

A combined model meta-analysis of aggregated and individual FEV1 data from randomized COPD trials

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Background

- Model-based meta-analysis (MBMA) allows integration of aggregated-level data (AD).
- AD are limited in information about interindividual variability (IIV) and the covariate relations.
- Combined modeling with both AD and individual patient-level data (IPD) may take advantage of the information in both data types and allow more informed clinical trial simulations for designing studies.
- Modelling data included aggregated-level data of a legacy MBMA model [2] from 298 studies of chronic obstructive pulmonary disease (COPD) [1], and individual patient-level data of two clinical trials [3,4], which were included in the above MBMA dataset.

Aim

This study aims to establish a combined model for the AD and IPD of COPD clinical trials, including to find suitable methods for estimating ISV/IIV and dealing with aggregation bias from exponential IIV and covariate correlations.

How to estimate inter-study variability (ISV) & interindividual variability (IIV) for rich aggregated data and sparse individual data?

$$FEV1 = B + DPS \cdot TIME + placebo\ effect + drug\ effect$$

Equation 1 Model structure.

FEV1: The endpoint, forced expiratory volume in one second; B: baseline; DPS: disease progression slope. TIME: study time. Placebo effect: Emax placebo effect versus time. Drug effect: EMAX/constant dose-responses were described for 23 compounds.

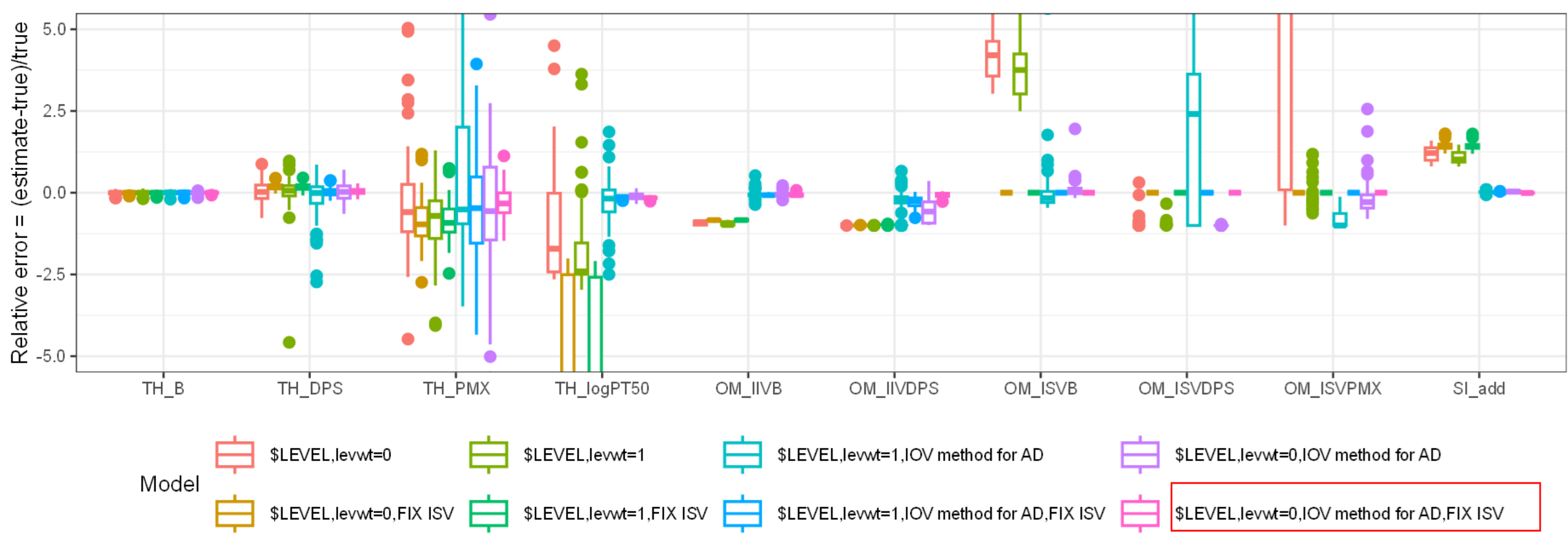


Figure 1 Stochastic simulation and estimations (SSE) results: comparison of different methods to estimate ISV and IIV in combined model.

The best method (red box): Applying \$LEVEL, levwt=0 (i.e., weights each level value equally regardless of subjects number per level value; levwt=1 means weight by subjects number). ISV from the original AD model were fixed. For the AD part, separate ETAs for each arm were used to estimate IIV (same as the method of inter-occasion variability (IOV) [6]). TH: theta; OM: omega; SI: sigma; PMX: maximal placebo effect; PT50: time when placebo effect reach 50%.

How to treat parameter with lognormal IIV when applied to aggregated data?

$P_{ijk} = \theta \cdot e^{\eta_{ijk}}$, $\eta \sim N(0, \omega^2)$ define a lognormal distribution of parameter P , where i: study, j: arm, k: individual.

$\bar{P}_{ij} = \text{mean}(P_{ijk}) = \frac{1}{N} \cdot (P_{ij1} + P_{ij2} + P_{ij3} + \dots + P_{ijN})$ define the P mean of one arm.

According to the central limit theory and properties of expectation and variance,

$$\bar{P}_{ij} \sim N(E(\bar{P}_{ij}), V(\bar{P}_{ij})), \text{ where } E(\bar{P}_{ij}) = E(P_{ijk}) = \theta \cdot e^{\frac{\omega^2}{2}}, V(\bar{P}_{ij}) = \frac{V(P_{ijk})}{N} = \frac{(e^{\omega^2} - 1) \cdot \theta^2 \cdot e^{\omega^2}}{N}.$$

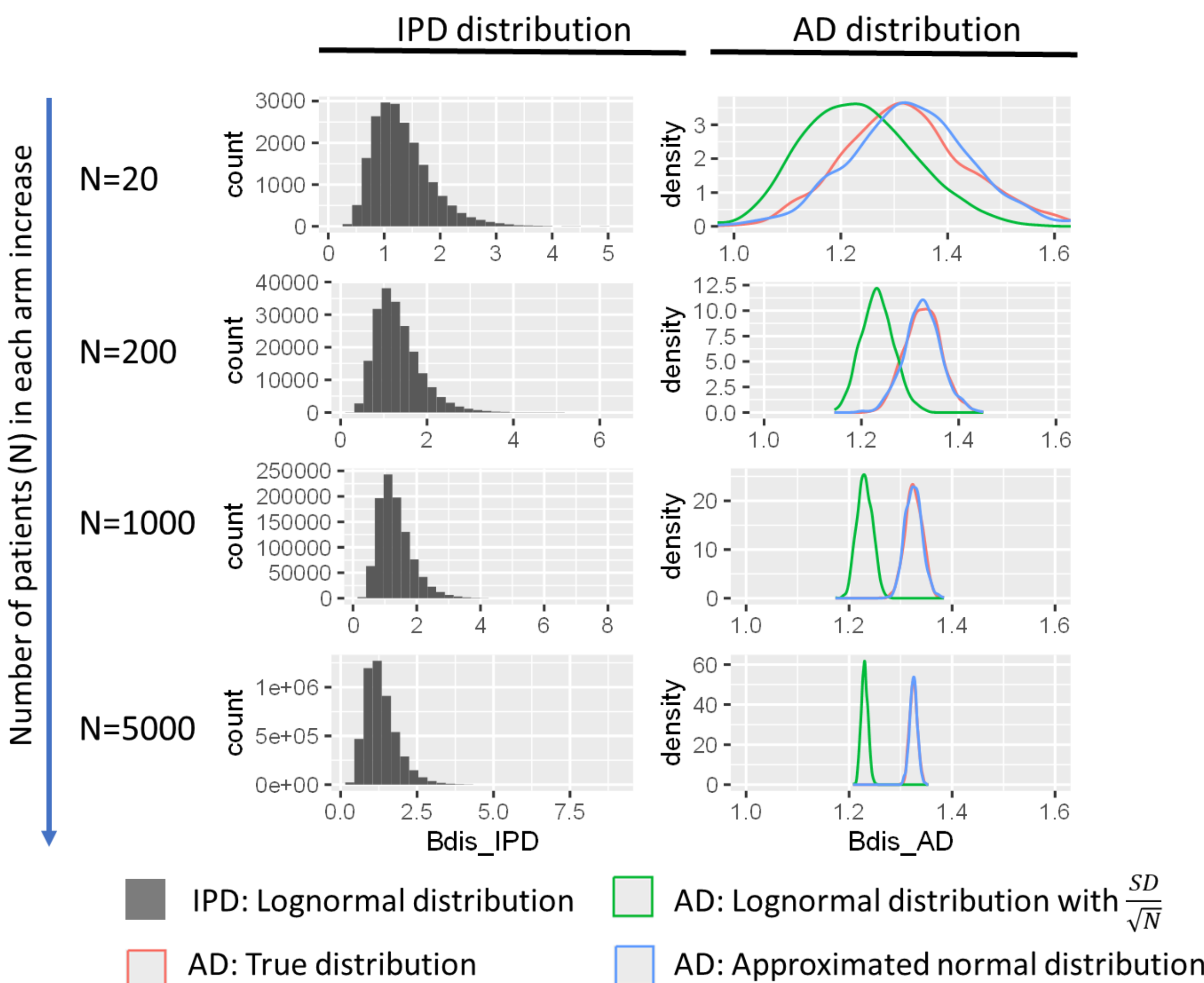


Figure 2 Simulations of distributions of individual/aggregated parameter: the approximated normal distribution showed no bias.

References: [1] [https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)) [2] Llanos-Paez et al. J Pharmacokinet Pharmacodyn. (2023) 50(4):297-314. [3] Kerwin et al. Respir Med. (2013) 107(4):560-9. [4] Martinez et al. Respir Med. (2013) 107(4):550-9. [5] Svensson et al. CPT Pharmacometrics Syst Pharmacol. (2022) 11(9):1210-1222. [6] Karlsson et al. J Pharmacokinet Biopharm. (1993) 21(6):735-50.

Conclusions

- ✓ The combined method of \$LEVEL and separate ETA (ETA is a vector containing random-effect in NONMEM) per arm for IIV and ISV fixed to AD only estimate was identified as the best method for this combined model with rich AD and sparse IPD.
- ✓ The distribution of the mean of parameters with lognormal IIV was approximated by a normal distribution according to the central limit theory.
- ✓ The covariates' correlation in AD were larger than IPD. This difference of correlation did not introduce aggregation bias according to SSE results.
- ✓ The combined modelling of AD/IPD was established for multiple COPD trials. New significant covariates (SEX&SMOKE on baseline) and multiple-level variabilities (ISV/IIV) were identified. Covariate/variability precisions were improved based on the combined modelling.

Is there a difference in covariates correlation between AD and IPD and does it introduce aggregation bias?

Table 1. Covariate correlations of AD and IPD.

Covariate	Correlation of IPD	Correlation of AD	Ratio of AD to IPD
AGE_SEX	0.135	0.301	2.232
AGE_COPD	0.013	0.251	19.403
AGE_SMOK	-0.318	-0.587	1.846
SEX_COPD	0.051	0.177	3.462
SEX_SMOK	-0.093	-0.484	5.198
COPD_SMOK	-0.014	-0.237	16.526

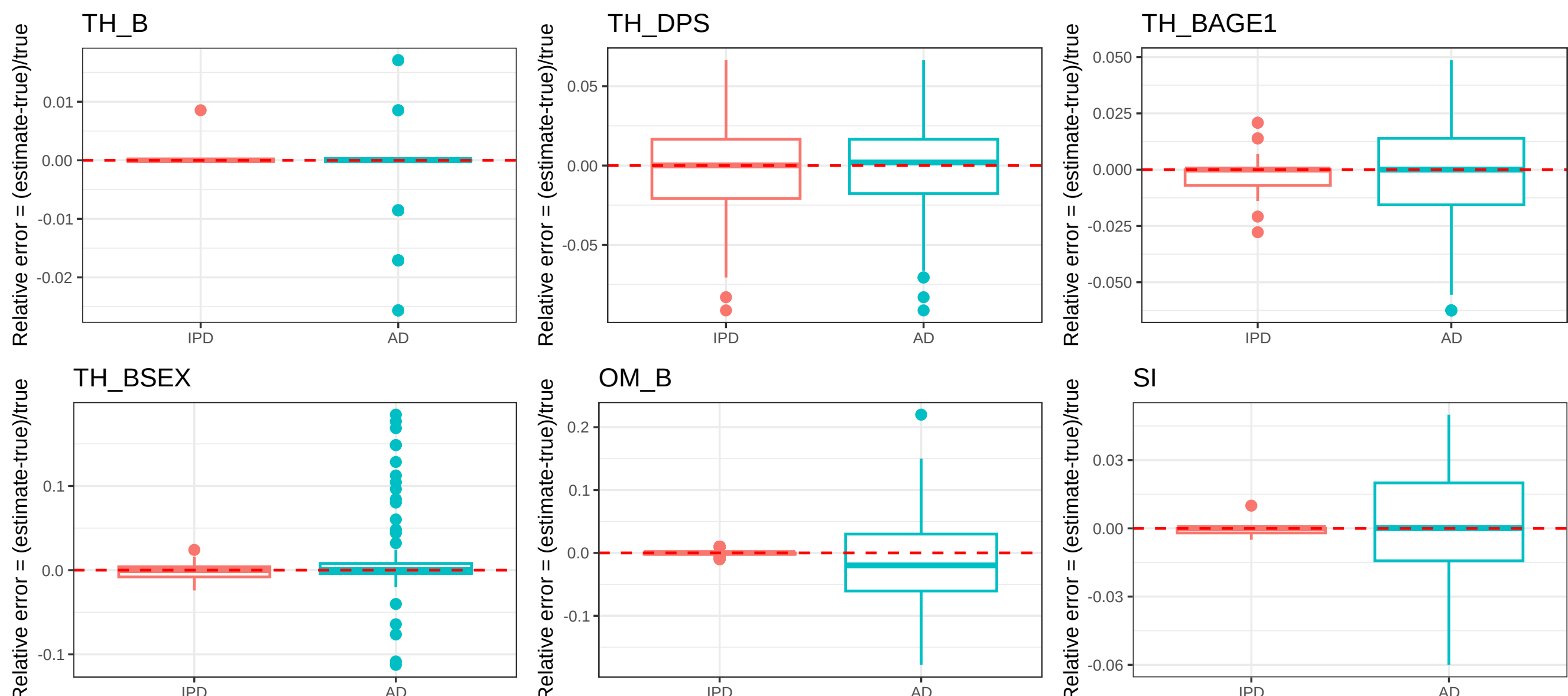


Figure 3 Relative estimation error of model parameters of SSE analysis.

The covariates AGE&SEX was simulate using two-layered (study & individual level) randomness and mean/variance/correlation as the real datasets. AD was the mean of IPD of each study. Estimation was performed on IPD&AD respectively.

Results of nonlinear combined model applying the methods of dealing with aggregation bias.

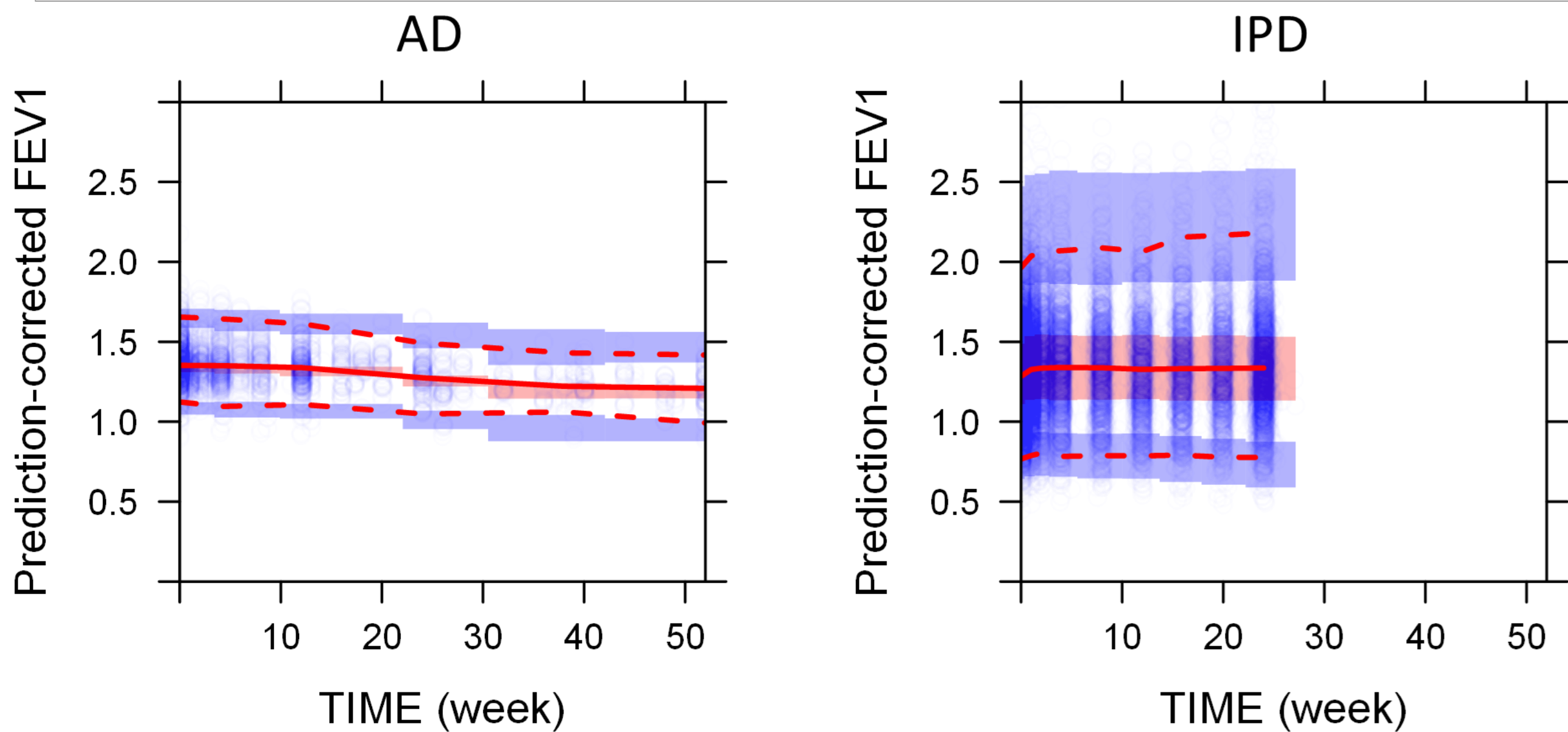


Figure 4 Visual prediction checks (VPC) of the combined model.

Table 2. Improvement on precisions of covariate/variability of the combined model.

RSE%	COPD on baseline	AGE on baseline	Baseline on anti-inflammatory drug effect	Baseline on bronchodilator effect	Baseline IIV
Original AD model	6.7	21.5	37.1	33.1	14.8
Combined model	1.8	3.8	25.4	15.3	1.4

Conflict of Interest: LY, CL-P, MJ and MOK declare that they have no conflict of interest. SY, CA and AB are GSK employees and hold GSK shares.

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