Translational Clinical Oncology
Pharmacometrics

Causal diagrams for understanding when correlations doesn't imply causation

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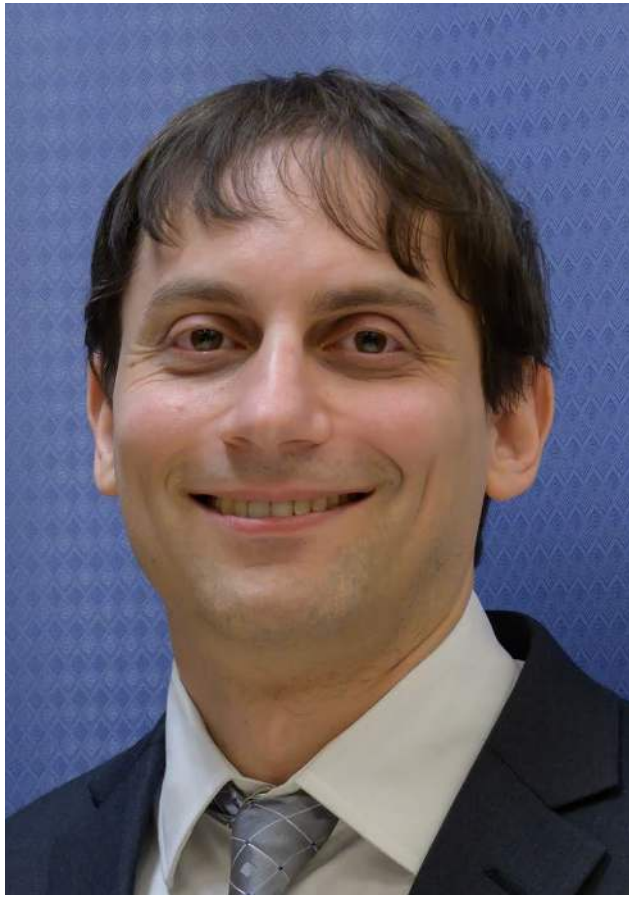
Who am I? Andy Stein

- **Group:** Pharmacometrics
- **What I do:**
  - Support quantitative analysis of early clinical trials, with a focus on identifying the right dose.
- **My background:**
  - Mechanical Engineering and Applied Mathematics
- **My passion:**
  - Learning and bringing insights from other fields into drug development and vice versa (environmental modeling, managing uncertainty, parenting)



Motivation – the importance of finding the right dose of a drug

- Tylenol helps to reduce pain and fever and is safe at daily doses ≤3,000 mg/day
- >5,000 mg/day can cause liver damage
- >10,000 mg/day can be lethal.
- You can learn about safety and efficacy from clinical trials
- Making best use of this data requires models to integrate the data

(paracetamol)

Johnson & Johnson

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Understanding which factors to control for (age) is critical

Pain & Fever

Children's TYLENOL® Oral Suspension

DOSE: Repeat every 4 hours as needed. Do NOT give more than 5 doses in 24 hours.
If possible, use weight to dose; otherwise, use age.

Use product only as directed.

ACTIVE INGREDIENT

Acetaminophen
160 mg (in each 5 mL)

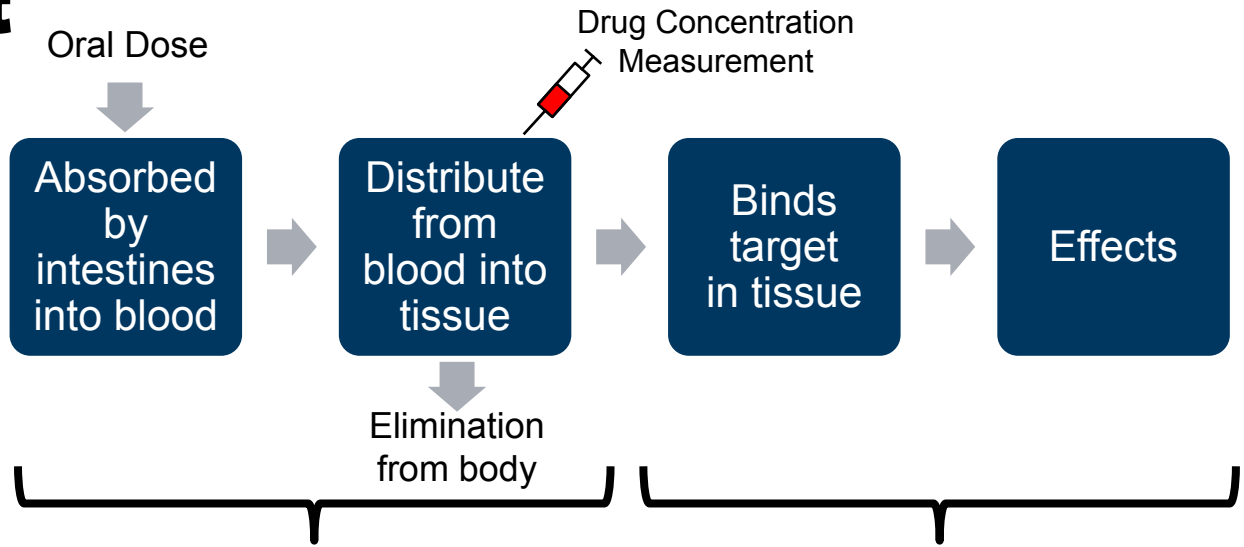
WEIGHT	AGE	DOSE
24-35 lbs	2-3 years	**5 mL** 
36-47 lbs	4-5 years	**7.5 mL** 
48-59 lbs	6-8 years	**10 mL** 
60-71 lbs	9-10 years	**12.5 mL** 
72-95 lbs	11 years	**15 mL** 

cine

Overview

- **Situation:**
  - We use models relating drug concentration to response to guide drug development.
  - Models are useful when they describe a **causal** relationship
  - If relationships are only correlative relationship, they can lead to poor decisions
- **Question:** How to assess whether a relationship is causal or just correlative?
- **Answer:** Causal diagrams can help identify confounders
- **Outline**
  - Introduce PKPD concepts and exposure-response modeling
  - Present two examples of exposure-response confounding
  - Introduce causal diagrams and their key structures
  - Conclude with COVID-19 example

The “PKPD” pathway of drug effect



Pharmacokinetics (PK):
How body affects drug

Should children and adults receive the same dose?

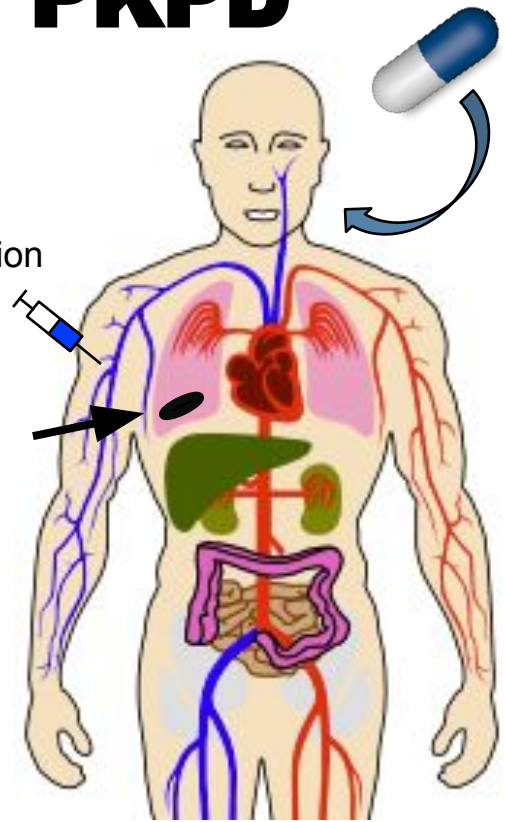
Pharmacodynamics (PD):
How drug affects body

What dose is needed to shrink a tumor without causing severe neutropenia

Measuring PKPD

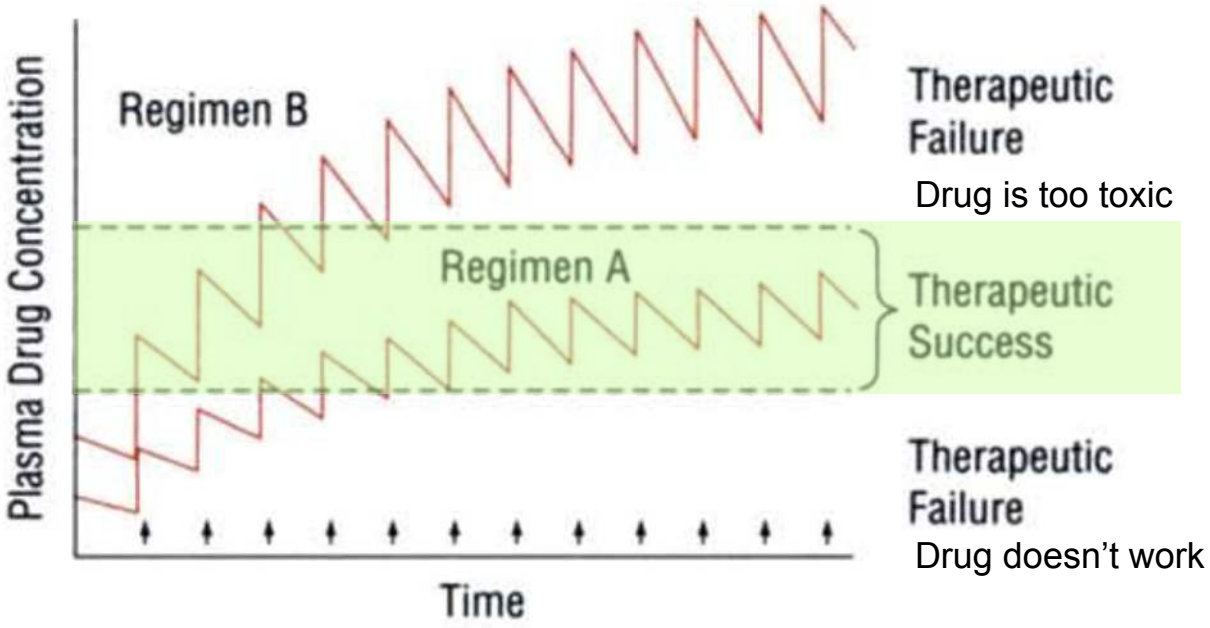
PK (Pharmacokinetics) example
Measurement of drug concentration from circulation

PD (Pharmacodynamics) example
Change in tumor size, as measured by X-Ray



Dose Regimen
- amount given
- frequency
- method (oral, patch, etc.)

Understanding PKPD can help in picking the optimal dose regimen

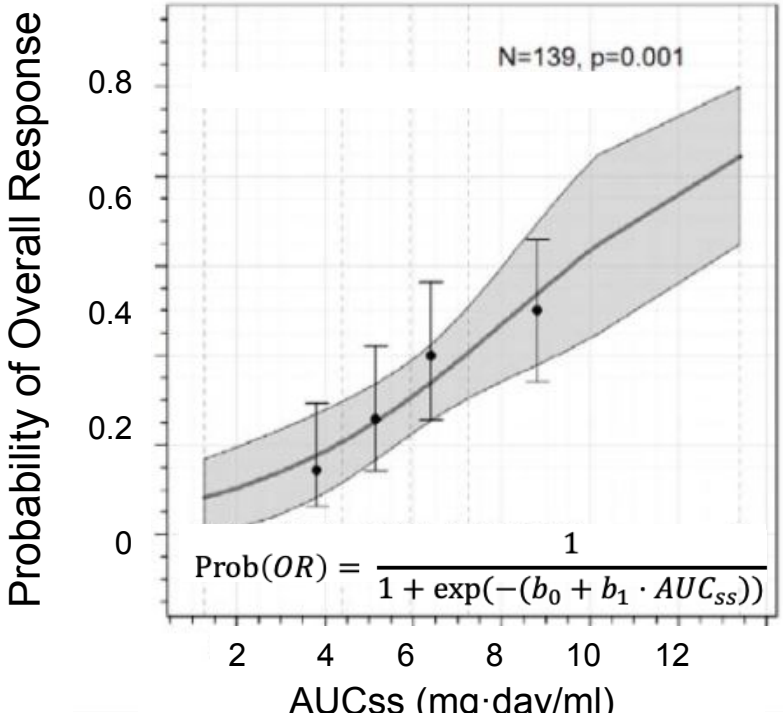


From Rowland and Tozer

Novartis was developing a PD-L1 Inhibitor. Other PD-L1 drugs on the market

- Atezolizumab dosed at 1200 mg q3w
- Our drug had similar properties to atezolizumab
- Is 1200 mg q3w the right dose for us?

Higher exposure of atezolizumab correlates with better response[1]



From Feb 2016 FDA Clin. Pharm. Review

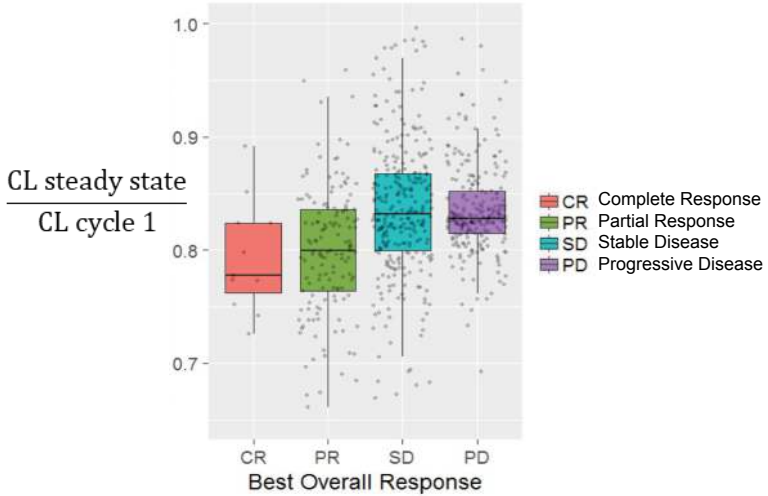
Atezolizumab, 1200 mg q3w

Only one dose tested

2nd Line Non Small Cell Lung Cancer (NSCLC)

Clearance decreases (and exposure increases) with improved response [1-2]

Atezolizumab in NSCLC
(observed for most PD-1, PD-L1 inhibitors)



$$AUC_{ss} = \frac{Dose}{CL \cdot \tau}$$

CL = clearance
τ = dosing interval
Lower clearance → Higher AUC

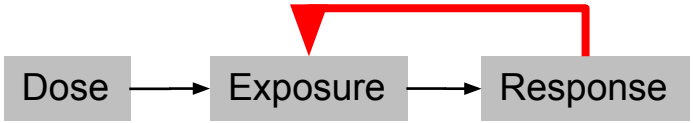
Cachexia in non-responders might lead to faster clearance of drug[3]

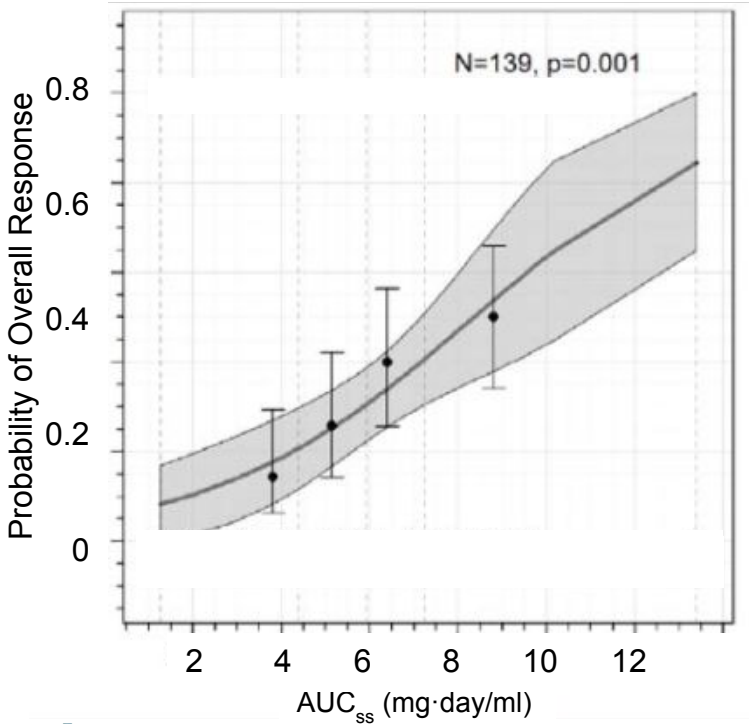
1. Liu, Chao, et al. "Association of Time-Varying Clearance of Nivolumab With Disease Dynamics and Its Implications on Exposure Response Analysis." *Clinical Pharmacology & Therapeutics* 101.5 (2017): 657-666.
2. FDA Clin Pharm Review for atezolizumab in NSCLC (2016)
3. Bajaj, G., et al. "Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors." *CPT: pharmacometrics & systems pharmacology* 6.1 (2017): 58-66.

Exposure drives response AND response drives exposure

Assumption

Reality
(sometimes)





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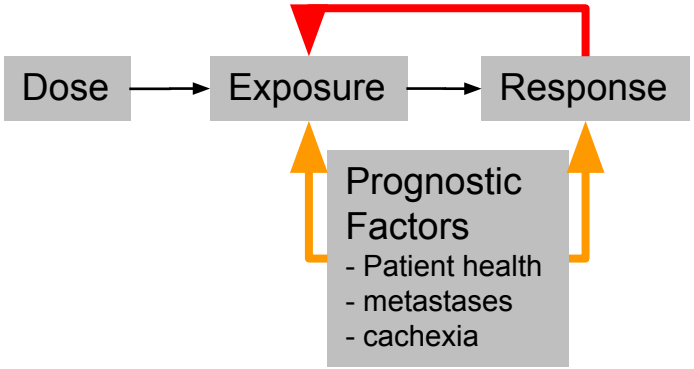
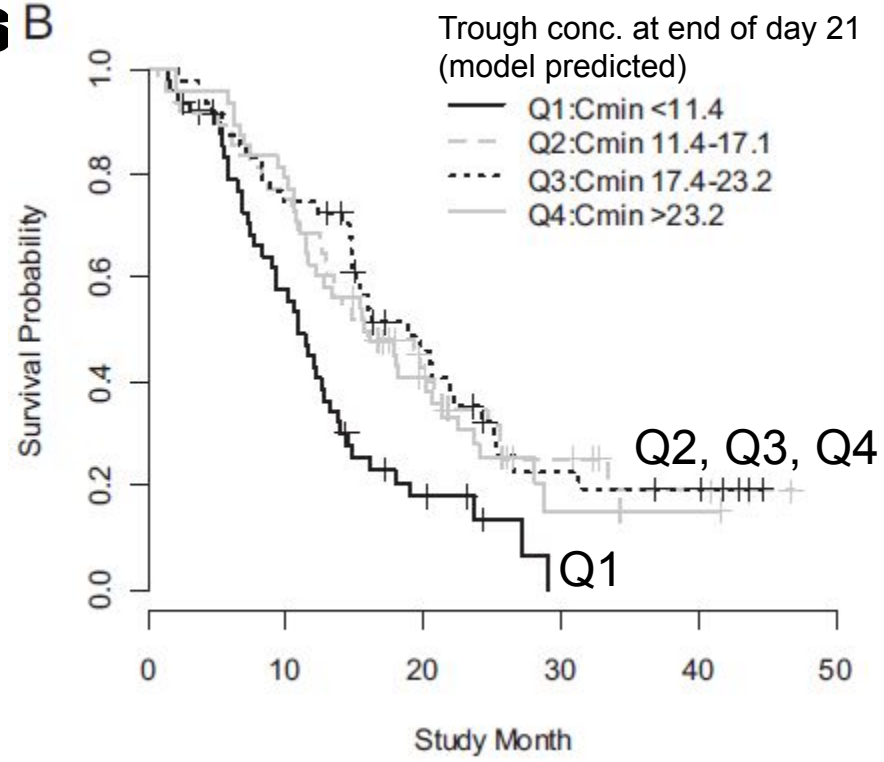
Prognostic factors may also confound the analysis

Assumption

Reality
(sometimes)



For trastuzumab in metastatic Gastric Cancer, exposure-OS relationship obs



1. Yang, Jun, et al. "The combination of exposure-response and case-control analyses in regulatory decision making." The Journal of Clinical Pharmacology 53.2 (2013): 160-166.

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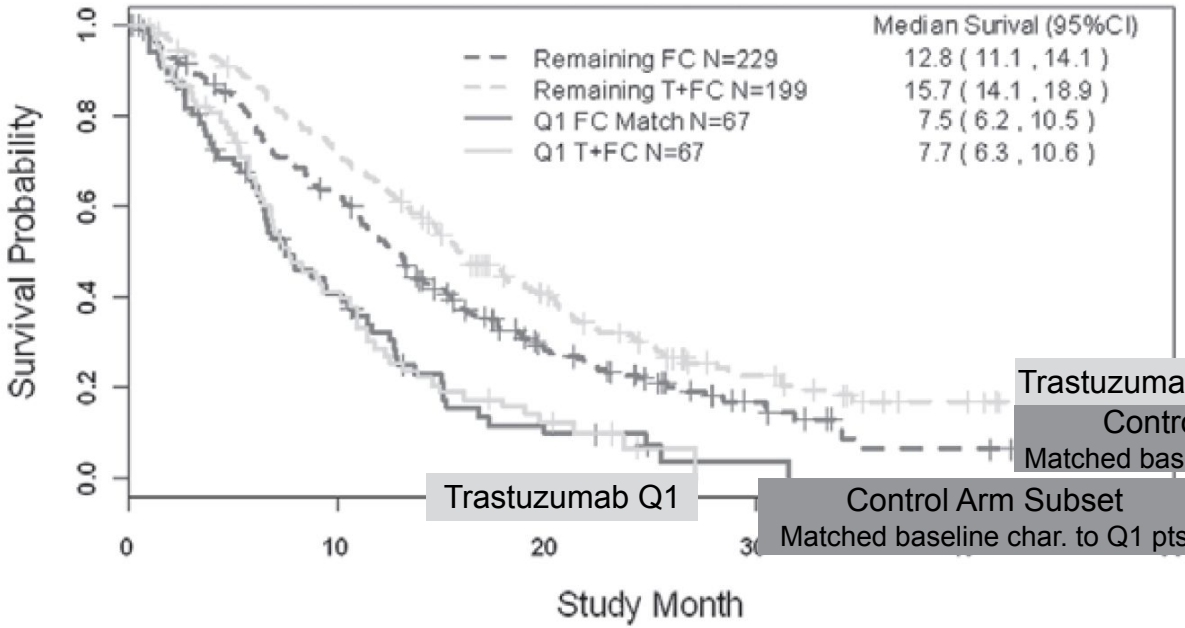
Poor response at Q1 exposure was due to prognostic factors affecting both exposure and response [1]



Key prognostic factors

- ECOG
- Prior gastrectomy
- # metastatic sites
- Asian ethnicity
- HER2 IHC score

1. Yang, Jun, et al. "The combination of exposure-response and case-control analyses in regulatory decision making." The Journal of Clinical Pharmacology 53.2 (2013): 160-166.

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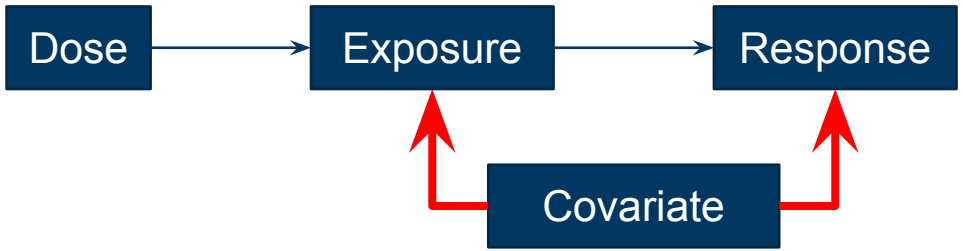
Draw a causal graph of the dose-exposure-biomarker-resp. relationship

Fork:

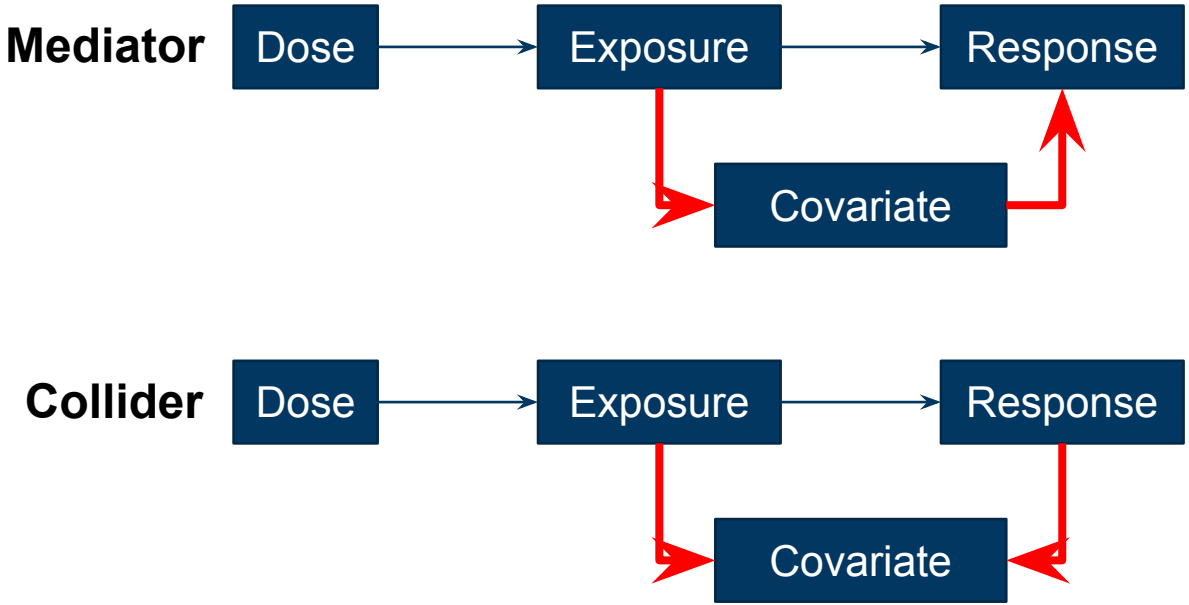
you must stratify by covariate, otherwise estimated E- relationship will not be causal



Simpson's Paradox:
https://en.wikipedia.org/wiki/Simpson%27s_paradox

Mediators and Colliders:

you must not stratify by covariate, otherwise E-R will be confounded [these are post-baseline covariates]



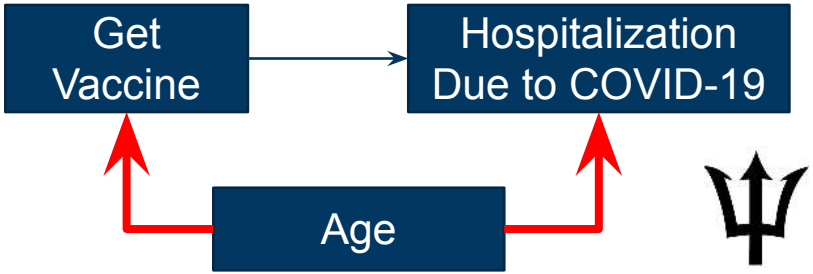
Feedback Loop:

You must think about the consequences of the feedback loop(s) and choose the appropriate analysis.

Using dose or exposure only at day 1 help avoid confounding.

1. https://arxiv.org/abs/1907.07271

COVID-19 example



Reason for confounding: Older people are both more likely to be vaccinated and more likely to be hospitalized, irrespective of vaccination.

1. https://www.covid-datascience.com/post/israeli-data-how-can-efficacy-vs-severe-disease-be-strong-when-60-of-hospitalized-are-vaccinated
Israel data with Pfizer Vaccine, August 2021

Age Group	Percent vaxxed	Severe Cases per 100k people		
		no vax	Vax	
All Ages	78%	16	5.3	68%
12-15	30%	0.30	<0.01*	>97%*
16-19	74%	1.6	<0.01*	>99%*
20-29	76%	1.5	<0.01*	>99%*
30-39	81%	6.2	0.20	97%
40-49	84%	17	1.0	94%
50-59	88%	40	2.9	93%
60-69	90%	77	8.7	89%
70-79	95%	190	20	89%
80-89	93%	250	48	81%
90+	91%	510	39	92%

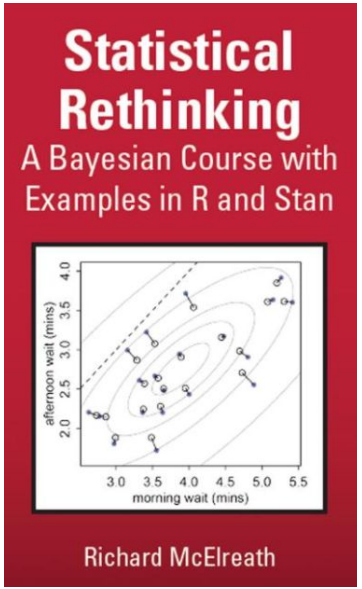
* Andy's guess for upper level of quantification

Drug development is challenging because biology is so complex

- Causal diagrams can help by identifying potentially confounding factors

Forks

Feedback Loops



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