

What are observational studies and how do they differ from clinical trials?

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Experimental/observational studies

- **Experimental study:** Investigator intervenes in the care of the patient in a pre-planned way and records the outcome
 - Randomised controlled trials; laboratory studies
- **Observational study:** Investigator does not intervene in the care of the patient, but simply records what happens
 - Cohort studies; case-control studies

Clinical studies – the evidence ‘hierarchy’

Meta-analyses/systematic reviews of well-designed and conducted studies

Randomised controlled trial (RCT)

Cohort study

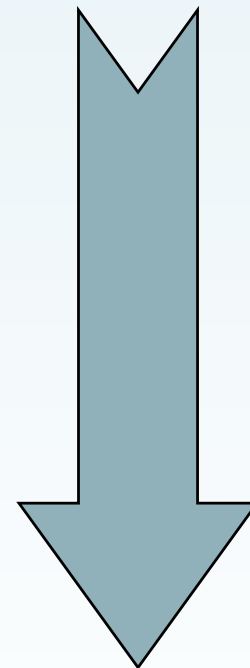
Case-control study

Cross-sectional study

Case series/case note review

‘Expert’ opinion

**BEST QUALITY
EVIDENCE**



**WORST QUALITY
EVIDENCE**

Assessing causality – Bradford Hill criteria

- Cause should precede effect
- Association should be plausible (i.e. biologically sensible)
- Results from different studies should be consistent
- Association should be strong
- Dose-response relationship between cause and effect
- Removal of cause should reduce risk of effect

Randomised controlled trials (RCTs)

- Experimental study in which treatments are allocated randomly to patients using process known as randomisation
- Ensures that characteristics of those in each treatment arm are broadly similar (any differences are due to chance)
- If there are differences in outcome, these are unlikely to be explained by baseline differences between the groups

Randomised controlled trials (RCTs)

- **Comparative** – comparison of two or more treatment strategies (e.g. new regimen vs. standard-of-care)
- **Control group** – enables investigator to estimate additional gain in outcome provided by the new drug over-and-above that which would have occurred anyway

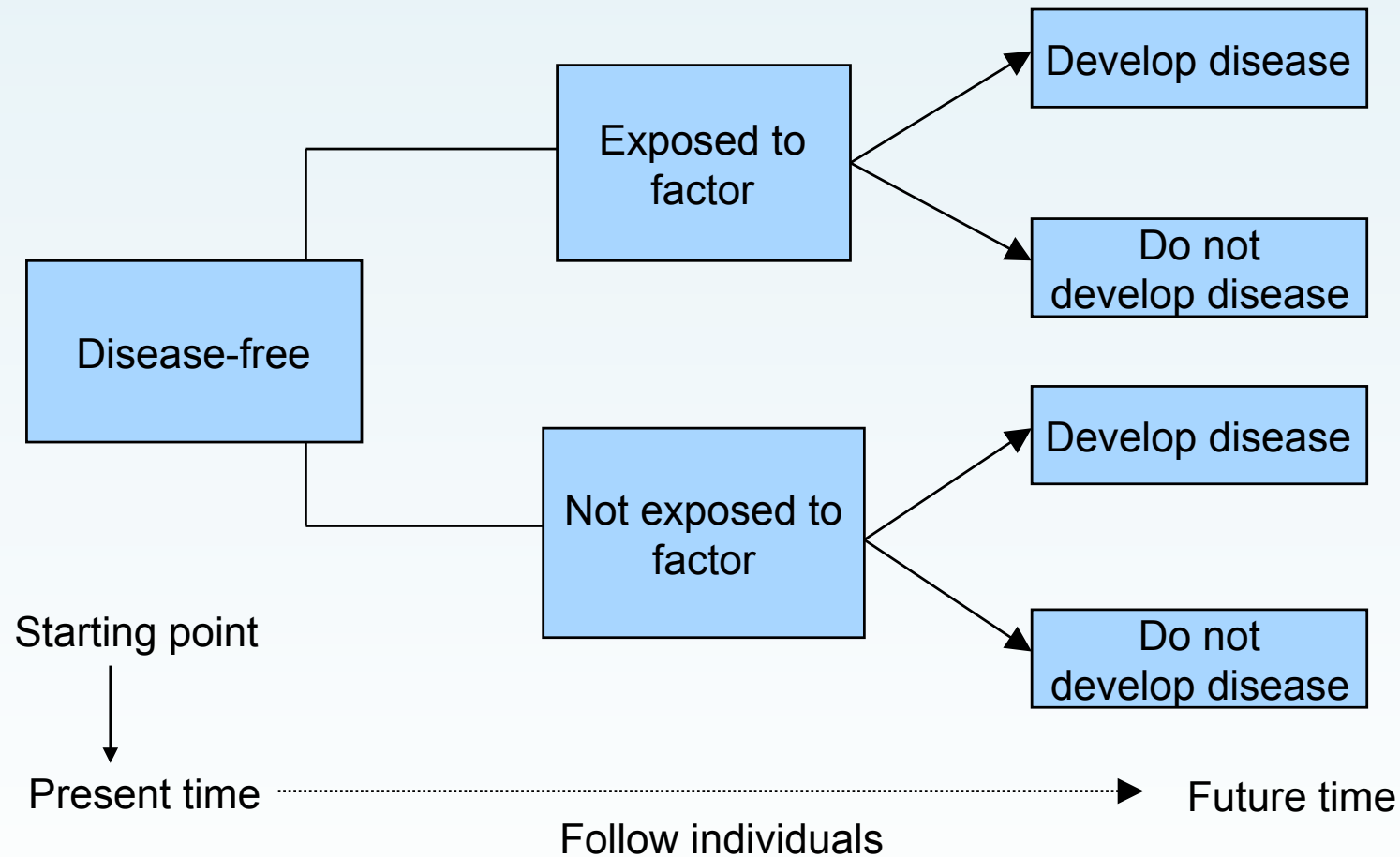
Limitations of RCTs

- Only possible if there is an 'intervention' to which people are willing to be randomised
- Patients in RCTs may be unrepresentative of clinic population, and management may be different – outcomes may differ from what would be expected
- May be short (48 weeks)
- May focus on two or three main treatment comparisons
- May focus on short-term surrogate marker changes rather than on longer-term clinical endpoints

Cohort studies

- Follow a group of individuals over time to assess the incidence of a disease (or some other outcome)
- Used to describe the effect of exposure to one or more factors of interest (potential 'risk' factors) on the incidence of the outcome
- Can be prospective or retrospective/historical

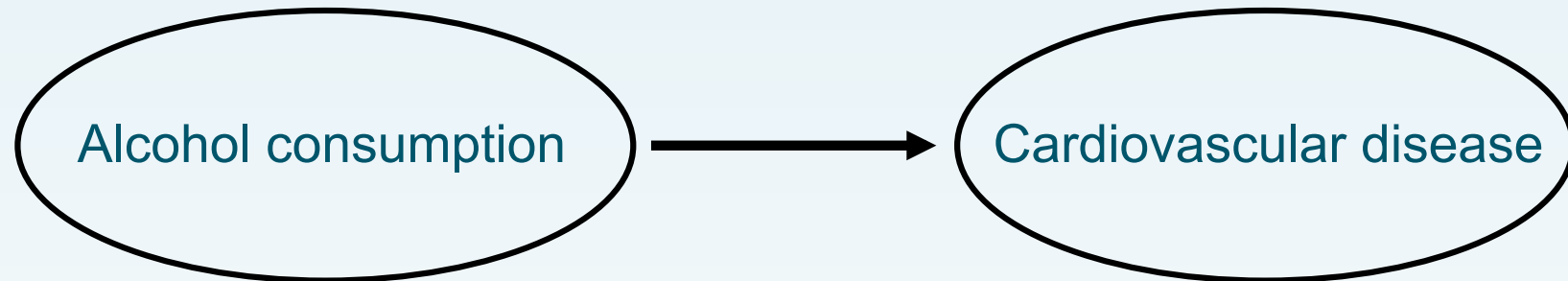
Cohort studies



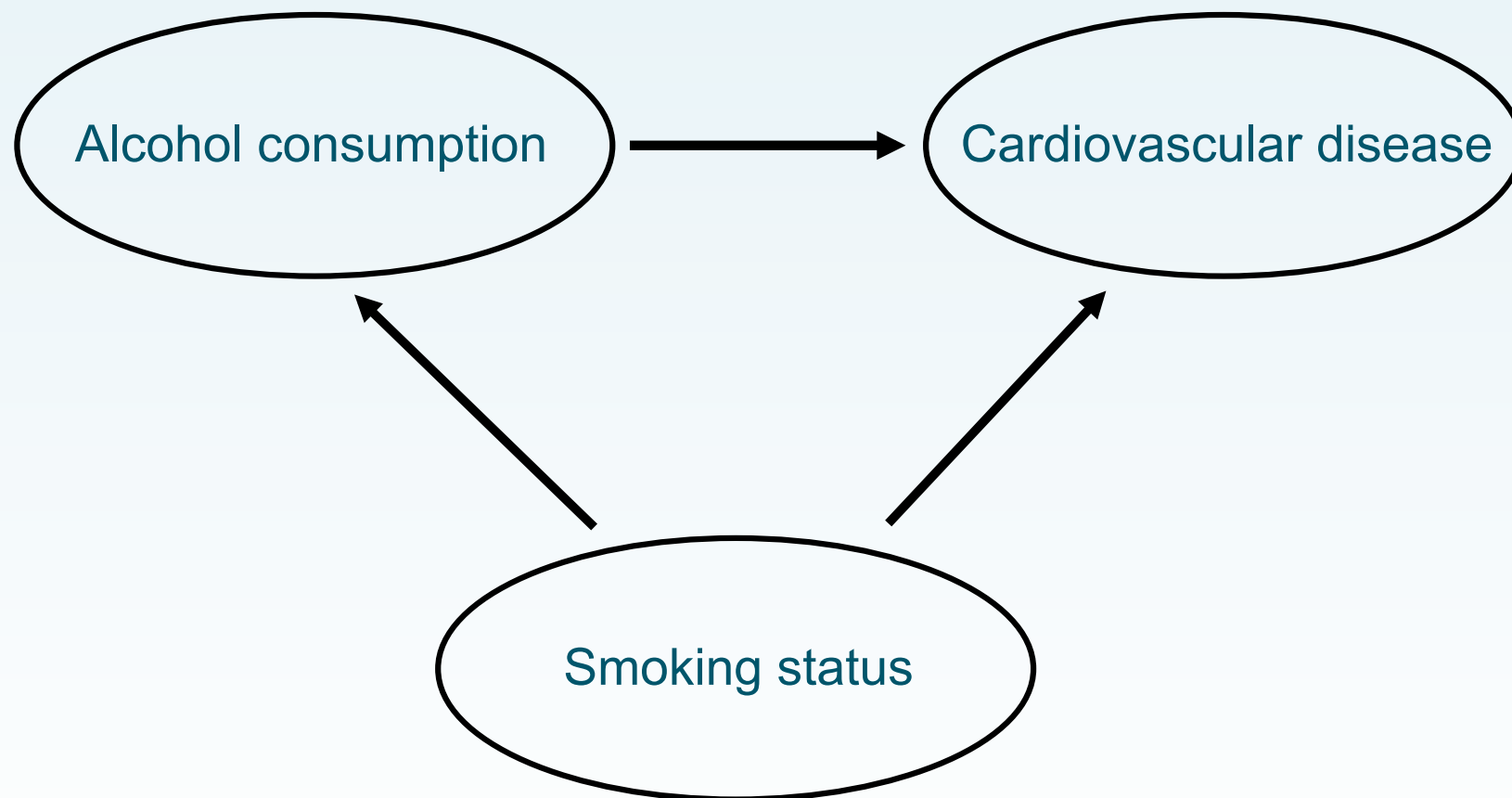
Cohort studies

- Can assess the temporal relationship between exposure and disease
- Can make some attempt to assess cause and effect (although RCTs are still preferable)
- BUT if disease is rare, the cohort may have to be very large and follow-up long (i.e. expensive) – may result in loss-to-follow-up
- Cohorts particularly vulnerable to bias due to confounding

Cohort studies – bias due to confounding



Cohort studies – bias due to confounding



Cohort design

- Fixed or closed cohort - new patients are unable to join the study
- Dynamic or open cohort - new patients are able to join the study
- Combination of fixed and dynamic

Cohort design – interval cohorts

- Patients often seen at a study site on regular occasions for study visits (e.g. 6-monthly)
- Participants may complete questionnaire on their health since last visit, treatments received, etc.
- Laboratory tests performed at pre-defined time intervals – this information is unlikely to be available at intervening times or when an event occurs, unless this coincides with study visit
- Patients must give consent to participate

Interval cohorts - example

- The Multicenter AIDS Cohort Study (MACS)
- HIV+ve and HIV-ve individuals from 4 centres in Baltimore, Chicago, Los Angeles and Pittsburgh
- Participants recruited from 1984-1985 (n=4954), 1987-1991 (n=668) and 2001-2003 (n=1351)
- Visits are bi-annual – at each visit, participants undergo detailed interview, physical examination, quality-of-life assessment and collection of blood for laboratory testing and storage

Cohort design – observational databases

- Utilise data that are already routinely collected as part of patient's medical care
- Patient does not have to attend for study visit or fill in any questionnaires
- Laboratory testing performed according to clinical need – will be more frequent if patient is ill or requires investigation
- Some data items may be difficult to collect if not part of routine care
- May or may not require patient consent, depending on local regulations in country

Observational databases – example

- The UK Collaborative HIV Cohort (CHIC) Study
- UK HIV Drug Resistance Database (UK HDRD)

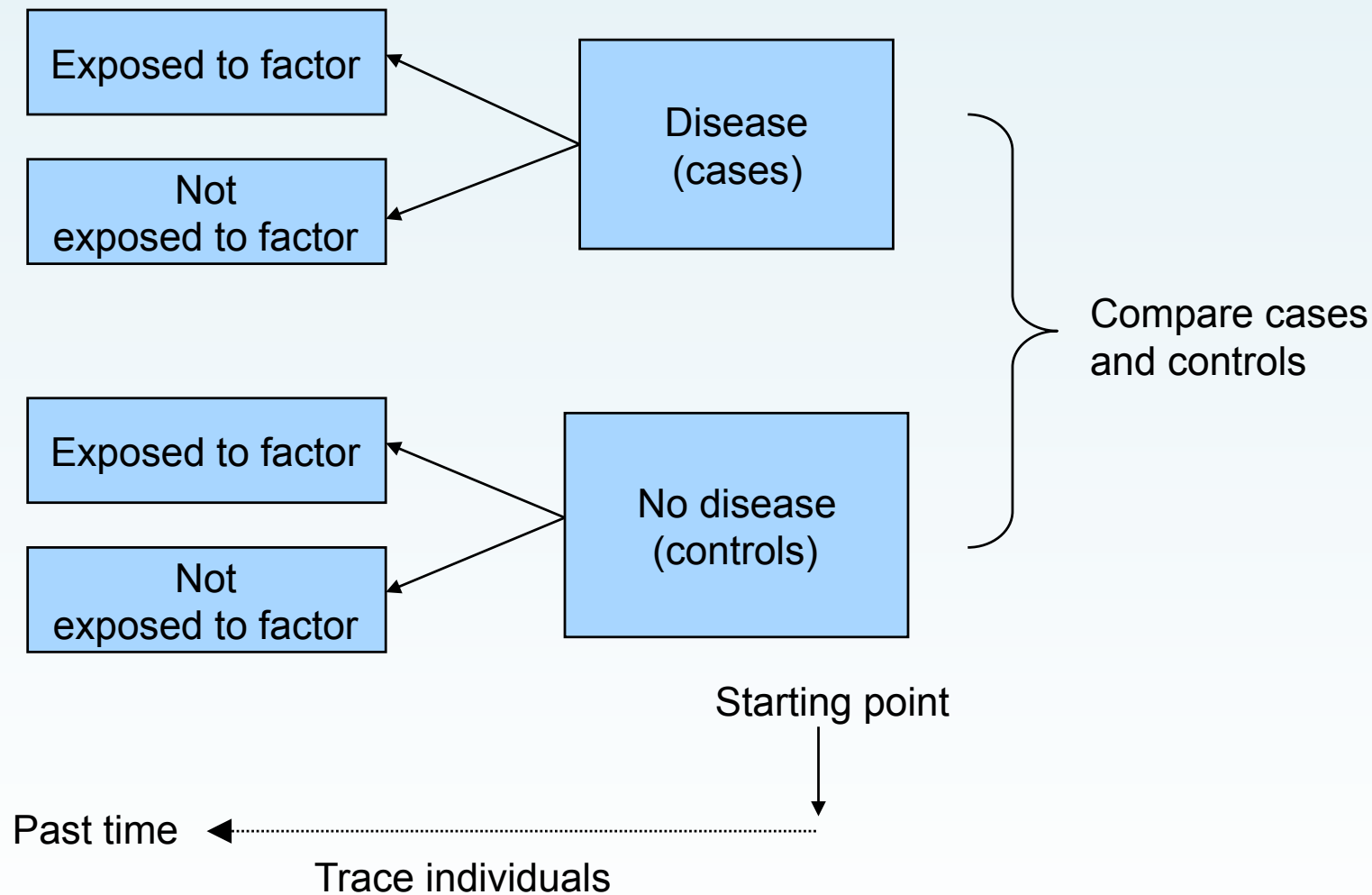
Cohort design

	Traditional cohort	Observational database
Study visits	At regular defined intervals	As and when patient attends for care
Data entry	Often form-based	Often electronic transfer of data
Representative?	May not be – patients must give consent	Often includes <i>all</i> patients – therefore representative
Loss to follow-up	May be substantial, but can be determined	May be difficult to assess as some patients attend infrequently
Data quality	Can introduce quality control measures	Difficult to regulate
Data items collected	Can determine at outset and change over time	May be difficult to influence

Case-control studies

- Retrospective studies in which a group of patients with a disease (**cases**) are compared to a group of patients without the disease (**controls**)
- Aim is to see whether exposure to any factor has occurred more or less frequently *in the past* in cases than controls

Case-control studies



Case-control studies

- Relatively cheap, quick and easy to carry out
- No loss-to-follow-up, and they are suitable for rare events
- However, the timing of events cannot always be reliably established; thus, difficult to assess **causality**
- Not possible to assess incidence
- Case-control studies particularly vulnerable to **recall bias**

Recall bias

- Tendency of cases to 'recall' information (particularly relating to exposures) differently to cases
- Can lead to apparent association between outcome and exposure, even if no association exists
- Example: cigarette smoking and lung cancer

Nested case-control studies

- Case-control study may often be nested within a larger cohort or RCT
- Provides a means of studying associations between novel biomarkers and disease outcome, particularly if these are expensive to measure
- May also be useful if additional data collection is required which cannot be performed through standard data collection mechanism
- Example: nested case-control study in SMART trial measured lipoprotein particles in 248 patients with a CVD event (cases) and 480 matched controls

Summary

RCTs

- No confounding
- Selected population
- Requires 'intervention' that patients can be randomised to
- Control external factors through experimental design

Cohorts

- Subject to confounding
- May/may not be selected population
- 'Intervention' must be in routine use in clinical care
- Have to use statistical methods to adjust for external factors