Introduction on common statistical methods in clinical ophthalmology

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30 May 2012

MERSEY POSTGRADUATE TRAINING PROGRAMME

Workshop Series: Basic Statistics for Eye Researchers and Clinicians

Outline

- Why statistics?
- Main statistical principles: variables, sample and inference
- Summary of most common statistical methods in clinical ophthalmology
- Department of Biostatistics at U of Liverpool. What do we do?
- References

Why is statistics needed?

- Statistics needed for ***objective evaluation*** of what is observed in clinical research
  - What the clinical data say
  - How certain we are of the message
  - How to assure data quality
  - Cost effectiveness of further studies
- Statistics as a ***communication tool***
  - Present findings convincingly
  - Understand and evaluate the findings of others

Research question

Design of study

Collecting data

Data analysis

Report

General steps in a research project

Fundamental statistical concepts: Variables

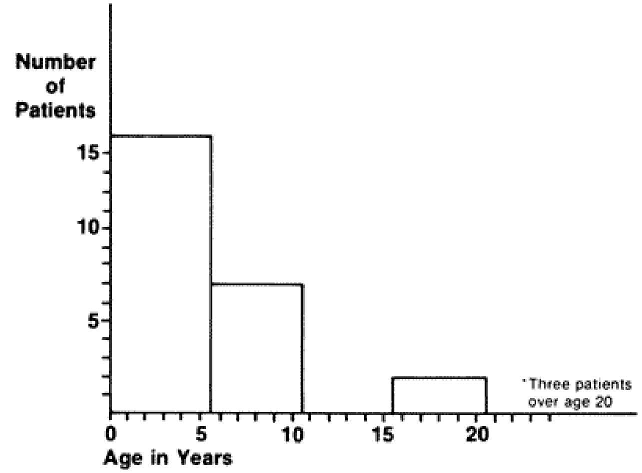
What we measure on subjects?

Variable

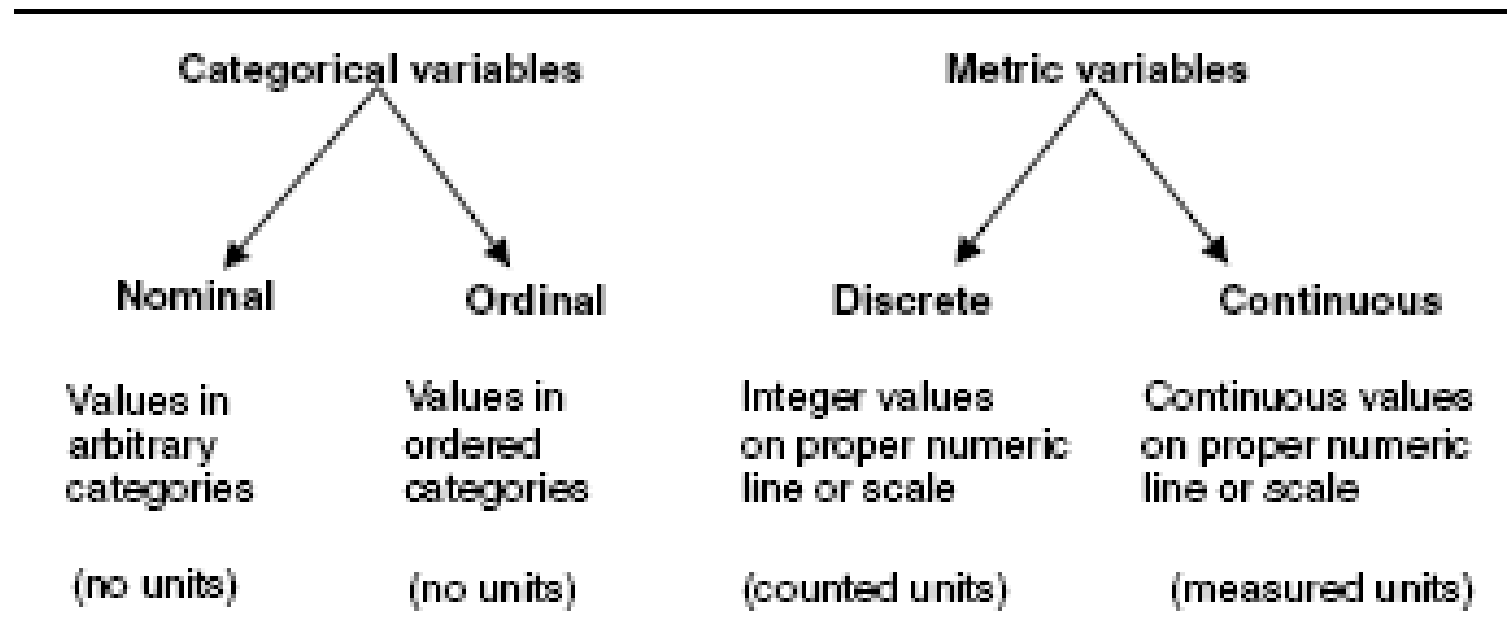
- It is something whose value can ***vary***. E.g. age, gender, visual acuity, degree to which laser scars are visible on a scan….

Data are values you get when you measure a variable.

- E.g. Age = 0.2, 0.5, 1.1, 1.2, 1.2, 1.3, 1.3, 1.4, 1.4, 2.3, 3.1, 3.3, 4.1, 4.6, 5.1,5.5, 5.6, 5.9, 6.1, 7.1, 7.3, 8.6, 8.7, 15.5, 17.7, 22.0, 33.2, 35.1 years
- Genger: Male and Female
- Visibility of laser scars on a scan: Impossible, Poor, Good, Very Good.
- ***Distribution*** is a "picture or map of data"



Types of variables i.e. types of data



E.g. Male/Female

Visibility of scar Poor/Good/Very Good

Number of scars in a retina

Age

Fundamental statistical concepts: Sampling and randomization

How to choose subjects for investigation?

In effectiveness studies how we allocate treatments to subjects?

Idea

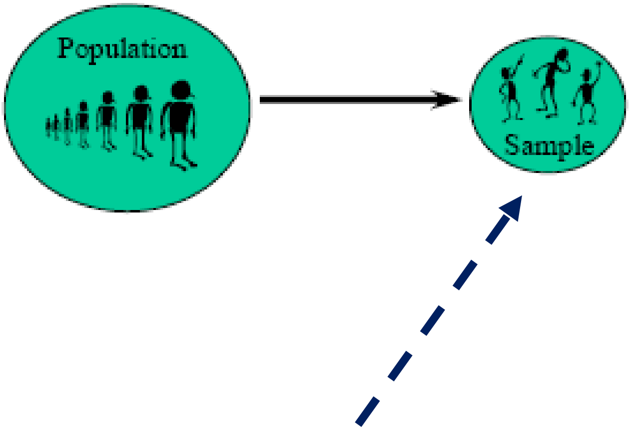
- We choose a ***sample*** of objects (patients or eyes) and we measure them to obtain data

Common study designs

- Observational studies vs. ***randomized*** controlled trials
- Prospective vs. retrospective
- Matched case-controls design vs. cohort studies

Main factors for selection of study design

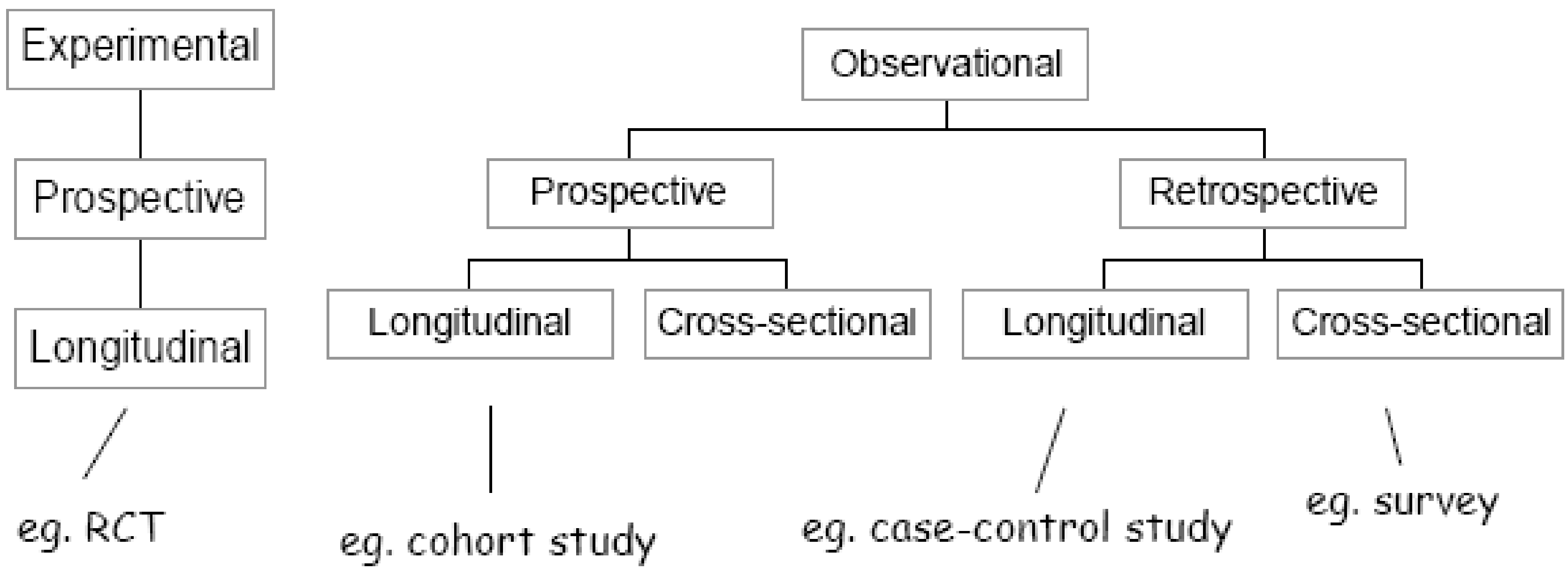
- ***Research question*** e.g. prevalence of disease, effectiveness of a treatment, factors related to AMD
- Resources, sources of bias, clinical importance



The objects who are studied act as a proxy for the total population of interest.

NB. In ophthalmology the object can be: eyes or patients.

Common Study Designs



Source: from the workshop slides of Biostatistics department "Statistical issues in the design and analysis of research projects"
Prospective = data collected prospectively, retrospective = data are recolled

Fundamental statistical concepts: Inference

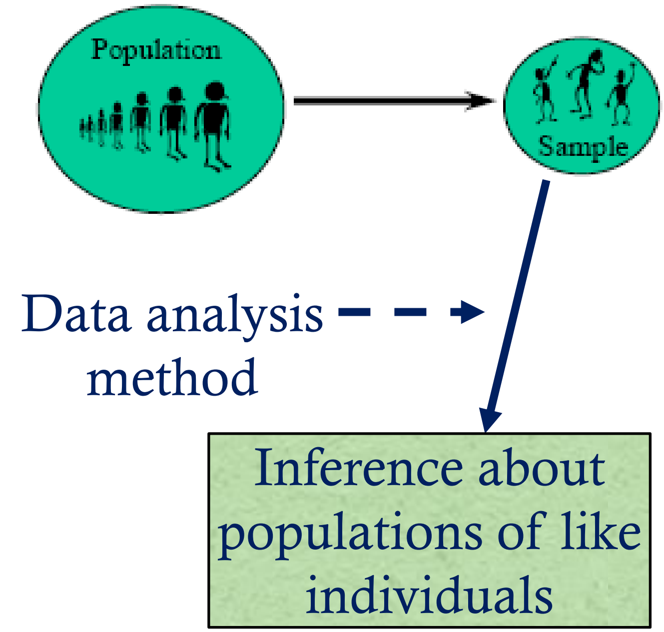
What the data say? How certain we are of the message?

Idea

- We use data collected on the sample to make ***statistical inference*** about the population of interest.
- i.e. from the sample we ***infer*** the properties of the population of the interest

Data analysis method is based on

- Assumptions about study design
- Assumptions about type s of variables (categorical…)
- Assumption of a model of how variables may be associated with each other (i.e. a model that has been proved already or is to be investigated),
- Probability laws (e.g. Law of large numbers)



NB. Statistical data analysis ***(inference)*** methods however sophisticated can not "rescue" a poor study design.

Example - Colour blindness

- We are interested in whether there is an association between colour blindness and gender.

- We asked 240 men and 260 women about color-blindness. The results of a survey are as follows:

	Normal colour vision	Colour blind	Total
Male	221	19	240
Female	254	6	260
Total	475	25	500

Example - Colour blindness

In sample 8% males and 2% females are colour blind

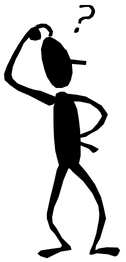
Does this mean that women are at less risk of becoming colour blind than men?

We rewrite research question into null hypothesis

- H_0: there is no association between colour blindness and gender

How to test the null hypothesis?

- We can use a method of comparison of proportions
- Results reported as Confidence Interval or P-value



Example - Colour blindness

- Confidence interval: range of plausible values for the "true" difference (usually use 95% certainty)
- Method of comparison of proportions
  - General formula (in large samples)

$$\text{estimate} \pm 1.96 \cdot \text{standard error}$$

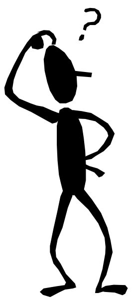
95% CI for $p_1 - p_2$ is (2%, 9%)

$\Rightarrow$ there is a significant difference in the proportion with colour blindness between the 2 groups at a 95% confidence level *(because value 0 is not in CI)*

Choosing the right statistical method for data analysis

Several factors to consider:

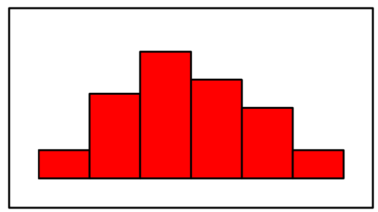
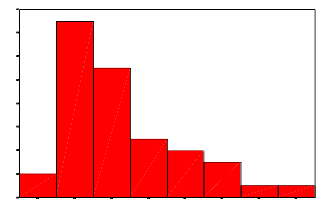
- ***Objective*** of the analysis
  - e.g. Estimating prevalence, comparison of groups, association between measures, instruments comparisons, …
- Type of data, i.e. ***categorical*** or ***continuous***
- Observations, i.e. ***independent*** or ***paired***
- Distribution of the data, i.e. ***symmetric*** or ***skewed***



NB. Always check if the ***assumptions*** of the statistical method are ***satisfied***

Comparisons of two groups

Type of Data

Categorical	Continuous Normal	Continuous Skewed
e.g. Color blindness yes/no or 3 severity grades of diabetic maculopathy		

Tests for differences, independent data:

Categorical	Continuous Normal	Continuous Skewed
Chi-square χ^2 test	t-test	Mann-Whitney U
Fisher's exact test		

Tests for differences, non-independent (paired) data:

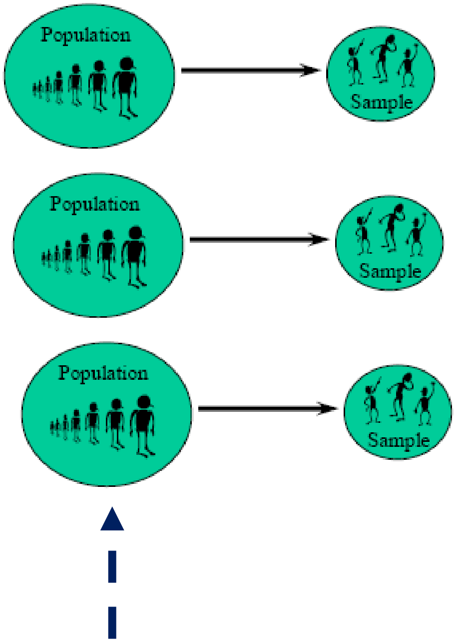
Categorical	Continuous Normal	Continuous Skewed
McNemar's test	Paired (single sample) t-test	Wilcoxon

Comparisons of two or more groups with respect to a continuous data

Analysis of variance (ANOVA)

- One-way ANOVA
  - It compares the 2 or more groups with respect to continuous data
  - E.g. Compare 3 grades of diabetic retinopathy with respect to retinal blood flow
- Two-way ANOVA
  - How is retinal blood flow varying across 3 grades of diabetic retinopathy and gender?

NB. Standard assumptions of ANOVA are
- Normal distribution of data
- and independent objects of analysis.

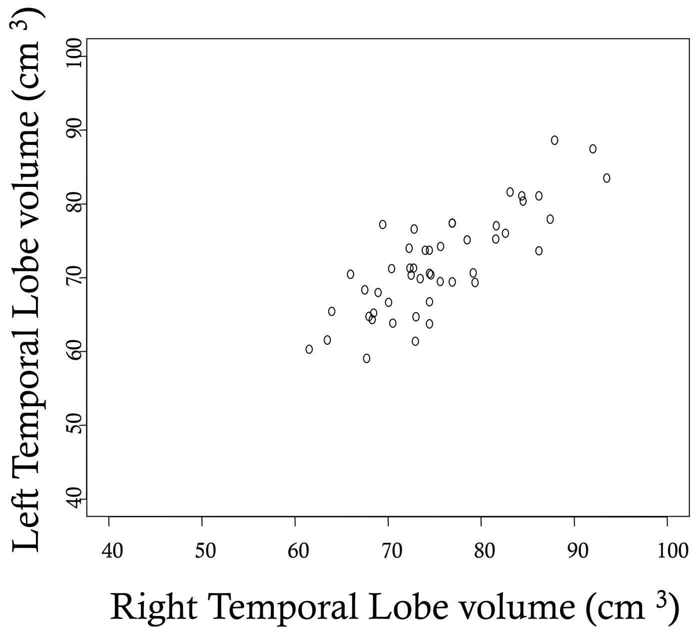


The three groups of interest defined by diabetic retinopathy stage.

Measuring association between two variables

Type of Data

Ordinal	Continuous
Spearman rank correlation coefficient	Pearson correlation coefficient
	Simple linear regression



Example of positive correlation in two continuous variables

NB. Correlation does ***not*** mean causation.

Agreement between two alternative ways of measurement

Test-retest or instrument comparisons

- Two typical questions
  - How well a new instrument replicates the measurements of other instrument? E.g. intraocular pressure measured via Goldmann applanation tonometrry or Perkins tonometer
  - Is there a good level of agreement between two raters (clinicians) using the same instrument?
- What methods are most common?
  - Kappa coefficient of agreement
  - Bland–Altman plot

NB. Pearson correlation coefficients is ***not*** applicable as it measure an association and not the agreement. Two instruments can correlate well and still disagree greatly.

List of more advanced statistical methods used in ophthalmic clinical research

- Repeated measures ANOVA
  Comparison of groups (novel therapy vs traditional therapy) when outcome (visual acuity in logMAR) is measured repeatedly on same subjects.
- Multiple linear regression
  How visual acuity (logMAR) depends on age (in years) while controlling for effect of other factors such as disease duration in years, and being on novel or traditional therapy.
- Linear mixed models, General estimating equations, Longitudinal analysis
  Same goal as linear regression, but it allows for correlation between objects of study i.e. correlation in measurements from two eyes
- Logistic regression
  How a visual acuity (dichotomously measured) depends on age while controlling for effect of other factors.
- Survival analysis methods
  Study the time to development of blindness.

Most common statistical issues in clinical ophthalmology

- How to measure the primary outcome?
  - E.g. How to measure visual acuity? Snellen Chart and Early Treatment Diabetic Retinopathy study Chart (ETDRS). No appropriate conversion exists.
- Dichotomizing the measurements?
  - E.g. to dichotomize the visual acuity measurements
  - It leads to loss of information, hence more patients needed for study.
- Eyes vs. patients as unit of randomization and analysis?
  - Measurements from two eyes of same patient may be ***correlated*** and hence carry less information than two eyes from two different patients; and standard data analysis methods are not appropriate.
- Multiple measures and multiple comparisons?
  - Performing statistical inference on multiple measures leads to significant results by ***chance***. This is overcome by using proper adjustments.

Department of Biostatistics at University of Liverpool. Some of the things that we do

- Teaching courses for NHS:
  - http://www.liv.ac.uk/medstats/courses.htm
  - Some courses:
    - Statistical issues in the design and analysis of research projects;
- Advise on analysis at design stage
- Advise on including funding for statistical support in grant applications
- May collaborate on every stage of clinical research
- We have academic staff specializing in statistics for ophthalmology

NB. Most of our courses are relevant to clinical ophthalmologists. However, ophthalmology has specific issues and challenges for which we plan to develop devoted workshops.

Resources

Books

- Practical statistics for medical research by Douglas G. Altman
- Medical Statistics from Scratch by David Bowers

Journals' with series on how to do statistics in clinical research

- American Journal of Ophthalmology has **Series on Statistics**
- British Medical Journal has series **Statistics Notes**

Guide on how to do clinical research in ophthalmology

- Clinical Research. A primer for Ophthalmologists. International Council of Ophthalmology. February 2009, http://www.icoph.org

Statistical papers with examples from ophthalmology

- Holopigian and Bach, A primer on common statistical errors in clinical ophthalmology, Doc. Ophthalmology, 2010
- Fan, Teo and Saw. Application of advanced statistics in ophthalmology. Inv Ophth and Visual Science, p 6059-6065, 2011.
- Bunce. Correlation, Agreement, and Bland-Altman Analysis: Statistical Analysis of Method Comparison Studies. Am J O 2010.
- Boscardin. The Use and Interpretation of Linear Regression Analysis in Ophthalmology Research. Am J O 2010.
- Wang and Attia. Study Designs in Epidemiology and Levels of Evidence. Am J O 2009

Statistical papers for general clinical research (relevant to clinical ophthalmology)

- Bland and Altman. Statistical methods for assessing agreement between two methods of clinical measurement, Lancet 1986.

Thank you for your attention

Questions?

Suggestions for topics for future workshops?

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