Get to Know Each Other Online: Have you ever….

6. Written a clinical research protocol?
7. Read a clinical research protocol?
8. Read a clinical journal article?

Overview

- Many different people take the course
  – Some first introduction, some advanced
- Tricks, tips, and concepts
- General objectives
  – Better consumer of medical and scientific literature
  – Enhance conversations inside research team [with study statisticians and epidemiologists]
  – Better science

Easy to Write

- The study will use a randomized, double-blind, controlled parallel arm design and an intent to treat analysis.
- Subjects/participants will be consented.

Not Easy

- To implement and maintain the integrity of
  – Randomization
  – Blinding/masking
  – Multiple study arms
  – Data collection
  – Transfer data to regulatory and other groups

Tonight's Objectives

- Identify study designs used in clinical studies, epidemiology and public health research
- Discuss masking/blinding, interventions, comparison groups

- Chapters 19, 29, 3rd Edition

Outline

➤ Where to start
- Taxonomy and examples
  – Some general vocabulary
  – Observational and interventional studies
- General good study design
  – Intervention and dose
  – Comparisons
- Conclusions
- Confounding and effect modification

Cervical Cancer

- Cultural
- Access
- Vinegar
- Diagnostic biomarker
  - High negative predictive value
  - Low cost
  - Fast
- Time table for treatment

Other Examples

- Cardiovascular disease
  - Weight
  - Hypertension
- Infectious diseases
- Data collection/mode of administration
  - Mobile health
- Combination of interventions

What is the question of interest?

- Interpreting work into new population
- Making decision about individual case
- Looking at changing a population
  - Diabetes management
- Differences between groups in a study
- Biomarker development? What kind of biomarker?
- Develop a new outcome?
- Level of evidence
- Evaluation of evidence

Analysis Follows Design

Questions → Hypotheses →

Experimental Design → Samples →

Data → Analyses → Conclusions

- Take all of your design information to a statistician early and often
  - Guidance
  - Assumptions

How a Statistician Sees a Research Study

- Everything impacts the statistical analysis

Outline

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Vocabulary

- Arm = Sample = Group
- Demonstrate superiority
  - Detect *difference* between
    - Groups
    - Treatments or study arms
- Demonstrate equally effective
- Demonstrate non-inferiority
- Patient vs. participant vs. subject

Study Design Taxonomy

- Intervention vs. Observational
- Longitudinal vs. Cross-sectional
- Prospective vs. Retrospective
- Blinded/Masked or Not Blinded/Masked
  - Single-blind, Double blind, Unblinded
- Randomized vs. Non-Randomized

Two Types of Research Studies

- Observational
  - Goal is to observe and collect data on characteristics of interest without influencing the participant, environment or disease course
- Experimental
  - Researcher deliberately influences course of events and investigates effects of an intervention on a carefully selected population of subjects
  - Experimental studies done on human subjects are referred to as clinical trials or clinical studies

Observational Studies

- Case Reports
- Case Series
- Cross-Sectional or Prevalence Surveys
- Case-Control Study
- Cohort Study (longitudinal)
- Natural History Studies
- Ecological Studies (data on population rather than individual level)

Quasi Experimental, One/Single Arm, or Non-Randomized Experimental Studies

- No control group
  - Early in investigation
- Concurrent control "group"
  - Treatment assignment not by randomization
- Historically controlled
  - Missing data
  - Poor data
  - Non-comparability of groups

Intervention Based Research Spectrum

- Epidemiology
- Quasi-experimental
- Pre-clinical studies
- Phase 0
- Phase I
- Early/Late Phase II
- Phase III
- Phase IV
- Dissemination and Implementation
- Comparative or Cost Effectiveness

Ideal Study - Gold Standard

- Treatment / control
- Parallel groups
- Superiority
- Prospective
- Double blind / masked
- Randomized

BMJ 14-20 Oct 2013

- Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis
- Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial

BMJ 14-20 Oct 2013

- Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study
- Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey

Distinguish

"Observational studies are often analyzed as if they had resulted from a controlled study, and yet the tacit assumption of randomness can be crucial for the validity of inference."

Copas, J.B. and Li, H.G. (1997). Inference for non-random samples (with discussion).
***Journal of the Royal Statistical Society*, 59: 55–95.**

Non-Randomized	Randomized
• Can ONLY show Association • You will never know all possible confounders!	• Can show Association AND Causality • Well done non-adaptive randomization → unknown confounders should not create problems

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Your Question Comes First

- May need to rewrite
- If you change your question later
  - May not have the power
  - May not have the data
- Need to know something about the population

THIS LECTURE:
FOCUS ON INTERVENTION STUDIES

26 OCTOBER 2015:
NON-INTERVENTION STUDIES
EPIDEMIOLOGY

Types of Randomized Studies

- Parallel Group – classic
- Sequential Trials – physical sciences
- Group Sequential trials – classic
- Cross-over – intervention washout
- Factorial Designs – independence
- Adaptive Designs – gaining popularity
- Enriched Enrollment – regression to the mean
- Cluster Randomized Designs

Parallel Group

- Randomize patients to one of X treatments
- Response
  – Measure at end of study
  – Change (delta) or % change from baseline
  – Repeated measures
  – Function of multiple measures

Variations on Parallel Group Designs

- Dose titration (with multiple study arms)
  - Titrate to the maximum tolerated dose within a subject
- Dose Escalation Studies (with a control arm that is simultaneously randomized to)
- Not all dose escalation and dose titration studies are randomized

Sequential Trials

- Not a fixed sample size/period
- Terminates when
  - One treatment shows a clear superiority or
  - It is highly unlikely any important difference will be seen
- Special statistical design methods

Group Sequential Trials

- Popular
- Analyze data after certain proportions of results available
- Early stopping
  - If one treatment clearly superior
  - Futility
  - Adverse events
- Careful planning and statistical design

At First Interim Analysis
(1/3 of projected infant infections)

P = 0.00006

DOD/BRB/NIAID
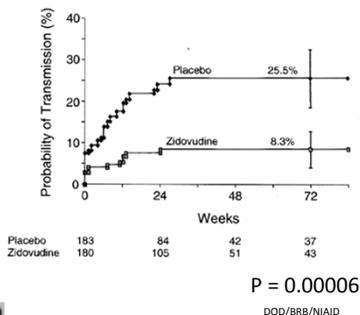
Preventing Mother-Infant HIV Transmission
(D.O. Dixon, NIAID)

- Zidovudine able to slow progression of HIV in adults with advanced disease
- AIDS Clinical Trials Group Protocol 076 designed to assess both safety and efficacy of Zidovudine in preventing transmission of HIV from infected (not advanced) women to their babies

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Preventing Mother-Infant HIV Transmission

- Powered (80%) to detect a 33% reduction of transmission rate (through 78 weeks of baby's life) relative to projected rate of 30%
- Target N was 748; began April 1991
- Projected accrual to take at least 5 years and 15% dropouts

Crossover Trial

- Cross over example
  - 2 treatments
  - 2 period crossover
- Use each patient as own control
- Must eliminate carryover effects
  - Need sufficient washout period
  - Not always known what length of time is needed
  - Not everything can wash out

Women's Alcohol Study
JNCI 2001

- Three 8-week dietary periods
  - 30 g alcohol/day
  - 15 g alcohol/day
  - 0 g alcohol/day [alcohol free beverage]
- *Order of assignment* to 3 alcohol levels was random
- Washout periods
- Double blind

Factorial Design

- Each level of a factor (treatment or condition) occurs with every level of every other factor
- Selenomethionine (Se) and Celecoxib (C) Gastroenterology 2002; 122:A71

SE Placebo	Selenium
C Placebo	C Placebo
SE Placebo	Selenium
Celecoxib	Celecoxib

Factorial Design

- Factor 1: Selenium
  - Yes, No
- Factor 2: Celecoxib
  - Yes, No

Factorial Design

	Se (Placebo)	Se (Real)
Celecoxib (Placebo)	Se Placebo C Placebo	Selenium C Placebo
Celecoxib (Real)	Se Placebo Celecoxib	Selenium Celecoxib

Factorial Design

	Se (Placebo)	Se (Real)
Celecoxib (Placebo)	Se Placebo C Placebo	Selenium C Placebo
Celecoxib (Real)	Se Placebo Celecoxib	Selenium Celecoxib

Factorial Design

- Power for the interaction or not?
- Is this a 4 arm study?
- 2-2 arm studies?

SE Placebo C Placebo	Selenium C Placebo
SE Placebo Celecoxib	Selenium Celecoxib

MsFLASH Factorial Design

	Yoga once a week, daily home practice	Aerobic exercise 3 times a week	Usual activity
Omega 3 supplement 615 mg gel capsule daily	15%	15%	20%
Placebo gel capsule	15%	15%	20%

Menopause, April 2014

Incomplete/Partial/Fractional Factorial Trial

- Nutritional Intervention Trial (NIT)
- 4x4 incomplete factorial
- A,B,C,D
- Did not look at all possible interactions
  - Not of interest (at the time)
  - Sample size prohibitive

Adaptive Designs

- Gaining popularity
- 2-8+ arms
- Dose ranging (perhaps)
- Smaller overall sample size (potentially)
- Run-in then analyze data continuously or at fixed points
- Need to be clear
  - What is adapted
  - When is it adapted
  - Based on what evidence does the adaptation take place, and who decides and implements

What are adaptive designs?

By adaptive design we refer to a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.

Gallo et al. (PhRMA Working Group) 2006

Wakim 2015

What are adaptive designs?

… an adaptive design clinical study *is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.*

FDA 2010

Wakim 2015

What is being adapted?
(Types of adaptations)

- Adaptive randomization
- Adaptive dose-finding (dose-ranging)
- Drop-the-loser (or pick-the-winner)
- Adaptive seamless phase II/III
- Biomarker-adaptive
- Group sequential methods
- Sample size re-calculation

Sanchez-Kam et al. 2014, Coffey et al. 2012, Chow & Chang 2008   Wakim 2015

Features of Adaptive Designs

- Their rules for adaptation are pre-specified in protocol

- Changes are made by design, not on an ad hoc basis

- They are not ad-hoc fixes for poorly-designed trials

- They require understanding by investigators, reviewers, DSMB members, and journal editors

Coffey et al. 2012, Gallo et al. 2006

Wakim 2015

Adaptive Designs

Advantages
Greater flexibility and more streamlined process

Disadvantages
Need for better quantification of statistical risks, e.g. statistical bias, potential increase in Type I error rate, risk of covariate imbalance

More upfront work and planning than in regular designs

Coffey 2013   Wakim 2015

Adaptive Designs

- Some act like group sequential designs
- Close an arm early
- Re-estimate sample size based on a nuisance parameter (variance)

- Big negative: any time a decision to continue is made, information is provided to the study investigators, public, investors….

Enriched Enrollment Designs

- Sometimes variant of crossover or n-of-1 study design
- Identify potential 'responders'
- Enter 'responders' on to 2nd prospective comparison study
- Results not generalizable to entire patient population
- Regression to the mean
  – Average 10 hot flashes a day for 14 days, and 3 on study in the placebo arm

Group or Cluster Randomized Studies

- Unit of randomization is not the individual
  – School
  – Community
  – Clinic
- Change eating patterns to impact obesity and other health outcomes
  – Altering supermarket environments
  – School based nutrition programs
- Charges for bed nets and impact on infant malaria cases

Outline

- ✓ Where to start
- ✓ Taxonomy and examples
  - ✓ Observational and interventional studies
- ➤ General good study design
  - ➤ What is the question
  - ➤ Comparisons
- Conclusions
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How good is the primary research question?

At the end of the day, when the clinical research is completed and the data analyzed, will the *answer* (whatever it is) to the *primary research question* advance scientific knowledge and/or clinical practice?

Wakim 2015

A good primary outcome measure is clinically meaningful and simple

Wakim 2015

How to Start Designing a Study

- Study aims, background, rationale
- Endpoints or outcome variables, other assessments
  - Specific variables, how measured, specific & sensitive to changes expected, reliability & validity of measure
- Inclusion/Exclusion criteria

How to Start Designing

- Accrual plan and preparatory tasks
  - Timeline for overall study
  - Timeline for individual study participant
- Treatments? Participant implications?
  - Product, dose, quality, administration, and reproducibility of interventions (including training)

Intervention Definition

- What is it; can someone replicate it?
- Dose; choices based on what?
- Does it interfere with patient management
- Generalizability often lost in quest for specificity
- Specify criteria for withdrawal from study or deviation from protocol or definitions
- List concurrent medications, procedures, etc. that are prohibited, permitted, must be recorded in certain way

What is a Dose?

- Number of sessions/pills/treatments/social media attempts
- Frequency
- Length of sessions (each, total treatment time)
- Amount of practice
- Leader
  - Contact time
  - Who that person is
- Many different combinations
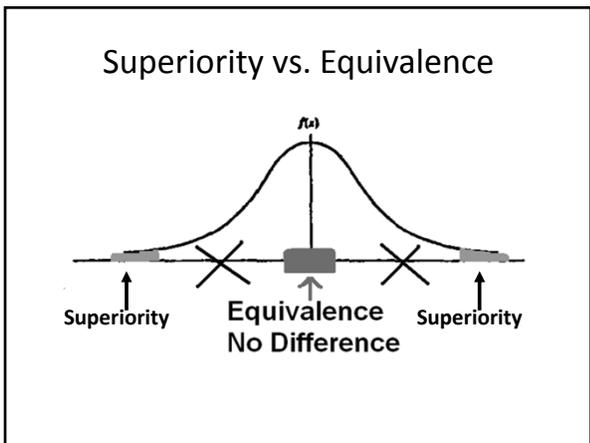
Practitioner Impact

- False negatives and positives
  - Details of protocol
- Examples
  - Massage for low back pain
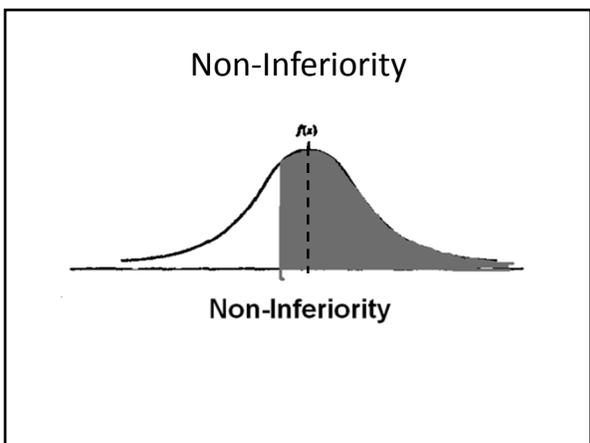 - Surgery
  - Prevention course

Study Analysis Population

- Mechanistic, proof of concept
  - Throw best at it
  - Per protocol
- General use
  - Like intent-to-treat analysis

- What is the question?

Intent-to-Treat versus Completers
"How Many in the Data Analysis"

- ITT = Intent-To-Treat analysis
  - Include all randomized (if randomized study)
  - Assume all study participants
    - Adhered to study regime assigned
    - Completed the study
- MITT = Modified ITT analysis
  - ITT, but only include people who start intervention they are assigned to
- Completers or Adherers analysis
  - Only the well behaved

Superiority vs. Equivalence

Superiority   Equivalence
No Difference   Superiority

Non-Inferiority

Non-Inferiority

Comparison Groups

- Experimental intervention vs control
- Case vs control
- Exposed vs unexposed
- Various levels of exposure
- Men vs women
- Old vs young
- BMI>25 vs ≤ 25
- Usual or standard care or practice
- History; pre-post

Placebo, Standard of Care, and Attention Controls

- Experimental treatment
  - Supportive care
  - Current treatment
- Yoga
  - Exercise or stretching
  - Cooking classes
  - Book club
  - Nothing

Control Usually Costs Money = Larger Sample Sizes

- Control everything except smallest element of intervention that you want to test
  - Be careful it is not too small a difference
- Consequences if study has
  - More control imposed
  - Less sensitive or precise outcome measures
- Plan accordingly

Differences

- Time at the intervention or study-participant contact
  - 1 to 3 hours / week
- Time spent at home
  - 15 to 60 minutes / day
- Have a 'match' in the control group or enough variance to put in the analysis

What is the control group?

- Placebo
- Most widely accepted treatment
- Standard treatment
- Most accepted prevention intervention
  - Condoms and HIV?
- Usual care
- Accepted means of detection or diagnostic test
- Non-diseased population

Control Groups

- Ethical
  - Control intervention itself
  - Assigning ANYONE meeting study criteria to ANY study group
- If "standard of care" (SOC) evidence: is really standard practiced usual care in that format?
- Good controls can always be masked?
  - No, sometimes IV versus pill of same medication
  - Try to mask interventions

No Placebo/Control = Problems

- People tend to do 'better' receiving some treatment, even placebo or standard of care
  - Care matters
  - Comparing a patient on treatment to baseline does not take this into account
- Comparing population incidence rate to beginning of program does not take into account many factors (may look worse before better)

No Control Group: Additional Problems

- No blinding
  - Researchers and participants tend to interpret findings in favor of new treatment
  - Investigator/participant bias
- No randomization
  - Impossible to distinguish effect of time from treatment effects
  - Confounding

What is the right control group for a randomized study?

- Waitlist control
- Placebo control
  - Remove 'active' component; may still have an impact on outcomes
- Active controls
  - Standard of care
  - Alternative intervention
  - Fewer parts of multi-part intervention
- Attention control
- No universally-appropriate control group

Controls Also Present in Many
Non-Randomized Studies such as
Case-Control Studies

- Siblings
- Community controls
- Hospital controls
- Worked in same area but not present for workplace exposure

- Match on many different variables or not
- Multiple control groups

Consider

- If it has effects
  – Positive
  – Negative
- Do the effects plateau?
- Time
  – Long term differences
  – Attenuation
  – Delayed response

Time and Other Elements

- Time is our favorite confounder in uncontrolled studies
  – Differential time participating is an issue
  – Differential drop-outs
  – Time in an environment, age, season
- Social support
  – Meeting in a group may have an impact
  – Talking to someone, empathy, may impact
- Exercise
  – Exercise helps cardiovascular risk factors
  – Exercise helps stress

Masking/Blinding

- Less common in non-randomized studies, but can mask outcome assessors as to hypothesis
- Specify whom to be masked, why, how, and to what
- Assess effectiveness of masking
- Specify criteria for unmasking, whom to be unmasked
- Mask determination of outcome so that reviewers are unaware of treatment assignment; provide information on "need to know" basis
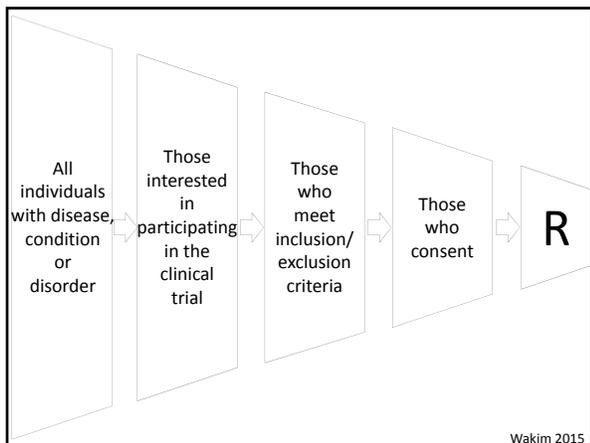
Reproducible Measurements:
Regardless of Study Design

- Well defined cohort
- Exclusion and inclusion criteria
- Study conduct
- Outcomes
- Study data, analyses

Biases in Clinical Research

Bias	Remedy
Selection/Assignment	Randomization
Treatment & Assessment	Masking Research Team
Response	Masking Participant
During Data "Cleaning"	Masking Assigned Treatment & Pre-specification
During Analysis	Intention to Treat (ITT) & Pre-specification
Publication	Trial Registration
Reporting	Pre-specification & Disclosure

Wakim 2015

| All individuals with disease, condition or disorder | → | Those interested in participating in the clinical trial | → | Those who meet inclusion/ exclusion criteria | → | Those who consent | → | R |

Wakim 2015

Studies ≠ Gold

- True for randomized and non-randomized studies
  - Volunteer bias
  - Inclusion/exclusion criteria
  - Measures
  - Artificial interventions/treatment definitions

Outline

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➢ Conclusions
• Confounding and effect modification

The PICO(T) Question

P: Population/disease
I: Intervention or Variable of Interest
C: Comparison group
O: Outcome
T: Time

In _____(P), how does _____(I) compared to _____(C) influence _____(O) during _____ (T)?

Example:
In patients ages 65 and older (P), how does the use of an influenza vaccine (I) compared to not receiving the vaccine (C) influence their risk of developing pneumonia (O) during the flu season (T)?

Stillwell et al. 2010; Wakim 2015; others

AND WHO CARES

Your Question Comes First

- May need to rewrite
- If you change your question later
  - May not have the power
  - May not have the data
- Need to know something about the population

Consider

- Questions you want to ask
- Hypotheses you want to test

- Key factors you wish to control
- Ethical issues and constraints
- What can be said with each control group?
  – More than one control group?

Outline

✓ Where to start
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✓ Conclusions
➢ Effect Modification and Confounding

Different Variables May Be

- Effect Modifier(s)
- Potential Confounder(s)
- Other things

- If measured these are usually "covariates" in the statistical model

Effect Modification

- Interaction
- Synergy
  - Could be larger or smaller
- Association between outcome and another variable (e.g. intervention) is modified by different levels of a third variable

Smoking, Asbestos, and Lung Cancer

- Smoking (alone) ↑ risk of lung cancer by A
- Asbestos exposure (alone) ↑ risk of lung cancer by B
- Smoking AND having asbestos exposure ↑ risk of lung cancer by MORE/LESS than A+B

Effect Modification

- A Short Introduction to Epidemiology
  - Neil Pearce chapter (2005)
- The phrase effect modification, defined for different professions
  - Biostatisticians, public health workers, physicians, lawyers, biologists, epidemiologists,….

Confounding

- Two or more variables
- Known or *unknown* to the researchers
- Confounded when their effects on a common response variable or outcome are mixed together

- Association between an exposure and outcome is misestimated due to the failure to account for a third factor (the confounder)


Consider

- Association observed between carrying matches in your pocket and lung cancer
  – Carrying matches causes lung cancer
  OR
  – Association between carrying matches and lung cancer is result of confounding by another unmeasured variable associated with both

(Pam Shaw, CTR Course 2013)

Coffee and Pancreatic Cancer

Coffee Drinking → Pancreatic Cancer

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Coffee and Smoking

Coffee Drinking
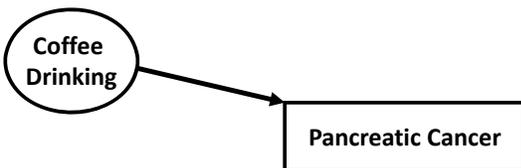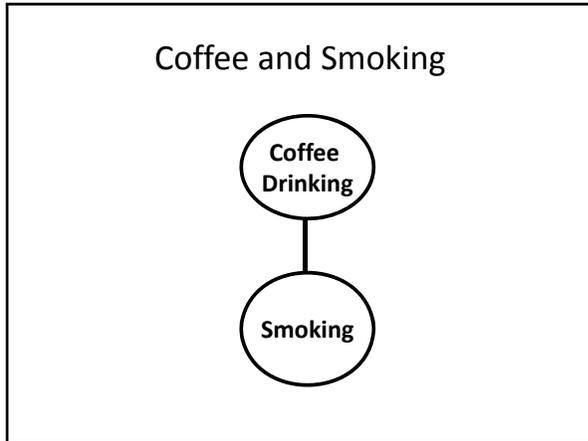
Smoking

Confounding Example

- Relationship between coffee and pancreatic cancer, BUT
- Smoking is a known risk factor for pancreatic cancer
- Smoking is associated with coffee drinking
  – Coffee drinking is associated with smoking
- Smoking is not a result of coffee drinking
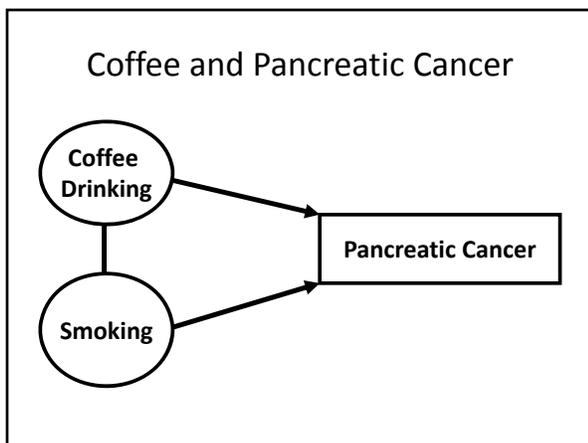
Coffee and Pancreatic Cancer

Coffee Drinking

Smoking

Pancreatic Cancer

What is Confounding

- If an association is observed between coffee drinking and pancreatic cancer
  - *Coffee actually causes pancreatic cancer, or*

Coffee Causes Pancreatic Cancer
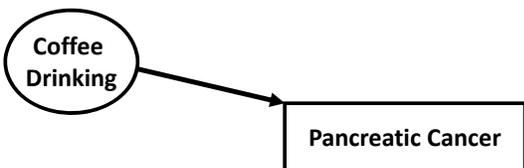
Coffee Drinking → **Pancreatic Cancer**

What is Confounding

- If an association is observed between coffee drinking and pancreatic cancer
  - Coffee actually causes pancreatic cancer, or
  - *The coffee drinking and pancreatic cancer association is the result of confounding by cigarette smoking*

Smoking is a Confounder: Coffee does NOT cause Pancreatic CA
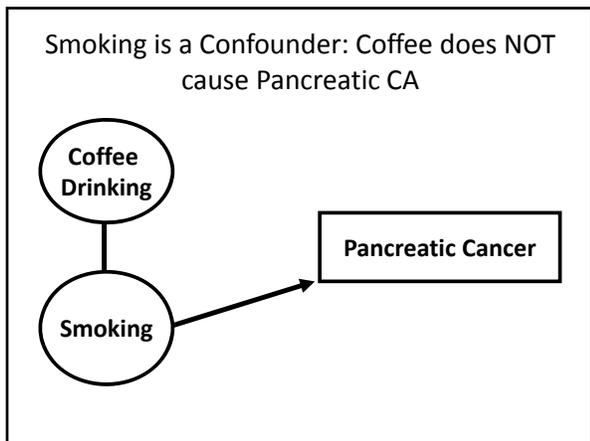
How to Handle Confounding

- Identify potential confounders
  – MEASURE THEM!
  – In the data analysis use
    • Stratification, or
    • Adjustment (add the variable to the model)
- Fear the unknown!

More to Confounding? Yes!

- Residual confounding
  – Poor measure of the confounder
    • Physical activity
  – Even when we put the confounder as measured in the model, not really explaining the effect of real physical activity in the model
- Example
  – Ever Smoked yes/no; pack years

Randomization =
No Confounders! Wrong!

- Side note
- Randomization helps protect against confounding
- Does not prevent confounding
- Non-random drop-out or attrition
- Patients testing substance
  - And then dropping out, or taking more of item

Confounding and Effect Modification

John Powers 35 March 2014 IPPCR
https://ippcr.nihtraining.com/lecture_detail.php?lecture_id=210&year=2013

Thanks!

- Please submit questions and comments electronically so all several thousands of us can share in the dialog