076 - Pages 1876-1898

076

Pages 1876-1898

Skewed distributions Skewed distributions • alphabetical order: mean - median - mode • '>' for positive, '<' for negative • Normal (Gaussian) distributions: mean = median = mode (bell-shaped) • Positively skewed distribution: mean > median > mode • Negatively skewed distribution mean < median < mode • To remember the above note how they are in alphabetical order, think positive going forward with '>', whilst negative going backwards '<' • Mean, median and mode are measures of central tendency • Descriptive statistics provide mean, median and mode values for a distribution Example: The annual numbers of reported cases of leptospirosis in the USA over the 5-year period from 1985 to 1990 were: 2, 1, 3, 4, 1, . What was the mean, median and modal number of cases per year? Answer: • The mean is found by summing all the values and dividing by 5; this gives a mean = 11/5=2.2 The mean is the average value of observations, and therefore very sensitive to extreme values in a distribution If the mean is greater than the median, this indicates a positive skew. • For the median and mode rewrite the values in ascending order: ie 1,1,2,3,4, • The median is the middle value when the values are placed in order = 2 For an even number of values it is halfway between the two middle values, If you forgot to sort the values before looking for the middle value, you will have got the incorrect answer = 3 The median is the observation that divides the frequency distribution by half and is equal to the 50th centile (lies exactly between each end of a range of values) It responds to the number of extreme observations but not their value, and therefore is useful as a measure of central tendency in extremely skewed distributions In a normal distribution the median equals the mean • The mode is the most common value; this is 1 , which occurs twice, whereas all other values occur only once mode is the most commonly observed value

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 17

Basic science Biostatistics & EBM

• The distribution sample means will be normally distributed even if the population values are not normally distributed. • The random sampling distribution of means would always tend to be normal, irrespective of the population distribution for which the samples were drawn. Hence, even if the population distribution is skewed or in any non-normal distribution, the sample means would be normally distributed.' • the mean of the random sampling distribution of means is equal to the

mean of the original population. • In a distribution skewed by the presence of a number of positive outliers Mean increases, median may increase, mode remains the same

---

Confidence interval and standard error of the mean • Definition of confidence interval a range of values for a variable of interest constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits* in simpler terms: a range of values within which the true effect of intervention is likely to lie • A confidence interval is needed for almost all statistical estimates, including sensitivity or specificity of a diagnostic test. • If the confidence interval includes the number 1, the trial did not find a statistically significant difference between the variables (this does not mean there was no difference) This means the association is not statistically significant and therefore the p value should be above 0.05. Key point • A 95% confidence interval: Most commonly, the 95% confidence level is used What is the best interpretation of the 95% confidence interval? We are 95% confident that the mean in the value is between confidence limits confidence interval at the 95% confidence level means that the confidence interval should contain the true effect of intervention 95% of the time. Standard error of the mean = standard deviation / square root (number of patients)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 A 95% confidence interval means that there is only a 5% chance that the true mean value for the variable lies outside the ranges quoted The 95% confidence limits will be the mean plus or minus 1.96 standard errors lower limit = mean - (1.96 * SEM) upper limit = mean + (1.96 * SEM) For example, in a study the mean height in a sample taken from a population is 183cm. You know that the standard error (SE) (the standard deviation of the mean) is 2cm. This gives a 95% confidence interval of 179-187cm (+/- 2 SE). meaning that there is a 5% chance that the true population mean is not included in this range, in other words a 95% chance that the true population mean is included within this range If the 95% confidence interval does not include 0 (zero), the difference is statistically significant If the p value is less than 0.05, statistically significant the 95% confidence interval should not include 0. • Standard error of the mean (SEM) The standard error of the mean (SEM) is a measure of the spread expected for the mean of the observations - i.e. how 'accurate' the calculated sample mean is from the true population mean SEM = SD / square root (n) where SD = standard deviation and n = sample size therefore, the SEM gets smaller as the sample size (n) increases standard error of the mean Gets smaller as the sample size increases Increasing the sample size will reduce the standard error of the mean and the width of the confidence interval. The standard error is Smaller than the standard deviation Assessment of significance (is the result statistically significant?) • If confidence interval does not include 1, this means the association is statistically significant and therefore the p value should be below 0.05. • A narrow confidence interval emphasises the significance of the result, but it is the pvalue that describes significance, not the confidence interval around it. • If there is no significant P-value given in the question, we can conclude that the association in the question is significant if the 95% confidence interval is very narrow (its range does not include the value 0). (e.g: 95% confidence interval 2 to 8)

Confounding variable • Is an extraneous variable in a statistical model that correlates (directly or inversely) with both the dependent variable and the independent variable. • To give a hypothetical example of a confounding variable: • A study shows that wearing sunglasses and putting on sun cream are linked - increases in sun cream sales are higher when sales of sunglasses increase. It could be that sun cream makes individuals wear sunglasses or that wearing sunglasses reminds people that they need to put on sun cream. However, there is a third "confounding" variable that affects

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 17

Basic science Biostatistics & EBM

BOTH sales of sunglasses and sun cream - the weather. It could be that hot, sunny weather makes people both put on sunglasses and apply sun cream. • Another example: In a case-control study on the association between cola drinking and type 2 diabetes => BMI is likely to be a confounding variable • In general, a randomised controlled trial eliminates confounding by known and unknown factors. • Stratified analysis eliminates the confounding of the stratified data. • Multivariable logistic regression can control and minimise confounding by simultaneous adjustment for multiple factors.

Correlation and linear regression Overview • The terms correlation and regression are related but are not synonymous. • Correlation is used to test for association between variables (e.g. whether salary and IQ are related). • Once correlation between two variables has been shown regression can be used to predict values of other dependent variables from independent variables. • Regression is not used unless two variables have firstly been shown to correlate. Correlation • The degree of correlation is summarised by the correlation coefficient (r). This indicates how closely the points lie to a line drawn through the plotted data. In parametric data this is called Pearson's correlation coefficient and can take any value between -1 to +1. • The value of 'r' (coefficient of variation) ranges from -1 to +1 • For example r = 1 - strong positive correlation (e.g. systolic blood pressure always increases with age) r = 0 - no correlation (e.g. there is no correlation between systolic blood pressure and age) r = - 1 - strong negative correlation (e.g. systolic blood pressure always decreases with age) • Whilst correlation coefficients give information about how one variable may increase or decrease as another variable increases they do not give information about how much the variable will change. They also do not provide information on cause and effect. • Correlation is summarised when using parametric variables by Pearson's correlation coefficient (represented by a small r). • In the situation of non parametric variables, Spearman's correlation coefficient is used. Spearman's correlation coefficient is usually represented by the Greek letter p (rho), or by rs. • In the case of dichotomous variables logistic regression is used. • Linear (or simple linear) regression is used when looking for association between two continuous variables, and multiple regression is used when looking for association between more than two continuous variables. Linear regression • In contrast to the correlation coefficient, linear regression may be used to predict how much one variable changes when a second variable is changed. • A regression equation may be formed, y = a + bx, where:

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 y = the variable being calculated a = the intercept value, when x = 0 b = the slope of the line or regression coefficient. Simply put, how much y changes for a given change in x x = the second variable

---

Correlation coefficient • The correlation coefficient measures the strength (and direction, if linear) of the relationship between two variables. • Correlation coefficient does not follow normal distribution. • Calculation of correlation coefficient does not need to assume normal distribution. • If there is perfect linear relationship with positive slope between the two variables, the correlation coefficient is 1. • If there is a perfect linear relationship with negative slope between the two variables, the correlation coefficient is -1. • A correlation coefficient of 0 means that there is no linear relationship between the variables. • The correlation is not necessarily linear • Correlation coefficient describes the linear relationship between two variables. If the relationship between them is not linear, it can be misleading and should not be used. • The correlation coefficient does not depend on sample size. Increasing the sample size will not change the correlation coefficient as its value does not depends on sample size. • The correlation coefficient can be a negative number. • The correlation coefficient can range from -1 to +1. • Correlation and regression are different. Correlation describes how closely two variables are associated. Regression allows you describe one variable with respect to the other in terms of an equation.

Screening test statistics Sensitivity = true positives / (true positives + false negatives) Specificity = true negatives / (true negatives + false positives) The rule of thumb is that a high sensitivity helps to rule out disease (SnOut) and a high specificity helps to rule in (SpIn) disease (Mnemonic "spin and snout")

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 17

Basic science Biostatistics & EBM Contingency tables • also known as 2 * 2 tables, are used to illustrate and calculate test statistics such as sensitivity. • TP = true positive; FP = false positive; TN = true negative; FN = false negative Disease present Disease absent Test positive TP FP Test negative FN TN The table below lists the main statistical terms used in relation to screening tests: Measure Formula Plain English Sensitivity TP / (TP + FN) Proportion of patients with the condition who have a positive test result Specificity TN / (TN + FP) Proportion of patients without the condition who have a negative test result Positive predictive value TP / (TP + FP) The chance that the patient has the condition if the diagnostic test is positive Negative predictive value TN / (TN + FN) The chance that the patient does not have the condition if the diagnostic test is negative Likelihood ratio for a positive test result sensitivity / (1 - specificity) How much the odds of the disease increase when a test is positive Likelihood ratio for a negative test result (1 - sensitivity) / specificity How much the odds of the disease decrease when a test is negative Sensitivity and specificity • Essentially a knowledge of the sensitivity/specificity is based on the disease state itself, whereas predictive values are based on the test result. • Sensitivity and specificity will not change with sample size. They will change only with: composition of the sample (especially if

subjects in the sample have different risks of disease) performance of the test diagnostic threshold, and The "gold standard" to be compared with. • The reliability of estimates of sensitivity, specificity, positive and negative predictive value will all increase with increasing sample size, which will reduce their confidence intervals. • Increasing the cut-off of a positive test result will decrease the number of false positives and hence increase the specificity.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Positive and negative predictive values • Positive and negative predictive values are prevalence dependent. The positive predictive value will increase and negative predictive value will decrease if the prevalence of the disease increases. Likelihood ratios • Likelihood ratios are not prevalence dependent. • If the sensitivity increases, the likelihood ratio of a positive test will increase. If the specificity decreases, the likelihood ratio of a positive test will decrease. • The likelihood ratio of negative test will increase if the specificity of the test is decreased. • The lower the likelihood ratio of a negative test, the less likely is the presence of disease • The likelihood ratio of a positive test helps to rule in disease and the likelihood ratio of a negative test helps to rule out disease. Posterior probability • Posterior probability = posterior odds / (1 + posterior odds) Posterior odds of having disease = prior odds × likelihood ratio. Prior odds of having disease = Prevalence(P) / (1 − P) Precision • quantifies a tests ability to produce the same measurements with repeated tests. MRCPUK-part-1-September 2009 exam: What is the correct formula to calculate the negative predictive value of a screening test? TN / (TN + FP) Incidence and prevalence

Incidence is the number of new cases per population in a given time period. Prevalence is the total number of cases per population at a particular point in time. • These two terms are used to describe the frequency of a condition in a population. • The incidence is the number of new cases per population in a given time period. • For example, if condition X has caused 40 new cases over the past 12 months per 1,000 of the population the annual incidence is 0.04 or 4%. • The prevalence is the total number of cases per population at a particular point in time. • For example, imagine a questionnaire is sent to 2,500 adults asking them how much they weigh. If from this sample population of 500 of the adults were obese then the prevalence of obesity would be 0.2 or 20%. Relationship • prevalence = incidence * duration of condition • in chronic diseases the prevalence is much greater than the incidence • in acute diseases the prevalence and incidence are similar. For conditions such as the common cold the incidence may be greater than the prevalence

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 17

Basic science Biostatistics & EBM

Relative risk Relative risk ratio (RRR) = EER / CER • Relative risk (RR) is the ratio of risk in the experimental group (experimental event rate, EER) to risk in the control group (control event rate, CER). EER = rate at which events occur in the experimental group CER = rate at which events occur in the control group • For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results Total number of patients

Experienced significant pain relief Paracetamol

Placebo

• Experimental event rate, EER = 60 / 100 = 0.6 Control event rate, CER = 20 / 80 = 0.25 Therefore the relative risk ratio = EER / CER = 0.6 / 0.25 = 2.4 • If the risk ratio is > 1 then the rate of an event (in this case experiencing significant pain relief) is increased compared to controls. It is therefore appropriate to calculate the relative risk increase if necessary (see below). • If the risk ratio is < 1 then the rate of an event is decreased compared to controls. The relative risk reduction should therefore be calculated (see below). • The relative risk is always positive • Relative risk reduction (RRR) or relative risk increase (RRI) is calculated by dividing the absolute risk change by the control event rate Using the above data, RRI = (EER - CER) / CER = (0.6 - 0.25) / 0.25 = 1.4 = 140% • Relative risk reduction = 1 − relative risk Remember that risk and odds are different. If 20 patients die out of every 100 who have a myocardial infarction, then the risk of dying is 20 / 100 = 0.2 whereas the odds are 20 / 80 = 0.25.

Numbers needed to treat and absolute risk reduction • Numbers needed to treat (NNT) is a measure that indicates how many patients would require an intervention to reduce the expected number of outcomes by one. • Example: if a study for stroke reveals that 20 patients need to be treated to prevent one event. • That means, if you treat a 1000 patients then you will expect to have 50 fewer strokes NNT= 1/absolute risk reduction Absolute risk reduction = (Control event rate) - (Experimental event rate)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• It is calculated by 1/(Absolute risk reduction) Experimental event rate (EER) = (Number who had particular outcome with the intervention) / (Total number who had the intervention) • Control event rate (CER) = (Number who had particular outcome with the control/ (Total number who had the control) • Absolute risk reduction = CER-EER or EER-CER • ARR = risk in control group - risk in treated group. For example: If a drug reduces the incidence of heart attacks from 12% to 8% then: The control event rate (CER) is 12% The experimental event rate (EER) is 8% The relative risk reduction (RRR) is 33% ([EER-CER/CER] x 100) The absolute risk reduction (ARR) is 4% (CER-EER) The number needed to treat (NNT) is 25 ([1/ARR] x 100) Number needed to harm • For many studies now, papers quote the number needed to harm. This uses the same principle to establish the difference in absolute risk of an adverse event occurring between two treatment strategies, calculating a number needed to harm by dividing 100 by the absolute risk. Hazard ratio • The hazard ratio (HR) is similar to relative risk but is used when risk is not constant to time. It is typically used when analysing survival over time • Example: A study is performed comparing two chemotherapy regimes for patients with small cell lung cancer. The end point of the study is survival time. Which one of the following types statistical measures is it most appropriate to compare survival time with? Hazard ratio

---

Odds and odds ratio Odds - remember a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome NOT a ratio of the number of

people who incur a particular outcome to the total number of people • Odds are a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome. The odds ratio may be defined as the ratio of the odds of a particular outcome with experimental treatment and that of control. Odds vs. probability In contrast, probability is the fraction of times you'd expect to see an event in many trials. When expressed as a single number probability is always between 0 and 1. So, if we take the example of rolling a dice: • the probability of rolling a six is 1/6 or 0.166666 • the odds of rolling a six is 1/5 or 0.2 • Odds ratios are the usual reported measure in case-control studies. It approximates to relative risk if the outcome of interest is rare. For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 17

Basic science Biostatistics & EBM

Total number of patients Achieved = 50% pain relief Paracetamol

Placebo

The odds of achieving significant pain relief with paracetamol = 40 / 20 = 2 The odds of achieving significant pain relief with placebo = 30 / 60 = 0.5 Therefore the odds ratio = 2 / 0.5 = 4

Pre- and post- test odds and probability Pre and post-test odds • Pre-test odds The odds that the patient has the target disorder before the test is carried out Pre-test odds = (pre-test probability/[1 – pre-test probability]). • Post-test odds The odds that the patient has the target disorder after the test is carried out Post-test odds = (pre-test odds x likelihood ratio). the likelihood ratio for a positive test result = sensitivity / (1 - specificity). Pre and post-test probability • Pre-test probability the proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence). For example, the prevalence of rheumatoid arthritis in the UK is 1%. • Post-test probability The proportion of patients with that particular test result who have the target disorder Post-test probability = (post-test odds/[1 + post-test odds]).

Screening: Wilson and Junger criteria

1. The condition should be an important public health problem
2. There should be an acceptable treatment for patients with recognised disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognised latent or early symptomatic stage
5. The natural history of the condition, including its development from latent to declared disease should be adequately understood
6. There should be a suitable test or examination
7. The test or examination should be acceptable to the population
8. There should be agreed policy on whom to treat

9. The cost of case-finding (including diagnosis and subsequent treatment of patients) should be economically balanced in relation to the possible expenditure as a whole
10. Case-finding should be a continuous process and not a 'once and for all' project

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

R-values • A positive R-value means that as one variable increases, so does the other • A negative R-value means that as one variable decreases, the other increases ie the correlation is inversed (A negative R-value indicates an inverse association) • association or lack of association is indicated by how close the value of R is to zero • statistical significance is denoted by its p-value • P-values < 0.05 are considered to be significant

---

Scales of measurement Data always come in one of the four scales of measurement: Nominal Data are divided into qualitative groups, such as hot/cold, with no implication of order. Ordinal Data are placed in an order (hot/hotter/hottest), although the absolute levels are unknown and no conclusion can be made about the size of the interval. Interval dividing a continuous measurement into groups (eg age groups).Data are placed in an order; and the exact value of the measurement is given, usually in measured quantities representing the difference between two measurements (81-90/91-100/101-110 °C). That is, differences between arbitrary pairs of measurements can be meaningfully compared. Ratios between numbers of the scale are not meaningful, so operations such as multiplication and division cannot be carried out directly. But ratios of differences can be expressed; for example, one difference can be twice Another lf the measurement scale does not have an absolute zero (ie no numbers exist below the zero) this is called interval data. Ratio Here, there is a value of 0 kelvin, and it isn't possible to get below this (ie absolute zero), therefore, the ratio between the values is meaningful, eg 271-280/281-290/291300 kelvin. Select Study Design to Match the Research Goals Objective Study design Describe of disease or spectrum Case series or report Cross sectional study Determine operating characteristics of a new diagnostic test Cross sectional study Describe prognosis Cohort study Determine cause-effect Cohort study Case control study Compare new interventions Randomised clinical trial summarize literature Meta-analysis

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 17

Basic science Biostatistics & EBM Select Study Design

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

The following table highlights the main features of the main types of study: Study type Key features Randomised controlled trial Participants randomly allocated to intervention or control group (e.g. standard treatment or placebo) Practical or ethical problems may limit use Cohort study Observational and prospective. Two (or more)are selected according to their exposure to a particular agent (e.g. medicine, toxin) and followed up to see how many develop a disease or other outcome. The usual outcome measure is the relative risk. Examples include Framingham Heart

Study Case-control study Observational and retrospective. Patients with a particular condition (cases) are identified and matched with controls. Data is then collected on past exposure to a possible causal agent for the condition. The usual outcome measure is the odds ratio. Inexpensive, produce quick results Useful for studying rare conditions Prone to confounding Cross-sectional survey Provide a 'snapshot', sometimes called prevalence studies Provide weak evidence of cause and effect

---

Systematic review (meta-analysis) • a study of studies. • statistical (quantitative) combination of results from two or more studies addressing the same research question. • Metanalysis= systematic reviews + Quantitative measures. • Usually used to treatment studies. • A 'meta-analysis' would look at combining all previous data,. This is likely to be the quickest option to complete, and also produces the highest level of evidence. • rapid and efficient • Publication bias might be present (positive results are published more often than the negative ones). • Publication bias can be examined by funnel plots if a sufficient number of studies is found. • Non-randomised or other studies may or may not be included. • However, randomised controlled trials usually have lower risk of bias and hence give us more confidence about validity of results and are preferred primary sources for systematic review. • Critical appraisal is an important part of systematic review and it has to be objectively performed using well-defined criteria or appraisal tools. Funnel plots - show publication bias in meta-analyses

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 17

Basic science Biostatistics & EBM

• Meta-analysis, that is, combining results numerically in a statistically appropriate way, though desirable, is not always feasible, depending on the availability of usable data and heterogeneity. (Meta-analysis is not always performed) • The search strategy in systematic review should be comprehensive involving electronic databases and other sources and using well-defined search terms. • Case-control studies are not usually included in the search of literature in systematic review • The research question is always focused • there are at least two authors to independently appraise the search results and primary studies. • It is not mandatory to exclude studies with missing data. • The effect size should not affect the weight of each study, although it will affect the final result. • Trial quality is usually not incorporated into meta-analysis nowadays since the weightings can be subjective and arbitrary. • The weight of each study should depend on the sample size • Funnel plots show publication bias in meta-analyses • Forest plot The most appropriate way of graphically depicting the results of metaanalysis. Fixed vs random effect model for meta-analysis The fixed effect model The random effects model the most commonly used model for meta-analysis. Provides the best estimate of the treatment effect attempts to provide one single best estimate of treatment effect. attempts to find an average treatment effect. assumes there is no heterogeneity between the trials. assumes heterogeneity assumes a single treatment effect allows multiple treatment effects.

Randomised controlled trial (RCT) Overview • The purpose of randomisation is to prevent systematic differences (bias) between treatment groups. Aim: to determine the possible effect of a

specific intervention on a given population Advantages • Minimizes bias • Can demonstrate causality Disadvantages • Cannot be used to evaluate rare diseases

 For rare diseases and exposures, case control studies are the best option. Although cohort studies are good for rare exposures, they are not good for rare diseases. • Cannot be used when treatments have well-known adverse side effects • Expensive and time-consuming Uses • the 'gold standard' for evaluating a new intervention • May be used to test an efficacy of a drug Study method • Randomization: Study participants are randomly allocated to either the treatment/intervention group or the control group to ensure that both groups have approximately the same baseline characteristics. • Blinding: the practice of not informing an individual or group about which study participants are part of the control group and which are part of the treatment group (used to reduce bias) • Classic errors in randomisation Consecutive sampling, which may well not be representative if the study time is short. Convenience sampling: strong potential for bias, with volunteers generally healthier than others. Judgmental sample: including those that you want only. The potential for systematic error is enormous. Methods of analysis for randomized controlled trials • Intention to treat analysis (ITT) Intention to treat analysis is a method of analysis for randomized controlled trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment. Include the patients who drop out in the final data set Intention to treat analysis is done to avoid the effects of crossover and drop-out, which may affect the randomization to the treatment groups. ITT helps to reduce bias by sticking to the original allocation of treatment and analysing the patient in that treatment group even if they do not receive the treatment ITT is considered to be the analysis which is least subject to bias. Considered the most robust • Per protocol analysis A per protocol analysis may exclude patients who suffered an event but then did not follow the protocol accurately, for example, a patient treated with the diabetes agent who was admitted to hospital, but missed one to two doses of medication.

Basic science Biostatistics & EBM

Case-control study Aim • to study if an exposure (i.e., a risk factor) is associated with an outcome (i.e., disease) Study method • Researchers begin by selecting patients with the disease (cases) and individuals without the disease (controls). • Controls are selected from the same source population and ideally have similar characteristics (e.g., gender, age) to the cases to reduce potential confounding. • The odds ratio is then determined between these groups. Advantages • Can be used to study rare diseases • Can be used to study diseases with long latency periods • A wide range of risk factors can be investigated • There is no loss to follow up • They are relatively cheap and quick to perform. Disadvantages • Recall and/or survivorship bias occurs in retrospective studies (have the greatest problems with recall bias) • Cannot be used to determine prevalence or incidence Example • A group of patients with histologically confirmed cervical cancer (cases) is

compared to otherwise similar patients without histologically confirmed cervical cancer (controls) for the presence of human papillomavirus (exposure).

Cohort study Aim • To study the incidence rate and whether a given exposure is associated with the outcome of interest A case-control study generally examines a small population group over a short period of time (less cost-intensive) and evaluates the association between multiple exposures and one outcome. A cohort study generally examines a large population over a long period of time (more cost-intensive) and determines how one exposure is associated with multiple outcomes In cohort studies, the study sample is selected based on exposure to a risk factor. In case-control studies, the study sample is selected according to having a disease or not, and then it is determined which participants were exposed to a risk factor.

Study method • The researchers gather a group of study participants who have common characteristics. • Participants are then classified into two groups: exposed and unexposed. • The incidence of the outcome of interest is compared between the two groups. Advantages • Less susceptible to recall bias than case-control studies. • Helps determine whether a given exposure plays a role in the development of a disease • Allows for the calculation of relative risk • Helps determine incidence • Can be used for rare exposures Disadvantages • When the outcome of interest is rare a very large sample size is needed (Insufficient for rare disease) • Prospective cohort studies are high-cost and time-consuming • In retrospective cohort studies, some data on predictors and confounders may be missing because the data was collected in the past. • Only assesses the exposures determined at the beginning of the study Types Types of cohort studies Prospective cohort study Retrospective cohort study Description Study begins before the groups develop an outcome of interest Exposure Study participants are categorized into an exposed group and an unexposed group. Outcome The participants are followed prospectively for a period of time to see whether there is a difference in the rate at which the exposed and unexposed groups develop the outcome of interest. Example Individuals with a smoking history of ≥ 1 pack of cigarettes a day (exposed group) are compared to individuals who are non-smokers to see if there is a difference in the proportion of patients in each group that develop lung cancer (e.g., the outcome) within a specific follow-up period. Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Study begins after the exposure and outcome of interest have already occurred Study participants are categorized into a group that was previously exposed to a given risk factor (exposed; e.g., smoking) and a group that was not (unexposed). Data previously collected about the participants is compared to see whether there was a difference in the rate at which the exposed and unexposed groups developed the outcome of interest (e.g., lung cancer) over a period of time. Individuals with a smoking history of ≥ 1 pack of cigarettes a day (exposed group) 5 years ago are compared to individuals who were non-smokers 5 years ago to see if there is a difference in the proportion of patients in each group that eventually develop

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 17

Basic science Biostatistics & EBM

Observational study • Disadvantages From association in an observational study, we cannot infer cause and effect

---

Biological assays • Biological assays are designed to measure the relative potency of different preparations.

Sequential trial • a trial in which the data are analysed after each participant's results become available and the trial continues until a clear benefit is seen in one of the comparison groups, could also be used to assess efficacy, but there would have to be a large expected difference from placebo. • 'Sequential' trial would be comparing one therapy to another sequentially (usually with wash out periods in between).

Crossover trial The principle of a crossover design is that a patient has one drug or treatment, then a washout period, and then another drug, and the effect is compared between the two in a single individual. For this reason it is a good study design for treatment of chronic conditions (eg: comparing analgesics in arthritis) but not appropriate for acute conditions. • In a crossover trial, the patient (who usually has a chronic stable disease) receives one drug (or placebo) and then the other drug after a washout period • Each patient will usually receive all drugs within the study • In this way, confounding can be greatly reduced • If a drug had long-lasting effects it may not be easy to see which of the trial drugs was having an effect • A self-limiting illness is difficult to study in this way • Because each person is acting as their own control, it is usually possible to use smaller numbers to get the same power. • If any treatment in a cross-over trial is a disease-modifier (in the most extreme case, kills or cures the patient), then the interpretation of results in any subsequent period becomes impossible. This is because disease modification implies that one course of the drug will permanently change the future timecourse of that patient's disease in some way, making a cross-over study un-interpretable. In this case a parallel trial is the only appropriate option.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Sampling • Sampling error arises when only a portion of the population is studied • Random sampling implies that the sample has been selected from a sampling frame in such a way that every individual has the same chance of being selected • The standard error of the mean is the standard deviation divided by the square root of the sample size, hence it must always be smaller than the standard deviation • Inference is the process of drawing conclusions about the population using the sample information • a sample statistic is a point estimate of a population parameter

---

Bias (Systematic error) Definition • An error in the study design or the way in which the study is conducted that causes systematic deviation of findings from the true value Types • Selection bias occurs when the study population is different from the population to whom the results will be applied and there is therefore said to be • Allocation bias occurs when patients are not randomly assigned to a particular treatment. • Assessment bias occurs when the observer knows which

treatment the subject is taking. • Observer bias is when one observer consistently under or over reports a particular variable. • Recall bias applies to case-control studies when a patient is more likely to remember a particular detail of exposure if they go on to develop the disease.

Study design: evidence and recommendations Levels of evidence • Ia - evidence from meta-analysis of randomised controlled trials • Ib - evidence from at least one randomised controlled trial • IIa - evidence from at least one well designed controlled trial which is not randomised • IIb - evidence from at least one well designed experimental trial • III - evidence from case, correlation and comparative studies • IV - evidence from a panel of experts

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 17

Basic science Biostatistics & EBM Grading of recommendation • Grade A - based on evidence from at least one randomised controlled trial (i.e. Ia or Ib) • Grade B - based on evidence from non-randomised controlled trials (i.e. IIa, IIb or III) • Grade C - based on evidence from a panel of experts (i.e. IV)

Study design: new drugs

Superiority trial a large sample size is required to demonstrate a significant difference When a new drug is launched there are a number of options available in terms of study design. One option is a placebo-controlled trial. Whilst this may provide robust evidence it may be considered unethical if established treatments are available and it also does not provide a comparison with standard treatments. Compare a new drug to an existing treatment • The statistician need to decide whether the trial is intended to show superiority, equivalence or non-inferiority: • Superiority one problem is the large sample size needed to show a significant benefit over an existing treatment • Equivalence an equivalence margin is defined (-delta to +delta) on a specified outcome. If the confidence interval of the difference between the two drugs lies within the equivalence margin then the drugs may be assumed to have a similar effect

• Non-inferiority similar to equivalence trials, but only the lower confidence interval needs to lie within the equivalence margin (i.e. -delta). Small sample sizes are needed for these trials. Once a drug has been shown to be non-inferior large studies may be performed to show superiority • It should be remembered that drug companies may not necessarily want to show superiority over an existing product. If it can be demonstrated that their product is equivalent or even non-inferior then they may compete on price or convenience. Phases of new drug development phase goal notes Animal trial Safety for testing the drug in humans Phase I • Initial safety most frequent side effects How the drug is Phase II Effectiveness The number of subjects ranges from a few dozen to about 300. Phase III Comparative efficacy (Effectiveness compared to commonly used treatment) (RCTs) • The number of subjects ranges from several hundred to about 3,000 • The best study for phase 3 is a randomised control study. Phase IV (post marketing) Side effects Enrolls a large number of patients, typically several thousands.

Graphical representation of data Charts and diagrams Quantitative data Qualitative data Histogram Scatter diagram The interpretation of novel findings in a published clinical research study • The trustworthiness of a study should depend solely on its scientific validity, that is, whether it is free of bias. • The conclusion should be treated with skepticism even if it is extensively peerreviewed
Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• conducted in healthy volunteers. • The number of subjects ranges from 20 to 80. metabolized and excreted. Bar diagram Pie diagram