Information anchored sensitivity analysis via multiple imputation

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Outline

- Trial primary analysis and missing data: asthma trial
- Reference based sensitivity analysis via Multiple Imputation
- Principles for variance estimation:
    1. Lower bound
    2. Information anchoring principle
- Theorem: Rubin's MI variance estimator gives information anchored sensitivity analysis

Outline

- Information anchored sensitivity analysis using the `δ-method': peer review trial
- Incorporating a prior distribution on δ
- Analysis of the peer review trial
- Conclusions

Example – asthma trial

- Placebo vs. Budesonide for patients with chronic asthma
- Forced Expiratory Volume in 1 second (FEV_1) recorded at baseline, 2, 4, 8 and 12 weeks
- Primary outcome: mean treatment group difference in FEV_1 at 12 weeks
- Only 37/90 Placebo and 71/90 Budesonide completed

Busse et al. (1998)

Trial primary analysis and missing data

- Any analysis must make an *untestable* assumption about the unobserved data
- Wrong assumption → biased treatment estimate
- Primary analysis – Missing-at-Random (MAR)
- A set of analyses where the missing data is handled in different ways as compared to the primary analysis should be undertaken

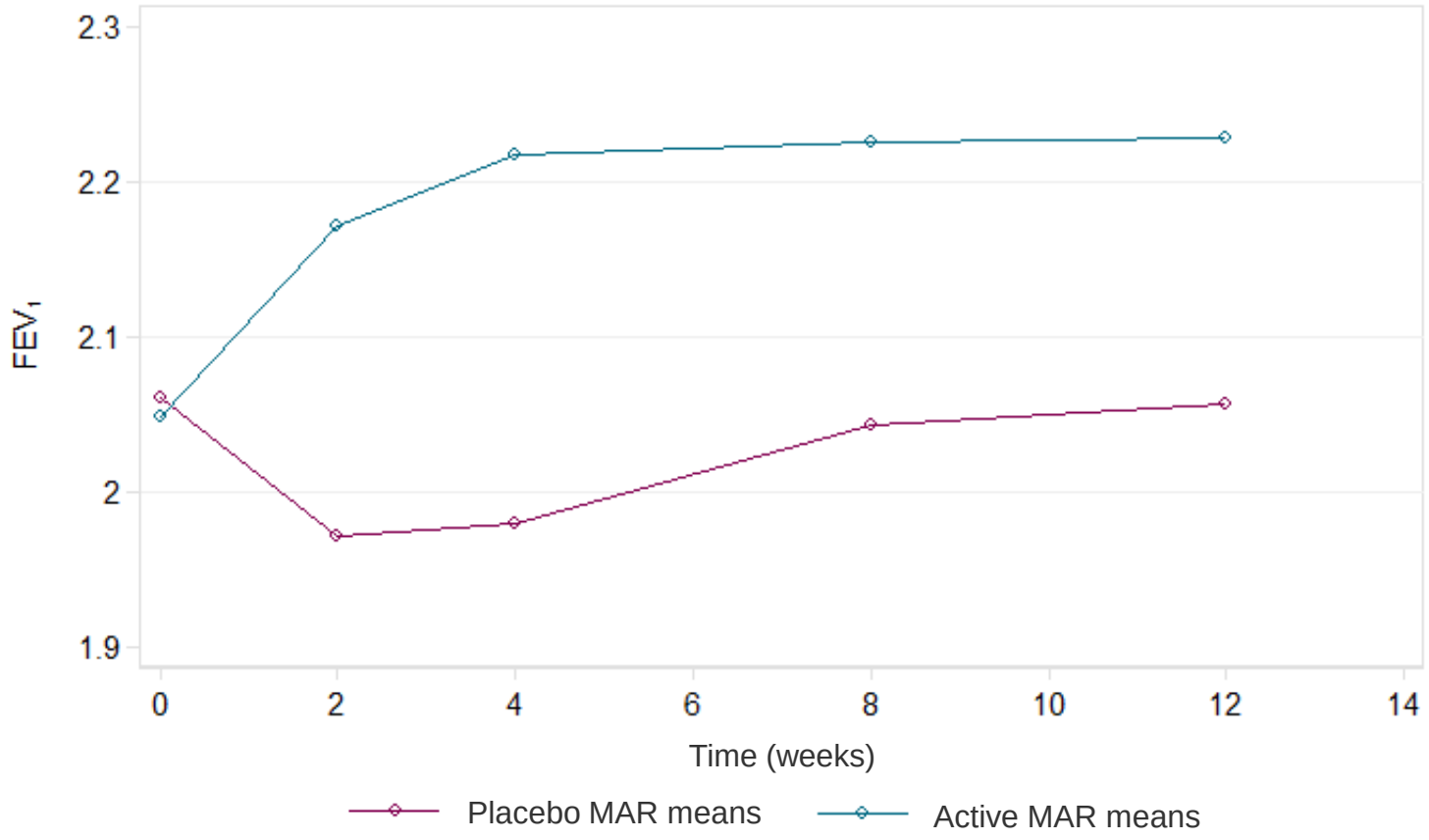
How should we do sensitivity analyses?

- Sensitivity analysis can use selection, latent variable or pattern mixture models

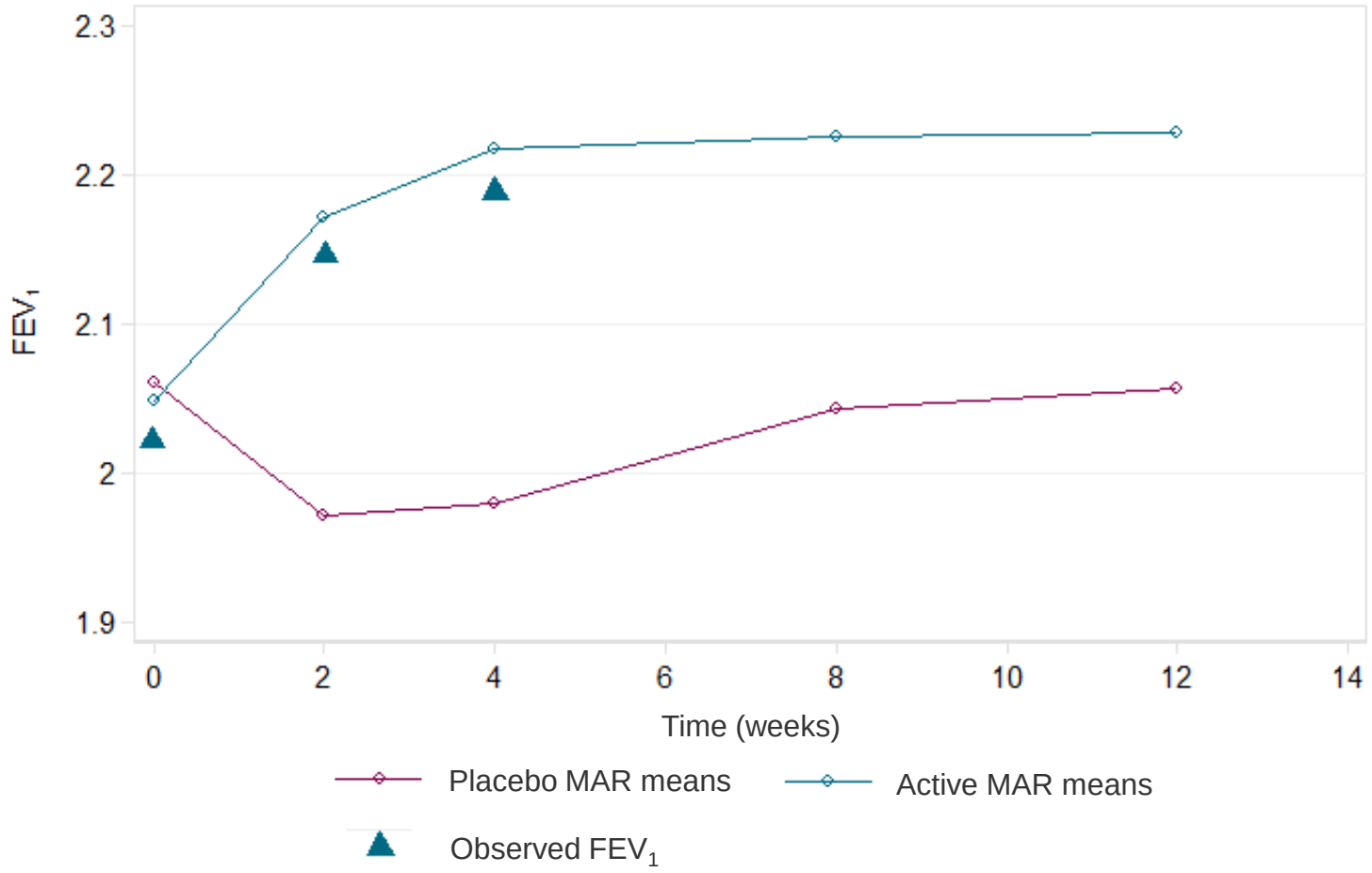
- Whatever our model, there are two broad approaches:
    1. Keep the design based analysis model used in primary analysis; vary the assumptions about the post-deviation data
    2. Formulate a separate analysis under each scenario

- Multiple Imputation (MI) is suited to the first approach as the imputation and analysis model are separate

Example – asthma trial - MAR



Example – asthma trial - MAR



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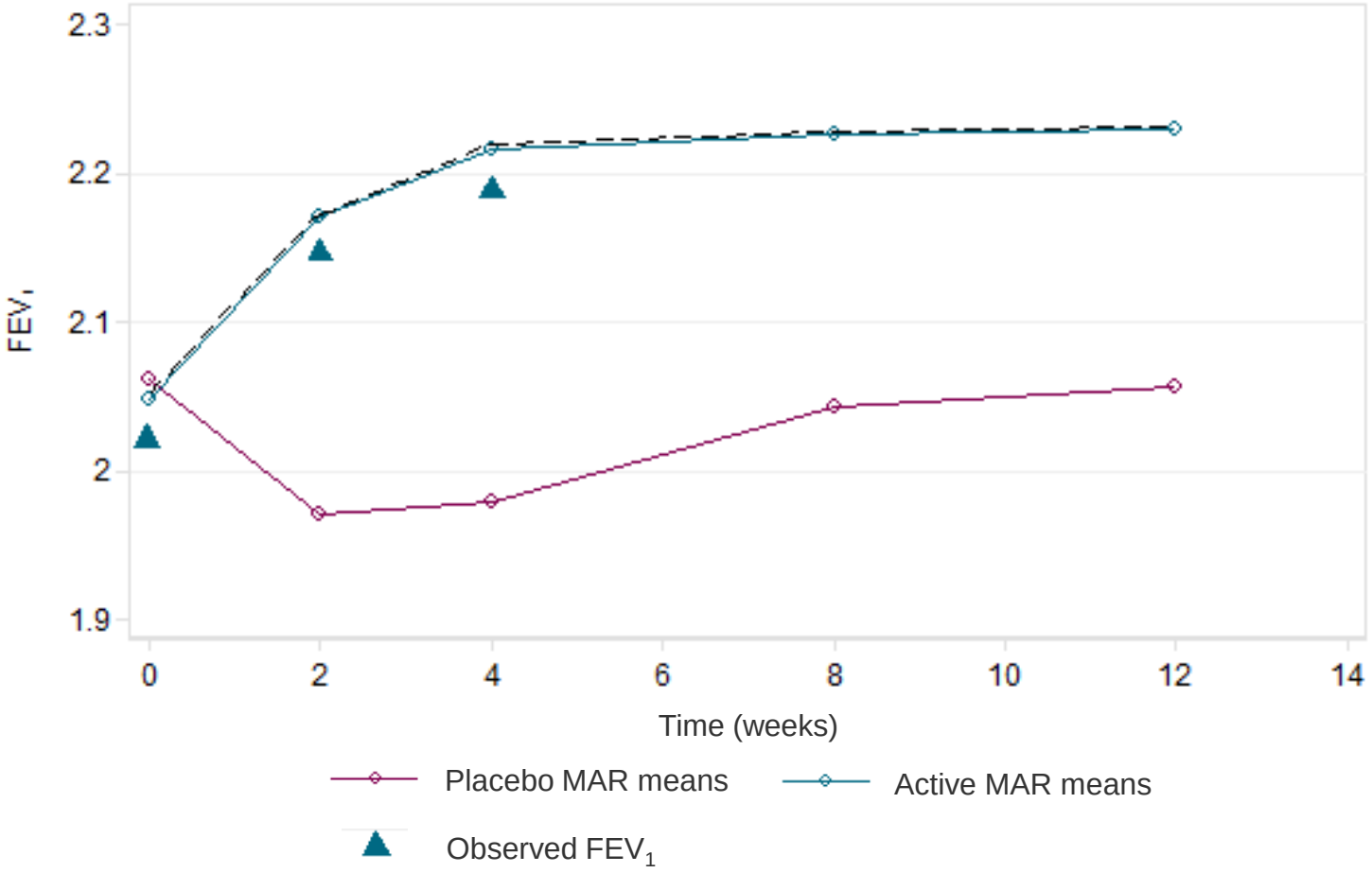

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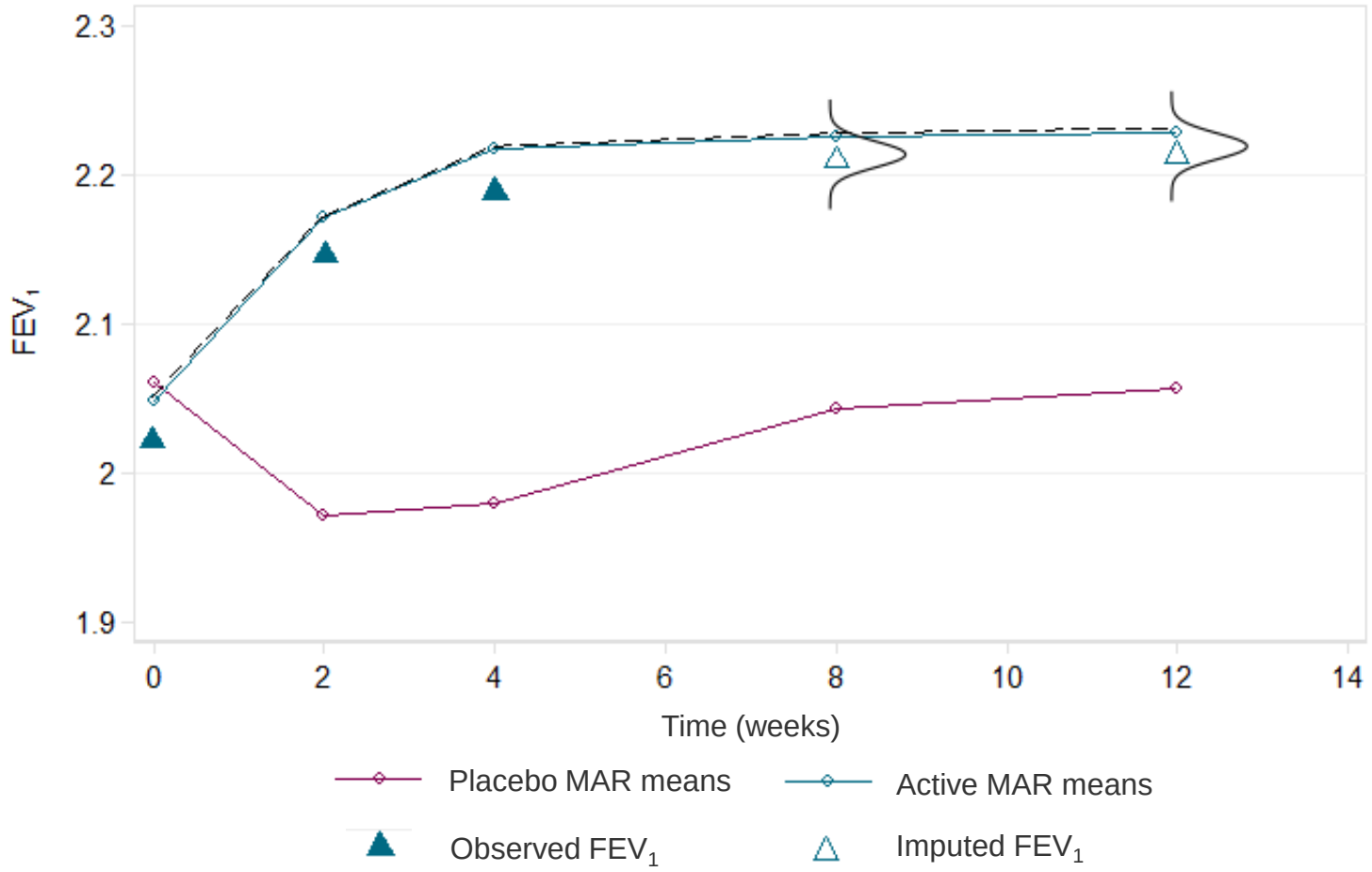
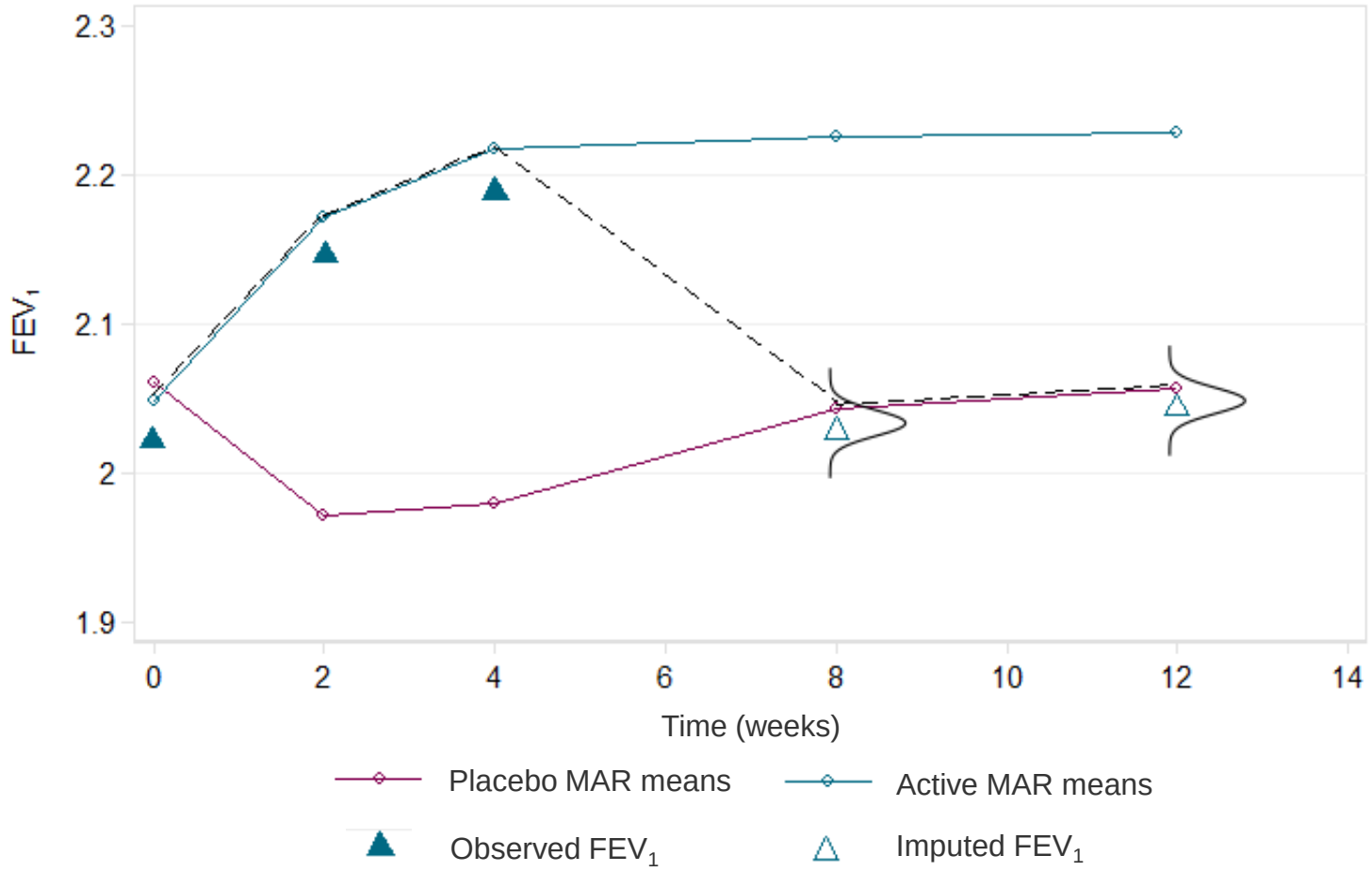
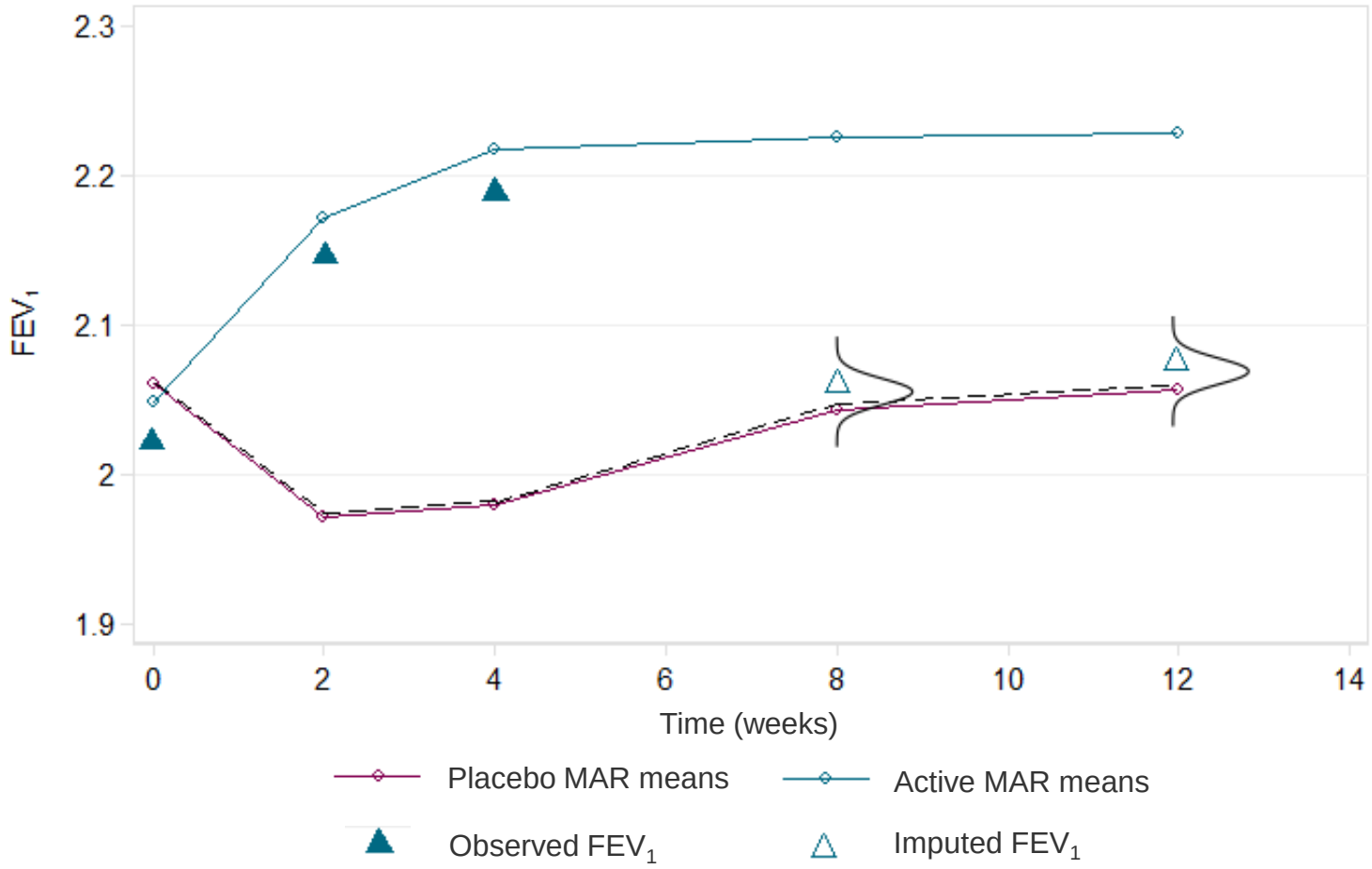


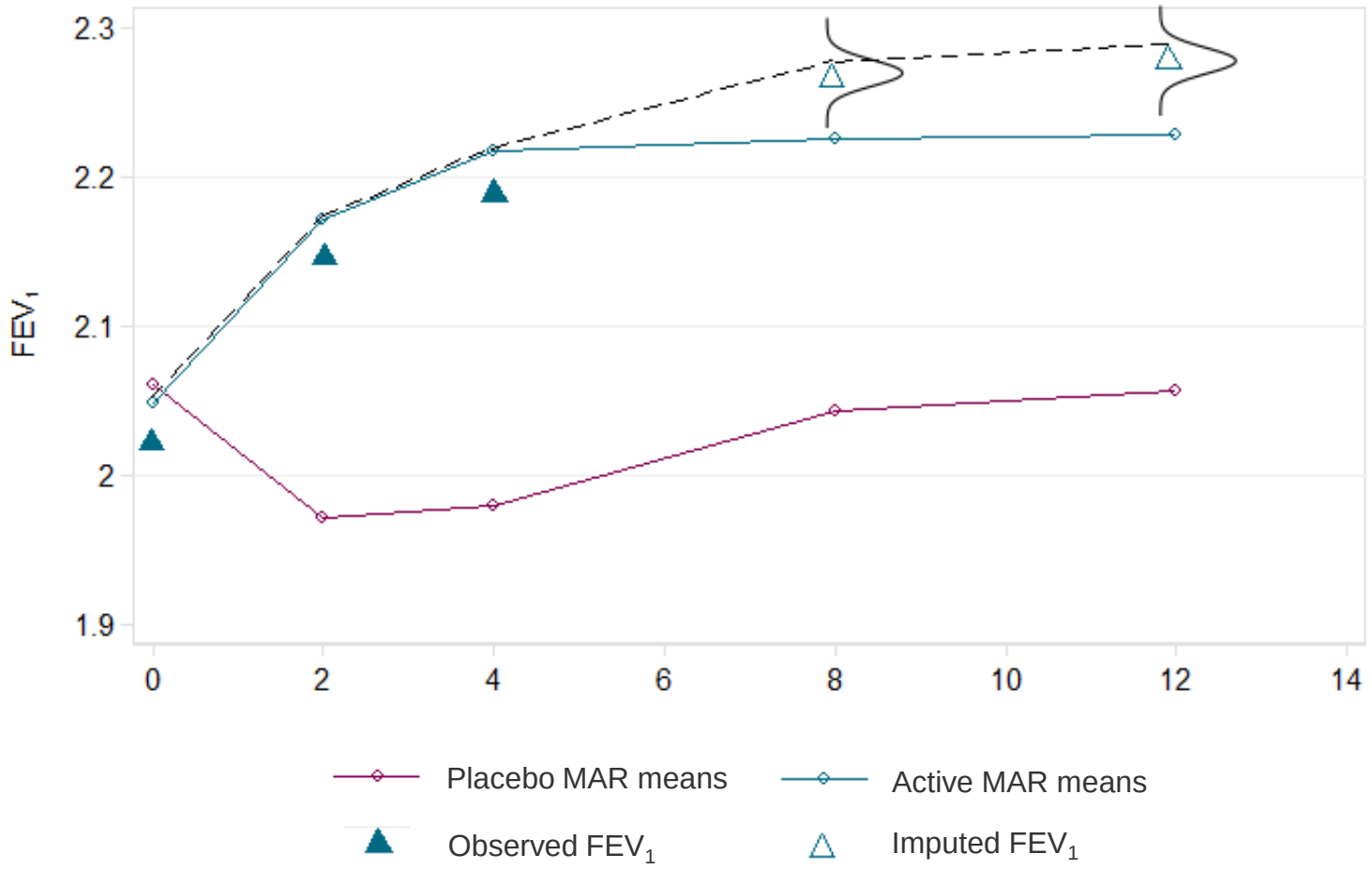
Example – asthma trial – Jump to reference



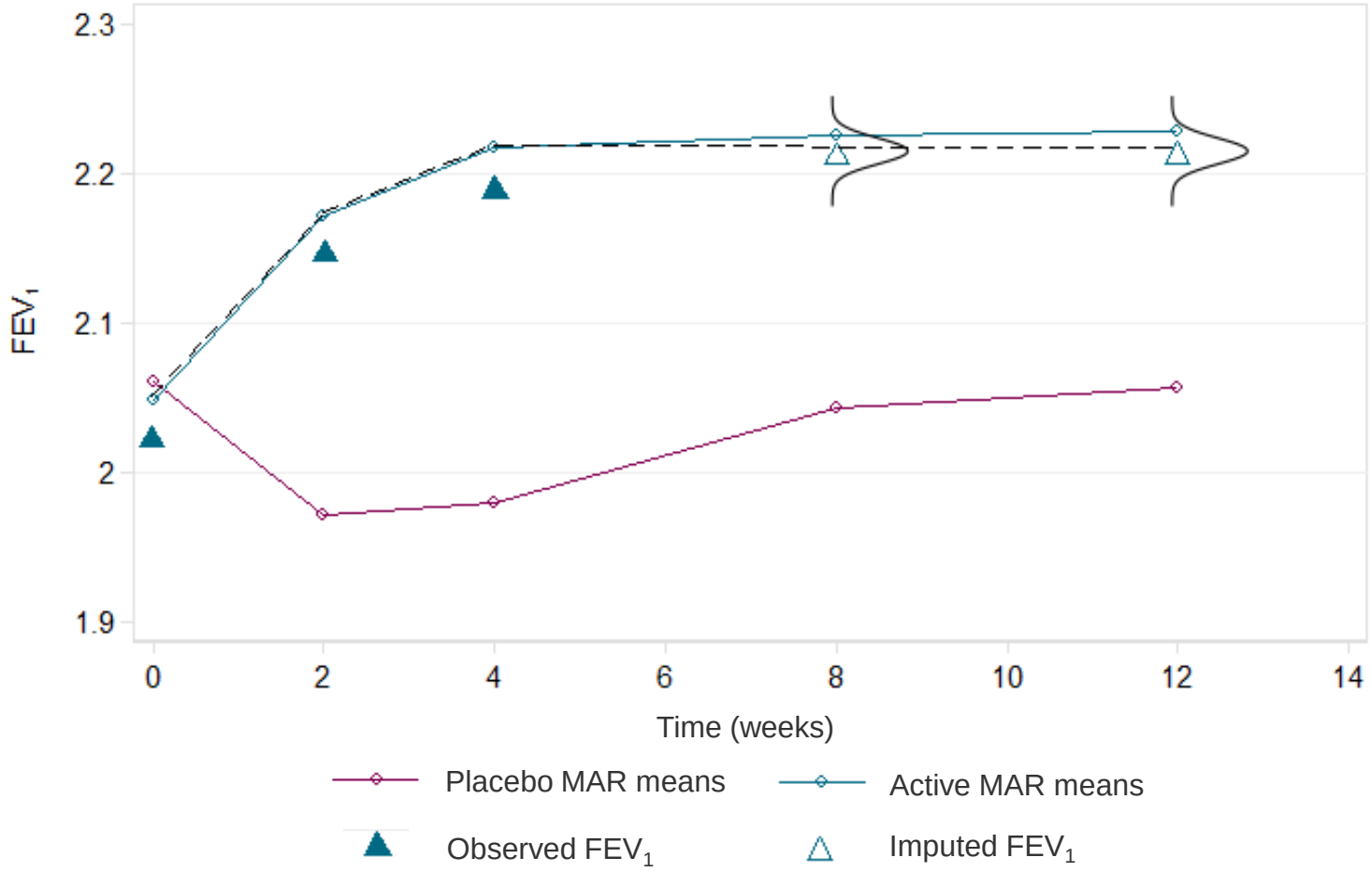
Example – asthma trial – Copy reference



Copy increments in reference



Last Mean Carried Forward



Reference based sensitivity analysis via MI

- Impute the missing data under a reference based assumption multiple times
- Analyse each imputed data set using the design based analysis model used in the primary analysis
- Get one overall treatment effect and estimate of variance using ***Rubin's rules***

Carpenter, Roger and Kenward (2013)

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Variance estimation

- We note that the imputation and analysis model are *uncongenial*
- For the unobserved cases the imputation model has structure that is additional to the analysis model
- The usual justification of Rubin's MI variance estimate does not hold
- We expect Rubin's MI Variance estimate to be conservative in a *long-run* sense

Meng (1994)

Principle 1 – Lower bound

Principle 1: With missing post-deviation data, to reflect the loss of information the variance of the MI treatment estimator should be larger than the variance we would obtain were we able to observe the post-deviation data

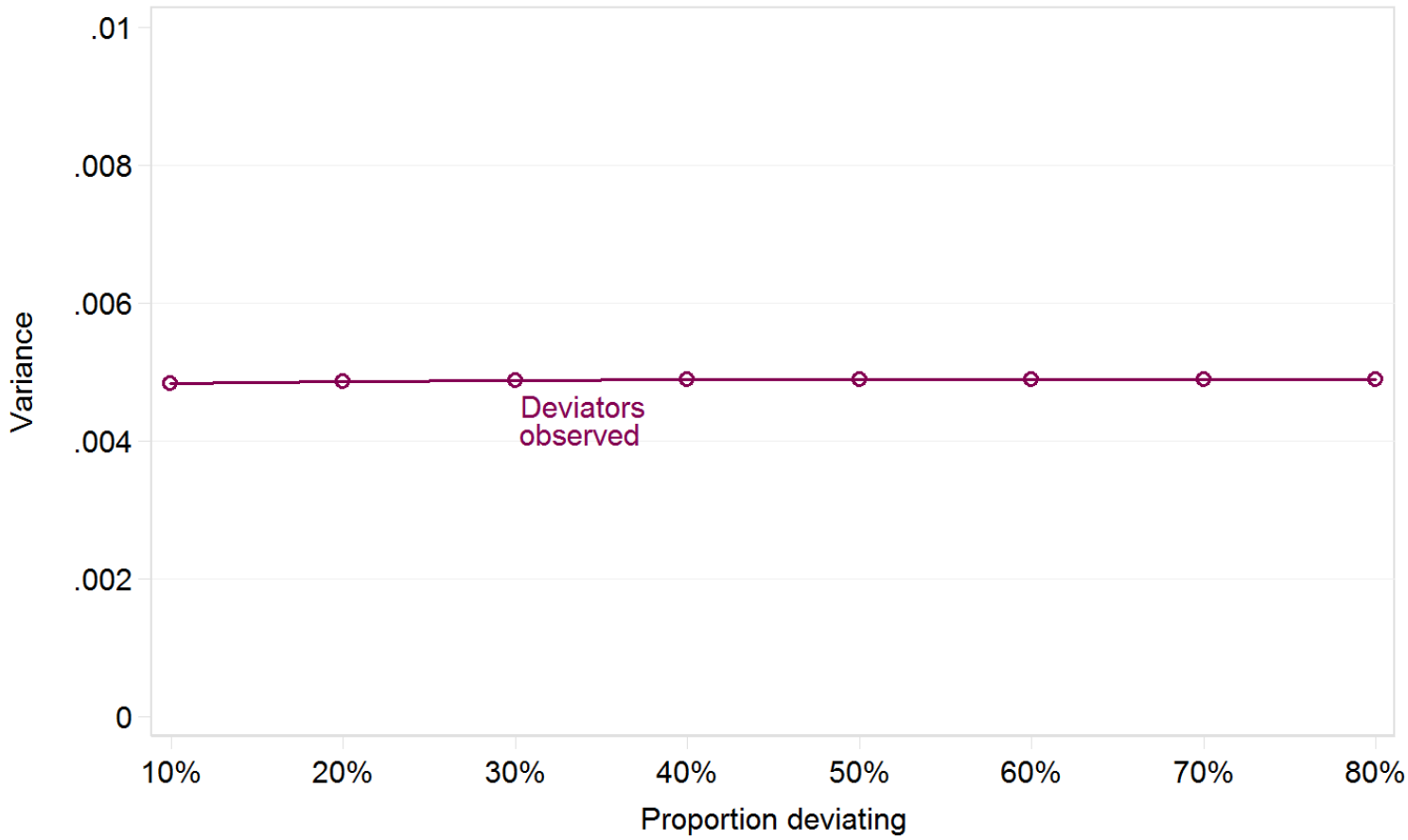
Simulation study

- Based on asthma RCT:
  - Placebo vs. Budesonide
  - FEV_1 recorded at baseline and a single follow-up
  - Data generation:

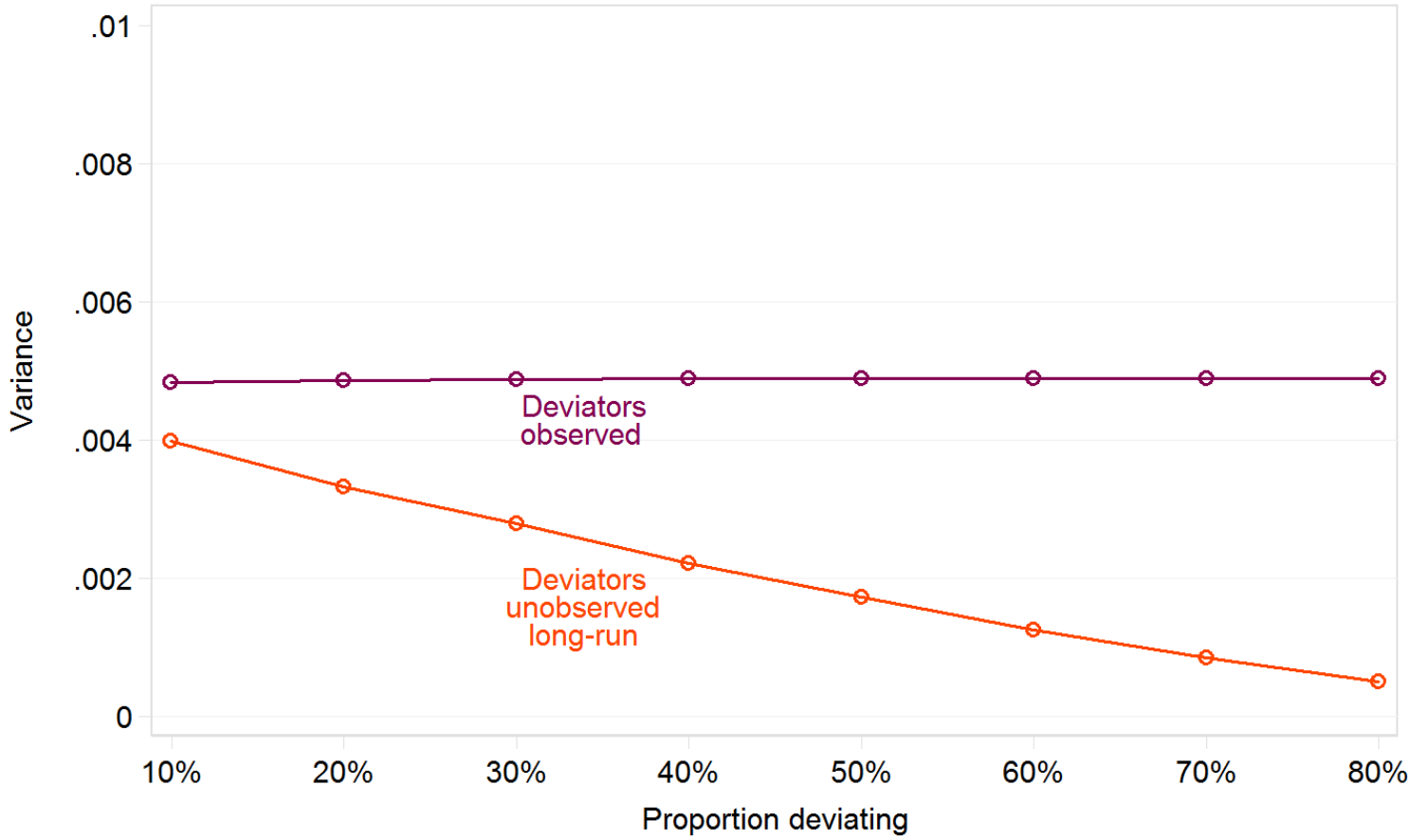
$$\mu_{budesonide} = [2.0, 2.2] \quad \mu_{placebo} = [2.0, 1.9] \quad \Sigma = \begin{bmatrix} 0.4 & 0.2 \\ 0.2 & 0.6 \end{bmatrix}$$

  - Primary outcome = mean treatment difference at follow-up
  - Suppose 10-70% patients in active arm deviate under Jump to reference (placebo)

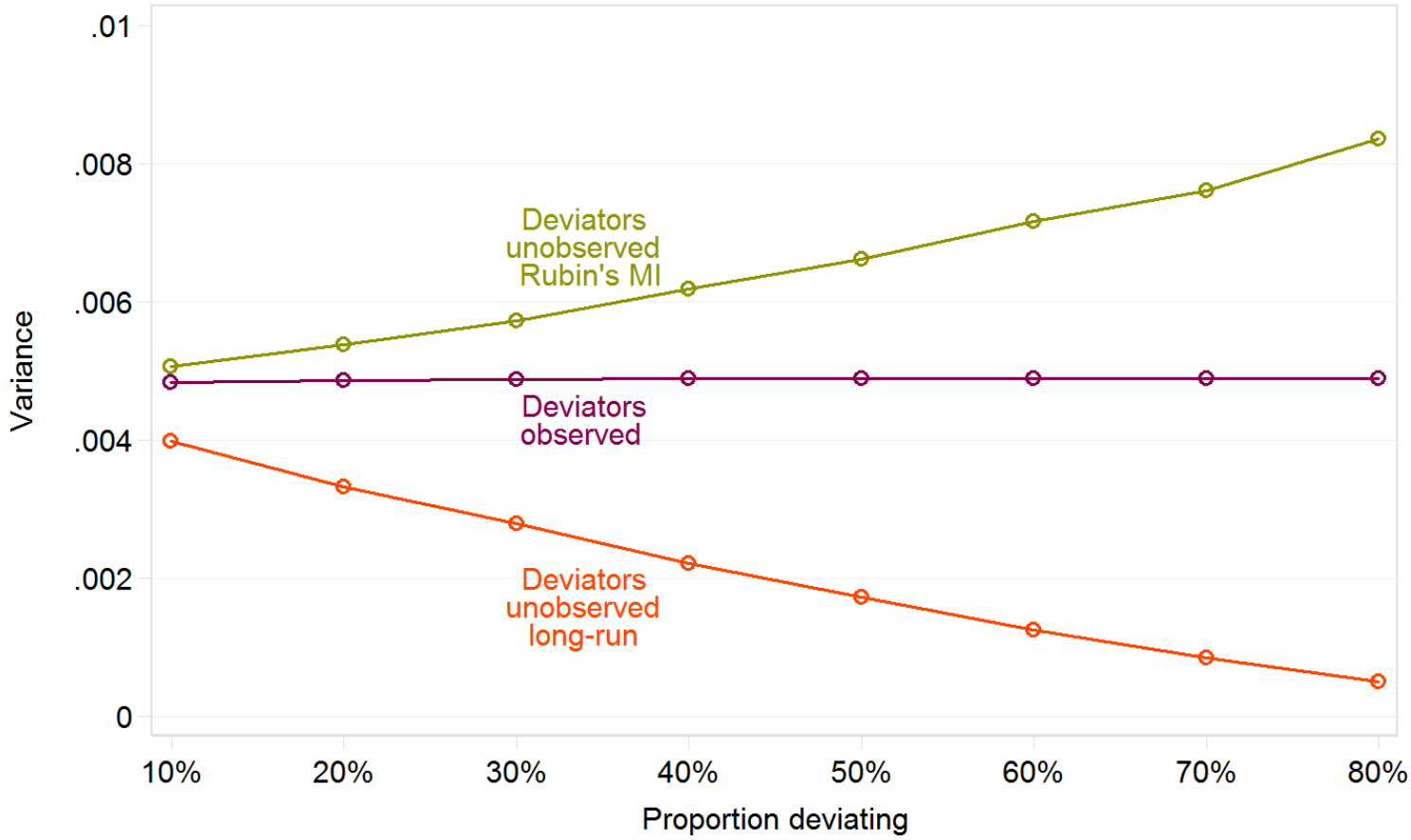
Observed post-deviation data



Long-run variance



Rubin’s MI variance



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- The long run variance of reference based MI estimator violates this principle as it substitutes the observed reference-arm mean for the mean of the unobserved active cases!

- Rubin's MI variance estimate meets this requirement

Principle 2 – Information Anchoring

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i.e. the increase in variance due to missing data in the primary analysis should be seen in sensitivity analysis

Information anchoring

- For the design based analysis model let,

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$$\frac{V_{missing,MAR}}{V_{full}}$$

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	Variance estimate
V_{full}	Full data; no deviations occur
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$$V_{anchored} = V_{full,ref} \times \frac{V_{missing,MAR}}{V_{full}}$$

How well do Rubin's rules approximate this?

- Proposition: In all settings where,

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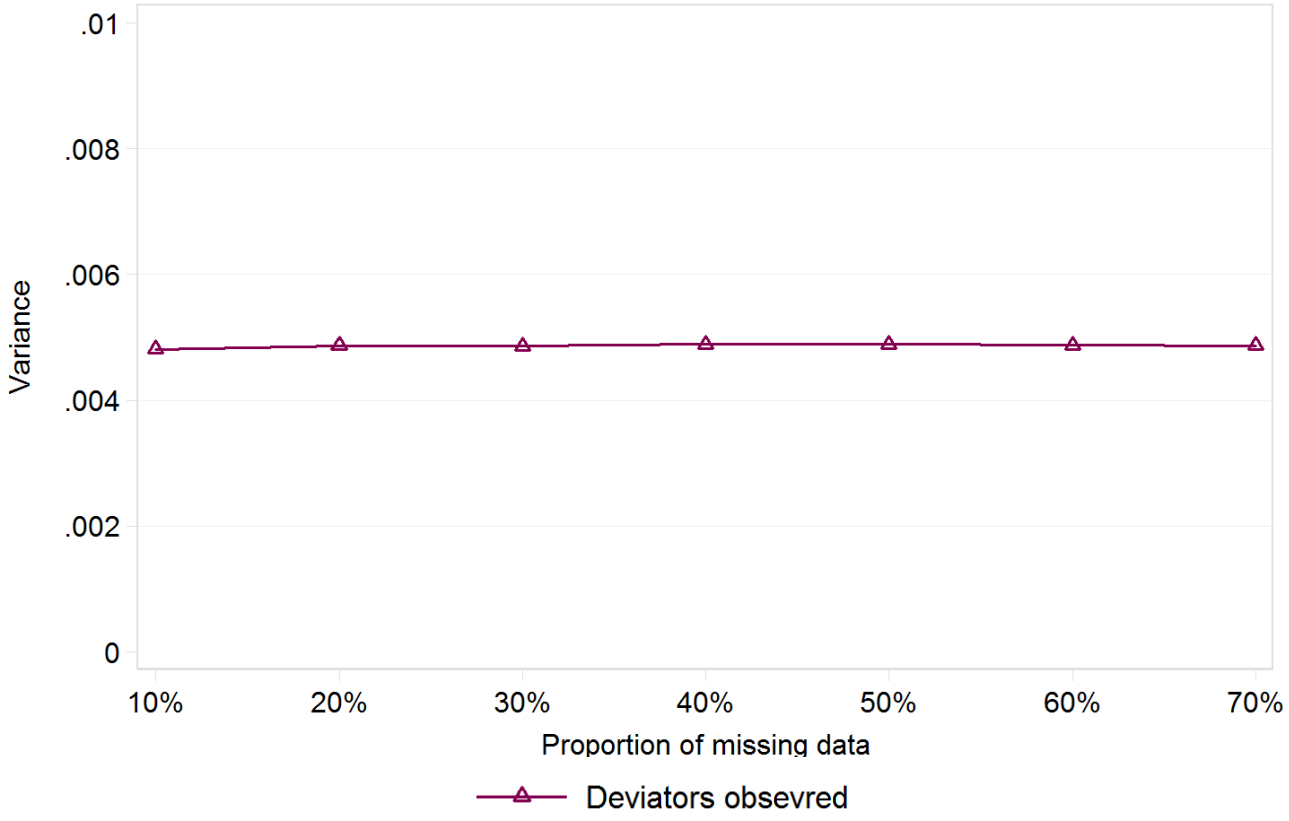
- Rubin's variance estimate is at most up to $O(n^{-2})$ information anchoring,

$$V_{Rubin} = V_{anchored} + O(n^{-2})$$

Simulation Study



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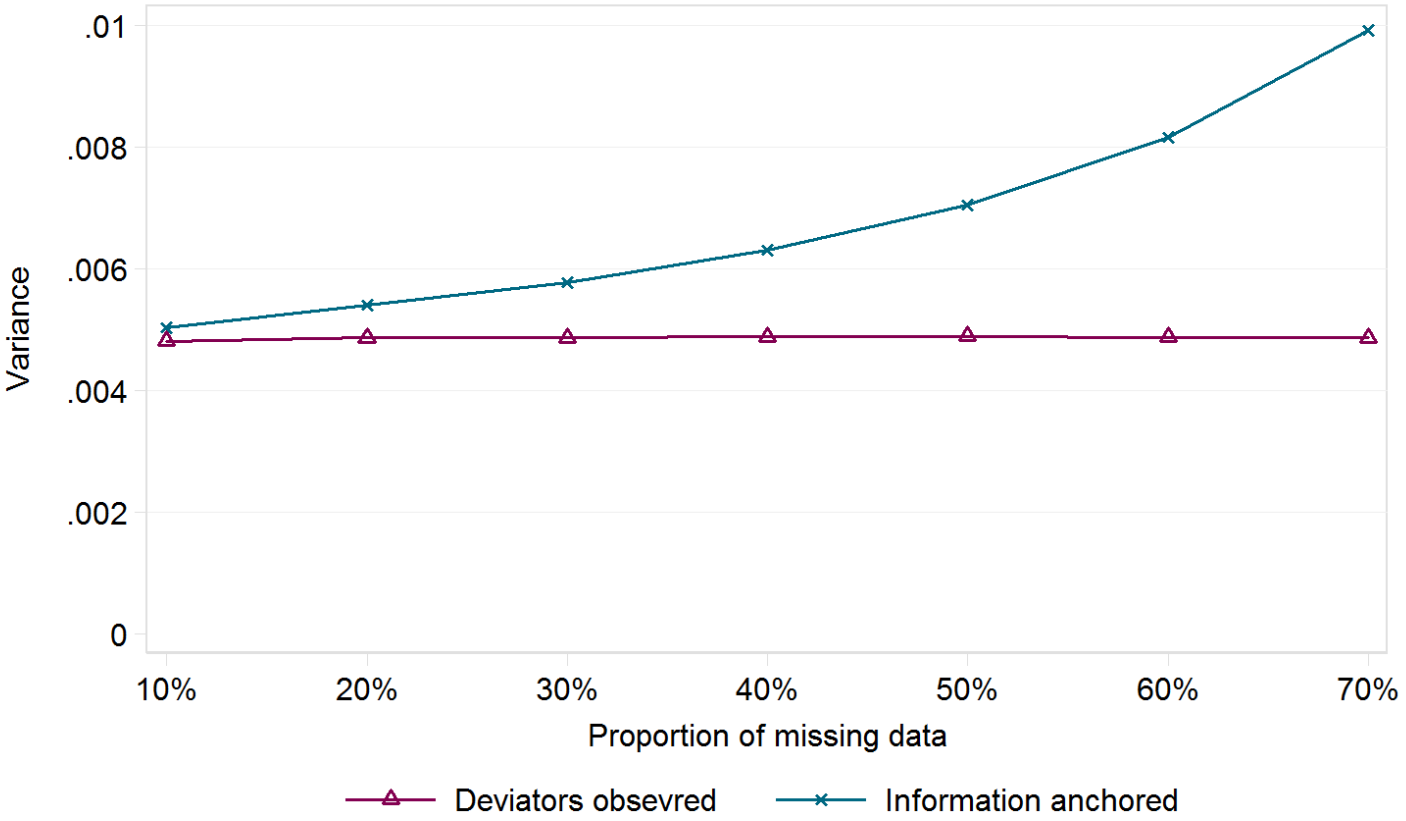
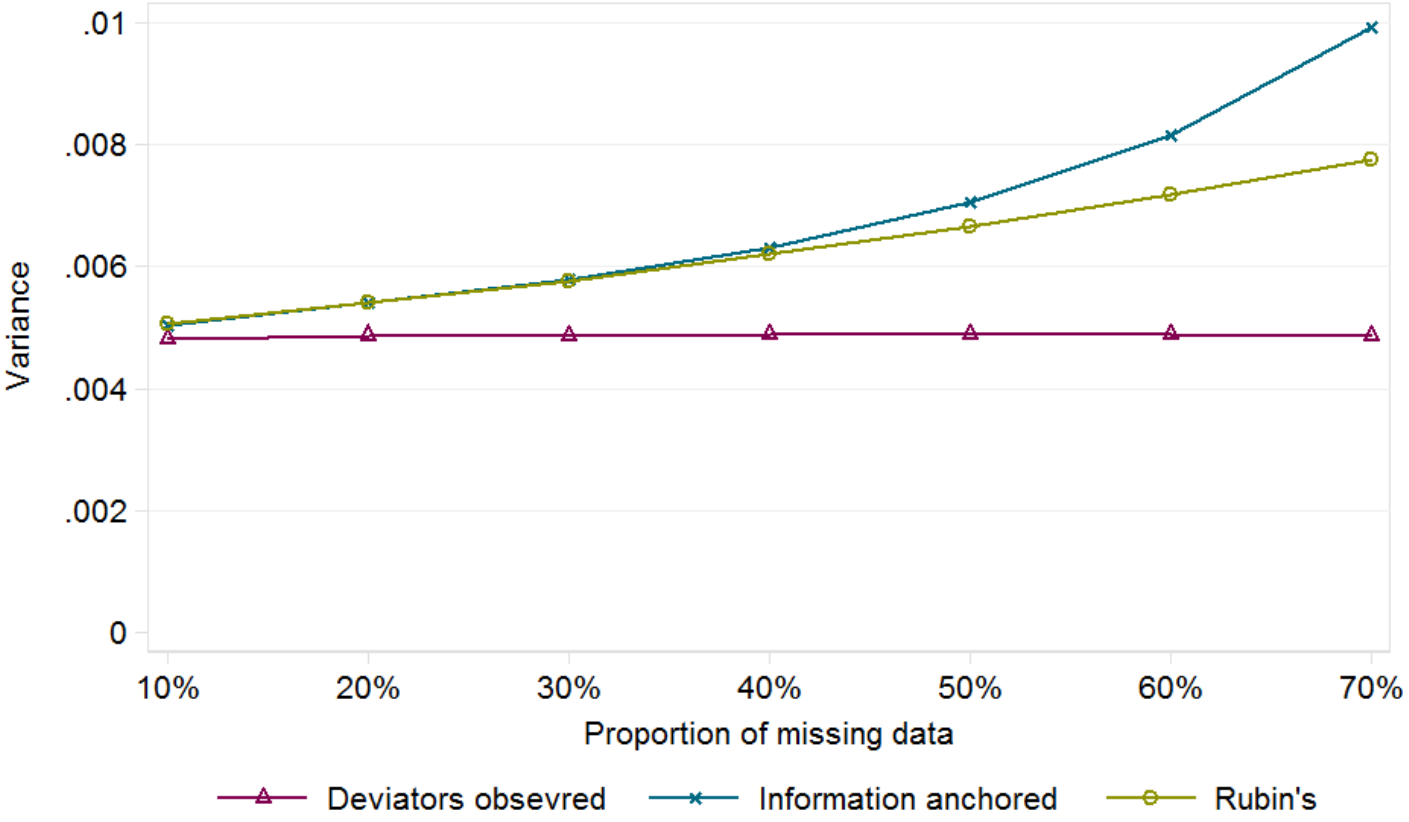


Rubin’s variance estimate



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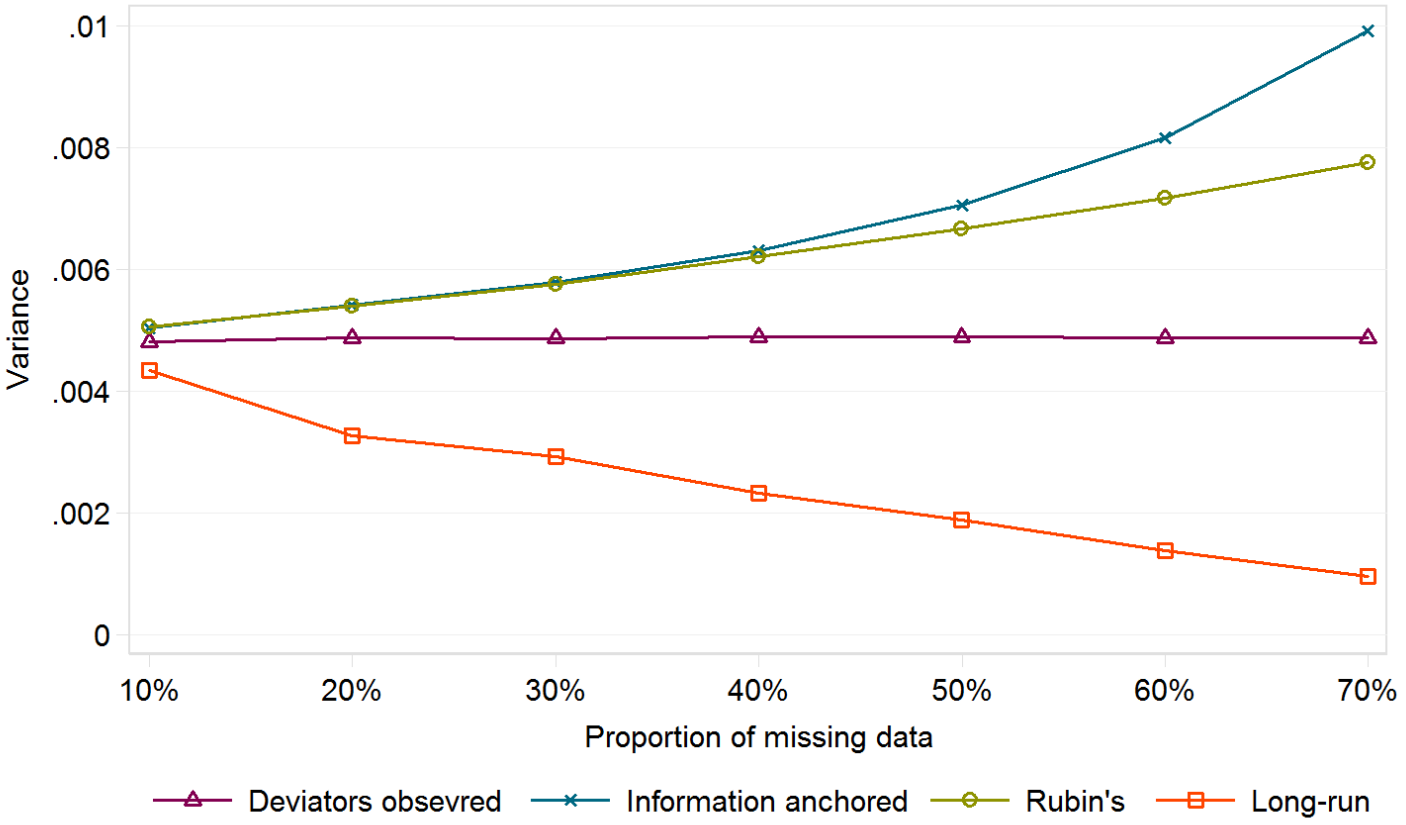


Software

- **mimix** implements the reference based MI procedures in Stata
- Download in Stata using **ssc install mimix**
- SAS Macros created by James Roger and the DIA working group available at www.missingdata.org.uk

What if deviators had a worse/better response post-deviation than those observed in their own treatment arm?

Example - peer review trial

No-training

Face-to-face training

Self-training

Example - peer review trial

No-training

Self-training

Example - peer review trial

No-training

Paper 1

Review Quality Index (0-5)

Self-training

Paper 1

Example - peer review trial

No-training

Paper 1

Paper 2

Review Quality Index (0-5)

Review Quality Index (0-5)

Self-training

Paper 1

Paper 2

Example - peer review trial

No-training

Paper 1
N = 173

Paper 2
N = 162

Review Quality Index (0-5)

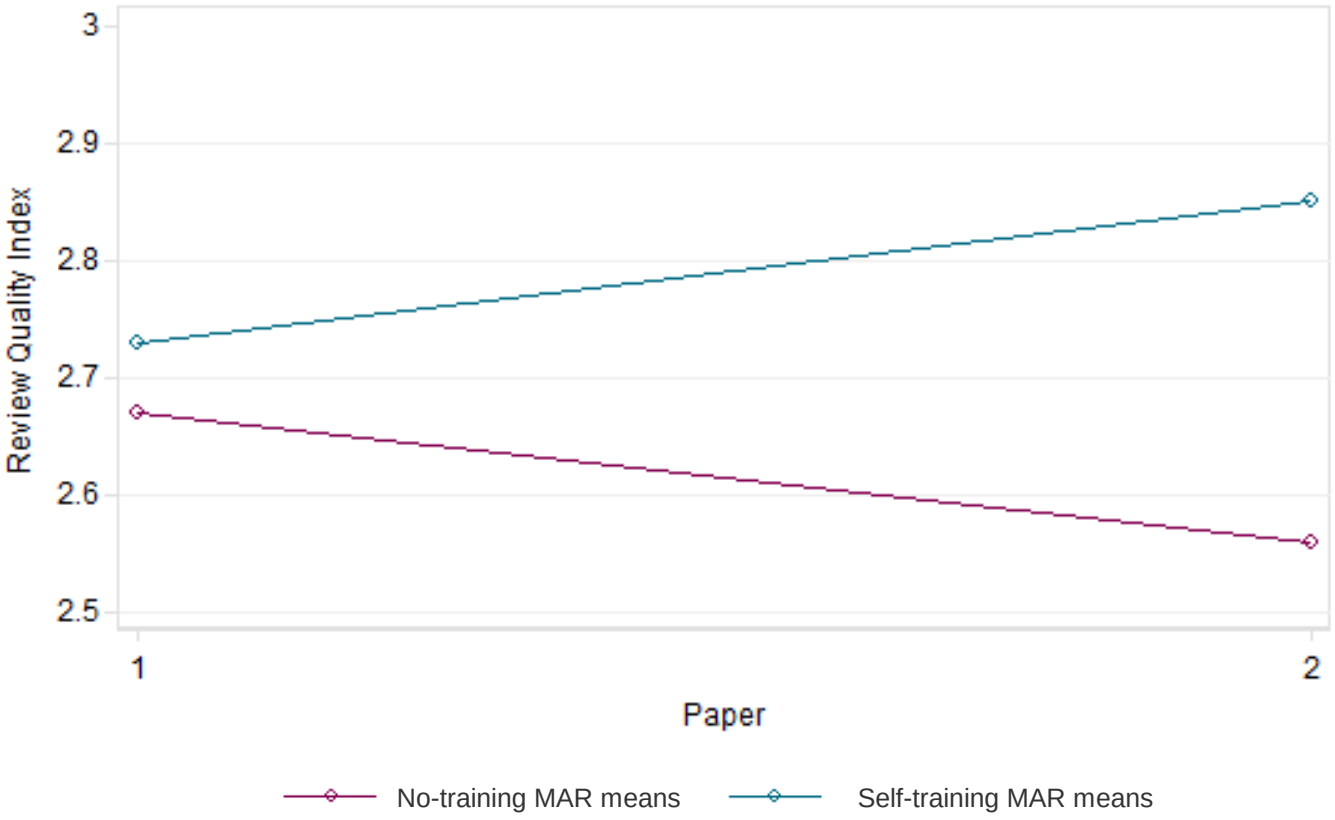
Review Quality Index (0-5)

Self-training

Paper 1
N = 166

Paper 2
N= 120

Example - peer review trial - MAR



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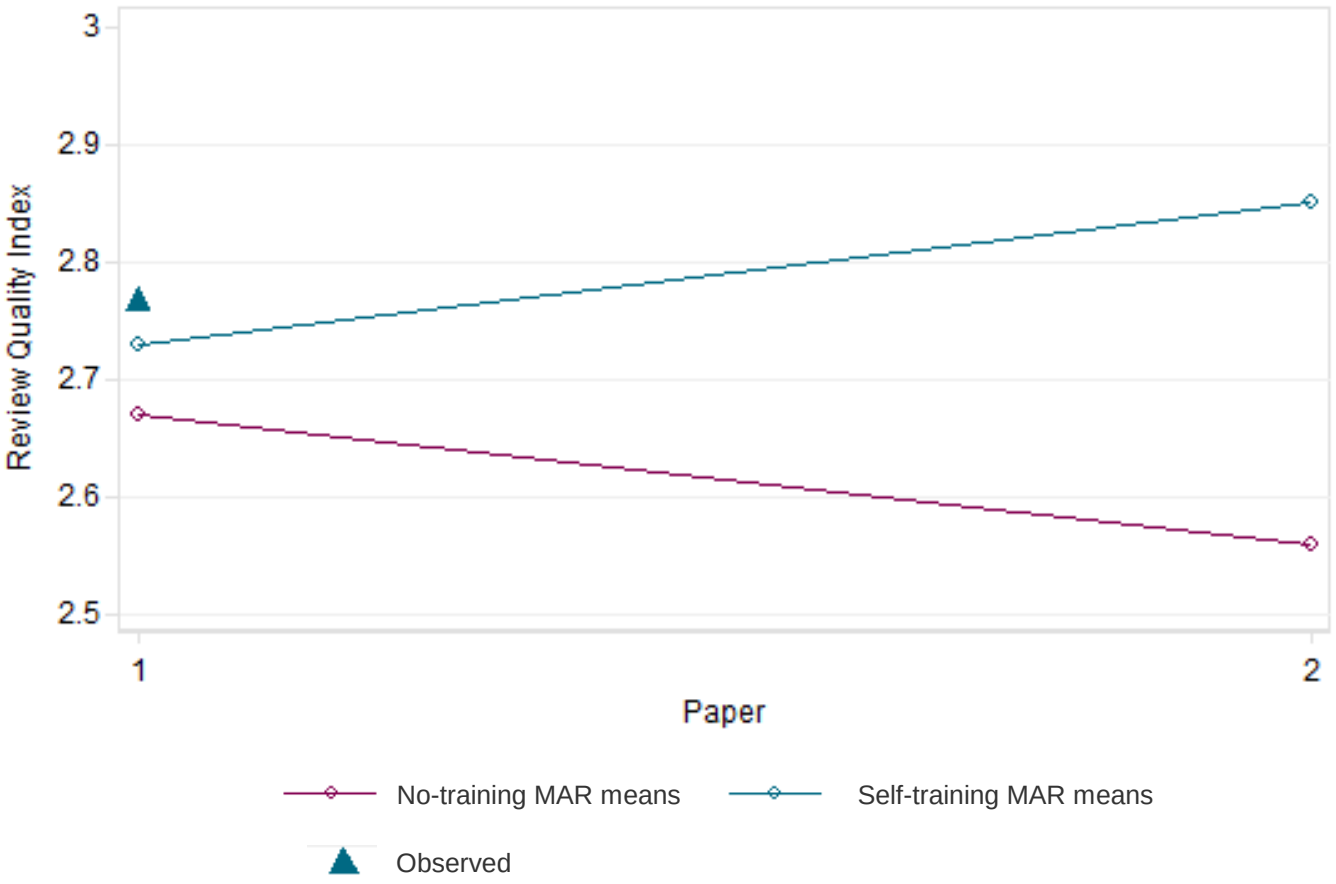

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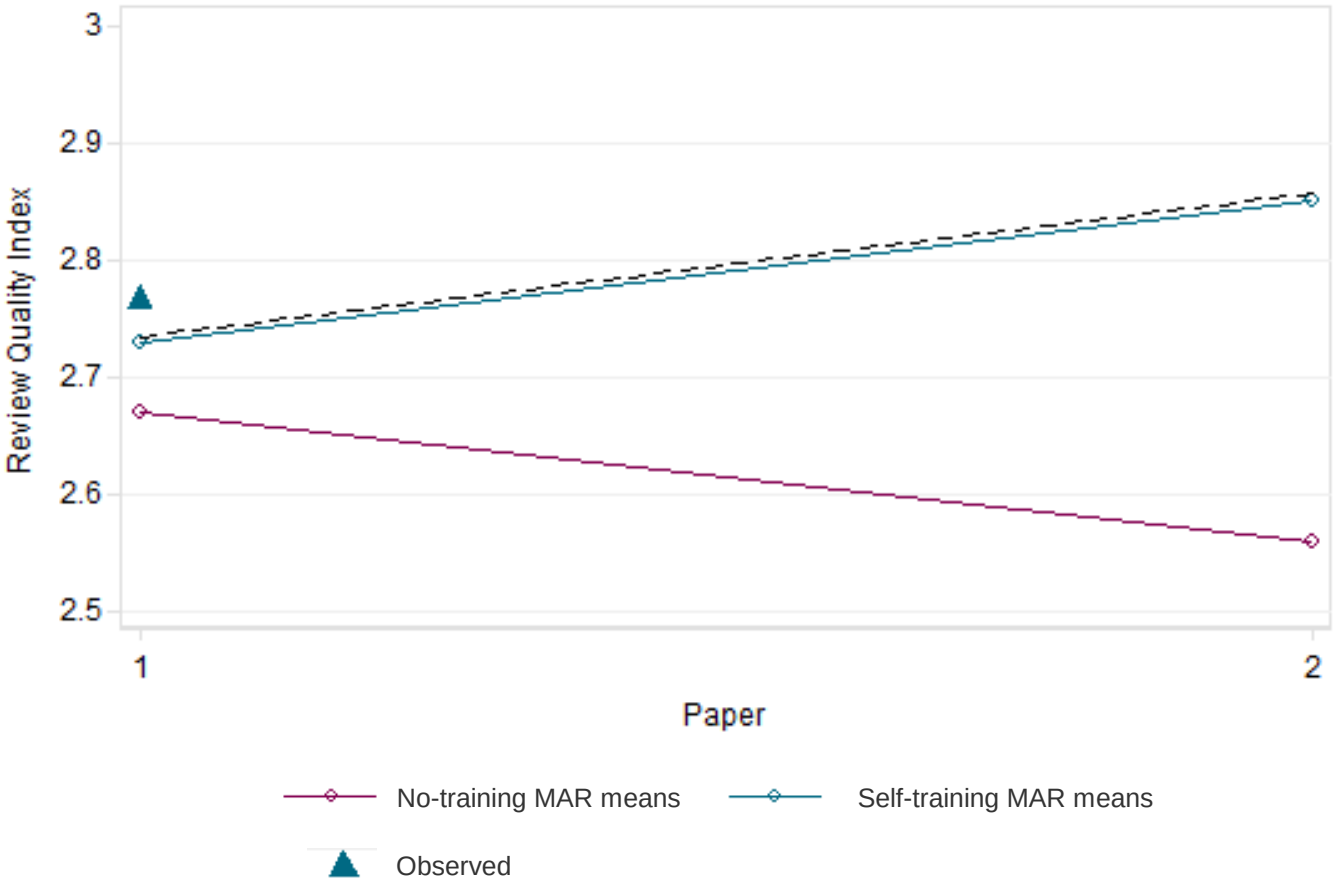

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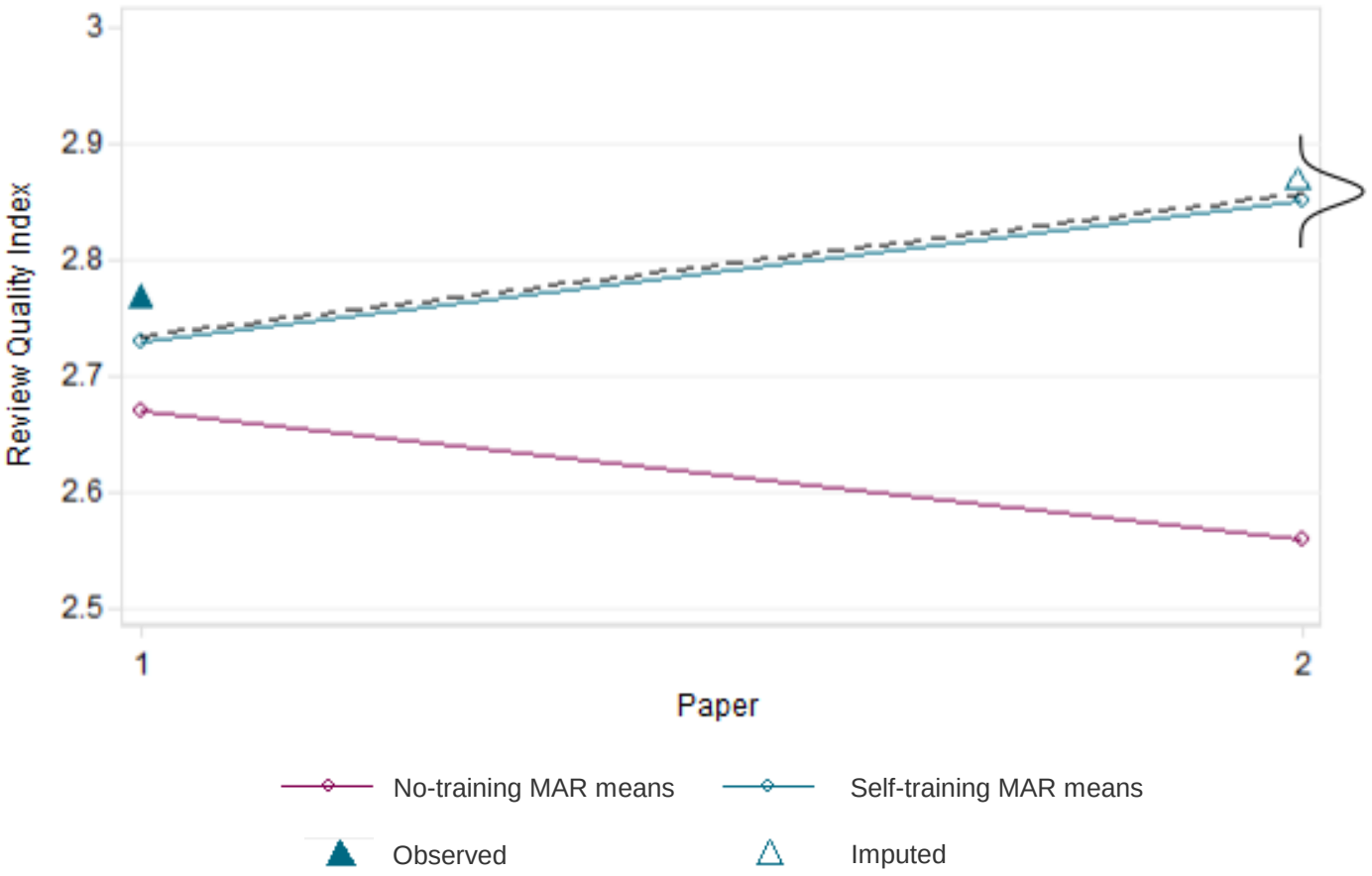

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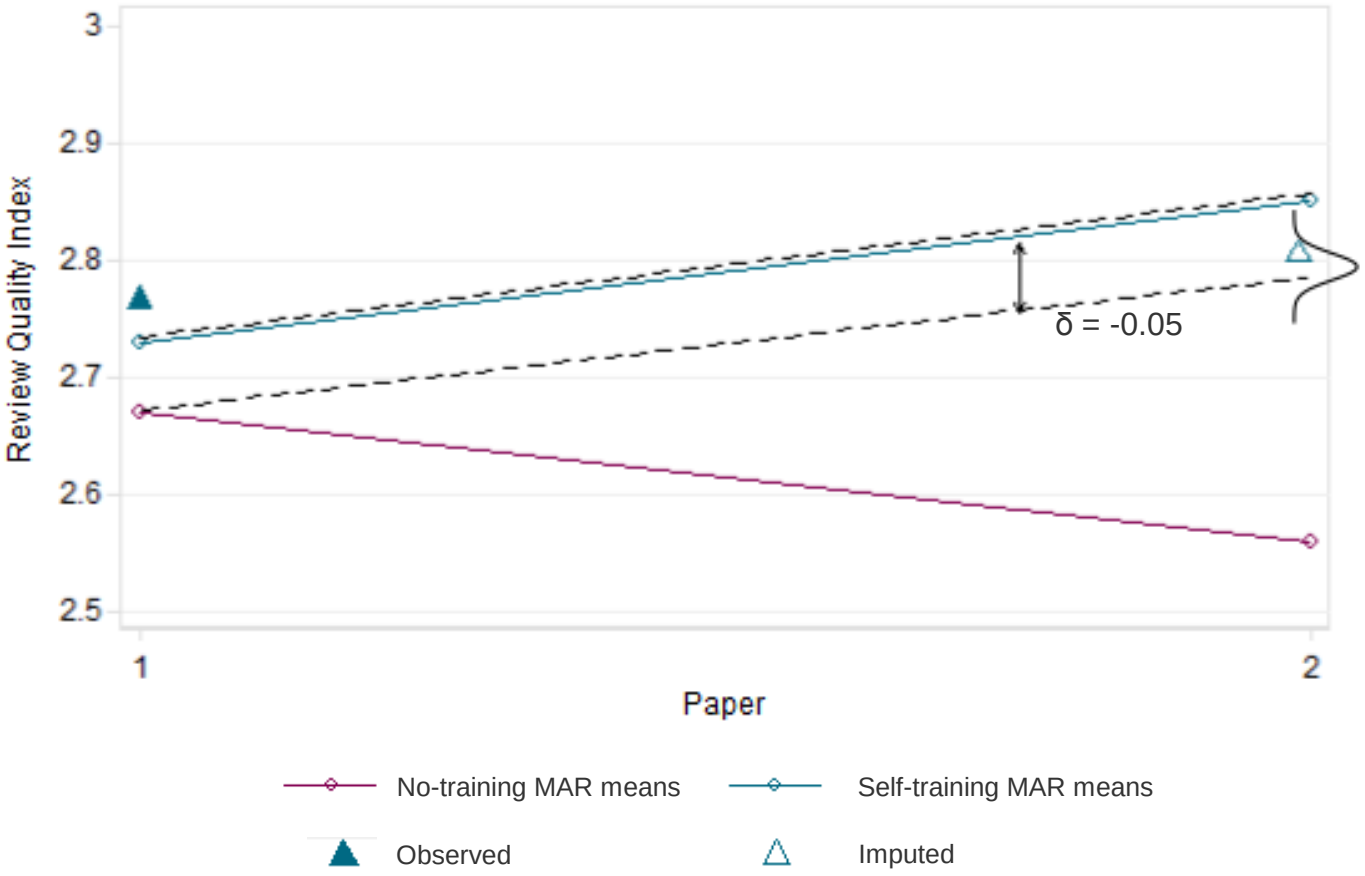

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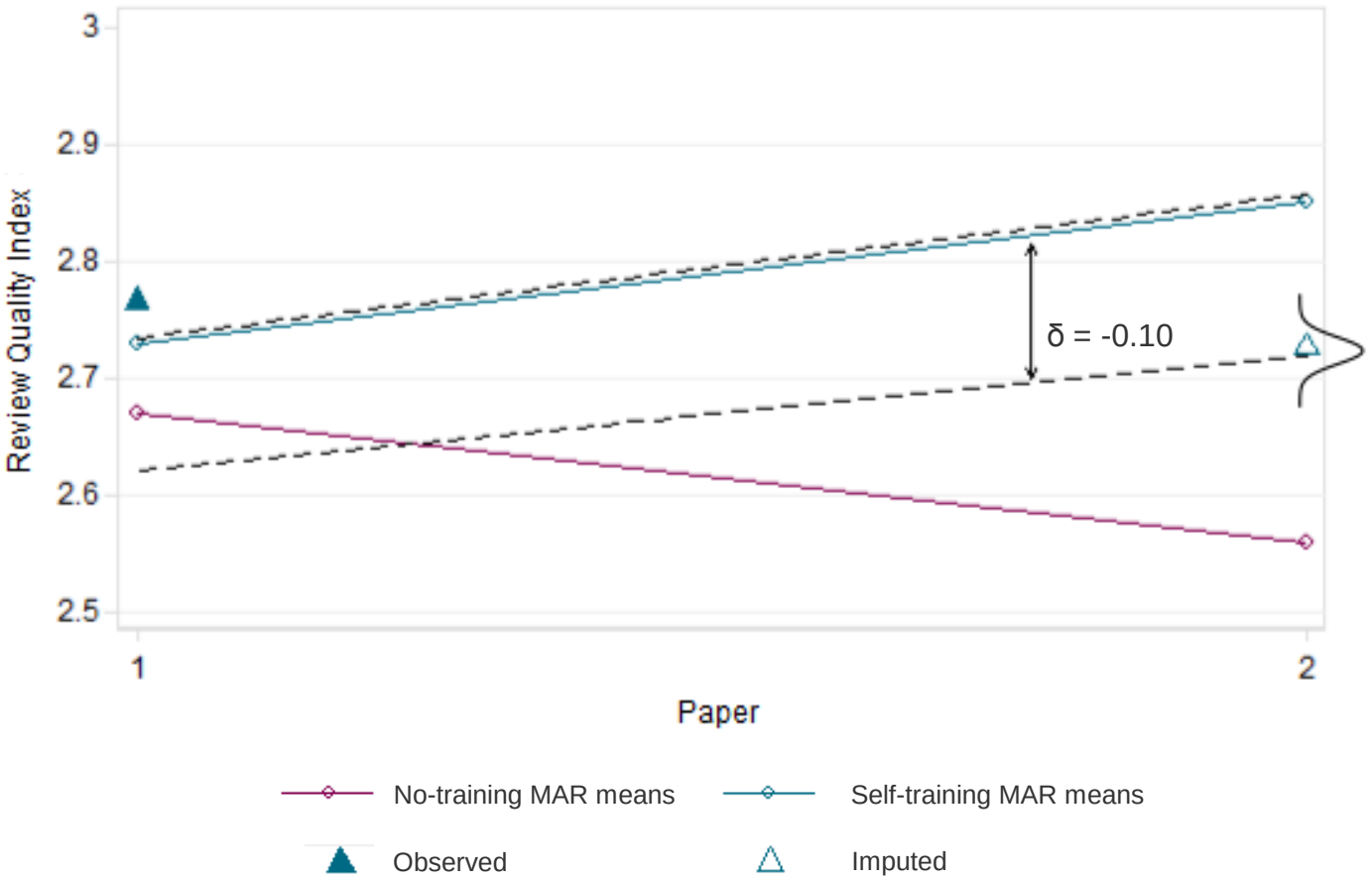
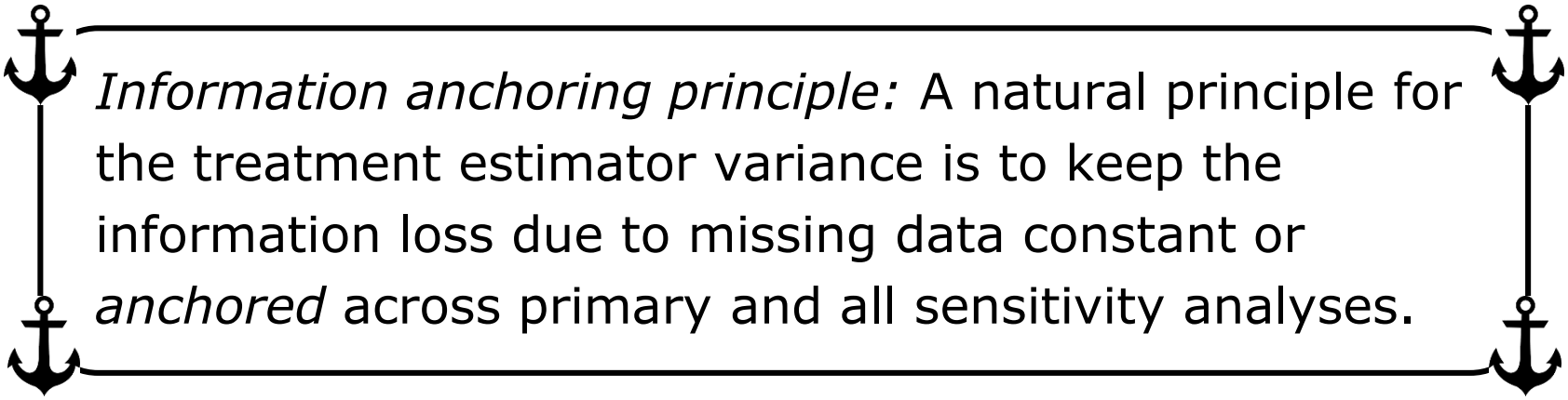


The `δ-method'

1. Impute the missing data under MAR ±δ
2. Repeat Step 1 for k = 1,…,K times.
3. Analyse each imputed data set using the design based analysis model
4. Get one overall treatment effect and estimate of variance using ***Rubin's rules***

Carpenter and Kenward (2008)

Principle for variance estimation



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Rubin’s variance estimate - the `δ-method’

- Rubin’s variance provides an excellent approximation for the information anchored variance with fixed delta,

$$V_{Rubin,\,\delta} = V_{anchored} + Q$$

where $\mathcal{O}(Q) < \mathcal{O}(V_{anchored})$

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- For a trial with single follow-up where π_d represents the proportion deviating,

$$Q = \frac{B_{MAR}}{W_{MAR}} \times \frac{\pi_d(1-\pi_d)\delta^2}{n}$$

Rubin's variance estimate - the `δ-method'

- For a longitudinal trial where $\pi_{d,j}$ represents the proportion deviating following time j for j=1,…,J-1,

$$Q = \frac{B_{MAR}}{W_{MAR}} \times \left[\sum_{j=1}^{J-1} \frac{\pi_{d,j}\left(1-\pi_{d,j}\right)\delta^2}{n}\right]$$

The `δ-method' - prior on δ

1. For imputation k draw $\delta_k \sim N(\delta, \sigma_\delta)$
2. Impute the missing data under MAR $\pm\delta_k$
3. Repeat Steps 1 and 2 for k = 1,…,K times.
4. Analyse each imputed data set using the design based analysis model
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Carpenter and Kenward (2008)

Rubin's variance estimate – prior on δ

- The information anchoring performance of Rubin's variance depends on the assumed variance for delta, σ_δ

- For a trial with a single follow-up where π_d represents the proportion deviating,

$$V_{Rubin,\,\delta} = V_{anchored} + Q + \boldsymbol{\pi_d{}^2 \sigma_\delta}$$

Rubin's variance estimate – prior on δ

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$$V_{Rubin,\,\delta} = V_{anchored} + Q + \sum_{j=1}^{J-1} \boldsymbol{\pi_{d,j}}^{2} \boldsymbol{\sigma_{\delta}}$$

Analysis of the peer review study

- White, Carpenter, Evans and Schroter elicited experts belief (N=22) about the mean difference between missing and observed outcomes

- Pooled prior (across treatment groups),

$$\delta_k \sim N(-0.21, 0.46^2)$$

Analysis of the peer review study

Analysis	Treatment Est (self – no training)	Std Err.	P-value
MI - MAR	0.234	0.071	0.001

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Analysis of the peer review study

- The `δ-method' with fixed δ anchors the loss of information in the primary analysis to a very good approximation
- A loss of information will occur when a prior distribution on δ is used *i.e. larger treatment estimator variance*
- Trialists should carefully consider the choice of δ when conducting sensitivity analysis via the `δ-method'

Conclusions

- The loss of information due to missing data across primary and design based sensitivity analysis should be constant
- Rubin's variance estimate anchors the loss of information in the primary analysis to a very good approximation in reference based settings
- With fixed δ adjustment Rubin's variance estimate also anchors the loss of information in the primary analysis to a very good approximation
- A loss of information will occur when a prior distribution on δ is used *i.e. larger treatment estimator variance*

Busse W, Chervinsky P, Condemi J, Lumry WR, Petty T, Rennard S, Budesonide delivered by turbuhaler is effective in a does dependent fashion when used in the treatment of adults patients with chronic asthma, *Journal of Allergy ad Clinical Immunology,* 101:457-463, 1998.

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