Biostatistics II: Hypothesis testing

Categorical data: McNemar test
Multiple testing problem

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In this Section

- McNemar test
- Examples
- Multiple testing

McNemar test: Theory

Assumptions

- The variables should be categorical
- Matched data (pairs)
- Pairs are independent of one another
- The levels (or categories) of the variables are mutually exclusive

McNemar test: Theory

Scenario

Is there a difference in the percentage of patients with asthma between the placebo and the drug group (matched data)?

	Drug (asthma)	Drug (no asthma)	Total
Placebo (asthma)	a	b	a + b
Placebo (no asthma)	c	d	c + d
Total	a + c	b + d	n

Hypothesis

$$H_0 : p_a + p_b = p_a + p_c \text{ and } p_c + p_d = p_d + p_b$$
$$H_1 : p_a + p_b \neq p_a + p_c \text{ and } p_c + p_d \neq p_d + p_b$$

$$H_0 : p_b = p_c$$
$$H_1 : p_b \neq p_c$$

McNemar test: Theory

Connection with regression

Conditional logistic model with one binary covariate

$$\pi = \frac{Pr(Y_{s,drug}=asthma \ \& \ Y_{s,placebo}=no\ asthma)}{Pr(Y_{s,drug}=asthma \ \& \ Y_{s,placebo}=no\ asthma)+Pr(Y_{s,drug}=no\ asthma \ \& \ Y_{s,placebo}=asthma)} = \frac{p_c}{p_c+p_b}$$

Hypothesis

$$H_0 : \beta = 0$$

$$\beta = \texttt{logit}(\pi) = 0$$

if we know that $\texttt{logit}(\pi) = \texttt{log}\left(\frac{\pi}{1-\pi}\right) \Rightarrow$

$$\beta = \texttt{log}\left(\frac{\frac{p_c}{p_c+p_b}}{1-\frac{p_c}{p_c+p_b}}\right) = \texttt{log}\left(\frac{\frac{p_c}{p_c+p_b}}{\frac{p_c+p_b-p_c}{p_c+p_b}}\right) = \texttt{log}\left\{\frac{p_c(p_c+p_b)}{p_b(p_c+p_b)}\right\} = \texttt{log}\left(\frac{p_c}{p_b}\right)$$

$$\beta = 0 \Rightarrow \texttt{log}\left(\frac{p_c}{p_b}\right) = 0 \Rightarrow \frac{p_c}{p_b} = 1 \Rightarrow p_c = p_b$$

McNemar test: Theory

Test statistic

$$X^2 = \frac{(b-c)^2}{b+c}$$

When the values in the contingency table are fairly small a "correction for continuity" may be applied to the test statistic:

$$X^2 = \frac{(|b-c|-1)^2}{b+c}$$

McNemar test: Theory

Sampling distribution

- χ^2-distribution with df = 1
- Critical value and p-value

Type I error

- Normally α = 0.05

Draw conclusions

- Compare test statistic (X^2) with the critical value or the p-value with α

McNemar test: Application

Scenario

Is there a difference in the percentage of patients with asthma between the placebo and the drug group (matched data)?

Hypothesis

$H_0 : p_b = p_c$
$H_1 : p_b \neq p_c$

McNemar test: Application

Collect and visualize data

	Drug (asthma)	Drug (no asthma)	Sum
Placebo (asthma)	8	13	21
Placebo (no asthma)	18	11	29
Sum	26	24	50

Test statistic

$X^2 = \frac{(b-c)^2}{b+c} = \frac{(13-18)^2}{13+18} = 0.81$ (with no continuity correction)

Degrees of freedom

$df = 1$

Type I error

$\alpha = 0.05$

McNemar test: Application

Critical values

Using R we get the critical values from the χ^2-distribution:
critical value$_\alpha$ = critical value$_{0.05}$

```r
qchisq(p = 0.05, df = 1, lower.tail = FALSE)
```

```
[1] 3.841459
```

McNemar test: Application

Draw conclusions

We reject the H_0 if:

- $X^2 >$ critical value$_\alpha$

We have $0.81 < 3.84 \Rightarrow$ we do not reject the H_0

Using R we obtain the p-value from the χ^2-distribution:

```
pchisq(q = 0.81, df = 1, lower.tail = FALSE)
```

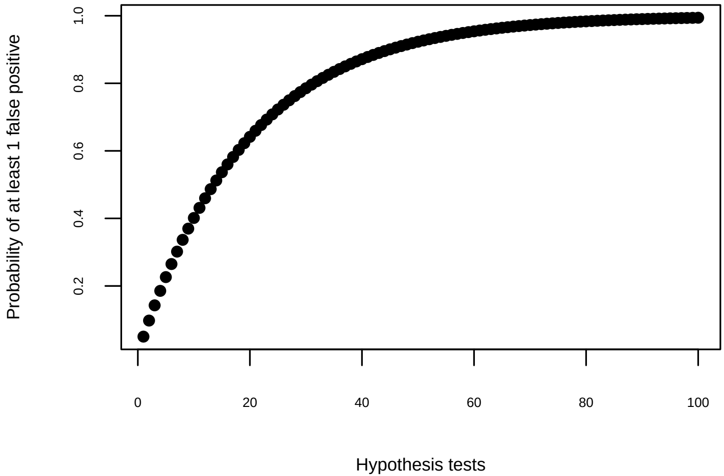
```
[1] 0.3681203
```

Multiple testing

- A single statistical test is rarely assumed
- If we perform m independent tests, what is the probability of at least 1 false positive?
  - P(Making an error) = α
  - P(Not making an error) = $1 - \alpha$
  - P(Not making an error in m tests) = $(1 - \alpha)^m$
  - P(Making at least 1 error in m tests) = $1 - (1 - \alpha)^m$

Multiple testing

Visualize this...



Multiple testing

Methods to adjust for multiple testing:

- **Bonferroni adjustment**: multiply the number of simultaneously tested hypothesis, e.g. $p - value = min(p - value * m, 1)$ or adjust the significant level to $\alpha = \alpha/m$
- **Holm adjustment**: $\alpha_i = \frac{\alpha}{m-i+1}$, where i is the order of the hypothesis - we start from the smallest to the largest p-value
- **Hochberg adjustment**: $\alpha_i = \frac{\alpha}{m-i+1}$, where i is the order of the hypothesis - we start from the largest p-value

Multiple testing

It is not as easy as you think

- What about the other institutions analyzing data from the same experiment?
- What about previous papers that were published on the same data?

Be transparent about what you have done!

- Report effect sizes, confidence intervals, and p-values (avoid arbitrary bounds, e.g $P < 0.05$; $P > 0.4$)
- Report whether you have adjusted for multiple testing or not

Multiple testing

Note that...

- In studies with a clear primary hypothesis, adjustment is not necessary
- If in one manuscript one or more secondary outcomes are presented, then adjustment for multiple comparisons may be considered

Take care: Strict rules such as always adjust for all comparisons will motivate authors to remove/ignore non significant results to decrease the number of comparisons

Further reading

- Althouse AD. Adjust for multiple comparisons? It's not that simple. The Annals of thoracic surgery. 2016 May 1;101(5):1644-5.
- Chen SY, Feng Z, Yi X. A general introduction to adjustment for multiple comparisons. Journal of thoracic disease. 2017 Jun;9(6):1725.