Valutazione del rischio di *bias* negli studi selezionati

Negrar, 5 aprile 2019

VALIDITA' INTERNA

La misura in cui uno studio riesce a cogliere la relazione «**vera**» fra due variabili

ERRORE CASUALE

ERRORE SISTEMATICO (BIAS)

ERRORE CASUALE

Errore che si verifica per effetto del caso

Replicazioni multiple della stessa misurazione producono differenti risultati in tutte le direzioni per variazioni casuali ma la media dà il risultato corretto

ERRORE SISTEMATICO

Errore che si verifica per la presenza di un fattore che distorce sistematicamente le osservazioni nella stessa direzione

Replicazioni multiple della stessa misurazione producono risultati sempre nella stessa direzione e “sbagliati”

Errore sistematico e validità interna di uno studio

- I risultati di uno studio sono tanto più validi (probabilmente veri) quanto meno esso è affetto da errori sistematici
- Gli errori sistematici vanno previsti ed evitati o ridotti in fase di disegno dello studio

Bias

Systematic distortion of the estimated intervention effect away from the truth, caused by **inadequacies** in the **design**, **conduct**, or **analysis** of a trial , or in the **publication of its results**. In other words, in a biased trial, **the results observed reflect other factors** in addition to (or, in extreme cases, instead of) the effect of the tested therapeutic procedure alone.

Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663–94

Bias is not the same as

Imprecision

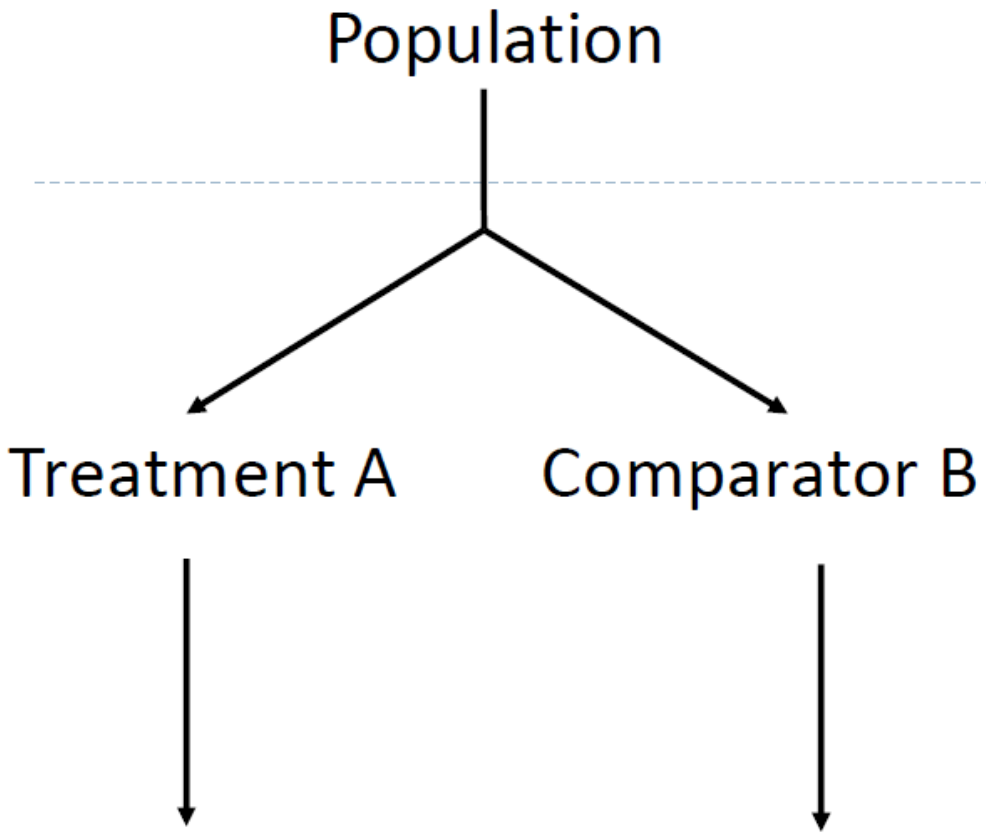
- random error due to sampling variation
- reflected in the confidence interval

Quality

- bias can occur in well-conducted studies
- not all methodological flaws introduce bias

Reporting

- good methods may have been used but not well reported



Bias

Selection bias

Performance bias

Detection bias

Attrition bias

Reporting bias

Randomizzazione

Sources of bias

Selection

Performance

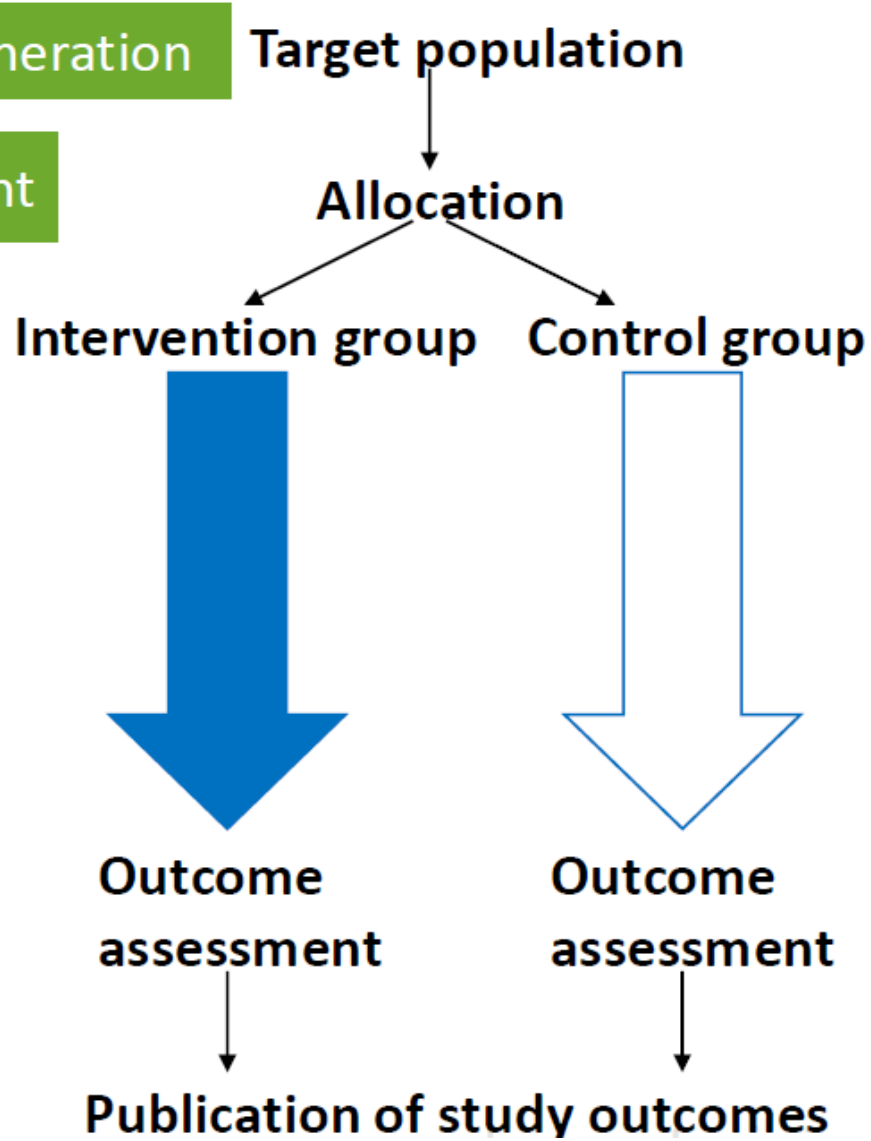
Detection

Attrition

Reporting

Random sequence generation

Allocation concealment



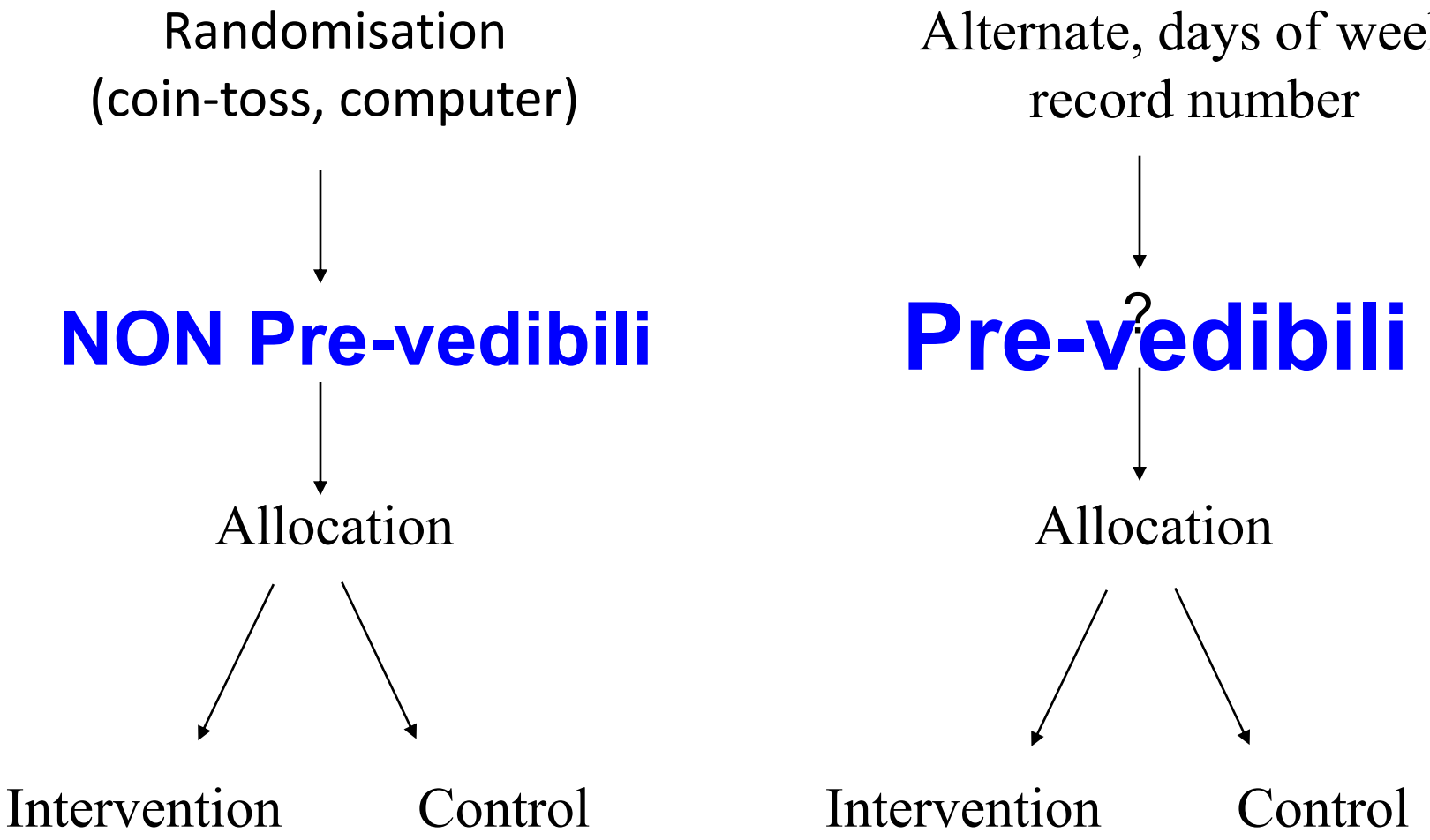
Why randomise?

At the End of a clinical trial..

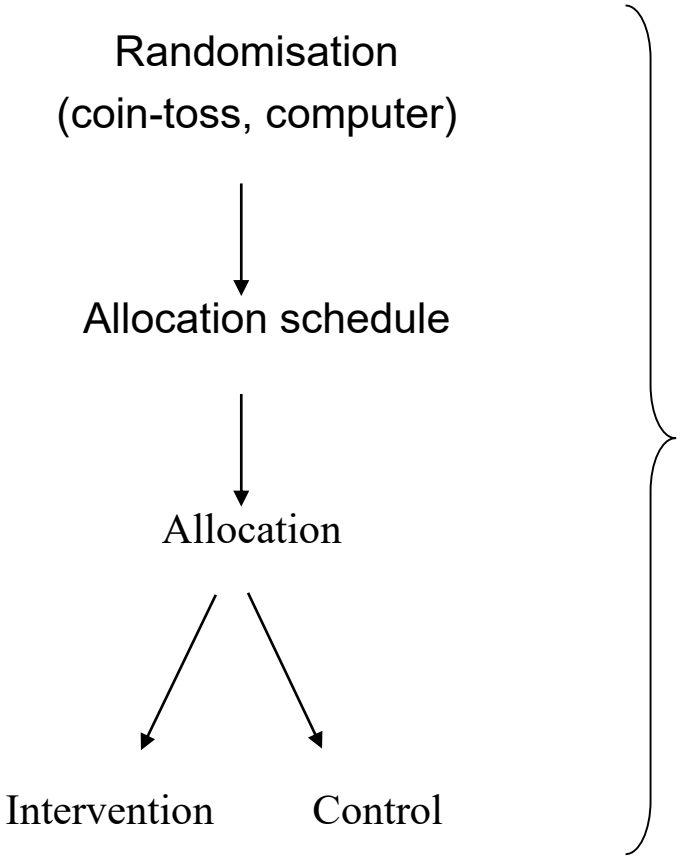
- **We find a difference in outcomes between intervention and control groups**
- **Possible explanations:**
  - **the intervention exhibits a real effect**
  - **the outcome difference is due to chance**
  - **there is a systematic difference (or bias) between the groups due to factors other than the intervention**
- **Randomisation prevents the third possibility**

Randomisation ensures similar levels of all risk factors (known and unknown)

RANDOMIZATION BIAS



RANDOMIZATION BIAS



- Recruiting selected individuals due to **knowledge of the next allocation**
- Manipulating allocations of people based on **personal believing**
- Exclusion of certain patients based on their **prognosis**

RANDOMIZATION COMPONENTS

Item	Descriptor
Sequence generation	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification)
Allocation concealment	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned
Implementation	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups

Selection bias

1. Sequence Generation

- **Adequate methods :**random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice. **(Low risk of bias)**
- **Inadequate methods**: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention (**High risk of bias**). **«quasi randomised studies «**

Baron Ja et al. A Trial of Calcium and Vitamin D for the Prevention of Colorectal Adenomas. N Engl J Med. 2015 Oct 15;373(16).

Randomization

- randomization by the coordinating center was performed with the use of computer-generated random numbers with permuted blocks and stratification according to clinical center, sex, anticipated colonoscopic examination at 3 years or 5 years, and full factorial randomization.

Selection bias

2) Mascheramento della assegnazione

- Chi recluta i pazienti e verifica se rispondono ai criteri di inclusione non sa a che gruppo verranno assegnati
- Chi assegna i pazienti ai gruppi non sa chi sono i pazienti

Selection bias

2. Mascheramento della assegnazione

Adequate methods: Investigators enrolling participants could not foresee assignment : central allocation (including telephone, web-based, and pharmacy-controlled, randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes. **Low risk of bias**

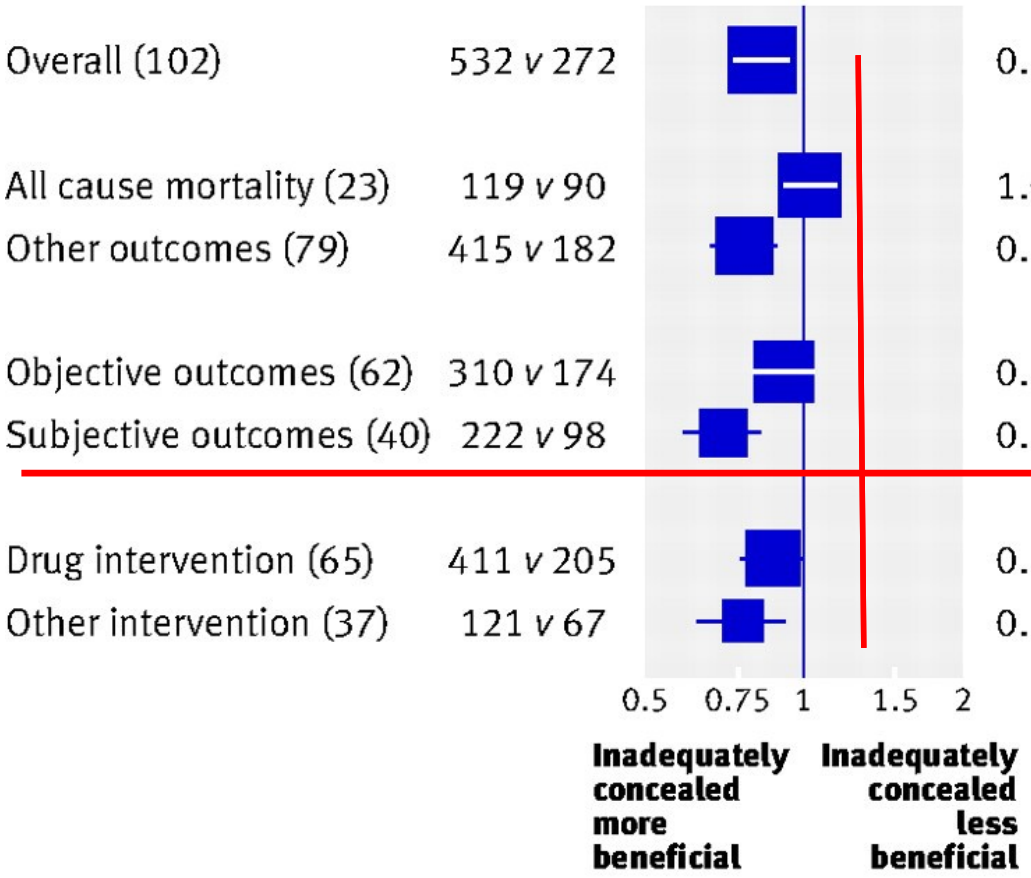
Inadequate methods: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure . **High risk of bias**


SORE THROAT?

ainers

Ratios of odds ratios comparing estimates of intervention effects 532 trials with inadequate or unclear allocation concealment versus 272 trials with adequate concealment

Comparison (No of meta-analyses)	No of trials*	Ratio of odds ratios	Ratio of odds ratios (95% CI)	P value of test of interaction	Variability in bias† (P value)
Overall (102)	532 *v* 272		0.83 (0.74 to 0.93)	–	0.11 (<0.001)
All cause mortality (23)	119 *v* 90		1.01 (0.90 to 1.15)	0.002	0.02 (0.24)
Other outcomes (79)	415 *v* 182		0.76 (0.66 to 0.87)		0.14 (<0.001)
Objective outcomes (62)	310 *v* 174		0.91 (0.80 to 1.03)	0.009	0.11 (<0.001)
Subjective outcomes (40)	222 *v* 98		0.69 (0.59 to 0.82)		0.07 (0.011)
Drug intervention (65)	411 *v* 205		0.87 (0.76 to 1.00)	0.27	0.09 (<0.001)
Other intervention (37)	121 *v* 67		0.77 (0.64 to 0.93)		0.16 (<0.001)



* Inadequately or unclearly concealed *v* adequately concealed

† Between-meta-analysis heterogeneity variance

Non accade MAI che allocation inadeguato dia risultati meno favorevoli per il trattamento sperimentale

Wood, L. et al. BMJ 2008;336:601-605

CECITA’

Sources of bias

Selection

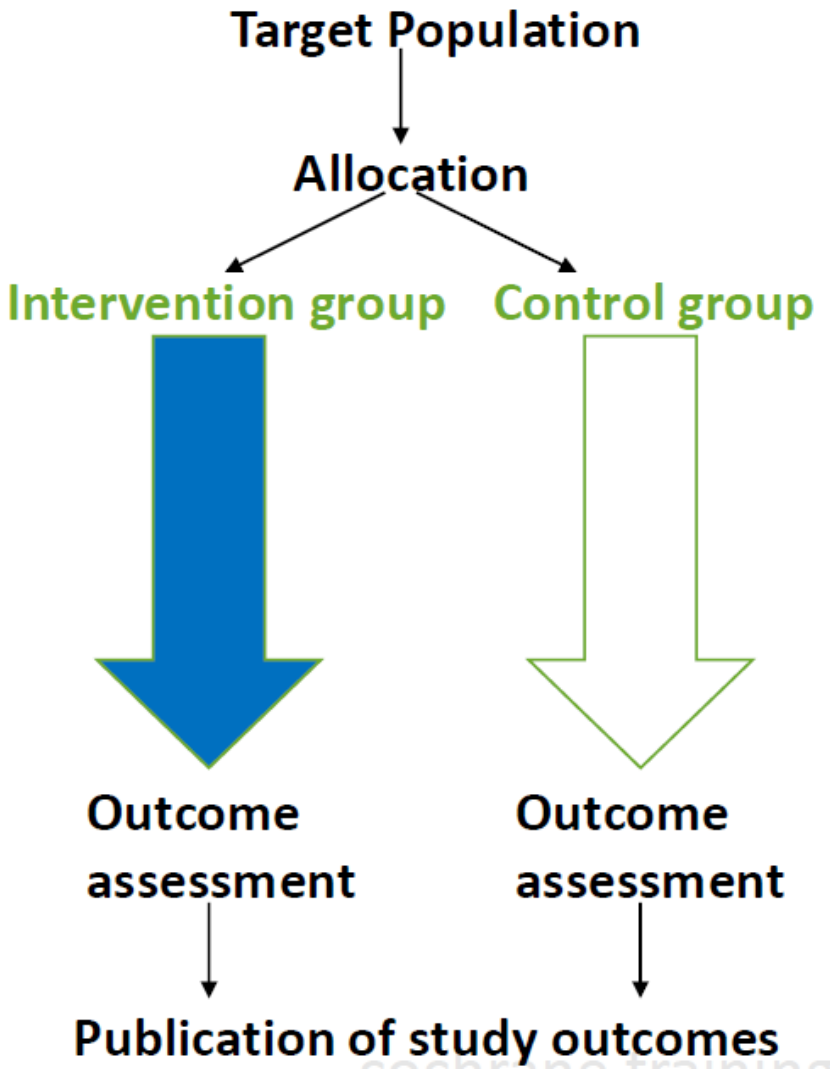
Performance

Blinding of participants, personnel

Detection

Attrition

Reporting



COSA POTREBBE FARE

- Usually reduces differential assessment
- May improve compliance and retention
- May reduce biased supplemental care or treatment (co-intervention) [and testing]

Confused Terminology of Single, Double, and Triple Blinding Permeates the Literature

- Physicians, textbooks, and journal articles vary greatly in interpretations and definitions

  [Devereaux et al. JAMA 2001; 285: 2000-3]

- Define "double-blind" inconsistently
  - Authors frequently fail to report their definitions clearly

- When I use "double-blind", participants, investigators, and assessors are blinded

- In reporting RCTs, authors should explicitly state what steps were taken to keep whom blinded

Performance bias (co-intervention)

- The interpretation of a randomized controlled trial relies on the assumption that any differences in outcome are the result of either chance (whose effects can be quantified) or of inherent differences between treatments.
- This assumption is invalid if the treatment groups are not handled equally with regard to all of the study procedures, a part the experimental treatment

Performance bias

Blinding of participants and providers

Rischio di bias dipende dal tipo di outcome !!

Low risk of bias : Blinding of participants and providers and unlikely that the blinding could have been broken

- No blinding or incomplete blinding, **but the outcome is not likely to be influenced by lack of blinding** (e.g. mortality, cancer incidence)

High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;

- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding

Sources of bias

Selection

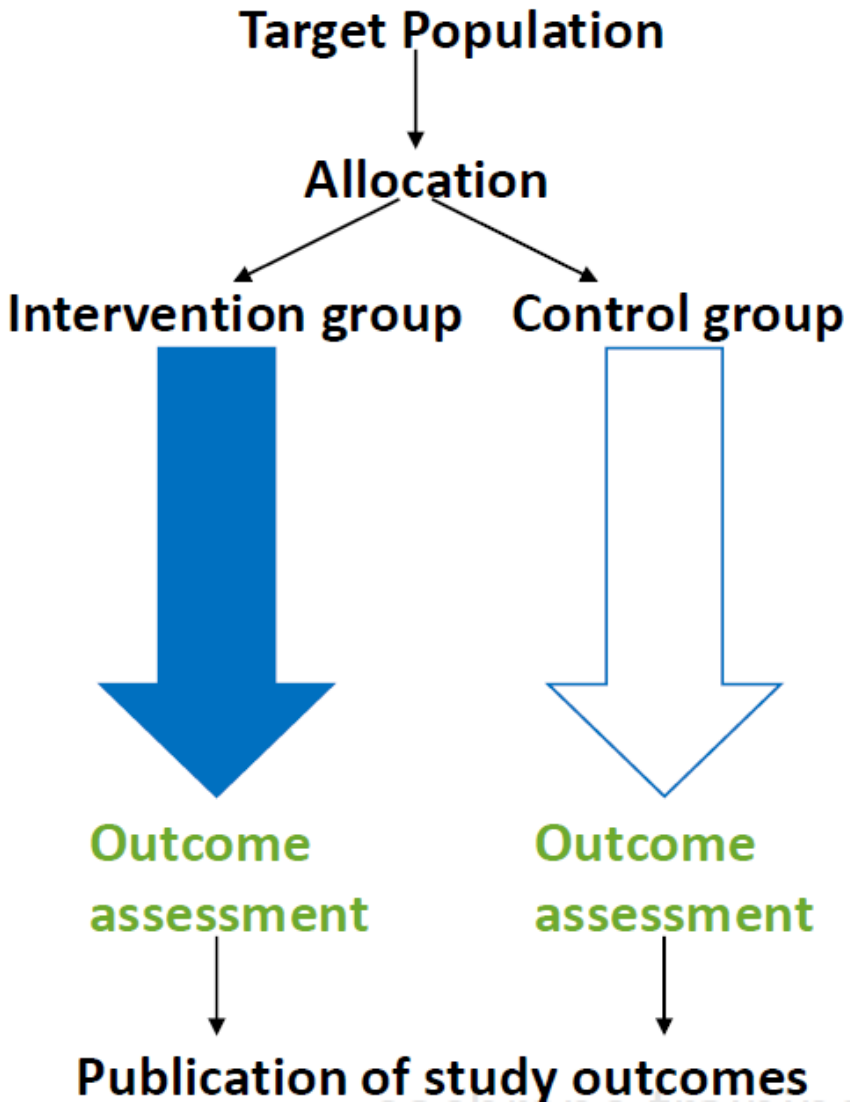
Performance

Detection

Attrition

Reporting

Blinding of outcome assessment



Detection bias

- When knowledge of the treatment assignment (by participants already recruited into a trial, investigators, or persons who analyze and report trial results) leads to systematic differences on the way the outcomes are assessed

Detection bias

Blinding of outcome assessor

Rischio di bias dipende dal tipo di outcome !!

Low risk of bias : Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken

- No blinding of outcome assessment, but the outcome measurement is not likely to be influenced by lack of blinding

High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;

- Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding

Detection bias

- Blinding? Double blinding? Triple blinding?
- Who needs to be blinded?
- Is the outcome sensitive to blinding?
  - Blinding: clearly very difficult in many intervention trials (i.e. surgical)
  - Solution: Blinded assessors should be used routinely for measuring outcome

Outcome assessor

- Participants (subiective outcomes)
- Investigator who collects outcome data
- Data manager
- Statistician
- Quando l'intervento non può essere fatto in cieco ma l'outcome è soggettivo è **fondamentale cercare di garantire la cecità di chi rileva i dati**
- **Non tutela dal detection bias del paziente**
- **Non tutela dal performance bias del medico**

Open studies (unblinded)

- Quando la cecità non è praticamente realizzabile (chirurgia, interventi educativi, psicosociali, riabilitazione, prevenzione primaria)
- Quando la cecità non è rilevante per il tipo di outcome (mortalità, incidenza di tumore, recidiva)
- **Risk of bias**: patients might under- or overreport treatment effects and side-effects, based on their confidence on the intervention (**detection bias**)
- Providers may give advice or prescribe additional therapy to the control group if they feel that these patients are disadvantaged in comparison to the active group, (**performance bias**)

Single-blinded studies

- the patient should be unaware of which treatment they are taking
- the investigators are aware
- **Risk of bias**: Providers may give advice or prescribe additional therapy to the control group if they feel that these patients are disadvantaged in comparison to the active group(**performance bias**)

Double-blinded studies

- neither the patient nor the provider knows the identity of the assigned intervention
- the validity of the study depends on the providers and participants remaining really blinded throughout the study .
- A study of a drug is easily unblinded if the medications are not identical in appearance

Double blind - double dummy

- Double dummy is a technique for retaining the blind when administering supplies in a clinical trial, **when the two treatments cannot be made identical**. Supplies are prepared for Treatment A (active and indistinguishable placebo) and for Treatment B (active and indistinguishable placebo). Subjects then take two sets of treatment; either A (active) and B (placebo), or A (placebo) and B (active).

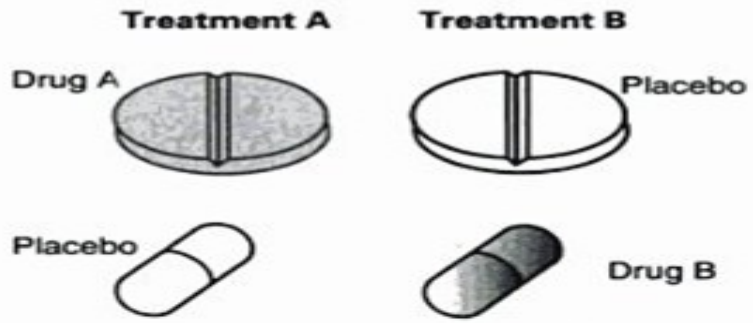


Fig. 2.7 The double-dummy technique. The patient always takes a tablet and a capsule. In treatment A, the tablet contains the active drug and the capsule contains the placebo. In treatment B, the capsule contains the active drug and the tablet contains the placebo.

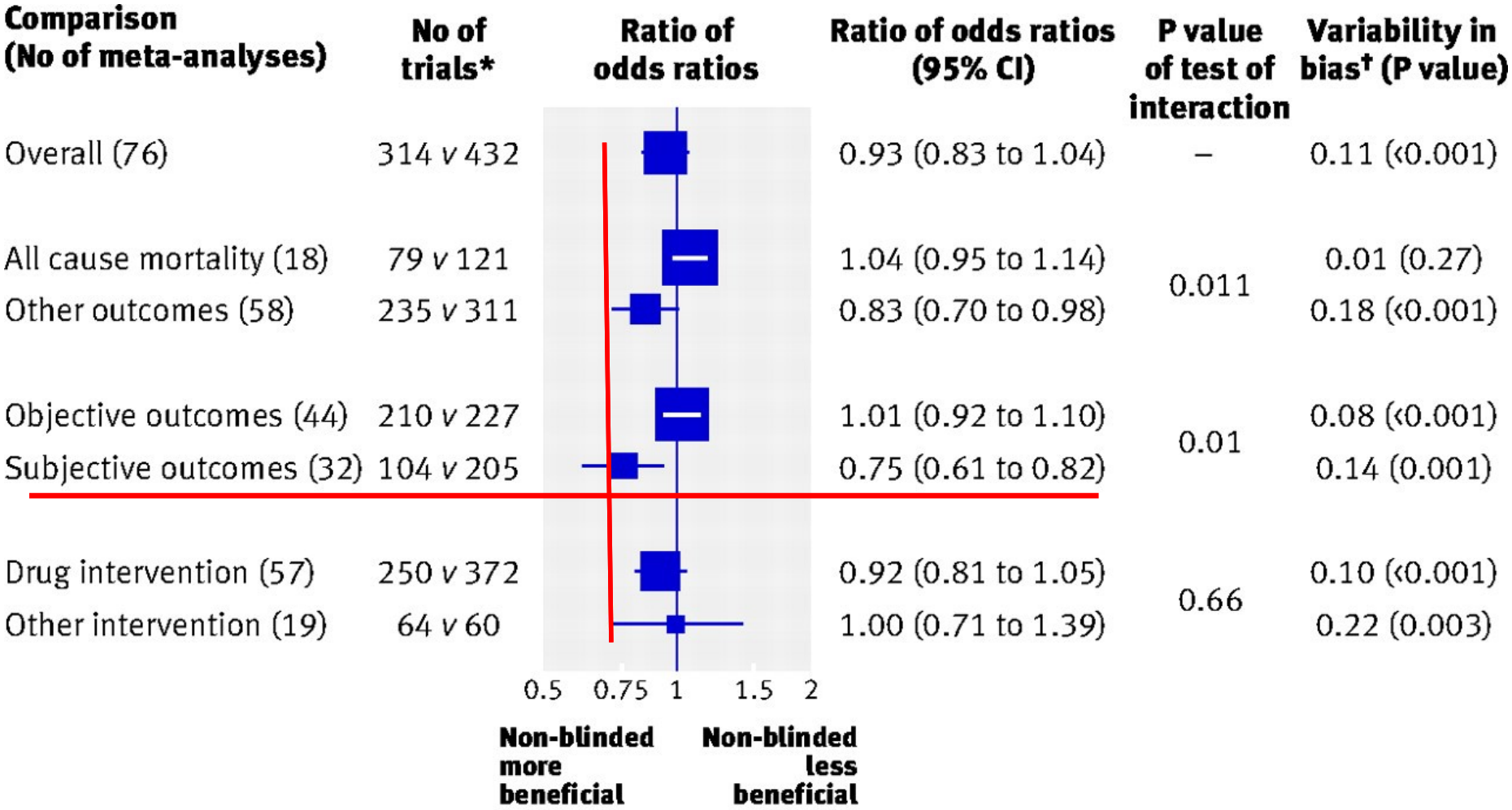
Triple-blinded studies

- Providers blinded
- Participants blinded
- All the sponsor's project team (eg, the project clinician, outcome assessor , statistician, and data manager) blinded
- Triple blinding is appropriate for studies in which the risk of adverse events due to the new or standard treatment is low, and should not be used for treatments where safety is a critical issue

Assessing trial blindness

- The degree to which the blinding was maintained in a study can be estimated by asking the patients to guess which group they were assigned to.
- If the mean result of the guesses is close to being 50% correct, the study was well blinded.
- A similar enquiry could be done with providers also.

Ratios of odds ratios comparing intervention effect estimates in 314 non-blinded trials versus 432 blinded trials.



* Non-blinded *v* blinded

† Between-meta-analysis heterogeneity variance

Wood, L. et al. BMJ 2008;336:601-605

Allocation concealment

•It prevents **selection bias** in intervention assignment by protecting the allocation sequence **before and until** assignment

•It can always be successfully implemented regardless of the study topic

≠

Blinding

•It seeks to prevent **performance and detection bias** by protecting the sequence **after** assignment

• Not always feasible – for example, in trials comparing surgical with medical interventions

6 ragioni per introdurre la cecità

- Se dite al paziente che è stato **randomizzato al placebo**, non è contento
- Se dite alle persone che l'efficacia del trattamento è dovuto **all'effetto placebo**, si arrabbiano
- Se dite al clinico che il paziente prende il trattamento**, il clinico vedrà un miglioramento** (anche in assenza di cambiamento)
- Se dite al paziente che non si dovrebbe grattare, **si gratta uguale, ma vi dice** che si gratta di meno (Effetto Rosenthal)
- Illusione di specifici effetti come **le tradizioni millenarie** sono molto radicate (agopuntura nei meridiani vs a caso)
- Avete inventato la panacea che, ogni volta che la somministrate, fallisce miseramente… cercate cercate fino a analizzare il beneficio su 100 variabili…(così funziona la statistica)

Attrition bias

- Quando **non tutti i soggetti randomizzati completano lo studio**
- i soggetti **non escono a caso dallo studio**: è possibile che quelli che escono siano sistematicamente diversi da quelli che non escono: i gruppi non sono più randomizzati
- **Validità esterna** : es: escono tutti i più giovani, o i meno gravi, o i maschi: posso trarre conclusioni solo su quelli che rimangono
- **Validità interna (Bias):** se la probabilità di uscire dallo studio è legata all'intervento o all'outcome, cioè se quelli che escono hanno sistematicamente probabilità più alte o più basse di avere l'outcome di quelli che restano

Attrition bias

- **Persi al follow up**: il soggetto sparisce non si hanno più informazioni
- **Uscito dallo studio** il soggetto interrompe il trattamento ma è reperibile (eventi avversi? Non efficace?)
- **Bassa compliance**: il soggetto riceve il trattamento ma in dosi e modalità diverse da quelle prescritte (eventi avversi? Trattamento poco accettabile?)
- **Missing data**: misurazioni ripetute: il soggetto riceve il trattamento ma non è presente a tutte le misurazioni dell'outcome (TD non consegnano le urine quando sono positive)

Attrition bias

Low risk of bias

- Numero di persi (piccolo) ma quanto? (<5-10%)
- Bilanciati fra i gruppi
- Riportate le ragioni (non differenti fra gruppi e non attribuibili agli interventi)
- Intention to treat
- Imputation of missing data

Attrition bias

Intention to treat analysis: all subjects analysed in the treatment group they were originally randomized, regardless if they actually received the assigned treatment or not

Imputation of missing data : es: considerare gli usciti come fallimenti terapeutici (TD); last observation carried forward

Per protocol analysis: only patients who received the treatment as described in the prtocol were analysed

Intention to treat:

- **effectiveness** (efficacia in pratica, efficacia del trattamento prescritto)
- Tiene conto anche della scarsa compliance, della difficoltà a somministrare il trattamento
- Tutela da attrition bias (mantiene la similitudine dei gruppi ottenuta con la randomizzazione

Per protocol:

- **efficacy** (efficacia in condizioni ottimali, efficacia della trattamento ricevuto nelle modalità previste)
- Può dare stime distorte se la non compliance e l'uscita dallo studio è legata al trattamento o all'outcome

Attrition bias

Low risk of bias

- No missing outcome data;
- the proportion of missing outcomes compared with observed event risk not enough to have a relevant impact on the intervention effect;
- Missing outcome data balanced in numbers across intervention groups, with similar reasons across groups;
- Missing data imputed using appropriate methods
- All patients analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)

High risk of bias:

- the proportion of missing outcomes compared with observed event risk enough to induce relevant bias in intervention effect estimate
- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;

What is publication bias (1)?

- Definition

"Publication bias refers to the greater likelihood that studies with positive results will be published"

JAMA 2002;287:2825-2828

What is publication bias (2)?

- An alternative definition:

Publication bias is the selective or *multiple* publication *or suppression* of trial results so that the scientific record is distorted

Extension: applied to trial parts - outcomes, subgroups, adverse events REPORTING BIAS

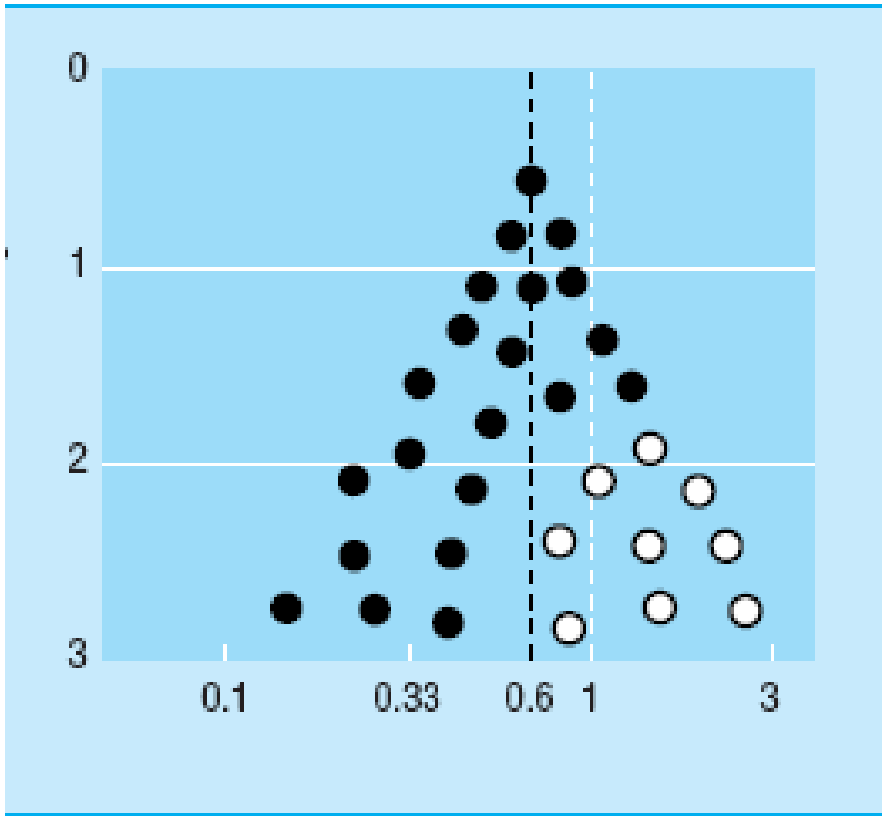
The likelihood of finding studies is related to the results of those studies (positive vs negative/detrimental)

Why does it matter?

- Distorts the scientific record
- Hides the “truth”
- Influences doctors’ decision making
- Misleads policy makers
- Causes harm to patients
- Costly for the health service
- A form of scientific and research misconduct

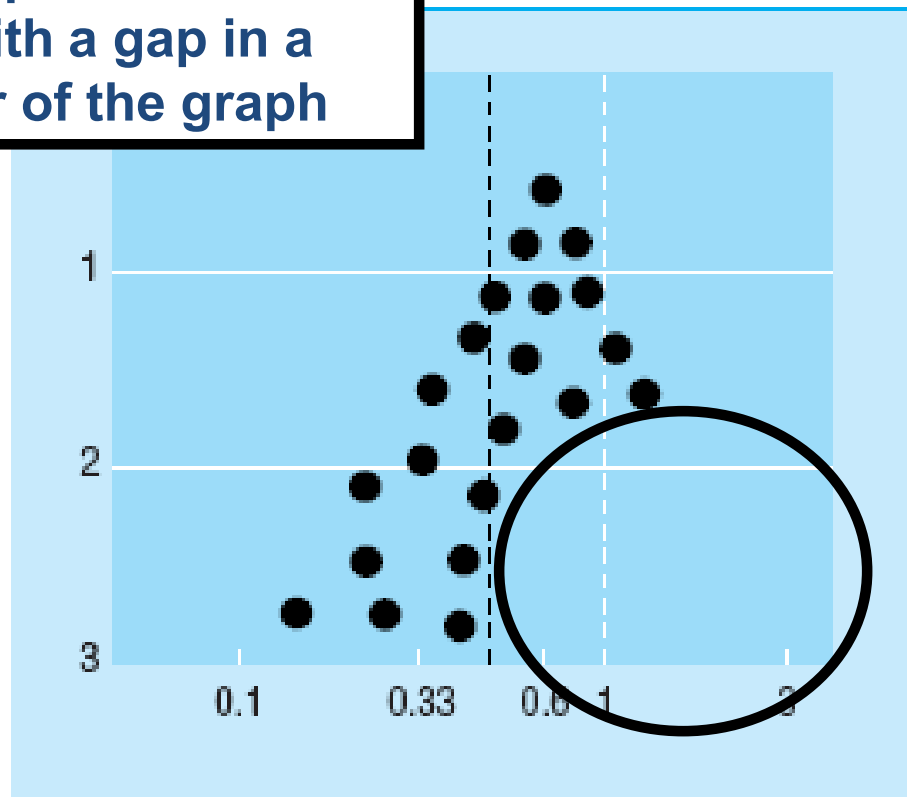
- TO U: It will matter if the studies you don’t find differ systematically from the ones you have found
- You might arrive at different answers, or even THE WRONG ANSWER

Publication of All Trials



Publication Bias

Asymmetrical appearance of the funnel plot with a gap in a bottom corner of the graph



Funnel plots

- A funnel plot is a scatter plot of treatment effect against a measure of study size / precision.

- Precision in the estimation of the true treatment effect increases as the sample size increases.
- Small studies scatter more widely at the bottom of the graph
- In the absence of bias the plot should resemble a symmetrical inverted funnel

Publication Bias

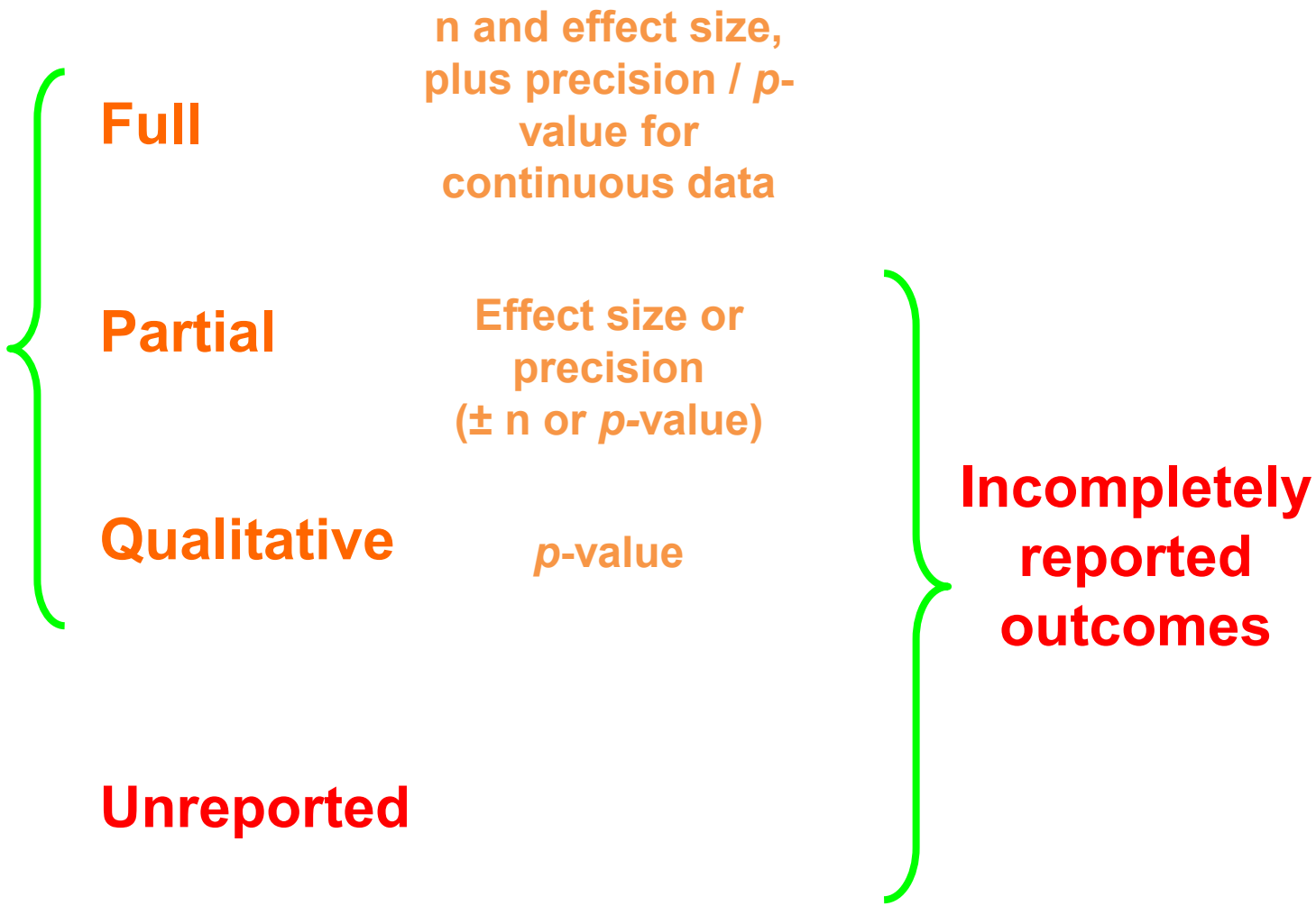
- **In this situation the effect calculated in a meta-analysis will overestimate the treatment effect**

- **The more pronounced the asymmetry, the more likely it is that the amount of bias will be substantial.**

Outcome reporting bias

Reporting bias is selection bias

- Reporting bias is perhaps the greatest source of selection bias
- Originally defined as the publication or non-publication of studies depending on the direction and statistical significance of the results
- Is a complex phenomenon


Full
n and effect size, plus precision / p-value for continuous data
Partial
Effect size or precision (± n or p-value)
Qualitative
p-value
Unreported
Incompletely reported outcomes

(Chan, 2004)

Results section

Table 2 Summary of methodological quality indicators of trials included in this systematic review of bupropion for smoking cessation in people with schizophrenia

Trials	Masking	Intention-to-treat analysis	Completeness of follow-up	Adherence monitoring	Matching of bupropion and placebo
Evins (2001)[32,34,36]	Double-blind (explicitly stated that participants were masked; otherwise unclear)	Explicitly stated in the report but it was not confirmed on study assessment	1/19 dropped out prior to medication (not included in analysis)	Yes	Yes
George (2002)[21,26,37,39]	Explicitly stated that participants, investigators and outcome assessors were masked to intervention	Specifically reported by the authors and this was confirmed on study assessment	5/32 dropped out during trial	Unclear	Yes
Evins (2005)[28–31]	Double-blind but details uncertain	Explicitly stated in the report but it was not confirmed on study assessment	4 dropped out prior to medication (not included in analysis); 10/53 dropped out at week 12; 9 more dropped out at week 24	Yes	Yes
Fatemi (2005)[20]	Double-blind (both participants and research staff)	Not stated and there was lack of confirmed intention-to-treat analysis on study assessment	1/10 dropped out from the study	Unclear	Unclear

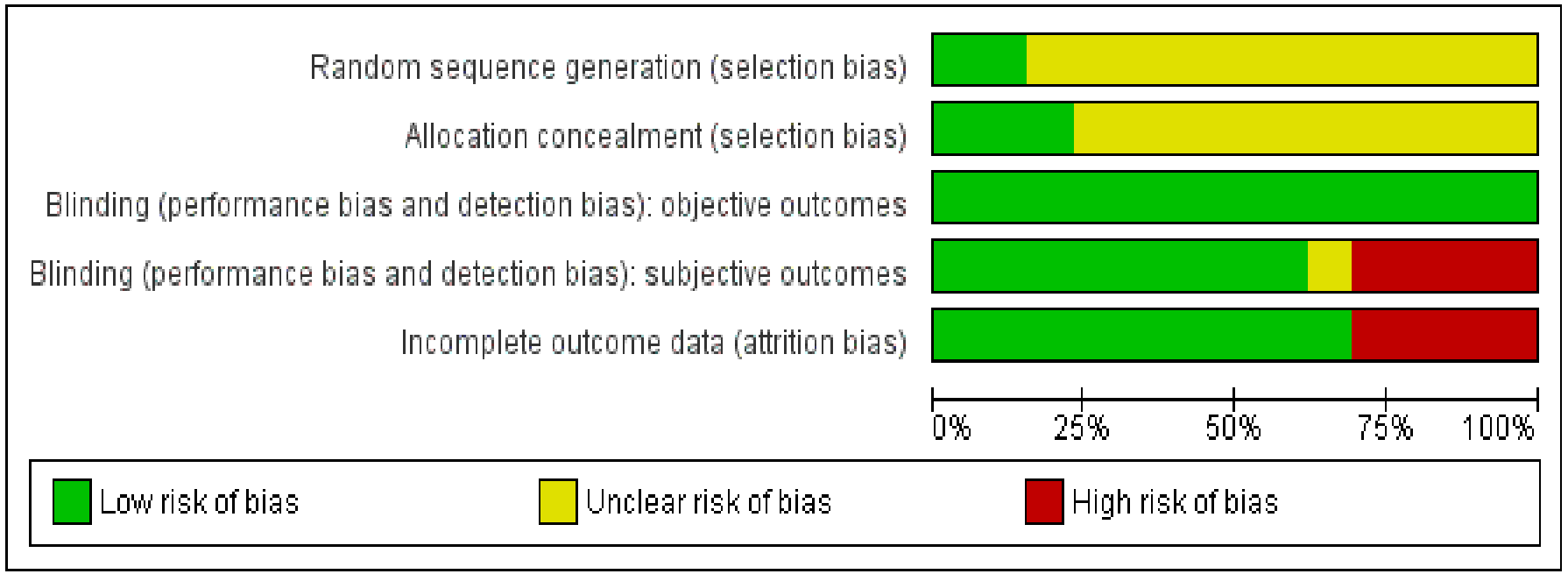
Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Low risk
Unclear risk
High risk

Footnotes

Summary results of risk of bias



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2