Basic types of study design

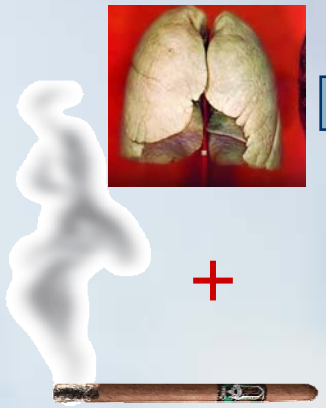
Assoc . Prof. Dr. Marius MARUSTERI
Medical Informatics and Biostatistics Dept.
University of Medicine and Pharmacy Tg. Mures, ROMANIA

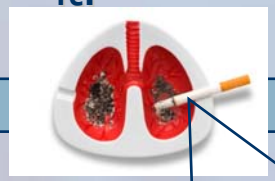
Some terminology....

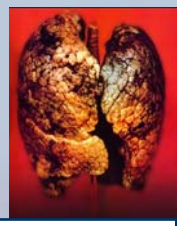
- A **hypothesis** (from Greek ὑπόθεσις; plural hypotheses) is a proposed explanation for an observable phenomenon.

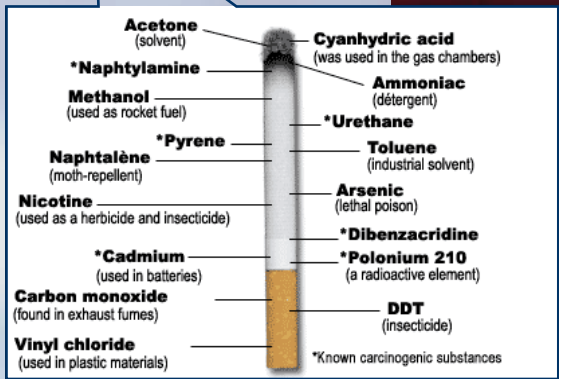
A **working hypothesis** is a hypothesis that is **provisionally accepted** when **no alternatives** are **available** or when the philosophical implications of the alternatives are considered to be absurd or otherwise undesirable.

For a hypothesis to be put forward as a **scientific hypothesis**, the **scientific method** requires that one can test it.









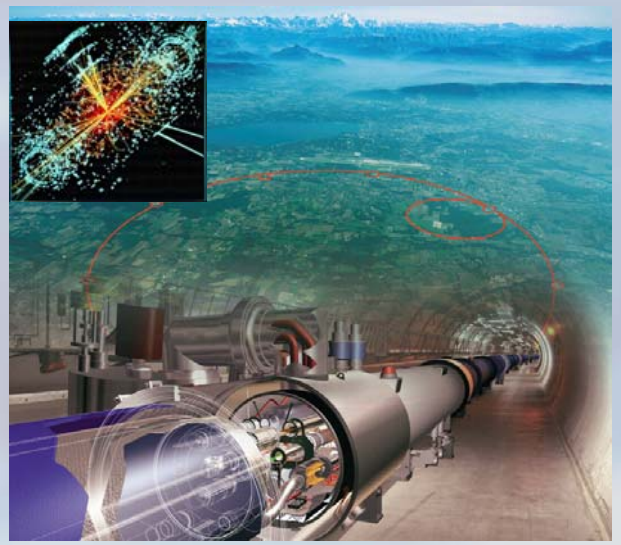
Some terminology....

Hypothesis

Working hypothesis

Scientific hypothesis, which requires **scientific method** to be able to test it.

The **Higgs Boson** is a hypothetical massive scalar elementary particle predicted to exist by the Standard Model in particle physics. At present there are **no known elementary scalar particles in nature.** The existence of the particle *is postulated as a means of resolving inconsistencies in current theoretical physics.* **The Higgs mechanism, which gives mass to vector bosons,** was theorized in 1964 by François Englert and Robert Brout ("boson scalaire"), in October of the same year by Peter Higgs, working from the ideas of Philip Anderson; and independently by Gerald Guralnik, C. R. Hagen, and Tom Kibble, who worked out the results by the spring of 1963.



LHC – Large Hadron Collider, 10 billion USD scientific device able to provide, in future, scientific information regarding the existence of Higgs Boson

Some terminology....

Hypothesis

Working hypothesis

Scientific hypothesis, which requires **scientific method** to be able to test it.

- **Scientific method** refers to a **body of techniques for investigating phenomena**, acquiring new knowledge, or correcting and integrating previous knowledge.
- To be termed **scientific**, a method of inquiry must be based on gathering **observable, empirical and measurable evidence subject** to specific principles of reasoning.
- A scientific method consists of the **collection of data through observation** and **experimentation**, and the **formulation and testing** of hypotheses.

RESEARCH

Research Methodology (Epidemiology) and (Bio)Statistics

Study design

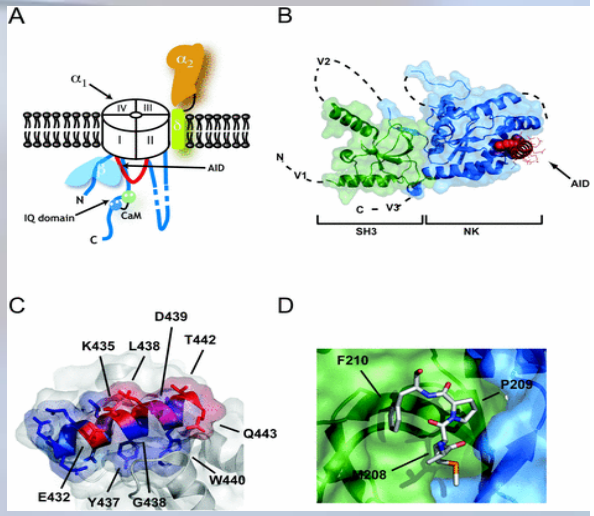
Studies

Research may be....

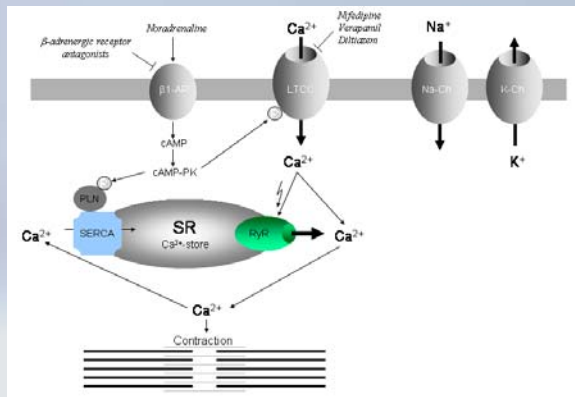
From the goal's viewpoint:

- **Fundamental** – with the goal to understand and/or to explain the mecanisms

- **Applicable** – applied science (e.g. in clinical practice, bioequivalence of drugs etc)



Calcium channels mechanism



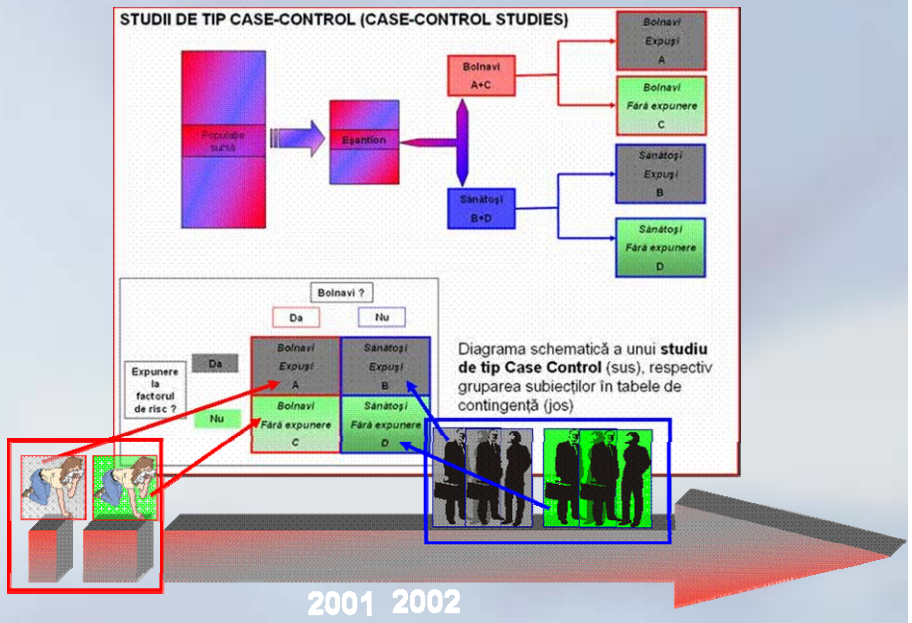
Calcium channels blockers

Research may be....

From the number (and importance) of the cases viewpoint:

- **Descriptive** – e.g. some specific cases or a (limited) number of cases (case reports or case series studies, for example) – which may generate a working hypothesis, but COULD NOT verify it.

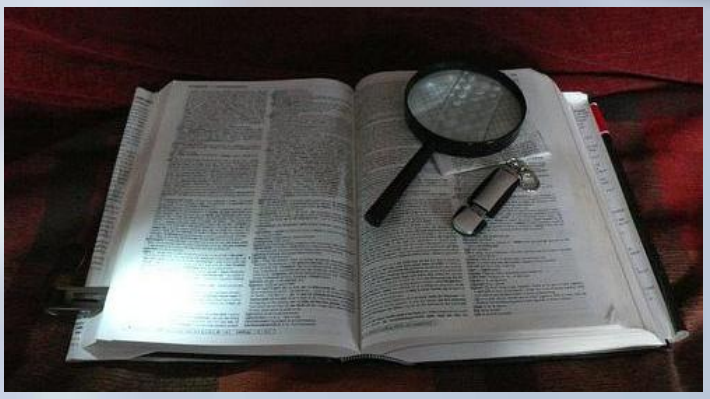
- **Analytic** – larger number of cases (e.g. samples, usually extracted/sampled from a population –cohort study for example), which could verify a working hypothesis and convert it, eventually, into a scientific hypothesis



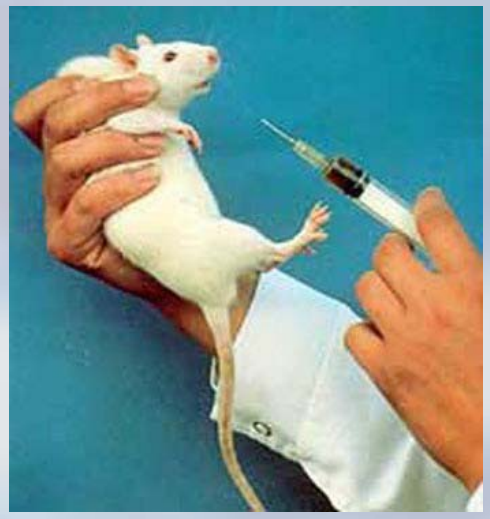
Research may be....

From the researcher involvement's viewpoint:

- **Observation** – where the researcher has no intervention
  - no intervention
  - low strength of evidence
  - NOT causality



- **Experiment**– where the researcher has to act in some way
  - controlled
  - high strength of evidence
  - causality



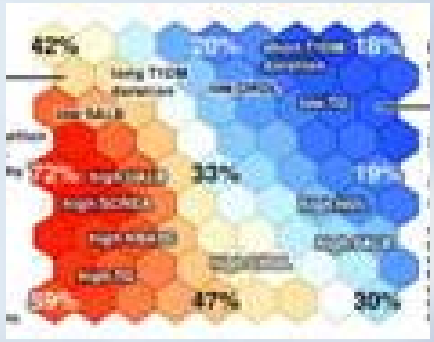
Research may be....

From the time perspective's viewpoint:

Cross-sectional ("snapshot")

time

retrospective



prospective

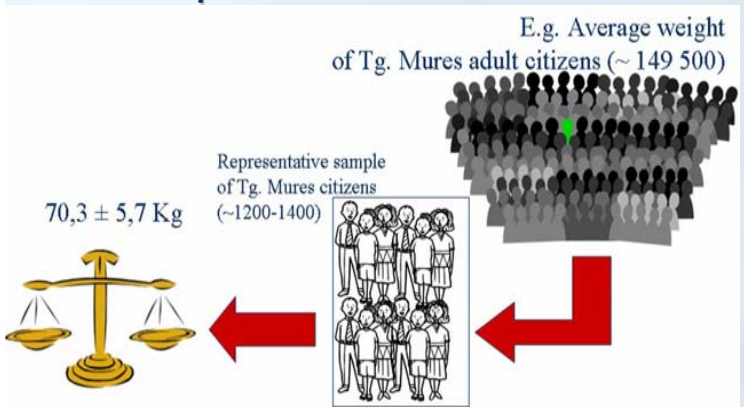
Research Methodology and Biostatistics....

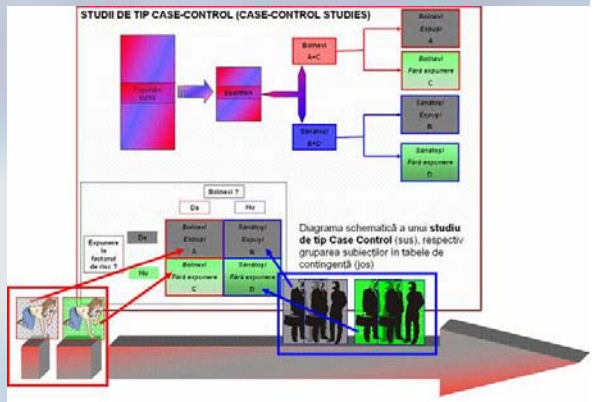
Research Methodology is the systematic study of methods that are, can be, or have been applied within a research.

In the medical field, a methodological approach of the research was extensively used in **epidemiology**, which **study the factors affecting the health and illness** of populations and is highly regarded in **evidence-based medicine** for identifying **risk factors for disease** and determining optimal treatment approaches to clinical practice.

Mathematical Statistics is the science which seeks to explain the "mass/global" phenomena through a relatively small number of observations.

Biostatistics is a branch of statistics, specialized in investigation of biological phenomena.





Epidemiological measures...

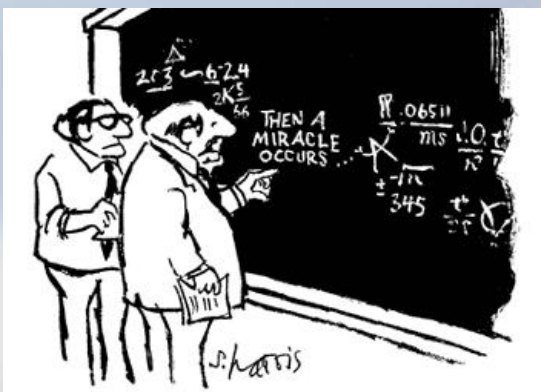
I. **Various types of ratio, proportions and rates**

II. **Measures of (disease) frequency or (disease) occurence**

- Incidence (number of new cases of disease during a given time period)
- Prevalence (number of cases that exist at a given point in time)

III. **Measures of association** (e.g. between a risk factor and a disease)

- Odds Ratio (OR)
- Relative Risk (RR)



"I think you should be more explicit here in step two."

Research process....

1) Choosing the research question

↓

2) Developing the protocol

↓

3) Pre-testing the protocol

↓

4) Carrying out the study

↓

5) Analyzing the findings

↓

6) Interpretation and results

secondary data analysis shortcut

Basic types of study design...

I. Descriptive studies (person, place and time)

- **Hypothesis generating**

They may be:

I.1. Studies that **describes single patient** or group of patients (individual) experience – e.g. **Case Report** or **Case Series** types of study

I.2. Examine characteristics of **entire populations** – e.g. **Correlational studies, Ecological studies** or **Cross-Sectional (or prevalence) Survey,** where, for example, exposure and disease status are simultaneously assessed in a population (a "snapshot" of the situation)

II. Analytic ("causal") studies

- **Hypothesis testing**

They may be:

II.1. Observational - investigator follows natural course of events. E.g.:

- **Case – Control study**
- **Cohort Study**

II.2. Experimental studies – Intervention of the investigator which "allocates" exposure and follows subjects. E.g.:

- **Randomized controlled trial (RCT)**
- **Bioequivalence testing**

Descriptive studies: …

- **Case Reports and Case Series**
  - Describes **single patient** or **group of patients experience**
  - **Most common form** of study published in medical journals
  - **Strength:**
    - May lead to **formulation of new hypotheses**
    - Important link between clinical medicine and epidemiology
    - **Cheap** and **not very** time-consuming
  - **Limitations:**
    - **Can not** be used to **test hypotheses**


JOURNAL OF MEDICAL CASE REPORTS

Case report

Coexistence of Mal de Meleda and congenital cataract in a consanguineous Tunisian family: two case reports


JOURNAL OF MEDICAL CASE REPORTS

Case report

Highly accessed Open Access

Hepatoprotective effects of Spirulina maxima in patients with non-alcoholic fatty liver disease: a case series

Aldo Ferreira-Hermosillo, Patricia V Torres-Duran and Marco A Juarez-Oropeza

Journal of Medical Case Reports 2010, **4**:103 doi:10.1186/1752-1947-4-103

Published: 7 April 2010

Descriptive studies: …

- **Correlational studies/Ecological studies**
  - Examine characteristics of **entire populations**
  - First step in examination of a **disease-exposure relationship**
  - **Strength:**
    - **Quick** and **inexpensive**, can be used as **first step**
  - **Limitations:**
    - Doesn't link **specific persons' exposure** with **specific outcome**
    - Can't control for potential confounding factors
    - Risk of **ecological fallacy -** often called an *ecological inference fallacy*, is an **error in the interpretation** of statistical data in an ecological study, **whereby inferences about the nature of specific individuals are based solely upon aggregate statistics collected for the group** to which those individuals belong. This fallacy assumes that individual members of a group have the average characteristics of the group at large.


Journal of Chronic Diseases
Volume 20, Issue 10, October 1967, Pages 769-779

doi:10.1016/0021-9681(67)90089-6 | How to Cite or Link Using DOI
Copyright © 1967 Published by Elsevier Inc.
Permissions & Reprints

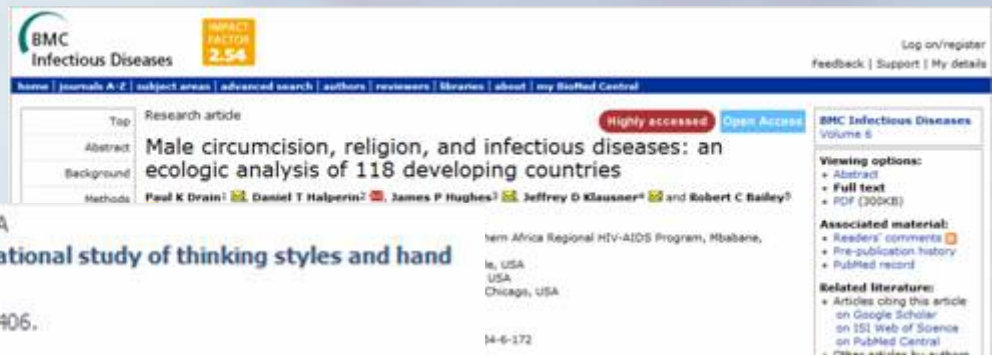
Cited By in Scopus (4)

Cigarette smoking and geographic variation in coronary heart disease mortality in the United States*1

Gary D. Friedman M.D., S.M. in Hyg.

Epidemiology Field and Training Station, Heart Disease Chronic Disease Control, Bureau of Disease Prevention Service, U.S. Department of Health, Education and Welf

Received 20 March 1967; Revised 23 June 1967. Avail


BMC Infectious Diseases

IMPACT FACTOR 2.54

Log on/register
feedback | Support | My details

home | journals A-Z | subject areas | advanced search | authors | reviewers | libraries | about | my BioMed Central

Top
Abstract
Background
Methods

Research article

Highly accessed | Open Access

Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries

Paul K Drain[1] Daniel T Halperin[2] James P Hughes[3] Jeffrey D Klausner[4] and Robert C Bailey[5]

BMC Infectious Diseases
Volume 6

Viewing options:
- Abstract
- Full text
- PDF (300KB)

Associated material:
- Readers' comments
- Pre-publication history
- PubMed record

Related literature:
- Articles citing this article on Google Scholar on ISI Web of Science on PubMed Central

2008: Sladek Ruth M; Bond Malcolm J; Phillips Paddy A

Why don't doctors wash their hands? A correlational study of thinking styles and hand hygiene.

American journal of infection control 2008;36(6):399–406.

Descriptive studies: …

- **Cross-Sectional (or prevalence) Survey**
  - **Exposure** and **disease status** are **simultaneously** assessed in a population ("snapshot" of the situation)
  - **Strength:**
    - Provides information about the **frequency and characteristics of a disease**
    - Useful for public health because is **fast, simple and usually involve low costs**
    - Can provide information concerning **the prevalence of disease** or other health outcome **in special groups** (e.g. occupations)
  - **Limitations:**
    - Can't determine whether **exposure preceded** or **occurred as a result of the disease**
    - Is the **sample representative**?
    - How about **rare diseases**?


BMC Infectious Diseases

IMPACT FACTOR 2.54

Log on/register
Feedback | Support | My details

home | journals A-Z | subject areas | advanced search | authors | reviewers | libraries | about | my BioMed Central

Top
Abstract
Background
Methods
Results
Discussion
Conclusion
Abbreviations
Competing interests
Authors'

Research article

Highly accessed | Open Access

A national cross-sectional study among drug-users in France: epidemiology of HCV and highlight on practical and statistical aspects of the design

Marie Jauffret-Roustide[1,2], Yann Le Strat[1], Elisabeth Couturier[1], Damien Thierry[3], Marc Rondy[2], Martine Quaglia[4], Nicolas Razafandratsima[4], Julien Emmanuelli[1], Gaelle Guibert[2], Francis Barin[3] and Jean-Claude Desenclos[1]

1 Infectious Diseases Departement, National Institute for Public Health Surveillance, Saint-Maurice, France
2 Center for Research in Psychotropics, Health, Mental Health and Society, UMR CNRS 8136, University Paris Descartes, Inserm U611, Paris, France
3 François-Rabelais University, Inserm ERI 19 and CHU Bretonneau, National Reference Center for HIV, Tours, France
4 National Institute of Demographic Studies, Paris, France

author email | corresponding author email

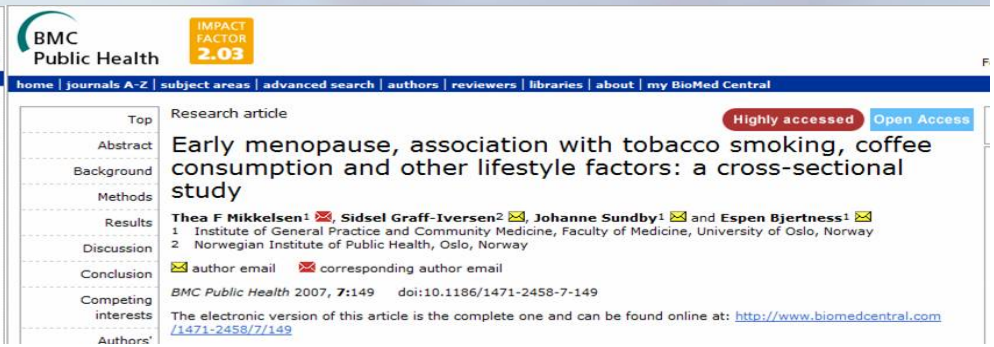
BMC Infectious Diseases 2009, **9**:113 doi:10.1186/1471-2334-9-113

BMC Infectious Diseases
Volume 9

Viewing options:
- Abstract
- **Full text**
- PDF (379KB)
- Additional files

Associated material:
- Readers' comments
- Pre-publication history
- PubMed record

Related literature:
- Articles citing this article on Google Scholar on ISI Web of Science on PubMed Central
- Other articles by authors


BMC Public Health

IMPACT FACTOR 2.03

home | journals A-Z | subject areas | advanced search | authors | reviewers | libraries | about | my BioMed Central

Top
Abstract
Background
Methods
Results
Discussion
Conclusion
Competing interests
Authors'

Research article

Highly accessed | Open Access

Early menopause, association with tobacco smoking, coffee consumption and other lifestyle factors: a cross-sectional study

Thea F Mikkelsen[1], Sidsel Graff-Iversen[2], Johanne Sundby[1] and Espen Bjertness[1]

1 Institute of General Practice and Community Medicine, Faculty of Medicine, University of Oslo, Norway
2 Norwegian Institute of Public Health, Oslo, Norway

author email | corresponding author email

BMC Public Health 2007, **7**:149 doi:10.1186/1471-2458-7-149

The electronic version of this article is the complete one and can be found online at: http://www.biomedcentral.com/1471-2458/7/149

Analytic studies - generalities

- Explicit **comparison** of **exposure** and **disease**
- Groups are assembled to determine whether **risk** is different for **exposed** and **unexposed**
- Appropriate **comparison group**
- **Hypothesis testing**

Two types

- **Observational** - natural course of events
- **Intervention/experiment** - investigator allocates exposure and follows subjects

Rom. J. Biophys. 2010 20(1): 47-59

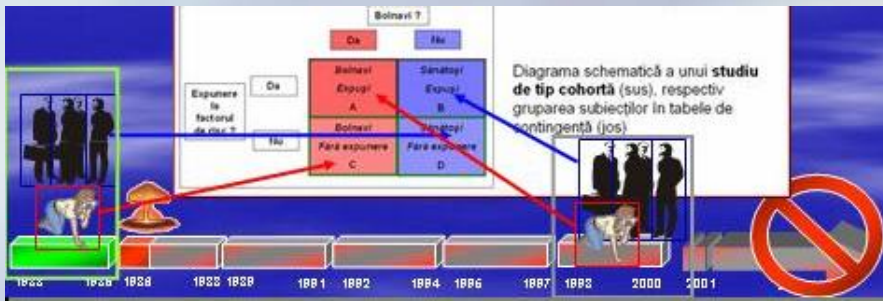
ACCIDENTAL IONIZING RADIATION AND ITS IMPACT ON THE POPULATION

MARIANA TILINCĂ*, M. MĂRUŞTERI**, JULIÁNNA SZAKÁCS***, I. NICOLAESCU***

*Department of Cellular and Molecular Biology, University of Medicine and Pharmaceutics, Târgu Mureş, Romania
**Department of Medical Informatics and Biostatistics, University of Medicine and Pharmaceutics, Târgu Mureş, Romania
***Department of Biophysics, Biotechnology, Medical and Pharmaceutical Physics, University of Medicine and Pharmaceutics, Târgu Mureş, Romania

Abstract. A study of the influence of accidental ionizing radiation due to the nuclear explosion in Chernobyl in 1986 on Mureş County population was performed. We studied the annual incidence of acute leukemia in Mureş County between 1983–2002, according to gender, origin, and type of disease. This study is a cohort type, based on ecological preponderance. Due to the existence of incomplete records in some clinics, we could not study the incidence of disease for more than 3 years in pre-Chernobyl period (1983–1985). Thus, we have grouped the post-Chernobyl interval in 5 periods of 3 years, to calculate and compare the cumulative incidence values. Regarding the total incidence of acute leukemia, there is a statistically significant positive association between the exposure to the risk factor (ionizing radiation) and the disease throughout all the studied periods during 1986–2000. Previous conclusions are also supported by the results of data analysis in case of grouping data according to criteria regarding the type of the disease, as well as demographic criteria. The results appear to contest the existence of a dose-response type relationship in case of our study.
Key words: ionizing radiation, acute leukemia, statistical analysis.

Retrospective cohort study



Analytic studies: Observational studies

- **Case-Control**
  - **Persons with disease**
  - **Comparison group**
  - **Non-randomized**
  - It is, usually, a **retrospective study**, but with proper arguments, it may be, rarely, **prospective** (e.g. *nested case-control study* in a population based cohort - In a **nested case-control study**, cases of a disease that occur in a defined cohort are identified and, for each, a **specified number of matched controls** is selected from among those in the cohort who have not developed the disease by the time of disease occurrence in the case).
- **Cohort**
  - Subjects classified on **basis of exposure of a factor**
  - **Follow-up** to determine **presence of disease**
  - It could be **prospective** or **retrospective study**

BMC Pulmonary Medicine

A case-control study on risk factors for early-onset respiratory tract infection in patients admitted in ICU

BMC Cancer

A prospective study of *Helicobacter pylori* in relation to the risk for pancreatic cancer

The aim of the present study was to investigate the association between H. pylori seropositivity and the risk for pancreatic cancer in a **nested case-control** study within a population based cohort.

BMC Infectious Diseases

Hyperglycemia in bacterial meningitis: a prospective cohort study

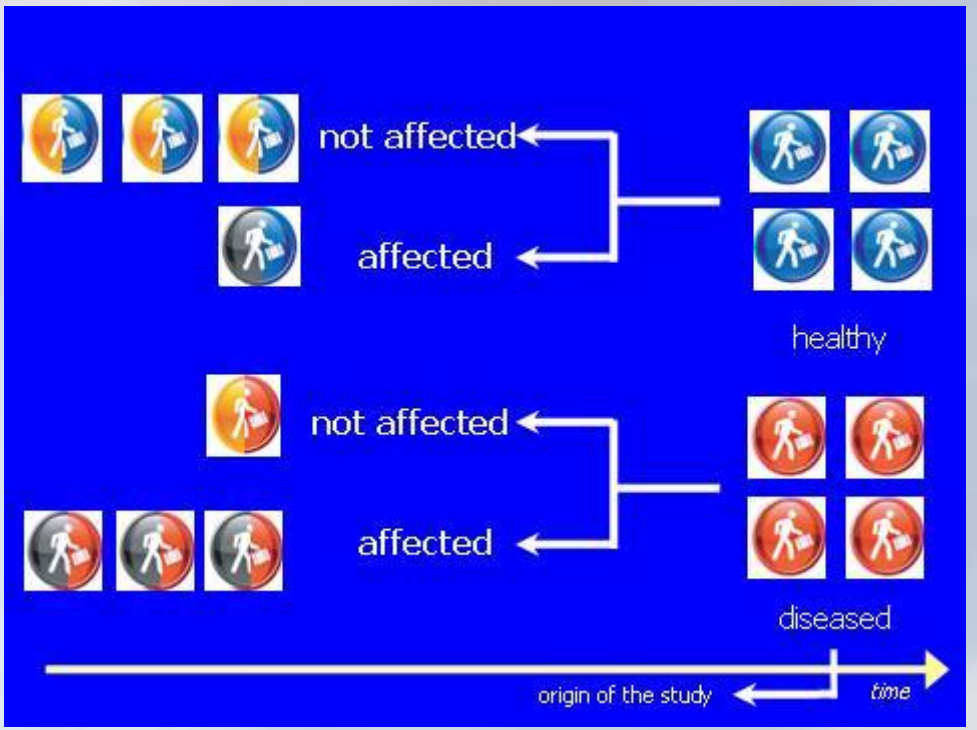
BMC Health Services Research

A retrospective cohort study on lifestyle habits of cardiovascular patients: how informative are medical records?

Analytic studies: Case-control studies

- **Case-Control studies**
- **Advantages**
  - Uniquely suited to diseases with **long incubation** periods
  - More efficient in terms of **time** and money (**low cost**)
  - Good for study of **rare disease**
  - Can look at **multiple exposures** (risk factors) for a single disease
- **Disadvantages**
  - Inefficient for evaluation of **rare exposures**
  - Cannot directly compute **incidence rates** of disease
  - **Temporal relationship** between exposure and disease may be **hard to establish**
  - Particularly prone to **bias** (selection and recall in particular)

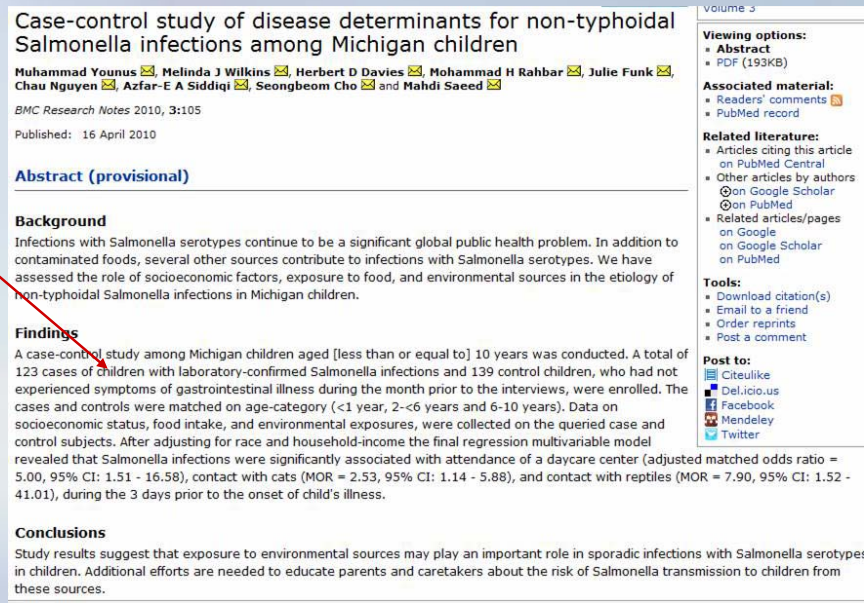
Flow chart:



Simundic AM, *Types of study design*, Intensive Course in Basic Biostatistics and Research Design, June 21-24, 2009, Targu Mures, Romania, Pre-congress event, 1st Congress of Romanian Association of Medical Laboratories.

Analytic studies: Case-Control studies - issues

- **Issues:**
  - **Definition** and **selection** of **cases**
  - **Incident** versus **prevalent** cases
  - **Source of controls:** hospital, general population, special series
  - **Number of control** groups
  - **Case/control ratio**
  - **Ascertainment** (non-random sampling) of **disease** and **exposure status**



Case-control study of disease determinants for non-typhoidal Salmonella infections among Michigan children

Muhammad Younus, Melinda J Wilkins, Herbert D Davies, Mohammad H Rahbar, Julie Funk, Chau Nguyen, Azfar-E A Siddiqi, Seongbeom Cho and Mahdi Saeed

BMC Research Notes 2010, **3**:105

Published: 16 April 2010

Abstract (provisional)

Background

Infections with Salmonella serotypes continue to be a significant global public health problem. In addition to contaminated foods, several other sources contribute to infections with Salmonella serotypes. We have assessed the role of socioeconomic factors, exposure to food, and environmental sources in the etiology of non-typhoidal Salmonella infections in Michigan children.

Findings

A case-control study among Michigan children aged [less than or equal to] 10 years was conducted. A total of 123 cases of children with laboratory-confirmed Salmonella infections and 139 control children, who had not experienced symptoms of gastrointestinal illness during the month prior to the interviews, were enrolled. The cases and controls were matched on age-category (<1 year, 2-<6 years and 6-10 years). Data on socioeconomic status, food intake, and environmental exposures, were collected on the queried case and control subjects. After adjusting for race and household-income the final regression multivariable model revealed that Salmonella infections were significantly associated with attendance of a daycare center (adjusted matched odds ratio = 5.00, 95% CI: 1.51 - 16.58), contact with cats (MOR = 2.53, 95% CI: 1.14 - 5.88), and contact with reptiles (MOR = 7.90, 95% CI: 1.52 - 41.01), during the 3 days prior to the onset of child's illness.

Conclusions

Study results suggest that exposure to environmental sources may play an important role in sporadic infections with Salmonella serotypes in children. Additional efforts are needed to educate parents and caretakers about the risk of Salmonella transmission to children from these sources.

Volume 3

Viewing options:
- **Abstract**
- PDF (193KB)

Associated material:
- Readers' comments
- PubMed record

Related literature:
- Articles citing this article on PubMed Central
- Other articles by authors on Google Scholar on PubMed
- Related articles/pages on Google on Google Scholar on PubMed

Tools:
- Download citation(s)
- Email to a friend
- Order reprints
- Post a comment

Post to:
Citeulike
Del.icio.us
Facebook
Mendeley
Twitter

Analytic studies: Case-Control analysis

Odds-Ratio is used for **case-control studies** because **persons are selected** based on **disease status**, so you **can't calculate risk of getting disease !**

	Disease+	Disease-
Exposed	a	b
Non-Exposed	c	d

$$\textbf{Odd-Ratio (OR)} = \frac{a/c}{b/d} = \frac{a \times d}{b \times c}$$

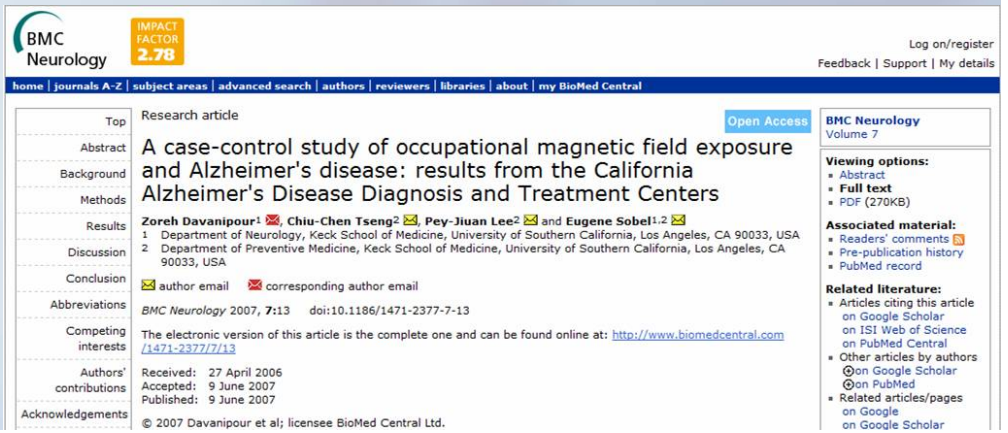
Interpretation of OR:

OR=1 - **No association** between exposure and disease. Incidence rates are identical between groups.

OR> 1 - **Positive association**

OR< 1 - **Negative association or protective effect**

Example: OR= 0.5 - half as likely to experience disease



BMC Neurology

IMPACT FACTOR 2.78

Log on/register

Feedback | Support | My details

home | journals A-Z | subject areas | advanced search | authors | reviewers | libraries | about | my BioMed Central

Top | Abstract | Background | Methods | Results | Discussion | Conclusion | Abbreviations | Competing interests | Authors' contributions | Acknowledgements

Research article

Open Access

A case-control study of occupational magnetic field exposure and Alzheimer's disease: results from the California Alzheimer's Disease Diagnosis and Treatment Centers

Zoreh Davanipour[1], Chiu-Chen Tseng[2], Pey-Jiuan Lee[2] and Eugene Sobel[1,2]

1 Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA

2 Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA

author email | corresponding author email

BMC Neurology 2007, **7**:13 doi:10.1186/1471-2377-7-13

The electronic version of this article is the complete one and can be found online at: http://www.biomedcentral.com/1471-2377/7/13

Received: 27 April 2006
Accepted: 9 June 2007
Published: 9 June 2007

© 2007 Davanipour et al; licensee BioMed Central Ltd.

BMC Neurology
Volume 7

Viewing options:
- Abstract
- **Full text**
- PDF (270KB)

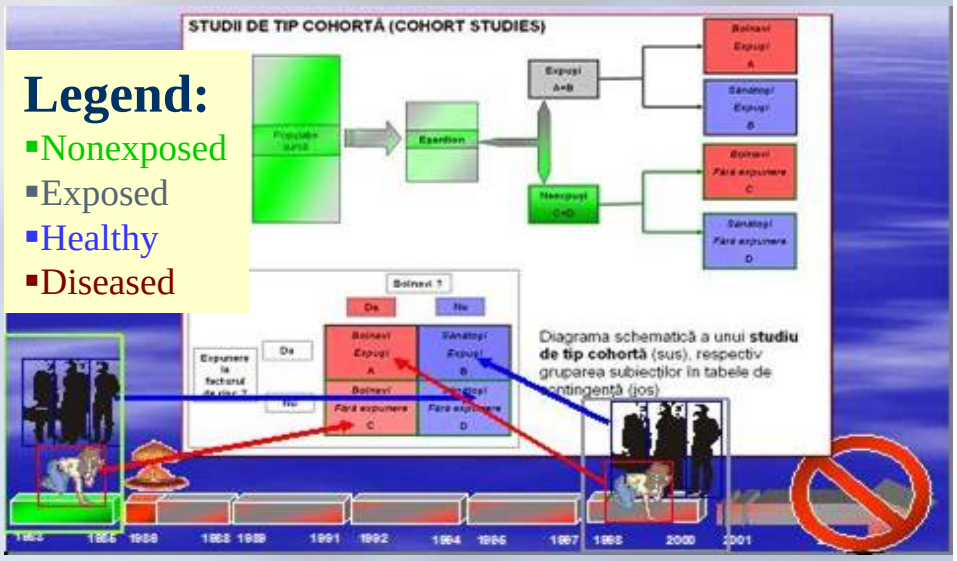
Associated material:
- Readers' comments
- Pre-publication history
- PubMed record

Related literature:
- Articles citing this article on Google Scholar on ISI Web of Science on PubMed Central
- Other articles by authors on Google Scholar on PubMed
- Related articles/pages on Google on Google Scholar

Analytic studies: Observational studies

- **Cohort studies**
- **Advantages**
  - Can **measure incidence** and thus **risk**
  - No recall bias
  - **Exposure** precedes **disease**
  - Can study **several diseases**
  - Can be very efficient for **rare exposure** (can sample on exposure status)
- **Disadvantages**
  - **Large number of subjects**/participants
  - Inefficient for **rare diseases**
  - **Long follow-up period**
    - Subjects may change health behaviors during course of study
    - Possible changes over time in ascertainment of disease
  - **patient drop-out**
  - **causality**
  - **Very costly**

Flow chart:



Prospective study

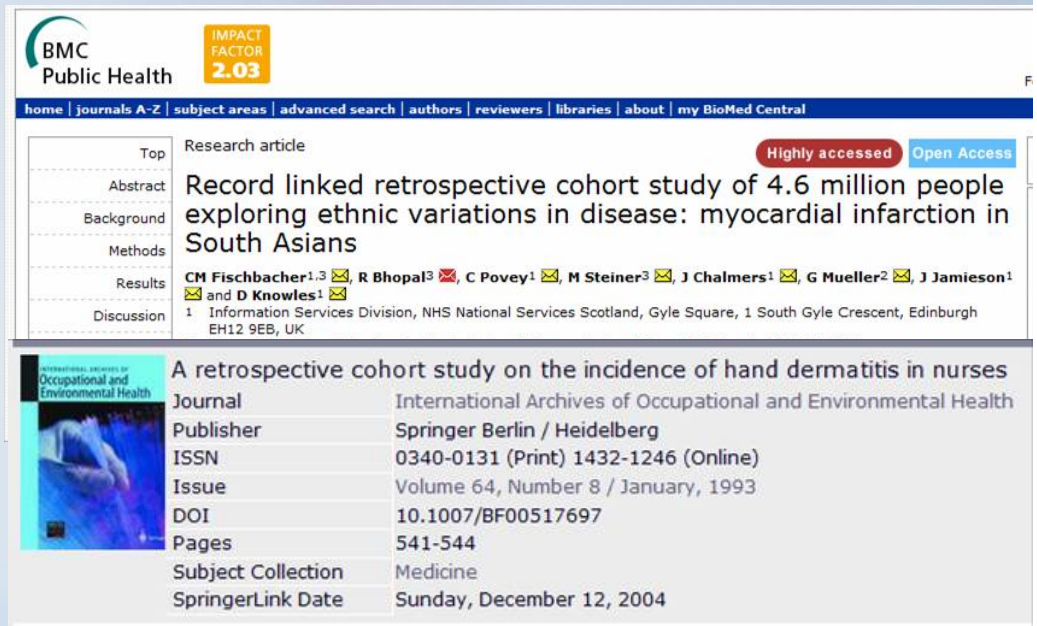
T_0 → T_1

T_{-1} ← T_0

Retrospective study

Analytic studies: Observational studies

- **Cohort studies – types:**
  - **PROSPECTIVE**
    - Study starts in the present and investigator observes cohort prospectively (i.e. into the future)
    - **Advantage:** Can collect whatever information you want
  - **RETROSPECTIVE**
    - Investigator identifies cohort retrospectively (i.e. in the past) and observes cohort through historical time
    - **Disadvantage:** You're stuck with what information was collected in the past.



Analytic studies: Cohort studies - issues

Issues:

- **Selection of the exposed population** (e.g. where they really at risk in the moment of Chernobyl accident ???)
- **Selection of comparison group** (in our case, incomplete medical records for some pre-Chernobyl period)
- **Source of exposure data**
- **Source of outcome data** ("theoretical" incidence reports from medical statistics institutes or confirmed cases in hospitals?)

Rom. J. Biophys. 2010 20(1): 47-59

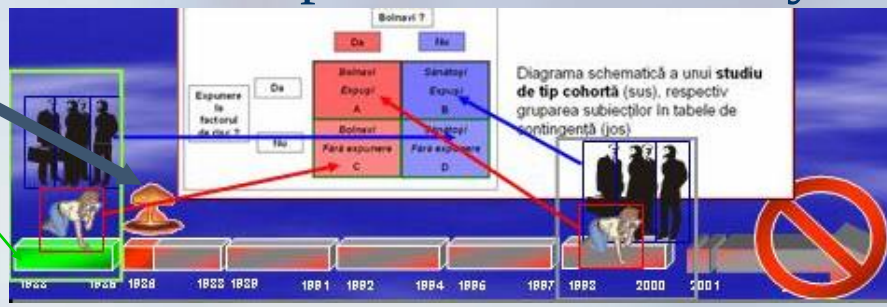
ACCIDENTAL IONIZING RADIATION AND ITS IMPACT ON THE POPULATION

MARIANA TILINCĂ*, M. MĂRUŞTERI**, JULIÁNNA SZAKÁCS***, I. NICOLAESCU***

*Department of Cellular and Molecular Biology, University of Medicine and Pharmaceutics, Târgu Mureş, Romania
**Department of Medical Informatics and Biostatistics, University of Medicine and Pharmaceutics, Târgu Mureş, Romania
***Department of Biophysics, Biotechnology, Medical and Pharmaceutical Physics, University of Medicine and Pharmaceutics, Târgu Mureş, Romania

Abstract. A study of the influence of accidental ionizing radiation due to the nuclear explosion in Chernobyl in 1986 on Mureş County population was performed. We studied the annual incidence of acute leukemia in Mureş County between 1983–2002, according to gender, origin, and type of disease. This study is a cohort type, based on ecological preponderance. Due to the existence of incomplete records in some clinics, we could not study the incidence of disease for more than 3 years in pre-Chernobyl period (1983–1985). Thus, we have grouped the post-Chernobyl interval in 5 periods of 3 years, to calculate and compare the cumulative incidence values. Regarding the total incidence of acute leukemia, there is a statistically significant positive association between the exposure to the risk factor (ionizing radiation) and the disease throughout all the studied periods during 1986–2000. Previous conclusions are also supported by the results of data analysis in case of grouping data according to criteria regarding the type of the disease, as well as demographic criteria. The results appear to contest the existence of a dose-response type relationship in case of our study.
Key words: ionizing radiation, acute leukemia, statistical analysis.

Retrospective cohort study



T_{-1} T_0

Contingency tables (2x2)

		Disease: Yes	Disease: No	Total
Exposure	Yes	a	b	a + b
	No	c	d	c + d
Total		a + c	b + d	a + b + c + d

Relative risk (RR)

Measure of association between exposure (risk factor) and disease (outcome)
Estimate the **magnitude** of this **association**

$$RR = \frac{\text{Incidence rate among exposed}}{\text{Incidence rate among unexposed}}$$

$$RR = \frac{\mathbf{a/(a+b)}}{\mathbf{c/(c+d)}}$$

a = number of individuals who are exposed and have the disease
b = number who are exposed and do not have the disease
c = number who are not exposed and have the disease
d = number who are both non-exposed and non-diseased

a + b = the total number of individuals exposed
c + d = the total number of unexposed
a + c = the total number with the disease
b + d = the total number without the disease
a + b + c + d = sum of all four cells and the total sample size for the study

Analytic studies: Cohort analysis

Interpretation of the results:

i) RR

ii) P value for the proper test (Chi square test, Chi square with Yates correction, Fischer exact test etc)

iii) CI 95% for RR.

Analogy Between Jury decisions and Statistical Tests		
	JURY	STATISTICAL
DECISION:	guilty/not guilty	reject/accept null
PRESUMPTION:	Presumed innocent	no association
STANDARD:	beyond a reasonable doubt	level of significance

Truth in population versus the results in a study sample

		Truth	
		Association (guilty)	No association (innocent)
Sample	Reject H_0 (guilty)	Correct	Type I error (alpha = 0.05)
	Fail to reject H_0 (not guilty)	Type II error (beta = 0.20)	Correct

Interpretation of Relative Risk (RR)

RR (OR)	CI 95 % Minimal value	CI 95 % Maximal value	P value	Interpretation
> 1	> 1	>> 1	≤ 0,05	**Positive association, statistically significant,** between exposure (risk factor) and disease
Positive association			**Statistically significant**	

RR (OR)	CI 95 % Minimal value	CI 95 % Maximal value	P value	Interpretation
< 1	<<1	< 1	≤ 0,05	**Negative association** (protective effect), **statistically significant,** between exposure (risk factor) and disease
Negative association or protective effect			**Statistically significant**	

RR (OR)	CI 95 % Minimal value	CI 95 % Maximal value	P value	Interpretation
> 1	< 1	> 1	> 0,05	**Positive association, statistically insignificant,** between exposure (risk factor) and disease
Positive association			**Statistically insignificant**	

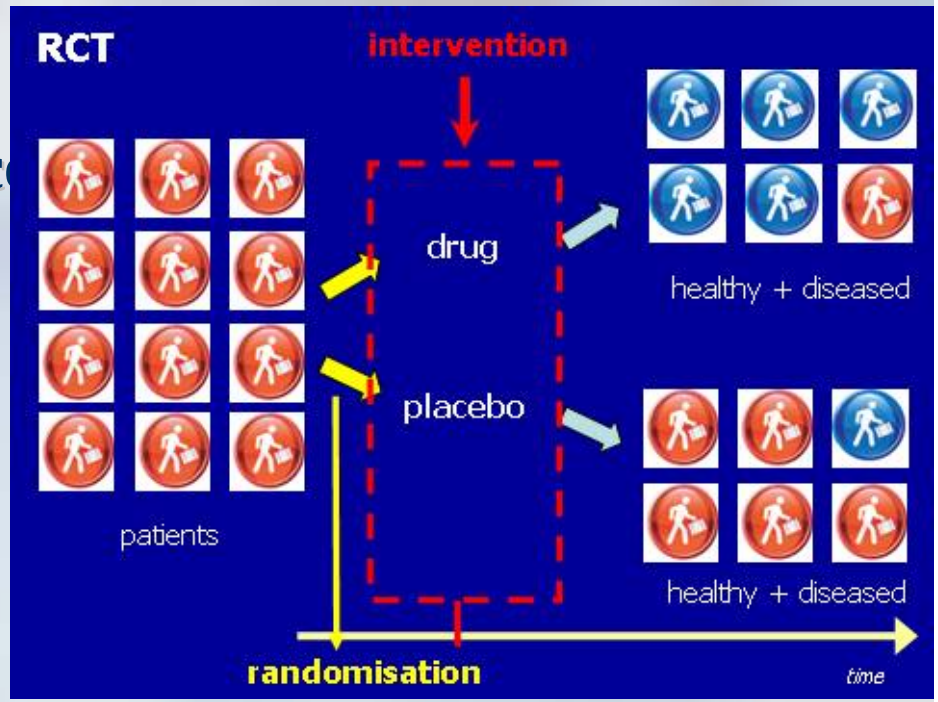
RR (OR)	CI 95 % Minimal value	CI 95 % Maximal value	P value	Interpretation
< 1	< 1	> 1	> 0,05	**Negative association** (protective effect), **statistically insignificant,** between exposure (risk factor) and disease
Negative association or protective effect			**Statistically insignificant**	

RR (OR)≅ 1 : No association between exposure (risk factor) and disease

Analytic studies: Intervention/Experimental studies

- **Experimental studies (e.g. Randomized Controlled Trials – RCT)**
  - Provides **most reliable evidenc**
  - **Randomization**
    - Controls for known risk factors
    - Controls for unknown risk factors
  - Useful for studying **small to moderate** effects
  - **Ethical considerations**
    - Human rights review
    - Data monitoring

Flow chart:



Simundic AM, *Types of study design*, Intensive Course in Basic Biostatistics and Research Design, June 21-24, 2009, Targu Mures, Romania, Pre-congress event, 1st Congress of Romanian Association of Medical Laboratories.

Analytic studies: Intervention/Experiment studies

Experimental studies (Randomized Controlled Trials – RCT)

- **Advantages**
  - **strength of evidence** (most scientist consider them to be the most reliable form of scientific evidence in the hierarchy of evidence that influences healthcare policy and practice)
  - it may study **different outcomes**
  - **control of bias** (systematic errors)
  - **causality**
- **Disadvantages**
  - **randomization** (is it ethical?)
  - **high cost**
  - **compliance**
  - **patient drop-out**


BMC Psychiatry

UNOFFICIAL IMPACT FACTOR 1.69

home | journals A-Z | subject areas | advanced search | authors | reviewers | libraries | about | my BioMed Central

Top
Abstract
Background
Methods
Discussion
Conclusion
Competing interests
Authors'

Research article

Open Access

Design and methods for a randomized clinical trial treating comorbid obesity and major depressive disorder

Kristin L Schneider[1], Jamie S Bodenlos[1], Yunsheng Ma[1], Barbara Olendzki[1], Jessica Oleski[1], Philip Merriam[1], Sybil Crawford[1], Ira S Ockene[2] and Sherry L Pagoto[1]

1 Department of Medicine, Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA, USA
2 Department of Cardiovascular Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA, USA

author email corresponding author email

BMC Psychiatry 2008, **8**:77 doi:10.1186/1471-244X-8-77


BMC Dermatology

home | journals A-Z | subject areas | advanced search | authors | reviewers | libraries | about | my BioMed Central

Top
Abstract
Background
Methods
Results
Discussion
Conclusion
Competing interests

Research article

Highly accessed Open Access

A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressings for the treatment of pressure ulcers [ISRCTN33429693]

Mohammad Taghi Hollisaz[1], Hossein Khedmat[2] and Fatemeh Yari[3]

1 Department of Rehabilitation, Baqyiatollah Hospital, Baqyiatollah University of Medical Sciences, Tehran, Iran
2 Department of Internal Medicine, Baqyiatollah Hospital, Baqyiatollah University of Medical Sciences, Tehran, Iran
3 Department of Biostatistics, Lorestan University of Medical Sciences, Khoramabad, Iran

author email corresponding author email

BMC Dermatology 2004, **4**:18 doi:10.1186/1471-5945-4-18

Randomized Controlled Trials – RCT - Classification

- **By study design**
  - **Parallel-group – each participant is randomized to a group,** and all the participants in the group receives (or does not receive) an intervention
  - **Crossover – over time, each participant receives (or does not receive)** an intervention in a random sequence
  - **Split-body – separate parts of the body of each participant** (e.g., the left and right sides of the face) are randomized to receive (or not receive) an intervention
  - **Cluster – pre-existing groups of participants (e.g., villages, schools)** are randomized to receive (or not receive) an intervention
  - **Factorial – each participant is randomized to a group that receives a particular combination** of interventions or non-interventions (e.g., group 1 receives vitamin X and vitamin Y, group 2 receives vitamin X and placebo Y, group 3 receives placebo X and vitamin Y, and group 4 receives placebo X and placebo Y)

An analysis of 616 RCTs indexed in PubMed, between December 2000 and December 2006, found that **78% were parallel-group**, **16% were crossover, 2% were split-body, 2% were cluster, and 2% were factorial.**

Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG (2010). The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. BMJ 2010;340:c723

Randomized Controlled Trials – RCT - Classification

- **By outcome of interest**

(efficacy vs. effectiveness)

- **Explanatory RCT - test "efficacy"** in a research setting with **highly selected participants** and under **highly controlled conditions**
- **Pragmatic RCT - test "effectiveness"** in everyday practice, with **relatively unselected participants** and **under flexible conditions**; in this way, pragmatic RCTs can **"inform decisions about practice"**

Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, Oxman AD, Moher D; CONSORT group; Pragmatic Trials in Healthcare (Practihc) group (2008). Improving the reporting of pragmatic trials: an extension of the CONSORT statement, BMJ 2008;337:a2390

Home > Comment > BMJ 2008;337:a2390, doi: 10.1136/bmj.a2390 (Published 11 November 2008)

This Article
Abstract FREE
PDF
Respond to this article
Alert me when this article is cited
Alert me when responses are posted
Alert me when a correction is posted
View citation map

Services
Email this article to a friend
Find similar articles in BMJ
Find similar articles in PubMed
Add article to my folders
Download to citation manager
Request Permissions

Citing Articles
Read articles citing this article

Published 11 November 2008, doi:10.1136/bmj.a2390
Cite this as: BMJ 2008;337:a2390

Research Methods & Reporting

Improving the reporting of pragmatic trials: an extension of the CONSORT statement

Merrick Zwarenstein, *director*[1,2,3], **Shaun Treweek**, *senior research fellow*[4,5], **Joel J Gagnier**, *post-graduate fellow*[5,6], **Douglas G Altman**, *director*[7], **Sean Tunis**, *director*[8,9,10], **Brian Haynes**, *Michael Gent professor and chair*[11], **Andrew D Oxman**, *senior researcher*[5], **David Moher**, *senior scientist*[12,13], for the CONSORT and Pragmatic Trials in Healthcare (Practihc) groups

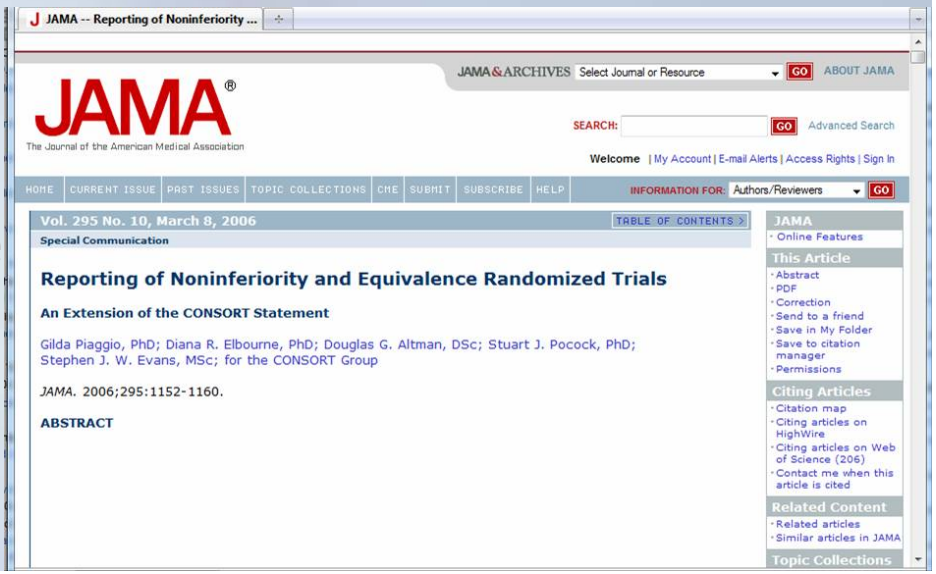
[1] Health Services Sciences, Sunnybrook Hospital, Toronto, Ontario, Canada, [2] Institute for Clinical Evaluative Sciences, Toronto Department of Health Policy, Management and Evaluation, University of Toronto, Toronto , [3] Division of International Health (IHCAR), Karolinska Institute, Stockholm, Sweden, [4] Clinical and Population Sciences and Education, University of Dundee, Dundee , [5] Norwegian Knowledge Centre for the Health Services, Oslo, Norway, [6] Faculty of Medicine, University of Toronto, [7] Centre for Statistics in Medicine, University of Oxford, Oxford, [8] Center for Medical Technology Policy, Baltimore, MD, USA, [9] Division of General Internal Medicine, Johns Hopkins School of Medicine, Baltimore, MD, [10] Center for Healthcare Policy, Stanford University School of Medicine, Palo Alto, CA, USA, [11] Department of Clinical Epidemiology and Biostatistics and Department of Medicine, McMaster University Faculty of Health Sciences, Hamilton, ON, Canada, [12] Clinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Canada, [13] Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa

Correspondence to: M Zwarenstein merrick.zwarenstein@ices.on.ca

Randomized Controlled Trials – RCT - Classification

- **By hypothesis (superiority vs. noninferiority vs. equivalence)**
  - **Superiority trials,** in which **one intervention** is **hypothesized to be superior to another** in a statistically significant way
  - **Noninferiority trials –** try **to determine** whether a **new treatment** is **no worse than a reference treatment**
  - **Equivalence trials -** in which the hypothesis is that **two interventions are indistinguishable** from each other

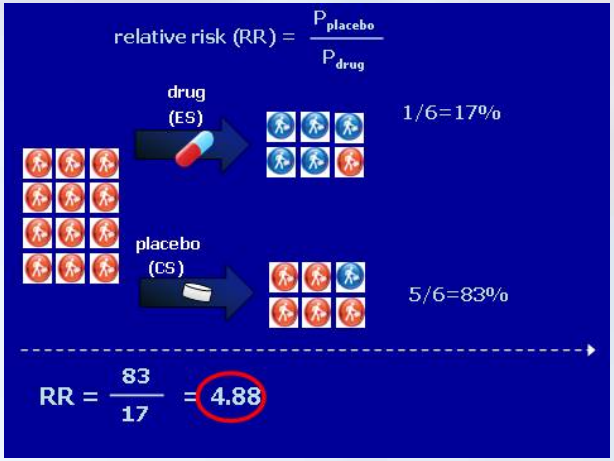
Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ; CONSORT Group (2006). "Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement". JAMA 295 (10): 1152–60



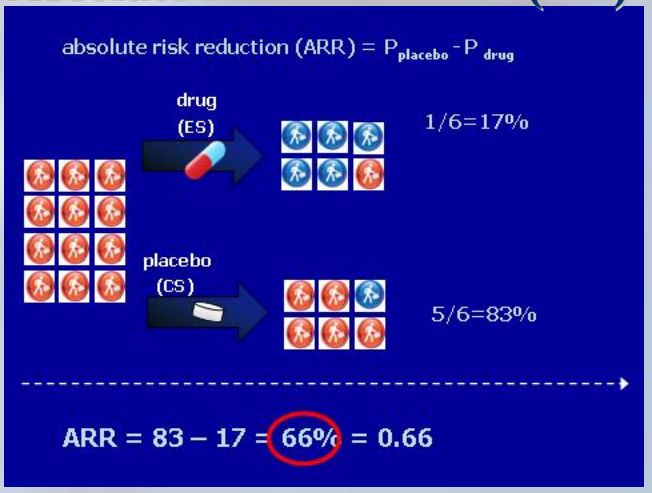
Analytic studies: RCT analysis

We may compute:

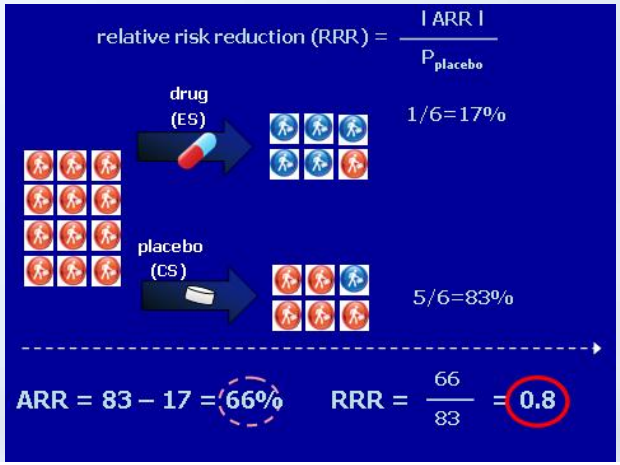
Relative Risk (RR)



Absolute Risk Reduction (RR)

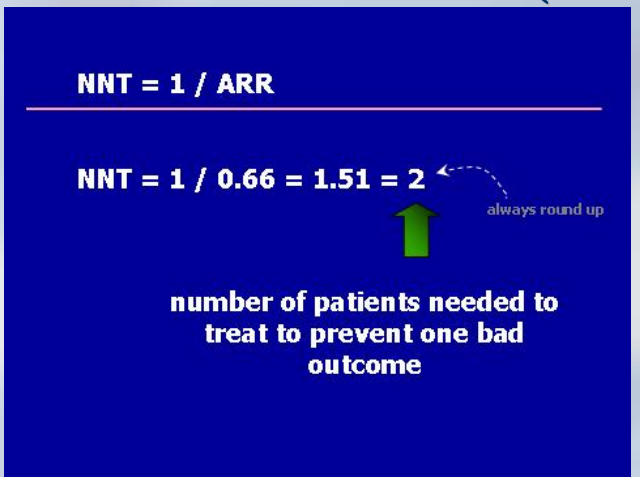


Relative Risk Reduction (RRR)



Simundic AM, *Types of study design*, Intensive Course in Basic Biostatistics and Research Design, June 21-24, 2009, Targu Mures, Romania,

Number Needed to Treat (NNT)



Strenght of evidence in various types of studies

Strenght of evidence

(Randomized) Clinical Trial - RCT

Cohort
Case-Control

Cross-sectional
Case Series
Case Reports

Analytic (experimental) studies

Analytic (observational) studies

Descriptive studies

Questions, when selecting a study design:

- **Scientific Knowledge ?**
  - New
  - Adding
  - Redoing / Confirming
- **Hypothesis?**
  - Generating
  - Testing
- **Epidemiologic / Statistical ?**
  - Disease
  - Exposure
  - Sample Size !
- **Resources ?** (usually a limiting factor)
  - Cost
  - Time

- **What disease is to be studied?**
  - Theoretical (e.g. incidence reports from governmental agencies, epidemiology books, other studies etc)
  - empirical based on diagnostic criteria
- **What exposure is to be studied?**
  - theoretical
  - empirical on the basis of criteria and examination methods used
- **What is the induction time,** that is, the time relation between exposure and effect (disease occurrence)?
- **What other factors may influence this association?**
  - theoretical
  - empirical on the basis of criteria and examination methods used

Issues in study design:

- Random or nonrandom sample?
- Sample size
- Random error
- Bias (systematic error)
- Association vs. Causation

Issues in study design:random or nonrandom sample?

- The best way to avoid a biased or unrepresentative sample is to select a **random sample**, also known as a probability sample.

A **random sample** is defined as a sample where the probability that any individual member from the population being selected as part of the sample is exactly the same as any other individual member of the population. Several types of random samples are simple random samples, systematic samples, stratified random samples, and cluster random samples.

- A sample that is not random is called a **nonrandom sample** or a nonprobability sample.

Nonprobability sampling include:

- **Convenience, Haphazard or Accidental sampling** - members of the population are chosen based on their relative ease of access.
- **Snowball sampling** - The first respondent refers a friend. The friend also refers a friend, etc.
- **Judgmental sampling** or **Purposive sampling** - The researcher chooses the sample based on who they think would be appropriate for the study.
- **Deviant Case**-Get cases that substantially differ from the dominant pattern (a special type of purposive sample)
- **Case study** - The research is limited to one group, often with a similar characteristic or of small size.
- **ad hoc quotas** - A quota is established (say 65% women) and researchers are free to choose any respondent they wish as long as the quota is met.

Issues in study design:sample size

- **How much error is acceptable?**

Alpha error/Type I error - rejecting null hypothesis when it is true

Finding an association that isn't real (False positive)

Beta error/Type II error - failing to reject null hypothesis when it is false

Missing an association that exists (False negative)

Power = 1 – Beta - Probability of observing an effect (association) in the sample if one exists

Example: B = 0.1 ---> Power = 90% chance of finding association

- **How large an effect do you expect to observe?**

Inverse relationship between **size of effect** and **sample size !!!**

- **How do you estimate effect? (clinically meaningful effect, pilot studies/other studies, informed guess)**
- **You may have to start with what you know you can do**
  - Available subjects
  - What's affordable (costs and time)

	Disease +	Disease -
Exposure +	5	2
Exposure -	4	3

Results

OR 1.9

P value (Chi square test) 0.6

CI 95% 0.2 to 17.3

	Disease +	Disease -
Exposure +	50	20
Exposure -	40	30

Results

OR 1.9

P value (Chi square test) 0.08

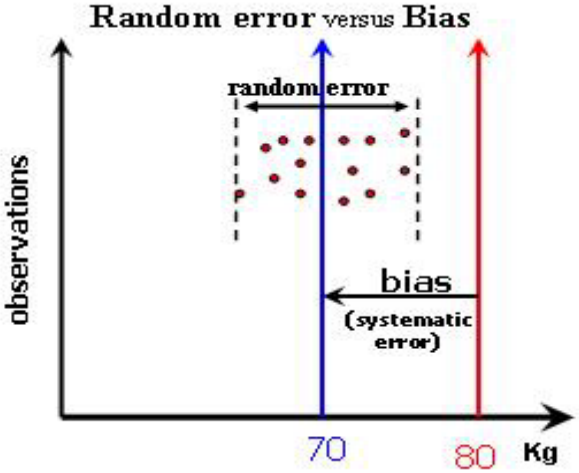
CI 95% 0.9 to 3.8

Issues in study design: steps in setting sample size

1. **State null hypothesis and alternative hypothesis**
2. **Select statistical test based on types of variables to be analyzed**
3. **Choose effect size - what do you expect to see?**
4. **Set alpha and beta levels (power of the study)**
5. **Calculate - use sample size table or computer program**

Issues in study design:random error and bias

- **Random error**
  - Random errors are errors in measurement **that lead to measured values being inconsistent when repeated measures** of a **constant attribute** or **quantity** are taken.
  - In a study design use the words **chance, luck of the draw**
- **How to reduce it?**
  - **Larger sample** produce **less variable estimate** and **more likely to reflect the experience of the total population**
  - ATTENTION! May be affected by both **the magnitude of the difference between groups** and **the sample size**
- **Bias (systematic error)**
  - **Any trend** in the collection, analysis, interpretation, publication or review of data **that can lead to conclusions** which are **systematically different from the truth.**



Issues in study design: types of bias

- **Types of bias**
  - selection bias
  - exclusion bias
  - prevalence / incidence bias
  - volunteer bias
  - compliance bias
  - performance bias
  - attrition bias (drop-out)
  - detection bias
  - response bias
  - information bias (recall bias, observer bias)
  - misclassification bias
  - funding bias
  - publication bias

  etc etc

- **Control of bias**

- Choice of study population
- Methods of data collection
  - Study Instruments
    - Objective questions
    - Objective measurements
  - Standardized techniques
    - Standard responses
    - Training
    - Blinding
- Use multiple sources of data for exposure and disease
- Minimize loss of follow-up

Issues in study design: association versus causation

- **We have to remember that:**
  - **Association** refers to **the statistical dependence between two variables**
  - **The presence of an association**, in no way implies that **the observed relationship** is one of **cause and effect.**

Criteria For Causality

- Can this **valid statistical association** be judged as **cause and effect**?
- **Strength of the association:**
  - Look at the magnitude of the observed association.
- **Biologic credibility of the hypothesis:**
  - Is there a known or postulated mechanism?
- **Consistency with other studies:**
  - Are these results consistent with others?
- **Time sequence:**
  - Does the exposure precede the outcome by a period of time consistent with any proposed biologic mechanism?
- **Dose-response relationship:**
  - Is there a gradient of risk with the degree of exposure?
- **Is the association specific?**
  - How many factors cause disease?
  - How many diseases are caused by the factor?