Observational Studies
Design of Epidemiologic Studies

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

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TO FINISH THE TEASER FROM THE LAST LECTURE…..

Different Variables May Be

- Effect Modifier(s)
- Potential Confounder(s)
- Other things
- If measured these are usually “covariates” in the statistical model

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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

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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

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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,….

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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)

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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)

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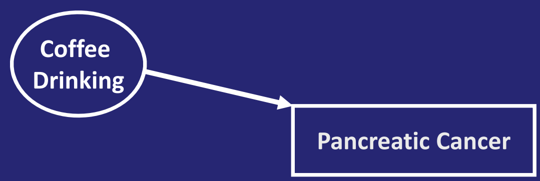
Coffee and Pancreatic Cancer



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Coffee and Smoking

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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

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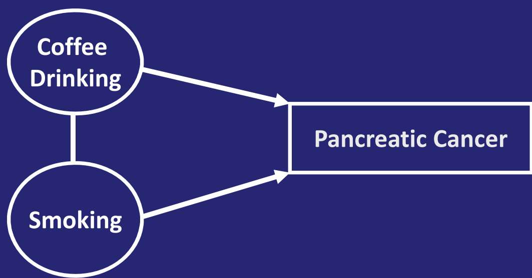
Coffee and Pancreatic Cancer



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What is Confounding

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

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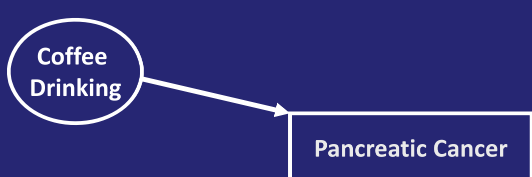
Coffee Causes Pancreatic Cancer



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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*

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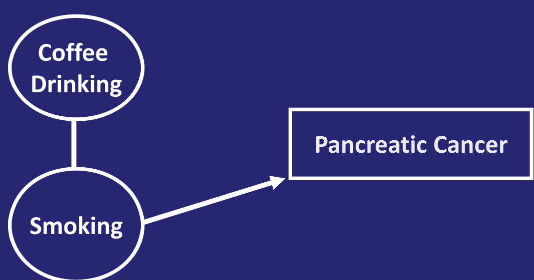
Smoking is a Confounder: Coffee does NOT cause Pancreatic CA



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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!

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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

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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

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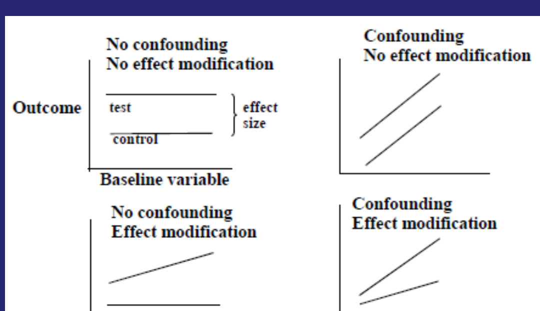
Confounding and Effect Modification



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

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Objectives

- Define epidemiology
- Identify common observational study designs and understand why they may or may not be used to answer a research question

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Chapter 18, 3rd Edition

- Thanks to Jerry Menikoff, OHRP, for rearranging, editing and providing comment on these slides

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Outline

- ➢ Definitions
- A few study designs
- Bias
- Conclusions

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What is Epidemiology?

- Study of the distribution and determinants of disease and injury in *human, animal, plant, or other* populations
  - [Human] disease does not occur at random
  - [Human] disease has causal and preventive factors that can be identified through systematic investigation of different populations or subgroups of individuals within a population
    - Hennekens and Buring, 1987

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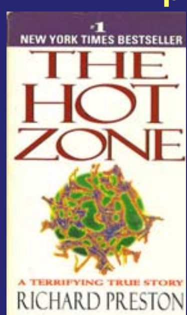
Think Outbreak
Epi - Epidemic



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What is Epidemiology?

- Studying epidemics
  - EIS (Epidemic Intelligence Service) at CDC
- Big cohort studies
  - Nurses Health Study
- Many things in between
- Considered (by some) cornerstone of Public Health Research

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Are all big epi studies refuted?

- All the epidemiologic studies prior to Women's Health Initiative (WHI)
  - They did not agree, really
  - Now with new statistical methods, well, hindsight was 20/20
  - Or adjust for socioeconomic status...
- Prevention hard to study except by epidemiology
- New York Times Magazine, 16 September 2007: http://tinyurl.com/5jjhkh

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Epidemiology is Hard

- Measure many things
- Measure each thing many different ways
- Measure each of those VERY accurately
  - Often
  - Do not lose any data
  - Same way every time
- You cannot know what you do not measure

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Epidemiology and Hypotheses

- Epidemiology is hypothesis generating evidence
  - Like circumstantial evidence in court?
- May be the only information outside of the laboratory
- Fundamental limitation of observational studies
  - Distinguish associations
  - CANNOT inherently determine causation

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Generating Hypotheses

- Epidemiology
- Clinician experience/observation
- Out of thin air

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Causal Inference in Observational Studies: Epidemiologic Criteria

A. Statistical significance
B. Strength of association (odds ratio, relative risk)
C. Dose-response relationships
D. Temporal sequence
E. Consistency of the association (internal "validity")
F. Replication of results (external validity)
G. Biological plausibility
H. Experimental evidence

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Experimental or Observational

- Epidemiologists used several different types of studies
  - Interventional or experimental
    - Researcher influences what happens to subjects (e.g., clinical trial)
    - Different concept for human subject protections
  - Observational
    - Descriptive (who, what, where, when)
    - Analytical (how, why)

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Outline

- ✓ Definitions
- ➢ A few study designs
- Bias
- Conclusions

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Observational Studies

- ➢ *Case Reports*
- ➢ *Case Series*
- Cross-sectional Surveys
- Case-Control Study
- Cohort Study

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Case Reports and Series

- Observations of patients with defined clinical characteristics
  - Certain disease
  - Cluster of symptoms
- Description of data without comparison groups
- Data from well defined group of people

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Case Reports and Series

- Clear definitions of phenomenon
- Same definitions for all individuals in series
- Observations reliable and reproducible

- GOOD observational studies very useful

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Descriptive Statistics

- Mean; median
- Standard deviation/error
- Proportions
- Confidence limits or intervals
- Separate data for subgroups
  - By sex, age, etc

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Case Reports and Series

- Hypothesis formation
- Natural history
- Clinical experience
- Biased patient selection?
- Generalizability of results?
- Chance or characteristic?

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Example

- Initial report of five cases of pneumocystis pneumonia in previously healthy, homosexual men
- US Centers for Disease Control and Prevention. Pneumocystis pneumonia-- Los Angeles. *MMWR* 1981; 30:250-2.

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Observational Studies

- ✓ Case Reports
- ✓ Case Series
- ➢ *Cross-sectional Surveys*
- Case-Control Study
- Cohort Study

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Cross-sectional or Prevalence Surveys

- Observe prevalence and characteristics of disease
- Participant characteristics in a well defined population

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Cross-sectional or Prevalence Surveys

- Define population
- Derive a sample of the population
- Define the characteristics being studied
  - Standardized *observations*
  - Clearly defined
  - Methods of data collection applied equally to all study participants

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Prevalence & Incidence Defined

- Prevalence
  - # with disease / # at risk
  - If you take a snap shot
  - How many diabetics in Brazil right now
  - Prevalence = Incidence * Duration
- Incidence
  - # NEW cases of disease (over a period of time) / # at risk during that period
  - How many new (incident) cases of diabetes diagnosed in 2007 / # who could develop disease in 2007

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What is Described in Tables

- Descriptive
  - How common is the factor?
  - Characteristics of a group
  - Distribution of factors of interest (e.g. age)
- Associative
  - Relationships between factors
  - How do those with one factor differ from those without?

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Cross-sectional or Prevalence Surveys

- Descriptive
  - Prevalence (% or cases per 10^5, etc)
  - Mean or median levels of relevant factors
  - Subset by important subgroups
- Analyses
  - Categorical
    - Chi-square test, Fisher's Exact test, logistic or ordinal regression
  - Continuous
    - t-Test, regression or other analyses

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Cross-Sectional Observational Studies

- Collect a representative sample
- Simultaneously classify by outcome and risk factor

		Outcome: Disease	Outcome: No disease
Risk Factor	Y		
	N		

Positive Attributes

- Inexpensive for common diseases
- More representative cases (vs. case series)
- Tend to be short (duration)
- Specific population
- Simultaneous wide variety of measurements

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Negative Attributes

- Unsuitable for rare diseases
- Unsuitable for disease of short duration
- High refusal rate → inaccurate prevalence estimates
- More expensive/time consuming than case control studies
- Time is the best/worst confounder of all

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Examples

- Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA* 2004;291:2847-50.
  - Measure height and weight in National Health and Nutrition Examination Survey (NHANES)
- Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 2007;298:2028-37.

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Observational Studies

- ✓ Case Reports
- ✓ Case Series
- ✓ Cross-sectional Surveys
- ➢ *Case-Control Study*
- Cohort Study

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Case Control Studies

- Observations regarding possible associations between a single outcome (usually a disease) and one or more hypothesized risk factors or exposures
- Well suited for studying
  - Rare diseases
  - Diseases with long latency periods
- Generally quicker and less expensive than cohort studies

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Case Control Studies

- Compare the prevalence or level of the possible risk factor between
  - Representative group of disease subjects
    - CASES
  - Representative group of disease-free
    - CONTROLS
- Same population

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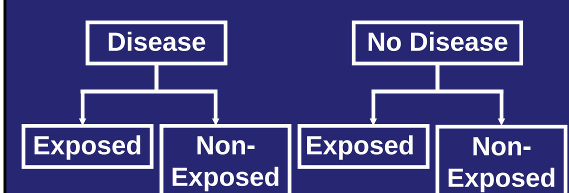
Case Control Studies



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Cases and Controls

- Cases represent all patients who develop disease
- Controls represent general ‘healthy’ population not developing the disease
- Information collected from cases and controls in the same way

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Cases

- Well defined population
  - Standardized selection criteria
  - Sometimes NESTED case control study (both groups nested in a large cohort study)
- Where?
  - Case registries
  - Admission records
  - Pathology logs
- High participation rate

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Controls

- Perfect control group?
  - Next to never exists
- Well defined population
  - Standardized selection criteria
- Sample of
  - General population (gen pop)
  - Neighborhood
  - Families
  - Hospital

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Case Control Studies

- Cost to obtain controls
- Multiple control groups!
  - Hospital control
  - Neighborhood control
- 'Adjustment' of results done during analysis (if subgroups large enough)

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Case Control Studies

- Again
  - All observations made using the same methods for cases and controls
  - Validity of measurement techniques established
- Selection, observation, and interviewer bias
- Use a 2x2 table

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Case Control Studies

Character-istic/ Exposure	Presence of Disease		Total
	Number with Disease	Number without Disease	
Present	a	b	a + b
Absent	c	d	c + d
Total	a + c	b + d	N

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Analyses

- Chi square or Fisher's exact tests
  - Proportion of cases exposed (a/a+c) compared to proportion of controls exposed (b/b+d)
- Continuous variables
  - Mean levels of cases compared to controls or non-diseased subjects using Student's t test, nonparametric tests, etc.
- Regression methods

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Positive Attributes

- Study the etiology of rare diseases
- Study multiple factors simultaneously
- Less time consuming and expensive
- 'If assumptions are met' associations and risk estimates are consistent with other types of studies

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Negative Attributes

- Do not estimate incidence
- Do not estimate prevalence
- Relative Risk indirectly measured
- Bias is an issue
- Hard to study rare exposure
- Temporal relationship difficult to document

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Example

- Case-control design was able to identify relationship of exposure to stilbesterol during mother's pregnancy with occurrence of rare tumor in female offspring many years later
- Herbst AL, Ulfelder H, Poskaner DC. Adenocarcinoma of the vagina: Association of maternal stilbesterol therapy with tumor appearance in young women. *N Engl J Med* 1974;284:878-881.

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Example

- Case-control design revealed unexpected link between intraocular lens material and risk of serious infection following cataract surgery.
- Menikoff JA, Speaker MG, Marmor M, Raskin EM. A Case-control Study of Risk Factors for Postoperative Endophthalmitis. *Ophthalmology* 1991;98:1761-1768.

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Observational Studies

- ✓ Case Reports
- ✓ Case Series
- ✓ Cross-sectional Surveys
- ✓ Case-Control Study
- ➢ *Cohort Study*

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Prospective or Longitudinal Cohort Studies

- Observations concerning associations between a given exposure (risk factor) and subsequent development of disease
- Examine multiple outcomes for a single exposure
- Directly calculate incidence of disease for each exposure group

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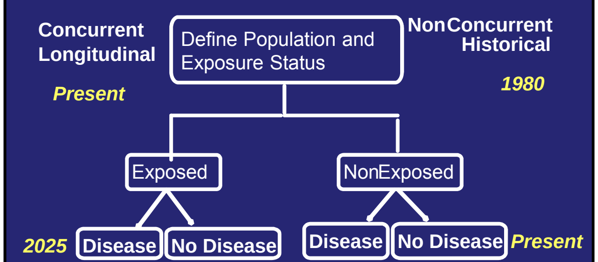
Prospective or Longitudinal Cohort Studies



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Concurrent Prospective

- Defined population is surveyed
- ID group with supposed risk factor
- ID similar group without risk factor
- Follow them forward in time
- Compare incidence rates between groups

- Could have a 0 in a cell on the 2x2 table

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Non-Concurrent or Retrospective

- Non-concurrent prospective study
  - Defined population with presence/absence of exposure ascertained in accurate, objective fashion in the past
    - Employment records
  - Data collected prospectively
- Retrospective study
  - Recall information
- Surveyed in present: disease occurrence
- Define incidence rates exposed/non-exposed

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Define Exposure, Non-Exposure

- Exposed and non-exposed are
  - Representative
  - Well-defined
- Absence of exposure (hard to be sure!)
  - Well defined
  - Assumed maintained in non-exposed during the study

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Outcomes Definitions

- Outcomes (disease outcomes) well defined prior to study
  - Not changed during course of study
- Death – easy to define, 'hard' outcome
- Subjective symptoms – harder to define

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Prospective or Longitudinal Cohort Studies

- Standard criteria applied to both exposed and non-exposed groups (again)
- Definitions of disease reliable and reproducible (again)
- Minimize loss to follow-up
  - Large non-response rates (>20%) raise questions as to the accuracy of the incidence rates

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Prospective or Longitudinal Cohort Studies

- Calculate incidence for the study period in exposed, unexposed, and test using Chi square (χ^2) or Fisher's exact test
- Measure association with relative risk (or odds ratio)
- 95% confidence limits
- Life-tables (another way to say "survival analysis")
- Regression

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Positive Attributes

- More representative of cases than case-control (incident cases)
- More natural history information
- Incidence rates available
- Relative risk directly estimated

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Positive Attributes

- 'Less' bias
- Relationship to exposure
- Temporal relationship
- Rare exposure with frequent cases among exposed

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Problematic Attributes

- LONG follow-up may be needed
- Free-living population follow-up is expensive
- Large population usually required
- Need baseline data
- Rare disease cannot be studied (rare exposures can be studied, though)
- Bias (loss to follow-up, assessment, etc)

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Prospective or Longitudinal Cohort Study Examples

- Prospective cohort study that showed early increase in risk of lung cancer and heart disease mortality and confirmed this over 50 years of follow-up
- Doll R, Hill AB. The mortality of doctors in relation to their smoking habits: A preliminary report. *Br Med J* 1954;228(i):1451-1455.
- Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years observations on male British doctors. *Br Med J* 2004;328:1519-1533.

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Prospective or Longitudinal Cohort Study Example

- Military medical records used to identify WW II head trauma exposure group and non-trauma comparison group who were traced and evaluated for dementia 50 years later
- Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology* 2000;55:1158-1166.

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Is enterovirus (EV) infection associated with increased risk of childhood type 1 diabetes in Taiwan? Identify the study design!

- National Health Insurance Research Database includes all claims data 2000-2008 for children 18 or younger; covers 99% of Taiwan residents
- Randomly sample with probability 0.5
- Identify children with first date of EV infection during 2000-2007 using set of ICD-9-CM codes
- Identify children without EV infection, excluding children with EV from 1996-2008 and then frequency match with sex and birth year
- Exclude children with prior diagnosis of type 1 diabetes

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Article

- Enterovirus infection is associated with an increased risk of childhood type 1 diabetes in Taiwan: a nationwide population-based cohort study
  - http://www.diabetologia-journal.org/files/Lin.pdf
- What are your thoughts about the questions raised by our course participant?
  - Are there internal or external validity issues with this cohort study?
  - What studies might follow this work?

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Longitudinal Study

- Robert M. Brackbill, James L. Hadler, Laura DiGrande, Christine C. Ekenga, Mark R. Farfel, Stephen Friedman, Sharon E. Perlman, Steven D. Stellman, Deborah J. Walker, David Wu, Shengchao Yu, and Lorna E. Thorpe
  Asthma and Posttraumatic Stress Symptoms 5 to 6 Years Following Exposure to the World Trade Center Terrorist Attack
  JAMA 2009;302:502–516

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Not All Cohort Studies Are Exposure Based

- Vegetarian diets and the incidence of cancer in a low-risk population. Tantamango-Bartley, Yessenia, Jaceldo-Siegl, Karen, Fan, Jing, Fraser, Gary. *Cancer Epidemiology, Biomarkers & Prevention (CEBP).* 2013 Feb, 22(2):286-94
- Pubmed ID: 23169929
- DOI: 10.1158/1055-9965.EPI-12-1060
- Adventist Health Study-2
  - 69 120 participants
  - 2 939 incident cancer cases

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Nested Studies

- Case-control
- Case-cohort

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Nested Case-Control

- Select from prospective cohort study
  - Stored samples
- Use baseline and follow up samples and data from newly occurring cases
  - Compare to matched or unmatched controls
- Efficient for expensive/difficult to measure
- Helps avoid selection and data collection biases
- Need to have enough cases in the cohort and need to store all the samples and data

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Nested Case-Cohort

- Select from cohort all incident cases and compare to random subset of non-cases
- Typically done when
  - Failure or event of interest is rare
  - Enormous resources to ascertain covariate values
- Very difficult to analyze

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Observational Studies

- Case Reports/Case Series
- Cross-sectional Survey
  - NHIS (National Health Interview Survey)
- Case-Control Study
  - Groups with or without outcome
  - Determine who was exposed to risk factor
- Cohort Study
  - Follow a group for a while
  - Cardiovascular Health Study

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Outline

- ✓ Definitions
- ✓ A few study designs
- ➢ Bias
- Conclusions

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A problem: Bias

- Bias – error due to difference between true value and values that are collected for the study
- Many types

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Selection Bias

- Prevalence Incidence bias
  - Exposed/impacted early? Might miss
    - Fatal episodes
    - Transient episodes
    - Silent cases
    - Case where evidence of exposure disappears with disease onset
- Non-respondent bias
  - Unwilling or unable to respond
  - Different exposures/outcomes from respondents?

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Observational or Interviewer Bias

- Diagnostic suspicion bias
- Exposure suspicion bias
- Recall bias
- Family information bias

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Outline

✓ Definitions
✓ A few study designs
✓ Bias
➢ Conclusions

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Observational Studies are Useful

- May be only alternative
  - Smoking in humans
  - Long term HAART treatment (antiretroviral therapy for HIV)
  - What happens in free living people (Cardiovascular Health Study)
- May be cheaper and faster than a trial

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Do Not Always Agree

- Hormone Replacement Therapy
- Observational trials
- Women's Health Initiative (WHI)
- Publication bias?
- Incorrect analyses of observational studies?
- Different populations?

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Observational Studies

- Why can observational studies only find a weaker degree of connection?
  - Subject to confounding
  - Can correct for what you know, but nothing to be done about the unknown
- Sometimes it is unethical to do a randomized trial (e.g. smoking)

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Design Issues

- Placebo effect
- Investigator and participant bias
- Unblinded treatment/assessment
- Regression to the mean
  - Natural reduction in disease activity over time
- Cheap, fast, get what you pay for

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Causation vs. Association

- Causation
  - Established by randomized experimental studies and clinical trials
- Association
  - Observational studies can merely find association between a risk factor and an response

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What do I do?

- Measure everything you can
- Build and investigate models
- Test those models on different data

- Try propensity scores
- Try other methods

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Yes there are problems, BUT

- One of the biggest mistakes is trying to design a randomized study when we need an observational study
- Alternative, predecessor, follow-up studies
- Population assessment

- It also is a mistake to refuse to do a creative randomized study

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Can we randomize in the following cases?

- Rapidly fatal disease with no treatment
  - Never forget, “no treatment” is a treatment alternative and sometimes a superior one
- Long latency period
- Breastfeeding
  - For what in whom? (ethics, preference)
- Second hand smoke
- Birth control
- Rare outcome

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How to Defend Non-Randomized Studies

- Randomization is a research ‘norm’
  - When a strong rationale is there, one deviates from the norm
- Admit limitations to non-randomized study
- Explain why randomization is far worse an option to answer the study question
- Document how minimizing problems with study approach

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Observation: the First Step

- Many crucial discoveries in medical history based on observations of a keen individual
  - Hand washing reduces infection
    - Sushruta 600 BC, Hippocrates 400 BC
  - Milk maids did not get small pox, led Edward Jenner to discovery of small pox vaccine 1796
    - Practice of variolation existed since 1000 BC in India, 10^{th} Century china
  - Cases of cholera clustered around a water source in 1854 outbreak
    - John Snow considered father of modern epidemiology

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More Information

- Publishing guidelines
  - STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)
  - MOOSE (Meta-analysis of Observational Studies in Epidemiology)
- CDC classroom and self-guided course information
  - www.cdc.gov/excite/classroom/intro_epi.htm
  - www.cdc.gov/osels/scientific_edu/ss1978/

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Thanks!

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

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Extra Material: Introduction to Odds Ratio (OR) and Relative Risk (RR)

Thanks to Steve Simon
http://www.pmean.com/01/oddsratio.html

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Ratios and Differences

- Odds ratios are common
  - Thanks, Logistic regression
- Many better understand risk ratios and risk differences
- Feasible for risk ratio and odds ratio to decrease and risk difference to increase
  - So what do you believe?
  - 2008 Stat Med Brumbeck and Berg

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Odds Ratios and Relative Risk (Risk Ratios)

- Both compare the relative likelihood of an even occurring between two distinct groups
- Both have limitations
- While relative risk (RR) seems more intuitive, sometimes it is unclear which RR we are comparing

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Statistics for Binary Data (1)

- Let p = probability of an event
  - 30-day survival in a study of septic patients
  - Proportion of TB cases that are MDR
- Relative risk (RR): p_1/p_2
  - Good for prospective studies
  - RR not valid in retrospective case-control studies, biased because probability of being a case is enriched by design

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Statistics for Binary Data (2)

- Odds = p/1-p
  - Used in logistic regression, especially in case-control studies when RR cannot be used
  - Example: for 6-sided die with rolls {1,2,3,4,5,6}
    - odds of rolling a 3 is 1/5; compare to Prob(3)=1/6.
    - the odds of rolling an even number is 3/3=1
- Odds are different from probability
- Comparing odds (odds ratio) different than RR (p_1/p_2).

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Odds Ratio (OR)

- Odds are related to probability
  - Odds = p/(1-p)
- Probability of horse winning race is 50%, odds are 1/1
- Probability of horse winning race is 25%, odds are 1/3 for win or 3 to 1 against win

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Case Control Studies

Character-istic/ Exposure	Presence of Disease		Total
	Number with Disease	Number without Disease	
Present	a	b	a + b
Absent	c	d	c + d
Total	a + c	b + d	N

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Odds

- If probability of diseased person being exposed is a/(a+c), odds are:

$$\frac{\frac{a}{a+c}}{1-\frac{a}{a+c}}$$

Odds and Odds Ratio

- Odds of exposure in cases: A/C
- Odds of exposure in controls: B/D

Odds Ratio (OR) = [A/C] / [B/D] = [AD] / [BC]

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Relative Risk (RR)

- Risk in exposed [A/(A+B)] divided by risk in unexposed [C/(C+D)]
- Simple comparison between two groups
- RR = 1 no difference in risk between the groups

- But not used in case-control studies unless…..

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Rare Disease, OR, RR

- A is small compared to B
  - All with exposure, # with disease vs. # without
- C is small compared to D
  - All without exposure, # w/ dx vs. # w/o dx
- Odds ratio estimates the relative risk well
  - OR is always further from unity
  - OR overestimates the magnitude of protective or harmful association

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Why we debate the interpretation

- Group A has 25% chance of death
- Group B has 50% chance of death
- Group B has it twice as bad! (Relative Risk)
- Nobody says they have an odds ratio of 3; that seems weird (true though)
  - Actually, sadly, someone will see the odds ratio and say that you are 3 times more likely to die in Group B. Which is False. They might say the odds are 3 times higher, which will be misinterpreted.

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More Interpretation

- 25% mortality from current weird flu
- New mutation
- 75% mortality
- Relative risk of 3, odds ratio of 9
- Risk difference has an even different interpretation.

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Use OR When

- Case Control Designs (except maybe rare events)
- Need covariate adjustment for confounders, etc
  - It is feasible to adjust a relative risk but tricky
- But be careful when prevalence is not rare
  - OR can get extreme values

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Relative Risk

- For every problem Relative Risk can be computed two possible ways
  - Risk of death, Risk of survival
  - Does an intervention increase the probability of breast feeding success, or decrease the probability of breast feeding failure
- Small relative change in the probability of one event's occurrence is usually associated with a large relative change in the even not occurring

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Risk: Difference vs. Ratio

- Difference in the absolute risks
  - Attributable risk
  - Excess risk attributable to exposure
- Relative Risk (RR)
  - Ratio of two absolute risks
- Hazard Ratio (HR)
  - Ratio between predicted risk of an event for member of A and that of a member of B, holding everything else constant
- Is ratio the best to talk to people?

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Difference vs. Ratio

- Invasive breast cancer WHI (JAMA 288[3]:321-33)
- Increase observed estrogen+progestin group
  - Difference in risk
    - 38 vs 30 per 10 000 person years
  - Hazard Ratio (HR)
    - 26%
- Is your personal risk 26%? No
- 8 more invasive breast cancers per 10 000 person years? Yes

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Ratios and Differences

- Odds ratios are common
  - Thanks, Logistic regression
- Many better understand risk ratios and risk differences
- Feasible for risk ratio and odds ratio to decrease and risk difference to increase
  - So what do you believe?
  - 2008 Stat Med Brumbeck and Berg

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Odds Ratios and Relative Risk (Risk Ratios)

- Both compare the relative likelihood of an even occurring between two distinct groups
- Both have limitations
- While relative risk (RR) seems more intuitive, sometimes it is unclear which RR we are comparing

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2 Examples (KC Mercy)

- Physician cardiac catheterization recommendations for patients with chest pain (watched videos)
- OR is 0.57 or 1.74
  - Authors report (Schulman et al 1999) physicians make different recommendations for male patients than for female patients

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Data

	No Cath	Cath	Total
Male	34 (9.4%)	326 (90.6%)	360
Female	55 (15.3%)	305 (84.7%)	360
Total	89	631	720

- Schwartz critique said OR overstated the effect
  - Relative Risk only 0.93 (reciprocal 1.07)
- But is it appropriate to look at 90.6% vs 84.7%?
- Comparing rates for recommending a less aggressive intervention (9.4% vs 15.3%)
  - Relative Risk 1.63, reciprocal 0.61

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Example

	Continued	Stopped	Total
Treatment	19 (37.3%)	32 (62.7%)	51
Control	5 (8.8%)	52 (91.2)	57
Total	24	84	108

- Look at 3mo, did breastfeeding (BF) continue with intervention? Or Stopped?
- ‘Failure’ RR=0.69 (recip 1.45)
  - OR=0.16 (recip 6.2)
- ‘Successful’ breastfeeding leads to different #s
- (do Survival analysis)

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Odds Ratio have this issue?

- OR is not dependent on focusing on one event's occurrence or the failure to occur, one is the reciprocal of the other
- But they have other issues

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What is Important

- Which event matters? Likely they both do
- Some say absolute changes in risk matter more
  - Who cares if you triple your risk of a rare outcome [well….] 3*0.00000001 is basically 0
  - 10% change in a common outcome is HUGE
- No wonder they say we lie with statistics

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Changes

- 10 fold increase in lung cancer death
- 2 fold increase in risk of death from heart disease
- But heart disease kills a lot more people in general
- This is why some people discuss number needed to treat (NNT) and number needed to harm (NNH)

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NNT (from pmean)

- Daily low dose aspirin for a year (genpop): NNT=102
  - One fewer stroke on average for what?
    - Rates may not be homogenous over time, so careful with the person years
- Giving prophylaxis antibiotic after a dog bite: NNT=16
  - For every 16 dog bites treated with antibiotics we see one fewer infection on average

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For Vaccines

- See lots of NNT, NNH and the balance between
- Numbers make ‘sense’ to people but they have strong assumptions

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