Three main categories of alternative explanation

- Chance - random error
- **Bias** - systematic error
- Confounding – third factor explaining an association

Bias

- is a systematic error in the design of an epidemiological study which leads to a distortion or error in the study results

Validity

- A study's results and conclusions are **valid** when they reflect the true relationship in the study population

- To assess the validity of findings we need to consider **alternative explanations** for the observed associations

Bias can affect

- Estimate of one variable

- Estimate of association between variables

Errors may be

- Non–differential vs. differential
  - ◦ error in one variable <u>not related</u> to / dependent on the value of other variables
  - ◦ error in one variable <u>is related</u> to value of other variable

- Selection vs. information
  - ◦ Related to <u>selecting</u> subjects into study
  - ◦ Related to collecting <u>information</u>

Two main types of bias

- Selection bias

  due to errors in the way sample is recruited

- Information bias

  due to errors in way in which information collected from the sample

Selection bias

- a distortion that results from procedures used to select subjects or their participation

- resulting in a difference in the characteristics between those who are included in the study and those in study population but not included in the study sample

Global perspective

- WEIRD samples
  - Over-reliance on samples drawn from populations that are White, Educated, Industrialized, Rich, and Democratic (Henrich, Heine, and Norenzayan)
  - Threat to validity (= generalizability to other populations)

Selection bias

- Selection of participants (random sampling)
- Participation rate, sample attrition

Information bias

- Errors in the way information about exposure or disease collected

- Misclassification - putting subjects in wrong category

- Eg. exposed as unexposed, case as control

Misclassification may be

- Random – above / below
- Systematic – all in one direction

- Non–differential (error in one variable not related to / dependent on the value of other variables)
- Differential (error in one variable is related to value of other variable

Non-differential misclassification:

- Tend to bias estimates towards null

- Cholesterol machine giving random readings

Differential misclassification

- Can distort associations, and can produce spurious associations

- Recall/reporting bias –
  - Error in way subjects give information
  - Correct and precise recall of information + willingness to share the information

- Observer bias
  - Error in way observers collect information

Recall bias

- Particular problem in retrospective studies
- Case may have better recall of exposure
  - Eg. mothers of babies with congenital abnormality
  - Diarrhoeal illness and food consumption
- In CS or CC studies when exposure & disease assessed at same time
  - Eg. depression and poor physical health
  - Often not conscious – placebo effect

Reporting bias

- Respondents may underestimate some behaviours eg. alcohol, smoking

Observer bias

- investigator classifies exposure differently in cases/control

or

- the investigator diagnoses disease differently in exposed/unexposed participants

and hence the results are distorted.

Interviewer bias

- Interviewer may probe cases more closely for exposure

- May look for endpoint more carefully in those exposed

Detection bias

- Differences in diagnostic criteria or reporting – often in multicentric/cross-national studies
- Differences in healthcare access

- These differences may be associated with exposure eg. social class/country

- Hence detail paid to ascertainment and validation of endpoints

What can we do to prevent / reduce bias?

Selection bias

- random sampling from study population

- strategies to reduce non–response e.g. repeat mailings, offering different times at clinic

- proper choice of control group in case-control studies

Recall / reporting bias

- recall bias – try to obtain objective information on past exposures wherever possible or use proxy information/informants
- reporting bias – include lots of different questions so that subjects are hypothesis blind
- trials should be controlled and blinded
  - Control (placebo) and experimental group
  - Double-blinding (both participants and interviewers are blinded)

Observer bias

- investigators blind to case / exposure status wherever possible
- use standardised instruments and protocols, back translations
- ideally use centralised measurement or calibrate instrument
- periodic check on staff to check for differences in procedures

Example - Child Behavior Checklist

CERTIFICATION

This is to certify that Corporate Translations, Inc. has performed the following procedures on the **Child Behavior Checklist for Ages 1 1/2 - 5 [CTi Job #: 59356]:**

- Two independent forward translations
- One harmonized forward translation
- One independent back-translation
- Reconciliation of back-translation and harmonized translation
- Review of back-translation by Survey Research Expert
- Review of harmonized translation by on-site sponsor representative
- Cognitive debriefing with five representative subjects who are parents of children ages 1 1/2-5 in Czech Republic
- Desktop publishing of previously validated translation
- Proofreading of previously validated translation

These documents were prepared by a team of translators and interviewers who are fully bilingual in both Czech for Czech Republic and English. All procedures were performed in accordance with current industry standards and FDA guidance.

Detection/diagnostic bias

- standardised diagnostic criteria

Bias: the silent menace

- Cannot be assessed numerically
- No software to identify bias
- If there is flaw in the design of the study increasing numbers will not get rid of it!
- Can only be assessed by careful evaluation of the design

Assessment of bias

- Non-responders questionnaire
- Baseline characteristics of those lost to follow can be analysed and compared to those remaining in study
- Objective validation of self-reported information
- Sensitivity analyses to estimate effect of bias

ELSPAC example

Prenatal psychosocial stress and children's sleep problems: Evidence from the ELSPAC-CZ study

Gabriela Ksinan Jiskrova[1] | Hynek Pikhart[1,2] | Martin Bobák[1,2] | Jana Klanova[1] | Irena Stepanikova[1,3]

11 years ($N = 4,371$). Approximately 50% of children remained in the study until the age of 11 years and ~20% until 19 years. Compared to women participating at the baseline, participants that remained in the study for its entirety were less commonly single (6.2% versus 8.9%) and aged <20 years at the time of delivery (6.5% versus 9.9%), and more often held a college degree (19.1% versus 7.1%; Piler et al., 2017).

ELSPAC example

The study has several limitations that need to be discussed. First, both exposure (PSLE) and outcome (child sleep problems) variables were reported by mothers; therefore, the association between the constructs may be inflated due to shared method variance. We addressed this issue by conceptualising PSLE and sleep problems as counts of the respective events or problems that occurred in a given time period, rather than as an individual interpretation of stress or the severity of sleep problems. However, despite our attempt to operationalise both constructs objectively, we cannot entirely rule out the potential impact of maternal factors (e.g. anxiety) on the reporting of PSLE and sleep problems. Objective measurement of sleep characteristics, e.g. by actigraphy, or by utilising multiple informants of child sleep problems, would improve the validity of sleep measurement.

Second, the ELSPAC-CZ data collection commenced in 1991–1992. Based on data from Czech Statistical Office (2020), mothers in 2019 were, on average, older, more educated, and less likely to be married than those in 1991–1992. At the same time, Czechoslovakia,

Third, there has been an attrition of the sample throughout the follow-up period. Given that children of younger and less educated mothers were more likely to drop out from the study, the results need to be generalised with caution. Lastly, due to the observational

Publication bias

High-impact journals prefer clear, positive results!

Bias in systematic reviews

Form of selection bias arising if null studies are not published

If not included the overall estimate is biased upwards

Minimised by searching grey literature, trial registers and conference proceedings to include null/negative results

e.g. the 'drug effectiveness cycle' (β-blocker-mortality example in session 7), selective serotonin reuptake inhibitors in treating depression

Publication bias

Failure to publish

- a negative or inconclusive trial result
- a small trial may be abandoned

Duplicate publication

- a large treatment effect
- need for research output

   Eg. nine trials of ondansetron (antiemetic) in 23 publications   Tramer et al BMJ 1997

How to avoid publication bias

- To make sure studies are not double counted
- To search for unpublished studies (e.g. contact researchers directly)
- To use non-English language publications
- Statistical checking (funnel plots: smaller studies report more extreme results)
- Registration of studies and to make sure all results are in public domain (not yet fully achieved)
- Trial registration: assigns unique trial identification numbers, and to record other basic information about the trial so that essential details are made publicly available
- From 2004 International Committee of Medical Journal Editors (ICMJE) would consider trials for publication only if they had been registered before the enrolment of the first participant

Funnel plot:

asymmetrical plot in the presence of bias: some smaller studies (open circles) are of lower methodological quality and therefore produce exaggerated effect estimates
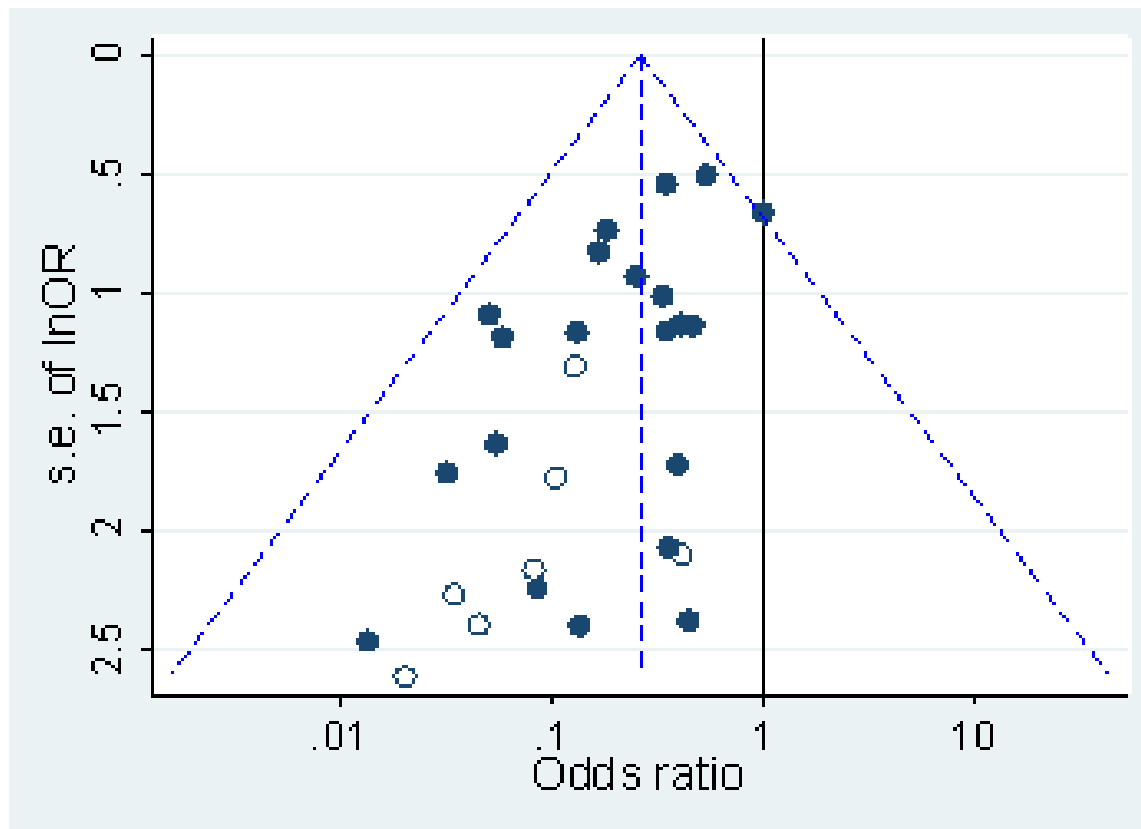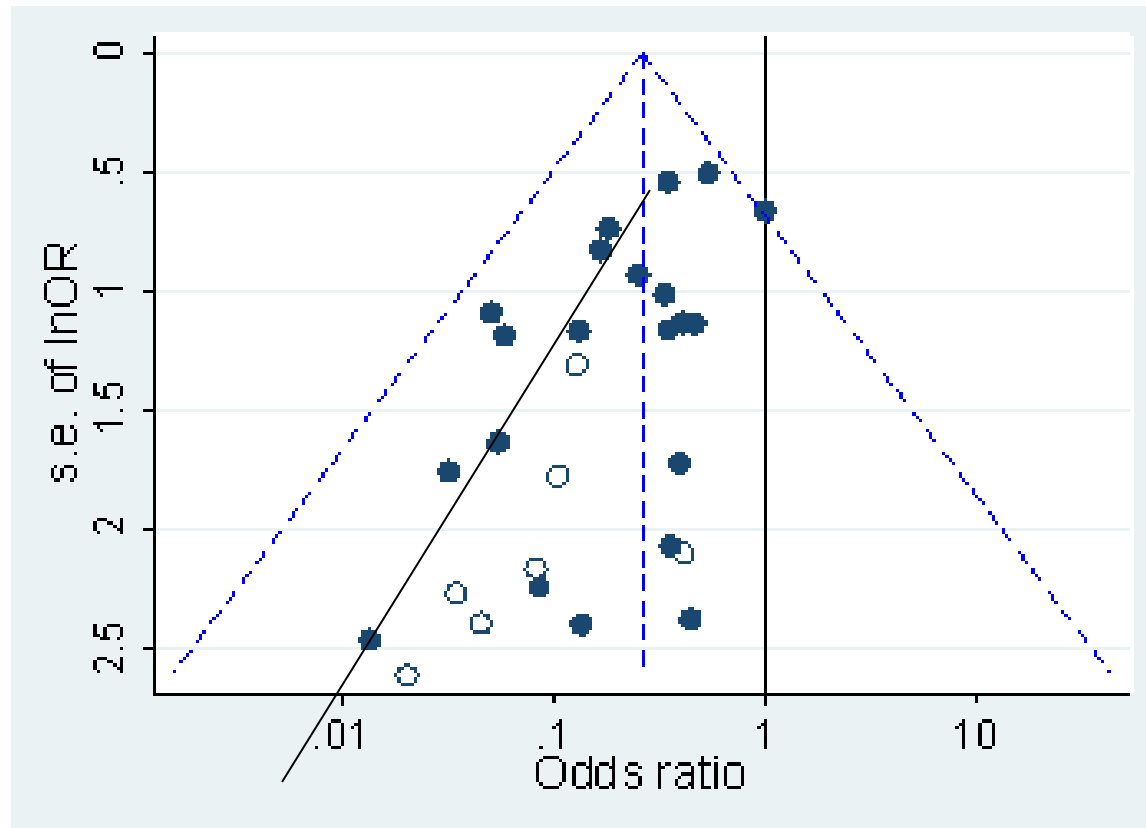
Funnel plot:

asymmetrical plot in the presence of bias: some smaller studies (open circles) are of lower methodological quality and therefore produce exaggerated effect estimates

Beta-blockers and total mortality after MI: meta-analysis

Year	Trials	Cumulative odds ratios (95% CI)
1972	A	
1974	B	
1974	C	
1977	D	P=0.02
1980	E	
1980	F	
1981	G	P=0.0001
1982	H	
1982	I	P<0.0001
1982	J	P<0.00001
1982	K	
1983	L	
1983	M	
1984	N	
1985	O	
1987	P	
1990	Q	P<0.00001

0.1   1   10

Favours β blocker   Favours control

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