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Understanding Effective Interventions

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Choosing the right study design

An early Clinical Trial

In the late 18th century, King Gustav III of Sweden decided that coffee was poison and ordered a clinical trial.

J Int Med, October 1991:289 -

Reprinted in Ann Intern Med 1992;117:30

Study design

- The king condemned a convicted murderer to drink coffee every day.
- Control: another murderer was condemned to drink tea daily.
- Outcome: death.
- Two physicians were appointed to determine the outcome.

Results

- The two doctors died first.
- The king was murdered.
- Both convicts enjoyed long life until the tea drinker died at age 83 (no age was given for the coffee drinker).

Discussion

One should not rely on such a small sample size. Perhaps the end point was too harsh.

The outcome of the trial had no effect on the decision makers. Coffee was forbidden in Sweden in 1794 and again in 1822.

Conclusions

None possible.

External events and other biases may have confounded the result.

Kings should not mess with clinical trials.



The Lancet published a series of papers in 2002 on conducting clinical research:

Grimes DA, Schulz KF. An overview of clinical research: The lay of the land. *Lancet* 2002;359:57-61.

Grimes DA, Schulz KF. Descriptive studies: What they can and cannot do. *Lancet* 2002;359:145-9.

Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002;359:248-52.

Grimes DA, Schulz KF. Cohort studies: Marching toward outcomes. *Lancet* 2002;359:341-5.

Schulz KF, Grimes DA. Case-control studies: Research in reverse. *Lancet* 2002;359:431-4.

Comparison



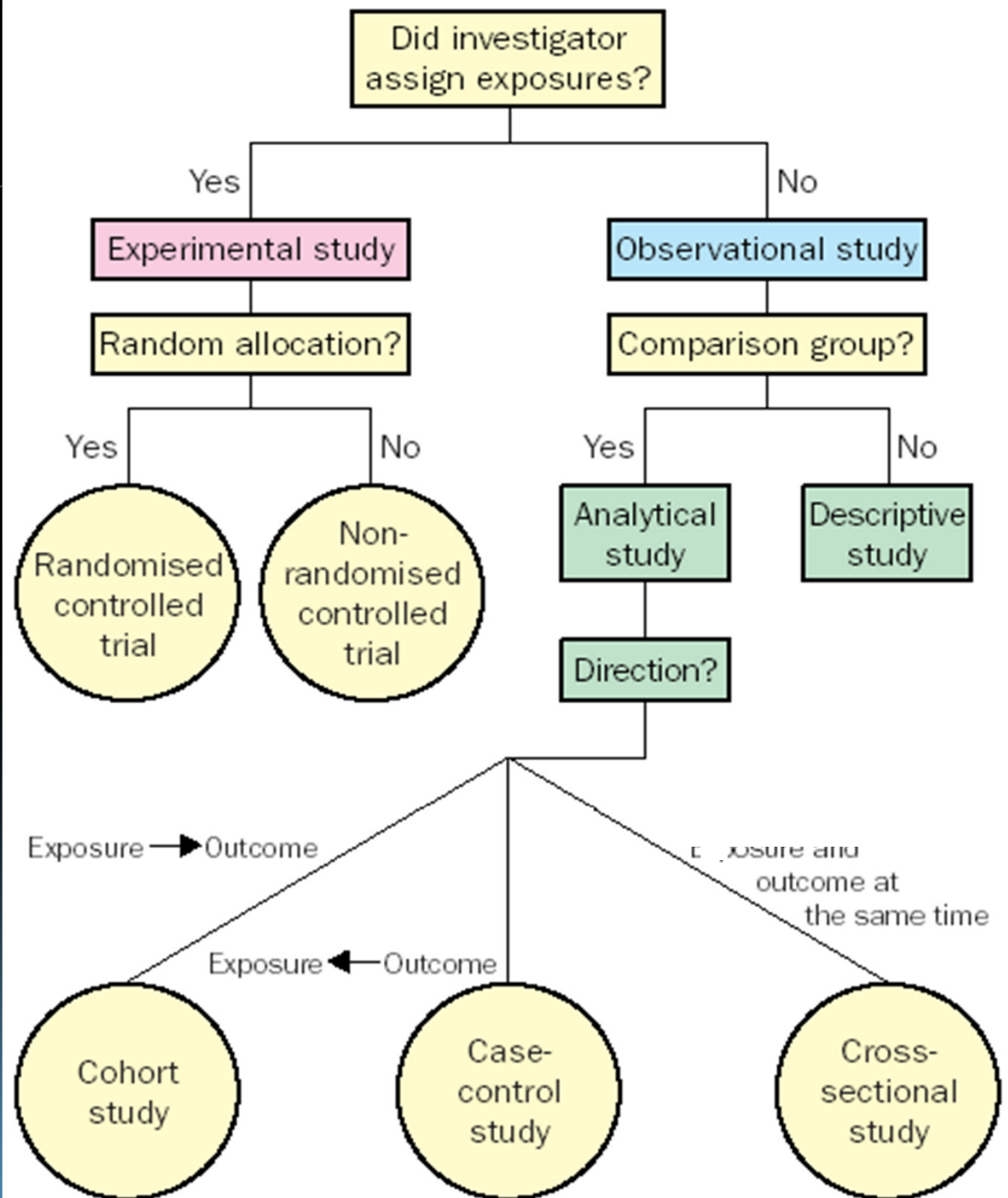
Qualitative

- Understanding
- Interview/observation
- Discovering frameworks
- Textual (words)
- Theory generating
- Quality of informant more important than sample size
- Subjective
- Embedded knowledge
- Models of analysis: fidelity to text or words of interviewees

Quantitative

- Prediction
- Survey/questionnaires
- Existing frameworks
- Numerical
- Theory testing (experimental)
- Sample size core issue in reliability of data
- Objective
- Public
- Model of analysis: parametric, non-parametric

Basic principles of study design

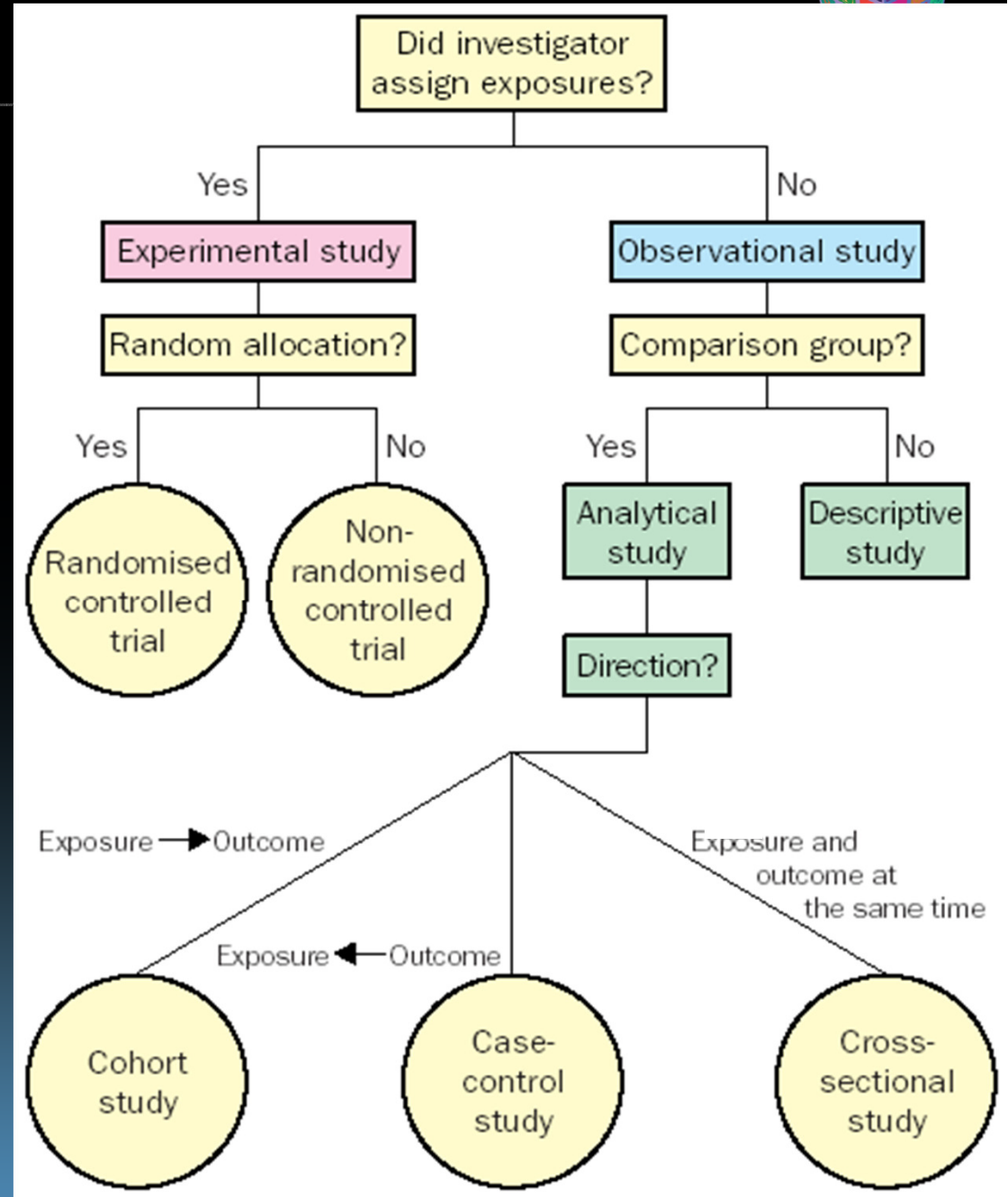


Quantitative designs



- **Observational**: studies that do not involve any intervention or experiment.
- **Experimental**: studies that entail manipulation of the study factor (exposure) and randomization of subjects to treatment (exposure) groups

Basic principles of study design



Observational Studies



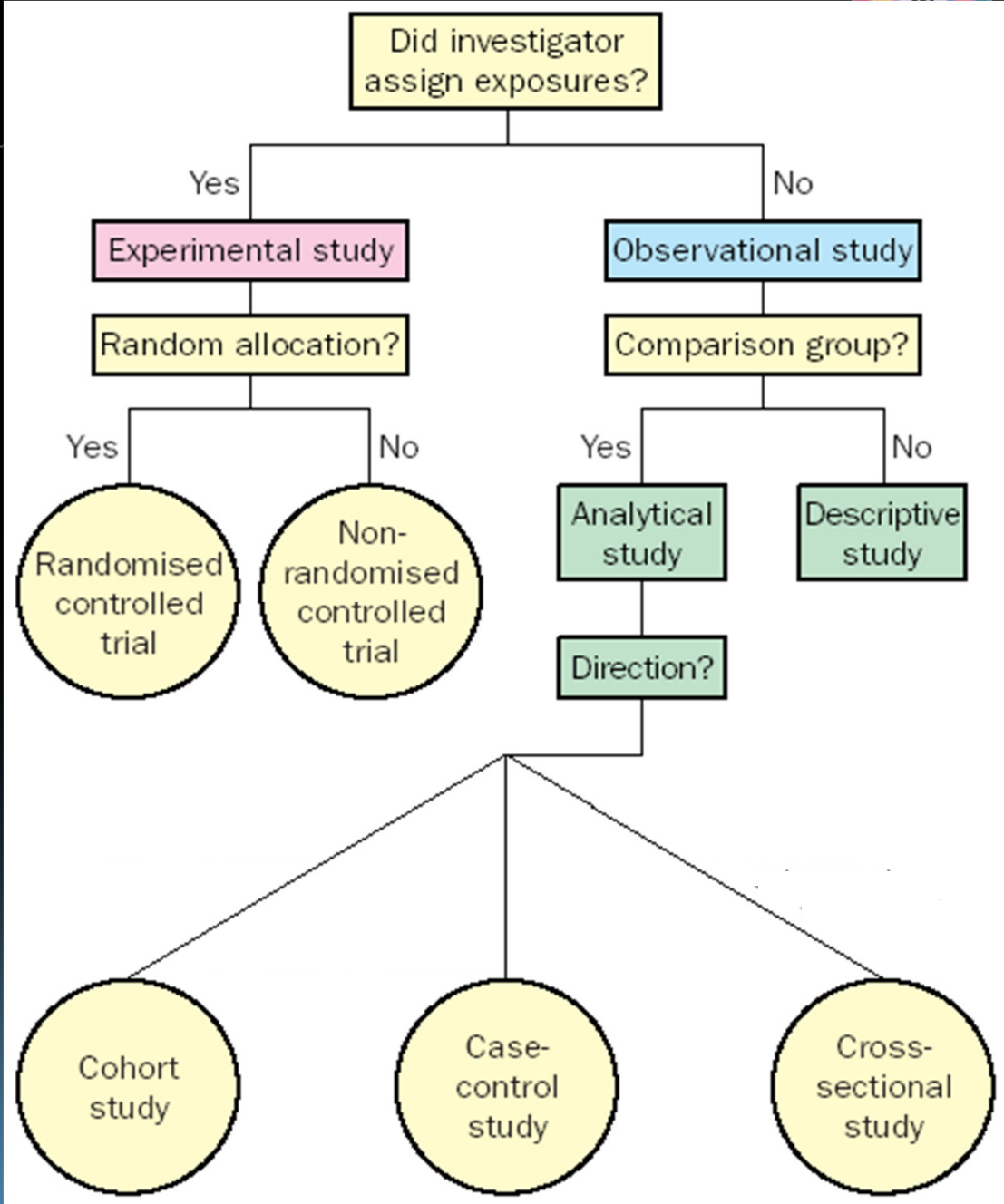
Dominate the literature

Funai et al.

Distribution of study designs
in four major US journals

Gynecol Obstet Invest 2001;51:8-11

Research

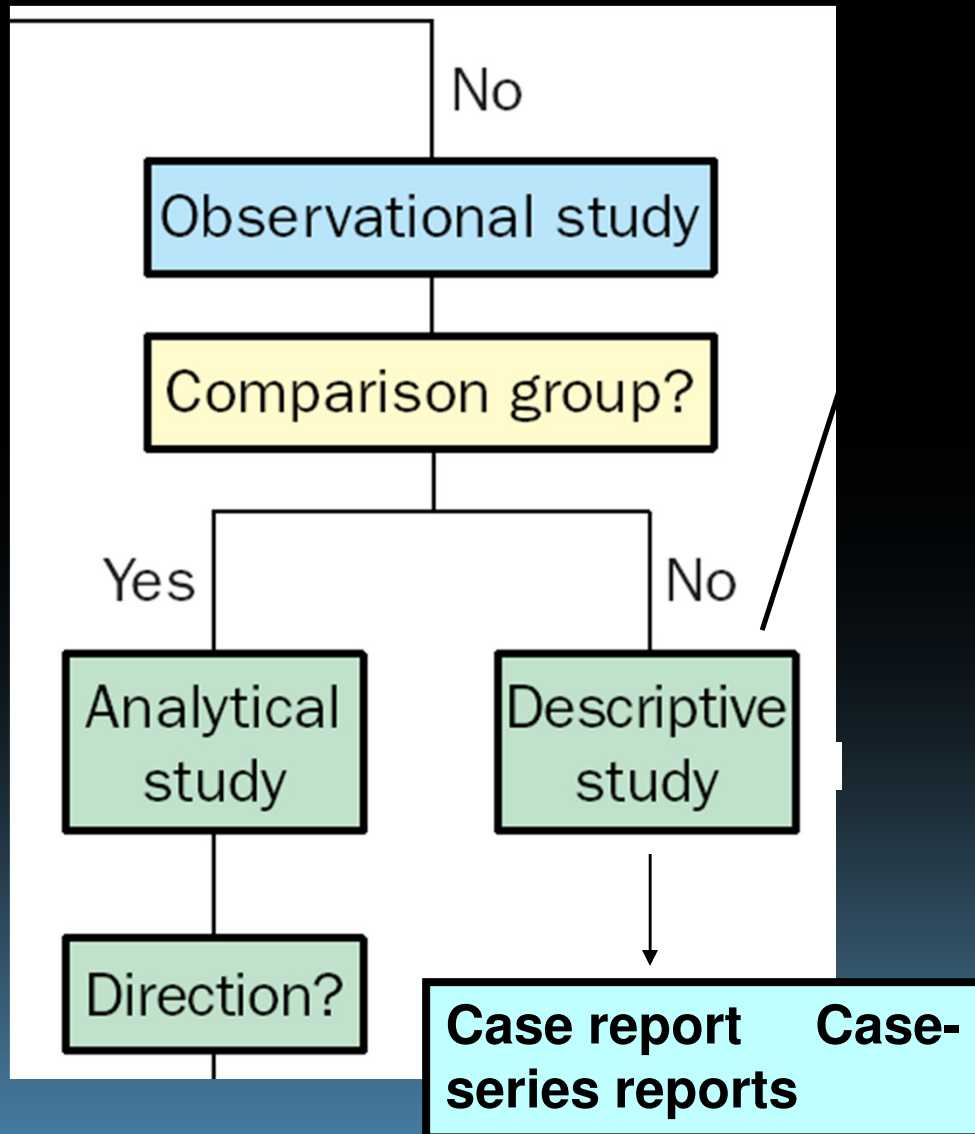


Observational Designs



- **Exploratory**: used when the state of knowledge about the phenomenon is poor: small scale; of limited duration.
- **Descriptive**: used to formulate a certain hypothesis: small / large scale. Examples: case-studies; cross-sectional studies
- **Analytical**: used to test hypotheses: small / large scale. Examples: case-control, cross-sectional, cohort.

Descriptive studies



1. Do not feature a comparison (control) group.
2. Often the first foray into a new area of medicine.
3. Describe the frequency, natural history, and possible determinants of a condition.
4. Hypothesis generation about the cause of the disease.
5. do not allow assessments of causal association.

Descriptive studies



Who, what, why, when, where

1. Who has the disease in question ?
2. What is the condition or disease being studied ?
3. Why did the condition or disease arise ?
4. Where does or does not the disease or condition arise ?

Teen fights for life after reaction to swine flu drug

7:00am Thursday 10th December 2009

 Print  Email  Share  Comments(12)

By Dan Hearn »

A TEENAGER is intensive care and fighting for her life after taking the swine flu drug Tamiflu.

Samantha Millard, of Purslane Drive, Bicester, has blisters all over her body and severe breathing difficulties after being prescribed the medication.

Last night the 18-year-old was in a critical condition and being treated in the specialist burns unit at Chelsea and Westminster Hospital after being transferred from Oxford's Churchill Hospital.

Doctors fear she may have the life-threatening Stevens-Johnson syndrome, which causes the skin to peel off.



Samantha Millard

Case report



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Toxic epidermal necrolysis associated with an influenza-like illness and oseltamivir phosphate

17 December 2009

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foundation year 1
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Chandakumar,
Suveer Singh,
Jorge
Leon-Villapalos,
Ruth Asher, Chris
Bunker, Carl
Heneghan, Vanessa
Venning

Send response to

journal:

Re: Toxic
epidermal
necrolysis
associated with an
influenza-like
illness and
oseltamivir

Dear Editor,

In December 2009, an 18-year-old girl, with a past medical history of occasional migraines and a low body mass index (BMI), experienced new onset symptoms of headache, sore throat, coryzal symptoms, myalgia and fever. Within 24 hours of the onset, she had telephoned her GP practice. The practice advised she contact the National Pandemic Flu Service who made a presumptive diagnosis of Swine-Origin Influenza A (H1N1) 2009 infection. She was prescribed oral oseltamivir (Tamiflu®) 75mg twice daily for five days.

After 24 hours and three doses of oseltamivir she noticed a rash over her abdomen. Her mother then contacted the GP who visited the patient and noted a widespread maculopapular rash over the trunk and upper limbs, associated tachycardia, pyrexia (temperature 39.4°C), significant cervical lymphadenopathy, bilateral conjunctivitis and pharyngitis. He prescribed oral penicillin V because of a concern about scarlet fever and advised the patient to stop oseltamivir. The next day the GP reviewed the patient noting blisters and erosions, particularly in the mouth and lips and referred the patient to the local dermatology team.

On examination at the department of dermatology she was alert and orientated but noted to have an extensive macular rash on the trunk and limbs with lesions forming a confluent sheet of erythema on the abdomen. Scattered targetoid lesions were present over the periphery of the trunk and proximal limbs. There were initially small discrete areas of blistering on the face and lower abdomen (Figure 1). Crusted erosions were visible on the lips and there was conjunctival suffusion. The rash was subjectively described as itchy but not painful. She was pyrexial (temperature 39.5 °C) and tachycardic but normotensive, normoxyaemic with a normal respiratory examination. Her initial blood tests showed a thrombocytopenia, elevated serum C-reactive protein, mildly deranged electrolytes and liver function and normal renal function (Table 1). Blood film showed toxic granulation. She was admitted to hospital, a skin biopsy was

Case-series: Clinical case series



- **Clinical case-series:** usually a coherent and consecutive set of cases of a disease (or similar problem) which derive from the practice of one or more health care professionals or health care setting,
- A case-series is, effectively, a register of cases.

Case-series: Clinical case series



- **Clinical case-series are of value in epidemiology for:**
 - Studying predictive symptoms, signs and tests
 - Creating case definitions
 - Clinical education, audit and research
 - Health services research
 - Establishing safety profiles

Case reports and case series from *Lancet* had significant impact on medical literature

Joerg Albrecht^{a,*}, Alexander Meves^b, Michael Bigby^c

^aDepartment of

^cDepartment of

J. Albrecht et al. / Journal of Clinical Epidemiology 58 (2005) 1227–1232

1229

Table 1
Summary of characteristics of case reports ($n = 64$)

	Number	Percentage
Frequency of being cited by other publications		
0	5	(8%)
1	8	(13%)
2–5	19	(30%)
6–10	9	(14%)
11–20	7	(11%)
21–50	11	(17%)
51–100	4	(6%)
336	1	(2%)
Reports that quote other reports or case series		
Yes	35	(55%)
No	29	(45%)
Case reports that were followed by published trials		
Yes	11	(17%)
No	53	(83%)
Case reports that were followed by trials in the current controlled clinical trials register (11/2002 ?)		
Yes	4	(6%)
No	60	(94%)
Outcome (overall impression)		
Success (total clearance of disease)	17	(27%)
Improvement	44	(69%)
Failure	3	(5%)
Reference to other case reports (or case series)		
Yes	35	(55%)
No	29	(45%)

Case
reports



Case reports

Joerg

^aDepartment of De

^cDepartment of Dermatol

Table 2
Summary of characteristics of case series (2 to 10 patients); (n = 39 case series)

	Number	Percentage
Frequency of being cited by other publications		
0	2	(5%)
1	5	(13%)
2-5	10	(26%)
6-10	4	(10%)
11-20	9	(23%)
21-50	6	(15%)
51-69	3	(8%)
Reports that quote other reports or case series		
Yes	21	(54%)
No	18	(46%)
Case reports that were followed by published trials		
Yes	12	(31%)
No	27	(69%)
Case reports that were followed by trials in the current controlled clinical trials register (11/2002)		
Yes	5	(13%)
No	34	(87%)
Number of patients		
2	11	(28%)
3	6	(15%)
4	3	(8%)
5	5	(13%)
6	3	(8%)
7	2	(5%)
8	3	(8%)
9	2	(5%)
10	3	(8%)
Not reported	1	(3%)
Case series that reported mixed response including patients where the treatment had failed		
Yes	4	(10%)
Case series that reported failure of treatment only		
Yes	4	(10%)
Case series that report improvement or cure, without failure		
Yes	31	(79%)
Reference to other case reports (or case series)		
Yes	17	(44%)
No	22	(56%)

Conclusions:

'Case reports and case series can be well received, and have significant influence on subsequent literature and possibly on clinical practice.'

Many were followed by clinical trials.

Often, report rare conditions for which trials may not be feasible.

Strong publication bias favouring positive results

Case series: what to look for



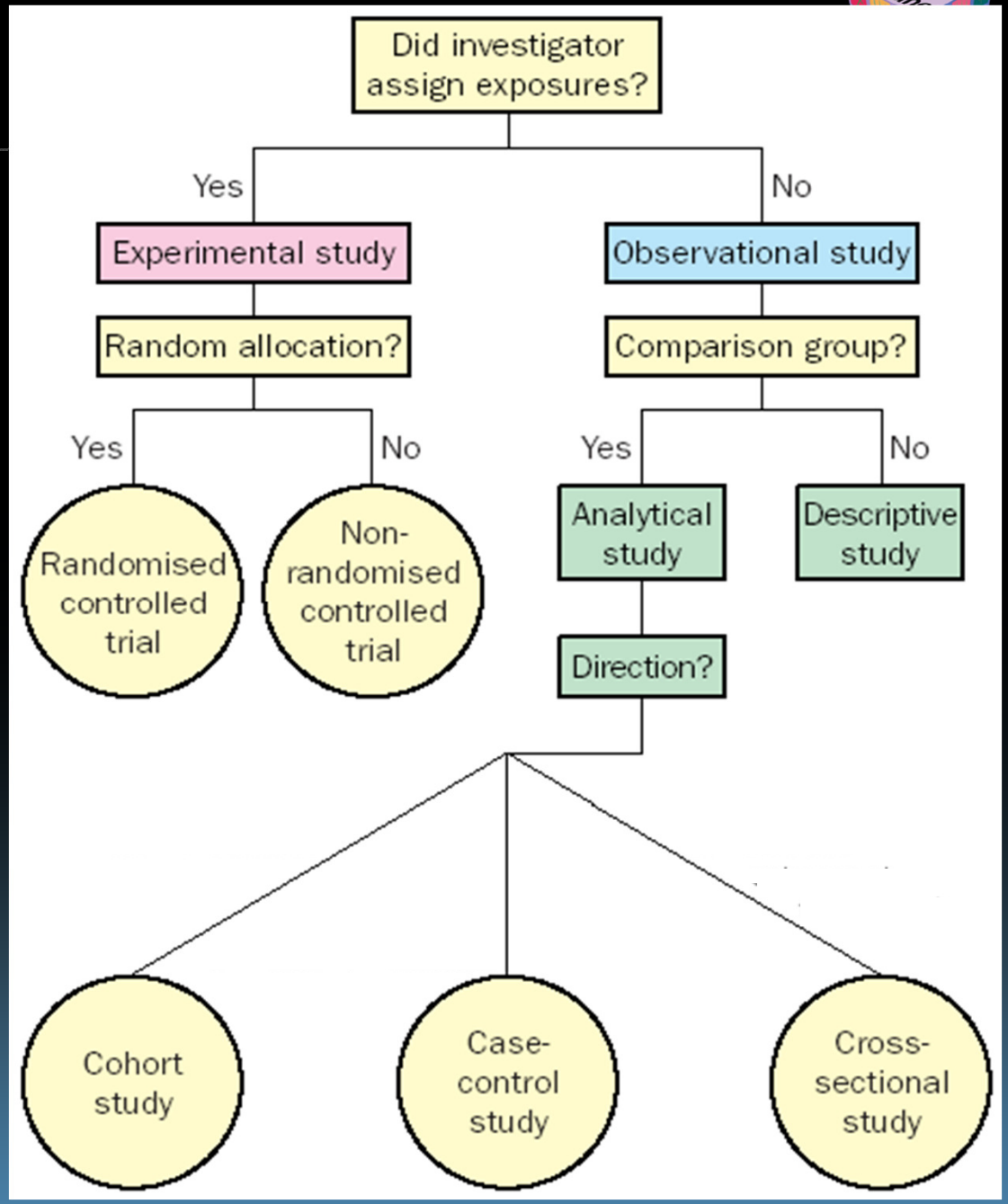
- The diagnosis (case definition) or, for mortality, the cause of death
- The date when the disease or death occurred (**time**)
- The place where the person lived, worked etc (**place**)
- The characteristics of the population (**person**)
- The opportunity to collect additional data from medical records (possibly by electronic data linkage) or the person directly
- The size and characteristics of the **population at risk**

Observational Designs



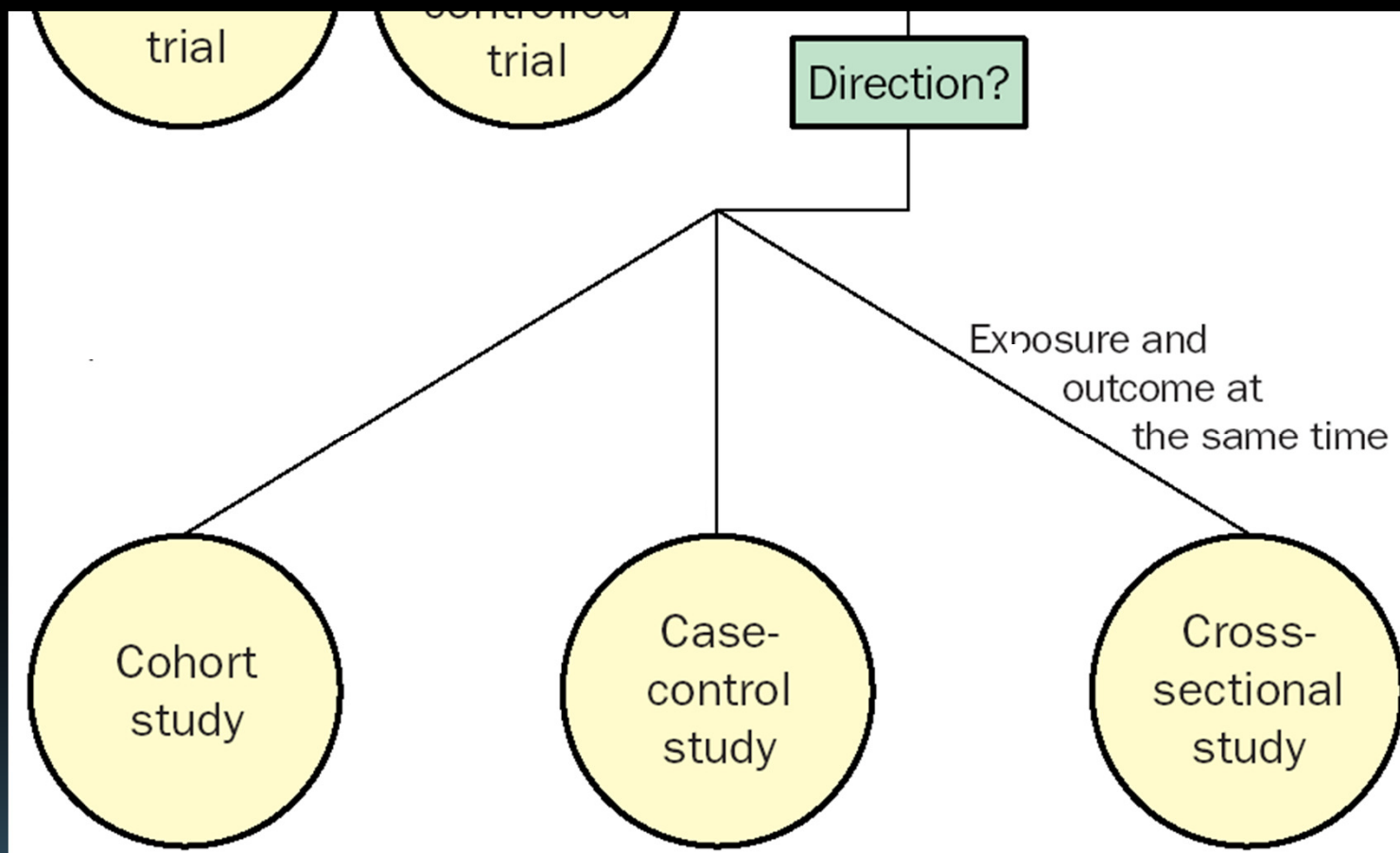
- **Exploratory:** used when the state of knowledge about the phenomenon is poor: small scale; of limited duration.
- **Descriptive:** used to formulate a certain hypothesis: small / large scale. Examples: case-studies; cross-sectional studies
- **Analytical:** used to test hypotheses: small / large scale. Examples: case-control, cross-sectional, cohort.

Research





Analytical Studies



Comparison of the Characteristics of

Cohort Study

&

Case-Control Studies

Usually very expensive

Complete source population denominator

Can calculate incidence rates or risks and their differences and ratios

Convenient for studying many diseases

Usually less expensive

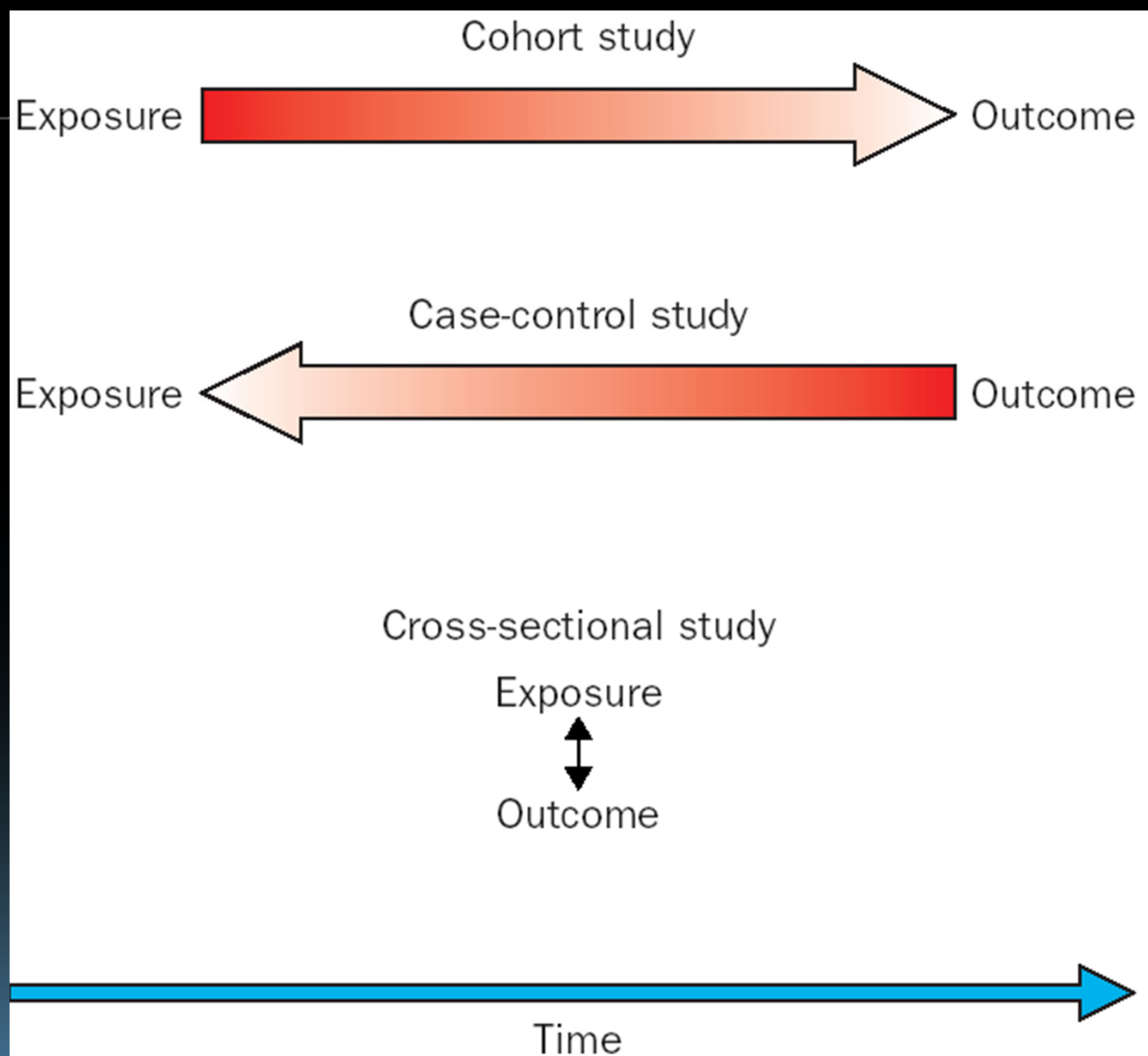
Sampling from source population

Can usually calculate only the ratio of incidence rates or risks

Convenient for studying many exposures



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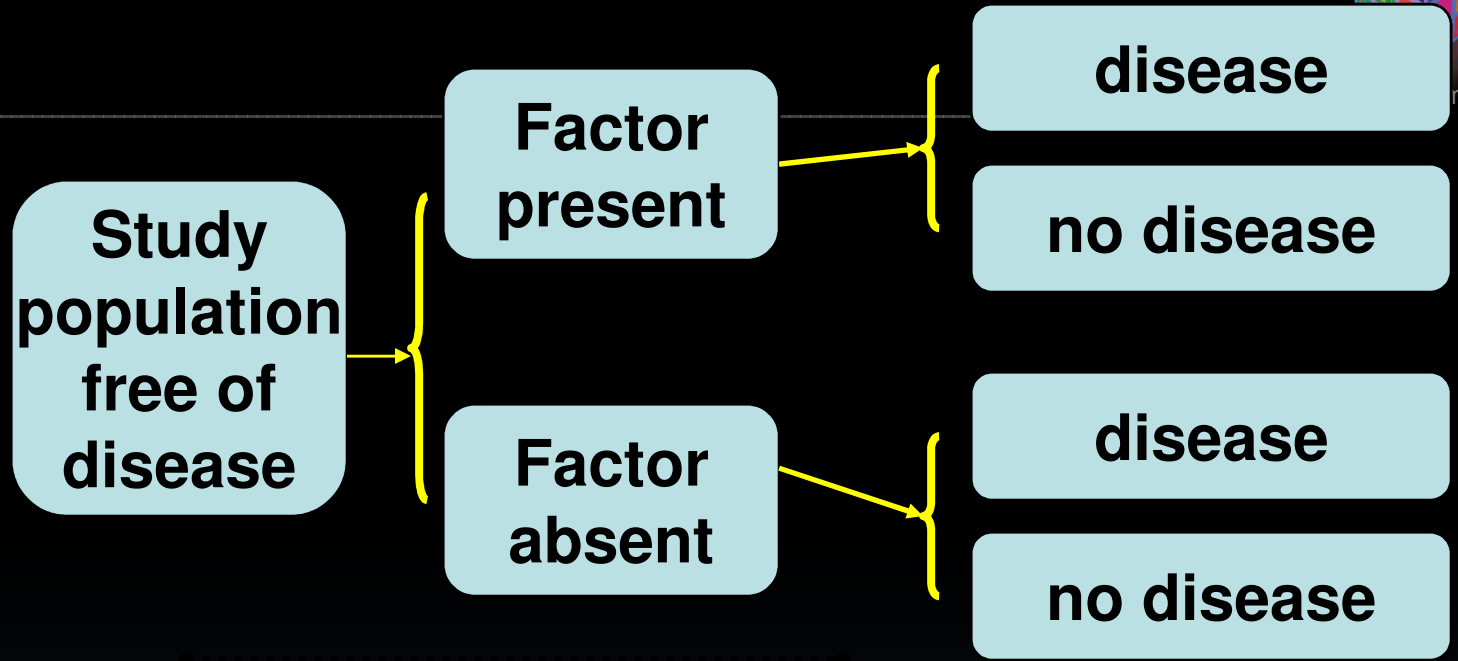


..... several famous
large cohort studies continue to
provide important information

*Ndoff R, Peto R, Boreham J, Sutherland I.
Smoking and dementia in male British doctors: prospective study.
BMJ 2000;320:1097-1102*

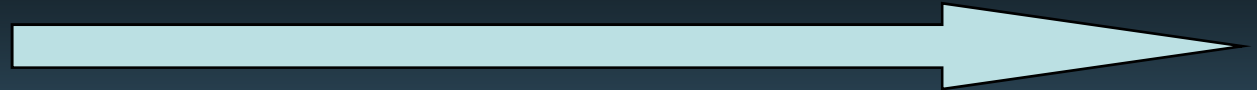


Cohort Design



present

future



time
Study begins here



Cohort Design

RANDOMIZATION

Study population free of disease

Factor present

Factor absent

disease

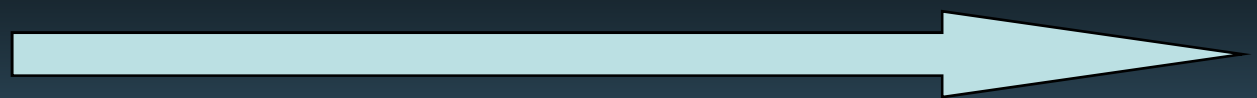
no disease

disease

no disease

present

future



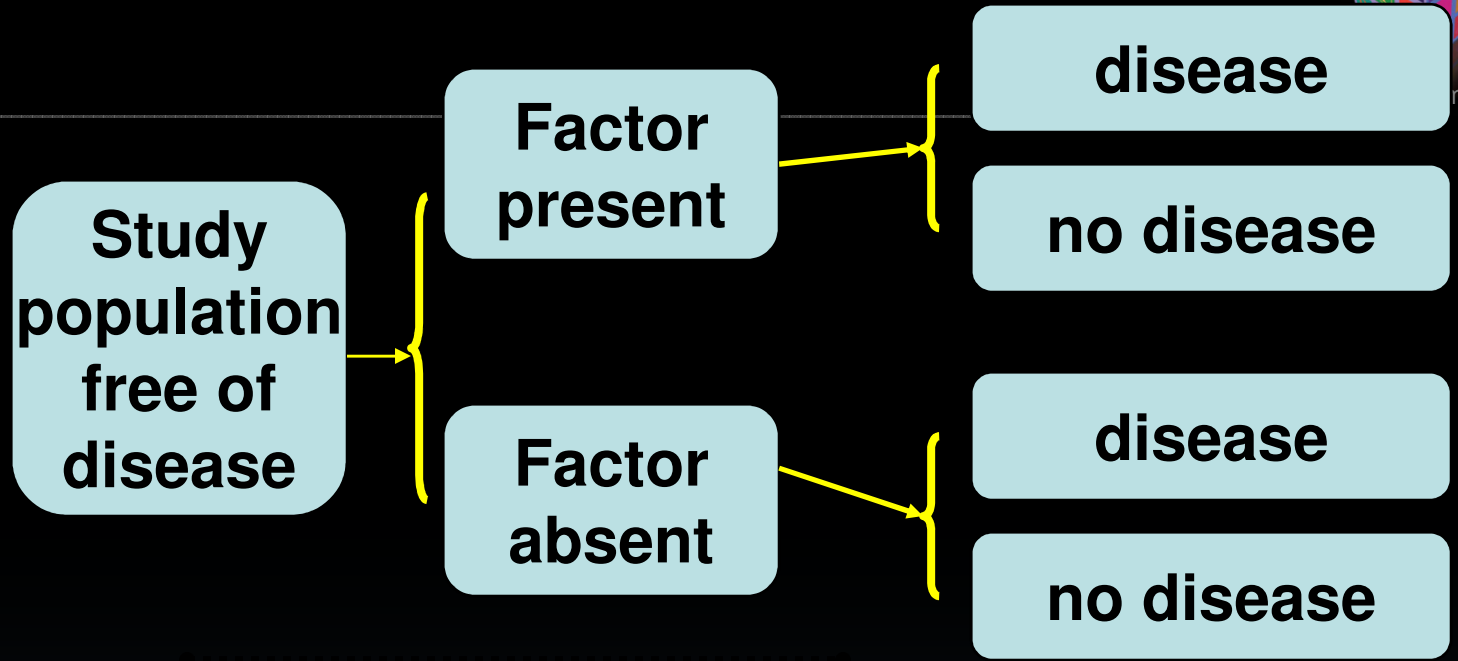
time



Study begins here

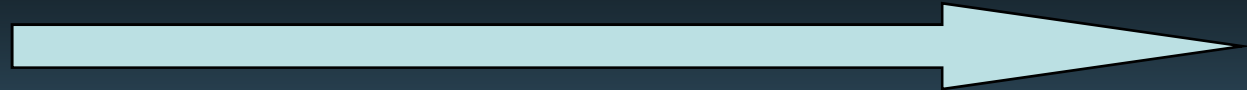


Cohort Design



present

future



Study begins here

Examples: *The Framingham study.*



- Began in 1948 with 5,209 participants
- – 5,123 spouses and children added in 1971
- Selection not based on exposures, but on stable population, wide spectrum of occupations,
- Single hospital, annual updated population list
- Allowed calculation of incidence rates and other descriptive measures for many outcomes



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Crunching the numbers

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"He's right! When you look at it that way, it's not so bad!"

Catching my eye today is this roll of toilet paper called, "Hemo Roll".



It's a product of Slovakia, made by a company named "Tento".

The paper is infused with herbal compounds that are claimed to help prevent hemorrhoid inflammation with continued use. According to the product's website...



RCT: Well conducted → no bias

- 5 patients with haemorrhoids received Hemo-Roll
- 5 people received placebo
- 4 out of 5 with Oximax got better
- 2 out of 5 with placebo got better



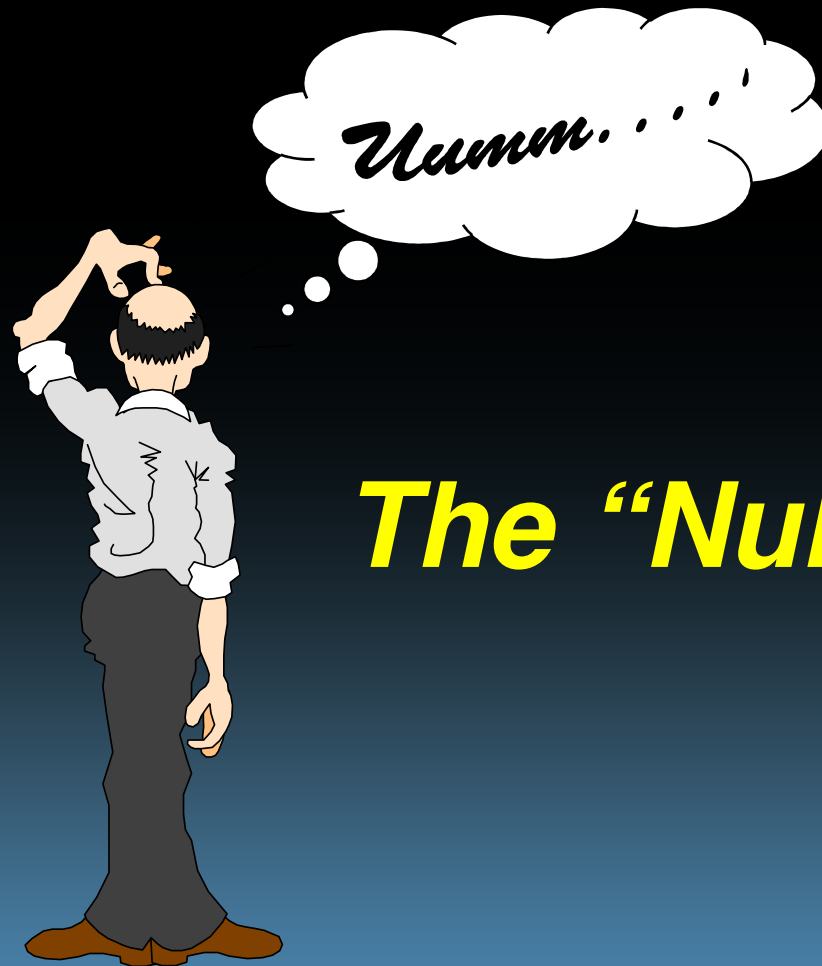
Participants are not convinced...

“It could have happened by chance!”

- So how many would you want before you believe the results?
- 10 in each arm?
- 20?
- 100?



It could have happened by chance
and nothing was really going on



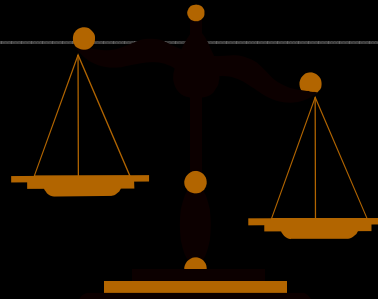
The “Null Hypothesis”



The p-value

- What does a p-value of 5 tell us?

It could have happened by chance



*what does $p=0.5$ mean?
So what does $p=0.05$ mean?*



0

Impossible

1

Definitely



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Number in treatment arm	5
Responders in treatment arm	4
Proportion responding in treatment arm	0.8
Number in control arm	5
Responders in control arm	2
Proportion responding in control arm	0.4
p-value	
	0.29



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Number in treatment arm	5	10
Responders in treatment arm	4	8
Proportion responding in treatment arm	0.8	0.8
Number in control arm	5	10
Responders in control arm	2	4
Proportion responding in control arm	0.4	0.4
p-value	0.29	0.09



Number in treatment arm	5	10	15	20	100
Responders in treatment arm	4	8	12	16	80
Proportion responding in treatment arm			0.8	0.8	0.8
Number in control arm			15	20	100
Responders in control arm			6	8	40
Proportion responding in control arm			0.4	0.4	0.4
p-value	0.29	0.09	0.03	0.01	<0.0001



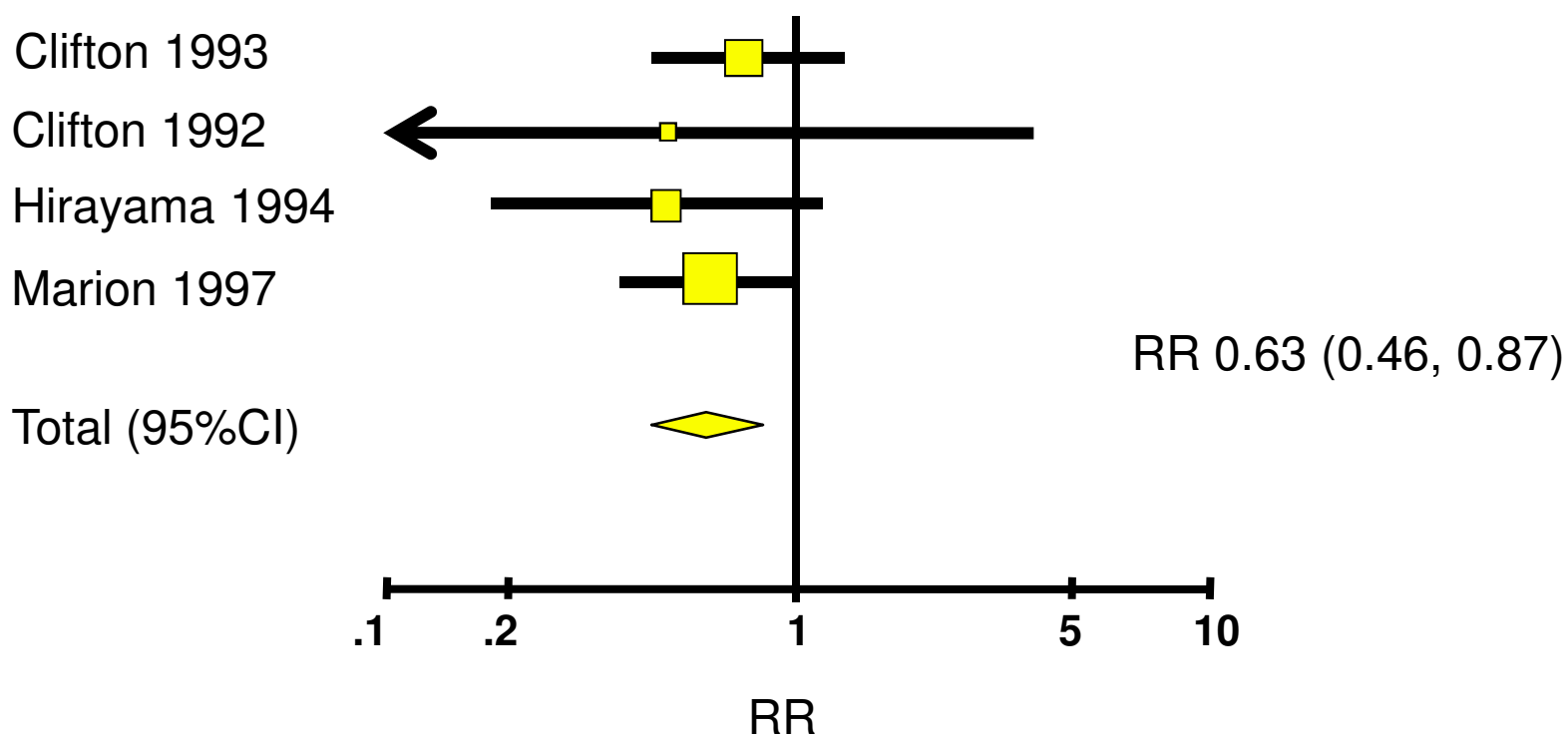
-
- Before I show the homeopathic dose of confidence intervals, let's explore your views...



Hypothermia vs. control

In severe head injury

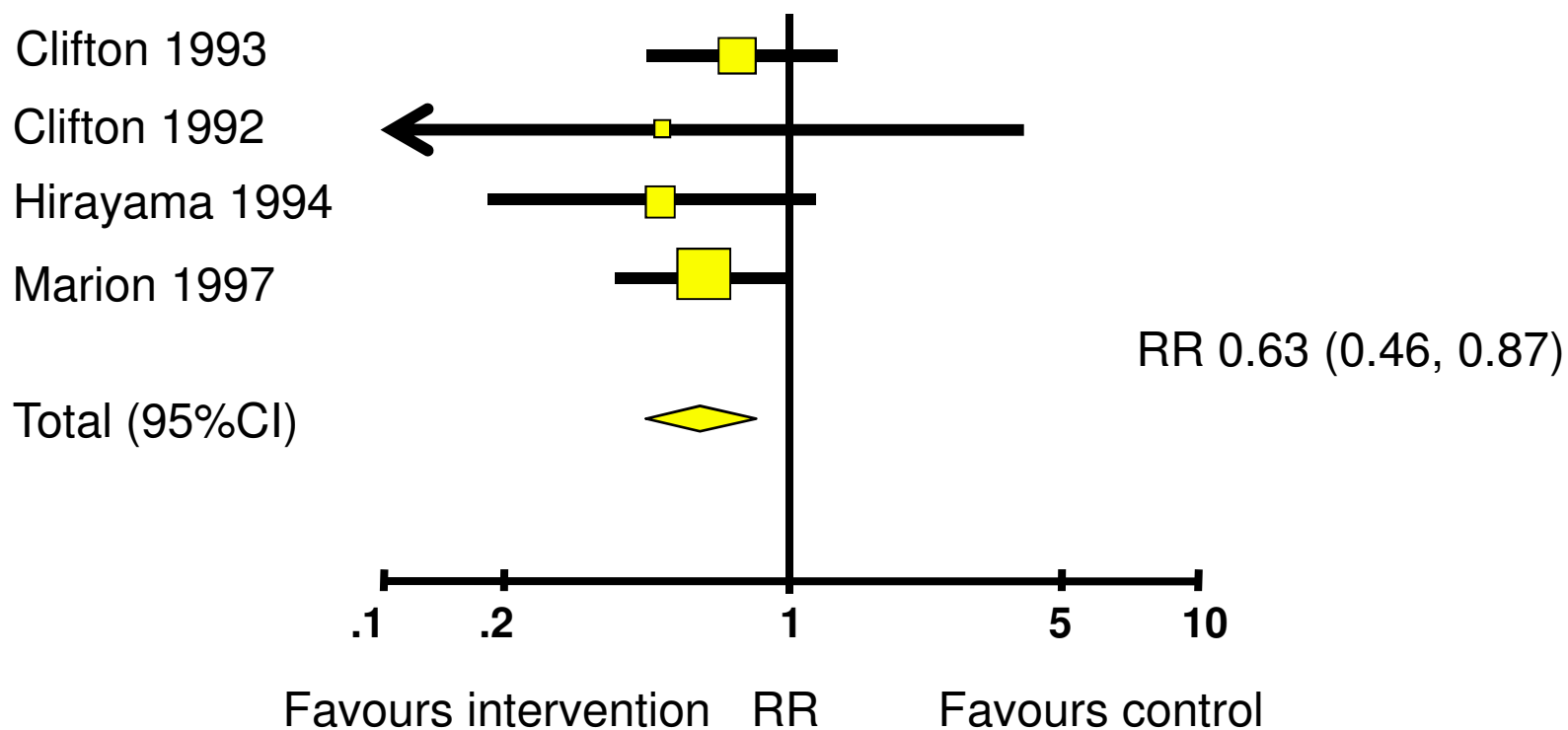
Mortality or incapacity (n=158)



ypothermia vs. control

In severe head injury

Mortality or incapacity (n=158)





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Natural frequency approach



Trial of Hemo-Roll 2



Control group

Intervention group

200 people

200 people

40 people have
haemorrhoids

20 people have
haemorrhoids

20%

10%

Natural frequencies

