Correcting for Confounding-by-Indication in Real Life Data: Does it Matter to the Decision Maker?

Panel: HTA based on health care system efficiency: using real-life data to improve health care management
HTAi 2011, Rio de Janeiro

Prof. Uwe Siebert, MD, MPH, MSc, ScD

Chair, Department of Public Health HTA, Austria
Adjunct Professor of Health Policy and Management, Harvard University, USA
Area Director, ONCOTYROL Center for Personalized Cancer Medicine, Austria

Acknowledgment

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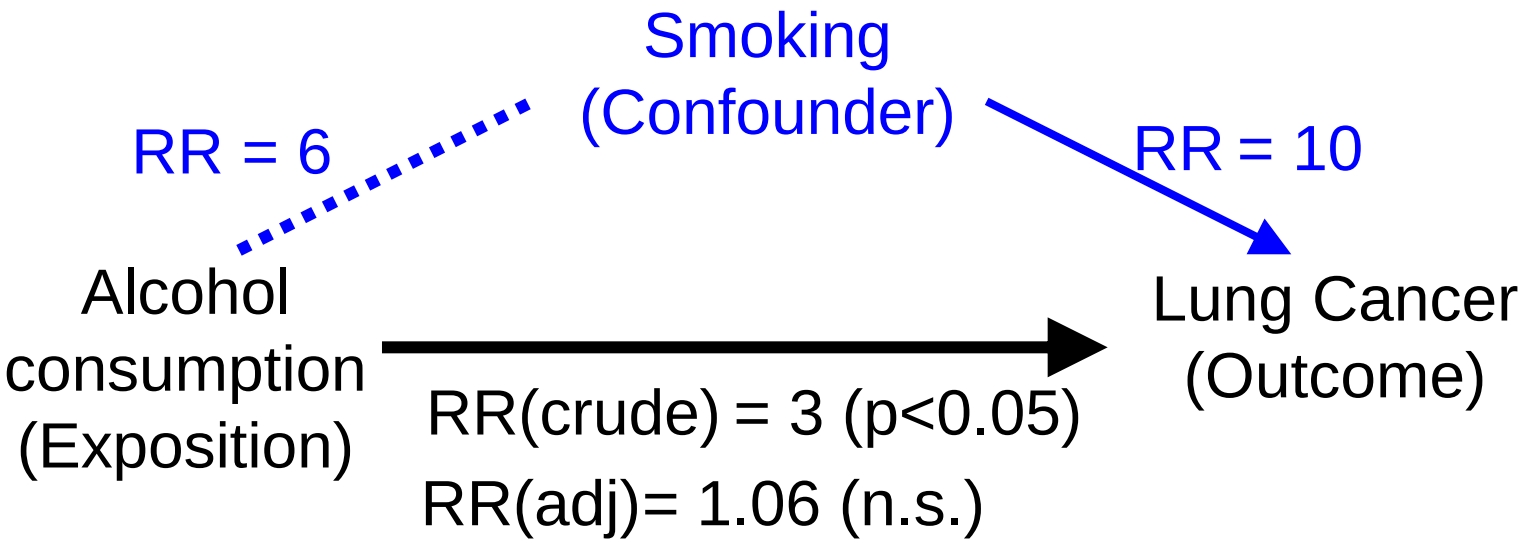
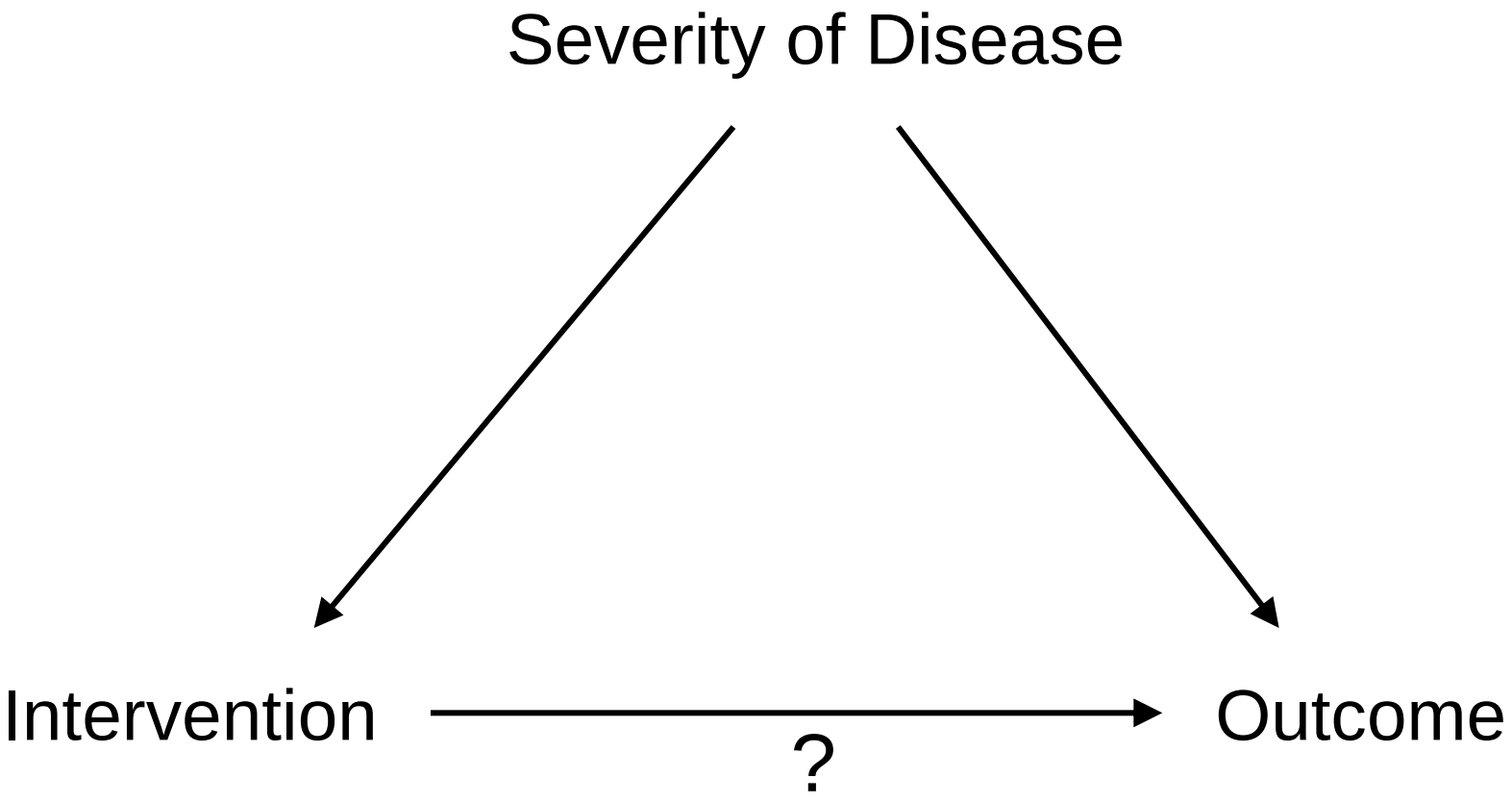
Overview

- Confounding
- Use of causal graphs to avoid bias in observational real-life data analysis
- Time-depending confounding by indication
- Dat requirements and challenges

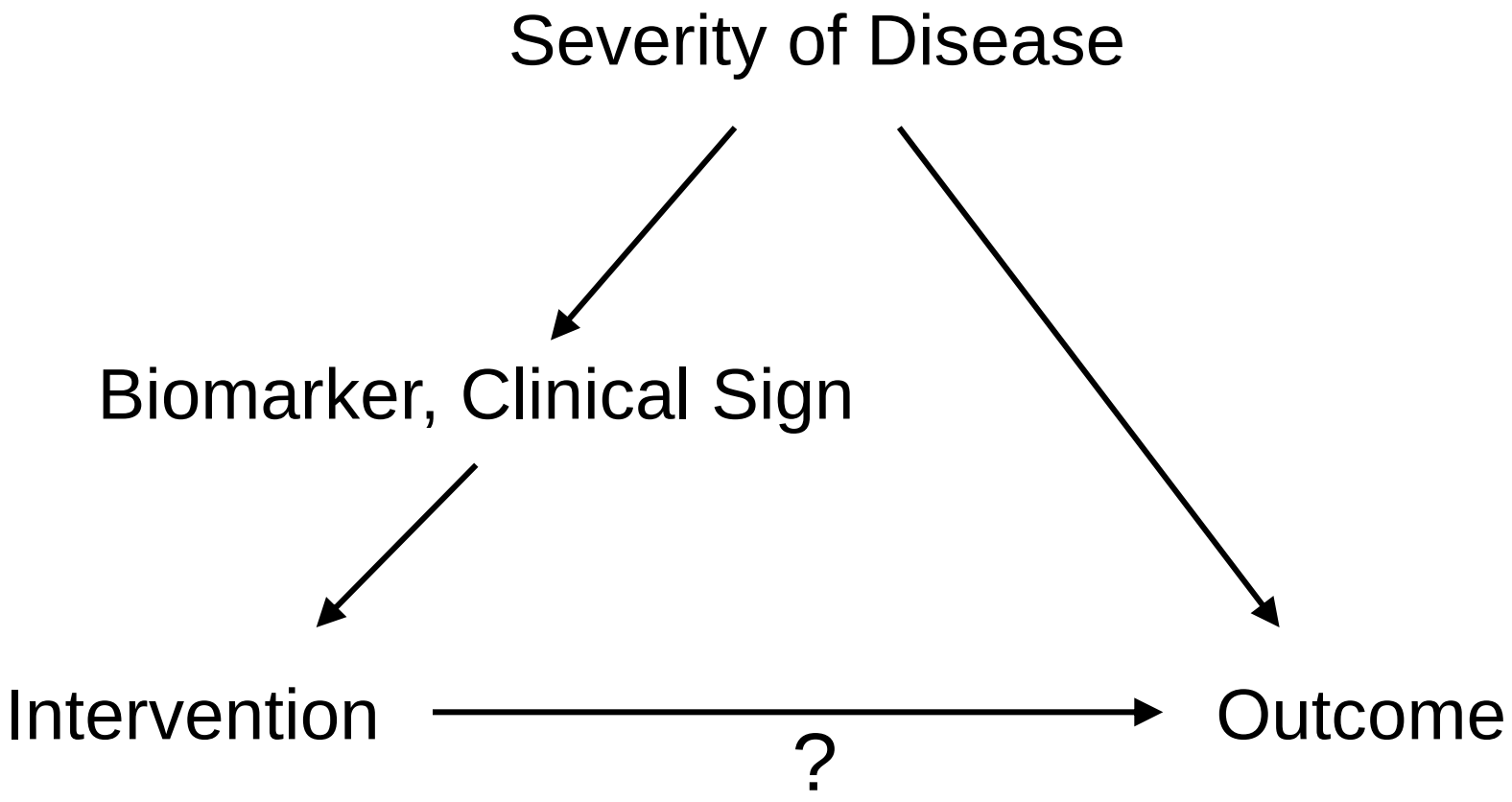
The Problem of Epidemiologic Studies: Confounding



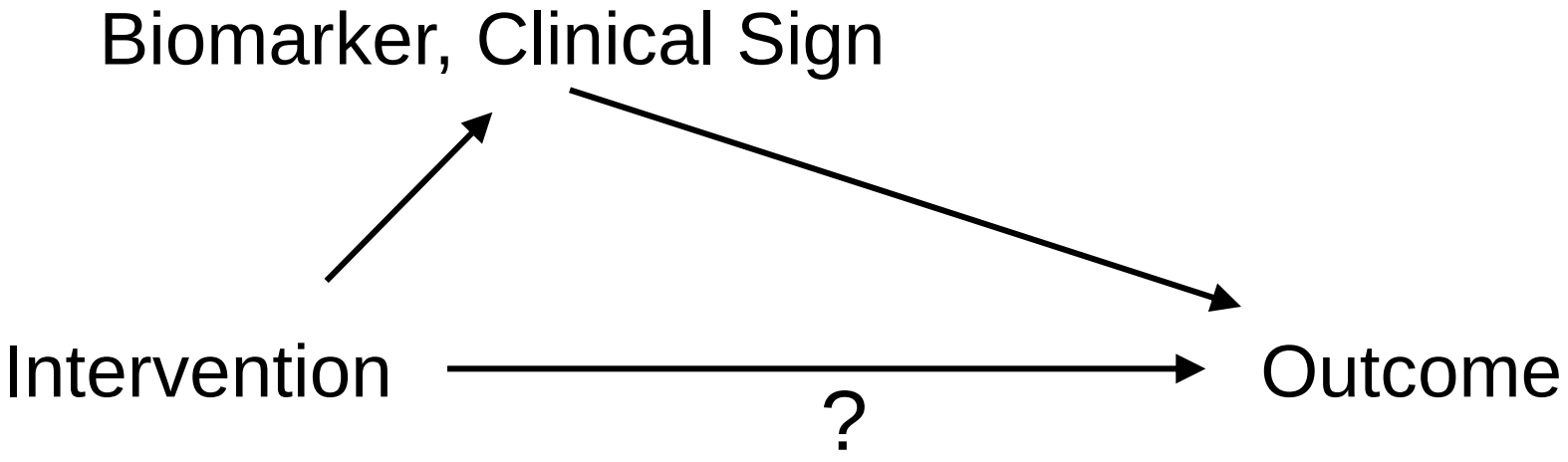
Confounding by Indication



Confounding by Indication



Intermediate Step



Example HIV Treatment -

The Multicenter AIDS Cohort Study (MACS)

Example MACS

Hernan MA. Brumback B. Robins JM.

Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men.

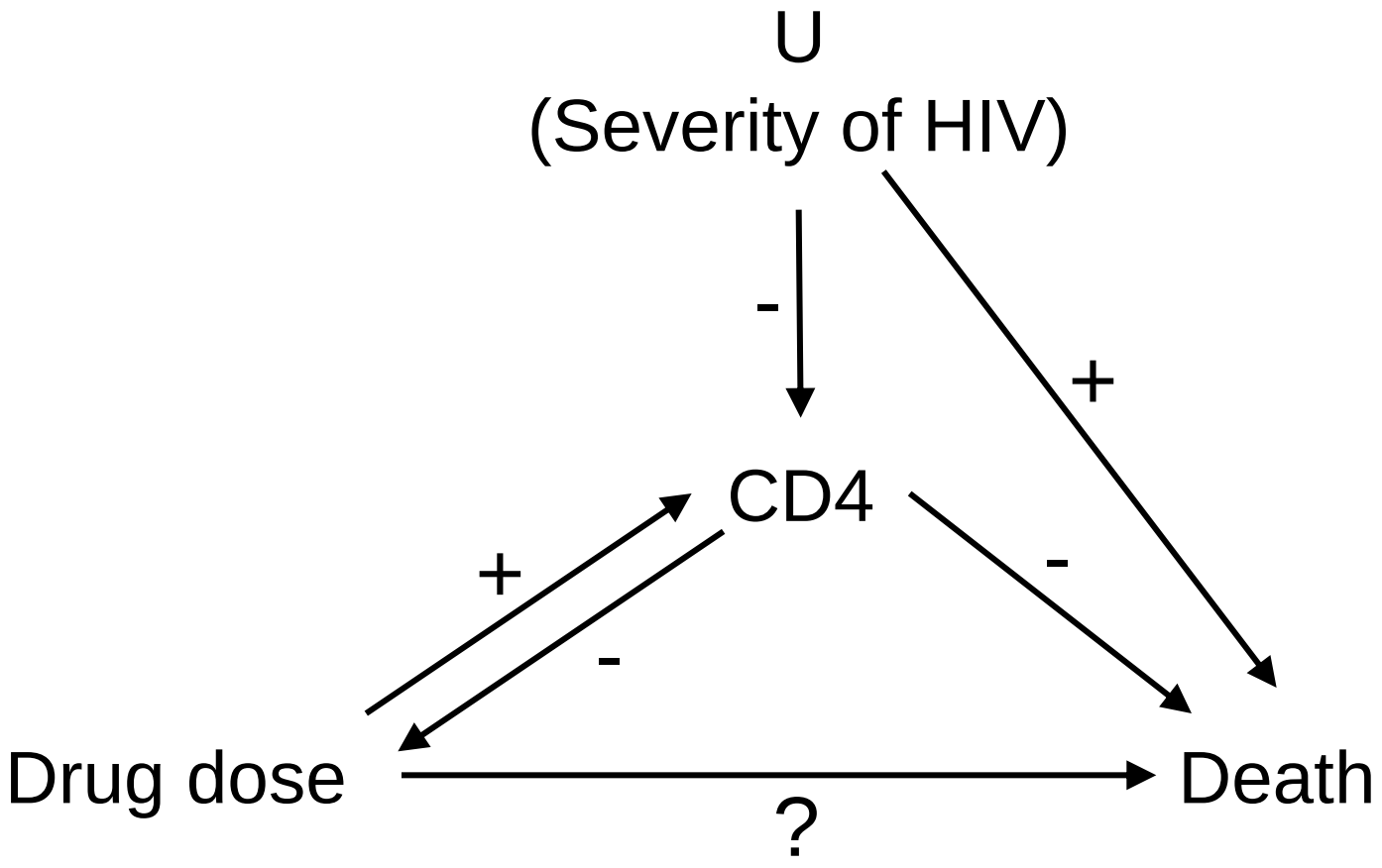
Epidemiology. 11(5):561-70, 2000

Story: Data from 2 small RCTs and the Multicenter AIDS Cohort Study (MACS)

Example MACS

- Intervention: Antiviral drug (dose)
- Outcome: Mortality
- Study design: Observational study

Example MACS

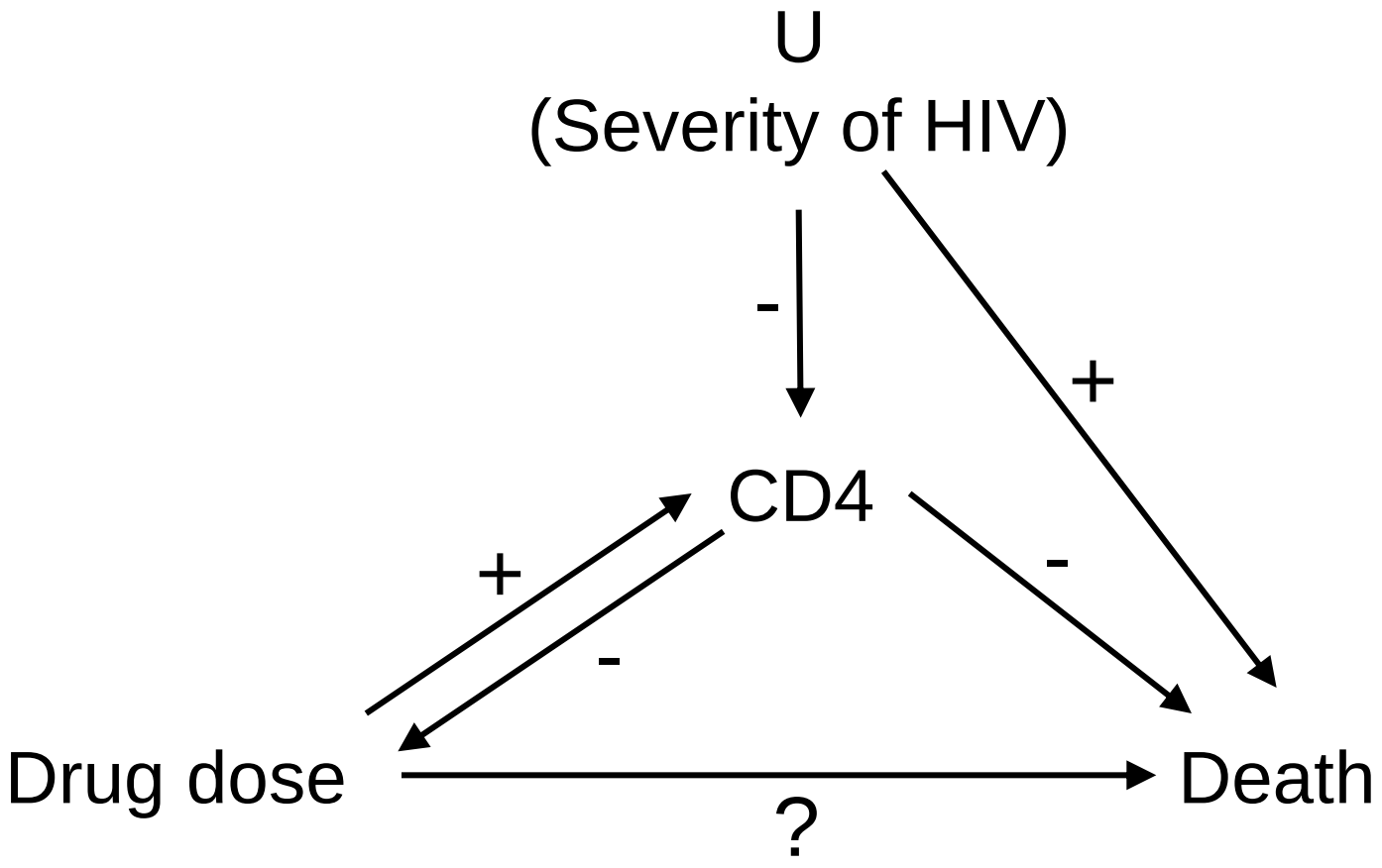


Example MACS

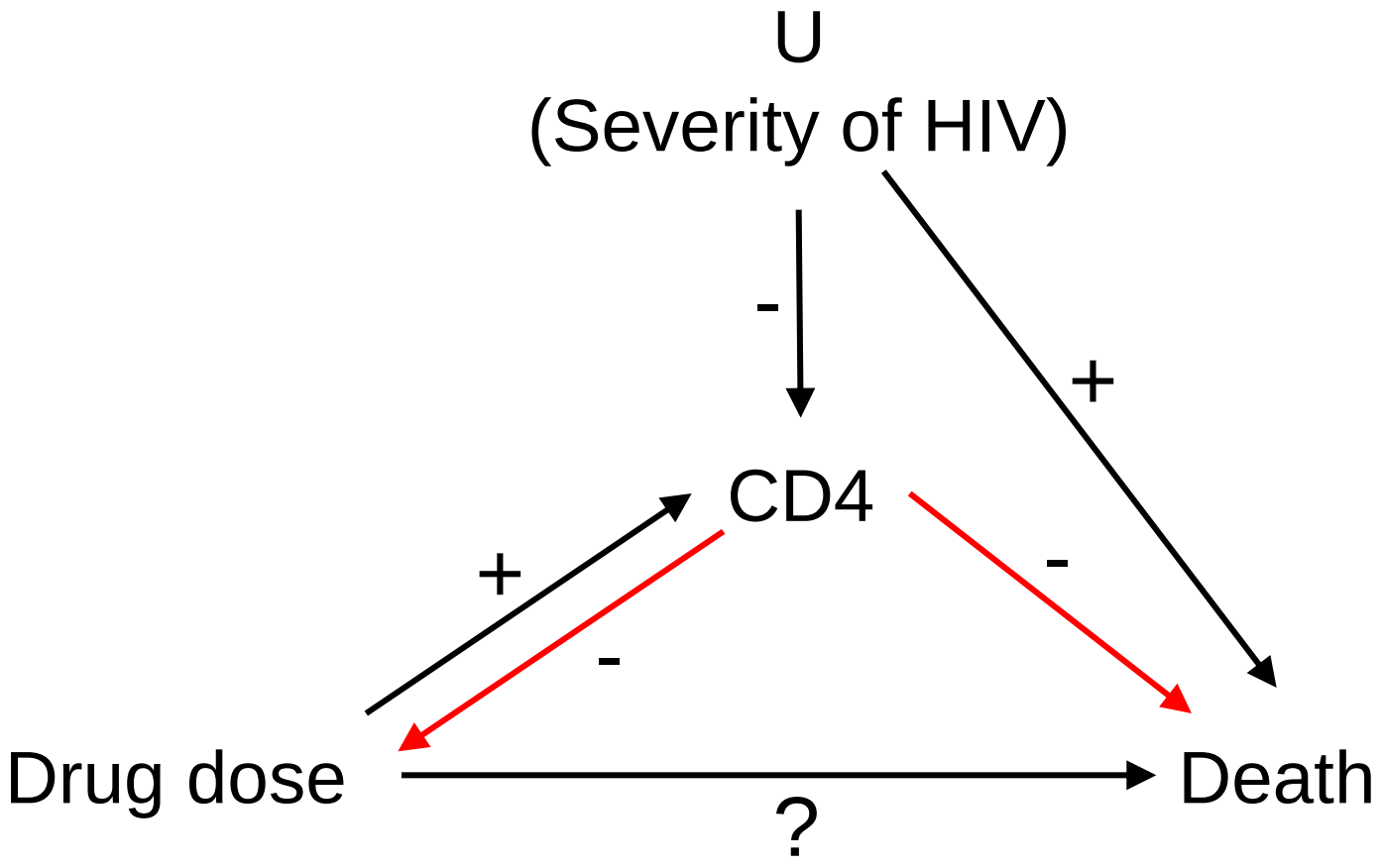
Analysis (high vs. low dose drug)	RR	Sign.
Not adjusted for CD4	3.6	p<0.05
Adjusted for CD4	2.3	p<0.05
Causal effect estimate	*?*	*?*

Data from Hernan MA, Brumback B, Robins JM. Epidemiology 2000

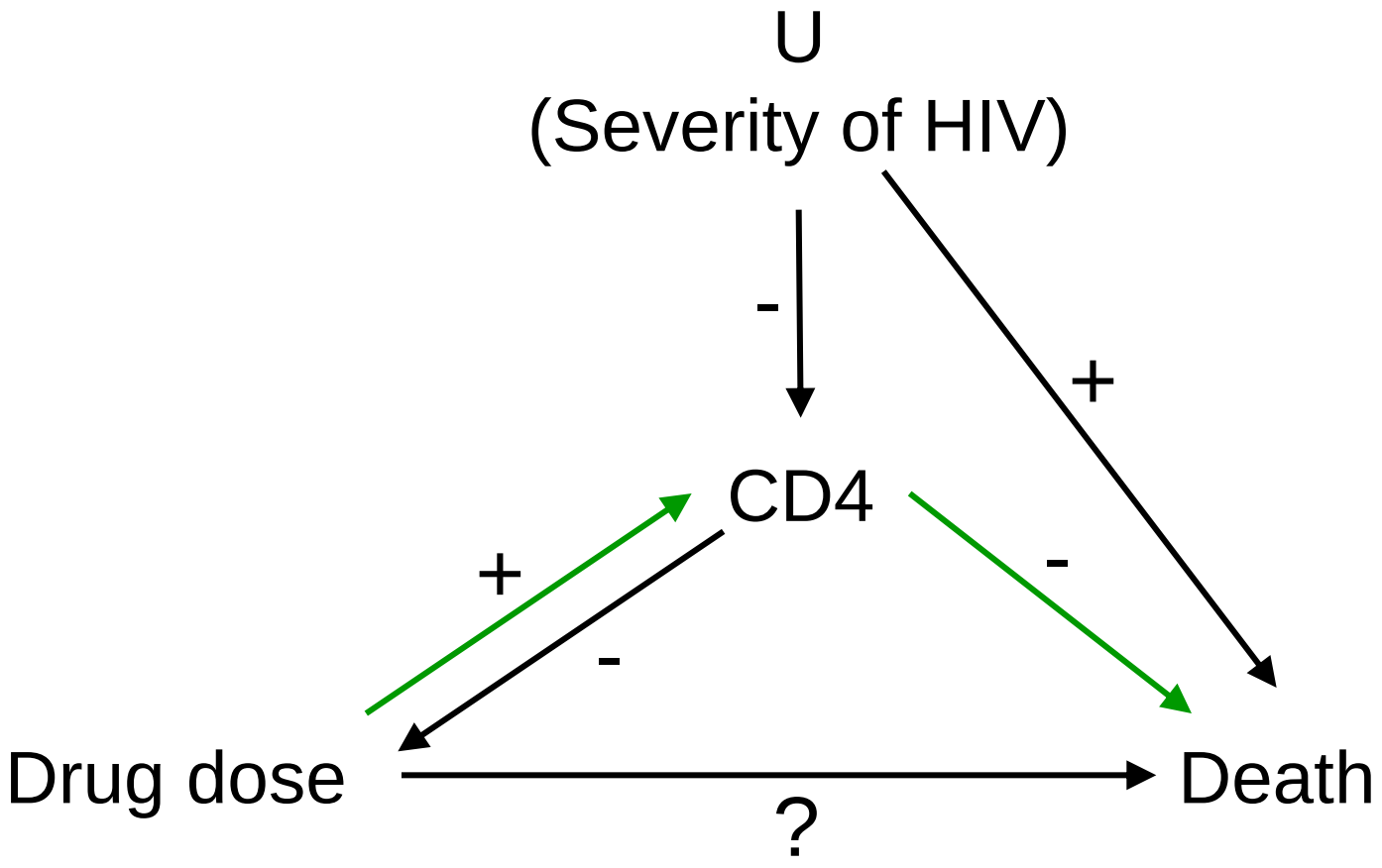
Example MACS



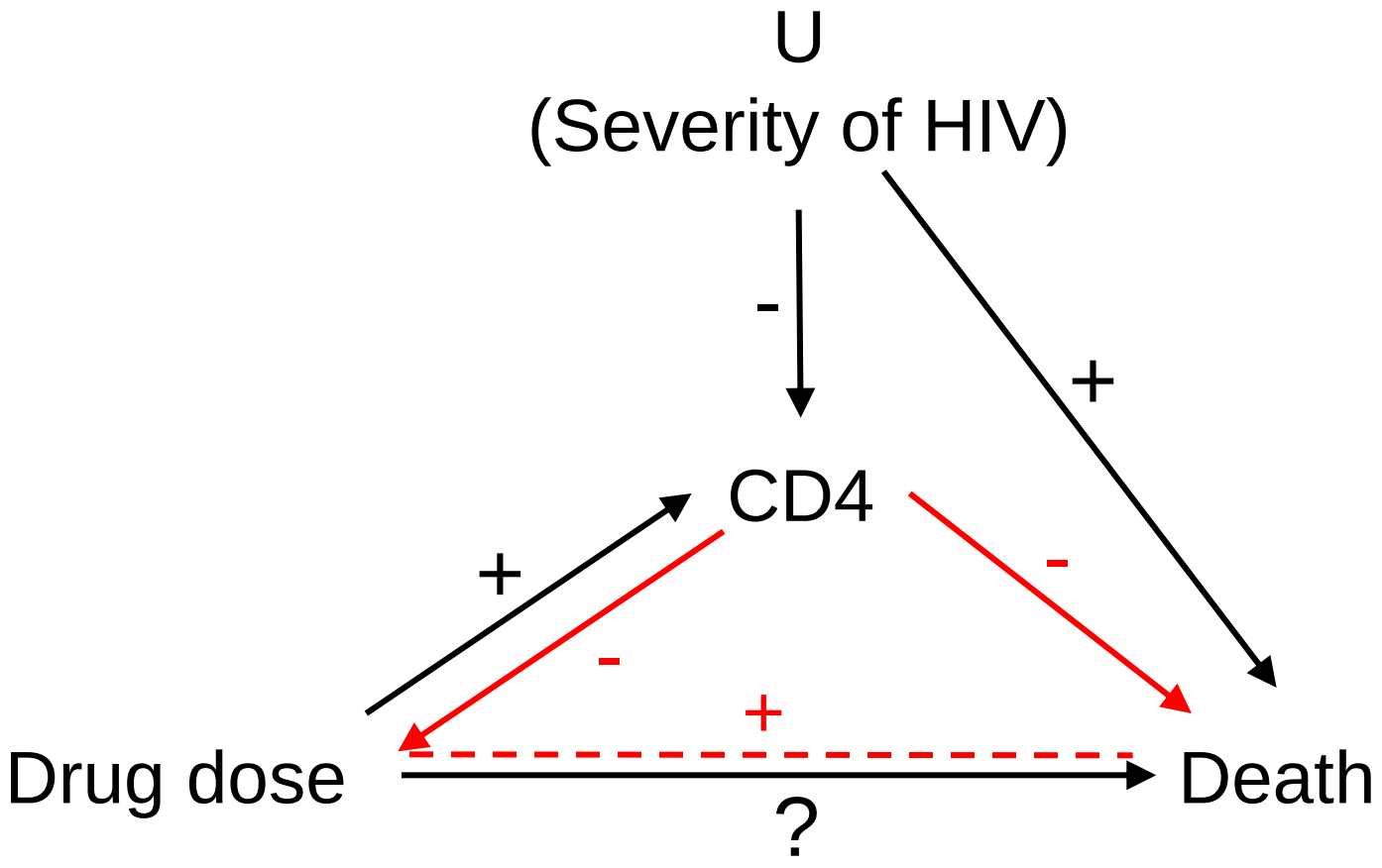
Example MACS



Example MACS

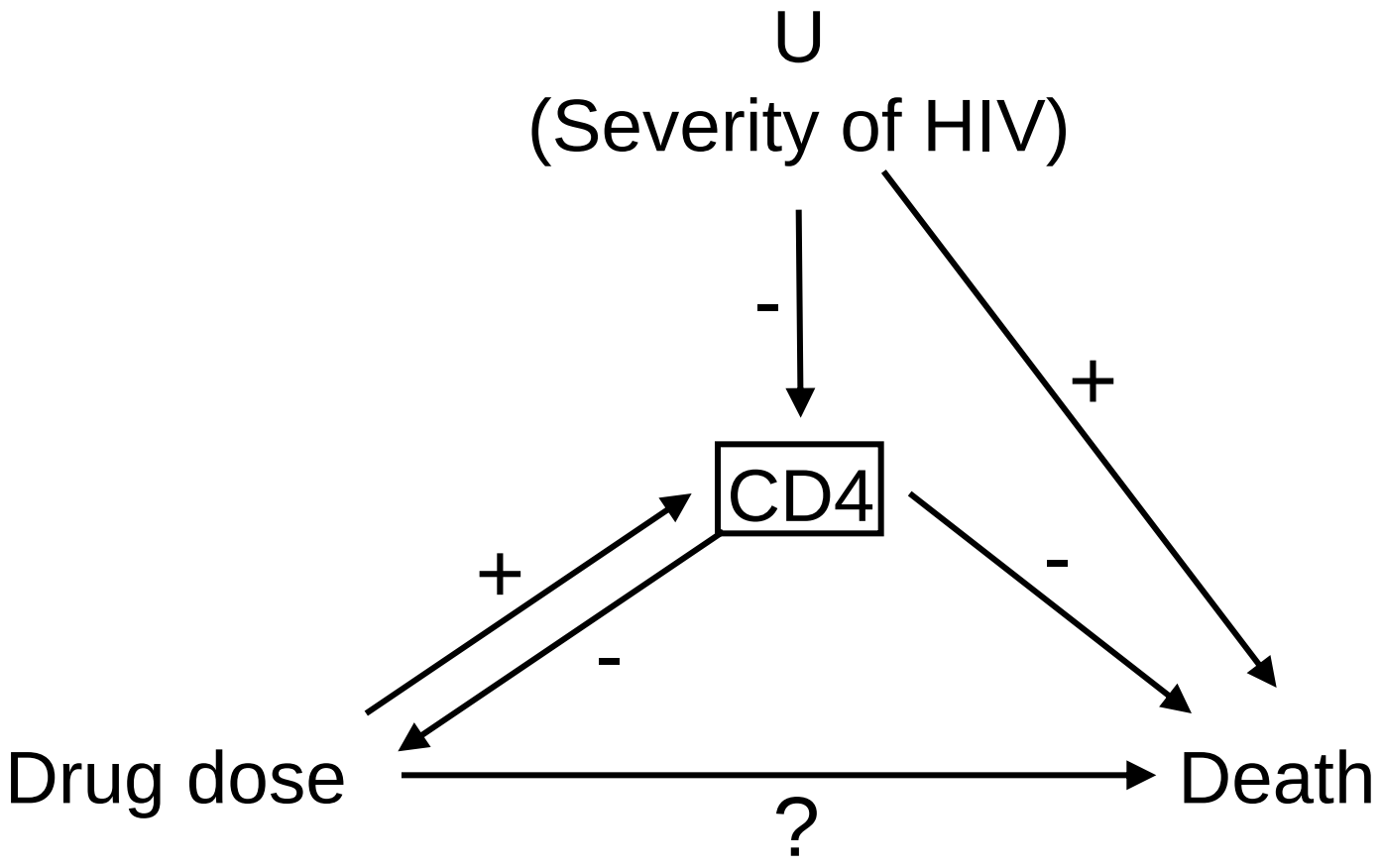


Example MACS

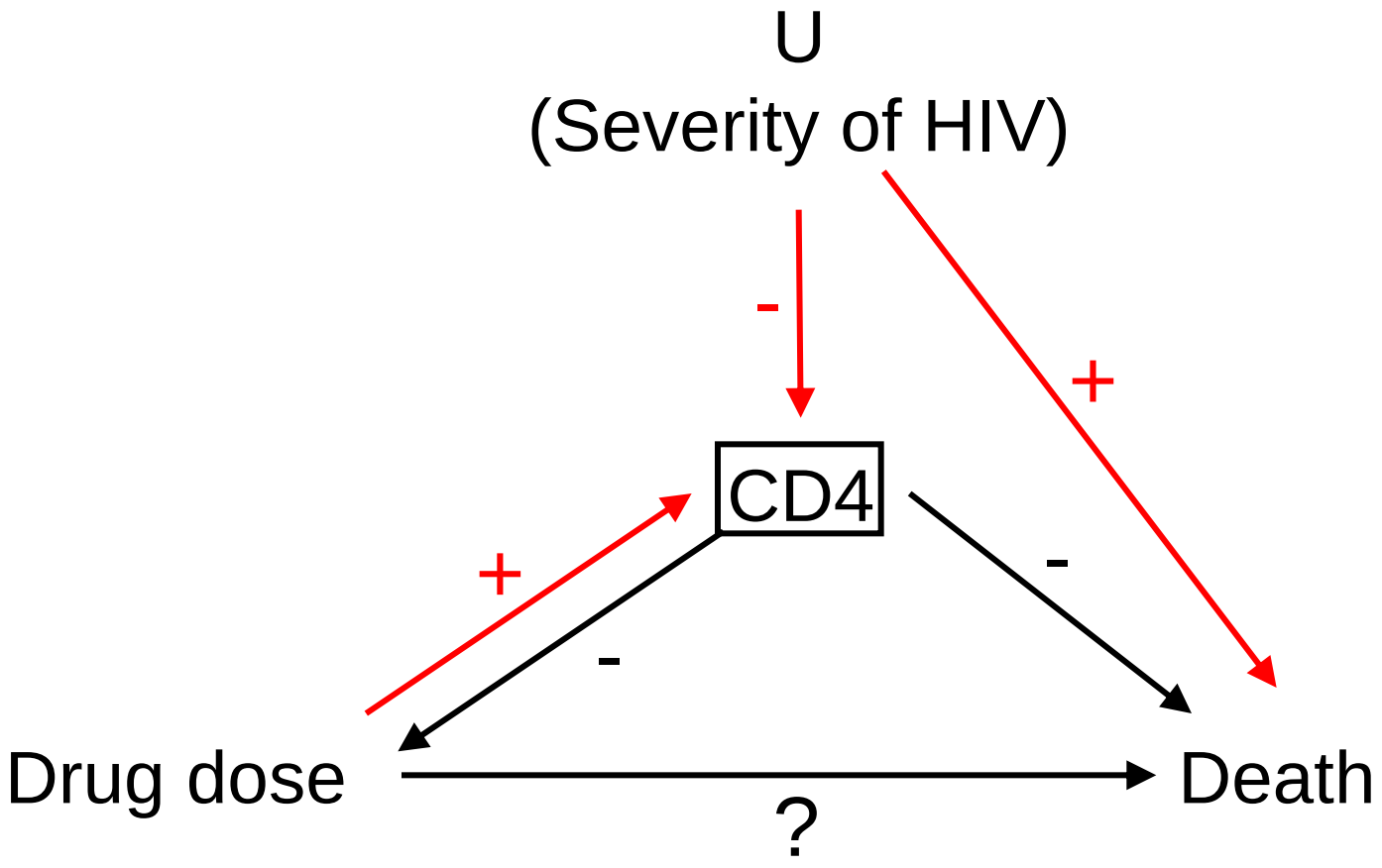


RR(not adjusted for CD4) = 3.6 ($p<0.05$) $\rightarrow$ biased

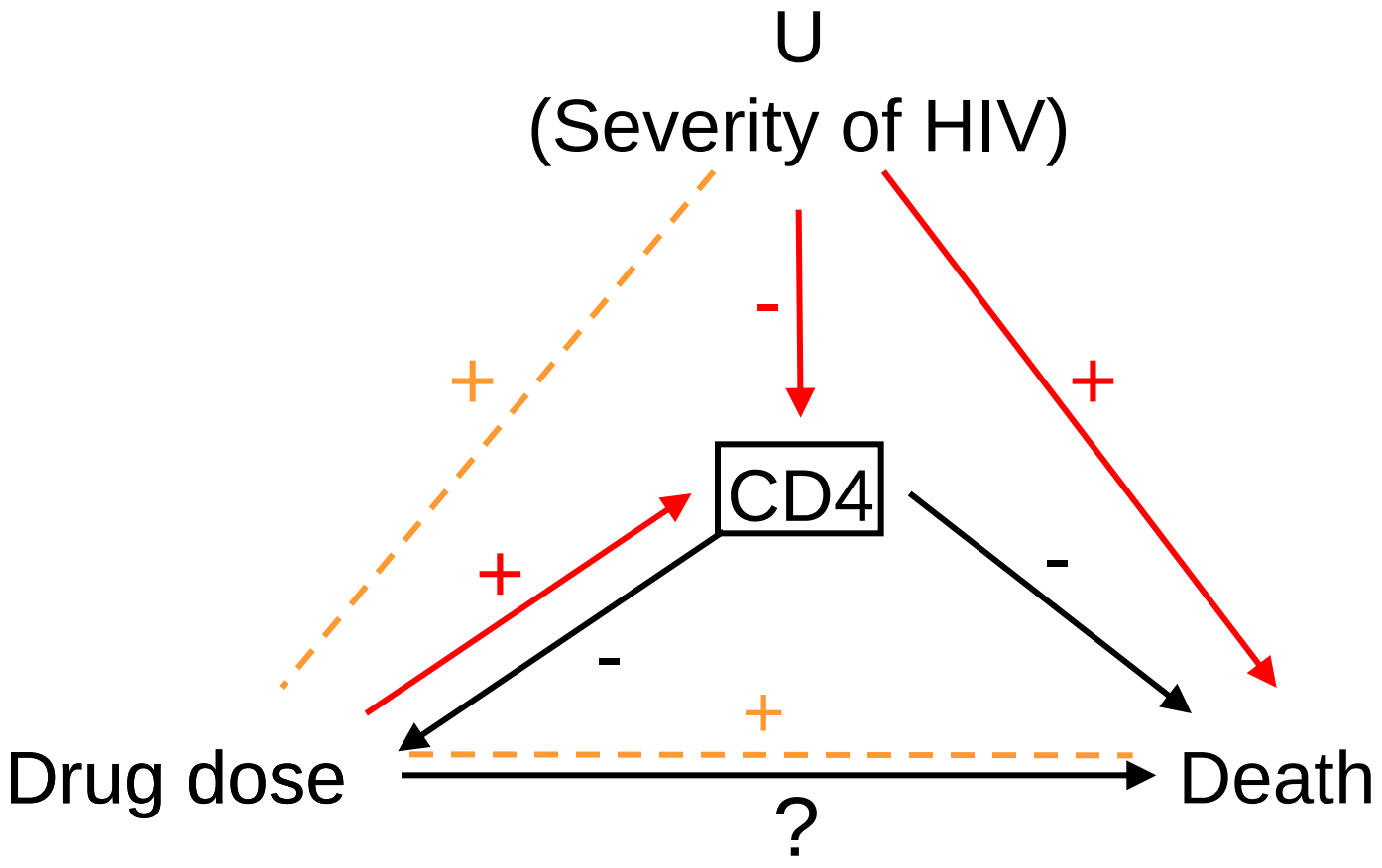
Example MACS



Example MACS



Example MACS



RR(adjusted for CD4) = 2.3 (p<0.05) → biased

Example MACS

Analysis (high vs. low dose drug)	RR	Sign.
Not adjusted for CD4	3.6	p<0.05
Adjusted for CD4	2.3	p<0.05
Causal effect estimate	*?*	*?*

Data from Hernan MA, Brumback B, Robins JM. Epidemiology 2000

Example MACS

Analysis (high vs. low dose drug)	RR	Sign.
Not adjusted for CD4	3.6	p<0.05
Adjusted for CD4	2.3	p<0.05
Marginal structural model (adjusting for time-dependent CD4)	0.7	p<0.05

Data from Hernan MA, Brumback B, Robins JM. Epidemiology 2000

Example HIV Treatment

Hernan MA. Brumback B. Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology. 11(5):561-70, 2000

Abstract:

Standard methods for survival analysis, such as the time-dependent Cox model, may produce biased effect estimates when there exist time-dependent confounders that are themselves affected by previous treatment or exposure. Marginal structural models are a new class of causal models the parameters of which are estimated through inverse-probability-of-treatment weighting; these models allow for appropriate adjustment for confounding. We describe the marginal structural Cox proportional hazards model and use it to estimate the causal effect of zidovudine on the survival of human immunodeficiency virus-positive men participating in the Multicenter AIDS Cohort Study. In this study, CD4 lymphocyte count is both a time-dependent confounder of the causal effect of zidovudine on survival and is affected by past zidovudine treatment. The crude mortality rate ratio (95% confidence interval) for zidovudine was 3.6 (3.0-4.3), which reflects the presence of confounding. After controlling for baseline CD4 count and other baseline covariates using standard methods, the mortality rate ratio decreased to 2.3 (1.9-2.8). Using a marginal structural Cox model to control further for time-dependent confounding due to CD4 count and other time-dependent covariates, the mortality rate ratio was 0.7 (95% conservative confidence interval = 0.6-1.0). We compare marginal structural models with previously proposed causal methods.

Another Example in HIV Treatment

Multicenter AIDS Cohort Study and Women's Interagency HIV Study

Example

- Intervention: HAART vs. No HAART
- Outcome: AIDS or death
- Study design: Observational study

TABLE 3. Estimated effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death for 1,498 human immunodeficiency virus-positive US men and women, 1995–2002

Model and HAART* use	No. of events	Person-years of follow-up	HR*	95% CI*
Unadjusted				
No HAART	238	3,581	1	
HAART	144	3,182	0.98	0.76, 1.26
Adjusted†			0.81	0.61, 1.07
Weighted†				
No HAART	246	3,586	1	
HAART	125	3,124	0.54	0.38, 0.78‡

* HAART, highly active antiretroviral therapy; HR, hazard ratio; CI, confidence interval.

† Both the adjusted standard model and the weighted marginal structural model accounted for the same set of covariates, namely age, gender, race, calendar year at entry, and baseline CD4 and RNA categories, as well as time-varying CD4 count, RNA level, symptoms related to human immunodeficiency virus, antiretroviral therapy, *Pneumocystis carinii* pneumonia prophylaxis, and number of days since the prior visit. The time-varying covariates were included as regressors in the adjusted standard model only.

‡ Robust 95% confidence interval.

Data from Cole et al. Am J Epidemiol 2003

*Time-Varying Confounding: Inverse-Probability of Treatment Weighting

ORIGINAL ARTICLE

Observational Studies Analyzed Like Randomized Experiments

An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease

Miguel A. Hernán,[a,b] *Alvaro Alonso,*[c] *Roger Logan,*[a] *Francine Grodstein,*[a,d] *Karin B. Michels,*[a,d,e] *Walter C. Willett,*[a,d,f] *JoAnn E. Manson,*[a,d,g] *and James M. Robins*[a,h]

Background: The Women's Health Initiative randomized trial found greater coronary heart disease (CHD) risk in women assigned to estrogen/progestin therapy than in those assigned to placebo. Observational studies had previously suggested reduced CHD risk in hormone users.

Methods: Using data from the observational Nurses' Health Study, we emulated the design and intention-to-treat (ITT) analysis of the randomized trial. The observational study was conceptualized as a sequence of "trials," in which eligible women were classified as initiators or noninitiators of estrogen/progestin therapy.

Results: The ITT hazard ratios (HRs) (95% confidence intervals) of CHD for initiators versus noninitiators were 1.42 (0.92–2.20) for the first 2 years, and 0.96 (0.78–1.18) for the entire follow-up. The ITT HRs were 0.84 (0.61–1.14) in women within 10 years of menopause, also present comparisons between these estimates and previously reported Nurses' Health Study estimates.

Conclusions: Our findings suggest that the discrepancies between the Women's Health Initiative and Nurses' Health Study ITT estimates could be largely explained by differences in the distribution of time since menopause and length of follow-up.

(*Epidemiology* 2008;19: 766–779)

Causal inferences are drawn from both randomized experiments and observational studies. When estimates from both types of studies are available, it is reassuring to find that

Hernán et al., Epidemiology, Nov. 2008

ISPOR RDB Analysis Task Force

Volume ** • Number ** • **
VALUE IN HEALTH

Good Research Practices for Comparative Effectiveness Research: Approaches to Mitigate Bias and Confounding in the Design of Nonrandomized Studies of Treatment Effects Using Secondary Data Sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part II

Emily Cox, PhD,[1] Bradley C. Martin, PharmD, PhD,[2] Tjeerd Van Staa, PhD, MD, MSc, MA,[3] Edeltraut Garbe, MD, PhD,[4] Uwe Siebert, MD, MPH, MSc, ScD,[5] Michael L. Johnson, PhD[6]

[1]Express Scripts, St. Louis, MO, USA; [2]Division of Pharmaceutical Evaluation and Policy, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [3]General Practice Research Database, London, UK; [4]Department of Clinical Epidemiology, Bremen Institute for Prevention Research and Social Medicine, Bremen, Germany; [5]Department of Public Health, Medical Decision Making and Health Technology Assessment, University of Health Sciences, Medical Informatics and Technology, Hall, Austria; Adjunct Professor of Public Health Policy and Management, Harvard University, Cambridge, MA, USA; [6]University of Houston, College of Pharmacy, Department of Clinical Sciences and Administration, Houston, TX, USA; Senior Scientist, Houston Center for Quality of Care and Utilization Studies, Department of Veteran Affairs, Michael E. DeBakey VA Medical Center, Houston, TX, USA

Cox et al., Value in Health 2009

Time-Depending Confounding

Traditional textbook techniques to control for time-independent confounding include restriction, stratification, matching, or multivariate regression analysis. However, these methods have been criticized for being inadequate to control for time-dependent confounding. Other methods such as g-computation, marginal structural models, or structural nested models have been suggested as approaches to this problem.

Cox et al., Value in Health 2009

Conclusions

- In “real-life” observational data evaluation, need to start analysis with a causal graph!
- Controlling for time-varying confounding
  - necessary in observational studies on treatment
  - necessary in risk factor intervention studies
  - provides “real” effect size even in RCTs (control for compliance)
  - usually requires longitudinal data and causal models
- Traditional adjustment methods (stratification, multivariate regression) may fail to control for time-dependent confounding

Challenges

- Causal methods are not yet covered in all epi textbooks, but first Macros (STATA) available
- Data analysis requires an epidemiologist familiar with causal methods
- HTA: CAVE meta-analysis of observational studies (control for confounding: yes/no/correct?)
- Decision modeling: CAVE modeling: are model inputs for intervened-on variables causal?

Other Examples

- Control for time-varying confounding
  - Witteman JC et al. (1998). G-estimation of causal effects: **isolated systolic hypertension and cardiovascular death** in the Framingham Study. American Journal of Epidemiology, 148:390-401.
- Control for confounding by indication
  - Cole SR et al. (2003). Effect of **highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death** using marginal structural models. Am J Epidemiol 2003;158(7):687-94.
- Multiple Interventions
  - Robins JM, Hernan M, Siebert U. (2004) **Effects of Multiple Interventions**. In: Ezzati M, Lopez AD, Murray CJL, eds. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors Vol I. Geneva: Worl Health Organization;2199-2238.
- Adjust for non-complicance in RCTs
  - Robins JM, Rotnitzky A. (2004). Estimation of treatment effects in **randomised trials with non-compliance** and a dichotomous outcome using structural mean models. Biometrika 91: 763-783.

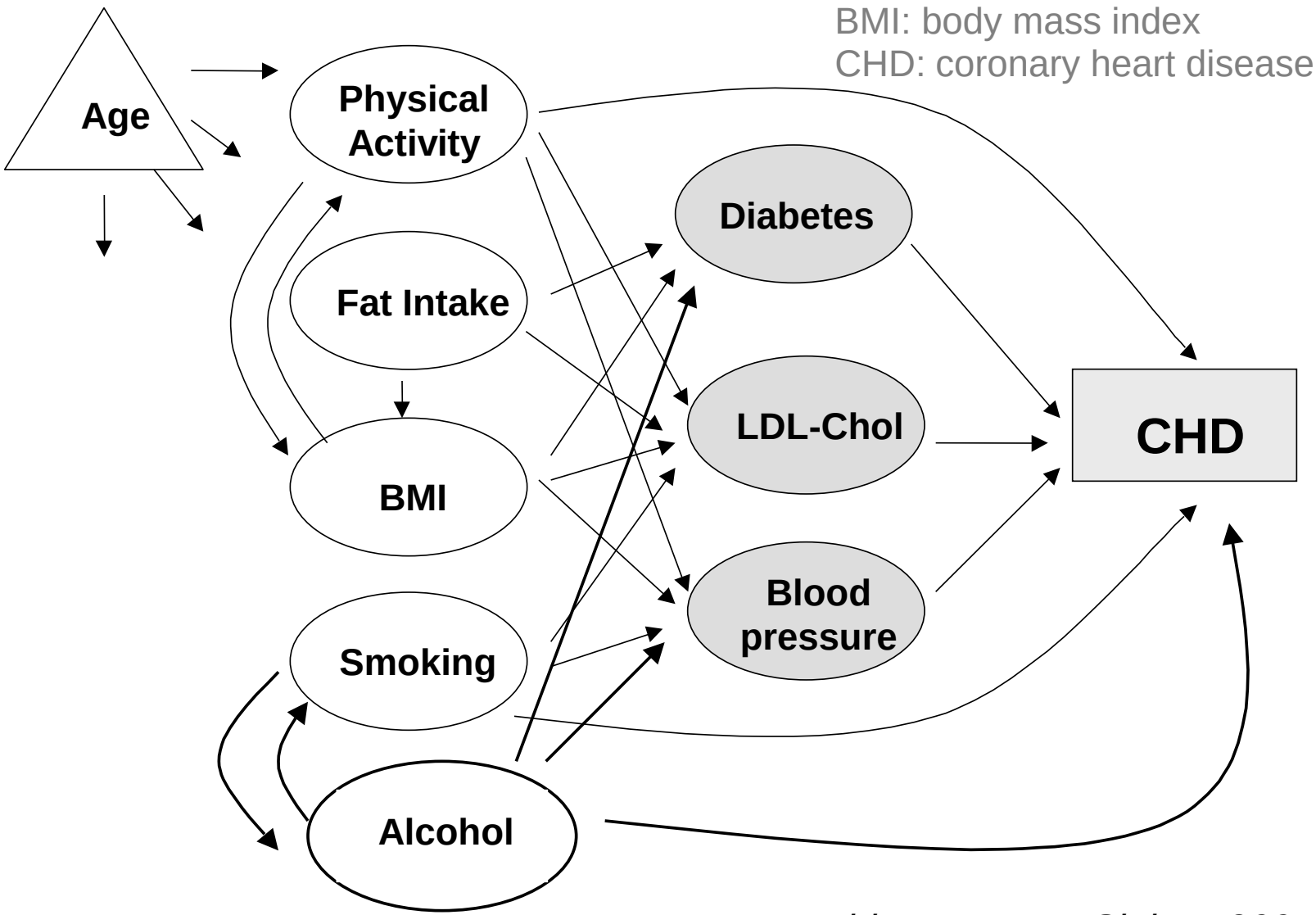
Other Examples

- Adjust for confounding after RCT becomes open label
  - Cook NR et al. (2002). Use of a marginal structural model to determine the **effect of aspirin on cardiovascular mortality** in the Physicians' Health Study. Am J Epidemiol;155(11):1045-53.
- Adjust for different second-line treatments
  - Yamaguchi T, Ohashi Y. (2004). Adjusting for **differential proportions of second-line treatment** in cancer clinical trials. Part I: structural nested models and marginal structural models to test and estimate treatment arm effects. Stat Med;23(13):1991-2003.
- Compare results from RCT and observational studies
  - Hernan MA et al. (2008). Observational studies analyzed like randomized experiments: an application to **postmenopausal hormone therapy and coronary heart disease**. Epidemiology;19(6):766-79.
- ITT analysis
  - van der Laan MJ et al. (2007). Causal Effect Models for Realistic Individualized Treatment and **Intention to Treat Rules**. The International Journal of Biostatistics 2007;3(1):1-52.

APPENDIX

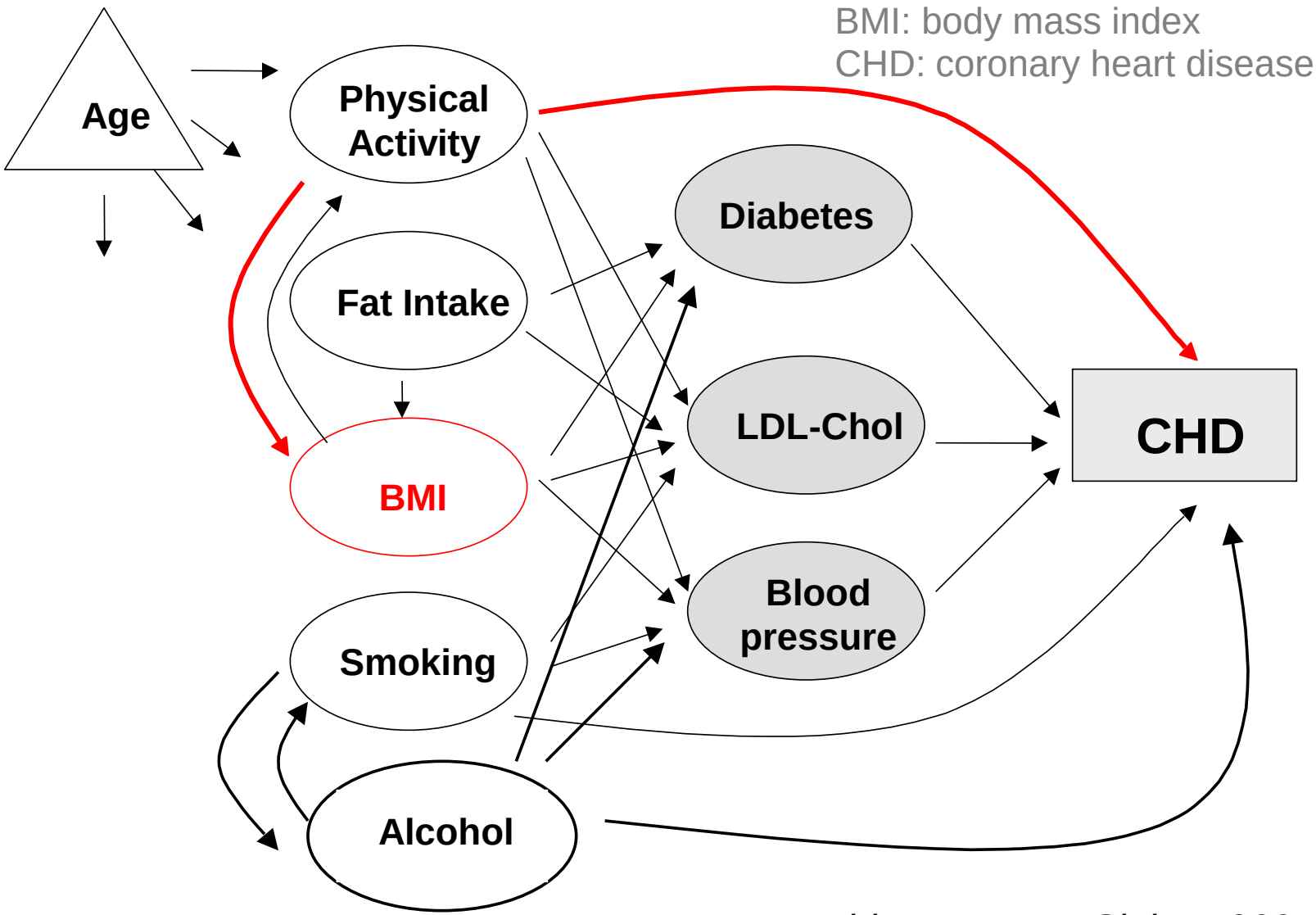
Risk Factor Interventions

Example: WHO-Project "Causal CHD Web"



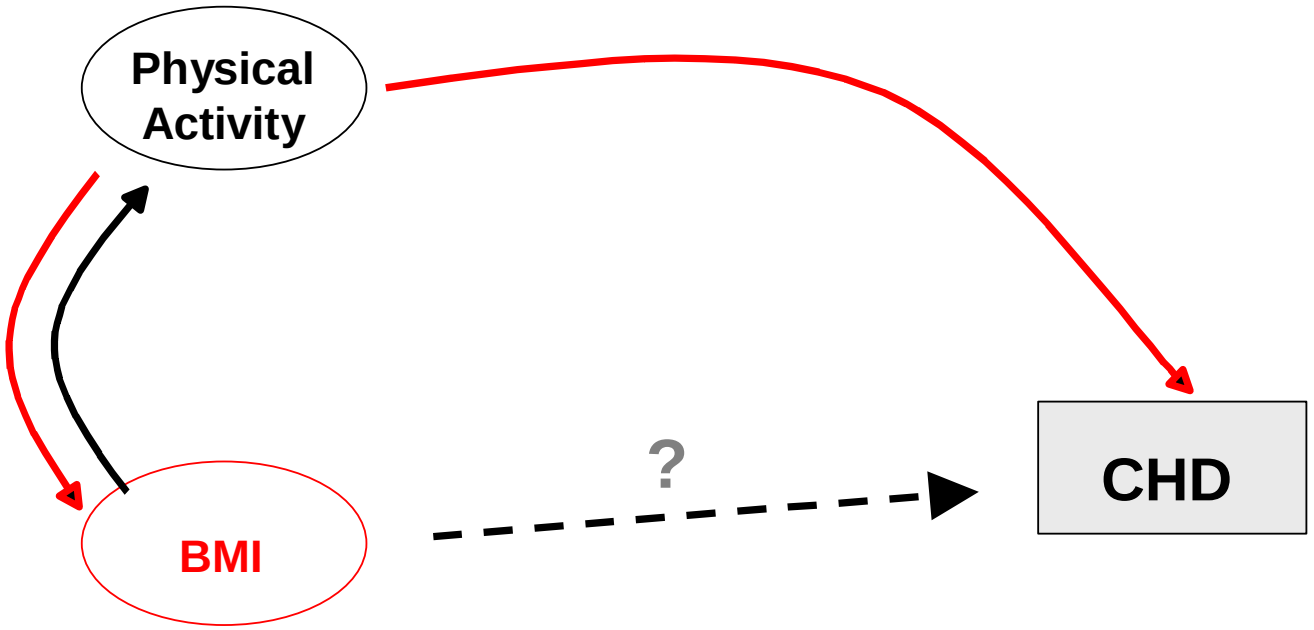
Robins, Hernan, Siebert 2005#

Example: WHO-Project "Causal CHD Web"

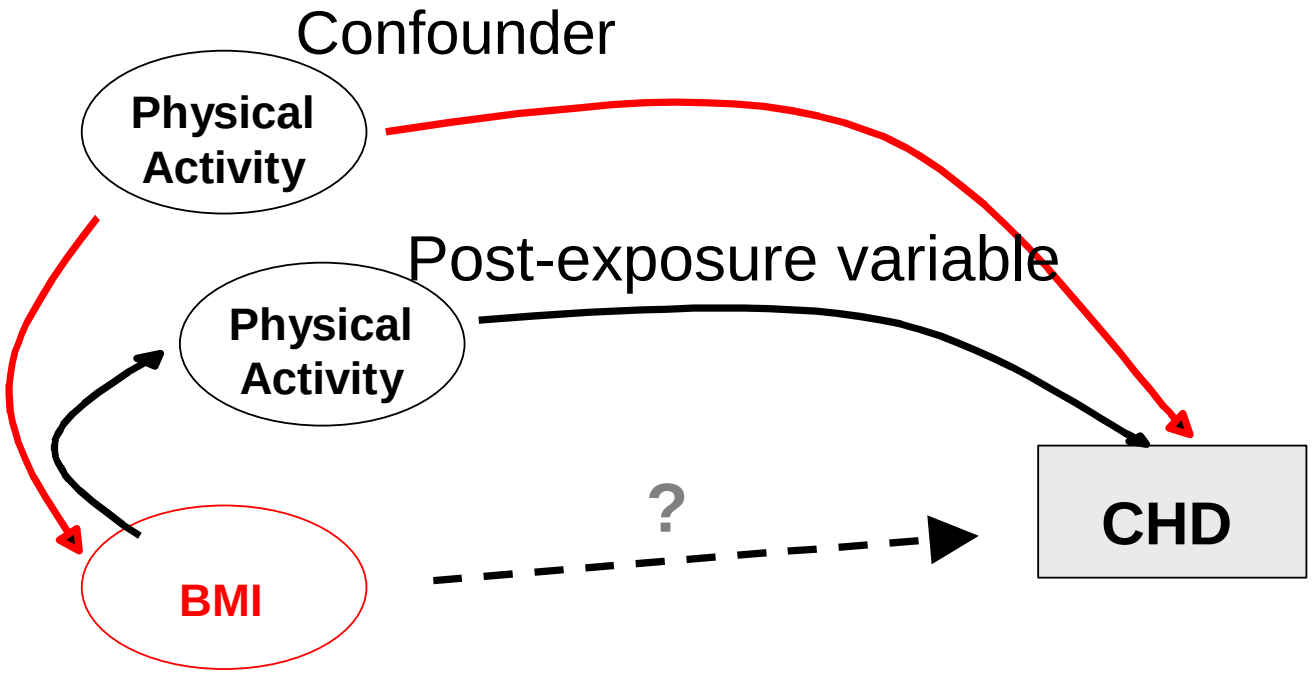


Robins, Hernan, Siebert 2005#

Causal diagram CHD



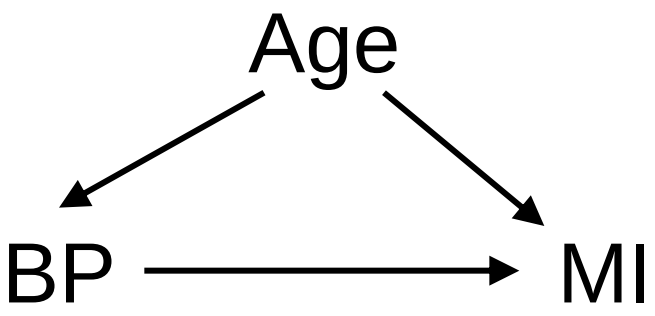
Causal diagram CHD



"Causal models": (epidemiologic) models adjusting for variables that simultaneously act as confounders and intermediate steps:

1) Nonparametric g-formula
2) Parametric g-formula
3) g-estimation
4) Marginal structural models

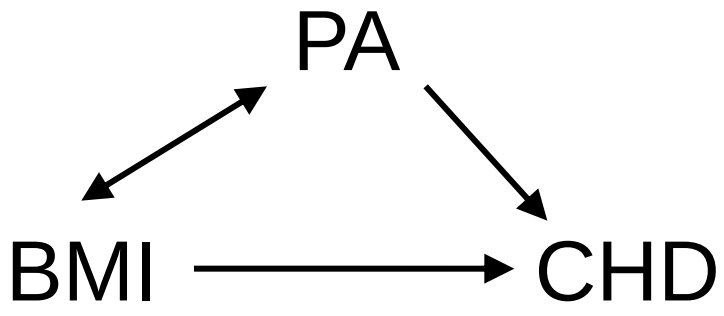
Confounding



Confounding

Age is a common cause of BP and MI

Traditional stratification or regression analysis works



Time-dependent confounding

PA is a common cause of BMI and CHD and is also affected by BMI

Traditional stratification or regression analysis fails

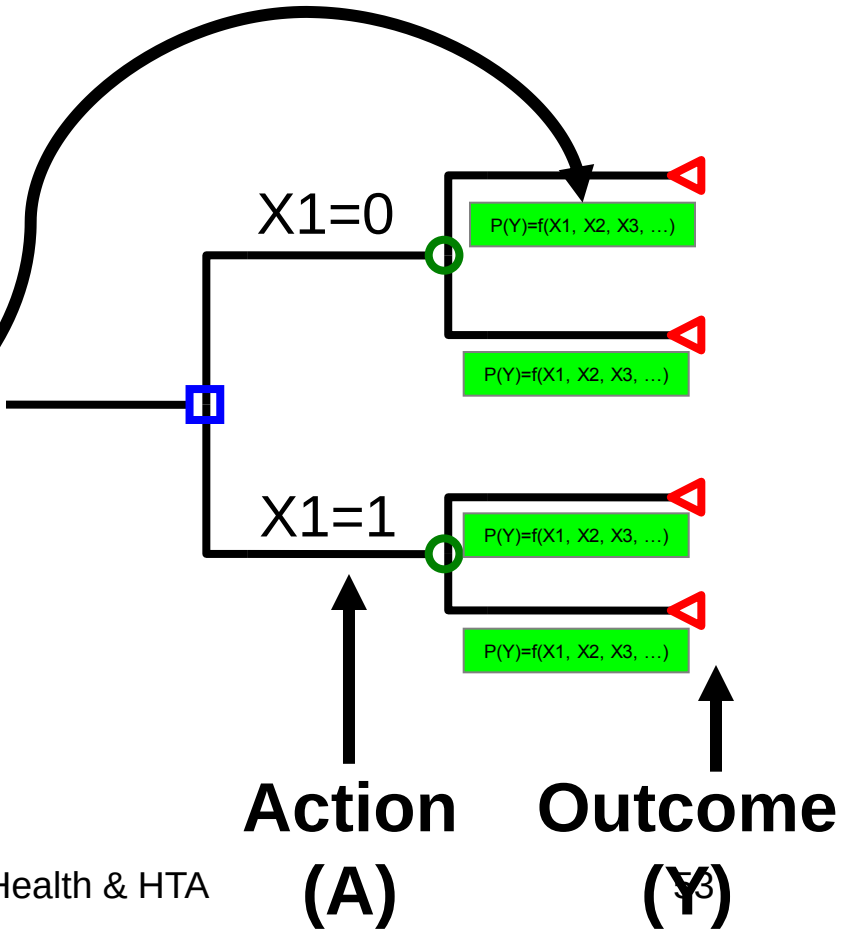
Cave Decision Analysts!

Effect Estimation and Decision Analysis

Observational Dataset

Statistical analysis

P(Y)=f(X1, X2, X3, …)



Examples:

- Framingham risk function
- Prediction functions in diabetes II
- Osteoporose risk function

…

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