WASHINGTON STATE UNIVERSITY

Types of Studies: An Overview

Questions from Last Class?

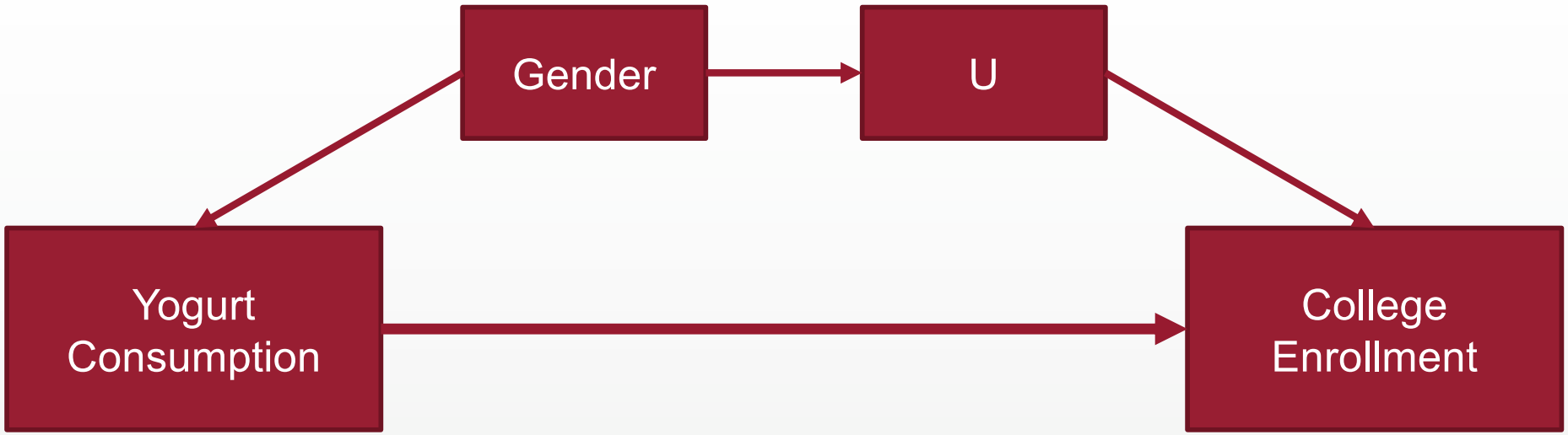
Problem Set 1

- Let's all hope you've turned in Problem Set 1
- Questions about it?

	Arrested	Not Arrested
Video Games	182	1802
No Video Games	425	3437

Risk in the Exposed: 182/(182+1802) = 0.09173387
Risk in the Unexposed: 425/(425+3437) = 0.1100466
Risk Ratio: 0.09173387/ 0.1100466 = 0.834
Risk Difference: 0.09173387 - 0.1100466 = -0.0183

Protective Risk Ratios (i.e. below one) will always have negative risk differences
The odds ratio question was sort of a trick. Remember, the rule is 10% in *all strata.* This was sort of an edge case.



Several of you suggested other, equally plausible potential mechanisms

https://s2.q4cdn.com/723557020/files/doc_downloads/GrubHub-Inc-Men-vs-Women-Eating-Preferences-White-Paper_v001_b3cw14.pdf

Effect Measure Modification

- This was mentioned in Charlie Poole's paper, but we haven't covered it yet
- Effect measure modification if the idea that, when we condition an effect on some variable Z, the relationship between the exposure and the outcome may be different in different levels of Z
- Indeed, we should probably expect this to be the case
- This is also called heterogeneity
- This is *also* called statistical interaction
- Note: Statistical interaction *does not imply* biological interaction

Effect Measure Modification Depends on Scale

- If effect measure modification is present, generally speaking *at most* one effect measure will be uniform across strata – the others may not be
- This means that whether effect measure modification is present depends on what effect measure you are looking at
- The difference between a confounder and an effect modifier is *murky at best* and may depend on if you can intervene, if the strata-specific elements are of interest, etc.

An Example

- Suppose we have a cohort of 50% men vs. women, and the average risk to men in the exposed arm is 0.5, and in the unexposed is 0.2.
- In women, it is 0.10 for exposed and 0.04 for unexposed
- RR in Men = 2.5
- RR in Women = 2.5
- RD in Men = 0.3
- RD in Women = 0.06

Additive vs. Multiplicative Effect Modification

- Additive Effect Modification: Does this appear when using risk differences?
- Multiplicative Effect Modification: does this appear when using risk ratios?

Example

- Suppose we're thinking about the risk of smoking and lung cancer
- But there's one group in your cohort that is exposed to periodic high levels of particulate matter (say, from wild fires) – does this change the effect between smoking and lung cancer?

Risks of Lung Cancer

	Smoking = 0	Smoking= 1
WF = 0	0.02	0.05
WF = 1	0.04	0.15

- We can ask if the effect of the two factors together exceeds their effect individually using risk differences
- $(p_{11} - p_{00}) - [(p_{10} - p_{00}) + (p_{01} - p_{00})] = p_{11} - p_{10} - p_{01} + p_{00}$
- 0.15 – 0.04– 0.05 + 0.02 =0.08
- An interaction > 0 is said to be positive or “super-additive”
- An interaction < 0 is negative or “sub-additive”

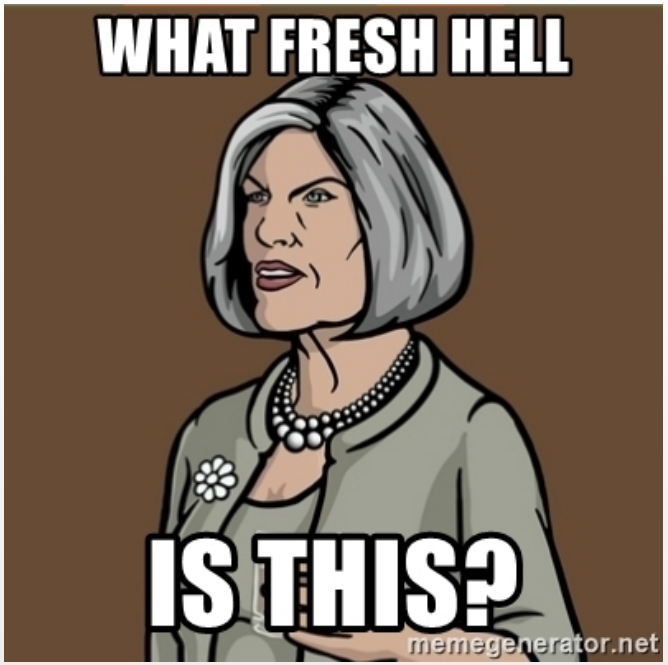
Risks of Lung Cancer

	Smoking = 0	Smoking= 1
WF = 0	0.02	0.05
WF = 1	0.04	0.15

- Now let's think on the multiplicative scale using relative risks
- $RR_{11} = p_{11}/p_{00} = 0.15/0.02 = 7.5$
- $RR_{10} = p_{10}/p_{00} = 0.04/0.02 = 2$
- $RR_{01} = p_{01}/p_{00} = 0.05/0.02 = 2.5$
- The measure of interaction here is $RR_{11}/(RR_{10} * RR_{01})$
- 7.5/(2*2.5) = 1.5
- If >1, positive interaction, if < 1 negative interaction

Non-collapsibility

- The odds ratio is what is known as non-collapsible
- This means that the association between the exposure and outcome across strata of some variable Z *will not* equal the marginal association between the exposure and outcome
- That is, the odds ratio for the study as a whole is not the weighted average of the stratum-specific odds ratios
- This can also occur for rate ratios and differences



An Example

- Suppose we have a cohort of 50% men vs. women, and the average risk to men in the exposed arm is 0.5, and in the unexposed is 0.2.
- In women, it is 0.08 for exposed and 0.02 for unexposed
- OR(Men) = [0.50/(1-0.50)]/[0.20/(1-0.20)] = 4.0
- OR(Women) = [0.08/(1-0.08)]/[0.02/(1-0.02)] = 4.3
- Risk overall would be 0.5(0.50) + 0.5(0.08) = 0.29 in the exposed
- 0.5(0.20) + 0.5(0.02) = 0.11 in the unexposed
- OR(All) = [0.29/1-0.29]/[0.11/1-0.11] = 3.30
- "the conditional odds ratios $OR_{AB|C}$ always move away from the null" – M. Hernan

Why Do We Care About This?

- This is a note of caution about how occasionally odd, unexpected, or "paradoxical" results can arise when using non-collapsible effect estimates.
- You can report the stratum specific estimates, the marginal estimate, or all of them, depending on what is of interest
- "In summary, a quantitative difference between conditional and marginal odds ratios in the absence of confounding is a mathematical oddity (no pun intended), not a reflection of bias. Such difference is irrelevant for the purposes of confounding adjustment because, in the absence of confounding by *C*, both the conditional and marginal odds ratios are valid. They just happen to be different."- M. Hernan (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3147074/)

Everything is a Cohort

- Remember that idea – that there is a cohort for all of these studies
- That does not mean we have (or can) observe that cohort, but this is useful as a framework

Case Series

- Just what it says on the tin – a series of cases
- Also known as anecdotes
- Not particularly good evidence, however they can be important
- Often the first way something will get reported
- Most epidemics are found by vigilant clinicians on the ground going “That’s odd…”

"The first three patients presented with severe acute illness characterized by headache, neck stiffness, photophobia, obtundation, and gastrointestinal symptoms, which made the initial diagnosis elusive….Because of the field conditions at the base and the severity of illness in the initial patients, one patient was evacuated to a U.S. military hospital in Germany, and 10 were evacuated to England. Two medical staff who treated the patients on the flight to England and a third contact at the hospital in England subsequently developed gastroenteritis…" Outbreak of Acute Gastroenteritis Associated with Norwalk-Like Viruses Among British Military Personnel --- Afghanistan, May 2002

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

https://www.cdc.gov/mmwr/preview/mmwrhtml/june_5.htm

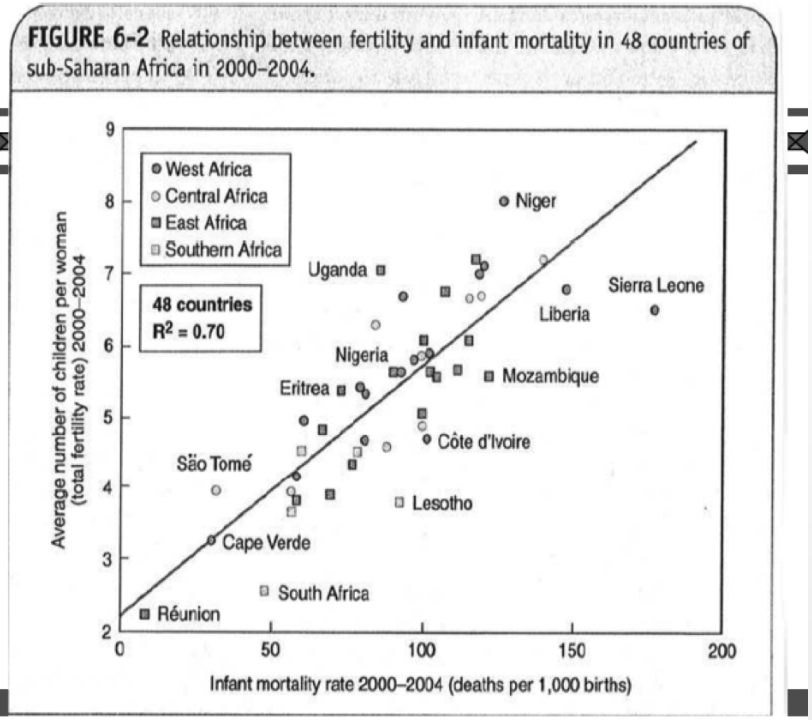
The Case Series Cohort

- What is the theoretical cohort for a case series?

Ecological Studies

- The unit of analysis is a population, rather than individuals
- Excellent use of pre-existing data, national level statistics, etc.
- Very efficient design, especially if using administrative data
- Cannot talk about individual factors of much beyond crude associations

The Ecologic Fallacy



- Consider this study of fertility and infant mortality
- There appears to be a strong association
- There's some credible "just so" studies one can tell to support this
- But do we know that the women who have more children are also the ones who have children die?

The Ecological Cohort

- What is the theoretical cohort for an ecological study?

Time Series Studies

- Looking at rates over a period of time
- How do these rates change?
- Again, we're looking at a population level measure, instead of individuals
- Time series analysis is difficult, and somewhat beyond the scope of this course in terms of how to perform it, though we will consider some examples for interpretation

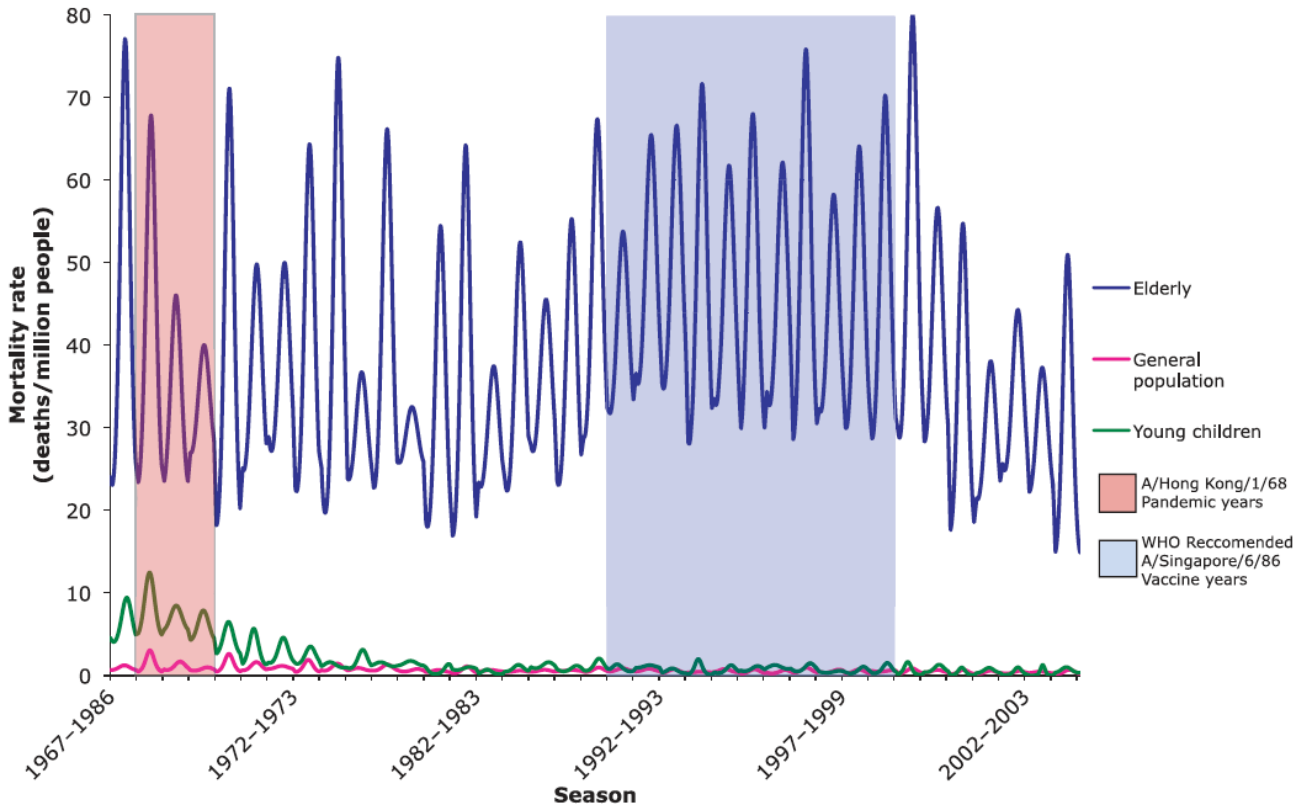
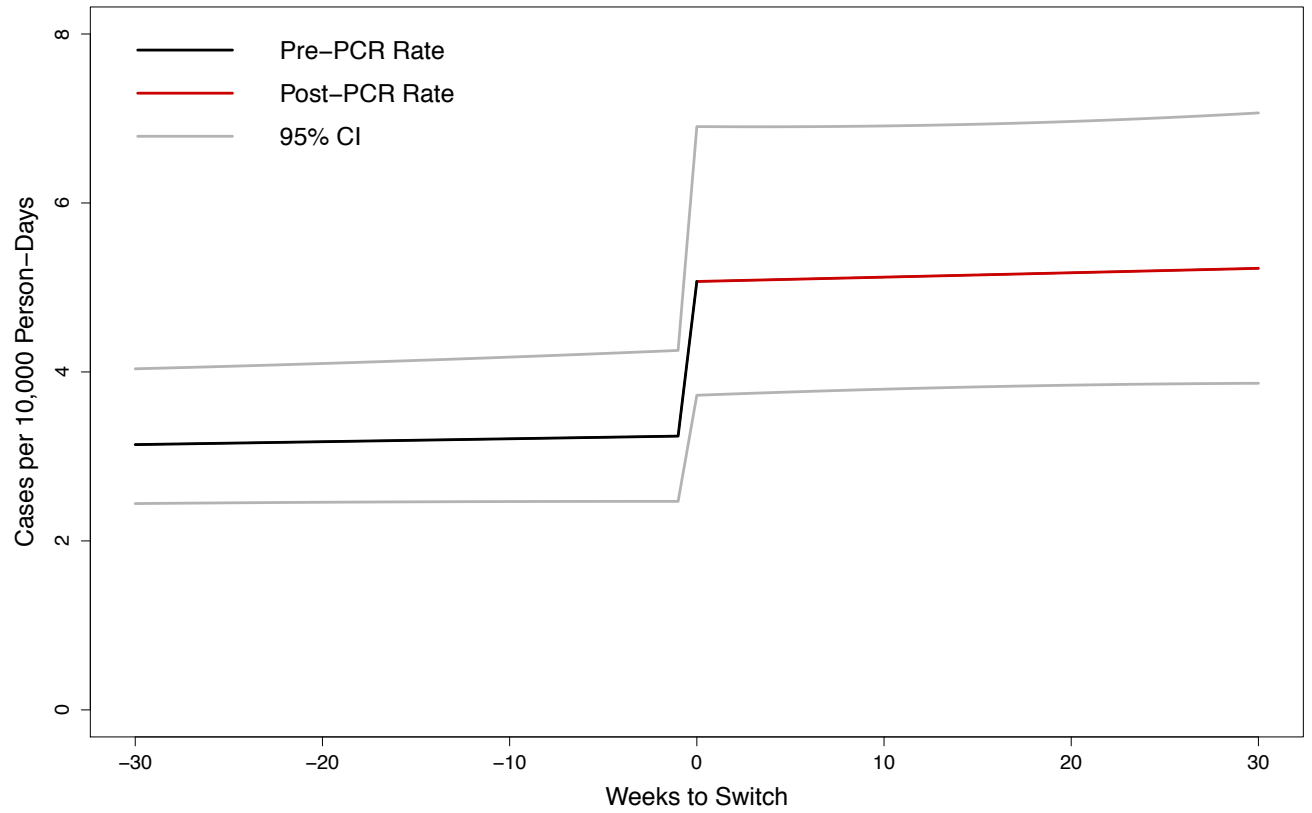


Figure 3. Smoothed harmonic time series for three population subgroups produced with Annual Harmonic Regression model. Periods of the pandemic circulation of A/Hong Kong/1/68 and the epidemic circulation of A/Singapore/6/86 are highlighted.

Time Series Studies and "Natural Experiments"

- Several study types try to examine natural experiments through the lens of time series studies
- Interrupted time series studies, which consider the impact of a single (or multiple) events, with or without a control group
- Difference-in-difference studies examine the change in one group over time compared to the change in another


Pre−PCR Rate
Post−PCR Rate
95% CI
Cases per 10,000 Person−Days
0
2
4
6
8
−30
−20
−10
0
10
20
30
Weeks to Switch

Tricks to ITS

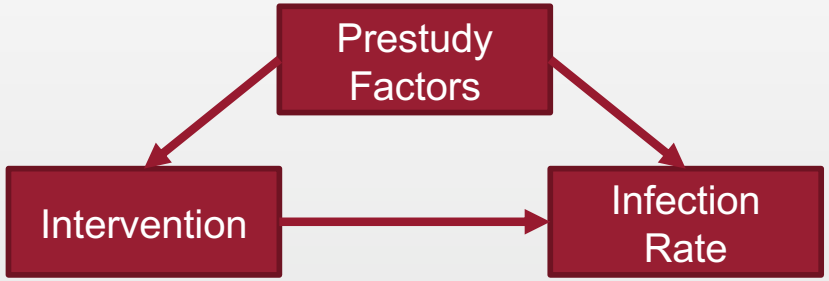
- What is time – absolute or relative?
- What is the event?
- How do controls experience the event?
- Confounding by indication
  - Often talked about it pharmacoepi – sicker patients get more aggressive drugs, which makes those drugs look like they're associated with bad outcomes
  - Are controls *different* in some way – site-level confounding by indication

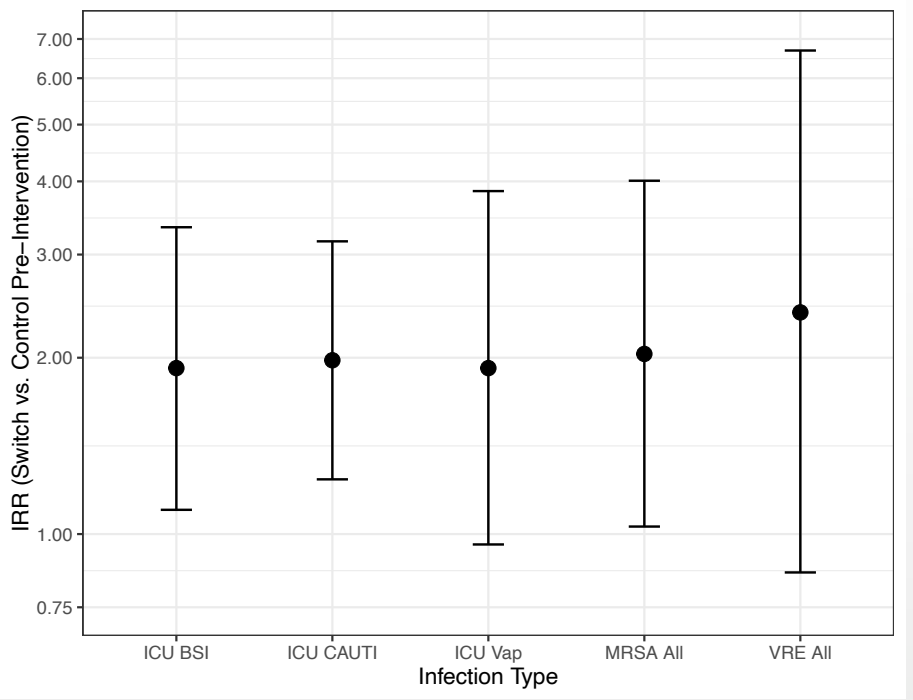
More About Control Groups

- "Control" feels really clear in a lab science or RCT context
- This means in natural experiments or "quasi-experimental" studies, people are often lured into a false sense of security about controls and what they mean

Confounding by Indication

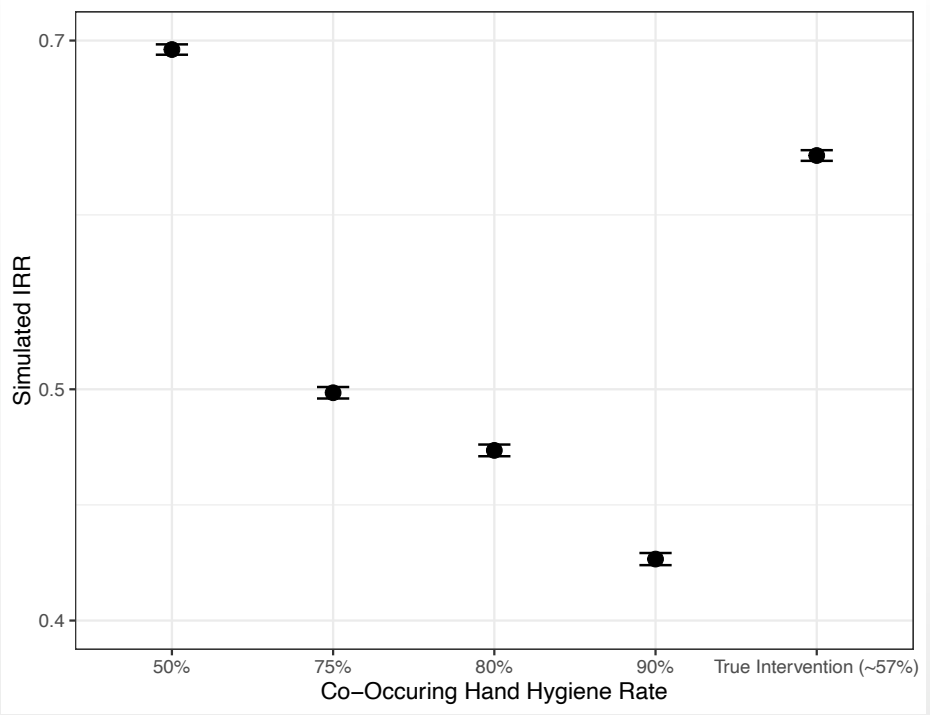
- Confounding by indication
  - Often talked about it pharmacoepi – sicker patients get more aggressive drugs, which makes those drugs look like they're associated with bad outcomes
  - Are controls *different* in some way – site-level confounding by indication





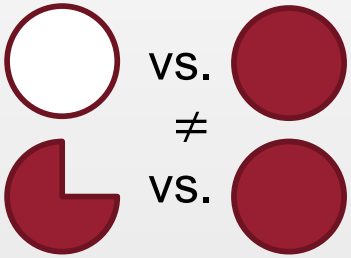
Co-Occuring Interventions

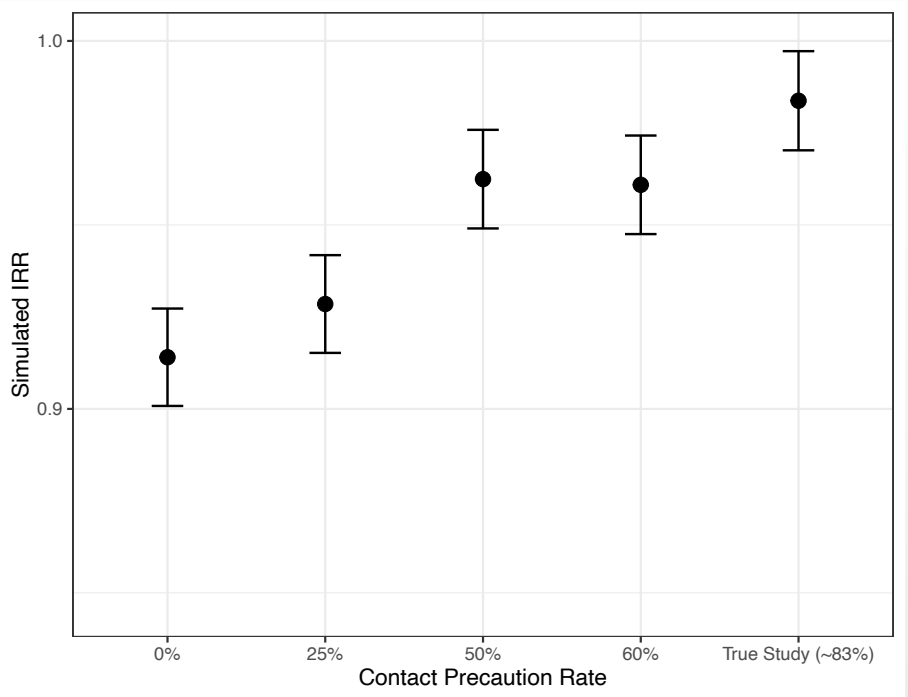
- Does the intervention induce a mediator as well as the direct effect?
- Does the control group experience having that mediator? For example, controls are often given literature and education
- Randomization doesn't fix this



Differing Baseline Levels of "Control"

- In many studies, control vs. treatment is assumed to be 0/1
- But what if it isn't – control can mean "business as usual"
- Randomization doesn't fix this





The Time Series Cohort

- What is the cohort for a time series?

Cross-Sectional Studies

- Draw a sample from a population at a given point in time
- Determine the relationship between exposure and outcome
- A cross-sectional studies is inherently only about a single point (or more commonly, a short period) of time
- Limited to collecting prevalence data

HSV-1 Prevalence in Lampang and Songkhla, Thailand

	Lampang*	Songkhla
HSV-1 +	1015	608
Total	1056	938
Prevalence	96.1%	64.8%

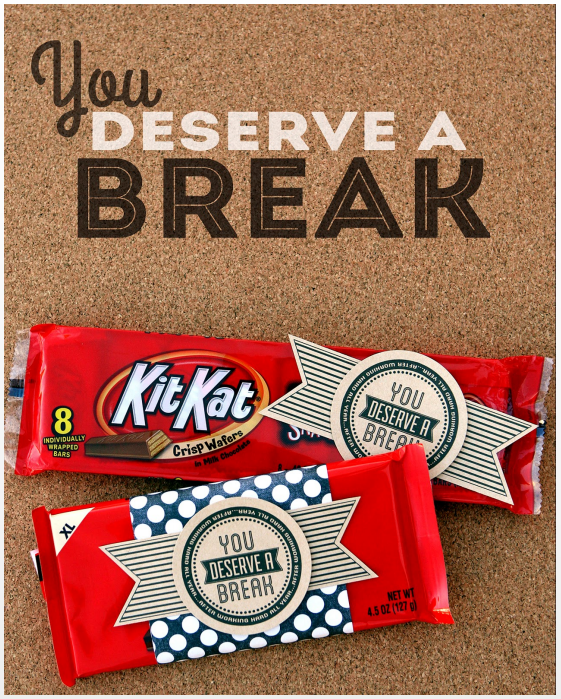
*Referent Category

Crude PR: 0.67

Cross-Sectional Cohort

- What is the cohort for a cross sectional study design?

Break Time


You
DESERVE A
BREAK
KitKat
8
Crisp Wafers
YOU DESERVE A BREAK
YOU DESERVE A BREAK
NET WT
4.5 OZ (127 g)

Case-Control Studies

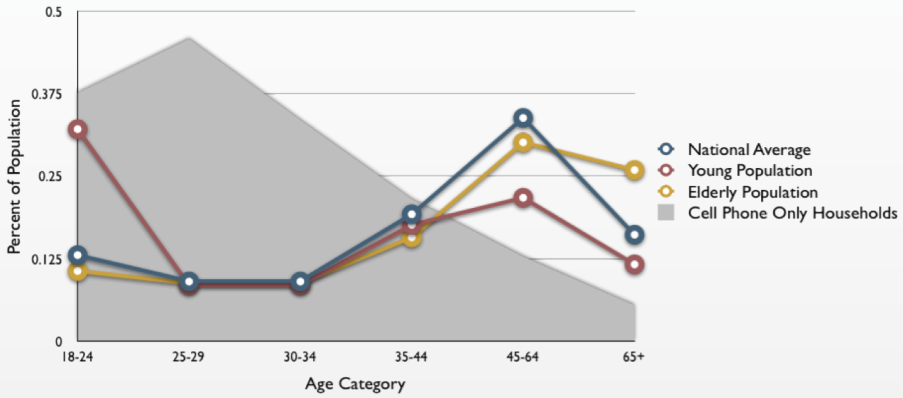
- Extremely common study design in epidemiology
- Cases are sampled from some source – a disease registry, hospitals, etc.
- Controls are sampled so that they come from the same population as the cases in some ratio (i.e. 1:1, 1:2, etc.)
- Examining the *distribution of the exposure* between cases and controls
- Here, we can't directly calculate risk, so we estimate using the odds ratio, usually via logistic regression

Where Do You Get Controls?

- Controls must come from the same source population as cases
- This is often trickier than it seems
- Examples:
  - Cases drawn from restaurant outbreak
    - Need *other restaurant goers*
  - Occupational exposures
    - Health worker bias
  - Hospitals
    - Different, unrelated wards – cases have access to healthcare

Random Digit Dialing

- Used to be a common way to recruit cases from a population – pick numbers associated with a geographically specific exchange
- In a simulation study where age was an unconfounded cause of a simulated outcome, accurately sampling cases and RDD sampling controls caused a considerable downward bias
- Sometimes enough to induce an association that wasn't present



Incidence Density vs. Prevalence Sampling

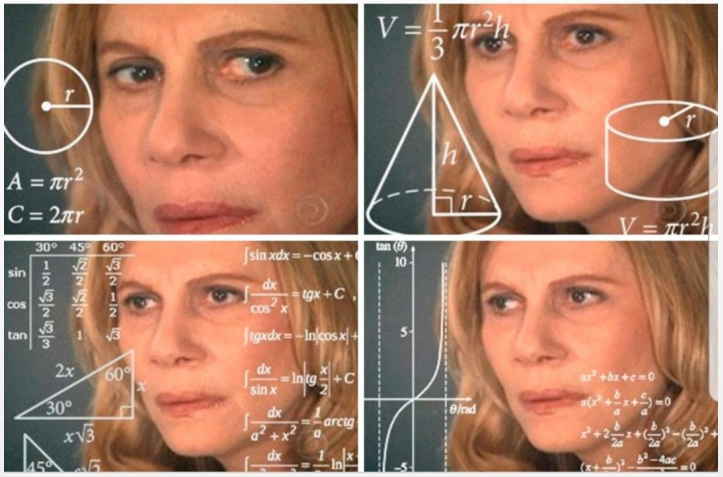
- What a case-control study is approximating depends on when controls are sampled
- Prevalence Sampling
  - Ascertain cases, collect controls once all cases are ascertained
  - Approximates a risk ratio
  - What people tend to think of when you say “case-control study”
- Incidence Density Sampling
  - Collect a control as each case is ascertained
  - Approximates a risk ratio
- Incidence density sampling *can* be done prospectively or retrospectively in some cases

Trohoc Fallacy

- Case-Control studies are not “backwards” cohort studies, where you start with the disease and reverse engineer
- This often leads people to believe that the cases and controls should be as similar as possible aside from their disease status
  - Preoccupation with healthy controls
- This is not the case – we are still interested in how these groups differ *by exposure*
- Controls should represent your study’s population at risk

This All Seems Very Complicated

- It is!
- Case-control studies are often taught very early because *analytically* they are very straightforward
- Logistic regression is basically bomb-proof
- Methodologically however they're quite complex



So Why Do a Case-Control Study?

- In a perfect world, we might never run a case-control study
- Case-control studies are *efficient* – that is you get a lot of inferential ability for relatively few study subjects
- Imagine an extremely rare outcome – non-motor vehicle fatalities from deer:human interaction
- Now imagine the size of the cohort you'd need to follow to get enough people with the outcome to do any sort of statistical analysis

This Is a Common Problem

- Studies are expensive
- Sophisticated lab tests are expensive – running an assay on a whole cohort for a rare outcome could be prohibitive
- There are time limitations for survey teams, medical chart review, etc.
- Study participation is not without risk – for example, consider a study that needs to take a biopsy or blood sample – you want to minimize the amount of those taken
- Imagine you're talking about some parts of veterinary epidemiology, and your study subjects must be euthanized afterwards

Cohort Studies

- We've discussed these as the sort of "Ur-Study" that other studies are, at least hypothetically, nested within
- Primarily group individuals by exposure status
- These studies allow you to estimate incidence, temporality is often much more clear, can consider multiple outcomes
- "Retrospective vs. Prospective"
  - This has to do with *when the outcome was known*, not just about data collection
  - Retrospective studies try to recreate exposure status after the fact

Fuzziness

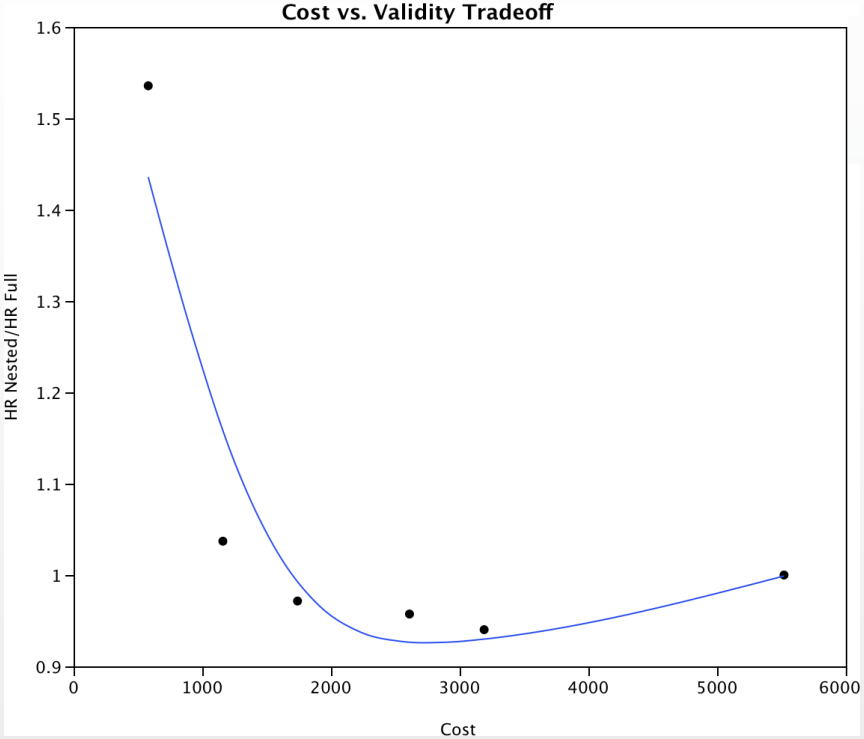
- Many of the objections to retrospective studies stem from concerns about the quality of information in the past
- Do we have good records, are they complete, etc.?
- For administrative records, you can imagine what's happening is that infinitely many prospective cohorts exist, but we only pick the interesting ones retrospectively (i.e. when a researcher actually goes into said data)
- Retrospective cohort studies *are* generally more efficient

More Complexity

- We've said that all studies are theoretically nested in a cohort
- Some studies are *actually* nested in a cohort study
- Usually for intensive analysis of some subgroup, exposure, etc.

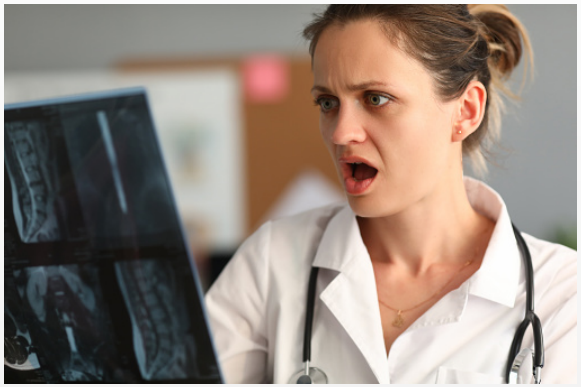
Within-Cohort Study Designs

- Nested Case-Control Studies
  - Case-Control taking place inside a cohort
  - Often trying to gain the efficiency of a case-control study for some biomarker or assay
  - For example, WGS
- Case-Cohort Study
  - Compare cases to a defined, random sub-cohort
- Case-Crossover Studies
  - Cases will serve as their own controls at later time points
  - Often used with administrative data on pharmaceuticals



Randomized Controlled Trials

- Special case of a cohort study
  - Many clinical researchers will shriek if you say that
- Rather than letting exposure be assigned by some natural process, exposure is assigned randomly
  - Drug vs. Placebo
  - Menu with printed calories vs. Menu without
- Blinded = Patients don't know what they got
- Double-blinded = Neither do the people administering the treatment
- Cohort is then followed over time



Why Do We Like RCTs?

- Remember confounding?
  - Controlling for confounding in other study designs is good at eliminating confounding, but imperfect
  - *Theoretically* randomizing exposure completely eliminates confounding
    - *In practice*, post-randomization changes between groups can re-introduce confounding
- Drawbacks
  - Just as hard, if not harder, to administer as cohorts
  - Not all exposures can be ethically randomized

Variations on the RCT

- Lots of variations on the RCT design, trying to preserve randomization while dealing with challenges
- "Block Randomization"
  - Population is organized into groups (blocks) and within each block assigned treatment randomly
  - Eliminates "nuisance factors" – for example, each person administering the treatment could be a block
- Multi-center Trials
  - RCT takes place in multiple sites, each *site* is randomized to a treatment
  - *Extremely* expensive
- Stepped Wedge
  - Everyone will receive the treatment eventually, the time until they receive it is randomized
- And others…

The Hierarchy of Evidence

- *Very* popular concept in biomedicine
- Used somewhat dogmatically
- Prioritizes internal validity
- Assumes the type of study is the primary driver of study quality
- Similarly, if case-control studies are efficient cohort studies, why are they lower?

Target Validity

- Internal validity: Accurately estimating the effect of an exposure within the study population
- External validity: Accurately estimating the effect of the exposure in the population of interest
- A study population is often *not* a random sample of the target population due to exclusion criteria, consent, reachability, etc.
- Target validity (aka target bias) is the sum of internal and external bias
- Difference between the true causal effect in the study population and what you estimated