Universidad del Cauca

ERASMUS UNIVERSITEIT ROTTERDAM

THE RESEARCH QUESTION AND STUDY DESIGNS

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Right problem and right question

"An approximate answer to the right problem is worth a good deal more than an exact answer to an approximate problem." ~ John Tukey

Research question

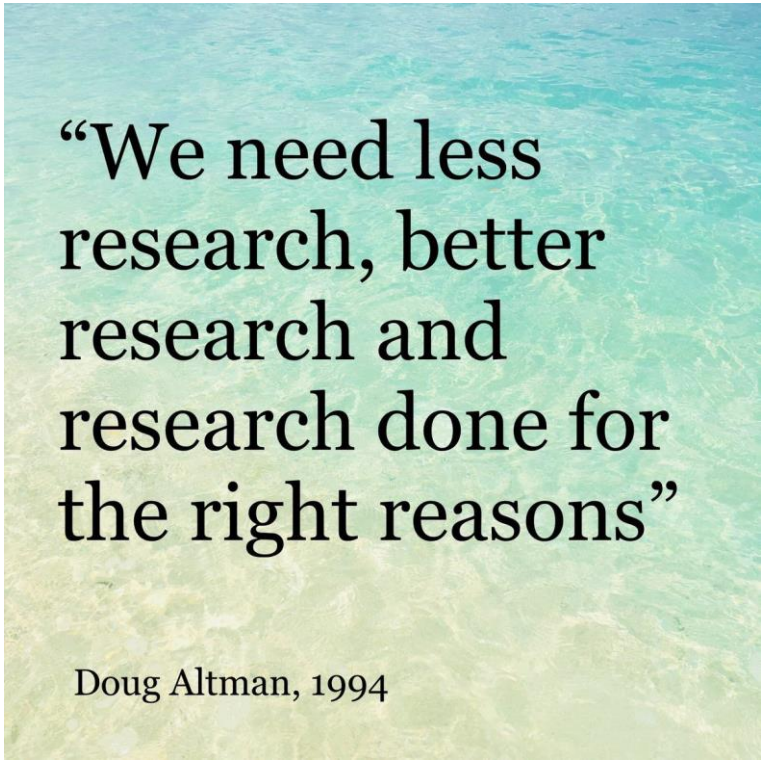
Feasible

Interesting

Novel

Ethical

Relevant



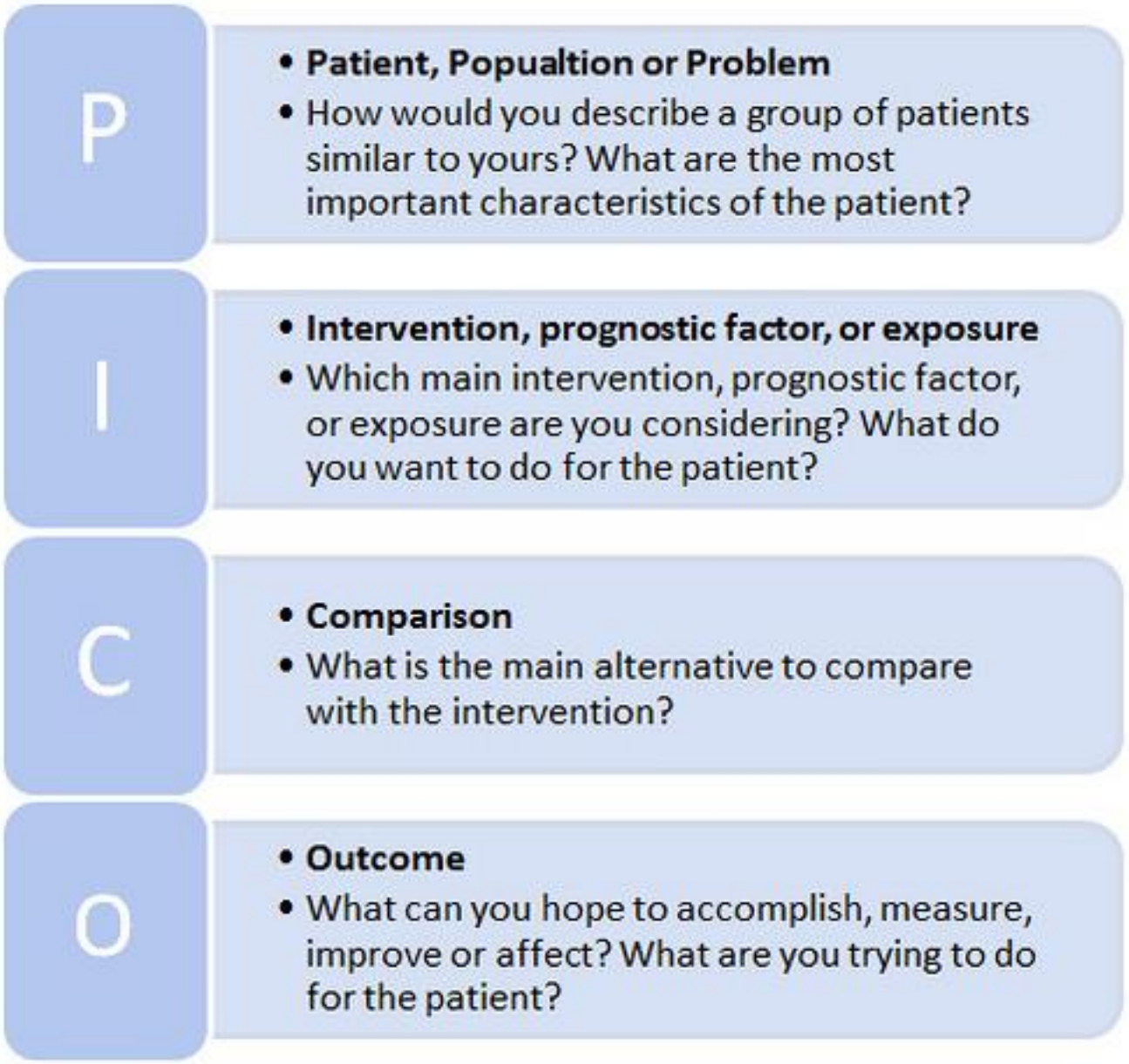
¿What is the research question?

Step 1. Determine the components of the research question and the type of question under study

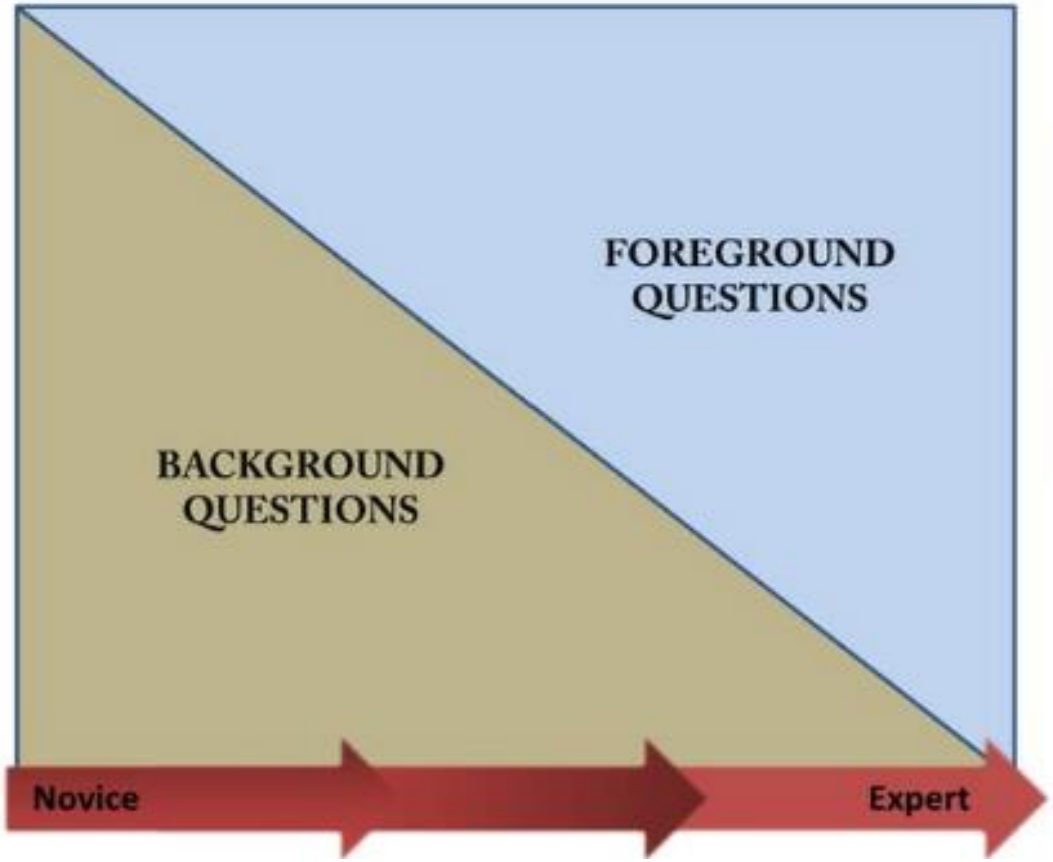
- PO. **P**opulation and **O**utcomes
- PICOt.

Step 2. Classify the type of research question

- Prevention
- Screening
- Diagnosis
- Prognosis
- Incidence
- Prevalence
- Etiology / Treatment
- Harm


P
• Patient, Popualtion or Problem
• How would you describe a group of patients similar to yours? What are the most important characteristics of the patient?
I
• Intervention, prognostic factor, or exposure
• Which main intervention, prognostic factor, or exposure are you considering? What do you want to do for the patient?
C
• Comparison
• What is the main alternative to compare with the intervention?
O
• Outcome
• What can you hope to accomplish, measure, improve or affect? What are you trying to do for the patient?

Background vs *Foreground questions*



Background Questions
- About conditions

Foreground Questions
- About choices

Background

- General knowledge
- General questions like
  - Who, what, when, where ...
  - Range reduction
  - PO Components

What is the incidence of postoperative nausea and vomiting after abdominal surgery?

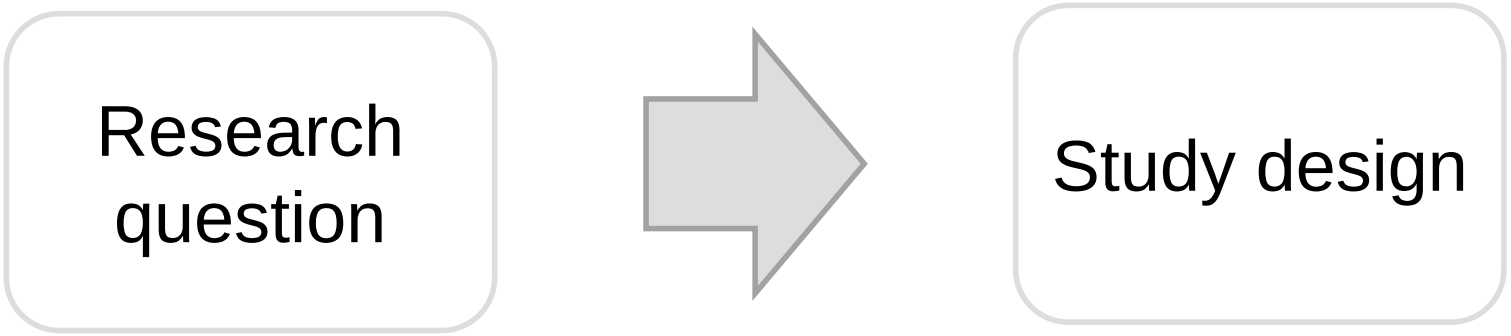
Who has the most postoperative pain experience after surgery?

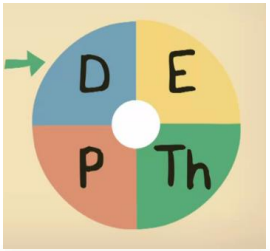
Foreground

- More specific
- PICO(t)
- Structured to facilitate its use and / or search
  - P - Population / Problem
  - I - Intervention / Exposure
  - C - Comparison / Control
  - O - Outcome
  - (t) - timeframe

What is the incidence of early postoperative cognitive decline in patients older than 60 years under general anesthesia compared to regional anesthesia?

Question and study design

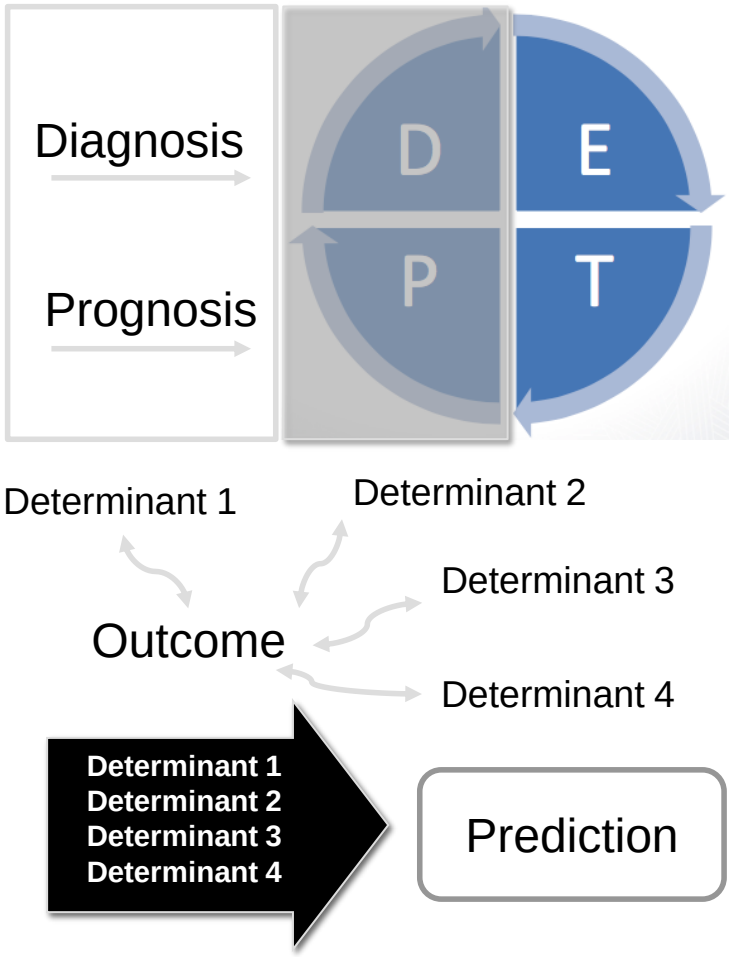




- Diagnosis
- Etiology / Causality
- Prognosis
- Treatment / Therapy

Methodological design

If there are unclear questions the design cannot be adapted appropriately and the horizon is lost, including the analytical and interpretive



Diagnosis

- Accurate identification of disease status
- Crucial to establishing "abnormality"
- It seeks to improve the diagnostic process

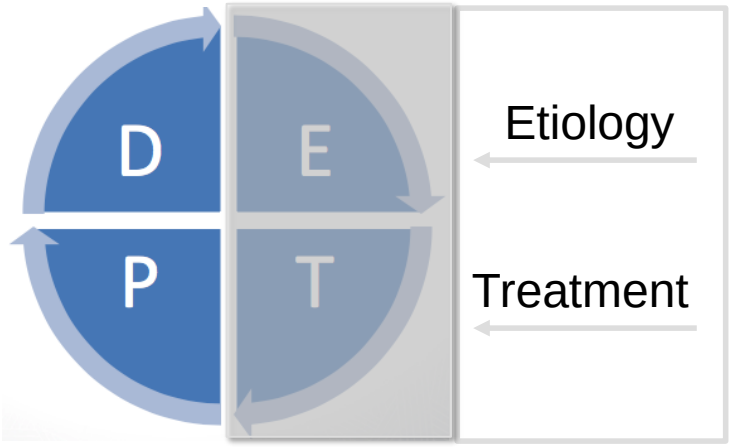
Prognosis

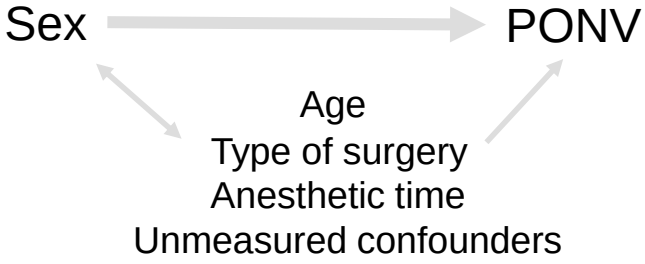
- Estimate a patient's prognosis (future)
- Important for everyone
- What happens if treatment is not started?

Examples

Does the use of troponin T in the postoperative period of non-cardiac surgery improve the diagnosis of acute coronary event if added to the classic signs and symptoms?

What is the **prognosis -in terms of mortality and morbidity-** at 30 days of patients diagnosed with acute perioperative myocardial infarction?





Etiology / Cause

- Origin and cause(s) of diseases
- Determinants in its occurrence (risk factors)
- Useful in prevention (counterfactual reasoning)
- Why?

C A U S A L

Treatment / Therapeutics

- Does treatment improve prognosis?
- Effect(s) of interventions
- Benefits -vs- side effects (safety)

Examples

- Is the anesthetic time a risk factors of early postoperative cognitive impairment in patients with outpatient surgeries older than 60 years?
-
- In patients undergoing outpatient surgery, does the administration of antiemetics prevent the occurrence of PONV?

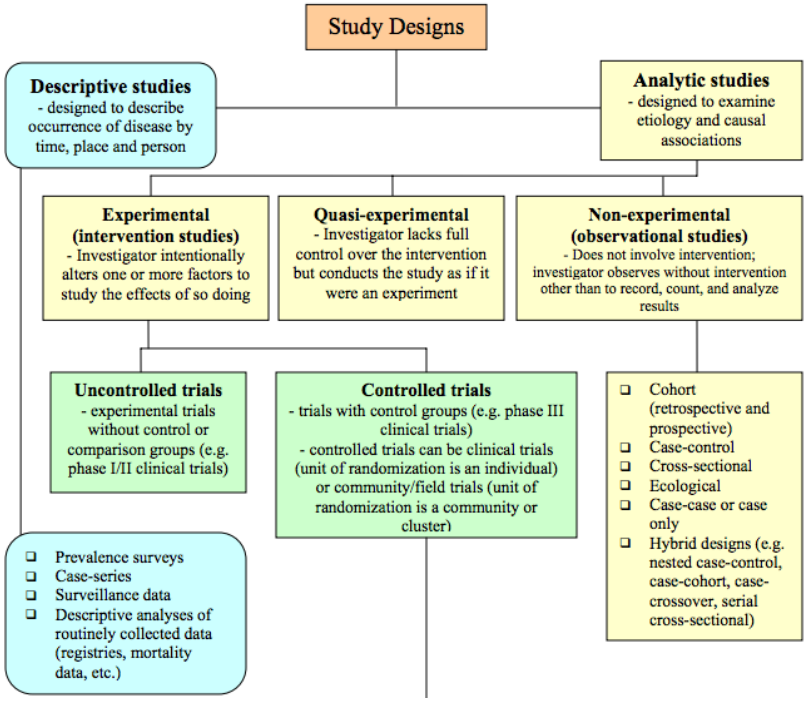
What is the frequency of respiratory complications in UCPA over a six-month period, in a medium-complex institution with a nursing-based recovery model?	**Incidence**
What is the quality of life in patients with chronic pancreatitis undergoing Whipple surgery compared to laparoscopic surgery?	**Prognosis**
What is the effectiveness of lidocaine use in reducing postoperative nausea and vomiting in pediatric patients?	**Treatment**
Is the use of ultrasound in the emergency room useful to detect the state of hypovolemic shock in traumatized patients?	**Diagnosis**
In adult patients taken to major non-cardiac surgery, is the preoperative glycemia a risk factor for the occurrence of infection in the first 30 postoperative days?	**Etiology / Cause**
What is the safety of using ketamine for sedation of mechanically ventilated patients diagnosed with severe SARS-CoV2 pneumonia?	**Harm**
What was the mortality from anti-personnel mines before and during the Colombian peace process?	**Prevalence / Incidence**

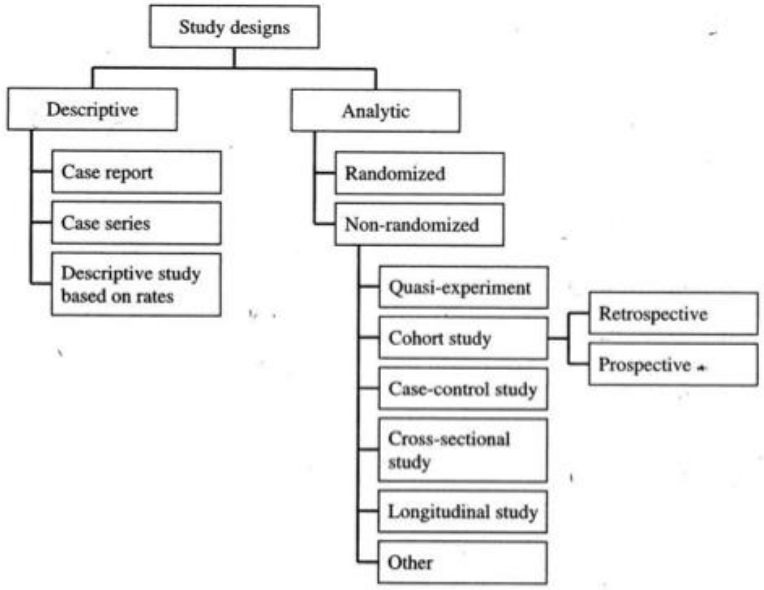
Question type	Research Designs
Effectiveness of an intervention	RCT > Experimental > RDD > CE
Diagnosis	Diagnostic test (Cross sectional*) > Cohort > RCT
Etiology / Cause	Cohort > Case-control > Cross sectional
Prognosis	Cohorte > RCT
Safety / Harm	RCT > Case-control > Cohort > Case Series > Case Report
Values and preferences	Qualitative research > Surveys (Cross sectional*)
Prevalence	Cross sectional > Cohort
Incidence	Cohort > RCT

The research process

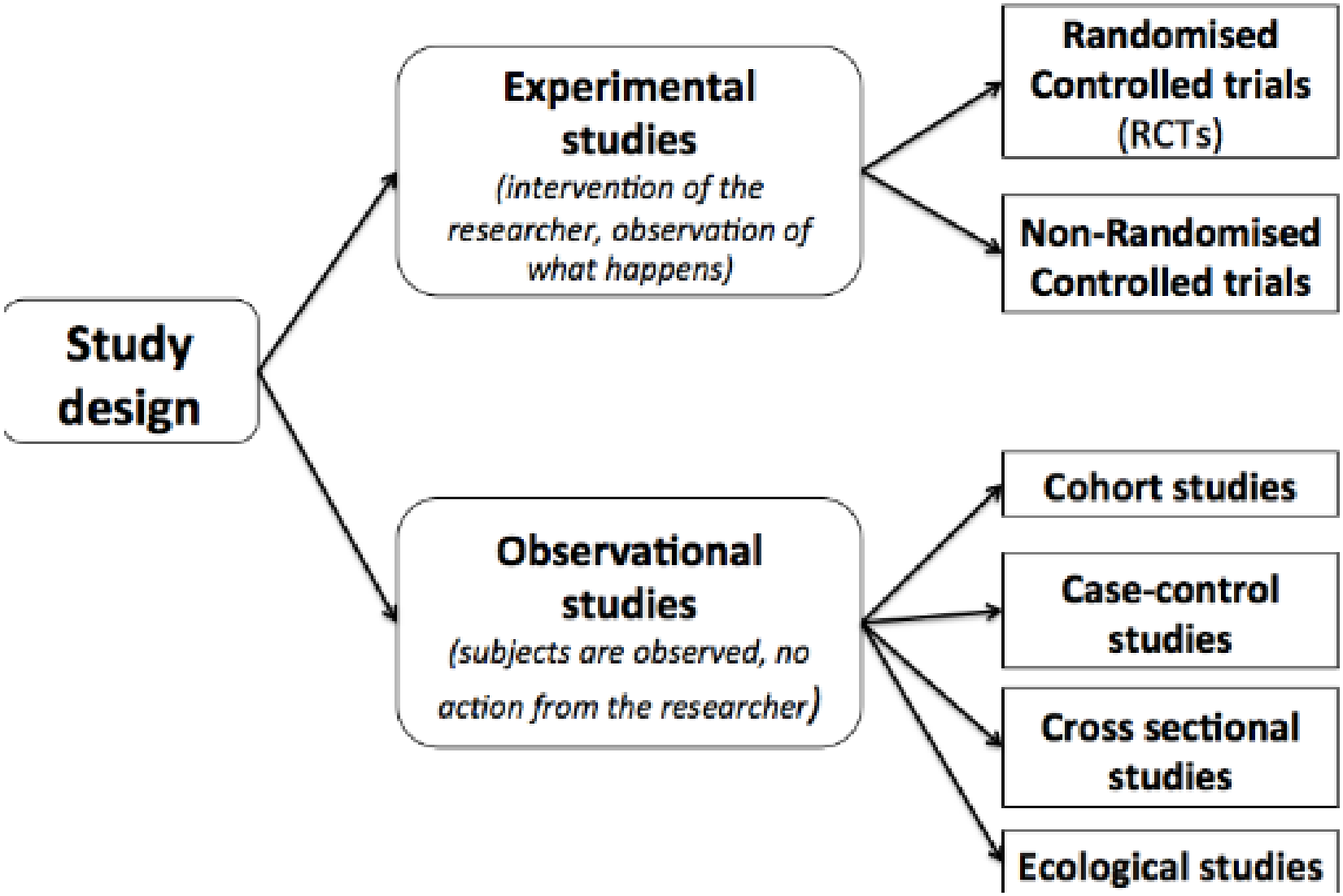
Element	Purpose
Research question(s)	Direct research It is the main objective of the process PICOt structured or unstructured
Background	Importance of the topic under study Existing knowledge and justification
Design	Strategy to find the answer Epidemiological methodology
Subjects under study	Selection of study participants Who they are and how they will be selected
Variables	What information will be collected Predictors, confounders, outcome(s)

Study designs





Koepsell & Weiss. Epidemiologic Methods. Oxford University Press, 2003



Grimes et al. Lancet 2002;359:57-61

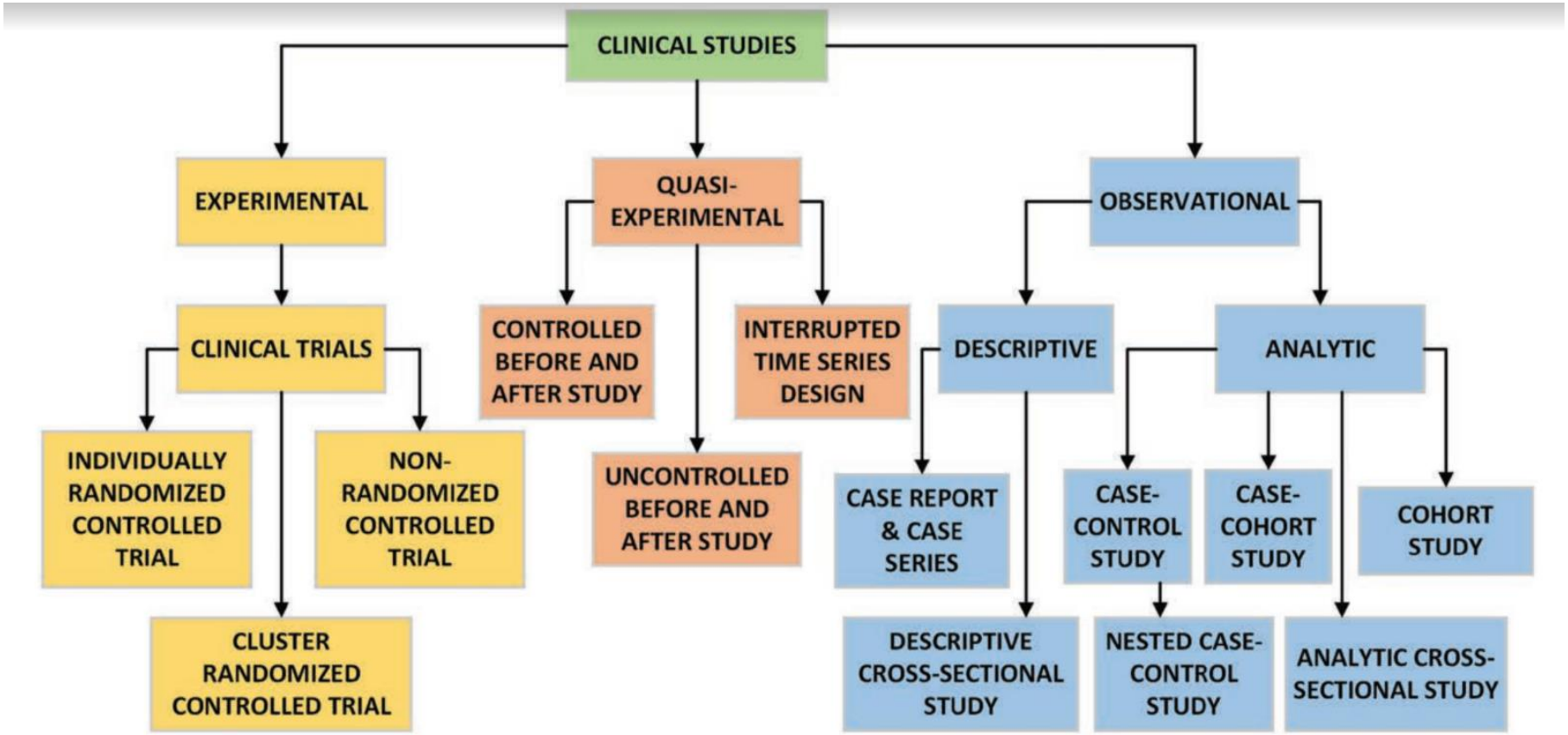


Figure 2. Research study design classification system or taxonomy.[1,4,11–13]

Prospective vs retrospective studies

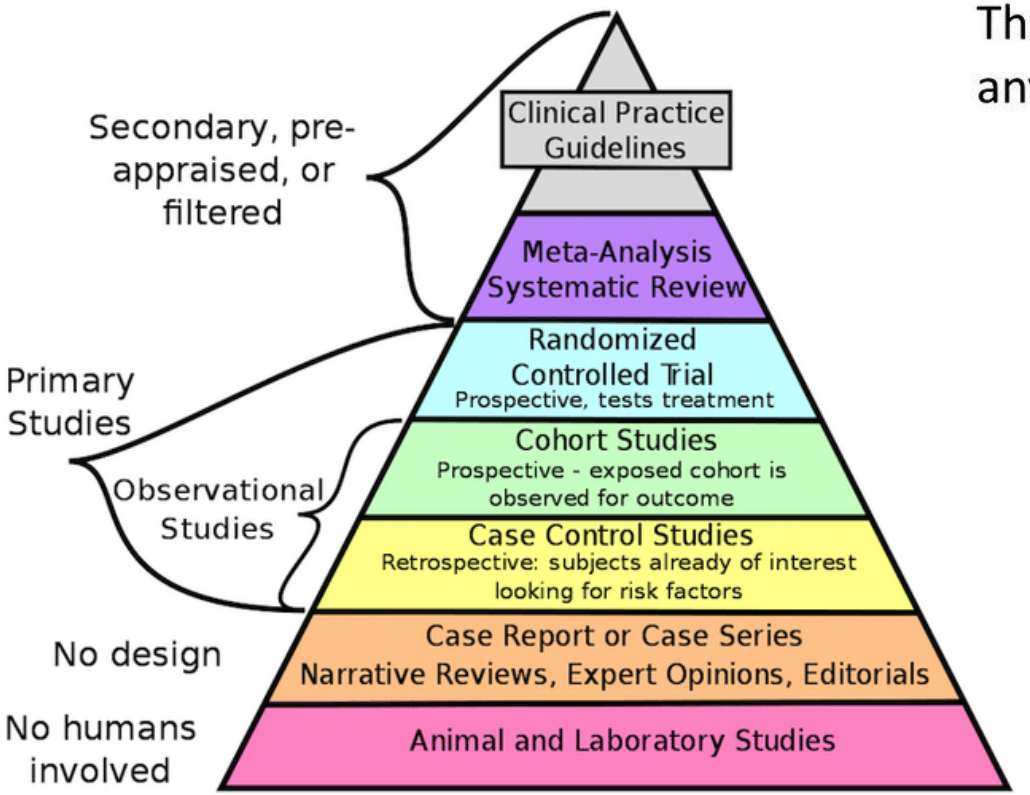
- It is not a good classification
- We must separate: the direction of exposure/outcome versus how the subjects were recruited

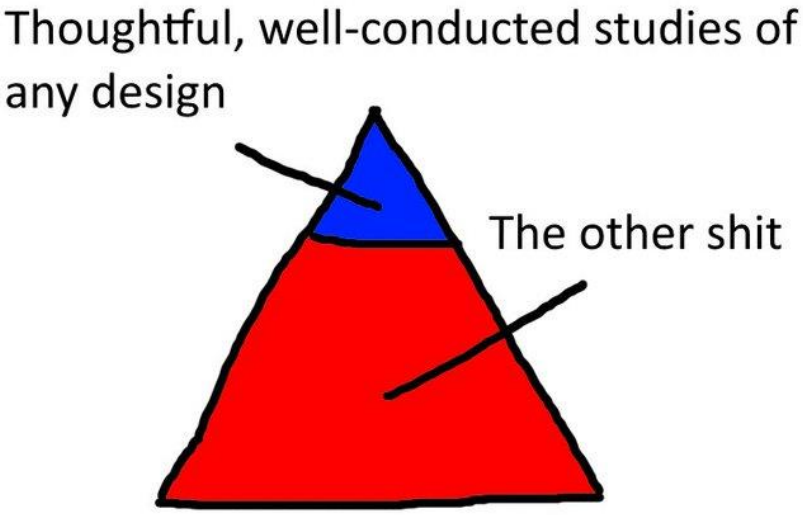
- Longitudinal o follow-up
  - It's also not very informative
  - RCTs and Cohort studies are longitudinal
  - Two designs without follow-up : CS, DTA

Key questions

1. Is there follow-up of participants from exposure(s) to outcome(s) ?
2. Was there follow-up (in the past)?
3. Is there an active intervention of the researcher or does it only observe what is happening?

Piramids? Not very accurate!





Cohort studies

- Population is an aggregate of subjects (share a condition)

- Closed cohorts
  - Group of subjects that are followed from a defined starting point to the occurrence of an outcome of interest
  - Cohort members do not change over time (except for mortality or lost of follow-up)
  - Individuals do not switch between exposure categories
  - Useful for short-term studies with high frequency of outcome

- Open cohorts or Dynamic population study DPS
  - Simulate real populations
  - Participants can enter or leave the study without compromising study´s integrity
  - Subjects under study contribute with person-time of exposure

“Cohort”

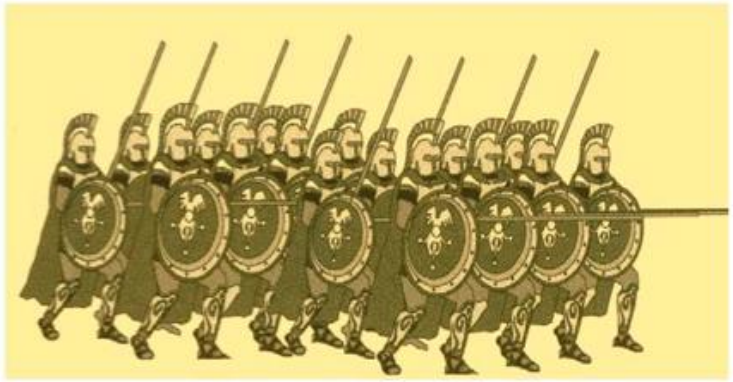


Figure 1: **An early cohort in search of favourable outcome**

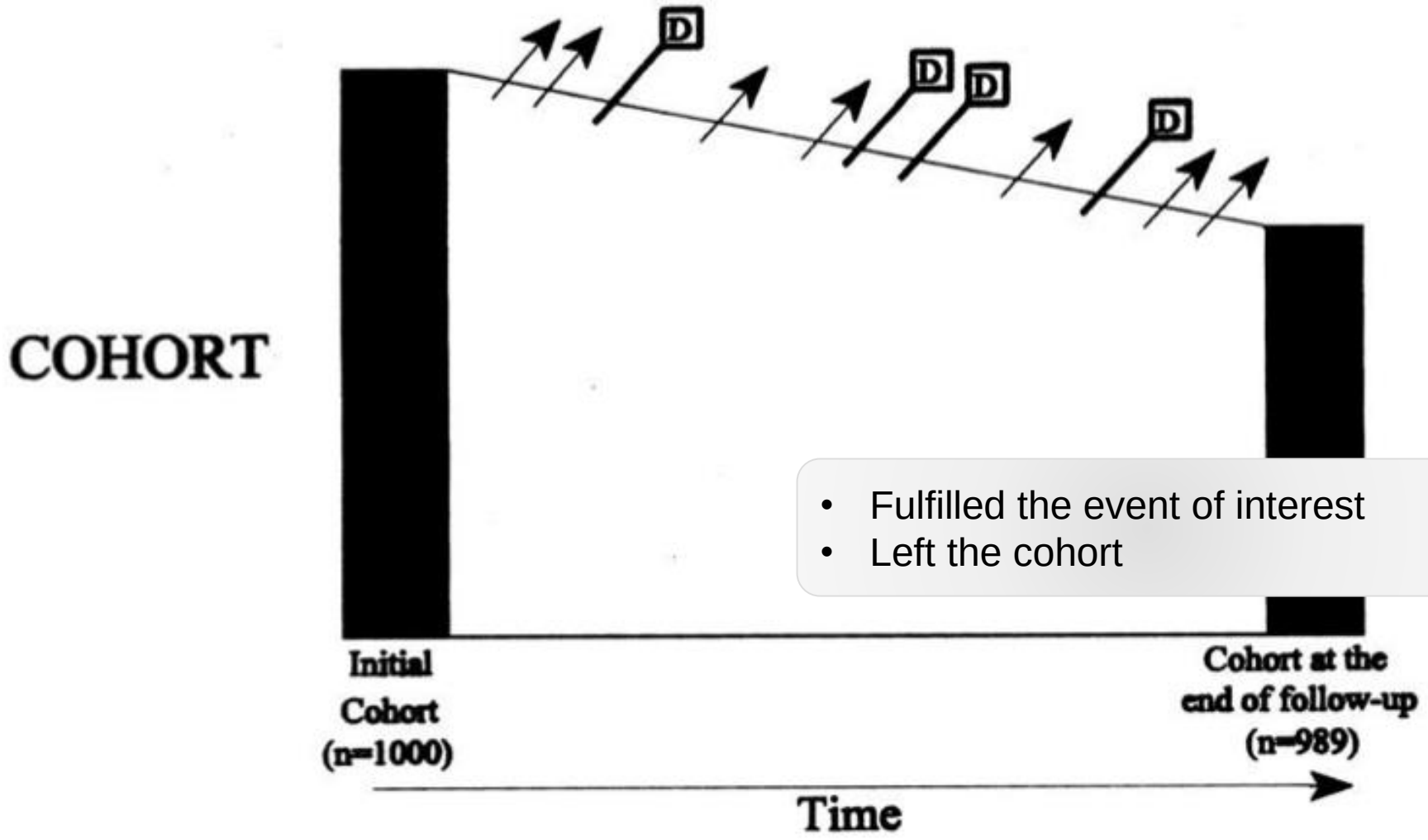
THE ROMAN LEGION

The Legion was split into 10 **Cohorts**.

The Cohorts were divided into **Centuries**. The First Cohort contained five centuries of 160 'crack troops.' The other cohorts contained six centuries of 80 men.

The centurion in charge of the First Cohort was called the **Primus Pilus**. He was the best!

1st cohort	2nd cohort	3rd cohort	4th cohort	5th cohort	6th cohort	7th cohort	8th cohort	9th cohort	10th cohort
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men



- Fulfilled the event of interest
- Left the cohort

Figure 1–13 Diagram of a hypothetical cohort of 1000 subjects. During the follow-up, four disease events (D) and seven losses to follow-up (arrows) occur, so that the number of subjects under observation at the end of the follow-up is 989.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Cohort studies

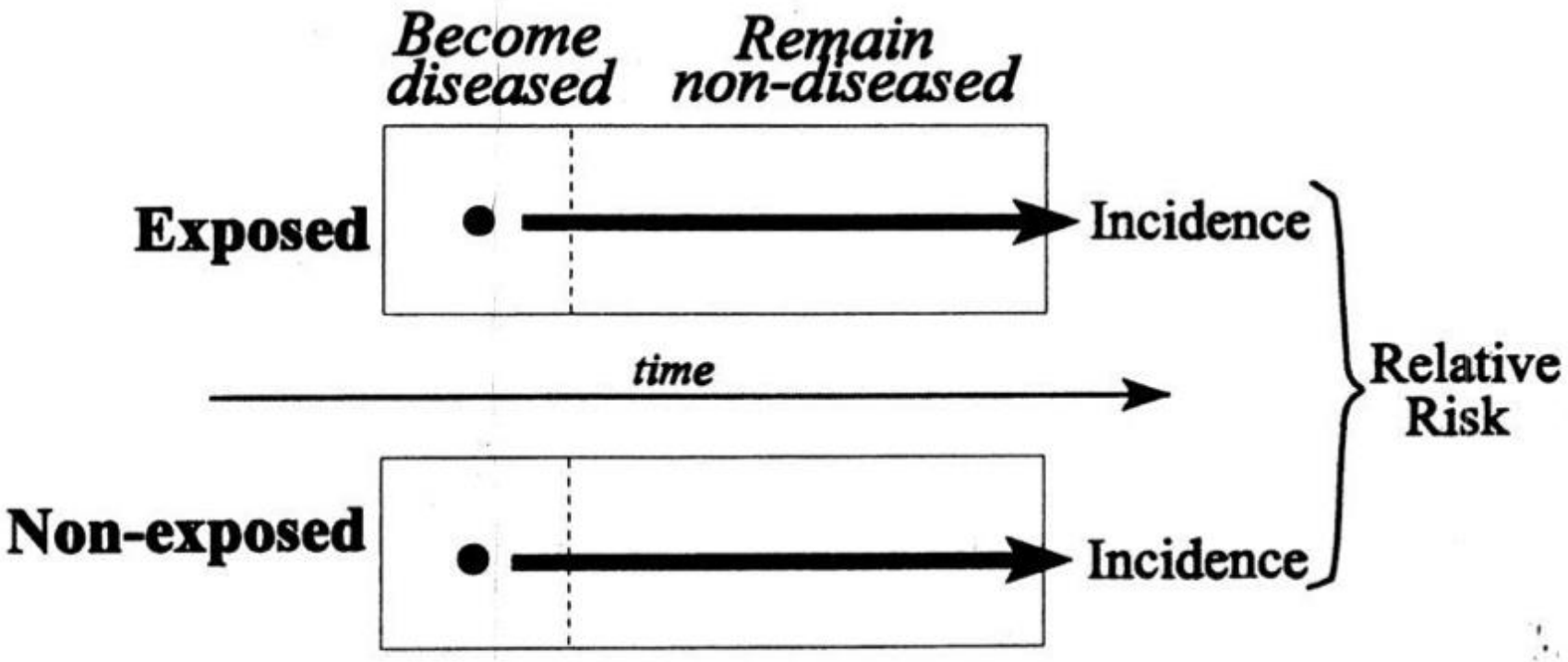
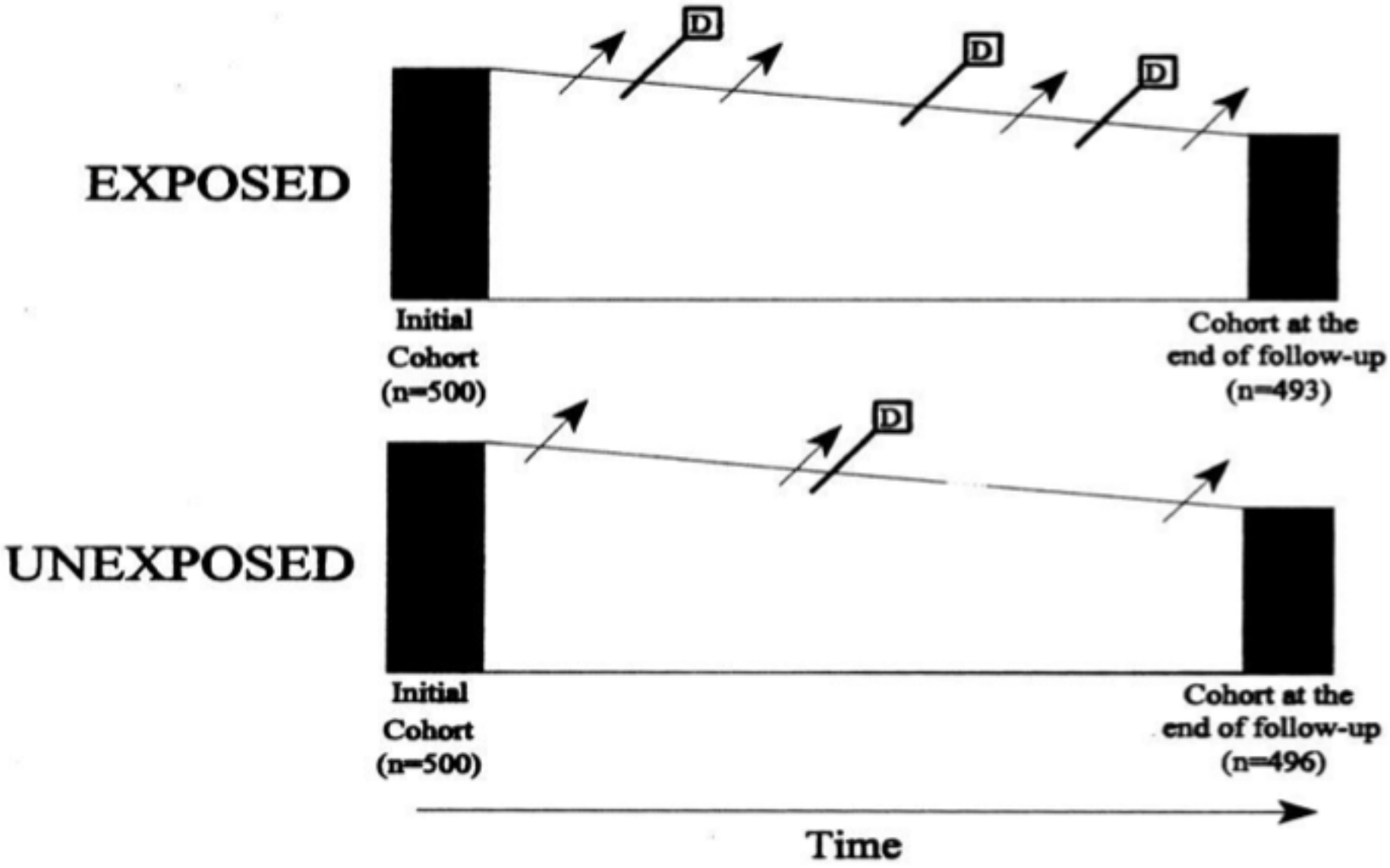
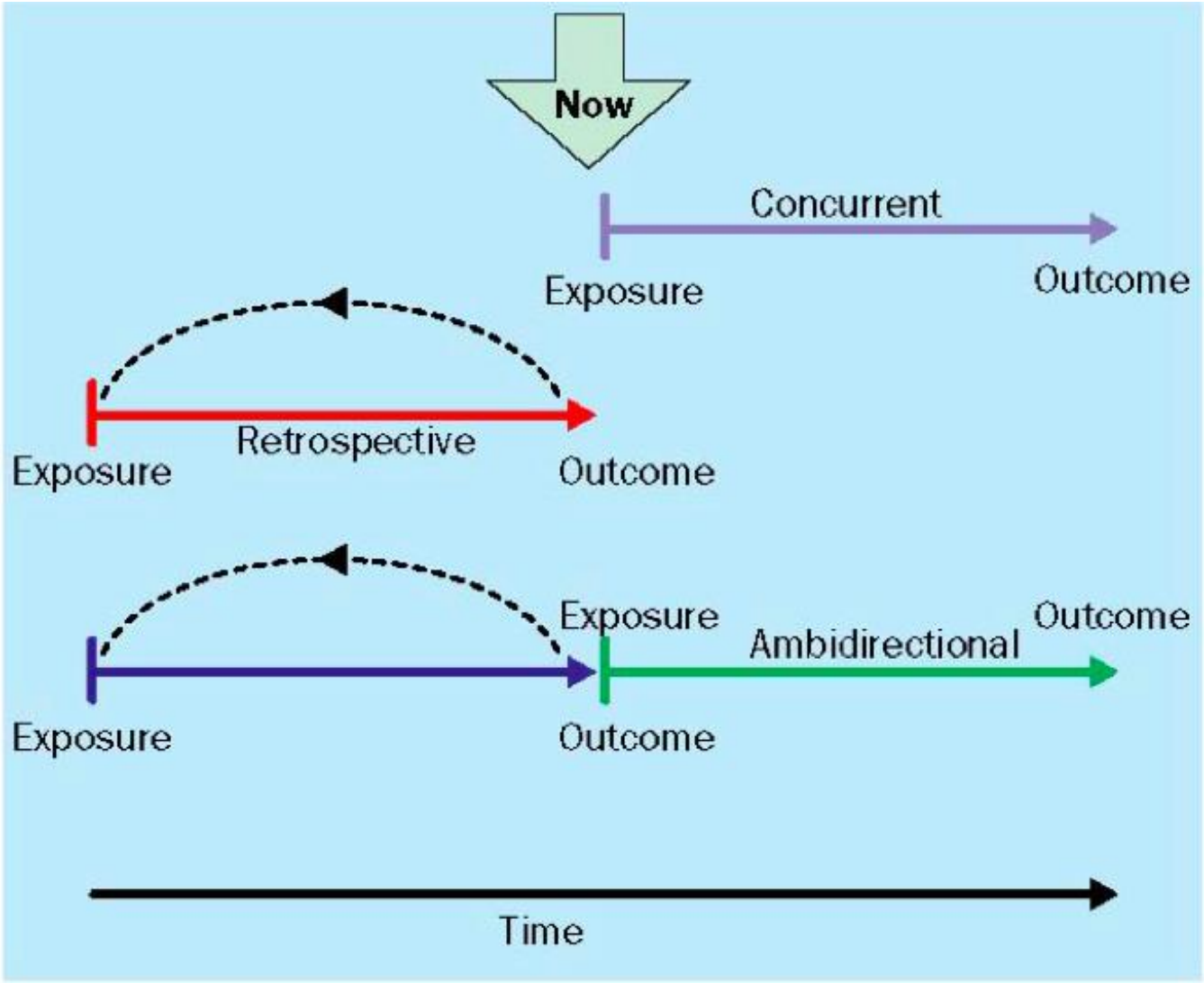


Figure 1–14 Basic analytical approach in a cohort study.


EXPOSED
D
D
D
Initial
Cohort
(n=500)
Cohort at the
end of follow-up
(n=493)
UNEXPOSED
D
Initial
Cohort
(n=500)
Cohort at the
end of follow-up
(n=496)
Time

Variations of cohort studies



Characteristics

Advantages

- Allow to quantify absolute risk and RR
- They follow the logic of the clinical question
- Assess exposure effects on several outcomes
- Useful in frequent outcomes

Disadvantages

- Economic costs
- Logistics costs
- Extended time
- May require large numbers of patients
- Losses during follow-up
-

Example. Rotterdam Study

- The Rotterdam Study is a prospective, population-based cohort study. The aim of the Rotterdam Study is to investigate factors that determine the occurrence of cardiovascular, neurological, ophthalmological, endocrinological, and psychiatric diseases in elderly people
- The study was established in 1990 by Prof. Albert Hofman of the department Epidemiology & Biostatistics at the Erasmus Medical Center in Rotterdam, the Netherlands
- Inhabitants of Ommoord, a suburb of Rotterdam, were invited to participate on a regular basis
- The findings of the Rotterdam Study have been presented in close to a 1,000 research articles and reports

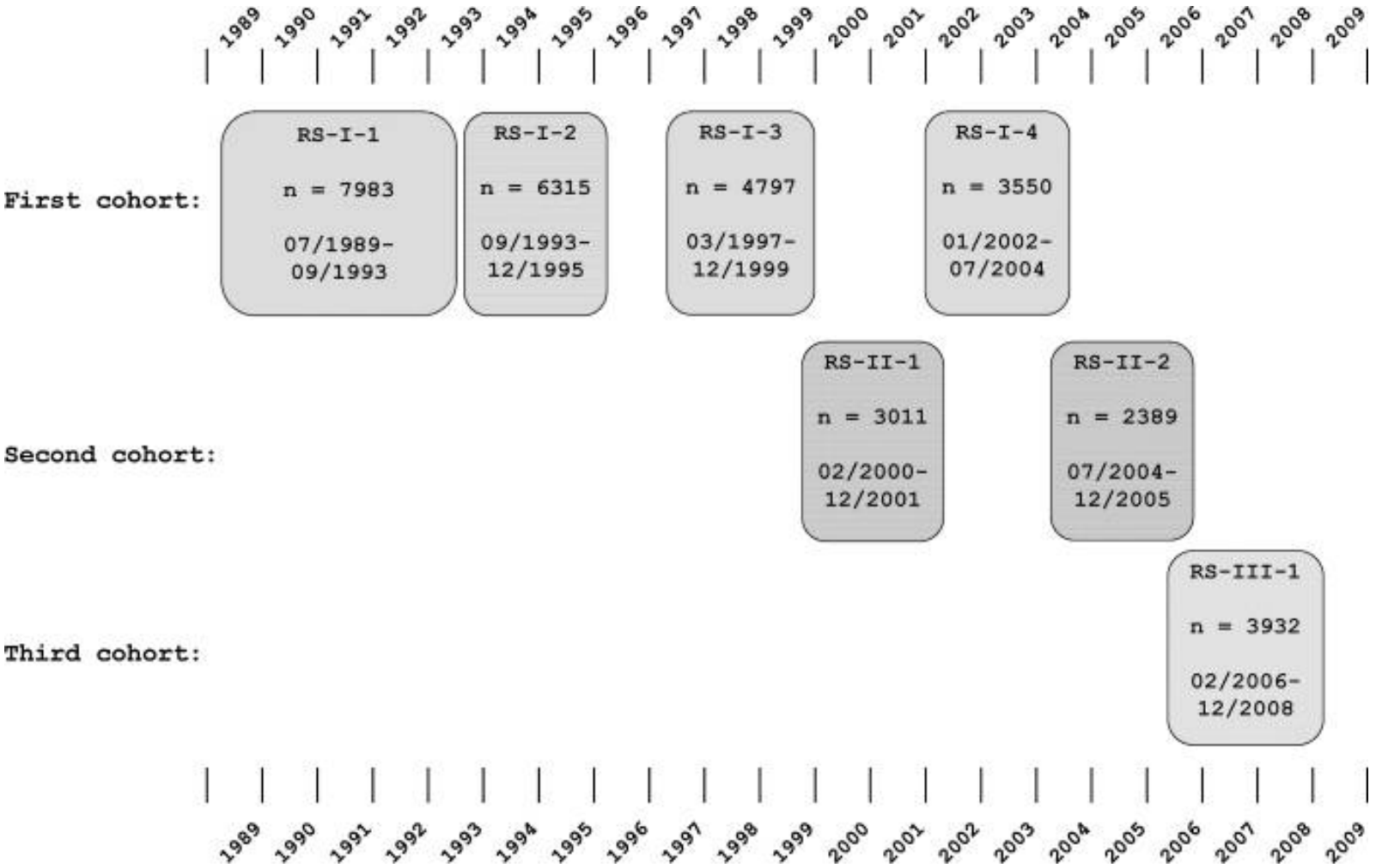


Diagram of examination cycles of the Rotterdam Study

Rotterdam Study

- The initial cohort (RS-I) started out in 1990 with 7,983 men and women aged 55 years and over. Follow-up visits were held in 1994-1995, in 1997-1999, 2002–2004, and 2009-2011.

Questions

- Cardiovascular diseases: What are the determinants of presence and progression of atherosclerotic vessel wall abnormalities and of occurrence of cardiovascular disease and what is the role of disturbances in hemostatic function ? Is progression of atherosclerosis in asymptomatic elderly subjects a prelude to cardiovascular events ?

- Neurologic diseases: What is the prevalence and incidence of various types of dementia and of Parkinson's disease, and which are the determinants?

- Locomotor diseases: What is the prevalence and incidence of vertebral and hip fractures and its determinants? What are the determinants of bone mineral density?

- Opthalmic diseases: What is the prevalence and incidence of age-related macula degeneration and of glaucoma, and which are the determinants ?

http://www.erasmus-epidemiology.nl/research/ergo.htm

Case-control study

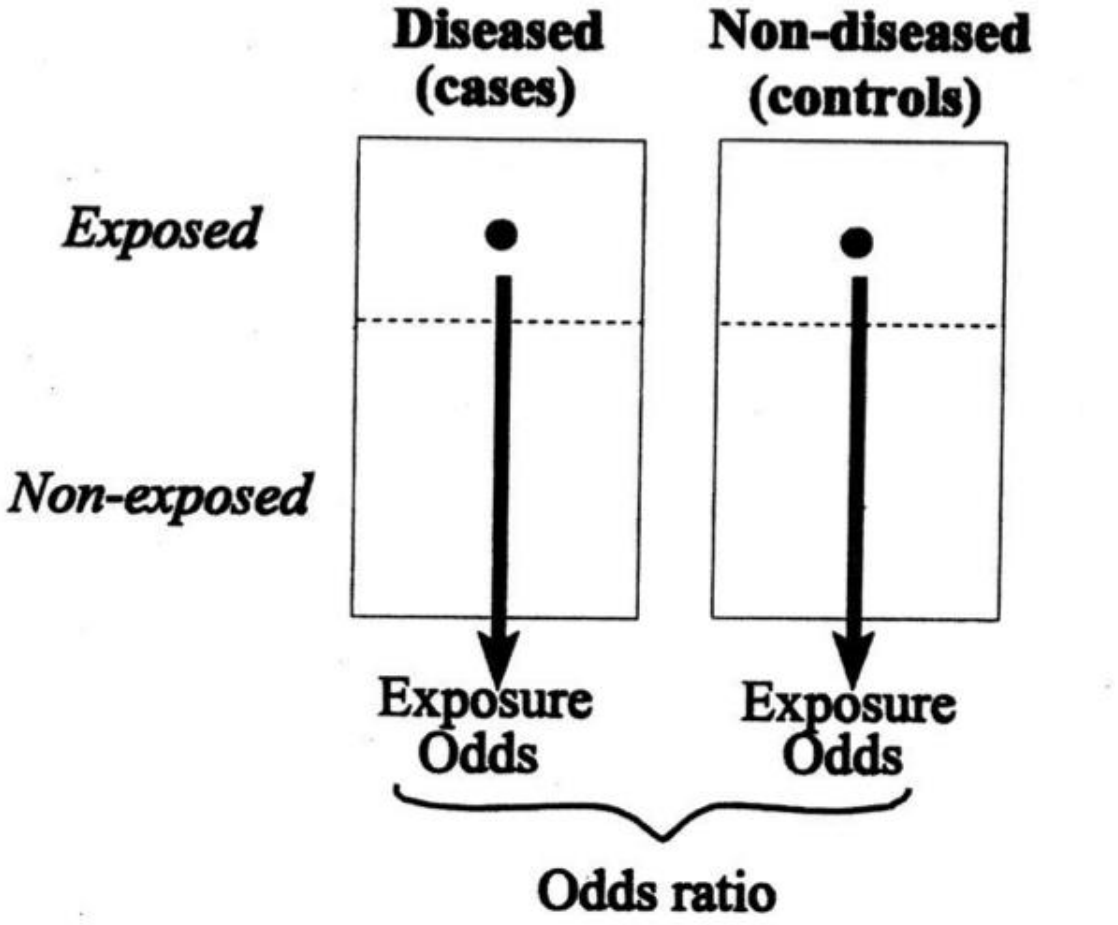
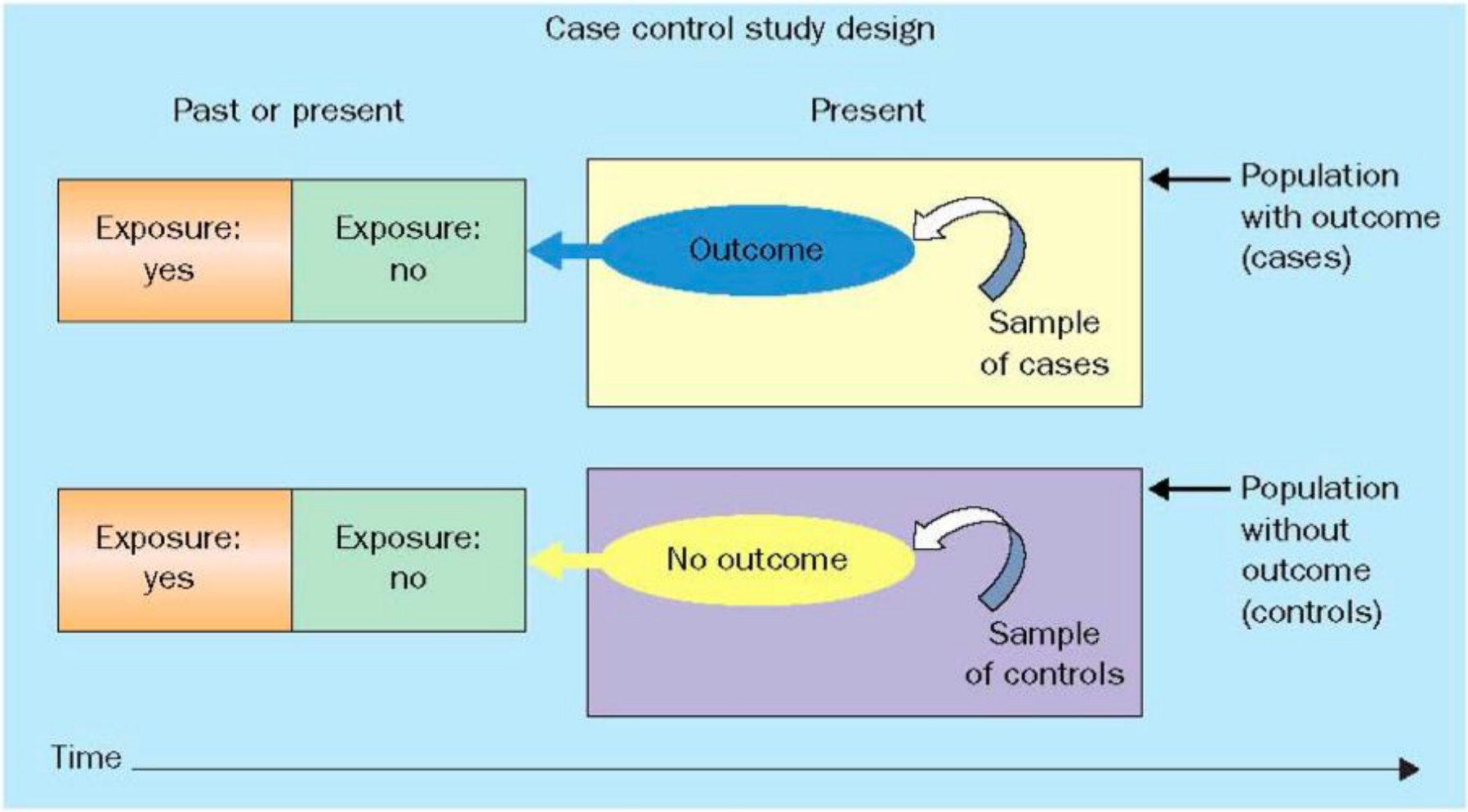
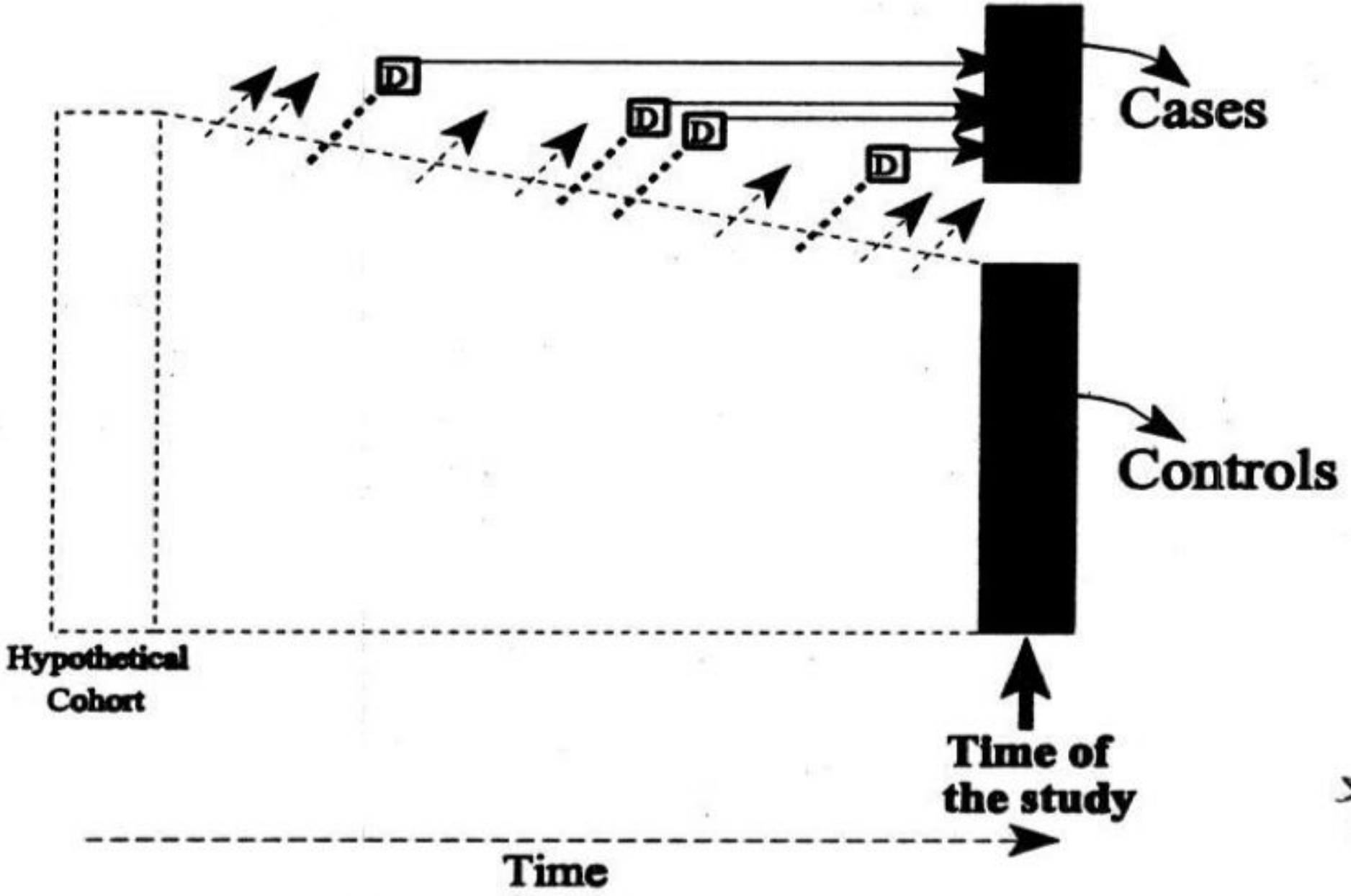


Figure 1–17 Basic analytical approach in a case-control study.



Schematic diagram of case-control study design


D
D
D
D
Cases
Controls
Hypothetical
Cohort
Time of
the study
Time

Samping strategies

- Controls should represent the distribution of exposure in the study
- Must be selected regardless of exposure

Characteristics

Advantages

- Efficiency in studying diseases (outcomes) or rare events
- Short time
- They have no follow-up
- Economic
- Relatively easy case identification

Disadvantages

- Biases in exposure measurement (misclassification)
- Difficulties in establishing controls
- They do not determine absolute risk or incidence or prevalence. They make an indirect estimate through odds.

Table 5–9 Comparison of the Characteristics of Cohort and Case-Control Studies

Cohort Study	Case-Control Study
Complete source population denominator experience tallied	Sampling from source population
Can calculate incidence rates or risks, and their differences and ratios	Can calculate only the ratio of incidence rates or risks (unless the control sampling fraction is known)
Usually very expensive	Usually less expensive
Convenient for studying many diseases	Convenient for studying many exposures
Can be prospective or retrospective	Can be prospective or retrospective

Example

		Lung Cancer: Case	Lung Cancer: Control
Tobacco Smoking	Yes	597	666
	No	8	114
		605	780
% Exposed to Tobacco		$\frac{597}{605} = 99\%$	$\frac{666}{780} = 85\%$

Source: Wynder and Graham. (1950). *JAMA*, 143: 329–336.

Cross sectional studies

- Prevalence studies

- A study that examines the relationship between a state of health-disease (exposure), other variables of interest that already exist and one or more outcomes, in a population in a given time

- The exposure-outcome relationship is measured in terms of prevalence

- Or according to the presence or absence of exposure in those who have or do not have the outcome

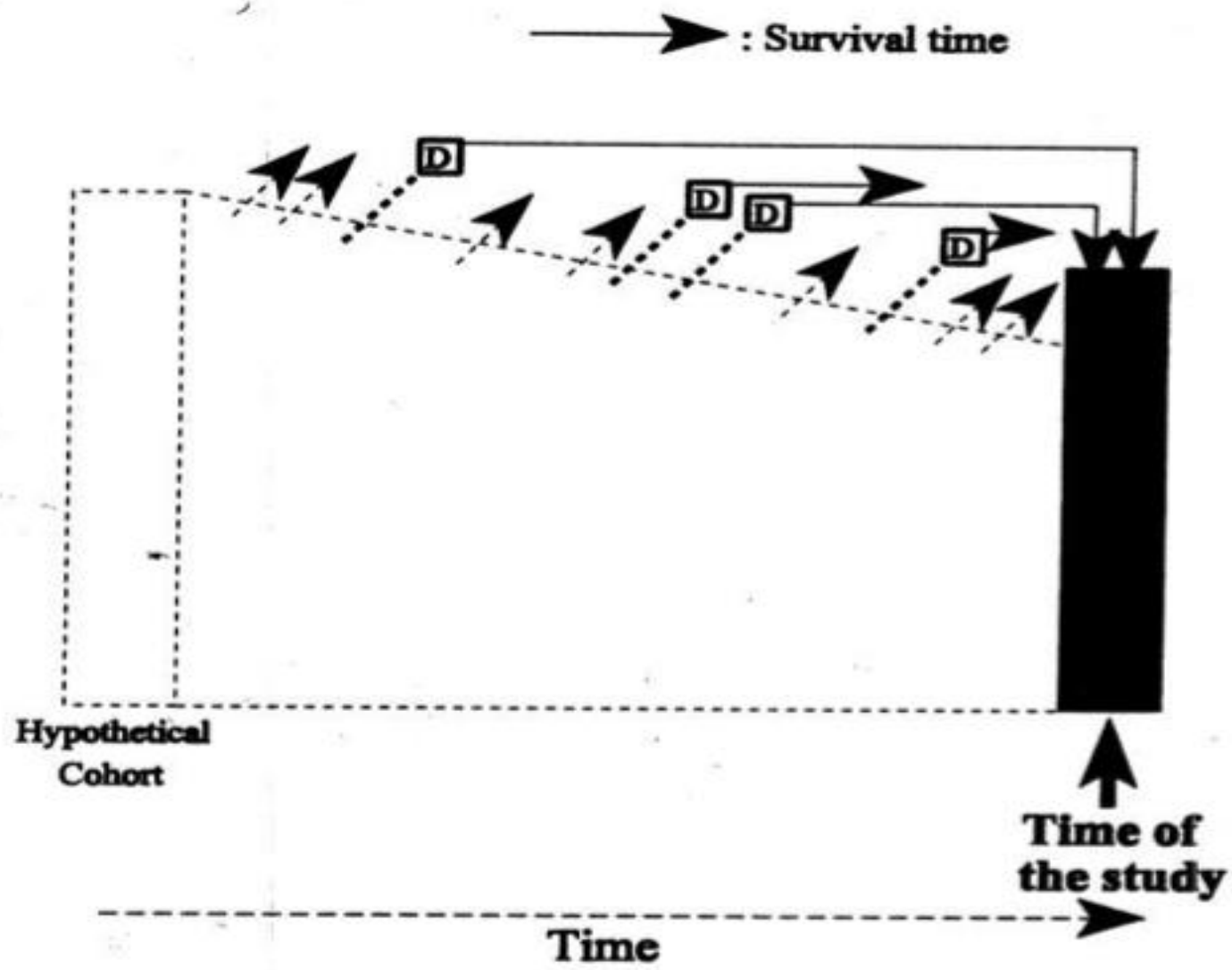


Figure 1–22 Schematic representation of a cross-sectional study, conceptually and methodologically analogous to the case-based case-control study represented in Figure 1–19, except that instead of explicitly selecting cases and controls, it selects a sample of the entire population. Broken diagonal lines with arrows represent losses to follow-up. Cases are represented by "D" boxes.

Characteristics

Advantages

- High control in subjects' selection and measurements
- There are no loss to follow-up
- Absence of waiting time
- Economic, fast studies
- First step for further studies

Disadvantages

- There are not a sequence of causality
- Not useful in rare diseases
- They do not determine incidence or absolute risk
- Potential bias

Example

- As part of a population-based screening program, a type of cross-sectional study, they evaluated the prevalence of microalbuminuria in relatives of patients with chronic kidney disease (CKD) compared with the general population. The investigators found that the prevalence of microalbuminuria was significantly greater in those with a family history of CKD than the prevalence in the age- and sex-matched control group.

- The prevalence of microalbuminuria was 9.5% in those with a family history of CKD. This was significantly greater than the prevalence of 1.4% in the age- and sex-matched control group with no family history of CKD.

- The prevalence of microalbuminuria in relatives of patients with CKD is greater than in an age- and sex-matched control group from the general population.

Bello AK, Peters J, Wight J, de Zeeuw D, El Nahas M; European Kidney Institute. A population-based screening for microalbuminuria among relatives of CKD patients: the Kidney Evaluation and Awareness Program in Sheffield (KEAPS). Am J Kidney Dis. 2008 Sep;52(3):434-43.

Observational study design measures of disease, measures of risk, and temporality.

Cross-sectional	Point prevalence Period prevalence	Odds ratio Prevalence odds ratio Prevalence ratio Prevalence difference	Retrospective
Case-control	None	Odds ratio	Retrospective
Retrospective and prospective cohort	Point prevalence Period prevalence Incidence	Odds ratio Prevalence odds ratio Prevalence ratio Prevalence difference Attributable risk Incidence rate ratio Relative risk Risk ratio Hazard ratio	Retrospective only Both retrospective and prospective Prospective only

Activity

Researchers investigated whether pioglitazone was associated with an increased risk of bladder cancer in people with type 2 diabetes. Use of pioglitazone, an oral antidiabetic agent in the thiazolidinedione class, is controversial.

A cohort of 115.727 patients with type 2 diabetes was established, with patients entering the cohort if they had been newly treated with oral hypoglycaemic agents. Patients were considered to have been exposed to pioglitazone if they had ever taken it, and measures of duration of use and cumulative dosage were recorded.

In the cohort 376 cases of bladder cancer were diagnosed. Patients were considered to be a case if their cancer was diagnosed at least one year after entry to the cohort, to account for latency. Each case was matched to as many as 20 controls on year of birth, year of cohort entry, sex, and duration of follow-up. A total of 6699 controls were identified. The researchers reported that the use of pioglitazone was associated with an increased risk of bladder cancer among people with type 2 diabetes.

Which one of the following study designs best describes that used above?

a) Case-control study
b) Cohort study
c) Cross sectional study
d) Nested case-control study

Diagnostic test assessment DTA

Useful to know the value of a new diagnostic method

Value is measured in sensitivity and specificity

The value of the test in the patient is measured in positive and negative predictive values

A "gold standard" is indispensable

All participants in the study

↓

New / Index test

↓

All participants undergo the new test and GS simultaneously or within a short interval to avoid changes in the diseases status.

↓

Gold Standard (GS)

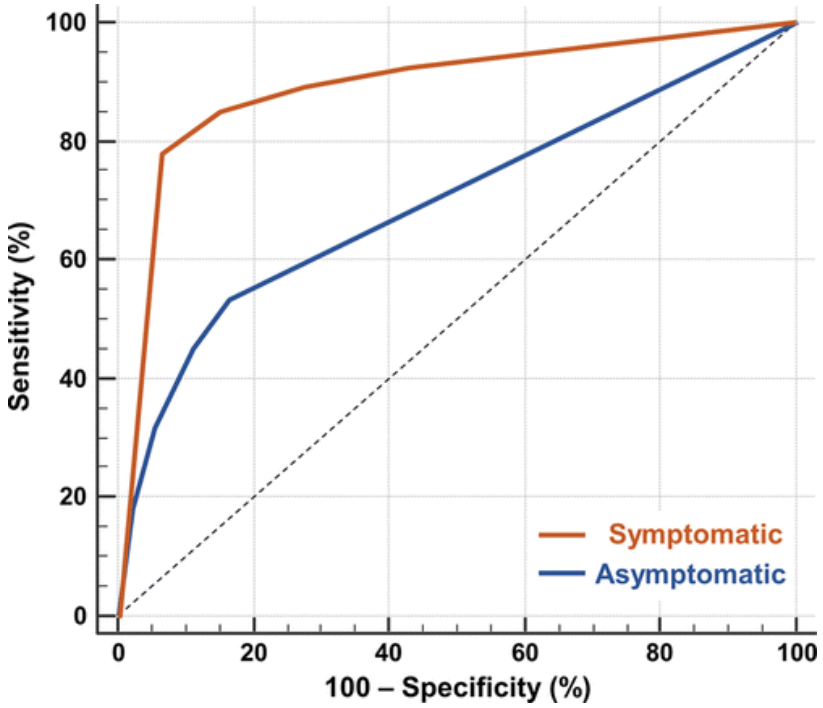
↓

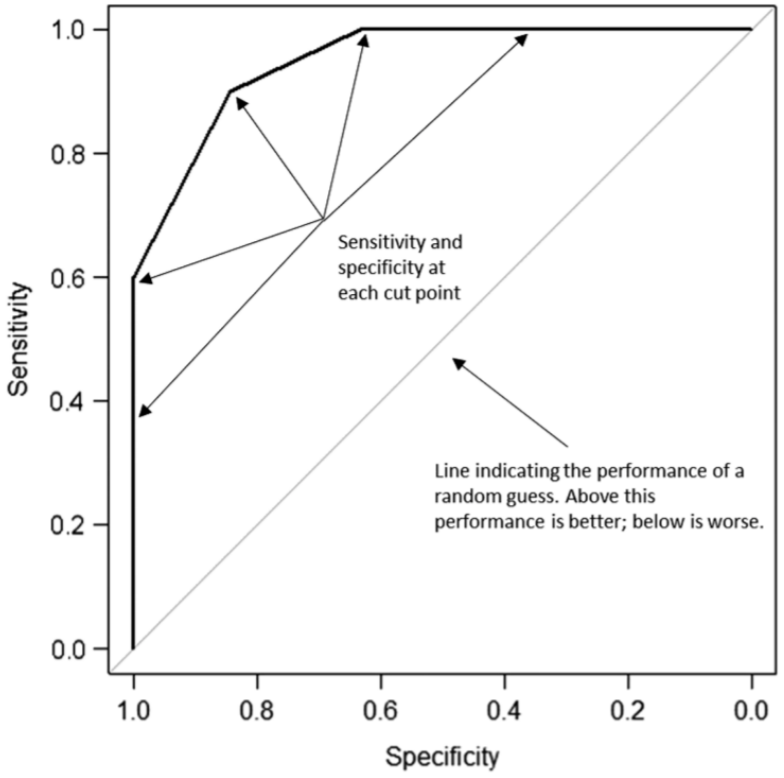
	Gold standard	
Index test	Positive	Negative
Positive	TP	FP
Negative	FN	TN

TP = true positive
TN = true negative
FP = false positive
FN = false negative

$$\text{Sensitivity} = \frac{TP}{TP + FN} \qquad \text{Specificity} = \frac{TN}{TN + FP}$$

Diagnostic performance





Reporte de caso / series de casos

- Describe las características de un paciente o un grupo de pacientes con similares características.
- Generalmente describen un nuevo hallazgo.
- Representan casi un tercio de las publicaciones
- Permiten la generación de hipótesis
- Son la interface entre la practica clínica y la epidemiología

Case series or cohort study?

- Understanding outcome as: "occurrence of a disease or a state associated with disease
  - Death
  - Metastasis in breast AC

- What is the inception point of the study
  - **Exposure**
    - Patients "free" or "without" the outcome and followed over time
    - Exposure(s) are varied characteristics fixed or not
    - Exposure may be binary (smoke/non-smoking) or continuous (blood pressure)

  - **Outcome**
    - Sampling people with a certain condition or disease

Case series or cohort study?

- The cohort study allows to directly estimate the absolute risk of occurrence of the outcome
- The absolute risk ratio is the relative risk RR

		Outcome / Disease		
Exposure		**Yes**	**No**	**Total**
	Exposed	a	b	**a+b**
	Non exposed	c	d	**c+d**
	Total	**a+c**	**b+d**	**a+b+c+d**

CI_{exp} = a/a+b

$CI_{non\ exp}$ = c/c+d

$$Relative\ risk\ or\ CIR = \frac{CIexp}{CIno\ exp} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

Case series or cohort study?

- Having a control group is not a requirement of cohort design since its objective may be:
  - Describe the course of the disease or the "prognosis"
  - It is important to clarify whether it pursues etiology (causality) or prognosis
  - The comparison group can be internal (Male/Female)

- Case series structure
  - By definition, it should sample subjects based on outcome or disease-associated status
  - There are two ways to sample for a series of cases
  - Patients with specific exposure and specific outcome
  - Patients with exposure-independent outcome (cc)

Case series or cohort study?

1. Patients with specific exposure and specific outcome
2. Patients with exposure-independent outcome (cc)

In none of the cases can the absolute risk of occurrence of the outcome be calculated directly

		Outcome		
Exposure		**Yes**	**No**	**Total**
	Exposed	a	b	**a+b**
	Non exposed	c	d	**c+d**
	Total	**a+c**	**b+d**	**a+b+c+d**

Difference between the two designs

- Cohort study: Sampling is exposure-based, has a follow-up period and the absolute risk of outcome can be directly calculated

- Case series: Only patients with the outcome are selected and do not allow the calculation of absolute ris
  - These may have an exposure or,
  - This may not be taken into account

Dekkers O, Egger M, Altman DG, Vandenbroucke JP. Distinguishing Case Series From Cohort Studies. Ann Intern Med. 2012;156:37-40.

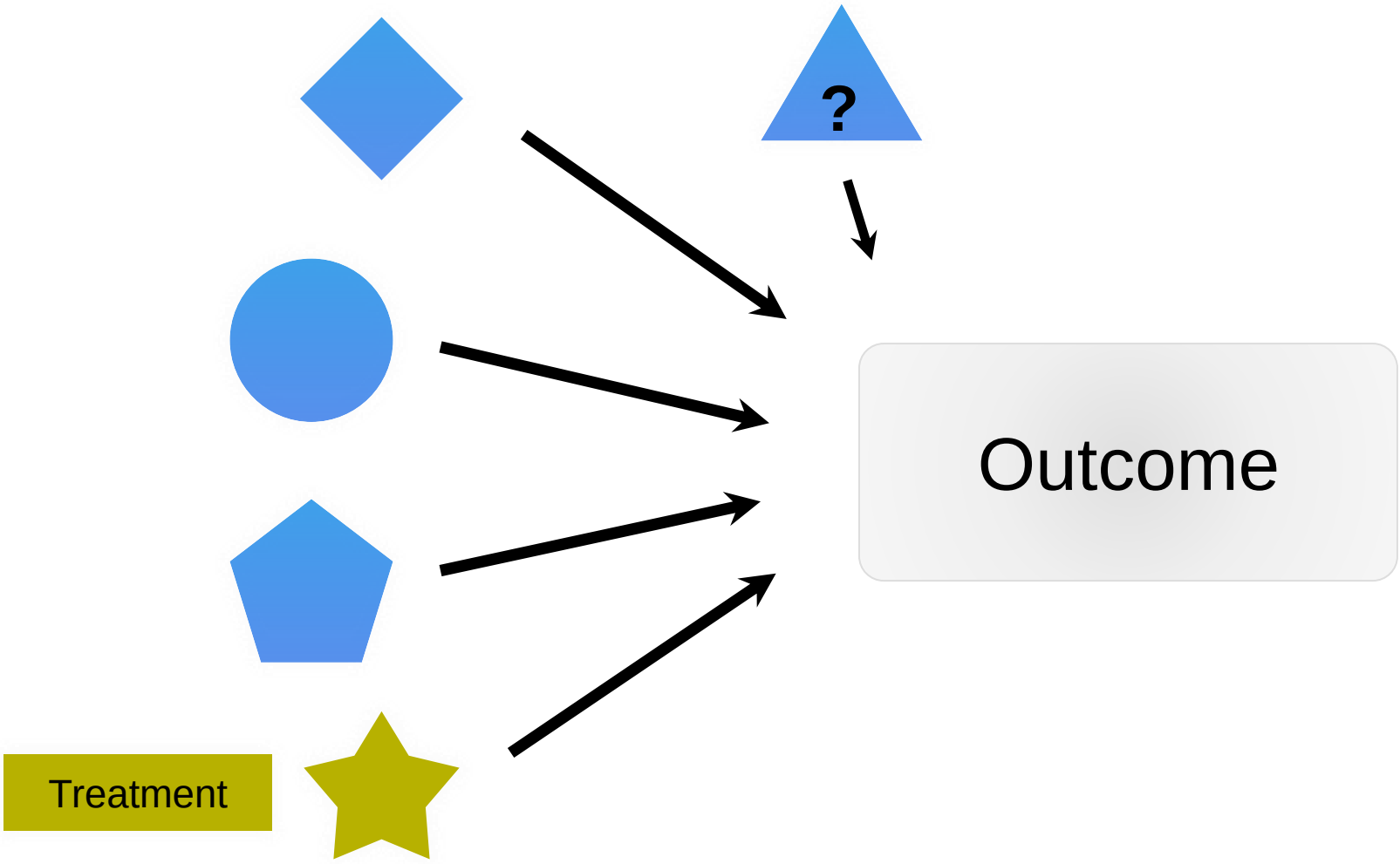
Key points

1. The number under study loses importance
   - A study of 5 patients with prosthetic reconstruction of the radial head is followed for 5 years and all remain with full functionality.
   - Functionality estimation?, is accurate? Confidence?

2. Selection biases or loss to follow-up may affect risk estimation

3. To investigate causality (etiology) or therapy almost always requires a control group (counterfactual thinking)

Randomized clinical trial



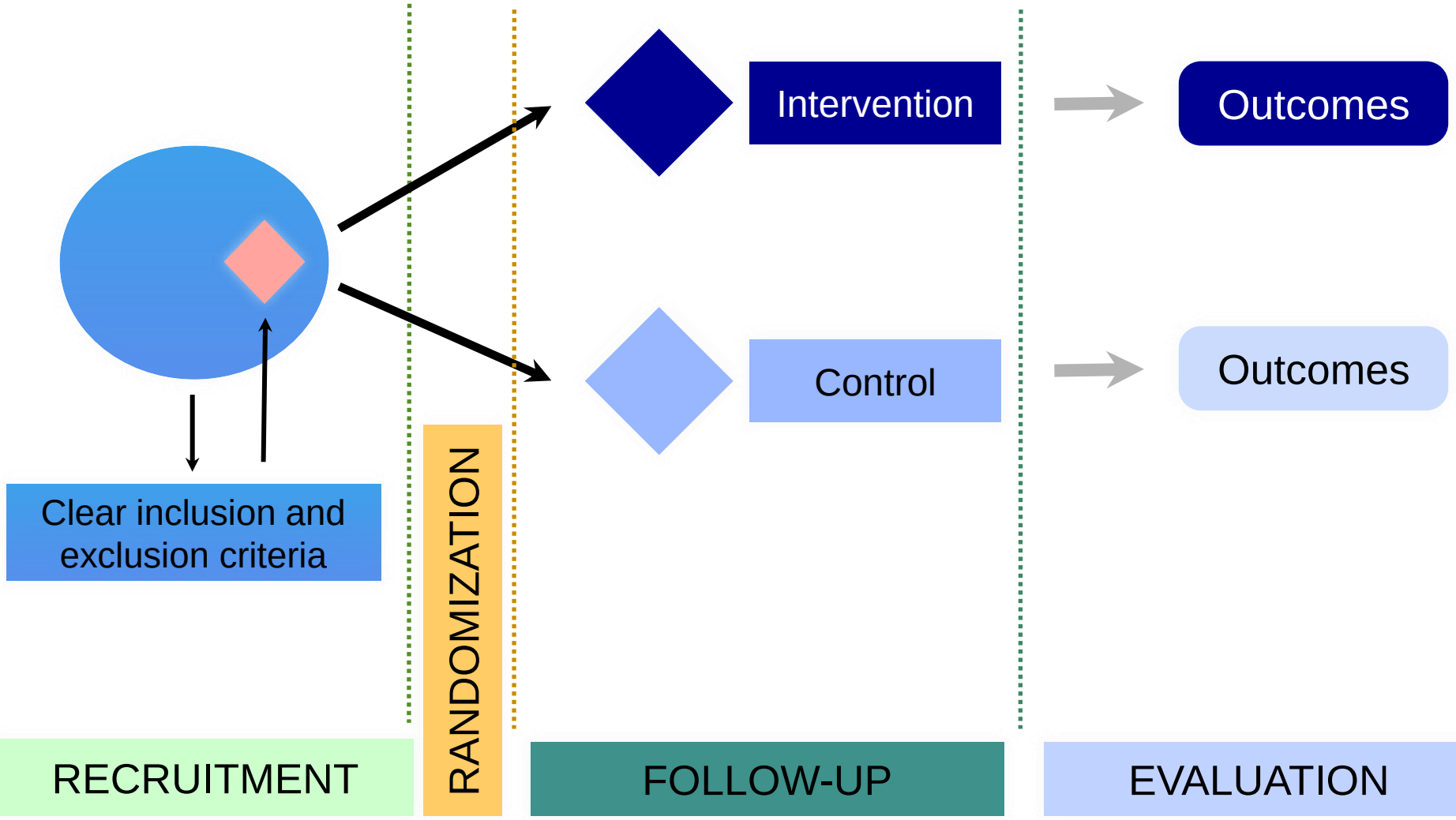
Randomized clinical trial

The clinical trial is a prospective human study that compares the effect of an intervention in a group with a control, in a disease or in a given condition.

Characteristics of clinical trials

- They are experiments in humans
- Studies in which the researcher establishes the population, assigns the intervention and decides who and how to evaluate the outcomes
- If well conducted, they provide high-quality **causal** evidence making them the substrate of systematic reviews of the literature and Evidence-Based Medicine.
- They are not the only source of causal evidence while they are not always feasible

Basic scheme



BRITISH MEDICAL JOURNAL

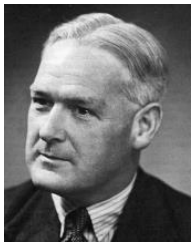
LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

- In 1948, Sir Austin Bradford Hill published the 1st RCT with strict concealed randomization of patients to treatment or control, and blinding of researchers to avoid bias



Medical Research Council (1948b).Streptomcin treatment of pulmonary tuberculosis: a Medical Research Council investigation. BMJ 2:769-782.

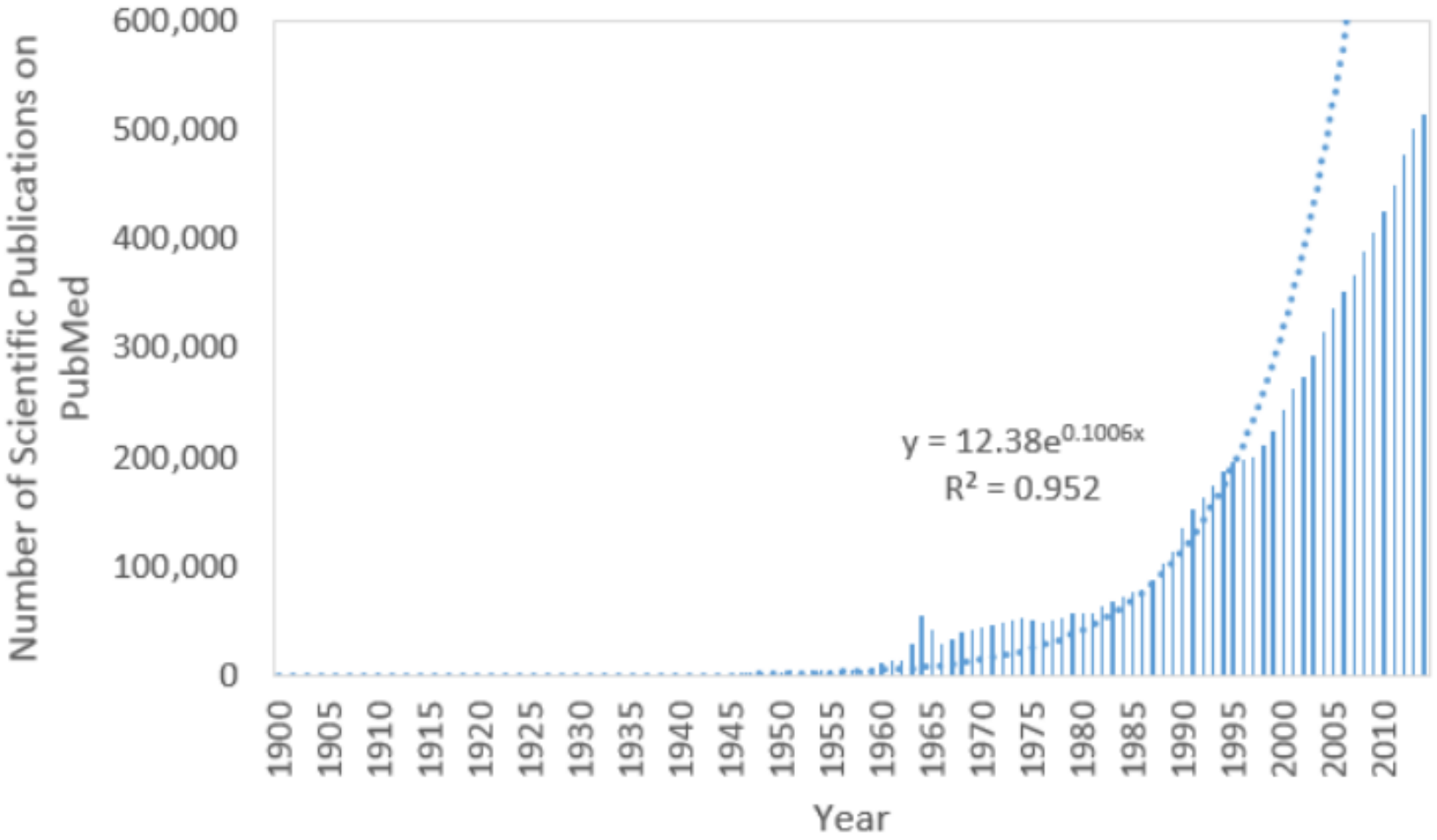
TABLE II.—*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement ..	28	51%	4	8%
Moderate or slight improvement	10	18%	13	25%
No material change	2	4%	3	6%
Moderate or slight deterioration	5	9%	12	23%
Considerable deterioration ..	6	11%	6	11%
Deaths	4	7%	14	27%
Total	55	100%	52	100%

	Alive	Dead	Total	
Streptomycin	51	4	55	→ 7 %
Placebo	38	14	52	→ 27 %

Systematic reviews

Balmoral Castle in Scotland

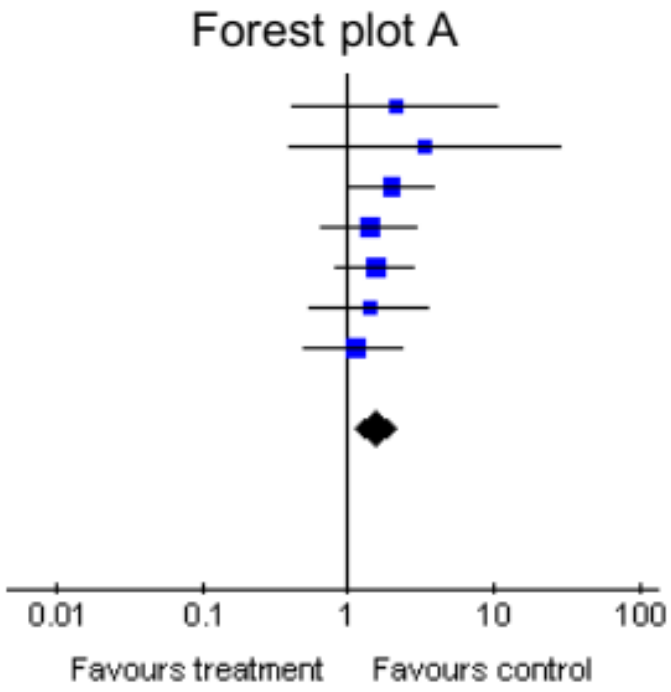

Number of Scientific Publications on PubMed
600,000
500,000
400,000
300,000
200,000
100,000
0
y = 12.38e^0.1006x
R² = 0.952
1900
1905
1910
1915
1920
1925
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
Year

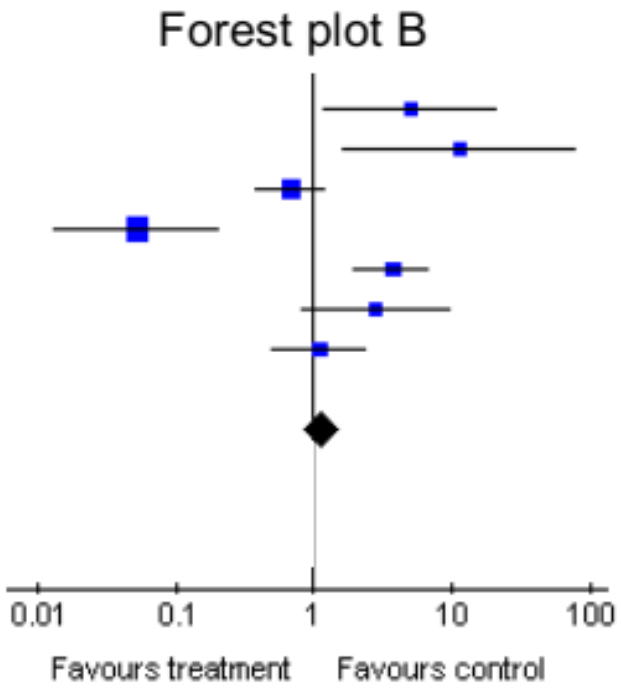
Why do we need systematic reviews

- Efficient way to access the body of research
  - Saves time required for search
  - Critical appraisal
  - Interpretation of the results
- They explore differences across studies and assess their validity (risk of bias)
- Reliable source for decision making (if well conducted
  - Unbiased selection of relevant information
  - Useful for decision-making in health care, policy development and **future research**

Systematic reviews

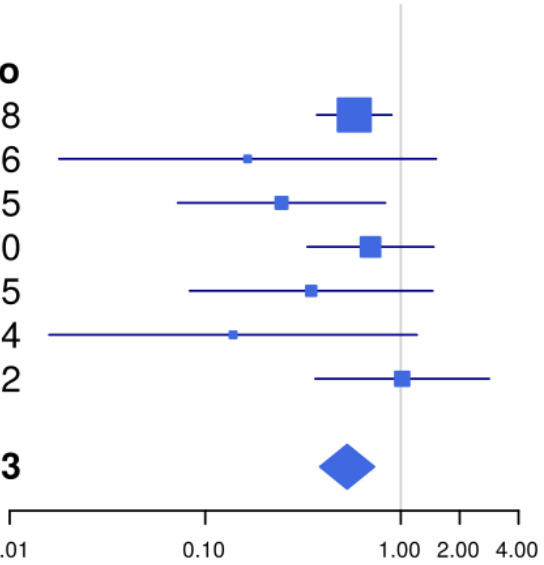
1. Defining the review question(s) and developing criteria for including studies
2. Searching for studies
3. Selecting studies and collecting data
4. Assessing risk of bias in included studies
5. Analyzing data and undertaking **meta-analyses**
6. Addressing reporting biases
7. Presenting results and “summary of findings” tables
8. Interpreting results and drawing conclusions


Forest plot A
0.01
0.1
1
10
100
Favours treatment
Favours control


Forest plot B
0.01
0.1
1
10
100
Favours treatment
Favours control

Forrest plot

Study	Deaths (corticosteroid)	Deaths (placebo)	Odds ratio
Auckland	36	60	0.58
Block	1	5	0.16
Doran	4	11	0.25
Gamsu	14	20	0.70
Morrison	3	7	0.35
Papageorgiou	1	7	0.14
Tauesch	8	10	1.02
Summary			**0.53**



Odds ratio with 95% confidence interval
(1=no effect, <1=treatment has fewer deaths)