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# TEACHING BIOSTATISTICS TO MEDICAL STUDENTS

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Statistical reasoning is applicable to all areas of medicine. The following few examples may serve to illustrate this.

*Example* 1. Reference ranges of "normal values" for various constituents in human plasma are to be based on accurate measurements in sufficiently large random samples of healthy individuals from relevant populations. Such a range is usually estimated from suitable percentiles of the observed frequency distribution, either non-parametric or based on a specific model like the gaussian distribution. The resulting ranges may be used by medical practitioners as an expedient to establish a diagnosis for an individual patient and later on for monitoring the course of the disease during a particular treatment regime.

*Example* 2. Evaluation of the merits of a new diagnostic test procedure either to confirm or to exclude a suspected disease, should be based on random samples from two populations, the first consisting of individuals with the disease truly present according to a so-called 'gold standard' and a second population of individuals with the disease truly absent by the same standard. Considering a certain diagnosis, a positive test should indicate that this is likely and a negative test that this is unlikely with respect to a particular patient. The merits of such a binary test are expressed in terms of sensitivity, specificity and predictive values, which may all be interpreted as conditional probabilities. In particular a predictive value may be derived from the values of sensitivity and specificity of a test together with the prevalence of the disease in the population concerned, by using Bayes' theorem:

$$P(D+|T+) = \frac{P(T+|D+)*P(D+)}{P(T+|D+)*P(D+)+P(T+|D-)*P(D-)}$$

or

$$pred.\ value = \frac{sens*prev}{sens*prev+(1-spec)*(1-prev)}$$

*Example* 3. Critical appraisal of the efficacy/safety balance of a new medical treatment requires, of course, relevant and reliable data. As a consequence careful design, execution and analysis of such a medical research project is required. The importance of this is clearly recognized by drug regulation authorities in Europe, Japan and U.S.A., as witnessed in various guidelines, for example the one by the European Commission on Good Clinical Practice, which states in its foreword: "good statistical design is an essential prerequisite for credibility of data". The best appreciated experimental design in clinical research, is the "parallel groups randomized controlled trial", particularly when definite answers are looked for. If a two-period cross-over comparative trial design is at all feasible, this comes next, but usually at a more preliminary stage of a research programme.

These three examples may suffice to explain why statistical methods are used abundantly in research papers in the medical literature. A medical doctor who wants to keep abreast of scientific progress in his field in order to strive for optimal patient care, will therefore be confronted with various aspects of statistical reasoning in his professional literature. Whether or not he has received any formal education in medical statistics he will anyway be involved in statistics, either only as a consumer or also as a producer when he is actively doing medical research and wants to publish his results. In the latter case, this may sometimes lead to peculiar applications of statistical models as illustrated with the following two examples.

*Example* 4. Some years ago, a paper in an international journal on growth and reproduction contained the graph shown in Fig. 1, which may be considered as an obvious example of statistical mis-modelling. It shows a linear regression model fitted to apparently heterogeneous data from 31 females. To point out albeit superfluously, some of the peculiarities:
– six distinct subgroups are involved, clearly different as to mean, variability and slope, but nevertheless pooled when fitting this model;
– values of $y - x$ are plotted against $x$, implying a built - in slope which is, of course, negative if $x$ and $y$ are uncorrelated;
– according to the text, for one subgroup (closed triangles) individuals with $x$ - values below 60 were excluded;
– a straight line was drawn even though both axes show interruptions either with or without change of scale.

*Example* 5. A paper in a medical journal contained a table showing data of a double blind efficacy study with a drug against insomnia (see

Table 1), which is clearly a specimen of sample size inflation. It bears on the results obtained during a seven days study with 78 patients. Obviously the study unit was not recognized since the seven answers from one patient were clearly counted as if given by seven different individuals. Moreover about 14% of the data were apparently missing, viz. 18% on drug and 11% on placebo.
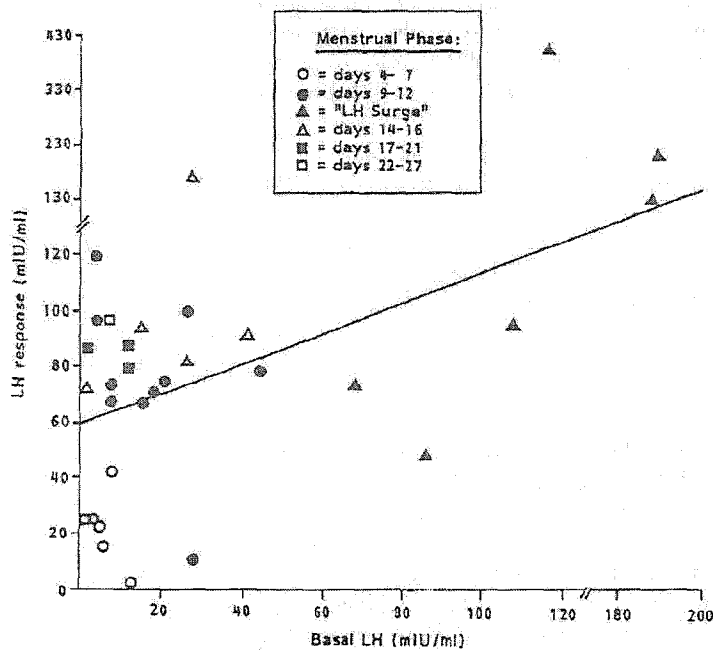


Figure 1. *Scatter diagram with regression line showing positive correlation between basal LH levels and response to LH-RH ($r = 0.55$, $p < 0.01$, $y = 58.8 + 0.8 x$) throughout the menstrual cycle.*

Table 1. *Quality of sleep: Did the medication help you to sleep?*

|                  | Helped | No help | Total |
|------------------|--------|---------|-------|
| Drug (n = 40)    | 216    | 13      | 229   |
| Placebo (n = 38) | 150    | 92      | 242   |
| Total            | 366    | 105     | 471   |

$\chi^2 = 70.84$; $P < 0.001$

These two examples may suffice to indicate that a basic knowledge of biostatistics is of prime relevance for every medical doctor. This brings us to the questions: when, what and how to teach biostatistics to medical students?

When exploring a way to successful teaching of biostatistics we may start by considering two theses:

– Medical students are generally well motivated but mainly for the study of medicine and not so much of chemistry, physics, statistics, etc.

– In order to practise medicine effectively in their later career medical students will need to know enough about biochemistry, biophysics, biostatistics, etc.

These statements may raise some questions:

– How to motivate medical students to take the study of biostatistics seriously?

– How to tailor a biostatistics curriculum to attain coverage of relevant subjects, make it interesting for medical students, and ultimately worthwhile in their opinion?

A successful method of approach to cover the second question, will most likely contribute to a favourable outcome with respect to the first one.

Let us now take up the question: When to teach? After what has been discussed so far, it may be argued that teaching biostatistics should be dispersed throughout the whole medical curriculum. However, the practice of everyday life in a medical school will in general set fairly strict limits to that idea. Moreover in our Medical School at the Erasmus University in Rotterdam, like in most medical schools, the medical curriculum contains also the related subjects epidemiology, social medicine, public health, clinical decision analysis and medical informatics. These subjects are taught partly parallel and in association with biostatistics and partly in other years. In this context we attained a satisfactory compromise: we are teaching obligatory courses in first year and in second year classes, and elective courses in later years.

The next question is: What to teach? In our opinion, given three different periods of study, teaching can be tailored to three levels of understanding:

– Initially the students learn to understand the line of thought in the application of statistical principles to the design and analysis of medical research; this part emphasizes a.o. study designs (including definition of study unit), data description, probability laws (applied to diagnostic problems), sampling distributions, statistical inference (confidence intervals; hypothesis testing; parametric and non-parametric; one and two samples); simple regression and correlation.

— In the second period the students read medical research papers and make a critical appraisal with respect to methodological issues; this part includes a.o. additional aspects of study designs, analysis of variance, evaluation of measurement methods, multiple and logistic regression, survival analysis.

— At the third stage the students, usually being involved in a (smaller part of a) research project, should practise the judicious application of methodological principles regarding design, analysis and interpretation; at this stage emphasis may be given to a special subject e.g. randomized controlled trials as a research design model in medicine.

With respect to the question: How to teach? I like to submit for your consideration a few general guidelines.

— Teaching biostatistics to medical students requires a well-balanced combination of lectures, tutorials and practicals. From our experience we strive for about an even distribution of them.

— When lecturing the teacher should resist the temptation to discuss statistical techniques as such, illustrating their use on invented data with a statement like "these are assumed to be realisations of indepedently distributed random variables".

— It is advisable to use actual data and to elaborate on the origin of the data and the way they were collected, stressing that this should flow from the medical question and from the design of the study. The student should thereby learn to formulate a plausible albeit tentative model of the data in concordance with the actual data generating process, as a basis for the statistical methods to be applied in order to (hopefully) answer the medical question in a reliable way. In our teaching we use as an initial and fairly simple example for this, a video film showing a doctor measuring systolic and diastolic blood pressures on twelve occasions. However, the students just hear the heartbeats as if from the stethoscope and see simultaneously only the scale of the manometer in the film, from which they have to read both blood pressure values. Their readings, as recorded on OCR-forms by the students and then further processed, form a unique data base. The twelve measurements, for example, of diastolic blood pressure represent six patients each measured twice in randomized order and blinded for the students. This makes it feasible during practicals to have students answer questions about inter-observer as well as intra-observer variation, while sitting at their PC's and using standard statistical software. They can easily produce histograms and descriptive statistics, test hypotheses, construct confidence intervals, perform regression and correlation analyses, etc. The students are usually well motivated to this, since their own data are involved and they know exactly how these were assembled.

— With respect to statistical inference, the student should be convinced of the relevance of confidence interval estimation of clinically important effects, instead of merely reporting P-values.

In conclusion, teaching of biostatistics to medical students should be carried out in a way:

— that makes clear that biostatistics is more than a "bag of tools" for data analysis per se;

— that does not leave the impression with the students that only the shape of the data matrix is important;

— that will overcome their lack of interest and motivation and instead convince the majority of the relevance of statistical methodology to medical practice and research.