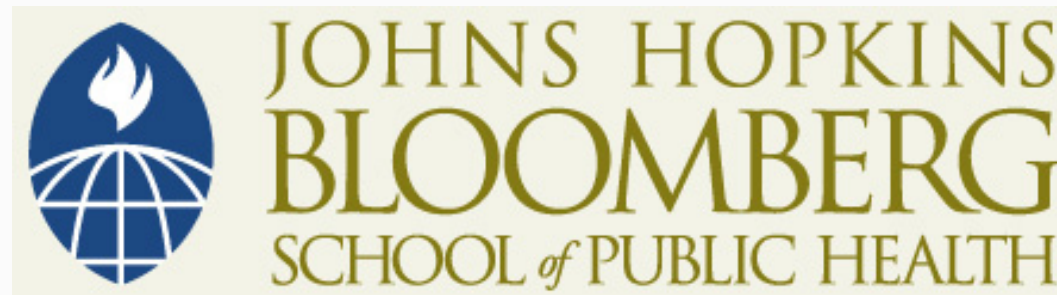


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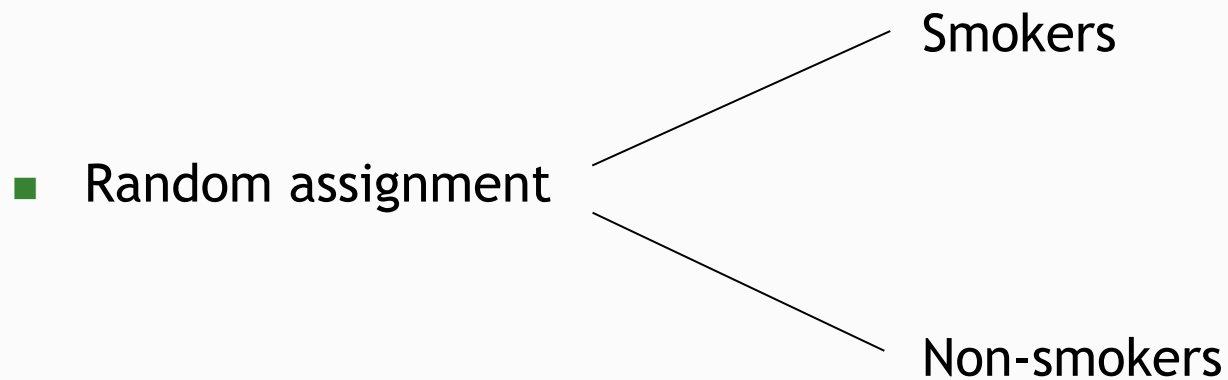
JOHNS HOPKINS
BLOOMBERG
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Section C

But John, What If Randomization Is Not Possible?

Randomization Is Not Always Possible!

- Unfortunately (at least for scientific purposes), you cannot always perform randomized trials!!



The Natural Experiment

- Almost as good as randomized study
- Individuals are assigned to groups because of completely “fortuitous reasons”
- Almost as good as randomized study
 - Assignment may not have been based on a random number table or the flip of a coin, but it is almost as good
 - Doesn't happen often, but when it does, it's good for researchers (but not necessarily for subjects in study)

Examples

- Cholera and water—classic public health study!
- In 1852, a law was passed which required only unpolluted parts of the Thames river to be used for drinking water
- There were multiple water companies in London at this time, including Lambert, Southwark, and Vauxhall
- Only Lambert complied with the law
 - Southwark and Vauxhall, as well as other companies, supplied customers with water from heavily polluted portions of the Thames

Cholera and Mortality in London—1800s

- Mortality rates per 100,000 persons by water company

	Water Company	
	Lambert	Southwark/ Vaughan
Pre Water Law	12.5	11.8
Post Water Law	3.7	13.0

Cholera and Mortality in London—1800s

- Is treatment assignment “random?”
- Are groups similar except for intervention (i.e., water companies)?
- Both water companies competed for the same customers and served residents all throughout London

Natural Experiment of HIV Etiology of AIDS

- HIV and hemophilia
- Mortality rates per 1,000 person-years among HIV infected and uninfected hemophiliacs in the United Kingdom*

	Uninfected	Infected
1985-1992	8.1	49.1
1977-1984	7.9	

Notes: * Darby, S., et al. (1995). Mortality before and after HIV infection in the complete UK population of haemophiliacs. UK Haemophilia Centre Directors' Organisation. *Nature*.

Natural Experiment of HIV Etiology of AIDS

- There were no other significant differences found between the infected and uninfected hemophiliacs

Non-Randomized Design: Observational Studies

- Studies in which subjects “self-select” to be in exposure groups (i.e., subjects are not randomized)
- Sometimes this is the only type of study that can be done
- Outcome/exposure relationships are of interest
 - Sometimes it is difficult to directly assess because of selection bias issues which may lead to systematic differences between the exposure groups other than the exposure of interest
 - Examples:
 - ▶ Smokers are more likely to drink alcohol
 - ▶ Vegetarians are more likely to exercise

Non-Randomized Design: Observational Studies

- Are children born to women who took Bendectin for nausea more likely to have birth defects?
- Observational study
 - Take a (random?) sample of mothers who gave birth in the past year
 - Compare Bendectin users vs. non-users

Observational Study

- A significant difference in the rates of birth defects could be explained by the following:
 - Bendectin causes birth defects
 - Mothers who took Bendectin also took other drugs (maybe those other drugs are related to birth defects)
 - Mothers who took Bendectin are different in other ways (medical, socioeconomic)

Observational Study

- Sometimes observational studies are performed to study results that will then be studied with a follow-up randomized trial

Beta Carotene and Cancer

- **“Abstract/Background.*** Observational studies suggest that people who consume more fruits and vegetables containing beta carotene have somewhat lower risks of cancer and cardiovascular disease and earlier basic research suggested plausible mechanisms. Because large randomized trials of long duration were necessary to test this hypothesis directly, we conducted a trial of beta carotene supplementation.”
- **“Conclusions.** In this (randomized) trial among healthy men, 12 years of supplementation with beta carotene produced neither benefit nor harm in terms of the incidence of malignant neoplasms, cardiovascular disease, or death from all causes. (*N Engl J Med* (1996) 334: 1145-9.)”

Notes: * Hennekens, C., et al. (1996). Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *The New England Journal of Medicine*.

Observational Study

- Sometimes this is the only type of study that can be performed
- Issues in selection bias can be addressed in analyses if factors related to both the outcome and exposure (confounders) can be accounted for
- How to account for?

Needle Exchange

- Montreal: relative risk of HIV infection for intravenous drug users (IVDUS) by needle exchange program participation

	RR of HIV	95% CI
Non-Participants	1.0	—
Consistent Users	10.2	3.3-31.5

Notes: * Bruneau, J., et al. (1997). High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: Results of a cohort study. *American Journal of Epidemiology*.

Needle Exchange

- Adjusted for . . .
 - I.V. drug use since last visit, number of times, borrowed I.V. equipment, number of times new equipment was used, practice of disinfection, matched on age, gender, language, year of birth

Needle Exchange

- New York City: relative risk of HIV infection for intravenous drug users (IVDUS) by needle exchange program participation

	RR of HIV	95% CI
Non-participants	1.0	-
Consistent users	0.3	0.1-0.7

Source: Des Jarlais, et al. (1996). HIV incidence among injecting drug users in New York City syringe-exchange programmes. *The Lancet*.

Needle Exchange

- Adjusted for the following . . .
 - Age, gender, race, frequency of injection
 - See also American Journal of Epidemiology, October, 1998, p. 713-716

Bruneau

- “It is possible that, despite the exhaustive data-driven process to identify confounders, some had been left unaccounted for . . . ”
- “None of the studies reported was a randomized clinical trial, so a causal link cannot be inferred . . . we could not control for whatever factors led some subjects to use the syringe exchanges (potential self-selection bias)”

Prospective Cohorts Studies

- Observational studies and natural experiments are also types of “prospective” cohort studies if the exposure of interest precedes the outcome in time
 - Blood transfusion preceded HIV seroconversion in hemophiliacs
 - Use of needle exchange preceded HIV seroconversion