Overview of Pharmacoepidemiology Research Methodology

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CPeRT Center for Pharmacoepidemiology Research and Training

ISPE

Course Overview: Monday 6/18

Topic	Time
Overview of Pharmacoepidemiology Research Methodology	10 am-12:00 PM
Cohort Studies	12:15 – 1:15 PM
Case-Control/Cross-Sectional Studies	2:15 – 4:15 PM
Statistical Test Selection	4:30 – 5:30 PM

Course Overview: Tuesday 6/19

Topic	Time
Databases for Pharmacoepidemiology Research	10 am-12:00 PM
Measurement of Exposure and Outcomes in Databases	12:15 – 1:15 PM
Confounding and Bias	2:15 – 4:15 PM
Protocol Development and Pharmacoepi Thought Exercises	4:30 – 5:30 PM

Learning Objectives

- **Understand importance of the study question/hypothesis to research**
- **Learn criteria supporting causal association**
- **Gain familiarity with study design options**
- **Learn measures of disease frequency, exposure effect**

Outline

- **Overview of the scientific method**
- **Criteria supporting causal association**
- **Options in research design**
- **Disease frequency and exposure effect**

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From The Book of Daniel, Chapter One

12 Try thy servants, I beseech thee, ten days; and let them give us pulse (leguminous plants) to eat and water to drink...

13 Then let our countenances be looked upon before thee; and the countenances of the youths who eat of the king's food...

14 So, he harkened unto them and tried them in this matter, and tried them ten days...

15 And at the end of ten days their countenances appeared fairer, and they were fatter in the flesh, than all of the youths that did eat of the king's food.

Galen, Second Century

All who drink of this remedy recover in a short time, except those whom it does not help, who all die.

Therefore, it is obvious that it fails only in incurable cases.

Lind's Treatise on Scurvy, Part 1

... I took twelve patients... (with) scurvy... Their cases were as similar as I could have them... They lay together in one place and had one diet common to all. Two of these were ordered each a quart of cider a day. Two others took twenty-five drops of elixir of vitriol three times a day upon an empty stomach. Two others took two spoonfuls of vinegar three times a day... Two of the worst patients were put upon a course of seawater. Of this they drank half a pint very day. Two others had each two oranges and one lemon given them every day.

C.P. Stewart and D. Guthrie, Eds. Edinburgh University Press, 1953.

Lind's Treatise on Scurvy, Part 2

The two remaining patients took an electuary recovered by a hospital surgeon made of garlic, mustard, balsam of peru and myrrh. The consequence was that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them being at the end of six days fit for duty. The other was the best recovered of any in his condition and was appointed nurse to the rest of the sick.

C.P. Stewart and D. Guthrie, Eds. Edinburgh University Press, 1953.

What is Research?

- **Systematic investigation into and study of materials, sources, etc. to establish facts and reach new conclusions**
- **Endeavor to discover new facts by a course of critical investigation**

[Oxford Concise Dictionary]

What is Research?

- **What we do when we have a question or problem we want to resolve**
- **We may think we know answer (obvious?)**
- **But until we subject problem to <u>rigorous scientific scrutiny</u>, our knowledge remains guesswork**

What is Research?

1. Formulate research question, hypothesis

↓

2. Determine how to answer questions
   - Have others examined it?
   - Use appropriate methods
   - Consider, mitigate limitations

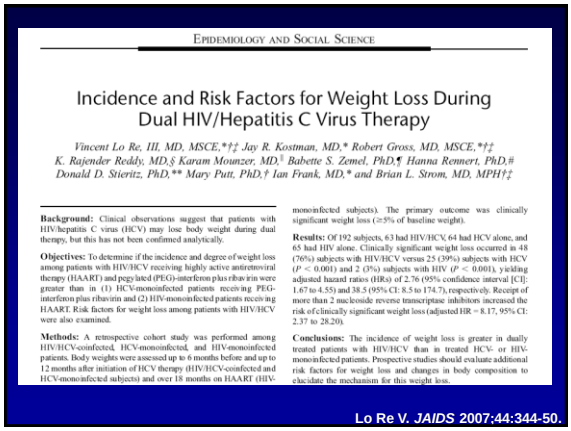
↓

3. Present your results, conclusions

Hypothesis: Prediction of Expected Outcome

- How manipulation of independent variables affects dependent variable
  - How much (magnitude)
  - In what way (direction)
- Description of relation between variables
  - Precision (e.g., cancer prevalence)

Hypothesis is tested in a study



EPIDEMIOLOGY AND SOCIAL SCIENCE

Incidence and Risk Factors for Weight Loss During Dual HIV/Hepatitis C Virus Therapy

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Background: Clinical observations suggest that patients with HIV/hepatitis C virus (HCV) may lose body weight during dual therapy, but this has not been confirmed analytically.

Objectives: To determine if the incidence and degree of weight loss among patients with HIV/HCV receiving highly active antiretroviral therapy (HAART) and peg/ated (PEG)-interferon plus ribavirin were greater than in (1) HCV-monoinfected patients receiving PEG-interferon plus ribavirin and (2) HIV-monoinfected patients receiving HAART. Risk factors for weight loss among patients with HIV/HCV were also examined.

Methods: A retrospective cohort study was performed among HIV/HCV-coinfected, HCV-monoinfected, and HIV-monoinfected patients. Body weights were assessed up to 6 months before and up to 12 months after initiation of HCV therapy (HIV/HCV-coinfected and HCV-monoinfected subjects) and over 18 months on HAART (HIV-monoinfected subjects). The primary outcome was clinically significant weight loss (≥5% of baseline weight).

Results: Of 192 subjects, 63 had HIV/HCV, 64 had HCV alone, and 65 had HIV alone. Clinically significant weight loss occurred in 48 (76%) subjects with HIV/HCV versus 25 (39%) subjects with HCV ($P < 0.001$) and 2 (3%) subjects with HIV ($P < 0.001$), yielding adjusted hazard ratios (HRs) of 2.76 (95% confidence interval [CI]: 1.67 to 4.55) and 38.5 (95% CI: 8.5 to 174.7), respectively. Receipt of more than 2 nucleoside reverse transcriptase inhibitors increased the risk of clinically significant weight loss (adjusted HR = 8.17, 95% CI: 2.37 to 28.20).

Conclusions: The incidence of weight loss is greater in dually treated patients with HIV/HCV than in treated HCV- or HIV-monoinfected patients. Prospective studies should evaluate additional risk factors for weight loss and changes in body composition to elucidate the mechanism for this weight loss.

Lo Re V. *JAIDS* 2007:44:344-50.

Definition: Epidemiology

- Study of distribution and determinants of disease in populations
- Basic science underlying much of public health and preventive medicine

Definition: Pharmacepidemiology

- Study of the uses and effects/side effects of drugs in populations
- Borrows from epidemiology and pharmacology
- Goal: Rational use of drugs to improve outcomes

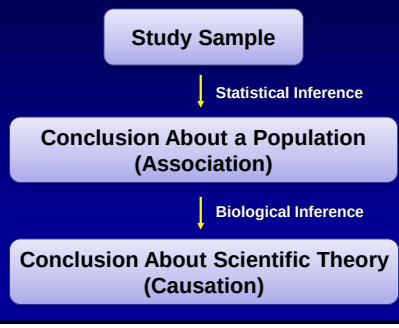
Definition: Biostatistics

- Statistical processes applied to biological data:
  - Collection
  - Analysis
  - Interpretation
- Concerned with application to biomedical sciences

Classical Scientific Method

- Observation of some phenomenon
  - Systematic, occasional, accidental
- Some idea of explanation (hypothesis)
  - Conjecture, intuition, guesswork
  - May be informed by related work
- Test (re-test) hypothesis

Overview of the Scientific Method



Outline

- Overview of the scientific method
- Criteria supporting causal association
- Options in research design
- Disease frequency and exposure effect

Types of Associations Between Factors Under Study

- None (independent)
- Artifactual association
  - Chance (unsystematic variation)
  - Bias (systematic variation)
- Indirect association
- Causal association (direct association)

Criteria Supporting Causal Nature of an Association

- Coherence with existing information
- Time sequence
- Specificity
- Consistence
- Strength of association
  - Quantitative strength
  - Dose-response relationship
  - Study design

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Options in Research Design

Descriptive Studies

- Case reports
- Case series
- Analysis of secular trends

Analytic Studies

- Case-control
- Retrospective cohort
- Prospective cohort
- Experimental

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Case Report

- Definition
  - Clinical description of single patient
- Use
  - Hypothesis generation
- Main limitation
  - Generalizability: patient may be atypical

Case Series

- Definition
  - Clinical description of patients with a disease
- Use
  - Characterization of the illness
- Main limitation
  - No control group: cannot determine which factors are unique to the illness

Analysis of Secular Trends (Correlational Studies)

- Definition
  - Compares geographical and/or time trends of an illness to trends in risk factors
- Use
  - Rapid, easy support/disproof of hypotheses
- Main limitation
  - Cannot differentiate among those hypotheses consistent with the data

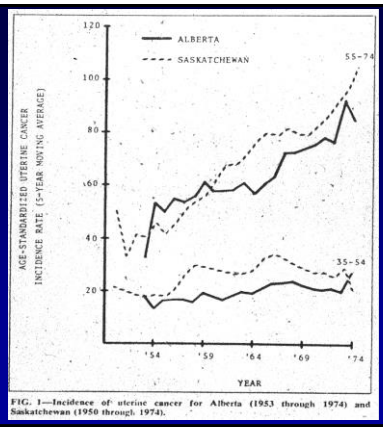
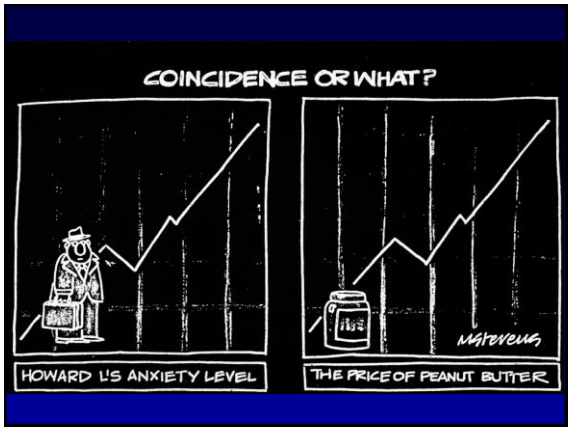


FIG. 1—Incidence of uterine cancer for Alberta (1953 through 1974) and Saskatchewan (1950 through 1974).



Options in Research Design

Descriptive Studies

- Case reports
- Case series
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Analytic Studies

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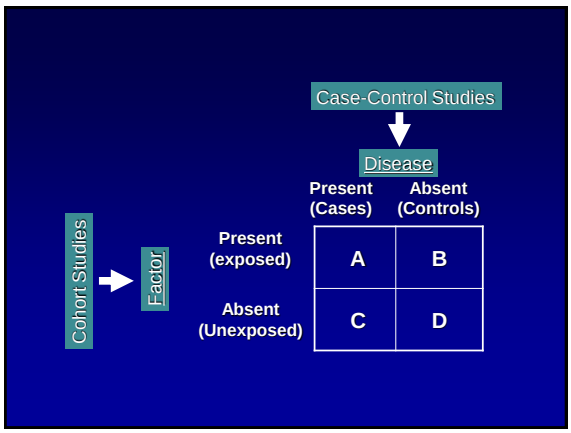
Case-Control Study

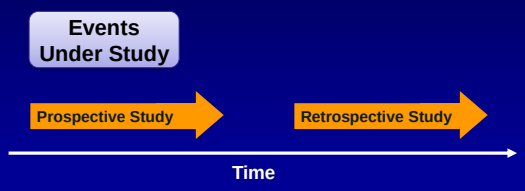
- Definition
  - Compares diseased to non-diseased patients, looking for differences in risk factors
- Use
  - Study risk factors for disease (esp. rare)
- Main limitation
  - Biases must be avoided (e.g., historically obtained data must be complete, accurate)

Cohort Study

- Definition
  - Compares patients with risk factor/exposure to others without for differences in outcome
- Use
  - Study any number of outcomes from singly risk factor/exposure
- Main limitation
  - Prolonged, costly

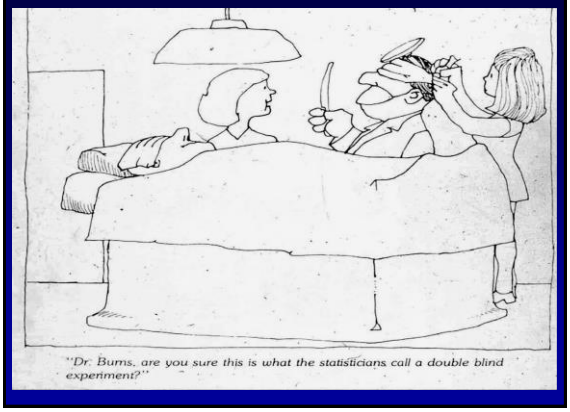


Retrospective vs. Prospective Studies



Experimental Study

- Definition
  - Risk factor/exposure of interest is controlled by investigator; randomization generally used
- Use
  - Most convincing demonstration of causality
- Main limitation
  - Logistical, ethical difficulties in application to human studies



Options in Research Design - 1

Descriptive Studies

- Case reports
- Case series
- Analysis of secular trends

Analytic Studies

- Case-control
- Retrospective cohort
- Prospective cohort
- Experimental

Options in Research Design - 2

- Options in directionality
  - Case-control study
  - Cohort study (follow-up)
    - Experimental study (clinical trial)
- Options in timing
  - Retrospective
  - Prospective
  - Cross-sectional (exposure, outcome measured at same time)

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Different Measures Express Disease Frequency and Exposure Effects

Measures of Disease Occurrence

- Prevalence
- Cumulative Incidence = Risk
- Incidence Rate = Incidence Density

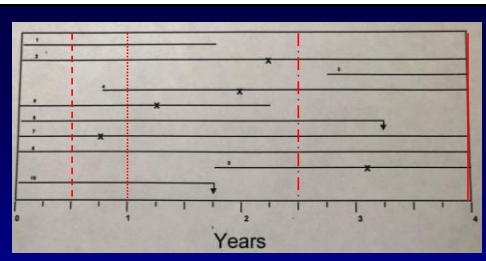
Measures of Exposure Effect

- Relative Risk
- Attributable Risk

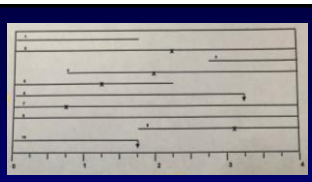
Prevalence

$$= \frac{\text{No. diseased persons}}{\text{Total population}} \text{ at a given point in time}$$

- Estimates burden of disease
- Useful in clinical assessment, decision-making
- Is a proportion (no units)
- Dependent on incidence, duration of disease

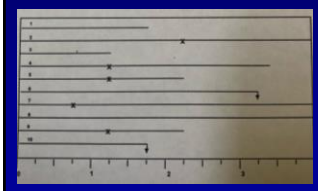


Time Point	Prevalence
0.5 years	0/7
1.0 years	1/8
2.5 years	3/6
4.0 years	4/6



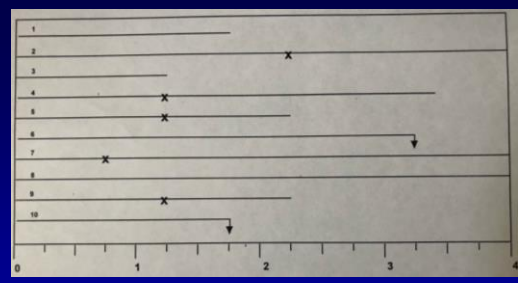
Calendar Years

Population's morbidity and mortality experience over calendar time



Years Study Time

Population's (viewed as a fixed cohort) morbidity and mortality experience over calendar time



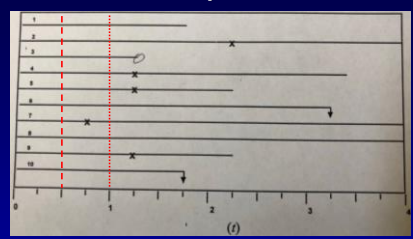
This fixed cohort has complete follow-up for 1.25 years

Cumulative Incidence

$$= \frac{\text{No. new cases of disease between } t_0 \text{ and } t_1}{\text{Total disease-free persons at risk at } t_0}$$

- Probability of disease over specified time period
- Assumes complete follow-up
- Is a proportion without units
- Must refer to a specific time frame

$$\frac{\text{No. new cases of disease between } t_0 \text{ and } t_1}{\text{Total disease-free persons at risk at } t_0}$$



Time Period (t_0-t)	Cumulative Incidence
0.5 years	0/10
1.0 years	1/10
2.0 years	?

Need Complete Follow-up!

Incidence Rate

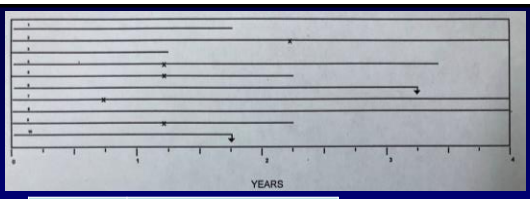
$$= \frac{\text{No. new cases of disease during time period}}{\text{Total person-time among individuals at risk}}$$

- Also referred to as "incidence density"
- Measure of occurrence of disease in susceptible
- Does not assume complete follow-up
- Units: events/person-time (e.g., months, years)

Incidence Rate

$$= \frac{\text{No. new cases of disease during time period}}{\text{Total person-time among individuals at risk}}$$

Sum of the time each individual is followed until the event, death, or loss to follow-up



Individual #	Person-Time
1	1.75 person-years
2	2.25 person-years
3	1.25 person-years
4	1.25 person-years
5	1.25 person-years
6	3.25 person-years
7	0.75 person-years
8	4.00 person-years
9	1.25 person-years
10	1.75 person-years

5 events observed

Total Person-time = 18.75 person-years

Incidence Rate

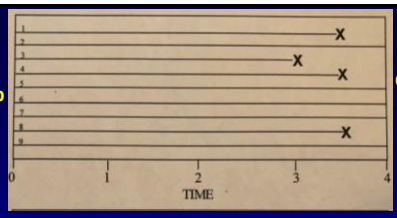
$$= \frac{\text{No. new disease events during time period}}{\text{Total person-time among individuals at risk}}$$

$$= \frac{5 \text{ events}}{18.75 \text{ person-years}} = 0.27 \text{ events/person-year}$$

Incidence Rates

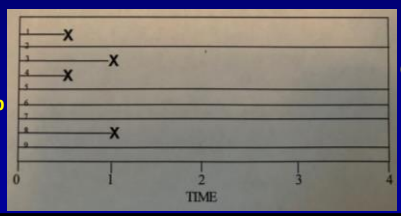
- Preferable to cumulative incidence if follow-up time is long
- Consider following two fixed cohorts with the same cumulative incidence at time = 4 years

Group A



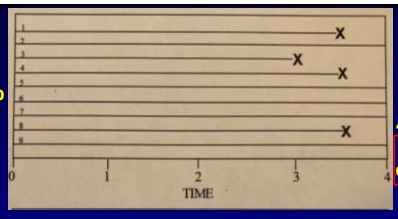
Cumulative Incidence (after t=4) =4/9

Group B



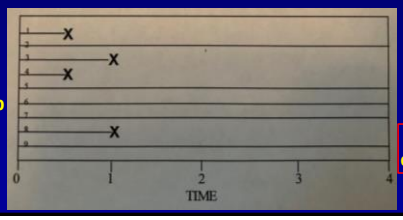
Cumulative Incidence (after t=4) =4/9

Group A



Incidence Rate= 4/33.5p-yrs =0.12 events/p-yr

Group B



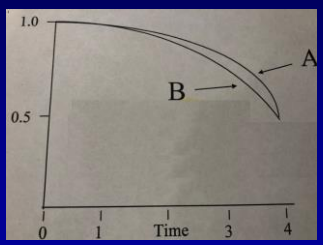
Incidence Rate= 4/23p-yrs =0.17 events/p-yr

- Identical cumulative incidence (risk) at 4 years for Groups A and B
- But figures visually demonstrate that Group B gets disease earlier than Group A
- Reflected by different incidence rates:
  - Incidence Rate$_A$ = 0.12 events/p-year
  - Incidence Rate$_B$ = 0.17 events/p-year
- Reflected by different survival curves

Survival Curves for Groups A and B

- Equal cumulative incidences over 0 – 4 years
- Different incidence rates

Proportion Surviving Without Disease



Belonging to Group A is preferable.

Relationship Between Incidence and Prevalence

Prevalence = Incidence x Average Duration of Disease

Assumption:

Dynamic Population in Steady State

Relative Measures of Effect

Attributable Risk

= Incidence Difference

= $\text{Incidence}_{\text{exposed}} - \text{Incidence}_{\text{unexposed}}$

Relative Risk (RR)

$$= \frac{\text{Incidence}_{\text{exposed}}}{\text{Incidence}_{\text{unexposed}}}$$

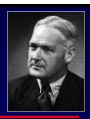
If $I_e = I_o$, then RR=1 (null effect)

RR and attributable risk provide complimentary information

Summary

- Focus on the study question, hypothesis
- Know criteria supporting causal assoc.
- Study design should be selected based on the research question
- Measures of disease frequency, exposure effect are used to report study results

Sir Austin Bradford Hill



"All scientific work is incomplete-- whether it be observational or experimental.

All scientific work is liable to be upset or modified by advancing knowledge.

That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Hill AB. *Proc R Soc Med* 1965:58;295.