Structural Nested Mean Models for Assessing Time-Varying Effect Moderation

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1 Warm-up: Why do we condition on pre-treatment variables S?

We want the effect of A on Y. Why condition on (adjust for) pre-treatment variables S?

1. **Confounding**: S is correlated with both A and Y. In this case, S is known as a "confounder" of the effect of A on Y.
2. **Precision**: S may be a pre-treatment measure of Y, or any other variable highly correlated with Y.
3. **Missing Data**: The outcome Y is missing for some units, S and A predict missingness, and S is associated with Y.
4. **Effect Heterogeneity**: S may moderate, temper, or specify the effect of A on Y. In this case, S is known as a "moderator" of the effect of A on Y. Formalized in next slide.

Effect Moderation in One Time Point

Definition: Fix $a \neq 0$. Let

$$\mu(s, a) \equiv E[Y(a) - Y(0) \mid S = s].$$

If $\mu(s, a)$ is non-constant in s, then S is said to be a *moderator* of the effect of a on Y.

Example: If the structural model for the conditional mean of $Y(a)$ given S is

$$E[Y(a) \mid S = s] = \beta_0 + \gamma_1 s + \beta_1 a + \beta_2 sa,$$

then $\mu(s, a) = \beta_1 a + \beta_2 sa$. In this example, S is a moderator of the effect of a on Y if $\beta_2 \neq 0$.

2 Time-Varying Effect Moderation

The focus of this paper is time-varying effect moderation.

The data structure in the time-varying setting is $\{S_1, a_1, S_2(a_1), a_2, Y(a_1, a_2)\}$.

Running Example, from the PROSPECT Study:

(a_1, a_2)	Time-varying treatment pattern; a_t is binary (0,1)
$Y(a_1, a_2)$	Depression at the end of the study; continuous
S_1	Suicidal Ideation at baseline visit; continuous
$S_2(a_1)$	Suicidal Ideation at second visit; continuous

Formal Definition of Time-Varying Causal Effects

Recall the data structure $\{S_1, a_1, S_2(a_1), a_2, Y(a_1, a_2)\}$.

Conditional Intermediate Causal Effect at $t = 1$:

$$\begin{aligned}\mu_{\mathbf{1}}(\mathbf{s_1}, \mathbf{a_1}) &\equiv E[Y(a_1, 0) - Y(0, 0) \mid S_1 = s_1] \\ &= a_1 \times H_1\beta_1 && \text{(Linear Parameterization)} \\ &\overset{\text{say}}{=} a_1 \times (\beta_{11} + \beta_{12}s_1) && \text{(Sample Model)}\end{aligned}$$

Conditional Intermediate Causal Effect at $t = 2$:

$$\begin{aligned}\mu_{\mathbf{2}}(\bar{\mathbf{s}}_{\mathbf{2}}, \bar{\mathbf{a}}_{\mathbf{2}}) &\equiv E[Y(a_1, a_2) - Y(a_1, 0) \mid S_1 = s_1, S_2(a_1) = s_2] \\ &= a_2 \times H_2\beta_2 && \text{(Linear Parameterization)} \\ &\overset{\text{say}}{=} a_2 \times (\beta_{21} + \beta_{22}(s_1 + s_2)/2) && \text{(Sample Model)}\end{aligned}$$

3 Robins' Structural Nested Mean Model

Recall the data structure $\{S_1, a_1, S_2(a_1), a_2, Y(a_1, a_2)\}$.

The SNMM for the conditional mean of $Y(a_1, a_2)$ given $\bar{S}_2(a_1)$ is:

$$E\big[Y(a_1, a_2) \mid \bar{S}_2(a_1) = \bar{s}_2\big] = \mu_0 + \epsilon_1(s_1) + \mu_{\mathbf{1}}(\mathbf{s_1}, \mathbf{a_1}) + \epsilon_2(\bar{s}_2, a_1) + \mu_{\mathbf{2}}(\bar{\mathbf{s}}_{\mathbf{2}}, \bar{\mathbf{a}}_{\mathbf{2}}), \qquad \text{where}$$

- $\epsilon_2(\bar{s}_2, a_1) = E[Y(a_1, 0) \mid \bar{S}_2(a_1) = \bar{s}_2] - E[Y(a_1, 0) \mid S_1 = s_1]$,
- $\epsilon_1(s_1) = E[Y(0, 0) \mid S_1 = s_1] - E[Y(0, 0)]$,
- $\mu_2(\bar{s}_2, a_2, 0) = 0$ and $\mu_1(s_1, 0) = 0$,
- $E_{S_2|S_1}[\epsilon_2(\bar{s}_2, a_1) \mid S_1 = s_1] = 0$, and $E_{S_1}[\epsilon_1(s_1)] = 0$.

4 Estimation in Time-Varying Setting

Recall that parametric models for our causal estimands μ_1 and μ_2 are based on the set of parameters $\beta = (\beta_1', \beta_2')'$.

The dissertation considers two estimators for β:

1. Proposed 2-Stage Regression Estimator
2. Robins' Semi-parametric G-Estimator

   *** We can use 2-Stage Estimator for starting guesses ***

Both estimators rely on Robins' **Consistency** and **Sequential Ignorability** assumptions. The 2-Stage Estimator relies more on modelling assumptions. We discuss these in turn, but first ...

What's wrong with the Traditional Estimator?

An **Example** of The **Traditional Estimator**: Apply OLS with

$$E(Y \mid \bar{S}_2 = \bar{s}_2, \bar{A}_2 = \bar{a}_2) = \beta_0^* + \eta_1 s_1 + a_1 \times (\beta_1^* + \beta_2^* s_1) + \eta_2 s_2 + a_2 \times (\beta_3^* + \beta_4^*(s_1 + s_2)/2)$$

- Possibly incorrectly specified nuisance functions.

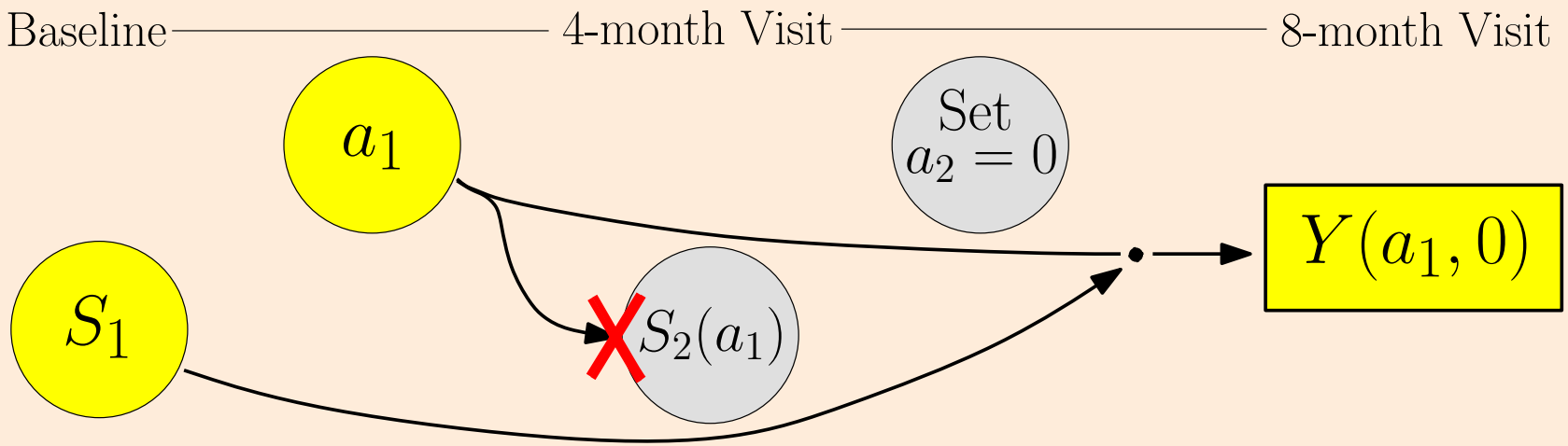
- Two problems arise when using the traditional regression estimator.

- These problems occur even in the absence of time-varying confounders (that is, even under Sequential Ignorability).

First problem with the Traditional Estimator

Recall the data structure $\{S_1, a_1, S_2(a_1), a_2, Y(a_1, a_2)\}$.

Wrong Effect

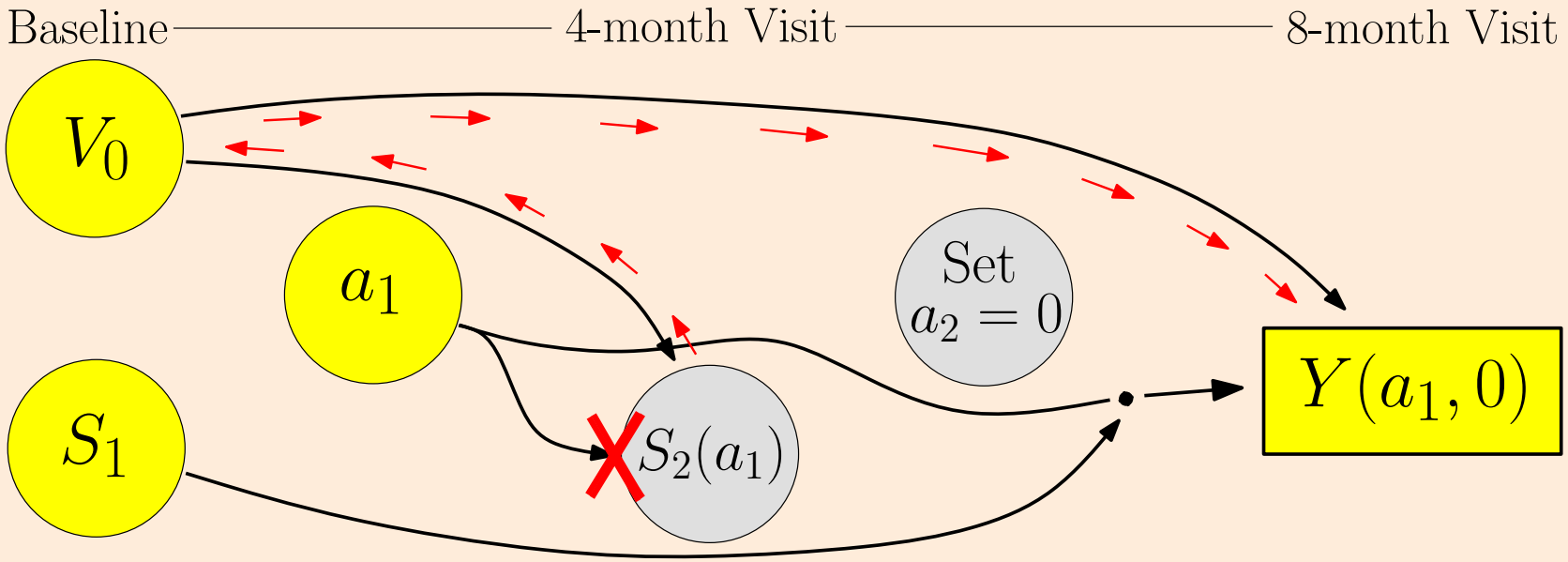


What about the effect transmitted through $S_2(a_1)$?

Second problem with the Traditional Estimator

Recall the data structure $\{S_1, a_1, S_2(a_1), a_2, Y(a_1, a_2)\}$.

Spurious Effect



Berkson's paradox; Judea Pearl's backdoor criterion

Parameterizing the Nuisance Functions

So we must parameterize the nuisance functions correctly.

Recall the constraints on the nuisance functions:

- $\epsilon_2(\bar{s}_2, a_1) = E[Y(a_1, 0) \mid \bar{S}_2(a_1) = \bar{s}_2] - E[Y(a_1, 0) \mid S_1 = s_1]$,
- $\epsilon_1(s_1) = E[Y(0, 0) \mid S_1 = s_1] - E[Y(0, 0)]$,
- $E_{S_2|S_1}[\epsilon_2(\bar{s}_2, a_1) \mid S_1 = s_1] = 0$, and $E_{S_1}[\epsilon_1(s_1)] = 0$.

Example parameterizations for the nuisance functions:

$$\epsilon_1(s_1) \overset{\text{say}}{=} \eta_{1,1}\big(s_1 - E(S_1)\big)$$

$$\epsilon_2(\bar{s}_2, a_1) \overset{\text{say}}{=} \big(\eta_{2,1} + \eta_{2,2} s_1\big)\big(s_2 - E(S_2(a_1) \mid S_1 = s_1)\big)$$

Proposed 2-Stage Regression Estimator

Recall that $E\big[Y(a_1, a_2) \mid \bar{S}_2(a_1) = \bar{s}_2\big] = \mu_2(\bar{s}_2, \bar{a}_2; \beta_2)$
$+ \epsilon_2(\bar{s}_2, a_1; \eta_2, \gamma_2) + \mu_1(s_1, a_1; \beta_1) + \epsilon_1(s_1; \eta_1, \gamma_1) + \mu_0.$

1. We have models for the μ's: $A_1 H_1 \beta_1$ and $A_2 H_2 \beta_2$; Set aside
2. Model $m_1(\gamma_1) = E(S_1)$, estimate γ_1 with GLM; model $m_2(s_1, a_1; \gamma_2) = E(S_2(a_1) \mid S_1 = s_1)$, estimate γ_2 with GLM
3. Construct residuals $\hat{\delta}_1 = s_1 - \hat{m}_1(\hat{\gamma}_1)$ and $\hat{\delta}_2 = s_2 - \hat{m}_2(s_1, a_1; \hat{\gamma}_2)$
4. Construct models for ϵ's: $G_1 \hat{\delta}_1 \eta_1 = G_1^* \eta_1$ and $G_2 \hat{\delta}_2 \eta_2 = G_2^* \eta_2$
5. Obtain $\hat{\beta}$ and $\hat{\eta}$ using OLS of $Y \sim [1, G_1^*, A_1 H_1, G_2^*, A_2 H_2]$

Robins' Semi-parametric G-Estimator

Robins' G-Estimator is the solution to these estimating equations:

$$0 = \mathbb{P}_n \left\{ \Big(Y - A_2 H_2 \beta_2 - b_2(\bar{S}_2, A_1)\Big) \times \Big(A_2 - p_2(\bar{S}_2, A_1)\Big) \times \begin{pmatrix} 0 \\ H_2' \end{pmatrix}' \right.$$

$$\left. + \Big(Y - A_2 H_2 \beta_2 - A_1 H_1 \beta_1 - b_1(S_1)\Big) \times \Big(A_1 - p_1(S_1)\Big) \times \begin{pmatrix} H_1' \\ \Delta'(H_1) \end{pmatrix}' \right\}$$

$$\Delta(H_1) = E\left[H_2 A_2 \middle| S_1, A_1 = 1\right] - E\left[H_2 A_2 \middle| S_1, A_1 = 0\right]$$

$$b_2(\bar{S}_2, A_1) = E\left[Y - A_2 H_2 \beta_2 \mid \bar{S}_2, A_1\right]$$

$$p_2(\bar{S}_2, A_1) = Pr\left[A_2 = 1 \mid \bar{S}_2, A_1\right]$$

$$b_1(S_1) = E\left[Y - A_2 H_2 \beta_2 - A_1 H_1 \beta_1 \mid S_1\right]$$

$$p_1(S_1) = Pr\left[A_1 = 1 \mid S_2\right]$$

5 Bias-Variance Trade-off

This discussion assumes true models for the causal effects, the μ_ts:

Robins' G-Estimator is unbiased if either p_t or b_t are correctly specified. So-called *double-robustness* property.

Robins' G-Estimator is semi-parametric efficient if p_t, b_t, and Δ are all correctly specified.

2-Stage Regression Estimator is unbiased only if the nuisance functions are correctly specified.

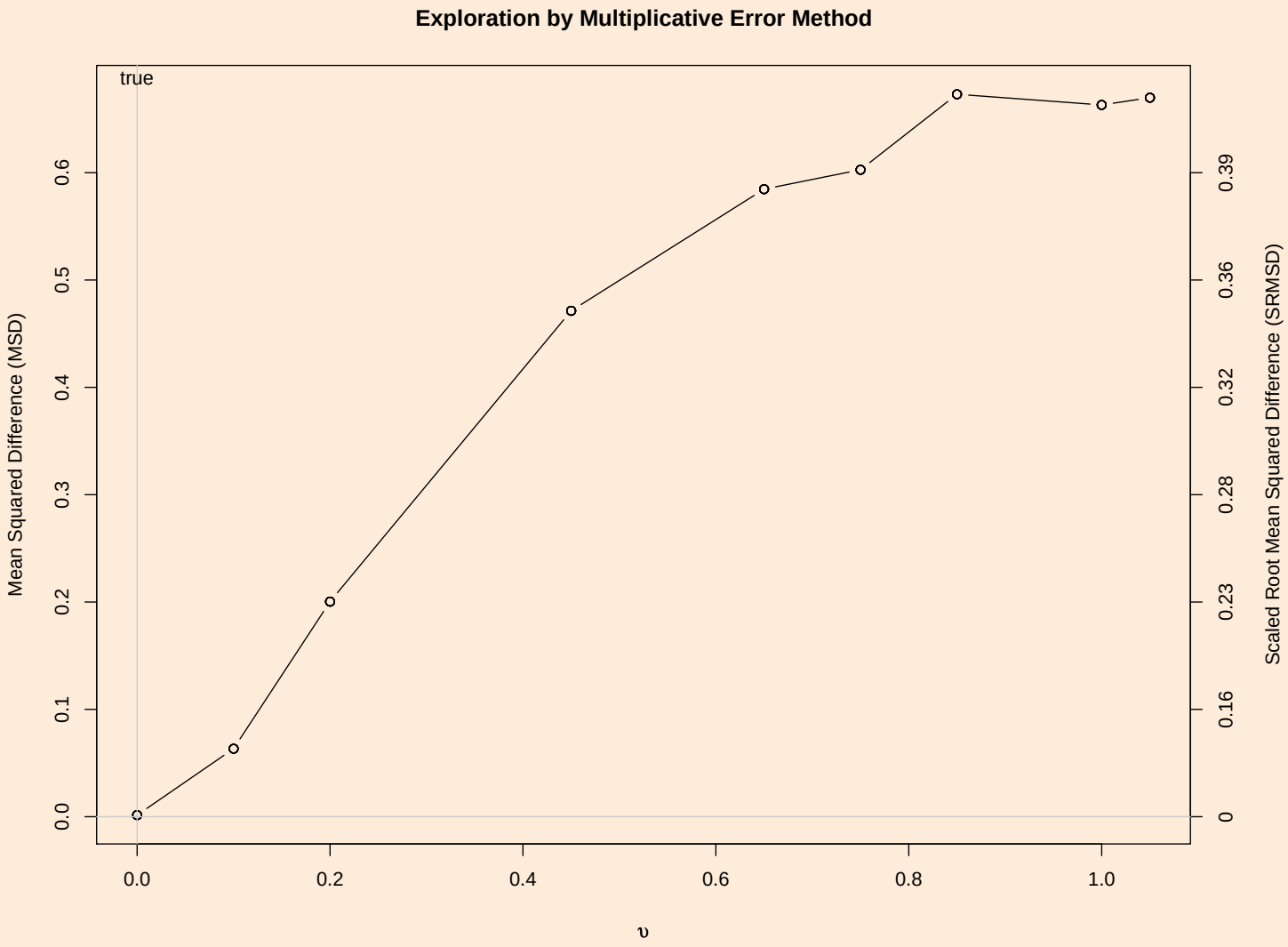
2-Stage Regression Estimator with correctly specified nuisance **is more efficient than** G-Estimator

But what happens as we mis-specify the nuisance functions?

A Simulation Study of the Bias-Variance Trade-off

1. Generate $Y \mid (\bar{S}_3, \bar{A}_3)$ SNMM; use $n = 600$
2. Move away from true model fit in a smooth and principled way
3. Fit 2-Stage Estimator and Robins' G-Estimator
4. Repeat $N = 1000$ times
5. Compare bias and variance of the 2-Stage Estimator versus the G-Estimator as you move away from true fit

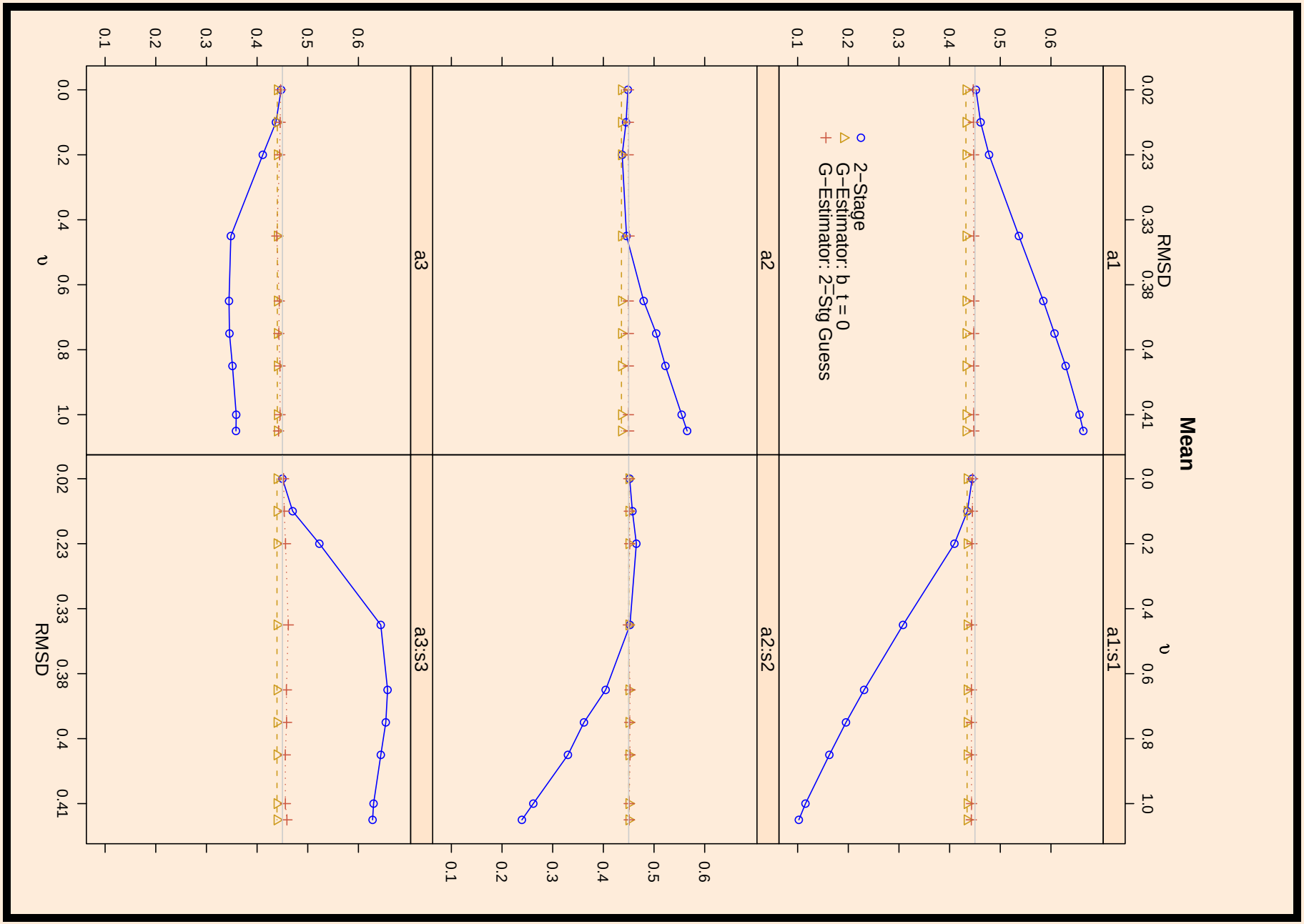
Mis-specifying ϵ_t's using $S^* = S \times N(1, \mathbf{sd} = \nu)$

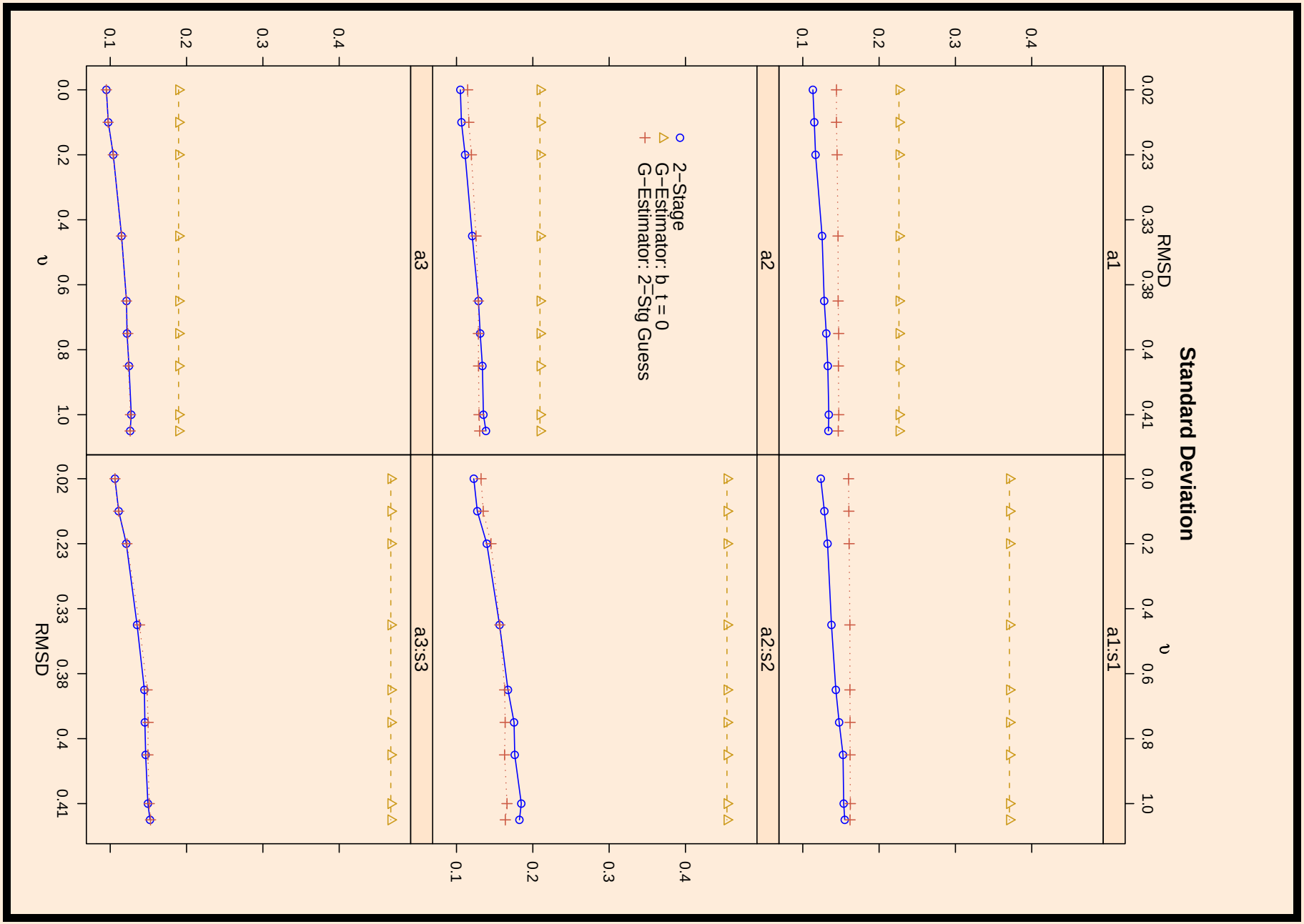


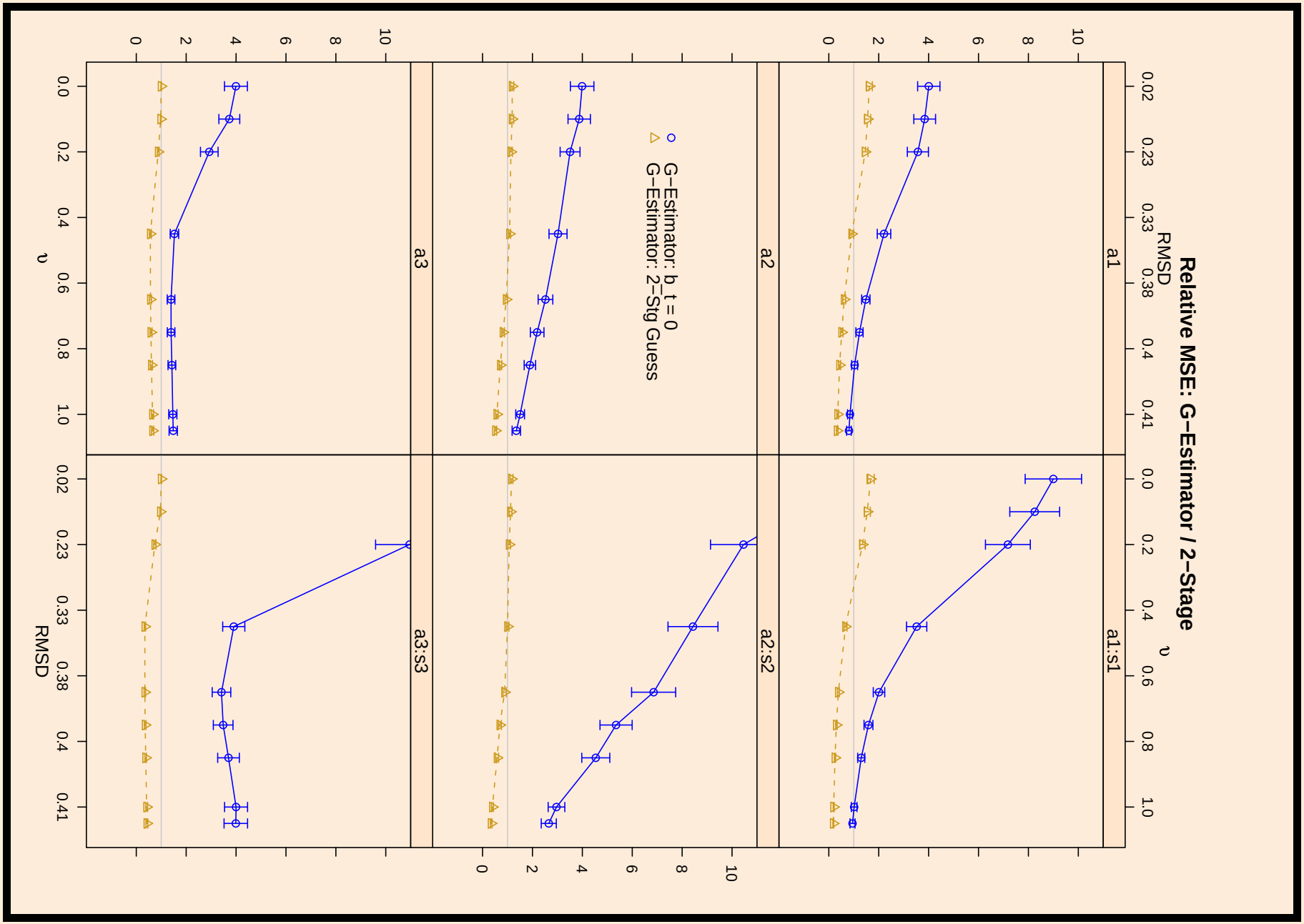
Results

Note two different fits for Robins' G-Estimator:

1. One using "bad" starting guesses (i.e., setting $b_t = 0$)
2. The other using the results of the 2-Stage Estimator as starting guesses


Mean
a1
a1:s1
a2
a2:s2
a3
a3:s3
RMSD
υ
2−Stage
G−Estimator: b_t = 0
G−Estimator: 2−Stg Guess


Standard Deviation
a1
a1:s1
a2
a2:s2
a3
a3:s3
RMSD
υ
2−Stage
G−Estimator: b_t = 0
G−Estimator: 2−Stg Guess


Relative MSE: G−Estimator / 2−Stage
a1
a1:s1
a2
a2:s2
a3
a3:s3
RMSD
υ
G−Estimator: b_t = 0
G−Estimator: 2−Stg Guess

6 Conclusions

1. The bias-variance trade-off is real and important.
2. The G-Estimator relies on good starting guesses.
3. With bad b_t guesses, the G-Estimator never dominates in terms of MSE.
4. With b_t guesses from 2-Stage Estimator, the G-Estimator starts to dominate when amount of mis-specifiction is between small and medium.
5. Standard errors are difficult for both estimators.
6. The 2-Stage Estimator is easy to carry out, intuitive, and can stand alone as its own estimator.

Thank you!
More Questions?