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Basic Knowledge in Common Clinical Statistical Methods

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Abstract

Advanced statistical methods reduce a complex problem to simple results in research. When the statistical methods are well-known, new dimensions will be brought to the subject. A strong structure will be constructed between the problem and the unbiased results.

Biostatistics concern with scientific method for collecting, organising, summarising data as well as drawing valid conclusion and making reasonable decision on the basis of such analysis in health domain. İt concern many different methods for clinical, basic and applied sciences to solve the complex problems. Today statistical methods are frequently used for every fields of medical research.

Biostatistics has reasonable proposals and methods for each steps of the problem solving in medical area. Statistical methods were developed for many different structure of the clinical design. Many design based on randomisation. Randomisation is important because if done properly it will minimise selection and other types of bias. In design of research, the researcher must learn and applied, internal and external randomisation to be unbiased. Except this, there are many important points in the statistical content that must be taken into account by the researcher in the study.

In the current review, basic knowledge of common clinical statistical methods was presented.

Key words: Sample size, sampling methods**,** clinical trials, regression and corelation

Introduction

Power And Sample Size İn Research

Sample size refers to the number of participants or observations included in a study Power refers to the possibility of finding a meaningful result(1). Power and sample size estimates are used to determine how many subjects are required to answer the survey(2).

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The null hypothesis

In a controlled experiment, the goal is usually to compare two or more vehicles. First, a "zero hypothesis" is created, indicating that there is no difference between the averages, and the aim of the experiment is to refute this zero hypothesis(3).

There are two hypotheses to consider:

1. The zero hypothesis is that there is no difference between the examined groups

2. Alternative hypothesis is the difference between the groups studied

We can make two types of errors when trying to determine whether the two groups are the same or different. These are called type I errors and type II errors.

It is said that there is a type I error when we misrepresent the null hypothesis and there is a difference between the two groups examined.

For type I error, we select a probability of <0.05. If we find a positive result, it means that the chance to find it will happen in less than 5%.This figure is called pα and is usually set by us early in planning.

The lower the level of significance, the lower the power, so using 0.01 will reduce our strength accordingly.(To avoid the type I error - that is, if we find a positive result, the chance to find it, or a larger difference happens in less than a% α of events). When we accept the null hypothesis incorrectly, it is said that there is no difference between the two groups and a type 2 error occurs. If there is a real difference between them, we express the probability of having a type II error and the probability of finding it. This figure is called pβ. There is less convention about the accepted pβ level, but 0.8-0.9 numbers are common (That is, if there is really a difference between them, then we will find it between 80% and 90%.).

Type II error avoidance is crucial to power calculations. The power of a study, β, is the probability of two groups to detect a predetermined measurement difference, if any, given a preset p value and a sample size N. Power calculations indicate how many patients are required to avoid type I or type II errors.

Strength refers to the number of patients required to avoid a type II error in a comparative study.

Sample size estimation is the term that applies to all types of work that only examines more than type II errors (2).

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Sampling Methods

Sampling is the process of selecting a group that will represent them from the population to be studied. The target audience is the group of people from which the sample can be taken A sample is a group of people participating in the research. These are called "participants". Expresses the extent to which we can apply the findings of our generalizability research to the target population(4)

Whichever method is chosen in an example, it is important that those people represent the entire population. This may include targeting hard-to-reach groups(5)

Sampling is of two types: probability sampling and non-probability sampling.

Probability Sampling Methods

1.Simple random sampling

Each individual is chosen by chance and every member of the population has a chance to be selected.

2.Systematic sampling

Individuals are selected at regular intervals. Ranges are selected to provide an adequate sample size

3.Stratified sampling

a method where the researcher divides the population into smaller groups that do not overlap but represent the entire population

4.Clustered sampling

The subgroups of the population are used as sampling units. The population is divided into subgroups known as randomly chosen clusters for inclusion in the study. Clusters are usually predetermined.

Non-Probability Sampling Methods

1.Convenience sampling

Participants are selected based on their willingness to participate.

2.Quota sampling

It is often used by market researchers. The interviewers are determined to have a certain type of quota to hire.

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3.Judgement (or Purposive) Sampling

Who will participate is determined by the request of the researcher. Researchers may indirectly choose a "representative" sample that suits their needs or approach individuals with specific characteristics.

4.Snowball sampling

It is a method that explores hard-to-reach groups. It is commonly used in social sciences. Existing subjects are asked to nominate other topics known to them so that the sample grows like a rolling snowball.

Probability sampling methods tend to be more time consuming and expensive than non-probability sampling(5).

How do you decide on the type of sampling to use?

The effectiveness of our sampling depends on several factors

- Take note of the research objectives. Often there should be a combination of cost, precision or accuracy
- Identify effective sampling techniques that could potentially meet the objectives of the research.
- Evaluate each of these methods and see if they help you achieve your goal.
- Choose the most appropriate method for research(6).

Clinical Trials

Clinical trials testing new treatments are partitioned into different stages, called phases. The phases of clinical trials are the steps in which scientists conduct experiments in an attempt to get adequate evidence for a process which might would be useful as a medical treatment. In the case of pharmaceutical study, the phases start with drug design and drug discovery then proceed on to animal testing.

If animal testing phase would be successful, they start the clinical phase of improvement by testing for safety in a few human subjects and expand to test in many study contributor to condition if the treatment is influential.

The earliest phase trials may study look at whether a drug is safe or the side effects it causes. Later phase trials intend to test whether a new treatment is better than existing treatments (7). There are 3 important phases of clinical trials; Phase 1,2,3. Phase 1 trials are the earliest phase trials and phase 3 are later phase trials. Some trials have an earlier stage called phase 0, and there are some phase 4 trials done after a drug has been licensed(Table 1.) (7).

Phase 0 Trials

Phase 0 is a new assignment for discretionary exploratory trials conducted in conformity with the United States Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies(8). An Important property of Phase 0 trials include the management of single subtherapeutic doses of the study drug to a little subject groups (10 to 20) to collect preliminary data on the agent's pharmacokinetics(9).

Phase I Trials

Phase 1 trials are the first stage of testing in human subjects(10). Phase 1 is designed to test the safety, side effects, best dose , formulation method for the drug(11). Phase 1 trials are not randomized, so this trials are vulnerable to selection bias(12). Normally, a small group of 20–100 healthy volunteers will be set up. The trials will be done on this group(10,13). These trials are frequently conducted in a clinical trial clinic, where the subject can be observed by full-time staff. The subject who gets the drug is generally observed until several half-lives of the drug have passed. In this phase, the safety (pharmacovigilance), tolerability, pharmacokinetics and pharmacodynamics of a drug are evaluated(14).

Phase II Trials

Once a dose or range of doses is determined, the following aim is to evaluate whether the drug has any biological activity or effect(15). Phase 2 trials are performed on larger groups (50–300 people).Phase 2 trials are designed to assess how well the drug works, as well as to continue Phase 1 safety assessments in a larger group of volunteers and patients. Failure to development process a new drug usually occurs in Phase 2 trials(15).

Phase III Trials

Phase 3 is designed to assess the success of the new intervention and its value in clinical practice. Phase III trials are randomized controlled mutlicenter trials on big patient groups (300–3,000 people) and this trials are intended at being the exact assessment of how effective the drug. Due to their size and relatively long period, Phase III trials are the time-consuming, most costly and difficult trials to design and operate of duration(15).

Phase IV Trials

Phase IV trial is additionally called post-marketing surveillance trial or unofficially as a confirmatory trial. Phase IV trials include the safety surveillance (pharmacovigilance) and continuing technical support of a drug after it get permission to be sold (for instance after confirmation under the FDA Accelerated Approval Program) (16).Detrimental impacts found by Phase IV trials may result in a drug being no longer sold.The least time period compulsory for Phase IV clinical trials is 2 years(7).

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Table I- Summary of clinical trial phases(7)

Phase	Number of people taking part	Is it randomised?	Primary goal	Dose
Phase 0	10 to 20 people	No	Testing a low dose of the treatment to check it isn't harmful	Very small, subtherapeutic
Phase 1	20 to 100 people	No	Finding out about side effects, and what happens to the treatment in the body	Often subtherapeutic, but with ascending doses
Phase 2	100 to 300 people	Sometimes	Finding out more about side effects and looking at how well the treatment works	Therapeutic dose
Phase 3	300 to 3000 people	Usually	Comparing the new treatment to the standard treatment	Therapeutic dose
Phase 4	Anyone seeking treatment	No	Finding out more about long term benefits and side effects	Therapeutic dose

In this section we will examine observational studies. We will consider for what studies they can be used, their advantages and disadvantages.

Cohort Studies

Cohort means "community of people with common characters". In cohort studies, different groups with different levels of risk factors are followed for a long time to see what results will be achieved. It is a method especially used in epidemiological studies. It can be done in two ways: prospective and retrospective. Prospective cohort studies are studies that start today and continue for a long time. Retrospective studies, on the other hand, are the studies performed by obtaining information and finding people in previous studies.

An example of a prospective cohort study is the study made by Viljakainen et al., the effect of maternal vitamin D values during their pregnancy on bone development in early childhood can be given (17)

Advantages of Cohort studies (18)

- It is suitable for understanding the causality of a factor.
- More than one result can be obtained depending on a factor.
- Different factor-result analysis can be performed by following more than one factor at the same time.
- Disease rates of those exposed and not affected can be calculated

Disadvantages of prospective cohort studies:

- May require long-term follow-up
- It may be necessary to work with a large number of people.
- Can be expensive to do
- Susceptible to loss to follow-up or withdrawals

Disadvantages of retrospective cohort studies:

- Open to recall or information bias
- Less control over variables

Evaluation of a cohort study; It includes the evaluation of whether or not the research design appropriate for the question to be investigated has been selected, the evaluation of the methodology, the appropriateness of the statistical methods used, the conflict of interest and how relevant the research is to practice sections. For this reason, it is recommended to use the STROBE (Strengthen the Reporting of Observational Studies in Epidemiology) guide when reporting a cohort study (19).

Case-Control Studies

Case-control studies investigate the causes by looking at a specific result. Individuals with cases (cases) and those who do not (control) are selected. It is important that these individuals are from the same population to prevent the election bias. Another point to note here is that the inclusion and exclusion criteria are clearly set. The historical data is then collected through interviews, questionnaires, or records (17).

Case-control studies are ideal for evaluating outcomes with long waiting times, as they result from the cause.

Advantages of case-control studies (18);

- Ideal for reviewing results with long waiting times
- Preparing faster
- Cheaper

- Fewer cases are needed
- Multiple causes or risk factors can be examined
- Existing data can be used

Disadvantages of case-control studies:

- Open to recall or information bias
- The information collected is difficult to validate
- Choosing an appropriate comparison group can be difficult

Descriptive Studies

Descriptive studies are used to describe the forms of the disease in relation to variables such as person, place, and time. It has four types: case reports, case series, cross-sectional studies, and ecological studies (20)

Case reports and case series: A case report refers to the outline of a patient with an uncommon illness or with synchronous prevalence of over one condition. A case series is analogous, except that it is associate aggregation of multiple (often solely a few) similar cases.

Cross-sectional studies: These studies include gathering information about the presence or level of one or more variables (health-related characteristic) of interest where located in a defined population at a given time.

These studies include gathering information about the presence or level of one or more variables (health-related characteristic) of interest in a defined population at a certain time. To be descriptive, these data should only be analyzed to determine the distribution of one or more variables.

These studies are ideal for measuring the prevalence of diseases, determining the risk factors of the population, determining the burden of disease and healthcare needs.

Ecological studies: These studies, also called correlational studies, examine the relationship between expose and outcome in populations rather than individuals.

This design is especially useful when exposure differences between individuals within a group are much smaller than exposure differences between groups. For example, the intake of certain food items is likely to vary less between people in a particular group, but may differ greatly between groups, for example, people living in different countries.

Problems that can be encountered in these studies:

1- Migration between regions
2- Different definitions for words
3- The exposure-outcome relationship at the group level may not be at the individual level

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4- A third factor may have caused the exposure-outcome relationship

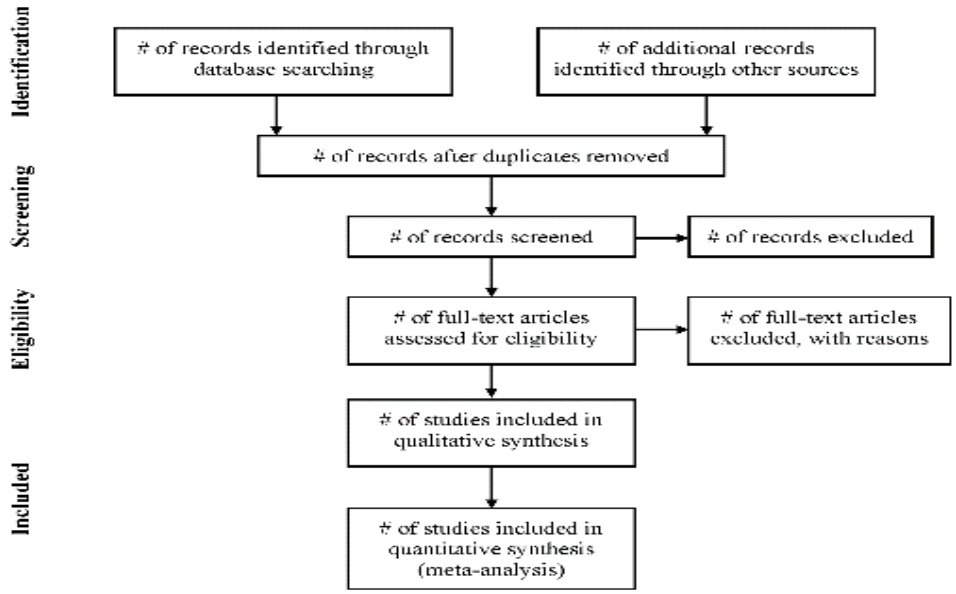
Cross-Sectional Studies

These studies evaluate a certain subject in a certain time section at the time we are in. It measures both exposure and outcome at the same time but does not say the relationship between them. These studies can be used in population-based questionnaires, prevalence estimates in clinical-based studies, and odds-ratio calculations (21).

Meta-Analysis

Meta-analysis studies examine more than one study on a subject in the past and provide a more accurate conclusion about that subject. This may be the effectiveness of a treatment or a risk factor for a disease. Meta-analyzes are done to evaluate the strength of evidence related to a disease and treatment. One goal is to determine if there is an effect; Another aim is to determine whether the impact is positive or negative and ideally to obtain a single summary estimate of the impact (22).PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) statement can be followed to make the study more effective while doing such studies. The PRISMA Statement has a 27-item checklist and a four-phase flow diagram.

PRISMA 2009 Flow Diagram (From Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006-12, For more information, visit www.prisma-statement.org)



It is characterized by a robust meta-analysis, a comprehensive and disciplined literature search. A clear definition of the hypotheses to be investigated forms the framework for such an investigation. According to the PRISMA statement, a clear question statement is addressed, referring to the participants, interventions, comparisons, results, and study design (PICOS).

Studies to be meta-analyzed are selected according to the inclusion criteria. If there is more than one hypothesis to be tested, separate criteria should be determined for each. Study design, including details of the method of randomizing subjects to treatment groups, eligibility criteria in the study, blinding, result evaluation method, and protocol deviations are important features that define the quality of the study.

One of the two methods to know when using meta-analysis is the fixed-effects model and the other is the random-effects model. The fixed effects model is based on the assumption that the only source of variation in the observed results occurs within the study; that is, the effect expected from each study is the same. Consequently, the models are assumed to be homogeneous; There is no difference in the underlying study population, no difference in subject selection criteria, and treatments are administered in the same way. Random effects models have a fundamental assumption that a distribution of effects exists, resulting in heterogeneity known as $\tau 2$ among study results. As a result, as the software evolved, random effect models that required more computing power became more frequent. This is desirable because the strong assumption that the relevant effect is the same in all studies is often untenable. Also, when statistical heterogeneity ($\tau 2$) is present in the results of studies in meta-analysis, the fixed effects model is not suitable. In the random effects model, studies are weighted by the inverse of their variance and heterogeneity parameter. Therefore, it is a more conservative approach with a wider confidence interval than the fixed effects model, where studies are weighted only by the inverse of their variance. The most commonly used random effects method is DerSimonian and Laird method.

Although the purpose of a meta-analysis is to find and evaluate all studies that meet the inclusion criteria, it is not always possible to obtain them. This is because large studies with positive results are published more than small ones with negative results.

It is important to examine the results of each meta-analysis for evidence of publication bias. The estimation of the probable magnitude of publication bias in the review and the approach to dealing with prejudice is natural in conducting many meta-analyzes. Various methods have been developed to evaluate the publication bias; most widely used one is funnel chart. A funnel plot is a scatter plot of a treatment effect versus a measure of study size. If there is no publication bias, the plan is expected to be symmetrical inverted funnel.

Classical meta-analysis, when comparing the two treatments, network meta-analysis (or multiple treatment meta-analysis) can provide estimates of the treatment efficacy of multiple treatment regimens, even when direct comparisons with indirect comparisons are not possible.

It can also be used to summarize the performance of diagnostic and prognostic tests.

Randomized Control Trial

In randomized controlled trials (RCTs), which are accepted as the gold standard in medical research, a group of participants meeting the inclusion and exclusion criteria is randomly

divided into two groups and receive different interventions. Random assignment indicates that each participant has the chance to distribute equally to the two groups. In some cases, these studies cannot be carried out for ethical reasons. For example, questions that may lead to being asked to take placebo instead of a treatment with known effect or ask individuals to try out experiences that will harm them (20).

There are different types of randomized studies (21);

Parallel: In this study, one group receives A treatment while the other receives B treatment.

Crossover: In this study, one group takes A treatment and then B treatment, while the other group follows the opposite.

Assumptions: In this study, a wait time is applied to clear the effects of the first treatment before the second treatment is applied after the first treatment.

Factorial: In these studies, two or more factors are included when randomizing, and the combined effect of these effects on a dependent variable can be investigated.

Cluster: Advantages may include the ability to examine interventions that cannot be directed to selected individuals (for example, a radio show about lifestyle changes) and the ability to control "contamination" among individuals (e.g. one person's behavior may affect another person's behavior). As a disadvantage, it can be said that the design and analysis are more complex, and more participants are needed to obtain the same statistical power.

Regression and Corelation

Methods that allow us to understand the relationship between variables and to predict the condition of patients regarding an interest variable are called correlation and regression.

Corelation investigate the strength of the connection between two variables, neither of which is viewed as the variable one is attempting to predict (the objective variable)(23). According to the study conducted in 2020 as an example of correlation, it has been concluded that serum magnesium has a significant negative correlation with fasting blood sugar, insulin and HOMA-IR, therefore it can be suggested that hypomagnesemia is one of the important predictors of type 2 diabetes mellitus (24).

Regression analusis investigates the ability of one or more factors, called independent variables, to predict a patient's condition in regard to the target or variable.

Independent and dependent variables can always be (with a wide range of values) or binary (yielding yes or no). regression models are often used to establish clinical prediction rules that help guide decisions in the clinic. In regression and correlation, clinicians should show more importance to the magnitude of the correlation and the predictive power of regression, whether it is statistically significant (23).

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Regression

The most preferred regression analysis method is multiple linear regression. other techniques such as linear regression, logistic regression, nonlinear regression and differential analysis are also covered by the term regression(25). Simple linear regression is not very preferred in medical research because it contains more than one predictive variable in most studies.

In the univariate statistical techniques such as simple linear regression, a single prediction variable is used, which can often be mathematically correct but clinically specious. The mathematical technique used to show the relationship between multiple independent predictive variables and a single dependent result variable is called multiple linear regression. multiple regression toward the mean is used in medical research and diagnostic and treatment concentrates within whichthe result depends on over one think about order to model observational data. Although it's generally limited to data that may be expressed by a linear function, it utilizes a well-developed mathematical framework that gives unique solutions and exact confidence intervals for regression parameters (26).

Corelation

In health-related studies, researchers often use correlations to assess the strength of the relationship between the 2 (continuous) variables measured. As an example, a possible relationship between high-sensitivity C-reactive protein (hs-CRP) and body mass index (BMI) can be considered. Although BMI is often considered a categorical variable, such as weak, normal, overweight, and obese, an uncategorized version will be more detailed so it may be more informative about identifying associations (27).

Relative Risk And Odds Ratio

Two of the most frequently used ratios in medical research are Relative Risk (RR) and Odds Ratio (OR). Relative Risk (RR) (also called the risk ratio) is often used to interpret the result of prospective studies (phase studies, cohort studies) (28).

Relative Risk is a ratio that shows the relation between the exposure and the result. We can find the Relative Risk by computing the ratio of the probability of a result in a group exposed to a certain factor to the probability of result in the control group (29).

The Relative Risk cannot be negative and it can be from 0 to infinity. If RR = 1, it is understood that exposure does not affect the result. Values other than 1.0; shows the difference between the two groups. RR < 1 shows that the risk of the result is decreased by exposure. RR > 1 shows that the risk of the result is increased by the exposure (30,31).

The Odds Ratio (OR) is often used in case-control studies. Odds of an event is the ratio of the likelihood of its occurrence to the likelihood of its nonoccurrence. To compute The Odds Ratio; the odds of an event in the exposure group must be divided by the odds of that event in the control group (32).

The Odds Ratio cannot be negative and it can take any value from 0 to infinity. Odds ratio (OR) can be interpreted according to the value it takes; when OR = 1, the certain factor (according to the reference) does not increase or decrease the likelihood of the situation. When OR <1, the

certain factor (according to the reference) has an effect that reduces the likelihood of the situation. When OR> 1, the certain factor (according to the reference) has an increasing effect on the likelihood of the situation (33).

Table 2. Comparison of the odds ratio and the relative risk (Source: Simon SD . Understanding the Relative Risk and the Odds Ratio . Journal of Andrology, Vol. 22, No. 4, July/August 2001)

Odds Ratio	Relative Risk
The null value is 1.0	The null value is 1.0
Difficult to interpret	Easy to interpret
Covariate adjustment is easy	Covariate adjustment is hard
Invariant to the labeling of events and nonevents	Labeling of events and nonevents creates ambiguity.

Conclusion

Biostatistics has reasonable proposals and methods for each steps of the problem solving in medical area. Statistical methods were developed for many different structure of the clinical design. Many design based on randomisation. Randomisation is important because if done properly it will minimise selection and other types of bias. In design of research, the researcher must learn and applied internal and external randomisation to be unbiased. Except this, there are many important points in the statistical content that must be taken into account by the researcher in the study

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