

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

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## Experimental/observational studies

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- **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

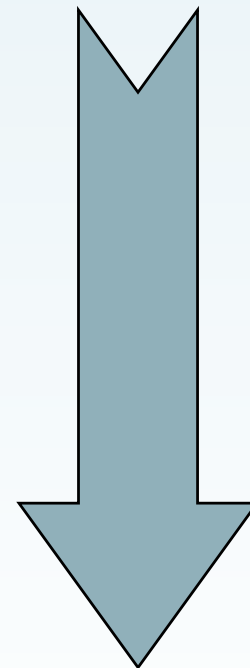
Case-control study

Cross-sectional study

Case series/case note review

‘Expert’ opinion

**BEST QUALITY  
EVIDENCE**



**WORST QUALITY  
EVIDENCE**

## Assessing causality – Bradford Hill criteria

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- 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)

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- 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)

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- **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

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- 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

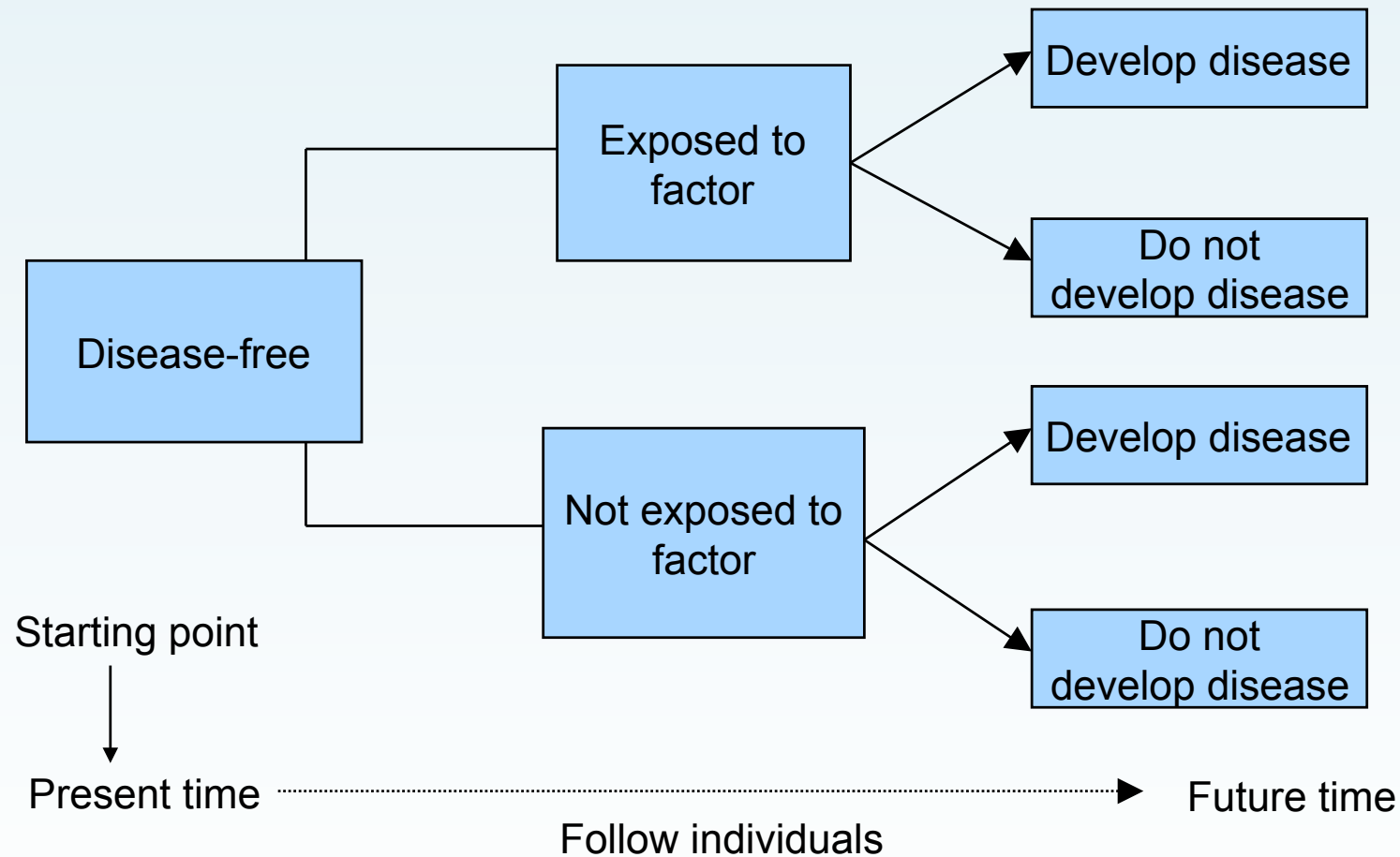
## Cohort studies

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- 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



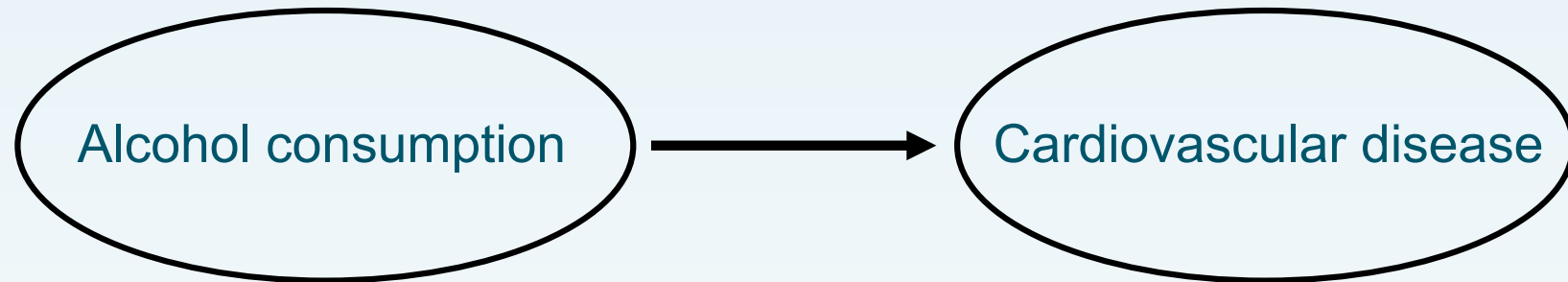
## Cohort studies

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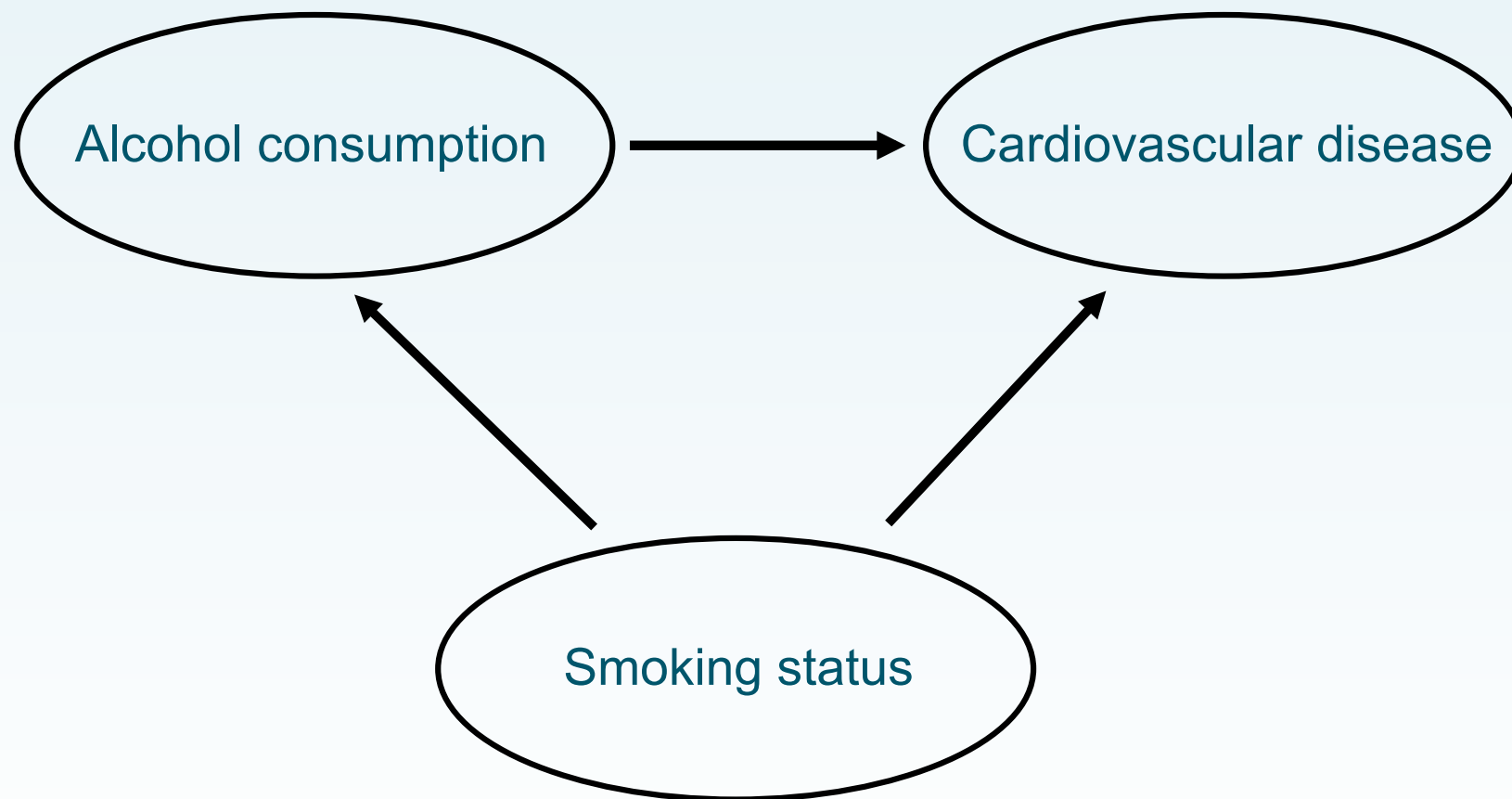
- Can assess the temporal relationship between exposure and disease
- Can make some attempt to assess cause and effect (although RCTs are still preferable)
- BUT if disease is rare, the cohort may have to be very large and follow-up long (i.e. expensive) – may result in loss-to-follow-up
- Cohorts particularly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

# Cohort studies – bias due to confounding

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## Cohort studies – bias due to confounding



## Cohort design

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- 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

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- 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

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- 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

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- 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

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

# Cohort design

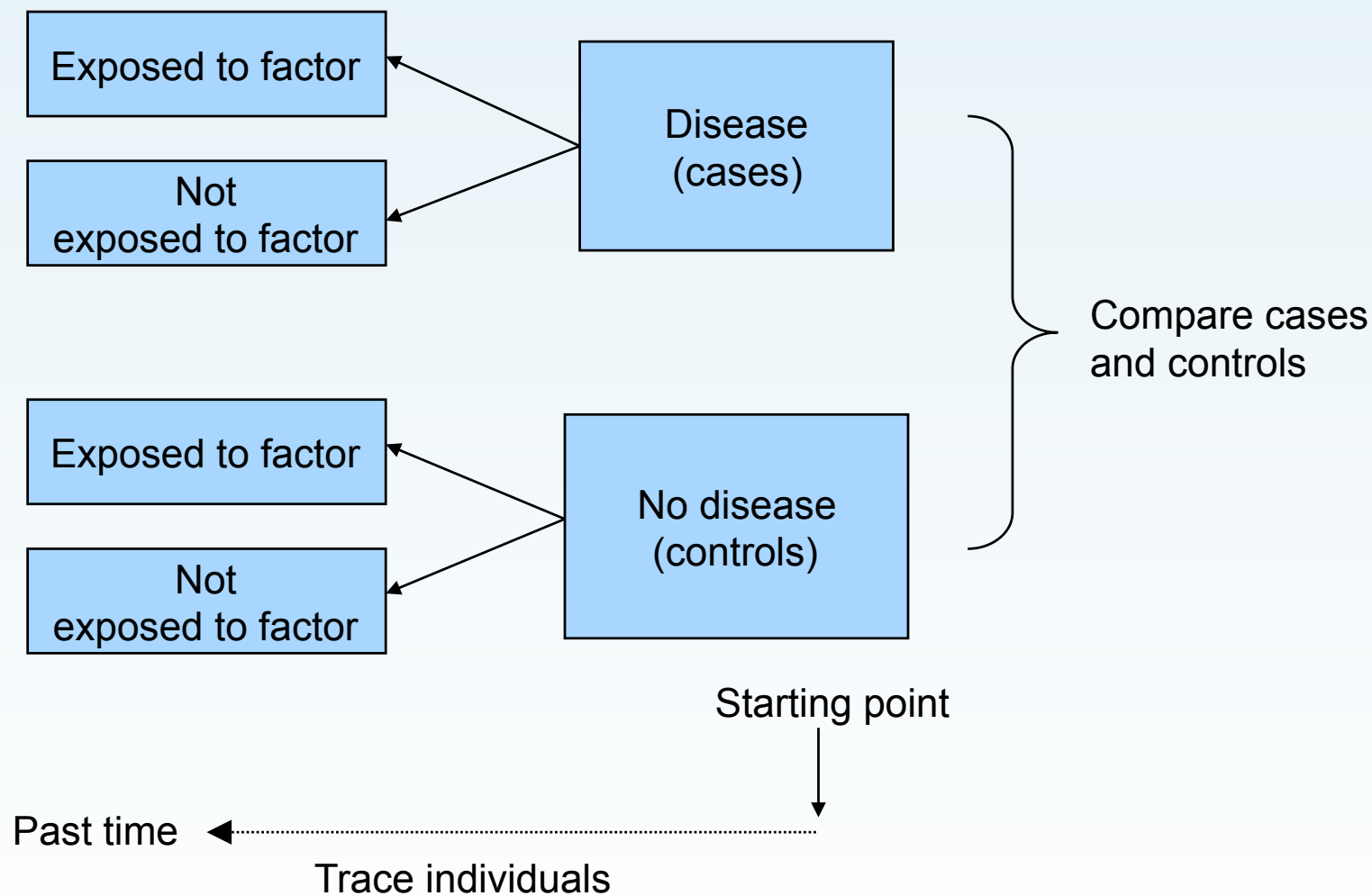
	<b>Traditional cohort</b>	<b>Observational database</b>
<b>Study visits</b>	At regular defined intervals	As and when patient attends for care
<b>Data entry</b>	Often form-based	Often electronic transfer of data
<b>Representative?</b>	May not be – patients must give consent	Often includes <i>all</i> patients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

## Case-control studies

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- 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

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- 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

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- 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

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- 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

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## **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