Overview of Epidemiological Study Designs

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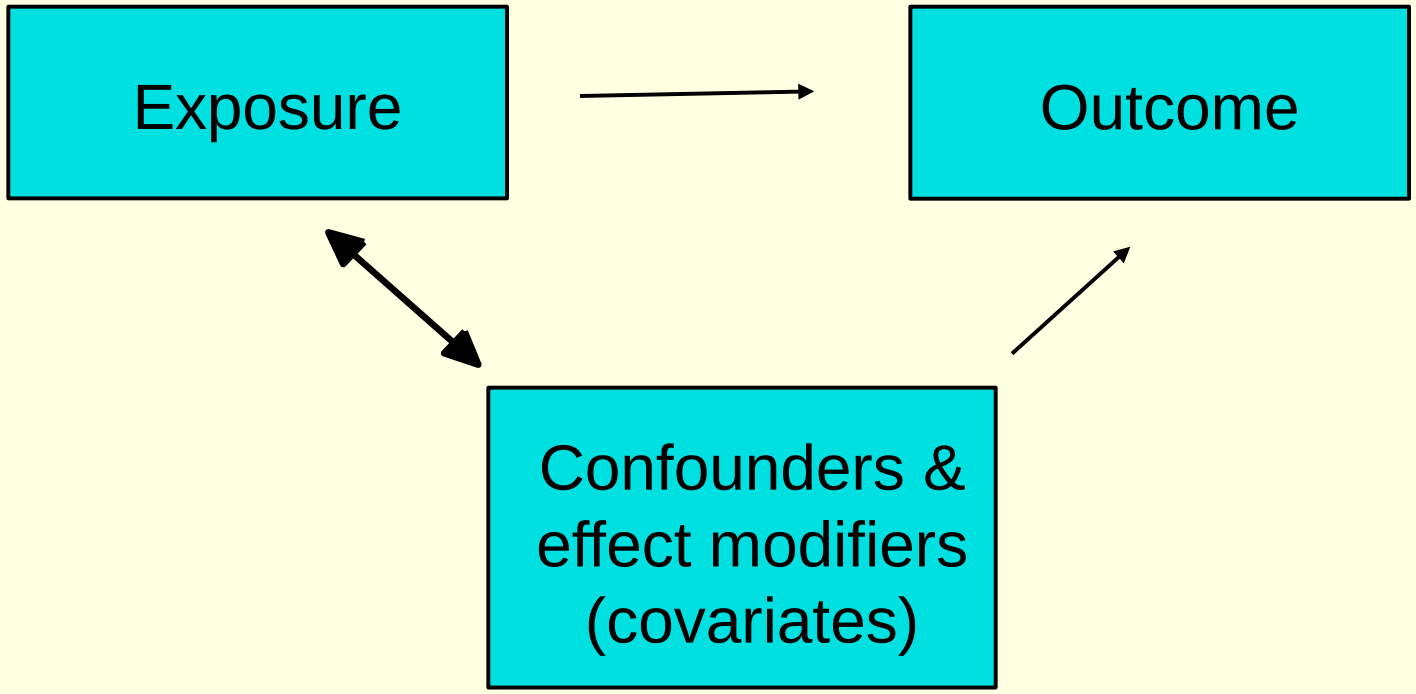
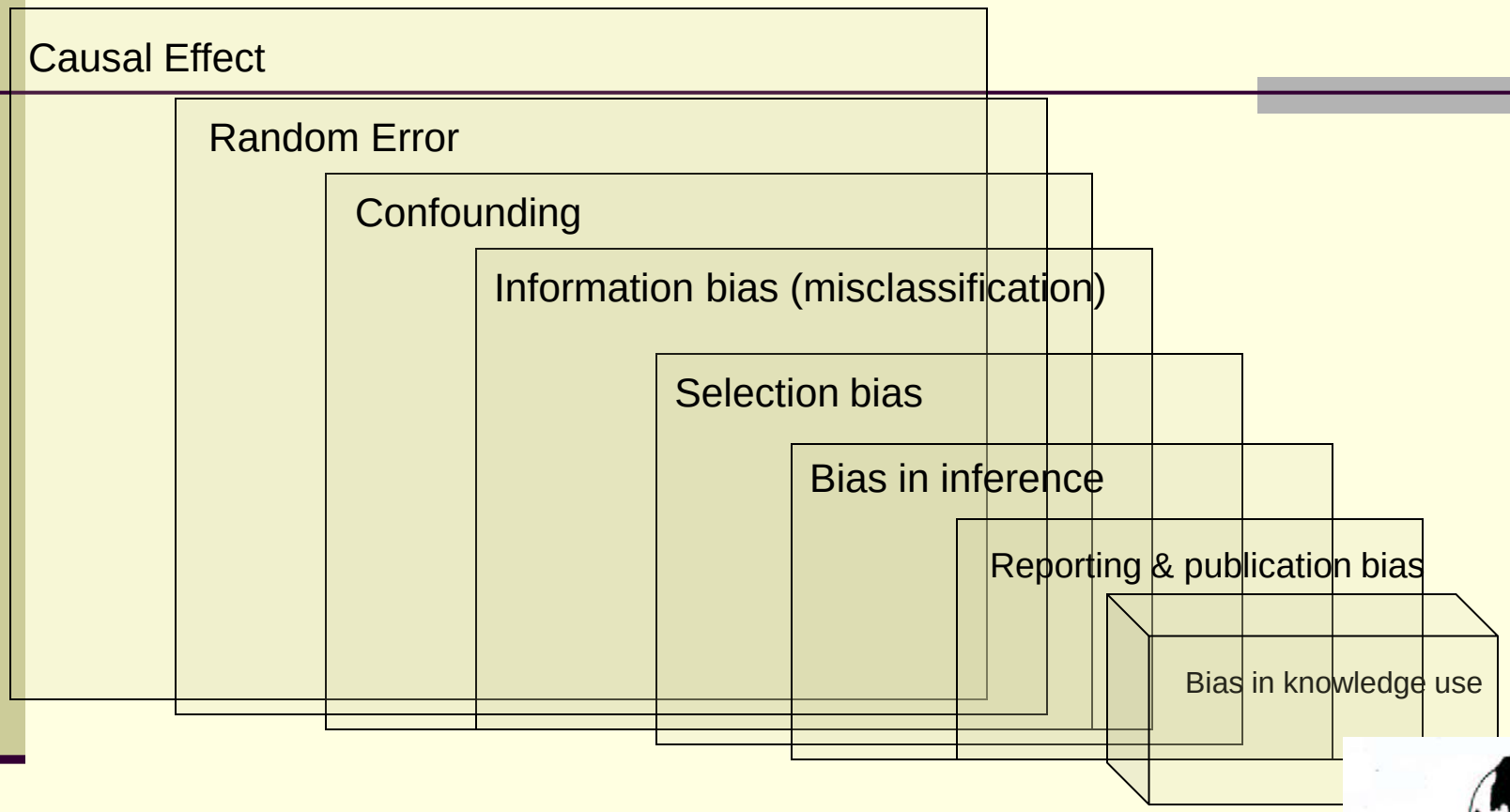
Exposures & Outcomes



Exposures & Outcomes

- A major goal of epi research is to explain patterns of disease occurrence and causation (etiology)
- Epi measurements are aimed at quantifying 3 things: exposures, confounders & outcomes
- Once quantified, the association between exposure and outcome is the central focus of epi studies
- There are many ways of evaluating the association between an exposure and an outcome: these are the different study designs

The best epidemiologic study will be one that captures the causal effect of interest with minimal distortion (error)

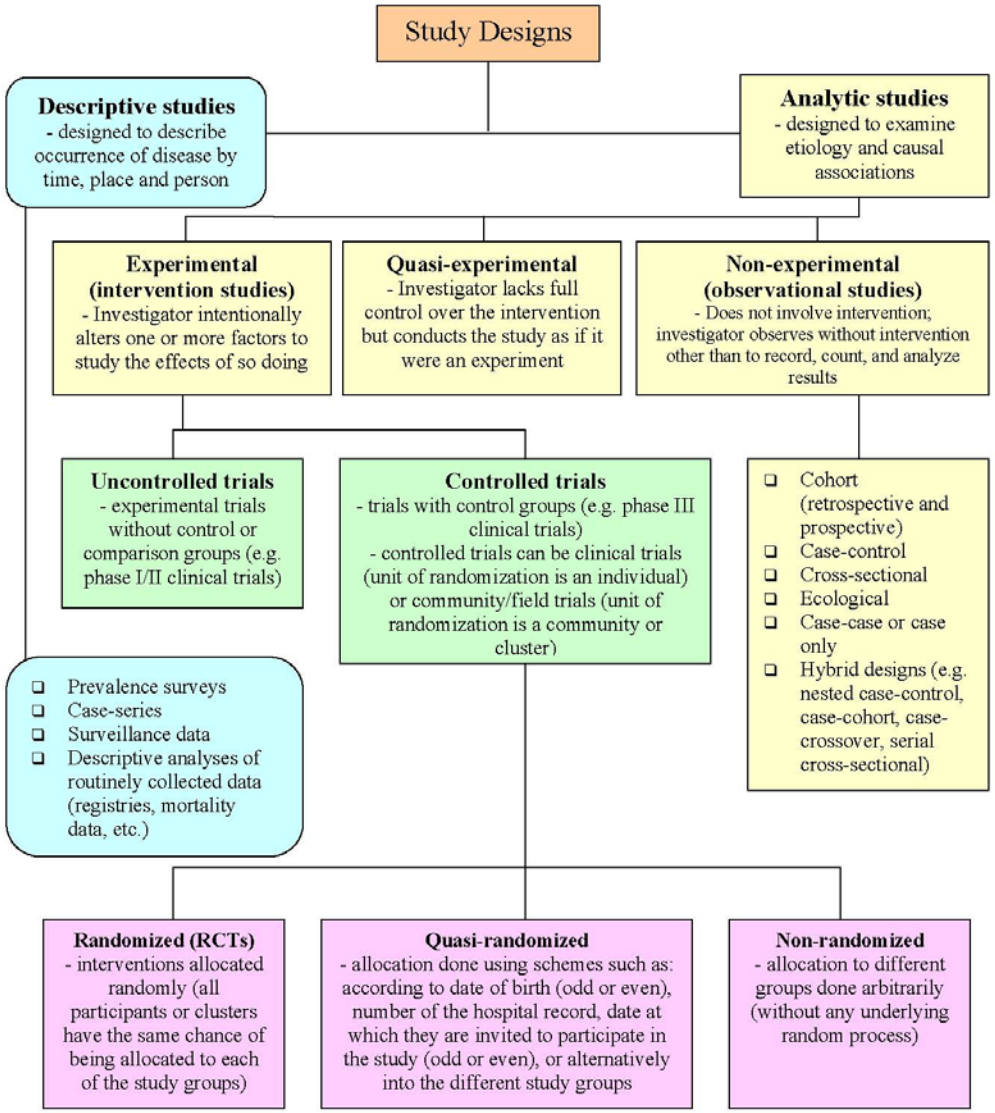


RR_{causal} "truth" → $RR_{association}$

Adapted from: Maclure, M, Schneeweis S. Epidemiology 2001;12:114-122.

Classification of study designs (Version 8)

(Qualitative studies are not included in this scheme; categories shown are not necessarily mutually exclusive, hybrid and mixed designs are possible)



Note: Systematic reviews and meta-analyses involve the secondary analysis and synthesis of original studies and are not considered in this classification system

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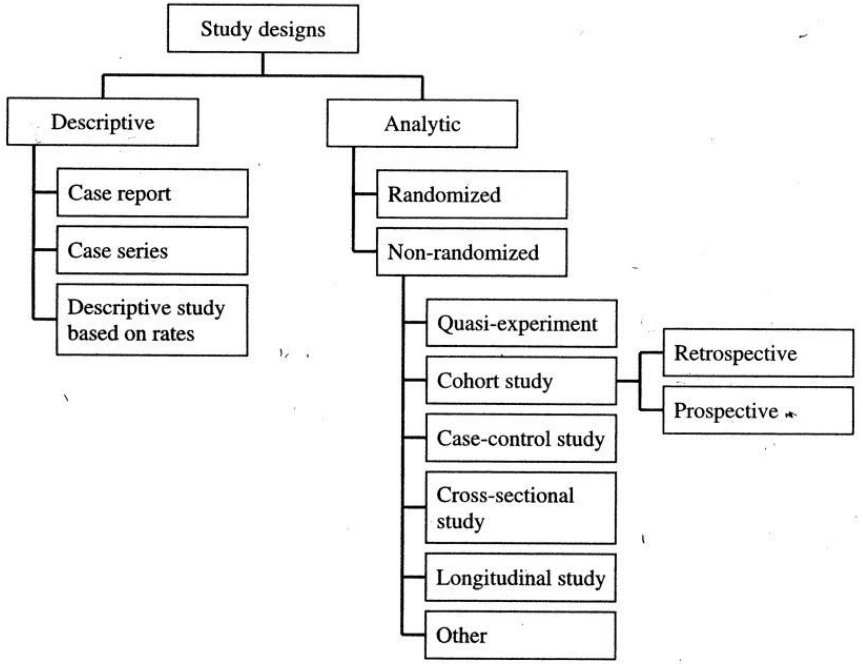


Figure 5–1. Major Epidemiologic Study Designs.

Koepsell & Weiss. Epidemiologic Methods. Oxford University Press, 2003

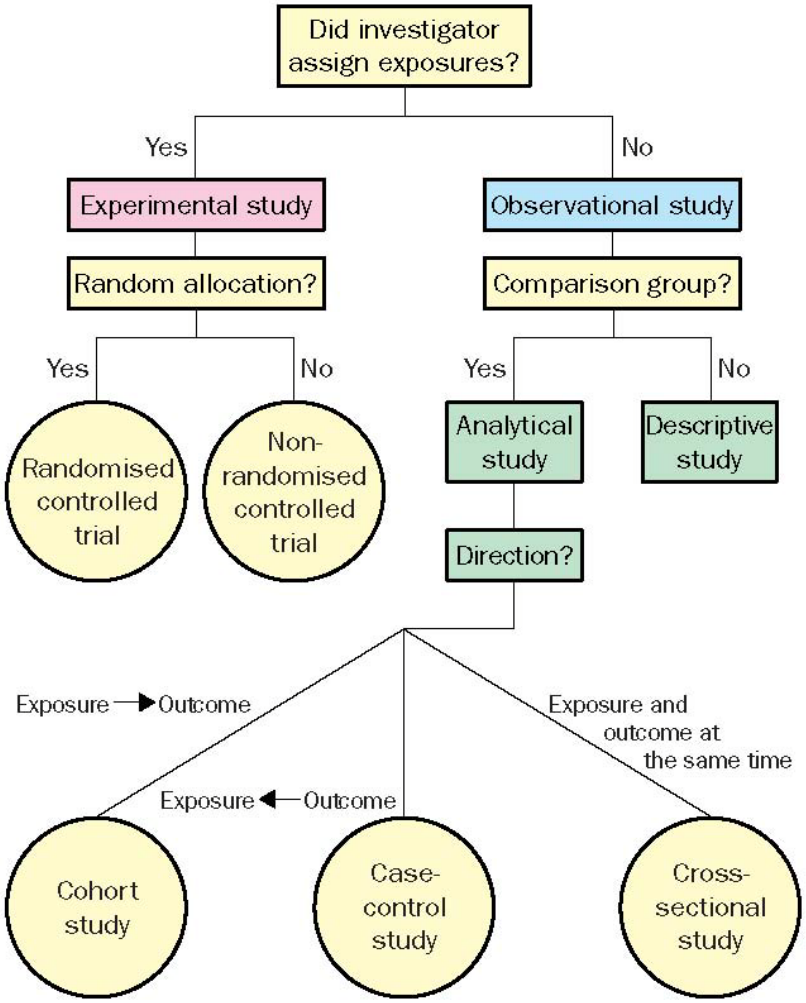


Figure 1: **Algorithm for classification of types of clinical research**

Grimes et al. Lancet 2002;359:57-61

Prospective vs. Retrospective studies

- NOT a good classification
- Need to separate: direction of the exposure/outcome analysis vs. how subjects were recruited into the study

- Also, “longitudinal or follow-up study” is not very informative:
  - RCTs are longitudinal
  - Cohort studies are longitudinal

Populations vs. cohorts

- A population is an aggregate of people
- 2 ways of defining a population based on membership:
  - based on a membership-defining event, with the membership commencing as of that event and lasting for ever thereafter
    - This is a “cohort”, a closed population, one that is closed for exit (e.g. a cohort of Nobel laureates or rock stars)
  - based on a membership-defining state, for the duration of that state, defining an open population, one that is open for exit, a population that is dynamic in the meaning of turnover of membership
- Cohort = closed for exit [some call it “closed or fixed population”]
- Population = open for exit [some call it “open or dynamic population”

[Source: Miettinen OS, 2007]

Cohort

Figure 1: **An early cohort in search of favourable outcome**

Grimes et al. Lancet 2002;359:341-45

THE ROMAN LEGION

The Legion was split into 10 **Cohorts**.

The Cohorts were divided into **Centuries**. The First Cohort contained five centuries of 160 'crack troops.' The other cohorts contained six centuries of 80 men.

The centurion in charge of the First Cohort was called the **Primus Pilus**. He was the best!

1st cohort	2nd cohort	3rd cohort	4th cohort	5th cohort	6th cohort	7th cohort	8th cohort	9th cohort	10th cohort
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
160 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men
	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men	80 men

http://www.caerleon.net/

Quiz: Who totally enjoys bashing up cohorts?

And the only cohort they were too gentlemanly to bash up?

Cohort: a simplistic view

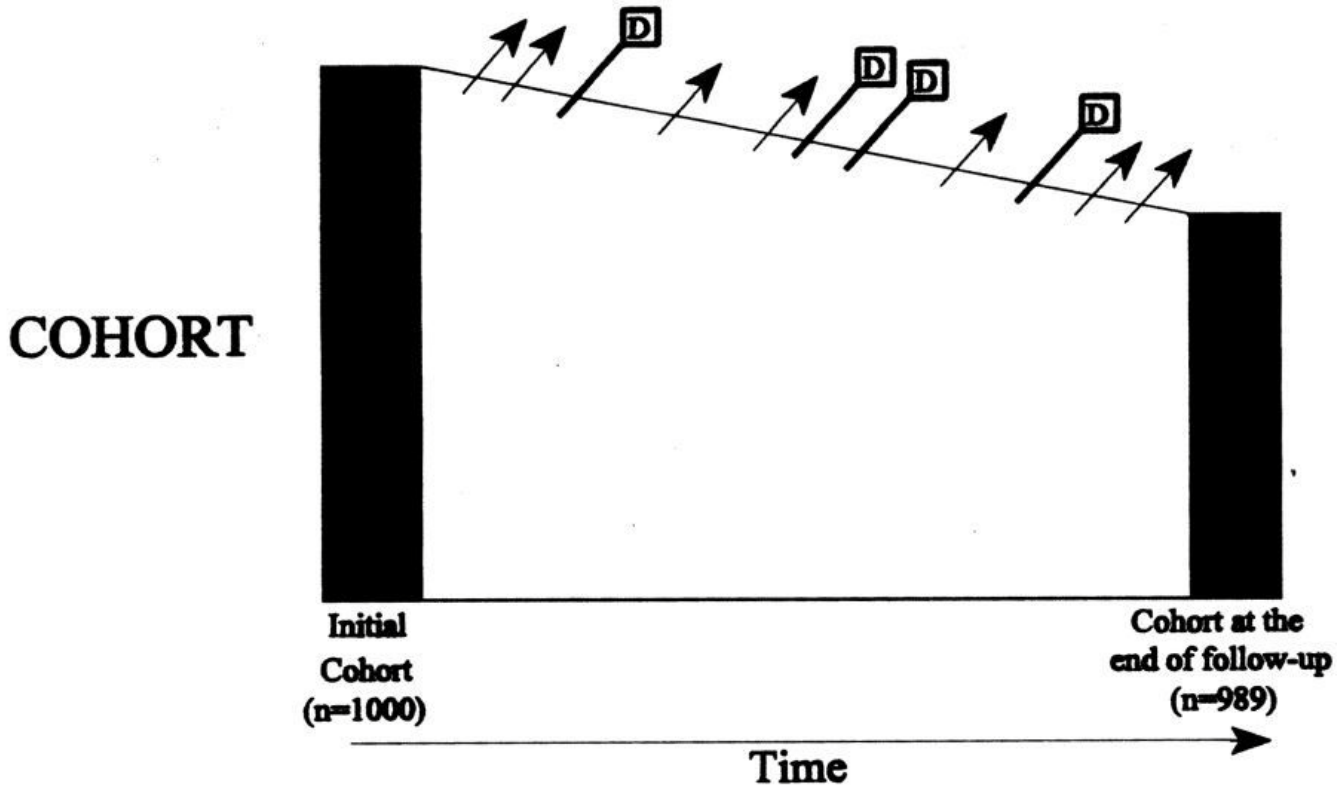


Figure 1–13 Diagram of a hypothetical cohort of 1000 subjects. During the follow-up, four disease events (D) and seven losses to follow-up (arrows) occur, so that the number of subjects under observation at the end of the follow-up is 989.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

A more sophisticated view: a “sea of person-time” in which all events occur

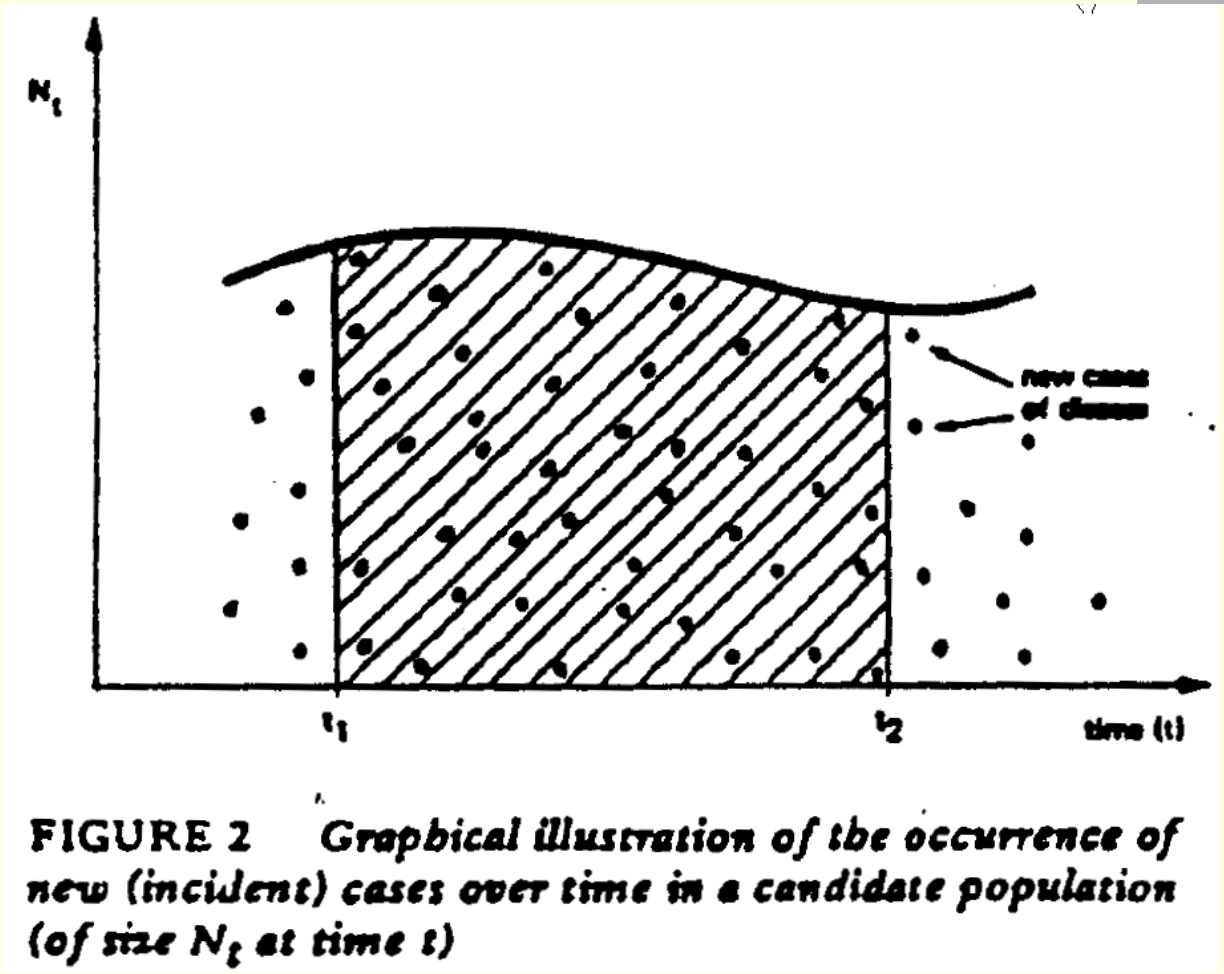
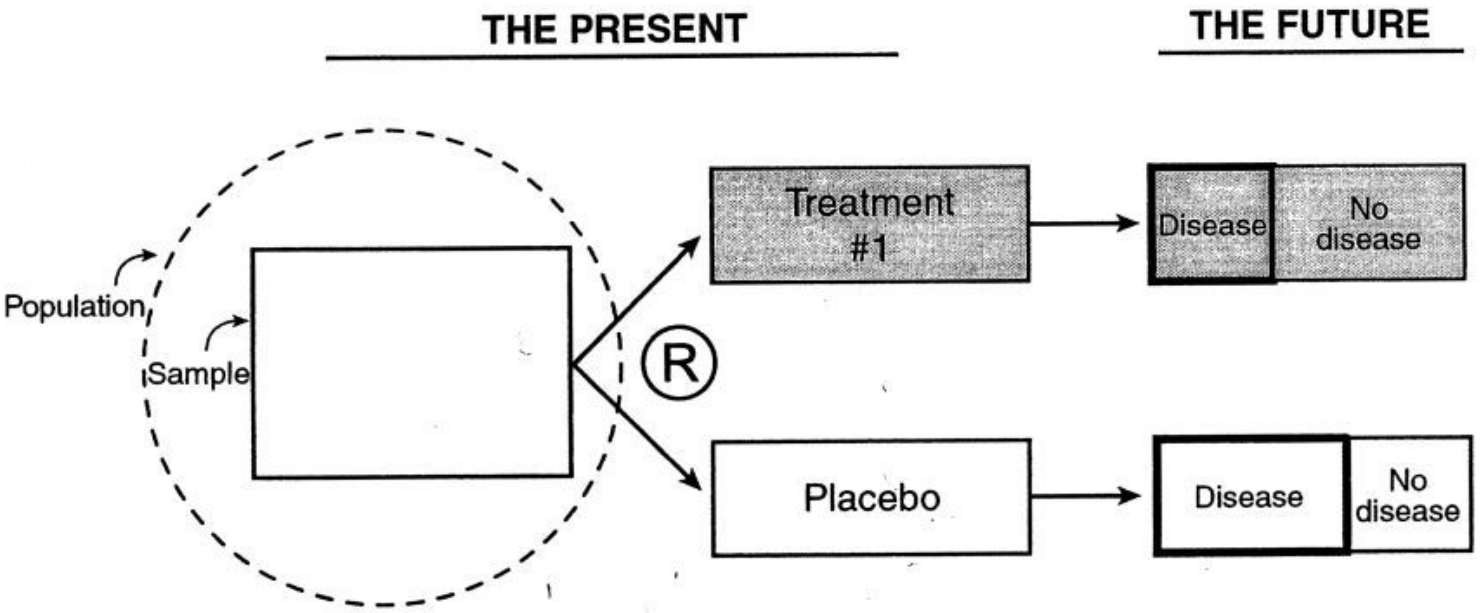


FIGURE 2 *Graphical illustration of the occurrence of new (incident) cases over time in a candidate population (of size N_t at time t)*

Morgenstern IJE 1980

Experimental designs

Simple, two-arm (parallel) RCT

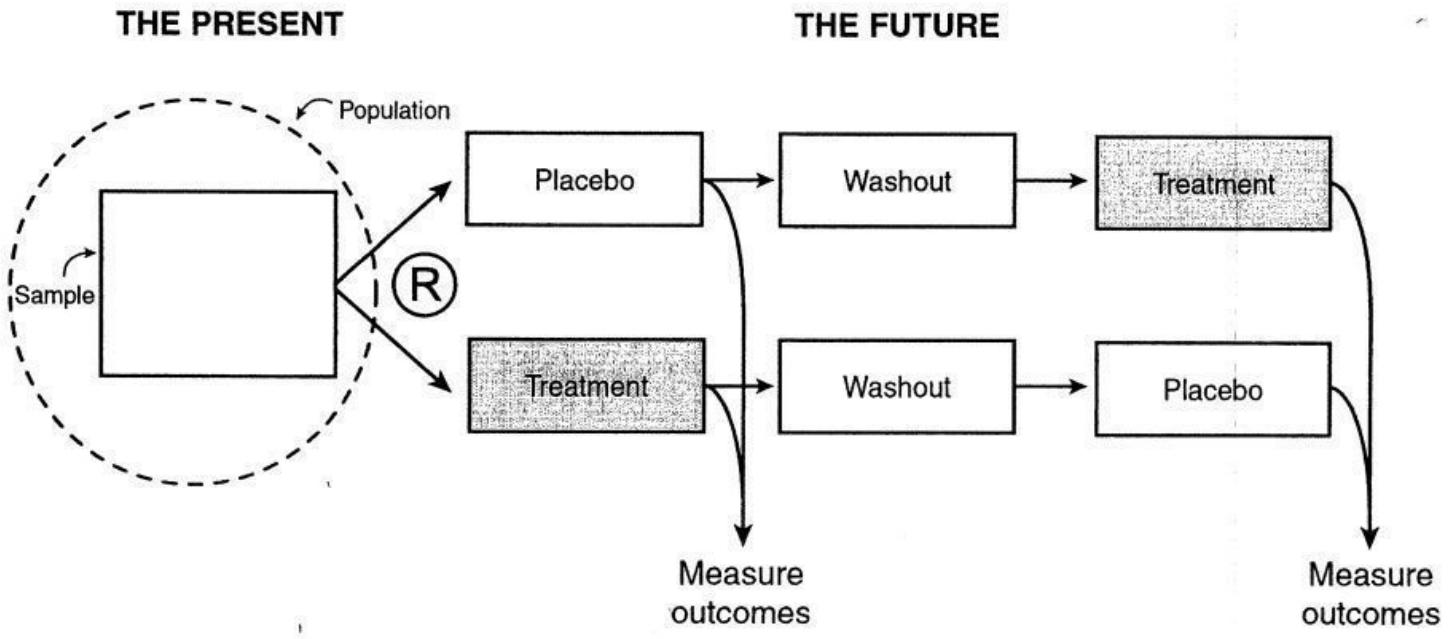


■ **FIGURE 10.1**

In a randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions (one should be a blinded placebo, if possible), (e) follows up the cohort, (f) measures outcome variables (blindly, if possible) and analyzes the results.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

Cross-over RCT design



■ **FIGURE 11.4**

In the cross-over randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions, (e) measures outcome variables, (f) allows washout period to reduce carryover effect, (g) applies intervention to former placebo group, (h) measures outcome variables again.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

Factorial RCT design

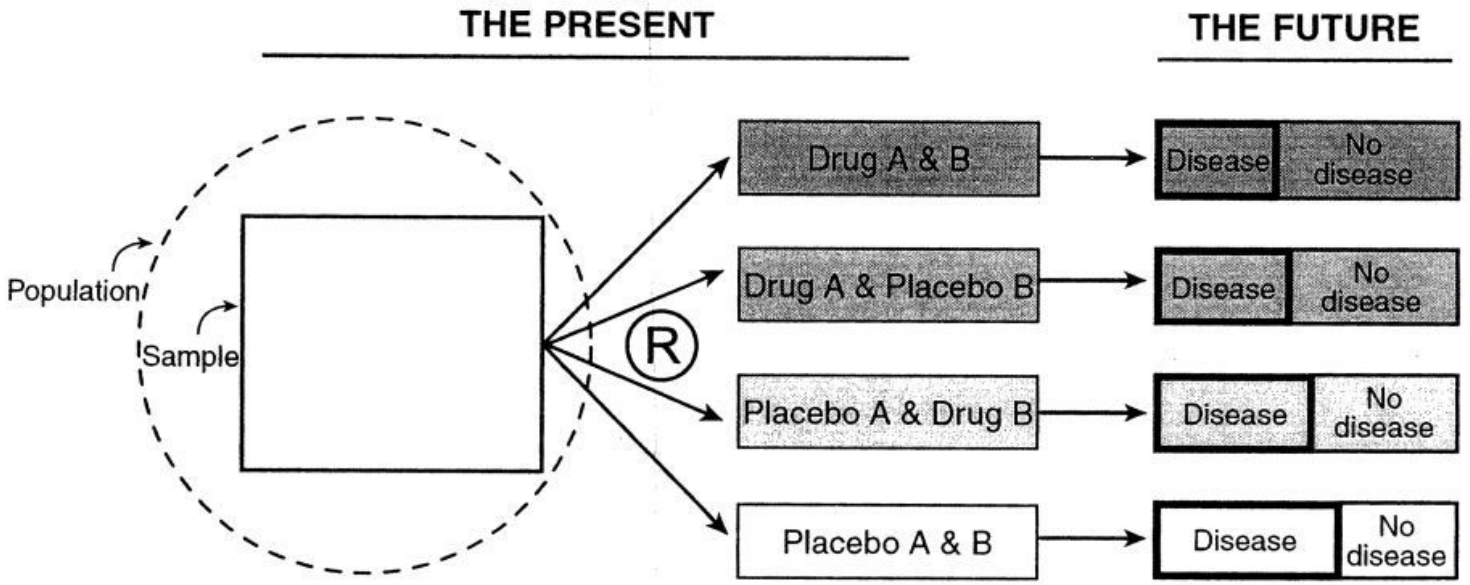


FIGURE 11.2

In a factorial randomized trial, the investigator (a) selects a sample from the population; (b) measures baseline variables; (c) randomly assigns two active interventions and their controls to four groups, as shown; (d) applies interventions; (e) follows up the cohorts; (f) measures outcome variables.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

ORIGINAL INVESTIGATION

A Randomized, Controlled Trial of the Effects of Remote, Intercessory Prayer on Outcomes in Patients Admitted to the Coronary Care Unit

William S. Harris, PhD; Manohar Gowda, MD; Jerry W. Kolb, MDiv; Christopher P. Strychacz, PhD; James L. Vacek, MD; Philip G. Jones, MS; Alan Forker, MD; James H. O'Keefe, MD; Ben D. McCallister, MD

Context: Intercessory prayer (praying for others) has been a common response to sickness for millennia, but it has received little scientific attention. The positive findings of a previous controlled trial of intercessory prayer have yet to be replicated.

Objective: To determine whether remote, intercessory prayer for hospitalized, cardiac patients will reduce overall adverse events and length of stay.

Design: Randomized, controlled, double-blind, prospective, parallel-group trial.

Setting: Private, university-associated hospital.

Patients: Nine hundred ninety consecutive patients who were newly admitted to the coronary care unit (CCU).

Intervention: At the time of admission, patients were randomized to receive remote, intercessory prayer (prayer group) or not (usual care group). The first names of patients in the prayer group were given to a team of outside intercessors who prayed for them daily for 4 weeks. Patients were unaware that they were being prayed for, and the intercessors did not know and never met the patients.

Main Outcome Measures: The medical course from CCU admission to hospital discharge was summarized in a CCU course score derived from blinded, retrospective chart review.

Results: Compared with the usual care group (n = 524), the prayer group (n = 466) had lower mean ± SEM weighted (6.35 ± 0.26 vs 7.13 ± 0.27; $P = .04$) and unweighted (2.7 ± 0.1 vs 3.0 ± 0.1; $P = .04$) CCU course scores. Lengths of CCU and hospital stays were not different.

Conclusions: Remote, intercessory prayer was associated with lower CCU course scores. This result suggests that prayer may be an effective adjunct to standard medical care.

Arch Intern Med. 1999;159:2273-2278

Non-experimental (observational) designs

Cohort study

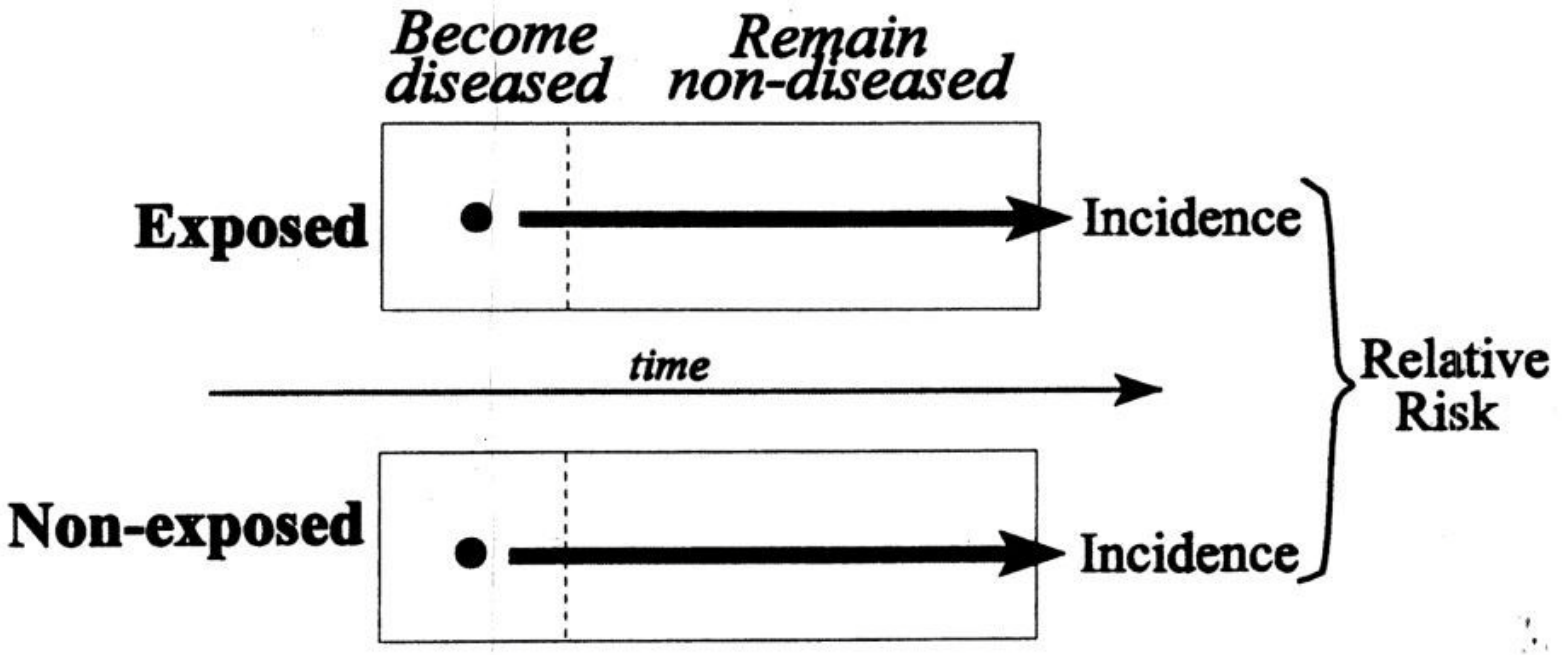


Figure 1–14 Basic analytical approach in a cohort study.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Cohort study

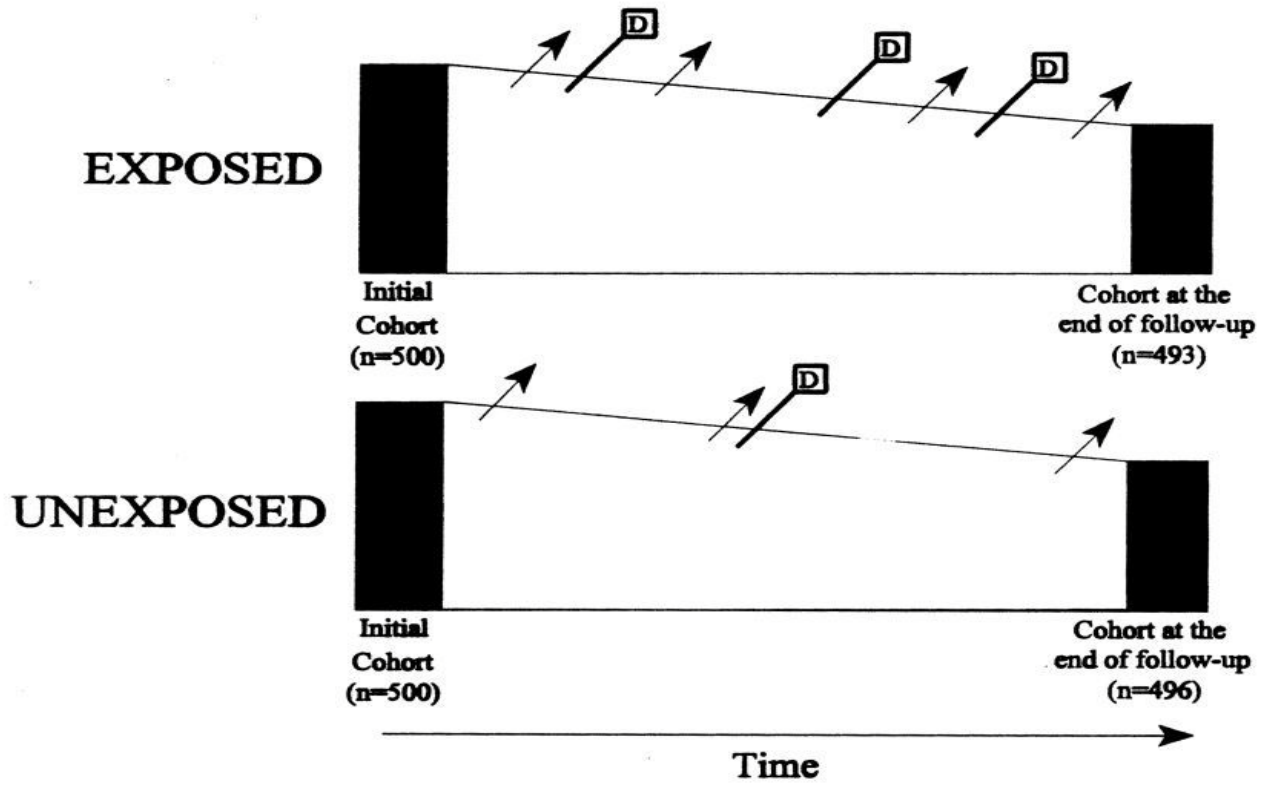


Figure 1–15 Same cohort study as in Figure 1–13, but the ascertainment of events and losses to follow-up is done separately among those exposed and unexposed.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Variants of cohort design

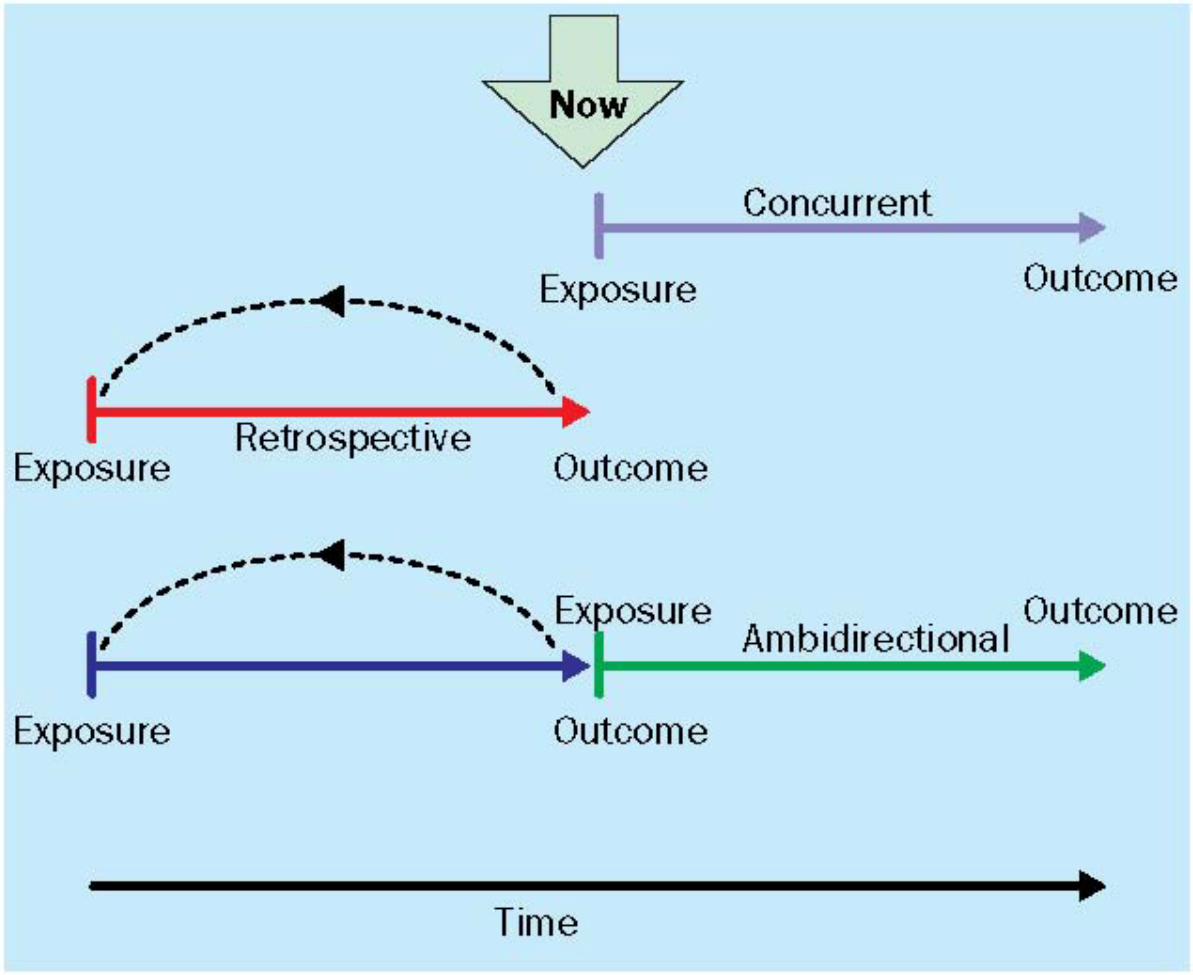


Figure 2: **Schematic diagram of concurrent, retrospective, and ambidirectional cohort studies**

Grimes et al. Lancet 2002;359:341-45

Pulmonary Function after Exposure to the World Trade Center Collapse in the New York City Fire Department

Gisela I. Banauch, Charles Hall, Michael Weiden, Hillel W. Cohen, Thomas K. Aldrich, Vasillios Christodoulou, Nicole Arcentales, Kerry J. Kelly, and David J. Prezant

Pulmonary Division, Department of Medicine, Montefiore Medical Center, and Biostatistics Division, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx; Bureau of Health Services, New York City Fire Department, Brooklyn; and Pulmonary Division, Department of Medicine, New York University School of Medicine, New York, New York

Rationale: On September 11, 2001, the World Trade Center collapse created an enormous urban disaster site with high levels of airborne pollutants. First responders, rescue and recovery workers, and residents have since reported respiratory symptoms and developed pulmonary function abnormalities.

Objectives: To quantify respiratory health effects of World Trade Center exposure in the New York City Fire Department.

Measurements: Longitudinal study of pulmonary function in 12,079 New York City Fire Department rescue workers employed on or before 09/11/2001. Between 01/01/1997 and 09/11/2002, 31,994 spirometries were obtained and the FEV_1 and FVC were analyzed for differences according to estimated World Trade Center exposure intensity. Adjusted average FEV_1 during the first year after 09/11/2001 was compared with the 5 yr before 09/11/2001. Median time between 09/11/2001 and a worker's first spirometry afterwards was 3 mo; 90% were assessed within 5 mo.

Main Results: World Trade Center–exposed workers experienced a substantial reduction in adjusted average FEV_1 during the year after 09/11/2001 (372 ml; 95% confidence interval, 364–381 ml; $p < 0.001$) This exposure-related FEV_1 decrement equaled 12 yr of aging-related FEV_1 decline. Moreover, exposure intensity assessed by initial arrival time at the World Trade Center site correlated linearly with FEV_1 reduction in an exposure intensity–response gradient ($p = 0.048$). Respiratory symptoms also predicted a further FEV_1 decrease ($p < 0.001$). Similar findings were observed for adjusted average FVC.

Conclusions: World Trade Center exposure produced a substantial reduction in pulmonary function in New York City Fire Department rescue workers during the first year after 09/11/2001.

service [EMS] workers) were present at the WTC site within the first week after 09/11/2001 and reported extensive exposures. Appropriate respiratory protection was initially not readily available; later, compliance was suboptimal (3). WTC exposure has since been implicated in "WTC cough," and upper and lower airway inflammation with airway obstruction and bronchial hyperreactivity (4–12).

In a previous cross-sectional stratified random sample of 319 WTC-exposed FDNY rescue workers 3 wk after 09/11/2001, we described pulmonary function declines that correlated with WTC dust exposure intensity (3). To define better the respiratory consequences of WTC exposure, we now report our analysis of longitudinal pulmonary function course from 1997 to 2002 in the entire FDNY WTC medical screening cohort ($n = 12,079$). Study objectives were to determine whether pulmonary function changed after 09/11/2001, and whether WTC exposure intensity affected pulmonary function and respiratory symptoms in an exposure intensity–response pattern after 09/11/2001. Some of the results of this study have previously been reported in the form of an abstract (13).

METHODS

The FDNY Bureau of Health Services performs periodic medical evaluations on all FDNY rescue workers approximately every 18 mo. Since 1997, these evaluations have included spirometry and a respiratory questionnaire. On 10/01/2001, the FDNY Bureau of Health Services started the FDNY WTC Medical Screening Program, which included

Case-control study

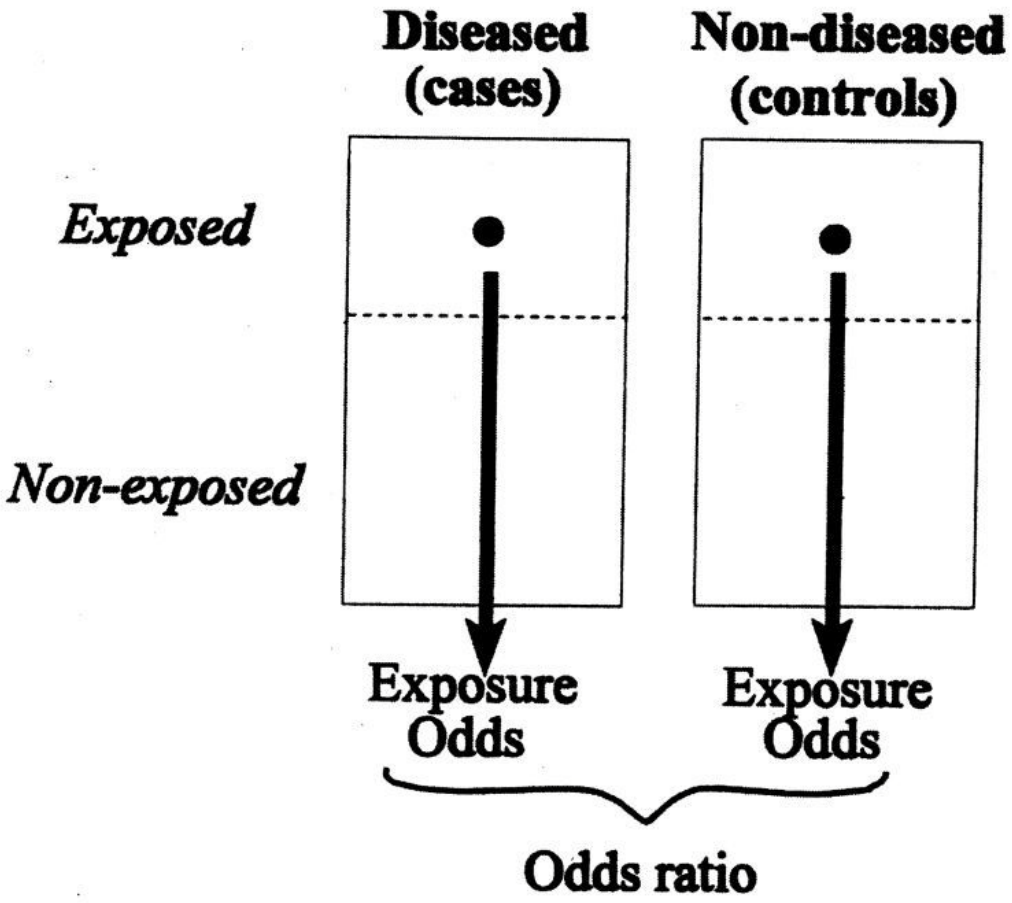
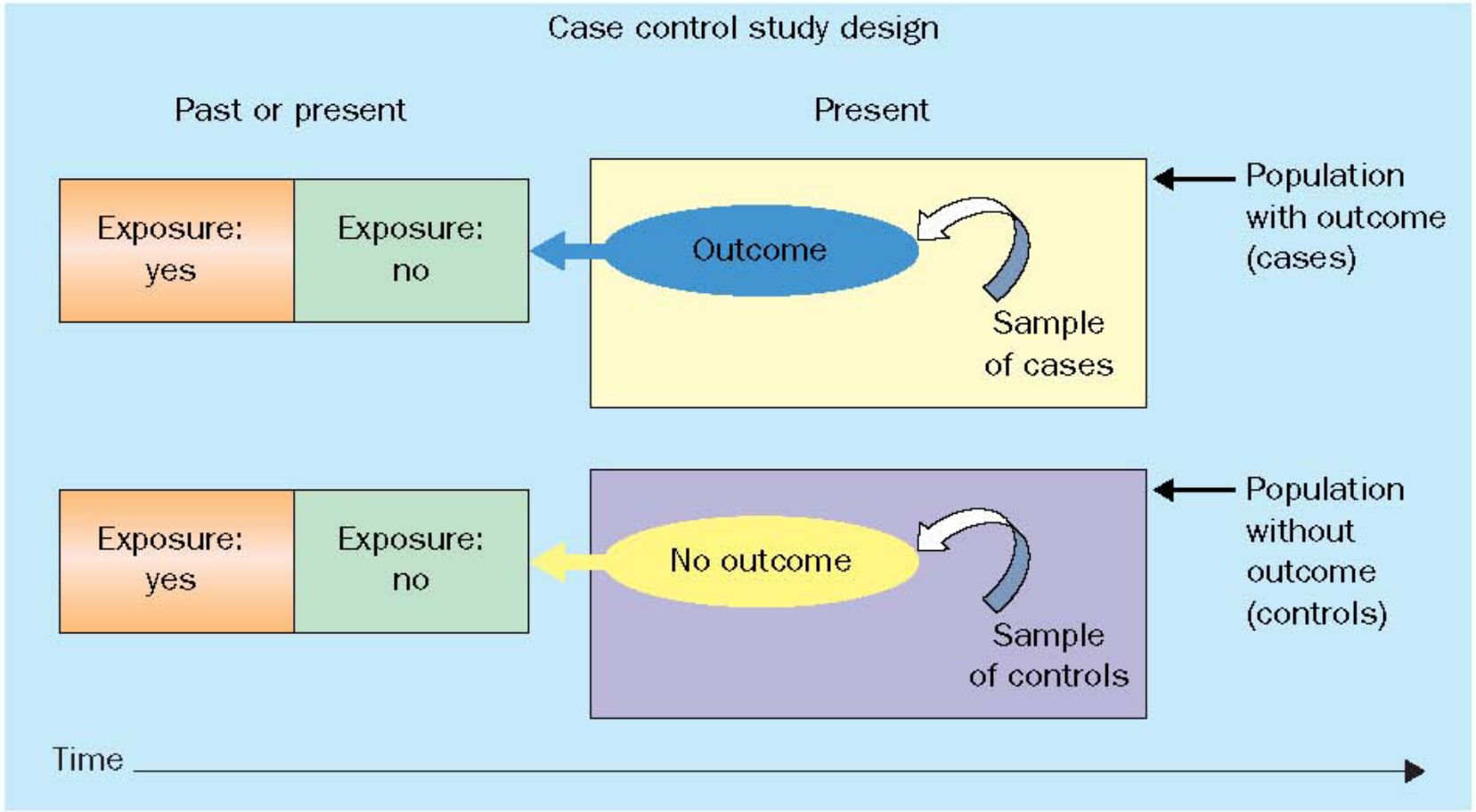


Figure 1–17 Basic analytical approach in a case-control study.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Case-control study



Schematic diagram of case-control study design

Grimes et al. Lancet 2002;359:431-34

Control sampling strategies

1) Cumulative sampling: from those who do not develop the outcome at the end of the study period (i.e. from the “survivors”)

2) Case-cohort (case-base; case-referent) sampling: from the entire cohort at baseline (start of the follow-up period)

3) Density sampling (risk-set sampling): throughout the course of the study, from individuals at risk (“risk-set”) at the time each case occurs

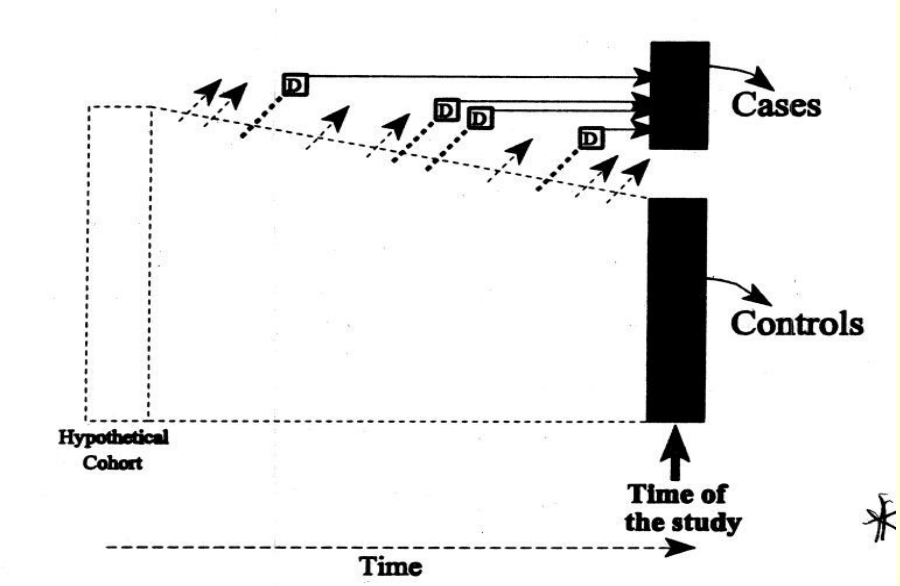


Figure 1–18 Hypothetical case-based case-control study, assuming that cases and controls are selected from a hypothetical cohort, as in Figure 1–13. The case group is assumed to include all cases that occurred in that hypothetical cohort up to the time when the study is conducted (“D” with horizontal arrows ending at the “case” bar): that is, they are assumed to be all alive and available to participate in the study; controls are selected from among those without the disease of interest (noncases) at the time when the cases are identified and assembled. Broken diagonal lines with arrows represent losses to follow-up.

•Controls should be representative of the person-time distribution of exposure (exposure prevalence) in the study base (i.e. be representative of the study base)
•Controls should be selected independent of the exposure

Mobile phone use and risk of acoustic neuroma: results of the Interphone case–control study in five North European countries

MJ Schoemaker*[,1], AJ Swerdlow[1], A Ahlbom[2,13], A Auvinen[3,10], KG Blaasaas[4], E Cardis[5], H Collatz Christensen[6], M Feychting[2], SJ Hepworth[7], C Johansen[6], L Klæboe[8], S Lönn[2], PA McKinney[7], K Muir[9], J Raitanen[10], T Salminen[3], J Thomsen[11] and T Tynes[8,12]

[1]Section of Epidemiology, Institute of Cancer Research, Brookes Lawley Building, Sutton SM2 5NG, UK; [2]Institute of Environmental Medicine, Karolinska Institute, Box 210, 171 77, Stockholm, Sweden; [3]STUK-Radiation and Nuclear Safety Authority, 00881 Helsinki, Finland; [4]Norwegian Armed Forces, Bygning 0028A, Sessvollmoen 2058, Norway; [5]International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Cedex 08, Lyon, France; [6]Institute of Cancer Epidemiology, Danish Cancer Society, Strandboulevarden 49, 2100 Copenhagen, Denmark; [7]Centre for Epidemiology and Biostatistics, University of Leeds, 30 Hyde Terrace, Leeds LS2 9LN, UK; [8]The Cancer Registry of Norway, Institute of Population-based Cancer Research, Montebello, 0310 Oslo, Norway; [9]Division of Epidemiology and Public Health, University of Nottingham, Nottingham NG7 2UH, UK; [10]Tampere School of Public Health, University of Tampere, Tampere 33014, Finland; [11]Department of Otolaryngology-Head and Neck Surgery, Gentofte Hospital, University of Copenhagen, DK-2900 Hellerup, Denmark; [12]Norwegian Radiation Protection Authority, PO Box 55, 1332 Osteras, Norway

There is public concern that use of mobile phones could increase the risk of brain tumours. If such an effect exists, acoustic neuroma would be of particular concern because of the proximity of the acoustic nerve to the handset. We conducted, to a shared protocol, six population-based case–control studies in four Nordic countries and the UK to assess the risk of acoustic neuroma in relation to mobile phone use. Data were collected by personal interview from 678 cases of acoustic neuroma and 3553 controls. The risk of acoustic neuroma in relation to regular mobile phone use in the pooled data set was not raised (odds ratio (OR) = 0.9, 95% confidence interval (CI): 0.7–1.1). There was no association of risk with duration of use, lifetime cumulative hours of use or number of calls, for phone use overall or for analogue or digital phones separately. Risk of a tumour on the same side of the head as reported phone use was raised for use for 10 years or longer (OR = 1.8, 95% CI: 1.1–3.1). The study suggests that there is no substantial risk of acoustic neuroma in the first decade after starting mobile phone use. However, an increase in risk after longer term use or after a longer lag period could not be ruled out.

British Journal of Cancer (2005) **93,** 842–848. doi:10.1038/sj.bjc.6602764 www.bjcancer.com
Published online 30 August 2005

Cross-sectional study

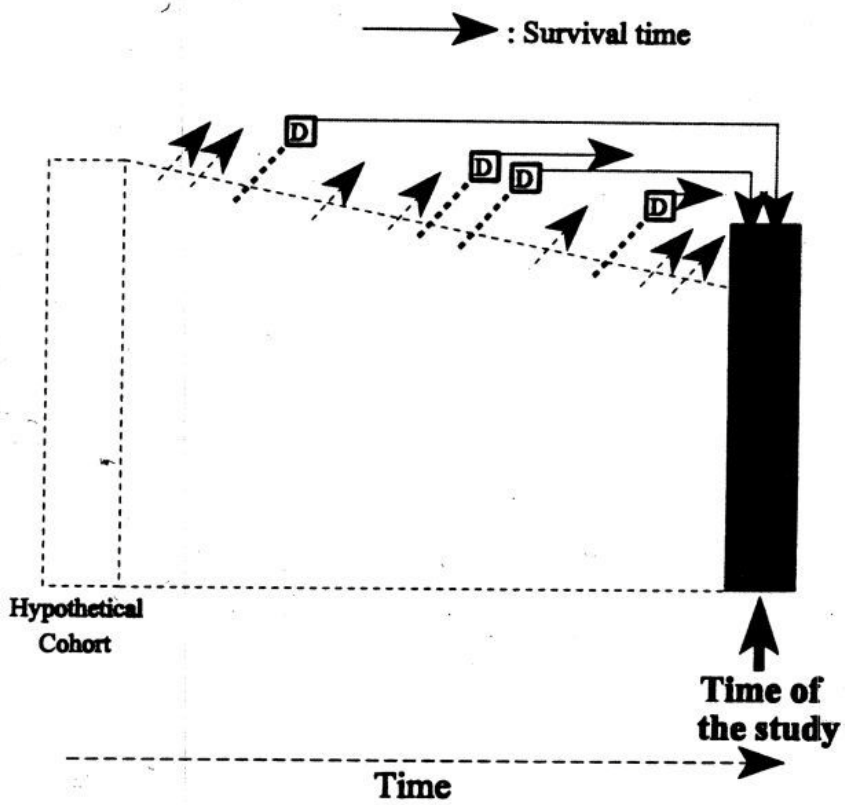


Figure 1–22 Schematic representation of a cross-sectional study, conceptually and methodologically analogous to the case-based case-control study represented in Figure 1–19, except that instead of explicitly selecting cases and controls, it selects a sample of the entire population. Broken diagonal lines with arrows represent losses to follow-up. Cases are represented by "D" boxes.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Respiratory Symptoms and Physiologic Assessment of Ironworkers at the World Trade Center Disaster Site*

Gwen Skloot, MD, FCCP; Michael Goldman, MD; David Fischler, MD; Christine Goldman, NP; Clyde Schechter, MA, MD; Stephen Levin, MD; and Alvin Teirstein, MD, FCCP

Study objectives: **To characterize respiratory abnormalities in a convenience sample of ironworkers exposed at the World Trade Center (WTC) disaster site for varying lengths of time between September 11, 2001, and February 8, 2002.**
Design: **Cross-sectional study.**
Setting: **The Mount Sinai Medical Center, a large tertiary hospital.**
Participants: **Ninety-six ironworkers engaged in rescue and recovery with exposure onset between September 11, 2001, and September 15, 2001, who responded to an invitation to undergo respiratory evaluation.**
Measurements: **Medical and exposure history, physical examination, spirometry, forced oscillation (FO), and chest radiographs. The relationships of prevalence of respiratory symptoms and presence of obstructive physiology to smoking, exposure on September 11, duration of exposure, and type of respiratory protection were examined using univariate and linear and logistic regression analyses.**
Results: **Seventy-four of 96 workers (77%) had one or more respiratory symptoms (similar in smokers [49 of 63 subjects, 78%] and nonsmokers [25 of 33 subjects, 76%]). Cough was the most common symptom (62 of 96 subjects, 65%), and was associated with exposure on September 11. Chest examination and radiograph findings were abnormal in 10 subjects (10%) and 19 subjects (20%), respectively. FO revealed dysfunction in 34 of 64 subjects tested (53%), while spirometry suggested obstruction in only 11 subjects (17%). Lack of a respirator with canister was a risk factor for large airway dysfunction, and cigarette smoking was a risk factor for small airway dysfunction. No other relationships reached statistical significance.**
Conclusions: **Respiratory symptoms occurred in the majority of ironworkers at the WTC disaster site and were not attributable to smoking. Exposure on September 11 was associated with a greater prevalence of cough. Objective evidence of lung disease was less common. Spirometry underestimated the prevalence of lung function abnormalities in comparison to FO. Continuing evaluation of symptoms, chest radiographs, and airway dysfunction should determine whether long-term clinical sequelae will exist.** ***(CHEST 2004; 125:1248–1255)***

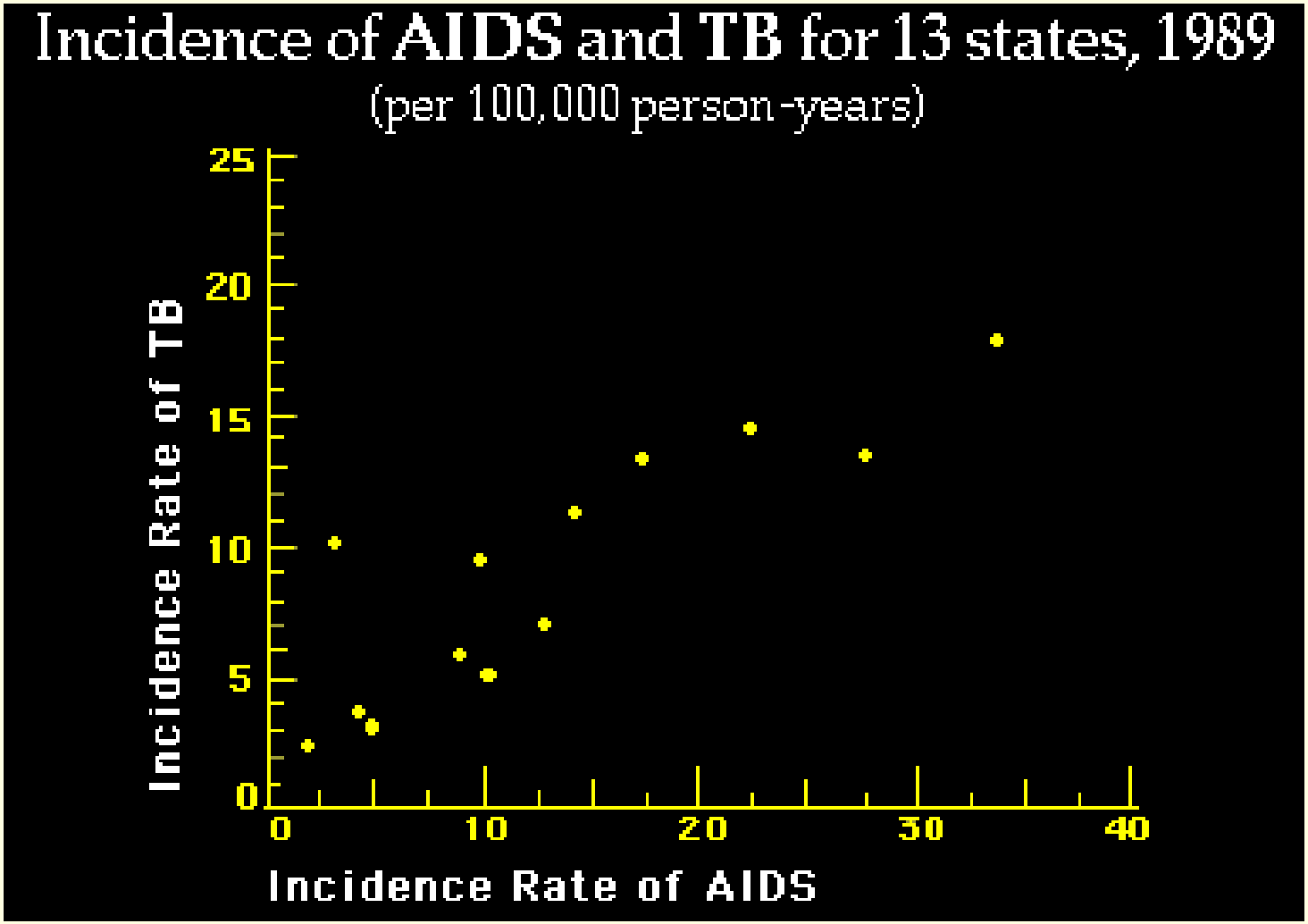
Key words: exposure; forced oscillation; ironworkers; September 11, 2001; spirometry; World Trade Center disaster

Abbreviations: AX = area of low-frequency reactance; f-d R = frequency dependence of resistance; $FEF_{25-75\%}$ = forced expiratory flow during 25% to 75% of FVC; FO = forced oscillation; IOS = Impulse Oscillation System; OR = odds ratio; R5 = respiratory resistance at 5 Hz; R5-R20 = respiratory resistance at 5 to 20 Hz; R20 = respiratory resistance at 20 Hz; WTC = World Trade Center

Ecologic Studies

- Explores correlations between aggregate (group level) exposure and outcomes
- Unit of analysis: not individual, but clusters (e.g. countries, counties, schools)
- Useful for generating hypothesis
- Prone to “ecological fallacy”
- Cannot adjust well for confounding due to lack of comparability (due to lack of data on all potential covariates)

Ecologic Studies: Correlation between TB and AIDS



Source: ActivEpi

Environmental Health: A Global Access Science Source

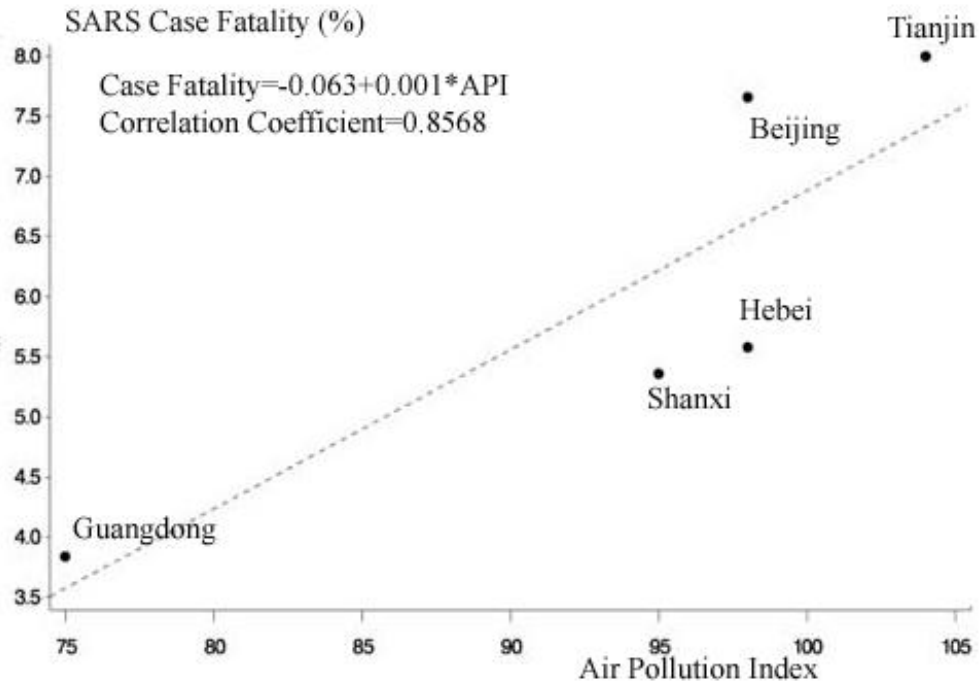
BioMed Central

Research

Open Access

Air pollution and case fatality of SARS in the People's Republic of China: an ecologic study

Yan Cui[1], Zuo-Feng Zhang*[1], John Froines[2], Jinkou Zhao[3], Hua Wang[3], Shun-Zhang Yu[4] and Roger Detels[1]



The Correlation and Association between Short-term Exposure to Ambient Air Pollution and Case Fatality of SARS in People's Republic of China.

Cui *et al. Environmental Health: A Global Access Science Source* 2003

Kraft Officials: Mac & Cheese Sales Predict Recession

NewsNet5.com
updated 2:49 p.m. ET, Tues., Dec. 2, 2008

Kraft officials said that they knew that a recession was on the horizon last year.

Company officials said the sales of Macaroni and Cheese began to spike last winter, reported consumer reporter John Matarese.

Officials said the sales of Kraft's Macaroni and Cheese is an accurate predictor of a recession.

More local links from WEWS

Monday's declaration by the National Bureau of Economic Research (NBER) that the US has been in a recession for more than a year is no surprise to buyers of Kraft Macaroni & Cheese, whose purchases jumped last winter.

Sales of Kraft's boxed mac-and-cheese rose to $193.1 million in the first quarter, 10 percent over the previous year, according to Information Resources Inc., a Chicago-based market-data company. They remained above 2007's level in the second and third quarters as shoppers turned to cheaper options in a sagging economy.

Importance of the research question

- “The question being asked determine the appropriate study architecture, strategy and tactics to be used - not tradition, authority, experts, paradigms or schools of though.”
  - Sackett, Wennberg 1997

- Good research starts with asking a clear, focused research question.
- How does one ask a focused research question?

How are these questions different?

- Does aspirin improve survival after myocardial infarction?

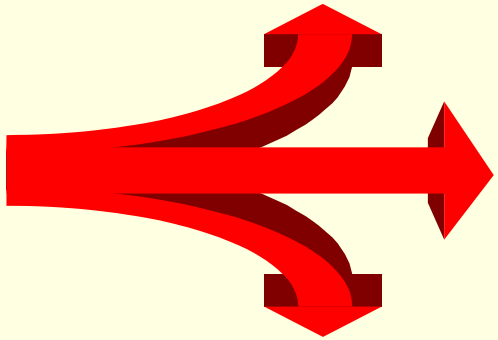
- In patients with first episode, acute myocardial infarction, does daily, low-dose, oral aspirin lead to higher survival rates as compared to placebo?

Types of questions (domains)

- Etiology [cohort, case-control]
- Therapy [RCT]
- Prognosis [cohort]
- Harm [cohort, case-control]
- Diagnosis [cross-sectional, case-control]
- Economic [cost-effectiveness analysis, etc.]

  - These domains are usually addressed by different study designs

Architecture of a focused question: a 4-part review question



P - Who is the patient or what problem is being addressed?

I/E - What is the intervention or exposure?

C – What is the comparison group?

O - What is the outcome or endpoint?

+ study design

Richardson et al. The well-built clinical question: a key to evidence-based decisions. ACP Journal Club 1995;A-12

Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med 1997;127:380-7.

Formulation of a therapy question

Intervention

Outcome

Is Zinc effective in treating cold?

Patient/problem

Intervention

In children with common cold, is oral Zinc effective in reducing the duration of symptoms, as compared to placebo?

Outcome

+ RCTs

Comparison

Formulation of an etiology question

Exposure

Outcome

Is alcohol a risk factor for dementia?

Patient

Exposure

Are adults who drink regularly at a greater risk of developing dementia as compared to those who do not drink at all?

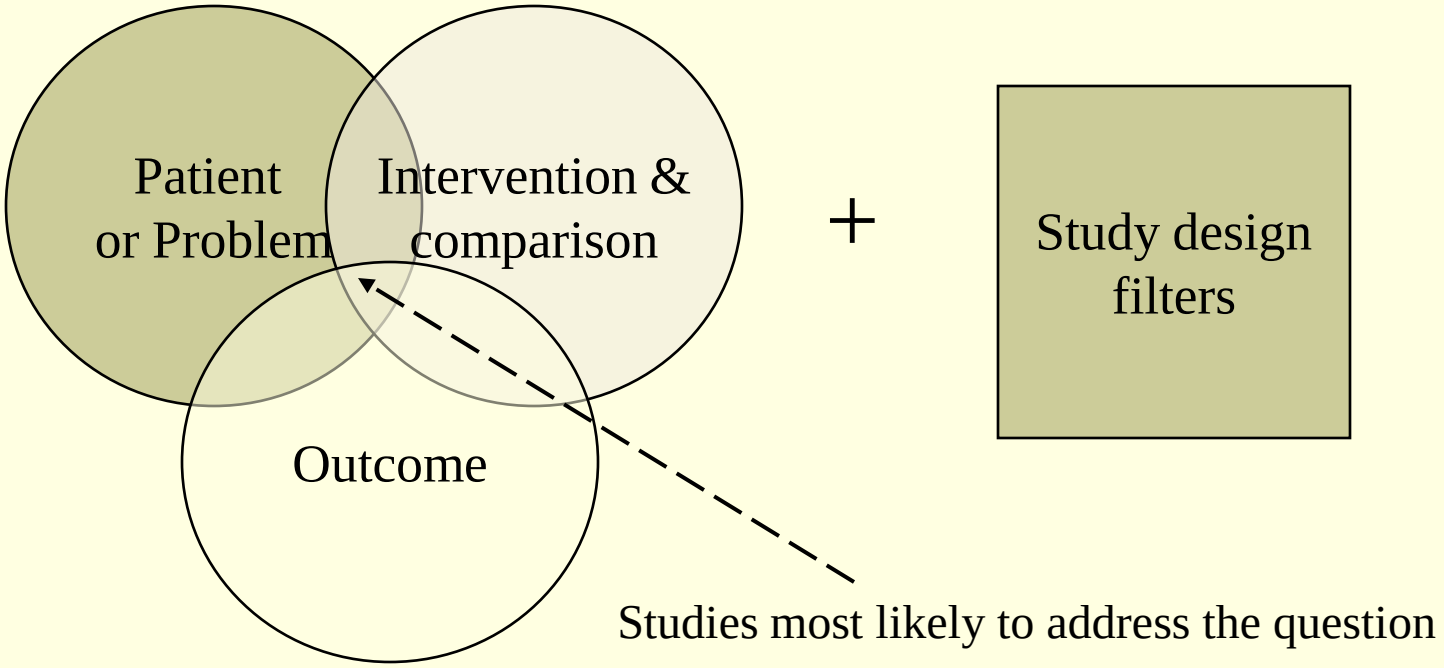
Outcome

+ cohort & case-control studies

Comparison

How a focused question also helps in searching for studies

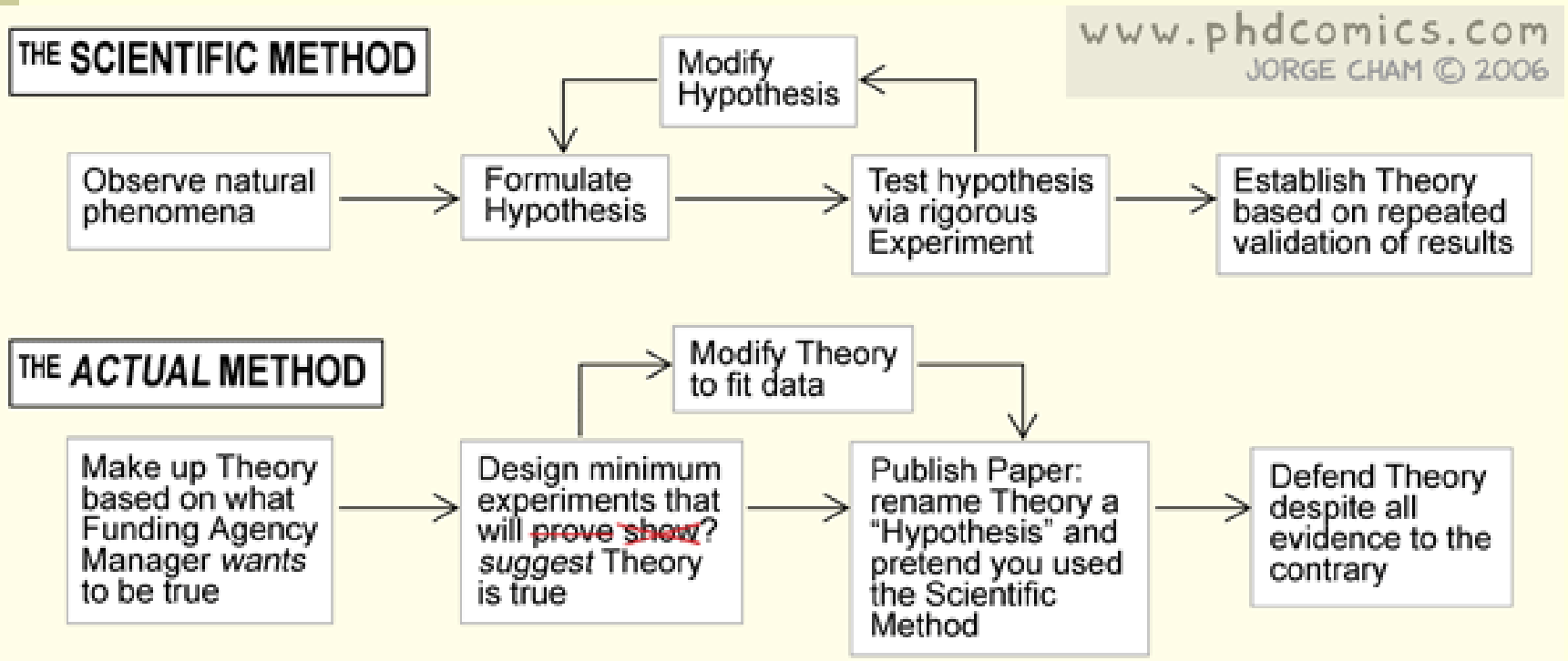
PICO + STUDY DESIGN FILTER



ALL OF YOU MUST LEARN HOW TO SEARCH PUBMED!

Readings for this week and next

- Rothman text:
  - Chapter 3: Measuring disease occurrence and causal effects
  - Chapter 4: Types of epidemiologic study
- Gordis text:
  - Chapter 2: Dynamics of disease transmission
  - Chapter 3 & 4: Measuring the occurrence of disease
- For ‘extra credit’: Asterix the Legionary


THE SCIENTIFIC METHOD
Modify Hypothesis
Observe natural phenomena
Formulate Hypothesis
Test hypothesis via rigorous Experiment
Establish Theory based on repeated validation of results
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THE ACTUAL METHOD
Modify Theory to fit data
Make up Theory based on what Funding Agency Manager wants to be true
Design minimum experiments that will prove show? suggest Theory is true
Publish Paper: rename Theory a "Hypothesis" and pretend you used the Scientific Method
Defend Theory despite all evidence to the contrary