# What is a randomised controlled trial?

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WITH THANKS TO PROF RICHARD EMSLEY AND DR LESLEY-ANNE CARTER

# Motivation

Our topic on this course is **testing health interventions.**

- *Does this treatment improve (or worsen) outcomes?*

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# Intervention?

Could be **all kinds of things** e.g:

A drug (paracetamol for pain relief)

A surgical procedure (coronary artery bypass for heart disease)

An AI algorithm (prognostic model for patients with heart failure)

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**Premise:** we have an obligation to test interventions in a robust manner.

- *Surprisingly controversial? What's the harm?*

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- *Surprisingly controversial? What's the harm?*
- *Treatments may make things worse, as well as better!*

**Question:** How can we do that?

- *Randomised controlled trials (or randomised clinical trials, RCTs).*

# What are randomised controlled trials (RCTs)?

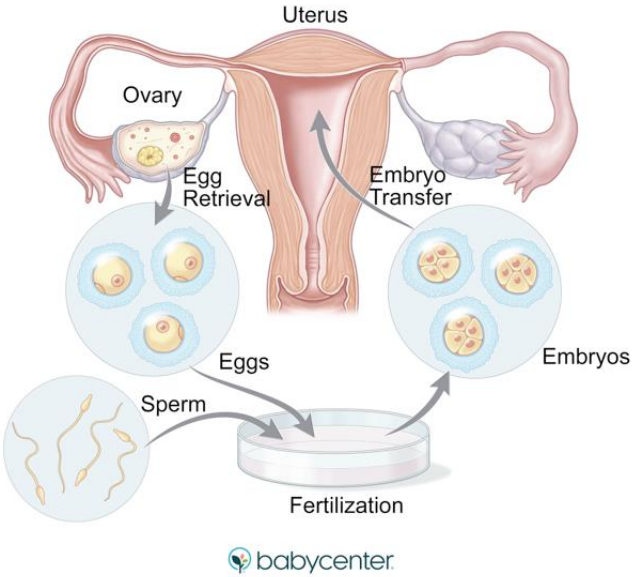
We will explain by contrasting to other types of **clinical studies** (*non-randomised, observational*).

# Some clinical background for our examples today

We are going to look at two examples relating to **in vitro fertilisation (IVF).**

People undergo IVF when they are having **fertility problems**.

The goal of treatment is to help them **have a baby**.



# Example of an RCT

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ORIGINAL ARTICLE

## A Randomized Trial of Endometrial Scratching before In Vitro Fertilization

Sarah Lensen, Ph.D., Diana Osavlyuk, M.Sc.,
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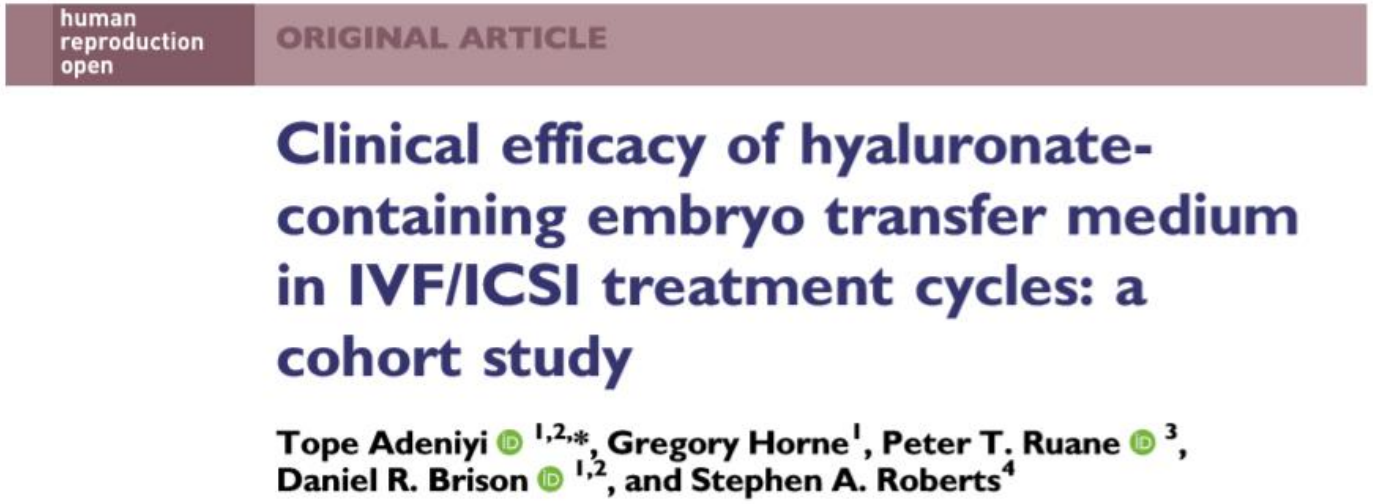
Q: If we scratch the inside of the uterus before in vitro fertilisation (IVF), does it improve the chance of having a baby?

# Example of a non-randomised study




- A cohort study
- Q: Does use of enriched embryo culture medium improve the chance of having a baby?
- 'Culture medium' is the liquid used to grow embryos in IVF.
- Will use these to illustrate key features of RCTs
- You will learn to **design, analyse**, **interpret** and **critically appraise** clinical studies on this unit.

# Much medical research is low quality

**Editorials**

**The scandal of poor medical research**

*BMJ* 1994 ; 308 doi: https://doi.org/10.1136/bmj.308.6924.283 (Published 29 January 1994)
Cite this as: *BMJ* 1994;308:283

"Much poor research arises because researchers feel compelled for career reasons to carry out research that they are ill equipped to perform, and nobody stops them." *Doug Altman, 1994.*

- Medical researchers routinely get the wrong answers to research questions, because they don't understand research design and statistical methodology.
- But bad research = bad medicine (and wasted resources).

# But good clinical research is hard

- Good clinical research: easier said than done
- Interpreting/ critically appraising isn't easy either
- There are many aspects to consider:

**Control group**
**Blinding**
**Analysis**
**Outcome assessment**
**Primary outcome**
**Sample size/ power**
**Randomisation**
**Allocation concealment**
**Choice of sample...**

We will learn about the importance of these features in this unit!

# Some terminology: treatment groups, control groups, and outcomes.

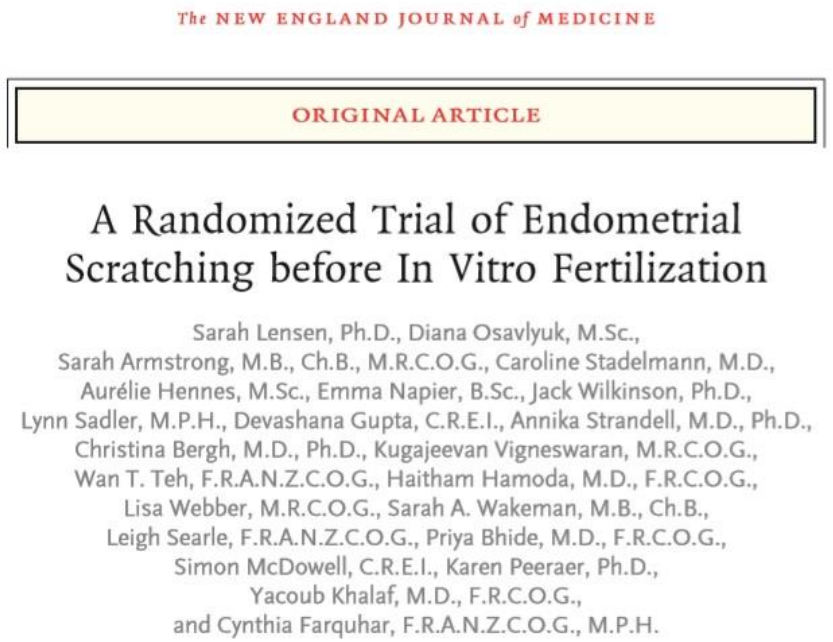
# Some terminology

**Treatment/ intervention/ exposure group:** used to mean the group of participants being given the treatment under evaluation in the study. (Also ‘experimental’ group/ treatment).

**Control group:** the group to which the treatment group is being compared.

# Treatment and control groups

**Treatment/ intervention/ exposure group:** used to mean the group of participants being given the treatment under evaluation in the study. (Also 'experimental' group/ treatment).



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- The **treatment group** underwent endometrial scratching before having IVF.
- A **control (comparator) group** underwent IVF without endometrial scratching. Note they still had some treatment (IVF).

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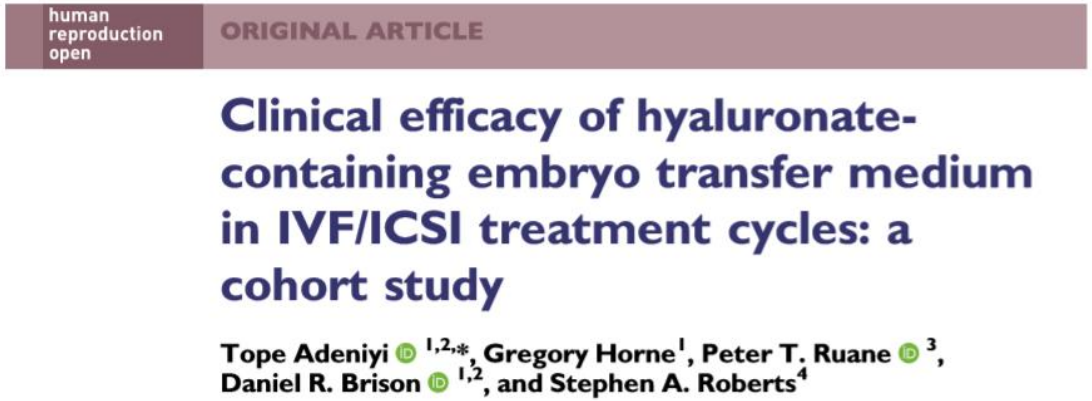



- The **treatment group(s)** had embryos cultured in enriched culture medium.
- A **control (comparator) group** had embryos cultured in normal culture medium.
- **Note:** this study actually considered two enriched groups.

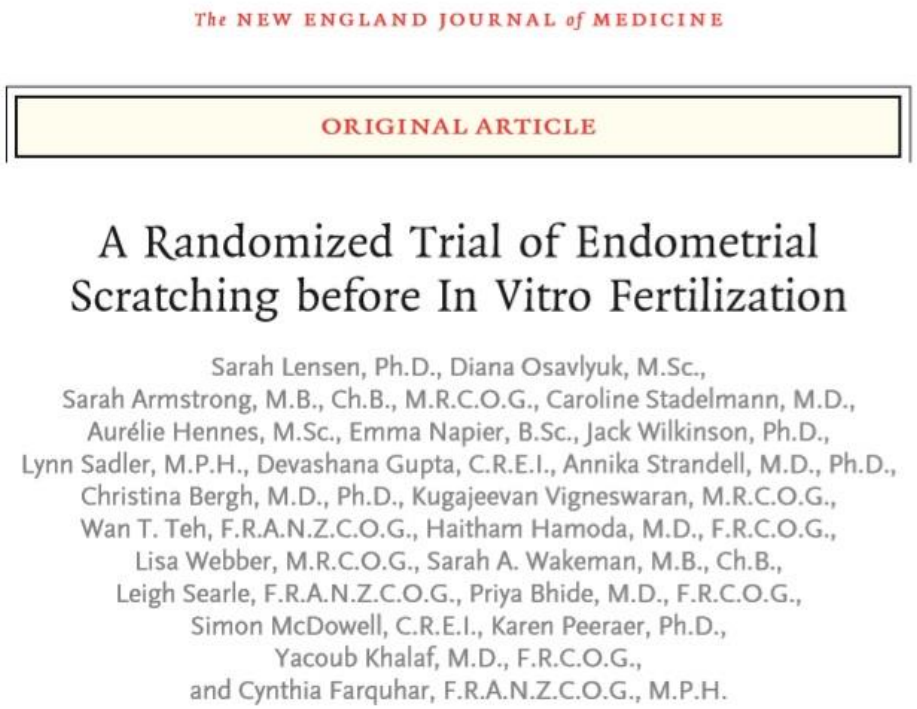
# Outcomes

**Outcome variable:** A measure of the patient's health post-treatment (e.g. how they responded to treatment … were patients' blood glucose levels 'better controlled' if they wore a blood glucose monitor?).

Often, we want to find out about the *effect* of the **treatment** on the **outcome** variable.

# Study outcomes

**Study outcome:** A measure of patient response to treatment. Used to evaluate the effect of the treatment/ intervention.



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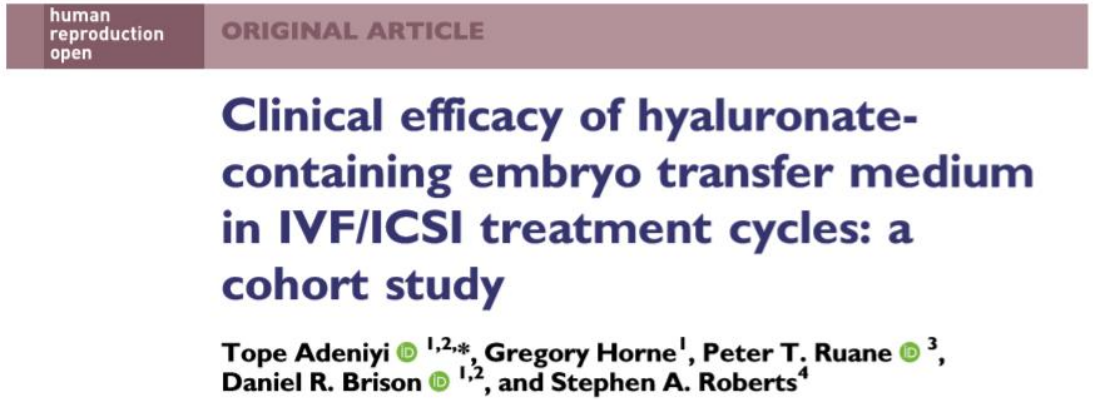
- The primary **outcome** of the study was live birth. Compared live birth rate (proportion of participants having live births) between treatment and control groups to determine whether endometrial scratching had any effect.

- Other, secondary **outcomes** included ongoing pregnancy, clinical pregnancy, ectopic pregnancy, pain during the procedure, neonatal outcomes…

# Study outcomes

**Study outcome:** A measure of patient response to treatment. Used to evaluate the effect of the treatment/ intervention.




- The primary **outcome** of the study was again live birth. Compared live birth rate (proportion of participants having live births) between treatment and control groups to determine whether enrichment had any effect.

Other, secondary **outcomes** included biochemical pregnancy, clinical pregnancy, multiple live births, early pregnancy loss, late miscarriage, neonatal outcomes…

# Does the treatment work?

A comparison between the responses (outcomes) in the treatment group vs the responses in the control group is used to test whether the treatment under study works.

# Why do we need control groups?

# Why do we need control groups?

Suppose you are ill, and we want to know whether we should give you a particular treatment, or some alternative (a *control*).

Ideally, to make that decision, we would like to know **what would happen to you** (that is, what your outcome would be) if we gave you each of the treatment and control.

We can give you one of them, and see what happens. But we will never know if that is better or worse than what **would have happened** if we had given you the other treatment instead.

RCTs are an attempt to estimate the 'what would have happened'.

More precisely, they attempt to estimate the **difference between outcomes** under the two possible scenarios – we call this difference the **treatment effect.**

# Why do we need control groups? Fundamental concept of causal inference

Receive treatment

Measured outcome

Receive control

Measure outcome

Comparison of outcomes *would* give an **individual treatment effect** (but we only see one of these!)

# Why do we need control groups? Fundamental concept of causal inference

Receive treatment

Measure outcome

Receive control


Measure outcome

Comparison of these outcomes **<u>will not give</u>** an individual treatment effect

# Why do we need control groups? Fundamental concept of causal inference

So we can't (usually) work out the *individual* treatment effect, without a time machine, or the ability to travel into parallel universes.

What about if we could take *everyone* who was ill with the same condition, and observe their outcomes under both treatments (we can't for most conditions – we still have no time machine - but imagine).

We could then calculate the individual treatment effects for everyone. And we could calculate the mean of these – the **average treatment effect.**

It turns out, if we *randomly allocate* (randomise) each person to receive either the treatment or control, then the difference in mean outcomes between groups is an **unbiased estimate of the average treatment effect.**

# Why do we need control groups? Fundamental concept of causal inference

Receive treatment

Measure outcome

Receive control

Measure outcome

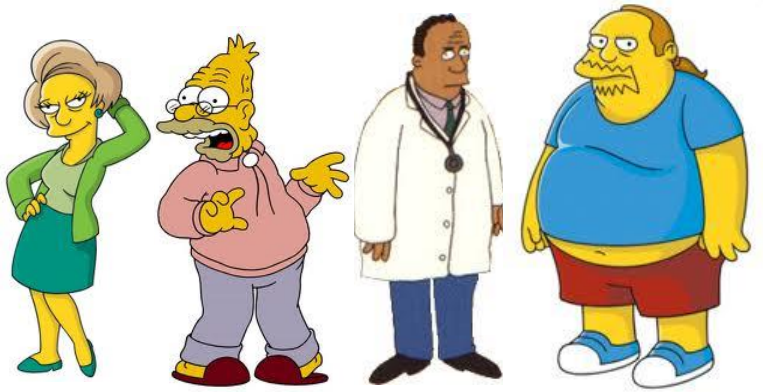
Comparison of average outcomes **defines** the **average treatment effect**

# Why do we need control groups? Fundamental concept of causal inference

Randomise treatment*

Measure outcome

Randomise control*



Measure outcome

*Or successfully control for confounding another way in a non-randomised study

Comparison of average outcomes **estimates** the **average treatment effect**

# Why do we need control groups? Fundamental concept of causal inference

Moreover, it turns out that if we take a random sample of people from the population of interest, and randomly allocate them to receive either treatment or control, then the *sample* average treatment effect is an estimate of the *population* average treatment effect! (caveats…)

Our estimate of the *average treatment effect* is usually the best estimate we can get of the *individual treatment effect*.

# Summarising

A comparison between the responses (outcomes) in the treatment group vs the responses in the control group is used to test whether the treatment under study works.

The question we are trying to answer is: are patients better off when given the treatment compared to how they *would have been* if they had been given the control?

We can't observe both possibilities in patients – we must observe one or the other (treatment or control). The other is *counterfactual.*

The comparison between treatment and control groups stands in for this impossible 'multiple reality' comparison, but we need to use random allocation (or successfully control for confounding in a non-randomised study)

# So control groups are essential

It follows that we can't usually determine whether or not a treatment works without a control group.

A common fallacy – looking to see if people in treatment group 'got better' or 'got worse'.

This doesn't tell us anything about the counterfactual – what would have happened to them otherwise.

Example: anti-ageing cream. After 40 years, participants look 20 years older. They 'got worse' = cream doesn't work?

# Why do we prefer random allocation to treatments?

# How is treatment allocated?

There are two generic types of research study:

- *Observational*
- *Experimental*

# Different types of research study

**Experimental studies**

We **do** manipulate the treatment variable – we decide who does and does not get treated

Then collect the data and compare outcomes between those treated and those untreated

# Different types of research study

**Observational studies**

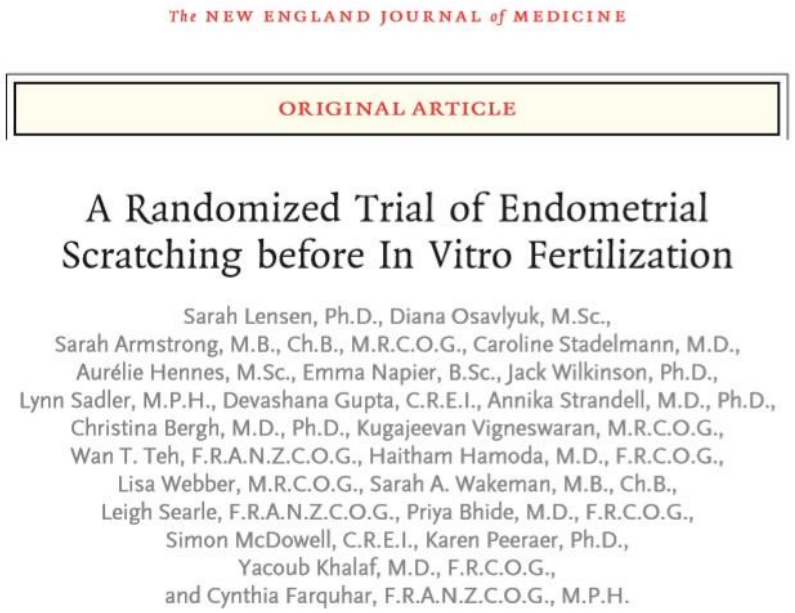
We do **not** directly manipulate the **treatment variable**

We then *observe* the outcome in people who have been treated, and compare to people who have not been treated.

# How is treatment allocated?

- How do we determine who ends up in the treatment or control groups?

In **experimental studies,** we have direct control over who enters the treatment and control groups.



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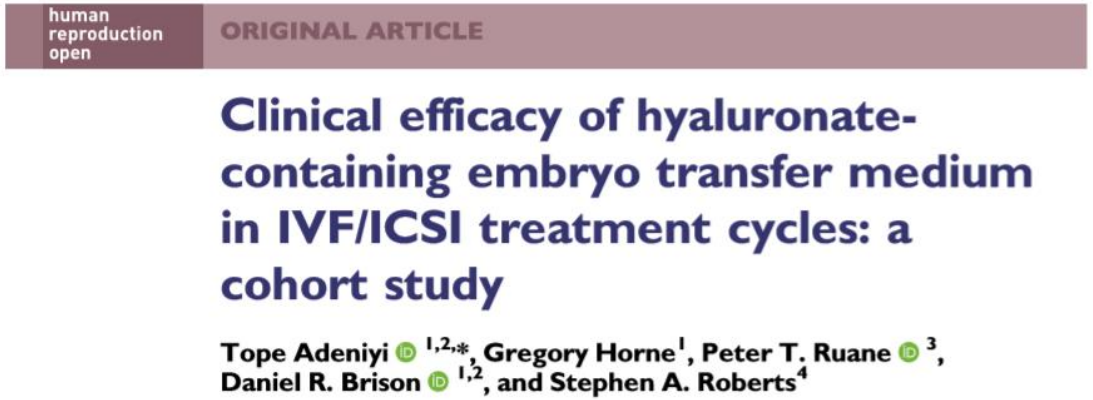
- A randomised controlled trial (RCT) is an example of an experimental study.
- Participants were randomly allocated to IVF with (treatment group) or without (control group) endometrial scratch.

# How is treatment allocated?

- How do we determine who ends up in the treatment or control groups?

In **observational studies**, we do not have direct control over this – we just observe the outcome in people who have been given the intervention, and compare to people who have not.




- A cohort study is an example of an observational study.
- It is also an example of a **non-randomised study of an intervention.**
- Changes in clinical practice in the centre: compared outcome of patients prior to and after introduction of HA-rich culture medium.

# Experimental vs observational studies

- All RCTs are experimental.

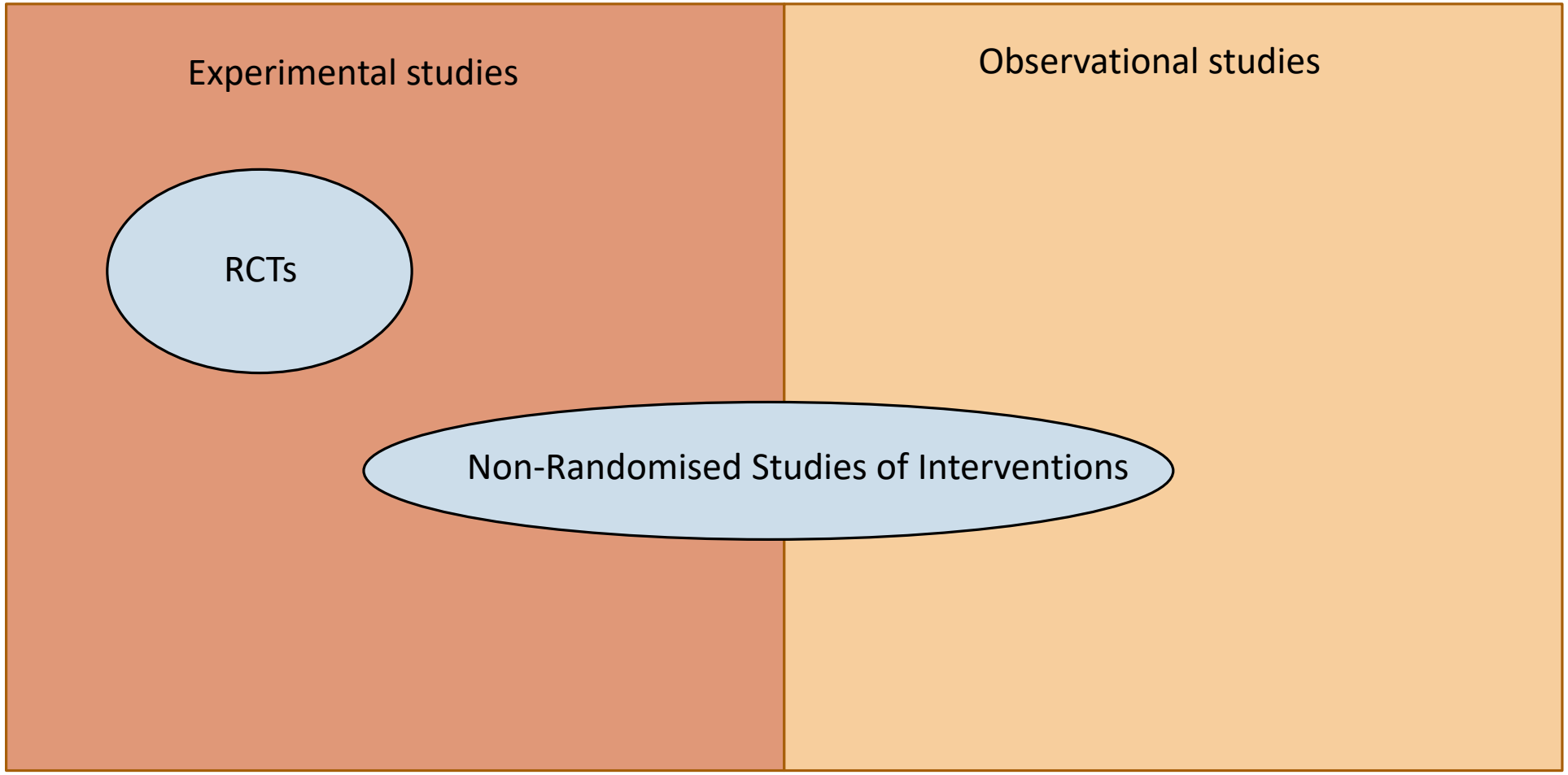
- But not all experimental studies are RCTs! People could allocate treatments in a non-random way (**non-randomised study of an intervention (NRSI)**).

- The distinction we are really interested in in this course is between RCTs and NRSI**.**

- NRSI may be observational or experimental.

- **Note:** there are lots of different study designs which could be called ‘observational’, but which have nothing to do with testing interventions (e.g. **developing** a clinical prediction model using electronic health records).

**RCTs are experimental studies, NRSI may be experimental or observational**



# What is Bias?

In medical research, **bias** occurs when some factor systematically corrupts the result of a study – it makes us get the wrong answer.

If there is bias: if we were to repeat the study many times over, our results would be too large or too small (or even in the wrong direction) compared to the truth (which we never know).

Bias can be introduced in two ways:

- Due to the **design** of the study.
- Related to properties of the method you use to **analyse** the data.

# What is Bias?

Bias, particularly relating to **design**, is a major concern in medical research.

It may occur in many different ways.

It is a greater problem in non-randomised studies than RCTs.

Next week, we will learn about different kinds of bias in RCTs, and how to prevent these

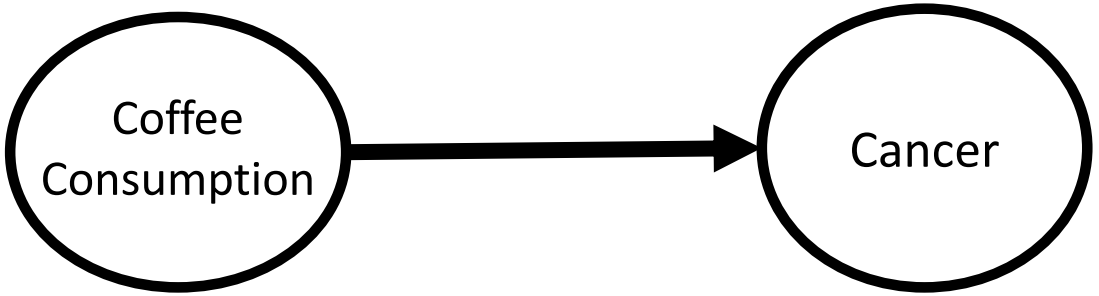
This week we will just consider a particular types of bias, called **confounding** bias.

# Why do we prefer random allocation?

- Main reason: non-randomised studies are subject to **confounding**.

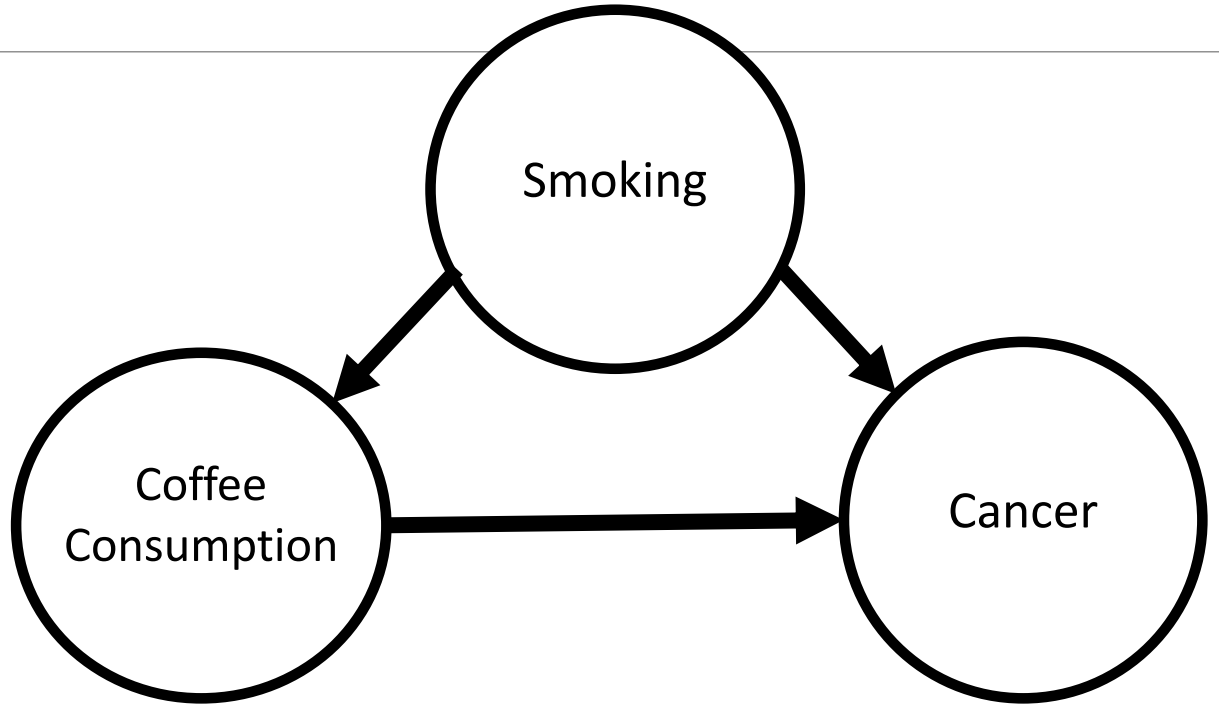
Example: coffee causes cancer

- Suppose an observational study suggests that coffee causes cancer:



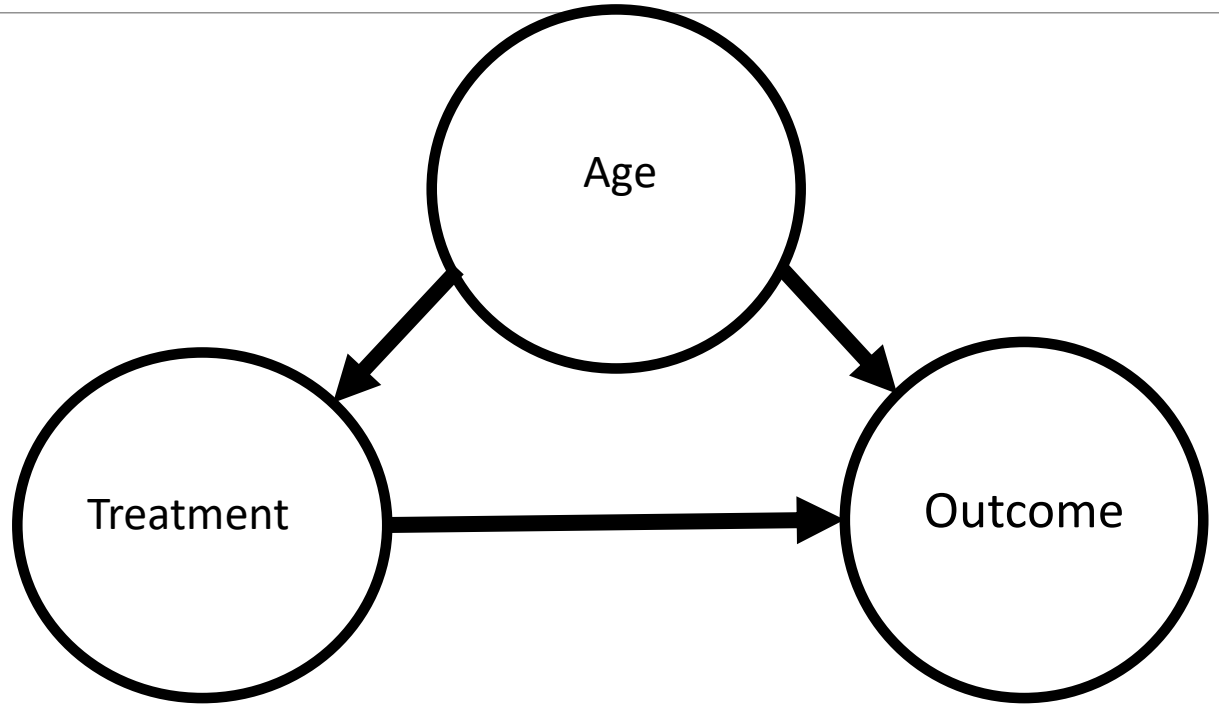

**Uh oh!**

# Confounding example: coffee causes cancer?




Maybe coffee drinkers tend to be smokers, and smoking causes cancer. If so, smoking is a confounder. It made us think that coffee caused cancer!

# Confounding in non-randomised studies




In NRSI, treatment and control groups might systematically differ in other ways (in addition to treatment received).

# What goes into the decision of how to treat a patient (shared decision making)?

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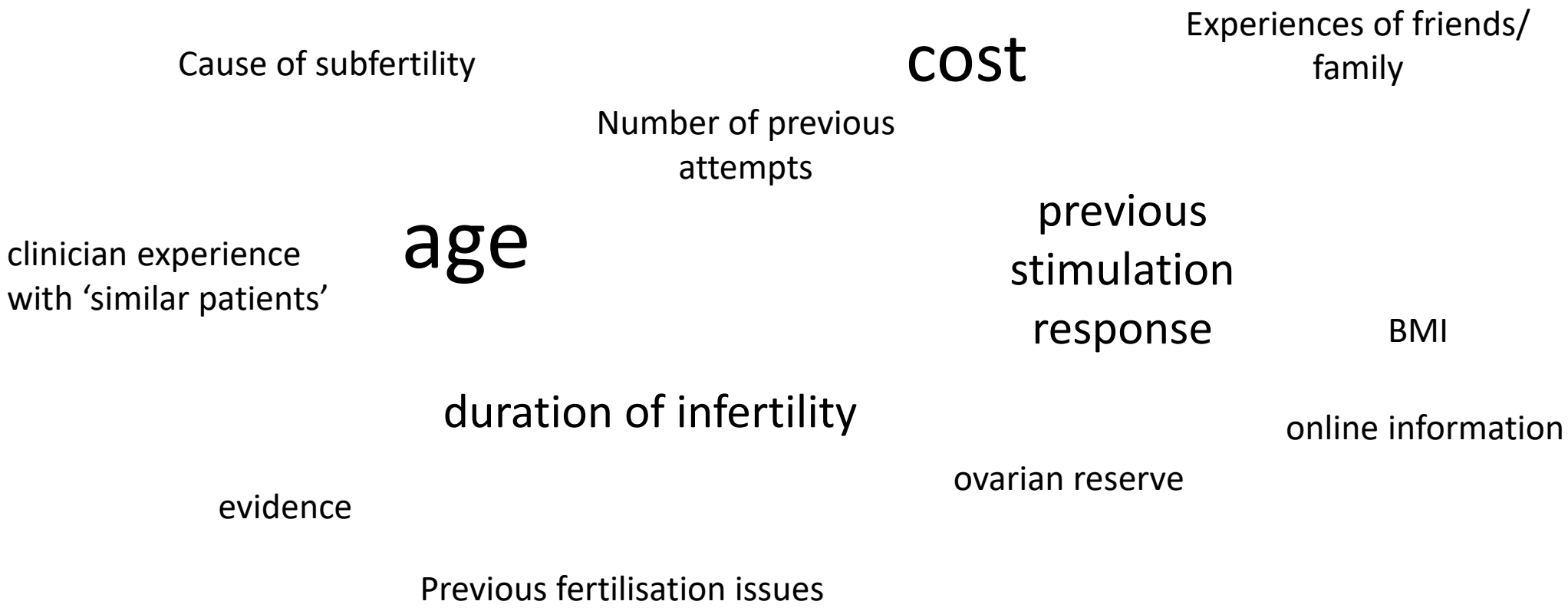


# These factors may be associated with other characteristics in complex ways

smoking

alcohol

ethnicity

Cause of subfertility

cost

Experiences of friends/ family

Number of previous attempts

metabolic disease

previous stimulation response

diet

clinician experience with ‘similar patients’

age

BMI

comorbidity

duration of infertility

online information

ovarian reserve

medical history

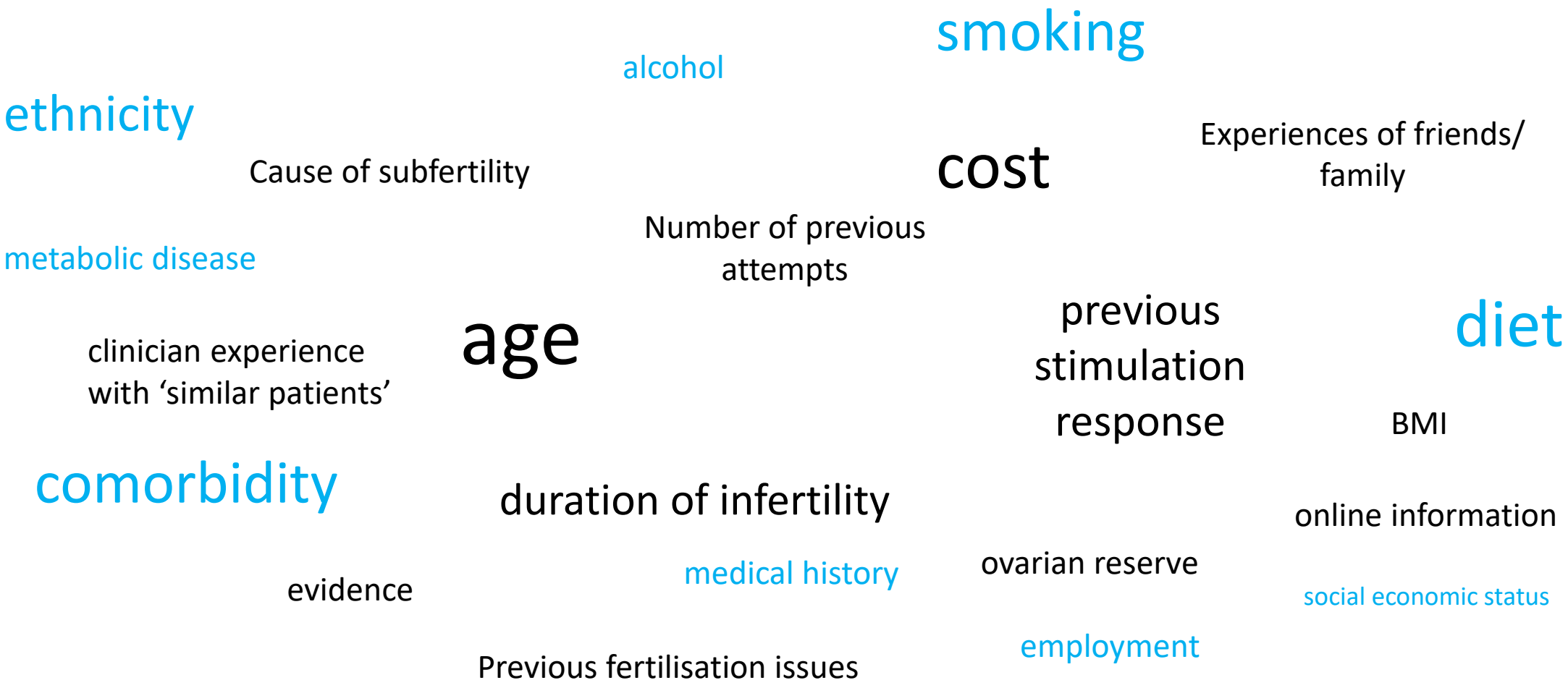
evidence

social economic status

employment

Previous fertilisation issues

# A treatment might be offered at some clinics, not others



# Possible differences between centres…

embryology lab conditions

smoking

alcohol

clinician experience

ethnicity

Cause of subfertility

cost

Experiences of friends/ family

Number of previous attempts

embryo selection procedures

metabolic disease

previous stimulation response

diet

clinician experience with ‘similar patients’

age

clinician skill

BMI

comorbidity

duration of infertility

online information

ovarian reserve

medical history

evidence

social economic status

employment

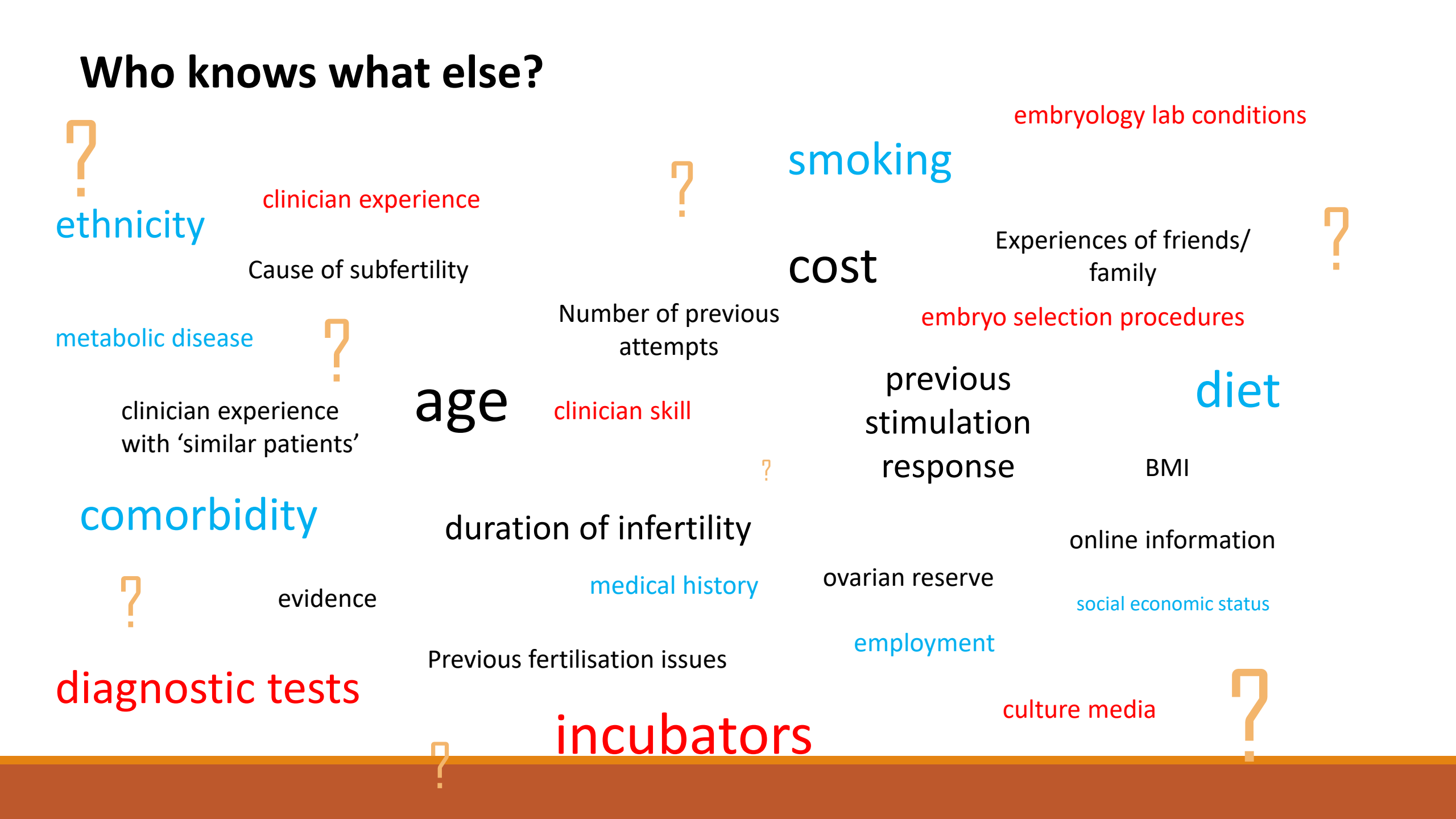
Previous fertilisation issues

diagnostic tests

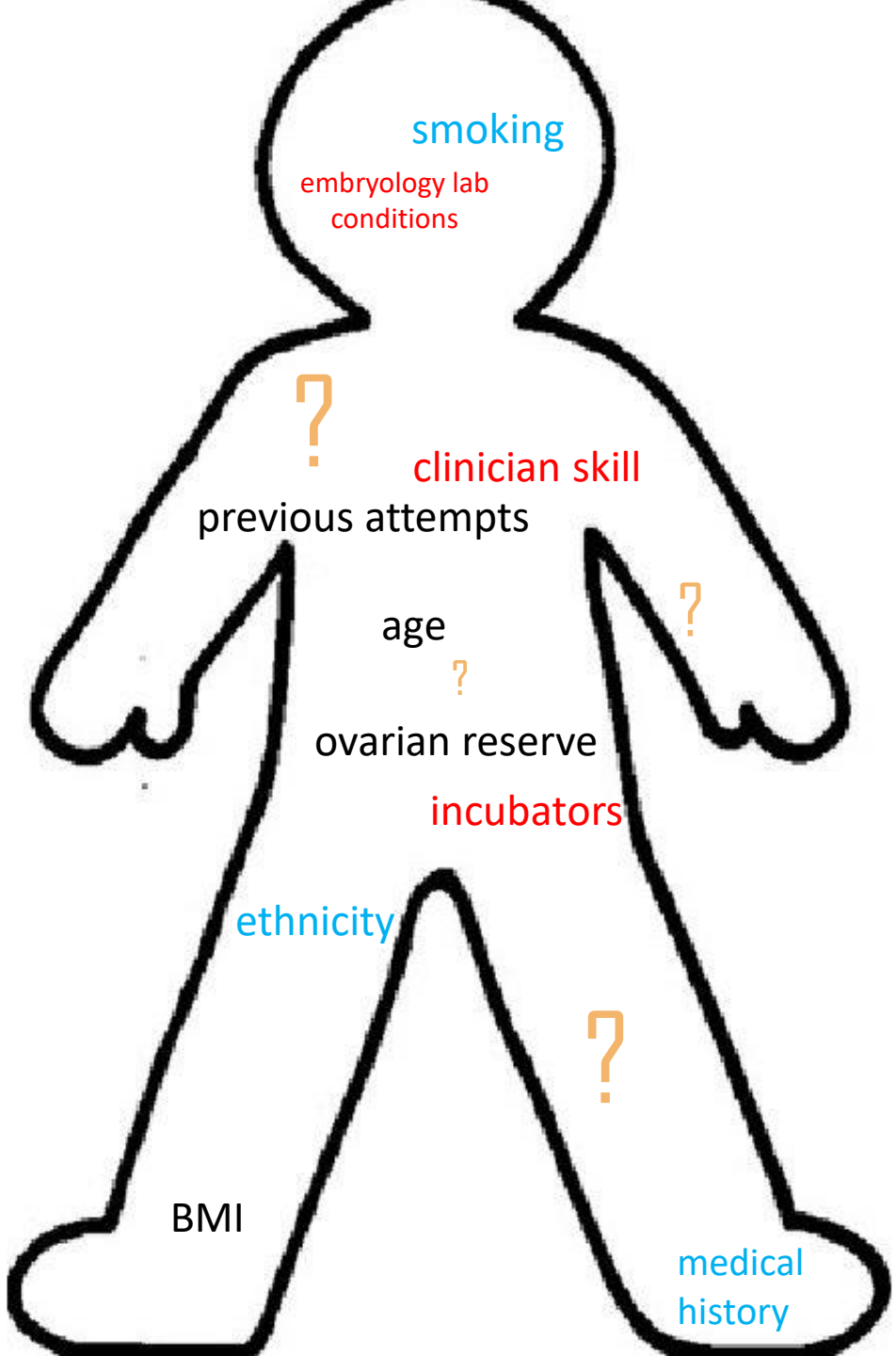
incubators

culture media

# Who knows what else?

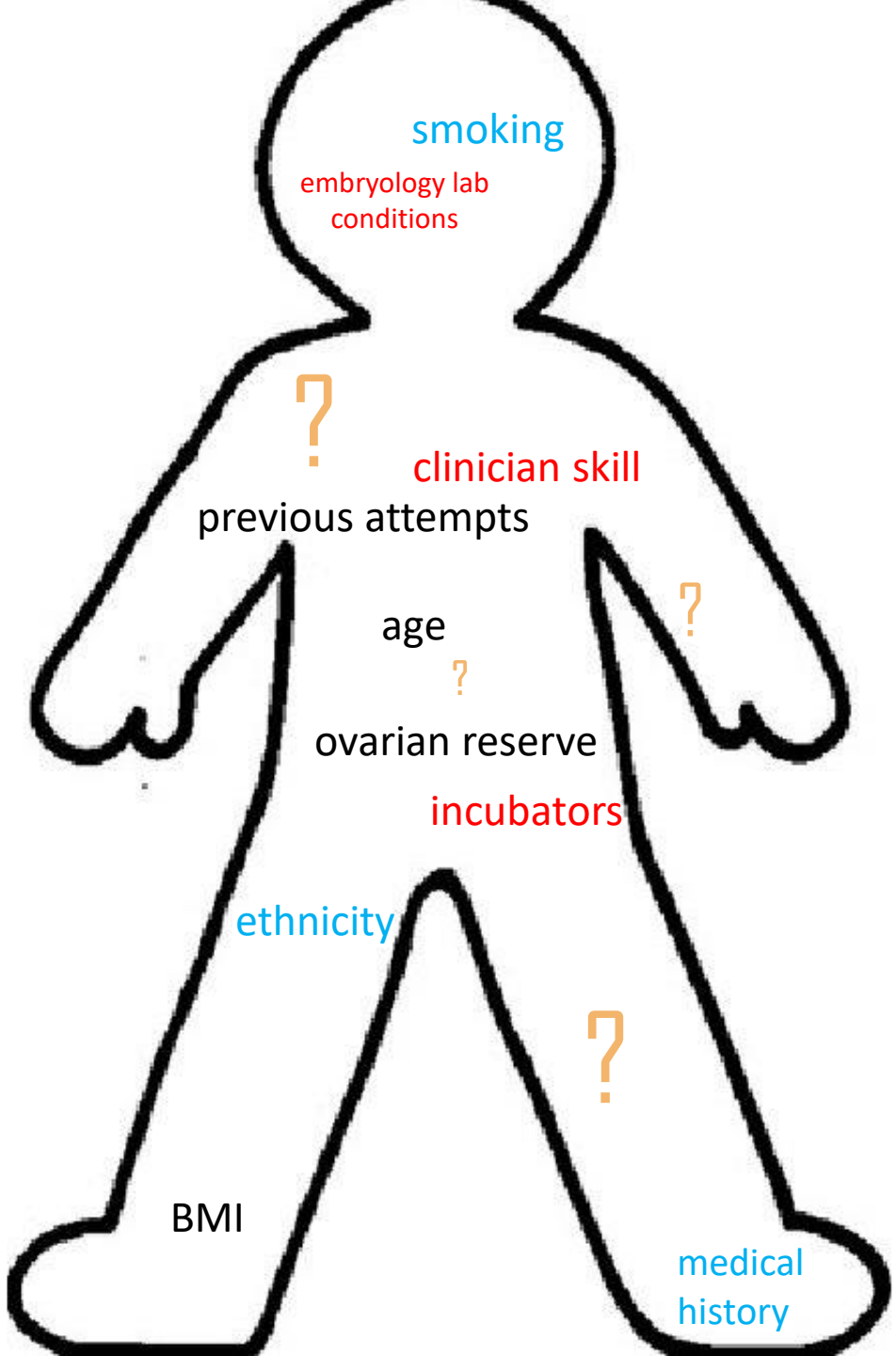


There is a unique ‘story’ or profile in the background, every time a patient is treated.



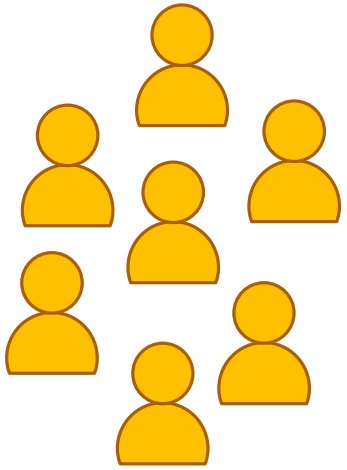
There is a unique ‘story’ or profile in the background, every time a patient is treated.

This profile determines whether or not treatment is likely to work.

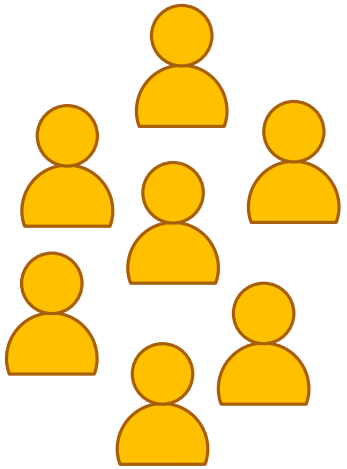


In NRSI, we take a group who were treated one way and compare them to a group who were treated a different way

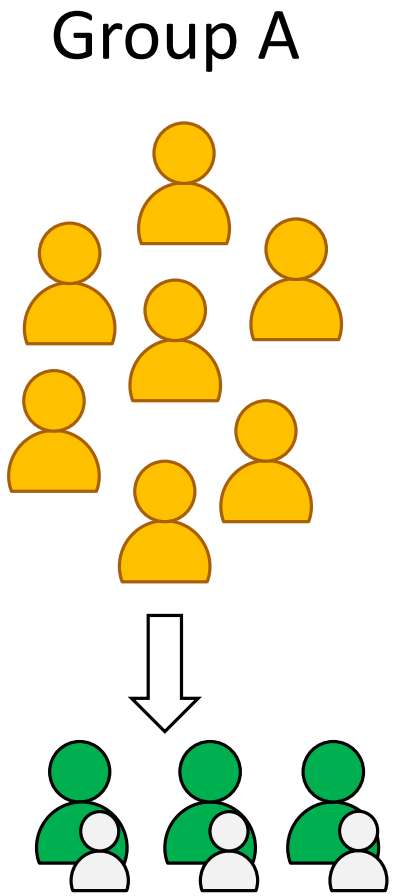
Group A

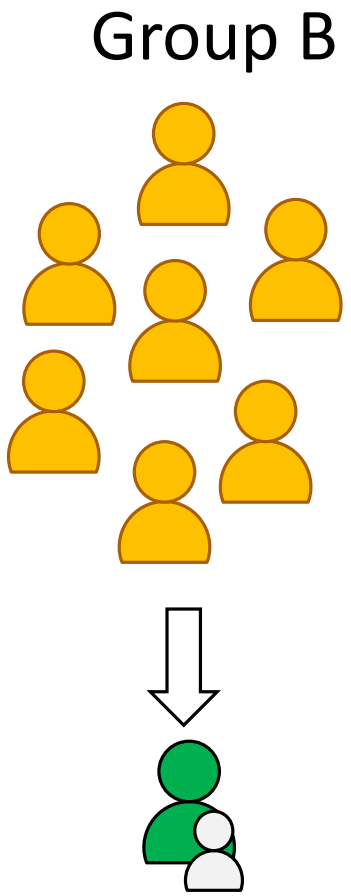


Group B



In NRSI, we take a group who were treated one way and compare them to a group who were treated a different way

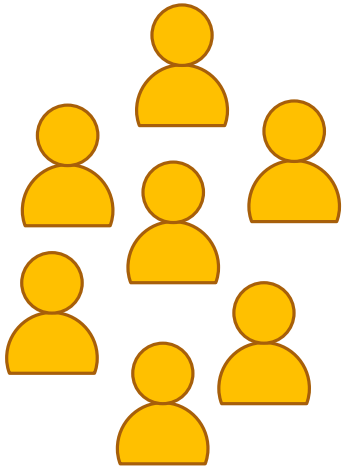


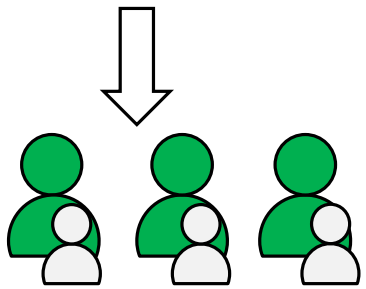



In NRSI, we take a group who were treated one way and compare them to a group who were treated a different way

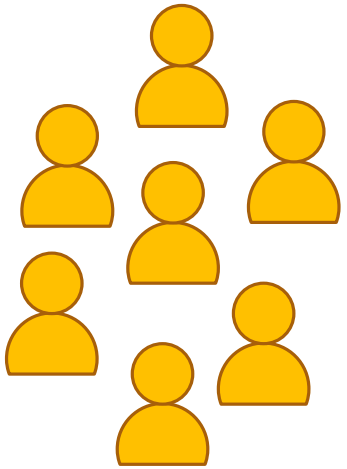
?
duration of infertility
social economic status ?
BMI
? age ?
culture media

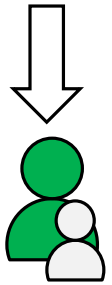
Group A





Group B





?
duration of infertility
social economic status ?
BMI
? age ?
culture media

# Dealing with confounding in non-randomised studies

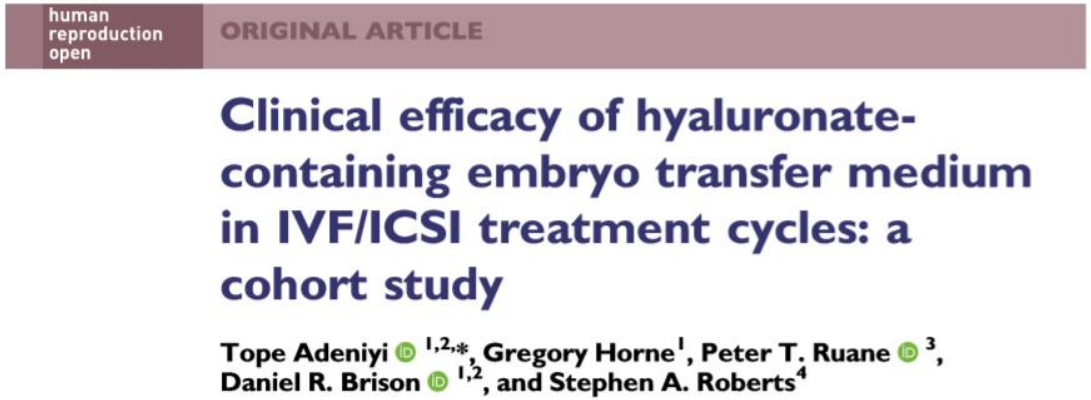
Without randomisation, treatment and control groups may **systematically** (as opposed to randomly) **differ** in terms of prognostic characteristics.

May also differ in terms of co-interventions: different incubators? Different lab conditions etc.

A simple comparison between groups no longer reflects the treatment effect – also reflects the fact that one group is older (for example).

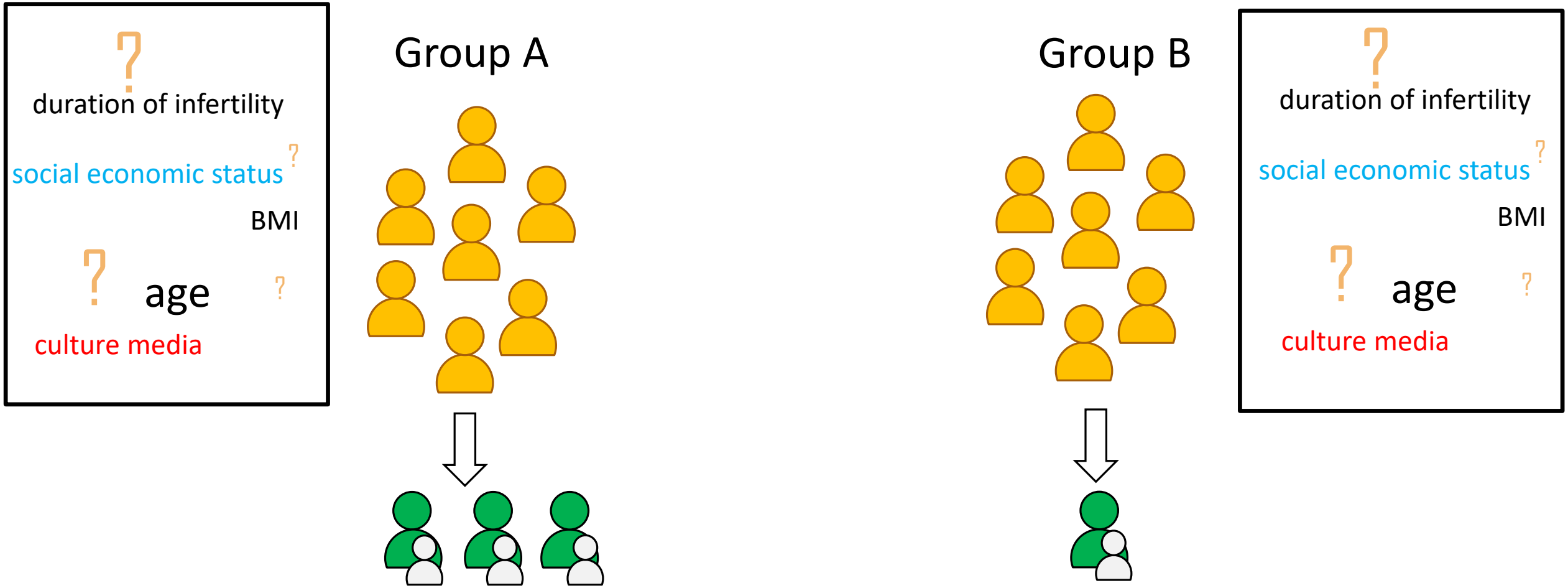
Usual approach is to try to **adjust** for confounding in the statistical analysis: regression, propensity score methods (or both at once).

# Example




- Used logistic regression to adjust for a number of measured confounders: incubator, number of embryos transferred, method of fertilisation (IVF vs ICSI), treatment attempt, embryo culture duration (2,3, or 5 days).

In NRSI, we take a group who were treated one way and compare them to a group who were treated a different way



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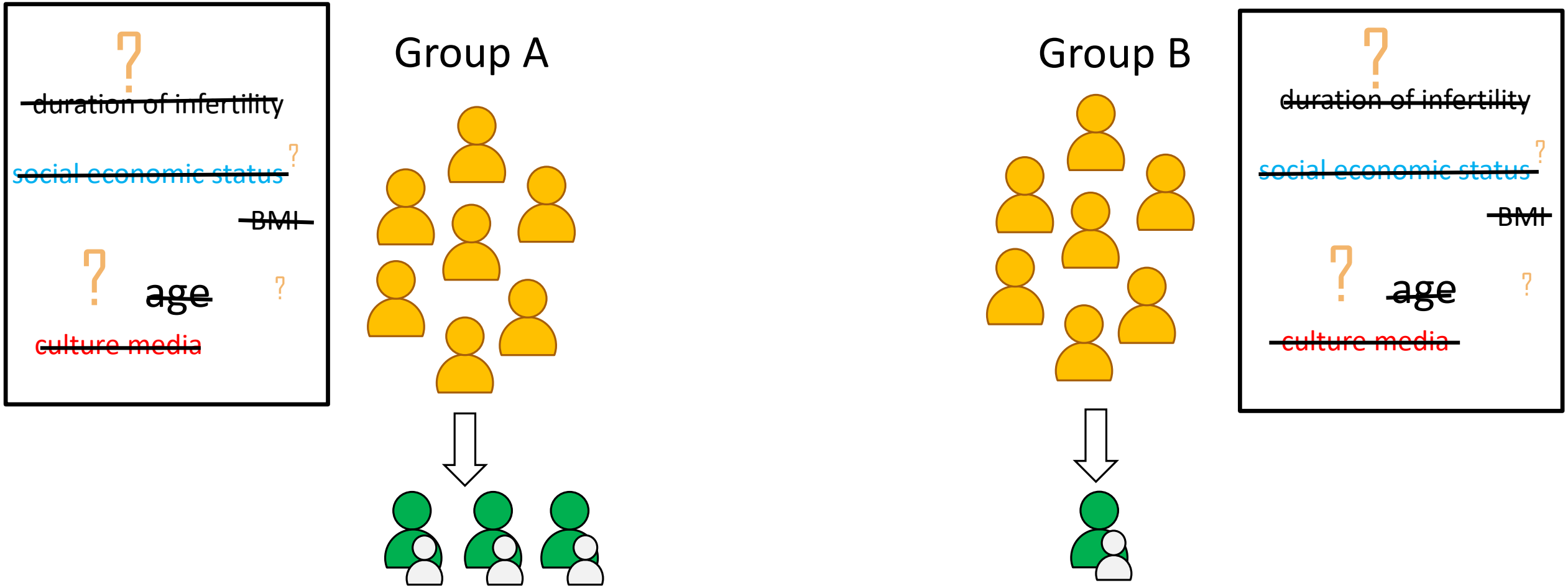


# Unmeasured Confounding

So how much unmeasured stuff is there? In any individual study, **we cannot know**

Analyses of non-randomised studies assume **no unmeasured confounding.**

**Unrealistic** to suppose we have measurements of everything, let alone good measurements (biology is really complex).

As such, we are usually left uncertain whether an observed difference between groups in an observational study is due to the treatment or due to unmeasured confounding.

# Unmeasured Confounding (2)

In practice, people adjust for a relatively modest number of variables

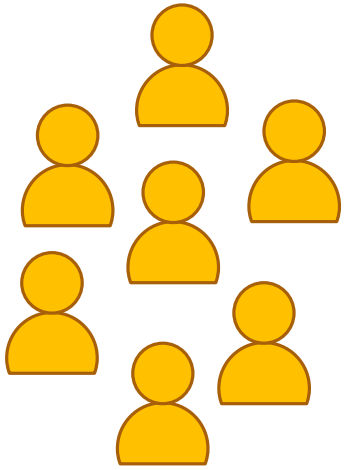
Complexity of the statistical method **does not change** this – can only include measured variables.

**Size of the dataset does not ameliorate this problem in any way.**

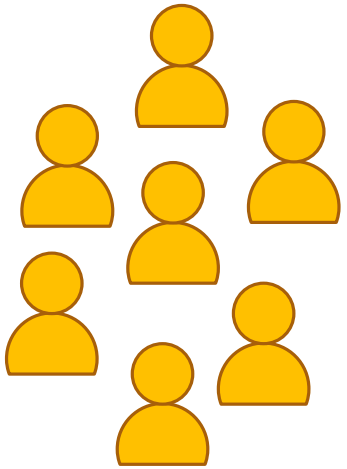
# Problem is comparing groups that systematically differ

?
duration of infertility
social economic status ?
BMI
? age ?
culture media

Group A



Group B

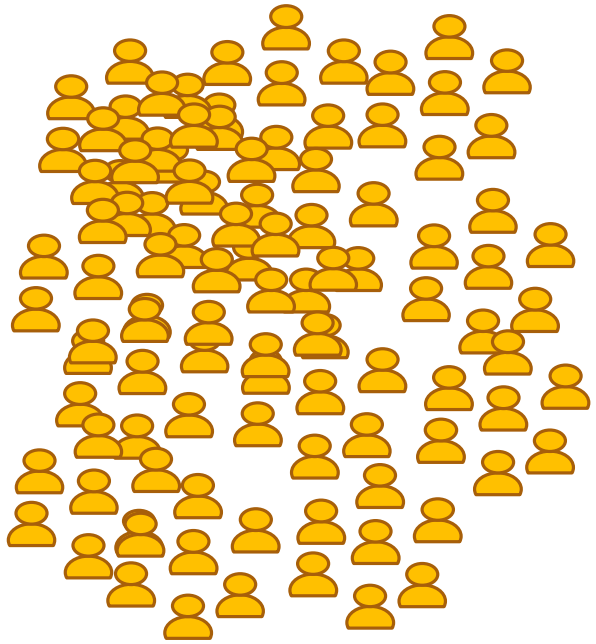


?
duration of infertility
social economic status ?
BMI
? age ?
culture media

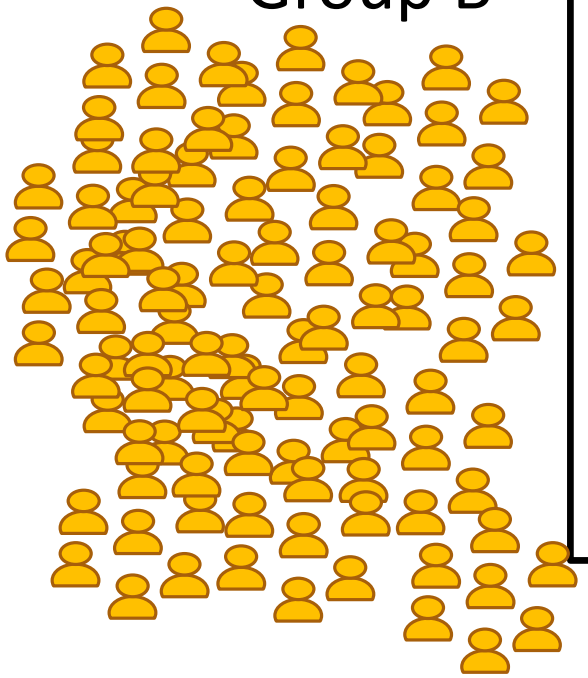
# This doesn’t change if you increase sample size

?
duration of infertility
social economic status ?
BMI
? age ?
culture media

Group A



Group B



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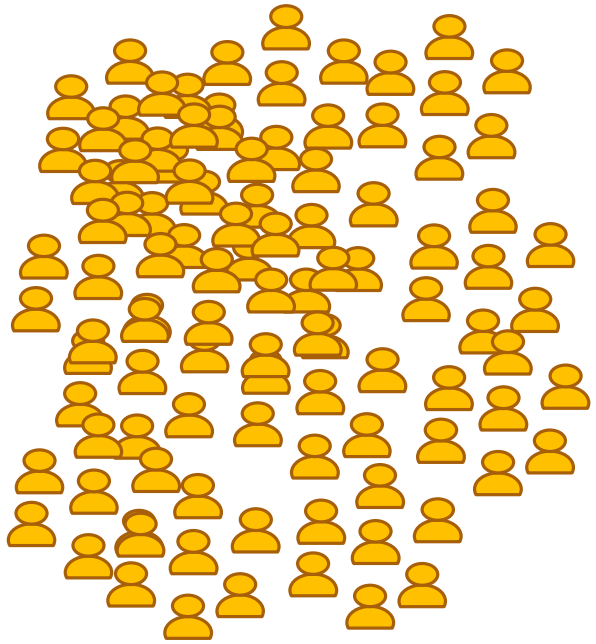
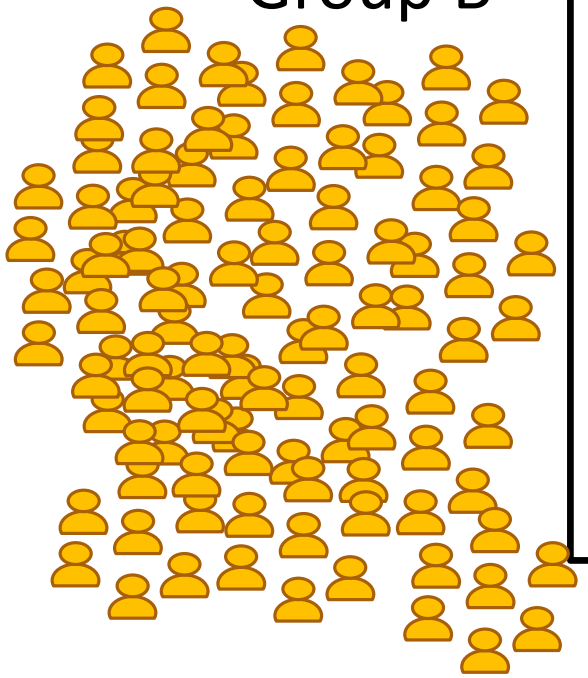
Group A



Group B



? duration of infertility

social economic status ?

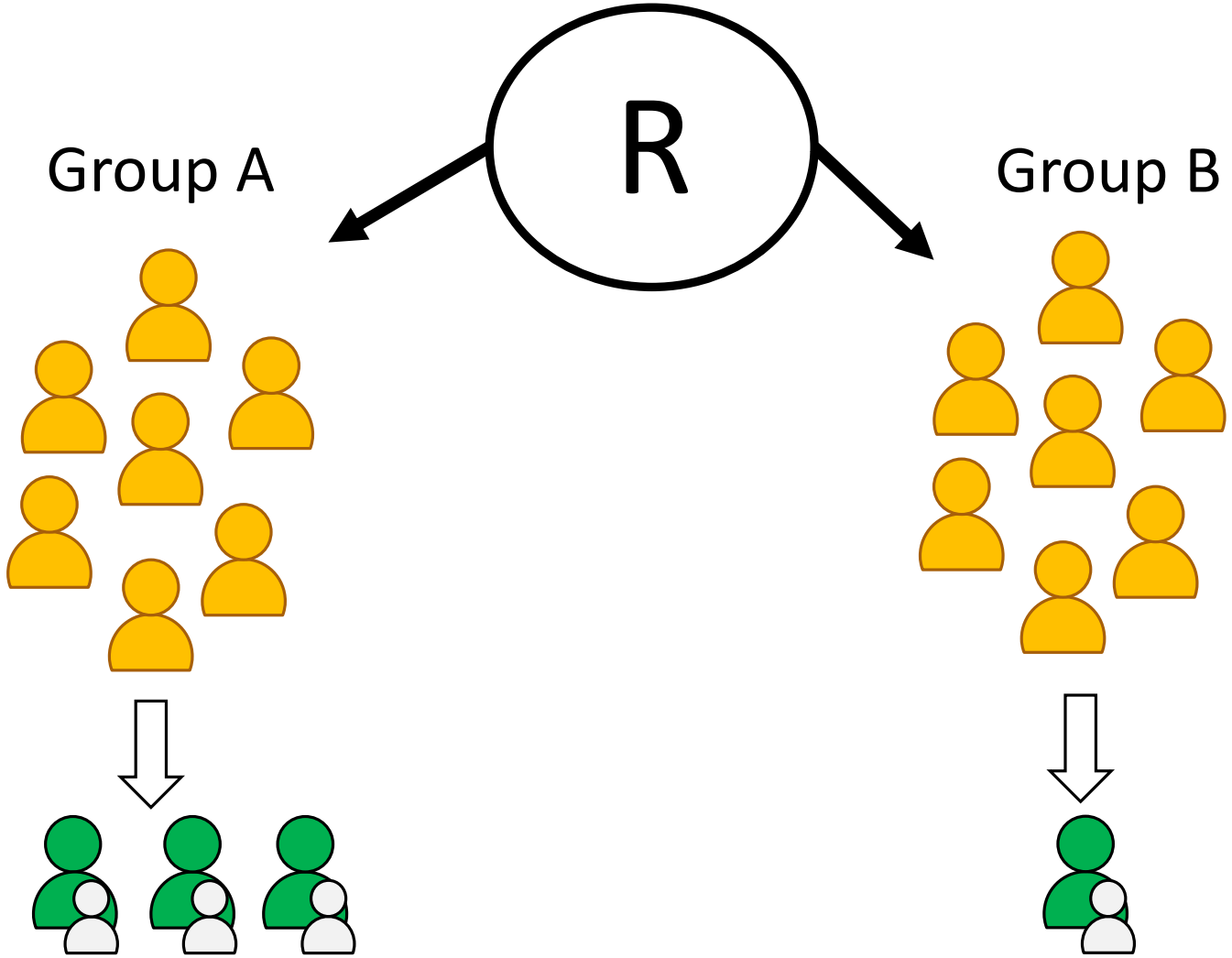
BMI

? age ?

culture media

… even if you make it really big!

In RCTs, we **randomly** allocate to groups



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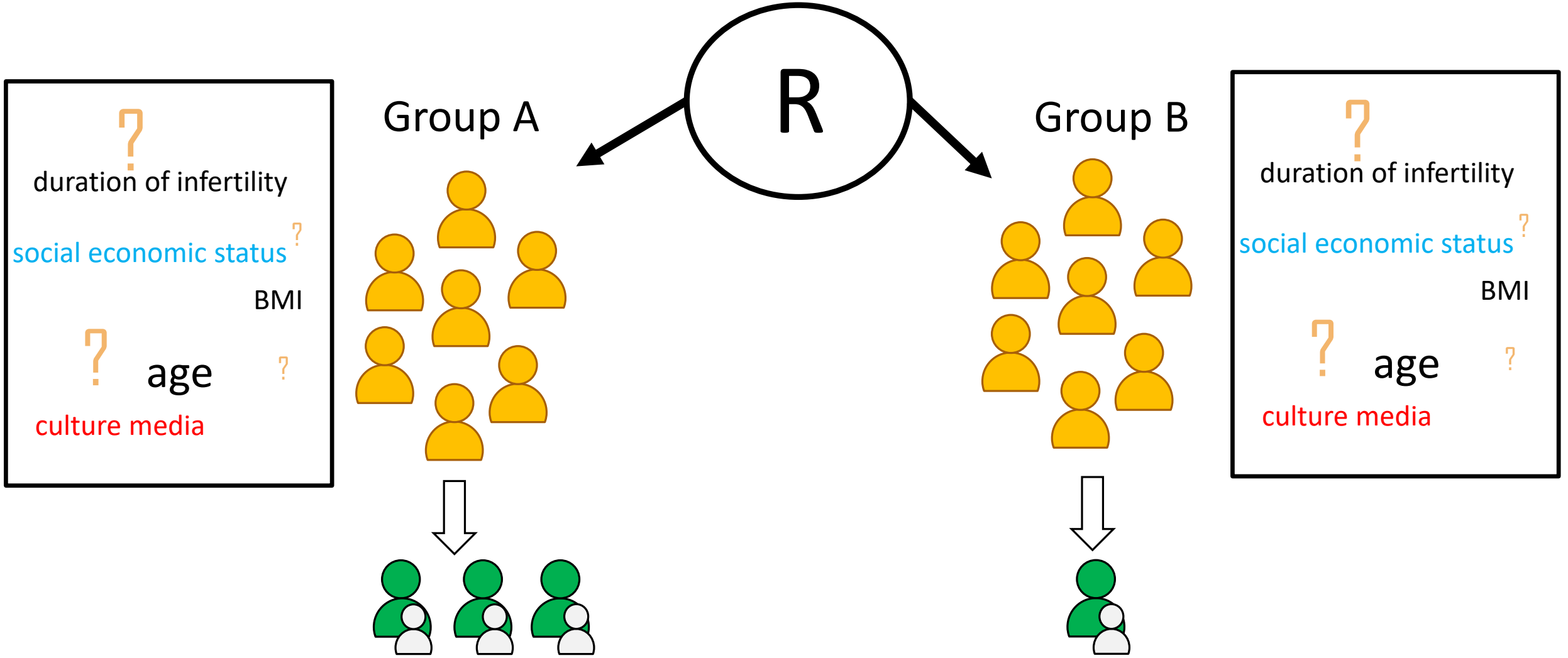

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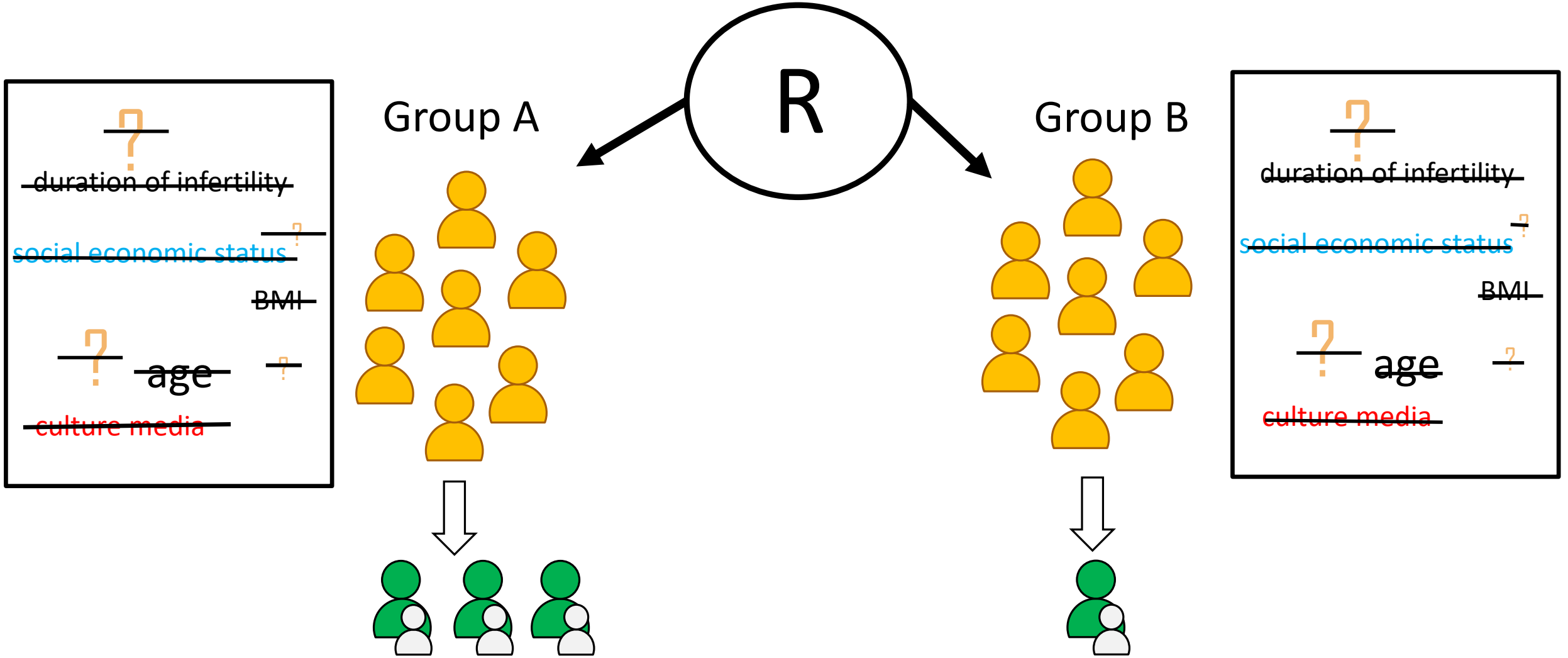
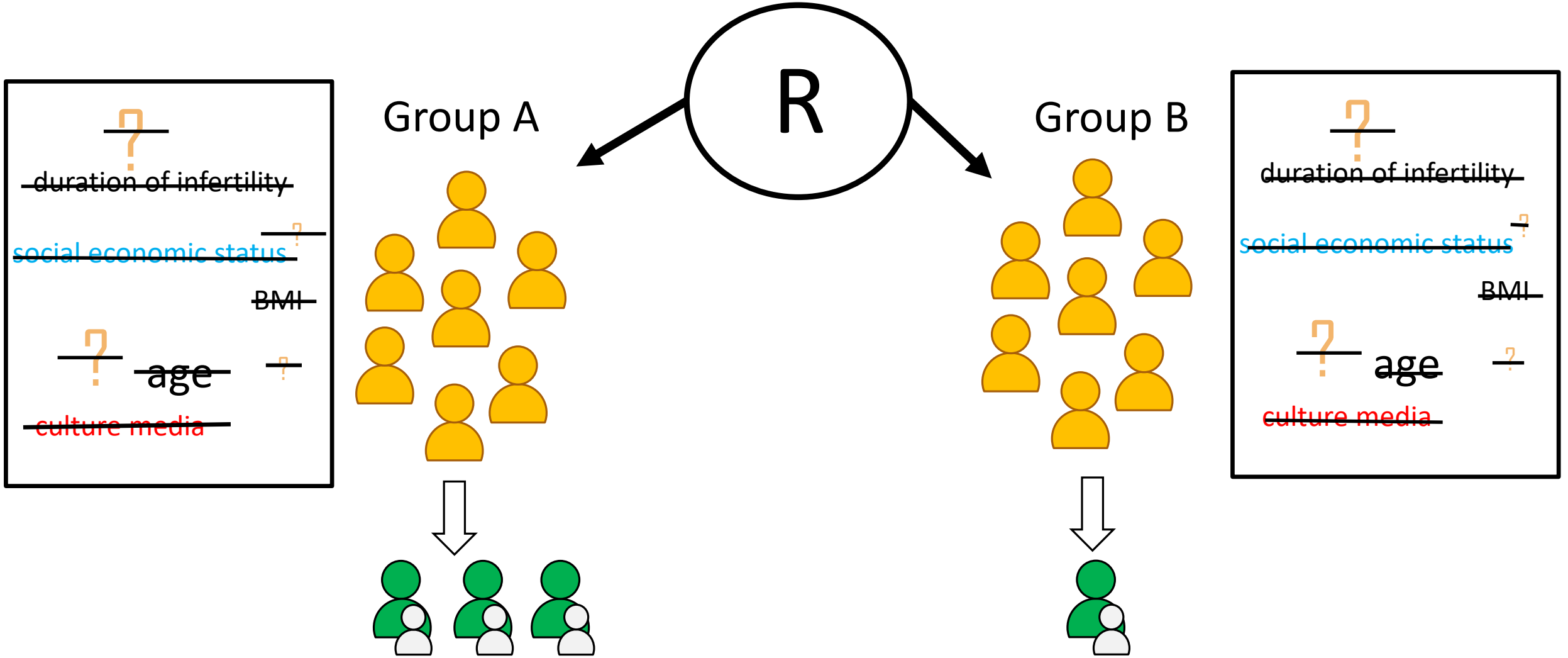
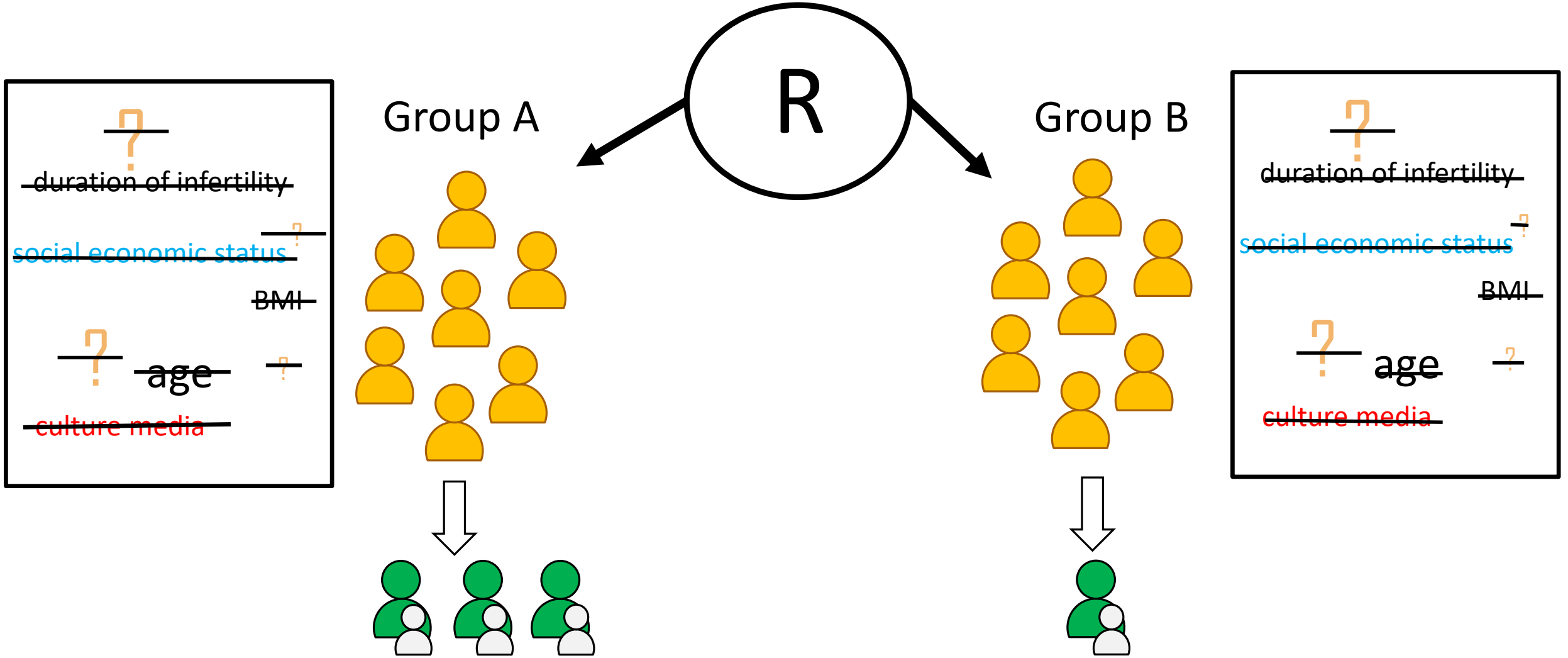


# In RCTs, we **randomly** allocate to groups




"But not everything will be perfectly balanced!"

# In RCTs, we **randomly** allocate to groups




RCTs do not require ‘balance’ on variables. The point is any **imbalance is random.** Analysis can then distinguish treatment effect from noise.

# Dealing with confounding using randomisation

- When we randomly allocate participants to treatment or control groups, **there is no confounding.**

- This doesn't mean (doesn't require) that the two groups are identical – as long as differences are *random,* our statistical tests will tell us allow us to consider whether we have evidence that a treatment works.

# Merits of RCTs vs NRSI

“NRSI studies can be larger”. True for observational NRSI, but size does not mitigate confounding in any way. Actually, in presence of confounding, increasing sample size makes you **less** likely to get the right answer, not more likely.

“Patients in observational NRSI are more representative”. True, but this actually doesn’t mean the results are more likely to represent what would happen in real clinical populations. The wrong answer doesn’t generalise to anybody.

Also worth noting that NRSI based on large retrospective datasets require that we use treatments on many patients before we know whether they work and whether they are harmful.

# Control groups, recruitment, and ethical issues in clinical trials

# Control groups

The simplest of clinical trial is a *case series* evaluation in which a group of patients who receive a new treatment are followed up and the outcome of treatment recorded.

The problem with case series evaluations of treatments is that it is impossible to know whether the observed outcome is

- the consequence of the treatment or
- the natural course of the disease,

  as some conditions can resolve without treatment. e.g. acute viral infections such as the common cold.

  Better name for case series might be **superstitious thinking!**

Don't need a control group if completely predictable results

- Should we use parachutes when jumping from a plane?
- **But we don't have a lot of 'parachutes' left in medicine.**

# Control groups

We need a control treatment against which a new treatment may be compared.

In most circumstances the control should be the current standard treatment if there is one. The effect of a new treatment is then measured relative to control.

Control group can be:

- Usual practice
- No intervention (this might be usual practice)
- Placebo (a dummy drug or treatment which looks, tastes, feels, smells … just like the real treatment, but is ‘inert’).

# Eligibility criteria

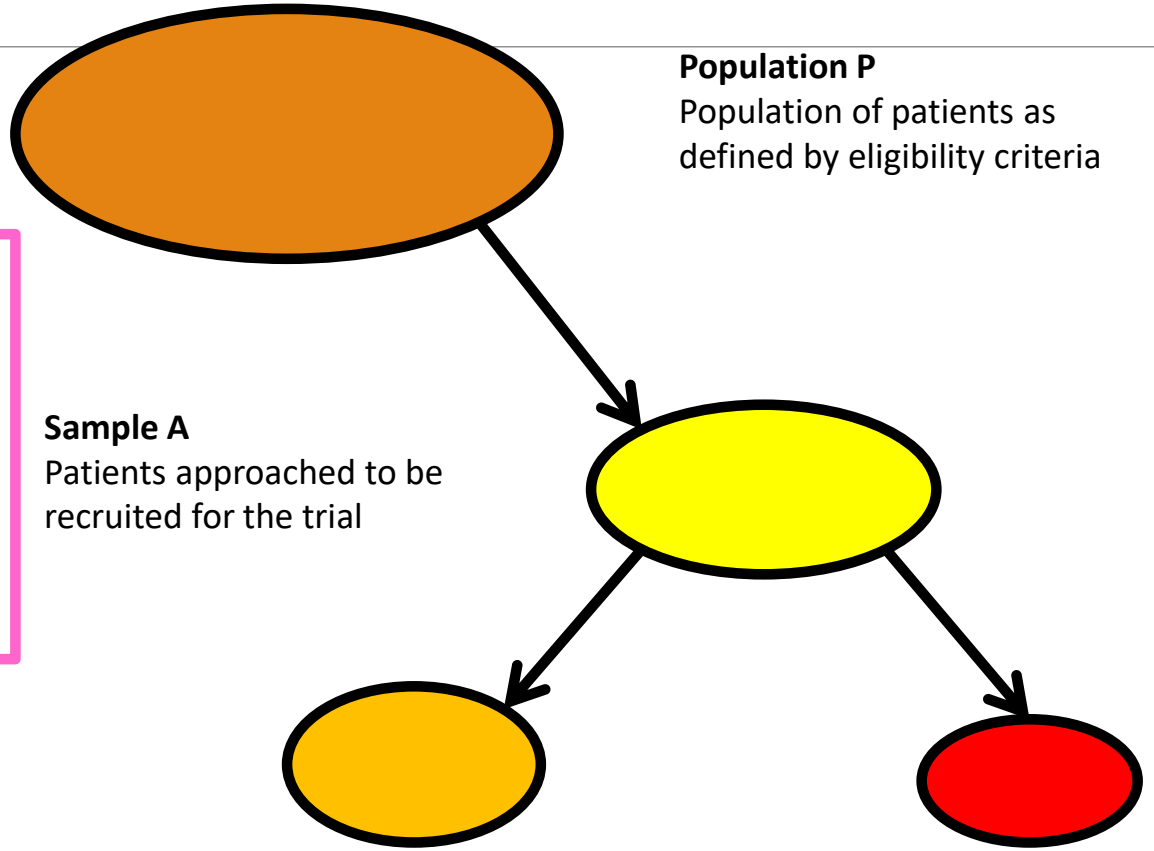
We use decision rules known as eligibility criteria to select potential participants for the trial.

There are two types of eligibility criteria:

- Inclusion criteria
- Exclusion criteria

“Eligible participants were all adults aged 18 or over with HIV who met the eligibility criteria for antiretroviral therapy according to the Malawian national HIV treatment guidelines (WHO clinical stage III or IV or any WHO stage with a CD4 count <250/mm3) and who were starting treatment with a BMI <18.5. Exclusion criteria were pregnancy and lactation or participation in another supplementary feeding programme.” BMJ 2009;338:1867-75.

# Ideal: recruitment to a randomised clinical trial



**Population P**
Population of patients as defined by eligibility criteria

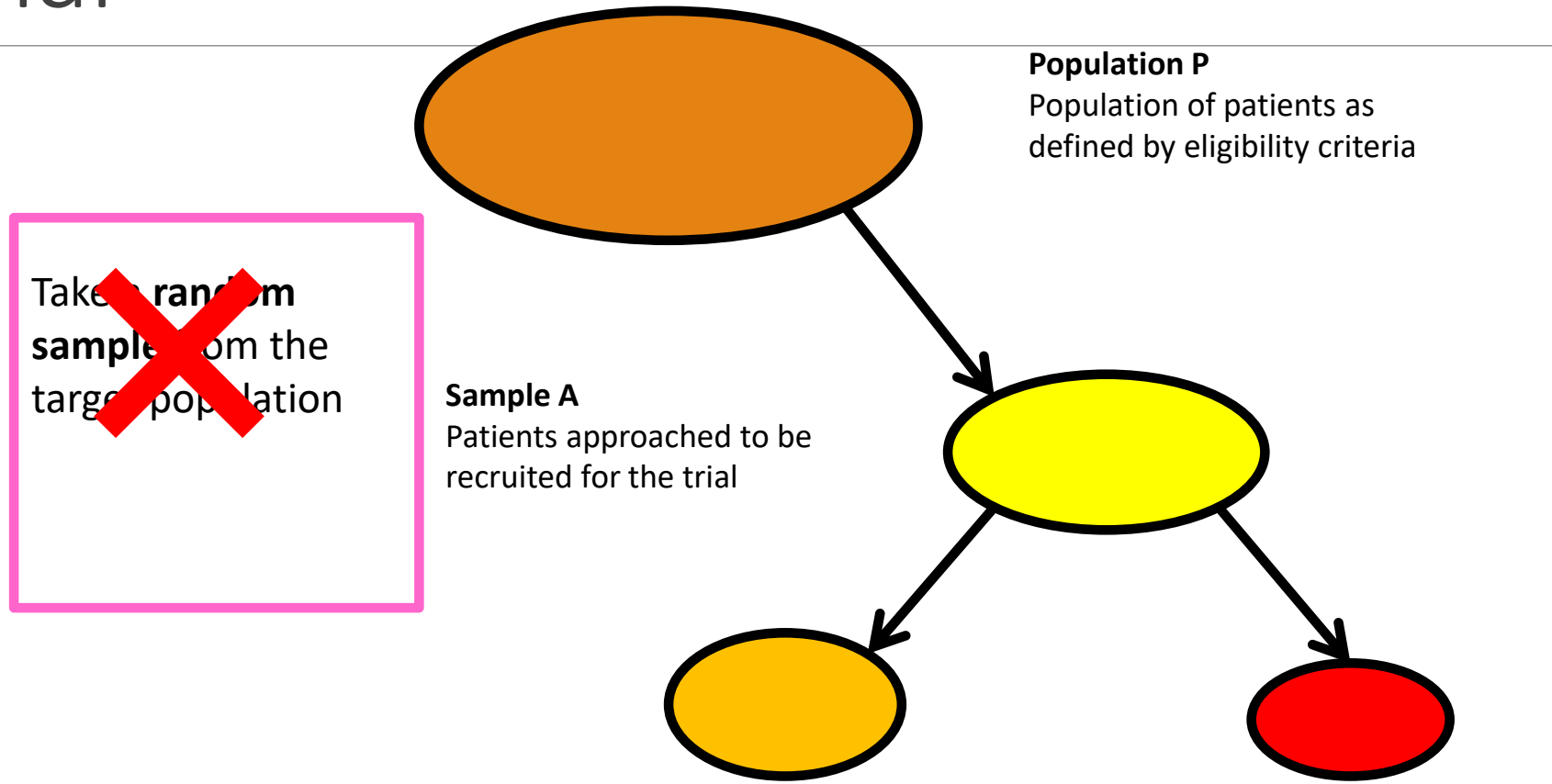
Take a **random sample** from the target population

**Sample A**
Patients approached to be recruited for the trial

**Sample B**
Patients formally in the trial

Eligible patients **not** entered into trial
e.g. refuse consent

# Ideal: recruitment to a randomised clinical trial



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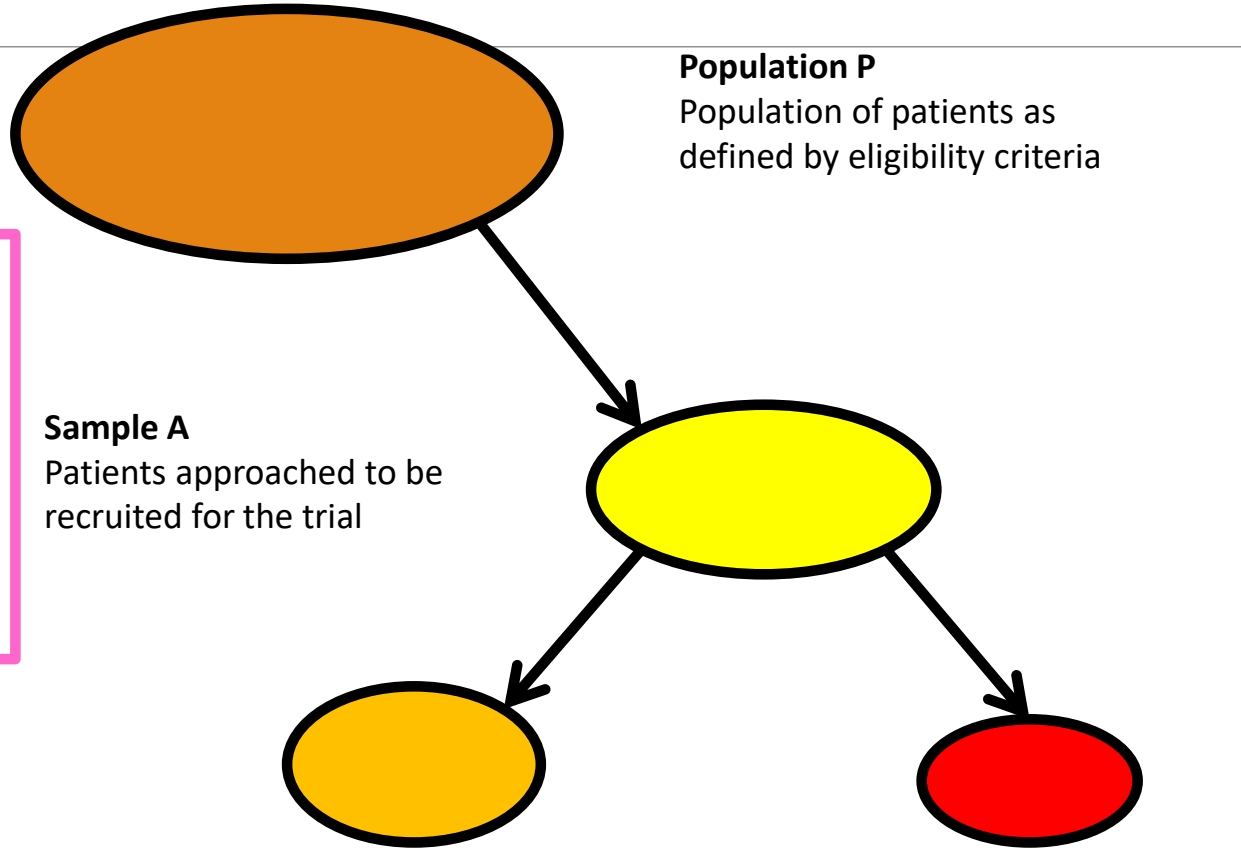


**Population P**
Population of patients as defined by eligibility criteria

Take a **random sample** from the target population

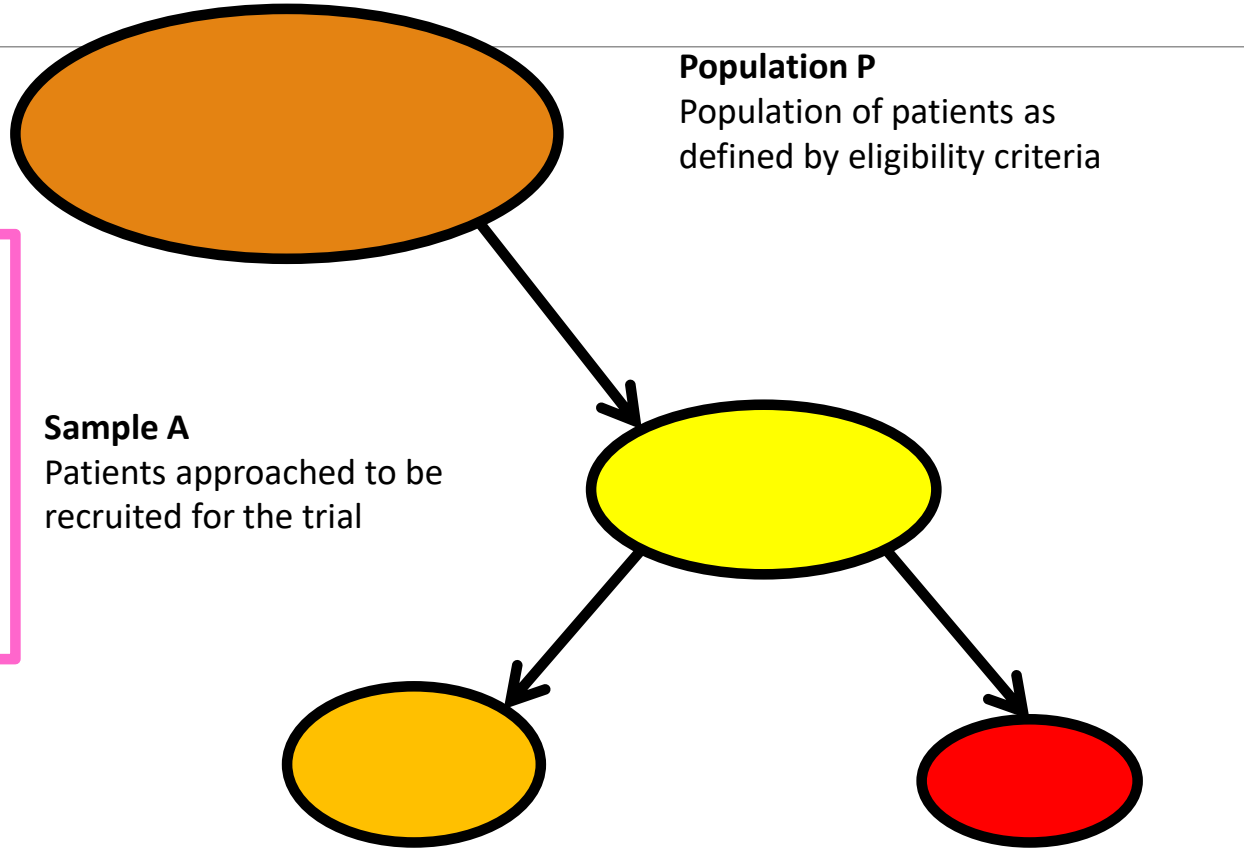
We never get a random sample

**Sample A**
Patients approached to be recruited for the trial

**Sample B**
Patients formally in the trial

Eligible patients **not** entered into trial
e.g. refuse consent

# Reality: recruitment to a randomised clinical trial



**Population P**
Population of patients as defined by eligibility criteria

Recruit patients meeting eligibility criteria who **consent**

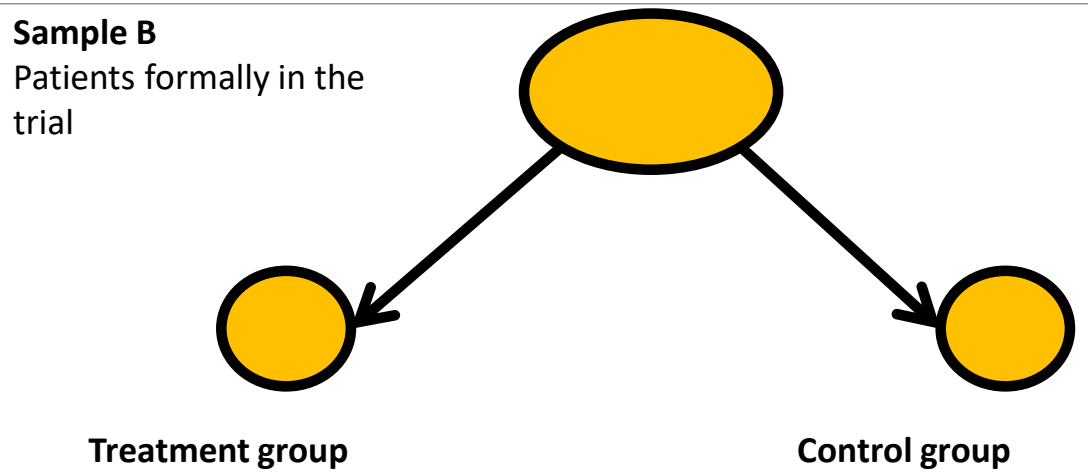
(not a random sample)

**Sample A**
Patients approached to be recruited for the trial

**Sample B**
Patients formally in the trial

Eligible patients **not** entered into trial
e.g. refuse consent

# Simple RCT model




Randomly allocate (randomise) our non-random sample to treatment or control

The (mean) difference in outcome between the two groups estimates the (average) treatment effect.

**Note that 'random sampling' and 'randomisation' are two different things!**

**In an RCT, we don't have random sampling, we do have random allocation (randomisation)**

# Ethical issues in clinical trials

**Ethical Principles**

1. Patients must never be given a treatment that is known to be inferior. Treatments should be in *equipoise*: there needs to be uncertainty regarding which treatment is better.

2. Prior to recruitment patients must be fully informed about possible adverse reactions / side-effects they may experience.

3. Once informed, they (or their representative in the case of non-competent patients) must give consent, preferably in writing.

4. Withholding consent must not compromise the patient's future treatment.

5. Patients who have entered a trial must be able to withdraw at any time.

# Ethical issues in clinical trials

**Mechanism to protection the interest of the patients**

- Ethics committee approval of research proposals.
- Individual informed consent by the patient to join a trial.
- Establishing an (independent) data monitoring [and ethics] committee (IDMC, DMC or DMEC) to monitor the progress of a trial, with specific emphasis on the safety of the intervention.
- The IDMC will report to a Trial Steering Committee (TSC) which is also primarily composed of people independent of the trial
- The TSC is usually the larger of the two committees, but each should include an independent statistician.

# Exercise – Early trial of the treatment of Scurvy (Lind, 1753 - www.jameslindlibrary.org )

"On 20 May 1747, I took 12 patients in the scurvy on board the 'Salisbury'. The cases were as similar as I could have them. They all … had … putrid gums, the spots and lassitude …"

"They laid together … and had one diet common to all … two cider, two others Elixir Vitril [$H_2SO_4$], two vinegar , two sea water, two oranges and lemons , the two remaining Nutmeg."

"One of the two receiving oranges and lemons recovered quickly and was fit for duty after 6 days. The second was the best recovered of the rest and assigned the role of nurse to the remaining 10 patients."

**What are the limitations of this study?**

# Exercise

a) In studies investigating the effect of an exposure on health, what is the difference between observational studies and experimental studies?

b) Give an example where it would **not** be ethical to conduct an experimental study in human subjects.