Identifying bias

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Conflict of interest

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- Gilead Sciences
- ViiV Healthcare
- Janssen-Cilag

Background

- When carrying out and appraising research, we must always be aware of any potential limitations of the study
- Many of the limitations of studies, particularly observational studies, are related to the potential for bias to occur
- We must consider the likely impact of any potential biases on our study – i.e. do we still believe the results?

Outline of session

- What is bias?
- Assessing time trends
- Selecting a representative sample
- Bias due to missing data and loss-to-follow-up
- Bias due to confounding
- Other common types of bias

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Bias

- Bias occurs when there is a systematic difference between the results from a study and the true state of affairs
- Bias is often introduced when a study is being designed, but can be introduced at any stage
- Appropriate statistical methods can reduce the effect of bias, but may not eliminate it totally
- Increasing the sample size *does not* reduce bias
- Preferable to design the study in order to avoid bias in the first place

Other forms of bias

- Many forms of bias exist – these can broadly be categorised as:
- Selection bias - occurs when patients included in the study are not representative of the population to which the results will be applied
- Information bias - occurs during data collection when measurements on exposure and/or outcomes are incorrectly recorded in a systematic manner
- Confounding may also result in bias

Selection bias

Can be due to:

- Ascertainment bias
- Attrition bias (loss-to-follow-up)
- Healthy entrant effect
- Response bias
- Survivorship bias

Information bias

Can be due to:

- Central tendency bias
- Lead-time bias
- Measurement bias
- Misclassification bias
- Observer bias
- Regression dilution bias
- Regression to the mean
- Reporting bias
- Publication bias

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Assessing time trends

- Analyses of cohort studies often involve the follow-up of individuals over a long period of time
- We may be interested in whether the incidence of an outcome has changed over time
- If we see a change, we have to question whether this is real, or whether it reflects other changes that may have occurred to the patients and/or their management

Initial viral load suppression after starting cART in UK CHIC Study

	50 copies/ml	
Year of starting cART	Median time to response (months)	% with response by 6 months
1998	9.3	36.1
1999	5.0	57.1
2000	5.2	56.8
2001	4.6	61.1
2002	5.2	56.8
2003	3.8	72.8
2004	3.6	74.0
2005	3.8	74.2
2006	3.5	76.5

Dramatic improvement in viral load suppression rates from 1998 to 2006

Initial viral load suppression after starting cART in UK CHIC Study

- Tempting to conclude that this is due to an improvement in the choice of antiretroviral drugs that are available
- However, could also be due to:
  - Changes in characteristics of patients starting cART (confounding)
  - Changes in viral load assay (i.e. lower limit of detection)
  - Changes in frequency of viral load monitoring
  - Reduced loss-to-follow-up in more recent years
  - Improved management of drug toxicities, resulting in fewer treatment discontinuations

Initial viral load suppression after starting cART in UK CHIC Study

	50 copies/ml		400 copies/ml	
Year of starting cART	Median time to response (months)	% with response by 6 months	Median time to response (months)	% with response by 6 months
1998	9.3	36.1	3.9	61.5
1999	5.0	57.1	2.5	75.5
2000	5.2	56.8	2.3	75.0
2001	4.6	61.1	2.0	79.1
2002	5.2	56.8	2.2	80.0
2003	3.8	72.8	1.8	88.1
2004	3.6	74.0	1.7	86.7
2005	3.8	74.2	1.9	88.0
2006	3.5	76.5	1.6	91.9

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Improvement still present, but less dramatic

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Selecting a representative sample

- For the results from our study to be reliable, we need to ensure that the sample we include in the study is representative of the population to which the results will be applied
- i.e. the characteristics of the sample should be similar to those of the population

Selecting a representative sample

Is the following sample likely to be representative of the population?

Population: all ART-naïve individuals infected with HIV who are starting HAART for the first time

Sample: individuals recruited to a clinical trial of a new HAART regimen at a large London clinic

Selecting a representative sample

Consider potential differences in…

- Patient demographics
- Geographical location
- Transmission groups
- Patient management/clinician views
- Clinical status
- Prior and future treatment options
- Availability of different antiretroviral drugs
- etc…

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Bias due to missing data

- Data are often missing in cohort studies
- This doesn’t reflect poor patient management, but reflects changing trends in patient monitoring as well as restricted access to laboratory data

Why are data sometimes missing?

- Lost-to-follow up: An individual is withdrawn from a study before completing follow-up; no further data are available
  - Individual moved house, side effects of medication…
- Missing study/clinic visit: An individual remains in a study, but misses a clinic visit
  - On holiday during study visit, felt too sick to attend…
- Missing data value: An individual attends the study visit at the required time, but not all tests are performed
  - Blood sample clotted, equipment broken, felt too sick to have a particular test performed…

Missing data

- Data may be missing on
  - outcomes/primary endpoints
  - exposures
  - confounders and effect modifiers
- Missing data shouldn't be a big concern for RCTS
  - Exposure of interest (randomised group) is always known, should be no confounders and standard methods exist for dealing with missing outcomes
- In cohort studies, however, missing data can be problematic due to the long follow-up and large numbers of individuals

Consequences of missing data

- Can introduce bias
  - Individuals without missing data may be different from those with missing data and therefore associations may be misspecified
- Leads to lack of precision/power
  - Fewer individuals can be included in analyses, and therefore we have less power to detect associations; CIs will be wider
- Although statistical approaches exist to account for missing data, better to ensure that as little data as possible are missing

Attrition bias

- Occurs when those who are lost-to-follow-up in a longitudinal study differ in a systematic way from those who are not lost-to-follow-up
- E.g. when conducting a study of mortality patterns in a cohort of patients starting HAART, if IDU are more likely to be lost-to-follow-up, then results may be biased
  - IDU more likely to have stopped ART?
  - IDU more likely to have died?

Dealing with loss-to-follow-up

- May be interested in an outcome at a point in time – e.g. had the patient died by 48 weeks?
- If individuals drop out of the study before 48 weeks, the outcome may not be observable for all individuals
- Use of survival analysis, rather than logistic regression, provides a solution when censoring occurs
- NOTE: approach is not helpful if the patients who drop out of the study tend to be the sickest patients (informative censoring)

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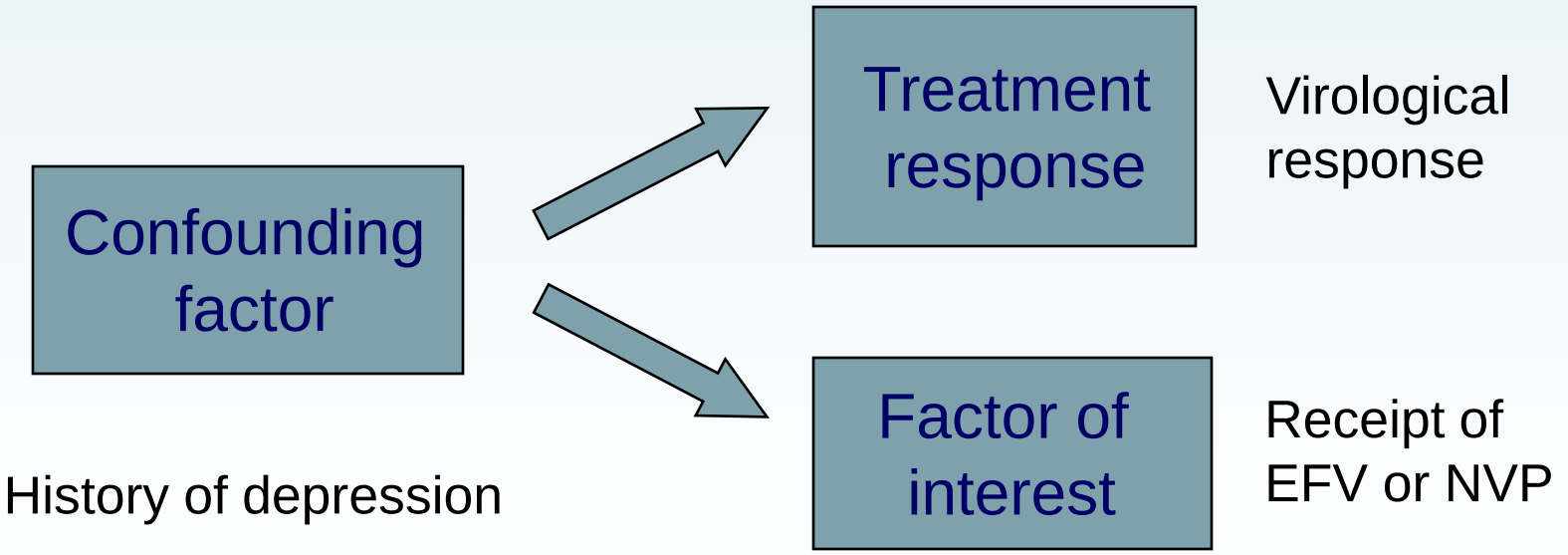
Bias due to confounding

- Occurs when a spurious association arises due to a failure to fully adjust for factors related to both the risk factor and outcome.



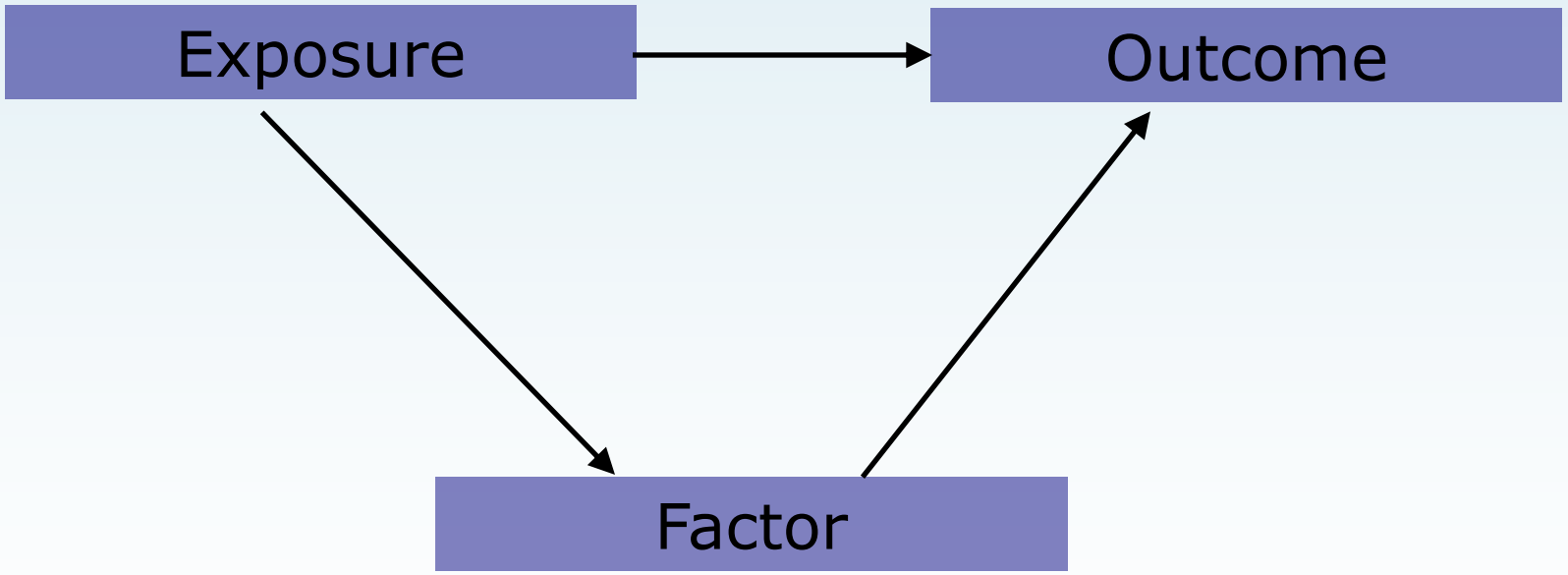
Dealing with confounding

- We use statistical methods (e.g. multivariable regression, propensity scores) to remove the effects of confounding
- Estimates from these models describe the relationship between a drug and a toxicity, after removing the effects of *known* confounders
- Whilst this approach is usually successful, all methods will give biased results if *unmeasured* (or unknown) confounding remains

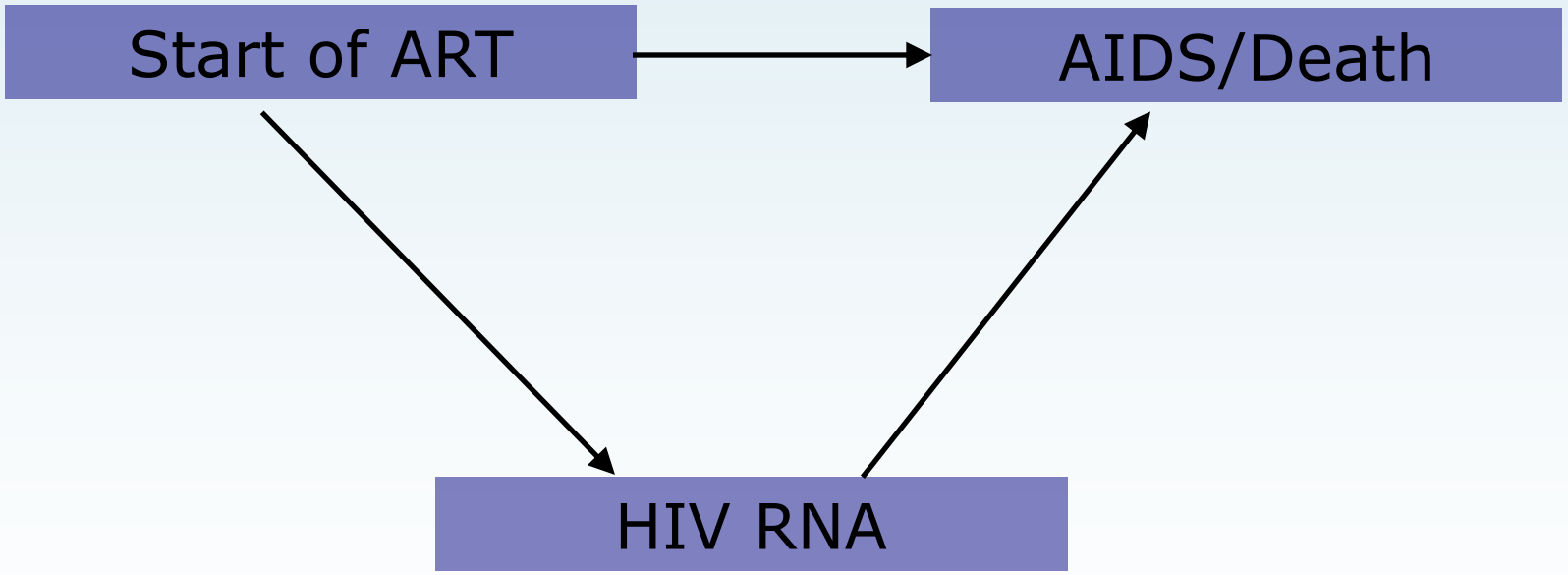
Factors on the causal pathway

- Generally use multivariable methods to control for confounding
- However, we must be careful when adjusting our analyses for factors on the causal pathway between the exposure and outcome
- This will lead to an attenuation of the true effect of the exposure

Factor on the causal pathway



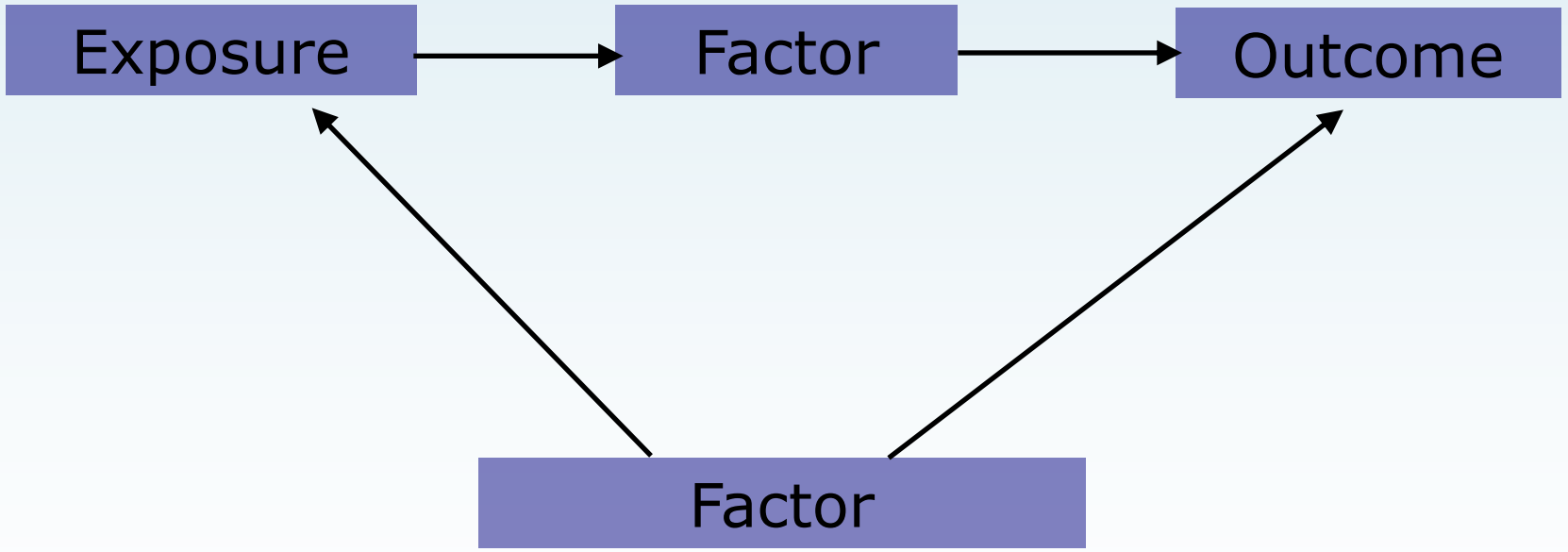
Factor on the causal pathway



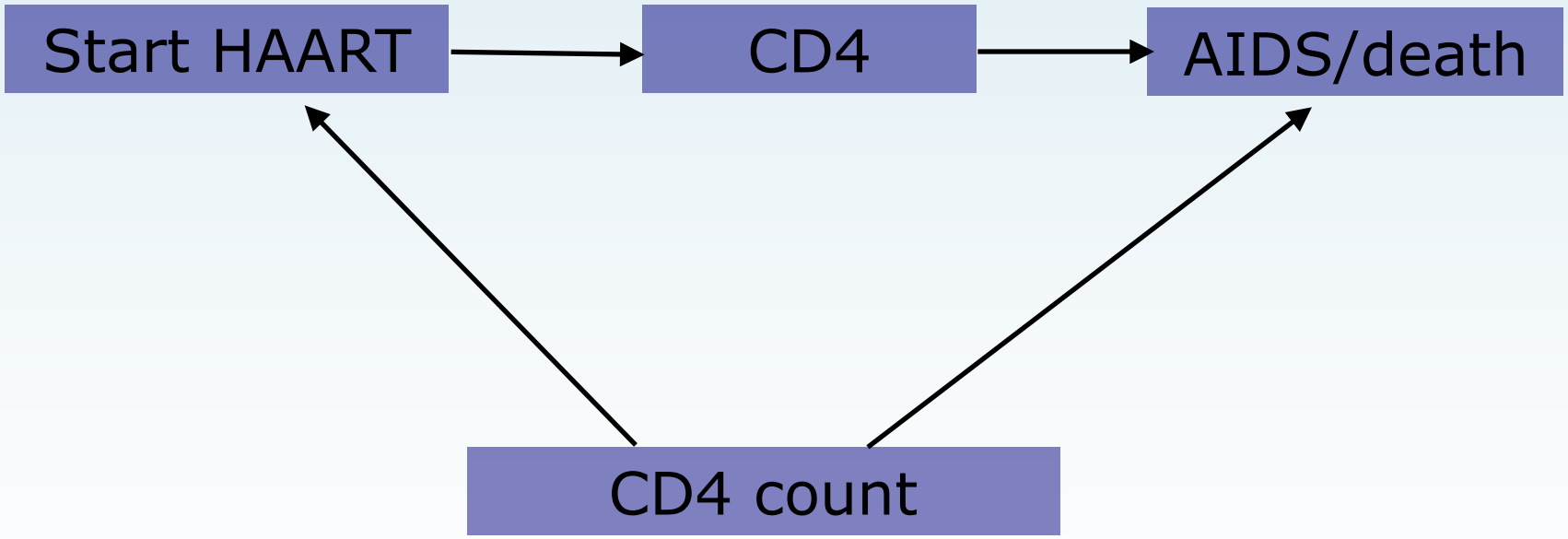
Time-dependent confounding

- Factors that are both on the causal pathway and are confounders can cause time-dependent confounding

Time-dependent confounding



Time-dependent confounding



Time-dependent confounding

- Factors that are both on the causal pathway and are confounders can cause time-dependent confounding
- Accounting for time-dependent confounding is not straightforward – methods such as marginal structural models (inverse probability weighting) or G-estimation are employed

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Observer bias

- Occurs when individuals change their behaviour when they know that they are in a study

  Example 1: Assessment of car speed by policemen in marked police cars

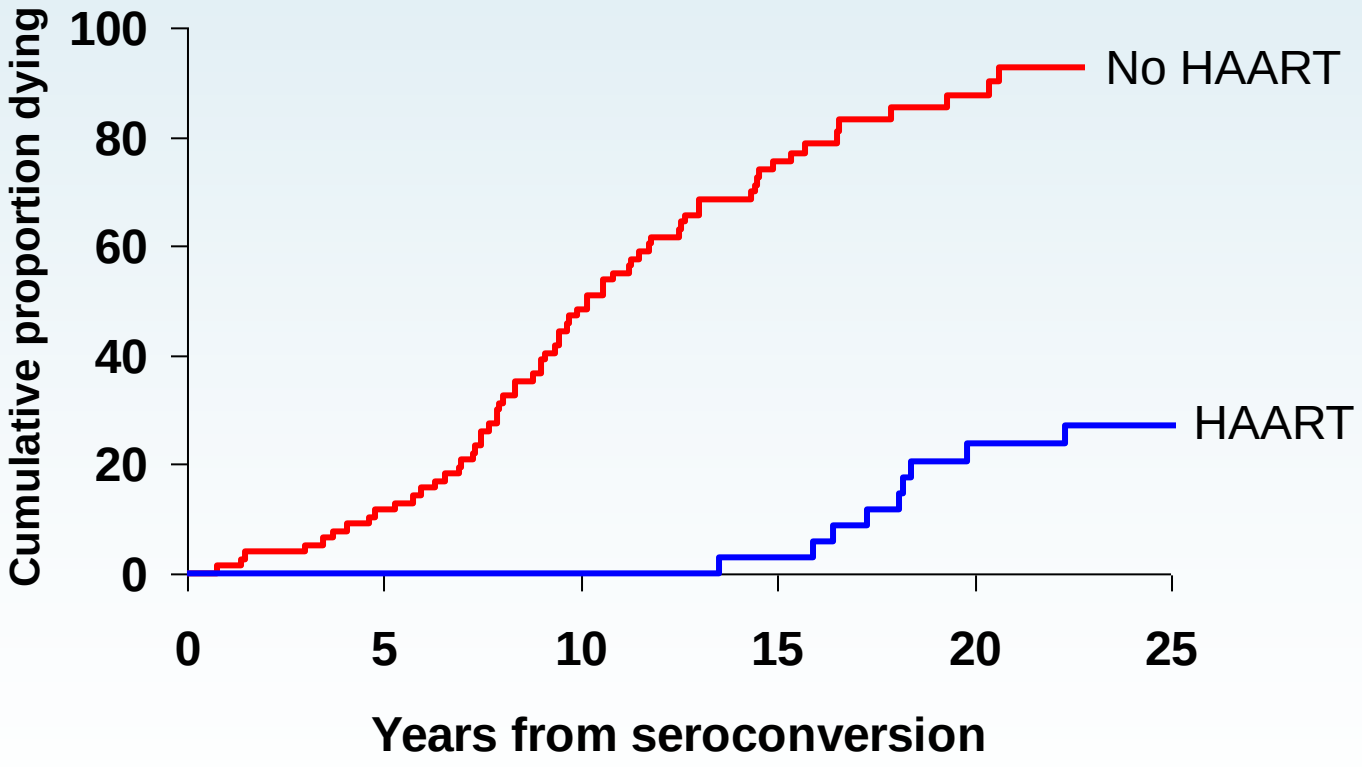
- Also occurs when observers over-emphasise something that they believe is related to the study, and under-emphasise things that they believe are unrelated

  Example 2: Assessments of potential drug toxicities in an unblinded randomised trial

Survivorship bias

- Occurs when survival is compared in patients who do/do not receive a particular intervention, when this becomes available at some stage in the future
- In order to receive the intervention, patients must have survived until its introduction; anyone who dies prior to this time will not be able to receive it
- It will appear that those who receive the intervention have particularly good survival compared to those who do not receive it

Example – mortality rates after HIV infection, stratified by receipt of HAART

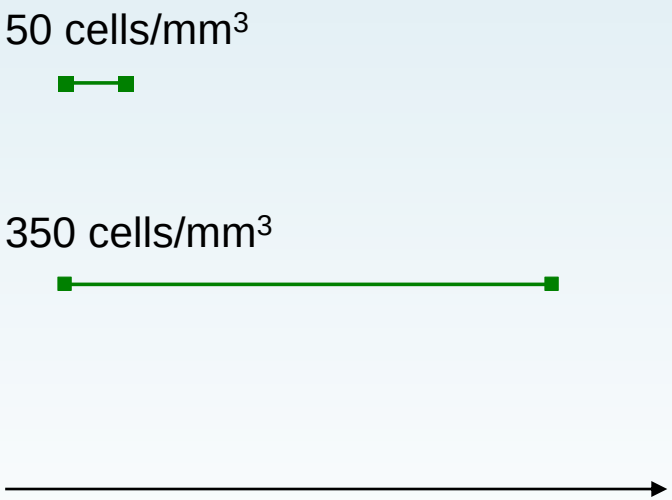


Royal Free Hospital Haemophilia Cohort, June 2005

Lead-time bias

- Clinical outcomes are generally better in those who start HAART at a higher CD4 count
- This has been used as justification for recommending that HAART is started at a higher CD4 count
- However, those starting treatment at lower CD4 counts have generally remained well long enough for their counts to fall to this level
- Furthermore, patients who died before their CD4 count fell to this level are after excluded from the analysis

Lead-time bias



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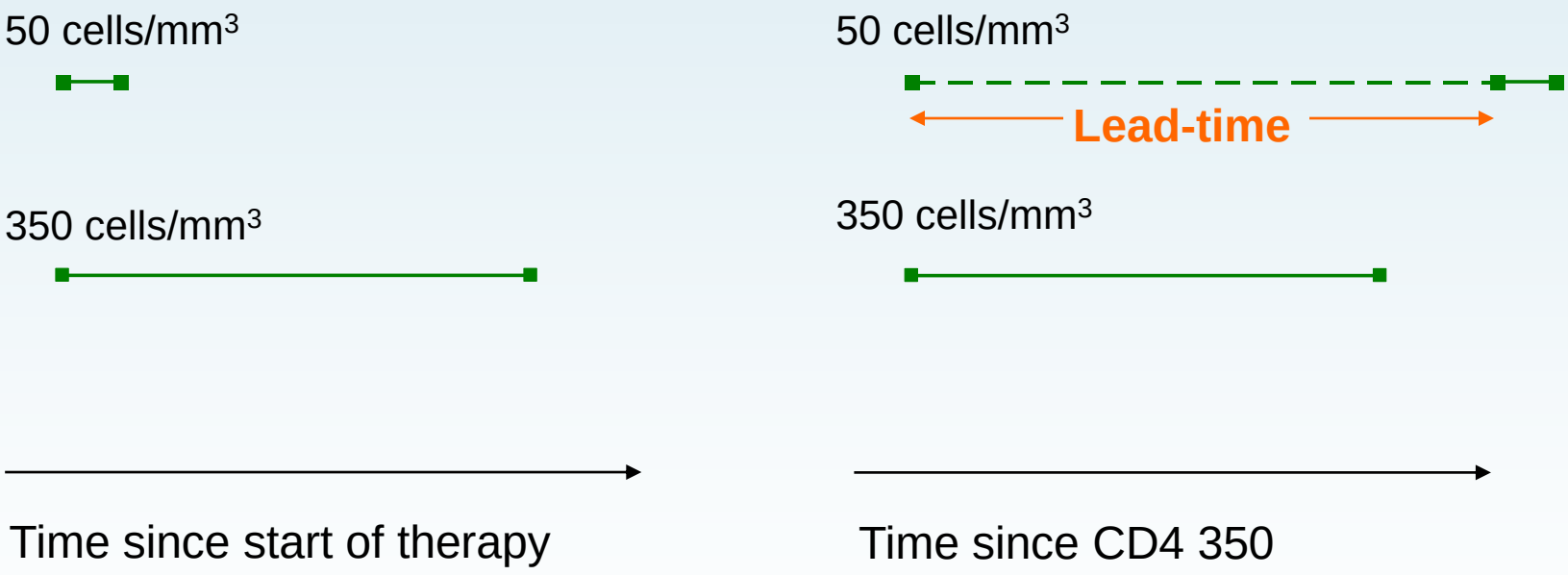
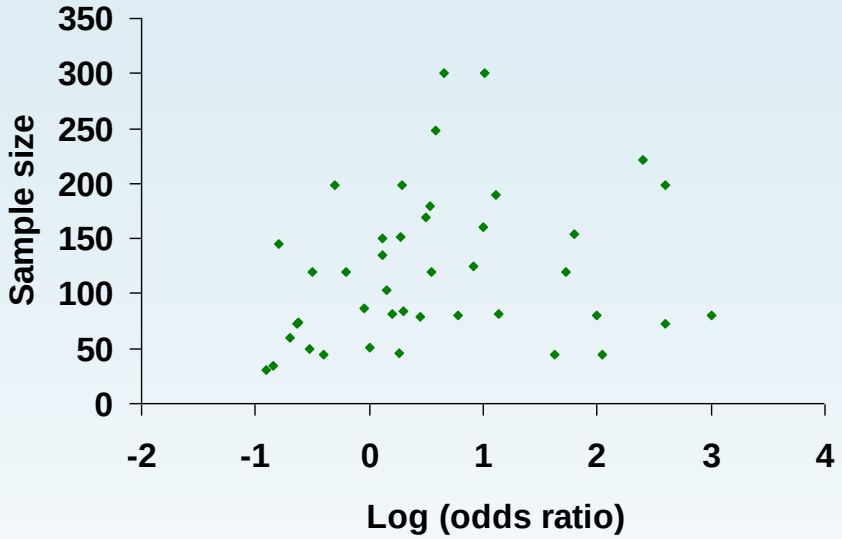


Publication bias

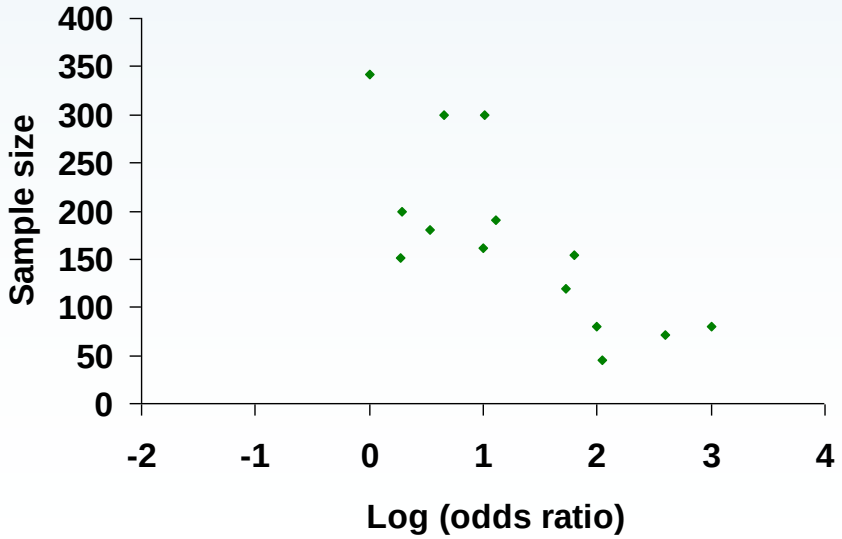
- Studies showing significant results more likely to be published than those showing non-significant results
- Bias is generally less marked when study is large
- When performing a systematic review it is important to obtain information on all studies performed, *whether or not* they have been published (e.g. abstracts, all journals including non-English language ones)
- Can investigate the possibility that publication bias exists by drawing a funnel plot

Funnel plots



No evidence of publication bias

Plot shows a good scatter of points around mean estimate – there is no 'hollowing'



Evidence of publication bias

The plot is non-symmetrical and hollow – the only studies to suggest a large treatment effect are small ones

Minimising bias at the design stage

- Select a representative sample
- Find ways to encourage high participation rates
- Be proactive in ensuring good follow-up on all patients; don’t wait for patients to return to clinic when they are ready!
- Remove as many logistical barriers to attendance as possible
- Where possible, attempt to ‘blind’ participants and observers to the study hypothesis, and use objective measurement tools

Summary

- Where possible we should design a study to minimise the opportunities for bias to arise
- During analysis, it is important to question whether bias may have been introduced at any stage (e.g. through loss-to-follow-up, missing data, differential follow-up, etc.)
- Appropriate statistical methods may then be used to minimise the impact of any bias
- Alternatively, if these methods are not practical, then it should still be possible to assess the direction of any bias