

Missing viral load measurements in HIV treatment trials: a comparison of approaches

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**Innovative Clinical
Trials Unit**

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Missing data are common in HIV treatment trials

Repeated measurements

In HIV treatment trials, viral load is measured repeatedly during follow-up, often over several scheduled visit windows, giving rise to missing data.

Dichotomisation

Viral load measurements are often dichotomised at a pre-specified threshold to flag raised measurements.

Composite endpoint

These raised measurement indicators are then combined to define virological failure.

Illustrative example

Attribute	Description
Population	Children and adolescents with HIV
Treatment	Experimental antiretroviral therapy vs standard care
Outcome	Virological failure: 2 consecutive viral loads ≥ 400 copies/mL, the first occurring at or after week 36
Intercurrent events & handling	None
Population-level summary	Difference in proportion with virological failure by 96 weeks

	Viral load result by visit window											Virological failure?
	0	4	12	24	36	48	60	72	84	96	108	
Patient 1	+	+	-	-	-	-	+	+	+	+	+	Yes
Patient 2	+	+	-	-	-	-	+	-	+	-	-	No
Patient 3	+	+	-	-	-	-	+	.	+	-	-	Not clear
Patient 4	+	+	-	-	-	-	+	.	.	.	.	Not clear

Virological failure – yes: patient 1 had a raised viral load at week 60, confirmed at week 72

Virological failure – no: patient 2 had isolated raised viral loads at weeks 60 and 84

How should data from patients 3 & 4 be handled?

	Viral load result by visit window											Virological failure?
	0	4	12	24	36	48	60	72	84	96	108	
Patient 1	+	+	-	-	-	-	+	+	+	+	+	Yes
Patient 2	+	+	-	-	-	-	+	-	+	-	-	No
Patient 3	+	+	-	-	-	-	+	.	+	-	-	Not clear
Patient 4	+	+	-	-	-	-	+	.	.	.	.	Not clear

Virological failure – not clear:

- Patient 3 had a raised viral load at week 60, could not be confirmed at week 72 due to missed visit; then an isolated raised viral load at week 84
- Patient 4 had a raised viral load at week 60, then was lost to follow-up

Simplest approach: complete case analysis (CCA)

	Viral load result by visit window											Virological failure?
	0	4	12	24	36	48	60	72	84	96	108	
Patient 1	+	+	-	-	-	-	+	+	+	+	+	Yes
Patient 2	+	+	-	-	-	-	+	-	+	-	-	No
Patient 3	+	+	-	-	-	-	+	.	+	-	-	Not clear
Patient 4	+	+	-	-	-	-	+	.	.	.	.	Not clear

} Included in analysis

} Excluded from analysis

Patients are excluded if any viral load measurement is missing

→ Lower efficiency, loss of power, potential bias depending on the missingness mechanism

Use available information: observed data analysis (ODA)

	Viral load result by visit window											Virological failure?
	0	4	12	24	36	48	60	72	84	96	108	
Patient 1	+	+	−	−	−	−	+	+	+	+	+	Yes
Patient 2	+	+	−	−	−	−	+	−	+	−	−	No
Patient 3	+	+	−	−	−	−	+	.	+	−	−	Not clear
Patient 4	+	+	−	−	−	−	+	.	.	.	.	Not clear

Use available information: observed data analysis (ODA)

	Viral load result by visit window											Virological failure?
	0	4	12	24	36	48	60	72	84	96	108	
Patient 1	+	+	-	-	-	-	+	+	+	+	+	Yes
Patient 2	+	+	-	-	-	-	+	-	+	-	-	No
Patient 3	+	+	-	-	-	-	+	↔	+	-	-	Yes
Patient 4	+	+	-	-	-	-	+	→				No

} Raised viral load at week 60, treated as confirmed at week 84

} Treated as isolated raised viral load at week 60

Gaps are 'ignored' when deriving the virological failure status

→ Uses more information than CCA, bias not clear

Multiple imputation (MI)

	Viral load result by visit window											Virological failure?
	0	4	12	24	36	48	60	72	84	96	108	
Patient 1	+	+	-	-	-	-	+	+	+	+	+	Yes
Patient 2	+	+	-	-	-	-	+	-	+	-	-	No
Patient 3	+	+	-	-	-	-	+	.	+	-	-	Not clear
Patient 4	+	+	-	-	-	-	+	.	.	.	.	Not clear

Multiple imputation (MI)

		Viral load result by visit window											Virological failure?
		0	4	12	24	36	48	60	72	84	96	108	
P _i	Patient 1	+	+	-	-	-	-	+	+	+	+	+	Yes
P _i	Patient 2	+	+	-	-	-	-	+	-	+	-	-	No
P _i	Patient 3	+	+	-	-	-	-	+	+	+	-	-	Yes
P _i	Patient 4	+	+	-	-	-	-	+	-	-	-	-	No

Treatment effect 1

Multiple imputation (MI)

		Viral load result by visit window											Virological failure?
		0	4	12	24	36	48	60	72	84	96	108	
Patient 1		+	+	-	-	-	-	+	+	+	+	+	Yes
Patient 2		+	+	-	-	-	-	+	-	+	-	-	No
Patient 3		+	+	-	-	-	-	+	+	+	-	-	Yes
Patient 4		+	+	-	-	-	-	+	+	-	-	-	Yes

Treatment effect 1

Treatment effect 2

Multiple imputation (MI)

Viral load result by visit window													Virological failure?
Viral load result by visit window													
Viral load result by visit window													
Viral load result by visit window													
P _i		0	4	12	24	36	48	60	72	84	96	108	Virological failure?
P _i	Patient 1	+	+	−	−	−	−	+	+	+	+	+	
P _i	Patient 2	+	+	−	−	−	−	+	−	+	−	−	No
P _i	Patient 3	+	+	−	−	−	−	+	−	+	−	−	Yes
P _i	Patient 4	+	+	−	−	−	−	+	−	+	+	−	Yes

Treatment effect 1

Treatment effect 2

Treatment effect 3

Multiple imputation (MI)

		Viral load result by visit window											Virological failure?
		0	4	12	24	36	48	60	72	84	96	108	
Patient 1		+	+	-	-	-	-	+	+	+	+	+	Yes
Patient 2		+	+	-	-	-	-	+	-	+	-	-	No
Patient 3		+	+	-	-	-	-	+	-	+	-	-	Yes
Patient 4		+	+	-	-	-	-	+	-	+	+	-	Yes

... M imputed datasets

Treatment effect 1

Treatment effect 2

Treatment effect 3

...

Treatment effect M

Pooled
treatment
effect, using
Rubin's rules

All missing viral load measurements are imputed using relationships with measurements at other visits (e.g. via multivariate imputation by chained equations, or MICE)

→ Uses all available information, allows for uncertainty, valid under MAR

Two approaches to MI

Dichotomisation of viral load measurements raises a further choice

Impute then dichotomise

IMPUTE Impute the missing continuous viral load measurements

DICHOTOMISE Apply the ≥ 400 c/mL threshold to the completed data to obtain the binary raised/not raised indicators

→ Candidate imputation models:

- **Linear regression (linreg)**: missing data (continuous) are imputed from linear regression models
- **Predictive mean matching (pmm)**: missing data (continuous) are imputed by borrowing observed values from patients with a similar predictive means

Dichotomise then impute

DICHOTOMISE Apply the ≥ 400 c/mL threshold to the observed data to obtain the binary raised/not-raised indicators

IMPUTE Impute the missing binary indicators

→ Candidate imputation model:

- **Logistic regression (logitreg)**: missing values (binary) are imputed from logistic regression imputation models

Aims of this work

A simulation study conducted to compare approaches for handling missing viral load data

1

Complete case analysis **cca**

Analysis restricted to only patients with complete follow-up viral load data

2

Observed data analysis **oda**

Pooled logistic regression using available information from all patients, without imputation

3

MI via multivariate imputation by chained equations

1. Impute then dichotomise

linreg and **pmm**

2. Dichotomise then impute

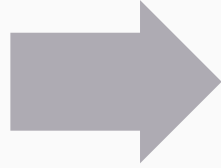
logitreg

Applied across all follow-up visits

Simulation procedure

Extract information from a real HIV treatment trial (ODYSSEY*)

- Missingness patterns
- Relationship between repeated viral load measurements



Perform simulations (5000 repetitions for each scenario)

- Simulate dataset containing full viral load measurements and treatment effect (**full data**)
- Make viral load data missing: MCAR & MAR mechanisms considered
- Handle the missing viral load using approaches under comparison

Methods are assessed on:

- Bias
- Standard errors (empirical, model-based)
- Coverage of 95% confidence intervals

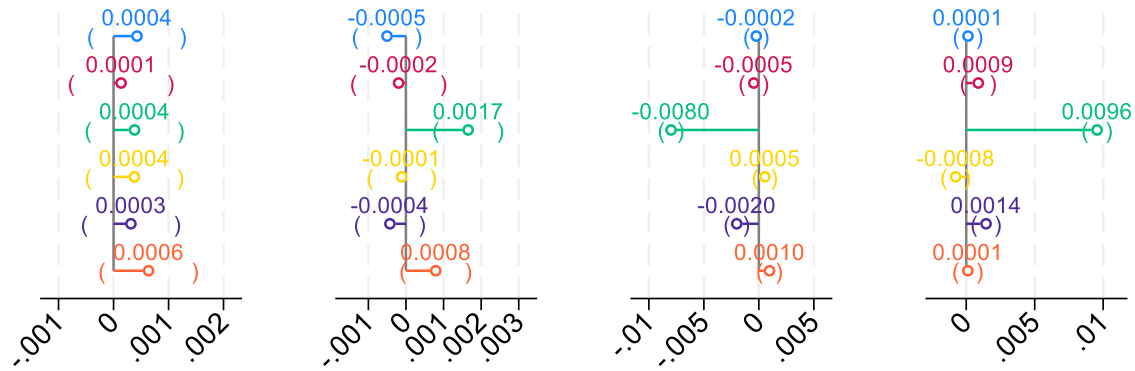
*Turkova A, White E, Mujuru HA, et al. Dolutegravir as first- or second-line treatment for HIV-1 infection in children. *N Engl J Med* 2021; 385: 2531–2543.

Bias

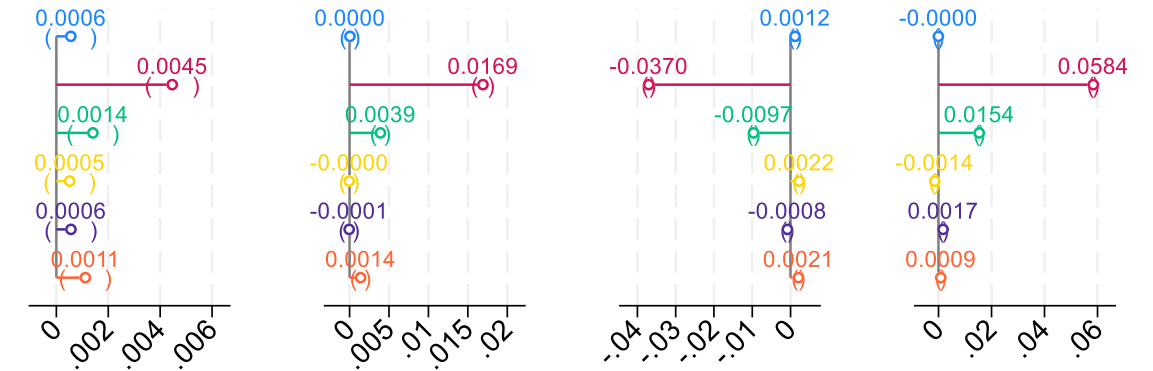
% incomplete cases soc:exp = 14:50 | 50:50 | 14:50 | 50:14

- full data
- cca
- oda
- linreg
- pmm
- logitreg

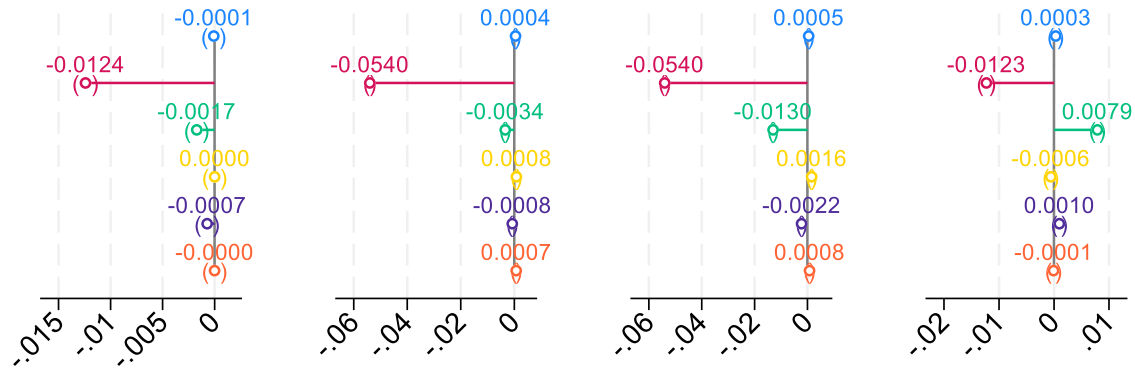
MCAR:MCAR



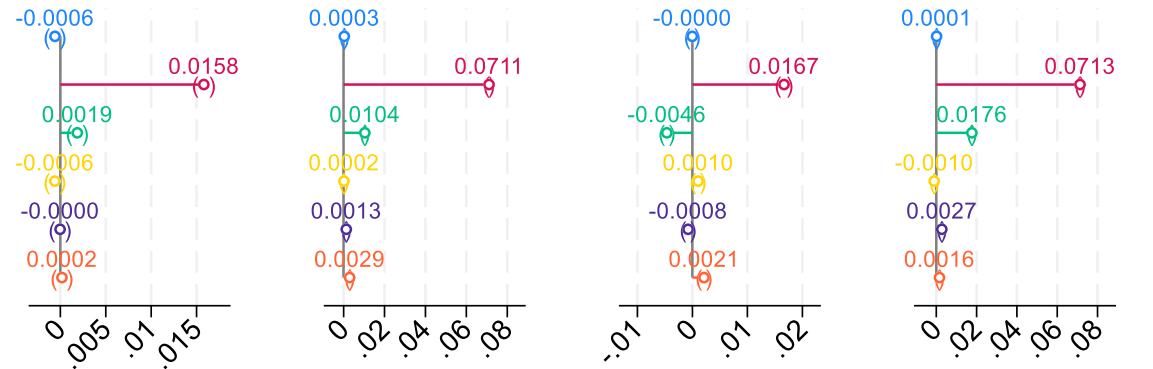
MAR:MAR



MCAR:MAR



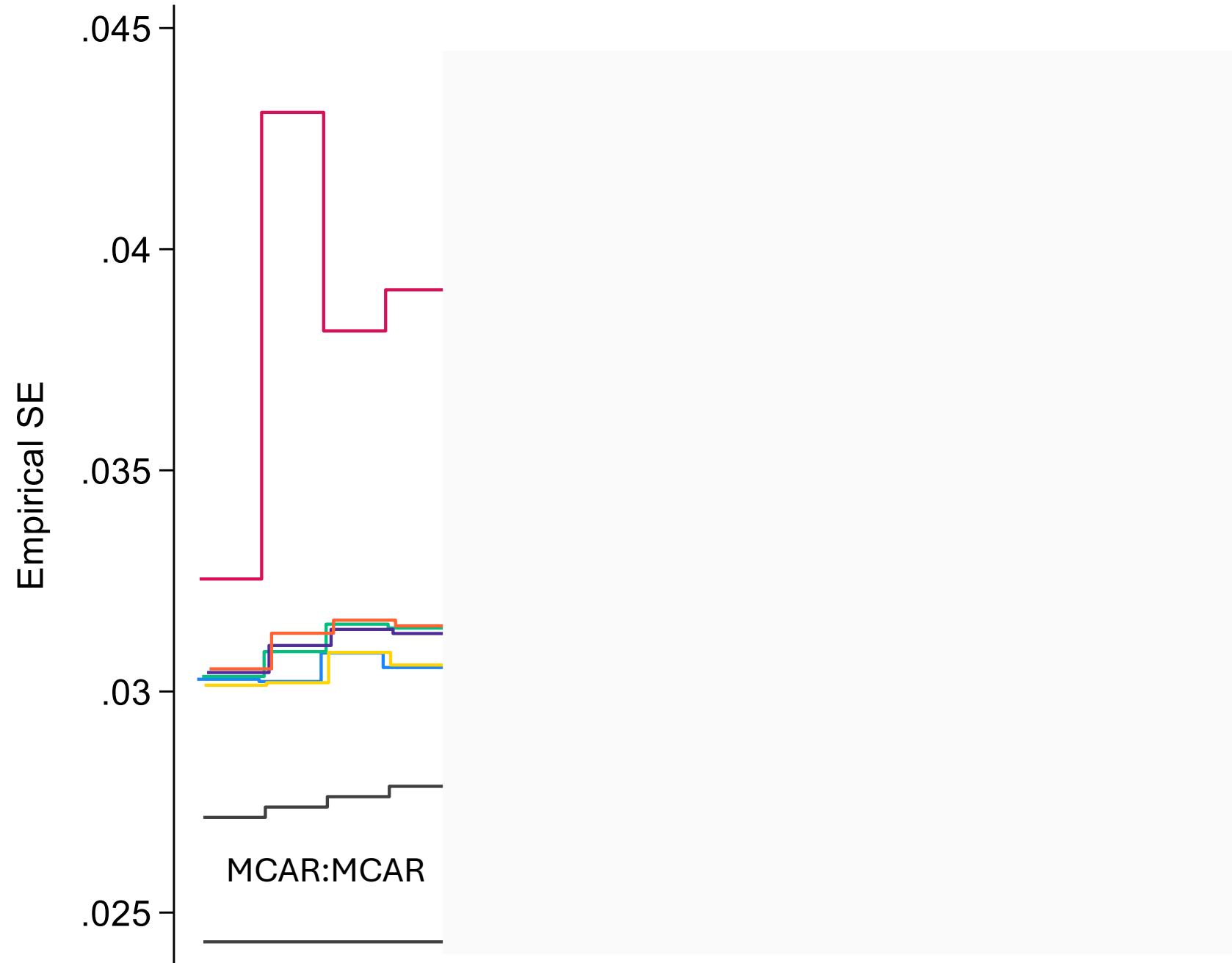
MAR:MCAR



Empirical SE

% incomplete cases soc:exp
14:14 | 50:50 | 14:50 | 50:14

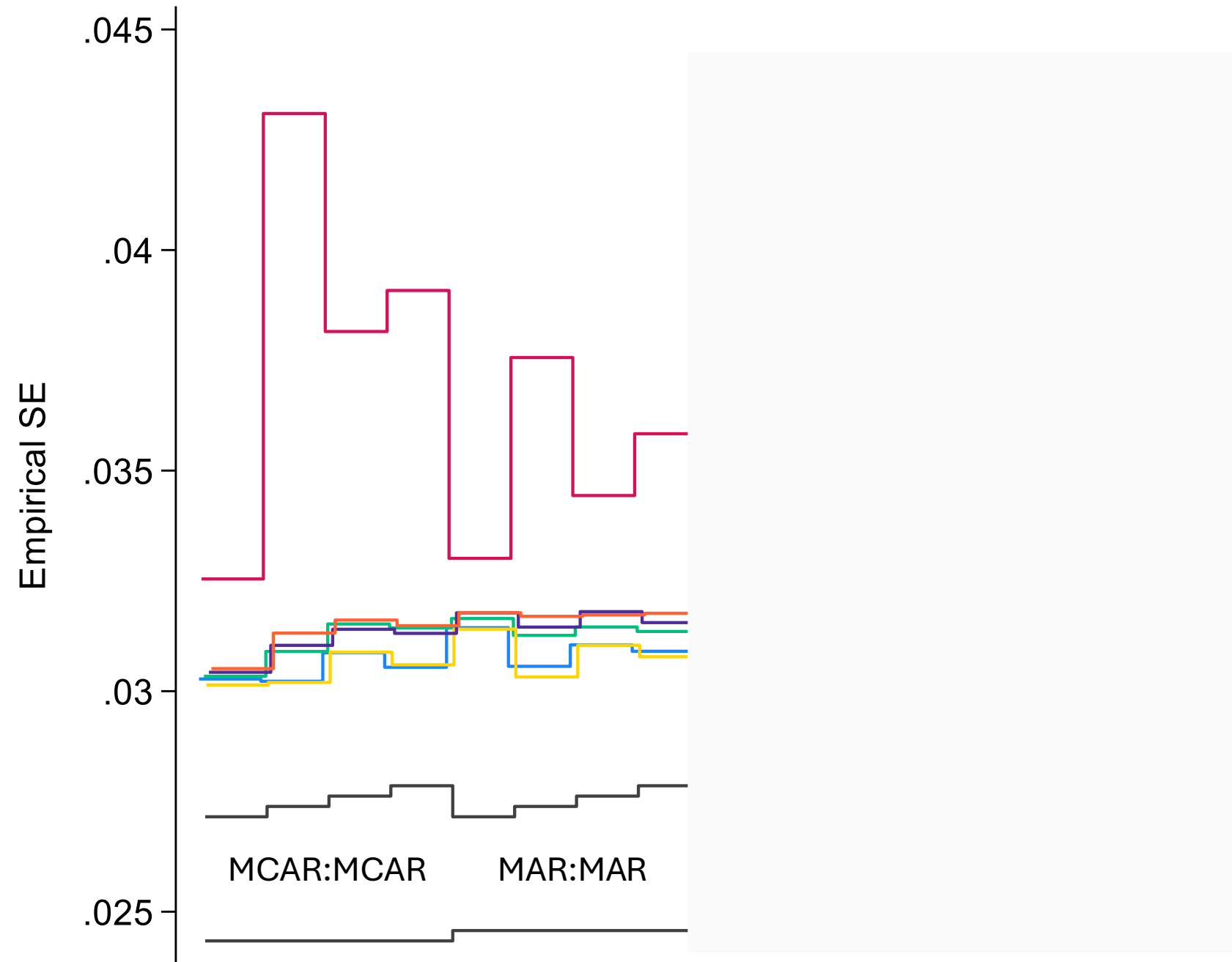
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— cca
— oda
— linreg
— pmm
— logitreg



Empirical SE

% incomplete cases soc:exp
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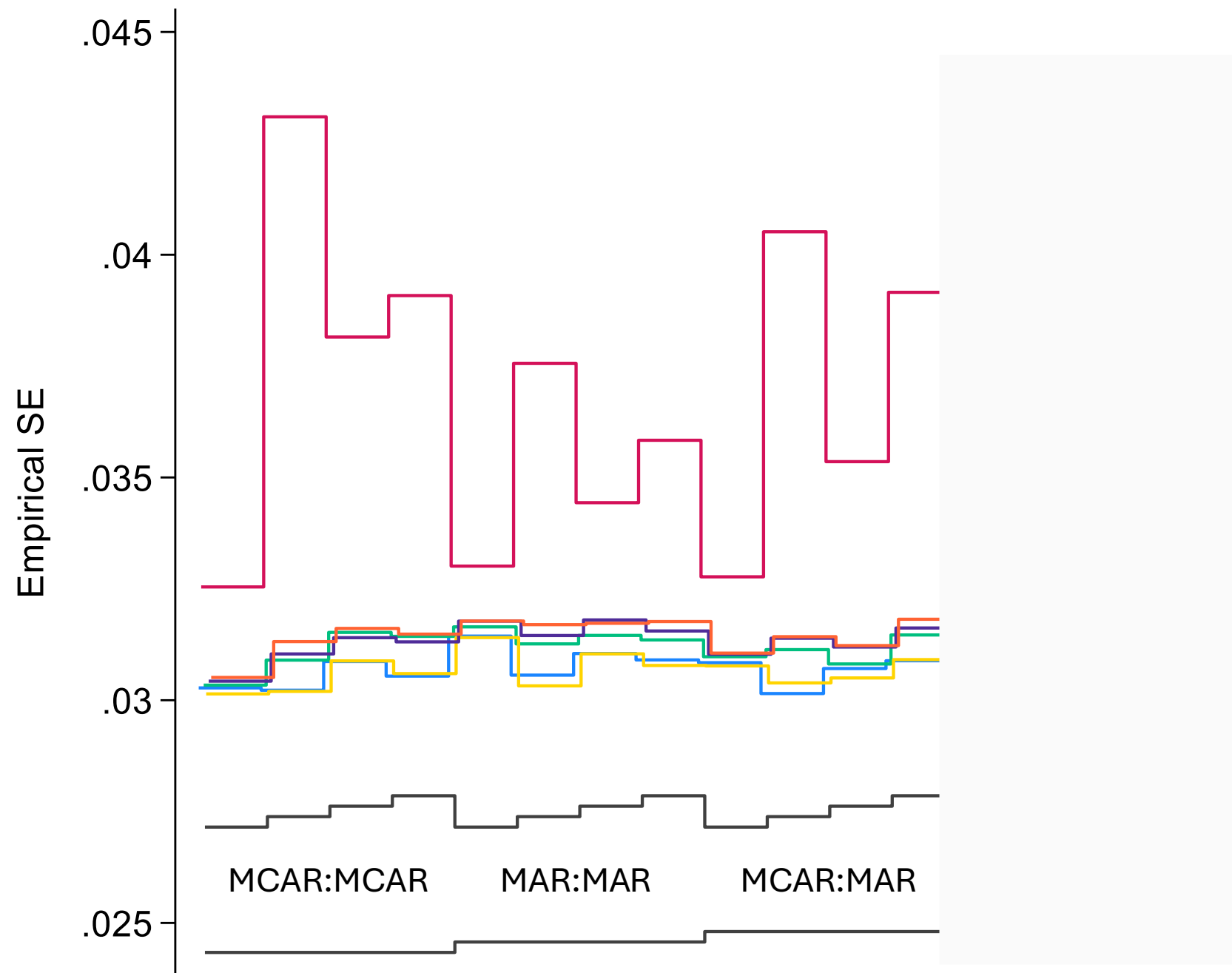
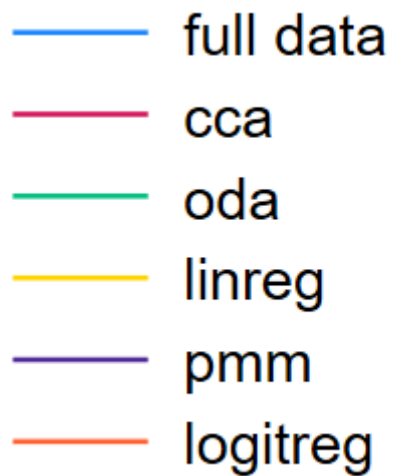
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— cca
— oda
— linreg
— pmm
— logitreg



Empirical SE

% incomplete cases soc:exp

14:14 | 50:50 | 14:50 | 50:14

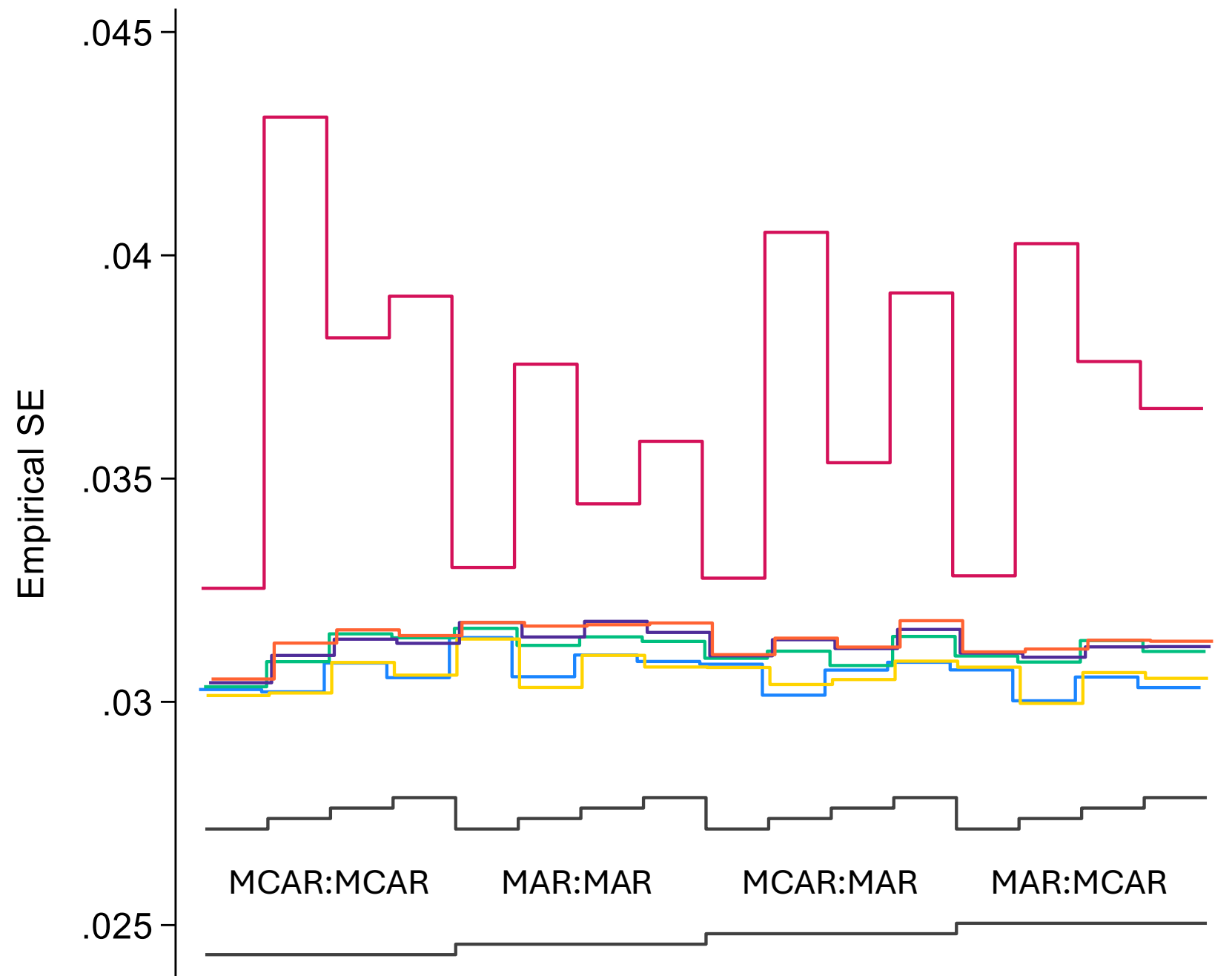


Empirical SE

% incomplete cases soc:exp

14:14 | 50:50 | 14:50 | 50:14

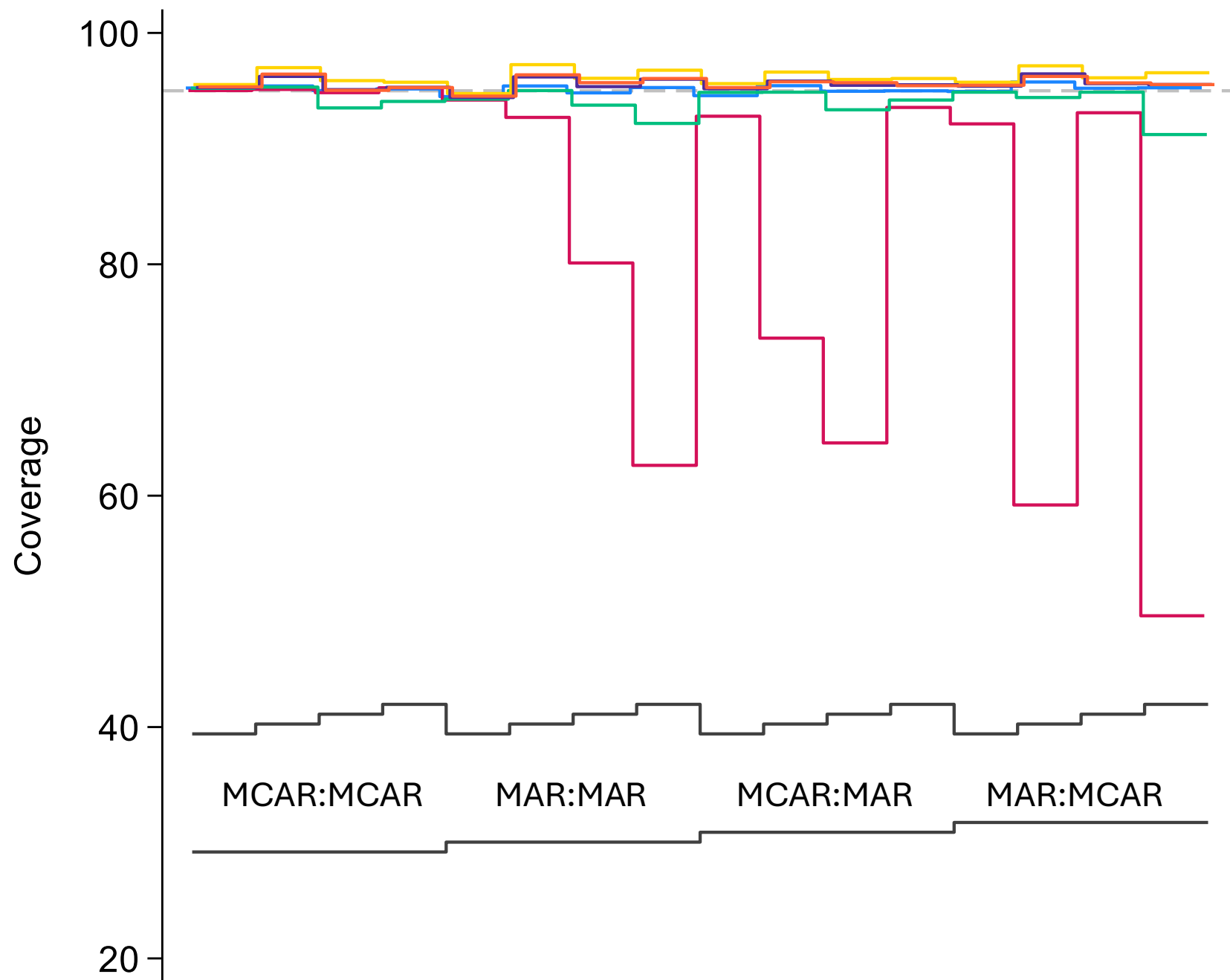
full data
cca
oda
linreg
pmm
logitreg



Coverage

% incomplete cases soc:exp
14:14 | 50:50 | 14:50 | 50:14

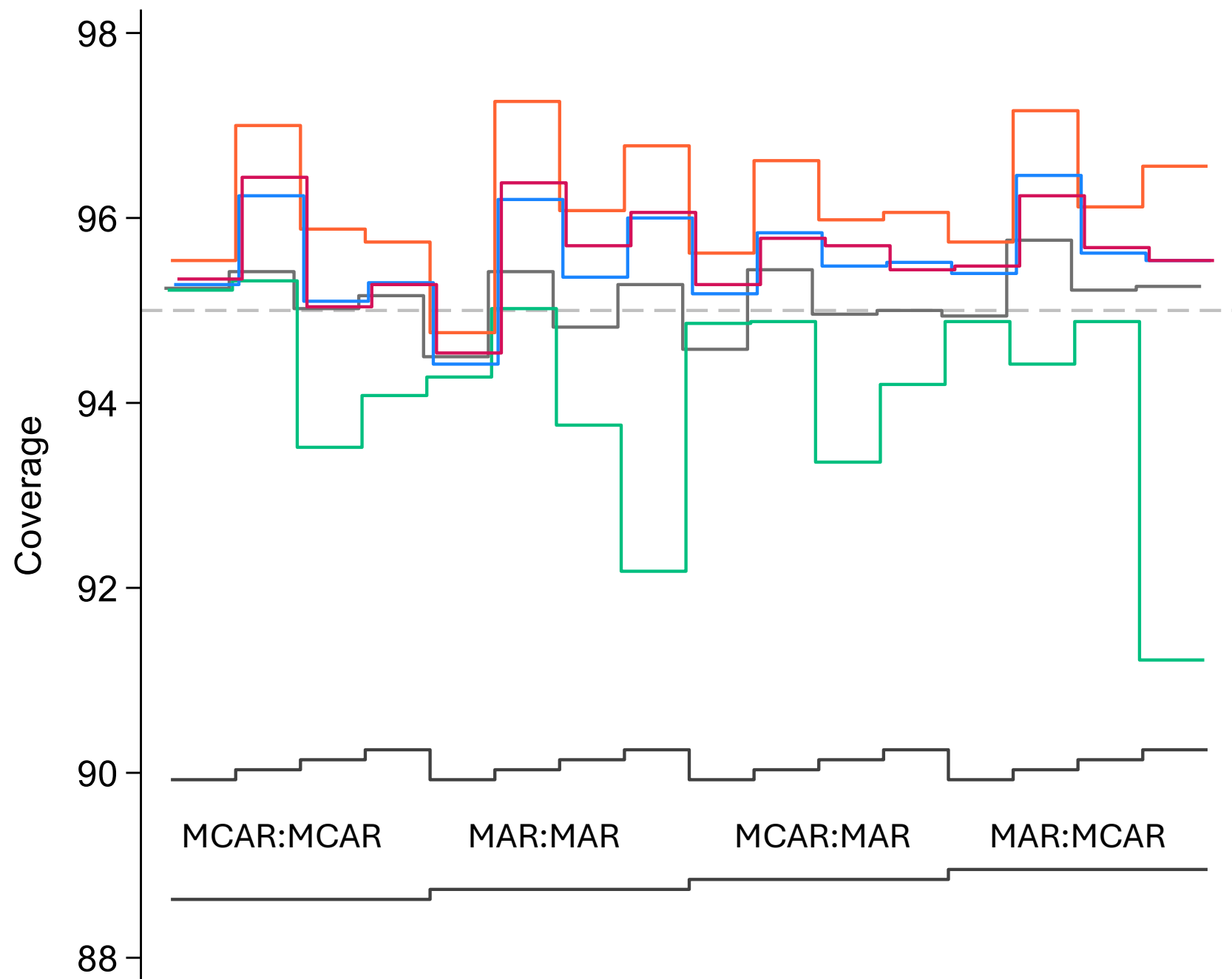
— full data
— cca
— oda
— linreg
— pmm
— logitreg



Coverage

% incomplete cases soc:exp

14:14 | 50:50 | 14:50 | 50:14



Summary of findings

Arm-specific missingness mechanism	Arm-specific proportion of incomplete cases	CCA	ODA	MI
Same MCAR:MCAR	Same	OK	OK for low % Biased otherwise	OK
	Different	OK	Biased	OK
Same MAR:MAR	Same	Biased	Biased	OK
	Different	Biased	Biased	OK
Different (MCAR: MAR; MAR: MCAR)	Same	Biased	Biased	OK
	Different	Biased	Biased	OK

Among MI methods:

- linreg generally has the smallest bias and empirical standard errors, but tend to over-cover
- Computational time: linreg and pmm are considerably faster than logitreg
- logitreg tends to be more prone to perfect prediction, especially with high proportions of missingness

Conclusion

- CCA can substantially reduce efficiency and lead to bias
- ODA is only valid in limited settings and should be used with caution
- MI provides a general solution and can handle MCAR and MAR mechanisms with moderate/high proportions of missing data
- MI of continuous data before dichotomisation is generally preferred