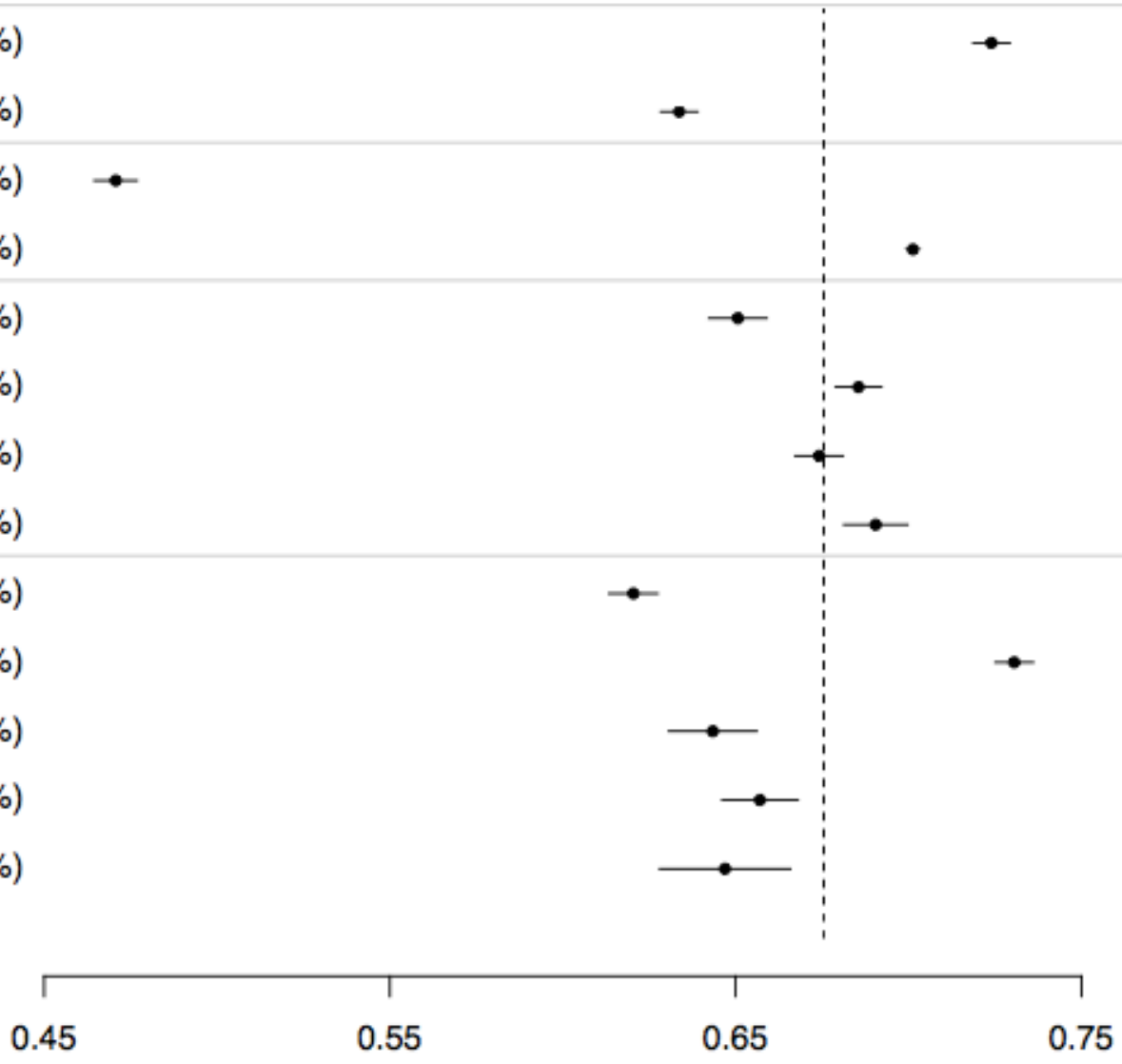
6. Hierarchical modeling and prior information

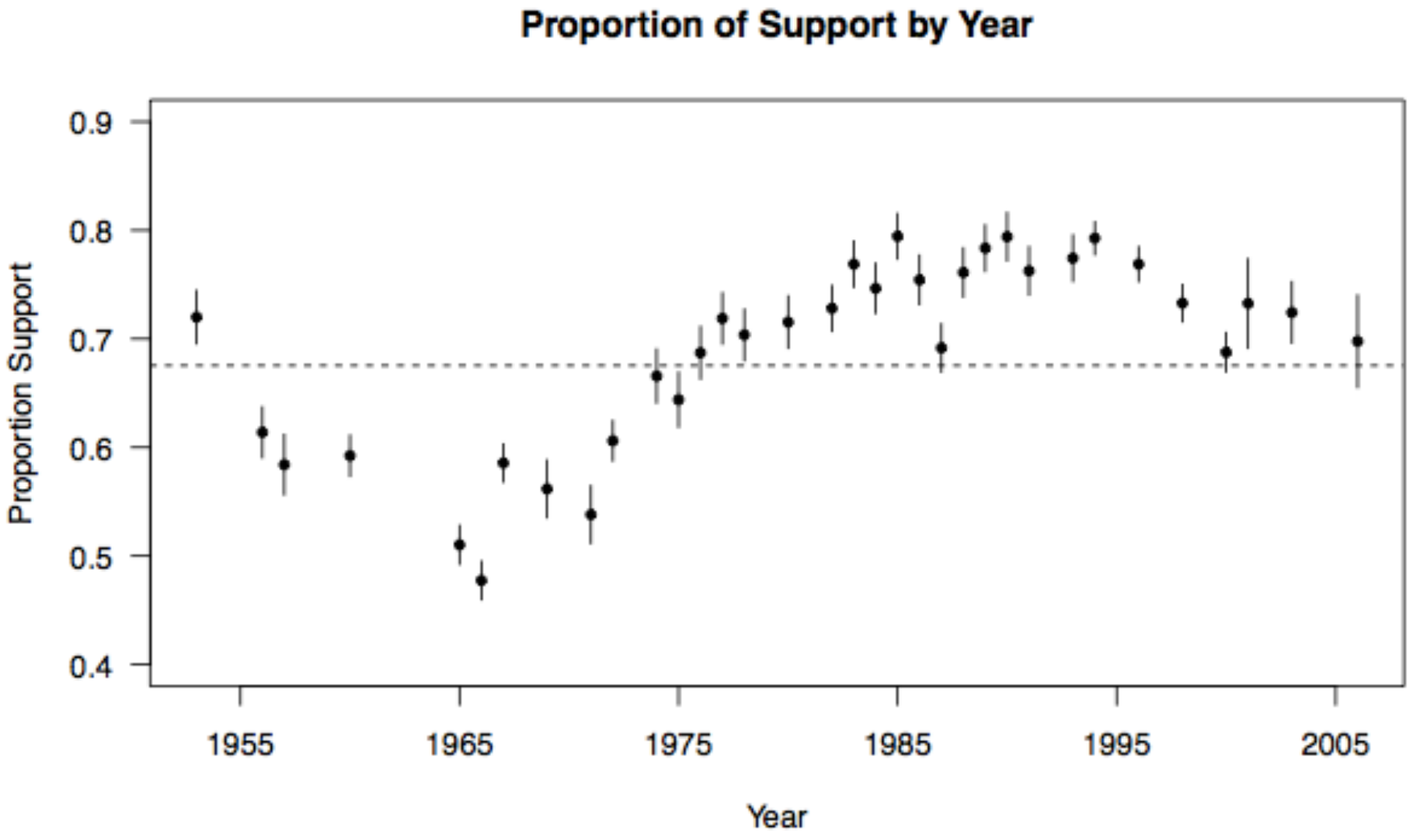
- State-level time series of death penalty opinions
- Population model in toxicology

Death penalty time series

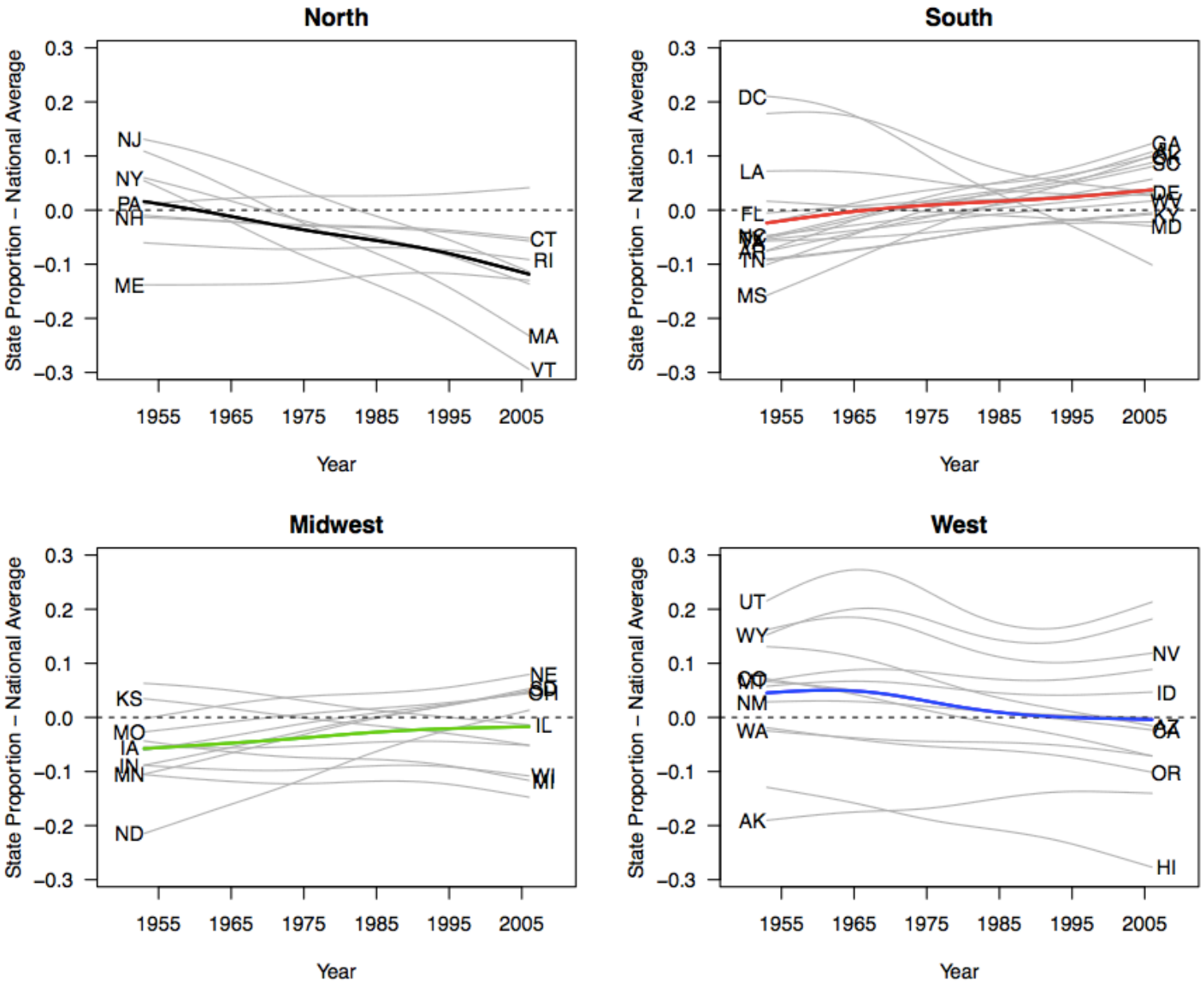
Category	Sample Size	Percentage
Men	26953	(46%)
Women	31300	(54%)
Black	6516	(11%)
Non–black	51737	(89%)
18–29	12460	(21%)
30–44	18619	(32%)
45–64	17526	(30%)
65+	9648	(17%)
Less than High School	18211	(31%)
High School	25010	(43%)
Some College	5415	(9%)
College grad	7170	(12%)
Grad School	2447	(4%)



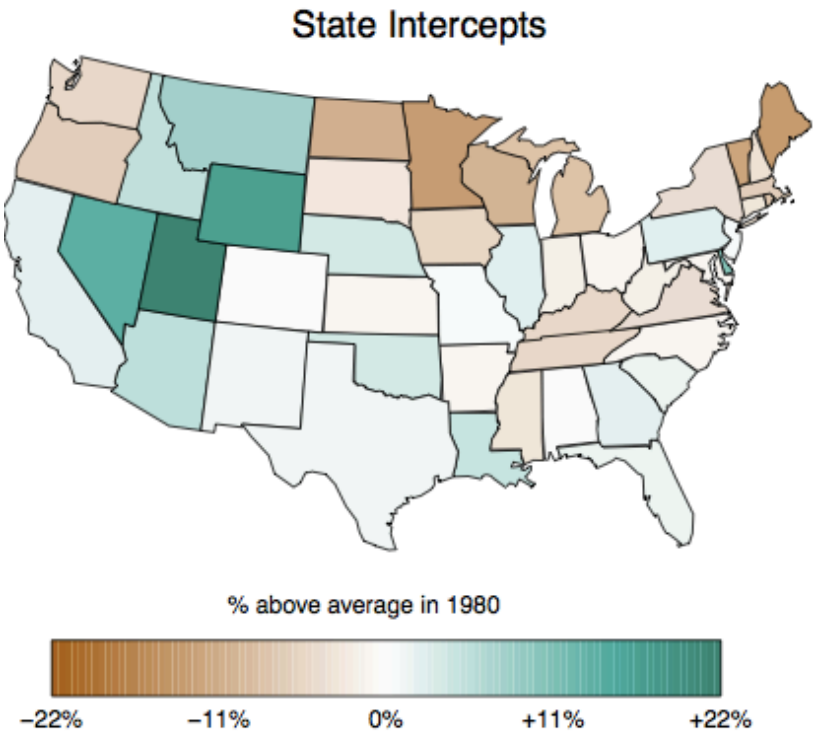
National demographic breakdown

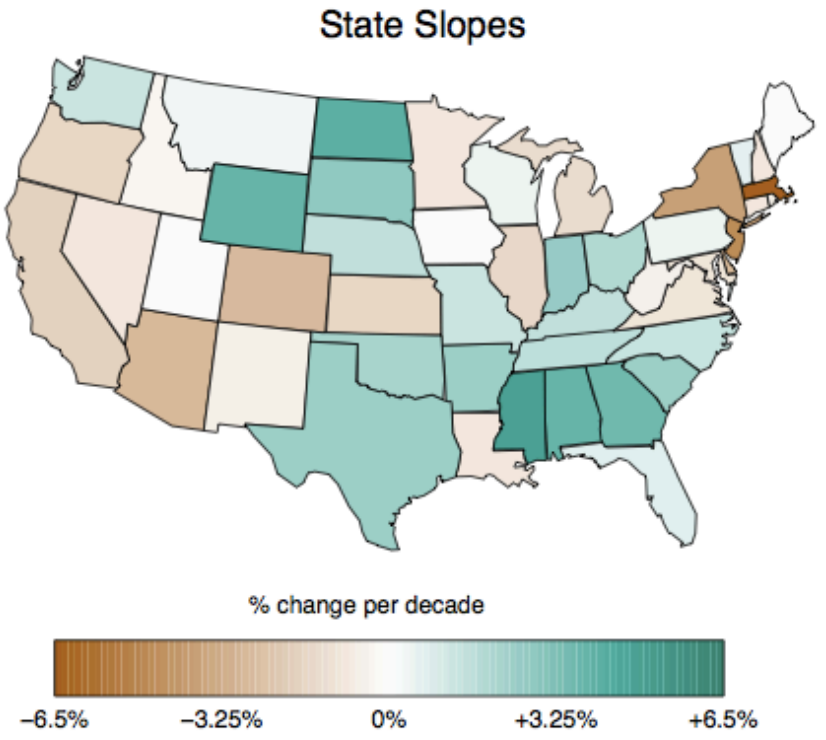


Trends by state

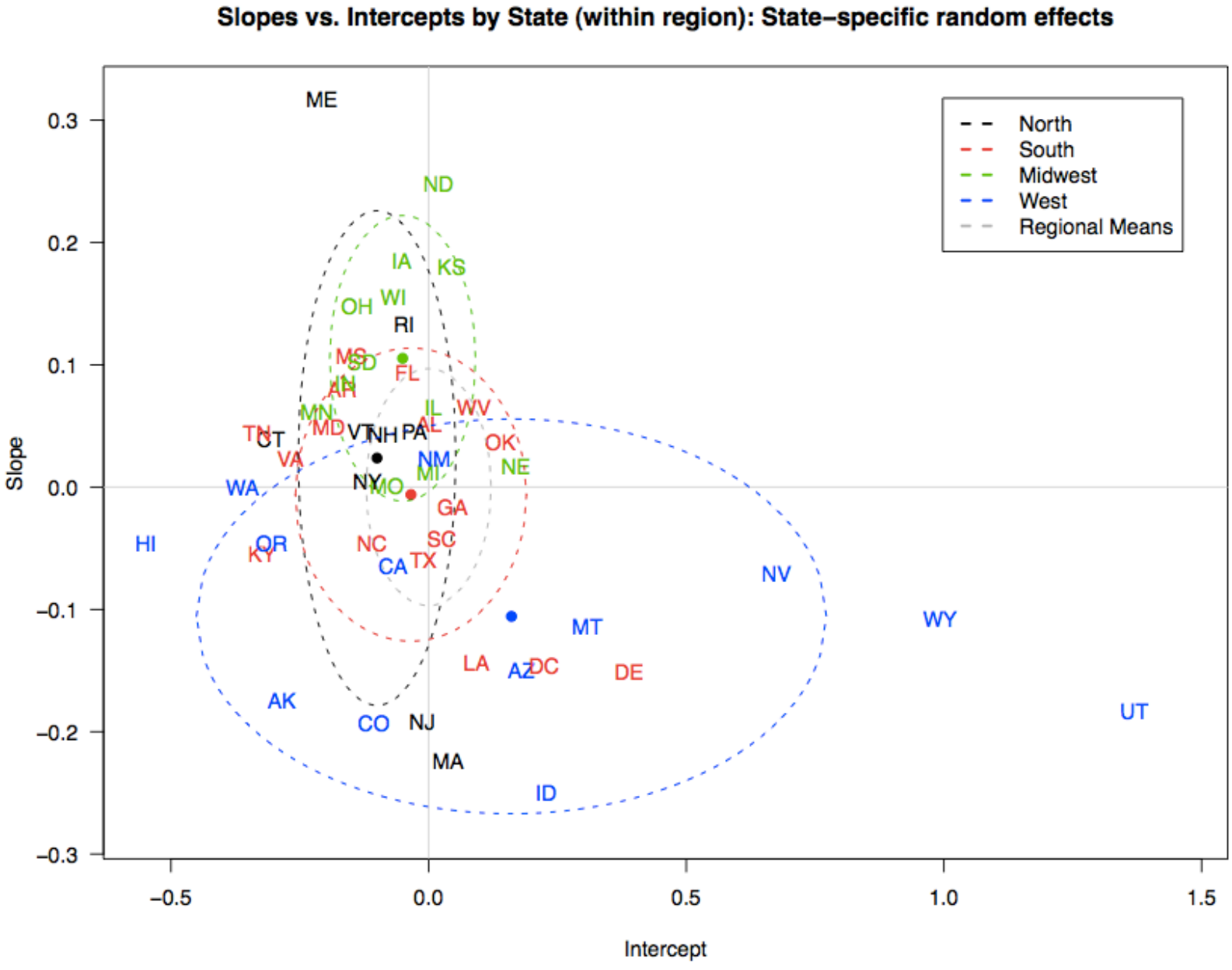


State intercepts and slopes

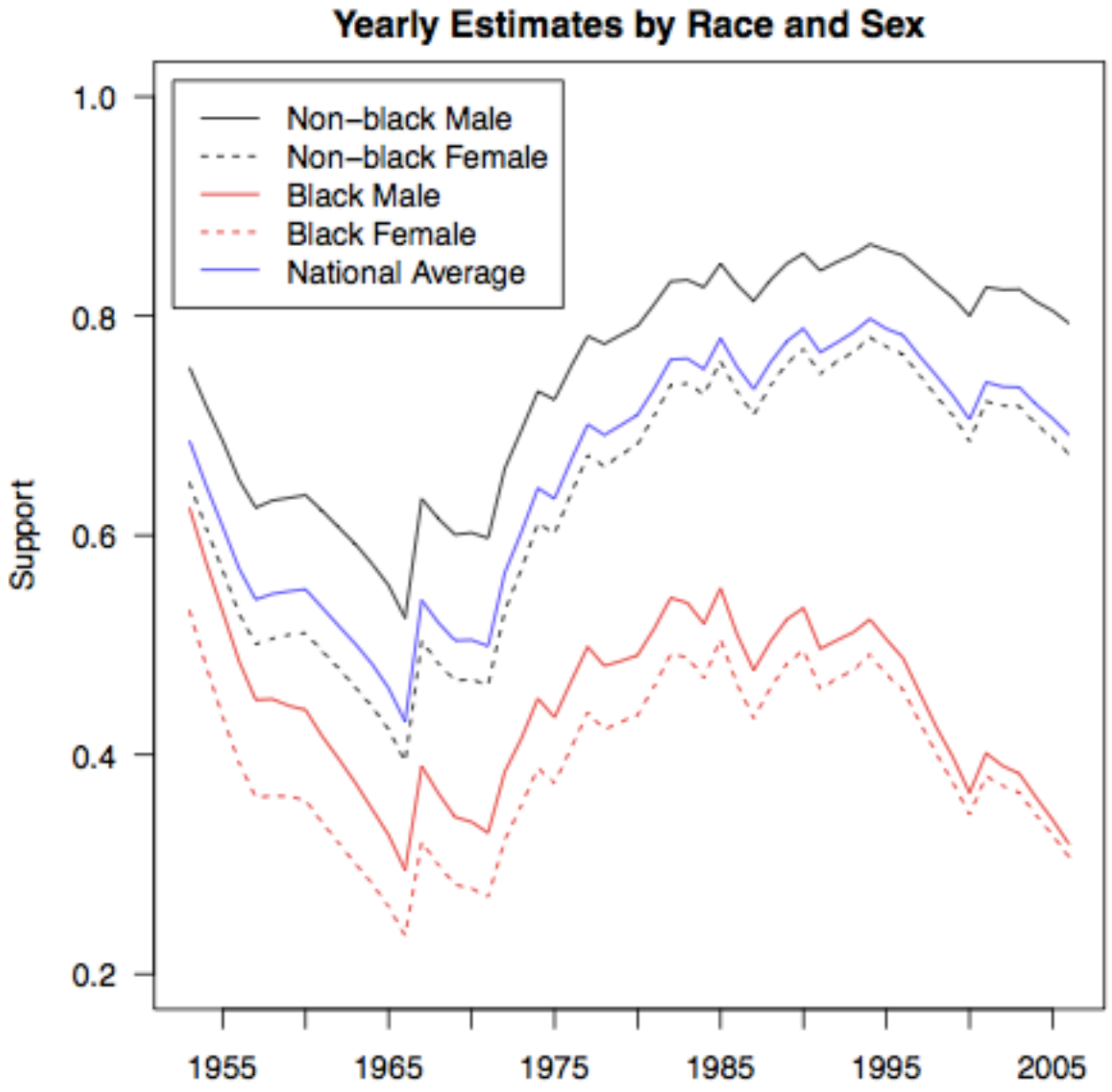




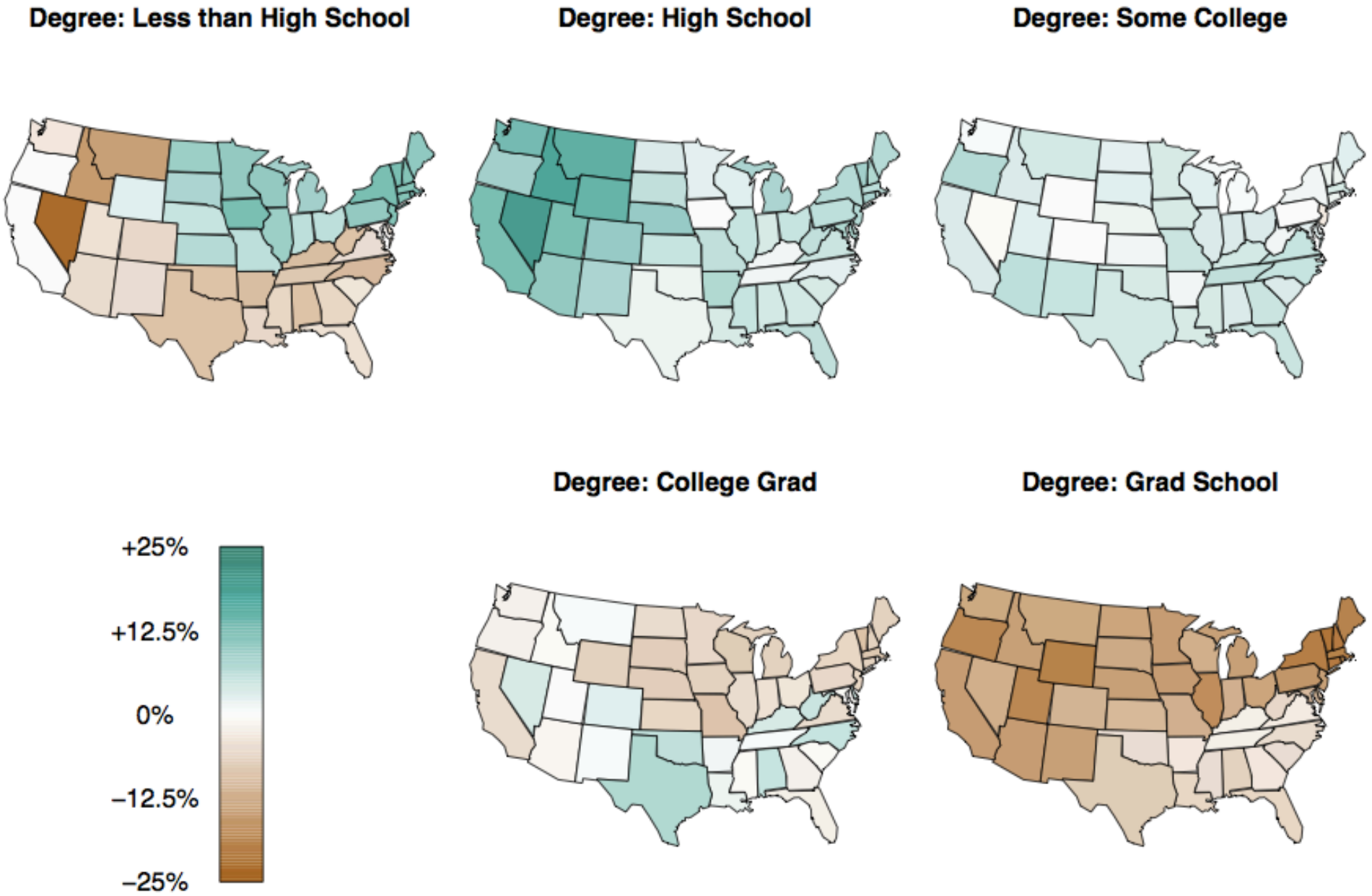
Unmodeled variation in state intercepts and slopes



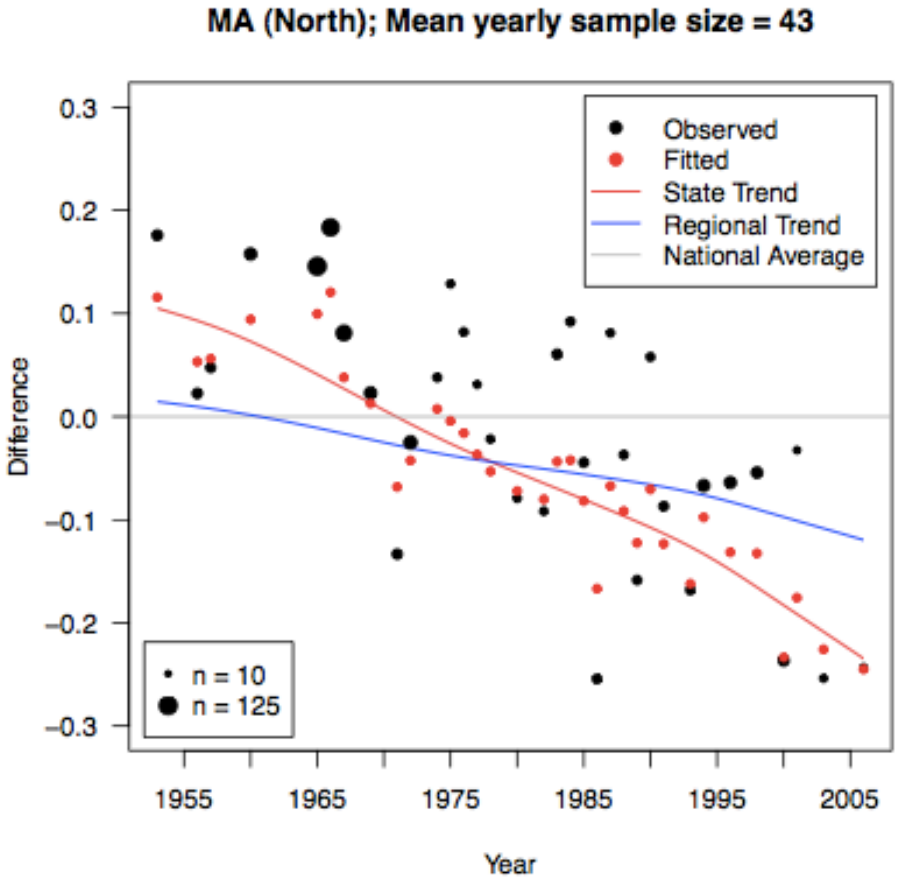
Trends by race and sex

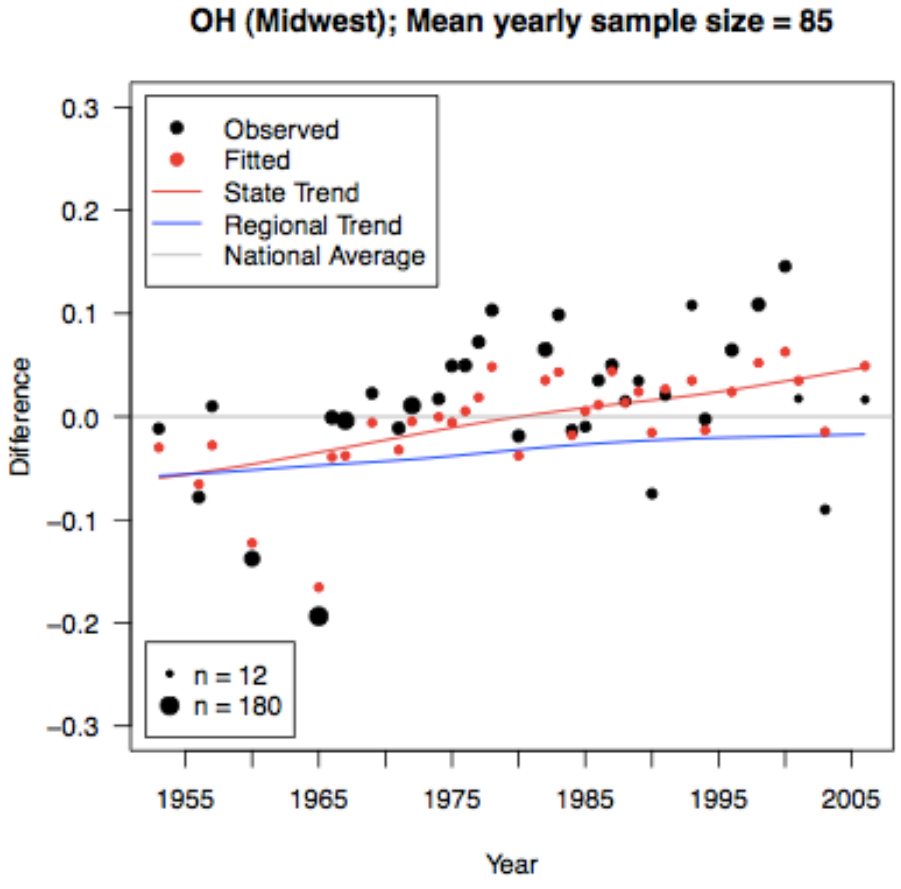


Support among different education levels



Close-up on two states (compared to U.S. avg)





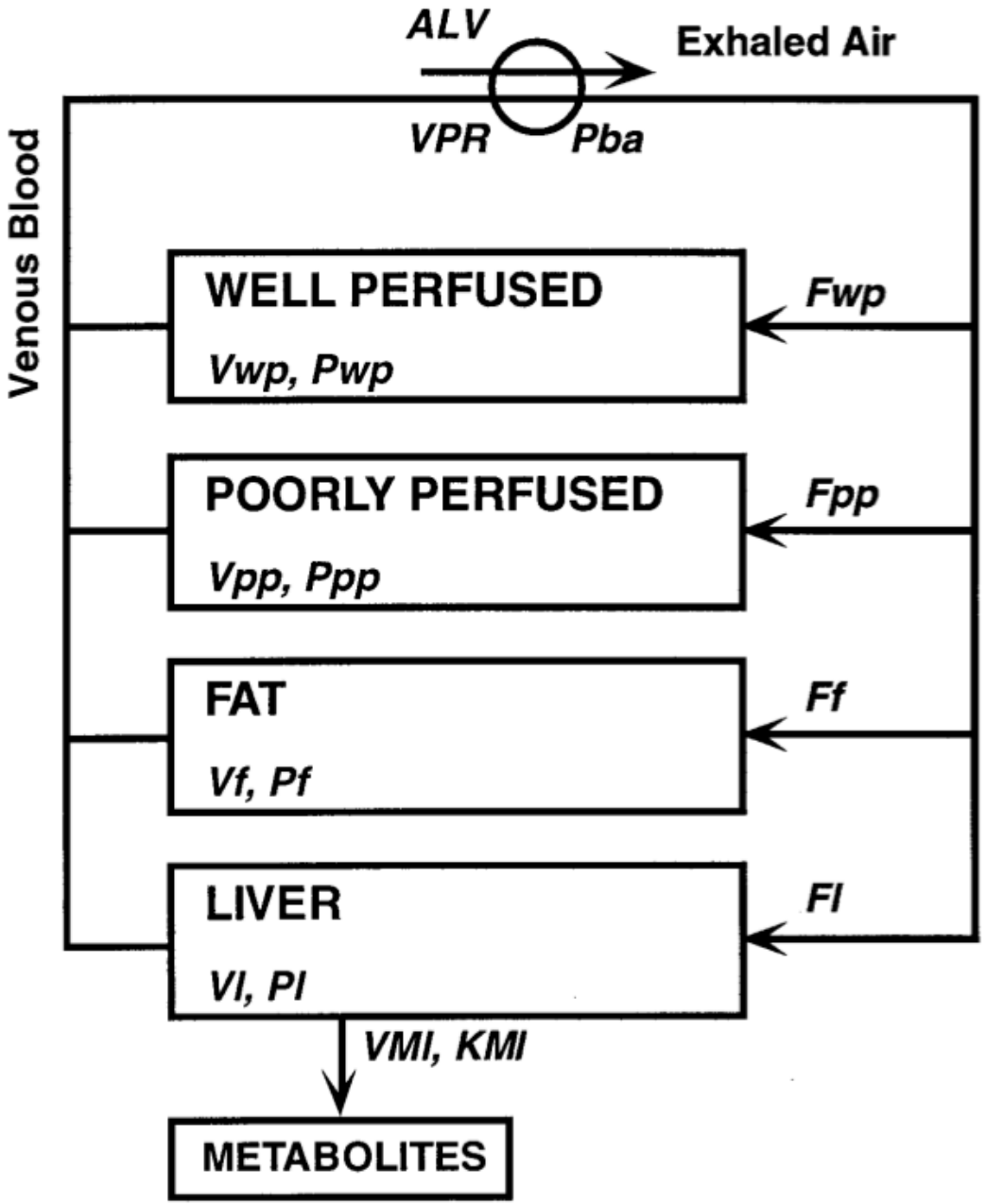
An example from toxicology

- Central story: 4-compartment model of toxicokinetics of perchloroethylene
- Bayesian inference combines prior information and data
- Unresolved questions
- How the model all fits together

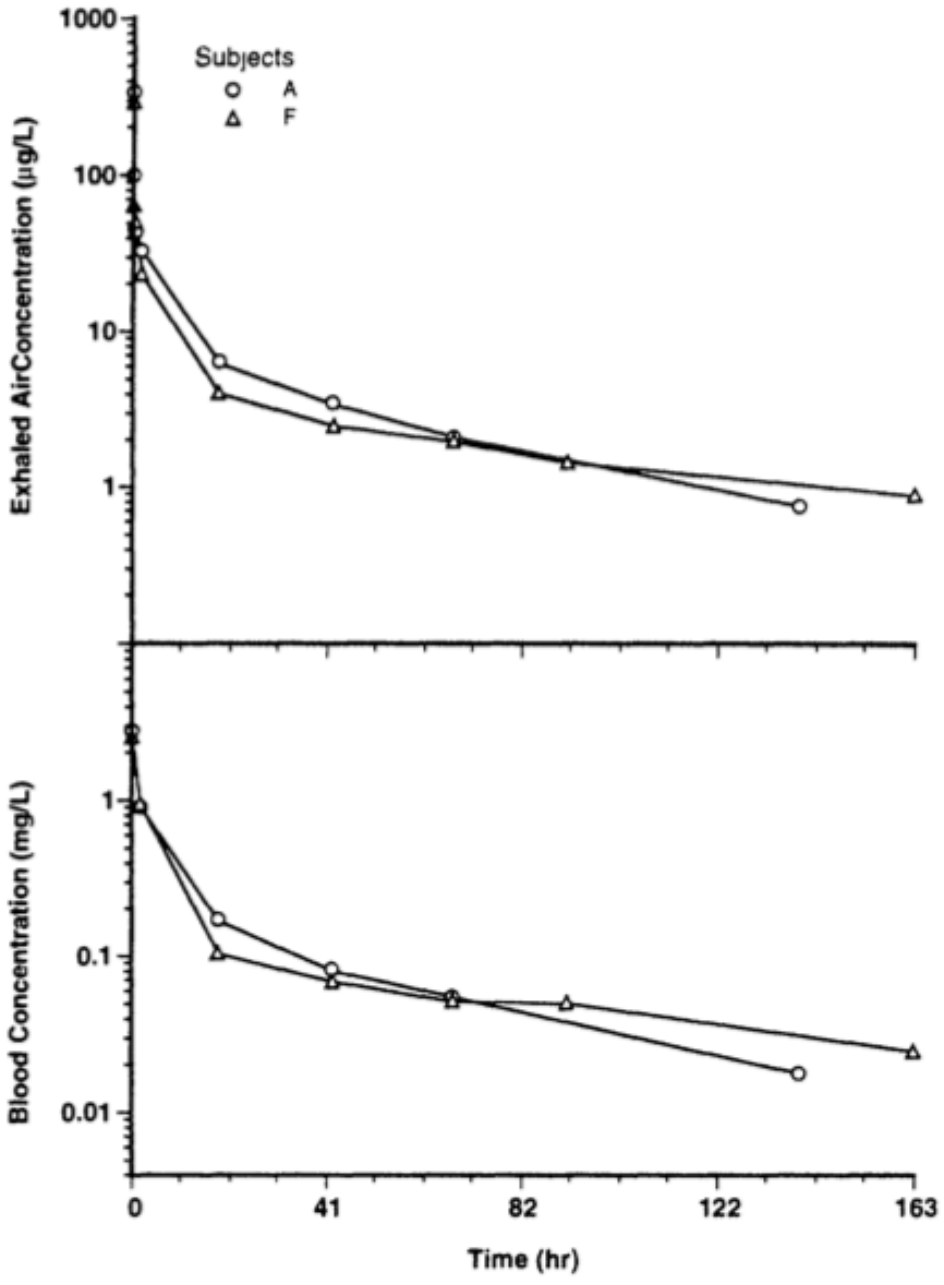
Toxicokinetics of perchloroethylene

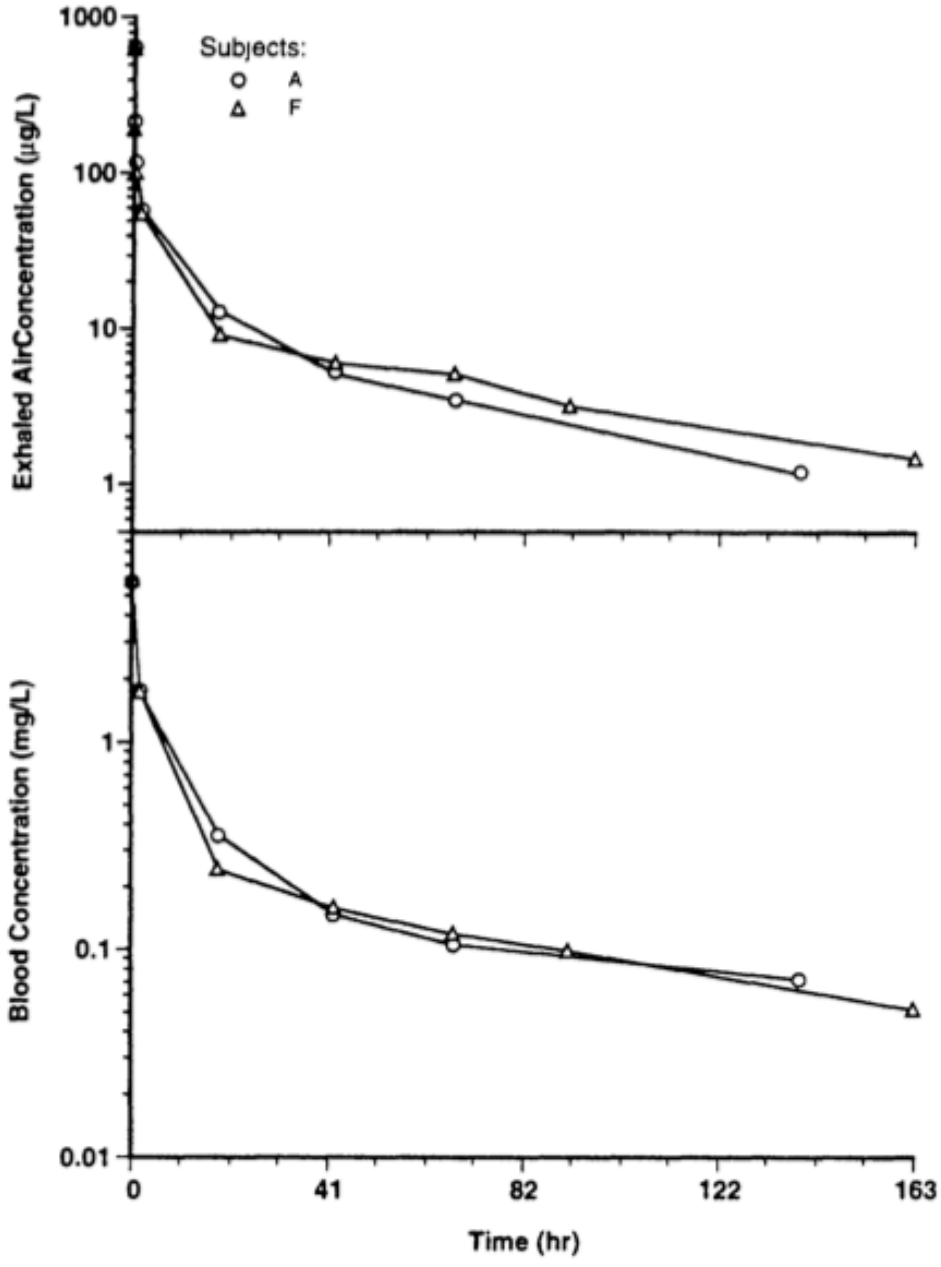
- Goal:
  - How much PERC is metabolized at low doses
  - Population distribution
- Experimental data: Expose 6 healthy volunteers to PERC for four hours, then measure concentrations in blood and air for 2 weeks
- 4-compartment model, metabolism in liver
- Our analysis:
  - Simple data-fitting did not work
  - Use Bayes to combine data and prior info within model

4-compartment model



Some data


Subjects
A
F
Exhaled AirConcentration (µg/L)
1000
100
10
1
Blood Concentration (mg/L)
1
0.1
0.01
0
41
82
122
163
Time (hr)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0.01
0
41
82
122
163
Time (hr)

Connections to general Bayesian principles

- Sometimes the model comes first, based on substantive considerations (toxicology, economics, . . .)
- Sometimes the model is chosen based on the data collection (traditional statistics of surveys and experiments)
- Other times the data come first (other statistics examples)
- Usually it's a mix
  - Discuss an example of prediction
  - Discuss an example of causal inference

Simple statistical ideas did not work

- Fitting 4-compartment model directly to data
- Assisted model fit
- 1 or 2-compartment model
- Simulation from prior distribution

Simple statistical ideas that did not work: Fitting 4-compartment model directly to data

- Nonlinear least squares
- Fitting to each person separately:
  - Unstable: approx 30 data points, 15 param
  - "8 kg liver"
- Pooling data and estimating parameters for "the standard man"
  - Not useful for our goal of population inference

Simple statistical ideas that did not work: Assisted model fit

- Set some parameters to fixed values (from the pharmacology literature)
- Estimate the other parameters
- Results:
  - Couldn't fit the data well
  - Difficult to get fixed values for PERC-specific parameters such as equilibrium concentration ratios

Simple statistical ideas that did not work: 1 or 2-compartment model

- Simpler model can be estimated easily and robustly
- Does not fit the data well
  - Most of the PERC leaves in a few hours, but some stays in the body after a week or more
- Not realistic for low-dose extrapolation

Simple statistical ideas that did not work: Simulation from prior distribution

- Get prior information on parameters from pharmacology literature
- Try to fit data within these prior constraints
- Does not fit the data well
- Difficult to get good prior information for PERC-specific parameters such as equilibrium concentration ratios

Bayesian inference

- 4-compartment model
- 15 parameters for each person
- Prior information
  - Strong for some parameters (e.g., volume of liver)
  - Weak for others (e.g., Michaelis-Menten coef)
  - Model includes uncertainty and variation
- Posterior simulation: random walk through parameter space
- Inference for parameters and predictions
- Model checking

Hierarchical prior distributions

- Prior distribution for a rate parameter in the metabolism, θ_j for person j
  - $\log \theta_j \sim N(\mu, \tau^2)$
  - $\mu \sim N(\log 16, (\log 10)^2)$
  - $\tau \approx \log 2$
- Large uncertainty, small variation
- Can learn about μ using data from several people
- Can't do this without a hierarchical model
- Transformations and prior correlations (why transformations are particularly important for Bayesians)

Hierarchical prior distributions

Parameter	*Population prior*
Ventilation/perfusion ratio (VPR)	1.6($\times\div$ 1.3) $\times\div$ 1.3
Blood flow, well-perfused tissues (Fwp)	.47($\times\div$ 1.17) $\times\div$ 1.17
Blood flow, poorly perfused tissues (Fpp)	.20($\times\div$ 1.22) $\times\div$ 1.22
Blood flow, fat (Ff)	.07($\times\div$ 1.27) $\times\div$ 1.27
Blood flow, liver (Fl)	.25($\times\div$ 1.15) $\times\div$ 1.15
Volume, well-perfused tissues (Vwp)	.27($\times\div$ 1.36) $\times\div$ 1.36
Volume, poorly perfused tissues (Vpp)	.55($\times\div$ 1.17) $\times\div$ 1.17
Volume, liver (Vl)	.033($\times\div$ 1.1) $\times\div$ 1.1
Partition coeff, blood/air (Pba)	12($\times\div$ 1.5) $\times\div$ 1.3
Partition coeff, well-perfused (Pwp)	4.8($\times\div$ 1.5) $\times\div$ 1.3
Partition coeff, poorly perfused (Ppp)	1.6($\times\div$ 1.5) $\times\div$ 1.3
Partition coeff, fat (Pf)	125($\times\div$ 1.5) $\times\div$ 1.3
Partition coeff, liver (Pl)	4.8($\times\div$ 1.5) $\times\div$ 1.3
Max metabolic rate in liver (VMl)	.042($\times\div$ 10) $\times\div$ 2
K_m in liver (KMl)	16($\times\div$ 10) $\times\div$ 1.5

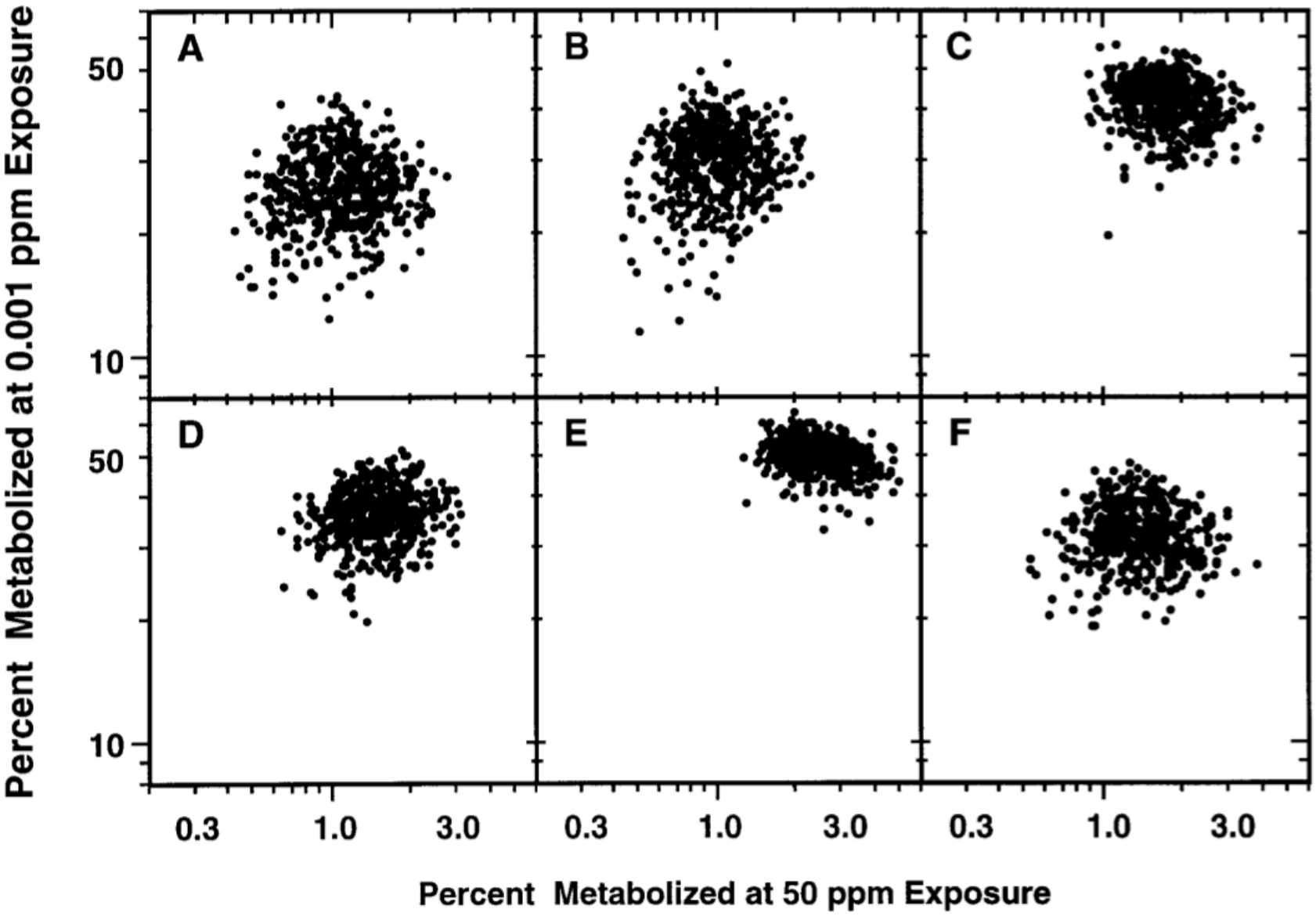
What we did

- Set up a hierarchical prior distribution with uncertainty and population variation for a 4-compartment model
- Fit the model to data (much computation)
- Checked inferences about parameters to see that they made sense
- Re-ran model under hypothetical low-dose, high-dose exposures

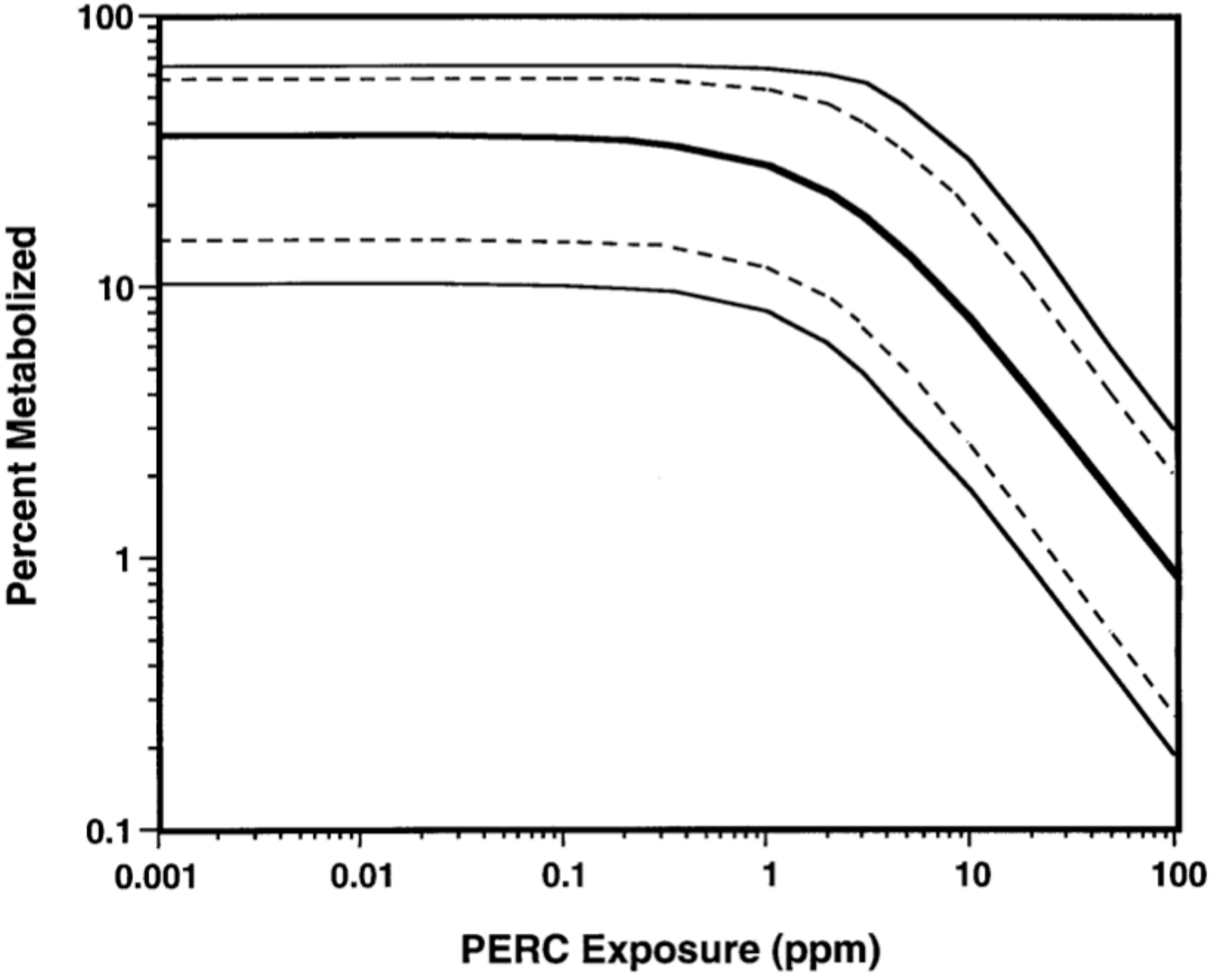
Fitting and using the model

- Computationally intensive: Each step requires evaluation of the numerical differential equation solver
- Check inferences: Do they make sense?
- Re-run the model several times to simulate what would happen under different conditions

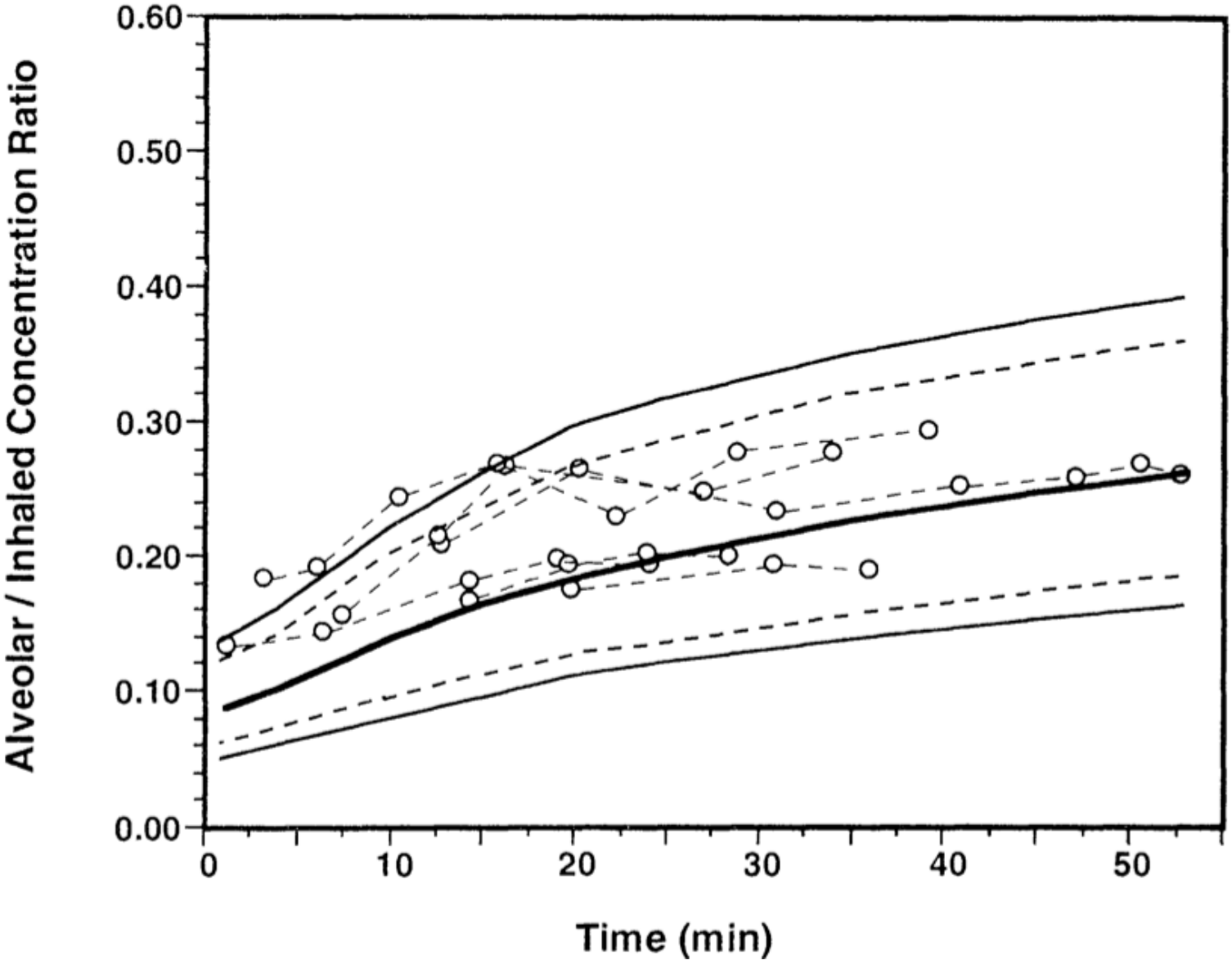
Inference for 6 individuals



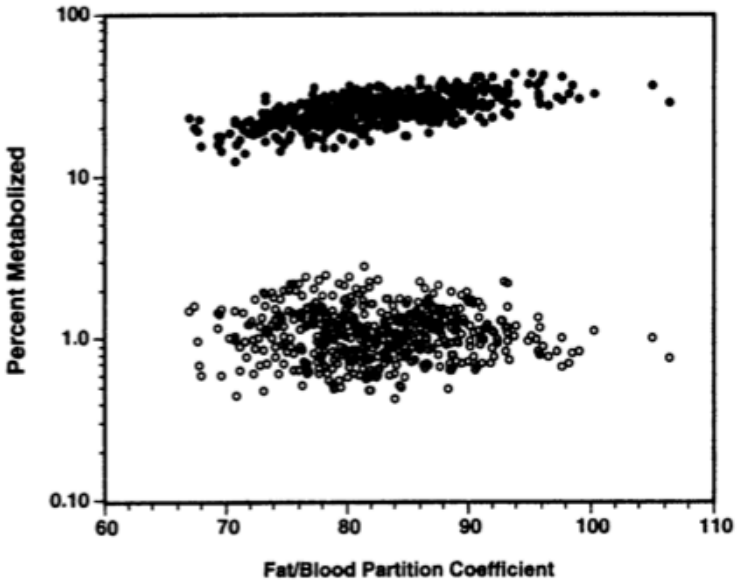
Inference for the population



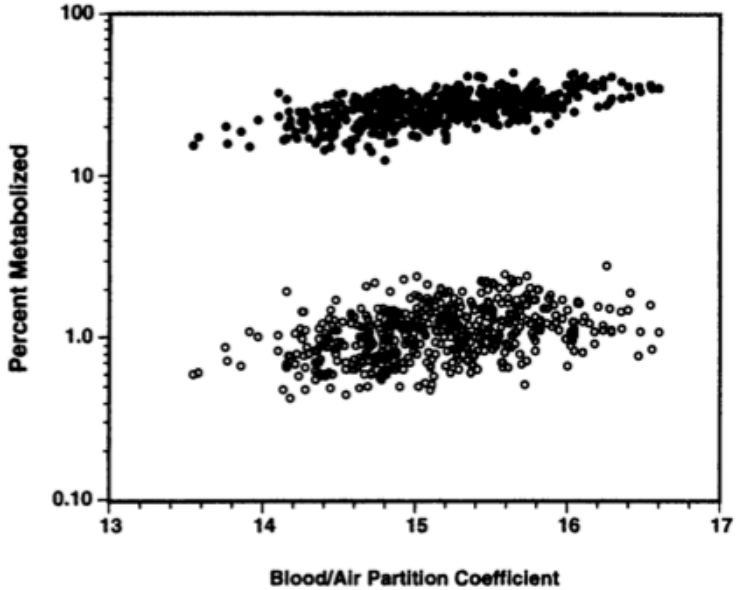
Prediction of data from a new study



Sensitivity to priors



(a)



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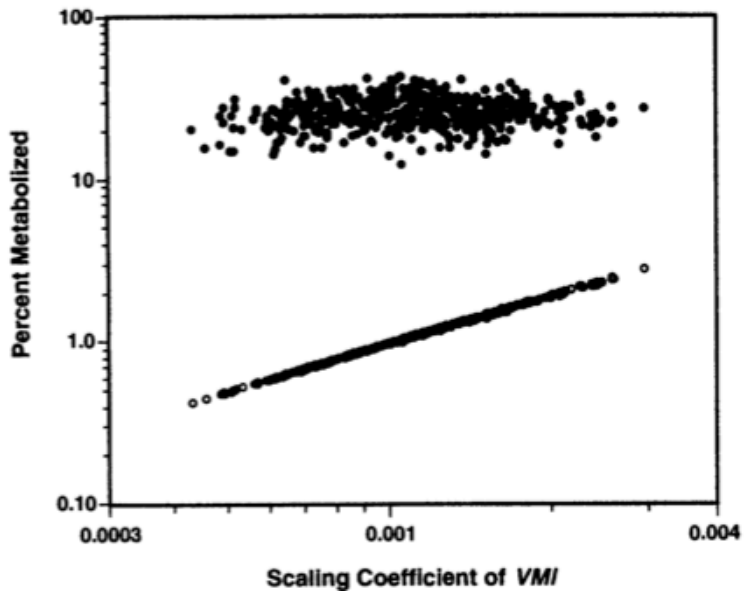

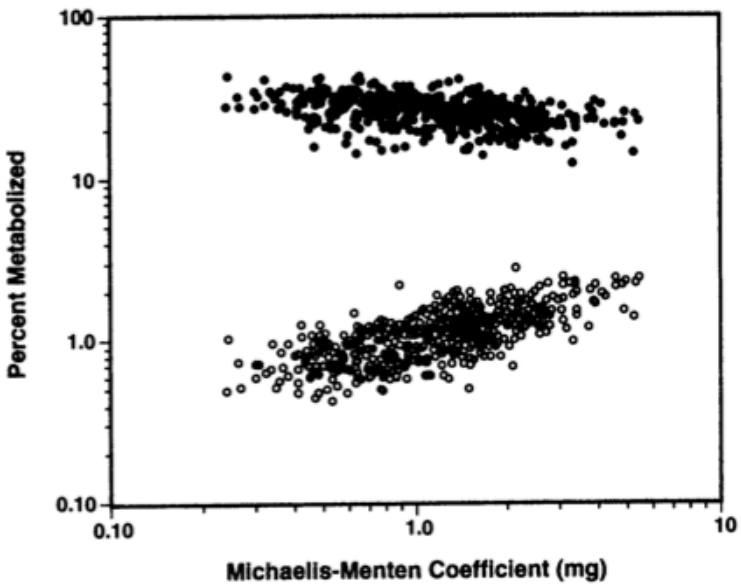

Putting it all together

(a) Physiological pharmacokinetic model
(b) Hierarchical population model
(c) Prior information
(d) Experimental data
(e) Bayesian inference
(f) Computation
(g) Model checking

- We need all of these!

(a) Physiological pharmacokinetic model

- Without a physiological model, there is no good way to get prior information on the parameters
- We need physiological parameters (not just curve-fitting of the data) to efficiently combine information across different people

(b) Hierarchical population model

- Without a population model, there generally are not enough data to estimate the parameters separately for each individual
- And there is too much variation among bodies (even among healthy young male volunteers) to pool all the data together and estimate common parameters

(c) Prior information
(d) Experimental data

- We need prior information. Otherwise, our estimates don't make sense (the 8 kg liver)
- We need experimental data to learn about perchloroethylene in particular

(e) Bayesian inference

- Find parameters that are consistent with both prior information and data (if such agreement is possible)
- Automatically includes uncertainty and variability, so inferences can be plugged in directly to risk assessment and decision analysis

(f) Computation

- Our models are big and nonlinear. Least squares, maximum likelihood, etc., are not enough
- We want to include more data from more patients

(g) Model checking

- Check inferences about parameters
  - Do they make sense?
  - Are they consistent with prior distributions
- Check fit to data
- Check predictions on new data

Using Bayesian ideas to improve existing analyses

- Regularization (for example, avoiding estimates on the boundary of parameter space)
- Accounting for uncertainty (especially for decisions)
- Checking model fit
- Using models to combine different sources of information (partial pooling)
- Better dialogue with subject-matter experts (more windows into the model and data)