University of Ioannina

School of Medicine

ΙΑΤΡΙΚΗ ΣΧΟΛΗ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ

The role of Randomized Controlled Trials

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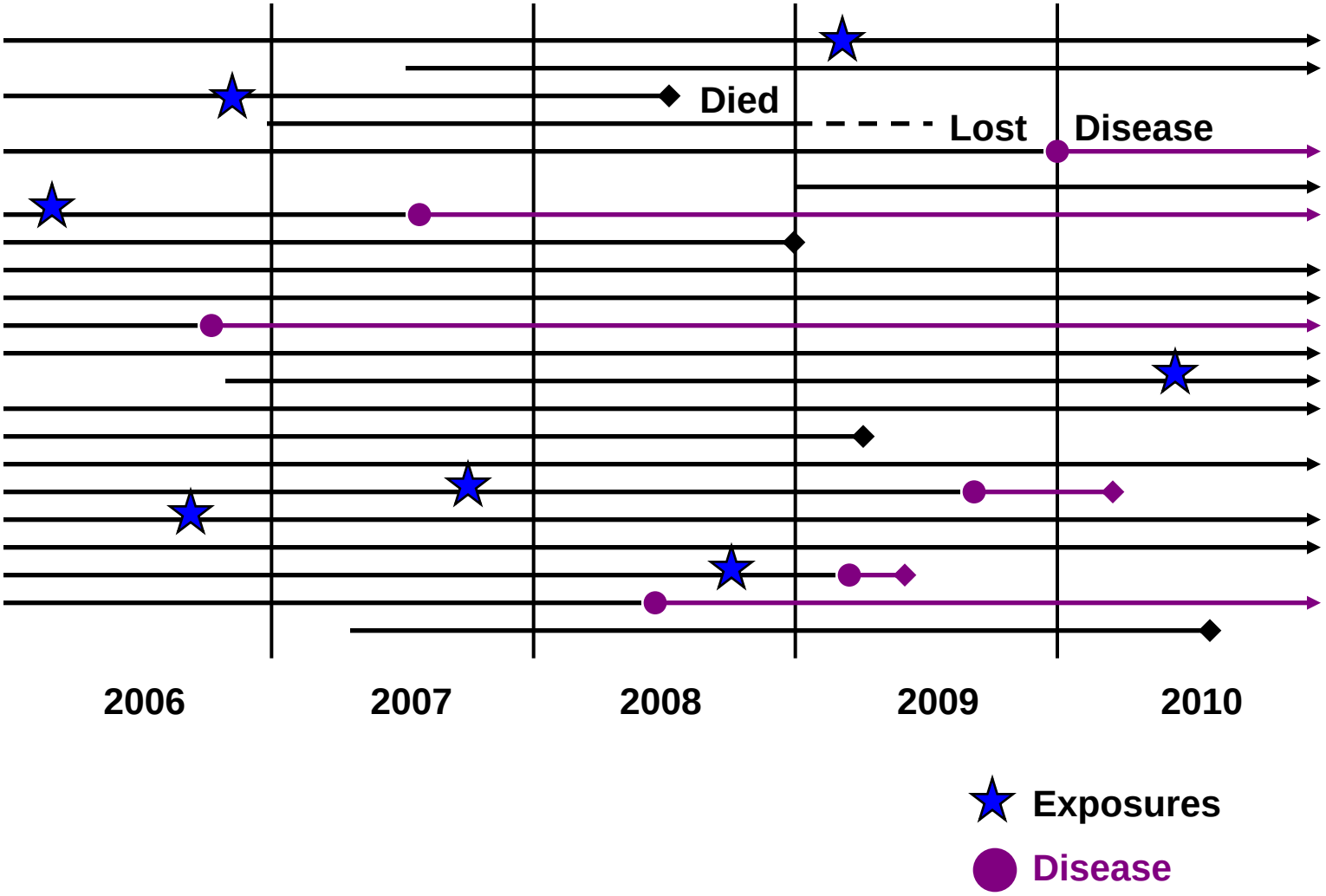
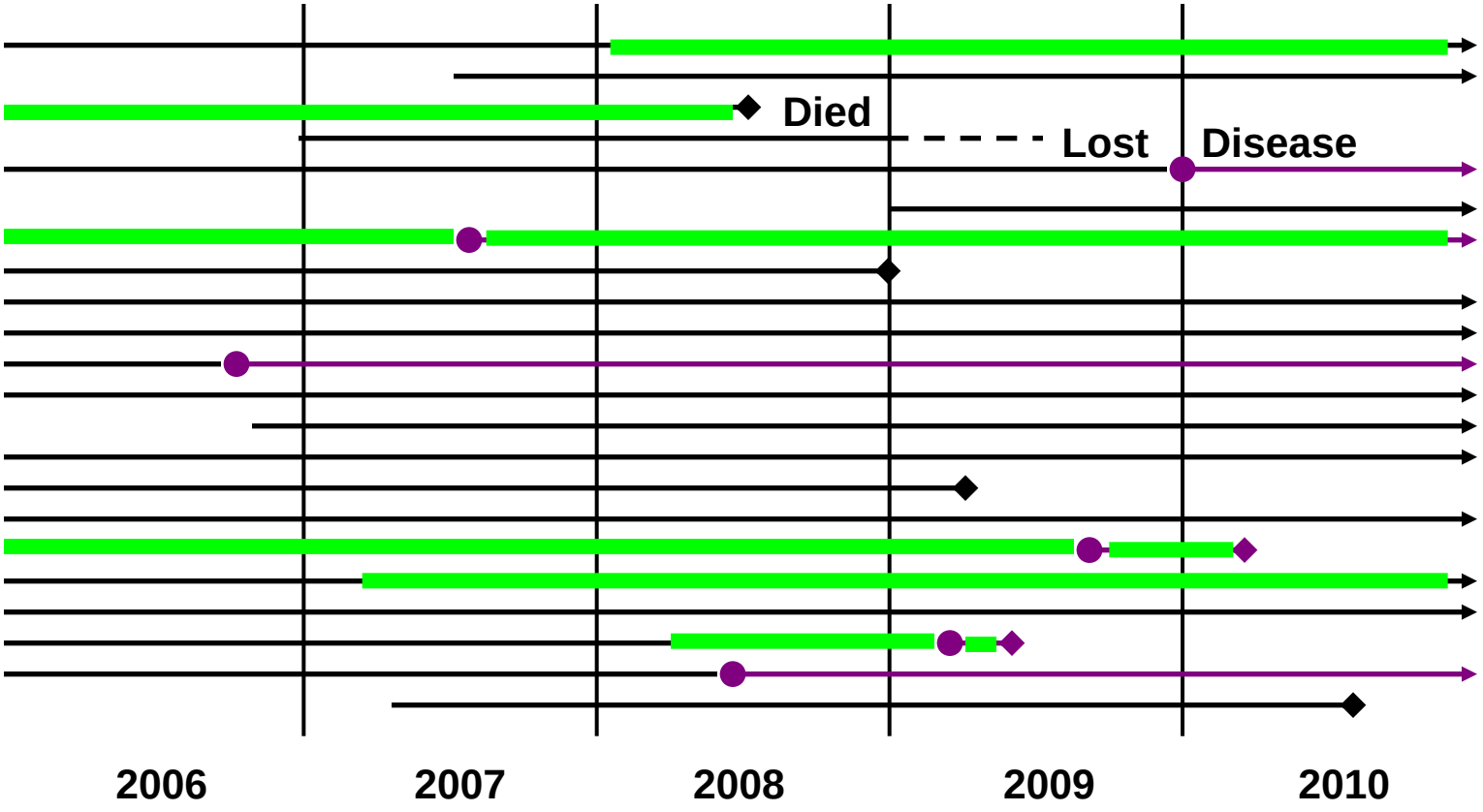
Outline

- Understanding study designs and the role of confounding
  - Observational studies (cross-sectional and cohort)
  - Confounding
- Randomized Controlled Trials (RCTs)
- How to run properly an RCT in order to minimize the risk of bias

The population of interest



The population of interest



1. Cross-sectional studies

- Snapshot in time (like a survey)
- Exposure and/or outcome measured at one point in time
  - Questions may relate to the past
- *Example: Survey of this room to associate the use of antidepressants with obesity*
  - Do you take antidepressant?
  - Is you BMI>30 ?

1. Cross-sectional studies

1. Cross-sectional studies

- Good
  - fine for life-long exposures (e.g. genetic) and certain outcomes that do not change with time (e.g. lipid levels?)
- Bad
  - Problems with causality

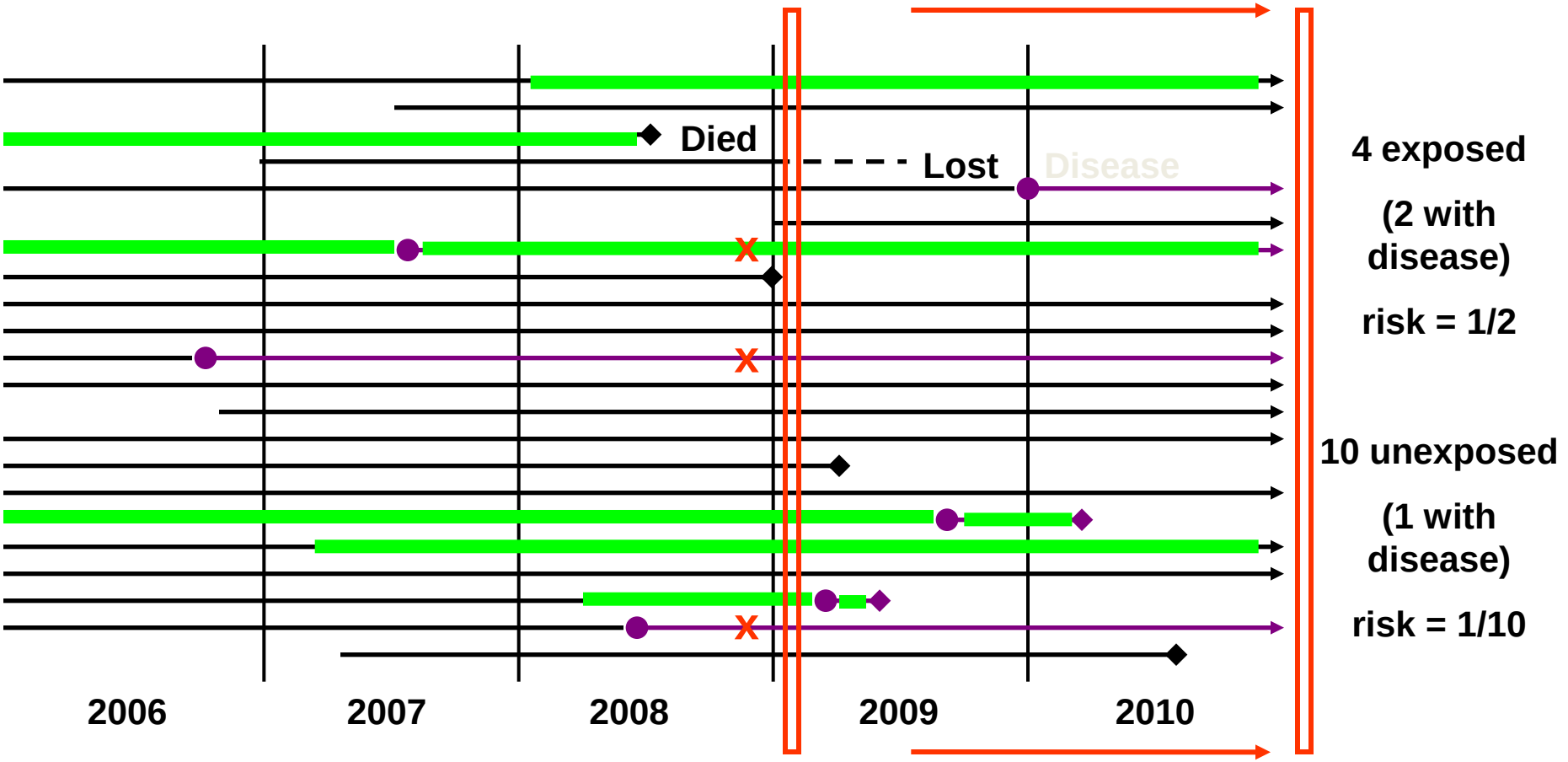
" is it the use of antidepressants that made you obese or is it the fact that you were obese that caused depression (and the prescription of antidepressants)?"

Antidepressant → Obesity

2. Cohort studies

- One defined group of people
- Follow-up over time, measuring exposures and outcomes
  - Exposures often measured at baseline
- Compare the outcome (e.g. disease rates) in exposed vs unexposed
- Also called longitudinal study

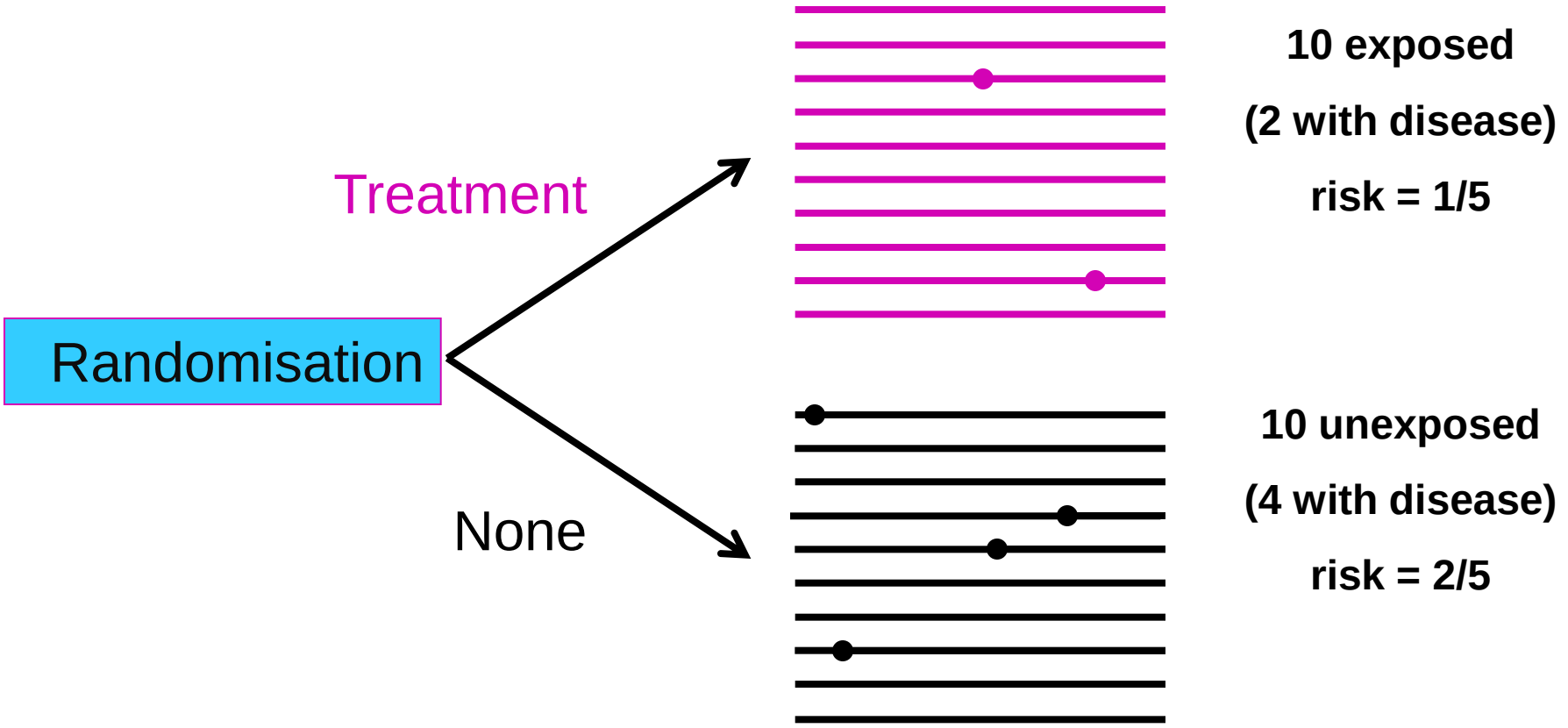
2. Cohort studies



2. Cohort studies: evaluation

- Good
  - whole population of interest
  - can look at many outcomes
  - time element
  - easier to disentangle causes and effects
    - You exclude the people that were obese before they started taking antidepressants
- Bad
  - unsuitable for rare disease (need lots of people)
  - expensive

3. Experimental studies: Randomized controlled trials (RCT)



3. RCTs: key issues

- Good
  - control over confounders (known and unknown)
- Bad
  - only for exposures you can control
    - i.e. healthcare interventions
  - typically can't look at rare outcomes (very expensive)

Why are RCTs better than observational studies?

- What is confounding?

Confounding

- Are Mercedes more safe than Porsche?

Confounding

- Cohort study for 1 year

	Porsche	Mercedes
At least one accident	47	26
None accident	53	74
All	100	100

- RR Porsche vs Mercedes = 47% over 26% = 1.81

Confounding

• Young people buy Porsche (and drive fast) – Mercedes is more popular among older drivers.

– Risk of a young driver to produce accident=50%

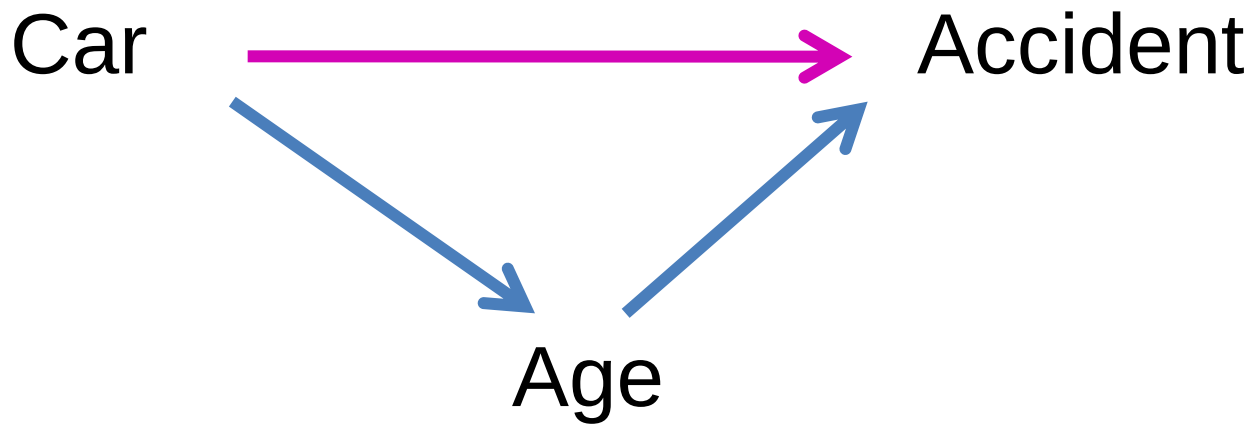
– Risk for older driver=2%

	Porsche	Mercedes
At least one accident	47	26
Younger than 45	45	10
Older than 45	2	16
None accident	53	74
Younger than 45	45	10
Older than 45	8	64
All	100	100
Younger than 45	90	20
Older than 45	10	80

$RR_{young}=1$

$RR_{older}=1$

Confounding



Omega 3 fatty acids and cardiovascular disease

THE INDEPENDENT

NEWSPAPER OF THE YEAR

INSIDE TODAY: INDEPENDENT EXTRA 8-PAGE PULL OUT

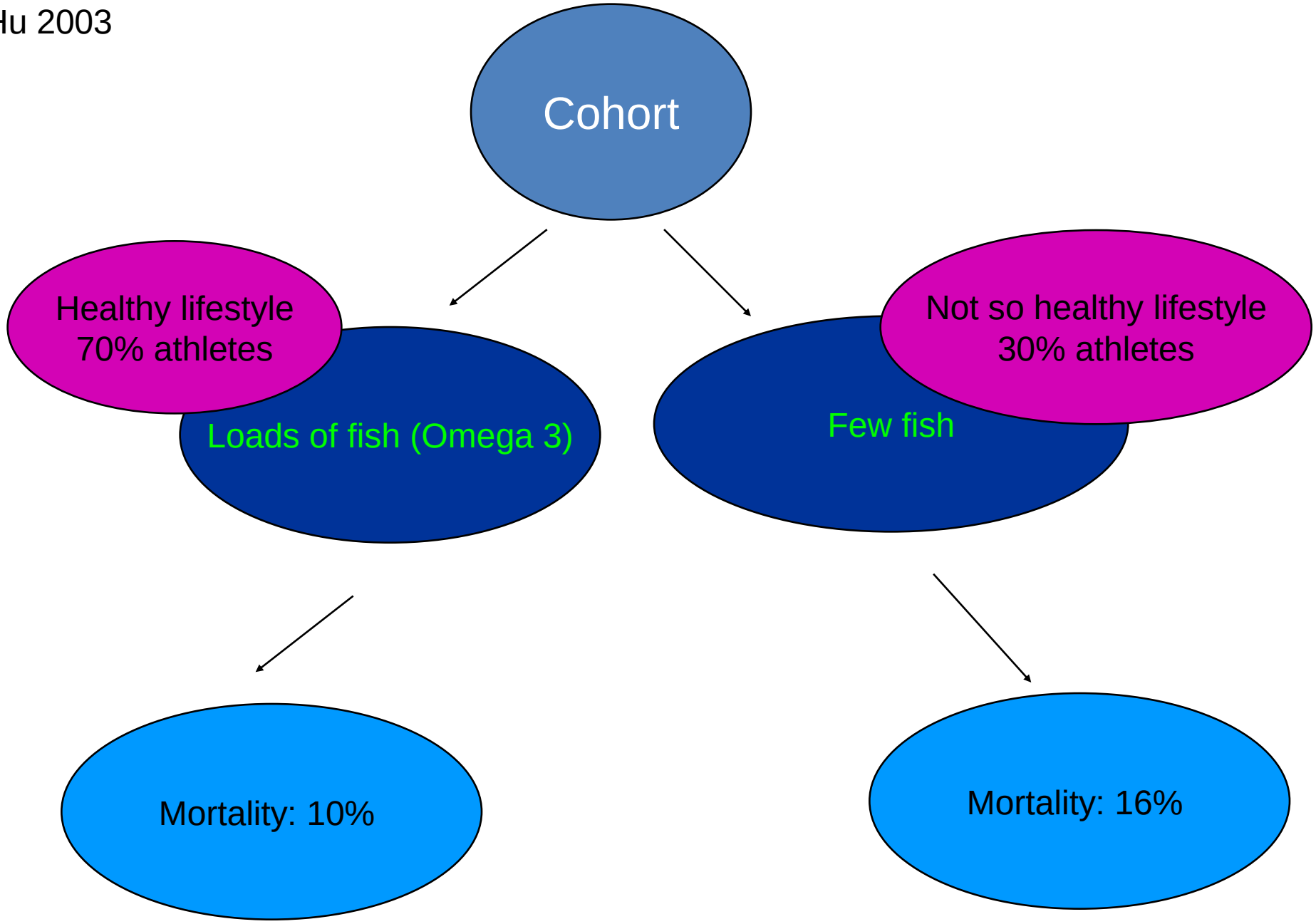
ME AND MY MOTHER

TRACEY EMIN • HOWARD JACOBSON • BIANCA JAGGER • JANET STREET-PORTER • TIM LOTT • JULIAN CLARY • PIERS MORGAN • AMY JENKINS • JEREMY HARDY • JULIE MYERSON • KATE FIGES

Debunked: the health benefits of oily fish

No evidence of protection against heart disease, strokes or cancer

Hu 2003

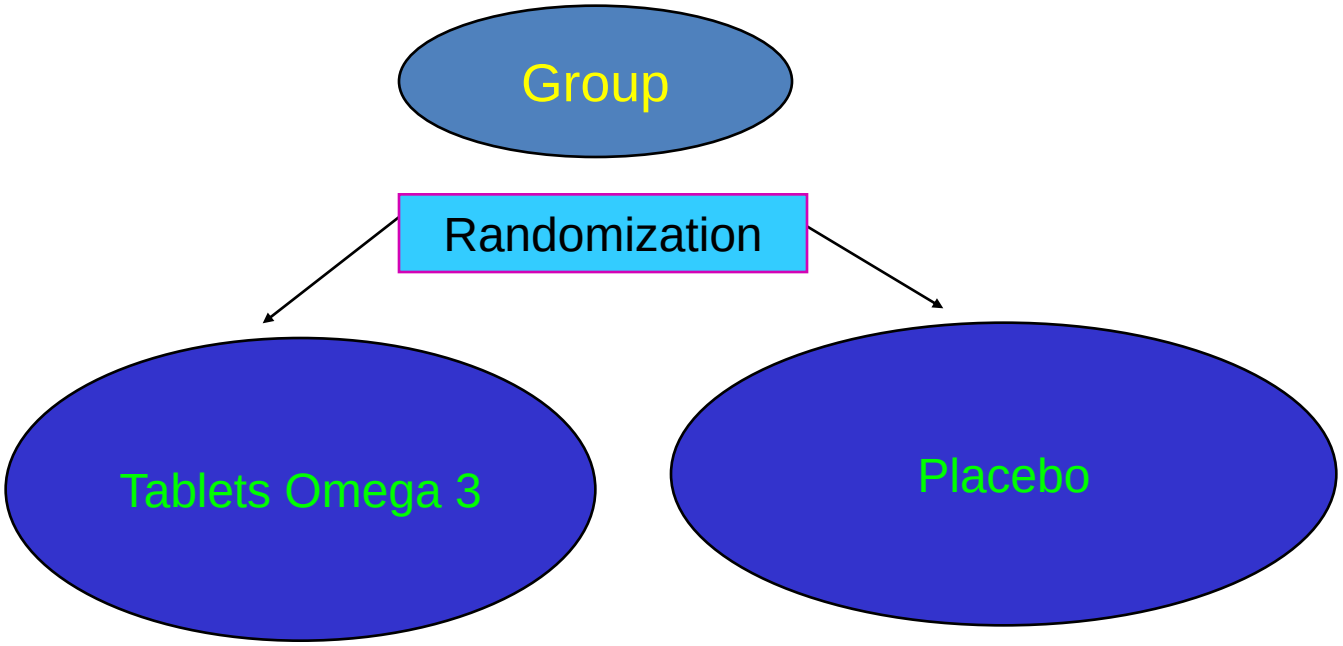

Cohort
Healthy lifestyle
70% athletes
Loads of fish (Omega 3)
Not so healthy lifestyle
30% athletes
Few fish
Mortality: 10%
Mortality: 16%

Dealing with confounding in observational studies

- Known confounding factors about can be adjusted by
  - Stratified analysis (e.g. per age group)
  - Using regression models
  - Logit(probability of death) = $a+\beta_1\times Omega3+\beta_2\times Age+\beta_3\times smoking$

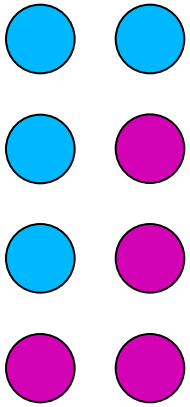
- But this can only be done for a limited amount of known confounding factors

Nielsen 2001



Randomization

Participants

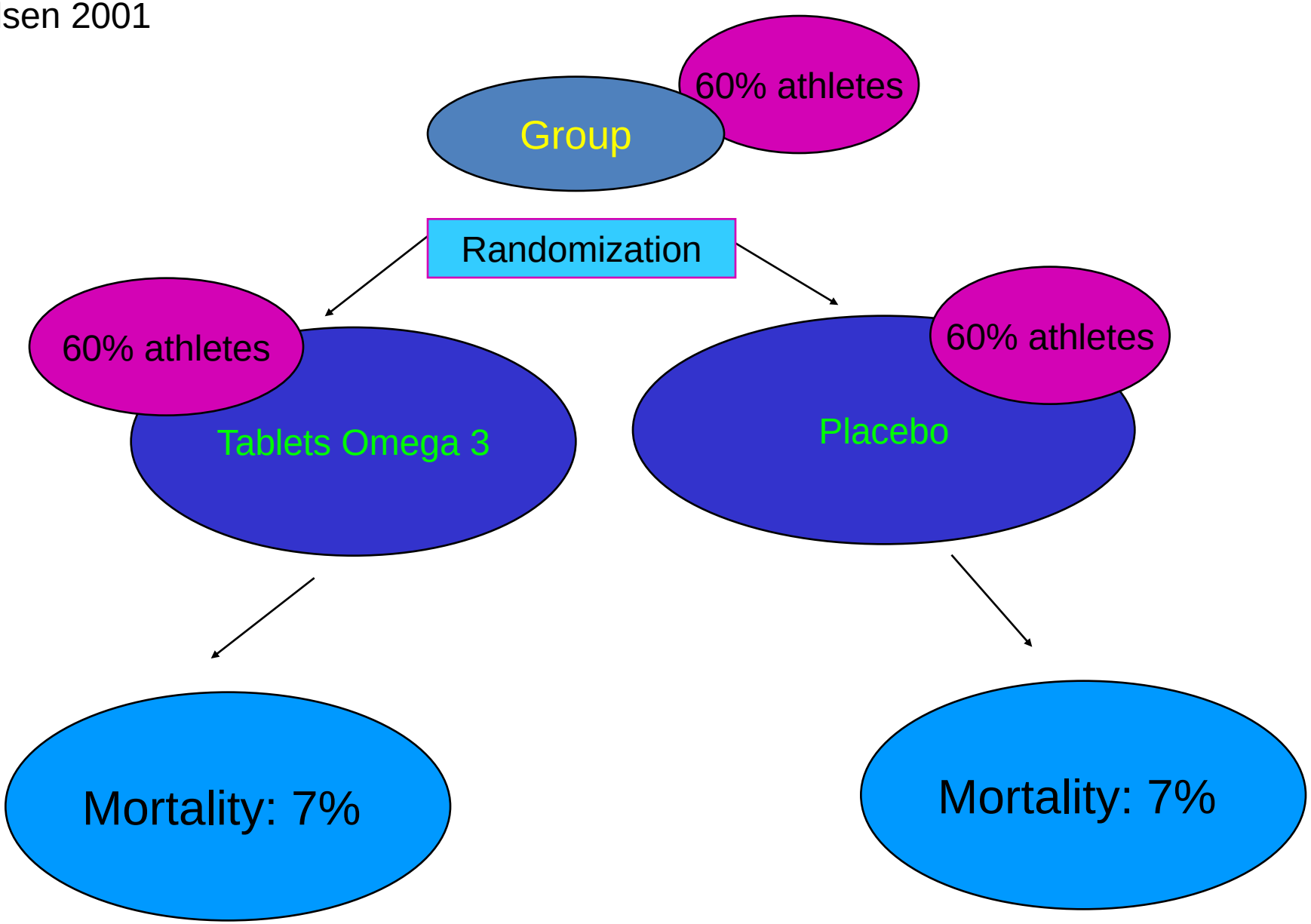


Omega 3

Placebo

By chance, all characteristics will be on average the same in the two groups
(of course we need a larger sample size...)

Nielsen 2001



Randomization controls for unknown factors too!

Levels of evidence

Recommendation	Level of Evidence	Type of Study
A	1a	Systematic review of RCTs
	1b	Individual RCT
B	2a	Systematic review of cohort studies
	2b	Individual cohort study
	3a	Systematic review of case control studies
	3b	Individual case control study
C	4	Case series/case report
D	5	Expert opinion, bench research

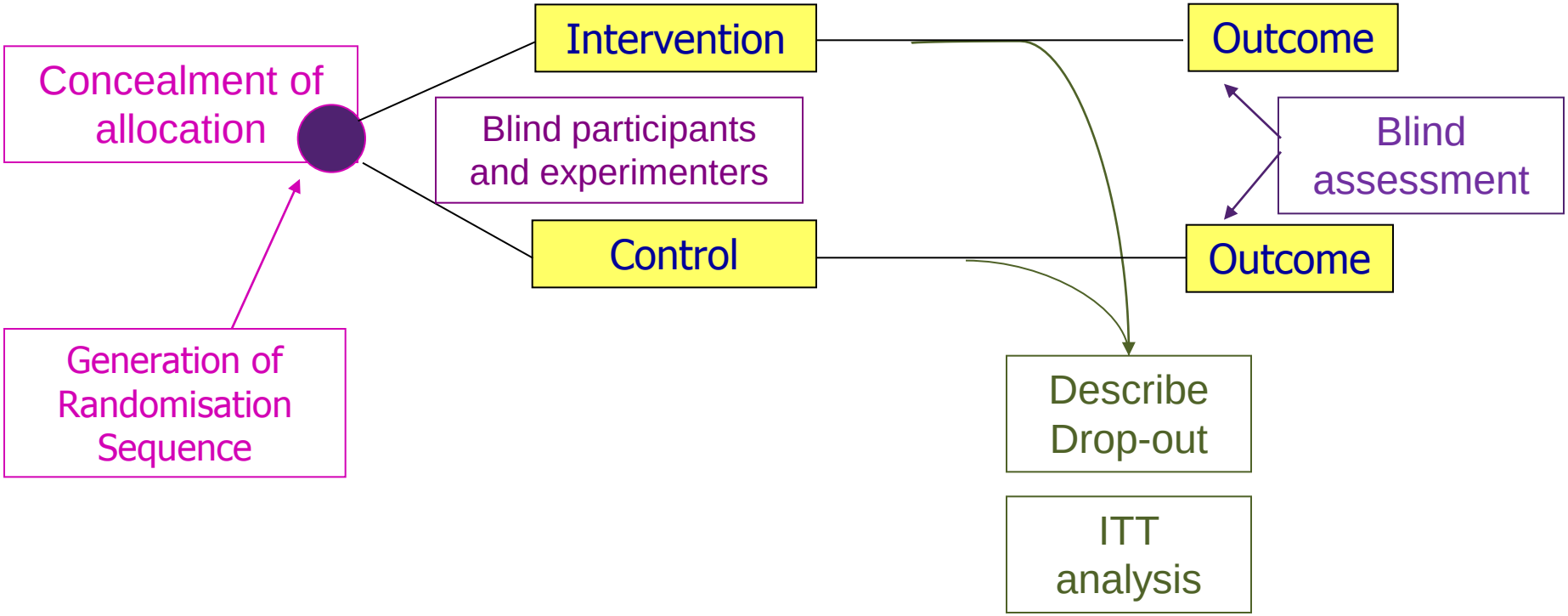
Not all RCTs are good

- RCTs can have important flaws in conduct and reporting
- Small and large studies can be bad of good
  - Although empirical evidence has shown small and old studies tend to be of less quality
- Credibility relates to the risk of bias in a study

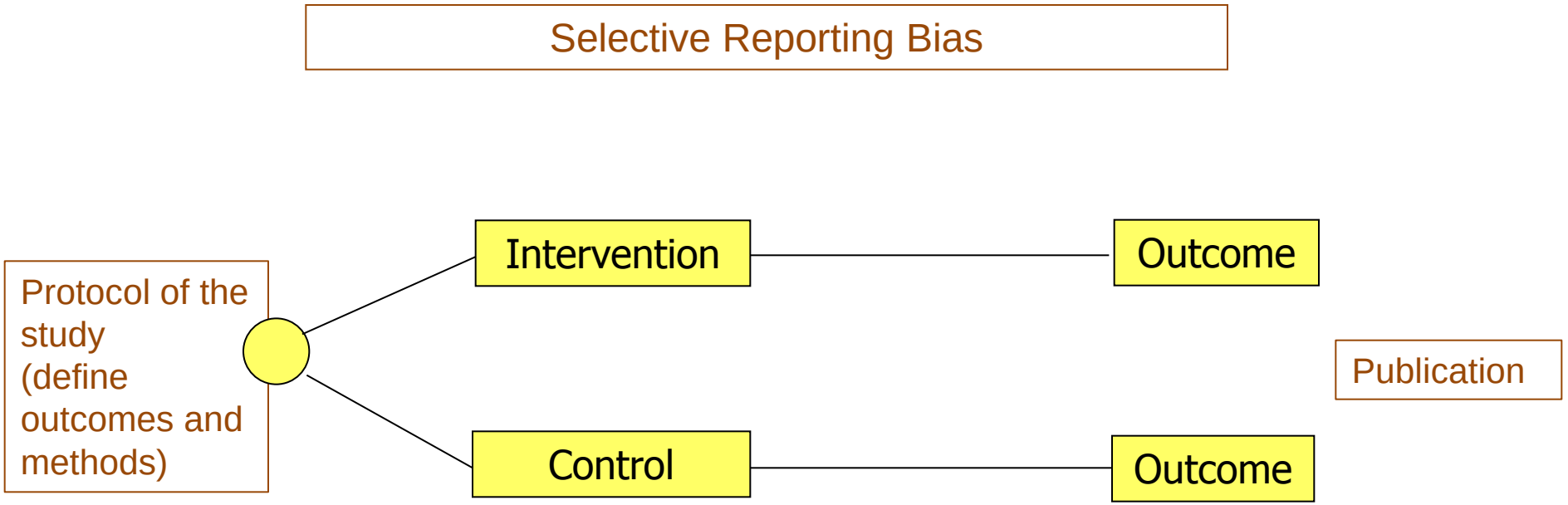
How to control bias in a RCT

Sources of bias in primary analysis

Selection bias | Performance bias | Attrition bias | Detection bias



Sources of bias in clinical trials



1. Generation of allocation sequence

- How will we decide who is going to which group? Was the process truly random?
- **Simple** (or complete) randomization
  - Any method that ensure that the chance that a patient receives either the test drug or the placebo is 50%
  - Randomization is performed independently for each patient
    - Eg Good randomization: Coin toss, random numbers table, computer
- **Block** randomization
  - Blocks of *k* patients are created such that balance is enforced within each block, e.g. *EECC*, *ECEC*, *ECCE*, *CEEC*, *CECE*, and *CCEE*
  - The blocks should be short enough to limit possible imbalance but should be long enough to avoid predictability
  - Is a *stratified randomization*

2. Allocation concealment

- Nobody (participants, clinicians etc) knows who is going to which group at the moment of randomization
- Common methods of ensuring allocation concealment:
  - Sequentially-Numbered, Opaque, Sealed Envelopes
  - Sequentially-numbered containers
  - Pharmacy controlled
  - Central randomization

2. Empirical evidence for the importance of allocation sequence

- Seven empirical studies
- Reasonably strong evidence: average 18% (95% CI 5% to 30%) exaggeration of odds ratios when allocation concealment is inadequate

Pildal et al (IJE 2007)

3. Blinding

- Who is blinded?
  - Participants
  - Providers of care
  - Researchers
  - Outcome assessors

- Open
- Single
- Double
- Triple
- …

"Do a double-blind test. Give the new drug to rich patients and a placebo to the poor. No sense getting their hopes up. They couldn't afford it even if it works."

3. Empirical evidence for blinding

- There is some evidence that failure *to blind outcome assessment* is associated with exaggeration of the treatment effectiveness by on average 14%
- The risk of bias is higher for subjective outcomes

Schulz 1995

4. Incomplete outcome

Why and when it is a problem?

Consider an intervention that is provided to stop alcoholism

	Stopped Drinking	**Remained in the study**	**Left the study**	**Total**
Intervention	**20**			**100**
Control	**10**			**100**

Risk Ratio between the randomized=2

4. Incomplete outcome

Why and when it is a problem?

Consider an intervention that is provided to stop alcoholism

	Stopped Drinking	**Remained in the study**	**Left the study**	**Total**
Intervention	**20**	**50**	**50**	**100**
Control	**10**	**80**	**20**	**100**

Risk Ratio between the randomized=2

Risk Ratio between those that remained in the study=3.2

4. Incomplete outcome

Why and when it is a problem?

Consider an intervention that is provided to stop alcoholism

	Stopped Drinking	Remained in the study	Left the study	Total
Intervention	**20** **70**	**50**	**50**	**100**
Control	**10**	**80**	**20**	**100**

Risk Ratio between the randomized=2

Risk Ratio between those that remained in the study=3.2

Risk Ratio assuming all people that left the intervention group did stop drinking whereas all that left the control group did not=7

4. Incomplete outcome: when does it introduce bias in the results?

- Random dropout
  - It's fine, don't worry
- Reasons for dropout related to randomisation or related to outcome
  - Introduces bias!!!
  - Example: trials on interventions for drinking cessation
- Different dropout percentage between the treatment and control group!
  - Study might have high risk of bias

Impact of missing data

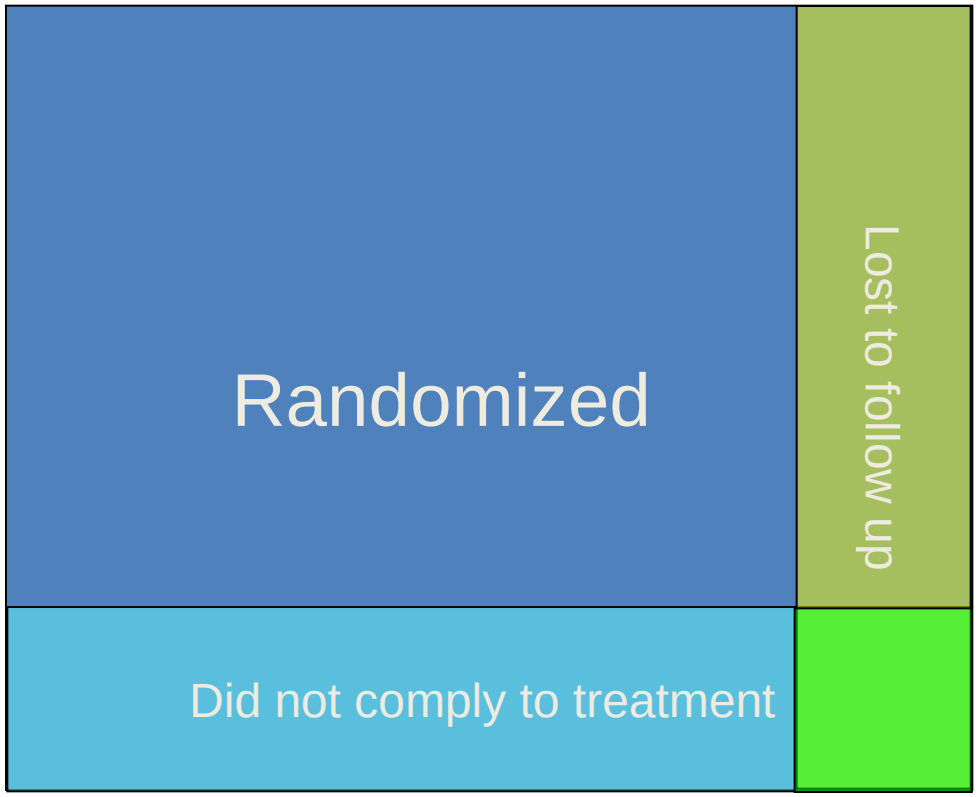
- Dichotomous

$$\frac{\#\text{missing}}{\#\text{events}}\uparrow \text{ then impact}\uparrow$$

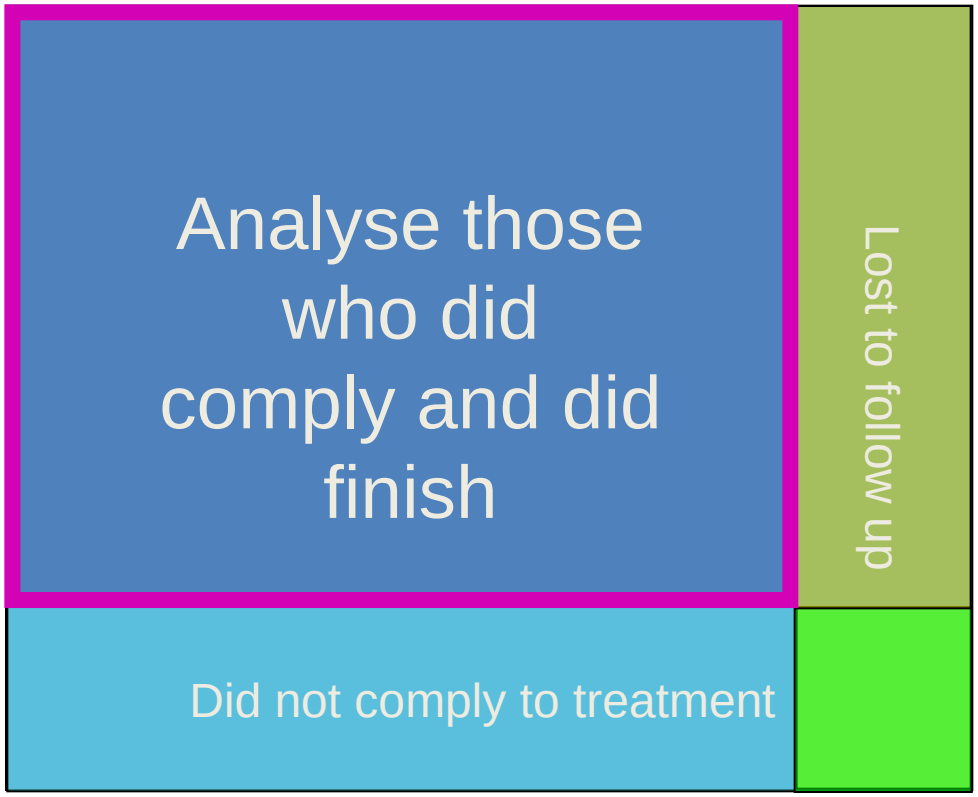
- Continuous

$$\%\text{missing}\uparrow \text{ then impact}\uparrow$$

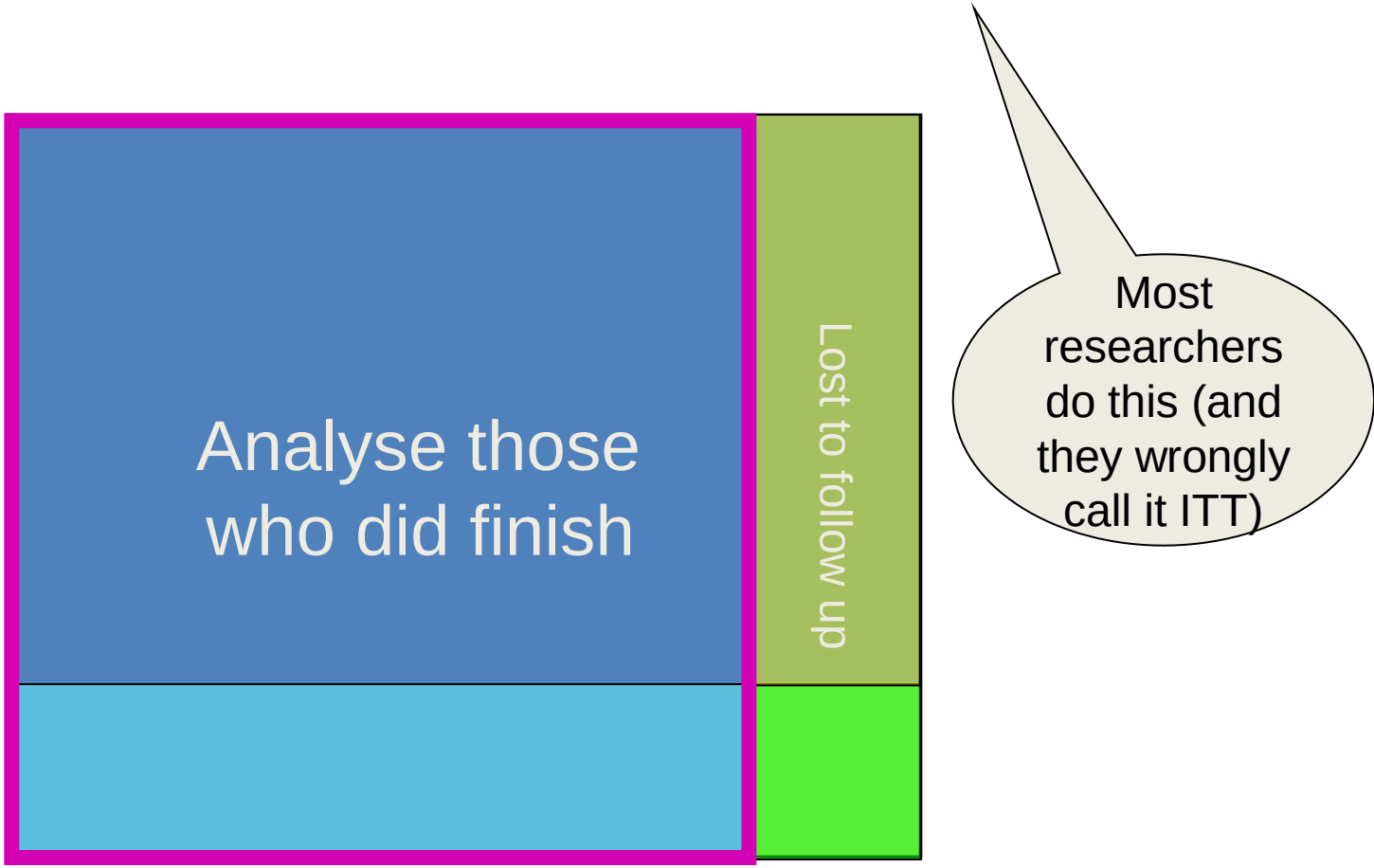
Intention To Treat analysis (ITT): What is it?



Per-protocol or treatment-received



Available cases analysis



True ITT

Because we want to estimate **the effectiveness** of the intervention under real circumstances and **not the efficacy** of the chemical substance or the nature of the intervention

Practical advise

- State explicitly what you mean by ITT as terms are often misused
- What to do when some individuals left the study and you can't find them
  - You can do ITT by 'imputing' missing data (ask for a statistician to help you) and do sensitivity analysis
  - Do available cases analysis but describe the numbers lost to follow-up and the reasons why they left the study.

5. Selective outcome reporting

- Bias due to data available being a biased ‘version’ of what has been done in practice
- Empirical evidence
  - strong;
  - 71% of outcomes with P<0.05 fully reported
  - 50% of outcomes with P>0.05 fully reported
  - 30% to 50% of primary outcomes changed between protocol and publication

Trial registration

- Registration of trials before their conduct to promote transparency of research

Statistical analysis

- Much easier compared to other designs
  - No need for adjustment for confounders
  - Baseline characteristics should be comparable between the group (when the trial is large enough)
- Be careful with subgroup analysis
  - Subgroups should be pre-specified in the protocol to avoid ‘fishing for significance’

Reporting

The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials

David Moher, MSc; Kenneth F. Schulz, PhD, MBA; and Douglas G. Altman, DSc, for the CONSORT Group* *Ann Intern Med.* 2001;134:657-662.

Table. Checklist of Items To Include When Reporting a Randomized Trial

Paper Section and Topic	Item Number	Descriptor	Reportec Page Nu
Title and abstract	1	How participants were allocated to interventions (e.g., "random allocation," "randomized," or "randomly assigned").	
Introduction			
Background	2	Scientific background and explanation of rationale.	
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	

Summarize

- RCTs are great (*in principal*) as they take control of all confounding factors, known and unknown
- A randomized trial should be undertaken with great care. You should
  - Register the protocol
  - Do properly the randomization, allocation concealment and blinding and try not to loose any participants
  - Report as per protocol

Acknowledgments

(for inspiring/sharing slides)
Julian Higgins
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