Statistical Issues

Designing Clinical Research

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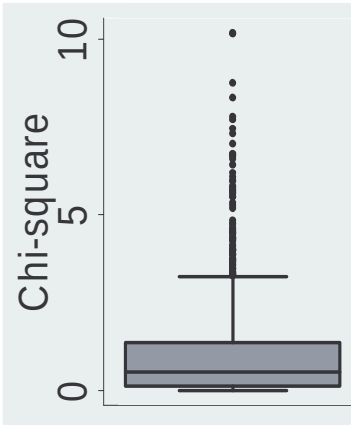
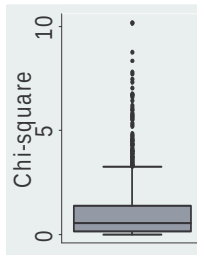


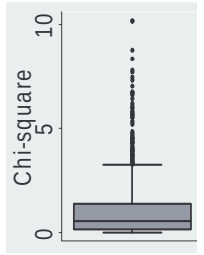
August 12, 2009

Statistics – a thumbnail sketch



- Introduction: Creutzfeld-Jakob disease
- Two minutes on statistical methods
- Box models
- Standard errors
- P-values
- Experiments for CJD
- Some analyses
- Summary

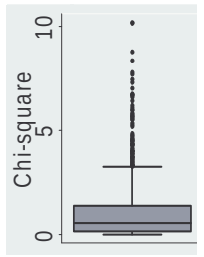
Introduction: CJD



EXAMPLE: Treating Creutzfeldt-Jakob disease (CJD) patients with quinacrine.

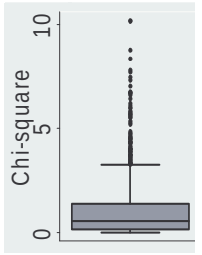
CJD is a rapidly progressing, fatal neurodegenerative disease. It is caused by an agent known as a “prion”, a proteinaceous infectious particle. Prions (Pree-ons) were discovered by Stanley Prusiner at UCSF, who was awarded the 1997 Nobel Prize for this work. Prions also cause mad cow disease in cattle and scrapie in sheep and goats.

Prions



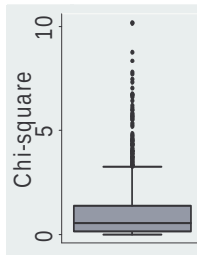
Prions are normal proteins found throughout the body and brain. In prion disease, this protein has the ability to take on an abnormal shape and acts as a template that converts normal prion proteins into this abnormal form. By this mechanism, abnormal prions accumulate within the brain, causing damage.

Treat CJD with quinacrine?



Quinacrine has been used for over 50 years as an antimalarial agent. It is generally well-tolerated with few side effects. In vitro experimentation suggests it may slow the conversion of normal prion to the abnormal form. Could treatment with quinacrine halt or slow progression of CJD?

Design an trial:



We can afford to recruit and sample 40 patients.

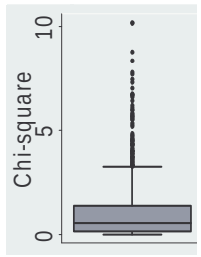
Outcomes:

1) Mini-mental state exam (MMSE). This is measured at baseline and 2 months. (MMSE0 and MMSE2). Ranges from 0 to 30.
2) Alive at 3 months (yes/no). (ALIVE)

And we'll also measure the

3) Barthel index: A measure of disability/activities of daily living. This is measured at baseline and 2 months. (BARTHEL0 and BARTHEL2). Ranges from 0 to 100.

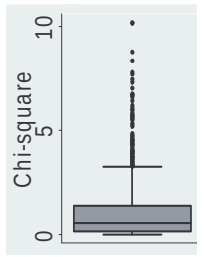
Two minutes on statistical methods



Type of outcome	Scenario: Change w/i a group	Compare two groups	Compare two groups after adjustment for confounder(s)
Binary	McNemar's test	Chi-square or Fisher's exact test	Logistic regression
Continuous	Paired t-test	Independent samples t-test	Multiple linear regression

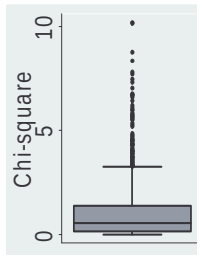
There are other data types, such as skewed continuous, count data, categorical, time-to-event, and ordered categorical. There are a multitude of other scenarios.

Box models



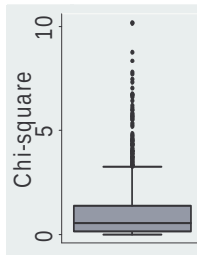
- Each box represents a target population. The box contains “tickets.”
- Each ticket represents one subject in the target population.
- The values on the tickets are the data values for that subject.
- Taking a ticket out of the box represents sampling that subject.

Using box models



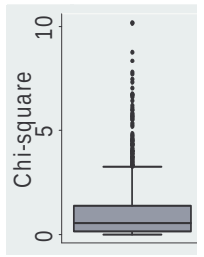
- The goal of statistical inference is to figure out something about the values on *all* the tickets in the box or boxes, based only getting to see a subset of the tickets.
- No box, no inference.

Using box models



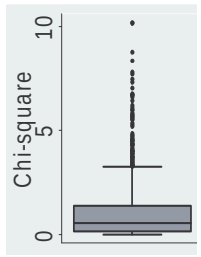
- We (usually) only get to do the real experiment once. But if we can devise a box model for the situation we can repeat a simplified version of the experiment an indefinite number of times. This allows us to quantify the degree of variation of sample statistics.
- With knowledge of the degree of variation of the sample statistics we can make inferences about all the tickets after seeing only some of them.

Standard errors



- A key ingredient in statistics is the *standard error or SE*. From sample to sample, calculated statistics approximate their average value, *give or take a standard error or two.*
- By knowing the SE you can delineate reasonable or unreasonable values of the unknown average values in the box.

Example: Box model for the proportion alive in the quinacrine group after three months.

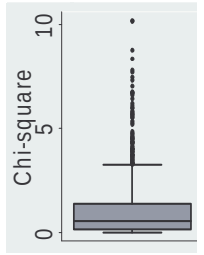


Box represents –

One ticket for each –

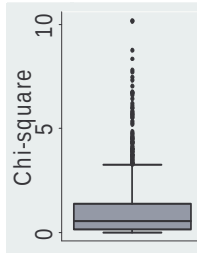
Tickets contain –

Using standard errors



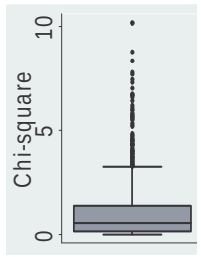
- Suppose a sample of 100 subjects (tickets) gives a proportion of 0.8 with a SE of 0.04. What can we say about the possibility that the true value (average if we emptied the box) is as low as 0.5?
- Range of reasonable values is 0.8 plus or minus 2×(0.04) or (0.72, 0.88).
- For this situation SE= $\sqrt{p(1-p)/n} = \sqrt{0.8(0.2)/100}$

P-values



- Another key idea in statistics is the *p-value*. A p-value measures the strength of the evidence *against* the null hypothesis. P-values range from 0 to 1 with values close to zero indicating the null hypothesis is false.

More on p-values

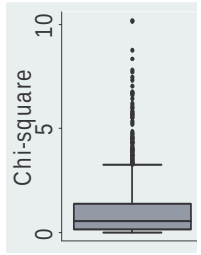


Here are rules of thumb for interpreting p-values:

- p<0.01 - strong evidence against the null hypothesis
- p<0.05 - evidence against the null hypothesis
- 0.05<p<0.10 - some evidence against the null hypothesis
- p>0.10 - No evidence against null hypothesis

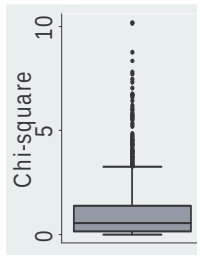
p<0.05 is widely accepted as the cutoff for declaring an alternative hypothesis supported and is termed *statistically significant.* Sometimes (unfortunately) shortened to “significant.”

Possible experiments



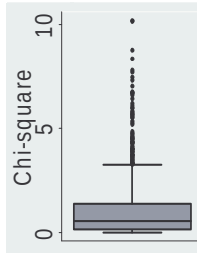
1) Compare change in MMSE (= MMSE2 – MMSE0) in a cohort of quinacrine treated subjects.
2) Compare change in MMSE in quinacrine and placebo subjects in an observational study.
3) Compare change in MMSE in quinacrine and placebo subjects in an RCT.
4) Compare mortality at 3 months in quinacrine and placebo subjects in an observational study.
5) Compare mortality at 3 months in quinacrine and placebo subjects in an RCT.

Issues for possible expts:



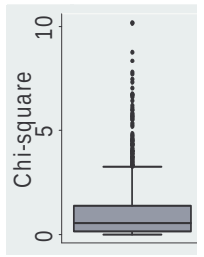
- Feasible?
- Advantages and disadvantages?
- Box model?
  - How many boxes?
  - What does each represent?
  - How many tickets?
  - What is on each ticket?
- Null hypothesis?
- Alternative hypothesis?
- How to decide between null and alternative?

Stata demonstration



- Sample 20 drug and 20 non-drug “patients” from the study population
- Run the appropriate statistical analysis
- Repeat

Summary



- Standard error: From sample to sample, calculated statistics approximate their average value, give or take a standard error or two.
- P-value <0.05 “statistically significant”. Measures the evidence against the null hypothesis.
- No box, no inference.