Odd cases and risky cohorts: Measures of risk and association in observational studies

Tom Lang
Tom Lang Communications and Training International, Kirkland, WA, USA

Correspondence to:
Tom Lang
10003 NE 115th Lane
Kirkland, WA 98033, USA
tomlangcom@aol.com
+1 425-242-1370

Abstract
Hundreds of statistical tests, procedures, and descriptive measures are used in clinical research. Risks, odds, and hazards are among the most common but not always the most understood. They are often used in all three types of observational studies in medicine and epidemiology – case-control, cross-sectional, and cohort studies – so a good understanding of what they are and are not is helpful in understanding these studies. Here, I briefly describe these measures, how they are used in observational studies, and how to interpret them.

Introduction
The three major types of observational studies in medicine and epidemiology – case-control, cross-sectional, and cohort studies – often involve three common measures of risk: odds, risks, and hazards and three common measures of association: odds ratios, risk ratios, and hazards ratios. Here, I briefly describe these measures, how they are used in observational studies, and how to interpret them.[1]

Measures of frequency
How often or how likely an event occurs can be indicated with a "measure of frequency."

Proportions
A ***proportion*** or fraction is a measure in which the numerator is a subset of the denominator: "fetal deaths ÷ all deaths". Proportions are often expressed as percentages: fetal deaths are a percentage of all deaths, for example.

Rates
A ***rate*** is a change in proportion over time, although sometimes the time period is assumed or not specified. For example, "the fetal survival rate was 90%" means that 90% of the infants alive at the beginning of a given period were alive at the end of the period.

Ratios
Finally, a ***ratio*** is a relationship between two independent quantities in which the numerator is *not* a subset of the denominator. For example, the fetal death ratio is expressed as "fetal deaths: live births."

Measures of risk
Prevalence
Prevalence (and incidence) are not strictly measures of risk, but they are relevant here.

Prevalence is the proportion of people with the disease divided by the total number of people in whom the disease can occur. Thus, it is the proportion of people with the disease at a given time:

The prevalence of prostate cancer in 2011 = 16.9 per 1,000 men, or 1.69%

Incidence
Incidence (sometimes called **instantaneous incidence**) is the *rate* at which new cases are diagnosed; that is, the number of new cases identified in a given (usually shorter) period among all people in whom the disease can occur:

The incidence of prostate cancer in 2012 = 105 per 100,000 men, or 0.11%

Another common incidence rate is ***cumulative incidence*** (also called the **incidence proportion** or **cumulative proportion**; no sense in making things easy), which is a measure of disease frequency during a longer period of time and often for a specific subpopulation:

The cumulative incidence of prostate cancer in black men up to age 69 years is 15.0%.

Risk

Risk is the probability or the frequency of an unfavourable event occurring during a given period of time. (Risk can also refer to positive events. In such cases, "risk for benefit," may be a more accurate term. We don't talk about the "risk of a happy marriage," for example). How risk is reported is important. A risk of 1 in 20 is often seen as lower than a risk of 1 in 43 when in fact it indicates a higher risk. Similarly, a risk of 1 in 20 appears to be lower than 10 in 200, although the risk is the same. Finally, a probability of 6 in 100 is the same as 6% and 0.06, but each tends to be interpreted differently.

Absolute risk, or simply **risk**, is the probability that a specified condition will affect the health of an individual or a population (in other words, the incidence):

$$\text{Risk of prostate cancer} = \frac{\text{No. men with prostate cancer}}{\text{No. men in whom prostate cancer can develop}}$$

In epidemiology, absolute risk may also require a defined geographical area and period. By convention, the estimated population on July 1 (mid-year) is used in the calculation.

$$\text{Absolute risk of prostate cancer for men living in London in 2017} = \frac{\text{No. of men in London with prostate cancer in 2017}}{\text{Estimated No. of men in London as of July 1, 2017, in whom prostate cancer could develop}}$$

The next several examples are based on a study in which 14 of 200 men with prostate cancer treated with resection died, whereas 30 of another 200 men with prostate cancer treated with watchful waiting died.

The absolute risk of death from prostate cancer with watchful waiting (no treatment) is 15% (30 ÷ 200). The absolute risk of death from prostate cancer with prostate resection is 7% (14 ÷ 200).

The **absolute risk difference, attributable risk,** or **absolute risk reduction (ARR)** is simply the difference between two absolute risks. Using the above example:

The absolute risk difference in mortality from prostate cancer treated with resection as opposed to watchful waiting is 8%. (From the above data, 15% – 7% = 8%). In other words, when compared to watchful waiting, resection reduces the risk of death by 8%.

The **relative risk reduction (RRR)** is the absolute risk difference expressed as a percentage of the risk of the control or untreated group. Again, using the above example:

The relative risk reduction in mortality from prostate cancer attributable to prostate resection is 53% (8% ÷ 15% = 0.533).

Odds

An **odds** is the probability of an event happening divided by the probability of it *not* happening. Odds is not the same as risk:

The *risk* (or probability or frequency) of drawing a heart from a deck of 52 cards is 13 ÷ 52 = 1/4 = 25%.

The *odds* of drawing a heart is the probability of drawing a heart divided by the probability of *not* drawing a heart: 13 ÷ 39 = 1/3 = 33%.

For uncommon outcomes, the odds and risk are similar. For example, the risk of drawing a face card from a deck is 12 ÷ 52, or about 0.23, whereas the odds are 12 ÷ 40, or about 0.30, not that much different from 0.23. For common outcomes, the odds will be higher than the risk: the risk of drawing a card with an even number (not counting face cards) is 20 ÷ 52, or about 39%, but the odds are 20 ÷ 32, or 63%, which is nowhere near the 39%.

In a clinical trial, the odds of death with watchful waiting was 0.18 (30 of 200 men who died ÷ 170 men who did not die) and with resection, 0.08 (14 of 200 men who died ÷ 186 men who did not die).

Odds (and odds ratios) are hard to understand, but they are necessary in retrospective studies and are the output of logistic regression analyses, which is a particularly useful statistical method.

Hazards

A **hazard rate** is an incidence rate: the number of new events per population at-risk per unit time. More precisely, a hazard is the "instantaneous event rate," or the probability that if an event has not occurred in one period, it will occur in the next. Notice that a hazard is a *rate* (the number of new events of disease per population at-risk *per unit time*; here, a year), whereas incidence is the *proportion* of new cases occurring *over a given period with many units of time*; that is, over several years vs. per year.

The hazard rate for death after radical prostatectomy was 0.4% at 5 years, 0.7% at 10 years, and 1% at 15 years.

Hazards rates are seen in time-to-event studies with binary (only two) outcomes, often alive or dead. They are the output of Cox proportional hazards regression analyses, which can also be used to identify which factors are associated with living or dying. They are also often indicated on Kaplan-Meier or survival curves, which show the incidence (death) rate at any given time in a study.

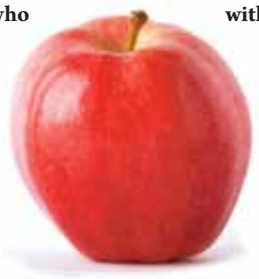
Measures of association

The association between two groups can be determined by dividing the value of a measure of risk in one group by that in another. The result is a ratio – a risk ratio, odds ratio, or hazards ratio. If the risk (or odds or hazards) is the same in the two groups, the ratio will be 1. By convention, risks greater than 1 are considered to be harmful or more common in one group than in the other, and those less than 1 are considered to be protective or less common than in the other.

Risk ratios

A ***risk ratio*** or **relative risk** is simply a ratio of two risks (Box 1).

The risk ratio of death from prostate cancer with watchful waiting is 2.14 (15% ÷ 7% = 2.14); men who choose watchful waiting over prostate resection are 2 times as likely to die from the disease as those who choose resection.



Because the risk ratio is the risk of one group divided by another, it matters which group is in the numerator and which is in the denominator: **If the risk ratio is 2, the risk for one group is 2 times (200%) as likely as it is for the other. If the risk ratio is 0.5, the risk for one group is half (50%) the risk of the other.**

Here, both ratios indicate that the risk in one group is twice as great as the risk in the other. Thus, by convention, protective factors are described with ratios of less than 1, and harmful factors are described with ratios of greater than 1.

Relative risk is not the same as the relative risk reduction. The relative risk is a ratio of two risks, whereas the relative risk reduction is the absolute risk reduction expressed as a percentage of the risk in the control group.

Odds ratios

The **odds ratio** is the odds for one group divided by that for another (Box 2). In the example, the *odds* of smokers having heart attacks is the number of smokers with heart attacks divided by *the number of smokers who did not have heart attacks*: 14 ÷ 22 = 0.636. The odds of non-smokers having heart attacks is: 5 ÷ 33, or 0.152. The odds ratio is: 0.636 ÷ 0.152 = 4.2, which means that the odds of smokers having a heart attack are 4.2 times as high as that of non-smokers.

To continue with the example of prostate cancer:

The odds ratio of dying with watchful waiting is 2.3 (17.6 ÷ 7.5).

Hazards ratios

A **hazard ratio** is a risk ratio or a ratio of *incidence rates*. (In contrast, odds ratios and risk ratios are ratios of *proportions*.)

Hazards ratios are found in time-to-event studies with binary outcomes (lived or died; cured or not) and are the output of Cox proportional hazards regression, which is used in "time-to-event" or survival analysis. (However, "survival" is not the endpoint, death is. "Time-to-event analysis" is thus the most accurate and preferred term.) Importantly, the outcome of time-to-the-event analysis is not the event itself, it is the *time* from a given starting point to the time when the event occurred. For example, the time between hospitalisation and death is what we are interested in, not in the death itself.

Prospective cohort studies: risks and hazards

Risk and risk ratios

In a cohort study, exposure is assessed before the outcome is measured. We assemble a sample of people who have the same characteristics of interest and follow them forward in time, looking for a specified outcome. For example, we could enroll a cohort of currently healthy people, record their exercise habits over several years, and wait to see which ones will have a heart attack. Because all participants were healthy at the beginning of the study, we can calculate the risks and risk ratios of heart attacks; we know "how many cards" we are starting with.

Hazards and hazards ratios

As with risk and risk ratios, we can use hazards and hazards ratios in prospective or cohort studies. The difference is that we can now determine the incidence of heart attack not only over the entire period of the study but for any given time in the study. That is, with risks, we are counting *the number of heart attacks* during the study period and dividing that number by the number of participants at risk for heart attack during the period. With hazards, we are collecting data on the *time* between the beginning of the study and each heart attack during the study. The hazards ratio gives us the average risk of having a heart attack at any given time during the study. We can also graph this "hazards function" as a Kaplan-Meier or survival curve.

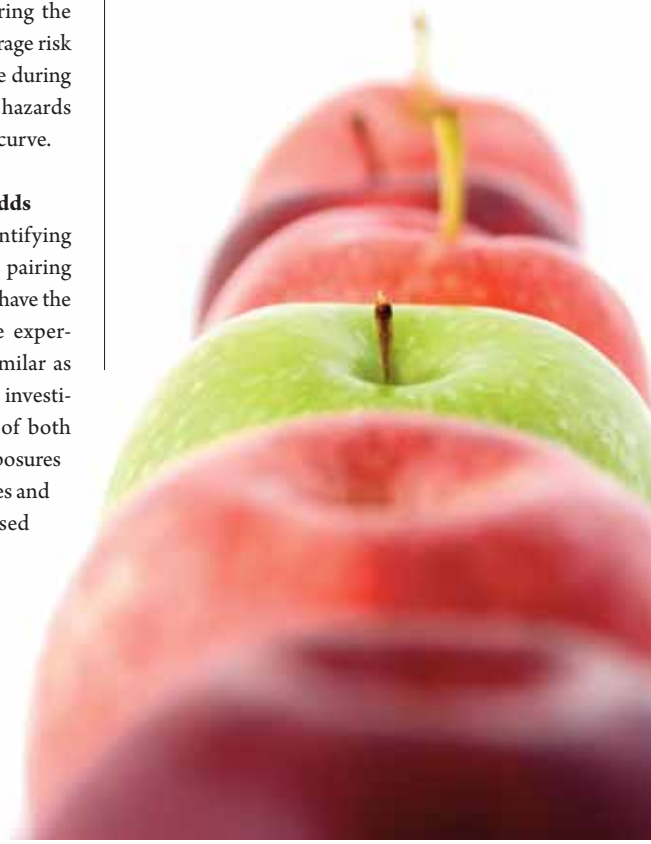
Retrospective case-control studies: odds

Case-control studies begin by identifying patients with a diagnosis (the cases), pairing them with a group of people who do not have the diagnosis but who otherwise have life experiences or personal characteristics as similar as possible to the cases (the controls). By investigating the history and characteristics of both groups, investigators hope to identify exposures or characteristics that differ between cases and controls. That is, outcomes are assessed before exposures.

Whereas risk and risk ratios are appropriate for prospective studies, odds and odds ratios are appropriate in retrospective studies. To continue the above example with playing cards, when we calculated the risk of drawing a heart, we knew how many cards were in the deck. In a prospective study, we know our sample has not yet experienced the event of interest, so the sample size is essentially "the number of cards in the deck."

In a retrospective study, however, we are starting with the event and looking back in time to find exposures that might be associated with the event. Thus, we don't know how many people *might* have been at risk for the exposure or the event: we don't know how many cards are in the deck, so to speak. We do know how many cases and controls we chose. That is, we can calculate the odds of the exposure for each group and compare the groups with the odds ratio (Figure 1).

Relative risk is not the same as the relative risk reduction. The relative risk is a ratio of two risks, whereas the relative risk reduction is the absolute risk reduction expressed as a percentage of the risk in the control group.



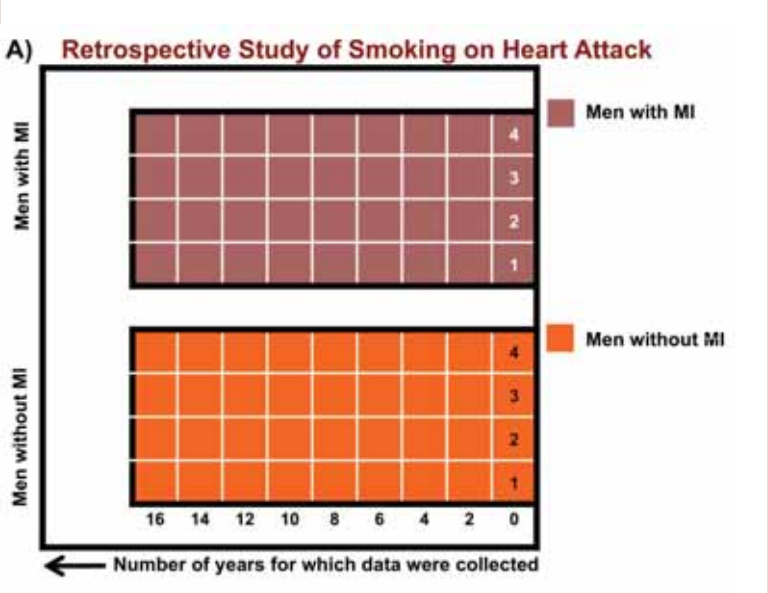
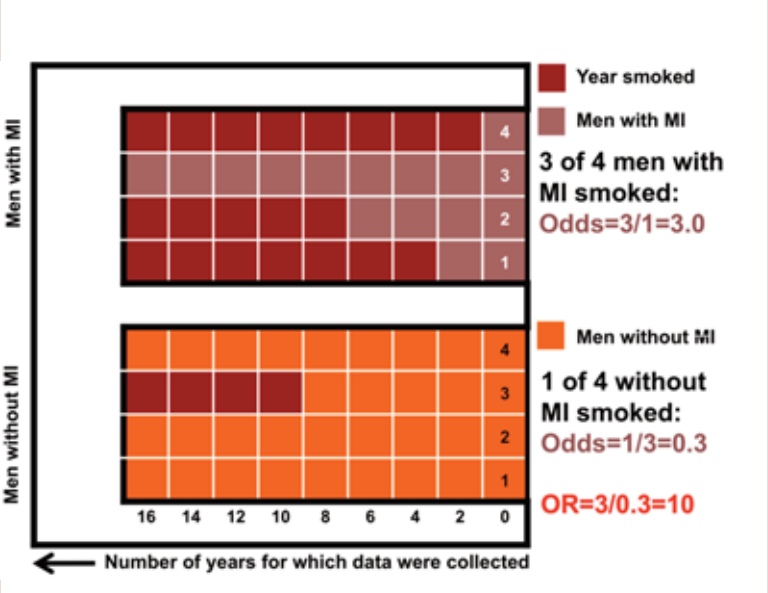
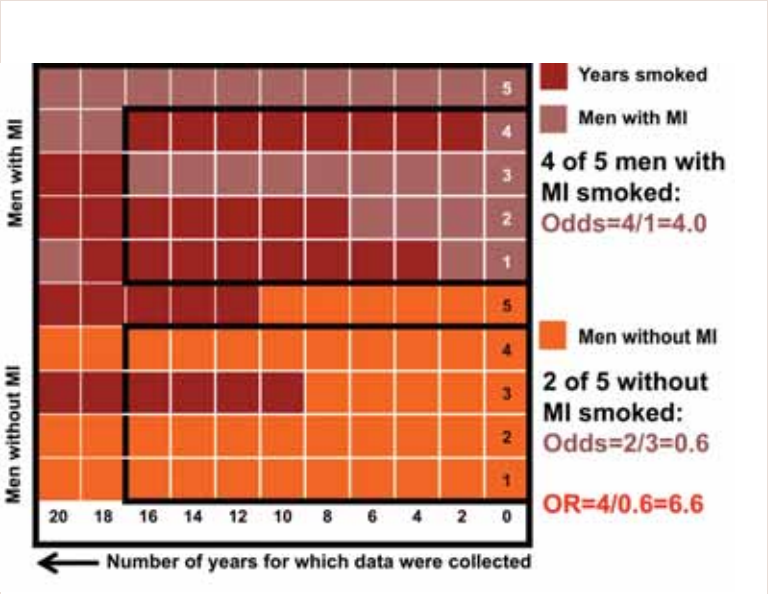


Figure 1. Odds and odds ratios: Example from a retrospective study on myocardial infarction (MI).
Odds and odds ratios are valuable in case-control studies because the true number of people at risk for the event is unknown. Thus, decisions about how many people to study and how far back in time to go may affect the results of the study.

(A) A planned case-control study for determining the association between smoking and heart attack. The 4 cases are men with heart attacks, and the 4 controls are men without heart attacks who have been matched with the cases on relevant criteria, such as age, occupation, and education. The study is looking for smoking behaviour over the past 16 years.



(B) The study as conducted revealed that 3 of the 4 cases and 1 of the 4 controls smoked at least some time during the study period. Thus, the odds of a heart attack among cases is 3 ÷ 1, or 3.0, and that for controls is 1 ÷ 3, or 0.3. The odds ratio was thus 3 ÷ 0.3, or 10. The odds of cases having a heart attack were 10 times as great as that of the controls.



(C) The study as conducted was based on the decisions by the researchers to study 4 cases and 4 controls over 16 years. Had they chosen to study 5 cases and 5 controls over 20 years, the results would have been different: the odds ratio would have been 6.6, not 10.

Box 1. Calculating risk and the risk ratio

Risk is the number of people in whom an event happened divided by the number of people in whom the event could happen. When calculating risk, the total number of people in each group (here, smokers and non-smokers) is the denominator. If these data were collected in a cross-sectional study, the term "prevalence risk ratio" might be used instead.

Smoking Status	Heart Attack	No Heart Attack	Total
Smokers	14	22	36
Non-smokers	5	33	38
Total	19	55	74

The risk of heart attack among smokers: 14 ÷ 36 = **0.39**
The risk of heart attack among non-smokers: 5 ÷ 38 = **0.13**
The risk ratio is 0.39 ÷ 0.13 = **3**
The risk of smokers having a heart attack is 3 times as high as that of non-smokers.

Box 2. Calculating odds and odds ratio

Odds is the probability of an event happening divided by the probability that it did not happen. If these data were collected in a cross-sectional study, the term prevalence odds ratio might be used instead.

Smoking Status	Heart Attack	No Heart Attack	Total
Smokers	14	22	36
Non smokers	5	33	38
Total	19	55	74

The odds of heart attack among smokers: 14 ÷ 22 = **0.636**
The odds of heart attack among non-smokers: 5 ÷ 33 = **0.152**
The odds ratio: 0.636 ÷ 0.152 = **4.2**
The odds of smokers having a heart attack is 4.2 times as high as that of non-smokers.
[a] The odds ratio can also be calculated as the "cross-product":
(14 × 33) ÷ (5 × 22) = **4.2**

Box 3. Various measures of the risk of death from prostate calculated from the same data

Absolute risks should always be reported because all other measures can be calculated from them. Natural frequencies are probably the most easily understood.

Measure	Value
Absolute risk with watchful waiting	15%
Absolute risk with resection	7%
Absolute risk reduction with resection	8%
Risk ratio for watchful waiting	2.14
Relative risk reduction with resection	53%
Odds with watchful waiting	0.18
Odds with resection	0.08
Odds ratio with watchful waiting	2.3
10-year hazard rate with resection	0.7%
Natural frequency, watchful waiting	15 of 100 men
Natural frequency, resection	7 of 100 men

Data are from a study of men with prostate cancer in whom 14 of 200 treated with resection died and 30 of 200 treated with watchful waiting died.

Cross-sectional surveys: risks and odds

Cross-sectional studies collect data about exposures and outcomes at a single point in time. From the survey results, we can also calculate risk and odds ratios These ratios are calculated and interpreted as above, but because the data are collected at a single point in time, they are referred to as the **prevalence risk ratio** (or simply, the **prevalence ratio**), and the **prevalence odds ratio** (Boxes 1 and 2).[2] Apparently, neither ratio is common in medical research.

Conclusion

Communicating risk effectively is not easy, in part because any of several measures can be reported, not all of which are easily understood (Box 3). Probably the most effective way to report risk is with **natural frequencies**, or percentages expressed in terms of 100 (or 1,000 or 10,000 people):

Of every 100 men with prostate cancer treated with watchful waiting, 15 will die.

However, whereas the mathematical aspects of risks are pretty straight forward, the psychological aspects are far more important and often counter to reality. We are more afraid of flying than of driving, despite the fact that flying is by far the safer way to travel. And that is a subject that must wait for a different article.

Conflicts of interest

I am the author of one of the two references cited.

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Author information

Tom Lang has been a medical-technical writer since 1975. Formerly Manager of Medical Editing Services for the Cleveland Clinic and Senior Scientific Writer at the New England Evidence-based Practice and Cochrane Centers, since 1999, he has been an international consultant in medical publications, providing both services and training in all aspects of reporting clinical research.