Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Copyright
National Institute for Health and Care Excellence [2017]. All rights reserved.
Contents

Appendix N: Clinical evidence – network meta-analysis: bias adjustment methods and results

N.1 Introduction

N.2 Methods

  N.2.1 Assumptions on the direction of bias

  N.2.2 Reporting of results

  N.2.3 Bias adjustment methods for SMD

  N.2.4 Bias adjustment methods for OR of response

  N.2.5 Bias adjustment methods for OR of discontinuation

N.3 Results: population with less severe depression

  N.3.1 Outcome: SMD

  N.3.2 Outcome: discontinuation

  N.3.3 Outcome: response (completers)

N.4 Results: population with more severe depression

  N.4.1 Outcome: SMD

  N.4.2 Outcome: discontinuation

  N.4.3 Outcome: response (completers)

N.5 References

N.6 Appendix 6: WINBUGS code

  N.6.1 Sample WinBUGS code – SMD bias analysis

  N.6.2 Sample WinBUGS code – Response bias analysis

N.7 Appendix 7: NMA posterior mean rank and 95% credible intervals by intervention (bias model)

  N.7.1 Population: LESS SEVERE depression

  N.7.2 Population: MORE SEVERE depression
Appendix N: Clinical evidence – network meta-analysis: bias adjustment methods and results

TSU, Bristol (Sofia Dias)

N.1 Introduction

Publication bias is known to affect results of meta-analyses in several clinical areas, including Depression (Trinquart et al. 2012; Moreno et al. 2011; Moreno et al. 2009, Driessen et al. 2015, Turner et al. 2008). It has been shown that published smaller studies tend to overestimate the relative treatment effect of interventions vs control, compared to larger studies (Moreno et al. 2011; Driessen et al. 2015, Turner et al. 2008, Chaimani et al., 2013). It is thought that these “small study effects” are a consequence of publication bias, where results from smaller, less precise, studies are unlikely to get published unless they show a large effect in the expected direction, whereas large studies tend to be published quickly, regardless of the magnitude and direction of effect.

When it is suspected that publication bias (small study effects) is present in a dataset, it is important to try to account for its impact on the results. A regression using a measure of study precision can be used to adjust for small study effects in meta-analysis, with the study variance being typically used to adjust for study size (Moreno et al. 2011; Chaimani et al. 2013). Similar regression methods can be used to estimate and adjust for bias in network meta-analysis (NMA) for a variety of risk of bias indicators (Dias et al. 2010).

The NMAs carried out for the Depression guideline were thought to be at risk of bias due to small study effects. A bias adjustment analysis based on the study variance was carried out to assess (1) whether there is evidence of small study bias, and (2) the sensitivity of the estimated relative effects to this bias, where it is present.

We focused on the main outcomes included in the economic model and informing the clinical decisions: the log odds ratio (OR) of discontinuation for any reason, the log OR of response in those who did not discontinue and the standardized mean difference (SMD) in depression scores.

The models for the main NMAs are reported separately (see Chapter 17). These models were adapted to estimate and adjust for potential small study/publication bias. The data informing the bias adjustment models are the same as in the main NMAs.

N.2 Methods

N.2.3 Assumptions on the direction of bias

The effect of small studies will be characterised by the variance of the effect of the treatment in arms 2, 3, ... of each trial, relative to the treatment in arm 1 of that trial. The Guideline Committee expressed the opinion that bias would act to favour active interventions when compared to a control, but that there would be no systematic preference for active interventions when compared to each other. These assumptions were supported by empirical evidence of the direction and magnitude of small study bias in meta-analyses of psychological interventions vs control (Driessen et al. 2015) and of antidepressants vs placebo (Turner et al. 2008).
The model therefore estimates a (possibly) non-zero mean bias, with an estimated variance, for comparisons of active interventions to controls, but forces the mean bias to be zero in active vs active comparisons, whilst still allowing a non-zero variance around this zero mean. This is to allow for the fact that small studies may exaggerate effects of one active intervention over another, but that this may cancel out across multiple studies, with no particular intervention being favoured across all studies (Dias et al. 2010). Further details on the bias model for each of the outcomes considered are given in Sections N.2.3 to N.2.5.

The treatments defined as controls by the Guideline Committee were those in the following classes:
1. Pill Placebo
2. Waitlist
3. Attention Placebo
4. TAU

while all other interventions were defined as active. See Chapter 17 for details on classes and treatment definitions.

The data were coded so that treatments are in ascending order by study arm, therefore control treatments are always in arm 1 of studies included in the NMA, although they may also be in arms 2, 3, etc, depending on the interventions considered in the trials. Treatment comparisons within a trial were defined as being of three types:
1. Control vs Control
2. Control vs Active
3. Active vs Active

with comparisons of types 1 and 3 having zero mean bias, whilst comparisons of type 2 estimate a possible non-zero mean bias, \( b \).

For each of the outcomes, the bias is assumed to exaggerate the relative treatment effect on the scale that is being estimated. So for SMD outcomes the bias, if present, is expected to be negative as that would indicate an overestimation of the reduction in depression scores in active interventions compared to controls in studies with larger variances (i.e. smaller studies). For OR outcomes the bias will be assumed to act on the log OR scale and is expected to be positive for the response outcome (increasing of the odds of response in active interventions compared to controls in studies with larger variances, i.e. favouring the active interventions) and negative for the discontinuation outcome (decreasing the odds of discontinuation).

A Bayesian framework is used to estimate all parameters, using Markov chain Monte Carlo simulation methods implemented in WinBUGS 1.4.3 (Lunn et al. 2013). Convergence was assessed using the Brooks-Gelman-Rubin diagnostic (Brooks et al. 1998; Gelman and Rubin 1992). Further iterations post-convergence were obtained on which all reported results were based. Sample WinBUGS code for each outcome is provided in Appendix 6.

### Reporting of results

For each of the NMAs considered, the median of the small study bias and the standard deviation around the mean bias will be reported along with their 95% Credible Intervals (CrI).

Networks for which the 95%CrI for the mean bias \( b \) does not contain zero will be considered to have evidence of small study bias. In random effects models, a substantial reduction of the between-study heterogeneity in relative treatment effects in the bias-adjusted model will also indicate evidence of bias. If bias adjustment explains a substantial amount of the observed between-study heterogeneity, then there is evidence that some of this heterogeneity was due...
The direction of the estimated bias will also be assessed. As it is expected that bias will favour active interventions, if the sign of the bias estimate suggest favouring the control interventions we will interpret these results with caution as they go against informed clinical opinion (see Section N.2.1.).

Adjusted relative intervention effects will also be reported as posterior median OR or SMD and 95% CrI compared to Pill placebo. However, these should be interpreted with caution for networks where there is no evidence of bias.

We also report the posterior median rank of each class (and 95% CrIs), with the convention that the lower the rank the better the class. Rank of interventions are presented in Appendix 7. Only interventions and classes of interest were included in the calculations of the rankings (see Chapter 17 for a list of these).

**N.2.34 Bias adjustment methods for SMD**

The bias model acts to change the relative treatment effects of the treatment in arm \( k \) compared to the treatment in arm 1 of each study \( i \) on the SMD scale, \( \hat{\delta}_{ik} \). This applies to the relative effects estimated from all included studies, whether the data are reported as change from baseline in measures of depression, depression measured at follow-up or as the number of responders to treatment. The model to pool these data is described in full in Section 17.2.5 of Chapter 17. The only change required to incorporate the bias adjustment is to change equation (3) of Chapter 17 to

\[
\theta_{ik} = \gamma_i + \hat{\delta}_{ik} + (\beta_{ik} \times V_{ik})
\] (1)

where \( \hat{\delta}_{ik} = \beta_{ik} = V_{i1} = 0 \), \( V_{ik} \) is the variance of the relative effect measure calculated for arm \( k \) of study \( i \) compared to arm 1, and \( \beta_{ik} \) represents the bias coefficient for the comparison of the treatment in arm \( k \) to the treatment in arm 1 of study \( i \) which is assumed to follow a Normal distribution

\[
\beta_{ik} \sim \text{Normal}(B, \kappa_{SMD}^2)
\] (2)

where \( B=b \) if the treatment in arm 1 of trial \( i \) is a control and the treatment in arm \( k \) is not (type 2) and \( B=0 \) if the comparison of treatment 1 to treatment \( k \) is active vs active or control vs control (types 1 and 3). The mean differences between the change from baseline for the treatment in arm \( k \) and the treatment in arm 1 of trial \( i \), \( \hat{\delta}_{ik} \), are modelled as in equation (4) of Chapter 17.

For trials reporting continuous measures of effect, \( V_{ik} \) is the variance of the SMD, calculated as the sum of the variances of the means in arms 1 and \( k \), divided by the square of the standardising constant (i.e. the pooled variance for that trial). For trials reporting the number of responders, the variance of the logOR of response in arm \( k \) compared to arm 1, \( V_{ik}^* \), is calculated for each trial and transformed to a variance on the SMD scale using the relationship

\[
V_{ik} = \frac{3}{\pi^2} V_{ik}^*
\] (3)
The mean bias $b$ is given a non-informative normal prior distribution $b \sim \text{Normal}(0,100^2)$. The between-study standard deviation around the mean bias, $\kappa_{SMD}$, is given a Uniform prior distribution with a lower bound of zero and upper bound chosen to capture all the observed variability. For the less severe network the upper bound was 5 and for the more severe network the upper bound was 50 as greater variability was observed.

**N.2.4.6 Bias adjustment methods for OR of response**

The bias model acts to change the relative treatment effects of the treatment in arm $k$ compared to the treatment in arm 1 of each study $i$ on the logOR scale, $\eta_{ik}$. This applies to the relative effects estimated from all included studies, whether the data are reported as the number of responders to treatment, change form baseline in measures of depression or depression measured at follow-up. The model to pool these data is described in full in Section 17.2.6 of Chapter 17.

For studies reporting the number of responders, the only change required to incorporate the bias adjustment is to write

\[
\text{logit}(p_{ik}) = \alpha_i + \eta_{ik} + (\beta_{ik}^* \times V_{ik}^*)
\]

(4)

where $\eta_{ii} = \beta_{ii}^* = V_{ii}^* = 0$, the logOR for the treatment in arm $k$ compared to the treatment in arm 1 of trial $i$, $\eta_{ii}$, are modelled as before and $V_{ik}^*$ is the variance of the logOR calculated for arm $k$ of study $i$ compared to arm 1.

Trials reporting continuous measures of effect provide information on SMDs which are then converted to logORs as described in Section 17.2.6 of Chapter 17 (Chinn 2000; Higgins and Green 2008). The variances of the logORs can be obtained by inverting the relationship in equation (3), where the variance of the SMD is calculated as described in Section N.2.3. The bias adjustment then acts on the converted logOR for arm $k$ compared to arm 1 of each study.

Parameter $\beta_{ik}^*$ represents the bias coefficient for the comparison of the treatment in arm $k$ to the treatment in arm 1 of study $i$ which is assumed to follow a Normal distribution

\[
\beta_{ik}^* \sim \text{Normal}(B^*, \kappa_{\text{LOG}}^2)
\]

(5)

where $B^*$=$b^*$ if the treatment in arm 1 of trial $i$ is a control and the treatment in arm $k$ is not (type 2) and $B^*$=0 if the comparison of treatment 1 to treatment $k$ is active vs active or control vs control (types 1 and 3).

The mean bias $b^*$ is given a non-informative normal prior distribution $b^* \sim \text{Normal}(0,100^2)$.

The between-study standard deviation around the mean bias is given a Uniform prior distribution with a lower bound of zero and upper bound of 5 which was sufficient to capture all the observed variability in the less severe and more severe networks.

**N.2.5 Bias adjustment methods for OR of discontinuation**

The bias model acts to change the relative treatment effects of the treatment in arm $k$ compared to the treatment in arm 1 of each study $i$ on the logOR scale. Only data on the number of discontinuations were included so the bias model is as described in equations (4) and (5), with $V_{ik}^*$ the variance of the logOR calculated for arm $k$ of study $i$ compared to arm 1.
N.3.1 Results: population with less severe depression

N.3.1.2 Outcome: SMD

A burn-in of 50,000 iterations was used after which a further 50,000 iterations were taken from 2 independent chains (total of 100,000 iterations). High autocorrelation is present in some parameters.

The NMA with bias adjustment showed a slightly improved fit to the data compared to the unadjusted NMA, although the DIC favoured the unadjusted NMA model and there was only a small reduction in the between-study heterogeneity when adjusting for bias (see Appendix 3 in Chapter 17).

Although the mean bias had a negative median (as expected), the 95%CrI included the possibility of a zero bias with moderate variability (Table 1 and Figure 1: Between-study variability in mean bias for the SMD in the less severe population). We therefore conclude that there is no evidence of small study bias in this network.

Table 1: Median and 95%CrI for the mean bias and its between study standard deviation for the SMD in the less severe population.

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>95%CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean bias, b</td>
<td>-0.22</td>
<td>(-1.93, 1.50)</td>
</tr>
<tr>
<td>Standard deviation of bias, (\kappa)</td>
<td>0.99</td>
<td>(0.05, 2.38)</td>
</tr>
</tbody>
</table>

Figure 1: Between-study variability in mean bias for the SMD in the less severe population

The SMD of interventions and classes for the bias adjusted model shows a small reduction in some relative effects, although since there was no evidence of bias these should be interpreted with caution (Figure 2 and Figure 3).
Figure 2: SMD of each intervention compared to Pill Placebo from the bias adjusted model. For intervention codes see Table 12 in Chapter 17.

Adjusted ranks for classes show no meaningful changes in class ranking, although there is added uncertainty in some rankings (Table 2).
We conclude that the NMA for SMD in the less severe population presented in Chapter 17 is robust to small study/publication bias.

### Table 2: Posterior median rank and 95%CrI from the bias adjusted analysis of the SMD for the population with less severe depression.

<table>
<thead>
<tr>
<th>Class</th>
<th>Posterior Median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined (IPT + AD)</td>
<td>2</td>
<td>(1, 13)</td>
</tr>
<tr>
<td>Combined (Short-term psychodynamic psychotherapies + AD)</td>
<td>2</td>
<td>(1, 18)</td>
</tr>
<tr>
<td>Long-term psychodynamic psychotherapies</td>
<td>5</td>
<td>(1, 18)</td>
</tr>
<tr>
<td>Self-help with support</td>
<td>5</td>
<td>(1, 16)</td>
</tr>
<tr>
<td>Combined (Cognitive and cognitive behavioural therapies + AD)</td>
<td>7</td>
<td>(1, 20)</td>
</tr>
<tr>
<td>Combined (Exercise + AD/CBT)</td>
<td>7</td>
<td>(1, 20)</td>
</tr>
<tr>
<td>Cognitive and cognitive behavioural therapies</td>
<td>8</td>
<td>(4, 13)</td>
</tr>
<tr>
<td>Behavioural therapies</td>
<td>8</td>
<td>(2, 19)</td>
</tr>
<tr>
<td>Psychoeducational interventions</td>
<td>9</td>
<td>(2, 19)</td>
</tr>
<tr>
<td>Exercise</td>
<td>10</td>
<td>(1, 20)</td>
</tr>
<tr>
<td>SSRIs</td>
<td>11</td>
<td>(4, 19)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapies</td>
<td>11</td>
<td>(4, 19)</td>
</tr>
<tr>
<td>Interpersonal psychotherapy (IPT)</td>
<td>11</td>
<td>(3, 20)</td>
</tr>
<tr>
<td>TCAs</td>
<td>12</td>
<td>(4, 19)</td>
</tr>
<tr>
<td>Self-help without support</td>
<td>12</td>
<td>(4, 20)</td>
</tr>
<tr>
<td>Counselling</td>
<td>13</td>
<td>(3, 20)</td>
</tr>
<tr>
<td>Pill placebo</td>
<td>15</td>
<td>(11, 18)</td>
</tr>
<tr>
<td>Attention placebo</td>
<td>16</td>
<td>(10, 19)</td>
</tr>
<tr>
<td>TAU</td>
<td>17</td>
<td>(13, 19)</td>
</tr>
<tr>
<td>Waitlist</td>
<td>19</td>
<td>(17, 20)</td>
</tr>
</tbody>
</table>

We conclude that the NMA for SMD in the less severe population presented in Chapter 17 is robust to small study/publication bias.

### N.3.2 Outcome: discontinuation

A burn-in of 50,000 iterations was used after which a further 50,000 iterations were taken form 2 independent chains (total of 100,000 iterations).

The NMA with bias adjustment showed a slightly improved fit to the data compared to the unadjusted NMA, although the DIC favoured the unadjusted NMA model and there was only a small reduction in the between-study heterogeneity when adjusting for bias (see Appendix 3 in Chapter 17).

The mean bias had a positive median (which is the opposite to the expected direction) and the 95%CrI included the possibility of a zero bias with small variability (Table 3 and Figure 4).

We therefore conclude that there is no evidence of small study bias in this network.

### Table 3: Median and 95%CrI for the mean bias and its between study standard deviation for the logOR of discontinuation in the population with less severe depression.

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>95%CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean bias, b</td>
<td>0.18</td>
<td>(-0.19, 0.47)</td>
</tr>
<tr>
<td>Standard deviation of bias, ( \kappa )</td>
<td>0.26</td>
<td>(0.02, 0.61)</td>
</tr>
</tbody>
</table>
Figure 4: Between-study variability in mean bias for the logOR of discontinuation in the less severe population.

The logOR of interventions and classes for the bias adjusted model shows some very small changes in relative effects. Since there was no evidence of bias these should be interpreted with caution (Figure 5 and Figure 6).

Figure 5: logOR of discontinuation of each intervention compared to Pill Placebo from the bias adjusted model. For intervention codes see Table 1 in Chapter 17.
Figure 6: logOR of discontinuation of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 1 in Chapter 17.

Table 4: Posterior median rank and 95%CrI from the bias adjusted analysis of the logOR of discontinuation for the population with less severe depression

<table>
<thead>
<tr>
<th>Class</th>
<th>Posterior Median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counselling</td>
<td>3</td>
<td>(1, 18)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>4</td>
<td>(1, 19)</td>
</tr>
<tr>
<td>Exercise</td>
<td>5</td>
<td>(1, 18)</td>
</tr>
<tr>
<td>Combined (Short-term psychodynamic psychotherapies + AD)</td>
<td>5</td>
<td>(1, 20)</td>
</tr>
<tr>
<td>Combined (Exercise + AD/CBT)</td>
<td>6</td>
<td>(1, 19)</td>
</tr>
<tr>
<td>Waitlist</td>
<td>7</td>
<td>(3, 15)</td>
</tr>
<tr>
<td>Cognitive and cognitive behavioural therapies</td>
<td>7</td>
<td>(3, 15)</td>
</tr>
<tr>
<td>Psychoeducational interventions</td>
<td>8</td>
<td>(1, 20)</td>
</tr>
<tr>
<td>Interpersonal psychotherapy (IPT)</td>
<td>8</td>
<td>(1, 20)</td>
</tr>
<tr>
<td>TAU</td>
<td>10</td>
<td>(5, 16)</td>
</tr>
<tr>
<td>Combined (IPT + AD)</td>
<td>10</td>
<td>(1, 20)</td>
</tr>
<tr>
<td>SSRIs</td>
<td>11</td>
<td>(4, 18)</td>
</tr>
<tr>
<td>Attention placebo</td>
<td>13</td>
<td>(4, 19)</td>
</tr>
<tr>
<td>Combined (Cognitive and cognitive behavioural therapies + AD)</td>
<td>13</td>
<td>(3, 20)</td>
</tr>
<tr>
<td>Pill placebo</td>
<td>14</td>
<td>(8, 19)</td>
</tr>
<tr>
<td>TCAs</td>
<td>15</td>
<td>(5, 20)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapies</td>
<td>15</td>
<td>(3, 20)</td>
</tr>
<tr>
<td>Self-help without support</td>
<td>15</td>
<td>(4, 20)</td>
</tr>
</tbody>
</table>
Depression in adults: treatment and management
Clinical evidence – network meta-analysis: bias adjustment methods and results

<table>
<thead>
<tr>
<th>Class</th>
<th>Posterior Median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural therapies</td>
<td>16</td>
<td>(4, 20)</td>
</tr>
<tr>
<td>Self-help with support</td>
<td>18</td>
<td>(6, 20)</td>
</tr>
</tbody>
</table>

We conclude that the NMA for discontinuation in the less severe population presented in Chapter 17 is robust to small study/publication bias.

N.3.3.3 Outcome: response (completers)

A burn-in of 100,000 iterations was used after which a further 200,000 iterations were taken form 2 independent chains (total of 400,000 iterations). High autocorrelation is present in some parameters.

The NMA with bias adjustment showed a substantially improved fit to the data compared to the unadjusted NMA with the DIC favouring the bias adjusted NMA model. There was also a substantial reduction in the between-study heterogeneity in the bias adjusted model (see Appendix 3 in Chapter 17).

The mean bias had a positive median (as expected) and the 95%CrI excludes the possibility of a zero bias although with moderate variability (Table 5 and Figure 7). We therefore conclude that there is strong evidence of small study bias in this network.

Table 5: Median and 95%CrI for the mean bias and its between study standard deviation for the logOR of responses in completers in the less severe population.

<table>
<thead>
<tr>
<th></th>
<th>median</th>
<th>95%CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean bias, b</td>
<td>1.48</td>
<td>(0.64, 2.34)</td>
</tr>
<tr>
<td>Standard deviation of bias, $\kappa$</td>
<td>0.68</td>
<td>(0.10, 1.29)</td>
</tr>
</tbody>
</table>

Figure 7: Between-study variability in mean bias for the logOR of response in completers in the less severe population.

The logOR of interventions and classes for the bias adjusted model show some reduction in magnitude of relative effects, which suggests that Classes TCA, SSRI, Cognitive and Cognitive behavioural therapies, Behavioural therapies and Combined IPT+AD, no longer have evidence of a beneficial effect, compared to Pill Placebo (Figure 8 and Figure 9). This reduction in class effects is due to the down-weighting and adjustment of the effects estimated in small studies to account for the bias (Dias et al. 2010).
Figure 8: logOR of response in completers of each intervention compared to Pill Placebo from the bias adjusted model. For intervention codes see Table 9 in Chapter 17.

Figure 9: logOR of response in completers of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 9 in Chapter 17.

Adjusted ranks for classes show some changes in class ranking (Error! Reference source not found.). The highest ranked class is unchanged but there are changes to the top 5 class rankings and their uncertainty.
We conclude that the results of the NMA for response in completers in the less severe population presented in Chapter 17 are sensitive to small study effects and the impact of the bias on conclusions should be assessed.

### N.4 Results: population with more severe depression

#### N.4.1 Outcome: SMD

A burn-in of 60,000 iterations was used after which a further 50,000 iterations were taken form 2 independent chains (total of 100,000 iterations). High autocorrelation is present in some parameters.

The NMA with bias adjustment showed no improvement in fit to the data compared to the unadjusted NMA with the DIC favouring the unadjusted NMA model. However, there was a substantial reduction in the between-study heterogeneity in the bias adjusted model (see Appendix 3 in Chapter 17).

The mean bias had a negative median (as expected) and the 95%CrI excludes the possibility of a zero bias although there is large between-study variability in bias (Table 7 and Figure 10). We therefore conclude that there is moderate evidence of small study bias in this network.
Table 7  Median and 95%CrI for the mean bias and its between study standard deviation for the SMD in the more severe population.

<table>
<thead>
<tr>
<th></th>
<th>median</th>
<th>95%CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean bias, b</td>
<td>-6.99</td>
<td>(-12.77, -1.19)</td>
</tr>
<tr>
<td>Standard deviation of bias, $\kappa$</td>
<td>9.61</td>
<td>(7.16, 12.74)</td>
</tr>
</tbody>
</table>

Figure 10: Between-study variability in mean bias for the SMD in the more severe population.

The SMD of interventions and classes for the bias adjusted model shows a small some relative effects. There are still no classes showing evidence of a compared to Pill Placebo. The only class with a higher standardized mean Waitlist (Figure 11: SMD of each intervention compared to Pill Placebo from the bias adjusted model. For intervention codes see Table 25 in Chapter 17.

and Figure 12: SMD of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 25 in Chapter 17).

Figure 11: SMD of each intervention compared to Pill Placebo from the bias adjusted model. For intervention codes see Table 25 in Chapter 17.
Figure 12: SMD of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 25 in Chapter 17.

Adjusted ranks for classes show some changes in class ranking (Table 8). The highest ranked classes are unchanged but there are changes to other class rankings and to the uncertainty in rankings.

Table 8  Posterior median rank and 95%CrI from the bias adjusted analysis of the SMD for the population with more severe depression

<table>
<thead>
<tr>
<th>Class</th>
<th>Posterior Median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined (Exercise + AD/CBT)</td>
<td>2</td>
<td>(1, 14)</td>
</tr>
<tr>
<td>Cognitive and cognitive behavioural therapies</td>
<td>3</td>
<td>(1, 10)</td>
</tr>
<tr>
<td>TCAs</td>
<td>5</td>
<td>(1, 12)</td>
</tr>
<tr>
<td>SSRIs</td>
<td>6</td>
<td>(2, 13)</td>
</tr>
<tr>
<td>Combined (Cognitive and cognitive behavioural therapies + AD)</td>
<td>6</td>
<td>(1, 16)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>7</td>
<td>(3, 13)</td>
</tr>
<tr>
<td>Behavioural therapies</td>
<td>7</td>
<td>(1, 16)</td>
</tr>
<tr>
<td>Pill placebo</td>
<td>8</td>
<td>(4, 14)</td>
</tr>
<tr>
<td>Interpersonal psychotherapy (IPT)</td>
<td>8</td>
<td>(1, 17)</td>
</tr>
<tr>
<td>Counselling</td>
<td>9</td>
<td>(1, 17)</td>
</tr>
<tr>
<td>Exercise</td>
<td>11</td>
<td>(2, 17)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapies</td>
<td>11</td>
<td>(2, 17)</td>
</tr>
<tr>
<td>Attention placebo</td>
<td>12</td>
<td>(5, 16)</td>
</tr>
<tr>
<td>TAU</td>
<td>13</td>
<td>(8, 16)</td>
</tr>
<tr>
<td>Self-help</td>
<td>13</td>
<td>(4, 17)</td>
</tr>
<tr>
<td>Self-help with support</td>
<td>15</td>
<td>(2, 17)</td>
</tr>
<tr>
<td>Waitlist</td>
<td>16</td>
<td>(11, 17)</td>
</tr>
</tbody>
</table>
N.4.24 Outcome: discontinuation

A burn-in of 80,000 iterations was used after which a further 100,000 iterations were taken form 2 independent chains (total of 200,000 iterations).

The NMA with bias adjustment showed a improved fit to the data compared to the unadjusted NMA, with the DIC favouring the bias-adjusted NMA model, although there was only a small reduction in the between-study heterogeneity when adjusting for bias (see Appendix 3 in Chapter 17).

The mean bias had a positive median (as expected) and although the 95% CrI included the possibility of a zero bias, there is a large probability that the bias is indeed positive. There was a large variability around the mean bias (Table 9 and Error! Reference source not found.). We therefore conclude that there is weak evidence of small study bias in this network.

Table 9 Median and 95% CrI for the mean bias and its between study standard deviation for the logOR of discontinuation in the more severe population.

<table>
<thead>
<tr>
<th></th>
<th>median</th>
<th>95% CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean bias, b</td>
<td>0.63</td>
<td>(-0.02, 1.32)</td>
</tr>
<tr>
<td>Standard deviation of bias, $\kappa$</td>
<td>0.66</td>
<td>(0.16, 1.19)</td>
</tr>
</tbody>
</table>

Figure 13: Between-study variability in mean bias for the logOR of discontinuation in the more severe population.

The logOR of interventions and classes for the bias adjusted model shows some small changes in relative effects with some relative effects reduced in are increased (Figure 14: logOR of discontinuation of each intervention compared to Pill Placebo from the bias adjusted model. For intervention codes see Table 14 in Chapter 17.

and Figure 15: logOR of discontinuation of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 14 in Chapter 17.)
Figure 14: logOR of discontinuation of each intervention compared to Pill Placebo from the bias adjusted model. For intervention codes see Table 14 in Chapter 17.

Figure 15: logOR of discontinuation of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 14 in Chapter 17.
Adjusted ranks for classes show some changes in class ranking (Table 10: Posterior median rank and 95% CrI from the bias adjusted analysis of the logOR of discontinuation for the population with more severe depression).

Table 10: Posterior median rank and 95% CrI from the bias adjusted analysis of the logOR of discontinuation for the population with more severe depression.

<table>
<thead>
<tr>
<th>Class</th>
<th>Posterior Median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>1</td>
<td>(1, 15)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapies</td>
<td>3</td>
<td>(1, 16)</td>
</tr>
<tr>
<td>Long-term psychodynamic psychotherapies</td>
<td>4</td>
<td>(1, 18)</td>
</tr>
<tr>
<td>Counselling</td>
<td>5</td>
<td>(1, 18)</td>
</tr>
<tr>
<td>Combined (Cognitive and cognitive behavioural therapies + AD)</td>
<td>5</td>
<td>(1, 14)</td>
</tr>
<tr>
<td>Self-help with support</td>
<td>7</td>
<td>(2, 17)</td>
</tr>
<tr>
<td>Waitlist</td>
<td>8</td>
<td>(3, 16)</td>
</tr>
<tr>
<td>TAU</td>
<td>9</td>
<td>(4, 16)</td>
</tr>
<tr>
<td>Cognitive and cognitive behavioural therapies</td>
<td>9</td>
<td>(3, 16)</td>
</tr>
<tr>
<td>Attention placebo</td>
<td>11</td>
<td>(3, 19)</td>
</tr>
<tr>
<td>Interpersonal psychotherapy (IPT)</td>
<td>12</td>
<td>(2, 19)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>13</td>
<td>(5, 17)</td>
</tr>
<tr>
<td>Self-help</td>
<td>13</td>
<td>(4, 19)</td>
</tr>
<tr>
<td>Combined (IPT + AD)</td>
<td>13</td>
<td>(2, 19)</td>
</tr>
<tr>
<td>Long-term psychodynamic psychotherapy individual + any SSRI</td>
<td>13</td>
<td>(2, 19)</td>
</tr>
<tr>
<td>TCA</td>
<td>14</td>
<td>(5, 18)</td>
</tr>
<tr>
<td>SSRI</td>
<td>15</td>
<td>(6, 19)</td>
</tr>
<tr>
<td>Pill placebo</td>
<td>17</td>
<td>(10, 19)</td>
</tr>
<tr>
<td>Behavioural therapies</td>
<td>18</td>
<td>(2, 20)</td>
</tr>
<tr>
<td>Psychoeducational interventions</td>
<td>20</td>
<td>(18, 20)</td>
</tr>
</tbody>
</table>

We conclude that the results of the NMA for discontinuation in the more severe population presented in Chapter 17 may be sensitive to small study effects and the impact of the bias on conclusions should be assessed.

N.4.30 Outcome: response (completers)

A burn-in of 50,000 iterations was used after which a further 100,000 iterations were taken form 2 independent chains (total of 200,000 iterations).

The NMA with bias adjustment showed some improved fit to the data compared to the unadjusted NMA with a similar DIC for the two models. There was also a small reduction in the between-study heterogeneity in the bias adjusted model (see Appendix 3 in Chapter 17).

The mean bias had a positive median (as expected) and the 95% CrI excludes the of a zero bias with low variability (Table 11: Median and 95% CrI for the mean bias and its between study standard deviation for the logOR of responses in completers in the more severe population. and Figure 16). We therefore conclude that there is evidence of small study bias in this network.
Table 11: Median and 95%CrI for the mean bias and its between study standard deviation for the logOR of responses in completers in the more severe population.

<table>
<thead>
<tr>
<th></th>
<th>median</th>
<th>95%CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean bias, b</td>
<td>1.38</td>
<td>(0.30, 2.64)</td>
</tr>
<tr>
<td>Standard deviation of bias, κ</td>
<td>0.86</td>
<td>(0.03, 2.08)</td>
</tr>
</tbody>
</table>

Figure 16: Between-study variability in mean bias for the logOR of response in completers in the more severe population.

The logOR of interventions and classes for the bias adjusted model shows some reduction in magnitude of relative effects (Error! Reference source not found. and Error! Reference source not found.).

Figure 17: logOR of response in completers of each intervention compared to Pill Placebo from the bias adjusted model. For intervention codes see Table 21 in Chapter 17.
Figure 18: logOR of response in completers of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 21 in Chapter 17.

Adjusted ranks for classes show no changes in ordering for the highest ranked although there is added uncertainty in class ranking (Table 12: Posterior median rank and 95%CrI from the bias adjusted analysis of the logOR of response in completers for the more severe population).

Table 12: Posterior median rank and 95%CrI from the bias adjusted analysis of the logOR of response in completers for the more severe population.

<table>
<thead>
<tr>
<th>Class</th>
<th>Posterior Median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural therapies</td>
<td>2</td>
<td>(1, 13)</td>
</tr>
<tr>
<td>Exercise</td>
<td>3</td>
<td>(1, 14)</td>
</tr>
<tr>
<td>Combined (Cognitive and cognitive behavioural therapies + AD)</td>
<td>4</td>
<td>(1, 13)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapies</td>
<td>5</td>
<td>(1, 13)</td>
</tr>
<tr>
<td>Counselling</td>
<td>5</td>
<td>(1, 13)</td>
</tr>
<tr>
<td>TCA</td>
<td>7</td>
<td>(2, 12)</td>
</tr>
<tr>
<td>Cognitive and cognitive behavioural therapies</td>
<td>7</td>
<td>(2, 13)</td>
</tr>
<tr>
<td>Attention placebo</td>
<td>8</td>
<td>(2, 14)</td>
</tr>
<tr>
<td>TAU</td>
<td>8</td>
<td>(4, 12)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>9</td>
<td>(2, 13)</td>
</tr>
<tr>
<td>SSRI</td>
<td>10</td>
<td>(3, 13)</td>
</tr>
<tr>
<td>Self-help</td>
<td>10</td>
<td>(2, 14)</td>
</tr>
<tr>
<td>Pill placebo</td>
<td>13</td>
<td>(6, 14)</td>
</tr>
<tr>
<td>Waitlist</td>
<td>13</td>
<td>(3, 14)</td>
</tr>
</tbody>
</table>
We conclude that the results of the NMA for response in completers in the more severe population presented in Chapter 17 may be sensitive to small study effects and the impact of the bias on conclusions should be assessed.

**References**


**Appendix 6: WINBUGS code**

**Sample WinBUGS code – SMD bias analysis**

```
# Normal likelihood, identity link: SMD with arm-based means
# Random effects model for multi-arm trials
model{
  # *** PROGRAM STARTS
```
for(i in 1:ns){  # LOOP THROUGH STUDIES
  w[i,1] <- 0   # adjustment for multi-arm trials is zero for control arm
  beta[i,1] <- 0  # no bias term in baseline arm
  V[i,1] <- 0  # no variance term in baseline arm
  delta[i,1] <- 0  # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,0.0001)  # vague priors for all trial baselines
}

# (1) CFB DATA
for(i in 1:nsCFB){
  # calculate pooled.sd and adjustment for SMD
  df[i] <- sum(nCFB[i,1:naCFB[i]]) - naCFB[i]  # denominator for pooled.var
  Pooled.var[i] <- sum(nvar[i,1:naCFB[i]])/df[i]
  Pooled.sd[i] <- sqrt(Pooled.var[i])  # pooled sd for study i, for SMD
  # H[i] <- 1 - 3/(4*df[i]-1)  # use Hedges' g
  H[i] <- 1  # use Cohen's d (ie no adjustment)
  for (k in 1:naCFB[i]){  
    se[i,k] <- sdCFB[i,k]/sqrt(nCFB[i,k])  
    var[i,k] <- pow(se[i,k],2)  # calculate variances
    prec[i,k] <- 1/var[i,k]  # set precisions
    y[i,k] ~ dnorm(phi[i,k], prec[i,k])  # normal likelihood
    phi[i,k] <- theta[i,k] * (Pooled.sd[i]/H[i])  # theta is stand mean
    # model for linear predictor, delta is SMD
    theta[i,k] <- mu[i] + delta[i,k] + beta[i,k] * V[i,k]
    dev[i,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])*prec[i,k]
    nvar[i,k] <- (nCFB[i,k]-1) * pow(sdCFB[i,k],2)  # for pooled.sd
  }
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:naCFB[i]])
}

# (2) BASELINE + FOLLOW-UP DATA (no CFB)
for(i in 1:nsBF){  # LOOP THROUGH STUDIES
  # calculate pooled.sd and adjustment for SMD
  df[i+nsCFB] <- sum(n[i,1:na[i]]) - na[i]  # denominator for pooled.var
  Pooled.var[i+nsCFB] <- sum(nvar[i,1:na[i]])/df[i+nsCFB]
  Pooled.sd[i+nsCFB] <- sqrt(Pooled.var[i])  # pooled sd for study i, for SMD
}
Depression in adults: treatment and management
Clinical evidence – network meta-analysis: bias adjustment methods and results

# H[i] <- 1 - 3/(4*df[i]-1)  # use Hedges' g
H[i+nsCFB] <- 1  # use Cohen's d (ie no adjustment)
for (k in 1:na[i]){  
yBF[i,k] <- yF[i,k] - yB[i,k]  # calculate mean CFB
seF[i,k] <- sdF[i,k]/sqrt(n[i,k])  # se at followup
seB[i,k] <- sdB[i,k]/sqrt(n[i,k])  # se at baseline

# variance of mean CFB, assuming correlation corr[i]
var[i+nsCFB,k] <- pow(seF[i,k],2) + pow(seB[i,k],2)
-2*(seF[i,k]*seB[i,k]*corr[i])
prec[i+nsCFB,k] <- 1/var[i+nsCFB,k]  # set CFB precisions
yBF[i,k] ~ dnorm(phi[i+nsCFB,k], prec[i+nsCFB,k])  # normal likelihood

# theta is standardised mean
phi[i+nsCFB,k] <- theta[i+nsCFB,k] * (Pooled.sd[i+nsCFB]/H[i+nsCFB])

# model for linear predictor, delta is SMD
theta[i+nsCFB,k] <- mu[i+nsCFB] + delta[i+nsCFB,k]
+ beta[i+nsCFB,k] * V[i+nsCFB,k]

# residual deviance contribution
dev[i+nsCFB,k] <- (yBF[i,k]-phi[i+nsCFB,k]) * (yBF[i,k]-phi[i+nsCFB,k])
* prec[i+nsCFB,k]

# variance of CFB, assuming correlation corrBF[i] (var is sd squared)
varBF[i,k] <- pow(sdF[i,k],2) + pow(sdB[i,k],2)
- 2*(sdF[i,k]*sdB[i,k]*corr[i])
nvarBF[i,k] <- (n[i,k]-1) * varBF[i,k]  # for pooled.sd
}

# summed residual deviance contribution for this trial
resdev[i+nsCFB] <- sum(dev[i+nsCFB,1:na[i]])

# (3) RESPONSE DATA (no CFB or BL+follow-up)
for(i in 1:nsR){  # LOOP THROUGH STUDIES
  df[i+nsCFB+nsBF] <- sum(nR[i,1:naR[i]]) - naR[i]  # denominator for pooled var
  Pooled.var[i+nsCFB+nsBF] <- sum(nvarR[i,1:naR[i]])/df[i+nsCFB+nsBF]
  Pooled.sd[i+nsCFB+nsBF] <- sqrt(Pooled.var[i])  # pooled sd for study i,
  for SMD  # H[i] <- 1 - 3/(4*df[i]-1)  # use Hedges' g
  H[i+nsCFB+nsBF] <- 1  # use Cohen's d (ie no adjustment)
  for (k in 1:naR[i]){  
r[i,k] ~ dbin(R[i,k], nR[i,k])  # binomial likelihood
  }
}
Depression in adults: treatment and management
Clinical evidence – network meta-analysis: bias adjustment methods and results

National Institute for Health and Care Excellence [2017]. All rights reserved.

```
R[i,k] <- phi.adj[i,k]
x[i,k] <- -(q[i]*yBR[i,k]+ phi[i+nsCFB+nsBF,k])/(sdBR[i,k] * sqrt(1+(1-q[i])*(1-q[i]-2*corrR[i])))
# adjust link function phi(x) for extreme values that can give numerical
# errors when x< -5, phi(x)=0, when x> 5, phi(x)=1
phi.adj[i,k] <- (step(5+x[i,k]) * step(x[i,k]-5)
    + step(5-x[i,k]) * step(x[i,k]+5) * phi(x[i,k]))*(1-
equals(x[i,k],5))
# correct for x=5
# theta is standardised mean
phi[i+nsCFB+nsBF,k] <- theta[i+nsCFB+nsBF,k]
    * (Pooled.sd[i+nsCFB+nsBF]/H[i+nsCFB+nsBF])
# model for linear predictor, delta is SMD
theta[i+nsCFB+nsBF,k] <- mu[i+nsCFB+nsBF] + delta[i+nsCFB+nsBF,k]
    + beta[i+nsCFB+nsBF,k] * V[i+nsCFB+nsBF,k]
# residual deviance contribution
rhat[i,k] <- R[i,k] * nR[i,k]
dev[i+nsCFB+nsBF,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])))
    + (nR[i,k]-r[i,k]) * (log(nR[i,k]-r[i,k]) - log(nR[i,k]-
rhat[i,k])))
# Sensitivity analysis
sdR[i,k] <- 0.693 + sdBR[i,k] * 3.266  # sd for response
sdR[i,k] <- sdBR[i,k]          # sd for response
nvarR[i,k] <- (nR[i,k]-1) * pow(sdR[i,k],2) # for pooled.sd
}
# summed residual deviance contribution for this trial
resdev[i+nsCFB+nsBF] <- sum(dev[i+nsCFB+nsBF,1:naR[i]])
# RE MODEL (CFB data)
for(i in 1:nsCFB){                    # LOOP THROUGH STUDIES WITH CFB DATA
    for (k in 2:naCFB[i]){              # LOOP THROUGH ARMS
        # model for bias parameter beta
        beta[i,k] ~ dnorm(mb[i,k], Pkappa)
        mb[i,k] <- A[CCFB[i,k]]
    }
}
```
\begin{verbatim}
V[i,k] <- (var[i,k]+var[i,1])/Pooled.var[i]
# trial-specific RE distributions
delta[i,k] ~ dnorm(md[i,k], taud[i,k])
md[i,k] <- d[tCFB[i,k]] - d[tCFB[i,1]] + sw[i,k]
# precision of RE distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
#adjustment, multi-arm RCTs
w[i,k] <- delta[i,k] - d[tCFB[i,k]] + d[tCFB[i,1]]
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
\end{verbatim}
beta[i+nsCFB+nsBF,k] ~ dnorm(mb[i+nsCFB+nsBF,k], Pkappa)
mb[i+nsCFB+nsBF,k] <- A[C[i,k]]

# calculate variance of log odds ratio for comparisons with arm 1
# check for zero or 100% events in arm k
aux.a[i,k] <- equals(r[i,k],0)*equals(r[i,k],nR[i,k])
# check for zero or 100% events in arm 1
aux.b[i,k] <- equals(r[i,1],0)*equals(r[i,1],nR[i,1])
aux[i,k] <- max(aux.a[i,k],aux.b[i,k])  # any zero or 100% events?
# add 0.5 if zero or 100% events
VLOR[i,k] <- 1/(r[i,k]+(0.5*aux[i,k])) + 1/(r[i,1]+(0.5*aux[i,k]))
+ 1/(nR[i,k]-r[i,k]+(0.5*aux[i,k]))
+ 1/(nR[i,1]-r[i,1]+(0.5*aux[i,k]))
V[i+nsCFB+nsBF,k] <- 0.30396 * VLOR[i,k]  # convert to var of SMD

# trial-specific RE distributions
delta[i+nsCFB+nsBF,k] ~ dnorm(md[i+nsCFB+nsBF,k], taud[i+nsCFB+nsBF,k])
md[i+nsCFB+nsBF,k] <- d[tR[i,k]] - d[tR[i,1]] + sw[i+nsCFB+nsBF,k]
# precision of RE distributions (with multi-arm trial correction)
taud[i+nsCFB+nsBF,k] <- tau *2*(k-1)/k
#adjustment, multi-arm RCTs
w[i+nsCFB+nsBF,k] <- delta[i+nsCFB+nsBF,k] - d[tR[i,k]] + d[tR[i,1]]
# cumulative adjustment for multi-arm trials
sw[i+nsCFB+nsBF,k] <-sum(w[i+nsCFB+nsBF,1:k-1])/(k-1)

} #

totresdev <- sum(resdev[])  # Total Residual Deviance (all data)
# Partial Residual Deviance
totresdev.p[1] <- sum(resdev[1:nsCFB])  # CFB data
totresdev.p[2] <- sum(resdev[nsCFB+1:nsCFB+nsBF])  # BL + Fup data
totresdev.p[3] <- sum(resdev[nsCFB+nsBF+1:nsCFB+nsBF+nsR])  # Response data
#
# Priors and model assumptions (classes)
d[1] <- 0  # treatment effect is zero for control arm
# no class treatments, vague priors for treatment effects
for (k in 2:4) { d[k] ~ dnorm(0, .0001) }
d[6] ~ dnorm(0, .0001)

# single treatment classes, borrowing variance
d[5] ~ dnorm(m[D[5]], prec2[13]) # variance from Counselling

# variance from CBT
for (k in 15:18) { d[k] ~ dnorm(m[D[k]], prec2[14]) }
d[27] ~ dnorm(m[D[27]], prec2[14]) # variance from CBT
for (k in 31:32) { d[k] ~ dnorm(m[D[k]], prec2[14]) }

# treatment effects from Class, estimate variance
for (k in 7:14) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
for (k in 19:26) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
for (k in 28:30) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }

# no class treatments: class effect = treat effect
m[1] <- 0

# priors for mean class effect
m[5] ~ dnorm(0, .0001)
for (k in 7:nc) { m[k] ~ dnorm(0, .0001) }
for (k in 1:nc) {
  sd2[k] ~ dnorm(0, tau2)I(0,)
  prec2[k] <- pow(sd2[k], -0.5)
}

#
tau2 <- pow(0.19, -2)
sdev ~ dunif(0, 20) # vague prior for between-trial SD
tau <- pow(sdev, -2) # between-trial precision

# mean bias: assumptions
\begin{verbatim}
A[1] <- 0           # control v control
A[2] <- b           # control v Active
A[3] <- 0           # Active v Active

# bias model prior for variance
kappa ~ dunif(0,50)
kappa.sq <- pow(kappa,2)
Pkappa <- 1/kappa.sq

# bias model prior for mean
b ~ dnorm(0,.0001)

# all pairwise differences
for (c in 1:(nt-1)) { for (k in (c+1):nt) { diff[c,k] <- d[k] - d[c] } }

# rank treatments
for(k in 1:7){ dR[k] <- d[k] }
dR[8] <- d[9]
for(k in 9:28){ dR[k] <- d[k+2] }
dR[29] <- d[32]

# pairwise SMDs for all possible class comparisons
for (c in 1:(nt-1)) {
  for (k in (c+1):nc) {
    diffClass[c,k] <- (m[k]-m[c])
  }
}
\end{verbatim}
N.6.20 Sample WinBUGS code – Response bias analysis

```
model{
  # *** PROGRAM STARTS
  for(i in 1:ns){
    # LOOP THROUGH STUDIES
    w[i,1] <- 0  # adjustment for multi-arm trials is zero for control arm
    beta[i,1] <- 0  # no bias term in baseline arm
    V[i,1] <- 0  # no variance term in baseline arm
    # RESPONSE DATA
    delta[i,1] <- 0  # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)  # vague priors for all trial baselines
    # CONTINUOUS DATA
    deltaX[i,1] <- 0  # treatment effect is zero for control arm
    muX[i] ~ dnorm(0,.0001)  # vague priors for all trial baselines
  }
}
```
# RESPONSE DATA
for(i in 1:nsR){                   # LOOP THROUGH STUDIES WITH RESPONSE DATA
  for (k in 1:naR[i]){             # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],nR[i,k])  # binomial likelihood

    # model for linear predictor
    logit(p[i,k]) <- mu[i] + delta[i,k] + beta[i,k] * V[i,k]
    rhat[i,k] <- p[i,k] * nR[i,k] # expected value of the numerators

    # Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k]) - log(rhat[i,k]))
    + (nR[i,k]-r[i,k]) * (log(nR[i,k]-r[i,k]) - log(nR[i,k]-
    rhat[i,k])))
  }
}
# Summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:naR[i]])
}
#
# (1) CFB DATA
for(i in 1:nsCFB){                 # LOOP THROUGH STUDIES WITH CFB DATA
  # calculate pooled.sd and adjustment for SMD
  df[i] <- sum(nCFB[i,1:naCFB[i]]) - naCFB[i] # denominator for pooled.var
  Pooled.var[i] <- sum(nvar[i,1:naCFB[i]])/df[i]
  Pooled.sd[i] <- sqrt(Pooled.var[i]) # pooled sd for study i, for SMD

  # H[i] <- 1 - 3/(4*df[i]-1)       # use Hedges' g
  H[i] <- 1                        # use Cohen's d (ie no adjustment)
  for (k in 1:naCFB[i]){           # LOOP THROUGH ARMS
    se[i,k] <- sdCFB[i,k]/sqrt(nCFB[i,k]) # calculate st error of CFB
    var[i,k] <- pow(se[i,k],2) # calculate variances of CFB
    prec[i,k] <- 1/var[i,k]      # set precisions of CFB
    y[i,k] ~ dnorm(phi[i,k], prec[i,k]) # normal likelihood
    phi[i,k] <- theta[i,k] * (Pooled.sd[i]/H[i]) # theta is stand mean

    # model for linear predictor, deltaX is SMD
    theta[i,k] <- muX[i] + deltaX[i,k]
    dev[i+nsR,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])*prec[i,k]
    nvar[i,k] <- (nCFB[i,k]-1) * pow(sdCFB[i,k],2) # for pooled.sd
# summed residual deviance contribution for this trial
resdev[i+nsR] <- sum(dev[i+nsR,1:naCFB[i]])
}

# (2) BASELINE + FOLLOW-UP DATA (no CFB)
for(i in 1:nsBF){
  # LOOP THROUGH STUDIES WITH BL + F-UP DATA
  # calculate pooled sd and adjustment for SMD
  df[i+nsCFB] <- sum(n[i,1:na[i]]) - na[i]  # denominator for pooled.var
  Pooled.var[i+nsCFB] <- sum(nvarBF[i,1:na[i]])/df[i+nsCFB]
  Pooled.sd[i+nsCFB] <- sqrt(Pooled.var[i+nsCFB])  # pooled sd for study
  for SMD  # H[i+nsCFB] <- 1 - 3/(4*df[i]-1)  # use Hedges' g
    H[i+nsCFB] <- 1  # use Cohen's d (ie no adjustment)
  for (k in 1:na[i]){  # LOOP THROUGH ARMS
    yBF[i,k] <- yF[i,k] - yB[i,k]  # calculate mean CFB
    seF[i,k] <- sdF[i,k]/sqrt(n[i,k])  # se at followup
    seB[i,k] <- sdB[i,k]/sqrt(n[i,k])  # se at baseline
    # variance of mean CFB, assuming correlation corr[i]
    var[i+nsCFB,k] <- pow(seF[i,k],2) + pow(seB[i,k],2) - 2*(seF[i,k]*seB[i,k]*corrBF[i])
    prec[i+nsCFB,k] <- 1/var[i+nsCFB,k]  # set CFB precisions
    yBF[i,k] ~ dnorm(phi[i+nsCFB,k], prec[i+nsCFB,k])  # normal likelihood
    # theta is standardised mean
    phi[i+nsCFB,k] <- theta[i+nsCFB,k] * (Pooled.sd[i+nsCFB]/H[i+nsCFB])
    # model for linear predictor, deltaX is SMD
    theta[i+nsCFB,k] <- muX[i+nsCFB] + deltaX[i+nsCFB,k]
    # residual deviance contribution
    dev[i+nsR+nsCFB,k] <- (yBF[i,k]-phi[i+nsCFB,k]) * (yBF[i,k]-phi[i+nsCFB,k]) * prec[i+nsCFB,k]
    # variance of CFB, assuming correlation corrBF[i] (var is sd squared)
    varBF[i,k] <- pow(sdF[i,k],2) + pow(sdB[i,k],2)
    - 2*(sdF[i,k]*sdB[i,k]*corrBF[i])
    nvarBF[i,k] <- (n[i,k]-1) * varBF[i,k]  # for pooled.sd
  }
  # summed residual deviance contribution for this trial
  resdev[i+nsR+nsCFB] <- sum(dev[i+nsR+nsCFB,1:na[i]])
}
# RE MODEL (Response data)
for(i in 1:nsR){
  # LOOP THROUGH STUDIES WITH RESPONSE DATA
  for (k in 2:naR[i]){  
    # LOOP THROUGH ARMS
    # calculate variance of log odds ratio for comparisons with arm 1
    # check for zero or 100% events in arm k
    aux.a[i,k] <- equals(r[i,k],0)*equals(r[i,k],nR[i,k])
    # check for zero or 100% events in arm 1
    aux.b[i,k] <- equals(r[i,1],0)*equals(r[i,1],nR[i,1])
    aux[i,k] <- max(aux.a[i,k],aux.b[i,k]) # any zero or 100% events?
    # add 0.5 if zero or 100% events
    V[i,k] <- 1/(r[i,k]+(0.5*aux[i,k])) + 1/(r[i,1]+(0.5*aux[i,k]))
    + 1/(nR[i,k]-r[i,k]+(0.5*aux[i,k]))
    + 1/(nR[i,1]-r[i,1]+(0.5*aux[i,k]))
    # model for bias parameter beta
    beta[i,k] ~ dnorm(mb[i,k], Pkappa)
    mb[i,k] <- A[CR[i,k]]
    delta[i,k] ~ dnorm(md[i,k], taud[i,k]) # trial-specific LOR distributions
    # mean of LOR distributions (with multi-arm trial correction)
    md[i,k] <- d[tR[i,k]] - d[tR[i,1]] + sw[i,k]
    # precision of LOR distributions (with multi-arm trial correction)
    taud[i,k] <- tau *2*(k-1)/k
    # adjustment for multi-arm RCTs
    w[i,k] <- (delta[i,k] - d[tR[i,k]] + d[tR[i,1]])
    # cumulative adjustment for multi-arm trials
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
  }
}

# RE MODEL (CFB data)
for(i in 1:nsCFB){
  # LOOP THROUGH STUDIES WITH CFB DATA
  for (k in 2:naCFB[i]){  
    # LOOP THROUGH ARMS
    # convert SMD to LOR
    deltaX[i,k] <- (delta[i+nsR,k]+beta[i+nsR,k]*V[i+nsR,k]) * ((sqrt(3))/3.1416)
Depression in adults: treatment and management
Clinical evidence – network meta-analysis: bias adjustment methods and results

Update 2017

# convert variance of SMD to variance of LOR for bias model
VSMD[i,k] <- (var[i,k]+var[i,1])/Pooled.var[i]
V[i+nsR,k] <- 3.2899 * VSMD[i,k]
# model for bias parameter beta
beta[i+nsR,k] ~ dnorm(mb[i+nsR,k], Pkappa)
mb[i+nsR,k] <- A[CCFB[i,k]]
# trial-specific RE distributions
delta[i+nsR,k] ~ dnorm(md[i+nsR,k], tau[i+nsR,k])
md[i+nsR,k] <- d[CFB[i,k]] - d[CFB[i,1]] + sw[i+nsR,k]
# precision of RE distributions (with multi-arm trial correction)
taud[i+nsR,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
w[i+nsR,k] <- delta[i+nsR,k] - d[CFB[i,k]] + d[CFB[i,1]]
# cumulative adjustment for multi-arm trials
sw[i+nsR,k] <- sum(w[i+nsR,1:k-1])/(k-1)
}
}
# RE MODEL (BL and F-up data)
for(i in 1:nsBF){
  # LOOP THROUGH STUDIES WITH BL + F-UP DATA
  for (k in 2:na[i]){# LOOP THROUGH ARMS
    # convert SMD to LOR
deltaX[i+nsCFB,k] <- (delta[i+nsCFB,k] + beta[i+nsCFB,k]*V[i+nsCFB,k]) * ((sqrt(3))/3.1416)
    # convert variance of SMD to variance of LOR for bias model
    VSMD[i+nsCFB,k] <- (var[i+nsCFB,k]+var[i+nsCFB,1])/Pooled.var[i+nsCFB]
    V[i+nsR+nsCFB,k] <- 3.2899 * VSMD[i+nsCFB,k]
    # model for bias parameter beta
    beta[i+nsR+nsCFB,k] ~ dnorm(mb[i+nsR+nsCFB,k], Pkappa)
    mb[i+nsR+nsCFB,k] <- A[C[i,k]]
    # trial-specific RE distributions
delta[i+nsCFB+nsR,k] ~ dnorm(md[i+nsCFB+nsR,k], tau[i+nsCFB+nsR,k])
    md[i+nsCFB+nsR,k] <- d[i,k] - d[i,1] + sw[i+nsCFB+nsR,k]
    # precision of RE distributions (with multi-arm trial correction)
taud[i+nsCFB+nsR,k] <- tau *2*(k-1)/k
    # adjustment, multi-arm RCTs
Depression in adults: treatment and management
Clinical evidence – network meta-analysis: bias adjustment methods and results

\[ w[i+\text{nsCFB}+\text{nsR},k] <- \delta[i+\text{nsR}+\text{nsCFB},k] \text{ - } d[t[i,k]] + d[t[i,1]] \]  # cumulative adjustment for multi-arm trials

\[ sW[i+\text{nsCFB}+\text{nsR},k] <- \sum(w[i+\text{nsCFB}+\text{nsR},1:k-1])/(k-1) \]

\[
\begin{align*}
\text{totresdev} & <- \sum(\text{readev}[i]) \quad \# \text{Total Residual Deviance (all data)} \\
\text{totresdev.p}[1] & <- \sum(\text{resdev}[1:\text{nsR}]) \quad \# \text{Response data} \\
\text{totresdev.p}[2] & <- \sum(\text{resdev}[\text{nsR}+1:\text{nsR}+\text{nsCFB}]) \quad \# \text{CFB data} \\
\text{totresdev.p}[3] & <- \sum(\text{resdev}[\text{nsR}+\text{nsCFB}+1:\text{nsCFB}+\text{nsBF}+\text{nsR}]) \quad \# \text{B + FL data} \\
d[1] & <- 0 \quad \# \text{treatment effect is zero for reference} \\
m[1] & <- 0 \quad \# \text{treatment effect is zero for reference class} \\
\end{align*}
\]

\# Priors and model assumptions (classes)

\# no class treatments

\[ d[2] \sim \text{dnorm}(0, .0001) \quad \# \text{vague prior for treatment effects} \]

\[ d[3] \sim \text{dnorm}(0, .0001) \quad \# \text{vague prior for treatment effects} \]

\[ d[4] \sim \text{dnorm}(0, .0001) \quad \# \text{vague prior for treatment effects} \]

\[ d[7] \sim \text{dnorm}(0, .0001) \quad \# \text{vague prior for treatment effects} \]

\# single treatment classes, borrowing variance

\[ d[16] \sim \text{dnorm}(\text{m}[D[16]], \text{prec2}[9]) \quad \# \text{variance from SSRI/TCA} \]

\[ x <- (1/\text{prec2}[8]) + (1/\text{prec2}[7]) \]

\[ \text{prec2}[9] <- 1/x \]

\[ d[17] \sim \text{dnorm}(\text{m}[D[17]], \text{prec2}[14]) \quad \# \text{variance from CBT} \]

\[ d[18] \sim \text{dnorm}(\text{m}[D[18]], \text{prec2}[14]) \quad \# \text{variance from CBT} \]

\[ d[26] \sim \text{dnorm}(\text{m}[D[26]], \text{prec2}[14]) \quad \# \text{variance from CBT} \]

\[ d[29] \sim \text{dnorm}(\text{m}[D[29]], \text{prec2}[14]) \quad \# \text{variance from CBT} \]

\# treatment effects from Class, estimate variance

for (k in 5:6) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
for (k in 8:15) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
for (k in 19:25) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
for (k in 27:28) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }

National Institute for Health and Care Excellence [2017]. All rights reserved.

37
Depression in adults: treatment and management
Clinical evidence – network meta-analysis: bias adjustment methods and results

# no class treatments: class effect = treat effect
# priors for mean class effect
m[5] ~ dnorm(0, .0001)
for (k in 7:nc){ m[k] ~ dnorm(0, .0001) }
tau2 <- pow(0.19,-2)
for (k in 1:8){
  sd2[k] ~ dnorm(0,tau2)I(0,)
  prec2[k] <- pow(sd2[k], -0.5)
}
for (k in 10:nc){
  sd2[k] ~ dnorm(0,tau2)I(0,)
  prec2[k] <- pow(sd2[k], -0.5)
}

# mean bias: assumptions
A[1] <- 0
# bias model prior for variance
kappa ~ dunif(0,5)
kappa.sq <- pow(kappa,2)
Pkappa <- 1/kappa.sq
# bias model prior for mean
b ~ dnorm(0,.0001)

# pairwise ORs and LORs for all possible treatment comparisons
for (c in 1:(nt-1)){
  for (k in (c+1):nt){
Depression in adults: treatment and management
Clinical evidence – network meta-analysis: bias adjustment methods and results

National Institute for Health and Care Excellence [2017]. All rights reserved.

```r
1 or[c,k] <- exp(d[k] - d[c])
2 lor[c,k] <- (d[k]-d[c])
3 }
4 }
5 # rank treatments
6 for(k in 1:8){ dR[k] <- d[k] }
7 dR[9] <- d[10]
8 for(k in 10:13){ dR[k] <- d[k+2] }
9 for(k in 14:ntR){ dR[k] <- d[k+3] }
10 for (k in 1:nt){
11 rk[k] <- nt+1-rank(d[],k)    # assumes events are "good"
12 # rk[k] <- rank(d[],k)        # assumes events are "bad"
13 best[k]  <- equals(rk[k],1)  # Smallest is best (i.e. rank 1)
14 # prob treat k is h-th best, prob[1,k]=best[k]
15 for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
16 }
17 for (k in 1:ntR){
18 rk2[k] <- ntR+1-rank(dR[],k)    # assumes events are "good"
19 # rk2[k] <- rank(dR[],k)       # assumes events are "bad"
20 best2[k]  <- equals(rk2[k],1)  # Smallest is best (i.e. rank 1)
21 # prob treat k is h-th best, prob[1,k]=best[k]
22 for (h in 1:ntR) { prob2[h,k] <- equals(rk2[k],h) }
23 }
24 
25 # pairwise ORs and LORs for all possible class comparisons
26 for (c in 1:(nt-1)) {
27 for (k in (c+1):nc) {
28 orClass[c,k] <- exp(m[k] - m[c])
29 lorClass[c,k] <- (m[k]-m[c])
30 }
31 }
32 # rank classes
33 for(k in 1:8){ mR[k] <- m[k] }
34 for(k in 9:ncR){ mR[k] <- m[k+1] }
35 for (k in 1:nc){
```
rkClass[k] <- nc+1-rank(m[],k)  # assumes events are "good"
bestClass[k] <- equals(rkClass[k],1)  # Smallest is best (i.e. rank 1)
# prob class k is h-th best, prob[1,k]=best[k]
for (h in 1:nc) { probClass[h,k] <- equals(rkClass[k],h) }
}
for (k in 1:ncR) {
    rkClass2[k]  <- ncR+1-rank(mR[],k)
    bestClass2[k]  <- equals(rkClass2[k],1)    # Smallest is best (i.e. rank 1)
    # prob class k is h-th best, prob[1,k]=best[k]
    for (h in 1:ncR) { probClass2[h,k] <- equals(rkClass2[k],h) }
}
# *** PROGRAM ENDS

N.7 Appendix 7: NMA posterior mean rank and 95% credible intervals by intervention (bias model)

N.7.16 Population: Less severe depression

Table 13: Discontinuation – bias adjusted results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Posterior median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directive counselling</td>
<td>5</td>
<td>(1, 44)</td>
</tr>
<tr>
<td>Yoga</td>
<td>6</td>
<td>(1, 43)</td>
</tr>
<tr>
<td>Emotion-focused therapy (EFT)</td>
<td>6</td>
<td>(1, 47)</td>
</tr>
<tr>
<td>Relational client-centered therapy</td>
<td>6</td>
<td>(1, 47)</td>
</tr>
<tr>
<td>Non-directive counselling</td>
<td>7</td>
<td>(1, 36)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>8</td>
<td>(1, 46)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapy individual + Any AD</td>
<td>9</td>
<td>(1, 39)</td>
</tr>
<tr>
<td>Third-wave cognitive therapy individual</td>
<td>10</td>
<td>(2, 31)</td>
</tr>
<tr>
<td>Exercise + CBT individual (under 15 sessions)</td>
<td>10</td>
<td>(1, 45)</td>
</tr>
<tr>
<td>CBT group (under 15 sessions)</td>
<td>14</td>
<td>(3, 34)</td>
</tr>
<tr>
<td>Rational emotive behaviour therapy (REBT)</td>
<td>14</td>
<td>(2, 42)</td>
</tr>
<tr>
<td>Exercise</td>
<td>16</td>
<td>(6, 32)</td>
</tr>
<tr>
<td>CBT individual (over 15 sessions)</td>
<td>16</td>
<td>(6, 31)</td>
</tr>
<tr>
<td>CBT individual (under 15 sessions)</td>
<td>17</td>
<td>(5, 36)</td>
</tr>
<tr>
<td>Waitlist</td>
<td>18</td>
<td>(6, 34)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapy individual + any SSRI</td>
<td>18</td>
<td>(1, 48)</td>
</tr>
<tr>
<td>Aerobic exercise (supervised) + sertraline</td>
<td>18</td>
<td>(3, 43)</td>
</tr>
<tr>
<td>Problem solving</td>
<td>19</td>
<td>(5, 41)</td>
</tr>
<tr>
<td>Psychoeducational group programme</td>
<td>20</td>
<td>(4, 42)</td>
</tr>
<tr>
<td>Interpersonal psychotherapy (IPT)</td>
<td>20</td>
<td>(6, 39)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>21</td>
<td>(7, 39)</td>
</tr>
</tbody>
</table>
### Table 14: Response (completers) – bias adjusted results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Posterior median rank</th>
<th>95% CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpersonal psychotherapy (IPT) + any AD</td>
<td>2</td>
<td>(1, 16)</td>
</tr>
<tr>
<td>Cognitive bibliotherapy</td>
<td>4</td>
<td>(1, 24)</td>
</tr>
<tr>
<td>Interpersonal psychotherapy (IPT) + imipramine</td>
<td>5</td>
<td>(1, 39)</td>
</tr>
<tr>
<td>Self-examination therapy</td>
<td>9</td>
<td>(1, 37)</td>
</tr>
<tr>
<td>CBT individual (over 15 sessions)</td>
<td>10</td>
<td>(4, 20)</td>
</tr>
<tr>
<td>Behavioural therapy (Lewinsohn 1976)</td>
<td>10</td>
<td>(1, 37)</td>
</tr>
<tr>
<td>Computerised-CBT (CCBT) with support</td>
<td>11</td>
<td>(1, 38)</td>
</tr>
<tr>
<td>Behavioural activation</td>
<td>12</td>
<td>(4, 27)</td>
</tr>
<tr>
<td>Coping with Depression course (individual)</td>
<td>12</td>
<td>(1, 37)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapy individual + any SSRI</td>
<td>12</td>
<td>(1, 38)</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>13</td>
<td>(3, 32)</td>
</tr>
</tbody>
</table>
### Table 15: SMD – bias adjusted results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Posterior Mean rank</th>
<th>95% Crls</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT individual (over 15 sessions) + desipramine</td>
<td>1</td>
<td>(1, 4)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapy individual + Any AD</td>
<td>3</td>
<td>(1, 9)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapy individual + Any SSRI</td>
<td>3</td>
<td>(1, 38)</td>
</tr>
<tr>
<td>Cognitive bibliotherapy with support</td>
<td>4</td>
<td>(1, 14)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapy individual</td>
<td>6</td>
<td>(3, 24)</td>
</tr>
<tr>
<td>Rational emotive behaviour therapy (REBT)</td>
<td>6</td>
<td>(3, 19)</td>
</tr>
<tr>
<td>Computerised psychodynamic therapy with support</td>
<td>8</td>
<td>(4, 23)</td>
</tr>
<tr>
<td>Coping with Depression course (group)</td>
<td>10</td>
<td>(3, 35)</td>
</tr>
<tr>
<td>Aerobic exercise (supervised) + sertraline</td>
<td>10</td>
<td>(4, 30)</td>
</tr>
</tbody>
</table>
## N.7.21 Population: More severe depression

### Table 16: Discontinuation – bias adjusted results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Posterior median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>2</td>
<td>(1, 30)</td>
</tr>
<tr>
<td>Yoga</td>
<td>2</td>
<td>(1, 31)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapy individual</td>
<td>7</td>
<td>(1, 26)</td>
</tr>
<tr>
<td>CBT individual (over 15 sessions) + any SSRI</td>
<td>8</td>
<td>(2, 26)</td>
</tr>
<tr>
<td>CBT individual (under 15 sessions) + amineptine</td>
<td>8</td>
<td>(1, 33)</td>
</tr>
<tr>
<td>Long-term psychodynamic psychotherapy individual</td>
<td>9</td>
<td>(1, 33)</td>
</tr>
<tr>
<td>Emotion-focused therapy (EFT)</td>
<td>10</td>
<td>(1, 38)</td>
</tr>
<tr>
<td>Non-directive counselling</td>
<td>10</td>
<td>(2, 36)</td>
</tr>
<tr>
<td>Relational client-centered therapy</td>
<td>10</td>
<td>(1, 38)</td>
</tr>
</tbody>
</table>
### Table 17: Response in completers – bias adjusted results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Posterior median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural activation (BA)</td>
<td>2</td>
<td>(1, 23)</td>
</tr>
<tr>
<td>Exercise</td>
<td>4</td>
<td>(1, 25)</td>
</tr>
<tr>
<td>Yoga</td>
<td>6</td>
<td>(1, 26)</td>
</tr>
<tr>
<td>CBT individual (over 15 sessions) + nortriptyline</td>
<td>7</td>
<td>(1, 25)</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapy individual</td>
<td>8</td>
<td>(2, 20)</td>
</tr>
<tr>
<td>Non-directive counselling</td>
<td>8</td>
<td>(2, 22)</td>
</tr>
<tr>
<td>Counselling (any type)</td>
<td>8</td>
<td>(1, 26)</td>
</tr>
<tr>
<td>CBT individual (under 15 sessions)</td>
<td>8</td>
<td>(3, 19)</td>
</tr>
</tbody>
</table>
## Table 18: SMD – bias adjusted results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Posterior median rank</th>
<th>95% CrIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third-wave cognitive therapy individual</td>
<td>4</td>
<td>(1, 24)</td>
</tr>
<tr>
<td>Exercise + Fluoxetine</td>
<td>4</td>
<td>(1, 19)</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>6</td>
<td>(2, 14)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>9</td>
<td>(4, 20)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>9</td>
<td>(4, 18)</td>
</tr>
<tr>
<td>CBT individual (over 15 sessions) + nortriptyline</td>
<td>10</td>
<td>(1, 29)</td>
</tr>
<tr>
<td>CBT individual (over 15 sessions) + Pill placebo</td>
<td>10</td>
<td>(1, 29)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>11</td>
<td>(6, 20)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>12</td>
<td>(6, 22)</td>
</tr>
<tr>
<td>CBT individual (under 15 sessions) + citalopram</td>
<td>12</td>
<td>(3, 26)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>13</td>
<td>(6, 24)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>13</td>
<td>(8, 23)</td>
</tr>
<tr>
<td>Behavioural activation (BA)</td>
<td>13</td>
<td>(3, 23)</td>
</tr>
<tr>
<td>Pill placebo</td>
<td>15</td>
<td>(10, 25)</td>
</tr>
<tr>
<td>Interpersonal psychotherapy (IPT)</td>
<td>15</td>
<td>(2, 28)</td>
</tr>
<tr>
<td>CBT individual (over 15 sessions)</td>
<td>15</td>
<td>(3, 27)</td>
</tr>
<tr>
<td>Emotion-focused therapy (EFT)</td>
<td>16</td>
<td>(2, 29)</td>
</tr>
<tr>
<td>Non-directive counselling</td>
<td>18</td>
<td>(4, 27)</td>
</tr>
<tr>
<td>CBT individual (under 15 sessions)</td>
<td>18</td>
<td>(8, 26)</td>
</tr>
<tr>
<td>Relational client-centered therapy</td>
<td>19</td>
<td>(2, 29)</td>
</tr>
<tr>
<td>Exercise</td>
<td>21</td>
<td>(8, 26)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Posterior median rank</td>
<td>95% CrIs</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-----------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Short-term psychodynamic psychotherapy individual</td>
<td>21</td>
<td>(8, 26)</td>
</tr>
<tr>
<td>Attention placebo</td>
<td>22</td>
<td>(8, 28)</td>
</tr>
<tr>
<td>Computerised-CBT (CCBT)</td>
<td>23</td>
<td>(11, 27)</td>
</tr>
<tr>
<td>TAU</td>
<td>25</td>
<td>(15, 28)</td>
</tr>
<tr>
<td>Cognitive bibliotherapy</td>
<td>26</td>
<td>(11, 29)</td>
</tr>
<tr>
<td>Computerised-CBT (CCBT) with support</td>
<td>27</td>
<td>(4, 29)</td>
</tr>
<tr>
<td>Waitlist</td>
<td>28</td>
<td>(21, 29)</td>
</tr>
<tr>
<td>Third-wave cognitive therapy individual</td>
<td>4</td>
<td>(1, 24)</td>
</tr>
</tbody>
</table>