National Institute for Health and Care Excellence

Consultation draft

Depression in adults: treatment and management

Appendix N2: Network meta-analysis - bias adjustment methods and results

NICE Guideline

Appendices

May 2018

Consultation draft

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

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2.1 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 variance of the relative treatment effects 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 Appendix N1). 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.

2.2 Methods

2.2.1 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).

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 mean. This allows for the fact that small studies may exaggerate effects of one active intervention over

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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 2.2.3 to 2.2.5.

The treatments defined as controls by the Guideline Committee were those in the following classes

1. Pill placebo
2. No treatment
3. Attention Placebo
4. TAU

while all other interventions were defined as active. See Appendix N1 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

Comparisons of types 1 and 3 are assumed to have zero mean bias, whilst comparisons of type 2 estimate a possibly 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 at the end of this document, in Appendix 6.

2.2.26 Reporting of results

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

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 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 suggests favouring the control

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interventions we will interpret these results with caution as they go against informed clinical opinion (see Section 2.2.1.).

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 Appendix N1 for a list of these).

2.2.30 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, for 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 1.2.5 of Appendix N1. The only change required to incorporate the bias adjustment is to change equation (3) of Appendix N1 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 Appendix N1.

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 (Chinn 2009, Higgins and Green 2008)

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

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, κ_{SMD}, is given a Uniform prior distribution with a lower bound of zero and upper bound chosen to capture all the observed

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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.

2.2.43 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, for 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 1.2.6 of Appendix N1.

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 1.2.6 of Appendix N1 (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 2.2.3. 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.

2.2.52 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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2.3 Results: population with less severe depression

2.3.1 Outcome: SMD – less severe depression

A burn-in of 70,000 iterations was used after which a further 140,000 iterations were taken from 2 independent chains (total of 280,000 iterations). High autocorrelation is present in some parameters.

We therefore conclude that there is strong evidence of small study bias in this network.

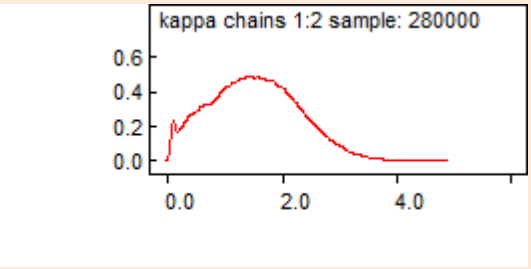
The bias adjusted NMA model showed a substantially improved fit compared to the unadjusted NMA model and the DIC favours the bias adjusted NMA model (Section 1.8 of Appendix N1). The bias adjusted model better predicted the data for Hermat-Far 2012 and Dunn 2005, compared to the unadjusted NMA model. These studies were poorly predicted by the unadjusted NMA model. There was a small reduction in the between-study heterogeneity in the bias adjusted NMA model (see Section 1.8 in Appendix N1). The median of the posterior distribution of the mean bias is negative (as expected) and the 95% CrI excludes the possibility of zero bias (Table 1). However there is considerable variability in mean bias (Figure 1). We therefore conclude that there is strong evidence of small study bias in this network.

We therefore conclude that there is strong 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 population with less severe depression.

	Median	95%CrI
mean bias, b	-2.23	(-4.31, -0.36)
Standard deviation of bias, κ	1.49	(0.15, 3.07)

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



The SMD of interventions and classes for the bias adjusted model shows a small reduction is some relative effects (Figure 7**Error! Reference source not found.** and Figure 8**Error! Reference source not found.**).

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

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% CrI
Combined (Counselling + AD)	2	(1, 21)
Combined (IPT + AD)	2	(1, 8)
Combined (Short-term psychodynamic psychotherapies + AD)	3	(1, 15)
Combined (Exercise + AD/CBT)	3	(1, 15)

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Class	Posterior median rank	95% CrI
Behavioural therapies (individual)	5	(1, 19)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	6	(2, 16)
Self-help with support	8	(3, 15)
Cognitive and cognitive behavioural therapies (individual)	8	(4, 16)
TCAs	10	(5, 18)
Exercise	12	(5, 21)
SSRIs	12	(7, 19)
Short-term psychodynamic psychotherapies	12	(3, 22)
Behavioural, cognitive, or CBT groups	14	(8, 20)
Combined (Self-help + AD)	14	(3, 23)
Psychoeducational interventions	15	(6, 21)
Interpersonal psychotherapy (IPT)	15	(4, 23)
Counselling	15	(5, 22)
Self-help without support	16	(9, 20)
Pill placebo	17	(12, 20)
Attention placebo	17	(6, 22)
TAU	21	(13, 23)
No treatment	22	(15, 23)
Problem solving	23	(11, 23)

We conclude that although there is some evidence of bias, the overall conclusions from the NMA for SMD in the population with less severe depression is robust to small study/publication bias.

Relative intervention and class effects versus pill placebo as well as the posterior median rank of each intervention are reported in the *'Bias adjustment'* worksheet of the respective excel file in Appendix N3.

2.3.27 Outcome: discontinuation for any reason – less severe depression

A burn-in of 30,000 iterations was used after which a further 60,000 iterations were taken form 2 independent chains (total of 120,000 iterations).

The NMA with bias adjustment showed a slightly improved fit to the data compared to the unadjusted NMA. The DIC for the adjusted and unadjusted model were similar although slightly smaller for the unadjusted NMA model. There was a small reduction in the between-study heterogeneity when adjusting for bias (see Section 1.8 in Appendix N1).

The mean bias had a negative median (which is in the expected direction) but the 95%CrI included the possibility of a zero bias although with moderate variability (Table 3 and Figure 2). 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	-0.12	(-0.46, 0.20)
Standard deviation of bias, κ	0.48	(0.13, 0.77)

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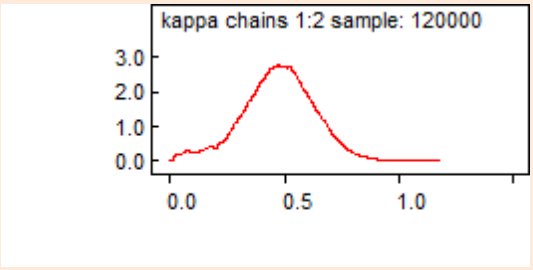
Figure 2: Between-study variability in mean bias for the logOR of discontinuation in the population with less severe depression.



The OR of interventions and classes for the bias adjusted model show some very small changes is relative effects (Figure 9 and Figure 10).

Adjusted ranks for classes (Table 4) show only small changes in class ranking when compared to the unadjusted NMA ranks. Since there was no evidence of bias these should be interpreted with caution.

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% CrI
Combined (Problem solving + AD)	3	(1, 24)
Mirtazapine	4	(1, 23)
No treatment	5	(1, 17)
Psychoeducational interventions	6	(1, 19)
Behavioural therapies (individual)	6	(1, 22)
Interpersonal psychotherapy (IPT)	9	(2, 21)
Problem solving	9	(2, 22)
Cognitive and cognitive behavioural therapies (individual)	9	(3, 17)
Combined (psych + placebo)	9	(1, 23)
Behavioural, cognitive, or CBT groups	10	(3, 21)
TAU	11	(3, 22)
Counselling	12	(3, 22)
Combined (IPT + AD)	12	(1, 25)
Exercise	14	(3, 23)
SSRIs	14	(6, 20)
Short-term psychodynamic psychotherapies	15	(3, 24)
Pill placebo	16	(9, 22)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	16	(3, 25)
Combined (Counselling + AD)	16	(1, 25)
Attention placebo	18	(5, 25)
Self-help without support	19	(10, 24)
TCAs	20	(11, 24)
Self-help with support	21	(11, 25)
Combined (Short-term psychodynamic psychotherapies + AD)	23	(6, 25)
Combined (Behavioural, cognitive, or CBT groups + AD)	25	(4, 25)

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We conclude that the NMA for discontinuation for any reason in the population with less severe depression presented in Appendix N1 is robust to small study/publication bias.

Relative intervention and class effects versus pill placebo as well as the posterior median rank of each intervention are reported in the *'Bias adjustment'* worksheet of the respective excel file in Appendix N3.

2.3.34 Outcome: response in completers

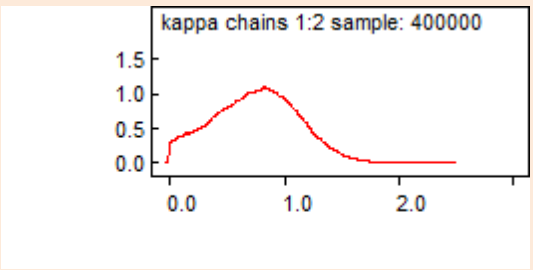
A burn-in of 121,000 iterations was used after which a further 200,000 iterations were taken form 2 independent chains (total of 400,000 iterations). High autocorrelation is present in some parameters.

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 (see Section 1.8 in Appendix N1). There was also a substantial reduction in the between-study heterogeneity in the bias adjusted model (see Section 1.8 in Appendix N1). The mean bias had a positive median (as expected) and the 95%CrI excluded the possibility of a zero bias although with moderate variability (Table 5 and Figure 3). 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 population with less severe depression.

	median	95%CrI
mean bias, *b*	1.54	(0.54, 2.53)
Standard deviation of bias, κ	0.76	(0.07, 1.45)

Figure 3: Between-study variability in mean bias for the logOR of response in completers in the population with less severe depression.



The OR of interventions and classes for the bias adjusted model show some reduction in magnitude of relative effects, which suggests that some classes no longer have evidence of a beneficial effect, compared to Pill Placebo Figure 11 and Figure 12). 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).

Adjusted ranks for classes show some changes in class ranking (Table 6). The highest ranked class is unchanged but there are changes to the top 5 class rankings and their uncertainty.

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% CrI
Combined (IPT + AD)	2	(1, 17)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	3	(1, 12)
Combined (Counselling + AD)	4	(1, 24)

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Class	Posterior median rank	95% CrI
Combined (Short-term psychodynamic psychotherapies + AD)	4	(1, 18)
Self-help without support	7	(2, 17)
Behavioural therapies (individual)	7	(2, 20)
Behavioural, cognitive, or CBT groups	8	(2, 17)
Cognitive and cognitive behavioural therapies (individual)	9	(3, 18)
TCAs	11	(4, 19)
SSRIs	11	(5, 18)
Exercise	12	(4, 21)
Mirtazapine	13	(1, 24)
Self-help with support	13	(3, 22)
Attention placebo	14	(3, 23)
Counselling	15	(4, 23)
Combined (Problem solving + AD)	15	(2, 24)
Short-term psychodynamic psychotherapies	16	(5, 23)
Interpersonal psychotherapy (IPT)	16	(5, 23)
TAU	17	(6, 23)
Problem solving	17	(7, 23)
Combined (Exercise + AD/CBT)	19	(5, 24)
Pill placebo	20	(15, 24)
Psychoeducational interventions	21	(8, 24)
No treatment	23	(15, 24)

We conclude that the results of the NMA for response in completers in the population with less severe depression presented in Appendix N1 are sensitive to small study effects and the impact of the bias on conclusions should be assessed.

Relative intervention and class effects versus pill placebo as well as the posterior median rank of each intervention are reported in the *'Bias adjustment'* worksheet of the respective excel file in Appendix N3.

2.47 Results: population with more severe depression

2.4.18 Outcome: SMD – more severe depression

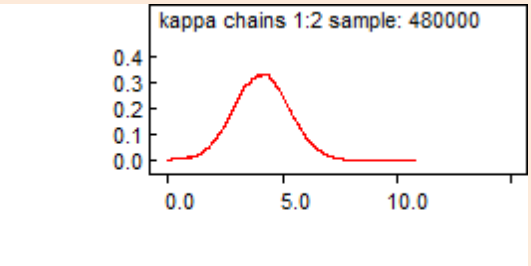
A burn-in of 120,000 iterations was used after which a further 240,000 iterations were taken form 2 independent chains (total of 480,000 iterations). High autocorrelation is present in some parameters.

The bias adjusted NMA model showed a substantially improved fit compared to the unadjusted NMA model and the DIC favours the bias adjusted NMA model (see Section 1.8 in Appendix N1). The bias adjusted model better predicted the data for Rush 1977, Torkan 2014, and Shamsaei 2008, compared to the unadjusted NMA model. These studies were poorly predicted by the unadjusted NMA model. There was a substantial reduction in the between-study heterogeneity in the bias adjusted NMA model (Section 1.8 of Appendix N1). The median of the posterior distribution of mean bias is negative (as expected), however the 95% CrI includes the possibility of zero bias (Table 7) and there is large between-study variability in bias (Table 7 and Figure 4). However, there is a large probability that the bias is indeed negative. There is not enough evidence to conclude the presence of small study bias in this network. However, results of the unadjusted model should be interpreted with caution due to the lack of adequate fit to the data.

Table 7 Median and 95%CrI for the mean bias and its between study standard deviation for the SMD in the population with more severe depression.

	median	95%CrI
mean bias, b	-4.28	(-10.19, 0.94)
Standard deviation of bias, κ	4.11	(1.7, 6.56)

Figure 4: Between-study variability in mean bias for the SMD in the population with more severe depression.



The SMD of interventions and classes for the bias adjusted model shows a small reduction is some relative effects and increased uncertainty (Figure 13 and Figure 14).

Adjusted ranks for classes show some changes in class ranking (Table 8). The highest ranked class is unchanged but there are changes to the top 5 classes 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% CrI
Combined (Exercise + AD/CBT)	1	(1, 2)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	3	(1, 14)
TCAs	4	(2, 11)
SSRIs	5	(2, 11)
Mirtazapine	6	(3, 13)
Pill placebo	7	(4, 13)
Interpersonal psychotherapy (IPT)	7	(2, 16)
Behavioural therapies (individual)	8	(2, 16)
Short-term psychodynamic psychotherapies	10	(2, 17)
Self-help with support	10	(2, 16)
Cognitive and cognitive behavioural therapies (individual) [CBT/CT]	10	(4, 16)
Self-help without support	12	(6, 16)
Counselling	13	(3, 17)
No treatment	14	(3, 17)
Attention placebo	14	(4, 17)
TAU	14	(7, 17)
Exercise	16	(3, 17)

We conclude that the results of the NMA for SMD in the population with more severe depression presented in Appendix N1 may be sensitive to small study effects although there is no clear evidence of bias.

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Relative intervention and class effects versus pill placebo as well as the posterior median rank of each intervention are reported in the *'Bias adjustment'* worksheet of the respective excel file in Appendix N3.

2.4.24 Outcome: discontinuation for any reason – more severe depression

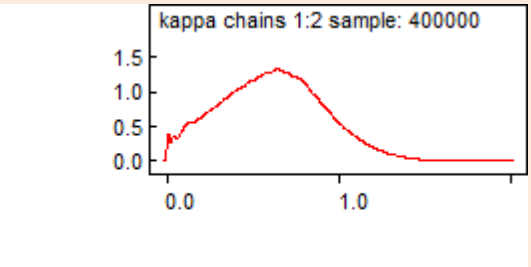
A burn-in of 60,000 iterations was used after which a further 200,000 iterations were taken from 2 independent chains (total of 400,000 iterations).

The NMA with bias adjustment showed an improved fit to the data compared to the unadjusted NMA, but there was no difference in the DIC and there was only a small reduction in the between-study heterogeneity when adjusting for bias (see Section 1.8 in Appendix N1). The mean bias had a positive median (as expected) but the 95%CrI included the possibility of a zero bias (Table 9). There was a large variability around the mean bias (Table 9 and Figure 5). We therefore conclude that there is no 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 any reason for the logOR of discontinuation for any reason in the population with more severe depression.

	median	95%CrI
mean bias, *b*	0.19	(-0.54, 0.94)
Standard deviation of bias, κ	0.61	(0.07, 1.21)

Figure 5: Between-study variability in mean bias for the logOR of discontinuation for any reason in the population with more severe depression.



The OR of interventions and classes for the bias adjusted model show only small changes in relative effects (Figure 15 and Figure 16).

Adjusted ranks for classes show some changes in class ranking but also increased uncertainty when compared to the unadjusted NMA results (Table 10).

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

Class	Posterior median rank	95% CrI
Problem solving	1	(1, 21)
Exercise	3	(1, 20)
Interpersonal psychotherapy (IPT)	5	(1, 19)
No treatment	6	(2, 18)
Counselling	7	(1, 21)
Cognitive and cognitive behavioural therapies (individual) [CBT/CT]	8	(3, 16)
Self-help with support	9	(2, 19)

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Class	Posterior median rank	95% CrI
Mirtazapine	10	(2, 18)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	10	(2, 19)
TAU	11	(4, 19)
TCAs	11	(3, 19)
SSRIs	12	(3, 19)
Behavioural therapies (individual)	13	(3, 21)
Behavioural, cognitive, or CBT groups	13	(3, 21)
Pill placebo	14	(5, 20)
Attention placebo	14	(3, 21)
Long-term psychodynamic psychotherapies	14	(2, 21)
Short-term psychodynamic psychotherapies	16	(2, 21)
Self-help without support	16	(8, 21)
Combined (Short-term psychodynamic psychotherapies + AD)	16	(2, 21)
Combined (Long-term psychodynamic psychotherapies + AD)	20	(5, 22)
Psychoeducational interventions	22	(20, 22)

We conclude that the results of the NMA for discontinuation in the more population with more severe depression presented in Appendix N1 are unlikely to be sensitive to small study effects.

Relative intervention and class effects versus pill placebo as well as the posterior median rank of each intervention are reported in the *'Bias adjustment'* worksheet of the respective excel file in Appendix N3.

2.4.37 Outcome: response in completers – more severe depression

A burn-in of 50,000 iterations was used after which a further 200,000 iterations were taken from 2 independent chains (total of 400,000 iterations).

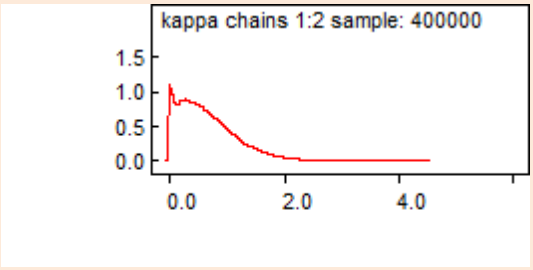
The NMA with bias adjustment showed a small reduction in the between-study heterogeneity but there was similar model fit and DIC for the adjusted and unadjusted models (see Section 1.8 of Appendix N1). The mean bias had a positive median (as expected) with moderate variance (Table 11 and Figure 6) but the 95%CrI included the possibility of a zero bias (Table 11), although with a high probability that it is indeed positive. There is therefore only weak 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 population with more severe depression.

	median	95%CrI
mean bias, b	1.41	(-0.17, 2.98)
Standard deviation of bias, κ	0.57	(0.02, 1.88)

Update 2018

Figure 6: Between-study variability in mean bias for the logOR of response in completers in the population with more severe depression.



The OR of interventions and classes for the bias adjusted model shows some reduction in magnitude of relative effects (Figure 17 and Figure 18).

Adjusted ranks for classes show small changes in ordering for the highest ranked classes, although with added uncertainty in class ranking (Table 12).

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

Class	Posterior median rank	95% CrI
Problem solving	1	(1, 2)
Behavioural, cognitive, or CBT groups	2	(1, 3)
No treatment	3	(2, 5)
Combined (IPT + AD)	5	(3, 19)
Interpersonal psychotherapy (IPT)	7	(4, 20)
Exercise	8	(4, 20)
Short-term psychodynamic psychotherapies	9	(4, 20)
Behavioural therapies (individual)	9	(4, 18)
Cognitive and cognitive behavioural therapies (individual) [CBT/CT]	9	(5, 14)
Self-help with support	10	(4, 20)
Counselling	10	(5, 19)
Combined (Short-term psychodynamic psychotherapies + AD)	11	(4, 20)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	12	(5, 19)
Attention placebo	13	(5, 20)
TCAs	13	(7, 18)
TAU	15	(8, 20)
Mirtazapine	15	(7, 19)
Self-help without support	16	(8, 20)
SSRIs	17	(10, 19)
Placebo	19	(14, 20)

We conclude that the results of the NMA for response in completers in the population with more severe depression presented in Appendix N1 are unlikely to be sensitive to small study effects.

Relative intervention and class effects versus pill placebo as well as the posterior median rank of each intervention are reported in the *'Bias adjustment'* worksheet of the respective excel file in Appendix N3.

Update 2018

2.51 References

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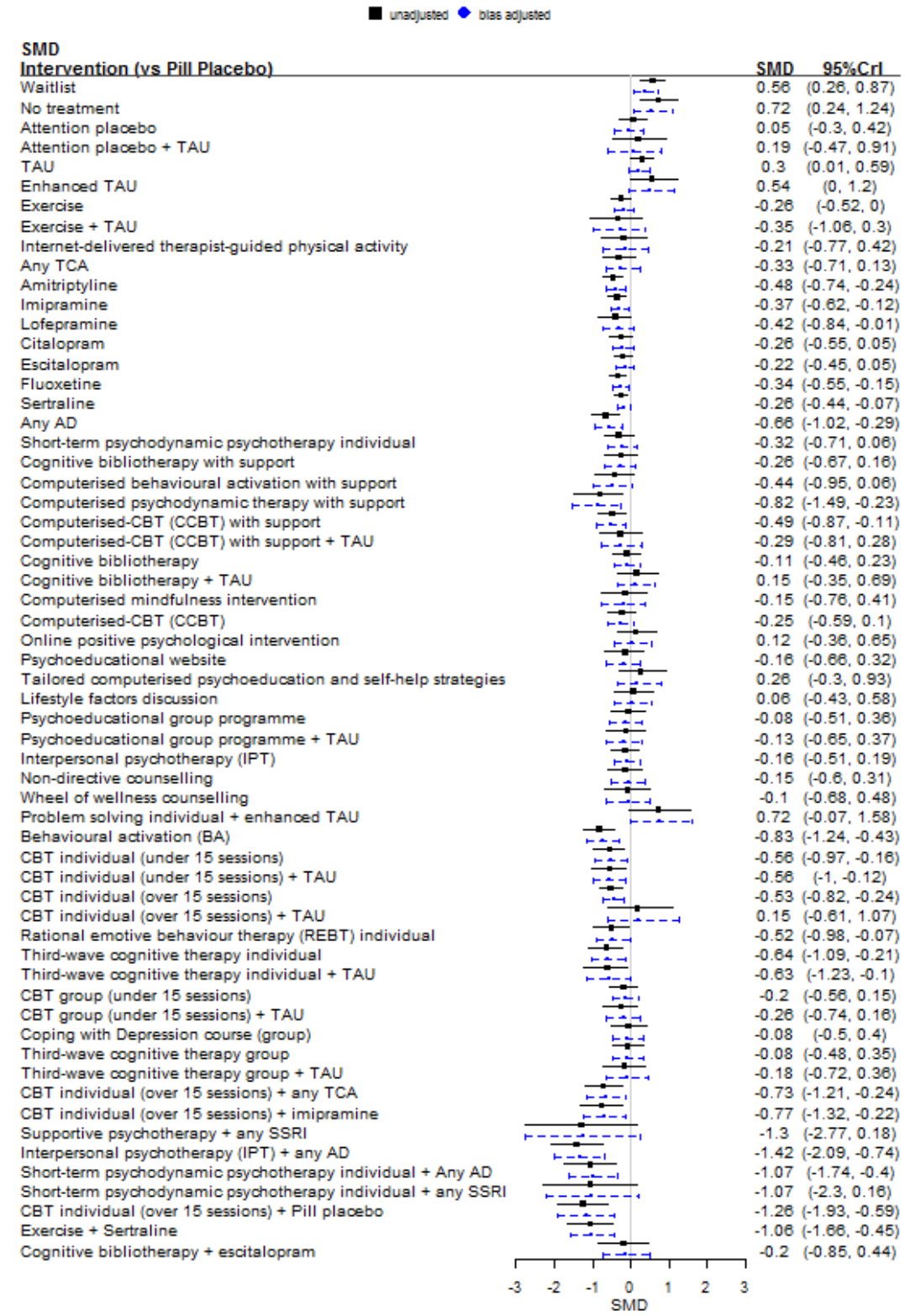
Update 2018

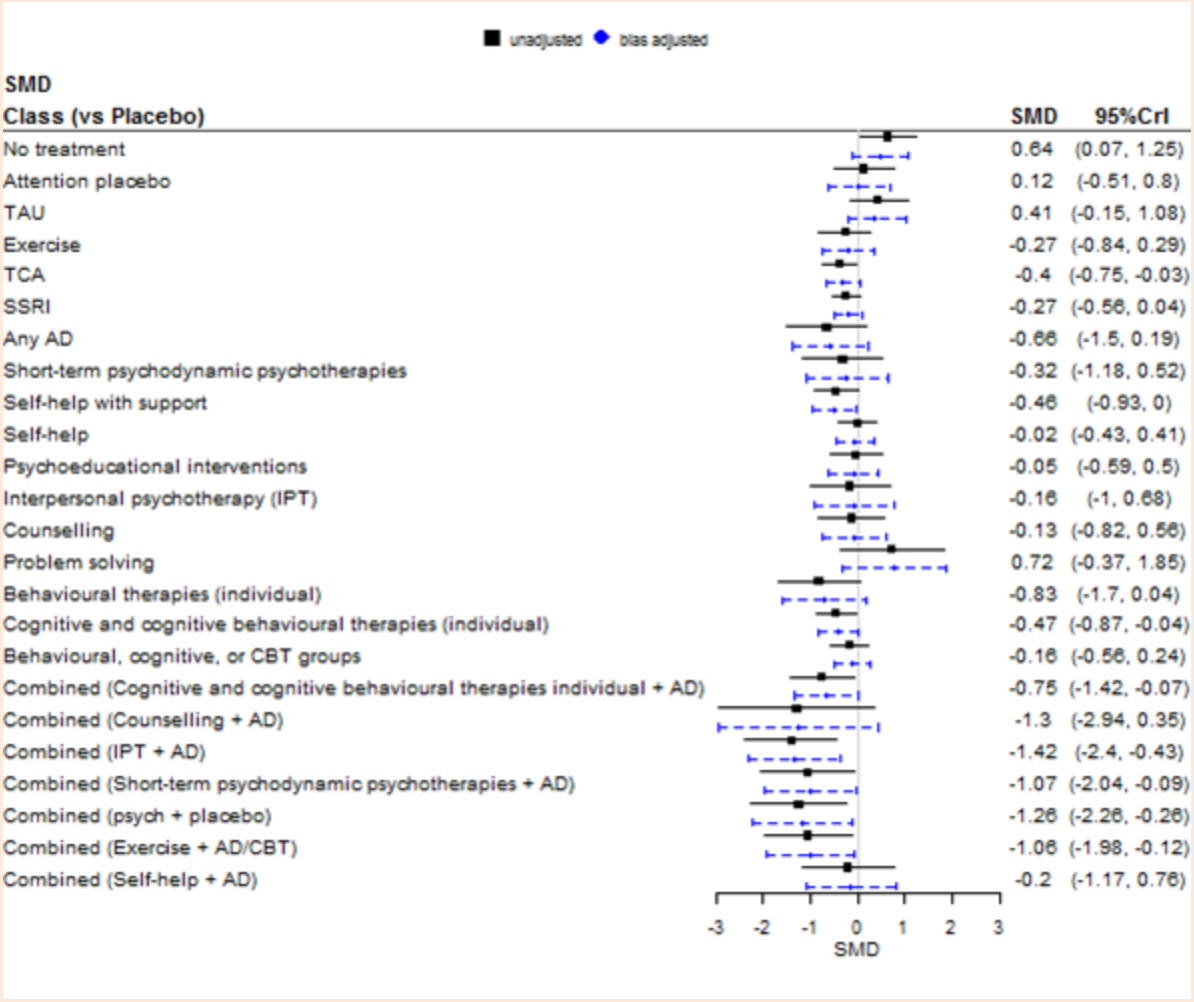
2.6 Forest plots (bias adjusted results): population with less severe depression

Figure 7: SMD of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models – less severe depression.



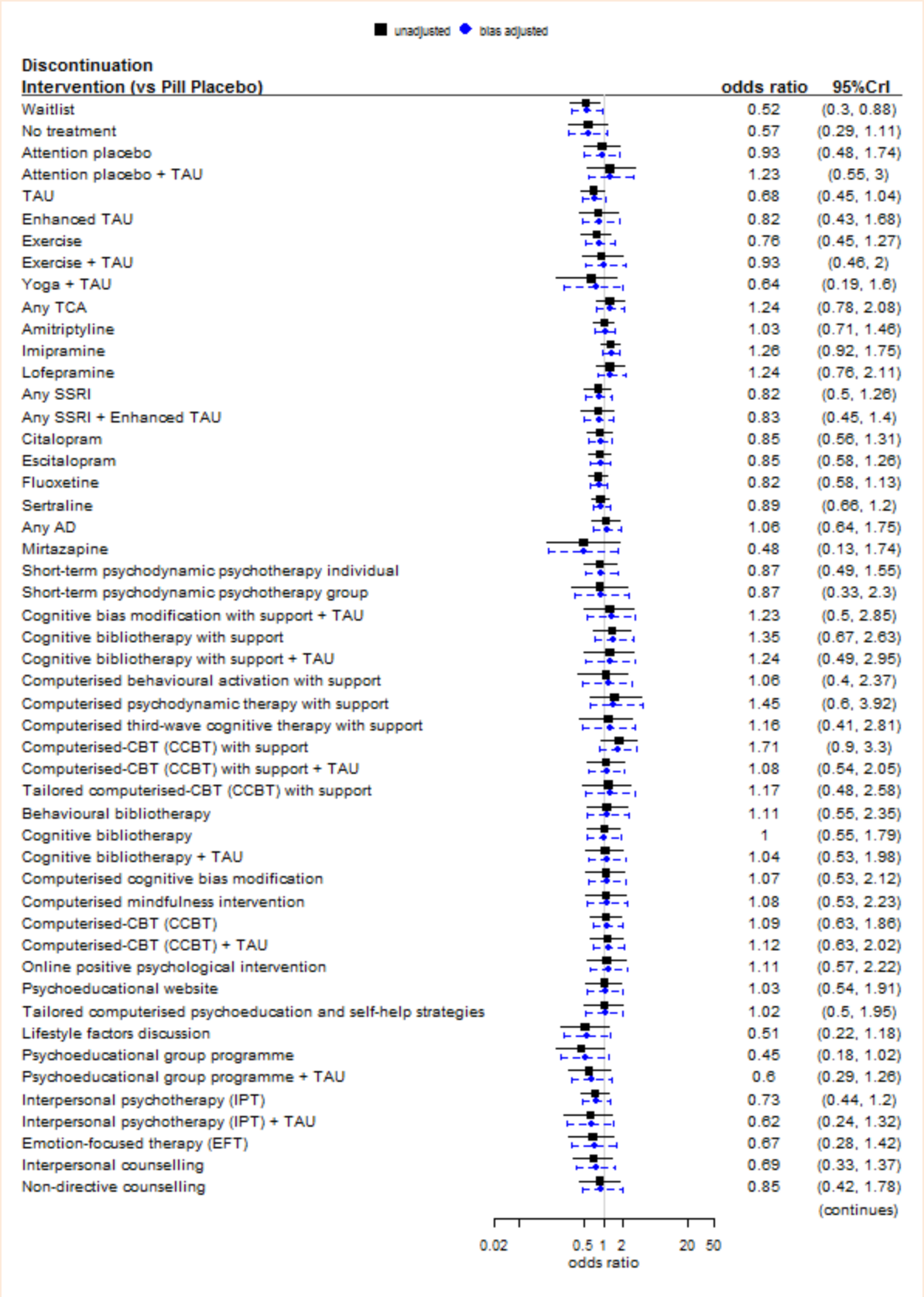
Update 2018

Figure 8: SMD of each class compared to Pill Placebo from the bias adjusted and unadjusted models – less severe depression.

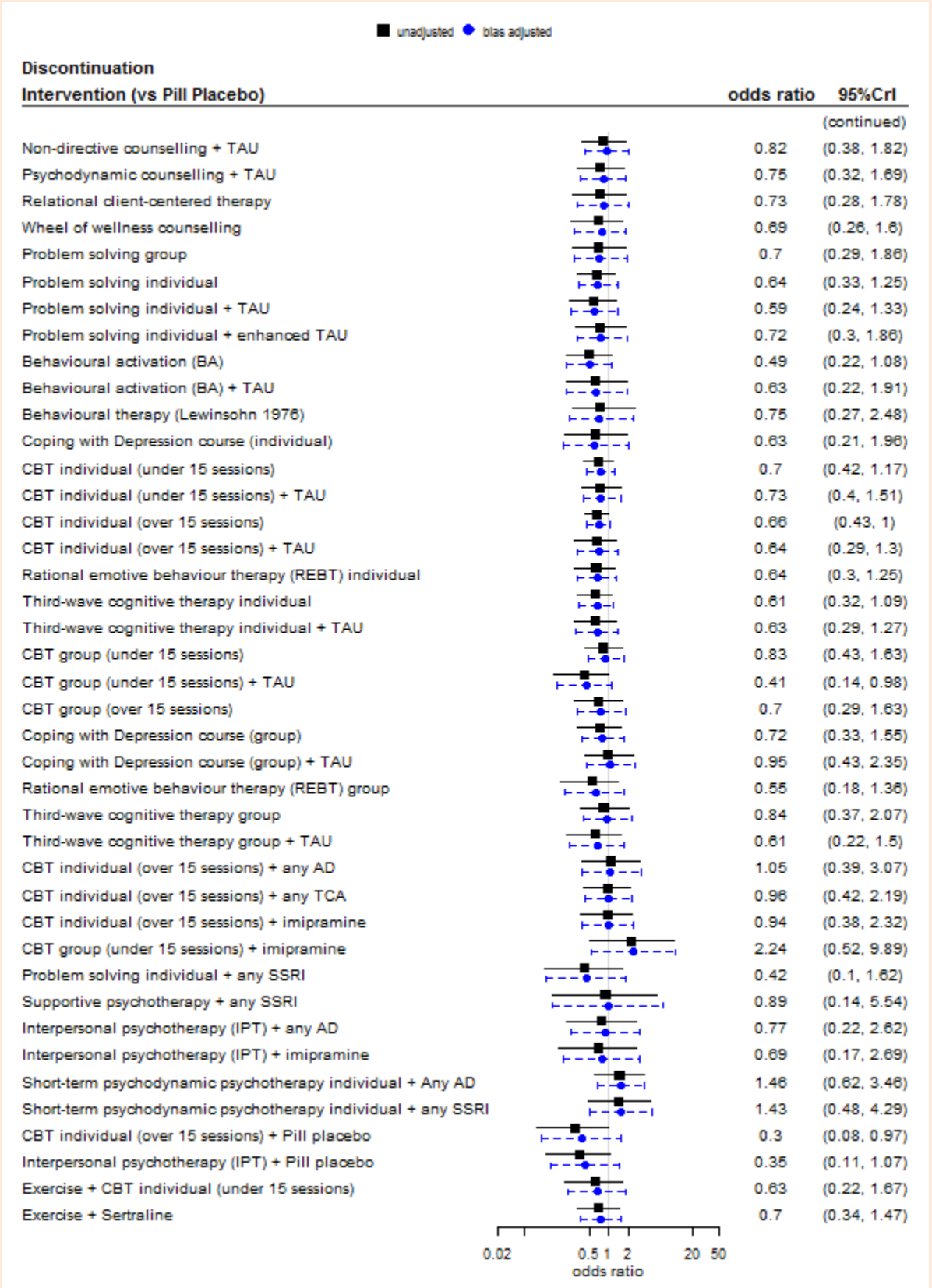


Update 2018

Figure 9: OR of discontinuation for any reason of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models (on a log scale) – less severe depression.

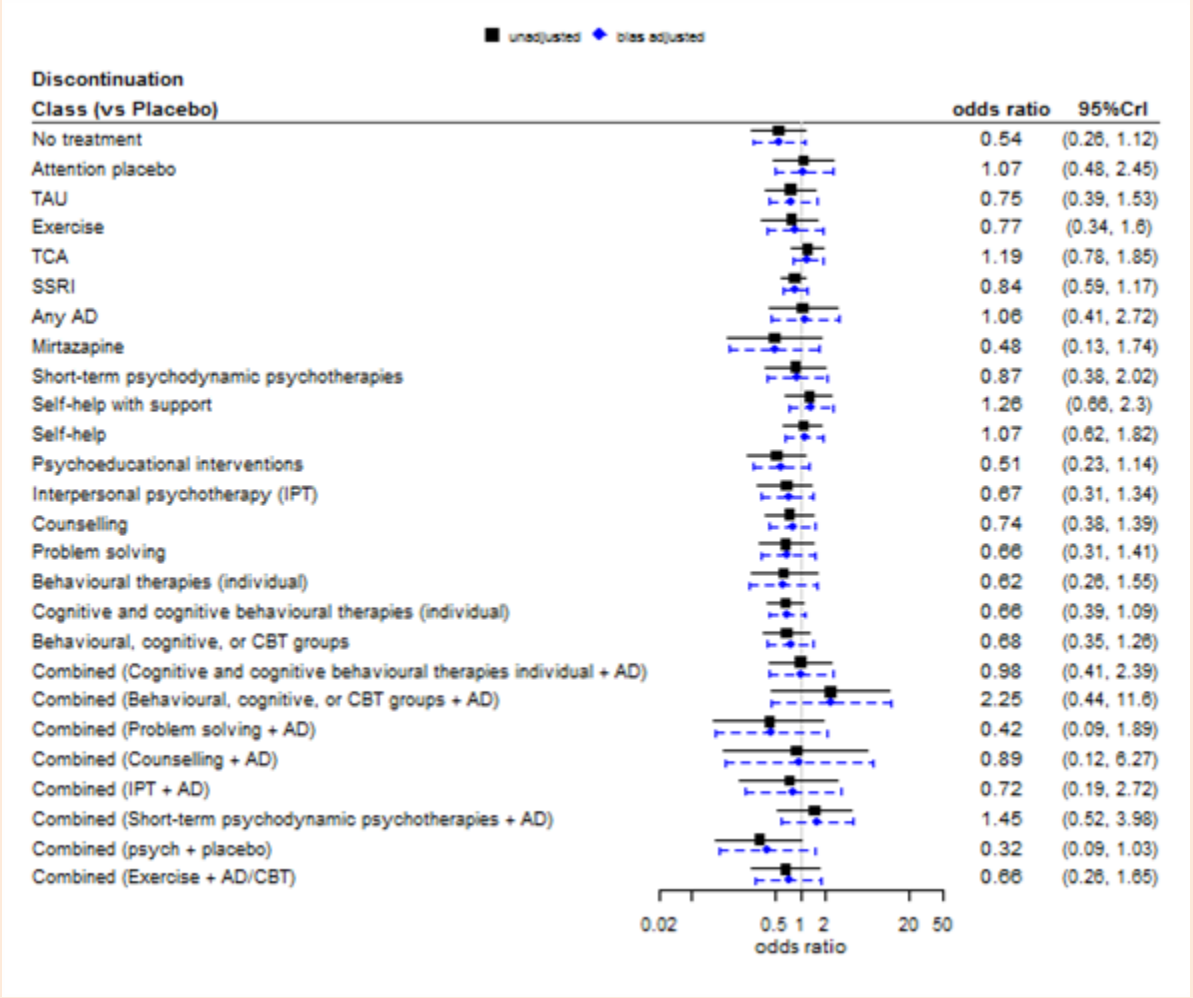


Update 2018



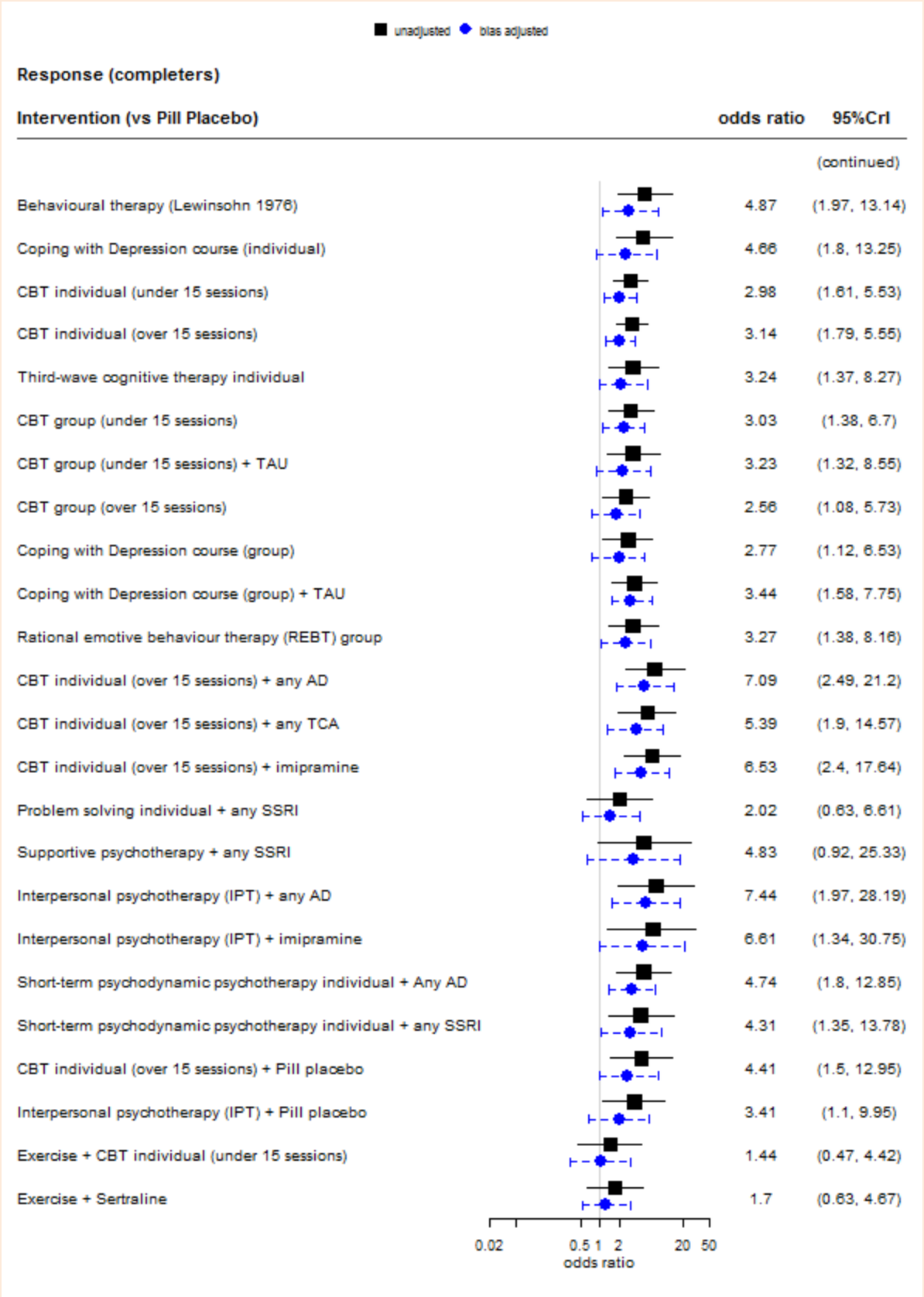
Update 2018

Figure 10: OR of discontinuation for any reason of each class compared to Pill Placebo from bias adjusted and unadjusted models (on a log scale) – less severe depression.



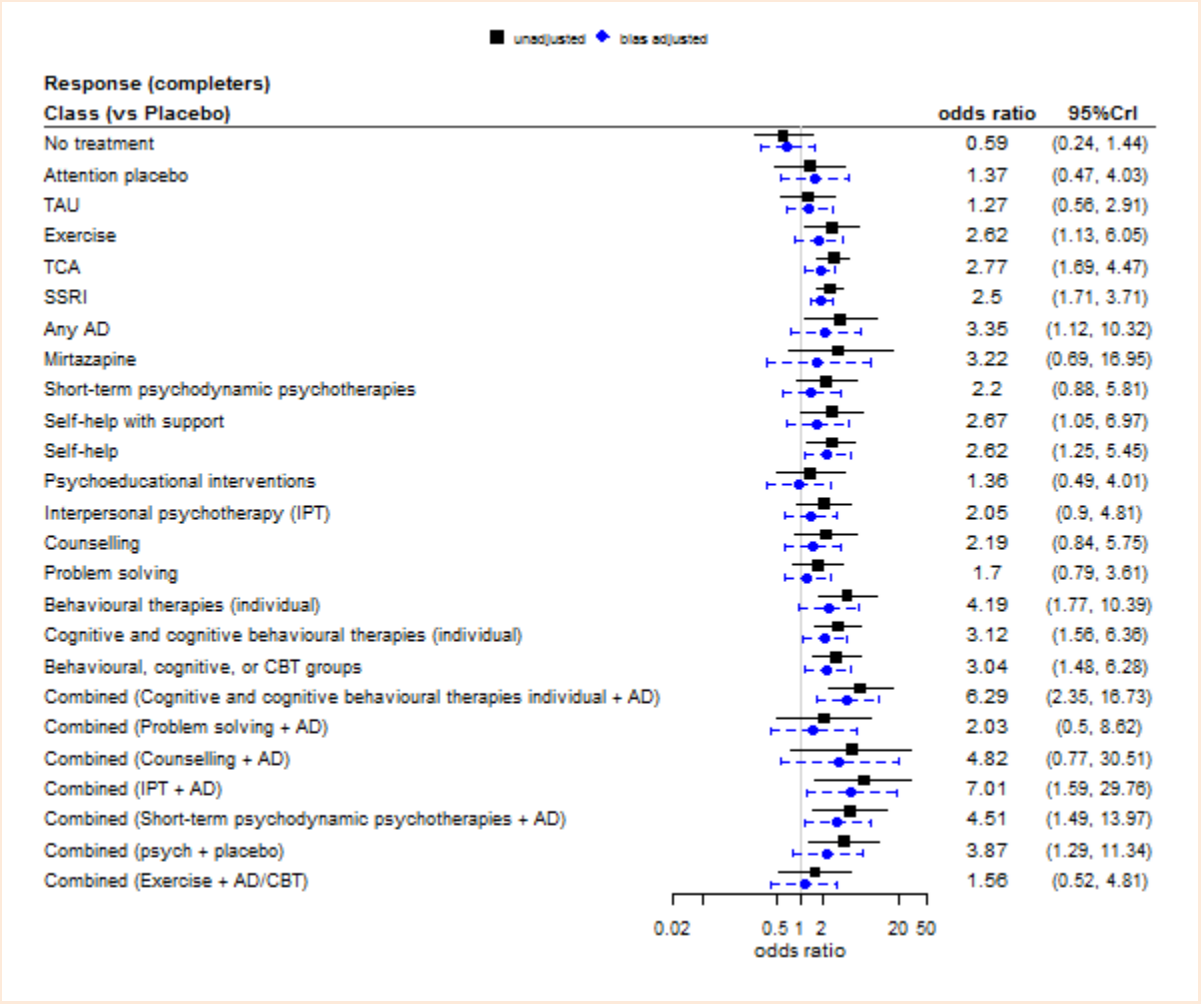
Update 2018

Figure 11: OR of response in completers of each intervention compared to Pill Placebo from the bias adjusted model and unadjusted models (on a log scale) – less severe depression



Update 2018

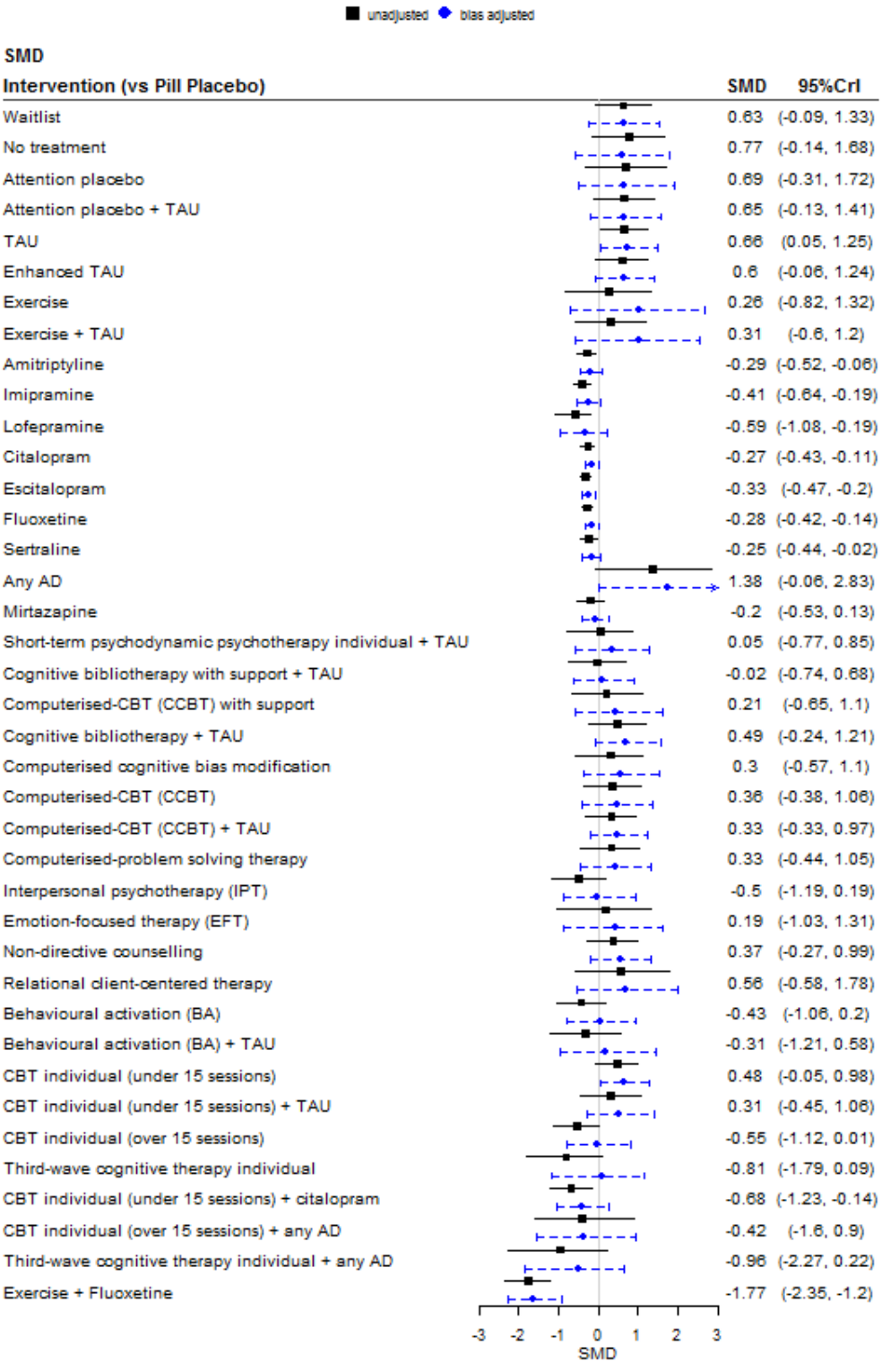
Figure 12: OR of response in completers of each class compared to Pill Placebo from the bias adjusted model and unadjusted models (on a log scale) – less severe depression.



Update 2018

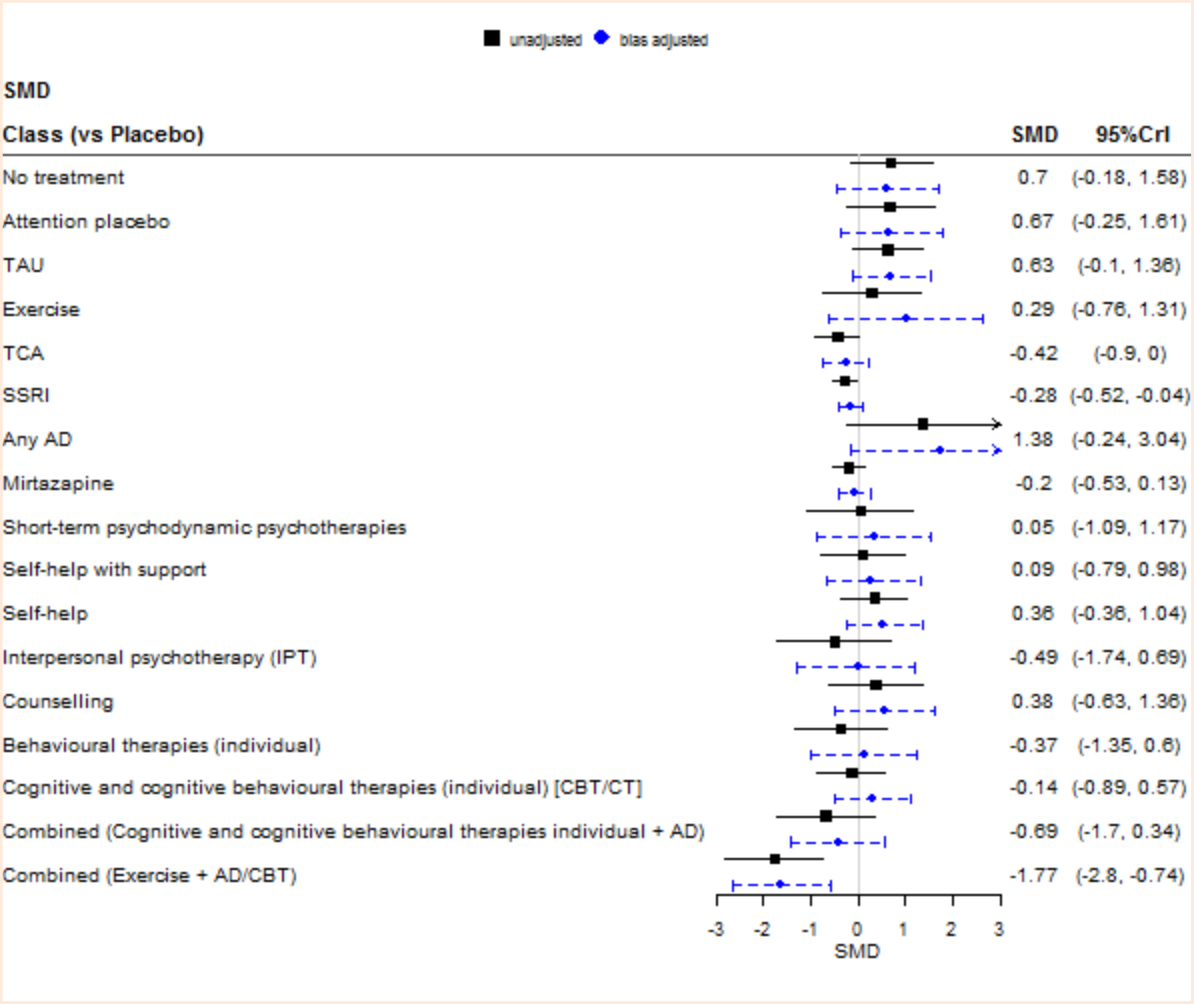
2.7 Forest plots (bias adjusted results): population with more severe depression

Figure 13: SMD of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.



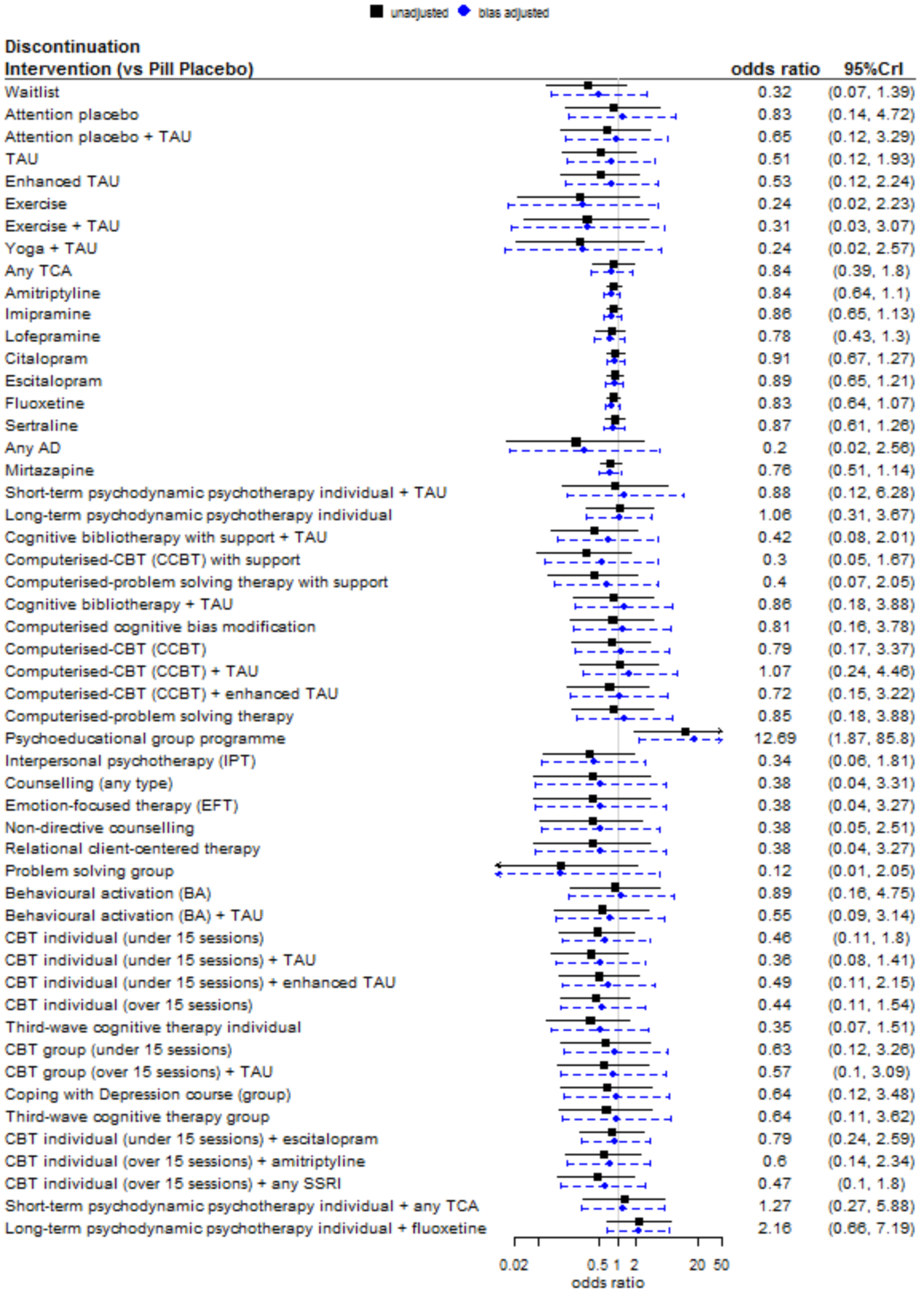
Update 2018

Figure 14: SMD of each class compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.



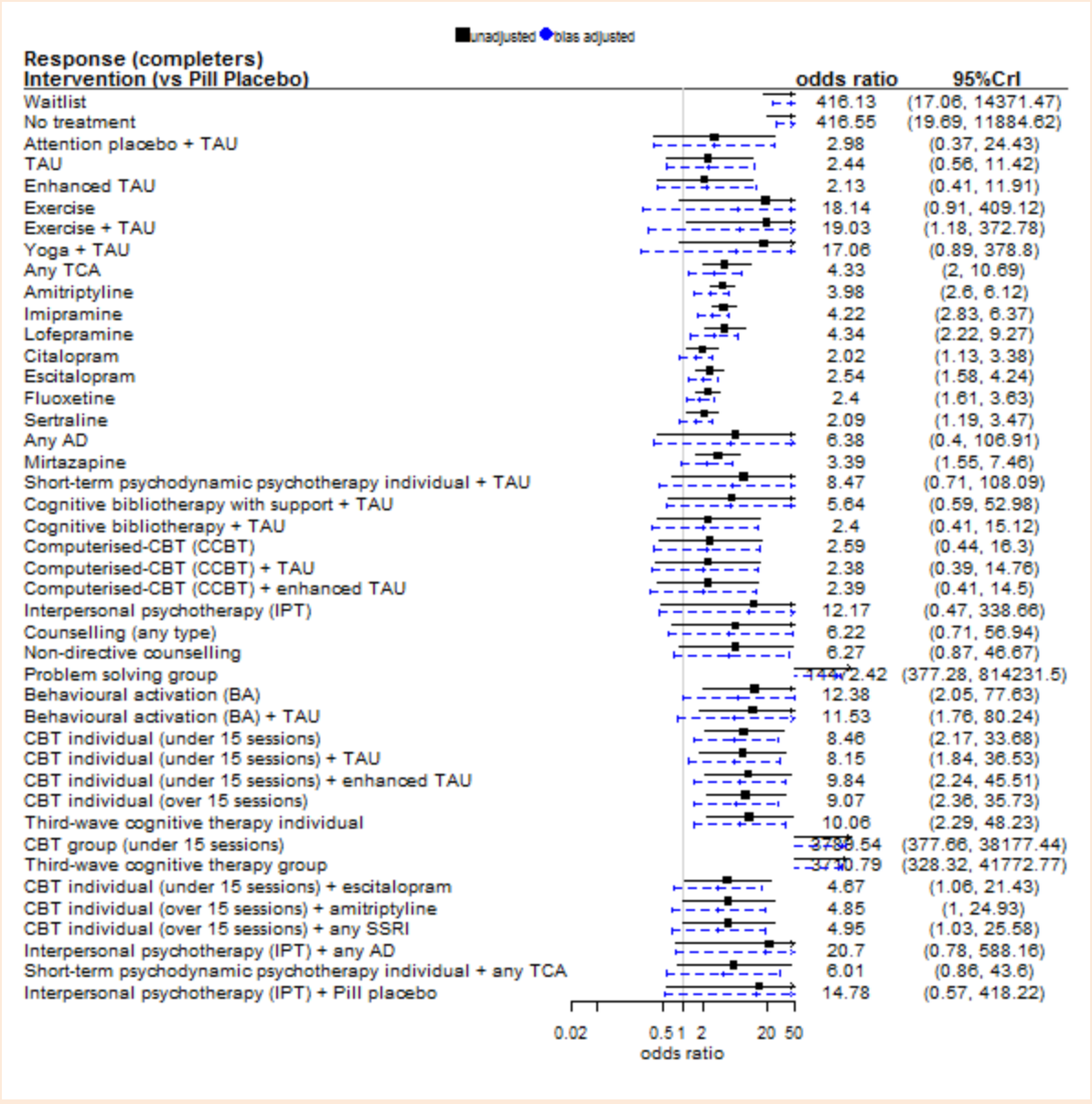
Update 2018

Figure 15: OR of discontinuation for any reason of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.



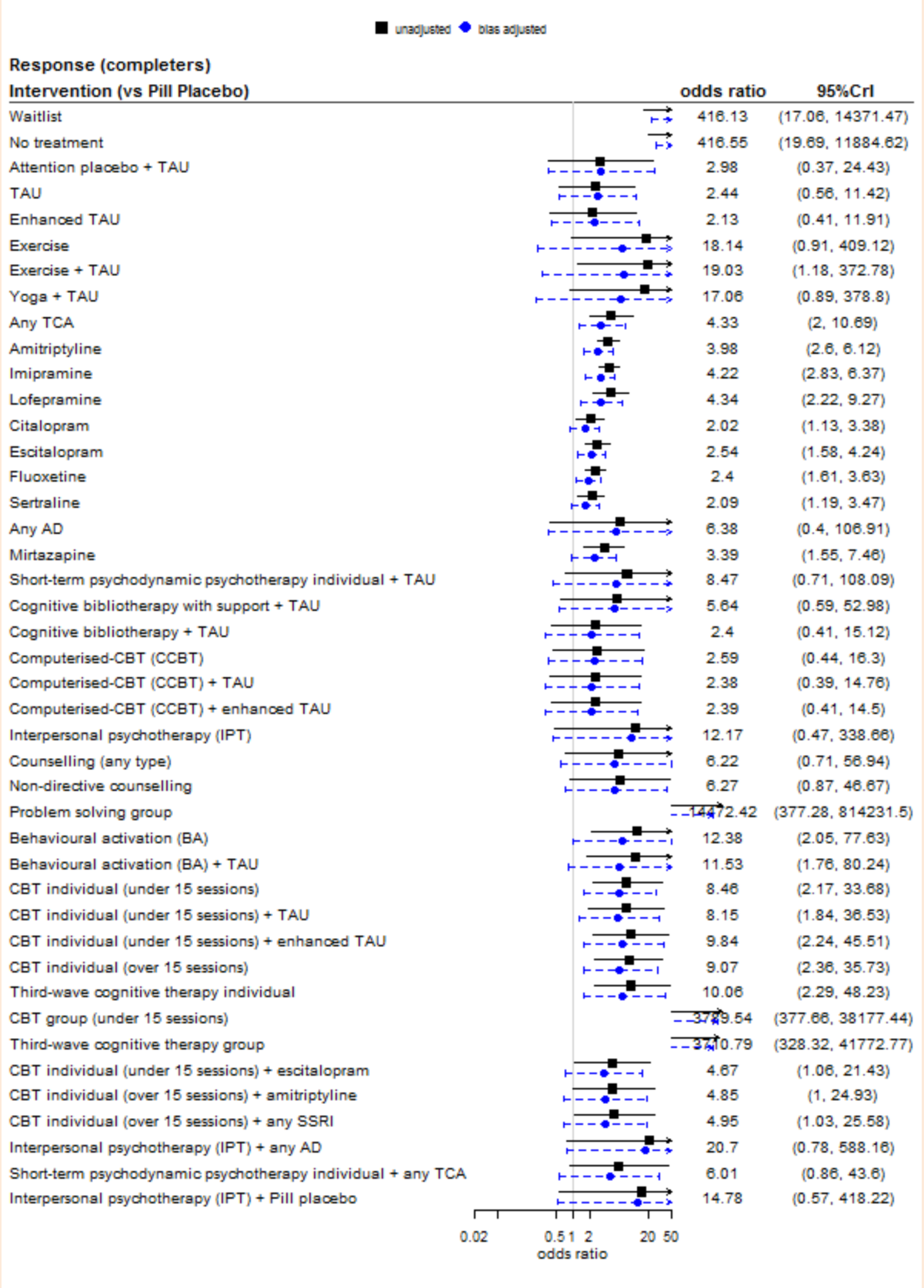
Update 2018

Figure 16 OR of discontinuation for any reason of each class compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.



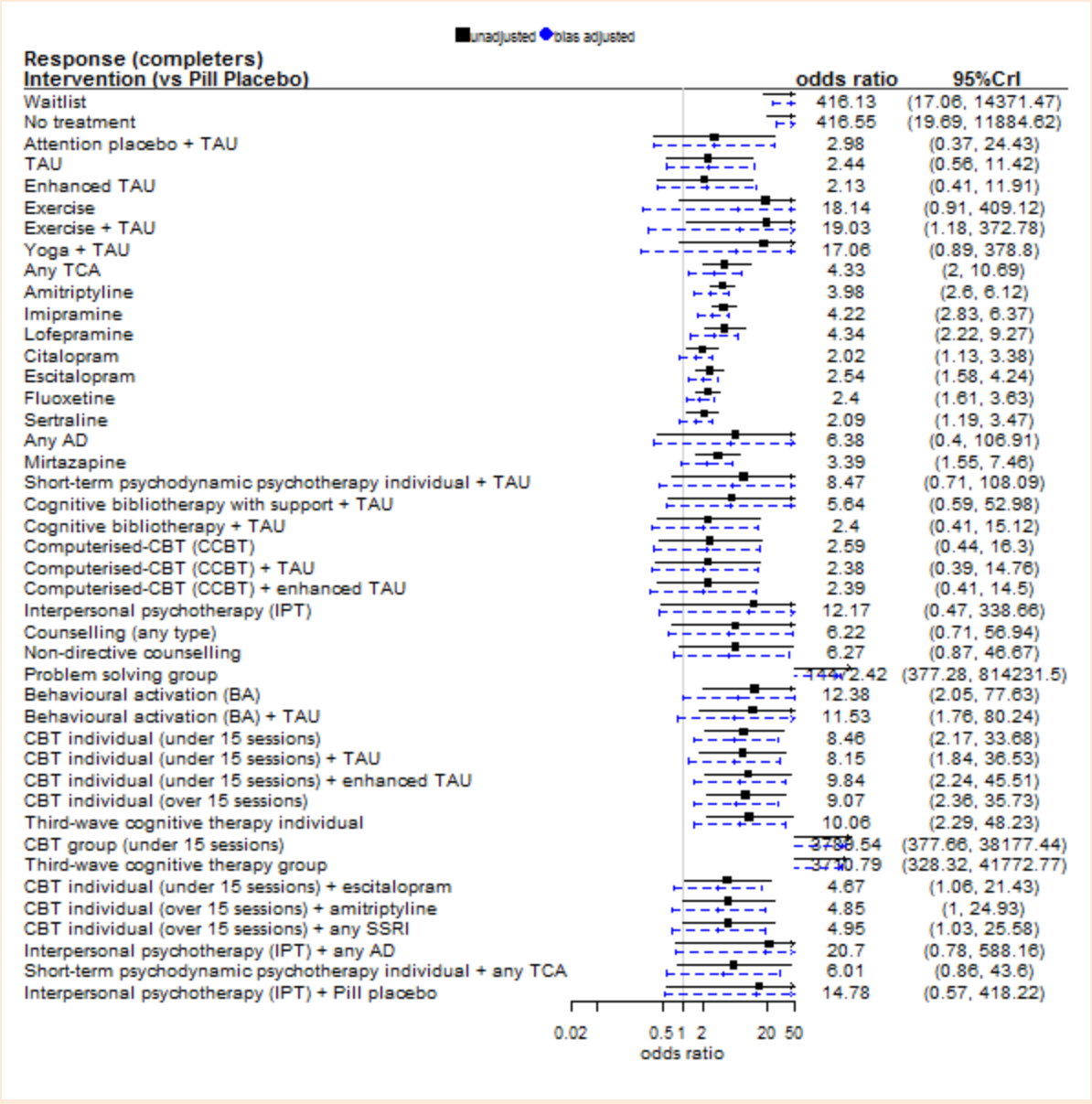
Update 2018

Figure 17: OR of response in completers of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.



Update 2018

Figure 18: OR of response in completers of each class compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depresssion.



Update 2018

2.8 Appendix 6: Sample WinBugs code

2.8.1 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
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 for study i, for SMD
  Pooled.sd[i] <- sqrt(Pooled.var[i])
#  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
```

Update 2018

```
  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 for study i, for SMD
  Pooled.sd[i+nsCFB] <- sqrt(Pooled.var[i+nsCFB])
#  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)
```

Update 2018

```
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 for study i, for SMD
  Pooled.sd[i+nsCFB+nsBF] <- sqrt(Pooled.var[i+nsCFB+nsBF])
#  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
    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] <-  4.24 + sdBR[i,k] * 0.73 # sd for response
```

Update 2018

```
    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]]
    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]]
```

Update 2018

```
    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
    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
```

Update 2018

```
    # 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 reference
treatment

     # vague prior for treatment effects (mirtazapine)
     d[18] ~ dnorm(0, .0001)

     # treatments borrowing variance
     # Variance from 'No treatment'
     for(k in 4:7) { d[k] ~ dnorm(m[D[k]], prec2[2]) }
     # Variance from 'Self-help with support'
```

Update 2018

```
      for(k in 8:9) { d[k] ~ dnorm(m[D[k]], prec2[11]) }
      # Any AD, variance from SSRIs & TCAS
      d[17] ~ dnorm(m[D[17]], prec2[8])      #prec2[8]=precision of
any AD class
      z <- (1/prec2[7]) + (1/prec2[6])  # sum of SSRI & TCA variances
      prec2[8] <- 1/z
      # Variance from Counselling
      d[19] ~ dnorm(m[D[19]], prec2[14])
      # Variance from CBT/CT
      d[27] ~ dnorm(m[D[27]], prec2[16])
      for(k in 31:32) { d[k] ~ dnorm(m[D[k]], prec2[16]) }
      # Variance from Combined (CBT/CT + AD)
      d[40] ~ dnorm(m[D[40]], prec2[17])

      # treatment effects from Class
      # No treatment
      for (k in 2:3){  d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
      # TCA, SSRI
      for(k in 10:16){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
      # Self-help with support, Self-help
      for(k in 20:26){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
      # Counselling
      for(k in 28:30){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
      # CBT/CT, Combined (CBT/CT + AD)
      for(k in 33:39){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }

#
m[1] <- 0
#treatments not belonging to a class
m[9] <- d[18]          #mirtazapine

# priors for mean class effect
for (k in 2:8){ m[k] ~ dnorm(0, .0001) }
for (k in 10:nc){ m[k] ~ dnorm(0, .0001) }
```

Update 2018

```
# priors for within-class variability
      for (k in 2:7){
      sd2[k] ~ dnorm(0,tau2)I(0,)      # prior for class variance
       prec2[k] <- pow(sd2[k], -1)
      }
      for (k in 9:nc){
      sd2[k] ~ dnorm(0,tau2)I(0,)      # prior for class variance
      prec2[k] <- pow(sd2[k], -1)
      }

tau2 <- pow(0.19,-2)                # informative prior 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(0,50)
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] }  }
# 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 2018

```
 }
#
for (k in 1:nt)  {
  rk[k]  <- rank(d[],k)           # lower values are "good"
  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) }
 }
#
# rank classes
for (k in 1:nc){
  rkClass[k] <- rank(m[],k)         # lower values 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) }
 }
}                                 # *** PROGRAM ENDS
```

2.8.2 Sample WinBugs code - Response bias analysis

```
# Random effects model for multi-arm trials
model{                              # *** PROGRAM STARTS
for(i in 1:ns){                     #   LOOP THROUGH ALL 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
```

Update 2018

```
  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]# model
for linear predictor
    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
```

Update 2018

```
    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
   }
  # 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
```

Update 2018

```
    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
```

Update 2018

```
    # 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)
 # 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)
   }
```

Update 2018

```
 }
# 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
    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]) # BL + FL
data
```

Update 2018

```
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)
# treatment effects from Class
for (k in 2:3){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
for (k in 10:19){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
for (k in 24:39){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
for (k in 42:65){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }

# variance from no treatment
for (k in 4:7){ d[k] ~ dnorm(m[D[k]], prec2[D[2]]) }
# variance from self-help with support
for (k in 8:9){ d[k] ~ dnorm(m[D[k]], prec2[D[11]]) }
# sum of variances from SSRI/TCAs
d[20] ~ dnorm(m[D[20]], prec2[8])
x <- (1/prec2[6]) + (1/prec2[7])
prec2[8] <- 1/x
# variance from counselling
for (k in 22:23){ d[k] ~ dnorm(m[D[k]], prec2[D[15]]) }
# variance from CBT/CT
for (k in 40:41){ d[k] ~ dnorm(m[D[k]], prec2[D[18]]) }
for (k in 72:73){ d[k] ~ dnorm(m[D[k]], prec2[D[18]]) }
# variance from CBT/CT + AD
for (k in 66:71){ d[k] ~ dnorm(m[D[k]], prec2[D[20]]) }
for (k in 74:75){ d[k] ~ dnorm(m[D[k]], prec2[D[20]]) }

# no class treatments [mirtazapine]
d[21] ~ dnorm(0, .0001)          # vague prior for treatment effects
m[9] <- d[21]                    # class effect = treat effect

for (k in 2:8){ m[k] ~ dnorm(0, .0001) }
```

Update 2018

```
for (k in 10:nc){ m[k] ~ dnorm(0, .0001) }
# priors for class precision
tau2 <- pow(0.19,-2)
for (k in 1:7){
  sd2[k] ~ dnorm(0,tau2)I(0,)   # informative prior for within-class st dev
  prec2[k] <- pow(sd2[k], -1) # within-class precision
 }
for (k in 9:nc){
  sd2[k] ~ dnorm(0,tau2)I(0,)   # informative prior for within-class st dev
  prec2[k] <- pow(sd2[k], -1) # 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 pair-wise comparisons
for (c in 1:(nt-1)){
  for (k in (c+1):nt){
    or[c,k] <- exp(d[k] - d[c])
    lor[c,k] <- (d[k]-d[c])
   }
 }
#
```

Update 2018

```
# pairwise differences for classes
for (c in 1:(nc-1)){
  for (k in (c+1):nc){
    diffClass[c,k] <- m[k] - m[c]
    orClass[c,k] <- exp(m[k] - m[c])
   }
 }
#
# rank treatments
#
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) }
 }
#
# rank classes
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) }
 }
}                                     # *** PROGRAM ENDS
```

2.8.3 Sample WinBugs code - Discontinuation bias analysis

```
# RE - random class effect model with bias adjustment for sample
size
# all active treatments same bias when compared to inactive
controls:
# TAU, Waitlist, Placebo, attention placebo, no treatment
# active-active comparisons have zero mean bias (but shared
variance)
```

Update 2018

```
model{
for(i in 1:ns){                    # LOOP OVER ALL 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
  for (k in 1:na[i]){              # LOOP OVER ARMS
    r[i,k] ~ dbin(p[i,k],n[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] * n[i,k]  # expected value of the numerators
    #Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  # Summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {             # RE model for treatment effects
    # 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],n[i,k])
    # check for zero or 100% events in arm 1
    aux.b[i,k] <- equals(r[i,1],0)+equals(r[i,1],n[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/(n[i,k]-r[i,k]+(0.5*aux[i,k]))
+ 1/(n[i,1]-r[i,1]+(0.5*aux[i,k]))
    # model for bias parameter beta
```

Update 2018

```
    beta[i,k] ~ dnorm(mb[i,k], Pkappa)
    mb[i,k] <- A[C[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[t[i,k]] - d[t[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[t[i,k]] + d[t[i,1]])
    # cumulative adjustment for multi-arm trials
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
 }
totresdev <- sum(resdev[])        # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
#


      # own class treatments with zero variance
      # vague prior for treatment effects (mirtazapine)
      d[22] ~ dnorm(0, .0001)

      # class treatments borrowing variance
      #Variance from 'No treatment'
      for(k in 4:7) { d[k] ~ dnorm(m[D[k]], prec2[2])}
      #Any AD, variance from SSRIs & TCAs
      d[21] ~ dnorm(m[D[21]], prec2[8]) # prec2[8]=precision of Any
AD class
      x <- (1/prec2[7]) + (1/prec2[6])  # sum of SSRI & TCA variances
      prec2[8] <- 1/x
      #Variance from Counselling
      for(k in 23:24) { d[k] ~ dnorm(m[D[k]], prec2[15])}
      #Variance from CBT/CT
```

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```
      for(k in 47:48) { d[k] ~ dnorm(m[D[k]], prec2[18])}
      for(k in 89:90) { d[k] ~ dnorm(m[D[k]], prec2[18])}
      #Variance from Combined [CBT/CT + AD]
      for(k in 82:88) { d[k] ~ dnorm(m[D[k]], prec2[20])}
      for(k in 91:92) { d[k] ~ dnorm(m[D[k]], prec2[20])}

      # treatment effects from Class
      #No treatment
      for (k in 2:3){  d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
      #Exercise; TCA; SSRI
      for (k in 8:20){  d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
      #Self-help with support; Self-help; psychoeducational
interventions
      for (k in 25:46){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
      #Counselling, Problem solving, behavioural therapies
(individual),
      #CBT/CT; Behavioural, cognitive, or CBT groups; Combined
(CBT/CT + AD)
      for (k in 49:81){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }



#
m[1]<-0     # treatment effect is zero for reference class
#treatments not belonging to a class
m[9] <- d[22]         #mirtazapine

# priors for mean class effect
for(k in 2:8) { m[k] ~ dnorm(0, .0001) }
for (k in 10:nc){  m[k] ~ dnorm(0, .0001)  }
#
# priors for within-class variability
  sd2[2] ~ dnorm(0,tau2)I(0,)  # informative prior for within-class
variance
  prec2[2] <- pow(sd2[2], -1)  # within-class precision
      for (k in 5:7){
```

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```
      sd2[k] ~ dnorm(0,tau2)I(0,)  # informative prior for within-class variance
      prec2[k] <- pow(sd2[k], -1)  # within-class precision
      }
      for (k in 11:13){
      sd2[k] ~ dnorm(0,tau2)I(0,)  # informative prior for within-class variance
      prec2[k] <- pow(sd2[k], -1)  # within-class precision
      }
      for (k in 15:20){
      sd2[k] ~ dnorm(0,tau2)I(0,)  # informative prior for within-class variance
      prec2[k] <- pow(sd2[k], -1)  # within-class precision
      }
tau2 <- pow(0.19,-2)

#
sd ~ dunif(0,5)      # vague prior for between-trial SD
tau <- pow(sd,-2)    # between-trial precision = (1/between-trial variance)
# 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 pair-wise comparisons
for (c in 1:(nt-1)){
  for (k in (c+1):nt){
    or[c,k] <- exp(d[k] - d[c])
```

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```
    lor[c,k] <- (d[k]-d[c])
   }
 }
#
# pairwise differences for classes
for (c in 1:(nc-1)){
  for (k in (c+1):nc){
    diffClass[c,k] <- m[k] - m[c]
    orClass[c,k] <- exp(m[k] - m[c])
   }
 }
#
# ranking on relative scale
for (k in 1:nt){
  rk[k] <- rank(d[],k)            # assumes events are "bad"
  best[k] <- equals(rk[k],1)      #calculate probability that treat k
is best
  # calculate probability that treat k is h-th best
  for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
 }
# rank classes
for (k in 1:nc){
  rkClass[k] <- rank(m[],k)
  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) }
 }
}
```

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