E350
Epidemiologie 2022

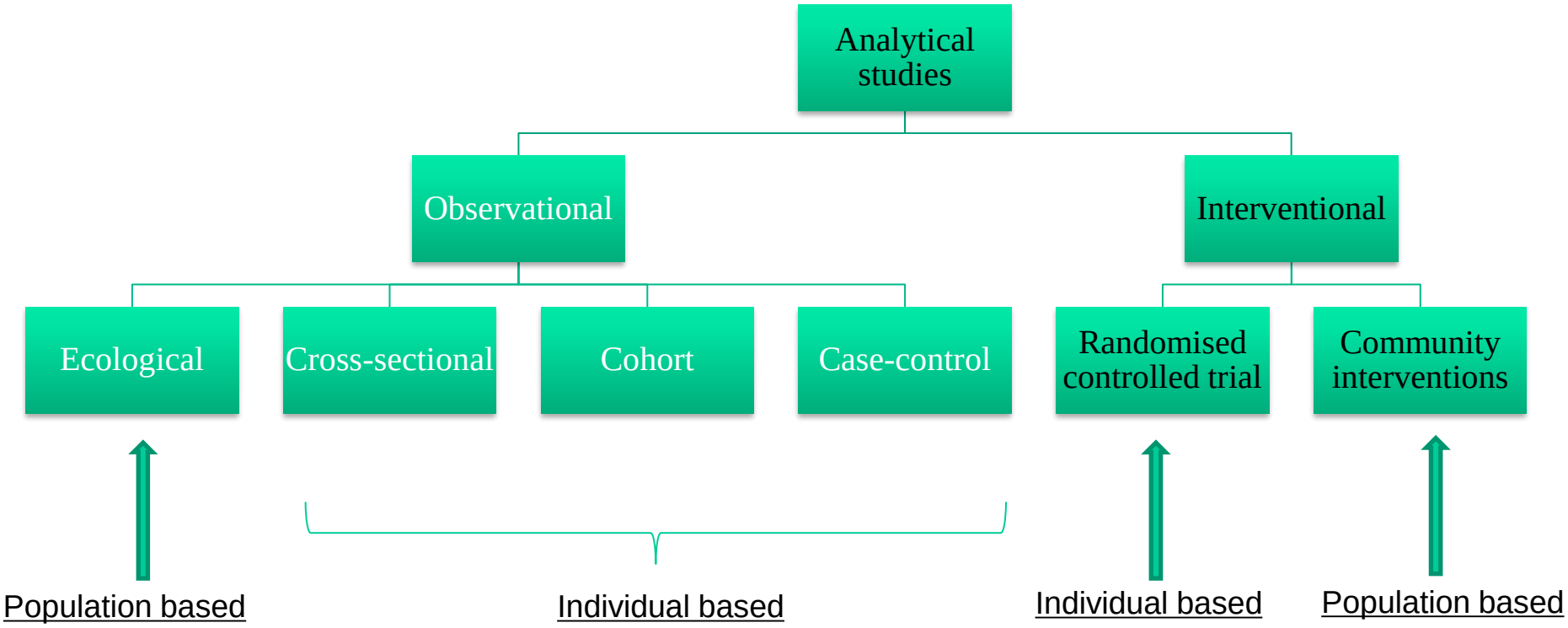
Intervenční studie
Mendelovská randomizace
Kritické hodnocení
Systematické přehledy literatury

Objectives

- Describe and understand the principles of
  - intervention studies,
  - Mendelian randomization
  - critical appraisal of evidence and systematic reviews
- Interpret results of these studies
- Describe a hierarchy of evidence
- Apply critical appraisal skills to examples of different studies

Interventional studies

Analytical studies



Main features of intervention studies

- An intervention study involves an **intentional change** in some aspect of environment or status of the subjects of the investigation.
- An intervention study is an EXPERIMENT intended to test a HYPOTHESIS
- Intervention studies differ from observational studies in that the researcher seeks to make **comparisons** (usually between two or more groups, but in some cases for the same group before and after) **that look at differences as a result of deliberate action rather than natural or found variation**.

Observation vs. Intervention studies

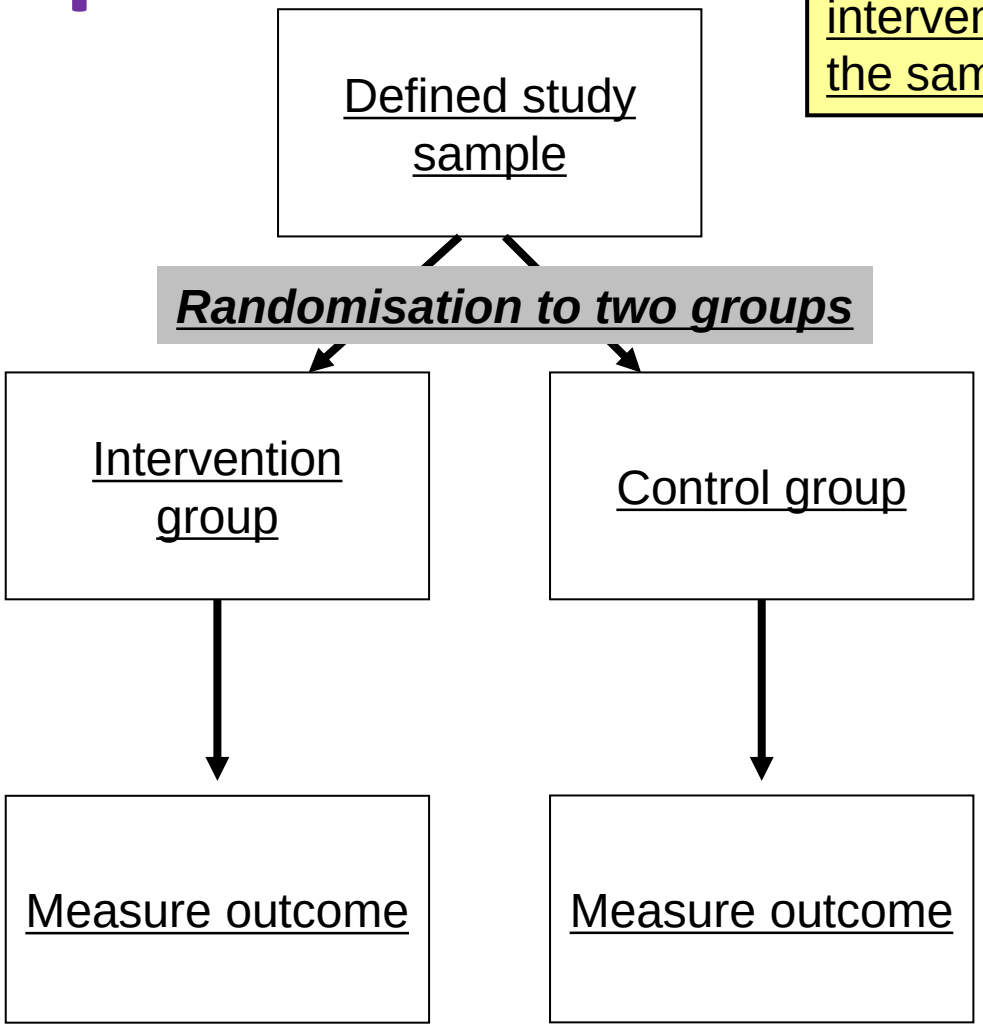
- **What is the difference between observation and intervention studies?**
  - Both can be used to compare differences between groups
  - Intervention studies involve exactly what they say; there is an intervention in one of the groups (at least). So, the research team does intervene rather than just observe the study participants

Randomised Controlled Trial (RCT)

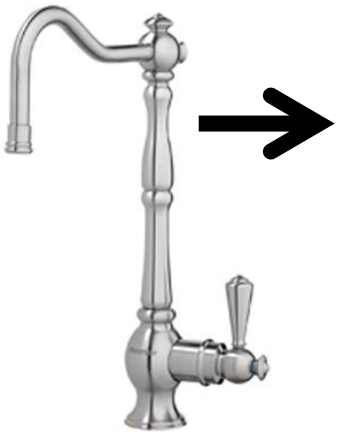
- A **randomised controlled trial (RCT)** is a type of perfect experiment.
- Participants are distributed on a strictly random or chance basis into **two groups** that do not differ in number or quality: the **control** and **intervention** groups.
- The **control group** receives no intervention or inactive or PLACEBO intervention or the “routine” care.
- The **intervention group** receives one single uniform intervention that we are testing.
- Groups should be equal apart from variable under test
- If the **condition (outcome)** inthe two groups **differs at the end** of the trial, then it **can only be the result of the intervention**.

The RCT concept

Everything except the intervention is (hoped to be) the same in the two groups



We may think experiments are done in a lab.



Bringing clean water to one village before another is also an experiment

Key issues in RCTs

- Careful entry criteria
- Assessment (Pre- & Post-intervention)
- Randomisation
- Allocation Concealment
- Blinding (Masking)
- Analysis – ITT
- Interpretation

Entry criteria

- Aim in any research is to draw conclusions about a population from a sample
- Representative sample

BUT

- In RCT participants often have a disease
- Participants must be able and willing to take part
- Compromise: exclusion criteria *vs.* ideal sample

Assessment

OUTCOME

- Careful selection of outcome
- Careful measurement of outcome
  - Reliability and responsiveness
  - Baseline assessments may prime participants

TIMING

- Sufficiently long after intervention to allow it to work
- Not so far after intervention that effect is lost
- Multiple follow-ups
  - Variation / change over time (short-term vs long-term)

Randomisation

- … is allocation of the units of analysis to the different experimental groups or conditions according to chance, such that each unit has an **equal probability of selection into each group**

- Most powerful way of ensuring characteristics **not** systematically allocated to a particular group

- Can randomise in groups (clusters)

The aim of randomisation is to…

create groups that are comparable with respect to known or unknown confounding factors

There are two steps in the process

1. Generating an **unpredictable** allocation sequence e.g. tossing a coin, using a computer random number generator
2. Concealing the allocation sequence from the investigators

Not always possible

Allocation concealment

- … is making sure that neither investigator nor patient can predict group assignment

Adequate methods

Off-site randomisation

Sequentially numbered, sealed, opaque envelopes

Not always possible!

Allocation concealment vs. Blinding: is there any difference?

- Allocation concealment: neither investigator nor participant can **predict** group assignment
- Blinding: neither investigator nor participant **knows** which group the participant is assigned to (double blinding); single blinding if only investigator is blinded
- How can you achieve this?
  - Allocation concealment: off-site randomisation
  - Blinding is not always feasible

Advantages of RCTs

- Experimental: groups treated similarly except intervention
- Randomisation: characteristics similarly distributed
- Blinding
  - patients
  - recorders
  - statisticians

Tells us difference at the end is due to intervention and not due to other factors (strong evidence for causation)

- ITT analysis

Prevents attrition bias

Gold-standard epidemiological study design to assess effectiveness of interventions

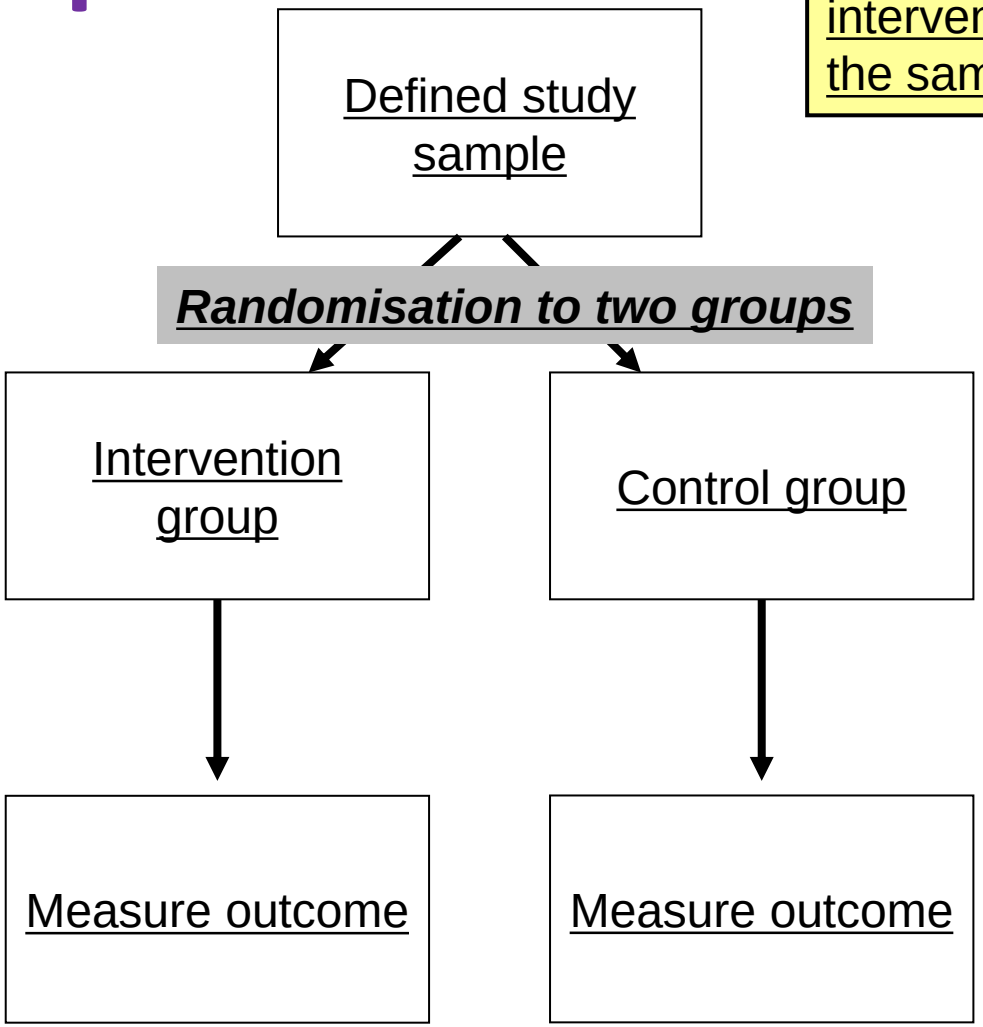
Summary

- Intervention studies are experiments (intentional change)
- RCTs are the gold-standard design for assessing the effectiveness of interventions
- Simple concept but many key features - need to carry out properly
- Randomisation is the most important, but others (generalisability/entry criteria, assessment, blinding, allocation concealment, ITT) also matter
- Not always applicable – PH interventions are more complex than a clear-cut simple experiment

Mendelian randomisation

The RCT concept

Everything except the intervention is (hoped to be) the same in the two groups



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Mendelian randomisation studies

Mendelian randomisation studies

- Observational design with (almost) RCT strengths
- Based on Mendel's second law: alleles of different genes assort independently of one another during gamete formation
- Inheritance of one trait should be independent of inheritance of other traits
- Genetic variant used as proxy for exposure is **unrelated** to conventional vascular risk factors and other disease marker

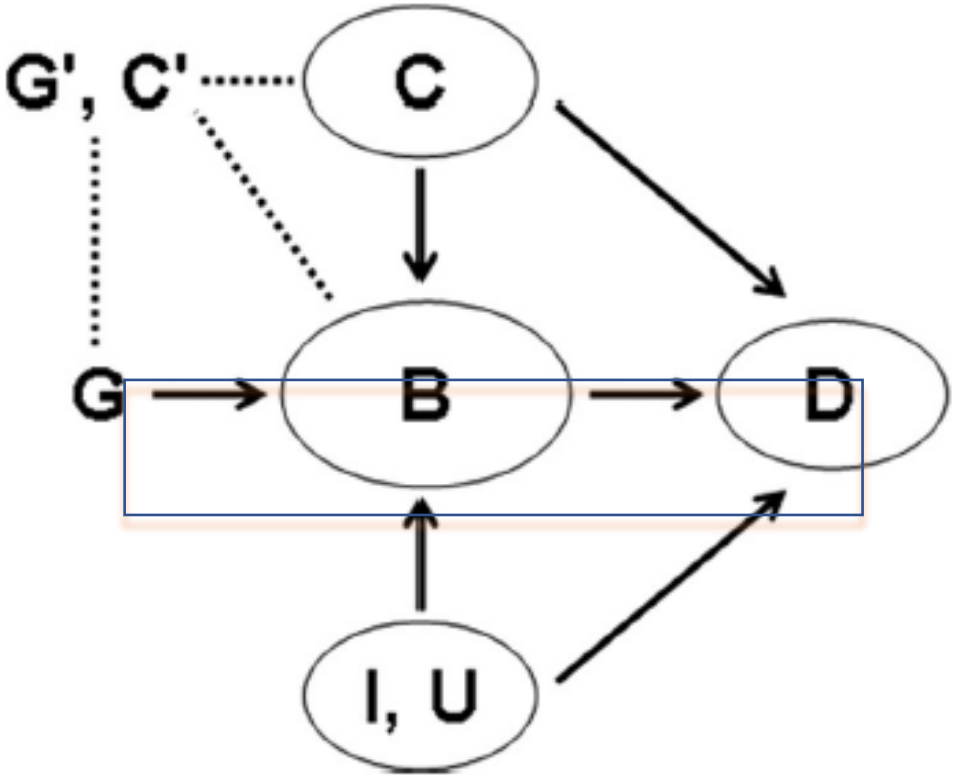
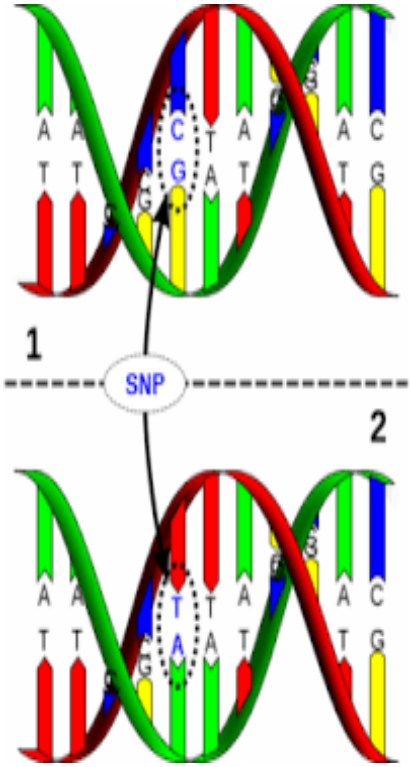


Fig. 1. Conceptualization of Mendelian randomization with interest in the relationship of a biomarker B with disease D with measured confounding variables C, unmeasured confounding variables U, unmeasured processes I affecting B and D, a polymorphism at a genetic locus G related to B, other genetic variants (G′) possibly related to G and B, and other individual characteristics (C′) possibly related to G, B, and D.

Glynn RJ,
Clinical Chemistry
56:3
388–390 (2010)

MR studies of biological or behavioural risk factors

- Identify genetic marker (often a SNP)
  - Associated with the risk factor
  - Not associated with the disease via other pathways (i.e. not associated with other risk factors)
- Estimate association between:
  - Genetic markers and RF
  - Observational RF and disease
  - Genetic marker and diseases
- Compare observational and MR associations
- Observational associations can be biased, confounded, MR should be unbiased

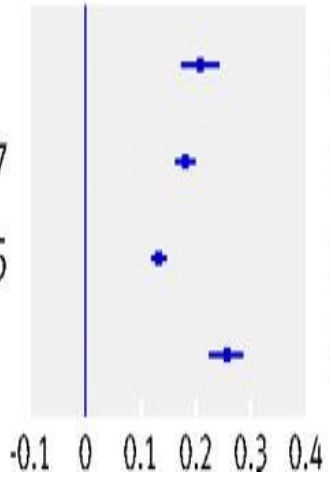


Example: CRP and cardiovascular disease

- Inflammation is associated with CVD
- C-reactive protein (CRP) is an inflammatory protein, is increased in inflammatory conditions (infection, chronic inflammations, injury-related inflammation etc)
- Easy and cheap to measure in blood
- Increased in patients with CVD
- Causal association?

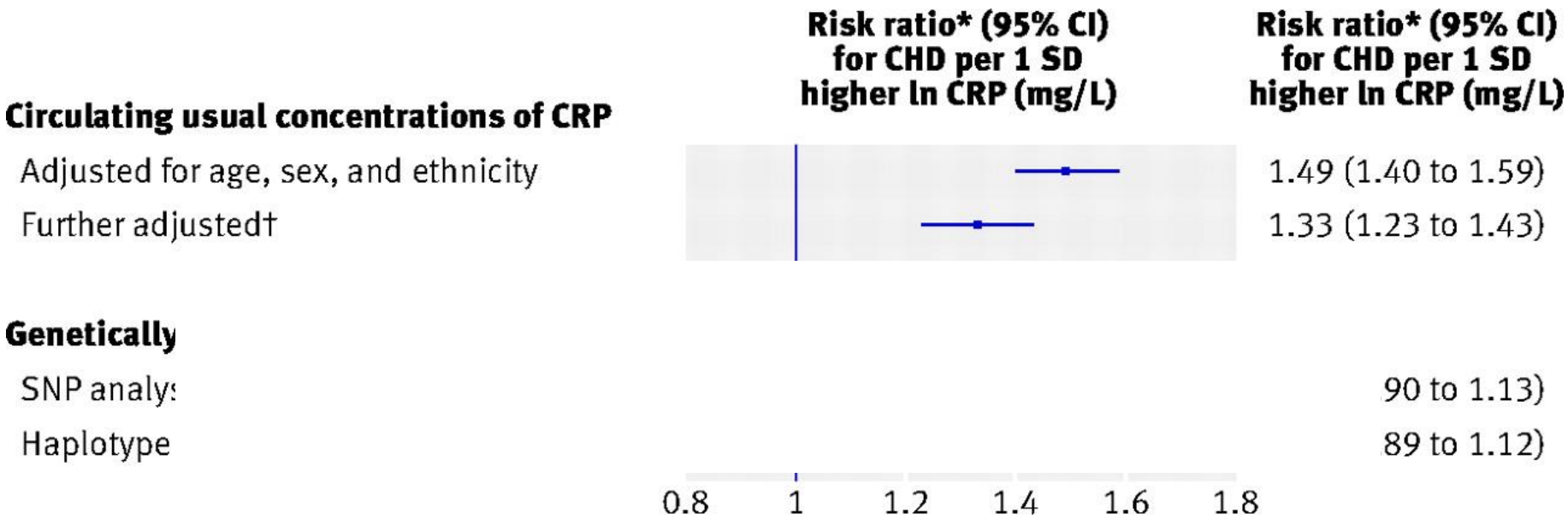
Estimates of association of each single nucleotide polymorphism with ln concentrations of C reactive protein

Single nucleotide polymorphism	Allele frequency*	No of studies/cases /participants†	Per allele higher mean ln CRP (95% CI), mg/L
rs3093077	0.06	19/15 133/96 807	
rs1205	0.67	43/40 527/172 567	
rs1130864	0.30	41/37 145/157 905	
rs1800947	0.94	31/31 636/93 507	



C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) BMJ 2011;342:bmj.d548

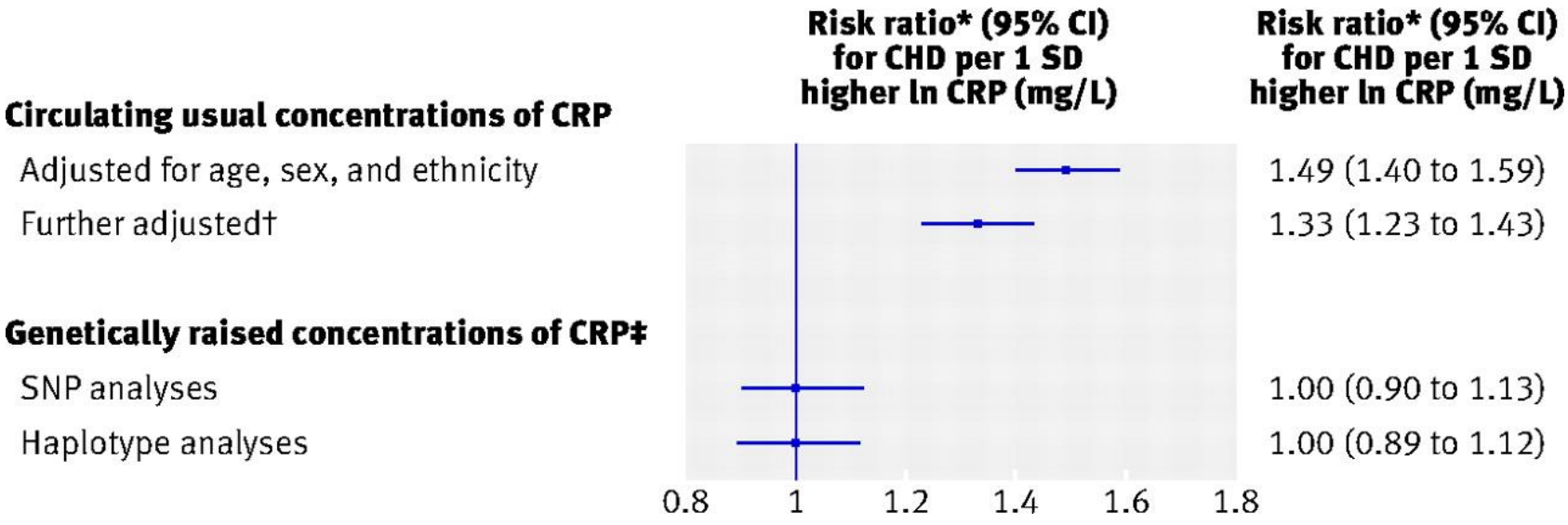
Association of circulating concentrations with risk of coronary heart disease (CHD)



***Corrected for regression dilution in C reactive protein and potential confounding factors**

C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) BMJ 2011;342:bmj.d548

Association of (1) circulating concentrations and (2) genetically raised concentrations of C reactive protein (CRP) with risk of coronary heart disease (CHD)



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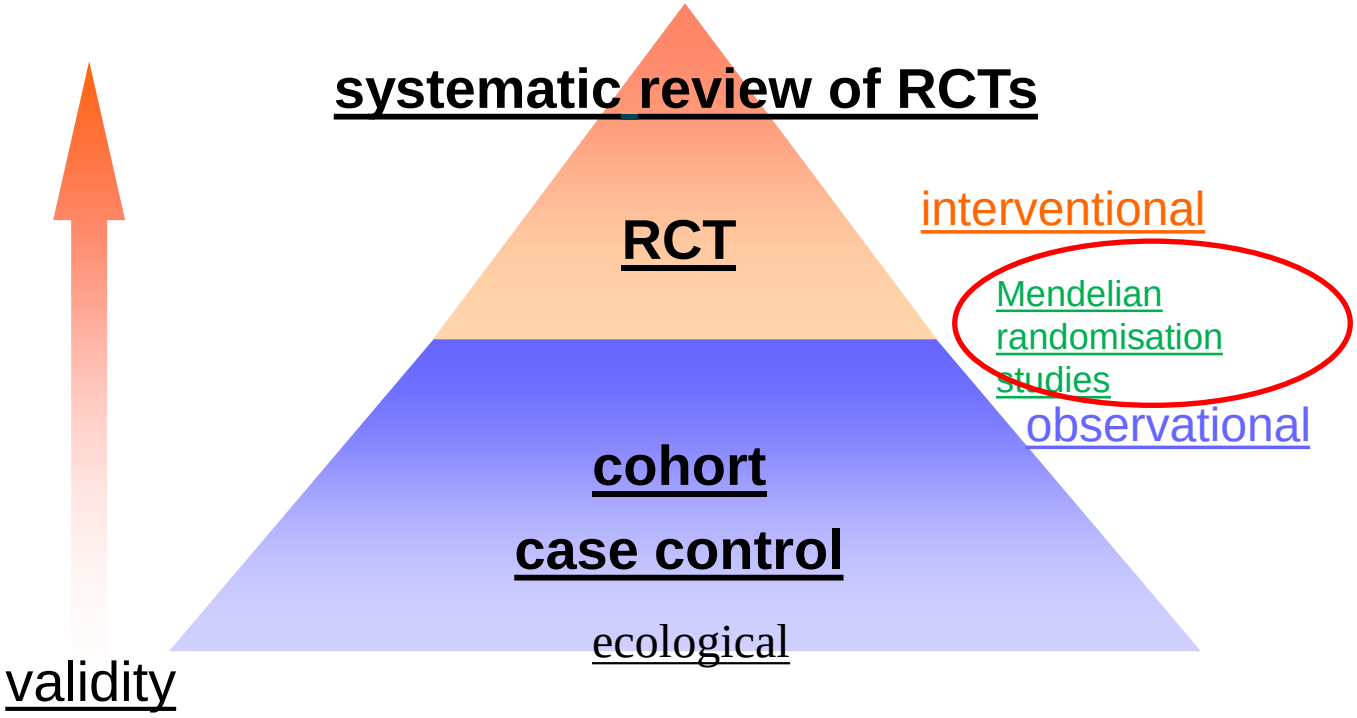
Assumptions / limitations

- A gene influences disease solely through B. This is unverifiable, as a single gene can influence disease risk through multiple pathways other than B (pleiotropy);
- Other alleles, G', may be correlated with G (linkage disequilibrium) and influence D through other pathways, thereby inducing confounding;
- Other characteristics of individuals at birth, C', that independently predict the development of D can be correlated with G (population stratification) or influence the expression of G (epigenetics),
- Both other alleles and patient characteristics can modify the effect of G on B, the effect of G on D, or both.

Types of comparisons in different types of studies

Study design	Type of comparison
Ecological studies	Comparing disease frequency between populations
Cross-sectional studies	Comparing disease frequency between persons with and without characteristic of interest
Cohort studies	Comparing disease incidence between exposed and unexposed persons
Case-control studies	Comparing frequency of (past) exposure between cases and healthy controls
Interventional studies	Comparing incidence of events in persons exposed to the intervention of interest and in control group
Mendelian randomisation	Comparing frequency of events in persons with and without genotype associated with exposure

hierarchy of major study designs



Critical appraisal

Introduction

- We frequently need evidence on which to base decisions about appropriate policy and how to spend public resources wisely
- Most of the same principles of appraisal apply for a other type of study and for policy appraisal
  - Evidence based medicine
  - Evidence based health policy
  - Evidence based …
- Sometimes there are few studies on a specific topic, other times there is large literature and many studies

What is critical appraisal?

“Critical appraisal is the process of carefully and systematically examining research to judge its trustworthiness, and its value and relevance in a particular context” (Burls 2009)

Why do we use critical appraisal?

Why do we use critical appraisal?

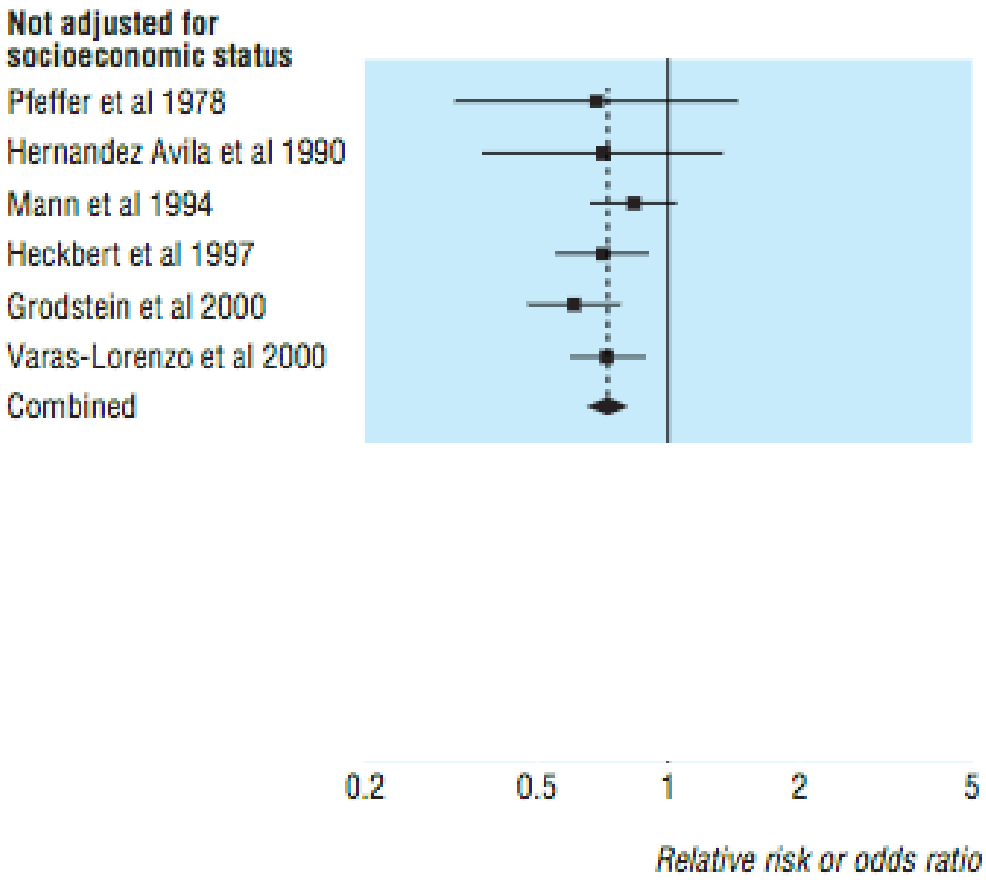
- Summarises and collates vast amount of research data
- To understand whether and how to apply findings from research, we need to assess quality, validity and applicability
- Informs clinical practice and public health policy
- Used to evaluate existing policy

What problems might exist in research?

What problems might exist in research?

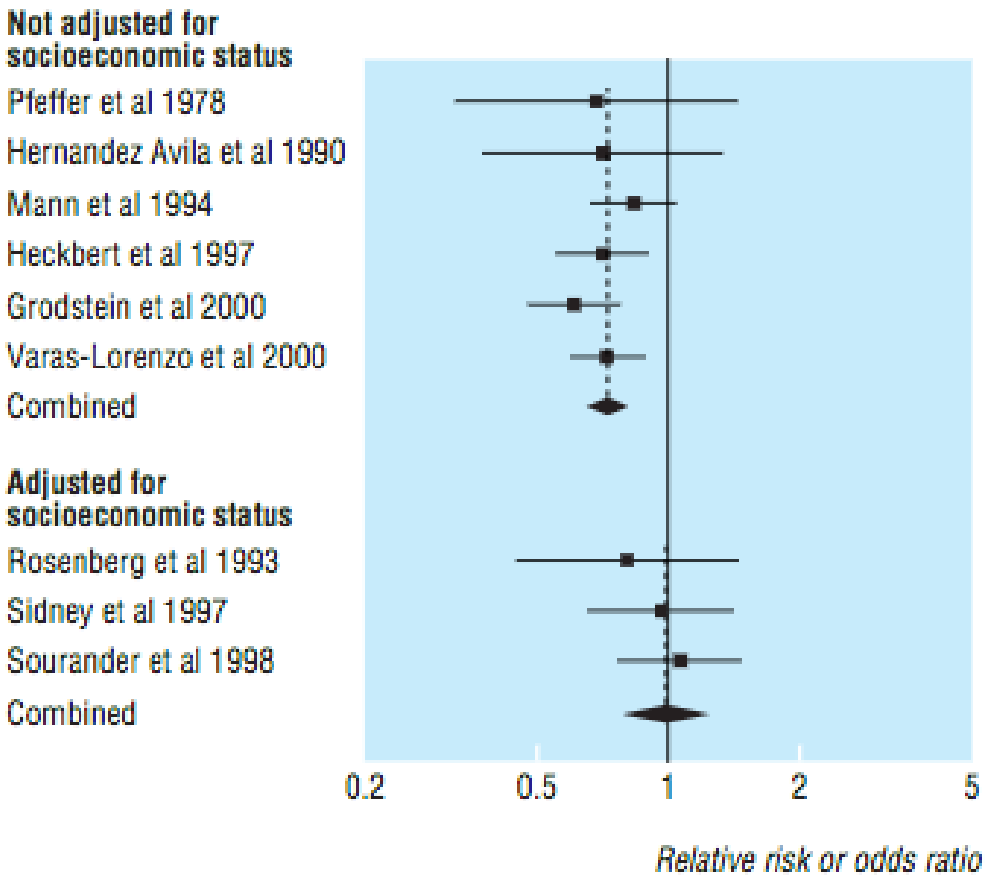
Deliberate research fraud is rare but research may have:

- Never been done
- Methodological limitations or inappropriate
- Poorly presented results
- Insufficient explanation of methods/results
- Misleading interpretation or conclusions
- Problems with generalisability
- Only been presented as a conference presentation / abstract



Meta-analysis of cohort studies and case-control studies of hormone replacement therapy and coronary heart disease. There is little evidence for a protective effect when analyses are adjusted for, in contrast to studies not adjusted for, socioeconomic status. Adapted from Humphrey et al, reference 7

http://www.bmj.com/content/bmj/329/7471/868.full.pdf



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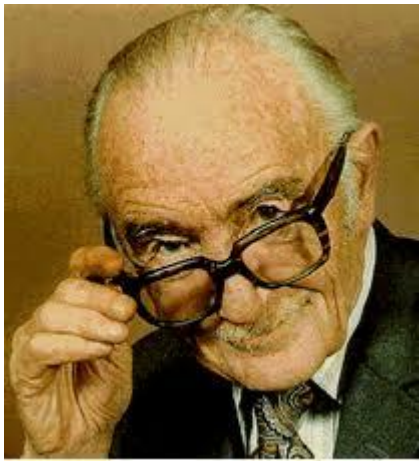
Cochrane.org

- International network with headquarters in the UK, a registered not-for-profit organization.

Purpose:

- To produce trusted and timely synthesized evidence addressing the most important questions for health decision making.
- There are now over 7,500 Cochrane Systematic Reviews published in the Cochrane Library.
- leading global advocate for evidence-informed health and health care.
- To inform health and care decisions by making evidence accessible, usable, and available to all.



Evidence-based medicine (EBM)

"Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."

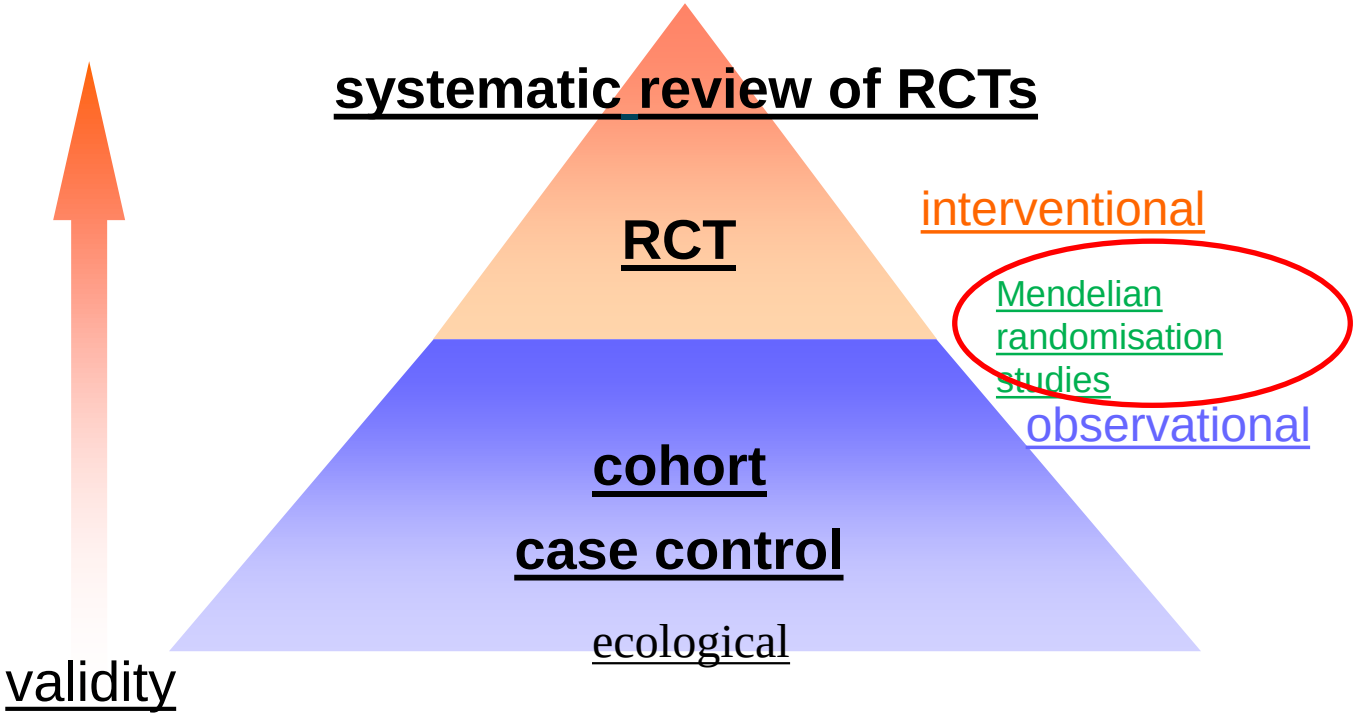
"No single study is sufficient for causal inference"

Sackett DL et al. Evidence-Based Medicine. 2nd edition. 2000. Churchill Livingstone. www.cebm.net

Putting research into context

- Single studies cannot be interpreted in isolation – we also need to evaluate existing literature relating to the question of interest
- Basing judgment about a particular intervention, treatment or 'risk factor' on only published material may lead to a biased picture because of *publication bias*
- Initiatives to compile information on all trials undertaken include:
  - **Cochrane collaboration - registers of trials and meta-analyses (www.cochrane.org)**
  - **"Amnesty" on unpublished trials, 1997**

hierarchy of major study designs



Tools for evaluating studies

- There are a number of guidelines/checklists for reporting and appraising different types of study designs:
  - **RCTs:** Consolidated Standards of reporting trials (CONSORT) www.consort-statement.org
  - **Observational studies:** Strengthening the reporting of observational studies in epidemiology (STROBE) www.strobe-statement.org
  - **Systematic reviews:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) www.prisma-statement.org
  - **All:** Enhancing the QUAlity and Transparency Of health Research (EQUATOR) www.equator-network.org

How do you do critical appraisal?

Consider…

- Central research question
- Study design
- Study population
- Exposures and outcomes
- Results and their interpretation
- Ethics
- Generalisability and public health implications

Appraisal of a single study

Central research question

- What is the central research question?
- Is it clear?
- Is it relevant?
- Does it contain a testable hypothesis?

Study design

- What is the study design?
- Is the study design appropriate for the question?
- Has it been properly carried out?
- Does it enable the central question to be answered?

Population

- What is the study population?
- How was the sample selected?
- What inclusion and exclusion criteria are used?
- How is this population and selection justified?

Exposures and outcomes

- What are the main exposures?
- What are the main outcomes?
- How are they defined and measured?
- Are there any problems in how this is done?

Results

- What is the main result?
- What is the size of effect?
- Is there a statistical difference?
- What sub-groups or secondary analyses have been considered?
- Are the results internally consistent and consistent with other literature?

Interpretation of results

- Chance
  - what is the study size and power?
  - Can the investigators exclude the role of chance?
- Confounding
  - Are appropriate confounders considered, measured and included in the analysis
- Bias
  - Selection of subjects into the study
  - Missing data (random / non-random) and follow-up
  - Measurement and procedure standardisation, validity and quality
- Causation

Appraisal of evidence from multiple studies

Types of review

- Systematic review

"the application of scientific strategies that limit bias by the systematic assembly, critical appraisal and synthesis of all relevant studies on a specific topic" (Cook et al, J Clin Epi 48:167-171)

- Narrative review

"summary of the information available to the author from the point of view of the author" (Kirkwood and Sterne, Essential Medical Statistics, p.372)

- Scoping review

"No universally accepted definition or purpose… allows for a more general question and exploration of the related literature, rather than focusing on providing answers to a more limited question"

(Peterson et al, J American Ass Nurse Practitioners, 29 (2017) 12-16)

Systematic reviews

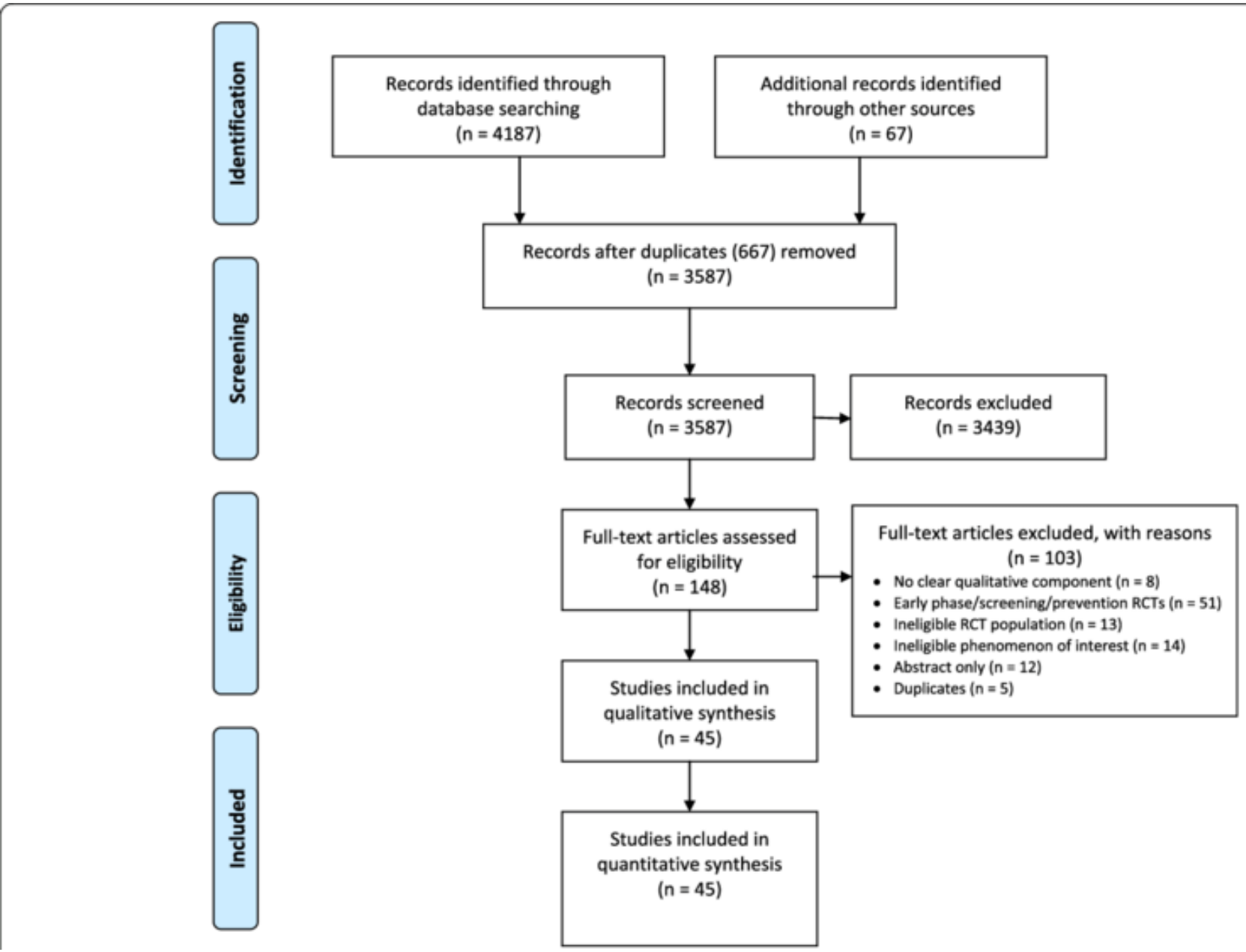
- Methods section with question
- Criteria for finding and including studies and extracting and analysing data (PRISMA diagram)
- Must be
  - Transparent
  - Replicable
  - Unbiased
- Two people to review studies
- Essential for developing evidence-based policy
- Big undertaking
- www.cochrane.org

Example of search strategy

(TITLE-ABS(precarity) OR TITLE-ABS(precariat) OR TITLE-ABS("precarious employment") OR TITLE-ABS("precarious work") OR TITLE-ABS("employment security") OR TITLE-ABS("employment insecurity") OR TITLE-ABS("secure employment") OR TITLE-ABS("insecure employment") OR TITLE-ABS("job security") OR TITLE-ABS("job insecurity") OR TITLE-ABS("low pay no pay cycle") OR TITLE-ABS("flexible labo*r") OR TITLE-ABS("dual labo*r") OR TITLE-ABS("temporary employment") OR TITLE-ABS("temporary contract*") OR TITLE-ABS("zero hour contract*") OR TITLE-ABS("gig economy") OR TITLE-ABS("contingent work*") OR TITLE-ABS("contingent employment") OR TITLE-ABS("secondary labo*r market") OR TITLE-ABS(flexicurity) OR TITLE-ABS("non-standard work") OR TITLE-ABS("non-standard employment") OR TITLE-ABS("non-standard contract*") OR TITLE-ABS(underemployment) OR TITLE-ABS("atypical work") OR TITLE-ABS("casual work*") OR TITLE-ABS("casual employment") OR TITLE-ABS("casual labo*r") OR TITLE-ABS("non-permanent employ*") OR TITLE-ABS("non-permanent work*") OR TITLE-ABS("exclusionary employment") OR TITLE-ABS("employment history*") OR TITLE-ABS("employment trajectory*") OR TITLE-ABS("employment transition*") OR

From Pulford et al, JECH, Nov 2022

Systematic review flowchart

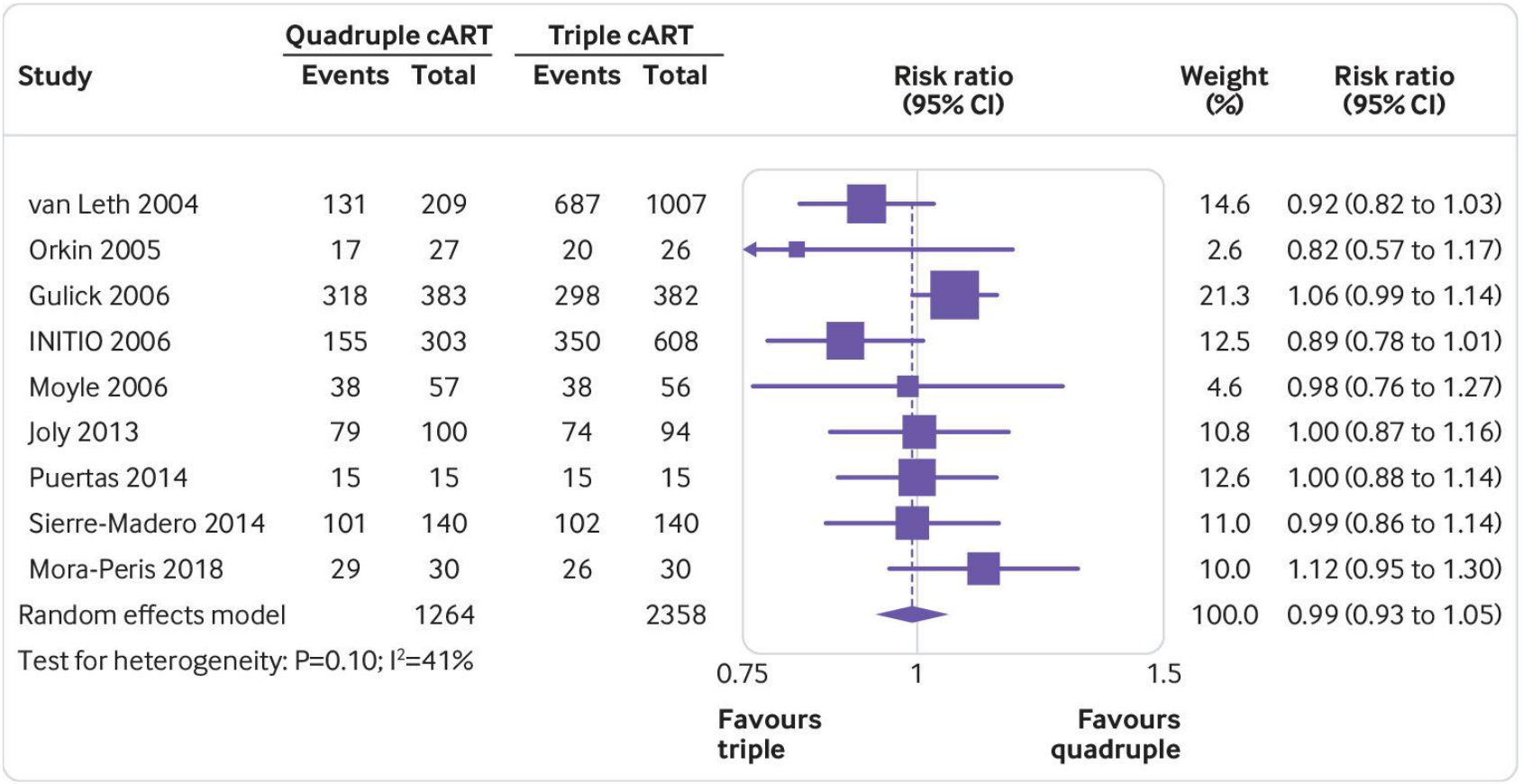


Meta-analysis

- Quantitative extension of systematic review approach
- Statistical methods for combining results of a number of published studies (particularly RCTs)
- Findings weighted by study size (and quality?)
- Is an association **consistent** in the literature?
  - Can a finding be replicated in different populations and types of studies?
  - Less likely that same biases / confounders are present in studies with different designs

Forest plot

Meta-analysis of comparative effects between quadruple and triple combination antiretroviral therapies (cART) as first line treatment for people with HIV, on undetectable HIV-1 RNA, from BMJ 2019;366:l4179



Study	Quadruple cART Events	Quadruple cART Total	Triple cART Events	Triple cART Total	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
van Leth 2004	131	209	687	1007		14.6	0.92 (0.82 to 1.03)
Orkin 2005	17	27	20	26		2.6	0.82 (0.57 to 1.17)
Gulick 2006	318	383	298	382		21.3	1.06 (0.99 to 1.14)
INITIO 2006	155	303	350	608		12.5	0.89 (0.78 to 1.01)
Moyle 2006	38	57	38	56		4.6	0.98 (0.76 to 1.27)
Joly 2013	79	100	74	94		10.8	1.00 (0.87 to 1.16)
Puertas 2014	15	15	15	15		12.6	1.00 (0.88 to 1.14)
Sierre-Madero 2014	101	140	102	140		11.0	0.99 (0.86 to 1.14)
Mora-Peris 2018	29	30	26	30		10.0	1.12 (0.95 to 1.30)
Random effects model		1264		2358		100.0	0.99 (0.93 to 1.05)

Test for heterogeneity: P=0.10; I^2=41%

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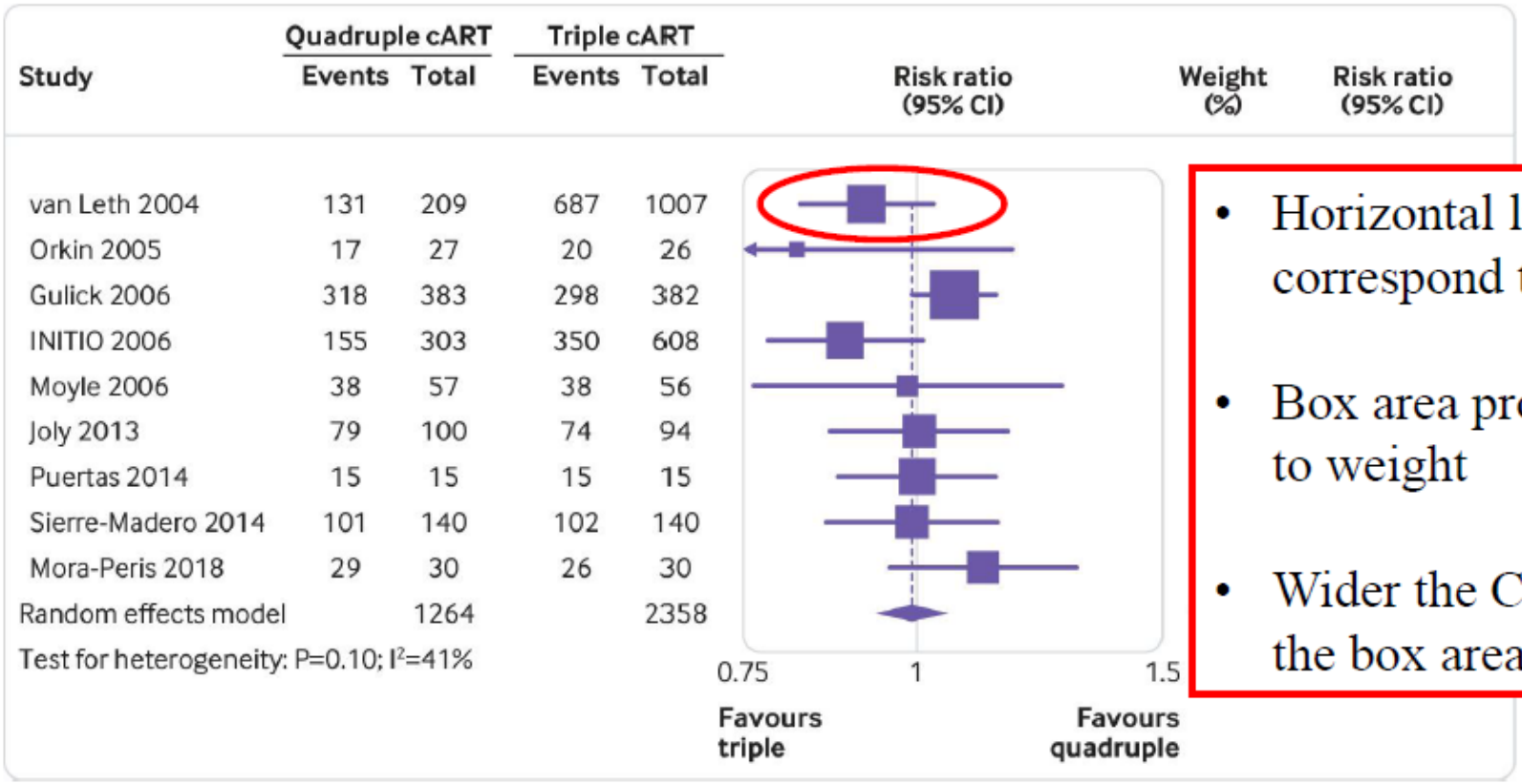
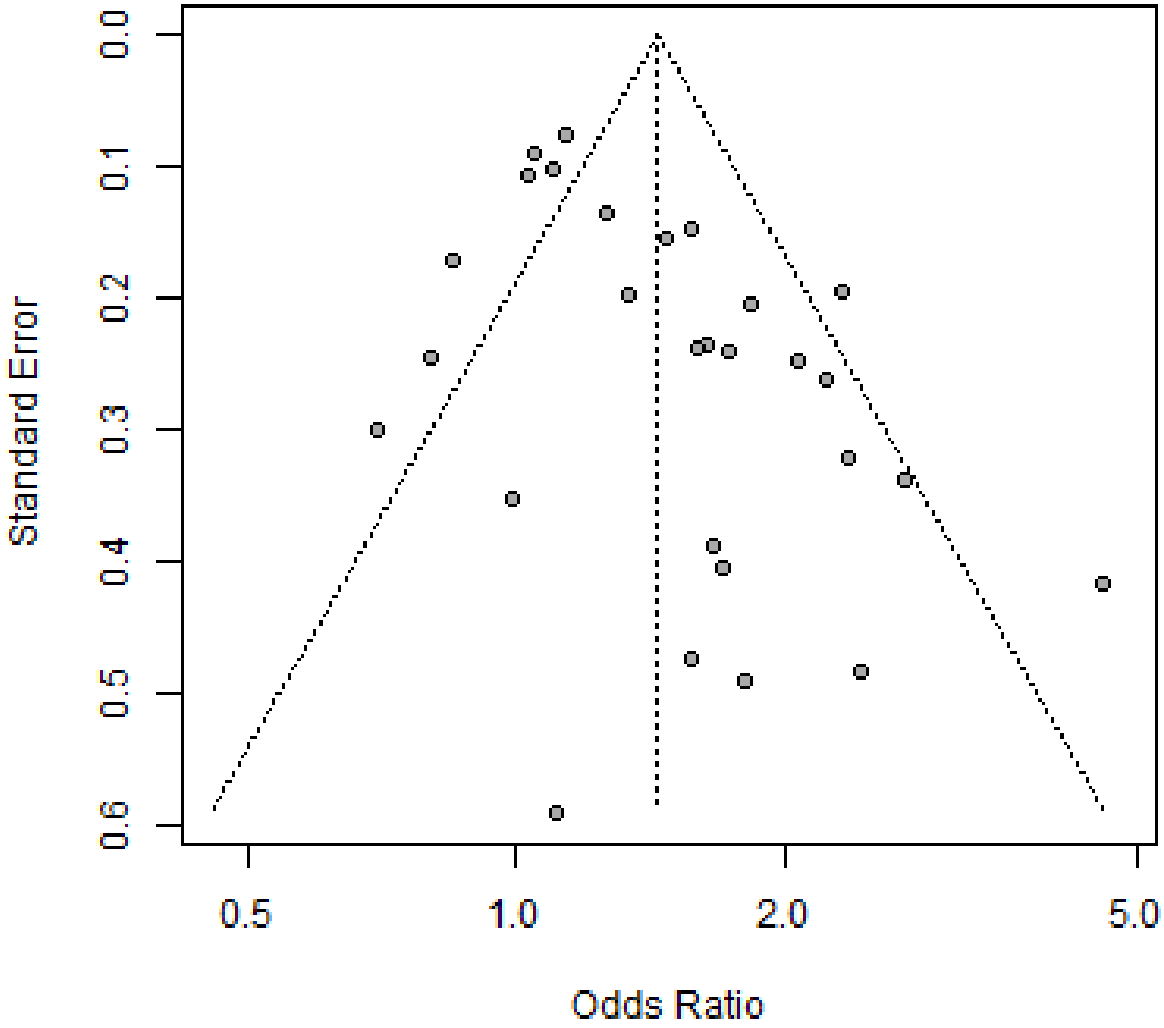


- Horizontal lines correspond to 95% CI
- Box area proportional to weight
- Wider the CI, smaller the box area

Potential limitations - Publication bias

- Statistically significant results are *more* likely to be published than statistically non-significant results
- Hence published studies may offer over-optimistic view of benefits of treatment
- Publication bias occurs especially for small studies

Funnel plot from a meta-analysis



What are the public health implications?

- Generalisability of the population and setting and intervention?
- Consider all important outcomes (exposure, outcome, covariates)
- Advantages and disadvantages
- Application in public practice
- How does this study fit with the existing research base?

In a nutshell

- Is the study valid?
- What are the results?
- Are the results useful?

Summary – critical appraisal

- Important to use a structured approach to assess the strengths and weaknesses of a paper
- Consider and be aware of all potential biases, confounders and role of chance when interpreting results of studies
- It is easy to find fault with all medical research studies
- The important thing to consider is whether the study is sufficiently well performed that you believe the results