

## Design of Epidemiologic Studies

Laura Lee Johnson, Ph.D.

Statistician

National Center for Complementary and  
Alternative Medicine

johnslau@mail.nih.gov

Fall 2008



---

---

---

---

---

---

---

---

## Objectives

- Intuitive understanding of some study designs and statistics used in public health research
- Understand and perform some simple but useful analyses & sample size calculations
- Little language to work with statisticians and epidemiologists



---

---

---

---

---

---

---

---

## Who are you?

- How many have had a class in biostatistics, epidemiology, or research design?
- How many have degrees in one of those fields?
- How many have attended a few lectures on those topics but nothing more?
- How many people know what logistic regression is and with the right computer, software, and data could implement it?
- Why did you sign up? How did you hear about this course?



---

---

---

---

---

---

---

---

## What I Hope You Learn

- Need to know something about the population under study
- Prevalence matters
  - Positive and negative predictive values, not only sensitivity and specificity
- IRB wants a sample size justification
- Competing risks are an issue in survival (time to event) analysis



---

---

---

---

---

---

---

---

## Epidemiology & Biostatistics

- Design of Epidemiologic Studies
- Clinical Study Development
- Issues in Randomization
- Principles of Hypothesis Testing
- Sample Size and Power
- Conceptual Approach to Survival Analysis



---

---

---

---

---

---

---

---

## What to Include in Design What to Include in Manuscript

- <http://www.consort-statement.org/>
  - Look at the Extensions (tab up top)
- QUOROM (meta analysis RCTs)
- MOOSE (meta analysis of observational studies)
- STROBE (epi)
- STARD (diagnostic accuracy)
- Many others



---

---

---

---

---

---

---

---

## Housekeeping

- Six lectures
  - Overlaps: complement and help lead you a bit deeper with each discussion
- Appendices, book and software lists are for your reference; I do not care what you use
- Slides: color (not needed) vs. bwprint



---

---

---

---

---

---

---

---

## 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



---

---

---

---

---

---

---

---

## Objectives: Design of Epi Studies Lecture

- What is Epidemiology?
- Along with the next few lectures, what are several types of studies



---

---

---

---

---


---

---

---

**Do Not Confuse**

- Association
- Causality
- Confounding



---

---

---

---

---

---


---

---

**Outline**

➤ *What is Epidemiology?*

- Vocabulary (1)
- Types of studies
- Questions



---

---

---

---

---


---

---

---

**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



---

---

---

---

---

---

---

---

## What is Epidemiology?

- Studying epidemics
  - EIS (Epidemic Intelligence Service) at CDC



---

---

---

---

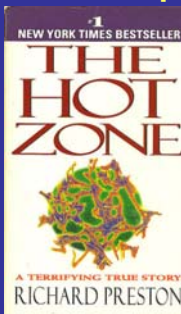
---

---

---

---

## EIS? Think Outbreak Epi - Epidemic



---

---

---

---

---

---

---

---

## 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



---

---

---

---

---

---

---

---

## Big Studies? Are They All Refuted?

- All the epidemiologic studies prior to Women's Health Initiative (WHI)
  - They did not agree, really
  - Now with new stat methods, well, hindsight was 20/20
  - Or adjust for SES.....
- Prevention?
- NYT Magazine Sept 16, 2007:  
<http://tinyurl.com/5jjhkh>



---

---

---

---

---

---

---

---

## What 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
- What you don't know and don't measure



---

---

---

---

---

---

---

---

## Epidemiology and Hypotheses

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



---

---

---

---

---

---

---

---

## Generating Hypotheses

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



---

---

---

---

---

---

---

---

## 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



---

---

---

---

---

---

---

---

## Outline

- ✓ What is Epidemiology?
- **Vocabulary (1)**
- Types of studies
- Questions



---

---

---

---

---

---

---

---

## Words I Might Use

- Model:  $y = \beta_0 + \beta_1x_1 + \beta_2x_2 + \varepsilon$
- Variable (in model) = Covariate = x
  - Treatment
  - Age
  - Gender
- Coefficient = Coef =  $\beta \approx$  Association
- Y is called outcome, endpoint, but not CAUSAL



---

---

---

---

---

---

---

---

## Covariates May Be

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



---

---

---

---

---

---

---

---

## 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



---

---

---

---

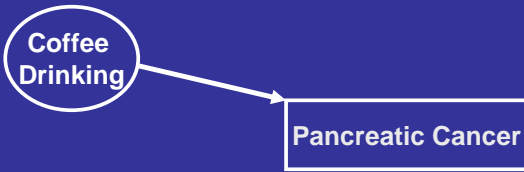
---

---

---

---

## Coffee and Pancreatic Cancer



---

---

---

---

---

---

---

---

## Coffee and 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 but it is not a result of coffee drinking



---

---

---

---

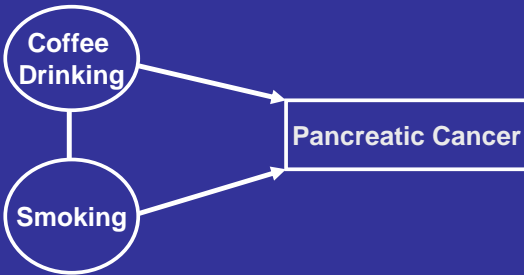
---

---

---

---

## Coffee and Pancreatic Cancer



---

---

---

---

---

---

---

---

## What is Confounding?

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



---

---

---

---

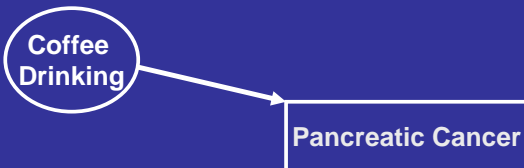
---

---

---

---

## Coffee Causes Pancreatic Cancer



---

---

---

---

---

---

---

---

## 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*



---

---

---

---

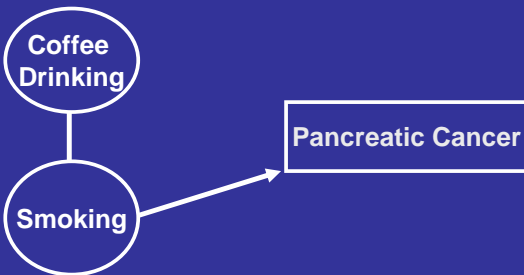
---

---

---

---

## Smoking is a Confounder: Coffee does NOT cause Pancreatic CA



---

---

---

---

---

---

---

---

## How to Handle Confounding

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



---

---

---

---

---

---

---

---

## Is there more to Confounding? Yes!

- Residual confounding
  - Poor measure of the confounder
    - For public health a big one: poor measure of physical activity
  - Even when you put the confounder as measured in the model, not really explaining the effect of (say) real physical activity in the model
- Ex: Ever Smoked yes/no; not pack years



---

---

---

---

---

---

---

---

## Randomization means 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 the item



---

---

---

---

---

---

---

---

## Effect Modification

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



---

---

---

---

---

---

---

---

## Smoking, Asbestos 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

- <http://tinyurl.com/66oxn6>
- The phrase effect modification, defined for different professions
  - Biostatisticians, public health workers, physicians, lawyers, biologists, epidemiologists,....



---

---

---

---

---

---

---

---

## Prevalence, Incidence,....

- Prevalence
  - # with disease / # at risk
  - If you take a snap shot
  - How many diabetics in the US 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 dx



---

---

---

---

---

---

---

---

## Sensitivity, Specificity

- Sensitivity: how good is a test at correctly IDing people who have disease
  - Can be 100% if you say everyone is ill (all have positive result)
  - Useless test with bad Specificity
- Specificity: how good is the test at correctly IDing people who are well
- ROC curves and Area Under the Curve (AUC; pAUC)



---

---

---

---

---

---

---

---

## Bias

- Selection Bias
- Observational or interviewer bias



---

---

---

---

---

---

---

---

## 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?



---

---

---

---

---

---

---

---

## Observational / Interviewer Bias

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



---

---

---

---

---

---

---

---

## What do I do?

- Measure everything you can
- Build and investigate models
- Test those models on different data
  
- Try propensity scores
- Try other methods



---

---

---

---

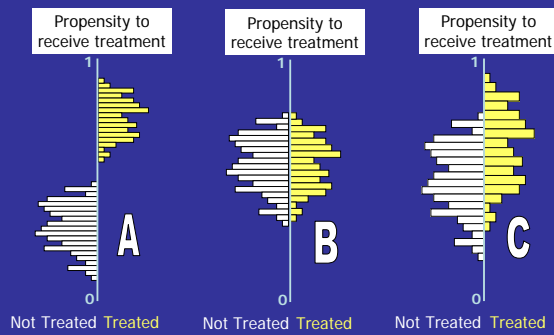
---

---

---

---

## How Much Overlap Do We Want?



---

---

---

---

---

---

---

---

## Outline

- ✓ What is Epidemiology?
- ✓ Vocabulary (1)
- *Types of studies*
  - Questions



---

---

---

---

---

---

---

---

## Study Design Taxonomy

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



---

---

---

---

---

---

---

---

## Ideal Study - Gold Standard

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



---

---

---

---

---

---

---

---

## Observational Studies

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



---

---

---

---

---

---

---

---

## 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



---

---

---

---

---

---

---

---

## Case Reports and Series

- Clear definitions of phenomenon
- Same definitions for all individuals in series
- Observations reliable and reproducible
- GOOD observational studies very useful



---

---

---

---

---

---

---

---

### Case Reports and Series - Analyses

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



---

---

---

---

---

---

---

---

### Case Reports and Series

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



---

---

---

---

---

---

---

---

### Case Reports and Series

- Initial report of five cases of pneumocystis pneumonia in previously healthy, homosexual men
- CDC. Pneumocystis pneumonia-- Los Angeles. *MMWR* 1981; 30:250-2.



---

---

---

---

---

---

---

---

## Observational Studies

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



---

---

---

---

---

---

---

---

## Crosssectional or Prevalence Surveys

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



---

---

---

---

---

---

---

---

## Crosssectional 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



---

---

---

---

---

---

---

---

## Crosssectional or Prevalence Surveys

- Present
  - Prevalence (% or cases per 10<sup>5</sup>, etc)
  - Mean or median levels of relevant factors
  - Subset by important subgroups
- Analyses
  - Categorical
    - Chi-square, Fisher's Exact Tests
  - Continuous
    - t-Test or other analyses



---

---

---

---

---

---

---

---

## Observational Studies

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

		Outcome	
		Disease	No disease
Risk Factor	Y		
	N		



---

---

---

---

---

---

---

---

## Crosssectional or Prevalence Surveys

- 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?



---

---

---

---

---

---

---

---

### Crosssectional or Prevalence Surveys

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



---

---

---

---

---

---

---

---

### Crosssectional or Prevalence Surveys

- 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



---

---

---

---

---

---

---

---

### Crosssectional or Prevalence Surveys

- 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.
  - Prevalence data on overweight and obesity using measured 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.



---

---

---

---

---

---

---

---

## Observational Studies

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



---

---

---

---

---

---

---

---

## Case Control Studies

- Observations regarding possible associations between a disease and one or more hypothesized risk factors



---

---

---

---

---

---

---

---

## 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



---

---

---

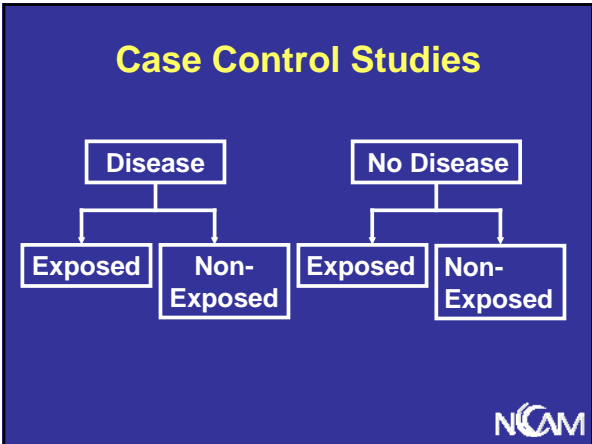
---

---

---

---

---




---

---

---

---

---

---

---

---

### Case Control Studies

- 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

NCAM

---

---

---

---

---

---

---

---

### Case Control Studies

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

NCAM

---

---

---

---

---

---

---

---

## Case Control Studies

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



---

---

---

---

---

---

---

---

## Case Control Studies

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



---

---

---

---

---

---

---

---

## 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



---

---

---

---

---

---

---

---

## 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



---

---

---

---

---

---

---

---

## Case Control Studies - 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 (especially in cross-sectional studies)
  - Mean levels of cases compared to controls or non-diseased subjects using Student's t test, non-parametric tests, etc.



---

---

---

---

---

---

---

---

## 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



---

---

---

---

---

---

---

---

## 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:  $B/D$

$$\text{Odds Ratio (OR)} = [A/C] / [B/D] = [AD] / [BC]$$



---

---

---

---

---

---

---

---

## Relative Risk (RR)

- Risk in exposed  $[A/(A+B)]$  divided by risk in unexposed  $[C/(C+D)]$
- But not used in case-control studies unless.....



---

---

---

---

---

---

---

---

## 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



---

---

---

---

---

---

---

---

## Case Control Studies

- 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



---

---

---

---

---

---

---

---

## Case Control Studies

- 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



---

---

---

---

---

---

---

---

## Case Control Studies

- 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.



---

---

---

---

---

---

---

---

## Observational Studies

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



---

---

---

---

---

---

---

---

## Prospective or Longitudinal Cohort Studies

- Observations concerning associations between a given exposure (risk factor) and subsequent development of disease



---

---

---

---

---

---

---

---

## Prospective or Longitudinal Cohort Studies

- 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




---

---

---

---

---

---

---

---

## Prospective or Longitudinal Cohort Studies

- If non-concurrent prospective study
  - Really, retrospective or historical control study
- Defined population with presence/absence of exposure ascertained in accurate, object fashion in the past
  - Employment records
- Surveyed in present: disease occurrence
- Define incidence rates exposed/non




---

---

---

---

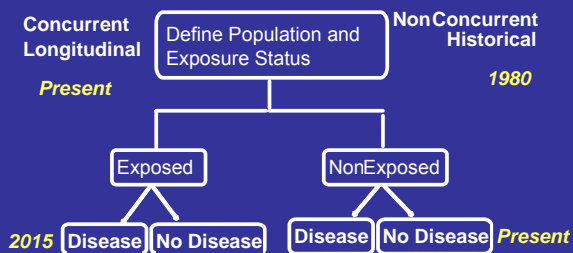
---

---

---

---

## Prospective or Longitudinal Cohort Studies




---

---

---

---

---

---

---

---

### Prospective or Longitudinal Cohort Studies

- Exposed and non-exposed are
  - Representative
  - Well-defined
- Absence of exposure
  - Well defined
  - Assumed maintained in non-exposed during the study



---

---

---

---

---

---

---

---

### Prospective or Longitudinal Cohort Studies

- 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



---

---

---

---

---

---

---

---

### 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



---

---

---

---

---

---

---

---

### Prospective or Longitudinal Cohort Studies

- Calculate incidence for the study period in exposed, unexposed, and test using Chi square ( $\chi^2$ ) or Fisher's exact test
- Measure association with relative risk (or odds ratio)
- 95% confidence limits (tomorrow)
- Life-tables (last lecture)



---

---

---

---

---

---

---

---

### Prospective or Longitudinal Cohort Studies

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



---

---

---

---

---

---

---

---

### Prospective or Longitudinal Cohort Studies

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



---

---

---

---

---

---

---

---

### Prospective or Longitudinal Cohort Studies

- 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 exposure, yes)
- Bias (loss to follow-up, assessment, etc)



---

---

---

---

---

---

---

---

### Prospective or Longitudinal Cohort Studies

- 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.



---

---

---

---

---

---

---

---

### Prospective or Longitudinal Cohort Studies

- 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.



---

---

---

---

---

---

---

---

## Summary



---

---

---

---

---

---

---

---

## 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



---

---

---

---

---

---

---

---

## Observational Studies are Useful

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



---

---

---

---

---

---

---

---

## Do Not Always Agree

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



---

---

---

---

---

---

---

---

## Questions?



---

---

---

---

---

---

---

---