EPI-546: Fundamentals of Epidemiology and Biostatistics

Course Notes – Frequency and Effect Measures

Mat Reeves BVSc, PhD

Outline:

I. Quantifying uncertainty (Probability and Odds)
II. Measures of Disease Frequency (Ratios, Proportions and, Rates)
III. Prevalence and Incidence Rates
IV. Risks and Measures of Effect

I. Quantifying Uncertainty - Probability and Odds

Medical data is inherently uncertain. To characterize uncertainty we can use words like "unlikely", "possible", "suspected", “consistent with”, or "probable" to describe gradations of belief. However, the exact meaning of these qualitative descriptions has been shown to vary tremendously between different clinicians. Fortunately, uncertainty can be expressed more explicitly by using probability ($P$). Probability expresses uncertainty on a numerical scale between 0 and 1, and is simply calculated as a proportion (i.e., $P = a / b$ where $a$ represents the number of “events” and $b$ the total number at risk). Using probability avoids the ambiguity surrounding the use of qualitative descriptions – especially those like "not uncommon", or "cannot be ruled out" that too often contaminate the medical literature.

Odds are an alternative method of expressing uncertainty, and represent a concept that many people have trouble grasping. Odds represent the ratio of the probability of the event occurring over the probability of the event not occurring or $P / (1 – P)$. For example, if the odds of an event X occurring are 1 : 9 (read as “one to nine”), this implies that the event X will occur once for every 9 times that event X will not occur. Or in 10 events X will occur once or 10% of the time.

Probability ($P$) and odds both quantify uncertainty and can be converted back and forth using the following formulas:

$$Odds = \frac{P}{1–P} \quad \text{and,} \quad P = \frac{Odds}{1 + Odds}$$

Example: The probability of diabetes in a patient is 5%, the odds of diabetes are:

$$Odds = \frac{.05}{1 - .05} = \frac{.05}{.95} = 1 : 19$$

Example: The odds of diabetes are 1 : 19, the probability of diabetes is:

$$P = \frac{1/19}{1 + 1/19} = \frac{0.05263}{1.05263} = 0.05 \text{ or } 5\%$$
The following table shows the relationship between probability and odds. Notice that there is little difference between probability and odds when the value of probability is small i.e., $\leq 10\%$, whereas the difference is quite marked for large probability values.

Table 1. Relationship between probability and odds

<table>
<thead>
<tr>
<th>Probability</th>
<th>Odds</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>4</td>
</tr>
<tr>
<td>0.67</td>
<td>2</td>
</tr>
<tr>
<td>0.60</td>
<td>1.5</td>
</tr>
<tr>
<td>0.50</td>
<td>1.0</td>
</tr>
<tr>
<td>0.40</td>
<td>0.67</td>
</tr>
<tr>
<td>0.33</td>
<td>0.5</td>
</tr>
<tr>
<td>0.25</td>
<td>0.33</td>
</tr>
<tr>
<td>0.20</td>
<td>0.25</td>
</tr>
<tr>
<td>0.10</td>
<td>0.11</td>
</tr>
<tr>
<td>0.05</td>
<td>0.053</td>
</tr>
<tr>
<td>0.01</td>
<td>0.0101</td>
</tr>
</tbody>
</table>

Using the equations provided above, practice converting probabilities to odds (and vice versa). The importance of being able to master this conversion will become more apparent when we discuss diagnostic (clinical) testing and Bayes’ Theorem in later lectures.

Note that in clinical epidemiology, probability and odds are often used to express a physician's opinion about the likelihood that an event will occur, rather than necessarily the absolute probability or odds that an event will occur. This emphasis on quantifying a physician's opinion will again become more evident when we come to discuss Bayes’ Theorem.

---

1 For those of you with more than a passing interest in betting, note that betting odds are typically odds against an event occurring, rather than the odds for an event occurring. For example, if at the track the odds for a horse to win a race are 4-1 (“four to one”), this means that 4 times out of five the horse would not be expected to win the race i.e., the probability of winning is only 20%. In the unusual race where there is a clear favourite, the odds are switched to become odds in favour of an event. This is indicated by the statement “odds on favourite”. For example, the statement “Rapid Lad is the 5-4 odds on favourite for the 2.30 pm Steeplechase”, means that 5 out of 9 times the horse would be expected to win (the probability is therefore 55% - which is still only about an even shot). Got it?
II. Measures of Disease Frequency

A fundamental aspect of epidemiology is to quantify or measure the occurrence of illness in a population. Obtaining a measure of the disease occurrence or impact is one of the first steps in understanding the disease under study.

Ratios, Proportions and Rates

There are three types of descriptive mathematical statistics or calculations which are used to describe or quantify disease occurrence: ratios, proportions and rates.

i. Ratios

A ratio is expressed as: \[ \frac{a}{b} \] ("a" is not part of "b")

where a and b are two mutually exclusive frequencies, that is to say the numerator (= a, the number on top of the expression) is not included in the denominator (= b, the number on the bottom of the expression).

Examples:

i) The ratio of blacks to whites in a particular school was 15/300 or 1:20. Note that the two quantities are mutually exclusive - blacks are not included as whites (and vice versa). The observed frequencies in a ratio are often re-expressed by dividing the smaller quantity into the larger one. Thus dividing 15 into 300 re-expresses the ratio in terms of 1 in 20.

ii) The ratio of spontaneous abortions to live births in a village was 12/156 or 1:13. Again note the exclusiveness of the two frequencies - abortions cannot be included as live births.

ii. Proportion

A proportion expresses a fraction in which the numerator (the frequency of disease or condition) is included in the denominator (population). Fractions may be multiplied by 100 to give a percentage.

\[ \text{Proportion} = \frac{a}{b} \] ("a" is included in "b")

\[ \text{Percentage} = \frac{a}{b} \times 100 = \% \]

Examples:

i) The proportion of blacks in the school was 15/315 = 0.048 or 4.8%.

ii) Of 168 women that were confirmed pregnant by ultrasound examination, 12 had spontaneous abortion, thus the proportion of abortions was 12/168 = 0.071 or 7.1%.

iii. Rates

Rates are special types of proportions which express the relationship between an event (e.g., disease) and a defined population-at-risk evaluated over a specified time period. The numerator is the number of affected individuals in a given time period, while the denominator is the population at risk over the same time period.
Page dimensions: 612.0x792.0

Mathew Reeves, PhD
© Department of Epidemiology, Michigan State Univ.

Rate = \frac{a}{b} \quad ("a" \text{ is included in } "b")
\quad ("b" \text{ represents population-at-risk})

The essential elements of any rate are the definition of both a population-at-risk and a specific time period of interest. As discussed below there are two types of rates commonly used as epidemiologic measures: the cumulative incidence rate and the incidence density rate.

III. Prevalence, Cumulative Incidence Rate and Incidence Density Rate

There are three basic measures of disease frequency used in epidemiology: prevalence, cumulative incidence and incidence density. These measures are commonly confused, so understanding the differences between these measures is critical.

i. Prevalence

The prevalence of disease is the proportion of the number of cases observed compared to the population at risk at a given point of time.

Prevalence = \frac{\text{Number of cases observed at time } t}{\text{Total number of individuals at time } t}

Prevalence refers to all cases of disease observed at a given moment within the group or population of interest, whereas incidence (with which it is often confused), refers to new cases that have occurred during a specific time period in the population.

Example: Calculation of the prevalence of diarrhea on a cruise ship

You are asked to investigate an outbreak of diarrhea on a cruise ship. On the day you visit the ship, you find 86 persons on the ship. Of these you find that 8 are exhibiting signs of diarrhea. The prevalence of diarrhea at this particular time is therefore \(\frac{8}{86} = 0.092\) or 9.2%.

Other examples:

i) The prevalence of glaucoma in a nursing home on March 24\textsuperscript{th} was \(\frac{4}{168} = 0.024\).

ii) The prevalence of smoking in Michigan adults as measured by the Behavioural Risk Factor Survey in 2002 was 26.5%.

Prevalence is a function of both the incidence rate (see below for definition of incidence) and the mean duration of the disease in the population.

Prevalence = \text{Incidence} \times \text{Duration}

So, for a given incidence rate, the prevalence will be higher if the duration of the disease is longer - as an example, the prevalence of arthritis in an elderly population is high since there is no cure for the condition so once diagnosed the person has it for the rest of their lives. The prevalence will also be affected by the mortality rate of the disease, a lower prevalence would result if the disease was usually fatal – as an example, the prevalence of rabies will always be extremely low because it is almost universally fatal. Incidence rather than prevalence is usually preferred in epidemiologic studies when the objective is
to convey the true magnitude of disease risk in the study population. Conversely, prevalence is often preferred to incidence when the objective is to convey the true magnitude of disease burden in the study population – particularly for chronic disease like arthritis, diabetes, mental health etc.

There are two different measures of disease incidence:

ii. **Cumulative Incidence Rate (Risk)**

The most commonly used measure of incidence – particularly in clinical studies is the cumulative incidence rate (CIR), which is also referred to as “risk”. The CIR is defined as the proportion of a fixed population that becomes diseased during a stated period of time. Cumulative incidence incorporates the notions of a population-at-risk and a specific time period, hence it is regarded as a rate.

\[
CIR = \frac{\text{Number of newly disease individuals for a specific time period}}{\text{Total number of population-at-risk for same time period}}
\]

The CIR has a range from 0 to 1 and must be accompanied by a specified time period to have any meaningful interpretation (this is because the proportion of the population affected generally increases over time, thus it is important to know over what time period the CIR is calculated). The CIR is a measure of the average risk, that is, the probability that an individual develops disease in a specified time period. For example, if a doctor tells you that the 5-year CIR of disease X is 10%, then this implies that you have a 10% risk of developing the disease over the next 5 years (note that the term “risk” may also be described as the “chance” or “likelihood” of developing the disease). Finally, note that in evidence-based medicine parlance the CIR is often referred to as the “event rate”, and in the context of randomized trials, the CIR in the control group is called either the control event rate (CER) or the baseline risk, whilst the CIR in the treatment group is called either the experimental event rate (EER) or treatment event rate (TER). (Note that the FF text also refers to CIR as the Absolute risk in Table 5.3)

**Other important CIRs:**

A specific type of CIR is the **Case-Fatality Rate** which is the proportion of affected individuals who die from the disease. In our cruise ship example, if 3 of the 8 affected people had died as a result of the diarrhea then the case-fatality rate would have been \( \frac{3}{8} = 0.37 \) or 37%. The case-fatality rate is usually associated with the seriousness and/or the virulence of the disease under study (the higher the case fatality rate the more virulent the disease).

Another specific type of CIR is the **Attack Rate** which is commonly used as a measure of morbidity (illness) in outbreak investigations. It is calculated simply as the number of people affected divided by the number at risk. For our cruise ship example, after 5 days of the outbreak 12 people developed diarrhoeal disease. The attack rate at that time was therefore \( \frac{12}{86} = 0.14 \) or 14%.

iii. **Incidence Density Rate**

A second type of incidence rate which is more commonly used in larger epidemiologic studies is the incidence density rate (IDR). The IDR is a measure of the instantaneous...
force or speed of disease occurrence.

\[
IDR = \frac{\text{Number of newly disease individuals}}{\text{Sum of time periods for all disease-free individuals-at-risk}}
\]

The numerator of the IDR is the same as the CIR – that is, the number of newly diseased individuals that occur over time. However, it is the denominator of the IDR that is different - it now represents the sum of the disease-free time experience for all the individuals in the population. The denominator of the IDR is termed "person-time" or "population time" and represents the total disease-free time experience for the population-at-risk (the concept of person-time is explained further below). The IDR ranges from 0 to infinity, while its dimensionality is the reciprocal of time i.e., time\(^{-1}\).

Whereas, the CIR simply represents the proportion of the population-at-risk who are affected over a specified time period, the IDR represents the speed or instantaneous rate at a given point in time that disease is occurring in a population. This is analogous to the speed with which a motor car is traveling - that is, miles per hour is an instantaneous rate which expresses the distance traveled for a given unit of time. An incidence rate of 25 cases per 100,000 population-years expresses the instantaneous speed which the disease is affecting the population. The IDR is a dynamic measure meaning it can change freely just as the speed of a car can. An IDR of 0 implies that the disease is not occurring in a population, whereas, an IDR of infinity is its theoretical maximum value and implies an instantaneous, universal effect on the population (if you want an example of this - think of a catastrophic event that kills everyone instantaneously! – this translates to a mortality rate of infinity).

The concept of person-time:
The calculation of "person-time" requires that the disease-free time contributed by each individual is summed across everyone in the population. As an example:

Scenario A: 100 people are followed for 1 year and all remain healthy, so they contribute 100 years of disease-free person-time (i.e., 100 x 1 year).

Scenario B: 200 people are followed for 6-months and all remain healthy, so they contribute 100 years of disease-free person-time (i.e., 200 x 0.5 year).

Scenario C: 100 people are followed for 1-year, 80 remain healthy but 20 develop disease at an average of 6-months. The total disease-free person-time is now 90 years (i.e., 80 x 1 year + 20 x 0.5-year).

The particular unit of "population time" (i.e., days, weeks, months, years) that is used depends entirely on the context of the study and the disease. In chronic disease studies, a standard measure is 100,000 person years, whereas in infections disease (especially outbreak investigations we might chose to express population time in terms of person-days or person weeks - whatever makes the most sense). Since it is obviously impractical to count the exact person-time for large populations it is usually approximated by estimating the population size midway through the time period. For example, to calculate the mortality rate for people 60 - 65 year of age in 2000, the population time can be
approximated by estimating the size of this population on July 1st, 2000 and expressing this value in person years.

**Other important IDR:**
A specific type of incidence rate is the mortality (death) rate, defined as the incidence rate of death per "population time". It is calculated by:

\[
\text{Mortality rate} = \frac{\text{Number of deaths during time period } t}{\text{Total population time at risk during time } t}
\]

The denominator for the mortality rate is again the population time. The mortality rate measures the speed of death in the population and is either calculated for all causes combined (so called “all-cause mortality”) or for a specific disease or cause (e.g., so called “disease specific mortality”). It should be clearly distinguished from the case-fatality rate described earlier. The denominator for the case-fatality rate is the number of affected individuals, not the population time at risk.

The use of the terms case fatality rate and mortality rate are often confused, yet they are very different as illustrated in the following example. A study by McGovern (NEJM, 1996;334:884-90) looked at trends in mortality and survival from acute myocardial infarction (MI) in the general population of Minneapolis, MN. They found the 28-day acute MI CFR for men and women to be 10% and 12%, respectively, while the mortality rates for acute MI in men and women were 110 per 100,000 person years, and 35 per 100,000 person years, respectively. So while the CFRs were very similar, the mortality rates were very different. Only the mortality rate confirms what your intuition tells you - that the mortality from MI is higher in men than women – in this case the death rate from acute MI is about 3 times higher.

Finally, for the mathematicians among you, the section at the very end of this chapter explains how the CIR and IDR are related to each other (this section is optional).

**IV. Risks and Measures of Effect**
In clinical studies it is common to calculate the risk or CIR of an event in different populations or groups. For example, in a randomized clinical trial (RCT) the risk or CIR of an event in the treated and control groups are calculated and compared (note that these risks may also be referred to as *event rates*). By taking either the *ratio* of these two measures or the *difference* in these two measures we can calculate two fundamental *measures of effect* - the *relative risk* and the *absolute risk* – that, in the case of an RCT, quantify the impact of the treatment.

To illustrate the calculation and interpretation of these measures, we will use the following data from an RCT designed to measure the mortality rate associated with two treatments (ligation and sclerotherapy) used for the treatment of bleeding oesophageal varices (Ref: Stiegmann et al, NEJM 1992;326:1527-32). The 65 patients treated with sclerotherapy are regarded as the control group (since that was the standard of care at the time), and the 64 treated with ligation were regarded as the “new” treatment group. The risk (or CIR) of mortality was calculated for each group:
Example – RCT of Endoscopic Ligation vs. Endoscopic Sclerotherapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Death</th>
<th>Survival</th>
<th>Risk ( t ) = 18 / 64</th>
<th>Risk ( c ) = 29 / 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligation ((t))</td>
<td>18</td>
<td>46</td>
<td>0.28</td>
<td>0.45</td>
</tr>
<tr>
<td>Sclerotherapy</td>
<td>29</td>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk \( t \) and Risk \( c \) represent the risk of death in the treatment and control groups, respectively. Risk \( c \) is often referred to as the baseline risk.

i. **Relative Risk (RR)**

In this RCT example, the Relative Risk (RR) is the ratio of the risk in the treated group (Risk \( t \) or TER), relative to the risk in the control group (Risk \( c \) or CER).

\[
RR = \frac{\text{Risk in treatment group}}{\text{Risk in control group}} = \frac{\text{Risk}_t}{\text{Risk}_c}
\]

The RR is a measure of the strength or magnitude of the effect of the new treatment on mortality, relative to the effect of the standard (control) treatment. In this example, the RR is 0.28/0.45 = 0.62, indicating that the risk of death after ligation is 0.62 times lower than the risk of death in the sclerotherapy treated group. In other words, the risk of death with ligation is 62% (or about \( \frac{2}{3} \)) of that of sclerotherapy (so if you needed treatment for oesophageal varices you’d probably pick treatment with ligation over sclerotherapy). Like all ratio measures the null value of the RR is 1.0 (i.e., the point estimate that indicates no increase or decrease in risk).

Although the RR is a very important measure of effect, it is somewhat limited in its clinical usefulness, since it fails to convey information on the likely effectiveness of clinical intervention - a better measure of the absolute benefit of intervention is given by the difference in risks between the two groups (i.e., absolute risk reduction (ARR)).

In the context of an epidemiologic study, specifically cohort studies, the RR measures the strength or magnitude of association between an exposure (or risk factor) and a disease or other outcome. It is calculated as the ratio of the risk in a group exposed to the risk factor, relative to the risk in an unexposed group. For example if the lung cancer mortality rate in lifetime heavy smokers (> 25 cigarettes/day) is 4.17 per 1,000 person years (which is equivalent to a CIR of 0.417% per year) and in lifetime non-smokers it is 0.17 per 1,000 person years (equivalent to a CIR of 0.017% per year), then the RR = 0.417/0.017 = 24.5, indicating that heavy smokers are almost 25 times more likely to die of lung cancer.
than non-smokers. One of the reasons that RR are favoured by epidemiologists is that they are in general, fairly constant across different populations, and so can be “transported” from one study to another (so, for example, the RR of 25 for lung cancer mortality due to heavy smoking was calculated from the famous British Doctors Study (Doll R et al, BMJ June 26th, 2004), it is likely that the effect of heavy smoking i.e., the RR is similar in the US or elsewhere).

A limitation of the RR calculated in cohort studies is that it is not a very useful measure of the impact of a risk factor on a population, since it does not include any information on the frequency or prevalence of the risk factor (e.g., smoking) in the population (see Population Attributable Risk Fraction).

Note that the Odds Ratio (OR) (see below) has a similar interpretation as the RR in that it also measures the strength or magnitude of the association between exposure and outcome.

Note that the RR is only used in study designs where the actual incidence or risk of an event can be measured i.e., RCTs and cohort studies. A general epidemiological rule for interpreting the magnitude of the RR (or OR) for a factor that increases risk of an outcome is that values of 2.0 or less are regarded as small, values of >2 - 5 are moderate, and those greater than 5 are large effects. For a factor that decreases risk the equivalent RR estimates for small, medium and large effects are >0.5, 0.5 - 0.2, and < 0.2, respectively. The magnitude of the RR is important to epidemiologists because the larger the value the less likely it is that the particular relationship is due to chance or other confounding biases. For example, one of the reasons that smoking is regarded as cause of lung cancer is that the RR for heavy smoking is ~25. It is extremely unlikely that such a large RR could be explained by some other confounding factor.

ii. The Relative Risk Reduction (RRR)

The Relative Risk Reduction (RRR) is a measure of effect that is commonly used in the context of the RCT. The RRR is nothing more than a re-expression or re-scaling of the information provided by the RR. However, in clinical environments the RRR has more direct meaning than the RR since it indicates by how much in relative terms the event rate is decreased by treatment.

The RRR is calculated by as the 1 – RR or by dividing the absolute risk reduction [ARR] (see below) by the baseline risk (Risk\(_c\)):

\[ RRR = 1 - RR \quad \text{or} \quad \frac{ARR}{Risk_c} = \frac{Risk_c - Risk_t}{Risk_c} \]

In our RCT example, the RRR is therefore 1 – 0.62 = 38% (or 0.45 - 0.28 / 0.45 = 38%). That is, the death rate is 38% lower after ligation treatment, compared to sclerotherapy treatment. Thus the RRR represents the proportion of the original baseline (or control) risk that is removed by treatment.
The RRR is applied in the context of a treatment that reduces the risk of some adverse outcome. The RRR indicates the magnitude of the treatment effect in relative terms. As a general rule, treatments with a RRR of 10% or less are regarded as having a small effect, those with a RRR of 10-30% are moderate, and those >30% are regarded as large treatment effects. (Note that in absolute terms, the effect of treatment would depend on both the RRR and the baseline risk - as quantified by the absolute risk reduction).

**iii. The Absolute Risk Reduction (ARR)**

A more clinically useful measure of the effect of a treatment is the absolute risk reduction [ARR] (also confusingly referred to as the attributable risk in the Fletcher text and may be called the risk difference (RD) elsewhere). The ARR is simply the absolute difference in risks between the control and treatment groups.

\[
ARR = Risk_c - Risk_t
\]

For the RCT example, the ARR is therefore \(0.45 - 0.28 = 0.17\) or 17%. The ARR represents the absolute difference in the risk of death between the two treatment groups. So the risk of death is 17% lower with ligation treatment, compared to sclerotherapy treatment. Like all difference measures the null value of the ARR is 0 (i.e., the point estimate that indicates no increase or decrease in risk).

The ARR is a simple and direct measure of the impact of treatment – in this example it tells you that 17% more patients treated with ligation will survive compared to using sclerotherapy. Contrast this information with that provided by the RR which tells you that ligation results in a death rate about 2/3rd that of sclerotherapy – the RR does not tell you about the absolute benefit or effect of the treatment (only its relative benefit). It is for this reason that the ARR is the preferred measure when discussing the benefits of clinical interventions at the individual patient level.

A critically important point about the ARR is that it will vary depending on what the baseline risk is in the control group (\(Risk_c\), as illustrated in the figure below. This figure shows the ARR for the same treatment effect (RRR = 0.33) for three populations that have baseline (control) risks or event rates of 30%, 10%, and 1%, respectively. Note that the ARR, which indicates the absolute impact of the treatment, varies from 10% in population 1 to a meager 0.33% on population 3. Thus the absolute benefit of treatment depends upon how much risk there is in the population before the treatment is applied (i.e., the baseline risk). When the baseline risk is high (as in population 1) the treatment can have a large impact (it will reduce the number of subjects who have the outcome by 10%), whereas when the baseline risk is low (population 3) the effect of treatment is minimal (it reduces the number of subjects who have the outcome by only 0.33%).

Since the magnitude of the baseline (control) event rate can vary widely from one population to another or from one age/sex/gender group to another, the ARR for a given treatment can vary markedly from one clinic or hospital to another. The bottom line is that an ARR calculated in one study or for one population **cannot** be directly applied (or transported) to another population.
Effect of different baseline risks on the ARR given a common RRR of 0.33

ARR= 10%  ARR= 3.3%  ARR = 0.33%

It is important to note that in contrast to the ARR we make an explicit assumption that the relative impact of an intervention (as measured by the RRR) is regarded as a constant entity – i.e., we assume that it does not change from one population to another. Thus, in the case of the treatment of oesophageal varices we assume that ligation treatment reduces the relative risk of death by 38% in all populations, whereas the absolute effect (as measures by the ARR) will be dependent on the baseline risk in the population. The assumption of constant RRR across all populations can of course be challenged as it is likely that the effect of treatment would differ across widely different populations.

iv. The Number Needed To Treat (NNT)
The number need to treat (NNT) illustrates the number of patients who would need to be treated in order to prevent one adverse event. It is calculated simply as the inverse of the ARR:

$$NNT = \frac{1}{ARR}$$

Using our RCT example, the NNT is $1/0.17 = 5.9$ (or 6). This means that for every 6 patients who received ligation treatment rather than sclerotherapy treatment, one death is prevented. The NNT can be seen as a simple re-expression of the information provided by the ARR, however, people have a hard time interpreting absolute probabilities (like an ARR of 17%). So converting these probabilities into “real numbers” (as the NNT does)

---

2 One last point about absolute risks. The ARR is used when the treatment group results in a lower event rate than the control group (i.e., when the RR is < 1.0), which is typical of therapeutic trials where the treatment is designed to reduce the occurrence of a bad outcome. However, treatments can also have harmful side effects. In this case we would see a RR of > 1, and would calculate an ARI or Absolute Risk Increase which would indicate in absolute terms how much more harmful events are seen in the treatment group. In turn, the ARI is used to calculate a NNH (number needed to harm), similar to the concept of the number need to treat. The potential confusion cause by referring to ARR or ARI is one of the reasons that the term risk difference (RD) – the absolute difference between two risks – is preferred by some.
provides more readily interpretable information. Note that since the ARR increases with increasing time it will have a concomitant effect on the NNT (which will get smaller), also just like the ARR, the NNT will be influenced by differences in baseline event rates.

The NNT is useful because it conveys the amount of work required to take advantage of the potential clinical benefit of an intervention. A high number indicates that a lot of effort will be expended to gain any benefit. For example, the 1-year NNT for primary stroke prevention in adults < 45 years of age using statin drugs is a staggering 13,000 – meaning that 13,000 patients would have to be treated with statins for one year to prevent one stroke event. However, the NNT for secondary stroke prevention (that is, among patients who have already suffered a stroke) using statins is only 57. Why would the NNT for the same drug be so different between these two applications?

The value of the NNT depends on the relative efficacy of the intervention (as indicated by the RRR) and the underlying baseline risk. This is demonstrated in the following table, notice the wide range of NNT values (Laupacis et al, NEJM 1988;318:1728-33):

<table>
<thead>
<tr>
<th>Base-line Risk (%)</th>
<th>Relative Risk Reduction (RRR)</th>
<th>0.5</th>
<th>0.25</th>
<th>0.20</th>
<th>0.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td></td>
<td>3</td>
<td>7</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>7</td>
<td>13</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>20</td>
<td>40</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>40</td>
<td>80</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>200</td>
<td>400</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>0.1</td>
<td></td>
<td>2000</td>
<td>4000</td>
<td>5000</td>
<td>10000</td>
</tr>
</tbody>
</table>

v. The Population Attributable Risk (PAR) and the Population Attributable Risk Fraction (PARF)

In terms of understanding the impact of a risk factor on the incidence of disease in the population at large it is necessary to know both the relative effect of the risk factor on disease risk (i.e., the RR), as well as the prevalence of the risk factor in the population. Clearly, a risk factor would be expected to result in more disease in a population if it is both strongly associated with disease risk (i.e., has a large RR) and is more common within the population. Two measures, the Population Attributable Risk (PAR) and the Population Attributable Risk Fraction (PARF), are used to quantify the impact of a risk factor on disease at the population level under the implicit assumption is that the risk factor is a *cause* of the disease.

The Population Attributable Risk (PAR) represents the excess disease in a population that is associated with a risk factor. It is calculated from the absolute difference in disease risks between the exposed and non-exposed groups (i.e., the risk difference [RD]) and the
prevalence (Prev) of the risk factor in the population i.e., PAR = RD x Prev. The PAR represents the excess disease (or incidence) in the population that is caused by the risk factor.

The Population Attributable Risk Fraction (PARF) represents the fraction of total disease in the population that is attributable to a risk factor. It is calculated as the PAR divided by the total incidence in the population. Thus it represents the proportion of the total incidence in the population that is attributable to the risk factor i.e., PARF = PAR/Total incidence. The PARF represents the maximum potential impact of prevention efforts on the incidence of disease in the population if the risk factor were eliminated. Again, the implicit assumption is that the risk factor is a cause of the disease, and that removing it would reduce the incidence of disease.

Example: Lung cancer mortality and smoking in British doctors (Data from earliest report on the cohort published by Doll and Hill, BMJ 1964 – See Table 5.4 in FF).
Total mortality rate from lung cancer= 0.56/1,000 person years
Mortality rate from lung cancer in ever smokers = 0.96/1,000 person years
Mortality rate from lung cancer in never-smokers = 0.07/1,000 persons years
RR of ever smoking and lung cancer death = 0.96/0.07 = 13.7
Prevalence of smoking (among British doctors in the 1950’s) = 56%

PAR = RD x Prev = [0.96 – 0.07] x 0.56 = 0.50/1,000 person years (or 0.05% per year). This represents the absolute excess of lung cancer mortality among the doctors due to smoking.

PARF = PAR/Total mortality = 0.50/0.56 = 89%. This represents the proportion of all lung cancer deaths in this population that is due to smoking (it indicates that the vast majority of lung cancer death is caused by smoking alone).

The PARF can also be calculated directly if the RR and prevalence are known using the following equation:

$$\text{PARF} = \frac{\text{Prev}.(\text{RR}-1)}{1 + \text{Prev}.(\text{RR}-1)}$$

So, if the RR = 13.7 and Prev = 56%, then the PARF = \([0.56(13.7-1)]/[1 + 0.56(13.7-1)] = 88\%\) (slight difference is due to rounding). Note that the potential impact of prevention efforts can be gauged by calculating the PARF using lower estimates of prevalence. For example if the prevalence of smoking was reduced to, say, only 10%, the PARF of smoking for lung cancer mortality would be reduced to 56% i.e., PARF = \([0.10(13.7-1)]/[1 + 0.10(13.7-1)]\).

The PAR and PARF indicate the potential public health significance of a risk factor. For example, a large risk that is very rare is unlikely to cause much disease in the population (and therefore has less public health significance), as opposed to a small risk that is very common which would lead to a high PARF with more public health significance. For example, a risk factor that has a big effect (i.e., RR= 10) but is rare (P = 0.1% or 0.001) has a PARF of 1%, whereas a risk factor that has a small effect (i.e., RR = 2) but is common (P = 40% or 0.4) has a PARF of 44%. (See the lecture on Cohort Studies for further discussion of the PARF).
The Odds Ratio (OR)

The Odds Ratio (OR) is the measure of effect of choice for case control studies (CCS), because the CCS design is not able to quantify the actual incidence or risk of disease in exposed and non-exposed groups. (see lecture 9 for further discussion) The OR is usually a good approximation of the RR – and it represents a clever fix to get around the problem that the case control design cannot generate the RR. As the name implies the OR is a ratio of odds, specifically, the odds of exposure in cases compared to the odds of exposure in controls. Like the RR the OR describes the magnitude or strength of an association between an exposure and the outcome of interest and like the RR its null value is 1.0. An OR > 1.0 indicates a positive association between the exposure and disease, while an OR < 1.0 indicates a negative association.

As an example of the calculation of an OR, imagine we had done a case control study rather than a cohort study to assess the relationship between ever smoking and death from lung cancer in the British doctors. We assess the smoking status in 100 lung cancer deaths (the cases) and 100 doctors who were alive or had died of something other than lung cancer (the controls). We get the following data:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lung CA Death</th>
<th>No Lung CA Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>95 (a)</td>
<td>56 (b)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>5 (c)</td>
<td>44 (d)</td>
</tr>
</tbody>
</table>

Odds of exposure: 95/5 = 19.0, 56/44 = 1.27

The OR is calculated as the ratio of the odds of exposure in the cases (i.e., 95/5) divided by the odds of exposure among the controls (i.e., 56/44) which equals 15.6. In this example the OR is a very good approximation of the RR that was generated from the cohort study design (i.e., 13.7). One would interpret the OR as saying that the odds of death due to lung cancer was 15.6 times higher in smokers compared to non-smokers. As a general rule the OR more closely approximates the RR when the outcome of interest is rare in the underlying population (i.e., <10%). In this case, the rate of lung cancer mortality in the overall population is very rare i.e., 0.56 per 1,000 persons/year (equivalent to 0.056% per year). The fact that the OR is a good estimate of the RR when the event or disease is rare also makes sense given the data in Table 1 which shows that the odds and probability are more alike when the risk is small (<10%).

Note that the OR was calculated using the numbers in the 4 cells labeled a, b, c, d –
specifically, a/c divided by b/d. The equation simplified to (a x d)/(b x c) which is known as the cross-product ratio. One advantage of the OR is that it is symmetrical, meaning that rather than calculating the odds of exposure in the cases relative to the controls, if you compare the odds of disease among the exposed (a/b) relative to the odds of disease amongst the non-exposed (c/d) you end up with the same OR (since both approaches reduce to the ad/bc cross product ratio) (See lecture on CCS design for more discussion of the OR).

While the OR is the effect measure of choice in CCS designs, another potential advantage of the OR is that it can be used in any other type of study design i.e., cross-sectional studies, cohort studies, RCTs, and meta-analyses. Although the OR is widely used across all sorts of designs the savvy reader should not forget that the OR has several disadvantages over the RR. These include:

1) The OR deviates from the true RR as the baseline risk in the untreated group (CER) increases – the effect is noticeable once the risk is > 10% which is often the case in RCTs, and the deviation can be substantial when baseline risk gets to be > 50%.
2) The OR deviates from the true RR as the treatment effect gets larger – the effect is particularly noticeable once the RR reaches < 0.75 or greater.
3) The OR is always further away from the null value (1.0) than the RR – thus the treatment effect is always over-estimated by the OR compared to the RR.
4) There is nothing clinically intuitive about the OR.

These disadvantages imply that when the data can be specified in terms of the RR i.e., the RCT or cohort design, then the RR should be the effect measure of choice.

**Optional section:**

What is the relationship between the CIR and the IDR?

Assuming a constant incidence rate (IDR) and no other causes of disease (i.e., competing risks). The relationship between the CIR and IDR is described by the following exponential function:

- \( CIR_t = 1 - e^{-IDR \Delta t} \) where \( t = \text{time} \)

When the IDR is small (< 0.1), then

- \( CIR_t \sim IDR \Delta t \)

So to estimate small risks, simply multiple the IDR by the time period. For example, if the IDR = 10 / 1,000 PY (equivalent to 1%), the 5-year CIR or risk is 5 x (10/1,000) or 5%.