Measuring association in contingency tables

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April 8

Hypothesis tests and confidence intervals

- Fisher's exact test and the χ^2-test can be used to calculate p-values and assess evidence against the null
- This null hypothesis can be loosely described as saying that there is "no association" between treatment/exposure and the outcome, or more formally as the hypothesis that the two events are independent
- However, we also need to be able to measure and place confidence intervals on effect sizes – otherwise, we have no way of assessing the practical and clinical significance of the association
- So we want a confidence interval ... but what do we want a confidence interval of?

Difference in proportions

- One way of measuring the strength of an association for categorical data is to look at the difference in proportions
- For example, in Lister's experiment, 46% of the patients who received the conventional surgery died, but only 15% of the patients who received the sterile surgery died
- The difference in these percentages is 31%

Flaws with the difference in proportions

- However, differences in proportions are not informative for rare events
- For example, in a rather famous study that made front-page headlines in the *New York Times*, 0.9% of subjects taking aspirin suffered heart attacks, compared to 1.7% of placebo subjects
- The difference in proportions, 0.8%, doesn't sound front-page-of-the-*New–York–Times*–worthy

The relative risk

- Instead, for proportions, we often describe the strength of an association using ratios
- When we said that the probability of suffering a heart attack was twice as large ($1.7/0.9 = 1.9$) for the placebo group as for the aspirin group, this is much more attention-grabbing
- Similarly for Lister's experiment: the risk of dying from surgery is three times lower ($46/15 = 3.1$) if sterile technique is used
- This ratio is called the *relative risk*, and it is usually more informative than the difference of proportions

Flaws with the relative risk

- The relative risk is a good measure of the strength of an association, but it too has flaws
- One is that it's asymmetric
- For example, the relative risk of dying is $46/15 = 3.1$ times greater with the nonsterile surgery, but the relative risk of living is only $85/54 = 1.57$ times greater with the sterile surgery

Relative risks and retrospective studies

- Another flaw is that it doesn't work with retrospective studies
- For example, consider the results of a classic case-control study of the relationship between smoking and lung cancer published in 1950:

	Cases	Controls
Smoker	688	650
Nonsmoker	21	59

- Is the probability of developing lung cancer given that a person smoked $688/(688+650) = 51\%$?

Relative risks and retrospective studies (cont'd)

- Absolutely not; this isn't even remotely accurate
- By design, this study included 709 people with lung cancer and 709 without; the fact that about 50% of smokers had lung cancer doesn't mean anything
- For retrospective and cross-sectional studies, then, we cannot calculate a relative risk
- This would require an estimate of the probability of developing a disease given that an individual was exposed to a risk factor, which we can only get from a prospective study
- Instead, retrospective studies give us the probability of being exposed to a risk factor given that you have developed the disease

Odds

- A slightly different measure of association, the *odds ratio*, gets around both of these flaws
- Instead of taking the ratio of the probabilities, the odds ratio is a ratio of the odds of developing the disease given risk factor exposure to the odds given a lack of exposure
- The *odds* of an event is the ratio of the number of times the event occurs to the number of times the event fails to occur
  - For example, if the probability of an event is 50%, then the odds are 1; in speech, people usually say that "the odds are 1 to 1"
  - If the probability of an event is 75%, then the odds are 3; "the odds are 3 to 1"

The symmetry of the odds ratio

- As advertised, the odds ratio possesses the symmetry that the relative risk does not
- For example, in Lister's experiment the odds of dying were $6/34 = .176$ for the sterile group and $16/19 = .842$ for the control group
- The relative odds of dying with the control surgery is therefore $.842/.176 = 4.77$
- On the other hand, the odds of surviving were $34/6 = 5.67$ for the sterile group and $19/16 = 1.19$ for the control group
- The relative odds of surviving with the sterile surgery is therefore $5.67/1.19 = 4.77$

An easier formula for the odds ratio

- Summarizing this reasoning into a formula, if our table looks like

a	b
c	d

then

$$\widehat{OR} = \frac{ad}{bc}$$

- Because of this formula, the odds ratio was originally called the "cross-product ratio"

There are two odds ratios

- Keep in mind that there are two odds ratios, depending on how we ordered the rows and columns of the table, and that they will be reciprocals of one another
- When calculating and interpreting odds ratios, be sure you know which group has the higher odds of developing the disease
- In Lister's experiment, the odds ratio for surviving with the sterile surgery was 4.77, but the odds ratio for surviving with the control surgery was $1/4.77 = 0.210$
- NOTE: When writing about an odds ratio less than 1, it is customary to write, for example, that "the sterile procedure reduced the odds of death by 79%"

Odds ratios and retrospective studies

- The symmetry of the odds ratio works wonders when it comes to retrospective studies
- So, in our case-control study of lung cancer and smoking, the odds ratio for smoking given lung cancer is

$$\begin{aligned}\widehat{OR} &= \frac{688 \cdot 59}{21 \cdot 650} \\ &= 2.97\end{aligned}$$

- However, this is also the odds ratio for lung cancer given smoking
- This is a minor miracle: we have managed to obtain a prospective measure of association from a retrospective study!
- Hence the popularity of the odds ratio: it can be used for any study design (prospective, retrospective, cross-sectional) that results in a 2x2 contingency table

Interpretation of odds ratios

- We will focus on odds ratios in this course, although it is worth noting that many researchers consider relative risks more easy to interpret, and prefer reporting them when possible
- Indeed, odds ratios are always larger in magnitude (i.e., further away from 1) than relative risks, something to keep in mind when interpreting clinical significance
- For example, we saw that for the Lister study, the relative risk was 3.1, while the odds ratio was 4.8
- An even more extreme example is the Nexium trial (recall that the healing rates in the two groups were 93% vs. 89%), where the relative risk is 1.04 but the odds ratio is 1.6

The χ^2-test and measures of association

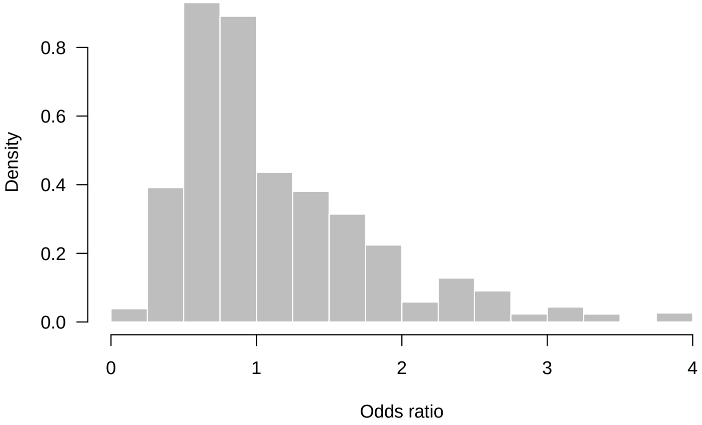
- Note that when the difference between two proportions equals 0, the relative risk equals 1 and the odds ratio equals 1
- Furthermore, when relative risk of disease given exposure equals 1, the relative risk of exposure given disease equals 1
- Indeed, all of these statements are equivalent to saying that exposure and disease are independent
- Thus, any one of these may be thought of as the null hypothesis of the χ^2-test
- This is why the null hypothesis is often loosely described as there being no "association" between exposure and disease

The odds ratio and the central limit theorem

- So far in this class, we've calculated confidence intervals for averages and percentages
- For both statistics, the central limit theorem guarantees that if the sample size is big enough, their sampling distribution will look relatively normal
- The central limit theorem, however, does not directly establish that the distribution of odds ratio will be normally distributed, and indeed, it tends to be skewed to the right

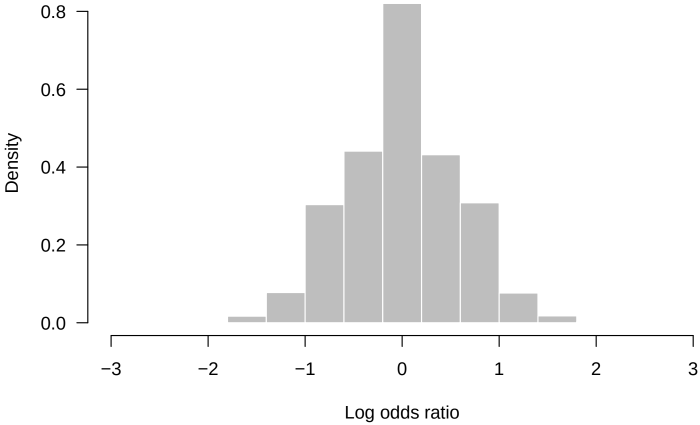
Simulation: The sampling distribution of the odds ratio

$n = 25$ per group



The log transform

However, look at the sampling distribution of the logarithm of the odds ratio:



Confidence intervals for the log odds ratio

- The log of the odds ratio is quite normal-looking and amenable to finding confidence intervals for using the central limit theorem/normal distribution
- Thus, the procedure that has been developed for constructing approximate confidence intervals for the odds ratio actually constructs confidence intervals for the log of the odds ratio
- Getting a confidence interval for the odds ratio itself then requires an extra step of converting the confidence interval back to the odds ratio scale

The standard error of the log odds ratio

It can be shown that a good estimate of the standard error of the log of the odds ratio is

$$SE_{lOR} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

where a, b, c, and d are the four entries in the contingency table

Confidence intervals for the odds ratio: procedure

The first three steps for constructing confidence intervals for the odds ratio should look familiar; the fourth will be new:

#1 Estimate the standard error of the log OR,
$SE_{lOR} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$

#2 Determine the values that contain the middle $x\%$ of the normal curve, $\pm z_{x\%}$

#3 Calculate the confidence interval for the log OR:

$$(L, U) = \left(\log(\widehat{OR}) - z_{x\%} \cdot SE_{lOR}, \, \log(\widehat{OR}) + z_{x\%} \cdot SE_{lOR}\right)$$

#4 Convert the confidence interval from step 3 back into the odds ratio scale to obtain the confidence interval for the odds ratio:

$$(e^L, \, e^U)$$

NOTE: "log" above refers to the natural log (sometimes abbreviated "ln"), not the base-10 logarithm

Confidence intervals for the odds ratio: example

To see how this works in practice, let's calculate a 95% confidence interval for the odds ratio of surviving with sterile surgery in Lister's experiment

#1 Estimate the standard error of the log odds ratio:

$$\begin{aligned} SE_{lOR} &= \sqrt{\frac{1}{34} + \frac{1}{6} + \frac{1}{19} + \frac{1}{16}} \\ &= 0.56 \end{aligned}$$

#2 As usual, 1.96 contains the middle 95% of the normal distribution

#3 Recall that the sample odds ratio was 4.77, so the log of the sample odds ratio is 1.56

#3 The 95% confidence interval for the log odds ratio is therefore

$$(1.56 - 1.96(0.56), 1.56 + 1.96(0.56)) = (0.47, 2.66)$$

Confidence intervals for the odds ratio: example (cont'd)

#4 The 95% confidence interval for the odds ratio is therefore

$$\left(e^{0.47}, e^{2.66}\right) = (1.60, 14.2)$$

- Note that the confidence interval doesn't include 1; this agrees with our test of significance
- Note also that this confidence interval is asymmetric (its right half is much longer than its left half) – this would be impossible to achieve without the log transform
- Now we have an idea of the possible clinical significance of sterile technique: it may be lowering the odds of surgical death by a factor of about 1.6, or by a factor of 14, with a factor of around 5 being the most likely

Reverse example

Note also the symmetry that arises if we had decided to calculate a confidence interval for the other odds ratio (the relative odds of dying on the sterile surgery):

- $\widehat{\mathrm{OR}} = 0.21$
- $\log(\widehat{\mathrm{OR}}) = -1.56$
- 95% CI for $\log(\widehat{\mathrm{OR}})$: (-2.66, -0.47)
- 95% CI for $\widehat{\mathrm{OR}}$: (0.07, 0.62)

Summary

- There are three natural ways to measure the association present in a 2×2 table:
  - Difference of proportions
  - Relative risk
  - Odds ratio
- One big advantage of the odds ratio is that it works equally well for both prospective and retrospective studies, unlike the other two
- Be able to construct confidence intervals for odds ratios