Hierarchy of Evidence

**Higher Quality Evidence**
- Systematic reviews of RCTs
- Randomized-controlled trials
- Cohort studies
- Case-control studies
- Case series and case reports
- Clinical observation/expert opinion

**Lower Quality Evidence**
Type of Studies

- **Non-experimental (Observational)**
  - Case report
  - Case series
  - Cross-sectional (survey)
  - Case-control
  - Prospective, observational (cohort)
- **Experimental**
  - Randomized, clinical trial (RCT)

Study designs

- **Observational studies:**
  - **Observe** both exposures and outcomes
- **Experimental studies (clinical trials)**
  - **Assign** exposures
  - **Observe** outcomes

Why we need Observational Studies

- **Important to establish associations** between exposures and clinical outcomes
- **Some exposures you can never randomize:** e.g. smoking, alcohol, lead exposure
- **Important to build hypotheses:** e.g. smoking associated with low serum beta carotene and high risk of cancer
Why Observational Studies are Dangerous

• Associations between exposures and clinical outcomes do not establish causality

• Residual Confounding

• Consumers and the press have a hard time refraining from jumping from associations to cause and effect

Study Design

• Design: Prospective, NIH-AARP Diet and Health Study

• Participants: 566,401 AARP members

• Exposure: Self reported Coffee Consumption from 24 hour dietary recall (2 days)

• Follow-up: 1995/6 to 2008
Results

Conclusions

• Inverse association of coffee consumption with deaths from all causes

• “Our results provides assurances with respect to concerns that coffee drinking might adversely affect health”
Message to Consumers

• "Coffee drinkers who worry about the jolt of java it takes to get them going in the morning might just as well relax and pour another cup."

• "The study will be cheered as excellent news by coffee drinkers, especially healthy people and those in the six-cups-a-day crowd."

OUTLINE

• History
• Definition/Terms
• Assumptions
• Advantages and disadvantages
• Examples
• Variation on a theme
STUDY DESIGNS AND CORRESPONDING QUESTIONS

- Ecologic
  - What explains differences between groups?
- Case Series
  - How common is this finding in a disease?
- Cross-sectional
  - How common is this disease or condition?
- Case-control
  - What factors are associated with having a disease?
- Prospective
  - How many people will get the disease? What factors predict development?

Cross-Sectional Study

Begin with: Defined Population

Then:
- Gather Data on Exposure and Disease
  - Exposed, with Disease
  - Exposed, No Disease
  - Not Exposed, with Disease
  - Not Exposed, No Disease

Case-Control Study

Begin with:
- “Cases” Disease
  - Exposed
  - Not Exposed
- “Controls” No Disease
  - Exposed
  - Not Exposed
Prospective Observational Studies

Defined Population

NON-RANDOMIZED

Exposed

Non-Exposed

Disease

No Disease

Disease

No Disease

Deaths rates* per 100,000 from tuberculosis, all forms, for Massachusetts, 1880 to 1930, by age and sex, with rates for cohort of 1880 indicated

<table>
<thead>
<tr>
<th>Age</th>
<th>1880</th>
<th>1890</th>
<th>1895</th>
<th>1900</th>
<th>1905</th>
<th>1910</th>
<th>1915</th>
<th>1920</th>
<th>1925</th>
<th>1930</th>
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<tbody>
<tr>
<td>0-4</td>
<td>1700</td>
<td>578</td>
<td>309</td>
<td>299</td>
<td>128</td>
<td>67</td>
<td>49</td>
<td>24</td>
<td>11</td>
<td>41</td>
</tr>
<tr>
<td>5-9</td>
<td>148</td>
<td>48</td>
<td>31</td>
<td>21</td>
<td>9</td>
<td>14</td>
<td>9</td>
<td>4</td>
<td>11</td>
<td>41</td>
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<td>10-19</td>
<td>126</td>
<td>118</td>
<td>60</td>
<td>63</td>
<td>43</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>20-29</td>
<td>444</td>
<td>3611</td>
<td>288</td>
<td>202</td>
<td>149</td>
<td>81</td>
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<td>30-39</td>
<td>378</td>
<td>368</td>
<td>296</td>
<td>203</td>
<td>164</td>
<td>115</td>
<td></td>
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<tr>
<td>40-49</td>
<td>364</td>
<td>336</td>
<td>253</td>
<td>253</td>
<td>178</td>
<td>118</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>366</td>
<td>325</td>
<td>267</td>
<td>252</td>
<td>171</td>
<td>127</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>475</td>
<td>340</td>
<td>304</td>
<td>246</td>
<td>172</td>
<td>95</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70+</td>
<td>672</td>
<td>396</td>
<td>343</td>
<td>163</td>
<td>127</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Deaths rates calculated per 100,000 from tuberculosis, all forms, for Massachusetts, 1880 to 1930, by age and sex, with rates for cohort of 1880 indicated.
“PROSPECTIVE” IN EPIDEMIOLOGY

• Clearly defined cohort (group, sample) of persons at risk followed through time
• Data regarding exposures (risk factors, predictors) collected prior to data on outcomes (endpoints)
• Protocol developed prior to data collection of research-grade data used for purpose of testing hypothesis (?)

2 x 2 TABLE

<table>
<thead>
<tr>
<th>Disease</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Exposure</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
</tr>
</tbody>
</table>

- Recruit 1,000 dialysis patients
- Measure Kt/V (dialysis treatment adequacy)
- Follow one year
- At the end of the year, count the deaths and compare mortality rates between the groups

RISK OF MORTALITY ASSOCIATED WITH Kt/V IN 1,000 DIALYSIS PATIENTS FOLLOWED FOR 1 YEAR

<table>
<thead>
<tr>
<th></th>
<th>Dead</th>
<th>Alive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Kt/V</td>
<td>125</td>
<td>275</td>
<td>400</td>
</tr>
<tr>
<td>High Kt/V</td>
<td>125</td>
<td>475</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>750</td>
<td>1,000</td>
</tr>
</tbody>
</table>

Relative Risk = 125/400 = 1.5
125/600
Odds Ratio = 125 / 275 = 1.7
125 / 475

Odds ratio are used to estimate how strongly a variable is associated with the outcome

Odds of dying is 1.7 times greater having a low Kt/V compared to having a high Kt/V
Types of Cohorts

- Occupational (e.g., Asbestos workers)
- Convenience (e.g., Precursors, Nurses)
- Geographic (e.g., Framingham, ARIC)
- Disease or Procedure
  - Natural History (e.g., Syncope, Lupus)
  - Outcomes Research (e.g., Dialysis, Cataracts)

PROSPECTIVE STUDY

ASSUMPTIONS

- Participants free of the disease at baseline
- Assessment of outcome not influenced by presence of risk factor or exposure (i.e., independent assessment)
- High follow up rate
  - Survival analysis assumes that persons lost to follow up have the same risk as those remaining in the study
  - Unreasonable assumption if follow up rate is low
  - 90% is gold standard, 70% acceptable—‘nonresponse bias’

PROSPECTIVE STUDY

ELIGIBILITY CRITERIA

- Balance generalizability (external validity) with ability to follow participants (internal validity)
  - Exclude persons who will be difficult to follow—intend to move, substance abuse, etc.
- Broad eligibility criteria important for representative prevalence and incidence measures
- For association studies (i.e., relative risk estimates), internal validity may be more important than generalizability
PROSPECTIVE STUDY
DATA COLLECTION

• Collect data on all important independent variables and confounders!
• Consider banking sera, DNA, and white cells as well as medical records to facilitate nested case-control studies and secondary analyses
• Blinded assessment of the outcome prevents bias, i.e., outcome classification unlikely to be affected by risk factor/exposure information.
• Obtain information to track persons through national death registry

PROSPECTIVE STUDY
ADVANTAGES

• Assess incidence
• Temporal relationship is clear
• Allows stronger causal inferences than cross-sectional and case-control studies
• Study rare exposures
• Study multiple outcomes
  Add new ones after baseline data collected

PROSPECTIVE STUDY
DISADVANTAGES

• May take a long time to complete
• Expensive, compared to case-control and cross-sectional studies
• Require considerable effort to maintain
• Limited to risk factors and exposure data collected at beginning of study. Usually cannot go back and add a new measure.
• Cannot study rare outcomes
Limitations of Observational, Non-Experimental Studies

• **Selection bias**: bias in selection of participants
• **Information bias**: bias in ascertainment of exposure or outcome status
• **Confounding** (possibly a bias as well): The association is real, but the inference is wrong.

Confounding

• **Confounder** - is an *extraneous variable* in a statistical model that correlates (positively or negatively) with both the *dependent variable* and the *independent variable*

• important to control for confounding to isolate the effect of a particular hazard

Hypothetical Causal Pathway

Potential Confounders

Grey Hair → Older Age → Higher Risk of CHD
Confounding by Indication

• Those who receive a therapy are placed on the therapy because it is clinically "indicated", and are therefore more or less likely to develop the outcome on that basis alone.

Ca++ Ch. Blockers

↓

Hx of Angina

? Myocardial Infarction

Confounding

• Confounding describes a relationship between TWO exposures and ONE outcome.

Coffee drinking

↓

Smoking

? Lung cancer

• Guilt by association: In this example, smoking is a confounder in the relationship between coffee and lung cancer.

Epidemiology in a box: The 2x2 table

• The EXPOSURE (E)
  Example: obesity

• The OUTCOME (D)
  Example: Hypertension

• Applicable to most study designs

\[ \begin{array}{cc|c}
   & \text{D}^+ & \text{D}^- \\
\text{E}^+ & a & b & a+b \\
\text{E}^- & c & d & c+d \\
\hline
a+c & b+d & \text{Total}
\end{array} \]
RISK OF LUNG CANCER ASSOCIATED WITH COFFEE DRINKING

<table>
<thead>
<tr>
<th>COFFEE</th>
<th>LUNG CA+</th>
<th>LUNG CA-</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>-</td>
<td>60</td>
<td>90</td>
</tr>
</tbody>
</table>

OR = \frac{90 \times 90}{60 \times 60} = 2.25

RR = \frac{90/150}{60/150} = 1.5

CONFOUNDING

Coffee not associated with cancer risk, but smoking is.
Apparent relation of coffee with cancer due to strong association of smoking with coffee intake.

WHEN SHOULD YOU DO A PROSPECTIVE STUDY?

- Common outcome
- Relatively short interval between baseline data collection and outcome
- Adequate resources to follow the cohort
- Identify risk factors preparatory to conducting a clinical trial
HISTORY OF THE PRECURSORS STUDY

- Idea proposed
- Grant submitted
- Grant funded
- Data collection begun on class of ’48
- 1,337 students entered

Over 1300 students (mainly white men) from the JHUSOM Classes of 1948-64. Baseline data collected in person in medical school. Follow-up data collected by yearly mailed questionnaires thereafter.
THE PRECURSORS STUDY  
DESIGN  

1948-1964  Present*  
History, Physical  Annual Follow-up  
Psychological  Exposure Measures  

BASELINE CHARACTERISTICS  

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>23.1</td>
<td>(2.5)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>125</td>
<td>(14)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>75</td>
<td>(9)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23</td>
<td>(3)</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>225</td>
<td>(41)</td>
</tr>
<tr>
<td>CPT response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-SBP, mmHg</td>
<td>12.0</td>
<td>(8.1)</td>
</tr>
<tr>
<td>-DBP, mmHg</td>
<td>15.0</td>
<td>(9.0)</td>
</tr>
<tr>
<td>-HR, beats/min</td>
<td>6.2</td>
<td>(8.7)</td>
</tr>
</tbody>
</table>

Continuous performance test – target (the letter S) and background stimuli (the letters, A, C, E, and T)  

RELATIVE RISK ESTIMATES FOR SUICIDE BY HNT ITEMS*  

<table>
<thead>
<tr>
<th>HNT item</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>4.2</td>
<td>(1.3, 13.9)</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>2.6</td>
<td>(0.8, 8.3)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>2.0</td>
<td>(0.6, 6.3)</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>1.7</td>
<td>(0.5, 5.8)</td>
</tr>
<tr>
<td>Urge to be alone</td>
<td>1.6</td>
<td>(0.5, 5.4)</td>
</tr>
</tbody>
</table>

*Based on a Proportional Hazards Regression Model including all five HNT items  
Graves and Thomas, 1991
RELATIVE RISK* OF DEVELOPING HYPERTENSION OVER 20-36 YEARS OF FOLLOW-UP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette Smoking</td>
<td>1.73</td>
<td>(1.15, 2.60)</td>
</tr>
<tr>
<td>Maternal hypertension</td>
<td>1.10</td>
<td>(0.64, 1.91)</td>
</tr>
<tr>
<td>Paternal hypertension</td>
<td>2.13</td>
<td>(1.29, 3.52)</td>
</tr>
<tr>
<td>Both parents with HTN</td>
<td>8.12</td>
<td>(4.47, 14.10)</td>
</tr>
<tr>
<td>Control SBP (mmHg)+</td>
<td>2.04</td>
<td>(1.43, 2.90)</td>
</tr>
<tr>
<td>Cold pressor SBP change</td>
<td>1.93</td>
<td>(1.26, 2.98)</td>
</tr>
</tbody>
</table>

*adjusted for baseline age, Quetelet (p>0.05)
+ for 20 mmHg increase

Menkes, 1989

RELATIVE RISK ASSOCIATED WITH A 36mg/dl DIFFERENCE IN SERUM CHOLESTEROL LEVEL IN MEDICAL SCHOOL IN 1,017 WHITE MEN: UNIVARIATE PROPORTIONAL HAZARDS ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th>&lt; 50 Years</th>
<th>50+ Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>CVD</td>
<td>37</td>
<td>1.93 (1.40-2.68)**</td>
</tr>
<tr>
<td>CHD</td>
<td>39</td>
<td>2.18 (1.54-3.10)**</td>
</tr>
<tr>
<td>MI</td>
<td>20</td>
<td>2.44 (1.82-3.68)**</td>
</tr>
<tr>
<td>Angina</td>
<td>16</td>
<td>1.75 (1.05-2.92)**</td>
</tr>
<tr>
<td>CVD Death</td>
<td>5</td>
<td>3.29 (1.53-7.06)**</td>
</tr>
<tr>
<td>Total Death</td>
<td>32</td>
<td>1.49 (1.02-2.19)**</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001

RELATIVE RISK OF SUBSEQUENT CHD (N=163) ASSOCIATED WITH CLINICAL DEPRESSION

<table>
<thead>
<tr>
<th>Adjusting Variables</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.8 (1.1-2.8)</td>
</tr>
<tr>
<td>Smoking+</td>
<td>1.8 (1.1-2.8)</td>
</tr>
<tr>
<td>Alcohol+</td>
<td>2.0 (1.2-3.2)</td>
</tr>
<tr>
<td>Coffee+</td>
<td>1.7 (1.1-2.7)</td>
</tr>
<tr>
<td>Baseline serum cholesterol, change in smoking+, incident hypertension+, and diabetes+</td>
<td>1.7 (1.0-2.9)</td>
</tr>
</tbody>
</table>

RESULTS FROM THE JOHNS HOPKINS PRECURSORS STUDY

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Disease</td>
<td>Anger, Depression, Gout,</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>Blood pressure, Adiposity</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Coffee</td>
</tr>
<tr>
<td>Knee Osteoarthritis</td>
<td>Knee injury</td>
</tr>
<tr>
<td>Depression</td>
<td>Insomnia</td>
</tr>
</tbody>
</table>

ASSOCIATIONS WITH CAREER ACHIEVEMENT IN 424 MALE ACADEMIC PHYSICIANS

<table>
<thead>
<tr>
<th>Scholastic Performance</th>
<th>Higher Rank</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOA</td>
<td>1.57***</td>
<td>3.09***</td>
</tr>
<tr>
<td>Top 1/3</td>
<td>1.37*</td>
<td>2.38***</td>
</tr>
<tr>
<td>Middle 1/3</td>
<td>1.24</td>
<td>1.54</td>
</tr>
<tr>
<td>Research Medical School</td>
<td>1.43***</td>
<td>2.58*</td>
</tr>
<tr>
<td>Age &lt; 25 yr</td>
<td>1.22**</td>
<td>1.42</td>
</tr>
</tbody>
</table>

INCIDENCE OF DIVORCE BY SPECIALTY

[Graph showing cumulative incidence of divorce by years of marriage for different specialties]
NONCONCURRENT PROSPECTIVE STUDIES

- Best of both worlds—fulfill criteria for temporality but don’t have to wait around for follow-up
- Uses data collected in the past, follow-up has already occurred, assess outcome in the present time
- Also called retrospective cohort studies, trohoc studies

CONCURRENT VS. NONCONCURRENT PROSPECTIVE STUDIES

**CONCURRENT VS. NONCONCURRENT PROSPECTIVE STUDIES**

<table>
<thead>
<tr>
<th>Concurrent</th>
<th>Nonconcurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Now</td>
<td>Past</td>
</tr>
<tr>
<td>Future</td>
<td>Now</td>
</tr>
<tr>
<td>Baseline exposure assessment</td>
<td>Outcome assessment</td>
</tr>
</tbody>
</table>

**CONCURRENT VS. NONCONCURRENT PROSPECTIVE STUDIES—BLOOD PRESSURE AND ESRD**

<table>
<thead>
<tr>
<th>Concurrent</th>
<th>Nonconcurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>1973</td>
</tr>
<tr>
<td>2007</td>
<td>1991</td>
</tr>
<tr>
<td>BP measurement</td>
<td>ESRD Incidence</td>
</tr>
</tbody>
</table>

**CONCURRENT VS. NONCONCURRENT PROSPECTIVE STUDIES—BLOOD PRESSURE AND ESRD**

<table>
<thead>
<tr>
<th>Concurrent</th>
<th>Nonconcurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP measurement</td>
<td>ESRD Incidence</td>
</tr>
<tr>
<td>1989</td>
<td>1973</td>
</tr>
<tr>
<td>2007</td>
<td>1991</td>
</tr>
</tbody>
</table>
MRFIT ESRD Study

1973  322,000 men screened  1989

Follow up for 16 years

1989  Obtain Medicare data on ESRD billing  2005

1991  Do analysis and publish results  2007

INCIDENCE OF ALL-CAUSE ESRD IN 322,000 MRFIT MEN

Klag, NEJM, 1991

INCIDENCE OF ALL-CAUSE ESRD BY 16 YEARS IN 322,000 MEN, MRFIT

Klag, NEJM, 1991
NESTED CASE-CONTROL STUDIES

- Uses incident cases from a prospective study
- Controls drawn from non-cases in the same study
- Data collected at baseline prior to development of disease
- Efficient and avoids usual limitations of case-control studies

NESTED CASE-CONTROL DESIGN

1. Identify cases
2. Draw sample of controls
3. Measure risk factors

NESTED CASE-CONTROL STUDIES
WHEN SHOULD THEY BE DONE?

- Limited number of cases in prospective study, e.g., rare outcomes like ESRD
- Efficient use of biological specimens and resources, e.g., serum bank
- Not enough resources to study all cases
- Avoids usual limitations of case-control studies, i.e., temporality fulfilled
CRITERIA FOR CAUSAL INFERENCE

- Experimental evidence
- Temporality
- Strength of the association
- Dose-response relationship
- Consistency in different populations
- Specificity - an exposure leads to only one disease
- Biologic plausibility
- Coherence
- Analogy

HIERARCHY OF STUDIES

- Randomized clinical trials
- Non-randomized clinical trials
- Prospective observational studies
- Case-control studies
- Cross-sectional studies
- Case series, case reports
- Ecologic statistics

STUDY DESIGNS AND CORRESPONDING QUESTIONS

- Ecologic
  - What explains differences between groups?
- Case Series
  - How common is this finding in a disease?
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  - How many people will get the disease?
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THANK YOU!