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CONFIDENCE INTERVALS FOR ASPIRIN / PLACEBO PATIENTS PROPABILITY OF SUSTAINING MYOCARDIAL INFARCTION

Statistical Methods, spring 2018

Exercise

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Introduction

In a famous clinical trial, acetylsalicylic acid's (aspirin) possibility to reduce cardiovascular mortality was studied. The original trial featured 22 071 participants, out of which 11 037 were randomly assigned to receive a 325 mg dose of aspirin every other day, while the remaining 11 034 received placebo. The average follow-up time was 60.2 months. The results display a 44 % reduction in risk of myocardial infarction (relative risk, 0.56; 95 percent confidence interval, 0.45 to 0.70; P<0.00001) in the aspirin group. [1]

The purpose of this exercise is to reiterate the analysis conducted in the 1989's Physicians Health Study and evaluate the probability of different populations sustaining heart attack. In particular, in this excersice three different methods will be utilized:

1. Binomial distribution fitting and getting maximum likelihood estimate for p as well as the 95 % CI's
2. Agresti-Coull method for getting the CI's as originally proposed in [2]
3. Bootstrapping method as originally proposed in [3]

Method 1

We use the following contingency table:

	Heart attack	**No heart attack**
Aspirin	139	10898
Placebo	239	10795

We model the problem with two binomial distributions, respectfully for the aspirin and placebo populations, where parameter p corresponds to a single participant's probability of sustaining a heart attack. From MATLAB's binofit-function we get the following results:

	$\hat{p}$	$\widehat{\Theta}_L$ (95 %)	$\widehat{\Theta}_U$ (95 %)
Aspirin	$12.6 * 10^{-3}$	$10.5 * 10^{-3}$	$14.9 * 10^{-3}$
Placebo	$21.7 * 10^{-3}$	$19.0 * 10^{-3}$	$24.6 * 10^{-3}$

Method 2

Agresti and Coull describe an alternative method for computing the CI's [2]. In particular, the upper (U.L) and lower (L.L) are given as:

$$U.L. = \frac{\hat{p} + \frac{z_{\alpha/2}^2}{2n} + z_{\alpha/2}\sqrt{\frac{\hat{p}(1-\hat{p})}{n} + \frac{z_{\alpha/2}^2}{4n^2}}}{1 + z_{\alpha/2}^2/n}$$

$$L.L. = \frac{\hat{p} + \frac{z_{\alpha/2}^2}{2n} - z_{\alpha/2}\sqrt{\frac{\hat{p}(1-\hat{p})}{n} + \frac{z_{\alpha/2}^2}{4n^2}}}{1 + z_{\alpha/2}^2/n}$$

Where

$$\hat{p} = \text{proportion of heart attacks in the sample}$$

$$z_{\alpha/2} = \text{a test quantity computed from standard normal distribution}$$

$$n = \text{sample size}$$

Utilizing this approach, we get:

	$\widehat{\Theta}_L$	$\widehat{\Theta}_U$
Aspirin	$10.6 * 10^{-3}$	$14.9 * 10^{-3}$
Placebo	$19.1 * 10^{-3}$	$24.6 * 10^{-3}$

Method 3

Bootstrapping method [3] was used, utilizing the following MATLAB code:

```
for i = 1:max_rounds
    na = sum(datasample(popula_aspirin,na_total));
    np = sum(datasample(popula_placebo,np_total));
    p_asp(i) = na / na_total;
    p_pla(i) = np / np_total;
    theta(i) = (na / na_total) / (np / np_total);
end
```

At each bs round, we take a random sample with replacement from each respective population. Subsequently, we compute the proportions of heart attack as well as the relative risk ratio between the populations. Repeating the process max_rounds times, we save the results from each resampling to their respective result vectors. Finally, the 95 % CI's are computed simply by taking the 2.5 and 97.5 percentiles from the resulting vectors from the bootstrap process. We get:

	$\widehat{\Theta}_L$	$\widehat{\Theta}_U$
Aspirin	$10.5 * 10^{-3}$	$14.8 * 10^{-3}$
Placebo	$19.0 * 10^{-3}$	$24.5 * 10^{-3}$
Risk ratio	0.46	0.72

A feasible point estimate for the risk ratio can be obtained in a straightforward manner, by computing from the original contingency table:

$$\frac{139}{139+10898} \Big/ \frac{239}{239+10795} \approx 0.58$$

Discussion

The CI's produced by the three different methods are in good agreement with each other and lead to the same conclusion. Based on the results, regular intake of aspirin does decrease the probability of heart attack on a statistically significant level[1]. The results are in good agreement with those reported in the original study [1]. Specifically, the maximum likelihood estimates $\hat{p} = 12.6 * 10^{-3}$ and $\hat{p} = 21.6 * 10^{-3}$ for aspirin and placebo groups respectfully, suggest a reduction in heart attack probability of ~42 %, while there is no overlap on the confidence intervals. Also, the 95 % risk ratio CI's (0.46, 0.72) obtained by the bootsrap method is close to that reported in the original paper (0.45, 0.70)

Attachments

1. MATLAB Code used in exercise: https://github.com/donkkis/aspirin/blob/master/aspirin_paho.m

[1] Speculatively, this could have something to do with aspirin's effect on blood density, although this is not by any means the primary subject of this exercise

REFERENCES

[1] Steering Committee of the Physicians' Health Study Research Group. 1989. Final Report on the Aspirin Component of the Ongoing Physicians' Health Study. Available https://www.nejm.org/doi/full/10.1056/NEJM198907203210301

[2] Agresti, A. and Coull, B. A. 1998. Approximate is better than exact for interval estimation of binomial proportions. The American Statistician, 52(2), 119-126.

[3] Efron, B., & Tibshirani, R. J. 1994. An introduction to the bootstrap. Chapman & hall/crc monographs on statistics & applied probability.