How do STC and ML-NMR Compare in Population Adjustment for ITC? Insights and Challenges

MSR108

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BACKGROUND

Problem: Indirect treatment comparisons (ITCs) face challenges when studies have different distributions of effect modifiers complicating the comparisons.

Current solution: Matching-adjusted indirect comparison (MAIC) is widely used but struggles when there is poor overlap in covariate distributions.

Challenge: Simulated treatment comparison (STC) and multi-level network meta-regression (ML-NMR) offer alternatives, but their comparative performance and ease of implementation are not well understood.

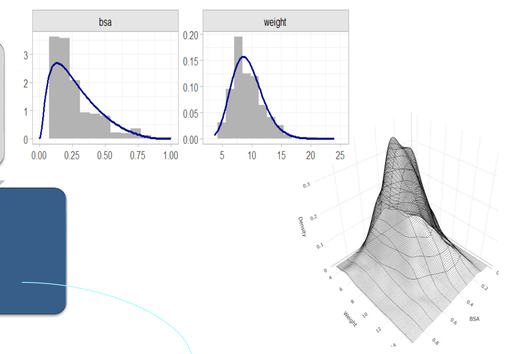
Objective: To replicate and compare results from STC and ML-NMR, focusing on ease of implementation and effectiveness in adjusting populations.

ML-NMR vs STC implementation steps:

Obtain correlations between each pair of effect modifying covariates(typically estimated from IPD)

Define marginal distributions for each covariate

Define joint distribution for covariates (e.g. using Gaussian copula)



STC

- Simulate (sample) from joint distribution corresponding to Aggregate Data (AgD) moments
- Fit regression model to IPD to estimate treatment interactions
- Predict outcomes in simulated AgD using IPD regression model ("Q-model")
- Estimate marginal treatment effects (within AgD population) as the difference between average predicted outcome in IPD vs aggregate outcome in AgD

ML-NMR

- Derive aggregate-level likelihood from individual-level likelihood
- Synthesis happens at the individual (conditional) level
- Integrate over the joint distribution of AgD covariates
- Estimate marginal treatment effects within target study (based on its covariate distribution)

Key differences between ML-NMR and STC

ML-NMR is a 1-stage approach; STC is a 2-stage approach

Treatment interactions for treatments in the AgD population are not parameterised in STC model

METHODS

We performed analyses of two illustrative ITCs in plaque psoriasis of etanercept versus secukinumab and ixekizumab versus secukinumab (**Fig. 1**) using:

- STC with G-computation[1]
- ML-NMR using the multinma R package[2]

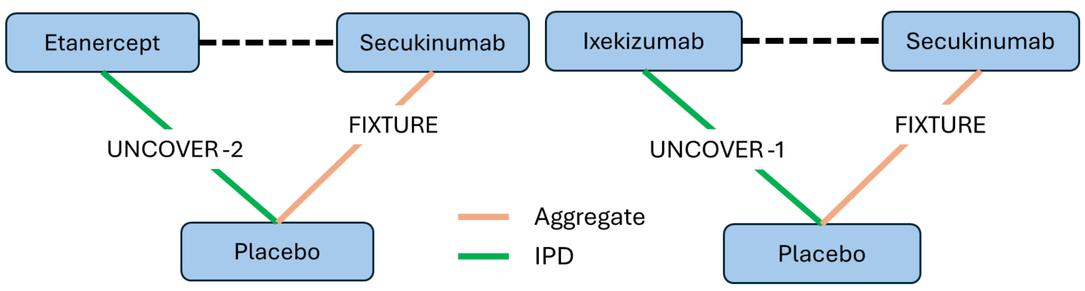
We adjusted for key effect modifiers (Table 1) assuming the same distributional relationships within both analyses and fitted the following models:

1. ***ML-NMR with independent effect modifiers*** *for each treatment (versus placebo)*
2. ***ML-NMR with shared effect modifier assumption*** *for each treatment (versus placebo)*
3. ***STC (Bayesian)***
4. ***STC (Frequentist)*** *without bootstrapping*
5. ***NMA*** *(assumes no effect modification)*

Estimands were the log-OR in the AgD population (FIXTURE) for:

- Secukinumab versus etanercept (ITC1)
- Secukinumab versus ixekizumab (ITC2)

Figure 1: Network plot showing studies and treatment comparisons in ITC1 (left figure) and ITC2 (right figure)



The dashed black line represents the comparison of interest within each ITC.

Table 1: Characteristics of included studies

Study	Data type	N	Body Surface Area (BSA)	Weight (kg)	Disease duration (yrs)	Previous systemic therapy	Psoriatic arthritis
UNCOVER-1	IPD	863	27.5 (17.2)	93.1 (26.2)	19.8 (12.1)	70.5%	26.8%
UNCOVER-2	IPD	524	26.9 (17.0)	92.6 (22.0)	19.2 (12.4)	60.7%	23.1%
FIXTURE	AgD	647	34.8 (19.2)	82.5 (21.0)	16.2 (12.0)	62.8%	15.2%

Continuous variables reported as mean (SD). IPD: individual participant data; AgD: aggregate data.

KEY FINDINGS

- **ML-NMR and STC** are fundamentally similar in approach, but our study shows that they *can* result in marked differences, depending on the **analytic choices, the data, and the assumptions regarding effect modification**
- **Reproducibility and transparency** is critical to ensuring analyses have been performed properly. Currently, analysts rarely report steps in detail and precise guidance is limited.
- A dedicated **R package for ML-NMR** provides consistency, though users need to be fully aware of what the default options imply for the model.

RESULTS

- Whilst for the ITC versus ixekinumab (ITC2), results were almost identical, STC and ML-NMR produced markedly different results for the ITC versus etanercept (ITC1) (**Fig. 2**).
- The degree of difference between the methods may depend on the relatively small number of events on Placebo in UNCOVER-2 and on the difference in the degree of effect modification between the two active treatments.
  - Secukinumab and Ixekinumab share the same mechanism of action (IL antagonist) and thus the degree of effect modification is likely to be similar.
  - Secukinumab and Etanercept have different mechanisms of action (IL antagonist and TNFα antagonist respectively) and thus effect modification likely differs.

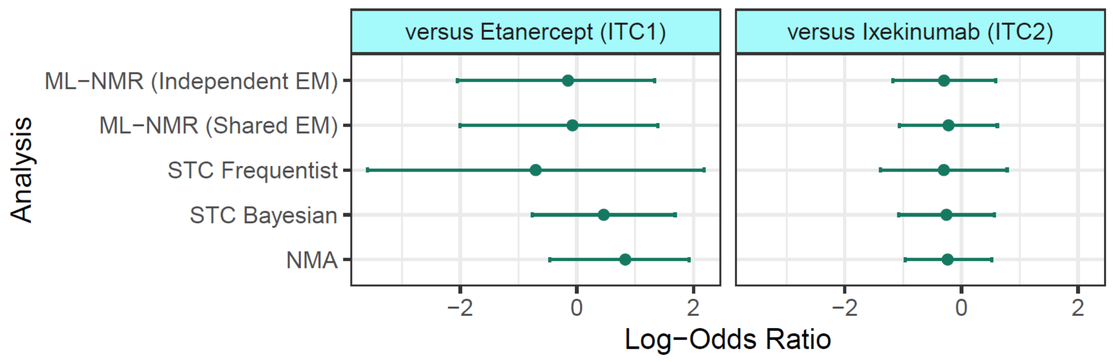
ML-NMR

- In principle, we expect that there may be very slight sharing of information on the treatment interactions from the AgD population. However, assuming shared versus independent effect modifiers has negligible impact in this scenario – a simple ITC when predicting treatment effect in the AgD population. More information would be available if there were multiple AgD studies informing the Secukinumab versus Placebo comparison.
- multinma facilitates consistency when using the default options, but these may not be applicable in all circumstances.

STC

- As a 2-stage approach, STC involves several steps performed at the discretion of the analyst that can impact estimates and precision. This may further complicate reproducibility of the same result.
- The Frequentist approach results in very wide 95%CIs. Uncertainty has not been properly accounted for (e.g. via bootstrapping), and prior information may play a role versus Etanercept (ITC1) where events are rare.
- Although not shown there, the number of simulated individuals impacts precision in both Frequentist and Bayesian analyses. A temptation might be to only simulate the same number of individuals as in the AgD population, but this inflates uncertainty.

Figure 2: Forest plot showing the marginal log-Odds Ratios for secukinumab versus either etanercept or ixekizumab in the FIXTURE population, estimated by the different covariate adjustment methods



EM: effect modifier.

CONCLUSIONS

- Contrary to what we might have expected, STC and ML-NMR *can* produce markedly different results. It is unclear whether analytic choices or differences in methodology leads to such pronounced discrepancies.
- The shared effect modifier assumption in ML-NMR allows estimation of treatment effects in IPD population. But this may introduce bias this assumption is not valid (e.g. due to a shared mechanism of action).

References.
1. Remiro-Azócar, A. et al. Res Synthesis Methods 2022; 13(6): 716-744.
2. Phillippo DM, et al. JRSSS-A: Statistics in Society 2020; 183(3): 1189–1210.

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