




# *Introduction to Biostatistics*
# *Lecture 6*

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## *What shall we learn today?*

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

An overly optimistic description: Lectures 3-5 but for categorical, rather than numerical, data.

For tables relating counts of a categorical variable, how can we test the distribution of values against

- a model (probability specification), or
- between subgroups.

We will start with the special case of dichotomous/binary data (event or non-event).



## *A note on categorical data*

We generally talk differently about categorical data depending on the number of unique values.

**Dichotomous/binary data** is typically yes/no- or event/non-event data. We talk about this data in terms of the probability of one of the events (often the one with the smallest probability). If **Prob**(event) is modelled, then **Prob**(non-event) is implicit (since **Prob**(non-event)=1-**Prob**(event)).

**"Non-binary" categorical data** has more than 2 values ($A$, $B$, $C$, ...). We talk about this data in terms of the entire *distribution*, i.e. the probability function ($\mathbf{Prob}(A), \mathbf{Prob}(B), \mathbf{Prob}(C), \ldots$). Of course we could omit one of these, since it would be implicit, but it is unconvenient.

## *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:

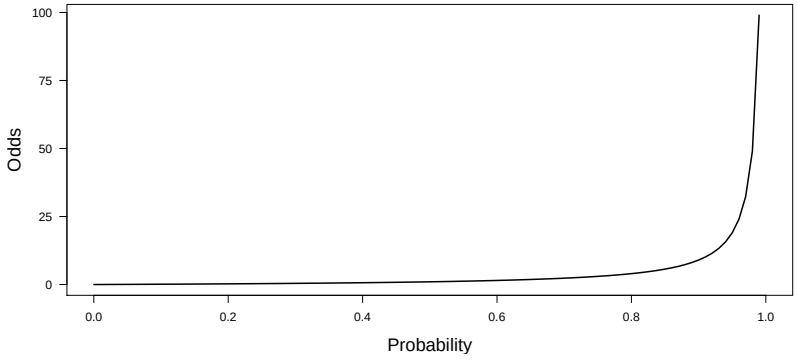
- **Risk** (probability of an unwanted event)
  Risk of bleeding $= 27/347 = 7.8\%$
- **Odds** (how much more likely it is, versus not, to experience an event)
  Odds of bleeding
  $$= \frac{27/347}{320/347} = \frac{27}{320} = 8.4\%$$

(Odds? Sometimes this is easier to model.)



## *Odds*

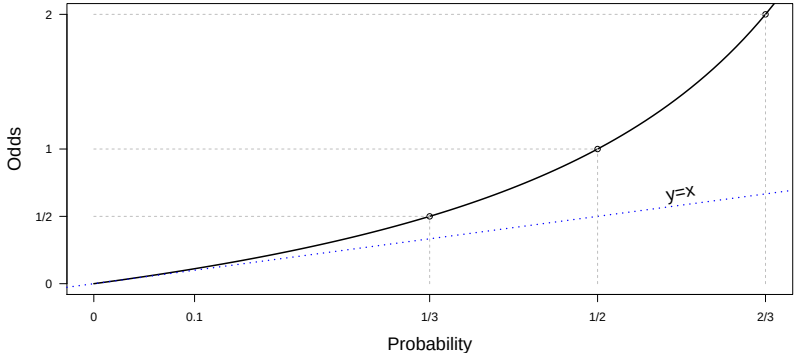
For an event with probability $p$, the odds is $p/(1-p)$.






## *Odds*

For small probabilities: odds $\approx$ probability.



## More on odds

- if an event has odds $\theta$, 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 you are 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 (RR)** $= \frac{27/347}{8/371} \approx 3.6$)
- **Odds ratio (OR)** $= \frac{27/320}{8/363} \approx 3.8$
- **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

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

For small values of $p_2$ and 'moderate' values of OR

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

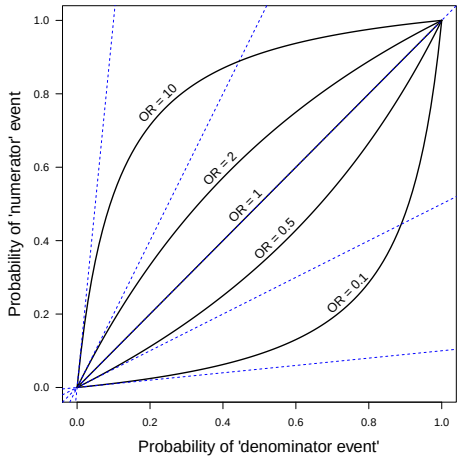
Deviation (%) between approximation and exact formula:

| **'denominator' ($p_2$)** | **Odds Ratio (OR)** | | | | |
|---|---|---|---|---|---|
| | 0.1 | 0.5 | 1 | 2 | 10 |
| 1 % | −0.9 | −0.5 | 0 | 1 | 9 |
| 5 % | −4.5 | −2.5 | 0 | 5 | 45 |
| 10 % | −9.0 | −5.0 | 0 | 10 | 90 |
| 50 % | −45.0 | −25.0 | 0 | 50 | 450 |



## OR and probabilities

The blue dotted lines are the approximations.



## *Fishers exact test*

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

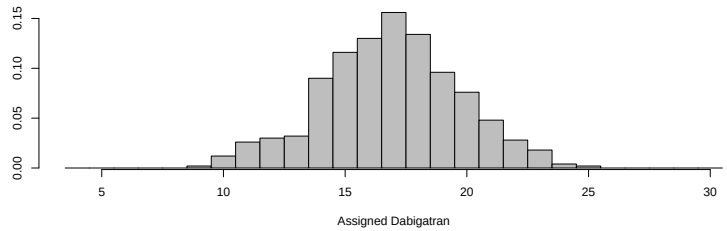
Suppose that whether a person bleeds or not is complete independent of intervention. ($H_0$: "odds ratio = 1".)

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 would expect $X$ to be 17-18, but is $X = 27$ within some acceptable range of possiblities?



Simulate (500 times) the experiment of randomly selecting 35 people from the study population and record the number who got dabigatran (15, 15, 16, 18, 16...)



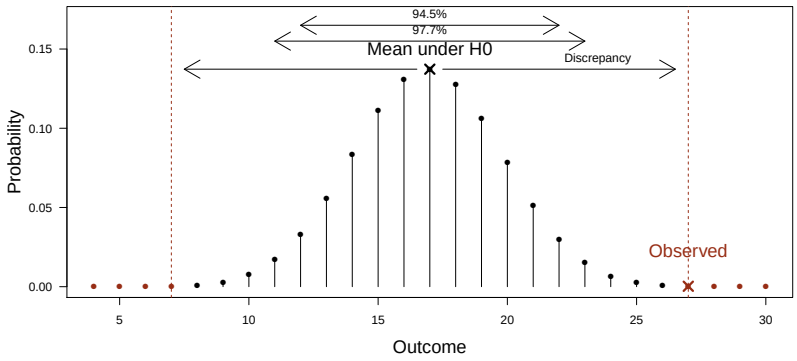

However, we can calculate *exactly* what the distribution of $X$ is *given* $H_0$ (in this case).

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.

## Risk Ratio?

So

> *The odds ratio of bleeding with dabigatran versus placebo is 3.8 (1.7–9.9).*

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) and thus the RR:

| OR | 1.7 | 3.8 | 9.9 |
|---|---|---|---|
| $p_1 =$ | 3.5% | 7.8% | 18% |
| RR = | 1.6 | 3.6 | 8.3 |

So

> *The risk ratio of bleeding with dabigatran versus placebo is 3.6 (1.6–8.3).*

(**N.B** The implied confidence interval (above) for $p_1$ is "too wide" since it takes to much uncertainty into account.)



## 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.)



## Have we exhausted the Dabigatran example yet?

**Summary of the dabigatran example**:

| Quantity | Estimate | Confidence interval |
|---|---|---|
| $p_1$ | 0.078 | $(0.050, 0.11)$ |
| $p_1 - p_2$ | 0.056 | $(0.024, 0.088)$ |
| OR (p1 vs. p2) | 3.82 | $(1.7, 9.9)$ |

## *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 |



## *McNemars test for paired data*

| | | new | | |
|---|---|---|---|---|
| | | no | yes | $\sum$ |
| market | 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, whereas the market leader 'creates' 15 reactions.

Switching from the market leader to the new product would benefit 15, make it worse for 5, and have no effect on 20. (In terms of skin reactions.)

A test statistic can be calculated. $p$-value for $H_0$:'no difference' is approx 4%.



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.*

**Note:**

One *can* estimate (and get confidence intervals) for $p_1$ and $p_2$ (risk of skin reaction with new and old, respectively).

*But* it is harder to quantify the SE for risk difference and OR, due to the dependence.



## *Other situations*

Twins being randomized to intervention or placebo:

| | | Placebo | |
|---|---|---|---|
| | | improvement | non |
| Intervention | improvement | a | b |
| | non | c | d |

Before/after data:

| | | Before | |
|---|---|---|---|
| | | event | non |
| After | event | 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 |



## $\chi^2$-tests

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

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

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

$\chi^2$ 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 $\chi^2$ distribution with a parameter (degrees of freedom) that depends on the situation.



## Comparing data to a model

$\chi^2$-analysis:

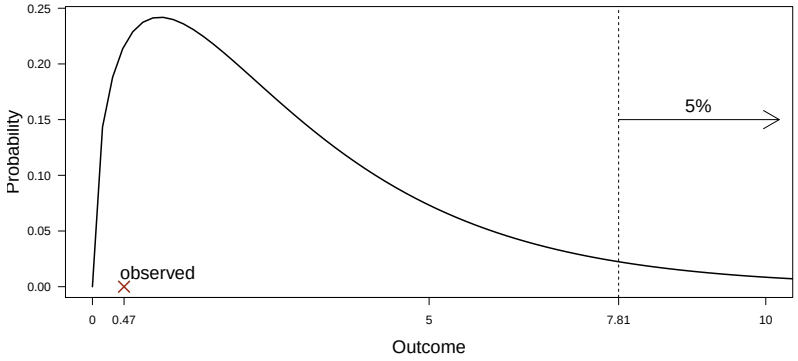
| Type | RY | RG | WY | WG | Sum |
|---|---|---|---|---|---|
| Data ($O$) | 315 | 108 | 101 | 32 | 558 |
| $H_0$ model ($p$) | 9/16 | 3/16 | 3/16 | 1/16 | 1 |
| Expected ($E = 558 \times p$) | 313.9 | 104.6 | 104.6 | 34.9 | 558 |
| $Q$, i.e. $(O-E)^2/E$ | 0.004 | 0.111 | 0.124 | 0.241 | 0.479 |
| Residuals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

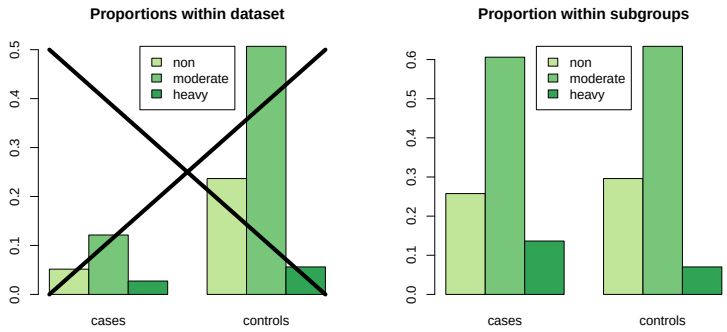
| | non | moderate | heavy | sum |
|---|---|---|---|---|
| cases | 34 | 80 | 18 | 132 |
| controls | 156 | 334 | 37 | 527 |
| sum | 190 | 414 | 55 | 659 |

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·$p$) | 38.1 | 82.9 | 11.0 | (132) |
| expected controls (527·$p$) | 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 $\chi^2$ with (rows-1)×(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).

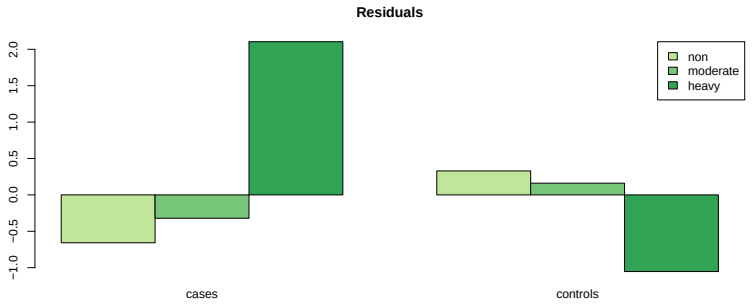
Do not forget to look at the estimates!

| | 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'.






## *$\chi^2$ on the dabigatran data*

The $\chi^2$ 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.)

| | | | Adjusted for size | | | |
|---|---|---|---|---|---|---|
| | Total | | Small stones | | 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.