ISPE Midyear Meeting 2013
Introduction to Pharmacoepidemiology

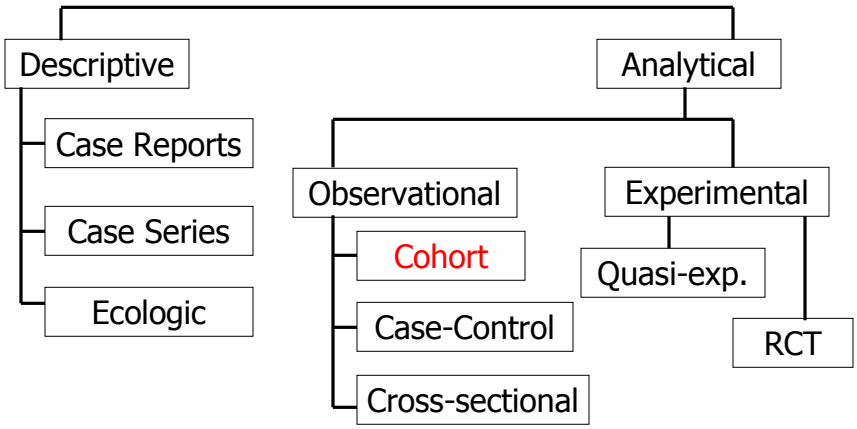
Cohort Studies

UF UNIVERSITY of FLORIDA

Conflict of Interest

- The views and opinions expressed in this presentation are solely mine and do not represent the position or opinion of ISPE or any other institution.
- I have no conflicts of interest to declare.

Types of Epidemiologic Studies



What is a cohort?

Cohort = basic tactical unit of a Roman legion

What is a cohort?

- Well-defined group of subjects
- Followed over time
- Observed for outcome(s) of interest

- Aim: To study how health status of cohort members change over time
  - How many subjects develop diabetes within one year of „follow-up“?
  - How does the average blood pressure change over one year of follow-up?
  - Among two subgroups defined by exposure, how does a particular outcome change/occur?

Closed versus open cohorts

- Closed = fixed
  - no subjects are added after enrollment; no exit allowed
  - Example: use of individuals in a cancer registry to estimate 1-year survival – if registrants are not lost to follow-up, entrance and exit are fixed
- Open = dynamic
  - subjects can move in and out
  - Example: use of a cancer registry for frequency estimates of cancer – the source population, e.g., residents of a particular state, is constantly changing.

Cohort entry and exit

- Definition of cohort entry
  - Data availability
  - Meet inclusion criteria
  - Specific event, e.g., onset of disease or start of therapy (inception cohort)
  - Matching criteria
- Definition of exit criteria
  - Data availability
  - Censoring criteria
  - Endpoint
  - Matching criteria

Examples

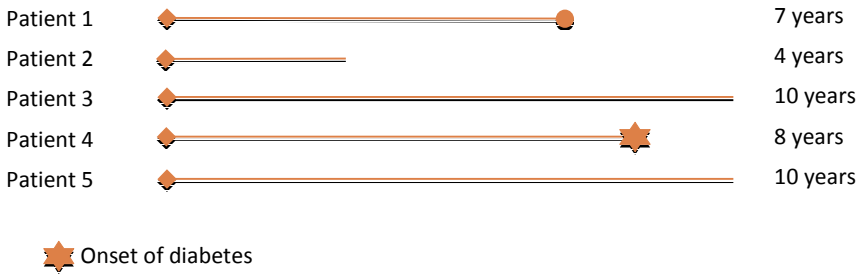
- Risk of MACE in new users of rosiglitazone versus pioglitazone (Graham et al, JAMA 2012)
  - Inception cohort: study entry at drug initiation following minimum of 6 months continuous eligibility and age >65
  - Censoring criteria: gap in TZD use >7days, non-endpoint hospitalization, study end
- Risk of sensorineural hearing loss in children with non-intact tympanic membranes and neomycin eardrops (Winterstein et al, Otolaryngol Head Neck Surg 2013)
  - Inception cohort: study entry at use of neomycin or quinolone ear drops within 12 months after tympanic membrane perforation
  - Fixed follow-up of 1 year thereafter, no censoring
- Any example for an open cohort design?

Measures of frequency and risk

Key outcome measures

- Incidence = measure of the risk of developing a certain (medical) condition over time
- Two measures of incidence:
  - Incidence proportion
  - Incidence density (=incidence rate)

Incidence measurement



Incidence proportion = (cumulative incidence) 1 / 5 = 0.2 (=20%)

Incidence density (incidence rate) = 1 / (7+4+10+8+10) person-years

= 1/39 PY= 0.0256 / 1 PY = **25.6 per 1000 PY**

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin vs Chlorthalidone

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Median follow-up was 3.3 years. A total of 365 patients in the doxazosin group and 608 in the chlorthalidone group had fatal CHD or nonfatal MI, with no difference in risk between the groups (relative risk [RR], 1.03; 95% confidence interval [CI], 0.90-1.17; P=.71).

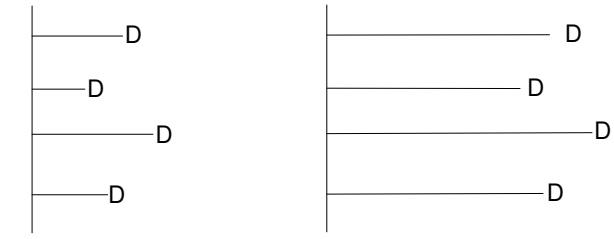
Total mortality did not differ between the doxazosin and chlorthalidone arms (4-year rates, 9.62% and 9.08%, respectively; RR, 1.03; 95% CI, 0.90-1.15; P=.56.)

Comparison of incidence rates

- Measure of of increased / decreased risk *relative* to a reference
  - Incidence rate ratio – ratio of two incidence rates (density)
  - Incidence risk ratio – ratio of two incidence proportions
- Absolute differences between risk are summarized by ARR (absolute risk difference)

$$\text{IRR} = \frac{\text{Incidence rate in exposed}}{\text{Incidence rate in unexposed}}$$

Incidence proportion – any problems?



Adapted from Rothman
Modern Epidemiology 2008

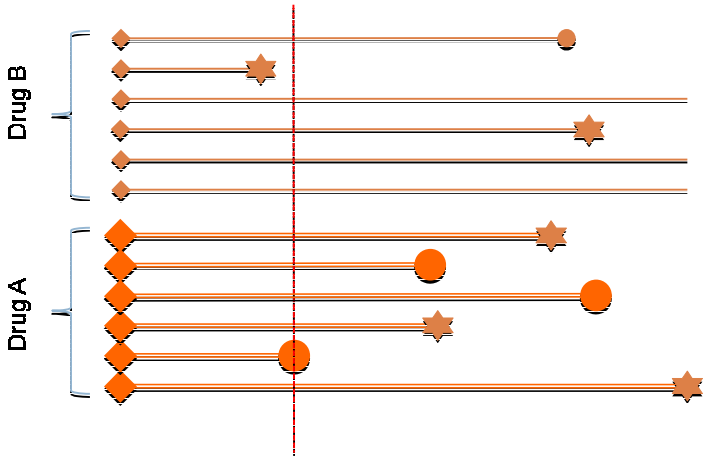
Time

D = Death

- Incidence proportion is 100% in both scenarios
- But is risk of death the same?
- Is incidence proportion useful in open cohorts?

Time at risk and differential loss to follow-up

How could incidence proportion be used in this cohort study?

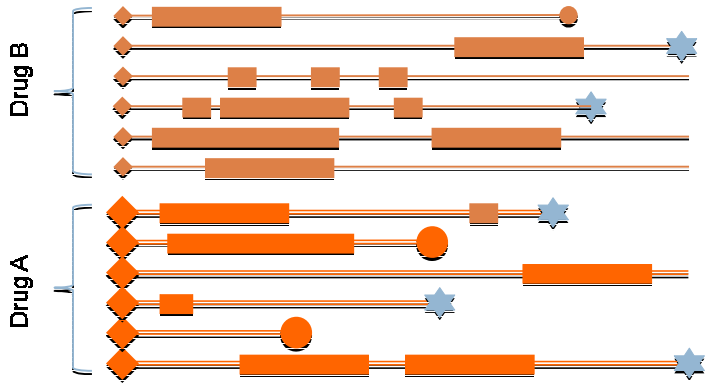


Competing causes – special case of loss to follow-up

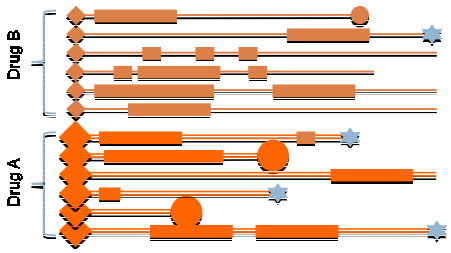
- Consider very effective drug to decrease cancer mortality
- Safety concern includes dementia
- What will use of incidence proportion show?

- Solution?

Other advantages of incidence density – changes in exposure status



Incidence density



Usually only <u>first</u> outcome of interest is considered

→ follow-up ends after first event

$$\text{Incidence density (or incidence rate)} = \frac{\text{Number of outcomes of interest}}{\text{Person time at risk}}$$

Summary

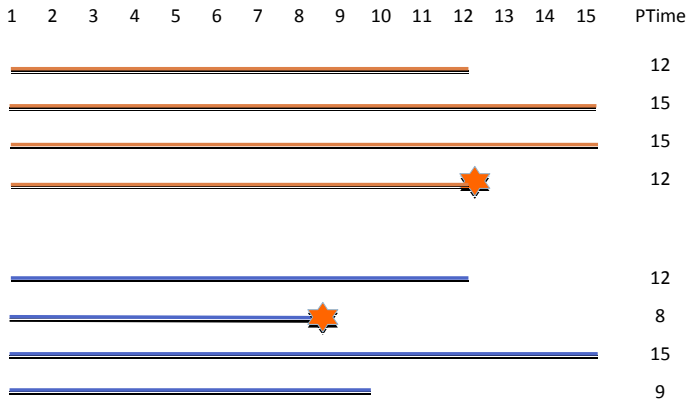
Incidence density of the more appropriate measure in most situations, because it:

- Accounts for time to event
- Accounts for competing causes
- Accounts for differences in follow-up times
- Helps to account for changes in exposure status

- Does incidence proportion include time in the denominator?

Classification of exposure

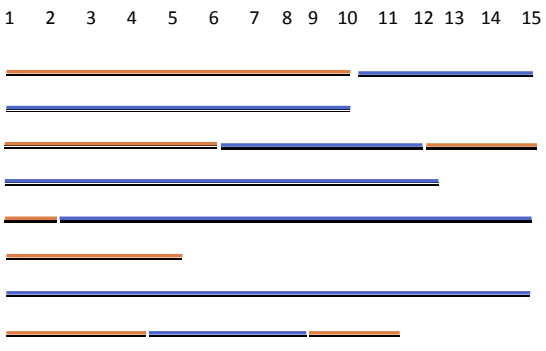
Classification of exposure



Example

- Risk of MACE in new users of rosiglitazone versus pioglitazone (Graham et al, JAMA 2012)
  - Inception cohort: study entry at drug initiation following minimum of 6 months continuous eligibility and age >65
  - Censoring criteria: gap in TZD use >7days, non-endpoint hospitalization, study end
  - Censoring also included a prescription for another TZD – follow-up restricted to periods of continuous use of original incident TZD

Time-dependent classification of exposure



PTime	Non	Current
15	10	5
10	0	10
15	8	7
12	0	12
15	2	13
5	5	0
15	0	15
11	7	4

Extended exposure periods

Strict definition of non-exposure times after drug supply is exhausted may be appropriate if:

- No residual drug effect exists
- Reason for discontinuation is not related to outcome
- Drug use does not continue in reality

Extended exposure time may be appropriate if:

- Effect is known to continue (contraceptive VTE risk)
- Drug supply is likely not exhausted (early prescription refill leading to gaps)
- Drug may have been stopped because of early outcome symptoms

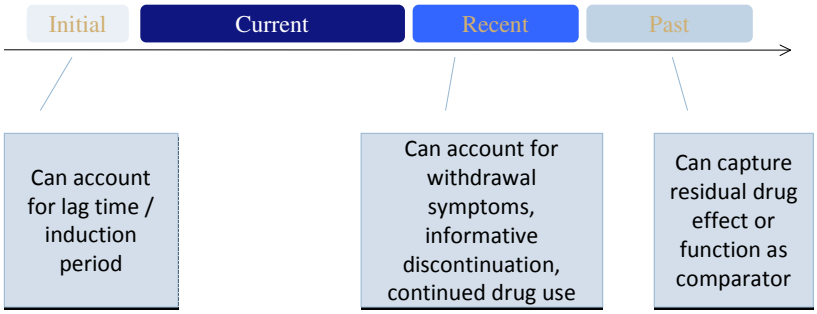
Example

- Risk of MACE in new users of rosiglitazone versus pioglitazone (Graham et al, JAMA 2012)
  - To guard against bias arising from informative censoring, any end point events occurring within 14 days following a gap in continuous treatment or admission to a hospital were counted in the analysis. This 14-day period of extended follow-up was not applied to thiazolidinedione switching, because it would not be possible to distinguish effects attributable to rosiglitazone from those attributable to pioglitazone, nor was it applied to censoring at the end of the study window because no data were collected after that date.

What if I don't know…

Exposure classification should be defined a priori, based on sounds reasoning, informed by sensitivity analyses

- *Pharmaco*epidemiology includes pharmacology
- Mechanism of exposure and exposure measurement



What if I do this wrong?

Assignment of exposure determines attribution of events. Erroneous attribution of event to no-use if subject was exposed will increase the incidence rate of the no-users and bias the comparison towards the null.

	True:	Found:
Drug	10/100	7/100
None	5/100	8/100

And consider this…

New user designs with censoring at switch is the cleanest solution but it may lose valuable follow-up time – and may not be possible if drug B is second choice.

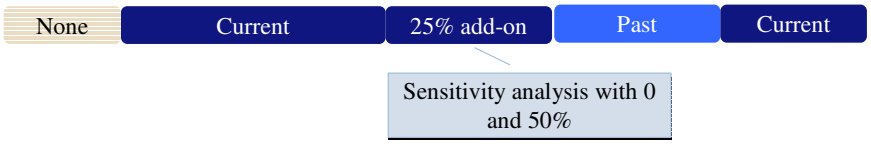
Observational research is not alone

- Among participants in the chlorthalidone group
  - 87.1% were taking chlorthalidone or another diuretic at 1 year, decreasing to 80.5% at 5 years;
  - 13.2% were taking a diuretic with a CCB (5.8% [n = 399]) or an ACE inhibitor (9.3% [n = 641]).
  - Only 9.0% were taking either a CCB (5.8% [n = 399]) or an ACE inhibitor (5.6% [n = 385]) without a diuretic at 5 years.

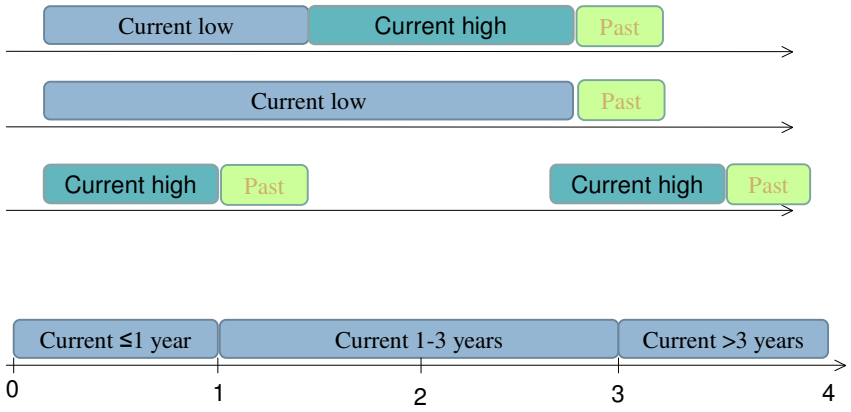
(ALLHAT, JAMA 2002)

Example

- Cardiac safety of stimulants in treatment of ADHD (Winterstein BMJ 2012)
  - Most states allow only 30-day refills – reduces guesses how long prescription might last (if used PRN)
  - But drug holidays are prevalent
  - Discontinuation may be due to tachycardia
  - Onset of ventricular arrhythmia may be immediate / etiology of AMI might require development of cardiomyopathy
  - No active comparator: emphasis on keeping exposed truly exposed and finding unexposed with no prior history of exposure

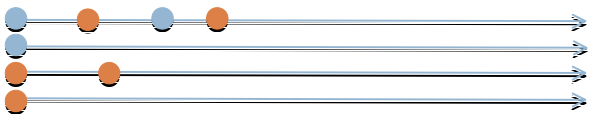


Just for fun: Classification according to dose or duration of use



Example

- Risk of sensorineural hearing loss in children with non-intact tympanic membranes and neomycin eardrops (Winterstein et al, Otolaryngol Head Neck Surg 2013)
  - Inception cohort: study entry at use of neomycin or quinolone ear drops within 12 months after tympanic membrane perforation
  - Fixed follow-up of 1 year thereafter, no censoring
  - Counter for the number of neomycin claims
  - Subjects were allowed to switch exposure
  - Covariate for # of quinolone or neomycin claims adjusted for confounding (repeated use)



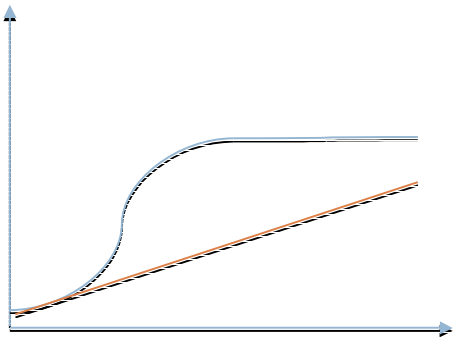
Example continued

Characteristics	No. of cases	Hazard ratio[†]	95% CI
Main exposure of interest			
Fluoroquinolone otic use	754	1.0	Ref.
Neomycin first dispensing	174	0.90	0.76-1.07
Neomycin second dispensing	42	**1.45**	**1.05-2.01**
Neomycin third or more dispensing	12	1.30	0.71-2.36
Covariates			
Age, yrs		**1.11**	**1.09-1.13**
Male		0.92	0.81-1.05
White vs. non-White		**1.30**	**1.14-1.48**
Total dispensing of ear drops		**1.21**	**1.14-1.28**

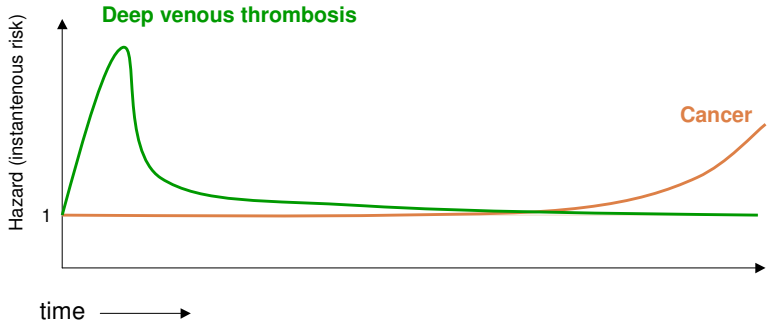
Time in studies of drug effects

Consideration of time

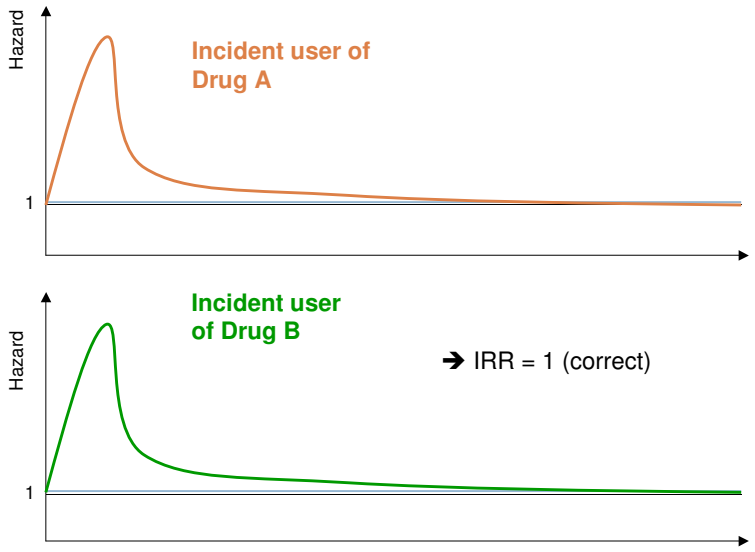
- Can be addressed with assignment of exposure or timing of follow-up
- Important in case of
  - Induction periods
  - Lag times
  - Changing hazard



Depletion of susceptibles

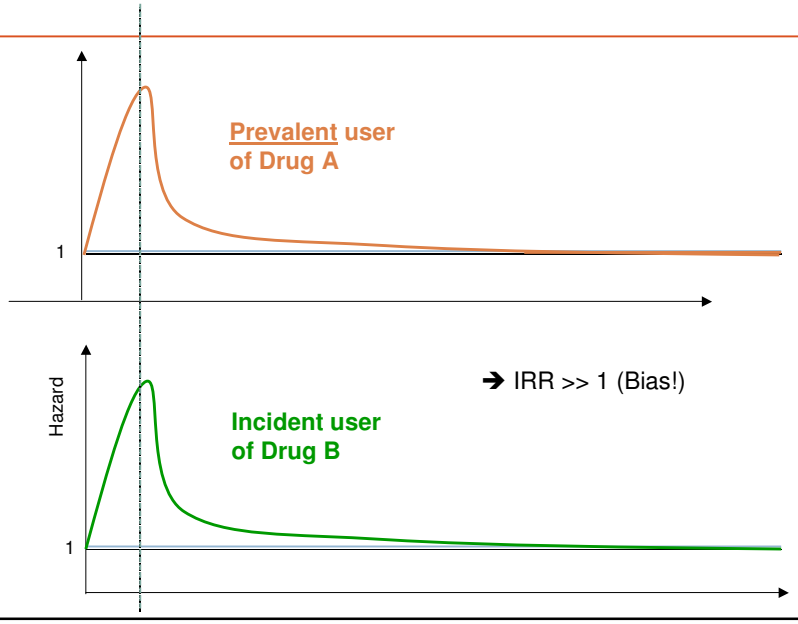


Depletion of susceptibles



➔ IRR = 1 (correct)

Depletion of susceptibles continued



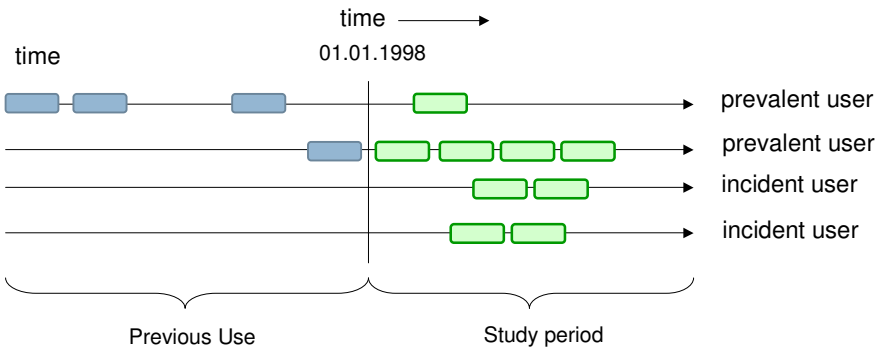
➔ IRR >> 1 (Bias!)

Remediation: New user designs

- Often used in pharmacoepi studies
- Looks like an RCT
- Follow-up starts with exposure → efficient
- Interpretation more straight forward
- Takes care of depletion of susceptibles

- Problems might occur in defining start of-follow-up in unexposed subjects
  ("immortal time bias")

Operationalizing "new use"



Long enough "Look-back" not always possible → include sensitivity analyses to study "depletion-of-susceptible" bias

To do list for a simple cohort study

1. Define the population of interest
2. Define how these subjects are sampled from the underlying source population
3. Define in- and exclusion criteria
4. Define and operationalize confounders
5. Explicitly (!) define date of cohort entry and cohort exit
6. Classify person time according to exposure
7. Sum-up person-time of the different exposure categories
8. Assign number of events to these categories
9. Calculate incidence(s) and incidence rates

Step 1-3

1. Define the population of interest (e.g. User of Drug A or Drug B)
2. Define how these subjects are sampled from the underlying source population
3. Define in- and exclusion criteria

- Similar to a randomized trial
- In- and exclusion criteria:
  - Well-defined population
  - Focus on population of interest (e.g. Patients with ADHD)
  - Can be used to reduce bias from confounding ("restriction") but might remove ability to explore effect modification (e.g., drug effect in high-risk groups)
  - Increase study efficiency (high background rate)
- Choice of comparator may be critical for confounding

Example: Stimulant safety study

Restriction versus ability to explore effect modification and maintain high background rate

- Literally no stimulant use occurred in patients on dialysis or post-organ transplant status
- But: proportion of children with congenital heart disease:
  - Unexposed 0.85%
  - Exposed 0.75%
- Background risk for serious cardiac events
  - Low-risk stratum: 3.1 per 100,000 patient-years
  - High-risk stratum: 99.1 per 100,000 patient-years

Choice of comparators

Ideal: Head-To-Head with very similar drug

- Reduces confounding
- Similar groups of patients (indication of use, comorbidity, etc.)
- New-user design preferred

Head-To-Head with inactive comparator drug

- For outcome acute MI → glaucoma medication
- Easy to define cohort entry
- It is ensured that all patients are under medical observation

Comparison with non-use

- Non-user often substantially different than user → confounding
- If feasible → Interpretation “straight forward”

Step 5

5. Explicitly (!) define date of cohort entry and cohort exit

- When to start follow-up ?
  - Calendar day
  - Event (day of ADHD diagnosis; first prescription of central nervous stimulant)
  - Time (365 days after inclusion into a registry) ...
- When to stop follow-up ?
  - End of study period (Dec 31, 2008)
  - Death / Loss-to-Follow-Up
  - Day of first occurence of outcome of interest

Step 7-9

7. Sum-up person-time of the different exposure categories
8. Assign number of events to these categories
9. Calculate incidence(s) and incidence rates

- 1. Crude estimates
- 2. Stratified analyses (e.g. by age, sex)
- 3. Multivariate modeling - for person-time based analyses (incidence density)
  - Poisson-Regression
  - COX-proportional hazard regression
  - If follow-up time is the same for all subjects: logistic regression

Summary: cohort study advantages

- Possible to study rare exposures
- Multiple outcomes can be studied (smoking --> lung cancer, COPD, larynx cancer)
- Exposure is assessed before outcome (no recall bias as in case control studies if prospective design)
- Exposure pattern can be fully explored
- Time-to-event analysis is possible (can estimate hazard function beforehand)
- Possible to estimate absolute risks (incidences)

Cohort studies - disadvantages

- Long duration (if prospective)
- Expensive
- Not efficient for rare outcomes
- Often not possible to study multiple exposures
- Might be problematic for diseases with long latency
- Assignment of exposure (with multiple categories) is cumbersome

FAQs

- Can one match in cohort studies?
- Can one vary exposure status in cohort studies?
- Can one study multiple exposures?
- Why are there “retrospective cohort studies”?
- Can one study multiple outcomes?
- Can subjects enter the cohort at different points in time?
- How do I determine when I should start to measure risk and when to stop?

Questions?