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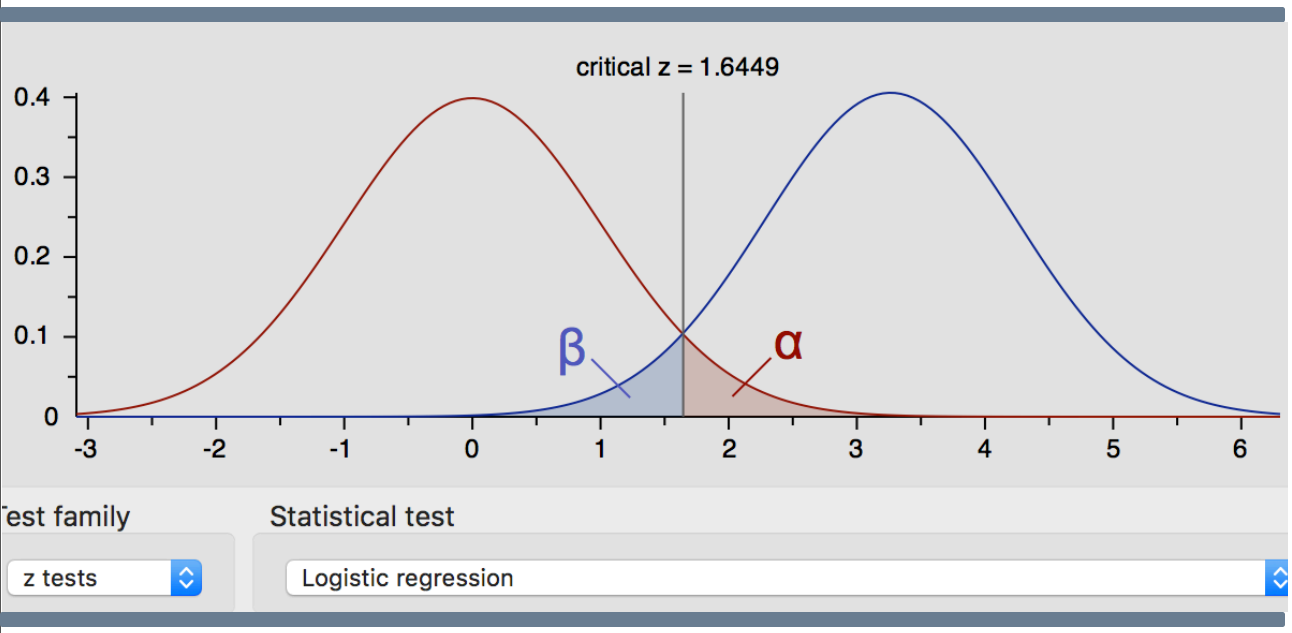
eahp
european association of hospital pharmacists



EAHP ACADEMY SEMINAR
30 September – 1 October 2017, Vienna, Austria

Hospital Pharmacy Practice Research– Scientific Quality

Statistical considerations and pitfalls

The limits of statistical testing

- Helena Jenzer, PhD, Hospital Pharmacist FPH
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Disclosure of conflicts of interest

- Nothing to declare
- My main interest is the patient's outcome (according to the Hippocratic Oath)
- No research funding from private sources

Evaluation of Learning Success

- Do genotypes and/or phenotypes and/or ethnicity have a major impact on the outcome of interventional studies? (y/n)
- Is Data Mining suitable for cohort studies with $100 \leq N \leq 1000$? (y/n)
- Are studies with a sample size below the calculated power likely to be approved by ethical committees? (y/n)

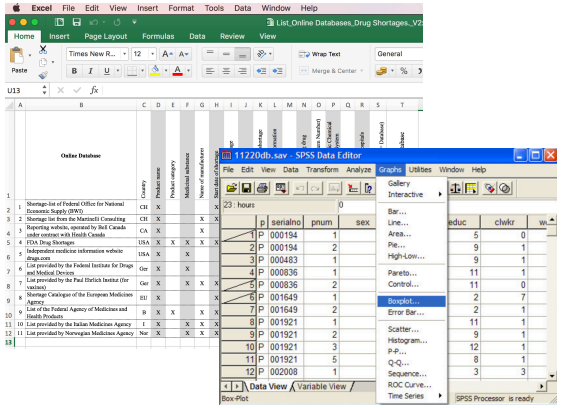
Overview

- Conversion of data to information
- Methodologies and Results Reporting
  - The Impact of Sampling and Recruitment on a wider generalisation of the conclusion
  - Sigmoid growth curves - Look at and Learn from Nature!
  - Data Mining
  - Systemati Review and Meta Analysis
- Summary

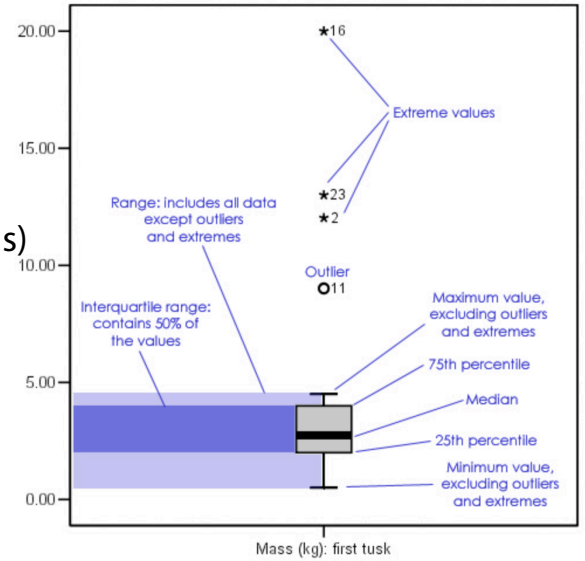
Conversion of data to information

- The importance of accuracy and precision
- Exposure and Outcome on the time line
- Accuracy and Precision
- Evidence

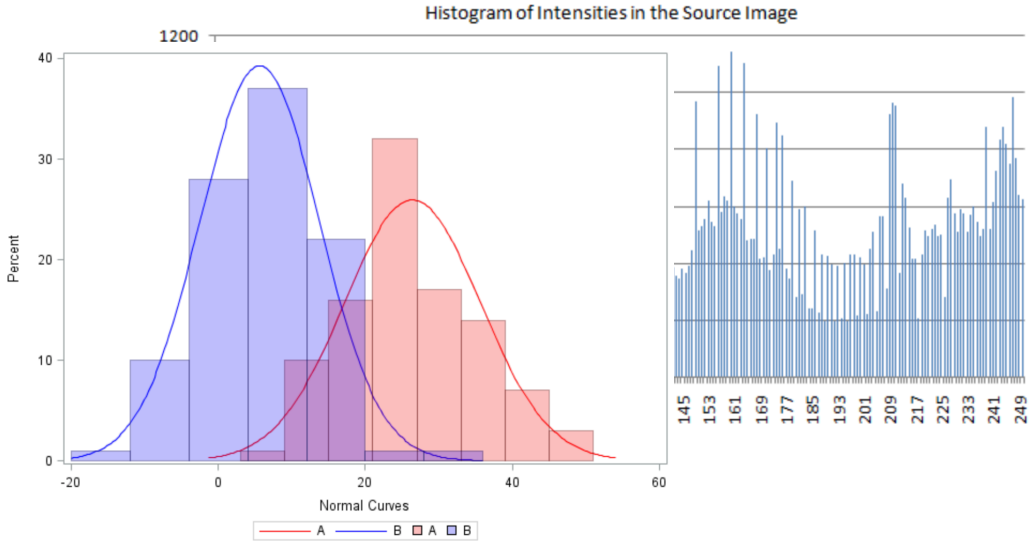
Statistics is a tool to convert data from qualitative or quantitative research into information



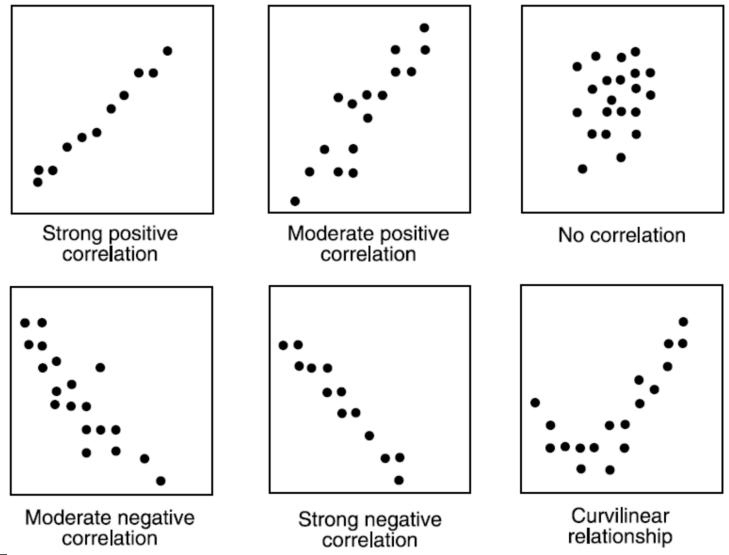
box plot
(median, 1/3 quartiles, max, min, 5/95 percentils)



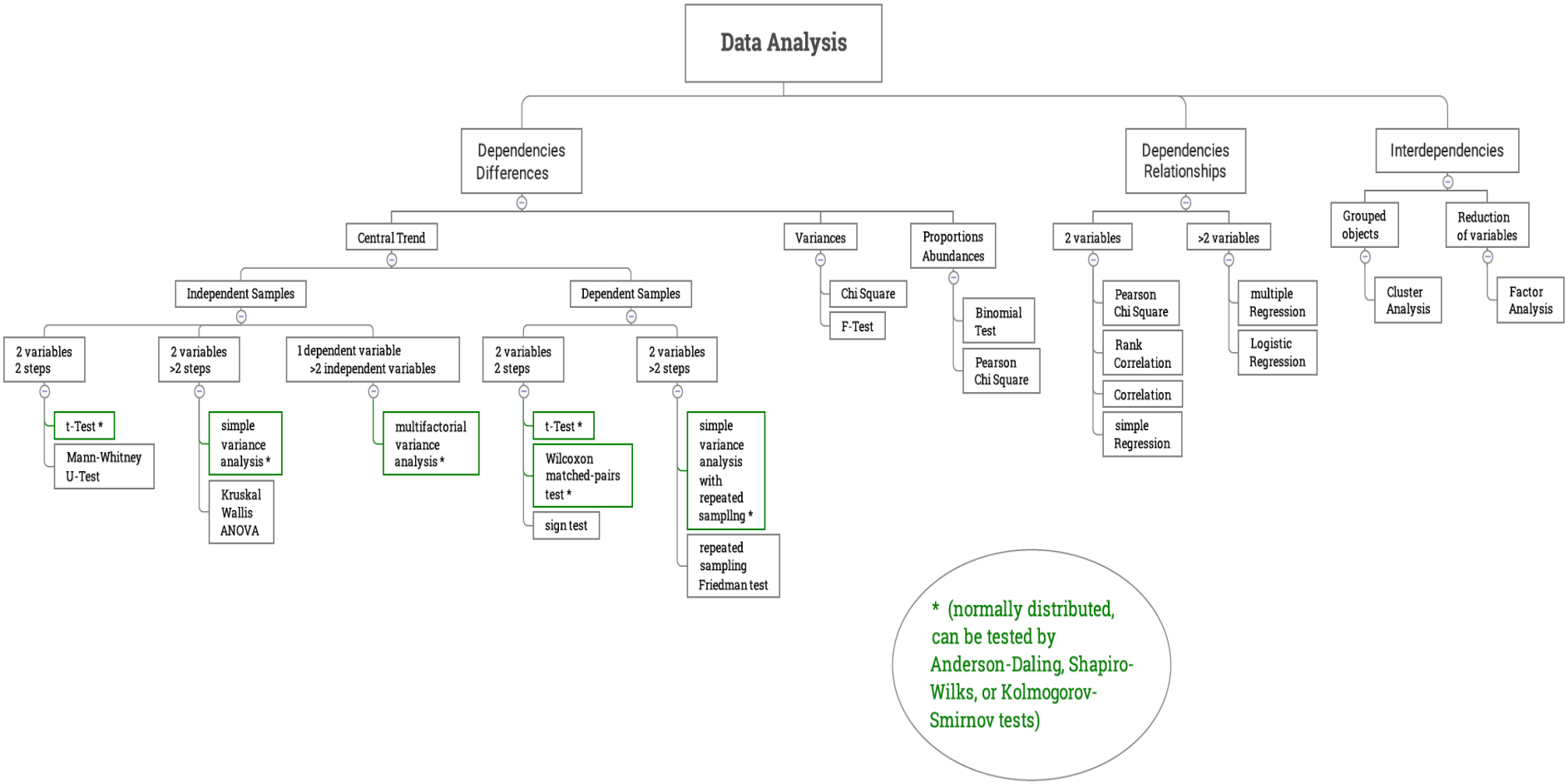
histograms (abundances)



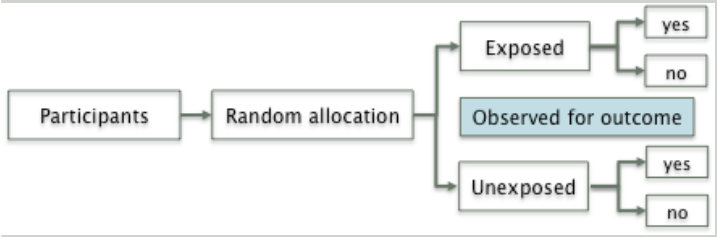
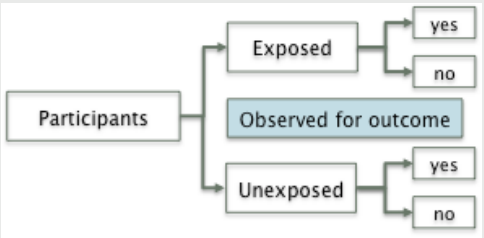
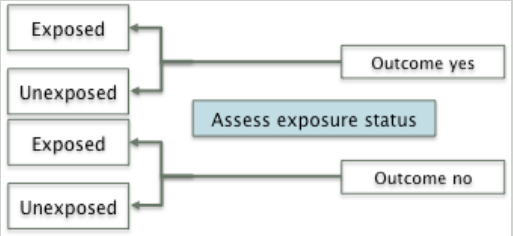
scatterplots
(multivariate data)



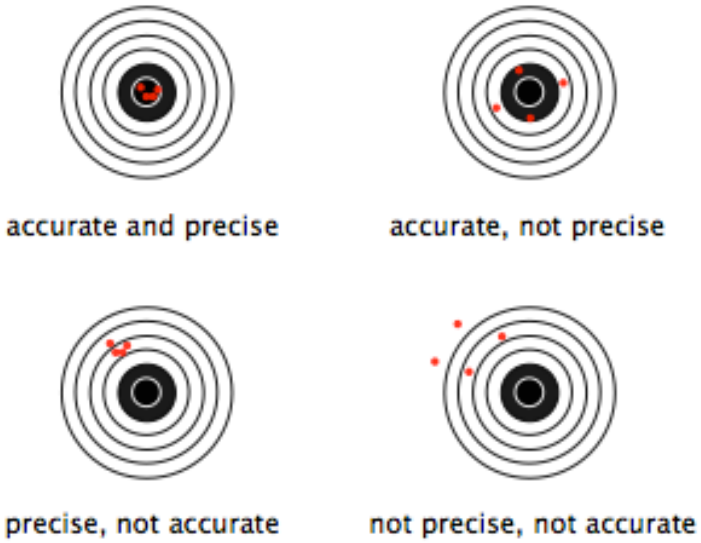
Static Data Analyses – Which data? Which test?

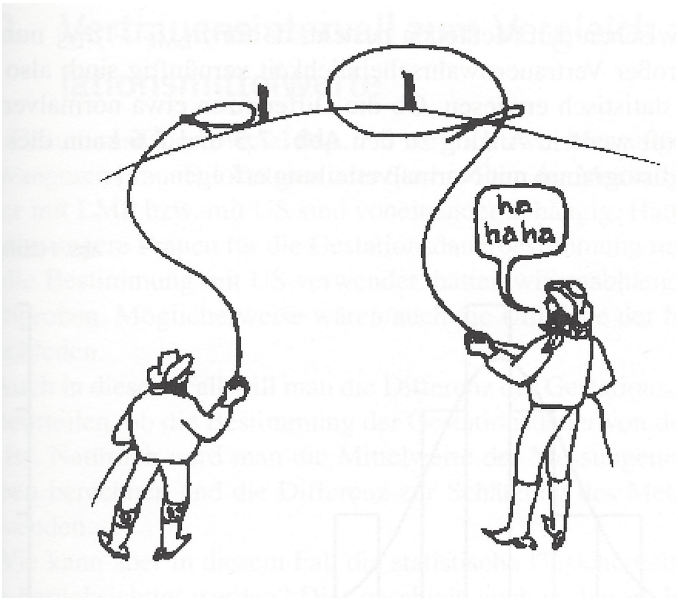


First things first - Exploring exposure and outcome

Study type	Visualisation
Randomised Clinical Trial RCT Randomised allocation to intervention Intervention occurs before the outcome Not always possible, e.g. smoking as intervention	
Cohort studies Observational (observed over time for the outcome) Lowest risk of bias Not always possible Not randomised to exposure	
Case-control studies Individuals with the (rare) outcome are identified and their exposure status is determined (OR as effect measure, best friend / seibling controlled) Risk of confounding: Is another cause possible? E.g. smoking and lung cancer Incidence itself cannot be measured	
Cross-sectional studies Exposure and outcome assessed at the same time Prevalence is measured, not incidence Recall errors (informations bias) Temporal relationship between exposure and outcome often not clear	

Clinical trials and analysis – accuracy and precision (ICH Guideline Q2 Analytical Validation)





- Analysis (Quality Control)
  - Accuracy
  - Precision (repeatability, intermediate precision)
  - Specificity, Sensitivity
  - Detection / Quantitation Limit, Linearity Range
- Exposure and Outcome
- Bias and Confounding
  - Bias = systematic deviation form target (no accuracy, by erroneous selection or information et cetera)
  - Confounding = alternative explanation for an association (e.g. genotype, further exposition(s), metastases / primary tumor, smoking and lung cancer)
- Statistical analysis aimed to produce an estimate of a treatment effect, thus
  - needs suitable Confidence Interval
  - is expected to provide evidence

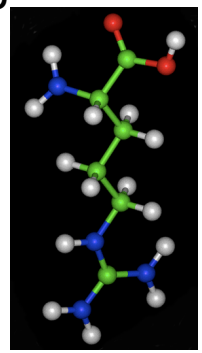
Evidence Levels - No evidence or evidence of no effect?

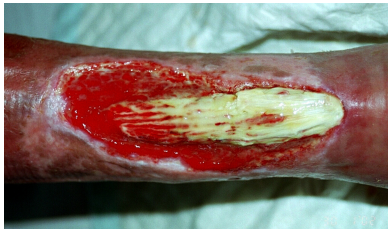
Recommendation Grade	Evidence Level	Criteria
A	1a	systematic Review of **RCT**s
	1b	single **RCT** with small CI
	1c	**Survival** Improvements (all patients died before therapy was available, now some or all patients survive with this therapy)
B	2a	systematic Review of **Cohort Studies**
	2b	single **Cohort Study**
	2c	**Outcome** Research
C	3a	systematic Review of **Case Control Studies**
	3b	single **Case Control Study**
C	4	**Case Series**
D	5	**Expert Opinion** on “First Principles”

- Philips B et al. Levels of Evidence. 2009. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009.

Examples - Unscientific Believe in Evidence

- 1. WHO: association of salt intake and non-communicable diseases
  - Target WHO: ≤ 5g / d, modified target in CH: ≤ 8g / d
  - Which is the henn, which is the egg?
  - Kidneys get more and more insufficient with age -> Hypertension
- 2. Semi-essential AA Arg and Gln supplementation in Wound Healing
  - *"The use of Gln and Arg in Wound Healing has only weak evidence… I recommend semi-essential amino acids only after refeeding and setting up protein and energy metabolism to avoid that amino acids are used to produce energy."*
    (a dietitian in a focus group interview)
  - Wrong use of Arg and Gln -> will never create the needed evidence
  - Biochemistry tells us: use in catabolic metabolic status
    - Glu needs ATP for the biosynthesis of Gln
    - Arg is used by two competing enzymes (arginase and NO-Synthase) in a catabolic metabolism such as hard-to-heal wounds
    - Thus, wrong use of these semi-essential AA
    - Thus, **evidence cannot be created with erroneous indication**
- Thus, evidence
  - is a pharmaco-epidemiologist‘s interest only
  - For dummies who do not know scientific basis
  - depends on the right use / indication of medicines



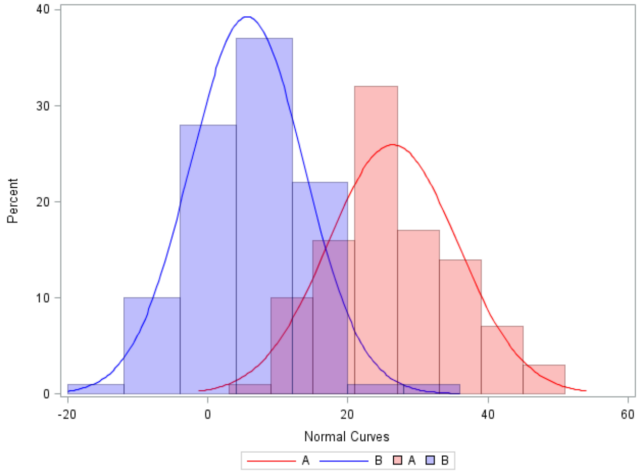


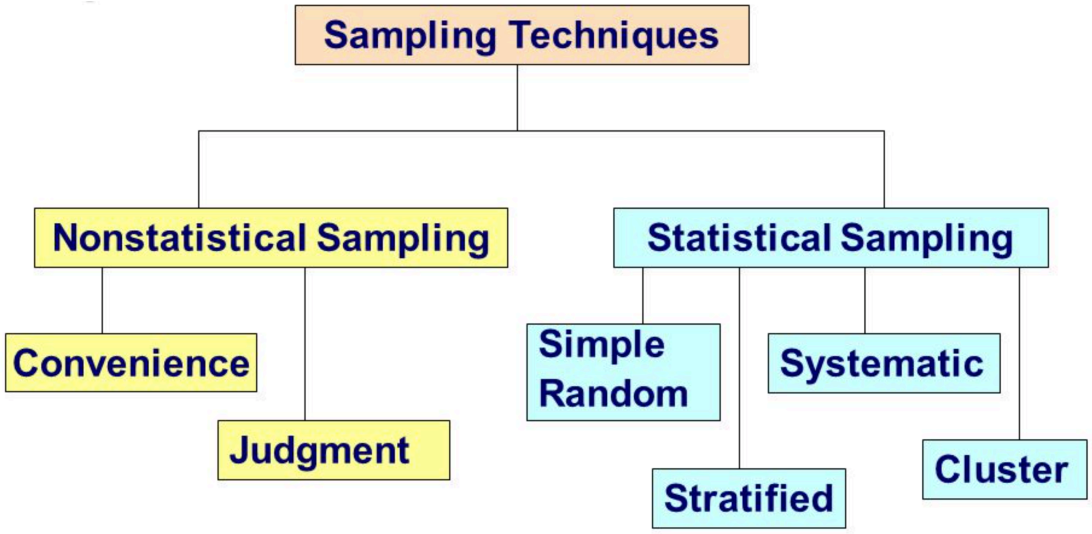
Methodologies - The Impact of Sampling and Recruitment on the wider generalisation

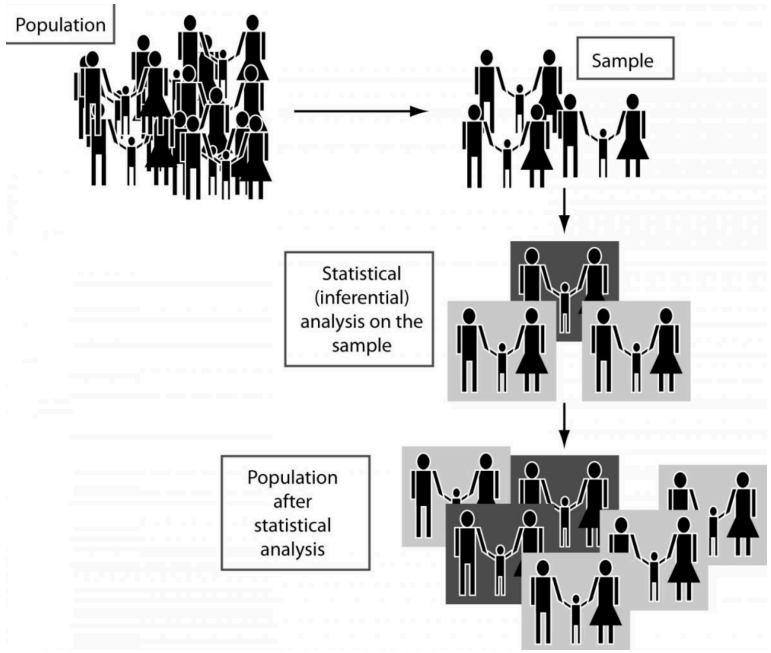
- Basic research
- Experimentation
- Identify research object and measure options

The sample – representative for the population?

- The sampling distribution is the distribution of a statistic across an infinite number of samples
  - How would you take a sample for quality control of a starting material for manufacturing?
  - Same procedure for recruitment of study participants? (different ethnicities! **Do not pool samples!**)





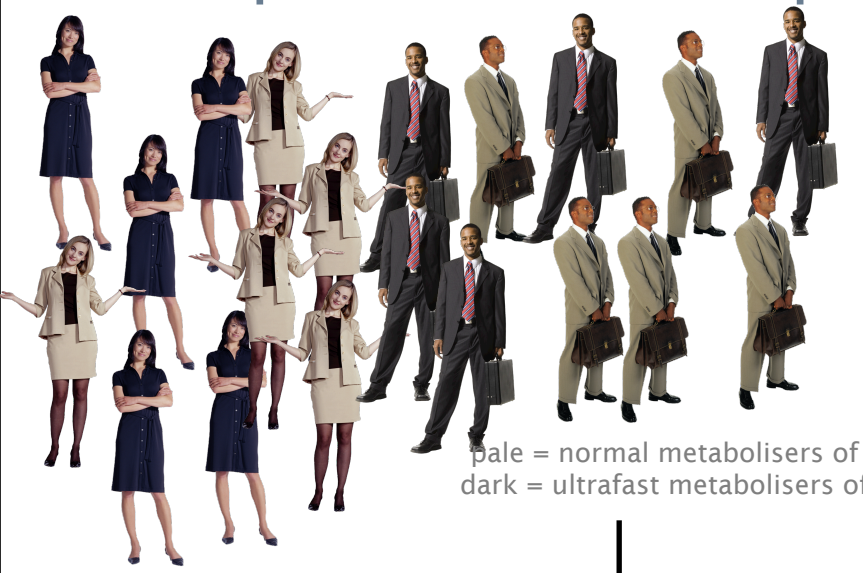


Beware of erroneous generalisations – include / exclude carefully to warrant representativity of sample

- Variables depending on a persons metabolism or being the result of it
  - Gender
  - Age
  - Ethnicity
  - BMI, body weight, lean body mass, fat mass
  - Behaviour (e.g. sedentary life style, high physical activity, nutrition)
  - Simple case – multi-morbid case
  - Social status
  - Regional localisation
  - Single- or multi-centre study
  - Literacy, education
- Independent variables
  - Microorganisms
- Why Rofecoxib (Vioxx®) had to be taken off the market?

Consider these variables (of the random sample) and parameters (of the population) also for evaluation and review of articles!

The importance of considering genetic heterogeneity and personalised requirements (many RCT are potentially wrong)



pale = normal metabolisers of new drug
dark = ultrafast metabolisers of new drug

randomisation

new active ingredient

existing reference

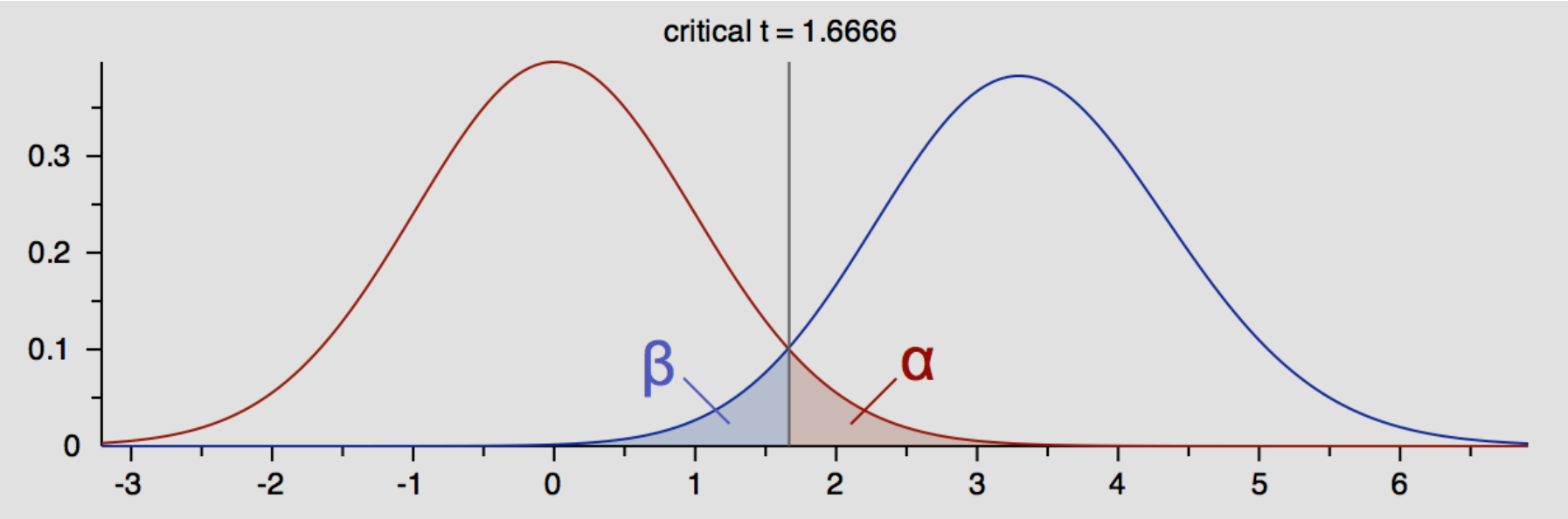
hypothesis: new drug is more effective

Treatment group

Ratio in treatment group: 3 normal, 7 fast
Better effect of new drug is not recognised
Hypothesis is rejected
Type II error

Reference group

Statistical Testing: Error probabilities α (error of the 1st kind) and β (error of the 2nd kind)?



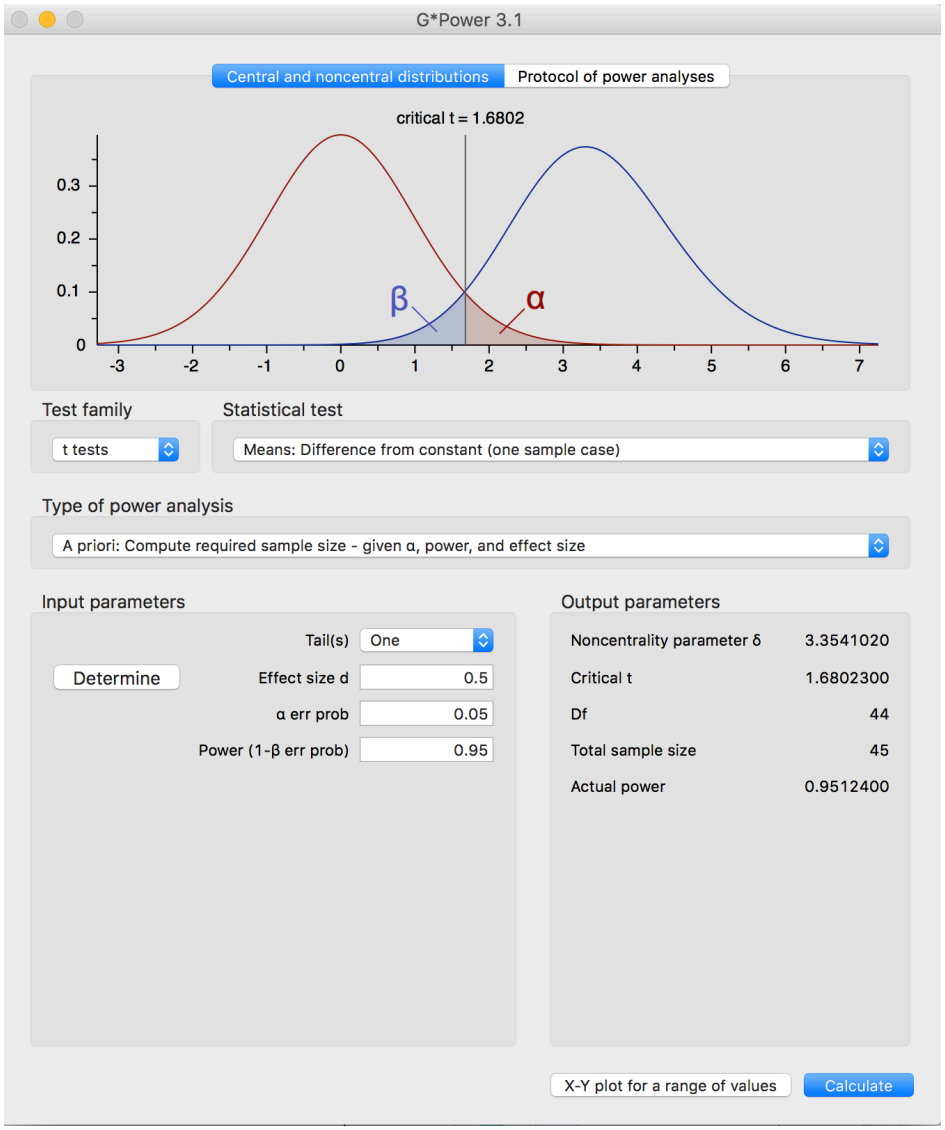
- Wrong attribution, if
  - a value of the red area is attributed to blue population
  - if a value of the blue area is attributed to red population
- d = power = 1-β = complement of the error probability of the 2nd kind

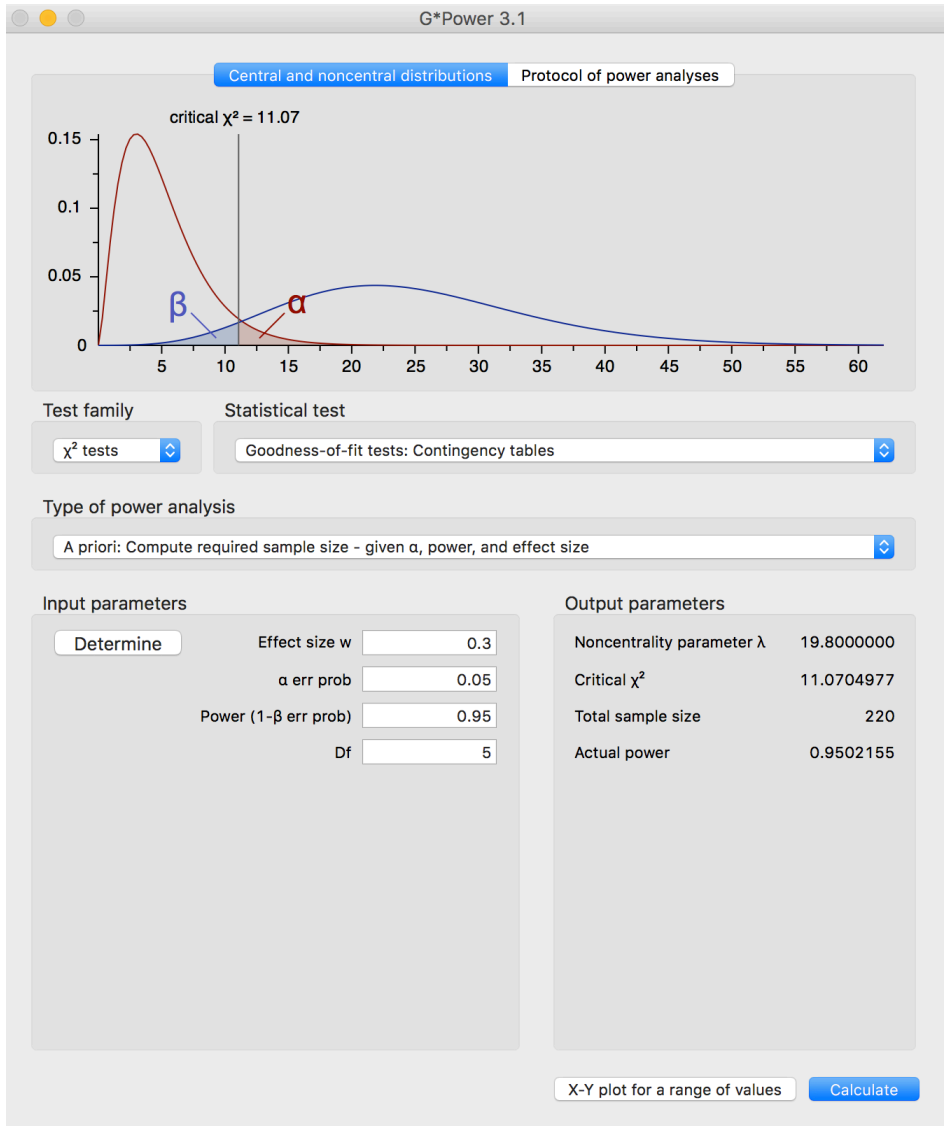
Power Analysis by aid of tables
(Power = complement of the error probability of a 2nd kind = 1 - β)

	α = 5%			α = 10%		
d	β = 5%	β = 7.5%	β = 10%	β = 5%	β = 7.5%	β = 10%
0.001 = 0.1%	47'409	41'675	37'516	37'516	32'436	28'779
0.002 = 0.2%	11'853	10'419	9'379	9'379	8'109	7'195
0.005 = 0.5%	1'897	1'667	1'501	1'501	1'298	1'152
0.01 = 1%)	475	417	376	376	325	288

- Example single random sample
  - Aim:
    - True H_0 rejected with α_{max} 5% and true H_1 rejected with β_{max} 5-10%
    - H_0: $\pi \leq x = \pi_0$, H_1: $\pi > x = \pi_0$ where x is a (literature) reference value, (e.g. a mortality rate)
- **In reality, N depends on practical issues: Cost? Time? Available patients?**

Power Analysis: Estimation of the required sample size (Power = complement of the 2nd kind error probability)





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

ABSTRACT

BACKGROUND

Observational cohort studies and a secondary prevention trial have shown an inverse association between adherence to the Mediterranean diet and cardiovascular risk. We conducted a randomized trial of this diet pattern for the primary prevention of cardiovascular events.

METHODS

In a multicenter trial in Spain, we randomly assigned participants who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). Participants received quarterly individual and group educational sessions and, depending on group assignment, free provision of extra-virgin olive oil, mixed nuts, or small nonfood gifts. The primary end point was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). On the basis of the results of an interim analysis, the trial was stopped after a median follow-up of 4.8 years.

RESULTS

A total of 7447 persons were enrolled (age range, 55 to 80 years); 57% were women. The two Mediterranean-diet groups had good adherence to the intervention, according to self-reported intake and biomarker analyses. A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). No diet-related adverse effects were reported.

CONCLUSIONS

Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events. (Funded by the Spanish government's Instituto de Salud Carlos III and others; Controlled-Trials.com number, ISRCTN35739639.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Estruch at the Department of Internal Medicine, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain, or at restruch@clinic.ub.es, or to Dr. Martínez-González at the Department of Preventive Medicine and Public Health, Facultad de Medicina–Clínica Universidad de Navarra, Irunlarrea 1, 31008 Pamplona, Spain, or at mamartinez@unav.es.

*The PREDIMED (Prevención con Dieta Mediterránea) study investigators are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Estruch and Martínez-González contributed equally to this article.

This article was published on February 25, 2013, and updated on February 27, 2014, at NEJM.org.

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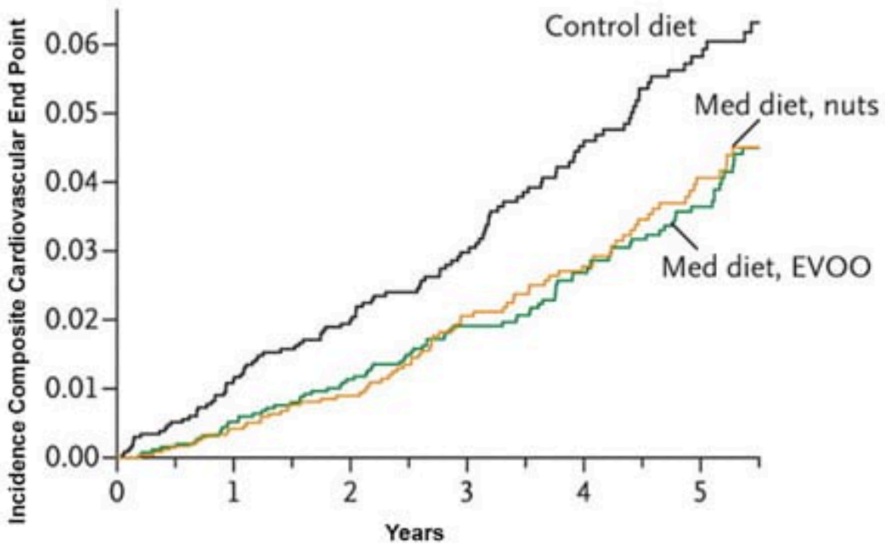
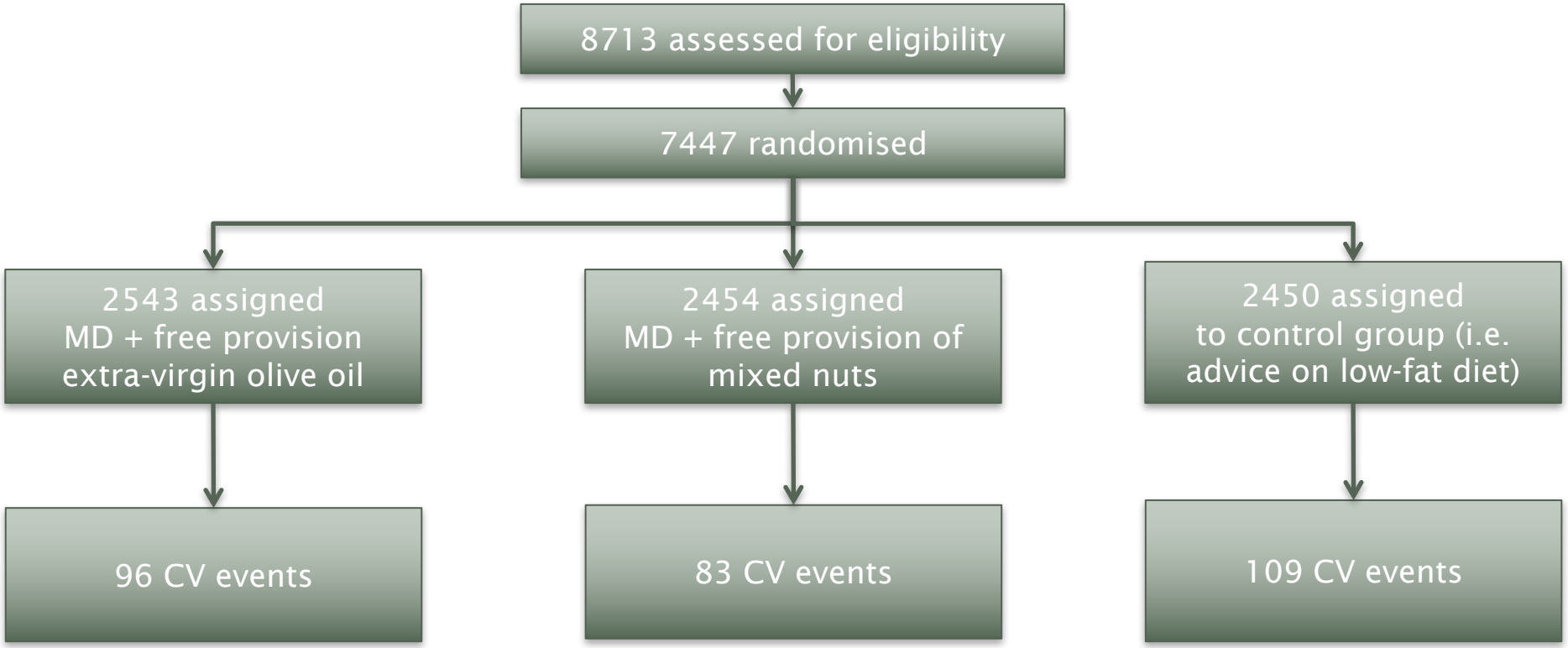


Example PREDIMED study

- Estruch R, et al. Primary prevention of cardiovascular disease with a mediterranean diet. NEJM 2013;368(14):1279-1290.
- Many objections due to **multiple bias, multiple confounding**
- Main objection: **Study population. Participants from the mediterranean region only. Cannot be extrapolated to other populations**



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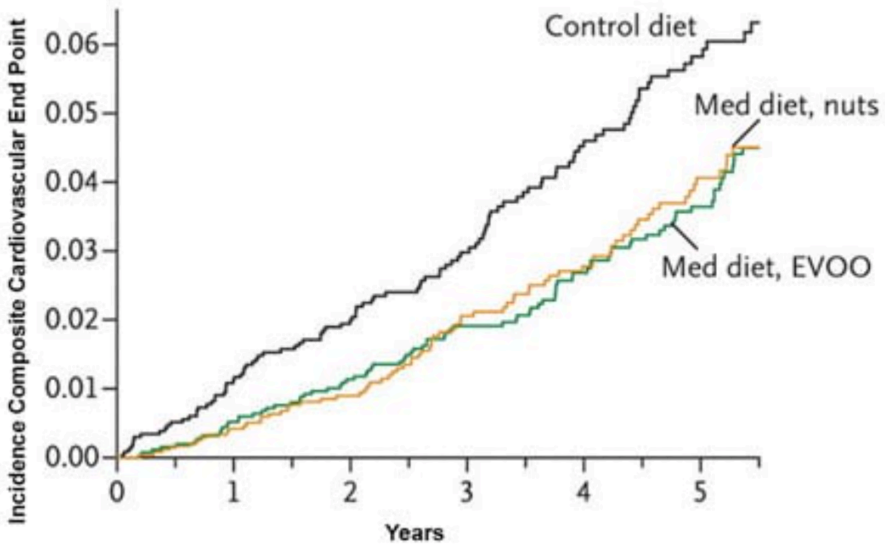


Main confounders:

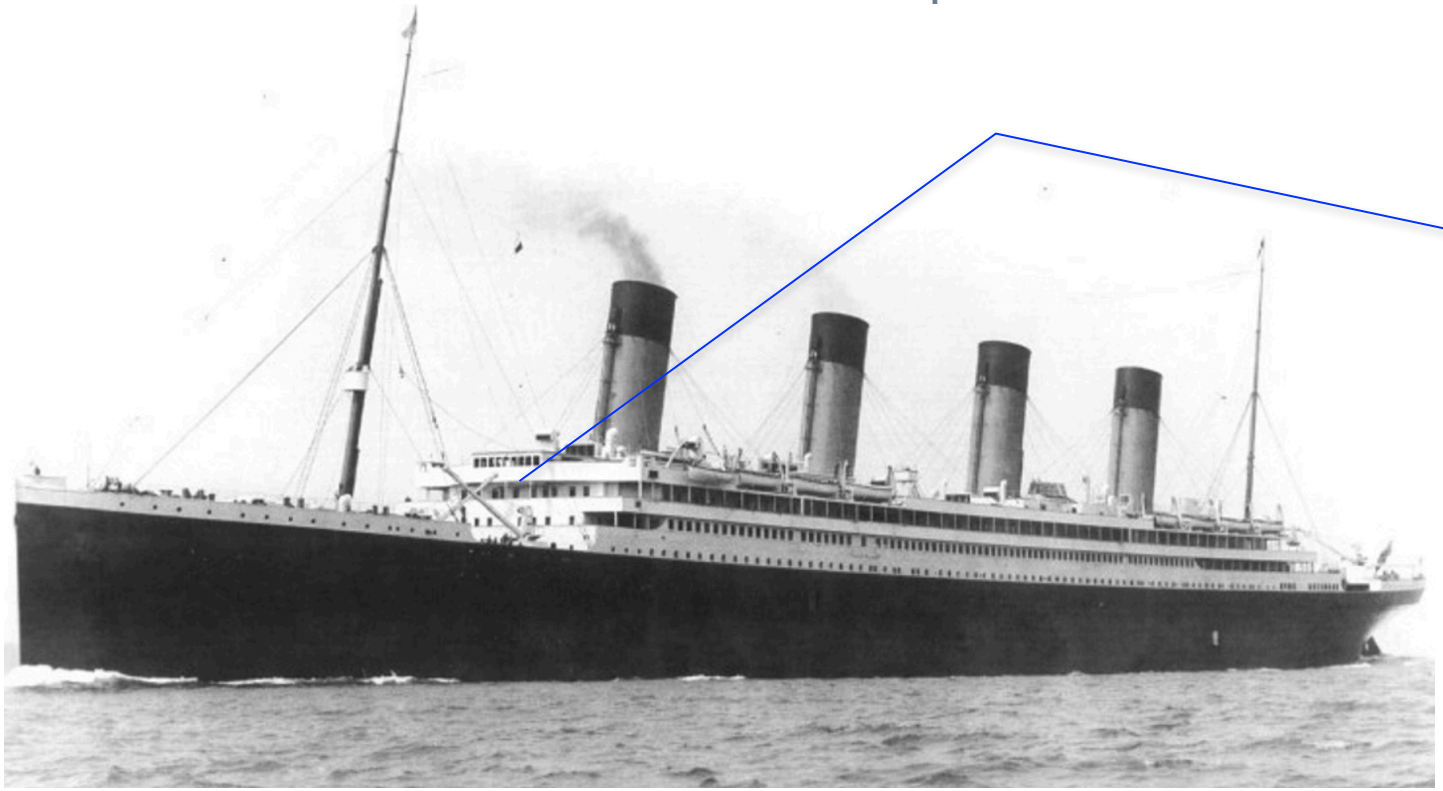
- only significant in men, not women
- risk of stroke down by 39% in the Mediterranean diet groups, but no significant difference in heart attacks
- dropout rates twice as high in the control group (11.3%), compared to the Mediterranean diet groups (4.9%)
- people with high blood pressure, lipid problems or obesity responded best
- no statistically significant difference in total mortality (risk of death)
- Study from Spain - may not be conclusive for other ethnicities

Nutritonal Medicine‘s Problem:
A matter of confounding with baseline characteristics

The captain‘s body weight

=

The ocean liner with the captain – The ocean liner alone



- Is the weight of the liner really constant? (no input/output allowed, e.g. blind passengers, whale hunting, seagulls, …)
- Compare: Are nutrition’s and wound healing’s blackboxes constant? Do not measing an artefact which has nothing to do with the object!

Methodologies - Sigmoid growth curves - Look at and Learn from Nature!

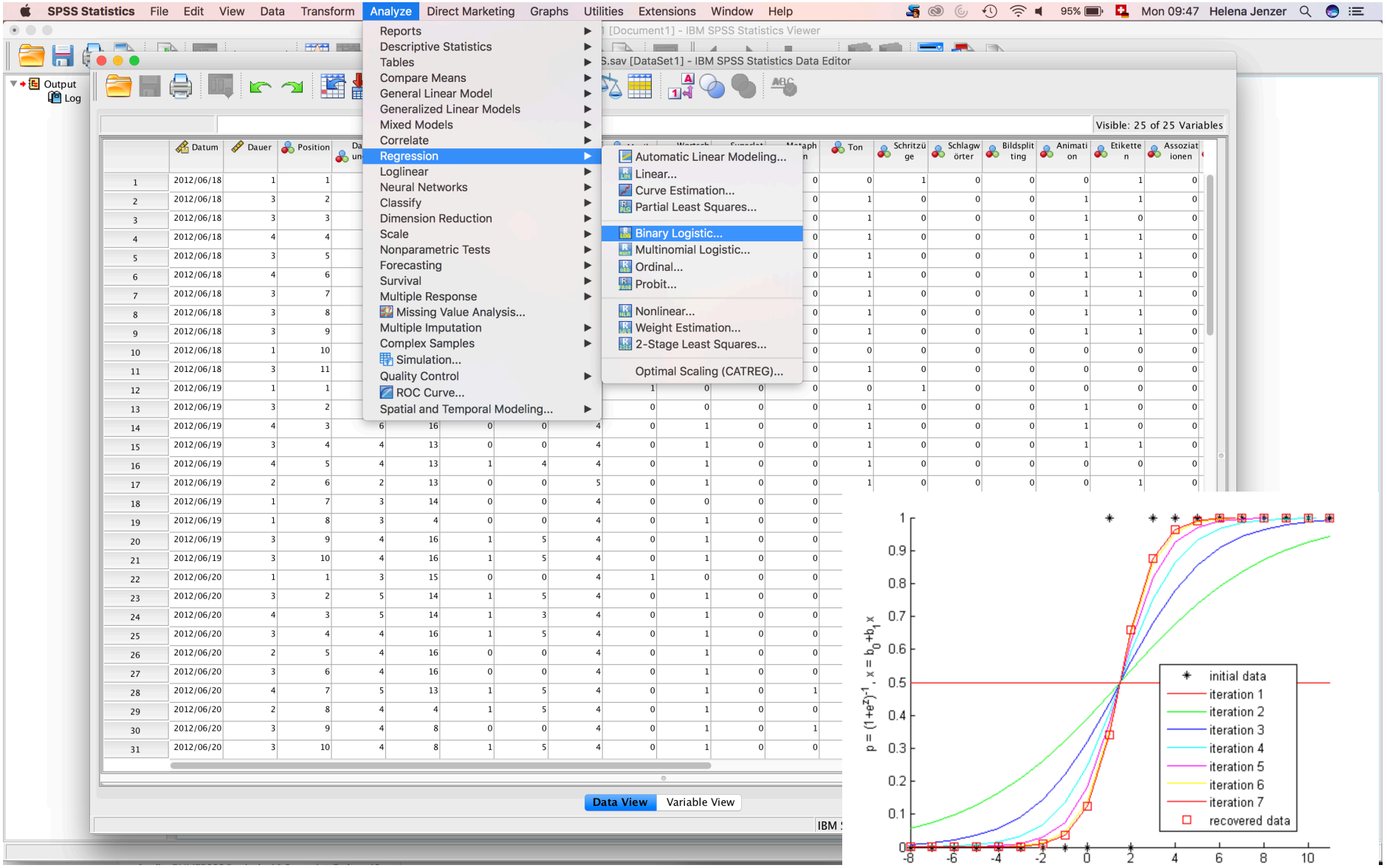
- Systems Dynamics in Complex Networks – COST Action CA15105 on Medicines Shortages
- Binary Logistic Regression

Observation time length: Effect on evidence?

Research area	Surrogate endpoint	Clinical outcome
Cardiology	Cholesterol level Blood pressure	CV-related mortality
Oncology	Tumor response	Cancer-related mortality
Infectiology	CD4 cell count	Development of AIDS HIV-associated mortality
Rheumatology	Bone mineral density	Osteoporosis-induced fractures

- Surrogate endpoint
  - Can be measured earlier in the course of a disease than clinical outcome
  - Less influence by competing risks
  - Reduction of sample size and of costs
  - **But: is not equal to the clinical outcome**

Binary Logistic Regression

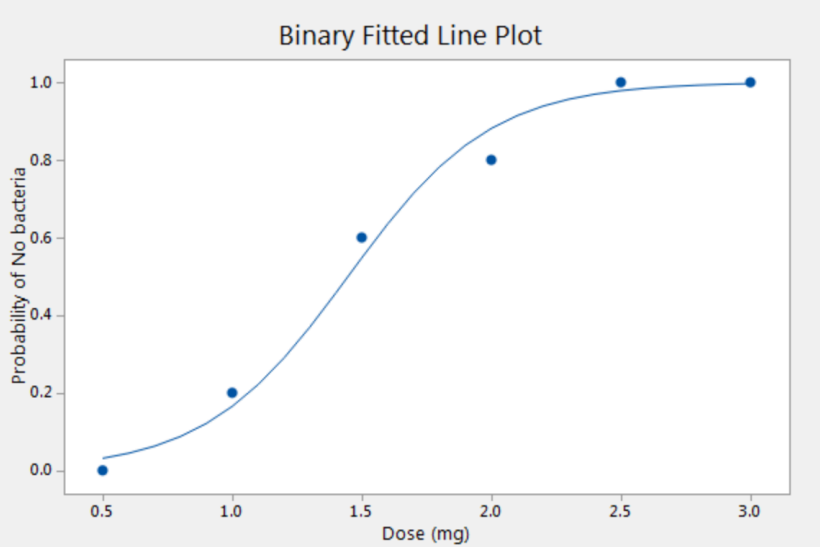


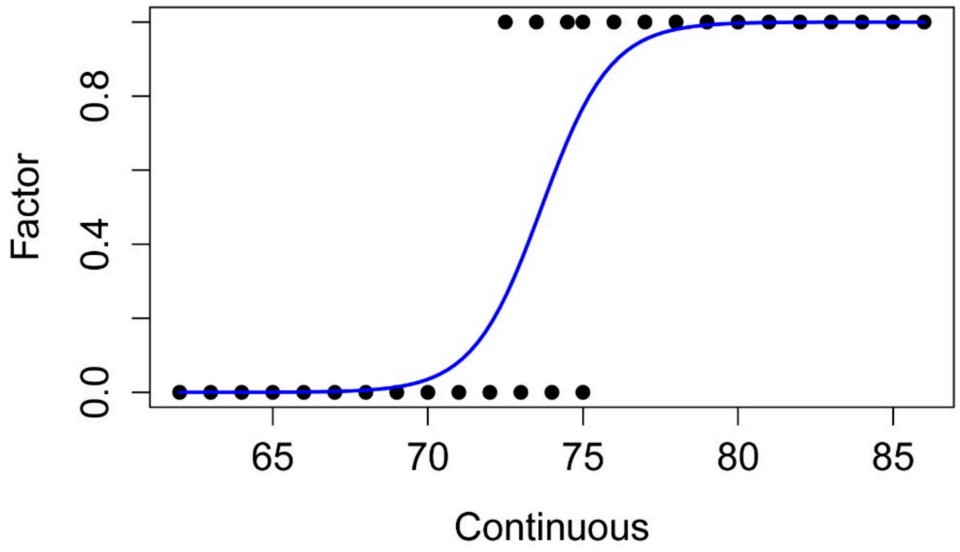
Binary Logistic Regression

- To analyse whether there is a dependency between multiple independent variables (x) and a binary dependent variable (y)
- Binary means y/n, male/female, taken/not taken...
- Logistic regression function

$$P(y=1) = 1 / (1 + e^{-(\beta 0 + \beta_1 * x_1 + \beta_2 * x_2 + \ldots \beta_k * x_k + \varepsilon)})$$

where β and ε are coefficients

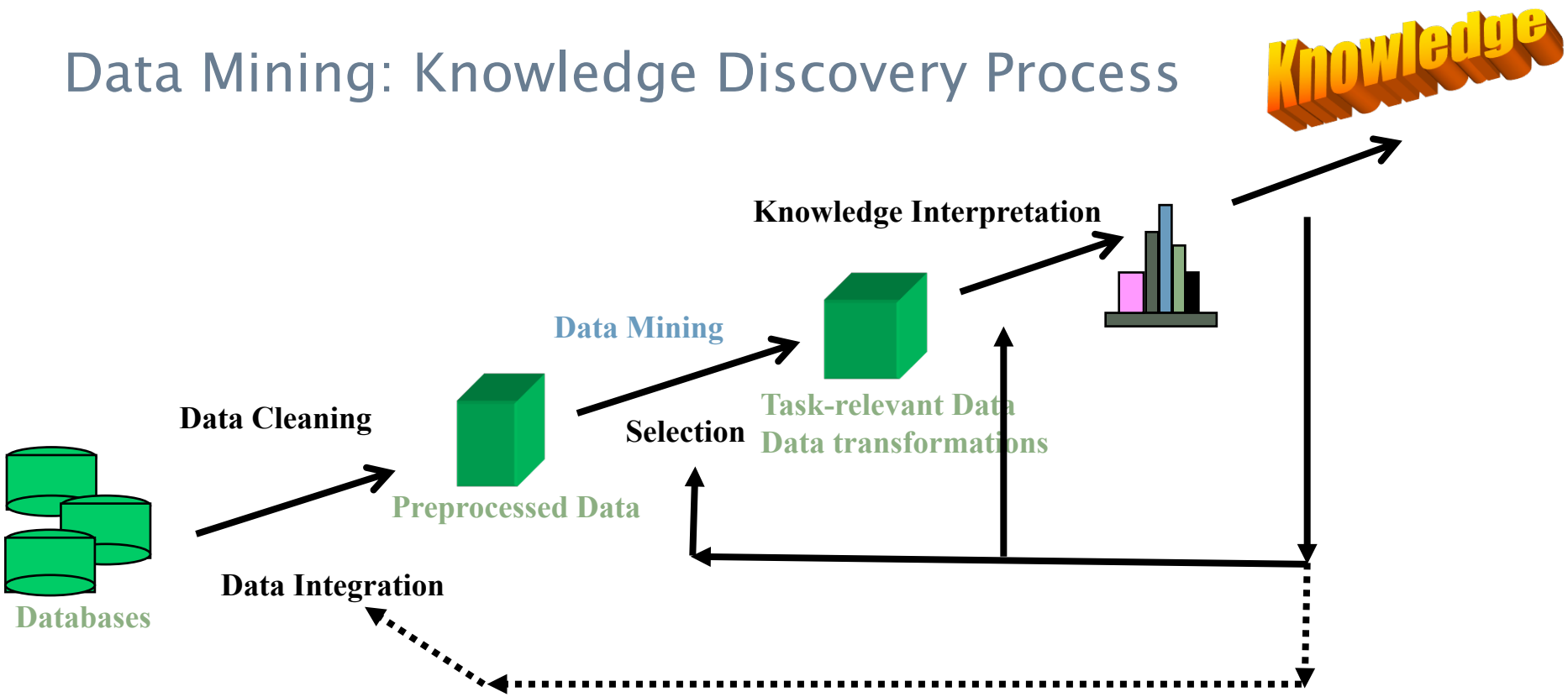




Methodologies - Data Mining (to find associations by experimentation rather than by project management)

- Big data
- Query & Answer
- Dig in the Data - Explore – Find rules - Create New Knowledge

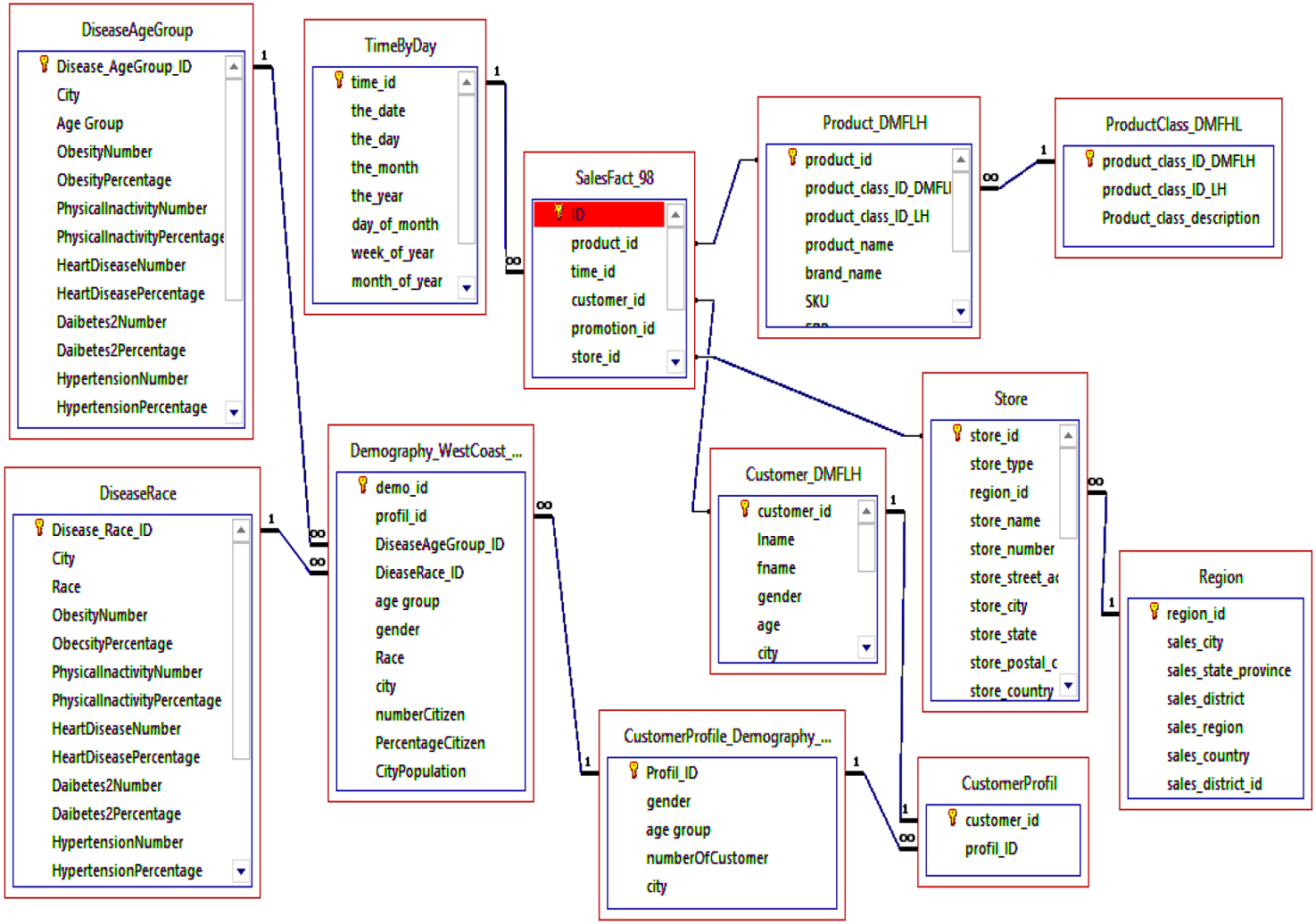
Data Mining: Knowledge Discovery Process



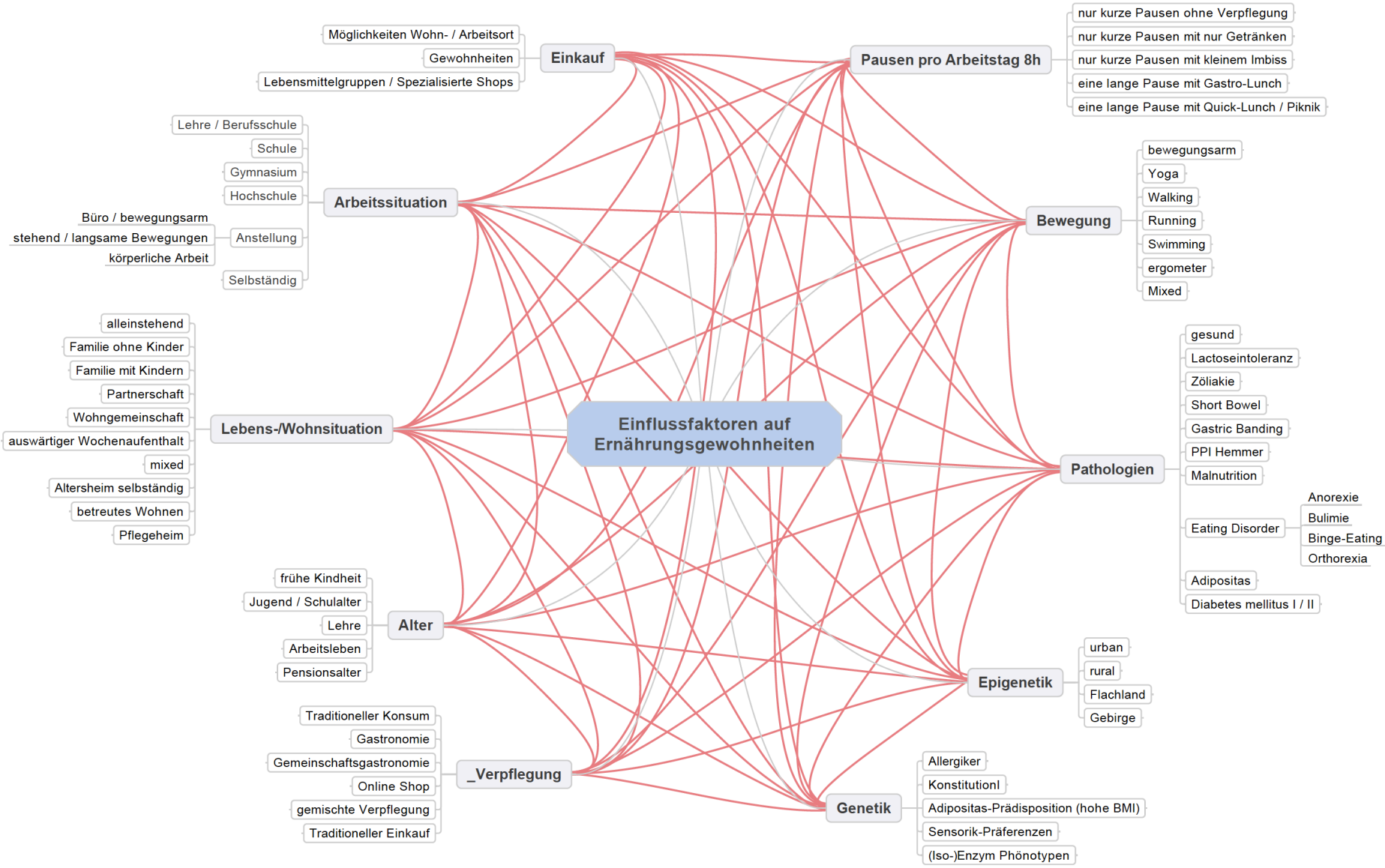
- Objective: To discover hidden patterns linked with non-communicable / lifestyle diseases
- **Difference between data mining and classical hypothesis-first statistical analysis**
  - **Classical Statistics to form evidence in support or against a hypothesis from a more limited set of data**
  - **Data Mining: to extract unknown relationships / clusters or recognize patterns in a huge dataset**
- Applied research in nutrition and dietetics: Dietary Patterns *(in pharmacotherapy: drug use)* and
  - Obesity (BMI >30)
  - Sedentary behavior: No exercise in the last 30 days
  - Hypertension and CV diseases
  - Type 2 Diabetes
  - Cancer
  - Mental disorders
  - Binge drinking

Data Mining needs big data

- Relate databases (Grocery Store, Demographical, and lifestyle diseases DB
- Clean, preprocess, integrate, build demographical classes (age, races)
- Q&A: find relevant associations and rules between dietary patterns, demographics and lifestyle diseases



Network of variables and their impacts on each other



Query & Answers – examples of identified patterns

- Rule 1: 25-34 years old from Los Angeles show the highest critical buy index for confectionary, salt containing, and high sodium content-products among all age groups from the same region, and tend to have a sedentary behavior as well as frequent binge drinking episodes.
  - Interpretation: This age group displays consumption and lifestyle behaviors that should be addressed as part of focused health promotion initiatives.
- Rule 2: 65-84 years old from Los Angeles show critical buy indexes of savory snacks and ready-to-eat products, both susceptible to contain high sodium levels. This group shows the highest hypertension and heart disease rates among all age groups as well
  - Interpretation Salt consumption behavior among this age group needs to be addressed in an effort to decrease cardiovascular disease rates.
- Rule 4: Critical buy indexes for pasta, bakery wares, rice and sugar has been noted among all age groups in Spokane
  - Interpretation: This may be associated with the generally high rates of obesity in Spokane.
- **Rule 7:** Caloric beverages with some nutrients show critical buy indexes among all age groups in Spokane.
  - **Interpretation:** Caloric beverages may contribute to the high prevalence of obesity. Preventive public health measures should tackle this issue.
- *Einsele F, Sadeghi L, Ingold R, Jenzer H. A study about discovery of critical food consumption patterns linked with lifestyle diseases using data mining methods. DOI: 10.5220/0005170402390245. In: Proceedings of the International Conference on Health Informatics (HEALTHINF-2015);239-245. ISBN: 978-989-758-068-0.*

Methodologies and Results Reporting

- Systematic Review
- Meta Analysis

Systematic Review vs Meta Analysis

- Difference
  - Statistical analysis aimed to produce an estimate of a treatment effect
    - It is appropiate and desirable to perform a systematic review of a body of data, may sometimes by inappropiate or even misleading to statistically pool results from separate studies -> resist temptation!
- Pooling
  - To estimate the effect of an intervention or determinant
  - Advantage:
    - Higher precision/more power
      - Detect small effects
      - Detect effects in subgroups
    - No increased validity
  - Two principles are important
    - Simply pooling the data and treating as one large study would fail to preserve randomisation and introduce bias and confounding
  - Calculating a mean is inappropriate
    - Small studies are subject to chance -> less weight

Validity of the sample‘s profile for other populations is not granted!

- Example (Forest PloT)
  Colditz GA, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. JAMA 1994;271(9):698-702.

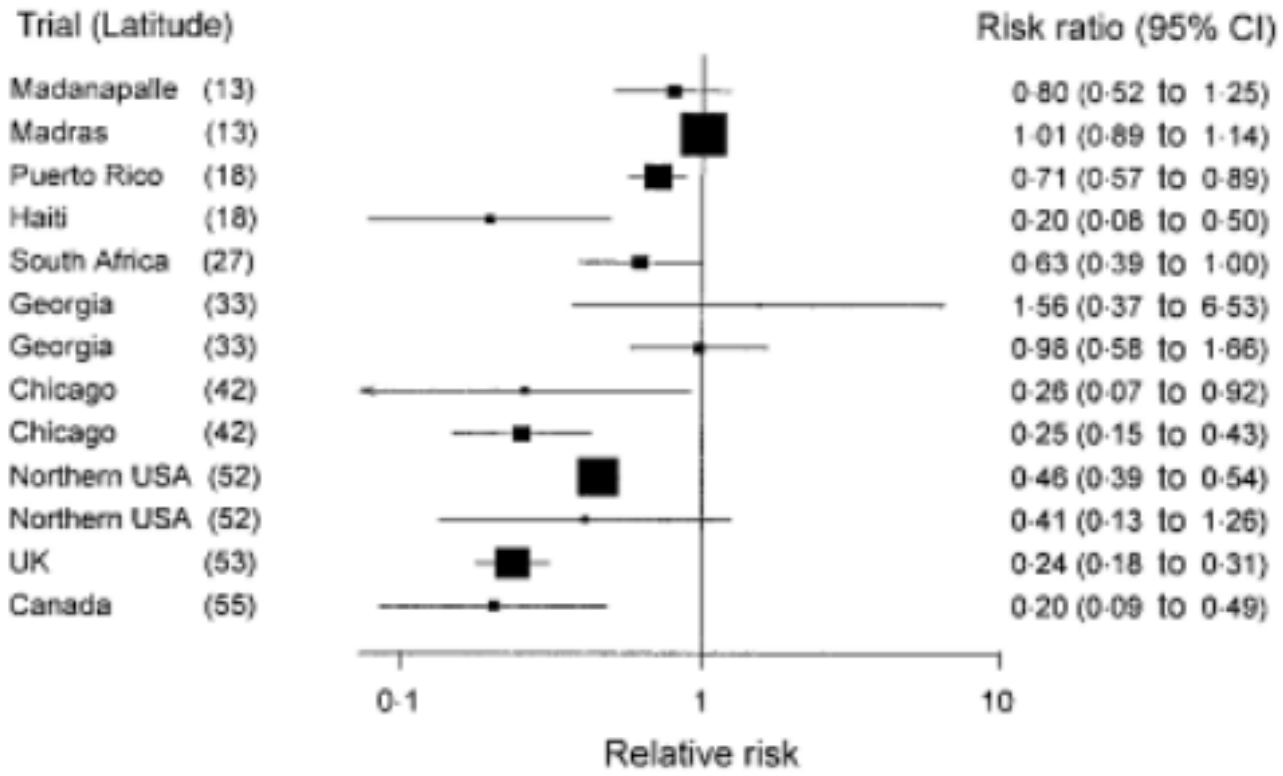


Figure 2.3 Forest plot of trials of BCG vaccine to prevent tuberculosis. Trials are ordered according to the latitude of the study location, expressed as degrees from the equator. No meta-analysis is shown. Adapated from Colditz *et al.*[32]

Meta Analysis pitfalls

- **Risk of heterogeneity**
  - If $p<0.05$ -> no homogeneity
- Qualitative data extraction
  - Population characteristics
  - Exposure/intervention
  - Outcome
  - Potential confounders
  - Study characteristics, including quality of study
- Quantitative data extraction
  - Normally distributed estimation of effect parameter
    - Dichotomous (RR, OR, RD, RRR, NNT)
    - Continuous (mean difference, standardized mean difference)
  - Variance (or SE) of this estimation
- **Bias**
  - Publication (Studies with significant results are more likely to get published)
  - Selection (Comparability of included patients)
  - Performance (Differences in care provided between groups)
  - Detection (Differences between groups how outcomes are determined)
  - Attrition (Differences between groups in withdrawals from study)

Meta Analysis – Risk of bias assessment (Cochrane)

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Summary

Summary

- The need of accuracy and precision (coping strategy against biases)
- Evidence can be obtained only with correct indication and use
- Multiple impacts of correct sampling (e.g. genotype, geographics)
- Power analysis to estimate required sample size
- Meta-analysis: beware of heterogeneity
- Data-Mining for pattern recognition
- Growth curves and binary logistic regression

Evaluation of Learning Success

- Do genotypes and/or phenotypes and/or ethnicity have a major impact on the outcome of interventional studies? (y/n)
- Yes, as long as the variables are part of the participants metabolism
- Is Data Mining suitable for cohort studies with $100 \leq N \leq 1000$? (y/n)
- No, because pattern recognition needs “big data”
- Are studies with a sample size below the calculated power likely to be approved by ethical committees? (y/n)
- Yes, as cost or availability of patients may be limited

That's all folks – questions or party?