

Getting started with Network Meta-analysis in Health Psychology

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Introduction

Meta-analysis has been an important evidence synthesis methodology in health psychology and indeed many health sciences for several decades now (Gurevitch, Koricheva, Nakagawa, & Stewart, 2018). Standard approaches to pairwise meta-analysis are clearly described in multiple accessible sources and commercial and free software to conduct meta-analyses are widely available (Borenstein, Hedges, Higgins &

Rothstein, 2011; Field and Gillett, 2010). The fundamentals of the method are usually covered in post-graduate training in health psychology and frequently in undergraduate psychology courses. In the context of the replication crisis in psychology, meta-analysis has achieved even greater importance and visibility over the last 5-10 years (Open Science Collaboration, 2015). For example, it can help health psychologists identify more precise estimates of the magnitude of intervention effects, moderators of interventions effects, publication biases and indeed the absence of efficacy for some widely advocated approaches in the health psychology intervention literature (Hollands et al., 2016).

Indeed, in the wider literature evaluating

complex interventions for health, standard pairwise meta-analysis is the data analytic mainstay of key evidence syntheses to inform healthcare practice. For example, provided that there are sufficient number of homogenous studies to synthesise, this approach is used in most Cochrane Reviews of RCT evaluations of healthcare interventions (Higgins & Green, 2011). One of the main limitations of pairwise meta-analysis, however, is that while it can tell whether an intervention works compared to something else e.g. 'treatment as usual' or a control condition, it cannot tell us which intervention is optimal out of all the available options for intervention. This is particularly problematic as many intervention approaches that may compete with each other for healthcare resources may not have been compared against each other within individual RCTs. Therefore, pairwise meta-analysis cannot address the critical research question of what intervention works best (Kanters et al., 2016).

A relatively recent data-analysis method where indirect comparisons can be made is known as **network meta-analysis or NMA** (Dias et al., 2018; Hutton et al., 2015). This approach has been developed over the last 10 to 15 years in the broader health literature and is gaining increasing prominence as a critical part of evidence synthesis, however the fundamentals are often unfamiliar to those working in health psychology and related fields (Molloy et al., 2018). In this paper, we will provide a short introduction to the key conceptual issues regarding NMA and a step-by-step tutorial, with accompanying annotated code, on the conduct of a NMA.

NMA can provide indirect comparison that allows

assessment of comparative effectiveness of interventions that may not have been compared against each other within a single trial. This can be achieved when a number of conditions are met with the most fundamental being that studies have a control, treatment as usual or other intervention condition that is shared among the studies being compared – that is, we have a connected network of treatments. This allows for an indirect comparison to be made such as the one outlined in Figure 1 below. In this example, a number of studies have compared Intervention A with Intervention C, while others have compared Intervention B with Intervention C. NMA can be applied to estimate the indirect comparison between Intervention A and Intervention B. If direct comparisons between Intervention A and Intervention B exist, these can be synthesised with the indirect comparisons to produce a more accurate NMA estimate. Naci and Ioannidis (2013) produced an evidence network with a similar structure in one of their analyses where they synthesised direct comparisons between physical activity interventions and usual care, direct comparisons between antihypertensive drug interventions and usual care, and indirect comparisons between physical activity interventions and antihypertensive drug interventions.

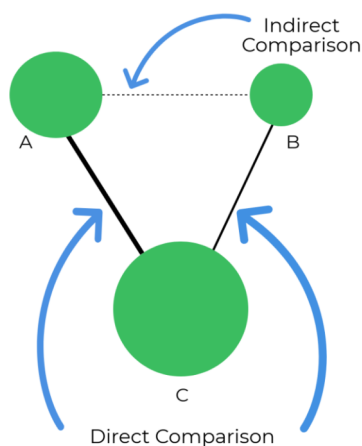


Figure 1. An evidence network including both direct and indirect comparisons.

The circles are referred to as nodes and represent each intervention. Their size usually represents the number of participants who received that intervention across all included studies. The lines connecting the nodes represent comparisons – solid lines indicate direct comparisons are present and dotted lines indicate that only indirect comparisons are possible. The thickness of the lines represents the number of studies which include that comparison.

In order to apply NMA validly, the assumption of *transitivity* must be met. When transitivity is present, it is assumed that any indirect comparison between two interventions in a network of evidence is a valid estimate of the direct comparison between these two interventions. When such direct comparisons do not exist, this assumption cannot be tested statistically. In these cases, transitivity can be qualitatively assessed by identifying potential effect modifiers (e.g. participant demographics, intensity of intervention, setting of intervention etc.) and assessing whether they are evenly distributed across the included studies (Salanti, 2012). When both direct and indirect comparisons exist, statistical tests of the *consistency* of the direct and indirect comparisons (i.e. their similarity) should be conducted (Dias et al., 2013).

Networks of Evidence in Health Psychology

There are specific considerations which need to be made when applying NMA to evidence from studies of behavioural interventions. This is because, in contrast to pharmacological interventions, on which the majority of studies applying NMA have focused so far, behavioural interventions are often made up of a number of different interacting components (Craig et al., 2013) and have much greater variation in the nature of their comparators (de Bruin et al., 2009).

This increases heterogeneity and affects the transitivity assumption.

The complex nature of behavioural interventions can affect transitivity because intervention components may be selected for specific groups or specific settings within the same patient population and this may introduce an uneven distribution of effect modifiers. Careful consideration of possible effect modifiers such as the setting, treatment intensity and participant characteristics is necessary. An extension of NMA – network meta-regression – can be applied to adjust for effect modifiers. Another important issue in considering evidence networks in health psychology is the content of control conditions. The control conditions to which behavioural interventions are compared are often complex too. Furthermore, they can vary significantly in their content which complicates the structure of the evidence network if several alternate interventions for a given behaviour and patient population are compared to several qualitatively different control conditions (de Bruin et al., 2009). The use of taxonomies developed within health psychology (e.g. Kok et al., 2016; Michie et al., 2013; Nudelman & Shiloh, 2015) can aid with the qualitative assessment of intervention components (including those within control conditions) and other effect modifiers.

When synthesising studies of complex interventions using traditional pairwise meta-analysis, we are forced to lump these interventions. This ignores the fact that these interventions are made up of a number of different components, the presence of which is likely to vary across the different interventions across the studies which are being synthesised. NMA allows us to represent different complex interventions as separate nodes in a network of evidence. Welton, Caldwell, Adamopoulos, & Vedhara (2009) explore four different modelling options for assessing the effects of components within complex interventions using NMA:

1. *Single Effect Model*: All behavioural treatments are grouped as one and compared to usual care.

2. *Additive Main Effects Model*: The effects of all components for each intervention are added together. This assumes that intervention components have independent treatment effects.

3. *Two-Way Interaction Model*: Allows for interactions between the components of each intervention. This assumes that the effect of one intervention component may enhance or diminish the effect of another intervention component.

4. *Full Interaction Model*: Each possible combination of components is treated as a different intervention.

The first model is simply a traditional pairwise meta-analysis model. The fourth model is analogous to a standard NMA model, where each treatment is considered separately. In many NMAs we do not need to consider the middle models as the issue of multiple components does not arise. However, although models 2 and 3 are under-utilised at present, we recommend implementation of these models in health psychology to learn more about the nature of interactions between intervention components in complex interventions. These models should be tested against one another to determine which fits the data best (Caldwell & Welton, 2016).

A Tutorial on Applying Network Meta-analysis to Complex Health Interventions

The next section will describe an NMA of behavioural interventions for reducing systolic blood pressure (SBP) by increasing adherence to antihypertensive medication. Data and annotated code for the analyses presented are available at <https://osf.io/6xp4s/>. Use of this code requires the installation of R (R Core Team, 2016), which we

recommend running through RStudio (RStudio Team, 2016), and WinBUGS (Lunn, Thomas, Best, & Spiegelhalter, 2000). The following steps should be undertaken when carrying out an NMA:

1. Conduct a systematic review to identify relevant studies and code interventions.
2. Extract data from each study.
3. Select and run models.
4. Interpret and report the results.

It is necessary that the search, screening, intervention coding, data extraction and analysis are carried out according to a pre-specified protocol. We recommend using both the PRISMA-P (Moher et al., 2015) and PRISMA-NMA (Hutton et al., 2015) checklists to guide the development of the protocol.

Systematic Review

A systematic review and meta-analysis was conducted by Morrissey et al. (2016) to examine the effect of medication adherence interventions on blood pressure control in hypertension. While the review focused on a pairwise meta-analysis, subsequent work on the dataset has allowed a network meta-analysis to be conducted on the interventions focused on reducing SBP. SBP was chosen rather than DBP for illustrative purposes as it is considered to be the most clinically relevant biomarker of hypertension (Basile, 2009).

Interventions were coded according to the context of the delivery. The variation in delivery contexts were considered a priori to be the intervention components contributing most to the heterogeneity among the interventions and coding the interventions in this way allowed us to answer a substantive research question about the optimal mode of delivery of adherence interventions for people with hypertension. This coding was done by one reviewer and based on the intervention description provided in each paper. Details of the coding can be seen in Table 1. Among the 12

included studies, 6 unique interventions were identified. However, one of these interventions was composed of two separate components which meant that we needed to consider the complex intervention models as detailed by Welton and colleagues (2009). Therefore, the four models described earlier were tested against each other to clarify whether a single treatment effect underlies the difference between the behavioural interventions and usual care (model 1), whether independent treatment effects for each intervention component sum together to produce the treatment effect (model 2), whether independent treatment effects for each intervention component interact to produce the treatment effect (model 3) or whether each combination of intervention components produces a unique treatment effect (model 4). For the *Single Effect Model*, we could only use 11 studies as Svarstad (2013) did not have an arm for usual care.

Data from RCTs

When modelling a continuous outcome the mean in each group at the start of the study (mean at baseline), the mean change in each group, and the standard deviation (SD) of the change in each group are required. All studies reported the mean at baseline and the mean change in each group, (or we were able to compute the mean change using mean of each group at follow-up). However, most studies reported the SD at baseline and follow-up as opposed to the SD of the change. Using Higgins & Green (2011), it is possible to compute a correlation coefficient from studies which report all three SDs (baseline, follow-up, and change), and then use this coefficient to impute the SD of the change. Two studies in our analysis (Marquez Contreras, 2005; Marquez Contreras, 2006) reported all three SDs. We therefore computed a correlation coefficient from these studies. However, the five arms from these studies had very different

Table 1. Description of included interventions.

Name	Intervention Type	Context
Amado 2011	Educational intervention	Primary care and home (materials)
Amado 2011	Usual care	Usual care Primary care and home
Dusing 2009	Supportive measures	(materials)
Dusing 2009	Usual care	Usual care
Friedberg 2014	Stage matched intervention	Home (telephone)
Friedberg 2014	Educational intervention	Home (telephone)
Friedberg 2014	Usual care	Usual care
Hosseinasab 2014	Self-monitoring of BP	Home (materials)
Hosseinasab 2014	Usual care	Usual care Primary care and home
Ma 2013	Motivational interviewing	(materials)
Ma 2013	Usual care	Usual care
Marquez Contreras 2005	Mail intervention	Home (materials)
Marquez Contreras 2005	Telephone intervention	Home (telephone)
Marquez Contreras 2005	Usual care	Usual care
Marquez Contreras 2006	Self-monitoring of BP	Home (materials)
Marquez Contreras 2006	Usual care	Usual care
Morgado 2011	Pharmacist intervention	Secondary care
Morgado 2011	Usual care	Usual care
	Positive affect and	Primary care and home
Ogedegbe 2012	educational intervention	(telephone) Primary care and home
Ogedegbe 2012	Educational intervention	(telephone) Primary care and home
Rudd 2004	Nurse management	(telephone)
Rudd 2004	Usual care	Usual care
Schroeder 2005	Nurse management	Primary care
Schroeder 2005	Usual care	Usual care Primary care and home
Stewart 2014	Pharmacist intervention	(materials)
Stewart 2014	Usual care	Usual care Primary care and home
Svarstad 2013	Pharmacist intervention	(materials)
Svarstad 2013	Patient information	Home (materials)
Tinsel 2013	Shared decision making	Primary care
Tinsel 2013	Usual care	Usual care Primary care and home
Wong 2013	Pharmacist intervention	(materials)
Wong 2013	Patient information	Usual care

correlation coefficients (0.22-0.71), with a weighted average (using the square root of the number of people in each arm) of 0.41. Two previous NMAs on blood pressure use a correlation coefficient of 0.5, which is close to the mean we obtained, so we also use 0.5 to impute the SD of the change for other studies (Follmann, Elliott, Suh, & Cutler, 1992; Welton et al., 2009). The choice of the correlation coefficient could potentially alter the results of the NMA, therefore we could test other values of the coefficient in what is known as a sensitivity analysis.

Models and Software

The NMA was carried out in WinBUGS (Lunn et al., 2000) using the R2WinBUGS package in R (Sturtz, Ligges, & Gelman, 2005). This is Bayesian software, based on Markov Chain Monte Carlo (MCMC), which uses an iterative process. When using MCMC we need to check for convergence by checking that the Brooks-Gelman-Rubin statistic is close to 1 (Gelman & Rubin, 1992, Brooks & Gelman, 1998). An acceptable threshold is generally 1.1. This is given by "Rhat" in the R2WinBUGS output.

We modelled an improvement in the SBP based on Schmitz and colleagues (2012) and Schmitz, Adams and Walsh (2013), with adjustments for multiple components based on work by Welton and colleagues (2009). These models use a random effects assumption which assumes that the true underlying effect can vary from study to study. These models are included in the appendix. As we have no treatment with three components the Two-Way Interaction Model and the Full Interaction Model simplify to be the same model, which we will refer to as the Interaction Model. We used the Deviance Information Criterion (DIC; Spiegelhalter, Best, Carlin, & Van Der Linde, 2002) to distinguish between the three different models. Differences greater than three are usually deemed to mean

that the model with the lower DIC has a better fit (Welton et al., 2009).

We checked for inconsistency by comparing our standard consistency model to an inconsistency model. The standard NMA (consistency) model assumes transitivity, i.e. it assumes that the estimate of the effect of treatment A relative to B must be equal to the sum of the estimate of C relative to A and the estimate of C relative to B. The inconsistency model, however, does not force this assumption, and instead estimates all relative treatment effects separately. For our analysis we used the interaction model specified by Dias and colleagues (2011) to check this assumption. We compared the deviance computed from both models, the DIC from both models, and the results of each treatment relative to usual care. Models are provided online. We expected a deviance contribution of approximately 1 from each datapoint, with higher deviances indicating a worse fit (Speigelhalter et al., 2002; Dias et al., 2011).

Methods for Summarising Results from the NMA

We calculated the difference in percentage reduction in all treatments versus usual care, taking the baseline value into account. As WinBUGS uses an iterative process we could store the rank of each intervention at each iteration of the MCMC chain, and use these values to estimate the probability of each intervention being in each position. We can then sum these probabilities to find the probability of each intervention being in each position or better, and plot these on a rankogram. Calculating the SUCRA (SUrface under the Cumulative RANking curve; Salanti, Ades, & Ioannidis, 2011) gives us a one number summary for each intervention. Possible SUCRA scores range from 0 to 1. A treatment with a value of 1 means that it is the best intervention with no uncertainty, and a value of 0 mean that it is the

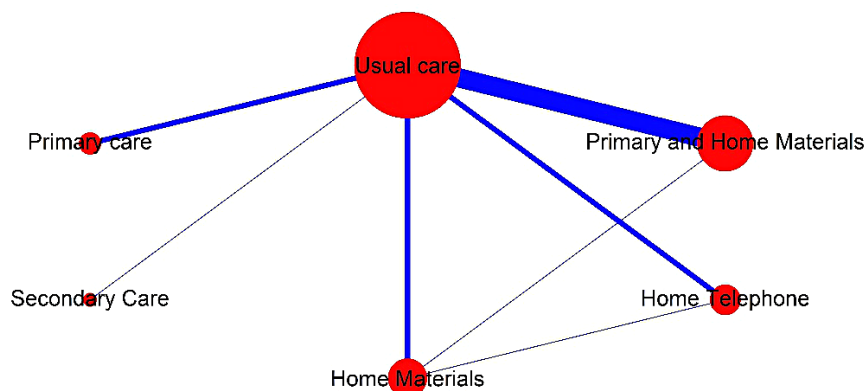


Figure 2. Network diagram (generated through pcnetmeta). Nodes and edges are proportional to the number of direct comparisons.

worst intervention with no uncertainty.

Results

Table 2. Percentage reduction in SBP for each treatment versus usual care.

Model	Intervention	Mean	SD	Lower CrI	Upper CrI
Single Main					
Effects Model	All Interventions	0.02	0.01	0.00	0.04
Additive Main Effects Model	Primary Care	0.00	0.02	-0.03	0.04
	Secondary Care	0.05	0.04	-0.02	0.12
	Home Telephone	0.00	0.02	-0.04	0.05
	Home Materials	0.02	0.02	-0.01	0.05
Interaction Model	Primary Care	0.01	0.03	-0.04	0.06
	Secondary Care	0.05	0.04	-0.03	0.13
	Home Telephone	0.01	0.02	-0.04	0.05
	Home Materials	0.02	0.02	-0.02	0.06
	Primary Care & Home Materials	0.02	0.02	-0.01	0.06

The network diagram can be seen in Figure 2. To compare the DIC across the three model we omitted the intervention study from Svarstad (2013) to ensure that we were comparing like with like. We found no difference between the three models. This is most likely due to the limited number of studies and, in particular, the fact that we only had one treatment node which involved more than one delivery context. We also compared the DIC using all 12 studies for the *Additive Main Effects Model* and the *Interaction Model*, and once again we found no difference. We therefore present the results of all three models.

The difference in percentage reduction in all treatments versus usual care is shown in Table 2. *The Single Effect Model* shows that the behavioural interventions grouped as one are superior to usual care at reducing SBP, with a Credible Interval (CrI), which does not span zero. However, for all other models all comparisons cross zero, which indicates that although the mean of each intervention is superior to usual care, we cannot be certain that these interventions have an effect on SBP compared to usual care.

The rankograms for the *Additive Main Effects Model* and the *Interaction Model* are shown in Figure 3. The SUCRA scores are shown in Table 3. We see that usual care is the lowest ranked intervention in each model. Secondary care is the

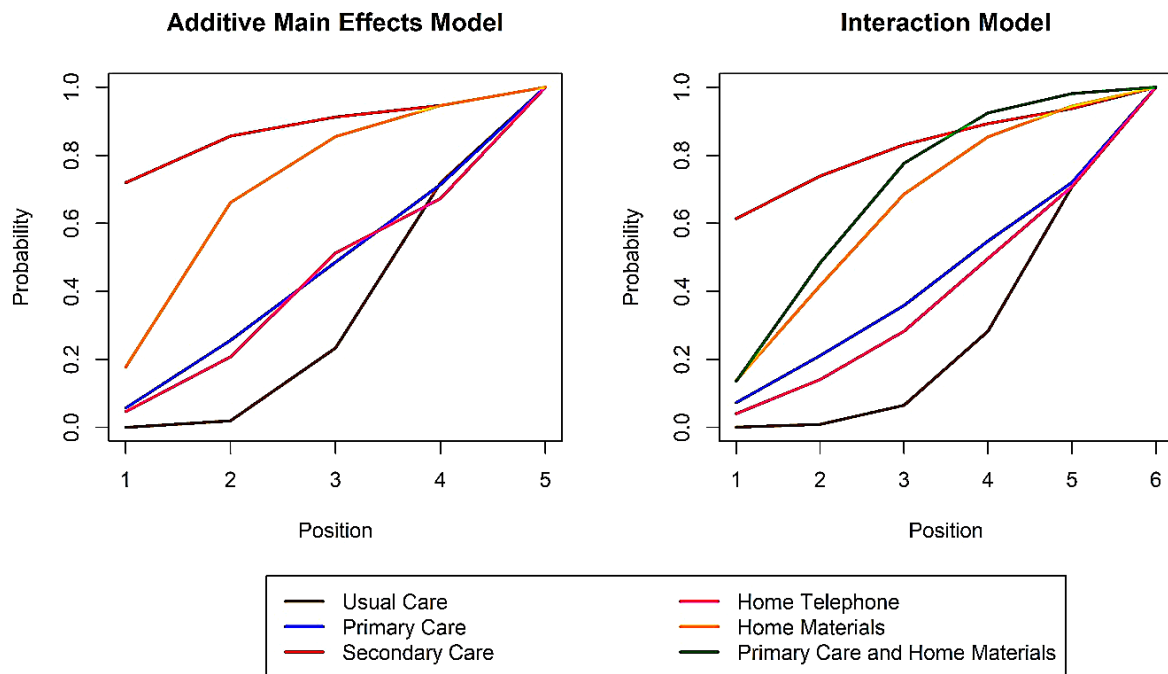


Figure 3. Rankogram for each treatment. At each point on the x-axis we see the probability of being in the nth position or better.

highest ranked intervention. It's worth noting that secondary care is the only intervention in our network that was included in one study only, so it may be that the intervention was applied particularly well in that study.

Checks for inconsistency

We can see from table 4 that the difference in DIC between the consistency and the inconsistency model is less than three so we find no meaningful difference in DIC. This indicates that it is correct to use the standard consistency model, which assumes transitivity. While there are some differences in the point estimates of some treatments versus usual care each mean is contained in the CrI of the other model. Figure 4 shows the deviance from the consistency model versus the deviance from the inconsistency model. Although there are some deviations from the line of equality, in absolute

terms the differences are quite small. Overall, we find no concerning evidence of inconsistency between the models and therefore it is likely that the transitivity assumption holds. Therefore, the set of studies that we have included are likely to be suitable to analyse in an NMA.

Further Learning for Applying Network Meta-Analysis in Health Psychology

The effective application of NMA to networks of evidence in health psychology will require knowledge and skill in describing components of behaviour change interventions, managing and modelling data from RCTs and using statistical software packages that are infrequently employed by health psychologists. We recommend that readers stay up-to-date with the statistical courses and workshops such as those offered by the

Table 3. SUCRA (SURface under the Cumulative RANking curve) score for each treatment. Higher values indicate better treatments. A treatment with a value of 1 means that it is the best intervention with no uncertainty, and a value of 0 mean that it is the worst intervention with no uncertainty.

Single Effect Model	Intervention Usual Care					
	0.99	0.02				
Additive Main Effects Model	Usual Care					
	Secondary	Home Materials	Primary	Home Tele	Care	
0.86	0.66	0.38	0.36	0.24		
Interaction Model	PC & Home Materials		Home Materials		Home Tele	Usual Care
	Secondary	Materials	Materials	Primary	Tele	Care
0.80	0.66	0.61	0.38	0.33	0.21	

Table 4. Comparison of results from the consistency and the inconsistency model for the full interaction model.

	Consistency Model				Inconsistency Model			
	Mean	SD	Lower CrI	Upper CrI	Mean	SD	Lower CrI	Upper CrI
Primary Care	0.01	0.03	-0.04	0.06	0.01	0.02	-0.03	0.05
Secondary Care	0.05	0.04	-0.03	0.12	0.05	0.03	-0.01	0.11
Home Telephone	0.00	0.02	-0.04	0.05	0.01	0.02	-0.02	0.05
Home Materials	0.02	0.02	-0.02	0.07	0.04	0.02	0.00	0.08
Primary Care & Home Materials	0.03	0.02	-0.01	0.06	0.01	0.01	-0.01	0.04
DIC	82.99				83.74			

University of Bristol, Oxford University, the Swiss Epidemiology Winter School and the Medical Research Council in the UK in order to avail of training in the application of NMA. A comprehensive treatment of NMA can be found in “Network Meta-analysis for Decision-making” by Dias and colleagues (2018). For a conceptual primer

on the use of NMA in health psychology and behavioural medicine, see the work of Molloy and colleagues (2018).

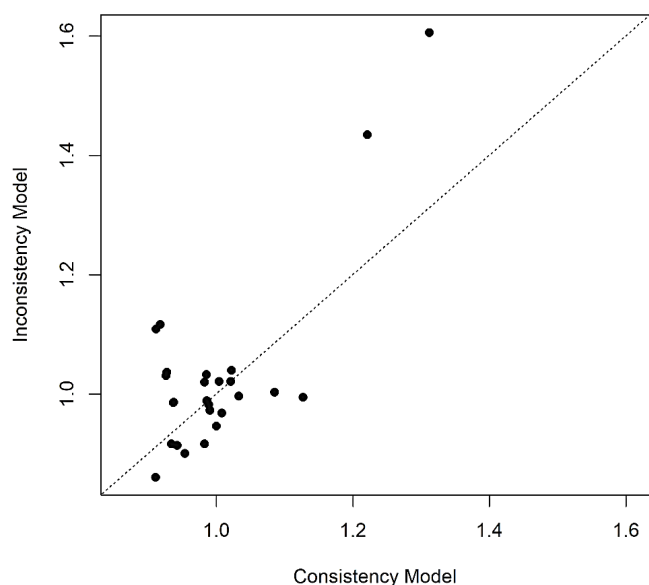


Figure 4. Deviance contribution from each study arm for the consistency model and the inconsistency model.

Conclusion

In this tutorial, we have discussed some basic concepts of NMA and demonstrated the application of NMA to a set of studies which examined the use of behavioural interventions to increase medication adherence in people with hypertension. By applying NMA to this network we have not only been able to address the question of whether these behavioural interventions work in terms of reducing blood pressure, but the more complex question of which intervention does this best by providing a ranking of behavioural interventions in terms of efficacy. However, due to the small number of studies, some uncertainty remains in these rankings.

Applying NMA in this manner is likely to have increasing importance for evidence synthesis in health psychology in the coming years. Appropriate application of the method requires adequate support from a multi-disciplinary team including biostatisticians to ensure that the synthesis of the evidence is reliable and valid. When used appropriately the method has the potential to

influence the role of the health psychology in the delivery of healthcare, as it can help reveal important insights into the comparative effectiveness of behavioural interventions in health.

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