Comparison of Population-Adjustment Methods for Indirect Treatment Comparisons – a Case Study in Plaque Psoriasis

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Objective

To compare three population-adjustment methods for indirect treatment comparisons (ITCs) – MAIC, plug-in means STC, and ML-NMR – in terms of their assumptions, target estimands, target populations, and practical feasibility, and to illustrate how these differences affect estimated treatment effects, uncertainty, and interpretation using a psoriasis case study.

Background

- The absence of head-to-head trials comparing treatments of interest necessitates ITCs; between-trial imbalances in effect-modifying covariates can bias anchored ITCs.
- Population-adjusted indirect comparisons (PAICs) reweight data (MAIC) or model the relationship between outcomes, treatment and patient characteristics (STC; ML-NMR), using a combination of individual patient data (IPD) and aggregate data.
- However, these methods differ, not only in overall approach (weighting versus regression), but also in targeted estimands. MAIC, ML-NMR and simulation-based STC target a marginal estimand (the average treatment effect in the target population), whereas plug-in-means STC yields an estimand combining (incompatible) conditional (the treatment effect for an individual with average characteristics) and marginal estimates (**Table 1**).[1,2]
- These distinctions are not always clear in publications, but matter for interpretation and subsequent decision-making: for non-collapsible effect measures such as odds ratios (ORs), conditional and marginal estimands do not generally coincide, which can yield conflicting treatment rankings. Typically, marginal estimands are more relevant than conditional estimands for decision-making and health economic modelling.[1]

Methods

- As a case study, anchored ML-NMR (using both conditional and marginal estimands), MAIC and plug-in means STC were compared with unadjusted (naïve) ITC using a plaque psoriasis dataset.[3]
- PAICs used IPD from UNCOVER-2 (ixekizumab, etanercept) and aggregate data from FIXTURE (secukinumab, etanercept) to indirectly compare IXE and SEC PASI 75 response (≥75% reduction in Psoriasis Area and Severity Index) at Week 12 (**Figure 1**), adjusting for five covariates (**Table 2**).
- The pooled FIXTURE population was the target population for all three approaches (required for MAIC and STC; elected for ML-NMR).
- Results were odds ratios (ORs; IXE vs. SEC), with 95% confidence interval (CI: MAIC, STC) or 95% credible interval (CrI: ML-NMR).
- Analyses were conducted in R Version 4.5.3, using *multinma* and *maicplus*.[3,4]

Results

- All PAICs had suitable diagnostics and yielded ORs (IXE vs. SEC) lower than the unadjusted OR. The point estimates using MAIC and ML-NMR (marginal estimand) were lower than those for STC and ML-NMR (conditional estimand).
- Uncertainty was greater for PAICs versus naïve comparison (**Figure 2**). This additional uncertainty arose from estimating covariate-treatment effect relationships in ML-NMR/STC, and from weighting and consequent reduced effective sample size (ESS) in MAIC (37.1% reduction).[5]
- Differences between methods may have resulted from: differences in target estimand, differences in estimation procedures, whether prediction or weighting; and data specific factors (e.g., degree of overlap between trials; number of covariates).[1,5]

Conclusion

MAIC, plug-in means STC and ML-NMR are not interchangeable, and the choice between them should be guided by desired interpretation (target estimand), target population of interest, and importance of simplicity of explanation of the methodology (**Table 1**). Sensitivity analyses may be warranted to ensure robustness of conclusions across population-adjustment approaches.

TABLE 1

Comparison of MAIC, STC, and ML-NMR across estimand, target population, inference framework, diagnostic, and relative strengths and limitations

	MAIC	Plug-in Means STC	ML-NMR
Approach	Method-of-moments weighting to match covariate means between UNCOVER-2 IPD and FIXTURE-reported means; marginal estimand in the FIXTURE population, uncertainty propagated via Sandwich estimator.	Logistic regression fitted to UNCOVER-2 IPD, with covariates centred at FIXTURE means; the modelled treatment effect at the mean covariates was compared with FIXTURE's marginal treatment effect.	Bayesian outcome model fitted to UNCOVER-2 IPD, with treatment effects transported to the FIXTURE population by integrating predictions over its covariate distribution.
Estimand targeted	Marginal	Quasi-conditional: Incompatible combination of conditional and marginal	Conditional or marginal
Target population	AgD trial population	AgD trial population	Specified based on population
Framework	Frequentist (CI)	Typically frequentist (CI)	Bayesian (CrI)
Key diagnostic reported	ESS	Standard frequentist	Standard Bayesian diagnostics
Pros	✓ Conceptually simple to understand, relative to ML-NMR ✓ Clearly defined marginal estimand	✓ Conceptually simple to understand, relative to ML-NMR ✓ Less susceptible to numerical issues with covariate overlap than MAIC	✓ Only method producing both conditional & marginal estimands ✓ Extends to larger networks ✓ Target population can be specified
Cons	✗ Restricted to the AgD trial population as the target population ✗ Limited to the two-study situation ✗ Numerically sensitive to poor covariate overlap, where low ESS can render results uninterpretable	✗ Restricted to the AgD trial population as the target population ✗ Limited to the two-study situation ✗ Plug-in-means targets neither a clean marginal nor fully conditional estimand (biased vs. both); this drawback is conceptually challenging to explain when acknowledging limitations of the approach ✗ Lack of clarity over robustness of results when covariate overlap is low	✗ Conceptually complex to explain methodology ✗ Lack of clarity over robustness of results when covariate overlap is low

TABLE 2

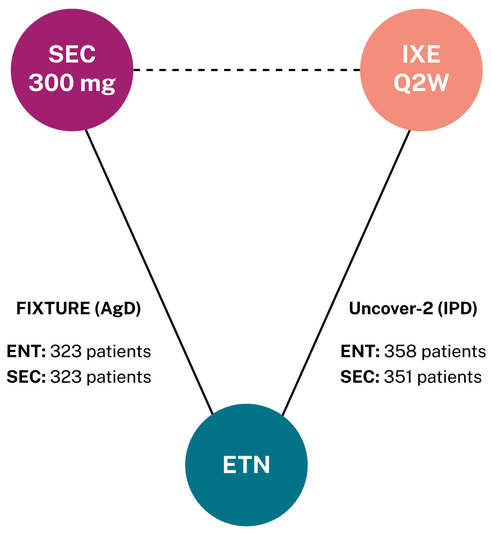
Covariate distributions in the UNCOVER-2 (IPD) and FIXTURE (AgD) trials

	Duration of psoriasis, Mean (SD)	Previous systemic treatment, Percentage	Body surface area (%), Mean (SD)	Weight, Mean (SD)	Psoriatic arthritis, Percentage
UNCOVER-2 (IPD trial): unweighted	18.5 (12.0)	62.4	25.5 (15.9)	90.8 (22.1)	23.2
UNCOVER-2 (IPD trial): MAIC-weighted	16.1 (10.7)	64.3	34.0 (22.2)	83.8 (19.8)	14.4
FIXTURE (AgD trial)	16.1 (12.1)	64.3	34.0 (18.6)	83.8 (21.1)	14.4

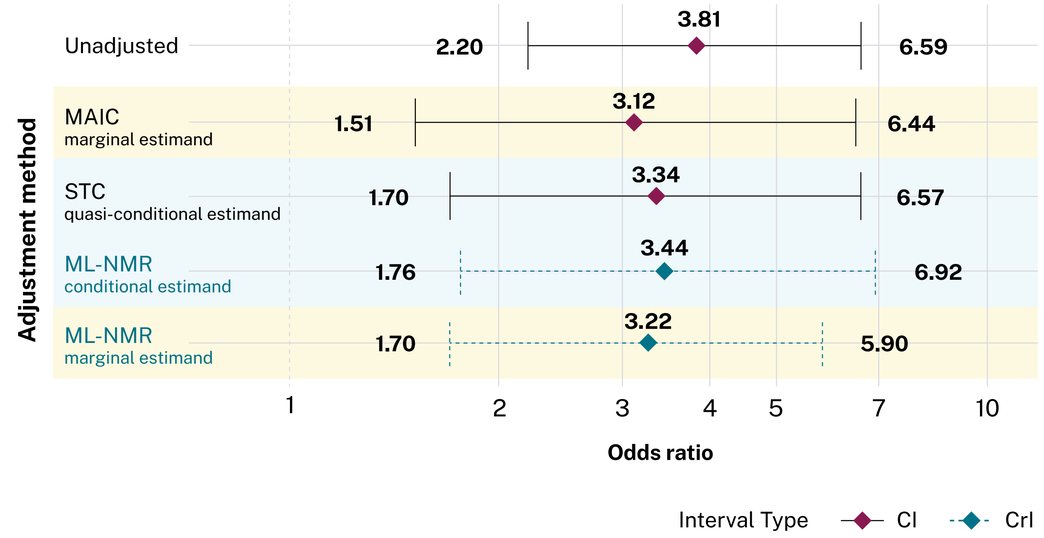
Note that these summary data limit to the treatment arms of interest for this analysis in each trial; as MAIC is the only weighting approach among the PAIC approaches included, it is the only one for which adjusted covariate distributions are relevant. For ML-NMR, distributions were assumed for each covariate based on visual inspection of the observed data.

FIGURE 1

A. Network plot



B. Forest plot of ORs (IXE vs SEC) with 95% CIs/CrIs (MAIC, STC, ML-NMR)



Abbreviations: AgD: Aggregate data; **CI:** confidence interval; **CrI:** credible interval; **ESS:** effective sample size; **ETN:** etanercept; **IPD:** individual patient data; **ITC:** indirect treatment comparison; **IXE:** ixekizumab; **MAIC:** Matching-Adjusted Indirect Comparison; **ML-NMR:** Multi-Level Network Meta-Regression; **OR:** odds ratio; **PASI:** Psoriasis Area and Severity Index; **SD:** standard deviation; **SEC:** secukinumab; **STC:** Simulated Treatment Comparison; **vs:** versus.

References: [1]Phillippo D.M. et al. Res Synth Methods 2025;16(2) :323-349; [2]https://pmc.ncbi.nlm.nih.gov/articles/PMC12527544/; [3]Phillippo D.M. multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data, R package version 0.9.1; [4]Chen G, Seo M, Gravestock I (2025). _maicplus: Matching Adjusted Indirect Comparison_. doi:10.32614/CRAN.package.maicplus <https://doi.org/10.32614/CRAN.package.maicplus>, R package version 0.1.2, https://CRAN.R-project.org/package=maicplus; [5]Phillippo D.M. et al. Stat Med 2020;39:4885-4911.

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