Life-course epidemiology

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Learning objectives

- Assessing the contributions of genetic, fetal, and childhood environmental factors to adult health
  - Metabolic syndrome and cardiovascular disease as examples
- Resources and methods for longitudinal studies of early-life influences on adult health

Life-course approach

- Effect of exposures (genetic, environmental, social) during gestation, childhood, adolescence and later life on development and outcome of disease
- Methods and resources in common with social sciences: education, deviance/crime, economics
  - Use of routine data to test whether secular trends are explained by cohort effects or period effects
  - Longitudinal studies
  - Follow-up of old studies for which records have been preserved: birth records, randomized trials in childhood
  - Exploit “natural experiment”, or instrumental variables that have unconfounded effects on pathway of interest

Long-term effects of pre-school education for disadvantaged children

Centers	Chicago Child-Parent	High/Scope Perry
Year began 1972	1962	1962
Location	Chicago, IL	Ypsilanti, MI
Sample size	1539	123
Research design	Matched neighborhoods	Randomized trial
Ages	3-4 years	3-4 years
Program schedule	Half-day, school year	Half-day, school year
High school graduation	62% v. 51%	65% v. 45%
Ever arrested as juvenile	17% v. 25%	16% v. 25%
Ever arrested as young adult	Not Measured	25% v. 40% (ages 19-24)
Adult Smoker	Not Measured	45% v. 56% (age 27)
Costs and Benefits (2006 dollars discounted at 3%)		
Cost	$ 8,224	$ 17,599
Crime Cost Savings	41100	198981
Earnings	34,123	74878
Total Benefits	$ 83,511	$ 284,086
B-C Ratio	10.1	16.1

Why is life-course approach hard?

- Cohort studies of chronic disease (eg Framingham, Nurses' Health Study)are usually established in middle age because investigators and funding agencies want results within a reasonable time frame
- Life course epidemiology usually relies on identifying datasets or cohort studies laid down decades earlier
  - Paper records may be destroyed, digital records may be unreadable
  - Data protection laws may limit use of old records

Is disease risk set early in life?

Mortality/incidence statistics:

- cohort effect for cervical cancer, period effect for CHD

Migrant studies:

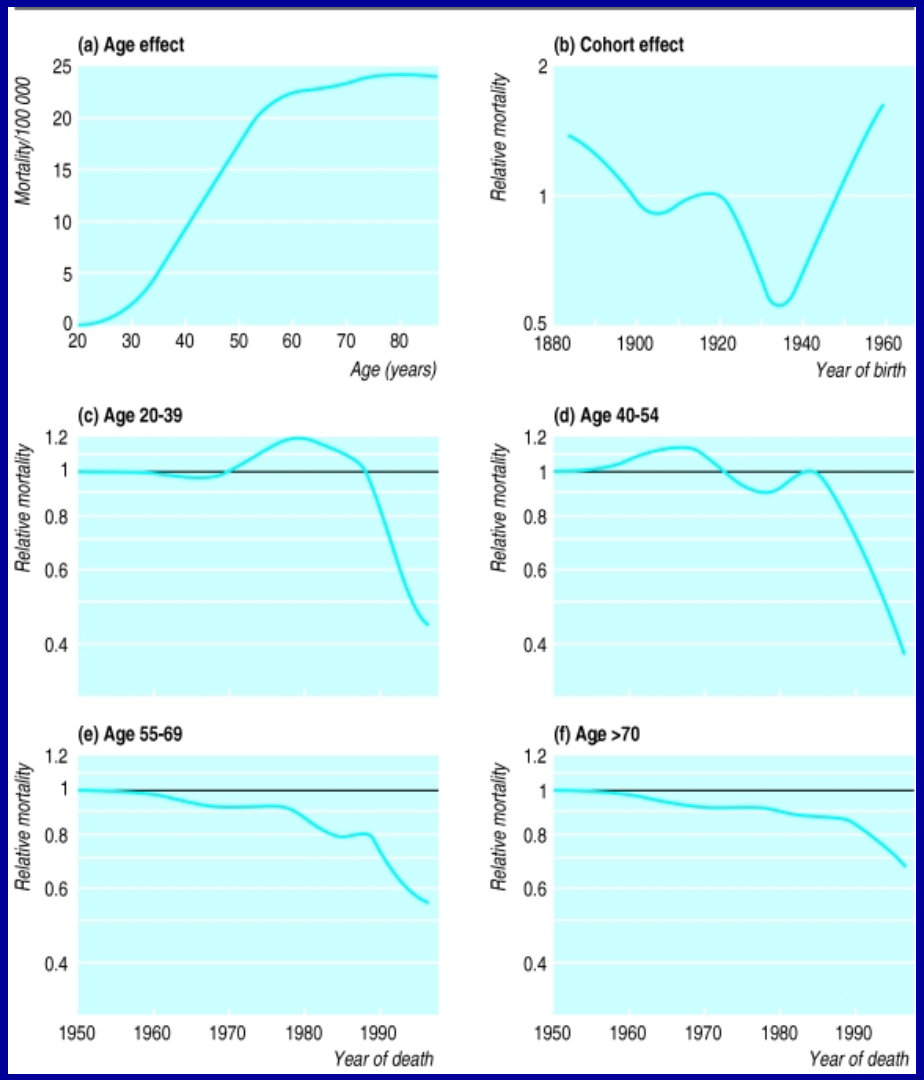
- colon cancer and breast cancer in Japanese-Americans,
- multiple sclerosis in migrants from UK to South Africa

- Experimental models
  - *critical periods* for development: e.g. visual cortex
- Observational studies of associations with traits that are set early in life
  - e.g. leg length as a proxy for childhood nutrition

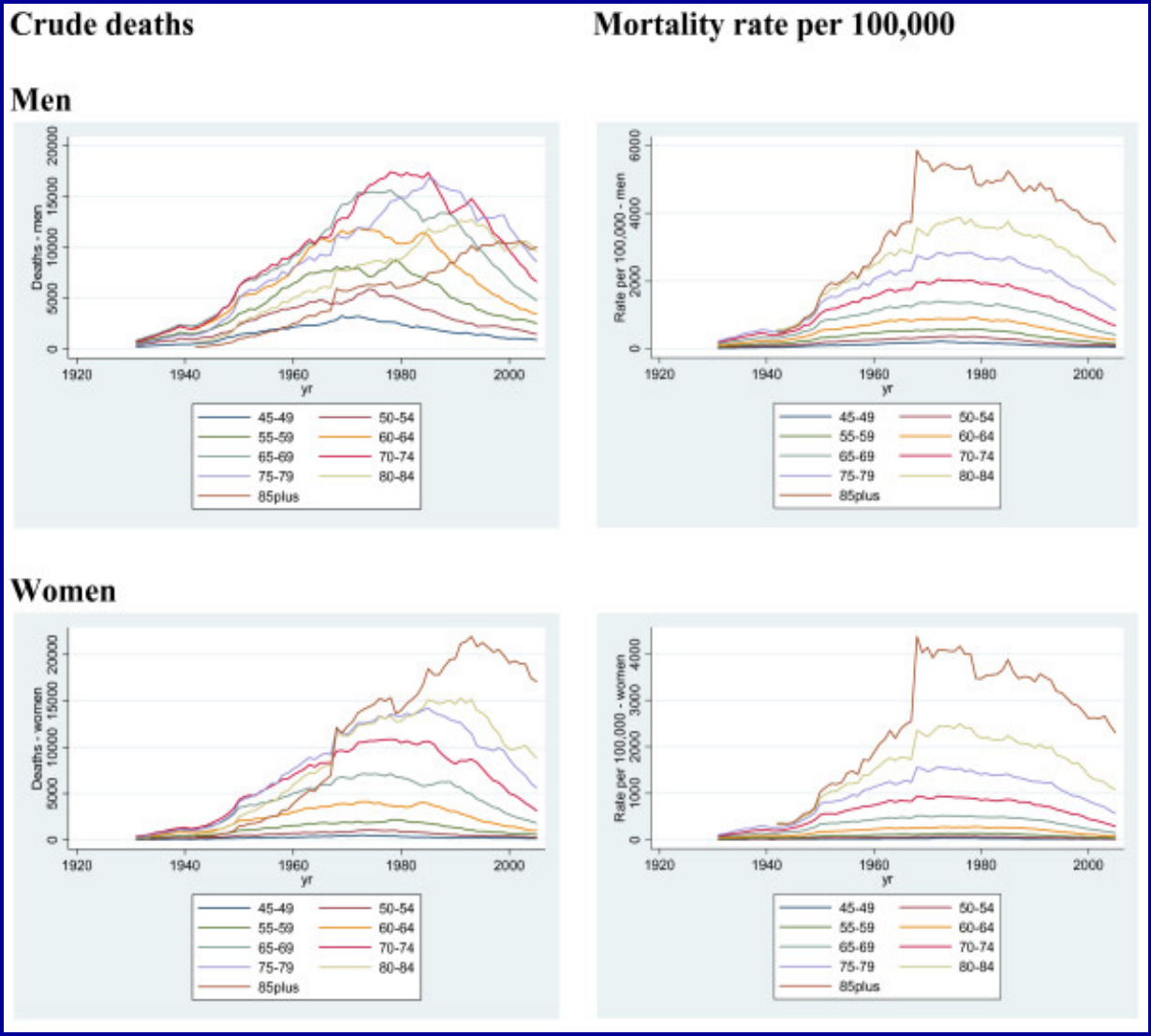
Age, period and cohort effect

- log failure rate (incidence, mortality)
  = mean + age effect + period effect + cohort effect
  - *period effect*: rates change for all age groups at same time
  - *cohort effect*: plots of log rate against age for successive birth cohorts are shifted up or down
- Inference is possible even though effects are not identifiable
  - because simpler models are more likely than complex models
  - Can distinguish period and cohort effects if there is a “turning point” when the trend reverses direction.

Age, period and cohort effects on cervical cancer mortality in E & W (Sasieni 1999)



Secular trend in CHD mortality in England & Wales 1931-2005: a period effect



How to distinguish between a cohort effect and a period effect in routine mortality data

- Plot age-standardized mortality rates
  - by calendar period
  - by birth cohort (e.g. 10-year age group)
- The evidence favours the simplest model that explains the data.

Cohort studies in the UK spanning birth to adulthood

- ONS Longitudinal Study: 1% of population with birth records, mortality, cancer registrations linked to Census records
- National birth cohorts with follow-up via questionnaire and physical examination:
  - 1946 (National Survey of Health and Development), 5362
  - 1958 (National Child Development Study), 17634
  - 1970 (British Cohort Study) 17196
    - data sharing established

Fetal origins hypothesis (Barker 1989)

- Ecological studies in Sweden and UK: correlation between infant mortality and later CHD/stroke mortality
- New cohorts assembled from birth records that included measurements of size at birth from 1920s in UK.
- Size at birth predicts blood pressure, Type 2 diabetes and mortality from coronary disease in adult life
- Effects of maternal undernutrition on blood pressure and glucose tolerance have been demonstrated in animal models

Ecological studies: infant mortality rates and average height predict stroke mortality

Correlation between stroke SMRs 1968–1978 and neonatal (N) and maternal (M) mortality death rates 1911-1914 in England & Wales

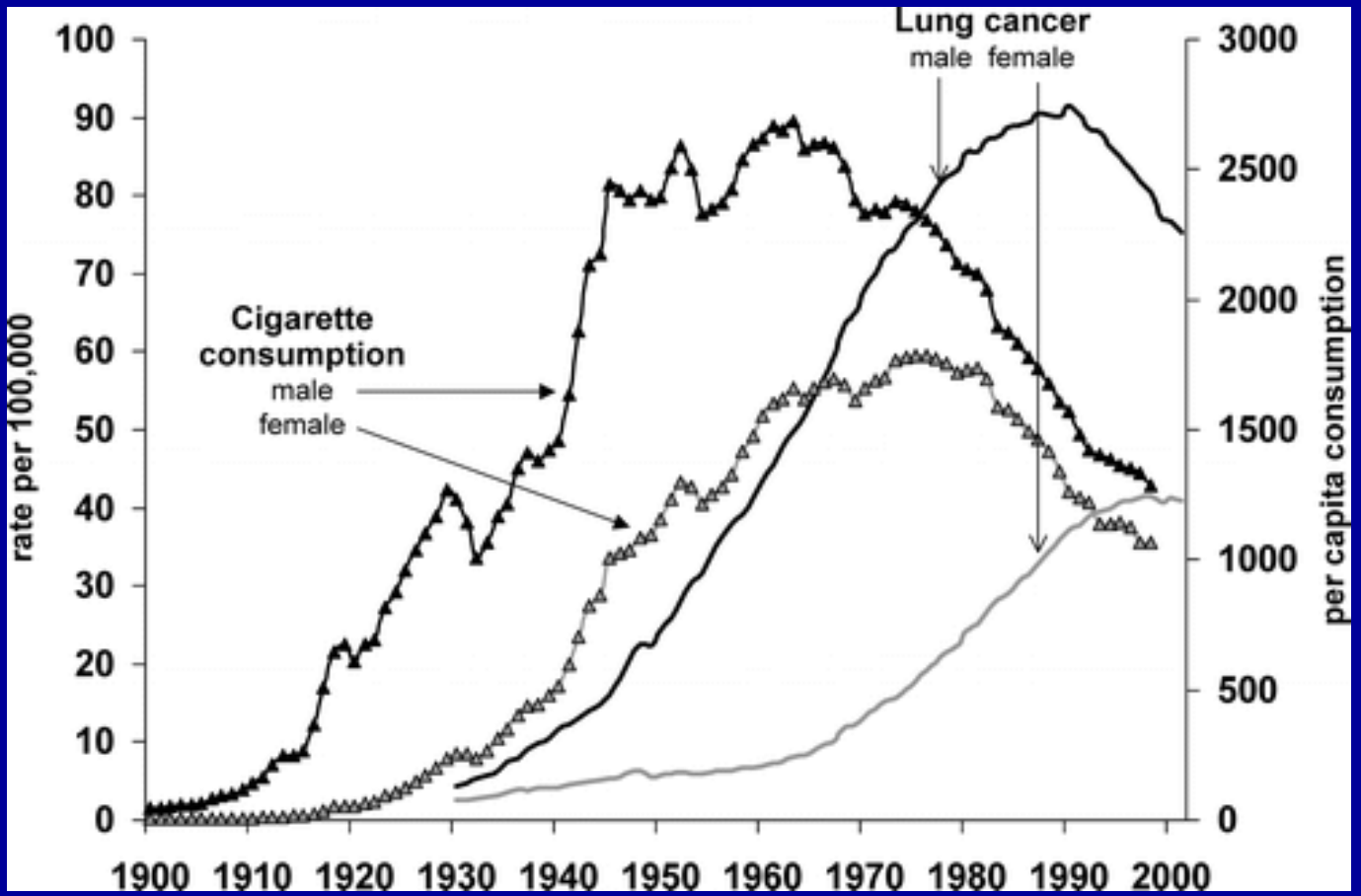
	Men	Women
N	0.61	0.54
M	0.61	0.53

Source: *Stroke.* 2003;34:1598.)

SMRs for stroke for counties grouped by average height

Height	Men	Women
Short	121	117
2	113	110
3	96	93
4	89	93
Tall	84	88

Sex-specific trends in smoking and lung cancer mortality: US



Lynch & Davey Smith Annu Rev Public Health. 2005;26:1-35

Association of metabolic syndrome with reduced size at birth

- Barker (1989): inverse relation of blood pressure with birthweight
- Hales (1991): inverse association of birthweight with impaired glucose tolerance - suggested effect mediated through impaired beta-cell function
- Barker (1993) - proposed that metabolic syndrome (defined as glucose intolerance, hypertension and lipid disturbances) should be renamed “small baby syndrome”

Longitudinal Study of Uppsala Men

Institute of Geriatrics, Uppsala, in collaboration with London School of Hygiene & Tropical Medicine

1920-24	births (1324 of 2322 records traced)
1970	2841 men resident in Uppsala
1970-73	2322 examined at age 50 (IVGTT on 1692)
1980-84	1860 examined at age 60 (fasting glucose ± oral glucose tolerance test)
1994-5	1221 examined at age 70 (euglycemic clamp study, oral glucose tolerance test)

Uppsala men: relation of birthweight to glucose intolerance at ages 60 and 70 years

Aged 60, N=961		Aged 70, N=589
Outcome	NIDDM	NIDDM / IGT
Prevalence	6%	28%
Birthweight quartile(lowest as baseline)	*Odds ratios (adjusted for body mass index at age 50)*	
1	1.00	1.00
2	0.78 (0.47-1.30)	0.78 (0.47-1.30)
3	0.38 (0.16-0.90)	0.48 (0.28-0.83)
4	0.54 (0.25-1.16)	0.49 (0.29-0.83)
Trend	p=0.005	p=0.001

Uppsala men: gradient of systolic blood pressure at age 50 by birthweight

Quartile of birthweight	Difference in systolic BP (adjusted for height and BMI)
1*	0
2	1.5 (-1.4,4.4)
3	-2.6 (-5.5,0.3)
4	-4.4 (-7.3,-1.5)
Trend	p<0.001

* Reference category

Uppsala birth cohort study: rate ratios for ischaemic heart disease mortality in men, by birthweight for gestational age

Quartile	Birthweight	Birthweight for gestational age
1*	1.00	1.00
2	0.84 (0.68, 1.03)	0.82 (0.67, 1.00)
3	0.74 (0.60, 0.91)	0.63 (0.50, 0.79)
4	0.70 (0.55, 0.86)	0.68 (0.55,0.85)
Trend	p=0.002	p<0.001

* Reference category

Total 636 IHD deaths

Is effect on diabetes mediated through impaired beta-cell function or through insulin resistance? - relation of birthweight to insulin levels in IVGTT at age 50 in Uppsala men (n=1324)

Partial correlations with birthweight (adjusted for adult BMI)

Sum of 4-, 6- and 8-minute insulin	-0.03 NS
Fasting insulin	-0.10 p=0.002
60-minute insulin	-0.10 p<0.001

Preston adults (n=103): Relation of fetal growth to insulin resistance measured by short insulin tolerance test

Ponderal index ($kg\ m^{-3}$)	Plasma glucose half-life (min)
< 20.6	20.6
-22.3	17.3
-25.0	17.9
>25.0	16.6

$p = 0.01$ for trend

Phillips DIW. *Diabetologia* 1994;**37**:150

Is there a specific association with thinness at birth? Uppsala men at age 60 years (n=1093): diabetes by birthweight and ponderal index

Birthweight (kg)	<3.25	>3.25	>3.75	>4.25
Prevalence (%)	8.1	4.7	5.2	4.0

Quintile of ponderal index	1	2	3	4	5
Prevalence (%)	11.9	5.2	3.6	4.3	3.5

p=0.001

Uppsala men: insulin sensitivity at age 70 by birthweight and gestational age

Gestational age	*Birthweight (kg)*			
	<3.25	3.25-	3.75-	4.25-
	M/I [g min^{-1} kg^{-1}(mU/l)$^{-1}$ × 100]			
<38 wk	5.5	4.0	-	-
≥38 wk	4.5	4.8	4.8	5.5

p=0.005 for interaction of birthweight x gestational age, adjusted for age and BMI

Relation of other features of metabolic syndrome to size at birth - Uppsala men at age 70

Birthweight (kg)	*<3.25*	*>3.25*	*>3.75*	*>4.25*	p-*value (BMI-adj)*
Waist girth	93.7	94.9	95.5	96.2	NS
Triglyceride	1.40	1.53	1.39	1.45	NS
HDL chol	1.29	1.26	1.27	1.31	NS
PAI-1 activity	18.7	19.1	16.8	14.3	<0.001

Byberg L. *Diabetologia* 1999

Small baby syndrome or insulin resistance syndrome? - summary of results on Uppsala men at ages 50, 60 and 70

- Reduced size at birth predicts:-
  - insulin resistance
  - raised blood pressure
  - diabetes and impaired glucose tolerance
  - raised PAI-1
- Reduced size at birth does not predict:-
  - raised plasma triglyceride
  - low HDL cholesterol
  - abdominal obesity

Conclusions: associations of metabolic disturbances with size at birth

- Relation of glucose intolerance with size at birth is mediated through insulin resistance
- In term births, inverse associations of raised blood pressure and glucose intolerance with birthweight are monotonic (rather than U-shaped)
- Specific associations with ponderal index or other measures of body proportions may result from failure to control for gestational age
- “Small baby syndrome” is a subset of the metabolic syndrome that excludes dyslipidaemia and abdominal obesity

What is the primary defect underlying the associations of size at birth with insulin resistance?

- Fetal genetic defect (Hattersley)
  - primary defect in insulin secretion or insulin action could cause reduced fetal growth and glucose intolerance in adult life
- Undernutrition in utero (Barker, Hales)
  - insulin resistance could be an adaptation to undernutrition: “thrifty phenotype” in populations with high rates of diabetes

Thrifty genotype or thrifty phenotype as explanation for between-population variation in risk of diabetes? relation of diabetes prevalence to European admixture in Nauruan islanders

Age	*% with European HLA types* Diabetic	Non-diabetic
20-44	6%	12%
45-59	9%	13%
60 +	5%	55%

Odds ratio for diabetes in those with European admixture = 0.31 (95% CI 0.11 - 0.81)

Serjeantson SW. *Diabetologia* 1983;**25**:13

Genetic models for relationship of insulin resistance to birthweight

- Tamemoto 1994 - in comparison with normal litter-mates, mice with the IRS-1 (insulin receptor substrate-1) gene deleted are 30% lighter at birth, and insulin resistant as adults.
- Human infants with (rare) genetic defects of insulin action are small at birth

Evidence for a primary role of undernutrition in utero

- Poulsen (1997): 14 MZ twin pairs discordant for NIDDM
  - Average difference in birthweight between diabetic twin and non-diabetic twin: 195 g (p=0.02)
- Ravelli (1998): follow-up of Dutch cohort exposed in utero to the 1944-45 famine
  - 2 h post-load plasma glucose 0.5 mmol/l higher in those exposed in late gestation

Effects of prenatal exposure to Dutch famine on mean systolic pressure

Timing of exposure	*Exposed - controls (mmHg)*
Early gestation	-1.7 (-5.6 to 2.2)
Mid-gestation	-0.6 (-3.9 to 2.7)
Late gestation	+1.3 (-1.9 to 4.4)

- 1 kg ↓ of birthweight was associated with ↑ of 2.7 mmHg (95% CI 0.3 to 5.1) in systolic pressure

Roseboom (1999)

Relation of diabetes prevalence to maternal weight and birthweight in southern India

Birthweight (kg)	<2.5	-2.9	>2.9
Prevalence	10%	19%	15%
Maternal weight during pregnancy (kg)	<43	-49	>49
Prevalence	10%	13%	24%

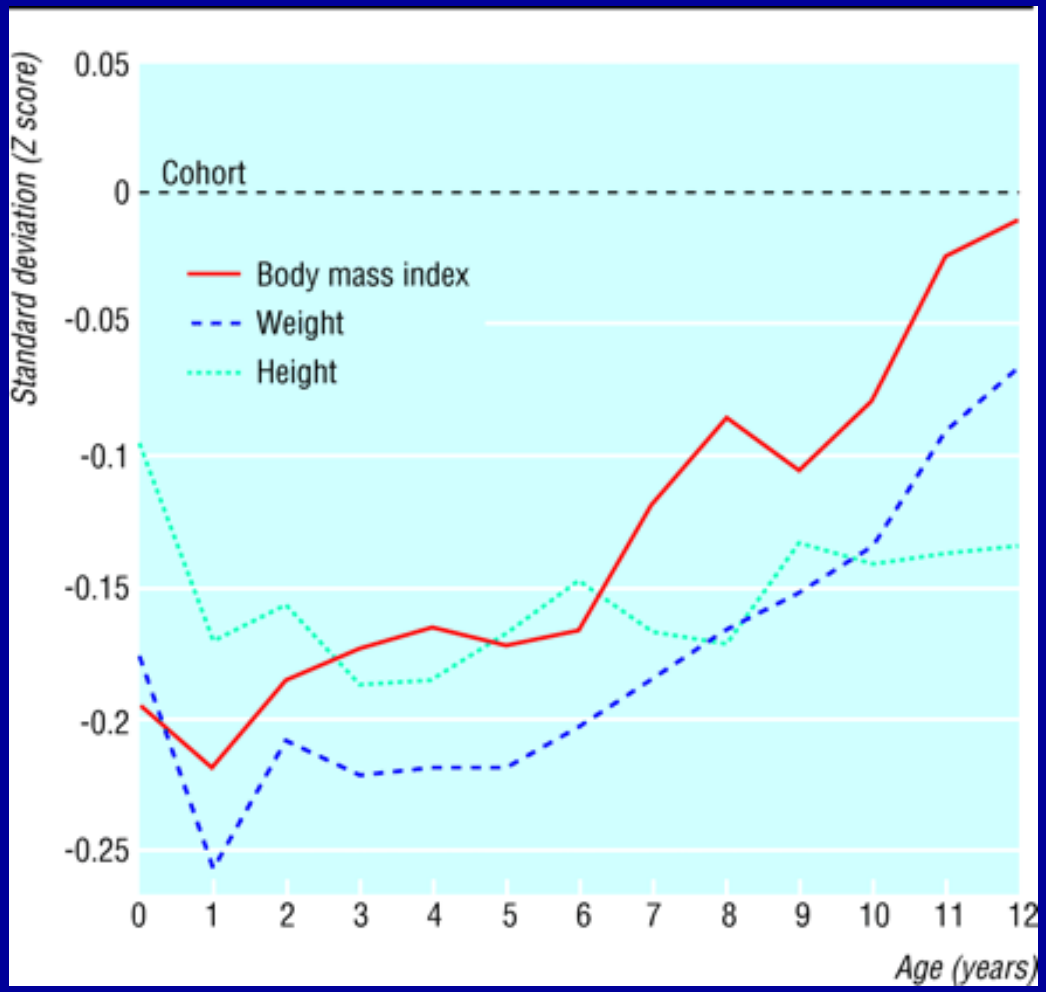
p=0.004 adjusted for offspring BMI

Fall CH *Diabetic Med* 1998;**15**:220

Conclusions: is “small baby syndrome” caused by genes or environment?

- Admixed populations: “thrifty phenotype” hypothesis does not explain variation in diabetes prevalence between high-risk and low-risk populations
- Associations are due to maternal environment not fetal genes
- Experimental studies suggest that fetal effects on glucose tolerance and blood pressure are mediated by alterations in glucocorticoid action
- Control of maternal hyperglycaemia in high-prevalence populations is important

Relative growth patterns for men dying of CHD compared with the general population



Source: Eriksson et al *BMJ* 2001;322:949-953

Growth after birth (1 SD increase in BMI at each age) and hazard ratio for CHD, stratified by ponderal index at birth

Age	Ponderal index <26	Ponderal index >26
1	0.89 (0.77-1.04)	0.80 (0.69-0.93)
3	1.06 (0.90-1.25)	0.73 (0.63-0.85)
5	1.13 (0.95-1.34)	0.72 (0.62-0.86)
7	1.22 (1.03-1.44)	0.75 (0.63-0.90)
9	1.20 (1.02-1.43)	0.77 (0.64-0.93)

Source: Eriksson et al *BMJ* 2001;322:949-953
PI= ratio of the cube root of mass (kg) divided by the height (cm)

Statistical modelling of longitudinal studies with measurements at different time points.

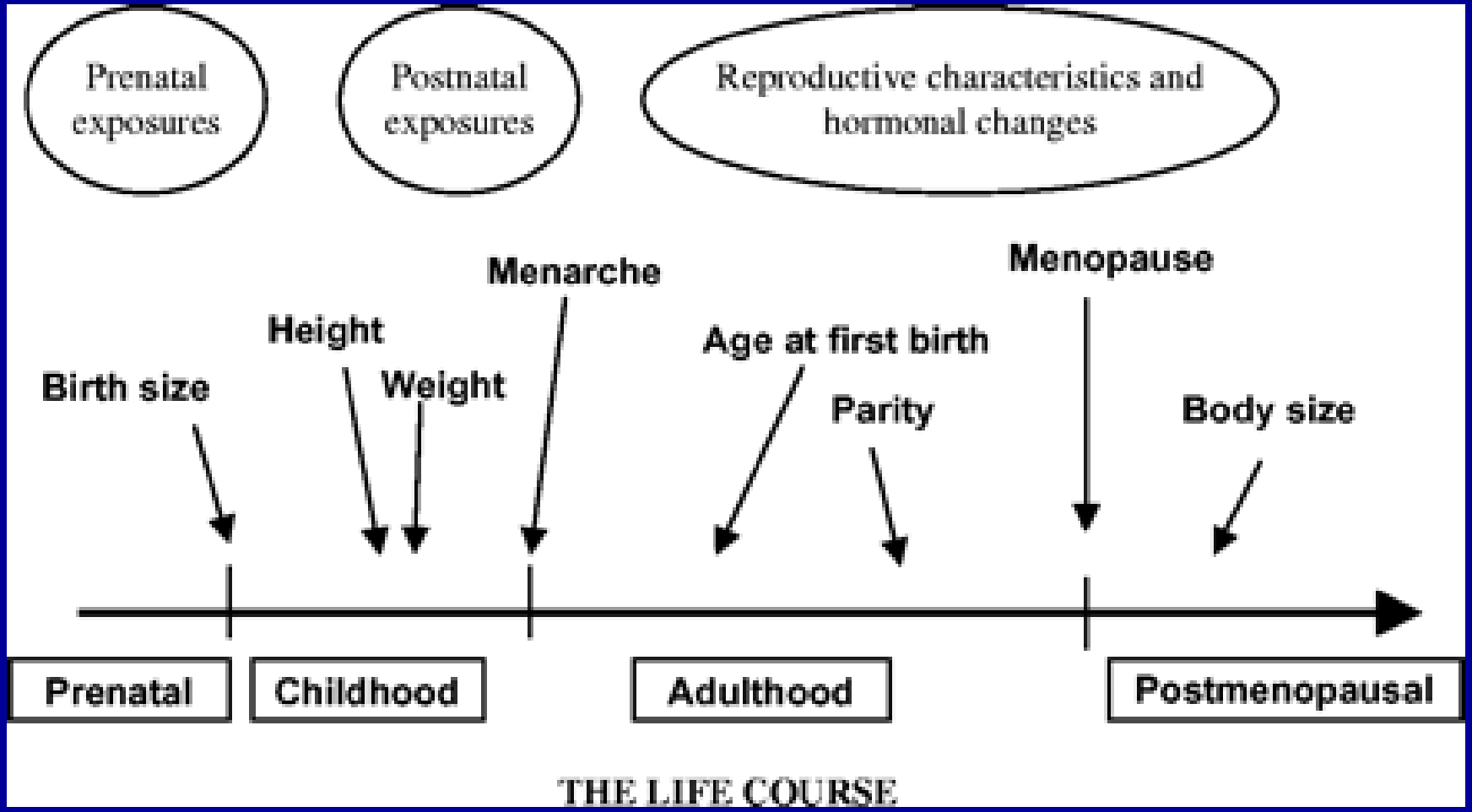
For exposure under study, other risk factors may be both causal and intermediate variables

Confounding may vary over time

Model can be specified as a graph of dependencies between random variables

Testing causal hypotheses is equivalent to inferring model parameters, or to choosing between alternative models

Risk factors for breast cancer



Source: de Stavola et al American Journal of Epidemiology 2006 163(1):84-96

Statistical analysis of effects via intermediate variables: graphical models

Classical approach: “estimate” model parameters

- analysis of covariance structures (structural equation modelling, path analysis)
- G-estimation for time-varying confounders

- Bayesian approach: model parameters are random variables
  - Calculate likelihood, or posterior density, as a function of the parameter of interest
  - Relies on computer simulation, using general-purpose software (BUGS, JAGS)

Limits to statistical inference from longitudinal studies

- Statistical methods can't overcome problems of unmeasured confounders and proxy measurements
- Can exploit natural experiments and *instrumental variables*
  - Statutory school-leaving age as an instrumental variable for assessing effect of extra year's schooling on life chances
  - Genotype as instrumental variable for a gene product or its metabolite (“mendelian randomization”)

Public health implications of effects of fetal/childhood growth on adult health

- Even where risk is set in early life, this does not exclude measures to reduce risk in adult life: eg. for Type 2 diabetes
- Pregnancy:
  - Size at birth is difficult to influence by dietary intervention
  - Control of maternal hyperglycaemia is important in high-risk populations
- Weight gain in infancy/childhood:
  - in infancy is associated with reduced risk of CHD
  - in later childhood is associated with increased risk CHD risk among those who were thin at birth
  - Risk factors that are set early in life may be amenable to later intervention
    - e.g. *H. pylori* infection as risk factor for stomach cancer

Public health implications of life-course research in epidemiology and social science

- Early life effects on physiological variables: insulin resistance, blood pressure, other cardiovascular risk factors are real
- but (except for exposures such as maternal hyperglycaemia or drugs) these physiological effects are small compared to
  - effects of risk factors such as obesity that are determined in adult life
  - early life effects mediated through socioeconomic status

Suggested reading

- Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges, and interdisciplinary perspectives. Int J Epidemiol 2002;31:285-93. http://ije.oupjournals.org/cgi/content/full/31/2/28
- Leon DA, Koupilova I, Lithell HO *et al*. Failure to realise growth potential *in utero* and adult obesity in relation to blood pressure in 50 year old Swedish men. *BMJ* 1996;**312:**401–06
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- Lynch JD, Smith GD. A life course approach to chronic disease epidemiology. Annu Rev Public Health. 2005;26:1-35