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## RELATIVE RISK, ODDS RATIO, ATTRIBUTABLE RISK AND NUMBER NEEDED TO TREAT

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## 1 EPIDEMIOLOGICAL INDICES

The research may or may not be epidemiological but there is a high likelihood that it would use the epidemiological indices discussed in this note. Rate, risk, hazard, incidence, and prevalence are everyday indices of disease occurrence that are used in a large number of research endeavours. Although these indices apparently look simple but many researchers are not fully comfortable in their usage. The following description should be helpful in that case.

### RATE, RISK, HAZARD, AND ODDS

Depending upon the focus, different indices are used to assess disease occurrence in a group of subjects. These can be explained as follows.

#### RATE AND RATIO

Akin to speed, rate is a measure of rapidity of occurrence of an event in a population. Thus time is an essential element of this concept. It has to be per unit of time – per day, per months, per year, etc. Rate is the frequency or the number of events that occur in a defined period of time divided by the population at risk for that event during that period. If the population varies from time to time within that period, such as at the beginning of the year and at the end of the year, it is conventional to use the average population, say at the middle of the year as an approximation. Here in lies the catch. If a city has a population of 10,000 at the beginning of the year and 6,000 perish due to a severe earthquake in the month of February, the mid-year population would be nearly 4,000 (some would die due to routine causes and some births may take place). In that case the death rate, since based on mid-year population, for that year would be  $6,000 / 1,000 / 4,000$  or 1,500 per 1,000 population, or 1.5 per person! This rate would be entirely different if earthquake deaths occur in the latter half of the year. This dramatic example illustrates that the mid-year or average population can be fallacious if deaths, for that matter any event for which rate is required, do not occur

regularly throughout the period at nearly a uniform rate. In fact the concept of rate is not applicable when such unusual spikes or dips occur.

Ratio is the frequency of one item compared to another. Albumin-globulin ratio as a biochemical parameter and embolus-to-blood ratio for Doppler are examples. Epidemiologists use sex ratio and dependency ratio. In all ratios, the two items under comparison are different entities, and none is part of the other.

### RISK AND HAZARD

In general conversation, risk and odds are used interchangeably. Actually they do not have same meaning. We shortly explain odds but risk is the chance that a person without the disease will develop the disease in a defined period. It can be any other event or outcome such as accidental injury and vision becoming <6/60. The term is generic and not restricted to adverse outcomes. It could be 'risk' of survival or risk of reduction in side-effects, or risk of conception. Risk could be 1 in 1000 or 0.05 or 0.20 but can not exceed one. It is a decimal number although often expressed as percentage. Although the implication is for future events but the calculation is based on previous experience. The denominator is the number of persons exposed to the risk and numerator is that part of the denominator that develops the outcome. For example, ten-year risk of coronary heart disease (CHD) may be 9% in a population of age 40–79 years. Such an estimate can be obtained only after follow-up of subjects for a 10-year period. This is based on past experience but would be used on future subjects. The population at risk for this calculation is not what was in the middle of the period but what was in the beginning of the period because all those are exposed to that risk. A measure of risk is the incidence rate, where also the denominator is the population at risk. This is discussed slightly later in this section.

Risk can not exceed one but hazard has no such restriction. If hundreds die within a few hours after plane crash, obviously the hazard of death is exceedingly high at that time than at a normal time. Hazard can be understood as the instantaneous rate of death — for that matter, of any event of interest. It is sometimes called the **force of mortality** for deaths, force of morbidity for ill-health, and force of event-occurrence in general. It can also be understood as the intensity with which events occur at a *point of time*. Hazard can increase steeply in situations such as calamity and epidemic. If constant over a period of time, hazard can be obtained by dividing the number of events in the target population by the exposure period.

In many research setups, hazard in the exposed group is compared with the hazard in the unexposed group, such as comparing the rate of adverse reactions in the test and the control group. In such setups, the interest generally is in the **hazard ratio** instead of hazard itself. Hazard of death due to local anaesthesia may be one in a 100,000 but it could be one in a thousand for general anaesthesia. Thus the latter is 100-times of the former. Hazard itself may continuously vary over the follow-up period but in many situations the hazard ratio remains constant throughout that period.

### ODDS

Now reverse the gear and consider the chance of presence of an antecedent in a group of subjects. If 67% of all hypertension are obese, the odds are said to be 67:33 or 2 to 1. A hypertensive is twice as likely to be obese as non-obese. This quirky measure is explained further in Section 2 but note at this stage that odds are generally calculated for an antecedent rather than an outcome.

## **INCIDENCE AND PREVALENCE**

Incidence and prevalence are among the most commonly used indices of disease occurrence. Yet the usage of these terms in literature is sometimes not appropriate.

### **INCIDENCE**

A prospective study is inherent in the definition of risk. Follow a group of persons without the outcome for a certain period and see in how many the outcome develops. A popular measure of risk is **incidence**. Risk is generally stated per person whereas incidence as percent or per thousand or even per million if it is very small. Both however express the same phenomenon. Both are based on new cases arising in a prefixed period of time. However, as already mentioned, risk has connotation for future. On the other hand, incidence is factual – based on empirical evidence.

The concept of incidence is based on the premise that the event of interest can occur only once in life-time of one person, or at least during the defined time period under review. But events such as asthma, otitis media, and angina can recur within a short period. The term then used is **incidence density**. This is comparable to hazard discussed earlier.

Another facet of incidence of disease is the **attack rate** used particularly for infectious diseases. This is the number of new spells (one person can have many spells such as of diarrhoea) in a specified time interval as percentage of the total population at risk during the same time interval. In case of epidemics, the denominator is the population exposed to the epidemic. It becomes **secondary attack rate** when the denominator is changed to subjects exposed to the primary cases. **Primary cases** are those that are already infected and capable of spreading infection.

### **PERSON-YEARS**

In many prospective studies, it is extremely difficult to follow each subject for the same length of time. For a study on breast cancer that is to be completed in five years, two to three years may be required for just enrolling the desired number of women with lump in breast. Once enrolled, some may quit the study and some could become untraceable after some time. Thus the duration of follow-up will vary from woman to woman. In such instances, one epidemiological tool is **person-years**. Just add years of follow-up for different women and get person-years. Use this to calculate incidence per 100 person-years. This concept assumes that the risk in, say, fourth year of follow-up is the same as in second year of follow-up. That is, the risk should be time-invariant. In most practical situations this condition is satisfied but watch out if this is indeed so in your research setup. An example where this does not hold is risk of kidney failure after transplantation. This risk is much more in the beginning than after two years of receiving the kidney.

The concept of person-years is useful also in the case of recurrent episodes in the same person. Time of follow-up after each episode can be added to calculate person-time. If the first child is followed-up for 12 months, second for 15 months and third for 10 months, and a total of 7 episodes of diarrhoea occurred, the incidence density is  $7 / (12+15+10)$  or 18.9 per 100 child-months.

### **PREVALENCE**

Opposed to incidence that relates to onset, cross-sectional surveys or descriptive studies give **prevalence** that measures the magnitude of presence of disease. If peptic ulcer is found

in 5% of adults of upper socio-economic status in a survey in Timbaktoo in the year 2005, this is the prevalence rate. Actually it is not a rate but is only a proportion. It does not measure speed of occurrence. Prevalence is an appropriate measure for chronic conditions and not for acute disorders. Note that prevalence counts all existing cases at a *point of time* whereas incidence counts new cases arising in a *period of time* such as per month or per year. Incidence is the inflow and prevalence is the stock. It is easy to imagine that larger the duration of disease, higher is the backlog and more is the prevalence if outflow in terms of remissions and deaths is not equally rapid. In the case of stable rates for extended times,

$$\text{Prevalence} = \text{Incidence} \times \text{Average duration of disease.}$$

Incidence is difficult to obtain because it requires a prospective study. Prevalence can be easily obtained by a cross-sectional study. Average duration of disease is generally known to the clinicians by experience, else can be obtained from records. When these two are available, incidence can be obtained by the preceding formula – thus saving the cost of a prospective study. However, the relation is not so simple in many situations due to changing rates and other intervening factors (see Box 1).

**Example 1: Prevalence from incidence of breast cancer**

Suppose an average of 3 new cases of breast cancer is detected each year per 1000 population of women of age 45-54 years in the hypothetical city of Narinagar. If the average duration of survival is 5 years, the prevalence of breast cancer at any point of time would be nearly ( $3 \times 5 =$ ) 15 cases per 1000 population of such women. If the population of such women is 30,000 in that city, expect to see 450 cases. Hospitals should be geared to meet the demand of services for 450 cases of breast cancer in that city.

**Box 1: Relation between incidence and prevalence is not so simple**

A basic assumption in the simple relationship we described in the text among incidence, prevalence and duration of disease is that these remain same over an extended period of time. This does not happen in many cases. Also there are other factors such as ageing and mortality that could affect this relationship.

Consider age-related cataract. The duration of this disease could be lifetime. The duration would cut-short by the general mortality, as well as by possibly accelerated deaths in cataract cases that may be in poor health compared to the non-cataract persons. Also, cataract can be ‘cured’ by procedures such as lens implant. And this would not be insignificant number of cases. Thus the simple relationship between incidence, prevalence and duration does not hold in this case.

A recent example is that of human immunodeficiency virus (HIV) infection. When the epidemic sets in, the infection quickly spreads to the high-risk subjects. The incidence steeply increases from year to year. It is not stable. It is surmised that the incidence reaches its peak level when the epidemic is around 12 years old. Then a plateau occurs before showing a decline. Because of these changes, the simple formula stated in the text is not applicable to HIV. Further, because of availability and affordability of antiretroviral therapy, death is postponed and the duration of acquired immunodeficiency syndrome (AIDS) disease has now considerably increased. Thus the prevalence has increased even in those

areas where incidence has remained constant or even reduced. Because of such instability, the formula linking incidence, prevalence and duration can not be used for HIV/ AIDS.

#### **RATE RATIO**

Since odds ratio and risk ratio are commonly used indices in medical research, these are discussed separately in Section 2. However, another index called rate ratio is also used in some situations. If 22 episodes of myocardial infarction (MI) occur in 480 person-years of follow-up of people of age 60 years and above with positive family history, the rate (incidence density) is  $22 \times 100 / 480 = 4.6$  MIs per 100 person-years. If this rate in those without family history is 2.7 MIs per 100 person-years, the rate ratio is  $4.6 / 2.7 = 1.7$ . Similar ratio can be obtained for prevalence rates also.

## **2 RELATIVE RISK, ODDS RATIO, AND ATTRIBUTABLE RISK**

We have already defined risk and odds. Risk is generally used for an outcome and odds is generally used for an antecedent. When comparing with another group, they are converted to indices such as relative risk, odds ratio, and attributable risk.

#### **RELATIVE RISK AND ODDS RATIO**

Whereas the absolute value of risk and odds is important in itself but the utility of these indices increases many-fold when their ratio is obtained relative to a comparison group. The comparison group generally is the control group. Such ratios are respectively called relative risk and odds ratio. The comparison groups should be similar in all respects except for the factor under consideration. If not, statistical methods of adjustment such as logistic regression are used.

#### **RELATIVE RISK (RR)**

Ratio of risk of an outcome such as disease in one group (say, the exposed group) to that in any other group (generally the control group – the unexposed group) is called the relative risk (or risk ratio). If relative risk (RR) of HIV infection in persons with STD versus those without STD is 6.5, it says that the persons with STD are 6.5 times as likely to contract the infection as are persons without STD—other factors remaining the same. A prospective study is required to calculate RR, and that could be very expensive. But it has future overtones. Assessment of relative risk is considered important to discuss the consequences with the patient, and in preparing a management strategy. Methods are available to check whether an RR is statistically significant.  $RR = 1$  implies that the two groups have same risk. Thus, significance here implies that RR is different from one.  $RR > 1$  has the usual meaning of increased risk but  $RR < 1$  could mean that there is a protective effect.

If risk in unexposed group is low, the relative risk can be a high value. If risk in the unexposed group is 2% and in the exposed group is 70%, the RR is 35. If the risk in the unexposed group is 60%, RR can not exceed  $100 / 60 = 1.67$ . Thus interpret an RR with caution.

## **ODDS RATIO (OR)**

Since case-control studies move from disease to the antecedent, they are relatively easy to conduct. For example, cases with pancreatitis and matched controls can be asked whether or not they smoke or smoked. Such a design gives the prevalence of smoking and no smoking in cases with pancreatitis and in the controls. If this prevalence of smoking in cases is 80% and of no smoking 20%, the odds of smoking in the cases of pancreatitis is 4:1. Similar odds can be calculated for controls. Controls in this setup are persons without the disease. Suppose the odds in them are 3:1. Thus the odds ratio (OR) is 4/3. When the prevalence of the disease is low, OR can be interpreted the same way as relative risk. This example is on pancreatitis whose prevalence is generally small in a population. Therefore, it can be safely concluded that the risk of pancreatitis in smokers is 4/3 times of that in nonsmokers. OR =1 indicates that the concerned factor is not a risk. Formulae are in Box 2.

## **OR VS. RR**

It can be mathematically shown that OR is approximately the same as RR when the prevalence of disease is low, say less than 5%. This equivalence property is extremely useful because most diseases have a low prevalence, and to obtain RR for them there is no need to conduct expensive prospective study. A retrospective study is much easier and requires fewer inputs, and would give an OR that fairly approximates RR. However, be careful. All diseases or health conditions are not rare. Anaemia in women in India is widespread, and nearly one-third of all births in India have low birth weight. Hypertension in India may be present in 20% or more adults in some segments of population. More than one-half of postmenopausal women are obese. In conditions such as these, OR can not be used as an approximation to RR.

Neither RR nor OR can be calculated if no event of interest occurs in the control group. If there is no person with exposure in the control group of a case-control study, the denominator for OR would be zero that would make it an impossible infinity. Same situation arises when all cases have the exposure. See denominator in the formulae in Box 2.

If the focus shifts from the occurrence of event to its nonoccurrence (e.g., survival instead of death), the only effect on OR is that it becomes inverse. But RR and its statistical significance can substantially change. This happens because the precision of estimated RR markedly differ when risk is low from the one when the risk is high. For this reason, decide before hand that the interest is in occurrence or nonoccurrence.

### **Example 2: Odds ratio in endometrial hyperplasia**

To study risk factors for endometrial hyperplasia, Ricci et al. (2002) examined 129 women aged 35-73 years with histologically confirmed complex endometrial hyperplasia (EH) without atypies in Italy during 1990-99, and 258 nonhysterectomized women aged 36-74 years from the same area as controls. **Odds ratio** for >12 years of education vs. <7 years was 2.8, for obesity 2.7, and for diabetes 2.2. For postmenopausal women only, the OR was 3.1 for use of hormone replacement therapy (HRT). On the basis of these odds ratios, which are substantially more than one, it can be concluded that high education, obesity, diabetes and HRT increase the risk of endometrial hyperplasia. Note that endometrial hyperplasia is a rare disease.

### **Example 3: Prevalence ratios as surrogate for risk ratios**

Brenner et al. (1999) report adjusted prevalence ratios for *H. pylori* infection among persons who consumed upto 10, 10-20 and 20+ gm of alcohol per day compared with nondrinkers as 0.93, 0.82 and 0.71, respectively in a German population of adults. This relationship became stronger when

recent drinkers were excluded. These results are based on prevalence rates and not risks. Thus these are **prevalence ratios**.

**Side note:** The findings support the hypothesis that moderate alcohol consumption may facilitate spontaneous elimination of *H. pylori* infection among German adults.

### Box 2: Formulas for various risks and ratios

We now put all types of risks and ratios together in a formula format. In these formulae, exposed group means the group in which the antecedent factor under study is present. The term disease is used for convenience but it can be any other outcome of interest. Risk measures can be calculated only if the study is prospective, and odds if it is retrospective.

Exposure (Antecedent)	Disease		Total
	Present	Absent	
Yes	$a$	$b$	$a+b$
No	$c$	$d$	$c+d$
Total	$a+c$	$b+d$	$n$

Risk = Absolute risk = Incidence rate =  $a/(a+b)$  in the exposed and  $c/(c+d)$  in the unexposed

Relative risk of the disease for an exposure

$$\begin{aligned}
 &= \frac{\text{Incidence rate of the disease in the exposed group}}{\text{Incidence rate of the disease in the unexposed group}} \\
 &= \frac{a/(a+b)}{c/(c+d)}
 \end{aligned}$$

Attributable risk = Risk difference

$$\begin{aligned}
 &= \text{Incidence rate of the disease in the exposed group} \\
 &\quad - \text{Incidence rate of the disease in the unexposed group} \\
 &= a/(a+b) - c/(c+d)
 \end{aligned}$$

$$\text{Attributable fraction} = \frac{\text{Attributable risk}}{\text{Incidence rate of the disease in the exposed group}}$$

$$\begin{aligned}
 \text{Population attributable risk} &= \text{Incidence rate in the exposed group} \\
 &\quad - \text{Incidence rate in the total population} \\
 &= \text{Attributable risk} \times \text{Prevalence of the exposure in the population}
 \end{aligned}$$

$$\begin{aligned}
 \text{Absolute risk reduction} &= \text{Incidence rate of disease before intervention} \\
 &\quad - \text{Incidence rate of the disease after intervention}
 \end{aligned}$$

$$\text{Relative risk reduction} = \frac{\text{Absolute risk reduction}}{\text{Incidence rate of disease before intervention}}$$

Odds =  $x/(1-x)$  if the antecedent is present in 100  $\times$  percent of the subjects

$$\text{Odds ratio} = \frac{\text{Odds in the diseased cases}}{\text{Odds in the nondiseased subjects}} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

## ATTRIBUTABLE RISK AND OTHER KINDS OF RISK MEASURES

Whereas it is customary to use ratio of risks for comparison of two groups but sometimes such a ratio provides a lop-sided story. Attributable risk and such other measures can be more appropriate in some situations.

### ATTRIBUTABLE RISK

The difference between the risk in exposed subjects and unexposed subjects is called attributable risk. If the risk of lung cancer among smokers is 7.6% and in nonsmokers of same age-gender is 1.2%, the risk attributable to smoking is  $(7.6 - 1.2) = 6.4\%$ . This can also be understood as **risk difference**. For this to be valid, it is necessary that the groups are similar with respect to all factors except the antecedent under review. That is, there is no other factor that can alter the risk.

Many times attributable risk gives more valid information to the health managers than the relative risk. This happens particularly when the disease is rare but occurs several times more frequently if a particular antecedent is present. Suppose cancer of throat has a risk of 0.0002 in nontobacco chewing persons but is 0.015 in those who chewed tobacco for 10 years or more. Thus the relative risk  $0.015/0.0002 = 75$ . But the attributable risk is only  $0.015 - 0.0002 = 0.0148$  (less than 1.5%). Changing habits of tobacco chewing will not make much of a difference to the *overall* incidence of cancer: RR = 75 notwithstanding. Later on we show that this is all the more true if only a small percentage such as 2% of the population chews tobacco. Attributable risk is better index of the public health importance of the risk factor in terms of the impact its reduction can make on the overall incidence of disease.

Why then RR is such a popular measure with researchers around the world? One reason is that it can be approximately estimated even by case-control studies. AR can not. The second is that RR often comes close to multiplying individual RRs when two independent factors act jointly in concert. This does not happen with AR. The third is that the same risk difference such as 4% between 60% and 64% has entirely different implications than between 2% and 6%. A large RR is a definite indicator of a strong association between an antecedent and outcome. Thus it is a better index of the aetiological role of a factor in disease.

### POPULATION ATTRIBUTABLE RISK

The example of 2% tobacco chewing population brings us to the concept of population attributable risk (PAR). This is obtained by multiplying attributable risk to the prevalence of the exposure. In our example,  $\text{PAR} = 0.0148 \times 0.02 = 0.000296$  or just about 3 in 10,000. This measures the impact of eliminating tobacco chewing from the entire population. This information is useful to the health managers. If it is impossible to completely remove tobacco chewing from a population, one can find what happens if the prevalence of tobacco chewing is brought down from the present, e.g., 2% level to 1%. Then,  $\text{PAR} = 0.0148 \times 0.01 =$   $\times$

0.000148 or about 1.5 in 10,000. If exposure is reduced to its one-half level, the PAR also comes down by the same proportion.

### **RELATIVE RISK REDUCTION**

For impact of intervention, another measure used is risk reduction. The absolute risk reduction is the same as AR whereas the relative risk reduction is AR as percentage of the risk in the exposed group. In our example, relative risk reduction is  $0.0148 / 0.015 \times 100 = 98.7\%$ . This percentage of risk *among tobacco chewers* would be reduced if tobacco chewing is eliminated. Do not over-rate it and realize that this percentage is out of 0.015 risk among the chewers. Importance of relative risk reduction can not be assessed without knowledge of the risk in the exposed group. A relative risk reduction of 25% could be from 4% to 3% or from 80% to 60%. For something like vaccine, relative risk reduction measures protective efficacy.

#### **Example 4: Relative risk reduction for smoking in ICU patients in UK**

Jones et al. (2001) included smoking cessation advice in a 6-week self-help ICU rehabilitation package after critical illness. In an RCT that included regular ward visitors as control, at the 6-month follow-up, previous smokers on rehabilitation package exhibited a **relative risk reduction** of 89% for smoking. Note in this case that the risk is of smoking and not of any disease.

**Side note:** It was concluded that the smoking cessation after critical illness is aided by the provision of a rehabilitation programme.

### **NUMBER NEEDED TO TREAT**

Among many kinds of risk measures, ensure in research that the one really appropriate for the study objectives and the one consistent with the design of the study is used.

Risk can be restated in a different manner that probably has better appeal. Think about the average number of patients that must be treated by drugs to prevent one cardiac event opposed to the number of patients that must be on exercise-diet therapy to prevent the same cardiac event. If drug treatment is required in 14 patients and exercise-diet therapy in 11 patients on average for prevention of one event, it can be easily inferred that exercise- diet therapy is more effective.

Number needed to treat (NNT) is the reciprocal of the absolute risk reduction. If the risk of cardiac event in control group is 12 per 100 person-years and in drug treatment group is 5 per 100 person-years, the absolute risk reduction is  $0.12 - 0.05 = 0.07$ . Thus the number needed to treat to prevent one cardiac event is  $1/0.07 = 14.3$ . If the incidence of cardiac event in exercise-diet therapy group is 3 per 100 person-years and 12 per 100 person- years in control as before, the absolute risk reduction is  $0.12 - 0.03 = 0.09$  and the number needed to treat is  $1/0.09 = 11.1$ .

Just as RR can be approximated by OR in special cases so can NNT. Thus, it is possible in some cases to calculate NNT through case-control studies as well. In most situations, however, an immaculately carried out RCT is needed to correctly calculate NNT.

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