Causal Inference, Bias, and Confounding

Part I

Guidelines for Causal Inference

Brandon Guthrie, PhD
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University of Washington
Importance of causal inference to epidemiologists

Influence decision-making about health and illness
- Individuals
- Clinicians
- Public health practitioners
  - Disease control
  - Non-infectious disease clusters
  - Public health surveillance
  - Public health program development

Guide research design/analysis
Koch’s causality criteria (1890)

An organism is regarded as a cause of a disease if:

1. It occurs in every case of the disease, and under circumstances that can account for the pathological changes and clinical course **NECESSARY**

2. It occurs in no other disease as a fortuitous and nonpathogenic organism **SPECIFIC**

3. After being isolated from the body, grown in pure culture and repeatedly passed, it induces the disease anew **SUFFICIENT**
Causal association in epidemiology

“Cause” is an event, condition, or characteristic that plays a role in producing an occurrence of the disease.

A cause is something that if it weren’t there, some of the disease wouldn’t happen.

NOT NECESSARY

A cause can be a contributing component of a more complex mechanism involving other factors.

NOT SUFFICIENT
Sir Austin Bradford Hill, CBE DSC FRCP FRS (1897-1991)
Causal Inference Guidelines

1. Randomized trial evidence exists
2. Temporal sequence is correct
3. Association is strong
4. Association is biologically plausible
5. Association is strongest when predicted to be so
6. Observed evidence is consistent
7. No alternative explanations exist
Randomized trials

Chance alone dictates which participants of the study are exposed.

Other factors don’t distort the results.
Randomized trials

Does male circumcision reduce the risk of HIV infection?

ANRS Orange Farm Study

- High prevalence of HIV
- Eligible men were sexually active and initially uncircumcised

Results

- Circumcised: 20/1,546 HIV infections
- Uncircumcised: 49/1,582 HIV infections

“Male circumcision provides a degree of protection against acquiring HIV infection, equivalent to what a vaccine of high efficacy would have achieved.”

Causal Inference Guidelines

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Correct temporal sequence

The cause **must** precede the effect

- Exposure must precede outcome by a period of time consistent with any proposed mechanism
- Existence of appropriate temporal sequence can be difficult to establish if there is a hypothesized short time from exposure to outcome
- Existence of appropriate temporal sequence can be difficult to establish from cross-sectional data
Results of a Cross-Sectional Study

<table>
<thead>
<tr>
<th>Menopausal status*</th>
<th>Mean serum cholesterol Mg/100ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>208</td>
</tr>
<tr>
<td>Post</td>
<td>218</td>
</tr>
</tbody>
</table>

* women aged 43-45 years
Correct temporal sequence

Results of a Longitudinal Study

Women who were pre-menopausal at 45 but whose periods stopped before 46

Women who were pre-menopausal through 51

Age in Years

Mean Serum Cholesterol

45 48 51
Alcohol consumption and endometriosis risk

A case-control study of risk factors for endometriosis:

- 88 cases with deep endometriosis
- 88 cases with peritoneal endometriosis
- 88 controls

In-person interview - current use of alcohol ascertained.

Women with deep endometriosis were nearly six times as likely as control women to report drinking every day.

Women with peritoneal endometriosis were no more likely than control women to drink.

Causal Inference Guidelines

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Strength of association

The magnitude of the ratio of incidence rates. The larger the value of the relative risk, the less likely the association is to be spurious. (AB Hill, 1965)

“Even as late as the second decade of the twentieth century, the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed to tar or mineral oils.” (Sir Richard Doll, 1964)

“For smokers, the risk of developing lung cancer was 9.9 times that of nonsmokers.”

“Consistent use of condoms results in 80% reduction in HIV incidence.” (Weller S and Davis K, 2002)
Causal Inference Guidelines

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Biological plausibility

Does hormonal contraceptive use increase the risk of HIV infection?

“The most popular contraceptive for women in eastern and southern Africa, a hormone shot given every three months, appears to double the risk the women will become infected with HIV, according to a large study published Monday.”

Hormonal contraceptives have effects on the vaginal environment

- Hormonal contraceptive use is associated cervical ectopy, which in turn is associated with increased susceptibility to HIV

- Hormonal contraceptives cause thinning of the vaginal epithelium

- Hormonal contraceptives cause increased inflammation in the genital tract

Causal Inference Guidelines

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### Strength of association: dose-response gradient

Cigarette smoking and lung cancer in men

<table>
<thead>
<tr>
<th>Cigarettes smoked per day</th>
<th>Annual death rate per 100,000</th>
<th>Relative lung cancer mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>1-9</td>
<td>56</td>
<td>4.6</td>
</tr>
<tr>
<td>10-19</td>
<td>90</td>
<td>7.5</td>
</tr>
<tr>
<td>20-39</td>
<td>159</td>
<td>13.1</td>
</tr>
<tr>
<td>40+</td>
<td>201</td>
<td>16.6</td>
</tr>
</tbody>
</table>
### Strength of association: exposure timing

**Menopausal estrogen use in women with endometrial cancer and controls**

<table>
<thead>
<tr>
<th>Years since first use</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used</td>
<td>1.0</td>
<td>Ref</td>
</tr>
<tr>
<td>1-2</td>
<td>1.2</td>
<td>0.4-3.7</td>
</tr>
<tr>
<td>3-4</td>
<td>5.4</td>
<td>2.5-11.5</td>
</tr>
<tr>
<td>5-7</td>
<td>4.7</td>
<td>2.6-8.4</td>
</tr>
<tr>
<td>8-10</td>
<td>11.7</td>
<td>6.2-21.8</td>
</tr>
</tbody>
</table>
GBS following influenza vaccination, 1976-77


Causal Inference Guidelines

1. Randomized trial evidence exists
2. Temporal sequence is correct
3. Association is strong
4. Association is biologically plausible
5. Association is strongest when predicted to be so
6. **Observed evidence is consistent**
7. No alternative explanations exist
Consistency of Evidence

Repeated observation of the association under different conditions of study

<table>
<thead>
<tr>
<th>Study location</th>
<th>Cases</th>
<th>Information obtained before or after death</th>
<th>Usual or last</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holland</td>
<td>62</td>
<td>After</td>
<td>Usual</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Last</td>
<td>4.9</td>
</tr>
<tr>
<td>U.K.</td>
<td>72</td>
<td>After</td>
<td>Last</td>
<td>8.8</td>
</tr>
<tr>
<td>N.Z.</td>
<td>473</td>
<td>After</td>
<td>?</td>
<td>3.3</td>
</tr>
<tr>
<td>Australia</td>
<td>42</td>
<td>After</td>
<td>Usual</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Before</td>
<td>Usual</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*RR for prone vs. other sleeping position
Does maternal smoking during pregnancy result in lower infant birthweight?
Temporal sequence

Retrospective cohort study

% low birthweight

Mothers never smoked 4%
Mothers smoked before pregnancy only 3%
Mothers smoked during pregnancy 11%
Strength of Association

Relative Risk \( = \frac{11}{4} = 2.8 \)

Smokers were nearly 3 times as likely as nonsmokers to have low birthweight babies.
Biological Plausibility

- Smoking reduces placental blood flow (nicotine causes vasoconstriction)
- Carbon monoxide causes fetal hypoxia
- Cyanide causes fetal growth retardation
Dose-response gradient

German female infants born in 1995–1997

mean birthweight (gms)

Cigarettes per day during pregnancy

<table>
<thead>
<tr>
<th>Cigarettes per day</th>
<th>Birthweight (gms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3400</td>
</tr>
<tr>
<td>1–5</td>
<td>3300</td>
</tr>
<tr>
<td>6–10</td>
<td>3200</td>
</tr>
<tr>
<td>11–15</td>
<td>3100</td>
</tr>
<tr>
<td>16–20</td>
<td>3000</td>
</tr>
<tr>
<td>21–60</td>
<td>2900</td>
</tr>
</tbody>
</table>
## Consistency of evidence

<table>
<thead>
<tr>
<th>Location</th>
<th>Study Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Retrospective cohort</td>
<td>200g lower birthweight</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Retrospective cohort</td>
<td>190g lower birthweight RR for low birthweight = 3</td>
</tr>
<tr>
<td>England (Low SES)</td>
<td>Retrospective cohort</td>
<td>RR for low birthweight = 2</td>
</tr>
<tr>
<td>Washington DC</td>
<td>Case-control</td>
<td>Women with low birthweight infants more likely to smoke (46% vs. 30%)</td>
</tr>
</tbody>
</table>
Does maternal smoking during pregnancy result in lower infant birthweight?
### Smoking and low birthweight, U.S., 1990-2005

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence of smoking in pregnancy</th>
<th>Low birthweight prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>18.4%</td>
<td>7.0%</td>
</tr>
<tr>
<td>1996</td>
<td>13.6%</td>
<td>7.4%</td>
</tr>
<tr>
<td>2002</td>
<td>11.4%</td>
<td>7.8%</td>
</tr>
<tr>
<td>2005</td>
<td>10.7%</td>
<td>8.2%</td>
</tr>
</tbody>
</table>
Causal Inference Guidelines

1. Randomized trial evidence exists
2. Temporal sequence is correct
3. Association is strong
4. Association is biologically plausible
5. Association is strongest when predicted to be so
6. Observed evidence is consistent
7. No alternative explanations exist
Causal Inference, Bias, and Confounding

Part II

Introduction to bias and confounding

Brandon Guthrie, PhD
Department Global Health
University of Washington
Alternative explanation: Bias

Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth.

- Affects internal validity
- Interferes with ability to infer causality
- Occurs during subject selection, information gathering, analysis, or reporting phases of study
Selection bias

A. Surveillance or detection bias

Procedures used to select subjects lead to a risk estimate among study subjects different from that obtainable from the entire population

- Caused by differential surveillance, diagnosis or referral into study (or self-referral)
- Can affect case-control, retrospective cohort studies
Selection bias

B. Nonresponse bias

Low participation or differential participation of cases and controls *may* lead to biased risk estimates (if participation is also related to exposure status)

- Differential in percentages of exposed and unexposed lost to follow-up *may* lead to biased risk estimates (if being lost is also related to disease status)

- Unpredictable direction of effect on association
Information bias

A. Interviewer bias

Systematic differences between subject groups in the way information on:

- exposure (case-control or retrospective cohort studies), or
- disease status (retrospective and prospective cohort studies and unmasked RCTs)

is solicited, recorded, or interpreted
Information bias

B. Misclassification of exposure or disease status

May be non-differential (same in cases and controls or in exposed and unexposed) or differential
Information bias: misclassification

Sources of *exposure* misclassification:

- Old exposure records inaccurate or incomplete (cohort)
- Subject unaware of exposure status (case-control)
- Subject dishonest about exposure status (case-control)

Impact of exposure misclassification:

Non-differential: biases association toward null value

Differential: Unpredictable direction
Information bias: misclassification

Sources of **disease** misclassification:

- Inaccurate or incomplete medical records information
- Limited accuracy of diagnostic tests
- Subject unaware of disease status
- Subject dishonest about disease status

Impact of **disease** misclassification:

- Non-differential: biases association toward null value
- Differential: unpredictable direction
Alternative explanation: Confounding

Association seen between exposure and disease is a distortion

Diagram:
- Exposure
- Factor
- Disease
Birth order and Down’s Syndrome risk

![Graph showing the prevalence of Down’s Syndrome risk across birth orders. The graph indicates an increase in prevalence per 1000 births with higher birth order numbers.]

Confounding

- Age is associated with birth order
- Age is associated with Down’s Syndrome

Age is a potential confounder of the association between birth order and Down’s Syndrome
Maternal age, birth order and Down’s Syndrome risk

Necessary conditions for confounding to occur

• Factor is associated with the disease of interest (or recognition of disease)
  ◦ Cause or correlate of cause

• Factor is associated with the exposure of interest

• Factor is not in the causal pathway between exposure and disease
Is the factor in the causal pathway?

Exposure determines presence or level of presumed confounder

Utilize non-epidemiologic (clinical) data to determine

Information may be inconclusive
Does drinking coffee increase the risk of myocardial infarction (MI)?

Case-control study with 150 cases, 150 randomly selected controls

- 90 of the cases routinely consumed 1 or more cups of coffee daily in the year before diagnosis
- 60 controls routinely consumed coffee in the same period

<table>
<thead>
<tr>
<th>Coffee</th>
<th>MI (cases)</th>
<th>no MI (controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>No coffee</td>
<td>60</td>
<td>90</td>
</tr>
</tbody>
</table>

\[
\text{OR} = \frac{(90 \times 90)}{(60 \times 60)} = 2.25
\]
## Confounder assessment

### 1. Association of factor and disease

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th></th>
<th>Nonsmokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI (cases)</td>
<td>no MI (controls)</td>
<td>MI (cases)</td>
</tr>
<tr>
<td>Coffee</td>
<td>80</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>No coffee</td>
<td>20</td>
<td>10</td>
<td>40</td>
</tr>
</tbody>
</table>

### Is smoking associated with MI risk?

<table>
<thead>
<tr>
<th></th>
<th>MI (cases)</th>
<th>no MI (controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

\[
OR = \frac{(20 \times 80)}{(10 \times 40)} = 4.0
\]
## Confounder assessment

### 2. Association of factor and exposure

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th></th>
<th>Nonsmokers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>20</td>
</tr>
<tr>
<td>No coffee</td>
<td>20</td>
<td>10</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

**Is smoking associated with coffee-drinking?**

<table>
<thead>
<tr>
<th></th>
<th>Non-Smokers</th>
<th></th>
<th>Smokers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No-Smokers</td>
<td></td>
<td>Coffee</td>
<td></td>
</tr>
<tr>
<td>Coffee</td>
<td>40</td>
<td>20</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>No coffee</td>
<td>10</td>
<td>80</td>
<td>10</td>
<td>80</td>
</tr>
</tbody>
</table>

\[
\text{OR} = \frac{(40 \times 80)}{(20 \times 10)} = 16.0
\]
Confounder assessment

3. Is the factor in the causal pathway?
When do confounder-disease and confounder-exposure associations result in confounding?

1. **Strong associations** between exposure and factor and between disease and factor exist

2. **Crude and stratum-specific** effect measures differ

3. **Crude and adjusted** effect measures differ

**Not based on statistical significance testing**
Coffee drinking and MI, potentially confounded by smoking

<table>
<thead>
<tr>
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<th>no MI (controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>No coffee</td>
<td>60</td>
<td>90</td>
</tr>
</tbody>
</table>

Crude OR = 2.25

**Smokers**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>No coffee</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

OR = \((80 \times 10) / (40 \times 20)\)
    = 1.0

**Nonsmokers**

<table>
<thead>
<tr>
<th></th>
<th>MI (cases)</th>
<th>no MI (controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>No coffee</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

OR = \((10 \times 80) / (20 \times 40)\)
    = 1.0
Confounding control – design phase

Randomization

• Removes associations between exposure and potential confounders (usually)

• Controls confounding by unknown or unmeasurable confounders

• Confounding may still occur due to “accident of randomization”
  ◦ Increase size of study
  ◦ Use stratified randomization methods
  ◦ Handle as for observational study
Confounding control – design phase

Restriction

• Require all members of study population to have same status on potential confounder(s)

• Most useful when most potential subjects have same status on potential confounder
  ◦ breast cancer – females
  ◦ veterans - males
  ◦ neonates – singletons

+ Enhances ability to make statistical inferences

- Reduces generalizability

- Eliminates ability to assess effect modification

- May be difficult (or expensive) to find sufficient subjects
Confounding control – design phase

Matching

**Cohort study:** Each exposed subject matched to ≥1 non-exposed subject(s) on potential confounder(s)

**Case-control study:** Each case matched to ≥1 control on potential confounder(s)

- Allows control for a few well-known strong risk factors
- Increases efficiency of case-control study

- Precludes examining matching factor(s) as risk factors
- Differential loss to follow-up may result in imbalance in matching factors
- Matching can create bias in case-control study
Confounding control – analysis phase

Rate adjustment

• Used to compare disease (or death) rates of two populations with different distributions of a characteristic when disease (or death) is related to that characteristic

• Remove effect of differences in population composition

• Combine category-specific rates into a single summary value by taking a weighted average of them

• Use arbitrarily chosen “standard population” with a known distribution of the characteristic of interest for category-specific weights
Rate standardization example

In Hospital A, there were 228 ICU deaths during the 3,200 ICU person-days accrued by their patients during one year.

In Hospital B, there were 110 ICU deaths, with 2,500 ICU person-days accrued in the corresponding time.

How does ICU mortality in Hospital B compare to that in Hospital A?

Crude ICU mortality rates

<table>
<thead>
<tr>
<th></th>
<th>Hospital A: 228/3,200</th>
<th>= 71.25 / 1000 person-days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital B: 110/2,500</td>
<td>= 44.00 / 1000 person-days</td>
</tr>
</tbody>
</table>

ICU mortality rate ratio for Hospital B / Hospital A:

= 44.00 / 71.25 = 0.62

ICU mortality rate difference for B - A:

= 44.00 – 71.25 = -27.25 / 1000 person-days
Rate standardization example

Is Hospital B’s ICU mortality rate better than Hospital A’s because Hospital B delivers better care, or because of something about Hospital A’s patients that would make them more likely to die even if they got good care?

The relevant factor might be the severity of illness, measured by Severity Score, if the two hospitals differ on the Severity Score distribution.

<table>
<thead>
<tr>
<th>Severity Score Category</th>
<th>Hospital A person-days:</th>
<th>Hospital B person-days:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>200</td>
<td>1500</td>
</tr>
<tr>
<td>20-39</td>
<td>1000</td>
<td>850</td>
</tr>
<tr>
<td>40+</td>
<td>2000</td>
<td>150</td>
</tr>
</tbody>
</table>
Rate standardization – Step 1

Choose a standard or reference population with a known distribution of the confounding factor.

Commonly used options:

- one of the two groups to be compared
- combination of the two groups to be compared
- Census population (age)
- IARC World standard population (age)
Rate standardization – Step 1

For this comparison we decide that the standard population will be the **combination of the two populations**, in terms of their severity score distribution (the confounding factor).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>200</td>
<td>1,500</td>
<td>1,700</td>
</tr>
<tr>
<td>20-39</td>
<td>1,000</td>
<td>850</td>
<td>1,850</td>
</tr>
<tr>
<td>40+</td>
<td>2,000</td>
<td>150</td>
<td>2,150</td>
</tr>
</tbody>
</table>

5,700
Rate standardization – Step 2

**Compute the rates in each level** of the confounding factor **within the exposed group** and then **within the unexposed group**.

<table>
<thead>
<tr>
<th>Severity Score</th>
<th># deaths</th>
<th># person days</th>
<th>Mort. Rate per 1,000 p-days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>3</td>
<td>200</td>
<td>15.0</td>
</tr>
<tr>
<td>20-39</td>
<td>25</td>
<td>1,000</td>
<td>25.0</td>
</tr>
<tr>
<td>40+</td>
<td>200</td>
<td>2,000</td>
<td>100.0</td>
</tr>
<tr>
<td>Hospital B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>40</td>
<td>1,500</td>
<td>26.7</td>
</tr>
<tr>
<td>20-39</td>
<td>40</td>
<td>850</td>
<td>47.1</td>
</tr>
<tr>
<td>40+</td>
<td>30</td>
<td>150</td>
<td>200.0</td>
</tr>
</tbody>
</table>
**Rate standardization – Step 3**

**Within each level** of the confounding factor, multiply the rates by the number of people in the standard population for the exposed group and then for the unexposed group.

This is the **number of expected** (or hypothetical) outcomes.
## Rate standardization – Step 3

<table>
<thead>
<tr>
<th>Severity Score</th>
<th>Stratum-specific mortality rate</th>
<th># in standard population</th>
<th>Hypothetical # of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hospital A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>15/1000 X</td>
<td>1,700</td>
<td>= 25.5</td>
</tr>
<tr>
<td>20-39</td>
<td>25/1000 X</td>
<td>1,850</td>
<td>= 46.3</td>
</tr>
<tr>
<td>40+</td>
<td>100/1000 X</td>
<td>2,150</td>
<td>= 215.0</td>
</tr>
<tr>
<td><strong>Hospital B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>26.7/1000 X</td>
<td>1,700</td>
<td>= 45.4</td>
</tr>
<tr>
<td>20-39</td>
<td>47.1/1000 X</td>
<td>1,850</td>
<td>= 87.1</td>
</tr>
<tr>
<td>40+</td>
<td>200/1000 X</td>
<td>2,150</td>
<td>= 430.0</td>
</tr>
</tbody>
</table>
Rate standardization – Step 4

Within each exposure group, sum the number of expected (hypothetical) outcomes. This gives you the total number of expected deaths separately in each exposure group.

Hospital A: \[25.5 + 46.3 + 215 = 286.8\] deaths

Hospital B: \[45.4 + 87.1 + 430 = 562.5\] deaths
Rate standardization – Step 5

Divide the total number of expected (hypothetical) outcomes for each exposure group by the total population from the standard population. Multiply by a constant and you have the adjusted (standardized) rates.

**Hospital A:** \( \frac{286.8}{5,700} = \frac{50.3}{1000} \text{ person-days} \)

**Hospital B:** \( \frac{562.5}{5,700} = \frac{98.7}{1000} \text{ person-days} \)

Severity score-adjusted risk of mortality in Hospital B compared with Hospital A:

**Ratio Hospital B / Hospital A** = \( \frac{98.7}{50.3} = 1.96 \)

**Difference (B - A)** = \( \frac{47.4}{1000} \text{ person-days} \)
Crude vs. stratum-specific rates vs. standardized rates

Crude rates
• Represent reality
• Useful for health services needs assessments

Stratum-specific rates
• Represent reality
• Detailed information useful
• Appropriate when stratum-specific effects differ
Final causal inference guideline: Specificity of the association

A certain exposure is associated with only one disease

“Probably should be deleted from the list” – Leon Gordis

Contradicted by known adverse effects of one exposure on multiple diseases

Smoking increases risk of: lung cancer
bladder cancer
pancreatic cancer
cardiovascular disease
emphysema
Usefulness of Specificity guideline

Specificity of exposure
Estrogen but not estrogen + progestin and endometrial cancer

Specificity with regard to susceptibility
Sulfa drugs and hemolytic anemia in G6PD‐deficient people

Specificity of outcome

<table>
<thead>
<tr>
<th>Years since 1st use</th>
<th>RR contralateral</th>
<th>RR ipsilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>5-9</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>≥ 10 yrs</td>
<td>1.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Mobile phone use and risk of glioma
Review of concepts of causation

1. Do we care if an exposure produces disease “directly” or “indirectly?”
One Causal Pathway Leading to Hepatitis in the 1930s

- Occurrence of Syphilis
  - Treatment of Syphilis
    - Intravenous Injection
      - Poor syringe hygiene
        - Infection with Hepatitis virus
2. In order to be considered causal, must the exposure have been present in all persons with the disease?
Lung cancer mortality in white male never smokers, ACS Cancer Prev. Study II

Lung cancer mortality in white male never- and current smokers, ACS Cancer Prev. Study II

![Graph showing lung cancer mortality in white male never- and current smokers.](image)

3. In order to be considered causal, must the exposure be capable of producing the disease on its own?
Gun ownership and homicide in the home

1860 homicides in three counties (Tenn., Wash., Ohio) were ascertained, 24% occurred in the home.

388 cases (homes where homicide occurred) were compared with 388 controls (homes in the same neighborhoods where homicides did not occur).

Handguns were present in 35.7% of the homes where homicides occurred.

Handguns were present in 23.3% of the homes where homicides did not occur.

Arriving at a tentative inference of “causal” or “noncausal” is a subjective process in which one judges how well the individual guidelines have been met.

“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 it appears to demand at a given time.”

- Sir Austin Bradford Hill, 1965