



Evidence generation in Medicine

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LEARNING OBJECTIVES:

- Recognise and understand different types of study design
- Understand which methods are used for which type of study
- Understand strengths and weaknesses of different types of study
- Understand the role of different study designs in terms of evidence
- Understand which studies are appropriate for which research questions

This topic was first introduced during the I IFMBE HTAD Summer School by Prof Saverio Stranges. His Lecture is available here:
<http://www.htad-ifmbe-elearning.org/courses/evidence-generation-in-medicine/>

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ETYMOLOGY/DEFINITIONS:

What is Epidemiology?

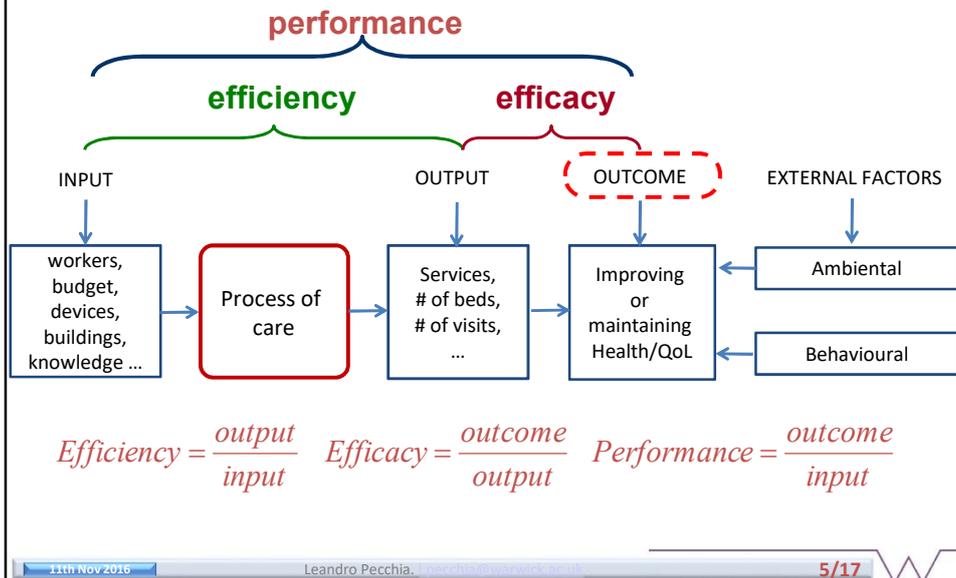
- Greek terms:
 - Epi: upon, among
 - Demos: people, district
 - Logos: study, word, discourse
- Epidemiology: “the study of what is upon the people”
- “The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems.” [Last, 1995]



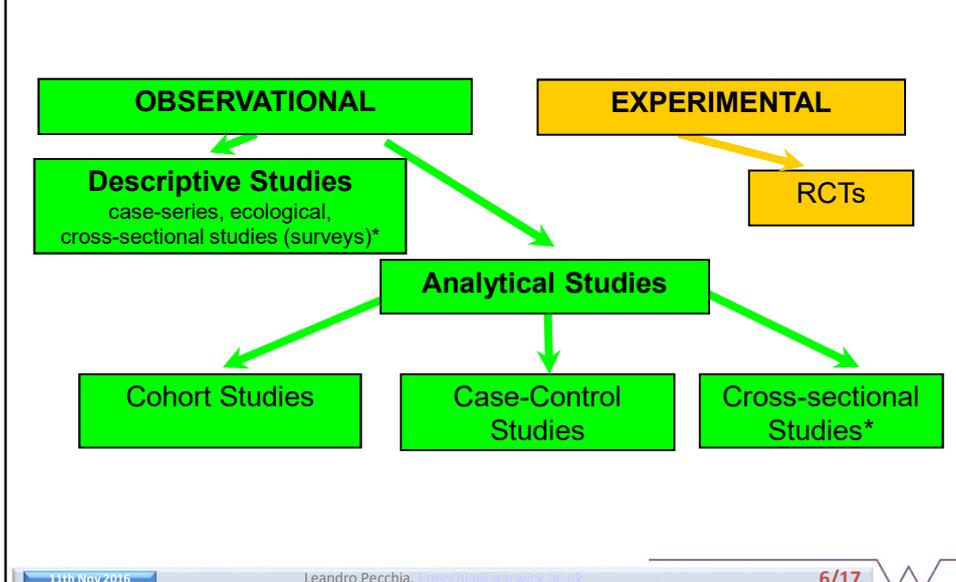
OBJECTIVES OF EPIDEMIOLOGICAL STUDIES

- “The goal in common in epidemiological studies is understanding the [true] **frequency**, **pattern**, and **causes** of disease in populations...” [Bhopal, 2002]
- Investigate disease aetiology
 - exposure → outcome relationship
 - interested in causal understanding
- Identify risk factors or protective effects
 - quantified in some way
 - absolute / relative risk (or protective effect)
- Evaluate health needs / disease / treatment and prevention strategies

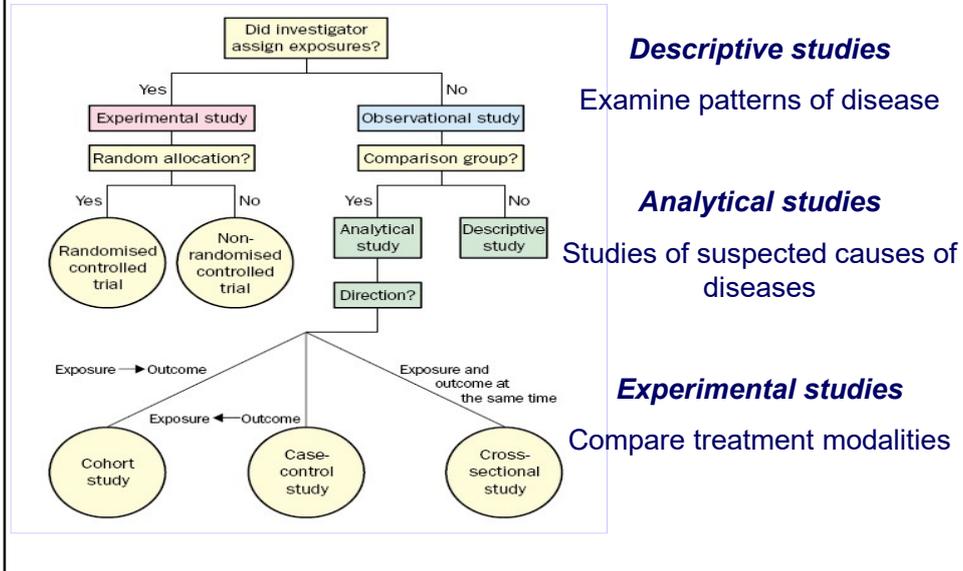
BEFORE STARTING, FEW DEFINITIONS



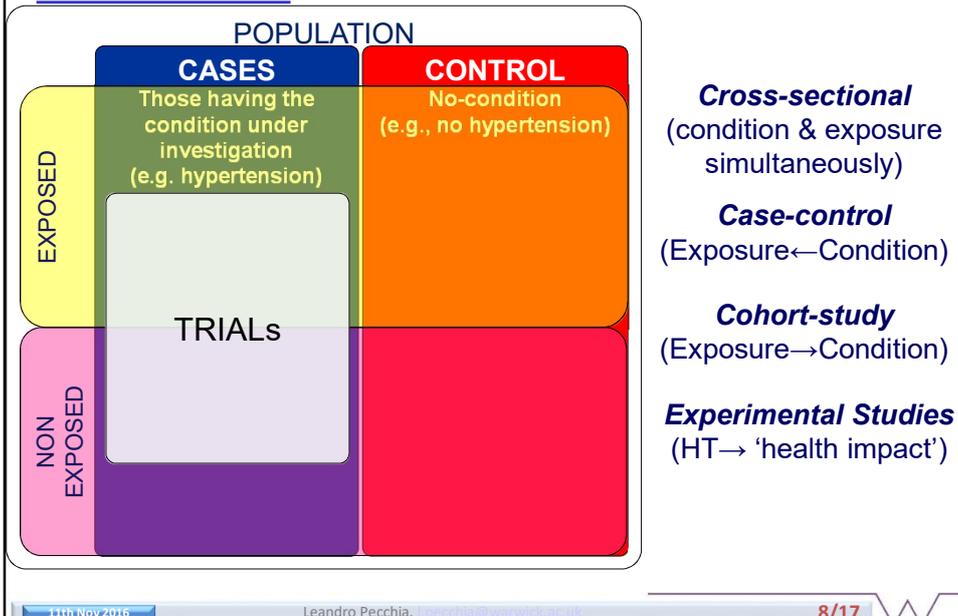
TYPES OF EPIDEMIOLOGICAL STUDIES



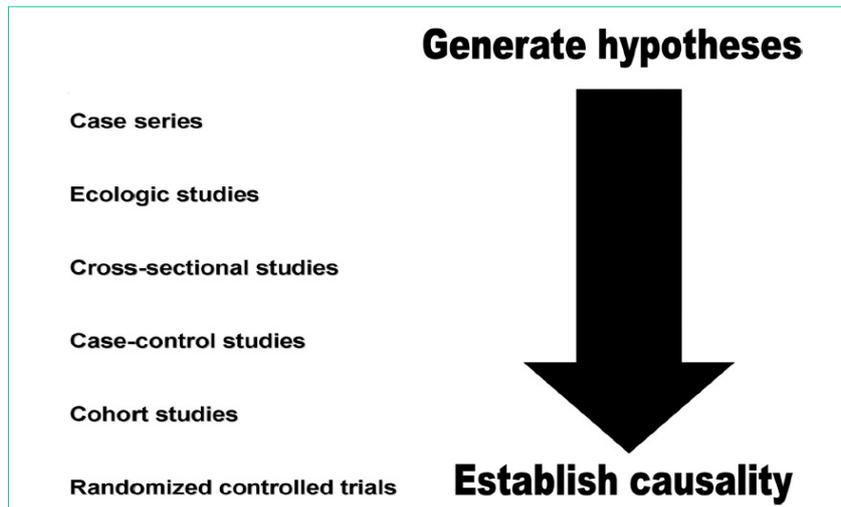
TYPES OF EPIDEMIOLOGICAL STUDIES



...in other words...

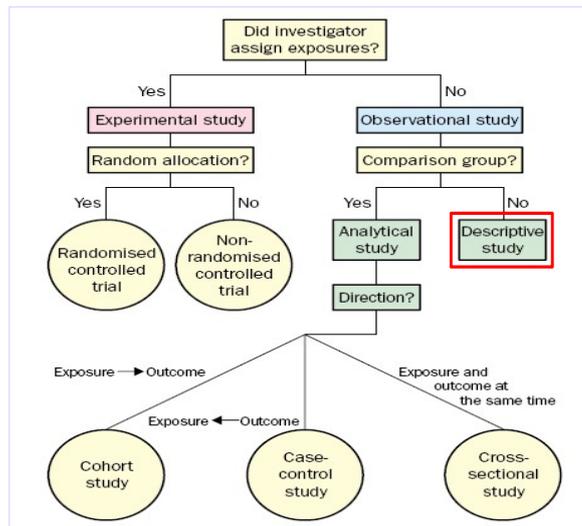


Different kinds for different purposes



Case series

Clinical case series – usually a consecutive set of cases of a disease (or other health issues) collected from a clinical practice/ hospital setting



Research article

[Open Access](#)

Diagnostic challenges of early Lyme disease: Lessons from a community case series

John Aucott*¹, Candis Morrison^{1,2}, Beatriz Munoz^{1,3}, Peter C Rowe^{1,4}, Alison Schwarzwald^{1,2} and Sheila K West^{1,3}

Abstract

Background: Lyme disease, the most common vector-borne infection in North America, is increasingly reported. When the characteristic rash, erythema migrans, is not recognized and treated, delayed manifestations of disseminated infection may occur. The accuracy of diagnosis and treatment of early Lyme disease in the community is unknown.

Methods: A retrospective, consecutive case series of 165 patients presenting for possible early Lyme disease between August 1, 2002 and August 1, 2007 to a community-based Lyme referral practice in Maryland. All patients had acute symptoms of less than or equal to 12 weeks duration. Patients were categorized according to the Centers for Disease Control and Prevention criteria and data were collected on presenting history, physical findings, laboratory serology, prior diagnoses and prior treatments.

Results: The majority (61%) of patients in this case series were diagnosed with early Lyme disease. Of those diagnosed with early Lyme disease, 13% did not present with erythema migrans; of those not presenting with a rash, 54% had been previously misdiagnosed. Among those with a rash, the diagnosis of erythema migrans was initially missed in 23% of patients whose rash was subsequently confirmed. Of all patients previously misdiagnosed, 41% had received initial antibiotics likely to be ineffective against Lyme disease.

Conclusion: For community physicians practicing in high-risk geographic areas, the diagnosis of Lyme disease remains a challenge. Failure to recognize erythema migrans or alternatively, viral-like presentations without a rash, can lead to missed or delayed diagnosis of Lyme disease, ineffective antibiotic treatment, and the potential for late manifestations.

Case series: advantages/disadvantages

Advantages:

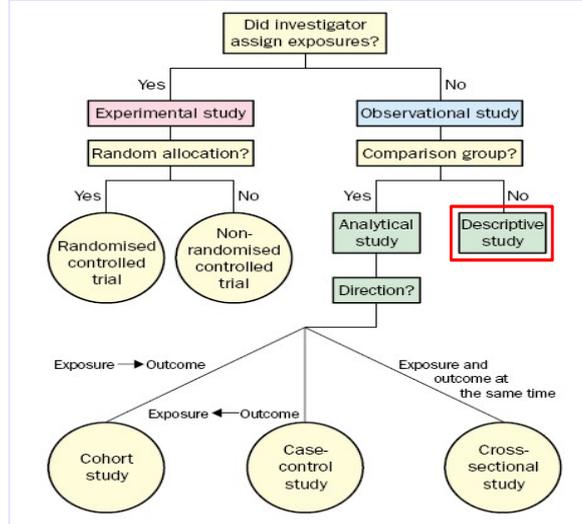
- Can broaden understanding of spectrum and natural history of disease
- Relatively cheap and relatively easy.
- Lay groundwork for more complex studies.

Disadvantages:

- Need other (comparison group/population) data to put them in context (e.g. to calculate rates)
- Difficult to know if data are complete/work out who's missing).

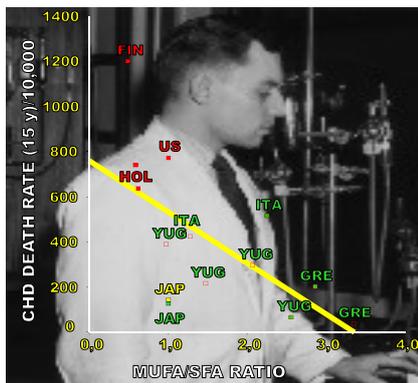
Ecological studies

Compares an area or population with another.
 e.g. the amount of alcohol drunk in France and UK and rates of cirrhosis in each country; the amount of saturated fats and rates of CVD across countries (Seven Countries Study)

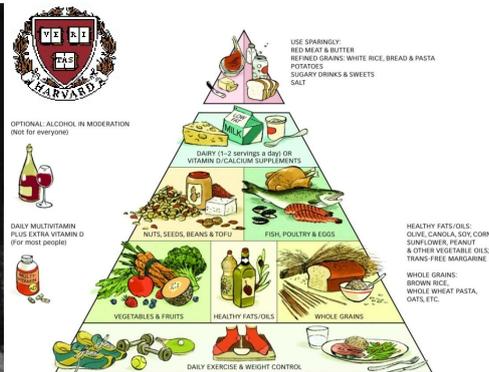


Ecological study:

The Seven Countries Study: Mediterranean Diet and CVD



A. Keys



Ecological Study:

Dietary Sodium vs. Blood Pressure

The INTERSALT Study

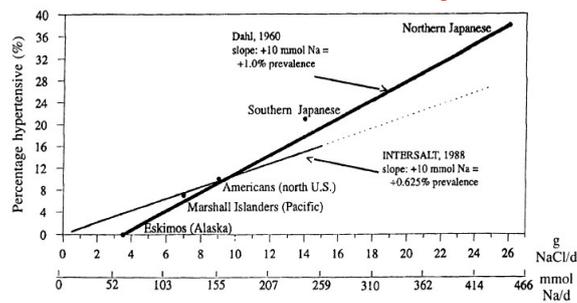


FIGURE 2. Average daily salt intake of population samples and prevalence of high blood pressure in studies by Dahl (42) and in the INTERSALT Study (14). INTERSALT criteria for high blood pressure were systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medication. $n = 52$ in the INTERSALT Study; values are adjusted for age and sex. A portion of this figure is reproduced with permission from Springer-Verlag (42).

Stamler J. Am J Clin Nutr. 1997;65:626S-42S

Ecological fallacy

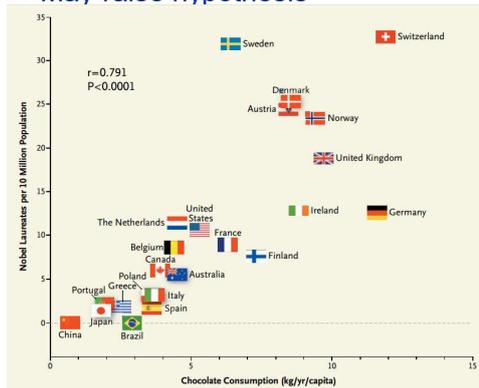
In 19th century Europe, suicide rates were higher in countries that were more heavily Protestant (Durkheim, 1897). This is an "ecological inference"-- a conclusion about individual behavior drawn from data about aggregate behavior...

The "ecological fallacy" consists in thinking that relationships observed for populations hold for individuals: if countries with more Protestants tend to have higher suicide rates, then Protestants must be more likely to commit suicide. (Freedman 2002)

Ecological studies: advantages/disadvantages

Advantages:

- Relatively cheap and simple to do
- May raise hypothesis



Disadvantages:

- Can't establish causation - only association
- Ecological fallacy
- Many of the disadvantages of cross sectional studies – with less reliable data collection!
- Confounding

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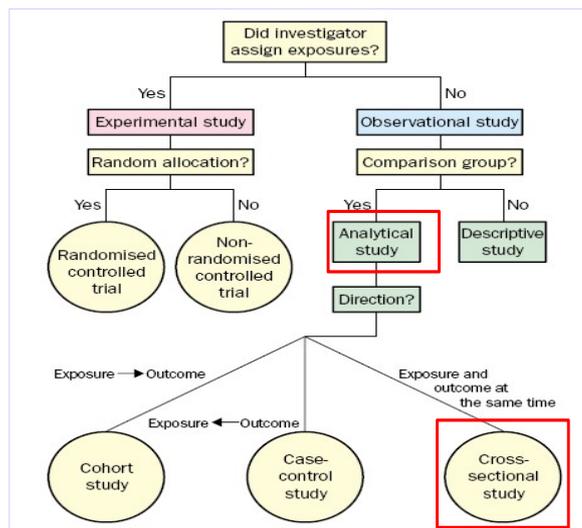
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Cross-sectional studies

A cross-sectional study is a study in which information is collected from each subject in the study population at one point in time. (Survey)

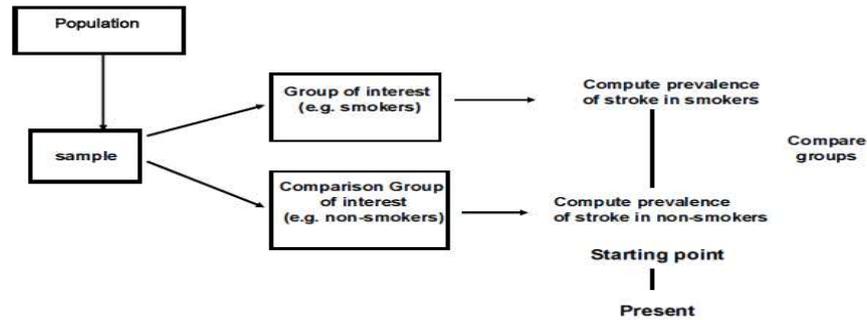
What for?

- to determine the prevalence of something (descriptive survey)
- to investigate possible associations between exposures and a particular outcome (analytical study)



Cross-sectional study

A TYPICAL CROSS-SECTIONAL STUDY



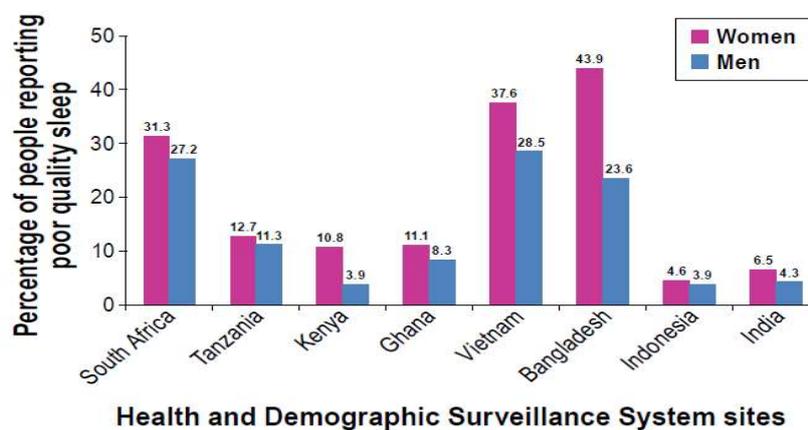
- A cross-sectional study is a single “snapshot” in time
- We can only study current diseases (prevalence)
- Examples include: Behavioural Risk Factor Survey, Health Survey for England

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Example 1: Prevalence of Sleep Problems in 8 countries across Africa & Asia, WHO study



Stranges S et al. Sleep. 2012;35:1173–1181.

Cross-sectional: advantages/disadvantages

Advantages:

- Relatively cheap and simple to do
- Good for examining exposures that do not change over time (e.g. sex)
- No exposure to harm or denial of beneficial therapy (“ethically safe”)
- May raise hypothesis

Disadvantages:

- Can't establish causation - only association
- Cannot measure incidence
- Confounding
- Recall bias
- Response rates

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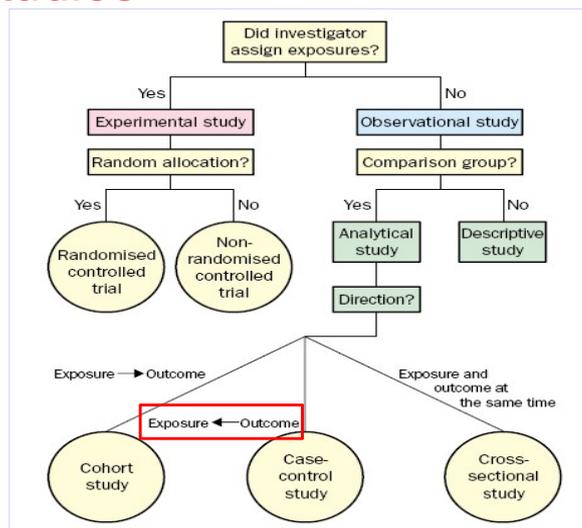
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Case-Control studies

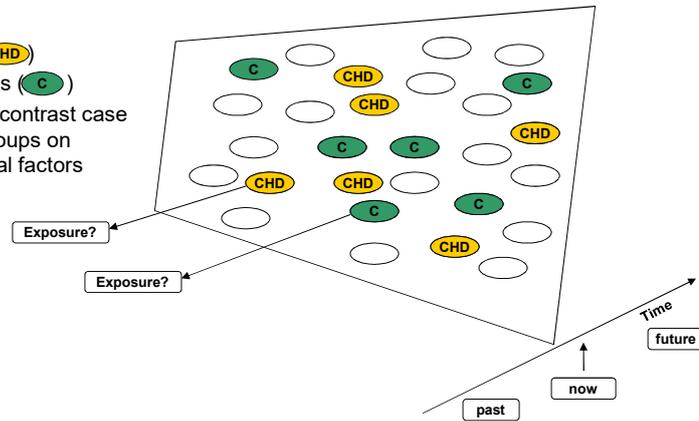
Case control studies involve comparing subjects with a condition (the cases) to subjects without the condition (the controls).

The level of exposure to a factor or factors is determined for both groups and compared. If the prevalence of exposure is higher in cases than in controls then the exposure might be a risk factor.



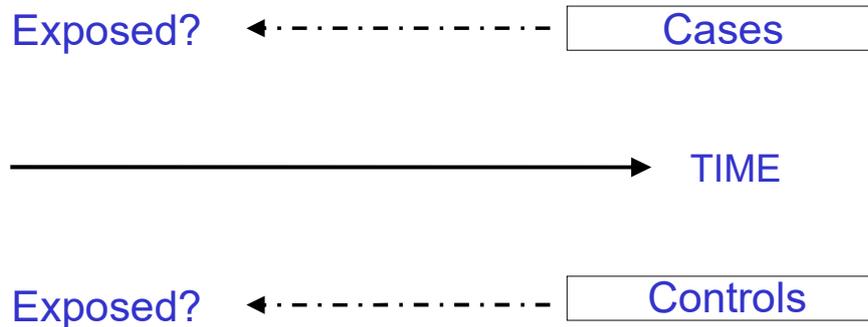
Population concept of a case-control study

- Find Cases (CHD)
- Define Controls (C)
- Compare and contrast case and control groups on potential casual factors

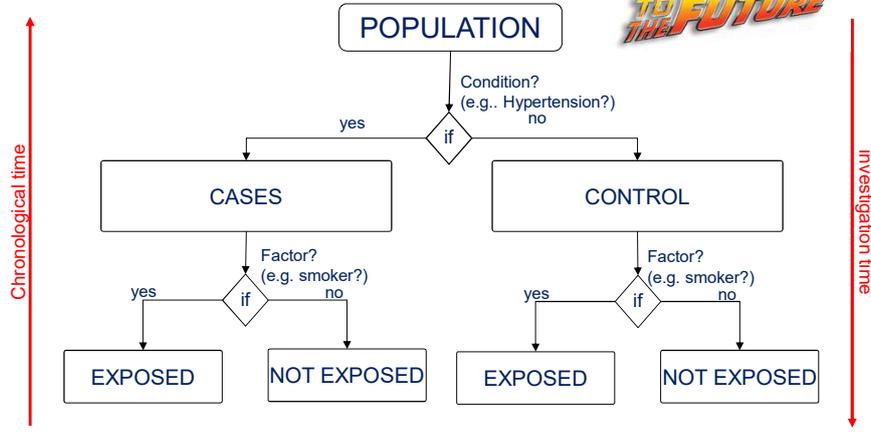


Source: Bhopal R. Concepts of Epidemiology: an integrated introduction to the ideas, theories, principles and methods of epidemiology. 2002

Case-control studies



Case-control study



Person-years observation in cohort studies

Disease	Person-years observation needed to yield 100 cases
CHD (cases)	10,000
CHD (deaths)	20,000
Lung cancer	50,000
Stomach cancer	200,000
Bladder cancer	1,000,000
Leukaemia	2,000,000

The Odds Ratio (OR) in the analysis of case-control studies

	Cases (diseased)	Controls (non-diseased)
Exposed	a	b
Unexposed	c	d

$$OR = \frac{a}{c} \div \frac{b}{d} = \frac{a \times d}{c \times b} = \frac{ad}{bc}$$

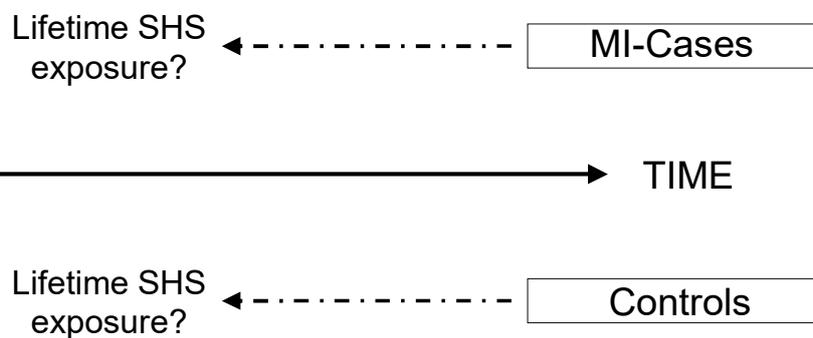
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Example Case-Control study (WNYHS):

Is Lifetime Second-hand Smoke (SHS) Exposure Associated with Risk of Myocardial Infarction (MI) in never smokers?



Western New York Health Study (WNYHS)

Results



SHS-Groups	Odds Ratios of MI
Lowest exposure (ref)	1.00
Middle	0.69 (0.44-1.09)
Highest exposure	1.19 (0.78-1.82)

No significant association between SHS and risk of MI in never smokers, but SHS exposure declined sharply in recent years

Stranges S et al. Arch Intern Med. 2006;166:1961-1967.

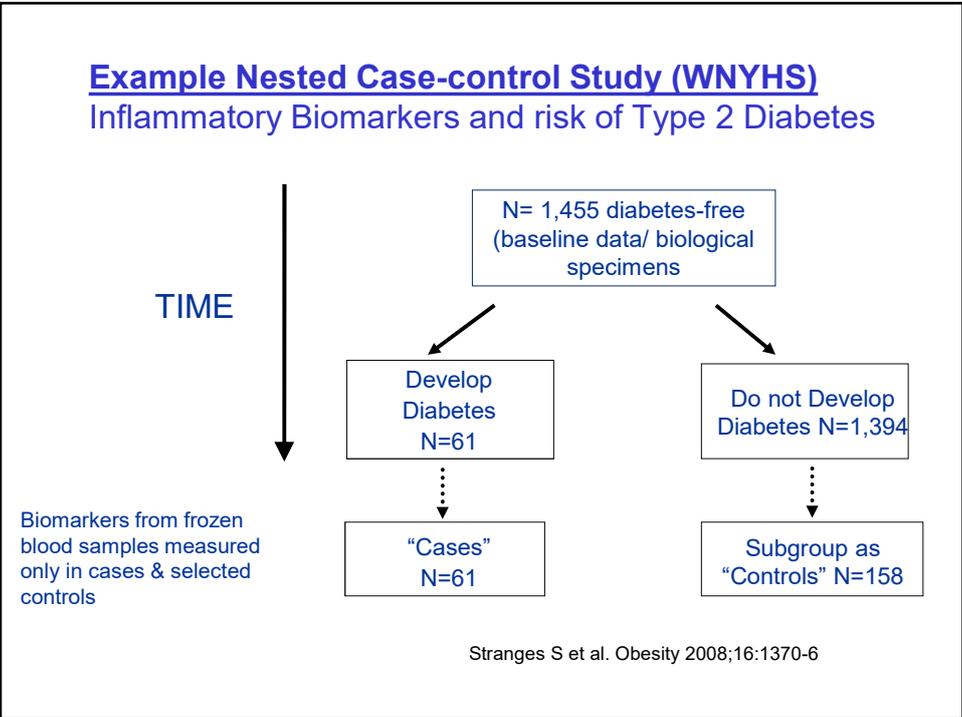
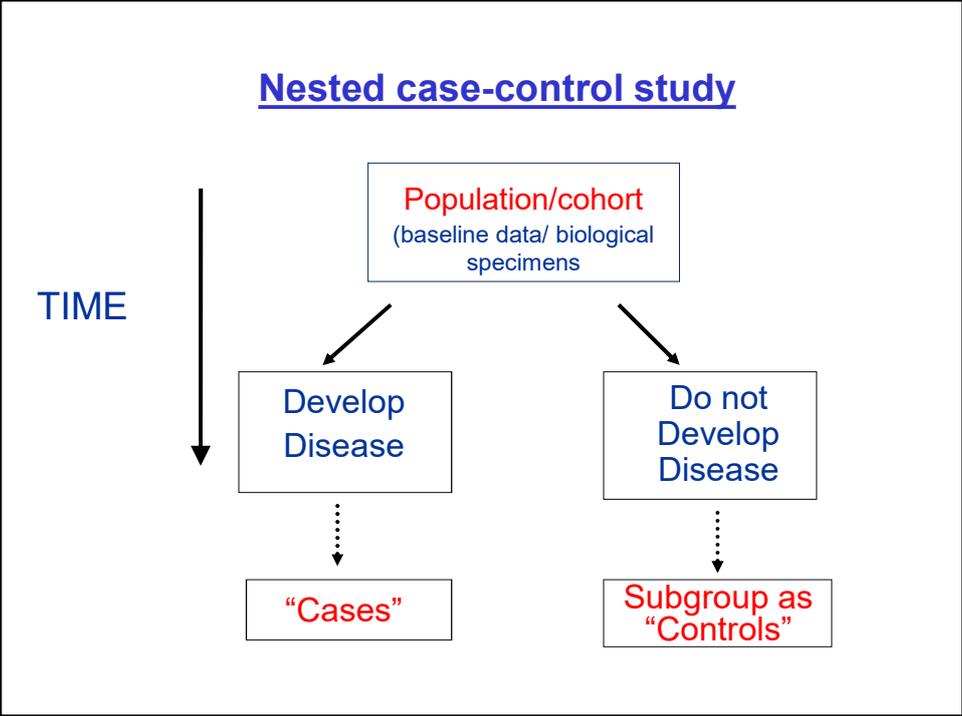
Conventional vs. nested case-control studies?

Conventional case-control study:

- retrospective collection of data (from recall)

Nested case-control study:

- 'nested' within a cohort study
- collection of data before disease has developed (from pre-existing records or biological samples)



Nested case-control studies

Advantages over conventional case-control studies:

- incidence rates can be calculated (sampling fractions known)
- population for sampling of controls is already defined
- data obtained before disease has developed, thus recall bias is eliminated

Advantages over conventional cohort studies:

- can collect more detailed information for a minority of participants; cost are dramatically reduced
- it is a cost-effective alternative to a full cohort analysis

Case-control studies: advantages/disadvantages

Advantages:

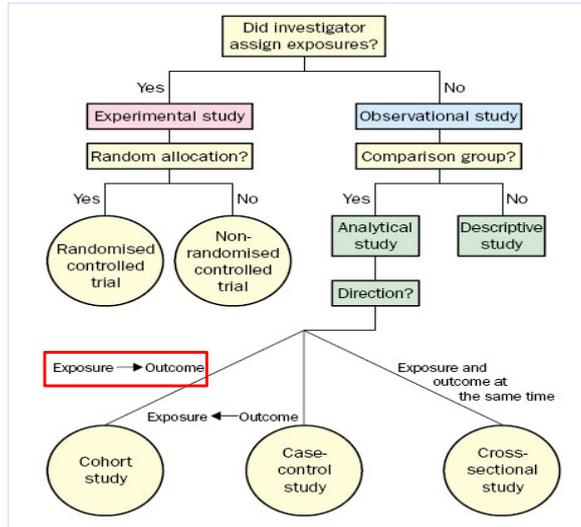
- relatively quick & cheap
- no loss to follow up
- Multiple exposures can be examined
- Rare diseases and diseases with long latency can be studied
- Suitable when randomization is unethical (alcohol and pregnancy outcome)

Disadvantages:

- prone to biases (e.g. recall)
- problems sorting out sequence of events
- not suitable for rare exposures
- cannot measure disease incidence
- Multiple outcomes cannot be studied

Cohort studies

- A cohort is a group of people who have something in common
 - Belonged to a specific group in the Roman army
 - Enrolled in medical course on the same day
 - Born in the same week
 - Worked in the same industry
 - Take the same drug
- A cohort study is one in which a group of people are followed up over time

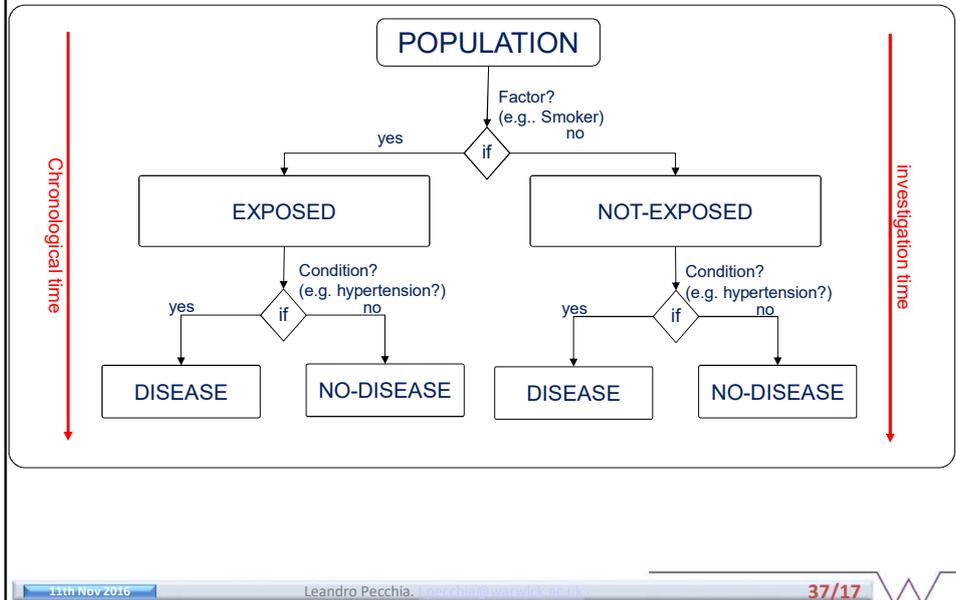


Cohort study

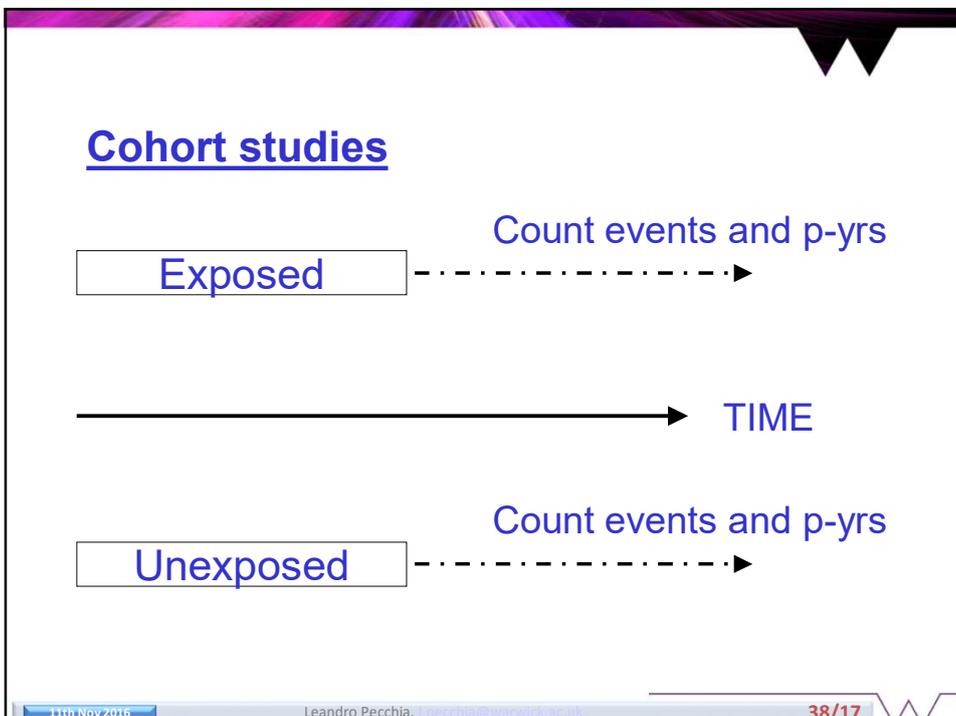
Two groups of people, one group exposed and another unexposed to a potential cause of disease, are followed-up over time and the incidence of the disease in one group is compared with the incidence in the other.



Case-control study



Cohort studies



Analysis of cohort studies – Incidence Rate Ratio (IRR) & Relative Risk (RR)

$$\text{IRR} = \frac{\text{Incidence in exposed}}{\text{Incidence in unexposed}}$$

$$\text{RR} = \frac{\text{Risk in exposed}}{\text{Risk in unexposed}}$$

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Analysis of cohort studies – Incidence Rate Ratio/Relative Risk

	Disease	No Disease
Exposed (person-years)	A	B
Unexposed (person-years)	C	D

$$\text{IRR} \approx \frac{A}{A+B} \div \frac{C}{C+D} = \frac{A \times (C+D)}{C \times (A+B)}$$

Cohort studies: advantages/disadvantages

Advantages:

- Can monitor changes over time
- May detect (causal) associations and time sequence
- Can establish population-based incidence
- Can examine rare exposures (asbestos > lung cancer)
- Multiple outcomes can be studied (smoking > lung cancer, COPD, larynx cancer, CVD)

Disadvantages:

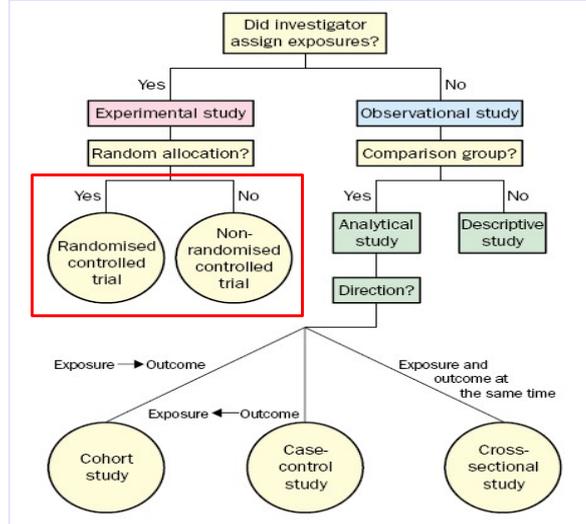
- Lengthy and expensive
- May require very large samples
- Not suitable for rare diseases
- Not suitable for diseases with long-latency
- Non-response, migration and loss-to-follow-up

Comparison between case-control and cohort studies

Case-control studies	Cohort studies
<ul style="list-style-type: none"> • Compares groups based on disease status • Quicker and so relatively cheaper • Not good for rare exposures • Can study a range of exposures for a single outcome or disease • Prone to information (recall) bias • Cannot establish that the exposure precedes the outcome/disease • Cannot measure incidence 	<ul style="list-style-type: none"> • Compares groups based on exposure status • Large and time-consuming and so relatively expensive • Not good for rare diseases • Can study a range of outcomes or diseases for each exposure • Prone to losses to follow-up & selection bias • Can establish that the exposure precedes the outcome/disease • Can directly measure incidence

Experimental Studies

- Randomised controlled trials (RCT)
 - Trial: an experiment or intervention (not passive observation)
 - Controlled: resemble laboratory experiment in basic science
 - Randomised: random allocation of exposure
- Therapeutic trials
- Preventive (or primary prevention trials)



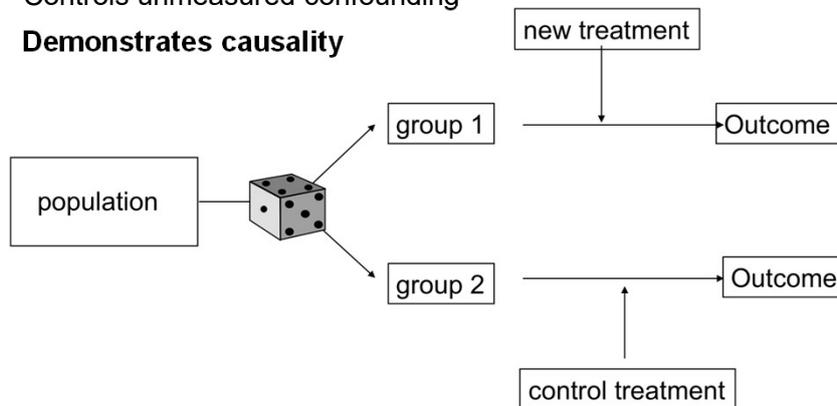
RCT

Should only be testing the effect of the intervention
everything else should be the same.

Investigator controls the intervention or treatment

Controls unmeasured confounding

Demonstrates causality



Purpose of RCT

To evaluate a new treatment

Scientifically

unbiased evaluation
controlled comparison

Safely

ethical considerations

Non-random trials

Patients are selected to receive new or standard treatment

- ❖ Selection bias (e.g. according to prognosis)
- ❖ Confounding – groups may differ systematically other than in the treatment given

Sampling

- ❖ Reference population
 - ❖ Group to which results are applicable (i.e. scope of PH impact of intervention)
- ❖ Experimental population
 - ❖ Group in which trial is conducted
 - ❖ Representative of reference population
 - ❖ Sample size
 - ❖ Sufficient number of outcomes
 - ❖ Follow-up
- ❑ Consider collecting baseline data and/or outcomes for those eligible but unwilling to participate

Randomisation

- ❖ Random allocation gives **equal chance** of receiving each treatment
- ❖ Groups likely to have **similar** characteristics by chance (distributes both known and unknown confounders equally between control and experiment groups)
- ❖ Reduces selection **bias** if patients enter trial before randomisation (recruit, consent, then randomise)
- ❖ Increased credibility

Randomisation

- o Toss unbiased coin
- o Random number tables
- o **Usually**, computer generated random numbers
- o Block randomisation: randomise subgroups
- o Factorial design: multistage randomisation (e.g. to aspirin & β -carotene)

The Placebo effect

“Even if the therapy is irrelevant to the patient’s condition, the patient’s attitude to his or her illness, and indeed the illness itself, may be improved by a feeling that something is being done about it” – Pocock SJ, 1983

- ❖ Hence, difference between new treatment and no treatment groups could be due to
 - ❖ **True treatment effect**
 - ❖ **placebo effect**

Allocation concealment

- ❖ Not disclosing to patients and those involved in recruiting trial participants the allocation sequence before random allocation occurs.
- ❖ The allocation sequence is the order in which participants are to be allocated to treatment. e.g. ABBA, BABB, BAAB, ABAA
- ❖ Allocation concealment meant that it was not possible to influence which patient received the next treatment in the sequence.
- ❖ It prevents subversion of the recruitment and treatment allocation of participants.

Blinding

Not disclosing to participants and outcome assessors the treatment allocations after random allocation.

- ❖ e.g. make treatment appear identical taste, appearance, texture, dosage regime, etc
- ❖ Compare active drug with a **placebo** (an inert substance similar in appearance, taste, texture...)
- ❖ **Single blind** – patient or clinician or assessor does not know the treatment allocation (*usually patient*)
- ❖ **Double blind** – two or more of patient, clinician, assessor does not know the treatment allocation (*usually patient + clinician/assessor*)

Follow-up: compliance

Reasons for noncompliance:

- ❖ Side effects, memory, etc.

To improve compliance

- ❖ Type of participants: high risk vs. healthy
- ❖ Frequent contacts with participants
- ❖ Duration of intervention
- ❖ Calendar packs
- ❖ Measuring compliance
 - ❖ Self-report
 - ❖ Pill count
 - ❖ Biochemical parameters to validate self-report
- ❖ Pursue follow-up data for all participants (complaint or not)

Analysis, interpretation

- ❖ **Chance:** sample size, (but also number of endpoints, differential compliance)
- ❖ **Selection bias:** randomisation, concealment
- ❖ Reporter bias & Observer bias: blinding
- ❖ **Confounding:** randomisation,
 - ❖ If baseline characteristics different adjust statistically

Preserve the power of randomisation: "once randomised, always analyse!"

Ethical issues

Random allocation versus best treatment for each individual patient

1. Reasonable uncertainty about which treatment is better (**clinical equipoise**)
2. Informed consent

Stopping rule

❖ Harm:

- Procedures in place for immediate un-blinding of clinician in the event of serious side effects or other clinical emergency
- Terminate study before originally scheduled if one treatment is clearly harmful

❖ Cost

- Terminate to save resources if preliminary data indicate clear benefit on the primary endpoint due to the intervention

RCT studies: advantages/disadvantages

Advantages:

- Designed to minimise bias and confounding
- Causality
- Disease events of interest always occur after study initiation – prospective
- Allows direct estimation of incidence in exposed and non-exposed

Disadvantages:

- expensive and time consuming
- ethical problems
- generalisability

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Synopsis of Different Study Designs

	Cross-sectional	Case-control	Cohort	RCT
Timing	short-term	short-term	long-term	variable
Exposure	simultaneous	retrospective	starting point	intervention
Disease status	simultaneous	starting point	prospective	prospective
Costs	variable	usually low	high	high
Ethics	standard	standard	complex	complex
Strengths	burden of disease	rare disease	temporality	gold standard for causality
Issues	confounding/ reverse causation	recall bias	Loss to follow-up	selection bias

Recommended Reading...

- Bhopal RS. Concepts of Epidemiology. Oxford University Press
- Gordis L. Epidemiology. W.B. Saunders Company
- Pocock SJ. Clinical trials: a practical approach. Wiley (Chichester)
- Jadad A. Randomised controlled trials. BMJ Books (London)