

Randomised Controlled Trials in the Social Sciences Conference
Missing Data in Randomised Trials — Overview and Strategies

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Acknowledgements

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● **Acknowledgements**

● Outline

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Critique of common methods

Missing At Random

Multiple Imputation under Missing At Random

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Outline

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- Acknowledgements

- **Outline**

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1. Missing data in trials— the need for a principled approach
2. Completers analysis
3. Imputation of simple mean
4. Imputation of regression mean
5. Last Observation Carried Forward
6. Multiple Imputation
 - assuming data are Missing At Random
 - assuming data are Missing Not At Random
7. Discussion

Why is this necessary?

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● **Why is this necessary?**

- Further...
- The E9 guideline, 1999
- Study validity and sensible analysis
- Why there can be no universal method:
 - Example: Trial of training to improve the quality of peer review
 - Key points for analysis
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Critique of common methods

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Discussion

Missing data are common.

However, they are usually inadequately handled in both epidemiological and experimental research.

For example, [14] reviewed 71 recently published BMJ, JAMA, Lancet and NEJM papers.

- 89% had partly missing outcome data.
- In 37 trials with repeated outcome measures, 46% performed complete case analysis.
- Only 21% reported sensitivity analysis.

Unfortunately, an update in 2014 [1] showed relatively little had changed, although Multiple Imputation [12] was much more commonly used.

Further...

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- Why is this necessary?
- **Further...**
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CONSORT guidelines state that the number of patients with missing data should be reported by treatment arm.

But [5] estimate that 65% of studies in PubMed journals do not report the handling of missing data.

[14] identified serious weaknesses in the description of missing data and the methodology adopted.

The E9 guideline, 1999

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- Missing data are a potential source of bias
- Avoid if possible (!)
- With missing data, a trial may still be regarded as valid if the methods are *sensible*, and preferably *predefined*
- There can be no universally applicable method of handling missing data
- The sensitivity of conclusions to methods should thus be investigated, particularly if there are a large number of missing observations

Guidelines downloadable from www.ich.org

The question is, how do we apply these principles in practice?

Study validity and sensible analysis

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Missing data are observations we intended to make but did not.

The sampling process involves both the selection of the units, and the process by which observations become missing — the *missingness mechanism*.

Thus for sensible inference, we need to take account of the missingness mechanism

By *sensible* we mean:

- Frequentist: nominal properties hold. Eg:
Estimators consistent; confidence intervals attain nominal coverage.
- Bayesian:
Posterior distribution is unbiased, correctly reflects loss of information due to missingness mechanism.

Why there can be no universal method:

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In contrast with the sampling process, which is usually known, the missingness mechanism is usually unknown.

The data alone cannot usually definitively tell us the sampling process.

Likewise, the missingness pattern, and its relationship to the observations, cannot identify the missingness mechanism.

With missing data, extra assumptions are thus required for analysis to proceed.

The validity of these assumptions cannot be determined from the data at hand.

Assessing the sensitivity of the conclusions to the assumptions should therefore play a central role.

Example: Trial of training to improve the quality of peer review

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The graph below shows selected results from a RCT of training to improve the quality of peer review of medical articles [10]. Background details are given on your practical sheet.



Key points for analysis

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- the question (i.e. the hypothesis under investigation) — missing data usually does not change this;
- the information in the observed data, and
- the reason for missing data.

We will consider the impact of various assumptions about the missing data.

Importantly, the data themselves do not tell us which assumptions are true.

We therefore want to explore whether our conclusions are robust to a range of plausible assumptions about the *distribution* of the missing values.

Note, we can't get back the missing values themselves!

Towards a systematic approach

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Therefore, although with missing data some information is irretrievably lost, we can often salvage a lot.

The success of the salvage operation depends on:

1. whether we can identify plausible reasons for the data being missing (called *missingness mechanisms*), and
2. the sensitivity of the conclusions to different missingness mechanisms.

A possible systematic approach is the following:

A systematic approach

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Investigators discuss possible missingness mechanisms, say A–E possibly informed by a blind review of the data, and consider their plausibility. Then

1. Under most plausible mechanism A, perform valid analysis, draw conclusions
2. Under similar mechanisms, B–C, perform valid analysis, draw conclusions
3. Under least plausible mechanisms, D–E, perform valid analysis, draw conclusions

Investigators discuss the implications, and arrive at a valid interpretation of the trial.

This approach broadly agrees with the E9 guideline.

Completers analysis

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● Completers analysis

● Simple (marginal) mean imputation

● Reviewer trial

● Regression mean imputation

● Reviewer Trial: regression mean imputation

● Last (Baseline) Observation Carried Forward (LOCF)

● Reviewer trial: BOCF

● General comments

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	Variables	
Unit	1	2
1	3.4	5.67
2	3.9	4.81
3	2.6	4.93
4	1.9	6.21
5	2.2	6.83
6	3.3	5.61
7	1.7	5.45
8	2.4	4.94
9	2.8	5.73
10	3.6	.

- Completers analysis deletes all units with incomplete data.
- In RCTs with single follow-up, OK if baseline variables predictive of outcome & missing data included.
- With longitudinal follow-up, likely both biased and inefficient.

Simple (marginal) mean imputation

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8	2.4	4.94
9	2.8	5.73
10	3.6	5.58

- Missing observations replaced by observed mean *for that variable*
- Inappropriate for categorical variables

- Reduces associations in data
- Variance underestimated

Reviewer trial

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Graphs by Training package

Treatment effect: 0.220, SE 0.059, $p < 0.001$

Regression mean imputation

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7	1.7	5.45
8	2.4	4.94
9	2.8	5.73
10	3.6	5.24

- Use regression, here OLS:
 $V_2 = \alpha + \beta V_1 + e$
- Using units 1–9 we get:
 $\hat{V}_2 = 6.56 - 0.366 \times (V_1)$.
- For unit 10 this gives
 $6.56 - 0.366 \times (3.6) = 5.24$.
- Now obtain unbiased estimators of means, associations, under MAR
- Variance still (often markedly) underestimated

Reviewer Trial: regression mean imputation

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Effect estimate: 0.237; SE: 0.0575, $p < 0.001$

Last (Baseline) Observation Carried Forward (LOCF)

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Time	Unit	
	1	2
1	2.1	3.4
2	3.8	3.9
3	3.8 ←.	2.6
4	3.8 ←.	1.9
5	3.8 ←.	2.2
6	3.8 ←.	2.2 ←.
⋮	⋮	⋮

- Makes strong, implausible assumptions
- Imputes a degenerate distribution
- Means and variances wrong
- In general neither conservative or liberal; bias depends on *unknown* treatment effect!
- See [8, 6, 2]

Baseline carried forward is a (worse) variant of LOCF

Reviewer trial: BOCF

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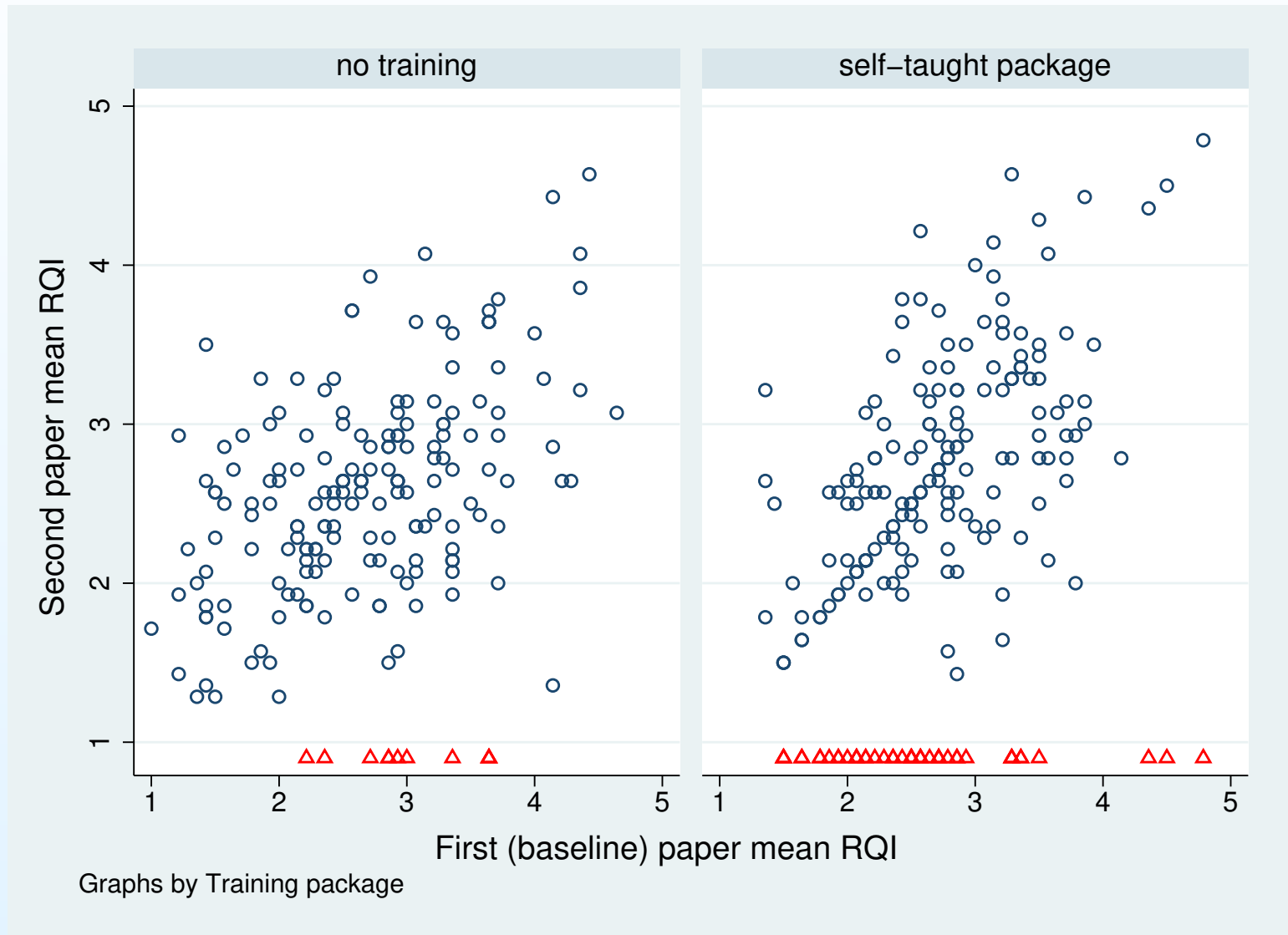
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Intervention effect: 0.153 , $SE=0.061$, $p = 0.013$

General comments

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MI: example

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Discussion

1. Single imputation methods generally put the ‘cart before the horse’—that is they adopt a simple approach to ‘complete’ the dataset, and then look for arguments to justify this.

Instead, we should — in consultation with those involved in the trial (particularly those collecting the data) — make contextually appropriate assumptions and then use a statistically principled method to draw inferences under those assumptions.

2. Further, when we use a single imputation method, our analysis cannot distinguish between observed and imputed data — they have the same status.

The consequence is that the standard error is underestimated, and may often be smaller than if we had no missing values!

A better starting assumption: Missing At Random (MAR)

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- A better starting assumption: Missing At Random (MAR)

- Example: Income and Job Type; true mean £45,000

- A note on the consequence of Missing At Random in regression

Multiple Imputation under Missing At Random

MI: example

Multiple Imputation under Missing Not At Random

Discussion

A more reasonable starting assumption is that, given baseline and early follow-up data, the distribution of outcome data is the same *whether or not we observe it*.

In Rubin's (1976) taxonomy of missing data [9], this is called 'Missing At Random'¹.

It corresponds to saying that *given the observed data* the probability of data being missing does not depend on the value of that data.

¹If the chance of the data being missing is unrelated to our inferential question (e.g. intervention effect) the data can be viewed as Missing Completely At Random (MCAR)

Example: Income and Job Type; true mean £45,000

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- A better starting assumption: Missing At Random (MAR)

- **Example: Income and Job Type; true mean £45,000**

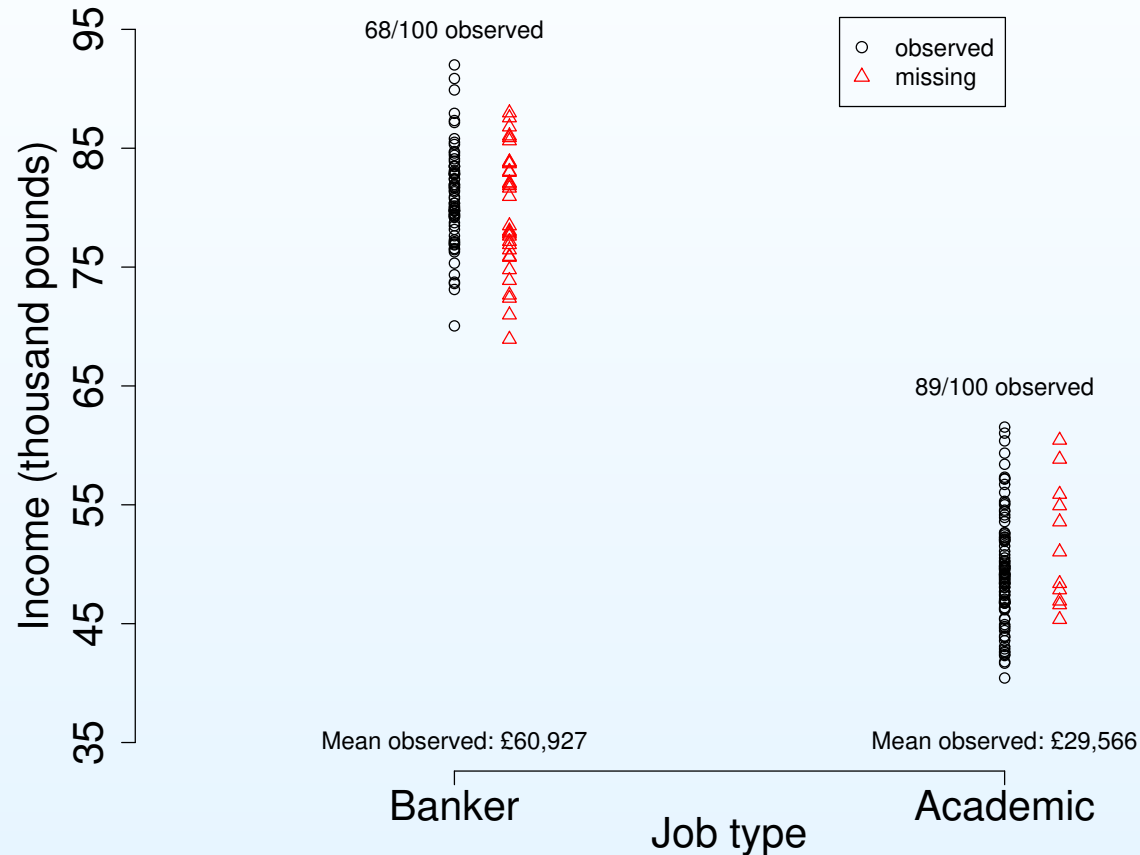
- A note on the consequence of Missing At Random in regression

Multiple Imputation under Missing At Random

MI: example

Multiple Imputation under Missing Not At Random

Discussion



Observed income: £43,149.

$$\text{MAR estimate: } \frac{100 \times 60,927 + 100 \times 29,566}{200} = £45,246$$

A note on the consequence of Missing At Random in regression

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- A better starting assumption: Missing At Random (MAR)
- Example: Income and Job Type; true mean £45,000
- A note on the consequence of Missing At Random in regression

Multiple Imputation under Missing At Random

MI: example

Multiple Imputation under Missing Not At Random

Discussion

- If the dependent variable is MAR *given the covariates* in a regression, then we get valid inference (the reverse is not true).
- In a RCT with longitudinal follow-up, if all observed repeated outcome measures are included in the model alongside the covariates, again we get valid inference under the MAR assumption.
- However, we need to choose the model carefully (cf Ch 2, [4], and impose minimal structure on the mean and covariance of the data.
- In many cases (e.g. GLMs), we may not want to include all the variables needed for a plausible MAR assumption in our model.
- In these settings, and when we move beyond MAR, of Multiple Imputation (MI) provides a practical approach.

Intuition for MI

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● Intuition for MI

- The idea:
- The key idea
- Intuition behind multiple imputation: 1
- Intuition behind multiple imputation: 2

MI: example

Multiple Imputation under Missing Not At Random

Discussion

Suppose our data set has variables X, Y with some Y values MAR given X . Using only subjects with both observed we can get valid estimates of the regression of Y on X .

We now show how MI works in this setting to also arrive at valid inference.

The attraction of MI for trials is that

1. we can include additional variables, not in our main analysis model, to improve the plausibility of MAR, and
2. we can explore the robustness of our inferences to departures from MAR.

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MI: example

Multiple Imputation under Missing Not At Random

Discussion

The idea:

1. Fit the regression of Y on X
2. Use this to impute the missing Y
3. With this completed data set, calculate our statistic of interest (e.g. sample mean, variance, regression of X on Y , regression of Y on X).

As we can only ever know the *distribution* of missing data (given observed), steps 2 & 3 have to be repeated, and the results averaged in some way.

The key idea

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MI: example

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The key idea is to use the data from individuals where both Y and X are observed to learn about the relationship between Y and X .

Then, if \tilde{X} represents the vector of X values from individuals with missing Y 's, we use this relationship to complete the data set by drawing the missing observations from $Y_M | \tilde{X}$.

We do this K (typically $\gg 5$) times, giving rise to K complete data sets.

We analyse each of these data sets in the usual way.

We combine the results using particular rules.

Suppose the analysis of interest is calculating the marginal mean of Y , or regressing X on Y .

Intuition behind multiple imputation: 1

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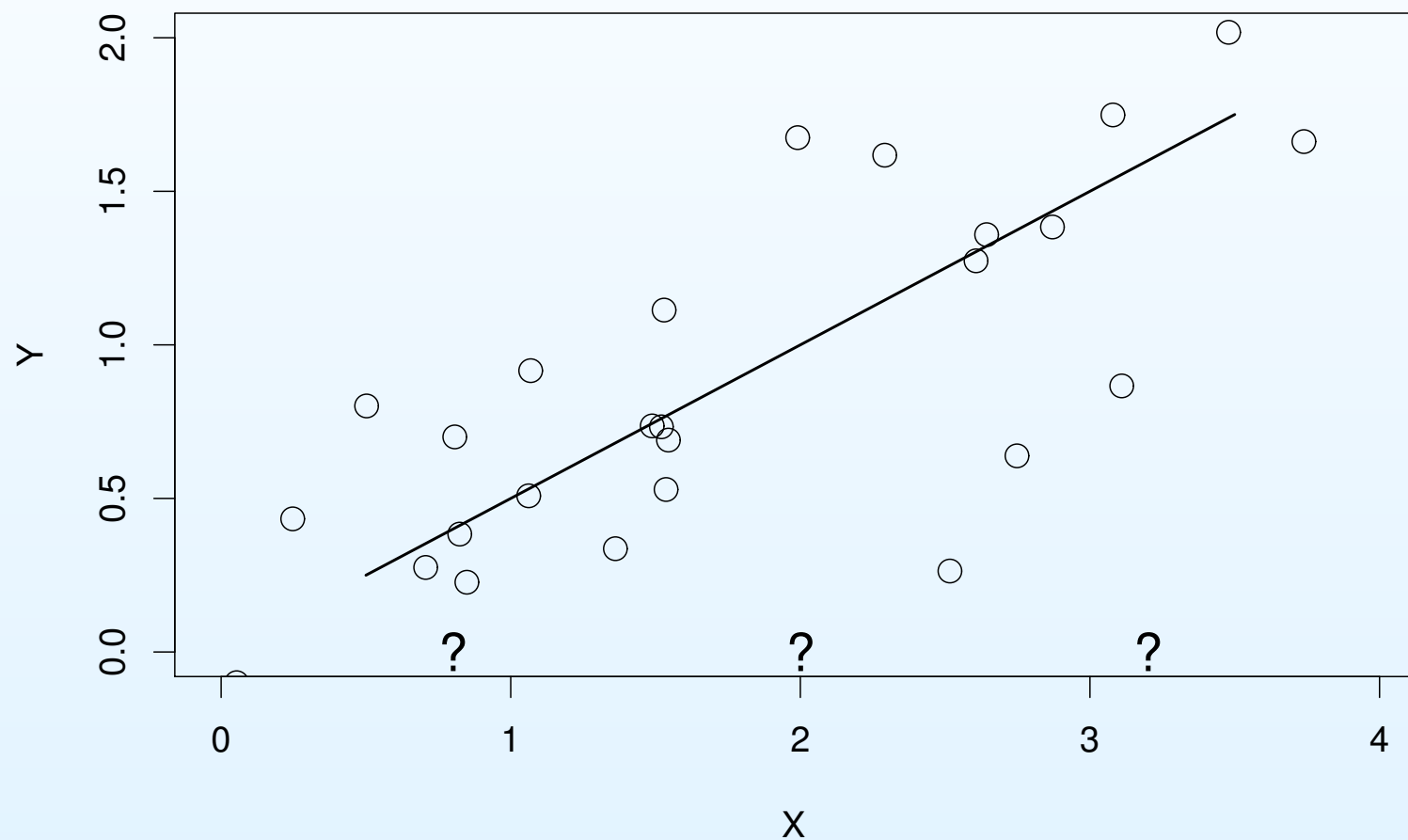
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- **Intuition behind multiple imputation: 1**
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MI: example

Multiple Imputation under Missing Not At Random

Discussion

Model observed pairs, denoted (Y_O, X) .



Intuition behind multiple imputation: 2

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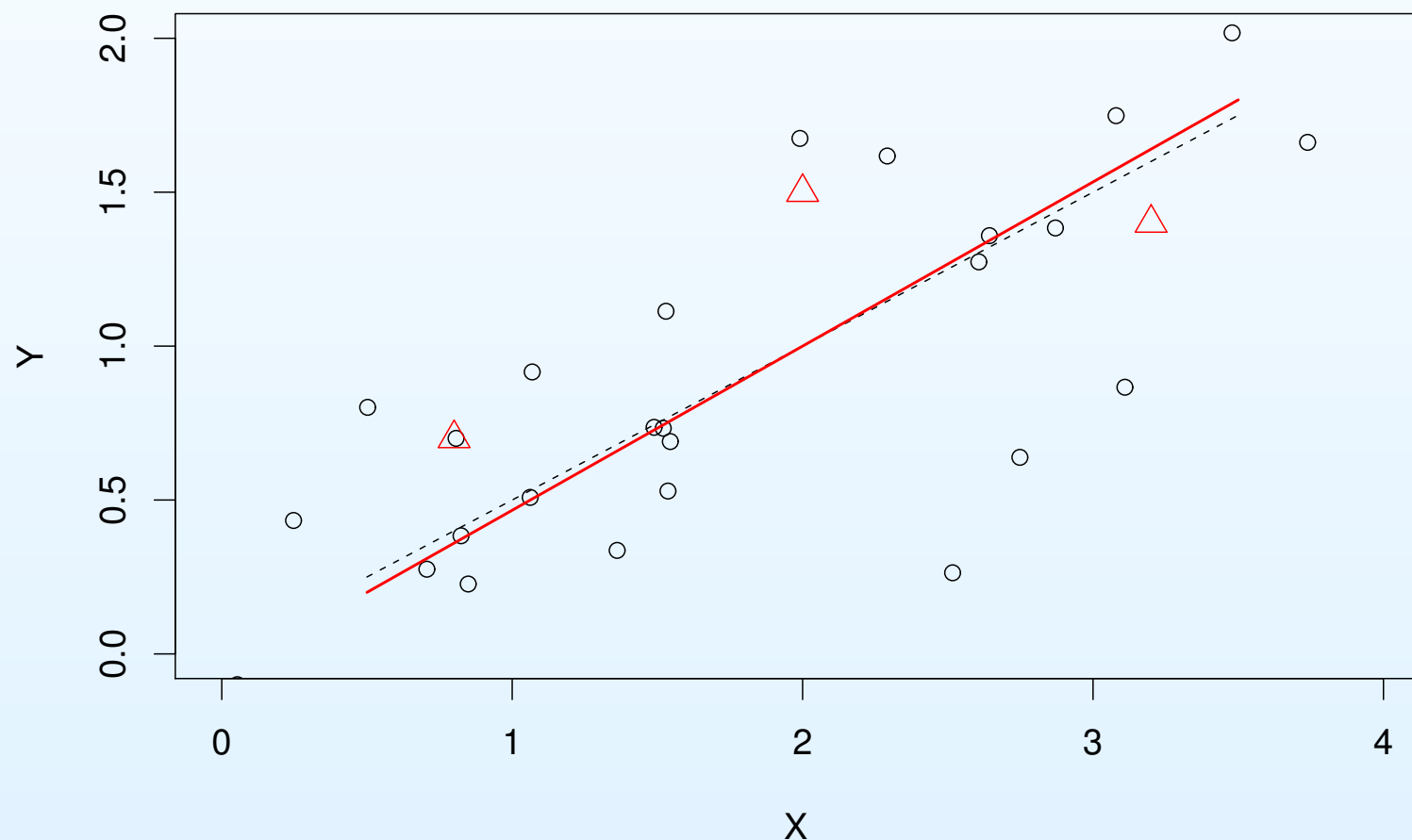
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MI: example

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Draw Y_M by (i) drawing from distribution of regression line (this gives us the solid (red) line below) (ii) then drawing from variability about that line.



Results of multiple imputation:

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● Results of multiple imputation:

● Notation for analyses of K imputed datasets

● Rubin's MI rules

● MI variance rule

● Inference for θ

● Video of multiple imputation

● MI under MAR for the reviewer data

● Comparison of MI and Complete Cases

Multiple Imputation under Missing Not At Random

Discussion

	Data		Imputation 1		Imputation 2		Imputation 3		Imputation 4	
Unit	Y	X	Y	X	Y	X	Y	X	Y	X
1	1.1	3.4	1.1	3.4	1.1	3.4	1.1	3.4	1.1	3.4
2	1.5	3.9	1.5	3.9	1.5	3.9	1.5	3.9	1.5	3.9
3	2.3	2.6	2.3	2.6	2.3	2.6	2.3	2.6	2.3	2.6
4	3.6	1.9	3.6	1.9	3.6	1.9	3.6	1.9	3.6	1.9
5	0.8	2.2	0.8	2.2	0.8	2.2	0.8	2.2	0.8	2.2
6	3.6	3.3	3.6	3.3	3.6	3.3	3.6	3.3	3.6	3.3
7	3.8	1.7	3.8	1.7	3.8	1.7	3.8	1.7	3.8	1.7
8	?	0.8	0.2	0.8	0.8	0.8	0.3	0.8	2.3	0.8
9	?	2.0	1.7	2.0	2.4	2.0	1.8	2.0	3.5	2.0
10	?	3.2	2.7	3.2	2.5	3.2	1.0	3.2	1.7	3.2

Notation for analyses of K imputed datasets

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Multiple Imputation under Missing Not At Random

Discussion

Analysing each imputed (i.e. 'completed') dataset the usual way (i.e. using the model intended if there were no missing data) gives us K estimates of the original quantity of interest, say θ . Denote these estimates $\hat{\theta}_1, \dots, \hat{\theta}_K$.

The analysis of each imputed data set will also give an estimate of the variance of the estimate $\hat{\theta}_k$, say $\hat{\sigma}_k^2$. Again, this is the usual variance estimate from the model.

Rubin's MI rules

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Rubin's MI rules combine these quantities to get our overall estimate and its variance using certain rules.

Let the multiple imputation estimate of θ be $\hat{\theta}_{MI}$. Then

$$\hat{\theta}_{MI} = \frac{1}{K} \sum_{k=1}^K \hat{\theta}_k.$$

MI variance rule

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Further define the within-imputation and between-imputation components of variance by

$$\hat{\sigma}_w^2 = \frac{1}{K} \sum_{k=1}^K \hat{\sigma}_k^2, \quad \text{and} \quad \hat{\sigma}_b^2 = \frac{1}{K-1} \sum_{k=1}^K (\hat{\theta}_k - \hat{\theta}_{MI})^2,$$

Then

$$\hat{\sigma}_{MI}^2 = \left(1 + \frac{1}{K}\right) \hat{\sigma}_b^2 + \hat{\sigma}_w^2,$$

so the estimated standard error of $\hat{\theta}_{MI}$ is $\hat{\sigma}_{MI}$.

Inference for θ

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To test the null hypothesis $\theta = \theta_0$, compare

$$\frac{\hat{\theta}_{MI} - \theta_0}{\hat{\sigma}_{MI}} \quad \text{to} \quad t_\nu,$$

where

$$\nu = (K - 1) \left[1 + \frac{\hat{\sigma}_w^2}{(1 + 1/K)\hat{\sigma}_b^2} \right]^2.$$

Thus, if $t_{\nu,0.975}$ is the 97.5% point of the t distribution with ν degrees of freedom, the 95% confidence interval is

$$(\hat{\theta}_{MI} - \hat{\sigma}_{MI}t_{\nu,0.975}, \quad \hat{\theta}_{MI} + \hat{\sigma}_{MI}t_{\nu,0.975})$$

Video of multiple imputation

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MI: example

- Results of multiple imputation:
- Notation for analyses of K imputed datasets
- Rubin's MI rules
- MI variance rule
- Inference for θ
- **Video of multiple imputation**
- MI under MAR for the reviewer data
- Comparison of MI and Complete Cases

Multiple Imputation under Missing Not At Random

Discussion

This video illustrates imputation of missing data using an asthma study.

The outcome is lung function 12 weeks after randomisation, and we adjust for baseline and estimate the treatment effect.

MI under MAR for the reviewer data

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Comparison of MI and Complete Cases

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Discussion

Analysis	Est	SE	p-value	95% CI
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Missing at random

Observed data	0.24	0.070	0.001	(0.10, 0.38)
MI under MAR, $K = 20$	0.23	0.071	0.002	(0.09, 0.37)

MNAR in the reviewer study

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● **MNAR in the reviewer study**

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Discussion

The practical sheet outlines why it is plausible that the missing RQIs in the reviewer trial are not MAR.

An attractive option is to elicit expert opinion on the difference between the observed and missing values. This can be viewed as attempting to quantify how experts would implicitly adjust their interpretation of the study due to the missing data. See [11, 7].

Prior elicitation for reviewer trial

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For the peer review study, [13] devised a questionnaire, designed to elicit experts' prior belief about the difference, δ , between the average missing and average observed review quality index in this study.

This was completed by 2 investigators and 20 editors and staff at the *British Medical Journal*.

The resulting distribution is negatively skewed, with mean -0.21 and SD 0.46 .

Unfortunately, it was not possible to collect information about how this was influenced by the randomised intervention (i.e. whether δ_N and δ_S have the same mean, and what their correlation is).

Elicitation of expert opinion

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We adopt a bivariate normal model approximation to the prior:

$$\begin{pmatrix} \delta_N \\ \delta_S \end{pmatrix} \sim N \left[\begin{pmatrix} -0.21 \\ -0.21 \end{pmatrix}, 0.46^2 \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix} \right]. \quad (1)$$

Because it was not possible to elicit a prior on ρ from the experts, we analyse the data with $\rho = 0$; assuming $\rho \geq 0$, this choice gives the largest standard error for the intervention effect.

Model

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Given a draw (δ_N, δ_S) from this distribution the *pattern mixture* model is

$$\text{RQI}_i = \beta_0 + \beta_1 \text{self-taught}_i + \beta_2 \text{baseline RQI}_i + e_i \quad \text{if RQI}_i \text{ observed,}$$

$$\begin{aligned} \text{RQI}_i = (\beta_0 + \delta_N) + (\beta_1 + \delta_S - \delta_N) \text{self-taught}_i \\ + \beta_2 \text{baseline RQI}_i + e_i \quad \text{if RQI}_i \text{ missing,} \end{aligned}$$

$$e_i \stackrel{iid}{\sim} N(0, \sigma^2). \quad (2)$$

Thus the mean review quality, relative to that in the observed data, is changed by δ_N in the no intervention arm and δ_S in the self-taught arm.

Using this information with MI

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We proceed as follows:

1. Fit the imputation model to the observed data. For $k = 1, \dots, K$, draw from the posterior distribution of the imputation model parameters $\theta^k = (\beta_0^k, \beta_1^k, \beta_2^k, \sigma^{2,k})$.
2. Draw (δ_N^k, δ_S^k) from (1)
3. Using the draws obtained in steps 1 and 2, impute the missing RQI_i^k using (2).

Steps 1–3 are repeated to create $K = 20$ imputed data sets. Then we fit the substantive model to each imputed data set and apply Rubin's rules.

One of the MNAR imputed datasets

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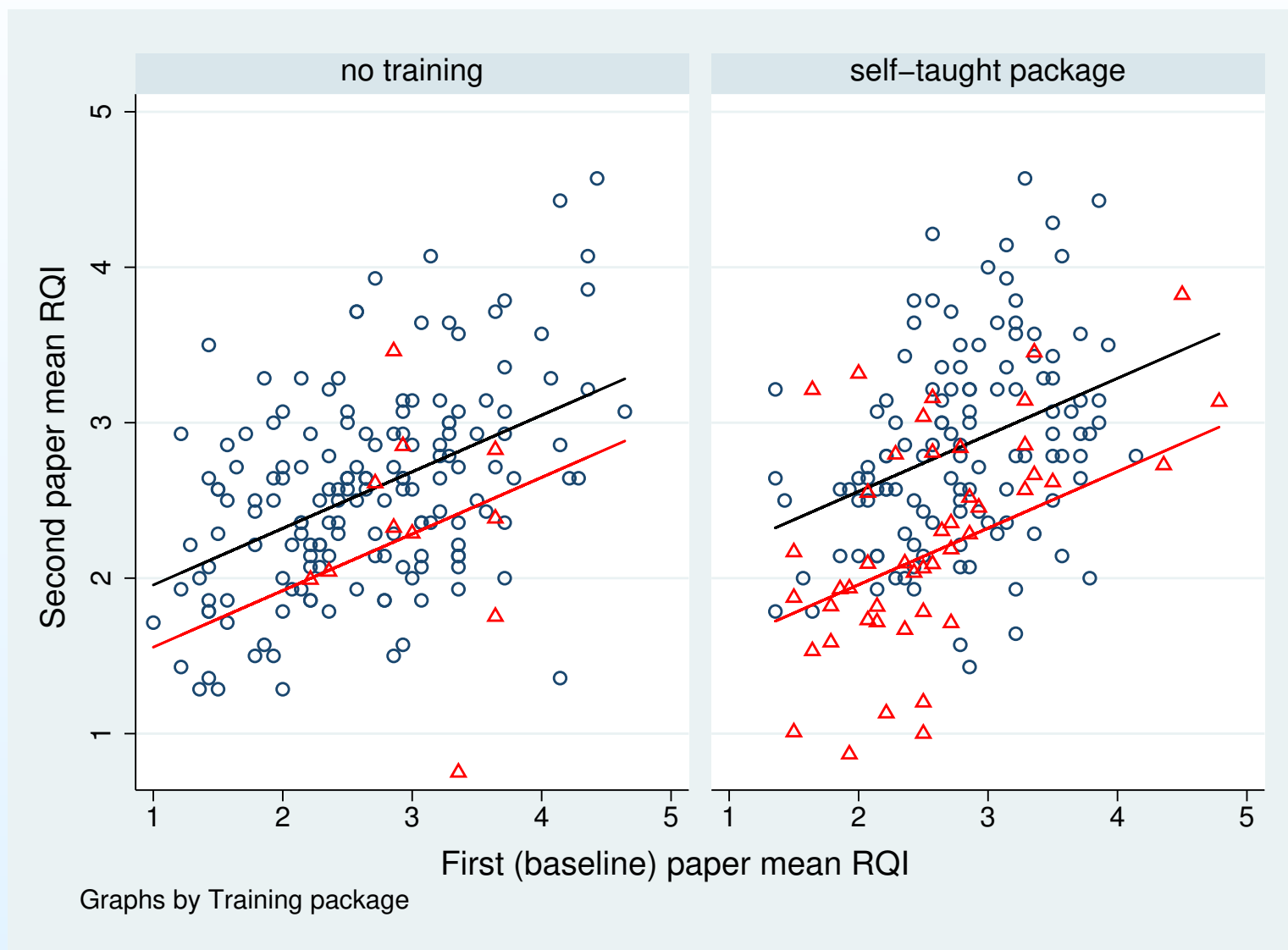
Multiple Imputation under Missing At Random

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Comparison of results

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Analysis	Est	SE	p-value	95% CI
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Missing at random

Observed data	0.24	0.070	0.001	(0.10, 0.38)
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MI under MAR, $K = 20$	0.23	0.071	0.002	(0.09, 0.37)
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Missing not at random

Experts' Prior:	0.21	0.178	0.250	(-0.158, 0.575)
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Summary & Discussion

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● **Summary & Discussion**

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- Missing data introduce ambiguity into the analysis, beyond the familiar sampling imprecision.
- Extra assumptions about the missingness mechanism are needed; these assumptions can rarely be verified from the data at hand.
- Sensitivity analysis is therefore important.
- Single imputation approaches should be avoided.
- MAR is a natural assumption for the primary analysis.
- Using MI for inference under MAR allows us to use all the longitudinal follow-up information and all baseline variables that are predictive of missing values.
- MI can also be used for sensitivity analysis, using the pattern mixture approach as illustrated above. More details and examples in [3]

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