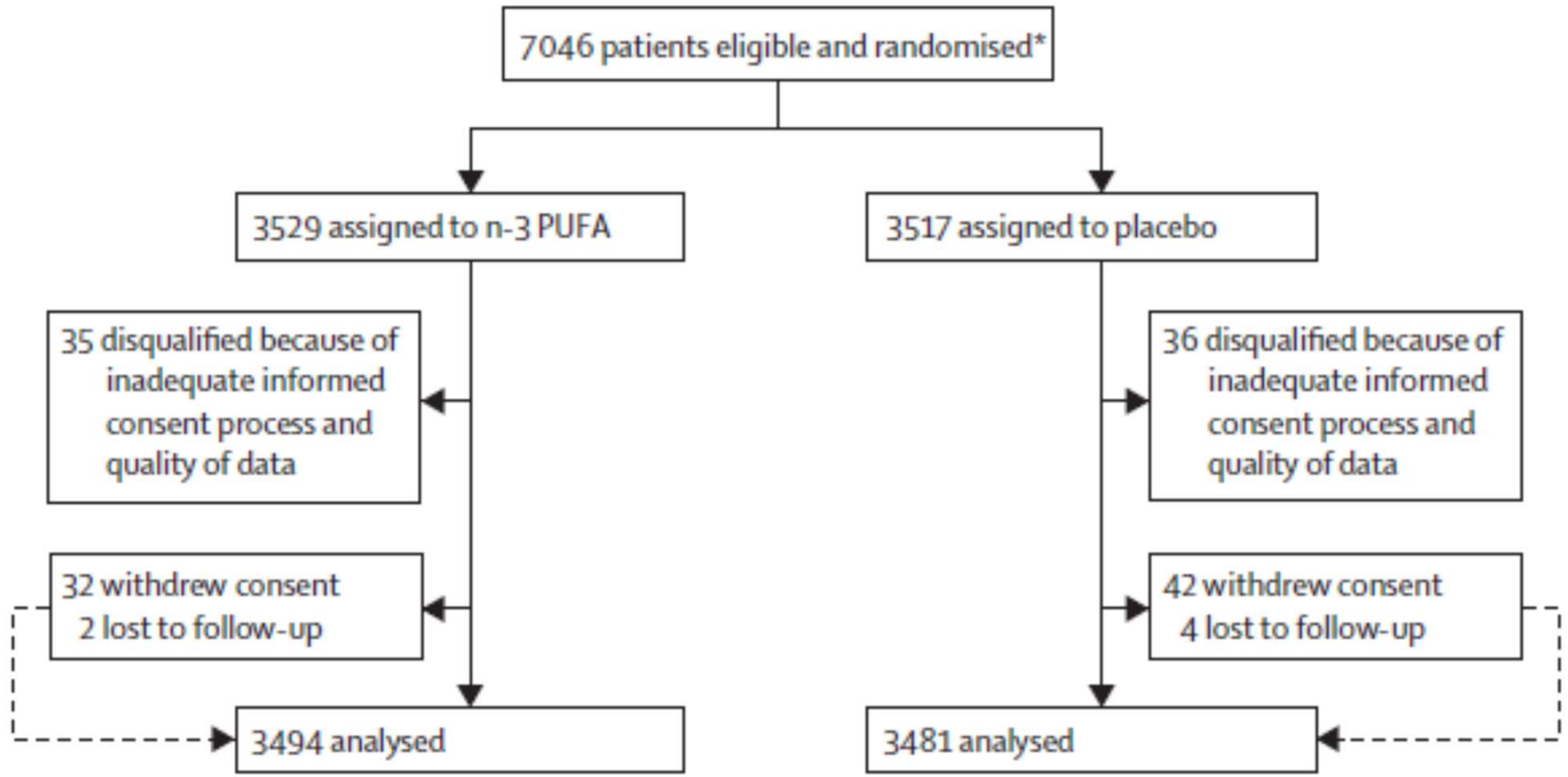
Hypothesis testing on two samples

Paola Rebora

Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial

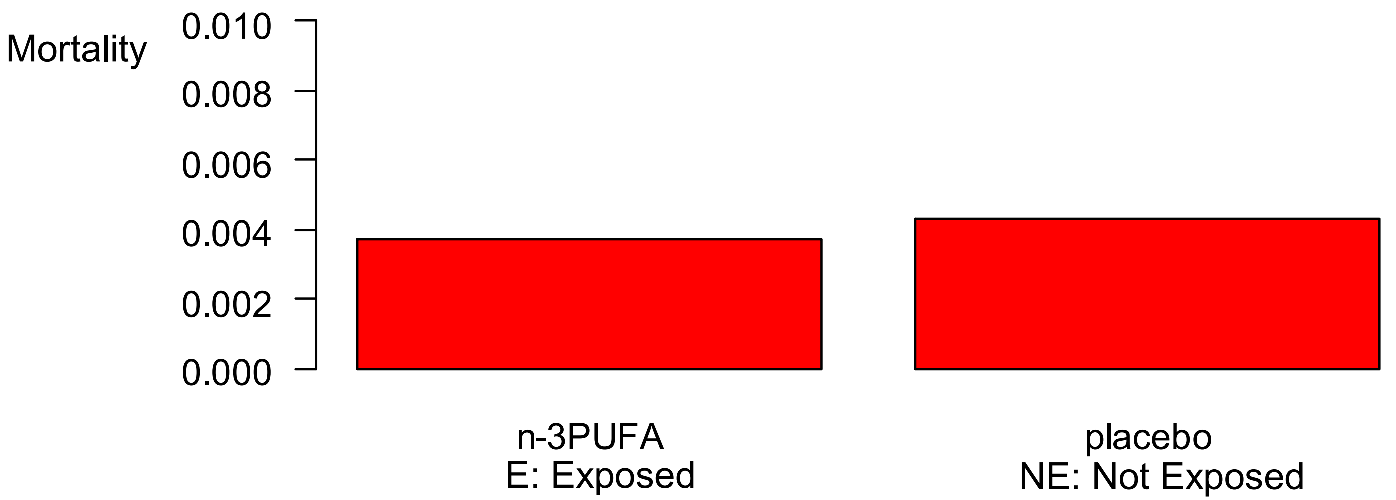
*GISSI-HF investiaators**



Did omega-3 affect the death?

Results from the first month of treatment on all cause death:
13 deaths in n-3 PUF arm (n=3494)
15 deaths in control arm (n=3481)
Use a 0.05 significance level to test the claim that first month mortality is different in the two groups.

Barplots of the outcome (mortality) in exposed and non exposed samples:



These barplots estimate the (unknown) distribution of the outcome variable Y in:
population of Not Exposed $Y_{NE} \sim Ber(\pi_{NE})$
population of Exposed $Y_E \sim Ber(\pi_E)$

Did omega-3 affect the death?

Use a 0.05 significance level to test the claim that first month mortality (π) is different in the two groups.

$$H_0: \pi_E = \pi_{NE}$$
$$H_1: \pi_E \neq \pi_{NE}$$

Requirements for hypothesis test comparing two proportions:

1. The sample proportions are from **two independent simple random samples** *(Samples are independent if the sample values selected from one population are not related to or somehow naturally paired or matched with the sample values selected from the other population.)*
2. For each of the two samples, there are at least 5 successes and at least 5 failures. (That is, $n*p \geq 5$ and $n*(1-p) \geq 5$ for each of the two samples).

Under these requirements :
The distributions of p_E can be approximated by a normal distribution with mean π_E and standard deviation $\sqrt{\pi_E(1-\pi_E)/n_E}$.
This apply also to the not exposed group.

Did omega-3 affect the death?

Given that

$$p_E \sim N(\pi_E; \sqrt{\pi_E(1-\pi_E)/n_E})$$

and

$$p_{NE} \sim N(\pi_{NE}; \sqrt{\pi_{NE}(1-\pi_{NE})/n_{NE}})$$

their difference:

$$(p_E\text{-}p_{NE}) \sim N\left(\pi_E - \pi_{NE}; \sqrt{\frac{\pi_E(1-\pi_E)}{n_E} + \frac{\pi_{NE}(1-\pi_{NE})}{n_{NE}}}\right)$$

NOTE: The variance of the differences between two independent random variables is the sum of their individual variances

Did omega-3 affect the death?

Under $H_0: \pi_E = \pi_{NE} = \pi$

$$(p_E - p_{NE}) \sim N\left(0; \sqrt{\frac{\pi(1-\pi)}{n_E} + \frac{\pi(1-\pi)}{n_{NE}}}\right)$$

Thus the quantity:

$$z = \frac{p_E - p_{NE}}{\sqrt{\frac{p(1-p)}{n_E} + \frac{p(1-p)}{n_{NE}}}}$$ is a standardised Gaussian

where $p = \frac{p_E n_E + p_{NE} n_{NE}}{n_E + n_{NE}} = \frac{f_E + f_{NE}}{n_E + n_{NE}}$

is the pooled estimate of the common value of π_E and π_{NE}

Hypothesis test on two proportions

$H_0: \pi_1 = \pi_2$
$H_1: \pi_1 \neq \pi_2$

$$z = \frac{p_1 - p_2}{\sqrt{\frac{p(1-p)}{n_1} + \frac{p(1-p)}{n_2}}}$$

Did omega-3 affect the death? Hypothesis test

$H_0: \pi_E = \pi_{NE}$

$H_1: \pi_E \neq \pi_{NE}$

$\alpha = 0.05$

Results from the first month of treatment on all cause death:

13 deaths in n-3 PUF arm (n=3494)

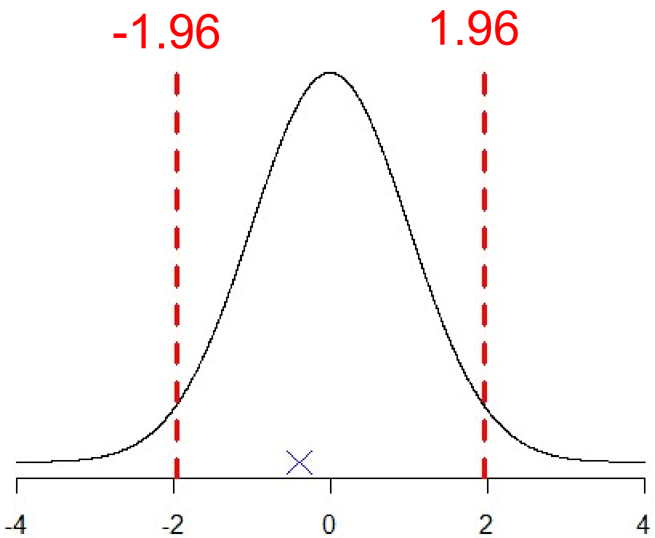
15 deaths in control arm (n=3481)

$$p_E = \frac{13}{3494} = 0.00372$$

$$p_{NE} = \frac{15}{3481} = 0.00431$$

$$p = \frac{13 + 15}{3494 + 3481} = 0.00401$$

$$Z = \frac{p_E - p_{NE}}{\sqrt{\frac{p(1-p)}{3494} + \frac{p(1-p)}{3481}}} = -0.3886$$



Cannot reject H_0:

the study does not suggest an impact of omega-3 on mortality in the first month of treatment

Did omega-3 affect the death?

P-value

$H_0 : \pi_E = \pi_{NE}$

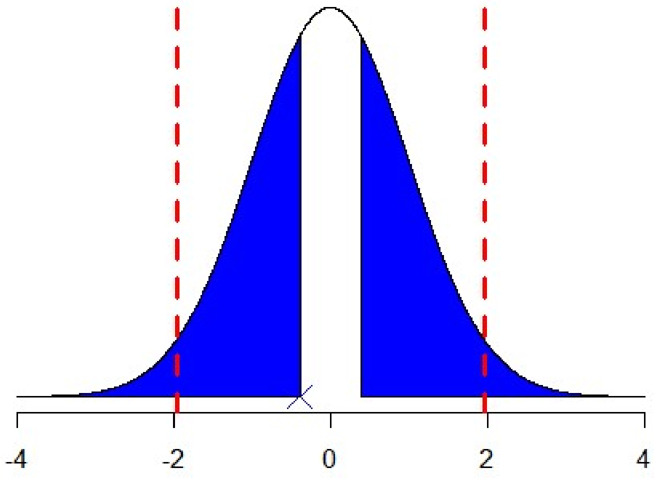
$H_1 : \pi_E \neq \pi_{NE}$

$\alpha = 0.05$

$$z = \frac{p_E - p_{NE}}{\sqrt{\frac{p(1-p)}{3494} + \frac{p(1-p)}{3481}}} = -0.3886$$

P-value=0.3488*2=0.6976

If omega-3 would not have any effect we would observe data like this around 70% of the times!



Did omega-3 affect the death?
Confidence interval at 95% confidence

α=0.05

Results from the first month of treatment on all cause death:

13 deaths in n-3 PUF arm (n=3494)

15 deaths in control arm (n=3481)

$$p_E = \frac{13}{3494} = 0.00372$$

$$p_{NE} = \frac{15}{3481} = 0.00431$$

$$\text{I.C.95\%:} p_E - p_{NE} \pm z_{\frac{\alpha}{2}} \sqrt{\frac{p_{E(1-p_E)}}{3494} + \frac{p_{NE(1-p_{NE})}}{3481}}$$

-0.000588±1.96*0.001514

I.C.95%:**[-0.003557; 0.002377]**

With 95% of confidence we can say that the advantage of omega-3 on early mortality will be included between 3.5 events less and 2.4 events more out of 1000 patients treated

Summary – inferential statistic on a dicotomous outcome

Estimate the percentage	⇒	confidence interval
Is the percentage higher than a reference value «x»?	⇒	one sample test (critical value or p-value method)
Is the percentage of group 1 higher than percentage of group 2?	⇒	two sample test (critical value or p-value method)
Quantify the difference in the percentage between group 1 and 2	⇒	confidence interval of the difference

The confidence interval shifts the attention
from STATISTICAL SIGNIFICANCE
to the CLINICAL RELEVANCE

Exercise

We want to test if two antiepileptic drugs (A and B) have different efficacy.
The effectiveness index adopted is the proportion of patients who, after one month from the start of therapy, reduced the frequency of the crisis by at least half.
We indicate with π_A and π_B the true effectiveness of treatments A and B.
330 subjects per group were sampled.
For reasons not dependent on either side effects or the efficacy of the drug, 18 patients treated with drug A and 24 patients treated with drug B were withdrawn from the study.
The effectiveness (reduction of the frequency of the crisis by at least half) was achieved in 240 patients who assumed drug A and on 210 patients who assumed drug B.

Test if the two antiepileptic drugs have different efficacy assuming a first type error of 5%.
Estimate the difference in efficacy of the two drugs.

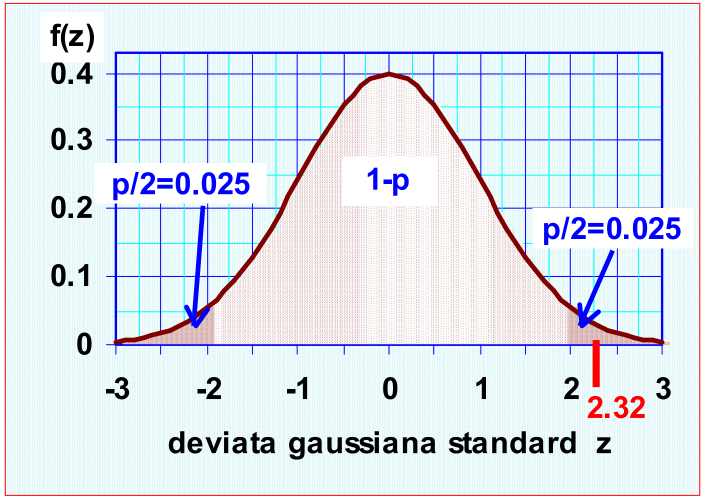
Exercise

$H_0: \pi_A = \pi_B = \pi$
$H_1: \pi_A \neq \pi_B$

α=0.05 Critical values $\pm$1.96

$$p_A = \frac{240}{312} = 0.769 \qquad p_B = \frac{210}{306} = 0.686 \qquad p = (240+210)/(312+306) = = 450/618 = 0.728$$

$$z = \frac{0.769 - 0.686}{\sqrt{0.728 \times 0.272 \times \left(\frac{1}{312} + \frac{1}{306}\right)}} = \frac{0.083}{0.0358} = 2.318 \qquad p = 2 * 0.01 = 0.02$$



2.318>1.96 reject the null hypothesis: the two drugs have different efficacy!

If there were no difference between the treatments, a result (in absolute value) equal or more extreme (in the tails of the distribution) than that observed would occur 2 times out of 100

Exercise: Estimate the difference in efficacy of the two drugs.

$$p_A = \frac{240}{312} = 0.769$$

$$p_B = \frac{210}{306} = 0.686$$

$$I.C._{1-\alpha} = (p_A - p_B) \pm z_{\alpha/2} \times \sqrt{\frac{p_A(1-p_A)}{n_A} + \frac{p_B(1-p_B)}{n_B}}$$

$$ES(p_A - p_B) = \sqrt{\frac{0.769 \times 0.231}{312} + \frac{0.686 \times 0.314}{306}} = 0.0357$$

I.C.95% = 0.083±1.96x0.0357 = [0.013; 0.153]

We can say with 95% confidence that with drug A, instead of drug B, we would get an increase in the number of patients who will reduce the frequency of the crisis by at least half from a minimum of 1.3 to a maximum of 15.3 out of 100 treated patients.

For monday

- Exercises on hypothesis test on proportions