MI and IPW methods for addressing both intermittent and monotone missingness in comparative effectiveness studies with time-varying confounding

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Outline

- Rationale
- Motivating example
- Simulation study
- Preliminary findings and next steps

Rationale

- **Routine data** increasingly used to establish the effectiveness and cost-effectiveness of health interventions
- **NICE** and other agencies now routinely use these data to supplement trial evidence (when this is limited/inexistent)
- One such area is the evaluation of treatment strategies sustained over time, i.e. **time-varying treatments**
- Central feature in these studies is that **treatment** status is **determined** at different points **over time**
- Patient's progression typically influences future treatments and outcomes, and is itself affected by previous treatments

Rationale

- In addition to the confounding a recurrent issue in these studies is **missing data**
- **Inverse probability weighting** (IPW) tends to be most suitable to handle monotone missing data but it is less practical to handle intermittent missing data. **Multiple Imputation** (MI) known for its flexibility to address intermittent patterns
- A few studies have **compared MI and IPW** for addressing data in studies with time-varying confounding
  - Moodie et al 2008
  - Vourli and Touloumi 2014
  - Liu et al 2019
  - Leyrat et al 2021
- Focused mostly on **missing confounders and one type of missingness (monotone)**

Aims and objectives

Aim: To contrast IPW and MI methods for handling both monotone and intermittent missing data in both outcomes and confounders

Objectives:

- To illustrate how to combine MI with IPW-based marginal structural models (MSMs)
- To assess the performance of MI and IPW in settings with both monotone and intermittent missingness:
  - **Method 1**: use IPW for both monotone and intermittent
  - **Method 2**: use IPW for monotone, and MI for intermittent
- To illustrate the methods in an evaluation of biologic drugs for patients with severe rheumatoid arthritis

Motivating example

Rheumatoid arthritis (RA) study

- RCTs showed some **biologics** (e.g. Etanercept) effectively slow RA progression and improves patients' HRQL over short-term
- **No randomised evidence** on the sustained effect of these biologics over long term (key parameter for CER – NICE decisions)
- We use **US National Data Bank** for rheumatic diseases and estimate 5-year effect of Etanercept vs other biologics on EQ-5D
- Restricted sample (N=13,002) to patients with severe RA who failed to respond to first-line treatment – **biologic initiators**
- Data are collected biannually as part of a clinical visit and also using patient-reported questionnaire

Missing data

id	time	At	Xt	Yt
1	1	A11	X11	.
1	2	A12	.	Y12
1	3	A13	.	.
1	4	A14	X14	Y14
2	1	A21	X21	Y21
2	2			
2	3			
2	4	A24	X24	Y24
3	1			
3	2	A32	X32	Y32
3	3	A33	X33	.
3	4	A34	X34	.
4	1	A41	X41	Y41
4	2	A42	X42	Y42
4	3	A43	X43	Y43
4	4			

TOTAL ~25% missing

Intermittent missing X and Y (5%)

Interval Censoring (10%)

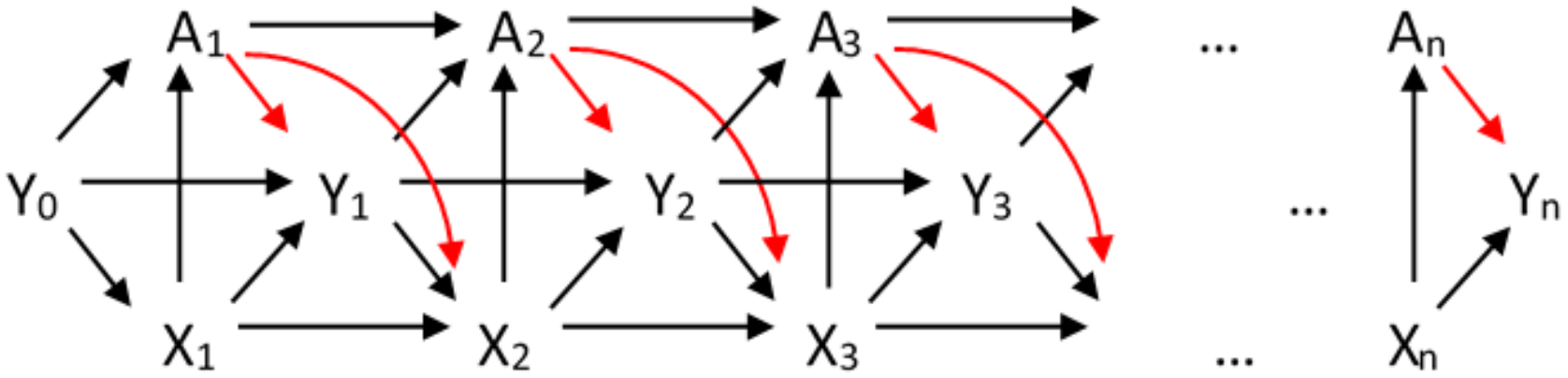
Left censoring (0.1%)

Monotone missing (4%)

Right censoring (6%)

Motivating example

Time-varying confounding



A – Treatment (1 if Etanercept, 0 otherwise)

X – Time-varying confounder (HAQ disability index)

Y – Outcome (EQ-5D)

Simplified DAG: e.g. - no direct long-term effects of A on Y or X

- no baseline variables

Confounding adjustment

Inverse probability weighting (IPW or IPTW)

- IPW re-weights individuals according to the probability of being assigned to treatment (conditional on observed confounders)

- We used the recommended stabilised weights (Daniel et al 2012):

$$SW_t = \prod_{t=1}^{T} \frac{P(A_t|\bar{A}_{t-1}, B)}{P(A_t|\bar{A}_{t-1}, \bar{Y}_{t-1}, \bar{X}_t, B)}$$

- The relationship between treatment and outcome can then be modelled using a MSM on re-weighted sample:

$$(Y^{\bar{a}_T}) = \beta_0 + \sum_{t=1}^{T} \beta_t a_t$$

Missing data methods

Method 1 – use IPW for both monotone and intermittent patterns

$$SC_t = \prod_{t=1}^{T} \frac{P(R_t = 1 | R_{t-1} = 1, B)}{P(R_t = 1 | \bar{A}_{t-1}, \bar{Y}_{t-1}, \bar{X}_{t-1}, R_{t-1} = 1, B)}$$

- Applied separately to monotone and intermittent missing data

- Discarded individuals when the treatment was missing at any point in time, had all outcome observations missing, or left censoring (to make it more comparable with simulations)

- $W_t = SW_t * SCm_t * SCi_t$

Missing data methods

Method 2 – use IPW for monotone and MI for intermittent missing data

For the IPW: $W_t = SW_t * SCm_t$

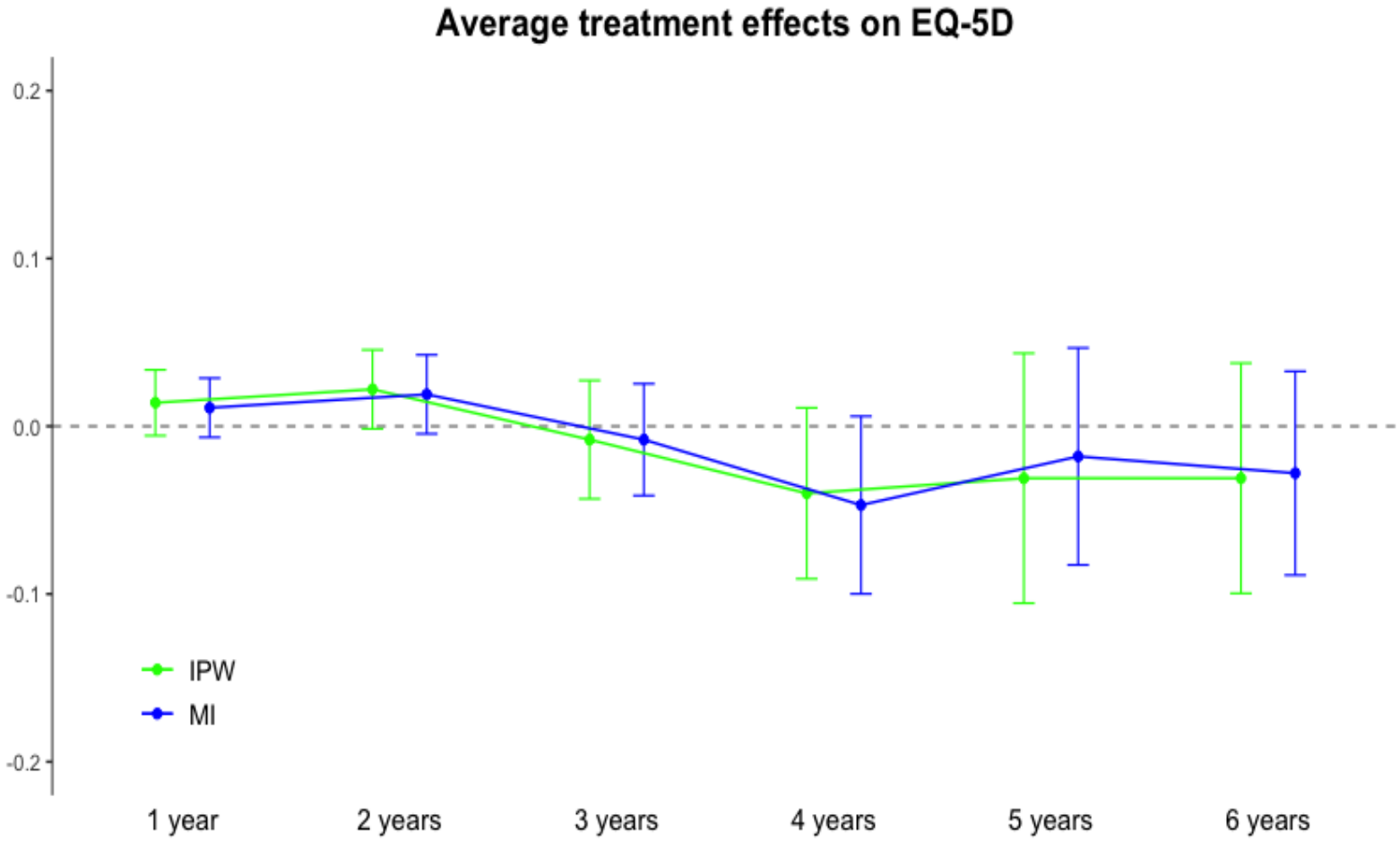
For the MI:

- Used chained equations and M = 10

-We followed Leyrat et al 2019's recommendations about combining MI with IPW weighting:

- Included outcome in the imputation model when imputing the confounders
- Applied Rubin's rules to treatment effects from MSM, rather than PS weights

RA study results



- Etanercept seems slightly more effective than other biologics in the first 2 years (as per trial evidence) but effect lost over time.

Simulations - DGP

Data generating process (in line with DAG above)

2 time-constant continuous and binary covariates (Ba, Bs)

1 time-varying continuous confounder (X)

1 time-varying binary treatment indicator (T)

1 continuous outcome (Y)

Baseline (Time 0)

$$Ba = 14 + 76 * beta(4.23, 2.7)$$

$$Bs = 1(unif(0,1) < 0.06)$$

$$T_0 = 0$$

$$X_0 = norm(1.09 + s * 0.1 + a * 0.00001, 0.714)$$

$$Y_0 = norm(0.842 - X_0 * 0.101 + s * 0.062 + 0.0001 * a, 0.152)$$

Simulations - DGP

Subsequent periods

$$\boldsymbol{X_t} = norm(1.62+0.38*X_{t-1} + 0.7 * T_{t-1} - 1.32 * Y_{t-1} + 0.016 * Bs + 0.001 * Ba, 0.716)$$

$$\boldsymbol{T_t} = 1(unif(0,1) < expit(-2.2 + 0.4 * X_t + 1.8 * T_{t-1} + 0.31 * Y_{t-1} + 0.041 * Bs + 0.025 * Ba))$$

$$\boldsymbol{Y_t} = norm(0.32 - 0.036 * X_t + 0.05 * T_t + 0.63 * Y_{t-1} - 0.01 * s + 0.0001 * a, 0.144)$$

Simulations – Missingness mechanism

Monotone/censored data ($C_0 = 0$) - MAR

$$\boldsymbol{C_t} = 1(unif(0,1) < (expit(-\beta_C - 2.1 * T_t + 0.25 * Bs + 0.025 * Ba) + C_{t-1} - \gamma_C)$$

Intermittent missing outcome - MAR

$$\boldsymbol{Mo_t} = 1(unif(0,1) < (expit(-\beta_{Mo} - 1.1 * T_t + 0.8 * Bs + 0.045 * Ba) + C_{t-1} - \gamma_{Mo})$$

Intermittent missing confounder - MAR

$$\boldsymbol{Mc_t} = 1(unif(0,1) < (expit(-\beta_{Mc} - 1.4 * T_t + 0.7 * Bs + 0.055 * Ba) + C_{t-1} - \gamma_{Mc})$$

Simulations - scenarios

12 SCENARIOS

- Missing outcome, confounder, or both, plus usual censoring
- % missingness (low vs high, i.e. 20% vs 40%)

Missing outcome	Missing confounder	Censoring	Level of missingness	β_C	β_{Mo}	β_{Mc}	γ_C	γ_{Mo}	γ_{Mc}
Yes	No	No	Low	3.113	3.215	3.720	0	0	1
No	Yes	No	Low	3.113	3.215	3.720	0	1	0
Yes	Yes	No	Low	3.113	3.215	3.720	0	0	0
Yes	No	Yes	Low	3.113	3.215	3.720	1	0	1
No	Yes	Yes	Low	3.113	3.215	3.720	1	1	0
Yes	Yes	Yes	Low	3.113	3.215	3.720	1	0	0
Yes	No	No	High	2.395	2.298	2.767	0	0	1
No	Yes	No	High	2.395	2.298	2.767	0	1	0
Yes	Yes	No	High	2.395	2.298	2.767	0	0	0
Yes	No	Yes	High	2.395	2.298	2.767	1	0	1
No	Yes	Yes	High	2.395	2.298	2.767	1	1	0
Yes	Yes	Yes	High	2.395	2.298	2.767	1	0	0

Simulations - results

Low missing data (true ATE is 0.2)

Y	X	Censoring	MI				IPW			
			Bias	MSE	Emp. SE	MC err.	Bias	MSE	Emp. SE	MC err.
Yes	No	No	1.28%	0.0105	0.0102	0.0003	0.78%	0.0161	0.0160	0.0005
No	Yes	No	1.20%	0.0099	0.0096	0.0003	1.58%	0.0194	0.0192	0.0006
Yes	Yes	No	1.22%	0.0101	0.0098	0.0003	1.46%	0.0164	0.0161	0.0005
Yes	No	Yes	2.12%	0.0115	0.0107	0.0003	1.38%	0.0137	0.0135	0.0004
No	Yes	Yes	0.98%	0.0106	0.0104	0.0003	1.84%	0.0148	0.0143	0.0004
Yes	Yes	Yes	1.46%	0.0110	0.0106	0.0003	1.68%	0.0139	0.0135	0.0004

- MI has the lowest empirical SE, mean square error and Monte Carlo error of bias.

Simulations - results

High missing data (true ATE is 0.2)

Y	X	Censoring	MI				IPW			
			Bias	MSE	Emp. SE	MC err.	Bias	MSE	Emp. SE	MC err.
Yes	No	No	1.10%	0.0116	0.0114	0.0004	1.03%	0.0297	0.0297	0.0009
No	Yes	No	1.17%	0.0099	0.0097	0.0003	2.33%	0.0477	0.0475	0.0015
Yes	Yes	No	1.19%	0.0108	0.0105	0.0003	1.19%	0.0393	0.0392	0.0012
Yes	No	Yes	3.01%	0.0149	0.0137	0.0004	1.44%	0.0241	0.0240	0.0008
No	Yes	Yes	0.63%	0.0130	0.0129	0.0004	2.22%	0.0311	0.0308	0.0010
Yes	Yes	Yes	1.42%	0.0135	0.0132	0.0004	2.31%	0.0250	0.0246	0.0008

- MI has the lowest empirical SE, mean square error and Monte Carlo error of bias.
- Bias is consistently low for both methods under all scenarios.

Preliminary findings

- **IPW straightforward to address censoring**, and hence why commonly used in epidemiological/biostatistical studies
- Our simulations suggest that **even in simple settings** with intermittent missing outcome IPW provides **less precise** estimates
- Impact more pronounced when both outcome and confounder are missing and **% missingness is relatively high**
- **In some settings IPW will be challenging**, say more than one outcome and several confounders missing
- **MI is computationally expensive**, particularly if combined with non-parametric Bootstrap

Next steps

What further simulated scenarios are warranted?

1. Allow more 'complex' MAR scenarios

- Allow Mc_t to be a function of Y, and
- Mo_t to be a function of X

2. Add 'Method 3' - use MI for both monotone and non-monotone missing.

- Don't expect much gain for MI
- Worth considering for completeness?