UPPSALA UNIVERSITET

KURS I FORSKNINGSMETODIK

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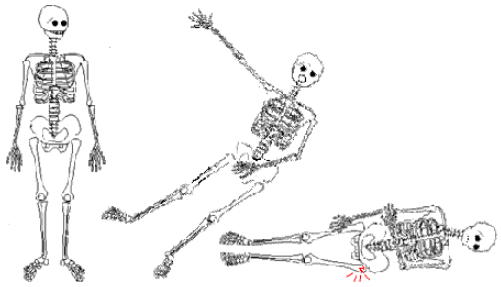
Dagens schema

Kl	
10-11	Crash course in epidemiology
11-12	DAG
13-14	DAG forts
14-15	Propensity score
15-17	Övningar DAG

Epidemiology – crash course

Karl.Michaelsson@surgsci.uu.se

Common in epidemiology research is that we observe and quantify prevalences and associations, normally without performing interventions among the study subjects



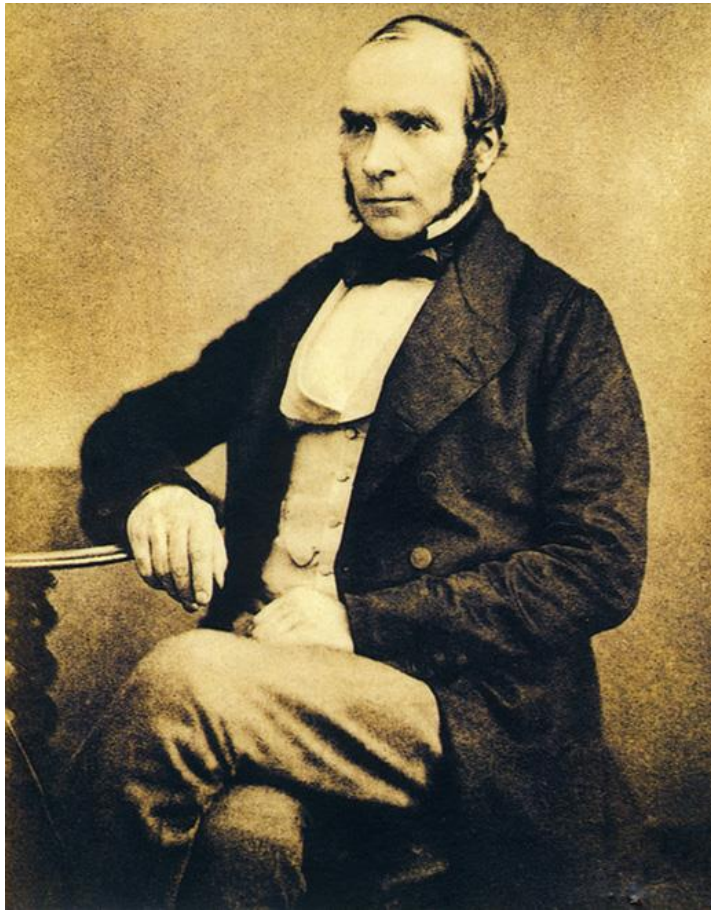
Examples

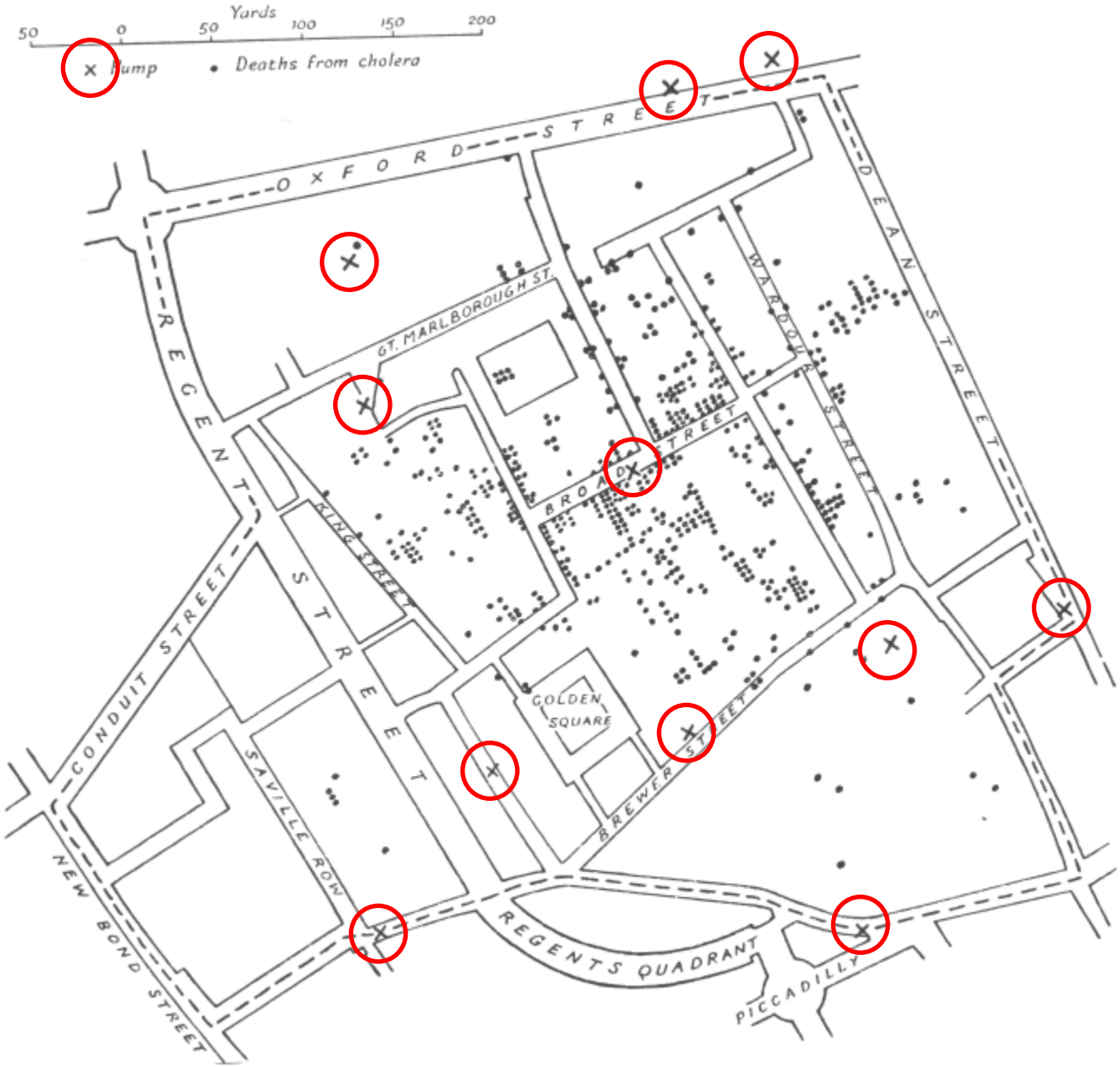
- Frequency of a disease/disease occurrence
- Mechanism behind the occurrence of …
- Prevention of…..
- Estimate the efficacy of treatment…
- Adverse effects of the treatment ….

From observation to prevention

John Snow 1813-1858

Stopped a cholera epidemic in London (1854) – how????




Yards
50
0
50
100
150
200
Pump
Deaths from cholera
OXFORD STREET
GT. MARLBOROUGH ST.
REGENT STREET
KING STREET
BROAD STREET
WARDOUR STREET
DEAN STREET
CONDUIT STREET
SAVILLE ROW
GOLDEN SQUARE
BREWER STREET
NEW BOND STREET
REGENTS QUADRANT
PICCADILLY

Mortality from cholera in the areas of London supplied by the Southwark and Vauxhall, and Lambeth Water Companies in 1849 and 1854

Districts with water supplied by	Number of deaths attributed to cholera	
	1849	**1854**
Southwark and Vauxhall Company	2261	2458
Lambeth Company	162	37
Both Companies	3905	2457

Mortality from cholera in three districts of London supplied by the Southwark and Vauxhall, and Lambeth Water Companies in 1854

Ratio 5.0/0.9 = 5.5

Districts with water supplied by	Population	Deaths from cholera	Cholera death rate per 1000 population
Southwark and Vauxhall Company	167,654	844	5.0

Mortality from cholera in the districts, related to source of individual water supply in the three groups of districts

Ratio 4.4/0.2 = 22

Districts with water supplied by	Water supply of individual houses	Population	Deaths from cholera	Cholera death rate per 1000 population
Southwark and Vauxhall Company	Southwark and Vauxhall Company	167,654	738	4.4
Lambeth Company	Lambeth Company	19,133	4	0.2

Some principal study designs and definitions

Study designs

Observational

- Cohort
- Case-control
- Cross-sectional
- Ecologic
- Case/case series

Interventional

- Randomized (blinded)
- Community-based intervention

Does the use of bicycle helmets reduce the risk of internal head injuries?

How to observe?

- What will happen with those exposed = helmet users and the ”non-exposed”? How many will have the outcome?
- Compared to what, who is not exposed?

- Ideal situation: to compare each individual during a period of exposure and during the same period with no exposure → ”counterfactual situation”

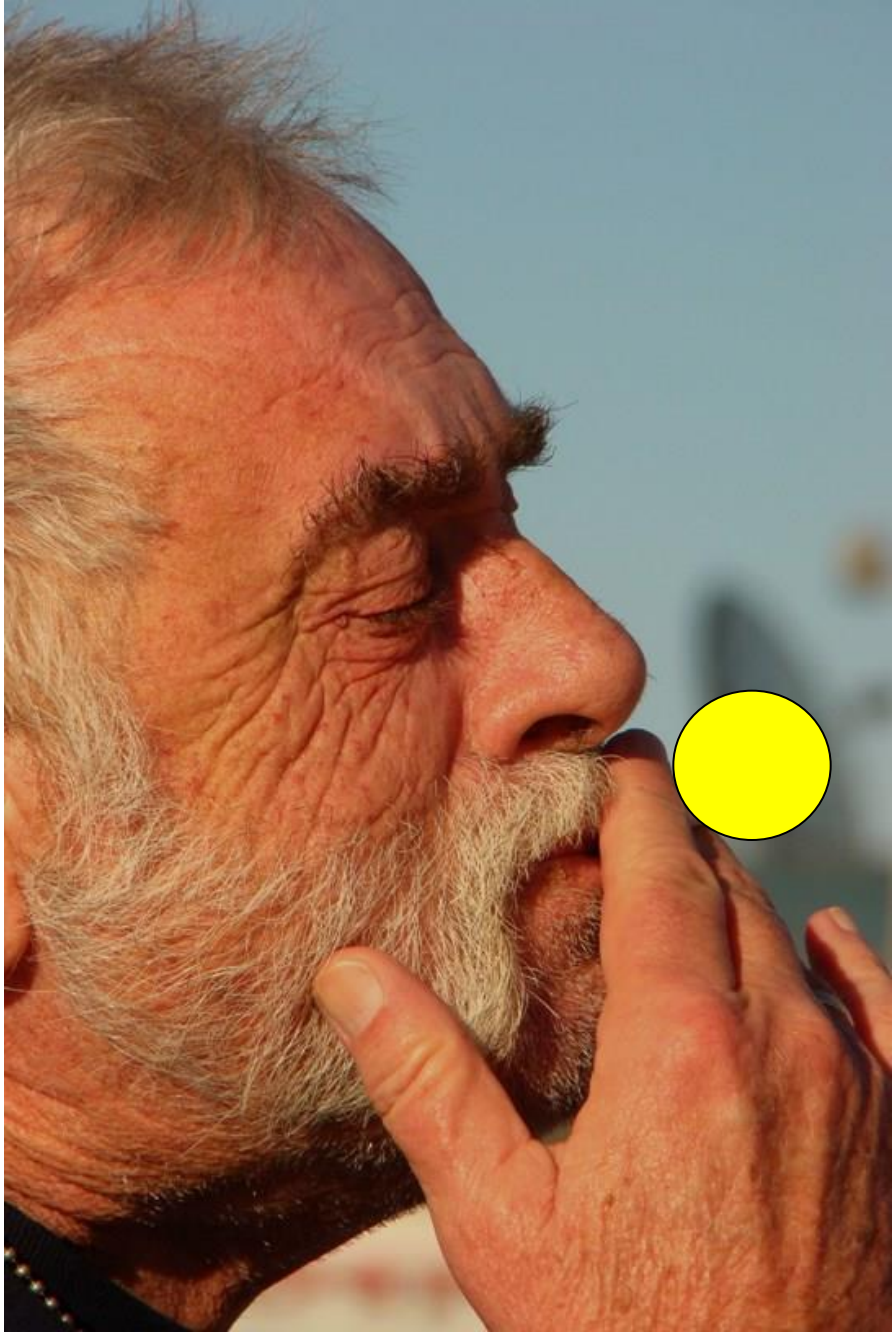


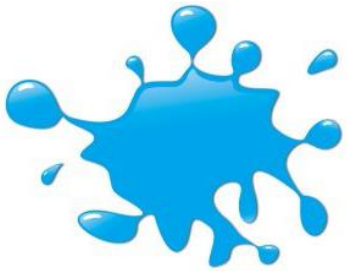
Foto: Shannon Pifko

- Ideal situation: to compare the same person during the same period of time but without the exposure → ”counterfactual situation”

… this is naturally not achievable!

- The practical solution is to compare with non-exposed individuals in the **study base**

Study base

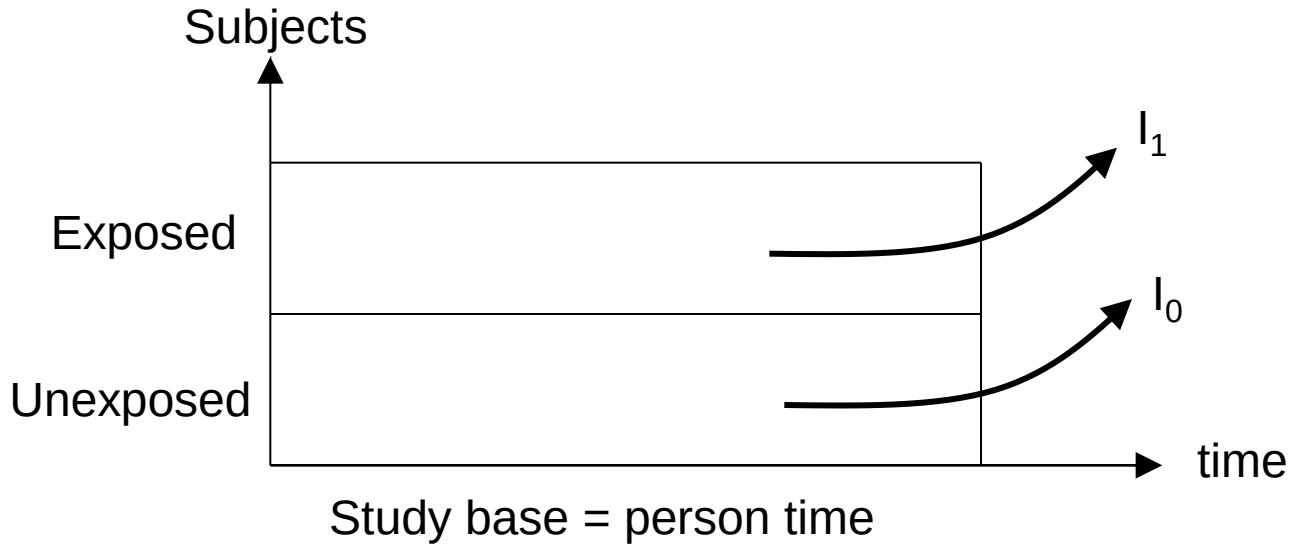


- A group of individuals followed during a defined period of time – some will develop the outcome and some will not… Person-years at risk of developing the disease

→ Your task is to gather information of those exposed and those nonexposed

→ Compare exposed with nonexposed

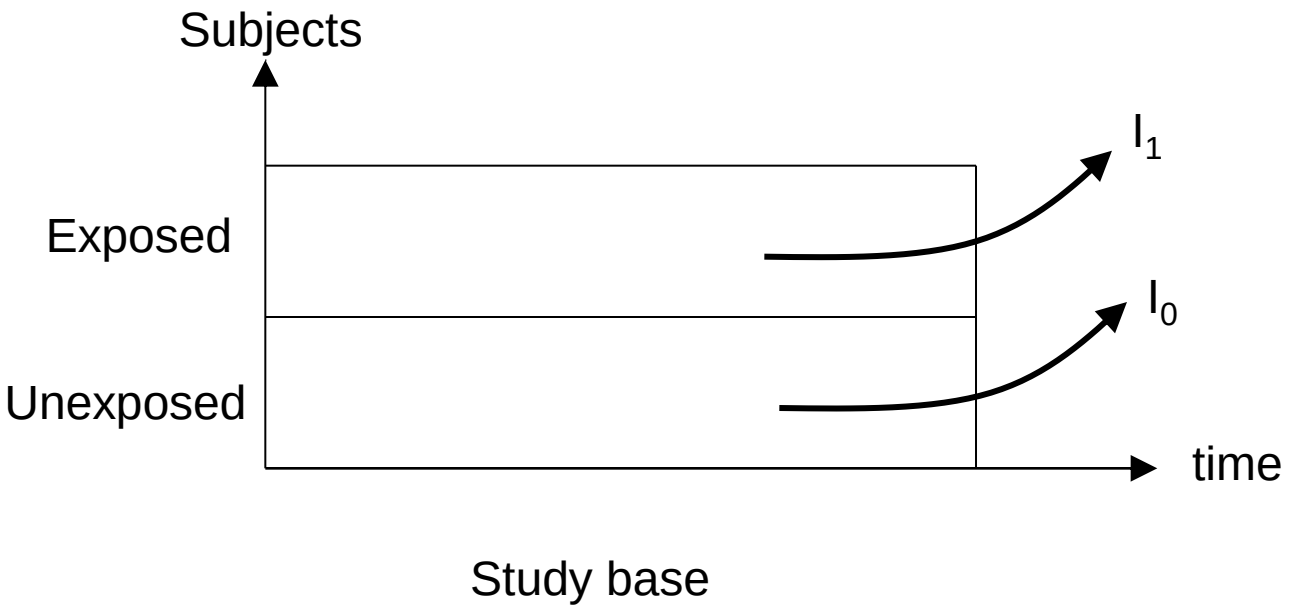
Study base

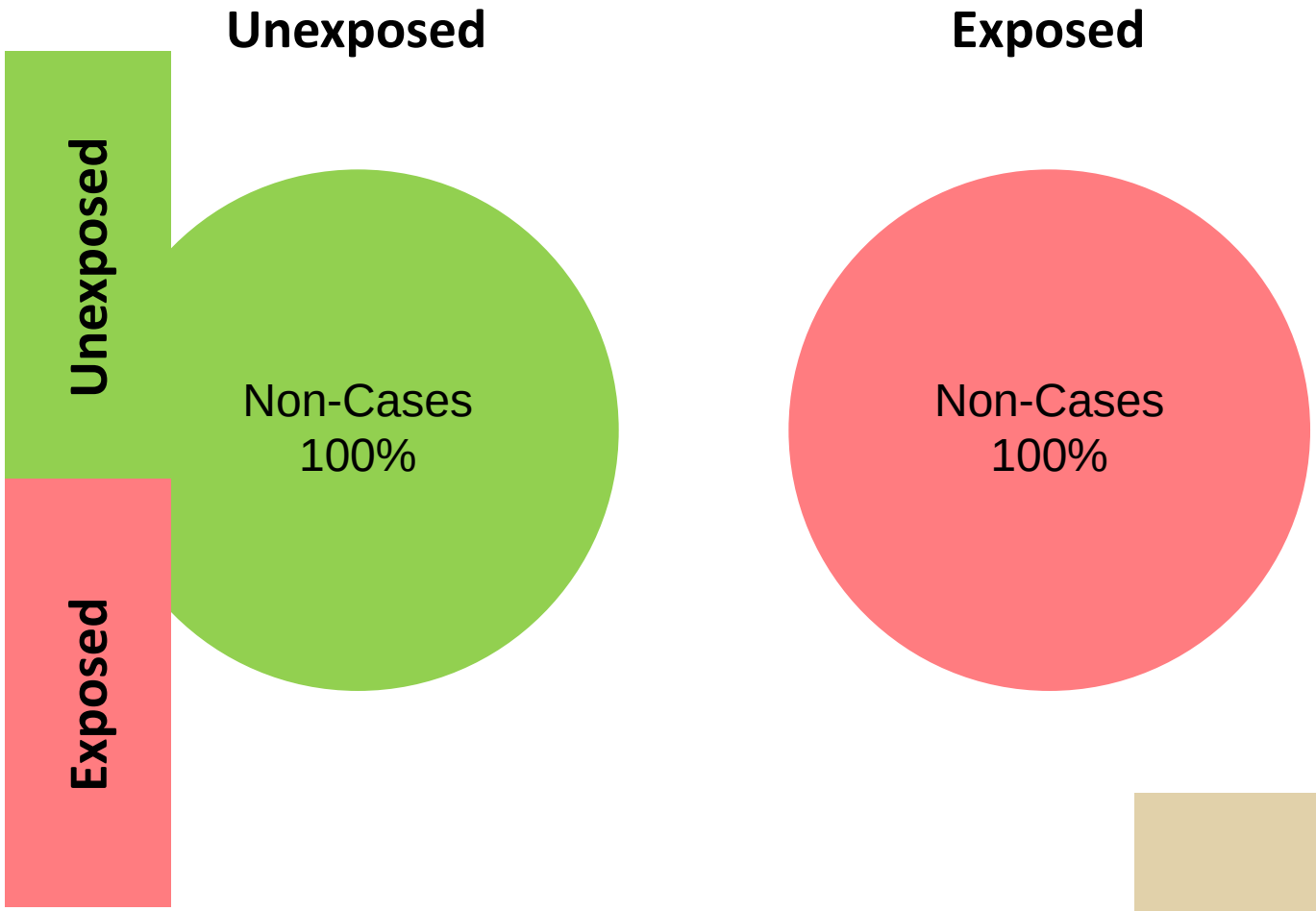

Subjects
Exposed
Unexposed
I_1
I_0
time
Study base = person time

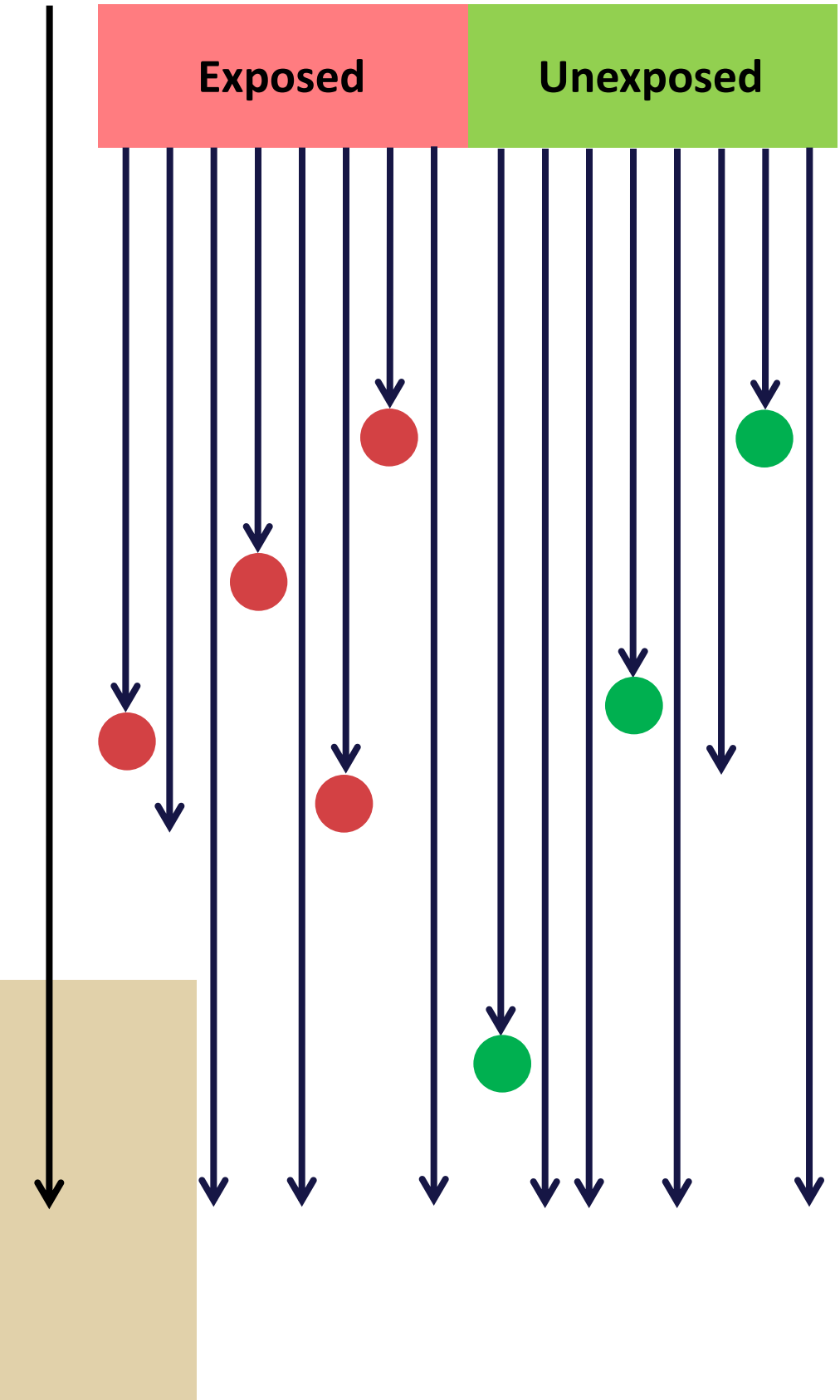
Cohort study

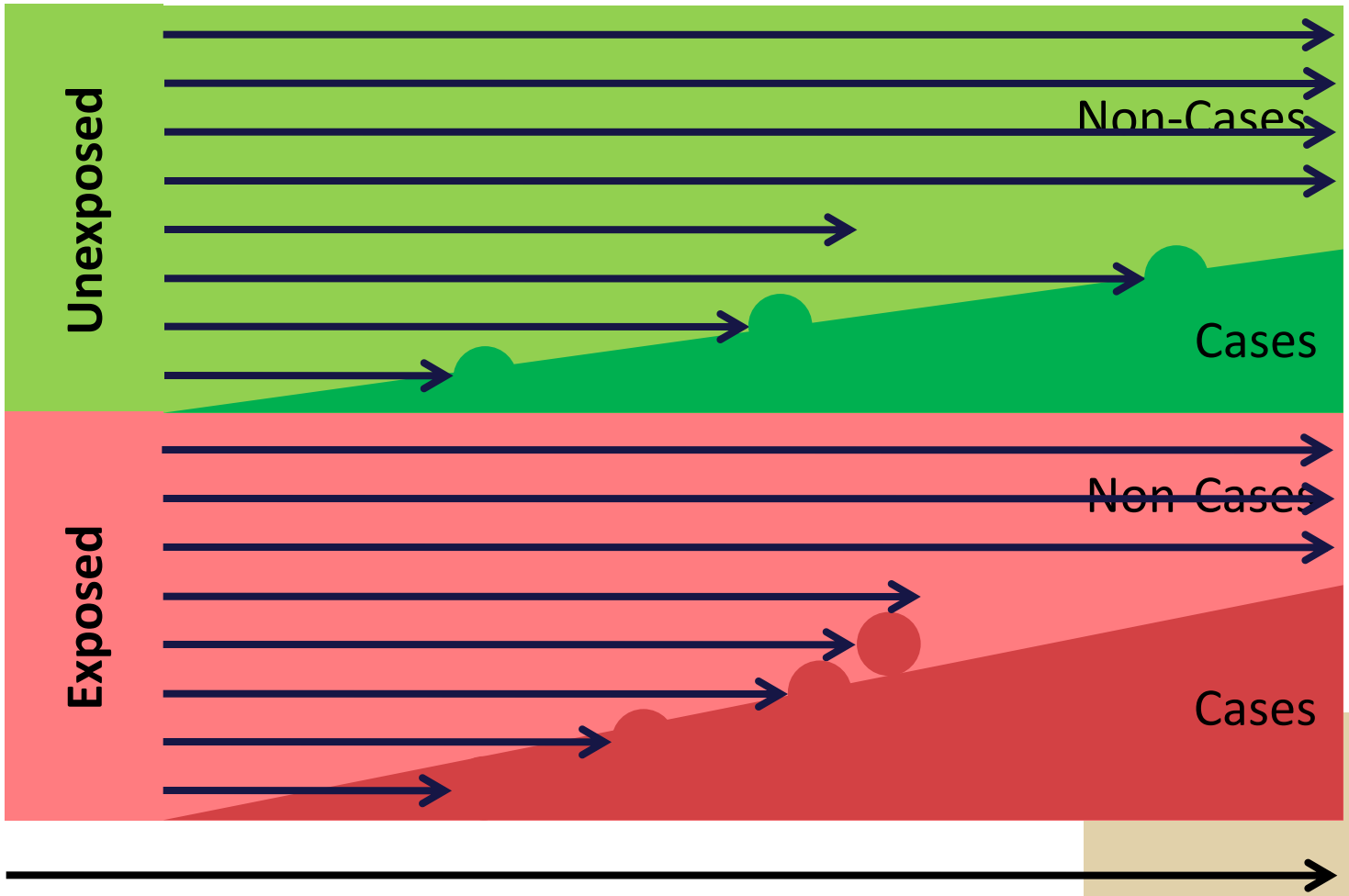
- Data collection in a well-defiend group of individuals followed by time
- Identify exposed and unexposed
- During follow-up, identify those with the outcome
- Compare the risk of the outcome among exposed subjects with unexposed individuals
- The exposure precedes the outcome

Cohort study




Unexposed
Exposed
Unexposed
Exposed
Non-Cases
100%
Non-Cases
100%


Exposed
Unexposed


Unexposed
Non-Cases
Cases
Exposed
Non-Cases
Cases

Cohort study

- Advantages
  - Good opportunity to examine cause and effect
  - Enables the study of changes by time
  - Several exposures and outcomes can be investigated
- Disadvantages
  - Often expensive
  - The exposure is not selected by chance
  - The outcome has to be sufficiently frequent

Randomized clinical trial

Subjects

Randomization

Exposed

Unexposed

I_1

I_0

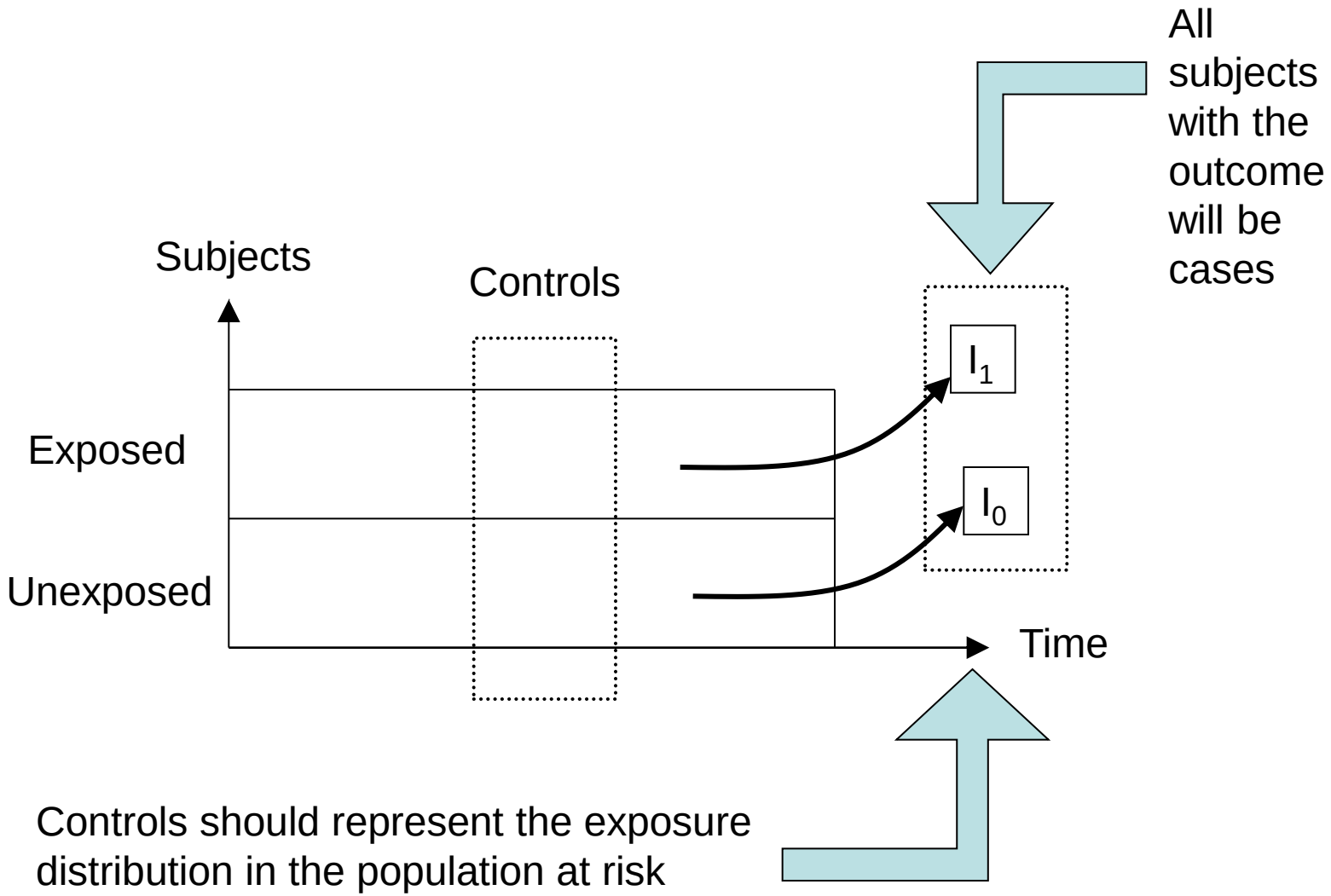
Time

Person time

RCT

- Advantages
  - Reduces the effect of confounding, measured and unmeasured
  - Highest evidence, especially a meta-analysis
- Disadvantages
  - Ethical problems
  - Often selected individuals included in the study – external validity?
  - Some research questions can’t be analyzed within a randomized study
  - Proper exposure window?

Case-control study

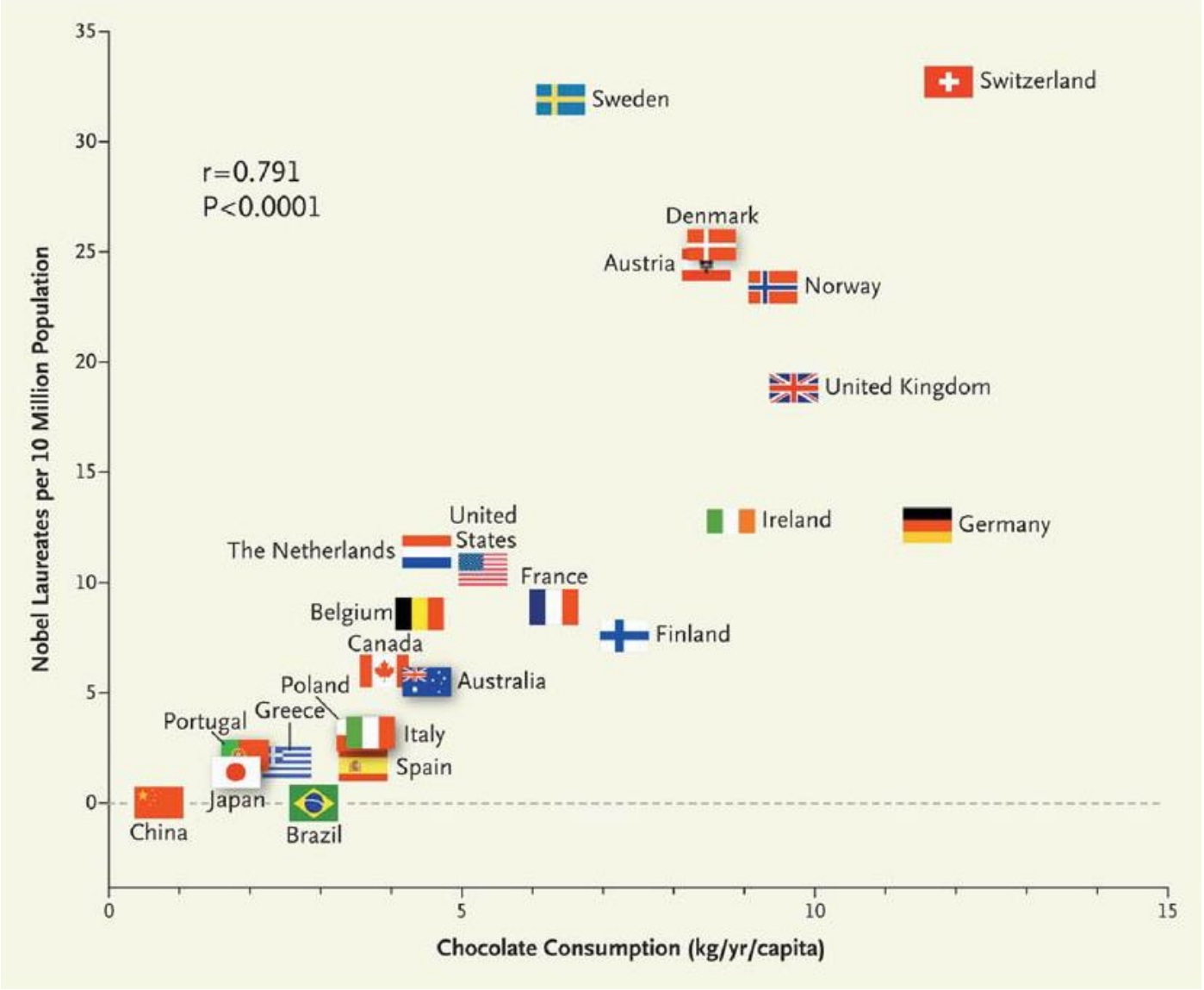


Cross-sectional study

- Hard to assess the cause and the effect
- Like a cohort study with no follow-up

Ecologic study

- Often the first step
- No individual level data



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

N Engl J Med Oct 2012

Questions

- Are the data in our study reliable?
- Can we trust our study results?
- Can we generalize our results?
- Can we in general trust results from epidemiological studies?

Ioannidis JP.
Why most published research findings are false.
PLoS Med. 2005 Aug;2(8):e124.

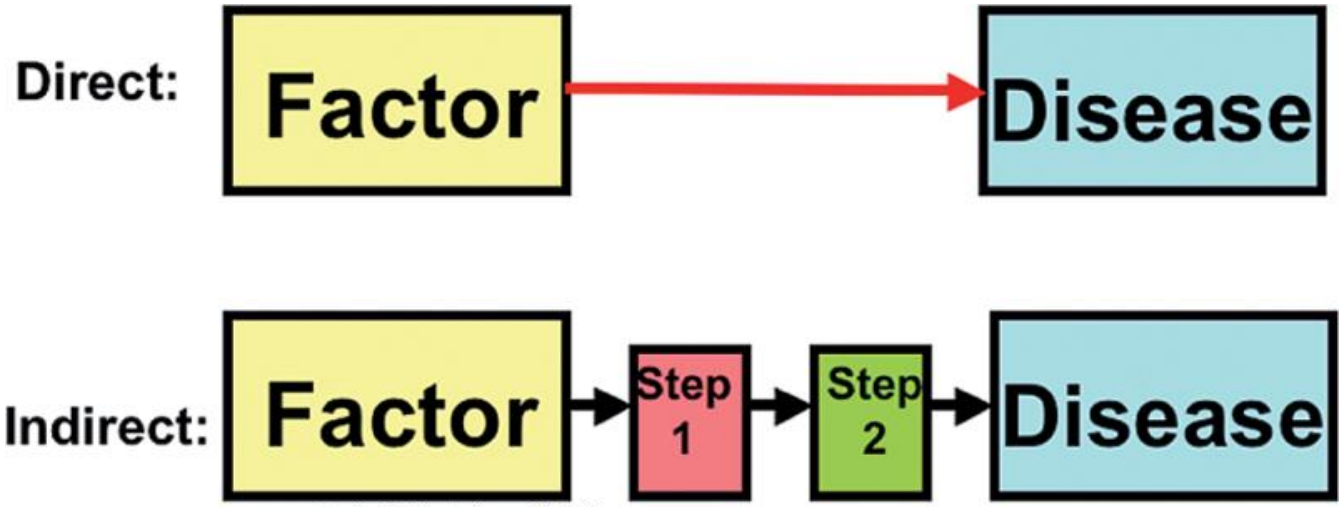
Validity

Key concepts

- **Causality**
- **Confounding**
- **Bias**

Causality

Cause and effect



Gordis: Epidemiology, 4th Edition.

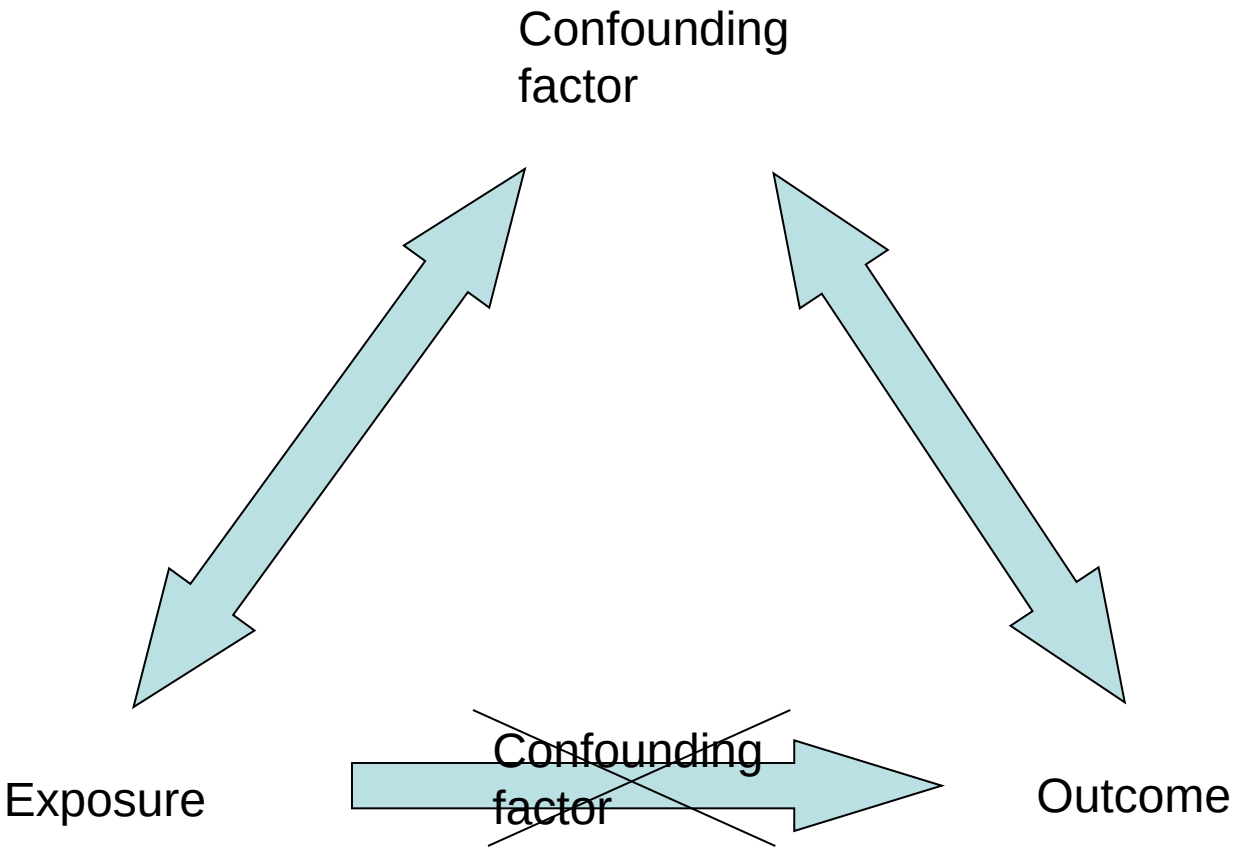
Confounding

- Confound: Mixing of effects
- Common in observational study designs

Common definition of confounding

- Associated with the exposure
- Associated with the outcome
- Not in the ”causal pathway” (not an intermediate)!

Classical way



Multiparity is associated with higher risk of Down’s syndrome

If we have identified the confounder, how can we deal with it?

1. **restriction**

2. **stratification**

3. **adjustment**

Bias (systematic error)

A difference between the true value and the observed value from any cause other than sampling variability

Selection bias

Scand J Med Sci Sports 2007: 17: 356–361
Printed in Singapore . All rights reserved
DOI: 10.1111/j.1600-0838.2006.00582.x

SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

Acute mortality during long-distance ski races (Vasaloppet)

B. Farahmand[1,2], U. Hållmarker[3], G. P. Brobert[1,2], A. Ahlbom[1,4]

[1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2]AstraZeneca R&D Södertälje, Södertälje, Sweden, [3]Department of Internal Medicine, Mora Hospital, Mora, Sweden, [4]Stockholm Center for Public Health, Stockholm, Sweden
Corresponding author: Bahman Farahmand, AstraZeneca R&D Södertälje, SE-151 85 Södertälje, Sweden. Tel: +46 8 553 236 87, E-mail: bahman.farahmand@astrazeneca.com

Accepted for publication 2 June 2006

were identified and compared with the corresponding expected numbers based on national death rates. *Results:* In total, 698 102 starters generated altogether 581 person-years of skiing. Overall, 13 deaths occurred compared with 1.68 expected during the skiing time, yielding a standardized mortality ratio (SMR) of 7.7 [95% confidence interval (CI) 4.1–13.2]. Twelve of the deaths were caused by

l deaths during the races been recommended to avoi

Selection bias vs confounding?

Selection bias – conditioning on common effects

Confounding – existence of common causes of exposure and outcome

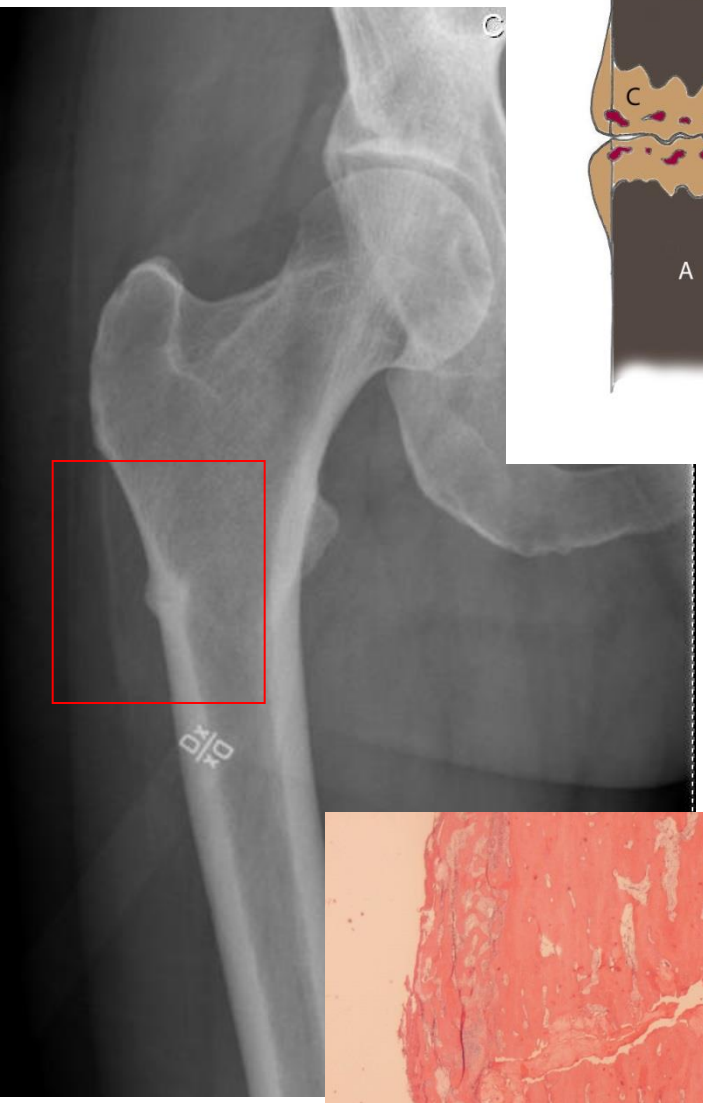
Information bias

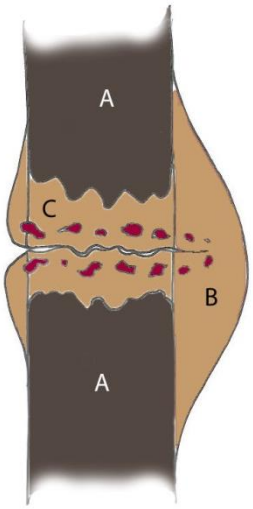
- Misclassification
- Recall bias
- Reporting bias

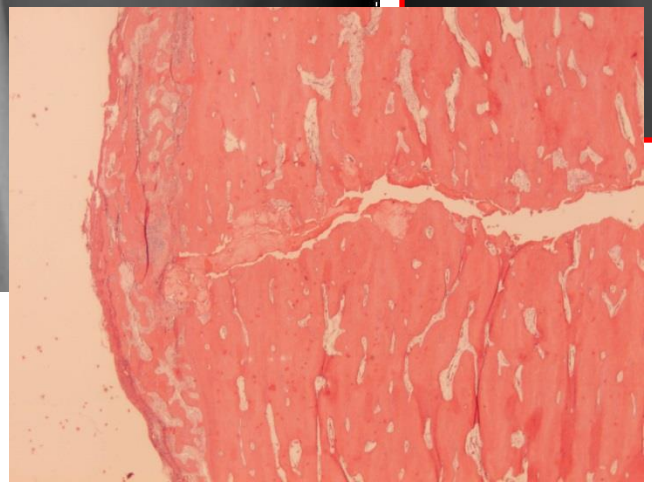
Atypical fractures….

Case reports

First report published in 2005




A
C
B
A



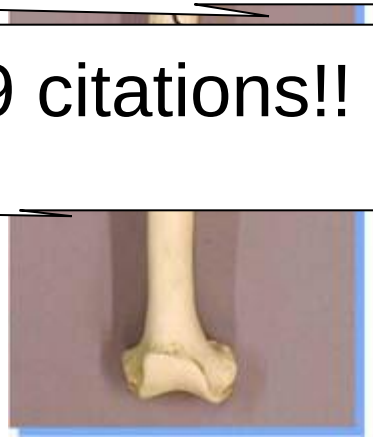
” We conducted two national register-based analyses to address atypical femur fractures as a potential adverse effect of alendronate.”

reports have found long-term am use to be common in patients with subtrochanteric or proximal diaphyseal femur fracture, raising concerns that these fractures could be a consequence of excessive suppression of bone turnover. Two national observational register-based studies were performed: (1) cross-sectional study (N =

” Patients with these atypical femur fractures were no more likely to be on alendronate treatment than patients with hip fractures.”

279 citations!!

Problem??



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 13, 2010 VOL. 362 NO. 19

Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur

Dennis M. Black, Ph.D., Michael P. Kelly, M.D., Harry K. Genant, M.D., Lisa Palermo, M.A., Richard Eastell, M.D., Christina Bucci-Rechtweg, M.D., Jane Cauley, Ph.D., Ping Chung Leung, M.D., Steven Boonen, M.D., Ph.D., Arthur Santora, M.D., Anne de Papp, M.D., and Douglas C. Bauer, M.D., for the Fracture Intervention Trial and HORIZON Pivotal Fracture Trial Steering Committees

ABSTRACT

Problem??

”no significant increase in risk associated with bisphosphonate use”

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bisphosphonate Use and Atypical Fractures of the Femoral Shaft

Jörg Schilcher, M.D., Karl Michaëlsson, M.D., Ph.D., and Per Aspenberg, M.D., Ph.D.

From the Department of Experimental and Clinical Medicine, Faculty of Health Science, Linköping University, Linköping (J.S., P.A.); and the Department of Surgical Sciences, Section of Orthopedics, and Uppsala Clinical Research Center, Uppsala University, Uppsala (K.M.) — both in Sweden. Address reprint requests to Dr. Aspenberg at the Department of Experimental and Clinical Medicine, Faculty of Health Sciences, Linköping University, SE-581 85 Linköping, Sweden, or at per.aspenberg@liu.se.

Drs. Schilcher and Michaëlsson contributed equally to this article.

N Engl J Med 2011;364:1728-37.

ABSTRACT

BACKGROUND

Studies show conflicting results regarding the possible excess ...fractures of the femoral shaft associated with bisphosphonate u...

METHODS

In Sweden, 12,777 women 55 years of age or older sustain... ...of the femur in 2008. We reviewed radiographs of 1234 of the 1271 wom... ...d a subtrochanteric or shaft fracture and identified 59 patients with ... ...ractures. Data on medications and coexisting conditions were obtained f... ...onal registries. The relative and absolute risk of atypical fractures associa... ...n bisphosphonate use was estimated by means of a nationwide cohort analy... ...he 59 case patients were also compared with 263 control patients who had or... ...y subtrochanteric or shaft fractures.

RESULTS

The age-adjusted relative risk of atypical fracture was 47.3 (95% confidence interval [CI], 25.6 to 87.3) in the cohort analysis. The increase in absolute risk was 5 cases per 10,000 patient-years (95% CI, 4 to 7). A total of 78% of the case patients and 10% of the controls had received bisphosphonates, corresponding to a multivariable-adjusted odds ratio of 33.3 (95% CI, 14.3 to 77.8). The risk was independent of coexisting conditions and of concurrent use of other drugs with known effects on bone. The duration of use influenced the risk (odds ratio per 100 daily doses, 1.3; 95% CI, 1.1 to 1.6). After drug withdrawal, the risk diminished by 70% per year since the last use (odds ratio, 0.28; 95% CI, 0.21 to 0.38).

CONCLUSIONS

...-based nationwide analyses may be reassuring for patients who ...though there was a high prevalence of current bisphosphonate use among patients with atypical fractures, the absolute risk was small.

(Funded by the Swedish Research Council.)

”relative risk of atypical fracture was 47.3”

”Although there was a high prevalence of current bisphosphonate use among patients with atypical fractures, the absolute risk was small.”

Kaiser Permanente study No 1

ORIGINAL ARTICLE

JBMR

Incidence and Demography of Femur Fractures With and Without Atypical Features

Adrianne C Feldstein,[1,2] Dennis Black,[3] Nancy Perrin,[1] A Gabriela Rosales,[1] Darin Friess,[4] David Boardman,[2] Richard Dell,[5] Arthur Santora,[6] Julie M Chandler,[7] Mary M Rix,[1] and Eric Orwoll[4]

Published 2012

OR 2.11 [95% CI, 0.99–4.49])


B/L
3
2

Kaiser Permanente study No 2

ORIGINAL ARTICLE

JBMR

Incidence of Atypical Nontraumatic Diaphyseal Fractures of the Femur

Richard M Dell,[1] Annette L Adams,[2] Denise F Greene,[1] Tadashi T Funahashi,[1] Stuart L Silverman,[3] Eric O Eisemon,[4] Hui Zhou,[2] Raoul J Burchette,[2] and Susan M Ott[5]

Published 2012

142 cases of atypical fracture

90% had taken bisphosphonates

Risk of atypical femoral fracture during and after bisphosphonate use.

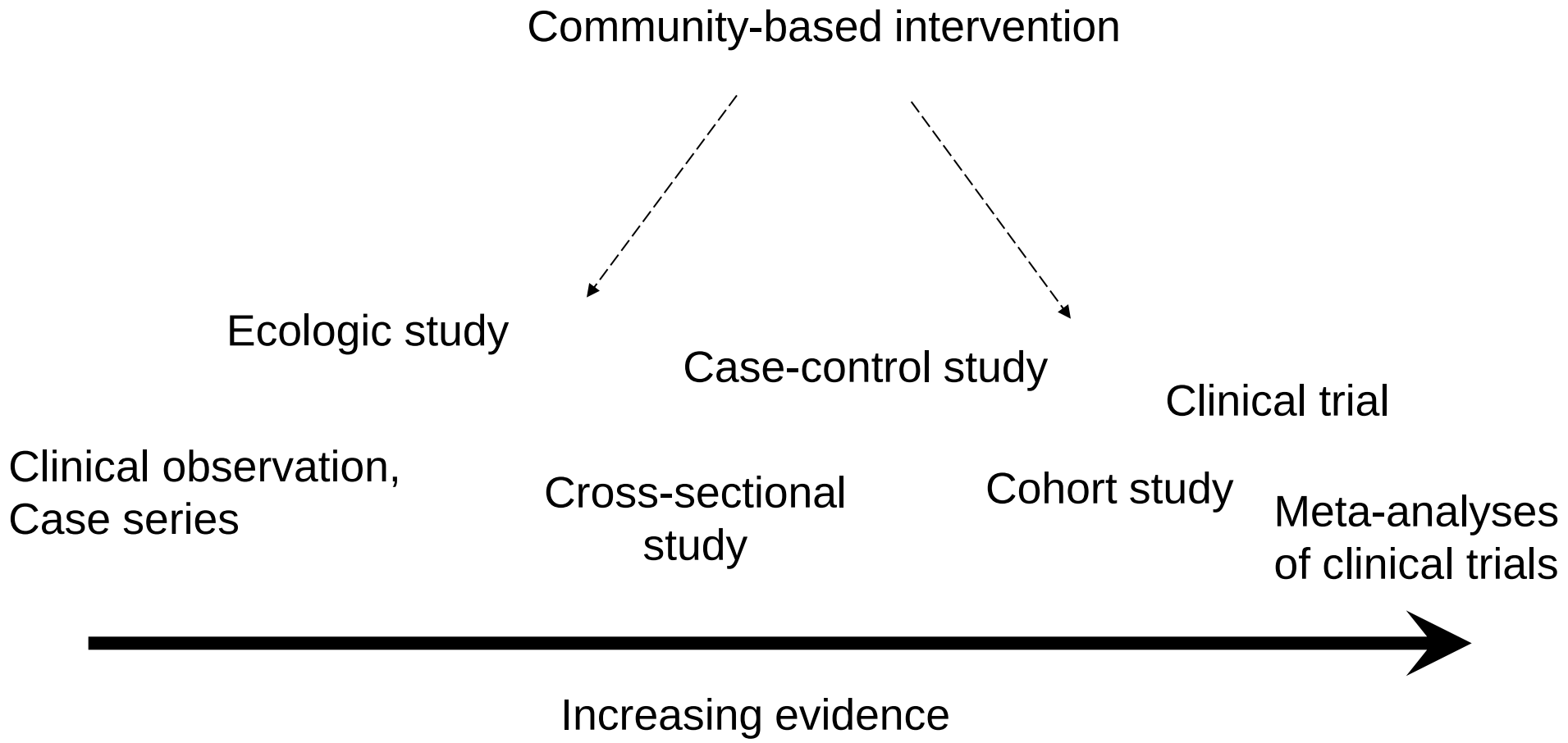
Schilcher J, Koeppen V, Aspenberg P, Michaëlsson K

N Engl J Med. 2014 Sep 4;371(10):974-6.

- RR >100 för behandling 4-5 år
- Kvinnor högre risk än män

NNH vs NNT?

Evidence based medicine – the study designs are graded on level of evidence



Does the use of bicycle helmets reduce the risk of internal head injuries?