
RACE NO.
2
8
MINUTES TO POST
APPROXIMATE ODDS
1
4
5
7
9
10
13
2
9-2
6
17
10
5-2
14
3
25
7
11
15
4
13
8
4
12
16

Introduction to Biostatistics
Lecture 6

Henrik Renlund

October 12, 2015

Uppsala Clinical Research Center

What shall we learn today?

Many analyses and concepts that relates to count data (tables).

For tables relating dichotomous data (event or non-event) what can be said about risk, both compared to a model and between subgroups?

For tables relating counts of a categorical variable, how can we test the distribution of values against a model or between subgroups.

Dabigatran data

Dagbigatran is an anticoagulant used for e.g. stroke prevention in patients with atrial fibrillation. The following example only looks at side effects.

718 people were randomized to Dabigatran or placebo and observed for some set time for bleeding.

id	intervention	bleeding
1	dabigatran	Yes
2	placebo	No
3	placebo	No
4	dabigatran	No
⋮	⋮	⋮
718	placebo	No

Tabulated data

	Bleeding		
	Yes	No	Sum
dabigatran	27	320	347
placebo	8	363	371
Sum	35	683	718

Measures for dabigatran:

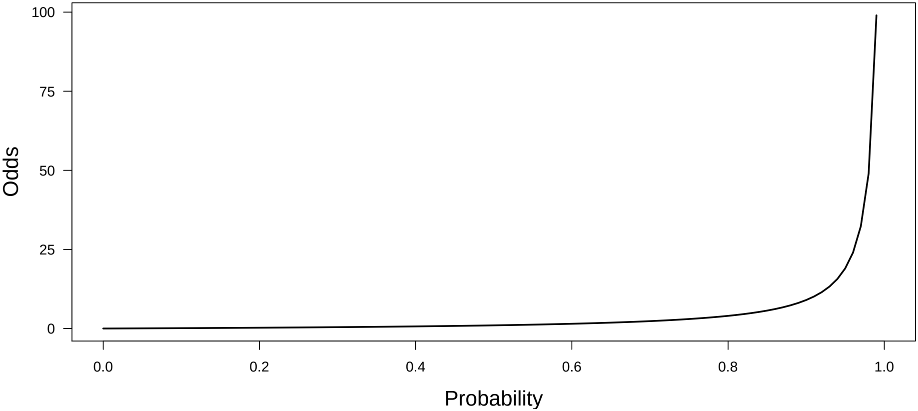
- Risk is probability of an unwanted event.
  Risk of bleeding $= 27/347 = 7.8\%$
- Odds is how much more likely it is to experience an event compared to not experience it. Odds of bleeding

$$= \frac{27/347}{320/347} = \frac{27}{320} = 8.4\%$$

(Odds? Sometimes this is easier to model.)

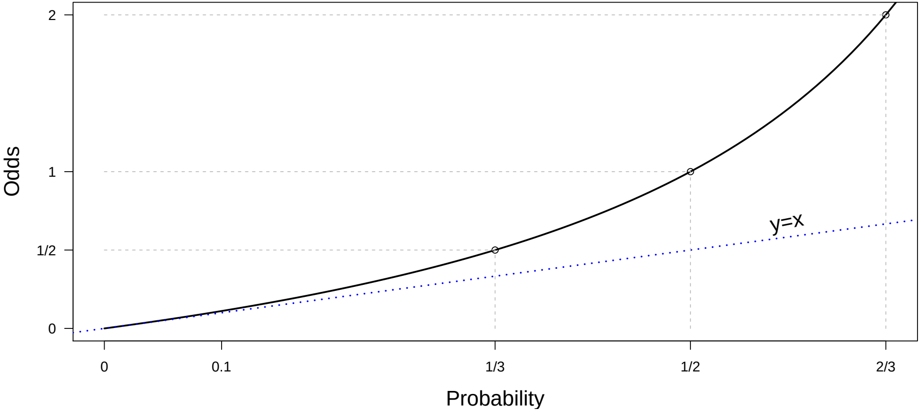
Odds

For an event with probability p, the odds is $p/(1-p)$.



Odds

For small probabilities: odds $\approx$ probability.



More on odds

- if an event has odds θ, then its probability p is $p = \theta/(1+\theta)$
  $\theta = 2$ corresponds to $p = 2/3$.
  $\theta = 1$ corresponds to $p = 1/2$.
  $\theta = 1/100$ corresponds to $p = 1/101$.

- in a betting game where you stand to win 1 unit of money, your stake S (*if this is kept when winning*) should not exceed the odds
  - 'expected' profit $= 1\frac{\theta}{1+\theta} - S\frac{1}{1+\theta} \geq 0$ is equivalent to $S \leq \theta$
  - If your offered x units of money for a game you think has odds 2 (in your favor) then do not bet more than $2x$.
    Betting $2x$ makes the game "fair".

- there are multiple systems of betting (sports) 'odds', that are not odds in the sense of this course!

Relational measures

	Bleeding		
	Yes	No	Sum
dabigatran	27	320	347
placebo	8	363	371
Sum	35	683	718

Measures for risk of dabigatran versus placebo

- (Risk ratio $= \frac{27/347}{8/371} \approx 3.6$)
- Odds ratio $= \frac{27/320}{8/363} \approx 3.8$
- Risk difference $= 27/347 - 8/371 \approx 0.056$

Odds ratio (OR)

The OR contains no information about the probabilities.
If you know the 'denominator' probability (p_2) then the 'numerator' probability (p_1) can be calculated

$$p_1 = \frac{\mathrm{OR} \cdot p_2}{1 + (\mathrm{OR} - 1) \cdot p_2}.$$

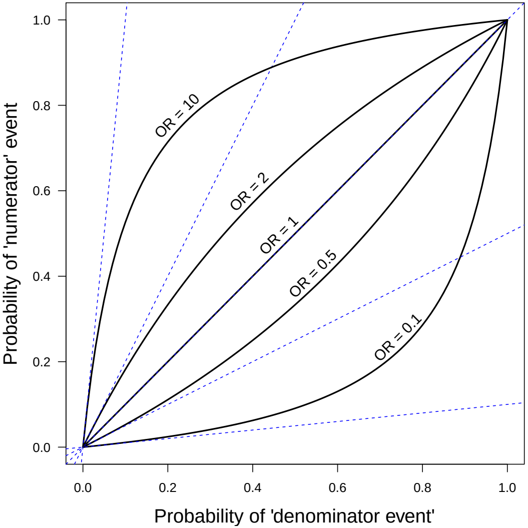
More importantly, for small values of p_2 and 'moderate' values of OR, one essentially has

$$p_1 \approx \mathrm{OR} \cdot p_2.$$

'denominator' (p_2)	**Odds Ratio (OR)**				
	0.1	0.5	1	2	10
0.01	0.0010	0.005	0.01	0.020	0.092
0.05	0.0052	0.026	0.05	0.095	0.340
0.1	0.0110	0.053	0.10	0.180	0.530
0.5	0.0910	0.330	0.50	0.670	0.910

OR and probabilities

The blue dotted lines are the 'corresponding slopes'.



Fishers exact test

	Bleeding		
	Yes	No	Sum
dabigatran	X	(347-X)	347
placebo	(35-X)	(683-347+X)	371
Sum	35	(683)	718

Suppose that whether a person bleeds or not is complete independent of intervention. (H_0: "odds ratio $= 1$".)

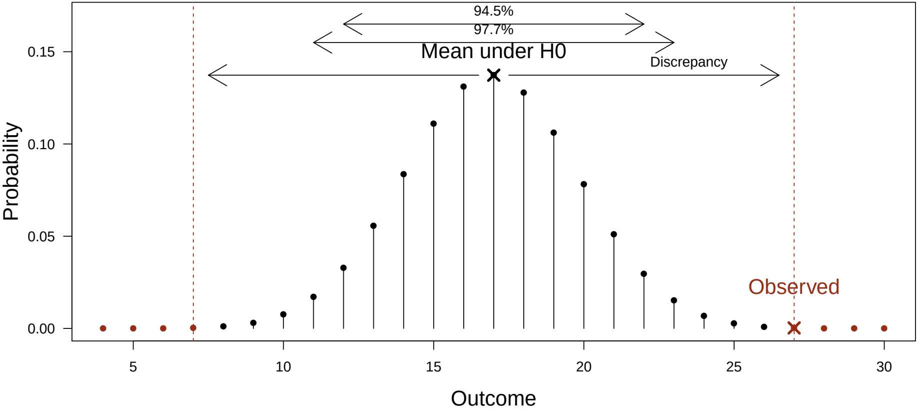
Then the 35 individuals who bled should be a random sample of the study population (of size 718) and we would expect that $X/35 = 347/718 \approx 48\%$.

We can calculate *exactly* what the distribution of X is *given* H_0.

The *p*-value is the probability of a discrepancy the size of that between the observed and the expected.

p-value in Fishers exact test

Sum the red values to get $p = 0.00045$.



More on Fishers exact test

My software produced the following output:

```
   Fisher's Exact Test for Count Data

data:  Dabigatran_example
p-value = 0.0004458
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
 1.659358 9.877595
sample estimates:
odds ratio
  3.821942
```

So odds ratio is between 1.7 and 9.9. (Allows for test of model.)
Probabilities are small, so risk of dabigatran is (approx.) between 1.7 and 9.9 times larger than placebo risk.

What question did we answer?

Calculating the OR is a very 'standard' analysis.

It is worth reiterating that this is a relative measure and answers a question along the lines of

> *how much does the odds of bleeding - measured in units of the placebo odds - change with this drug? Answer: 3.83 (1.66–9.88).*

The placebo risk is $p_2 = 8/371 \approx 2.2\%$ so we can use an earlier formula to get $p_1 =$ risk with dabigatran:

OR	1.66	3.82	9.88
$p_1 \approx$	3.6%	8.2%	21%
$p_1 =$	3.5%	7.8%	18%
RR =	1.6	3.6	8.3

In a sense this gives us a confidence interval p_1 but it is "too" wide since it takes into account the uncertainty of p_2.

Absolute risk

What can we say about the *absolut* risk of bleeding with dabigatran?

This was covered by Lars in Lecture 3! (Genotype example.)

The risk estimate $27/347 = 0.078$ has a standard error (SE) given by

$$\sqrt{\frac{0.078(1-0.078)}{347}} = 0.0144.$$

This yields a 95% confidence interval given by

$$(0.078 \pm 1.96 \cdot 0.0144) = (0.050, 0.11).$$

(This allows for test of model.)

Risk difference

What is the *difference* in risk between dabigatran and placebo?
This has (almost) been covered by Lars. One needs to know that for two **independent** estimators (having SE_1 and SE_2) the SE for their difference is given by

$$\sqrt{SE_1^2 + SE_2^2}.$$

Risk	Estimate	Standard error
dabigatran	$p_1 = 27/347 = 0.078$	$\sqrt{p_1(1-p_1)/347} = 0.0144$
placebo	$p_2 = 8/371 = 0.022$	$\sqrt{p_2(1-p_2)/371} = 0.0075$
difference	$p_1 - p_2 = 0.056$	$\sqrt{0.0144^2 + 0.0075^2} = 0.0162$

We get a 95% confidence interval for the difference with

$$(0.056 \pm 1.96 \cdot 0.0162) = (0.024, 0.088).$$

(This allows for test of model.)

Cosmetic skin testing

To prove a new product is hypoallergenic it should provoke no more skin reactions than current market leader.

To test a new product 40 individuals got both products applied to to patches of skin and observed for reaction (yes/no)

id	new	market
1	no	no
2	yes	no
3	no	no
⋮	⋮	⋮
40	yes	yes

Is the new product as good as the market leader?

The following table is *not* appropriate to answer that question.

	no	yes
old	22	18
new	32	8

The rows are dependent. This makes e.g. test of risk difference faulty.

McNemars test for paired data

	new		
market	no	yes	Sum
no	17	5	22
yes	15	3	18
Sum	32	8	40

McNemars test only considers the pairs were the results are different.

With new product there are 8 reactions but 3 of them would have happened anyway. The new product 'creates' 5 reactions.

Similarly, the market leader 'creates' 15 reactions.
(15 benefits, 5 are worse off and 20 are unchanged.)

A test statistic is created using '5' and '15'. p-value for H_0:'no difference' is approx 4%.

Other situations

Twins being randomized to intervention or placebo:

	Placebo	
Intervention	improvement	non
improvement	a	b
non	c	d

Case control study:

	Cases	
Controls	exposure	non
exposure	a	b
non	c	d

Mendel's pea experiment

One of Mendels pea-experiments was a (dihybrid) cross between the genes for round/wrinkled seeds and yellow/green seeds.

Type	RY	RG	WY	WG	Sum
Count (O)	315	108	101	32	558

According to his theory, these should appear in ratios of 9:3:3:1.
So, we have a model for $X =$"the type":

Value v	RY	RG	WY	WG
Prob$(X = v)$	$9/16$	$3/16$	$3/16$	$1/16$

χ^2-tests

χ^2 tests are applied to tabulated data (i.e. the 'counts'), typically categorical data.

Like the t-test, we can use χ^2 to compare a sample against a model or, compare 2 or more samples against each other.

χ^2-tests can be applied to all tables (non-paired data) presented so far.

χ^2 tests typically calculate a test statistic Q according to the formula

$$Q = \sum \frac{(\text{observed - expected})^2}{\text{expected}}.$$

Q is compared to a χ^2 distribution with a parameter (degrees of freedom) that depends on the situation.

Comparing data to a model

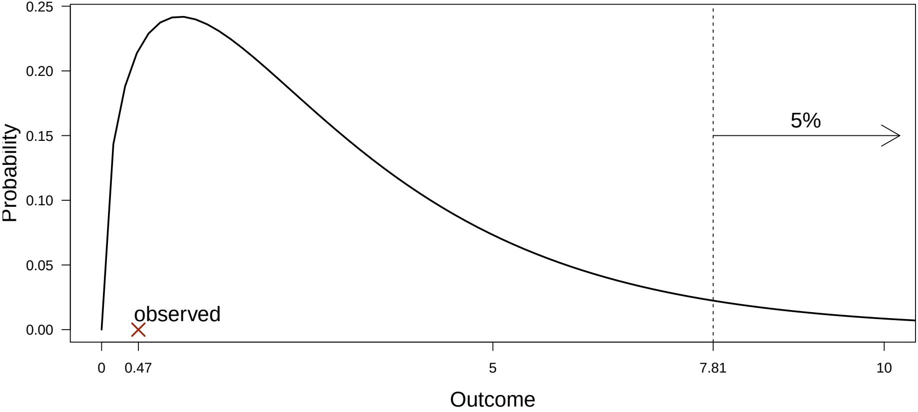
χ^2-analysis:

Type	RY	RG	WY	WG	Sum
Data (O)	315	108	101	32	558
H_0 model (p)	$9/16$	$3/16$	$3/16$	$1/16$	1
Expected ($E = 558 \times p$)	313.9	104.6	104.6	34.9	558
Q, i.e. $(O-E)^2/E$	0.004	0.111	0.124	0.241	0.479
Residuals $(O-E)/\sqrt{E}$	0.127	0.367	-0.318	-0.467	

If H_0 is correct then Q should be (approximately) $\chi^2(3)$.
(3 $=$ the number of categories -1.)

Mendels hypothesis seems ok

The observed test statistic 0.47 is compatible with H_0.



Comparing distributions

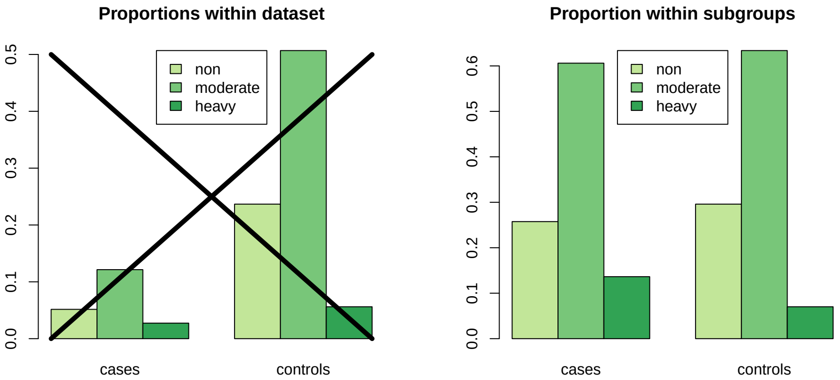
A case control study of coronary heart disease and drinking (none, moderate, heavy). Cases were matched on age, gender and smoking habits.

	non	moderate	heavy	sum
cases	34	80	18	132
controls	156	334	37	527
sum	190	414	55	659

Does drinking habits differ between cases and controls?
If they do not (H_0), their distributions should be close to

non	moderate	heavy
28.8% (190/659)	62.8% (414/659)	8.3% (55/659)

Visualizing the distributions



Are drinking categories equidistributed for cases and controls?

	non	moderate	heavy	Sum
observed cases	34	80	18	132
observed controls	156	334	37	527
sum	190	414	55	659
prop. (p=sum/659)	0.29	0.63	0.08	(1)
expected cases ($132 \cdot p$)	38.1	82.9	11.0	(132)
expected controls ($527 \cdot p$)	152.0	331.0	44.0	(527)
Q cases ((Obs.-Exp.)^2/Exp.)	0.43	0.10	4.4	Tot:
Q controls	0.11	0.026	1.1	6.2

The test statistic $Q = 6.2$ should be compared to a χ^2 with (rows-1)$\times$(columns-1)=1*2=2 degrees of freedom.
$p = \textbf{Prob}(Q > 6.2) = 0.045$.

So the difference between cases and controls is statistically significant.

The large sample size gives this test a lot of power (ability to find differences).

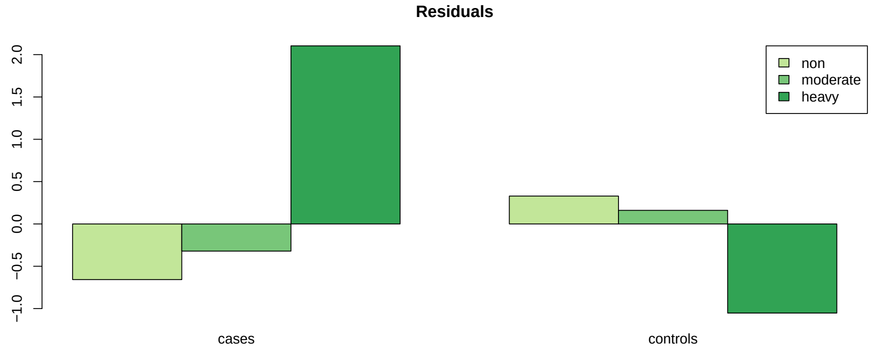
Do not forget to look at the estimates!

	non	moderate	heavy
proportion cases	0.26	0.61	0.13
proportion controls	0.30	0.63	0.07
proportion total	0.29	0.63	0.08

Whether these differences are significant in any other sense is for the researcher to discuss.

Which categories deviate?

One can also look at the 'residuals'.



χ^2 *on the dabigatran data*

The χ^2 test can also be applied to our dabigatran data.

It tests if the distribution of complications (bleeding/not) is the same for the two groups.

Output from my software:

```
#   Pearson's Chi-squared test with Yates'
#   continuity correction
#
#   data:  bord
#   X-squared = 11.05, df = 1, p-value = 0.0008869
```

(Recall that Fisher's exact test gave $p = 0.0004458$.)

Adjusting for a confounder

Comparison of open surgery (OS) and percutaneous nephrolithotomy (PN) for removal of kidney stones.
(Data illustrates Simpson's paradox.)

	Total		Adjusted for size: Small stones		Adjusted for size: Large stones	
	OS	PN	OS	PN	OS	PN
Success	273	289	81	234	192	55
Failure	77	61	6	36	71	25
Odds (for success)	3.5	4.7	13.5	6.5	2.7	2.2
Odds ratio (OS / PN)	0.75		2.1		1.2	

Here it seems like we should adjust for stone size.
The Mantel-Haenszel test is a way to analyse several contingency tables.

Adjusting for multiple confounders

In observational studies we typically gather more information. E.g.

Ind.	Bleeding	DE Dose	Age	Gender	Weight	...
1	Yes	50	75	M	83	...
2	No	75	64	F	77	...
⋮	⋮	⋮	⋮	⋮	⋮	

When medicine is not randomized a simple cross tabulation analysis of 'Bleeding' versus 'DE Dose' is likely to be confounded.
One way to deal with this is to do a logistic regression. More on that in Lecture 10.

References

- Chapters 23-25: Petrie & Sabin. *Medical Statistics at a Glance*, Wiley-Blackwell (2009).
- Grant, R. L.: Converting an odds ratio to a range of plausible relative risks for better communication of research findings, *BMJ* **348** (2014) 7 pages.