

Addressing Confounding Bias in Exposure–Response Analysis — Evaluating Instrumental Variable Strategies

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Introduction

Exposure–response analyses are important to determine dose individualization. Randomization of subjects to multiple dose levels in clinical trials enables an unbiased estimation of the dose–response relationship. However, drug exposure is determined by several physiological factors at the subject level which often cannot be randomized. These factors may also influence drug response, thus causing confounding in the exposure–response (E–R) relationship. This is particularly problematic when the studied dose range is narrow.

The aim of this study is to examine the confounding bias in estimation of PKPD relationships in randomized dose controlled (RDCT) trials, under multiple designs and modelling approaches. Specifically, we evaluate approaches that utilize randomized dose assignment in RDCTs as an Instrumental Variable to identify causal effects of the exposure.

Methods

X represents observed covariates, and the subscripts IV and RE represent instrumental variable and random effect, respectively.

1. Predictor Substitution approach (PS)^{2,3,4} Using instrument–predicted exposure to estimate the E–R relation

$$Y_{PK} = f(\theta_{PK}, \eta_{PK}, Dose, X) + \epsilon_{PK}, \quad Y_{PD} = g(\theta_{PD}, \eta_{PD}, f(\theta_{PK}, Dose, X), X) + \epsilon_{PD}$$

2. Control Function approach (CF)^{3,5} Using the residual from instrument–exposure estimation as a covariate in E–R relation

$$Y_{PK} = f(\theta_{PK}, \eta_{PK}, Dose, X) + \epsilon_{PK}, \quad Y_{PD} = g(\theta_{PD}, \eta_{PD}, C_{obs}/C_{ipred}, X) + \theta_{res}r_f + \epsilon_{PD}$$

3. PKPD correlated model (PCM) A simultaneous estimation model accounting for correlation between IIVs of PK and PD

$$Y_{PK} = f_{PCM}(\theta_{PK}, \eta_{PK}, Dose, X) + \epsilon_{PK}, \quad Y_{PD} = g(\theta_{PD}, \eta_{PD}, f_{PCM}(\theta_{PK}, \eta_{PK}, Dose, X), X) + \epsilon_{PD}, \text{ with } corr(\eta_{PK}, \eta_{PD}) \neq 0$$

4. Double relations model (DRM) A novel approach based on utilizing the Instrument to obtain separate estimates for fixed and random effects components of the E–R relationship

$$Y_{PK} = f_{DRM}(\theta_{PK}, \eta_{PK}, Dose, X) + \epsilon_{PK}, \quad Y_{PD} = Y_{PD,IV} + Y_{PD,RE} + \epsilon_{PD},$$

$$\text{where } Y_{PD,IV} = g(\theta_{PD,IV}, \eta_{PD,IV}, f_{DRM}(\theta_{PK}, Dose, X), X), \text{ and}$$

$$Y_{PD,RE} = g(\theta_{PD,RE}, \eta_{PD,RE}, f_{DRM}(\theta_{PK}, \eta_{PK}, Dose, X) - g(\theta_{PD,RE}, \eta_{PD,RE}, f_{DRM}(\theta_{PK}, Dose, X), X))$$

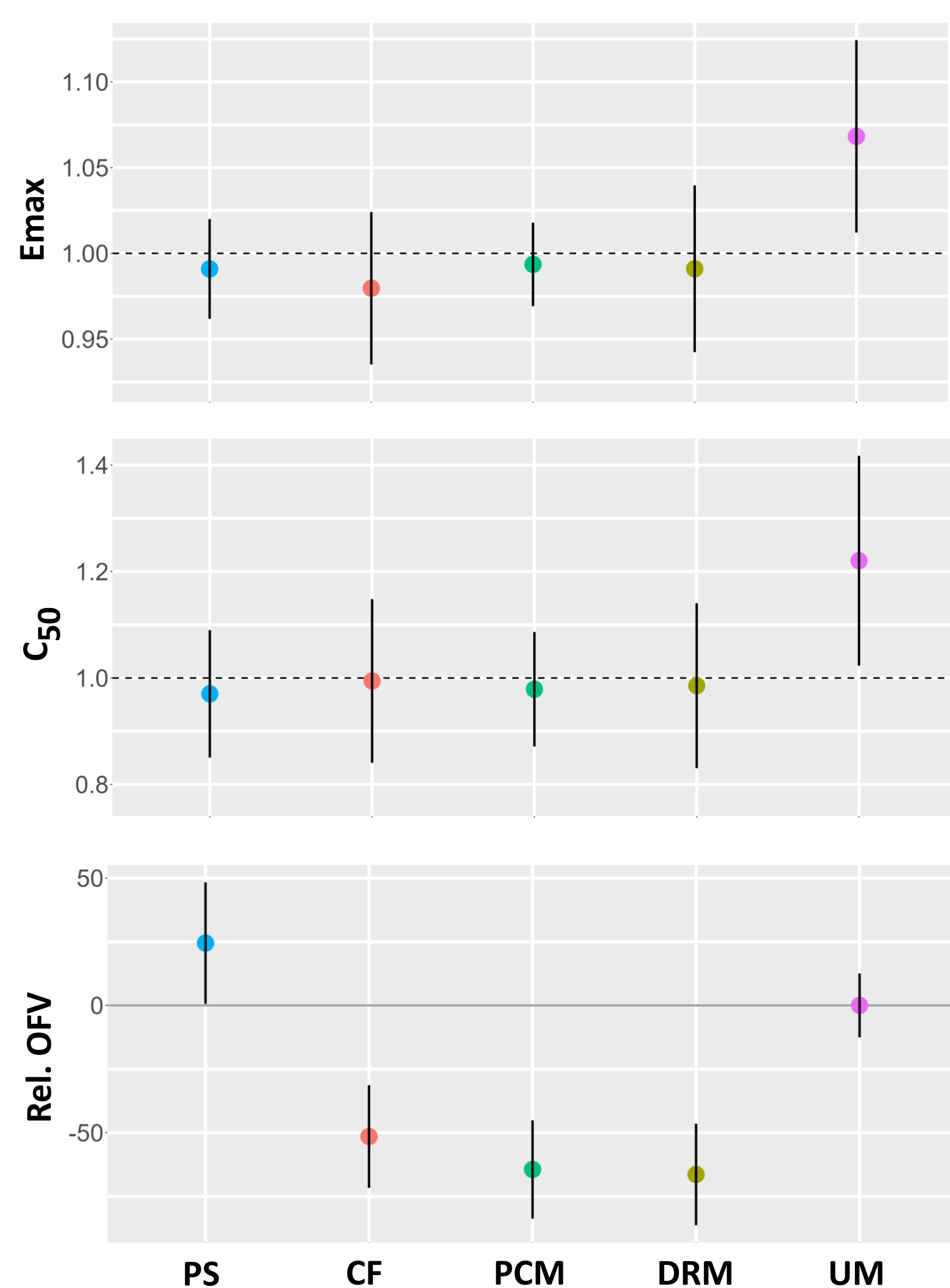
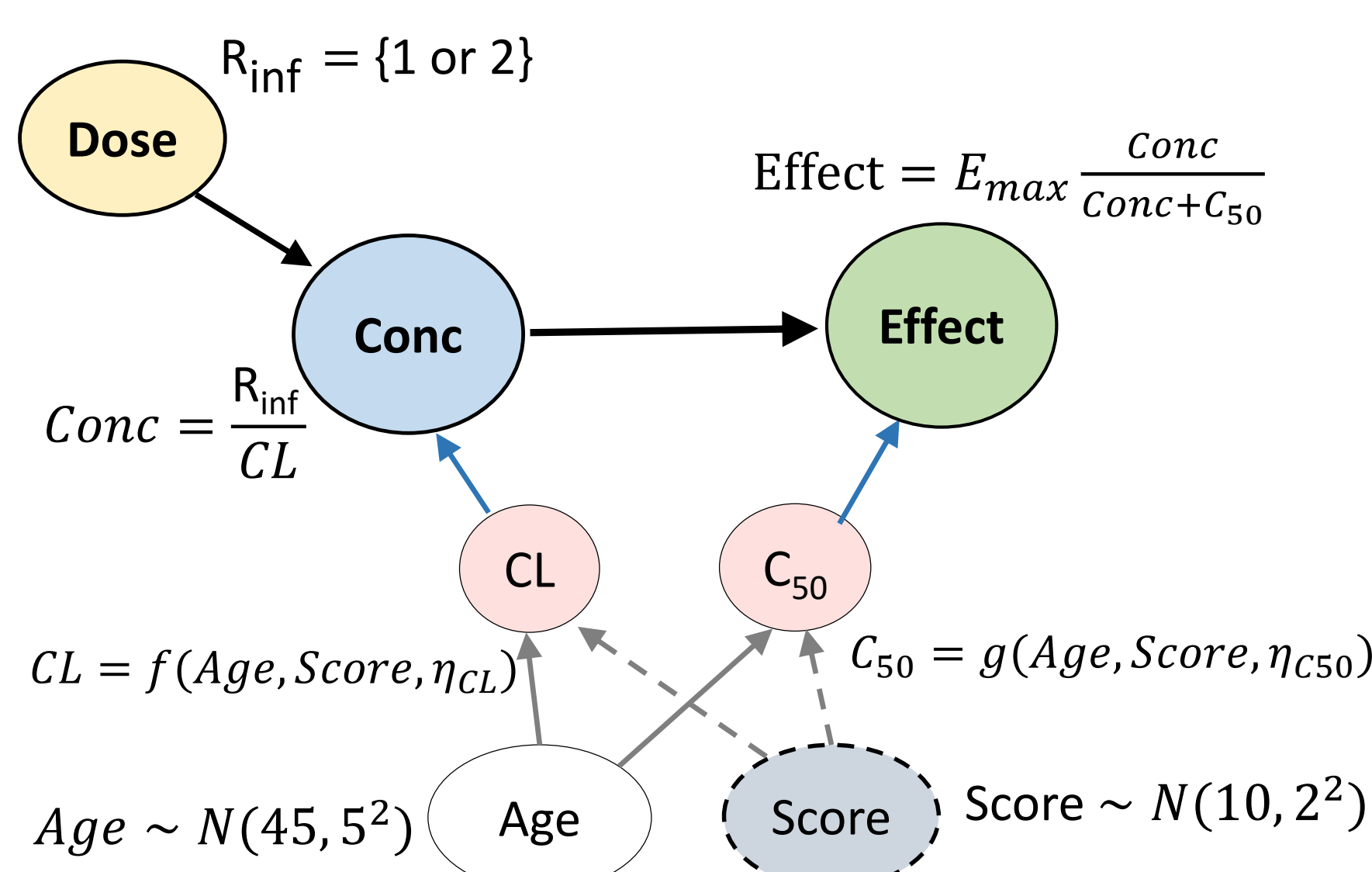
5. Unadjusted Model (UM) For comparison $Y_{PD} = g(\theta_{PD}, \eta_{PD}, C_{obs}/C_{ipred}, X) + \epsilon_{PD}$

Conclusions

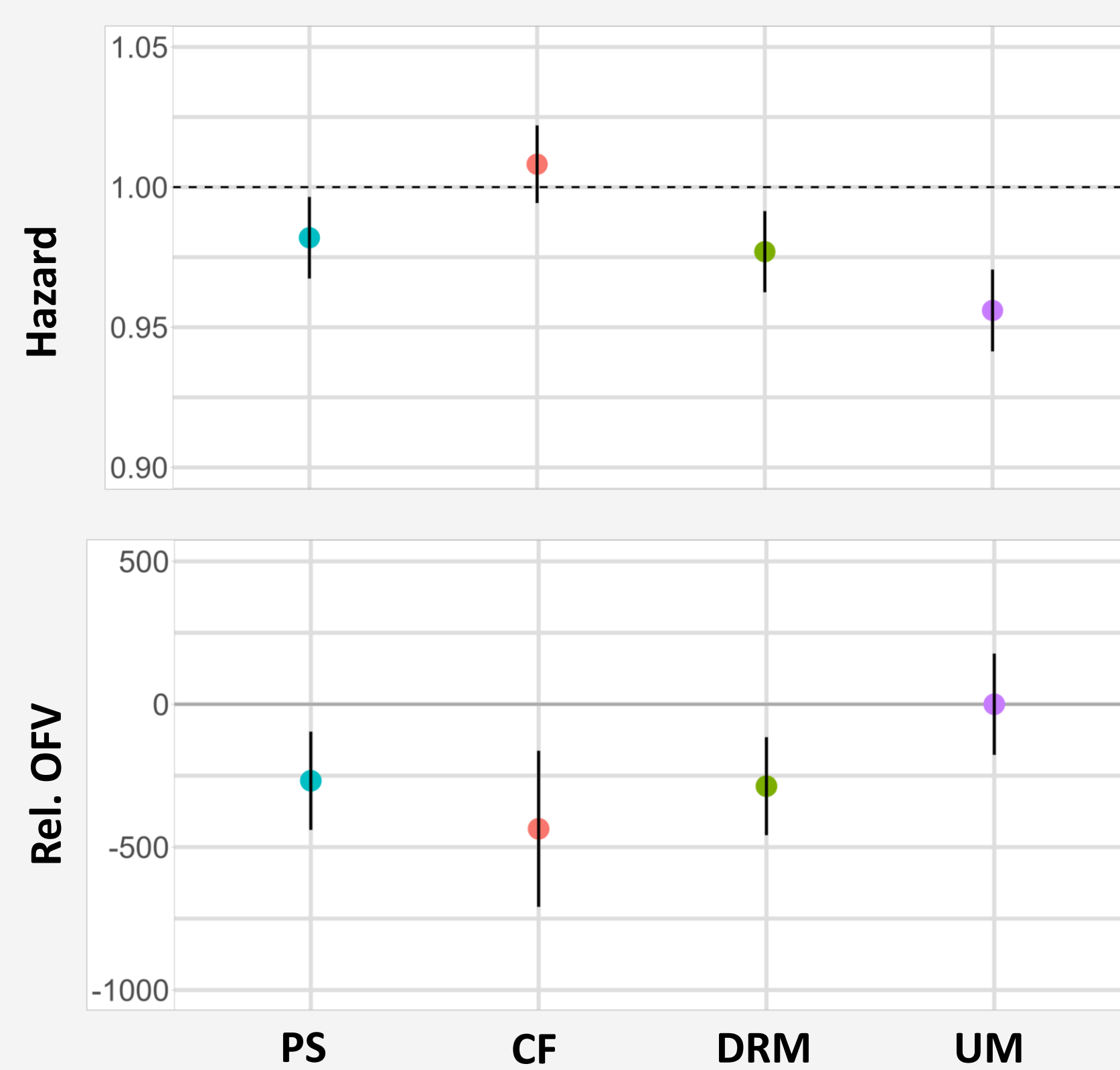
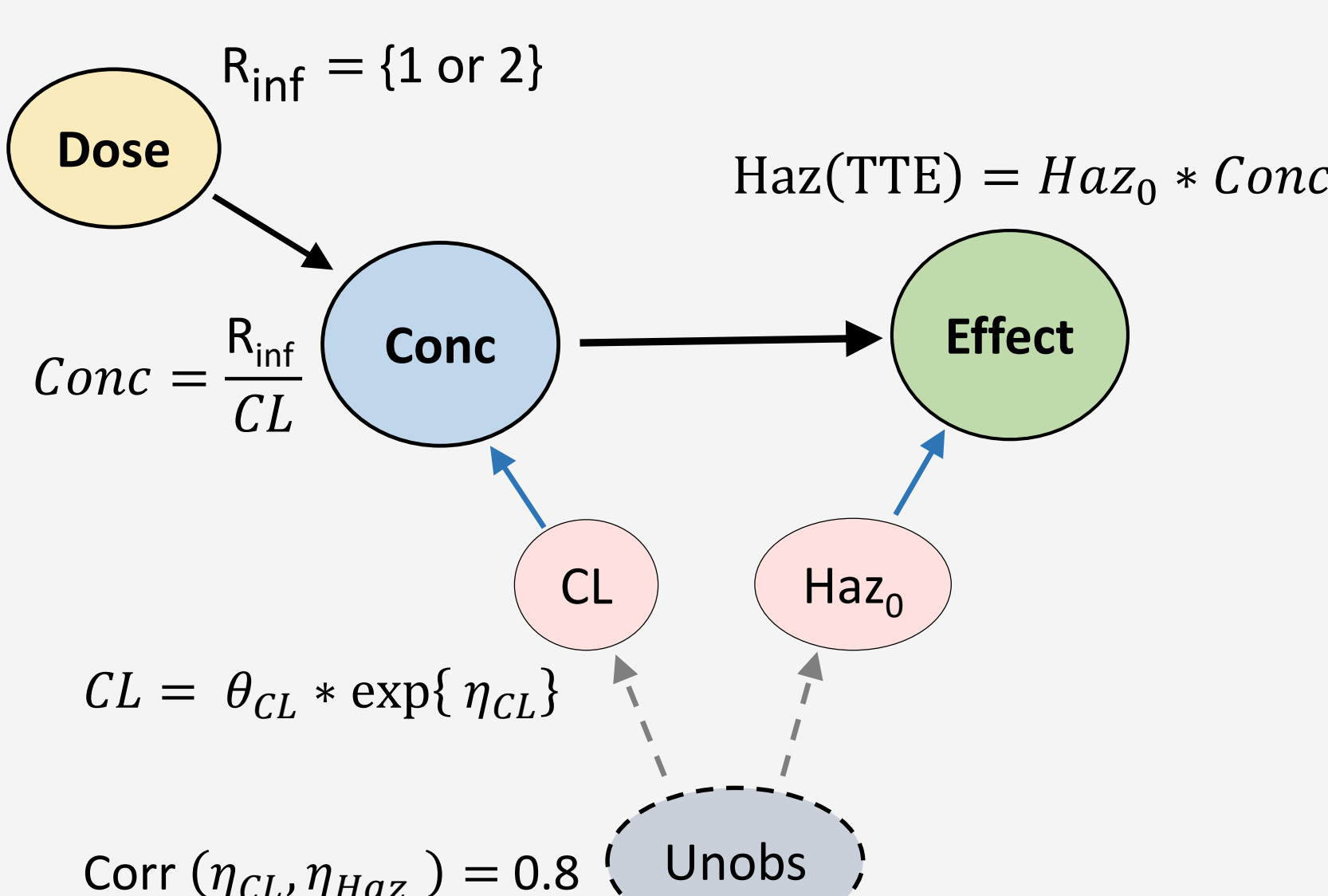
- The instrumental variable approaches PS and CF leverage the randomized dose as an instrument. While CF performs well across designs, PS shows more varied results.
- The novel DRM also performs well across designs, and has the additional advantage of separating out the fixed effects and random effects components of the exposure–response relationship for comparison.
- Accounting for correlation in random effects between exposure and response in the estimation (PCM) provided the best results. However, this may not always be applicable (e.g. Design 2) and identification of the right correlation pattern may be difficult in practice.

Results

Design 1: Single effect observation



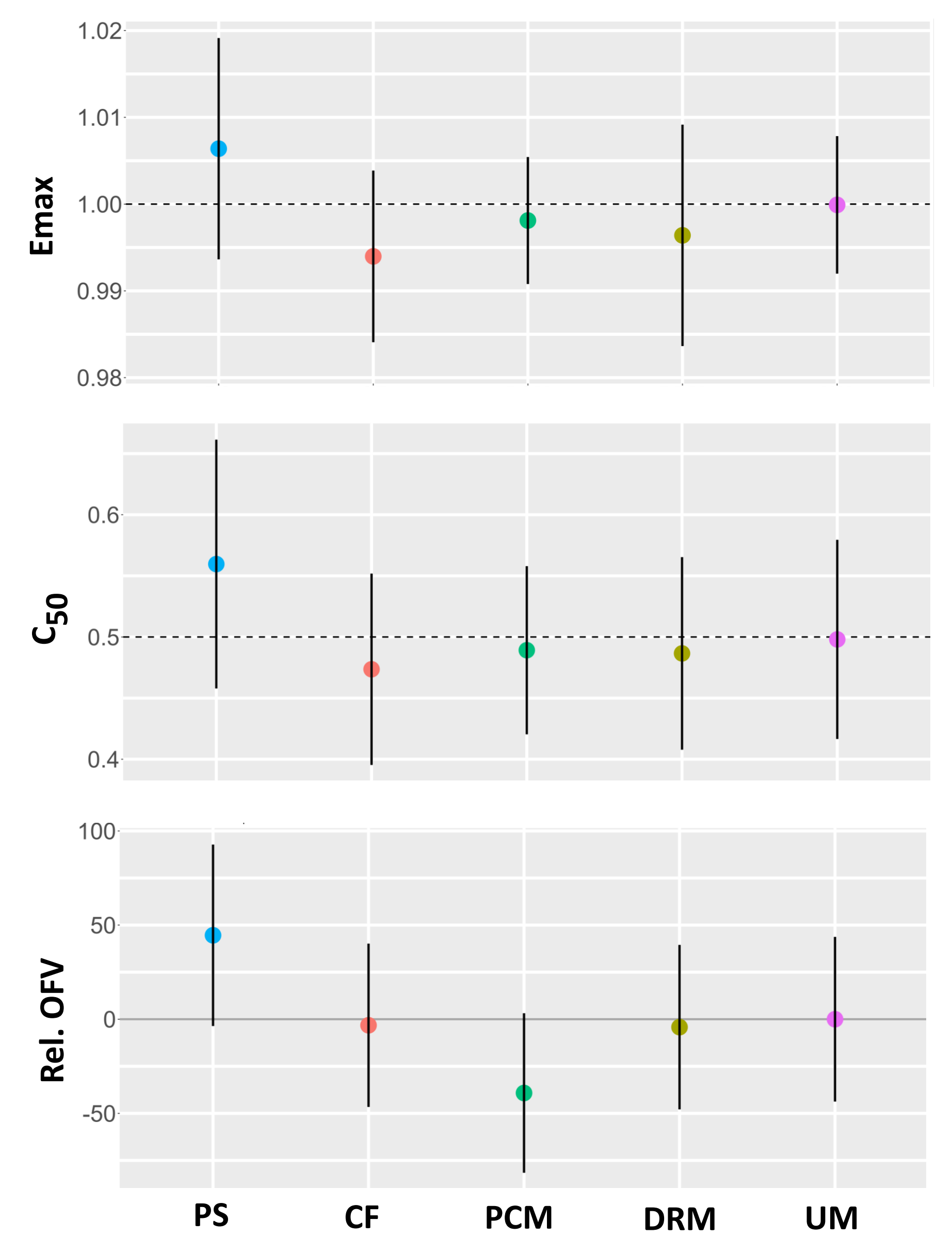
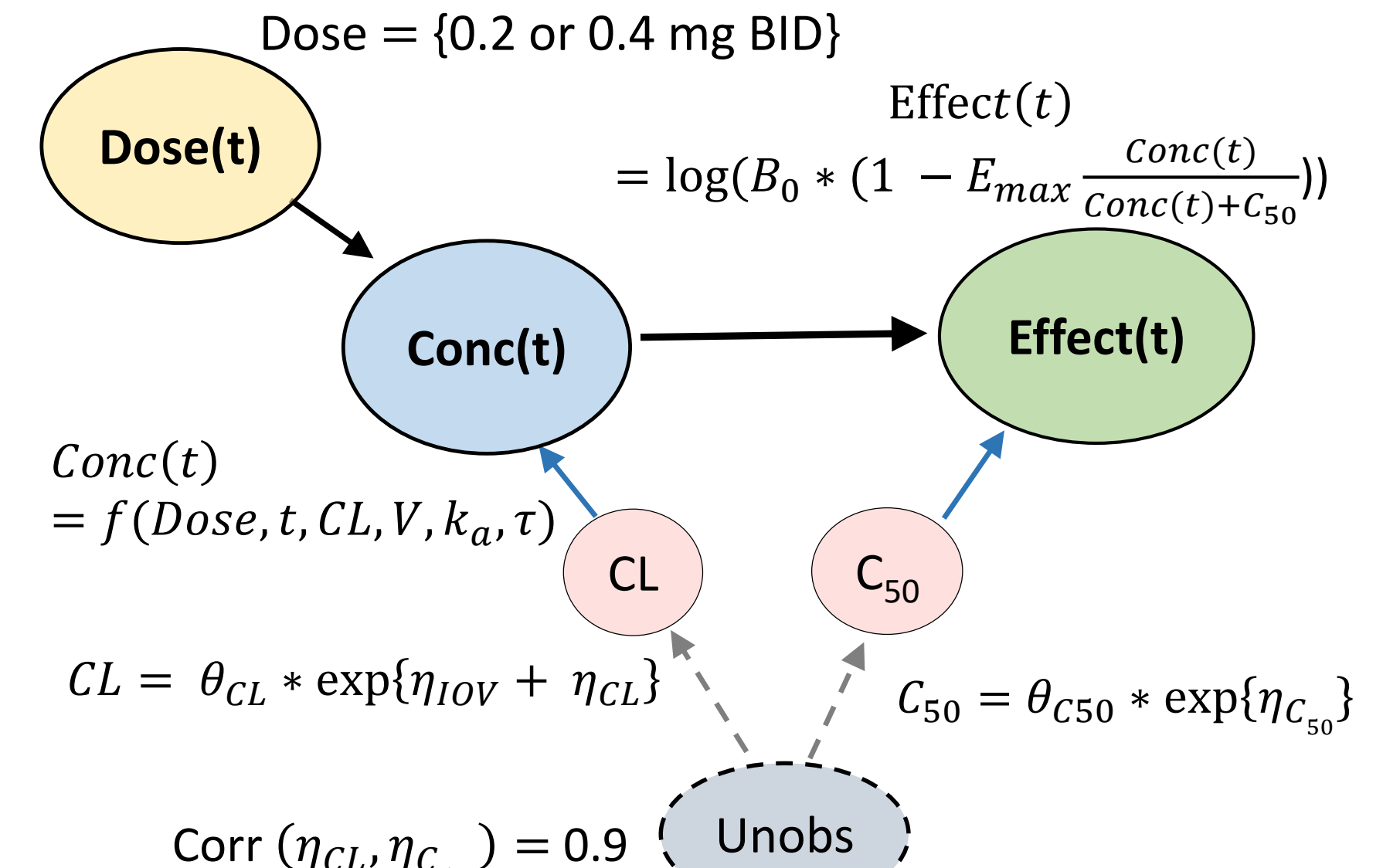
Design 2: PK Time-to-Event Model



Design 1 (N=100) and Design 2 (N=5000) simulate scenarios with a single dose and a single response. Design 3 (N=53) simulates a multi-dose and multi-response scenario based on a PKPD model for moxonidine-noradrenaline¹. Each scenario is based on 500 simulations.

Model performance is assessed using bias and standard deviation of the parameter estimates relative to the simulated values (indicated by dotted line), as well as the mean and standard deviation of the model OFV relative to the mean OFV of the Unadjusted Model (UM).

Design 3: Repeated Measures



References

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