Bringing together causal inference & pharmacometrics

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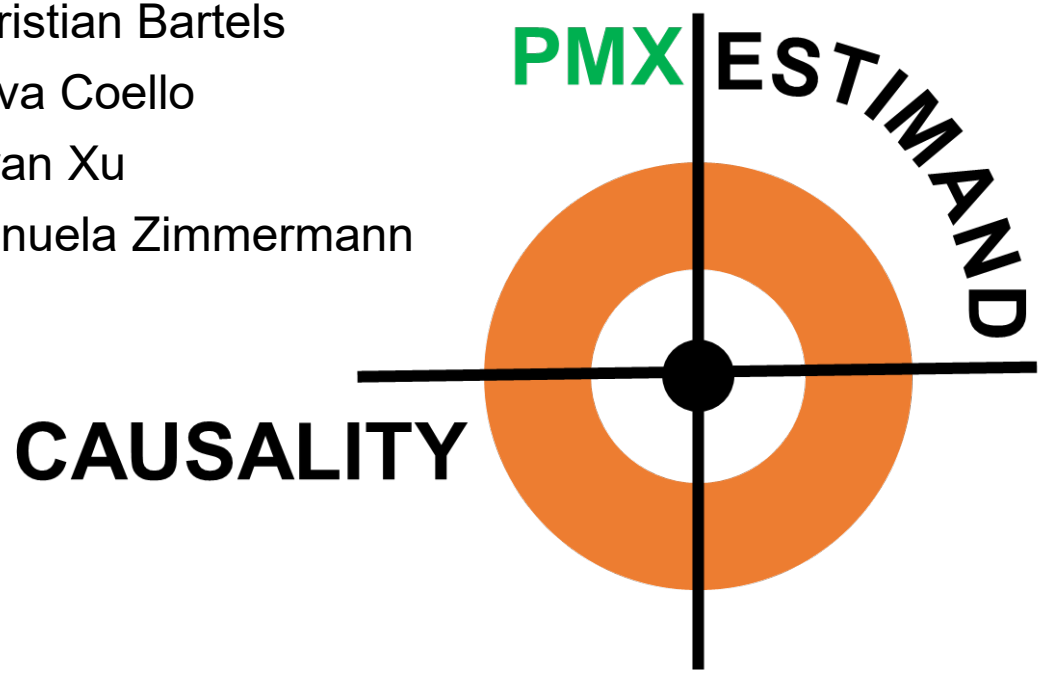

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ISoP SxP webinar

May 23rd 2025:

Correcting for confounding in longitudinal experiments: positioning NLME as implementation of standardization using latent exchangeability

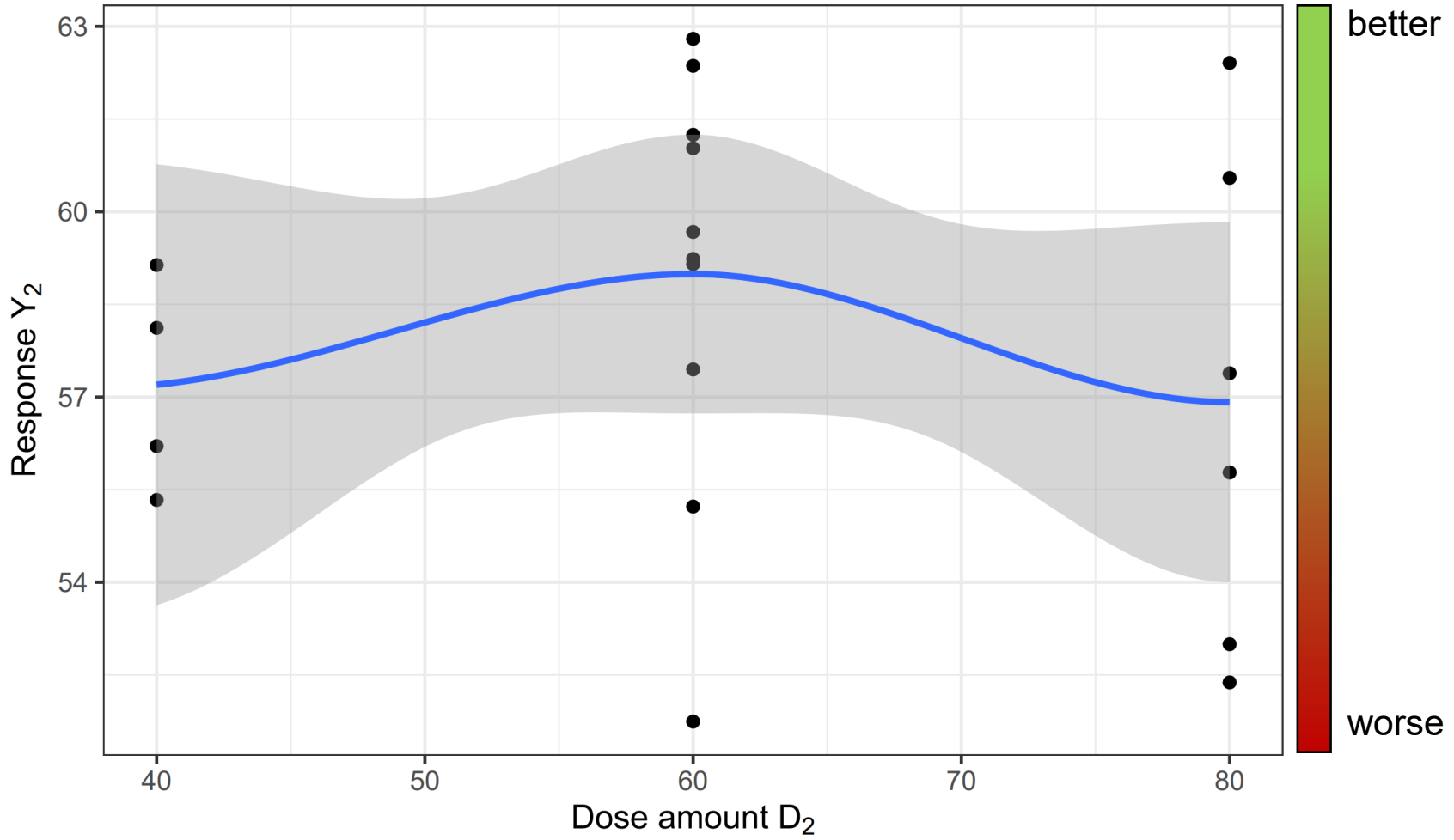
PAGE conference

June 6th 2025:

Performing causal inferences with pharmacometrics models

Does this ‘drug’ tend to have a beneficial dose-response relationship?

Submit your answer



Does this ‘drug’ tend to have a beneficial dose-response relationship?

Too nebulous!

We first need to get clarity on:

- What exactly do we want to estimate?
- How can we use the available data target this question?

What exactly do we want to estimate?

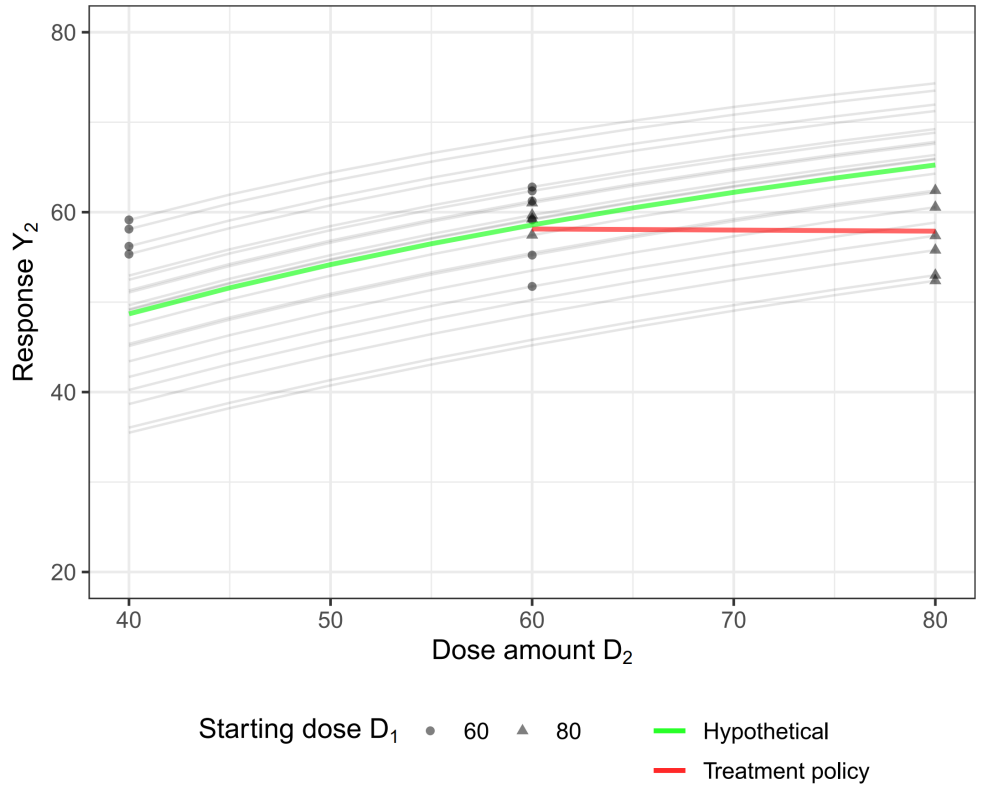
Different interventions whose causal effect we might be interested in (c.f. estimands framework):

- Treatment policy estimand: $f\left(Y_2^{D_1=d}\right) = f(Y_2|D_1 = d)$

  What would the expected response be if all patients are assigned to the dose d?
- Hypothetical estimand: $f\left(Y_2^{D_1=d,D_2=d}\right)$

  What would the expected response be if all patients are assigned to dose d and are forced to adhere?

⇒ **Need to be explicit and precise in which dose-response relationship we target**
⇒ **The estimator depends on the estimand**



Note: For simplicity, we assume only two time points/periods, and that all patients initiate treatment at their assigned dose level.

30 years ago…

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.

Intention-to-treat provides valid estimates and associated tests and intervals for the effect on outcome of *assignment to therapy* in the clinical trial (so-called use-effectiveness[4]). Intention-to-treat analysis does not provide valid significance levels, estimates, or interval estimates either for use-effectiveness in regular medical practice or for the effect of the *actually administered therapy* (so-called method-effectiveness). The latter is, however, arguably more relevant to medical decisions than is use-effectiveness, and trials should be designed and analyzed to provide estimates of it as well.

Additional challenges for answering “What if…” questions (hypothetical estimands)

Hypothetical estimands describe the outcome of a hypothetical intervention (‘contrary to fact’)

The potential outcome under this intervention is generally not observed in all patients

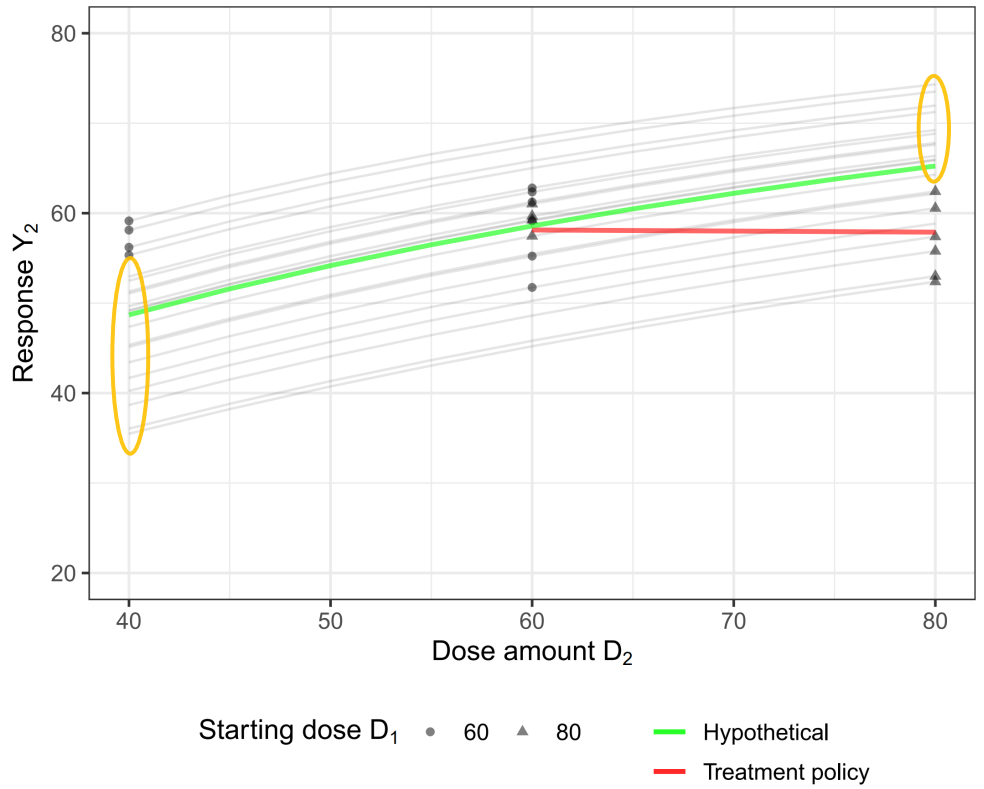
⇒ In general, there is selection bias in whose potential outcomes are (un)observed

⇒ Requires more assumptions compared to the other estimands (*previous slide*)

⇒ If assumptions are violated: bias

To avoid/reduce bias:

- Be explicit and precise when defining the estimand
- Explicitly state & carefully assess assumptions (requiring cross-functional domain knowledge)



How were the data generated?

D_1, D_2: Dose

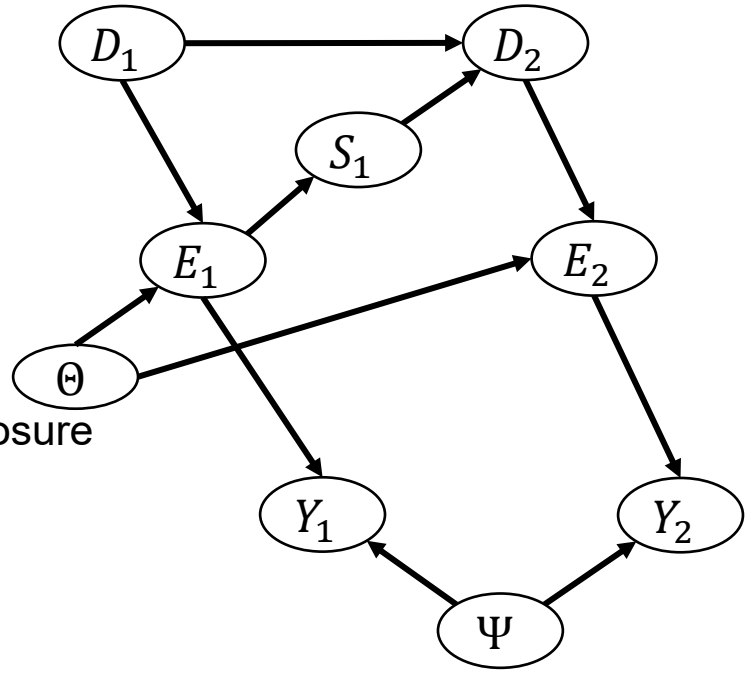
S_1: Safety measure

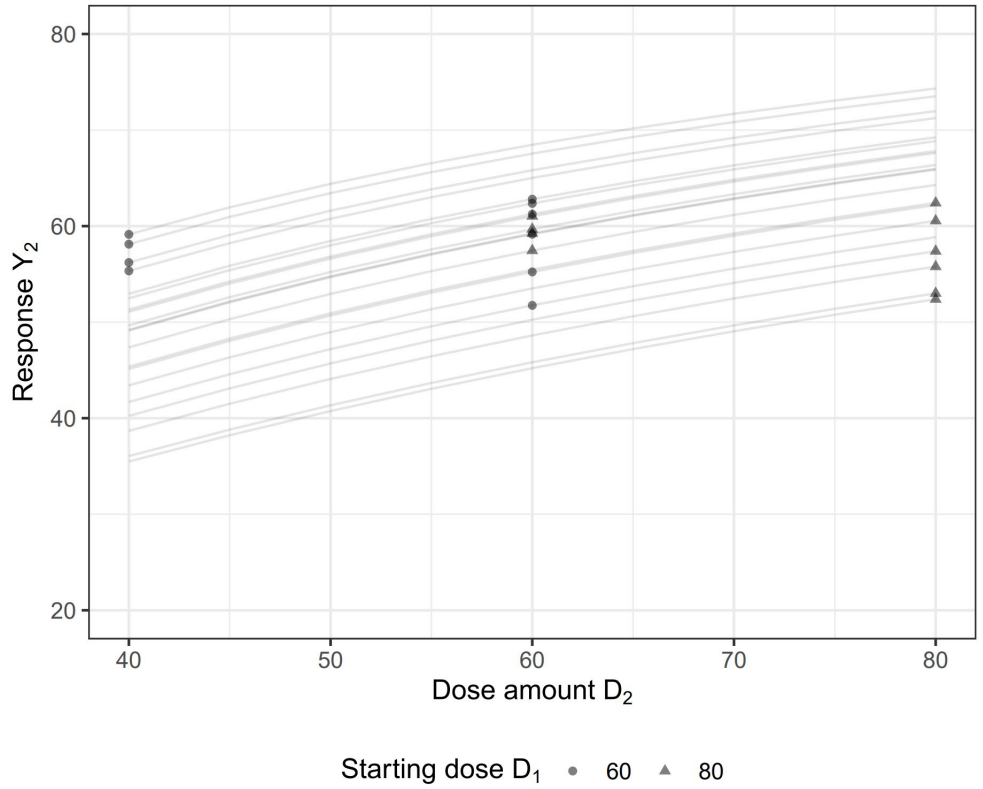
E_1, E_2: Exposure (PK)

Θ: Individual parameters characterizing dose-exposure

Y_1, Y_2: Response (PD)

Ψ: Individual parameters characterizing exposure-response





Note: This DAG is a simplified version, e.g. only including direct effects.

How do we estimate hypothetical estimands in pharmacometrics, conceptually?

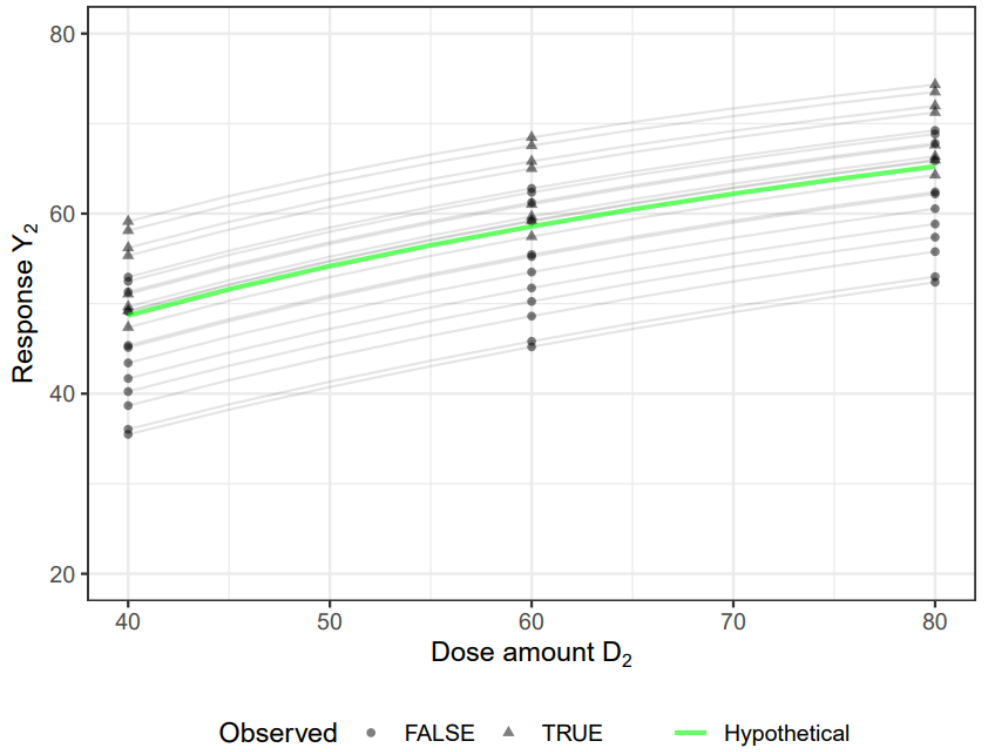
Hypothetical estimand: $f\left(Y_2^{D_1=d,D_2=d}\right)$

What would the response be if all patients are assigned to dose d and are forced to adhere?

Assumption: potential individual dose-response relationship is independent of the observed treatment history

⇒ Use individual parameters to predict potential outcome in the hypothetical setting of interest

⇒ No direct arrows from doses into individual parameters



A causal inference perspective on the pharmacometric NLME approach

Causal inference:

- Association is causation if there are no open confounding paths
- Confounding paths (e.g. $D_2 \leftarrow S_1 \leftarrow E_1 \leftarrow \Theta \rightarrow E_2 \rightarrow Y_2$) can be blocked by conditioning on a variable on the confounding path
- **Adjustment formula (standardization):**

$$f\left(Y_2^{D_1=d,D_2=d}\right) = \int_\theta f(\theta)\, f\left(Y_2 \mid \Theta=\theta, D_1=d, D_2=d\right) d\theta$$

Assumptions

Distribution of individual parameters

Conditional outcome model as a function of dose and individual parameters

D_1, D_2: Dose

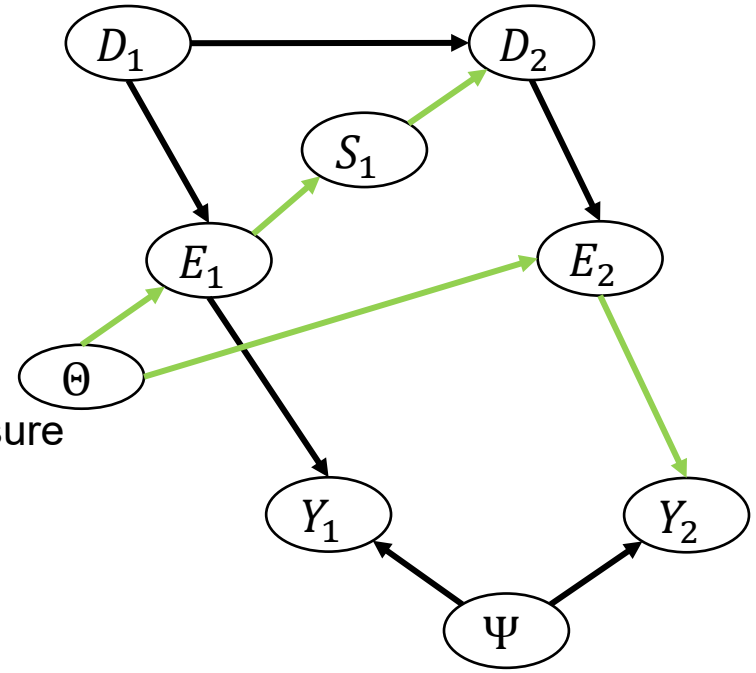
S_1: Safety outcome

E_1, E_2: Exposure (PK)

Θ: Individual parameters characterizing dose-exposure

Y_1, Y_2: Response (PD)

Ψ: Individual parameters characterizing exposure-response



Two potential sources of confounding

PK: Safety (exposure)-driven intercurrent events, e.g.

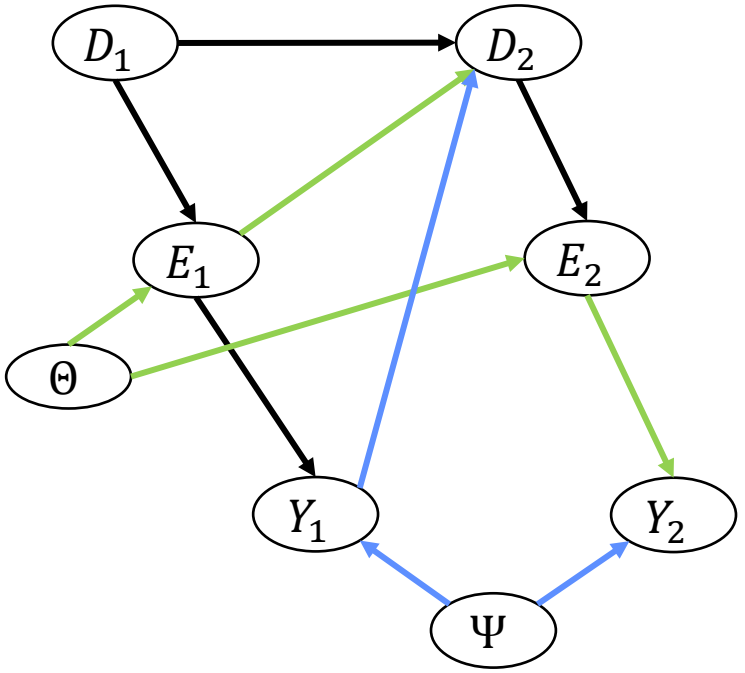
- Down-titration due to safety concerns related to drug exposure
- Note: Safety events are not of direct interest here
  ⇒ not explicitly shown

PD: Efficacy-driven intercurrent events, e.g.

- Stop up-titration when target systolic blood pressure is reached

The two scenarios might appear similar in the DAG, but there are important differences:

- PK (pharmacokinetic) models are often reliable
- PD (pharmacodynamics) is usually more challenging to model



Simulation re-estimation study inspired by trials

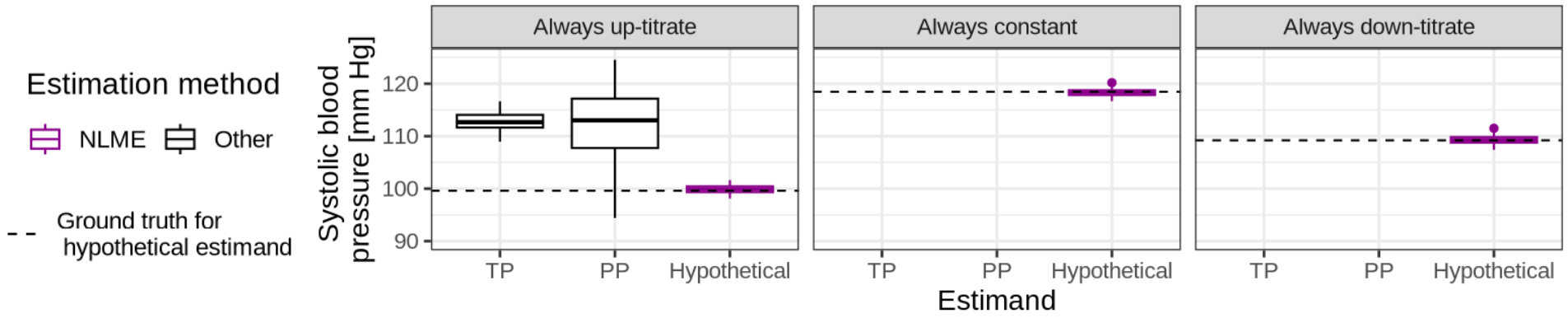
Simulation – re-estimation study inspired by real-world study (blood pressure lowering drug)

Estimates of three different treatment effects based on three distinct (hypothetical) scenarios of dose adaptation.

For comparison: summarizing the observed data via treatment policy (TP) and per-protocol (PP) estimators yields different estimates. This is expected as they target distinct estimands.

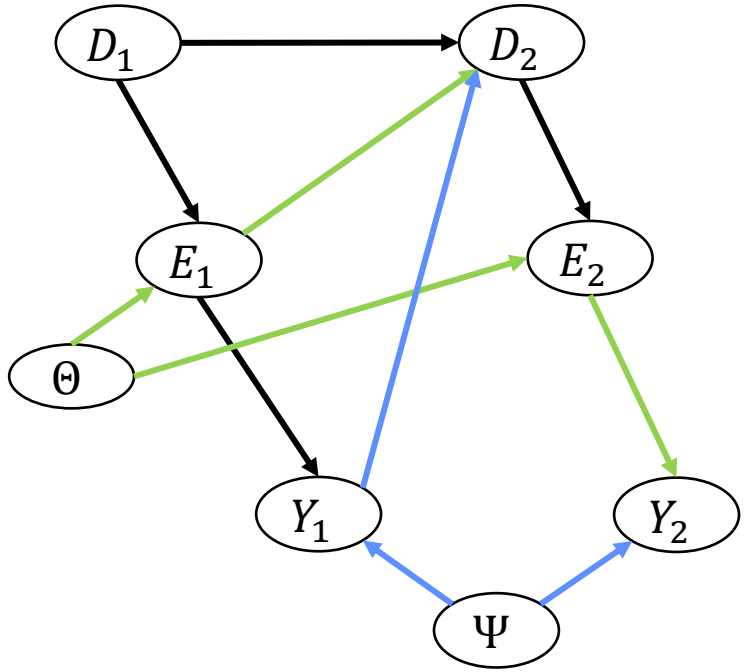
Note: only 3.5% of patients in the study follow the regimen of interest for the estimand.

	Enforce up-titrations	Forbid dose changes	Enforce down-titrations
Starting dose level	2	3	6
'Adherence' level in data	**3.5 %**		



When did we observe unbiased estimates from a popPKPD approach?

Dose adaptations due to	PK data	PD data	Unbiased estimate of hypothetical estimand?
Exposure (safety)	Rich	Rich	**Yes**
	Rich	At end of study	**Yes**
Efficacy	Rich	Rich	**Yes**
	Rich	At end of study	**No** Why? Impossible to estimate individual PD parameters and correct for confounding • Model diagnostics can help detect inappropriate adjustments



Summary & Conclusion

Be explicit & precise about

- what we want to estimate (the *estimand*), and
- our assumptions, including on the data-generating process (e.g. visualized using *causal diagrams*)

In pharmacometrics, we often make the (implicit) assumption that we have sufficient data to infer all random effects of a popPKPD model

Bartels *et al.* (2024): Conditioning on the individual parameters of an NLME model blocks confounding paths

If some assumptions are not met:

Active area of research (Novartis PMX initiative on Causality & Estimands, INVENTS (WP 1.2), cross-industry & academia working group on Causal Inference in PMX,…), building on earlier work e.g. by *Sheiner et al.* (1989): Study designs for dose-ranging

- Reach out if you'd like to collaborate

Making formal causal inferences can increase the value and impact of our work!

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Thank you