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Using R Software to Conduct Network Meta-Analysis on Diabetes Data

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Abstract

A meta-analysis's goal is typically to quantify the total treatment effect and draw conclusions regarding the differences in effects between the two treatments. Meta-analysis is a quantitative method for combining the findings of several studies in the social and medical sciences. A meta-analysis might be of three typical forms. Network-wide, pairwise, and multivariate meta-analyses are all possible. The integrated assessment of more than two treatments is generally made possible by network meta-analysis (NMA). Mainly, frequentist and Bayesian frameworks are used to categorize statistical methods to NMA. Because a portion of NMA includes indirect, repeated comparisons, as network meta-analyses grow more popular, it is critical to introduce the method to readers and provide information on how to interpret the results. This chapter defines words used in NMA, provides an overview of pertinent statistical concepts, and uses an example of a network containing diabetes treatments and the R program to demonstrate the NMA analytic method based on the frequentist and Bayesian framework. The article's goal is to compare the fundamental ideas and analyses of NMA with diabetes data and employed treatment approaches.

Keywords: Network meta-analysis (NMA), diabetes treatment, R software, frequentist and Bayesian frameworks, statistical methods in meta-analysis

INTRODUCTION

Meta-analysis is used to combine the findings of multiple studies, and the overall effect size is considered valid only if certain assumptions are met [1]. The growing number of alternative medical treatment choices has created a demand for comparative efficacy studies [2, 3]. Other methodological strategies are needed because randomized controlled trials that compare various treatment options are usually ruled impracticable. A meta-analysis integrated into a systematic review is often regarded as a beneficial statistical tool because it allows the combination of data from multiple studies to offer a complete estimate of the treatment effect.

However, typical meta-analyses have a significant constraint in that only two therapies can be examined simultaneously. When there are multiple treatment options to consider, a series of individual meta-analyses can provide only partial information because they can only answer questions about pairs of treatments, making optimal clinical decisions difficult. After all, each meta-analysis is only one component of the overall picture. The need for a method to compile evidence from various therapies is increasing [4].

A network meta-analysis (NMA) was created to synthesize data from several randomized trials and assess the relative efficacy of various therapies [5–7]. It is sometimes referred to as a multiple treatment meta-analysis or mixed-treatment

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comparison. This approach is predicated on the analysis of direct data, which comes from studies that directly randomize treatments of interest, and indirect data, which comes from studies that contrast treatments of interest with a common comparator [8].

Some applications and methodological publications [2, 9, 10] have commented on the benefits of network analysis as it has grown in popularity. Figure 1 shows the total number of published NMA papers published. The publication of network meta-analyses is on the rise.

The basic assumptions of pairwise meta-analysis and NMA are similar, but because NMA is used less often, it has been criticized more [11].

Methodologically, logically, and statistically more rigorous assumptions on similarity, transitivity, and consistency made by NMA [12–17] are because it should be determined whether any of these is satisfied [15, 18–21].

There are several ways to determine how much each comparison's direct and indirect evidence contributes to its own NMA estimate when it comes to NMA, but it is less clear how to characterize each study's contribution to a different estimate of the treatment effect. Numerous recommendations, each based on a distinct methodology, have been made in the literature; however, many of them have drawbacks, and their conclusions typically contradict each other [20, 22–24]. Several studies have examined the relative strengths of direct and indirect evidence. Among these is the "back calculation" method [21] developed by Dias. Other methods have been suggested that use a Bayesian framework [25].

There is also one proposed frequentist framework [13]. 'Node splitting' was proposed as an alternative by Dias and other people. Node splitting determines indirect evidence by modeling all studies that provide direct information [25]. Others referred to this procedure as 'side splitting' after it was modified [26, 27]. Different meanings of "side" have been assigned to it in the literature. For instance, White [27] defines it as an edge in a network graph, while others [28, 29] see it as an acronym for "Separating Indirect and Direct Evidence," or SIDE.

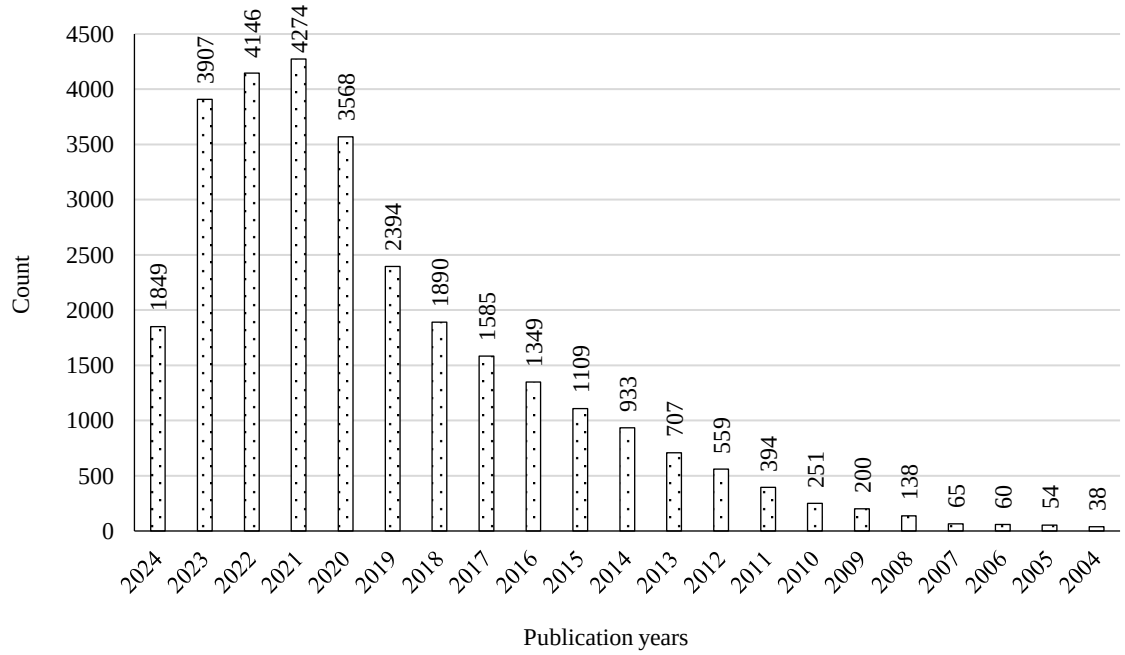

Figure 1. The number of papers containing network meta-analyses (retrieved from Web of Science through June 2024).

Regardless of the analytical model selected, there are six fundamental procedures that any NMA ought to take. These steps include.

1. understand network geometry,
2. comprehend important ideas and presumptions,
3. carry out analysis and provide findings,
4. evaluate the model's assumptions using both local and global testing,
5. establish a ranking system for competing interventions.
6. conduct heterogeneity and sensitivity analyses.

Because it aids in visualizing the studies that are currently accessible and the body of evidence across many comparisons, a network plot is essential to an NMA. In this type of graph, every treatment or comparator found in the review is represented by a node and the studies that visually demonstrate a direct comparison between two interventions are depicted by edges connecting the appropriate nodes. Figure 2 shows a network plot of our scenario.

A type 2 diabetes treatment network is shown in Figure 2. The lines connecting the treatment nodes indicate which comparisons were performed in the randomized trials. The absence of a line connecting two nodes indicates that no studies (i.e., direct evidence) have been conducted to compare the two medications. An NMA simultaneously examined the data from all randomized trials. Even if no trials have compared these two therapies, an NMA can be used to assess their relative effectiveness.

If there is direct evidence (e.g., metf vs. sulf in Figure 2), the NMA can integrate direct and indirect estimates. Then, a mixed effect size can be calculated by averaging the direct evidence, that is, studies that directly compare metf and sulf—and indirect evidence—that is, studies that compare metf and acar through placebo. The network formed by comparing metf against acar, acar against placebo, and metf against placebo in a study is sometimes referred to as a loop of evidence.

An NMA can use both direct and indirect evidence. Empirical research can provide more precise estimates of the impacts of an intervention than either a single direct or indirect estimate [30, 31].

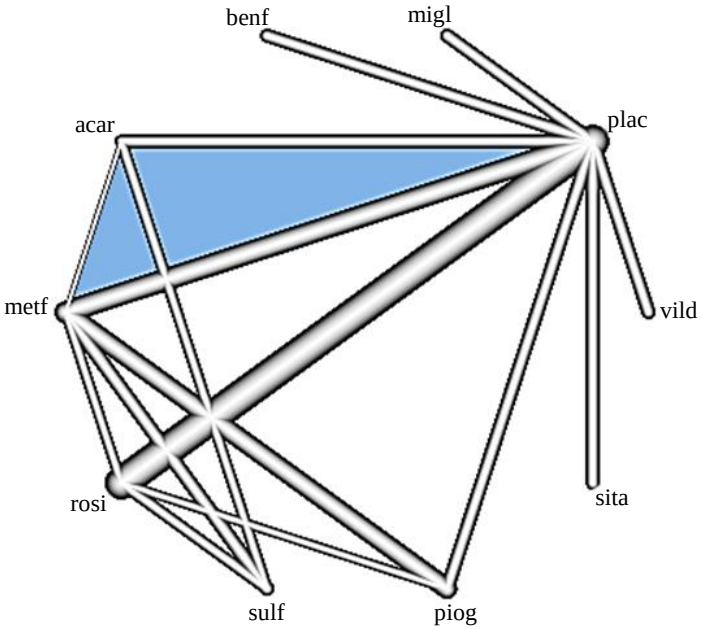

Figure 2. An illustration of the network created for the diabetes data using the netgraph function.

Simultaneous comparison of all interventions of interest for a particular outcome allowed us to assess their relative ranking within the same analysis. The structure of the paper is as follows. We present an overview of the NMA techniques found in our literature search in the following sections. Section 2 introduces fundamental concepts and core techniques for NMA. Section 3 uses diabetes treatment data as an example. The final section summarizes our research, and the results obtained through NMA diabetes data using the R tool.

CONCEPTUAL PROBLEMS AND PRESUMPTIONS IN NETWORK META-ANALYSIS

In an NMA, there may be several therapeutic options for a given health issue. NMA stands out by combining direct and indirect estimations to determine the relative impact of each treatment, enabling the selection of the most effective course of action. Studies that compare two treatments, A and B, head-to-head (AB studies), can be used to make direct comparisons. Studies comparing these two therapies to a common comparator therapy C, known as AC and BC studies [27], can also provide an indirect approximation. The mixed-treatment impact can be computed by integrating direct and indirect estimates, as illustrated in the left panel of Figure 3.

As demonstrated in the example in the right panel of Figure 2, there may be numerous direct and multiple indirect estimates obtained through numerous different comparators for treatment comparison inside such a network.

All these data may be compared using NMA to obtain an internally consistent summary of the relative contributions of each therapy. Regarding the applicability of employing indirect treatment comparisons (indirect evidence) in decision-making, researchers are still at odds. Strong justification exists for not using these results, especially in cases where there are direct treatment comparisons (direct evidence) [32–35]. Hence, confounding factors (e.g., when randomized AB and AC trials are consistently different from BC) may make indirect treatment comparisons more vulnerable to skewed treatment effect estimates [30] and prejudice in selection (for instance, when the study's comparator is chosen in accordance with the relative treatment effect) [36].

Indirect Comparisons

Examine Trial 1, a two-arm study comparing B to A, and Trial 2, a two-arm study comparing C to B. An indirect comparison of "C–A" may be achieved as $\hat{\delta}_{indirect}^{AC} = \hat{\delta}_1^{AB} + \hat{\delta}_2^{BC}$ if the estimated effect sizes in these trials are in $\hat{\delta}_1^{AB}$ Trial 1 and $\hat{\delta}_2^{BC}$ Trial 2. If the underlying treatment effects have the following relationships with one another, the network of these three trials can only be considered consistent:

$$\hat{\delta}_3^{AC} = \hat{\delta}_1^{AB} + \hat{\delta}_2^{BC} \tag{1}$$

Here, $\hat{\delta}_1^{AB}$,$\hat{\delta}_2^{BC}$ and $\hat{\delta}_3^{AC}$ represent the actual effects of these three investigations. It is improbable that Equation (1) holds true in practice for a particular set of three trials such as those mentioned above. In the following sections, these two ideas are discussed in further detail [37].

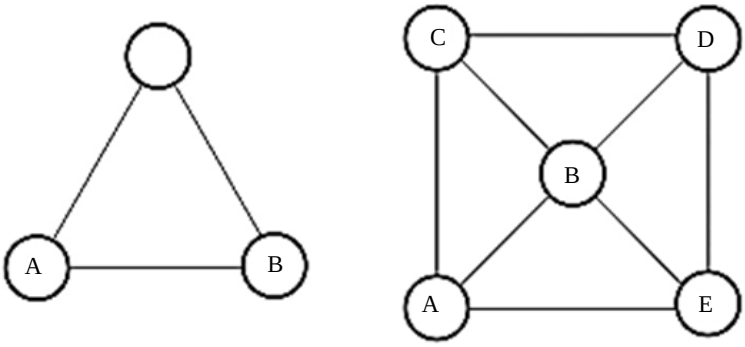

Figure 3. Direct comparisons are shown by lines, and each circle represents an intervention.

Heterogeneity

Heterogeneity in the meta-analysis, which refers to the circumstances in which several studies addressing the same research topic have disparate underlying values with respect to the effect measure underestimation, has been extensively studied in the literature to date. If the study index is altered while the treatment comparison remains unchanged, the heterogeneity in the NMA scenario can be explained. In particular, if $\hat{\delta}_i^{AB} \neq \hat{\delta}_j^{AB}$ can demonstrate that there is heterogeneity for comparison 'B–A' for a pair of studies i and j. Heterogeneity is an essential part of meta-analyses [38].

The use of a random effects model is a common technique used to account for heterogeneity. This assumes that the main effect in several comparisons originates from a single distribution, which is often a normal distribution.

$$\hat{\delta}_i^{JK} \sim N\left(\delta^{JK}, \tau_{JK}^2\right)$$

employing values AB, AC, or BC in the running example for pairwise comparison JK [37]

Consistency

Consistency is a statistical representation of the transitivity [12]. Another technique for making implicit judgments about the feasibility of the transitivity assumption is to examine the network for consistency. Consistency is the statistical concordance between direct and indirect visible sources of information. A basic network can have only three treatments: A, B, and C.

For a single comparison, the best possible relationship between direct and indirect evidence is often determined by using a consistency equation.

$$\delta^{AC} = \delta^{AB} + \delta^{BC} \tag{2}$$

JK represents the average effect size across all the comparison studies. For comparison, JK, and dJK denote a fixed (common) treatment effect in a fixed effect meta-analysis paradigm that does not presume heterogeneity. We call evidence that meets the consistency equation "showing consistency." Figure 4(a) depicts a three (non-touching) solid-edge relationship triangle in a network with only two-arm trials. A two-arm experiment comparing two treatments at the opposing ends of an edge is represented by one or more edges. To show that there is no contradiction (inconsistency) between the three edges, that is, because Equation (2) is true, we draw a solid line for each of the three edges [37].

Loop Inconsistency

The consistency Equation (2) may not hold when studies concentrating on numerous treatment comparisons are sufficiently different from one another that their effect sizes change; as a result, the effect sizes are not "added up" around the loop in the diagram. This is known as loop inconsistency and is demonstrated by drawing edges with various line styles (Figure 4(b)). Only when discrete comparisons are conducted in at least three different research groups (e.g., studies 'B-A', 'C-A', and 'C-B') may loop inconsistency arise. This is only possible when we obtain estimates of an impact magnitude that are both direct and indirect (for instance, when 'C-B' is estimated both directly and indirectly through 'A') [37]. The following list of causes of loop consistency includes the following examples.

Multi-arm Trials

Network meta-analyses typically include trials with more than two treatment arms. In fact, almost one-quarter of randomized trials have more than two arms [39], so it is critical to choose proper procedures when dealing with the situation. The concept of loop inconsistency in evidence networks with several experimental arms has become increasingly challenging. A multi-arm study cannot account for loop inconsistencies.

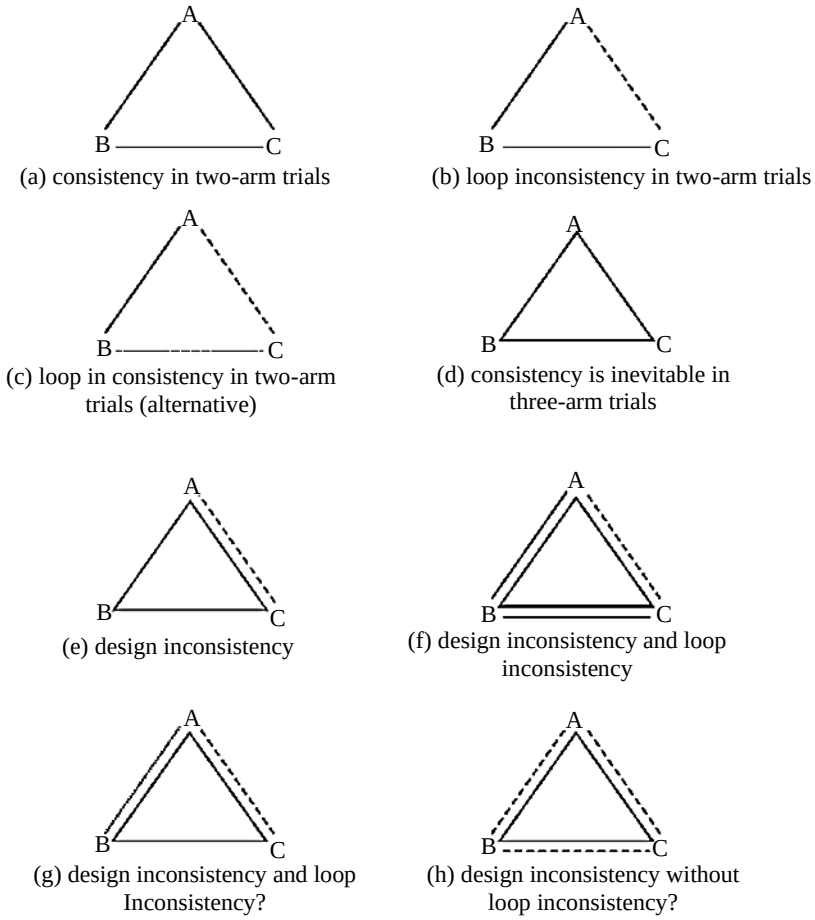

Figure 4. Consistency, loop inconsistency, and design inconsistency are graphically shown.

Therefore, consistency in a network may arise observationally (assuming that assumptions about the equality of direct and indirect comparisons hold across studies), architecturally (because all trials contain all treatments), or through a combination of the two. Furthermore, loop inconsistency cannot be correctly described using Equation (2) because the average effect size δ^{JK} now corresponds to pairwise comparisons derived from a combination of potentially inconsistent loops (e.g., from two-arm trials) and naturally consistent loops (e.g., from multi-arm trials). In our illustrations, multi-arm trials are represented by a closed (merged) polygon [37] (Figure 4(d)).

Transitivity

NMA aims to enhance the process of choosing between different treatments for a particular audience and a specific health condition. Therefore, the estimates meant to be estimated in an NMA are the mean relative treatment effect sizes of therapies that are anticipated to compete with one another in the target population. NMA adopts the same set of assumptions as pairwise meta-analysis [40], but it also adopts another assumption that can be difficult to check [41], which is called transitivity [42]. Also known as similarity [43, 44], or exchangeability [45]. Transitivity is the ability to gather information about one treatment C through comparisons between A, B, and C, and between C and another therapy. Although this assumption cannot be statistically tested, it can be conceptual and epidemiological [21]. According to the transitivity assumption, (indirect) insights into the AB comparison can be obtained by direct evidence from AC and BC investigations. However, this begs the question of whether the distribution of effect modifiers—variables or traits that modify the observed relative effects, such as treatment dose and participant mean age—between the AC and BC trials has changed significantly, offering insights into the indirect comparison [42, 46].

Consequently, one way to assess the validity of the transitivity assumption is to search for significant shifts in the distribution of effect modifiers within the body of research. Assuming that the trials are identical, transitivity may be reasonable if the relative treatment impact does not have any unknown modifiers. [47]. If substantial differences are detected and adequate data are provided, the transitivity of the network can be improved using network meta-regression. A meta-analysis of trials examining fluoride treatments administered to prevent dental cavities revealed that the definition of a placebo varied between fluoride toothpaste and fluoride rinse studies [48], raising questions about the viability of the transitivity assumption.

Another example was studied by Julious and Wang [49], who examined how the population's changing placebo response over time can distort the results of indirect comparisons when a placebo is used as an intermediate comparator. An indirect estimate for A against B may be biased; for example, if studies evaluating therapy A versus placebo are older than studies comparing treatment B versus placebo, another method to express the transitivity assumption is to assume that, regardless of the treatments compared in each study, the true relative effect of A against B is the same in the fixed effects model or may vary between trials in the random effects model [45, 50], that any treatments that are absent from a trial are absent at random [51]. Alternatively, the selection of treatment comparisons in trials has no bearing on the relative efficacy of the various therapies.

Lastly, another way to hypothesize this assumption is to say that the included patients can be assigned at random to any of the therapies in the network [21].

However, this does not imply that the transitivity assumption is always true. It should be observed that, as previously mentioned, the transitivity assumption is functionally untestable, and the lack of statistical inconsistency offers no evidence to support its validity.

Design Inconsistency

The 'design' of a study refers to a collection of treatments that are compared inside the study, which differs from traditional interpretations of the term. Design inconsistency refers to discrepancies in effect sizes between studies that used distinct sets of treatments. It is implicitly expected that multiple designs, including different treatment sets, can act as proxies for one or more significant modifiers of effect while still permitting this flexibility.

Similarity

To compare clinical trial research, it is important to use similar methodologies [12, 48]. The methodological assessment of the resemblance between the selected articles was qualitative rather than statistically testable. The population, intervention, comparison, and outcome (PICO) technique [17] was used to assess similarity. The analysis compared studies based on four criteria: clinical characteristics of study individuals, therapeutic interventions, comparative therapies, and outcome measures. Failure to satisfy the similarity assumption has a detrimental effect on the other two assumptions [46]. Furthermore, it is imperative to confirm the existence of the heterogeneity error [18, 52].

NETWORK DIAGRAMS

A network diagram is a tool for visually representing the organizational structure of a network of interventions [12]. A graph such as this is made up of lines that display direct comparisons between pairs of treatments that are currently accessible and nodes that reflect the interventions in the network. Figure 3 shows an example of a network diagram with four interventions. In this example, discrete lines that constitute a closed triangular loop are inserted to demonstrate the existence of three-arm research. It should be noted that this method of presenting multi-arm research may result in intricate and meaningless network diagrams in which a tabular style may be more appropriate for displaying multi-arm studies.

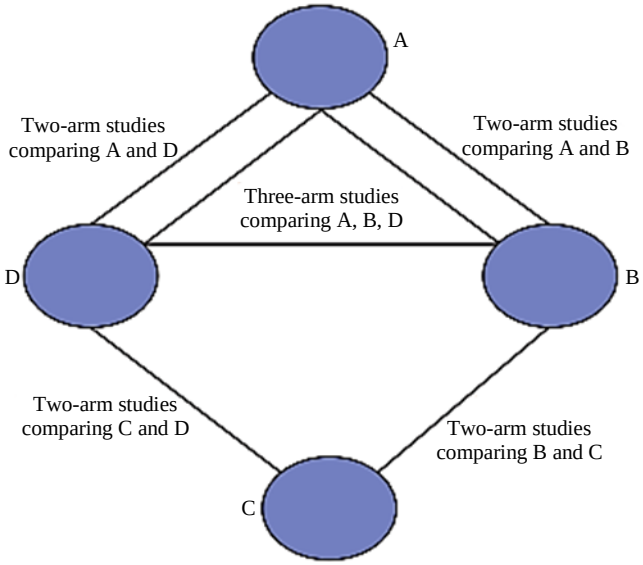

Figure 5. An illustration of a network diagram showing information on the existence of multi-arm randomized trials and four competing interventions.

ILLUSTRATING EXAMPLE

The goal of the diabetes NMA was to determine how adding various oral glucose-lowering drugs to baseline sulfonylurea therapy in people with type 2 diabetes would affect their HbA1c levels. A systematic literature search was conducted on all relevant articles published between January 1993 and June 2009 in MEDLINE and Embase. The search parameters used in the strategy were "humans," "sulfonylurea or sulphonylurea," and "randomized controlled trials." Combining the key terms from the Medical Subject Headings "chlopropamide," "glibenclamide," "glyburide," "gliclazide," "glimepiride," "glipizide," "gliquidone," and "tolbutamide" with the term "RCT" verified this exploratory search. There were no language restrictions. The R software was used for analysis.

Senn [53] provided an original dataset that we employed in our first NMA. This dataset included effect size data from randomized controlled studies that compared different diabetic treatments. The mean difference (MD) of the post-test HbA1c levels for individuals with diabetes was calculated for all comparisons. This figure represents the glucose concentration in the blood, which was intended to be reduced using diabetic medications. As can be seen, the data consists of seven columns and 28 rows representing treatment comparisons. The effect size of each comparison is shown in the first column (TE) along with the matching standard error.

The impact size data that has already been generated for each comparison is not available. The terms treat1.long, treat2.long, treat1, and treat2 refer to the two therapies being compared. Since the variables treat1 and treat2 only contain a shortened form of the full treatment name, they are unnecessary, and we can now use the netmeta function to fit our original NMA model. Now, we can examine the outcomes of our first model, which assumes a fixed effects model. We can now create our network graph (Figure 2) after establishing our NMA model. This network graph conveys several different forms of information.

- First, using our network's basic comparison structure, we can determine which treatments are compared with the original data.
- Second, there are edges with varying thicknesses, which indicates the frequency of this particular comparison in our network. Numerous studies have compared rosiglitazone with placebo.
- Our network included one multiarm study (indicated by a blue triangle). Next, by determining the extent to which each comparison's direct and indirect contributions contribute to the rate, we may concentrate on direct and indirect evidence in our network. Direct.evidence.plot is the name of the function that was developed.

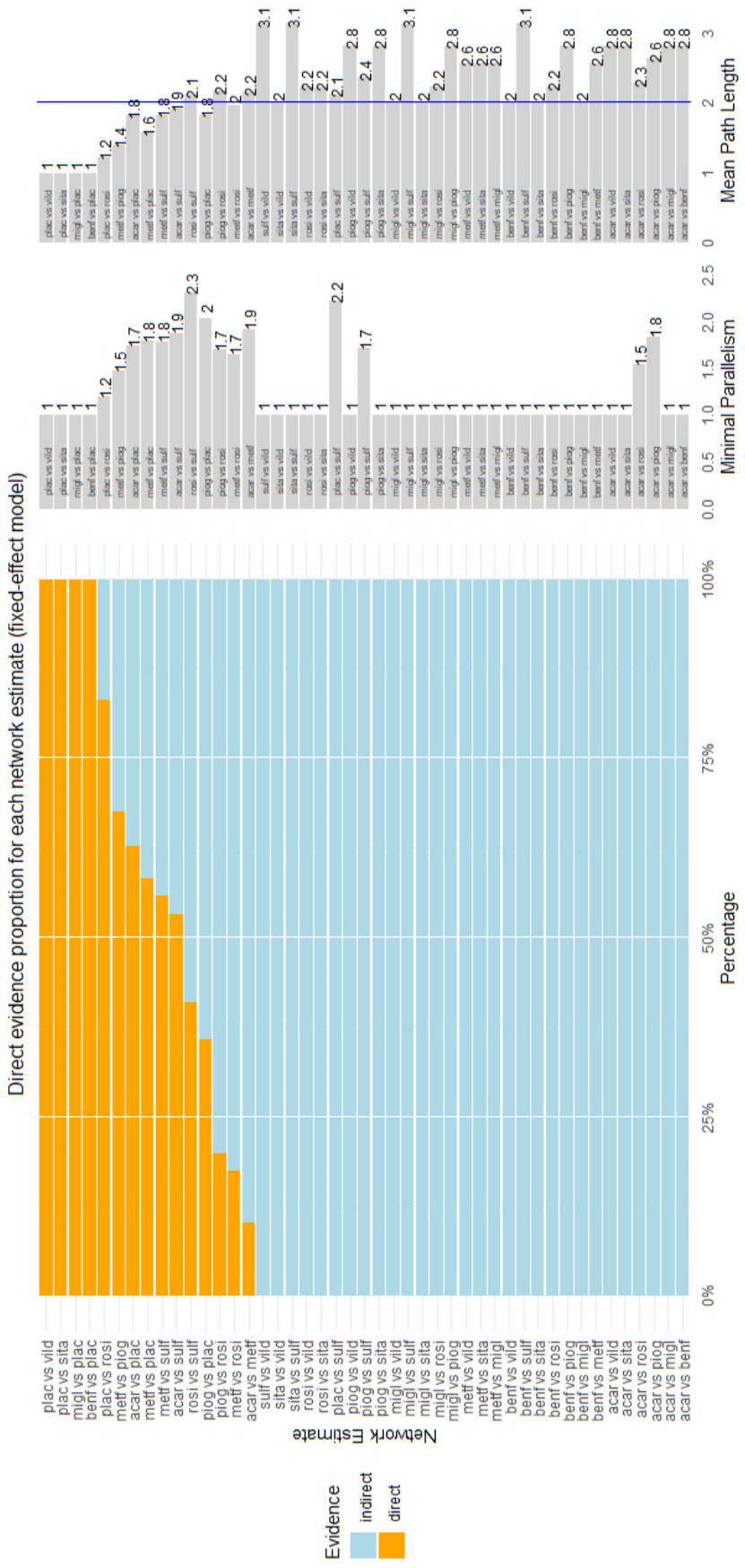

Figure 6. Direct evidence proportion for each network estimate.

As shown in Figure 6, our network model contains many estimations that can only be inferred indirectly. The Figure 6 provides two additional metrics: Minimal parallelism and mean path length for each comparison. König [54] noted that lower values of minimal parallelism and mean path length > 2 indicate that caution should be exercised when interpreting the results for a specific comparison. The predictions of our network can then be verified for every possible combination of treatments. To do this, we can use the result matrices stored in our netmeta results object, which follow the fixed effects paradigm.

With a few preprocessing steps, the matrix can be made more readable. First, we extract the matrix from our data and round the numbers into three digits.

```
       acar   benf   metf   migl   piog   plac  rosi   sita   sulf   vild
acar  0.000  0.078  0.287  0.117  0.239 -0.827 0.374 -0.257 -0.388 -0.127
benf -0.078  0.000  0.209  0.039  0.161 -0.905 0.297 -0.335 -0.466 -0.205
metf -0.287 -0.209  0.000 -0.170 -0.048 -1.114 0.088 -0.544 -0.675 -0.414
migl -0.117 -0.039  0.170  0.000  0.123 -0.944 0.258 -0.374 -0.504 -0.244
piog -0.239 -0.161  0.048 -0.123  0.000 -1.066 0.135 -0.496 -0.627 -0.366
plac  0.827  0.905  1.114  0.944  1.066  0.000 1.202  0.570  0.439  0.700
rosi -0.374 -0.297 -0.088 -0.258 -0.135 -1.202 0.000 -0.632 -0.762 -0.502
sita  0.257  0.335  0.544  0.374  0.496 -0.570 0.632  0.000 -0.131  0.130
sulf  0.388  0.466  0.675  0.504  0.627 -0.439 0.762  0.131  0.000  0.261
vild  0.127  0.205  0.414  0.244  0.366 -0.700 0.502 -0.130 -0.261  0.000
```

When we evaluate the fact that a “triangle” in our matrix has too much redundant information, the bottom triangle can be replaced by an empty value.

```
     acar  benf    metf    migl    piog     plac     rosi    sita     sulf     vild
acar "0"   "0.078" "0.287" "0.117" "0.239"  "-0.827" "0.374" "-0.257" "-0.388" "-0.127"
benf "."   "0"     "0.209" "0.039" "0.161"  "-0.905" "0.297" "-0.335" "-0.466" "-0.205"
metf "."   "."     "0"     "-0.17" "-0.048" "-1.114" "0.088" "-0.544" "-0.675" "-0.414"
migl "."   "."     "."     "0"     "0.123"  "-0.944" "0.258" "-0.374" "-0.504" "-0.244"
piog "."   "."     "."     "."     "0"      "-1.066" "0.135" "-0.496" "-0.627" "-0.366"
plac "."   "."     "."     "."     "."      "0"      "1.202" "0.57"   "0.439"  "0.7"
rosi "."   "."     "."     "."     "."      "."      "0"     "-0.632" "-0.762" "-0.502"
sita "."   "."     "."     "."     "."      "."      "."     "0"      "-0.131" "0.13"
sulf "."   "."     "."     "."     "."      "."      "."     "."      "0"      "0.261"
vild "."   "."     "."     "."     "."      "."      "."     "."      "."      "0"
```

The netleague() function provides a straightforward way to export all estimated effect sizes. This function can build a matrix identical to that described above. However, as would be gained if a traditional meta-analysis were carried out for each comparison, the upper triangle in the matrix produced by this function will only represent the pooled effect sizes from the direct comparisons that are available in our network. Certain fields in the upper triangle are unfilled because not all comparisons have direct evidence. The lower triangle in this example displays the NMA effect sizes for each comparison.

The main advantage of this function is that it allows us to display both effect size estimates and confidence intervals together in each cell. We only need to provide the number of digits we want our estimates to have behind the comma and the style of the confidence interval brackets. In an NMA, the most interesting issue is which intervention works best. The netrank() function, which is implemented in netmeta, can perform this type of treatment ordering from most to least useful. The netrank() function is based on a frequentist treatment ranking algorithm that uses P-scores.

These P-scores indicate the degree of confidence that one treatment is superior to another. This P-score is the same as the SUCRA score [55]. Our netmeta object is required as an input by the function. Moreover, it is necessary to supply a small-value parameter, which establishes whether smaller effect

sizes in comparison signify a beneficial ("good") or detrimental ("bad") influence. Let us now look at the output of our example.

```
      P-score
rosi   0.9789
metf   0.8513
piog   0.7686
migl   0.6200
benf   0.5727
acar   0.4792
vild   0.3512
sita   0.2386
sulf   0.1395
plac   0.0000
```

The drug rosiglitazone has the greatest P-score, as can be shown, indicating that it might be especially helpful. The placebo, on the other hand, has a P-score of zero, confirming our suspicion that it is not the optimal treatment option. However, it should be highlighted that simply having the highest score does not guarantee that treatment is the best [56]. Using the "weakest" treatment for comparison, network forest plots are a useful tool for displaying uncertainty in our network. Moreover, forest plots can be used for this purpose. The reference group of the forest plot can be specified using group argument.

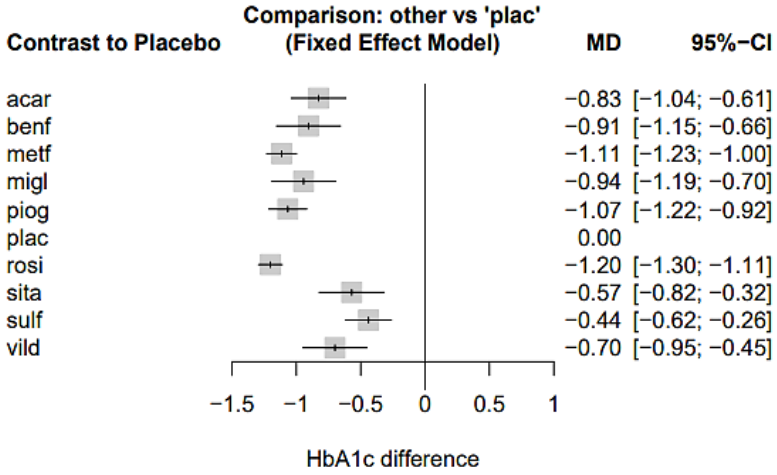

Figure 7. The fixed effect model forest plot uses a placebo as the reference.

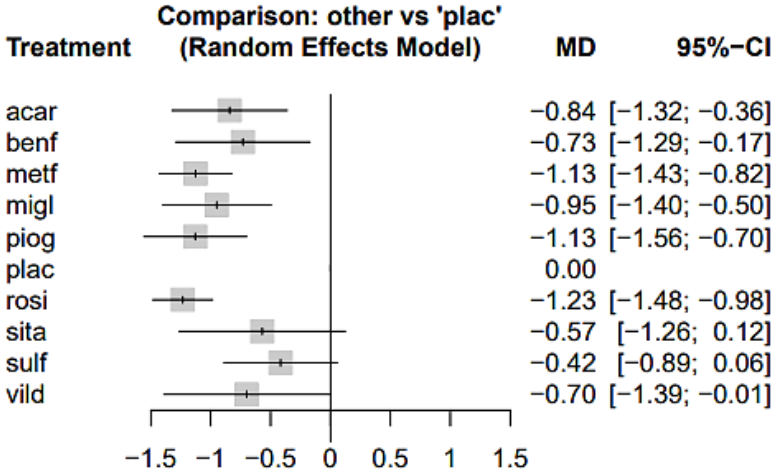

Figure 8. Random effects model forest plot using placebo as the reference.

Currently, it appears that the results are less clear than they were previously, and multiple effective treatments with overlapping confidence intervals were found.

It is now evident that there are many high-performance therapies with overlapping confidence ranges, making the results more perplexing than previously believed. This means that we cannot make a solid decision on which treatment is best, but we can see that several therapies are more effective than the placebo.

Breakdown of Statistics on Heterogeneity

One can separate the Q total statistic (of the "whole network") into two Q statistics: one to evaluate design inconsistency ("between designs"), and the other to quantify heterogeneity across studies with the same design ("within designs"). The groupings of treatments compared to each other in a study established the design.

```
                         Q df         pval
Total            96.98555 18 7.871369e-13
Within designs   74.45528 11 1.723944e-11
Between designs  22.53027  7 2.057014e-03
```

Using the fixed effects model for this study, it is evident that there is a great deal of heterogeneity and inconsistent practices within and between designs. The contribution of each design can be used to further decompose the overall within-design heterogeneity.

```
                design      Q df     pval
1          acar vs sulf  0.000  0       NA
2          metf vs piog  0.000  0       NA
3          metf vs rosi  0.187  1 6.65e-01
4          metf vs sulf  0.000  0       NA
5          piog vs rosi  0.000  0       NA
6          plac vs acar  0.000  0       NA
7          plac vs benf  4.381  1 3.63e-02
8          plac vs metf 42.164  2 6.98e-10
9          plac vs migl  6.449  2 3.98e-02
10         plac vs piog  0.000  0       NA
11         plac vs rosi 21.273  5 7.19e-04
12         plac vs sita  0.000  0       NA
13         plac vs vild  0.000  0       NA
14         rosi vs sulf  0.000  0       NA
15 plac vs acar vs metf  0.000  0       NA
```

As can be seen, the NMA contains 26 trials with 15 different designs. The remaining design-specific Q statistics are zero with no degrees of freedom because there are only five designs for which there is more than one investigation. Except for design metf:rosi (p = 0.67), heterogeneity was greater than expected between contributing studies for all four designs, with metf:plac significantly more (p < 0:0001). This could have sources that are found in a substantive application, in which case, the analysis can be adjusted.

```
                    Q df  pval tau.within
Between designs 2.194  7 0.948       0.38
```

As can be seen, the NMA contains 26 trials with 15 different designs. The remaining design-specific Q statistics are zero with no degrees of freedom because there are only five designs for which there is more than one investigation. Except for design metf:rosi (p = 0.67), heterogeneity was greater than expected between contributing studies for all four designs, with metf:plac significantly more (p < 0:0001). This could have sources that are found in a substantive application, in which case, the analysis can be adjusted.

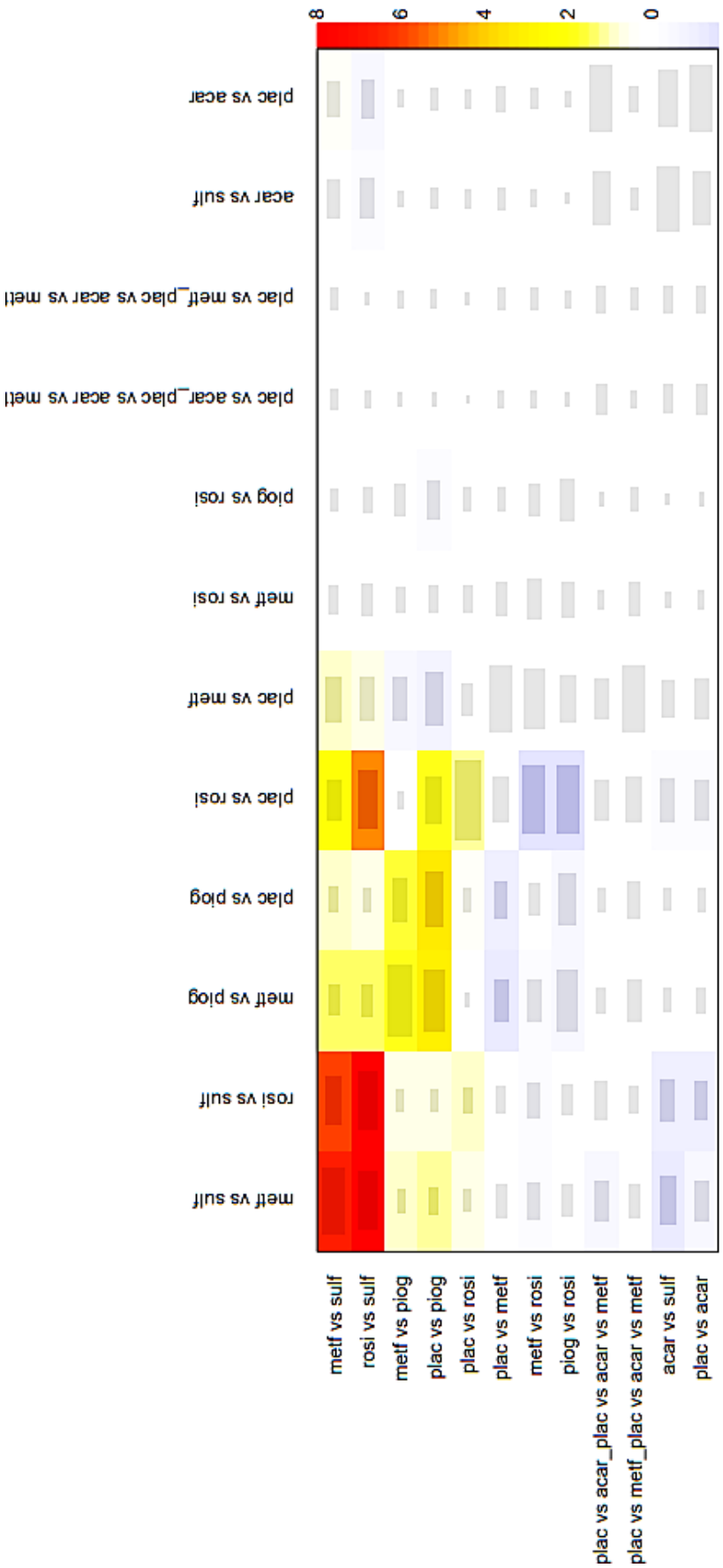

Figure 9. Senn data example's net heat plot based on a fixed effect model.

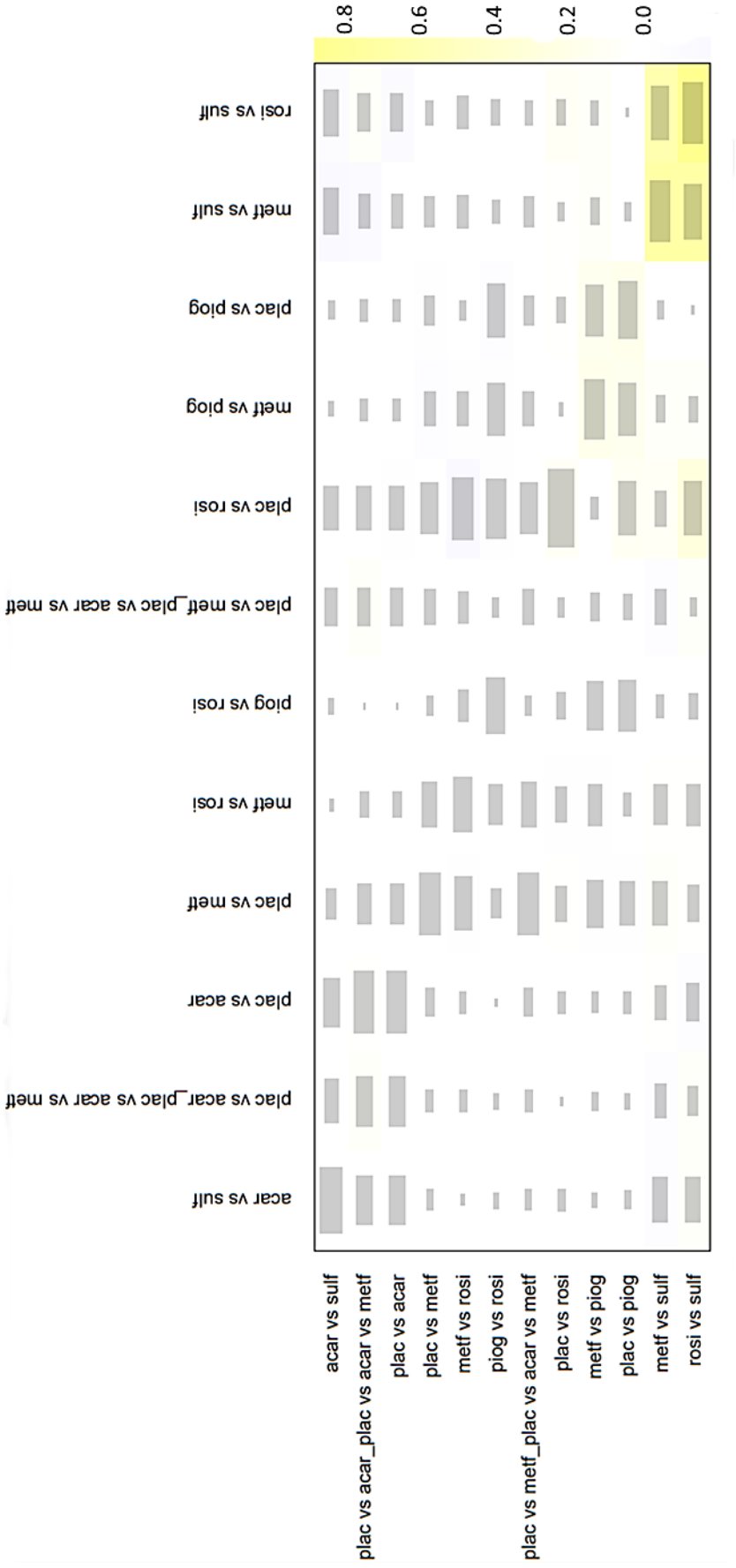

Figure 10. Senn data example's net heat plot from a random effects model.

By producing a quadratic matrix, this function makes it possible to compare every element in a row with every other element in each column. It is important to note that the rows and columns relate to specific designs rather than to all treatment comparisons in our network. Thus, rows and columns were produced by the multi-arm study comparing "Plac," "Metf," and Acar. As we are dealing with instances of disagreement between direct and indirect data, this chart does not include comparisons of treatments with only one type of evidence (direct or indirect evidence).

Additionally, there were two noteworthy features of the net heat plot: 1. Boxes in gray color. The gray boxes for each design comparison indicate how essential one treatment comparison is when calculating another. The comparison becomes increasingly significant when the box is larger. This can be studied simply by looking through the plot rows one by one and then determining which columns have the greatest gray boxes. Where the row and column comparisons cross, the boxes are large, which is a common result and indicates that direct evidence is used. For example, when the "Plac vs. Rosi2" row and the "Plac vs. Rosi2" column converge, a large gray box may be seen [57].

The irregularity of the row is emphasized by the vibrant backdrops, which vary in hue from blue to red, and can be connected to the design of the column. Inconsistent fields are highlighted in red in the upper-left corner. For example, the entry in the column "Metf vs. Sulf" is highlighted in red in the row "Rosi vs. Sulf." This suggests that there is an incompatibility between the data and the data that supports the "Metf vs. Sulf" estimate.

A huge gray box is located at the junction of the "Plac vs. Rosi2" row and the "Plac vs. Rosi2" column [57]. The irregularity of the row is emphasized by the different backdrops, which range in color from blue to red and are related to the design of the column. Inconsistent fields are indicated in red in the upper-left corner. For instance, in the "Rosi vs. Sulf" row, the entry in the "Metf vs. Sulf" column is underlined in red. This indicates that the data used to support the "Metf vs. Sulf" estimates are inconsistent with the other data.

Net Splitting

Another method for confirming the consistency in our network is called net splitting, which is also called device splitting. By dividing our network estimates into direct and indirect contributions, we can account for discrepancies in individual comparisons within our network using this technique. to produce a net split and to evaluate the outcomes. In this case, the p-value column contains crucial data. If the value in this column is $p < 0.05$, an appreciable difference (inconsistency) exists between the indirect and direct estimates. When the fixed effects model is applied, it is evident from the results that there are, in fact, few comparisons that demonstrate appreciable differences between direct and indirect evidence. Figure 11 illustrates how the netsplit results can be presented using a forest chart that includes all comparisons with direct and indirect evidence.

CONCLUSION

NMA has the potential to be a strong tool for estimating and comparing treatment effects in a specific region by incorporating all available information. A diabetic example has been used to illustrate this method [53], which demonstrates how to graph the network and carry out several analytics. The extent of information collected in a specific treatment comparison via indirect evidence, as well as the extent of heterogeneity, are two crucial components of NMA. The net heat graph transmits information about both, and the program enables the breakdown of heterogeneity within and between the designs. It is worthwhile to look into this further if there is clinically significant heterogeneity because it is not feasible.

Because the software currently does not support covariate adjustment, one method is to undertake study-specific (preferably individual participant data) studies with proper covariate adjustment before using the software presented here to perform an NMA.

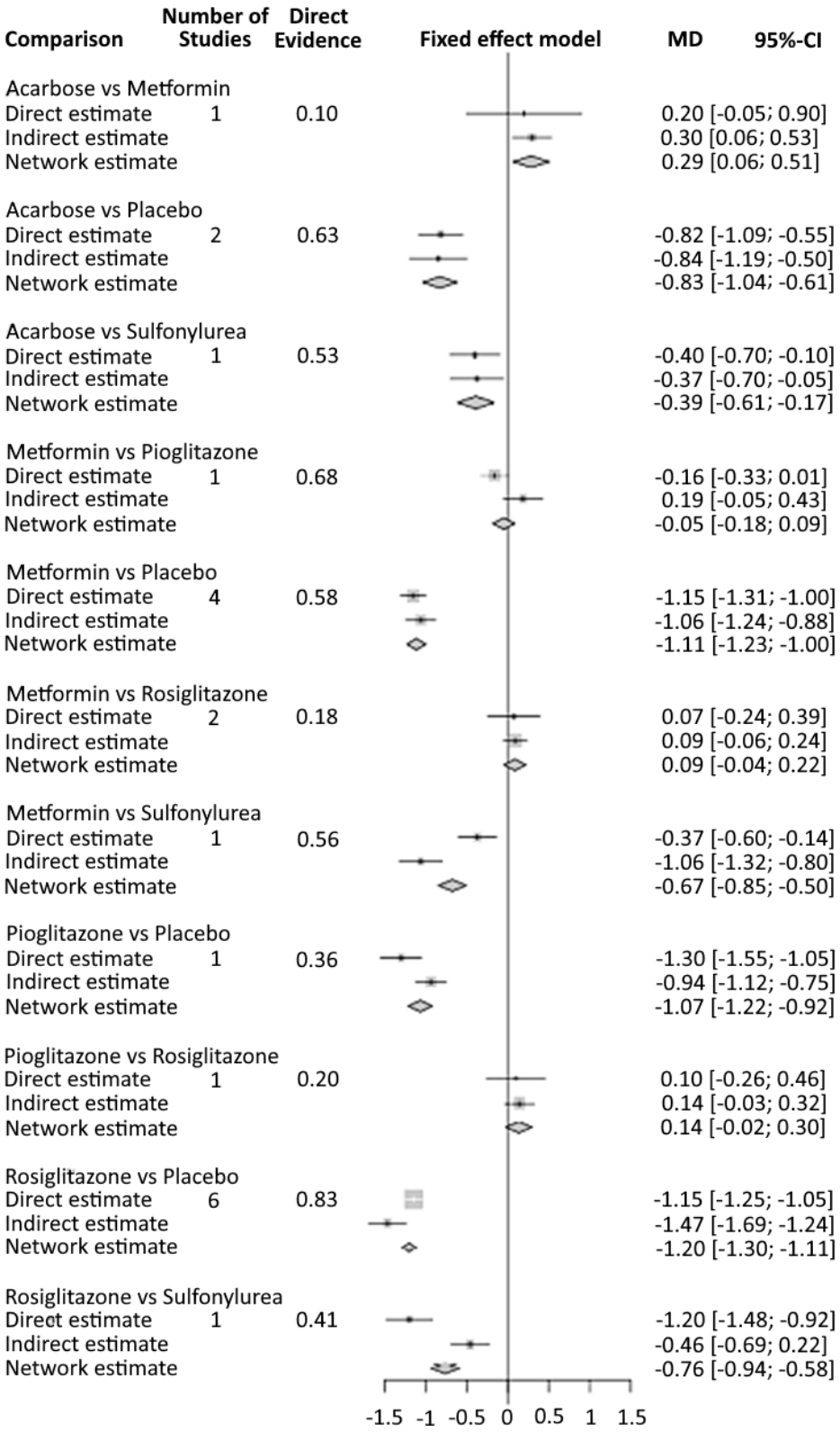

Figure 11. Example of the net split-plot of Senn data using a fixed effect model.

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