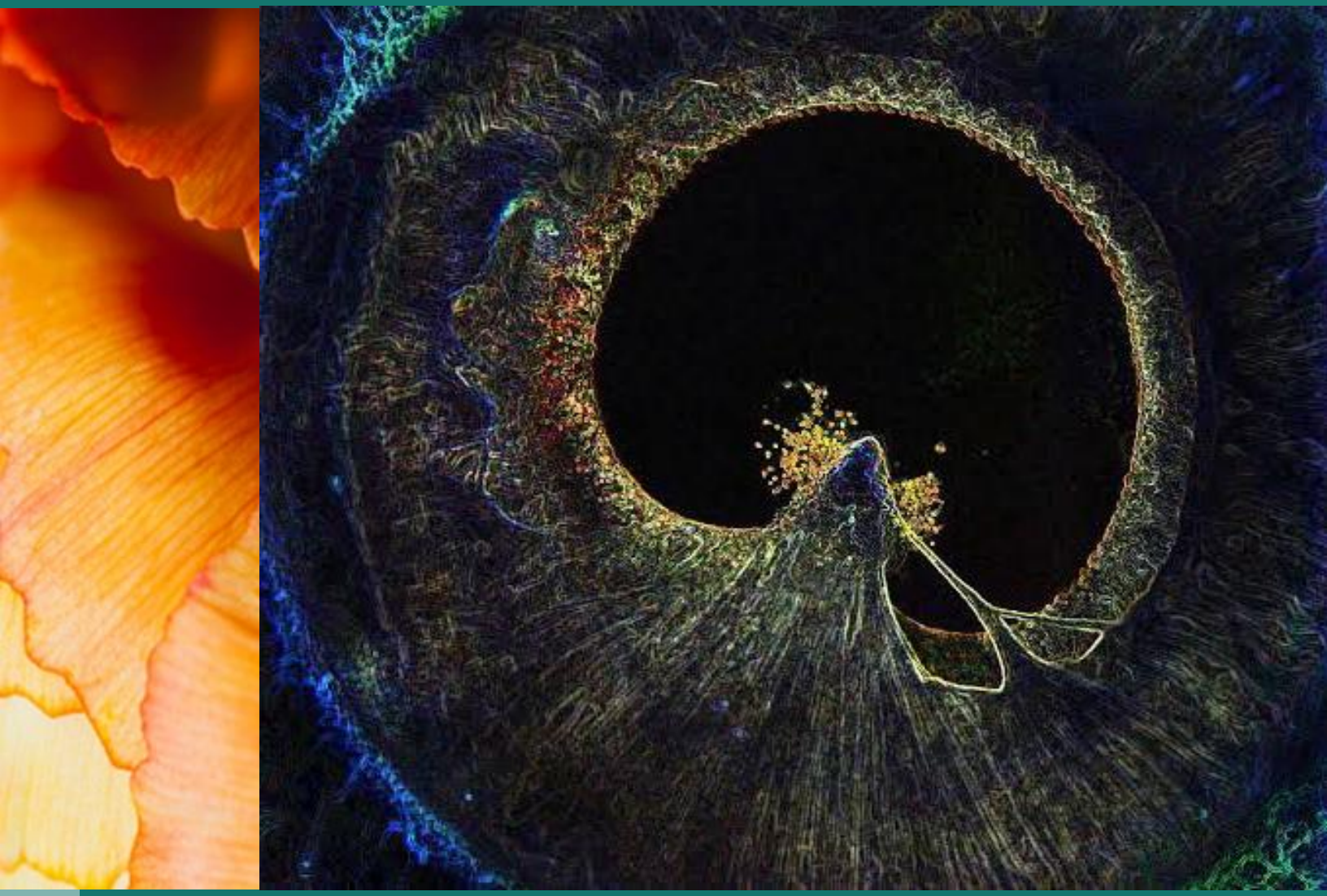

Epidemiology for Ophthalmologist

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EPIDEMIOLGICAL CONCEPTS

Good epidemiological skills are needed for every ophthalmologist to read scientific articles critically before implementing the result to the daily practice. This review provides basic epidemiological research concept about introduction to epidemiology, study designs and interpretation of the findings. To get a better understanding, all examples are taken from the ophthalmology literature.

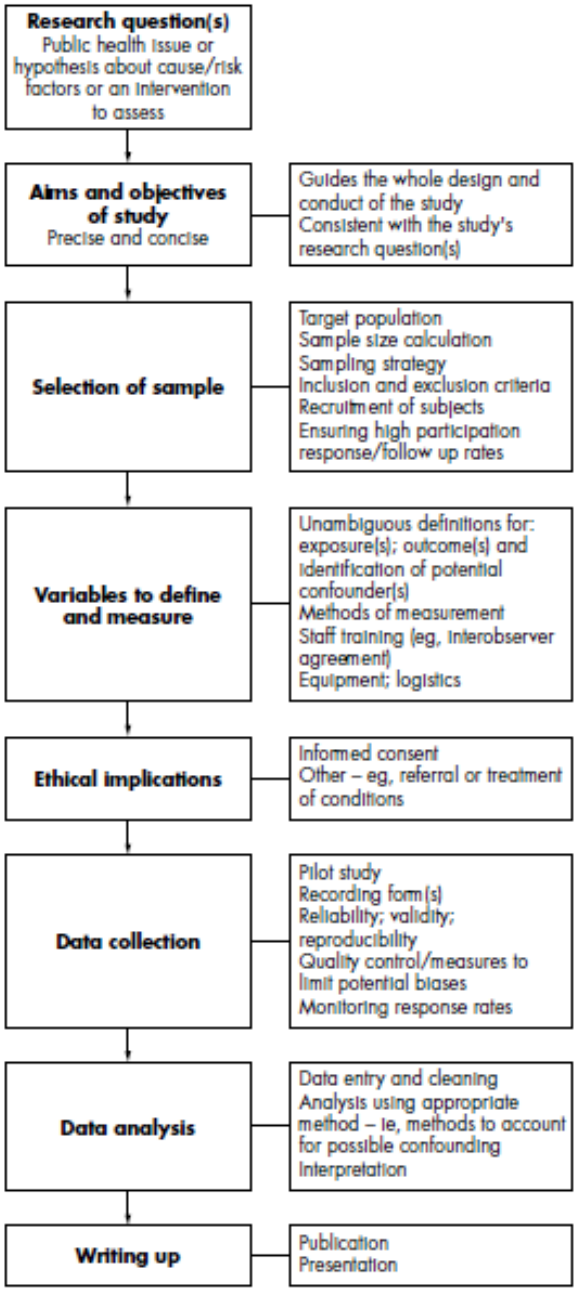


Figure 1. Designing epidemiological study[1]

CONTENTS

Case Definition

Epidemiological research starts with the definition of the disease or condition of interest and based on the ability to quantify the occurrence of disease in populations. This requires a clear definition of what is meant by a case. As an example, a case might be the individual in a population who has the disease, health disorder, or suffers the event of interest. Once a case definition has been decided, the number of cases can be determined. However, changing the definition of the case will change the estimated burden of disease. In Ophthalmology the main concern is visual blindness. In terms of blindness, World Health Organization (WHO) set the case definition as presenting visual acuity (VA) of <3/60 in the better eye, or a central visual field of <10°.[1,2,3]

"The epidemiological definition of a case is not necessarily the same as the ordinary clinical definition and, in most circumstances, epidemiologists may have to rely on diagnostic tests that are less invasive and cheaper than those normally used by clinicians."

Population and Sampling

Measuring the condition of interest in the whole population is sometimes not feasible. In order to overcome this condition, a group of samples is taken from the target population. Target population can be the whole population of a country or region, or the population defined by particular characteristics. The sample of individual should be randomly selected from the population of interest so that every person in the population has an equal chance of being selected. In order to represent the population, we also need to consider the sampling distribution and variation. The larger the sample, the smaller the sampling variation would extent, thus the more reliable result of the study.[1,2]

Measures of the Burden of Disease

The most used measures of disease burden are prevalence and incidence.

Prevalence

Prevalence is the number of cases of disease in a population at one point in time. Prevalence is also defined as a proportion of the total number of persons in that population. Thus, prevalence is a proportion, not a rate. Prevalence measure of the burden of disease in a population at specified point in time. The number of prevalence is obtained from surveys and is useful for the policy maker and administrator to allocate health care resources. In a recent national survey of blindness in Bangladesh, a sample of 11.624 individuals aged >30 was examined, of whom 162 had a VA of ,3/60 in the better eye. The prevalence of blindness was therefore 162/11.624, or 1.39%. So, the national (age standardised) estimate of 650 000 people are blind in those aged >30.[1,2,4-6]

$$Prevalence = \frac{Number\ of\ cases\ in\ a\ defined\ population\ at\ one\ point\ in\ time}{Number\ of\ persons\ in\ the\ defined\ population\ at\ the\ same\ point\ in\ time}$$

Incidence

Not like prevalence that relates on existing cases, incidence relates to new cases. Incidence measures the number of new cases of disease that develop in a population of individuals at risk during a specified time interval. Incidence not only depends on the frequency of the new cases, but also the duration of the disease. There are three measures of incidence: cumulative incidence, odds of disease, and incidence rate. [1,2,4,5]

a. Cumulative Incidence (Risk)

Cumulative incidence, or also known as risk, is the number of new cases that occur in a population which is initially free of disease at baseline who subsequently develop the disease over a specified period of time. This measure will be interpreted as the probability that the subject will develop a disease in the specified time interval. Cumulative incidence has no time limits but must be clearly specified. As an example, approximately seven million people become blind every year so, there are seven million incident cases of blindness per year. The disease free population at risk is 6000 million (global population) minus the number of existing cases of blindness (50 million), giving 5950 million. The global cumulative incidence of blindness in the year 2000 was therefore approximately 0,1%, or seven million divided by 5950 million.[1,5,7,8]

$$\text{Risk} = \frac{\textit{Number of}\ \text{new}\ \textit{cases}\ \text{of disease in a given time period}}{\textit{Number}\ \text{disease – free persons at the start of that time period}}$$

b. Odds of Disease

Odds of disease to non-disease measures the total number of cases by the number of persons which is still free of disease at the end of the study.[2,4]

$$\text{Odds of disease} = \frac{\textit{Number of}\ \text{persons who did become a case of disease in a given time period}}{\textit{Number}\ \text{of persons who did not become a case in that time period}}$$

c. Incidence Rate

The incidence rate or the cumulative incidence presumes that the whole population at risk has been followed up since the beginning of the study period for a specified period of time. Incidence rate uses person time at risk as the denominator, rather than the population at risk. During the follow up of a group of people who are initially free of disease at baseline, each subject may develop the disease of interest, be lost to follow up, develop a competing disease or die, or remain disease free. The calculation starts at the enrolment of the study and stops when one of the occasions occurs or reaches the end of the follow up period. To calculate the incidence rate, we divide the number of incident cases that occur during follow up by the total person time at risk (Box 1).[1,4,5,9]

$$\text{Incidence Rate} = \frac{\textit{Number of}\ \text{new}\ \textit{cases}\ \text{in a given time period}}{\text{Total person-time at risk during that period}}$$

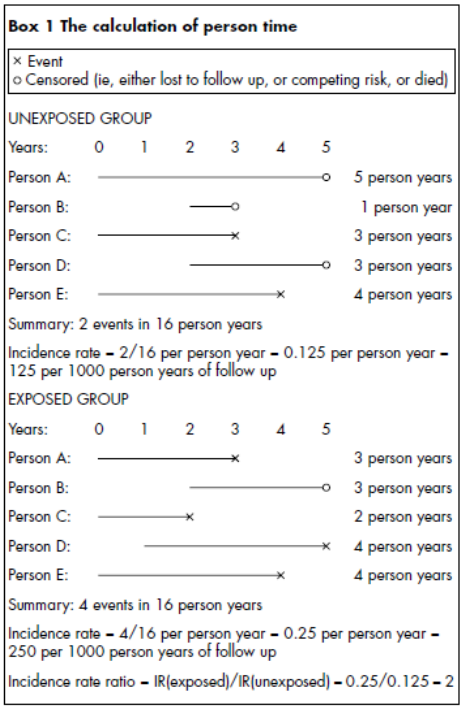
Measures of Associations

Epidemiological research is aimed to find the association between risk factor and outcome. To explore this, there is a need to compare the prevalence or incidence in a group of subjects exposed to the risk factor with the incidence or prevalence in a group of subjects not exposed. From this calculation we can get the relative measure of the effect of the exposure of the disease. This is called the measures of relative risk. Type of measures that can be calculated to estimate the magnitude of an association between exposure and disease are the risk ratio or cumulative incidence ratio (CIR), the rate ratio or the Incidence rate ratio (IRR), and the odds ratio. [1,2,4,5]

$$Risk\ ratio = \frac{Risk\ (cumulative\ incidence)\ in\ the\ exposed\ group}{Risk\ (cumulative\ incidence)\ in\ the\ unexposed\ group}$$

$$Rate\ ratio = \frac{Incidence\ rate\ in\ the\ exposed\ group}{Incidence\ rate\ in\ the\ unexposed\ group}$$

$$Odds\ ratio = \frac{Odds\ of\ disease\ in\ the\ exposed\ group}{Odds\ of\ disease\ in\ the\ unexposed\ group}$$



Confidence Interval

After observing proportion in a random sample, it is important to set an interval of possible value where the true population proportion might lie. The number of 95% confidence interval is the most common statistical technique to display the degree of uncertainty that attached to any proportion. In the national survey of blindness in Bangladesh the 95% confidence interval for the estimate of the number of blinds ranged from 524.000 to 725.800 blind people. The interpretation of 95% confidence intervals is that in that 95% of the time lies the true value for the population. However, there is 5% of risk that the true population lies outside the interval. Confidence interval also depends on the number of sample size. Estimation of 95% confidence interval will be wide on small study and reflect imprecise measures of the burden of disease. At the times when the 95% confidence interval does not include the null value, it usually reflects a result that is statistically significant.[1,4,5]

INTERPRETING RESULTS

Studies are conducted to find out the true association between the disease and associated exposure. Before drawing any conclusions, we ought to make sure that the result were not result of chance, bias, or confounding. [1,2]

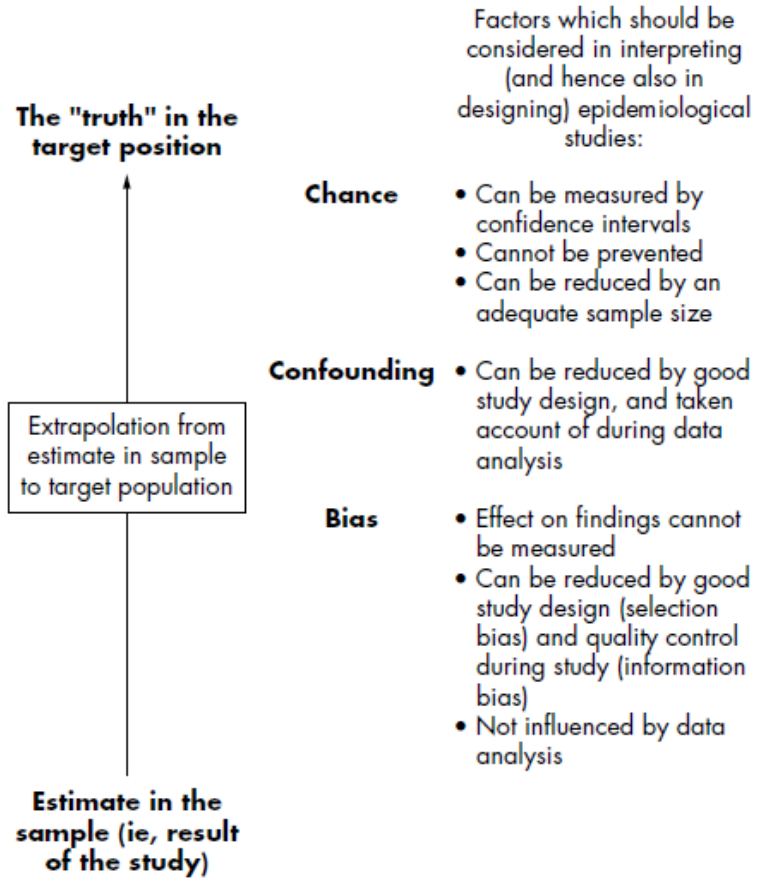


Figure 2. Schematic presentation of how chance, bias, and confounding can mislead the true finding of the study[1]

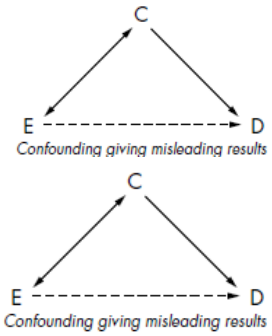
Chance

Sampling variation caused by random error is called chance. Due to chance, different random subject of the population will result in distinct result. During the sampling process, some samples might show estimation higher than the true value and so do the opposite. The magnitude of chance or random error depends on the size of the sample. The larger the sample, the more accurate the estimation would be and would more likely to show the true proportion of the population. [1,2,4,7]

Confounding

Epidemiology study is concerned with establishing association between exposure and disease, but all associations are potentially influenced by the effects of confounding. Confounding happens when the association between an exposure and outcome is distorted by the presence of a third factor. To be a confounder, a variable must be associated with the exposure and also independently associated with the outcome, but not be the casual pathway to the disease. Confounding can be controlled through three approach in the design of the epidemiological study: Randomisation, restriction, and matching. It can also be controlled in the analysis by using stratification and statistical modelling. [1,2,4,7]

A study was undertaken in Australia to assess whether ultraviolet radiation (exposure) was associated with cataract (disease).7 The authors reported a statistically significant positive correlation and argued for the avoidance of sunlight as a preventive measure. However, less wealthy people were more likely to be exposed to sunlight, and poverty is independently related to the prevalence of cataract. The association between sunlight and cataract may, therefore, have been confounded by poverty. If everyone in the study had the same status with respect to the confounder (for example, all came from the same socioeconomic group) then the factor could no longer exert a confounding influence. [1,10]



Bias

Epidemiological study might be influenced by a non-random error which is called bias. Bias, or systematic error, is the deviation of results from the truth. Systematic error leads to incorrect estimation of the exposure effect on the outcome of interest. There are two major types of bias: selection bias and information bias. Selection bias is caused by systematic differences in characteristics between the participants of the study and those who were eligible but did not take part, or those who dropped out during the study. Information or measurement bias occurred by inaccuracy in the measurement of exposure or disease that resulted in different quality of information or classification of disease. For example, Selection bias could arise in a study to find the association between physical disability and age-related macular degeneration (AMD). If people who are both physically disabled and have AMD are preferentially included in the study (for example, are more likely to be found at home). This could produce a spurious association between physical disability and AMD. Statistic could not solve the problem of bias. In contrast with the random error, systematic error does not depend on the sample size. The degree of the result deviation caused by bias cannot be measured but can be minimized by a good study design and the quality of data collection. [1,2,4,7,11]

Causation

When the effect of confounding, chance and bias are controlled, the causation can be enforced for the association between exposure and outcome. To prove the causality, Bradford-Hill criteria must be fulfilled. The Bradford-Hill criteria consist of temporality, strength of evidence, coherence, experimental evidence, plausibility, dose response relation, specificity, consistency, and analogy. [1,2,4,7]

STUDY DESIGN

Study designs used in the epidemiological study can be divided as descriptive or analytical study (cross sectional, cohort, case control) and intervention study (randomised control trial). In the Descriptive or analytical study, the investigator observes the events without any manipulation. On the other hand, during the interventional study, the investigator manipulates the exposure to access the effect on the outcome.[1,2]

Study design	Type of information collected	How this information can be used
Descriptive and analytical studies	• Burden of disease (prevalence and incidence) • Distribution of disease, with • identification of high risk groups • Risk factors for disease (aetiology)	Policy Advocacy Priority setting Planning and resource allocation Target setting Evaluation Impact assessment
Intervention studies	• Effectiveness of preventive measures • Effectiveness of treatments	Health promotion Preventive measures Therapeutic interventions
Meta-analysis and systematic reviews	• Summary of evidence of effectiveness of preventive measures • Summary of evidence of effectiveness of treatments	Policy Guidelines Planning

Figure 3. Types and use of epidemiological study[1]

Cross Sectional Study

Cross sectional study is a simple form of epidemiological study in form of a survey where the data about exposure and/or outcome is gathered from the subject at one point in time. The measure of the outcome obtained from a cross sectional study is prevalence. Cross sectional study is usually done to observe exposure and outcome of a sample that reflect the population. [1,2,12]

The result of the study can be beneficial for the public health planners and administrators to allocate the health care resources in the community. It can also be used to monitor intervention or disease trends to see the impact on the prevalence of the outcome. Cross sectional study can be quickly performed with less budget economically than other types of study. There are two types of cross-sectional study: descriptive or analytical. In the descriptive study, only the information about the exposure and the outcome is gathered. While in the analytic cross-sectional study, the association between the exposure and the outcome is measured. However, we must bear in mind that association does not equal causation. This is due to the fact that both the exposure and the outcome are measured at the same point of time. [1,4,7]

Study Illustration:

Bourne et al conducted a cross sectional survey in Bangkok to estimate the burden of glaucoma. They sampled 701 people aged >50 years and examined them for glaucoma. The estimated prevalence of glaucoma was 3.8% but was higher in women (6.0%) than men (3.2%), giving a prevalence ratio of 1.86 (95% CI: 0.9 to 4.0). Since the 95% confidence interval included the null value, the "truth" may be that there is no sex difference in glaucoma prevalence. [12]

Cohort Study

Cohort study measures the predictors of disease incidence. Cohort study take individuals free from the disease of interest and classify them into ''exposed'' or ''unexposed'' group with respect to the risk factor desired. This study allows us to examine a relatively rare exposure. The subjects are followed over time and the number of incident cases of the disease is recorded. The incidence is then calculated for the exposed and unexposed group and the incidence ratio is estimated. Participants of cohort studies can be enrolled at the beginning only (close cohort study) or can be enrolled over time (open cohort study). Cohort studies can be referred as prospective study because they look forward from exposure to disease. Major advantage of this study is that we are possible to measure several disease outcomes. However, loss to follow up can happen and lead to selection bias. Cohort studies usually estimate the risk or rate of disease in different exposure group. [1,2,4,7]

The example provided illustrates the problem of loss to follow up, which is often encountered by cohort studies. Another problem is competing risks which happened when cohort subjects die or develop other diseases. True cumulative incidence is then underestimated.

Study Illustration:

Bowman et al conducted a closed cohort study in the Gambia to examine the association between trichiasis (exposure) and corneal visual loss (outcome). In the beginning, 639 people with trachomatous lid scarring but without corneal visual loss were identified. Subject from the exposed group had trichiasis while others did not (unexposed group). After 12 years, 326 of the initial cohort were retraced. Of the 26 people with trichiasis at baseline (exposed group) two had developed corneal visual loss (CI: 2/26 or 7.7% over 12 years), compared to six of the 295 people with trachomatous lid scarring without trichiasis (unexposed group) (CI: 6/295 or 2.0% over 12 years). The cumulative incidence rate comparing the exposed and unexposed groups was 3.78 (95% CI: 0.80 to 17.81). It shows that the 12 year risk of developing corneal visual loss was almost four times higher in people with trichiasis at baseline compared to those without. However, only 326 of the initial cohort of 639 were traced, and it was not known what happened to the remaining 313 people in terms corneal visual loss.[13]

This problem can be overcome by using person time analyses and calculating incidence rates. The main drawback is that most disease examined are rare, we either need a large sample or long follow up to accumulate enough cases to have enough power to have meaningful outcome. Due to this, cohort studies are expensive and time consuming. [1,2,7]

Case Control Study

Case-control studies are used to study the etiology of the disease. Case-control studies are conducted by identification by a group of people who have the disease of interest (cases) as well as people without the disease (controls). The controls should be selected from the same population and matched so that they represent the exposure distribution in the source population. The ratio of cases to controls can be one to one or more than one per case to increase the statistical power of the study. The prevalence of exposure is then measured and compared in the two groups. [1,2,4,7]

Study Illustration:

Minassian et al conducted a hospital-based case control study to investigate the association between childbearing and risk of cataract in young women. Cases were women aged 35–45 with bilateral 'senile' cataract attending an eye hospital in central India. Controls were women of the same age with clear lenses from the same hospital. Cases and controls were interviewed about their history of pregnancy and childbirth. The number of live births was statistically significantly higher in cases than in controls and a dose-response relation between childbearing and risk of cataract was apparent. [14]

The odds of exposure in cases (number exposed versus unexposed) is compared to the odds of exposure in controls, to assess the exposure-disease association. Because the ratio of cases was determined by the researchers, case-control cannot be used to estimate the burden of disease. Case-control studies are relatively quick and cheap to carry out. They can also be used to investigate rare diseases and multiple exposures. It is usually the optimal study design to study disease outbreaks. Recall bias and information bias however might happen. There is also the potential for selection bias, particularly in the selection of the controls. [1, ,2,4]

Randomised Controlled Trials

A randomised controlled trial (RCT) is an intervention study. Researchers starts with two (or more) groups of participants which then classified as the intervention group and the control or comparison group. RCTs are used to assess the benefit therapeutic measures such as new drug or treatment and preventive measure such as health education. People were selected and randomised to receive either the intervention (treatment under investigation) or the control (placebo or standard treatment). In order to make the intervention and control groups as similar as possible to important confounders (both known and unknown), randomisation should be done. Both groups are monitored over time for the defined outcomes and this allowed the relative risk to be calculated. [1,2,4,7]

Study Illustration:

Kahook et al conducted a multicentre, pararel-group RCT in New Jersey, to provide novel pharmacotherapies that evaluate efficacy and long-term safety of IOP lowering drug. In the study 756 eligible patients with elevated IOP were randomised to received netarsudil 0.02% once a day (q.d), netarsudil 0.02% twice a day (b.i.d), or timolol 0.5% b.i.d for 12 months. Both the participants and investigators were blinded to the treatment group status. The primary outcome was evaluated using mean IOP from week 2 to month 12. Mean IOP decreased from a baseline IOP of 22.5-22.6 mm Hg to 17.9-18.8 mm Hg, 17.2-18.0 mm Hg, and 17.5-17.9 mm Hg for netarsudil q.d., netarsudil b.i.d., and timolol, respectively, over 12 months. This result showed the persistence of ocular hypotensive efficacy of netarsudil.[15]

Data analysis should only take account of the treatment group to which they were assigned (intent to treat analyses) to avoid breaking the randomisation. This study is usually blinded so the participants in an

RCT often will not know whether they are receiving the intervention or the control. Ideally the investigator will also be unaware of their treatment status (double blinded/ masked). Blinding helps to reduce information bias. Compared to other types of study, RCTs are often held up as the gold standard of study designs. The result of RCT are reliable because the effects of confounding, selection bias, and information bias have been minimised. However, ethical considerations are more important in interventional studies compared to other studies. In designing RCTs there must therefore be a state of equipoise where the potential benefits of a new treatment are equally and oppositely outweighed by the potential harm. RCTs are expensive, take a long time to generate results.[1,2,4]

CONCLUSION

Every study started with a research question which can be answered by conducting studies on a sample of people. Before starting a research, the purpose of the study must be clear as well as the study design, methodology, and research analysis. Good epidemiological skills are needed for every ophthalmologist to read scientific articles critically and when conducting their own research.

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