AN EXTENSION OF UNANCHORED MATCHING-ADJUSTED INDIRECT COMPARISON TO VERIFY THE RESULTS OF THE COMPARISONS BETWEEN POORLY OVERLAPPING STUDIES

Parkitny M[1,2], Wojciechowski P[1], Aballea S[3], Toumi M[2,4]
[1] Clever-Access, Krakow, Poland, [2]Aix-Marseille University, Marseille, France, [3]InovIntell, Rotterdam, SouthHolland, Netherlands [4]Clever-Access, Paris, France

MSR27

BACKGROUND

Unanchored matching-adjusted indirect comparison (MAIC[1]) becomes unfeasible when trial populations lack overlap in key prognostic factors or effect modifiers. Poor overlap reduces the effective sample size (ESS), weakening MAIC reliability. Consequently, poorly overlapping variables are often excluded, leading to 'incomplete models' that are prone to bias.

OBJECTIVE

We investigate the consequences of using incomplete models and identify the conditions associated with the highest risk of bias in MAICs using small, single-arm studies. We propose a method to assess how poorly overlapping parameters affect unanchored MAIC outcomes.

METHODS

SIMULATIONS

The simulation study assessed the impact of omitting binary or continuous variable in unanchored MAIC. Individual patient data for studies A and B were generated, then aggregated for B. Study A samples ranged from 20 to 200 patients, the impact of a poorly overlapping variable x_{poor} on the outcome (β_3) was between 5% and 50% of the treatment effect. The tested overlap levels varied from very poor to full overlap.

The data were generated using the following model:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_{poor} + \beta_{trt} + \epsilon,$$

where: y denotes the outcome, x_1 and x_2 - continuous covariates with good and average overlap, x_{poor} - a binary or continuous covariate with varying overlap. The parameters were set: $\beta_0 = 0.1$, $\beta_1 = 0.2$, $\beta_2 = -0.1$, and $\beta_{trt} = 2$ for A and B. The mean difference ($\hat{\mathrm{d}}_{AB}$), with true value of 0, was estimated.

EXTENSION OF MAIC (EMAIC)

The algorithm for EMAIC was designed to evaluate the reliability of MAIC in the presence of binary, poor overlap variable:

1. **Conduct incomplete MAIC** between A and B without x_{poor}.
2. **Balance $\boldsymbol{x_{poor}}$** by sampling weighted patients (A_0^*) from overrepresented subgroup (A_0) and shifting them to underrepresented subgroup (A_1).
3. **Adjust the outcomes** for patients from A_0^* using k potential β_3^i values from the prespecified interval ($i = 1, \dots, k$):
$$y_p^i = \begin{cases} y_p + \beta_3^i, & if\ p \in A_0^* \\ y_p, & otherwise \end{cases}.$$
4. **Estimate the effects of A in population B** $\left(\hat{d}_A^i(B)\right)$ using adjusted outcomes y^i and incomplete MAIC weights:
$$\hat{d}_A^i(B) = \frac{\sum_{p \in A} w_p * y_p^i}{\sum_{p \in A} w_p}, \text{ for } i = 1, \dots, k.$$
5. **Conduct indirect comparisons:**
$$\hat{\mathrm{d}}_{AB}^i = \hat{d}_A^i(B) - \hat{d}_B, \text{ for } i = 1, \dots, k.$$
6. **Find $\boldsymbol{\beta}^*$**, for which results of the incomplete MAIC change in significance.

RESULTS

SIMULATIONS

A total of 1,000 datasets were generated for each of the 72 scenarios. The results for binary x_{poor} are presented.

Figure 2 highlights that incomplete MAIC results were biased when the overlap was average and the impact of the variable on outcomes was moderate or high. At very poor and poor overlap, the incomplete MAIC yielded biased results, regardless of the strength of the association between variables.

Higher variability in the estimated treatment effects using the full MAIC was observed when the overlap was very poor. Additionally, smaller samples were associated with greater variability in treatment effects for both methods.

Table 1. %ESS and SE for different scenarios.

Overlap	N	Full MAIC % ESS (mean)	Full MAIC SE (mean)	Incomplete MAIC % ESS (mean)	Incomplete MAIC SE (mean)
Very poor	20	19	0.31	57	0.11
	100	6	0.26	62	0.06
	200	4	0.21	62	0.05
Poor	20	29	0.24	58	0.12
	100	24	0.11	62	0.07
	200	23	0.08	62	0.06
Average	20	44	0.18	57	0.14
	100	47	0.08	62	0.07
	200	47	0.06	63	0.06
Full	20	54	0.16	58	0.15
	100	61	0.07	62	0.07
	200	62	0.06	63	0.06

Table 1 shows that including x_{poor} decreased ESS, particularly when overlap was poor, with reduction exceeding 80% at very poor overlap. The standard error (SE) of treatment effects in the full MAIC increased as overlap worsened.

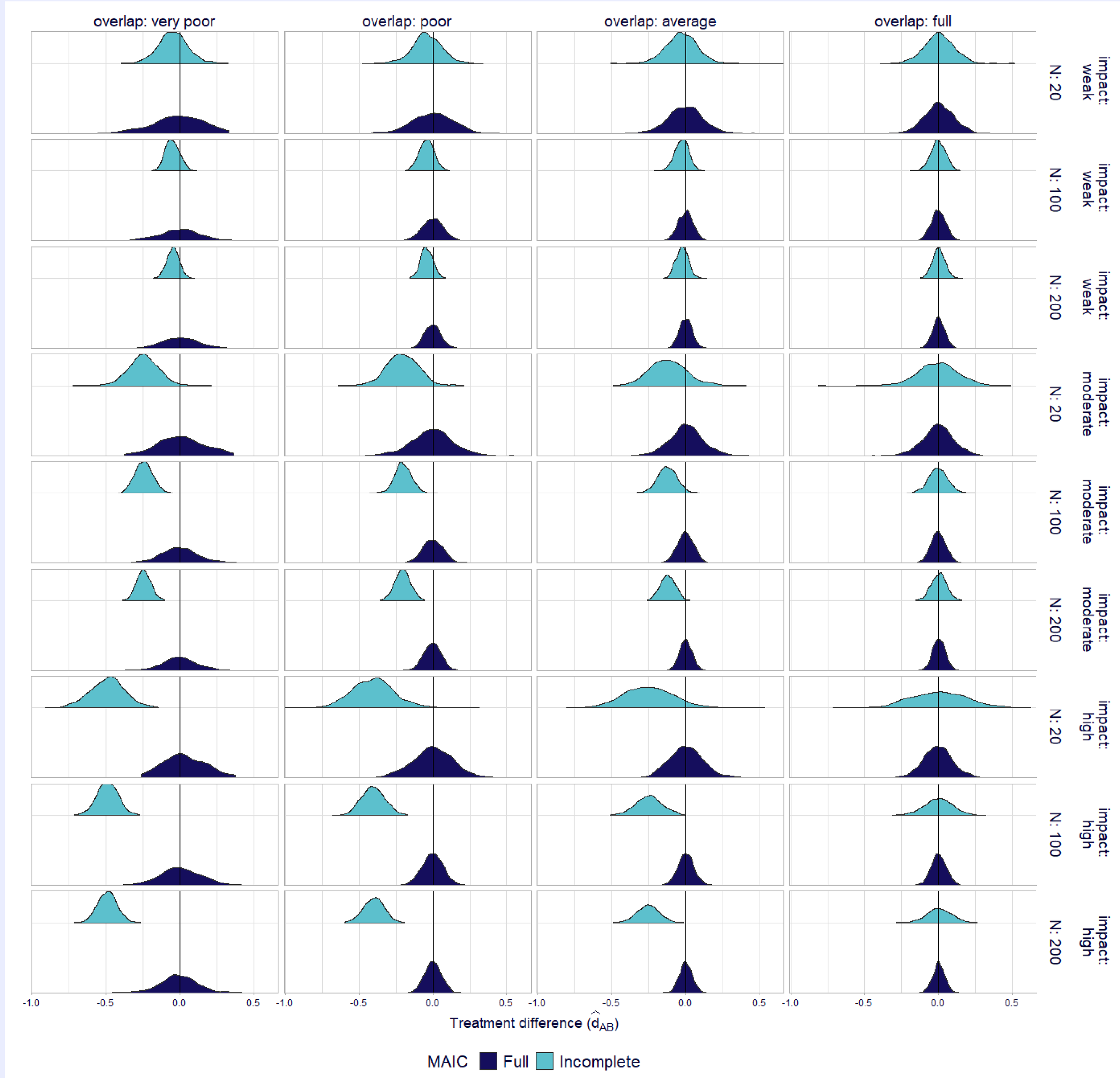

Figure 2. Relative treatment effects for different scenarios.

EXTENSION OF MAIC

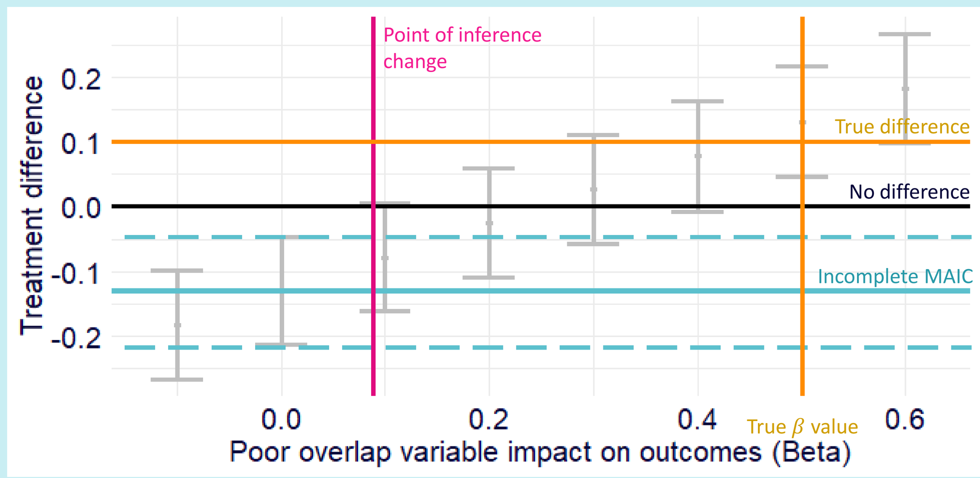

Figure 3. Application of EMAIC – Case 1

Case 1: Full MAIC unfeasible.

Observation: Even a weak impact of omitted x_{poor} can alter the incomplete MAIC conclusions.

Conclusion: Incomplete MAIC unreliable and unsuitable for use.

Case 2: Full MAIC is associated with low ESS (3%) and 1% of patients dominating the results. EMAIC was employed as a confirmatory analysis.

Observation: As long as the considered value of β is not greater than 2.5 times its true value, the analysis will conclude correctly that there is a significant difference between treatments.

Conclusion: Provided we have an approximate understanding of the impact of the poor overlap variable on the outcomes, we can determine whether the conclusion of the incomplete MAIC is reliable.

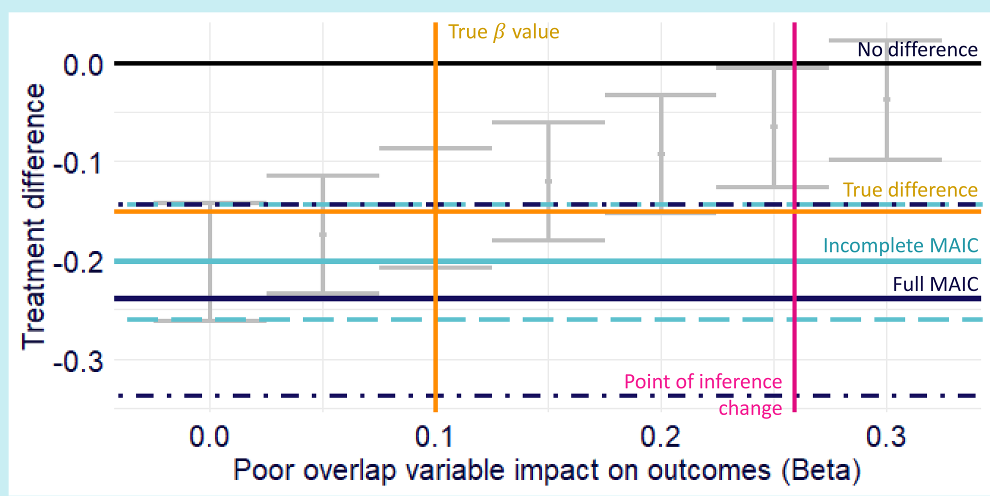

Figure 4. Application of EMAIC – Case 2

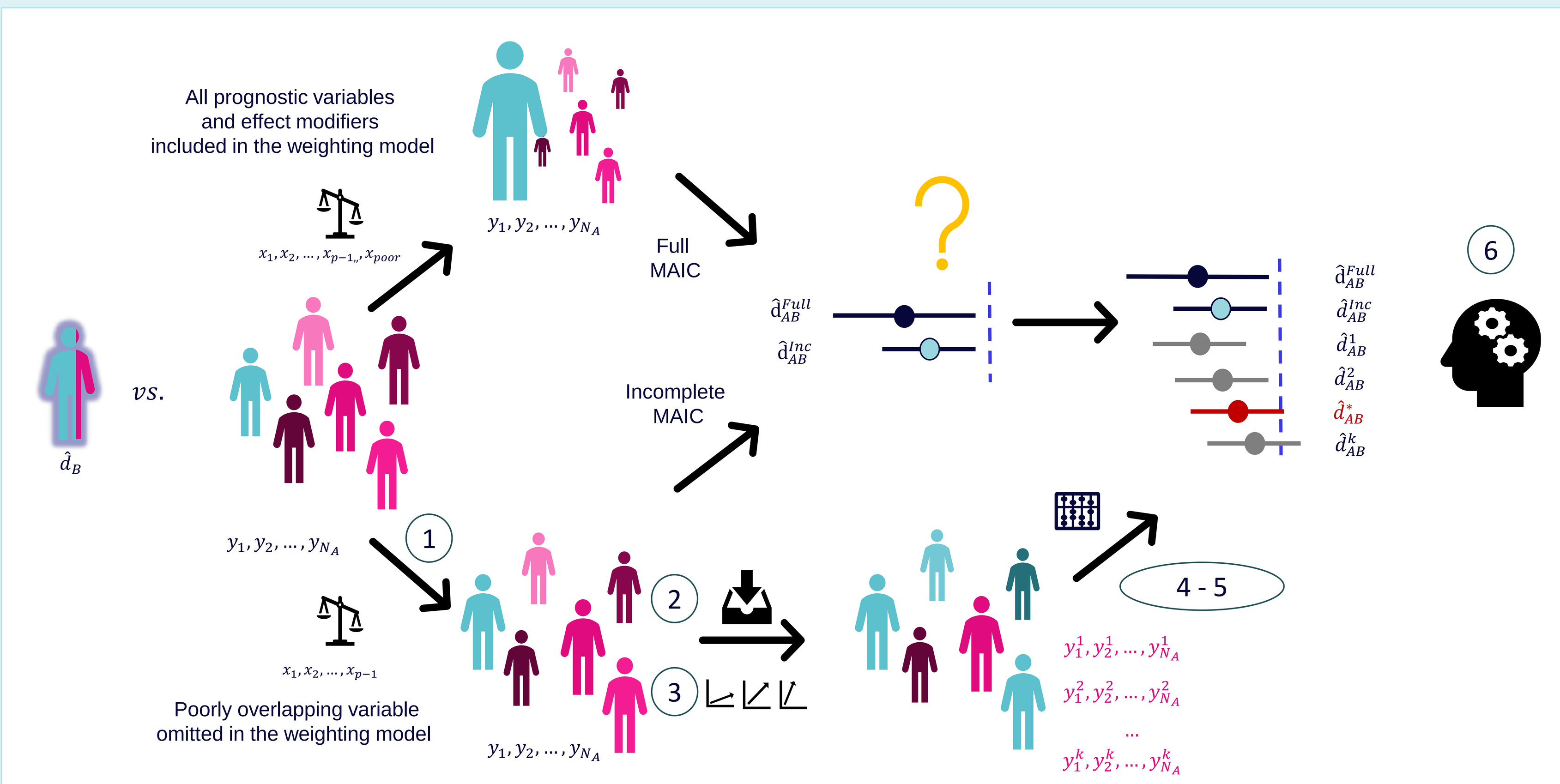

Figure 1. Overview of the EMAIC algorithm

The algorithm assumes the use of nonparametric bootstrap[2] to compute standard error (SE) of $\hat{d}_A^i(B)$. The approach can be extended for a continuous x_{poor}.

CONCLUSIONS

The simulation study showed that bias occurs in incomplete MAICs when the omitted variable has a moderate to strong association with outcomes, especially with poor overlap. Therefore, incomplete MAICs should not be used alone.

When full MAIC is unfeasible, an extended approach allows for investigating the bias of incomplete MAIC and reintroduces the omitted variable into the inference. If the variable's impact is deemed unlikely to alter conclusions, the incomplete MAIC results can be considered reliable.

REFERENCES

1. Signorovitch JE, Wu EQ, Yu AP, et al. DOI: 10.2165/11538370-000000000-00000
2. Efron B, Tibshirani R. DOI: 10.1214/ss/1177013815