Cardiovascular Disease and Hormone Therapy

Week 2

Objectives

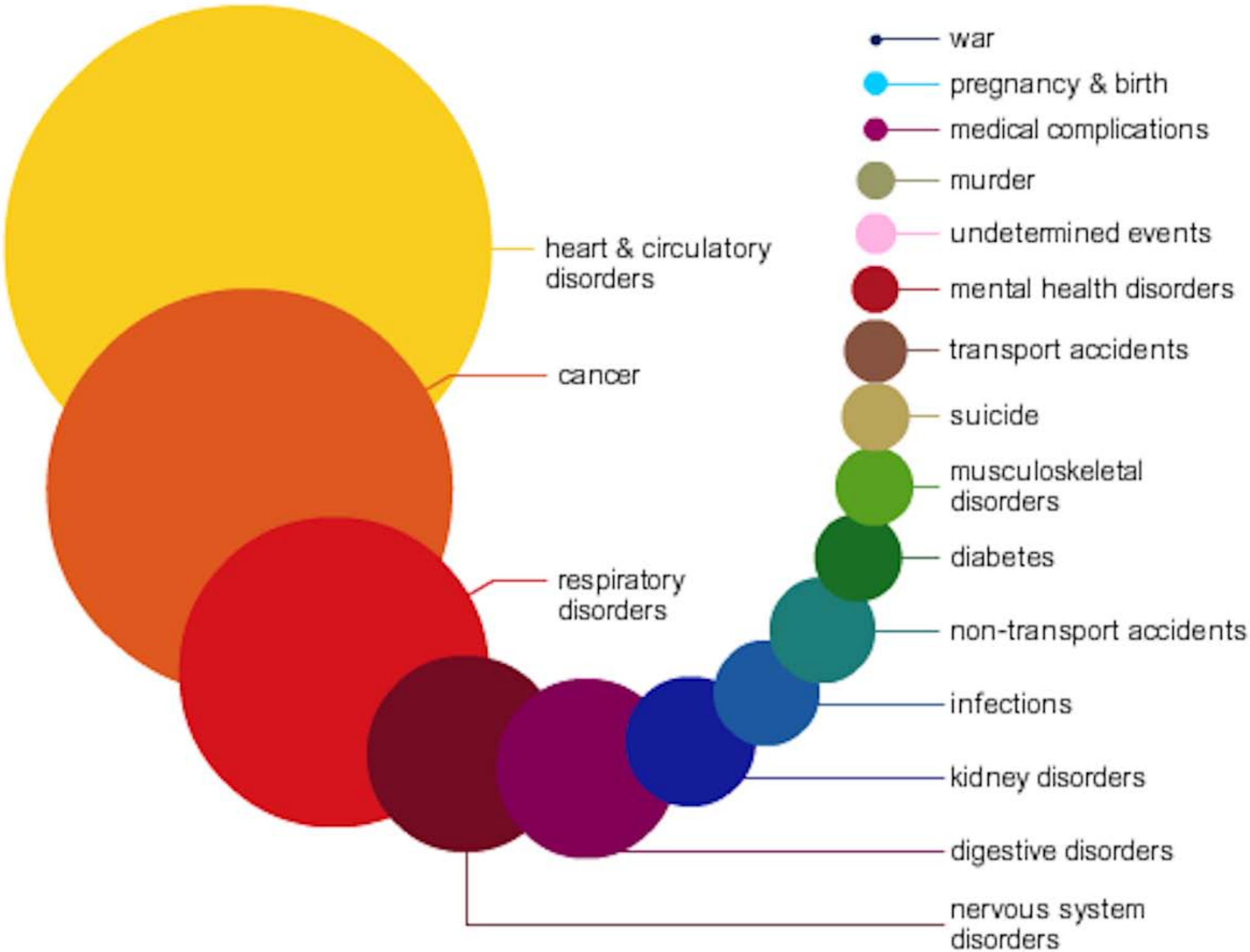
1. Learn about cardiovascular disease including sex-linked biology and gender aspects

2. Introduce study designs

3. Learn about the hormone therapy controversy including the centrality of study designs

Cardiovascular Disease

- Class of diseases involving heart & blood vessels
- Many related to atherosclerosis
    - Plaque builds up in artery walls
- Includes
    - Myocardial infarction (heart attack)
    - Ischemic stroke
    - Congestive heart failure
    - Arrhythmias (slow, fast, irregular)

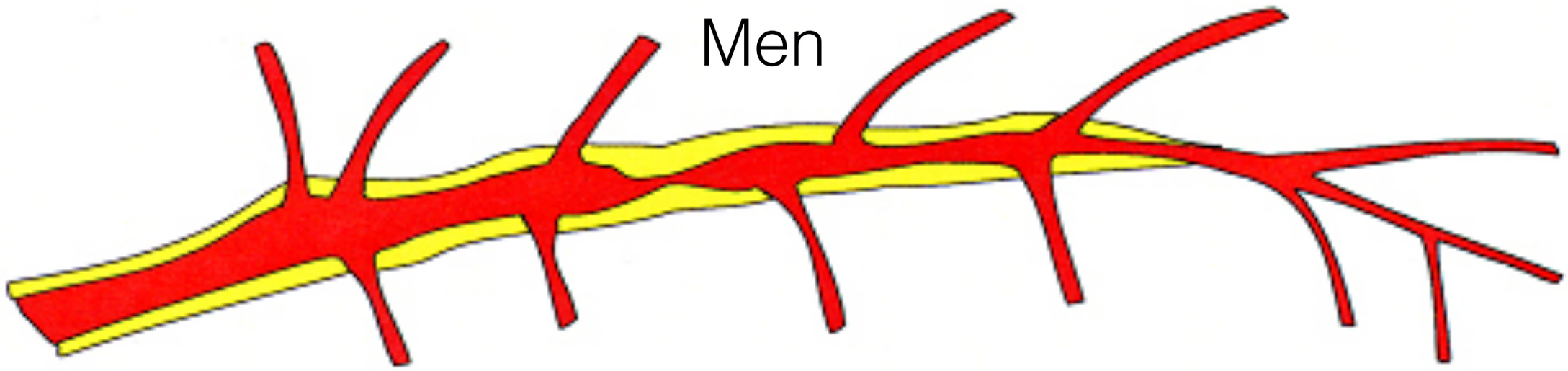

heart & circulatory disorders
cancer
respiratory disorders
war
pregnancy & birth
medical complications
murder
undetermined events
mental health disorders
transport accidents
suicide
musculoskeletal disorders
diabetes
non-transport accidents
infections
kidney disorders
digestive disorders
nervous system disorders

Cardiovascular Disease in Women

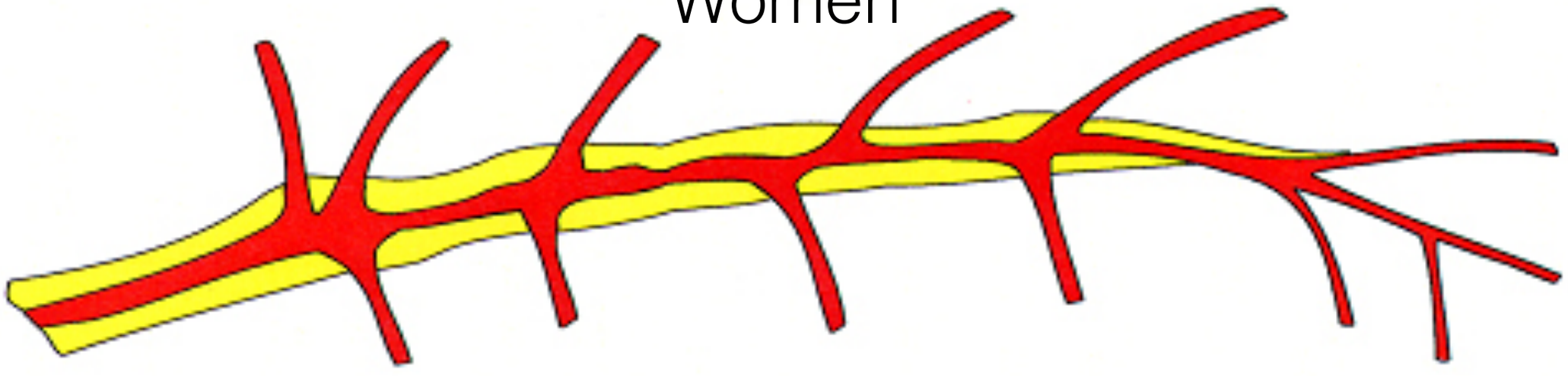
- Underlying physiology may be different
- First myocardial infarction 10 years later
  - More likely to die
- May experience different symptoms
- Some risk factors more common, powerful
- Under-diagnosed and under-treated

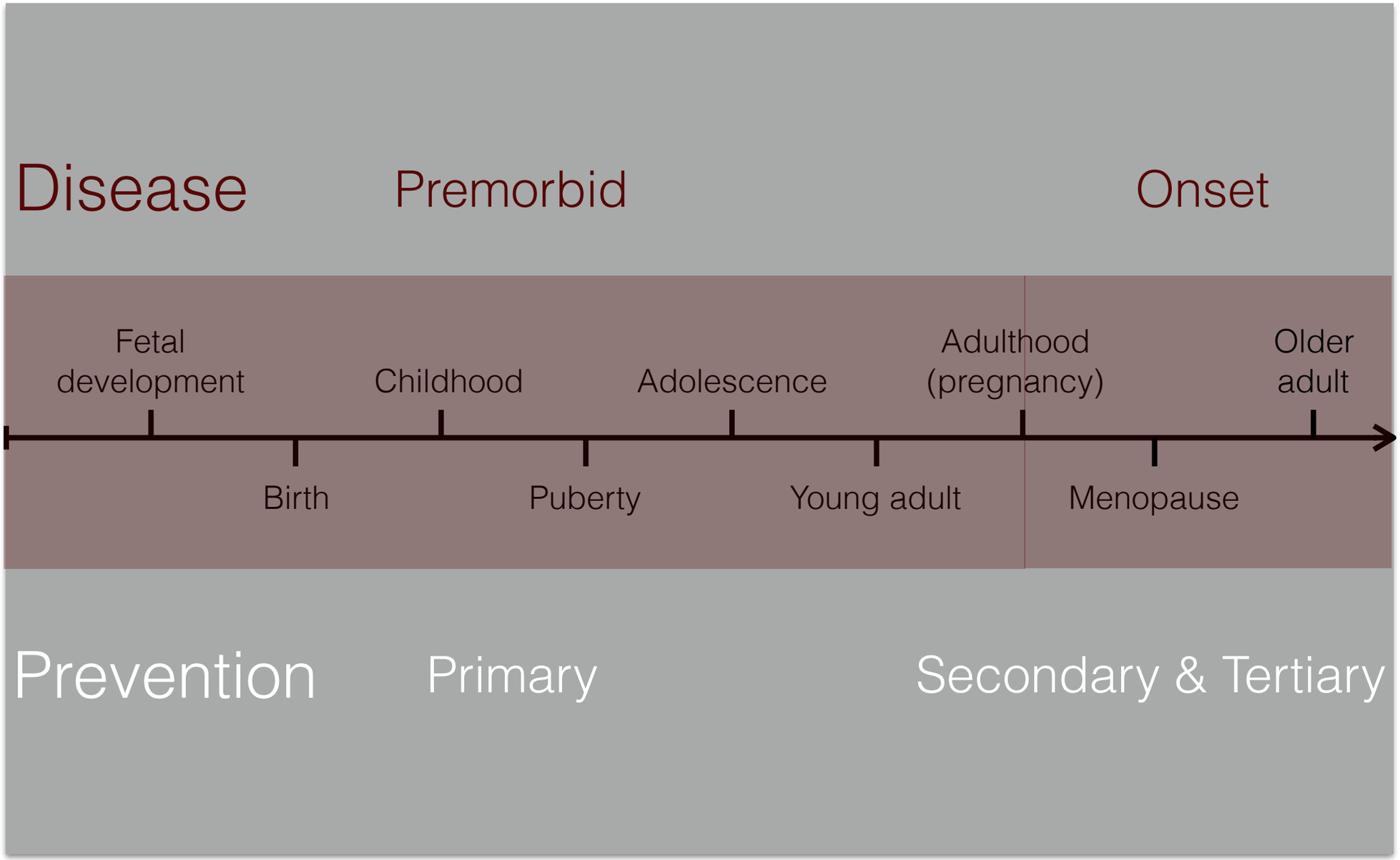
Artery Blockage

Men



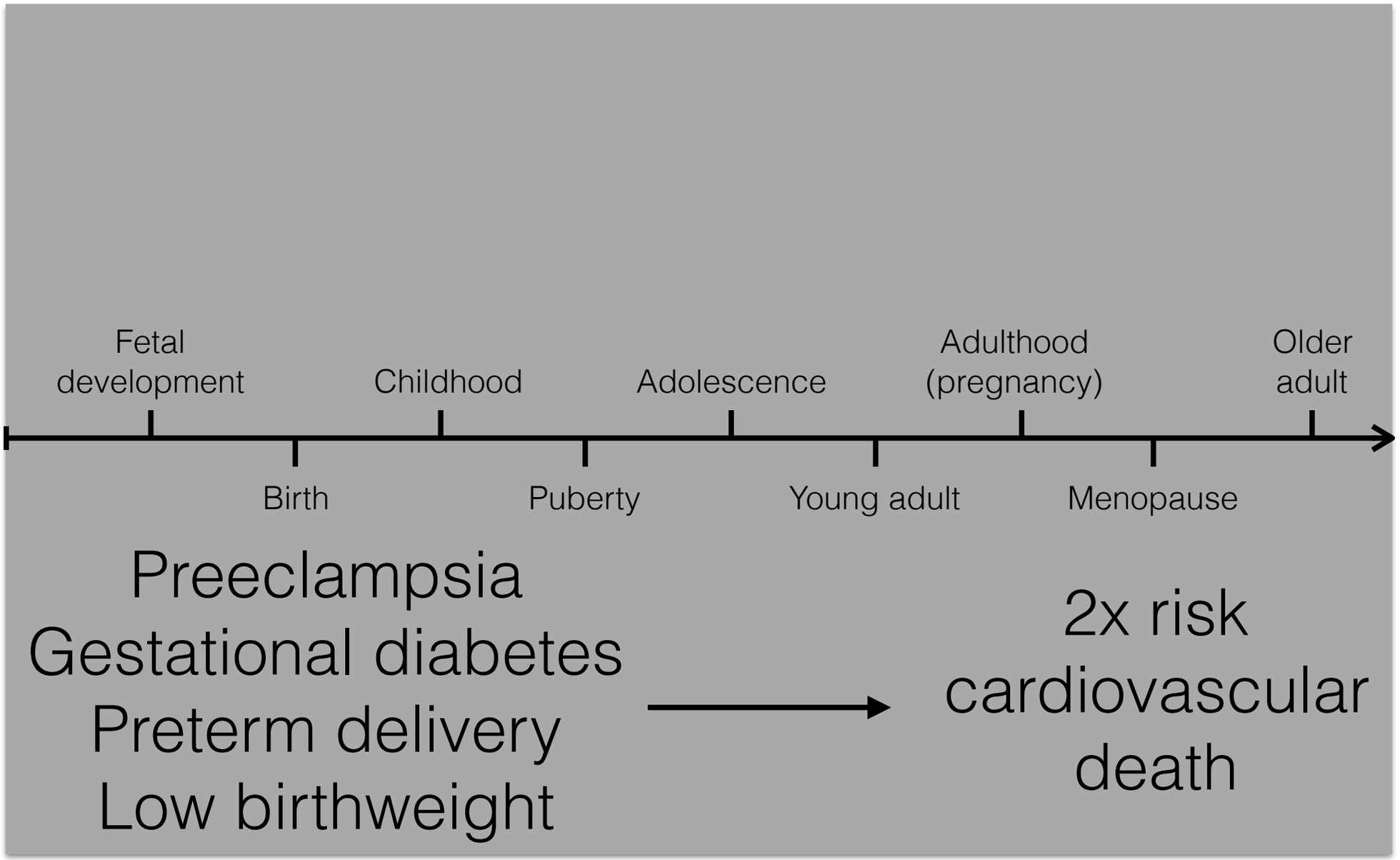
Women





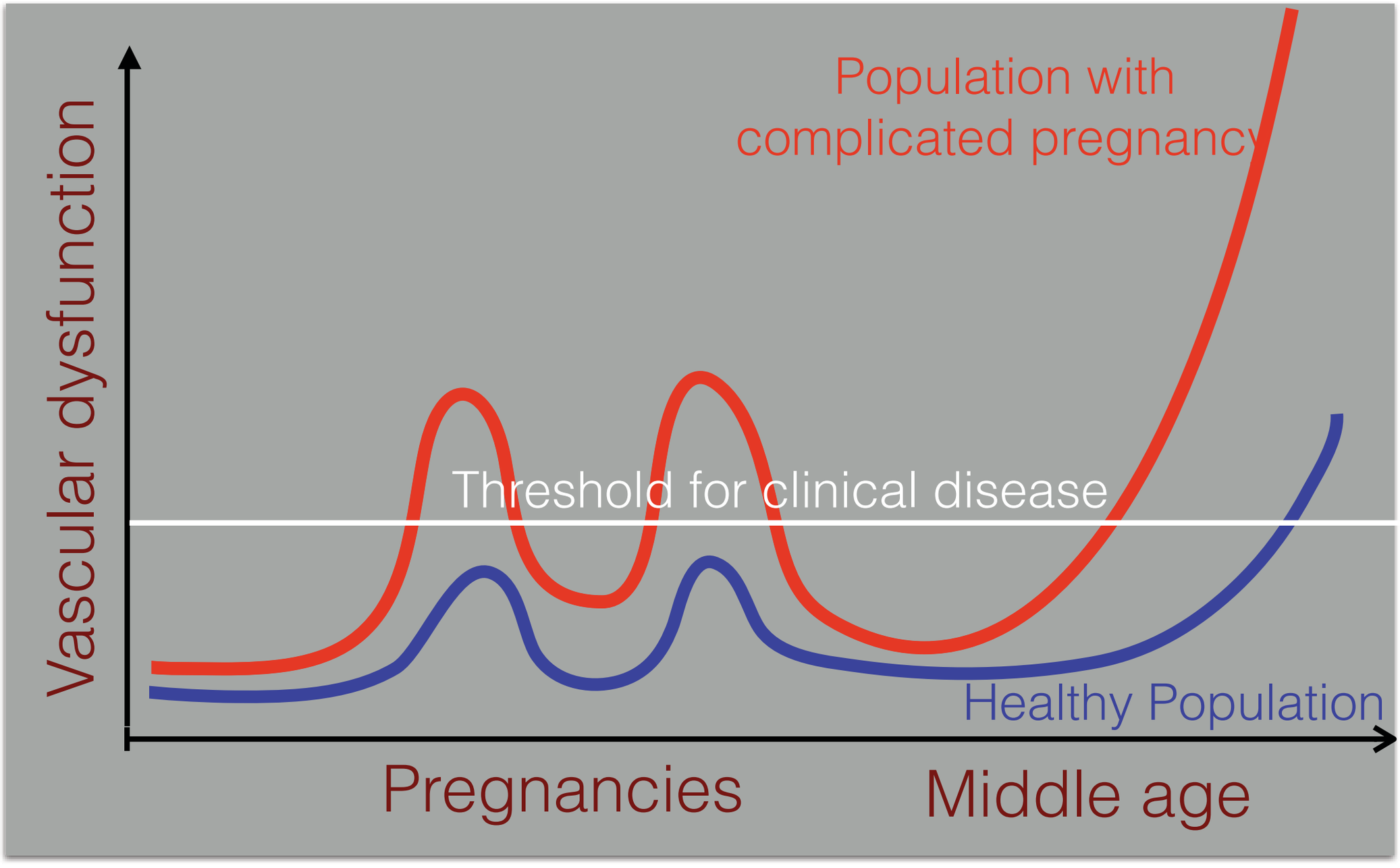
Chronic Disease Prevention

Across the Lifespan



Reproductive Health & Chronic Disease

Linkage



Pregnancy as Stress Test

for Cardiovascular Disease

Satter *BMJ* 2002

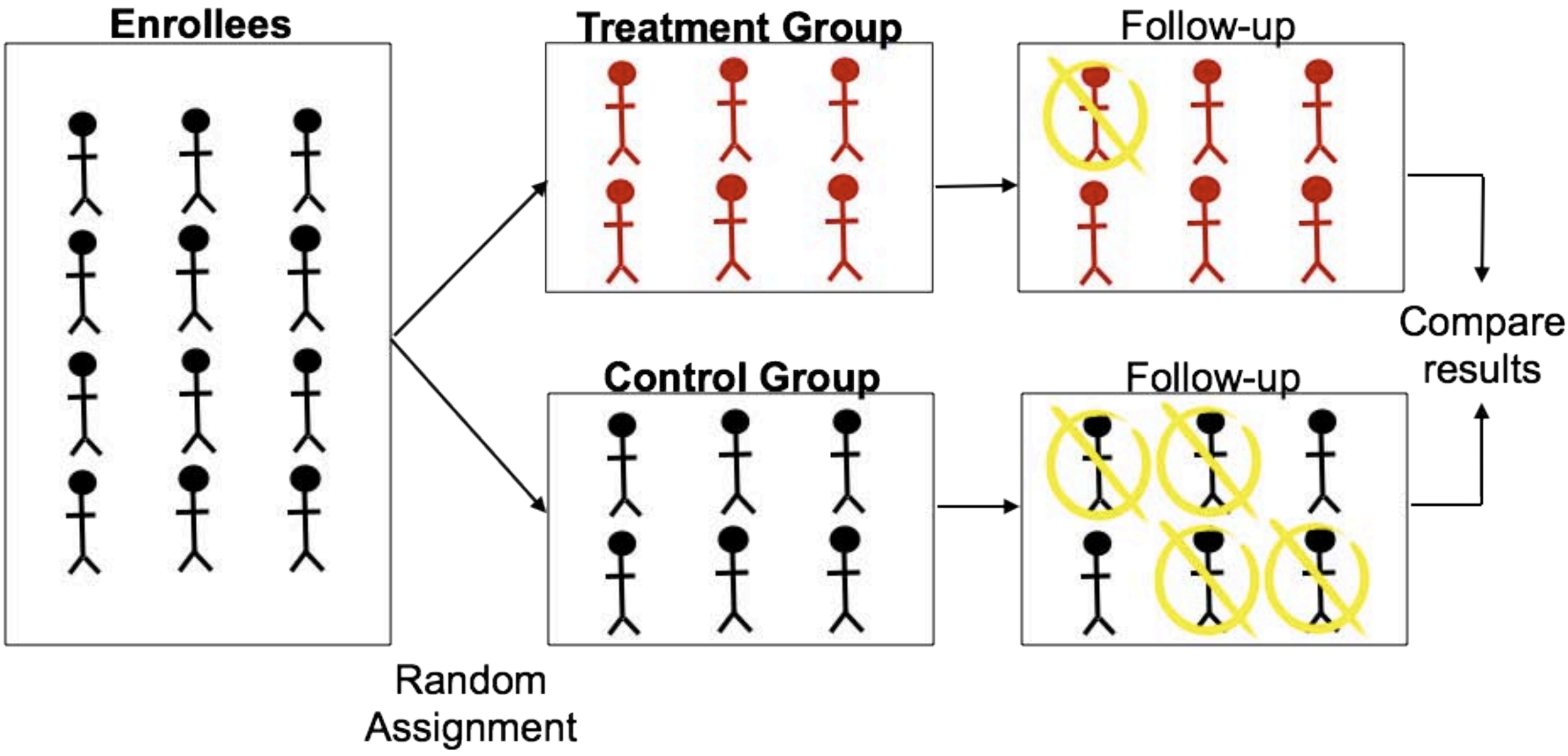
Study Designs

Experimental

- Randomized controlled trial (RCT)

Non-experimental or observational

- Case series
- Ecological/Correlational
- Cross-sectional
- Cohort
- Case-control
- And many more...



Randomized Controlled Trial

Randomized Controlled Trial

- Structure
  - Defined by investigator assignment
- Prospective
- Measures of association include
  - Will cover more next class
  - Risk Ratio, Risk Difference, Odds Ratio
- Classic example
  - Women's Health Study
    - Tested the effects of lower-dose aspirin and vitamin E in preventing CVD and cancer among 39,876 U.S. female health professionals, over age 45 at baseline
    - Funded by the NIH; based at BWH; industry provided drugs

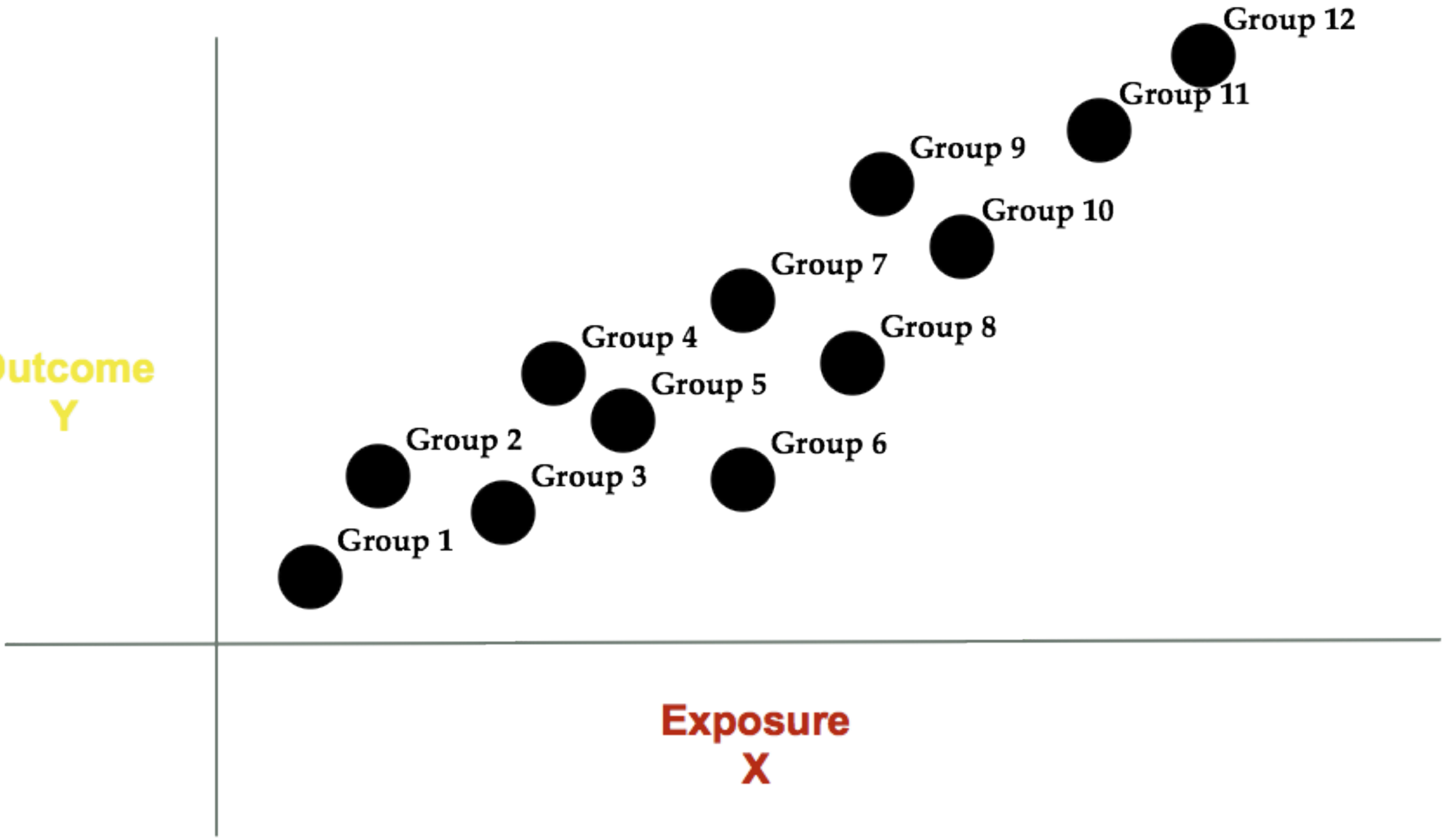
Randomized Controlled Trial

Strengths include

- Minimizes confounding by known and unknown factors
- Greater degree of control over exposure
- Information can be collected on multiple outcomes with little cost increase

Weaknesses include

- Ethical issues
- Time consuming
- Costs and feasibility
- Must select appropriate exposure, dosing, and duration
- Compliance, loss-to-follow-up, misclassification
- Need equipoise



Ecologic/Correlational

Ecologic/Correlational

- Structure
  - Information on exposure and/or disease is available on a group level not an individual level
- Estimate measures include
  - Risk Ratio, Risk Difference, Odds Ratio
- Classic example
  - Cell phones and brain cancer
    - Compare national prevalence of each

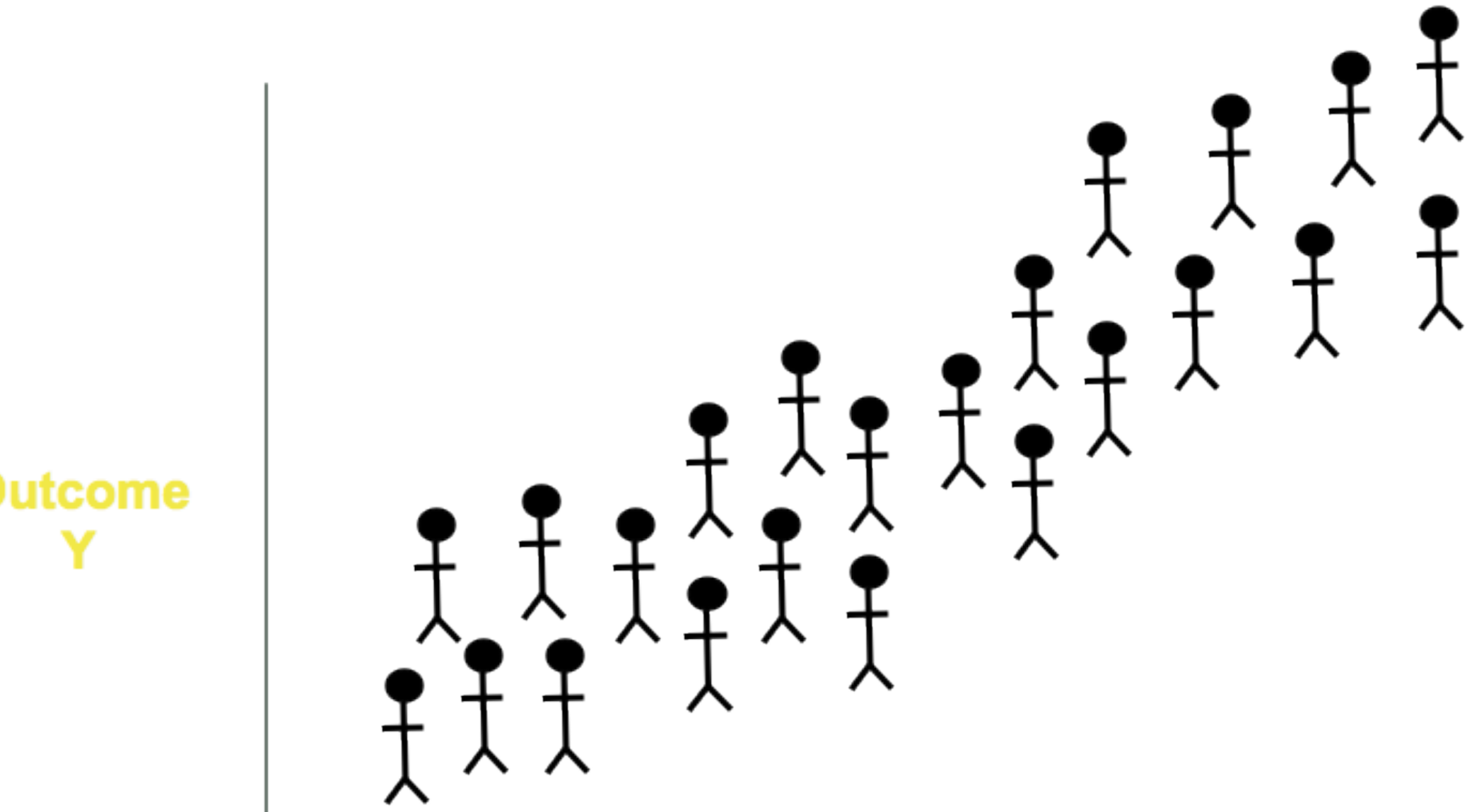
Ecologic/Correlational

Strengths include

- Quick
- Inexpensive
- Large sample

Weaknesses include

- Often have a poor measure of exposure
- No information on if the “exposed” are getting the disease
- Aggregate association may not reflect individual level association
- No data to control individual level confounding



Cross-Sectional

Cross-Sectional

- Structure
  - Data on individual level, exposure and outcome reflect same time period
- Estimate measures include
  - Risk Ratio, Risk Difference, Odds Ratio
- Classic example
  - National Health and Nutrition Examination Survey (NHANES)
    - Started 1960s, series of surveys
    - Based at CDC

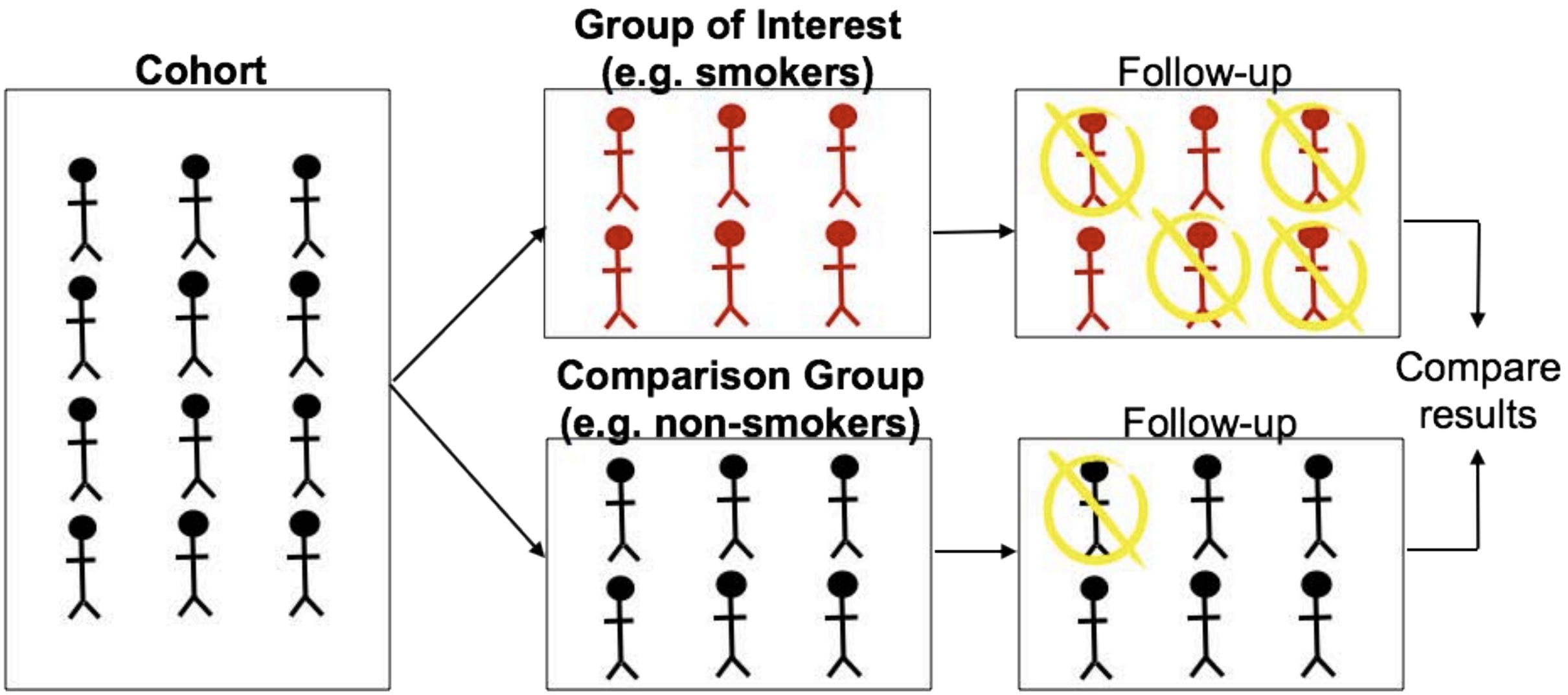
Cross-Sectional

Strengths include

- Quick
- Inexpensive

Weaknesses include

- Can’t access temporality


Cohort
Group of Interest
(e.g. smokers)
Follow-up
Compare
results
Comparison Group
(e.g. non-smokers)
Follow-up

Cohort

Cohort

- Structure
  - Select subjects on the basis of exposure status
- General or special exposure
- Prospective or retrospective
- Estimate measures include
  - Risk Ratio, Risk Difference, Odds Ratio
- Classic example
  - Nurses' Health Study

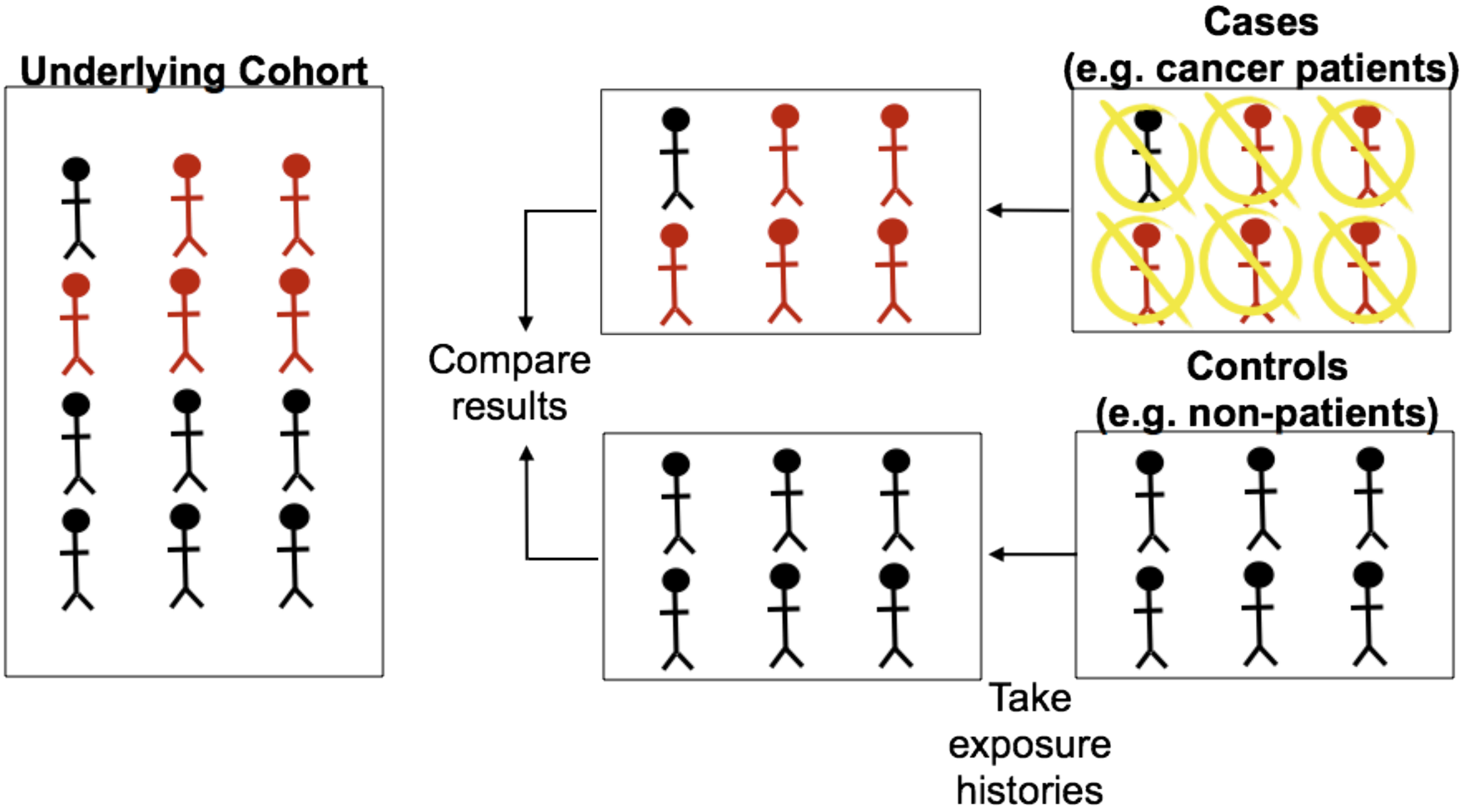
Cohort

Strengths include

- Observing people as naturally conduct lives
- Recall bias eliminated
- Good for rare exposures
- Establish temporality
- Can estimate risk (unlike case-control)

Weaknesses include

- Time consuming
- Expensive
- Difficult for rare diseases



Case-control

Case-control

- Structure
  - Select subjects on the basis of disease status
  - Retrospective
- Effect measures
  - Odds ratio
- Classic example
  - Doll and Hill's smoking and lung cancer study

Image courtesy of Roman Pavlyuk on flickr. License CC BY.

Case-control

Strengths include

- Fast
- Good for rare outcomes
- Short follow-up is ideal for acute epidemic outbreaks of short duration

Weaknesses include

- Difficult for rare exposures
- Can only study one exposure/outcome relationship
- Limited exposure information
- Selecting appropriate controls challenging

Study Design Overview

Case series

- Careful, detailed report of a series of patients, highlight factors that could be related to outcome

Randomized controlled trial

- Structure of cohort study, but exposure is allocated by investigator

Correlational (ecologic) study

- Data from entire populations to compare disease frequencies among different groups during the same period of time, or among the same population at different times

Cross-sectional study

- Snapshot in time: information on exposure and outcome of individuals assessed at the same point of time for all subjects

Case-control study

- Observational study with selection into study on basis of outcome status

Cohort study

- Observational study with selection into study on basis of exposure status

Study Design Exercise

1. For each description below: Identify the study design used and indicate the main feature that led you to choose that study design. Study design options include:

    - case series
    - randomized controlled trial
    - correlational (ecologic) study
    - cross-sectional study
    - case-control study
    - cohort study

Study Design Exercise

a. In 1980, an investigator noted that there was substantial variability in per capita fat consumption among 25 European countries.

   The investigator then also assessed the 1980 coronary heart disease mortality rates in these countries in order to determine whether an association between per capita fat consumption and coronary heart disease mortality in these countries exists.

Correlational (ecologic): data are collected on population-level, not individual-level

Study Design Exercise

b. In a study of menstrual abnormalities in females after treatment for childhood cancer, the investigators are enrolling two groups of women who were treated for childhood cancer between 1974 and 1980:

(1) women who were treated with chemotherapy and

(2) women who were treated with surgery.

The frequency of menstrual abnormalities occurring from the time of treatment through the end of 2004 will be evaluated.

Cohort: comparing a group who was exposed (surgery) to a group who were not exposed (not surgery, chemotherapy)

Study Design Exercise

c. In a study of electric blanket use during pregnancy and its effect on miscarriage, women who are hospitalized for a clinical miscarriage and an age-matched sample of women who are hospitalized for the delivery of a live born infant are being enrolled.

All subjects are being interviewed to determine their pattern of electric blanket use during the pregnancy that just ended.

Case-control: comparing a group with the outcome (miscarriage) to a group without the outcome (live born infant)

Study Design Exercise

d. A physician at MIT Medical is concerned that a high level of self-perceived stress during college is a risk factor for a subsequent clinical diagnosis of depression.

She plans on reviewing all of the MIT Medical records in fall 2015.

She will identify a group of students who have had a clinical diagnosis of depression, and ask these students about their previous self-perceived stress levels.

Case-series: describing a series of patients with the outcome, with no comparison group

Study Design Exercise

e. A researcher hypothesizes that practicing Tai Chi may lower rates of falls among elderly individuals.

She enrolls 1,000 individuals aged 65 years or old and assigns half of them to a Tai Chi program and half of them to usual activities.

She then compares the two groups with respect to their rates of falls in the next two years.

Intervention: exposure (Tai Chi) was assigned, not self-selected

Study Design Exercise

2. Dietary flavonoids, found in chocolate and plant-based foods, are associated with improved cognitive performance

   A researcher hypothesized that chocolate consumption may improve not only an individual's cognitive performance, but also the performance of whole populations

   - However, measures of cognitive performance of entire populations are not publicly available for his analysis

He decided to use the number of Nobel laureates per capita in 22 countries as a surrogate marker for cognitive functioning of the population

He also obtained information on the per capita yearly chocolate consumption for these same 22 countries

Study Design Exercise

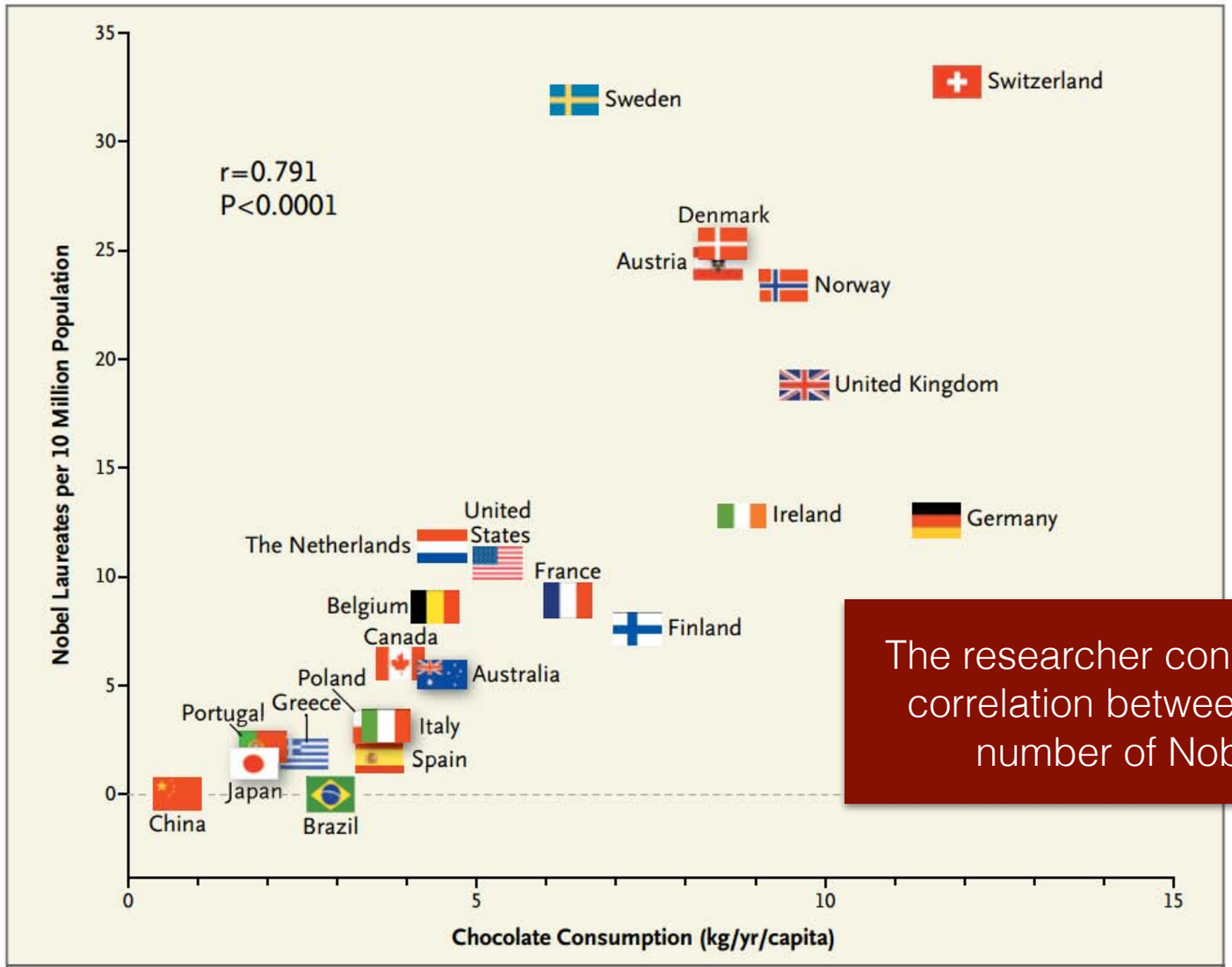


Figure 1. **Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.**

The main figure from his analysis

The researcher concluded there "is a surprisingly powerful correlation between chocolate intake per capita and the number of Nobel laureates in various countries."

Messerli *NEJM* 2012

Study Design Exercise

a. Discuss three possible explanations for why the authors could have observed an association between chocolate consumption and the number of Nobel laureates from a country.

Chocolate consumption influences the number of Nobel laureates. Chocolate consumption has been associated with improved cognitive function and this improved cognitive function could lead to more Nobel laureates.

Nobel laureates influence chocolate consumption. People who win Nobel prizes may be more likely to consume chocolate because they are aware of the positive health benefits of chocolate consumption; celebratory events associated with a citizen winning a Nobel prize may increase national chocolate consumption.

The number of Nobel laureates and the per capita chocolate consumption are **both influenced by a common underlying mechanism**. Socioeconomic differences or geographic and climatic factors may explain the association. For example, those countries with higher chocolate consumption may also have higher per capita income which could be associated with strong educational systems. Stronger educational systems should result in more Nobel prize winners.

Study Design Exercise

b. Discuss the limitations to the interpretation of the data from this study that are inherent in an ecologic/correlational study.

The data in this paper are collected at the national level and we **do not have individual level data**. We are unable to determine if those citizens who consume the most chocolate are also the citizens who are awarded Nobel prizes.

The author only has information on the **average amount** of chocolate consumed by citizens of each country. We do not know if everyone in that country is consuming the average level of chocolate.

The authors are **unable to control for confounding** by other variables (for example, age or socioeconomic status).

Finally, the author **does not have information about the timing** of chocolate consumption and the awarding of Nobel prizes. We do not know if these levels of chocolate consumption reflect consumption prior to Nobel prizes being awarded.

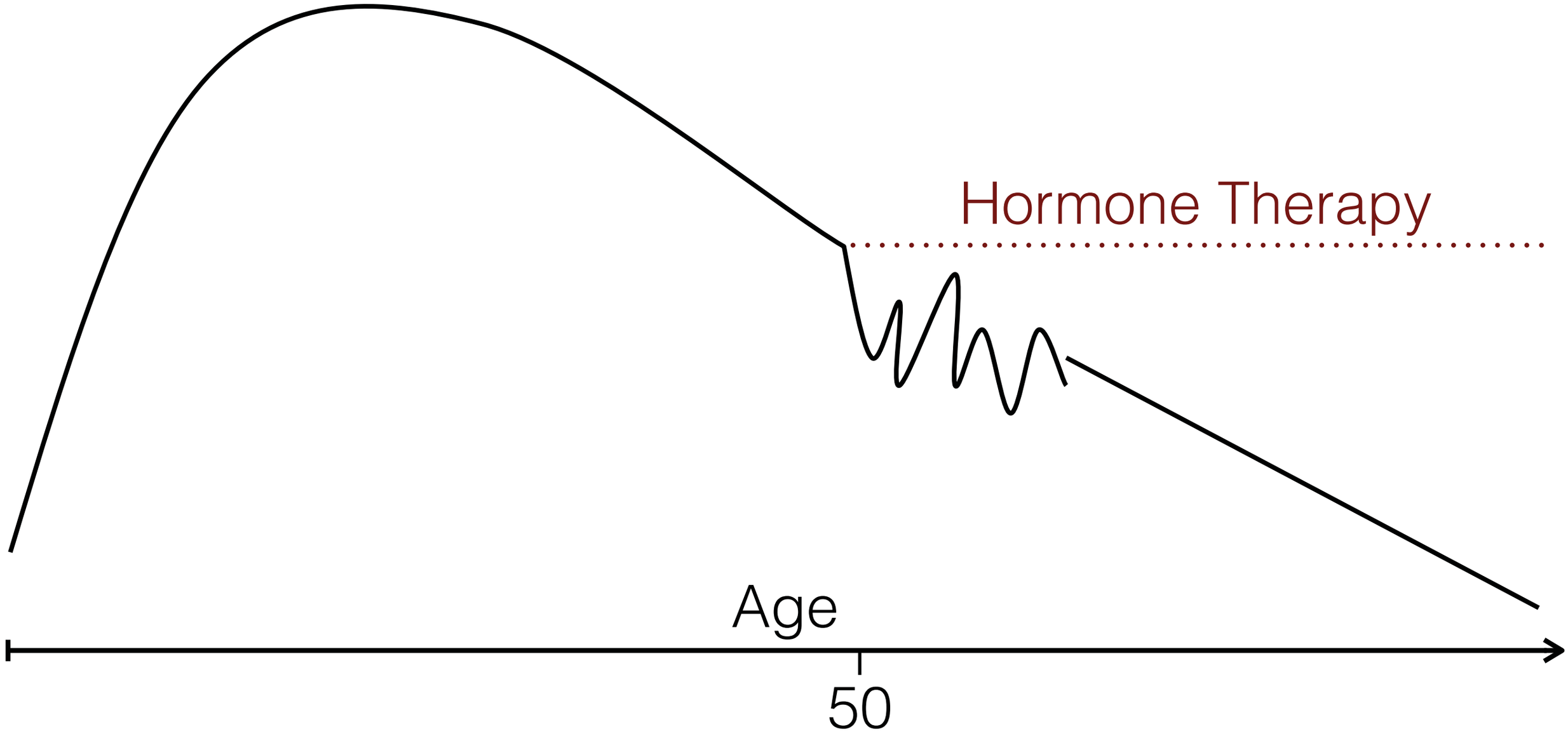
Hormone Therapy

Should women take HT?
Which women?
Which HT?
When? How long?

Indications

- Hot flashes
- Night sweats
- Vaginal dryness
- Urethritis
- Osteoporosis

Estrogen Levels



Feminine Forever

- Defines natural human condition as a disease
- Cure: “off-label,” unapproved use of a drug that healthy people would take every day for the rest of their lives
- Proselytizes can accomplish more than symptom relief
- Receives payments for the book/speaking tours from pharma

Endometrial Cancer

- Estrogen alone (unopposed)
  - 5-y use: 4-5 fold increase
  - 10-y use: 10-fold increase
- Estrogen + progesterone (opposed)
  - No association
- Reason to oppose estrogen
- Rare: ~55,000 cases diagnosed in U.S. in 2015

Cardiovascular Disease

- Meta-analysis of 40 observational studies
  - Ever vs. never HT use: RR=0.65 (95%CI 0.59-0.68)
  - Current use: RR=0.50 (95% CI 0.45-0.56)
- Common: 1 in 3 women die in U.S. in 2015

Grodstein and Stampfer *Prog Cardiovasc Dis* 1995

Nurses' Health Study

Nurses' Health Study I (NHSI)

- 121,701 female nurses
- 30-55 years of age (1976)
- Married

Nurses' Health Study II (NHSII)

- 116,609 female nurses
- 25-42 years of age (1989)

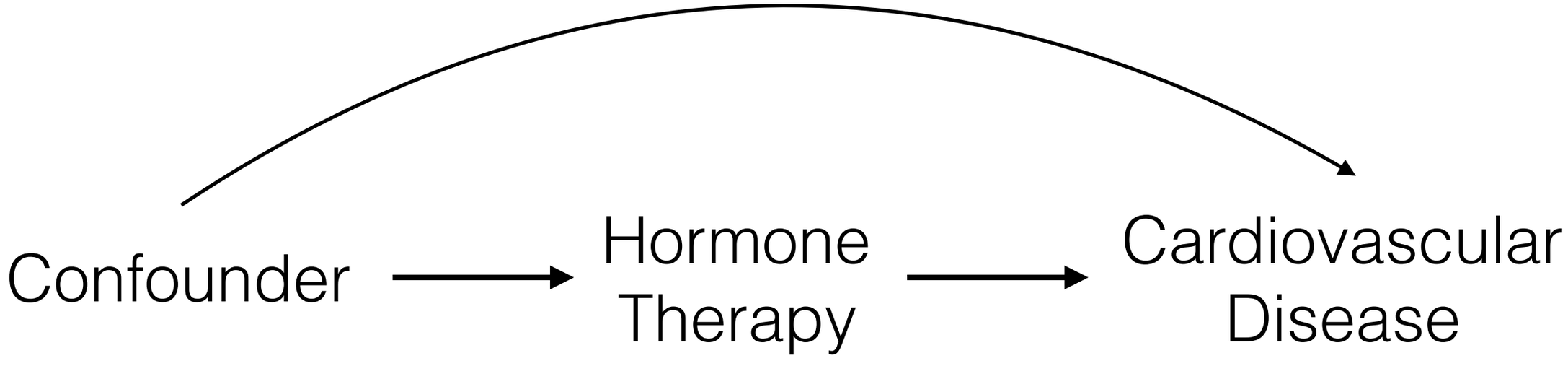
Mailed biennial questionnaires

Cooperative, >90% follow-up

Medical knowledgable -> accurate

Homogenous education, career, and race

Confounding



Users vs non-users:
Leaner
Smoke less
More physically active
More educated
More likely to see physician

Bernadine Healy

Head of the National Institutes of Health & American Red Cross

Launches $625 million Women's Health Initiative

Women's Health Initiative

Established in 1991, 8-12 year intervention

Multi-center randomized controlled trial, UW lead

161,809 women, aged 50-79

Three main areas

- Hormone therapy and cardiovascular disease
- Fat intake and breast cancer
- Calcium/vitamin D and osteoporotic fractures

Largest randomized trials to date

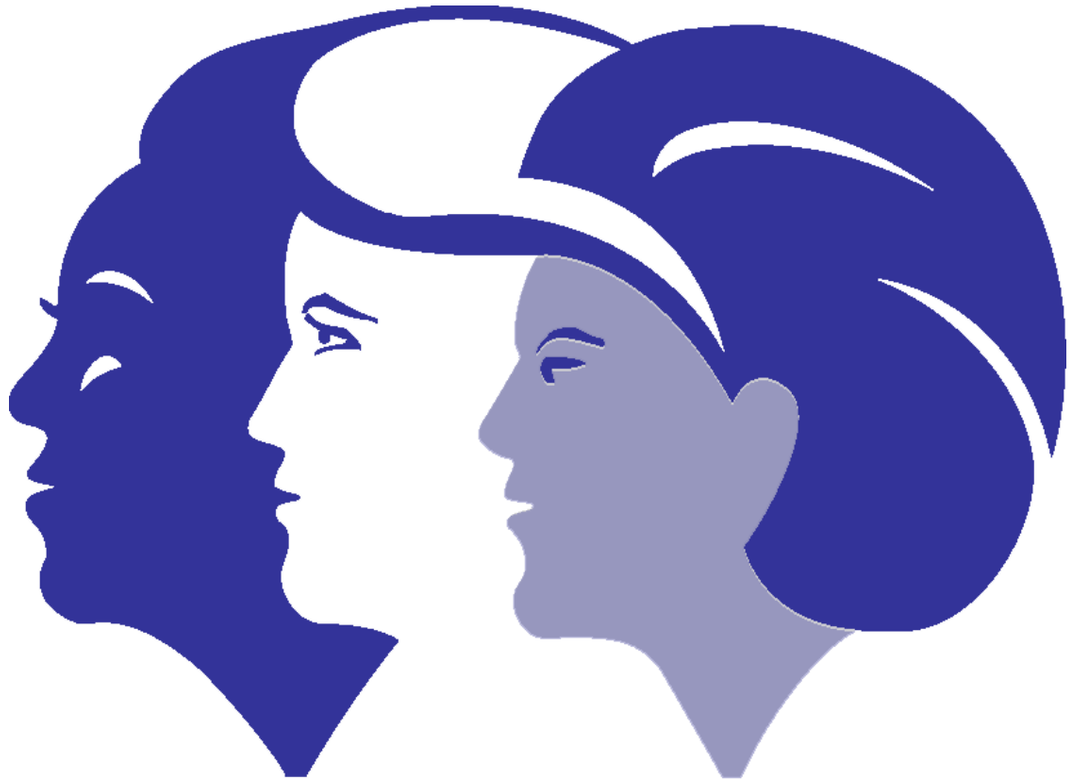
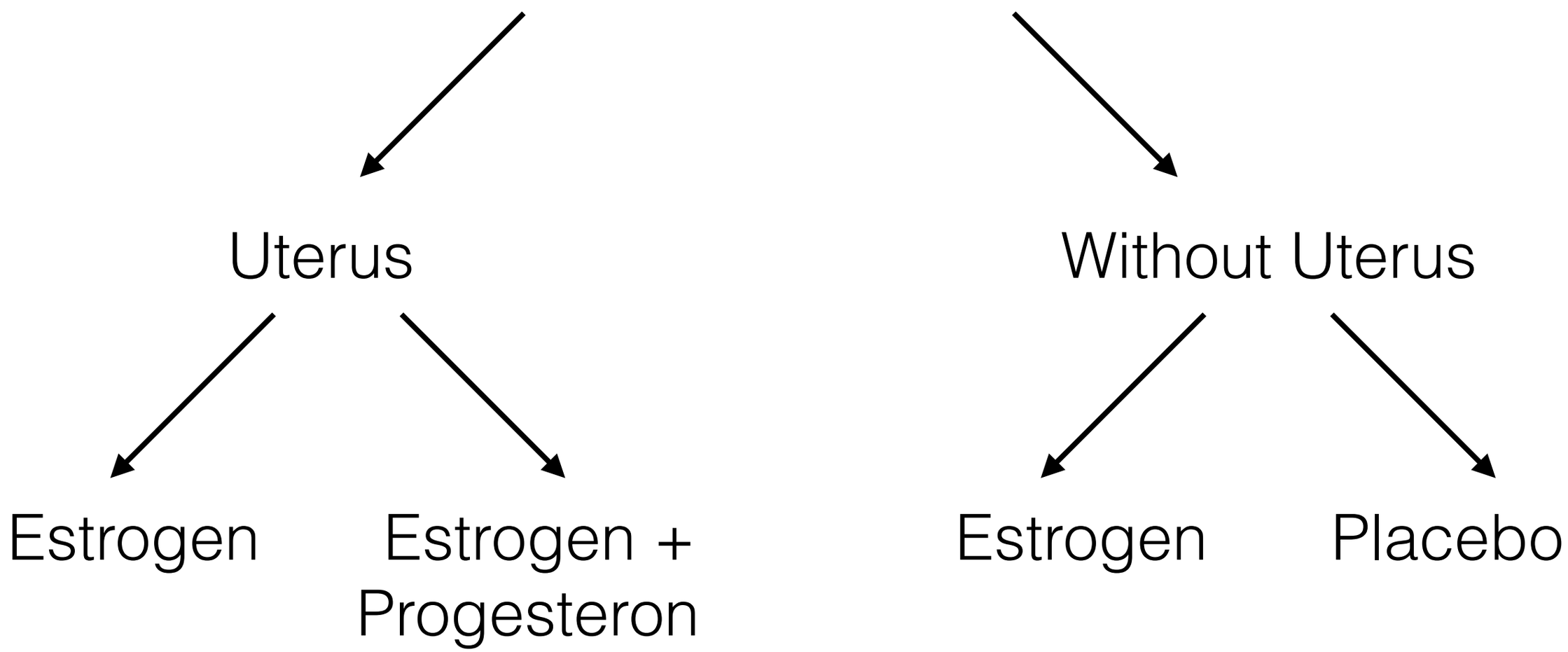


Image courtesy of the Women's Health Intiative. This image is in public domain. Source: Wikimedia Commons.

Study Design



Trial Stopped

- Study participants informed twice about slight excess risk for CVD among hormone therapy users

- In 2002, prematurely stopped the estrogen + progesterone component after 5.6 years of follow-up

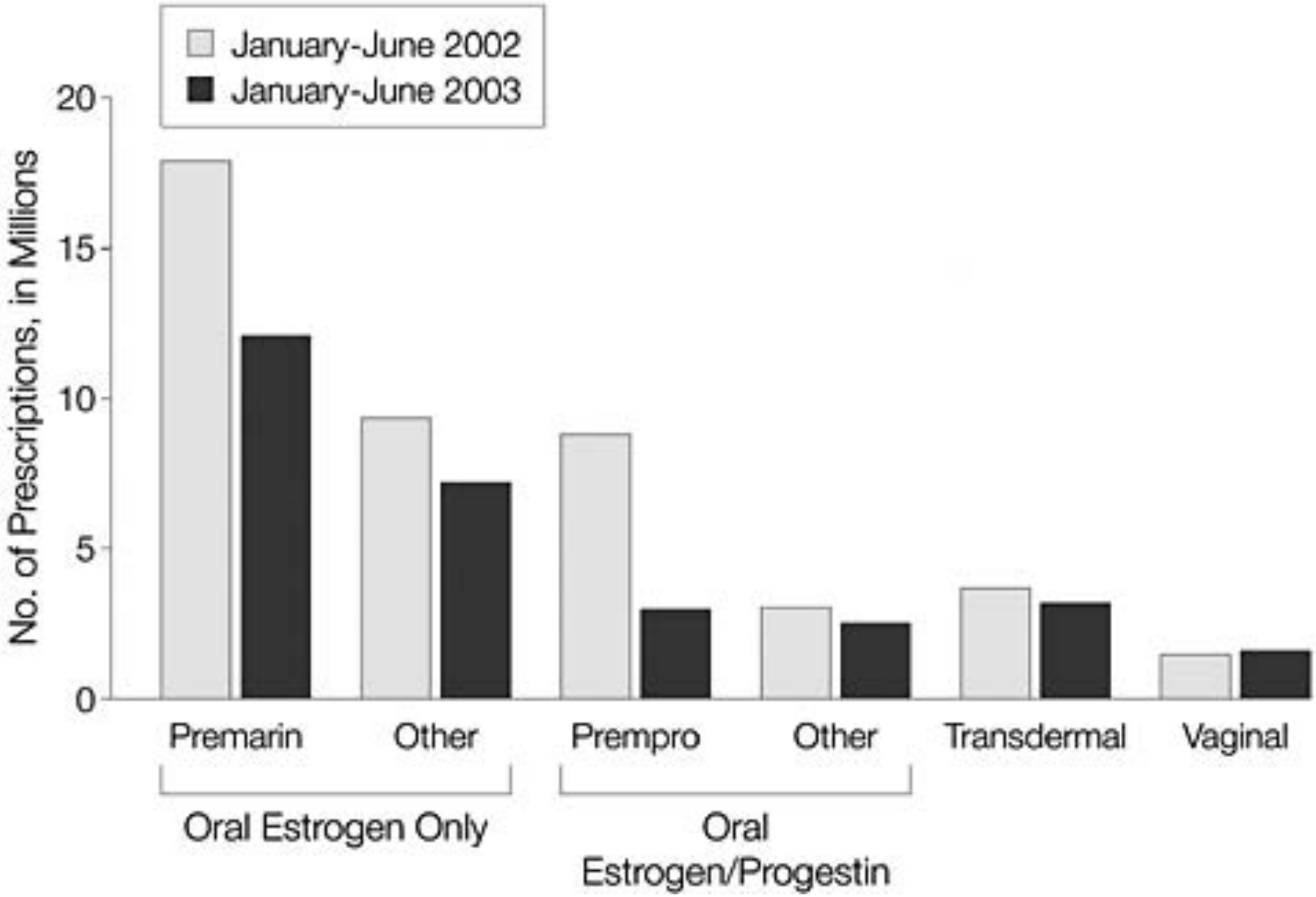
- In 2004, prematurely stopped the estrogen only component after 7 years of follow-up

Trial Stopped

	Cases	Hazard Ratio (95% CI)
Venous Thromboembolism	218	2.11 (1.58-2.50)
Stroke	212	1.41 (1.07-1.85)
CHD	286	1.29 (1.02-1.63)
Breast Cancer	290	1.26 (1.00-1.59)

WHI Investigators *JAMA* 2002

Prescriptions Decrease



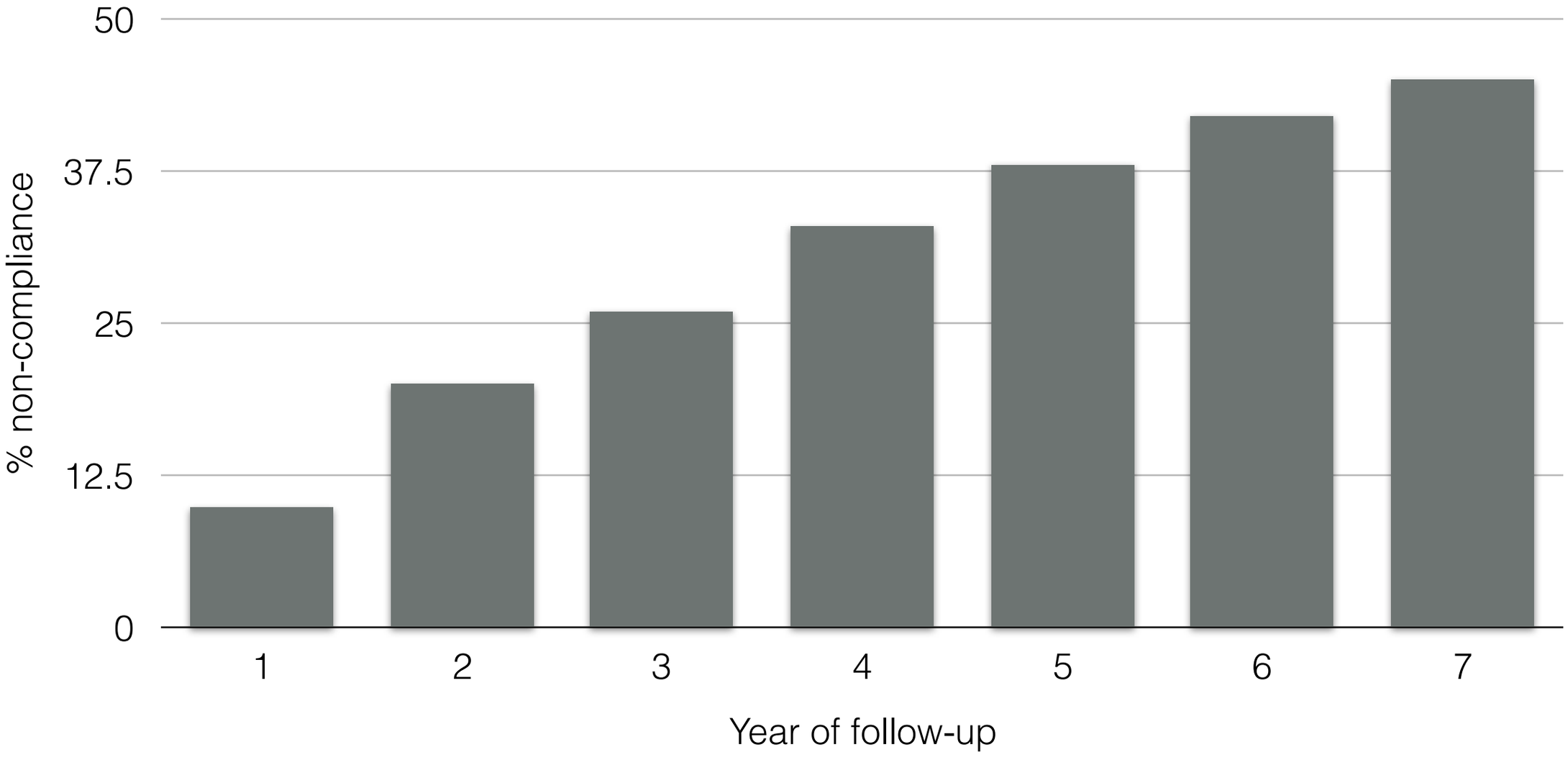
WHI Investigators *JAMA* 2004

How can we explain
the discordant findings from
observational studies and
randomized clinical trials?

Confounding

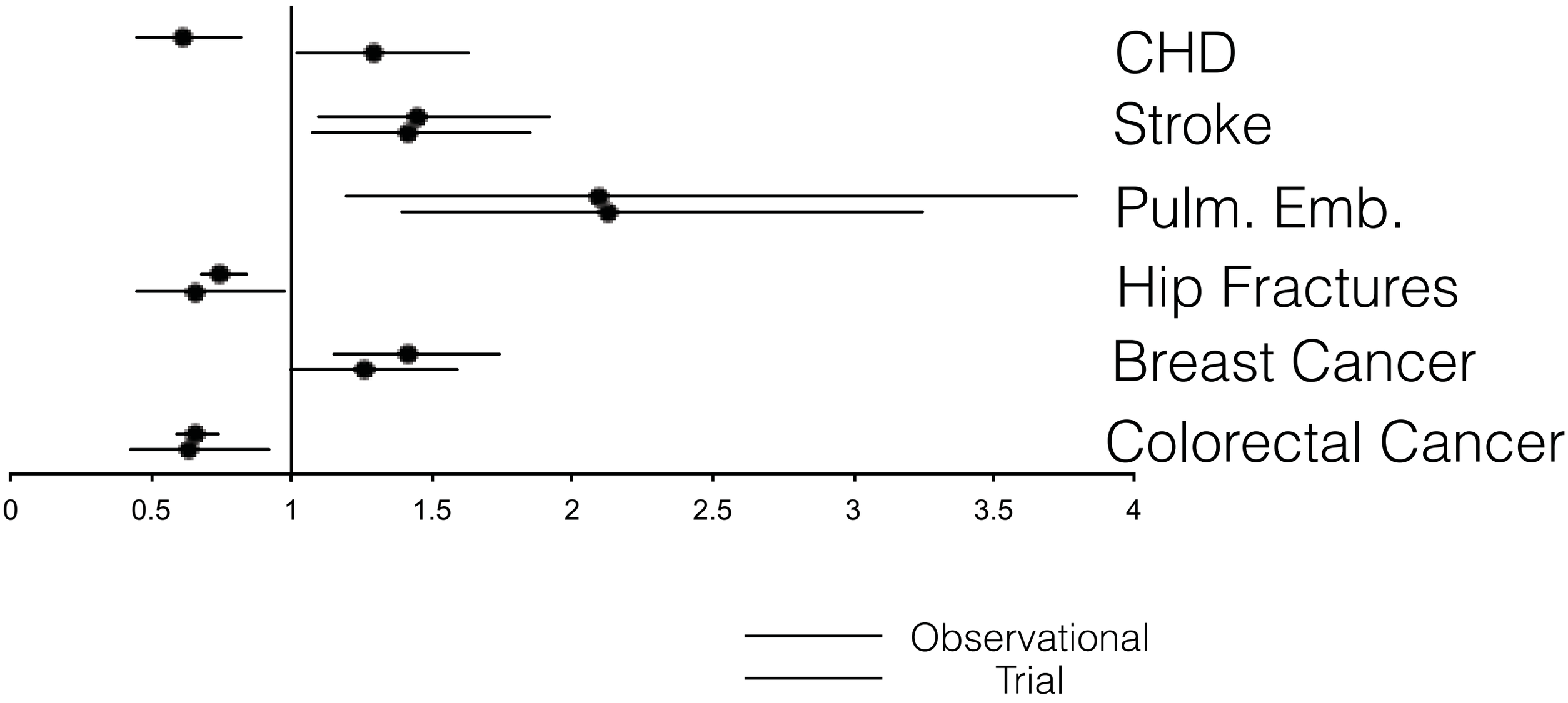
- Users in observational studies may be healthier
  - Unmeasured & residual confounding
- Users in trial are randomly assigned
  - No confounding

Trial Non-compliance



WHI Investigators *JAMA* 2002

Observational vs Trial Results



Michels and Manson *Circulation* 2003

Different Populations

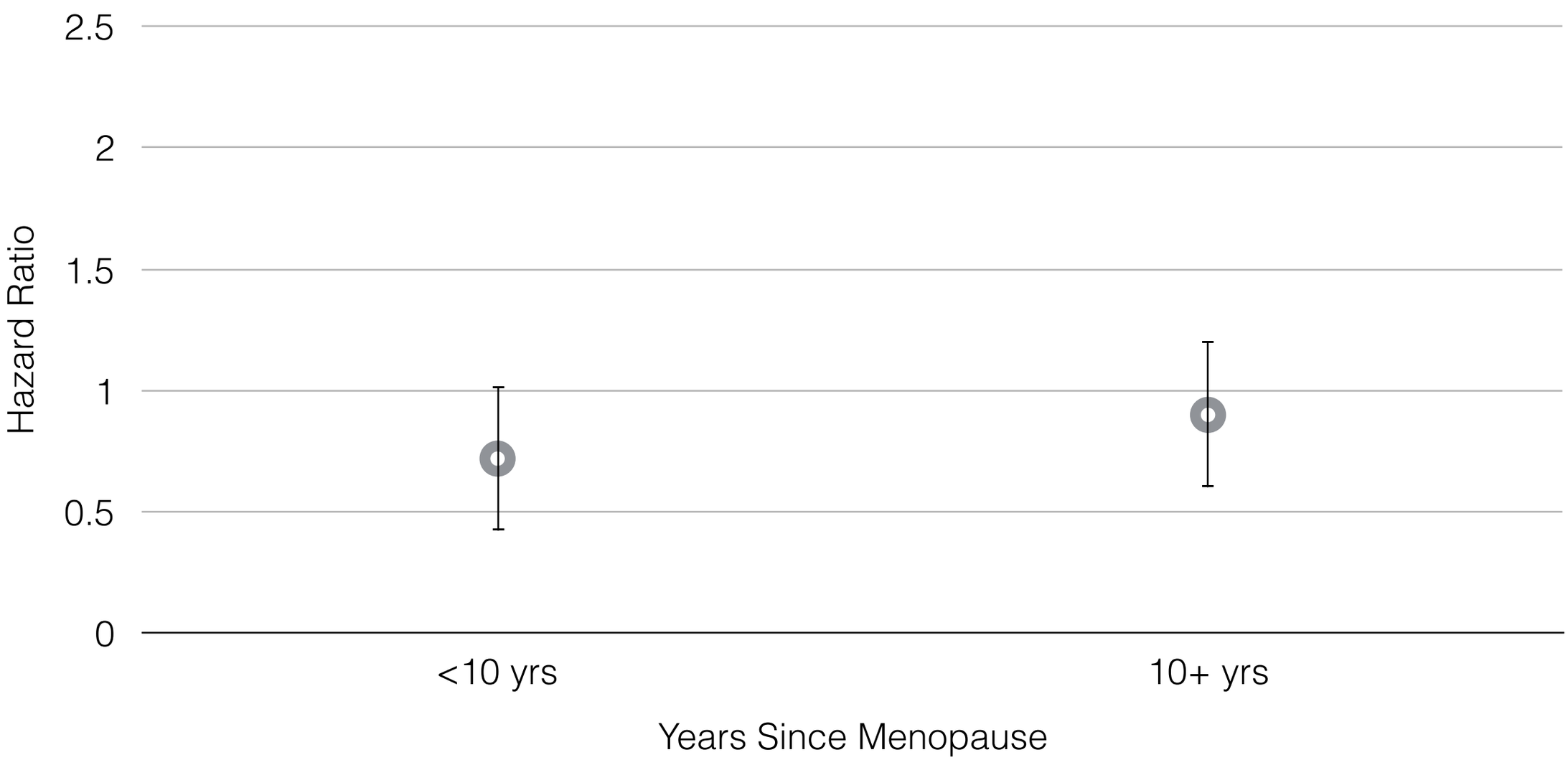
Observational

- Elected to use HT
- Presumably a considerable proportion has menopausal symptoms
- Started HT when they reached menopause

Trial

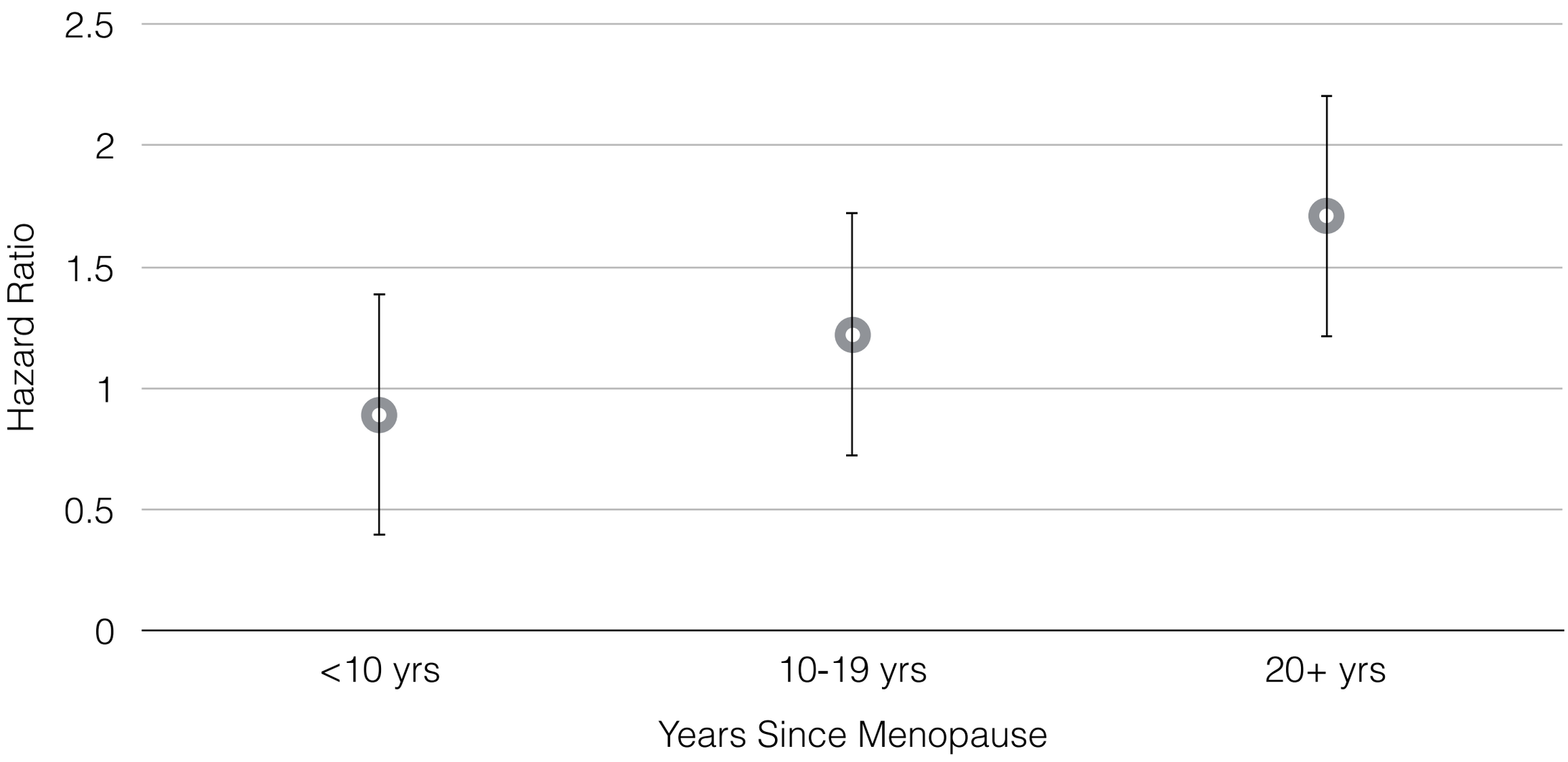
- Willing to start taking HT at the flip of a coin
- Had no or only mild menopausal symptoms
- Started taking HT several years into menopause
- 70% overweight
- Possibly unhealthy lifestyle (29% also in diet trial)

CHD in Observational



Grodstein et al. *J Women's Health* 2006

CHD in Trial



Manson et al. *NEJM* 2003

Conclusions

Observational

- Results give effect of hormone therapy on CHD
- Among women **with** menopausal vasomotor **symptoms** (i.e., hot flashes) who **initiate** hormone therapy **at onset** of menopause

Trial

- Results give effect of hormone therapy on CHD
- Among women **without** menopausal vasomotor **symptoms** (i.e., hot flashes) who **initiate** hormone therapy **well into** their menopause

Conclusions

- Menopausal symptoms should govern decision
- Short-term use may be sufficient for many women to ease into menopause
- Should not be routinely prescribed for all women entering menopause
- Selected subgroups may benefit
- Minimize dose and duration
- Re-asses use at regular intervals
- Consider alternative options

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