Odds, risk, hazards, etc
Interpretation of randomized controlled trials

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Sydney, Australia
What I am going to cover ...

- Randomized controlled trial (RCT)
- Concept of "risk"
- Interpretation of RCT data
Evidence based medicine vocabulary

- **Efficacy**
- **Intention-to-treat**
- **Likelihood ratio**
- **OR**
- **RR**
- **RRR**
- **NNH**
- **Time-to-event analysis**
- **ARR**
- **Sensitivity**
- **P-value**
- **95% CI**
- **Risk versus benefit**
- **Meta-analysis**
- **Effect size**
- **Cost-benefit**
- **Effectiveness**
- **Cost-effective**
- **DB-PC-RCT**
- **NNT**
- **HR**
- **Population attributable risk**
Randomized controlled trial
Randomized controlled trial

An experiment in which subjects are randomly allocated into groups, usually called study and control groups, to receive or not to receive an experimental preventive or therapeutic procedure, maneuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups, respectively.
Randomized controlled trial

- An important advance in the history of medical science
- Gold standard for evaluating efficacy (and safety?) of an intervention
- Allow cause-effect inference

(But it is probably the worst method for evaluating an individual patient)
Randomized controlled trial

• First RCT: use of streptomycin in the treatment of TB
• Sir Bradford Hill and Sir Richard Doll
Photograph courtesy of Ernie Branson.
The main idea of RCT

Randomized into groups

Follow-up

Comparison of outcome

Rx

Placebo
The "risk" concept
“Risk factor”

- A concept originated from the Framingham Heart Study (Dr. William Kannel in 1961, *Ann Int Med*)

- **Risk factor** – a measurable characteristic causally associated with increased disease frequency

- The concept changed the way medicine is practised
• Risk – *Probability of adverse and undesirable event during a period*

• Characteristics
  – Probability
  – Time
  – Undesirable event
• **Disease**
  
  – a binary trait (yes/no)
  
  – applicable to an individual

• **Risk of disease**
  
  – a continuous trait (0 – 1)
  
  – applicable to a *group* of individuals
• Hazard can be confusing!

• Short: A hazard is *the rate at which events occur*

• Long: A hazard (H) is the ratio of the *probability of an event* occurring in a short time interval (P) over the *length of time* (L)

• In other words,

\[ P = H \times L \]
An example: Dubbo Osteoporosis Epidemiology Study

1287 women aged 60+

Osteoporosis 345 (27%)

Fracture: 137
Risk: 137/345 = 0.40

Non-osteoporosis 942 (73%)

Fracture: 191
Risk: 191/942 = 0.20

Nguyen et al., JBMR 2005
• *Odds* - a risk-related concept

• Odds = ratio of the probability of occurrence of an event to that of non-occurrence

• If $P$ is the risk of fracture, the *odds of fracture* is defined as

$$odds = \frac{P}{1 - P}$$
Odds is **not** risk!
Metrics of effect in RCT
Metrics of effect in RCT

• Relative metrics
  – Relative risk (risk ratio)
  – Odds ratio
  – Hazards ratio

• Absolute metrics
  – Absolute risk difference
  – Number needed to treat (NNT)
373,092 Women Initiated Screening

18,845 Provided Consent and Reported No Hysterectomy

16,608 Randomized

8,506 Assigned to Receive Estrogen + Progestin
- Status on April 30, 2002
  - 7,968 Alive and Outcomes Data Submitted in Last 18 mo
  - 307 Unknown Vital Status
  - 231 Deceased

8,102 Assigned to Receive Placebo
- Status on April 30, 2002
  - 7,608 Alive and Outcomes Data Submitted in Last 18 mo
  - 276 Unknown Vital Status
  - 218 Deceased
## Results (year 5 data)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E+P (n = 5964)</th>
<th>Placebo (n = 5566)</th>
</tr>
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<td>Invasive breast cancer</td>
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How do we assess the effect?

WHI, JAMA 2002; 288:321-333
# WHI data – risk of cancer

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\[ Risk_1 = \frac{34}{5964} = 0.0057 \quad Risk_0 = \frac{12}{5566} = 0.0022 \]
Risk ratio (RR)

• Commonly referred to as Relative Risk

• Definition of RR

\[ RR = \frac{Risk_1}{Risk_0} = \frac{Risk(Rx)}{Risk(control)} \]
Meaning of RR

$$RR = \frac{Risk_1}{Risk_0} = \frac{Risk(Rx)}{Risk(control)}$$

- RR = 1, there is no effect
- RR < 1, beneficial effect
- RR > 1, harmful
WHI data – breast cancer RR

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\[
Risk_1 = \frac{34}{5964} = 0.0057 \quad Risk_0 = \frac{12}{5566} = 0.0022
\]

\[
RR = \frac{0.0057}{0.0022} = 2.59
\]
Doctors say: 1% breast cancer risk

Patient hears: 99% chance of no breast cancer

Do you Feel Lucky?
WHI data – an alternative expression

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<td>Risk of inv breast cancer</td>
<td>0.00570</td>
<td>0.00216</td>
</tr>
<tr>
<td>Risk of NON-cancer</td>
<td>0.99430</td>
<td>0.99644</td>
</tr>
</tbody>
</table>

\[
RR = \frac{0.9943}{0.99644} = 0.9964
\]

It seems that there was no effect!
• Risk ratio is a asymmetric measure
• Odds ratio (OR) = ratio of two odds
• OR is symmetric (nice property!)
Odds ratio (OR)

- Odds1 = odds of event in the Rx group
- Odds0 = odds of event in the control group

\[ OR = \frac{Odds_1}{Odds_0} \]

- OR = 1, there is no effect
- OR < 1, beneficial effect
- OR > 1, harmful
## An example of OR

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</tr>
<tr>
<td>Risk of inv breast cancer (P)</td>
<td>0.00570</td>
<td>0.00216</td>
</tr>
<tr>
<td>Risk of NON-cancer (1-P)</td>
<td>0.99430</td>
<td>0.99644</td>
</tr>
<tr>
<td>Odds: P / (1-P)</td>
<td>0.00573</td>
<td>0.00216</td>
</tr>
</tbody>
</table>

\[
OR = \frac{0.00573}{0.00216} = 2.65
\]
An example of OR – demonstration of symmetry

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<td>0.99644</td>
</tr>
<tr>
<td>Odds: (1-P) / P</td>
<td>174.4</td>
<td>462.8</td>
</tr>
</tbody>
</table>

$$OR = \frac{462.8}{174.4} = 2.65$$
A comparison between RR and OR

- **RR = 2.59**: Relative to placebo, E+P increased the risk of invasive breast cancer by 2.6 times.

- **OR = 2.65**: Relative to placebo, E+P increased the odds of invasive breast cancer by 2.6 times.

- Risk is not odds!
But be careful with odds ratio!

- OR can exaggerate an effect, particularly in studies with common events.
- Consider the following "discrimination study"
Figure 1. Patients as Portrayed by Actors in the Video Component of the Survey. Panel A shows a 55-year-old black woman, Panel B a 55-year-old black man, Panel C a 70-year-old black woman, Panel D a 70-year-old black man, Panel E a 55-year-old white woman, Panel F a 55-year-old white man, Panel G a 70-year-old white woman, and Panel H a 70-year-old white man.

Logistic regression analysis indicated that women (odds ratio, 0.60; 95 percent confidence interval, 0.4 to 0.9; $P=0.02$) and blacks (odds ratio, 0.60; 95 percent confidence interval, 0.4 to 0.9; $P=0.02$) were less likely to be referred for cardiac catheterization than men and whites, respectively. Analysis of race–sex interactions showed that black women were significantly less likely to be referred for catheterization than white men (odds ratio, 0.4; 95 percent confidence interval, 0.2 to 0.7; $P=0.004$).

<table>
<thead>
<tr>
<th></th>
<th>Catheterization</th>
<th>No Catheterization</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>652</td>
<td>68</td>
<td>720</td>
</tr>
<tr>
<td>Black</td>
<td>610</td>
<td>110</td>
<td>720</td>
</tr>
</tbody>
</table>
### Table 2. Presentation of Study Findings in Selected Major News Media.

<table>
<thead>
<tr>
<th>Source*</th>
<th>Headline</th>
<th>Characterization of Primary Finding</th>
<th>Interpretation</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nightline*7</td>
<td>“A Recent Study Shows That Doctors Diagnose Black and White Patients Differently”</td>
<td>“In our main analysis we found that blacks were 40 percent less likely to be referred for cardiac catheterization compared to whites.”</td>
<td>“A recent study shows that doctors diagnose black and white patients differently.”</td>
<td>“It’s having an adverse effect on the health of their patients and there is growing statistical evidence that if a patient is black he or she is significantly likely to get a lesser quality of medical care.”</td>
</tr>
<tr>
<td>USA Today6</td>
<td>“Heart Care Reflects Race and Sex, Not Symptoms”</td>
<td>“Blacks and women with chest pain are 40% less likely than whites or men to be referred by physicians for cardiac catheterization.”</td>
<td>“Race and sex of patients with chest pain influence whether they’re sent for the most definitive test for heart disease.”</td>
<td>“. . . the new study truly does indicate that a bias exists.”</td>
</tr>
<tr>
<td>Washington Post5</td>
<td>“Georgetown University Study Finds Disparity in Heart Care; Doctors Less Likely to Refer Blacks, Women for Cardiac Test”</td>
<td>“Physicians said they would refer blacks and women to heart specialists for cardiac catheterization tests only 60 percent as often as they would prescribe the procedure for white male patients.”</td>
<td>“Doctors are far less likely to recommend sophisticated cardiac tests for blacks and women than for white men with identical complaints of chest pain.”</td>
<td>“Authors suggest the differences are the consequences of race and sex bias [and that] the attitudes demonstrated in the survey exist in all medical specialties . . . you don’t have to be consciously racist to see the influence of race and gender playing out in treatment. That’s what this study confirms.”</td>
</tr>
<tr>
<td>Los Angeles Times4</td>
<td>“Heart Study Points to Race, Sex Bias”</td>
<td>“[Doctors] refer blacks and women to heart specialists 60% as often as they would white male patients.”</td>
<td>“Doctors are far less likely to recommend sophisticated cardiac tests for blacks and women than for white males.”</td>
<td>“Authors suggest the differences are the consequences of race and sex bias.”</td>
</tr>
<tr>
<td>Wall Street Journal1</td>
<td>“Study Suggests Race, Sex Influence Physicians’ Care”</td>
<td>“Doctors are only 60% as likely to order cardiac catheterization for women and blacks as for men and whites.”</td>
<td>“Women and blacks complaining of chest pain are less likely than men and whites to receive the best cardiac testing.”</td>
<td>“Unconscious prejudices among doctors may help explain [the findings].”</td>
</tr>
<tr>
<td>New York Times3</td>
<td>“Doctor Bias May Affect Heart Care, Study Finds”</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Since the *Wall Street Journal* and *New York Times* stories were based on the same Associated Press report, the characterization of the primary finding, interpretation, and stated implication were the same in the two newspapers. The quotations in the table are from the *New York Times*. 
Where is the truth?

<table>
<thead>
<tr>
<th></th>
<th>Catheterization</th>
<th>No catheterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>610</td>
<td>110</td>
</tr>
<tr>
<td>White</td>
<td>652</td>
<td>68</td>
</tr>
</tbody>
</table>

$OR = \frac{610 \times 68}{110 \times 652} = 0.59$

$P_{\text{black}} = \frac{610}{720} = 0.847$

$P_{\text{white}} = \frac{652}{720} = 0.906$

$PR = \frac{0.847}{0.936} = 0.94$

WHY?
# Relationship between OR and RR

Odds ratio is an *estimate* of relative risk

<table>
<thead>
<tr>
<th></th>
<th>Event</th>
<th>No event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Group 2</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

\[
RR = \frac{a}{a + b} \cdot \frac{c}{c + d}
\]

When \(a\) and \(b\) are small (relative to \(c\) and \(d\))

\[
RR \approx \frac{a}{b} \cdot \frac{ad}{bc} ; \quad OR \approx \frac{ad}{bc}
\]
Odds ratio overestimates relative risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of disease</th>
<th>Odds of disease</th>
<th>Comparison between RR and OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 ($p_1$)</td>
<td>Group 2 ($p_2$)</td>
<td>Nhóm 1 ($odd_1$)</td>
</tr>
<tr>
<td>1</td>
<td>0.001</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>0.01</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.02</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.15</td>
<td>0.05</td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
<td>0.30</td>
<td>0.11</td>
</tr>
<tr>
<td>6</td>
<td>0.15</td>
<td>0.45</td>
<td>0.18</td>
</tr>
<tr>
<td>7</td>
<td>0.20</td>
<td>0.60</td>
<td>0.25</td>
</tr>
<tr>
<td>8</td>
<td>0.25</td>
<td>0.75</td>
<td>0.33</td>
</tr>
<tr>
<td>9</td>
<td>0.30</td>
<td>0.90</td>
<td>0.43</td>
</tr>
<tr>
<td>10</td>
<td>0.33</td>
<td>0.99</td>
<td>0.49</td>
</tr>
</tbody>
</table>
For a constant RR, OR increases with background risk.
Absolute metrics
**Problem with RR: background risk**

<table>
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<th>Study 1</th>
<th></th>
<th>Study 2</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Rx</td>
<td>Placebo</td>
<td>Rx</td>
</tr>
<tr>
<td>N</td>
<td>100</td>
<td>100</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>Disease</td>
<td>20</td>
<td>10</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Risk (%)</td>
<td>20</td>
<td>10</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>RR</td>
<td>0.50</td>
<td></td>
<td>0.50</td>
<td></td>
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Absolute risk reduction

- $P_1$: risk of disease in Rx
- $P_0$: risk of disease in controls

$$\text{ARR} = P_1 - P_2$$
### WHI data – Absolute difference

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\[
Risk_1 = \frac{34}{5964} = 0.0057 \quad Risk_0 = \frac{12}{5566} = 0.0022
\]

\[
ARR = 0.0057 - 0.0022 = 0.0035
\]
Absolute Risk Reduction

- ARR = 0.0035

- Difficult to understand!

- Hard to convey to patients (and the public)
The “number needed to treat” turns 20 — and continues to be used and misused

Finlay A. McAlister MD MSc

Key points

• The number needed to treat is a useful measure for counselling patients about their potential to benefit from a particular intervention.
• It is sometimes used as a basis for comparing 2 or more therapies; however, it is important to appreciate that this number is not therapy-specific, but rather it is specific to the results of a single comparison.
• If it is to be used to compare treatments, the therapies must have been tested in similar populations with the same condition at the same stage, using the same comparator, time period and outcomes.
• The factors that influence the number needed to treat beyond the efficacy of the treatment must be taken into account to avoid drawing erroneous conclusions when comparing numbers needed to treat for 2 or more interventions.
NNT – number needed to treat


• Number of patients need to be treated in order for one to benefit

• Definition of NNT:

\[ NNT = \frac{1}{ARR} = \frac{1}{Risk_1 - Risk_0} \]
## WHI data – NNT (hip fracture)

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\[
Risk_1 = \frac{5}{5964} = 0.00084 \quad Risk_0 = \frac{8}{5566} = 0.0014
\]

\[
ARR = 0.00084 - 0.0014 = 0.00060
\]

\[
NNT = \frac{1}{0.00060} = 1670
\]
### NNH – number needed to harm

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\]

\[
ARR = 0.0057 - 0.0022 = 0.0035
\]

\[
NNH = \frac{1}{0.0035} = 286
\]
NNT is dependent on baseline risk

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Risk profile</th>
<th>Placebo</th>
<th>Active</th>
<th>NNT</th>
</tr>
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<tbody>
<tr>
<td>VERTEBRAL FRACTURE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIT-I</td>
<td>Alendronate</td>
<td>Prev fx, T &lt; -2.5</td>
<td>0.150</td>
<td>0.080</td>
<td>14</td>
</tr>
<tr>
<td>Proof</td>
<td>Calcitonin</td>
<td>Prev fx, T &lt; -2.5</td>
<td>0.156</td>
<td>0.108</td>
<td>21</td>
</tr>
<tr>
<td>MORE-2</td>
<td>Raloxifene</td>
<td>Prev fx, T &lt; -2.5</td>
<td>0.212</td>
<td>0.147</td>
<td>15</td>
</tr>
<tr>
<td>VERT-US</td>
<td>Risedronate</td>
<td>Prev fx, T &lt; -2.5</td>
<td>0.163</td>
<td>0.113</td>
<td>20</td>
</tr>
<tr>
<td>VERT-MN</td>
<td>Risedronate</td>
<td>Prev fx, T &lt; -2.5</td>
<td>0.290</td>
<td>0.181</td>
<td>9</td>
</tr>
<tr>
<td>Neer, 2001</td>
<td>PTH 20 mg</td>
<td>Prev fx, T &lt; -2.5</td>
<td>0.140</td>
<td>0.050</td>
<td>11</td>
</tr>
<tr>
<td>Neer, 2001</td>
<td>PTH 40 mg</td>
<td>Prev fx, T &lt; -2.5</td>
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<td>FIT-2</td>
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<td></td>
<td>Alendronate</td>
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<td>0.021</td>
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<td>MORE</td>
<td>Raloxifene 60</td>
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<td>0.023</td>
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<tr>
<td></td>
<td>Raloxifene120</td>
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<td>0.028</td>
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<tr>
<td>TROPOS</td>
<td>Strontium</td>
<td>T&lt;-2.5</td>
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<tr>
<td>Strontium</td>
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<td>Prev fx</td>
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<td>8</td>
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<td>HORIZON</td>
<td>Zoledronate</td>
<td>Prev fx</td>
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NNT và baseline risk

Number needed to treat (NNT) vs. Incidence of vertebral fracture in placebo group

- NNT: Number needed to treat
- Baseline risk: Baseline risk for vertebral fracture in the placebo group.

Graph shows the relationship between the number needed to treat (NNT) and the incidence of vertebral fracture in the placebo group.
Risk communication
The effect of risk framing (communication)

Which (hypothetical) study is more likely to be funded?

Prescription of drug

Questionnaire A on relative risk reduction

1. A cholesterol lowering drug treatment reduces the relative risk of a fatal and non-fatal myocardial infarction by 34%. This result is significant.

2. A cholesterol lowering drug treatment reduces the relative risk of a fatal myocardial infarction by 26%. This result is not significant.

3. A cholesterol lowering drug treatment increases the total mortality by 5.7%. This result is not significant.

4. During a cholesterol lowering drug treatment, 71 patients have to be treated for five years to prevent one fatal or non-fatal myocardial infarction. This result is significant.

Questionnaire B on absolute risk reduction

1. A cholesterol lowering drug treatment reduces the incidence of fatal and non-fatal myocardial infarction by 14 per 1000 patients and five years of treatment. This result is significant.

2. A cholesterol lowering drug treatment decreases the incidence of fatal myocardial infarction by one per 1000 patients and five years of treatment. This result is not significant.

3. A cholesterol lowering drug treatment increases the total mortality by 1.2 deaths per 1000 patients and five years of treatment. This result is not significant.

4. During a cholesterol lowering drug treatment 71 patients have to be treated for five years to prevent one fatal or non-fatal myocardial infarction. This result is significant.
RR result and prescription of drug

Score of treatment initiation

Myocardial infarction

Relative risk
Absolute risk
Summary

- RR is a common effect size measure
- OR is an estimate of relative risk
- For diseases with high risk, OR tends to overestimate effect size.
- Presentation of RR can influence decision-making
- NNT is probably more useful than RR/OR, but watch out for background risk
"Medicine is a science of uncertainty and an art of probability" (William Osler)

There will always be a need for “art of medicine” to interpret risk predictions and use them to inform patient decisions.