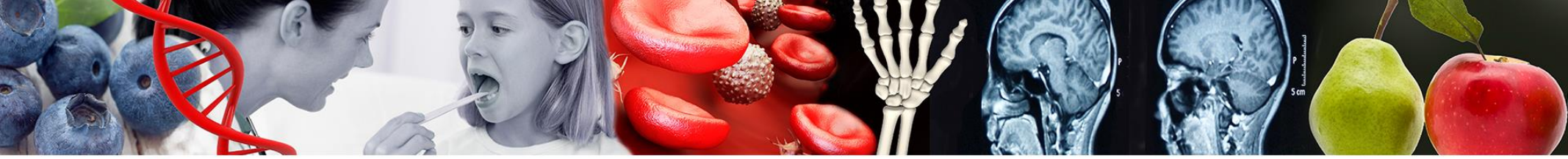


UiO : Institutt for medisinske basalfag
Det medisinske fakultet

MF9130E – Introductory course in statistics, spring 2024

Lecture: Study designs: epidemiological designs and concepts, principles of clinical trials

Jo S Stenehjem (slides also by Marit B Veierød),
Senior Researcher, Dept of Biostatistics, University of Oslo
Senior Researcher, Dept of Research, Cancer Registry of Norway

Outline

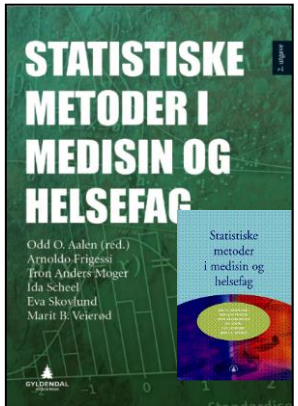
- 08.30-10.00: Part I. Epidemiological studies
  - 09.40-10:00: Mini-groups, discussion
- 10.00-10.15: Break
- 10:15-11.30: Part II. Clinical studies/summary
  - 10:10-11:30: Mini-groups, discussion
- 11:30-11:45: Part III. Questions

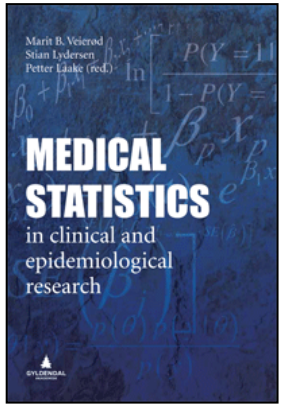
Readings/literature

- Kapittel 9&10. Aalen (red), Frigessi, Moger, Scheel, Skovlund, Veierød. Statistiske metoder i medisin og helsefag. Gyldendal Akademisk 2006
- Chapter 34. Kirkwood, Sterne. *Medical Statistics*. 2nd ed. Blackwell Science Ltd 2003'

Additional readings:

- Chapter 1. Veierød, Lydersen, Laake (eds.) *Medical statistics in clinical and epidemiological research*. Gyldendal Akademisk, 2012. www.medicalstatistics.no
- Laake, Hjartåker, Thelle, Veierød (red). Epidemiologiske og kliniske forskningsmetoder. Gyldendal akademisk, 2007.





Learning outcomes

The participants shall get a basic understanding in the following areas: Elementary probability; probability distributions: binomial distribution and normal distribution; design of clinical trials and epidemiological studies; statistical theory of estimation; construction of confidence intervals; testing statistical hypotheses; analysis of paired data and comparison of two samples; analysis of tables; linear regression analysis with one or several explanatory variables; survival analysis.

Learning outcomes for the lecture

- Know the key-features of different designs
- When we can use different designs
- Pros and cons with different designs
- Briefly methods used for the different designs – more later this week

Outline Part I. Epidemiological studies:

- Overview
- Ecological
- Cross-sectional
- Case-control
- Cohort
- Summary methods
- Case: Group discussion

Epidemiology definition (Porta, 2014):

The study of the occurrence and distribution of health-related events, states and processes in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems.

Epidemiologi definisjon (Porta, 2014):

The study of the occurrence and distribution of health-related events, states and processes in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems.

- *Occurrence and distribution (norsk: forekomst)*
- *Health-related events, states and processes (norsk: utfall/sykdom)*
- *Populations (norsk: befolkninger)*
- *Determinants (norsk: årsaker)*

Simple definition

The study of distribution and causes of disease in a population

Distribution and causes of disease

At the core of epidemiology lies the ability to acquire knowledge about the causes and distribution of a disease

We have to ask ourselves:

- *Who get sick? (distribution)*
- *Why does some get sick, while others does not? (causes)*

Distribution

The distribution may be studied by some central axes:

- **Time:** How does the disease distirubtion develop over time? Does it change?
- **Age:** Is the incidence different in different age group?
- **Place:** Is the incidence different at different places?

Causes / exposures – some examples

External factors

- Occupation
- Environment
- Biological (virus, bactera, toxines)
- Diagnostic pressure?

Host factors

- Chronic diseases
- Immunological

Does the incidence differ among the exposed vs the unexposed?

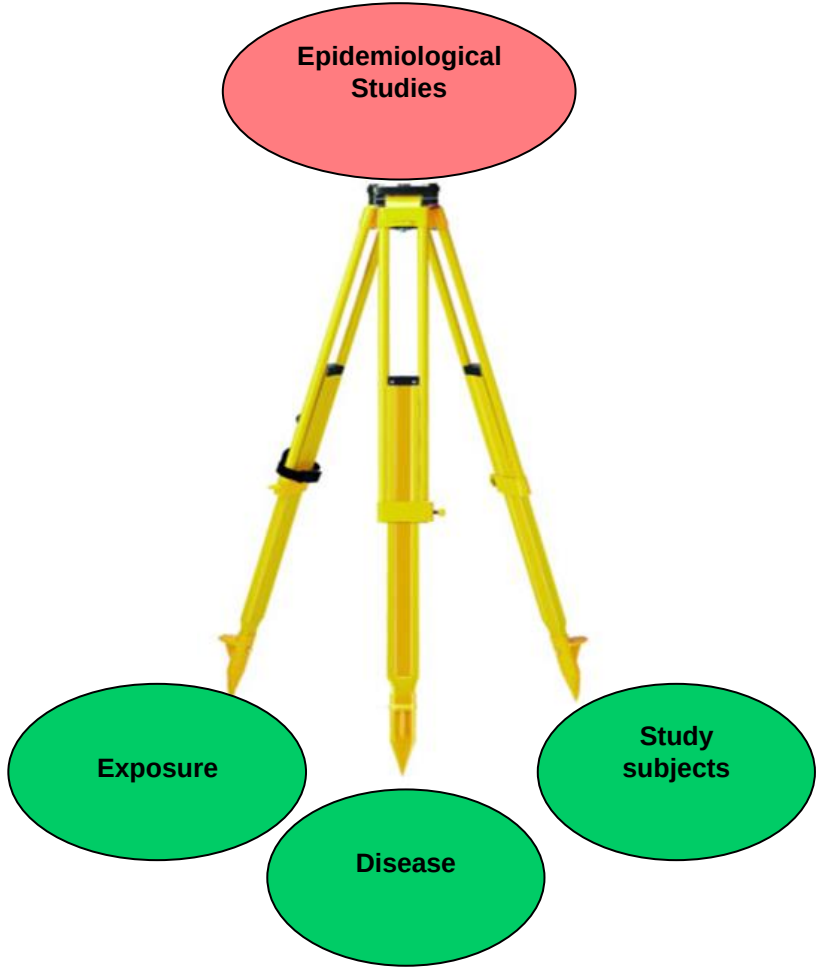
Tripod - analogy

Analogy to taking photos:

Epidemiological studies are like photo cameras on tripods; they need three legs to not give a biased picture of reality

Epidemiological studies precision and validity depend on:

- Good exposure data
- Good endpoint data
- Good control on the population



Observational designs

- Ecological studies
- Cross-sectional studies
- Case-control studies
- Cohort studies

Ecological studies

Comparison of the frequency of disease in different populations with an average distribution of the exposure within these populations – group level comparisons

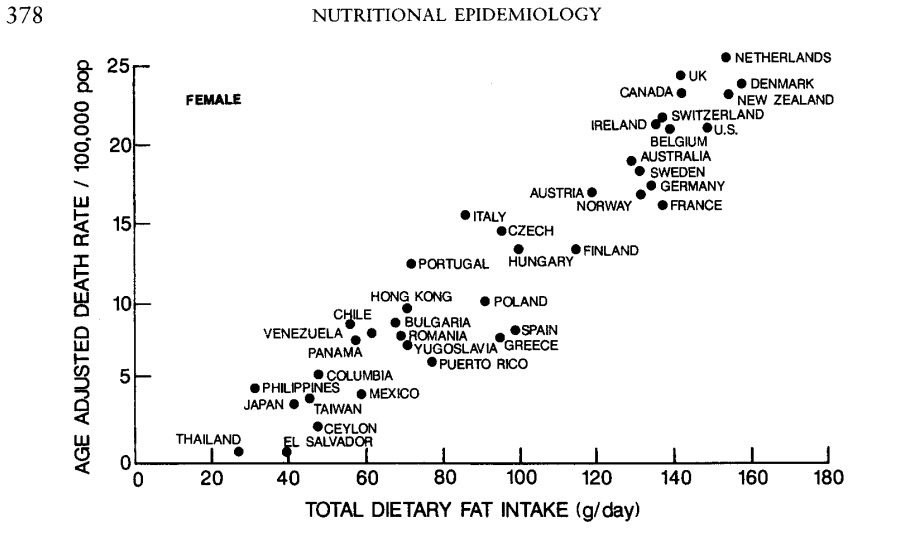


Figure 16–1. Relationship of national per capita fat intake with risk of breast cancer mortality. (From Carroll, 1975; reproduced with permission.)

Ecological studies cont.

- Armstrong and Doll (1975) studied the association between per capita meat consumption and incidence of colon cancer, based on data from 23 countries. A very strong correlation between meat consumption and colon cancer was observed. Pearson's correlation coefficient was 0.89 for women and 0.85 for men.

- Exposure and outcome are measured at the group level

Ecological studies cont.

Stat. sig. correlation between number of familial hypercholesterolemia diagnoses and statin users.

However, we cannot claim any causal relation in this study, and studies of data at an individual level are warranted to adequately address the association between statin use and genetically verified FH.

Contents lists available at ScienceDirect
Atherosclerosis
journal homepage: www.elsevier.com/locate/atherosclerosis

Genetic testing is essential for initiating statin therapy in children with familial hypercholesterolemia: Examples from Scandinavia

Karianne Svendsen [a,b,1,*], Gisle Langslet [a,1], Henriette W. Krogh [b], Jonas Brinck [c,d], Ib Christian Klausen [e], Jo S. Stenehjem [f,g], Kirsten B. Holven [b,h], Martin P. Bogsrud [h,i], Kjetil Retterstøl [a,b]

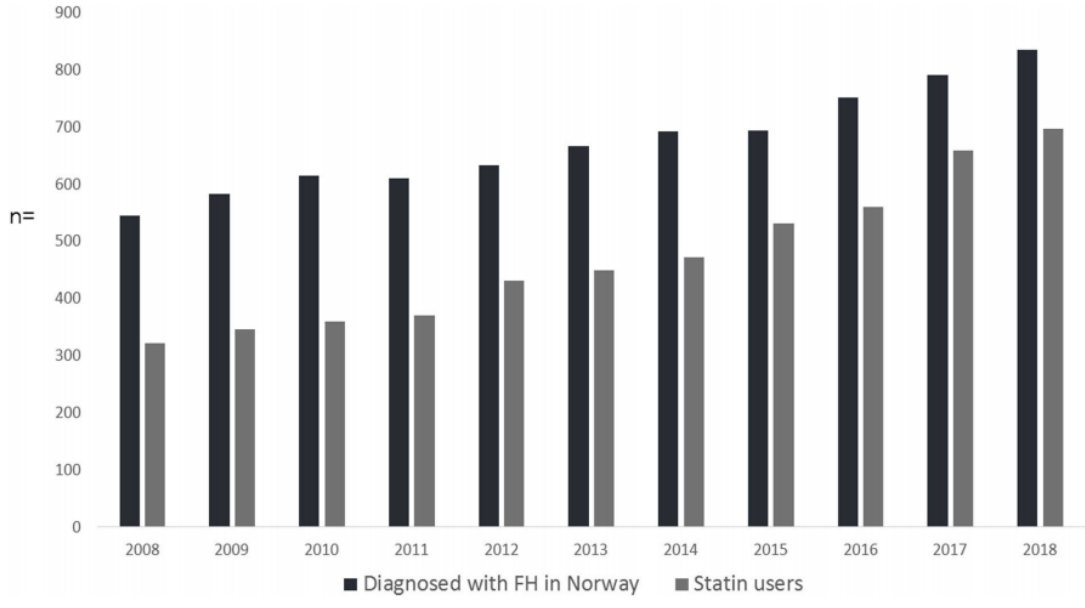


Fig. 3. Number of genetically diagnosed children aged 10-19 years with familial hypercholesterolemia and number of statin/statins + ezetimibe users in corresponding age group in Norway between 2008 and 2018.
The Kendall's tau correlation = 0.96, $p < 0.001$.

Ecological studies cont.

The NEW ENGLAND JOURNAL of MEDICINE

Chocolate Consumption, Cognitive Function, and Nobel Laureates

Franz H. Messerli, M.D.

DISCUSSION

The principal finding of this study is a surprisingly powerful correlation between chocolate intake per capita and the number of Nobel laureates in various countries. Of course, a correlation between X and Y does not prove causation but indicates that either X influences Y, Y influences X, or X and Y are influenced by a common underlying mechanism. However, since chocolate consumption has been documented to improve cognitive function, it seems most likely that in a dose-dependent way, chocolate intake provides the abundant fertile ground needed for the sprouting of Nobel laureates. Obviously, these findings are hypothesis-generating only and will have to be tested in a prospective, randomized trial.

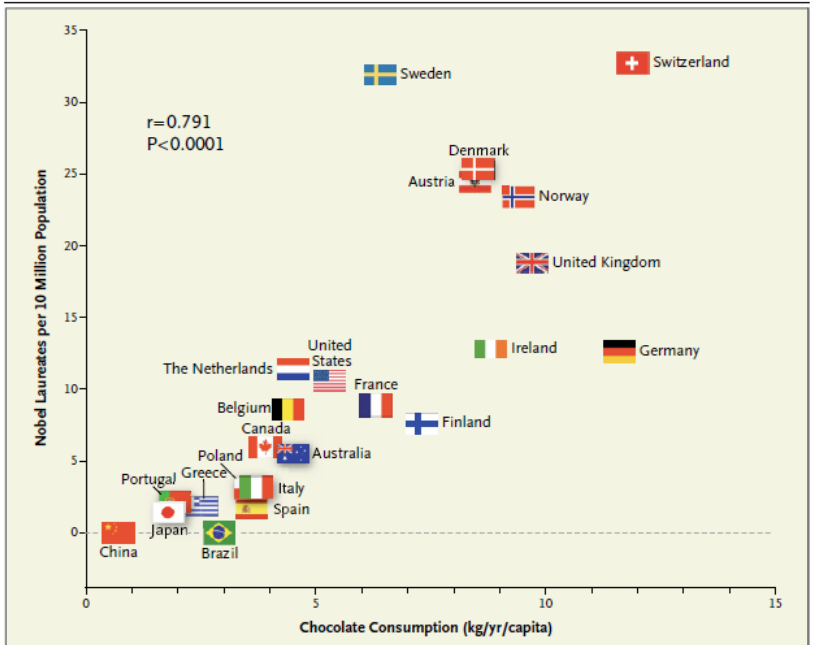


Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

Ecological studies cont.

Disadvantages:

- Not data at an individual level
- Does not indicate whether or not it is individuals with high exposure that get sick.
- Proper control for confounding by other factors is not possible.
- Ecological studies alone are insufficient to form a basis for public health guidelines.

Advantages:

- Heterogeneity in the exposure
- May be used to describe group phenomena – e.g. political elections

Ecological studies cont.

Methods used

- Correlations
- Comparison of group-level prevalence or incidence rates
- Regression techniques to examine trends in rates; i.e. to check if rates have changed significantly over time.

Observational designs

- Ecological studies
- Cross-sectional studies
- Case-control studies
- Cohort studies

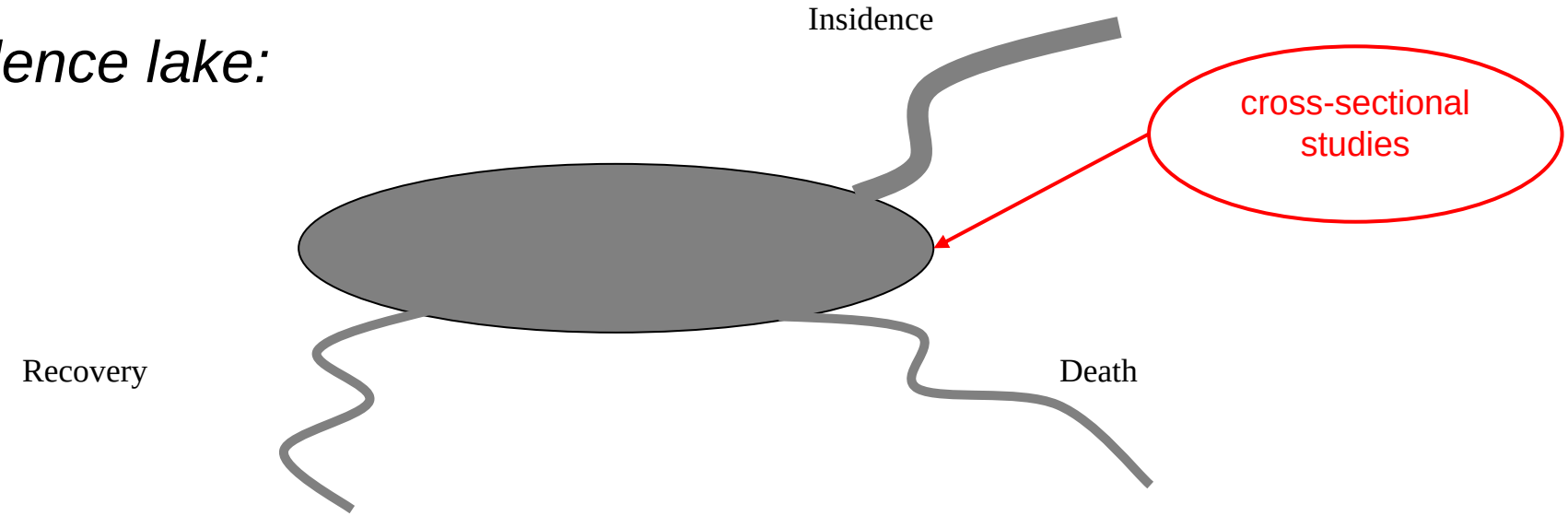
Cross-sectional studies

- Useful to determine the prevalence of a specific characteristic, disease, or exposure, at a given specified time.
- Form the basis for administrative and political decisions.

Cross-sectional studies

- **Prevalence** measures *burden* of disease
- **Insidens** measures *risk* of disease

Prevalence lake:



Cross-sectional studies cont.

Example 1 (Lien et al., UNGHUBRO)

- A cross-sectional population-based survey was conducted with10th-grade students in Oslo, Norway (n = 5498). Hopkins Symptom Checklist and Strengths and Difficulties Questionnaire to assess mental health outcomes.
- **Conclusion:** High consumption levels of sugar-containing soft drinks were associated with mental health problems even after adjustment for possible confounders.
- **Question:** Soft drinks causes psychological distress or distressed adolescents choose to drink sugar-containing soft drinks?

Cross-sectional studies cont.

Example 2: from the HUNT-study

- Consist of several cross-sectional surveys conducted in the Nord-Trøndelag county
- **Aim:** To examine the association between adiposity, physical activity and hypertension
- **Question:** By using data measured at the same time from HUNT 1, can we say anything about causality?
  - Physical inactivity may lead to hypertension
  - Hypertension may lead to inactivity
- **Important:** Cross-sectional studies may be transformed to a longitudinal study.
- Longitudinal study=linkage of two or more cross-sectional studies and thereby establish a temporal component.

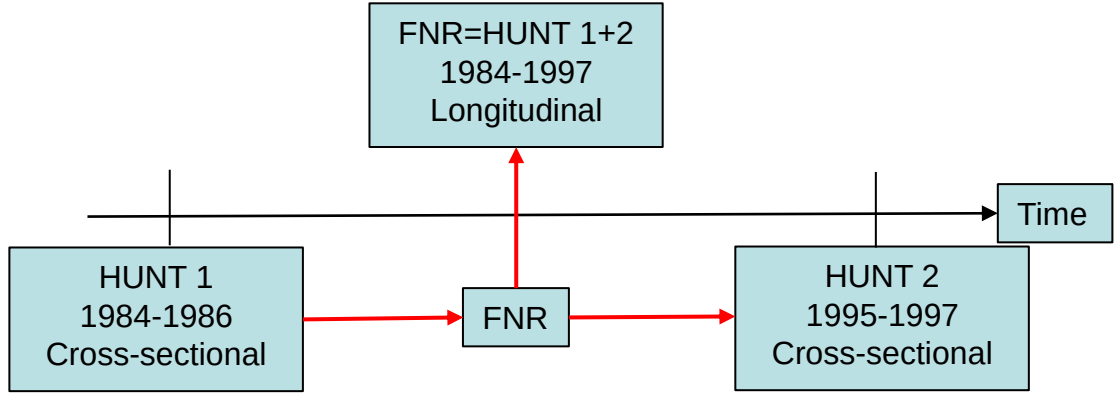
Journal of Human Hypertension
https://doi.org/10.1038/s41371-018-0042-5

ARTICLE

Adiposity, physical activity, and risk of hypertension: prospective data from the population-based HUNT Study, Norway

Jo S. Stenehjem[1] · Kirsti V. Hjerkind[1] · Tom I.L. Nilsen[2,3]

Received: 29 November 2017 / Revised: 21 January 2018 / Accepted: 29 January 2018



Cross-sectional studies cont.

Example 3: from the HUNT-study

- **Aim:** To examine the association between physical activity and colorectal cancer risk
- **Methods:** Linkage between HUNT1 and CRN. Prospective follow-up 1984-2002
- **Important:** Cross-sectional studies may be transformed to a cohort study by linkage to registries.
- We could ask about cancer in HUNT1 1984-1986, but then we would not know whether:
  - PA→cancer ?
  - Cancer→PA ?

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION

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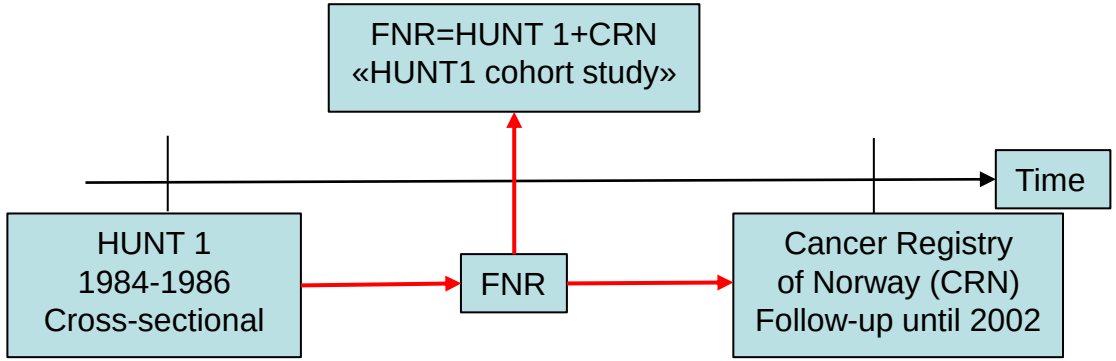
Research Articles

Recreational Physical Activity and Cancer Risk in Subsites of the Colon (the Nord-Trøndelag Health Study)

Tom I.L. Nilsen, Pål R. Romundstad, Hermod Petersen, David Gunnell, and Lars J. Vatten

DOI: 10.1158/1055-9965.EPI-07-0746 Published January 2008



Cross-sectional studies cont.

Disadvantages:

- Both exposures and outcomes are sampled at the same time. Dimension of time not taken into account, and no follow-up.
- Cannot address causation, since we do not know when exposure occurred relative to the outcome.

Advantages:

- Resource efficient (time and cost)
- Can study many variables (exposures and outcomes)

Cross-sectional studies cont.

Methods used

- Regression analysis that do not rely on a temporal component:
  - Logistic regression
  - Linear regression
  - Poisson regression

Typical effect measure

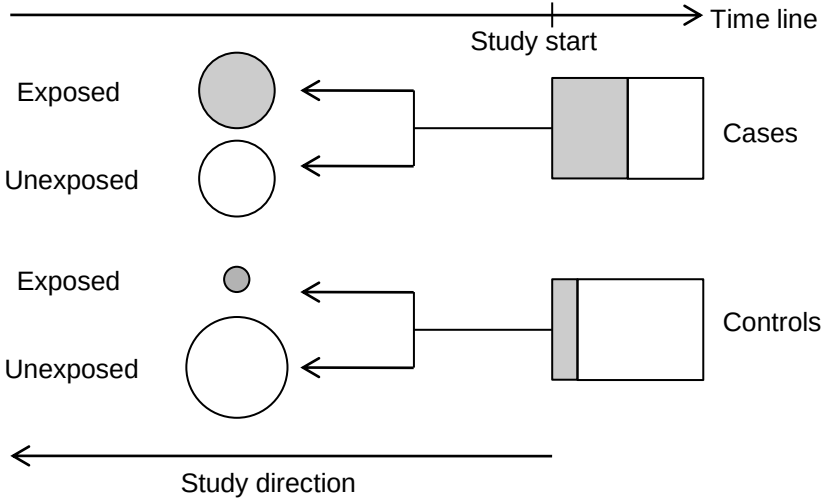
- Regression coefficient (linear regression)
- Risk/probability ratio (Poisson regression without person time)
- Odds ratio (logistic regression)

Observational designs

- Ecological studies
- Cross-sectional studies
- Case-control studies
- Cohort studies

Case-control studies

- We start with the cases and collect information about exposures from the past
- Next, we contact controls who are disease-free and collect information about exposures from the past



Case-control studies cont.

Example (Aydin et al.)

The CEFALO Study

- Identified childhood tumors in the Cancer Registry of Norway.
- Research groups travelled across Norway to inteview cases and controls about mobile phone use and potential confounding factors

DOI: 10.1093/jnci/djr244
Advance Access publication on July 27, 2011.

ARTICLE

Mobile Phone Use and Brain Tumors in Children and Adolescents: A Multicenter Case–Control Study

Denis Aydin, Maria Feychting, Joachim Schüz, Tore Tynes, Tina Veje Andersen, Lisbeth Samsø Schmidt, Aslak Harbo Poulsen, Christoffer Johansen, Michaela Prochazka, Birgitta Lannering, Lars Klæboe, Tone Eggen, Daniela Jenni, Michael Grotzer, Nicolas Von der Weid, Claudia E. Kuehni, Martin Röösli

Manuscript received February 9, 2011; revised May 27, 2011; accepted June 7, 2011.

Correspondence to: Martin Röösli, PhD, Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Socinstrasse 57, PO Box, 4002 Basel, Switzerland (e-mail: martin.roosli@unibas.ch).

Case-control studies cont.

Example (Østerlind et al.)

- All patients 20-79 yrs diagnosed with malignant melanoma 1/10-82 - 31/3-85 in a region of East-Denmark, identified by Danish Cancer Registry
- April 1984 controls randomly drawn from the national population registry, same age group and geographic region
- Cases and controls examined and interviewed

IJC International Journal of Cancer

Article

The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors

A. Østerlind, M. A. Tucker, K. Hou-Jensen, B. J. Stone, G. Engholm, O. M. Jensen

First published: 15 August 1988 | https://doi.org/10.1002/ijc.2910420210 | Citations: 120

Case-control studies cont.

Example (Østerlind et al.) cont.

	≥5 nevi	No nevi
Cases	76	231
Controls	39	635

$$OR = \frac{76 \cdot 635}{39 \cdot 231} = 5.4$$

95% CI (3.5, 8.1)

Logistic regression adjusted for age, freckles, hair color, skin color:
OR=5.1 (95% CI (3.3, 7.9)).

For rare diseases like melanoma *OR*≈RR

Case-control studies cont.

- Controls must be drawn from the same source population as the cases.
- The statistical power can be increased by inclusion of more than one control per case (rare diseases or when case acquisition is expensive).
- Some studies are matched, e.g., by age and sex. Individual matching must be taken into account in the statistical analysis. Not possible to study the effect of a matching variable.

Case-control studies cont.

Odds ratio in case-control studies:

- Important: Depends on the sampling of controls:
- Selected from person-time at risk (the study base available for matching at each case's diagnosis): odds ratio = rate ratio
- Selected from persons at risk (the base-population at risk at the beginning of follow-up): odds ratio = risk ratio
- Selected from survivors (the population at risk at the end of follow-up): odds ratio = odds ratio

International Journal of Epidemiology
© International Epidemiological Association 1993

Vol. 22, No. 6
Printed in Great Britain

What Does the Odds Ratio Estimate in a Case-Control Study?

NEIL PEARCE*,†

Pearce N (Department of Medicine, Wellington School of Medicine, PO Box 7343 Wellington, New Zealand). What does the odds ratio estimate in a case-control study? *International Journal of Epidemiology* 1993; **22**: 1189–1192.

The use of the term 'odds ratio' in reporting the findings of case-control studies is technically correct, but is often

Case-control studies cont.

Advantages:

- Generally relatively quick and inexpensive to implement
- Appropriate for rare diseases
- Wide range of exposures can be studied
- Well-suited when exposure assessment is demanding (e.g. biomarkers).

Disadvantages:

- Inappropriate for rare exposures
- Only possible to study one disease.
- Exposure is recorded after disease diagnosis. Recall bias may occur.

Case-control studies cont.

Methods used

- Regression techniques
  - Logistic regression
  - Conditional logistic regression (matched studies)

Typical effect measures

- Odds ratio (logistic regression with control-sampling among survivors)
- Risk ratio (logistic regression with control-sampling among persons at risk)
- Rate ratio (logistic regression control-sampling among from person-time at risk incidence density sampling)

Case-control studies cont.

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Case-control studies cont.

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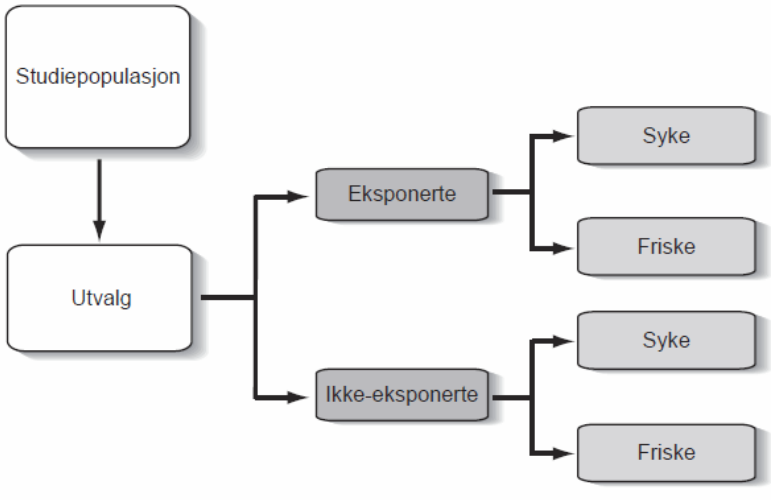
Observational designs

- Ecological studies
- Cross-sectional studies
- Case-control studies
- Cohort studies

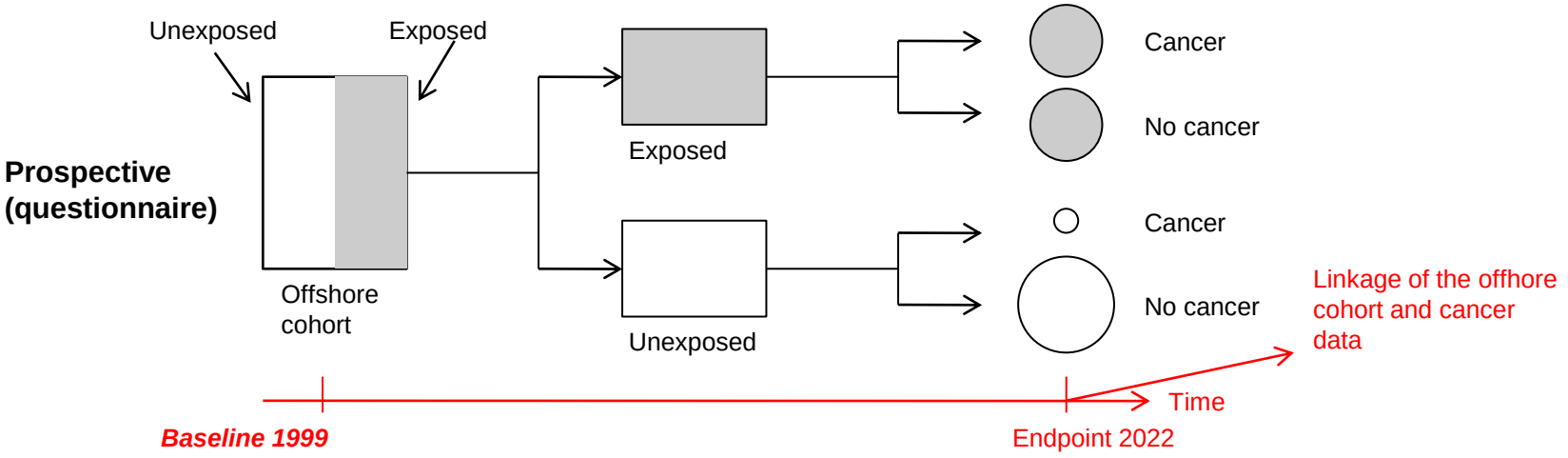
Cohort studies

A group of subjects, a cohort, is followed forward in time. Exposure recorded at study start, before disease diagnosis. Disease incidence is recorded during follow-up.



Cohort studies cont.

Example of the Cancer Registry of Norway's Offshore Worker Cohort



Cohort studies cont.

Effect measure: Incidence rate ratio (IRR)

$$IRR = \frac{insidence\ rate\ \ among\ the\ exposed}{insidence\ rate\ among\ the\ non-exposed}$$

Cohort studies cont.

	Exposed	Non-exposed
No. with outcome	s_e	s_0
No. of person-years	t_e	t_0
Incidence rate	IR_e	IR_0

$$IRR = \frac{IR_e}{IR_0} = \frac{s_e / t_e}{s_0 / t_0}$$

95% CI:

$$(IRR \cdot e^{-1.96\sqrt{1/s_e + 1/s_0}}, IRR \cdot e^{1.96\sqrt{1/s_e + 1/s_0}})$$

Cohort studies cont.

Example (Veierød et al.) The Women's Lifestyle and Health Cohort Study

106 379 women aged 30-50 in 1991/92 repsonded to a questionnaire
on sun tanning habits.
Followed up until 31-Dec-1999

<u>Sunbrun at age 10-19 years and melanoma:</u>

- Exposed:
  21 273 with sunburns ≥2 times/yr: 55 got melanoma
- Unexpoed
  22 747 had never been sunburned: 22 got melanoma

Cohort studies cont.

Example (Veierød et al.) cont.: The Women's Lifestyle and Health Cohort Study

	Sunburn ≥2 times/yr 10-19 yrs	Never sunburned 10-19 yrs
No. of melanoma cases	55	22
No. of person years	173 216	177 537
Insidence rate	0.000317	0.000124

$$IRR = \frac{55/173\ 216}{22/177\ 537} = 2.56$$

95% KI (1.56, 4.20)

Poisson regression adjusted for age, region of residence, and hair color:

IRR=2.42 (95% CI (1.46, 4.02))

Cohort studies cont.

Advantages:

- Exposure is assessed before disease diagnosis (recall bias not an issue as in case-control studies).
- Several exposures and outcomes can be studied, exposure can be updated during follow-up, and incidence rate is easily estimated.

Disadvantages:

- Can be unsuitable for rare diseases which would require large cohorts. Long follow-up may be necessary, and thus the study may become expensive.
- Disease diagnosis may evolve over time, and loss to follow-up can also occur.

Cohort studies cont.

Methods used

- Regression analysis (time-to-event)
  - Poisson regression
  - Cox regression

Typical effect measures

- Incidence rate ratios (Poisson regression)
- Hazard ratios (Cox regression)

Summary methods for observational designs

Multivariable regression techniques play an essential role in the adjustment for confounding :

- Linear or logistic regression in ecological and cross-sectional studies
- Logistic regression in case-control studies (conditional logistic regression if the study is matched on an individual level)
- Cox or Poisson regression in cohort studies

Overview:
Observational designs

- Ecological studies
- Cross-sectional studies
- Case-control studies
- Cohort studies

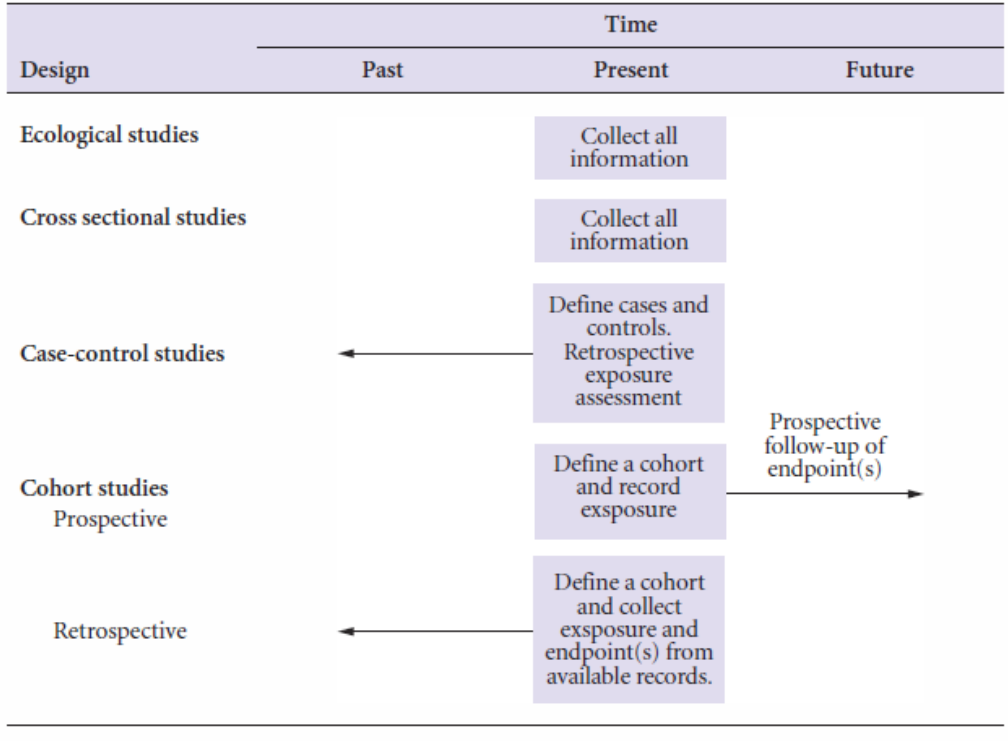


Table 1.2 in Veierød M.B., Lydersen S., Laake P. (eds.) *Medical statistics in clinical and epidemiological research*. Gyldendal Akademisk, 2012. www.medicalstatistics.no

Many more….

- Retrospecitive cohort study
- Nested case-control study
- Case-cohort study
- Case-crossover study
- Matched cohort study

15 min break

Outline Part II. Clinical studies/summary:

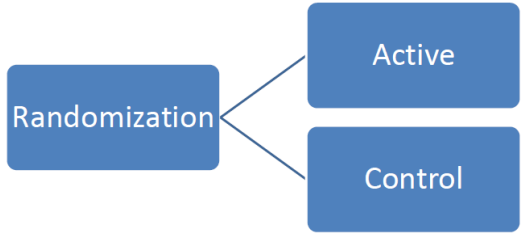
- Evidence and RCT
- Study planning
- RCT designs
- Randomization
- Blinding
- RCT analyses
- Summary and bias
- Case: Group discussion

Clinical research definition (National Institutes of Health, 2011):

Medical research that involves people
to test new treatments and therapies

Evidence and RCT - Randomized controlled trial

- Gold standard for evaluating health care interventions in clinical and epidemiological research.
- ≥2 interventions are compared, one is control.
- Study participants allocated at random to eliminate bias
- Blinding of the group assignment to the clinicians/caregivers, and the assessors is recommended (if possible) to avoid bias.



Evidence and RCT cont.

Intervention

- Biomedical or behavioural

  For example

  – Medication
  – Surgery
  – Diet
  – Physical activity
  – Physiotherapy
  – Acupuncture
  – Information

Study planning

Predefined and registered protocol must include

1. Aim
2. Hypotheses
3. Study sample (inclusion/exclusion criteria)
4. Study conduct
5. Randomization
6. Variables
7. Sample size
8. Procedures
9. Handling missing values
10. Statistical analysis

Aim

Example

- To investigate whether a new drug has a different effect than standard treatment on a specific disease

Purpose ⟷ Hypothesis

Hypothesis: Specification of the null-hypothesis

- $H_{0:}$ A and B do not have different effect
- H_A: A and B do have different effect

(two-sided test)

A and B could be for example

- A=New treatment,
  B=Standard treatment
- A=New treatment,
  B=Placebo

Inclusion/Exclusion criteria

- Factors that allow someone to participate in a clinical trial are *inclusion criteria*. Those that exclude or not allow participation are *exclusion criteria*.

- Consider generalization

Variables

Examples on different treatments/interventions and outcomes :

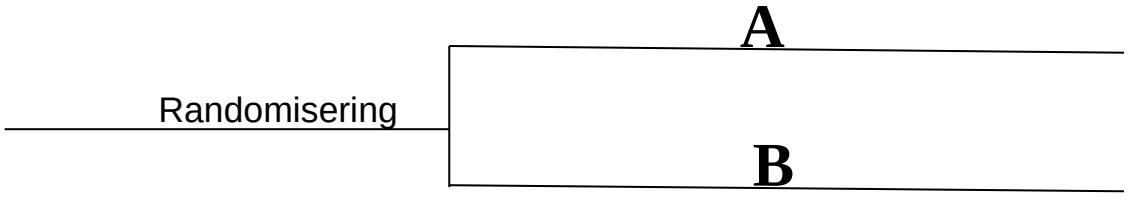
- Example 1:
  - Treatment: medication
  - Outcome: survival after cancer
- Example 2:
  - Treatment: Physical activity
  - Outcome: Quality of life after cancer
- Example 3:
  - Treatment: Vitamin D
  - Outcome: Lung function after COVID-19

Sample size

- Another lecture

RCT designs

Parallel group study



Intervention groups are independent and the analysis consists of *between subject* comparisons. Simplest and most commonly used RCT design is the individually randomized, two group, parallel study.

RCT designs cont.

Parallel group study

Advantages:

- Behandlingsresultatene fra de forskjellige gruppene kan være uavhengige
- Ingen carry-over effekt som vi skal se at vi kan ha i kryss-over studier

Disadvantages:

- Gruppene kan initialt bli lite sammenlignbare, kan ofte løses ved blokkrandomisering (kommer snart)
- Antall pasienter kan bli stort spesielt hvis vi har mange grupper der hver gruppe bør ha en viss størrels

RCT designs cont.

Parallel group study: example

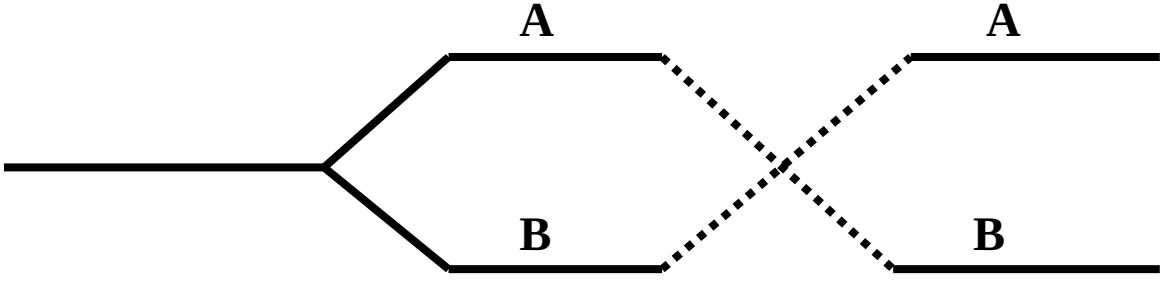
The International Neonatal Immunotherapy Study (INIS) Collaborative Group (NEJM 2011)

- *Parallel group* RCT
- Immune globulin vs placebo in the treatment of neonatal sepsis, a major cause of death in newborn infants.
- *n*=3493 infants that were receiving antibiotics for the treatment of proven or suspected serious infection.
- *Double-blind* study: infants were randomly assigned to treatment in a blinded fashion and both treatments were given as identical injections (immune globulin, *n* = 1759; placebo, *n* = 1734).
- *Primary outcome* was death or disability when the child was two years old.

RCT designs cont.

Crossover study

- Sometimes convenient to perform *within-subject* comparisons, e.g., to evaluate medications with a limited therapeutic window in cases of chronic disease.
- Each participant is randomly allocated to an intervention sequence and receives each intervention, one after the other.



RCT designs cont.

Crossover study cont.

Advantages:

- Within-subject measurements usually have less variation than between-subject variation, i.e., smaller study sample is required than in a parallel group study.
- The participant is its own control, can discover patient preferences, e.g., in a study comparing treatments for migraine.

Disadvantages:

- Total study period is longer, all participants must complete all intervention periods to prevent loss of power.
- Not appropriate for curable short-term diseases.

Randomization – why do it?

- Why? To remove investigator bias in the allocation of participants and tends to produce study groups comparable with respect to known as well as unknown risk factors.

- Why? To prevent that the estimated treatment effects are biased by confounding factors.

Randomization cont.

Simple randomization

Example

Two treatments A and B.

Randomization

- Coin
- List of random digits (computer generated or from a table)

  Digits 0-4 gives A, 5-9 gives B:

  0 5 2 7 8 4 3 gives A B A B B A A
- Computer programs and websites for randomization

Easy to implement, and completely unpredictable. May result in a substantial imbalance in group size between the interventions.

Randomization cont.

Block randomization

Aim: balanced groups

Example
Two treatments A and B

- 4 patients per block.
- List of random numbers where
  1: AABB, 2: ABAB, 3: ABBA,
  4: BBAA, 5: BABA, 6: BAAB
  (0, 7-9 ignore).
- 0 5 2 7 8 4 3 ... gives
  - BABA ABAB - - BBAA ABBA..

  Slightly predictable: allocation of the first three subjects is known, the investigator can then predict the allocation of the next subject. Can be avoided if the block sizes are varied at random, for example, between four, six, and eight.

Randomization cont.

Stratified randomization

- Stratify with respect to known prognostic factors.
- The number of subjects within a stratum can be small, so blocked randomization is recommended within each stratum to ensure balanced allocation.

Table 5.5. An example of random permuted blocks within strata for a trial in primary breast cancer (A [illegible] placebo)

Age:	< 50	⩾ 50	< 50	⩾ 50
No. of positive axillary nodes:	1–3	1–3	⩾ 4	⩾ 4
	B	B	A	B
	A	B	A	A
	B	A	B	[illegible]
	A	A	B	B
	A	A	B	A
	B	A	A	B
	A	B	B	B
	B	B	A	A
	A	B	B	B
	B	A	A	B
	B	A	B	A
	A	B	A	A
	B	A	B	A
	B	B	A	B
	A	B	A	A
	⋮	⋮	B	⋮
		⋮	⋮	

- OBS: Block randomization and stratified randomization is not the same!
- We block to secure equal N
- We stratified to get groups with equal values on important prognostic variables
- Blocking and stratification can be combined

Eksempel:

Randomization cont.

Example Rossebø et al.:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

Anne B. Rossebø, M.D., Terje R. Pedersen, M.D., Ph.D.,
Kurt Boman, M.D., Ph.D., Philippe Brudi, M.D., John B. Chambers, M.D.,
Kenneth Egstrup, M.D., Ph.D., Eva Gerdts, M.D., Ph.D.,
Christa Gohlke-Bärwolf, M.D., Ingar Holme, Ph.D.,
Y. Antero Kesäniemi, M.D., Ph.D., William Malbecq, Ph.D.,
Christoph A. Nienaber, M.D., Ph.D., Simon Ray, M.D.,
Terje Skjærpe, M.D., Ph.D., Kristian Wachtell, M.D., Ph.D.,
and Ronnie Willenheimer, M.D., Ph.D., for the SEAS Investigators*

Randomization cont.

Example Rossebø et al. cont.:

SEAS placebo group. During this process, neither the patients nor the investigators were aware of study-group assignments. After a 4-week run-in period in which all patients were given single-blind placebo tablets and were instructed to follow a lipid-lowering diet according to the recommendations of the National Cholesterol Education Program,[36] eligible patients underwent randomization in a 1:1 fashion in blocks of two to receive either simvastatin–ezetimibe or placebo (Fig. 1).

Gives a clear description of the method of randomization

Randomization cont.

Example Rossebø et al. cont.:

- 1:1 , equal sample size in the two groups
- Two treatments, blocks of two patients. E.g. used list of random numbers and assigned:
  - AB for digits 0-4
  - BA for digits 5-9
- Randomization list:

0	5	2	7	8	Etc
AB	BA	AB	BA	BA	Etc

Blinding

Blinding of participants. Two purposes:

- Placebo effect
  - Knowledge of the treatment may affect the outcome
- Information bias
  - Knowledge of the treatment may affact the participants reporting of symptoms

Blinding of MD / researcher to avoid biased medical treatment/follow-up care

Blinding cont.

- Double blinded study: Neither the patient nor the investigator or the person who evaluate the response, know what treatment the patient gets

- The purpose of bliniding is to reduce both known and unknown errors. All patients have equal expectations to the treatment, get the same care and the same unbiased evaluation

Statistical analysis

- Intervention effects in RCTs may often be analyzed by a ***univariable method***, a method involving only one exposure and the outcome.
- Parallel group study:
  - **Continuous outcome**: a *t*-test can be used to study differences in the outcome between two intervention groups or a one-way analysis of variance if more than two groups are compared
  - **Categorical outcome**: Pearson's chi-squared test can be used to compare a dichotomous outcome in two or more groups in large samples
  - **The outcome is an event, i.e., time to event data**: Kaplan-Meier plots of estimated survival functions in the intervention groups and comparison of two survival curves by the logrank test

Statistical analysis cont.

- Interventions are assigned by randomization to eliminate confounding bias, and adjustment by a ***multivariable method*** may be less necessary than in observational studies.
- Regression is often used to adjust for baseline measurements (Vickers and Altman, BMJ 2001)
- Confounding may still occur. For a variable to be a confounder in an RCT, it must differ between the comparison groups and predict the outcome of interest (CONSORT). A multivariable method is used when adjustment is sensible (Moher et al., BMJ 2010). See also review by Yu et al (Trials 2010)
- It is recommended to adjust for stratification variables

Eksempel:

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and Ronnie Willenheimer, M.D., Ph.D., for the SEAS Investigators*

STATISTICAL ANALYSIS

The study outcomes were analyzed according to the intention-to-treat principle. The study had a power of 90% to detect a reduction of 22% in the relative risk of the primary outcome. For all time-

Statistical analysis cont.

Intention-to-treat analysis

- If some subjects do not follow the allocated intervention, an ***intention-to-treat*** analysis is recommended to avoid bias (Moher et al., BMJ 2010). Then all subjects are included in the analysis in the groups to which they were originally allocated.

Statistical analysis cont.

Intention-to-treat:

biased against finding an effect (concervative)

(Some patients may receive the other group's treatment, the treatment difference may be smaller than it should be)

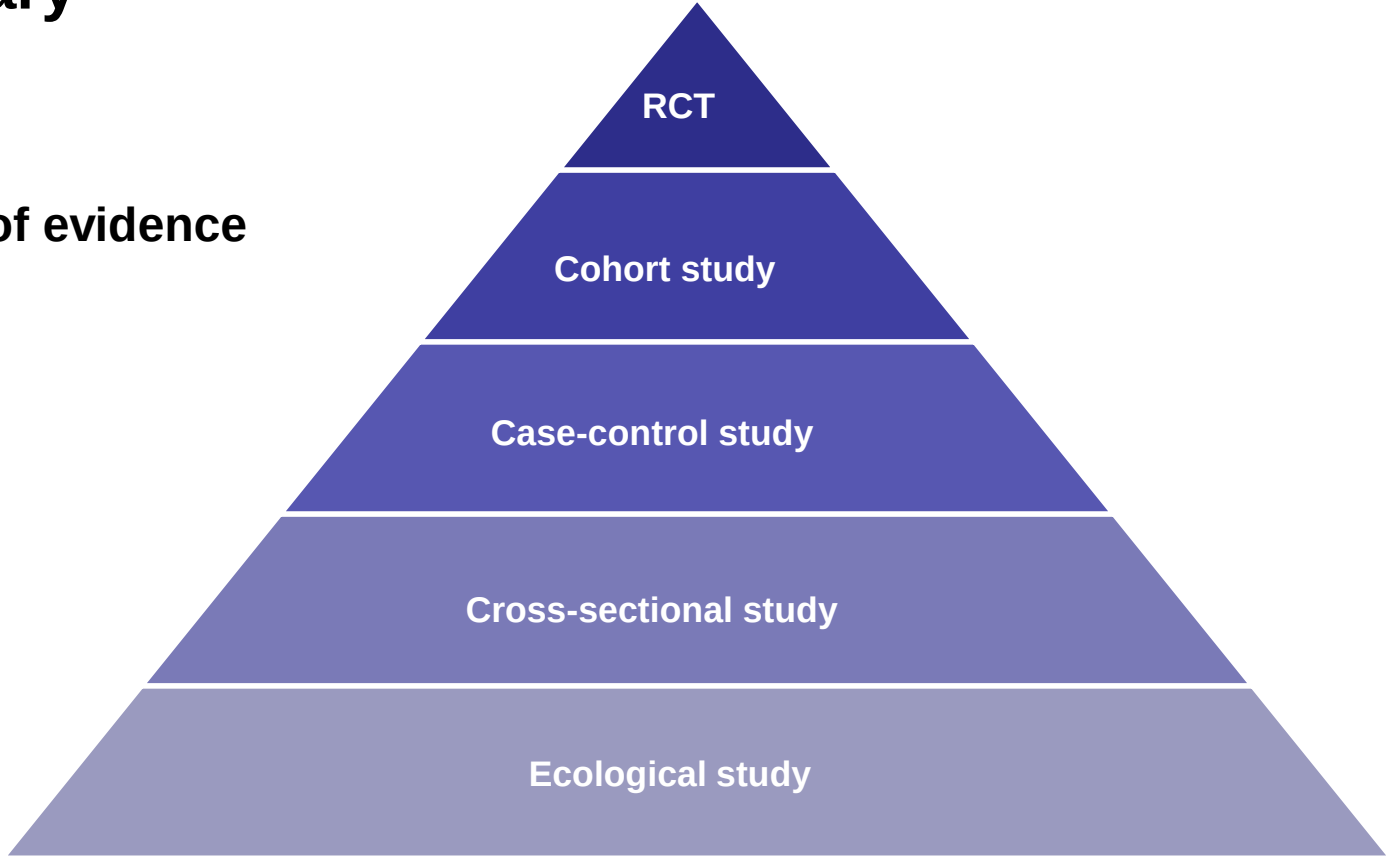
Analysing by treatment actually received

(on treatment analysis/per protocol):

biased in favour of showing a difference

Summary

Pyramid of evidence



Summary

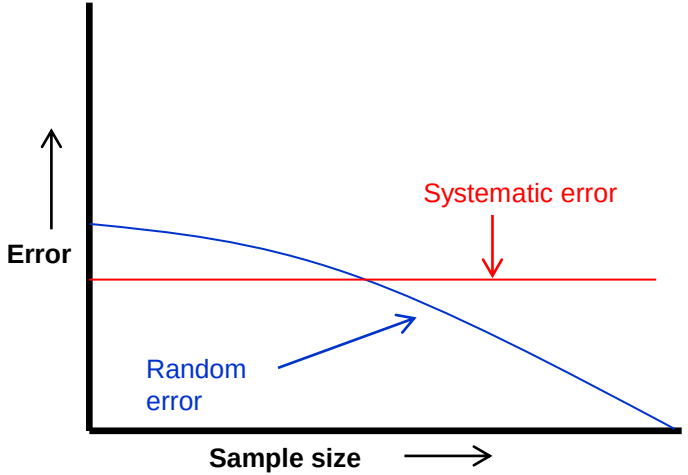
Grading the evidence in terms of causality of a supposed association

Study type	Reasoning
Ecological study	Descriptive; association on group level may be used for **development of broad hypotheses**
Cross-sectional study	Descriptive; individual association may be used for **development and specification of hypotheses**
Case-control study	Increased prevalence of risk factor among diseased **may indicate a causal relationship**
Cohort study	Increased risk of disease among exposed **indicates a causal relation**
Intervention study	Modification (reduction) of the incidence rate of the disease **confirms a causal relationship**

Ahrens et al., 2005

Summary

Random and systematic error



Summary

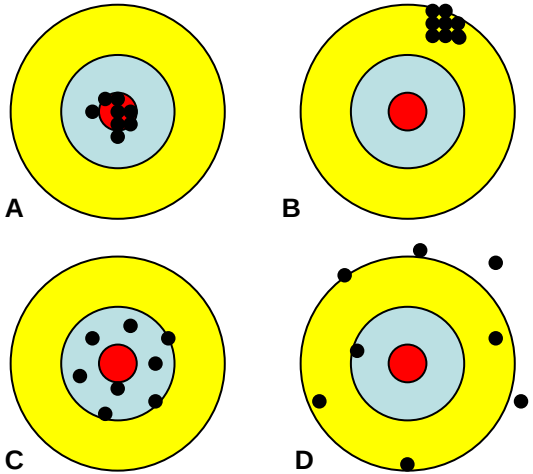
Random and systematic error cont'd

A: Low random and low systematic error = high precision and high validity

B: Low random and high systematic error = high precision and low validity

C: High random and low systematic error = low precision and high validity

D: High random and High systematic error = low precision and low validity



Summary

Internal and external validity

- Inadequacies in the design, conduct, or analysis of a study will give biased effect estimates.
- ***Internal validity*** implies that there is no bias in the way the data is collected, analyzed, and interpreted.
- Internal validity is a prerequisite for ***external validity***, i.e., generalizability of the study results to subjects outside the study sample.

Summary

Confounding

Confounder

A confounder is a variable that is

1) associated with the disease (either as a cause or a proxy for a cause but not as an effect of a disease),
2) associated with the exposure, and
3) not an effect of the exposure

Rothman KJ. Epidemiology. An Introduction. (2002)

Summary

Bias

- **Selection bias:** the study participants' representativeness in relation to the source population, can result from procedures used to select study participants.

- **Information bias:** occurs when exposure and/or disease are measured with measurement errors. The errors are typically due to instrument error and/or sampling error. Both systematic and random errors may cause biased effect estimates.

- **Confounding:** see previous slides

Questions

- Epost: j.s.stenehjem@medisin.uio.no

Summary methods for observational designs

Table 1.4 Regression models.

Outcome	Regression model	Effect estimate	Chapter
Continuous data	Linear regression	Regression coefficient, $\hat{\beta}$	4
Nominal data			
Two categories	Logistic regression	Odds ratio, $\widehat{OR} = e^{\hat{\beta}}$	3
>Two categories	Multinomial logistic regression	Odds ratio, $\widehat{OR} = e^{\hat{\beta}}$	3
Ordinal data	Ordinal logistic regression	Odds ratio, $\widehat{OR} = e^{\hat{\beta}}$	3
Count data	Poisson regression	Rate ratio, $\widehat{RR} = e^{\hat{\beta}}$	6
Time to event data	Cox regression	Hazard ratio, $\widehat{HR} = e^{\hat{\beta}}$	5
	Poisson regression	Incidence rate ratio, $\widehat{IRR} = e^{\hat{\beta}}$	6

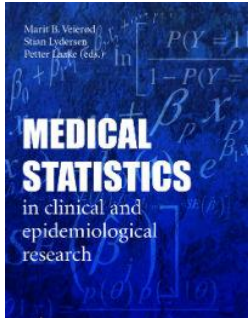


Table 1.4 in Veierød M.B., Lydersen S., Laake P. (eds.) *Medical statistics in clinical and epidemiological research*. Gyldendal Akademisk, 2012. www.medicalstatistics.no