# Matched Pairs
## McNemar's Test

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Everything discussed thus far has implicitly assumed that the observations in our data were independent. In many cases, assuming independence is a realistic assumption.

Correlated data can occur in many ways:

- Repeated measurements on the same subject, across time or across experimental conditions.

- Subjects that are close to each other in some respect, e.g. family members in vaccine studies.

- Unmeasured covariates that are associated with the variable of interest.

# Introduction

Generally speaking, correlated data does not bias our estimates. Inference on the other hand, is almost ways impacted by correlation by impacting standard errors.

Recall that for two random variables $Y_i$ and $Y_j$

$$V(Y_i + Y_j) = V(Y_i) + V(Y_j) + 2\mathrm{Cov}(Y_i, Y_j)$$

where $\mathrm{Cov}(Y_i, Y_j) = 0$ under indepepndence.

For example, if data are positively correlated (positive covariance), then assuming independence will give standard errors that are too small.

# Matched Pairs

*Matched pairs data* occurs when we have two samples of data. There is a natural pairing between each subject in one sample with a subject in the other sample.

Because of this matching, we expect these subjects within a pair to be correlated with each other and treating them as independent would be incorrect.
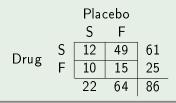
In a *crossover study* subjects are given one treatment and a response is measured. Then, they are given a second treatment and response is again measured and for each subject. Yields two (very correlated) responses: success or failure under each of the two treatments.

## Example (Crossover Study: Drug vs Placebo)

Consider 86 subjects. Randomly assign each to either "drug then placebo" or "placebo then drug". Binary response (S,F) for each.

| Treatment | S | F | Total |
|-----------|-----|-----|-------|
| Drug | 61 | 25 | 86 |
| Placebo | 22 | 64 | 86 |

To reflect the dependence and looking at the full information

|  |  | Placebo S | Placebo F |  |
|------|---|-----|-----|-----|
|  | S | 12 | 49 | 61 |
| Drug | F | 10 | 15 | 25 |
|  |  | 22 | 64 | 86 |

# Marginal Homogeneity

Represent probabilities in previous example

|       |   | Placebo |         |          |
|-------|---|---------|---------|----------|
|       |   | S       | F       |          |
| Drug  | S | $\pi_{11}$ | $\pi_{12}$ | $\pi_{1+}$ |
|       | F | $\pi_{21}$ | $\pi_{22}$ | $\pi_{2+}$ |
|       |   | $\pi_{+1}$ | $\pi_{+2}$ | 1        |

## Definition (Marginal Homogeneity)

There is *marginal homogeneity* if

$$\pi_{1+} = \pi_{+1} \Leftrightarrow \pi_{12} = \pi_{21}$$

since

$$\pi_{1+} - \pi_{+1} = (\pi_{11} + \pi_{12}) - (\pi_{11} + \pi_{21}) = \pi_{12} - \pi_{21}$$

Under $H_0$: marginal homogeneity

$$\frac{\pi_{12}}{\pi_{12} + \pi_{21}} = \frac{1}{2}$$

with $n_{12}$ and $n_{21}$ each having equal probability of contribution, $1/2$, to $n^\star = n_{12} + n_{21}$.

$$n_{12} \sim \text{Bin}(n^\star, 0.5) \;\Rightarrow\; z = \frac{n_{12} - n^\star/2}{\sqrt{n^\star \left(\frac{1}{2}\right)\left(\frac{1}{2}\right)}} = \frac{n_{12} - n_{21}}{\sqrt{n_{12} + n_{21}}} \overset{\text{approx.}}{\sim} N(0, 1)$$

with inference similar to introductory statistics "z-test".

Using the normal approximation to the binomial we are assuming that $n^\star \times (1/2) > 5$. Some authors suggest $> 10$ or even $> 25$.

Equivalent to a z-test you may see

$$z^2 = \frac{(n_{12} - n_{21})^2}{n_{12} + n_{21}} \sim \chi_1^2 \equiv [N(0, 1)]^2$$

and the p-value being the area to the right (because we squared, only nonnegative values possible).

To create a $100(1 - \alpha)\%$ CI for $\pi_{1+} - \pi_{+1}$

$$\underbrace{p_{1+} - p_{+1}}_{\frac{n_{12} - n_{21}}{n}} \mp (z_{1-\alpha/2}) \frac{1}{n} \sqrt{n_{12} + n_{21} - \frac{(n_{12} - n_{21})^2}{n}}$$

# McNemar's Test

## Remark

Depending on the situation, such as, if it is desirable $n_{12}$ to be large then a 1-sided test of CI might yield some gain in power.

- Hypothesis $H_a : \pi_{12} > \pi_{21}$, p-value=$P(Z \geq z)$ area to the right (using normal distribution).
- CI use $+z_{1-\alpha}$

## R

Use `mcnemar.test(x, y = NULL, correct = TRUE)`
The continuity correction for using a continuous distribution to approximate the discrete binomial, is the default setting. Also recommended to use `mcnemar.exact{exact2x2}` which uses the exact Binomial test and does not require $n^{\star} \times (1/2) > 5$.

## Example (Crossover Study: Drug vs Placebo continued)

$$
\begin{array}{ccc}
 & & \text{Placebo} \\
 & & \text{S} \quad\ \text{F}
\end{array}
$$

|  |  | Placebo S | F |  |
|---|---|---|---|---|
| Drug | S | 12 | 49 | 61 |
|  | F | 10 | 15 | 25 |
|  |  | 22 | 64 | 86 |

$$
z = \frac{49 - 10}{\sqrt{49 + 10}} = 5.1 \qquad \text{and p-value} < 0.0001
$$

Evidence that probability of success is higher for drug than placebo. The 95% CI for $\pi_{1+} - \pi_{+1}$ is

$$
\frac{49}{86} - \frac{10}{86} \mp 1.96 \frac{1}{86} \sqrt{49 + 10 - \frac{(49 - 10)^2}{86}} \longrightarrow (0.31, 0.60)
$$

Probability of success under drug is larger than that under placebo.

## Example (continued)

```
> mcnemar.test(crossover,correct=FALSE)


McNemar's chi-squared = 25.78, df = 1, p-value = 3.827e-07


> require(exact2x2)
> mcnemar.exact(crossover)


Exact McNemar test (with central confidence intervals)


b = 49, c = 10, p-value = 2.706e-07
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
  2.451984 10.849724
sample estimates:
odds ratio
       4.9
```

# McNemar-Bowker

For larger than $2 \times 2$ tables, $k \times k$ tables, McNemar's test is generalized as the *McNemar-Bowker* symmetry test for testing

$$H_0 : \pi_{ij} = \pi_{ji}, \quad \text{for all pairs}$$

However, it may fail if there are 0's in certain locations in the matrix.

### R

Use `nominalSymmetryTest{rcompanion}`

`nominalSymmetryTest(x, method = "fdr", digits = 3, ...)`

For examples see https://rcompanion.org/handbook/H_05.html

# We learned

- New methodology needed for inference with correlated data
- McNemar's test for matched pairs data