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Depression in adults: treatment and management

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

NICE Guideline

Appendices

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Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

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

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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.2.1 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).

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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.

N.2.2 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

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to the different effects reported by small studies and bias adjusted results should be considered.

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, δ_{ik}. This applies to the relative effects estimated from all included studies, whether the data are reported as change form 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

$$\theta_{ik} = \gamma_i + \delta_{ik} + (\beta_{ik} \times V_{ik}) \quad (1)$$

where $\delta_{i1} = \beta_{i1} = V_{i1} = 0$, V_{ik} is the variance of the relative effect measure calculated for arm *k* of study *i* compared to arm 1, and β_{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

$$\beta_{ik} \sim \text{Normal}(B, \kappa^2_{SMD}) \quad (2)$$

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*, δ_{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 [11,12]

$$V_{ik} = \frac{3}{\pi^2} V^*_{ik} \quad (3)$$

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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, κ_{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 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, η_{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

$$\text{logit}(p_{ik}) = \alpha_i + \eta_{ik} + \left(\beta^*_{ik} \times V^*_{ik}\right) \quad (4)$$

where $\eta_{i1} = \beta^*_{i1} = V^*_{i1} = 0$, the logOR for the treatment in arm *k* compared to the treatment in arm 1 of trial *i*, η_{ik}, 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 describe 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 β^*_{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

$$\beta^*_{ik} \sim \text{Normal}(B^*, \kappa^2_{LOR}) \quad (5)$$

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.

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N.3 Results: population with less severe depression

N.3.1 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).

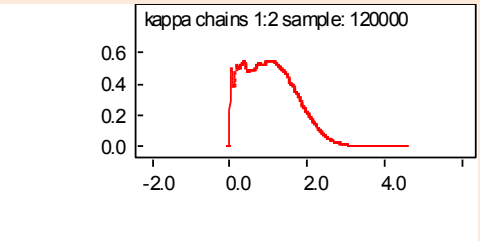
Although the mean bias had a negative median (as expected), the 95%CrI included the possibility of a zero bias with moderate variability (Table 1 and Figure 1: Between-study variability in mean bias for the SMD in the less severe population

. 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.

	Median	95%CrI
mean bias, b	-0.22	(-1.93, 1.50)
Standard deviation of bias, κ	0.99	(0.05, 2.38)

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 is some relative effects, although since there was no evidence of bias these should be interpreted with caution (Figure 2 and Figure 3).

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Figure 2: SMD of each intervention compared to Pill Placebo from the bias adjusted model. For intervention codes see Table 12 in Chapter 17

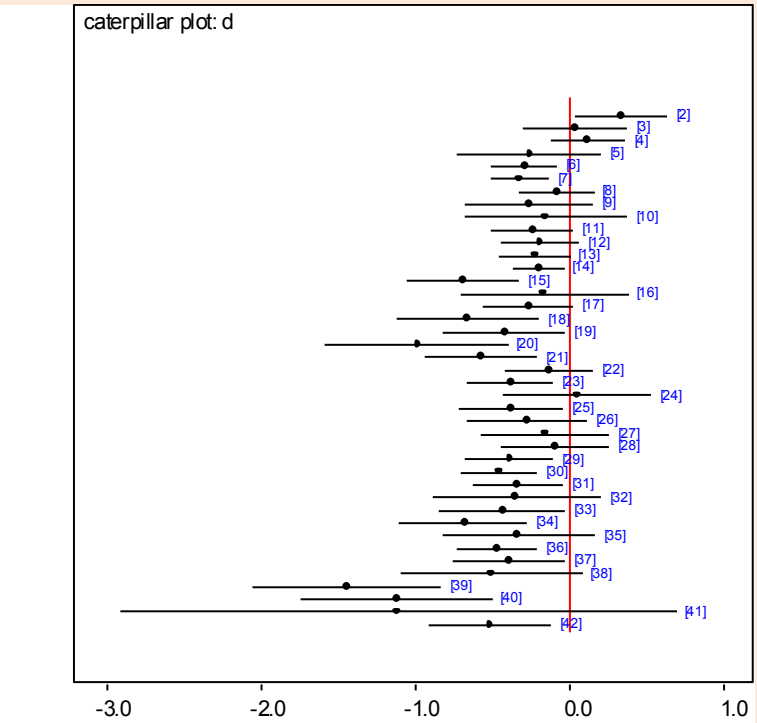
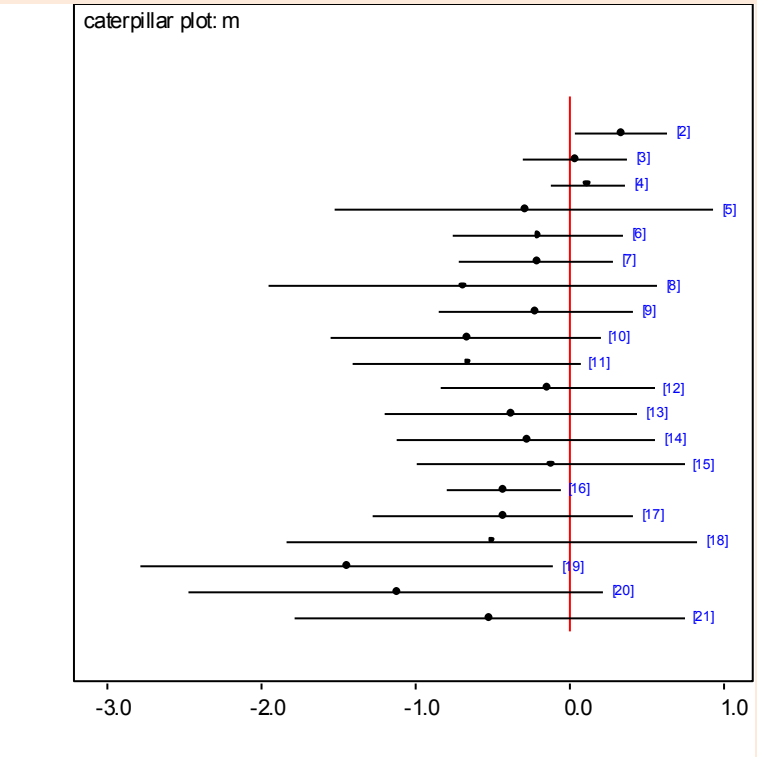


Figure 3: SMD of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 12 in Chapter 17.



Adjusted ranks for classes show no meaningful changes in class ranking, although there is added uncertainty in some rankings (Table 2).

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

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

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

N.3.25 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.

	Median	95%CrI
mean bias, b	0.18	(-0.19, 0.47)
Standard deviation of bias, κ	0.26	(0.02, 0.61)

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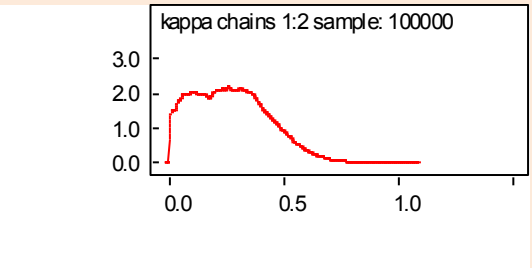
Figure 4: Between-study variability in mean bias for the logOR of discontinuation in the less severe population.



The logOR of interventions and classes for the bias adjusted model shows some very small changes is 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.

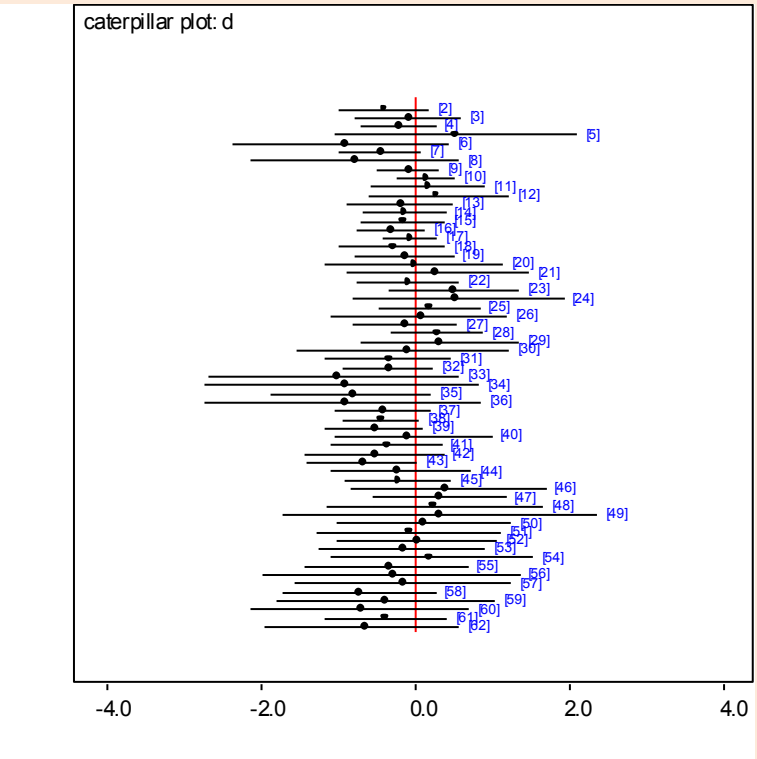


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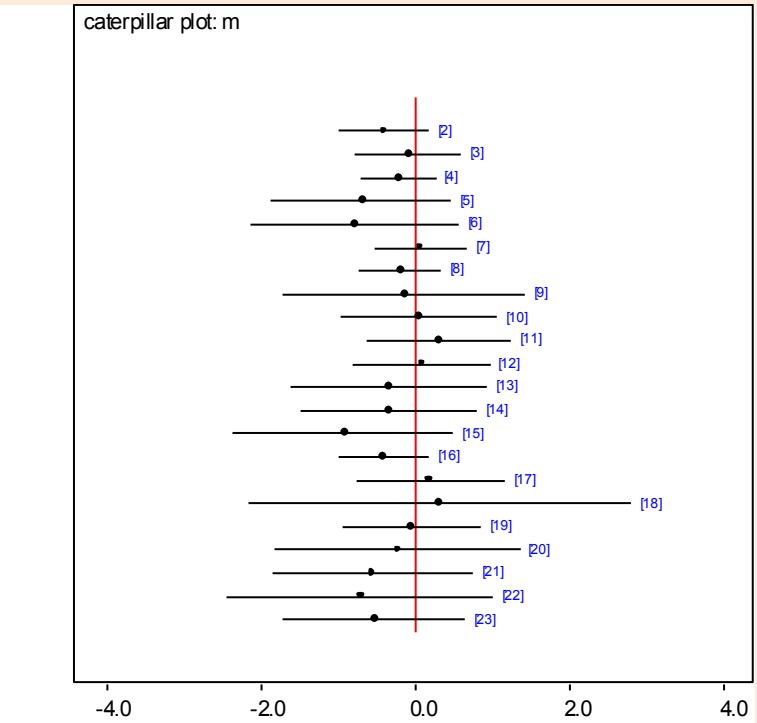
Figure 6: logOR of discontinuation of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 1 in Chapter 17.



Adjusted ranks for classes show some small changes in class ranking, although there is added uncertainty in rankings (Table 4).

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

Class	Posterior Median rank	95% CrIs
Counselling	3	(1, 18)
Mirtazapine	4	(1, 19)
Exercise	5	(1, 18)
Combined (Short-term psychodynamic psychotherapies + AD)	5	(1, 20)
Combined (Exercise + AD/CBT)	6	(1, 19)
Waitlist	7	(3, 15)
Cognitive and cognitive behavioural therapies	7	(3, 15)
Psychoeducational interventions	8	(1, 20)
Interpersonal psychotherapy (IPT)	8	(1, 20)
TAU	10	(5, 16)
Combined (IPT + AD)	10	(1, 20)
SSRIs	11	(4, 18)
Attention placebo	13	(4, 19)
Combined (Cognitive and cognitive behavioural therapies + AD)	13	(3, 20)
Pill placebo	14	(8, 19)
TCAs	15	(5, 20)
Short-term psychodynamic psychotherapies	15	(3, 20)
Self-help without support	15	(4, 20)

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Class	Posterior Median rank	95% CrIs
Behavioural therapies	16	(4, 20)
Self-help with support	18	(6, 20)

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

N.3.33 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.

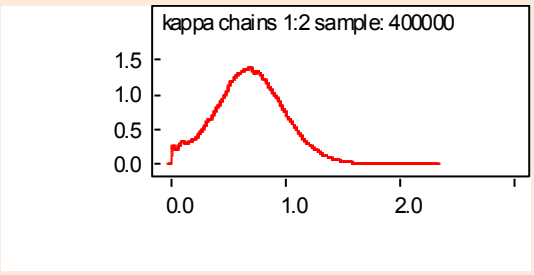
The NMA with bias adjustment showed a substantially improved fit to the data compared to the unadjusted NMA with the DIC favouring the bias adjusted NMA model. There was also a substantial reduction in the between-study heterogeneity in the bias adjusted model (see Appendix 3 in Chapter 17).

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.

	median	95%CrI
mean bias, b	1.48	(0.64, 2.34)
Standard deviation of bias, κ	0.68	(0.10, 1.29)

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).

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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.

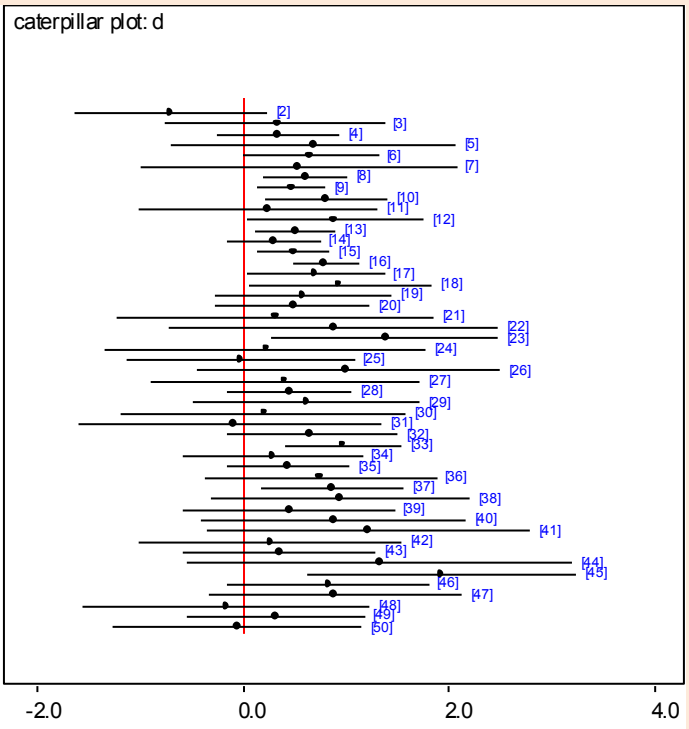
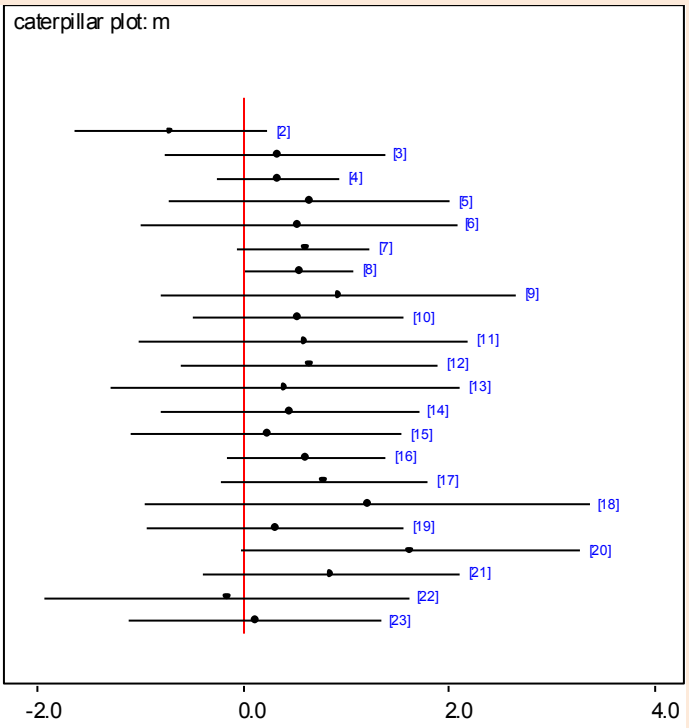


Figure 9: logOR of response in completers of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 9 in Chapter 17.



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.

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Table 6: Posterior median rank and 95%CrI from the bias adjusted analysis of the logOR of response in completers for the population with less severe depression.

Class	Posterior Median rank	95% CrIs
Combined (IPT + AD)	1	(1, 16)
Behavioural therapies	6	(1, 17)
Combined (Short-term psychodynamic psychotherapies + AD)	6	(1, 18)
Exercise	8	(1, 19)
Self-help without support	8	(1, 18)
Cognitive and cognitive behavioural therapies	8	(2, 16)
TCA	9	(2, 17)
SSRI	9	(3, 17)
Self-help with support	9	(1, 19)
Mirtazapine	10	(1, 20)
Short-term psychodynamic psychotherapies	10	(2, 19)
Psychoeducational interventions	11	(1, 20)
Interpersonal psychotherapy (IPT)	11	(1, 20)
Attention placebo	12	(2, 19)
TAU	12	(6, 17)
Counselling	13	(2, 20)
Combined (Cognitive and cognitive behavioural therapies + AD)	13	(2, 20)
Combined (Exercise + AD/CBT)	15	(3, 20)
Pill placebo	16	(11, 19)
Waitlist	20	(15, 20)

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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.48 Results: population with more severe depression

N.4.19 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.

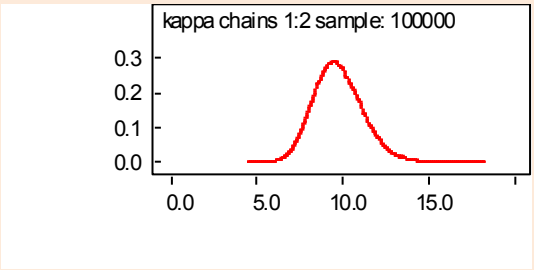
The NMA with bias adjustment showed no improvement in fit to the data compared to the unadjusted NMA with the DIC favouring the unadjusted NMA model. However, there was a substantial reduction in the between-study heterogeneity in the bias adjusted model (see Appendix 3 in Chapter 17).

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.

	median	95%CrI
mean bias, b	-6.99	(-12.77, -1.19)
Standard deviation of bias, κ	9.61	(7.16, 12.74)

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.

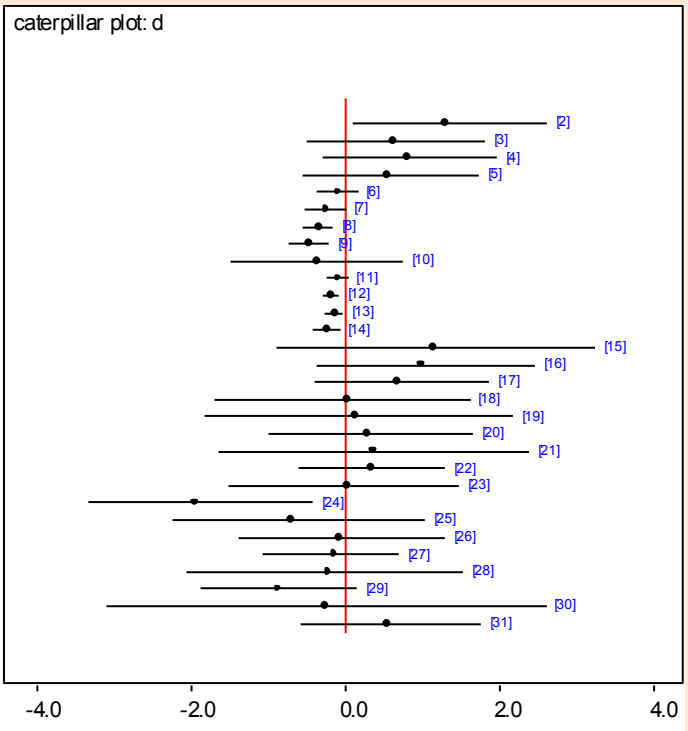


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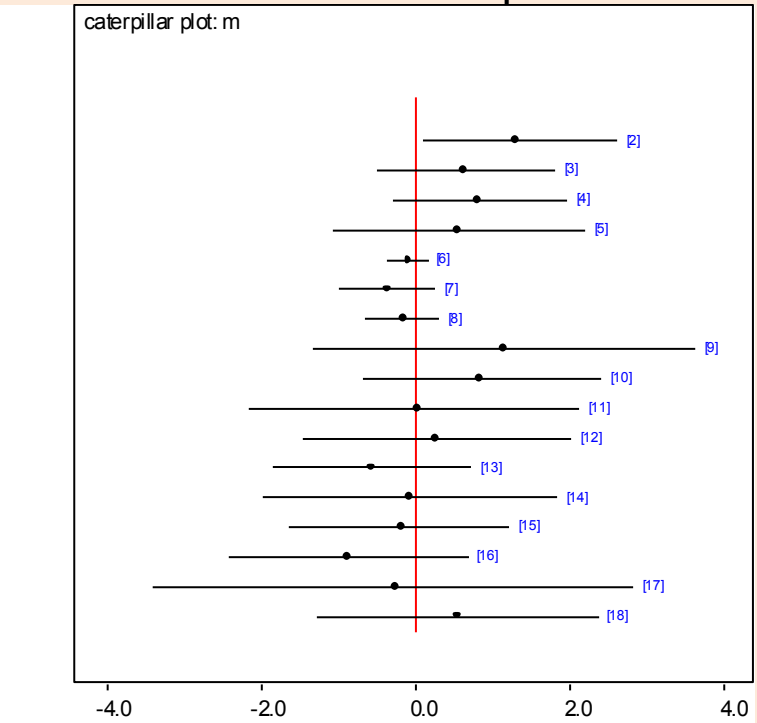
Figure 12: SMD of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 25 in Chapter 17



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

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

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

N.4.24 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).

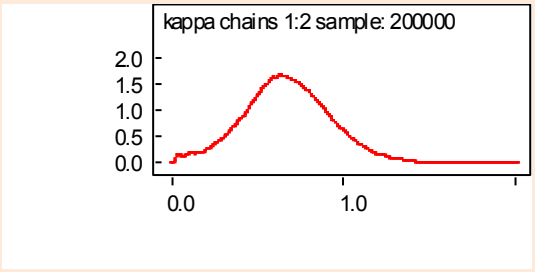
The NMA with bias adjustment showed a improved fit to the data compared to the unadjusted NMA, with the DIC favouring the bias-adjusted NMA model, although there was only a small reduction in the between-study heterogeneity when adjusting for bias (see Appendix 3 in Chapter 17).

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.

	median	95%CrI
mean bias, b	0.63	(-0.02, 1.32)
Standard deviation of bias, κ	0.66	(0.16, 1.19)

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 is 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.

).

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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.

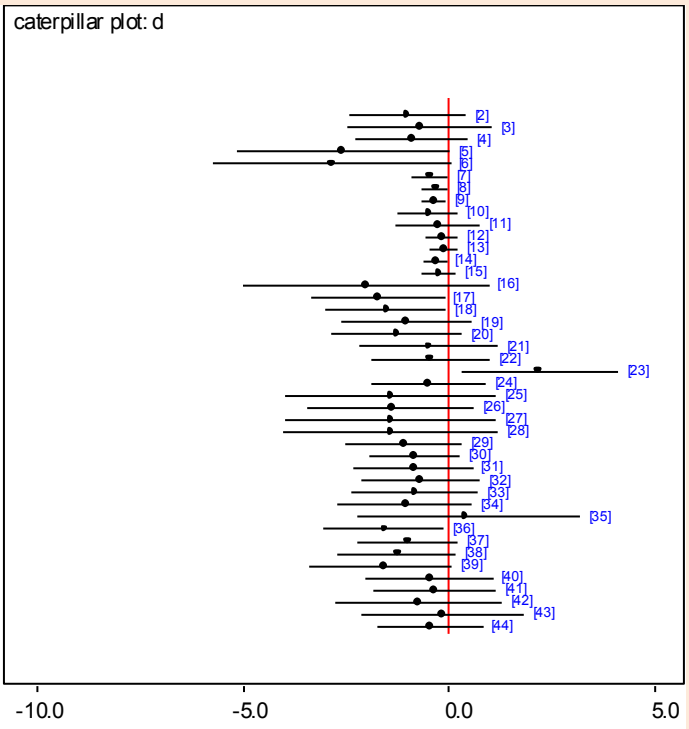
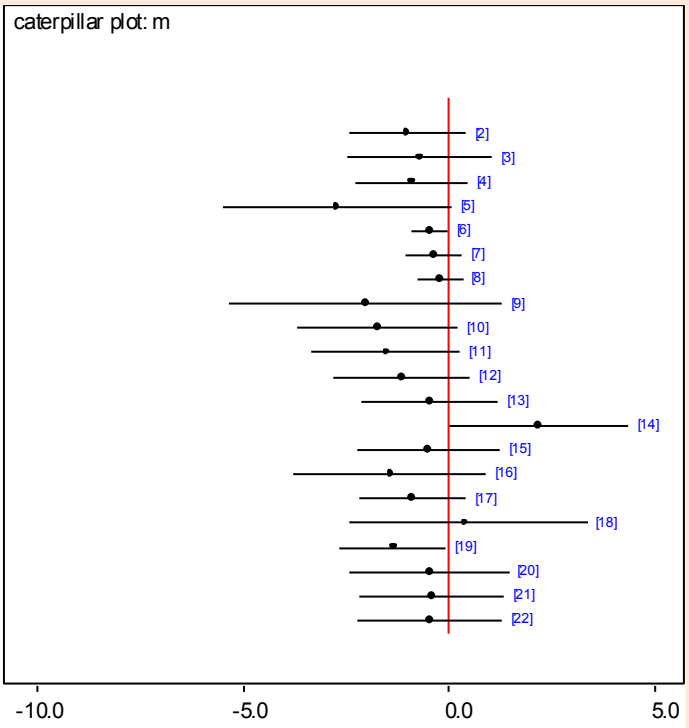


Figure 15: logOR of discontinuation of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 14 in Chapter 17.



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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.

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

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.

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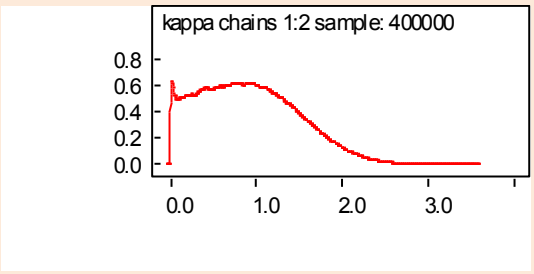
Table 11: Median and 95%CrI for the mean bias and its between study standard deviation for the logOR of responses in completers in the more severe population.

	median	95%CrI
mean bias, b	1.38	(0.30, 2.64)
Standard deviation of bias, κ	0.86	(0.03, 2.08)

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

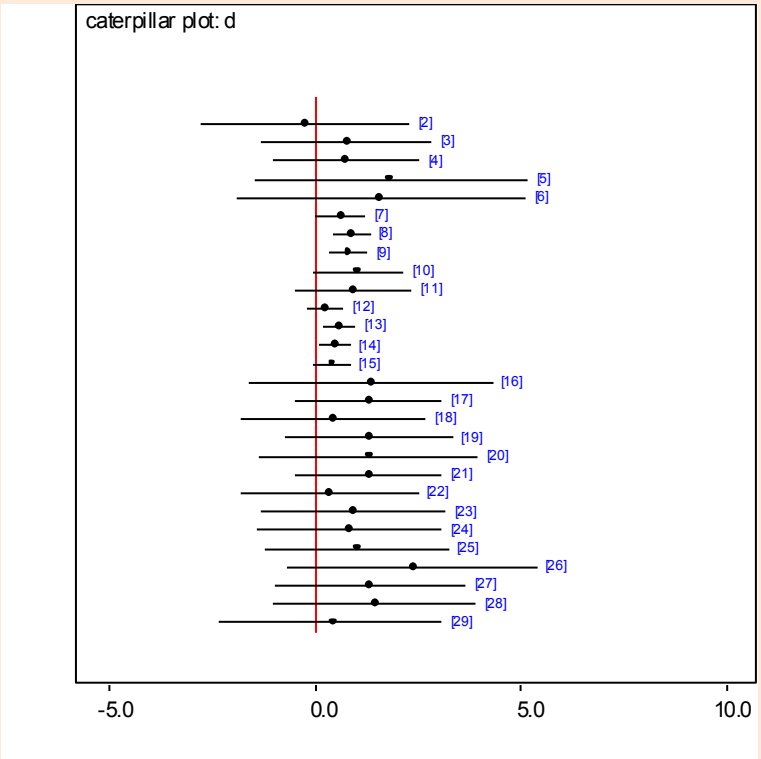


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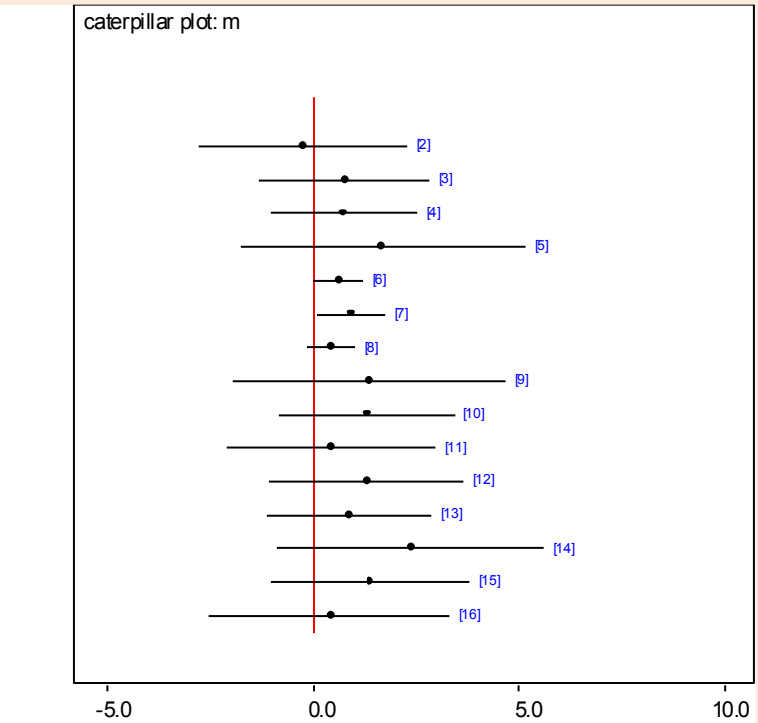
Figure 18: logOR of response in completers of each class compared to Pill Placebo from the bias adjusted model. For class codes see Table 21 in Chapter 17.



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.

Class	Posterior Median rank	95% CrIs
Behavioural therapies	2	(1, 13)
Exercise	3	(1, 14)
Combined (Cognitive and cognitive behavioural therapies + AD)	4	(1, 13)
Short-term psychodynamic psychotherapies	5	(1, 13)
Counselling	5	(1, 13)
TCA	7	(2, 12)
Cognitive and cognitive behavioural therapies	7	(2, 13)
Attention placebo	8	(2, 14)
TAU	8	(4, 12)
Mirtazapine	9	(2, 13)
SSRI	10	(3, 13)
Self-help	10	(2, 14)
Pill placebo	13	(6, 14)
Waitlist	13	(3, 14)

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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.

N.5 References

Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. *Journal of Computational and Graphical Statistics.* 1998;7(4):434-455.

Chaimani A, Vasiliadis HS, Pandis N, Schmid CH, Welton NJ, Salanti G. Effects of study precision and risk of bias in networks of interventions: a network meta-epidemiological study. *International Journal Of Epidemiology.* 2013;42:1120-1131.

Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med.* 2000;19:3127-3131.

Dias S, Welton NJ, Marinho VCC, Salanti G, Higgins JPT, Ades AE. Estimation and adjustment of bias in randomised evidence by using Mixed Treatment Comparison Meta-analysis. *Journal of the Royal Statistical Society (A).* 2010;173(3):613-629.

Driessen E, Hollon SD, Bockting CLH, Cuijpers P, Turner EH. Does Publication Bias Inflate the Apparent Efficacy of Psychological Treatment for Major Depressive Disorder? A Systematic Review and Meta-Analysis of US National Institutes of Health-Funded Trials. *PLOS ONE.* 2015;10(9):e0137864.

Gelman A, Rubin DB. Inferences from iterative simulation using multiple sequences. *Statistical Science.* 1992;7:457-472.

Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008].* Chichester: The Cochrane Collaboration, Wiley; 2008.

Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D. *The BUGS book.* Boca Raton, FL: CRC Press; 2013.

Moreno SG, Sutton AJ, Ades AE, Cooper NJ, Abrams KR. Adjusting for publication biases across similar interventions performed well when compared with gold standard data. *Journal of Clinical Epidemiology.* 2011;64(11):1230-1241.

Moreno SG, Sutton AJ, Turner EH, et al. Novel methods to deal with publication biases: secondary analysis of antidepressant trials in the FDA trial registry database and related journal publications. *BMJ.* 2009;339:b2981.

Trinquart L, Chatellier G, Ravaud P. Adjustment for reporting bias in network meta-analysis of antidepressant trials. *BMC Medical Research Methodology.* 2012;12:150.

Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine.* 2008;358:252-260.

N.6 Appendix 6: WINBUGS code

N.6.1 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
```

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```
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,.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)      # calcultate 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(nvarBF[i,1:na[i]])/df[i+nsCFB]
  Pooled.sd[i+nsCFB] <- sqrt(Pooled.var[i])# pooled sd for study i, for SMD
```

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```
#  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
  # calculate pooled.sd and adjustment for SMD
  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
```

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```
    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))
           + 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]]
```

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```
    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)
   }
 }
# RE MODEL (BL and F-up data)
for(i in 1:nsBF){                    # LOOP THROUGH STUDIES WITH BL+FUP
DATA
  for (k in 2:na[i]){                # LOOP THROUGH ARMS
    # model for bias parameter beta
    beta[i+nsCFB,k] ~ dnorm(mb[i+nsCFB,k], Pkappa)
    mb[i+nsCFB,k] <- A[CBF[i,k]]
    V[i+nsCFB,k] <- (var[i+nsCFB,k]+var[i+nsCFB,1])/Pooled.var[i+nsCFB]
    # trial-specific RE distributions
    delta[i+nsCFB,k] ~ dnorm(md[i+nsCFB,k], taud[i+nsCFB,k])
    md[i+nsCFB,k] <- d[t[i,k]] - d[t[i,1]] + sw[i+nsCFB,k]
    # precision of RE distributions (with multi-arm trial correction)
    taud[i+nsCFB,k] <- tau *2*(k-1)/k
    #adjustment, multi-arm RCTs
    w[i+nsCFB,k] <- delta[i+nsCFB,k] - d[t[i,k]] + d[t[i,1]]
    # cumulative adjustment for multi-arm trials
    sw[i+nsCFB,k] <-sum(w[i+nsCFB,1:k-1])/(k-1)
   }
 }
# RE MODEL (Response data)
for(i in 1:nsR){                     # LOOP THROUGH STUDIES WITH RESPONSE
DATA
  for (k in 2:naR[i]){               # LOOP THROUGH ARMS
    # model for bias parameter beta
```

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```
    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
```

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```
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
m[2] <- d[2]
m[3] <- d[3]
m[4] <- d[4]
m[6] <- d[6]
#
# 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,)          # prior for class precision
  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
```

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```
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]
#
for (k in 1:nt)  {
  rk[k]  <- rank(d[],k)
  best[k]  <- equals(rk[k],1)    # Smallest is best (i.e. rank 1)
  # prob treat k is h-th best, prob[1,k]=best[k]
  for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
 }
for (k in 1:ntR){
#  rk2[k] <- ntR+1-rank(dR[],k)     # assumes events are "good"
  rk2[k] <- rank(dR[],k)      # assumes events are "bad"
  best2[k]  <- equals(rk2[k],1)    # Smallest is best (i.e. rank 1)
  # prob treat k is h-th best, prob[1,k]=best[k]
  for (h in 1:ntR) { prob2[h,k] <- equals(rk2[k],h) }
 }
# 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])
```

Update 2017

```
   }
 }
# rank classes
for(k in 1:16){  mR[k] <- m[k] }
mR[17] <- m[18]
for (k in 1:nc){
  rkClass[k] <- 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]  <- 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.6.2 Sample WinBUGS code – Response bias analysis

```
# 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
  # 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
 }
#
```

Update 2017

```
# 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)      # calcultate 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
   }
```

Update 2017

```
  # 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 i,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]])
 }
#
```

Update 2017

```
# 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)
```

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], taud[i+nsR,k])
    md[i+nsR,k] <- d[tCFB[i,k]] - d[tCFB[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[tCFB[i,k]] + d[tCFB[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+nsR+nsCFB,k] +
beta[i+nsR+nsCFB,k]*V[i+nsR+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], taud[i+nsCFB+nsR,k])
    md[i+nsCFB+nsR,k] <- d[t[i,k]] - d[t[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
```

Update 2017

```
    w[i+nsCFB+nsR,k] <- delta[i+nsR+nsCFB,k] - d[t[i,k]] + d[t[i,1]]
    # cumulative adjustment for multi-arm trials
    sw[i+nsCFB+nsR,k] <-sum(w[i+nsCFB+nsR,1:k-1])/(k-1)
   }
 }
#
# Calculate residual deviance
totresdev <- sum(resdev[])            # Total Residual Deviance (all data)
totresdev.p[1] <- sum(resdev[1:nsR])  # Response data
totresdev.p[2] <- sum(resdev[nsR+1:nsR+nsCFB]) # CFB data
totresdev.p[3] <- sum(resdev[nsR+nsCFB+1:nsCFB+nsBF+nsR]) # B + FL data
d[1] <- 0                    # treatment effect is zero for reference
treatment
m[1] <- 0                    # treatment effect is zero for reference class
#
# Priors and model assumptions (classes)
# no class treatments
d[2] ~ dnorm(0, .0001)         # vague prior for treatment effects
d[3] ~ dnorm(0, .0001)         # vague prior for treatment effects
d[4] ~ dnorm(0, .0001)         # vague prior for treatment effects
d[7] ~ dnorm(0, .0001)         # vague prior for treatment effects
#
# single treatment classes, borrowing variance
d[16] ~ dnorm(m[D[16]], prec2[9])  # variance from SSRI/TCA
x <- (1/prec2[8]) + (1/prec2[7])
prec2[9] <- 1/x
d[17] ~ dnorm(m[D[17]], prec2[14])  # variance from CBT
d[18] ~ dnorm(m[D[18]], prec2[14])  # variance from CBT
d[26] ~ dnorm(m[D[26]], prec2[14])  # variance from CBT
d[29] ~ dnorm(m[D[29]], prec2[14]) # 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]]) }
```

Update 2017

```
#
# no class treatments: class effect = treat effect
m[2] <- d[2]
m[3] <- d[3]
m[4] <- d[4]
m[6] <- d[7]
# 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,)   # informative prior for within-class st dev
  prec2[k] <- pow(sd2[k], -0.5) # within-class precision
 }
for (k in 10:nc){
  sd2[k] ~ dnorm(0,tau2)I(0,)   # informative prior for within-class st dev
  prec2[k] <- pow(sd2[k], -0.5) # within-class precision
}
#
sdev ~ dunif(0,5)                # vague prior for between-trial SD
tau <- pow(sdev,-2)              # between-trial precision
# mean bias: assumptions
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(0,5)
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){
```

Update 2017

```
    or[c,k] <- exp(d[k] - d[c])
    lor[c,k] <- (d[k]-d[c])
   }
 }
# rank treatments
for(k in 1:8){ dR[k] <- d[k] }
dR[9] <- d[10]
for(k in 10:13){  dR[k] <- d[k+2] }
for(k in 14:ntR){ dR[k] <- d[k+3] }
for (k in 1:nt){
  rk[k] <- nt+1-rank(d[],k)       # assumes events are "good"
#  rk[k] <- rank(d[],k)          # assumes events are "bad"
  best[k]  <- equals(rk[k],1)    # Smallest is best (i.e. rank 1)
  # prob treat k is h-th best, prob[1,k]=best[k]
  for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
 }
for (k in 1:ntR){
  rk2[k] <- ntR+1-rank(dR[],k)       # assumes events are "good"
#  rk2[k] <- rank(dR[],k)            # assumes events are "bad"
  best2[k]  <- equals(rk2[k],1)  # Smallest is best (i.e. rank 1)
  # prob treat k is h-th best, prob[1,k]=best[k]
  for (h in 1:ntR) { prob2[h,k] <- equals(rk2[k],h) }
 }
#
# pairwise ORs and LORs for all possible class comparisons
for (c in 1:(nt-1)) {
  for (k in (c+1):nc)  {
    orClass[c,k] <- exp(m[k] - m[c])
    lorClass[c,k] <- (m[k]-m[c])
   }
 }
# rank classes
for(k in 1:8){ mR[k] <- m[k] }
for(k in 9:ncR){ mR[k] <- m[k+1] }
for (k in 1:nc){
```

Update 2017

```
  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.7.1 Population: Less severe depression

Table 13: Discontinuation – bias adjusted results

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

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Intervention	Posterior median rank	95% CrIs
Interpersonal psychotherapy (IPT) + imipramine	22	(1, 49)
Third-wave cognitive therapy group	24	(5, 46)
TAU	25	(13, 37)
Behavioural activation	25	(6, 43)
Interpersonal psychotherapy (IPT) + any AD	27	(2, 49)
Citalopram	28	(8, 44)
Escitalopram	28	(8, 44)
Cognitive bibliotherapy	28	(9, 43)
CBT group (over 15 sessions)	28	(6, 48)
Attention placebo	30	(9, 45)
Amitriptyline	30	(12, 44)
Short-term psychodynamic psychotherapy individual	30	(10, 45)
Self-examination therapy	30	(2, 49)
CBT individual (over 15 sessions) + amitriptyline	30	(3, 49)
Sertraline	31	(16, 43)
Pill placebo	33	(20, 43)
Psychodynamic counselling	33	(4, 49)
Tailored computerised-CBT (CCBT) with support	36	(5, 49)
Lofepramine	38	(12, 49)
Computerised-CBT (CCBT) with support	39	(20, 47)
Short-term psychodynamic psychotherapy group	40	(8, 49)
Coping with Depression course (individual)	40	(4, 49)
Computerised-CBT (CCBT)	41	(28, 47)
Online positive psychological intervention	42	(12, 49)
Coping with Depression course (group)	42	(16, 49)
Behavioural therapy (Lewinsohn 1976)	43	(8, 49)
Cognitive bibliotherapy with support	44	(25, 49)
Computerised psychodynamic therapy with support	45	(9, 49)

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Table 14: Response (completers) – bias adjusted results

Intervention	Posterior median rank	95%CrI
Interpersonal psychotherapy (IPT) + any AD	2	(1, 16)
Cognitive bibliotherapy	4	(1, 24)
Interpersonal psychotherapy (IPT) + imipramine	5	(1, 39)
Self-examination therapy	9	(1, 37)
CBT individual (over 15 sessions)	10	(4, 20)
Behavioural therapy (Lewinsohn 1976)	10	(1, 37)
Computerised-CBT (CCBT) with support	11	(1, 38)
Behavioural activation	12	(4, 27)
Coping with Depression course (individual)	12	(1, 37)
Short-term psychodynamic psychotherapy individual + any SSRI	12	(1, 38)
Lofepramine	13	(3, 32)

Intervention	Posterior median rank	95%CrI
Short-term psychodynamic psychotherapy individual + Any AD	13	(2, 35)
Sertraline	14	(4, 27)
Third-wave cognitive therapy individual	15	(2, 38)
Exercise	18	(6, 32)
CBT individual (under 15 sessions)	18	(4, 35)
Amitriptyline	19	(6, 33)
Emotion-focused therapy (EFT)	19	(3, 38)
Psychodynamic counselling	20	(4, 37)
Mirtazapine	22	(1, 41)
Citalopram	22	(8, 35)
Fluoxetine	23	(9, 35)
Short-term psychodynamic psychotherapy individual	23	(9, 36)
Interpersonal psychotherapy (IPT)	24	(10, 36)
Coping with Depression course (group)	24	(6, 38)
Psychoeducational group programme	25	(4, 40)
Problem solving	25	(10, 37)
Attention placebo	27	(5, 40)
TAU	27	(13, 37)
Escitalopram	28	(12, 38)
Cognitive bibliotherapy with support	28	(3, 41)
CBT group (under 15 sessions)	28	(9, 40)
Aerobic exercise (supervised) + sertraline	28	(7, 39)
CBT individual (over 15 sessions) + amitriptyline	29	(4, 41)
Computerised-CBT (CCBT)	30	(4, 41)
Non-directive counselling	30	(4, 41)
Pill placebo	35	(25, 40)
Online positive psychological intervention	35	(12, 40)
Exercise + CBT individual (under 15 sessions)	35	(8, 41)
Relational client-centered therapy	36	(6, 41)
Waitlist	40	(34, 41)

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Table 15: SMD – bias adjusted results

Intervention	Posterior Mean rank	95% CrIs
CBT individual (over 15 sessions) + desipramine	1	(1, 4)
Short-term psychodynamic psychotherapy individual + Any AD	3	(1, 9)
Short-term psychodynamic psychotherapy individual + Any SSRI	3	(1, 38)
Cognitive bibliotherapy with support	4	(1, 14)
Short-term psychodynamic psychotherapy individual	6	(3, 24)
Rational emotive behaviour therapy (REBT)	6	(3, 19)
Computerised psychodynamic therapy with support	8	(4, 23)
Coping with Depression course (group)	10	(3, 35)
Aerobic exercise (supervised) + sertraline	10	(4, 30)

Intervention	Posterior Mean rank	95% CrIs
Third-wave cognitive therapy group	12	(6, 23)
CBT individual (under 15 sessions)	13	(7, 22)
CBT group (over 15 sessions)	14	(5, 32)
Long-term psychodynamic psychotherapy individual	15	(5, 31)
Online positive psychological intervention	16	(6, 30)
Non-directive counselling	16	(8, 28)
Behavioural activation	16	(5, 31)
Cognitive bibliotherapy	17	(8, 28)
CBT group (under 15 sessions)	18	(4, 36)
Third-wave cognitive therapy individual	18	(5, 36)
CBT individual (over 15 sessions)	19	(8, 31)
Exercise	20	(9, 30)
Enhanced TAU	22	(12, 30)
Psychoeducational group programme	22	(7, 35)
Amitriptyline	23	(6, 36)
Short-term psychodynamic psychotherapy group	23	(12, 33)
Lofepramine	24	(9, 35)
Escitalopram	25	(13, 33)
Citalopram	27	(11, 35)
Fluoxetine	27	(17, 33)
Sertraline	27	(7, 38)
Interpersonal psychotherapy (IPT)	28	(10, 37)
Computerised-CBT (CCBT) with support	30	(18, 35)
Directive counselling	31	(17, 37)
Pill placebo	33	(28, 37)
Attention placebo	34	(23, 37)
Computerised-CBT (CCBT)	35	(16, 38)
TAU	36	(32, 37)
Waitlist	38	(36, 38)

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N.7.21 Population: More severe depression

Table 16: Discontinuation – bias adjusted results

Intervention	Posterior median rank	95% CrIs
Exercise	2	(1, 30)
Yoga	2	(1, 31)
Short-term psychodynamic psychotherapy individual	7	(1, 26)
CBT individual (over 15 sessions) + any SSRI	8	(2, 26)
CBT individual (under 15 sessions) + amineptine	8	(1, 33)
Long-term psychodynamic psychotherapy individual	9	(1, 33)
Emotion-focused therapy (EFT)	10	(1, 38)
Non-directive counselling	10	(2, 36)
Relational client-centered therapy	10	(1, 38)

Intervention	Posterior median rank	95% CrIs
Counselling (any type)	10	(1, 38)
Computerised-CBT (CCBT) with support	12	(3, 32)
CBT individual (over 15 sessions) + nortriptyline	12	(2, 34)
CBT individual (under 15 sessions)	15	(5, 32)
Waitlist	16	(5, 34)
Cognitive bibliotherapy with support	16	(4, 36)
Third-wave cognitive therapy individual	16	(3, 37)
CBT individual (over 15 sessions) + imipramine	16	(4, 35)
TAU	18	(8, 33)
CBT group (under 15 sessions)	19	(6, 36)
CBT individual (over 15 sessions)	20	(7, 34)
Third-wave cognitive therapy group	20	(5, 37)
CBT individual (over 15 sessions) + Pill placebo	21	(2, 39)
Attention placebo	22	(5, 38)
Problem solving	22	(8, 37)
Mirtazapine	26	(9, 36)
Lofepramine	26	(7, 38)
Cognitive bibliotherapy	26	(7, 39)
Computerised-CBT (CCBT)	26	(12, 38)
Interpersonal psychotherapy (IPT)	26	(7, 38)
Interpersonal psychotherapy (IPT) + any TCA	26	(5, 39)
Long-term psychodynamic psychotherapy individual + fluoxetine	27	(4, 39)
Amitriptyline	29	(12, 36)
Fluoxetine	29	(12, 36)
Sertraline	30	(13, 38)
CBT individual (under 15 sessions) + Pill placebo	31	(5, 39)
Citalopram	32	(15, 38)
Escitalopram	33	(16, 38)
Pill placebo	35	(21, 39)
Behavioural activation (BA)	37	(5, 40)
Psychoeducational group programme	40	(38, 40)

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Table 17: Response in completers – bias adjusted results

Intervention	Posterior median rank	95% CrIs
Behavioural activation (BA)	2	(1, 23)
Exercise	4	(1, 25)
Yoga	6	(1, 26)
CBT individual (over 15 sessions) + nortriptyline	7	(1, 25)
Short-term psychodynamic psychotherapy individual	8	(2, 20)
Non-directive counselling	8	(2, 22)
Counselling (any type)	8	(1, 26)
CBT individual (under 15 sessions)	8	(3, 19)

Intervention	Posterior median rank	95% CrIs
CBT individual (over 15 sessions) + any SSRI	8	(1, 24)
Lofepramine	11	(1, 23)
Amitriptyline	12	(2, 20)
CBT group (under 15 sessions)	12	(2, 25)
Third-wave cognitive therapy individual	12	(2, 25)
Attention placebo	14	(3, 25)
Third-wave cognitive therapy group	14	(2, 25)
TAU	15	(7, 24)
Mirtazapine	16	(3, 24)
Escitalopram	16	(4, 23)
Fluoxetine	18	(6, 24)
Cognitive bibliotherapy	18	(4, 26)
CBT individual (over 15 sessions) + Pill placebo	18	(2, 26)
Sertraline	19	(6, 25)
CBT individual (over 15 sessions)	19	(5, 26)
Citalopram	21	(8, 25)
Pill placebo	24	(11, 26)
Waitlist	24	(4, 26)

Table 18: SMD – bias adjusted results

Intervention	Posterior median rank	95% CrIs
Third-wave cognitive therapy individual	4	(1, 24)
Exercise + Fluoxetine	4	(1, 19)
Lofepramine	6	(2, 14)
Amitriptyline	9	(4, 20)
Sertraline	9	(4, 18)
CBT individual (over 15 sessions) + nortriptyline	10	(1, 29)
CBT individual (over 15 sessions) + Pill placebo	10	(1, 29)
Escitalopram	11	(6, 20)
Fluoxetine	12	(6, 22)
CBT individual (under 15 sessions) + citalopram	12	(3, 26)
Mirtazapine	13	(6, 24)
Citalopram	13	(8, 23)
Behavioural activation (BA)	13	(3, 23)
Pill placebo	15	(10, 25)
Interpersonal psychotherapy (IPT)	15	(2, 28)
CBT individual (over 15 sessions)	15	(3, 27)
Emotion-focused therapy (EFT)	16	(2, 29)
Non-directive counselling	18	(4, 27)
CBT individual (under 15 sessions)	18	(8, 26)
Relational client-centered therapy	19	(2, 29)
Exercise	21	(8, 26)

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Intervention	Posterior median rank	95% CrIs
Short-term psychodynamic psychotherapy individual	21	(8, 26)
Attention placebo	22	(8, 28)
Computerised-CBT (CCBT)	23	(11, 27)
TAU	25	(15, 28)
Cognitive bibliotherapy	26	(11, 29)
Computerised-CBT (CCBT) with support	27	(4, 29)
Waitlist	28	(21, 29)
Third-wave cognitive therapy individual	4	(1, 24)

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