Toxic exposures to the fetus and adult health

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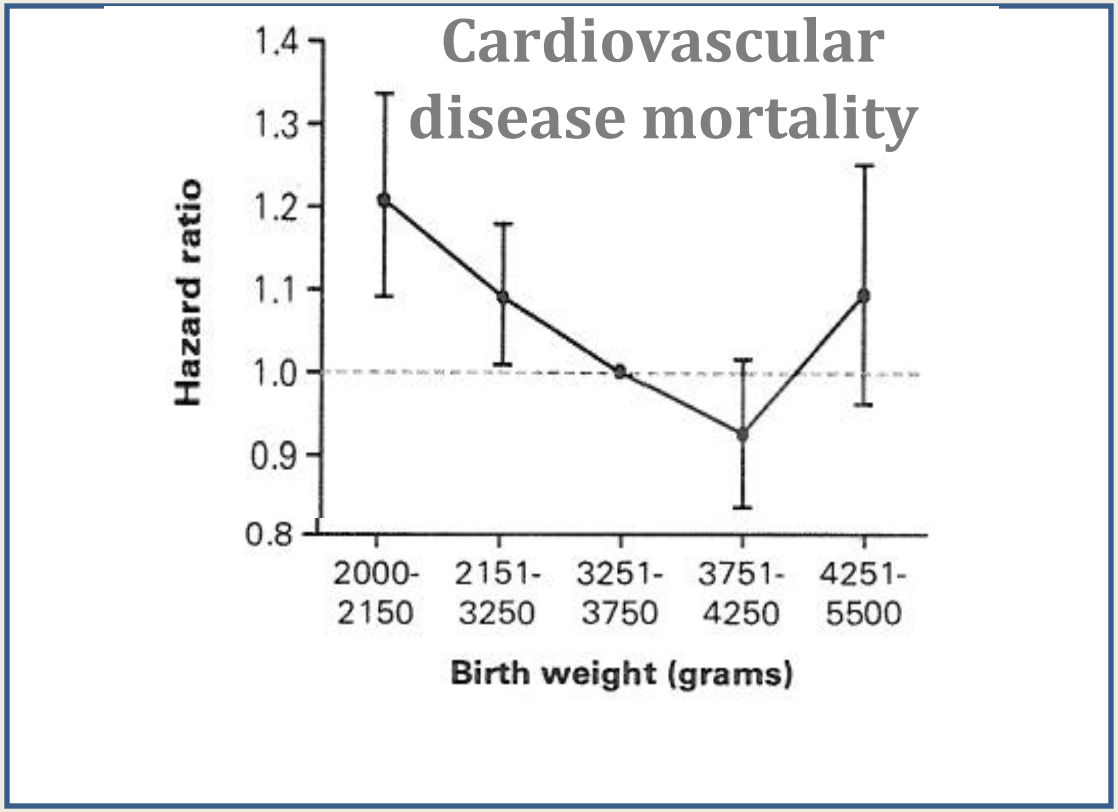
Outline

1. A note on Barker and birth weight
2. Fetal exposures and adult health
   - Transplacental carcinogens
   - Other effects
3. The challenges for public health

1. A note on Barker and birth weight

- Birth weight is associated with adult cardiovascular risk

Birth weight as a predictor of CVD mortality

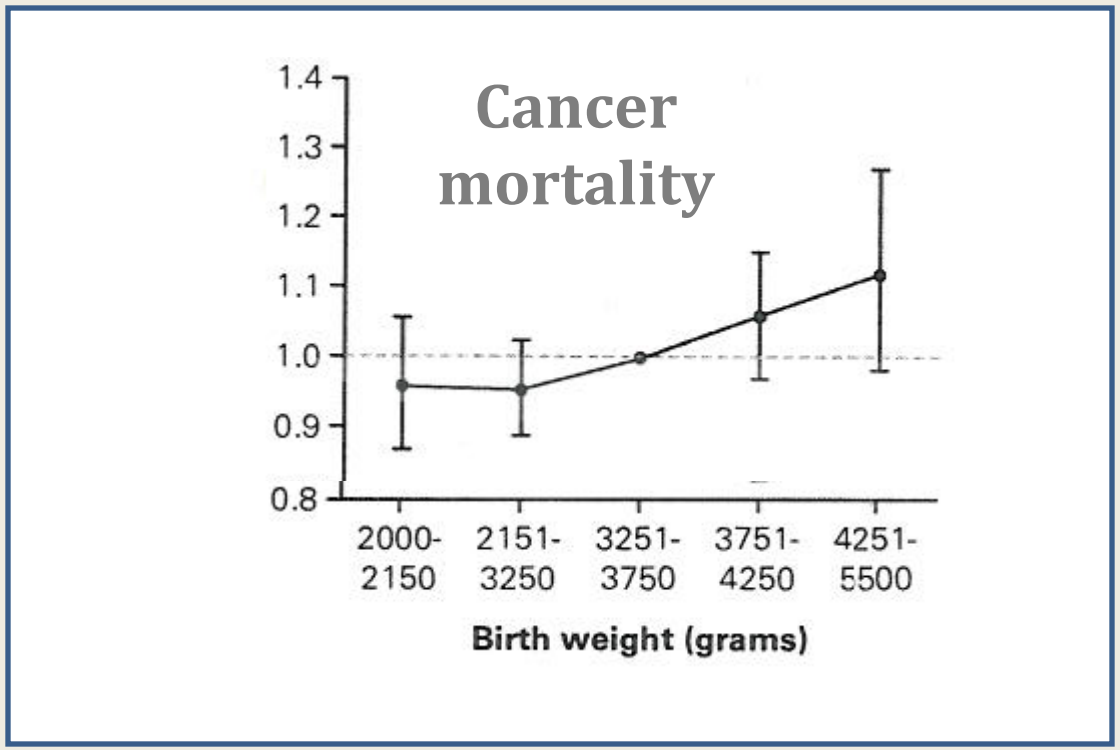


JL Baker et al, *Epidemiology*, 2008

1. A note on Barker and birth weight

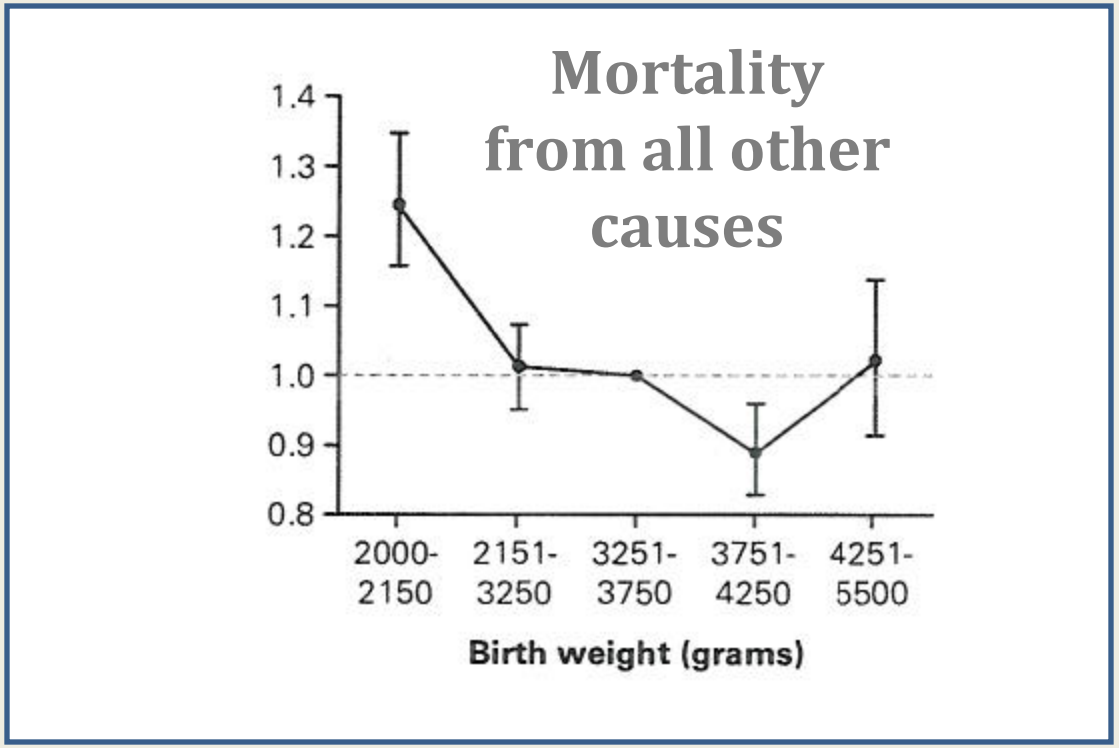
- Birth weight is associated with adult cardiovascular risk
- Barker's hypothesis: nutrition affects metabolism and cardiovascular health
- Birth weight is in fact related to many aspects of adult health

Birth weight as a predictor of adult mortality



JL Baker et al, *Epidemiology*, 2008

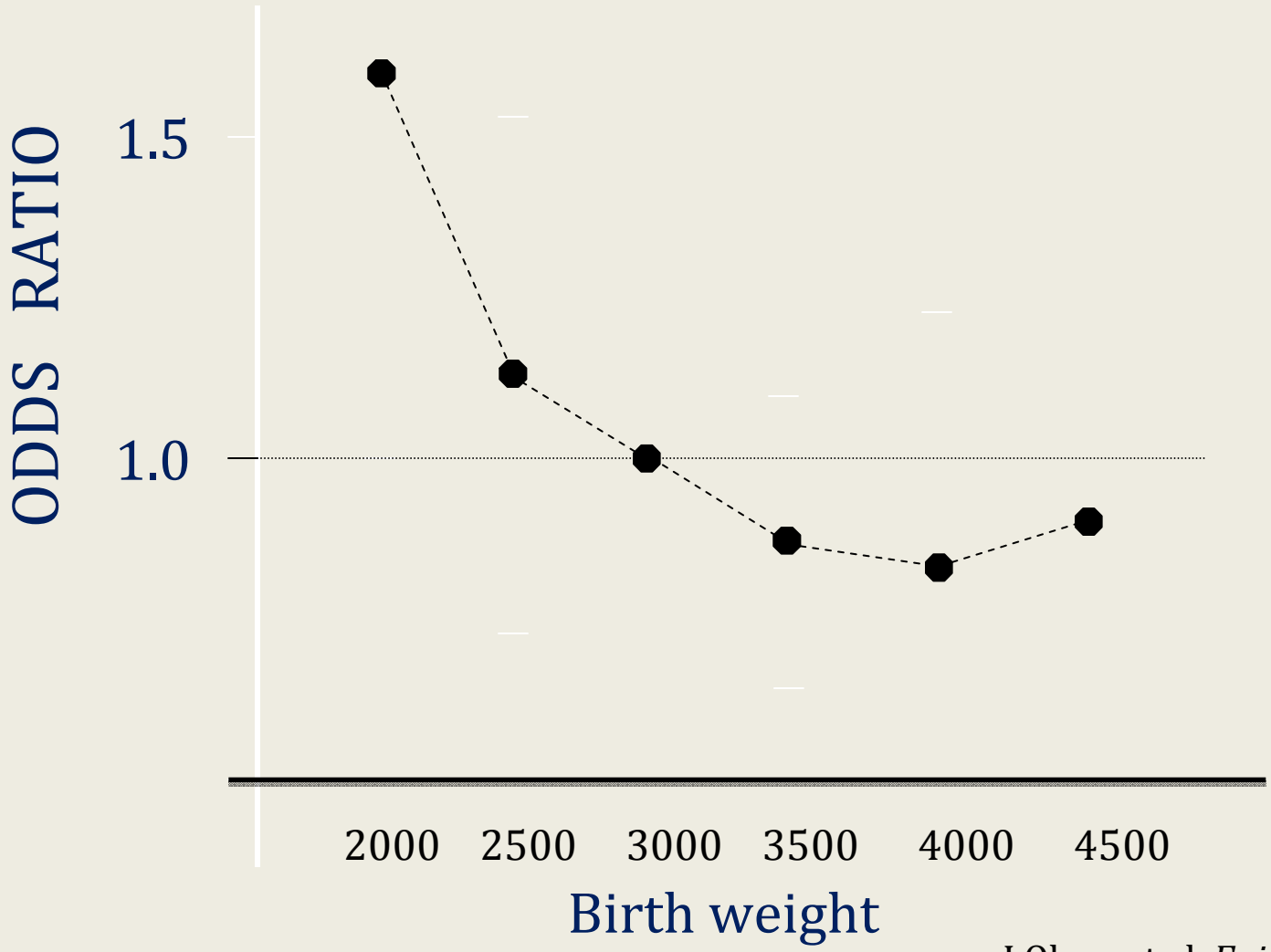
Birth weight as a predictor of adult mortality



JL Baker et al, *Epidemiology*, 2008

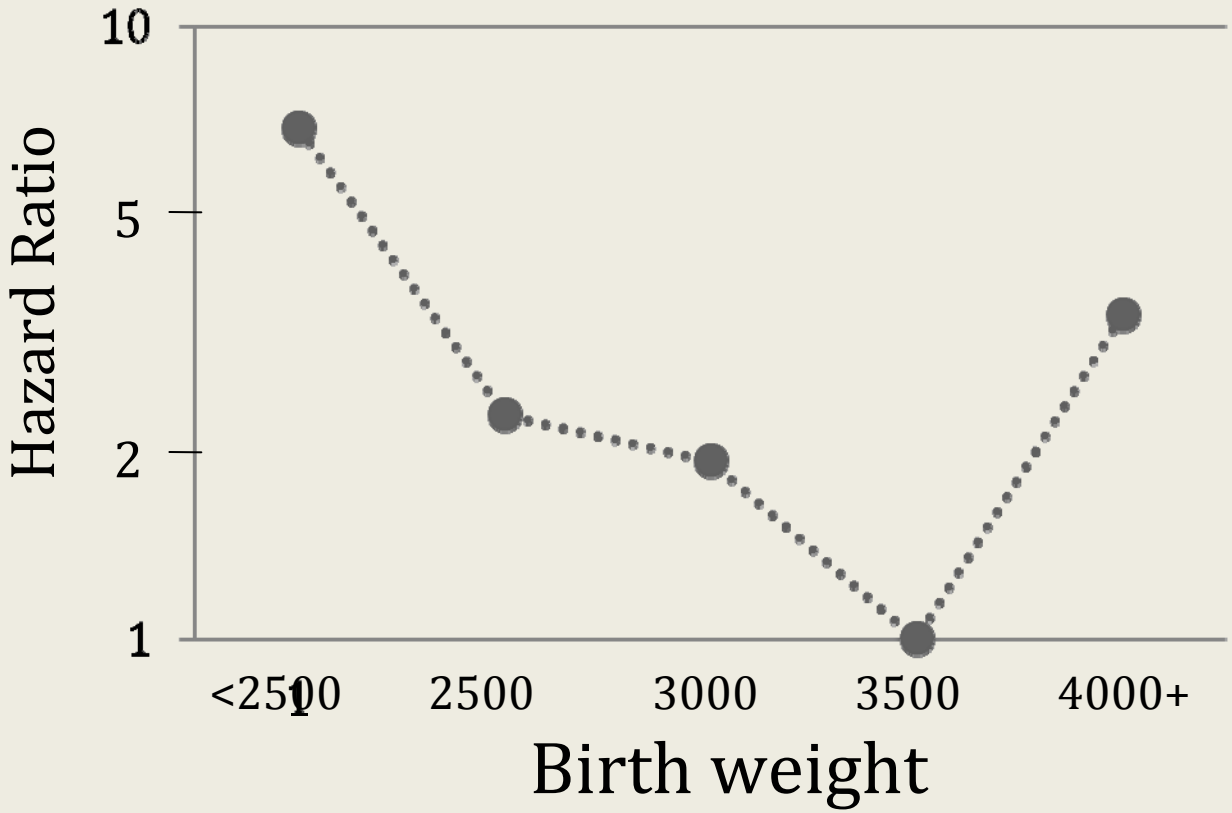
Birth weight is also a predictor of adult *morbidity*

Birth weight as a predictor of hearing impairment (Danish military)



J Olsen et al, *Epidemiology*, 2001

Birth weight as a predictor of schizophrenia (Swedish military)



D Gunnell et al, *AJE*, 2001

How can we explain this wide range of associations with birth weight?

- Does “fetal nutrition” affect more aspects of health than we realize?
- Or are there confounding factors (for example, genes, or fetal exposures) that link fetal growth and adult health?

2. Effects of fetal exposures on adult health

The story of diethylstilbestrol (DES)

Diethylstilbestrol (DES)

An estrogen pill prescribed to about 4 million pregnant women 1941- 1971

Diethylstilbestrol (DES)

1971: DES discovered to cause a very rare vaginal cancer in young women exposed in utero.

Drug was immediately banned.

An estimated 500 cases have been attributed to DES.

“Transplacental carcinogenesis”

DES triggered extensive research on fetal exposures that can cause cancer later in life.

Exposing animal fetuses to toxins can produce many types of cancers

lung cancer

ovarian cancer

lymphoma/leukemia

nervous system tumors

kidney cancer

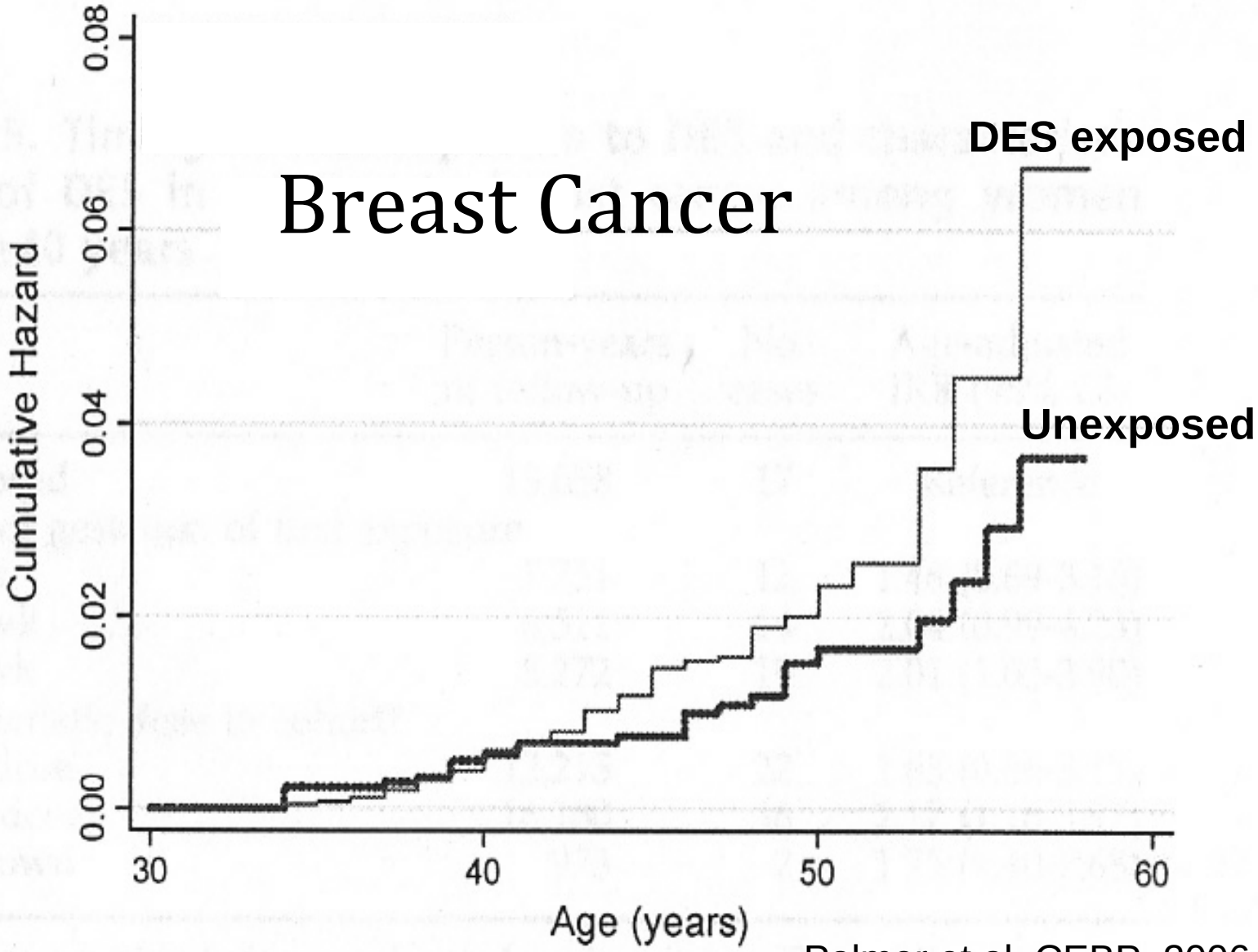
liver cancer

breast cancer

Anderson, *Envir Health Perspec,* 2000

Transplacental carcinogenesis

- Do other prenatal exposures besides DES cause cancer in humans?
  - None known.
- DES may cause other cancers.



Palmer et al, CEBP, 2006

Diethylstilbestrol (DES)

- Once the cancer effects were recognized, other problems also became apparent.

DES causes major reproductive problems in women who were exposed as fetuses.

Infertility	RR =	2 to 4
Miscarriage	RR =	1.5 to 2
Tubal pregnancy	RR =	4 to 8
Preterm delivery	RR =	2 to 3

Consequences of in utero exposure to DES

est. 100,000 women made sterile

300,000 preterm births

10,000 neonatal deaths

10,000 cerebral palsy, other preterm-related handicaps

Troubling questions about DES

What if DES had not caused a rare and unusual cancer?

Would we have noticed an increase in infertility or preterm births among some women?

If we had noticed, would we have thought to ask about women's exposures 20 or 30 years earlier?

If we asked, would women know?

Do fetal exposures affect other aspects of adult health?

- Maternal smoking
  - Decreased sperm quality of sons
  - Male infertility
  - Female infertility

Do fetal exposures affect other aspects of adult health?

- 1918 Influenza epidemic

  Fetal exposure associated with

  - adult disability
  - lower achieved education
  - diabetes
  - stroke

D Almond et al, *Am Econ Rev*, 2005, *J Political Econ*, 2006

3. The challenges for public health

- Methods
- Data
- Hypotheses

METHODS

Exciting new methods for longitudinal data

- Marginal structural models
  - confounding factors that change over time
- Hierarchical models
  - several levels of causation, for example neighborhood effects and individual exposures

How often do we have data good enough to apply these methods?

DATA

- Early exposures are usually difficult or impossible to reconstruct
- When data are available, they are usually imprecise, can be biased
- But a bigger problem is trying to figure out what data we need
  - What are the right questions to ask?

HYPOTHESES

- Animal studies
- Generalizing from past examples
- Changes in disease incidence with no known cause
- The “astute clinician” – or astute public health worker?

HYPOTHESES:
Which exposures?

LEARNING FROM WHAT WE KNOW:

- Rubella → Infections
- Alcohol → Self-administered drugs
- DES Prescribed drugs
- Environmental?

HYPOTHESES: Which outcomes?

- Testicular cancer
- Asthma
- Obesity?
- Autism?
- Health endpoints associated with birth weight

IN SUM

- Fetal life and infancy are vulnerable periods
- The effects of toxic exposures to fetus and infant may not be obvious until later in life
- Possible outcomes are diverse
- The threats are real, their extent unknown
- Effects may never be discovered if we don't consider their possibility