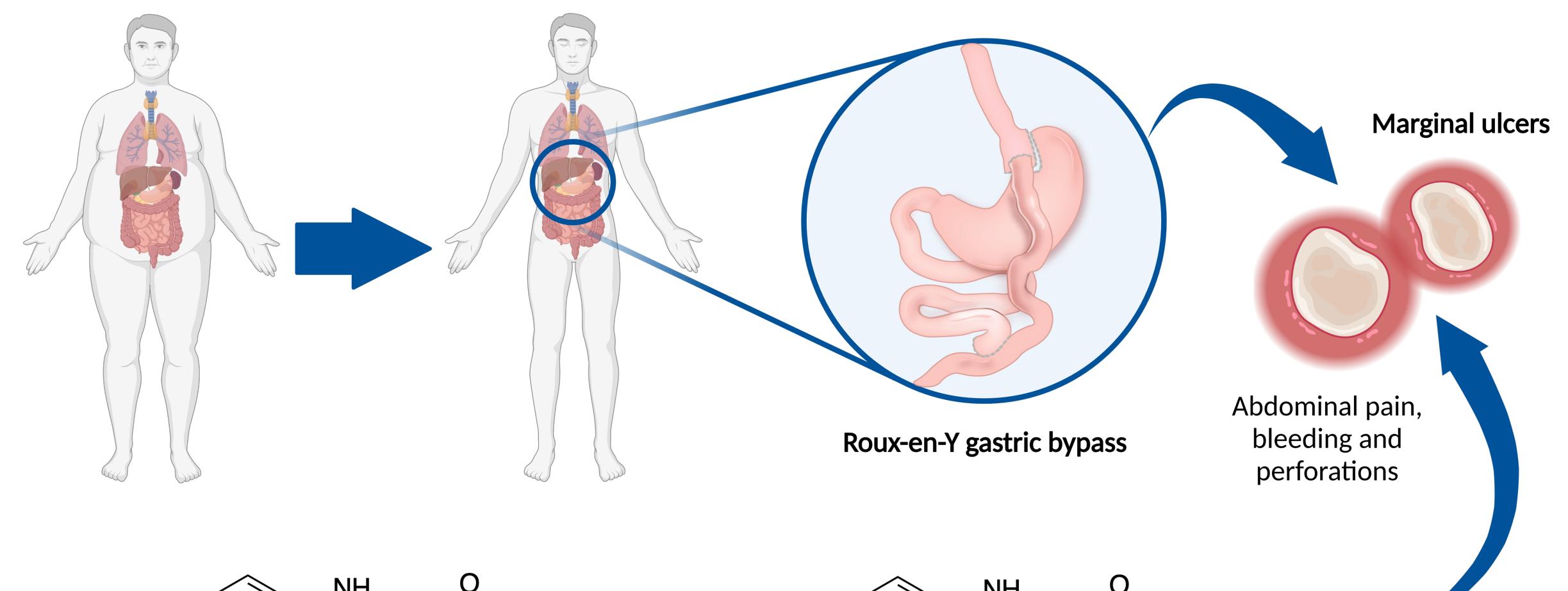


The down-regulation of CYP3A4 and CYP2C19 in obese patients is restored after gastric bypass: PBPK modeling for omeprazole as a probe drug

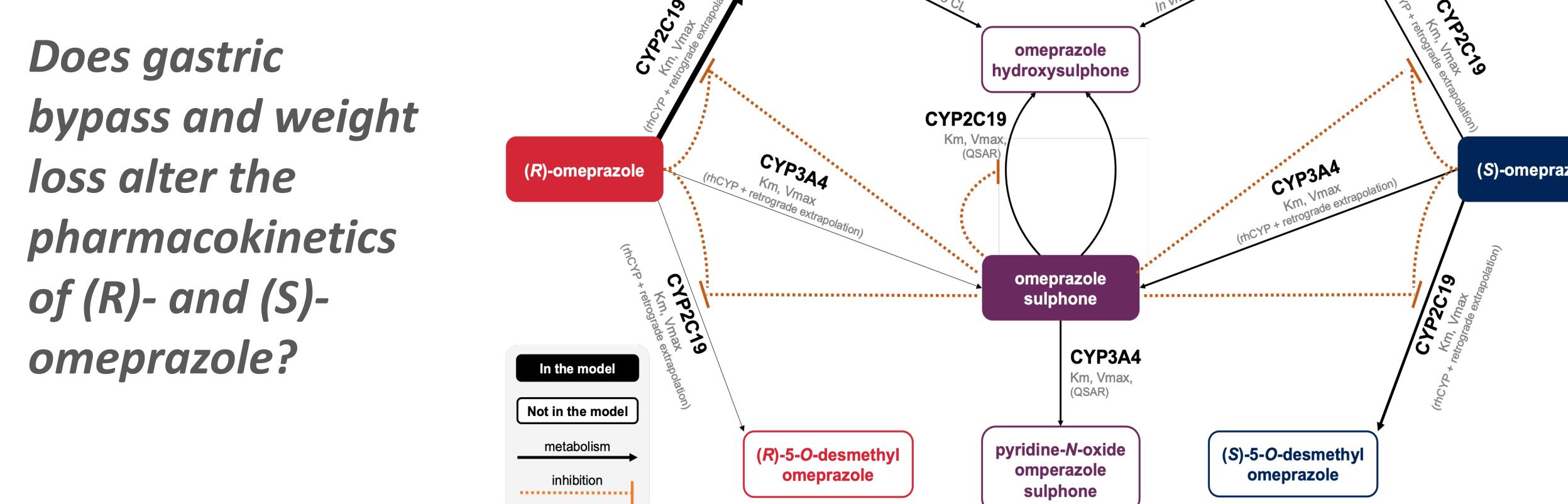
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Background



Does gastric bypass and weight loss alter the pharmacokinetics of (R)- and (S)-omeprazole?



Results

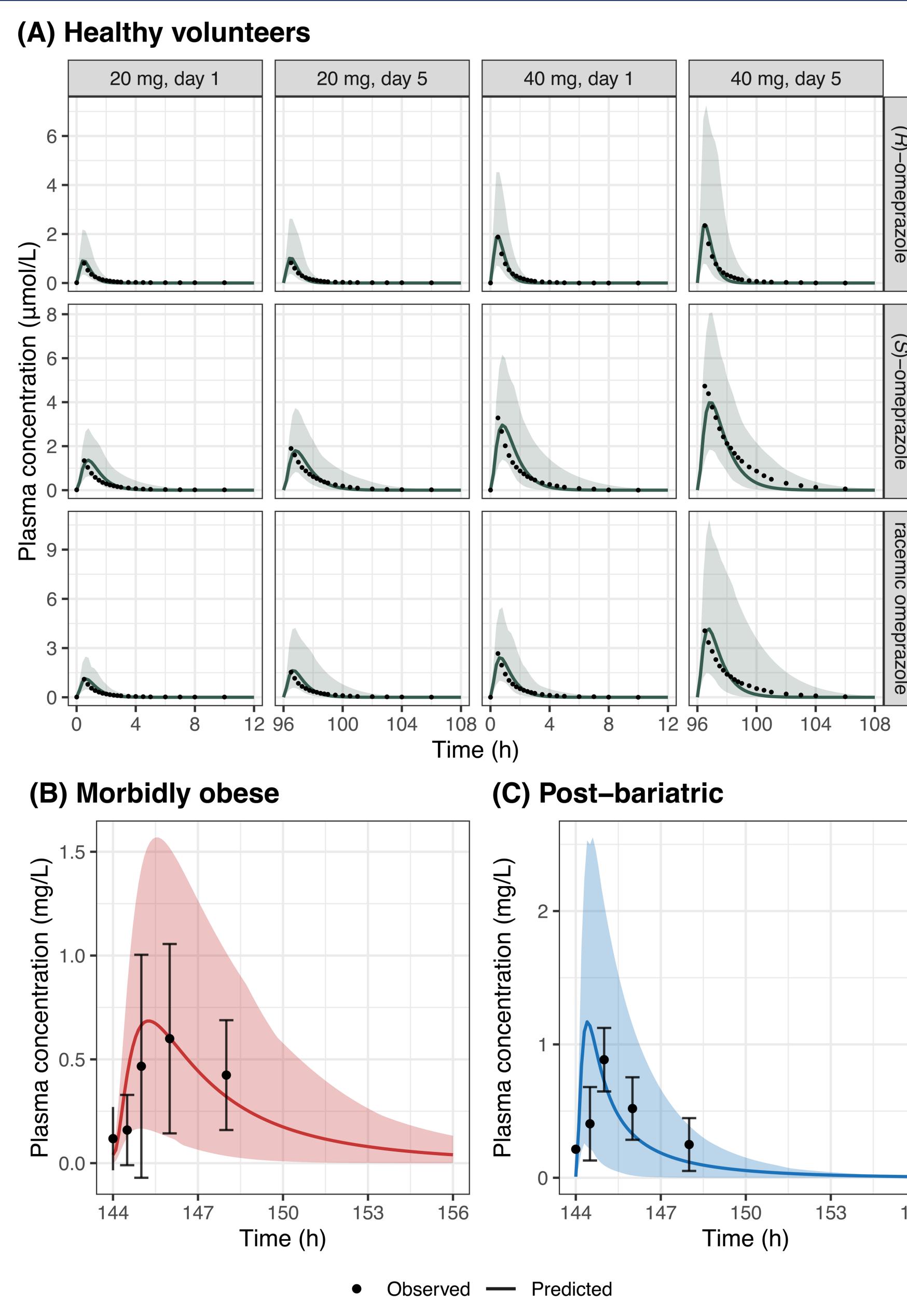


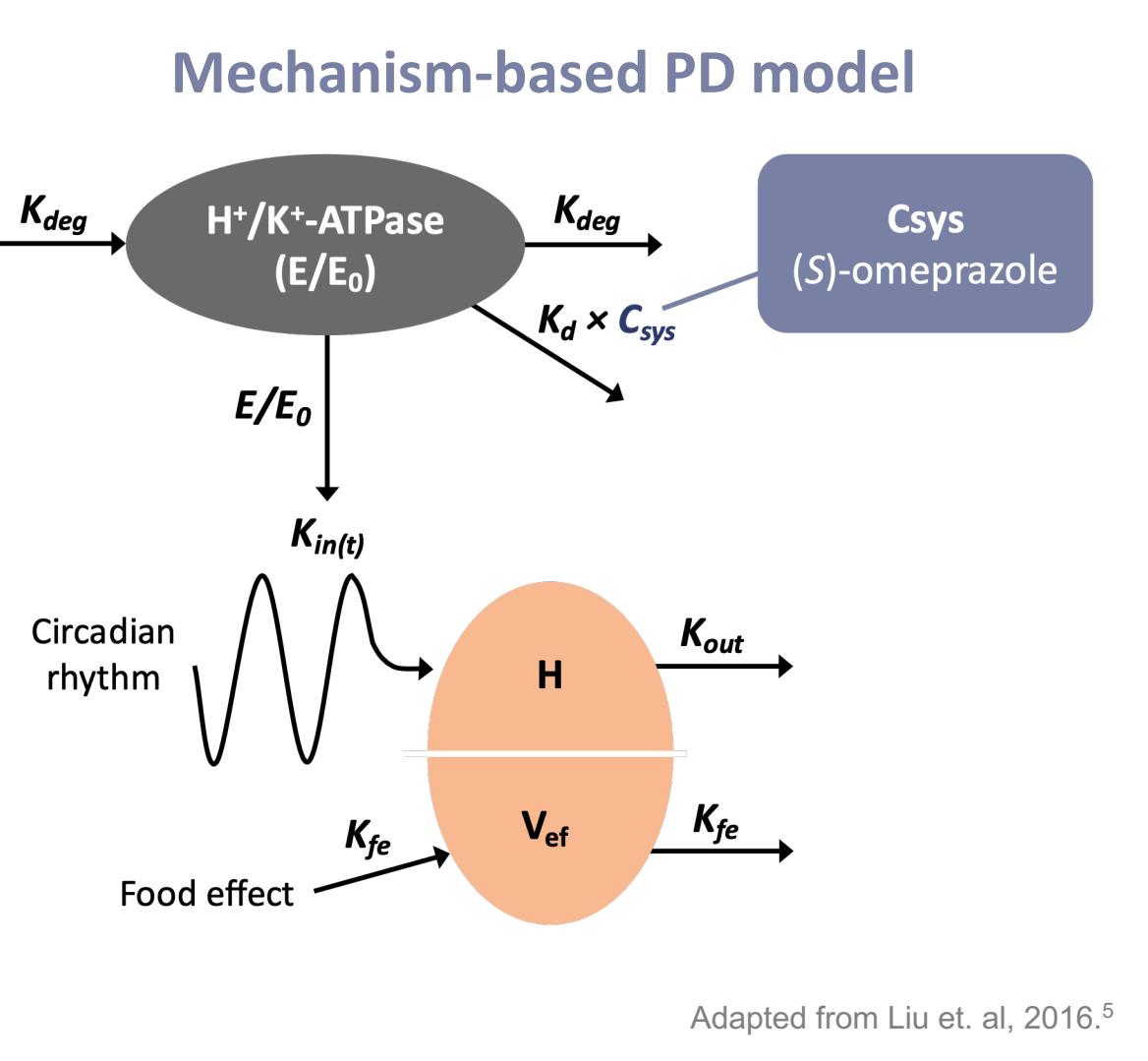
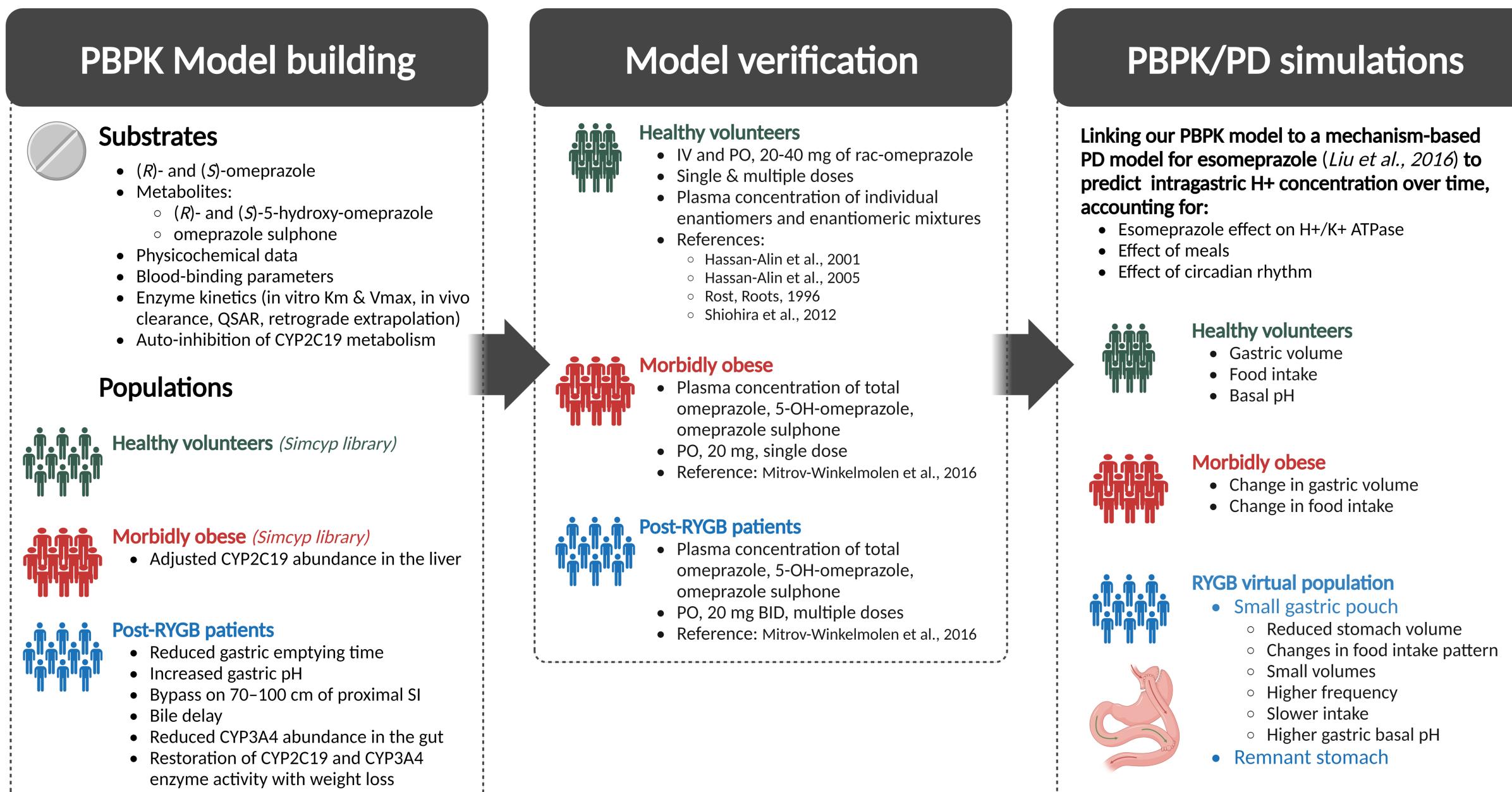
Figure 1. Predicted vs. observed plasma concentration. (R)-, (S)-, and racemic omeprazole in healthy volunteers¹ (A), and morbidly obese² (B) and post-bariatric subjects (C).²

The model accurately describes the PK of omeprazole and its metabolites

Objectives

- Characterize the effect of obesity and weight loss progression after gastric bypass on the pharmacokinetics of (R)- and (S)-omeprazole and its main metabolites
- Explore the effect of (S)-omeprazole on gastric pH after the Roux-en-Y gastric bypass

Methods



Results

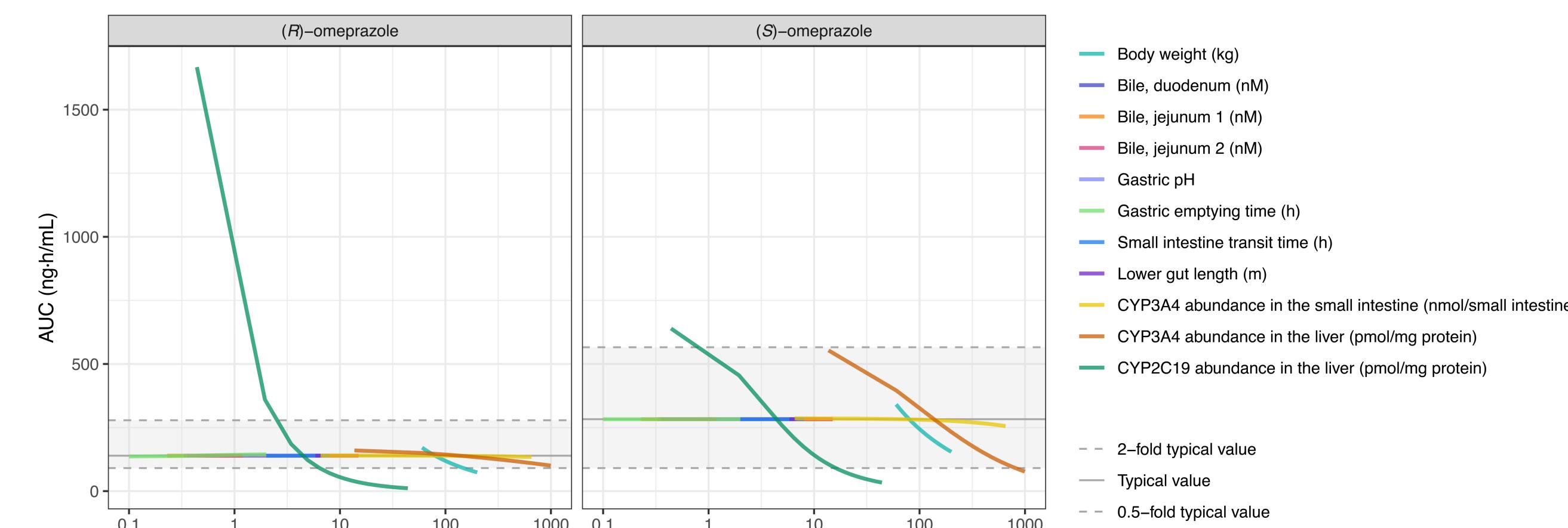


Figure 2. Parameter sensitivity analysis of dependent variables affecting the AUC of (R)- and (S)-omeprazole.

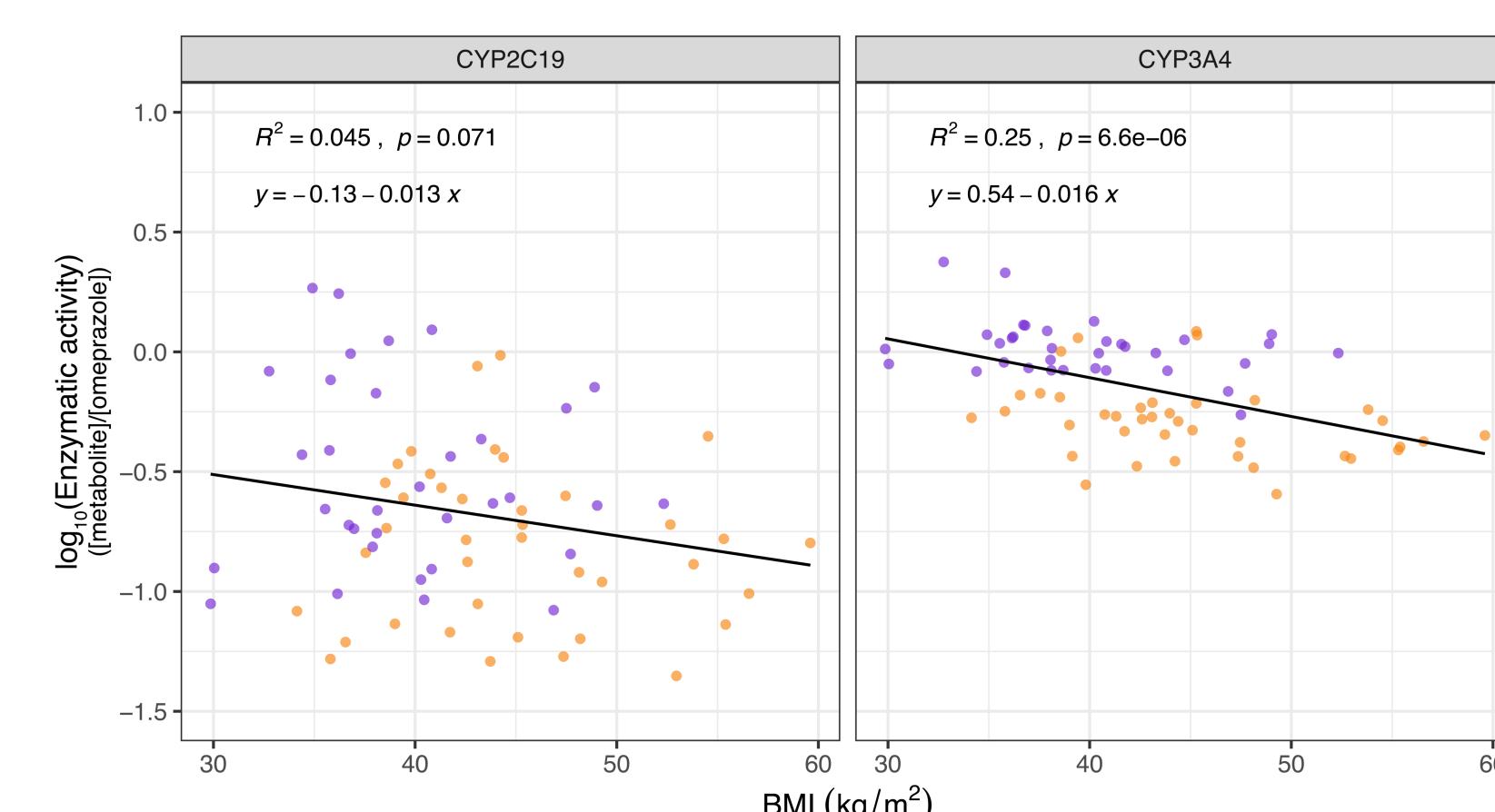


Figure 3. Correlations of enzymatic activity for CYP2C19 and CYP3A4 by BMI in clinical data.²

Table 1. Total abundances of CYP2C19 and CYP3A4 in simulated populations.

Population	Total abundance (μmol)		
	[Geometric mean (90% CI)]	CYP2C19	CYP3A4
Healthy volunteer	0.25 (0.22–0.28)	7.12 (6.56–7.73)	
Morbidly obese	0.20 (0.18–0.23)	5.30 (4.85–5.80)	
Post-bariatric	0.24 (0.21–0.28)	8.00 (7.30–8.76)	

Local Sensitivity Analysis showed the hepatic abundance of CYP2C19 and CYP3A4 are the main factors impacting AUC

Clinical data² showed the in vivo activities of CYP2C19 and CYP3A4 are reduced in obese subjects, and is restored with weight loss

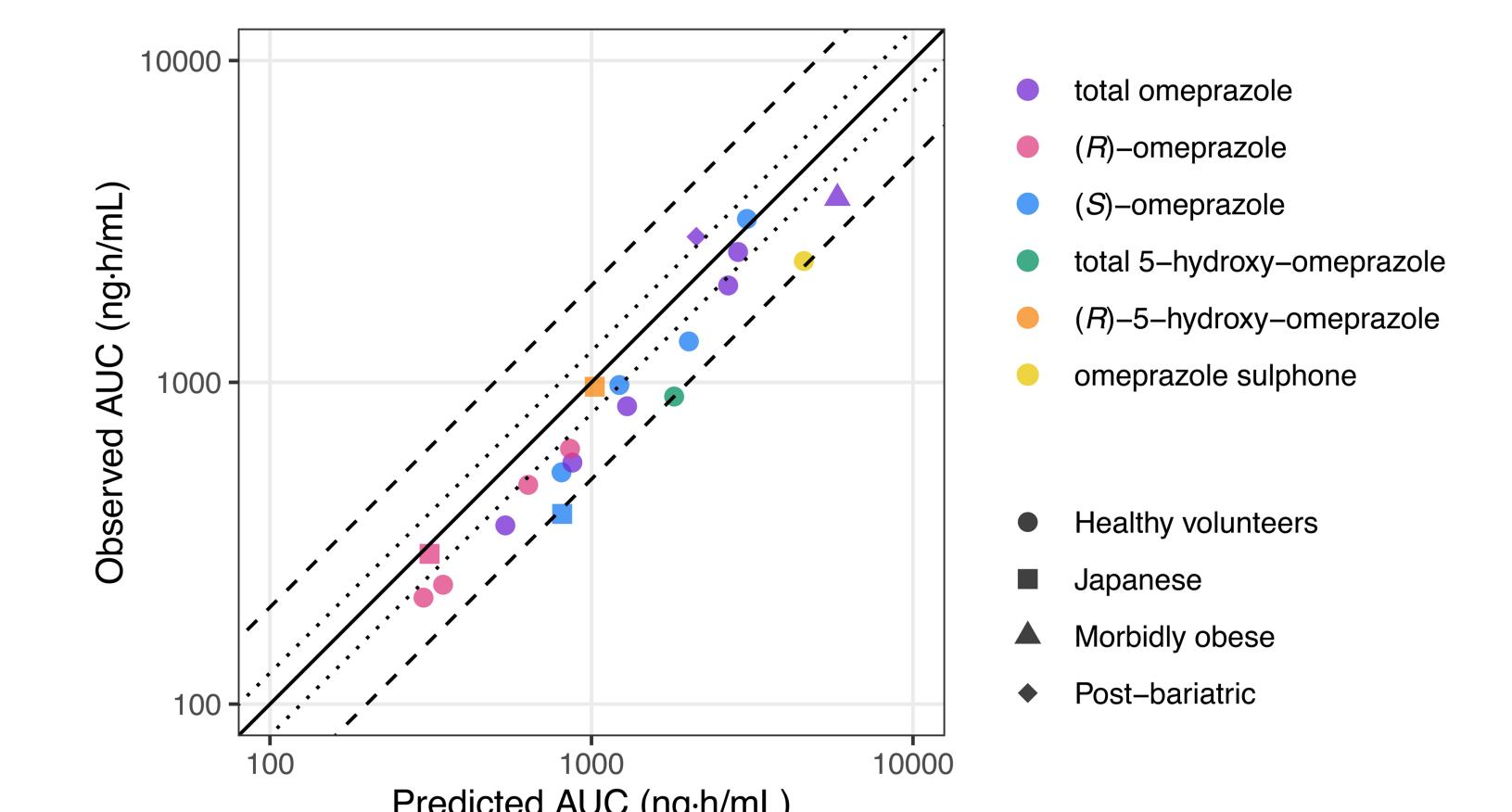


Figure 4. Goodness of fit plot illustrating the model performance. The solid line represents the line of identity, the dotted lines indicate 1.5-fold deviation; the dashed lines indicate two-fold deviation.^{1–4}

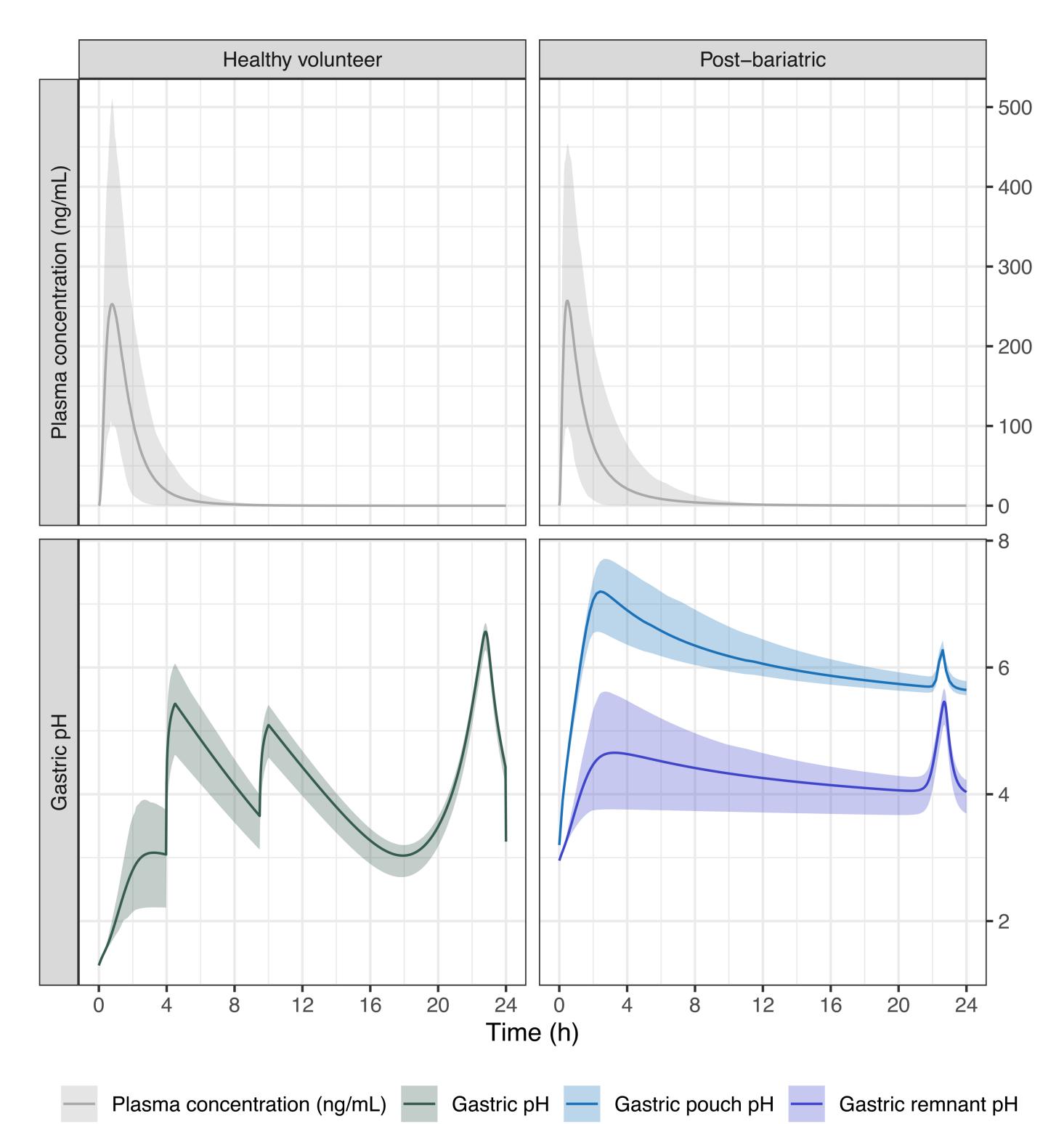
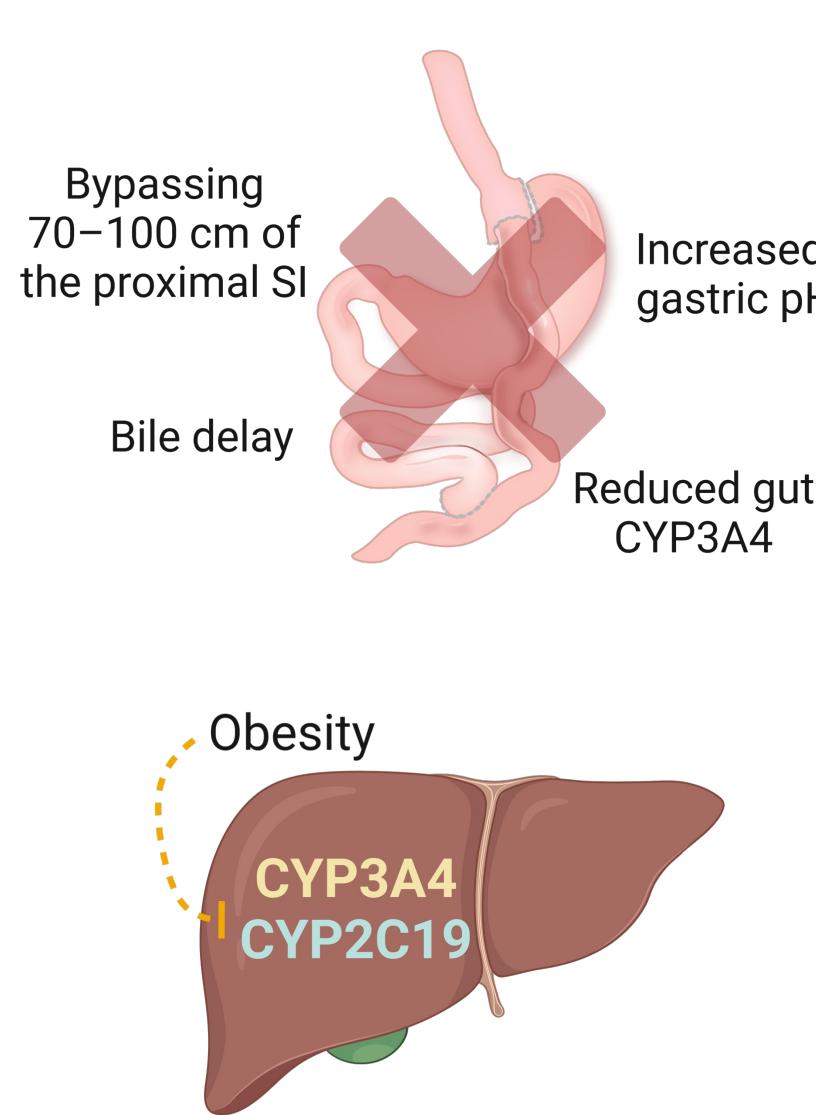


Figure 5. PBPK/PD simulation of the effect of (S)-omeprazole in healthy volunteers and post-bariatric populations.

Conclusions

- We successfully developed a PBPK model incorporating mechanism-based and competitive inhibition for (R)- and (S)-omeprazole, and its main metabolites in healthy volunteers, morbidly obese and post-Roux-en-Y gastric bypass patients
- The regulation of hepatic CYP2C19 and CYP3A4 significantly influences the exposure to (S)-omeprazole, whereas the regulation of hepatic CYP2C19 enzyme has a major impact on (R)-omeprazole exposure
- The link of a mechanism-based PD model to explore the effect of (S)-omeprazole and Roux-en-Y gastric bypass showed the pH is significantly increased in these subjects compared to healthy volunteers, and the dietary regimen, consisting of fractionated small meals, does not impact the pH of the gastric pouch due to the low volume of the meals and higher basal pH

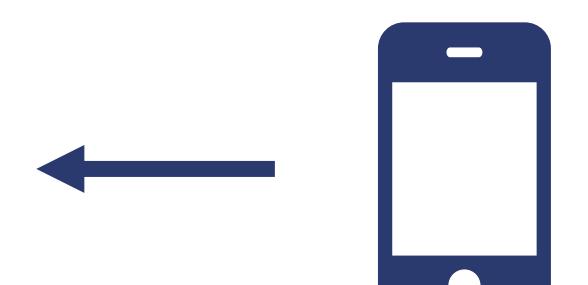


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Additional information



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