Epidemiologic study designs

and critical appraisal of scientific papers

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eahp
european association
of hospital pharmacists
making the difference in medication

Bio sketch

- MD, PhD in epidemiology
- Associate professor of Epidemiology at UMC Utrecht
- Research focus on methods for causal research

- “I have no potential conflict of interest”

Outline

- Epidemiologic research
- Measures of association
- Study designs
- Critical appraisal of scientific papers

Epidemiologic research

Descriptive (prediction)

- Diagnosis (predicting the presence/absence of disease)
- Prognosis (predicting the future course of disease)

Causal

- Etiology (causes of disease)
- Therapeutic (treatment effects)

Aim of pharmacoepidemiologic research

To quantify the relation between exposure and the occurence of a particular outcome for a specific patient population

- Domain: patient group / population of interest
- Exposure: pharmacological treatment
- Outcome: clinical endpoint

Often *causal* research

Epidemiology is comparative research

Research goal:

To ***quantify the relation*** between exposure and the occurence of a particular outcome for a specific patient population

'Quantify the relation' =

Make a comparison between those who are exposed and those who are 'something else'

Example: Statins and muscle pain

Occurence of disease

Incidence of the disease:

- no. new cases

- in population 'at risk'

- Cumulative incidence ('risk')

  - no. cases / no. at risk

  - in a certain time period (e.g. 1 year)

- Incidence density ('rate')

  - no. cases / total amount of observation time

- A----------x--Moves away
- B----------x----------Death
- C-------breast cancer/death
- D----------x---------- alive
- E----------x--------lost to follow-up
- F----------x----------alive
- G----------x----------breast cancer/death
- H----------x-Myocardial infarction/death
- I--------death
- J----------x----------alive
- K----------lost to follow-up
- L----------x----------moves from the area
- M--------1----------2--x----------3----------4----------alive

- CI mortality = 5 / 13 = 38% in 5 years
- ID mortality = 5 / 42 person years = 12 / 100 person years

Measures of association

- Relative measures of association (‘relative risk’)
  - Risk ratio (cumulative incidence ratio)
  - Rate ratio (incidentie density ratio)
  - Odds ratio

- Absolute measures of assocation
  - Risk difference
  - Rate difference
  - (Odds difference)

Choice of measure of association depends on

1. Type of outcome (categorical / continuous)
2. Duration of follow-up
3. …

Example:

- Oral antidiabetic treatment vs. placebo
- myocardial infarction (yes / no)
- 1 year of follow-up

How to quantify association?

Relative measures of association

	Event			
	Yes	No	Total	Person time
Active treatment	A	B	N_1	PT_1
Placebo	C	D	N_0	PT_0

- Risk ratio: $[A/N_1] / [C/N_0]$
- Rate ratio: $[A/PT_1] / [C/PT_0]$
- Odds ratio: $[A/B] / [C/D] = A*D/(B*C)$

Relative measures of association

	Event			
	Yes	No	Total	Person years
Active treatment	100	900	1000	950
Placebo	400	600	1000	800

- Risk ratio: [100/1000] / [400/1000] = 0.25
- Rate ratio: [100/950] / [400/800] = 0.21
- Odds ratio:[100*600] / [900*400] = 0.17

Risk ratio = 0.25

- *"During 1 year of follow-up, the risk in the intervention group is 0.25 times the risk in the placebo group."*
- *"The intervention decreases the risk of an event during the first year of follow-up by a factor 4."*

Rate ratio = 0.21

- *"The event rate in the intervention group is 0.21 times the event rate in the placebo group."*
- *"The intervention decreases the event rate by a factor 4.8."*

Absolute measures of association

	Event			
	Yes	No	Total	Person time
Active treatment	A	B	N_1	PT_1
Placebo	C	D	N_0	PT_0

- Risk difference: $[A/N_1] - [C/N_0]$
- Rate difference: $[A/PT_1] - [C/PT_0]$

Absolute measures of association

	Event			
	Yes	No	Total	Person time
Active treatment	100	900	1000	950
Placebo	400	600	1000	800

- Risk difference: [100/1000] - [400/1000] = -0.30
- Rate difference: [100/950] - [400/800] = -0.39

Risk difference = -0.3

- *"During 1 year of follow-up, the risk in the intervention group is 0.3 less than the risk in the placebo group."*
- *"The intervention decreases the risk of an event during the first year of follow-up by 0.3."*

Rate difference = -0.39

- *"The event rate in the intervention group is 0.39 less than the event rate in the placebo group."*
- *"The intervention decreases the event rate by 0.39."*

- **Acute** condition, fixed duration of follow-up, competing events can be ignored:
  - RD, RR, or OR
  - OR is easier, but overestimates RR if outcome is not rare (i.e., > 10%)

- **Chronic** condition, variable duration of follow-up, competing events cannot be ignored:
  - Rate ratio (HR) is the only valid choice!
  - Based on time-to event / survival analysis

- Impact of relative effect (RR) depends on incidence of the outcome…
  - Example: RR = 0.8
    - Cumulative incidence= 0.0001
    - If treated, cumulative incidence = 0.00008

    - Cumulative incidence= 0.1
    - If treated, cumulative incidence = 0.08

- Impact of absolute effect (RD) captures incidence of the outcome…
  - RD = -0.02
    - Cumulative incidence= 0.1
    - If treated, cumulative incidence = 0.08
  - 1/RD = NNT (‘number needed to treat’)
  - RD = -0.02 → treat 50 patients in order to prevent 1 event

Study designs

- Cross-sectional
- Follow-up (cohort)
- Case-control

- Don’t use the terms ‘prospective’ / ‘retrospective’

Cross-sectional study

- Exposure and outcome measured at the same time
- Hard to disentangle causes and effects
- Not very useful in pharmacoepidemiology (except pharmacogenomics?)

Follow-up and case-control

- Exposure and outcome measured at different moments in time
- Chronological order may help to make causal claim
- Key designs in pharmacoepidemiology

Follow-up studies

- Study groups based on exposure status
- Comparison of outcome status among groups of exposed and unexposed subjects

Follow-up studies in PE

- In large electronic health record database:
  - Identify users of treatment of interest
  - Identify appropriate comparator group (e.g. alternative drug)
  - For both groups, collect information on possible outcomes
  - Note: timing is often of major importance

Analysis of follow-up study

	Event			
	Yes	No	Total	Person years
Treatment A	100	900	1000	950
Treatment B	400	600	1000	800

Comparison of treatment groups:

- Risk ratio: [100/1000] / [400/1000] = 0.25
- Rate ratio: [100/950] / [400/800] = 0.21

Case-control studies

- Study groups based on outcome status
- Comparison of exposure status among cases and controls

- Typical way of clinical reasoning to identify causes of disease

  Examples:

  – HIV
  – Deep venous thrombosis
  – Reye’s syndrome

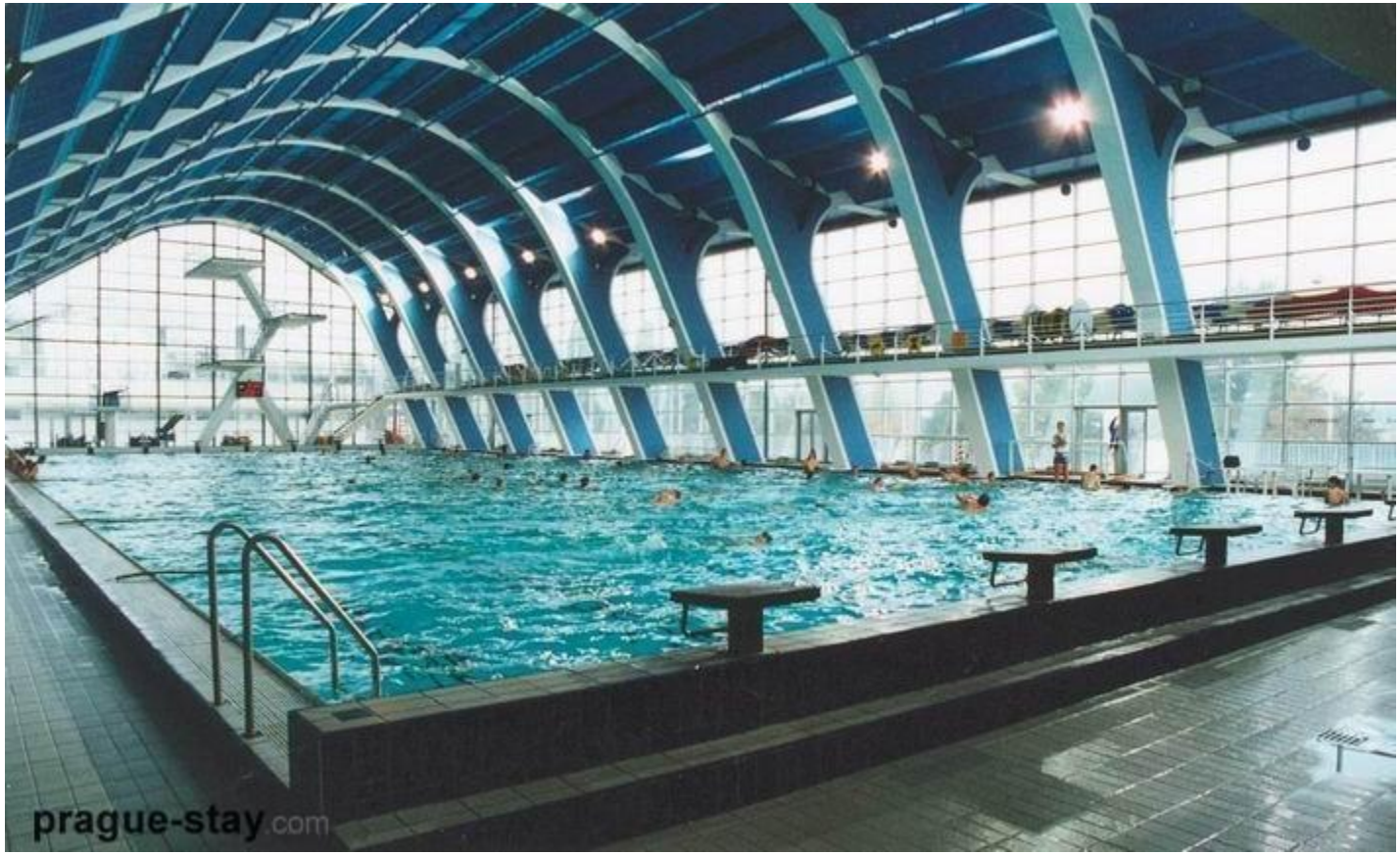
Case-control studies[2]

- Cases: those with the outcome of interest
- Controls…

  should provide information on usual exposure status

  (NOTE: not exposure status among those without the outcome!)

Swimming pool



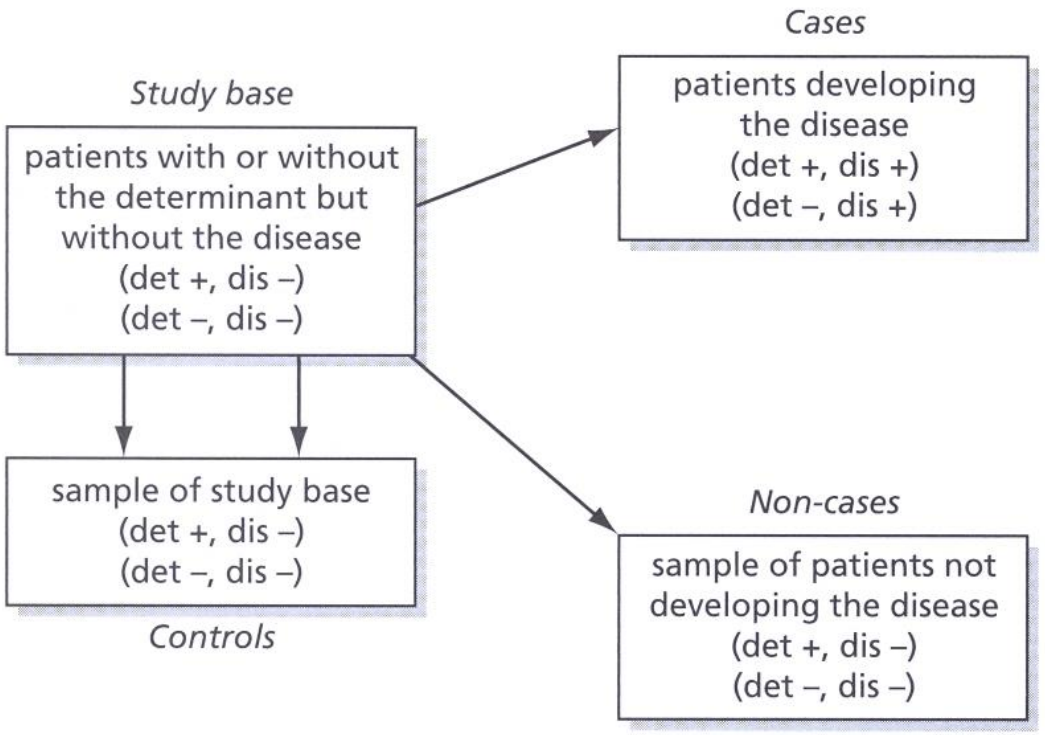


FIGURE 9.1 Case control study. Abbreviations are det, determinant; dis, disease.

Grobbee & Hoes, Clinical Epidemiology, 2008

Case-control study = Efficiency

e.g.
- disease is rare
- assessment exposure is expensive
- many exposure categories of interest
- long/unknown latency period

	Event			
	Yes	No	Total	Person time
Treatment A	400	600	1000	800
Treatment B	100	400	500	450
Total	500	1000	1500	1250

- Risk ratio = (400/1000) / (100/500) = 2.0
- Rate ratio = (400/800) / (100/450) = 2.25
- Odds ratio = 400*400 / (600*100) = 2.7

	Event			
	Yes	No	Total	Person time
Treatment A	400	99 600	100 000	99 800
Treatment B	100	49 900	50 000	49 950
Total	500	149 500	150 000	149 750

- Rate ratio = (400/99800) / (100/49950) = 2.0
- Follow-up study rather inefficient
- Case-controle is much more efficient!

	Case	Control
Treatment A	400	333
Treatment B	100	167
Total	500	500

Controls are a sample of person time:

Odds ratio = 400*167/ (333*100) = 2.00 [=rate ratio!!]

Note: No prevalence / cumulative incidence / incidence density

	Follow-up	Case-control
Comparison of …	Exposure groups	‘Outcome’ groups (cases vs. controls)
Measures of association	Absolute / relative risks / rates etc.	Odds ratio
Efficiency	Depends on availability of data and incidence of the outcome	Often more efficient than follow-up study
Bias		More prone to selection bias??

Critical appraisal of scientific papers

- Don’t let the terminology fool you!
- Try to reconstruct how they did the study

Critical appraisal of scientific papers

1. **Research question?**
   Exposure / Outcome / Domain
2. **Study population (in- / exclusion criteria)?**
3. **Definition of exposure?**
4. **Definition of outcome?**
5. **Design (follow-up / case-control)**
6. **Potential for bias (e.g. selective treatment allocation)?**

Br J Surg. 2014 Jul;101(8):966-75. doi: 10.1002/bjs.9517. Epub 2014 May 21.

Statin use and rupture of abdominal aortic aneurysm.

Wemmelund H[1], Høgh A, Hundborg HH, Thomsen RW, Johnsen SP, Lindholt JS.

Author information

Abstract

BACKGROUND: Ruptured abdominal aortic aneurysm (rAAA) is associated with high mortality. Research suggests that statins may reduce abdominal aortic aneurysm (AAA) growth and improve rAAA outcomes. However, the clinical impact of statins remains uncertain in relation to both the risk and prognosis of rAAA.

METHODS: This nationwide, population-based, combined case-control and follow-up study included all patients (aged at least 50 years) with a first-time hospital admission for rAAA and 1 : 1 matched AAA controls without rupture in Denmark from 1996 to 2008. Individual-level data on preadmission drug use, co-morbidities, socioeconomic markers, healthcare contacts and death were obtained from Danish nationwide registries.

RESULTS: The study included 3584 cases and 3584 matched controls. Current statin use was registered for 418 patients with rAAA (11·7 per cent) and 539 AAA controls (15·0 per cent), corresponding to an age- and sex-matched odds ratio (OR) of 0·70 (95 per cent confidence interval (c.i.) 0·60 to 0·81) for rAAA in current statin users versus never users. The decreased risk of rAAA remained after adjustment for potential confounding factors (adjusted OR 0·73, 0·61 to 0·86). The overall 30-day mortality rate from time of hospital admission among patients with rAAA was 46·1 per cent in current statin users compared with 59·3 per cent in never users (adjusted mortality rate ratio (MRR) 0·80, 95 per cent c.i. 0·68 to 0·95). Patients who had formerly used statins did not have reduced mortality (adjusted MRR 0·98, 0·78 to 1·22).

CONCLUSION: Statin use was associated with a reduced risk of rAAA and lower case fatality following rAAA. These results support current guidelines that recommend statin therapy in patients diagnosed with AAA.

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BMJ. 2014 May 29;348:g3244. doi: 10.1136/bmj.g3244.

Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases.

Dormuth CR[1], Filion KB[2], Paterson JM[3], James MT[4], Teare GF[5], Raymond CB[6], Rahme E[7], Tamim H[8], Lipscombe L[3]; Canadian Network for Observational Drug Effect Studies Investigators.

⊕ Collaborators (13)

⊕ Author information

Abstract

OBJECTIVE: To evaluate the incremental increase in new onset diabetes from higher potency statins compared with lower potency statins when used for secondary prevention.

DESIGN: Eight population based cohort studies and a meta-analysis.

SETTING: Six Canadian provinces and two international databases from the UK and US.

PARTICIPANTS: 136,966 patients aged ≥ 40 years newly treated with statins between 1 January 1997 and 31 March 2011.

METHODS: Within each cohort of patients newly prescribed a statin after hospitalisation for a major cardiovascular event or procedure, we performed as-treated, nested case-control analyses to compare diabetes incidence in users of higher potency statins with incidence in users of lower potency statins. Rate ratios of new diabetes events were estimated using conditional logistic regression on different lengths of exposure to higher potency versus lower potency statins; adjustment for confounding was achieved using high dimensional propensity scores. Meta-analytic methods were used to estimate overall effects across sites.

MAIN OUTCOME MEASURES: Hospitalisation for new onset diabetes, or a prescription for insulin or an oral antidiabetic drug.

RESULTS: In the first two years of regular statin use, we observed a significant increase in the risk of new onset diabetes with higher potency statins compared with lower potency agents (rate ratio 1.15, 95% confidence interval 1.05 to 1.26). The risk increase seemed to be highest in the first four months of use (rate ratio 1.26, 1.07 to 1.47).

CONCLUSIONS: Higher potency statin use is associated with a moderate increase in the risk of new onset diabetes compared with lower potency statins in patients treated for secondary prevention of cardiovascular disease. Clinicians should consider this risk when prescribing higher potency statins in secondary prevention patients.