# Multilevel Network Meta-Regression (ML-NMR): Some Practical Experiences from an Industry Perspective

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## INTRODUCTION

- Standard indirect comparison (e.g. Bucher) or network meta analysis (NMA) require aggregate data (AgD) and assume that effect modifiers are balanced across trial populations. Anchored population-adjusted indirect comparisons utilise individual patient data (IPD) from at least one trial to adjust for differences in observed effect modifiers. However, current matching-adjusted indirect comparisons and simulated treatment comparison methods are limited to one-to-one trial comparisons and cannot extrapolate to other target populations
- Multilevel network meta-regression (ML-NMR) has been recently introduced as a new methodology for indirect treatment comparisons in situations where IPD are available for some but not all trials within a network of trials[1, 2]
- When implemented in a Bayesian framework, ML-NMR retains the flexibility and extensibility of Bayesian NMA, allowing prior information to be used, data types with differing likelihoods to be included, and the analysis to be embedded in a probabilistic cost-effectiveness framework[1]
- ML-NMR allows accounting for effect modifiers across multiple studies and comparison in any target population within a given covariate distribution, meaning that
  - comparisons can be made in each of the included trial populations in a connected evidence network[1, 2] and
  - extrapolations to other target populations relevant for decision making can be made

## OBJECTIVE

- To present a case study in the setting of large-scale randomized trials, highlighting how typical issues such as missing data can be dealt with using ML-NMR

## METHODS

- A ML-NMR was conducted in a Bayesian framework,[1] using the multinma R package,[3] to compare efficacy outcomes of semaglutide 2.0 mg versus dulaglutide 3.0 mg and 4.5 mg for the treatment of type 2 diabetes using IPD from the SUSTAIN FORTE and SUSTAIN 7, and AgD from the AWARD-11 randomised controlled trials in a connected evidence network (**Figure 1**)
- For IPD, missing data were imputed using multiple imputation and the multiply imputed data sets were incorporated into the ML-NMR model as described by Gelman et al[4]
- A shared effect modifier assumption[5, 6] was chosen to make the model estimable. As data for dulaglutide (3.0 mg and 4.5 mg) were only available on aggregate level (AWARD-11), it was assumed that the potential effect modifier interaction coefficients were identical for all dulaglutide dose levels
- To explore the impact of adjustment for potential effect modifiers, an unadjusted analysis using standard Bayesian NMA methodology was also conducted

**Figure 1**: Network graph

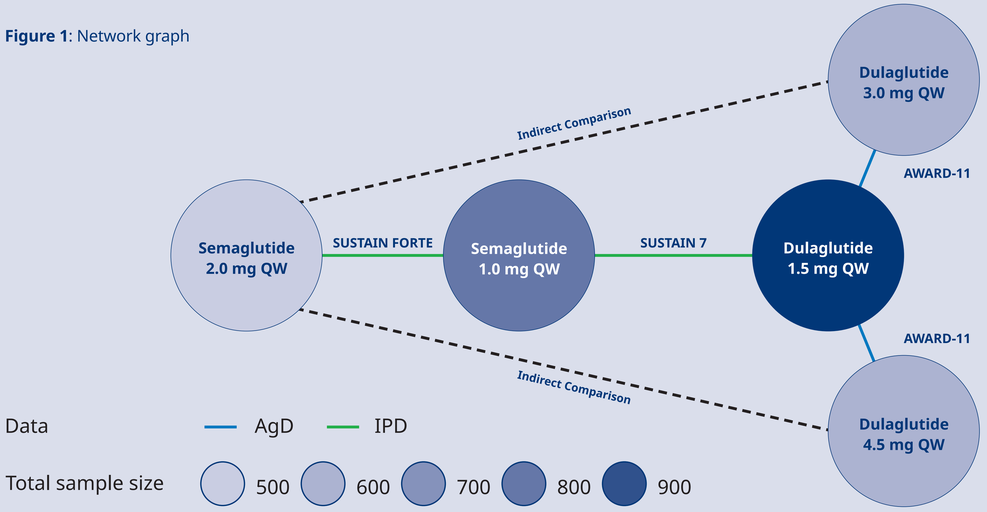


**Table 1**: Mean values of effect modifiers in the target population

| Target population | Mean values of effect modifiers in the target populations | | | | |
|---|---|---|---|---|---|
| | AWARD 11 | SUSTAIN 7 | SUSTAIN FORTE | SUSTAIN FORTE subpopulations | |
| | | | | High BL $HbA_{1c}$ (BL $HbA_{1c}$>9%) | High BL BMI (BL BMI ≥ 35 kg/m²) |
| $HbA_{1C}$ BL (%) | 8.6 | 8.2† | 8.9 | 9.5 | 8.9 |
| BMI BL, kg/m² | 34.2 | 33.3† | 34.6 | 34.5 | 41.0 |
| Diabetes Duration, years | 7.6 | 7.5† | 9.5 | 9.8 | 8.2 |

**Table 2:** Change from baseline in $HbA_{1c}$, % – semaglutide 2.0 mg vs dulaglutide 3.0 mg and 4.5 mg

| Target population | Results for ML-NMR study population (ETD, 95% CrI) | | | | | Results for fixed-effects NMA |
|---|---|---|---|---|---|---|
| | AWARD 11 | SUSTAIN 7 | SUSTAIN FORTE | SUSTAIN FORTE subpopulations | | |
| | | | | High BL $HbA_{1c}$ (BL $HbA_{1c}$>9%) | High BL BMI (BL BMI ≥ 35 kg/m²) | |
| Semaglutide 2.0 mg – dulaglutide 3.0 mg | –0.44 (–0.68, –0.20) | –0.41 (–0.67, –0.16) | –0.46 (–0.71, –0.21) | –0.51 (–0.82, –0.20) | –0.42 (–0.72, –0.13) | –0.47 (–0.69, –0.23) |
| Semaglutide 2.0 mg – dulaglutide 4.5 mg | –0.28 (–0.52, –0.03) | –0.25 (–0.51, 0.01) | –0.30 (–0.55, –0.05) | –0.35 (–0.66, –0.04) | –0.26 (–0.56, 0.04) | –0.31 (–0.53, –0.08) |

†Only semaglutide 1.0 mg and dulaglutide 1.5 mg arm
Abbreviations: AgD, aggregate data; BL, baseline; BMI, body mass index; CrI, credible interval; ETD, estimated treatment difference; $HbA_{1c}$, glycated haemoglobin; IPD, individual patient data; ML-NMR, multilevel network meta-regression; NMA, network meta analysis; QW, once weekly

## RESULTS

- The ML-NMR analysis was adjusted for baseline glycated haemoglobin ($HbA_{1c}$), body mass index (BMI), and diabetes duration as potential effect modifiers, thereby accounting for differences in baseline characteristics among trials (**Table 1**)
- Convergence of the Markov chain Monte Carlo algorithms was reached, and treatment differences for the indirect comparisons of semaglutide 2.0 mg versus dulaglutide 3.0 mg and 4.5 mg could be estimated alongside 95% credible intervals in the multiple imputation setup (**Table 2**)
- The ML-NMR approach allowed for robust indirect comparison of changes in $HbA_{1c}$ associated with semaglutide 2.0 mg compared with dulaglutide 3.0 mg and 4.5 mg and showed consistent results regardless of the target population used in analyses (**Table 2**)
- Estimation of treatment effects was also done for other target populations of interest e.g. a population of patients with high baseline $HbA_{1c}$ > 9.0% and high baseline BMI ≥ 35 kg/m² (**Table 2**)
- Comparison with NMA without adjustment for potential effect modifiers supported the findings of the ML-NMR analysis, confirming no appreciable impact of effect modification on the results of the analysis (**Table 2**)

## CONCLUSION

- From an industry perspective, the benefit of ML-NMR lies primarily in the possibility of adjustment of studies within a network, combining the most valuable elements of adjusted indirect comparison and NMA
- ML-NMR offers the ability to more fully leverage IPD in indirect treatment comparisons
- This case study suggests that ML-NMR is well suited for application in a typical production setting, offering an accessible yet flexible option for coherently accounting for the totality of evidence across both IPD and AgD

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