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Research Strategies and Design

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Abstratct

A research strategy is a step by step plan of action that gives direction to your thoughts and efforts, enabling you to conduct research systematically and on schedule to produce quality results and detailed reporting. The research design refers to the overall strategy that you choose to integrate the different components of the study in a coherent and logical way, thereby ensuring you will effectively address the research problem; it constitutes the blueprint for the collection, measurement, and analysis of data. This article discuss the principles, methods, and strategies useful in the planning, design and evaluation of research.

Introduction

The selection of a research strategy is the core of a research design and is probably the single most important decision the investigator has to make. Therefore, the development of a research strategy is the main focus of this manual. Essential components of the research design and the scientific basis for these will be discussed in the following chapters.

The research strategy must include the definition of the population of interest, the definition of variables (characteristics of the individuals in this population), their status and relationships to one another. In testing a hypothesis, for example, an investigator may be able to assign the independence or exposure variable to a number of subjects in the study, and withhold it from others (controls) while controlling for other extraneous or confounding variables. This strategy constitutes an experiment and covers hypothesis testing through intervention.

Another investigator may choose to compare people with and without exposure to a factor, and to analyse the incidence of a disease in these groups to find out if the disease is related to the

exposure. This constitutes an analytical study, of which there are many varieties; this type of study also incorporates the testing of hypotheses. Still another investigator may simply describe the distribution of a phenomenon or the outcome of a programme. This constitutes a descriptive study with no intervention and no prior hypothesis.

In all of the above situations, observations are made on a group of people, and inferences are made about relationships or associations of various 'exposures' to 'outcomes'. The inferences reached are always subject to uncertainty due to the variation of characteristics across the population. The accuracy of the inference depends, therefore, on the accuracy of the information collected and on the representativeness of the subjects observed to the larger group of subjects in the population, as well as on the accuracy of the statistical methods used to draw the inference. In order to develop a good research strategy, we need to understand the nature of these 'errors' or 'variations' and the methods available to measure the errors.

Errors in the inference

Two common sources of error that need to be controlled result from problems with 'reliability' and 'validity'. Our inference should have high reliability (if the observations are repeated under similar conditions, the inferences should be similar) and high validity (the inference should be a reflection of the true nature of the relationship). The reliability and validity of inferences depend on the reliability and validity of the measurements (are we measuring the right thing, and with accuracy?) as well as the reliability and validity of the samples chosen (have we got a true representation of the population that we are drawing inferences from?). The reliability of a sample is achieved by selecting a large sample, and the validity is achieved by ensuring the sample selection is unbiased. In statistical terms, reliability is measured using 'random error' and validity by 'bias'.

Reliability

Reliability of measurements

If repeated measurements of a characteristic in the same individual under identical conditions produce similar results, we would say that the measurement is reliable. If independent, repeated observations are taken and the probability distribution is identified, the standard deviation of the observations provide a measure of reliability. If the measurement has high reliability, the standard deviation should be smaller. One way to increase the reliability is to take the average of a number of observations (the average having a smaller standard deviation – known as standard error of the mean [sem] – than the standard deviation of the individual observations).

Reliability of study

A result is said to be reliable if the same result is obtained when the study is repeated under the same conditions. The natural variability in observations among individuals in the population is commonly known as random error. For example, if one is measuring the systolic blood pressure (SBP) of individuals, it has been observed that the measurements in large groups of people would follow a 'normal' distribution, so that the standard deviation of SBP is used as a measure of random error in SBP measurements. Clearly, if the standard deviation is small, repeated studies

from this population are bound to come up with similar results. If the standard deviation is large, different samples from the same population will tend to differ substantially. Since we are often dealing with summary measures from samples that have standard deviations inversely proportional to the square root of the sample size, increasing the sample size increases the reliability of these measures.

Validity

A measurement is said to be valid if it measures what it is supposed to. If a measurement is not valid, we say it is 'biased'. Bias is a systematic error (as opposed to a random error) that skews the observation to one side of the truth. Thus, if we use a scale that is not calibrated to zero, the weights we obtain using this scale will be biased. Similarly, if a sample is biased (for example, more males in the sample than the proportion of males in the population, or selecting cases from a hospital and controls from the general community in a case-control study), the results tend to be biased. Since it is often difficult to correct for biases once the data have been collected, it is always advisable to avoid bias when designing a study

Experimental versus observational strategies

Although an experiment is an important step in establishing causality, it is often neither feasible nor ethical to subject human beings to risk factors in etiological studies. Instead, epidemiologists make use of 'natural experiments', when available, or they resort (more frequently) to analytical observational studies or quasi-experiments. However, there is one area of epidemiology in which experimental strategies are used extensively: this is the area of clinical and field trials for testing new drugs or intervention programmes.

Advantages of the experimental approach include the following:

- The ability to manipulate or assign independent variables. This is by far the most distinct advantage of experimental strategies. It is readily illustrated by clinical trials, described in Chapter 4, in which cases of a specific disease are deliberately assigned (in random order, or by matching) to treatment and to control groups. For example, in an evaluation of the efficiency of intrauterine devices, women of a certain age and with certain other characteristics may be assigned at random or in matched pairs to physicians and nurses. A criterion for evaluation, such as the frequency of complications, is compared in the two groups. It may also be possible to manipulate the degree of exposure or the dose of the treatment.
- The ability to randomize subjects to experimental and control groups. Randomization makes it more likely that the distribution of some extraneous variables will be equalized between the two groups, although it is still necessary in the analysis to compare the distribution of these variables to ensure the validity of inferences drawn from the study. It is also possible in experiments (and also in some observational studies) to use matching in conjunction with randomization. In addition, randomization provides a basis for the calculation of appropriate probabilities of error in the inference.

- The ability to control confounding and eliminate sources of spurious association. Most of the other factors that interfere with the association under study can more easily be controlled in experiments (especially in animals) than in observational studies.
- The ability to ensure temporality. Determining which variables precede and which are the consequences of the intervention is more feasible in experimental studies than it is in some analytical studies, particularly those of the case-control and cohort designs.
- The ability to replicate findings. Experiments are often more replicable than observational studies. Replication satisfies the consistency requirement in causation. In practice, however, few clinical trials are exactly replicated.

All in all, the evidence for causal relationship is more compelling if it comes from a carefully executed experimental study, because selection factors that inadvertently bias observational studies can virtually be eliminated by the process of randomization. However, other sources of bias are not automatically controlled by randomization.

The limitations of the experimental approach are sometimes overlooked, as the impressive advantages of experiments have led some people to reject evidence for causation if it is not based on experiments. If we were limited to the experimental approach, however, we would have to abandon most of the evidence upon which significant advances in public health have been made. Experiments also have the following limitations:

- Lack of reality. In most human situations, it is impossible to randomize all risk factors except those under examination. Observational methods deal with more realistic situations.
- Difficulties in extrapolation. Results of experiments in animal models, which are rigorously controlled, cannot readily be extrapolated to human populations.
- Ethical problems. In human experimentation, people are either deliberately exposed to risk factors (in etiological studies) or treatment is deliberately withheld from cases (intervention trials). It is equally unethical to test the efficiency or side-effects of new treatments without critical evaluation in a small group of human subjects. (See also Chapter 10.)
- Difficulties in manipulating the independent variable. It is virtually impossible, for instance, to assign smoking habits at random to the experimental and control groups.
- Non-representativeness of samples. Many experiments are carried out on captive populations or volunteers, who are not necessarily representative of the population at large. Experiments in hospitals (where the experimental approach is most feasible and is frequently used) suffer from several sources of selection bias.

Descriptive studies

Definition

When an epidemiological study is not structured formally as an analytical or experimental study, i.e. when it is not aimed specifically to test a hypothesis, it is called a descriptive study, and belongs to the observational category of studies. The wealth of material obtained in most descriptive studies allows the generation of hypotheses, which can then be tested by analytical or experimental designs. A survey, for example a prevalence survey, could also be defined as a descriptive study, as it covers the elements of descriptive study.

Conduct of descriptive studies

Descriptive studies entail the collection, analysis and interpretation of data. Both qualitative and quantitative techniques may be used, including questionnaires, interviews, observations of participants, and service statistics, as well as documents describing communities, groups, situations, programmes and other individual or ecological units. The distinctive feature of this approach is that its primary concern is with description rather than with the testing of hypotheses or proving causality. The descriptive approach may, nevertheless, be integrated with or supplement methods that address these issues, and may add considerably to the information base.

Kinds of descriptive studies

Case series

This kind of study is based on reports of a series of cases of a specific condition, or a series of treated cases, with no specifically allocated control group. These represent the numerator of disease occurrence, and should not be used to estimate risks.

In an attempt to make such series more impressive, clinicians may calculate proportional distribution, which consists simply of percentages of the total number of cases that belong to a specific category of age, sex, ethnic group or other characteristic. These numbers are not rates, because the denominator still represents the cases and not the population at risk.

Community diagnosis or needs assessment

This kind of study entails collection of data on existing health problems, programmes, achievements, constraints, social stratification, leadership patterns, focal points of resistance or high prevalence, or groups at highest risk. Its purpose is to identify existing needs and to provide baseline data for the design of further studies or action.

Epidemiological description of disease occurrence

This common use of the descriptive approach entails the collection of data on the occurrence and distribution of disease in populations according to specific characteristics of individuals (e.g. age, sex, education, smoking habits, religion, occupation, social class, marital status, health status, personality), place (rural/urban, local, subnational, national, international) and time (epidemic, seasonal, cyclic, secular). A description may also be given of familial characteristics such as birth order, parity, family size, maternal age, birth interval or family type.

Descriptive cross-sectional studies or community (population) surveys

Cross-sectional studies entail the collection of data on, as the term implies, a cross-section of the population, which may comprise the whole population or a proportion (sample) of it. Many cross-sectional studies do not aim at testing a hypothesis about an association, and are thus descriptive. They provide a prevalence rate at a particular point in time (point prevalence) or over a period of time (period prevalence). The study population at risk is the denominator for these prevalence rates.

Included in this type of descriptive study are surveys in which the distribution of a disease, disability, pathological condition, immunological condition, nutritional status, fitness, or intelligence, etc., is assessed. This design may also be used in health systems research to describe 'prevalence' by certain characteristics – pattern of health service utilization and compliance – or in opinion surveys. A common procedure used in family planning and in other services is the KAP survey (survey of knowledge, attitudes and practice).

Ecological descriptive studies

When the unit of observation is an aggregate (e.g. family, clan or school) or an ecological unit (a village, town or country) the study becomes an ecological descriptive study.

As mentioned earlier, hypothesis testing is not generally an objective of the descriptive study. However, in some of the above studies (cross-sectional surveys, ecological studies) some hypothesis testing may be appropriate. Moreover, description of the data is also an integral part of the analytical study.

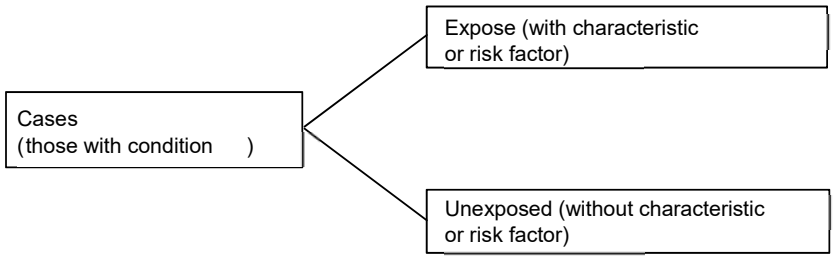
Analytical strategies in epidemiology

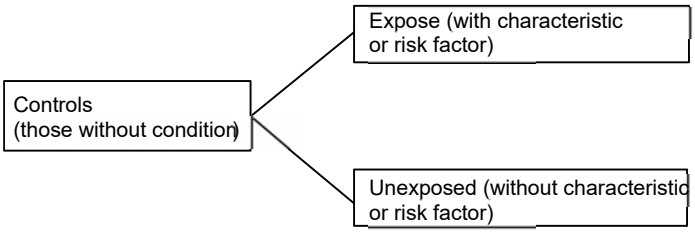
Observational studies, where establishing a relationship (association) between a 'risk factor' (etiological agent) and an outcome (disease) is the primary goal, are termed analytical. In this type of study, hypothesis testing is the primary tool of inference. The basic approach in analytical studies is to develop a specific, testable hypothesis, and to design the study to control any extraneous variables that could potentially confound the observed relationship between the studied factor and the disease. The approach varies according to the specific strategy used.

Case-control studies

The simplest and most commonly used analytical strategy in epidemiology involves the case-control study. It is designed primarily to establish the causes of diseases by investigating associations between exposure to a risk factor and the occurrence of disease. The design is relatively simple, except that it is backward-looking (retrospective) based on the exposure histories of cases and controls. With this type of study, one investigates an association by contrasting the exposure of a series of cases of the specified disease with the exposure pattern of carefully selected control groups free from that particular disease (Figure 2.1). Data are analysed to determine whether exposure was different for cases and for controls. The risk factor is something that happened or began in the past, presumably before disease onset, e.g. smoking, or a previous infection or medication. Information about the exposure is obtained by taking a history and/or from records. Occasionally, the suspected factor or attribute is a permanent one, such as blood group, which can be ascertained by clinical or laboratory investigation. A higher frequency of the attribute or risk factor among

FIGURE 2.1 DESIGN OF A CASE-CONTROL STUDY





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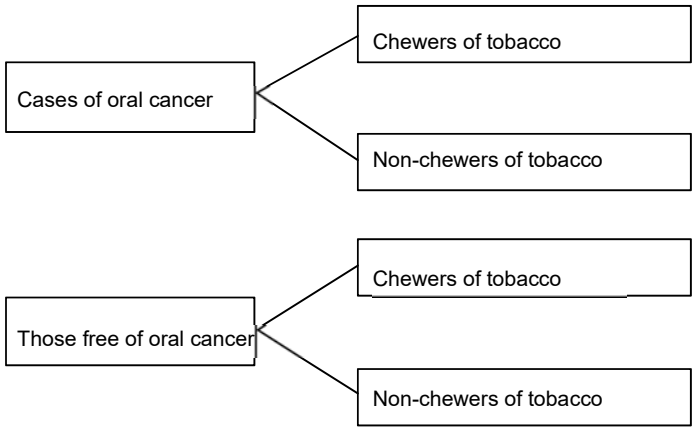


cases than among controls is indicative of its association with the disease/condition – an association that may be of etiological significance. In other words, if a greater proportion of cases than controls give a history of exposure, or have records or indications of exposure in the past, the factor or attribute can be suspected of being a causative factor.

Selection of cases

What constitutes a case in the study should be clearly defined with regard to the histological type and other specific characteristics of the disease, such as date of diagnosis, geographical location, etc. Cases that do not fit these criteria should be excluded from the study. This design is particularly efficient for rare diseases, because all cases that fit the study criteria in a particular setting within a specific period are usually included. This allows for a reasonable number of cases to be included in the study without waiting for the occurrence of new cases of the disease, which might take a long time.

For reasons of convenience and completeness of case records, the cases identified for case-control studies are often those from a hospital setting, from physicians' private practices, or from disease registries. Newly diagnosed cases within a specific period (incident cases) are preferred to prevalent cases, since such a choice may eliminate the possibility that long-term survivors of a disease were exposed to the investigated risk factor after the onset of the disease.

The selection of cases should be such that the study results are reliable and valid. For these reasons, the following guidelines should be used when selecting cases in a case-control study:

a. The criteria for inclusion in the study (what constitutes a case) and criteria for exclusion from the study must be clearly specified; this will improve the validity of the results;

b. The sources of cases may be:

- all cases admitted to or discharged from a hospital, clinic, or private practice within a specified period;
- all cases reported or diagnosed during a survey or surveillance programme within a specified period;
- incident or newly diagnosed cases;
- incident cases in an ongoing cohort study or in an occupational cohort (sometimes called a nested casecontrol study);
- deaths with a record of causes of death, and fulfilling other criteria for the study;
- case units with a prescribed health outcome;

c. If the number of cases is too large, a probability sample may be used;

d. Cases selected for the study should be representative of all cases of the disease under consideration.

Selection of controls

It is crucial to set up one or more control groups of people who do not have the specified disease or condition in order to obtain estimates of the frequency of the attribute or risk factor for comparison with its frequency among cases. This is the most important aspect of the case-control study, as biases in the selection of controls may invalidate the study results, and bias in the selection of controls is often the greatest cause for concern when analysing data from case-control studies.

a. The sources of comparison groups may be:

- a probability sample of a defined population, if the cases are drawn from that defined population;
- a sample of patients admitted to, or attending the same institution as the cases;
- a sample of relatives or associates of the cases (neighbourhood controls);
- a group of persons selected from the same source population as the cases, and matched with the cases for potentially confounding variables;

- on other risk factors (other than the one under consideration);

b. The selection of controls may involve matching on other risk factors:

• Matching means that controls are selected such that cases and controls have the same (or very similar) characteristics other than the disease and the risk factor being investigated. The characteristics are those that would confound the effect of the putative risk factor,

i.e. these characteristics are known to have an association with the disease, and may be associated with the risk factor being studied. The purpose of the matching is to ensure comparability of these characteristics for the two groups, so that any observed association between the putative risk factor and the disease is not affected by differential distribution of these other characteristics. It is common to match for age, sex, race and socioeconomic status in case-control studies on diseases, as we know all of these factors affect the incidence of most of the diseases. Matching may be done on an individual basis (one-to-one matching) or on a group basis (frequency matching). Individual matching is preferable, because of the ease of analysis accounting for matching. The disadvantages of matching include a loss of precision and overmatching. Also, once a matched design is used, the matching variable is eliminated from consideration, and therefore it cannot be investigated for etiological association with the disease. For example, if we matched for marital status in a study of breast cancer, we would not know whether single or married women had different risks for breast cancer. Many epidemiologists prefer to conduct studies without matching, and use statistical methods to adjust for possible confounding during analysis, because of the increased precision and the ability to investigate any possible interaction effects. The use of unmatched controls, obtained through random sampling, allows
greater flexibility in studying various interactions. What is most important is that information on potential confounding factors should be collected in the study, so that these can be adjusted in the analysis.

c. The number of control groups may vary. It is sometimes desirable to have more than one control group, representing a variety of disease conditions other than that under study and/or non-hospitalized groups. Use of multiple controls confers three advantages:

- If the frequency of the attribute or risk factor does not differ from one control group to another, but is consistently lower than that among the cases, this increases the internal consistency of the association;
- If a control group is taken of patients with another disease, which is independently associated with the risk factor, the difference in the frequency of the factor between cases and controls may well be masked. In such a case, the use of another control group will save the research project;
- Multiple controls provide a check on bias.

The impact of poorly chosen controls on the conclusions of a case-control study is commonly exemplified by Pearl's study in 1929. Pearl compared 816 malignancies identified among 7500 autopsied cases at the Johns Hopkins Hospital in Baltimore, Maryland, USA with 816 non-malignant autopsied cases matched at death for age, sex, race and date of death. Lesions of active tuberculosis were found in 6.6% of cases and in 16.3% of controls, which led to the conclusion that there was antagonism between tuberculosis and cancer. This finding could not be corroborated in animal experiments. One explanation for Pearl's findings is that his control

group inadvertently included many individuals who had died of tuberculosis, because tuberculosis patients were more frequently autopsied than were patients with other causes of death, and were thus unrepresentative of the general population of deaths.

Collection of data on exposure and other factors

Often data are collected through interviews, questionnaires and/ or examination of records. Occasionally, clinical and laboratory examinations are carried out, but often this is not possible, especially if the 'cases' include past cases which may also include some deaths. The following precautions should be taken when deciding on the datacollection strategy:

- observation should be objective, or, if obtained by survey methods, well standardized;
- the investigator or interviewer should not know whether a subject is in the case or control group (blinding);
- the same procedures, e.g. interview and setting, should be used for all groups.

Multifactorial case-control studies

The common form of case-control study addresses one main factor or attribute at a time. It is possible, however, to investigate several exposure factors in the same study. For example, in a study in three states in the USA with a population of 13 million, all mothers of leukaemic children of 1-4 years old (diagnosed in 1959-67) were interviewed. As controls, a sample of 13 000 other women was taken. Four factors were considered, two preconceptional (preconceptional radiation and previous reproductive wastage) and two post-conceptional (in utero irradiation and viral infection during pregnancy). Analysis showed that each factor was related to leukaemia in their children (Gibson et al.,1968). Further analysis was conducted for combinations of factors, where the estimated relative risk in the absence of any of the four factors was made equal to 1.0, as shown in Table 2.1.

It is apparent that the effect was the greatest among women with all four factors, and that there is synergism between the factors.

Advantages of case-control studies

The following are examples of the advantages of case-control studies:

- feasible when the disease being studied occurs only rarely,
  e.g. cancer of a specific organ;
- relatively efficient, requiring a smaller sample than a cohort study;
- little problem with attrition, as when follow-up requires periodic investigations and some subjects refuse to continue to cooperate;
- sometimes they are the earliest practical observational strategy for determining an association (e.g. use of diethylstilbesterol and clear-cell adenocarcinoma of the vagina in daughters).

Enhancement of the validity of case-control studies

Ways in which one can increase the validity of a study include ensuring that:

- the cases are representative of all cases in a particular setting;
- the controls are similar to cases with respect to risk factors other than the study factor;
- multiple controls are used with consistent results;
- cases and controls are truly selected independently of exposure status;
- the sources of bias are mitigated, or at least shown not to have affected the results. (A common example is the British study of smoking and lung cancer by Doll and Hill (1952). After the cases and controls had been interviewed, it was discovered that some of the cases had been wrongly diagnosed as cancer. Reanalysis showed the persistence of the association and indicated that, in the study, the fact of being told that they had lung cancer did not bias the respondents with regard to the history they gave of smoking);
- repeated studies in different settings and by different investigators confirm each other (for example, the association between smoking and lung cancer has been reported by over 25 investigators from ten countries);
- it is possible to demonstrate a dose-response or gradient relationship (for example, several case-control studies showed that the number of cigarettes smoked per day was related to the risk of lung cancer);
- a hybrid design of case-control study nested in a cohort study with a defined population is used; this is a most powerful strategy.

Disadvantages and biases of case-control studies

The following are some of the problems associated with casecontrol studies:

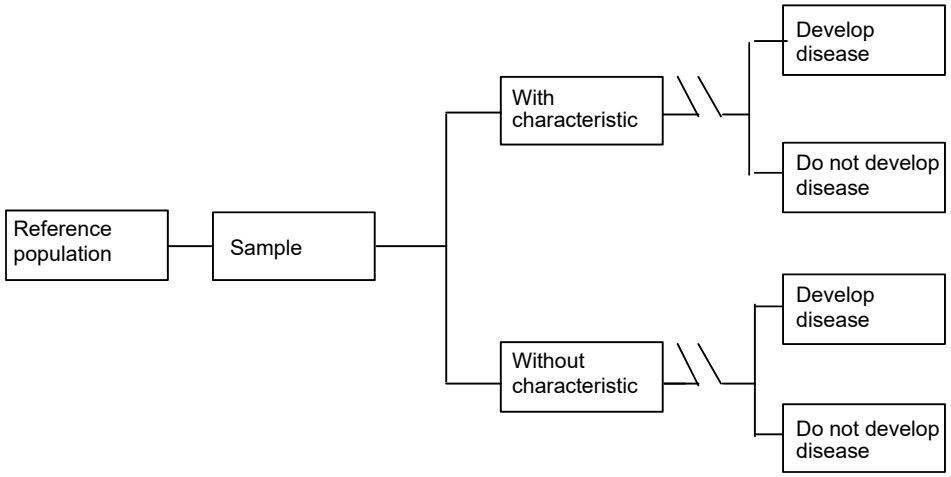
- the absence of epidemiological denominators (population at risk) makes the calculation of incidence rates, and hence of attributable risks, impossible;
- temporality is a serious problem in many case-control studies where it is not possible to determine whether the attribute led to the disease/condition, or vice versa;
- there is a great risk of bias in the selection of cases and controls. This is particularly serious when a single control group is related to the risk factor under investigation;
- it may be very difficult or impossible to obtain information on exposure if the recall period is long;
- selective survival, which operates in case-control studies, may bias the comparison; there is no way of ascertaining whether the exposure was the same for those who died and those who survived;
- because most case-control studies are performed in hospitals, they are liable to Berkson's fallacy, or the effect of differing admission policies and rates;
- measurement bias may exist, including selective recall and misclassification (putting cases in the control group, or vice versa); there is also the possibility of the Hawthorne effect: with repeated interviews, respondents may be influenced by being under study;

- case-control studies are incapable of disclosing other conditions related to the risk factor: for example, in a study of the side-effects of oral contraceptives, one has to know their side-effects before a case-control design can be set up.

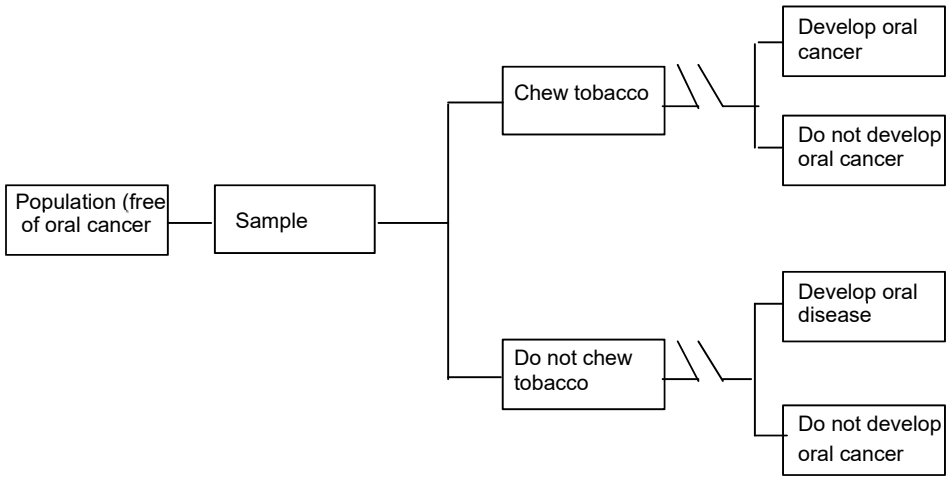
Prospective cohort studies

The common strategy of cohort studies is to start with a reference population (or a representative sample thereof), some of whom have certain characteristics or attributes relevant to the study (exposed group), with others who do not have those characteristics (unexposed group). Both groups should, at the outset of the study, be free from the condition or conditions under consideration. Both groups are then observed over a specified period to find out the risk each group has of developing the condition(s) of interest. This is illustrated diagrammatically in Figure 2.2.

FIGURE 2.2 DESIGN OF A COHORT (PROSPECTIVE) STUDY



Example



Design features

a. Selection of cohort:

- a community cohort of specific age and sex;
- an exposure cohort, e.g. radiologists, smokers, users of oral contraceptives;
- a birth cohort, e.g. school entrants;
- an occupational cohort, e.g. miners, military personnel;
- a marriage cohort;
- a diagnosed or treated cohort, e.g. cases treated with radiotherapy, surgery, hormonal treatment.

The usual procedure is to locate or identify the cohort, which may be a total population in an area or sample thereof. b. Data to be collected:

- data on the exposure of interest to the study hypotheses;
- data on the outcome of interest to the study hypotheses;
- characteristics of the cohort that might confound the association under study.

c. Methods of data collection

Several methods are used to obtain the above data, which should be on a longitudinal basis. These methods include:

- interview surveys with follow-up procedures;
- medical records monitored over time;
- medical examinations and laboratory testing;
- record linkage of sets with exposure data and sets with outcome data, e.g. work history data in underground mines with mortality data from national mortality files.

In a conventional cohort study, an initial cross-sectional study is often performed to exclude persons with the outcome of interest (disease) and to identify the cohort that is free from the disease.

Measures of frequency

Two methods are commonly used in cohort studies to measure the incidence of the disease (condition) under investigation: a. Cumulative incidence

This index of disease frequency is based on the total population at risk which was, at entry to the study, free of the disease under investigation. The incidence of the disease is calculated for each stratum of exposure to the risk factor, and is the ratio of the number of new cases or events in a specified period of observation, to the total population at risk during that period.

This incidence measure provides an estimate of the probability or risk of developing disease among all members of the group who were included in the study at its initiation, and were at risk of disease. Because cumulating all new cases in the total population at risk derives the measure, the term 'cumulative incidence' has been applied. Cumulative incidence is a proportion, not a rate, and can vary from 0 to 1, that is, no less than 0% and no more than 100% of the population at risk can acquire the disease.

This measure of disease frequency is calculated as if all units or individuals had the same period of observation, but new cases are no longer at risk once they develop the disease.

b. Incidence density (person-time approach)

This approach is an improvement over the conventional measure of incidence, because it takes into consideration both the number observed and the duration of observation for each individual. Thus, if 30 individuals were observed as follows: 10 for two years, 5 for three years, and 15 for four years, they would contribute (10x2)+(5x3)+(15x4) = 95 person-years of observation, which would become the denominator. The numerator is the number of new cases observed in these groups over the specified period of time. This gives an incidence rate per person-year, called the incidence density. Person-years do not represent the number of persons: 400 person-years of observation could represent 400 persons each observed for one year, or 40 persons each observed for 10 years. Two drawbacks of this measure are that the exact time when the disease occurs often cannot be ascertained, and that the rate of disease development over time is not necessarily constant.

The basic measures of effect used in cohort studies are the relative risk (RR), attributable risk (AR), population attributable risk (PAR), population attributable risk percent (ARP%), and etiologic fraction (EF). These measures will be discussed in detail in Chapter 7.

Advantages of cohort studies

The following are some of the advantages of a cohort study compared with a case-control study:

- Because of the presence of a defined population at risk, cohort studies allow the possibility of measuring directly the relative risk of developing the condition for those who have the characteristic, compared to those who do not, on the basis of incidence measures calculated for each of the groups separately.
- In a cohort study, it is known that the characteristic precedes the development of the disease, since all the subjects are free of disease at the beginning of the study; this allows for a conclusion of cause-effect relationship (a necessary, but not sufficient, condition).

- Because the presence or absence of the risk factor is recorded before the disease occurs, there is no chance of bias being introduced due to awareness of being sick as in encountered in case-control studies.
- There is also less chance of encountering the problem of selective survival or selective recall, although selection bias can still occur because some subjects who contracted the disease will have been eliminated from consideration at the start of the study.
- Cohort studies are capable of identifying other diseases that may be related to the same risk factor.
- Unlike case-control studies, cohort studies provide the possibility of estimating attributable risks, thus indicating the absolute magnitude of disease attributable to the risk factor.
- If a probability sample is taken from the reference population, it is possible to generalize from the sample to the reference population with a known degree of precision.

Disadvantages of cohort studies

The following are some of the disadvantages of cohort studies:

- These studies are long-term and are thus not always feasible; they are relatively inefficient for studying rare conditions.
- They are very costly in time, personnel, space and patient follow-up.
- Sample sizes required for cohort studies are extremely large, especially for infrequent conditions; it is usually difficult to find and manage samples of this size.
- The most serious problem is that of attrition, or loss of people from the sample or control during the course of the study as a result of migration or refusal to continue to participate in the study. Such attrition can affect the validity of the conclusion, if it renders the samples less representative, or if the people who become unavailable are different from those actually followed up. The higher the proportion lost (say beyond 10-15%) the more serious the potential bias.
- There may also be attrition among investigators who may lose interest, leave for another job, or become involved in another project.
- Over a long period, many changes may occur in the environment, among individuals or in the type of intervention, and these may confuse the issue of association and attributable risk.
- Over a long period, study procedures may influence the behaviour of the persons investigated in such a way that the development of the disease may be influenced accordingly (Hawthorne effect). This problem is more likely to occur in studies involving repeated contact with participants, as in studies of diet or the use of contraceptives. The participants may modify their diet or shift to another contraceptive method because of repeated probing. Behavioural changes are also a serious problem in opinion surveys, acceptability studies and psychological investigations, such as studies of the psychological sequelae of sterilization.
- A serious ethical problem may arise when it becomes apparent that the exposed population is manifesting significant disease excess before the follow-up period is completed.

It must be emphasized that, although the cohort study is close to the randomized trial (experiment) in terms of epidemiological power, it may still have problems of validity. Care must be taken to ensure that it satisfies other requirements of epidemiological research, particularly with regard to appropriate sampling, construction of comparison groups, handling of missing data, application of appropriate statistical methods and other prerequisites for a sound research design.

Historical (retrospective) cohort studies

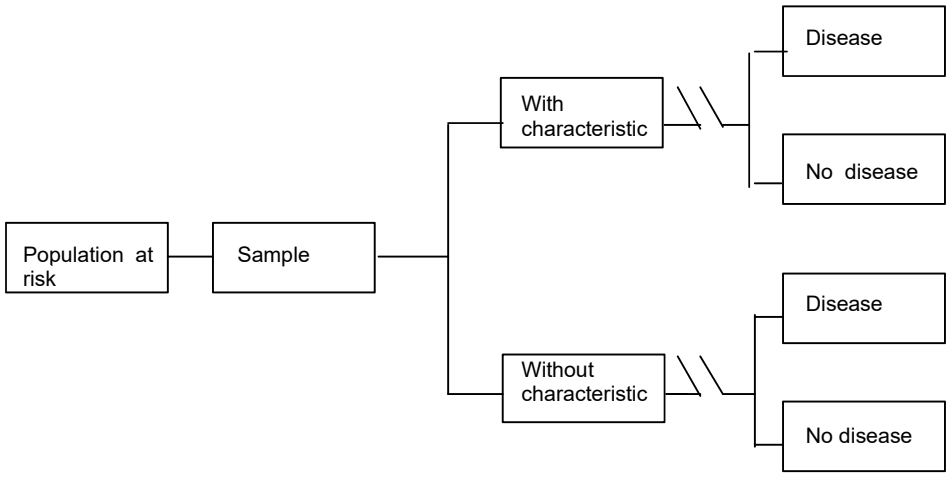
In a prospective cohort study, the investigators or their substitutes are typically present from the beginning to the end of the observation period. However, it is possible to maintain the advantages of the cohort study without the continuous presence of the investigators, or having to wait a long time to collect the necessary data, through the use of a historical or retrospective cohort study. The design of such a study is illustrated in Figure 2.3.

A historical cohort study depends upon the availability of data or records that allow reconstruction of the exposure of cohorts to a suspected risk factor and follow-up of their mortality or morbidity over time. In other words, although the investigator was not present when the exposure was first identified, he reconstructs exposed and unexposed populations from records, and then proceeds as though he had been present throughout the study.

Historically constructed cohorts share several advantages of the prospective cohort. If all requirements are satisfied, a historical cohort may suffer less from the disadvantages of time and expense. Historical cohort studies have, however, the following disadvantages:

- All of the relevant variables may not be available in the original records.
- It may be difficult to ascertain that the study population was free from the condition at the start of the comparison. This problem does not exist if we are concerned with deaths as indicators of disease.

FIGURE 2.3 DESIGN OF A HISTORICAL (RETROSPECTIVE) COHORT STUDY



Investigation begins here and reconstructs the history of exposure and development of disease

Time >

- Attrition problems may be serious due to loss of records, incomplete records, or difficulties in tracing or locating all of the original population for further study.
- These studies require ingenuity in identifying suitable populations and in obtaining reliable information concerning exposure and other relevant factors. Examples of such population groups include members of health insurance plans, military personnel, industrial groups (such as miners), professional groups, members

Prognostic cohort studies

Prognostic cohort studies are a special type of cohort study used to identify factors that might influence the prognosis after a diagnosis or treatment. These follow-up studies have the following features:

- The cohort consists of cases diagnosed at a fixed time, or cases treated at a fixed time by a medical or surgical treatment, rehabilitation procedure, psychological adjustment or vocational adjustment.
- By definition, such cases are not free of a specified disease, as in the case of a conventional cohort study (but are free of the 'outcome of interest').
- The outcome of interest is usually survival, cure, improvement, disability, vocational adjustment, or repeat episode of the illness, etc.

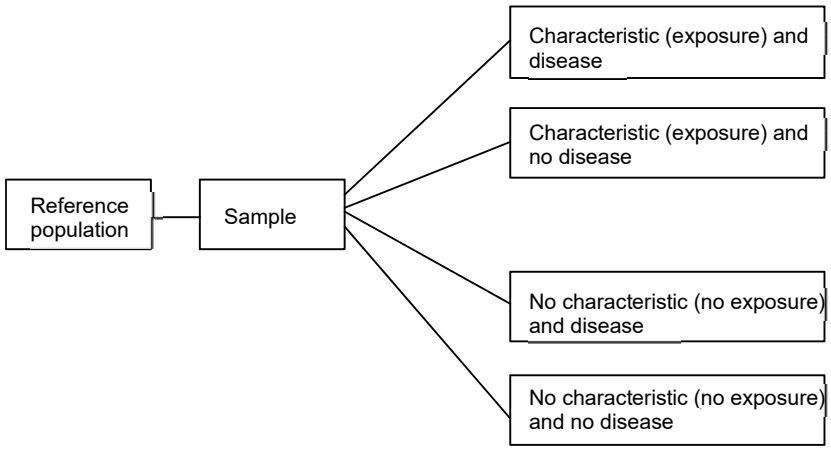
Analytical cross-sectional studies

In an analytical cross-sectional study, the investigator measures exposure and disease simultaneously in a representative sample of the population. By taking a representative sample, it is possible to generalize the results obtained in the sample for the population as a whole. Cross-sectional studies measure the association between the exposure variable and existing disease (prevalence), unlike cohort studies, which measure the rate of developing disease (incidence). Rare diseases, conditions of short duration, or diseases with high case fatality are often not detected by the one-time snapshot of the crosssectional study. Therefore, cross-sectional studies are more appropriate for measuring the relationship between fairly permanent characteristics in individuals and chronic diseases or stable conditions.

Design

Cross-sectional studies are represented in Figure 2.4. They usually start with a reference population, from which a random sample is taken. Data are collected at the same time on the risk factor or characteristic and the condition.

FIGURE 2.4 DESIGN OF A CROSS-SECTIONAL STUDY



Advantages of cross-sectional studies

The following are some advantages of cross-sectional studies:

- Cross-sectional studies have the great advantage over case-control studies of starting with a reference population from which the cases and controls are drawn.
- They can be short-term, and therefore less costly than prospective studies.
- They are the starting point in prospective cohort studies for screening out already existing conditions.
- They provide a wealth of data that can be of great use in health systems research.
- They allow a risk statement to be made, although this is not precise.

Disadvantages of cross-sectional studies:

- They provide no direct estimate of risk.
- They are prone to bias from selective survival.
- Since exposure and disease are measured at the same point in time, it is not possible to establish temporality (i.e. whether the exposure or presence of a characteristic preceded the development of the disease or condition).

Ecological studies

In ecological studies, the unit of observation is an aggregate, a geographical administrative locality, a cluster of houses, a town, a whole country, etc. They may take any of the following forms:

- descriptive
- case-control
- cross-sectional
- cohort, or

- experimental.

Some specific forms of ecological studies are discussed below.

Aggregate analysis of national figures

These studies consist of an aggregate analysis of the correlation between a study factor and a disease (or mortality from a specific cause) in the geographical locale. They do not offer information on the exposure status of the individuals afflicted with or dead from the specific cause. Instead, the level of experience in the geographical unit or country is taken as a surrogate measure for all the individuals in that unit or country. Examples include:

- ecological correlation of per capita consumption of cigarettes and level of mortality from lung cancer;
- ecological correlation of water hardness and mortality from cardiovascular disease;
- maps of cancer frequency in a country and their interpretation by national cancer research authorities;
- ecological correlation of birth rate with gainful employment of women outside the home.

Time-series ecological studies

A variety of ecological studies may add a time-series dimension by examining, still on an aggregate basis, whether the introduction of a factor into a geographical area was associated with an increase in morbidity or mortality, or whether intervention in a geographical area reduced the morbidity or mortality. A good example is the study of death certificates for US women of reproductive age between 1961 and 1966 (Markush and Siegel, 1969), to find out whether there had been an increase in mortality from thromboembolism in women after the introduction of oral contraceptives in 1960-61.

Disadvantages and biases in ecological studies

While such studies are of interest as sources of hypotheses and as initial or quick methods of examining associations, they cannot be used as the basis for making causal inference. Their most serious flaw is the risk of ecological fallacy, when the characteristics of the geographical unit are incorrectly attributed to the individuals. Other sources of confounding are possible since many risk factors have a tendency to cluster in certain geographic areas. Thus, air pollution, heavy industry, ageing and crowding correlate to cities. The death of a person from heart disease may have little or no relationship to the presence of heavy industry.

Comparison of the three major analytical strategies

The major attributes of the three major strategies, the casecontrol, cohort and cross-sectional study, are outlined in Table 2.2. Note that an experiment (a clinical trial, for example) has the same properties as the prospective cohort study, except that the exposure variable (usually an intervention) is deliberately assigned to experimental and control groups.

TABLE 2.1 ESTIMATED RELATIVE RISKS FOR LEUKAEMIA IN CHILDREN 1-4 YEARS OF AGE FOR COMBINATIONS OF RISK FACTORS

No. of preconceptional factors	No. of post-conceptional factors		
	None	One	Two
None	1.0	1.1	1.8
One	1.2	1.6	2.7
Two	1.9	3.1	4.6

TABLE 2.2 COMPARISON OF THREE ANALYTICAL STRATEGIES

Attribute	Type of analytical strategy		
	Cohort	Case-control	Cross-sectional
Classification of population	Population free from condition or disease, with or without characteristic	Cases with condition (disease) with or with-out the characteristic, and controls	Populations without identification of condition or characteristic
Sample represented	Non-diseased	Uncertain: the source population of the cases is unknown	Survivors at a point or period in time
Temporal sequence	Prospective or retrospective	Retrospective	Contemporary or retrospective
Function	Compares incidence rates in exposed and unexposed	Compares prevalence of exposure among cases and controls	Describes association between exposure and disease simultaneously

Outcome	Incidence of disease in exposed and unexposed	Prevalence of exposure in cases and controls	Prevalence of disease in exposed and unexposed
Risk measure	Relative risk, attributable risk	Odds ratio (estimate of relative risk)	Prevalence ratio (inexact estimate of relative risk); also odds ratio
Evidence of causality	Strong	Needs more careful analysis	Only suggestive
Bias	Easy to manage	Needs more effort and sometimes very difficult to manage	May be very difficult to manage

Choice of strategy

The bases for choosing one of the research strategies are summarized in Table 2.3.

TABLE 2.3 CHOICE OF STRATEGY

Basis	Cohort	Case-control	Cross-sectional
Rare condition	Not practical	Bias	Not appropriate
To determine a precise risk	Best	Only estimate possible	Gives relative prevalence, not incidence
To determine whether exposure preceded disease	Best	Not appropriate	Not appropriate
For administrative purposes	Not appropriate	Not appropriate	Best
If attrition is a serious problem	Not appropriate	Attrition is usually minimal	Attrition may have occurred before the study
If selective survival is problem	Best	Not appropriate	Not appropriate

If all factors are not known	Best	Not appropriate	Less appropriate
Time and money	Most expensive	Least expensive	In between

References and further reading

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