A Primer in Epidemiology to Guide Vaccine Claims of Harm

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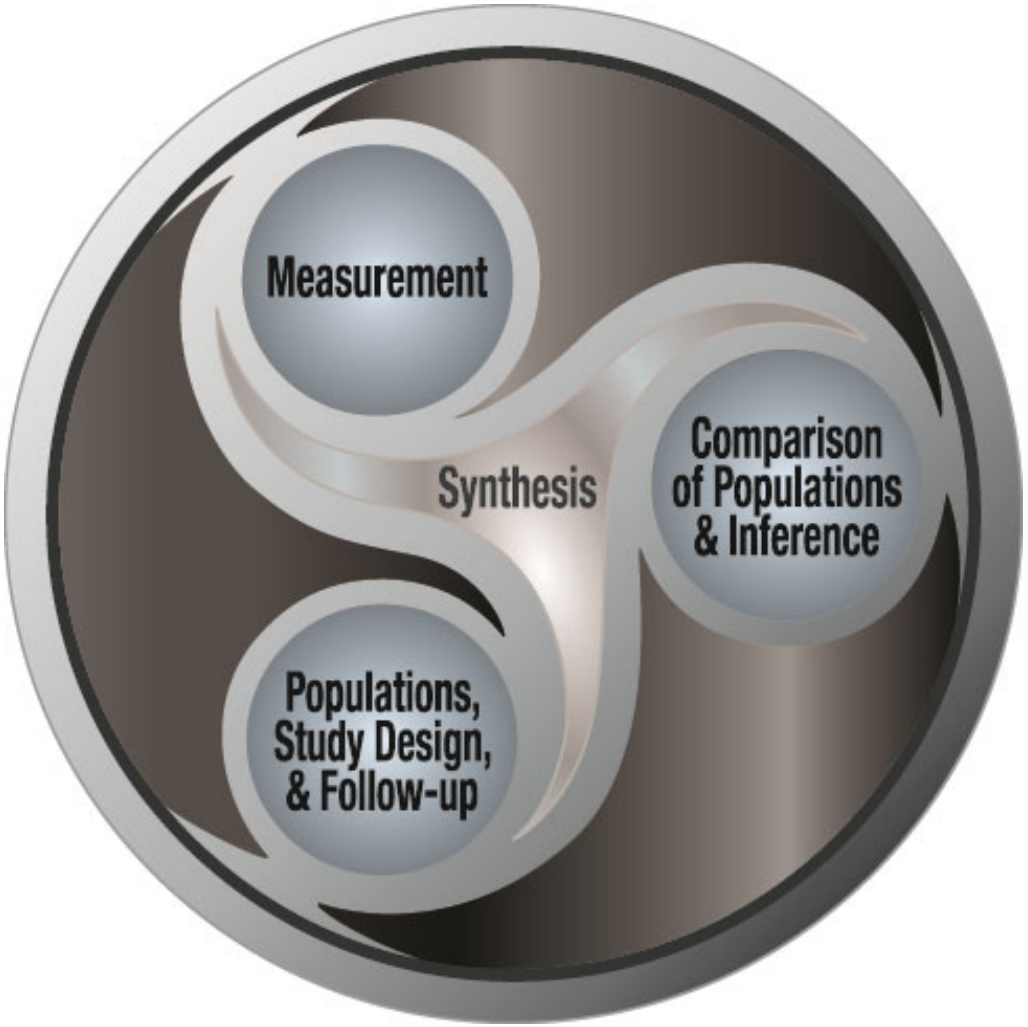
Plan for this session

- The concept, rationale and approaches used in epidemiological investigations
- Observational vs. Experimental designs
- Common pitfalls in drawing inference from study findings
- Relevance for judging vaccine harms
- Save some time for questions (please post in the chat)

JHU vision of epidemiology

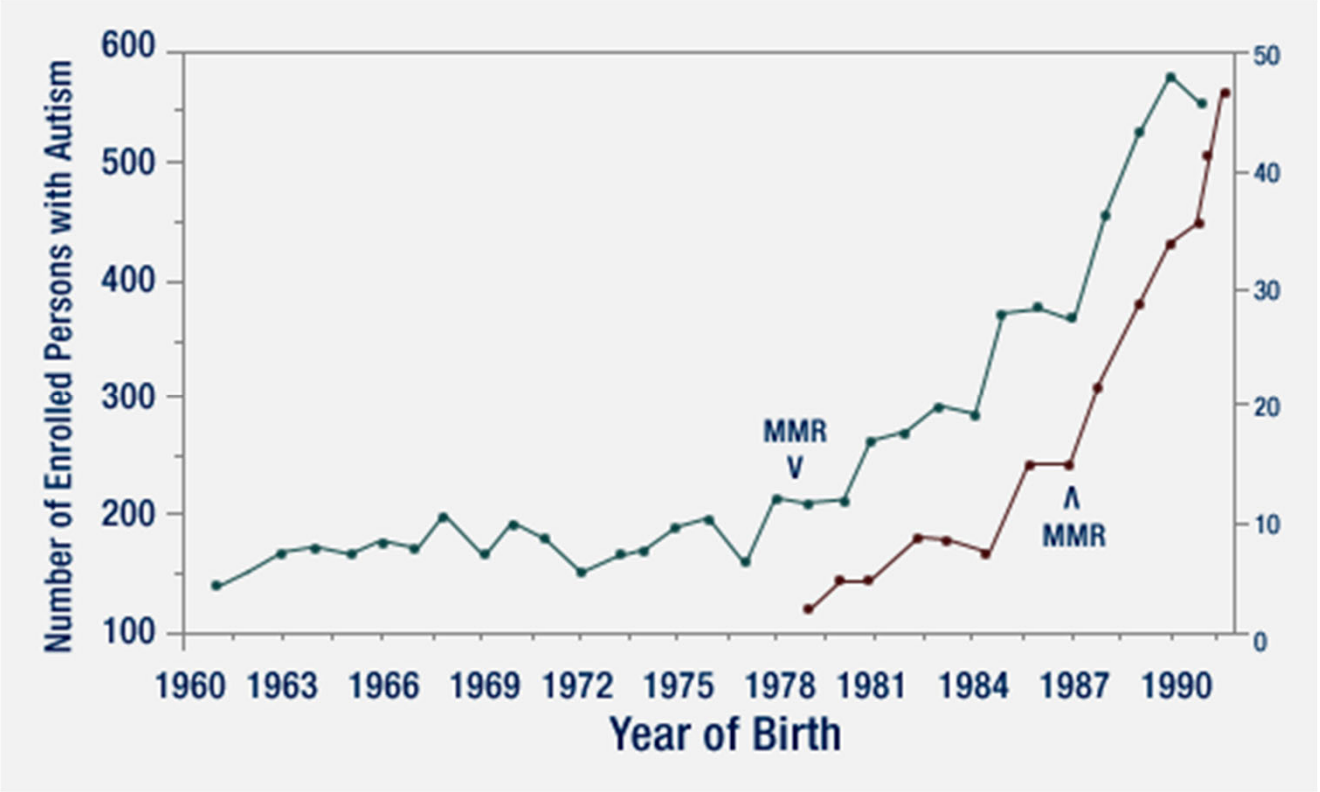


What is Epidemiology?

"The study of the distribution and determinants of health and disease in human populations to enable health services to be planned rationally, disease surveillance to be carried out, and preventive and control programs to be implemented and evaluated."

World Health Organization

Does MMR vaccine cause autism?



http://www.choosinghope.com/vacine/vacine.asp

Does nut consumption reduce mortality?

Assuming meta-analysis of cohort studies represents life span-long causal associations,

For a baseline life expectancy of 80 years,

Eating 12 hazelnuts daily (1 ounce)

Prolongs life by 12 years (i.e., 1 year per hazelnut)

Schwingshackl et al., AJCN 2017;105:1462-73

Why Do We Want to Identify Groups At High Risk for Diseases?

1. To study factors associated with increased disease risk

2. To direct prevention and screening programs for early detection to appropriate populations

Epidemiological Reasoning

Step 1

Determine whether there is or is not an association between a factor or characteristic ("*exposure*") and the development of a disease ("*outcome*"):

- by studying the characteristics of groups
- by studying the characteristics of individuals.

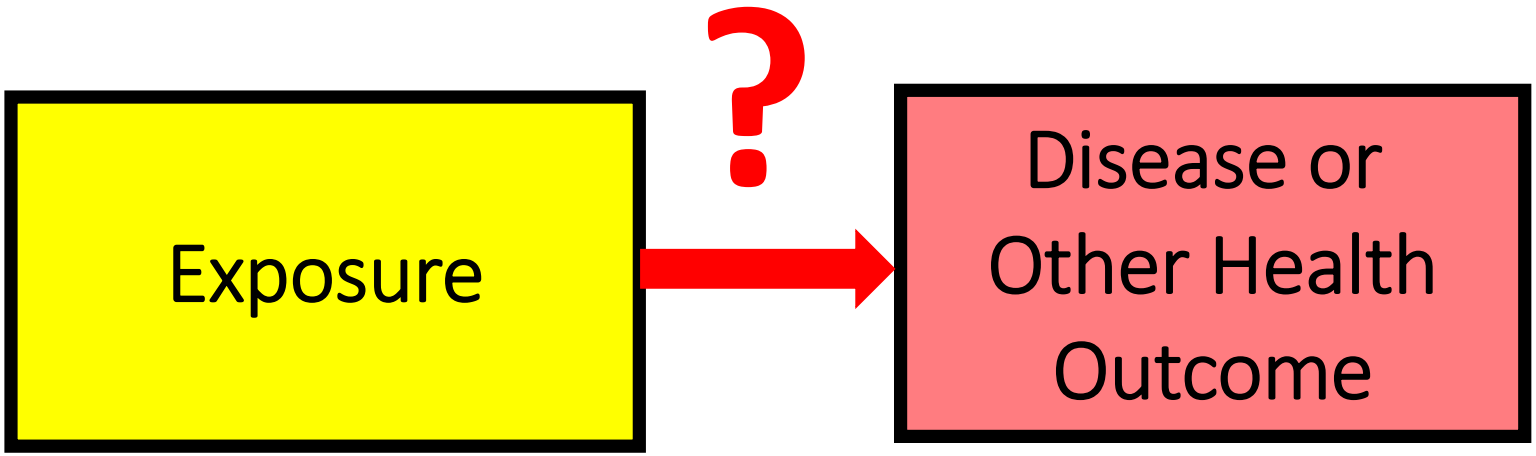
Epidemiological Reasoning

Step 2

Derive appropriate inferences regarding a possible causal relationship from the patterns of association which have been found.

Look out for those epidemiologic *illusions*
("*confounding*")

The ultimate question for Epidemiology



- **Distribution of disease and its determinants is the domain of descriptive epidemiology**

  Analysis of disease patterns according to the characteristics of the person, place and time

  Who is getting the disease?
  Where is it occurring?
  How is it changing over **time**?
  Does some *exposure* seem to be linked to an *outcome*?

Observational (Descriptive) study designs

Case reports and case series

Exploratory ecological designs

Cross-sectional surveys

Cohort Studies

Outbreak of Electronic-Cigarette–Associated Acute Lipoid Pneumonia — North Carolina, July–August 2019

Weekly / September 13, 2019 / 68(36);784–786

On September 6, 2019, this report was posted online as an MMWR *Early Release.*

Kevin Davidson, MD[1]; Alison Brancato, MS[1]; Peter Heetderks, MD[1]; Wissam Mansour, MD[1]; Edward Matheis, MD[1]; Myra Nario, MS[1]; Shrinivas Rajagopalan, MD, PhD[2]; Bailey Underhill, MS[1]; Jeremy Wininger, MS[1]; Daniel Fox, MD[1]

Ecological Studies

- Key features that differentiate ecological studies:
  1. Population = unit of analysis (not individuals)
  2. Exposure status = property of the population
- Often the first step in determining whether an association exists
- Problem: we do not know if individual risk equates to group risk

Dietary fat intake and breast cancer by country

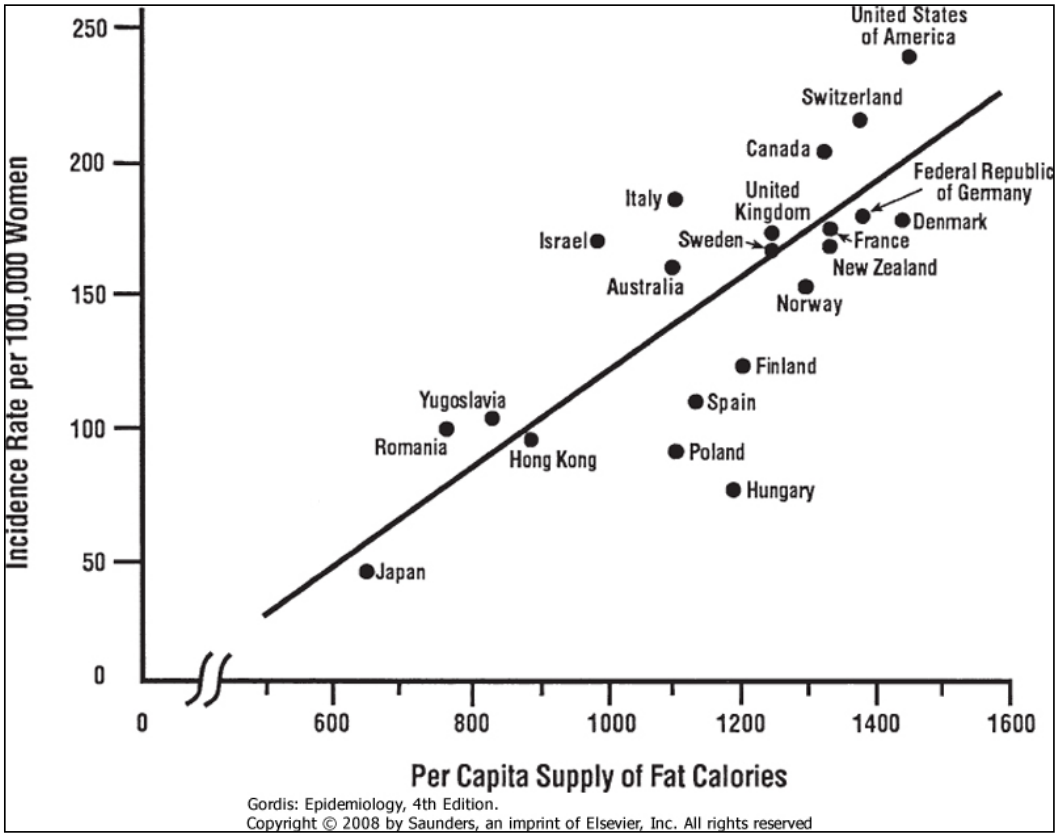


Figure 14-4 Correlation between dietary fat intake and breast cancer by country. (From Prentice RL, Kakar F, Hursting S, et al: Aspects of the rationale for the Women's Health Trial. J Natl Cancer Inst 80:802-814, 1988.)

Sources of bias in cross-sectional studies

- *Response bias* – those who participate are systematically different from those who do not respond or refuse
- *Acquiescent response style* – respondents try to "look good" for the interviewer
- *Interviewer biases* (leading the witness)

However, these biases are often seen in other epidemiologic study designs as well!

How do we interpret an association?

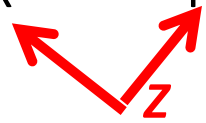
- If there seems to be an association between exposure and outcome (e.g., increased cholesterol and CHD), we have to confront several issues:
  1. **Identify prevalent cases** (not incident cases), which may not be representative of the population of cases
     - Including only prevalent cases excludes deaths
     - The association may reflect survival after developing the disease (CHD) and not the risk of developing the disease

Issues in interpreting an association

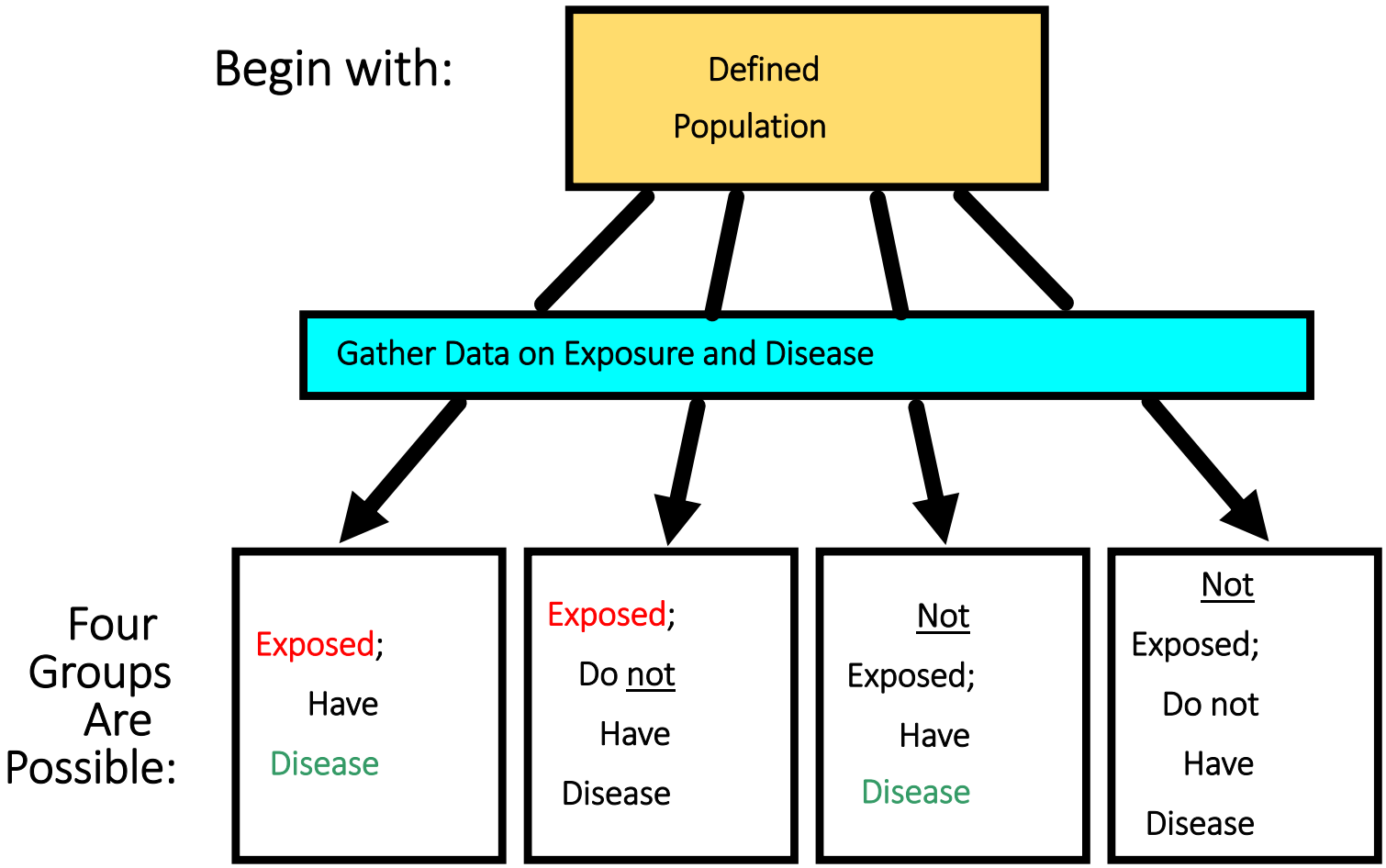
2. **Cannot establish temporality** between exposure and outcome in cross-sectional studies

   - If exposure does not precede disease, association cannot reflect a causal relation

X ===➔ Y (hypothesized)
Y ===➔ X (in reality?)
X ===== Y



Cross-Sectional Study - I



Key Features of Cross-sectional Studies

- Examines exposure prevalence and disease prevalence *simultaneously*
- Cannot infer temporal sequence between exposure and outcome (especially if exposure can change)
- Preponderance of *prevalent* cases of long duration
- Healthier participants/*volunteers* a concern

Analytical Epidemiology: Why?

- *Determining risk factors and causes of disease*

  Is childhood obesity associated with increased incidence of Type 2 diabetes?

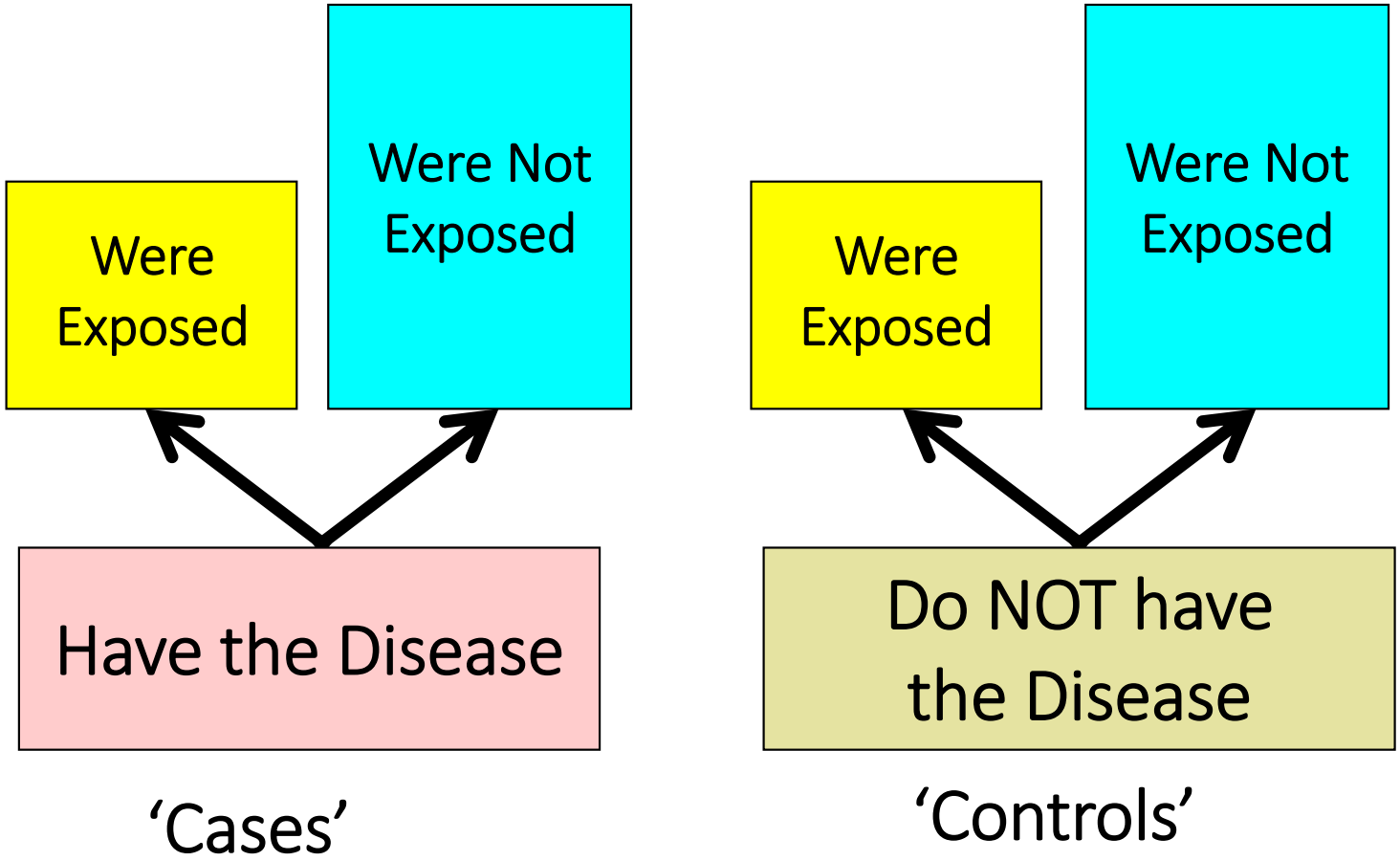
- *Evaluating preventive and therapeutic interventions that alter the course of disease*

  Does beginning HIV treatment earlier (at higher CD4 levels) lead to better health outcomes (non-detectable viral load) and reduce transmission?

Examples of Analytic Study Designs

- Case-control studies
- Cohort studies
- Randomized trials

Design of a Case-Control Study



Advantages of a Case-Control Design

- When the disease is rare (low prevalence)
- Relatively short time to complete
- Relatively inexpensive
- Possible to study associations of a disease with several exposures

Problems of Recall In Case-Control Studies

Limitations in human ability to recall

Recall Bias -- Cases may remember their exposure more than controls do

Cases may also attribute exposures

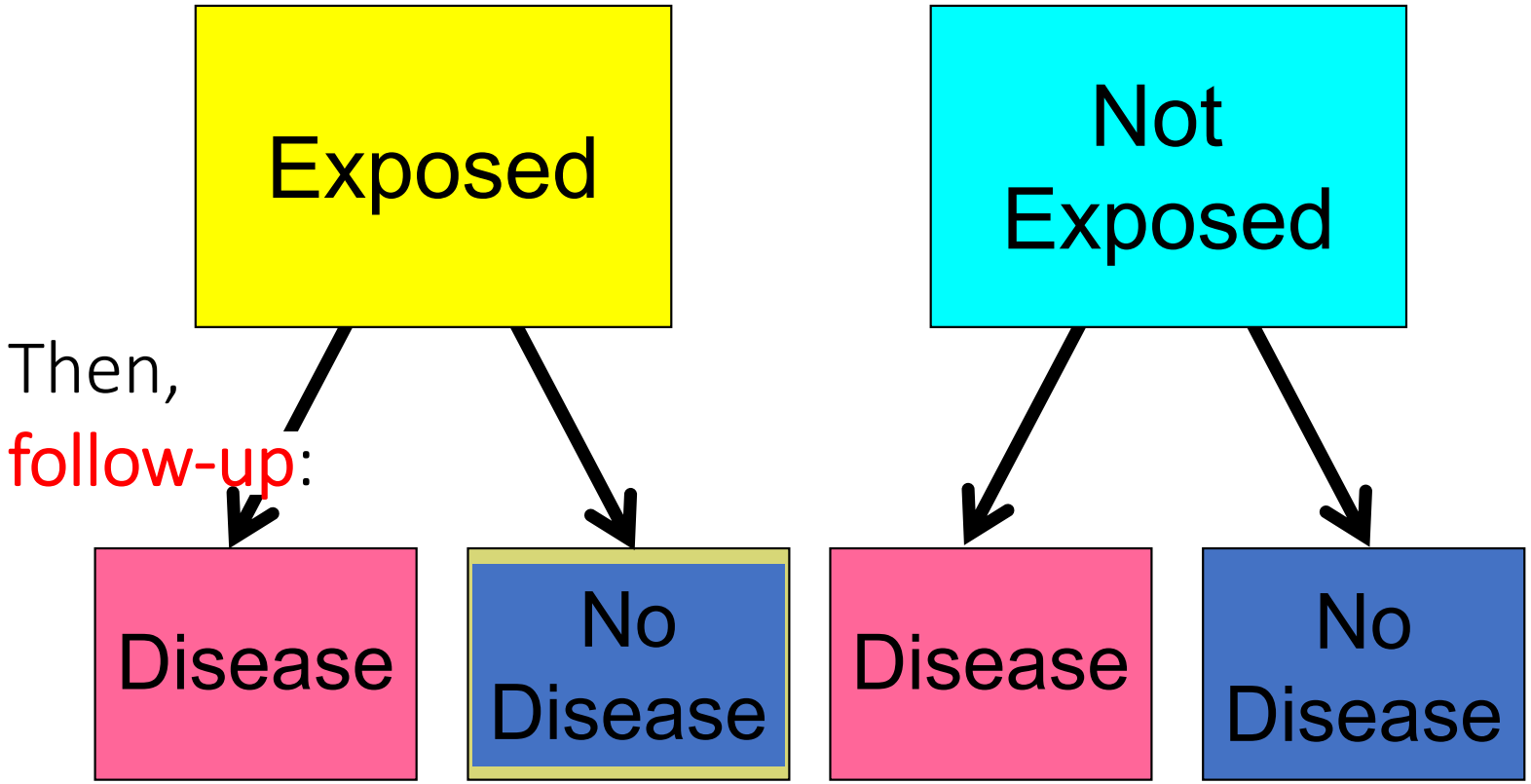
An Artificial Association Resulting From Recall Bias

Example: A study of maternal infections during pregnancy and congenital malformations

Assume:	CASES (congenital malformations)	CONTROLS (no malformations)
True Incidence of Infection	15%	15%
% of Infections Recalled	90%	10%
Infection Rate as Ascertained by Interview	13.5%	1.5%

Design of a Cohort Study

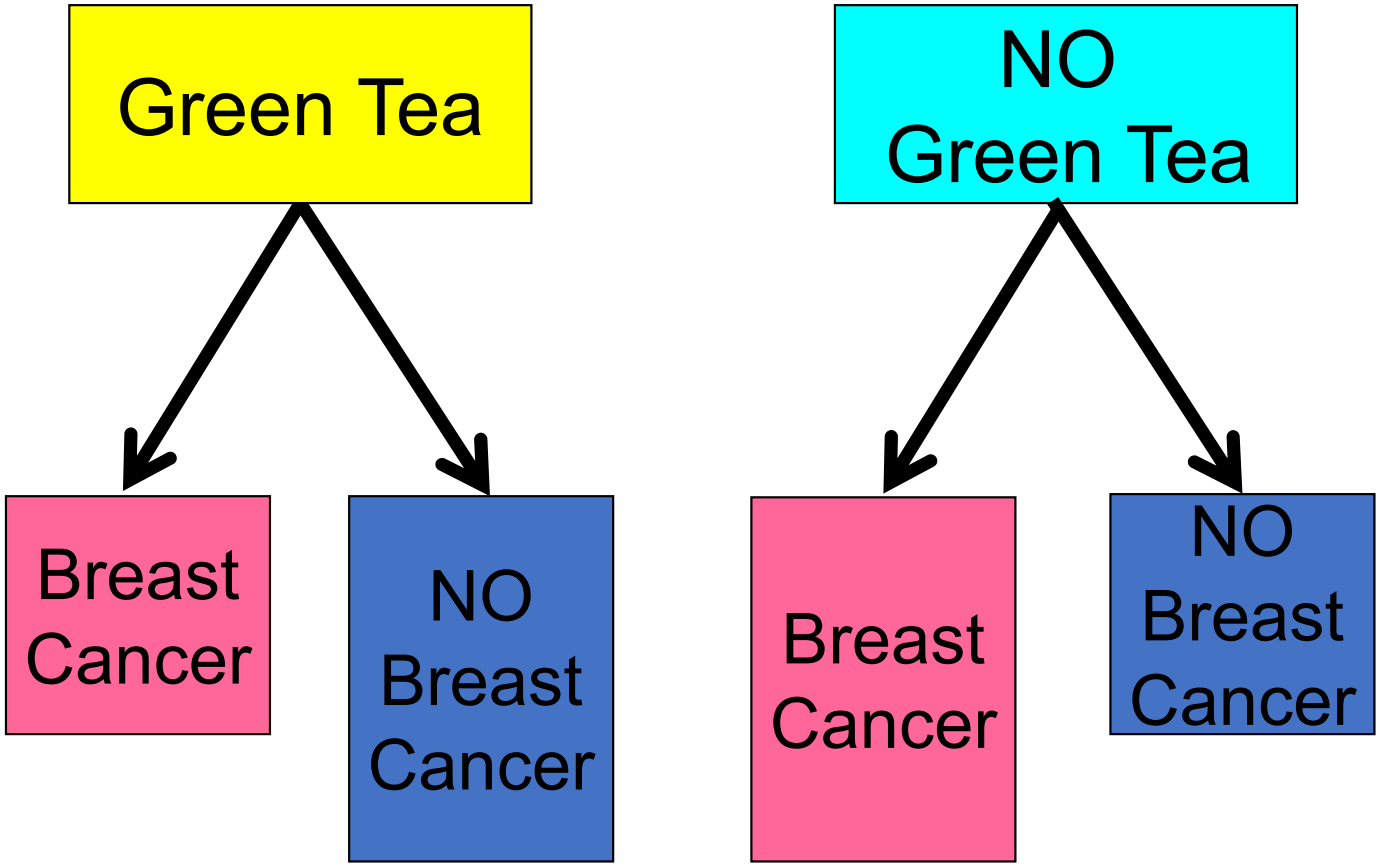
Start with:



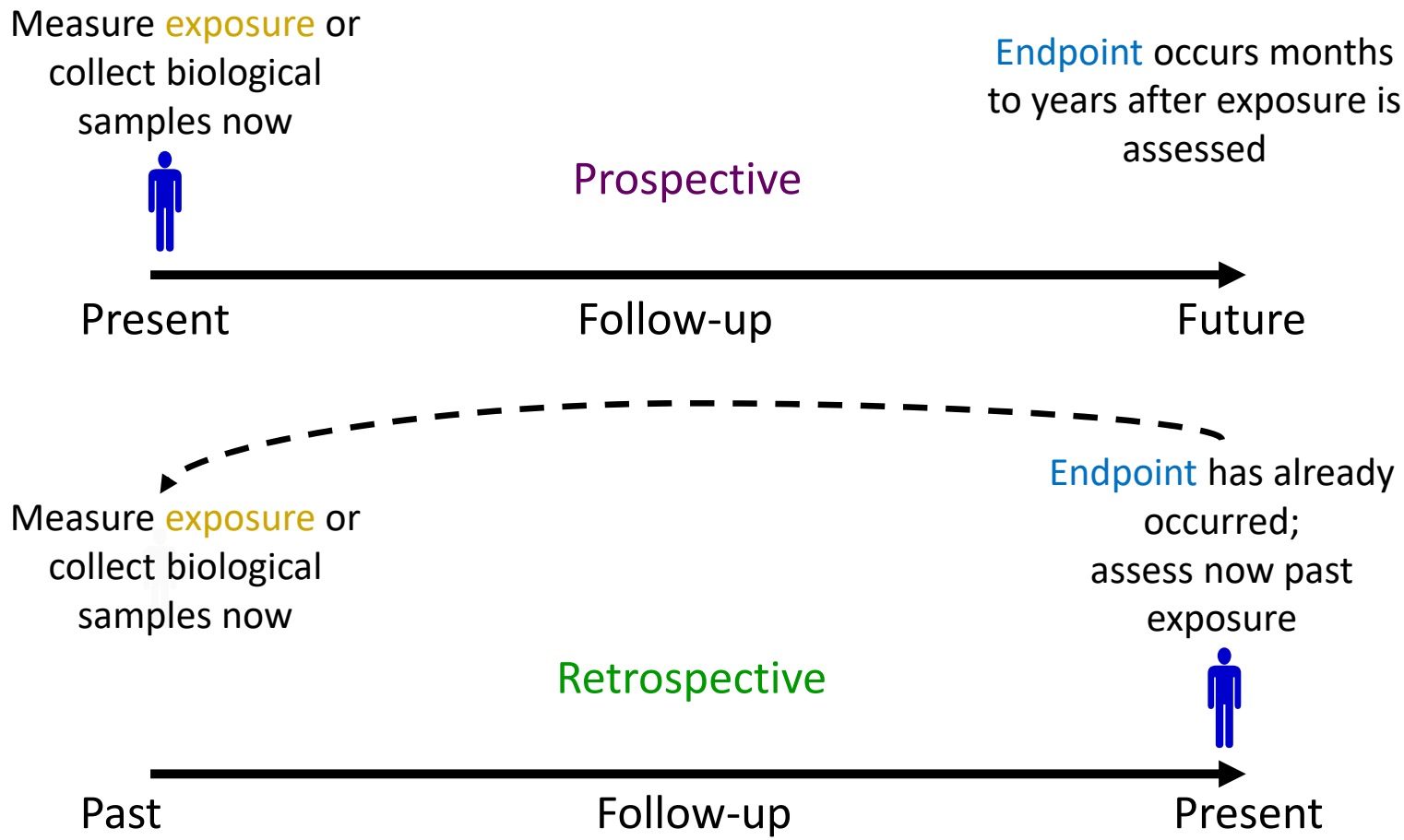
For a defined standard period of time

Cohort Study of Green Tea and Breast Cancer

If there was an association, we could expect to find:



Cohort Studies: Prospective vs. Retrospective



Types of Cohort Study Populations

- Single-site cohort
- Multicenter cohort
- ‘Collaborative cohorts’
- Population-based sample
  - For an identified source population, a probability sample may be taken

Advantages of Cohort Studies

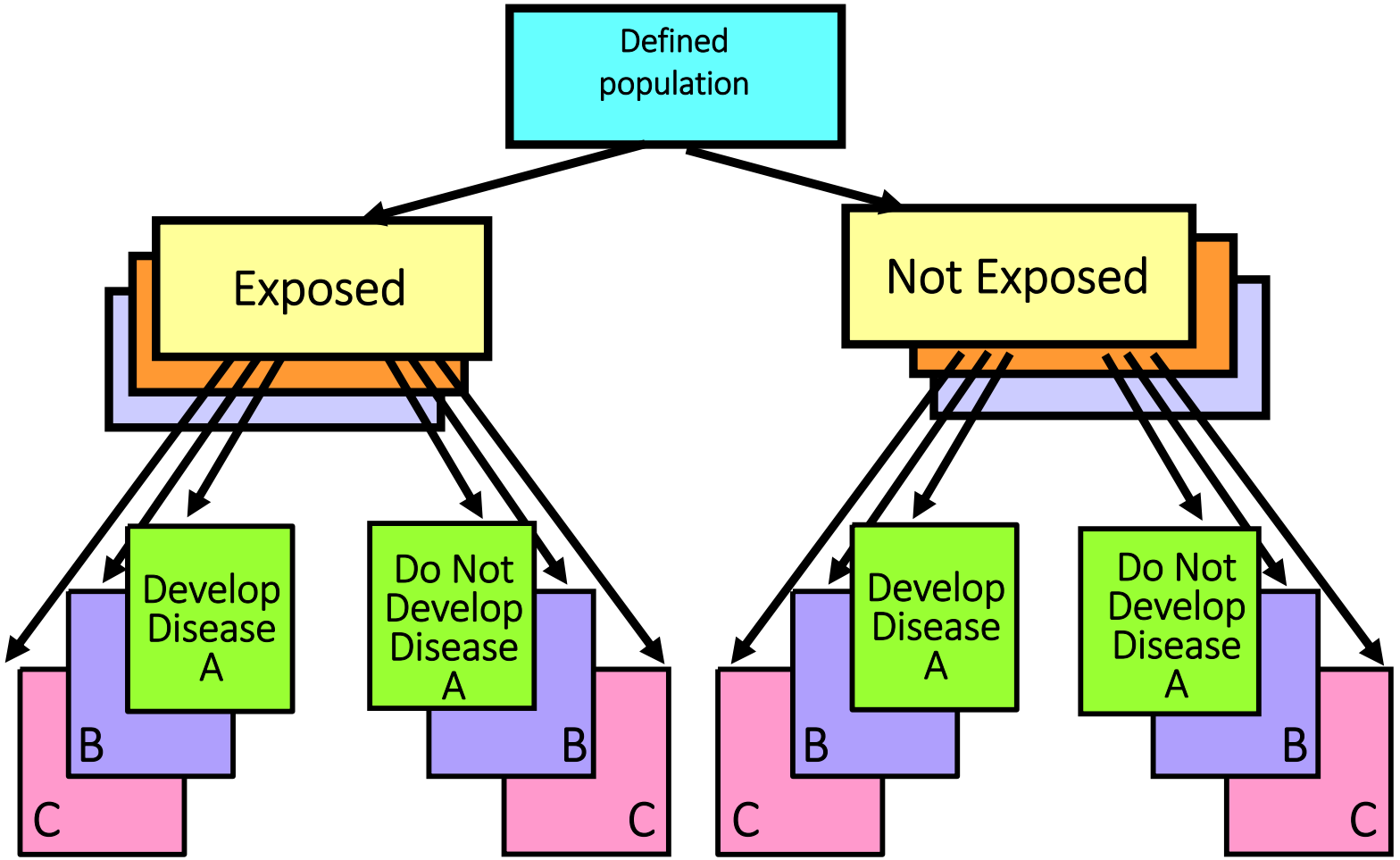
Can assess several outcomes simultaneously

Control of time and outcome measurements

Less potential for bias than case-control studies but same potential for confounding

Matching and masking possible

In a Cohort Study Starting With a Defined Population, We Can Study Multiple Exposures and Multiple Outcomes



Disadvantages of Cohort Studies

Requires large samples

Requires long follow-up

Not efficient for rare outcomes

if exposure is low

Financially costly

Cohort members “choose” exposures

themselves (not under our control)

Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis

Deborah Donnell, Jared M Baeten, James Kiarie, Katherine K Thomas, Wendy Stevens, Craig R Cohen, James McIntyre, Jairam R Lingappa, Connie Celum, for the Partners in Prevention HSV/HIV Transmission Study Team*

Lancet 2010; 375: 2092–98
Published Online
May 27, 2010

Summary

Background High plasma HIV-1 RNA concentrations are associated with increased risk of HIV-1 transmission. Initiation of antiretroviral therapy (ART) reduces plasma HIV-1 concentrations. We aimed to assess the effect of ART use by patients infected with HIV-1 on risk of transmission to their uninfected partners.

Among 3,381 couples, only 1 of 103 genetically-linked transmissions was among an infected participant starting HAART early – 92% reduction in transmission

Lancet 2010;375:2092-8

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Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*

RCT of 1,763 HIV discordant couples in 13 countries, where half started HAART immediately or at CD4 <200

– 96% reduction in HIV transmission

Interventions that can be evaluated by RCT

- Drugs, vaccines and other treatments of disease
  - Versus control (no treatment, placebo or active treatment)
- Medical and health care technology
- Comparative effectiveness research
- Primary prevention
  - Community health programs
- Behavioral interventions (primary & secondary)

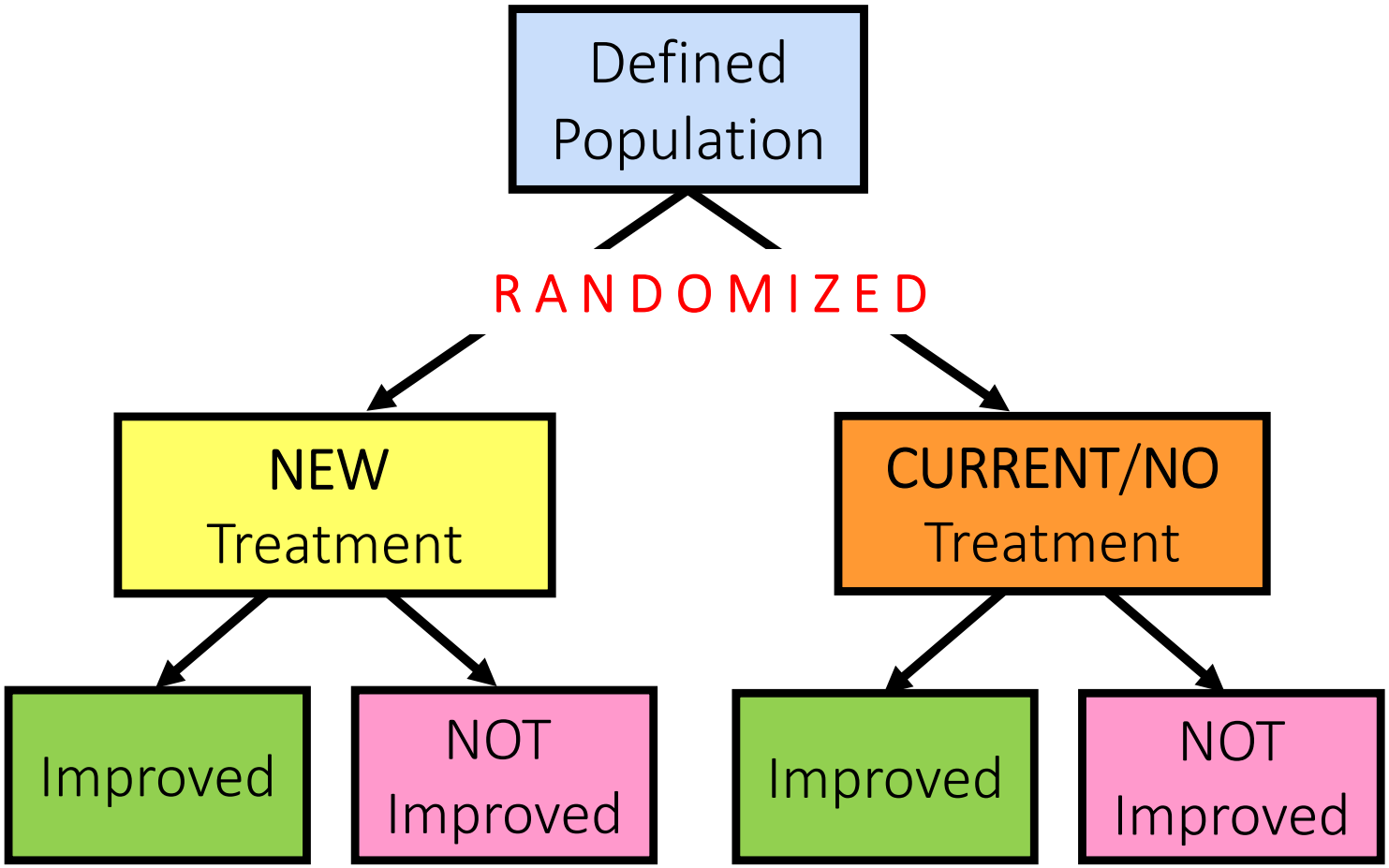
Treatment Comparisons

- ***Superiority*** trials: one treatment is better than the other
  - Define *a priori* a clinically important difference

- ***Equivalence*** or ***Non-inferiority*** trials: two treatments are equal (within some small margin)

  - Must be "much" smaller than clinically important difference
  - Sometimes larger sample sizes are needed because you are trying to "prove" that difference between treatments is small

Design of a Controlled Trial



ORIGINAL CONTRIBUTION JAMA-EXPRESS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10 000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10 000 person-years.

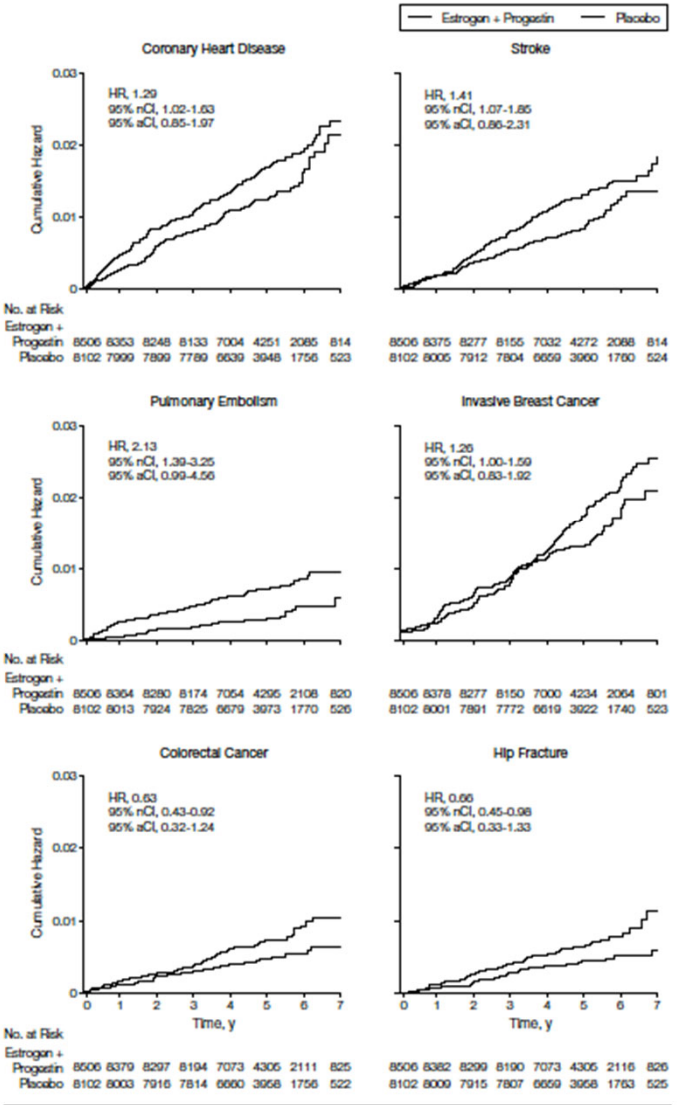
Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:321-333 www.jama.com

For editorial comment see p 366.

Author Information and Financial Disclosures appear at the end of this article.

Figure 3. Kaplan-Meier Estimates of Cumulative Hazards for Selected Clinical Outcomes



What does randomization do?

- Ensures that participant assignment to treatment is unbiased…..
  - Treatment given is not influenced by provider bias or patient prognosis - avoids “confounding by indication”
  - Treatment groups are comparable at the start of the study

How different is a RCT from Cohort ?

- Not very much!

- Difference is that the exposure is randomly assigned in the RCT, whereas the exposure occurs naturally ("in nature") in the cohort (or observational) study

Why is randomization important?

- Primary: to remove the potential for **bias** in the choice of treatment (treatment selection bias, confounding by indication)

- Secondary: to increase the likelihood of balance between groups for known and ***unknown*** risk factors

- Tertiary: to provide a probability basis for statistical testing

Trials versus Observational Studies

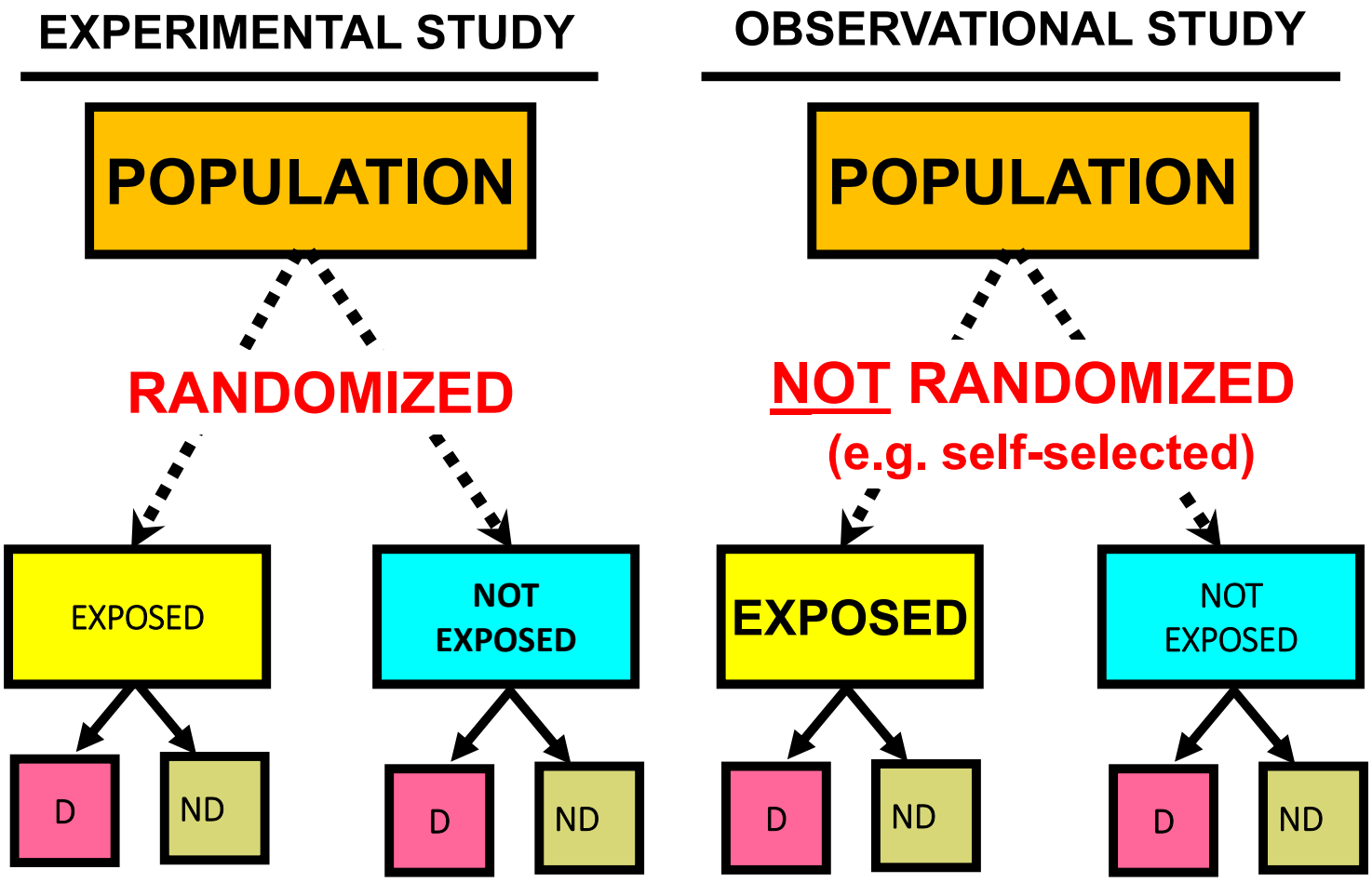
Experimentation vs. **observation**:

- Experimentation: "exposure" is directed (or "manipulated") by the researcher;

  exposure is the experimental intervention
- Observation: exposure is observed by the researcher as it plays out over time naturally

Controlled trials differ from other epidemiologic studies in that they are experimental rather than observational

Experimental vs. Observational Approach



So, at the end of the day, how do you know if vaccination leads to injury?

Have other sources of bias been addressed?

Is the evidence consistent with other findings?

Did the exposure (vaccination) precede the outcome?

Is the evidence from a controlled trial? If not, are the methods used appropriate?

Questions?