Research Confuses Me: What is the Difference Between Case-Control and Cohort Studies in Quantitative Research?

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What is the difference between a cohort and a case-control trial? And why is it important? As a student, it is sometimes difficult to appreciate the difference between these two study methods, and why should it matter to us anyway? After all, we study medicine to treat patients, not statistics. Study methodologies were for the scientists; we are clinicians. Fast forward to clinical practice, and the importance of research design becomes apparent. As medical doctors we treat patients, but we also look at the bigger picture: why is this happening to this patient? Why is this patient more likely to be affected than another? In order to truly care for patients it is necessary to search and query and that means doing, or being able to properly interpret, research.

The most fundamental point of both cohort and case-control trials is that they are *observational trials*. Unlike randomised controlled trials (RCTs), where the researchers actively divide participants into control and comparison groups, observational trials are more passive: here the researchers literally observe participants. The major drawback is the potential for bias: apparent differences may be due to known or unknown confounders.[1] However, in emotive or ethically difficult areas (e.g., obstetrics or paediatrics) or in situations when blinded randomisation is not possible (e.g., surgical procedures) they may be the best quality evidence available.

To illustrate the differences between the two study types, a good example is the history of research into lung cancer. We all know that *smokers are more likely to develop lung cancer*, but where did that knowledge come from? And what if you look at this from the other direction: *"How many persons with lung cancer were smokers?"* These two ways of looking at a question illustrate the differences between a cohort and a case-control trial perfectly. In fact, over fifty years ago in the UK a young doctor and a statistician asked just that same question and decided to use these two methods to find an answer.

Case-Control

How many people with lung cancer were smokers?

Sir Richard Doll (an epidemiologist) and Sir Austin Bradford Hill (a statistician) started off by looking at patients with lung cancer: the "cases". They then picked a group of controls, patients without lung cancer but in hospital for another reason. Looking back in time (*retrospectively*) they tried to ascertain what the cases had been exposed to that made them more likely to develop lung cancer than the controls.[2] The cases were divided into those exposed to smoking and those unexposed. A similar group (in this case, other hospital patients) were similarly divided into exposed and unexposed groups (Figure 1). Due to the risk of confounding (see below) the researcher then assumes (and hopes!) that the cases and controls come from the same population.[3] So the key features to a case-control trial are retrospective and comparison.[4]

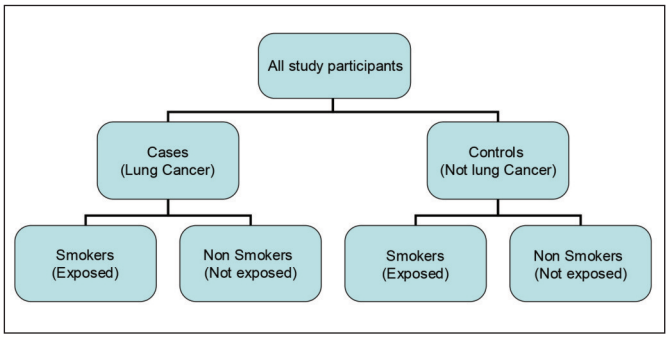

Figure 1 Case Control Trial

The difficulty can, sometimes, be deciding who has been exposed or unexposed: smoking might be obvious, but what do you do with ex-smokers? And what if the exposure is not obvious: how many mothers, for example, would know if they took certain medications during pregnancy? While those who have the disease may have searched for a cause, those without the disease may never be aware of the exposure they had. This can lead to "recall bias" as participants may deny having been exposed, simply because the exposure meant nothing to them.[4]

A second difficulty is choosing your controls: what if Doll and Hill had chosen patients with emphysema? Their smoking outcome (lung cancer versus emphysema) would have been different but their smoking habits might have been the same. These are called confounders: factors which link two groups and suggest a causal relationship. While some confounders are obvious (e.g., grey haired people have higher surgical mortality) others are not so obvious (e.g., eating eggs increases your risk of a myocardial infarction, or is this confounded by regularly eating fried bacon with these eggs?). This is another advantage of RCTs over observational trials: RCTs balance groups for confounders that have not yet been described.[3]

Case-control trials are usually retrospective, so the data are usually ready to be collected; therefore the study is cheaper and quicker to complete than a prospective trial. This is an advantage when studying diseases with a long latency period. Equally, if you are researching a rare disease or outcome using a cohort study, it would require huge numbers of exposed persons and many years to obtain enough people who develop the rare outcome. Therefore, a case-control trial (where the participants have already developed the rare outcome) is a more efficient use of resources and would require a smaller sample size[5]. However, the information available is limited by what other people thought was important at the time the data were recorded and this, in itself, may lead to bias.

The key featuress to case-control trials, therefore, are outcome, (usually) retrospective, rare outcome or long latency period. It is, however, also possible to have prospective case-control trials: take for example a study of serum lipoprotein as a risk factor for coronary heart disease. Here, the participants (men aged 50 years) had blood samples taken and frozen. Fast forward six years, through which the men were followed to see whether they had developed coronary heart disease or not. Those who had (the cases) were compared to randomly selected controls from the remaining participants. The blood samples of the two groups were compared to see if they differed with respect to their concentration of serum lipoprotein(a). This meant that not all the blood samples needed to be analysed, but that the cases could be accurately compared to controls for exposure to differing concentrations of lipoprotein(a) (this is an example of a nested case-control trial, that is, a case-control trial nested within a cohort trial[5]).

The main disadvantage of prospective case-control trials is that the ratio of cases to controls is artificially 'created', meaning that the prevalence of the condition cannot be estimated from the data collected and so absolute risks and, therefore, relative risks cannot be estimated either. Therefore, odds ratios are given for any risk factors.

Cohort

Smokers are more likely to develop lung cancer

The key features to a cohort trial is to follow a group of exposed persons forward in time to see if they develop the outcome.[6] For example, if people are followed prospectively to evaluate if smokers are more likely to develop cancer than non-smokers. (There are also retrospective cohort trials but for the moment, the key features to a cohort trial are exposure and prospective. Thus a cohort trial is also termed a *prospective* trial). In epidemiology, a cohort is a defined population that is followed prospectively to see who develops an illness. No new additions are made, and an attempt is made to follow all those who comprised the original group.[7]

In Doll and Hill's study where the outcome was lung cancer, the study would require years of follow up to see if any of the participants would ever develop the disease. (There's no point in stopping follow up at twenty years if patients may be diagnosed after twenty-five years). Due to the time and effort required, it is first important to at least have a basis for your hypothesis: this is why many researchers start with a case-control trial (as Doll and Hill did). Another disadvantage of the time required for the study is the loss to follow up: how do you keep in contact with your original study group? Doll and Hill very sensibly decided to have as their cohort doctors registered with the General Medical Council (the GMC, the professional organisation for medical doctors in the UK). So they would have a group of participants who would be easier to follow (as they needed to remain registered with the GMC) and would also, appreciate the importance of participation in such a study.

The cohort trial of British medical doctors has been published every five years since 1954[9], the last update being published in 2004.[10] The original trial gained worldwide notice, and resulted in similar trials starting in other countries, including the Nurses Health study in the US.[11] Information obtained on multiple outcomes in smokers was obtained which has significantly changed medical treatment. However, this is a very long-term study and involved significant work from the authors and their support teams.

The advantage of cohort studies over case-control studies is that as long as a representative cohort has been recruited, then prevalence, absolute and relative risks can be estimated readily for any risk factors.

Table 1 Key features comparing case control vs. Cohort studies

Case control Studies	Cohort Studies
Starts with the disease	Starts with the exposure
Usually retrospective	Usually prospective
Odds ratio	Relative risk
Usually quicker to perform	Usually longer to perform
Good to study rare disease	Good to study rare exposures

In summary, case-control trials and cohort trials are easily confused, so the key features are shown in Table 1. Both are observational trials. However, case-control trials compare cases with controls to investigate what each group was exposed to such that cases become cases and the controls remain controls. So, the key features to case-control trials are retrospective (usually) and outcome. In contrast, cohort trials only investigate one group and usually follow them forward in time to see if they develop a disease. Therefore, the key features to cohort trials are exposure and prospective (usually).

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What is a Randomised Controlled Trial?

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The basics

A randomised controlled trial (RCT), also known as a randomised controlled clinical trial, is a study in which participants are assigned randomly to one of two or more arms (groups with different interventions) of a clinical trial. Occasionally, a placebo is used as one of the interventions, but, generally, if there is a recognised and accepted intervention that works (the "gold standard"), then a new drug, device or intervention is tested against this gold standard rather than against placebo. Where a gold standard drug or intervention exists, it would be unethical to randomise to a placebo and, by doing so, make an effective treatment unavailable to some participants. Generally, RCTs are conducted because there is equipoise (or uncertainty) about whether a new intervention is potentially better than an existing one. The trialists (the team of people that plan, conduct, supervise and analyse the results of the trial) start with the hypothesis that there is no difference between the two interventions (this is "the null hypothesis"). The purpose of the RCT is to reject or accept the null hypothesis. If they manage to reject the null hypothesis, they can accept the "alternative hypothesis", i.e., that there is a difference between the two interventions.

Blinding

RCTs can be, but are not always, blinded. Blinding means that someone who plays an active part in the trial does not know what treatment (new intervention, gold standard or placebo) has been assigned to each participant. Trials can be single-blinded, double-blinded or even triple-blinded depending on how many types of people involved in the trial are blinded. For example, the participant could be blinded and not know what intervention they are assigned to. Or the medical doctor who deals with all the participants might not know to which intervention each participant is assigned. Or the statistician who reviews all the datasets and performs the statistical analysis might not know which group of participants has been assigned to which intervention. As you can imagine, if the participants are blinded, then there is less likelihood that they will complain of symptoms or side-effects that are known to be associated with either the new intervention, or the gold standard, or placebo. Similarly, a blinded doctor is less likely to assess patients in a biased way. To avoid the bias the statistical tests should be chosen prior to starting the RCT along with the rationale given for choosing them). Everybody has biases – even you!

Random Allocation

RCTs by definition, randomly allocate participants to the different arms. This is designed to mimic chance, and to ensure that there is no difference between groups. A good trial published in a journal will show the characteristics of the various intervention groups summarised (usually in a table) and compared (often with p values and confidence intervals, though not always) to prove to the reader that there are no differences at baseline.
Randomisation does not mean assigning alternate treatments to every second patient, nor assigning intervention A to patients who present on Mondays, Wednesdays and Fridays and intervention B to all others; if a well-meaning, but biased, physician wants his favourite patient to be assigned to intervention A he can tell that patient to come in on the day that intervention will be assigned; this is known as selection bias. Randomisation is designed to prevent biases, as well as to ensure "same-ness" between the assignment groups. The best method of randomisation is to use computer software to generate a sequence of random numbers, where each number refers to one of the interventions.

Sample Size Calculations

Calculating the number of patients needed for a trial is important.[1] If you can show that a new intervention is statistically significantly better than the old intervention by randomising fifty patients, you can avoid the expense of randomising and treating one hundred patients (which would also be unethical if the new treatment was beneficial). On the other hand twenty-five patients might not be enough to detect a statistically significant difference, even if a difference truly does exist (this is a type II error). In other words the 'power' of the study was too low to show the difference. To avoid costly errors when planning a trial, trialists use a nomogram (e.g., Altman's nomogram[2]) inputting three pieces of information: the required level of statistically significant difference (usually to 0.05 or 0.01 level); a pre-determined difference between the interventions that would be clinically relevant; and the power of the study (the risk of making a type 2 error), which the trialists choose to set at a pre-determined level (often around 80%). This nomogram then calculates how many patients are needed to show this predetermined clinical difference, at the predetermined power and level of statistical significance. This is the total number of participants needed to complete the trial. Most trialists will try to recruit more than this, to allow for drop-outs during the study period. Sample sizing software can also be used to calculate the