# Pharmacoepidemiology

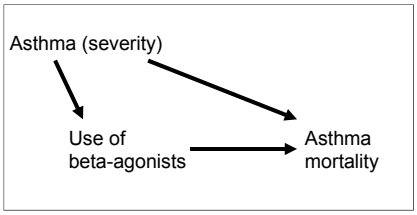
## Lesson 4: Methodological Challenges

Confounding
Selection Bias





## Teaching Example for Confounding by Indication




Crane J, Pearce N, Flatt A, Burgess C, Jackson R, Kwong T, Ball M, Beasley R. Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. Lancet. 1989 Apr 29;1(8644):917-22.

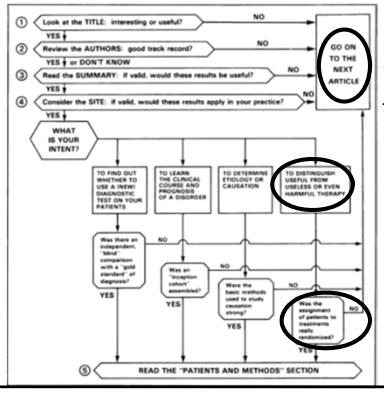
Walker AM, Lanes SL. Misclassification of covariates. Stat Med 1991; 10:1181-96.

Blais L, Suissa S. Confounding by indication and channeling over time: the risks of beta 2-agonists. Am J Epidemiol. 1996 Dec 15;144(12):1161-9.

Pearce N. The use of beta agonists and the risk of death and near death from asthma. J Clin Epidemiol 2009;62:582-7.



## Intractable Confounding




Sackett DL. How to read clinical journals: I. Why to read them and how to start reading them critically. CMAJ 1981;124:555-8.



## Intractable Confounding

- Miettinen Stat Med. 1983;2:267-71: "control of the indication in non-experimental terms is commonly infeasible owing to the complexity and subtlety of the indication"
- Yusuf, Collins, Peto. Stat Med 1984;3:409-22: "For the realistic assessment of the effects of today's widely practicable treatments on mortality from the currently common neoplastic diseases or the currently common vascular diseases, the use of 'historical controls', 'databases', or whatever, is of little real value, for such methods may introduce moderate biases"
- EBM working group JAMA 1992;268:2420-5: "The criteria should not be presented in such a way that fosters nihilism (if the study is not randomized, it is useless and provides no valuable information)"

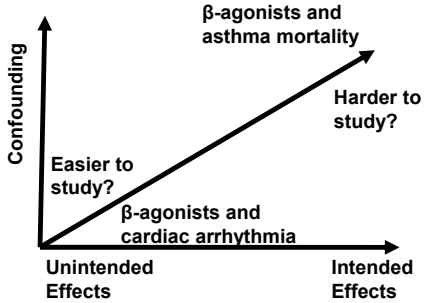


## Confounding by Indication

- Good prescribing leads to confounding of drug effects on intended outcomes
- More severe disease more likely to
  - Be treated (with higher doses)
  - Have higher risk of adverse outcomes
- Assessment of severity of disease
  - Often difficult
  - Intractable for intended effects (Miettinen 1983; Yusuf, Collins, & Peto 1984)
- Drug looks BAD compared with **NON-USERS**!



## Potential for Confounding by Indication




Also: Statins and CVD vs. statins and rhabdomyolysis
Cave: Frequent overlap of risk factors!

## BTW: Confounding by Indication?

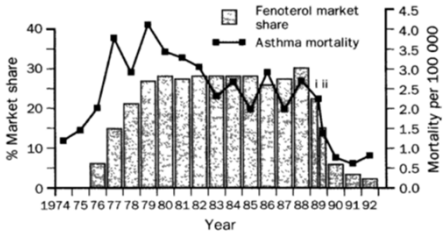
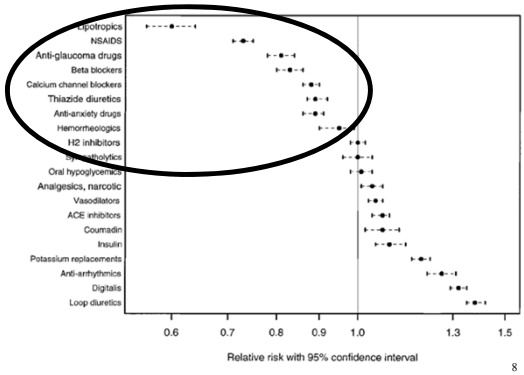



Figure 1: **Inhaled fenoterol market share and annual asthma mortality in persons aged 5–34 years**
The data for 1989 are divided into two 6-month periods because the first Department of Health warnings about the safety of fenoterol were issued in mid-1989.

Pearce N et al. End of the New Zealand asthma mortality epidemic. Lancet 1995;345: 41-4.

Maybe, but not entirely!

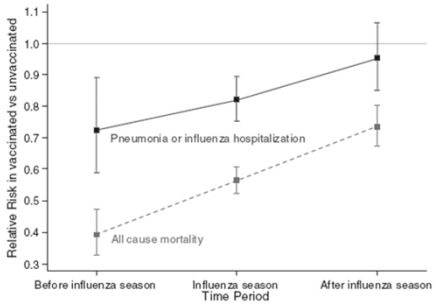
## Paradoxical Drug Relations in Elderly




RR for 1-year mortality, hospitalized Medicare population. Glynn RJ et al. Epidemiology 2001



## Paradoxical Vaccine Relations in Elderly




RR for mortality in >65-year old HMO population
Jackson LA et al. Int J Epidemiol 2006



## Frailty

- End of life loss of
  - Weight
  - Physical function
  - Cognitive function
- Recognized by healthcare professionals
- Reduces likelihood of receiving/staying on preventive therapies
  - Focus on main medical problem (Redelmeier et al. 98)
  - Little expected benefit (competing risks; Welch et al. 96)

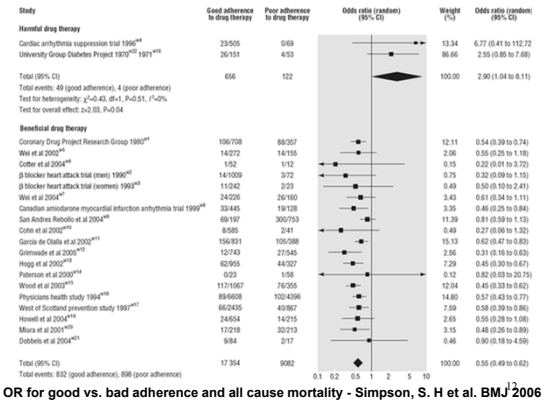


## Confounding by Frailty in Population Based PE Studies

- Individuals close to death are
  - Less likely to receive preventive treatments
    - E.g., statins, flu vaccination
  - More likely switched to palliative treatments
    - E.g., opiates instead of NSAIDs
  - More likely to receive certain classes of drugs
    - E.g., loop diuretics vs. other diuretics
- Paradoxical drug mortality associations
- Drug looks GOOD compared with **NON-USERS**!

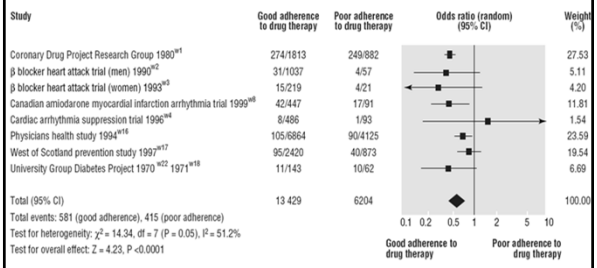


## Adherence to Harmful/Beneficial Drug Therapy and Mortality




**OR for good vs. bad adherence and all cause mortality - Simpson, S. H et al. BMJ 2006**

## Adherence to Placebo and Mortality




**OR for good vs. bad adherence and all cause mortality - Simpson, S. H et al. BMJ 2006**

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## Selection bias in RCTs

- Simpson et al. meta-analysis of 21 trials (BMJ 2006)
- Good vs. poor adherers to active treatment 45% reduced odds of death
- Good vs. poor adherers to placebo 44% reduced odds of death
- Better adherence associated with lower mortality (except when therapy harmful)
- Similar issue with persistence on preventive drugs?

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## Statin Persistence

**Table 3. Association Between Adherence to Statin Therapy and Risk of Health-Related Events**

| Outcome | More Adherent Event Rate, /100 Person-Years | Less Adherent Event Rate, /100 Person-Years | Unadjusted HR | 95% Confidence Limits for HR | Adjusted HR | 95% Confiden Limits for HI |
|---|---|---|---|---|---|---|
| Accident events | | | | | | |
| Both sexes (n=141 086) | | | | | | |
| Burn | 0.28 | 0.36 | 0.78 | (0.71–0.87) | 0.88 | (0.79–0.97) |
| Fall | 0.53 | 0.54 | 0.98 | (0.90–1.06) | 0.90 | (0.83–0.98) |
| Fracture | 2.20 | 2.38 | 0.93 | (0.89–0.96) | 0.92 | (0.88–0.96) |
| Motor vehicle accident | 1.48 | 2.25 | 0.66 | (0.63–0.69) | 0.75 | (0.72–0.79) |
| Open wound | 2.44 | 2.74 | 0.89 | (0.86–0.92) | 0.91 | (0.88–0.95) |
| Poisoning | 0.32 | 0.41 | 0.78 | (0.71–0.86) | 0.86 | (0.78–0.94) |
| Workplace accident | 1.31 | 2.13 | 0.62 | (0.59–0.65) | 0.77 | (0.74–0.81) |
| All (first occurrence) | 7.38 | 9.39 | 0.79 | (0.77–0.81) | 0.85 | (0.83–0.87) |
| Screening events | | | | | | |
| Both sexes (n=141 086) | | | | | | |
| Eye examination | 3.58 | 2.93 | 1.21 | (1.17–1.26) | 1.08 | (1.05–1.12) |
| Fecal occult blood test | 8.06 | 6.14 | 1.31 | (1.27–1.34) | 1.21 | (1.18–1.24) |
| Sigmoidoscopy | 0.53 | 0.49 | 1.09 | (1.00–1.18) | 1.07 | (0.98–1.16) |
| All (first occurrence) | 12.01 | 9.28 | 1.28 | (1.25–1.31) | 1.17 | (1.15–1.20) |

BC data; Dormuth et al. Circulation 2009

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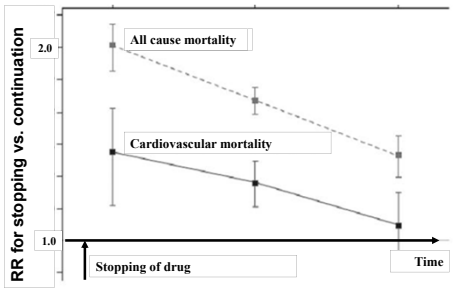
## Sick Stopper?




Adapted from Jackson LA et al. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. Int J Epidemiol 2006.
Note: Bias most pronounced immediately after stopping!

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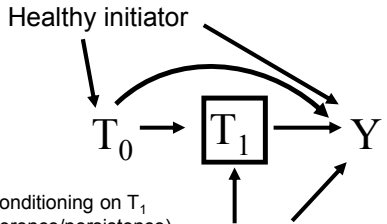
## Healthy User Bias DAG




Conditioning on $T_1$ (adherence/persistence) opens time-varying confounding path or introduces selection bias when censoring

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## Confounding at Initiation Versus on Treatment

- At drug initiation: not affected by actual treatment
  - By logic
  - Cave: still affected by outcome prediction
- Solution:
  - Condition (implicitly) on indication
    - Active comparator, new user study design

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## Confounding on Treatment (Time-Varying)

- Stopping/switching after initiation:
  - **More complex than at initiation**
  - Likely affected by prior treatment, e.g.,
    - Lack of effectiveness
    - Side effects
  - Hard (impossible?) to predict
- Solution:
  - Censor? -> introduces selection bias
  - Initial treatment (IT) carried forward
  - G-methods (dependent on prediction)

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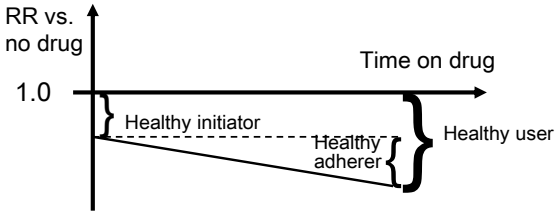
## Bias Over Time on Preventive Drug Compared with Non-Use

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## Confounding – Selection Bias

- Real threats to validity of PE studies
- Think "conditional on measured covariates"
- Prevalent users affected by both!
- Solution (just a hint):
  - Think "What is the RCT I would like to do?"
    - Intervention usually means "new user"
    - New use of "placebo" unobservable -> active comparator
    - Active comparator implicitly conditions on indication (and medicalization, frailty, etc.)
  - Everything after initiation: similar to RCT
    - Initial treatment carried forward (IT) avoids selection bias
    - Cave G-methods dependent on prediction adherence/persistence
- Study design more important than analysis

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