Study Design

The main types of study design are meta-analysis or systematic review, controlled trials, which are ideally randomised controlled trials; the observational study group which includes cohort, case-control and cross sectional studies, case series and case reports, and laboratory or experimental trials. There is a huge number of study designs, most of which are a sub-type of one of these classifications.

By the end of this section you will have an overview of study design and advantages and disadvantages of each

Why understand study design?

An understanding of study design will enable you to:

- select a suitable study design for your own research project
- critically evaluate reports in the published literature and elsewhere, for example, the media
- assess the strength of evidence supported by a particular study, depending on its design

CJ Mann has published an excellent summary of study design in the Emergency Medicine Journal, citing real-world examples of some classic designs (1). See also the British Medical Journal's series 'Epidemiology for the Uninitiated' https://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated.

The 'evidence pyramid' cartoon below shows the theoretical hierarchy of the strength of evidence reflected by the various types of study. Study designs nearer to the top of the pyramid are likely to be less biased and thus provide stronger evidence for a conclusion than those further down the pyramid. It is important to remember that this is a guide, not a hard and fast rule. Strength of evidence is governed by the quality of the study, including internal and external validity, as well as the design. A well designed and conducted cohort study probably provides stronger evidence for a given proposition than a poorly conducted randomised controlled trial.

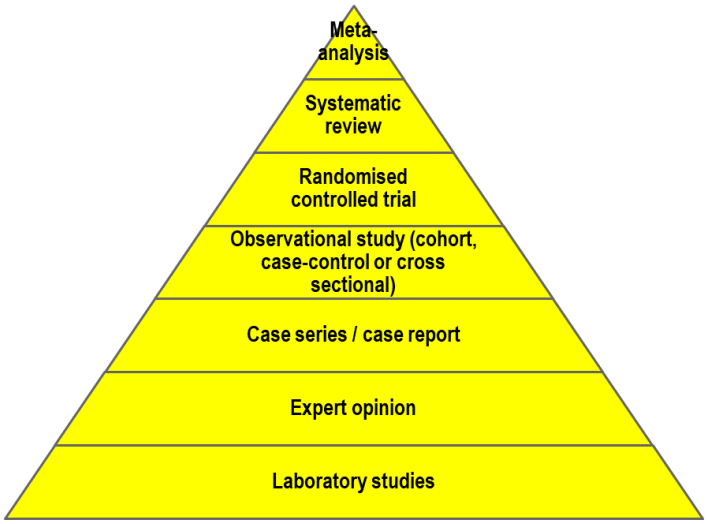

Figure 1. The 'evidence pyramid'.

Study Design: types of study

Terminology: exposures and outcomes

Epidemiological terminology can be confusing to people who are primarily clinicians. Epidemiologists and clinical researchers talk about 'exposures' and 'outcomes'. An exposure is the event or risk factor that happens FIRST and causes or influences what happens – the outcome.

An 'exposure' can be a medical or surgical treatment, such as a drug or type of surgical procedure. It can be a risk factor, which could be a literal exposure such as exposure to lead or sunlight, or a protective factor such as eating a healthy diet or sunscreen. Exposures are also called 'interventions'; you can understand this in the context of drugs, surgical procedures, diet, physiotherapy and a host of other things which might be recommended to patients.

The 'outcome' always comes AFTER the exposure. For example, chronic exposure to lead, particularly in children, causes neurological damage, here neurological damage would be the outcome. Eating a healthy diet would be an exposure which is a modifiable risk factor, which would protect a person from obesity and cardiovascular disease.

Figure 2 depicts lead as the 'exposure' and neurological damage as the 'outcome'.

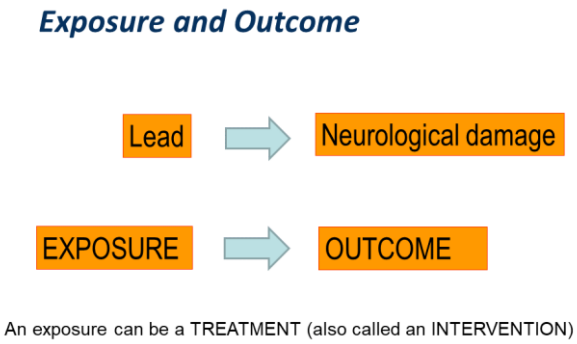

Figure 2. Exposure to lead leads to an outcome of neurological damage.

Having fair skin is an example of a risk factor that would make a person susceptible to sunburn (Figure 3).

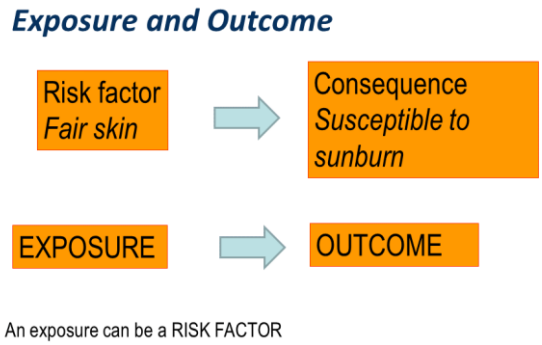

Figure 3. Exposure to 'fair skin' is a risk factor for sunburn if you spend too long in the sun.

Study Design: types of study

Randomised controlled trial and epidemiological observational study designs are discussed first, a grasp of features of these designs makes it easier to appreciate the features of other types of study. Other study designs include meta-analyses and systematic reviews, case series and case reports.

Different types of study can be distinguished on

i) how the study participants or subjects are selected, according to the exposure and outcome, and

ii) who allocates the study subject to which group.

In a randomised controlled trial (RCT), the study subjects are randomly allocated to an exposure (treatment) BY THE INVESTIGATOR. Each subject has an equal chance of being allocated to either group.

In a cohort study, the subjects are selected on their exposure status.

In a case-control study, subjects are selected on their disease (outcome) status.

In a cross sectional study or survey, a representative sample of the population is selected, and disease and exposure status determined after selection (Figure 4).

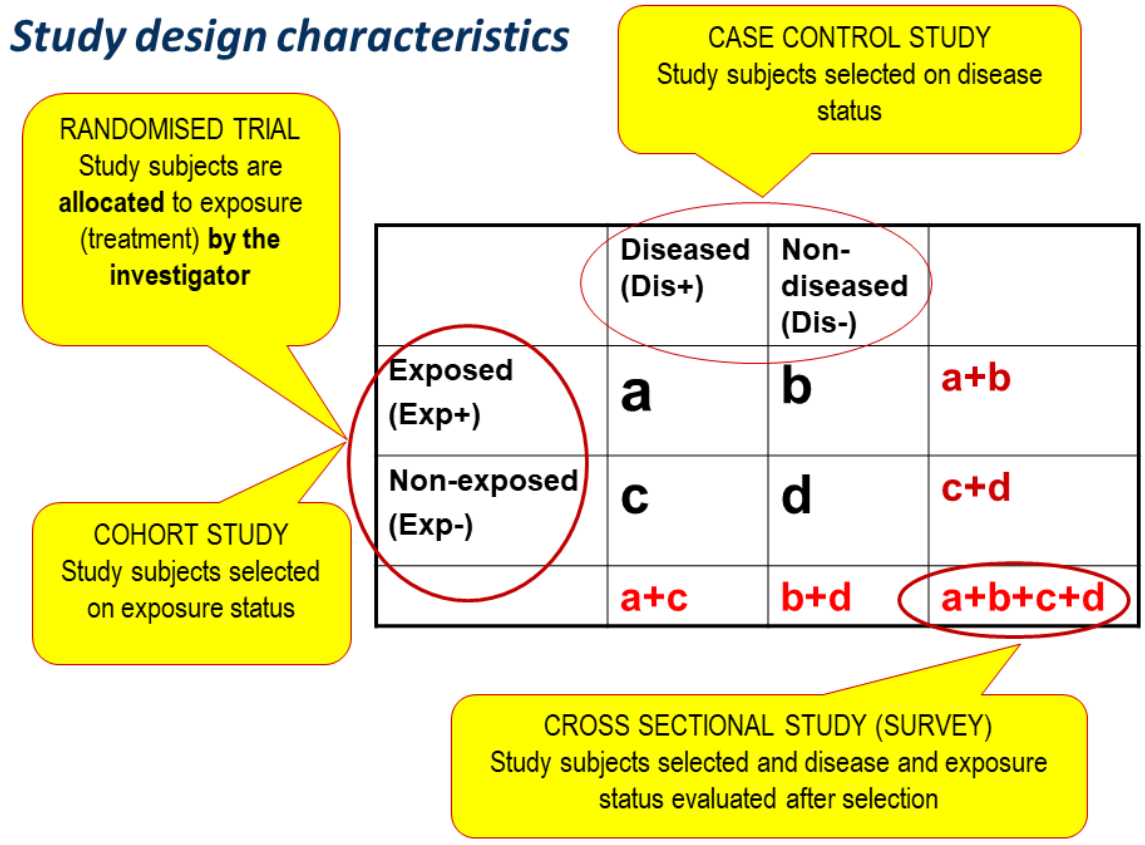

Figure 4. In controlled trials, subjects are allocated to exposed or non-exposed groups by the researcher. In cohort studies, subjects are classified as exposed or non-exposed, but NOT allocated to exposure or non-exposure by the researcher. In case-control studies, subjects are selected on the basis of being a case or being a control. In cross sectional studies, a representative sample of the population is selected, then exposure and outcome determined AFTER selection.

The various methods of subject selection are not only features of study design, but the method of selection dictates how the sample size will be determined. For more detail, see the section on sample size calculation.

As an aside, we talk about epidemiological study designs loosely in contrast to those which are traditionally derived from agricultural studies, such as factorial and latin square designs, although there is considerable crossover. These latter types of study are not discussed here.

Intervention studies versus observational studies

Intervention studies are those in which the researcher allocates some type of intervention or treatment to two or more groups of subjects. The randomised controlled trial is the prototype intervention study. Studies conducted using laboratory or field animals are often intervention studies based on a randomised controlled trial design. The randomised controlled trial is the gold standard for pharmacological studies.

Observational studies are those in which the researcher merely observes the effect of some exposure on two or more groups of subjects. Cohort, case-control and cross sectional studies are the classic observational study designs, often known as 'epidemiological' studies. Case series and case reports are by their nature observational studies.

Randomised controlled trials

In a randomised controlled trial, the effect of two or more interventions on a particular outcome is compared. The key distinguishing feature of a randomised controlled trial is that participants are randomised to the treatment or exposure groups by the researcher.

In a controlled trial (sometimes known as a clinical trial, although 'clinical trial' is not a very precise term), the researcher allocates the study subjects into treatment and control groups. It is possible to conduct a study which is controlled (there is a control group which does not receive the treatment of interest) but not randomised. Such studies are likely to be biased and their conclusions unreliable. They are unfortunately common in the medical and scientific literature.

In order to make a valid comparison of the outcome depending on which the treatment to which a subject is assigned, the study groups need to be similar at baseline. If the study is not randomised, there is a high probability that the groups will NOT be similar at baseline, i.e. the beginning of the study. Methods of allocating subjects to groups on the basis of, for example, every second patient, or patients in every second week, are not reliable in producing groups which are similar at baseline.

Randomisation

To overcome the challenge of creating groups which are similar at baseline, subjects should be formally randomised to one group or another (usually a treatment and control group). The key point is that each subject must have an equal chance of being allocated to one group or the other. Randomisation is usually done using computerised randomisation schedule.

Table 1 below shows you what a such a randomisation schedule looks like. In this example showing the randomisation schedule for the first ten participants, each participant in the study (identified by study number, Study_no_) is randomised to either treatment A or B. This particular example also illlustrates the concept of 'block' randomisation. Participants are randomised in blocks of four or six (the researcher can select any block size) to ensure that the number of subjects receiving each treatment are approximately the same at the end of the study. The block size itself is randomised, so that researchers cannot predict which treatment an individual participant receives.

Study Design: types of study

	id	stratum	block.id	block.size	treatment
1	Study_no_001	Centre1	B01	4	B
2	Study_no_002	Centre1	B01	4	B
3	Study_no_003	Centre1	B01	4	A
4	Study_no_004	Centre1	B01	4	A
5	Study_no_005	Centre1	B02	6	B
6	Study_no_006	Centre1	B02	6	A
7	Study_no_007	Centre1	B02	6	B
8	Study_no_008	Centre1	B02	6	A
9	Study_no_009	Centre1	B02	6	A
10	Study_no_010	Centre1	B02	6	B

Table 1. Example of randomisation using a computer program. The column headings are 'id', which gives the study number of the participant; 'stratum', which in this case indicates that the participant is from centre 1; 'block.id' and 'block.size', which indicate the block and size of the block';treatment, which indicates whether the participant has been randomized to either treatment A or B. Randomisation has been performed in 'blocks', so that regardless of when recruitment finishes, there are roughly the same number of subjects allocated to the two treatments. You can see that the first block contains 4 subjects, the second block contains six subjects. The table does not indicate which of the treatments A or B is the active or placebo/reference treatment. This table was generated using R software(2) with the 'blockrand' package.

Be suspicious if you read a paper which does not state whether, or how, randomisation was done!

Distinguishing features, advantages and disadvantages of randomised controlled trials are shown in Table 2.

Features of randomised controlled trials	Advantages of randomised controlled trials	Disadvantages of randomised controlled trials
• Subjects are allocated to groups by the researcher • A valid randomisation technique must be used, so that groups are similar at baseline (except for the intervention of interest); each subject has an equal chance of being allocated to any particular group • Subjects should not know which treatment they are getting (if they know they are getting a placebo they will expect it 'not to work') (Blinding) • Researchers measuring the outcome should not know which treatment the study subject has had (If they know the subject has had the active treatment they might nudge the outcome up to a 'better' outcome unconsciously or even consciously ('Double Blinding')	• The 'gold standard' for evaluating therapies with the least chance of bias if the study is well conducted • Unknown factors which might influence the outcome are equally distributed between the control and treatment groups • Specifically, avoid confounding – 'confounders' which might have caused the effect instead of the treatment are equally distributed in each group due to randomisation	• Take a lot of time and organisation (randomisation, blinding, staff) • Expensive • Unethical where the exposure might cause harm.

Table 2. Features, advantages and disadvantages of randomised controlled trials.

Study Design: types of study

Subtypes of randomised controlled trials: parallel and crossover designs

There are many subtypes of randomised controlled trials. The main ones are parallel group and crossover designs.

In parallel group study, two or more groups are run in parallel at the same time – this is the most common design.

In a crossover study, each subject receives both the treatment and control intervention, with each subject acting as their own control. The order or treatment is randomised. Half the subjects get the active intervention first, and the other half get the placebo. After a 'washout period', subjects receive whichever treatment they did not get during the first 'arm'. This design is suited to conditions in which the severity of disease does not fluctuate over time, where the treatment is expected to have an effect in a relatively short time and to 'wear off' quickly, i.e. have a short duration of action. It is very important that there is an adequate washout period so that the treatment during the first period does not affect the outcome during the second period. Crossover trials may need fewer subjects than parallel group trials, but the analysis is more complex than for parallel group trials.

There are many more complex designs based on the idea of random allocation.

Example of a randomised controlled trial

You can find many examples of good randomised controlled trials in your own field of interest. To give you an example of one of the early landmark randomised controlled trials, in 1948 the British Medical Research Council conducted a trial of streptomycin in tuberculosis (3), a serious and lethal lung disease (Figure 5). The famous epidemiologist and statistician Austin Bradford-Hill was on the Medical Research Council committee and performed the randomisation. Fifty-five 55 patients were randomly allocated by the researchers to streptomycin plus bed-rest, and 52 to bed-rest alone. Patients in the treatment group were given two grams of streptomycin intramuscular daily in four divided doses for four months. All patients received 6 months bed-rest. At the end of the trial only 4/55 (7%) of the treatment group had died, compared with 14/52 (27%) of the bed rest group (Table 3). This difference was statistically significant at $p<0.01$.

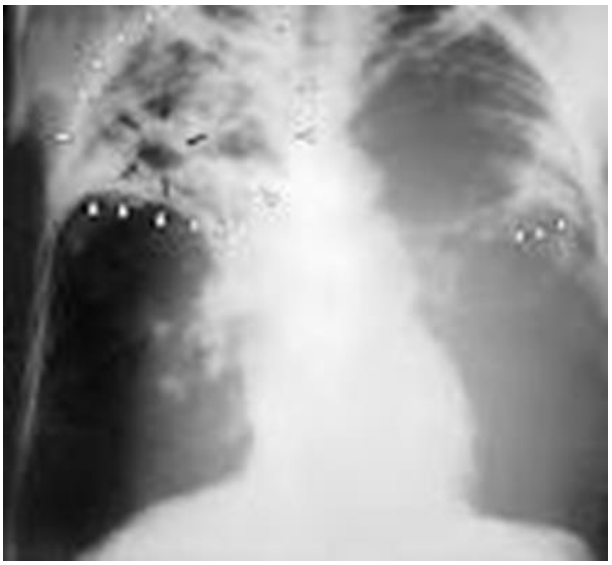

Figure 5. X-ray of a tubercular lung.This image is in the public domain and comes from comes from the Centers for Disease Control and Prevention's

Study Design: types of study
Public Health Image Library (PHIL), with identification number #2543.See https://en.wikipedia.org/wiki/Tuberculosis#/media/ File:Tuberculosis-x-ray-1.jpg

To put this in the context of our two-by-two contingency table, the results of the trial look like this:

	Died	Lived	
Streptomycin plus bed rest	4	51	55
Bed rest alone	14	38	52
	18	89	107

Table 3. Results of the trial of streptomycin as a treatment for pulmonary tuberculosis conducted by the British Medical Council. Streptomycin treatment reduced the proportion of people dying, $p<0.01$ (chi-square test). The odds ratio is (4/51)/(14/38) = 0.22, suggesting a highly protective effect. The relative risk is (4/55)/(14/52) = 0.26, consistent with a highly protective effect of streptomycin on the risk of death.

Epidemiological studies

The three main types of observational study are cohort studies, case-control studies and cross sectional studies or surveys.

Cohort studies

In a cohort study, subjects are selected by the investigator on the basis of exposure and followed over time to determine the outcome (Figure 6).

Referring to Figure 4, you can see that subject selection on exposure is similar to that of randomised trials, with the critical difference that the researcher does not assign the exposure in cohort studies, but merely observes the outcome in subjects who already fall into an exposure group. Cohort studies are the best design for exposures which are likely to be associated with harm, and thus it would be unethical to assign subjects to an exposure groups. For example, it would be unethical to assign people to smoke cigarettes, to have a bicycle accident resulting in fracture. It would be impractical as well as unethical to assign an incidentally occurring exposure such as diabetes or asthma if you wanted to determine a long-term outcome of such a condition.

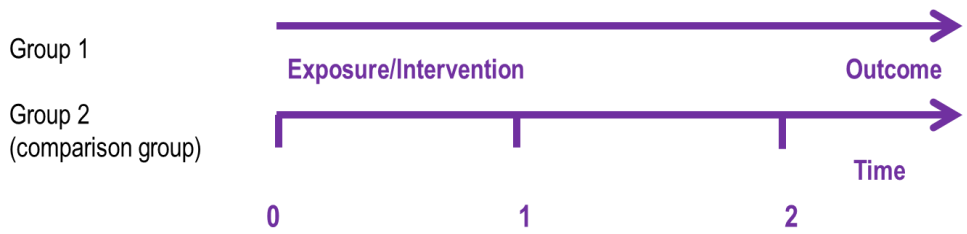

Figure 6. In a cohort study, exposed and non-exposed groups are followed over time to determine which subjects in each group get the outcome. The diagram depicts two groups. The line indicates a timeline at time zero, the start of the study, through time 1 to time 2 and beyond. The two groups are followed over time and then the outcome determined.

Study Design: types of study

Characteristic features, advantages and disadvantages of cohort studies are shown in Table 4.

Features of cohort studies	Advantages of cohort studies	Disadvantages of cohort studies
• The researcher looks for subjects who receive the exposure but DOES NOT decide who will get the exposure • The researcher then tries to find similar subjects who have not received the exposure • SUBJECTS ARE SELECTED ON EXPOSURE • and a NON-EXPOSED group selected • The outcome is determined after following the subjects over time.	• You can calculate relative risk and disease odds ratio • You can infer causation, because the hypothesised 'cause' comes temporally before the outcome, i.e. comes before the outcome in time, similar to a randomised controlled trial • Incidence of disease in exposed and unexposed subjects can be calculated • In prospective studies, data collection will be well designed and complete (hopefully) and bias due to faulty recall of events, particularly exposures, is minimised • It is theoretically possible to undertake a retrospective cohort study, if there are very good records and complete databases available.	• Exposed and unexposed proportions in the target population cannot be estimated • Unsuitable for rare diseases because large numbers of subjects would need to be studied • Potentially long duration of follow-up • Dropouts to follow-up are likely and maintaining follow-up is difficult • Control of extraneous variables may be incomplete • Potentially expensive

Table 4. Features, advantages and disadvantages of cohort studies.

Example of a cohort study: the British Doctors Study

The British doctor study, led by Sir Richard Doll, is a famous cohort study where British doctors were grouped according to whether they smoked or not. The study began in 1951. At the time there was controversy about whether or not smoking was harmful. It would have been unethical to randomise subjects to either smoke or not smoke, so the researchers selected a well-defined group, British doctors, and divided them into a 'smoking' and 'non-smoking' cohort, and followed them over time. By 1954 it was apparent that smoking was related to a number of adverse outcomes, including premature death, lung cancer, myocardial infarction and respiratory disease.

- Outcome was death / cause of death
- The study showed that smoking was related to premature death, lung cancer, myocardial infarction and respiratory disease
- Reports were published in 1954 and 1956 (4-6)

Case-control studies

In a case control study, subjects are selected according to their disease or outcome status. 'Cases' are individuals who have the disease of interest, and 'controls' are subjects similar to the cases except for their disease status. Case control studies are good for rare diseases, because there may be very few cases in many hundreds or thousands of people or animals. If you selected a cohort-type design, you would have to select a large number of subjects with and without the hypothesised exposure or cause and follow them for a long time for only a very few cases to develop. This is not often feasible. Controls may be 'matched' on particular characteristics. Selection of controls is often difficult. Characteristic features, advantages and disadvantages of case-control studies are shown in Table 5.

Features of case-control studies	Advantages of case control studies	Disadvantages of case control studies
• SUBJECTS ARE SELECTED ON DISEASE • and a comparable NON-DISEASED group selected • Cases selected first • Controls selected as close as possible to cases except for disease or outcome of interest • (i.e. controls are 'matched' to the cases either as a group or on an individual basis) • 'Look backward' to see what the exposure was	• Good for diseases with long incubation periods • Quick to organise and conduct • Relatively cheap • Require relatively few subjects • Sometimes can use existing records • No risk to subjects • Allow assessment of multiple exposures	• Can't estimate exposed and unexposed proportions in target population • May be recall bias for exposure • May be hard to validate exposure • Incomplete control of extraneous variables • Difficult to select control group • Incidence of disease in exposed and unexposed subjects can't be estimated

Table 5. Features, advantages and disadvantages of case control studies.

Example of a case-control study: Helicobacter pylori & gastritis

Barry Marshall, a young resident at the Royal Perth Hospital, and Robyn Warren, a pathologist at the same hospital, were interested in a spiral bacterium they had noticed on endoscopic gastric biopsies of people with gastritis (7, 8). They hypothesised that these hitherto unknown and unidentified bacteria were associated with gastritis. From a sample of 100 people undergoing gastroscopy for various reasons, they selected those with gastritis and those without gastritis, and compared their exposure to the as yet unclassified organism (Table 6).

	Gastritis	No gastritis	
Helicobacter positive on biopsy	55	2	57
Helicobacter negative on biopsy	14	29	43
	69	31	100

Table 6. Two by two contingency table for association of gastritis with the presence of Helicobacter pylori in gastric biopsy specimens. There was a statistically significant association between gastritis and bacteria, p<0.0001. Adapted from Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Barry J Marshall and J. Robyn Warren. Lancet 1984;1311-1314.

They found a significant association between gastritis and the presence of bacteria in the biopsy specimen ($p<0.0001$).

This data was published in the Lancet in 1984. Warren and Marshall, having had their initial abstract rejected by the organisers of a local scientific conference in 1983, went on to win a Nobel Prize. See (https://www.nhmrc.gov.au/media/podcasts/2009/conversation-professor-barry-marshall).

Cross sectional studies (surveys or prevalence studies)

In a cross sectional study or survey (sometimes known as a prevalence study), a representative sample of the population is taken. Then both exposure and outcome are ascertained after participant recruitment. A cross sectional study may be undertaken over a short specified time period – capturing a 'snapshot' in time, for example in prevalence surveys.

A cross sectional study may also be longitudinal – observations are repeated over time to provide information about the course of disease over time and space, for example to estimate incidence risk or incidence rate. These type of studies are also known as panel studies.

Features, advantages and disadvantages of cross sectional studies are shown in Table 7.

Study Design: types of study

Features of cross sectional studies	Advantages of cross sectional studies	Disadvantages of cross sectional studies
• In a cross sectional study, A REPRESENTATIVE SAMPLE OF THE POPULATION IS TAKEN • Exposure and outcome are ascertained after data collection • May be cross sectional – undertaken over a short specified time period – a single 'snapshot' in time (eg prevalence surveys) • May be longitudinal – observations are repeated over time to provide information about the course of disease over time and space (eg incidence risk or incidence rate)	• If a random sample of the target population is selected, can estimate prevalence and proportion of exposed and unexposed subjects in the target population • Quick to conduct • Relatively cheap • Sometimes can use current records • No risk to subjects • Can assess multiple exposures and outcomes	• Unsuitable for rare diseases • Unsuitable to diseases of short duration • Hard to control extraneous variables • Can't estimate incidence in exposed and unexposed individuals • Can't determine cause and effect (temporal exposure to outcome sequence can't be evaluated)

Table 7. Features, advantages and disadvantages of cross sectional studies.

Example of a cross sectional study

To estimate the prevalence and type of bacteria and fungi harboured by normal horse eyes, Hampson et al surveyed 95 client-owned horses attending veterinary hospitals for unrelated reasons (9). Breed, age, sex, purpose, housing and climatic conditions were investigated as risk factors for bacterial or fungal culture status. Bacterial isolates were cultured from 187/190 (984%) of eyes and fungal isolates from 111/190 (58.4%) of eyes. There was no significant effect of any of the hypothesised risk factors on bacterial or fungal culture status.

Example of cross sectional panel data

Figure 7 shows the number of laboratory confirmed cases of influenza in Australia by state from 2008 to 2017. Figure 8 shows the rate per 100,000 population. Data is from the National Notifiable Diseases Surveillance system http://www9.health.gov.au/cda/source/cda-index.cfm.

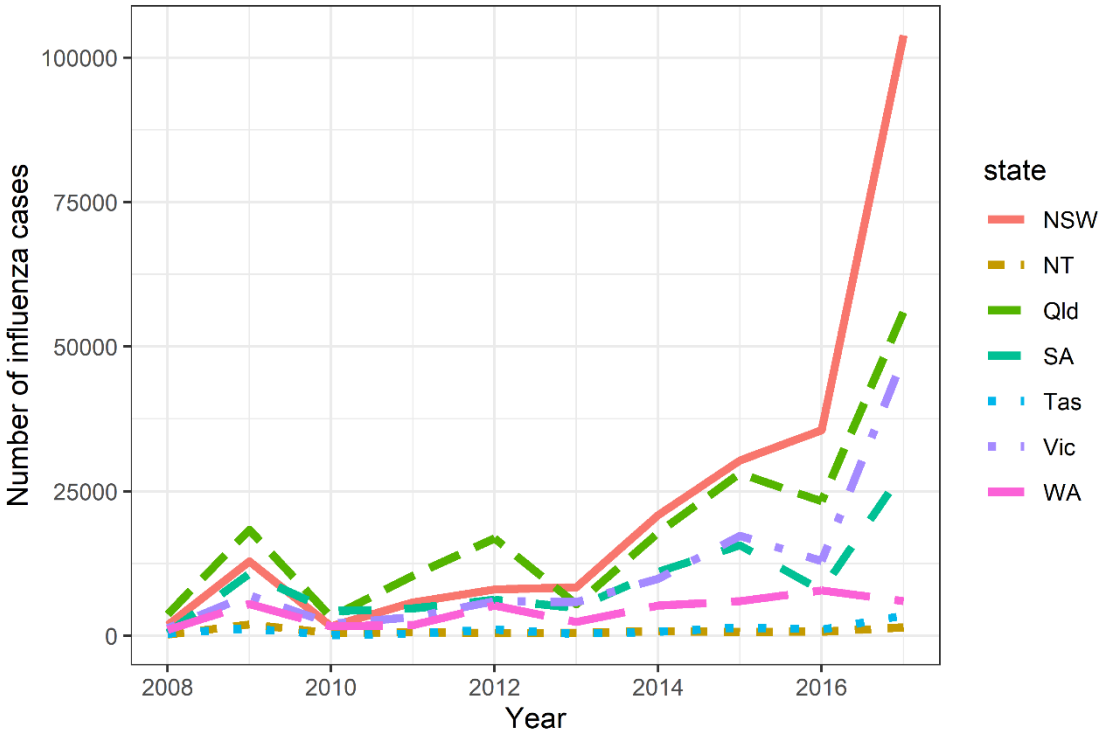

Figure 7. Cross sectional panel data example. Number of laboratory confirmed influenza in Australia from 2008 to 2017. Source:

http://www9.health.gov.au/cda/source/pub_influ.cfm

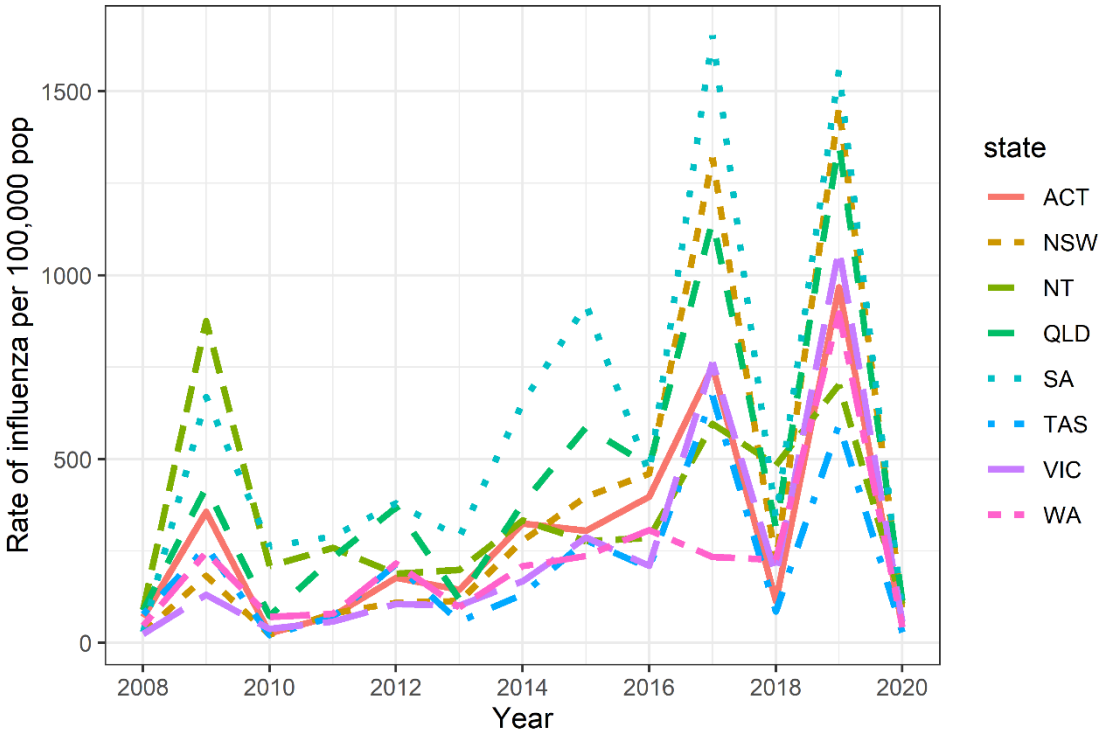

Figure 8. Cross sectional panel data example. Rate per 100,000 population of laboratory confirmed influenza in Australia from 2008 to 2020. Source: http://www9.health.gov.au/cda/source/rpt_4_sel.cfm

Study Design: types of study
In the influenza example, it is likely that different subjects were observed over time to determine their disease status. Some panel studies survey the same individuals at multiple time points.

Case series and case reports

Case series and case reports have no control group, so apparent effects of treatment are very unreliable indicators of the success of any therapy, because disease may fluctuate or resolve naturally.

Case series and case reports are very important in flagging the emergence of new diseases and recognition of syndromes. There are many examples of important conditions which were identified initially through case series or case reports, including

- HIV/AIDS
- Hendra Virus disease (10)
- Cystic Fibrosis (11)

Laboratory or experimental studies

In the context of human medicine, laboratory studies or experimental studies are usually like a randomised controlled trial but conducted under artificial, controlled circumstances. There studies are generally conducted in species other than humans, and even for those species, are not 'real world' as the animals are husbanded under very artificial conditions and indeed are usually themselves very genetically homogeneous and often genetically modified.

These studies are very important for basic science but are not generalisable directly to clinical practice.

Systematic reviews

In a systematic review, all relevant studies are systematically identified, appraised and summarised using explicit and reproducible methods. There should be a formal written protocol, which distinguishes systematic reviews from 'narrative' reviews, where studies may be selected for review according to the preferences of the reviewer. Selecting and including studies according to well defined rules helps reduce bias. The characteristic features of a systematic review are that there is a well-designed PICO format research question, and that the search strategy is designed and specified before the literature search is undertaken. The search terms, databases to be searched, inclusion and exclusion criteria are explicitly defined.

Meta-analysis

In a meta-analysis, as for a systematic review, results from all relevant studies are systematically identified, appraised and summarised using explicit and reproducible methods. Additionally, the results for each included report are analysed statistically to give an overall summary result. Results are often reported using a Forest Plot (12).

In a forest plot, a summary statistic for each included study, often a Risk Ratio or Odds Ratio, along with the corresponding 95% confidence interval, is depicted. An overall summary statistic, weighted for the number of subjects in the constituent studies, is shown at the bottom. A forest plot derived from hypothetical data comprising an active treatment and placebo treatment is shown in Figure 9 (13). The 'treatment' was protective of disease in all the trials, with the Risk Ratios ranging from 0.14 to 0.44. All the upper 95% confidence intervals were less than one, indicating that each study would have shown a statistically significant effect of treatment. The overall weighted Risk Ratio was 0.32 (CI 0.19 – 0.54). The I^2 statistic indicates moderate heterogeneity, and the Q statistic (Cochrane's Q) at p = 0.11, indicates that heterogeneity was not statistically significant. See Martin Bland's presentation

Study Design: types of study
https://www-users.york.ac.uk/~mb55/msc/systrev/week7/hetpub-compact.pdf - for more explanation.

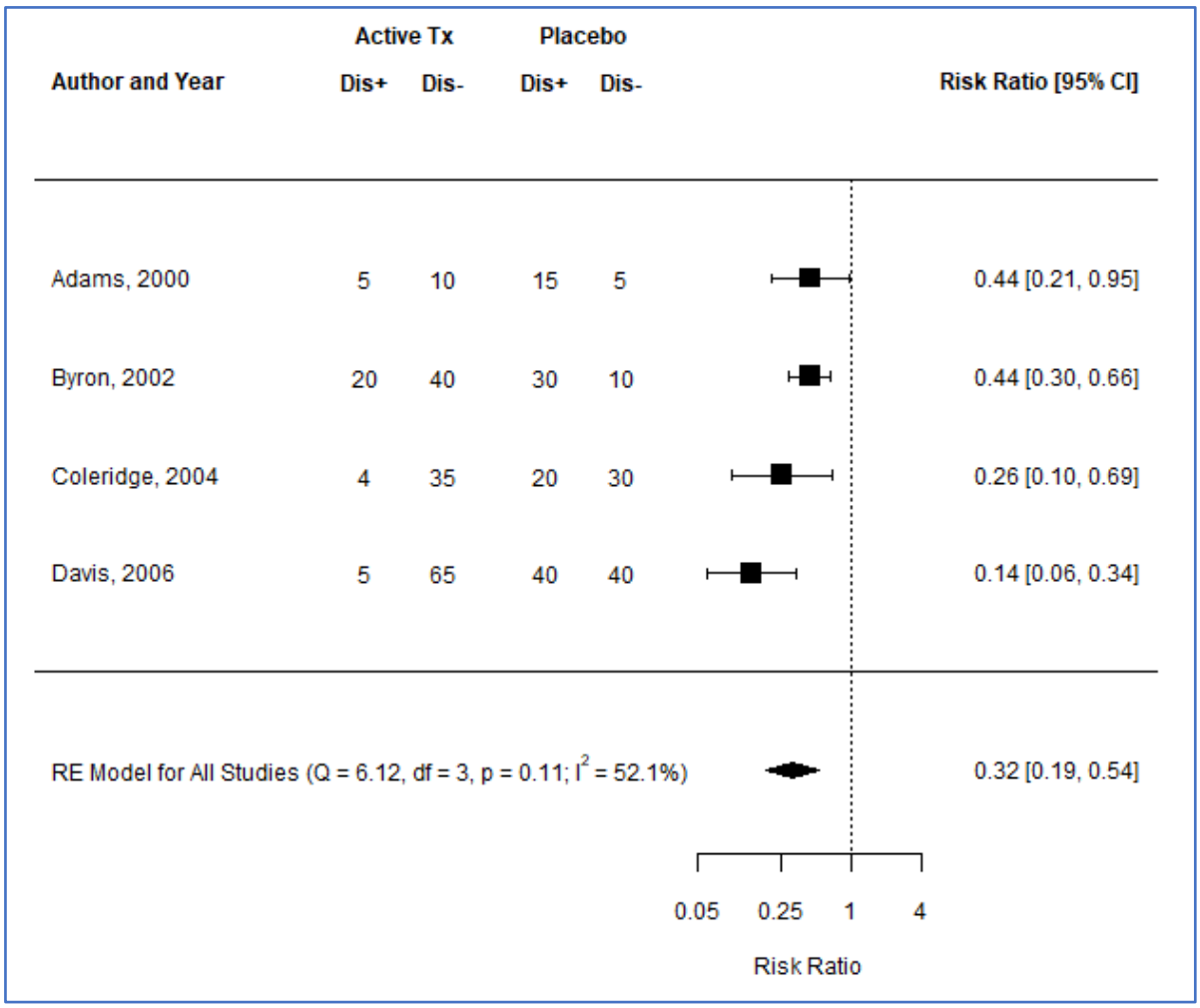

Figure 9. A forest plot using hypothetical data. All the four studies indicated a protective effect of treatment, as did the weighted Relative Risk for all studies combined.

Example of meta-analysis: streptokinase for acute myocardial infarction.

In 1992, Joseph Lau and colleagues conducted a meta-analysis of mortality after treatment of myocardial infarction with intravenous streptokinase (14). Such studies had been carried out from 1959 and were still being carried out at the time of publication of the analysis. The overall pooled Odds Ratio showed that streptokinase is highly effective at reducing mortality.

The authors then performed a cumulative meta-analysis, systematically adding patients from each trial by year. This cumulative meta-analysis technique showed that by the time 2,432 patients had been evaluated, there was a clear advantage of streptokinase; this would have been known by 1973, years before 'clotbusters' became routine therapy for myocardial infarction, had researchers run this analysis as new data came to light.

One lesson from this is that in many cases, it may be important to do a meta-analysis before conducting a new study - the answer may already be out there!

Study Design: types of study

References

1. Mann, CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003;20(1):54-60. Epub date: 2003/01/21. doi: PMID 12533370.

2. R Core Team (2017). R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2018. Vienna, Austria. URL https://www.R-project.org/.

3. Streptomycin treatment of pulmonary tuberculosis. A Medical Research Council Investigation. Br Med J. 1948;2(4582):769-782. Epub date: 1948/10/30. doi: PMID 18890300. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2091872/

4. Doll, R, Hill AB. The mortality of doctors in relation to their smoking habits; a preliminary report. Br Med J. 1954;1(4877):1451-1455. Epub date: 1954/06/26. doi: PMID 13160495.

5. Doll, R, Hill AB. Lung cancer and other causes of death in relation to smoking; a second report on the mortality of British doctors. Br Med J. 1956;2(5001):1071-1081. Epub date: 1956/11/10. doi: PMID 13364389.

6. Doll, R, Hill AB. The mortality of doctors in relation to their smoking habits: a preliminary report. 1954. BMJ. 2004;328(7455):1529-1533; discussion 1533. Epub date: 2004/06/26. doi: 10.1136/bmj.328.7455.1529. PMID 15217868.

7. Marshall, BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;1(8390):1311-1315. Epub date: 1984/06/16. doi: 10.1016/s0140-6736(84)91816-6. PMID 6145023.

8. Warren, JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet. 1983;1(8336):1273-1275. Epub date: 1983/06/04. doi: PMID 6134060.

9. Hampson, EGCM, Gibson JS, Barot M, Shapter FM, Greer RM. Identification of bacteria and fungi sampled from the conjunctival surface of normal horses in South-East Queensland, Australia. Vet Ophthalmol. 2019;22(3):265-275. Epub date: 2018/07/03. doi: 10.1111/vop.12587. PMID 29963751.

10. Selvey, LA, Wells RM, McCormack JG, Ansford AJ, Murray K, Rogers RJ, Lavercombe PS, Selleck P, Sheridan JW. Infection of humans and horses by a newly described morbillivirus. Med J Aust. 1995;162(12):642-645. Epub date: 1995/06/19. doi: PMID 7603375.

11. Clague, S. Dorothy Hansine Andersen. Lancet Respir Med. 2014;2(3):184-185. Epub date: 2014/03/14. doi: 10.1016/s2213-2600(14)70057-8. PMID 24621679.

12. Lewis, S, Clarke M. Forest plots: Trying to see the wood and the trees. British Medical Journal. 2001;322:1479-1480. Epub date: doi: 10.1136/bmj.322.7300.1479 PMID

13. Viechtbauer, W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software. 2010;36(3):1-48. Epub date: doi: PMID

14. Lau, J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med. 1992;327(4):248-254. Epub date: 1992/07/23. doi: 10.1056/nejm199207233270406. PMID 1614465.