Global Sensitivity Analysis for Repeated Measures Studies with Informative Drop-out: A Semi-Parametric Approach

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Sensitivity Analysis

- Consider follow-up randomized study designs that prescribe measurements of an outcome of interest to be taken on each study participant at fixed time-points.
- Focus on monotone missing data pattern
- Interest is in a comparison of treatment arm means at the last scheduled visit.

Notation

- K scheduled post-baseline assessments.
- There are then $(K+1)$ missing data patterns characterized by the last visit an individual was seen, i.e., $0, \ldots, K$.
- The $(K+1)$st missing data pattern represents individuals who complete the study.
- Let Y_k be the outcome scheduled to be measured at visit k, with Y_0 denoting the baseline measure (which is always observed).
- Let $Y_k^- = (Y_0, \ldots, Y_k)$ and $Y_k^+ = (Y_{k+1}, \ldots, Y_K)$.

Notation

- Let R_k be the indicator of being on study at visit k.
- $R_0 = 1$; $R_k = 1$ implies $R_{k-1} = 1$.
- Let C be the last visit that the patient is on-study: $C = \max\{k : R_k = 1\}$.
- The observed data for an individual is $O = (C, Y_C^-)$.
- We consider each treatment arm separately, and want to estimate $\mu = E[Y_K]$.

Asssumptions

- Inference about the treatment arm means requires two types of assumptions:
  - (i) *unverifiable* assumptions about the distribution of outcomes among those with missing data and
  - (ii) testable assumptions that serve to increase the efficiency of estimation.

Sensitivity Analysis

- Type (i) assumptions are necessary to identify the treatment-specific means.
- Since type (i) assumptions are not testable, it is essential to conduct a sensitivity analysis, whereby the data analysis is repeated under different type (i) assumptions.
- There are an infinite number of ways of positing type (i) assumptions.
- Ultimately, these assumptions prescribe how missing outcomes should be "imputed."

Class of Type (i) Assumptions

For $k = 0, ..., K-1$,

$$\text{logit } P[C = k | C \geq k, Y_K^-] = h_k(Y_k^-) + \alpha r(Y_{k+1})$$

where

$$\begin{aligned} h_k(Y_k^-) &= \text{logit } P[C = k | C \geq k, Y_k^-] - \\ &\quad \log\{E[\exp(\alpha r(Y_{k+1}))| C \geq k, Y_k^-]\} \end{aligned}$$

$r(Y_{k+1})$ is a specified increasing function of Y_{k+1} and α is a sensitivity analysis parameter.

Class of Type (i) Assumptions

- $\alpha = 0$ is missing at random
- α quantifies the influence of Y_{k+1} on the decision to drop-out between k and $k+1$.

Identification Formula

$$\mu(P) = E\left[\frac{I(C = K)Y_K}{\prod_{k=0}^{K-1}(1 + \exp(h_k(Y_k^-) + \alpha r(Y_{k+1})))^{-1}}\right]$$

where P is the distribution of the observed data, characterized by

$$P[C = k | C \geq k, Y_k^-]$$

and

$$f(Y_{k+1} | C \geq k, Y_k^-)$$

- These conditional distributions can't be estimated at fast enough rates so a plug-in estimator of μ will converge at $\sqrt{n}$ rates.

Type (ii) Assumptions

First-order Markov assumptions:

$$P[C = k | C \geq k, Y_k^-] = P[C = k | C \geq k, Y_k]$$

and

$$f(Y_{k+1} | C \geq k, Y_k^-) = f(Y_{k+1} | C \geq k, Y_k)$$

- Non-parametric smoothing with respect to the covariate Y_k using a Gaussian kernel.
- Estimate optimal smoothing parameters using a weighted squared-error loss function and 10-fold cross validation.

Estimation of μ

- Plug-in estimator can still suffer from non-standard asymptotics.
- To correct this problem, we use a one-step estimator:

$$\text{plug-in} + \text{average of estimated influence function}$$

(Newey, Hsieh, Robins, 1998)

Uncertainty

- In finite-samples, influence function based confidence intervals, non-parametric bootstrap and parametric bootstrap don't work well.
- Double bootstrap works much better.

Case Study: Chronic Schizophrenia

- Major breakthroughs have been made in the treatment of patients with psychotic symptoms.
- However, side effects associated with typical and atypical neuroleptics have limited their usefulness.
- RIS-INT-3 (Marder and Meibach, 1994, Chouinard *et al.*, 1993) was a multi-center study designed to assess the effectiveness and adverse experiences of four fixed doses of risperidone compared to haliperidol and placebo in the treatment of chronic schizophrenia.

RIS-INT-3

- At selection, patients were required to have a PANSS (Positive and Negative Syndrome Scale) score between 60 and 120.
- Prior to randomization, there was a single-blind, one-week washout phase during which all anti-psychotic medications were to be discontinued.
- If acute psychotic symptoms occurred, patients were randomized to a double-blind treatment phase, scheduled to last 8 weeks.
- Patients were randomized to one of 6 treatment groups: risperidone 2, 6, 10 or 16 mg, haliperidol 20 mg, or placebo.
- Dose titration occurred during the first week of the double-blind phase.

RSIP-INT-3

- Patients scheduled for 5 post-baseline assessements at weeks 1,2,4,6, and 8 of the double-blind phase.
- Primary efficiacy variable: PANSS score
- 521 patients randomized to receive placebo ($n = 88$), haliperidol 20 mg ($n = 87$), risperidone 2mg ($n = 87$), risperidone 6mg ($n = 86$), risperidone 10 mg ($n = 86$), or risperidone 16 mg ($n = 87$).

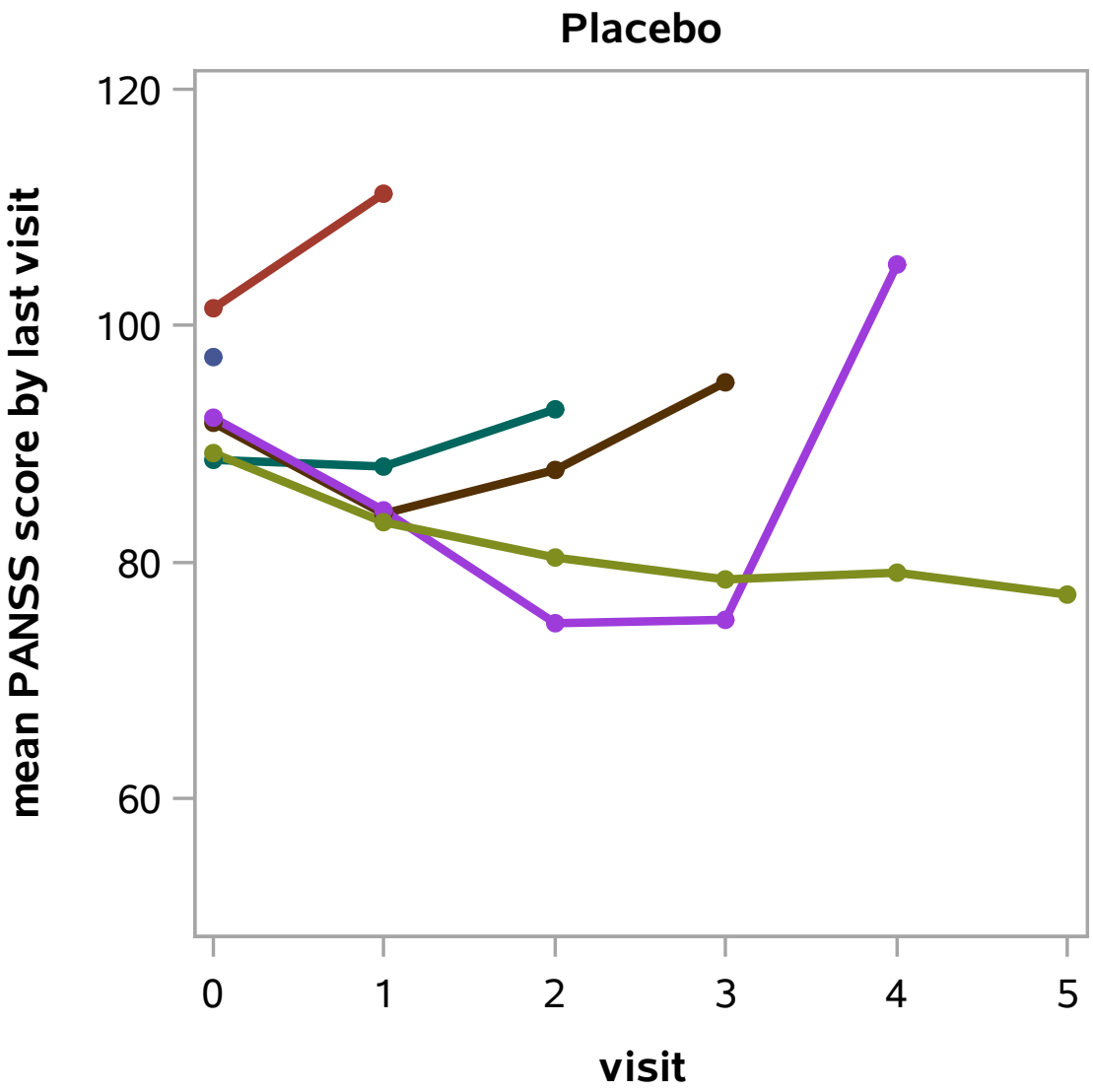
Premature Withdrawal

- Only 49% of patients completed the 8 week treatment period.
- The most common reason for discontinuation was "insufficient response."
- Other main reasons included: adverse events, uncooperativeness, and withdrawal of consent.

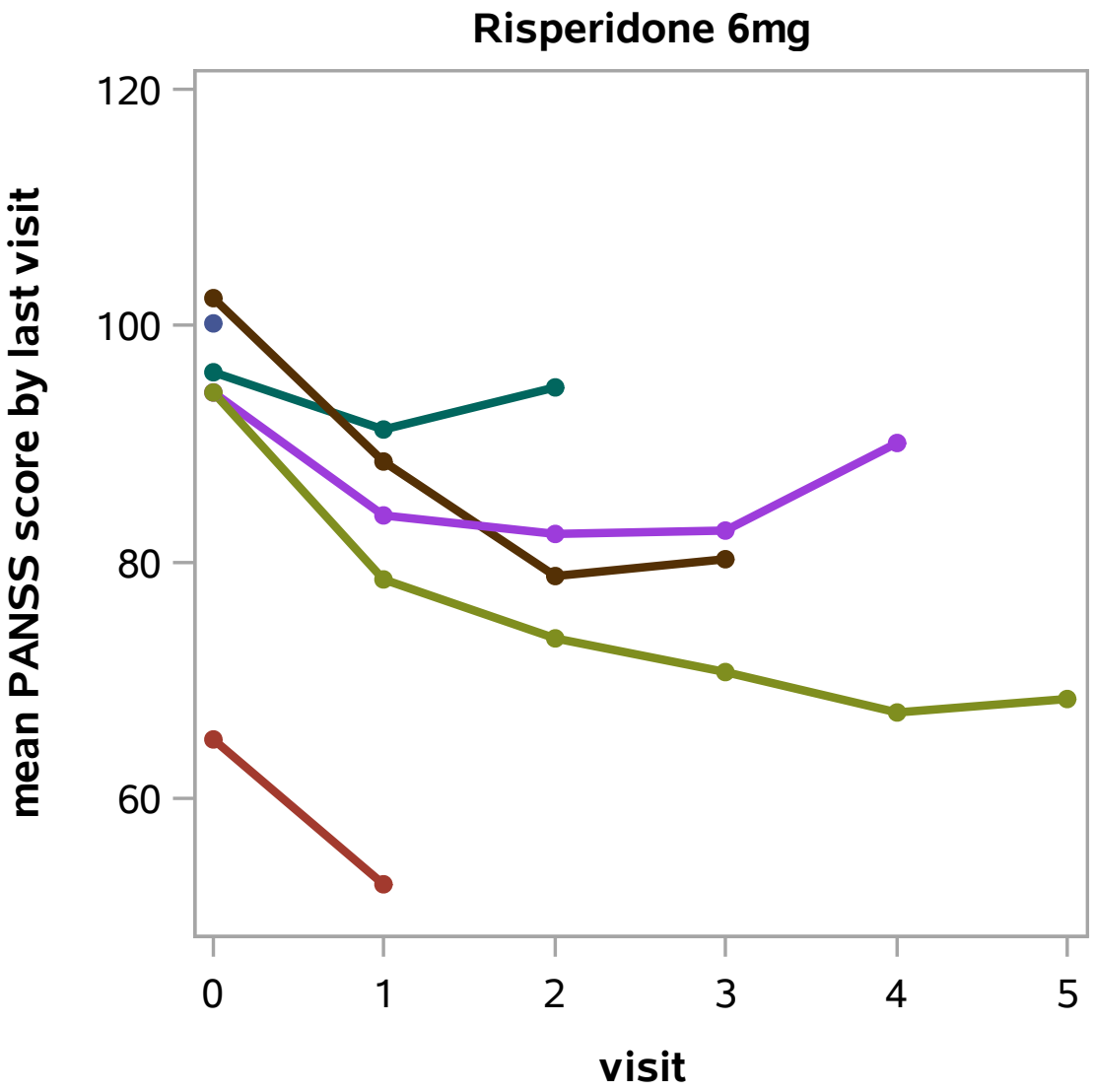
Premature Withdrawal

	Placebo ($n = 88$)		Haliperidol ($n = 87$)		Risp 2mg ($n = 87$)		Risp 6mg ($n = 86$)		Risp 10mg ($n = 86$)		Risp 16 mg ($n = 87$)	
Completed	27	31%	36	41%	36	41%	53	62%	48	56%	54	62%
Withdrawn	61	69%	51	59%	51	59%	33	38%	38	44%	33	38%
Lack of Efficacy	51	58%	36	41%	41	47%	12	14%	25	29%	18	21%
Other	10	11%	15	17%	10	11%	21	24%	13	15%	15	17%

Observed Data



Observed Data



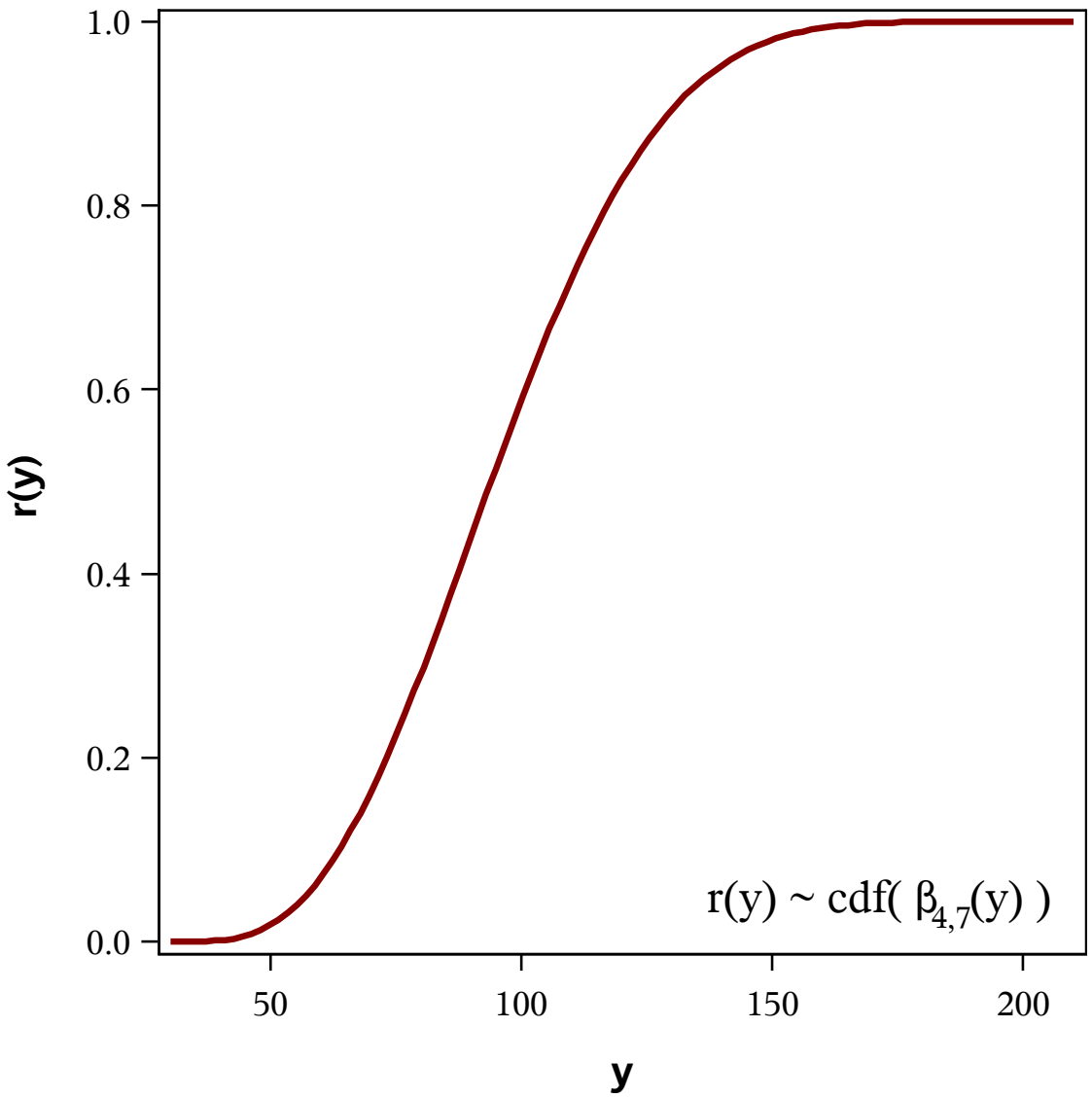
Central Question

What is the difference in the mean PANSS scores at week 8 between risperidone at a specified dose level vs. placebo in the counterfactual world in which all patients were followed to that week?

Notation

- $K = 5$ scheduled post-baseline assessments.
- Y_k is PANSS score
- Higher PANSS indicates greater mental illness.

Bias Function



Sensitivity Analysis

Consider two patients who are on study through visit k and have the same history of measured factors through that visit. Suppose that the first and second patients have PANSS score at visit $k+1$ of y_{k+1} and y^*_{k+1}, respectively $(y_{k+1} < y^*_{k+1})$.

The logarithm of the ratio of the odds of last being seen at visit k as opposed to remaining on study for the second versus the first patient is equal to $\alpha\{r(y^*_{k+1}) - r(y_{k+1})\}$.

Sensitivity Analysis

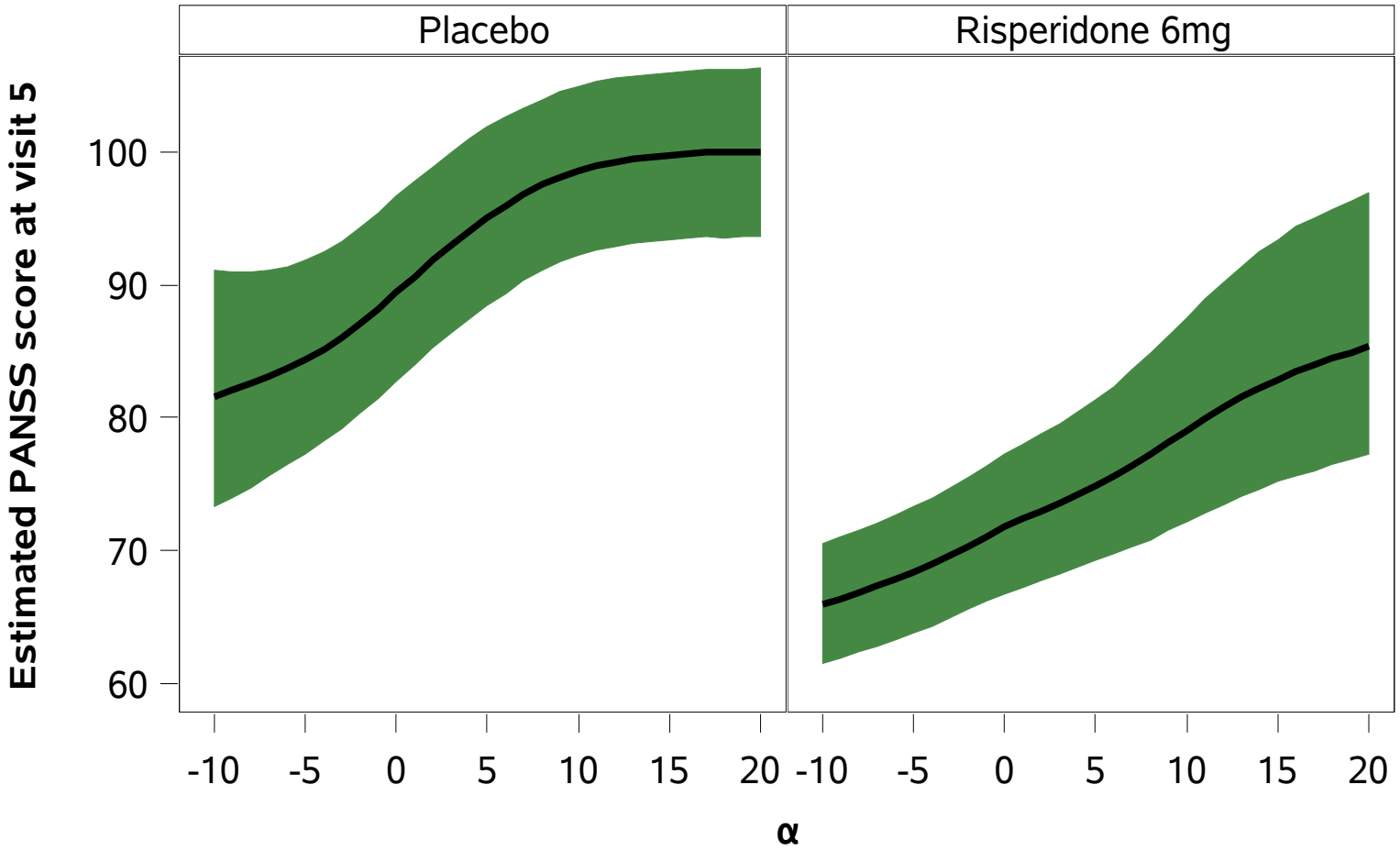
y^*_{k+1}	y_{k+1}	Log Odds Ratio
50	30	$\alpha 0.02$
60	40	$\alpha 0.07$
80	60	$\alpha 0.22$
100	80	$\alpha 0.30$
120	100	$\alpha 0.24$
140	120	$\alpha 0.12$
160	140	$\alpha 0.04$
180	160	$\alpha 0.01$
200	180	$\alpha 0.00$

Sensitivity Analysis

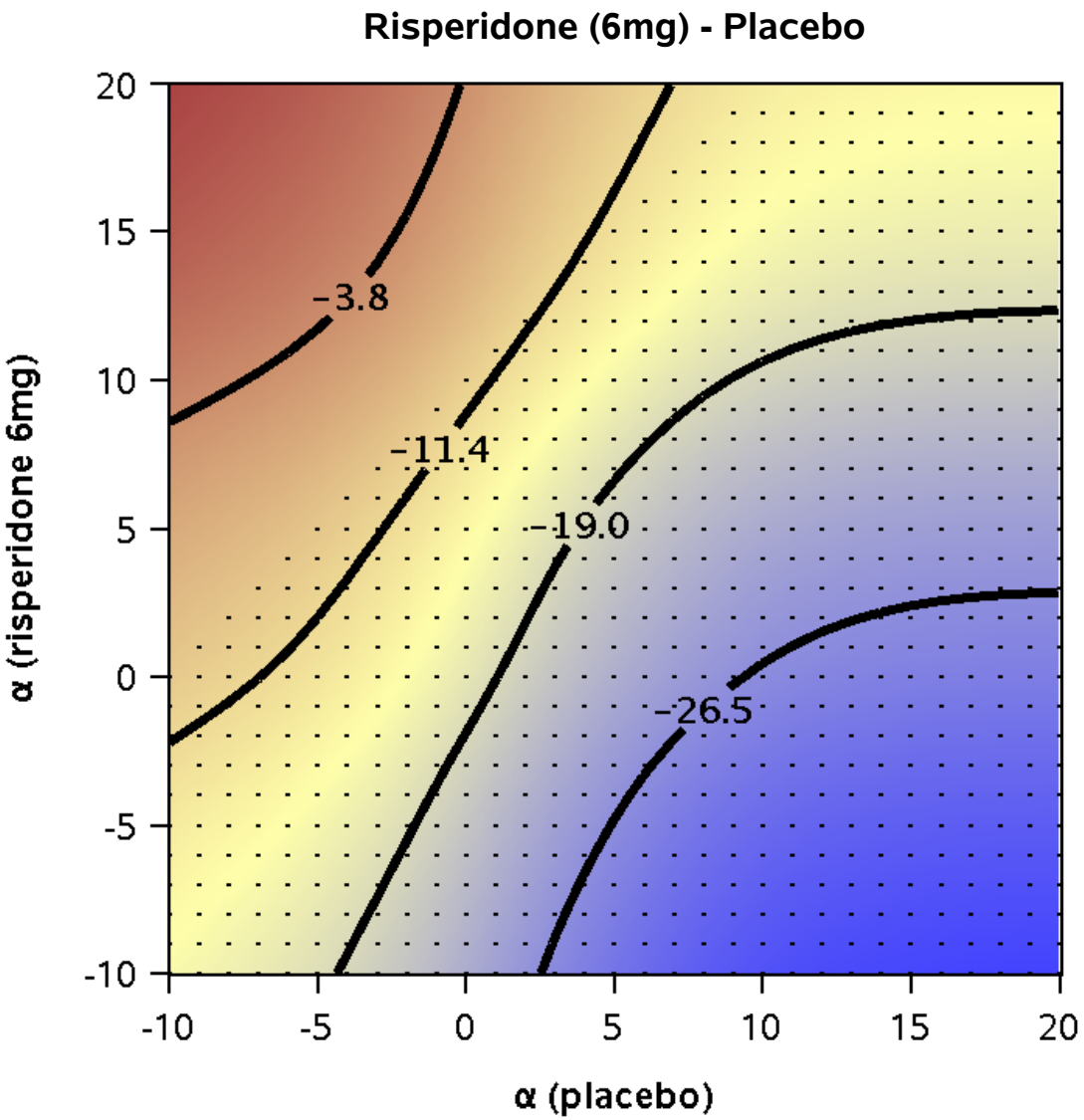
We assumed that $-10.0 \leq \alpha \leq 20.0$

When $\alpha = 4$, a patient with a PANSS score at visit $k+1$ of 100 (120;80) vs. a patient with a PANSS score at visit $k+1$ of 80 (100;60), has 3.3 (2.6;2.4) times the odds of last being seen at visit k vs. remaining on study.

Results


Placebo
Risperidone 6mg
Estimated PANSS score at visit 5
100
90
80
70
60
-10
-5
0
5
10
15
20
α

Results


Risperidone (6mg) - Placebo
α (risperidone 6mg)
α (placebo)
20
15
10
5
0
-5
-10
-10
-5
0
5
10
15
20
−3.8
−11.4
−19.0
−26.5

Results

- Inference is robust to deviations from MAR.
- 6mg risperidone is superior to placebo in reducing symptoms.

Software

www.missingdatamatters.org