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INTRODUCTION

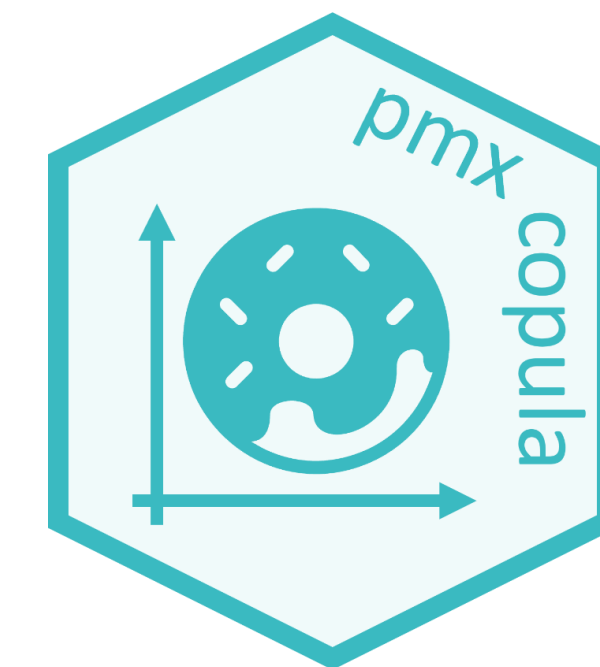
Background

- Incorporating **realistic patient covariates**, i.e. virtual populations, is crucial to achieving realistic model-informed precision dosing.
- **Copulas** can correctly account for covariate distributions, both **marginal distributions** and the **dependency structure**.
- Realistic virtual populations can be simulated from copulas [1,2].

- Copulas that have been evaluated and verified can be **easily shared** and **reused**.
- The **evaluation tools** for copula-based covariate simulation are lacking.

Aim

To streamline the application of copulas in pharmacometric workflows by developing **pmxcopula**, an integrated R package with easy-to-use functions for copula evaluation and application.



WORKFLOW & EXAMPLE

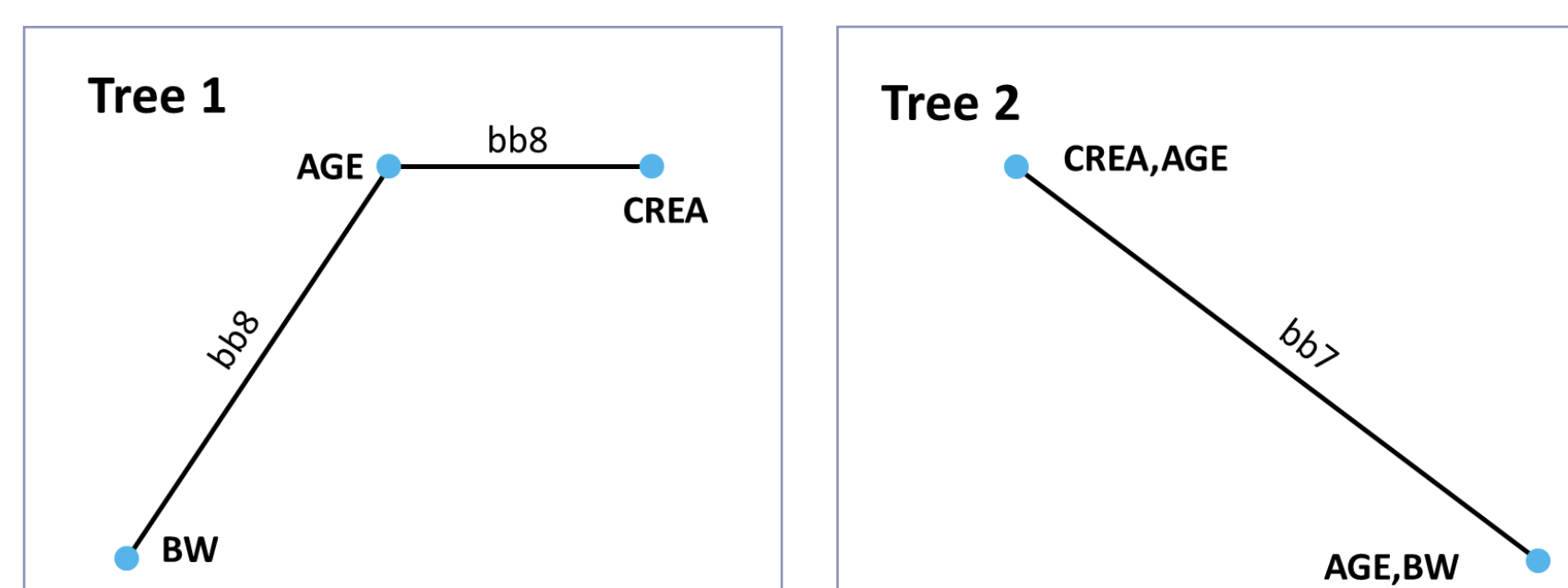
1. Copula Estimation

Estimate the copula model

```
pediatric_cop <- vine(pediatric_3cov)
```

Visualize the tree structure of copula

```
plot(pediatric_cop$copula)
```



Simulate for evaluation

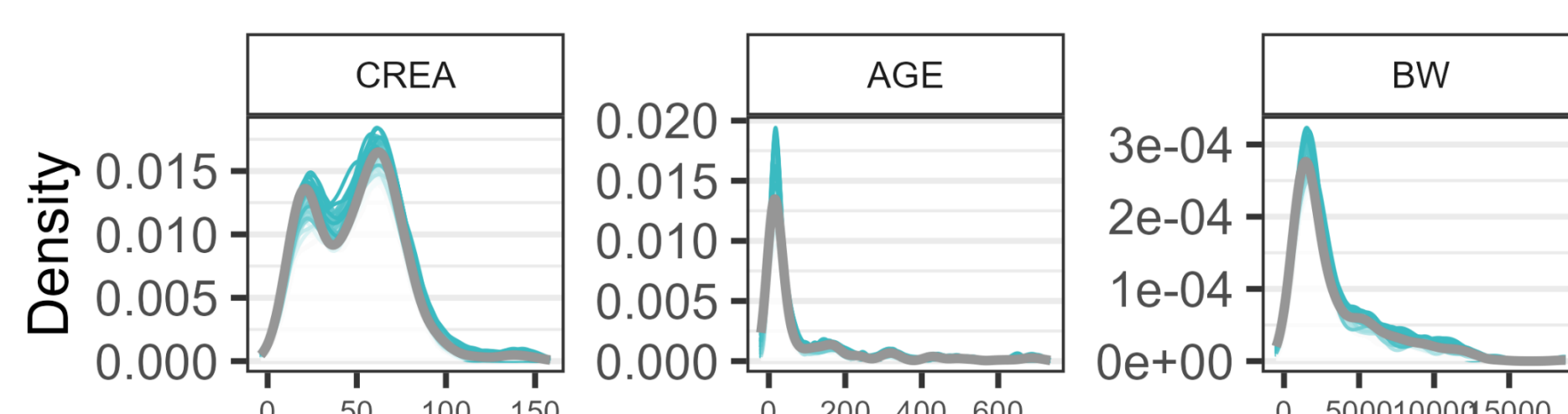
Copula evaluation is implemented using a simulation-based strategy.

```
# 100 simulations of the real-world population  
pediatric_sim <- rcopula(pediatric_cop, 100)
```

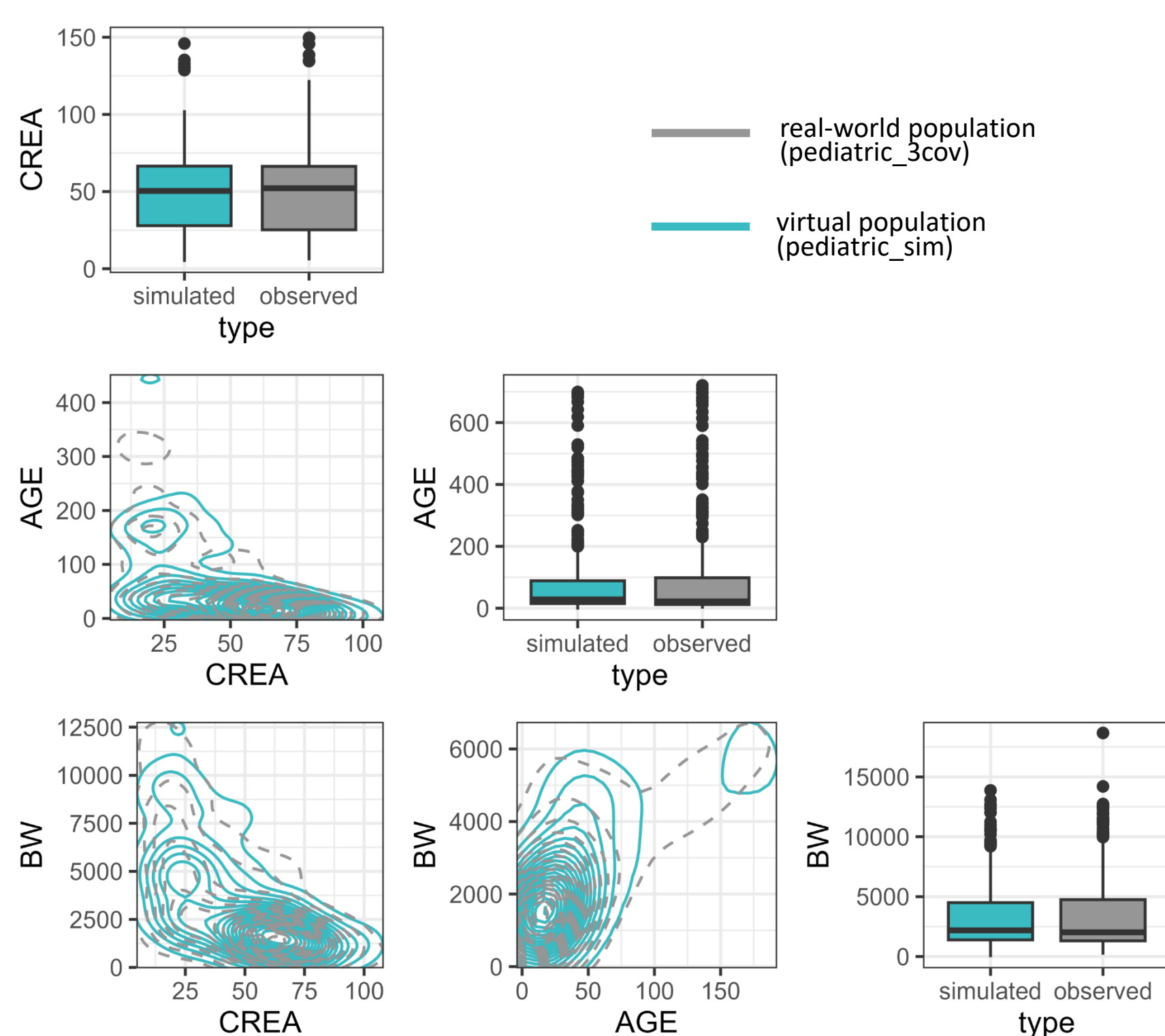
2. Copula Evaluation | pmxcopula

Visualize the distribution

```
# marginal distribution  
plot_1dlist(pediatric_sim, pediatric_3cov,...)
```

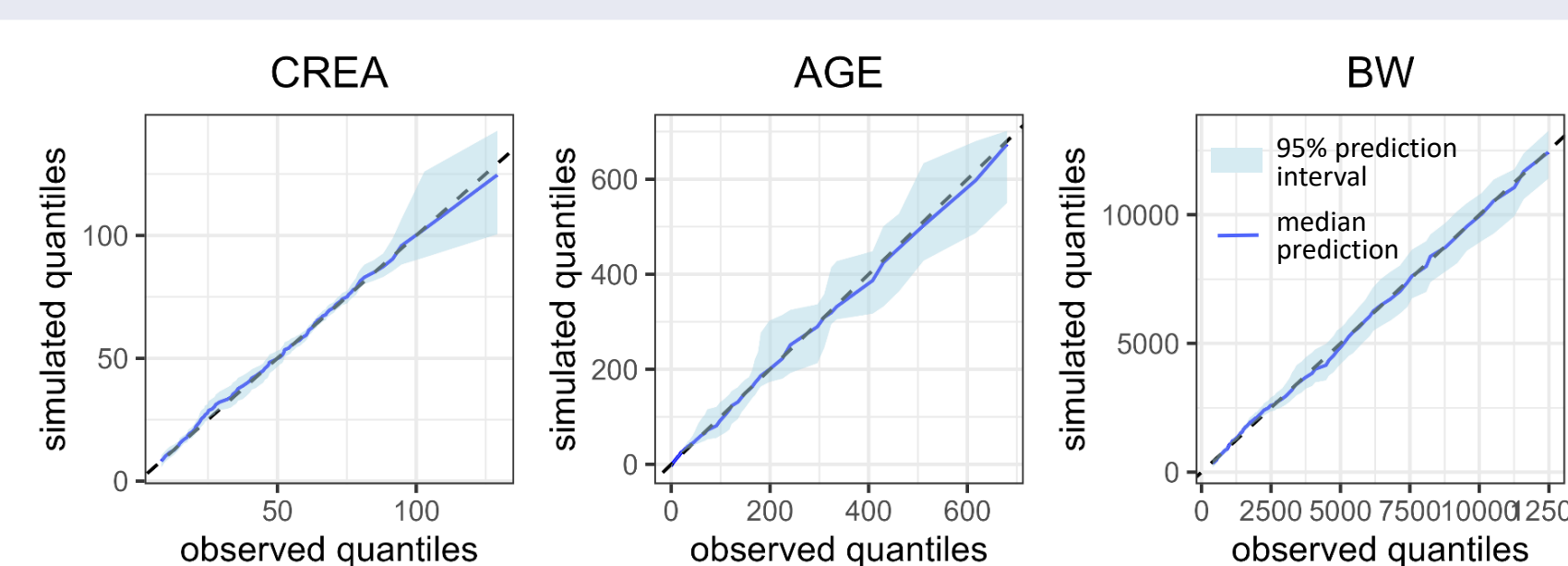


```
# dependency structure  
plot_mvdist(pediatric_sim, pediatric_3cov,...)
```

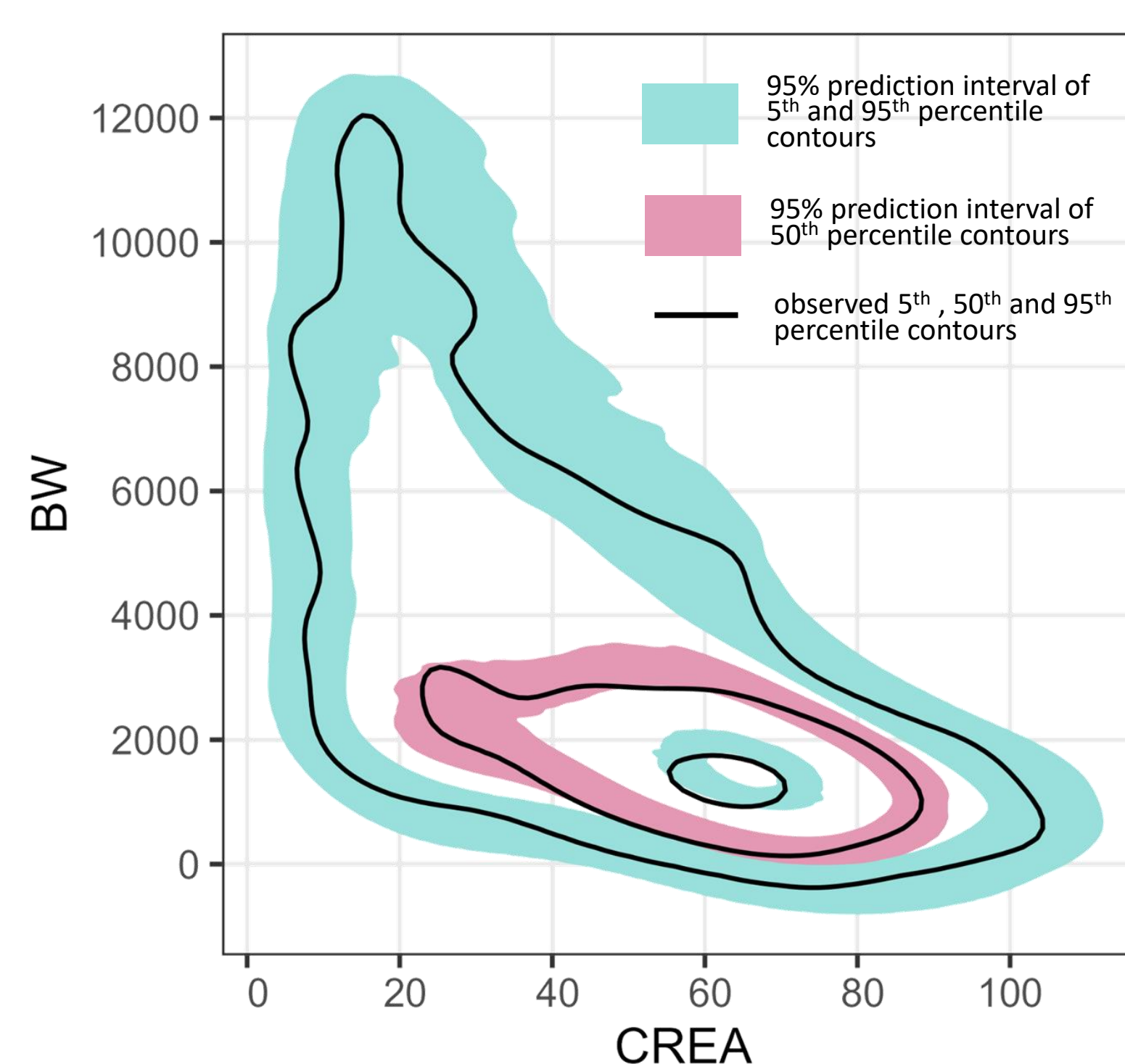


Plot visual predictive checks

```
# marginal prediction intervals  
# qqplot, based on univariate percentiles  
plot_qq(pediatric_sim, pediatric_3cov,...)
```

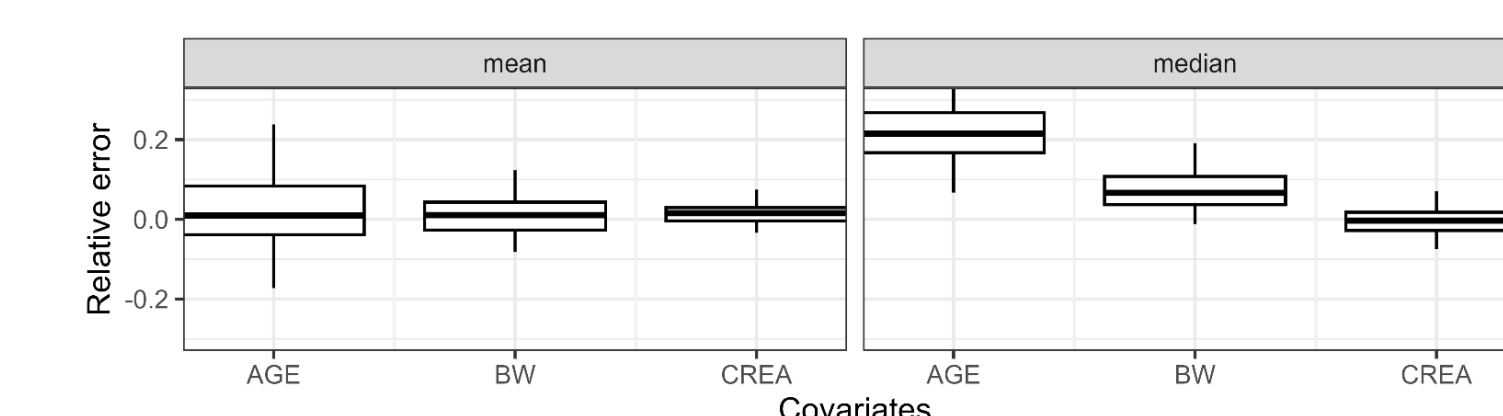


```
# dependency prediction intervals  
# donutVPC, based on bivariate density contours  
donutVPC(pediatric_sim, pediatric_3cov,...)
```

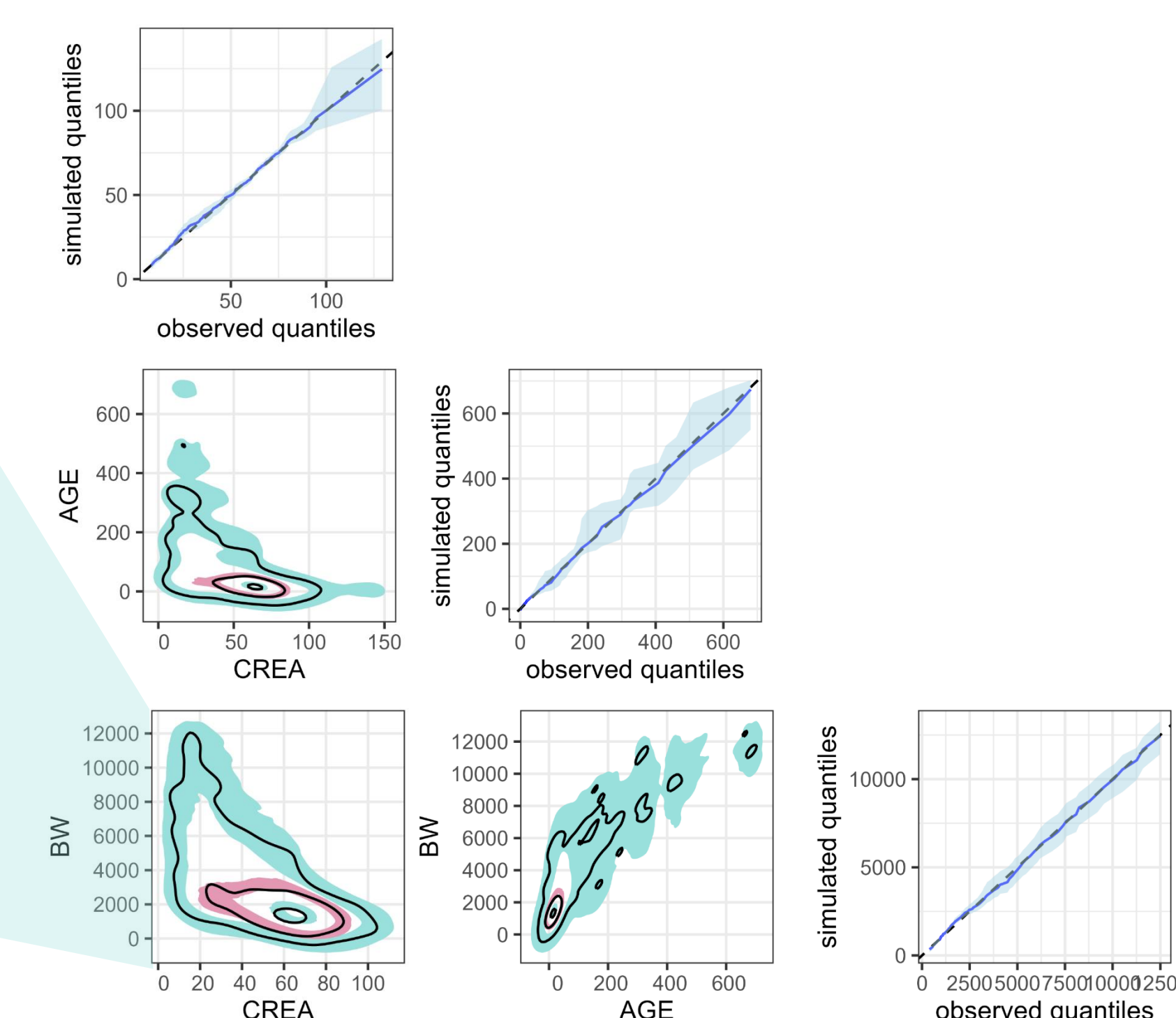


Calculate predictive metrics

```
# marginal metrics  
# mean, median, SD and percentiles  
calc_margin(pediatric_sim,  
  pediatric_3cov,  
  c("mean", "median"))
```



```
# dependency metrics  
# correlation and overlap metric  
calc_dependency(pediatric_sim,  
  pediatric_3cov,...)
```



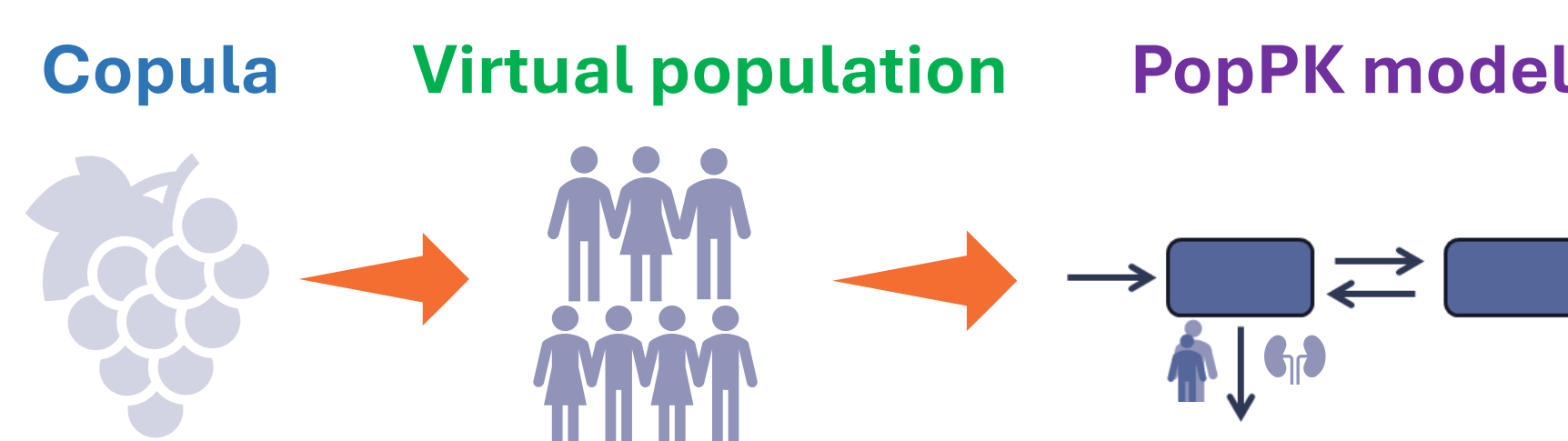
3. PMX Application

Generate virtual population of interest

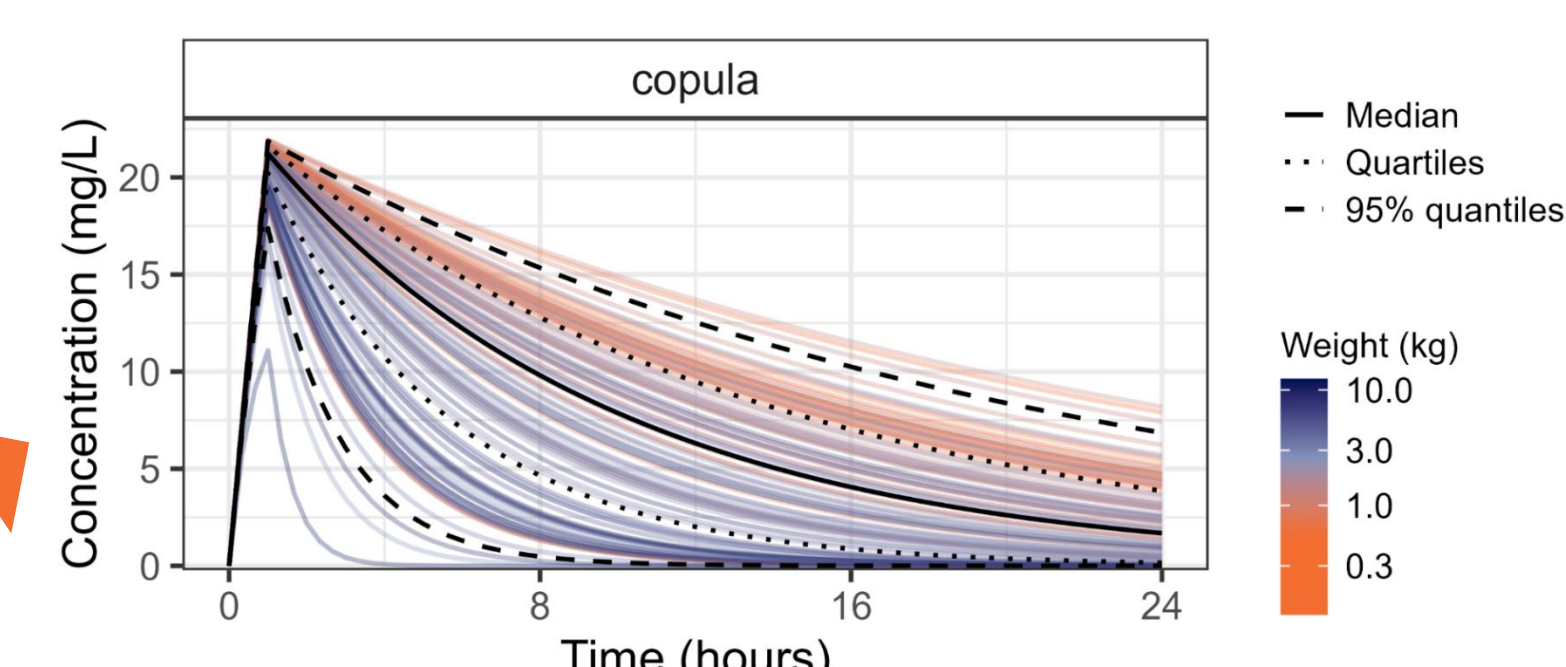
```
# generate 1000 individuals aged 0~60 days  
pediatric_VP <- rscopula(  
  pediatric_cop,  
  n_sim = 1000,  
  xmin = c(NA, 0, NA),  
  xmax = c(NA, 60, NA),  
  category = NULL,  
  var_types = c("c", "c", "c"))
```

Simulate PK/PD with virtual population

```
sim_PK <- mod %>% rxSolve(et,  
  iCov = pediatric_VP)
```



Simulated PK profiles



CONCLUSIONS

- **pmxcopula** provides copula **evaluation tools** and a **step-by-step tutorial** to perform covariate simulation using copulas.
- The evaluation tools provided apply to covariate simulation methods, **including but not limited to copulas**.

Get started devtools::install_github("vanhasseltlab/pmxcopula")