THE RISKS AND HAZARDS OF INTERPRETING AND REPORTING HEALTH STUDY MEASURES: A SIMPLE, PRACTICAL OVERVIEW

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ABSTRACT

To ensure accurate interpretation and reporting of study findings, medical communicators should understand several key measures that are used to determine the efficacy of interventions in health studies. This article 1) provides a practical overview of important measures of effect typically used in health studies, including absolute risk, absolute risk reduction, relative risk, relative risk reduction, odds ratio, hazard ratio, and number needed to treat; 2) covers the use and misuse of these methods; and 3) gives examples of how these measures should be correctly interpreted and reported.

Health studies, such as randomized clinical trials, are critical in assessing the effect of particular exposures and interventions. The results of these studies represent the cornerstone of evidence upon which decisions are made relating to medical practice and public health.[1] In health studies, outcomes of interest are often compared between 2 or more study groups with various measures to determine the effect of a particular exposure or intervention (Table 1). For many medical communicators without a strong statistical background, critically appraising, accurately interpreting, and appropriately reporting the results of health studies can be a challenge.

A lack of familiarity with measures of effect can result in a misinterpretation of a study's results. An excellent example of this comes from the media's interpretation

Table 1. Summary of Common Measures of Effect Used to Determine the Absolute and Relative Effects of Interventions or Exposures

Definition	Range of Values
Absolute Risk (AR)	
Probability of a binary event[a] occurring in a given population over a defined period	• Expressed as a percentage, fraction, number (1, event will always occur; 0, event will never occur), or rate (events per person-years at risk)
Absolute Risk Reduction (ARR) or Absolute Risk Difference	
Arithmetic difference (not ratio) in AR between 2 study groups (control group AR – treated group AR)	• Typically expressed as a percentage (0%, no difference between control and treated groups)
Relative Risk (RR)	
Probability of an outcome in treated/ exposed group divided by the probability of the same outcome in control/unexposed group	• RR = 1, risk of outcome identical in both groups • RR <1.0, risk of outcome lower among treated/ exposed vs control/unexposed • RR >1.0, risk of outcome greater among treated/ exposed vs control/unexposed
Relative Risk Reduction (RRR)	
Represents the magnitude of risk diminished by treatment: 1 - RR	• Typically expressed as a percentage (0%, treatment produces no reduction in risk; 100%, treatment reduces all risk)
Odds[b] Ratio (OR)	
Odds of an event in the treated/ exposed group divided by the odds of the same event in the control/ unexposed group	• OR = 1, odds of outcome identical in both groups • OR <1.0, odds of outcome lower among treated/exposed vs control/unexposed • OR >1.0, odds of outcome greater among treated/exposed vs control/unexposed
Hazard[c] Ratio (HR)	
Ratio of the event rate in the treated/ exposed group to that in the control/ unexposed group	• The larger the HR, the greater the chance that the end point will occur sooner in a treated patient than in a person in the control group • HR = 1, treatment produces no effect • HR = 2, twice as many treated patients (vs control patients) experience an event • HR = 0.5, half as many treated patients (vs control patients) experience an event
Number Needed to Treat (NNT)	
Number of patients who must be treated to obtain the desired outcome in 1 patient: 1 ÷ ARR or 1 ÷ (incidence in untreated population × RRR)	• Ranges from 1 (favorable outcome expected to occur in every patient receiving therapy) to infinity • The greater the NNT, the closer the treatment approaches no effect beyond control

[a] *A binary event has only 2 possible outcomes (eg, dead or alive, fracture or no fracture).*

[b] *The odds of an outcome is determined by dividing the probability that an outcome occurs by the probability that it does not. The probability of an outcome is determined by dividing the number of times it occurs by the total number of observations.*[10]

[c] *A hazard represents the rate at which events happen.*[14,17]

of a study by Schulman et al[2] published in *The New England Journal of Medicine*. The purpose of the study was to investigate whether a patient's race and sex influence a physician's decision to request diagnostic cardiovascular procedures to manage chest pain. The study found that both women and black individuals were less likely than men and white individuals to be referred for cardiac catheterization; referral rates were 84.7% for women and black people, and 90.6% for men and white people (odds ratio = 0.6).

As reviewed by Schwartz et al,[3] major news media picked up on this article and, focusing on the odds ratio, ran headlines such as "Heart Care Reflects Race and Sex, not Symptoms" and "A Recent Study Shows That Doctors Diagnose Black and White Patients Differently." The basic message reported by the media was that, compared with white individuals and men, black individuals and women were 40% less likely to be referred for cardiac testing. This interpretation, however, misrepresented the study's results. While many factors contributed to this misunderstanding, an important aspect was how the media inappropriately equated odds ratio with relative risk.[3] When the same results were analyzed more appropriately in terms of relative risk, it was apparent that black individuals and women were 0.93 (ie, 84.7% ÷ 90.6%) times less likely to be referred than white individuals and men—in other words, physicians were actually 7% (not 40%) less likely to order cardiac catheterization tests for black or female patients than for their white or male counterparts.

To help medical communicators more capably interpret different measures of effect, we review how key outcome measures can be calculated from health research data, the advantages and disadvantages of each measure, and potential pitfalls in the interpretation of each measure. Particular emphasis is placed on distinguishing between relative risk and odds ratio, since these terms often lead to confusion and misinterpretation of the results of health studies. Throughout, we present the topics without the use of technical jargon or complex equations, making it easier to gain insight into these measures. Readers who want a more in-depth understanding of these topics are encouraged to attend an AMWA epidemiology workshop.

ABSOLUTE RISK

Absolute risk is the chance of a particular dichotomous outcome (such as dead/alive or fracture/no fracture) occurring over a defined period in a given population (eg, patients of a given age with stated risk factors).[4,5] Absolute risk is calculated by dividing the number of patients experiencing an outcome by the total number of patients in that particular group.

An example of how to calculate absolute risk is given in the Box at right with data from a randomized controlled trial comparing the effect of vitamin D3 supplementation with placebo on seasonal influenza A in children.[6] The absolute risk of seasonal influenza A in children in the placebo group was 18.6% over 17 weeks. Absolute risk can be expressed as a percentage (as in this example), as a fraction, as a number between 1 (ie, the event always occurs) and 0 (ie, the event never occurs), or as a rate, such as events per person-years at risk (ie, the actual time in years that all patients contributed to the observation period).

ABSOLUTE RISK DIFFERENCE

The arithmetic difference (not the ratio) in absolute risk between the control and treatment groups represents the *absolute risk difference*.[7] With use of the same data in the Box, the decrease in risk (ie, the absolute risk reduction) of seasonal influenza A developing as a result of vitamin D3 supplements is calculated as follows: 18.6% –10.8% = 7.8%. Stated another way, vitamin D3 supplements reduced the absolute risk of seasonal influenza A by 7.8% (ie, 0.078) over 17 weeks.

Absolute risk difference is often used to facilitate risk management in clinical practice and in related situations (eg, health policy decisions) and is a helpful tool for developing health care treatment strategies.[4] Absolute risk difference provides information on whether a particular intervention will be clinically meaningful in general terms, but it is not an easily comprehensible measure of the effects of an intervention. Nevertheless, an important aspect of determining the absolute risk difference in a clinical trial is that it permits calculation of a more user-friendly and more easily conceptualized outcome measure—the number needed to treat (discussed below).[5,8]

Example of How to Calculate Absolute Risk, Absolute Risk Reduction, Relative Risk, and Relative Risk Reduction[a]

- A total of 430 children were randomly assigned to receive either placebo or vitamin D3 for up to 17 weeks (334 children [167 per group] completed the study)
- Number of cases of influenza A:
  18 occurred in 167 children receiving vitamin D3, and 31 occurred in 167 children receiving placebo
- Absolute risk of influenza A over 17 weeks
  –Placebo group: 31 ÷ 167 = 18.6%
  –Vitamin D3 group: 18 ÷ 167 = 10.8%
- Absolute risk reduction over 17 weeks: 18.6% – 10.8% = 7.8%
- Relative risk: 10.8% ÷ 18.6% = 0.58
- Relative risk reduction:
  100 x (1– 0. 58) = 42%

[a]Data in the example are from a randomized, double-blind, placebo-controlled trial of the effect of vitamin D3 supplements on seasonal influenza A (diagnosed by influenza antigen testing of nasopharyngeal swabs) in children.[6]

RELATIVE RISK AND RELATIVE RISK REDUCTION

The most frequently used method of summarizing treatment effects of event outcomes in health studies is to cal-

culate the relative risk. *Relative risk* is the probability (ie, the incidence) of an outcome in an active-treatment group divided by the probability (ie, the incidence) of the same outcome in a control or placebo group.[9] A relative risk of 1 indicates that the risk of an outcome is identical in both groups; a relative risk less than 1.0 indicates that the risk is lower among treated/exposed persons than among control/unexposed persons; and a relative risk greater than 1.0 indicates that the risk is higher among treated/exposed persons than among control/unexposed persons.

With use of the data in the Box, the relative risk of seasonal influenza A is calculated by dividing the risk of influenza in the vitamin D3 group by the risk of influenza in the placebo group: 10.8% ÷ 18.6% = 0.58.

A related term, relative risk reduction, expresses the absolute risk reduction as a percentage of the risk or incidence in the untreated group. When simplified, relative risk reduction is calculated as 100 times the difference of 1 minus the relative risk. With use of the data in the Box, the relative risk reduction is calculated as follows: (1 – 0.58) × 100 = 42%. In other words, vitamin D3 supplements resulted in a 42% relative risk reduction in seasonal influenza A infection compared with placebo.

It is important to recognize that, for both relative risk and relative risk reduction, the same proportional reduction occurs regardless of the magnitude of the absolute values. For example, a 75% relative risk reduction would apply equally to a change in the absolute risk from 24 to 6, from 16 to 4, from 4 to 1, or from 1 to 0.25, but the absolute risk difference would vary (18, 12, 3, or 0.75, respectively). Thus, without knowledge of the baseline absolute risk (ie, the incidence rate) in the control group, it is not possible to fully appreciate the impact of a particular intervention on the basis of relative risk or relative risk reduction alone. A physician may be swayed to initiate a new therapy on the basis of clinical trial results that showed a 50% reduction in outcome compared with standard therapy but may be less impressed if an absolute risk of 2 in 1,000 decreased to 1 in 1,000, even though this also represents a 50% reduction in risk. In general terms, the efficacy of a treatment (in relation to control or another treatment) can be adequately assessed by relative risk reduction, but the absolute risk and the absolute risk difference are needed to provide the context in order to more completely appreciate the effect of a treatment on the population of interest.

ODDS RATIO

The *odds* of an event (a within-group measure) is determined by dividing the probability that an outcome occurs by the probability that it does not. The probability of an outcome is calculated by dividing the number of times it occurs by the total number of observations.[10] The *odds ratio* (a between-group measure) is defined as the odds of an event in the experimental or exposed group divided by the odds of the same event in the control or unexposed group as follows:

$$\text{Odds Ratio} = \frac{\text{Exp Group Positive} \div (\text{Exp Group Total} - \text{Exp Group Positive})}{\text{Control Group Positive} \div (\text{Control Group Total} - \text{Control Group Positive})}$$

where Exp indicates experimental or exposed.

The following 2 examples illustrate how to calculate the odds ratio. In a hypothetical randomized trial conducted over 5 years, 70 of 100 adult women gained bone (determined by bone densitometry) while receiving antiresorptive therapy and 10 of 100 adult women gained bone while taking placebo. The simple odds (within group) of gaining bone is 7 to 3 for women receiving antiresorptive therapy compared with the odds of 1 to 9 for women taking placebo; the odds ratio (between groups) is therefore (7/3) ÷ (1/9) = 21. These results indicate that the odds of gaining bone with antiresorptive therapy is 21 times the odds of gaining bone with placebo. In contrast, the relative risk (a between-group measure) calculated with the same data would be 70% ÷ 10% = 7. Thus, patients receiving antiresorptive therapy are 7 times more likely to gain bone than patients taking placebo.

In the above example, the odds ratio is greater than 1 because the odds of the outcome (gained bone) is greater among treated patients than control patients. For some trials, however, the odds of an outcome (eg, fracture, hospitalization, death) is lower among treated patients than control patients, and, thus, the odds ratio indicating treatment benefit is less than 1. This is illustrated by a second example, which involves a published randomized trial that compared the effect of either intensive therapy or standard therapy (control) for glycemia on the progression of diabetic retinopathy in patients with type 2 diabetes.[11] At 4 years, 104 of 1,429 patients (7.3%) had progression of diabetic retinopathy in the intensive therapy group and 149 of 1,427 patients (10.4%) had progression in the standard therapy (control) group. The simple odds of progression were 104 ÷ (1,429 – 104) = 1/12.74 or 0.0785 for patients receiving intensive therapy and 149 ÷ (1,427 – 149) = 1/8.58 or 0.1166 for patients receiving standard therapy; the odds ratio is therefore 0.0785 ÷ 0.1166 = 0.67. These results indicate that the odds of progression with intensive therapy is 0.67 times the odds of progression with standard therapy, corresponding to a relative odds reduction (analogous to relative risk reduction) of 33% (1 – 0.67 = 0.33 or 33%). The relative risk calculated with the same data would be 7.3% ÷ 10.4% = 0.7 (ie, a 30% relative risk reduction).

In the second example, the odds ratio is numerically comparable to the relative risk because the outcome occurs infrequently (<11%). However, when the specific outcome occurs frequently (such as in the hypothetical example above), the odds ratio poorly approximates to relative risk (21 vs 7,

respectively) and may seemingly overestimate the treatment effect—the greater the frequency of the outcome, the greater the exaggeration of effect.[9,12] The study by Schulman and colleagues[2] illustrates an extreme case of this phenomenon. In that study, the event rate (referral for catheterization) was extremely common (>85% of patients).[3] In those circumstances, the odds ratio poorly approximated to the relative risk, actually magnifying the observed effect by almost 600%. When the incidence rate is greater that 10%, it is unwise to interpret the odds ratio with the simplified language afforded by the relative risk.

The main disadvantages of using odds ratio rather than relative risk are that 1) it provides only an approximated estimate of the effect of interest and 2) the concept of odds tends to be more difficult for most people to grasp. In contrast, the interpretation of relative risk is more intuitive and is generally easier to comprehend since the ratio of actual event rates is closer to what most people think of when they consider the likelihood of an event occurring. However, for some study designs, notably case-control studies, incidence rates are not available, and, thus, relative risk is impossible to compute. A case-control study is designed to quantify the relationship between exposure variables (eg, smoking) and disease by comparing individuals with the disease of interest (cases) with a random sample of individuals without the disease (controls).[13] In this setting, only odds ratios can be calculated, and this is done with use of the odds of exposure rather than outcome.[10]

HAZARD RATIO

The *hazard ratio* is commonly calculated to analyze statistical differences in survival or time-to-event data between treatment groups.[14,15] Time to event represents the period in a clinical trial (or other health study) from recruitment to the occurrence (usually the first occurrence) of a disease end point, the resolution of a sign or symptom, or the censoring of a given participant's follow-up (eg, as a result of being lost to follow-up, dying of another cause, or withdrawing from the study). The hazard ratio is a ratio of event rates over time and is not strictly equivalent to relative risk, which is a ratio of event numbers, although sometimes the 2 concepts have been used interchangeably.[14]

The interpretation of the hazard ratio depends on the nature of the event. When the absence of an event is beneficial (eg, absence of cancer), a hazard ratio less than 1 indicates a beneficial outcome of therapy compared with the control. However, when the presence of an event is beneficial (eg, the disease is cured), a hazard ratio greater than 1 indicates a desirable outcome.

An example of how the hazard ratio can show differences undetectable by analysis of the relative risk or odds ratio is illustrated by a simple hypothetical clinical trial designed to compare the occurrence of a particular clinical event (eg, a fracture) over 10 years in 2 groups of patients (10 in a treatment group and 10 in a placebo group). In this hypothetical trial, the same number of fractures (3) occurred in each group; however, in the placebo group, all 3 fractures occurred at year 1, and in the treatment group, all 3 fractures occurred at year 9.

To calculate the hazard ratio, the event rate for each group is calculated from the total number of person-years at risk. For the placebo group, the total number of person-years at risk is calculated as follows: $(7 \times 10) + (3 \times 1) = 73$ person-years. The fracture rate is therefore $3 \div 73 = 0.04$ (ie, 4 patients per 100 person-years at risk). In the treatment group, the total number of person-years at risk is greater because more patients lived a longer period before a fracture occurred: $(7 \times 10) + (3 \times 9) = 97$ person-years. The fracture rate for the treatment group is therefore $3 \div 97 = 0.03$ (ie, 3 patients per 100 person-years at risk). The corresponding hazard ratio, $0.03 \div 0.04 = 0.75$, indicates that, compared with placebo, the treatment produced a 25% risk reduction in fractures over 10 years, calculated as $100 \times (1–0.75)$.

Interestingly, the corresponding 10-year fracture odds ratio is $(3/7) \div (3/7) = 1$, and the 10-year fracture relative risk is $30\% \div 30\% = 1$. Both indicate the absence of a difference in the incidence of fracture over the entire study period.

Kaplan-Meier curves provide a simple means of visualizing the cumulative proportion (or percentage) of patients surviving or experiencing an event at multiple time points and can provide useful information about temporal trends. The Figure shows Kaplan-Meier curves for the time to treatment failure in a placebo-controlled trial of antimicrobial therapy for acute otitis media in children.[16] A total of 161 children received amoxicillin-clavulanate or placebo over 7 days, and the time to treatment failure was determined. As shown in the Figure, the curves separated early and remained separate. The hazard ratio (0.38) showed that amoxicillin-clavulanate resulted in a 62% attenuation in the progression to treatment failure, calculated as $100 \times (1 – 0.38)$.

It is clear from these analyses that clinically relevant outcomes between groups can be easily missed when only 1 time point is used (eg, the end of a trial). Important temporal patterns, such as early worsening of diabetic complications, latency periods for cancers, and acute effects of hormone-replacement therapy on cardiovascular disease, can therefore be missed by focusing only on single point-in-time comparisons, such as relative risk or odds ratio analyses.

The overall hazard ratio, though, does not give any information about the relative speed or how much faster a particular end point might occur in 1 group compared with another.[17] Instead, the hazard ratio indicates the chance that a treated person who has not had an event at 1 time point will have that event at a subsequent time point compared with people in

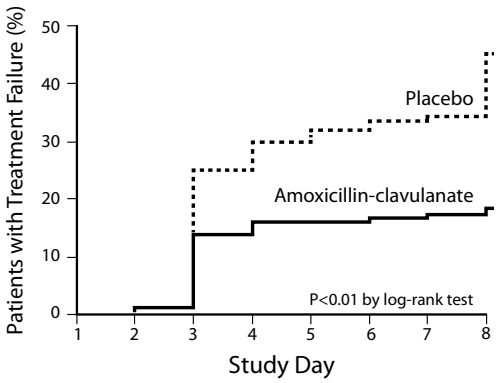

Figure 1. *Kaplan-Meier curves for time to treatment failure in a randomized clinical trial comparing amoxicillin-clavulanate with placebo for acute otitis media in children. Kaplan-Meier curves essentially show a "picture" of the event rate over time. Treatment failure was based on the child's overall condition (including adverse events) and otoscopic signs of acute otitis media. From Tähtinen et al[16]; used with permission from the Massachusetts Medical Society.*

a control group (or in another treatment group).[14,17] The larger the hazard ratio, the greater the chance that the end point will occur sooner in a person in a treatment group than in a person in a control group. A hazard ratio of 2.0, however, does not indicate that an event will occur twice as quickly in 1 group as in another.[14] It is true, though, that the person has twice the risk of experiencing the outcome compared with a person in the other group.

NUMBER NEEDED TO TREAT

The *number needed to treat* indirectly gives an estimate of the risk-benefit profile of a particular therapy. In other words, it provides an estimate of the number of people who would need to be exposed to potential drug risks and side effects to prevent 1 person from experiencing a particular outcome. The number needed to treat can also be used to provide an estimate of the cost of therapy for a particular outcome (ie, how many people need to receive the treatment to avert 1 unwanted outcome), thereby better enabling a rough assessment of the cost-effectiveness of different agents.[7] This concept can also be applied to similar measures (number needed to harm, number needed to screen, etc).

The scale for the number needed to treat theoretically ranges from 1 to infinity. A number needed to treat of 1, which is rarely found in practice, indicates that a favorable outcome would be expected to occur in every person receiving the therapy (but not in any person receiving the control).[18] The greater the number needed to treat, the closer the treatment approaches a neutral outcome (ie, no effect beyond placebo). A number needed to treat of negative 1 indicates the worst-case scenario, in which everyone who receives the control (but not the therapy) experiences a favorable outcome.[18]

The number needed to treat can be calculated as the reciprocal of the absolute risk reduction.[5,8] For example, in the Heart Protection Study, a randomized controlled trial with patients at high cardiovascular risk, the absolute risk of all-cause mortality over 5 years was 12.93% (1,328 deaths among 10,269 patients) in the simvastatin group and 14.68% (1,507 deaths among 10,267 patients) in the placebo group over 5 years.[19] The absolute risk reduction resulting from exposure to simvastatin is 1.75% (ie, 14.68% – 12.93%). Stated another way, simvastatin reduced the absolute risk of dying by 1.75% (0.0175) over 5 years. The number needed to treat is therefore 57 (ie, 1 ÷ 0.0175). This means that 57 people would need to be treated with simvastatin over a 5-year period to prevent the death of 1 person.

The number needed to treat can also be calculated by determining how many clinical events have been averted (or caused) by a specific exposure or intervention. In the Heart Protection Study example, 1,468 persons in every 10,000 would be expected to die within 5 years (ie, the rate in the placebo group). However, the study's results suggest that the use of simvastatin would decrease this death rate to 1,293 per 10,000 every 5 years. Therefore, simvastatin appears to have averted 175 deaths per 10,000 people over a 5-year period. This means that 1 death would be expected to be averted for every 57 people treated (ie, 10,000 ÷ 175).

Finally, the number needed to treat may be computed from the baseline risk in the untreated (reference) population and the relative risk reduction attributed to therapy. For example, assuming a relative risk reduction of 30% (0.3) and a spontaneous risk of events of 10% (0.1), the number needed to treat is 33, calculated as 1 ÷ (0.3 × 0.1). A simple nomogram has been proposed to allow rapid calculation of number needed to treat from these 2 variables.[20] It is tempting to use the placebo group in a clinical trial as a reference population, but care should be exercised in this scenario because clinical trial populations are usually subject to inclusion and exclusion criteria and, thus, do not generally reflect the broader population. The incidence in the placebo group is not a surrogate for the incidence in the general population. In addition, it is preferable to use a relative risk reduction derived from a combined analysis of multiple randomized clinical trials rather than from a single study.

Although it is a clinically useful tool, the number needed to treat has limitations and should not be used to compare different outcomes across disease conditions. Its numerical values should ideally be considered inextricably linked to a specific disease, intervention, and duration of study.[9] Thus, it is inappropriate to directly compare number needed to treat values among different trials when the therapeutic intervention, outcome, disease (and severity), and specified observation period are not the same.

SUMMARY

Relative risk, its companion relative risk reduction, and hazard ratio are the preferred measures for summarizing data comparing treatment interventions, with the proviso that they are also considered in relation to absolute differences, since ratios may appear to exaggerate clinical effects. The odds

ratio is more complicated to calculate and understand, and it should be considered only cautiously (and in certain circumstances) as a reasonable approximation of an applicable relative risk. However, when the event rate is low (usually <15%), the odds ratio may be considered a reasonable approximation of the relative risk. Although the absolute risk difference does not provide a measure of the proportional effects of an intervention, it does provide useful information about whether a particular intervention will be clinically meaningful in general terms. The absolute risk difference and the number needed to treat should not be used to compare the efficacy of interventions among different clinical trials and are useful only if the true risk (ie, the underlying baseline incidence rate) of the population of interest is known (ie, the risk obtained from epidemiologic data).

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