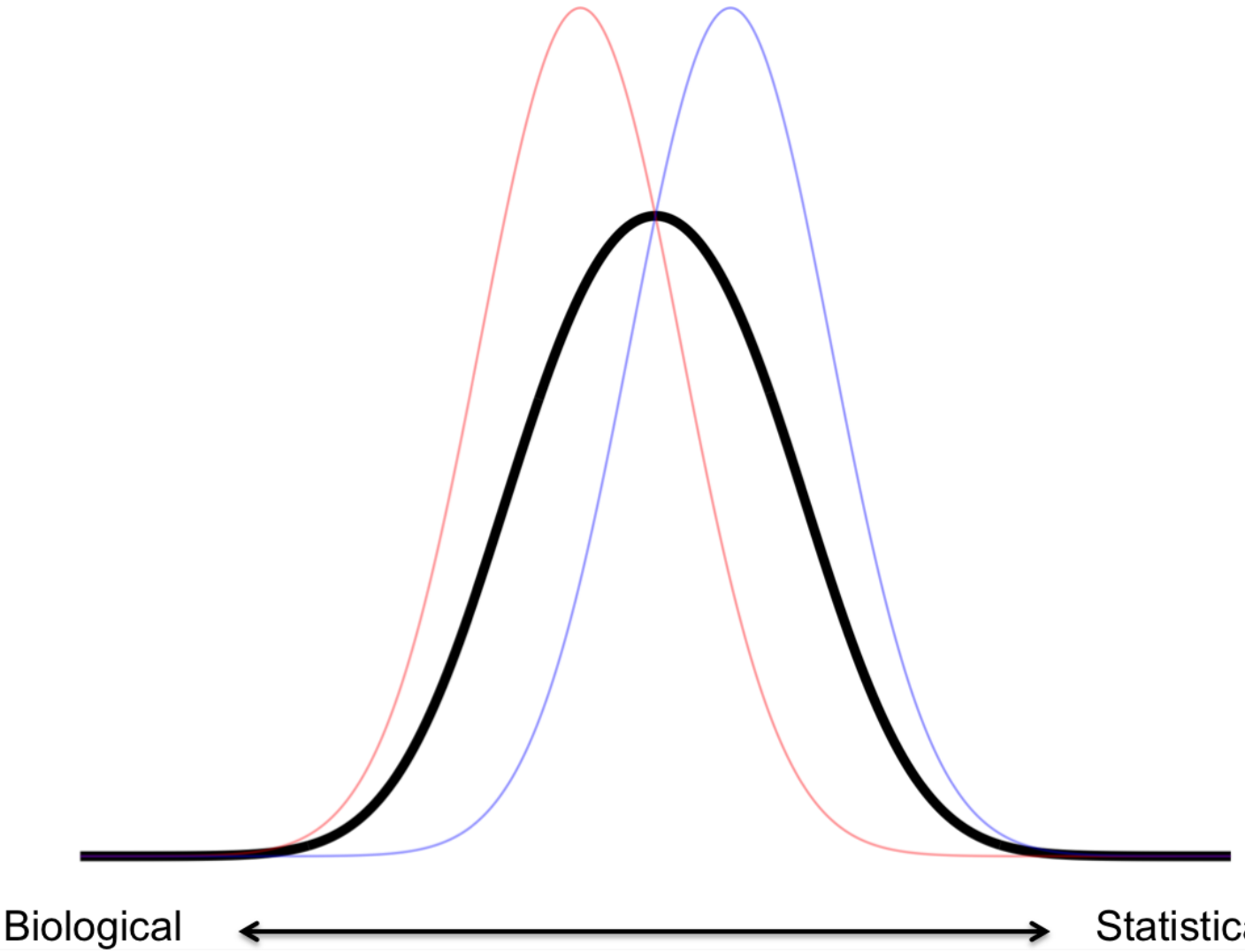
METRUM
RESEARCH GROUP

Causal models with pharmacometric applications

Jonathan L. French, ScD

Metrum Research Group LLC

October 24, 2016


Biological
Statistical

Why do we build models?

- To describe data
  - “To describe the relationship between Drug X exposure and response rate“
- To make predictions
  - New dosing, new populations, etc.
- For causal inference
  - “If we were to increase exposure in this population of patients, how would we expect the response rate to change? “
  - Mechanistic models are helpful, but we still need to account for potentially confounding variables

Causal inference in exposure-response has been a topic of interest lately . . .

The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

The Journal of Clinical Pharmacology
53(2) 160–166

DOI: 10.1177/0091270012445206

Jun Yang, PhD[1], Hong Zhao, PhD[1], Christine Garnett, PharmD[1], Atiqur Rahman, PhD[1], Jogarao V. Gobburu, PhD[1], William Pierce, PharmD[2], Genevieve Schechter, MD[2], Jeffery Summers, MD[2], Patricia Keegan, MD[2], Brian Booth, PhD[1], and Yaning Wang, PhD[1]

2012

Exposure–Response Relationship of T-DM1: Insight Into Dose Optimization for Patients With HER2-Positive Metastatic Breast Cancer

J Wang[1], P Song[1], S Schrieber[1], Q Liu[1], Q Xu[2], G Blumenthal[3], L Amiri Kordestani[3], P Cortazar[3], A Ibrahim[3], R Justice[3], Y Wang[1], S Tang[2], B Booth[1], N Mehrotra[1] and A Rahman[1]

2015

CCR Perspectives in Drug Approval

Clinical Cancer Research

FDA Approval Summary: Ramucirumab for Gastric Cancer

Sandra J. Casak[1], Ibilola Fashoyin-Aje[1], Steven J. Lemery[1], Lillian Zhang[2], Runyan Jin[2], Hongshan Li[2], Liang Zhao[2], Hong Zhao[2], Hui Zhang[3], Huanyu Chen[3], Kun He[3], Michele Dougherty[4], Rachel Novak[4], Sarah Kennett[4], Sachia Khasar[1], Whitney Helms[1], Patricia Keegan[1], and Richard Pazdur[3]

2015

But causal inference isn't a new topic . . .

Pitfalls in Retrospective Analysis in Search of Concentration-Effect Relationships

Carl Peck, Tom Ludden

Leiden University, The Netherlands, and CDER, FDA, USA

1994

Intention-to-treat analysis and the goals of clinical trials

Lewis B. Sheiner, MD, and Donald B. Rubin, PhD[a]

San Francisco, Calif. and Cambridge, Mass.

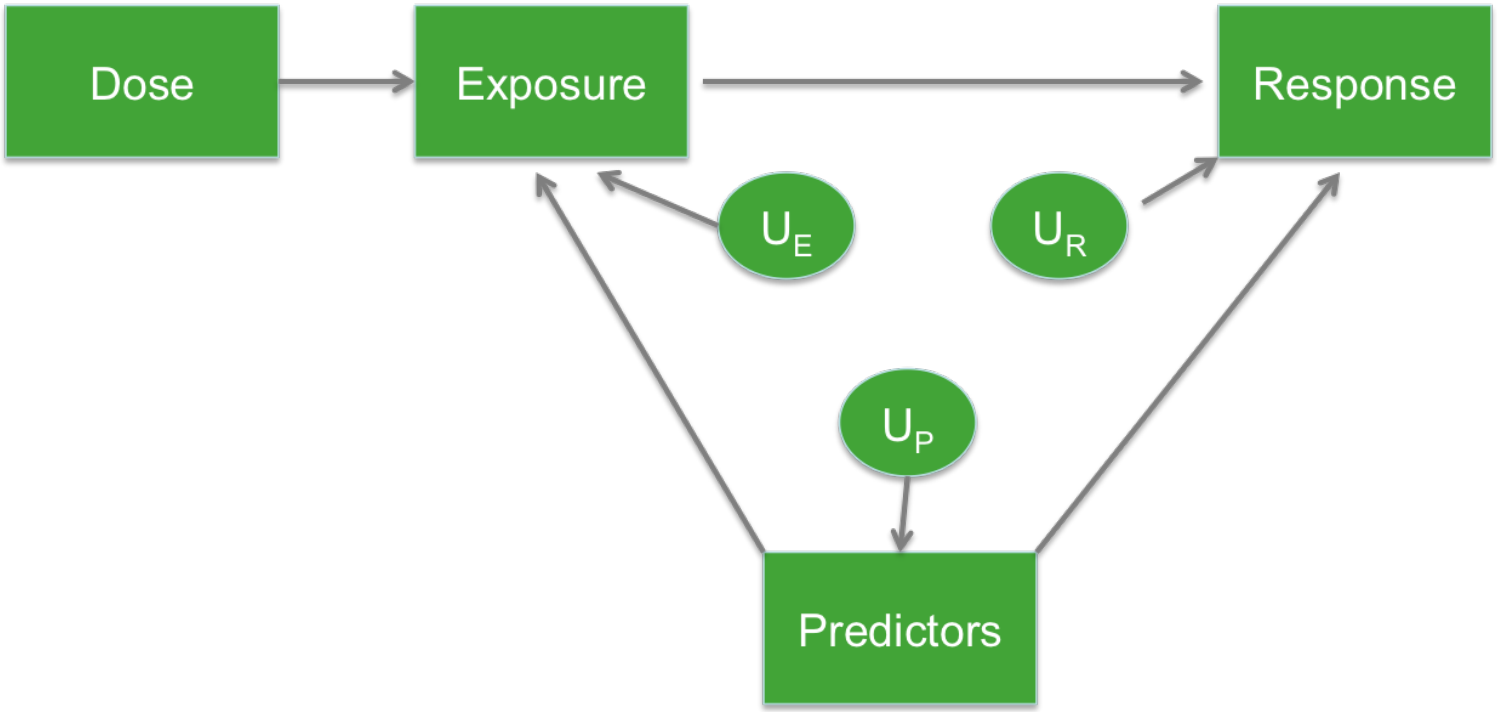
1995

Diagnostics for confounding in PK/PD models for oxcarbazepine

Jerry R. Nedelman[1,*,†], Donald B. Rubin[2] and Lewis B. Sheiner[3,✠]

2007

In all of those examples, exposure is an outcome

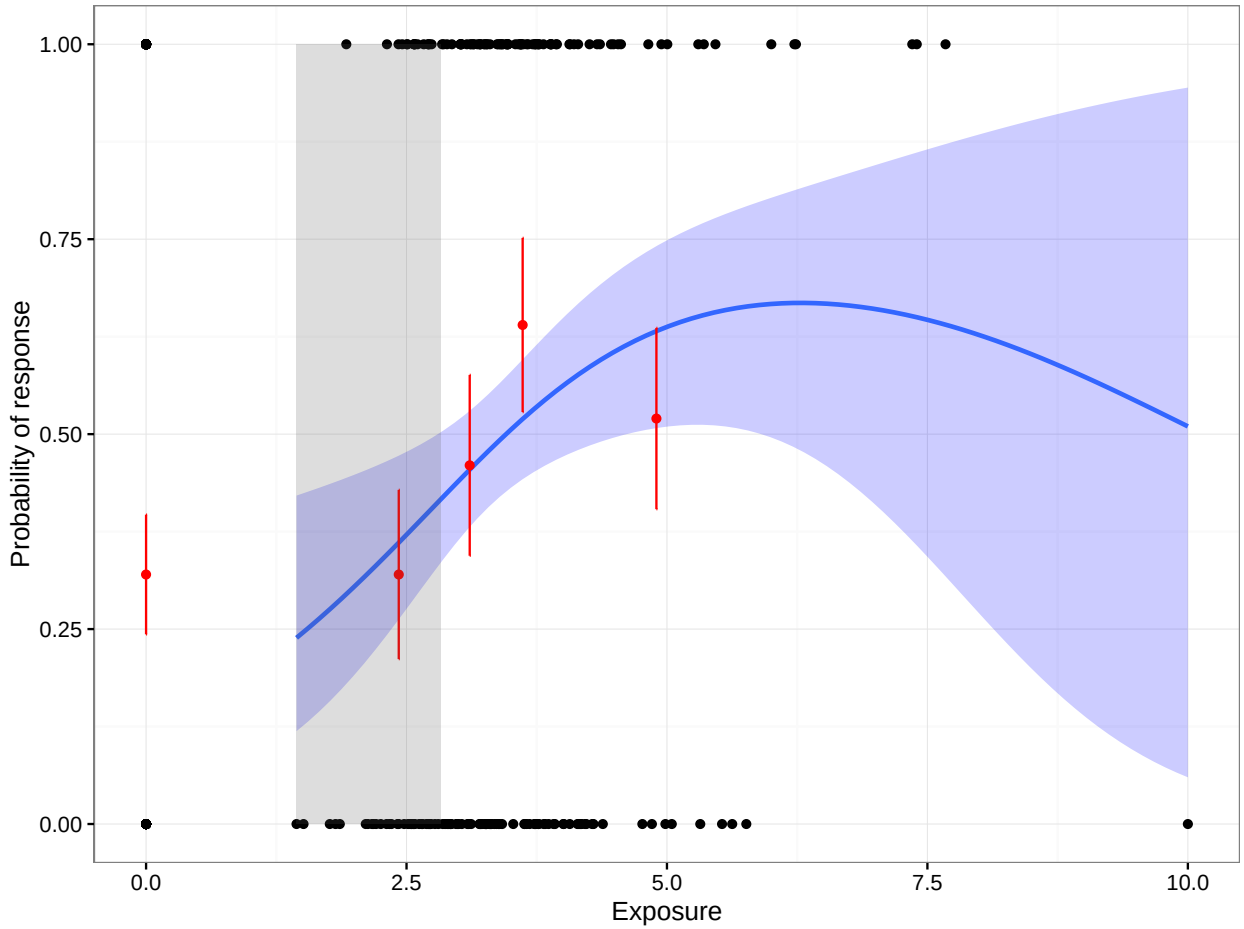


When there are predictors of both exposure and response, need to consider employing tools from the analysis of observational data.

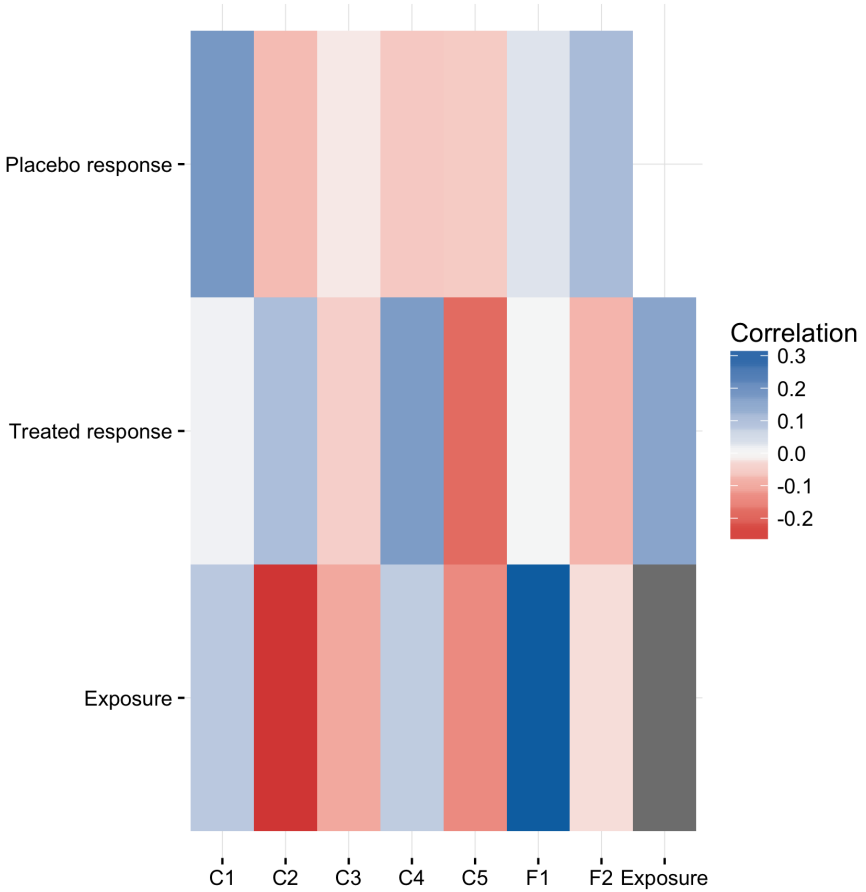
Motivating (fake-data) example

- You are on a drug development team developing a large molecule (MRG-001) for the treatment of oblivio.
- Your team has run one randomized, Phase 2 study comparing a single dose of MRG-001 to placebo.
- The outcome of interest is binary (responder/non-responder)
- There are several covariates (X) that are known to be prognostic for exposure which may also be predictive of the outcome (Y)

There is a fairly clear relationship between exposure and response



There are some predictors related to both exposure and response



Variable	Placebo	Q1	Q2	Q3	Q4
N	100	50	50	50	50
response	0.32	0.32	0.46	0.64	0.52
exposure	0	2.43	3.11	3.61	4.9
C1	39.6	34.9	31.3	37.8	37.4
C2	70.8	77	69.4	64.9	61.3
C3	957	1440	1160	1010	994
C4	36.1	33.3	35.7	37.2	36.3
C5	19.4	26.8	26	16.9	20.3
F1	0.57	0.26	0.46	0.56	0.78
F2	0.42	0.6	0.5	0.52	0.5

Questions of interest

- What is your estimate of the effect of exposure for this *population as a whole*?
- What is your estimate of the effect of exposure in *patients with low exposure*?

These questions relate to estimating the causal effect of exposure on response.

Techniques such as case-matching (case-control) analyses aren't ideally suited to answer these questions.

A general roadmap for causal questions

1. Specify knowledge about the system to be studied using a causal model
2. Specify the observed data and their link to the causal model
3. Specify the target causal quantity
4. Assess identifiability
5. State the statistical estimation problem
6. Estimate
7. Interpret

Peterson and van der Laan, Epidemiology, 25(3) 418-426, 2014

A general roadmap for causal questions

1. Specify knowledge about the system to be studied using a causal model
2. Specify the observed data and their link to the causal model
3. Specify the target causal quantity
4. Assess identifiability
5. State the statistical estimation problem
6. **Estimate**
7. **Interpret**

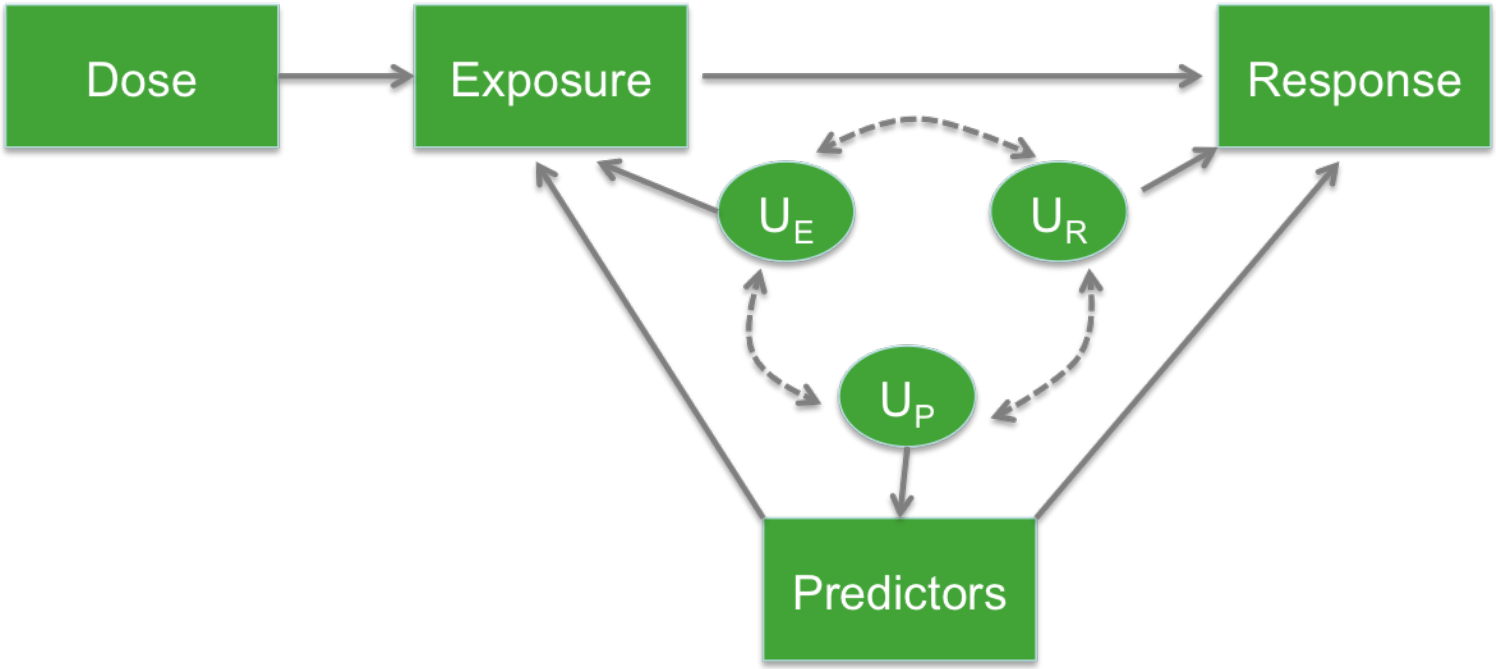
Peterson and van der Laan, Epidemiology, 25(3) 418-426, 2014

A general roadmap for causal questions

1. **Specify knowledge about the system to be studied using a causal model**
2. Specify the observed data and their link to the causal model
3. **Specify the target causal quantity**
4. Assess identifiability
5. State the statistical estimation problem
6. **Estimate**
7. **Interpret**

Peterson and van der Laan, Epidemiology, 25(3) 418-426, 2014

Specifying knowledge about the system



- Encoding what we know (and don't know) in a causal graph can be an important first step.
- Correlations between error terms (U_E,U_R,U_P) may be induced by unmeasured variables.
  - Assessing the potential impact of unmeasured confounders (Nedelman et al., 2007)

Potential outcomes and the assignment mechanism

- Let $Y_i(e)$ be the potential outcome for patient i at exposure $(E) = e$
  - $Y_i(e)$ is the outcome we would observe if a patient i had $E = e$
  - We typically only observe $Y_i(e)$ for one (or a few) values of e
  - Counterfactual potential outcomes are the values of $Y_i(e)$ that we don't observe
- The assignment mechanism is the (stochastic) process that assigns exposure
  - For a concentration-controlled trial, this is completely random
  - For a dose-controlled trial, it may depend on observed (and/or unobserved) covariates

Causal effects are differences in potential outcomes

- We will define individual causal effects in terms of differences in potential outcomes
  - Causal effect at $E = e$: $Y_i(e) - Y_i(0)$
  - But, we've only observed $Y(e)$ for one value of e
- So, we will calculate the population causal effect
  - The expected difference between the mean response at $E = e$ and $E = 0$
  - Expectation is taken with respect to the distribution of X
- Conditioning on X this is
  $E_Y(Y|X = x, E = e) - E_Y(Y|X = x, E = 0)$
- If we average over the distribution of X, this is
  $E_X\left[E_Y(Y|X = x, E = e) - E_Y(Y|X = x, E = 0)\right]$

Calculating the population (average) causal effect

$$
\begin{aligned}
ACE &= E_X\left[E_Y(Y|X=x, E=e) - E_Y(Y|X=x, E=0)\right] \\
&= \sum_x \left\{E_Y(Y|X=x, E=e) - E_Y(Y|X=x, E=0)\right\} p(X=x)
\end{aligned}
$$

The probability distribution for X comes from the population of focus.

- Enrolled population
- Low exposure patients

We estimate population causal effect as

$$
\widehat{ACE} = \frac{1}{n_{pop}} \sum_{i \in P} \widehat{E}_Y(Y|X=x_i, E=e) - \widehat{E}_Y(Y|X=x_i, E=0)
$$

Causal effects should be model-independent

$$ACE = E_X\left[E_Y(Y|X = x, E = e) - E_Y(Y|X = x, E = 0)\right]$$

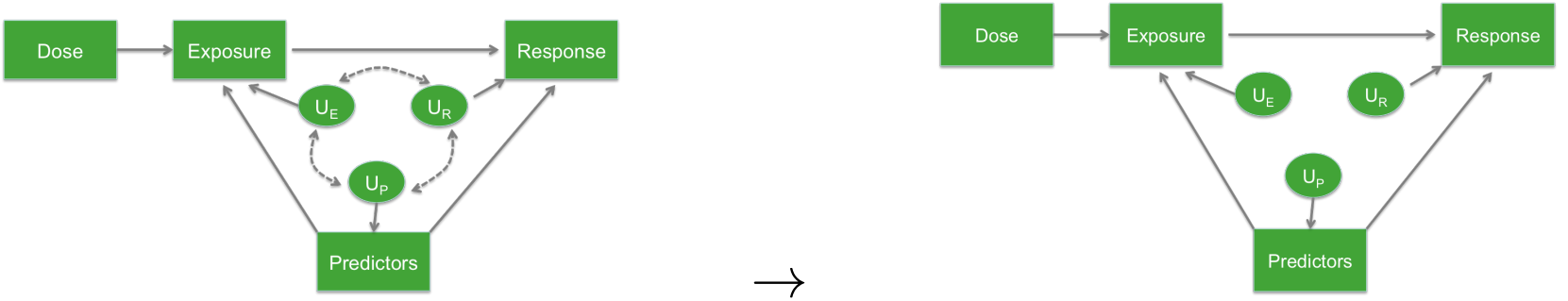
The definition of causal effects does not depend on any particular model.

It could be calculated using

- parametric or non-parametric regression model
- machine learning
- model averaging

How does this relate to the motivating example?

Given the graphical model and causal effect of interest, we're ready to make inference.



$$ACE = E_X\left[E_Y(Y|X = x, E = e) - E_Y(Y|X = x, E = 0)\right]$$

Estimated exposure-response model

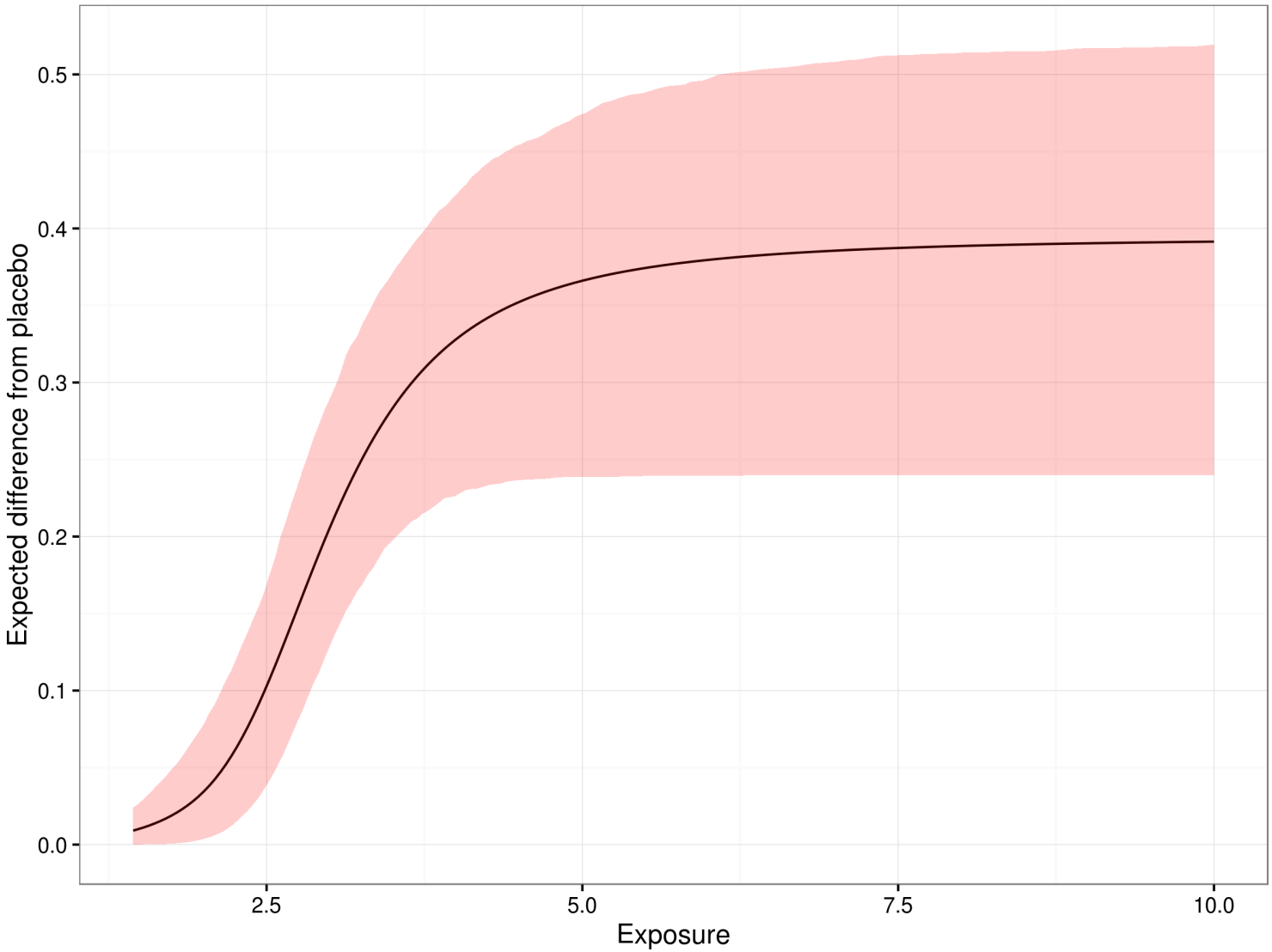
- Suppose we've arrived at the following model:

$$
\begin{aligned}
Y_i &\sim \text{Bernoulli}(p_i) \\
X_i &= (C1_i, C2_i, C3_i, C4_i, C5_i, F1_i, F2_i) \\
\text{logit}(p_i) &= \text{BSL}_i + \frac{\text{Emax}_i \; E_i^{\theta_8}}{\text{E50}^{\theta_8} + E_i^{\theta_8}}
\end{aligned}
$$

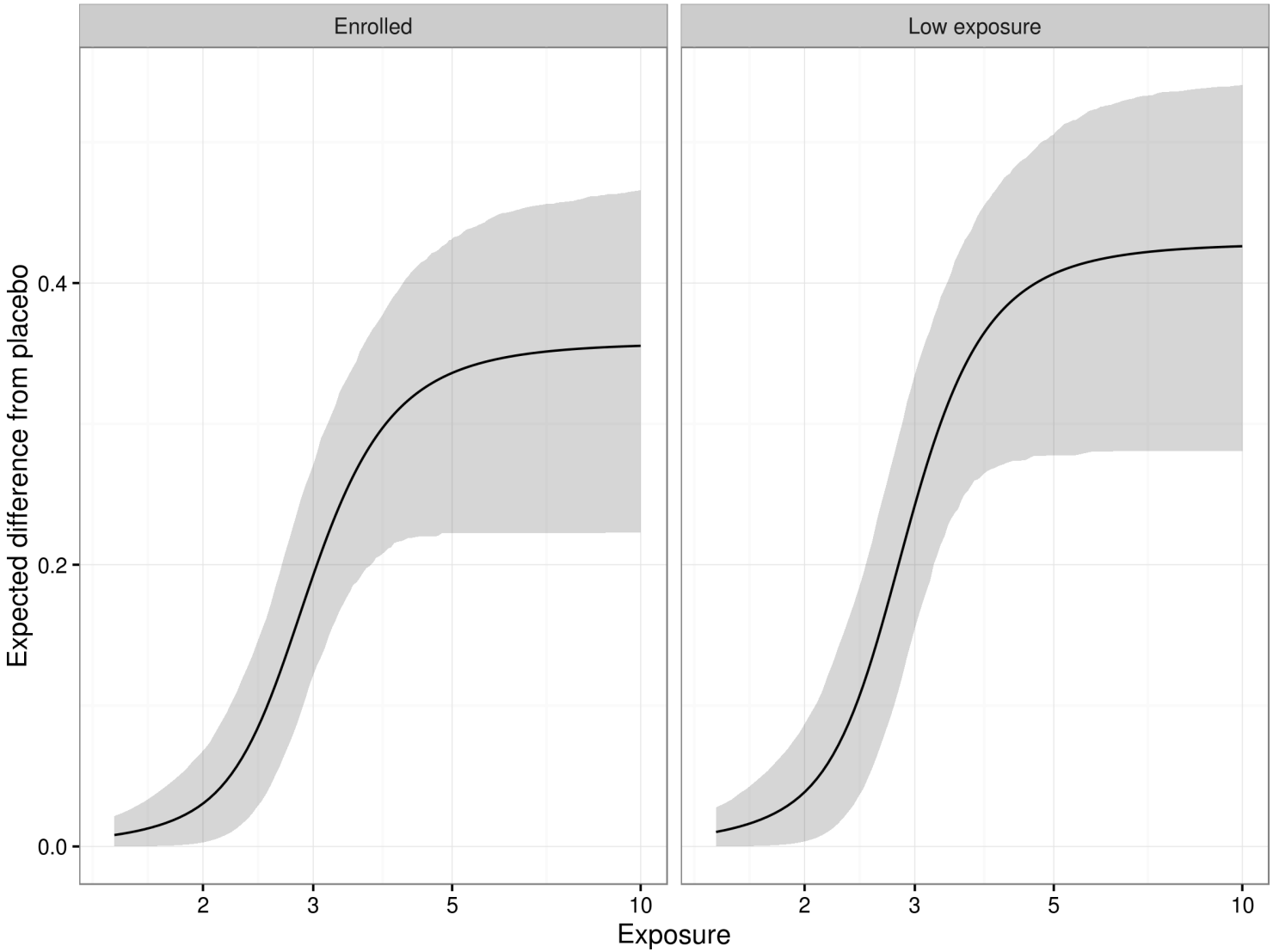
$$
\begin{aligned}
\text{BSL}_i &= \theta_0 + \theta_1 C1_i + \theta_2 C2_i + \theta_3 C3_i + \theta_4 F1_i \\
\text{Emax}_i &= \theta_5 + \theta_6 C1_i + \theta_7 C2_i
\end{aligned}
$$

Model-predicted difference from placebo

$$E(Y|X = \text{reference}, E = e) - E(Y|X = \text{reference}, E = 0)$$



Average casual effect in different populations



A few odds and ends

- There are many important details (and assumptions) of causal inference that I've skipped over!
- I have presented one simple example of using the formal framework of causal analysis in pharmacometrics
  - A randomized dose ranging design could have helped dramatically
  - Other models could have been used instead of logistic regression
    - "Estimation procedures should be tailored to provide high-quality answers to questions of scientific interest" – Gruber & van der Laan
- As M&S scientists move toward using observational databases (e.g., EHR), causal tools will be increasingly more important.

Summary

- Exposure is an *outcome*
- Think about causal effects in terms of *potential outcomes*.
- In order to make clear causal inference, we should define a *target causal quantity (and population)* of interest.

Acknowledgements

Jayson Wilbur
Jim Rogers
Dan Polhamus
Yoni Sidi
Marc Gastonguay

Ben Arnold
David Benkeser

References

- Casak et al. FDA Approval Summary: Ramucirumab for Gastric Cancer. *Clin Cancer Res.* 2015; 21(15): 3372-6.
- Gruber S and van der Laan MJ. Consistent causal effect estimation under dual misspecification and implications for confounder selection procedures. *Stat Meth Med Res.* 2015; 24(6): 1003-8.
- Nedelman JR, Rubin DB, and Sheiner LB. Diagnostics for confounding in PK/PD models for oxcarbazepine. *Stat Med.* 2007; 26:290-308.
- Peck C and Ludden T. Pitfalls in Retrospective Analysis in Search of Concentration-Effect Relationships. PAGE 3 (1994) Abstr 867 [www.page-meeting.org/?abstract=867]
- Petersen ML and van der Laan MJ. Causal Models and Learning from Data: Integrating Causal Modeling and Statistical Estimation. *Epidemiology.* 2014; 25(3): 418-425.
- Sheiner LB and Rubin DB. Intention-to-treat analysis and goals of clinical trials. *Clin Pharm Ther.* 1995; 57: 6-15.
- Wang J et al. Exposure-Response Relationship of T-DM1: Insight into Dose Optimization for Patients with HER2-Positive Metastatic Breast Cancer. *Clin Pharmacol Ther.* 2015; 95(5)
- Yang JY et al. The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making. *J Clin Pharmacol.* 2012; 53(2): 160-6.