

Modelling UACR as a clinical endpoint



UPPSALA
UNIVERSITET

Gustaf Wellhagen^{1,2}, Bengt Hamrén¹, Maria Kjellsson², Magnus Åstrand¹

III-72

Clinical Pharmacology & Safety Sciences, R&D BioPharmaceuticals, AstraZeneca, Gothenburg, Sweden¹, Department of Pharmaceutical Biosciences, Uppsala University²

Introduction

- Clinical studies in patients with chronic kidney disease (CKD) often use urinary albumin-to-creatinine ratio (UACR), as an endpoint in phase 2
- UACR is highly variable between individuals and occasions, and also within individuals
- Different statistical methods to analyze such data are available, e.g.:
 - Analysis of variance or analysis of covariance (ANOVA/ANCOVA), which disregard much of the information
 - Mixed-effect Model Repeated Measures (MMRM), which makes no/few assumptions regarding the response
- We have investigated **dose-response characterization within the MMRM framework** to assess if it can improve precision and better describe dose-response, compared to more conventional MMRM and ANOVA/ANCOVA

Objectives

To investigate the **precision** and **accuracy** of placebo-adjusted change from baseline of UACR ($\Delta\Delta\text{UACR}$) with different methods: MMRM (1) with or (2) without a dose-response relationship and (3) a dose-response relationship of only the end-of-study data using ANOVA/ANCOVA.

Conclusions

- All three methods well predicted the outcome for the highest dose at the end-of-study
- A dose-response relationship improved the precision of predictions compared to standard MMRM, especially for lower dose arms
- MMRM with dose-response had the highest precision in all cases**
- This can improve decision-making in clinical development when uncertainty is high, e.g. with a variable biomarker such as UACR

Discussion

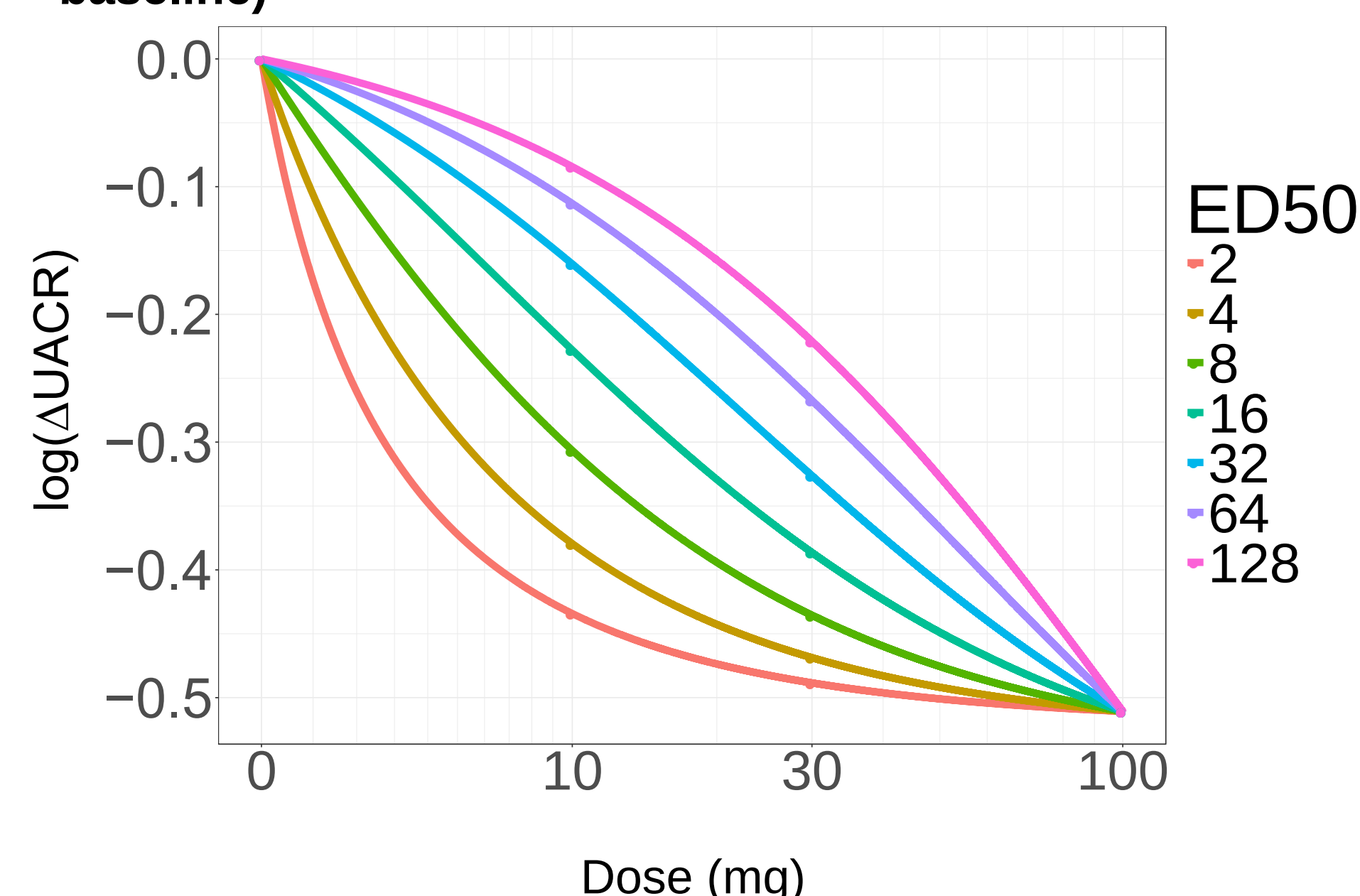
- Further knowledge about a compound's dose-response relationship can be gained by modelling all data at hand (from all visits and dose arms)
- The MMRM with dose-response is a simple and parsimonious addition to MMRM
- MMRM with dose-response had lower bias than ANOVA/ANCOVA, and higher precision for lower doses
- The bias with all methods was relatively small
- The highest bias was around 10% of the maximal effect, for lower dose arms when ED50 was high, for ANOVA/ANCOVA and around 2.5% for MMRM with dose-response
- The standard MMRM will always be unbiased as each visit is estimated independently
- Possible future investigations:
 - We have assumed an Emax dose-response, other functions could be explored as well



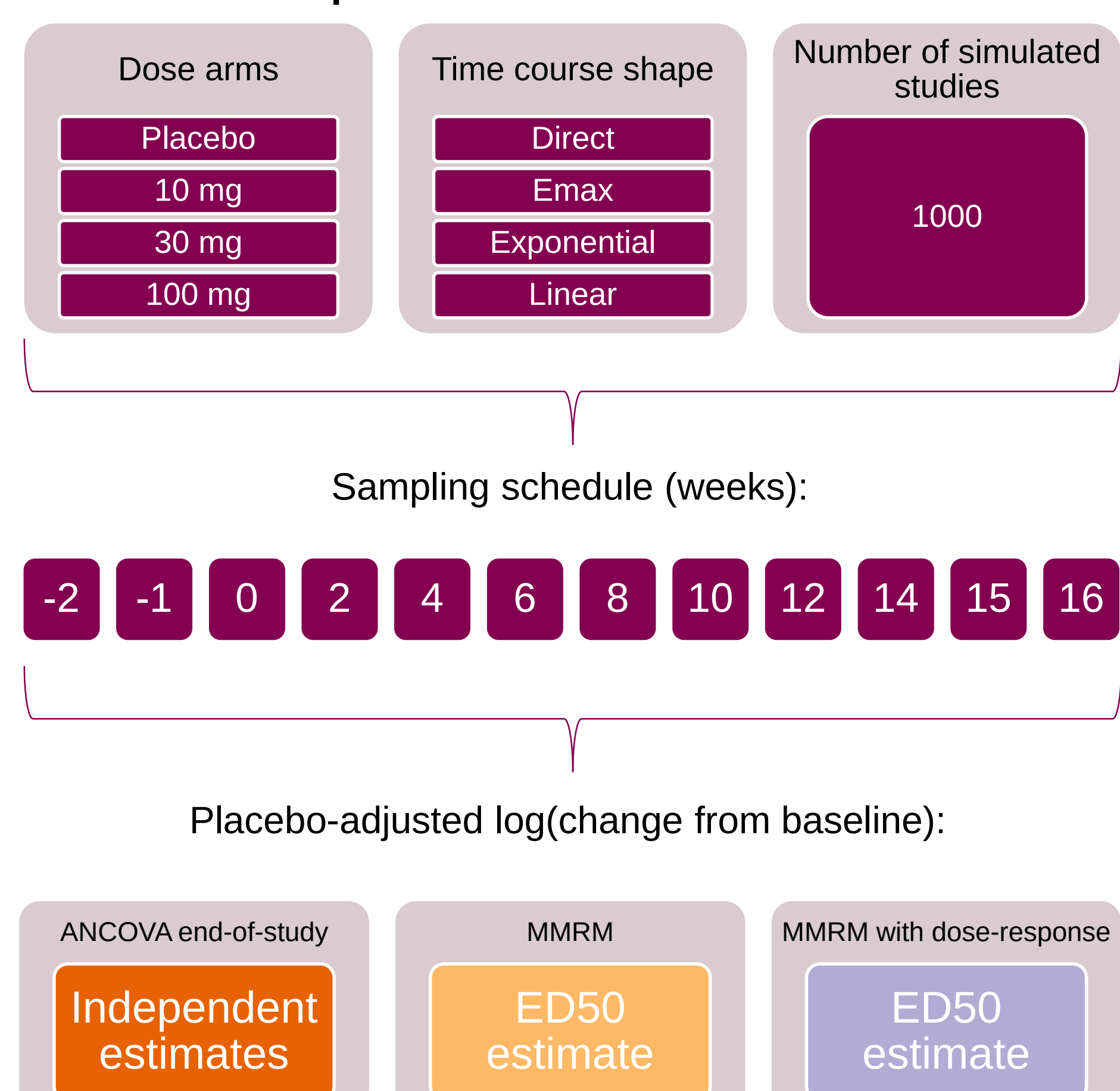
Methods

A true dose-response model following an Emax shape with varying ED50 was assumed. A first-order autoregressive model (AR1) was assumed for the correlation of residuals. The sample size was set to provide a power of 95% for detecting a 40% reduction in $\log(\text{UACR})$ between the highest dose arm and placebo at end-of-study.

Figure 1: True dose-response relationship at end-of-study via Emax function, $\log(\text{UACR change from baseline})$



Simulation setup:



Results

Figure 2: Simulation example, mean placebo-adjusted $\log(\text{change from baseline})$ and average 95% confidence intervals with ED50=32 mg and linear time course

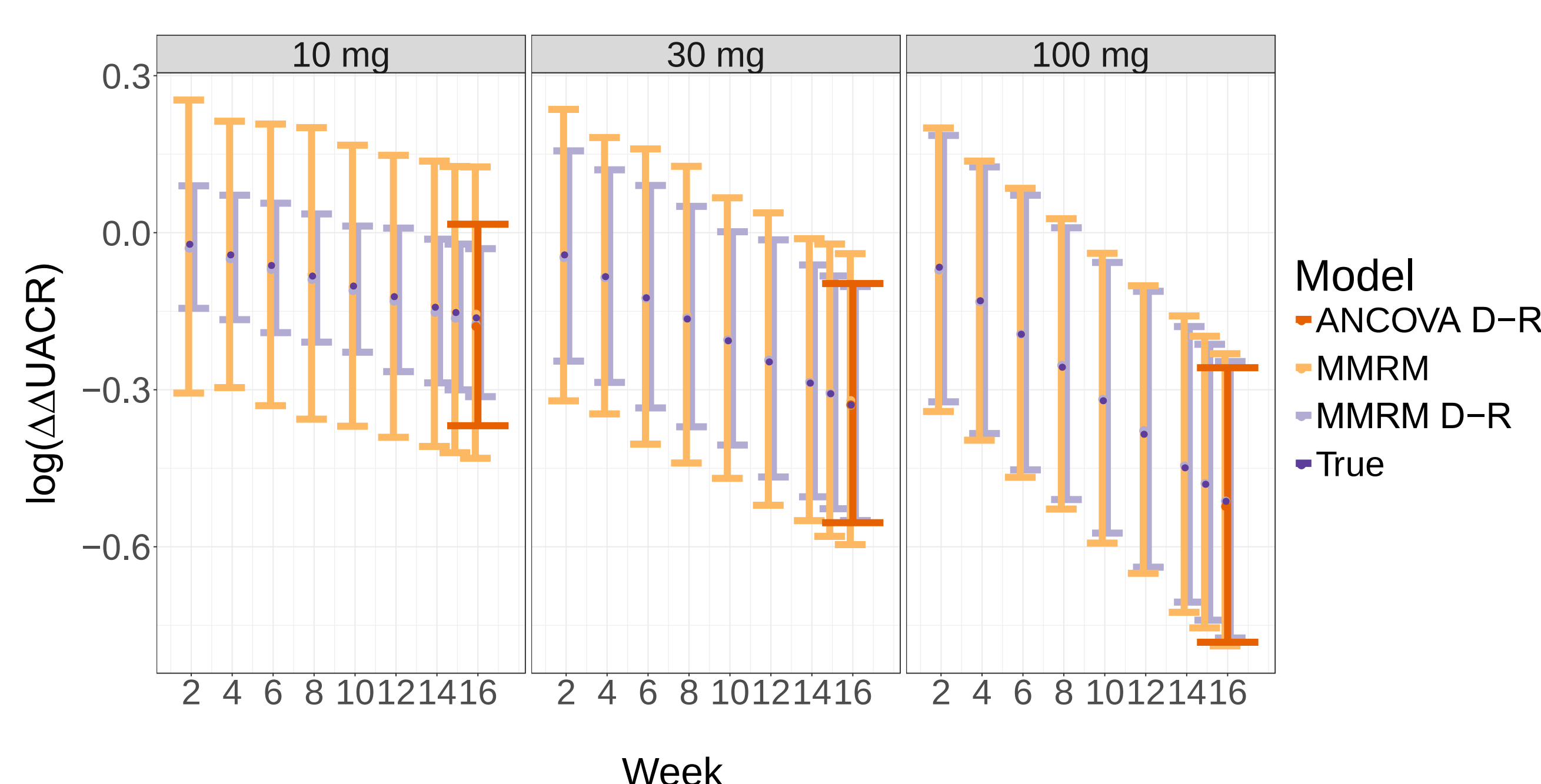


Figure 3: $\sqrt{\text{Mean squared error at last visit (MSE = variance + bias}^2\text{)}}$

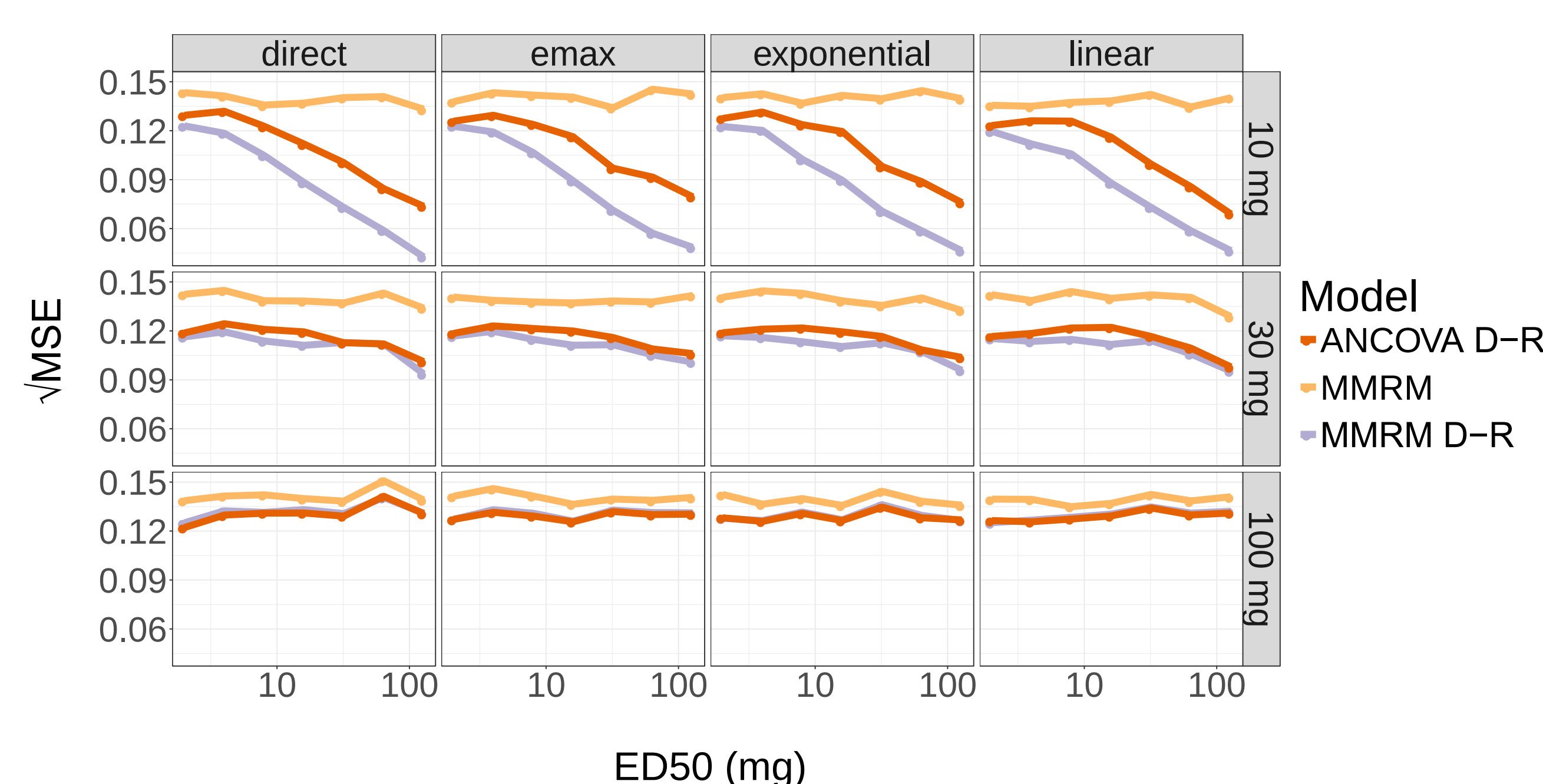
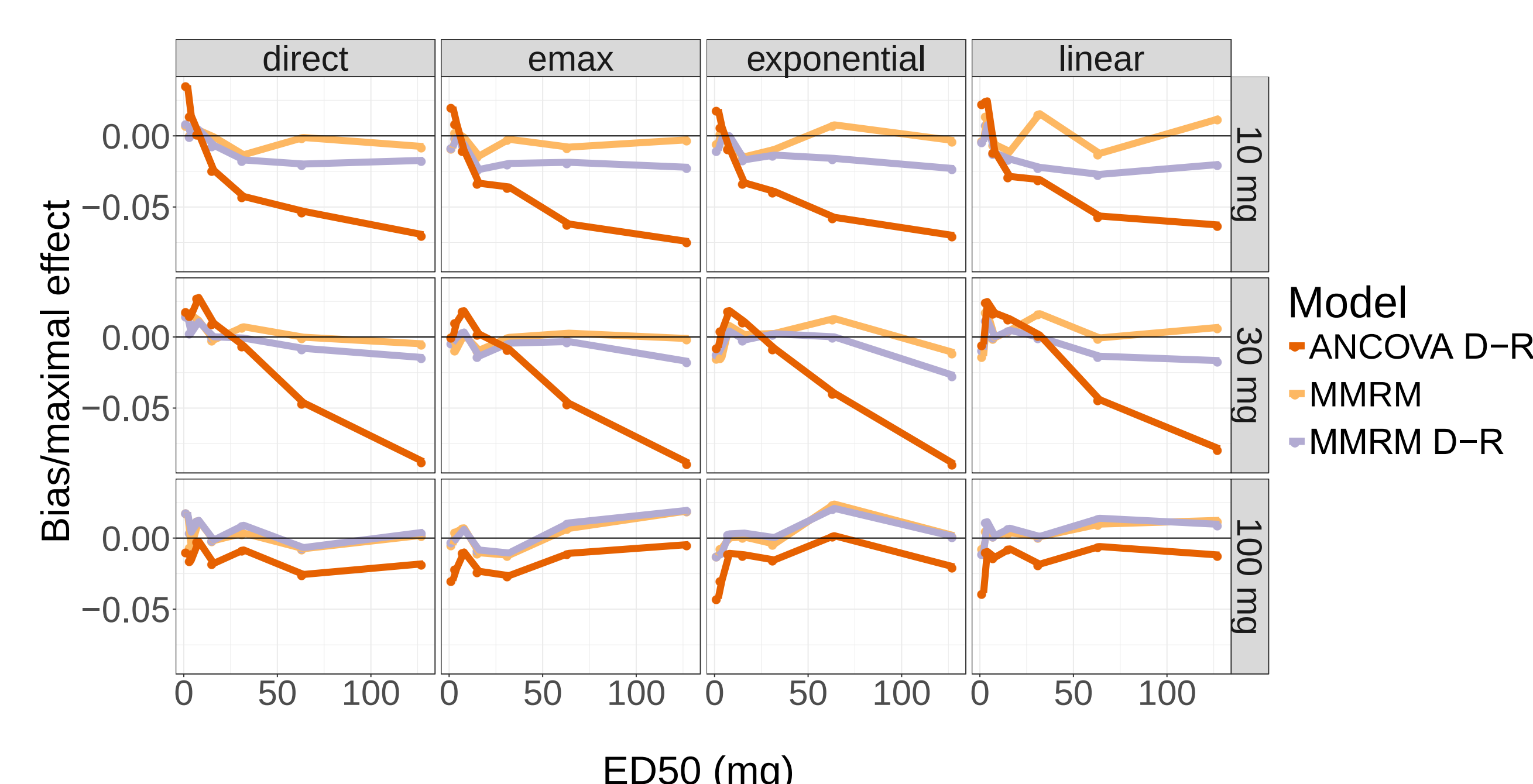


Figure 4: Bias relative to maximal effect, at last visit



The estimation was successful for all cases except one study (out of 28000), when ED50 was 128 mg and the time course was direct.

To the left is depicted an example of the simulated results, where ED50 was 32 mg and the time course of the drug effect was linear. All models have similar predictions and uncertainties of the effect at end-of-study for the highest dose, but for other time points and dose arms the precision is improved when a dose-response relationship is assumed.

The square root of MSE is a measure of both variance and bias. As the bias was very low (see below) this is close to an estimate of the standard deviation. The dose-response-informed models have smaller variance with higher ED50 (excluding the highest dose), while the MMRM has constant variance.

The bias was at most up to ~10% of the maximal effect (40% reduction) for the dose-response-informed models at end-of-study. All models were practically unbiased for the highest dose arm, and the MMRM models were always practically unbiased.

References

- R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.