University of BRISTOL

# Cardiovascular Disease:

## Scientific Challenges and Opportunities

CHILDREN OF THE 90s

MRC Centre for Causal Analyses in Translational Epidemiology

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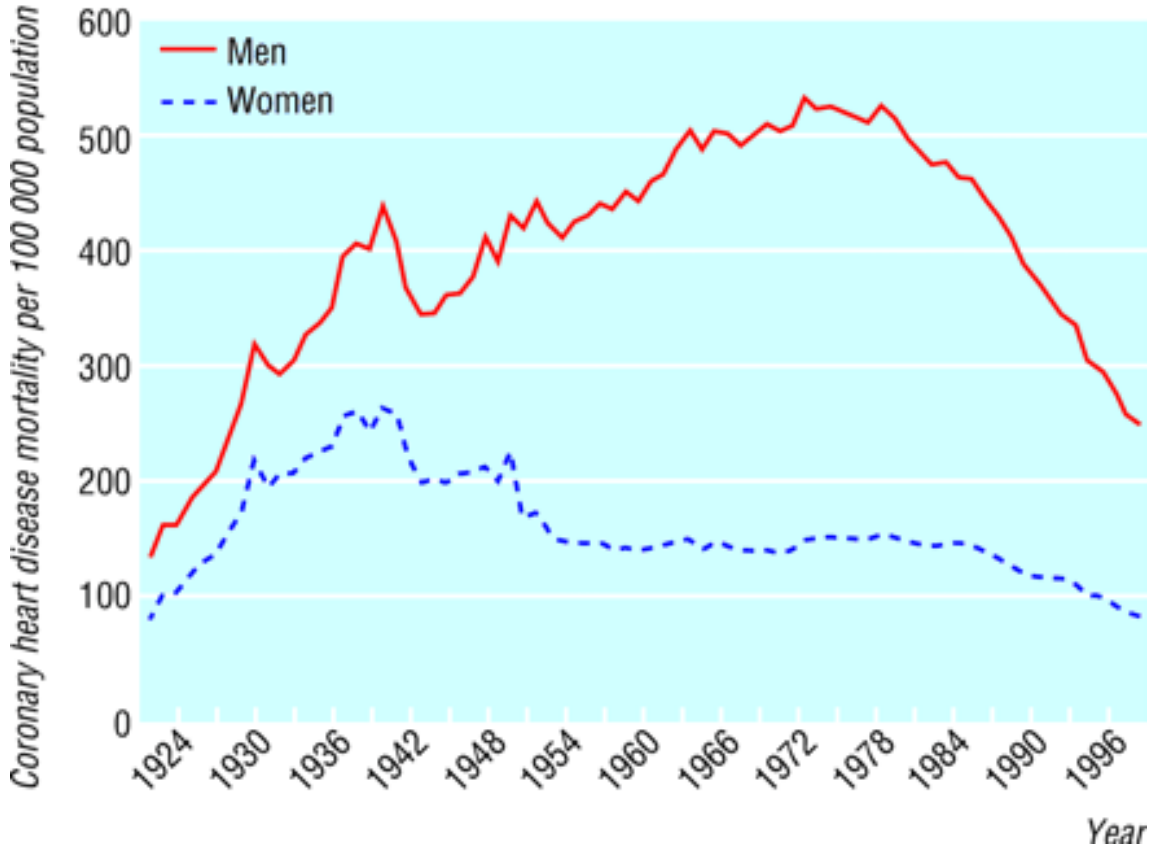
# Cardiovascular disease




Lawlor et al. BMJ 2001

# Cardiovascular disease

- CHD and stroke are rare until middle age
- Adult risk factors: diet, smoking, lack of physical activity, hypertension, adult obesity

- Why are birth cohorts important in cardiovascular disease research?

- Cardiovascular disease pathology starts early in life

# Coronary artery disease in young US war fatalities

**Korean war - early 1950s** (Enos et al, JAMA 1953)

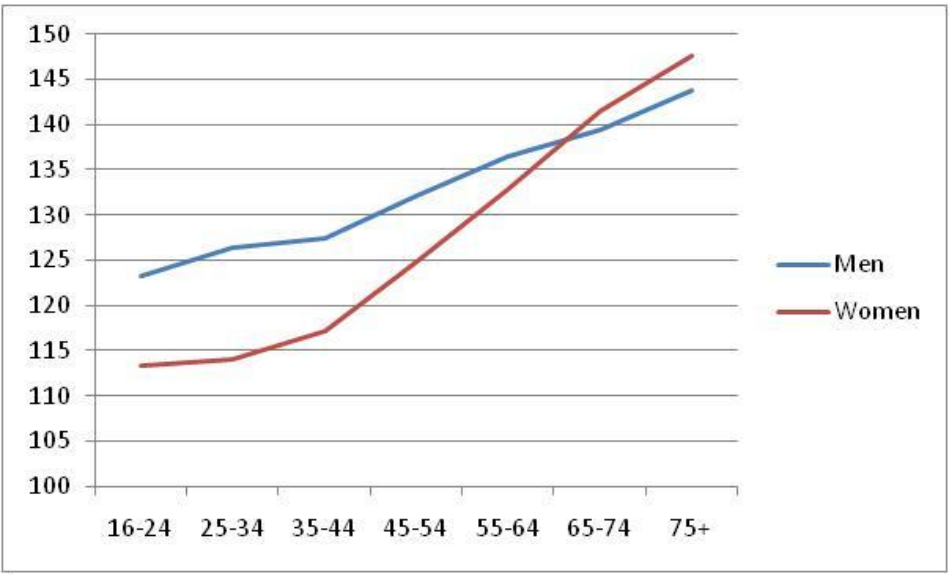
- 200 autopsied combatants, mean age = 22 years
- 77% evidence of atherosclerosis
- 15% clinically significant narrowing of vessel(s)

**Vietnam war - late 1960s** (McNamara et al, JAMA 1971)

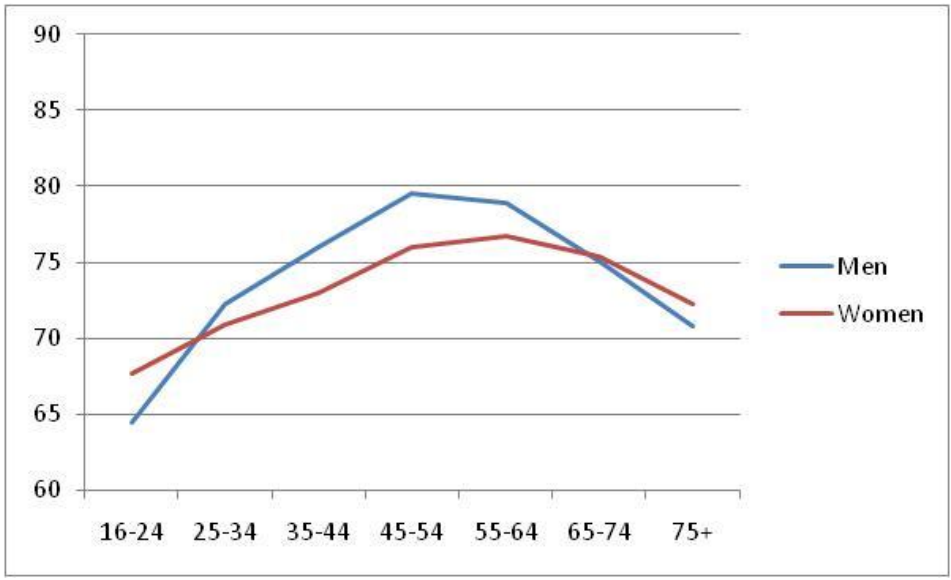
- 105 autopsied combatants, mean age = 22 years
- 45% evidence of atherosclerosis
- 5% clinically significant narrowing of vessel(s)

# Mean BP by age in England

SBP

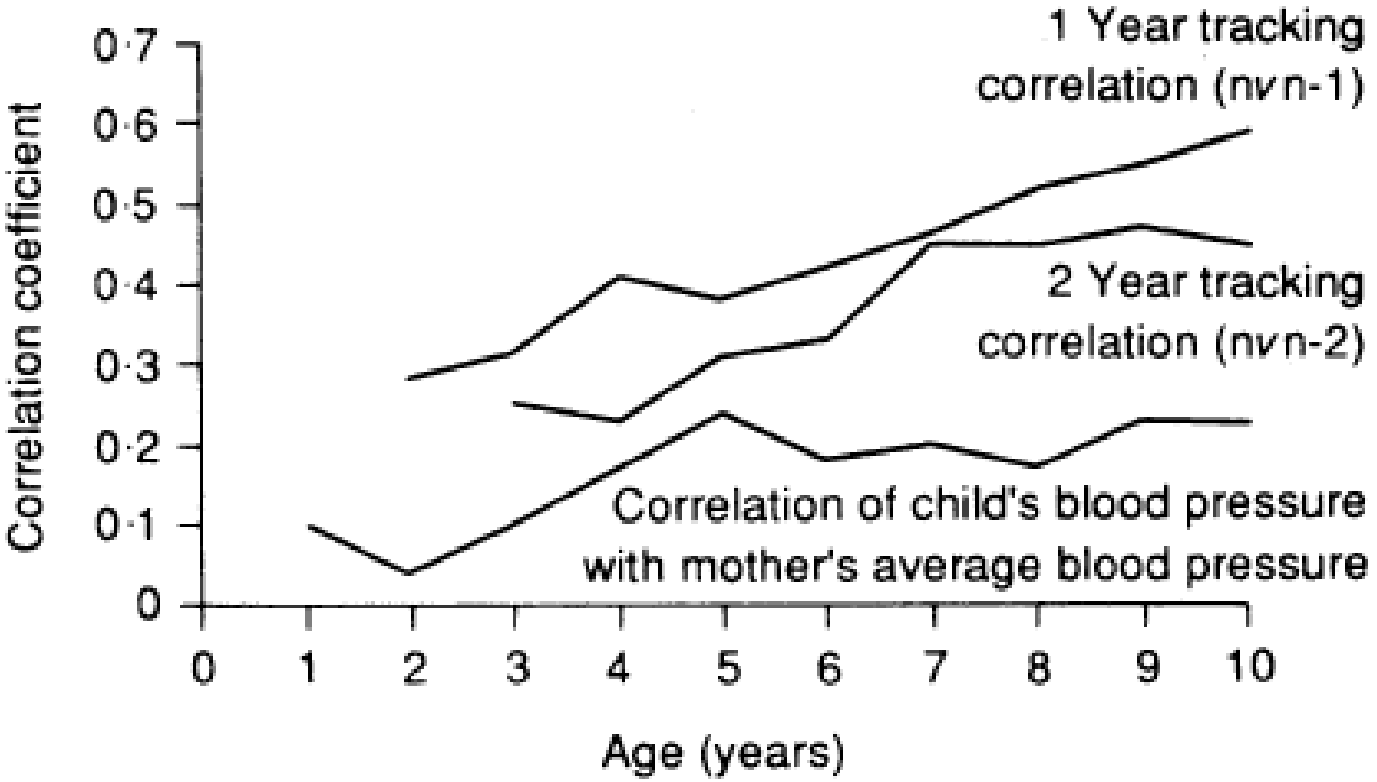



DBP




HSE 2003

# Tracking correlations of BP




*Correlation coefficients for tracking and mothers' average blood pressure with increasing age*

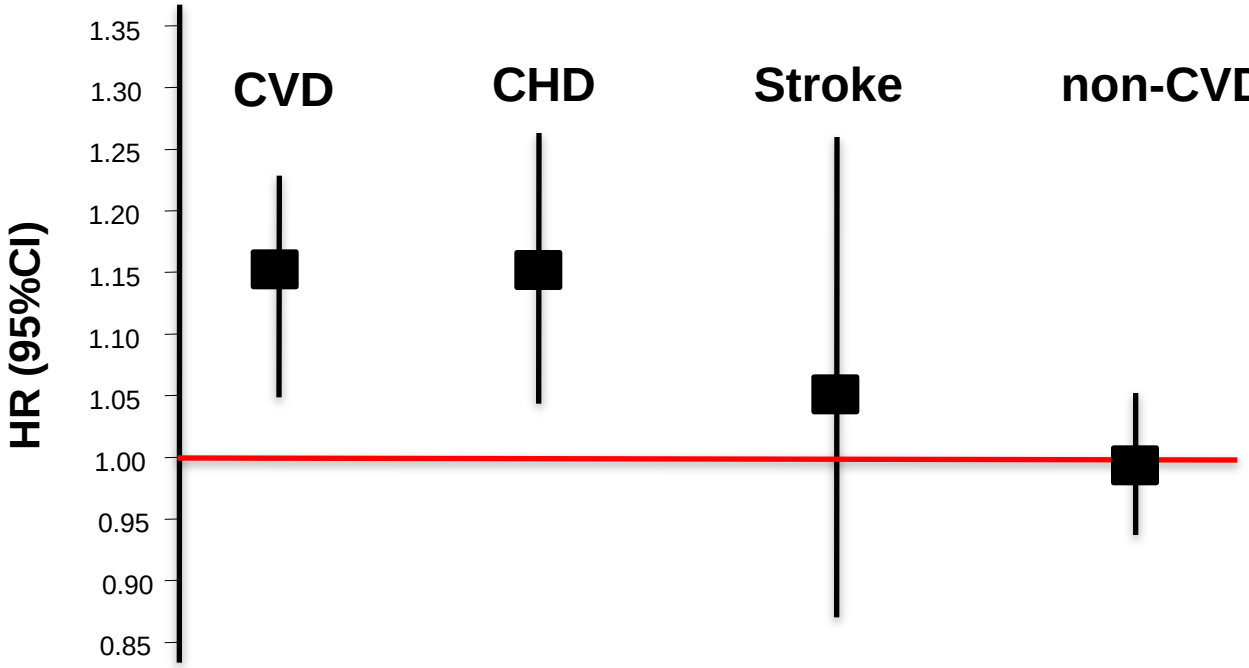
de Swiet et al. BMJ 1992

# Tracking correlations of lipids from childhood to adulthood

| | Girls | Boys |
|---|---|---|
| **Total Cholesterol** | | |
| 2-8 years | 0.48 | 0.53 |
| 9-14 years | 0.42 | 0.45 |
| **LDLc** | | |
| 2-8 years | 0.48 | 0.51 |
| 9-14 years | 0.44 | 0.50 |
| **HDLc** | | |
| 2-8 years | 0.23 | 0.04 |
| 9-14 years | 0.34 | 0.43 |
| **Triglycerides** | | |
| 2-8 years | 0.32 | 0.18 |
| 9-14 years | 0.25 | 0.42 |

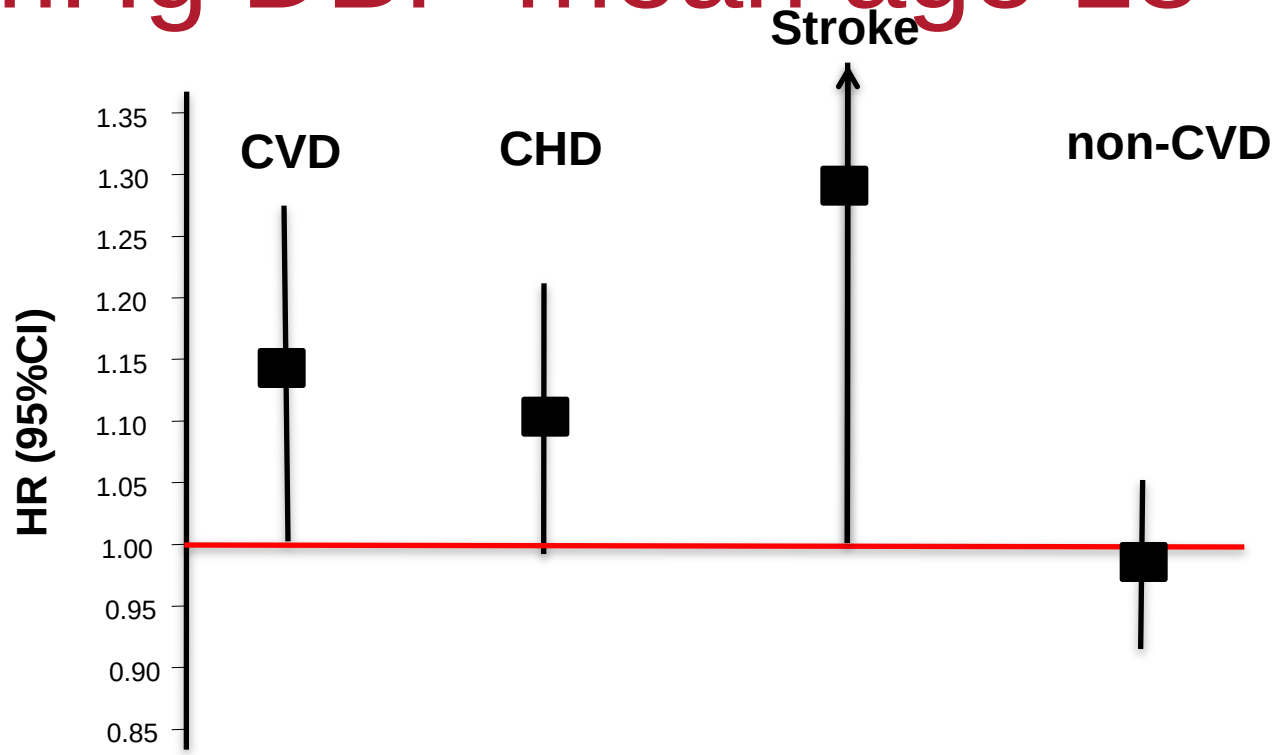
Webber LS, et al. AJE 1991

# Hazard ratio of mortality per 10mmHg SBP mean age 18




McCarron P, et al. Lancet 2000

# Hazard ratio of mortality per 10mmHg DBP mean age 18




McCarron P, et al. Lancet 2000

# Association of childhood (age 12-18) risk factors with CIMT measured 21 years later

**Table 4.** Multivariable Model of the Relationships Between Risk Variables Measured at Ages 12-18 Years and Common Carotid Artery Intima-Media Thickness Measured 21 Years Later (n = 1170)*

| Risk Variable | Regression Coefficient† | SE | *P* Value |
|---|---|---|---|
| Male sex | 0.023 | 0.006 | <.001 |
| Age | 0.002 | 0.001 | .24 |
| LDL-C | 0.010 | 0.003 | .001 |
| Body mass index | 0.009 | 0.003 | .007 |
| Systolic blood pressure | 0.013 | 0.003 | <.001 |
| Smoking (no/yes) | 0.016 | 0.007 | .02 |

Abbreviation: LDL-C, low-density lipoprotein cholesterol.
*Mean age at time of first measurement, 14.9 (SD, 2.4) years.
†Expressed in millimeters for a 1-unit change in age (year) and a 1-SD change in other continuous variables and for the presence or absence of smoking.

Raitakari OT, et al. JAMA 2003

# Association of adult (age 33-39) risk factors with CIMT measured at same time

**Table 3.** Multivariable Model of the Relationships Between Current Risk Variables and Common Carotid Artery Intima-Media Thickness in Adults Aged 29 Through 39 Years (N = 2229)*

| Risk Variable | Regression Coefficient† | SE | *P* Value |
|---|---|---|---|
| Male, sex | 0.009 | 0.004 | .02 |
| Age | 0.026 | 0.002 | <.001 |
| LDL-C | 0.004 | 0.002 | .06 |
| Body mass index | 0.011 | 0.002 | <.001 |
| Systolic blood pressure | 0.010 | 0.002 | <.001 |
| Smoking (no/yes) | 0.011 | 0.004 | .004 |

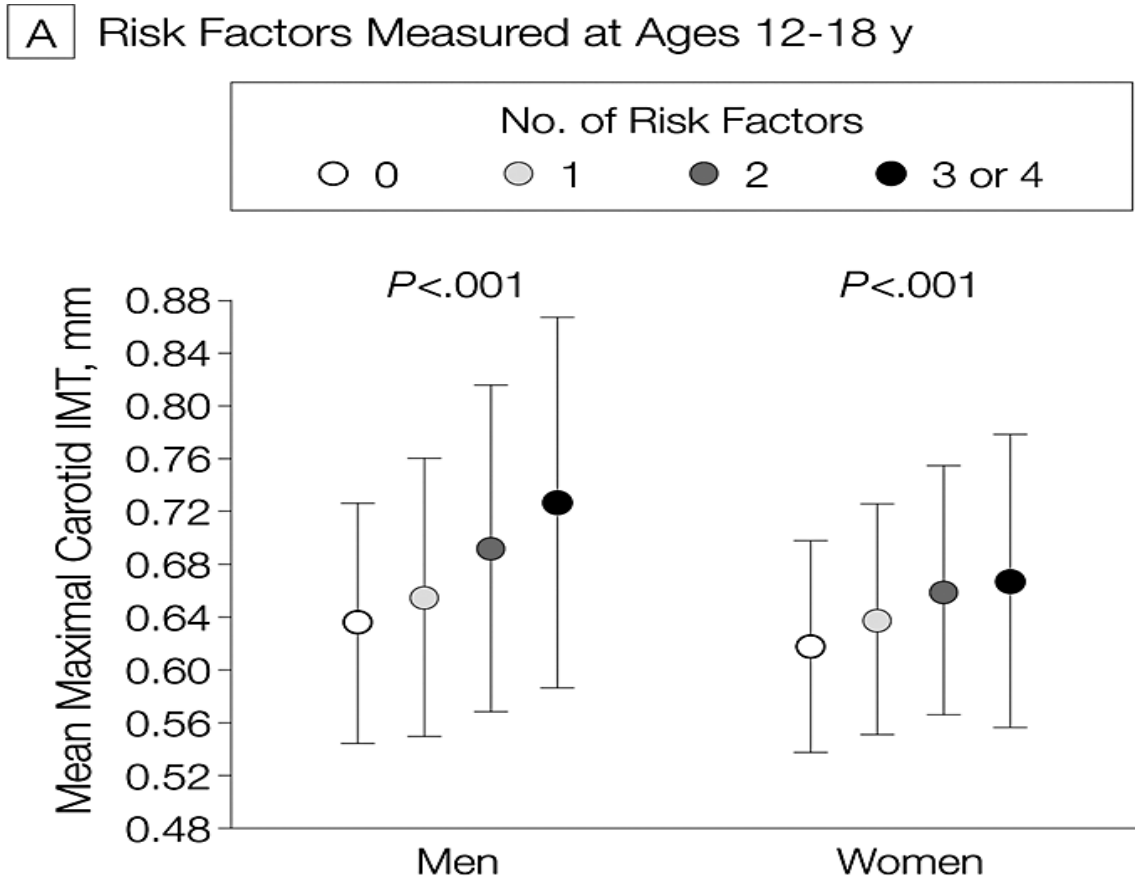
Abbreviation: LDL-C, low-density lipoprotein cholesterol.

*Diastolic blood pressure was also a significant correlate of intima-media thickness (*P*<.001) when entered into the model instead of systolic blood pressure.

†Expressed in millimeters for a 5-unit change in age (year) and a 1-SD change in other continuous variables and for the presence or absence of smoking.

Raitakari OT, et al. JAMA 2003

# Number of childhood risk factors and CIMT in adulthood




Raitakari OT, et al. JAMA 2003

# Early life influences on CVD

## Birth size & CVD

- Low birth weight ~ CVD and risk factors

- Possible interpretations:

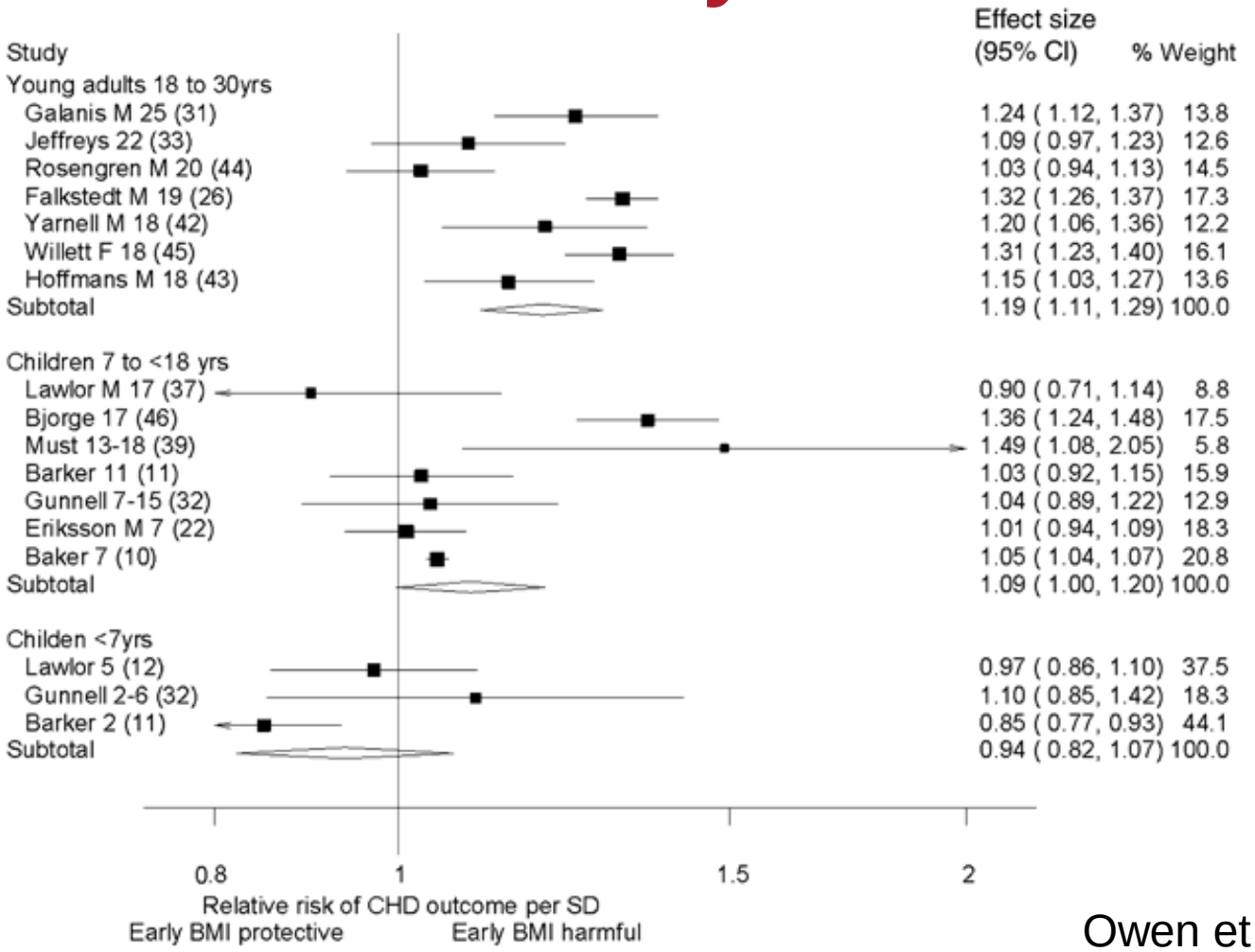
1. Programming of CVD risk by impaired intrauterine nutrition/growth
2. Genetic variants that affect both foetal growth and insulin resistance
3. Confounding (e.g. by SEP, shared familial behaviours), statistical artefact or publication bias

# Early life influences on CVD

## Infant growth & CVD

- Small birth size and rapid growth?
- Sensitive or critical periods of growth?
- Development of adiposity

# Child obesity & adult CHD




Owen et al. Int J Obesity 2009

# Behavioural risk factors for CVD

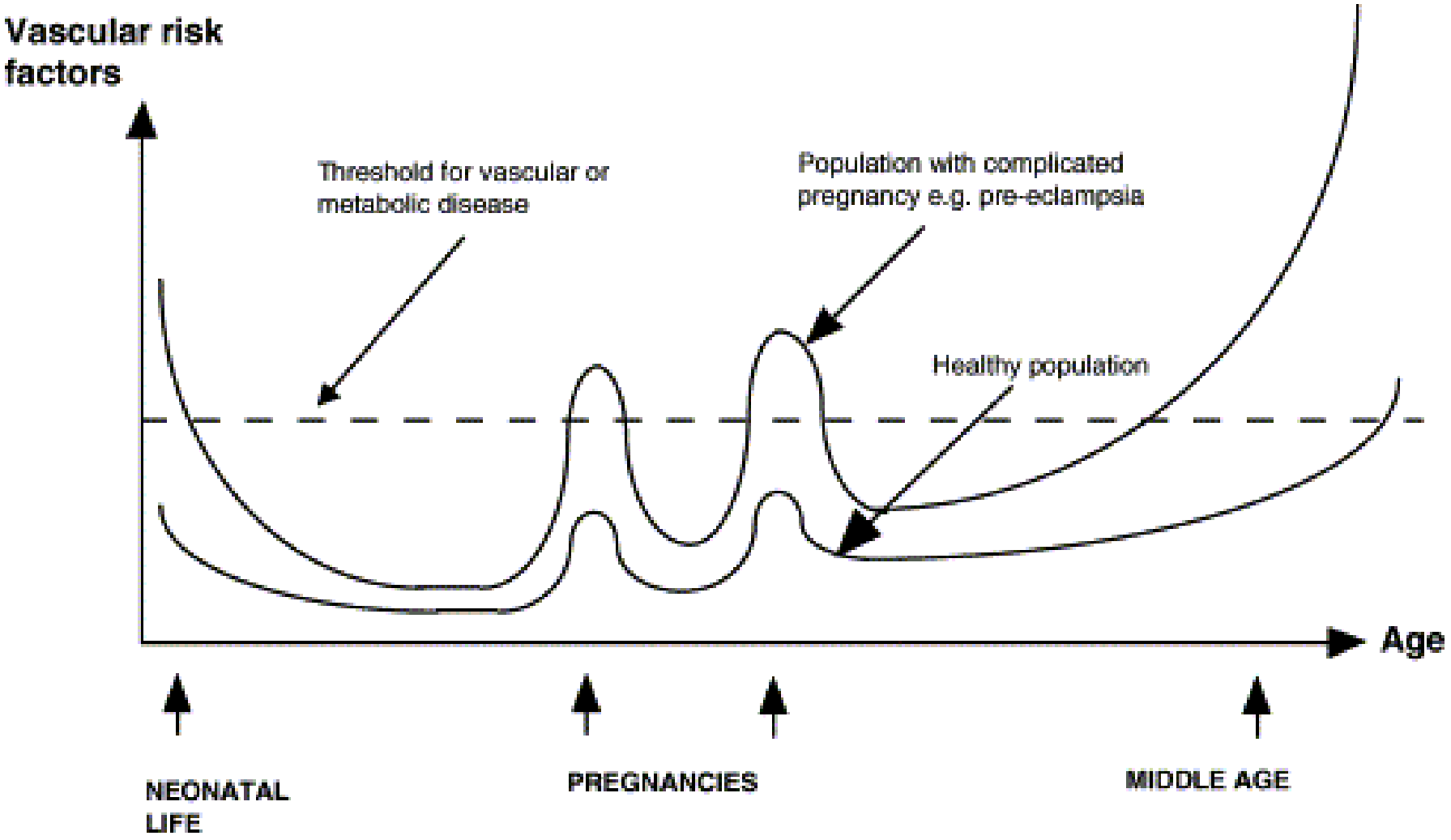
- Established in childhood
- Interventions to reduce risky behaviours in adults tend to have modest success (thus early intervention may be important)

# CVD and pregnancy

- Behaviour change in pregnancy

# CVD and pregnancy

- Pre-eclampsia, gestational hypertension, gestational diabetes
- Relatively little is known on the causes, full consequences and how to prevent




Sattar. Atherosclerosis 2004

# Gestational weight gain & CVD risk factors in offspring

- Long term risks and benefits to mother and child poorly understood
- ?Appropriateness of recent guidelines

Fraser et al. Circulation 2010

- Challenges in cardiovascular disease research

# Cohort effects

# Long lag times

# Causality

- Causal associations of early life factors and CVD?

Study designs to give clues to causality:

- Mendelian randomisation
- Family-based studies
- Cohort comparisons

# The ideal cohort study

- Large
- Siblings, both parents
- Repeat measures during pregnancy
- Repeat measures of behaviours and biomarkers for both parents and children
- Follow-up from pre-conception to into late adulthood

# So…

- Collaboration
- Cohort comparisons
- Compare across generations
- Family-based studies
- Mendelian randomisation

# Global life course epidemiology

- CVD rates increasing in LMICs
- Little research
- Big differences from HICs

- Need for collaboration, but also investment in cohort studies in LMICs

# Thank you

- Debbie Lawlor
- Abigail Fraser