Statistical Modeling for Clinical Trials

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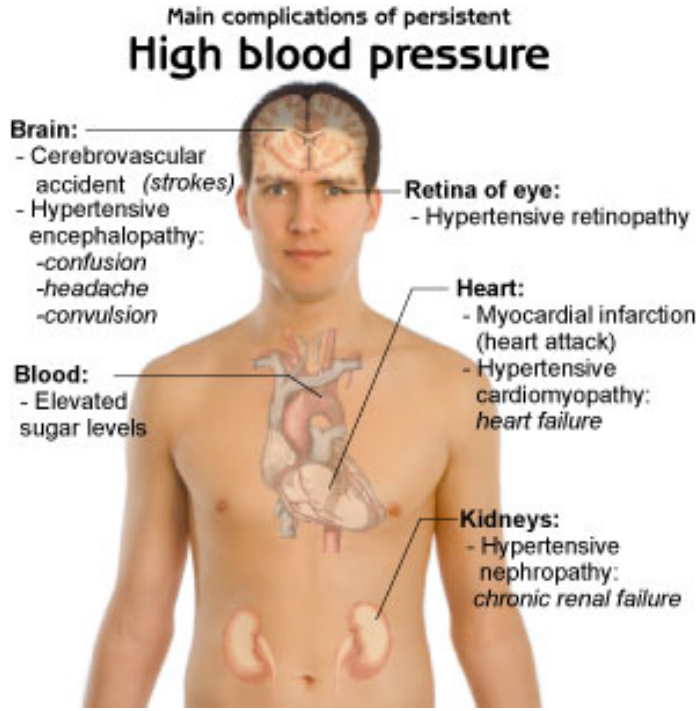
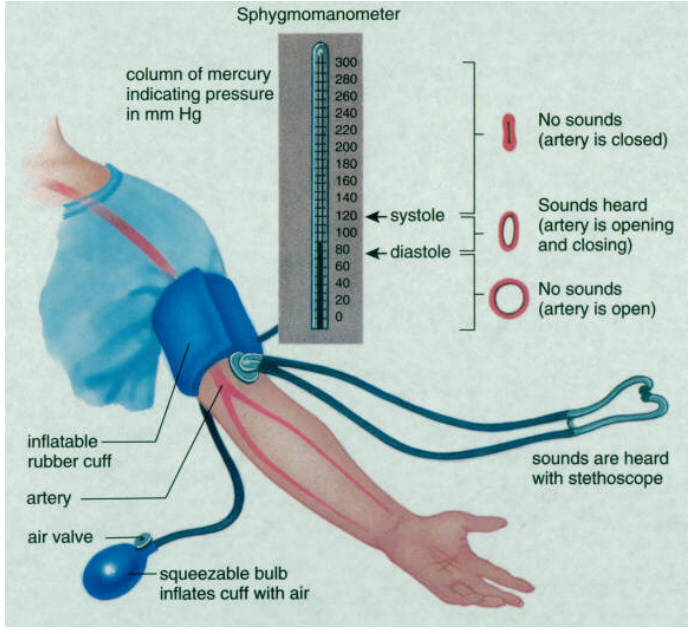
Dangers and Solutions of Hypertension



- Lifestyle interventions - ineffective, lack of consistency
- Medication - effective

Hypertension



For our purposes high blood pressure (BP) is defined:

- having systolic BP above 140 mm Hg
- top measurement

Medications

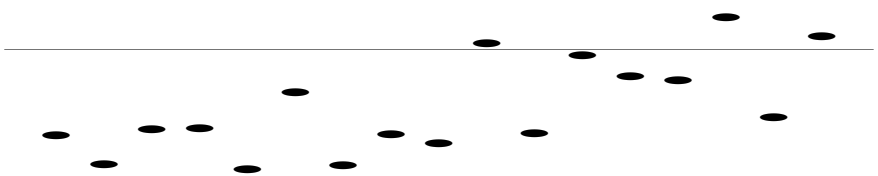
- Lower systolic blood pressure (BP) by about 10 mm Hg
- Sales are approximately $35 billion per year
- When BP is lowered through medication you generally stay on these for life
- Do the drugs have benefits after you stop taking them?

AstraZeneca's TRial Of Preventing HYpertension (TROPHY) examined this question — Do the effects of candesartan continue after treatment has ceased?

TROPHY

Trial Of Preventing HYpertension

- 809 participants with systolic blood pressure (BP) 130 - 139 mm Hg randomised
- Treatment - two years, then two year follow up
- Placebo - 4 years of monitoring
- Measurements every 3 months
- 69% of those diagnosed with hypertension did so by having 3 measurements above 140 mm Hg
- Treatment 53.2%, Placebo 63.0% cumulative diagnosis



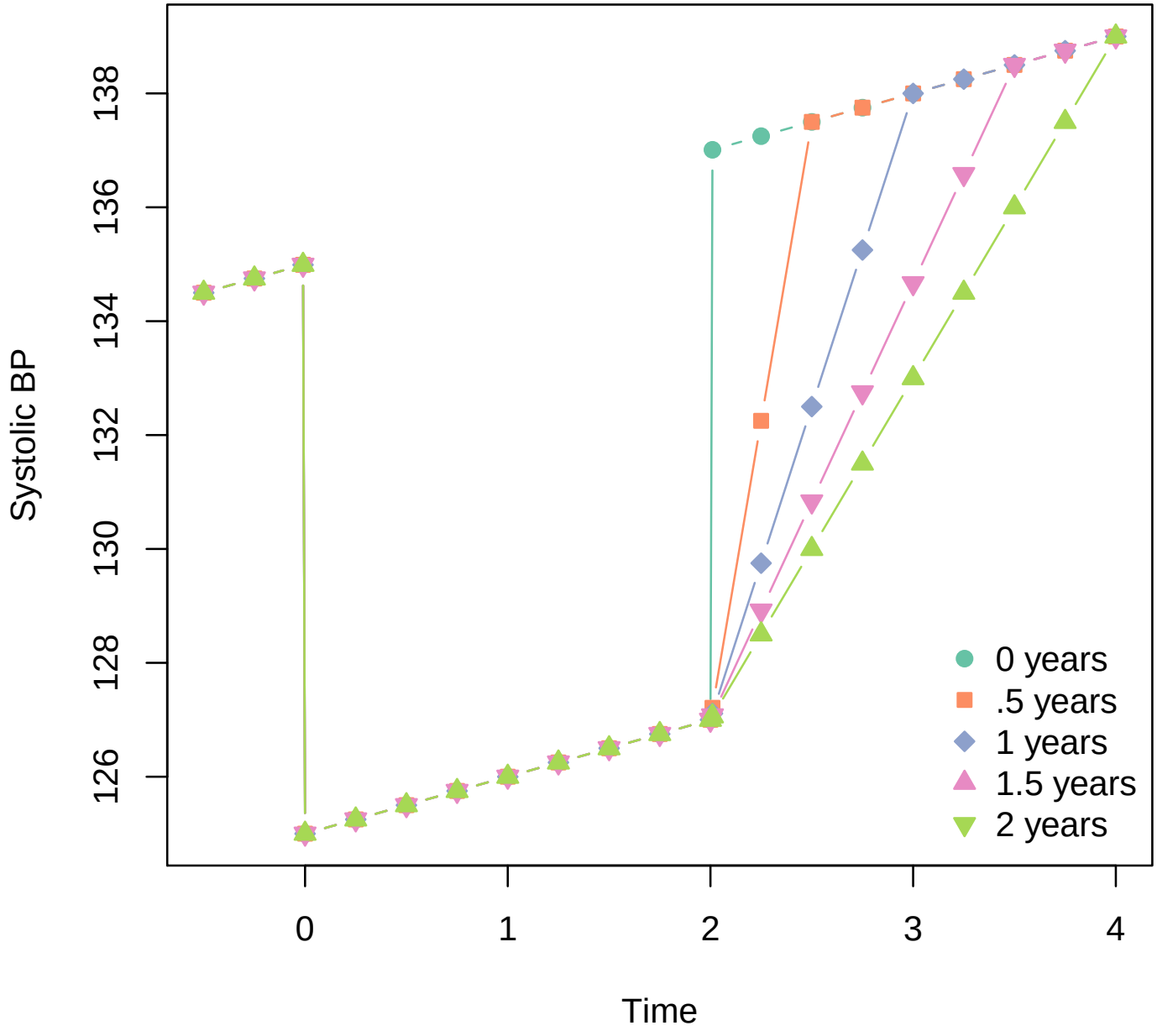
Concluded that "...the effect of active treatment on delaying the onset of hypertension can extend up to 2 years after the discontinuation of treatment. "
High-impact paper with the conclusions:

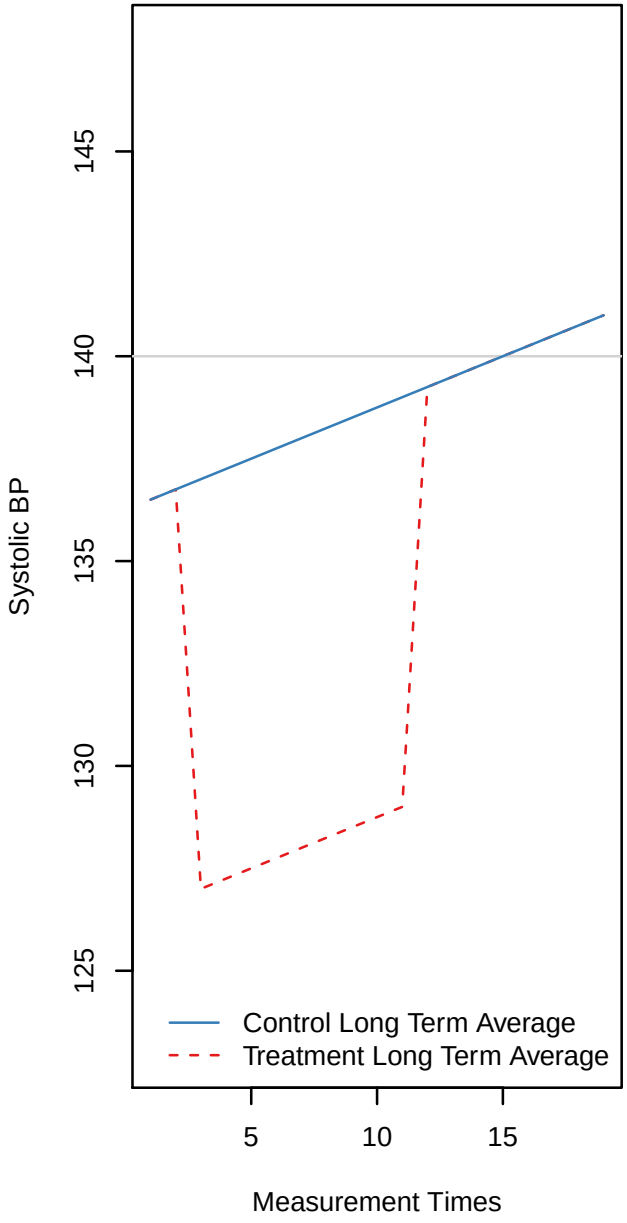
- Control group had 240 participants develop hypertension while the candesartan group had 208 $P < .0007$
- Treatment of prehypertensives is beneficial

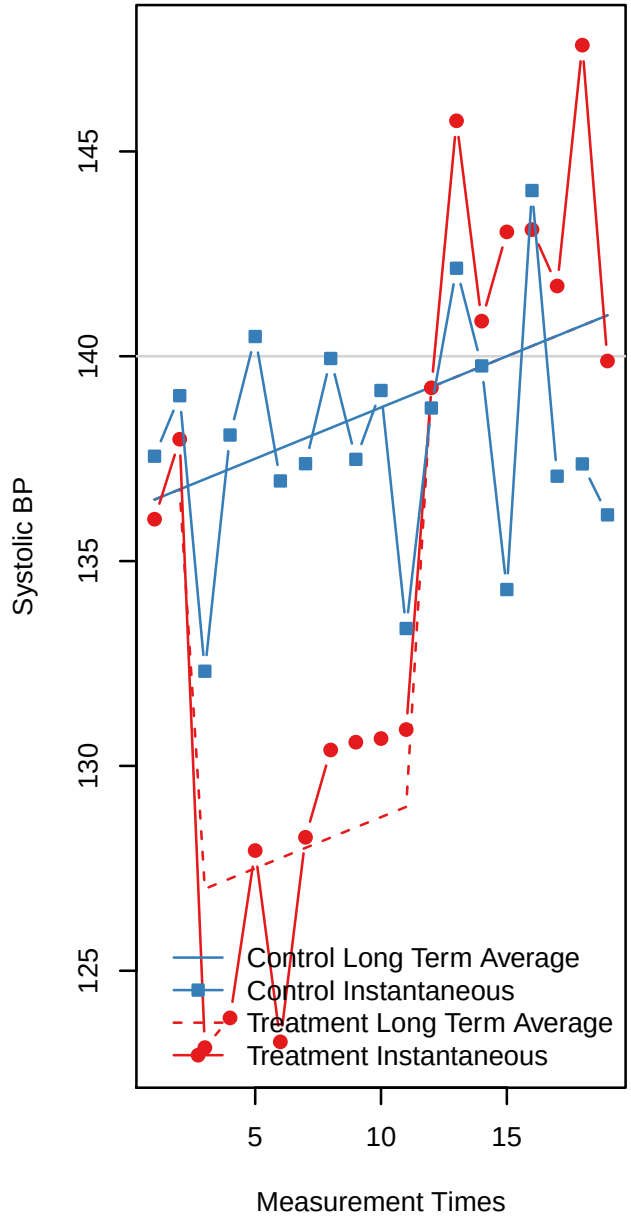
Lifestyle Interventions

Carryover of medication is suprising; duration of effects of short lifestyle interventions is important.

Carryover


Systolic BP
126
128
130
132
134
136
138
0
1
2
3
4
Time
0 years
.5 years
1 years
1.5 years
2 years


Systolic BP
145
140
135
130
125
5
10
15
Measurement Times
Control Long Term Average
Treatment Long Term Average


Systolic BP
145
140
135
130
125
5
10
15
Measurement Times
Control Long Term Average
Control Instantaneous
Treatment Long Term Average
Treatment Instantaneous

Criticisms of TROPHY's analysis

Meltzer (2006)

- "idiosyncratic primary endpoint seriously impairs external applicability"

Persell and Baker (2006)

- Cumulative diagnosis rates would differ even with identical underlying BP

Lumley, Rice and Psaty (2008)

- Simulations conducted to replicate TROPHY outcomes
- Without carryover, similar cumulative incidences of hypertension were found in 80% of studies

Complications

Our modeling must consider the following:

- Noisy measurement
- Exceeding a threshold
- Treatment after diagnosis - measurements no longer used

Approaches for developing methodologies which test a carryover hypothesis:

- Attempt to remedy TROPHY design
  - Parallel design
  - Crossover design
  - A 3 arm study with both parallel, crossover, and control
- Potential ways to do an analysis
  - Linear mixed model

Approaches for developing methodologies which test a carryover hypothesis:

- ~~Attempt to remedy TROPHY design~~
  - ~~Parallel design~~
  - ~~Crossover design~~
  - ~~A 3 arm study with both parallel, crossover, and control~~
- Potential ways to do an analysis
  - Linear mixed model

Missing At Random - linear mixed model

Justification:

- Longitudinal data (correlated)
- Diagnosis results in treatment in a way that we understand
- Our data is *missing at random*: probability of dropout depends ONLY on past observed values
- We can find consistent estimates of carryover parameters if we model correlation correctly

Linear Mixed Model - Completely Random

We model BP using:

$$Y_i = a_i + b_i t_i + c_i X_{it} + d_i Z_{it} + \epsilon_{it}$$

- Y_i is the blood pressure (BP) measurement
- a_i estimates the intercept, b_i estimates the trend
- c_i estimates the treatment effects
- d_i estimates the carryover
- X_{it} is 1 if person i is on treatment at time t and 0 otherwise
- Z_{it} starts at 1 when someone stops treatment and decreases linearly to 0 over the carryover period.

Linear Mixed Model - Random Intercept

We model BP using:

$$Y_i = a_i + \beta t_i + \gamma X_{it} + \delta Z_{it} + \epsilon_{it}$$

- Y_i is the blood pressure (BP) measurement
- a_i estimates the intercept
- β is the average trend
- γ is the average treatment effects
- δ is the average carryover
- X_{it} is 1 if person i is on treatment at time t and 0 otherwise
- Z_{it} starts at 1 when someone stops treatment and decreases linearly to 0 over the carryover period.

Correlation Structure

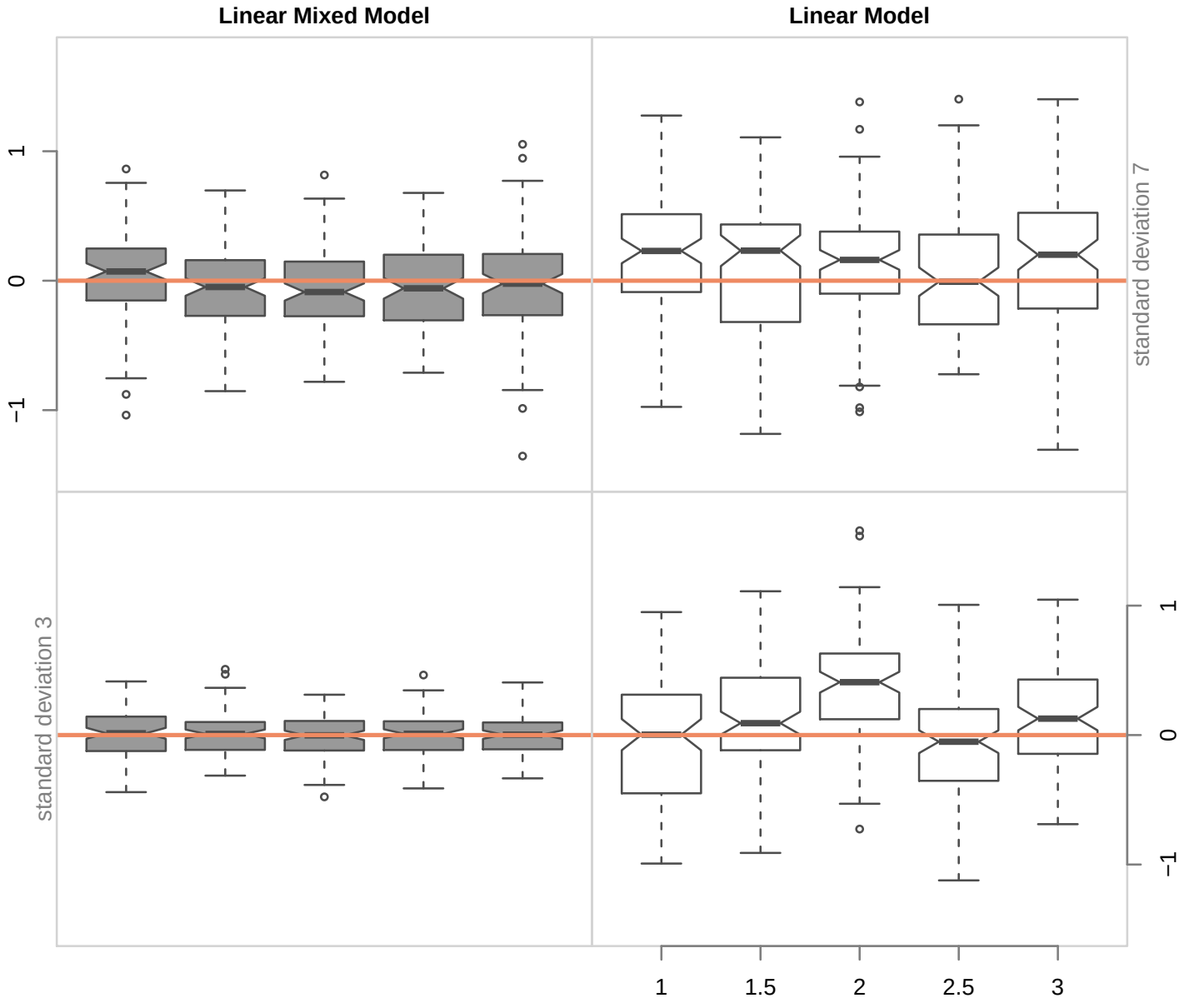
- analysis of real data is necessary
- scheduled to arrive in July
- actually arrived on 20 Nov!!!!
- we fit a model with all random effects to simulated data

We use a linear mixed model for continuous BP with all random effects to find the MLE of:

$$\begin{pmatrix} a_i \\ b_i \\ c_i \\ d_i \end{pmatrix} \sim N \left[\begin{pmatrix} \alpha \\ \beta \\ \gamma \\ \delta \end{pmatrix}, \mathbf{\Sigma} \right]$$

where $\mathbf{\Sigma}$ is the covariance matrix.

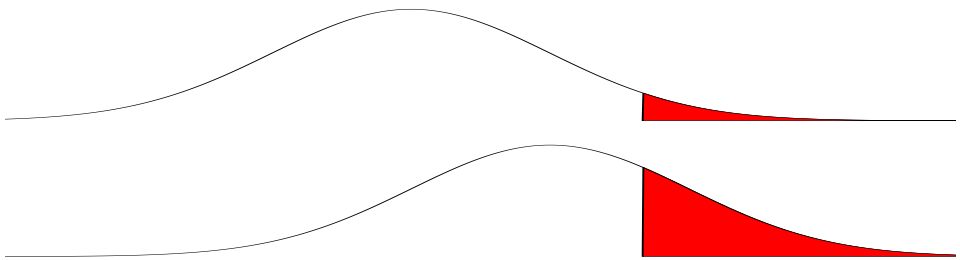
Bias in Estimates



Future Work

From here we will find:

- Modeling systolic and diastolic blood pressure jointly
- Relative risk



For further reading

S. D. Persell and D. W. Baker.
Studying interventions to prevent the progression from prehypertension to hypertension: Does TROPHY win the prize?
American Journal of Hypertension, 19(11):1095–7, 2006.

J. I. Meltzer.
A specialist in clinical hypertension critiques the TROPHY trial.
American Journal of Hypertension, 19(11), 2006.

More reading

T. Lumley, K. M. Rice, and B. M. Psaty.
Carryover effects after cessation of drug treatment: Trophies or dreams?
American Journal of Hypertension, 21:14–16, 2008.

S. Julius, S. D. Nesbitt, B. M. Egan, M. A. Weber, E. L. Michelson, N. Kaciroti, H. R. Black, R. H. Grimm, F. H. Messerli, and S. Oparil.
Feasibility of treating prehypertension with an angiotensin-receptor blocker.
New England Journal of Medicine, 354(16):1685–97, 2006.