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Prospective Evaluation of a Population Pharmacokinetic Model of Pantoprazole for Obese Children

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Introduction

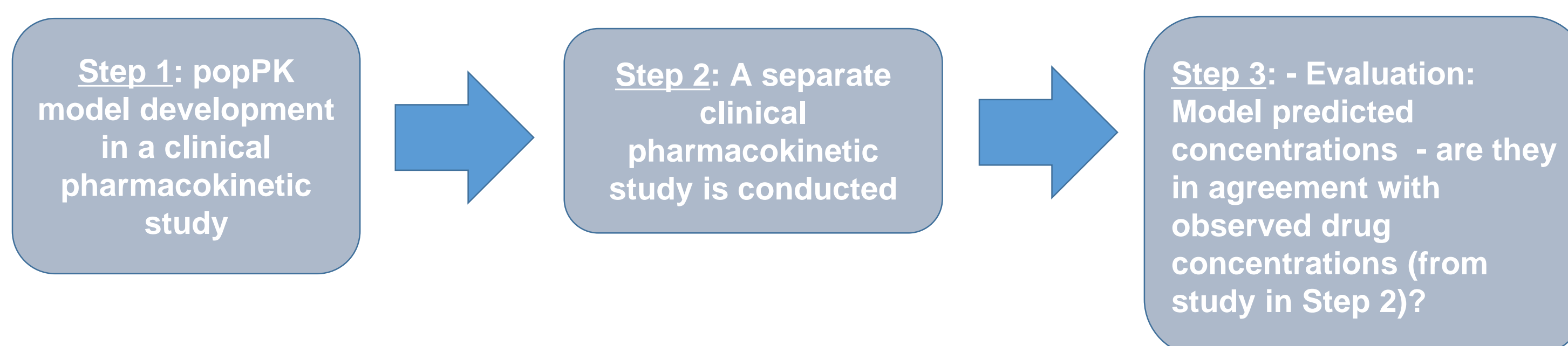
Proton pump inhibitors are commonly prescribed medications for children. Current dosing of proton pump inhibitors (PPIs) relies on weight-based strategies (e.g., mg/kg, weight-tiered). Such dose selection may not be appropriate for obese children, as it could result in over- or under-dosing with subsequent toxicities (i.e., infection, osteopenia) or treatment failure. Since obese children are 6-times more likely to suffer from gastroesophageal reflux disease, and PPIs have become some of the most commonly prescribed drugs to children, there is a critical need to characterize the drivers of variability in systemic exposure to PPIs, other than pharmacogenetic (i.e., CYP2C19 genotype), for obese children.

Objective

We previously developed a population pharmacokinetic (popPK) model of pantoprazole (PAN) for obese children. Our objective was to evaluate the predictive performance of this model in an independent cohort of normal weight, overweight and obese children.

Methods

Figure 1. Approach to Evaluation of a Population Pharmacokinetic (popPK) Model.



Details on prospective evaluation of a popPK model (Step 3).

- **Identify model structure:** 2-compartment structural model with modified first-order absorption ($k_a=7.3 \text{ hr}^{-1}$)
- **Collect typical population parameters and covariate relationships.** Covariates identified to affect PAN PK are weight and CYP2C19 genotype.
- **Predict PAN PK.** Predictions are based on dose, sampling times, and covariates from 57 children.
- **Assess general model predictive performance:** visually and by relative root mean squared error (RMSE)
- **Assess model performance by weight category:** by ratio of predicted-to-observed area under the concentration time curve (AUC)

Results

Figure 2. Time-course of pantoprazole (PAN) plasma concentrations. Following oral administration of a single dose pantoprazole, a total of 546 plasma samples were collected at designated time points from 57 subjects.

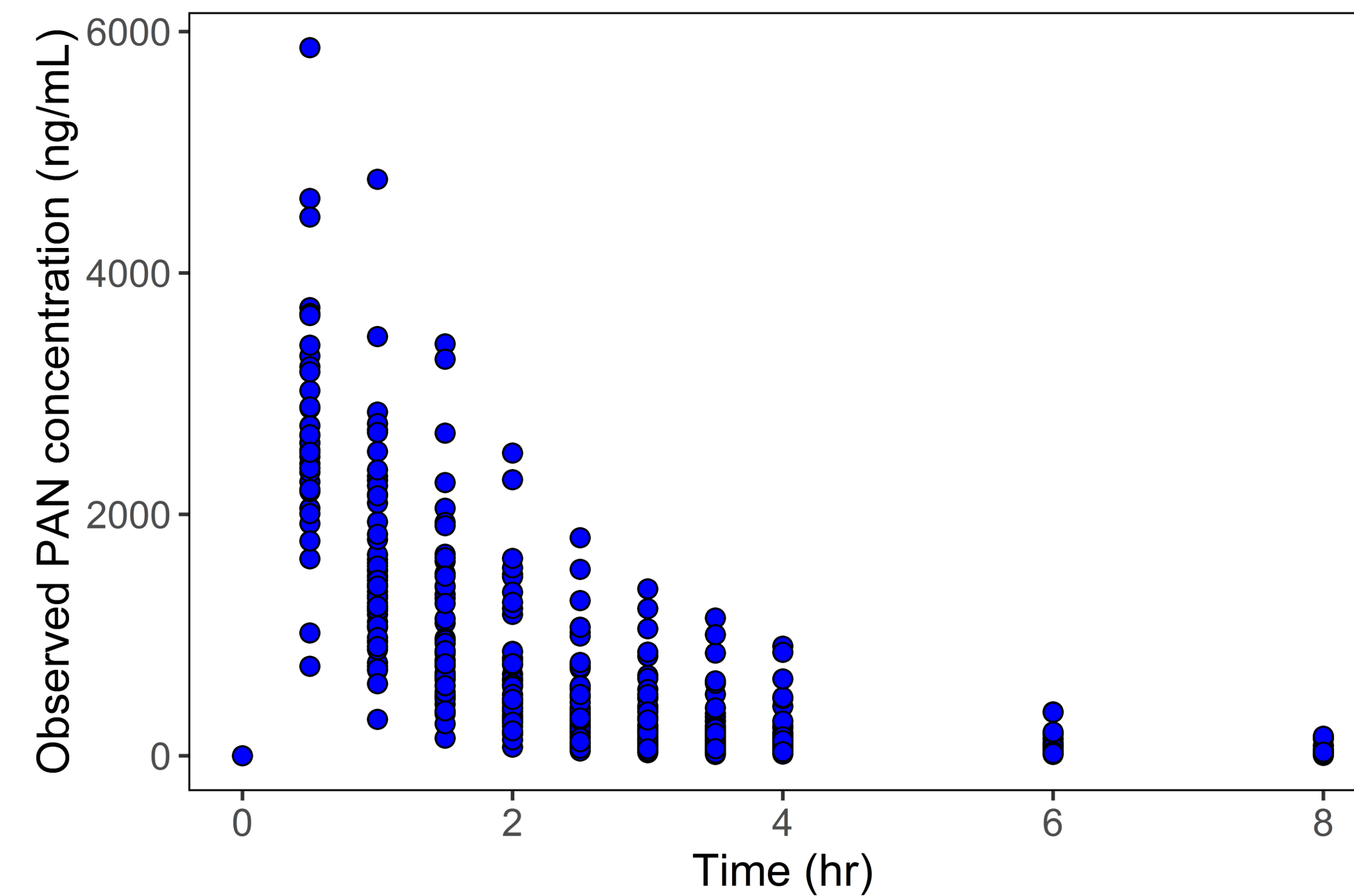


Table 1. Drug formulation and patient demographics from a published popPK study and CMH cohort. In both studies, children were enrolled prospectively and received a single oral dose of pantoprazole based on their respective lean body weight. CYP2C19 phenotype was assigned according to the characterized genotypes of each subject: Intermediate metabolizer (IM): CYP2C19*1*2 or *2*17; Normal metabolizer (NM): CYP2C19*1*1 or *1*17.

	Published popPK study	CMH cohort
Drug formulation	PAN delayed release	PAN immediate release
Number of patients (M/F)	N=40 (18/22)	N=57 (24/33)
Age range (yr)	6-17	6-17
Weight category	Obese (n=40)	Normal (n=29), Overweight (n=16), Obese (n=12)
Weight range (kg)	32.4-131.6	18.5-124
BMI range	22.1-42.0	15-41.72
CYP2C19 phenotype	IM=18 NM=21	IM=13 NM=44

Results

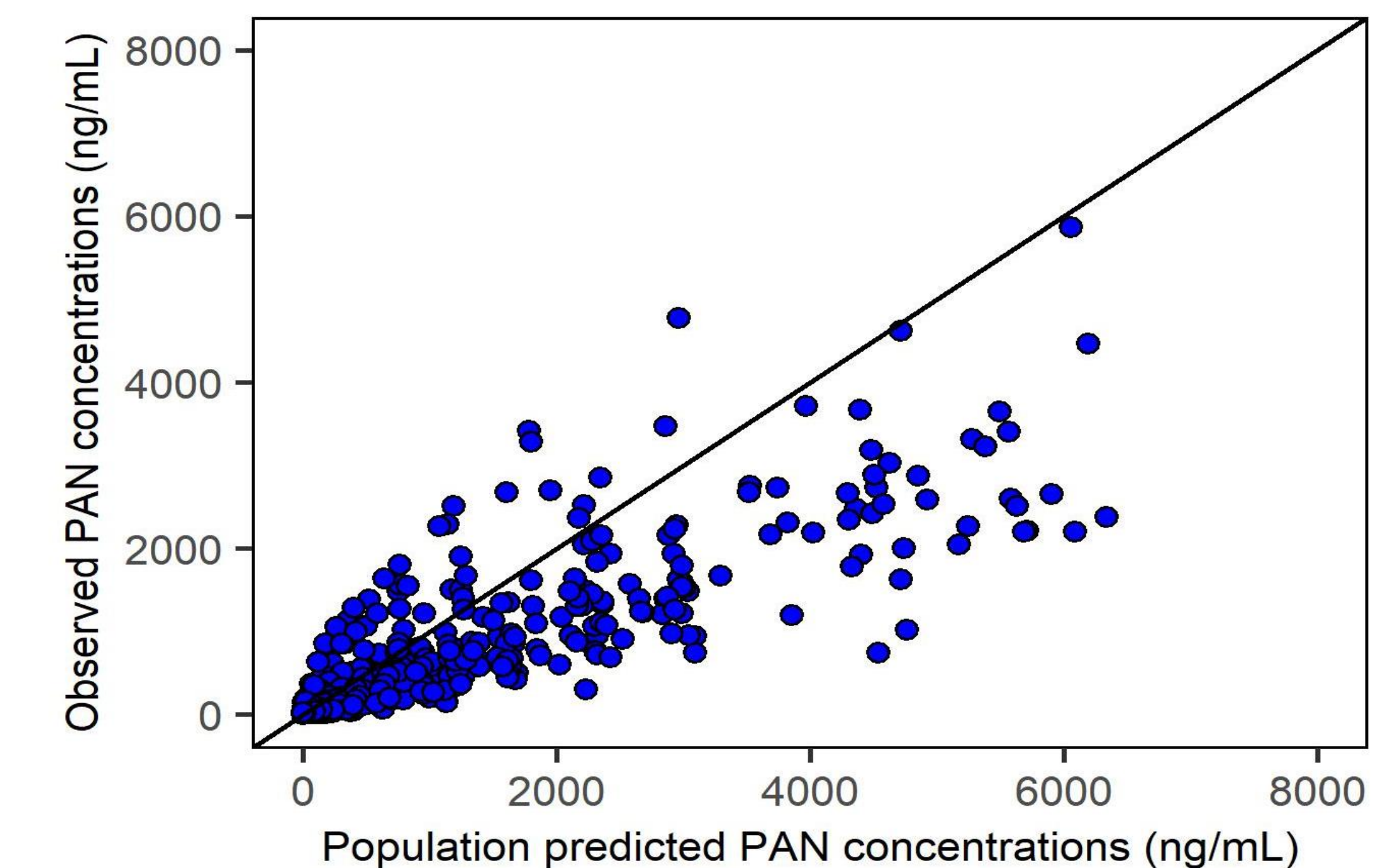


Figure 3. Comparison of observed and population predicted PAN concentrations. The popPK model generally overpredicted PAN concentrations (RMSE = 194%). The overprediction is mostly noticed at higher concentrations.

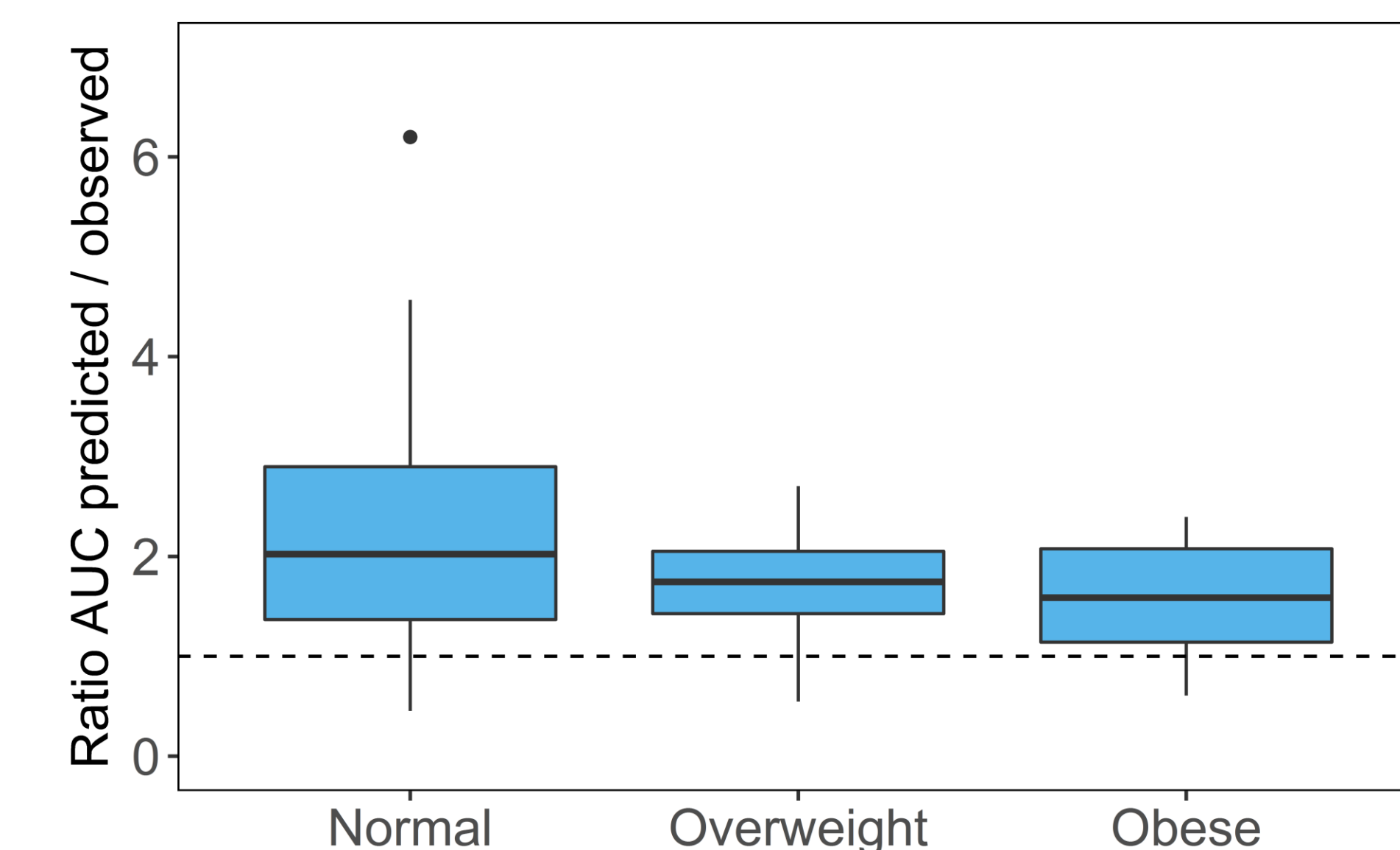


Figure 4. PAN predicted / observed AUC ratios stratified by weight category. The AUC ratios were not significantly different among normal, overweight and obese groups (2.2 vs. 1.7 vs. 1.5, $p=0.06$); however, a trend toward a better model prediction is seen in obese children.

Conclusions

- Overprediction of observed PAN concentrations may be due to differences in PAN formulation (delayed vs. immediate release) between studies.
- Ongoing study of a delayed release PAN will assess formulation effect, which will allow further refinement of existing popPK model.
- Our ultimate goal is to identify appropriate dosing strategy for PAN and other PPIs to prevent over- or under-dosing.

References

Shakhnovich et al. A Population-Based Pharmacokinetic Model Approach to Pantoprazole Dosing for Obese Children and Adolescents. Pediatric Drugs 2018. PMID: 30097906