



Objectives

Lung function is an important indicator of asthma [1]. Although the relationship between aging and lung function in healthy people has been previously studied [2], lung function progression in asthma has not been similarly explored [1]. This study aimed to quantify lung function, expressed as FEV1, progression of asthma and to evaluate short-term and long-term effects after formoterol and terbutaline treatments.

Methods

The FEV1 data set was collected pre- and 30 min post-dose in two randomized (terbutaline or formoterol), double-blind, multi-centre, parallel designed 12-months clinical trials [3] in 1130 patients (nobs=16610) with intermittent or mild persistent asthma.

The equation for healthy subjects [4] was re-estimated to quantify lung function progression in asthma (Figure 1). Drug effects, aging effects, and the difference between intermittent asthma and mild persistent asthma were analyzed in NONMEM. Visual predictive checks (VPCs) were employed for model evaluation.

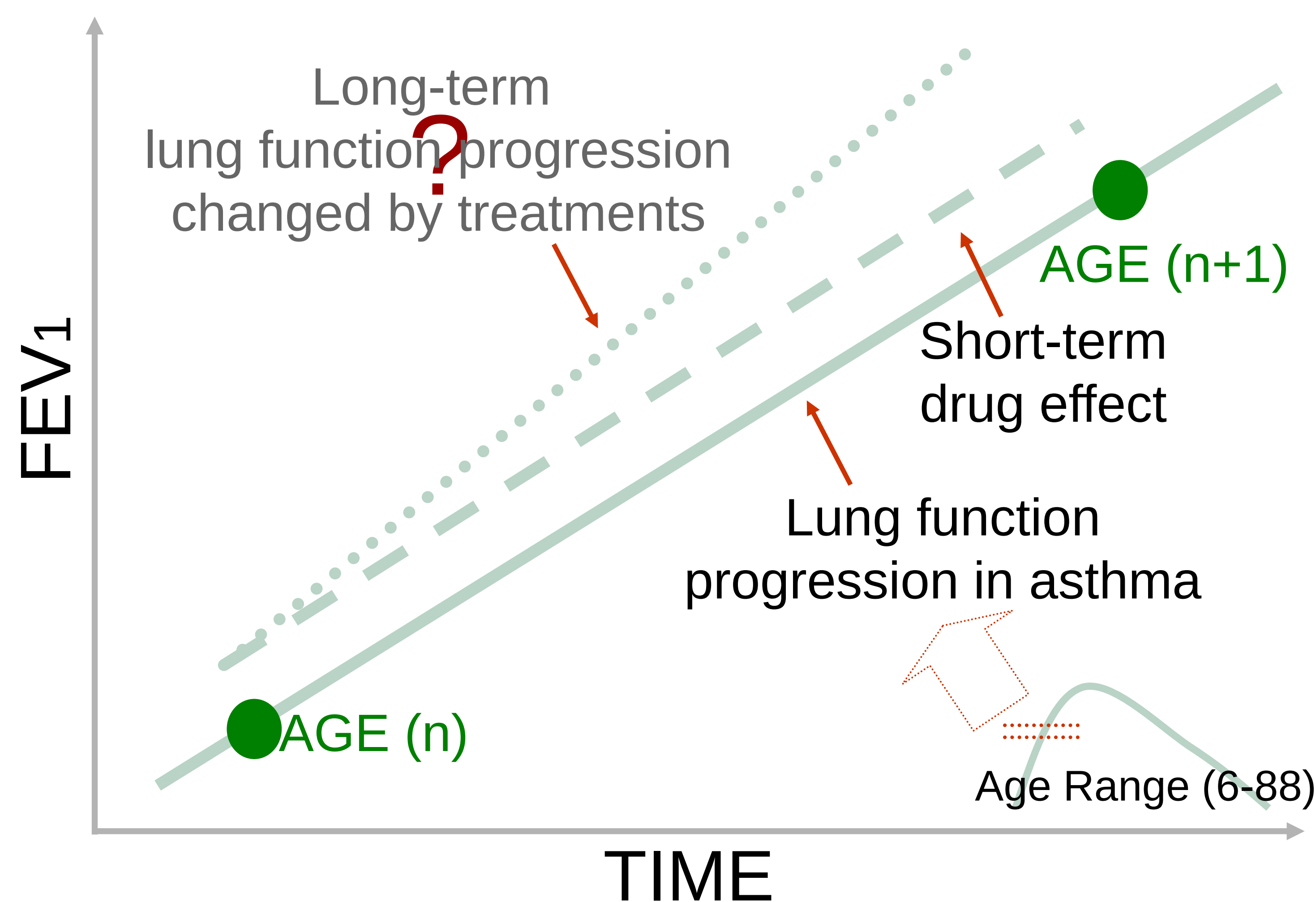


Figure 1. Three components of lung function in asthma: progression, short-term drug effect, and long-term lung function progression changed by treatments.

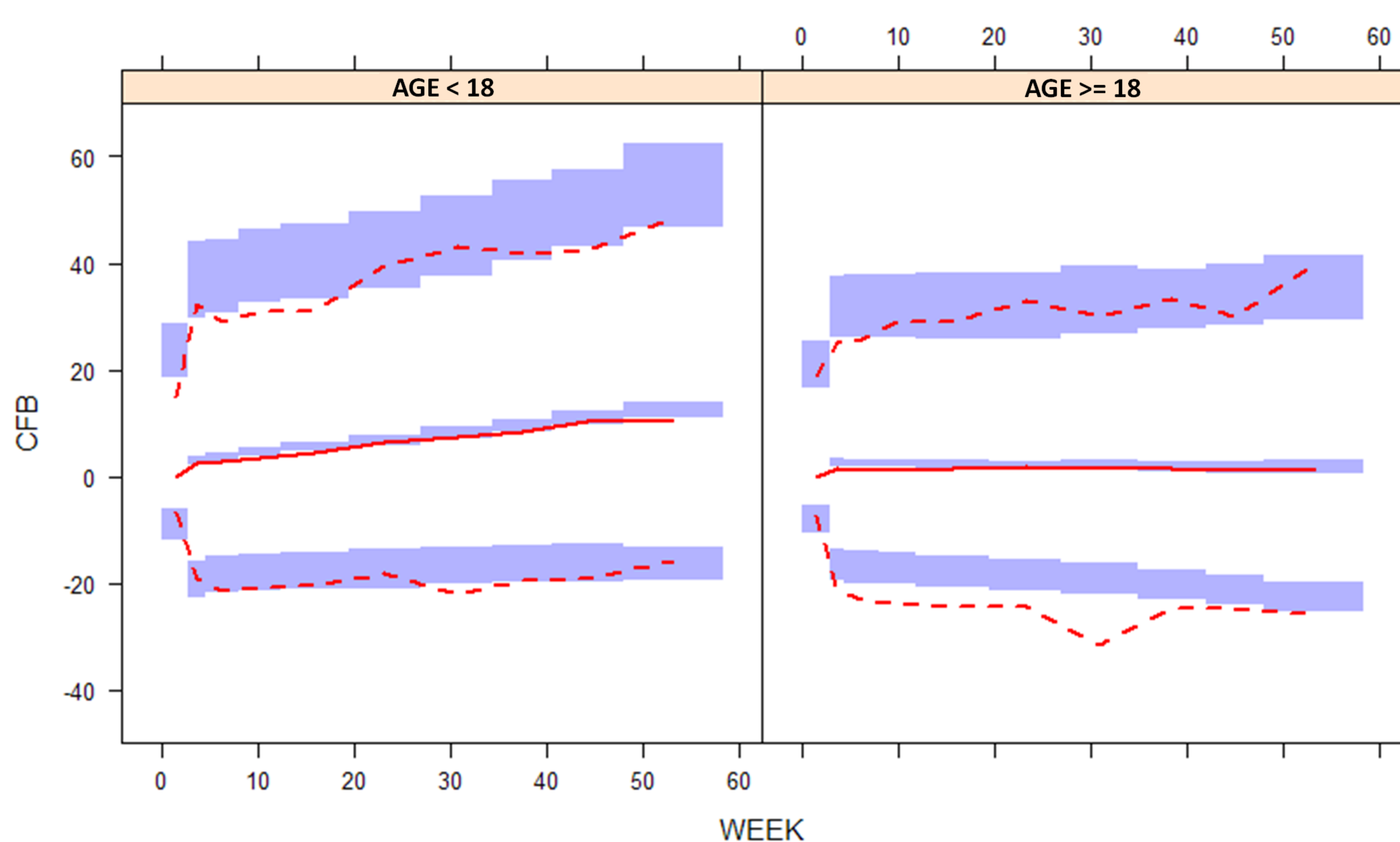


Figure 2. VPCs. Change from baseline (CFB) vs time in study. Red lines are 5th, 50th and 95th intervals of observed data. Shaded areas are 95% CIs for the 5th, 50th and 95th prediction intervals based on simulated data.

Results

The model described the data well. The difference in lung function progression between intermittent asthma and mild persistent asthma was not significant. FEV1 in asthma could be quantified as: $FEV1 = \text{EXP}(0.174 \cdot \text{LOG}(\text{AGE}) + 0.122 \cdot \text{LOG}(\text{WT}) + 0.0168 \cdot \text{HT} - 0.00141 \cdot \text{WT} - 0.011 \cdot \text{AGE} - 2.33)$; (IIV 14%). VPCs based on AGE, WT and HT (Figure 3) revealed that the predictions were in accordance with observations. Change from baseline (Figure 2) shows that lung function increases before 18 years old.

Based on the above FEV1 progression function, the drug effects of formoterol and terbutaline, regardless of asthma status (intermittent or mild persistent), were determined to be similar (Figure 4). The acute improvement of lung function after treatments was about 6% (IIV 46%). The change in FEV1 during the study period was in agreement with ageing of the patients, without any long-term drug-effect on lung function.

Conclusions

Lung function progression of asthma was quantified. Formoterol and terbutaline equally improved lung function 30 min post-dose, but no long-term influence from drug therapy was evident on lung function progression. This study also proposed a population approach to model chronic disease progression from normal clinical trial designs.

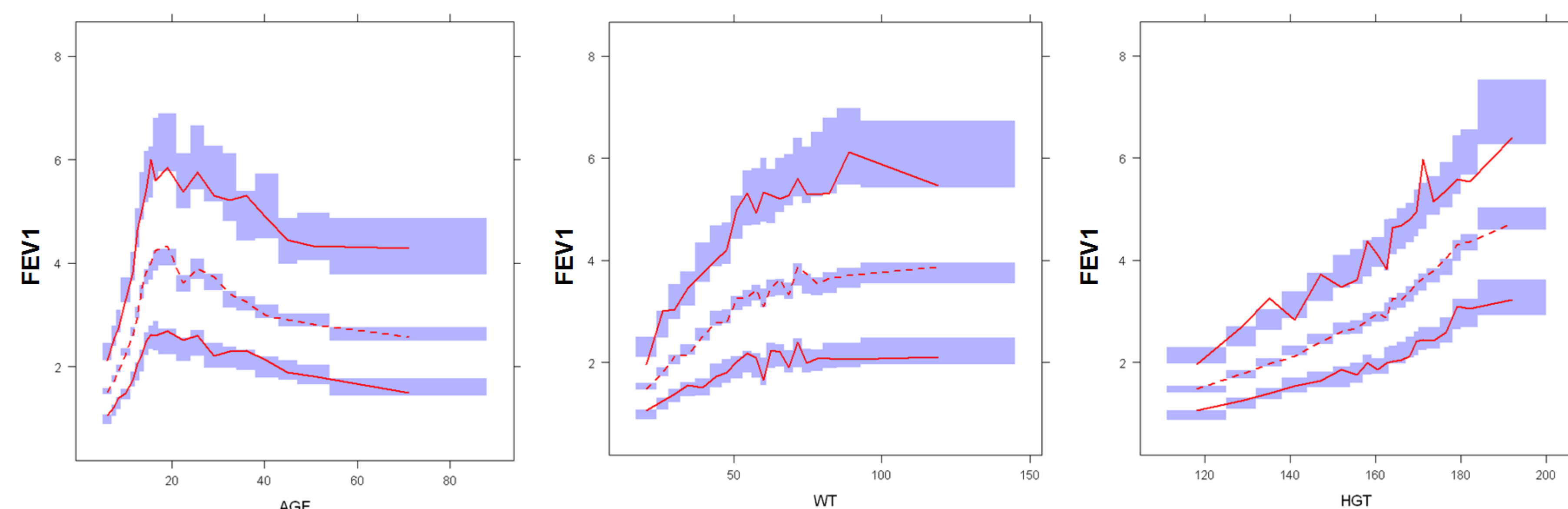


Figure 3. VPCs. Lung function vs age, weight, height in asthma. Red lines are 5th, 50th and 95th intervals of observed data. Shaded areas are 95% CIs for the 5th, 50th and 95th prediction intervals based on simulated data.

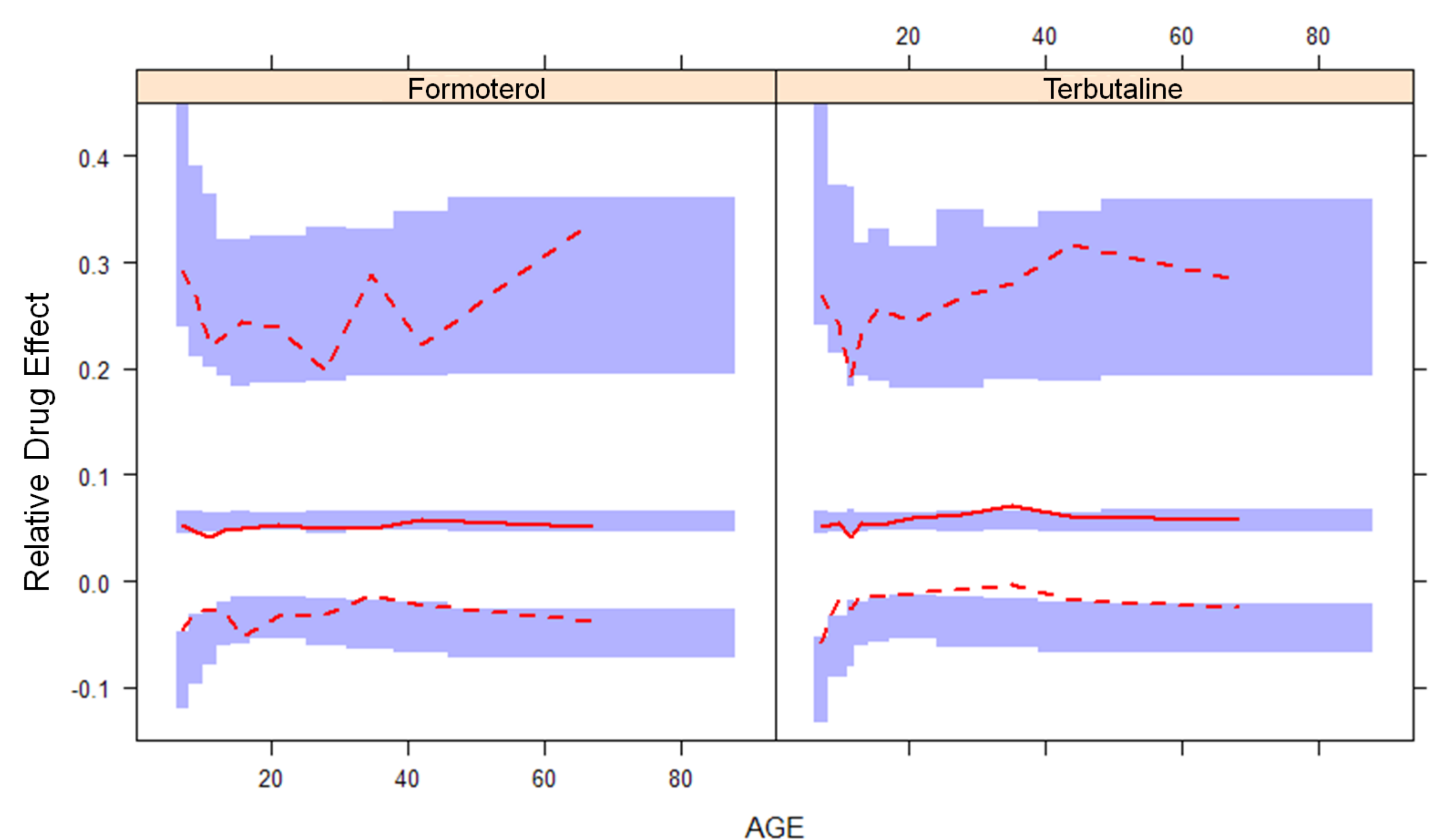


Figure 4. VPCs of Relative Drug Effect for Formoterol and Terbutaline. Relative drug effect = (Postdose – Predose)/Predose. Red lines are 5th, 50th and 95th intervals of observed data. Shaded areas are 95% CIs for the 5th, 50th and 95th prediction intervals based on simulated data.

References

1. Pedersen, S. Am J Respir Crit Care Med; 2004; **170**(3): p. 206-207.
2. Chan, P.L. and N.H. Holford. Annu Rev Pharmacol Toxicol; 2001; **41**: p. 625-59.
3. Chuchalin, A., et al. Respir Med; 2005; **99**(4): p. 461-70.
4. Kristufek, P., et al. Bull Eur Physiopathol Respir; 1987; **23**(2): p. 139-47.