Criteria of the research (article) to be published in international peer review journal”
Workshop

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Associate Editor Journal of Sexual Medicine

Think first

- What is the purpose of my article?
- Is it an important question my study deals with
- Why is it important to investigate or examine the subject of the article?
- Do I have a clear research question ?
- Have others already done this work? Is my work original
- Which are the methods best suited for my research question ?
- Are there different methods suitable?
- What types of statistics would I need ?
- Based on the necessary numbers is my study feasible ?
- What do I claim to have found out? Are the findings clearly stated?
- How does this advance knowledge in the field?

You are the reviewer
First Read Considerations

Keep a pen and paper handy when skim-reading.

Try to bear in mind the following questions - they'll help you form your overall impression:

- What is the main question addressed by the research? Is it relevant and interesting?
- How original is the topic? What does it add to the subject area compared with other published material?
- Is the paper well written? Is the text clear and easy to read?
- Are the conclusions consistent with the evidence and arguments presented? Do they address the main question posed?
- If the author is disagreeing significantly with the current academic consensus, do they have a substantial case? If not, what would be required to make their case credible?
- If the paper includes tables or figures, what do they add to the paper? Do they add understanding or are they superfluous?

A writer‘s and reviewer‘s guide

- **Problem statement**
- **Review of the literature**
- **Purpose, aims, hypothesis**
- **Method**
  - **Sample**
    - **Size, relationship to population**
    - **Selection Recruitment**
  - **Design**
    - **Type of Study; relationship between variables (independent, dependent)**
  - **Data collection**
    - **Instruments for outcome measures**
    - **Application**
  - **Data analysis**
    - **Statistical tests level of significance**
- **Results**
  - **Clear and understandable writing and visualization**
  - **Importance and validity**
- **Discussion:**
  - **Findings and interpretation**
  - **Strength and weaknesses**
  - **Differences and similarities in relation to other studies**
  - **Open questions and future research**
  - **Conclusion**

The Introduction

A well-written introduction:

- Sets out the argument
- Summarizes recent research related to the topic
- Highlights gaps in current understanding or conflicts in current knowledge
- Establishes the originality of the research aims by demonstrating the need for investigations in the topic area
- Gives a clear idea of the target readership, why the research was carried out and the novelty and topicality of the manuscript

Originality and Topicality

Originality and topicality can only be established in the light of recent authoritative research. For example, it's impossible to argue that there is a conflict in current understanding by referencing articles that are 10 years old.

Authors may make the case that a topic hasn't been investigated in several years and that new research is required.

This point is only valid if researchers can point to recent developments in data gathering techniques or to research in indirectly related fields that suggest the topic needs revisiting. Clearly, authors can only do this by referencing recent literature. Obviously, where older research is seminal or where aspects of the methodology rely upon it, then it is perfectly appropriate for authors to cite some older papers

- Editors say, *"Is the report providing new information; is it novel or just confirmatory of well-known outcomes*?"

Aims

It's common for the introduction to end by stating the research aims. By this point you should already have a good impression of them - if the explicit aims come as a surprise, then the introduction needs improvement.

Take your time to come to a clear formulation of your research aim. The best way is to put it into the form of a research question !!!!!!!!!

- **Describing a population**
- **Finding associations**
- **Testing a hypothesis**
- **Looking for causality**

Materials and Methods

Sample

- Size, relationship to population
- Selection Recruitment

Design

- Type of Study; relationship between variables (independent, dependent)

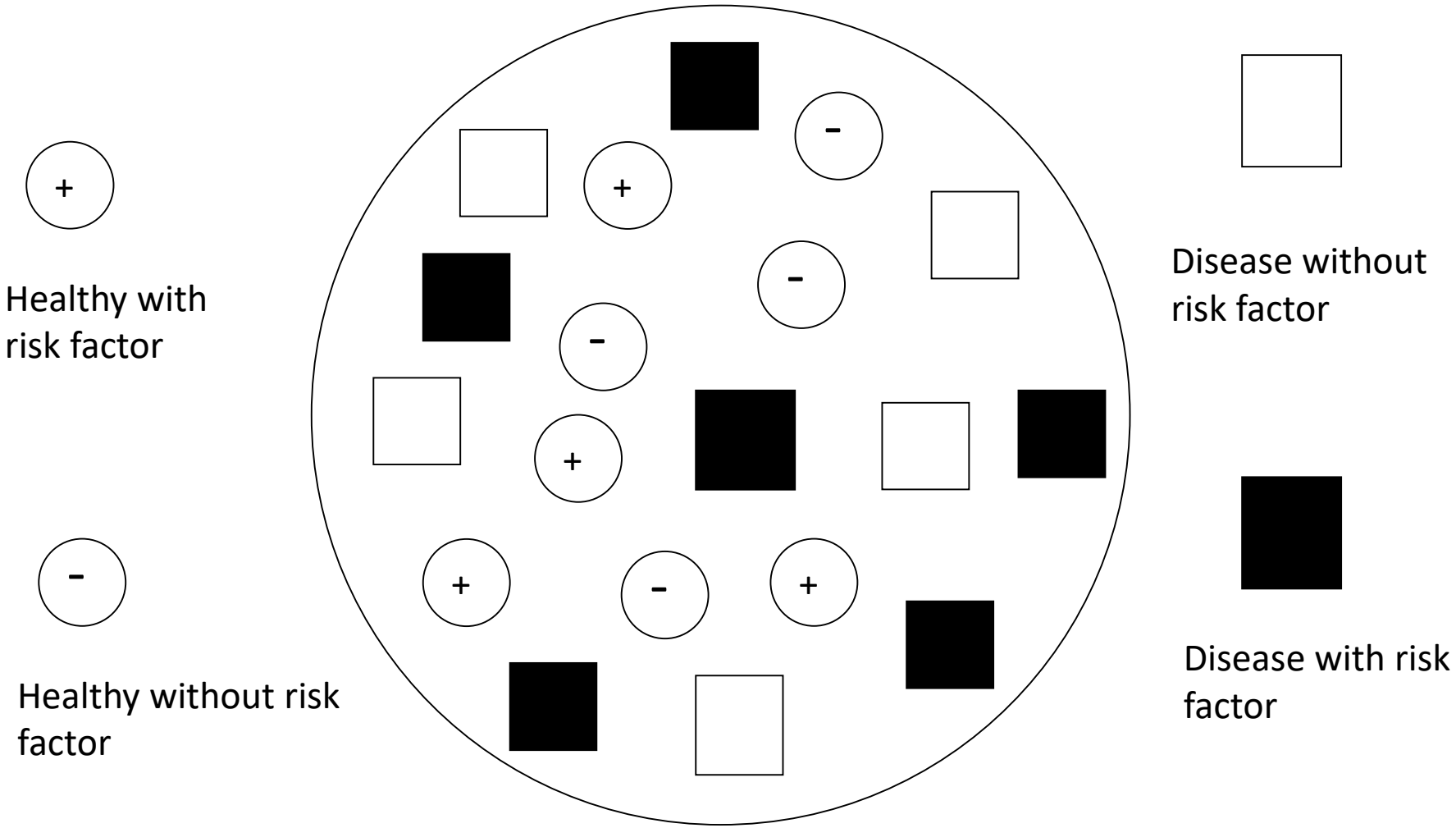
Data collection

- Instruments for outcome measures
- Application

Data analysis

- Statistical tests level of significance

Cross Sectional – Prevalence study



Cross Sectional – Prevalence study

- Quick and easy access to data
- Description of frequency
- Can be the start for the fromulation of an hypthesis

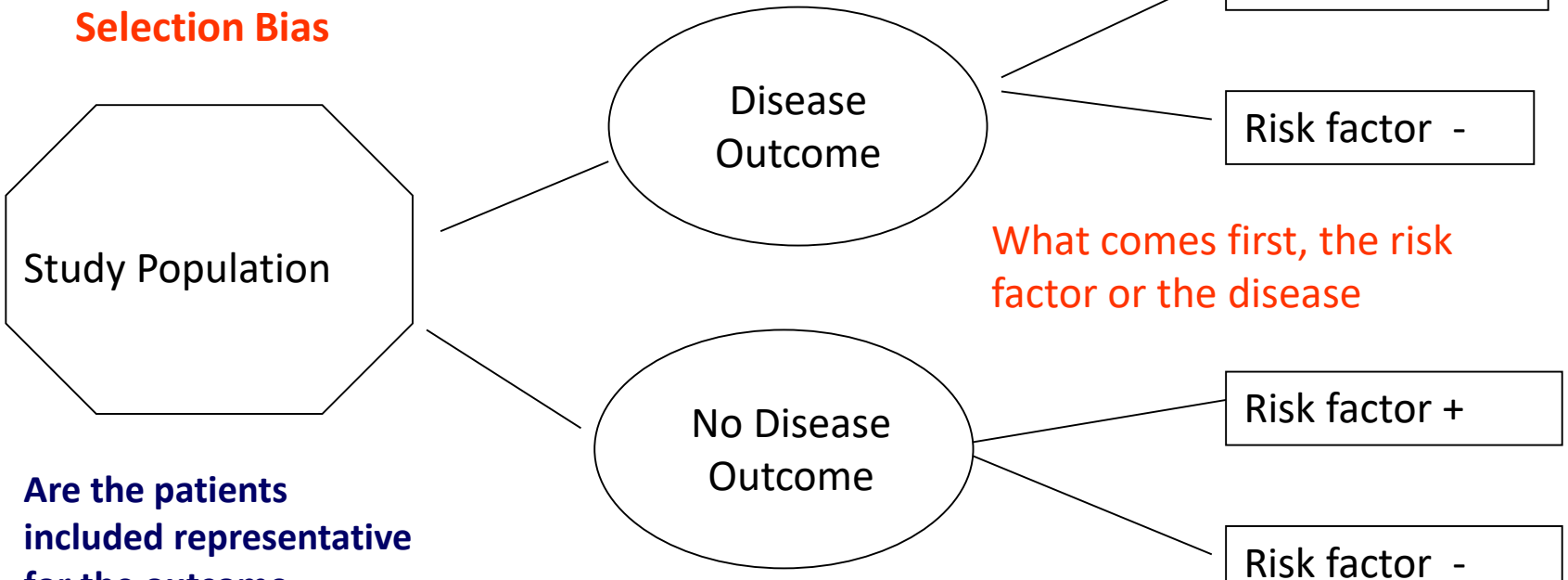
Start

Measure, Compare

Recall Bias

Information Bias

Population and Selection Bias



What comes first, the risk factor or the disease

Are the patients included representative for the outcome (disease) ? What about prevalence and incidence

Restrospective data collection with missing data

Do healthy and ill patients remember the same way ?

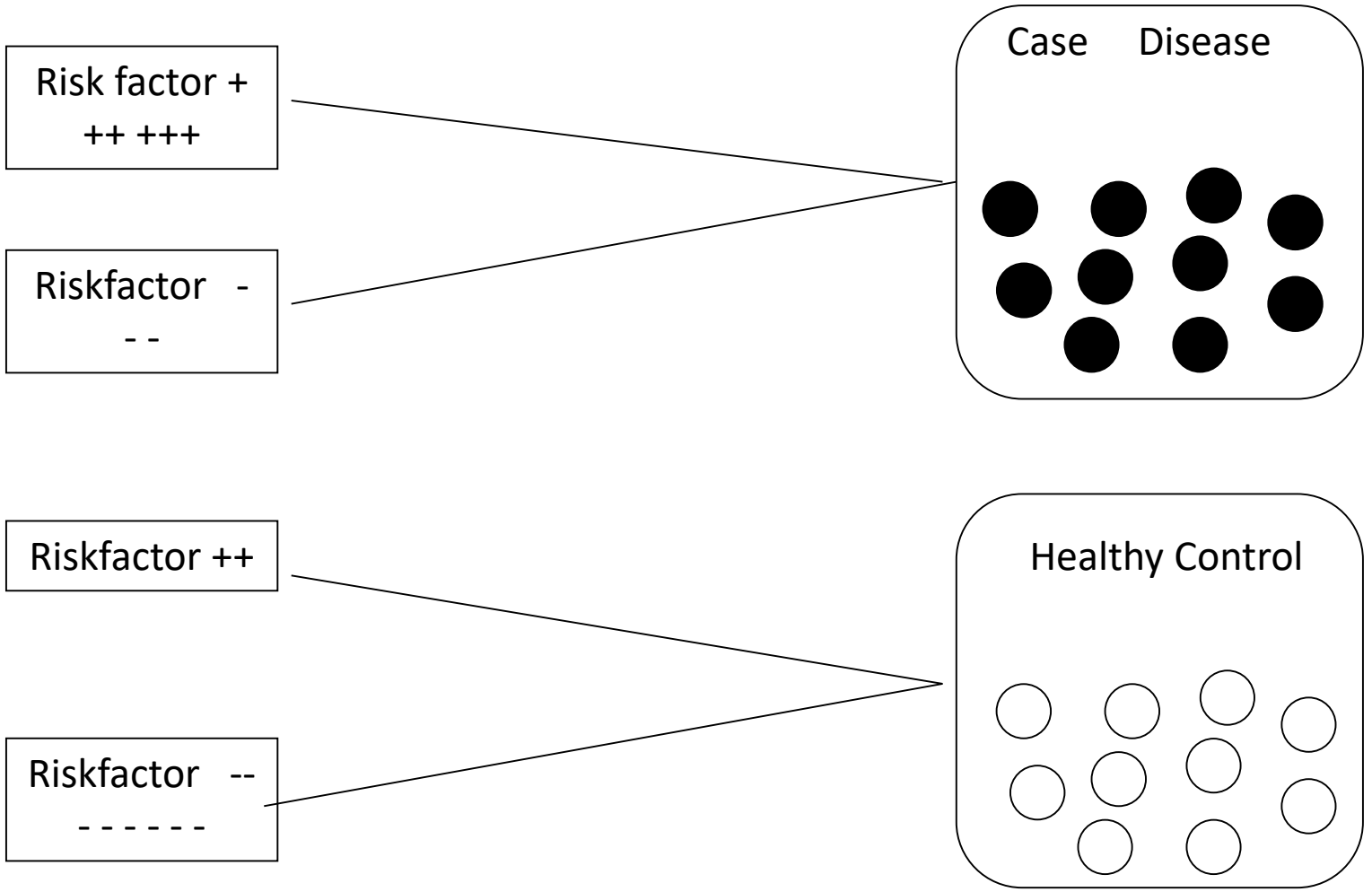
Present

Cross sectional

Cross Sectional – Prevalence Study

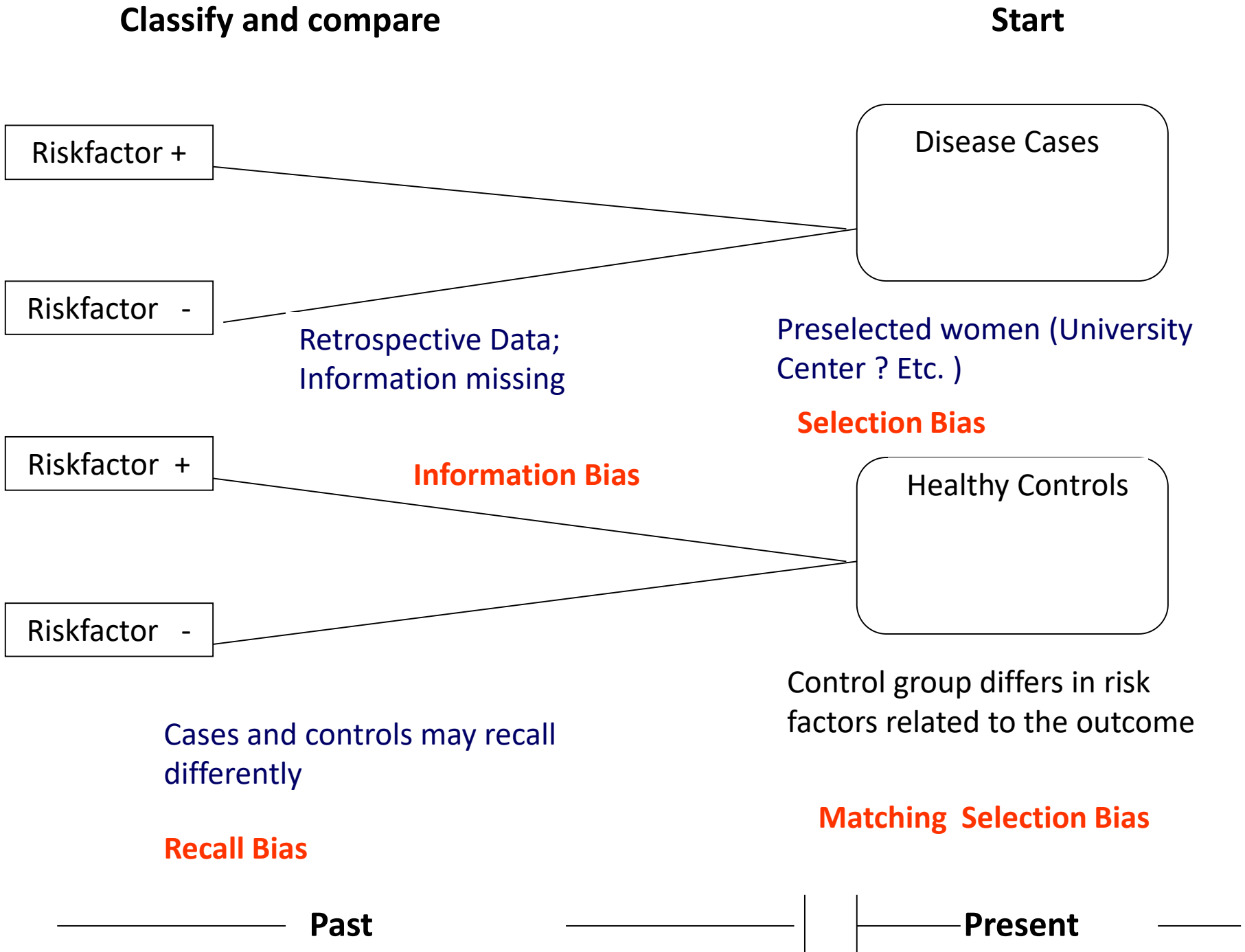
- Difficult to compare because incidence and prevalence are mixed
- Only hypothesis formation, no prove for association.
- Caveat:
  - Selection Bias
  - Information Bias
  - Recall Bias

Case Control



Case Control

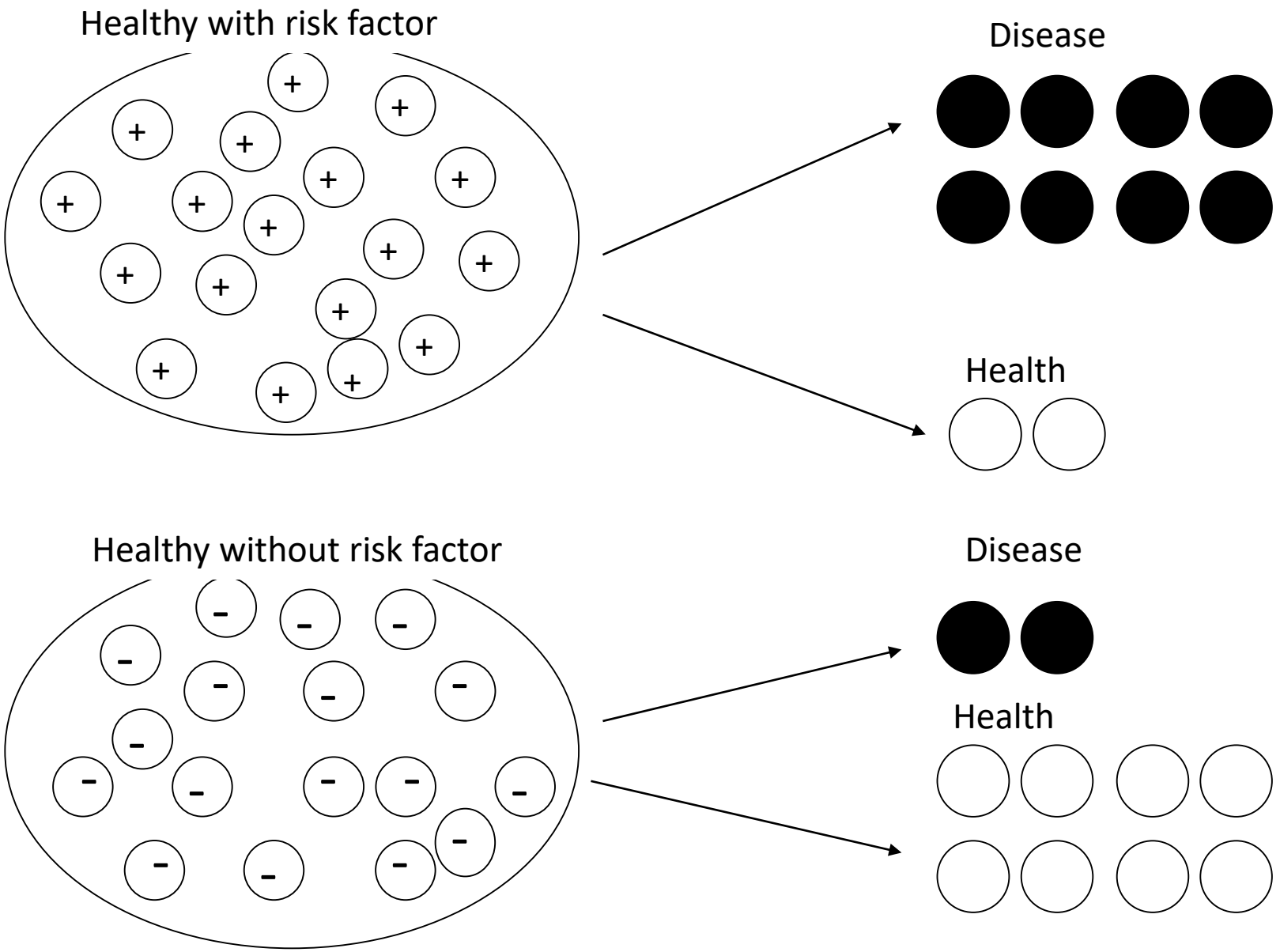
- Rare diseases can be studied
- Some explanatory power
- Quick access to data
- Not expensive
- Several risk factors can be examined at the same time


Classify and compare
Start
Riskfactor +
Riskfactor -
Disease Cases
Retrospective Data;
Information missing
Preselected women (University Center ? Etc.)
Selection Bias
Riskfactor +
Information Bias
Healthy Controls
Riskfactor -
Control group differs in risk factors related to the outcome
Cases and controls may recall differently
Matching Selection Bias
Recall Bias
Past
Present

Case Control

- Selection of cases:
  - Are cases representative for the population with the outcome ?
- Selection of controls
  - Controls should come from the same population and should be different from cases only by the characteristic of disease
    - Patients with different diseases
    - Random sample of the population
    - Friends of relatives of the case
- Caveat:
  - Matching Selection Bias
  - Recall Bias

Cohort Study



Cohort Study

- Prospective data collection; risk factor comes before outcome etc.
- Allows observation of incidence instead of prevalence
- Rare and multiple risk factors can be studied

Start

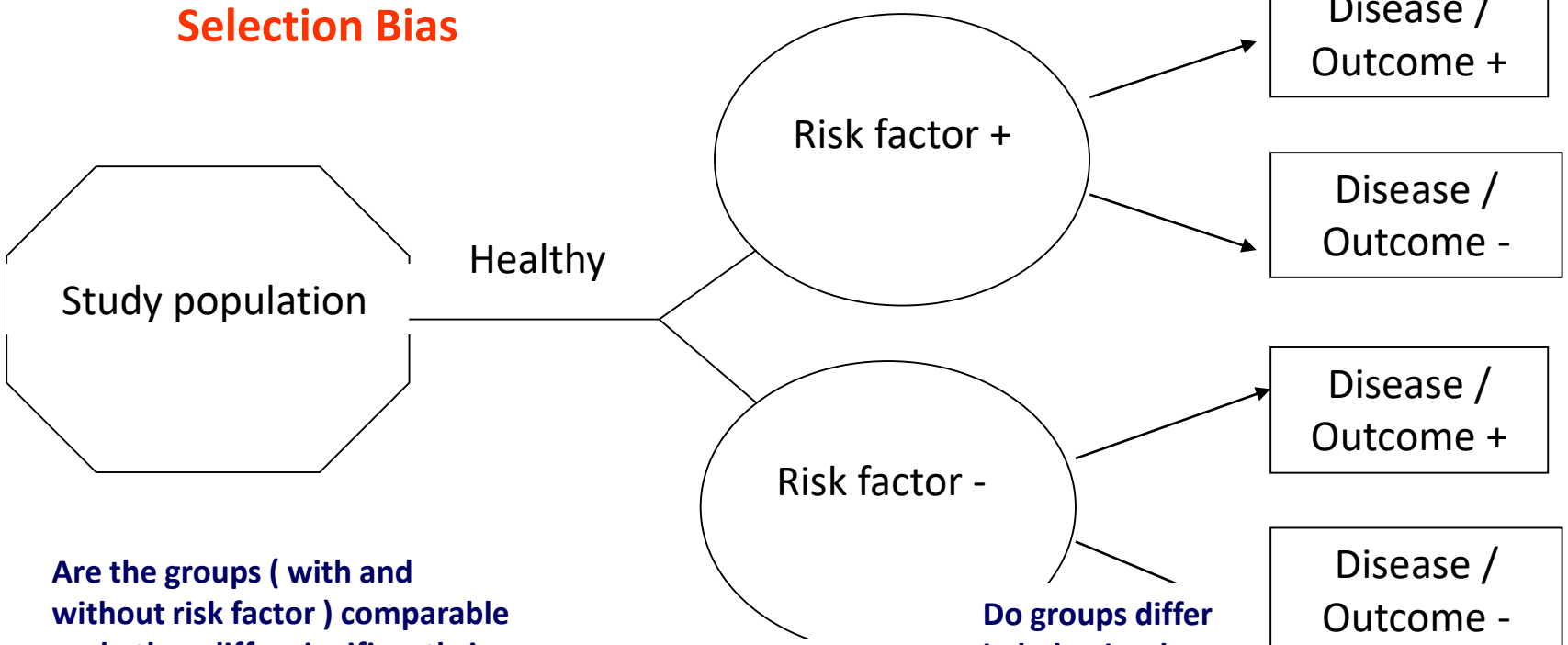
Measure classify

Messen, Vergleichen

Attrition and Surveillance Bias,

Detection Bias

Selection Bias



Are the groups (with and without risk factor) comparable or do they differ significantly in factors related to the outocme

Do groups differ in the loss to follow up

Do groups differ in behavioral changes that are related to the outcome

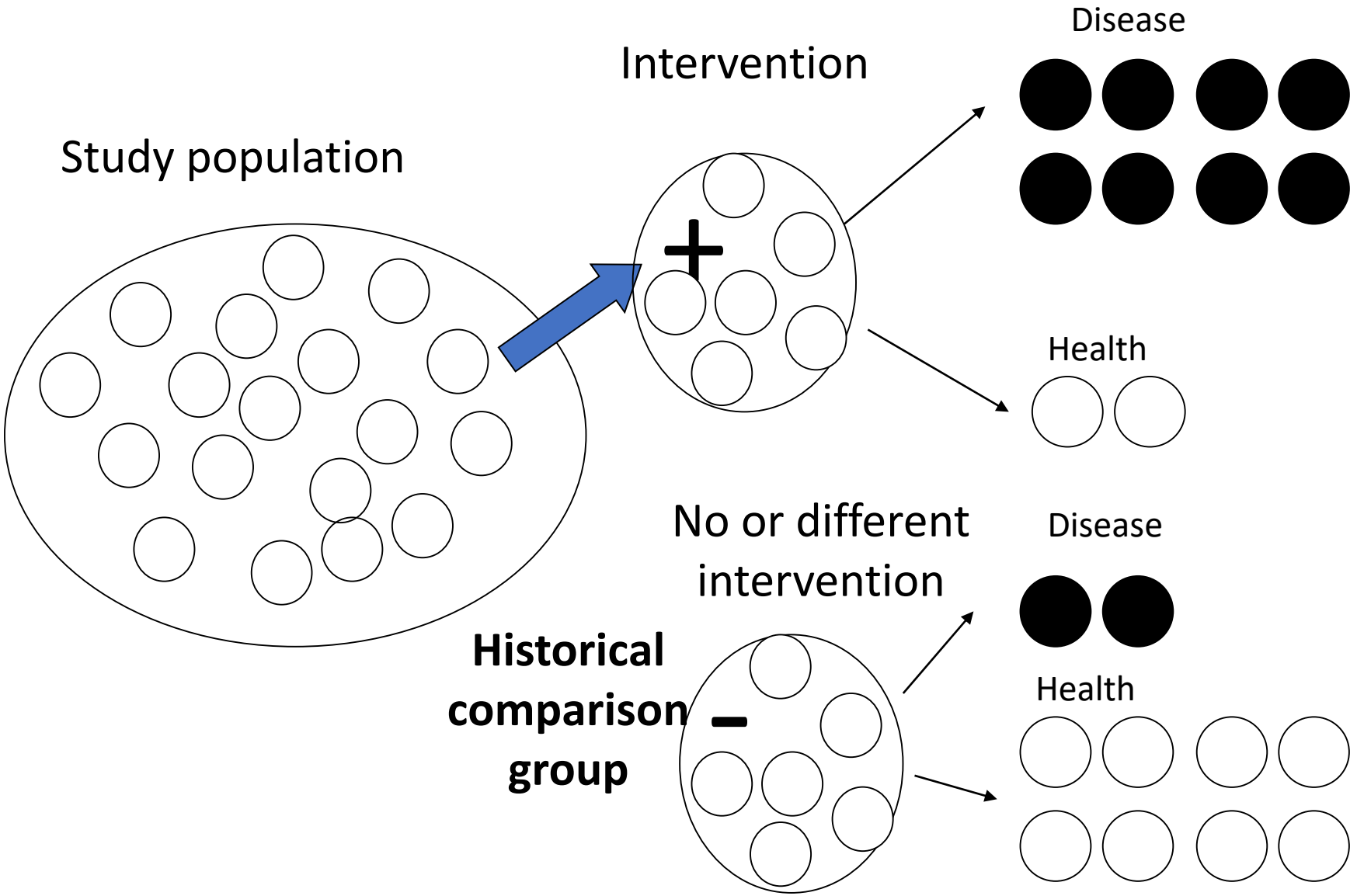
Are both groups examined with teh same frequency by the same quality

PRESENT — Quality of observation — Future

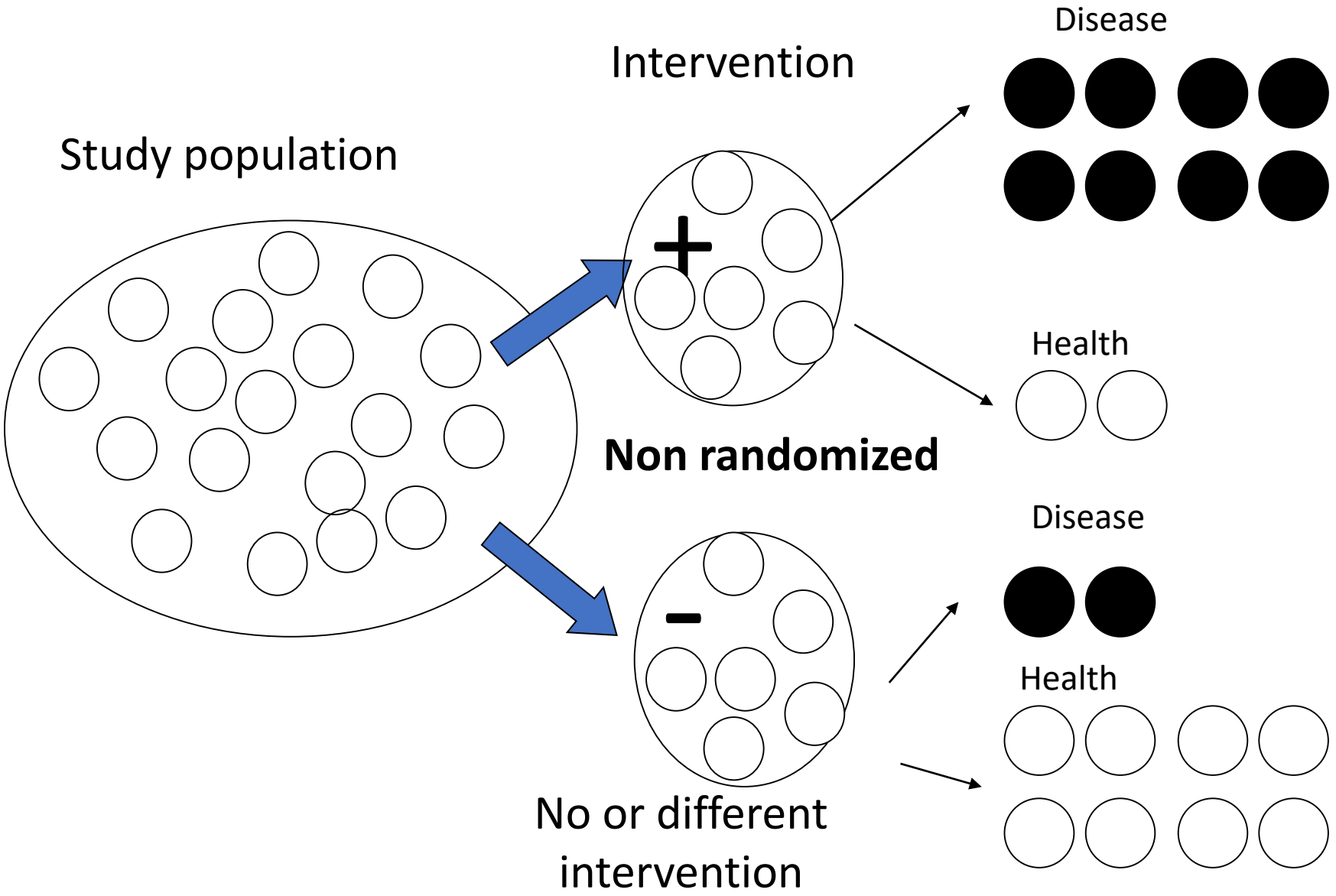
Cohort Study

- Rare outcomes are difficult to assess, because of the large number of participants needed
- To observe many participants is expensive
- Caveat:
  - Selection Bias
  - Attrition Bias, Drop outs
  - Detection Bias
  - Confounders in the course of the observation

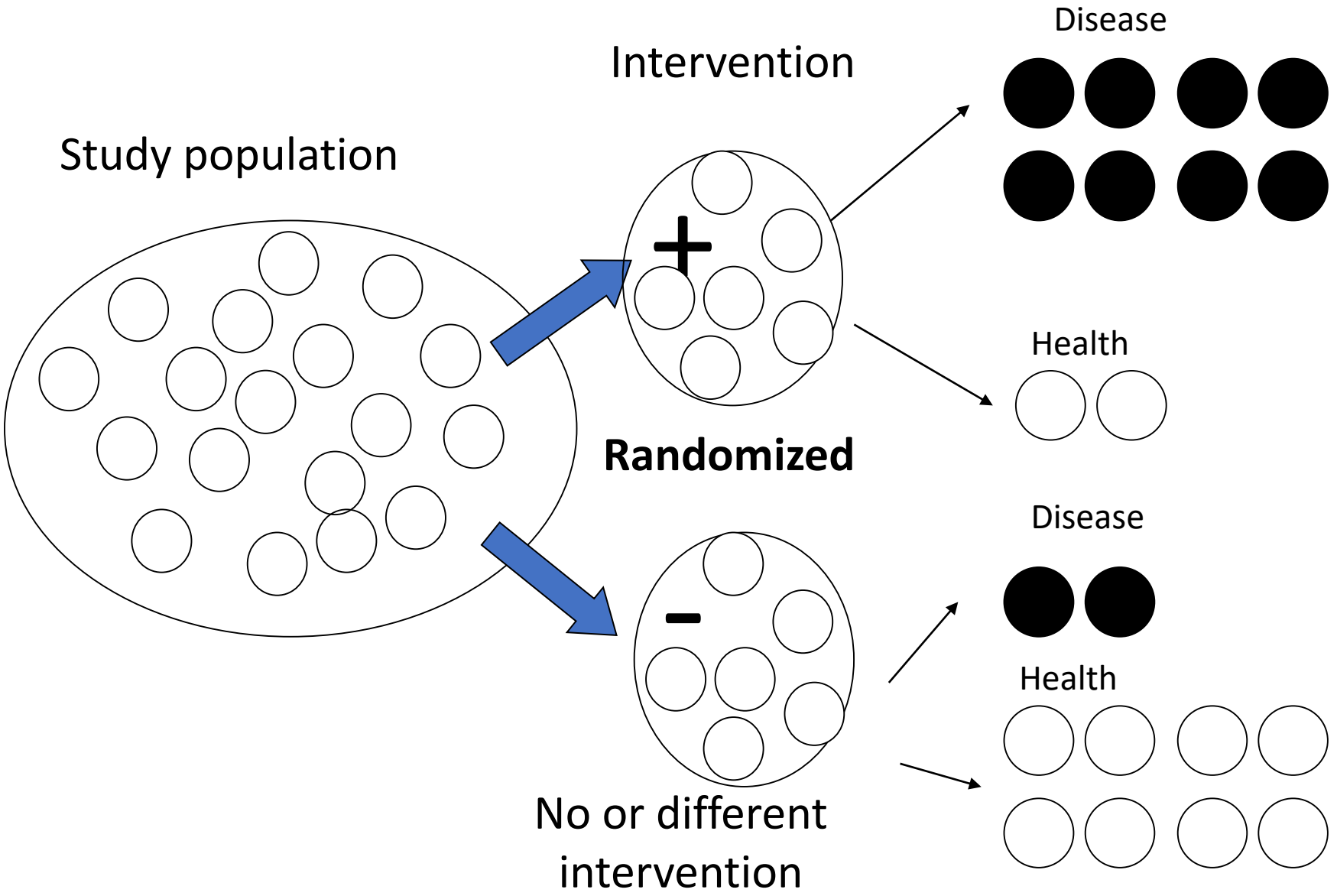
Clinical Trials



Clinical Trials



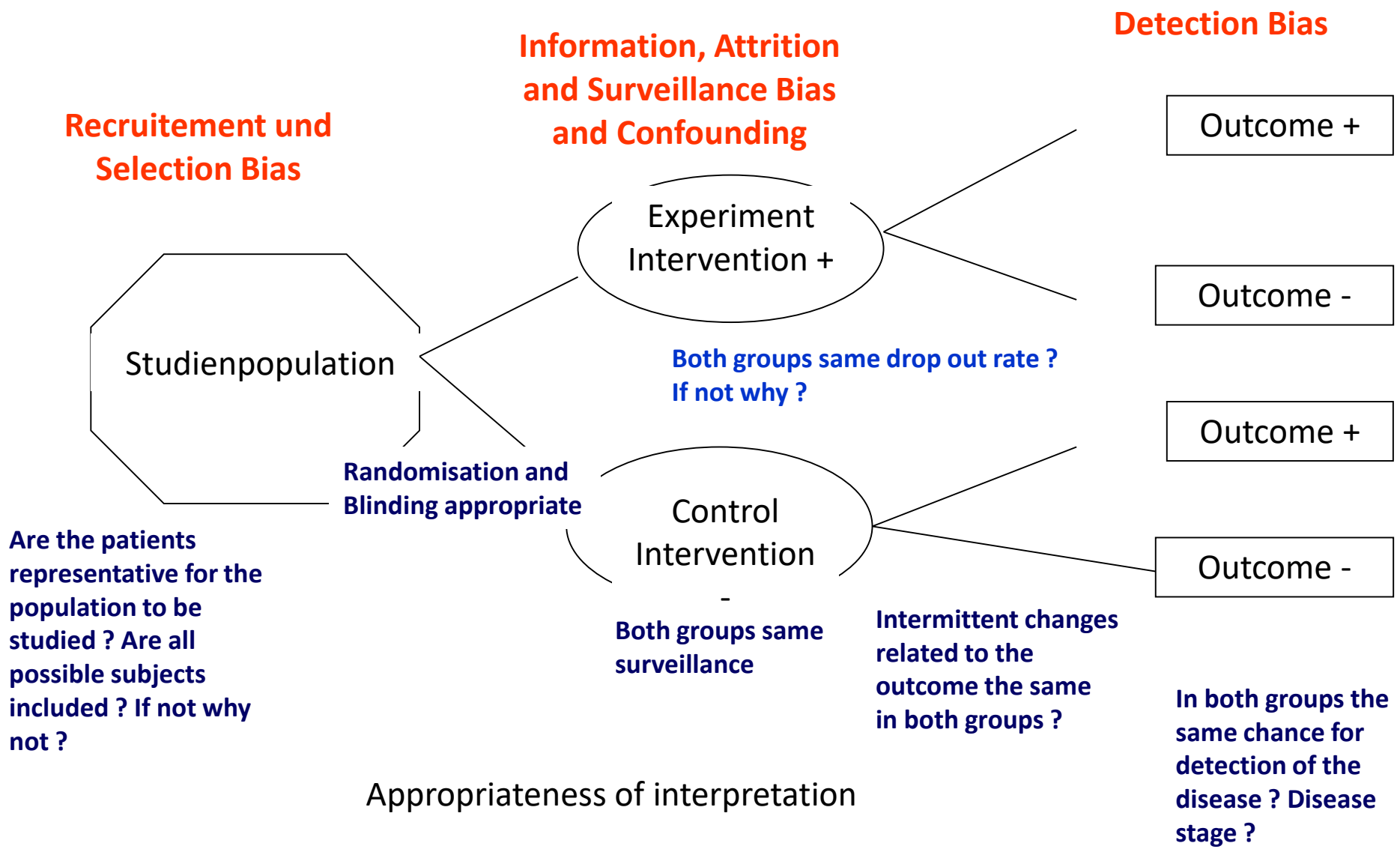
Clinical Trials



The controlled intervention studies

- The author controls the intervention
- Data are assessed prospectively in a standardized manner
- In randomized trials there is a high probability that known and unknown risk factors are equally distributed among the intervention and the comparison group

Start **Allocation** **Measure, Compare**



Appropriateness of interpretation

Statistical Errors

PRESENT FUTURE

Intervention Studies RCT

- Expensive and complicated
- External validity frequently questionable because of „narrow“ inclusion criteria
- Caveat:
  - Are the subjects included respresentative for the condition to be studied and are all suitable subjects included ? Recruitement Bias
  - Who was not included and why ? Selection Bias
  - How was the randomization made ? Allocation Bias
  - Was blinding maintained ? Information Bias
  - Have both groups the same chance for detection of the outcome ? Detection Bias
  - How many dropouts in each group and why ? Attrition Bias
  - In the course of the study where there changes with possible influence on the outcome ? Confounding
  - Other possible confounders (age?)

Bias and Confounders

- **Bias:** An error in the planning, performance or interpretation of a study, which leads to a systematic distortion of the outcome to measure. The study is invalid.
- **Confounder:** Factors which influence independently of the study design the outcome to measure. Frequently confounders are at the same time associated with the risk factor and the outcome. It is possible to adjust for confounders

Selection of Statistics

- Type of Data
- Estimated direction of change or difference (one direction, two directions)
- Distribution of Data
- Study design: Independent data; Paired data – (repeated measurements with the same patient or matched groups)
- Number of groups

Types of variables

Categorial Nominal Data	**Male, female, black, blue, green, brown colour of the eyes**
Categorifal Ordinal data	**Ranking: mild, medium, severe (objective and subjective)**
Numerical data (Interval, Discrete)	**Data with defined numbers exp. Days of hospital stay etc.**
Numerical data (Interval, Continuous)	**keine diskreten Schritte; fortlaufende Messwerte; Grösse, Gewicht, Laborwerte**

Types of statistics

Objective of the Test	**Parametric continuous data**	Example	**Non Parametric, intervall discrete ordinal, non normally distributed data,**	Example
Comparison of independent samples	**Unpaired T Test**	Prolacatin Values in swiss and migrant women	**Mann Whitney U Test**	Exam scores among male and female medical students
Comparison of 2 measurements in one sample	**Paired T Test**	Prolactin Values before and after Dostinex	**Wilcoxon matched pair test**	Depression Score before and after intervention

Types of statistics

Objective	**Parametric**	Example	**Non parametric**	Beispiel
Comparison of 3 or more samples	**Analysis of variance**	**Testosterone values in eumenorrhoic, PCO and perimenopausal women**	**Kruskal Wallis Test**	**Exam scores in swiss and turkish male and female medical students**
Comparison of 3 or more measurements in the same sample	**Repeated measure-ment ANOVA**	Blood glucose 1,2,3, hours after intake of sugar	**Friedmann ANOVA**	Depression Score 1,2,3 weeks after Intervention

Types of statistics

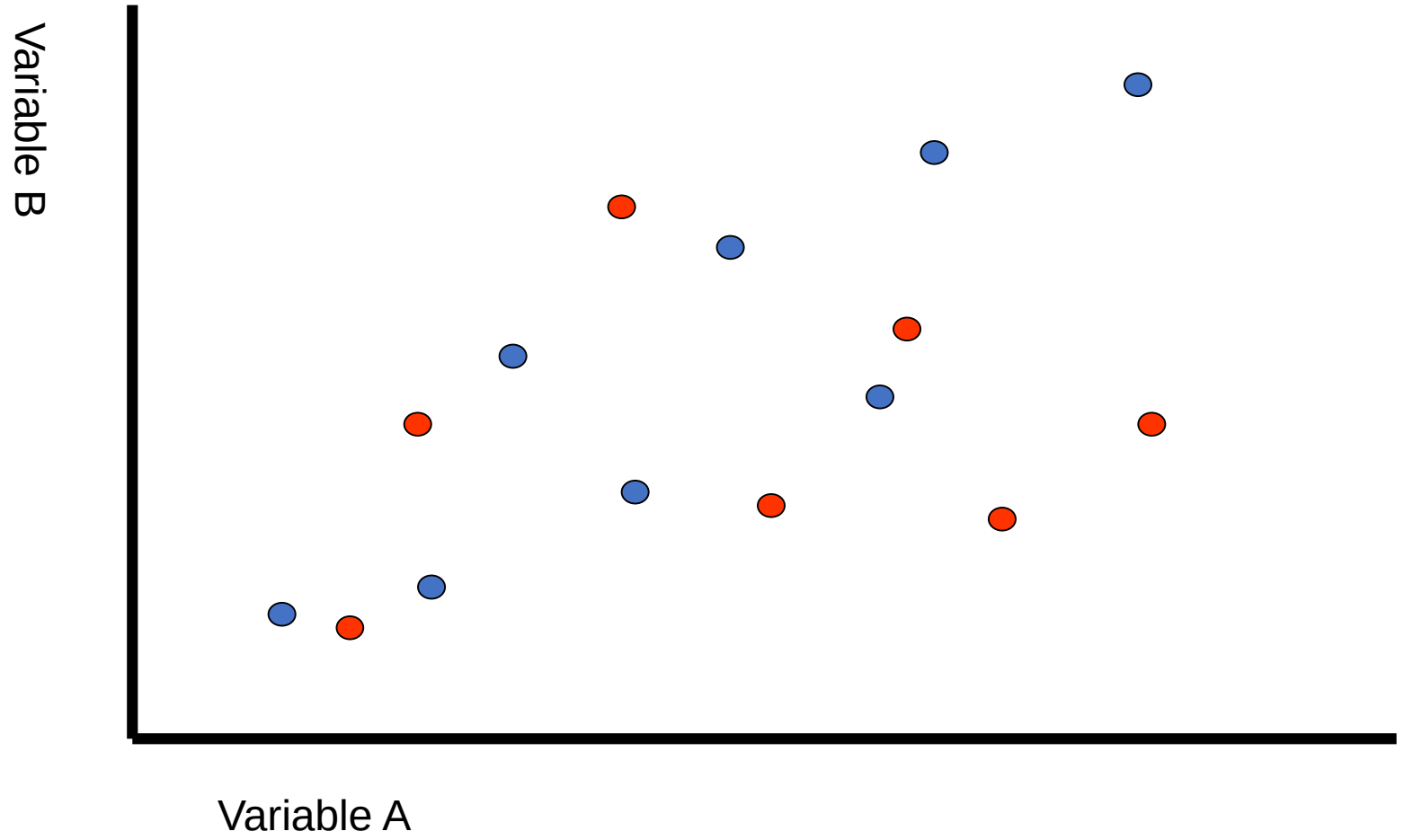
Objective			**Non parametric, categorical dichotomous, nominal**	Example
Comparison of 2 or more independent Data groups			**Chi Square, Fisher‘s exact Test**	**Difference between two drugs with a binary outcome (healed, non healed)**
Comparison of 2 or more dependent data groups			**Mc Nemar Test**	**Comparison of a mammogram by two radiologists**

Correlation

- **Correlation evaluates the strength of linear relationships or associations between variables. How closely are patients‘ weights and blood pressure related to one another**
- **The correlation coefficient measures the degree in which changes in one variable are associated with changes in the other variable.**
- **The relationship can have 2 directions: Positive correlation and negative correlation**

Correlation

The strength of the relationship

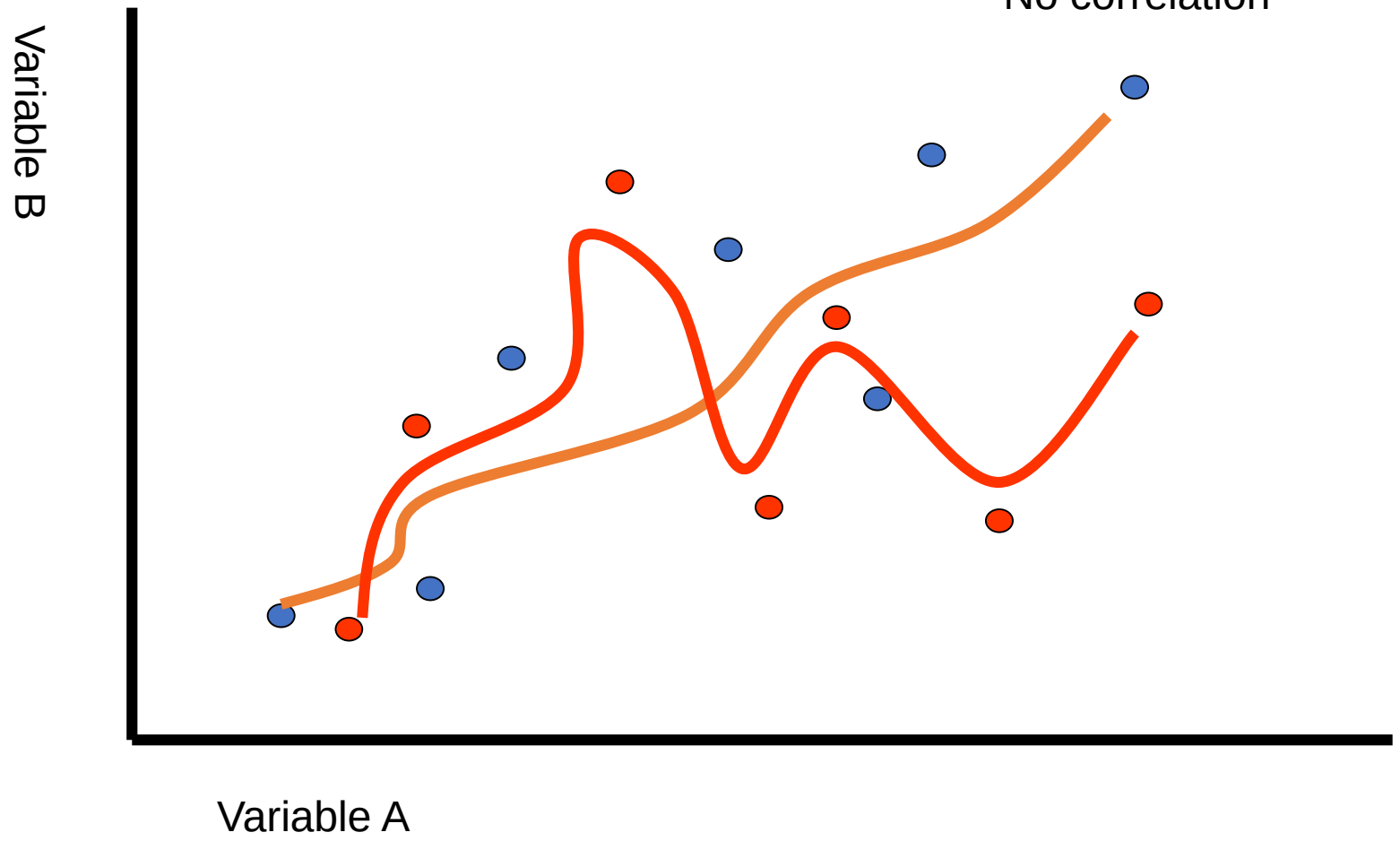


Correlation

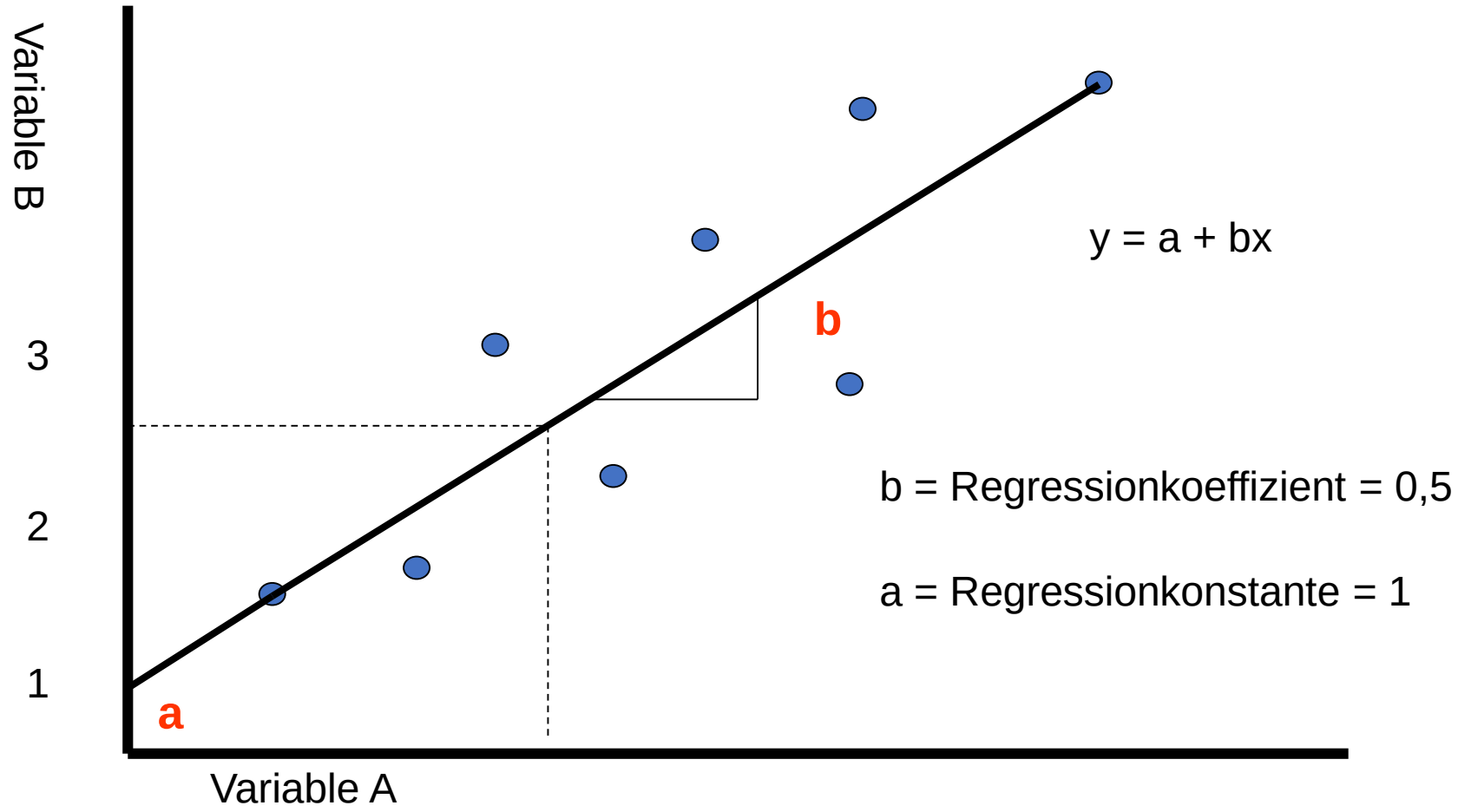
Correlation Coefficient = 1
strongest Korrelation

Correlation Coefficient = 0
No correlation

Strenght of realtionsip



Regression


Variable B
3
2
1
a
b
Variable A
y = a + bx
b = Regressionkoeffizient = 0,5
a = Regressionkonstante = 1

Regression

- Lineare Regression:
  - Prediction of variable B by values of variable A
- Logistic Regression:
  - Probability of variable A, that variabel B belongs in one of two groups (healthy versus ill)
  - Frequently used in case control studies

Choice of appropriate statistical significance test to be used in bivariate Analysis (Analysis of one independent variable and one dependent variable)

First Variable	Second Variable	Examples	Appropriate test or tests of significance
Continuous	Continuous	Age (C) and systolic blood pressure (C)	Pearson correlation coefficent (r); linear regression
Continuous	Ordinal	Age (C) and satisfaction (O)	Spearman correlation or ANOVA or F-test
Continuous	Dichotomous unpaired	Systolic blood pressure and gender	Student‘s t
Continuous	Dichotomous paired	Difference blood pressure before and after treatment	Paired t Test
Continuous	Nominal	Hemoglobin (C) and blood type (N)	ANOVA (f-Test)

Choice of appropriate statistical significance test to be used in bivariate Analysis (Analysis of one independent variable and one dependent variable)

First Variable	Second Variable	Examples	Appropriate test or tests of significance
Ordinal	Ordinal	Correlation of satisfaction with care and serverity of illness	Spearman correlation coefficient(rho); Kendall
Ordinal	Dichotomous unpaired	Satisfaction and gender	Mann-Whitney U Test
Ordinal	Dichotomous paired	Difference in satisfaction before and after intervention	Wilcoxon matched-pairs signed-ranks test
Ordinal	Nominal	Hemoglobin (C) and blood type (N)	Kruskal-Wallis Test

Choice of appropriate statistical significance test to be used in bivariate Analysis (Analysis of one independent variable and one dependent variable)

First Variable	Second Variable	Examples	Appropriate test or tests of significance
Dichotomous	Dichotomous unpaired	Success/Failure in treated/untreated group	Chi square test; Fisher exact probability test
Dichotomous	Dichotomous paired	Change in success/failure rate before versus after treatment	Mc-Nemar chi-square test
Dichotomous	Nominal (N)	Success/failure and blood type	Chi square test
Nominal	Nominal	Ethnicity and blood type	Chi square test

Choice of appropriate procedure to be used in multivariable analysis (Analysis of one dependent variable and more than on independent variable)

Dependent Variable	Independent Variable	Appropriate Procedure or Procedures
Continuous	All are categorical	Analysis of Variance (ANOVA)
Continuous	Some are categorical and some are continous	Analysis of Covrariance (ANCOVA)
Continuous	All are continuous	Multiple linear regression
Ordinal		No formal multivariable procedure for ordinal dependent variable. Either treat the variables as if they were continuous or perform log-linear analysis

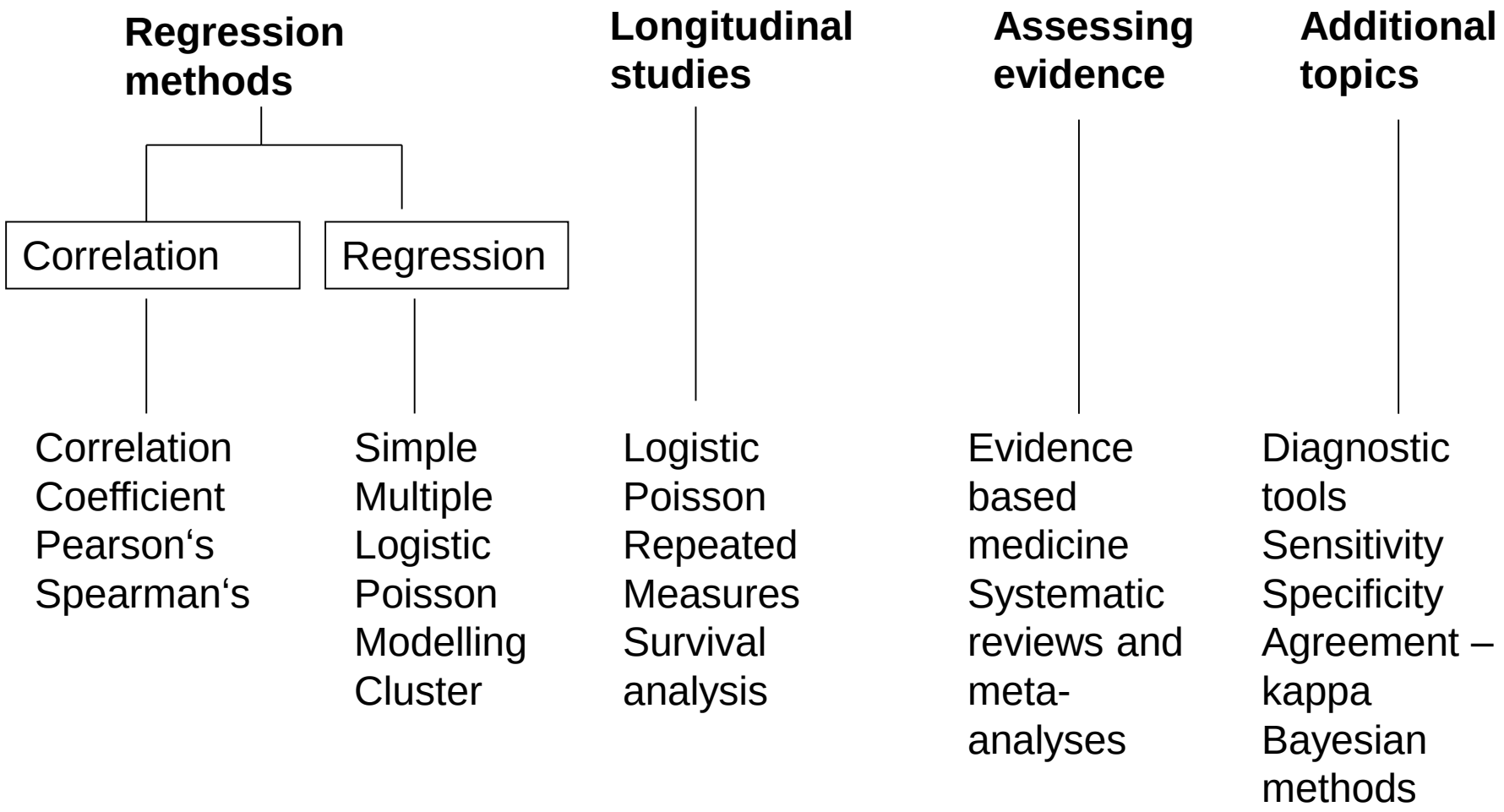
Choice of appropriate procedure to be used in multivariable analysis (Analysis of one dependent variable and more than on independent variable

Dependent Variable	Independent Variable	Appropriate Procedure or Procedures
Dichotomous	All are categorical	Logistic regression; log - linear analysis
Dichotomous	Some are categorical and some are continous	Logistic regression
Dichotomous	All are continuous	Logistic regression; discriminant function analysis

Choice of appropriate procedure to be ussed in multivariable analysis (Analysis of one dependent variable and more than on independent variable

Dependent Variable	Independent Variable	Appropriate Procedure or Procedures
Nominal	All are categorical	Log-linear analysis
Nominal	Some are categorical and some are continuous	Group the continuous variables and perform log-linear analysis
Nominal	All are continuous	Discriminant function analysis; group the continuous variables and perform log-linear analysis

Flow chart for further analysis



Results and Discussion

They should start by describing in simple terms what the data show

They should make reference to statistical analyses, such as significance or goodness of fit

If you find yourself looking at a piece of information from which you cannot discern a story, then you should ask for improvements in presentation. This could be an issue with titles, labels, statistical notation or image quality.

Where information is clear, you should check that:

- The results seem plausible, in case there is an error in data gathering
- The trends you can see support the paper's discussion and conclusions
- There are sufficient data. For example, in studies carried out over time are there sufficient data points to support the trends described by the author?

Structured Discussion

- **Findings and interpretation**
- **Strength and weaknesses**
- **Differences and similarities in relation to other studies**
- **Open questions and future research**

Conclusions

This section is usually no more than a few paragraphs and may be presented as part of the results and discussion, or in a separate section.

The conclusions should reflect upon the aims - whether they were achieved or not and in case of not why not

Reporting negative outcomes

List of References

- **Accuracy**

Where a cited article is central to the author's argument, you should check the accuracy and format of the reference - and bear in mind different subject areas may use citations differently. Otherwise, it's the editor’s role to exhaustively check the reference section for accuracy and format.

- **Adequacy**

✓ You should consider if the referencing is adequate:

✓ Are important parts of the argument poorly supported?

✓ **Are there published studies that show similar or dissimilar trends that should be discussed?**

✓ If a manuscript only uses half the citations typical in its field, this may be an indicator that referencing should be improved - but don't be guided solely by quantity

✓ **References should be relevant, recent and readily retrievable**

- **Balance**

✓ Check for a well-balanced list of references that is:

✓ **Helpful to the reader**

✓ **Fair to competing authors**

✓ **Not over-reliant on self-citation**

✓ **Gives due recognition to the initial discoveries and related work that led to the work under assessment**

You should be able to evaluate whether the article meets the criteria for balanced referencing without looking up every reference.

List of References

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List of References

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Your report

Summary

- Give positive feedback first. Authors are more likely to read your review if you do so. But don't overdo it if you will be recommending rejection
- Briefly summarize what the paper is about and what the findings are
- Try to put the findings of the paper into the context of the existing literature and current knowledge
- Indicate the significance of the work and if it is novel or mainly confirmatory
- Indicate the work's strengths, its quality and completeness
- State any major flaws or weaknesses and note any special considerations. For example, if previously held theories are being overlooked

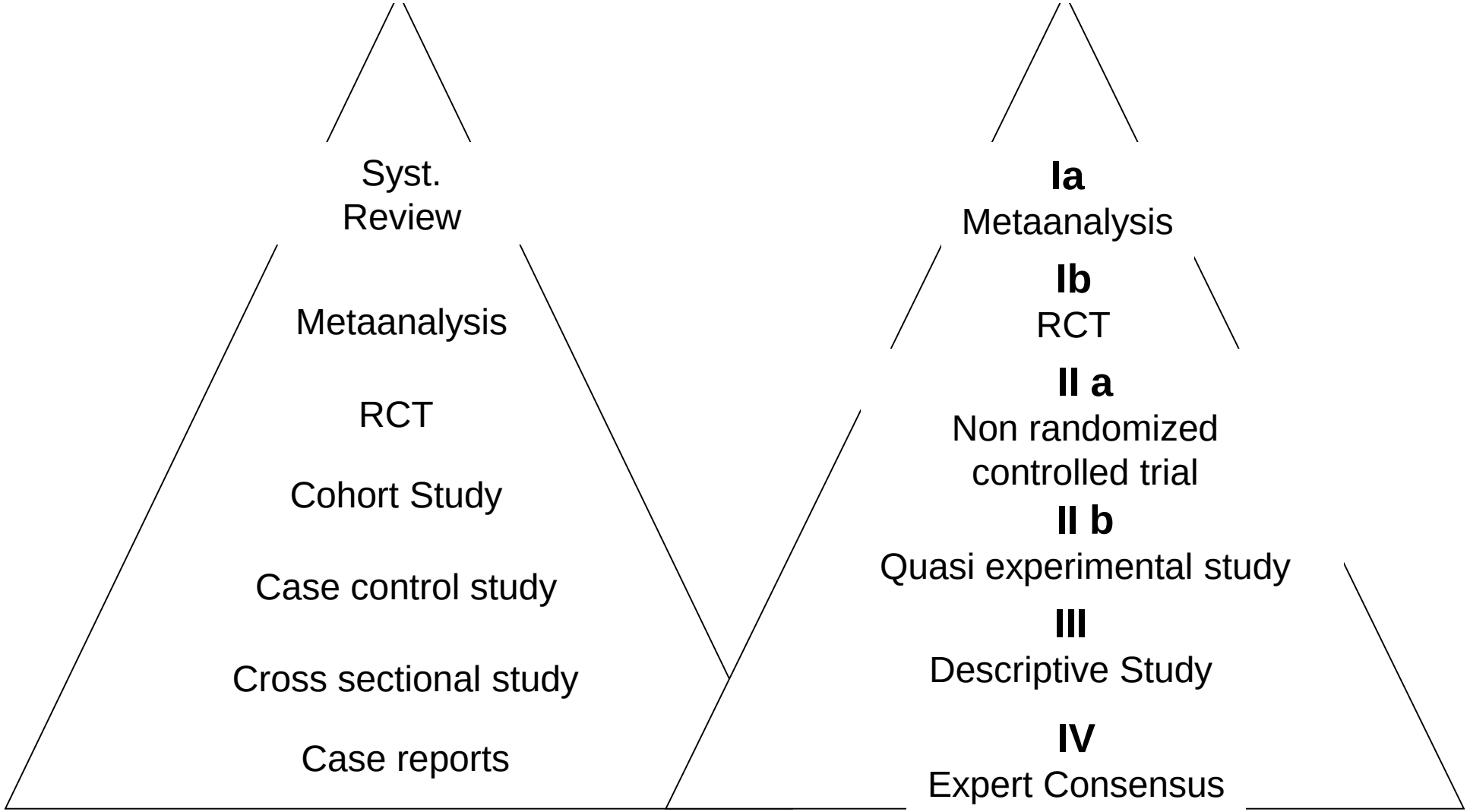
Major Issues

- Are there any major flaws? State what they are and what the severity of their impact is on the paper
- Has similar work already been published without the authors acknowledging this?
- Are the authors presenting findings that challenge current thinking? Is the evidence they present strong enough to prove their case? Have they cited all the relevant work that would contradict their thinking and addressed it appropriately?
- If major revisions are required, try to indicate clearly what they are
- Are there any major presentational problems? Are figures & tables, language and manuscript structure all clear enough for you to accurately assess the work?
- Are there any ethical issues? If you are unsure it may be better to disclose these in the confidential comments section

Minor Issues

- Are there places where meaning is ambiguous? How can this be corrected?
- Are the correct references cited? If not, which should be cited instead/also? Are citations excessive, limited, or biased?
- Are there any factual, numerical or unit errors? If so, what are they?
- Are all tables and figures appropriate, sufficient, and correctly labelled? If not, say which are not

Hierarchy of probability knowledge



Systematic review

- Very powerful
- **Reviews all literature**
  - search engines,
  - other languages,
  - references of references,
  - raw data,
  - expert views,
  - non peer reviewed data

- Trials must meet eligibility criteria
- It may exclude articles if considered not robust or fitting criteria
- Tabulates the original data
- Assembles the data set
- Analyses all results
- Conclusions are reliable & accurate

Introduction to Meta-Analysis

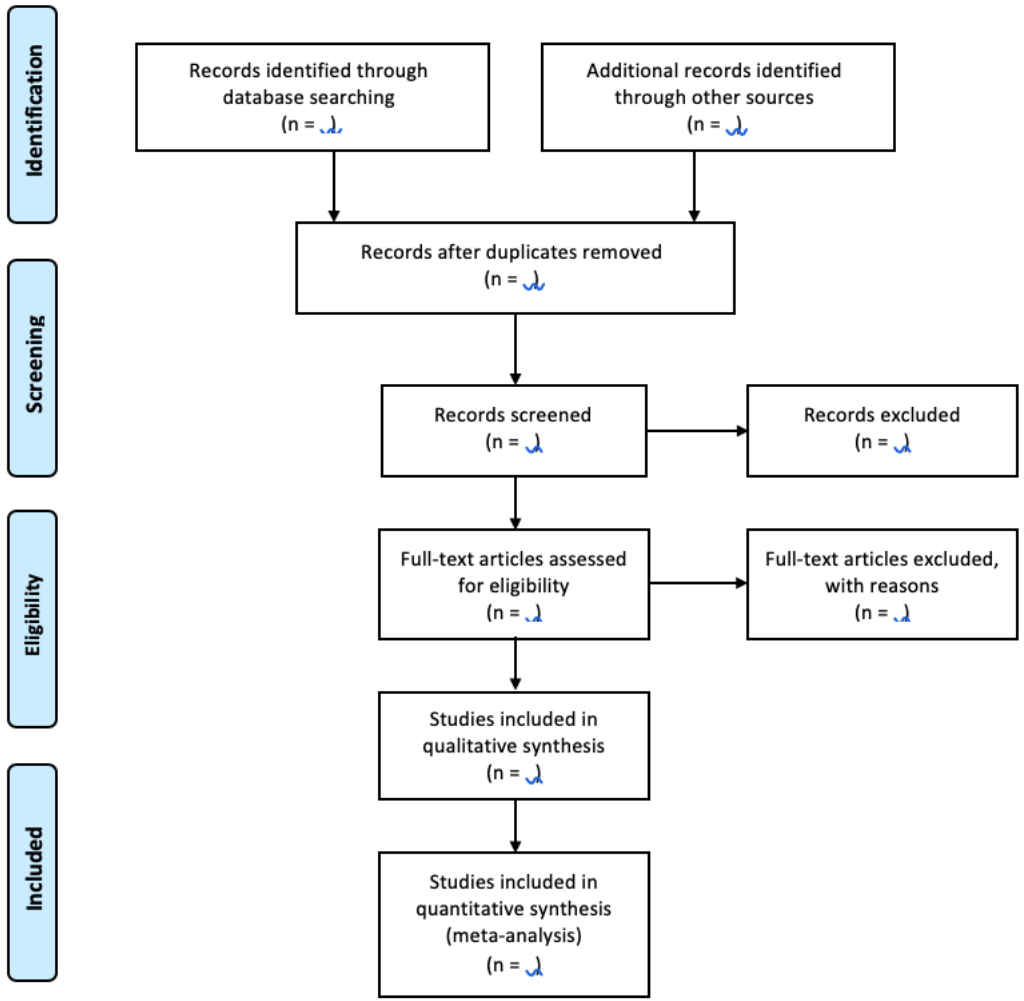
Michael Borenstein

Larry Hedges

Hannah Rothstein

July 1, 2007
www.Meta-Analysis.com

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097

For more information, visit www.prisma-statement.org.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PROSPERO: International prospective register of systematic reviews

A database of systematic review protocols

Logon to **PROSPERO: International prospective register of systematic reviews**

Description

PROSPERO is a database of systematic review protocols, that is, reviews currently being undertaken. Researchers are encouraged to register their review in PROSPERO when they start, and to record their progress. Registration in PROSPERO can help avoid duplication and we recommend you search it before you start your systematic review.

PROSPERO is maintained by the Centre for Reviews and Dissemination, University of York

Help: **Search advice** is available **here**

Figure 2: Forest plot of comparison: Testosterone versus Comparator: Satisfying Sexual Events by Menopausal Status (A)

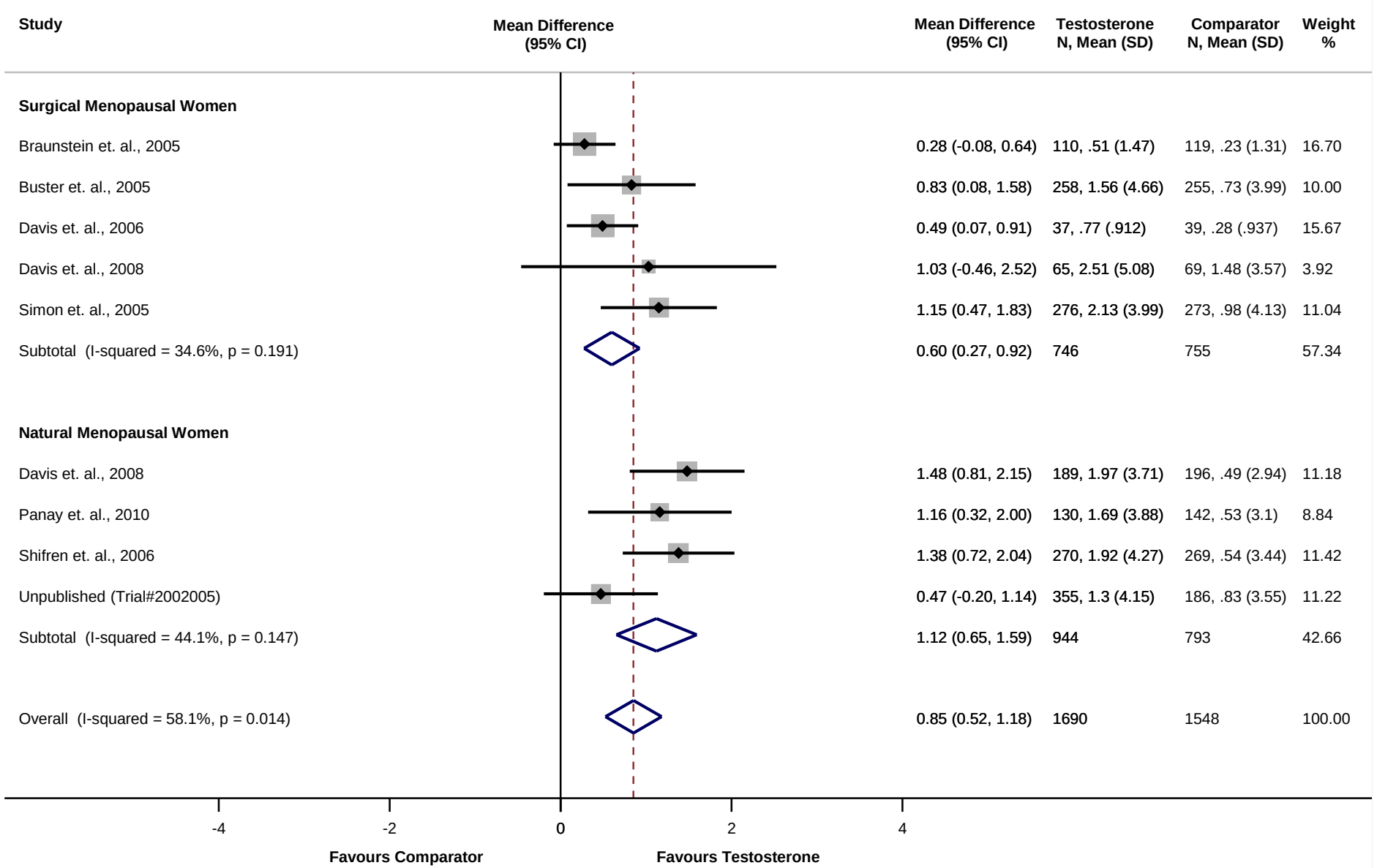


Figure 2: Forest plot of comparison: Testosterone versus Comparator: Satisfying Sexual Events by Menopausal Status (B)

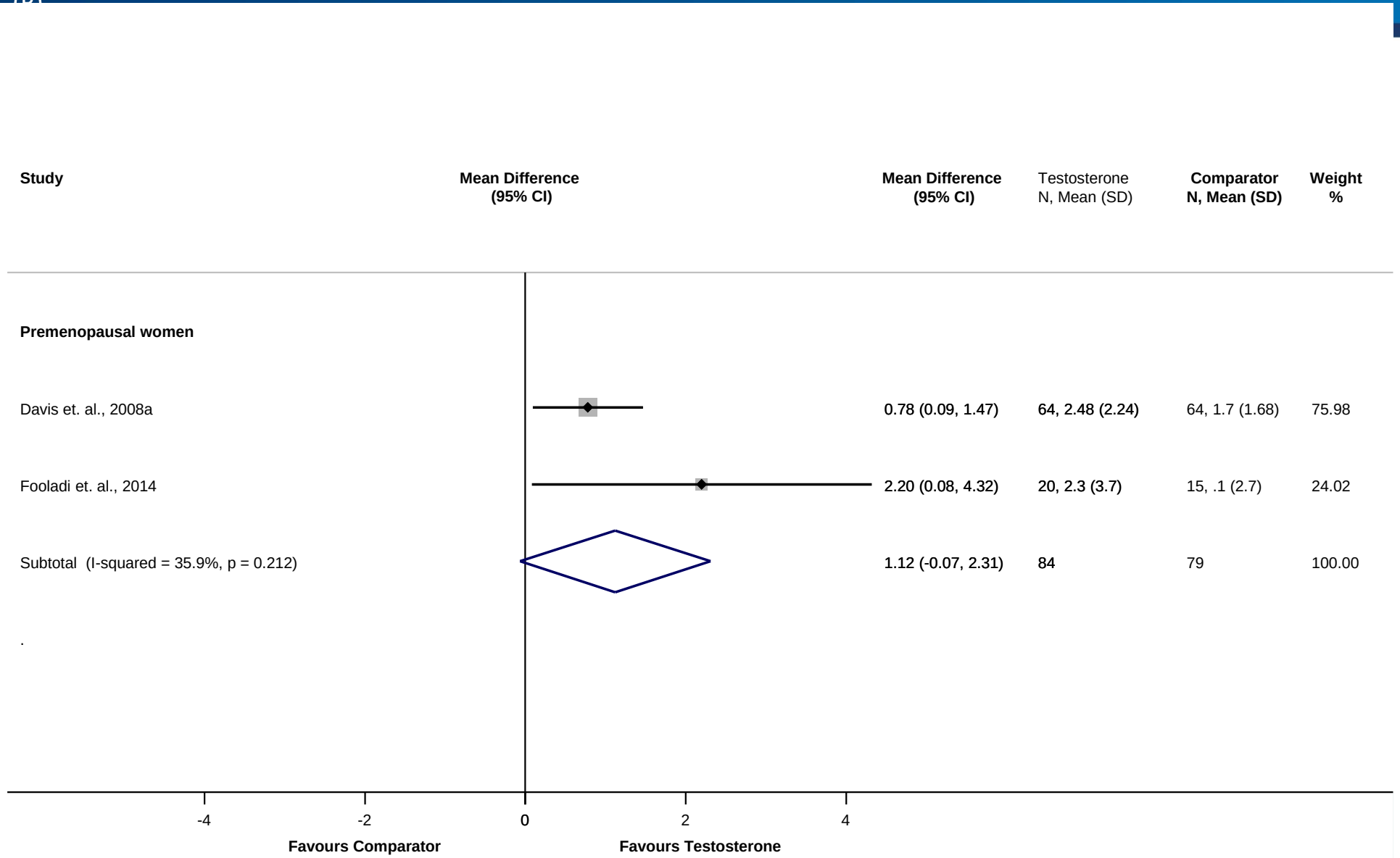


Figure 2: Forest plot of comparison: Testosterone versus Comparator: Satisfying Sexual Events by Mode of Oestrogen (E) Administration
(C)

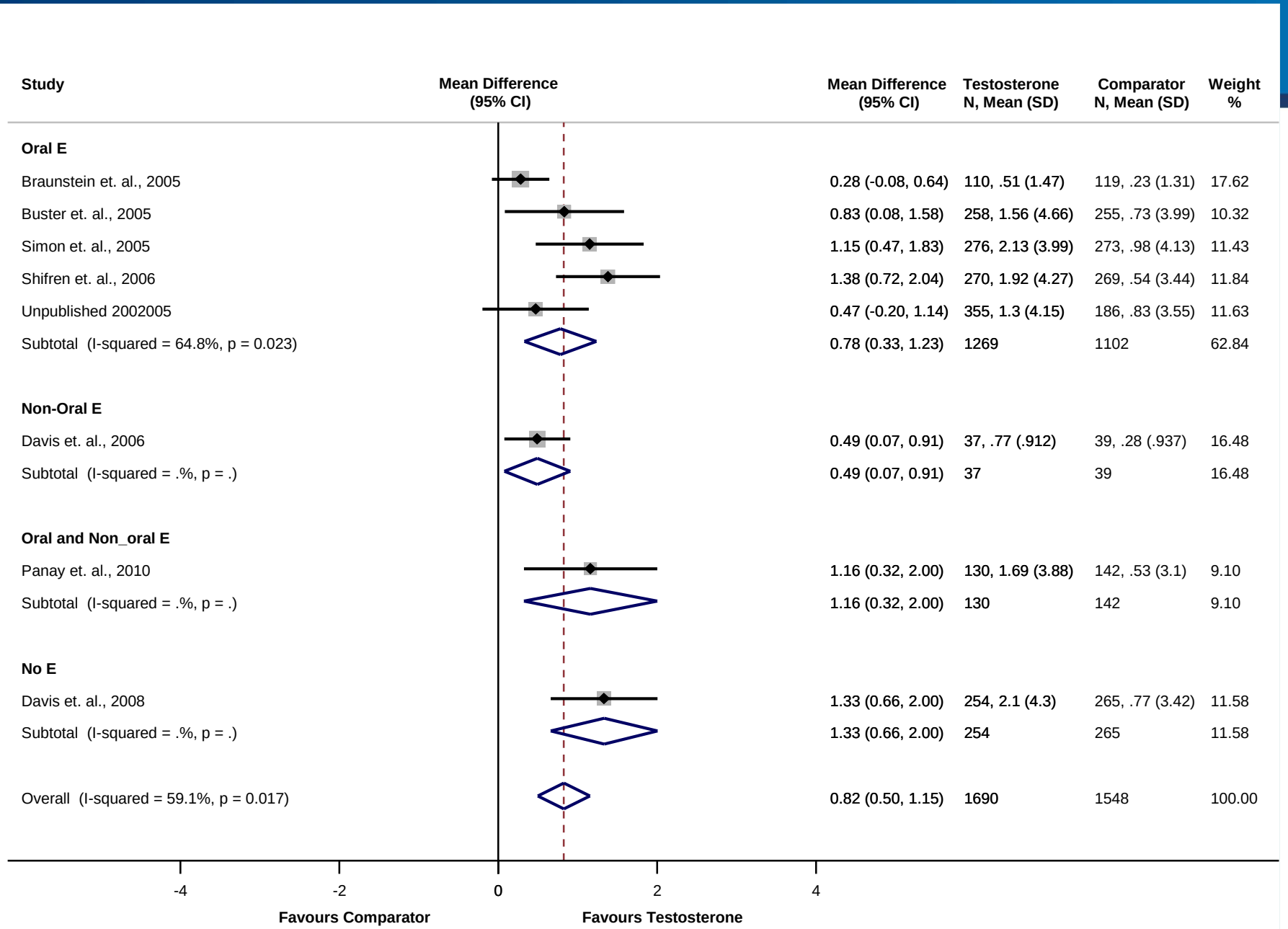


Figure 2.1: Forest plot of comparison: Testosterone versus Comparator: Sexual Desire by Menopausal Status (A)

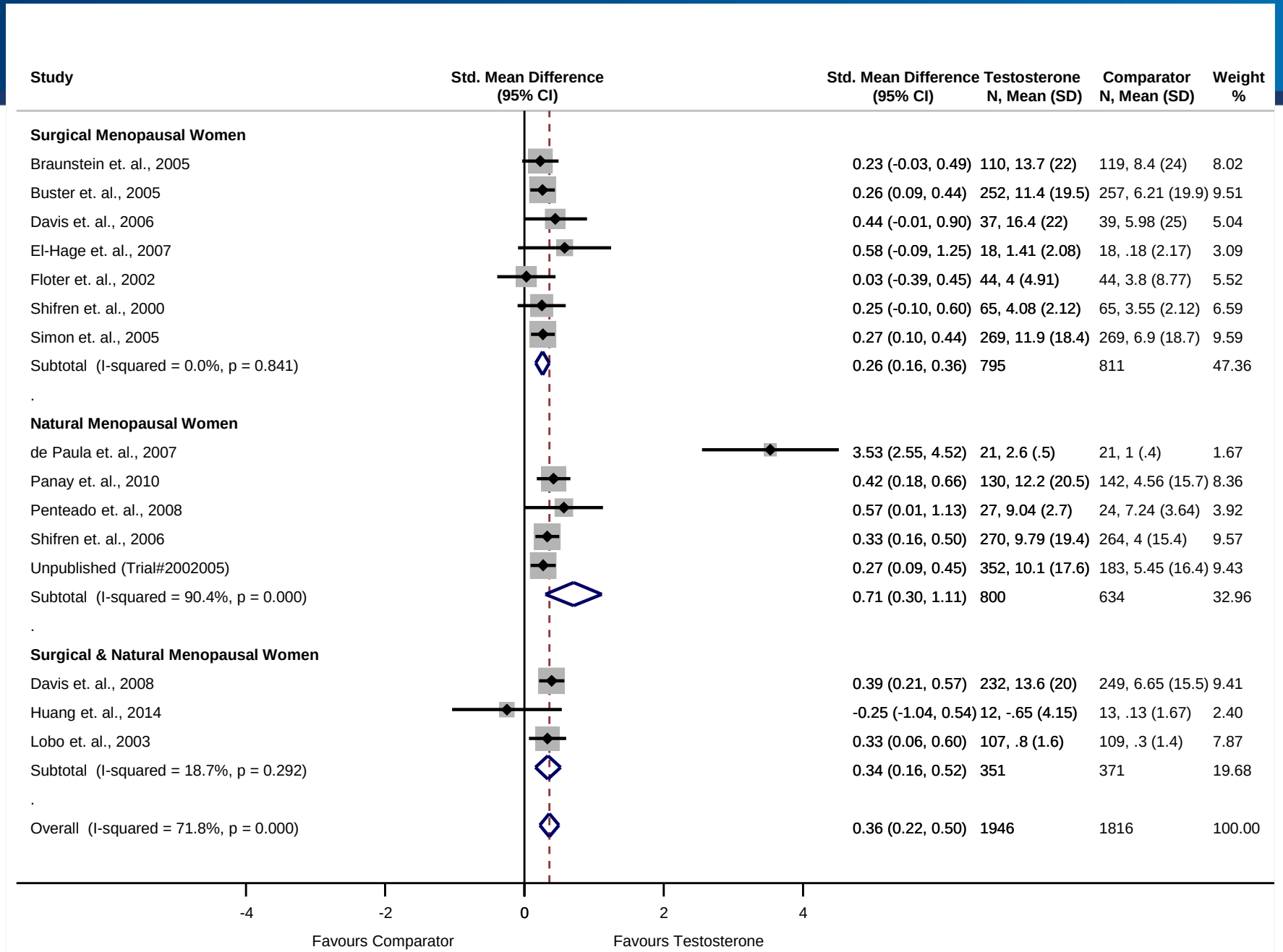


Figure 2.1: : Forest plot of comparison: Testosterone versus Comparator: Sexual Desire by Menopausal Status (B)

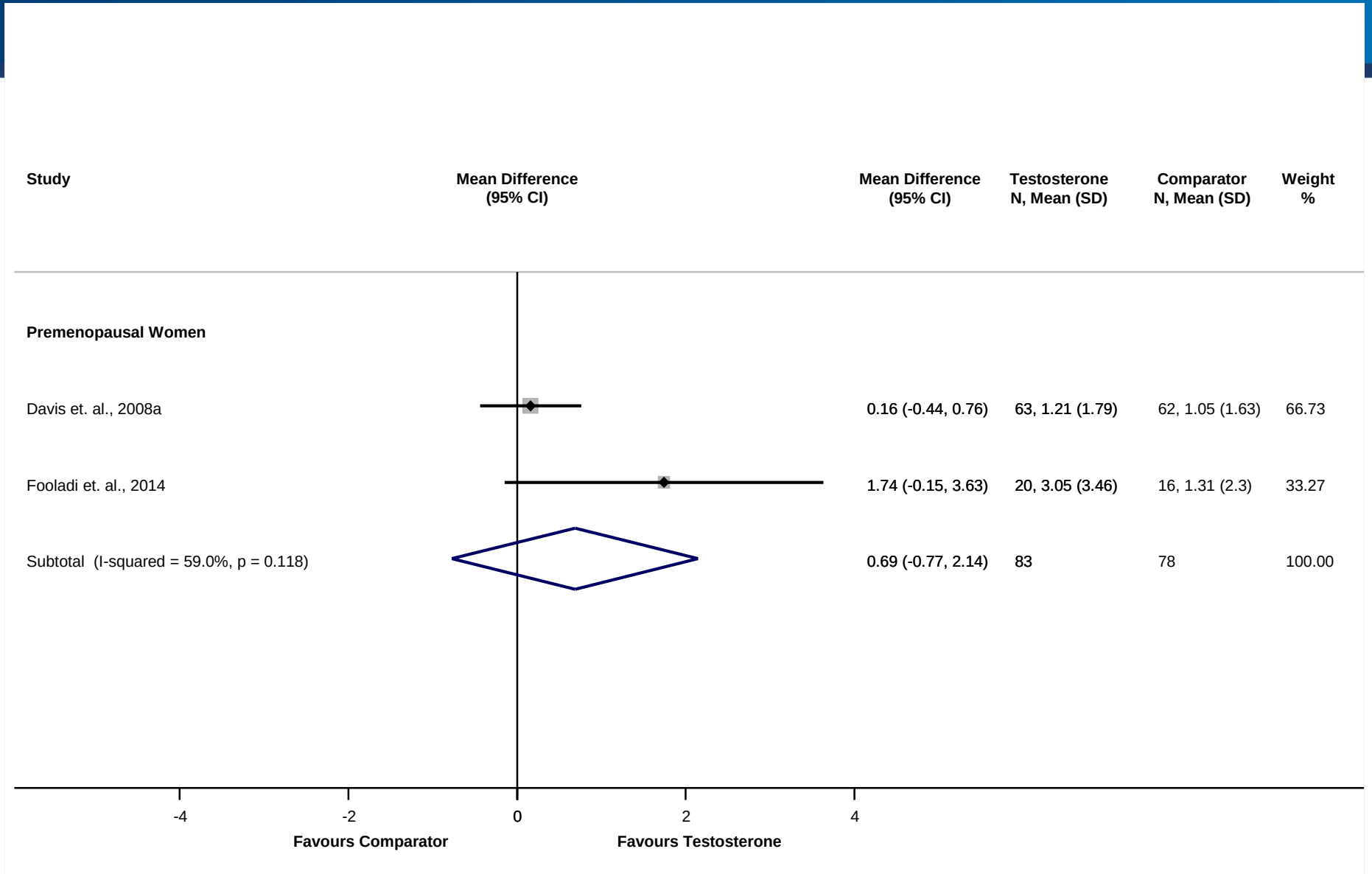
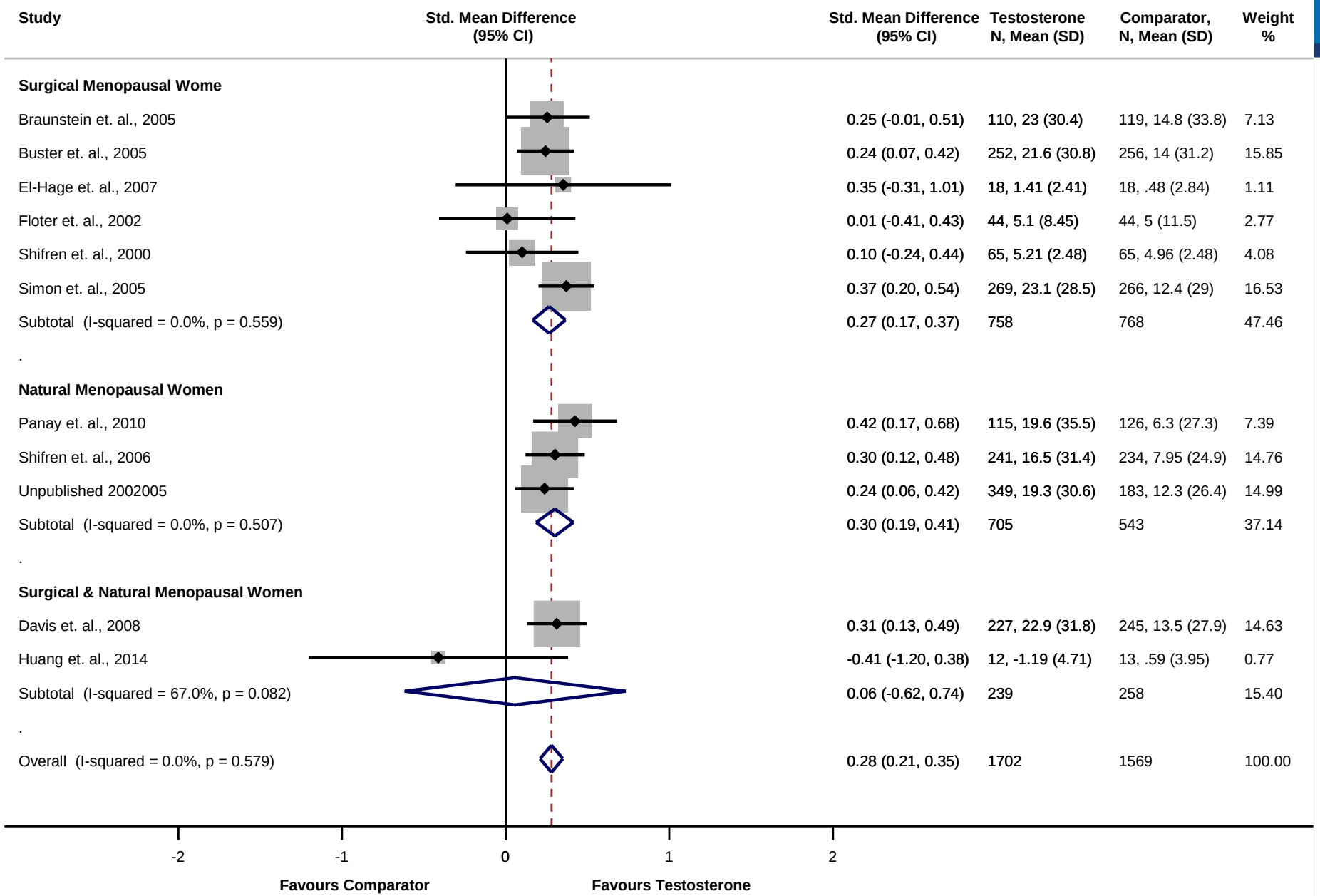


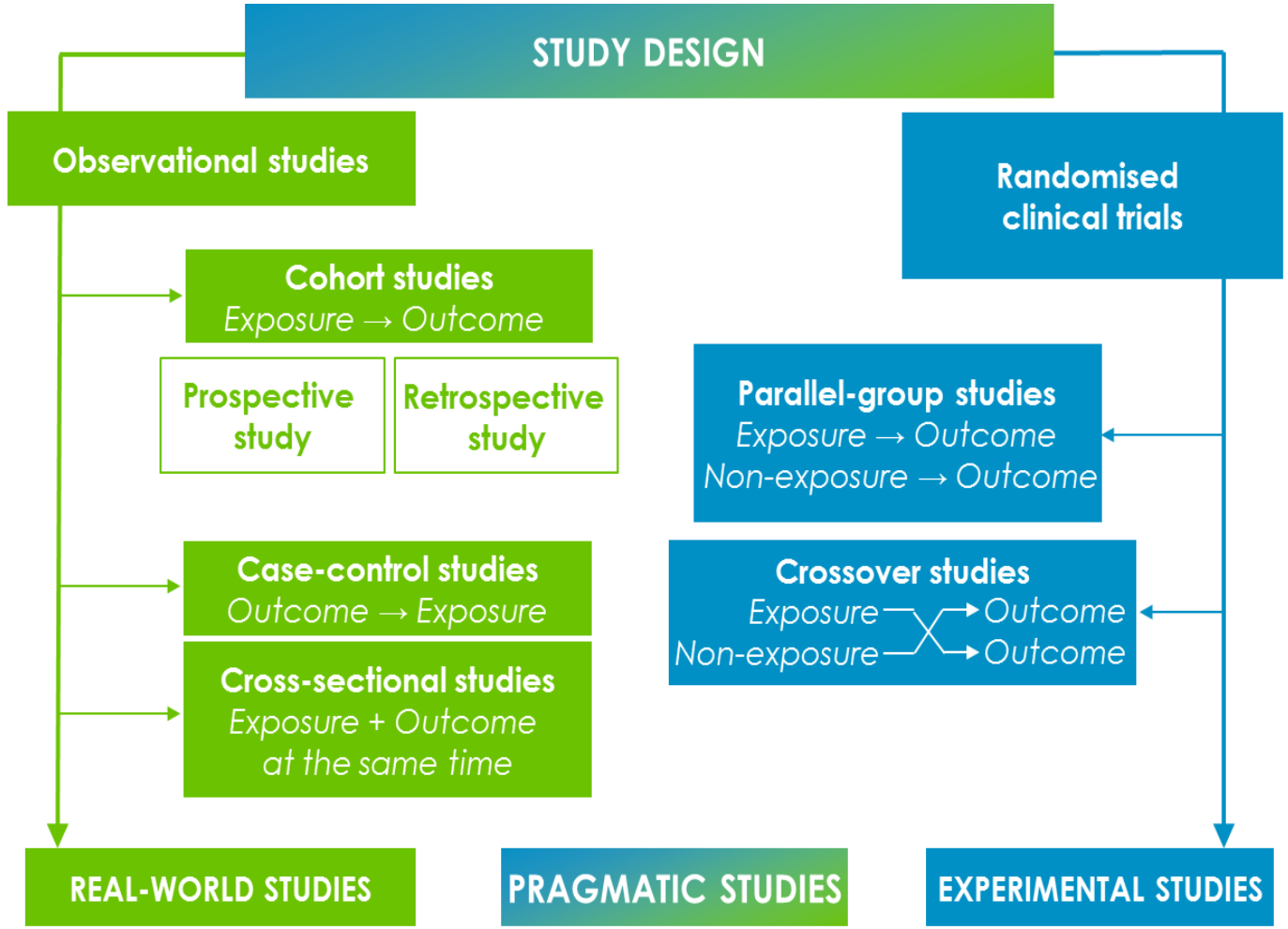
Figure 2.2: Forest plot of comparison: Testosterone versus Comparator: Arousal by Menopausal Status



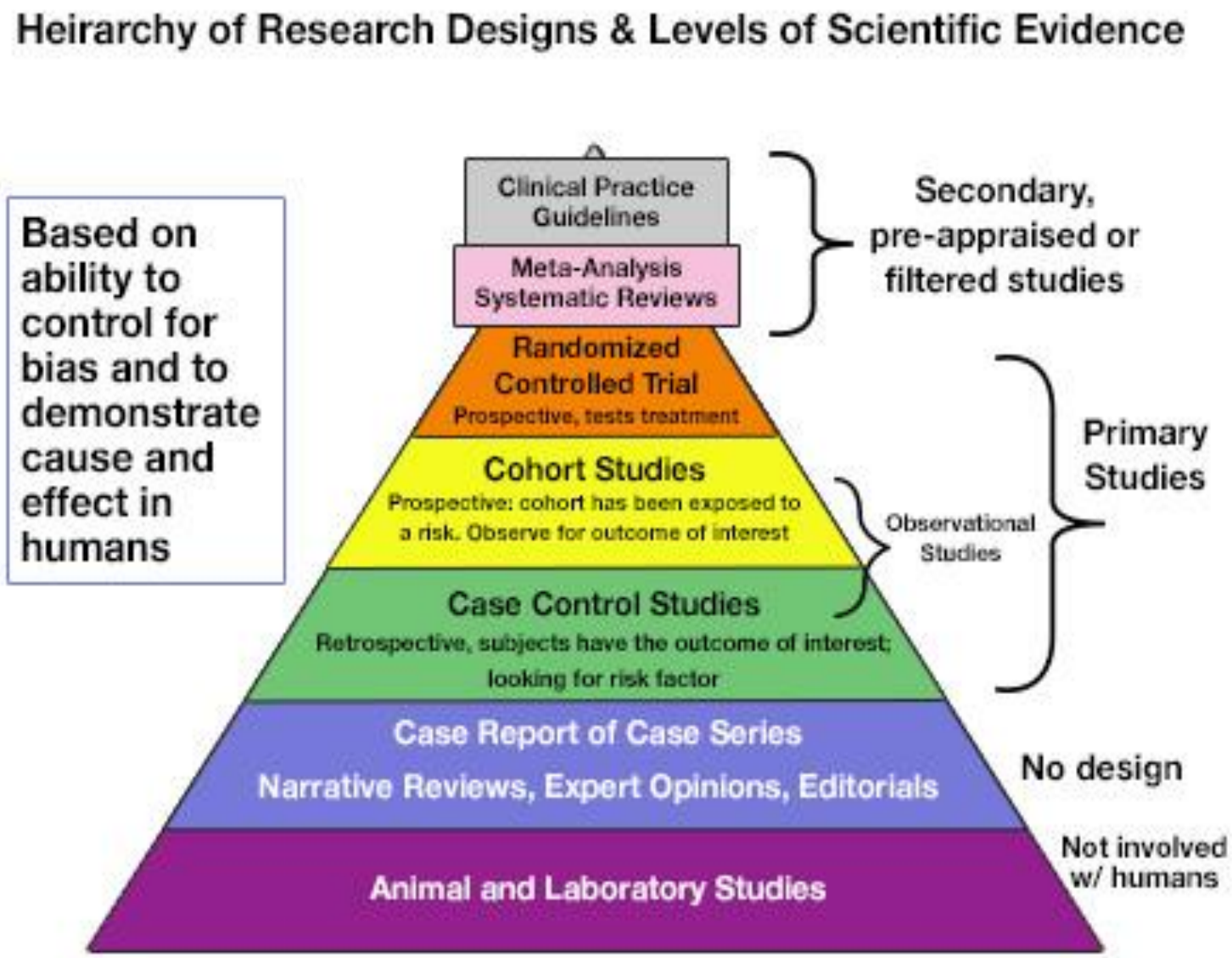
Why do we need real life data for contraceptive counseling and care

- Preventing unwanted pregnancies can be achieved by a large number of methods and interventions
- Contraception is therefore a field in which there is no single solution (therapy) for the problem (unwanted pregnancies) but there are many different solutions.
- The challenge for the practitioner is to find the best method for the individual woman (tailor contraception)
- To do this the HCP needs evidence based information about
  - The efficacy, side effects, benefits of each method
  - Information about **the efficacy, side effects, benefits of different methods in different women**

Where do we get the evidence from ?



How do we get evidence-based knowledge?



The advantages of RCTs

RCT			
Well defined selected patient	Well defined drug	Well defined patient behaviour	Well defined outcome • Efficacy • Side effects

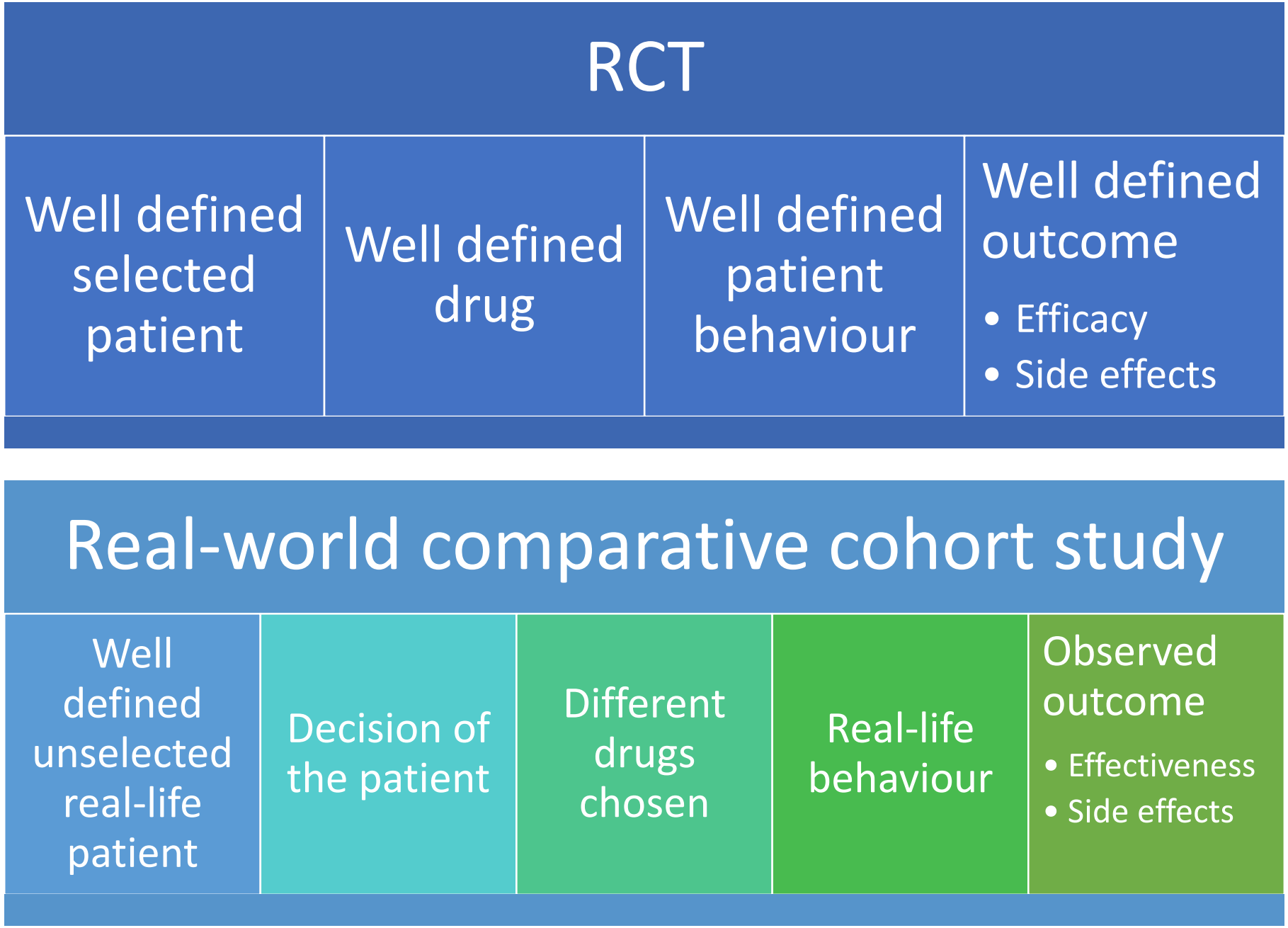
Infer Causality

Limitations of Randomized controlled trials

RCT
Expensive
Time consuming
Strict exclusion and inclusion criteria may cause study population to differ from target population
Treatment efficacy is evaluated, involving strict treatment strategies and/or patient monitoring that may not be practical in a real-world setting
Potentially unethical (e.g. teratogenic effects)
Achieving adequate sample sizes for statistical power can be difficult

The potential of real world data

Observational study
Lower costs
Less time consuming (capital importance when public safety is at stake, and regulatory actions must be taken)
Representative of target population
Treatment effectiveness under real-world conditions is evaluated
Avoids ethical issues in e.g. the study of noxious exposures
Large sample sizes ensure statistical power


RCT
Well defined selected patient
Well defined drug
Well defined patient behaviour
Well defined outcome
• Efficacy
• Side effects
Real-world comparative cohort study
Well defined unselected real-life patient
Decision of the patient
Different drugs chosen
Real-life behaviour
Observed outcome
• Effectiveness
• Side effects

Definition of real-world data

- Data generated from experience with routine medical care that has been systematically recorded in a manner that can be used for research purposes
- Derived from heterogenous, large populations (real populations!)

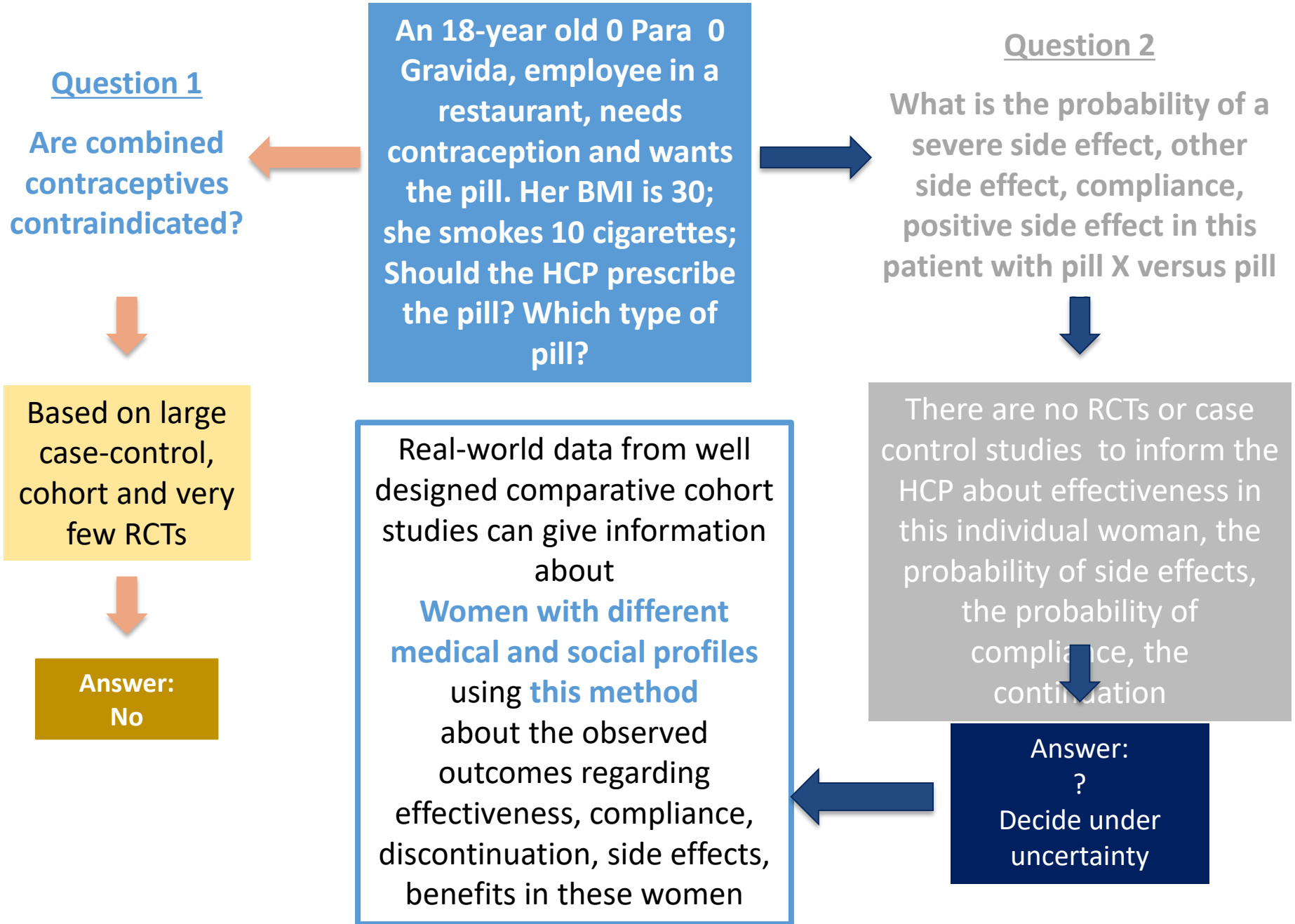
Rationale for growing significance of real-world data over time

- As experience is accumulated over time, our ability to detect treatment effects that exist (statistical power) increases
  - As more emphasis is placed on effectiveness, real-world data become more relevant
  - Quick responses are increasingly important in managing public health issues
  - New analytical methods are being actively developed in an attempt to mimic effectiveness RCTs from observational data

Why do we need real-world data for contraceptive counselling and care ?

- The HCP needs evidence-based:
  - Information about the efficacy, side effects, benefits of each method
  - Information about the efficacy, side effects, benefits of different methods in different women

- RCTs
- Prospective cohort studies
- Well-designed comparative cohort studies


An 18-year old 0 Para 0 Gravida, employee in a restaurant, needs contraception and wants the pill. Her BMI is 30; she smokes 10 cigarettes; Should the HCP prescribe the pill? Which type of pill?
Question 1
Are combined contraceptives contraindicated?
Based on large case-control, cohort and very few RCTs
Answer: No
Question 2
What is the probability of a severe side effect, other side effect, compliance, positive side effect in this patient with pill X versus pill
There are no RCTs or case control studies to inform the HCP about effectiveness in this individual woman, the probability of side effects, the probability of compliance, the continuation
Answer: ? Decide under uncertainty
Real-world data from well designed comparative cohort studies can give information about
Women with different medical and social profiles
using this method
about the observed outcomes regarding effectiveness, compliance, discontinuation, side effects, benefits in these women

A 42 year old II para II Grav complains about acne, depressed mood, irregular cycles with heavy menstrual bleeding and lack of desire.
Her BMI is 28 kg/m². She smokes 5 cigarettes.
She needs effective contraception; practiced NFP (calendar method) previously

Question 1

Is there a contraindication to COCs, progestogen-only pill, Copper IUD, Mirena?

Based on large case-control, cohort and very few RCTS

Answer:
COC WHO category II
Other methods Category I

Question 2

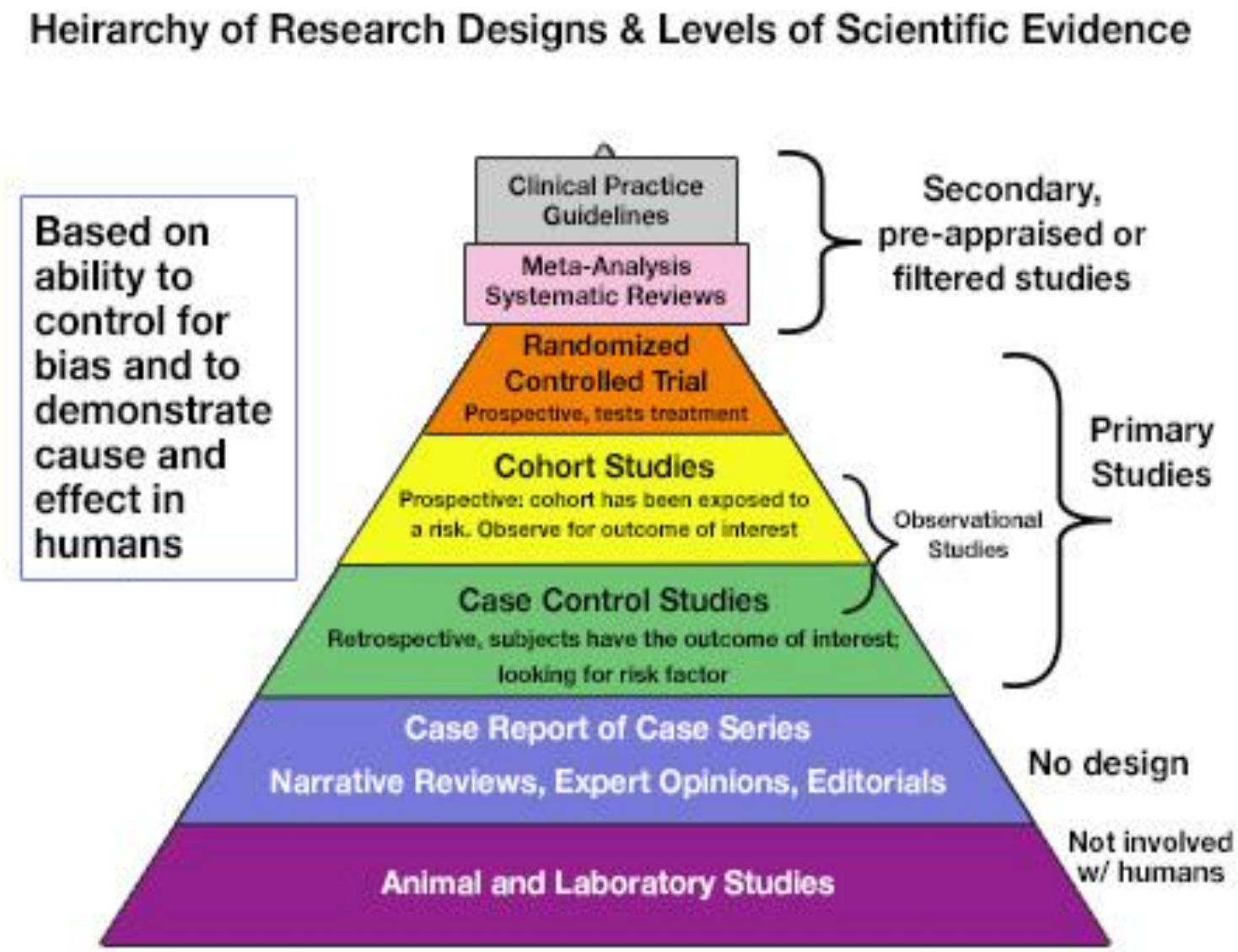
What is the probability of a severe side effect, other side effects, compliance, positive side effects in this patient in case of COC, POP, Copper IUD, Mirena?

There are no RCTs or case control studies to inform the HCP
about effectiveness in this individual woman, the probability of side effects, the compliance, the continuation of these different methods

Answer:
?
Decide under uncertainty

Real-world data from well designed comparative cohort studies can give information about women **with similar risk profiles** using **different methods** about the observed outcomes regarding efficacy, compliance, discontinuation, side effects, benefits, etc

How do we get evidence-based knowledge?



Limitations of observational studies (1)

- Careful study design and analysis is needed to avoid bias arising from:
  - Differences between individuals exposed and unexposed to treatment
    - Unlike in RCTs, people in real-life who receive drugs are quite different from those who don't
      - Confounding by indication is a generalized problem in this setting
      - In order to avoid this problem, it might be desirable to compare drugs with similar indications/contraindications, or to use methods that adjust for confounding factors such as prior comorbidity (e.g. matched designs, regression models, propensity scores, etc.)
  - Incomplete data on predictors
    - Adjustment for confounding factors is mandatory when analysing these data
    - All relevant factors must be available, and such data should be confirmed as being as valid and complete as possible

Limitations of observational studies (2)

- Careful study design and analysis is needed to avoid bias arising from:
  - Incomplete data on events
    - Identification of all relevant events should be ensured, as well as that all identified events are actually relevant
    - Validation studies are key here to ensure both sensitivity and specificity of investigational strategy
  - Selection procedure
    - This is particularly important in (but not exclusive of) case-control studies
    - Controls should be representative of the population that gave rise to the cases, and must be sampled independently of exposure
    - It is also important that exposure status is not influenced by individual responses to a drug (e.g. selection of prevalent users should be avoided)

Key indicators of quality (1)

- Prior evidence obtained from the resource is compatible/replicated with other resources (e.g. RCTs, other observational studies, incidence rates estimated from disease registries, etc.)
  - Availability of data on all predictors of the conditions under study:
    - Comorbidity
    - Prior drug use
    - Life-style factors (e.g. smoking, alcohol)
    - Demographics (e.g. age, gender, body mass index, deprivation, etc.)
    - Identification of study events using clear and reproducible investigational strategies, based on a combination of diagnostic codes, free text, and laboratory test values (if applicable)

Key indicators (2)

- Validation studies
  - Data should not only be available but have their validity verified by other studies
    - Such studies are commonly performed to compare data recorded in a computerised database with that on paper medical records, or on other databases (e.g. comparison of hospitalizations recorded in a primary care database with those recorded in a secondary care database)
    - They are key for validating the methods/steps used to identify study events
  - Proper analysis is needed to ensure that spurious effects of confounding factors are avoided

Guidelines to evaluate observational studies

Real-world application	Standard/Guideline
Study design	• Agency for Healthcare Research Quality (AHRQ): Developing a protocol for observational comparative effectiveness research [AHRQ 2013] • European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist for study protocols [ENCePPa] • ENCePP Guide on methodological standards in pharmacoepidemiology (Revision 5) [ENCePPb] • International Society For Pharmacoeconomics and Outcomes Research (ISPOR) Good research practices for retrospective database analysis task force report (Parts I, II, and III) [Berger 2009; Cox 2009; Johnson 2009]
Data interpretation	• The GRACE checklist: A validated assessment tool for high quality observational studies of comparative effectiveness [Dreyer 2016]
Data reporting	• The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [von Elm 2008]

The aim
Is the research question and hypothesis clearly stated
Is background information important for the research question summarized
Is the design of the study clearly described.
What type of observational study is performed
The sample:
Is it clearly defined. Are all important variables relative to the outcome assessed
Are the data controlled and validated
The exposure:
Is it clearly described (types and duration)
The outcome:
What is measured and how is it measured? Data validation
Statistical methods
Are they appropriate
Discussion:
Are possible confounders addressed. Strength and weaknesses of the study.

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Contraception xx (2016) xxx – xxx

Contraception

Original research article

Impact of estrogen type on cardiovascular safety of combined oral contraceptives☆,☆☆,★

Jürgen Dinger[a,*], Thai Do Minh[b], Klaas Heinemann[b]

[a]*Pharmacoepidemiology, Berlin, Germany*

[b]*ZEG—Berlin Center for Epidemiology and Health Research, Berlin, Germany*

Received 14 March 2016; revised 14 June 2016; accepted 17 June 2016

Objectives:

The International Active Surveillance study "Safety of Contraceptives: Role of Estrogens" (INAS-SCORE) investigated the cardiovascular risks associated with the use of a combined oral contraceptive (COC) containing dienogest and estradiol valerate (DNG/EV) compared to established COCs in a routine clinical setting.

Research questions

Association between different Ocs (independent variable) and Cardiovascular risk (dependent variable)-

Routine setting-

ELSEVIER

Contraception xx (2016) xxx – xxx

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Study Design: Transatlantic, prospective, noninterventional cohort study conducted in the United States and seven European countries with two main exposure groups and one exposure subgroup: new users of DNG/EV and other COC (oCOC), particularly levonorgestrel containing COCs (LNG).

All self-reported clinical outcomes of interest (OoI) were validated via attending physicians and relevant source documents.

Main OoI were serious cardiovascular events (SCE), particularly venous thromboembolic (VTEs) events. Comprehensive follow-up procedures were implemented.

Statistical analyses were based on Cox regression models.

Study Design ?

Sample ?

Outcome : Self reported SCE, VTE

Validation of outcome:

Follow up procedures.

Statistics: Cox regression

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Contraception

Contraception xx (2016) xxx – xxx

Original research article

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Results:

A total of **50,203 new COC users** were followed up for up **to 5.5 years (mean value, 2.1 years).**

Overall 20.3% and 79.7% of these women used DNG/EV and oCOC (including 11.5% LNG users), respectively.

A low loss to follow-up of 3.1% was achieved.

Based on 47 (VTE) and 233 (SCE) events, the primary analysis (European data set) yielded adjusted hazard ratios for DNG/EV vs. oCOC of 0.4 and 0.5, respectively. The upper bounds of the 95% confidence intervals were 0.98 (VTE) and 0.96 (SCE).

The corresponding hazard ratios for DNG/ EV vs. LNG showed similar point estimates but the confidence intervals included unity.

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Conclusion: DNG/EV is associated with similar or even lower cardiovascular risk compared to oCOC and LNG.

Implication Statement: A COC containing DNG and EV is associated with similar or even lower cardiovascular risk compared to COCs containing levonorgestrel or other progestogens.

Discussion

Strength

- Prospective comparative cohort design
- Availability of important confounder information
- Validation of outcomes
- Comprehensive long term outcomes with low loss to follow up
- Independent blinded adjudicated outcomes
- Appropriate statistic tests
- Typical user study population
- Reproducibility of typical time pattern of VTE risk
- Supervision by an independent Safety Monitoring Board

Weaknesses

- Selection bias ?
- Misclassification ?
- Diagnostic bias possible
- It is not possible to infer causality
- Hazard Ratios in a low region

How can we perform evidence-based practice?

The Evidence-Based Medicine triad

(see D.L. Sackett et al, BMJ 1996; 312: 71-72)

Evidence-based good clincial practice: A combination of experimental research and clinical experience

- Real-world cohort studies
- Variability of patients

- Real-world cohort studies
- Accumulated practice experience

- Experimental Studies

Need for practicitioners to refer to accumulated practice experience (number of patients, time of observation)

5 A's of evidence-based practice process

- Ask
- Acquire
- Appraise
- Apply
- Analyze