

# Bayesian models for smaller trial sizes

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R in Pharma

Aug 16, 2018

Daniel Lee

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*Generable*

The story you're about to hear is true.

Only the names, data, model, and a few other things have been changed to protect the innocent.

# Early signals of efficacy in Phase I/II trials

## A Bayesian approach with Stan and R

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**Generable**

# What are we after?

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- ▶ Quantifying the efficacy of a treatment.

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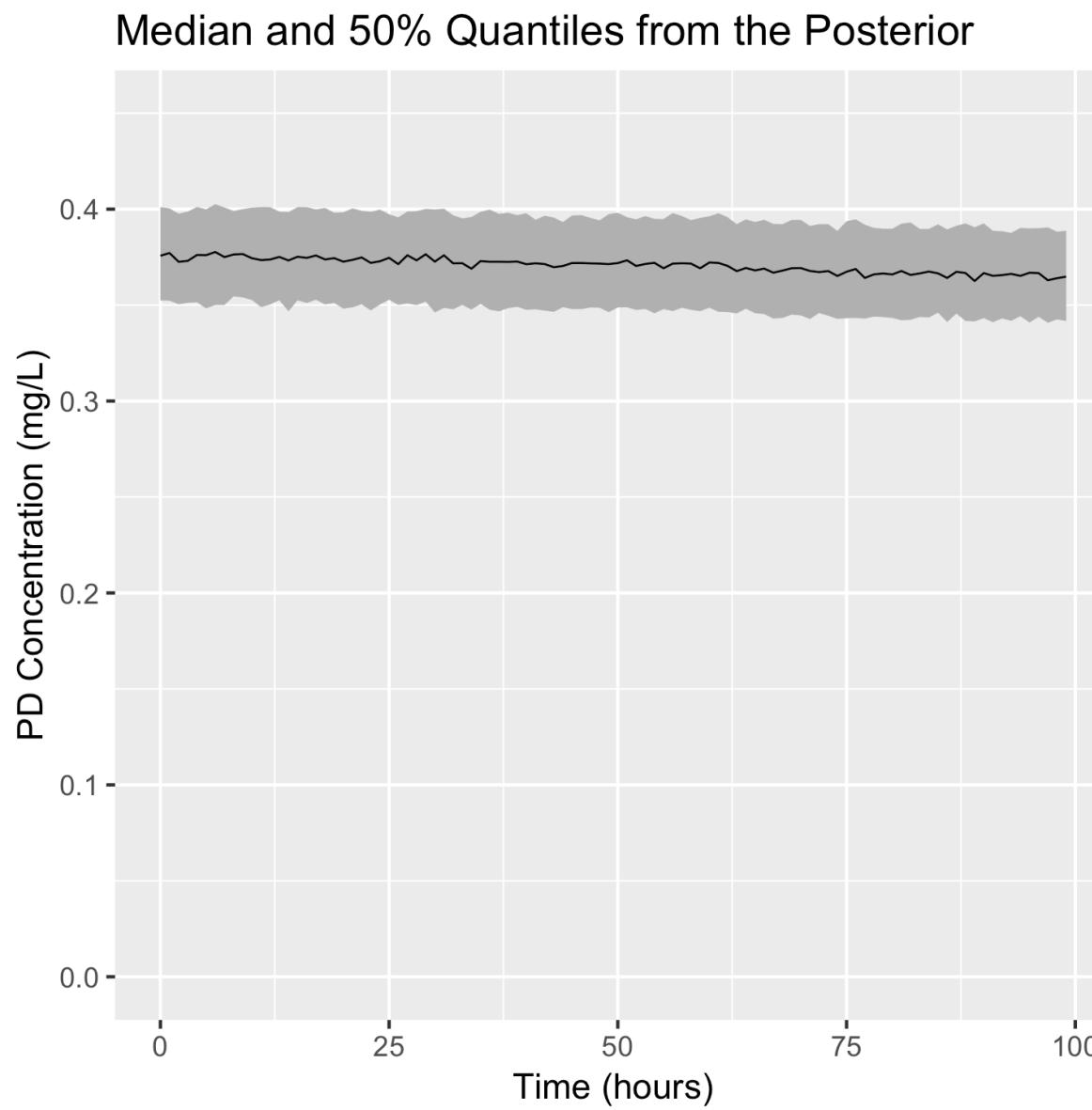
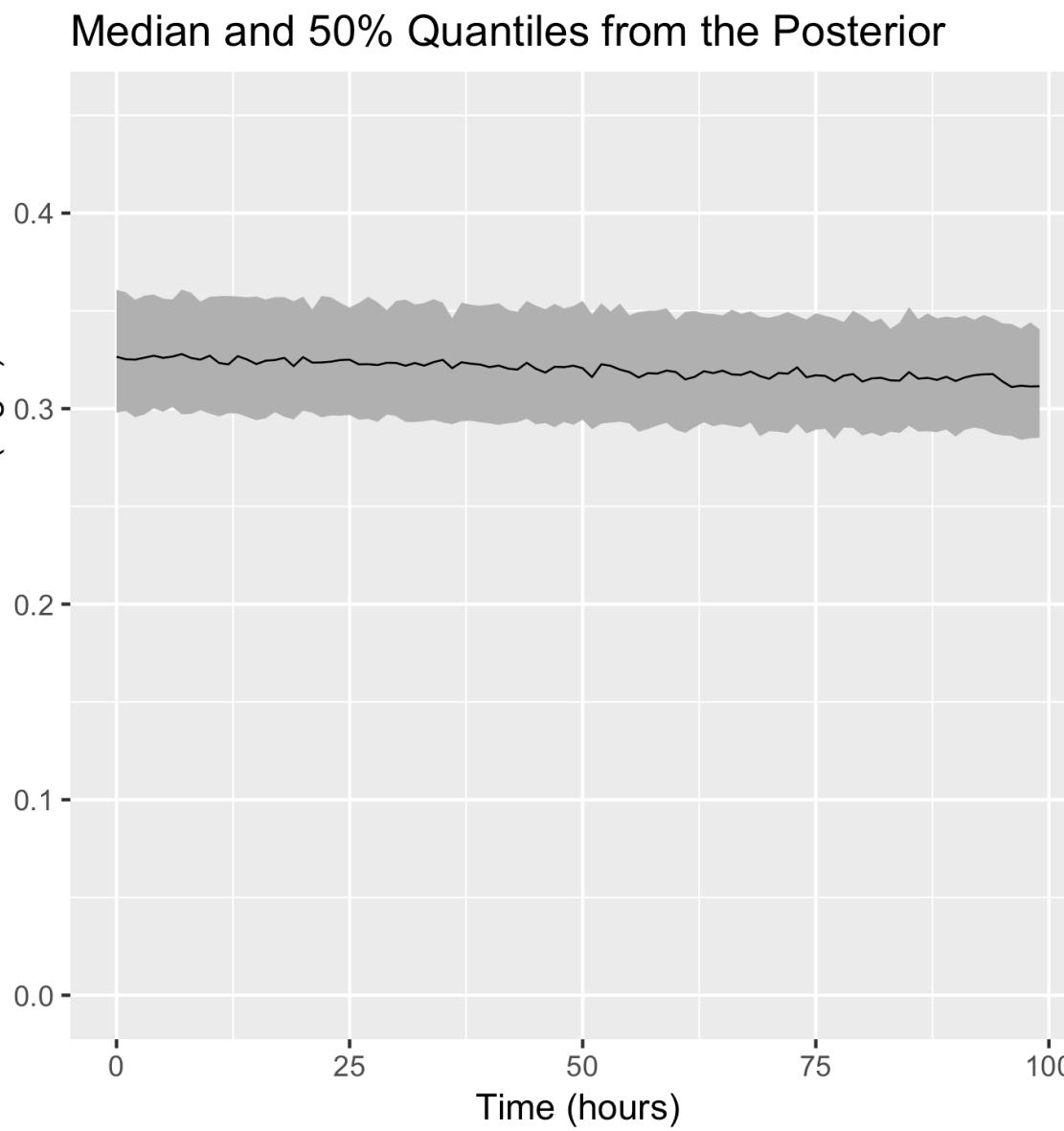
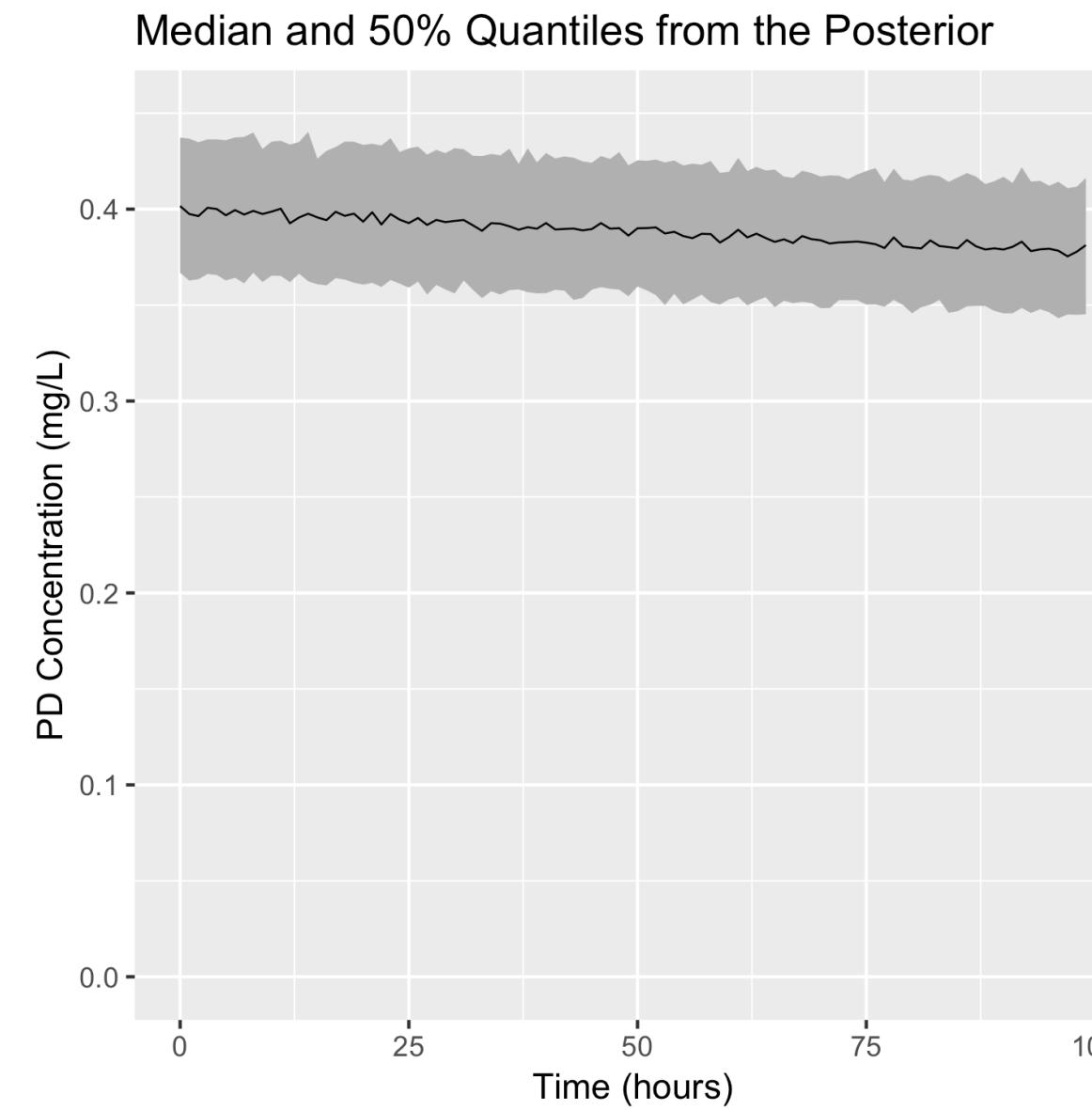
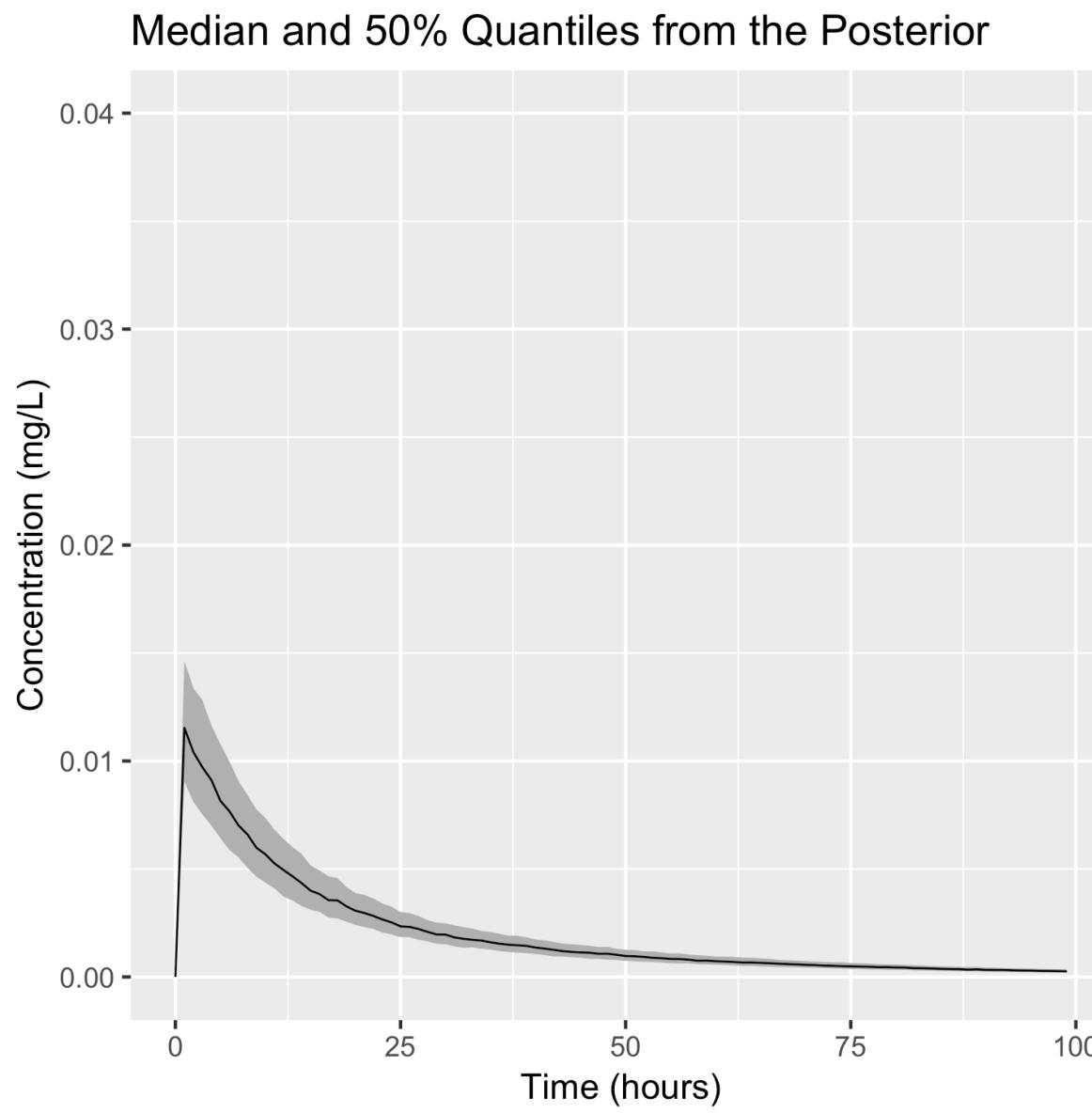
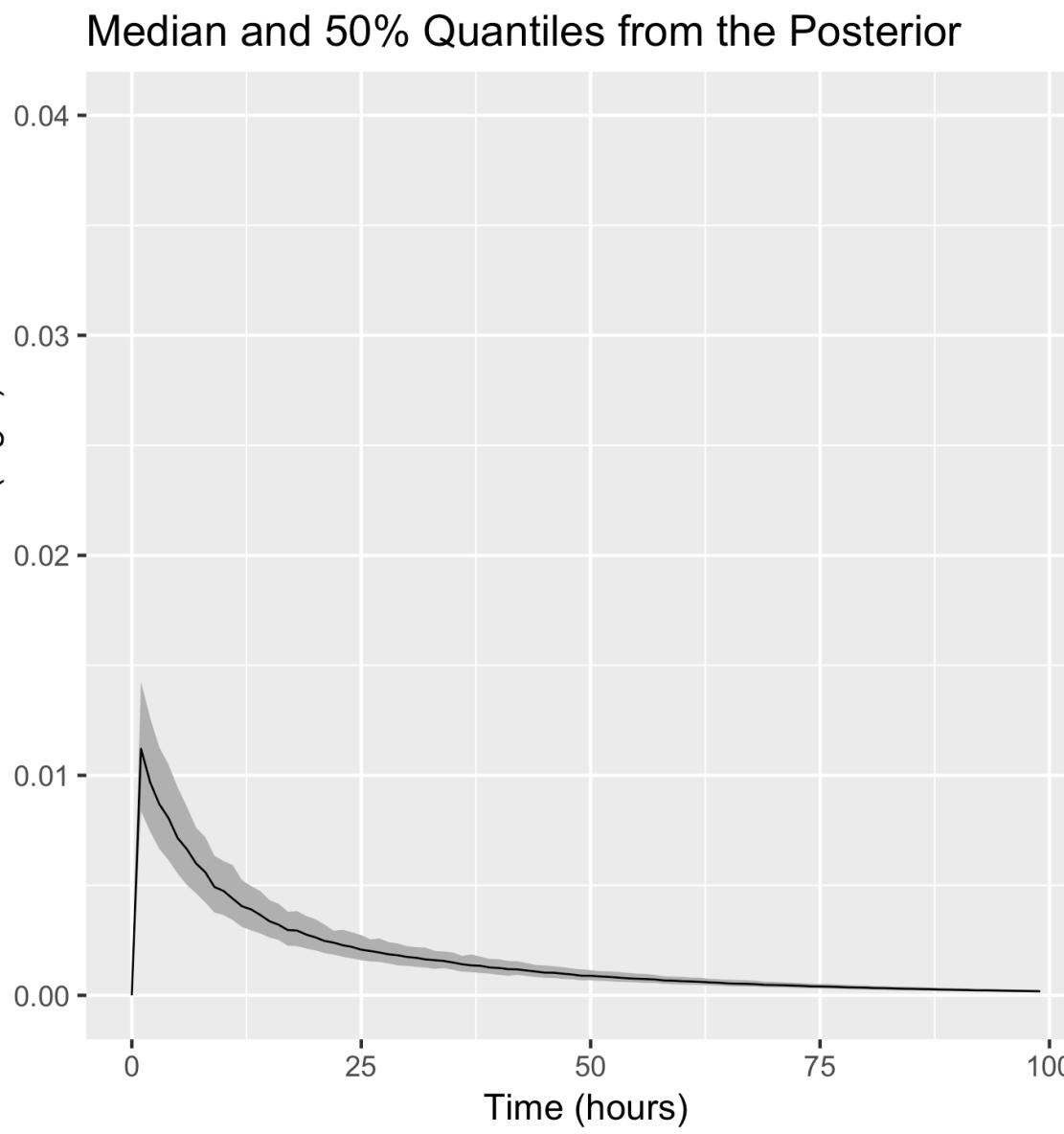
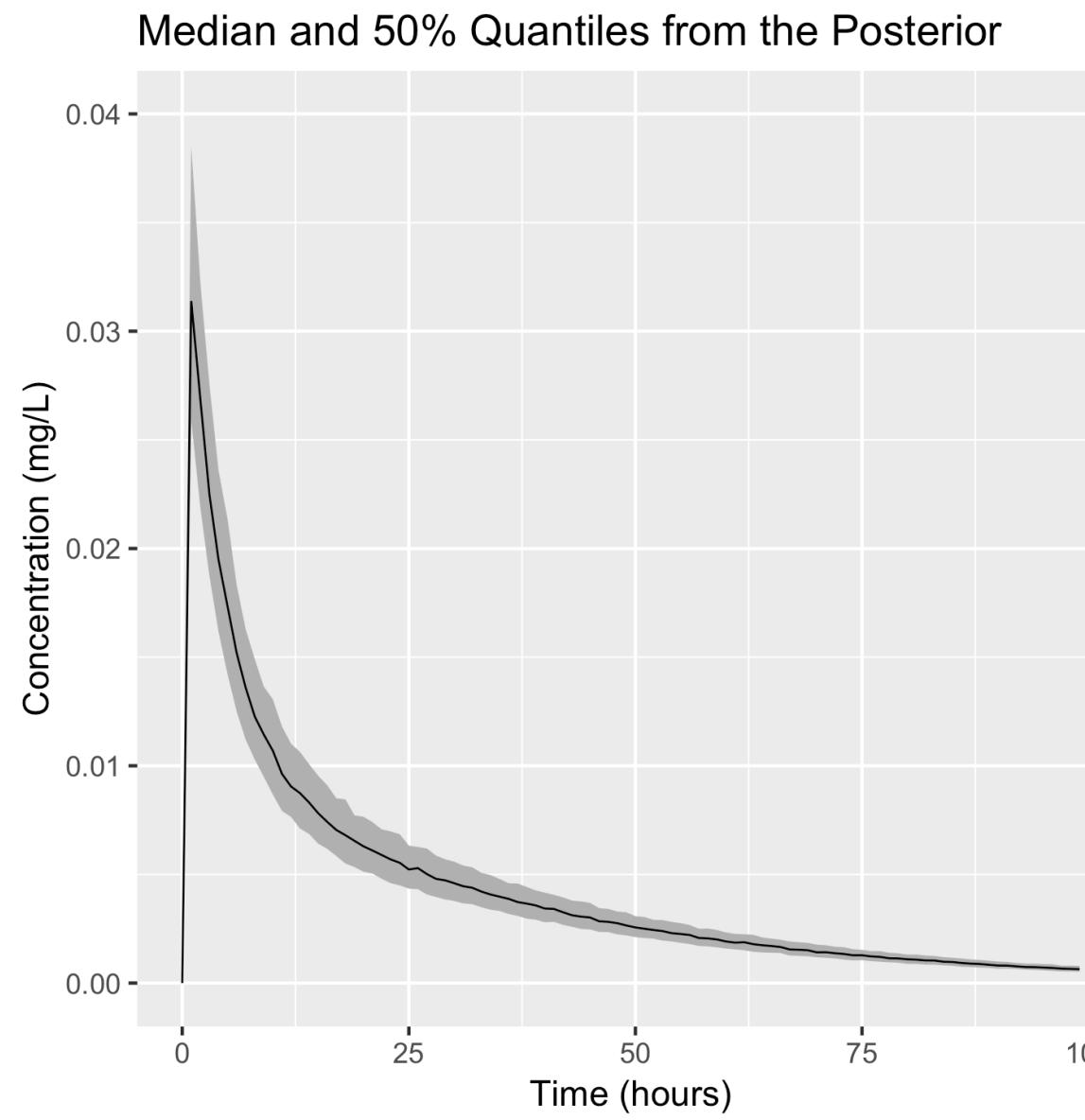
- ▶ Quantifying the efficacy of a treatment.
- ▶ Traditional:
  - ▶ Phase I: 20-100 healthy volunteers
  - ▶ Phase II: several hundred people with the disease

# What are we after?

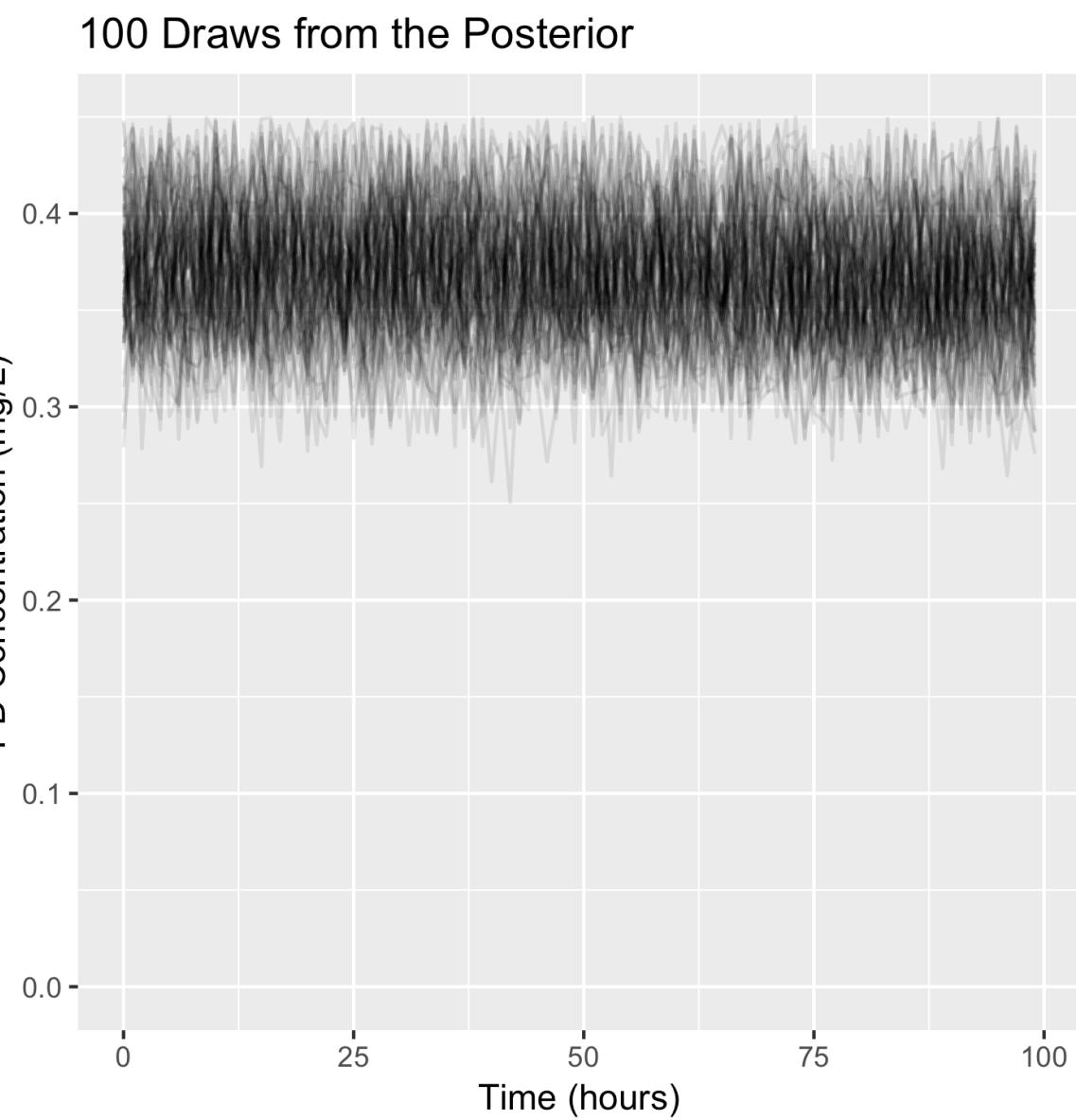
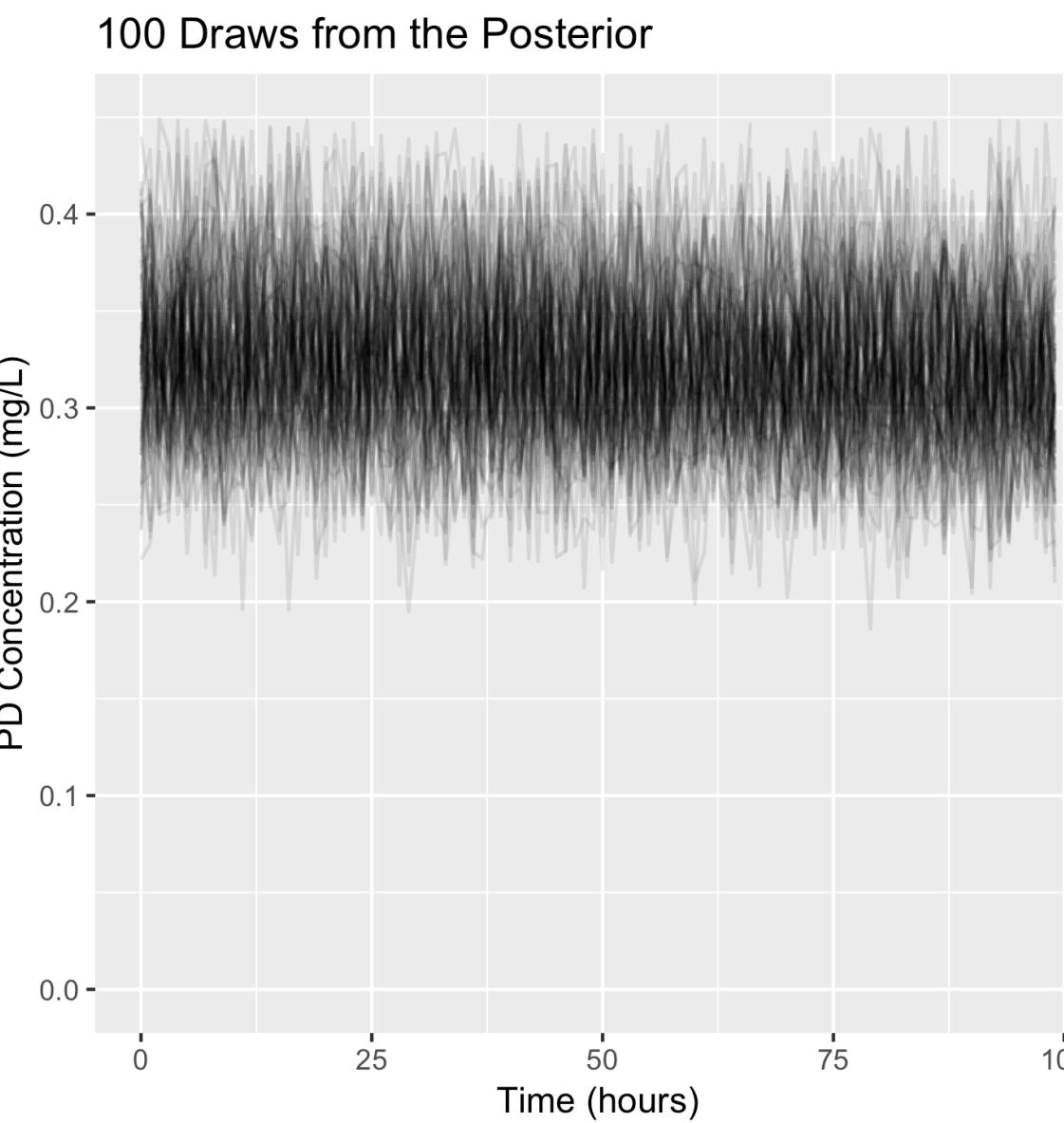
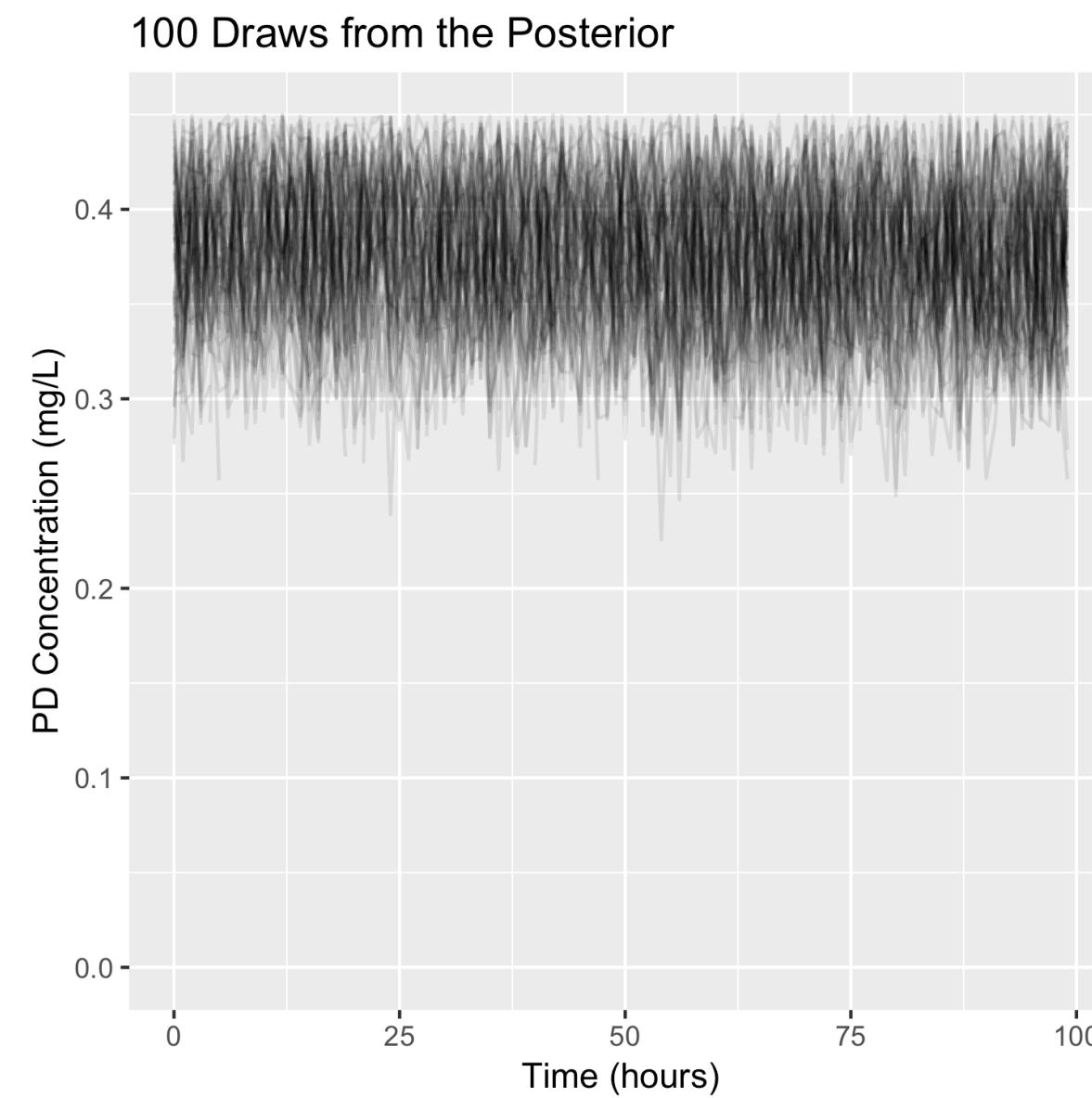
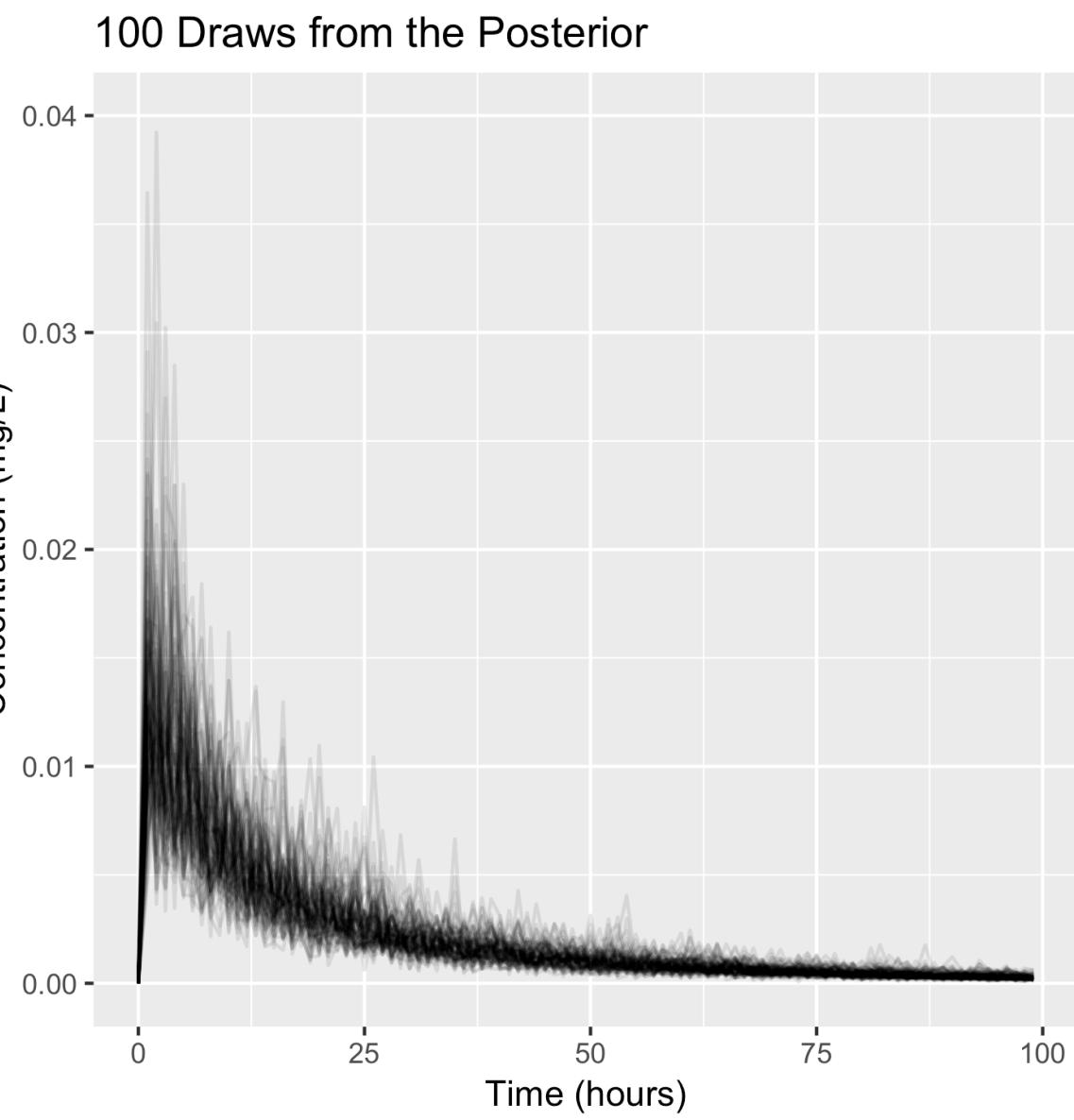
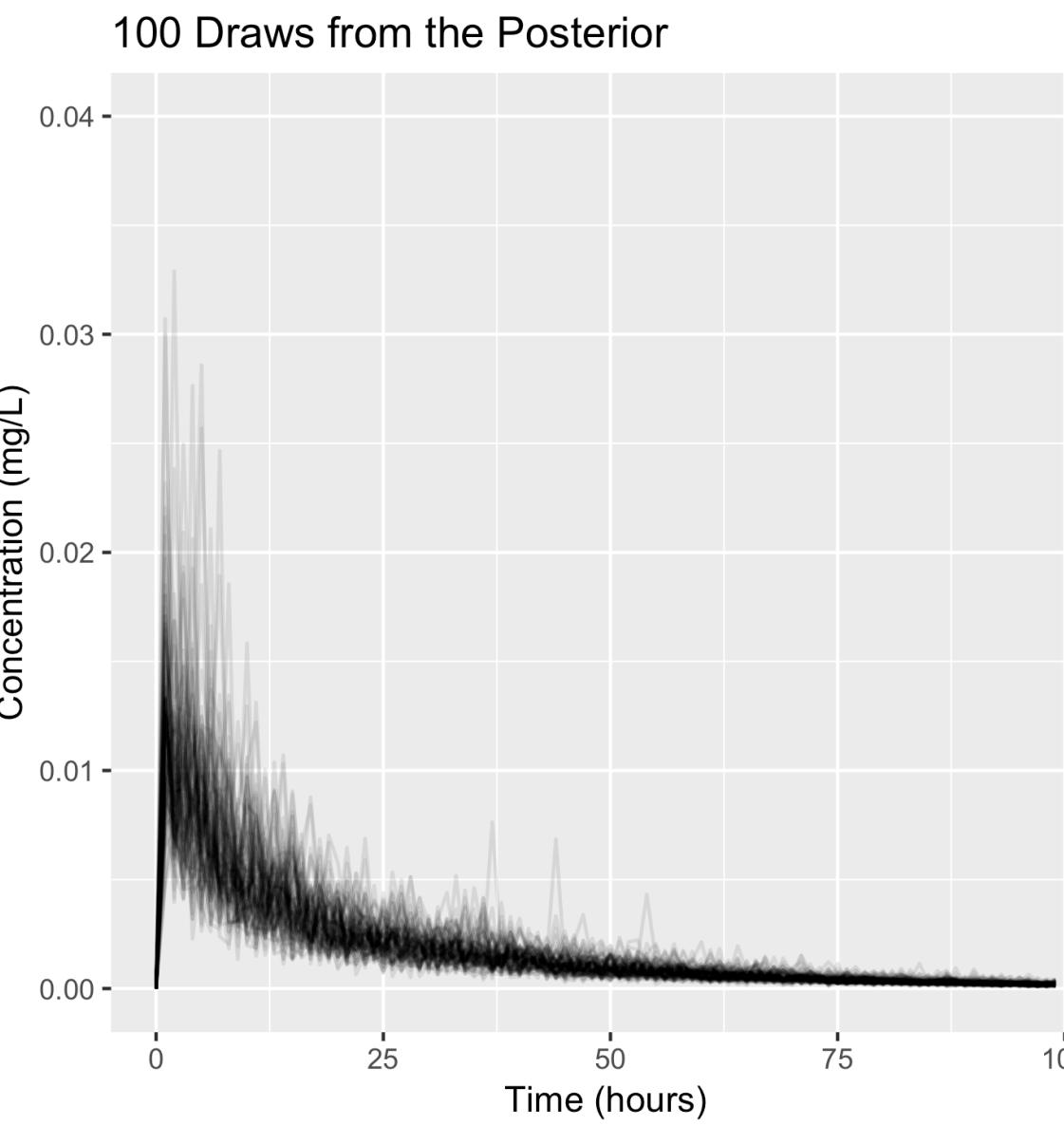
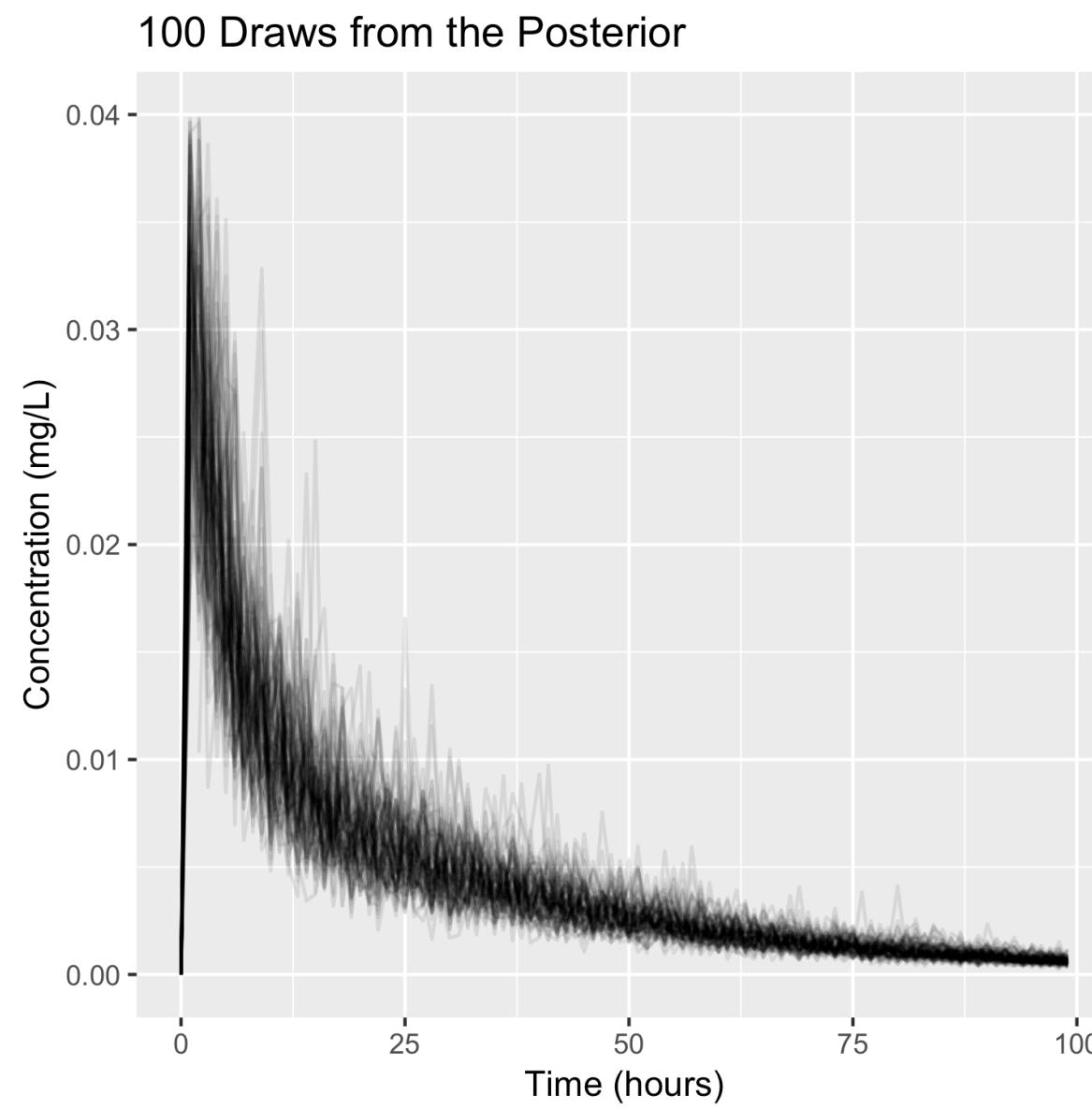
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- ▶ Quantifying the efficacy of a treatment.
- ▶ Traditional:
  - ▶ Phase I: 20-100 healthy volunteers
  - ▶ Phase II: several hundred people with the disease
- ▶ Rare disease:
  - ▶ Phase I/II: < 50 people
- ▶ Can get early signal of efficacy?

# These might look familiar...



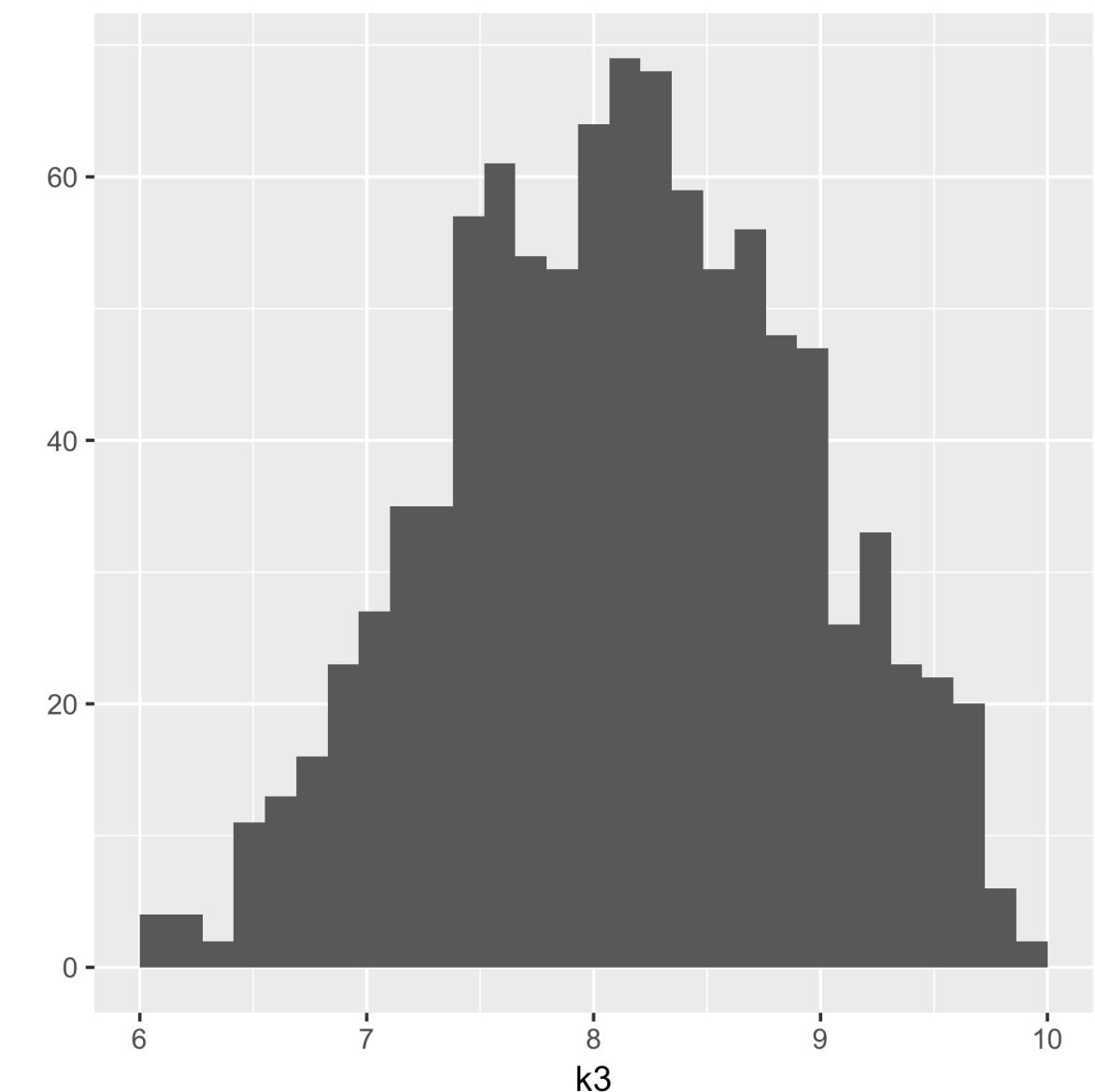
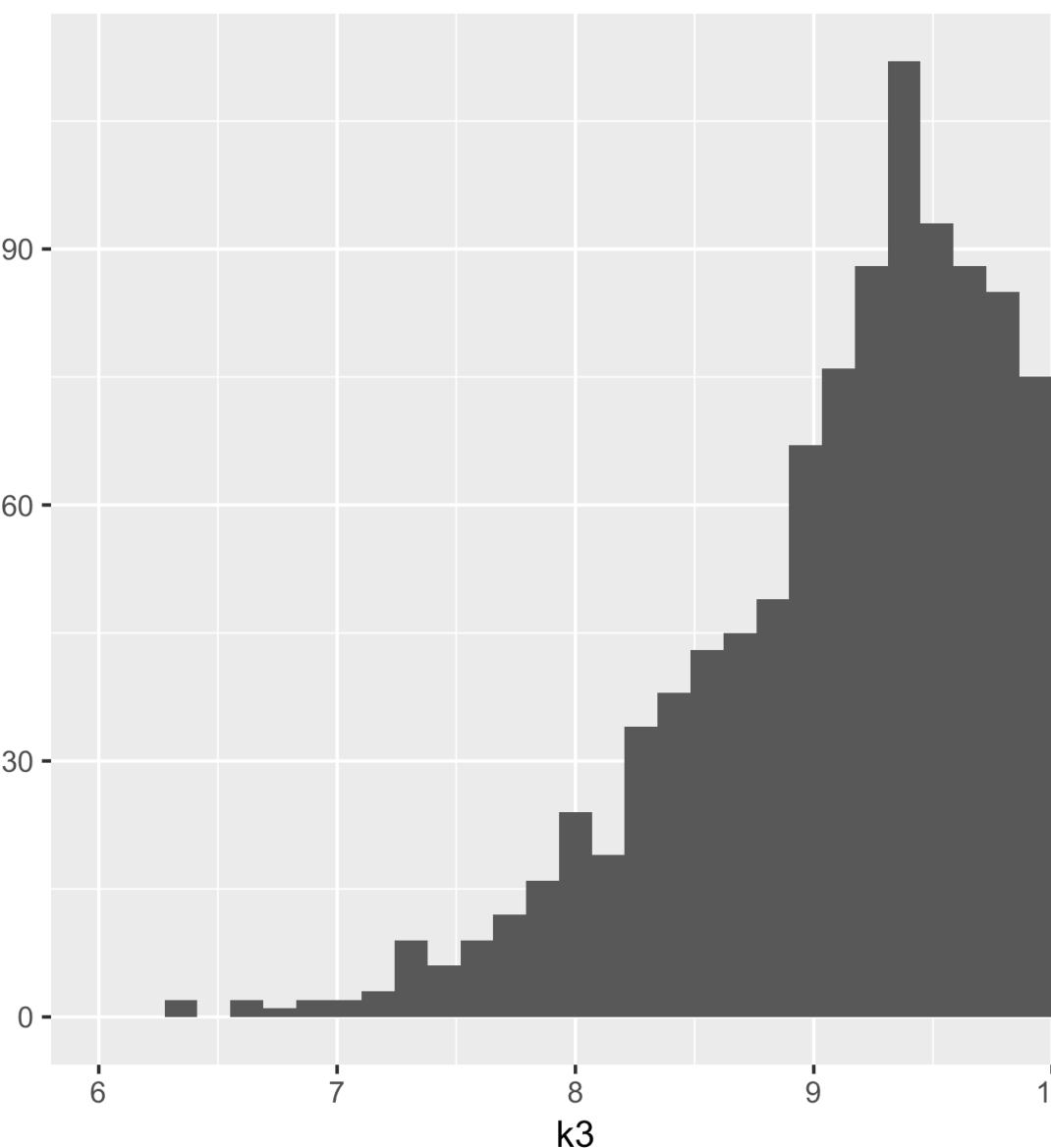
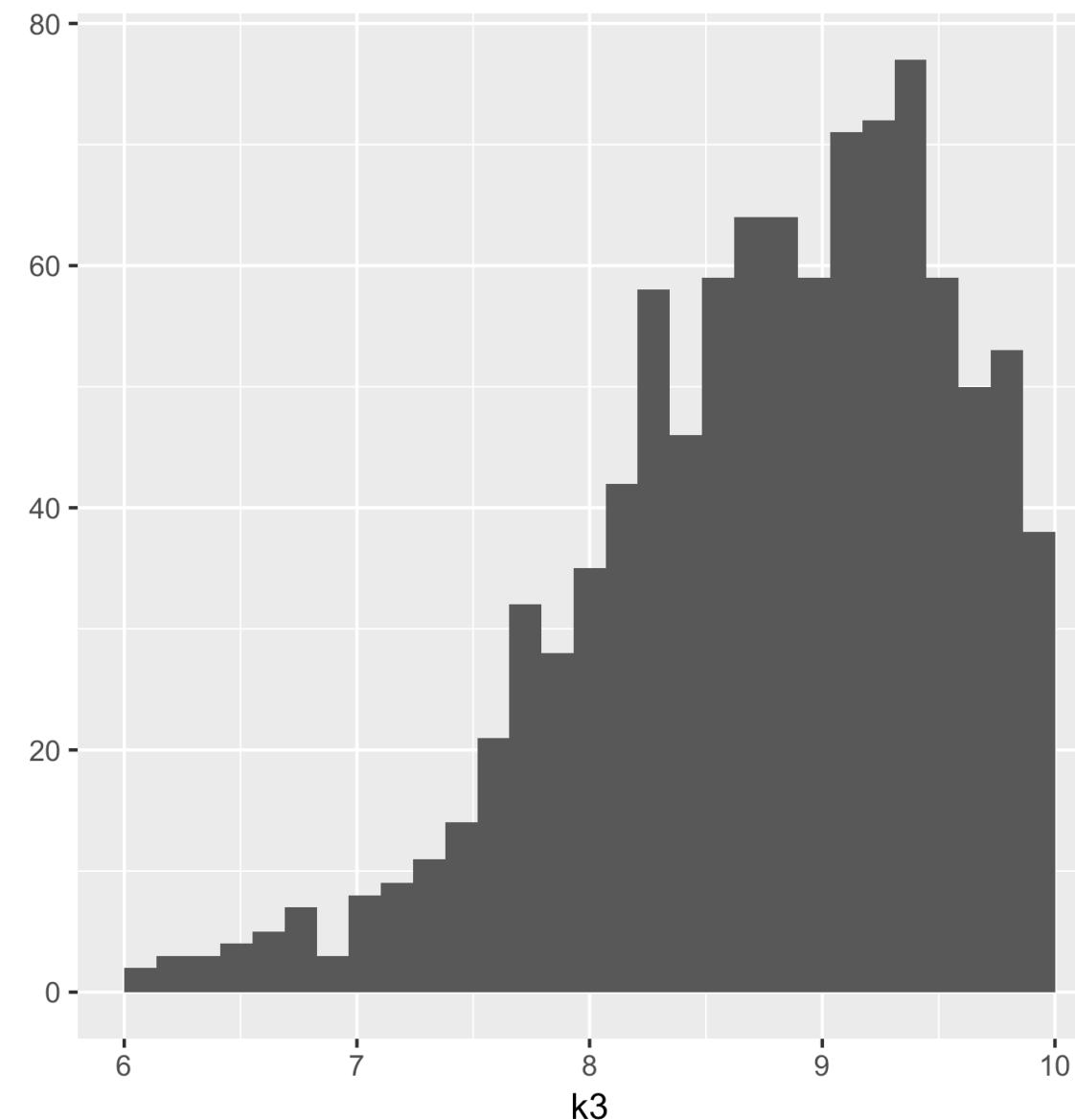
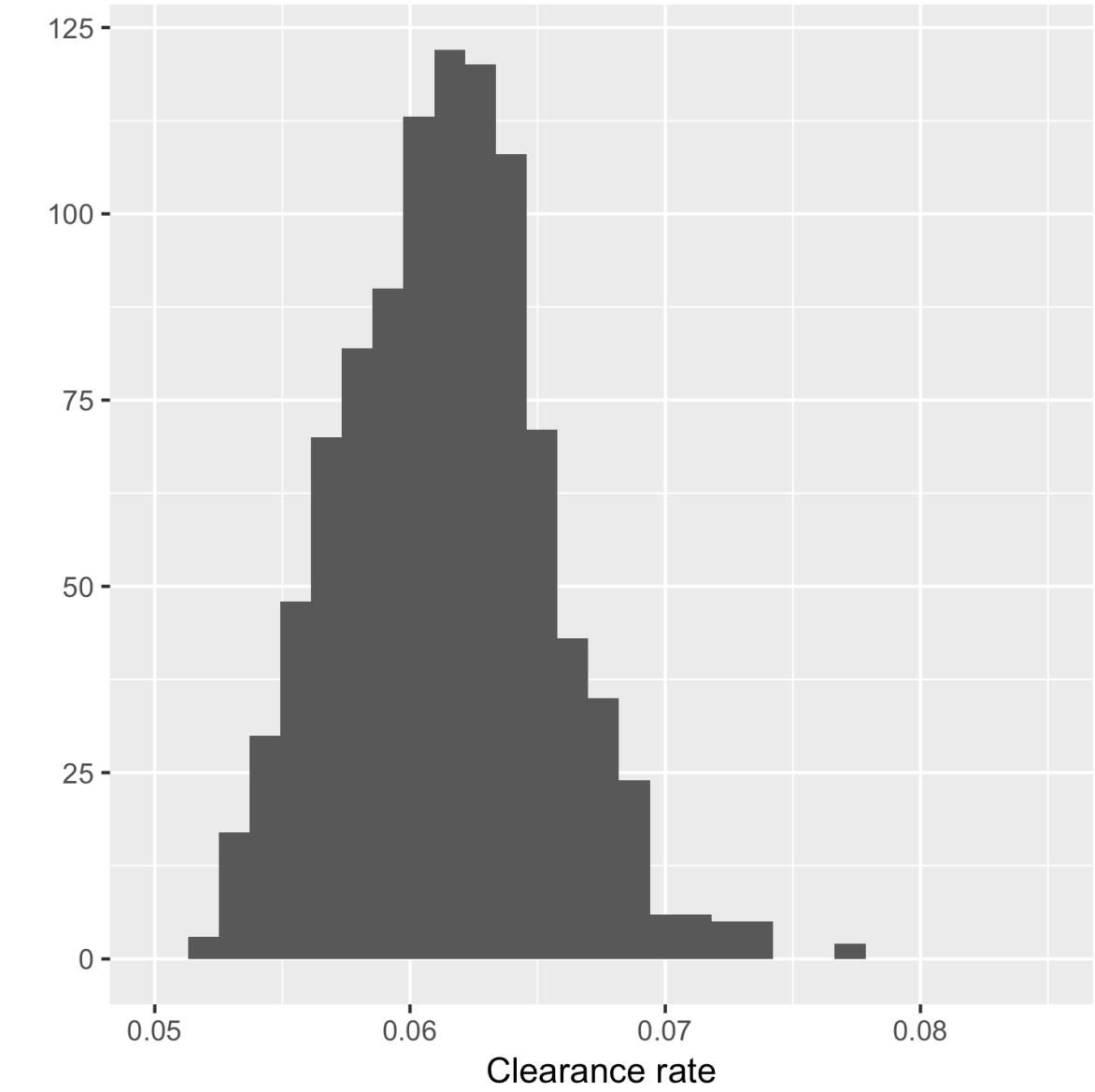
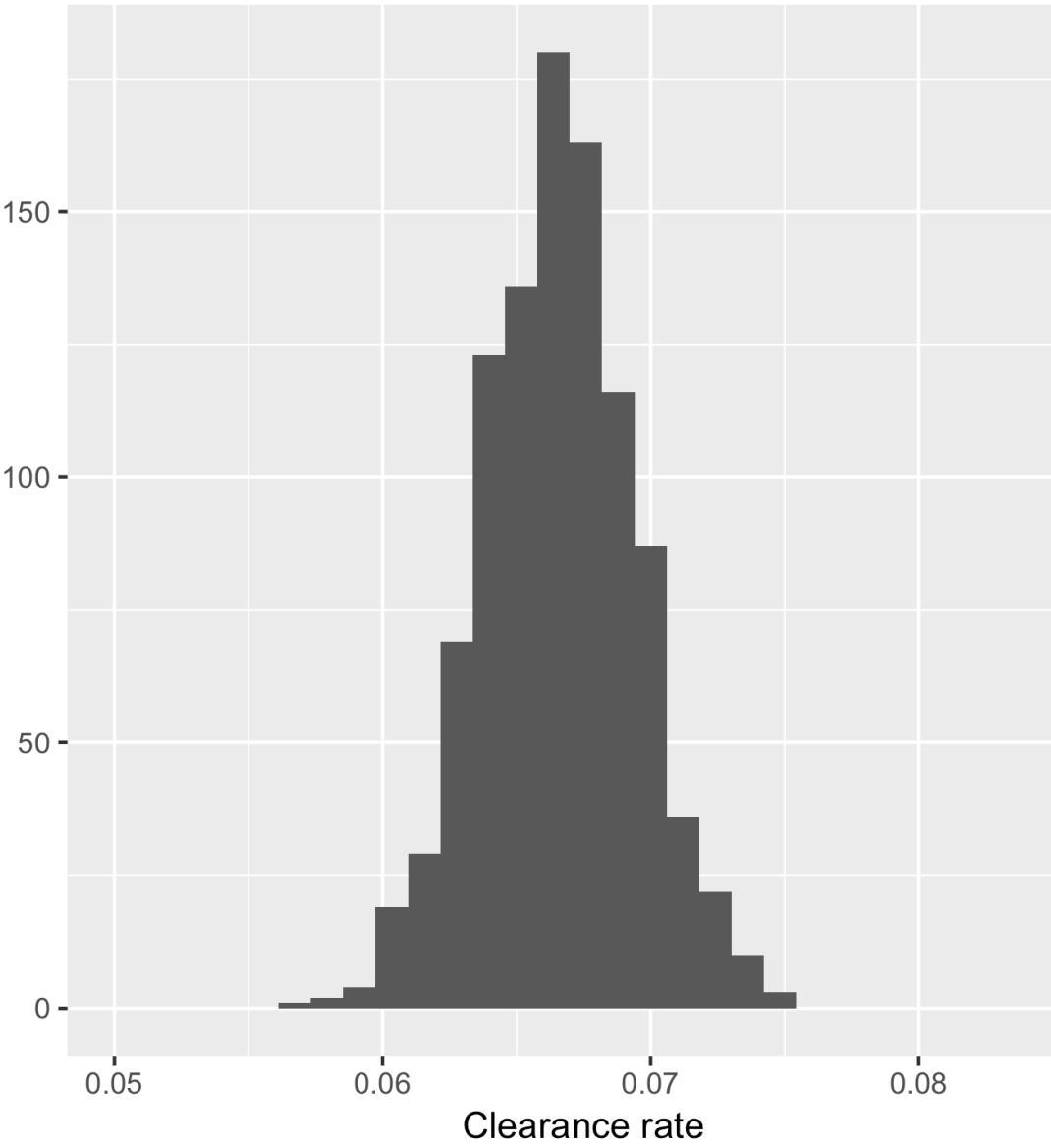
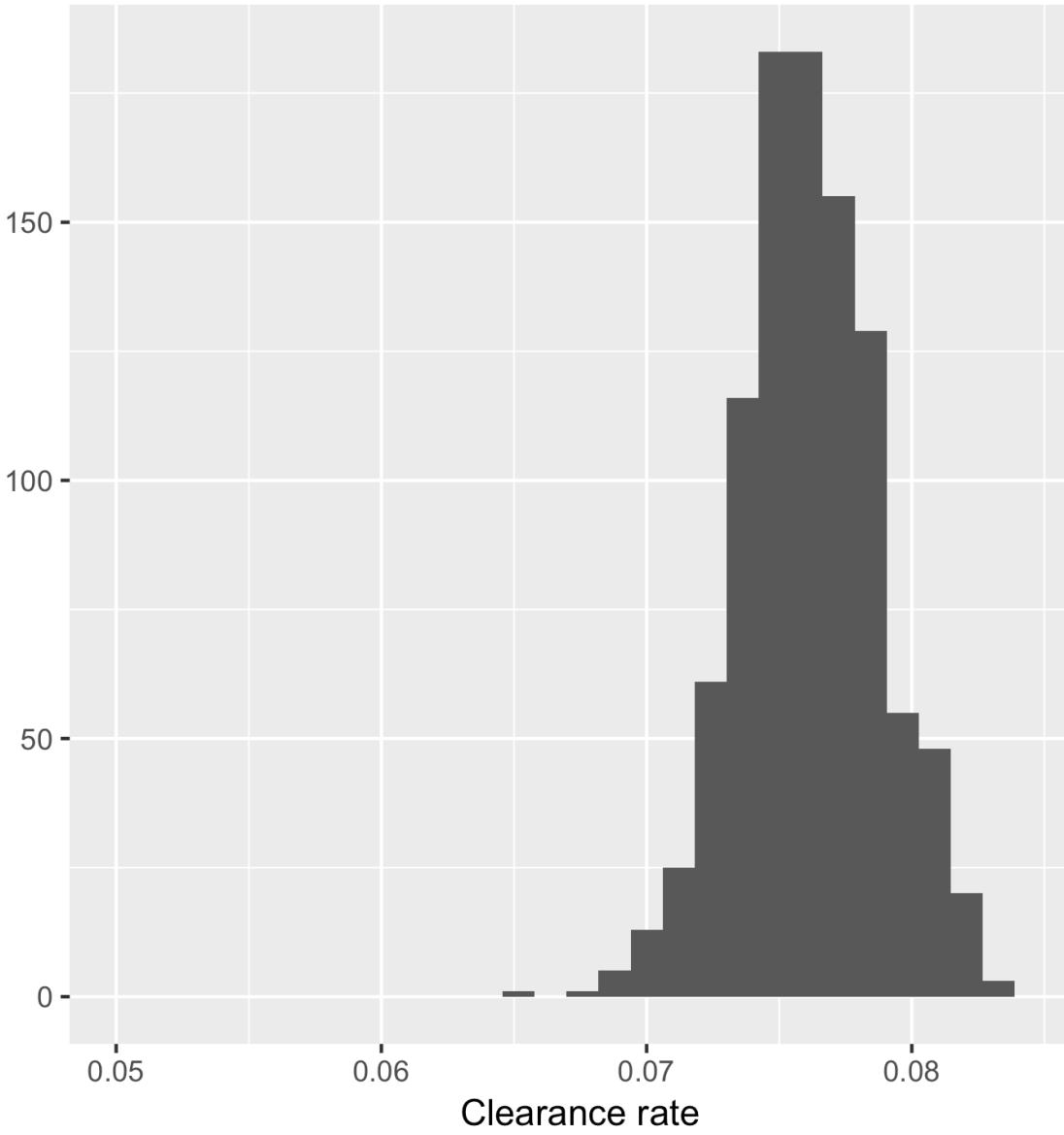
# But it represents much more



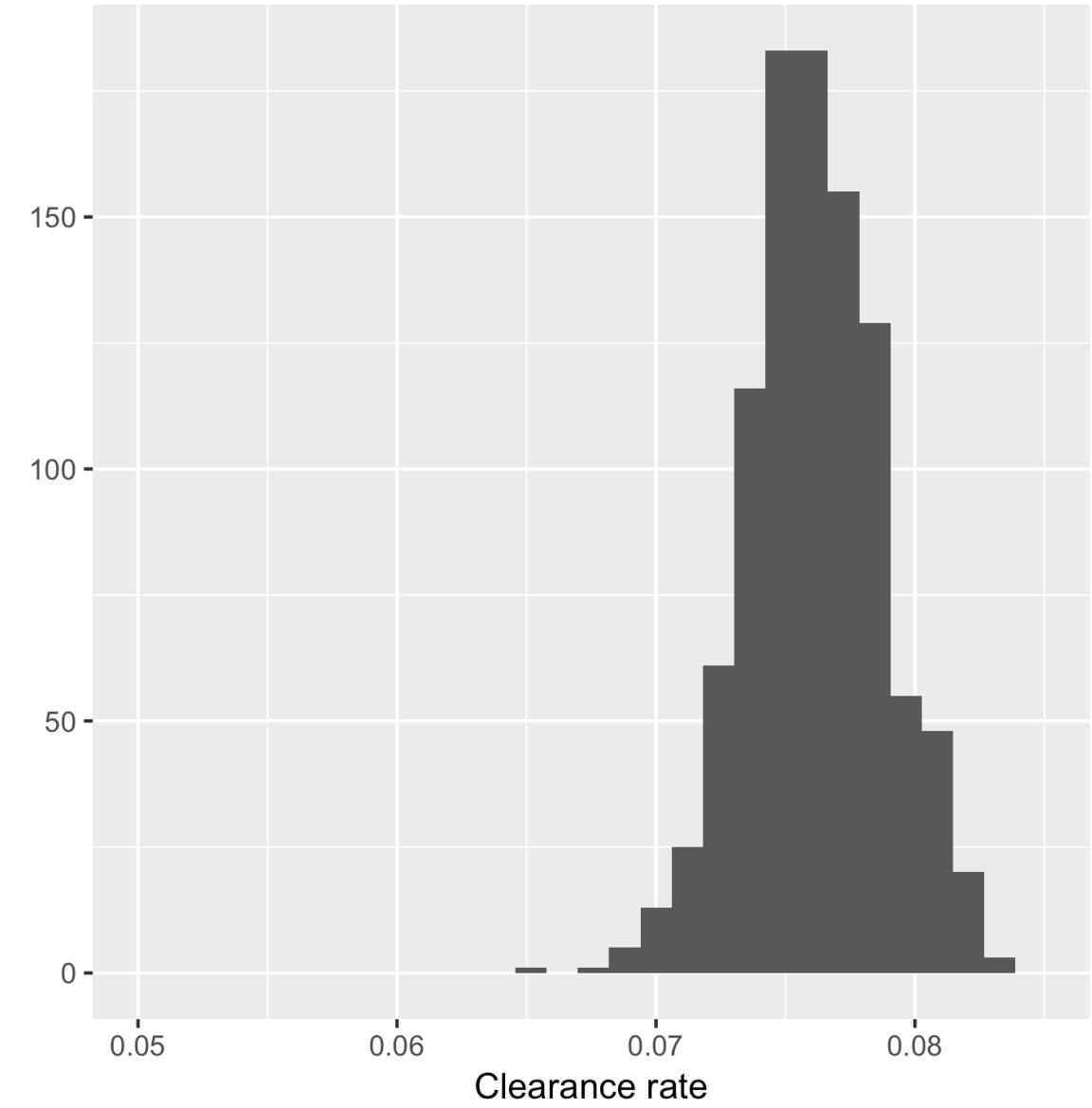
# So... why is this different?

- ▶ We're fitting the PK / PD model jointly.
- ▶ Parameter estimates are distributions, not single points.
- ▶ If the model is correct,  
this is what we believe with the right level of certainty.
- ▶ All of this on small data.

# Parameter estimates are distributions



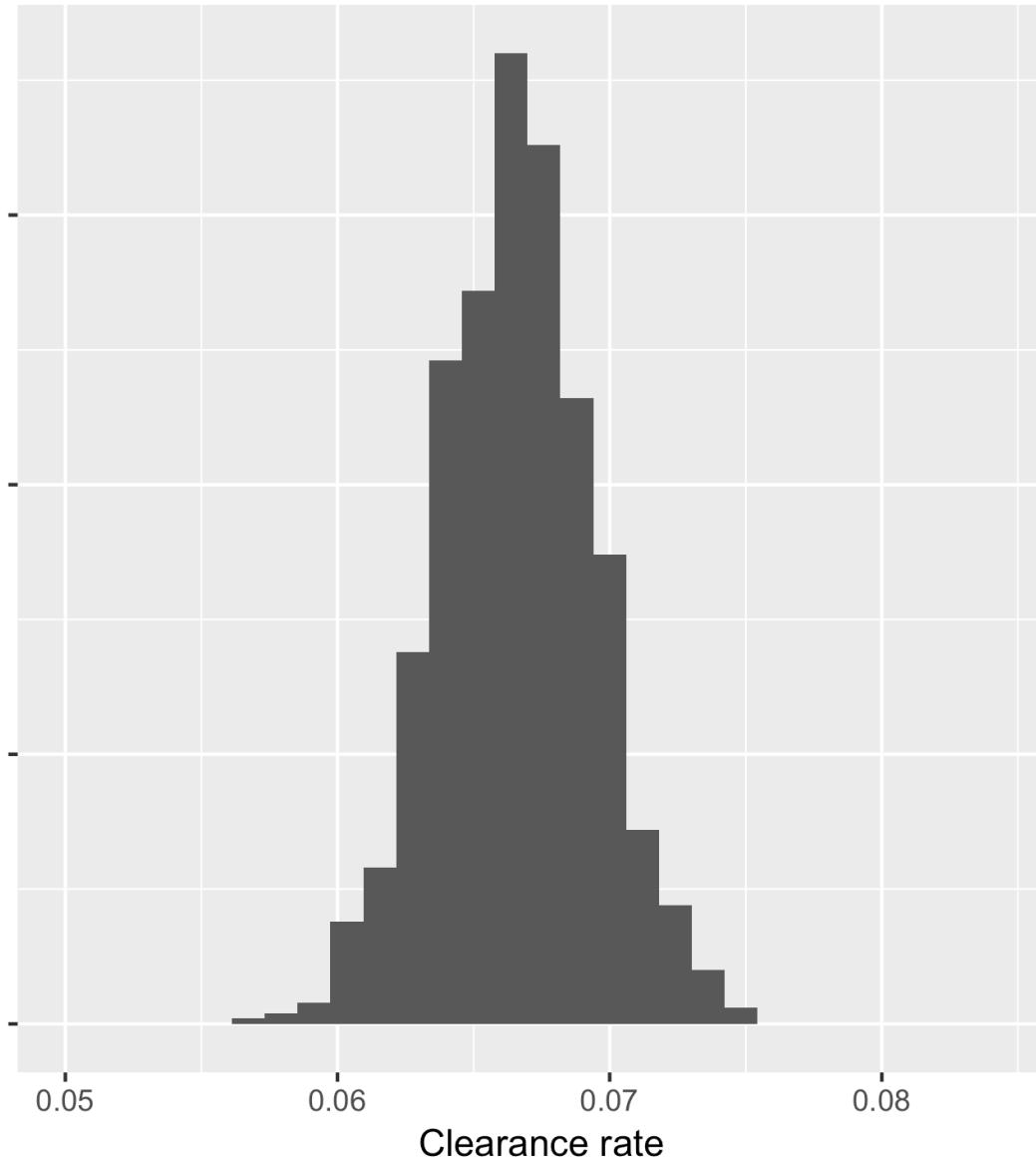
# $\Pr(\text{CI} > 0.07) ?$



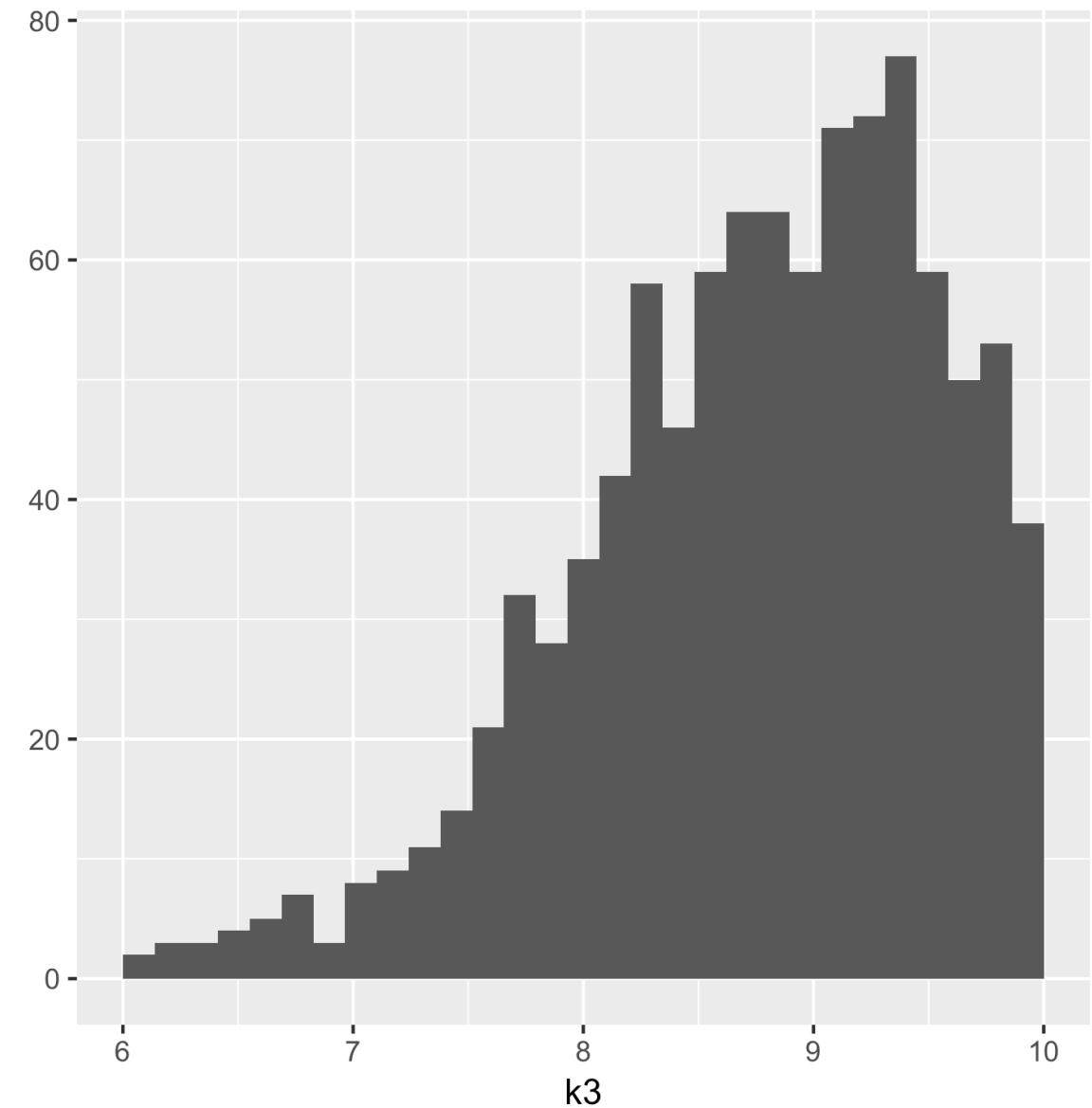
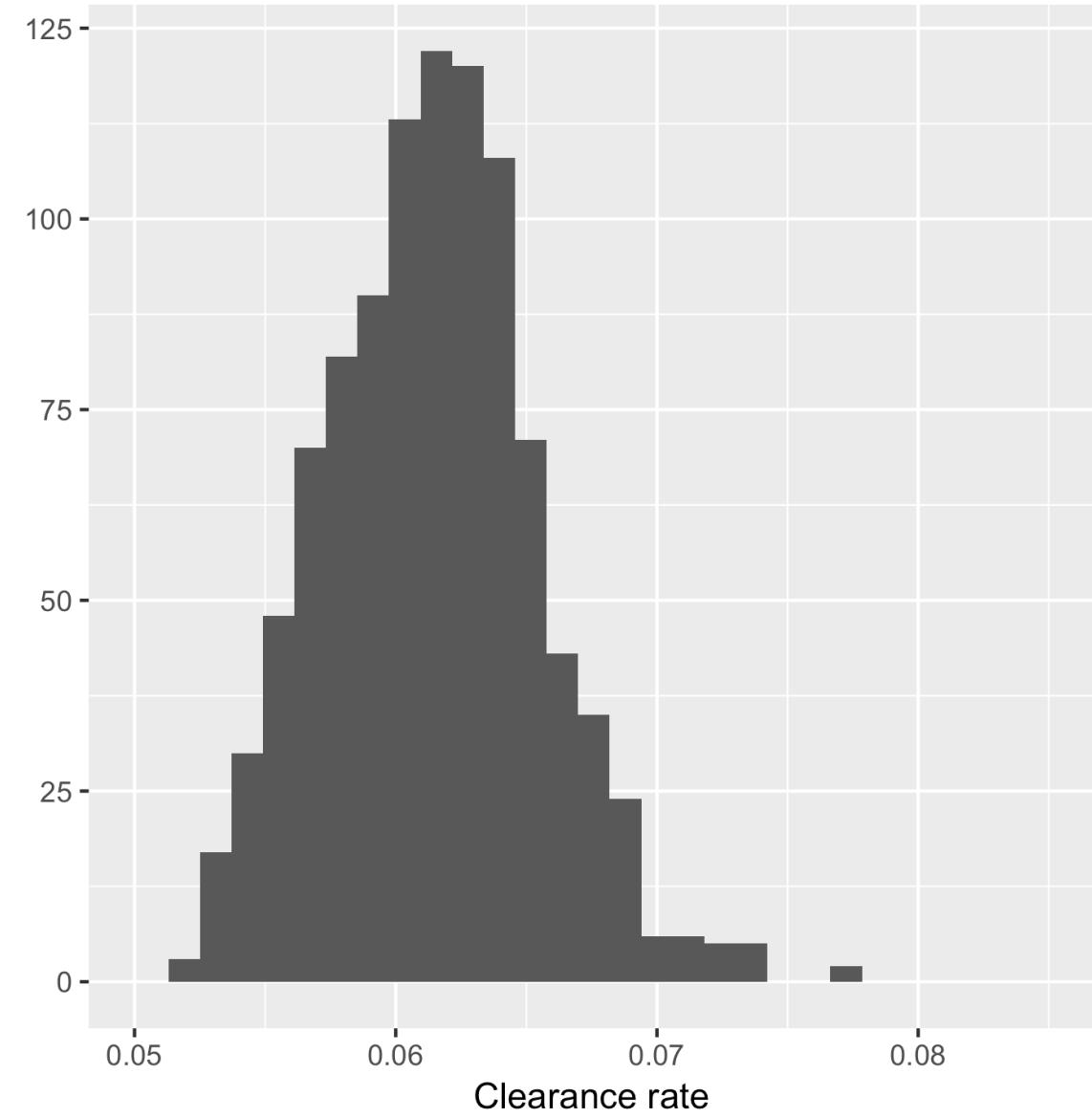
0.99

0.10

# $\Pr(k_3 < 7) ?$

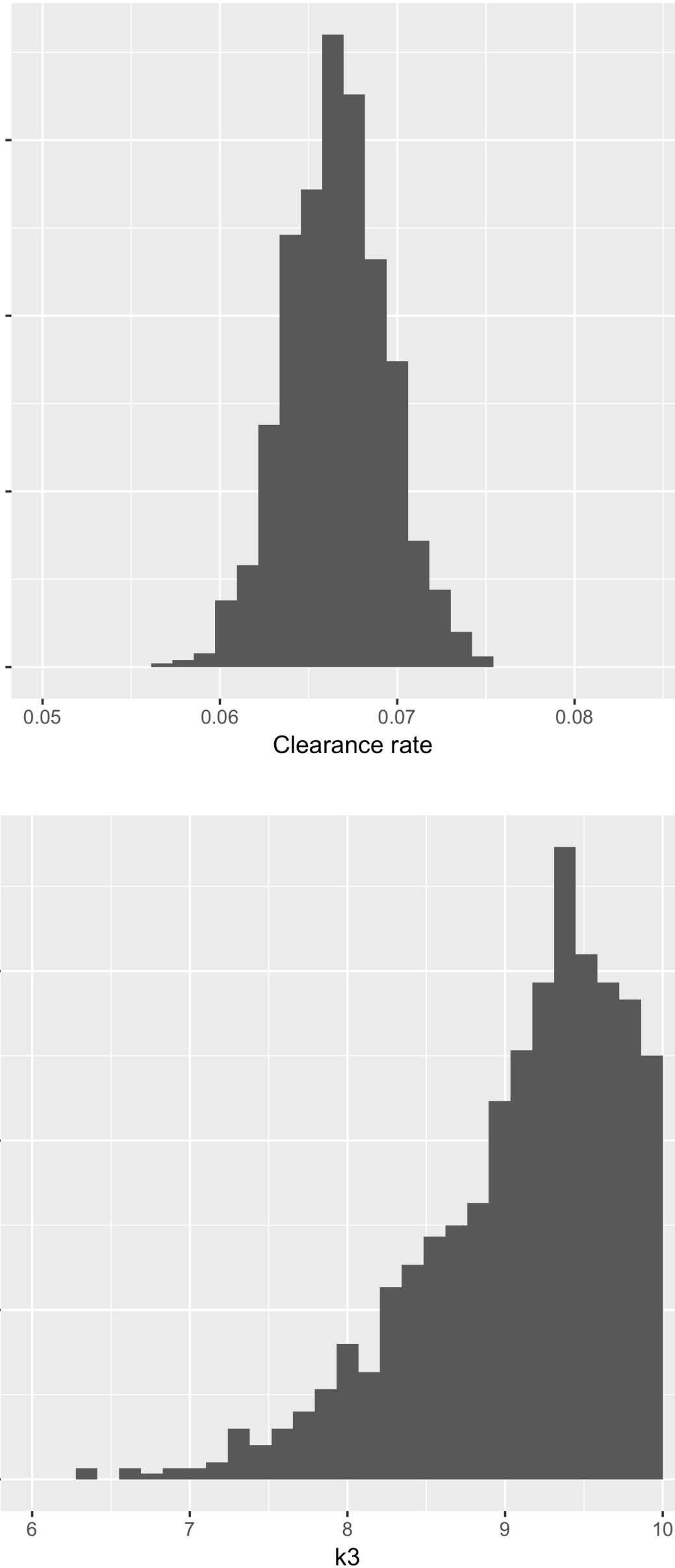


0.02

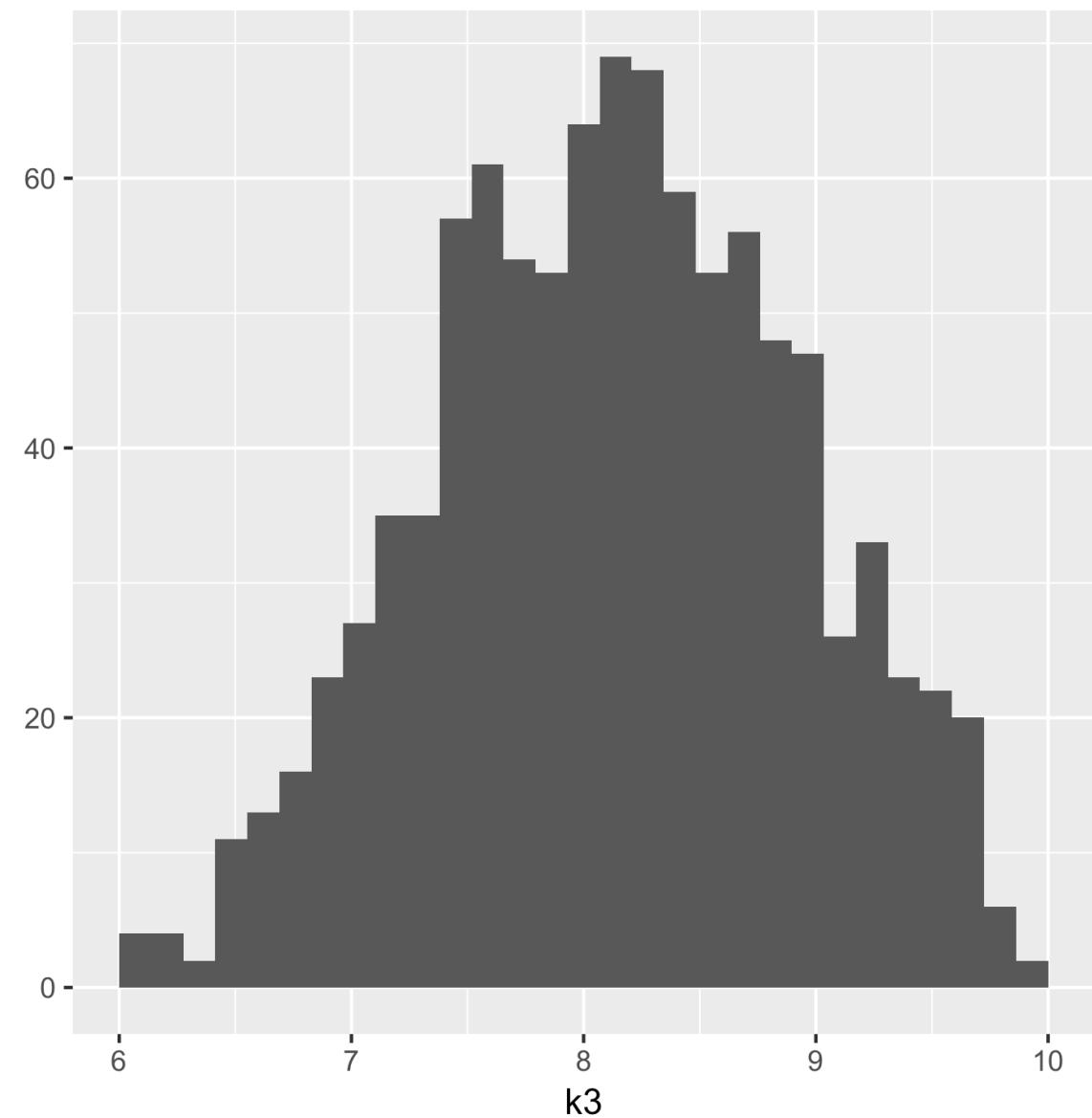


0.17

0.07

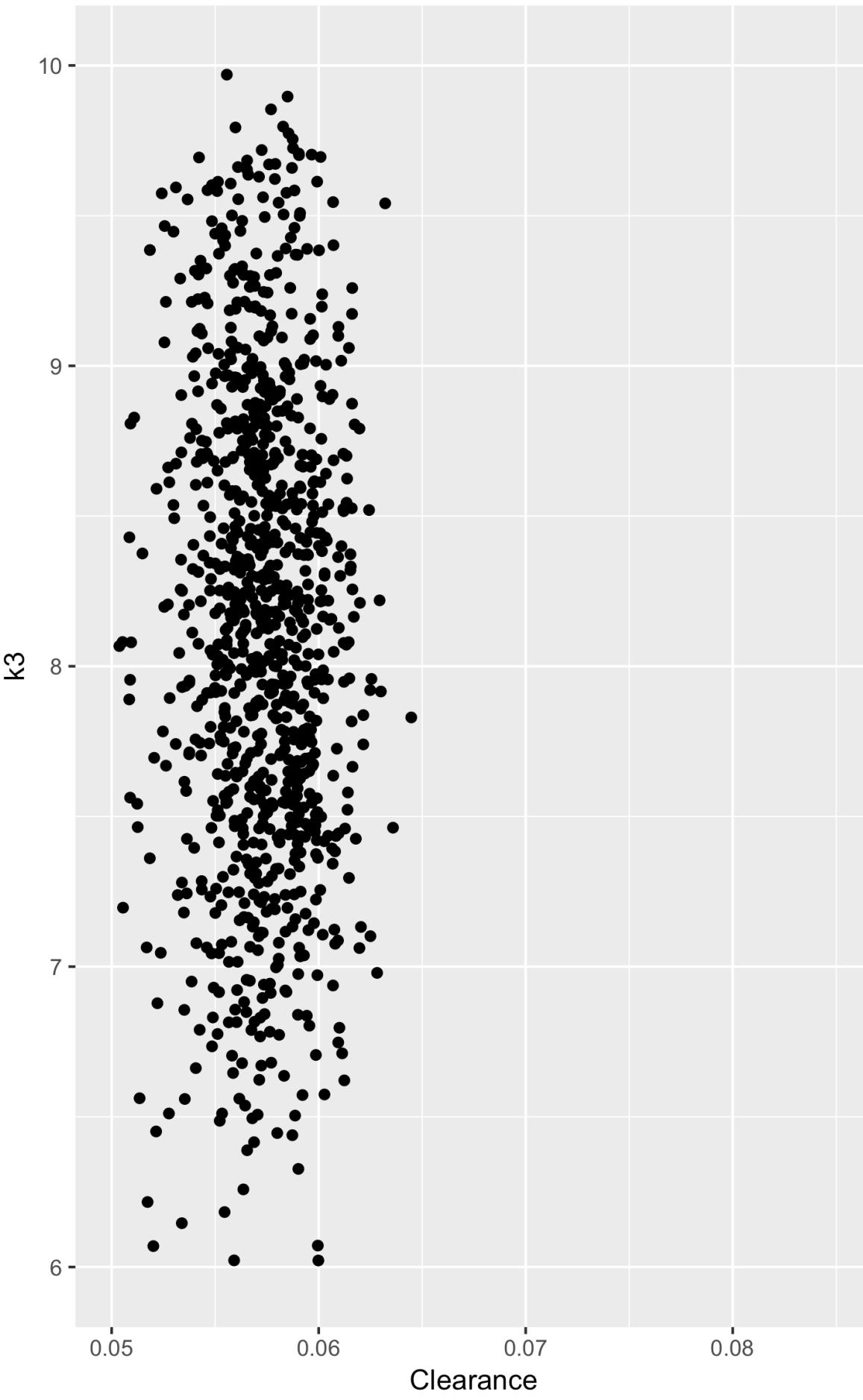
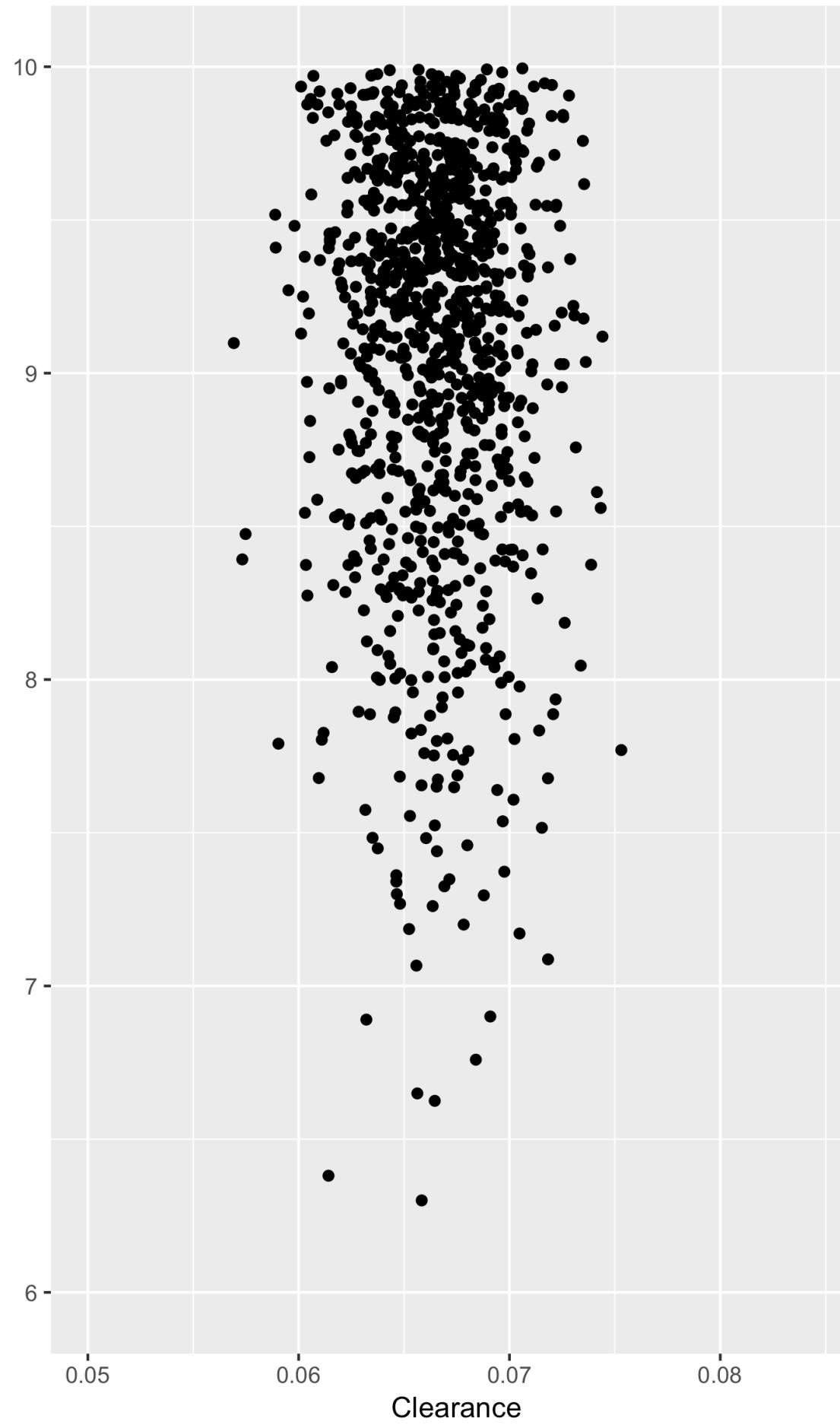
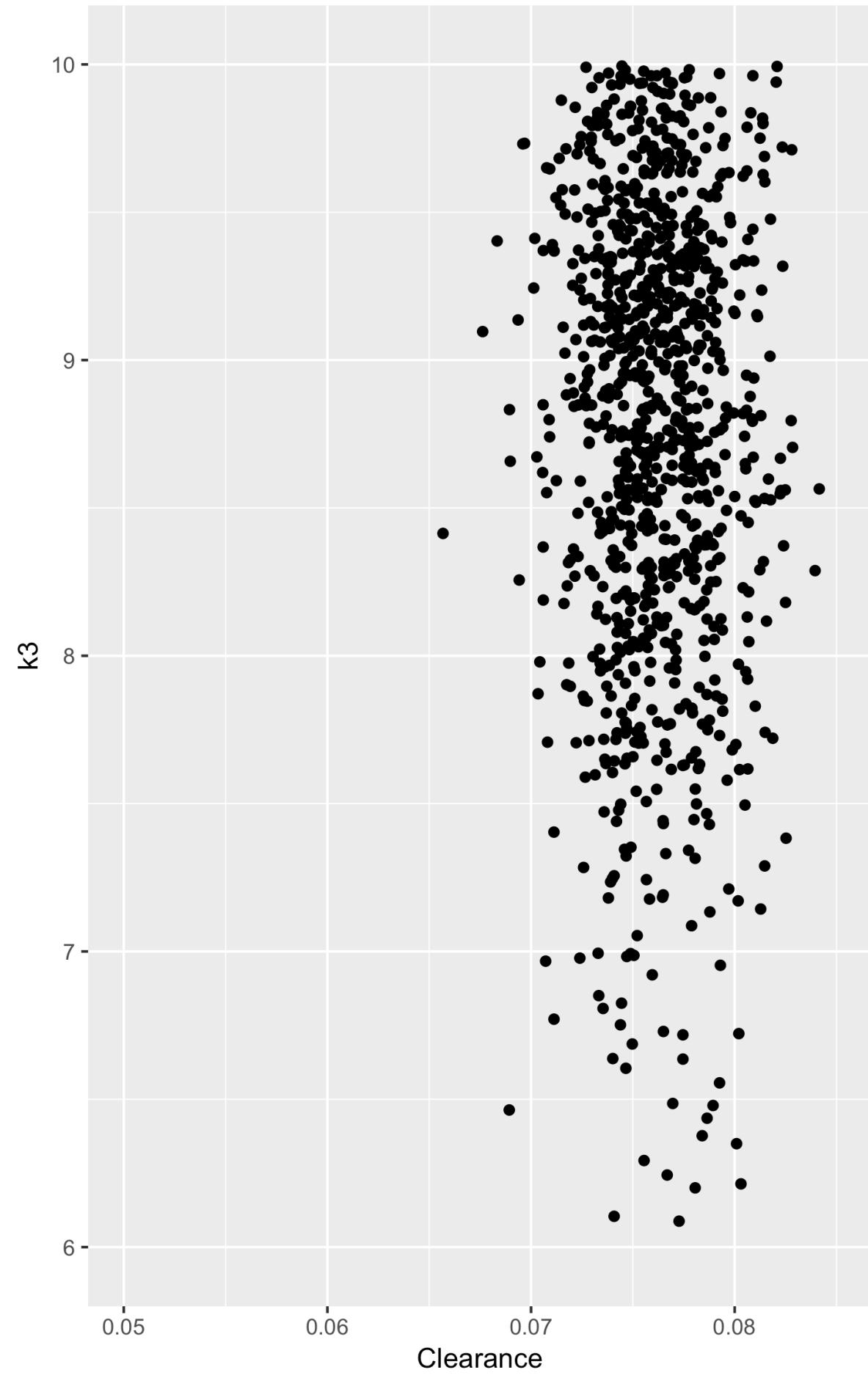


0.44



# But it's really high dimensional

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# How do we do this with such little data?

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- ▶ We embrace what we know

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(structure + prior information)

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- ▶ We embrace what we know
  - ▶ Pharmacometrists are our friends  
(structure + prior information)
  - ▶ Generative modeling
    - ▶ 2 compartment ODE for PK  
(3 individual parameters)
    - ▶ 2 compartment ODE for PD  
(4 individual parameters)
    - ▶ 10 shared parameters
    - ▶ Lognormal measurement model + with censoring  
(lower limit of quantification)

# Simple Stan Program

Knowns:

$$X, y$$

Unknowns:

$$\theta$$

Model:

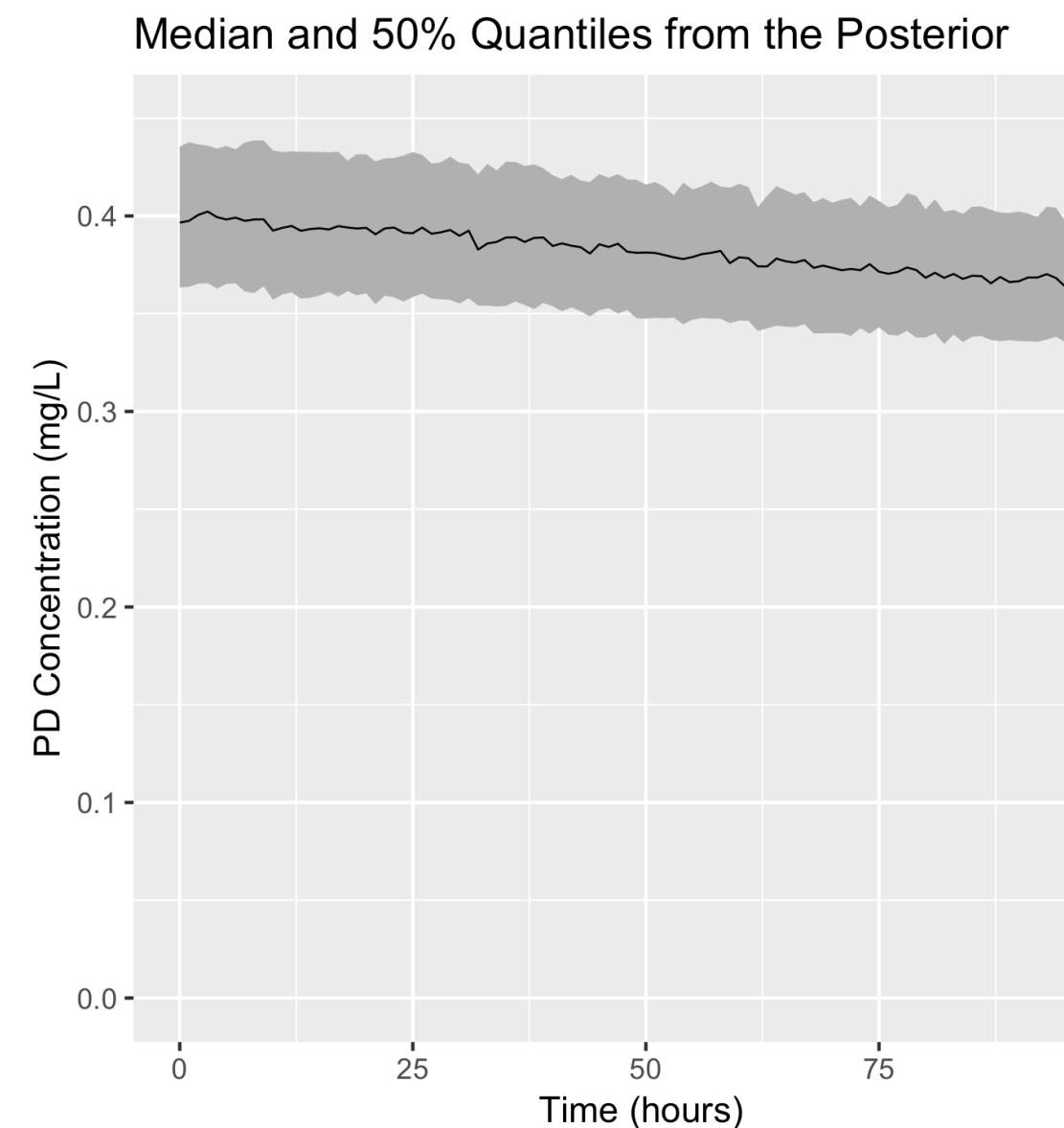
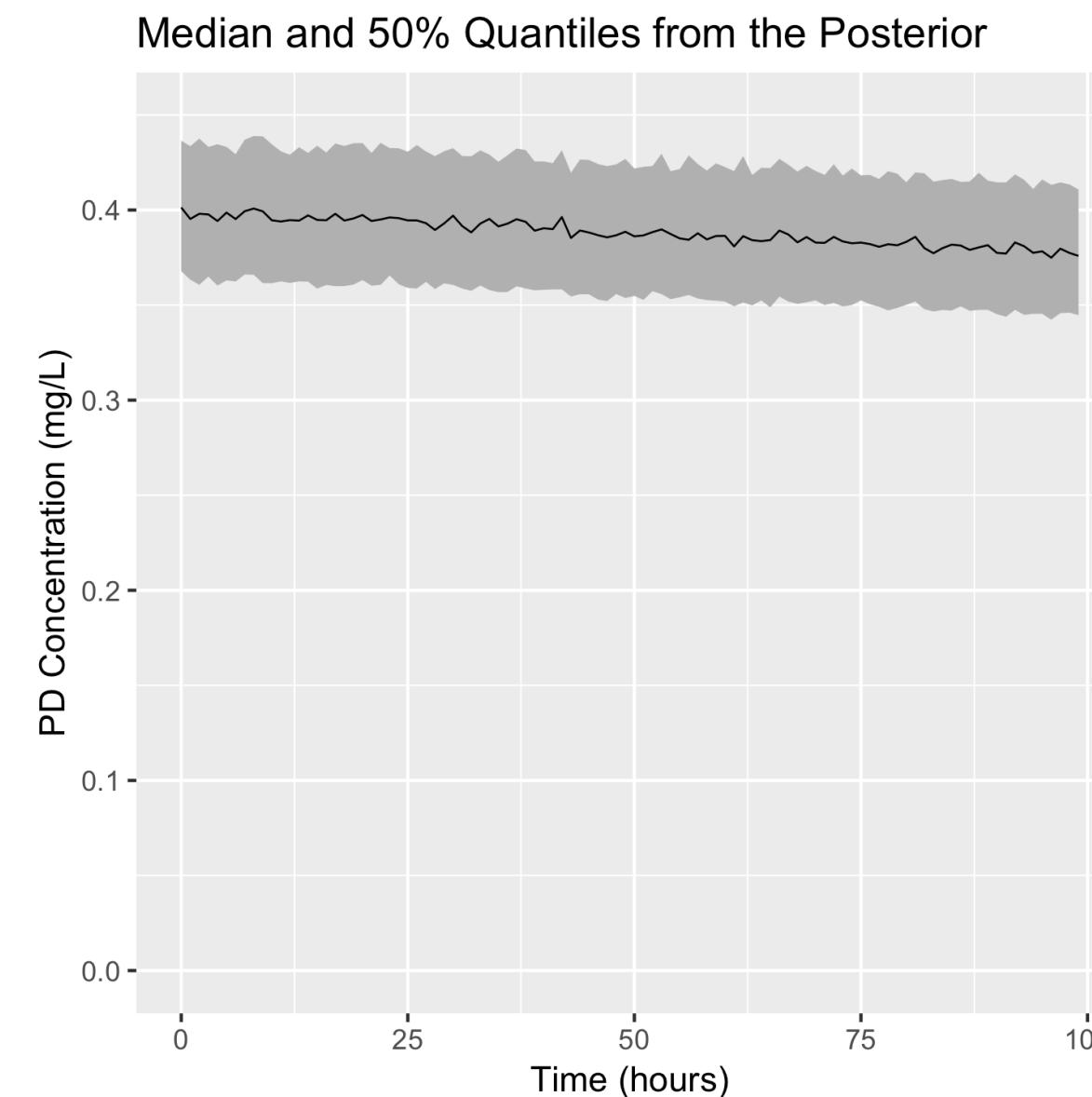
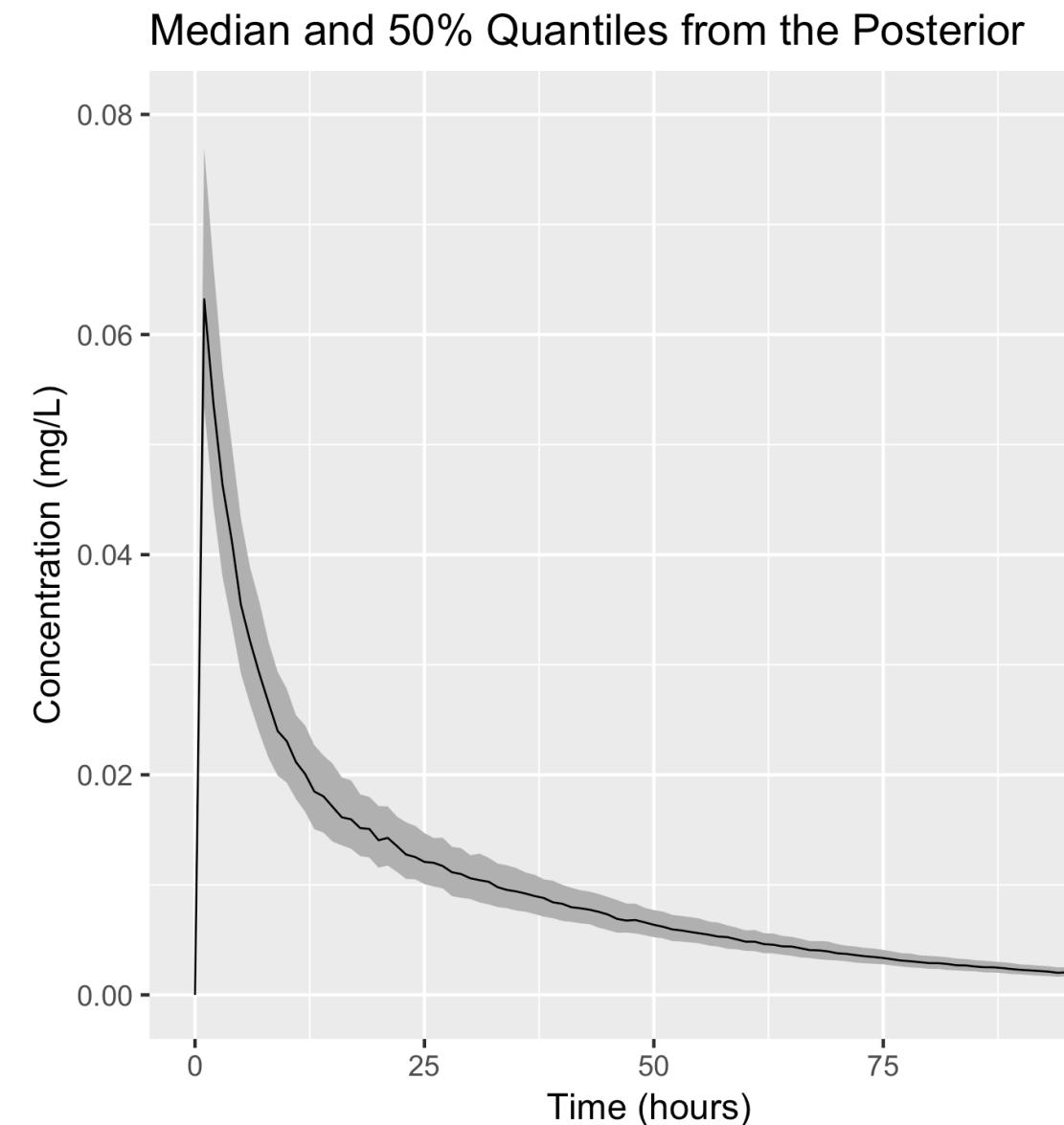
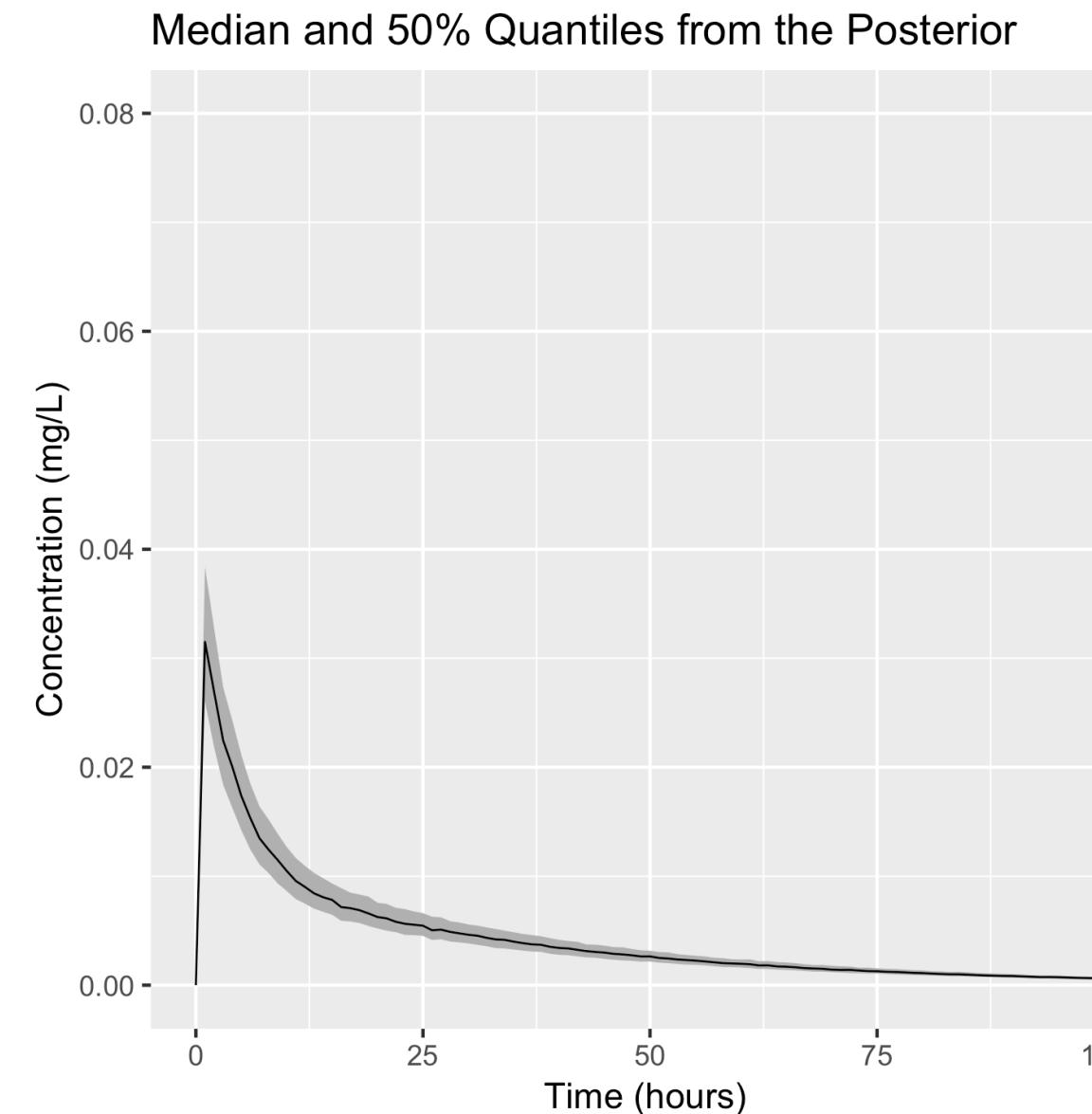
$$\log(p(y|X, \theta)) + \\ \log(p(\theta))$$

Predictions:

$$p(\tilde{y}|y)$$

```
1  data {
2      int<lower=1> N;
3      int<lower=1> K;
4      matrix[N, K] X;
5      vector[N] y;
6  }
7  parameters {
8      real alpha;
9      vector[K] beta;
10     real<lower=0> sigma;
11 }
12 model {
13     y ~ normal(X * beta + alpha, sigma);
14     alpha ~ normal(0,10);
15     beta ~ normal(0,10);
16     sigma ~ cauchy(0,10);
17 }
18 generated quantities {
19     vector[N] y_rep;
20     for (n in 1:N)
21         y_rep[n] = normal_rng(X[n,] * beta +
22                               alpha, sigma);
23 }
```

# We can ask counterfactual questions



If we went from 3 mg to 6 mg:

- ▶ Pr(higher dose is more effective)?

1

- ▶ Expected effect of increased dose?

0.012

Thank you