

## Risk Assessment II: Odds Ratio

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The most direct way to determine if an exposure is associated with a condition is to prospectively follow 2 groups, one exposed and one unexposed, and observe the frequency with which each group develops the condition. Relative risk, discussed in the first part of this 2-part series on risk assessment (*Hospital Physician*, October 2005), reflects the magnitude of the difference in the frequency of an outcome between groups. For a given exposure (and exposure could mean exposure to a risk factor or exposure to a treatment), the relative risk of an outcome is calculated as:

$$\text{Relative risk} = \frac{\text{Risk of the outcome with exposure}}{\text{Risk of the outcome without exposure}}$$

Consider a study of 1000 people in which 500 are treated with a new drug and 500 are treated with placebo. If 5 in the treatment group (1%) and 10 in the placebo group (2%) have heart attacks, the relative risk of heart attack with treatment would be 0.01/0.02, or 0.5. The risk of heart attack with treatment is one half the risk without treatment.

The relative risk tells us the precise proportional difference in risk between groups, and, as we saw in the previous article, can be easily calculated when groups with known outcome frequencies are studied. There are situations (eg, case-control studies) when all the necessary information to calculate a relative risk may not be available, but we still wish to measure the association between a risk factor and an outcome. Another frequently presented measure of this association is the odds ratio.

### WHEN THERE IS NO DENOMINATOR

Calculating relative risk requires knowing the risk of an outcome with and without exposure. To determine risk, you must know not only the frequency of an outcome but also the size of the groups at risk. If you followed a defined group prospectively, you could precisely calculate the proportion that develops a condition of interest. When you have a nearly "captive population" (eg, those with a particular kind of insurance who would almost certainly seek medical care in a particu-

lar setting), you can make reasonable assumptions about the size of the population, and thus make reasonable estimates of the true risk.

What if you are suspicious that a particular exposure might increase the risk of developing a particular condition? Say you identify a group of patients with a cancer and wish to determine if a particular exposure is a risk factor. It would be impractical, particularly if you are dealing with a rare condition, and unethical, to expose disease-free individuals to the potential risk factor and measure the frequency of cancer development. You could, however, review the records of those with cancer and determine how many of them were exposed to the potential risk factor. You could then create a group of people otherwise similar, but without cancer, and determine the proportion of this group that was exposed to the potential risk factor. By performing this case-control study and comparing the proportion of those exposed with cancer (the cases) to those exposed but without cancer (the controls), you can gain insight into the risk factor's association with the cancer. This comparison is typically presented as the odds ratio.

### CALCULATING AN ODDS RATIO

Continuing the above example, say you identify 50 patients (cases) with cancer, review their medical records, and determine that 10 of them were exposed to the risk factor in question. You then identify a comparison group of 50 cancer-free individuals (controls), review their medical records, and determine that 2 were exposed to the risk factor. (You need not have the same number of controls as cases; the number used will influence the statistical tests but not the method of determining the odds ratio.) Ten of 50 individuals with cancer were exposed, giving a probability of exposure among cases of 20%. Two of 50 without cancer were exposed, giving a probability of exposure among controls of 4%. The odds ratio is calculated as:

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$$\text{Odds ratio} = \frac{\text{Odds of exposure in those with the condition}}{\text{Odds of exposure in those without the condition}}$$

Recall that odds is calculated from probability as:

$$\text{Odds} = \frac{\text{Probability}}{1 - \text{Probability}}$$

From our example, the probability of exposure in those with disease was 20%, or 0.2, so the odds of exposure in those with disease is:

$$0.2 / (1 - 0.2) = 0.2 / 0.8 = 0.25$$

Similarly, the odds of exposure for those without disease is:

$$0.04 / (1 - 0.04) = 0.04 / 0.96 = 0.04167$$

The odds ratio is calculated as the ratio of the odds of exposure in those with disease to those without disease; in this case, the odds ratio is 0.25/0.04167, or 6.

This means that the odds of finding the risk factor in someone with the condition is 6 times the odds of finding the risk factor in someone without the condition. Note the subtle difference in the meaning of odds ratio and relative risk; a relative risk of 6 would mean the condition was 6 times more likely to develop in someone exposed than in someone unexposed.

If the data are expressed in a 2 × 2 table, there is a shortcut to calculating the odds ratio.

	Condition	
	+	-
Risk +	A	B
Risk -	C	D

The odds ratio can be calculated as: AD/BC (The derivation of this formula is shown after the answers to the Practice Questions at the end of this article.) Substituting from our example:

	Condition	
	+	-
Risk +	10	2
Risk -	40	48

And the odds ratio is then:

$$(10 \times 48) / (2 \times 40) = 480 / 80 = 6$$

Do not be tempted to use a 2 × 2 table constructed to calculate an odds ratio to calculate a relative risk. Doing so in this case would imply that your population has a prevalence of disease of 50%. (I mention this here be-

cause it is a common mistake, and the resulting wrong answer is typically provided on multiple-choice tests!)

### INTERPRETING ODDS RATIOS

As with relative risk, an odds ratio greater than 1 implies a positive association between the exposure and the condition of interest; an odds ratio less than 1 implies a negative association. An odds ratio of 1, like a relative risk of 1, implies no association between the exposure and the condition. As with relative risk, research papers reporting odds ratio typically will report the 95% confidence intervals (CI) around the measured odds ratio. Realize that the odds ratio presented in a research paper is an estimate of the true odds ratio, and if the 95% CI includes the value 1, this implies that the odds ratio obtained in the study is statistically consistent with a true odds ratio of 1, and you cannot properly accept that the true odds ratio is different from 1. This is why you might see the odds ratio for a risk factor calculated as 1.2, implying an increased risk, but if the 95% CI is 0.9 to 1.5 (including the value 1), the risk will be considered “not statistically significantly different.”

### ODDS RATIO VERSUS RELATIVE RISK

As a measure of the association between a risk factor and a condition, relative risk is superior to odds ratio and should be determined over the odds ratio wherever feasible. Unlike odds ratio, relative risk presents the precise proportional difference in risk of an outcome after an exposure, and this is typically what we are most interested in clinically. Reliance on odds ratio data should be reserved for situations (eg, rare conditions) where prospective study and determination of relative risk is not feasible.

It is essential to understand that odds ratio is not the same as relative risk, and relative risk is not the same as odds ratio. Both measure an association between a risk factor and an outcome, but relative risk is related to the difference in outcomes with and without a risk factor, and odds ratio is related to the difference in the presence of a risk factor in those with and without a condition. The difficulty in distinguishing these concepts is made worse by the observation that across much of the range of disease frequency and risk factor presence, the odds ratio and relative risk will turn out to be similar numbers (though at extremes of disease prevalence or risk factor presence the odds ratio and relative risk will diverge). Consider both relative risk and odds ratio to be measures of association between a condition and a risk factor, but remember they measure different things and should not be considered equivalent.

**SOME LIMITATIONS OF STUDIES PRESENTING ODDS RATIO**

There are many sources of bias that might affect the reliability of data used in a case-control study and thus impact the veracity of the odds ratio. Patients with and without disease may recall exposures differently, or clinicians may record the presence of a risk factor with different frequencies if they know a patient has or does not have a particular condition. This recall and recording bias will tend to inflate the odds ratio for a risk factor. Although every effort should be made to have the control group as similar as possible to the case group, it is always possible that the groups could be systematically different in ways that could affect the results. Only a careful review of a study’s methods can help you determine the potential effect of a group’s composition on the results. A future article in this series will discuss common biases in the medical literature and how to identify them.

Note also that, unlike randomized controlled trials, case-control trials cannot confirm a cause-and-effect relationship but can only measure an association. There is always the possibility that some unconsidered confounder is the “real” cause of the condition. Although you might be able to perform a study and generate a relative risk or odds ratio greater than 1 suggesting that an increase in ice cream sales is associated with an increase in drowning, both are likely increased due to warm weather and not a cause-and-effect relationship.

This anticipates an additional limitation of retrospective studies, particularly case-control studies: clustering. If it were true that outcomes were distributed not only randomly, but also evenly, then any apparent clustering of outcomes around an exposure (eg, cancers in those living near electrical wires) would imply that the exposure is a cause. Consider a disease with a known prevalence of 1 in 100,000: in a population of 1 million, you would expect to find 10 cases. If you had one hundred cities each with 1 million people, all cities would not have 10 cases. Some cities might have 10, 5, 20, 1 or none. There would likely be a normal distribution of case frequencies across all cities, with the overall average being 10 per city. It would be more likely that someone in a city with an excess of cases (greater than 10) would seek to determine if there was a local risk factor for the condition that explained the excess cases, and anything unique to the city (eg, a power plant, a factory) might be studied as a risk factor. A case-control study may very well result in an odds ratio considerably greater than 1 (implying association) for the potential risk factor and the condition. There may

or may not be a real association between this risk factor and the disease, so before the potential risk factor is deemed a certain culprit, it is essential that the study be repeated in other settings. Unfortunately, more media attention is typically given to a first study finding an association between a disease and an exposure than to later studies refuting an association.

**SUMMARY**

The relative risk is the ratio of the frequency of an outcome between an exposed and unexposed group. This ratio expresses how many more times likely an outcome is in an exposed group. When you do not know the size of the population, and therefore cannot determine the risk of an outcome with exposure, you can determine an odds ratio by comparing a group with the condition to one without, and assessing how much more likely the exposure is to be found in those with the condition compared to those without. This type of case-control study is particularly useful when studying rare conditions or in other settings when it would be impractical or unethical to perform a prospective study.

**PRACTICE QUESTIONS**

1. You are attempting to establish a link between diets high in trans fatty acids and early heart disease. You identify 50 patients with early heart disease and determine through interviews that 25 had diets high in trans fatty acids. You then gather 150 controls who do not have early heart disease but are of similar age, sex, and socioeconomic status and determine that 50 had diets high in trans fatty acids. From the data you collected, calculate the odds ratio for trans fatty acid consumption and early heart disease.
2. If you determine from reliable data that 10% of people in your community have early heart disease, and the proportion of those with diets high in trans fatty acids turns out to be the same in those with and without early heart disease as it was in question 1, what is the relative risk of heart disease with a diet high in trans fatty acids?

**ANSWERS**

1.  $2 \times 2$  method:

	Condition	
	+	-
Risk +	25(A)	50(B)
Risk -	25(C)	100(D)

$$\begin{aligned} \text{Odds ratio} &= (A \times D) / (B \times C) \\ &= (25 \times 100) / (25 \times 50) = 2 \end{aligned}$$

Longhand: probability of a high trans fatty acid diet with early heart disease is:

$$25/50 = 0.5, \text{ odds} = P / (1 - P) = 0.5 / 0.5 = 1.$$

Probability of a high trans fatty acid diet without early heart disease is:

$$50/150 = 0.3333, \text{ odds} = 0.3333 / 0.6666 = 0.5$$

Odds ratio is 1/0.5, or 2.

2. The easiest way to solve problems like this is to construct a 2 × 2 table by working backwards from the prevalence. Imagine a population of 1000 people. If 10% have early heart disease, that means 100 have early heart disease and 900 do not. Since from the first problem 50% of those with early heart disease had diets high in trans fatty acids, and 1/3 of those without early heart disease had diets high in trans fatty acids, your 2 × 2 table would look as follows:

	Condition		
	+	-	
Risk +	50	300	350
Risk -	50	600	650
	100	900	

The risk of early heart disease in those with a diet high in trans fatty acids is 50/350, the risk of early heart disease in those without a diet high in trans fatty acids is 50/650, and the relative risk is then:

$$(50/350) / (50/650) = 650/350 = 1.86.$$

### DERIVATION OF AD/BC FOR ODDS RATIO

Consider a 2 × 2 table for a risk factor and a condition:

	Condition	
	+	-
Risk +	A	B
Risk -	C	D

The odds ratio is calculated as:

$$\frac{\text{Odds of exposure in those with the condition}}{\text{Odds of exposure in those without the condition}}$$

Odds of exposure in those with the condition is calculated as:

$$\frac{\text{Probability of exposure in those with condition}}{1 - \text{Probability of exposure in those with condition}}$$

Probability of exposure in those with the condition is:

$$\frac{A}{A + C}$$

so the odds of exposure in those with the condition is:

$$\frac{A}{A + C} \bigg/ 1 - \frac{A}{A + C}, \text{ and}$$

$$1 - \frac{A}{A + C} = \frac{A + C}{A + C} - \frac{A}{A + C} = \frac{C}{A + C}$$

Substituting, the odds of exposure with the condition is:

$$\frac{A}{A + C} \bigg/ \frac{C}{A + C} = \frac{A}{C}$$

Similarly, the odds of exposure in those without the condition is:

$$\frac{B}{B + D} \bigg/ 1 - \frac{B}{B + D} =$$

$$\frac{B}{B + D} \bigg/ \frac{B + D}{B + D} - \frac{B}{B + D} =$$

$$\frac{B}{B + D} \bigg/ \frac{D}{B + D} = \frac{B}{D}$$

The odds ratio is then:

$$(A/C) / (B/D) = (AD) / (BC)$$

**HP**

### SUGGESTED READING

Guyatt G, Rennie D. User's guide to the medical literature. Chicago: American Medical Association Press; 2002.

Riegelman RK, Hirsh RP. Studying a study and testing a test. 3rd ed. Boston: Little, Brown and Company; 1996.

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### EDITOR'S NOTE

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