EP16: Missing Values in Clinical Research: Multiple Imputation

3. Analysis & Pooling

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Analysis Step

Multiple imputed datasets:

X_1	X_2	X_3	X_4
1.4	9.2	1.8	2.0
0.5	12.4	2.3	0.1
-0.5	10.7	2.6	-1.6
⋮	⋮	⋮	⋮

X_1	X_2	X_3	X_4
1.4	13.3	1.8	2.0
0.5	12.4	2.1	0.6
-0.5	10.2	2.6	-1.7
⋮	⋮	⋮	⋮

X_1	X_2	X_3	X_4
1.4	10.0	1.8	2.0
0.5	12.4	2.2	-1.4
-0.5	8.6	2.6	-1.0
⋮	⋮	⋮	⋮

Analysis Step

Analysis model of interest, e.g.,

$$x_1 = \beta_0 + \beta_1 x_2 + \beta_2 x_3 + \beta_3 x_4 + \varepsilon$$

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Multiple sets of results:

	est.	se
β_0	-0.15	0.22
β_1	0.16	0.02
β_2	-0.59	0.03
β_3	0.28	0.03

	est.	se
β_0	0.19	0.16
β_1	0.14	0.01
β_2	-0.59	0.03
β_3	0.20	0.03

	est.	se
β_0	0.04	0.22
β_1	0.14	0.01
β_2	-0.58	0.03
β_3	0.28	0.03

Pooling

Why pooling?

Recall from Section 1:
We need to represent missing values by a **number of imputations**.
➡ *m* imputed datasets

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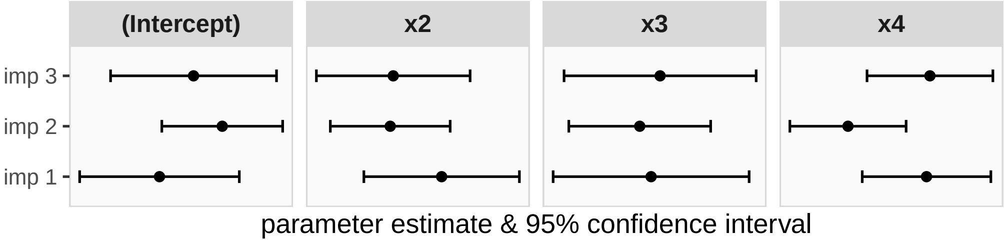
We want to **summarize** the results and describe **how (much) the results vary** between the imputed datasets.

Pooling

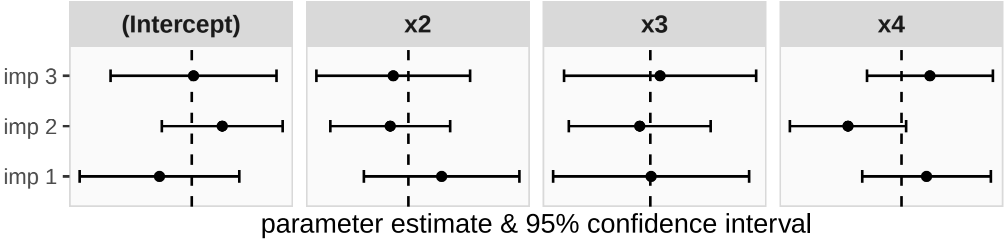
In the results from multiply imputed data there are **two types of variation/uncertainty**:

- **within** imputation (represented by the confidence intervals)
- **between** imputation (horizontal shift between results)



Pooling

To summarize the results, we can take the mean of the results from the separate analyses. This is the **pooled point estimate**.



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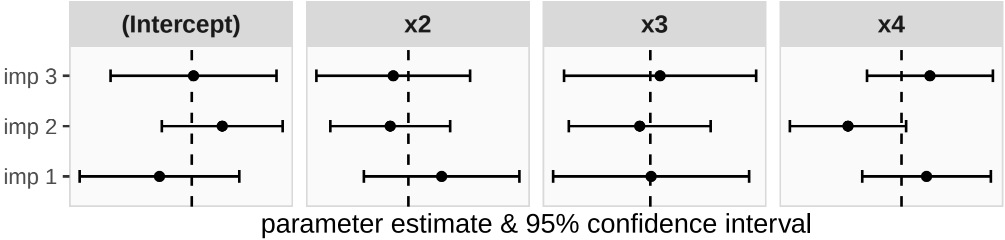

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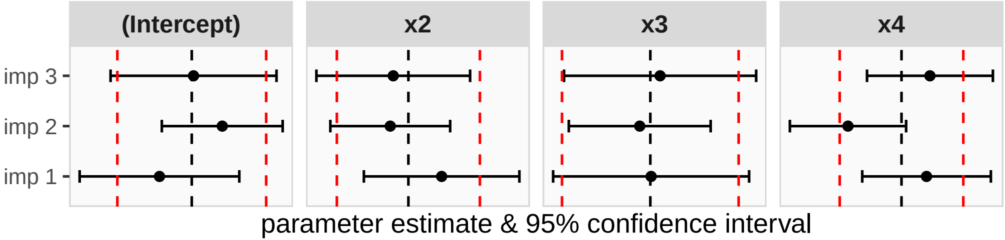


But does the same work for the standard error (or bounds of the CIs)?

The averaged CI's (marked in red) seem to underestimate the total variation (within + between).

Rubin's Rules

The most commonly used method to pool results from analyses of multiply imputed data was introduced by Rubin (1987), hence **Rubin's Rules**.

Notation:
m: number of imputed datasets
Q_ℓ: quantity of interest (e.g., regr. parameter β) from ℓ-th imputation
U_ℓ: variance of Q_ℓ (e.g., $var(\beta) = se(\beta)^2$)

Pooled parameter estimate:

$$\bar{Q} = \frac{1}{m}\sum_{\ell=1}^{m}\hat{Q}_\ell$$

Rubin's Rules

The **variance** of the pooled parameter estimate is calculated from the **within and between imputation variance**.

Average within imputation variance:

$$\bar{U} = \frac{1}{m} \sum_{\ell=1}^{m} \hat{U}_\ell$$

Between imputation variance:

$$B = \frac{1}{m-1} \sum_{\ell=1}^{m} \left(\hat{Q}_\ell - \bar{Q}\right)^T \left(\hat{Q}_\ell - \bar{Q}\right)$$

Total variance:

$$T = \bar{U} + B + B/m$$

Rubin's Rules

Confidence intervals for pooled estimates can be obtained using the **pooled standard error** $\sqrt{T}$ and a **reference** t **distribution** with degrees of freedom

$$\nu = (m-1)\left(1 + r_m^{-1}\right)^2,$$

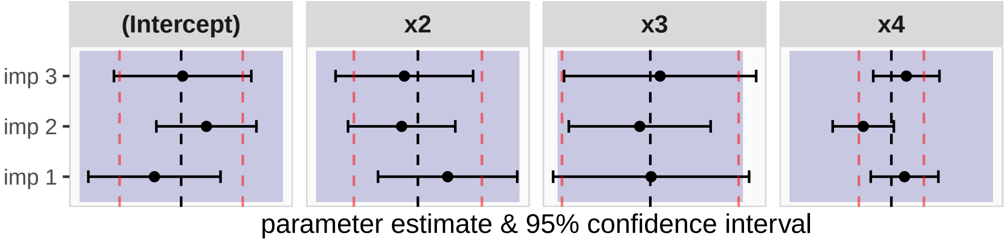
where $r_m = \frac{(B+B/m)}{\bar{U}}$ is the relative increase in variance that is due to the missing values.

The $(1-\alpha)$ **100% confidence interval** is then

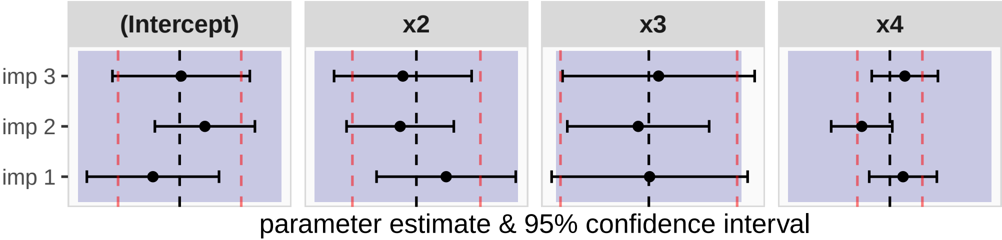
$$\bar{Q} \pm t_\nu(\alpha/2)\sqrt{T},$$

where t_ν is the $\alpha/2$ quantile of the t distribution with ν degrees of freedom.

Rubin’s Rules



Rubin's Rules



The corresponding **p-value** is the probability

$$Pr\left\{F_{1,\nu} > \left(Q_0 - \bar{Q}\right)^2 / T\right\},$$

where $F_{1,\nu}$ is a random variable that has an F distribution with 1 and ν degrees of freedom, and Q_0 is the null hypothesis value (typically zero).

References

Rubin, D. B. (1987). *Multiple imputation for nonresponse in surveys.* Wiley. https://books.google.nl/books?id=0KruAAAAMAAJ