New directions in ageing research: life course epidemiology and cross-cohort comparisons

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Acknowledgements

- MRC Lifelong Health and Ageing team
  - Dr Rachel Cooper, Stephanie Black
  - Prof Diana Kuh
- University College London
- Australia Department of Health and Ageing
- NHMRC

Outline of the talk

- Introduction to life course epidemiology
  - Life course models
  - Methodology to test life course hypotheses
- Cross-cohort comparisons
- Family based studies
- Challenges & future directions

Life course studies

Cohort studies with information from at least one developmental stage (gestation, childhood, adolescence) and in adult life

Revival of life course & social perspective in epidemiology

Dissatisfaction with

Degenerative model:

- Concerns the identification of adult factors associated with time and speed of degeneration in function

- Pays little attention to processes that lead up to the peak in physiological condition (eg lung function)

Revival of life course & social perspective in epidemiology

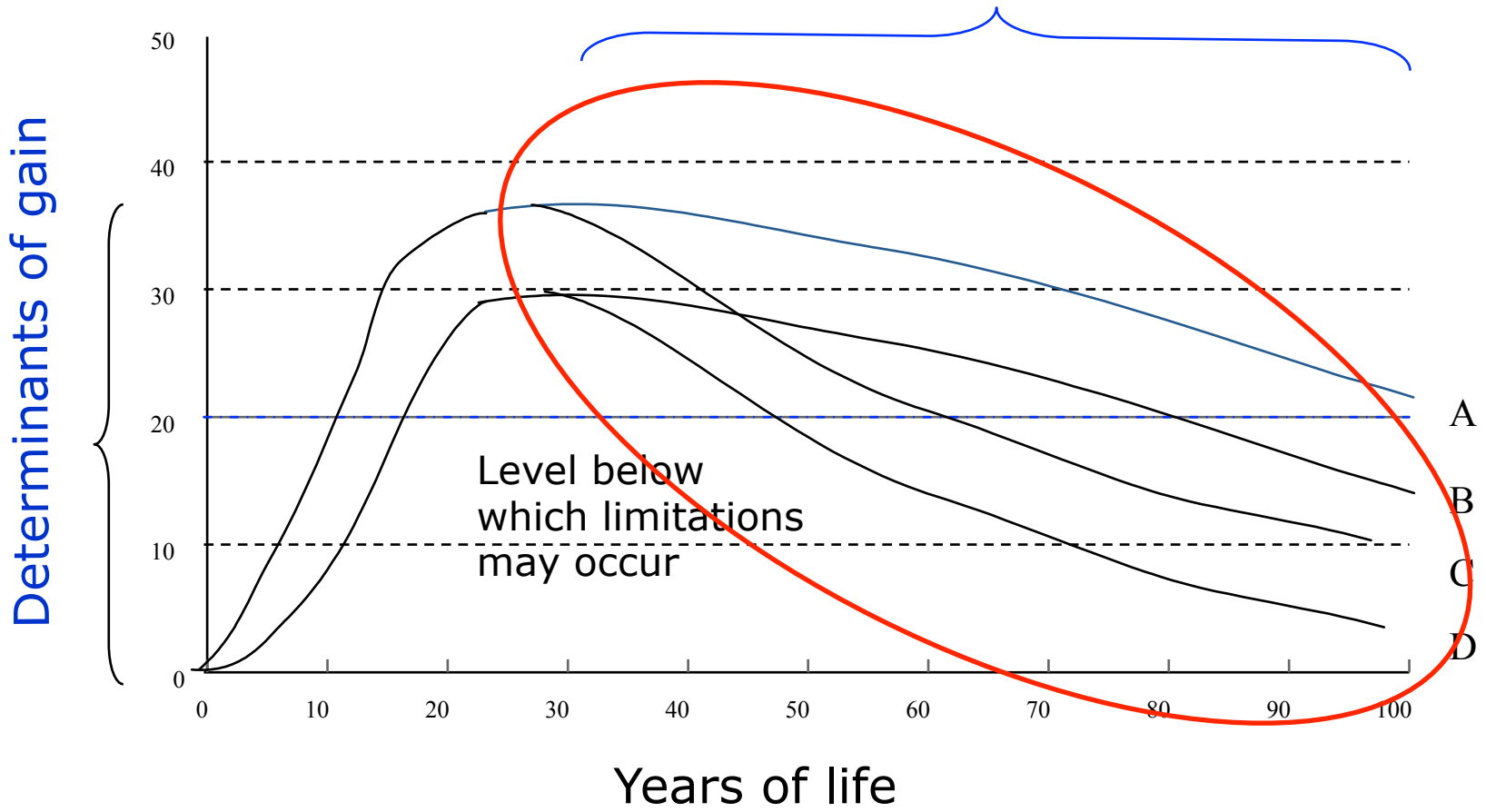
Development model of disease causation

- Childhood origins of adult disease
  - Natural history studies of children showing "tracking" of conventional risk factors
    - Early social conditions ⇒ CVD (Forsdahl)
    - Under-nutrition in utero ⇒ CVD (Barker)

- Evidence from maturing birth cohort studies

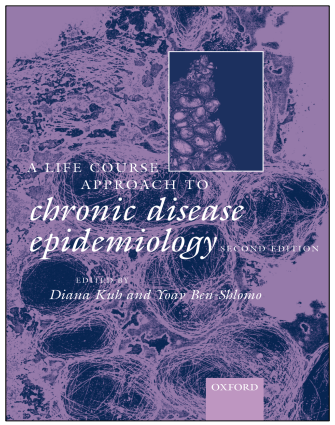
Physiological life course trajectories

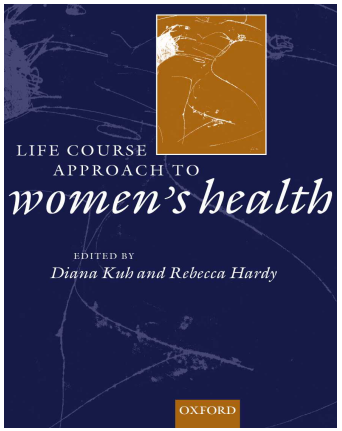
(adapted from Sheik and Strachan 2004)

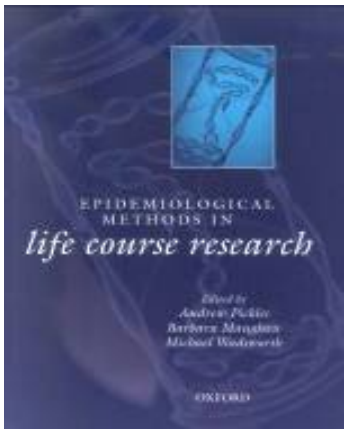


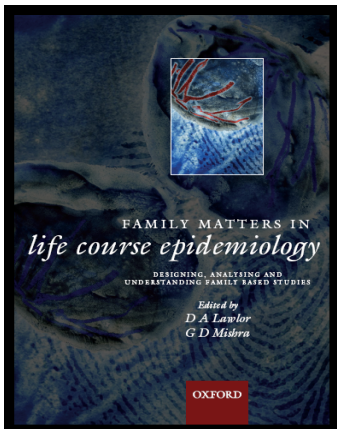
What is life course epidemiology?

- It investigates the long term effects on chronic disease risk *and ageing* of physical and social hazards during gestation, childhood, adolescence, young adulthood, and later adult life (*and across generations*)





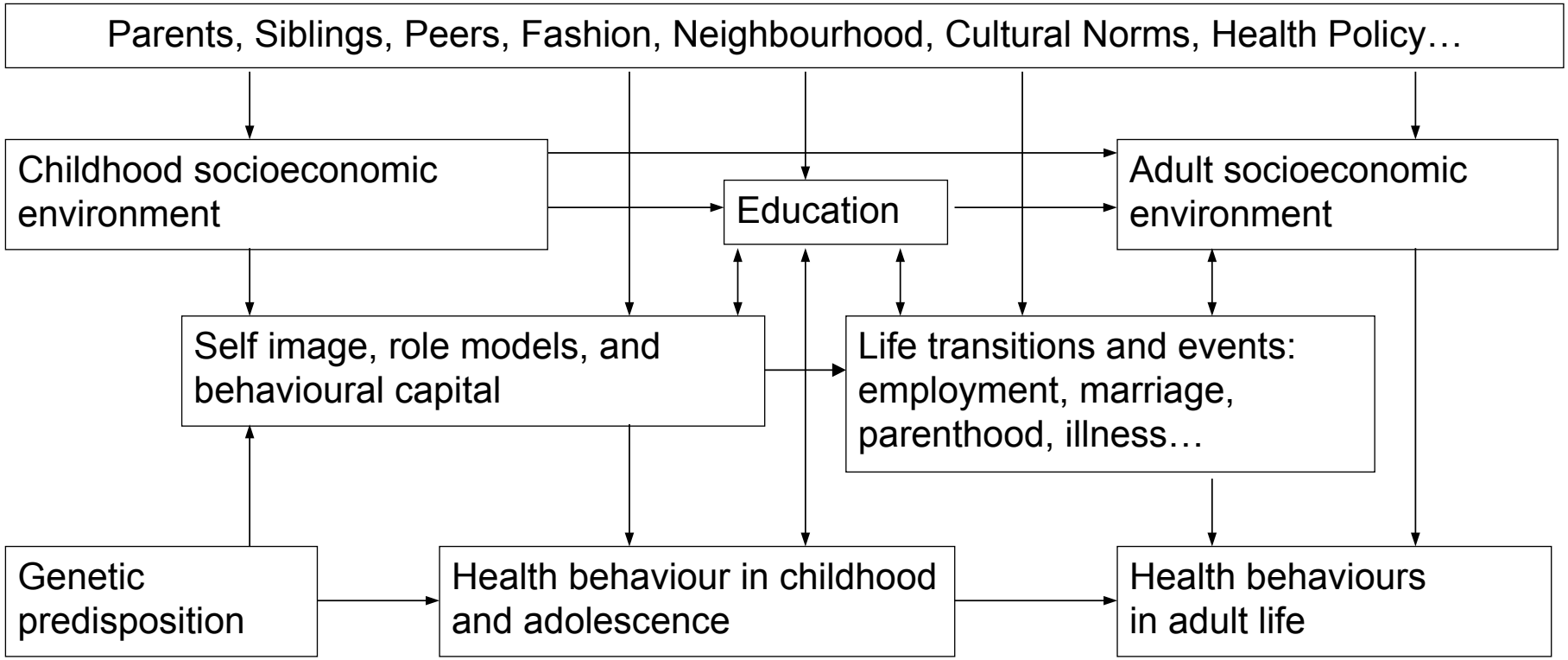




Life course epidemiology models

- Models are fundamental to this approach
- Address questions of type, timing and targeting of exposures/interventions
- May be used in combination to form an overall conceptual framework for analysis

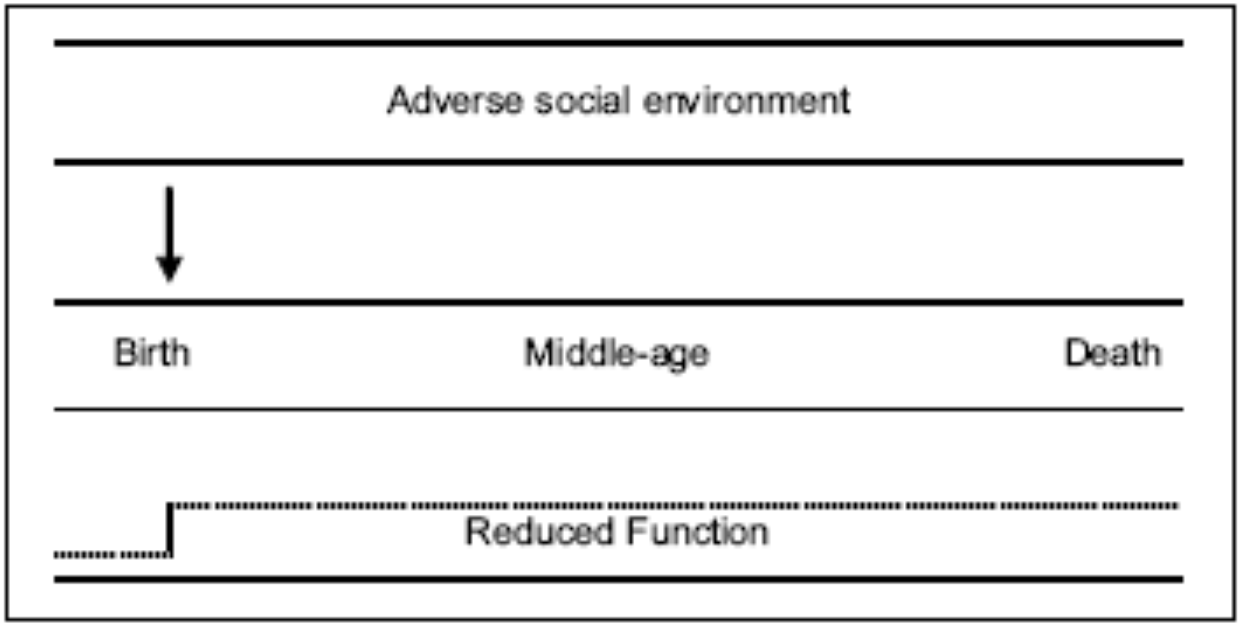
Developmental life course framework: pathways between childhood socioeconomic environment and adult health behaviours



Mishra, Ben-Shlomo, Kuh, 2010

1. “Critical” periods

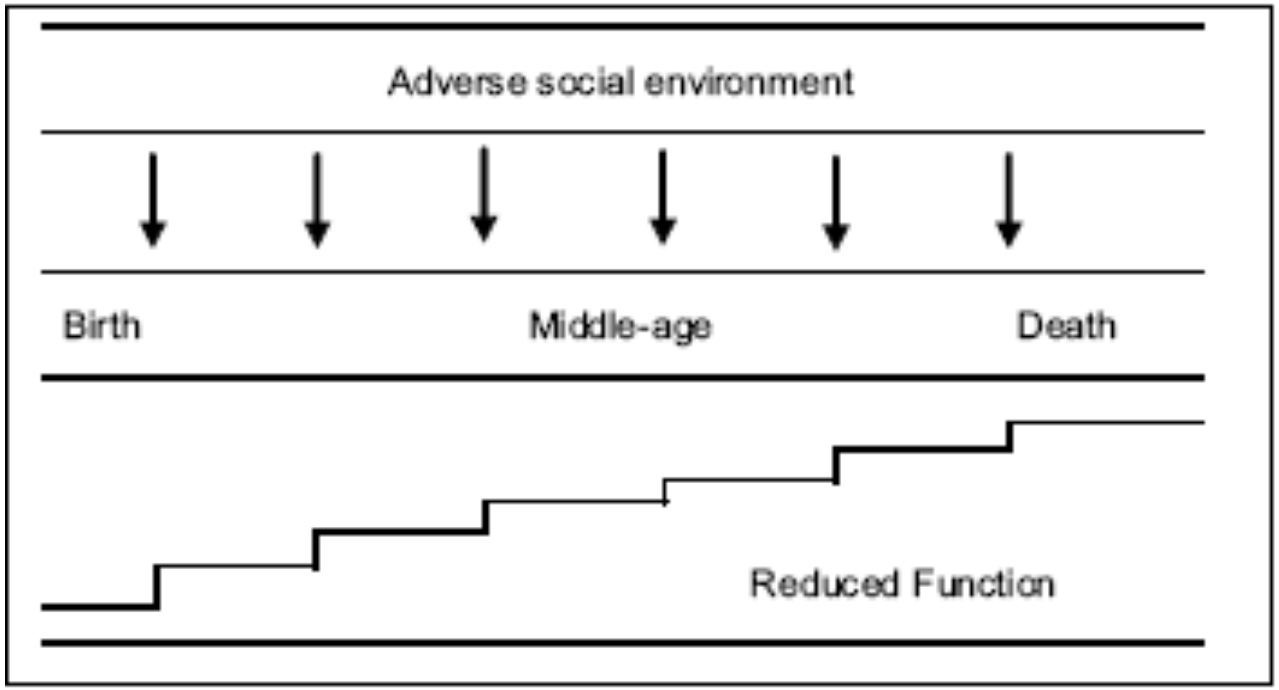
- pays attention to the timing of exposure
- assumes irreversible changes in body systems, usually at vulnerable phase of life



Rosvall et al. 2006

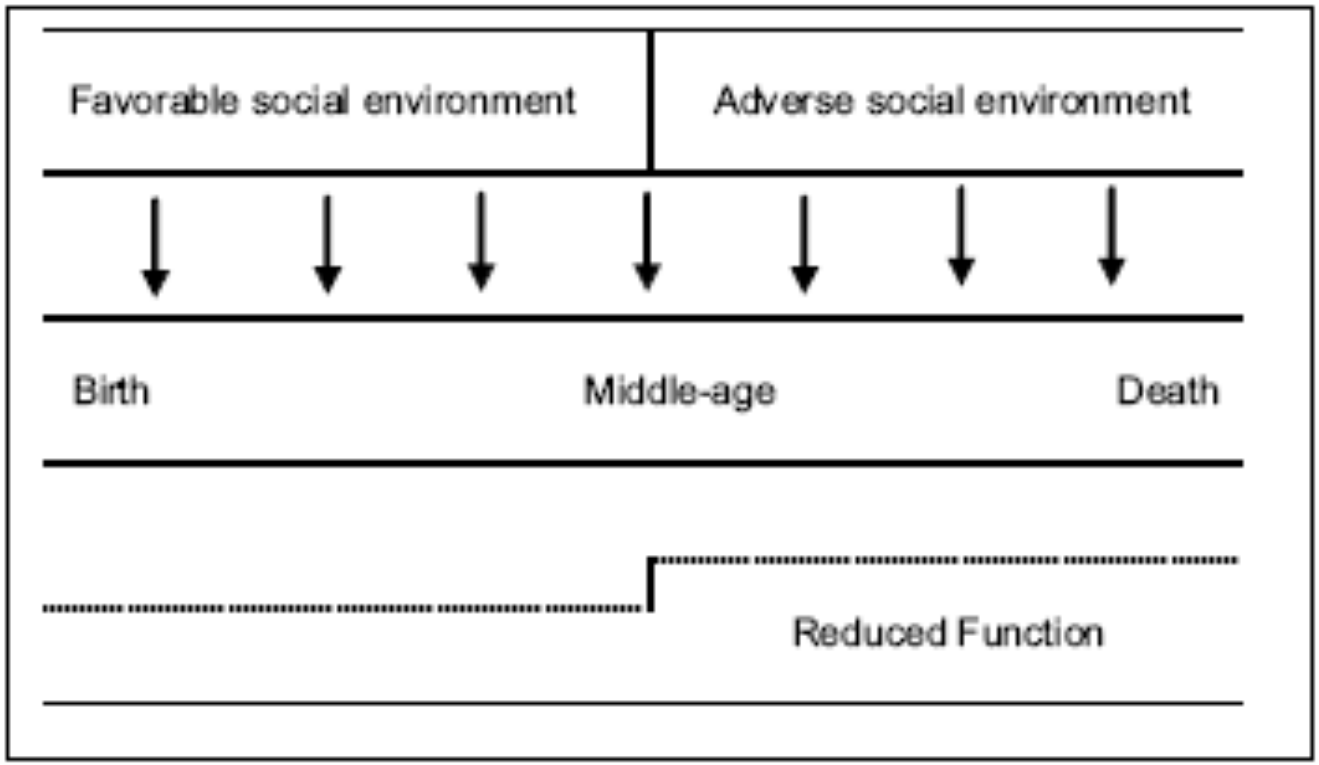
2. Accumulation of risk

- Relationship between time spent in adverse SEP across life course and increased risk of chronic disease, early mortality



3. Social mobility

- Earlier effects of SEP on health differs across levels of a later factor (adult SEP) – interaction



Can we disentangle the different life course models?

PERGAMON

Social Science & Medicine 58 (2004) 1555–1562

SOCIAL SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

Can we disentangle life course processes of accumulation, critical period and social mobility? An analysis of disadvantaged socio-economic positions and myocardial infarction in the Stockholm Heart Epidemiology Program

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Can we disentangle the different life course models?

METHODOLOGY

A structured approach to modelling the effects of binary exposure variables over the life course

Gita Mishra,[1*†] Dorothea Nitsch,[2†] Stephanie Black,[1] Bianca De Stavola,[2] Diana Kuh[1] and Rebecca Hardy[1]

International Journal of Epidemiology 2009; 38:528-537

Example: results from the MRC 1946 Birth cohort study

What is the relationship between social class across the life course and adult BMI?

Relationship between social class across the life course and Adult BMI		Partial F-test against saturated model
		p-value
Women		
No effect		<0.001
Accumulation of risk		**0.214**
Critical period#	*age 4*	0.018
	age 26	<0.0001
	age 43	0.003
Social mobility	adult	<0.0001
	any mobility	<0.0001
Men		
No effect		0.002
Accumulation of risk		0.060
Critical period	*age 4*	**0.359**
	age 26	0.015
	age 43	0.002
Social mobility	adult	0.002
	any mobility	0.006

Moving beyond single study associations

- Inter-cohort research
  - Investigate relationship between exposures and outcomes in different cohorts studies (and at different times)
  - To determine the extent that the findings are consistent

HALCyon
Healthy Ageing across the Life Course

The Halcyon is a fabled bird identified with the kingfisher (from the Halcyonidae family). The Halcyon is supposed to have the power to calm the wind & the waves during the winter solstice while it nested on the sea. 'Halcyon days' refer to a period of peace & prosperity.

LHA is leading a collaborative programme:

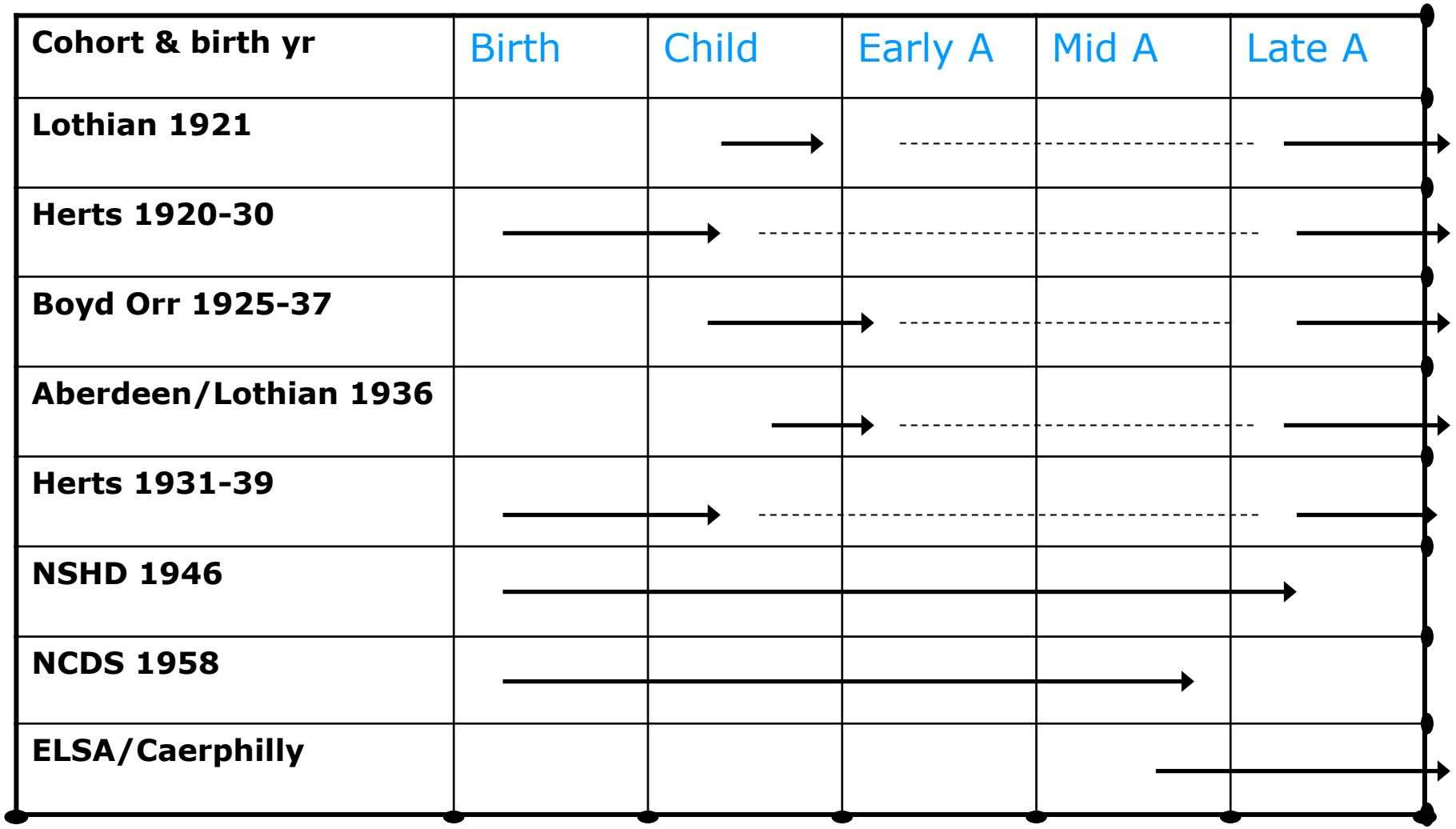
- 9 UK cohorts born 1921 to 1958
- 23 investigators, 19 collaborators
- 8 projects

Aim is to improve the lives of older people by understanding how healthy ageing is influenced by factors operating across the whole of life.

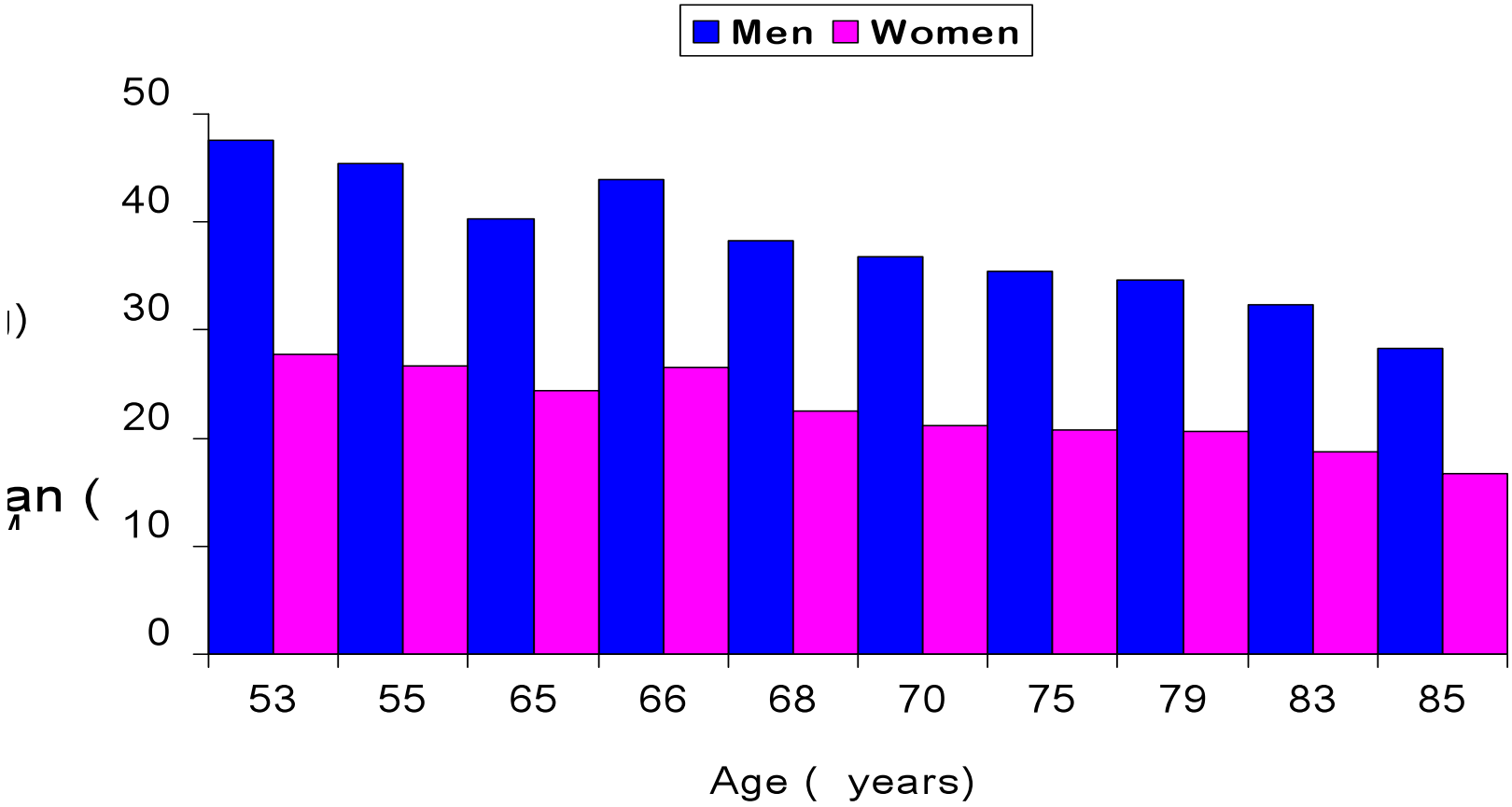
Indicators of healthy ageing being studied include:

- the capacity to undertake the physical and mental tasks of daily living;
- social and psychological wellbeing;
- genetic and other biological ageing processes.

HALCyon life course cohorts



Grip strength (kg) by age using HALCyon cohorts



Physical capability

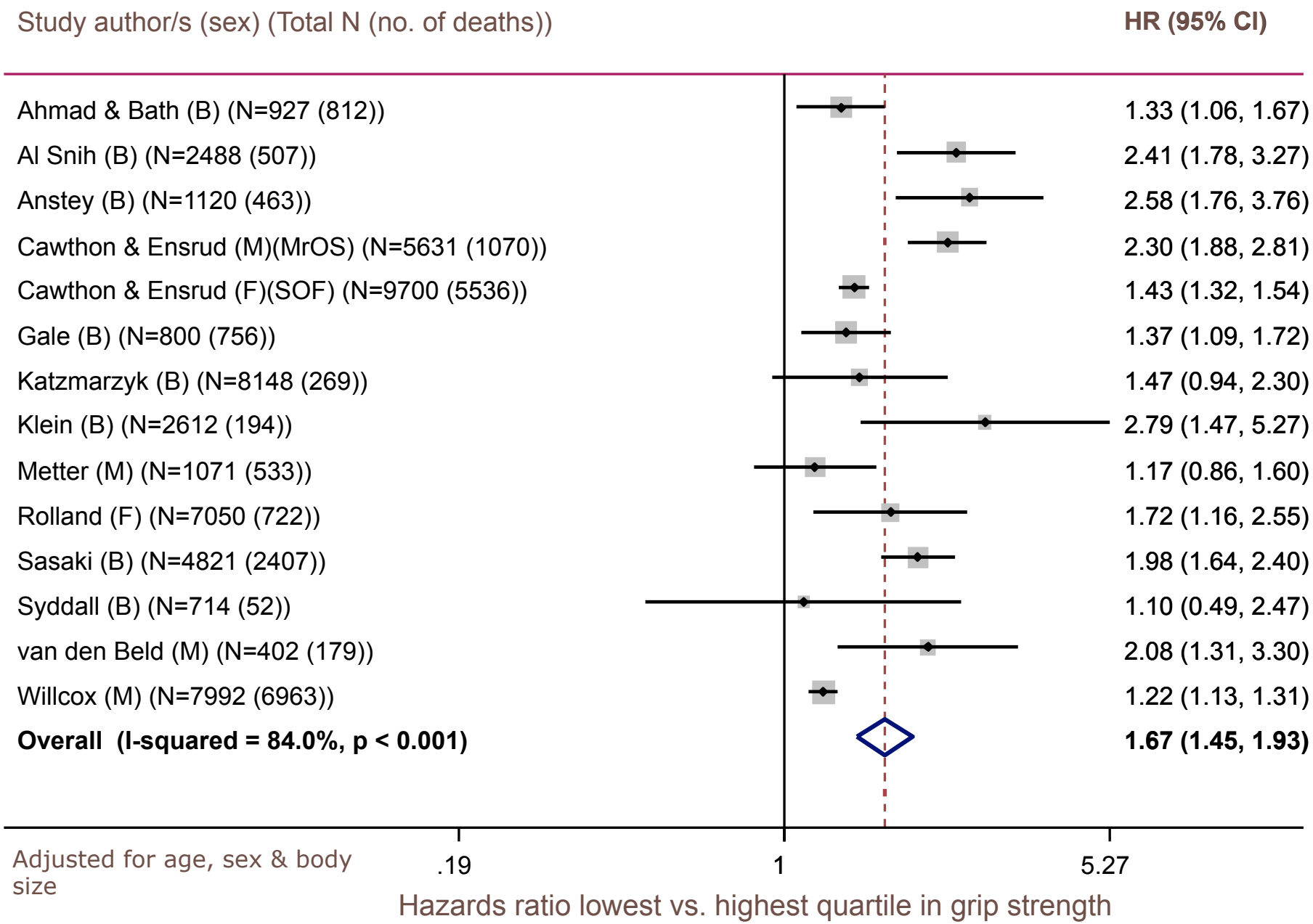
- The ability to perform physical tasks in order to function independently in daily life

- Objective measures include: grip strength, chair rises, gait speed and standing balance

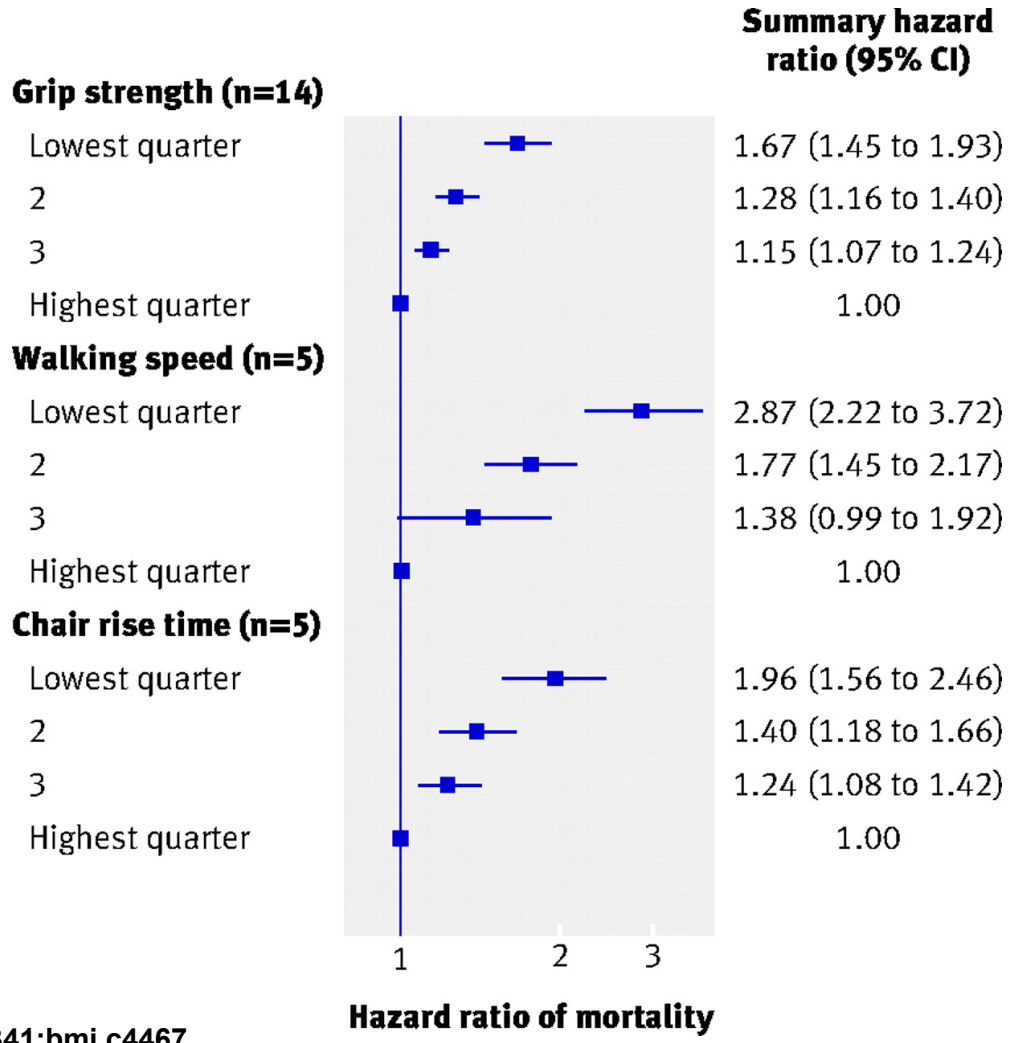



Slides courtesy of Rachel Cooper, MRC LHA

Hazards ratios of mortality comparing lowest with highest quartile



Summary hazard ratios of mortality from meta-analyses comparing each quarter of grip strength, walking speed, and chair rise time with highest quarter, including results adjusted for age, sex (where appropriate), and body size (n=number of data points included in meta-analysis).



Cooper R et al. BMJ 2010;341:bmj.c4467

BMJ

Summary of findings

- There is consistent evidence of associations between baseline measures of grip strength, chair rise time & walking speed and all-cause mortality in community-dwelling older populations

- The association of grip strength with mortality is also found in populations <60yrs

- There is also some evidence of associations between standing balance and mortality in elderly populations

Explanation of findings

- Objective measures of physical capability as markers of:
  - sub-clinical disease or biological ageing
  - 'system integrity'
  - lifetime exposure to risk factors

- Greater 'physical reserve' → increased chance of survival
- Confounding
- Low physical capability levels → disease

Time to raise the bar

To improve population health, life course epidemiology has to go beyond describing associations

- Are the association causal?
- What are the mechanisms?
- How do observed associations operate across generations?
- How do different risk factors interact across the life course?

Example – results from a large Danish Record Linkage study

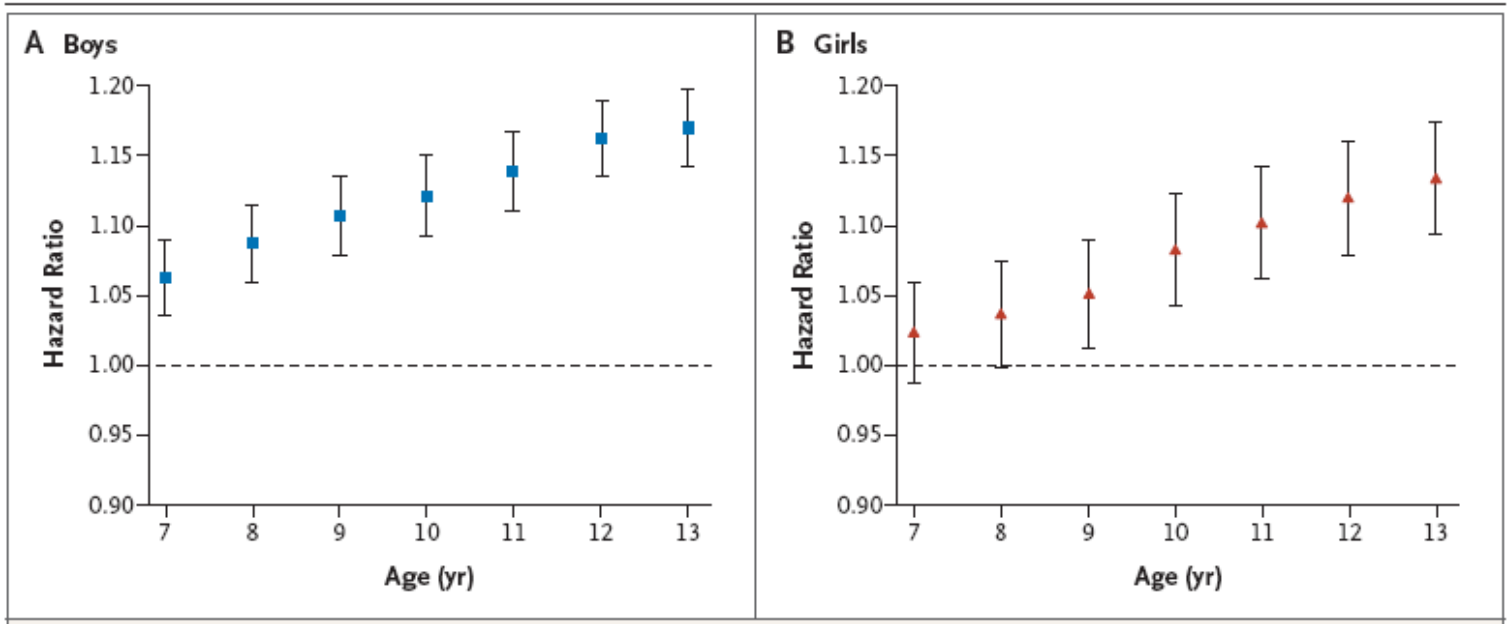


Figure 1. Body-Mass Index (BMI) in Childhood and the Risk of Coronary Heart Disease (CHD) in Adulthood.

The graphs depict the association between childhood BMI and the risk of having a CHD event (nonfatal or fatal) in adulthood. Hazard ratios and 95% confidence intervals are given for a 1-unit increase in BMI z score at each age from 7 to 13 years. The data are from 139,857 boys (Panel A) and 136,978 girls (Panel B) in the Copenhagen School Health Records Cohort. The associations were linear within each age, since trend tests resulted in the rejection of the alternative of nonlinearity modeled as a restricted cubic spline with five knots (all P values >0.15).

Baker et al. *NEJM* 07; 357(23). pp 2329-37

How to translate the findings into relevant public health messages

- To what extent is the association (between childhood BMI and adult CHD risk) causal or explained by confounders such as SES, lifestyle characteristics?

- If causal, to what extent is the assoc. mediated by changes to metabolic and vascular changes in childhood that are permanent even if the child were to lose weight?

- If causal, to what extent is the association mediated by adult obesity

- Would **family-based interventions**, aimed at preventing obesity in all family members (adults and children), provide the most effective and cost-effective means of preventing obesity and hence CHD?

Causality and observational epidemiology?

In the absence of RCTS in observational studies

- Natural experiments – Dutch winter famine study, migration study

- Mendelian randomisation

- ***Family based studies***

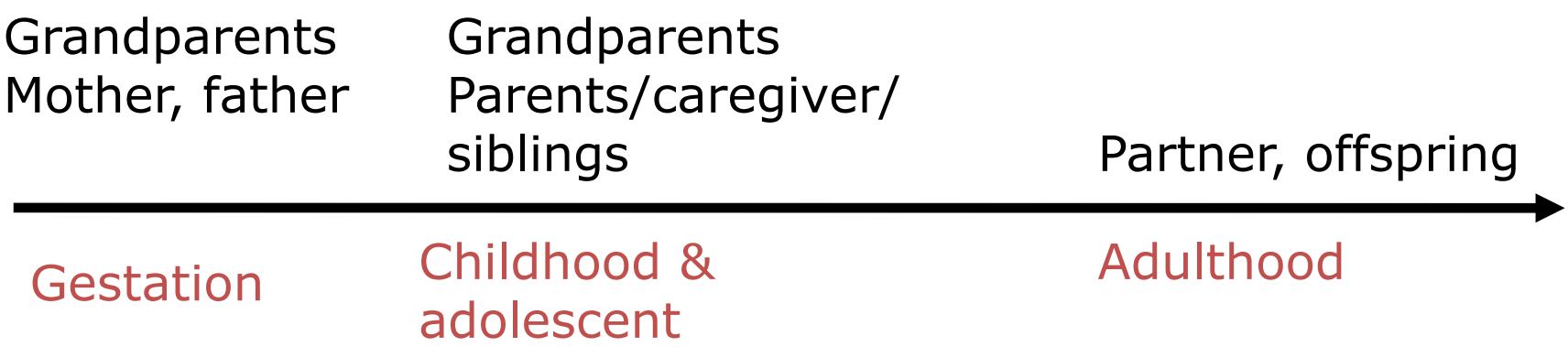
Note of caution – based on conditions and assumptions, care is required in the interpretation

Family based studies in life course epidemiology

1. Family directly affect ones health

2. Different family members have different impact, and at different stages of the life course

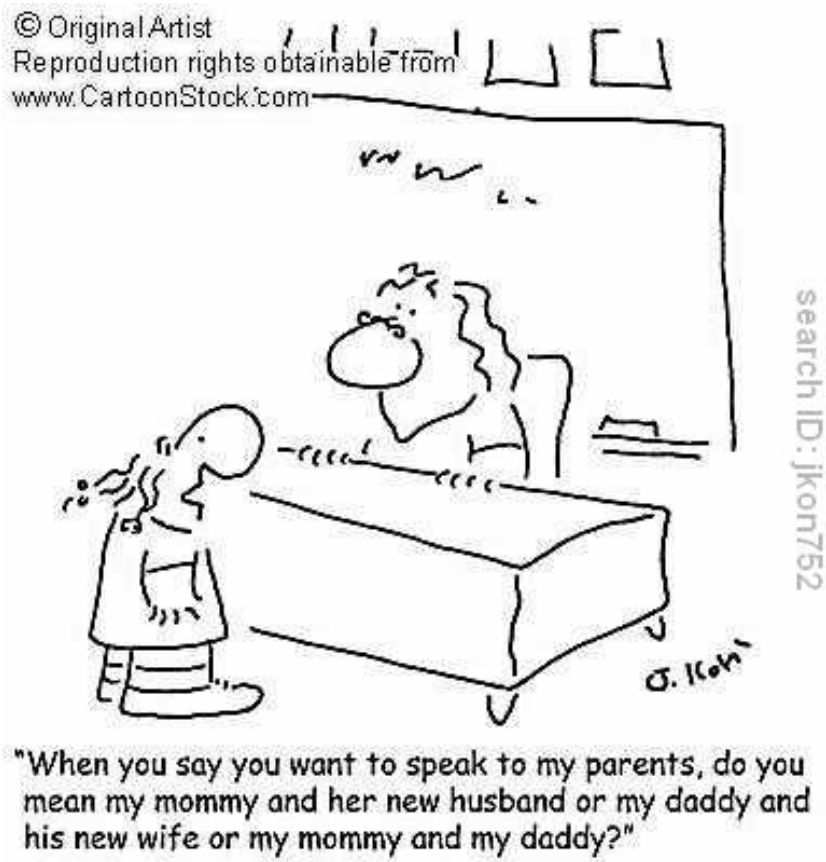
   - relevant for timing of exposure



Family based studies

3. Comparing relationships within and between family members can help clarify mechanisms underlying and help determine causality

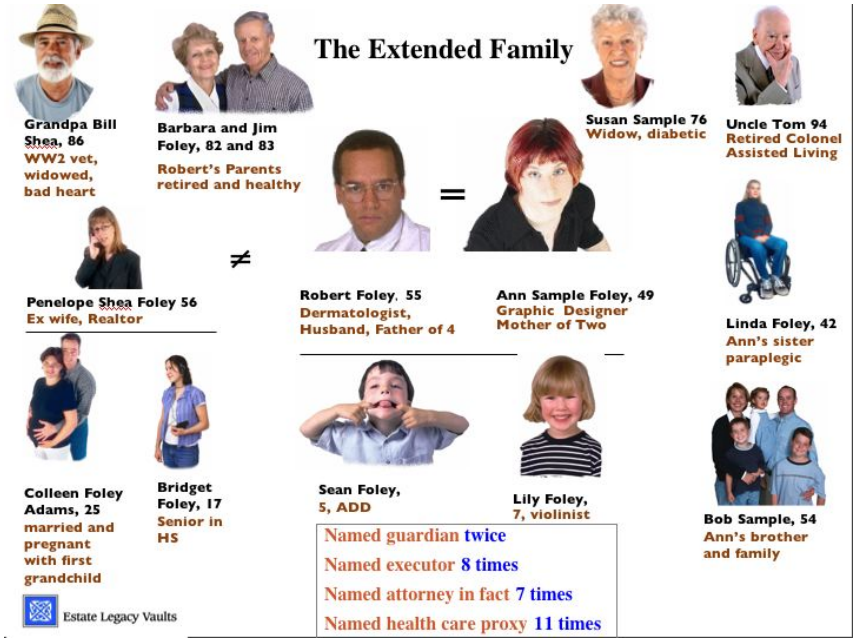
What are families?



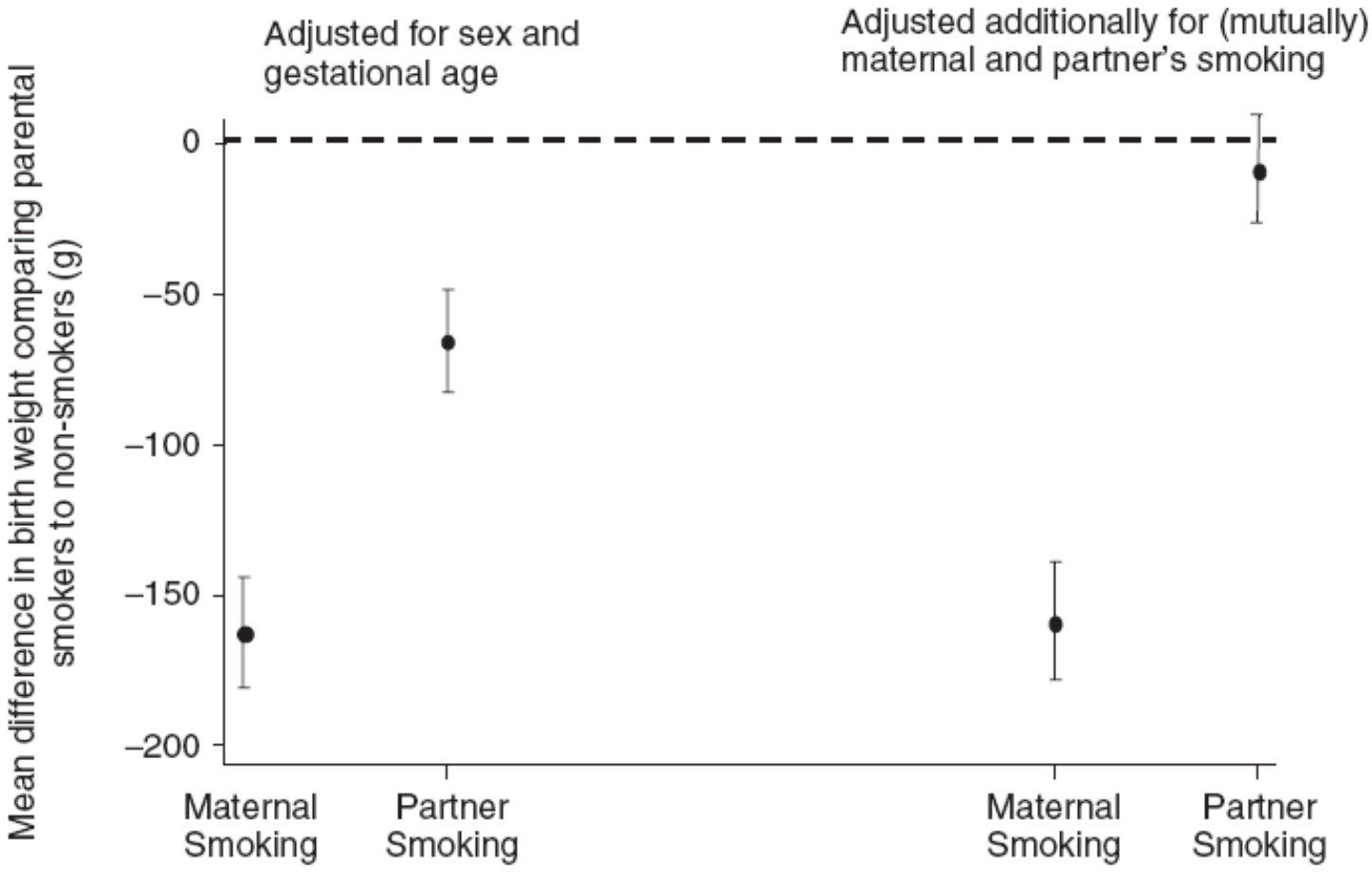
"When you say you want to speak to my parents, do you mean my mommy and her new husband or my daddy and his new wife or my mommy and my daddy?"

Types of family based studies

- Intergenerational
  - Maternal / offspring
  - Grandparents
- Siblings
  - Full sibling/ half sibling
  - adopted / migration
- Twins
  - monozygotic and dizygotic twins



Exposure in parents with health related outcome in their offspring (ALSPAC)



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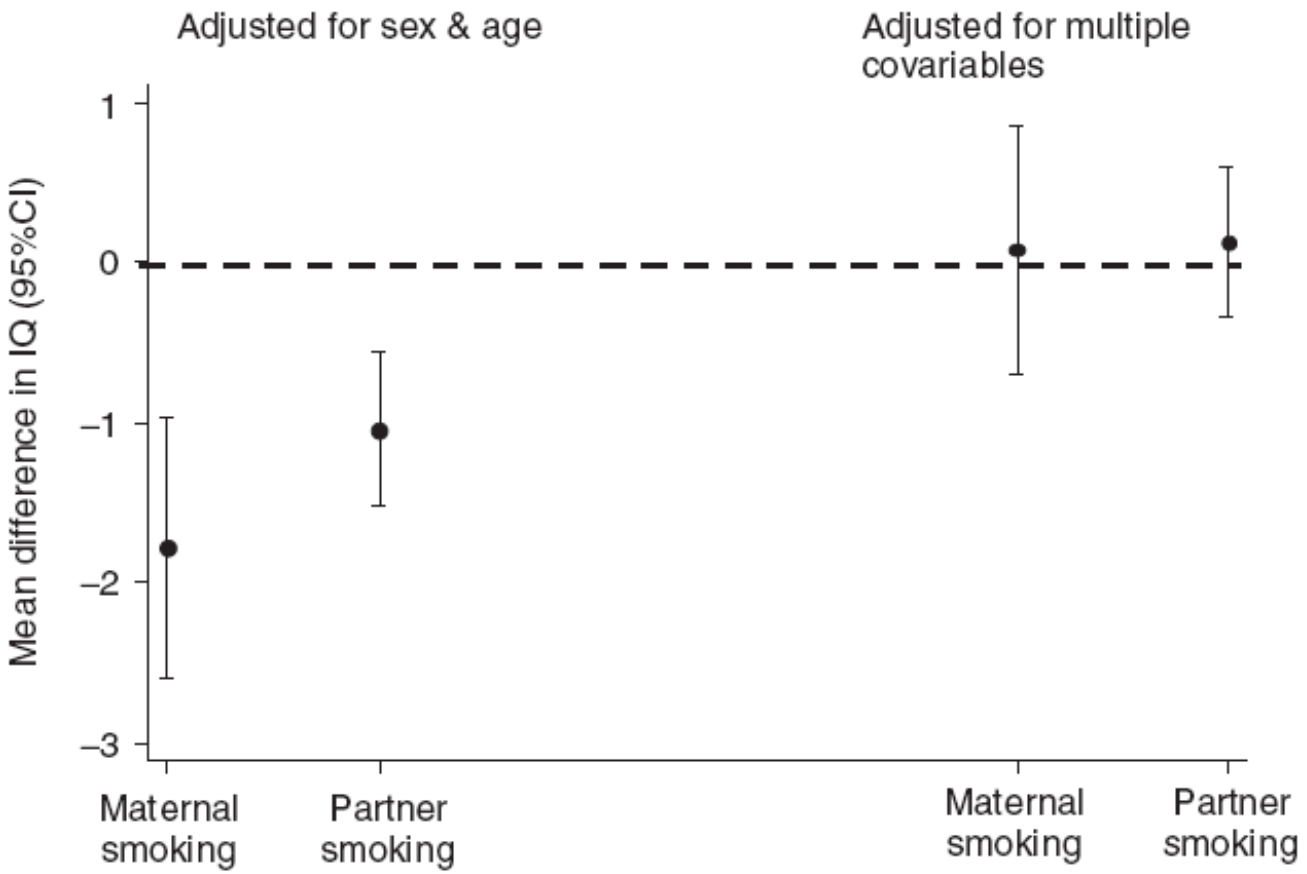
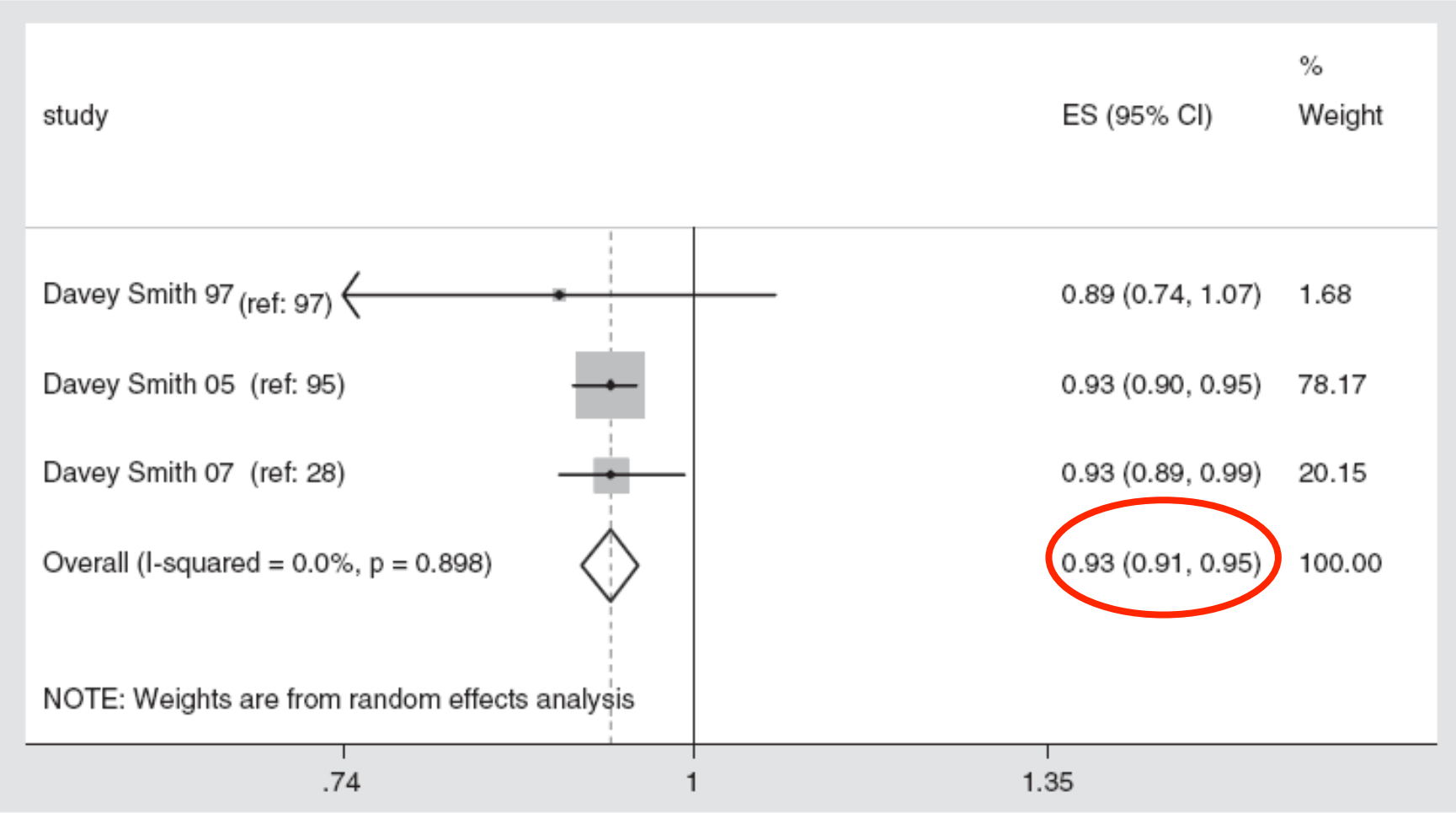


Mean difference childhood IQ at age 8

Use of offspring as proxies for parental exposures

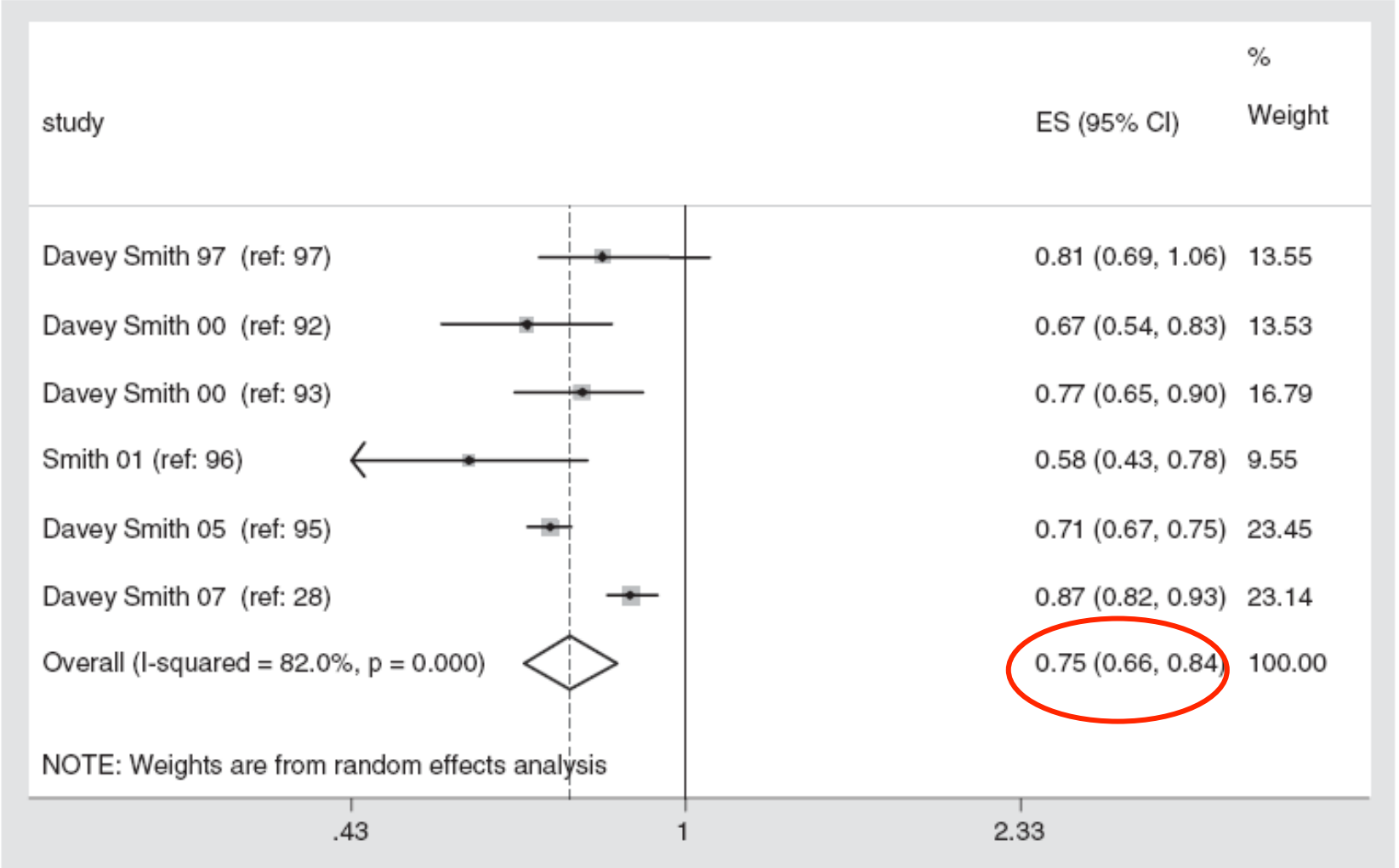
- Parental CVD risk and offspring birthweight
  - Birthweight as a marker for health outcomes in later life.
  - If BWt— CVD association is due to genes from both parents
    - ↑ BWt ↓ CVD risks in both mothers & fathers

Offspring birth weight with father's CVD mortality



Lawlor et al, chp 2

Offspring birth weight with mother's CVD mortality



Lawlor et al, chp 2

Interpretation of results

The stronger association with maternal CVD risk may be due to:

- Fetal programming: fetal undernutrition in the mother programmes her CVD risk and leads to low BWt in her offspring - due to smaller pelvic size
- Direct effect of maternal health behaviour (smoking, poor diet, heavy alcohol use..)
- Maternal imprinting – a gene with pleiotropic effects resulting in low BWt and insulin/resistance/CVD risk
- Paternal misclassification – not the biological father

Lawlor et al, chp 2

Challenges dealing with family-based data in life course epidemiology

- Representativeness and generalisability
  - Exposures 5 or 6 decades ago will be different to today's generation
  - Nature of families and how they relate to each other have changed
  - Findings may not be generalisable to different populations (different geography, ethinicity)
- Examine association in different cohorts, ethnic groups etc (Systematic reviews & meta-analyses)

Other Methodological challenges

- Sample size and statistical power
- Missing data and attrition
- Measuring exposures and outcome
- Analytical strategy

Future Family Based Studies

Study	Country	Years of Recruitment	Age at enrolment	Study sample size
Jerusalem Perinatal Study[10,11]	Israel	1964–1976	At birth	92 408 births
Tasmanian Infant Health Survey (TIHS)[12]	Australia	1988–1995	Post-natal (4 days)	10 627 babies
Avon Longitudinal Study of Parents and Children (ALSPAC)[8]	U.K.	1990–1992	Pre-natal	14 541 pregnancies, 14062 live births
Birth Defects Surveillance System for the Collaborative Project China (BDSS-China)[13]	China	1993–1995	Pre-conception, pre-natal	247 831
Danish National Birth Cohort (DNBC)[14]	Denmark	1996–2002	Pre-natal	101 042 pregnancies
Norwegian Mother and Child Cohort Study (MoBa)[15]	Norway	1999–2007	Pre-natal	100 000 planned (77 000 by Oct 2006)[16]
Infancia y Medio Ambiente (INMA)[17]	Spain	2001–2005	Pre-natal	3100 planned (3500 by Oct 2006)[18]
China Children and Families Cohort Study (CCFC)	China	2006–2007	Pre-conception, pre-natal	300 000 planned
Born in Bradford[19]	U.K.	2006–2008	At birth	10 000 planned
National Children's Study (NCS)[9]	U.S.	2008–2012	Pre-conception, pre-natal	100 000 planned
Etude Longitudinale Française depuis l'enfance (ELFE)[20]	France	2008–2009	At birth	20 000 planned

Cohort studies described during the 2005 Second International Childhood Cancer Cohort Consortium Workshop. Others planned in Canada, Brazil, New Zealand, Mexico, Korea, Japan and Germany

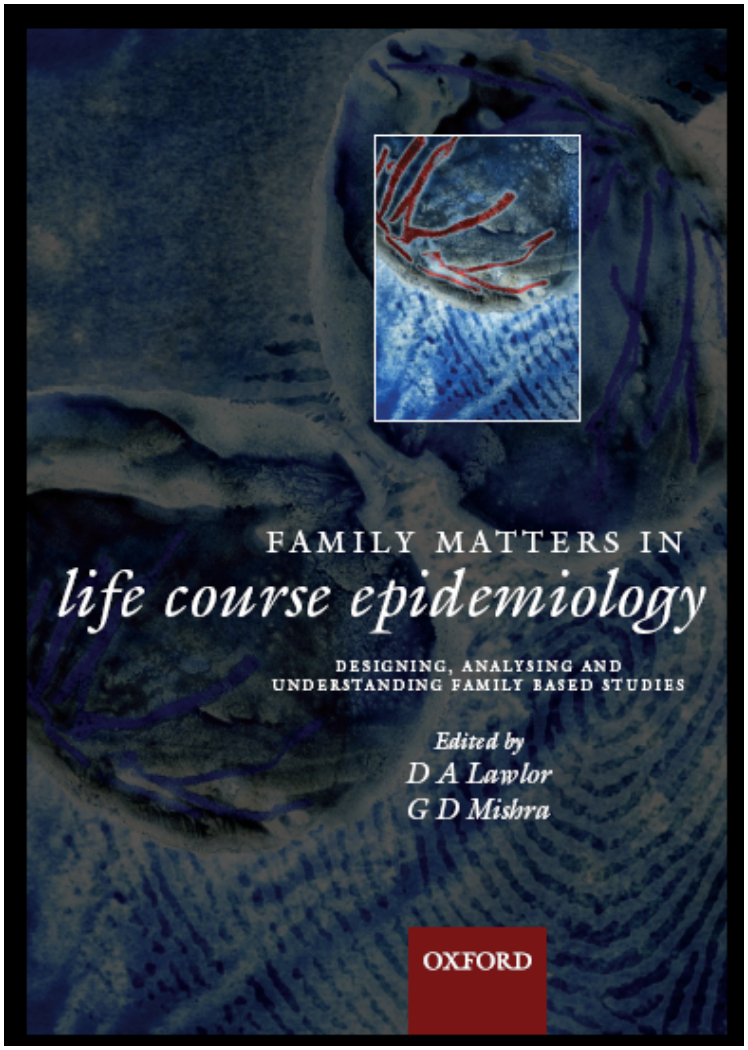
Conclusion

- Represents new territory in scientific terms – eg using observational studies to establish causal pathways rather that associations

- Family based studies should also incorporate new emerging interests in other fields such
  - the role of built environment in public health
  - the new implications of climate change

- We all should work together more closely in order to share knowledge, skills, and study resources.

Thank You for listening!



April 2009

The family- that dear octopus from whose tentacles we never

quite escape nor,

in our inmost hearts, ever quite wish to.

Dodie Smith Dear Octopus – A comedy. Act III, Scene 2. 1938