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Illustrating the Assumptions of Meta-Regression in Treatment Networks

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Abstract

Background

Network meta-analysis (NMA) is a common statistical method used to synthesize evidence across multiple studies, enabling simultaneous comparison of multiple competing

treatments for a given condition. Network meta-regression (NMR) extends NMA by adjusting treatment effect estimates based on study-level characteristics, helping to explain residual heterogeneity. Despite its usefulness, NMR adoption as a technique has been limited due to conceptual complexity, implementation challenges, and limitations in sparse-data settings. NMR model coefficients follow independent, exchangeable, or common assumptions, each applied with or without enforcing consistency among treatment comparisons. However, choosing between these models is complex, as different modeling assumptions can lead to varying results and interpretations depending on factors like model fit and data availability. Additionally, before fitting NMR models without consistency, meta-analysts must also consider potential data directionality, where certain study characteristics (e.g., sponsorship) may systematically bias treatment effect estimates.

Methods

We present frequentist tools for NMR and evaluate the properties of four different modelling assumptions achievable via design matrix modifications to the standard NMA model. Based on these properties, we provide recommendations for NMR implementation that account for data availability and the research question of interest. We also offer guidance on interpreting treatment-by-covariate interactions in the context of underlying NMR assumptions.

Results

We illustrate the different NMR modeling assumptions using a network of ten diabetes treatments. Findings highlight the impact of data directionality in models without consistency in the treatment-by-covariate interactions. Differences across modeling assumptions underscore the importance of carefully considering both the network structure and the characteristics of included studies when implementing NMR.

Conclusion

This work elucidates crucial NMR assumptions and demonstrates the importance of the network structure for NMR. The introduced tools can streamline the implementation of NMR,

facilitating the exploration of sources of heterogeneity and inconsistency in NMA and expanding tools available to researchers in the field of evidence synthesis.

Keywords: network meta-analysis, network meta-regression, small data, directionality, consistency assumption

1. Introduction

In medical decision-making, network meta-analysis (NMA) provides a tool for the quantitative synthesis of multiple independent studies, typically aiming to estimate relative treatment effects between multiple treatments[1–7]. However, heterogeneity among studies and comparisons poses an important challenge in NMA and is often addressed via quantification of heterogeneity through a random-effects model. Identifying sources of heterogeneity in meta-analysis is crucial for accurate interpretation of NMA results, and network meta regression (NMR) provides one such method to explore sources of heterogeneity. For example a NMR performed for 13 covariates (e.g. study year and sponsorship etc.) in a network of 21 antidepressant treatments for adults with major depressive disorder[8] showed that older studies had larger effects in placebo controlled trials. Since heterogeneity may result from study-specific conditions, the presence of heterogeneity suggests potential interactions between treatment comparisons and study-specific attributes[3,9–13]. The resulting estimates enable the identification of potentially important sources of heterogeneity, relevant subgroups, and effect modifiers, and treatment effect for groups of particular interest, which may help refine medical decision-making[10]. In scenarios where residual between-study variability is considerably reduced by the interaction, the NMR may provide clinically relevant insight[10,14].

While accessible tools for meta-regression are implemented in pairwise meta-analysis, NMR's added complexities have received little attention in the literature[3,10,13,15,16]. Due to the

lack of frequentist NMR tools and guidance, analysts who may be primarily familiar with in frequentist settings may switch to Bayesian implementations when NMR tools are needed, which lead to subtle but nuanced changes in implementation and interpretations[17,18]. In order to account for the multiple treatment comparisons, analysts need to identify relevant assumptions for the incorporation of evidence across studies and the consistency of comparisons[10,16,19]. Existing research highlights NMR's ability to refine NMA by clarifying small study effects and addressing inconsistencies in aggregate data, especially in Bayesian settings[3,16,20–25]. Ideally, researchers would have access to individual participant data (IPD), which enables the use of more powerful and explanatory techniques such as IPD-NMR and multi-level NMR to examine effect modifiers and adjust treatment effects[5,26,27]. However, since IPD is often unavailable due to several potential obstacles, such as data acquisition, aggregate data NMR techniques provide practical tools for evidence synthesis in the absence of IPD[28,29]. In aggregate data NMR, there remains a need to examine NMR and its assumptions to clarify NMR concepts and provide tools that improve the accessibility and interpretability of NMR.

In the present paper, we explore NMR for aggregated data in a frequentist setting in order to clarify the assumptions made in the implementation of NMR and their impact on parameter estimation. We begin with an overview of the standard NMA model, implemented as a form of multivariate meta-analysis. Then, we introduce NMR models in the frequentist setting by adapting the NMA model's design matrix. NMR model coefficients follow independent, exchangeable, or common assumptions, each applied with or without enforcing the consistency assumption among treatment comparisons. Exchangeable across study assumptions require adaptations beyond the design matrix, and are not included in the design matrix-based frequentist NMR implementations. In total, we examine four different design matrix modifications to the standard NMA model and demonstrate the landscape of assumptions and their benefits and limitations available in NMR. We present an interpretation guide, and tools in the R package **netmeta** to simplify the application of NMR[30].

1.1.Hypothetical Network

NMR assumptions are sensitive to the structure of the available evidence network. To illustrate the impact of the assumptions on the estimation, we use a hypothetical dataset of four study designs, and four treatments (A, B, C, and D) (**Table 1**). The hypothetical dataset contains a multi-arm study with treatments A, B, and D, to display the impact of network geometry on NMR's relationship to traditional NMA. Although NMR can be applied with any type of covariate, for simplicity in this hypothetical example we assume a continuous covariate.

2. Methods

2.1.Standard Network Meta-Analysis Model

Suppose a network of N studies comparing T treatments. Let $y_{i,b_{(i)}k}$ denote the relative treatment effect between treatments k and an arbitrarily chosen study reference treatment $b_{(i)}$ in study $i = 1,2,\dots,N$, where $k, b_{(i)} \in K_i$, and K_i denotes the total number of arms in study i. Treatment effects $y_{i,b_{(i)}k}$ are extracted from each study i, along with their known variances $\sigma^2_{b_{(i)}k}$. For simplicity, in the remainder of the manuscript, we assume that a common reference treatment exists across all studies in the network, so that $b = b_{(i)}, \forall i$. We further assume that treatment b is the global reference treatment in the network. Then a random-effects NMA model can be expressed in a hierarchical form as[31,32],

$$\begin{aligned} \boldsymbol{y} &\sim \boldsymbol{N}(\boldsymbol{\delta}, \mathbf{V}) \\ \boldsymbol{\delta} &\sim \boldsymbol{N}(\mathbf{X}\boldsymbol{\mu}, \boldsymbol{\Sigma}) \end{aligned} \tag{1}$$

where $\boldsymbol{y} = \left[y_{i,bk}\right]' i = 1,2,\dots,N$ denotes a vector of length $\sum_{i=1}^{N}(K_i - 1)$ containing all study-specific treatment effects in the network. Vector $\boldsymbol{\delta} = \left[\delta_{i,bk}\right]' i = 1,2,\dots,N$ is also of

length $\sum_{i=1}^{N}(K_i - 1)$ and refers to the true study specific treatment effect estimates between a treatment $k \in K_i$ and the common reference $b \in K_i$ in study $i = 1,2, \dots N$.

Two variance-covariance matrices, namely $\mathbf{V}$ and $\mathbf{\Sigma}$, representing the within and across study variance-covariance matrices, respectively, are embedded in the NMA model of equation (1). The within study matrix $\mathbf{V}$ is a known block diagonal matrix with diagonal elements $\mathbf{V_i}$ of dimension $(K_i - 1) \times (K_i - 1)$. For a study i in the network, the diagonal elements of each matrix $\mathbf{V_i}$ correspond to the study-specific known variances $\sigma^2_{i,bk}$, while off-diagonal elements include the respective covariances between all study-specific treatments effects $y_{i,bk}$ for each multi-arm study. Across-study variances, referring to the heterogeneity in the network, are included in equation (1) via the block diagonal matrix $\mathbf{\Sigma}$, with diagonal elements equal to $\mathbf{\Sigma_i}$, which have the same dimensions as the matrices $\mathbf{V_i}$. Following convention, we assume a common heterogeneity parameter τ^2 across all pairwise comparisons in the network. In this case the diagonal elements of each matrix $\mathbf{\Sigma_i}$ are equal to τ^2, while the off diagonal elements are equal to 0 for two arm studies and $\frac{\tau^2}{2}$ for multi-arm studies[33,34].

The parameters of interest in equation (1) are the NMA treatment effects $\boldsymbol{\mu}$ and the heterogeneity parameter τ^2. Under the assumption of consistency the NMA treatment effect between any two treatments t_1 and t_2 ($t_1, t_2 = 1,2, \dots, T$ and $t_1 \neq t_2$) can be obtained via the consistency equations[31,32,35,36]

$$\mu_{t_1 t_2} = \mu_{b t_2} - \mu_{b t_1} \qquad (2)$$

This reduces the total number of treatment effect parameters that we need to estimate from $\binom{T}{2}$ to $T - 1$, referring to the estimates of all treatments in the network versus the arbitrarily chosen global reference treatment $b = 1,2, \dots, T$. These $T - 1$ parameters μ_{bk} are called basic parameters. The rest of the parameters, known as functional parameters, are

obtained via equation (2) as linear combinations of the basic parameters. The consistency equations are embedded in the NMA model of equation (1) via the design matrix **X** which has dimension equal to $\sum_{i=1}^{N}(K_i - 1) \times (T - 1)$ and maps the observed treatment effects of each study to the basic parameters μ_{bk}. For example, in the hypothetical network of section 1.1 the design matrix for the first four studies example has the form[37],

$$\boldsymbol{X} = \begin{matrix} \\ \text{Study 1} \\ \text{Study 2} \\ \text{Study 3} \\ \text{Study 4} \\ \text{Study 4} \end{matrix} \begin{matrix} \begin{pmatrix} \mu_{AB} & \mu_{AC} & \mu_{AD} \end{pmatrix} \\ \begin{pmatrix} 1 & 0 & 0 \\ -1 & 1 & 0 \\ 0 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix} \end{matrix}$$

where each row represents a study, and each column represents a basic parameter. Overall, equations (1) and (2) define the standard NMA model. The estimation of the unknown parameters is possible in both frequentist and Bayesian settings. Under a frequentist model, the estimation of the basic parameters $\boldsymbol{\mu}$ is possible using the weighted least squares approach,

$$\hat{\boldsymbol{\mu}} = \left(\mathbf{X}'\left(\mathbf{V} + \hat{\boldsymbol{\Sigma}}\right)^{-1}\mathbf{X}\right)^{-1} \mathbf{X}'\left(\mathbf{V} + \hat{\boldsymbol{\Sigma}}\right)^{-1}\boldsymbol{y} \tag{3}$$

with $var(\hat{\boldsymbol{\mu}}) = \left(\mathbf{X}'\left(\mathbf{V} + \hat{\boldsymbol{\Sigma}}\right)^{-1}\mathbf{X}\right)^{-1}$ where an estimate $\hat{\boldsymbol{\Sigma}}$ of the between studies variance-covariances matrix $\boldsymbol{\Sigma}$ can be obtained using various methods such as the restricted maximum likelihood (REML) or the Der-Simonian Laird approaches[38,39].

2.2. Network Meta-Regression Models

Incorporating the heterogeneity parameter in a random-effects NMA model is usually only the first step to account for the between study heterogeneity[40–43]. Often, investigators are interested in explaining the between study heterogeneity by accounting for treatment-by-covariate interactions via NMR models. Let c_i denote the value of a covariate C in study $i =$

$1,2,\ldots,N$. This can be either a continuous or a categorical covariate. Then, a NMR model can be parametrized as,

$$\boldsymbol{y} \sim \boldsymbol{N}(\boldsymbol{\delta}, \mathbf{V}) \tag{4}$$

$$\boldsymbol{\delta} \sim \boldsymbol{N}(\mathbf{X}^{*}\boldsymbol{\theta}, \boldsymbol{\Sigma})$$

where $\boldsymbol{\theta} = [\boldsymbol{\mu}, \boldsymbol{\beta}]'$ represents the vector of unknown parameters including both the NMA treatment effect estimates $\boldsymbol{\mu}$ and the new regression coefficients $\boldsymbol{\beta}$ which refer to the treatment-by-covariate interactions. In the remainder of the manuscript, we refer to treatment-by-covariate interactions as interactions.

The exact dimensions of the design matrix $\mathbf{X}^{*}$ and the length of the vector $\boldsymbol{\theta}$ depends on the underlying analysis-relevant assumptions regarding interactions $\boldsymbol{\beta}$, such as the assumption of interaction consistency. Similar to the treatment effect consistency, interaction consistency for $\boldsymbol{\beta}$ would imply that[40,42,43],

$$\beta_{t_1 t_2} = \beta_{bt_2} - \beta_{bt_1} \tag{5}$$

As in NMA models, the consistency equations here allow us to connect the basic regression coefficients (i.e. $\beta_{bt_k}, k = 1,2,\ldots,T$) with the remaining functional coefficients. However, in cases where the assumption of consistency for the NMA treatment effects is weak, investigators might prefer not to impose the additional assumption of consistency for the interaction terms. In such cases, other NMR models, such as those assuming consistent NMA treatment effects but unrelated mean interaction effects (UMIE), may be a viable alternative.

UMIE NMR models relax the consistency assumption in the interactions, limiting evidence synthesis for each interaction coefficient to direct comparisons. The interaction terms are no longer split into basic and functional components, thus there is no global reference treatment across all interaction parameters in the network. In this setting, reference treatment groups should be carefully defined at the study level to ensure that all studies directly

investigating the comparison of any two treatments t_1 and t_2 are synthesized in a meaningful direction.

In some cases, it is meaningful if the comparison of any two treatments in the network t_1 and t_2 are synthesized in a common direction such that one treatment is always the comparator and the other is always the reference. This can be easily achieved if investigators define treatment directionality based on the alphabetical order of treatment names. However, with UMIE models, investigators could also define directionality based on specific treatment attributes. For example, Chaimani et al.[44] proposed defining directionality using an indicator variable Z_{j,t_1t_2} describing whether treatment t_1 is 'favored' over treatment t_2 in study $i = 1,2,\dots N$. We follow a similar rationale and, for beneficial outcomes, we define the directionality variable as,

$$Z_{i,t_1t_2} = \begin{cases} -1, \text{if } t_1 \text{ is } 'favored' \text{ over } t_2 \\ 0, \text{if neither } t_1 \text{ nor } t_2 \text{ is } 'favoured' \\ 1, \text{if } t_2 \text{ is } 'favored' \text{ over } t_1 \end{cases} \quad (6)$$

These indicator variables can be embedded directly in the design matrix $\mathbf{X}^*$ of UMIE models. Note that for multi-arm studies, similar to the unrelated mean effect (UME) NMA models[45], UMIE models can have different parameterizations depending on which treatment is defined as the study reference, according to the directionality variable. For example, if directionality is defined based on the alphabetical order of treatments, then a three-arm study investigating treatments A, B, and C will contribute evidence to the interaction estimation of contrasts AB and AC, but not BC as treatment A is the study reference in this case. However, the study would still inform the treatment effect estimation due to the assumption of treatment effect consistency in equation (2). The adjusted treatment effects, μ_{bk} represent the expected consistent treatment effect at covariate value, $C = 0$. Changing the centering value of the covariate alters the location at which consistent treatment effects are estimated and may impact

205 both the magnitude of resulting interaction terms and adjusted effects, depending on data
206 availability.

207 The final decision as to when one treatment is 'favored' over another in each study is
208 always context-specific and should rely on clinical judgment. One example where such a
209 directionality parameter may be useful is in networks that include both sponsored and
210 public/non-profit studies. In this context, investigators might define directionality such that a
211 treatment is considered 'favored' if it is sponsored, and 'not favored' if it is not. The resulting
212 interaction estimate would then reflect how a unit increase in covariate C affects the NMA
213 treatment effect estimate for the comparison between sponsored versus non sponsored
214 treatments. If treatments in all studies are neither 'favored' nor disadvantaged relative to each
215 other due to the study conditions, then the covariate should not be included in the UMIE NMR
216 because the interaction is not estimable, as all values of Z_{i,t_1t_2} become zero, indicating a lack
217 of directionality, reducing the model to a traditional NMA.

218 In addition to considerations around the consistency assumptions, we further investigate
219 two assumptions concerning the relationship between the basic regression coefficients[40,42,43].
220 These coefficients can either be assumed independent or merged into a common coefficient
221 across all pairwise comparisons in the network. Note that the consistency assumption in the
222 treatment effects $\boldsymbol{\mu}$ can also be removed. However, in our work, we always assume that the
223 main NMA treatment effects are subject to the consistency assumption from equation (2).

224 Overall, the combination of the interaction consistency options on $\boldsymbol{\beta}$ and the choice of
225 either independent or common interactions yield four different NMR models that will be
226 discussed in the remainder of this section. An overview of these NMR models is available in

Table 2. The final decision regarding the appropriateness of each NMR model is always context specific and depends on several factors such as the model fit, data availability, and clinical relevance. Assuming a network composed of multiple studies with the study designs illustrated in the hypothetical data, **Figure 1** shows the influence of network geometry on NMR covariate estimation. Across all four NMR models, the least squares estimates of $\boldsymbol{\theta}$ and their variances can be obtained from equation (7) as,

$$\widehat{\boldsymbol{\theta}} = \left(\mathbf{X}^{*\prime}\left(\mathbf{V}+\widehat{\boldsymbol{\Sigma}}\right)^{-\mathbf{1}}\mathbf{X}^{*}\right)^{-1}\ \mathbf{X}^{*\prime}\left(\mathbf{V}+\widehat{\boldsymbol{\Sigma}}\right)^{-\mathbf{1}}\boldsymbol{y}$$

$$var\left(\widehat{\boldsymbol{\theta}}\right) = \left(\mathbf{X}^{*\prime}\left(\mathbf{V}+\widehat{\boldsymbol{\Sigma}}\right)^{-\mathbf{1}}\mathbf{X}^{*}\right)^{-1} \tag{7}$$

2.2.1. Network Meta-Regression with Interaction Consistency: Independent Interactions

Under the assumption of independent interactions, each of the total $\binom{T}{2}$ treatment comparisons in the network has its own interaction term, and under the assumption of consistency, the model attempts to estimate only $T-1$ basic regression coefficients β_{bk}. The remaining $\binom{T}{2}-(T-1)$ functional interaction coefficients are estimated via the interaction consistency equation (5). In this case the vector of the unknown parameters $\boldsymbol{\theta} = [\boldsymbol{\mu}, \boldsymbol{\beta}]'$ has length $2(T-1)$ as it contains both the $T-1$ basic treatment effect parameters μ_{bk} and the $T-1$ basic regression parameters β_{bk}. Across all the different pairwise comparisons in the network this NMR model estimates in total $T(T-1)$ basic and functional parameters in terms of both main NMA treatment effects and regression coefficients.

The consistency equations for the main treatment effects and interactions are embedded in the design matrix $\mathbf{X}^*$ which in this case has dimensions $\sum_{i=1}^{N}(K_i - 1) \times 2(T-1)$. For example, fitting a NMR model with consistent and independent $\boldsymbol{\beta}$ in terms of the hypothetical network in Section 2.1 is possible using the following design matrix,

$$\mathbf{X}^* = \begin{array}{c} \\ \text{Study 1} \\ \text{Study 2} \\ \text{Study 3} \\ \text{Study 4} \\ \text{Study 4} \end{array} \begin{array}{c} \begin{array}{cccccc} \mu_{AB} & \mu_{AC} & \mu_{AD} & \beta_{AB} & \beta_{AC} & \beta_{AD} \end{array} \\ \begin{pmatrix} 1 & 0 & 0 & c_1 & 0 & 0 \\ -1 & 1 & 0 & -c_2 & c_2 & 0 \\ 0 & 1 & 0 & 0 & c_3 & 0 \\ 1 & 0 & 0 & c_4 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & c_4 \end{pmatrix} \end{array}$$

where the values $c_i, i = 1,2 \ldots, N$ represent the study specific values of covariate C while the signs of all elements of $\mathbf{X}^*$ refer to the consistency equations (2) and (5). The total number of interaction parameters estimated in this hypothetical example, assuming sufficient data, are graphically illustrated in

Figure 1I.

The interpretation of the parameters $\boldsymbol{\beta}$ quantifies the magnitude of the NMA treatment effect change given a 1-unit increase in the covariate C. Here we should also note that in the presence of sparse networks, where limited evidence exists for some treatments, the capacity of the NMR model with independent interaction terms can be severely limited. Therefore, we recommend that, before fitting this NMR model, investigators should first assess its appropriateness by considering both clinical judgment and the overall data availability required to obtain $T(T-1)$ estimates.

2.2.2. Network Meta-Regression with Interaction Consistency: Common Interactions

In the presence of limited direct evidence or sparsely connected treatments, users may prefer to rely on the common interaction assumption, which is more robust in sparsely connected networks, as it only estimates a single interaction for the model. With this assumption, an NMR model assumes a common interaction term across all comparisons in the network. In this case the vector of unknown parameters $\boldsymbol{\theta}$ has length equal to T, referring to the $T-1$ parameters in terms of the main NMA treatment effects and one additional parameter β_c reflecting the common interaction term across all comparisons. Interestingly, under the assumption of consistency, only studies containing the global reference treatment b contribute to the estimation of the common interaction term β_c. Due to the consistency equation from equation (5), the functional terms are fixed to 0, as $\beta_{t_1t_2} = \beta_{bt_2} - \beta_{bt_1} = \beta_c - \beta_c = 0$. Overall, the total number of basic and functional estimates obtained from such a NMR is equal to $\binom{T}{2} + 1$.

Under these settings, the design matrix $\mathbf{X}^*$ has dimension equal to $\sum_{i=1}^{N}(K_i - 1) \times T$. For example, fitting a NMR model with consistent and common interaction β_c in terms of the hypothetical network in Section 2.1 is possible using the following design matrix,

$$\boldsymbol{X} = \begin{array}{c} \\ \text{Study 1} \\ \text{Study 2} \\ \text{Study 3} \\ \text{Study 4} \\ \text{Study 4} \end{array} \begin{pmatrix} \mu_{AB} & \mu_{AC} & \mu_{AD} & \beta_{AK} \\ 1 & 0 & 0 & c_1 \\ -1 & 1 & 0 & 0 \\ 0 & 1 & 0 & c_3 \\ 1 & 0 & 0 & c_4 \\ 0 & 0 & 1 & c_4 \end{pmatrix}$$

where the first three columns embed the consistency equations in terms of the basic NMA treatment effects μ_{AB}, μ_{AC} and μ_{AD} as shown in equation (2), and the last column represent the values c_i of the covariate C across all studies. Here, the value c_2 has been replaced with zero to reflect that, under the model settings, only studies containing the global reference treatment, treatment A in this example, contribute in the estimation of the common interaction term β_c. The total number of interaction parameters estimated in this case are illustrated in

Figure **1II.**

The interpretation of the parameters β_{AK} here quantifies the magnitude of the NMA treatment effect change for a unit increase of covariate C, for any comparisons containing the global reference treatment. In such NMR models particular emphasis should be placed on the choice of the global network reference treatment, as different choices can lead to different estimates $\hat{\beta}_{AK}$ and address different clinical questions, as the reference treatment is an integral aspect of the research question. Particularly, selecting a treatment that only occurs once in the network as a global reference may lead to non-estimation of $\hat{\beta}_{AK}$ in the frequentist setting.

Overall, the choice of a NMR with a common interaction term β_{AK} can be particularly relevant in scenarios where the objective is not to estimate comparison-specific interactions, when a treatment behaves differently from others in the network. For instance, when assessing how assigning Non-directive supportive therapy (NDST) as a control treatment affects the magnitude of the treatment effects, researchers may be interested in obtaining a global estimate $\hat{\beta}_c$ rather than a comparison specific interaction, while maintaining the comparison granularity for treatment effect estimates[46]. Moreover, as discussed in Section 3.2.1, the presence of sparse networks can severely affect the performance of a NMR model with independent interactions. In such situations, adopting a common interaction term not only simplifies the estimation process but also enhances precision, as the available evidence is pooled to estimate a single interaction parameter.

2.2.3. Unrelated Mean Interaction Effects (UMIE): Independent Interactions

Assuming a UMIE NMR model with independent interactions implies that, for each pairwise comparison between treatments t_1 and $t_2 = 1,2,\dots T$ in the network, the respective interaction term $\beta_{t_1 t_2}$ is estimated based only on the available direct evidence for that specific comparison, without considering any indirect evidence. Consequently, in such NMR models, an estimate of $\beta_{t_1 t_2}$ can be obtained only if the direct comparison between treatments t_1 and t_2 is informed by at least two studies in the network with varying values $c_i, i = 1,2,\dots N$ for the covariate of interest C. Note that, since the consistency assumption from equation (2) still applies here, the NMA treatment effects are estimated based on both direct and indirect evidence.

For UMIE models with independent interaction terms the exact length of the vector $\boldsymbol{\theta}$ depends on the number of pairwise treatment comparisons in the network that are directly observed. A fully connected network where all direct comparisons contain more than one study would allow the estimation of all possible interactions $\beta_{t_1 t_2}$. In independent UMIE models the vector of unknown parameters $\boldsymbol{\theta}$ has a length equal to $(T-1) + \binom{T}{2}$, where the first part relates to the $(T-1)$ basic NMA treatment effects and the second part relates to the $\binom{T}{2}$ interaction terms. Similarly, the dimension of the design matrix $\mathbf{X}^*$ in this UMIE model is $\sum_{i=1}^{N}(K_i - 1) \times \left[(T-1) + \binom{T}{2}\right]$.

In terms of the hypothetical example in Section 2.1 a UMIE model with independent interactions would have a design matrix equal to

$$\mathbf{X}^{*} = \begin{array}{c} \\ \text{Study 1} \\ \text{Study 2} \\ \text{Study 3} \\ \text{Study 4} \\ \text{Study 4} \end{array} \begin{array}{c} \begin{pmatrix} \mu_{AB} & \mu_{AC} & \mu_{AD} & \beta_{AB} & \beta_{AC} & \beta_{AD} & \beta_{BC} & \beta_{BD} & \beta_{CD} \end{pmatrix} \\ \begin{pmatrix} 1 & 0 & 0 & Z_{1,AB}c_1 & 0 & 0 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 & 0 & Z_{2,BC}c_2 & 0 & 0 \\ 0 & 1 & 0 & 0 & Z_{3,AC}c_3 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & Z_{4,AB}c_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & Z_{4,BD}c_4 & 0 \end{pmatrix} \end{array}$$

where again the first three columns embed the consistency equations in terms of the basic NMA treatment effects μ_{AB}, μ_{AC} and μ_{AD} as shown in equation (2). The rest of the columns relate with the $\binom{4}{2} = 6$ interaction terms. The values of the variables Z depend on the definition of the directionality. **Table 1** includes a pseudo-directionality indicating which treatment is the comparator and which is the reference in each study. The remaining comparisons either do not include any direct studies (e.g. BC), or neither treatment is favorable relative to the other (e.g. AD), and therefore an interaction term cannot be estimated in these cases (

Figure **1III).** Particularly, in the multi-arm studies 4 and 8 the contrast AD involves a comparison between two comparators and therefore it is not accounted for in the model parametrization. This can also be seen considering the definition of the directionality parameter from equation (6), as in this case $Z_{4,AD} = 0$. Consequently, an estimate $\hat{\beta}_{AD}$ cannot be obtained from this UMIE model and only zeros are added in the respective column six of $\mathbf{X}^*$. The study references in **Table 1** involve mixed directionality within a treatment comparison for contrast AB (**Figure 2**). In study 1, A is reference in the AB comparison, and in study 4, B is serves as the reference in the AB comparison. Such scenarios could occur if the references are defined based on a study specific treatment attribute such as sponsorship or control treatment designation[46].

Alternatively, directionality for the UMIE model can use a consistent directionality parameter within comparisons such that within the AB comparison, A is always reference and B is always comparator. When an independent UMIE model uses a consistent directionality parameter within each comparison, the independent interaction terms of the UMIE model have the same interpretation as those in the independent NMR model assuming consistency. However, the core distinction between these two models lies in the amount of information required to estimate all the interactions of interest. The NMR model with consistent independent interactions, estimates the $T - 1$ basic interaction terms and, ultimately, all $\binom{T}{2}$ interactions via the consistency equations using equation (5). Conversely, the UMIE model can estimate all $\binom{T}{2}$ interactions only in the presence of a fully connected network, where each pairwise comparison is investigated in at least two studies having varying values of the covariate C.

2.2.4. Unrelated Mean Interaction Effects (UMIE): Common Interactions

UMIE models can also assume a common interaction term across all comparisons in the network. In this case the length of the vector of the unknown parameters $\boldsymbol{\theta}$ is equal to T, referring to the $T-1$ basic parameters related to the NMA treatment effects and a single parameter β_c related to the common interaction term. The respective design matrix $\mathbf{X}^*$ of this model has dimension equal to $\sum_{i=1}^{N}(K_i-1)\times T$.

In UMIE models with a common interaction term, all pairwise comparisons with a non-zero directionality value contribute to the estimation process, even if they are derived from a single study. However, as in UMIE models with independent interactions, pairwise comparisons that appear solely through multi-arm studies where neither treatment is 'favored' relative to the other are not included in the analysis. With common interactions, consistent directionality for comparisons in fully connected loops leads to mixed directionality across treatment comparisons, as shown in **Figure 2** where in the AB study B is comparator, and in the BC study B is reference, despite theoretically allowing consistent direction within each treatment comparison. Thus, the interpretation of UMIE models with the common interaction are highly dependent on the directionality definitions.

Given these considerations the respective design matrix $\mathbf{X}^*$in terms of the hypothetical data of Section 2.1 would have the following form

$$\mathbf{X}^* = \begin{array}{c} \\ \text{Study 1} \\ \text{Study 2} \\ \text{Study 3} \\ \text{Study 4} \\ \text{Study 4} \end{array} \begin{array}{c} \begin{pmatrix} \mu_{AB} & \mu_{AC} & \mu_{AD} & \beta_Z \end{pmatrix} \\ \begin{pmatrix} 1 & 0 & 0 & Z_{1,AB}c_1 \\ -1 & 1 & 0 & Z_{2,BC}c_2 \\ 0 & 1 & 0 & Z_{3,AC}c_3 \\ 1 & 0 & 0 & Z_{4,AB}c_4 \\ 0 & 0 & 1 & Z_{4,BD}c_4 \end{pmatrix} \end{array}$$

where again the first three columns embed the consistency equations in terms of the basic NMA treatment effects μ_{AB}, μ_{AC} and μ_{AD} as shown in equation (2) while the signs in the last column relate with the definition of the pseudo-directionality variable inequation (6).

The distinction between the UMIE model with a common interaction term and the UMIE model with independent interaction terms is that the former synthesizes evidence from pairwise comparisons investigated within a single interaction, provided that a direction can be specified for the comparison based on the definition of the directionality parameter. For the context of UMIE models, the estimate $\hat{\beta}_Z$ is interpreted as the change in the NMA treatment effect estimates between any two contrasts in the network in the presence of the directionality condition, per unit increase in the covariate C. UMIE contexts imply that $\hat{\beta}_Z$ now adjusts the NMA estimates for all contrasts in the network (

Figure **1 IV**). Previous work showed the ability of the UMIE model with a common across studies assumption to explore the association between a one-unit increase in standard error and treatment effects between older and newer treatments[44].

2.3. Implementation of Network Meta-Regression in R

The frequentist NMR model in **netmeta** is a multivariate meta-regression model that allows users to estimate NMR models with interaction consistency with either common or independent across study interaction structures as described in Sections 2.2.1 and 2.2.2. Implementation first requires a standard **netmeta** object[30]. The following syntax fits the NMA model using a contrast-based dataset named *mydata_contrast* with placebo as the reference treatment:

```
nma <- netmeta(mydata_contrast, reference.group = "placebo")
```

For NMR, users must specify the covariate of interest (e.g. *year_cent*), along with the assumptions and reference treatment. For example, the following syntax can be used to fit an NMR model under an independent-unrelated structure with consistency:

```
nmr_ind_contrast <- netmetareg(nma, covar = year_cent, consistency = TRUE,
assumption = "independent", reference.group = "placebo")
```

The argument 'assumption' allows users to specify either "independent" or "common" across studies interactions. By default, the model output summarizes the basic parameters. The summary function provides estimates for all comparisons considering the underlying modeling assumptions

```
summary(nmr_ind_contrast)
```

Further details regarding the netmetareg() function and its output are available in the documentation.

3. Results

3.1. Clinical Example and Network Meta-Analysis

A previously published meta-analysis of glucose-lowering agents consists of data from 26 trials containing ten treatments, including placebo (**Figure 3I**)[47]. The dataset reports study-level continuous outcomes, defined as either the mean change in glycated hemoglobin (HbA1c) measurements or mean of raw HbA1c measurements at follow-up. NMA results of the estimated mean differences between treatments and residual heterogeneity (τ^2=0.11) have previously been described elsewhere in both frequentist and Bayesian NMA contexts[47,48]. Using NMR, we can explore potential interactions between treatment comparisons and available covariates, such as study year and standard error from this dataset, to quantify potential setting-specific contributors to heterogeneity between the studies. To further illustrate the relationship between of covariate definitions and model assumptions, we introduce two hypothetical variables, study level sponsorship and treatment level sponsorship. Treatment level sponsorship within comparisons is summarized in **Figure 3II**.

3.2. Network Meta-Regression

To illustrate the NMR models and explore residual heterogeneity found in the NMA, we examined the treatment-covariate interactions two study-level covariates, study year and sponsorship, and a contrast-level covariate, standard error. Furthermore, we explored treatment-covariate-covariate interactions between each of the aforementioned covariates and two arm-level covariates, treatment sponsorship and order using UMIE models. Each model provided

unique estimates of the adjusted treatment effect and interaction coefficient. Results of the frequentist NMA and NMR implementations for treatment year are shown in *(***Figure 4***),* with additional NMR results of other covariates available in the supplementary material. The results of analyses from the Bayesian settings are also available in the supplementary material.

3.3. Independent Interactions under Consistency

When implementing the independent NMR model under consistency we used placebo as the network-wide reference treatment for all treatment-by-covariate interactions. Most treatments had interactions for both treatment effects and treatment-by-covariate interactions as shown for study year in the upper right triangle of Figure 5. The model, which reduced residual heterogeneity (τ^2=0.07) relative to the NMA, quantified how changes in the study year influenced treatment effect estimates in comparisons with sufficient data, alongside corresponding adjusted treatment effects.

In 1994, the earliest study year, the largest estimated difference to the standard NMA was in the comparison of sulfonylurea versus benfluorex. The NMR estimated a mean difference (MD) in HbA1c of -1.87 (95%CI: -3.58 to -0.16), whereas the standard NMA model estimated a MD of 0.31 (95%CI: -0.42 to 1.05) for the treatment effect. The corresponding interaction estimate indicated an increase in the mean difference in HbA1c of 0.31 (95% CI: 0.08 to 0.55) with each increasing year. The model did not estimate treatment-by-covariate interactions for comparisons involving sitagliptin and vildagliptin, which were sparsely connected within the network and each appeared in only one study. The model continued to estimate the treatment effects containing the two treatments, and thus assumed that the treatment effects remained unchanged across years.

3.4. Common Interactions under Consistency

We also used placebo as the network-wide reference to implement the common NMR model under consistency, which yielded reduced heterogeneity (τ^2=0.10) compared to the NMA. Study year was associated with an average increase in the mean difference of HbA1c of 0.02 (95%CI: -0.02 to 0.07) per year for all treatments compared to placebo. The estimated treatment effects were adjusted accordingly, and for the year 1994, the corresponding mean difference in HbA1c for sulfonylurea versus placebo was -0.59 (95% CI: -1.17 to -0.02).The interaction term captures the impact of a one-unit change in the study year on the relative treatment effect of each non-placebo treatment compared to placebo (**Figure 6I**). To maintain consistency, the model assumes that there is no change across years in the relative treatment effect between comparisons that do not involve placebo. One such comparison, sulfonylurea versus benfluorex, thus has an estimated mean difference in treatment effect of 0.34 (95% CI: -0.36 to 1.05) across all time points, which is higher than its unadjusted treatment effect in the standard NMA model.

3.5. Unrelated Mean Interaction Effects with Common Interactions

For illustrative purposes, the study-specific reference treatment is defined using a hypothetical treatment sponsorship variable (**Figure 3II*)***. The common UMIE model results in a heterogeneity variance estimate of 0.10 and incorporates evidence from sparsely connected treatment comparisons, such as sulfonylurea versus rosiglitazone, providing adjusted treatment effect estimates for all treatments in the dataset (**Figure 6II**). The single treatment-by-covariate interaction of 0.01 (95% CI: -0.01 to 0.03) quantifies the relationship between study year and treatment effect when using hypothetical treatment sponsorship as a directionality variable. These interactions are assumed to apply uniformly to all treatment comparisons, including sulfonylurea versus placebo and sulfonylurea versus benfluorex, indicating the impact of a one-unit change in the year on the relative treatment effect for any sponsored treatment compared to any non-sponsored treatment in the network.

3.6. Unrelated Mean Interaction Effects with Independent Interactions

Using treatment order to attain consistent directionality within comparisons, the treatment-by-covariate interactions in the UMIE models with independent interactions represent the effect of a one-unit change in the study year on the relative treatment effect for each treatment compared to the preceding treatment within the specified comparison as shown in the bottom left triangle of the figure (**Figure 5**). In this case, the reference treatment in each study was naively defined as placebo, where available, and then the first alphabetically ordered treatment in the study otherwise (**Figure 3II***)*. Using this treatment order as the directionality parameter showed decreased heterogeneity relative to the NMA (τ^2=0.07), and this model estimated an MD in treatment effects for 1994 when benfluorex is favored relative to placebo of -0.07 (95% CI: -1.12 to 0.97), which decreased by 0.08 (95% CI: -0.18 to 0.03) per additional year. When using hypothetical treatment sponsorship as a directionality parameter, rather than treatment order, the estimated heterogeneity increased (τ^2=0.14) and the estimated MD in treatment effects for benfluorex and placebo containing comparisons was -0.34 (95% CI: -1.21 to 0.52), which decreased by 0.06 (95% CI: -0.04 to 0.15) per additional year when either is sponsored. Although the UMIE model is designed to estimate all possible treatment contrasts, the model cannot leverage information from purely indirect comparisons. As no study simultaneously includes both sulfonylurea and benfluorex, this NMR model cannot estimate an interaction and only estimate a constant treatment effect across all values of the study year covariate.

4. Discussion

In this work, we introduce four frequentist NMR models under different assumptions regarding interaction consistency (consistency vs UMIE) and the structure of covariate-by-treatment interactions (independent vs. common) by varying the design matrix structure of the

vary the multivariate meta-analysis. In contrast to standard NMA, where the choice of a reference treatment is arbitrary, the definition of the reference treatment in the design matrix plays a pivotal role in NMR model specifications. To our knowledge, this work presents the first implementation of NMR models in a frequentist framework using design matrices explicitly constructed to reflect the underlying assumptions. Existing approaches have primarily focused on Bayesian estimation[10,40,49,50]. Within the frequentist framework, we introduce the netmetareg() function within the **netmeta** R package to streamline the implementation of NMR models[30]. These frequentist implementations directly provide variance-covariance estimates, enabling projection without model refitting. They also remove the need for covariate centering for numerical stability, instead allowing for informative centering, which is critical for the interpretability of estimates in UMIE models[41]. We also propose a graphical toolkit in the appendix to support the visualization of NMR results and illustrate our findings in a clinical example of diabetes treatments.

NMR models assuming consistency require a single network-wide reference treatment that appears in more than one study. In contrast, UMIE models, which do not impose the consistency assumption on interaction terms, rely solely on directly observed comparisons and are not dependent on a single reference treatment. In UMIE models, reference treatments are defined at the study level, and the choice study specific reference treatments, or directionality, affects estimation. Regardless of consistency, the frequentist implementations in **netmeta** can estimate separate interactions for each treatment comparison, or merge the interactions across comparisons by using common interactions.

A limitation of this work is the lack of NMR models with exchangeable interactions[40,50]. These models share objectives with models assuming common interactions in NMR, but introduce an additional variance term for the interactions that cannot be represented through design matrix modifications alone. In addition, the proposed frequentist implementations do not circumvent fundamental limitations in meta-regression. Though data are curated identified

from randomized evidence, subgroups and indirect comparisons are observational when analyzed across studies in NMR[51,52]. Consequently, NMR findings should be interpreted as exploratory and not causal[16]. When using aggregated patient-specific covariate information, NMR analyses may be subject to aggregation bias. In such cases, individual patient data are preferable, but are often difficult to obtain in practice[53]. Our work focuses on scenarios where only aggregated data are accessible, a common situation in applied research, which is suitable for exploring study level covariates such as risk of bias, study year, and standard error.

When planning and interpreting NMR analyses, researchers should weigh both clinical and practical considerations. Covariates should be pre-specified in the study protocol, and sensitivity analysis can investigate the impacts of modeling assumptions and analysis schemes. Where data are sufficient, the tools and model structures proposed in this work extend the available resources for conducting NMR analyses in applied settings

5. Conclusion

This work introduces frequentist tools and practical guidance for NMR implementation and interpretation to represent key modeling assumptions about consistency and treatment-by-covariate interactions. The proposed tools and guidance enhance interpretability and standardization of NMR implementation, broadening the methodological options for researchers conducting evidence synthesis with study-level covariates. Using NMR, researchers can explore effect modification and compare treatment effects across different levels of a covariate to explain heterogeneity in treatment networks. Identifying and addressing sources of heterogeneity using NMR allows for more reliable estimation of treatment effects, improved interpretation of variability, and enhanced treatment decision-making. Consequently, we believe this work offers practical guidance and tools for evidence synthesis.

6. Abbreviations

NMA: Network Meta-Analysis

NMR: Network Meta-Regression

IPD: Individual Participant Data

UMIE: Unrelated Mean Interation Effects

UME: Unrelated Mean Effect

HbA1c: glycated hemoglobin

MD: Mean Difference

SE: Standard Error

7. Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

The analyses based on example data is fully described in the article. The original data for the applied example can be found in the the original publication(47) (https://doi.org/10.1177/0962280211432220).

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

NK led the project as the primary researcher in the initial development of code and manuscript content. AN initiated and conceptualized this project. TE and AN provided supervision and methodological refinements throughout the project. GS and NK created the R code and

contributed to software. TE and NK wrote the main manuscript. JM, ES, and ME provided clinical context and application insights. AN, TE, GS, JM, ES, and ME critically revised the article. AN and ES acquired funding. All authors contributed to reviews and editing. All authors approved the final version.

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9. Table and Figure Legends

Table 1: Hypothetical Data

Hypothetical network of 4 treatments. c: observed covariate value, y: observed effect, $SE(y)^2$: observed study variance

Study Design ID	Study	Observed Covariate	Study Reference	Treatment	Observed Effect	Observed Variance
1	Study 1	c_1	Reference	A	y_{1A}	$SE(y_{1A})^2$
1	Study 1	c_1	Comparator	B	y_{1B}	$SE(y_{1B})^2$
2	Study 2	c_2	Reference	B	y_{2B}	$SE(y_{2B})^2$
2	Study 2	c_2	Comparator	C	y_{2C}	$SE(y_{2C})^2$
3	Study 3	c_3	Reference	A	y_{3A}	$SE(y_{3A})^2$
3	Study 3	c_3	Comparator	C	y_{3C}	$SE(y_{3C})^2$
4	Study 4	c_4	Comparator	A	y_{4A}	$SE(y_{4A})^2$
4	Study 4	c_4	Reference	B	y_{4B}	$SE(y_{4B})^2$
4	Study 4	c_4	Comparator	D	y_{4D}	$SE(y_{4D})^2$

Table 2: Interpretation of Covariate Assumptions

Summary of the included across study and consistency assumptions in aggregate data meta-analyses

	Interaction Definition Assumptions		**Consistency Imposed at**
	Independent	***Common***	
Question Addressed by the model interaction term	I. For every possible comparison of two treatments, t_1 and t_2, regardless of whether they are observed, how does the average treatment effect between t_1 and t_2 change among studies with differing levels of the covariate X?	II. How does the average treatment effect between the network-wide reference treatment, b, and all other treatments in the network change among studies with differing levels of the covariate X?	***Treatment Effect and Interaction Consistency***
Reference Type	Network-Wide		
Question Addressed by the model interaction term	III. For observed comparisons of two treatments, t_1 and t_2, how does the average treatment effect between the study-specific reference treatments t_1 and each comparator treatment t_2 change among studies with differing levels of the covariate X?	IV. How does the average treatment effect between all study-specific reference treatments t_1, and all other treatments, t_2, in a given study change among studies with differing levels of the covariate X?	***Only Treatment Effect Consistency (UMIE)***
Reference Type	Study-Specific		

Figure 1: Visualizing Assumption Estimation Capabilities in a Network

Interaction estimation capabilities for each assumption in the hypothetical network of 4 treatments. Solid lines indicate that the interaction could be estimated with sufficient data. Dotted lines indicate non-estimation or an estimation of 0 for the interaction. Arrow heads indicate the direction of favorability in the underlying direct comparison. Treatment D is the reference treatment in models with consistency. UMIE models do not have a network wide reference treatment and therefore each comparison contains a study specific reference.

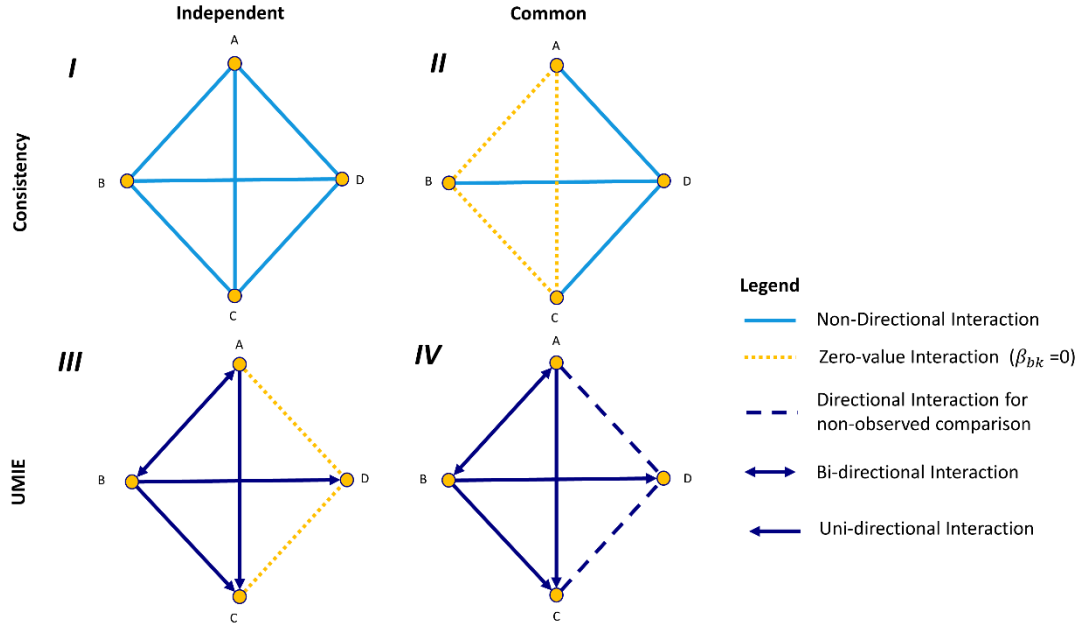


Figure 2: Mixed Directionality

Mixed Directionality in the hypothetical data. Yellow bars indicate non-favored treatments, or study specific references. Blue bars indicate favored treatments.

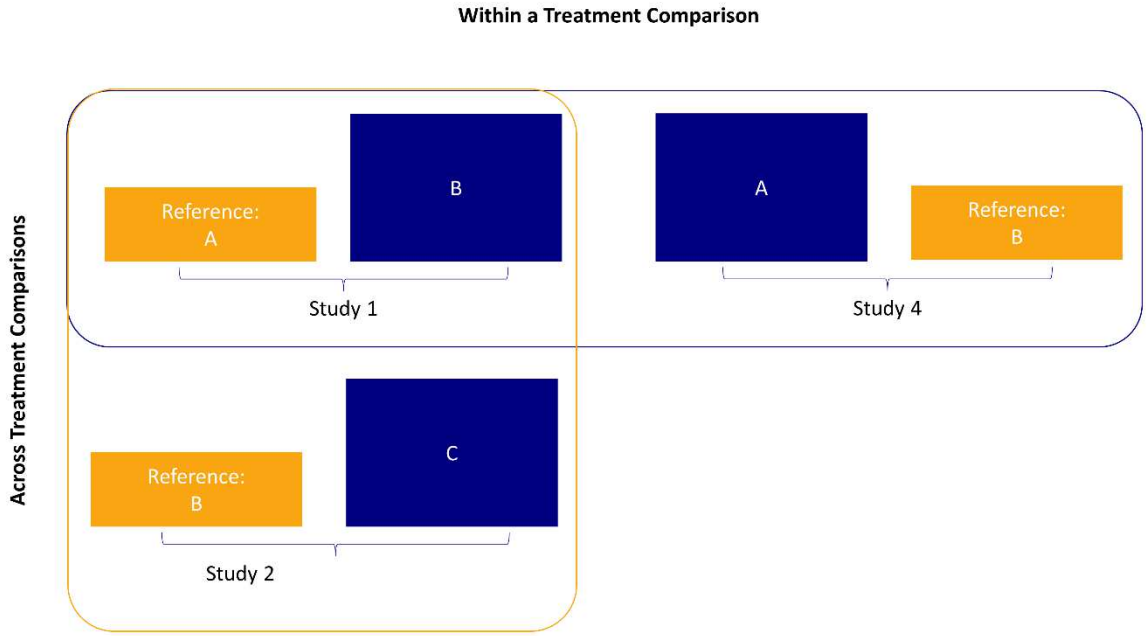
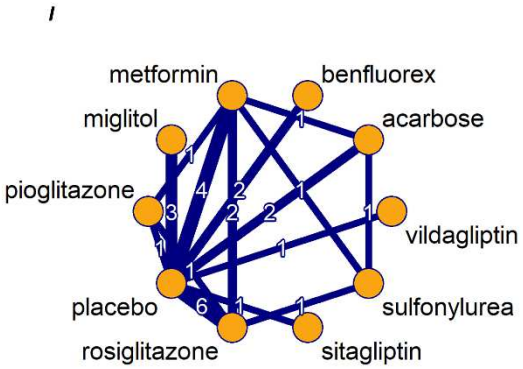


Figure 3: Network Plot

Network of trials and treatments for the diabetes example and direction in UMIE models[47]. Arrows in panel II determine which treatment is favored in the UMIE models and correspond to treatment order and the hypothetical treatment sponsorship variable.



II

Reference Treatment	Directionality defined by „Treatment Sponsorhip ALT"	Treatment Order	Comparator Treatment	Number of studies
acarbose	–	–	metformin	1
metformin	→	→	pioglitazone	1
metformin	←	→	rosiglitazone	2
pioglitazone	→	→	rosiglitazone	1
acarbose	→	→	sulfonylurea	1
metformin	→	→	sulfonylurea	1
rosiglitazone	→	→	sulfonylurea	1
placebo	→	→	acarbose	2
placebo	**↔**	**→**	**benfluorex**	**2**
placebo	**↔**	**→**	**metformin**	**4**
placebo	↔	→	miglitol	3
placebo	→	→	pioglitazone	1
placebo	**↔**	**→**	**rosiglitazone**	**6**
placebo	→	→	sitagliptin	1
placebo	→	→	vildagliptin	1

Figure 4: Fairy Light Plot All Models

Estimated mean difference of HbA1c for the year 1994 by type of analysis, for each treatment comparison. Values less than 0 favor the depicted reference treatments. Values greater than 0 favor the depicted comparator treatment.

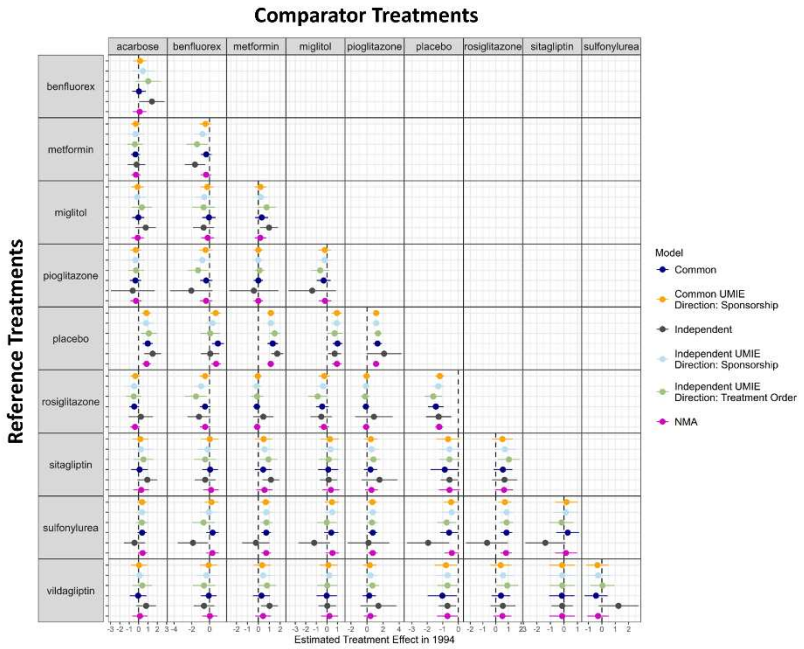


Figure 5: Independent Flashlight Plots

Estimated mean difference of HbA1c since 1994 across study years for each treatment comparison in the independent-unrelated consistency and UMIE models. Directionality indicates whether the comparator or reference treatment was favored within the study in the UMIE model

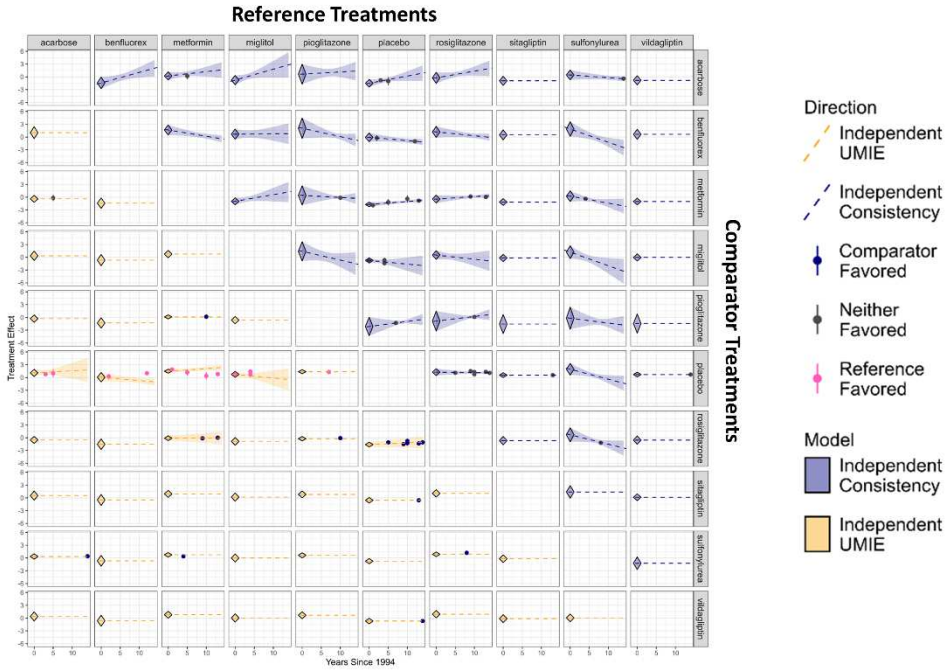
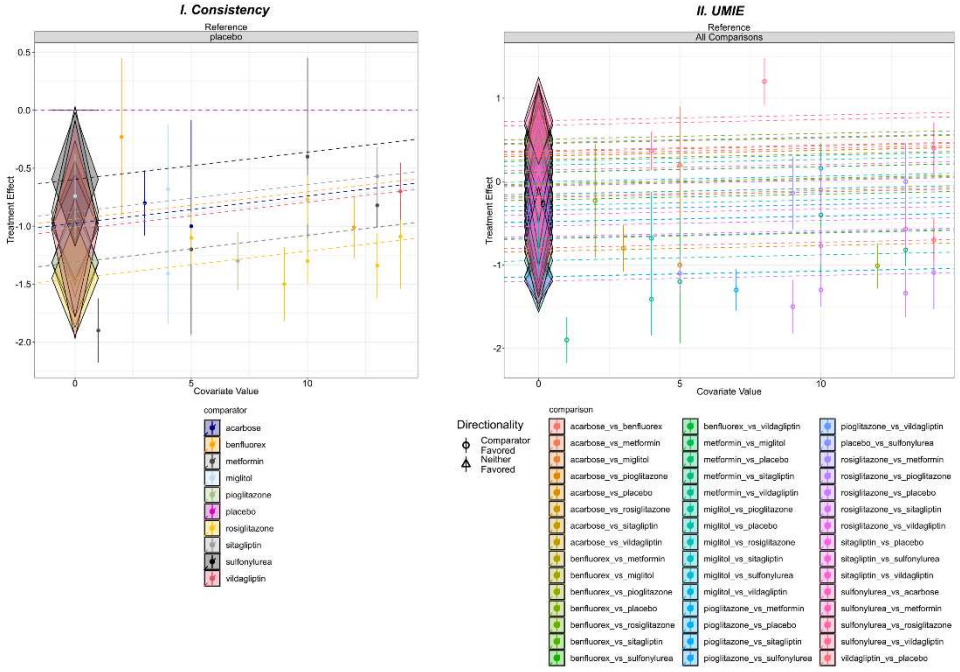


Figure 6: Common Firefly Plots

Estimated mean difference of HbA1c since 1994 across study years for each treatment compared to placebo in the common model with consistency.

Estimated mean difference of HbA1c since 1994 across study years for each treatment comparison in the common UMIE model. Directionality indicates whether the comparator or reference treatment was favored within the study



Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementTablesIllustratingAssumptionsMetaRegressionTreatmentNetworks10.xlsx
- SupplementIllustratingAssumptionsMetaRegressionTreatmentNetworks10.docx