

# **Clinical statistics for non-statisticians: Day two**

Steve Simon

## **Re-introduce yourself**

Here's one more interesting number about myself

- 51: I started running when I was 51.

Tell us one more interesting number about yourself.

## **Outline of the three day course**

- Day one: Numerical summaries and data visualization
- Day two: Hypothesis testing and sampling
- Day three: Statistical tests to compare treatment to a control and regression models

My goal: help you to become a better consumer of statistics

## Day two topics

- Hypothesis testing
  - What does a p-value tell you
  - Why you might prefer a confidence interval
  - What sample size do you need
  - How does a Bayesian data analysis differ
  - What should you do if you do not have a hypothesis to test

## Day two topics (continued)

- You may see this on day 3 instead.
- Sampling
  - What do you gain with a random sample
  - When might you prefer a non-random sample
  - When should you use randomization or blinding
  - What are the benefits of matching
  - How can you ensure that your sampling approach is ethical

## Bad quiz question

A research paper computes a p-value of 0.45. How would you interpret this p-value?

1. Strong evidence for the null hypothesis
2. Strong evidence for the alternative hypothesis
3. Little or no evidence for the null hypothesis
4. Little or no evidence for the alternative hypothesis
5. More than one answer above is correct.
6. I do not know the answer.

## **A bad confidence interval**

A research paper computes a confidence interval for a relative risk of 0.82 to 3.94. This confidence interval tells that the result is

1. statistically significant and clinically important.
2. not statistically significant, but is clinically important.
3. statistically significant, but not clinically important.
4. not statistically significant, and not clinically important.
5. The result is ambiguous.
6. I do not know the answer.

## Bayesian question

A Bayesian data analysis can incorporate subjective opinions through the use of

1. data shrinkage.
2. a prior distribution.
3. a posterior distribution.
4. p-values.
5. I do not know the answer.



## P-values

- Most commonly reported statistic
  - Also sharply criticized
  - Requires a research hypothesis
- Two alternatives
  - Confidence intervals
  - Bayesian analysis
- What to do when no research hypothesis

## What is a population?

- Population: a group that you wish to generalize your research results to. it is defined in terms of
  - Demography,
  - Geography,
  - Occupation,
  - Time,
  - Care requirements,
  - Diagnosis,
  - Or some combination of the above.

## **Example of a population**

All infants born in the state of Missouri during the 1995 calendar year who have one or more visits to the Emergency room during their first year of life.

## What is a sample?

- Sample: subset of a population.
- Random sample: every person has the same probability of being in the sample.
- Biased sample: Some people have a decreased probability of being in the sample.
  - Always ask “who was left out?”

## An example of a biased sample

- A researcher wants to characterize **illicit drug use in teenagers**. She distributes a questionnaire to students attending a local public high school
- (in the U.S. high school is grades 9-12, which is mostly students from ages 14 to 18.)
- Explain how this sample is biased.
- Who has a decreased or even zero probability of being selected.

*Type your ideas in the chat box.*

## Fixing a biased sample

- Redfine your population
  - Not all teenagers,
    - but those attending public high schools.

## What is a parameter?

- A parameter is a number computed from a sample.
  - Examples
    - Average health care cost associated with the 29,637 children
    - Proportion of these 29,637 children who died in their first year of life.
    - Correlation between gestational age and number of ER visits of these 29,637 children.
  - Designated by Greek letters ( $\mu$ ,  $\pi$ ,  $\rho$ )

## What is a statistic?

- A statistic is a number computed from a sample
  - Examples
    - Average health care cost associated with 100 children.
    - Proportion of these 100 children who died in their first year of life.
    - Correlation between gestational age and number of ER visits of these 100 children.
  - Designated by non-Greek letters ( $\bar{X}$ ,  $\hat{p}$ ,  $r$ ).



## What is Statistics?

- Statistics
  - The use of information from a sample (a statistic) to make inferences about a population (a parameter)
    - Often a comparison of two populations

## What is the null hypothesis?

- The null hypothesis ( $H_0$ ) is a statement about a parameter.
- It implies no difference, no change, or no relationship.
  - Examples
    - $H_1 : \mu_1 - \mu_2 \neq 0$
    - $H_0 : \pi_1 - \pi_2 \neq 0$
    - $H_0 : \rho \neq 0$

## What is the alternative hypothesis?

- The alternative hypothesis ( $H_1$  or  $H_a$ ) implies a difference, change, or relationship.
  - Examples
    - $H_1 : \mu_1 - \mu_2 \neq 0$
    - $H_1 : \pi_1 - \pi_2 \neq 0$
    - $H_1 : \rho \neq 0$

## Hypothesis in English instead of Greek

- Only statisticians like Greek letters
  - Translate to simple text
  - For two group comparisons
    - Safer, more effective
  - For regression models
    - Trend, association

## Use PICO

- P = patient population
- I = intervention
- C = control
- O = outcome

## Example of text hypotheses (1/2)

- “... the objective of this 78-week randomised, placebo-controlled study was to determine whether treatment with nilvadipine sustained-release 8 mg, once a day, was effective and safe in slowing the rate of cognitive decline in patients with mild to moderate Alzheimer disease.”
  - Lawlor B, Segurado R, Kennelly S, et al. Nilvadipine in mild to moderate Alzheimer disease: A randomised controlled trial. PLoS Med. 2018; 15(9): e1002660. DOI: 10.1371/journal.pmed.1002660

## **PICO for this study**

- P = patients with mild to moderate Alzheimer disease
- I = Nilvadine
- C = placebo
- O = cognitive function

## Example of text hypotheses (2/2)

- “... we investigated trends in BCC incidence over a span of 20 years and the associations between incident BCC and risk factors in a total population of 140,171 participants from 2 large US-based cohort studies: women in the Nurses’ Health Study (NHS; 1986–2006) and men in the Health Professionals’ Follow-up Study (HPFS; 1988–2006).”
  - Wu S, Han J, Li WQ, Li T, Qureshi AA. Basal-cell carcinoma incidence and associated risk factors in U.S. women and men. *Am J Epidemiol.* 2013; 178(6): 890–897. DOI: 10.1093/aje/kwt073



## **PICO for this study**

- P = female nurses/male health professionals
- I = various risk factors
- C = absence of various risk factors
- O = presence/absence of BCC

## One-sided alternatives

- Examples
  - $H_1 : \mu_1 - \mu_2 > 0$
  - $H_1 : \pi_1 - \pi_2 > 0$
  - $H_1 : \rho > 0$
- Changes in only one direction expected
- Changes in opposite direction uninteresting

## **Passive smoking controversy**

- EPA meta-analysis of passive smoking
  - Criticized for using a one-sided hypothesis
  - Samet JM, Burke TA. Turning science into junk: the tobacco industry and passive smoking. *Am J Public Health*. 2001;91(11):1742–1744.

## What is a decision rule? (1/3)

- Example

- $H_0 : \mu_1 - \mu_2 = 0$
- $H_1 : \mu_1 - \mu_2 \neq 0$
- $t = (\bar{X}_1 - \bar{X}_2) / se$
- Accept  $H_0$  if  $t$  is close to zero.

## What is a decision rule? (2/3)

- Example

- $H_0 : \pi_1 - \pi_2 = 0$
- $H_1 : \pi_1 - \pi_2 \neq 0$
- $t = (\hat{p}_1 - \hat{p}_2) / se$
- Accept  $H_0$  if  $t$  is close to zero.

## What is a decision rule? (3/3)

- Example
  - $H_0 : \rho = 0$
  - $H_1 : \rho \neq 0$
  - $t = r / se$
  - Accept  $H_0$  if  $t$  is close to zero.

## What is a Type I error?

- A Type I error is rejecting the null hypothesis when the null hypothesis is true
  - False positive
  - Example involving drug approval: a Type I error is allowing an ineffective drug onto the market.
- $\alpha = P[\text{Type I error}]$

## What is a Type II error?

- A Type II error is accepting the null hypothesis when the null hypothesis is false.
  - False negative result
  - Usually computed at MCD
  - An example involving drug approval: a Type II error is keeping an effective drug off of the market.
- $\beta = P[\text{Type II error}]$
- Power =  $1 - \beta$



## What is a p-value?

- Let  $t =$ 
  - $(\bar{X}_1 - \bar{X}_2) / \text{se}$ , or
  - $(\hat{p}_1 - \hat{p}_2) / \text{se}$ , or
  - $r / \text{se}$
- p-value = Prob of sample result,  $t$ , or a result more extreme,
  - **assuming the null hypothesis is true**
- Small p-value, reject  $H_0$
- Large p-value, accept  $H_0$

## Alternate interpretations

- Consistency between the data and the null
  - Small value, inconsistent
  - Large value, consistent
- Evidence against the null
  - Small, lots of evidence against the null
  - Large, little evidence against the null

## What the p-value is not (1/2)

- A p-value is NOT the probability that the null hypothesis is true.
  - $P[t \text{ or more extreme} \mid \text{null}]$  is different than
  - $P[\text{null} \mid t \text{ or more extreme}]$ 
    - $P[\text{null}]$  is nonsensical
    - $\mu$ ,  $\pi$ , or  $\rho$  are unknown constants (no sampling error)

## What the p-value is not (2/2)

- Not a measure FOR either hypothesis
  - Little evidence **against** the null  $\neq$  lots of evidence **for** the null
- Not very informative if it is large
  - Need a power calculation, or
  - Narrow confidence interval
- Not very helpful for huge data sets

## Pop quiz, revisited

A research paper computes a p-value of 0.45. How would you interpret this p-value?

1. Strong evidence **for** the null
2. Strong evidence **for** the alternative
3. Little or no evidence **for** the null
4. Little or no evidence **for** the alternative
5. More than one answer above is correct.
6. I do not know the answer.

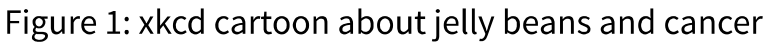


Figure 1: xkcd cartoon about jelly beans and cancer

## What is p-hacking?

- Abuse of the hypothesis testing framework.
  - Run multiple tests on the same outcome
  - Test multiple outcome measures
  - Remove outliers and retest
- Defenses against p-hacking
  - Bonferroni
  - Primary versus secondary
  - Published protocol

## **What is a confidence interval?**

- Range of plausible values
  - Tries to quantify uncertainty associated with the sampling process.



## Example of a confidence interval

- Homeopathic treatment of swelling after oral surgery
  - 95% CI: -5.5 to 7.5 mm
  - Lokken P, Straumsheim PA, Tveiten D, Skjelbred P, Borchgrevink CF. Effect of homoeopathy on pain and other events after acute trauma: placebo controlled trial with bilateral oral surgery BMJ. 1995;310(6992):1439-1442.

## Confidence interval interpretation (1 of 7)

---

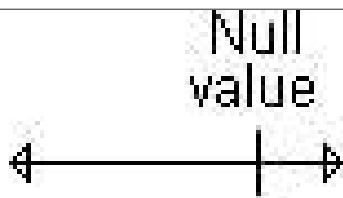


Figure 2: Interval that contains the null value

## Confidence interval interpretation (2 of 7)

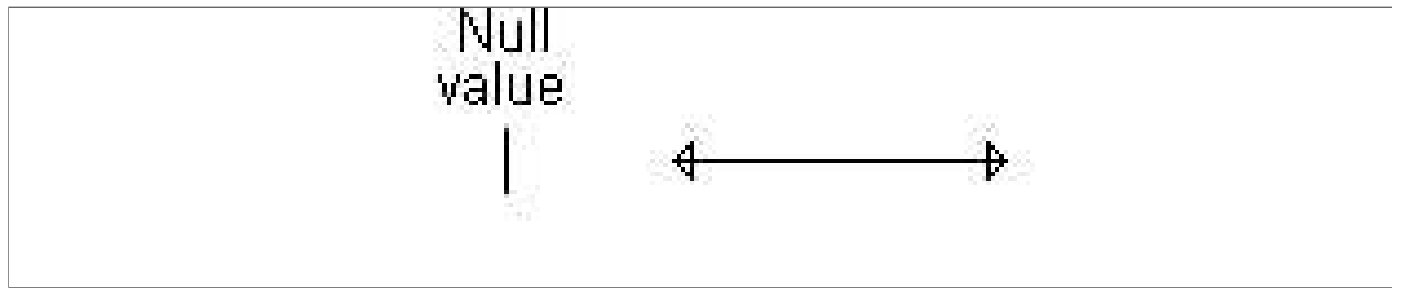


Figure 3: Interval entirely above the null value

## Confidence interval interpretation (3 of 7)

---

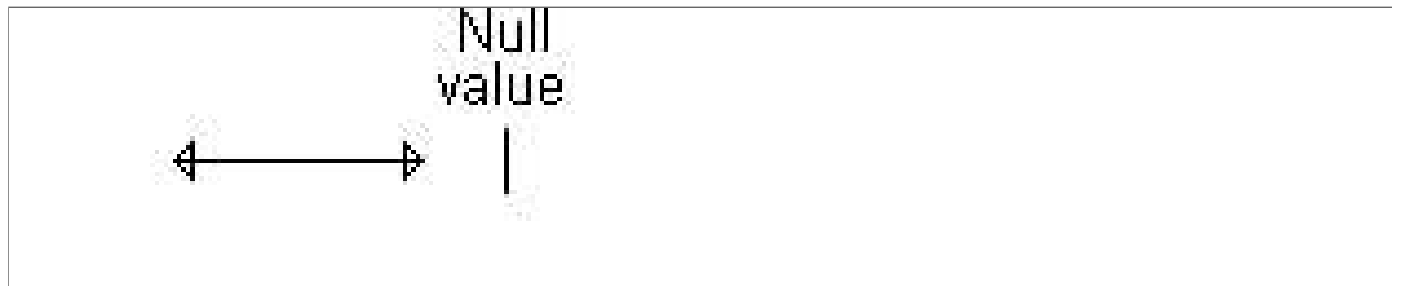


Figure 4: Interval entirely below the null value

## Confidence interval interpretation (4 of 7)

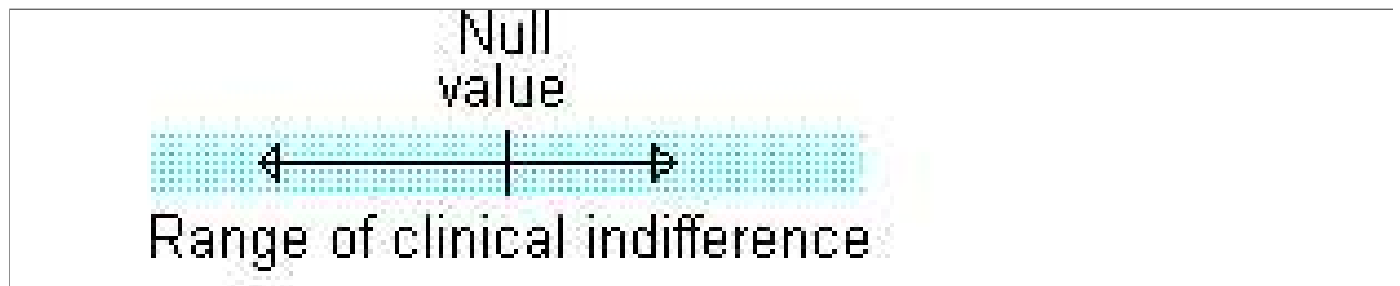


Figure 5: Interval entirely inside the range of clinical indifference

## Confidence interval interpretation (5 of 7)

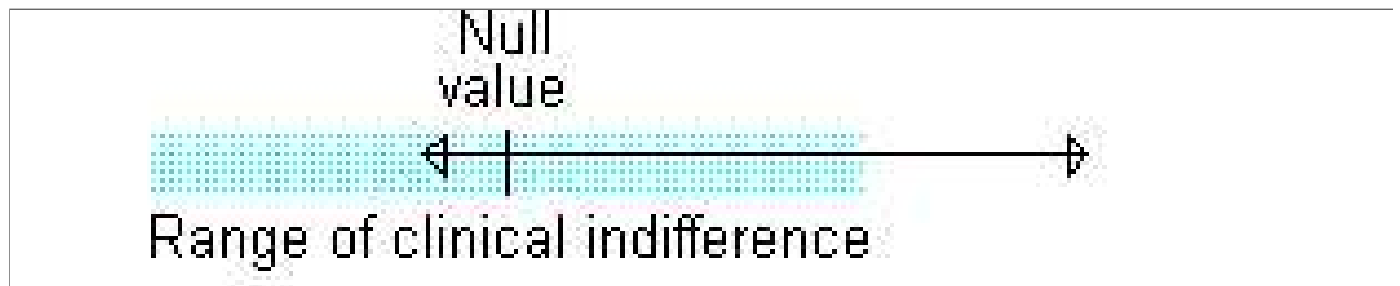


Figure 6: Interval partly inside/outside range of clinical indifference

## Quiz question, revisited

A research paper computes a confidence interval for a relative risk of 0.82 to 3.94. This confidence interval tells that the result is

1. statistically significant and clinically important.
2. not statistically significant, but is clinically important.
3. statistically significant, but not clinically important.
4. not statistically significant, and not clinically important.
5. The result is ambiguous.
6. I do not know the answer.

## Confidence interval interpretation (6 of 7)

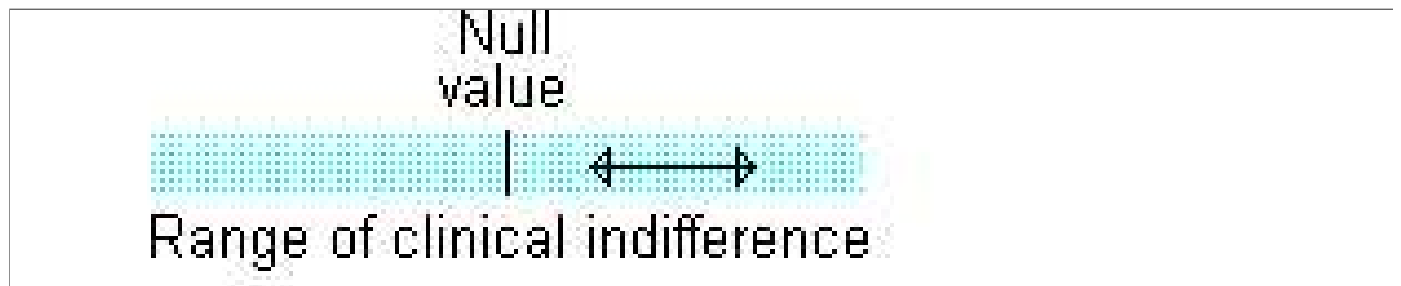


Figure 7: Confidence interval that contains the null value



## Confidence interval interpretation (7 of 7)



Figure 8: Confidence interval entirely outside the range of clinical indifference

## Why you might prefer a confidence interval

- Provides same information as p-value,
  - Clinical importance
  - Distinguish between
    - definitive negative result, or
    - more research is needed

## **What sample size do you need?**

- Sackett's formula
- Rules of thumb
- Confidence interval width
- Power calculations
- Post hoc power - never!
- Effect sizes - never!

[CMAJ](#). 2001 Oct 30; 165(9): 1226–1237.

PMCID: PMC8158

PMID: [1170691](#)

Why randomized controlled trials fail but needn't: 2. Failure to employ physiological statistics, or the only formula a clinician-trialist is ever likely to need (or understand!]

[David L. Sackett](#)

Figure 9: Sackett 2001, PMID:

$$\text{Confidence} = \frac{\text{Signal}}{\text{Noise}} \times \sqrt{\text{Samplesize}}$$

Figure 10: Formula found in Sackett 2001

## Rules of thumb

- Rule of 50
  - Only for binary outcomes
  - Total sample size is irrelevant
  - Strive for 25/50 **events** in each group
- Rule of 16
  - $ES = MCD/\sigma$
  - $n = 16/ES^2$

## Confidence interval width

- How narrow do you want your confidence interval?
  - Algebraic solution
    - $\pm t_{0.975} SE = \pm MCD$
    - $SE = S_p \sqrt{1/n_1 + 1/n_2}$
    - Solve for  $n_1$  and  $n_2$
    - Usually assume  $n_1 = n_2$
  - Trial and error

## Power calculations

- Need to specify MCD
- Power =  $P[\text{Reject } H_0 \mid MCD] = 0.9$
- =  $P[\bar{X}_1 - \bar{X}_2 > t_{0.975} SE \mid MCD] = 0.9$ 
  - Solve for n1 and n2.



## Formal software for sample size calculations

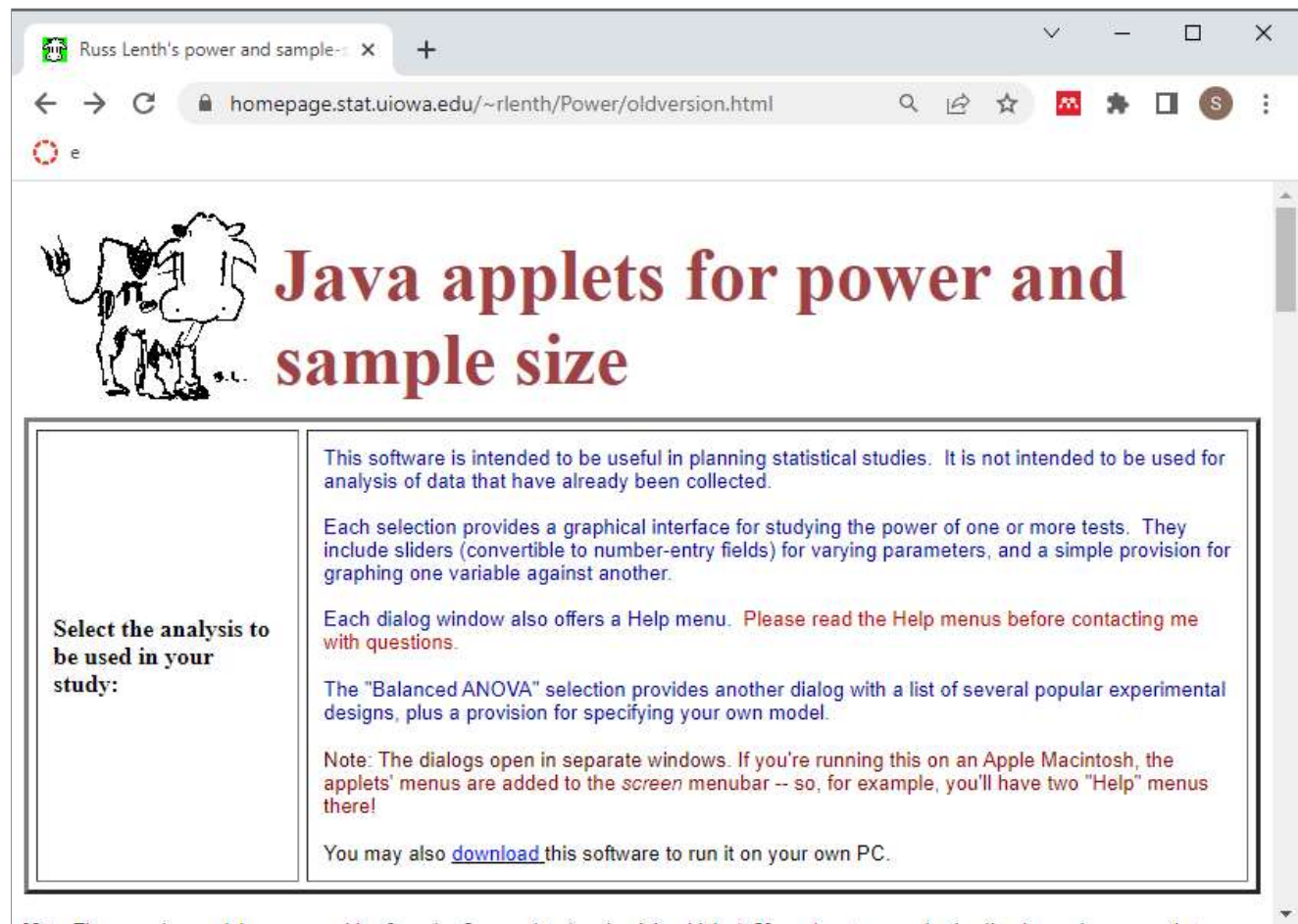


Figure 11: Lenth Power and Sample Size software

## **Post hoc power, effect sizes - never!**

- Power must be calculated prior to data collection
- Effect sizes are only an intermediate calculation
  - Do not reflect clinical judgement
  - Always start with MCD
- Effect sizes also are not a useful summary statistic

## Criticisms of hypothesis testing (1 of 4)

- Criticisms of the binary hypothesis
  - Dichotomy is simplistic
  - Point null is never true
  - Cannot prove the null
- Possible remedy
  - $H_0 : -\Delta \leq \mu_1 - \mu_2 \leq \Delta$

## Criticisms of hypothesis testing (2 of 4)

- Criticisms of the p-value
  - Not intuitive, easily misunderstood
  - “results more extreme”
  - Ignores clinical importance
  - Does not measure uncontrolled biases

## Criticisms of hypothesis testing (3 of 4)

- General criticisms
  - Too hard to reject  $H_0$
  - Too easy to reject  $H_0$
  - Too reliant on a single study
  - Thoughtless application

## Criticisms of hypothesis testing (4 of 4)

<u>P-VALUE</u>	<u>INTERPRETATION</u>
0.001	HIGHLY SIGNIFICANT
0.01	
0.02	
0.03	
0.04	SIGNIFICANT
0.049	
0.050	OH CRAP. REDO CALCULATIONS.
0.051	ON THE EDGE OF SIGNIFICANCE
0.06	
0.07	HIGHLY SUGGESTIVE, SIGNIFICANT AT THE $P < 0.10$ LEVEL
0.08	
0.09	
0.099	HEY, LOOK AT THIS INTERESTING SUBGROUP ANALYSIS
$\geq 0.1$	

Figure 12: Cartoon showing interpretation of various p-values

## **What should you do if you do not have a hypothesis to test?**

- Descriptive statistics
  - Include confidence intervals
- Qualitative data analysis

---

# Teaching Inference about Proportions Using Bayes and Discrete Models

Jim Albert  
Bowling Green State University

*Journal of Statistics Education* v.3, n.3 (1995)

---

Albert 1995



## Bayes rule

- $P(H|E) = P(E|H)P(H)/P(E)$ 
  - H = hypothesis
  - E = evidence (data)

## Prior

- $P[H]$  is prior
  - Subjective prior
    - Contrast optimistic/pessimistic perspectives
    - Incorporate prior knowledge
  - Flat (non-informative prior)

[illegible]

Figure 13: Empty table for prior probabilities

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														
16														

		0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
Control survival probability	0.05	0.0333									
	0.15		0.0333								
	0.25			0.0333							
	0.35				0.0333						
	0.45					0.0333					
	0.55						0.0333				
	0.65							0.0333			
	0.75								0.0333		
	0.85									0.0333	
	0.95										0.0333
		Sum = 0.33333									

Figure 14: Table with diagonal priors

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														
16														

		ECMO survival probability									
		0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
Control survival probability	0.05										
	0.15	0.0074									
	0.25	0.0074	0.0074								
	0.35	0.0074	0.0074	0.0074							
	0.45	0.0074	0.0074	0.0074	0.0074						
	0.55	0.0074	0.0074	0.0074	0.0074	0.0074					
	0.65	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074				
	0.75	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074			
	0.85	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074		
	0.95	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	

Sum = 0.3333

< >

Shell

Diagonal

Lower triangle

Upper triangle

...

+

:

Figure 15: Table with lower triangle of prior probabilities

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1														
2														
3														
4			ECMO survival probability											
5			0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95		
6		0.05		0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074		
7		0.15			0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074		
8		0.25				0.0074	0.0074	0.0074	0.0074	0.0074	0.0074	0.0074		
9		0.35					0.0074	0.0074	0.0074	0.0074	0.0074	0.0074		
10	Control	0.45						0.0074	0.0074	0.0074	0.0074	0.0074		
11	survival	0.55							0.0074	0.0074	0.0074	0.0074		
12	probability	0.65								0.0074	0.0074	0.0074		
13		0.75									0.0074	0.0074		
14		0.85										0.0074		
15		0.95											0.0074	
16														Sum = 0.3333

Figure 16: Table with upper triangle of prior probabilities







	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1														
2	<div> <div>Bayes rule: <math>P(H E) = \frac{P(E H) P(H)}{P(E)}</math></div> </div>													
3														
4	ECMO survival probability													
5		0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95			
6	0.05	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000			
7	0.15	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000			
8	0.25	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000			
9	0.35	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002		
10	0.45	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0004		
11	0.55	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0006		
12	0.65	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0006		
13	0.75	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0004		
14	0.85	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0001		
15	0.95	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000		
16														

Sum = 0.0027

<

>

...

Upper triangle

Prior

Likelihood

Product

P

...

+

:

◀

▶

Figure 19: Product of prior and likelihood



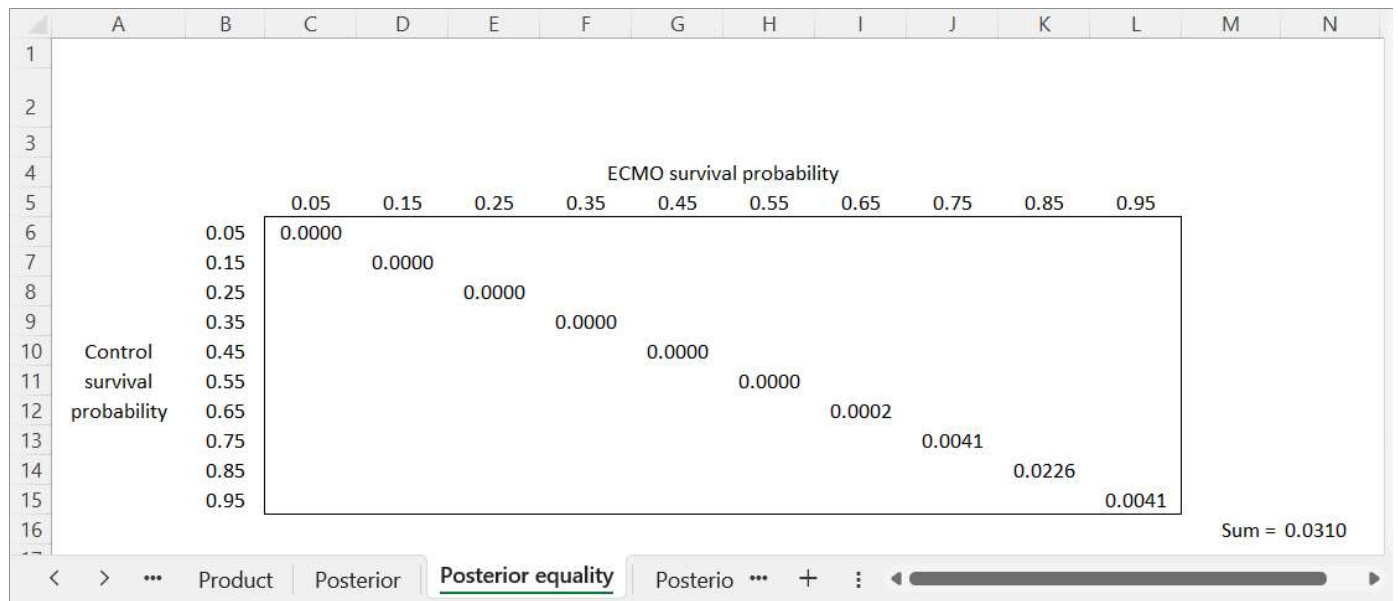


Figure 21: Posterior probability of equality

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1														
2														
3														
4					ECMO survival probability									
5					0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
6		0.05				0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
7		0.15					0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0012
8		0.25						0.0000	0.0000	0.0000	0.0000	0.0001	0.0020	0.0153
9		0.35							0.0000	0.0000	0.0000	0.0004	0.0086	0.0649
10	Control	0.45								0.0000	0.0010	0.0200	0.1503	
11	survival	0.55									0.0015	0.0299	0.2244	
12	probability	0.65										0.0298	0.2238	
13		0.75											0.1375	
14		0.85												
15		0.95												
16														

Sum = 0.9110

Posterior equality Posterior superiority

Table of superiority posterior probabilities

## **Criticisms of Bayesian data analysis**

- Choice of prior distribution is arbitrary
- Probability of a hypothesis is absurd
- Requires strong distributional assumptions
- Computationally intensive

## **Areas where Bayesian data analysis excel**

- Imputation
- Latent models
- Random effects/hierarchical models
- Incorporating historical data

## Repeat the bad quiz question

A research paper computes a p-value of 0.45. How would you interpret this p-value?

1. Strong evidence for the null hypothesis
2. Strong evidence for the alternative hypothesis
3. Little or no evidence for the null hypothesis
4. Little or no evidence for the alternative hypothesis
5. More than one answer above is correct.
6. I do not know the answer.

### **Repat the bad confidence interval question.**

A research paper computes a confidence interval for a relative risk of 0.82 to 3.94. This confidence interval tells you that the result is

1. statistically significant and clinically important.
2. not statistically significant, but is clinically important.
3. statistically significant, but not clinically important.
4. not statistically significant, and not clinically important.
5. ambiguous.
6. I do not know the answer.



## **Repeat of Bayesian question**

A Bayesian data analysis can incorporate subjective opinions through the use of Bayes rule.

1. data shrinkage.
2. a prior distribution.
3. a posterior distribution.
4. p-values.
5. I do not know the answer.

## Summary

In today's class, you learned about

- p-values,
- confidence intervals,
- justifying your sample size, and
- Bayesian data analysis

*Are there any questions?*