form one stage within this broader sequence, which begins with laboratory studies using animal models, thence to human testing:

Phase I: The new drug or treatment is tested in a small group of people for the first time to determine safe dosage and to identify possible side effects.

Phase II: The drug or treatment is given to a larger group at the recommended dosage to determine its efficacy under controlled circumstances and to evaluate safety. This is generally not a randomized study.

Phase III: The drug or treatment is tested on large groups to confirm effectiveness, monitor side effects, compare it to commonly used treatments, and to collect information for the safe use of the drug. Phase III testing normally involves a series of randomized trials. At the end of this phase, the drug may be approved for public use. The approval may limit how the drug can be used, for instance in specific diseases or in certain age groups.

Phase IV: After the treatment enters the marketplace, information continues to be collected to describe effectiveness on different populations and to detect possible side effects. This does not involve an RCT and is called post-marketing surveillance; it is based on reports of side effects from physicians (and patients) so it requires the active participation of treating physicians and is necessary to detect rare or slowly developing side effects.

see Links: The clinical trials registry

5.7 Observational Studies

In observational studies, the researcher observes what happens to people under exposure conditions that have been self-selected or have been determined by influences outside the control of the researcher. The researcher can choose what exposures to study, but does not influence them. As this is a non-randomized design, the major problem in inferring causation is that the exposed and unexposed groups may differ on other key factors that may themselves be true causes of the outcome, rather than the characteristics under study. Such factors are known as confounders.

Descriptive studies

Descriptive studies describe how things are; they do not set out to test hypotheses. For instance the Canadian Community Health Survey describes health and health habits in the Canadian population, or a family physician might describe the demography of patients attending her practice. They are usually cross-sectional in design. Surveys are often used in a descriptive manner, for example to establish disease prevalence, or to record who uses health services and what patients think of them. This kind of information can be useful for clinicians deciding what kinds of information to offer their patients, or what services they ought to provide. They are particularly useful for public health and health care planning. Descriptive information is often collected by surveys or by surveillance programmes, covering person, place, and time of disease occurrences.

Analytical studies

The critical distinction between a descriptive and an analytical study is that the latter is designed to test a hypothesis. When an outcome variable, such as heart disease, is studied in relation to an exposure variable such as body weight, the study does more than count: it tests a hypothesis predicting an association between the two. Analytical observational studies can be of three types, depending on the time sequence and sampling procedures used to collect data.

Cross-sectional studies

Here, subjects are selected irrespective of the presence or absence of the characteristics of interest for hypothesis testing. One of the most common cross-sectional analytical studies is the survey, in which a random sample is drawn to give an accurate representation of the population. It is similar to a descriptive survey except that the purpose of the analysis is to record associations between variables, rather than merely to report frequencies of their occurrence.

As an example of a cross-sectional study, a researcher might draw a random sample of people to test hypotheses concerning the association between feelings of stress and the use of medical services. The researcher might ask whether people had visited a doctor in the last 2 weeks, and if they were under stress in the last year. Suppose the sample included over 18,000 people about stress and doctor visits, producing the following result:

Table 5.5: Stress and physician visits: calculating the association between two variables

		Doctor visit in the last 2 weeks?		
		yes	no	Total
Stress in the last year?	yes	1,442	3,209	4,651
	no	2,633	11,223	13,856
	Total	4,075	14,432	18,507

Note that this result can be reported in either of two ways:

1. Of those who suffered stress in the last year, 31% (1442/4651) visited their doctor in the last 2 weeks compared with only 19% (2633/13856) of those who did not suffer stress.

2. Of those who visited their doctor in the last 2 weeks, 35% (1442/4075) suffered stress in the previous year, compared with 22% (3209/14432) of those who did not visit their doctor.

Either approach is correct. The researcher is free to decide which way to report the results; the study design allows both types of analysis. All that can be concluded is that there is an association between the two variables. It might be supposed that stress predisposes people to visit their doctor, or could it be that the prospect of a visit to the doctor causes stress, or perhaps something else (fear of an underlying illness?) causes both? This study cannot provide support for an inference of causation because in this cross-sectional study it is impossible to know if stress pre-dated the doctor visit.

see Nerd's Corner: Ecological studies

Cohort studies

A cohort is a group of people who can be sampled and enumerated, who share a defining characteristic and who can be followed over time: members of a birth cohort share the same year of birth, for example. Cohort studies of health commonly study causal factors; the characteristic of interest is usually some sort of exposure that is thought to increase the likelihood of a health outcome. A cohort study typically begins with a sample of people who do not have the disease of interest; it collects information on exposure to the factor being studied, and follows exposed and unexposed people over time (Figure 5.2). The numbers of newly occurring (incident) cases of disease are recorded and compared between the exposure groups. Cohort studies are also known as longitudinal or follow-up studies.

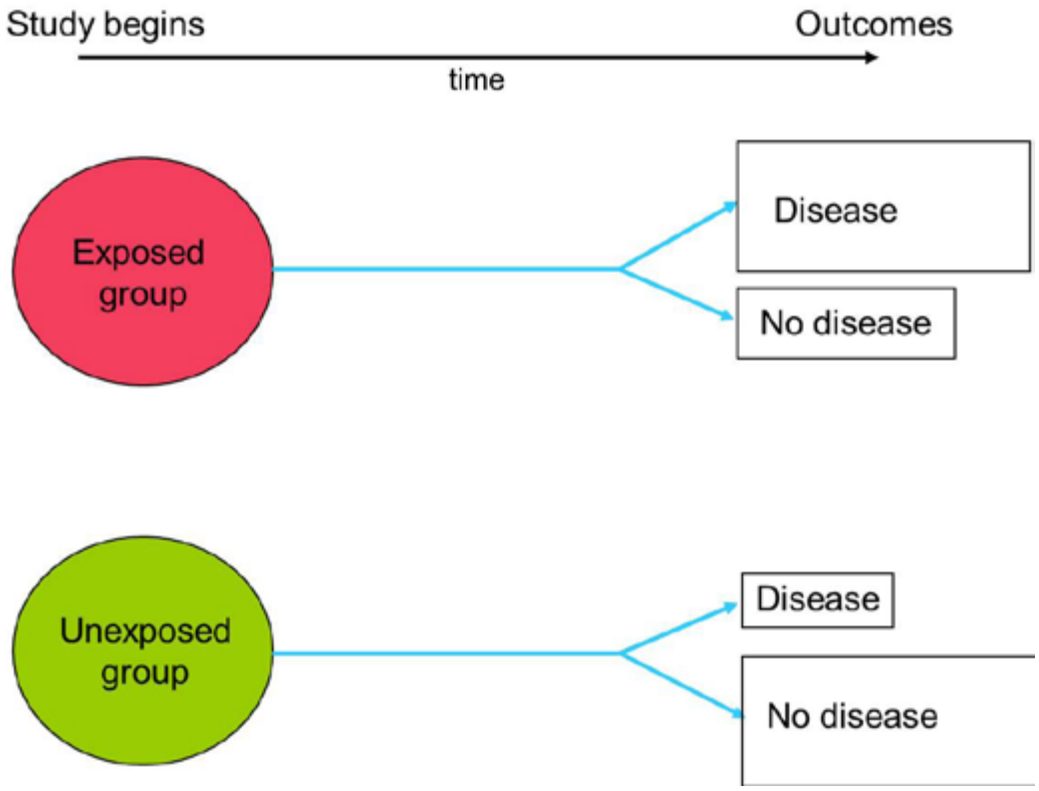

Figure 5.2: Schema of a cohort study

see Nerd's Corner: Cohort

In simple cohort studies the results can be fitted into a "2 by 2" table (2 rows by 2 columns: don't count the Total column).

Table 5.6: Generic format for a 2 x 2 table linking an exposure to an outcome.

	Outcome (e.g., disease) present	Outcome (e.g., disease) absent	Total
Exposure (or risk factor) present	a	b	a + b
Exposure (or risk factor) absent	c	d	c + d

The incidence, or risk of disease in the exposed group, is calculated as a / (a + b). Correspondingly, the risk in the non-exposed people is c / (c + d). These risks can be compared to get a risk ratio (often called a relative risk, or RR) that gives an estimate of the strength of the association between the exposure and the outcome: [a/(a + b)] / [c/(c + d)]. A relative risk of 1.0 indicates that exposed people are neither more nor less likely to get the disease than unexposed people: there is no association between exposure and disease. A relative risk greater than 1.0 implies that, compared to a person not exposed to the factor, a person who has been exposed has a greater chance of becoming diseased, while a relative risk of less than 1.0 implies a protective effect, that is exposed people have a lower chance of becoming diseased compared to unexposed people. The fact that exposure was recorded before the outcomes is the main advantage of cohort studies; they can clearly establish the causal criterion of a temporal sequence between exposure and outcome as long as study participants truly did not have the disease at the outset. Furthermore, because recording of exposures and outcomes is planned from the beginning of the study period, data recording can be standardized.

Definition of exposure groups

Imagine a cohort study designed to test the hypothesis that exposure to welding fumes causes diseases of the respiratory tract. The sample could be drawn on the basis of a crude indicator of exposure, such as using occupation as a proxy (welders are assumed to be exposed; a non-welding occupations would be presumed to be unexposed). This approach is frequently used in occupational and military epidemiology. A more detailed alternative would be to quantify levels of exposure (e.g., from the person's welding history); this requires considerably more information but would permit dose-response to be estimated - one of the criteria for inferring causation (see Table 5.4). In an extension of this quantified approach, a cohort study might not select an unexposed group to follow, but rather select a sample of individuals with sufficient variability in their exposure to permit comparisons across all levels of exposure, or to permit mathematical modelling of exposure. Cohort studies of diet, exercise, or smoking often use this approach, deriving information from a baseline questionnaire. This approach has been used in community cohort studies such as the Framingham Heart Study.

see Illustrative Material: The Framingham Study

see Here be Dragons: A cohort study proves?

Case-control studies

Case-control studies (see Case-control study in Glossary) compare a group of patients with a particular outcome (e.g., cases of pathologist-confirmed pancreatic cancer) to an otherwise similar group of people without the disease (the controls). As shown in Figure 5.3, reports or records of exposure (e.g., alcohol consumption) before the onset of the disease are then compared between the groups. The name of the design reminds you that groups to be compared are defined in terms of the outcome of interest: present (cases) or absent (controls).

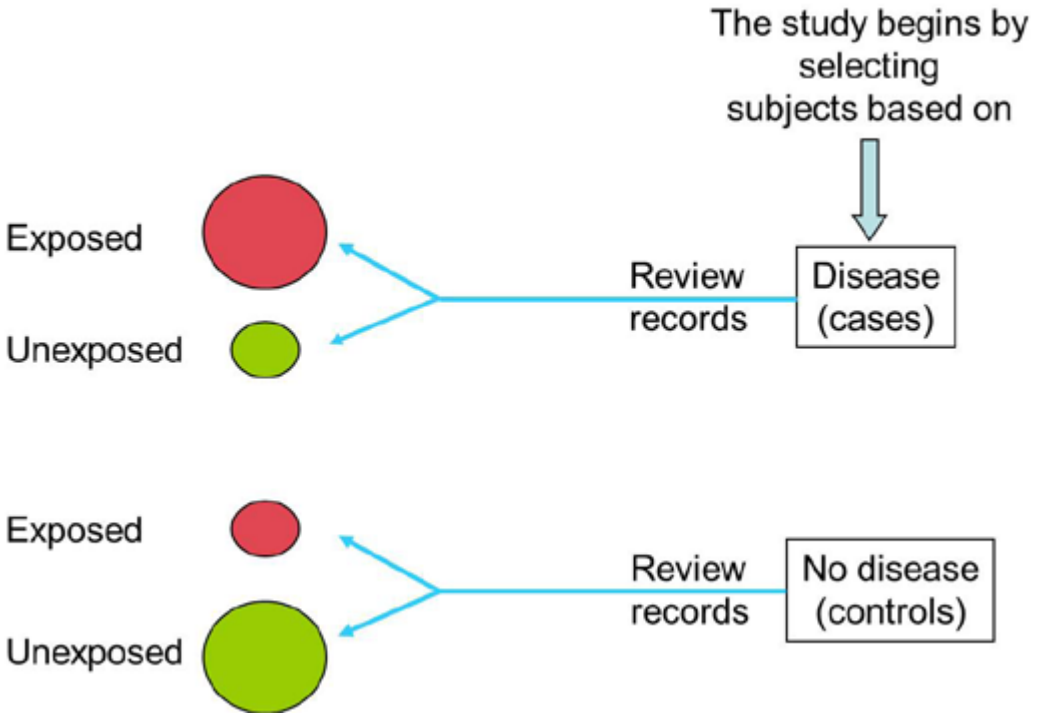

Figure 5.3: Schema of a case-control design

Notice that a case-control study does not allow the calculation of the incidence or risk of the disease, because it begins with people who already have it and a predetermined number who do not. Therefore, a risk ratio cannot be calculated. Instead, the study identifies the exposure status of a sample of cases and another of controls. This information allows the calculation of the odds of a case having been exposed the ratio of a:c in the 2 x 2 table (Table 5.7). This can be compared to the odds of a control having been exposed, the ratio of b:d. The result of the case-control study is then expressed as the ratio of these 2 odds, giving the Odds Ratio (OR): (a/c) / (b/d). To make the calculation easier, this is usually simplified algebraically to ad/bc.

Table 5.7: Generic 2 x 2 table for calculating an odds ratio

	Outcome (or disease) present	Outcome (or disease) absent
Outcome (or disease) present	a	b
Exposure (or risk factor) absent	c	d

The OR calculated from a case-control study can approximate a relative risk, but only when the disease is rare (say, up to around 5% in the sample, as is the case for many chronic conditions). The interpretation of the value of an OR is the same as a RR. Like a relative risk, an OR of 1.0 implies no association between exposure and disease. A value over 1.0 implies a greater chance of diseased people having been exposed compared to controls. A value below 1.0 implies that the factor is protective. This might occur, for example, if a case-control study showed that eating a low fat diet protected against heart disease.

Key contrast between cohort and case-control studies

In cohort studies, the participants groups are classified according to their exposure status (whether or not they have the risk factor).

In case-control studies, the different groups are identified according to their health outcomes (whether or not they have the disease).

see Here be Dragons: Prospective or retrospective?

5.8 Measures of Risk: Attributable Risk and Number Needed to Treat

The RR and OR indicate how much an individual's risk of disease is increased by having been exposed to a causal factor, in relative terms. Both statistics answer the question "Compared to someone without the risk factor, how many times as likely am I to get the disease?", giving the answer as a ratio: "You are twice as likely", or "10% more likely". A patient's question, however, often concerns absolute risk, which relates to disease incidence and answers the question "What is my chance of getting the disease (in the next year, ten years, my lifetime)?" The answer is given as a proportion, such as 1 in 10, or 1 in 100. An important point to bear in mind when communicating with a patient is that if the disease is rare, the RR of having a risk factor can appear quite frightening 100% greater risk of death in the next year even though the absolute risk is small. A relative increase of 100% on an absolute risk of 1 in a million is still only 2 in a million.

Judging the magnitude of a risk introduces the concept of attributable risk, which indicates the number of cases of a disease among exposed individuals that can be attributed to that exposure:

Attributable risk = Incidence in the exposed group – incidence in the unexposed.

This tells us how much extra disease has been caused by this exposure, in absolute terms: 1 case per million persons in the example above. In the case of a factor that protects against disease, such as a vaccination, it tells us how many cases can be avoided. Sometimes this value is expressed as a proportion of the incidence in exposed persons, yielding the exposed attributable fraction, EAF:

$$EAF = [Incidence_{(exposed)} - Incidence^{(unexposed)}] / Incidence_{(exposed)}$$