Maternal and child nutrition: effects on health and development throughout the life course

Christine P. Stewart, MPH, PhD

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Outline

- Nutrition and epidemiologic transition
- Nutrition in pregnancy
- ‘Barker hypothesis’ and the fetal origins of disease
- Life course approach to nutritional epidemiology
- Selected example: Obesity and diabetes during pregnancy

Background

- Deficiencies during pregnancy or early childhood have been associated with an increased risk of mortality, morbidity, poor growth, and poor cognitive performance.
- Overweight, obesity and associated co-morbidities are growing in prominence in many parts of the world
- The consequences of obesity in pregnancy have only recently begun to be studied

The Nutrition Transition

Urbanization, economic growth, technological changes for work, leisure, and food processing

Pattern-3: Receding famine

- Starchy, low variety, low fat, high fiber foods
- Labor-intensive work/leisure

MCH deficiencies, stunting

Slow mortality decline

Pattern-4: Degenerative disease

- Increased fat, sugar, processed foods
- Shift in technology of work and leisure

Obesity emerges, bone density prob.

Altered life expectancy, ↑ NR-NCD

Pattern-5: Behavior change

- Reduced fat, increased fruits/veg, fiber
- Purposeful change in recreation & leisure activities

↓ body fatness, ↑ bone health

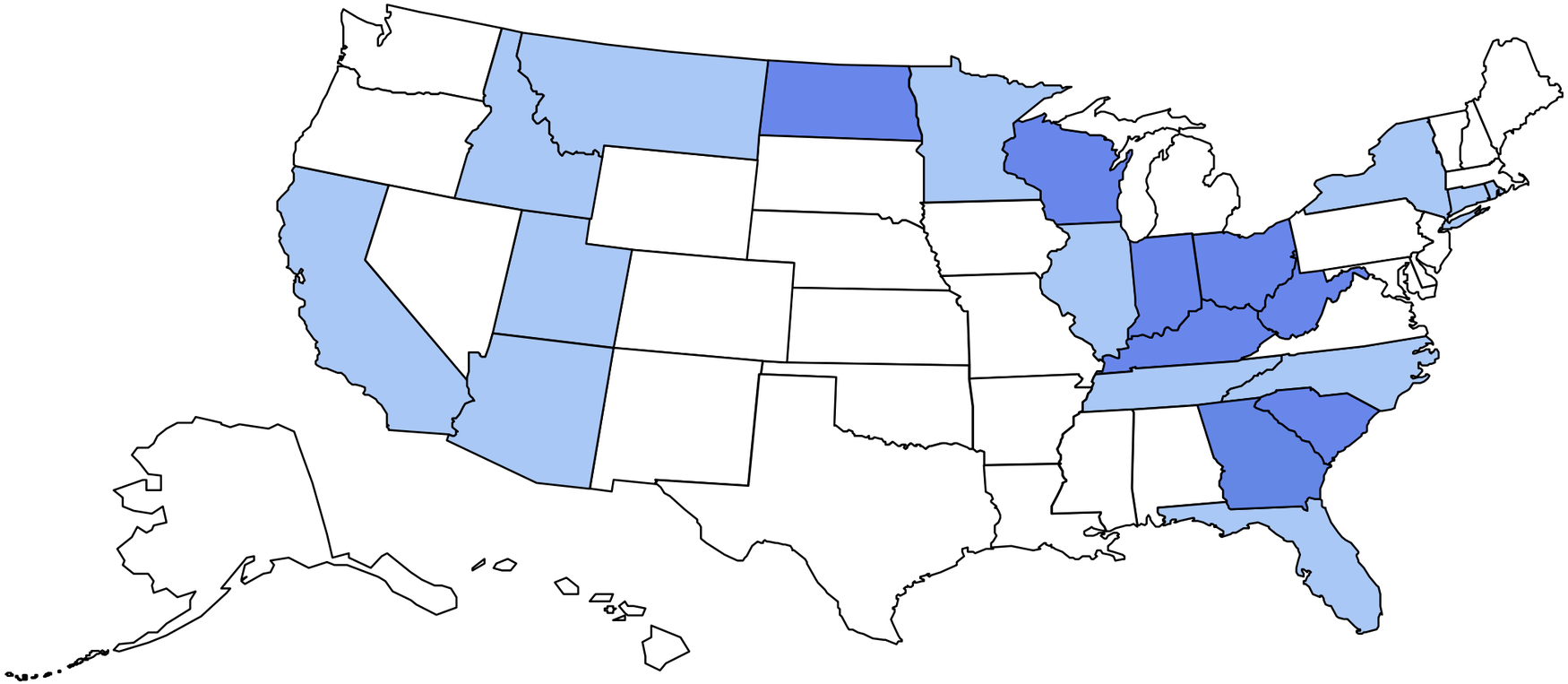
Healthy aging, ↓ NR-NCD

Adapted from Caballero & Popkin, 2002

Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



No Data <10% %–14%

Obesity Trends* Among U.S. Adults

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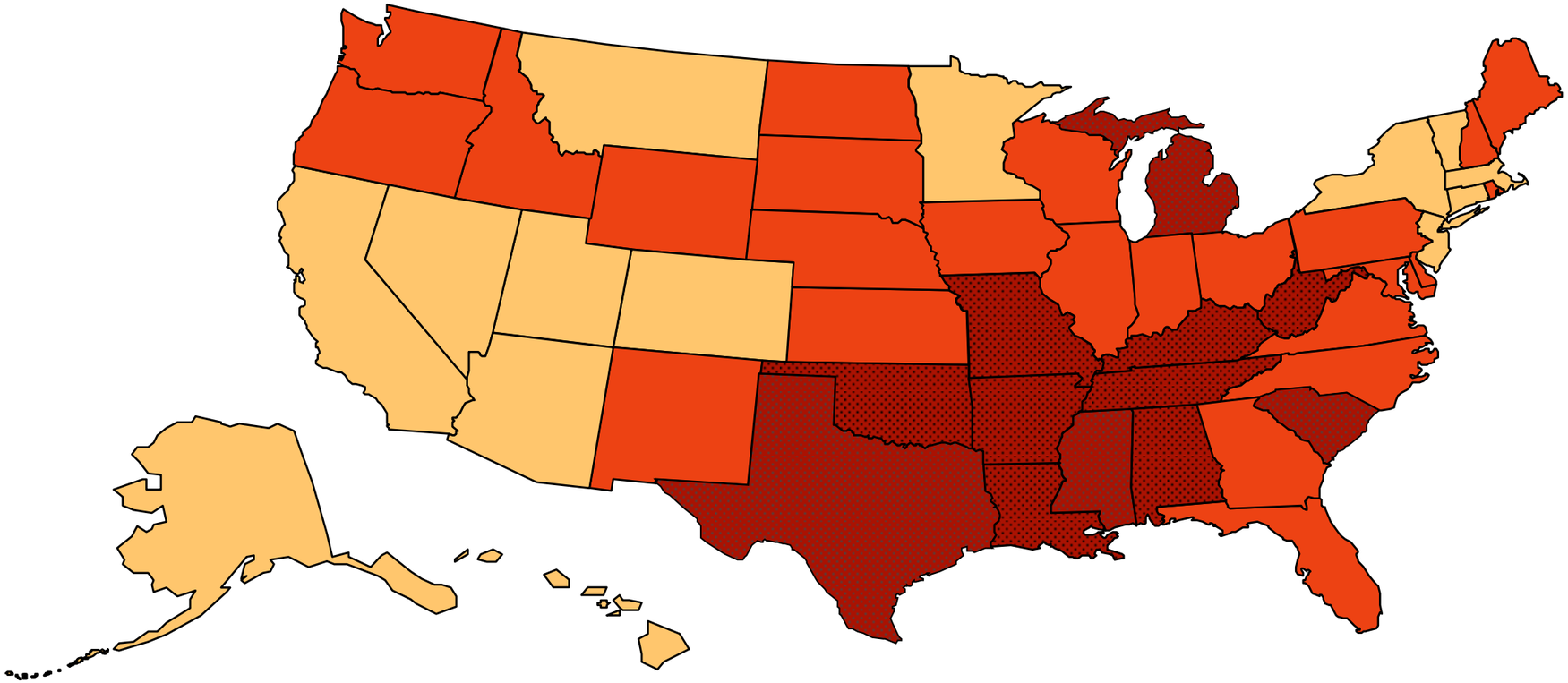


No Data | <10% | 10%–14% | 15%–19% | 20%–24% | 25%–29% | ≥30%

- While the United States is an extreme example, populations globally are undergoing dramatic transitions in health and nutrition patterns
- Individuals within those populations are undergoing dramatic transitions in diet, environmental exposures, and disease risk within their own lifetimes

"Epidemiologic Transition": Changes in leading causes of death over the past century

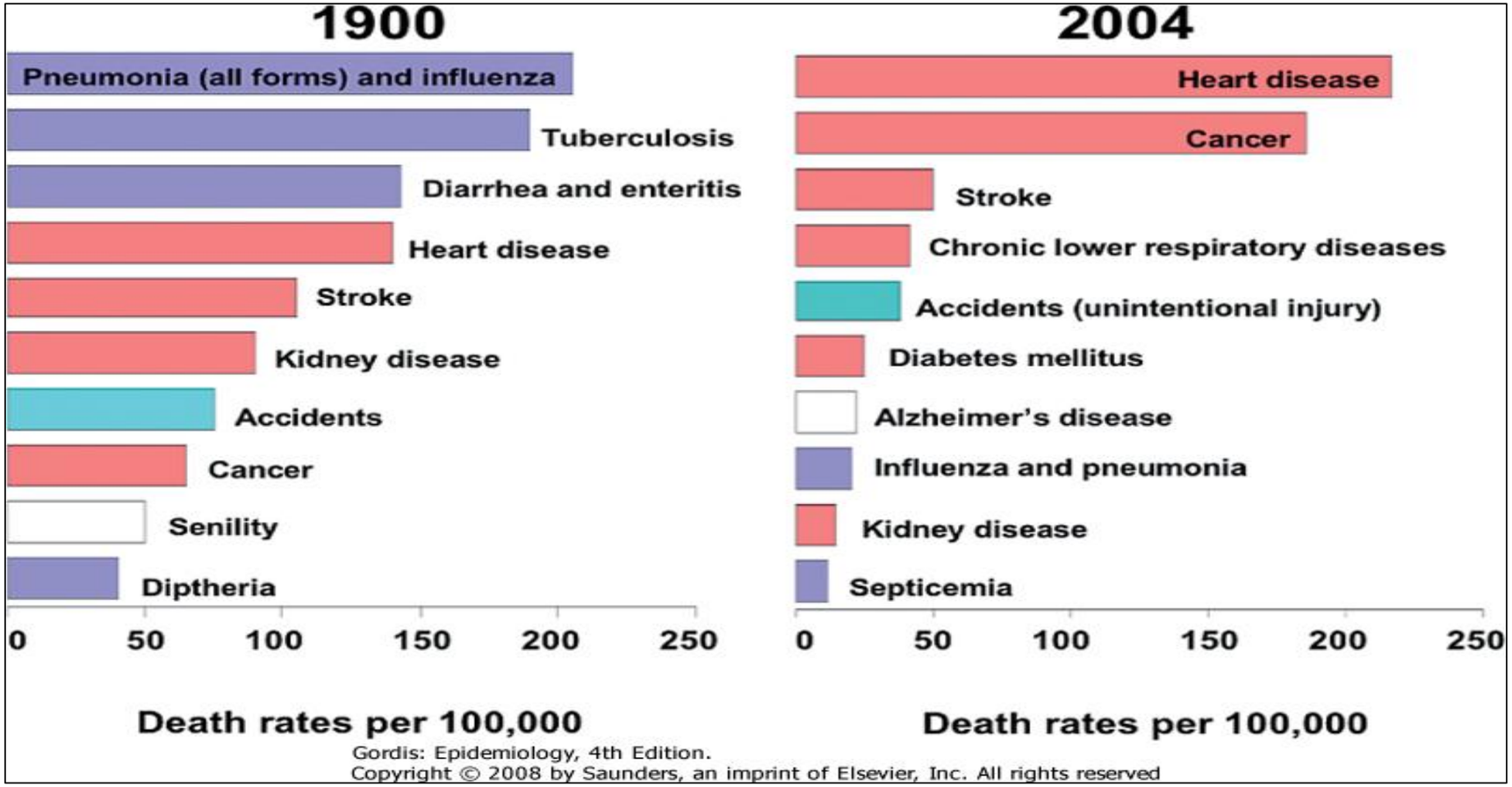


Figure 1-2 Ten leading causes of death in the United States, 1900 and 2004. Although the definitions of the diseases in this figure are not exactly comparable in 1900 and 2004, the bars in the graphs are color coded to show chronic diseases (salmon), infectious diseases (purple), injuries (aqua), and diseases of aging (white). (Redrawn from Grove RD, Hetzel AM: Vital Statistics Rates of the United States, 1940-1960. Washington, DC, US Government Printing Office, 1968; and National Center for Health Statistics: National Vital Statistics Report, vol 54, no 19, June 28, 2006.)

NUTRITION IN PREGNANCY

Nutrient metabolism

- Fetus receives nutrient supply from across the placenta via either active transport or facilitated diffusion
- Changes in nutrient metabolism in pregnancy are driven by:
  - Hormonal changes
  - Fetal demands
  - Maternal nutrient supply

Nutrient metabolism

- Types of adjustment
  - Accretion of new tissues or deposition in maternal stores
  - Redistribution among tissues
  - Increased turnover or rate of metabolism
  - Increased efficiency of nutrient absorption

Nutrient metabolism

- Fasting and postprandial glucose levels increase to delivery glucose needed for fetal growth.
- Elevated hormone levels increase insulin resistance, peaks in 3rd trimester.

Physiologic changes related to pregnancy

- Gastrointestinal function
  - Reduced intestinal motility, which leads to increased gastric emptying time (increased heartburn and constipation)
  - Decreased smooth muscle tone resulting in increased water absorption
  - Increased intestinal absorption of nutrients such as iron, calcium and vitamin B12
  - Increased colonic absorption of water and sodium

Physiologic changes related to pregnancy

- Renal function
  - Renal plasma flow increases by 50-80%
  - Glomerular filtration rate increases by 50%
  - Increased urinary excretion of glucose, amino acids, and other nutrients
  - Sodium and water retention increases

Physiologic changes related to pregnancy

- Cardiovascular function
  - Increased cardiac output (amount of blood pumped per beat per minute)
  - Expansion of blood volume
    - ~43% increase in plasma volume
    - ~30% increase in number of blood cells (expansion of the red blood cell mass)

Changes in food intake during pregnancy

- Some factors explaining changes in food intake:
  - Morning sickness/ food aversions
  - Cravings
  - Taboos, food beliefs
  - Changes in taste acuity (ex. salt)
  - Nutritional counseling

Nutrient requirements of pregnancy

- Nutrient requirements increase with pregnancy, but not proportionally
- Maternal behavioral changes augment physiologic changes to meet nutrient requirements
- A limit exists to the physiologic capacity to adjust metabolism. When that limit is exceeded, fetal growth & development are impaired

LONG-TERM CONSEQUENCES OF UNDER- AND OVER-NUTRITION DURING PREGNANCY

Developmental origins of health and disease hypothesis

- Early life nutritional and environmental factors may impact later life disease risk
- Earlier research focused predominantly on fetal growth restriction (indicated by lower birth weight) and adult chronic disease risk

“Barker’s” Hypothesis

Infant mortality rates, 1901-1910

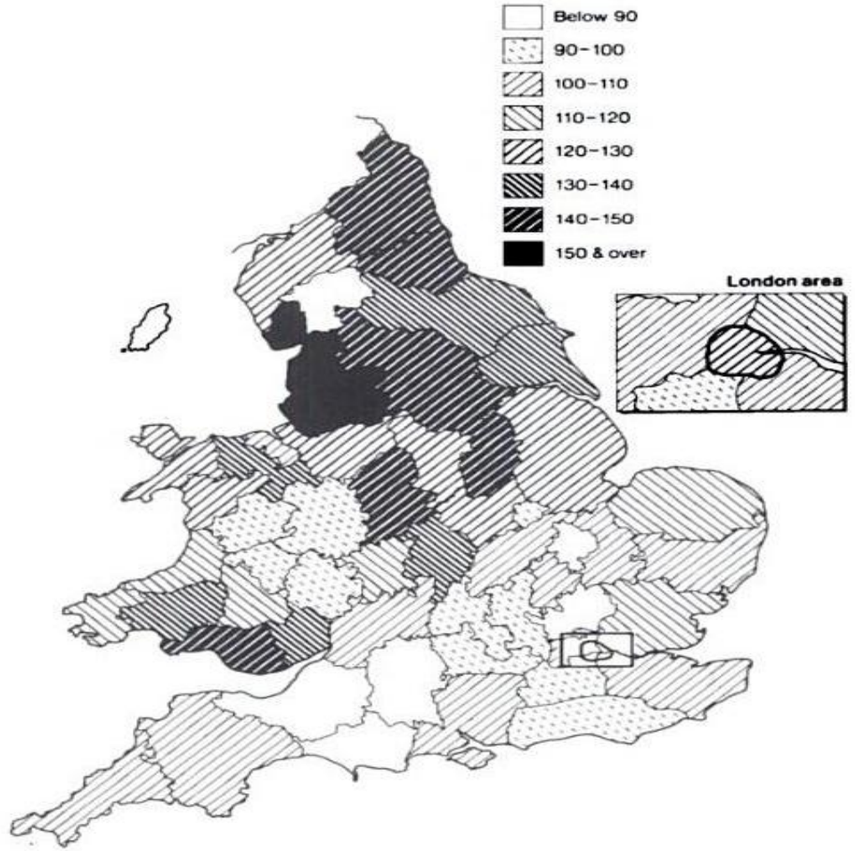
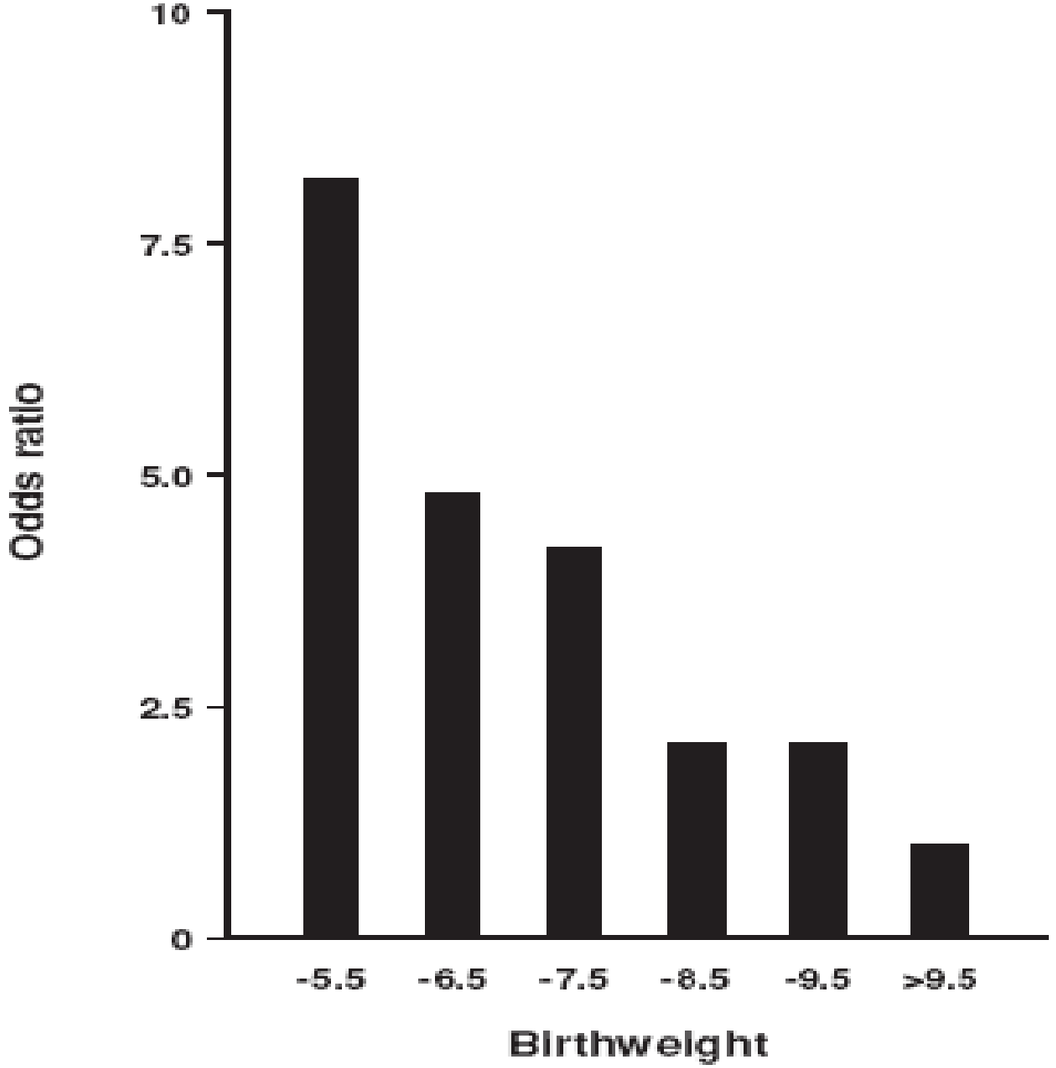


Fig. 1.3 Infant mortality rates per 1000 births in England and Wales during 1901–10.

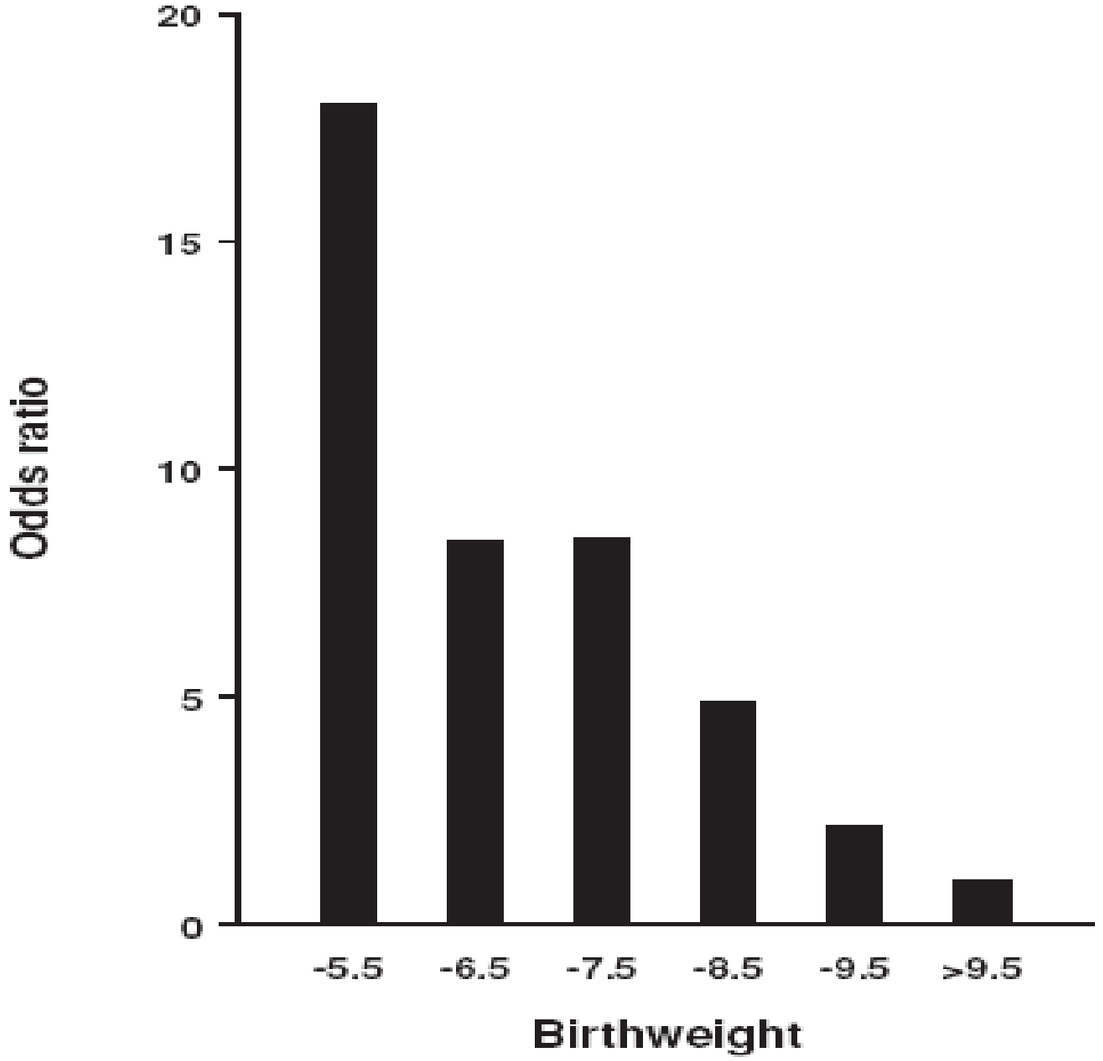
CHD mortality rates, 1968-1978

Fig. 1.2 Standardised mortality ratios (SMR) for coronary heart disease in England and Wales among men aged 35–74 years during 1968–78.

Barker, Mothers, babies and health in later life, 1998



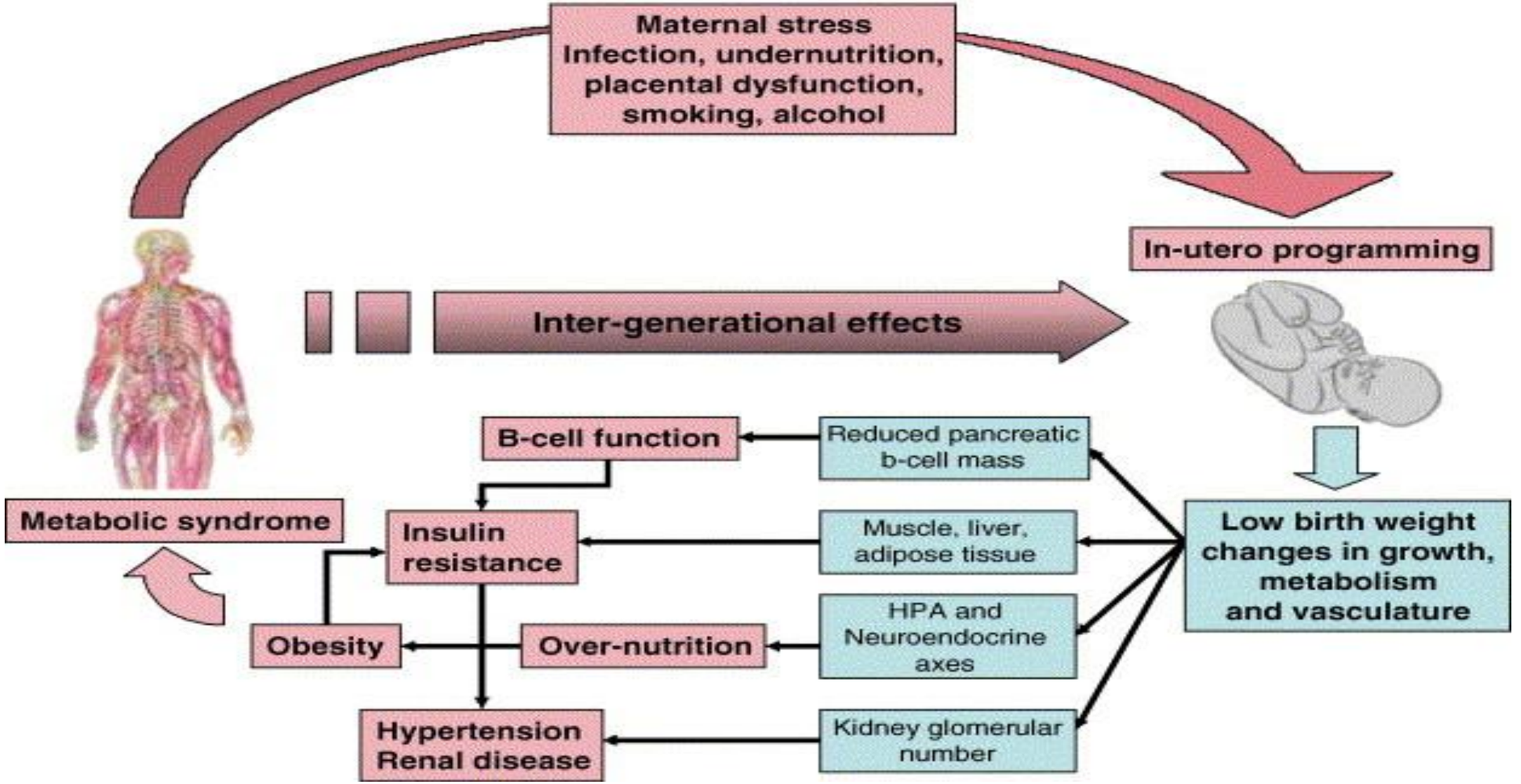
Odds ratios for impaired glucose tolerance or Type II diabetes among 64 yr old men in Hertfordshire (adjusted for adult BMI)



Odds ratios for metabolic syndrome among men in Hertfordshire (adjusted for adult BMI)

Hales & Barker, 2001

The Thrifty Phenotype Hypothesis



D.S. Fernandez-Twinn , S.E. Ozanne, Physiology & Behavior Volume 88, Issue 3 2006 234 - 243

The Dutch Famine

- Late 1944-May 1945
- Food supplies in the northern and western regions of the Netherlands were halted due to a German blockade
- A harsh winter froze the canals, effectively cutting off the vital supply routes
- Food rations dropped to 500 calories per day
- 18,000 people died due to starvation during the famine

The Dutch “Hunger Winter” of 1944

Dutch Famine

- Summary of findings in 50 year old survivors
  - Exposed in early gestation
    - Higher BMI & waist circumference (among women) (Ravelli 1999)
    - Higher ratio of LDL to HDL cholesterol (Roseboom 2000)
    - Increased risk of CVD (OR=3.0) (Roseboom 2000), though findings have been mixed (Lumey 2012)
    - Lower selective attention span in late adulthood (de Rooij 2010)
  - Those exposed during mid- or late gestation had:
    - Born small and stayed small throughout their lives
    - Reduced glucose tolerance (Ravelli 1998)
  - Those exposed in mid-gestation had:
    - Increased risk of microalbuminuria (OR=3.2) (Painter 2005)
    - Increased risk of obstructive airways disease (OR=1.7) (Lopuhaa 2000)

Epigenetics

We certainly need to remember that between genotype and phenotype, and connecting them to each other, there lies a whole complex of developmental processes.

E.H. Waddington, 1942

Epigenetics

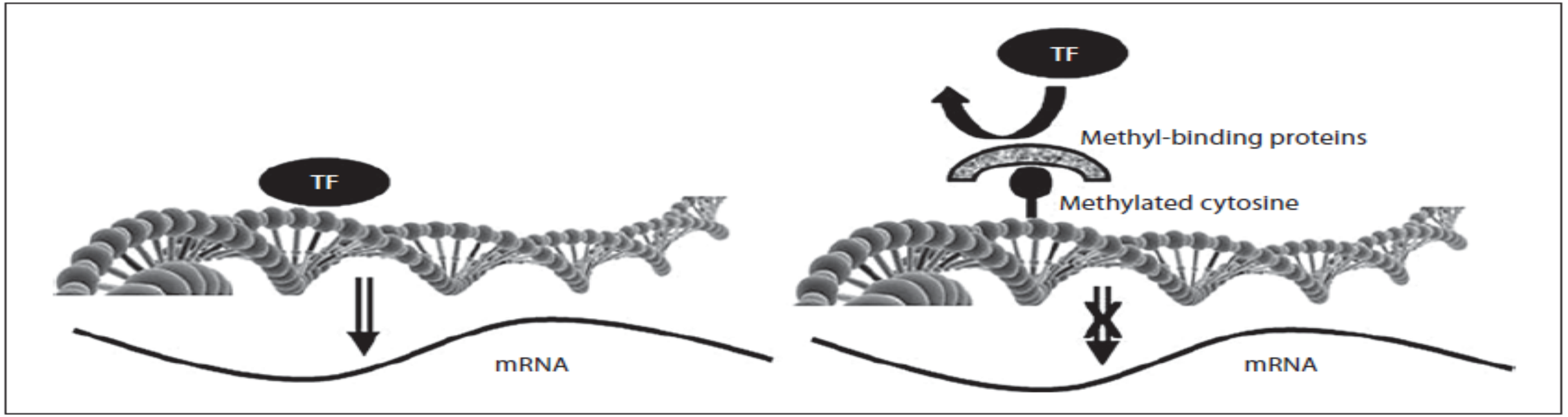


Fig. 2. Epigenetic regulation of gene expression. Normally, genes are expressed when transcriptions factors (TF) bind to DNA and activate the gene (left panel). One mechanism for controlling gene expression uses methylation of cytosines in DNA. When this methylation is present, proteins are attracted to the methylated site, and this blocks off access for the transcription factor and the gene cannot be turned on.

- DNA methylation
- Histone modification
- Non-coding RNAs

Zeisel, 2012

The ‘fetal origins of disease’

- Animal evidence has been fairly strong and consistent:
  - Global nutrient restriction, restriction in methyl-donor nutrients (folate, B6, B12, choline), some minerals (Zn, Mg) has adverse effects on cardiovascular development, renal development, insulin signaling, body composition
  - Effects are exacerbated when exposed to a ‘high fat’ or ‘western’ diet postnatally

The ‘fetal origins of disease’

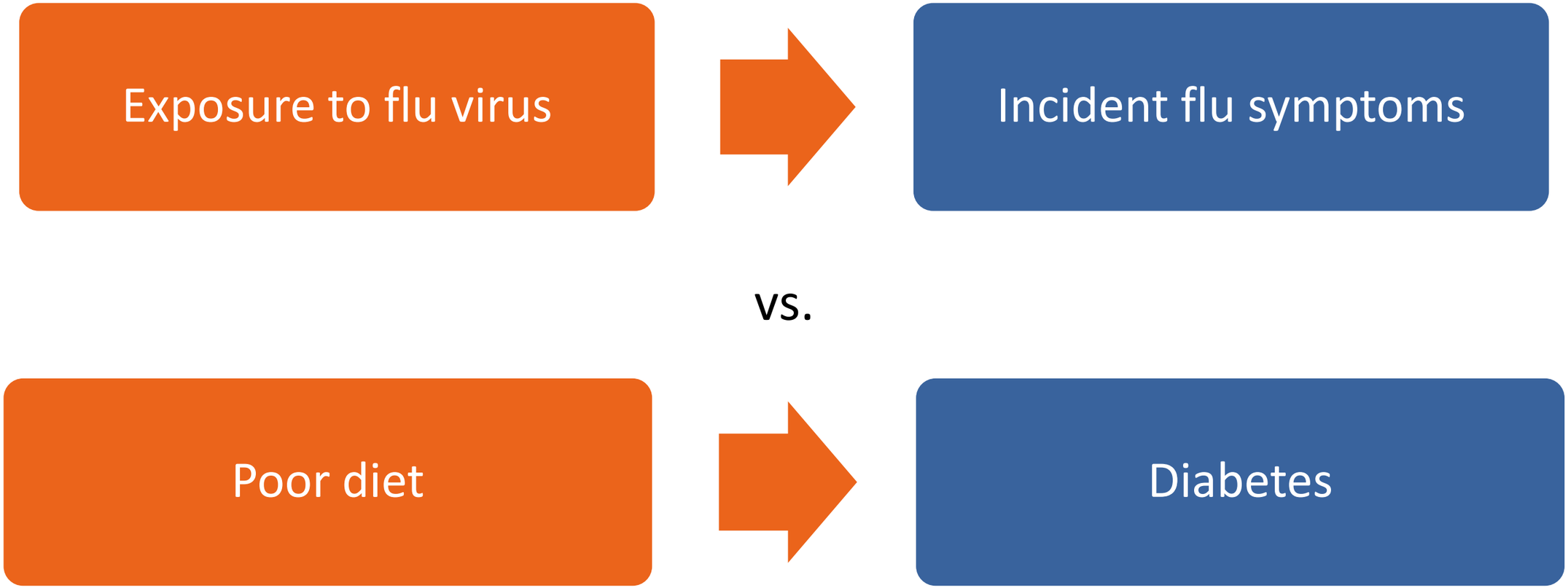
- Human evidence has been mixed
  - Long duration of time needed for follow-up contributes to selection bias
    - Large losses to follow-up
    - Survivor bias
  - Confounding by socioeconomic factors, other environmental exposures
  - Difficulty to disentangle prenatal from postnatal effects
  - Difficulty in determining metabolic pathways when ‘insult’ may have occurred decades prior

Evolutions in epidemiologic thinking

- The field of epidemiology developed predominantly as a study of infectious disease epidemics
- Over time, there has been a transition from infectious disease to chronic disease as the primary cause of morbidity and mortality in many countries. Resulting need for new ways of thinking to understand disease causality.
- More recently, investigators have taken a ‘life course’ approach to study a variety of health and disease outcomes related to both under- and over-nutrition (among other exposures) during fetal development and beyond.

Differences in ways of thinking about disease causality

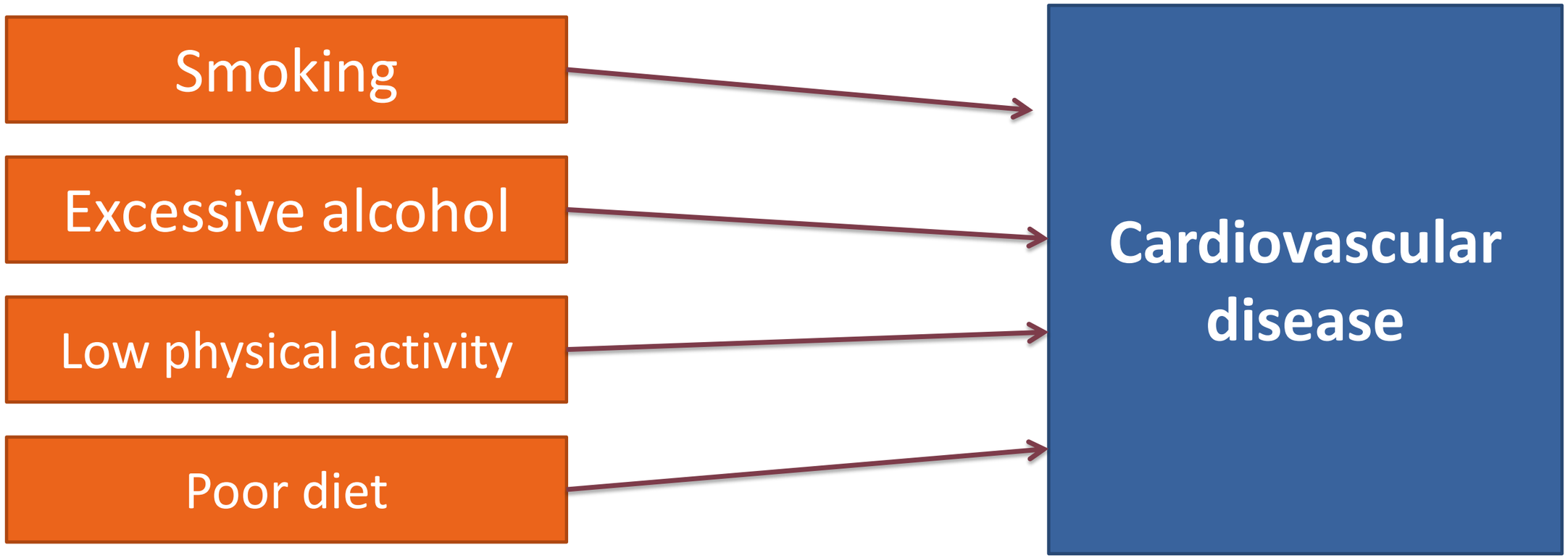
How long would you have to wait to see an outcome?



What causes disease?

Adult risk factors

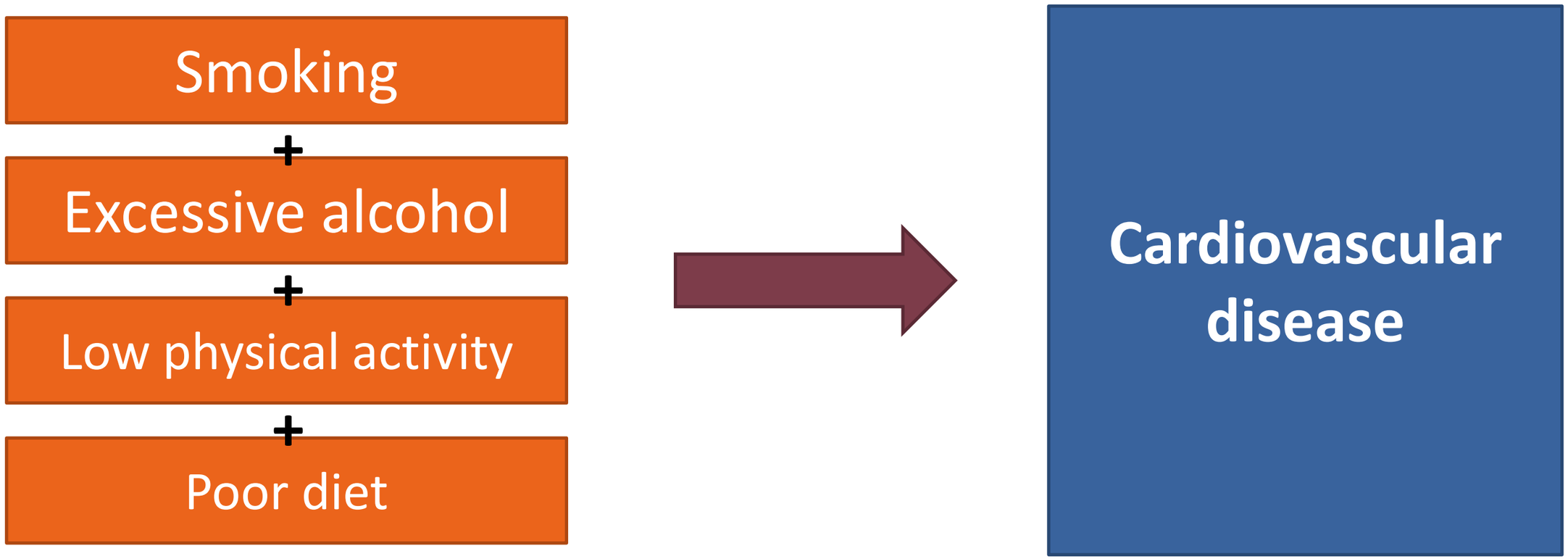
Does each factor independently cause CVD?



What causes disease?

Adult risk factors

Do you need a combination of risk factors to cause CVD?

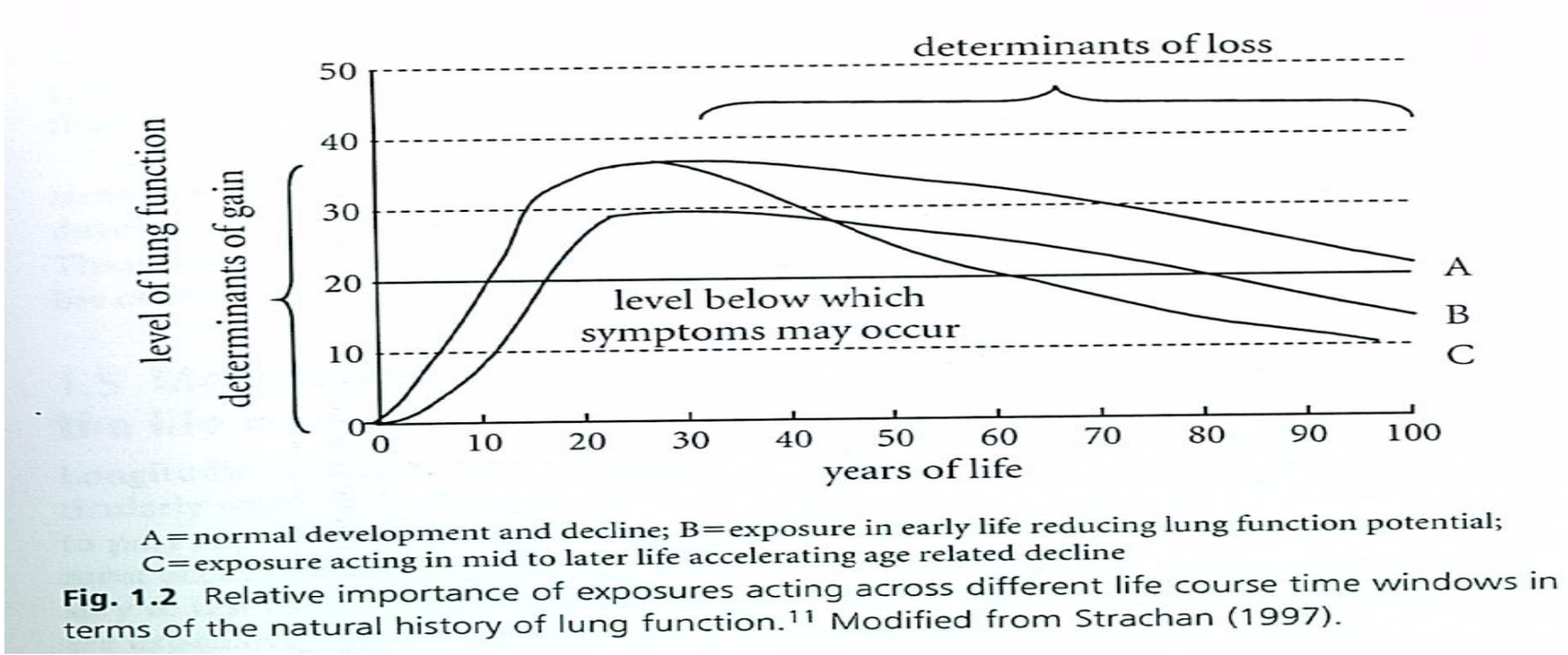


What causes disease?

Factors in childhood

Are there critical periods of life in which you are most sensitive to risk?

Lung function



A=normal development and decline; B=exposure in early life reducing lung function potential; C=exposure acting in mid to later life accelerating age related decline

Fig. 1.2 Relative importance of exposures acting across different life course time windows in terms of the natural history of lung function.[11] Modified from Strachan (1997).

Kuh & Ben-Shlomo, 2007

What causes disease?

Factors in fetal development and infancy

Are there critical periods of life in which you are most sensitive to risk?

Brain development

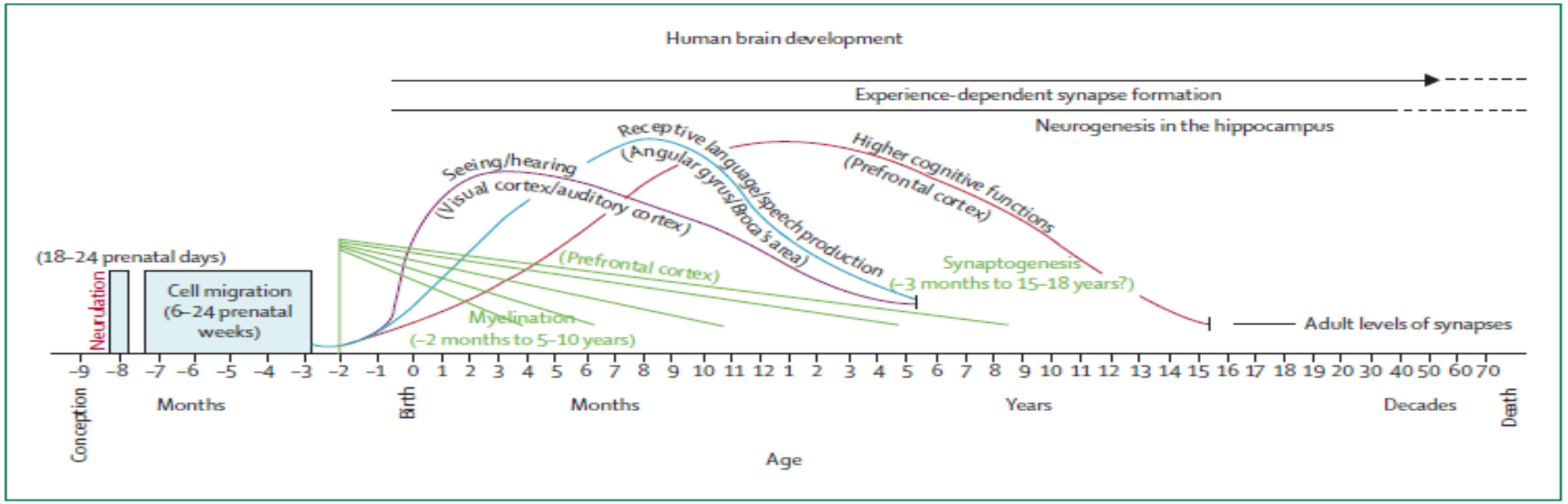
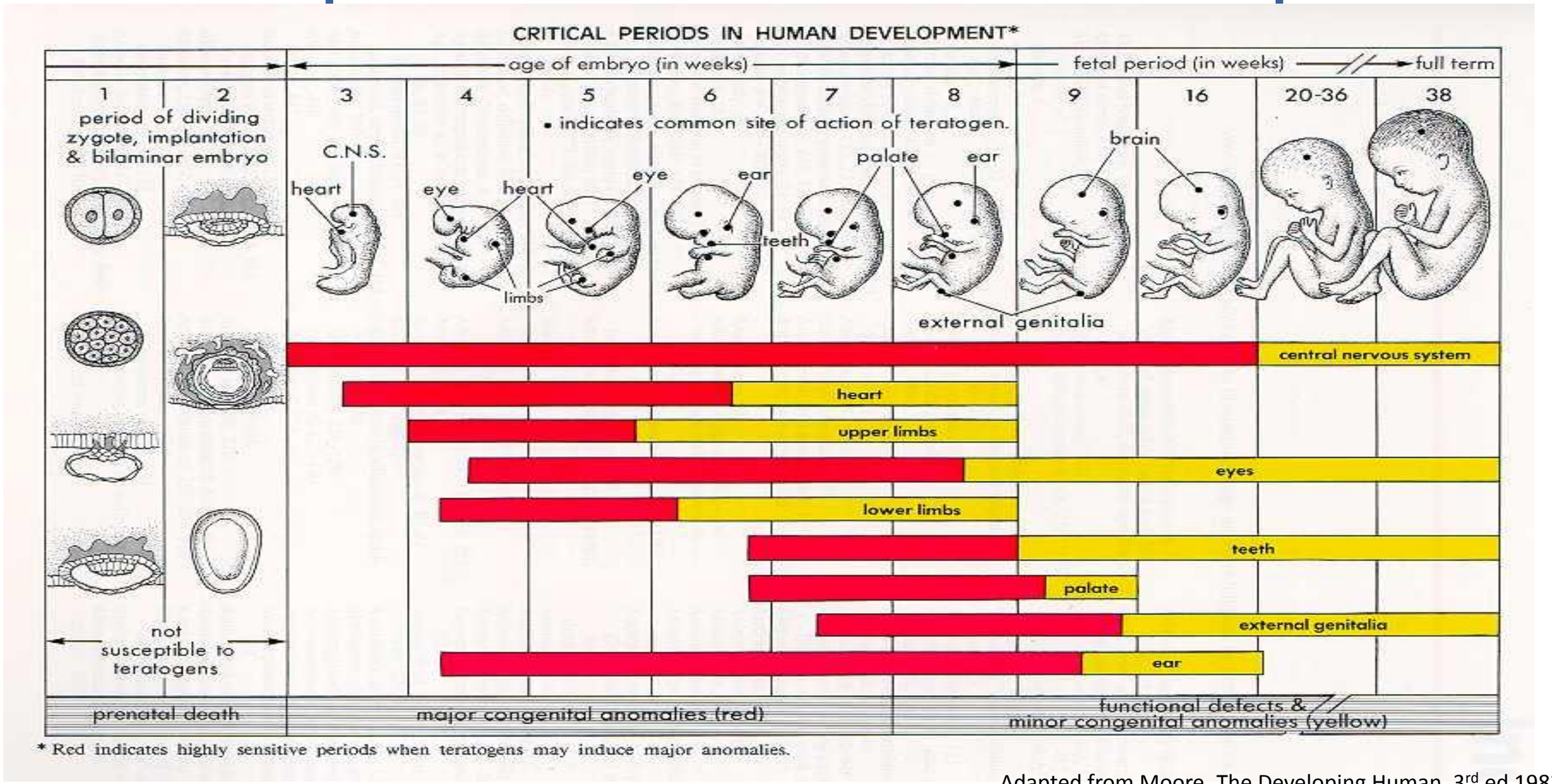


Figure 1: **Human brain development**
Reproduced with permission of authors and American Psychological Association[17] (Thompson RA, Nelson CA. Developmental science and the media: early brain development. *Am Psychol* 2001; **56:** 5–15).

Grantham-McGregor, 2007

Critical periods of human development



* Red indicates highly sensitive periods when teratogens may induce major anomalies.

Adapted from Moore, The Developing Human, 3rd ed 1982

CONSEQUENCES OF OVERWEIGHT/OBESITY AND COMPLICATIONS DUE TO DIABETES DURING PREGNANCY

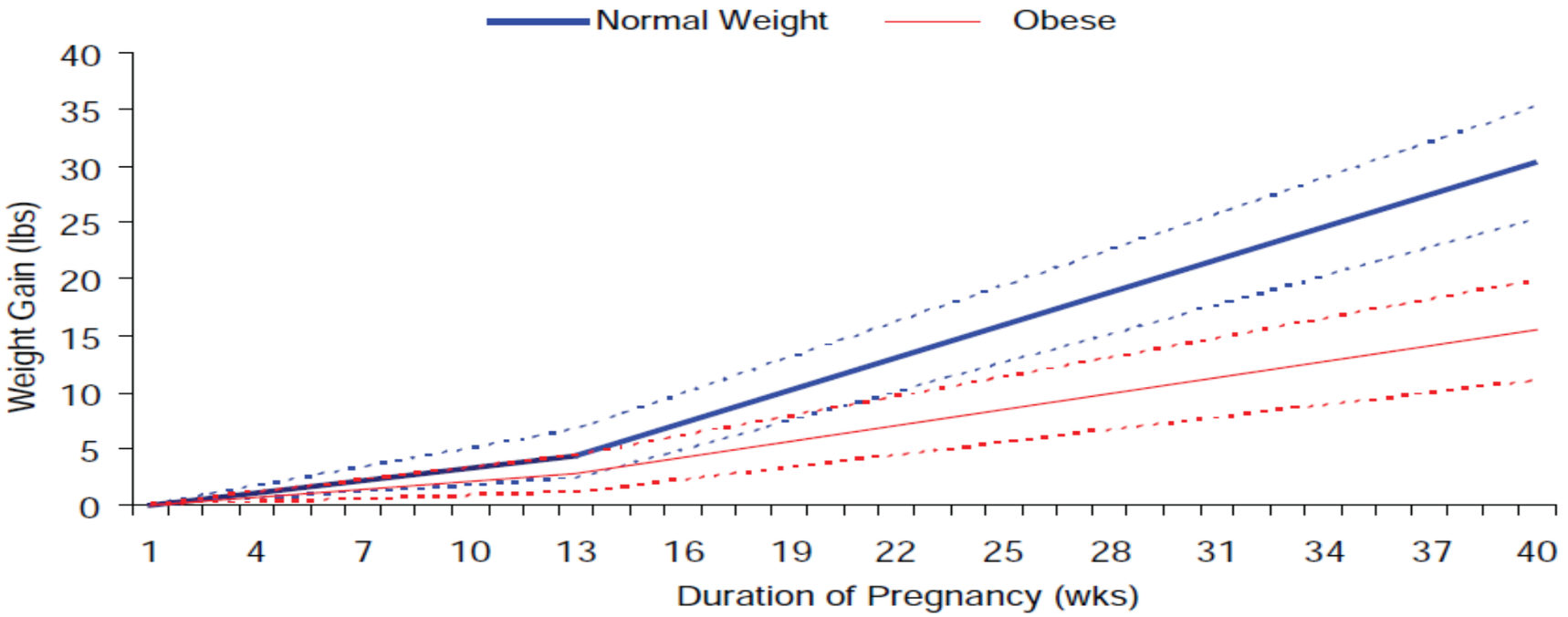
Weight gain recommendations

Pre-pregnancy BMI	BMI (kg/m^2)	Total weight gain range	Rates of weight gain in 2nd & 3rd trimester (mean range in lbs/wk)
Underweight	<18.5	28-40	1 (1-1.3)
Normal weight	18.5-24.9	25-35	1 (0.8-1)
Overweight	25.0-29.9	15-25	0.6 (0.5-0.7)
Obese (includes all classes)	≥30.0	11-20	0.5 (0.4-0.6)

IOM, 2009

Recommended weight gain for normal weight and obese mothers

FIGURE 1: WEIGHT GAIN COMPARISON BETWEEN NORMAL WEIGHT AND OBESE BMI CATEGORIES

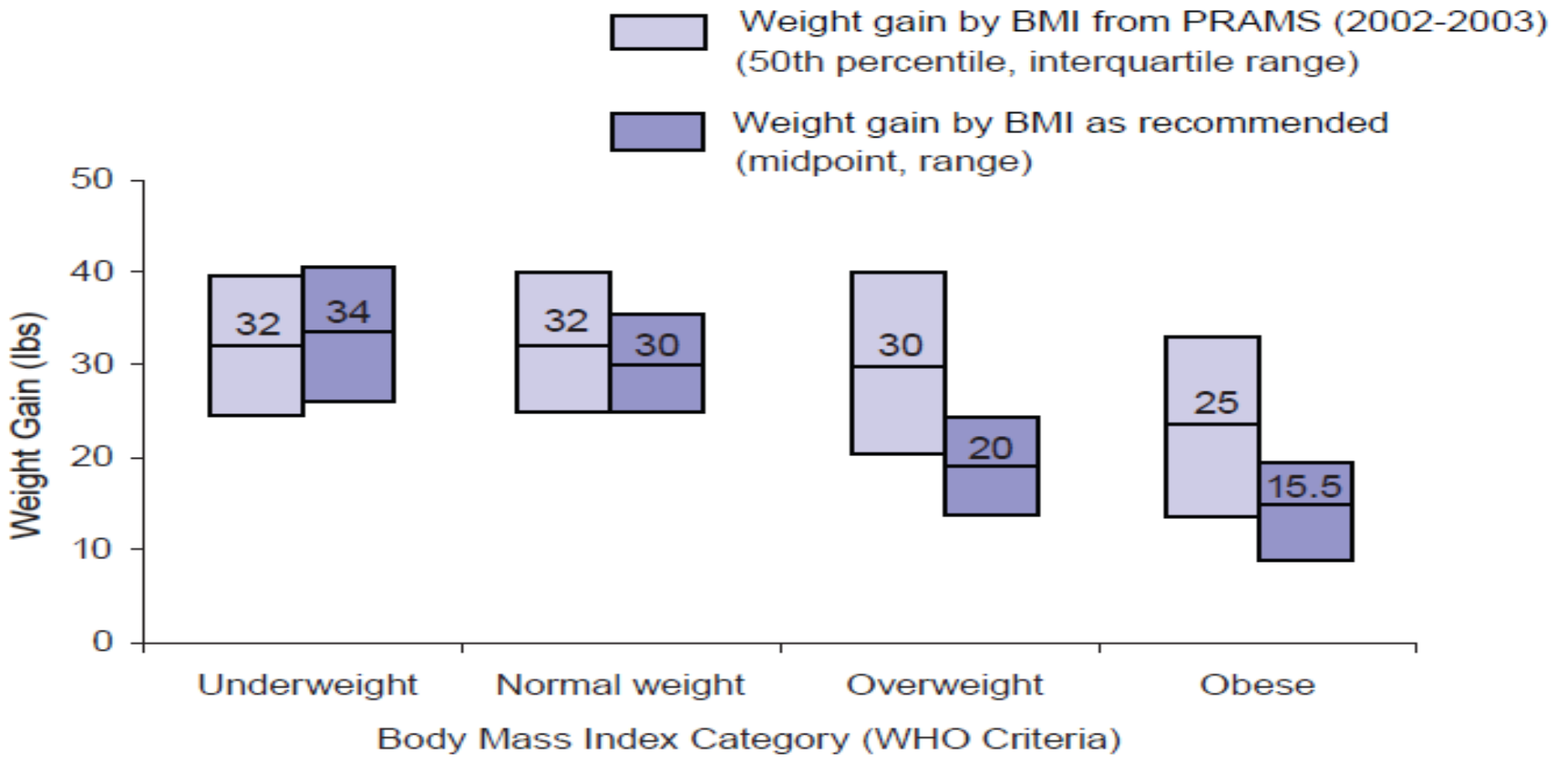


The difference between the median (solid lines) and range (dotted lines) of recommended weight gain for pregnant women within normal weight (BMI 18.5-24.9 kg/m2) and obese (BMI > 30.0 kg/m² categories is shown in Figure 1.

IOM, 2009

Recommendations vs. reality

FIGURE 2: CURRENT TRENDS IN WEIGHT GAIN DURING PREGNANCY COMPARED TO THE RECOMMENDED GUIDELINES

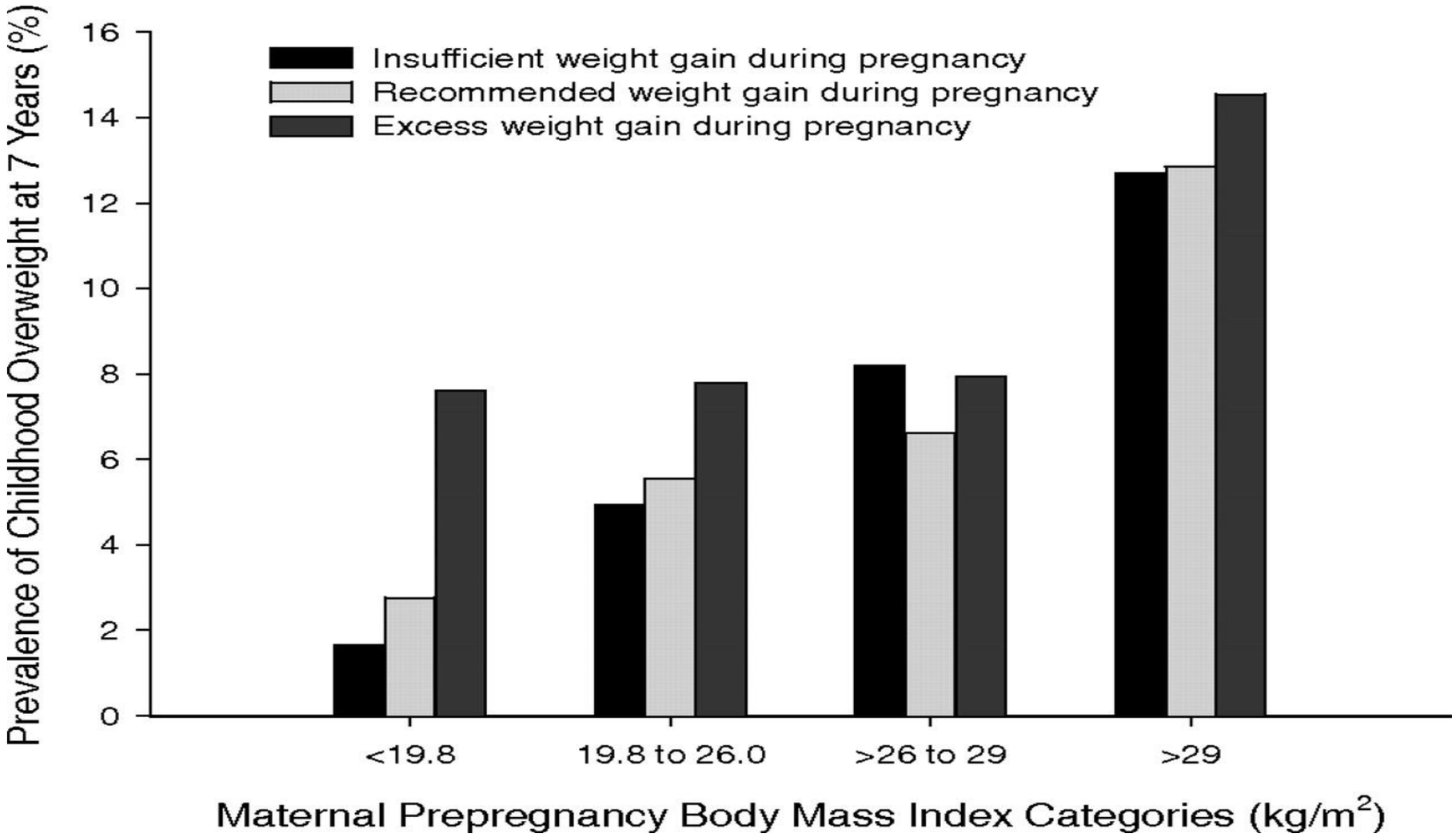


Comparison of weight gain by BMI category between data reported in the Pregnancy Risk Assessment Monitoring System (PRAMS), 2002-2003, and weight gain as recommended in the new guidelines.The number in the center represents the midpoint, and the boxes represent the ranges in weight gain for each body mass index (BMI) category.

IOM, 2009

Prevalence of childhood overweight at 7 y by maternal pre-pregnancy BMI categories and gestational weight gain categories.

The American Journal of Clinical Nutrition



Wrotniak B H et al. Am J Clin Nutr 2008;87:1818-1824

©2008 by American Society for Nutrition

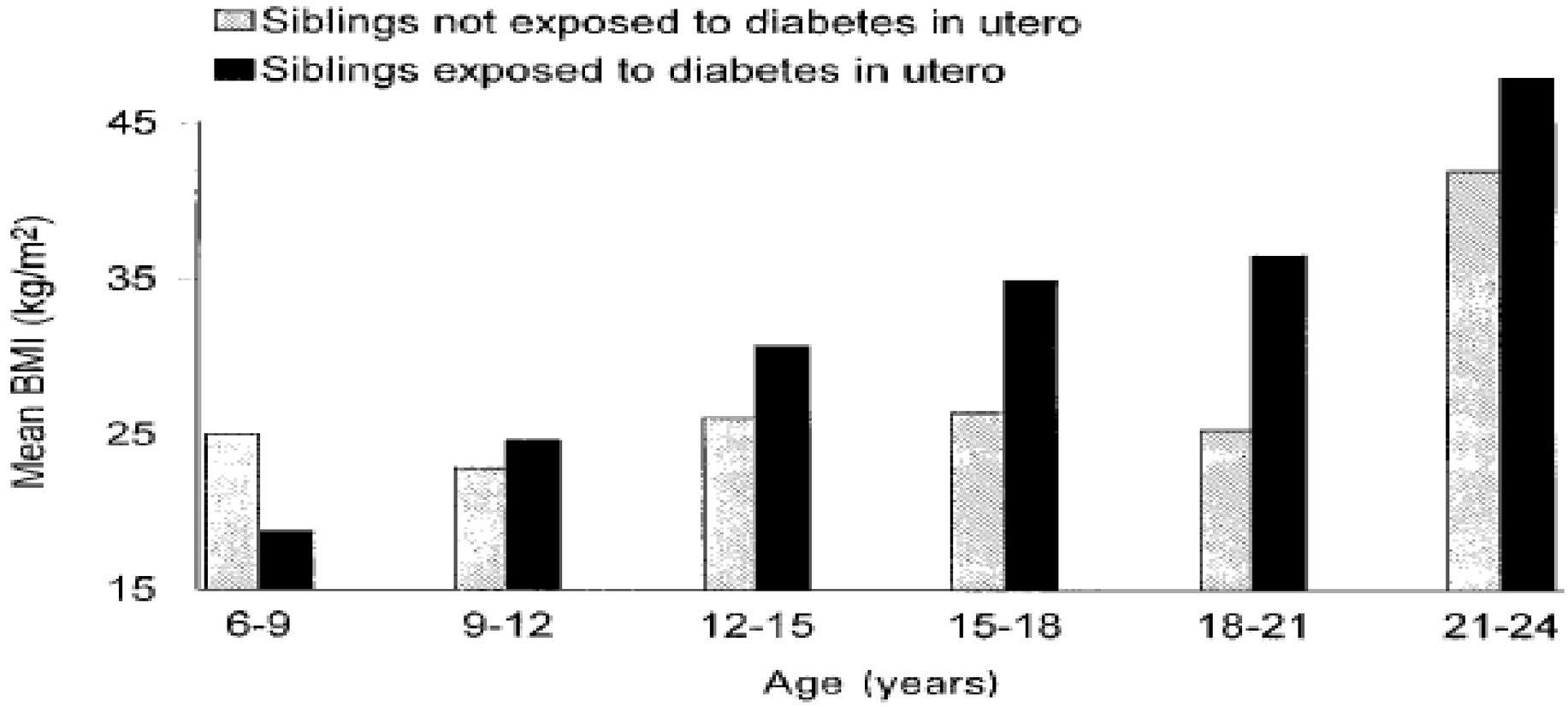
Diabetes during pregnancy

- Infants of diabetic mothers are at significantly greater risk of spontaneous abortion, stillbirth, congenital malformations, morbidity and mortality
- 3-10% of pregnancies in the United States are affected by abnormal glycemic control, 80% of these are gestational diabetes (GDM)
- GDM is strongly associated with obesity (Chu, 2007):
  - Overweight women: 2.1 fold greater risk
  - Obese women: 3.6 fold greater risk
  - Morbidly obese women: 8.6 fold greater risk

Diabetes during pregnancy

- Fetus is exposed to hyperglycemia, resulting in increased fetal insulin levels that serves as a growth promoter and storage of excess energy as fat
- Fetal macrosomia may result

Mean BMI in siblings exposed and unexposed to a diabetic intrauterine environment



Dabelea et al, 2000

Table 4 Associations of gestational diabetes with childhood overweight from logistic regression models

Outcomes	Model 1		Model 2	
	OR[a]	95% CI	OR[b]	95% CI
Overweight at age 3 ($n = 10{,}413$)	1.39	0.79, 2.43	1.22	0.69, 2.15
Overweight at age 4 ($n = 11{,}919$)	2.09*	1.35, 3.21	1.81*	1.18, 2.86
Overweight at age 7 ($n = 22{,}768$)	1.68*	1.31, 1.16	1.61*	1.07, 1.28

OR odds ratio

* $P < 0.5$

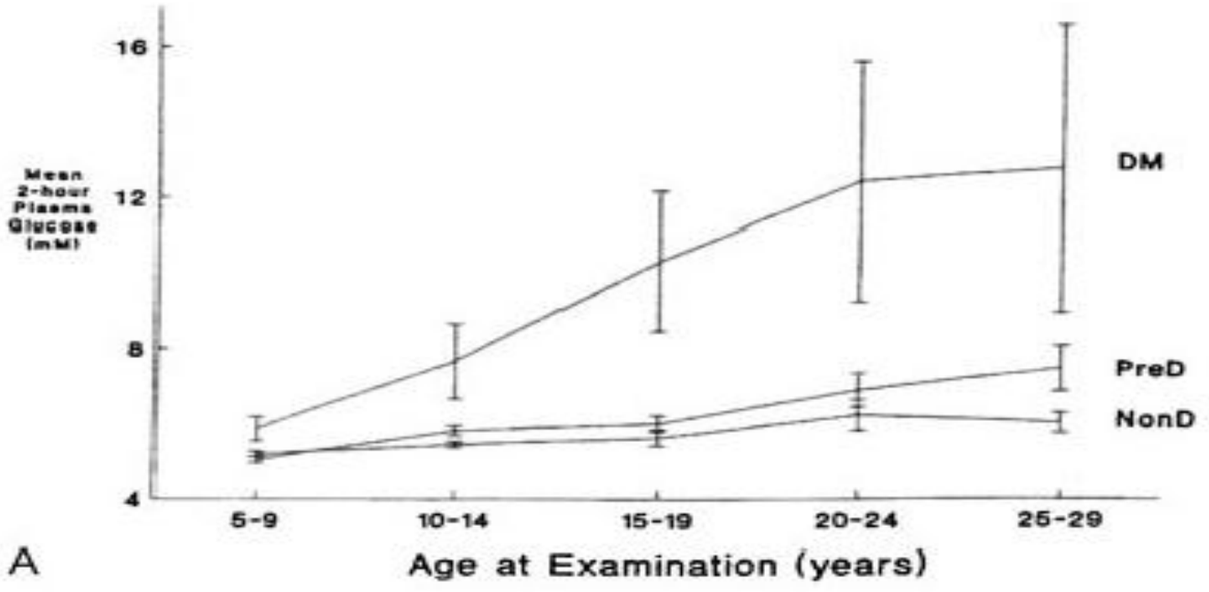
[a] Adjusted for maternal age, maternal pregnancy BMI, pregnancy weight gain, family income

[b] Adjust for maternal age, maternal pregnancy BMI, pregnancy weight gain, family income, and birth weight

Fraser et al, 2012

Risk of diabetes in offspring of diabetic mothers (Pima Indians)

Glucose intolerance



Prevalence of Diabetes

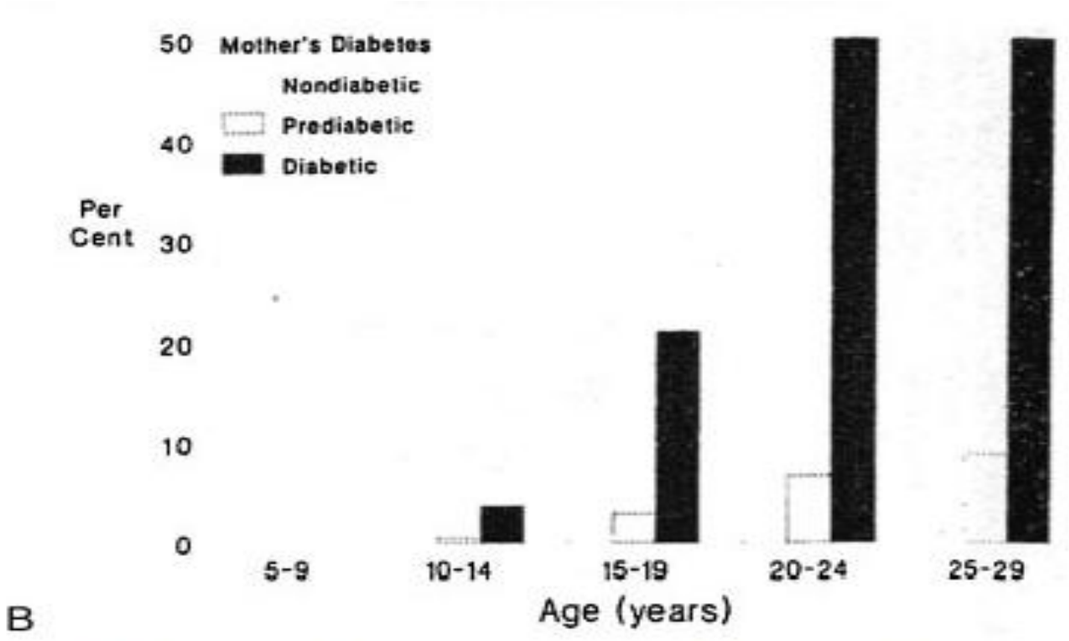


Figure 1 (A and B) Rates of glucose intolerance and diabetes in children born to diabetic women (DM), prediabetic women (PreD), and nondiabetic women (NonD).

Fetal hyperinsulinemia

- Fetal hyperinsulinemia in response to maternal hyperglycemia is a strong predictor of impaired glucose tolerance in later life
- In animal models, fetal hyperinsulinemia elevates expression of neuropeptide Y (NPY) in the hypothalamus that results in hyperphagia and weight gain in postnatal life

Diabetes during pregnancy: Iron metabolism

- Uncontrolled glycemia during pregnancy can result in fetal hypoxemia
- The fetus responds by increasing oxygen carrying capacity of the red blood cell mass.
- With RBC mass expansion of up to 30%, fetal iron demands are greatly increased
- Placenta up-regulates iron transport, but cannot fully compensate for higher requirements
- The fetus draws down fetal liver iron stores
  - 55% reduction in heart iron
  - 40% reduction in brain iron

Diabetes during pregnancy: cognitive impairments

- Reduced performance on tests of general development in infancy and toddlerhood (deRegnier et al 2000)
- Modest reduction in performance on learning and memory tasks in 3.5 y old children (Riggins et al 2009)
- Reduced school performance, educational attainment, and IQ (Fraser et al 2012)
- Impairments are generally mild to moderate, so may be possible to compensate with targeted interventions

Conclusions

- Nutrition during fetal development can have a life-long impact on health and disease risk
- Understanding the consequences of nutritional deficiencies or excesses in pregnancy requires a life-course approach, an understanding of the physiology of pregnancy, and of biologic ‘critical windows’ of development