Network meta-analysis report from the NICE Guidelines TSU for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

TSU, Bristol (Hugo Pedder, Debbi Caldwell and Nicky J Welton)

Acknowledgements: Caitlin Daly, Edna Keeney and Sofia Dias for their contributions to the previous versions of the report for the 2017 and 2018 guideline consultation drafts

Introduction

The purpose of this analysis was to estimate the comparative effectiveness of various interventions for treating a new episode of less severe depression or more severe depression in adults. In total 674 studies were included in these analyses comparing 153 interventions and combinations of interventions.

The outcomes analysed were: discontinuation for any reason; discontinuation due to side effects; remission; response; and standardized mean difference (SMD) on a continuous measurement on various depression scales.

Methods

Network meta-analysis

In order to take all trial information into consideration network meta-analyses (NMA) were conducted. NMA is a generalization of standard pairwise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials (Caldwell 2005; Dias 2013; Lu 2004). A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from an A versus B trial, is the same as the relative effect between A and B estimated indirectly from A versus C and B versus C trials. NMA techniques strengthen inference concerning the relative effect of two treatments by including both direct and indirect comparisons between treatments, and, at the same time, allow simultaneous inference on all treatments while respecting randomisation (Caldwell 2005; Lu 2004).

Simultaneous inference on the relative effects of all treatments is possible whenever treatments are part of a single “network of evidence”, that is, every treatment is linked to at least one of the other treatments under assessment. The correlation between the random effects of multi-arm trials (that is, those with more than 2 arms) in the network is taken into account in the analysis (Dias 2013). In a NMA we assume that intervention A is similar (in dose, administration etc.) when it appears in the A vs B and A vs C studies and also that every patient included the network could have been assigned to any of the interventions (Caldwell 2005) – a concept called ‘joint randomisability’ (Salanti 2012).

In the situation where a study compared two treatments that were coded the same way (based on the review protocol), following previous guidelines, we have included them as separate arms. Any differences between the treatments in these arms therefore contributed to between-study SD.

A Bayesian framework is used to estimate all parameters, using Markov Chain Monte Carlo (MCMC) simulation methods implemented in WinBUGS 1.4.3 (Lunn 2000 & 2013). The network reference treatment was selected as the best-connected intervention in the network

as this improved model stability and reduced the number of MCMC simulations required for model convergence. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic (Brooks 1998) and was satisfactory by 80,000 simulations for all outcomes (Gelman 1992). A further simulation sample of at least 20,000 iterations post-convergence was obtained on which all reported results were based. Sample WinBUGS code is provided in supplement B5, appendix 1, and full WinBUGS files are included which contain the precise number of simulations for convergence and number of iterations monitored for each outcome.

For binary data, studies with zero or 100% events in all arms were excluded from the analysis because these studies provide no evidence on relative effects (Dias 2011). For studies with zero or 100% events in one arm only, we planned to analyse the data without continuity corrections where computationally possible. Where this was not possible, we used a continuity correction where we added 0.5 to both the number of events and the number of non-events, which has shown to perform well when there is an approximate 1:1 randomisation ratio across intervention arms (Sweeting 2004). For the small number of studies in which there was not an approximate 1:1 randomisation ratio, a continuity correction that was weighted by the reciprocal of the opposite group arm size was used (Sweeting 2004). For studies with >2 arms we extended this weighted continuity correction by using a weighting that was a sum of the sample size in the other treatment arms in the study, and then standardised the weights so that they summed to 1.

Reporting of results

Network diagrams are presented for each population and outcome. The edges (lines) connecting each pair of interventions represent a direct comparison.

Relative intervention effects are reported in the "*Effect size vs Reference*" worksheets of the Excel files included in supplement B6 as posterior median log-odds ratios (log-OR) or standardised mean differences (SMD) and 95% Credible Intervals (CrIs) compared to either Pill placebo (for NMAs of more severe depression) or Treatment As Usual (TAU) (for NMAs of less severe depression). The full list of ORs and SMDs for each intervention and class compared to every other are reported in the "*Treatment Direct Effects*" and "*Class Direct Effects*" worksheets of the Excel files included in supplement B6, respectively.

We also report posterior mean rank of each class, along with the posterior median and 95% CrIs, with the convention that the lower the rank the better the class. These can be found in the "*Ranks*" worksheet of the Excel files included in supplement B6. Only interventions and classes of interest were included in the calculations of the rankings. The interventions that were included in the NMA in order to provide links to the networks but were deemed not of interest by the committee and were therefore excluded from the rankings were:

- No treatment
- Any psychotherapy
- CBT individual (15 sessions or over) + pill placebo
- CBT individual (under 15 sessions) + pill placebo
- Interpersonal psychotherapy individual + pill placebo
- Non-directive/supportive/person-centred counselling + pill placebo
- Computerised-CBT + TAU
- Progressive muscle relaxation individual + pill placebo
- Any SSRI
- Any TCA
- Imipramine
- Any AD

The classes that were included in the NMA in order to provide links to the networks but were deemed not of interest for decision-making by the committee and were therefore excluded from the rankings were

- No treatment
- Any psychotherapy
- Cognitive and cognitive behavioural therapies individual + placebo
- Interpersonal psychotherapy individual + placebo
- Counselling individual + placebo
- Self-help + TAU
- Relaxation individual + placebo
- Any AD

Class models

Classes are groups of interventions which are thought to have similar effects. Class models were used so that strength could be borrowed across treatments in the same class and to reconnect disconnected networks. For all outcomes, random class effect models were used which assume that the effects of treatments in a class are distributed around a common class mean, m_{class}, with a within-class variance, τ^2_{class}. In this way treatment effects are shrunk towards a class mean and can borrow strength from other elements of the class, whilst still estimating distinct effects for each treatment.

The pooled relative treatment effects were assumed to be exchangeable within class:

$$d_{1,k} \sim N\left(m_{D_k}, \tau^2{}_{D_k}\right)$$

where $d_{1,k}$ is the effect of intervention *k* relative to intervention 1, and D_k indicates the class to which treatment *k* belongs.

We note that an error was made in the coding of Interpersonal counselling individual + venlafaxine. This was coded in the dataset as belonging to the Counselling individual + AD class, when it should have been coded as belonging to the Interpersonal psychotherapy (IPT) individual + AD class. This was corrected for SMD outcomes, but for other outcomes the incorrect coding persists. However, this only causes a difference in coding for 13 participants in several of the more severe NMAs. A sensitivity analysis was conducted to assess the impact of this in SMD in more severe depression (see Sensitivity analyses: post-hoc).

For treatments belonging to a class with only one or two treatments in a particular analysis there is insufficient evidence to estimate the within-class variance, however we would still expect there to be heterogeneity between the within class treatment effects. For this reason, the within-class variance was shared with another similar class in the model, where the variability between treatment effects might be expected to be similar. The following rules applied where there was limited information with which to estimate separate class variances (e.g. where classes had only one or two treatments) but variance could be shared with another class for which it could be more reliably estimated. The following variance sharing rules were used when necessary:

- The following classes shared variance with Behavioural therapies individual:
  - Cognitive and cognitive behavioural therapies individual
- The following classes shared variance with Cognitive and cognitive behavioural therapies individual:
  - Behavioural therapies individual

  - Behavioural therapies group
  - Cognitive and cognitive behavioural therapies group
  - Problem solving individual
  - Problem solving group
  - Counselling individual
  - Interpersonal psychotherapy (IPT) individual
  - Psychoeducation group
  - Self-help
  - Self-help with support
  - Long-term psychodynamic psychotherapies individual
  - Short-term psychodynamic psychotherapies individual
  - Short-term psychodynamic psychotherapies group
  - Mindfulness or meditation individual
  - Relaxation individual
  - Cognitive and cognitive behavioural therapies individual + placebo
  - Interpersonal psychotherapy (IPT) individual + placebo
  - Counselling individual + placebo
  - Relaxation individual + placebo
  - Acupuncture
  - Cognitive and cognitive behavioural therapies individual + AD
  - Acupuncture + counselling individual
- The following classes shared variance with Cognitive and cognitive behavioural therapies group:
  - Music therapy group
  - Mindfulness or meditation group
  - Relaxation group
  - Peer support group
  - Yoga group
- The following classes shared variance with Self-help with support:
  - Exercise individual
  - Exercise group
- The following classes shared variance with SSRIs:
  - TCAs
  - SNRIs
- The following classes shared variance with Acupuncture:
  - Sham acupuncture
  - Light therapy
  - Acupuncture + AD
  - Sham acupuncture + AD
  - Light therapy + AD
- The following classes shared variance with Cognitive and cognitive behavioural therapies individual + AD:
  - Self-help + TAU
  - Behavioural therapies individual + AD
  - Cognitive and cognitive behavioural therapies group + AD

  - Problem solving individual + AD
  - Long-term psychodynamic psychotherapy individual + AD
  - Interpersonal psychotherapy (IPT) individual + AD
  - Counselling individual + AD
  - Self-help + AD
  - Short-term psychodynamic psychotherapies individual + AD
  - Psychoeducation group + AD
  - Peer support group + AD
  - Mindfulness or meditation group + AD
  - Relaxation individual + AD
  - Exercise individual + AD
  - Exercise group + AD
  - Yoga group + AD
  - Cognitive and cognitive behavioural therapies individual + exercise group
  - Cognitive and cognitive behavioural therapies group + exercise group
- The following class used the maximum of either the SSRI class variance or the TCA class variance:
  - Any AD
- The following class used the maximum of either the Cognitive and cognitive behavioural therapies individual class variance or the Cognitive and cognitive behavioural therapies group class variance:
  - Any psychotherapy

The following treatments were not allocated to a class, and a single intervention effect estimated (equivalent to a class-effect model with within-class variability ($\tau^2_{D_k} = 0$)):

- Pill placebo
- Attention placebo
- No treatment
- Waitlist
- TAU
- Enhanced TAU
- Mirtazapine
- Trazodone

These assumptions were based on the committee's expert opinion.

If class variances could not be estimated for any psychological/physical/combined therapies (i.e. the absence of class variance information on both Behavioural therapies individual *and* Cognitive and cognitive behavioural therapies individual), then the class variance was shared with the class that had the maximum class variance.

The within-class mean treatment effects were given vague priors m_{class} ~ N(0,100^2) and the within-class standard deviations (SD) were given vague uniform priors τ_{class} ~ Uniform(0,5). In cases where there was evidence that the prior constrained the posterior, the upper limit was extended to 7.

For treatments connected by only a single, small study with zero responders in one of the connecting arms, this sometimes led to convergence issues that could not be resolved without making additional strong assumptions. In these cases, the treatments were

effectively disconnected from the network, meaning that relative effects for them compared to other treatments in the network could not be estimated, and thus are not presented.

Intervention effects are reported for both individual treatments and classes of treatments.

Inconsistency checking

Consistency between the different sources of indirect and direct evidence was explored statistically by comparing the fit of a model assuming consistency with a model which allowed for inconsistency (also known as an unrelated mean effect model) at the treatment-level, whilst still modelling class effects.

Goodness of fit was measured using the posterior mean of the residual deviance, which is a measure of the magnitude of the difference between the observed data and their model predictions (Spiegelhalter 2002). Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points (Spiegelhalter 2002). We also report the Deviance Information Criterion (DIC), which penalises model fit with model complexity (Spiegelhalter 2002). Finally, we report the between studies standard deviation (heterogeneity parameter) to assess the degree of statistical heterogeneity. If the inconsistency model had the smallest posterior mean residual deviance or heterogeneity then this indicated potential inconsistency in the data. In comparing models, differences of ≥5 points for posterior mean residual deviance and DIC were considered meaningful (Spiegelhalter 2002), with lower values being favoured.

Dev-dev plots that plotted individual deviance contributions from both consistency and inconsistency models for each data point are presented for each outcome. Data in which these contributions are substantially different indicate a better fit in either the consistency or inconsistency model and warrant a closer inspection. These points are named and highlighted in the dev-dev plots.

Direct estimates from the unrelated mean effect model are reported in the separate spreadsheets of results for each outcome (supplement B6), and these can be compared to NMA estimates from the consistency models. To identify comparisons for which there was likely to be a discrepancy between direct and indirect estimates, we estimated the indirect evidence contributions by subtracting the direct evidence contributions estimated using the unrelated mean effects model from the NMA estimates estimated using the consistency model, assuming normality of the posterior distributions:

$$d_{ind} = \frac{d_{nma}(w_{dir} + w_{ind}) - w_{dir}d_{dir}}{w_{ind}}$$

Where d_{ind} is the indirect relative effect, d_{nma} is the mixed relative effect estimated from the NMA, d_{dir} is the direct relative effect estimated from the inconsistency model, for a given treatment comparison. w_{nma}, w_{dir} and w_{ind} are the inverse-variance weights, calculated as $\frac{1}{\sigma^2_{nma}}$, $\frac{1}{\sigma^2_{dir}}$ and $\frac{1}{\sigma^2_{ind}}$ for the mixed, direct and indirect effects respectively; σ_{nma} and σ_{dir} are the standard deviations of the posterior distributions for the corresponding relative effects; σ_{ind} is the standard error for the indirect relative effect, calculated as:

$$\sigma_{ind} = \sqrt{\frac{\sigma^2_{nma}\sigma^2_{dir}}{\sigma^2_{dir} - \sigma^2_{nma}}}$$

The difference between direct and indirect estimates can then be estimated, and a Wald test can be used to test whether direct and indirect evidence are in agreement. We acknowledge

that the posterior distributions may not be normally distributed, and hence we use this approach as a heuristic to identify comparisons in which direct and indirect evidence are likely to strongly disagree, given the large number of comparisons in many of the networks.

WinBUGS codes for inconsistency models are provided in supplement B5, appendix 6.

SMD analysis: methods

We wished to include as many trials and information as possible in each analysis even when data were reported in different ways. This meant transforming the data in some cases. For the SMD analysis we wanted to conduct a NMA on the mean difference in change from baseline (CFB) (for which standard methods are available, see Dias 2011). The data required for each arm of each study are the mean CFB, the standard deviation in CFB and the total number of individuals in that arm (or the standard error of the mean change from baseline).

However, some studies did not report these data, and instead reported

a) the baseline and endpoint means, standard deviations and number of individuals, for each arm of the study;

b) the number of individuals responding to treatment in each arm of each study, out of the total number of individuals, defined as those improving by more than a certain percentage from baseline;

Studies reporting outcomes a) or b) above also provide information on the mean change from baseline, through the relationship between the underlying continuous scale and the measurements that can be derived from it.

For our analysis, if CFB data were available in a study we used those data. If that study did not report CFB but reported baseline and endpoint data we used the baseline and endpoint data and transformed it to CFB. If a study reported neither CFB nor baseline and endpoint data but did report response, we used the response data and transformed it to CFB. For using intention-to-treat data we required that the number of participants randomised be reported, whilst for per-protocol data we required that the number of completers be reported. If these were not reported consistently for continuous data on CFB, baseline or endpoint, then we preferred to use the number of individuals responding to treatment and derive the continuous results from this.

Notation

To transform the data we assumed that n_{ik} individuals are randomised to each arm k (k>1) of study i=1,…,M, on which the following outcomes are recorded for individual j=1,…,n_{ik}:

x_{jik} - the score at baseline for individual j in arm k of trial i, on a given continuous scale;

y_{jik} - the score at follow-up for individual j in arm k of trial i, on a given continuous scale;

c_{jik} - the change from baseline for individual j in arm k of trial i, on a given continuous scale, where $c_{jik} = y_{jik} - x_{jik}$;

R_{jik} - response status at endpoint for individual j in arm k of trial i, defined as **at least a q_i*100% reduction** of the endpoint measurement on a given continuous scale, compared to baseline, i.e.

$$R_{jik} = \begin{cases} 1 & \text{if } y_{jik} - x_{jik} \leq -q_i x_{jik} \\ 0 & \text{otherwise} \end{cases} \quad (1)$$

Note that different studies may have used a different cut-off *q* (although they would be expected to be the same for all arms of a study), and these are therefore indexed by study.

Reported outcomes

Studies may report all or some of the following observed outcomes

$m_{X,ik}$ - the observed mean at baseline in arm *k* of trial *i*, on a given continuous scale;

$sd_{X,ik}$ - the observed standard deviation at baseline in arm *k* of trial *i*, on a given continuous scale;

$m_{Y,ik}$ - the observed mean at endpoint in arm *k* of trial *i*, on a given continuous scale;

$sd_{Y,ik}$ - the observed standard deviation at endpoint in arm *k* of trial *i*, on a given continuous scale;

$m_{C,ik}$ - the observed mean change from baseline in arm *k* of trial *i*, on a given continuous scale;

$sd_{C,ik}$ - the observed standard deviation in change from baseline in arm *k* of trial *i*, on a given continuous scale;

ρ_{ik} - the observed correlation between baseline and endpoint scores measured on the same individual in arm *k* of trial *i*. (Although this is rarely reported directly, it can be calculated when the means and standard deviations at baseline, endpoint and from the CFB are provided);

$r_{resp,ik}$ - the number of individuals achieving response in arm *k* of trial *i*, with response defined in equation (1).

Relationship between different outcomes

We assume that for each patient the baseline and endpoint measurements are sampled from a bivariate Normal distribution. Thus for all patients in arm *k* of trial *i*, we assume that their baseline, X_{ik}, and endpoint measurements Y_{ik}, are independent and identically distributed as

$$\begin{pmatrix} X_{ik} \\ Y_{ik} \end{pmatrix} \sim \mathrm{N}_2\left(\begin{pmatrix} \mu_{X,ik} \\ \mu_{Y,ik} \end{pmatrix}, \begin{pmatrix} \sigma^2_{X,ik} & \rho_{ik}\sigma_{X,ik}\sigma_{Y,ik} \\ \rho_{ik}\sigma_{X,ik}\sigma_{Y,ik} & \sigma^2_{Y,ik} \end{pmatrix}\right) \quad (2)$$

with $\mu_{X,ik}$ and $\mu_{Y,ik}$ representing the means and $\sigma^2_{X,ik}$ and $\sigma^2_{Y,ik}$ the variances at baseline and endpoint for individuals in arm *k* of trial *i*, respectively, and ρ_{ik} being the within arm and study correlation between baseline and endpoint measurements on the same individuals.

We define the mean change from baseline in arm *k* of trial *i* as $\theta_{ik} = \mu_{Y,ik} - \mu_{X,ik}$ as the parameter of interest.

NMA model for continuous outcomes

With continuous outcome data, meta-analysis is usually based on the sample means, with standard errors assumed known. Here we are interested in modelling the mean changes from baseline, which are assumed to be approximately normally distributed, with likelihood

$$m_{C,ik} \sim N\left(\theta_{ik}, se_{C,ik}^2\right)$$

The parameter of interest is the mean, θ_{ik}, of this distribution. For a random effects model we write

$$\theta_{ik} = \gamma_i + \delta_{ik} \quad (3)$$

where γ_i are the trial-specific effects of the treatment in arm 1 of trial *i*, treated as unrelated nuisance parameters, and the δ_{ik} are the trial-specific treatment effects of the treatment in arm *k* relative to the treatment in arm 1 in that trial, where $\delta_{i1} = 0$. The trial-specific random effects δ_{ik}, represent the mean differences between the change from baseline for the treatment in arm *k* and the treatment in arm 1 of trial *i* and, in a random effects model,

$$\delta_{ik} \sim \text{Normal}(d_{t_{i1},t_{ik}}, \tau_{study}^2) \quad (4)$$

where τ_{study}^2 denotes the between-study heterogeneity, assumed common to all treatment comparisons and $d_{t_{i1}t_{ik}} = d_{1,t_{ik}} - d_{1,t_{i1}}$ are the pooled mean differences, defined by the consistency equations ($d_{11} = 0$). The fixed effect model is obtained by replacing equation (3) with $\theta_{ik} = \gamma_i + d_{1,t_{ik}} - d_{1,t_{i1}}$. Where studies with more than 2 arms are present, a correlation is induced in the trial specific effects δ_{ik} so equation (4) is replaced by a multivariate normal distribution with correlation equal to 0.5 (Dias 2011; Higgins 1996).

Likelihood and link functions for studies reporting other outcomes

- Studies reporting mean and variance at endpoint

From the joint bivariate normal distribution in equation (2) we know that

$$\left(Y_{ik} - X_{ik}\right) \sim N\left(\theta_{ik}, \sigma_{X,ik}^2 + \sigma_{Y,ik}^2 - 2\rho_{ik}\sigma_{X,ik}\sigma_{Y,ik}\right) \quad (5)$$

Therefore, studies not reporting change from baseline but reporting the mean and variance at baseline and endpoint also provide information on the parameter of interest θ_{ik}, the mean change from baseline.

For these studies we can calculate the mean change from baseline as $m_{C,ik} = m_{Y,ik} - m_{X,ik}$. Using equation (5), the likelihood can be written as

$$m_{C,ik} \sim N\left(\theta_{ik}, se_{X,ik}^2 + se_{Y,ik}^2 - 2\rho_{ik}se_{X,ik}se_{Y,ik}\right)$$

Provided the standard errors at baseline and endpoint can be obtained and that we have information on the within-study correlation, the remaining model is given in equations (3) and (4) can be used to pool the mean differences in change from baseline.

- Studies reporting number of responders

Using equation (1), the probability of response for individuals in arm *k* of trial *i* is defined as

$$R_{ik} = \Pr(Y_{ik} - X_{ik} \leq -qX_{ik}) \tag{6}$$

Conditioning on the baseline value X_{ik} we have

$$Y_{ik} \mid X_{ik} \sim N\left(\mu_{X,ik}(1-\rho_{ik}) + \theta_{ik} + \rho_{ik}X_{jik}, (1-\rho_{ik}^2)\sigma_{X,ik}^2\right) \tag{7}$$

thus,

$$\begin{aligned} R_{ik} \mid X_{ik} &= \Pr_{Y|X}\left(Y_{ik} < (1-q)X_{ik}\right) \\ &= \Phi\left(aX_{ik} + b\right) \end{aligned} \tag{8}$$

with

$$a = \frac{1-q-\rho_{ik}}{\sigma_{X,ik}\sqrt{1-\rho_{ik}^2}}\ ,\ b = -\frac{\mu_{X,ik}(1-\rho_{ik}) + \theta_{ik}}{\sigma_{X,ik}\sqrt{1-\rho_{ik}^2}}$$

Therefore the unconditional probability of response in arm *k* of trial *i* is

$$R_{ik} = E_{X_{ik}}\left[\Phi\left(aX_{ik} + b\right)\right] \tag{9}$$

It can be shown that

$$E_X\left[\Phi\left(aX + b\right)\right] = \Phi\left(\frac{aE(X) + b}{\sqrt{1 + a^2 Var(X)}}\right) \tag{10}$$

thus the probability of response for individuals in arm *k* of trial *i* can be written as

$$R_{ik} = \Phi\left(\frac{-(q\mu_{X,ik} + \theta_{ik})}{\sigma_{X,ik}\sqrt{1 + (1-q)(1-q-2\rho_{ik})}}\right) \tag{11}$$

Therefore, studies not reporting the change from baseline or endpoint measures, but providing information on the probability of response, also provide information on the parameter of interest, the mean change from baseline θ_{ik}.

These studies have a binomial likelihood

$$r_{resp,ik} \sim \text{Binomial}(R_{ik}, n_{ik})$$

Provided the baseline mean and standard deviation for each study are reported and that we also have information on the correlation between baseline and endpoint scores in each arm of each study, we can replace these as if they are known into equation (11) and then use equations (3) and (4), as before.

Prior distributions and computation

In this case non-informative prior distributions are chosen for the pooled treatment effects, relative to treatment 1, d_{1k}, k=2,…,nt , where nt is the number of treatments in the network

$$d_{1k} \sim \text{Normal}(0, 100^2) \quad (12)$$

and a Uniform prior between 0 and 5 is chosen for the between-study heterogeneity, which is thought to be sufficiently wide to capture the variability in difference in mean change from baseline across trials making the same comparisons.

An informative prior distribution for the within class standard deviation is given as detailed under '*Class models*'.

Analysis on the SMD scale

In this case, studies also used different underlying continuous scales on which they report the means or the number of responders. As the methods noted above are study and arm specific, they apply regardless of which scale was used in that trial, although care needs to be taken to ensure that the pre-specified cut-offs *q* and *h* are appropriate for the scale used in a particular study.

Pooling of the difference in means across different scales is not appropriate. A common approach is to use the SMD, where the mean difference is divided by a standardising constant, which can be the population standard deviation for each scale (if known), or its estimate, s_i. We use the baseline SD as the standardising constant because it is not influenced by treatment, so better reflects the SD of the outcome scale in the RCT population (Daly 2021).

The standardising constant can be adjusted in different ways (Cooper 2009). We use Cohen's d (Cohen 1969), but the analysis using another standardising constant can be done following the same principles.

The SMD for arm *k* of study *i* compared to arm 1 of study i, λ_{ik} , is given as

$$\lambda_{ik} = \frac{m_{ik} - m_{i1}}{s_i} \quad (13)$$

where s_i in a two arm study is given as

$$s_i = \sqrt{\frac{(n_{i1}-1)sd^2_{i1} + (n_{i2}-1)sd^2_{i2}}{n_{i1} + n_{i2} - 2}} \quad (14)$$

and in a three arm study is given as

$$s_i = \sqrt{\frac{(n_{i1}-1)sd^2_{i1} + (n_{i2}-1)sd^2_{i2} + (n_{i3}-1)sd^2_{i3}}{n_{i1} + n_{i2} + n_{i3} - 3}} \quad (15)$$

The likelihood for each study reporting the various outcomes are as before, but the parameter of interest is now the SMD λ_{ik} . Thus the model is defined as

$$\lambda_{ik} = \gamma_i + \delta_{ik} \quad (16)$$

This model is linked to the mean change from baseline through the following relationship

$$\theta_{ik} = \lambda_{ik} s_i \quad (17)$$

Prior distributions can be defined as before.

Response analysis: methods

The economic model is driven by the probabilities of response on each treatment which are informed both by studies reporting response and studies reporting continuous measures. Again we wanted to include as much data as possible in the analysis. For studies not reporting response we transformed the continuous data first to the SMD scale and then to response. The data required for each arm of each study are the number of individuals responding to treatment in each arm of each study, out of the total number of individuals, defined as those improving by more than a certain percentage from baseline;

However, some studies did not report these data, and instead reported

a) the mean CFB, the standard deviation in CFB and the total number of individuals in that arm (or the standard error of the mean change from baseline);

b) the baseline and endpoint means, standard deviations and number of individuals, for each arm of the study.

Studies reporting outcomes a) or b) above also provide information on the probability of response through the relationship between the underlying continuous scale and the measurements that can be derived from it.

For this analysis, if response data were available in a study we used those data. If that study did not report response but reported CFB we used the CFB data and transformed these to response. If a study reported neither response nor CFB but did report baseline and endpoint data, we used the baseline and endpoint data and transformed these to response.

Continuous SMD data were converted to LOR following the approach recommended by the Cochrane collaboration (Higgins 2011). For trials reporting response the following model was used:

$$r_{ik} \sim \text{Binomial}(p_{ik}, n_{ik})$$

where r_{jk} is the number of individuals achieving response in arm k of trial j, n_{jk} is the total number of individuals in arm k of trial j, and p_{jk} is the probability of response in arm *k* of trial *j*. These probabilities are modelled on the log-odds scale as:

$$\text{logit}(p_{ik}) = \alpha_i + \eta_{ik}$$

where η_{ik} represents the relative treatment effect of the treatment in arm *k* compared with the treatment in arm 1 in trial *i*, on the log-odds ratio (LOR) scale and $\eta_{i1} = 0$. Thus $\eta_{ik} > 0$ favours the treatment in arm *k* and $\eta_{ik} < 0$ favours the treatment in arm 1.

The LOR of response can be related to a notional SMD for response using the formula (Chinn 2000):

$$LOR_{\text{Re}sponse} = \frac{\pi}{\sqrt{3}} SMD_{\text{Re}sponse} \quad (18)$$

noting the change in sign to retain the interpretation of a positive LOR favouring treatment *k*.

The LOR was obtained by transforming the treatment effect from the SMD scale using equation (18). So, the treatment effect on response is informed by the treatment effect in studies on the pooled scale of symptoms as:

$$\eta_{ik} = \left(-\frac{\pi}{\sqrt{3}} \delta_{ik} \right)$$

Standard NMA random and fixed effects model can used to pool η, as described in section '*SMD analysis: methods'* under subsection '*NMA model for continuous outcomes*'. Prior distributions can also be defined as before.

Sample WinBUGS code for both the SMD and response analyses is provided in supplement B5, appendix 1.

Information on within-study correlation and standard deviation at follow-up

To apply the methods described in sub-sections of '*Likelihood and link functions for studies reporting other outcomes*' within section '*SMD analysis: methods*' we needed information on a) the correlation between baseline and endpoint scores and b) the relationship between standard deviations (SDs) at baseline and endpoint.

For a) we identified 35 studies in our dataset that provided information on mean and SD at baseline, mean and SD at endpoint and the mean and SD of change from baseline (supplement B5, appendix 2). The correlations had a median of 0.31 (Inter-Quartile Range: 0.18-0.47), and this value was used for subsequent calculations. In the 2017 and 2018 guideline consultation drafts, a sensitivity analysis exploring different values for the correlation was performed (0.5 or 0.3), which was found to have very little effect. However in that version, unlike in our current analysis, there were also insufficient data points to empirically inform the correlation.

For b) we plotted the SDs at baseline and endpoint from every study that reported both by group of intervention and population (Figure 68 and Figure 69). The blue line on these plots is the regression line with 95% confidence interval and the red line is the line of equality where y=x. The regression equation is also shown. We used the regression equation to predict SD at endpoint from SD at baseline in studies where SD at endpoint was not reported using the regression equations given. No sensitivity analysis was conducted on this, but 2017 and 2018 guideline consultation drafts explored this and found that results were very similar between SDs predicted using a regression equation, and SDs predicted assuming that baseline and endpont were equal.

Figure 68. Plot of SDs at baseline and endpoint – More severe depression.

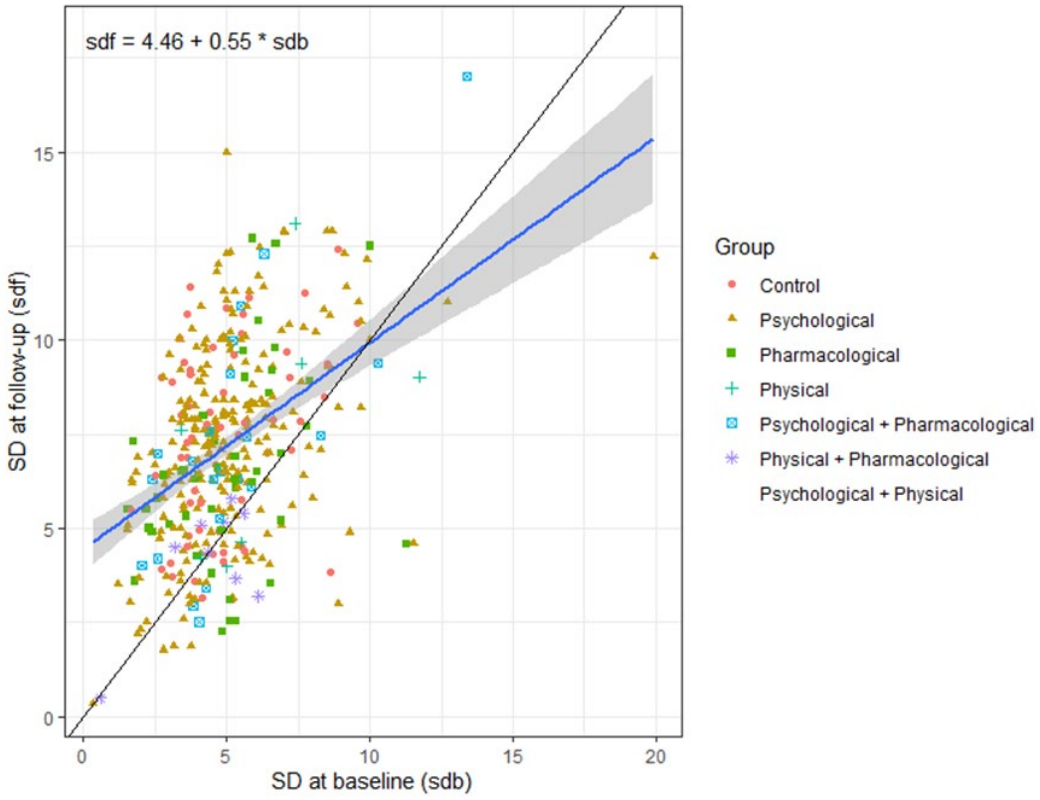
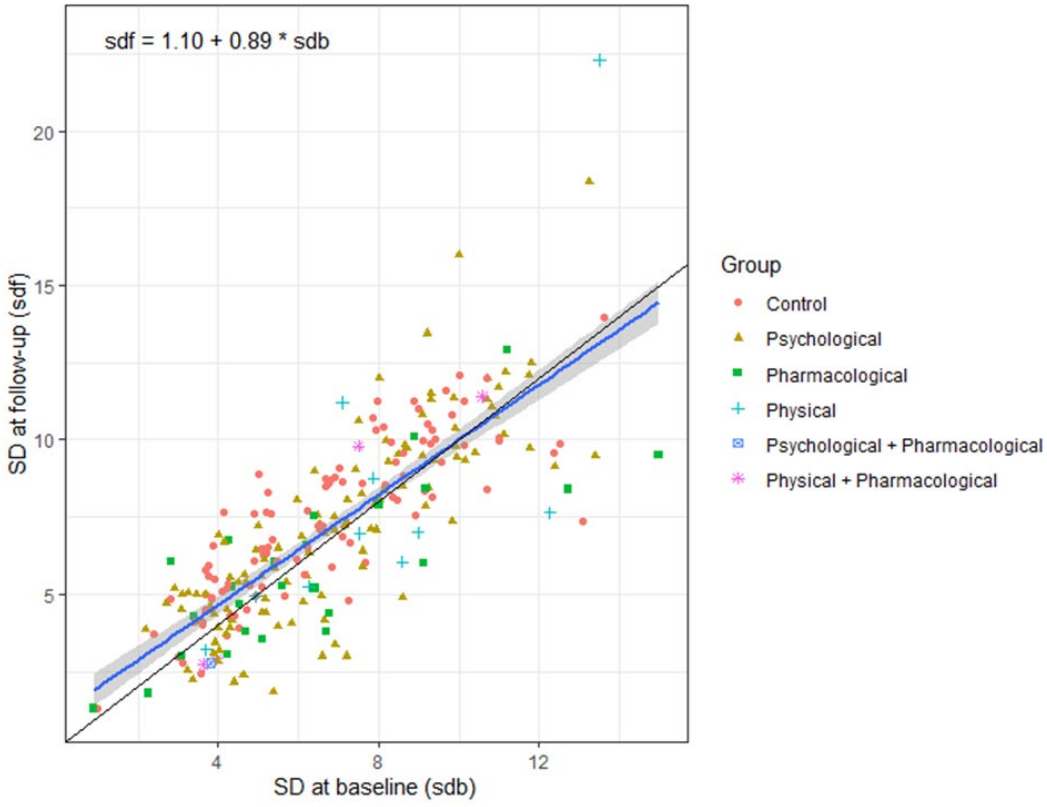


Figure 69. Plot of SDs at baseline and endpoint – Less severe depression.



Pre-specified sensitivity analyses

In selected outcomes (discontinuation due to any reason, response in completers, and Standardised Mean Differences) in both less severe and more severe depression, we evaluated the potential for small study bias using the methods reported by Dias 2010. Adjusting for small study effects captures a range of potential biases that are associated with smaller studies, including, but not restricted to, publication bias. In the absence of sufficient information to explore other risk of bias domains, the best proxy available is to explore the effect of study size, which is often associated with risk of bias indicators. The analysis of small study effects has the benefit that all studies can be included in the analyses simultaneously, thus increasing power to detect any effect.

Bias was assumed in comparisons of active interventions vs inactive control, and no bias was assumed between inactive control comparisons, as well as between active intervention comparisons. Additionally, in comparisons where counselling was the control intervention, bias against counselling was assumed. The bias was assumed to be of the same magnitude across all potentially biased comparisons.

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 outcome scale being modelled (SMD or logOR). This applies to the relative effects estimated from all included studies, whether the data are reported as change from baseline in measures of depression, depression measured at endpoint or as the number of responders to treatment. The only change required to incorporate the bias adjustment is to change equation (3) to

$$\theta_{ik} = \gamma_i + \delta_{ik} + \left(\beta_{ik} \times V_{ik}\right)$$

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

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

where *B*=*b* if the treatment in arm 1 of trial *i* is a control and the treatment in arm *k* is not and *B*=0 if the comparison of treatment 1 to treatment *k* is active vs active or control vs control.

Bias-adjusted models were compared to random effects consistency models using DIC. If the bias-adjusted model had a DIC that was lower by ≥5 then results from this were reported over the unadjusted model (Spiegelhalter 2002).

WinBUGS codes for bias-adjusted models are provided in supplement B5, appendix 6.

For Standardised Mean Differences, a non-pharmacological subgroup of the overall dataset was analysed separately as a further sensitivity analysis. This excluded any studies that investigated pharmacological interventions in any arm.

Results for adults with a new episode of less severe depression

Outcome: Discontinuation (for any reason)

This analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients randomized. After excluding trials with zero events in all arms or with the number events equal to the denominator in all arms, 120 trials of 75 interventions and 34 classes were included for this outcome (Table 111,

Figure 70, Figure 71). A continuity correction was applied to data in 7 studies containing at least one zero cell to stabilize the results.

Lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, as well as minimal improvement in the prediction of data in individual studies by the inconsistency model, suggested that there was no evidence of inconsistency (supplement B5, Table 3.1 in appendix 3; Figure 72). The between-study heterogeneity was very similar in consistency and inconsistency models.

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The bias parameter for comparisons with active versus control or counselling treatments was estimated to be 0.14 (95%CrI -0.26, 0.58). Although the between study heterogeneity was slightly reduced (supplement B5, Table 3.1 in appendix 3; Figure 72), the DIC remained the same as in the base-case consistency model. Further details are given in 'Sensitivity Analyses' section). Results from the bias-adjusted model and from the base-case unadjusted model can be found in Excel files in supplement B6 ("*Depression NMA less severe DISCONany bias-adjusted*.xlsx" and *"Depression NMA less severe DISCONany base-case.xlsx"*, respectively).

Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.53\ (95\%\ \mathrm{CrI}\ 0.38\ \mathrm{to}\ 0.70)$). Waitlist was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.1 & 4.2 in appendix 4).

Table 111. Interventions, classes and number of patients randomised (N). Discontinuation (for any reason) analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Waitlist	3785	Waitlist	1	3785	
2	Pill placebo	621	Placebo	2	621	
3	Attention placebo	795	Attention placebo	3	795	
4	No treatment	1713	No treatment	4	1713	
5	TAU	1005	TAU	5	1005	
6	Enhanced TAU	96	Enhanced TAU	6	96	
7	Behavioural activation (BA) individual	153	Behavioural therapies individual	7	153	1
8	Behavioural activation (BA) group	107	Behavioural therapies group	8	373	1
9	Coping with Depression course (group)	266				
10	CBT individual (15 sessions or over)	90	Cognitive and cognitive behavioural therapies individual	9	663	1
11	CBT individual (under 15 sessions)	402				
12	Third-wave cognitive therapy individual	171				
13	CBT group (15 sessions or over)	47	Cognitive and cognitive behavioural therapies group	10	483	2
14	CBT group (under 15 sessions)	283				

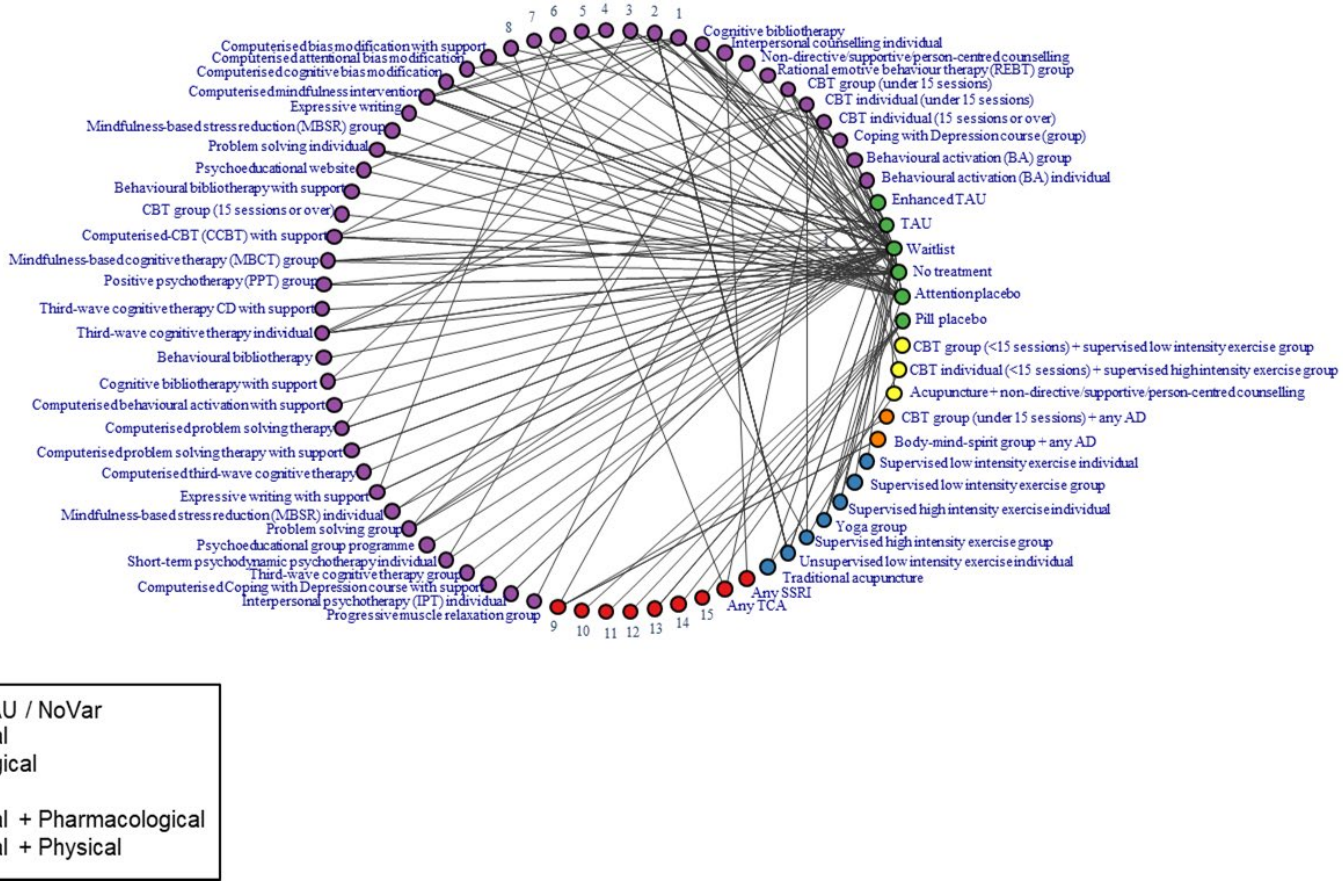
15	Positive psychotherapy (PPT) group	89				
16	Rational emotive behaviour therapy (REBT) group	15				
17	Third-wave cognitive therapy group	49				
18	Problem solving individual	159	Problem solving individual	11	159	1
19	Problem solving group	168	Problem solving group	12	168	1
20	Non-directive/supportive/person-centred counselling	125	Counselling individual	13	125	1
21	Interpersonal counselling individual	27	Interpersonal psychotherapy (IPT) individual	14	135	1
22	Interpersonal psychotherapy (IPT) individual	108				
23	Psychoeducational group programme	23	Psychoeducation group	15	23	1
24	Behavioural bibliotherapy	13	Self-help	16	5733	3
25	Cognitive bibliotherapy	427				
26	Computerised-CBT (CCBT)	3173				
27	Computerised attentional bias modification	154				
28	Computerised behavioural activation	159				
29	Computerised cognitive bias modification	76				
30	Computerised Coping with Depression course	292				
31	Computerised expressive writing	44				
32	Computerised mindfulness intervention	645				
33	Computerised positive psychological intervention	440				
34	Computerised problem solving therapy	101				
35	Computerised third-wave cognitive therapy	31				
36	Expressive writing	13				
37	Psychoeducational website	165				
38	Behavioural bibliotherapy with support	67	Self-help with support	17	1391	4
39	Cognitive bias modification with support	32				
40	Cognitive bibliotherapy with support	125				
41	Computerised-CBT (CCBT) with support	428				
42	Computerised behavioural activation with support	41				
43	Computerised Coping with Depression course with support	36				

44	Computerised problem solving therapy with support	124				
45	Computerised third-wave cognitive therapy with support	82				
46	Expressive writing with support	125				
47	Third-wave cognitive therapy CD with support	331				
48	Short-term psychodynamic psychotherapy individual	53	Short-term psychodynamic psychotherapies individual	18	53	1
49	Mindfulness-based stress reduction (MBSR) individual	20	Mindfulness or meditation individual	19	20	1
50	Mindfulness-based cognitive therapy (MBCT) group	167	Mindfulness or meditation group	20	375	5
51	Mindfulness-based stress reduction (MBSR) group	70				
52	Mindfulness meditation group	138				
53	Progressive muscle relaxation individual	15	Relaxation individual	21	15	1
54	Progressive muscle relaxation group	63	Relaxation group	22	63	2
55	Any SSRI	28	SSRIs	23	462	6
56	Citalopram	27				
57	Fluoxetine	81				
58	Sertraline	326				
59	Amitriptyline	90	TCAs	24	208	7
60	Any TCA	13				
61	Imipramine	73				
62	Lofepramine	32				
63	Any AD	107	Any AD	25	107	8
64	Traditional acupuncture	40	Acupuncture	26	40	1
65	Supervised high intensity exercise individual	39	Exercise individual	27	235	9
66	Supervised low intensity exercise individual	61				
67	Unsupervised low intensity exercise individual	135				
68	Supervised high intensity exercise group	121	Exercise group	28	181	4
69	Supervised low intensity exercise group	60				
70	Yoga group	78	Yoga group	29	78	2
71	CBT group (under 15 sessions) + any AD	35	Cognitive and cognitive behavioural therapies group + AD	30	35	1
72	Body-mind-spirit group + any AD	44	Mindfulness or meditation group + AD	31	44	1
73	Traditional acupuncture + non-directive/supportive/person-centred counselling	40	Acupuncture + counselling individual	32	40	1

74	CBT individual (under 15 sessions) + supervised high intensity exercise group	21	Cognitive and cognitive behavioural therapies individual + exercise group	33	21	1
75	CBT group (under 15 sessions) + supervised low intensity exercise group	35	Cognitive and cognitive behavioural therapies group + exercise group	34	35	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 70. Network diagram of interventions. Discontinuation (for any reason).



1 Computerised CBT (CCBT), 2 Computerised behavioural activation, 3 Computerised Coping with Depression course, 4 Computerised expressive writing, 5 Computerise positive psychological intervention, 6 Computerised third wave cognitive therapy with support, 7 Mindfulness meditation group, 8 Progressive muscle relaxation individual, 9 Any AD, 10 Amitryptyline, 11 Citalopram, 12 Fluoxetine, 13 Imipramine, 14 Lofepramine, 15 Sertraline.
Without the use of a class model Pill placebo, Interpersonal counselling individual, Amitriptyline, Any SSRI, Citalopram, Fluoxetine, Imipramine, Lofepramine and Sertraline would be disconnected from the rest of the network.

Figure 71. Network diagram of classes. Discontinuation (for any reason).

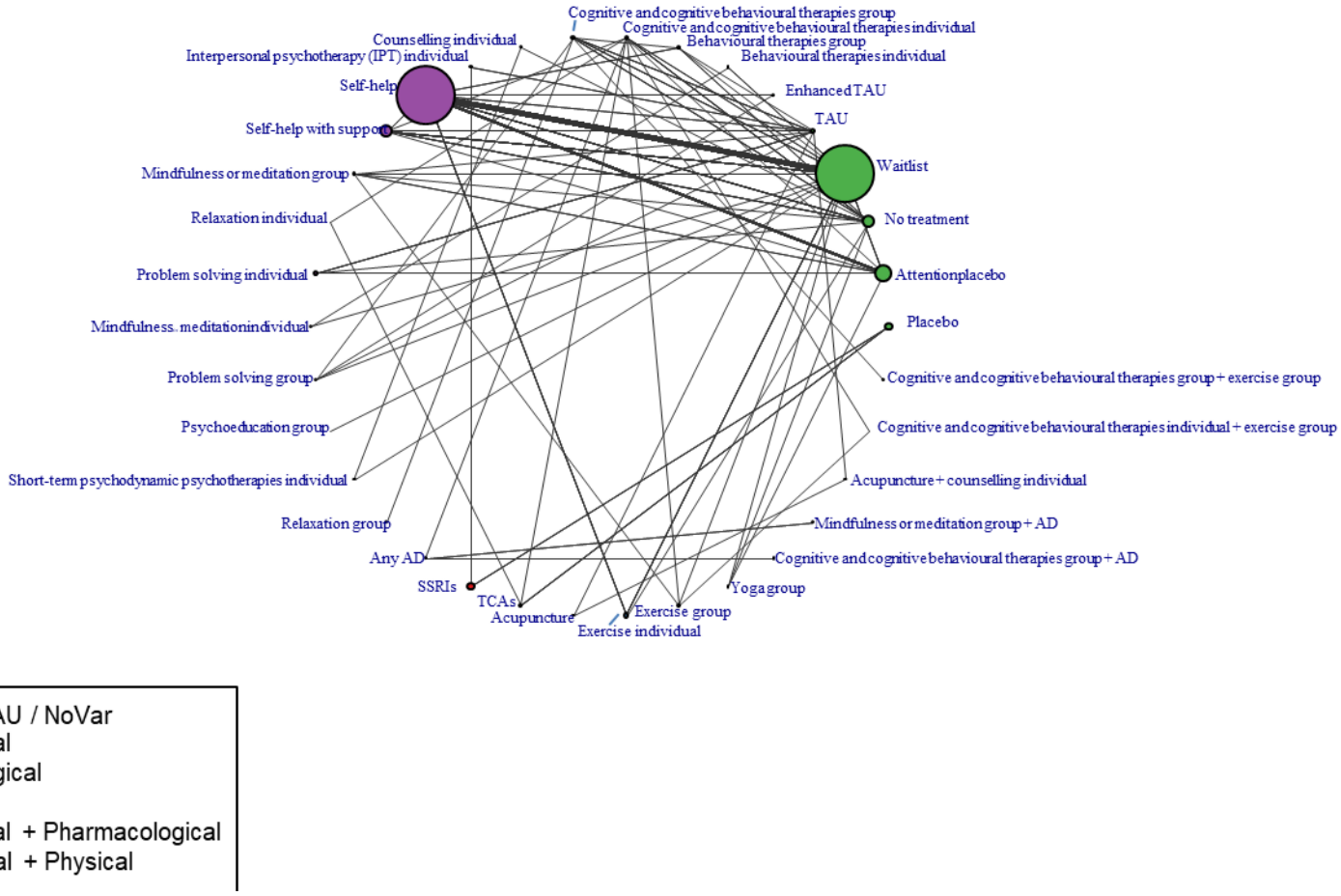
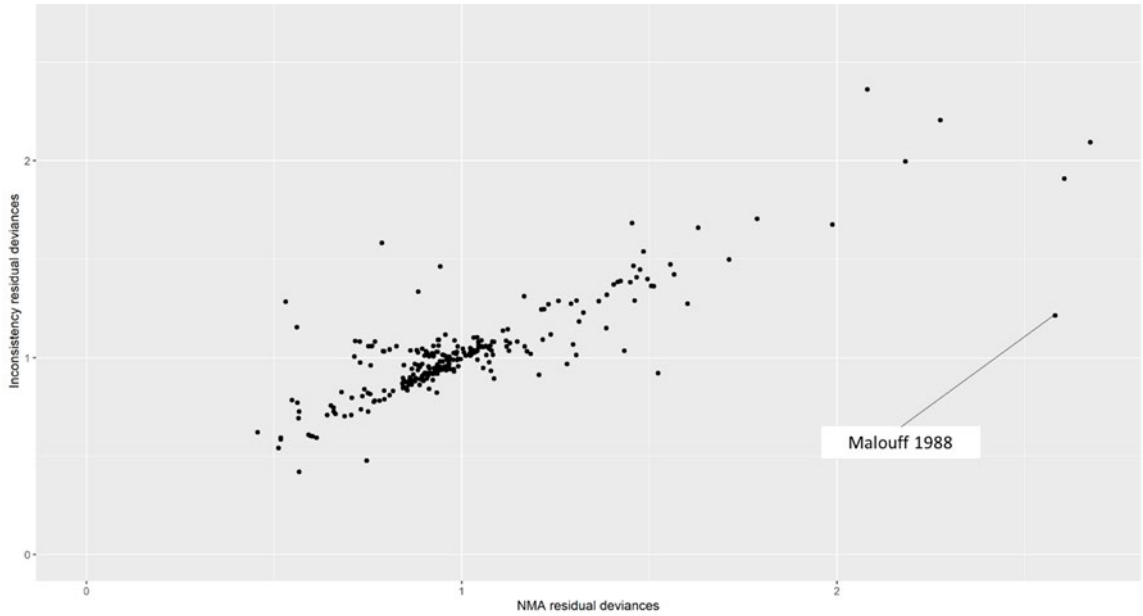


Figure 72. Deviance plot. Discontinuation (for any reason).



There is evidence of only two interventions having a decreased odds of discontinuation compared to TAU (supplement B5, Figure 4.1 in appendix 4):

- No treatment
- Waitlist

There is no clear evidence of any intervention having an increased odds of discontinuation compared to TAU, nor is there evidence of any classes of interventions having a decreased or increased odds of discontinuation compared to TAU (supplement B5, Figures 4.1 & 4.2 in appendix 4). For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

The highest ranked class is Psychoeducation group with a posterior median rank of 4th (95% CrI 1st to 25th) (Table 112). The lowest ranked classes are TCAs, Problem solving group and Enhanced TAU (Table 112). We note however the wide credible intervals in the all ranks, reflecting the uncertainty in which class or treatment is best.

Table 112. Posterior mean and median rank and 95% credible intervals by class. Discontinuation (for any reason).

Class	Posterior mean rank	Posterior median rank (95% CrI)
Psychoeducation group	6.1	4 (1, 25)
Short-term psychodynamic psychotherapies individual	8.2	6 (1, 27)
Waitlist	9.9	10 (5, 16)
Cognitive and cognitive behavioural therapies individual	9.9	9 (3, 23)
Counselling individual	10.0	8 (1, 28)
Cognitive and cognitive behavioural therapies individual + exercise group	11.1	9 (1, 30)
Relaxation group	11.4	7 (1, 32)
Behavioural therapies individual	11.4	8 (1, 31)
Yoga group	12.6	10 (1, 32)

Acupuncture + counselling individual	13.2	11 (1, 31)
Mindfulness or meditation group	13.5	13 (2, 30)
Attention placebo	15.2	15 (9, 23)
Acupuncture	15.7	15 (2, 31)
Mindfulness or meditation individual	15.8	15 (1, 32)
Exercise individual	15.8	15 (2, 31)
Cognitive and cognitive behavioural therapies group + AD	16.6	16 (1, 32)
Mindfulness or meditation group + AD	16.8	17 (1, 32)
TAU	18.1	18 (10, 26)
Exercise group	18.2	18 (6, 29)
Cognitive and cognitive behavioural therapies group	18.3	19 (4, 31)
Self-help	19.3	19 (13, 26)
SSRIs	19.8	22 (2, 32)
Self-help with support	20.2	20 (12, 28)
Problem solving individual	20.7	22 (4, 31)
Placebo	20.8	24 (2, 32)
Behavioural therapies group	20.8	22 (7, 31)
Cognitive and cognitive behavioural therapies group + exercise group	21.6	24 (3, 32)
Interpersonal psychotherapy (IPT) individual	21.8	23 (6, 32)
Relaxation individual	21.9	26 (2, 32)
TCAs	23.2	27 (3, 32)
Problem solving group	24.7	27 (6, 32)
Enhanced TAU	25.5	27 (13, 32)

Outcome: Discontinuation due to side effects

There were insufficient studies and interventions available to be able to fit a NMA with random class effects. Therefore, a simpler fixed class model was fitted, in which all interventions within a class were assumed to have the same effect. As this outcome informed the guideline economic analysis, details of this analysis are provided in appendix J, under '*Relative effects on efficacy, acceptability and tolerability of treatments for a new depressive episode and methods of evidence synthesis*'. Results are also summarised in supplement B5, Figures 4.3 & 4.4 in appendix 4.

Outcome: Remission in completers

This remission analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients who completed treatment. After excluding trials which did not report remission in completers, trials with zero events in all arms, trials with the number events equal to the denominator in all arms, and 2 trials that were disconnected from the network, 27 trials of 27 interventions and 17 classes were included for this outcome (Table 113, Figure 73, Figure 74). A continuity correction was applied to data in 2 studies containing at least one zero cell to stabilize the results.

Lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, as well as minimal improvement in the prediction of data in individual studies by the inconsistency model, suggested that there was no evidence of inconsistency (supplement B5, Table 3.3 in appendix 3; Figure 75). The between-study heterogeneity was very similar in consistency and inconsistency models. Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} =$

0.53 $(95\%$ CrI 0.38 to $0.70))$. Waitlist was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.5 & 4.6 in appendix 4).

Posterior mean residual deviances were the same in the NMA random effects consistency model and the inconsistency model, and DIC was slightly lower. In addition to minimal improvement in the prediction of data in individual studies by the inconsistency model, this suggested that there was no evidence of inconsistency (supplement B5, Table 3.3 in appendix 3; Figure 75). However, both models poorly predicted data from two studies (Yang 2015, Rosso 2017), both of which investigated No treatment compared to an intervention from the Self-help class. The between-study heterogeneity was very similar in consistency and inconsistency models. Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.35$ $(95\%$ CrI 0.02 to $0.89)$). Waitlist was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.5 & 4.6 in appendix 4).

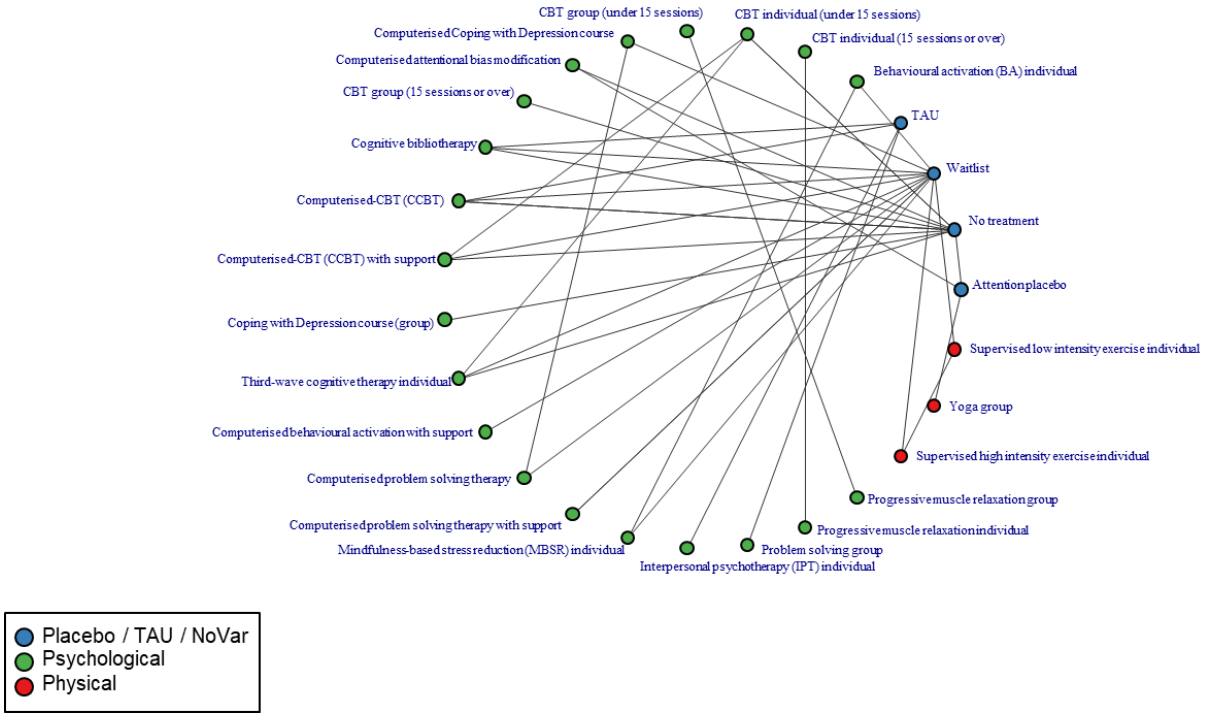
Table 113. Interventions, classes and number of patients (N) included in remission in completers analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Waitlist	414	Waitlist	1	414	
2	Attention placebo	38	Attention placebo	2	38	
3	No treatment	671	No treatment	3	671	
4	TAU	371	TAU	4	371	
5	Behavioural activation (BA) individual	15	Behavioural therapies individual	5	15	1
6	Coping with Depression course (group)	61	Behavioural therapies group	6	61	1
7	CBT individual (15 sessions or over)	12	Cognitive and cognitive behavioural therapies individual	7	194	1
8	CBT individual (under 15 sessions)	89				
9	Third-wave cognitive therapy individual	93				
10	CBT group (15 sessions or over)	42	Cognitive and cognitive behavioural therapies group	8	107	1
11	CBT group (under 15 sessions)	65				
12	Problem solving group	86	Problem solving group	9	86	1
13	Interpersonal psychotherapy (IPT) individual	58	Interpersonal psychotherapy (IPT) individual	10	58	1
14	Cognitive bibliotherapy	205	Self-help	11	795	2
15	Computerised-CBT (CCBT)	460				
16	Computerised attentional bias modification	28				
17	Computerised Coping with Depression course	51				
18	Computerised problem solving therapy	51				
19	Computerised-CBT (CCBT) with support	133	Self-help with support	12	263	1

20	Computerised behavioural activation with support	40				
21	Computerised problem solving therapy with support	90				
22	Mindfulness-based stress reduction (MBSR) individual	18	Mindfulness or meditation individual	13	18	1
23	Progressive muscle relaxation individual	12	Relaxation individual	14	12	1
24	Progressive muscle relaxation group	61	Relaxation group	15	61	1
25	Supervised high intensity exercise individual	14	Exercise individual	16	29	1
26	Supervised low intensity exercise individual	15				
27	Yoga group	15	Yoga group	17	15	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 73. Network diagram of all studies included in analysis by intervention. Remission in completers.



Without the use of a class network CBT group (under 15 sessions), CBT individual (15 sessions or over), Progressive muscle relaxation group and Progressive muscle relaxation individual would be disconnected from the rest of the network and would have to be excluded from the analysis.

Figure 74. Network diagram of all studies included in analysis by class. Remission in completers.

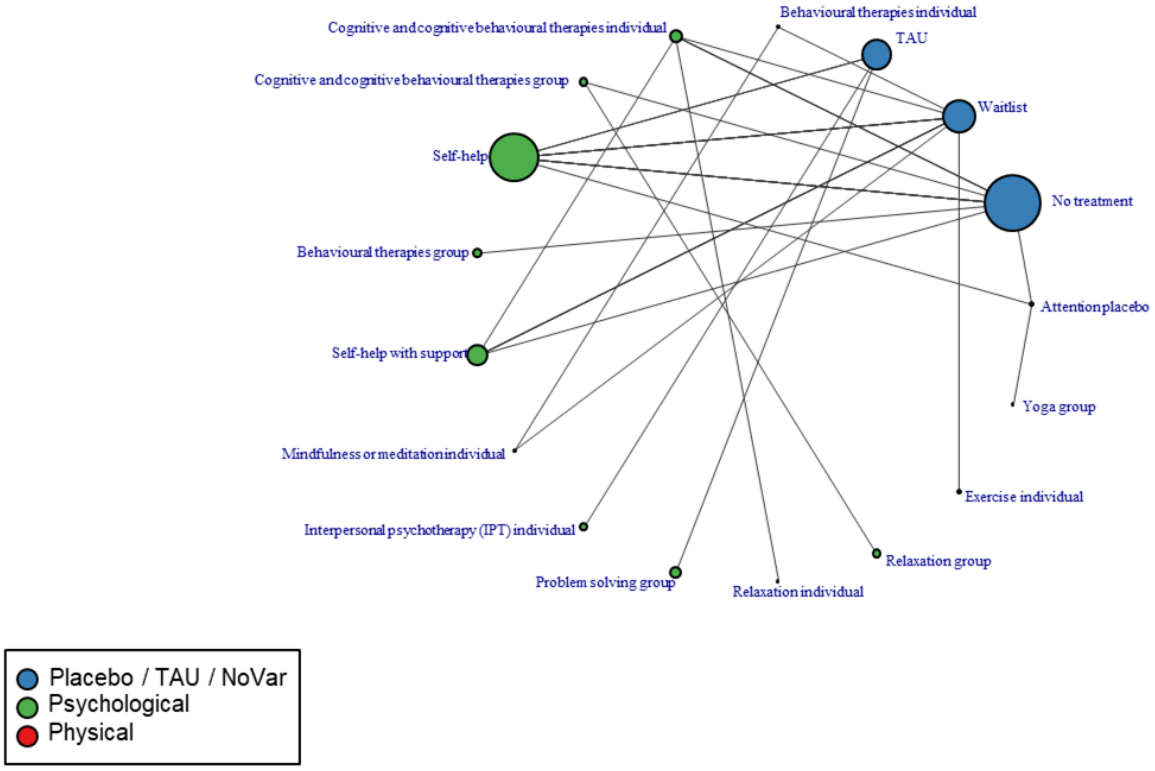
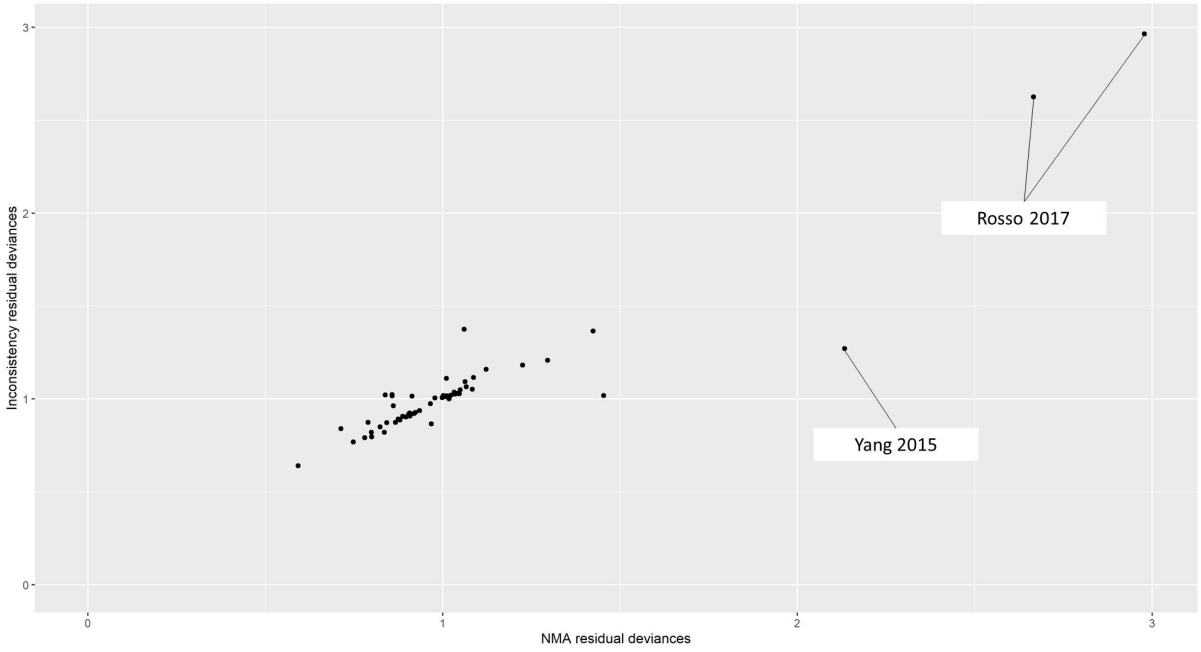


Figure 75. Deviance plot. Remission in completers.



The interventions for which there is evidence of an increased odds of remission compared to TAU are the following (supplement B5, Figure 4.5 in appendix 4):

- CBT individual (under 15 sessions)
- Computerised behavioural activation with support

- Computerised problem solving therapy with support
- Problem solving group
- Supervised high intensity exercise individual
- Supervised low intensity exercise individual
- Third-wave cognitive therapy individual

There is no evidence that any interventions have a decreased odds of remission compared to TAU.

The classes for which evidence suggests an increased odds of remission compared to TAU are the following (supplement B5, Figure 4.6 in appendix 4):

- Exercise individual
- Problem solving group

There is also some evidence to suggest an increased odds of remission for Self-help with support compared to TAU. There is no evidence that any classes have a decreased odds of remission compared to TAU. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Problem solving group is the highest ranked class with a posterior median rank of 1st (95% CrI 1st to 6th). The lowest ranked class is Self-help at 16th (95% CrI 6th to 16th) (Table 114).

The highest ranked intervention is Problem solving group with a posterior median rank of 1st (95% CrI 1st to 5th). The lowest ranked intervention is Attention placebo at 25th (95% CrI 8th to 26th) (Excel file in supplement B6: *"Depression NMA less severe REMIScompleters"*, *"Ranks"* worksheet).

Table 114. Posterior mean and median rank and 95% credible intervals by class. Remission in completers.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Problem solving group	1.8	1 (1, 6)
Exercise individual	3.5	3 (1, 10)
Yoga group	5.2	3 (1, 15)
Self-help with support	5.7	5 (2, 11)
Cognitive and cognitive behavioural therapies individual	6.2	6 (3, 12)
Behavioural therapies individual	6.4	6 (1, 15)
Mindfulness or meditation individual	7.3	7 (2, 15)
Self-help	8.3	8 (4, 12)
Behavioural therapies group	8.7	9 (3, 15)
Cognitive and cognitive behavioural therapies group	8.9	9 (3, 15)
Interpersonal psychotherapy (IPT) individual	10.9	11 (3, 16)
TAU	11.3	11 (7, 15)
Relaxation group	12.5	14 (3, 16)
Waitlist	12.7	13 (9, 15)
Relaxation individual	13.0	15 (3, 16)
Attention placebo	13.7	15 (6, 16)

Outcome: Remission in those randomised

An additional remission analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients randomised. After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 26 trials of 25 interventions and 16 classes were included for this outcome (Table 115, Figure 76, Figure 77).

Posterior mean residual deviances and DIC were similar in the NMA random effects consistency model and the inconsistency model, and there was no clear improvement in the prediction of data in individual studies by the inconsistency model. This suggested that there was no evidence of inconsistency (supplement B5, Table 3.4 in appendix 3; Figure 78). However, both models poorly predicted data from two studies (Yang 2015, Rosso 2017), both of which investigated No treatment compared to an intervention from the Self-help class. The between-study heterogeneity was very similar in consistency and inconsistency models. Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.45$ (95% CrI 0.05 to 1.03)). No treatment was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.7 & 4.8 in appendix 4).

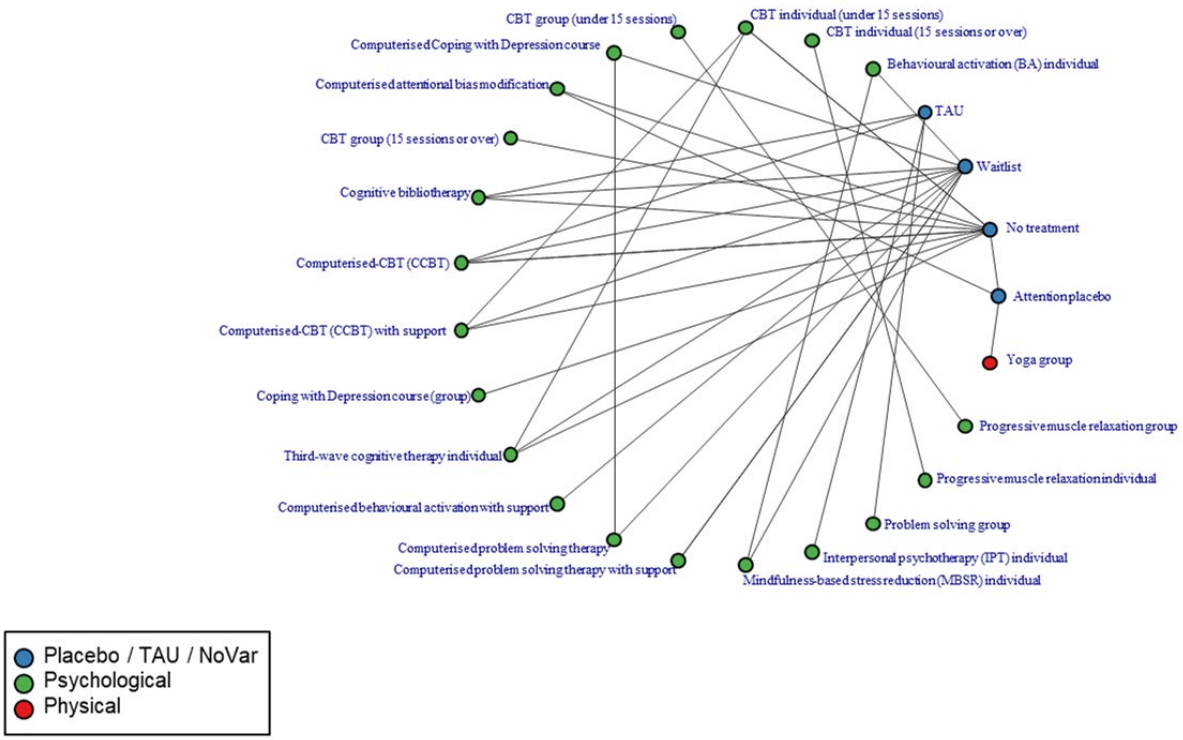
Table 115. Interventions, classes and number of patients (N) included in remission in those randomised analysis.

	Intervention	N	Class		N	Variance Sharing*
1	No treatment	751	Waitlist	1	751	
2	Attention placebo	46	Attention placebo	2	46	
3	Waitlist	468	No treatment	3	468	
4	TAU	437	TAU	4	437	
5	Behavioural activation (BA) individual	16	Behavioural therapies individual	5	16	1
6	Coping with Depression course (group)	68	Behavioural therapies group	6	68	1
7	CBT individual (15 sessions or over)	12	Cognitive and cognitive behavioural therapies individual	7	233	1
8	CBT individual (under 15 sessions)	116				
9	Third-wave cognitive therapy individual	105				
10	CBT group (15 sessions or over)	47	Cognitive and cognitive behavioural therapies group	8	117	1
11	CBT group (under 15 sessions)	70				
12	Problem solving group	89	Problem solving group	9	89	1
13	Interpersonal psychotherapy (IPT) individual	69	Interpersonal psychotherapy (IPT) individual	10	69	1
14	Cognitive bibliotherapy	287	Self-help	11	1050	1
15	Computerised-CBT (CCBT)	559				
16	Computerised attentional bias modification	28				
17	Computerised Coping with Depression course	88				

18	Computerised problem solving therapy	88				
19	Computerised-CBT (CCBT) with support	184	Self-help with support	12	348	1
20	Computerised behavioural activation with support	40				
21	Computerised problem solving therapy with support	124				
22	Mindfulness-based stress reduction (MBSR) individual	20	Mindfulness or meditation individual	13	20	1
23	Progressive muscle relaxation individual	15	Relaxation individual	14	15	1
24	Progressive muscle relaxation group	63	Relaxation group	15	63	1
25	Yoga group	20	Exercise individual	16	20	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 76. Network diagram of all studies included in analysis by intervention. Remission in those randomised.



Without the use of a class network CBT group (under 15 sessions), CBT individual (15 sessions or over), Progressive muscle relaxation group and Progressive muscle relaxation individual would be disconnected from the rest of the network and would have to be excluded from the analysis.

Figure 77. Network diagram of all studies included in analysis by class. Remission in those randomised.

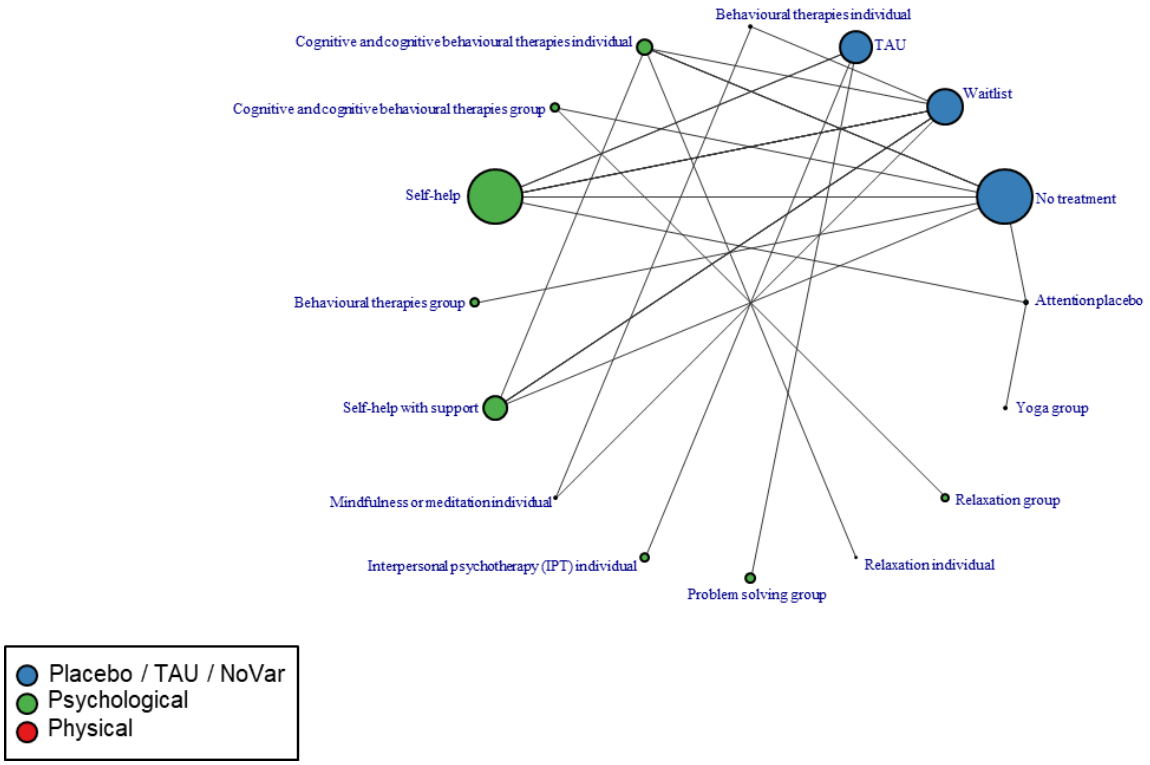
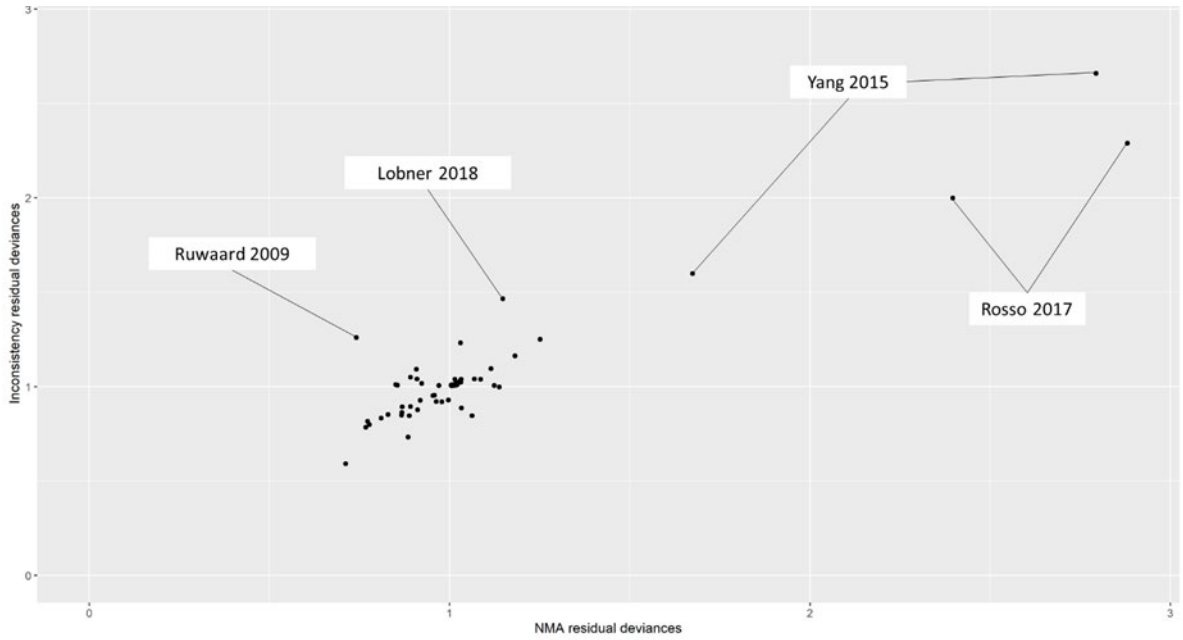


Figure 78. Deviance plot. Remission in those randomised.



The only intervention for which there is evidence of an increased odds of remission compared to TAU is Problem solving group (OR: 28.79; 95%CrI: 7.32, 117.92) (supplement B5, Figure 4.7 in appendix 4). The high efficacy shown here was driven by results from one study (Vazquez 2013/Otero 2015/Lopez 2020) with 173 participants randomised. Problem solving group is the only intervention in its class, which explains why this is also the only class for which there is evidence of increased odds of remission compared to TAU (supplement B5, Figure 4.8 in appendix 4). There was no evidence that any intervention or class had a decreased odds of remission compared to TAU.

Problem solving group is the highest ranked class at 1st (95% CrI 1st to 5th) (Table 116). The highest ranked intervention, Problem solving group (1st, 95% CrI 1st to 5th), is the only treatment within this class (Excel file in supplement B6: *"Depression NMA less severe REMISitt.xlsx"*, *"Ranks"* worksheet). The lowest ranked class is Relaxation individual (15th, 95% CrI 5th to 15th), and the lowest ranked intervention is Progressive muscle relaxation individual (24th, 95% CrI 9th to 24th), which is the only intervention in the Relaxation individual class.

Table 116. Posterior mean and median rank and 95% credible intervals by class. Remission in those randomised.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Problem solving group	1.6	1 (1, 5)
Yoga group	4.6	3 (1, 14)
Cognitive and cognitive behavioural therapies individual	5.4	5 (2, 11)
Behavioural therapies individual	5.5	4 (1, 13)
Self-help with support	5.7	6 (2, 10)
Mindfulness or meditation individual	6.6	6 (2, 14)
Cognitive and cognitive behavioural therapies group	7	7 (2, 13)
Behavioural therapies group	7.5	7 (2, 14)
Self-help	7.7	8 (4, 11)
Interpersonal psychotherapy (IPT) individual	9.8	10 (3, 15)
TAU	10.3	10 (5, 14)
Relaxation group	10.5	12 (2, 15)

Outcome: Response in completers

As mentioned in the methods section, this analysis included trials reporting three types of data:

a) Number of individuals responding to treatment in each arm of each study, out of the total number of individuals, defined as those improving by more than a certain percentage from baseline

b) Mean change from baseline (CFB), the standard deviation in CFB and the total number of individuals in that arm

c) Baseline and endpoint means, standard deviations, and number of individuals, for each arm of the study

The response analysis was first carried out only in those who completed treatment, using WinBUGS code given in supplement B5, appendix 1. After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 12 trials reported response. Out of the remaining studies, 8 reported change from baseline in completers (but not response) and 56 reported baseline and final scores in completers (but not response or change from baseline). This meant that 76 trials of 56 interventions and 27 classes were included in the analysis for this outcome (Table 117, Figure 79, Figure 80).

Although posterior mean residual deviances were very similar between the random-effects NMA consistency model and the inconsistency model, between-study heterogeneity was considerably lower in the inconsistency model, and prediction of some data points was substantially improved in the inconsistency model (supplement B5, Table 3.5 in appendix 3; Figure 81). These were strongly suggestive of inconsistency, particularly in 4 studies

comparing Waitlist, No treatment, Behavioural activation (BA) group and CBT group (under 15 sessions) (Zemestani 2016, Yang 2018, Gordon 1987, Zemstani 2017).

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The bias parameter for comparisons with active versus control or counselling treatments was estimated to be 0.66 (95%CrI -0.95, 2.35). The between study heterogeneity was substantially reduced (supplement B5, Table 3.5 in appendix 3), though it had a wide 95%CrI, and the prediction of data points improved such that these were similar between the bias-adjusted consistency NMA and the inconsistency model. This suggests that heterogeneity and inconsistency could be explained by small study effects. However, the residual deviance and DIC were similar between the base-case and bias-adjusted models, and for this reason the base-case model was selected. Results are therefore based on the random-effects consistency NMA model. Results from the base-case unadjusted model and from the bias-adjusted model can be found in Excel files in supplement B6 (*"Depression NMA less severe RESPcompleters base-case.xlsx" and "Depression NMA less severe RESPcompleters bias-adjusted.xlsx"*, respectively).

High between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.96\ (95\%\ CrI\ 0.71\ to\ 1.28)$). Waitlist was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.9 & 4.10 in appendix 4).

Table 117. Interventions, classes and number of patients (N) included in response in completers analysis.

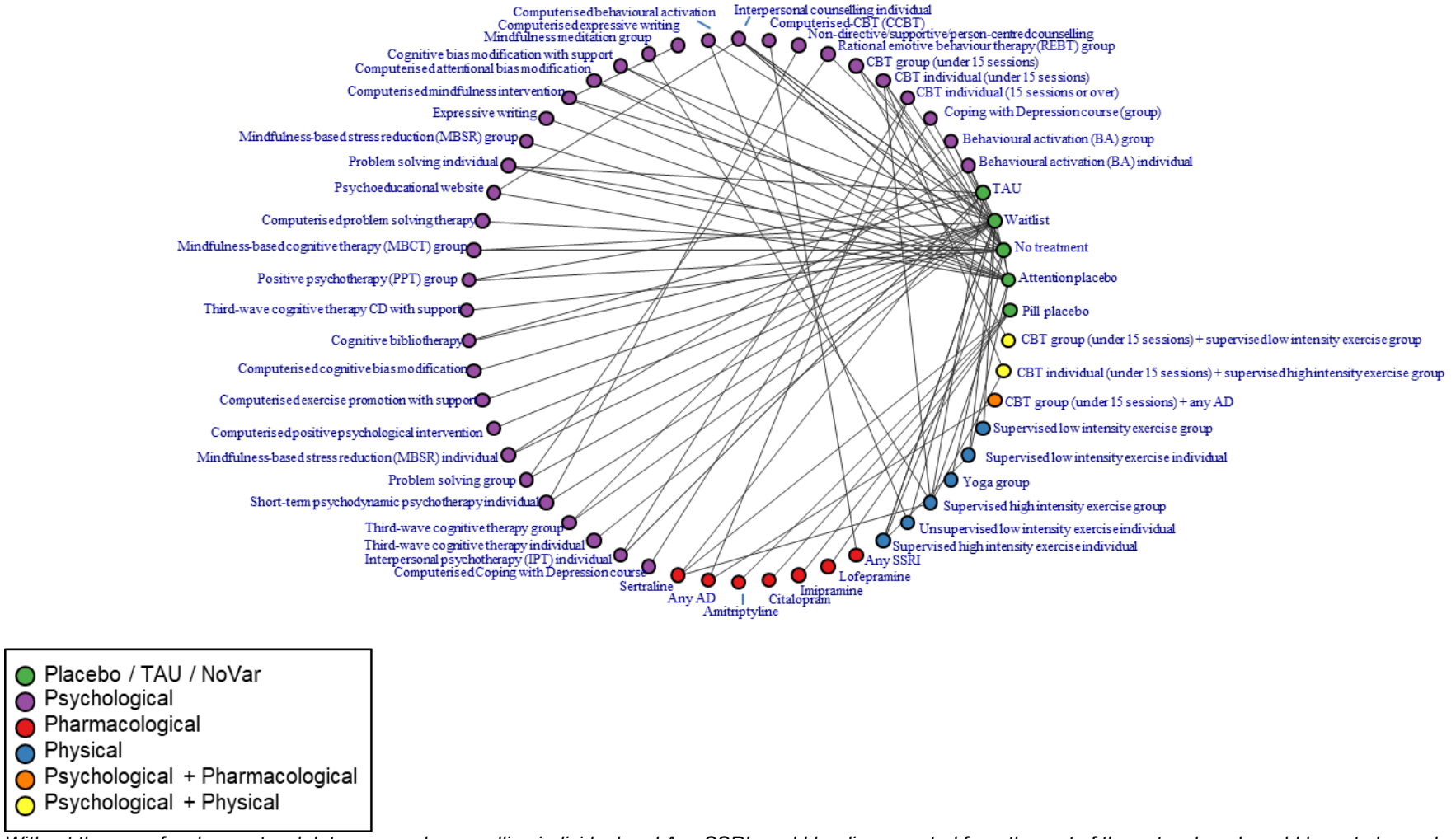
	Intervention	N	Class		N	Variance Sharing*
1	Waitlist	772	Waitlist	1	772	
2	Pill placebo	219	Placebo	2	219	
3	Attention placebo	417	Attention placebo	3	417	
4	No treatment	1033	No treatment	4	1033	
5	TAU	395	TAU	5	395	
6	Behavioural activation (BA) individual	111	Behavioural therapies individual	6	111	1
7	Behavioural activation (BA) group	47	Behavioural therapies group	7	171	1
8	Coping with Depression course (group)	124				
9	CBT individual (15 sessions or over)	68	Cognitive and cognitive behavioural therapies individual	8	361	1
10	CBT individual (under 15 sessions)	233				
11	Third-wave cognitive therapy individual	60				
12	CBT group (under 15 sessions)	59	Cognitive and cognitive behavioural therapies group	9	164	1
13	Positive psychotherapy (PPT) group	76				
14	Rational emotive behaviour therapy (REBT) group	14				
15	Third-wave cognitive therapy group	15				

16	Problem solving individual	98	Problem solving individual	10	98	1
17	Problem solving group	15	Problem solving group	11	15	1
18	Non-directive/supportive/person-centred counselling	39	Counselling individual	12	39	1
19	Interpersonal counselling individual	17	Interpersonal psychotherapy (IPT) individual	13	142	1
20	Interpersonal psychotherapy (IPT) individual	125				
21	Cognitive bibliotherapy	137	Self-help	14	1508	2
22	Computerised-CBT (CCBT)	607				
23	Computerised attentional bias modification	76				
24	Computerised behavioural activation	122				
25	Computerised cognitive bias modification	20				
26	Computerised Coping with Depression course	67				
27	Computerised expressive writing	36				
28	Computerised mindfulness intervention	174				
29	Computerised positive psychological intervention	95				
30	Computerised problem solving therapy	25				
31	Expressive writing	13				
32	Psychoeducational website	136				
33	Cognitive bias modification with support	20	Self-help with support	15	327	3
34	Computerised exercise promotion with support	24				
35	Third-wave cognitive therapy CD with support	283				
36	Short-term psychodynamic psychotherapy individual	43	Short-term psychodynamic psychotherapies individual	16	43	1
37	Mindfulness-based stress reduction (MBSR) individual	18	Mindfulness or meditation individual	17	18	1
38	Mindfulness-based cognitive therapy (MBCT) group	73	Mindfulness or meditation group	18	179	1
39	Mindfulness-based stress reduction (MBSR) group	15				
40	Mindfulness meditation group	91				
41	Any SSRI	24	SSRIs	19	98	4
42	Citalopram	24				
43	Sertraline	50				
44	Amitriptyline	62	TCAs	20	146	4
45	Imipramine	61				
46	Lofepramine	23				

47	Any AD	50	Any AD	21	50	4
48	Supervised high intensity exercise individual	43	Exercise individual	22	189	3
49	Supervised low intensity exercise individual	25				
50	Unsupervised low intensity exercise individual	121				
51	Supervised high intensity exercise group	136	Exercise group	23	178	3
52	Supervised low intensity exercise group	42				
53	Yoga group	40	Yoga group	24	40	1
54	CBT group (under 15 sessions) + any AD	32	Cognitive and cognitive behavioural therapies group + AD	25	32	1
55	CBT individual (under 15 sessions) + supervised high intensity exercise group	18	Cognitive and cognitive behavioural therapies individual + exercise group	26	18	1
56	CBT group (under 15 sessions) + supervised low intensity exercise group	25	Cognitive and cognitive behavioural therapies group + exercise group	27	25	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 79: Network diagram of all studies included in analysis by intervention. Response in Completers.



Without the use of a class network Interpersonal counselling individual and Any SSRI would be disconnected from the rest of the network and would have to be excluded from the analysis.

Figure 80. Network diagram of all studies included in analysis by class. Response in Completers.

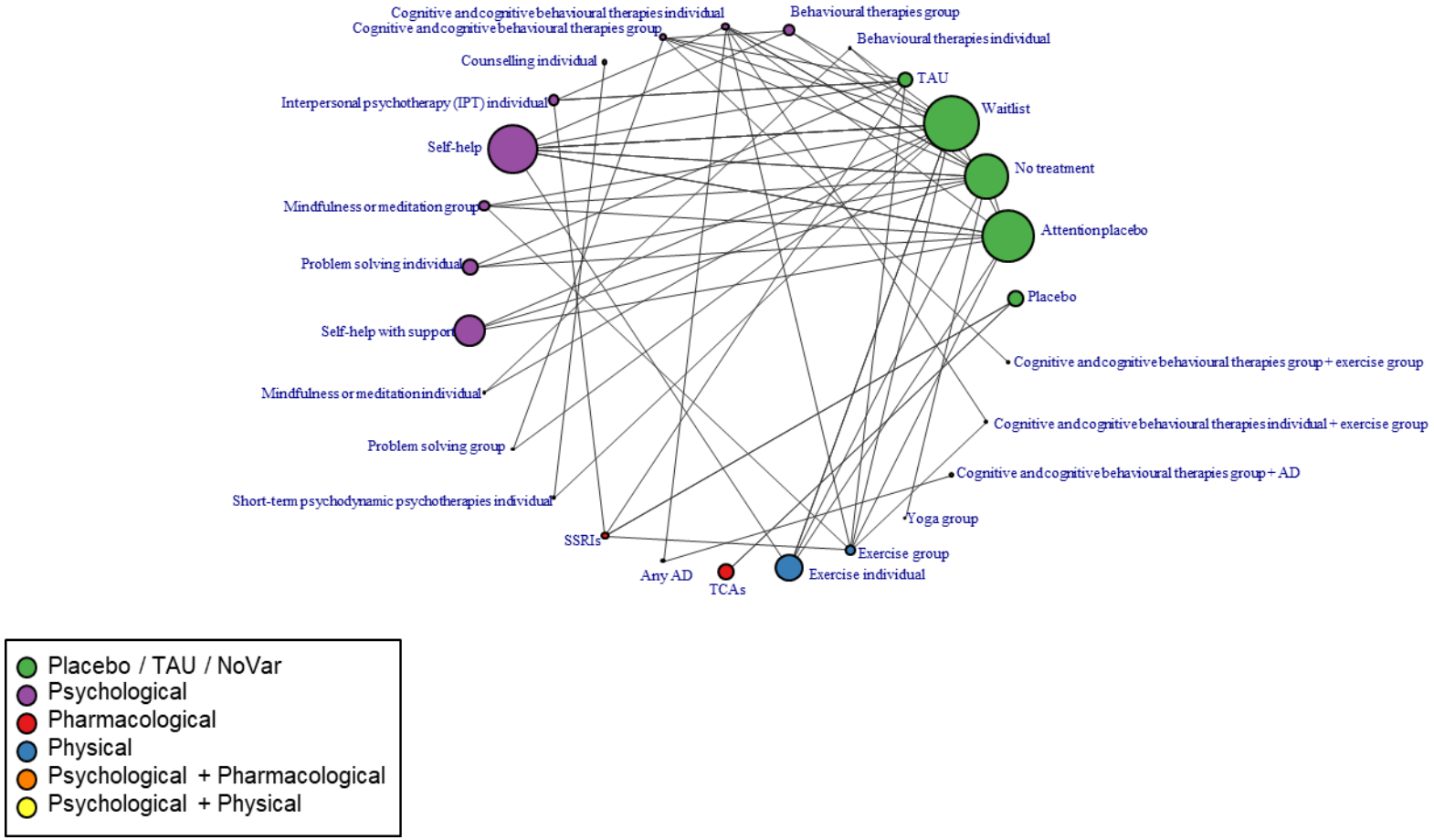
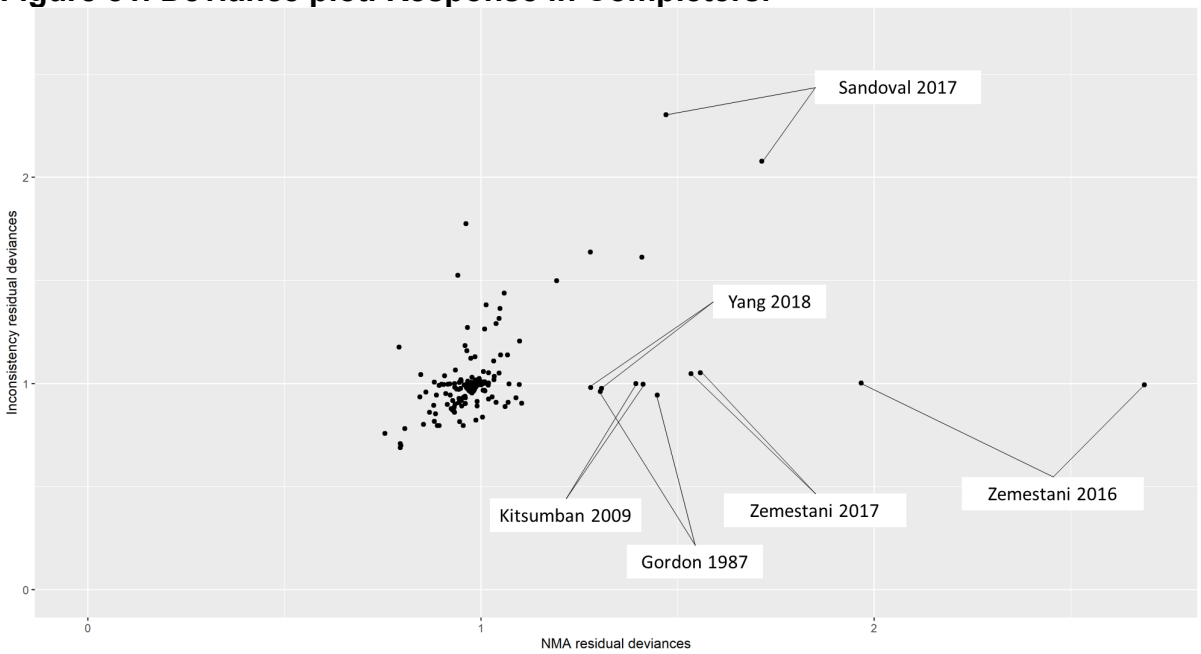


Figure 81. Deviance plot. Response in Completers.



There is evidence of an increased odds of response in completers compared to TAU for the following interventions (supplement B5, Figure 4.9 in appendix 4):

- Amitriptyline
- Behavoural activation (BA) group
- CBT group (under 15 sessions)
- CBT group (under 15 sessions) + supervised low intensity exercise group
- CBT individual (under 15 sessions)
- Imipramine
- Lofepramine
- Mindfulness-based cognitive therapy (MBCT) group
- Mindfulness meditation group
- Pill placebo
- Positive psychotherapy (PPT) group
- Rational emotive behaviour therapy (REBT) group
- Sertraline
- Third-wave cognitive therapy group
- Yoga group

There is no evidence of a reduction in the odds of response for any interventions compared to TAU.

The classes for which there is evidence of an increased odds of response compared to TAU are the following (supplement B5, Figure 4.10 in appendix 4):

- Cognitive and cognitive behavioural therapies group
- Cognitive and cognitive behavioural therapies group + exercise group
- Pill placebo
- TCAs

There is no evidence of any classes having a decreased odds of response compared to TAU. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Cognitive and cognitive behavioural therapies group + exercise group is the highest ranked class with a posterior median rank of 1st (95% CrI 1st to 6th) (Table 118). CBT group (under 15 sessions) + supervised low intensity exercise group is the only intervention in this class, and it is also the highest ranked intervention at 1st (95% CrI 1st to 4th) (Excel file in supplement B6: *"Depression NMA less severe RESPcompleters base-case.xlsx"*, *"Ranks"* worksheet). Cognitive and cognitive behavioural therapies group is the second highest ranked class at 4th (95% CrI 2nd to 12th). The lowest ranked class and intervention is Waitlist, with a posterior median class rank of 24th (95% CrI 20th to 25th) and a posterior median intervention rank of 51st (95% CrI 48th to 52nd). The lowest ranked active class is Problem solving individual at 20th (95% CrI 5th to 25th) (Table 118).

Table 118. Posterior mean and median rank and 95% credible intervals by class. Response in Completers.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Cognitive and cognitive behavioural therapies group + exercise group	1.5	1 (1, 6)
Cognitive and cognitive behavioural therapies group	5	4 (2, 12)
TCAs	6.1	5 (1, 19)
Yoga group	8.1	6 (1, 24)
Placebo	9.2	8 (3, 21)
Behavioural therapies group	9.7	9 (2, 21)
Problem solving group	10.6	9 (2, 25)
SSRIs	11.3	10 (3, 23)
Cognitive and cognitive behavioural therapies group + AD	11.6	10 (1, 25)
Behavioural therapies individual	11.9	11 (2, 24)
Mindfulness or meditation individual	12.2	11 (2, 25)
Cognitive and cognitive behavioural therapies individual	12.4	12 (4, 22)
Mindfulness or meditation group	12.5	12 (4, 22)
Short-term psychodynamic psychotherapies individual	12.9	12 (2, 25)
Interpersonal psychotherapy (IPT) individual	13.9	14 (4, 24)
Exercise group	14.3	14 (6, 23)
Counselling individual	14.6	15 (2, 25)
Exercise individual	15.3	15 (7, 23)
Self-help with support	16.1	16 (7, 24)
Self-help	16.2	16 (10, 21)
Cognitive and cognitive behavioural therapies individual + exercise group	16.3	18 (3, 25)
Problem solving individual	18.7	20 (5, 25)
Attention placebo	20.1	20 (15, 24)
TAU	21.1	21 (15, 25)
Waitlist	23.6	24 (20, 25)

Outcome: Response in those randomised

The response analysis was also carried out in all patients randomized, including those who discontinued treatment, using WinBUGS code given in supplement B5, appendix 1.

After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 11 trials reported response. A continuity correction was applied to data in 1 of these studies containing a zero cell to stabilize the results. From other studies in the dataset, 6 reported change from baseline (but not response) and 58 reported baseline and final scores (but not response or change from baseline). This meant that 75 trials of 53 interventions and 26 classes were included in the analysis for this outcome (Table 119, Figure 82, Figure 83). Any AD, Mindfulness group + AD, Non-directive/supportive/person-centred counselling and Short-term psychodynamic psychotherapy individual were disconnected from the network, so studies comparing these treatments were excluded.

No evidence of inconsistency was identified with the NMA model having a similar posterior mean residual deviance and lower DIC and between study heterogeneity (supplement B5, Table 3.6 in appendix 3). The inconsistency model did not predict the data substantially better for any data points, although both consistency and inconsistency models provided a poor fit for Zemestani 2016, which compared Waitlist, Behavioural activation (BA) group and Third-wave cognitive therapy group (Figure 84). Reported results are therefore based on the random-effects NMA model, assuming consistency. High between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.76\ (95\%\ \text{CrI}\ 0.55\ \text{to}\ 1.01)$). No treatment was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.11 & 4.12 in appendix 4).

Table 119. Interventions, classes and number of patients (N) included in response in those randomised analysis.

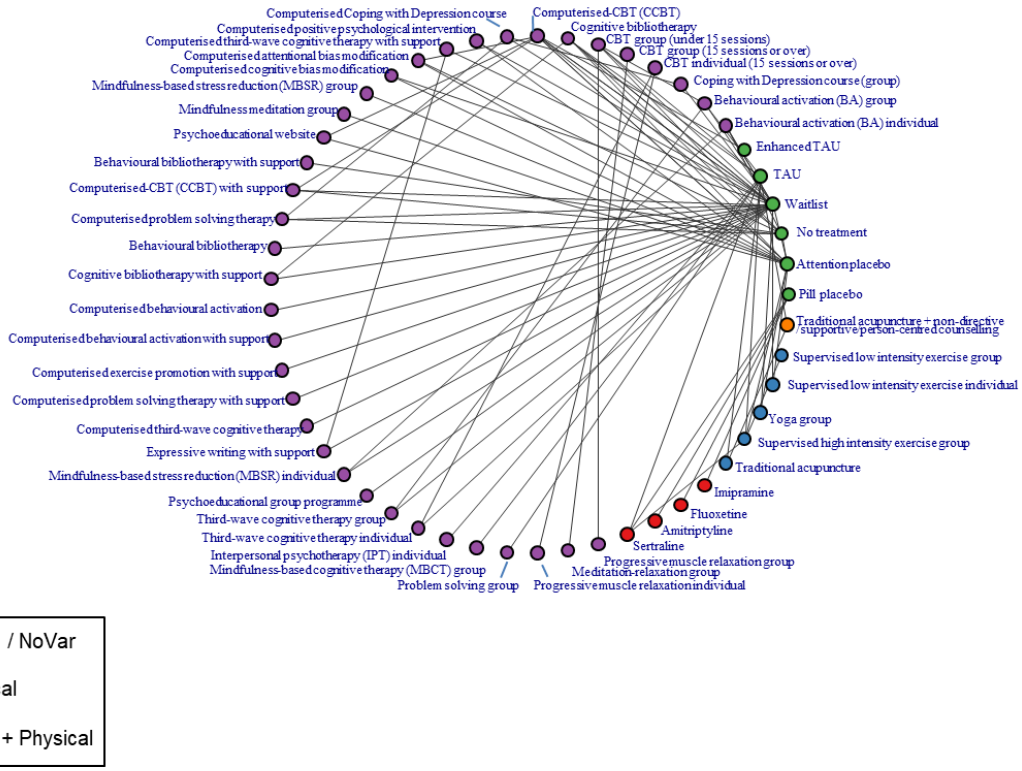
	Intervention	N	Class		N	Variance Sharing*
1	Waitlist	3144	Waitlist	1	3144	
2	Pill placebo	303	Placebo	2	303	
3	Attention placebo	727	Attention placebo	3	727	
4	No treatment	718	No treatment	4	718	
5	TAU	623	TAU	5	623	
6	Enhanced TAU	36	Enhanced TAU	6	36	
7	Behavioural activation (BA) individual	65	Behavioural therapies individual	7	65	1
8	Behavioural activation (BA) group	85	Behavioural therapies group	8	184	1
9	Coping with Depression course (group)	99				
10	CBT individual (15 sessions or over)	56	Cognitive and cognitive behavioural therapies individual	9	121	1
11	Third-wave cognitive therapy individual	65				
12	CBT group (15 sessions or over)	10	Cognitive and cognitive behavioural therapies group	10	341	1
13	CBT group (under 15 sessions)	267				

14	Third-wave cognitive therapy group	64				
15	Problem solving group	89	Problem solving group	11	89	1
16	Interpersonal psychotherapy (IPT) individual	69	Interpersonal psychotherapy (IPT) individual	12	69	1
17	Psychoeducational group programme	22	Psychoeducation group	13	22	1
18	Behavioural bibliotherapy	13	Self-help	14	4373	2
19	Cognitive bibliotherapy	516				
20	Computerised-CBT (CCBT)	2541				
21	Computerised attentional bias modification	181				
22	Computerised behavioural activation	10				
23	Computerised cognitive bias modification	55				
24	Computerised Coping with Depression course	190				
25	Computerised positive psychological intervention	439				
26	Computerised problem solving therapy	232				
27	Computerised third-wave cognitive therapy	31				
28	Psychoeducational website	165				
29	Behavioural bibliotherapy with support	67	Self-help with support	15	849	3
30	Cognitive bibliotherapy with support	125				
31	Computerised-CBT (CCBT) with support	262				
32	Computerised behavioural activation with support	40				
33	Computerised exercise promotion with support	24				
34	Computerised problem solving therapy with support	124				
35	Computerised third-wave cognitive therapy with support	82				
36	Expressive writing with support	125				
37	Mindfulness-based stress reduction (MBSR) individual	20	Mindfulness or meditation individual	16	20	1
38	Meditation-relaxation group	13	Mindfulness or meditation group	17	197	1
39	Mindfulness-based cognitive therapy (MBCT) group	76				
40	Mindfulness-based stress reduction (MBSR) group	70				
41	Mindfulness meditation group	38				
42	Progressive muscle relaxation individual	15	Relaxation individual	18	15	1

43	Progressive muscle relaxation group	63	Relaxation group	19	63	1
44	Fluoxetine	78	SSRIs	20	159	4
45	Sertraline	81				
46	Amitriptyline	90	TCAs	21	163	4
47	Imipramine	73				
48	Traditional acupuncture	40	Acupuncture	22	40	1
49	Supervised low intensity exercise individual	71	Exercise individual	23	71	3
50	Supervised high intensity exercise group	42	Exercise group	24	52	3
51	Supervised low intensity exercise group	10				
52	Yoga group	65	Yoga group	25	65	1
53	Traditional acupuncture + non-directive/supportive/person-centred counselling	40	Acupuncture + counselling individual	26	40	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 82. Network diagram of all studies included in analysis by intervention. Response in those randomised.



Without the use of a class network CBT group (15 sessions or over) and Meditation-relaxation group would be disconnected from the rest of the network and would have to be excluded from the analysis. Any AD, Mindfulness group + AD, Non-directive/supportive/person-centred counselling and Short-term psychodynamic psychotherapy individual were excluded from the NMA as they were disconnected from the network.

Figure 83. Network diagram of all studies included in analysis by class. Response in those randomised.

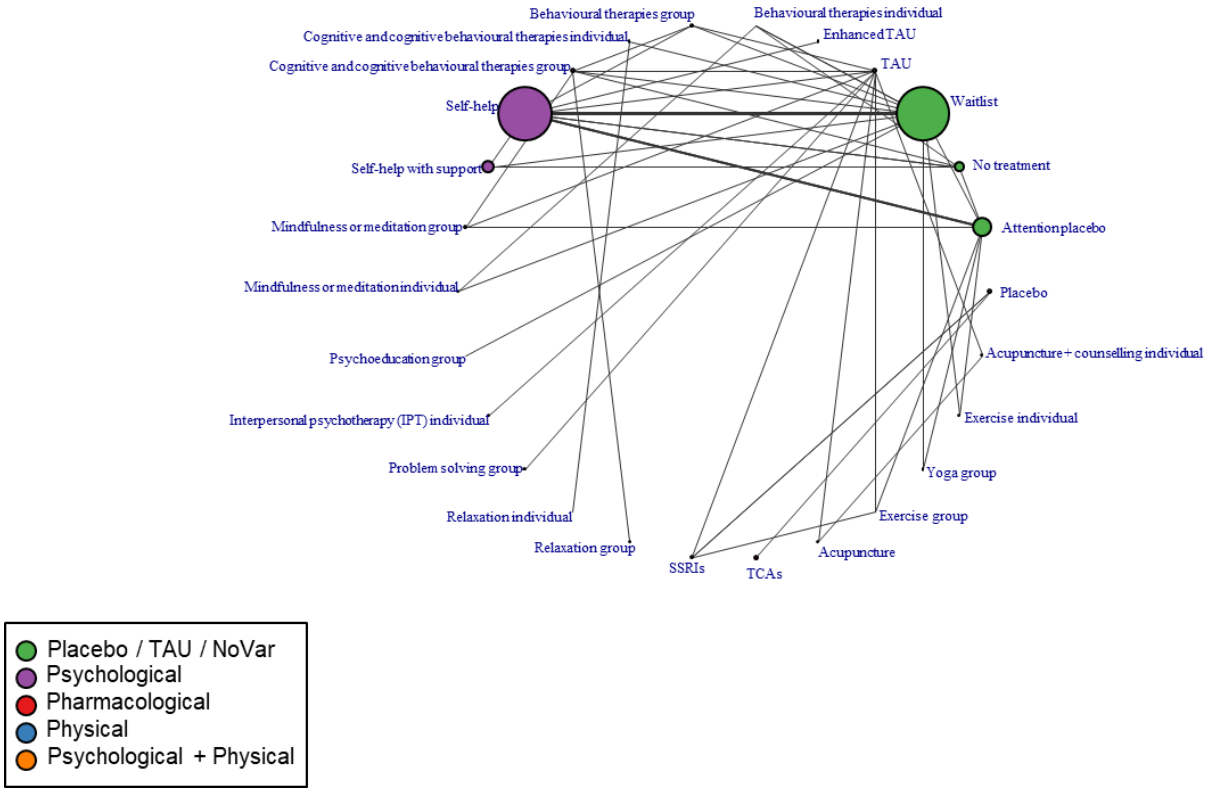
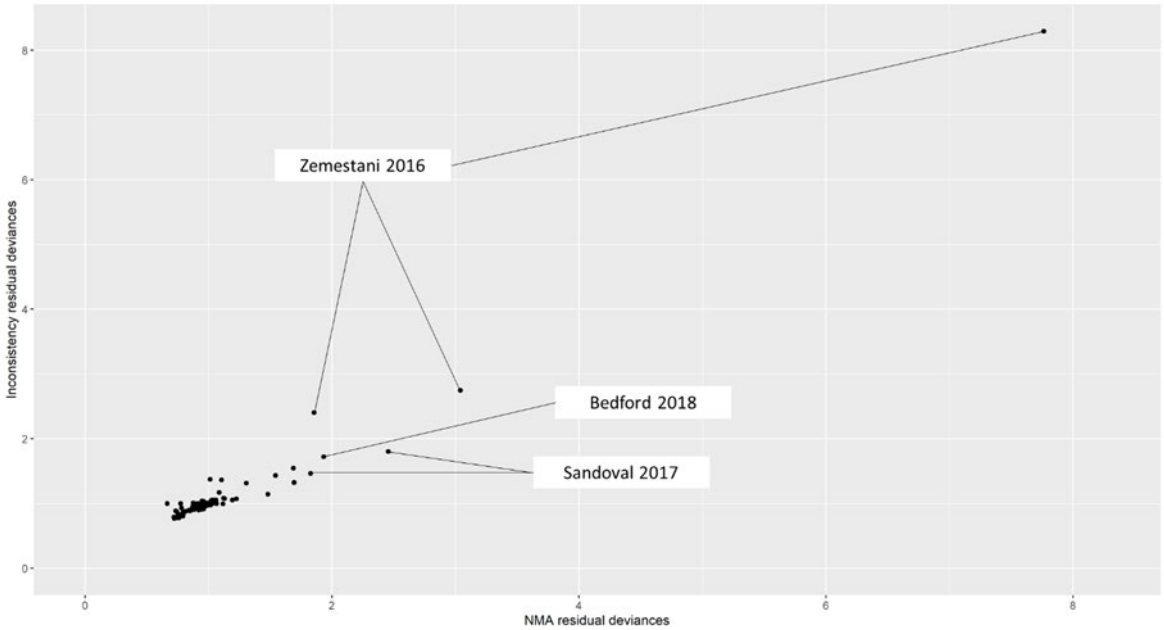


Figure 84. Deviance plot. Response in those randomised.



There is evidence of an increased odds of response compared to TAU for the following interventions (supplement B5, Figure 4.11 in appendix 4):

- Amitriptyline
- Behavioural activation (BA) group
- Behavioural activation (BA) individual
- CBT group (under 15 sessions)

- Fluoxetine
- Imipramine
- Pill placebo
- Problem solving group
- Sertraline
- Supervised high intensity exercise group
- Third-wave cognitive therapy group
- Traditional acupuncture + non-directive/supportive/person-centred counselling

There was no evidence that any interventions had a lower odds of response compared to TAU.

The classes for which there is evidence of an increased odds of response compared to TAU are the following (supplement B5, Figure 4.12 in appendix 4):

- Cognitive and cognitive behavioural therapies group
- Exercise group
- Pill placebo
- Problem solving group
- TCAs

There was no evidence that any class had a lower odds of response compared to TAU. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Whilst there was considerable uncertainty in rankings, TCAs and Problem solving group had the highest posterior median rank (3rd, 95% CrI 1st to 20th and 3rd, 95% CrI 1st to 18th respectively). The highest ranked intervention is Amitryptiline with a posterior median rank of 3rd (95% CrI 1st to 38th) (Excel file in supplement B6: *"Depression NMA less severe RESPitt.xlsx"*, *"Ranks"* worksheet). The lowest ranked classes are Waitlist (22nd, 95% CrI 18th to 25th) and Relaxation individual (25th, 95% CrI 4th to 25th) (Table 120).

Table 120. Posterior mean and median rank and 95% credible intervals by class. Response in those randomised.

Class	Posterior mean rank	Posterior median rank (95% CrI)
TCAs	4.5	3 (1, 20)
Problem solving group	4.9	3 (1, 18)
SSRIs	6.3	5 (1, 21)
Placebo	6.8	5 (2, 19)
Cognitive and cognitive behavioural therapies group	8.3	8 (2, 18)
Behavioural therapies group	8.9	8 (2, 20)
Exercise group	9.3	9 (2, 20)
Acupuncture + counselling individual	10.3	9 (1, 24)
Behavioural therapies individual	10.4	10 (1, 23)
Yoga group	10.5	10 (1, 24)
Acupuncture	10.8	10 (1, 24)
Mindfulness or meditation individual	11.1	10 (1, 24)
Cognitive and cognitive behavioural therapies individual	12.2	12 (1, 24)

Mindfulness or meditation group	12.8	13 (4, 22)
Exercise individual	14.2	14 (5, 23)
Self-help	15.2	15 (10, 19)
Psychoeducation group	15.4	16 (2, 25)
Self-help with support	15.6	16 (10, 21)
Relaxation group	15.9	17 (2, 25)
Interpersonal psychotherapy (IPT) individual	18.5	20 (4, 25)
Attention placebo	19.1	19 (14, 23)
TAU	19.6	20 (14, 24)
Enhanced TAU	21	22 (11, 25)
Relaxation individual	21.5	25 (4, 25)
Waitlist	22.1	22 (18, 25)

Outcome: SMD

As mentioned in the methods section, this analysis also included trials reporting three types of data:

a) Mean change from baseline (CFB), the standard deviation in CFB and the total number of individuals in that arm

b) Baseline and endpoint means, standard deviations, and number of individuals, for each arm of the study

c) Number of individuals responding to treatment in each arm of each study, out of the total number of individuals, defined as those improving by more than a certain percentage from baseline

This analysis was carried out on all patients randomized where possible, using WinBUGS code given in supplement B5, appendix 1. However, if trials only reported the number of completers then these were also included. After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 10 trials reported CFB. Out of the remaining studies, 115 reported baseline and follow-up scores (but not CFB) and 2 reported response (but not CFB or baseline and follow-up). This meant that 127 trials of 76 interventions and 34 classes were included in the analysis for this outcome (Table 121,

Figure 85, Figure 86). Although for other outcomes Interpersonal counselling + AD was incorrectly included in the class of Counselling + AD, for SMD (both less severe and more severe) this intervention was correctly coded in Interpersonal psychotherapy (IPT) individual + AD. Results are therefore shown here for the correct class coding. A post-hoc sensitivity analysis was conducted to assess the impact of this in more severe SMD (Sensitivity analyses: post-hoc).

No evidence of inconsistency was identified with the NMA model having a slightly lower DIC, and similar between study heterogeneity (supplement B5, Table 3.7 in appendix 3). The inconsistency model did not predict the data substantially better for any data points (Figure 87). Between study heterogeneity was lower in the bias-adjusted model that accounted for small study effects (performed as a prespecified sensitivity analysis) (supplement B5, Table 3.7 in appendix 3). The negative bias parameter (-2.96; 95%CrI: -5.11 to -0.91) indicated that smaller studies had larger effects favouring active interventions versus control interventions or counselling. Reported results are therefore based on the bias-adjusted random-effects NMA model, assuming consistency. Results from the bias-adjusted model and from the base-case unadjusted model can be found in Excel files in supplement B6 ((*"Depression NMA less severe SMD bias-adjusted.xlsx"* and *"Depression NMA less severe SMD base-case.xlsx"*, respectively).

Moderate between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.23$ (95% CrI 0.10 to 0.47)). Attention placebo was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.13 & 4.14 in appendix 4).

Table 121. Interventions, classes and number of patients (N) included in SMD analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Attention placebo	935	Attention placebo	1	935	
2	Pill placebo	301	Placebo	2	301	
3	No treatment	1478	No treatment	3	1478	
4	Waitlist	3555	Waitlist	4	3555	
5	TAU	815	TAU	5	815	
6	Enhanced TAU	36	Enhanced TAU	6	36	
7	Behavioural activation (BA) individual	147	Behavioural therapies individual	7	147	1
8	Behavioural activation (BA) group	117	Behavioural therapies group	8	340	1
9	Coping with Depression course (group)	223				
10	CBT individual (15 sessions or over)	123	Cognitive and cognitive behavioural therapies individual	9	481	1
11	CBT individual (under 15 sessions)	233				
12	Third-wave cognitive therapy individual	125				
13	CBT group (15 sessions or over)	10	Cognitive and cognitive behavioural therapies group	10	480	2
14	CBT group (under 15 sessions)	316				

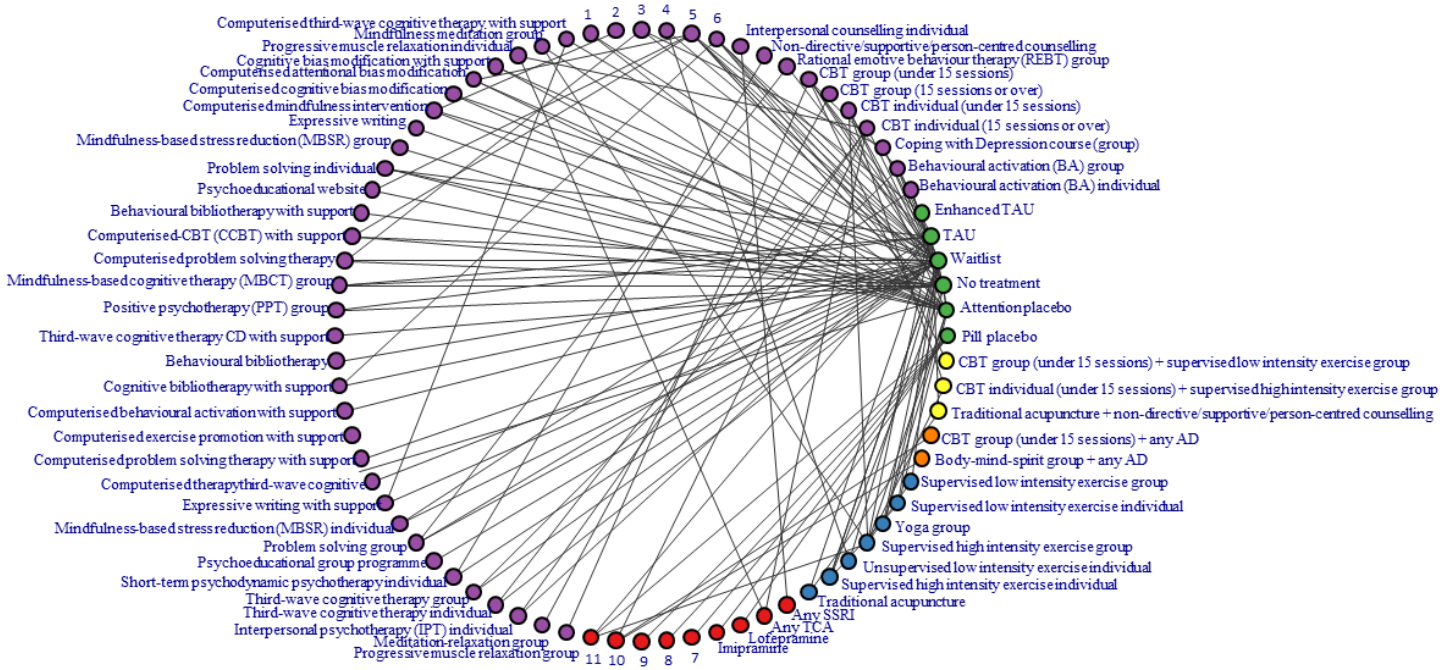
15	Positive psychotherapy (PPT) group	76				
16	Rational emotive behaviour therapy (REBT) group	14				
17	Third-wave cognitive therapy group	64				
18	Problem solving individual	98	Problem solving individual	11	98	1
19	Problem solving group	104	Problem solving group	12	104	1
20	Non-directive/supportive/person-centred counselling	55	Counselling individual	13	55	1
21	Interpersonal counselling individual	17	Interpersonal psychotherapy (IPT) individual	14	153	1
22	Interpersonal psychotherapy (IPT) individual	136				
23	Psychoeducational group programme	22	Psychoeducation group	15	22	1
24	Behavioural bibliotherapy	13	Self-help	16	4922	3
25	Cognitive bibliotherapy	516				
26	Computerised-CBT (CCBT)	2619				
27	Computerised attentional bias modification	230				
28	Computerised behavioural activation	122				
29	Computerised cognitive bias modification	75				
30	Computerised Coping with Depression course	257				
31	Computerised expressive writing	36				
32	Computerised mindfulness intervention	174				
33	Computerised positive psychological intervention	439				
34	Computerised problem solving therapy	232				
35	Computerised third-wave cognitive therapy	31				
36	Expressive writing	13				
37	Psychoeducational website	165				
38	Behavioural bibliotherapy with support	67	Self-help with support	17	1286	4
39	Cognitive bias modification with support	20				
40	Cognitive bibliotherapy with support	125				
41	Computerised-CBT (CCBT) with support	396				
42	Computerised behavioural activation with support	40				

43	Computerised exercise promotion with support	24				
44	Computerised problem solving therapy with support	124				
45	Computerised third-wave cognitive therapy with support	82				
46	Expressive writing with support	125				
47	Third-wave cognitive therapy CD with support	283				
48	Short-term psychodynamic psychotherapy individual	49	Short-term psychodynamic psychotherapies individual	18	49	1
49	Mindfulness-based stress reduction (MBSR) individual	20	Mindfulness or meditation individual	19	20	1
50	Meditation-relaxation group	13	Mindfulness or meditation group	20	376	5
51	Mindfulness-based cognitive therapy (MBCT) group	149				
52	Mindfulness-based stress reduction (MBSR) group	85				
53	Mindfulness meditation group	129				
54	Progressive muscle relaxation individual	13	Relaxation individual	21	13	1
55	Progressive muscle relaxation group	63	Relaxation group	22	63	2
56	Any SSRI	24	SSRIs	23	207	6
57	Citalopram	24				
58	Fluoxetine	78				
59	Sertraline	81				
60	Amitriptyline	67	TCAs	24	136	6
61	Any TCA	10				
62	Imipramine	36				
63	Lofepramine	23				
64	Any AD	65	Any AD	25	65	6
65	Traditional acupuncture	40	Acupuncture	26	40	1
66	Supervised high intensity exercise individual	43	Exercise individual	27	250	7
67	Supervised low intensity exercise individual	86				
68	Unsupervised low intensity exercise individual	121				
69	Supervised high intensity exercise group	147	Exercise group	28	199	8
70	Supervised low intensity exercise group	52				
71	Yoga group	73	Yoga group	29	73	2
72	CBT group (under 15 sessions) + any AD	32	Cognitive and cognitive behavioural therapies group + AD	30	32	1
73	Body-mind-spirit group + any AD	15	Mindfulness or meditation group + AD	31	15	1

74	Traditional acupuncture + non-directive/supportive/person-centred counselling	40	Acupuncture + counselling individual	32	40	1
75	CBT individual (under 15 sessions) + supervised high intensity exercise group	18	Cognitive and cognitive behavioural therapies individual + exercise group	33	18	1
76	CBT group (under 15 sessions) + supervised low intensity exercise group	25	Cognitive and cognitive behavioural therapies group + exercise group	34	25	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 85. Network diagram of all studies included in analysis by intervention. SMD.



1 Computerised positive psychological intervention; 2 Computerised expressive writing; 3 Computerised Coping with Depression course; 4 Computerised behavioural activation; 5 Computerised-CBT (CCBT); 6 Cognitive bibliotherapy; 7 Fluoxetine; 8 Citalopram; 9 Amitriptyline; 10 Any AD; 11 Sertraline
Without the use of a class network CBT group (15 sessions or over), Interpersonal counselling individual, Meditation-relaxation group and Any SSRI would be disconnected from the rest of the network and would have to be excluded from the analysis.

Figure 86. Network diagram of all studies included in analysis by class. SMD.

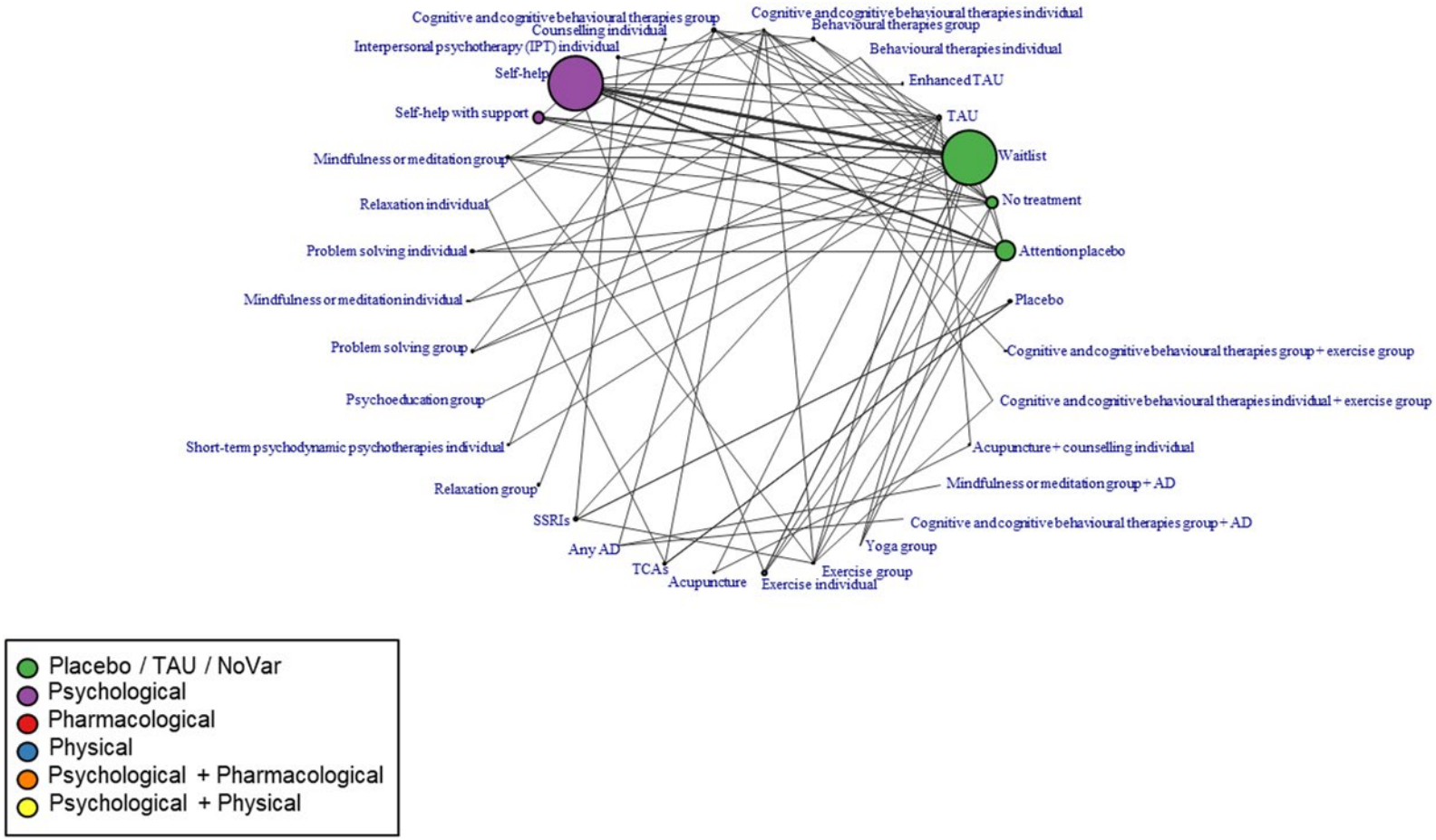
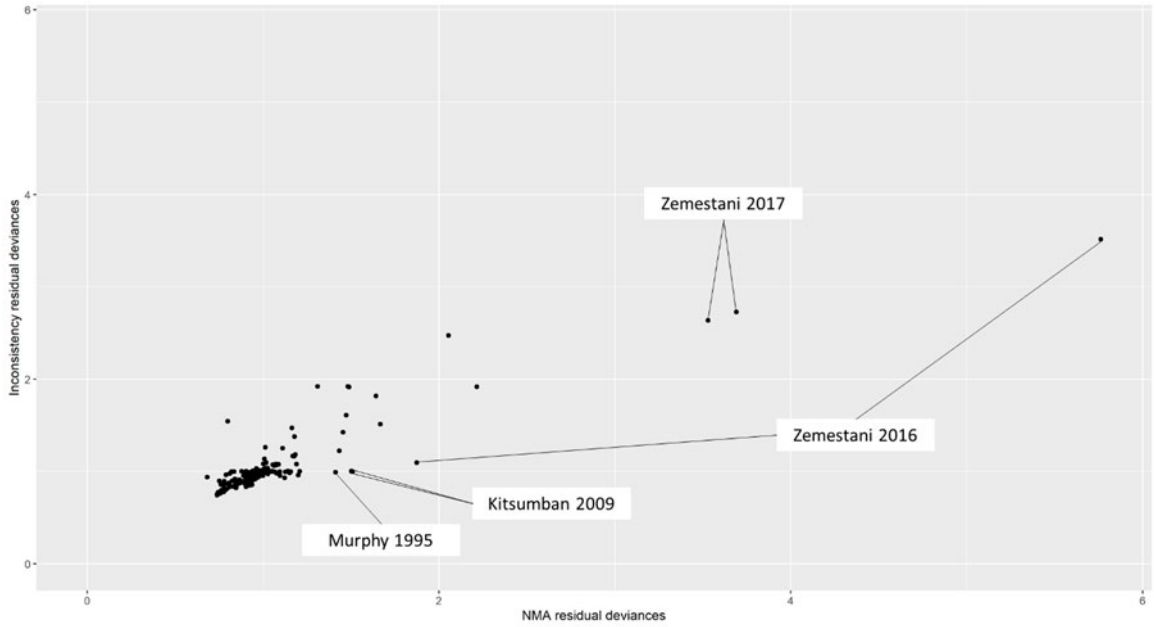


Figure 87. Deviance plot. SMD.



There is evidence of a decreased SMD in depression (lower SMD corresponds to improved outcomes) compared to TAU for the following interventions (supplement B5, Figure 4.13 in appendix 4):

- Behavioural activation (BA) group
- CBT group (under 15 sessions)
- CBT group (under 15 sessions) + supervised low intensity exercise group
- CBT individual (15 sessions or over)
- Meditation-relaxation group
- Mindfulness-based cognitive therapy (MBCT) group
- Mindfulness mediation group
- Positive psychotherapy (PPT) group
- Problem solving group
- Third-wave cognitive therapy CD with support
- Third-wave cognitive therapy group
- Third-wave cognitive therapy individual
- Traditional acupuncture + non-directive/supportive/person-centred counselling

There was no evidence that any interventions have a higher SMD compared to TAU.

The classes for which there is clear evidence suggesting a lower SMD in depression compared to TAU are the following (supplement B5, Figure 4.14 in appendix 4):

- Cognitive and cognitive behavioural therapies group
- Cognitive and cognitive behavioural therapies group + exercise group.

However, there is also some evidence to suggest lower SMD compared to TAU in Cognitive and cognitive behavioural therapies individual, Self-help and Self-help with support.

The only class for which there was some evidence of a higher standardized mean difference compared to TAU is Waitlist. For many classes, effects were more uncertain than at the

intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Cognitive and cognitive behavioural therapies group + exercise group is the highest ranked class with a posterior median rank of 2nd (95% CrI 1st to 14th). This class contained only one intervention, CBT group (under 15 sessions) + supervised low intensity exercise group, which was also the highest ranked intervention (1st, 95% CrI 1st to 6th). The lowest ranked intervention is Waitlist at 44th (95% CrI 42nd to 44th) (Excel file in supplement B6: *"Depression NMA less severe SMD bias-adjusted.xlsx"*, *"Ranks"* worksheet). The lowest ranked class is Waitlist, with a posterior median rank of 27th (95% CrI 21st to 31st), and the lowest ranked active class is Problem solving individual (27th, 95% CrI 6th to 32nd) (Table 122).

Table 122. Posterior mean and median rank and 95% credible intervals by class. SMD.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Cognitive and cognitive behavioural therapies group + exercise group	2.919	2 (1, 14)
Problem solving group	6.607	5 (1, 26)
Cognitive and cognitive behavioural therapies group	9.553	9 (3, 22)
Mindfulness or meditation group + AD	12.22	7 (1, 32)
Behavioural therapies group	13.09	12 (3, 28)
Cognitive and cognitive behavioural therapies individual	13.14	12 (4, 27)
TCAs	13.27	12 (3, 29)
Cognitive and cognitive behavioural therapies group + AD	13.34	9 (1, 32)
Acupuncture + counselling individual	13.37	12 (2, 31)
Yoga group	13.83	12 (2, 31)
Acupuncture	14.26	13 (2, 31)
Mindfulness or meditation group	14.47	14 (4, 28)
Behavioural therapies individual	14.72	13 (2, 31)
Placebo	15.09	14 (4, 29)
SSRIs	15.9	15 (4, 30)
Mindfulness or meditation individual	16.09	14 (1, 32)
Short-term psychodynamic psychotherapies individual	16.49	15 (2, 32)
Interpersonal psychotherapy (IPT) individual	16.93	17 (4, 30)
Relaxation group	17.84	18 (3, 32)
Exercise group	17.91	18 (1, 32)
Self-help with support	18.22	18 (11, 25)
Relaxation individual	18.39	19 (1, 32)
Counselling individual	19.2	21 (2, 32)
Exercise individual	19.43	20 (4, 31)
Self-help	19.51	20 (13, 25)
Cognitive and cognitive behavioural therapies individual + exercise group	19.78	22 (2, 32)
Psychoeducation group	20.8	23 (3, 32)
Attention placebo	21.52	22 (14, 28)
Problem solving individual	24.28	27 (6, 32)
TAU	24.35	25 (18, 30)
Enhanced TAU	24.9	26 (11, 32)

Waitlist	26.56	27 (21, 31)

Results for adults with a new episode of more severe depression

Outcome: Discontinuation (for any reason)

This analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients randomized. After excluding trials with zero events in all arms and trials with the number events equal to the denominator, 402 trials of 74 interventions and 39 classes were included for this outcome (Table 123, methods, under 'Class models'

Figure 88,

Figure 89). A continuity correction was applied to data in 2 studies containing at least one zero cell to stabilize the results.

Although there was lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, the between-study heterogeneity was lower in the inconsistency model (supplement B5, Table 3.8. in appendix 3). The prediction of individual studies was similar in both models, apart from for one study (Sun 2013) (Figure 90). This was for a zero arm to which a continuity correction had been added.

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The bias parameter for comparisons with active versus control or counselling treatments was estimated to be -0.35 (95%CrI -0.76, 0.04). The between study heterogeneity was slightly reduced and the DIC was lower than in the base-case consistency model (supplement B5, Table 3.8 in appendix 3). Further details are given under '*Sensitivity Analyses*'. Results from the bias-adjusted model and from the unadjusted base-case consistency model can be found in Excel files in supplement B6 ("*Depression NMA more severe DISCONany bias-adjusted.xlsx*" and *"Depression NMA more severe DISCONany base-case.xlsx"*, respectively).

Reported results are based on the bias-adjusted random effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.28\ (95\%\ \mathrm{CrI}\ 0.22\ \mathrm{to}\ 0.33)$). Pill placebo was used as the network reference treatment, and reported relative effects are presented compared to this (supplement B5, Figures 5.1 & 5.2 in appendix 5).

Table 123. Interventions, classes and number of patients (N) included in Discontinuation (for any reason) analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	16577	Placebo	1	16577	
2	Attention placebo	36	Attention placebo	2	36	
3	No treatment	764	No treatment	3	764	
4	Waitlist	580	Waitlist	4	580	
5	TAU	266	TAU	5	266	
6	Enhanced TAU	37	Enhanced TAU	6	37	
7	Mirtazapine	2637	Mirtazapine	7	2637	
8	Trazodone	1430	Trazodone	8	1430	
9	Behavioural activation (BA) individual	595	Behavioural therapies individual	9	595	1
10	Behavioural activation (BA) group	15	Behavioural therapies group	10	46	1
11	Coping with Depression course (group)	31				
12	CBT individual (15 sessions or over)	461	Cognitive and cognitive behavioural therapies individual	11	771	1
13	CBT individual (under 15 sessions)	287				
14	Third-wave cognitive therapy individual	23				
15	CBT group (under 15 sessions)	162	Cognitive and cognitive behavioural therapies group	12	162	1

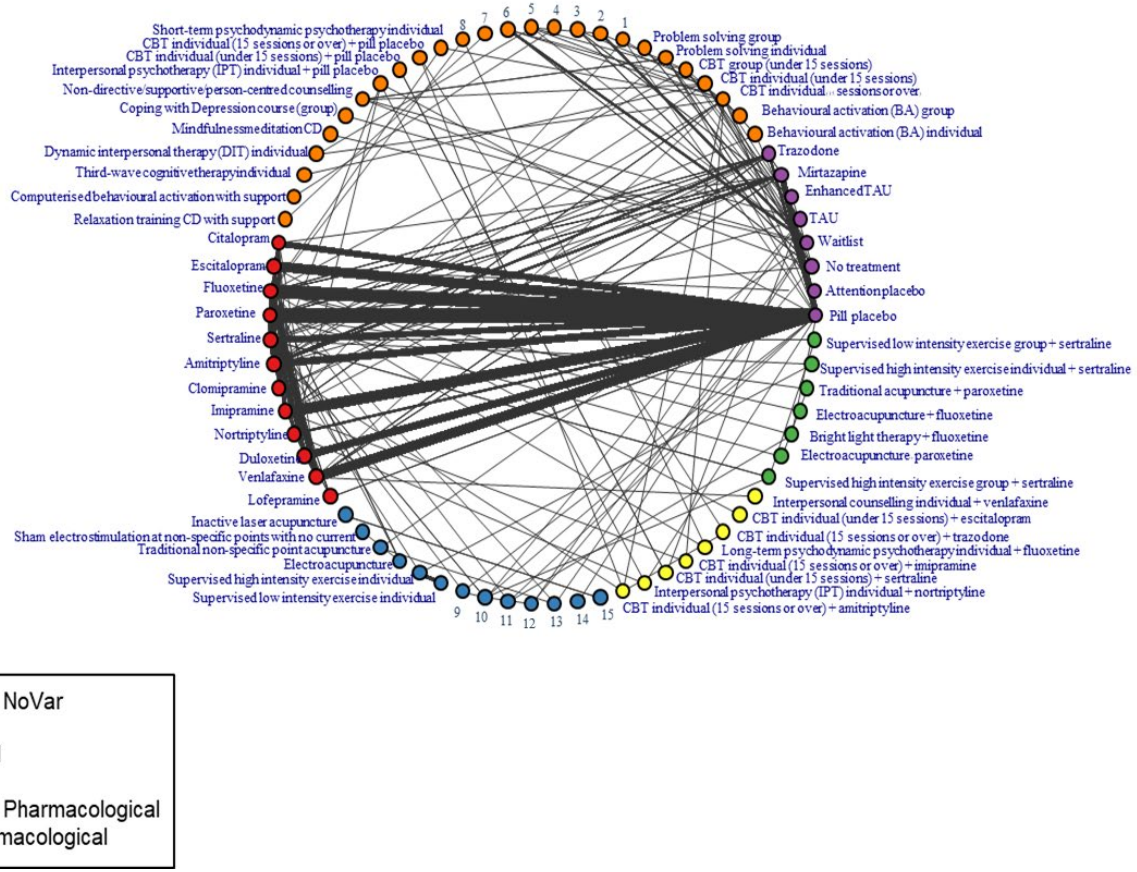
16	Problem solving individual	448	Problem solving individual	13	448	1
17	Problem solving group	58	Problem solving group	14	58	1
18	Non-directive/supportive/person-centred counselling	332	Counselling individual	15	332	1
19	Interpersonal psychotherapy (IPT) individual	63	Interpersonal psychotherapy (IPT) individual	16	63	1
20	Cognitive bibliotherapy	169	Self-help	17	477	2
21	Computerised-CBT (CCBT)	115				
22	Mindfulness meditation CD	39				
23	Psychoeducational website	154				
24	Cognitive bibliotherapy with support	67	Self-help with support	18	556	3
25	Computerised-CBT (CCBT) with support	290				
26	Computerised behavioural activation with support	159				
27	Mindfulness meditation CD with support	20				
28	Relaxation training CD with support	20				
29	Long-term psychodynamic psychotherapy individual	90	Long-term psychodynamic psychotherapies individual	19	90	1
30	Dynamic interpersonal therapy (DIT) individual	73	Short-term psychodynamic psychotherapies individual	20	129	1
31	Short-term psychodynamic psychotherapy individual	56				
32	CBT individual (15 sessions or over) + pill placebo	14	Cognitive and cognitive behavioural therapies individual + placebo	21	97	1
33	CBT individual (under 15 sessions) + pill placebo	83				
34	Interpersonal psychotherapy (IPT) individual + pill placebo	48	Interpersonal psychotherapy (IPT) individual + placebo	22	48	1
35	Citalopram	3523	SSRIs	23	28464	4
36	Escitalopram	5627				
37	Fluoxetine	7766				
38	Paroxetine	8362				
39	Sertraline	3186				
40	Amitriptyline	3778	TCAs	24	7782	5
41	Clomipramine	601				
42	Imipramine	2585				

43	Lofepramine	296				
44	Nortriptyline	522				
45	Duloxetine	5226	SNRIs	25	10251	4
46	Venlafaxine	5025				
47	Inactive laser acupuncture	36	Sham acupuncture	26	117	1
48	Sham electrostimulation at non-specific points with no current	29				
49	Traditional non-specific point acupuncture	52				
50	Electroacupuncture	112	Acupuncture	27	255	1
51	Laser acupuncture	41				
52	Traditional acupuncture	102				
53	Supervised high intensity exercise individual	162	Exercise individual	28	336	3
54	Supervised low intensity exercise individual	121				
55	Unsupervised high intensity exercise individual	53				
56	Supervised high intensity exercise group	124	Exercise group	29	167	3
57	Supervised low intensity exercise group	43				
58	Yoga group	30	Yoga group	30	30	1
59	Bright light therapy	32	Light therapy	31	32	1
60	CBT individual (15 sessions or over) + amitriptyline	50	Cognitive and cognitive behavioural therapies individual + AD	32	246	6
61	CBT individual (15 sessions or over) + imipramine	25				
62	CBT individual (15 sessions or over) + trazodone	11				
63	CBT individual (under 15 sessions) + escitalopram	52				
64	CBT individual (under 15 sessions) + sertraline	108				
65	Long-term psychodynamic psychotherapy individual + fluoxetine	91	Long-term psychodynamic psychotherapy individual + AD	33	91	6
66	Interpersonal psychotherapy (IPT) individual + nortriptyline	16	Interpersonal psychotherapy (IPT) individual + AD	34	16	6
67	Interpersonal counselling individual + venlafaxine	13	Counselling individual + AD	35	13	6
68	Supervised high intensity exercise individual + sertraline	84	Exercise individual + AD	36	84	6
69	Supervised high intensity exercise group + sertraline	97	Exercise group + AD	37	134	6
70	Supervised low intensity exercise group + sertraline	37				
71	Electroacupuncture + fluoxetine	48	Acupuncture + AD	38	160	1

72	Electroacupuncture + paroxetine	58				
73	Traditional acupuncture + paroxetine	54				
74	Bright light therapy + fluoxetine	29	Light therapy + AD	39	29	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 88. Network diagram of all studies included in analysis by intervention. Discontinuation (for any reason).



1 Interpersonal psychotherapy (IPT) individual; 2 Cognitive bibliotherapy; 3 Computerised CBT (CCBT); 4 Psychoeducational website; 5 Cognitive bibliotherapy with support; 6 Computerised CBT with support; 7 Mindfulness meditation CD with support; 8 Long-term psychodynamic therapy individual; 9 Unsupervised high intensity exercise individual; 10 Supervised high intensity exercise group; 11 Supervised low intensity exercise group; 12 Bright light therapy; 13 Traditional acupuncture; 14 Yoga group; 15 Laser acupuncture
Without the use of a class network the following treatments would be disconnected from the rest of the network and would have to be excluded from the analysis: Psychoeducational website, Mindfulness meditation CD with support, Inactive laser acupuncture, Computerised behavioural activation with support, Relaxation training CD with support, and Laser acupuncture

Figure 89. Network diagram of all studies included in analysis by class. Discontinuation (for any reason).

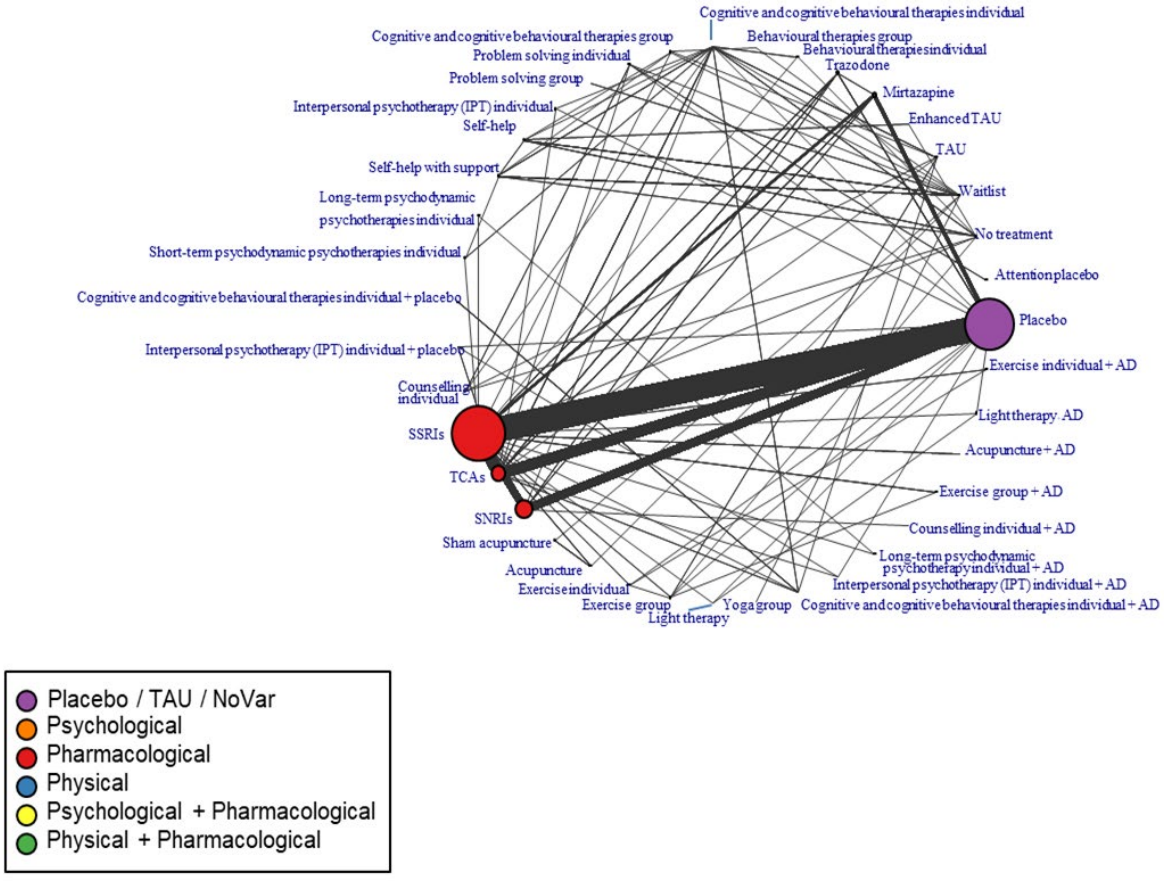
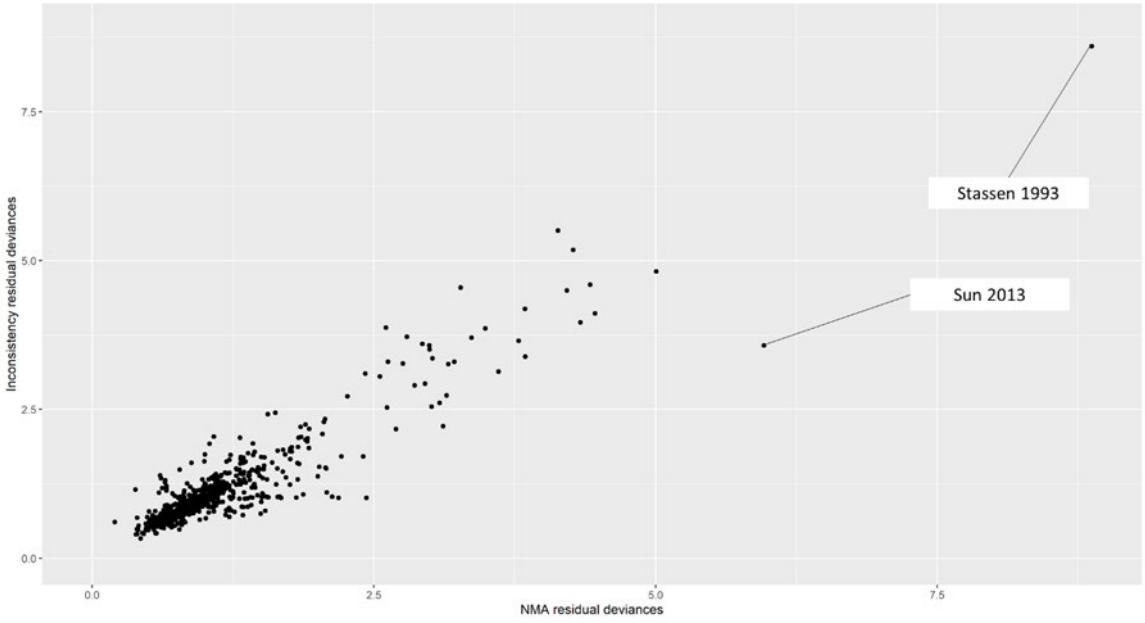


Figure 90. Deviance plot. Discontinuation (for any reason).



There is evidence of a decreased odds of discontinuation (lower OR corresponds to lower discontinuation) compared to Pill placebo for the following interventions (supplement B5, Figure 5.1 in appendix 5):

- Behavioural activation (BA) individual
- CBT individual (15 sessions or over)
- Enhanced TAU
- Escitalopram
- Fluoxetine
- No treatment
- Sertraline
- Waitlist

There was evidence of increased odds of discontinuation compared to Pill placebo for Trazodone.

The classes for which there is clear evidence suggesting a lower odds of discontinuation compared to Pill placebo are the following (supplement B5, Figure 5.2 in appendix 5):

- Enhanced TAU
- No treatment
- SSRIs
- Waitlist

The only class for which there was evidence of a higher odds of discontinuation compared to Pill placebo is Trazodone. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Enhanced TAU is the highest ranked class with a posterior median rank of 2nd (95% CrI 1st to 12th). The lowest ranked class is Trazodone 30th (95% CrI 23rd to 34th) (Excel file in supplement B6: *"Depression NMA more severe DISCONany bias-adjusted.xlsx"*, *"Ranks"* worksheet and Table 124).

Table 124. Posterior mean and median rank and 95% credible intervals by class. Discontinuation (for any reason).

Class	Posterior mean rank	Posterior median rank (95% CrI)
Enhanced TAU	2.7	2 (1, 12)
Waitlist	9.3	9 (3, 20)
Attention placebo	10.3	7 (1, 32)
Light therapy + AD	10.8	6 (1, 35)
Interpersonal psychotherapy (IPT) individual + AD	11.2	7 (1, 35)
Behavioural therapies individual	11.3	10 (2, 29)
Problem solving individual	11.4	10 (2, 30)
Interpersonal psychotherapy (IPT) individual	12.1	11 (2, 31)
TAU	12.1	11 (3, 27)
Self-help	12.2	10 (1, 34)
Sham acupuncture	12.3	10 (2, 32)
Long-term psychodynamic psychotherapies individual	14.8	13 (2, 33)
Cognitive and cognitive behavioural therapies individual	16.3	16 (6, 30)
Cognitive and cognitive behavioural therapies individual + AD	16.5	16 (3, 33)
Counselling individual	17.1	16 (4, 33)
Light therapy	17.9	17 (2, 36)

Acupuncture	18.3	17 (5, 34)
Cognitive and cognitive behavioural therapies group	19.5	19 (3, 35)
Yoga group	19.8	19 (2, 36)
Exercise individual	20.1	20 (3, 35)
Acupuncture + AD	21.1	21 (4, 35)
Exercise group + AD	21.7	22 (3, 36)
SSRIs	21.9	22 (15, 28)
Behavioural therapies group	21.9	22 (4, 36)
Exercise individual + AD	23.1	25 (3, 36)
Short-term psychodynamic psychotherapies individual	23.2	24 (6, 35)
Mirtazapine	23.9	24 (16, 31)
Placebo	24.5	25 (18, 30)
Counselling individual + AD	25	32 (1, 36)
Long-term psychodynamic psychotherapy individual + AD	25.1	29 (3, 36)
SNRIs	25.2	25 (18, 31)
Self-help with support	25.3	27 (7, 36)
TCAs	25.9	26 (18, 32)
Exercise group	26	29 (4, 36)
Problem solving group	26.6	33 (2, 36)
Trazodone	29.9	30 (23, 34)

Outcome: Discontinuation due to side effects

This analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients who discontinued treatment. After excluding trials with zero events in all arms or with number events equal to the denominator in all arms, 278 trials of 22 interventions and 11 classes were included for this outcome (Table 125, Figure 91, Figure 92). 2 studies were excluded because they were disconnected from the network. A continuity correction was applied to data in 5 studies containing at least one zero cell to stabilize the results.

Although there was lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, the between-study heterogeneity was lower in the inconsistency model (supplement B5, Table 3.9 in appendix 3). However, the prediction of individual studies was similar in both models (Figure 93).

Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.44$ (95% CrI 0.33 to 0.55)). Pill placebo was used as the network reference treatment, and reported relative effects are presented compared to this (supplement B5, Figures 5.3 & 5.4 in appendix 5).

Table 125. Interventions, classes and number of patients (N) included in Discontinuation due to side effects analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	4231	Placebo	1	4231	
2	Mirtazapine	692	Mirtazapine	2	692	
3	Trazodone	365	Trazodone	3	365	

4	Interpersonal psychotherapy (IPT) individual + pill placebo	17	Interpersonal psychotherapy (IPT) individual + placebo	4	17	1
5	Citalopram	661	SSRIs	5	6445	1
6	Escitalopram	1108				
7	Fluoxetine	1831				
8	Paroxetine	2082				
9	Sertraline	763				
10	Amitriptyline	963	TCAs	6	2096	2
11	Clomipramine	174				
12	Imipramine	759				
13	Lofepramine	80				
14	Nortriptyline	120				
15	Duloxetine	1272	SNRIs	7	2478	1
16	Venlafaxine	1206				
17	Bright light therapy	4	Light therapy	8	4	Max(1,2)
18	Interpersonal psychotherapy (IPT) individual + nortriptyline	10	Interpersonal psychotherapy (IPT) individual + AD	9	10	Max(1,2)
19	Electroacupuncture + fluoxetine	2	Acupuncture + AD	10	14	Max(1,2)
20	Electroacupuncture + paroxetine	9				
21	Traditional acupuncture + paroxetine	3				
22	Bright light therapy + fluoxetine	2	Light therapy + AD	11	2	Max(1,2)

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 91. Network diagram of every study included in analysis by intervention. Discontinuation due to side effects

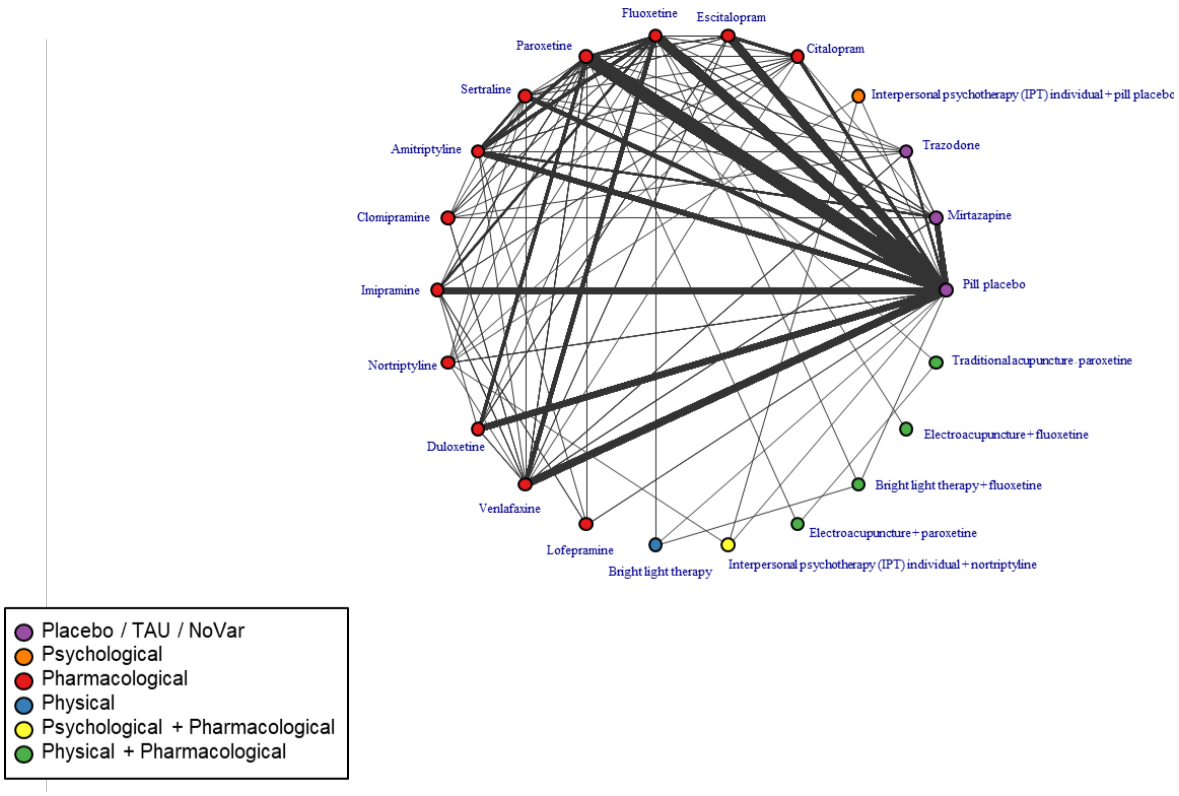


Figure 92. Network diagram of every study included in analysis by class. Discontinuation due to side effects.

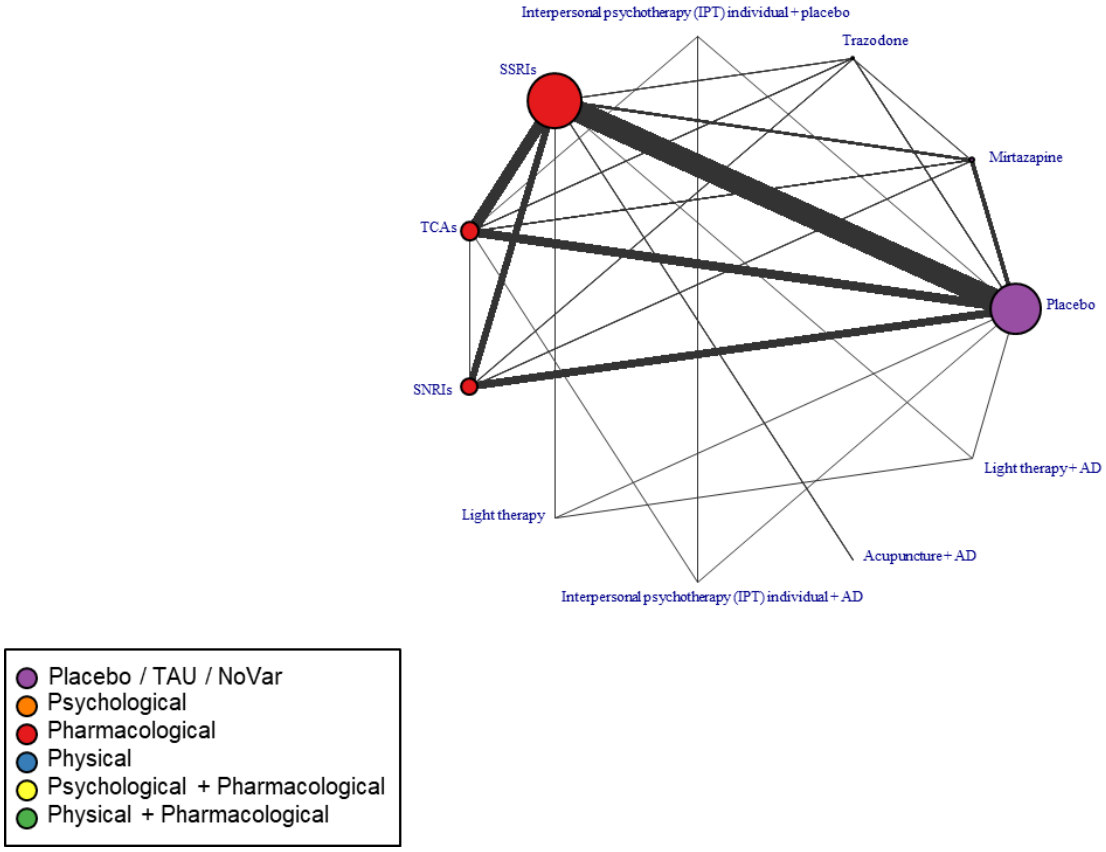
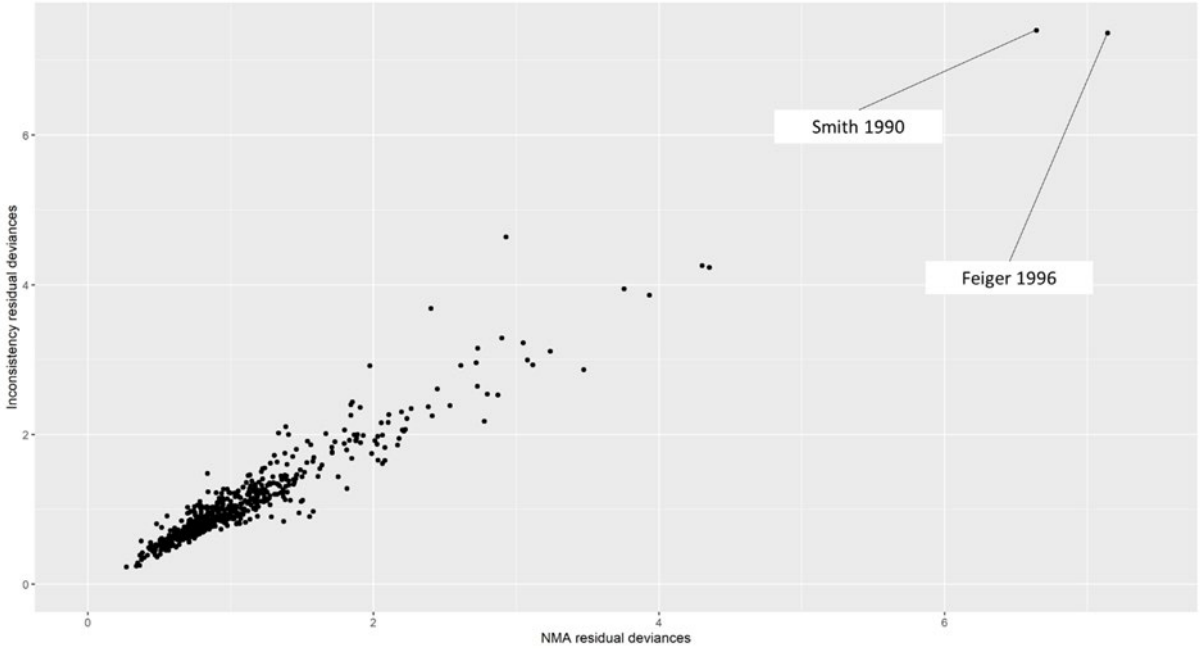


Figure 93. Deviance plot. Discontinuation due to side effects.



There is evidence suggesting that the following interventions have an increased odds of discontinuation due to SE compared to Pill placebo (supplement B5, Figure 5.3 in appendix 5):

- Clomipramine
- Duloxetine
- Escitalopram
- Fluoxetine
- Imipramine
- Lofepramine
- Mirtazapine
- Nortriptyline
- Paroxetine
- Sertraline
- Trazodone
- Venlafaxine

The classes for which there is evidence of having an increased odds in discontinuation due to SE are the following (supplement B5, Figure 5.4 in appendix 5):

- Mirtazapine
- Trazodone
- TCAs
- SSRIs

Placebo is the highest ranked class at 2nd (95% CrI 1st to 4th) (Table 126) and the highest ranked intervention at 2nd (95% CrI 1st to 5th) (Excel file in supplement B6: "*Depression NMA more severe DISCONse.xlsx*", "Ranks" worksheet). The lowest ranked intervention is Electroacupuncture + paroxetine with a posterior median rank of 18th (95% CrI 2nd to 20th). The lowest ranked class is TCAs with a posterior median rank of 9th (95% CrI 6th to 10th).

Table 126. Posterior mean and median rank and 95% credible intervals by class. Discontinuation due to side effects.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Placebo	2.2	2 (1, 4)
Light therapy	3.5	2 (1, 10)
Interpersonal psychotherapy (IPT) individual + AD	4.2	3 (1, 10)
SSRIs	4.6	5 (2, 7)
Mirtazapine	4.8	5 (2, 7)
Light therapy + AD	6.1	7 (1, 10)
Trazodone	6.3	6 (3, 9)
SNRIs	7.0	7 (4, 9)
Acupuncture + AD	7.9	9 (2, 10)
TCAs	8.4	9 (6, 10)

Outcome: Remission in completers

This analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients who completed treatment. 185 trials of 65 interventions and 35 classes were included in the analysis for this outcome (Table 127,

Figure 94, Figure 95). A continuity correction was added to data from 1 study (Sun 2010), and another study (Reynolds 1999a) was excluded because all participants in all arms experienced remission.

Although there was lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, the between-study heterogeneity was lower in the inconsistency model (supplement B5, Table 3.10 in appendix 3). The prediction of individual studies was notably worse in one study (Rush 1977/Kovacs 1981), which investigated CBT individual (15 sessions or over) versus Impiramine (Figure 96).

Results are based on the random-effects NMA model, assuming consistency. Low between trial heterogeneity was observed for this outcome (τ_{study}=0.14 (95% CrI 0.02 to 0.24)). Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.5 & 5.6 in appendix 5).

Table 127. Interventions, classes and number of patients (N) included in Remission in completers analysis.

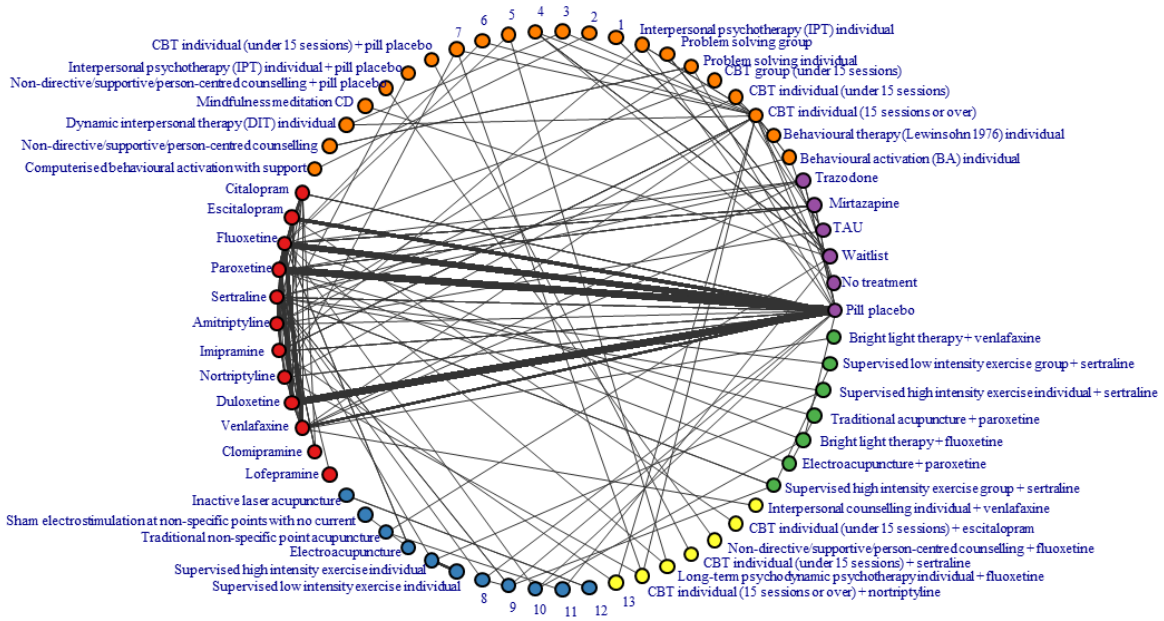
	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	5850	Placebo	1	5850	
2	No treatment	299	No treatment	2	299	
3	Waitlist	309	Waitlist	3	309	
4	TAU	45	TAU	4	45	
5	Mirtazapine	645	Mirtazapine	5	645	
6	Trazodone	552	Trazodone	6	552	
7	Behavioural activation (BA) individual	320	Behavioural therapies individual	7	330	1
8	Behavioural therapy (Lewinsohn 1976) individual	10				
9	CBT individual (15 sessions or over)	391	Cognitive and cognitive behavioural therapies individual	8	440	1
10	CBT individual (under 15 sessions)	49				
11	CBT group (under 15 sessions)	32	Cognitive and cognitive behavioural therapies group	9	32	1
12	Problem solving individual	191	Problem solving individual	10	191	1
13	Problem solving group	47	Problem solving group	11	47	1
14	Non-directive/supportive/person-centred counselling	103	Counselling individual	12	103	1
15	Interpersonal psychotherapy (IPT) individual	89	Interpersonal psychotherapy (IPT) individual	13	89	1
16	Cognitive bibliotherapy	147	Self-help	14	327	1
17	Mindfulness meditation CD	35				
18	Psychoeducational website	145				
19	Cognitive bibliotherapy with support	38	Self-help with support	15	323	1
20	Computerised-CBT (CCBT) with support	165				

21	Computerised behavioural activation with support	120				
22	Long-term psychodynamic psychotherapy individual	73	Long-term psychodynamic psychotherapies individual	16	73	1
23	Dynamic interpersonal therapy (DIT) individual	59	Short-term psychodynamic psychotherapies individual	17	101	1
24	Short-term psychodynamic psychotherapy individual	42				
25	CBT individual (15 sessions or over) + pill placebo	17	Cognitive and cognitive behavioural therapies individual + placebo	18	38	1
26	CBT individual (under 15 sessions) + pill placebo	21				
27	Interpersonal psychotherapy (IPT) individual + pill placebo	22	Interpersonal psychotherapy (IPT) individual + placebo	19	22	1
28	Non-directive/supportive/person-centred counselling + pill placebo	11	Counselling individual + placebo	20	11	1
29	Citalopram	1041	SSRIs	21	10361	2
30	Escitalopram	2457				
31	Fluoxetine	3001				
32	Paroxetine	3110				
33	Sertraline	752				
34	Amitriptyline	486	TCAs	22	1204	3
35	Clomipramine	135				
36	Imipramine	318				
37	Lofepramine	55				
38	Nortriptyline	210				
39	Duloxetine	3674	SNRIs	23	5949	2
40	Venlafaxine	2275				
41	Inactive laser acupuncture	33	Sham acupuncture	24	100	4
42	Sham electrostimulation at non-specific points with no current	22				
43	Traditional non-specific point acupuncture	45				
44	Electroacupuncture	67	Acupuncture	25	145	4
45	Laser acupuncture	36				
46	Traditional acupuncture	42				
47	Supervised high intensity exercise individual	109	Exercise individual	26	242	5
48	Supervised low intensity exercise individual	83				
49	Unsupervised high intensity exercise individual	50				
50	Supervised high intensity exercise group	80	Exercise group	27	80	1
51	Bright light therapy	28	Light therapy	28	28	4

52	CBT individual (15 sessions or over) + imipramine	16	Cognitive and cognitive behavioural therapies individual + AD	29	100	6
53	CBT individual (15 sessions or over) + nortriptyline	18				
54	CBT individual (under 15 sessions) + escitalopram	40				
55	CBT individual (under 15 sessions) + sertraline	26				
56	Long-term psychodynamic psychotherapy individual + fluoxetine	62	Long-term psychodynamic psychotherapy individual + AD	30	62	6
57	Interpersonal counselling individual + venlafaxine	11	Counselling individual + AD	31	24	6
58	Non-directive/supportive/person-centred counselling + fluoxetine	13				
59	Supervised high intensity exercise individual + sertraline	44	Exercise individual + AD	32	44	6
60	Supervised high intensity exercise group + sertraline	82	Exercise group + AD	33	114	6
61	Supervised low intensity exercise group + sertraline	32				
62	Electroacupuncture + paroxetine	49	Acupuncture + AD	34	100	4
63	Traditional acupuncture + paroxetine	51				
64	Bright light therapy + fluoxetine	27	Light therapy + AD	35	52	4
65	Bright light therapy + venlafaxine	25				

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 94. Network diagram of every study included in analysis by intervention. Remission in Completers.



1 Cognitive bibliotherapy; 2 Psychoeducational website; 3 Cognitive bibliotherapy with support; 4 Computerised CBT (CCBT) with support; 5 Long-term psychodynamic psychotherapy individual; 6 Short-term psychodynamic psychotherapy individual; 7 CBT individual (15 sessions or over) + pill placebo; 8 Unsupervised high intensity exercise individual; 9 Supervised high intensity exercise group; 10 Bright light therapy; 11 Traditional acupuncture; 12 Laser acupuncture; 13 CBT individual (15 sessions or over) + imipramine

Without the use of a class network the following treatments would be disconnected fro the rest of the network and would have to be excluded from the analysis: Psychoeducational website, CBT individual (under 15 sessions) + pill placebo, Non-directive/supportive/person-centred counselling + pill placebo, Inactive laser acupuncture, Computerised behavioural activation with support, CBT individual (under 15 sessions) + sertraline, Non-directive/supportive/person-centred counselling + fluoxetine, and Laser acupuncture

Figure 95. Network diagram of every study included in analysis by class. Remission in Completers.

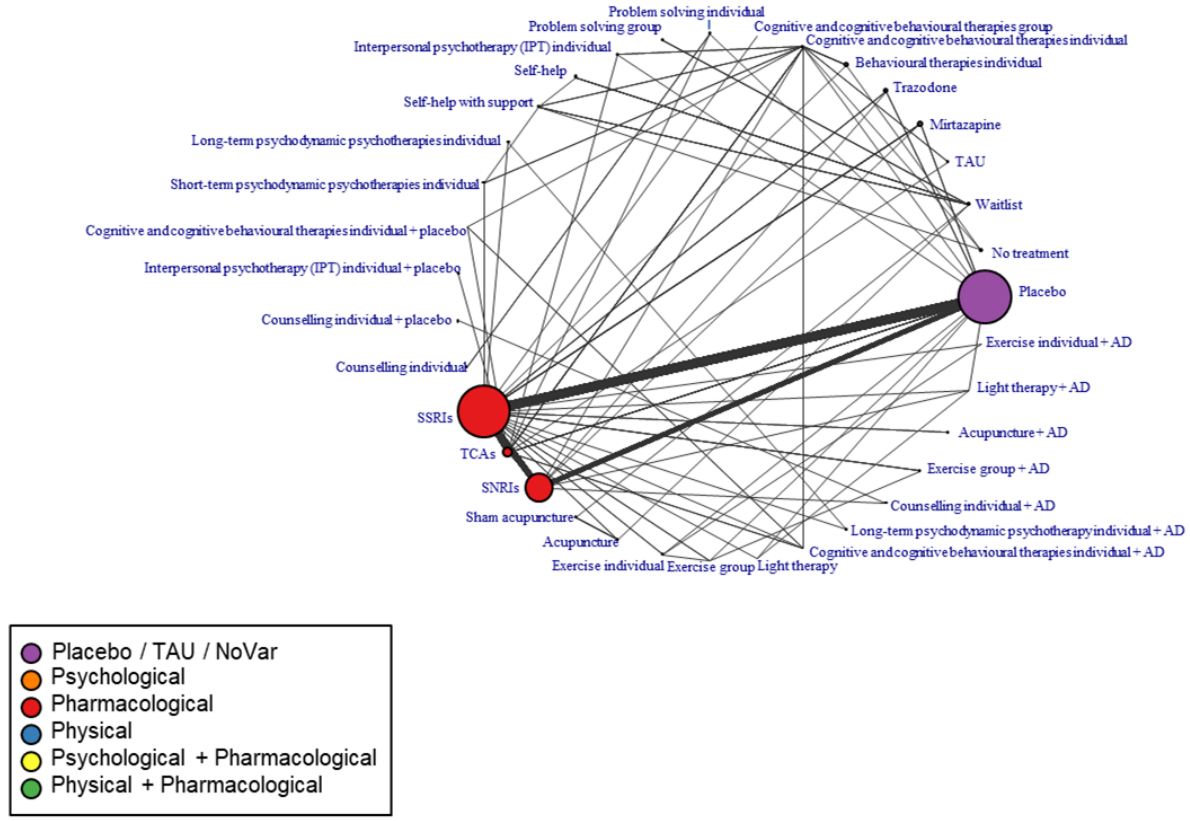
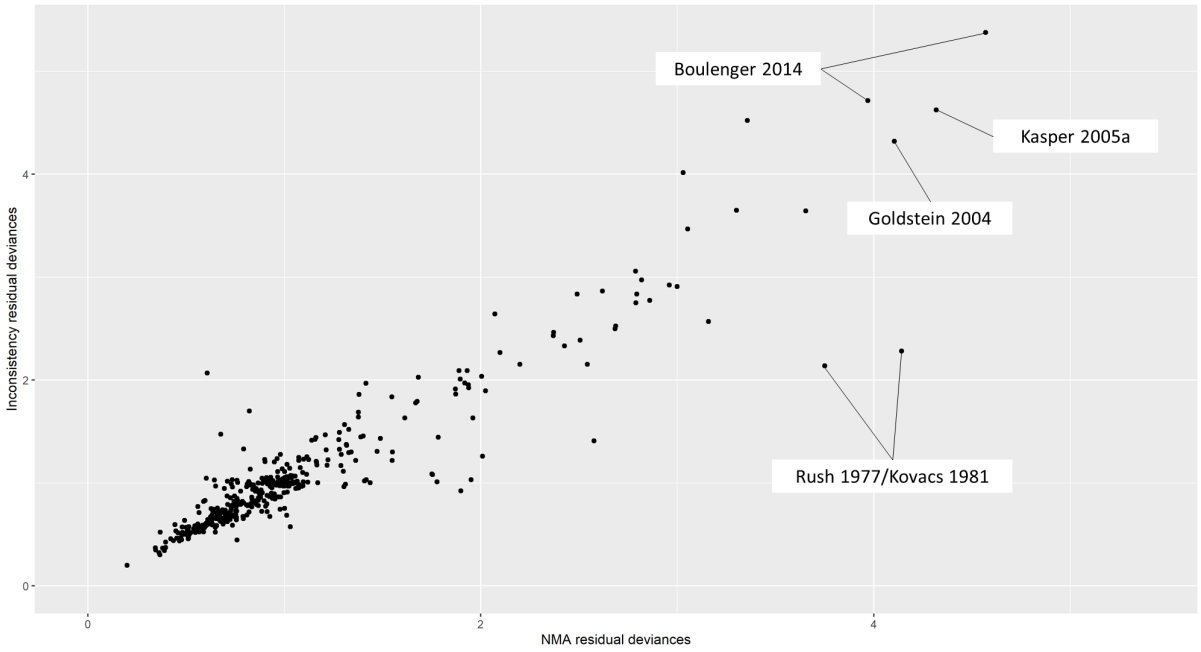


Figure 96. Deviance plot. Remission in Completers.



There is evidence suggesting the interventions with an increased odds of remission compared to Pill placebo are the following (supplement B5, Figure 5.5 in appendix 5):

- Amitriptyline

- Behavioural activation (BA) individual
- Bright light therapy
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + impiramine
- CBT individual (15 sessions or over) + nortriptyline
- CBT individual (15 sessions or over) + pill placebo
- CBT individual (under 15 sessions) + escitalopram
- CBT individual (under 15 sessions) + pill placebo
- Citalopram
- Clomipramine
- Cognitive bibliotherapy
- Computerised-CBT (CCBT) with support
- Duloxetine
- Dynamic interpersonal therapy (DIT) individual
- Electroacupuncture + paroxetine
- Escitalopram
- Fluoxetine
- Imipramine
- Interpersonal psychotherapy (IPT) individual
- Long-term psychodynamic psychotherapy individual
- Long-term psychodynamic psychotherapy individual + fluoxetine
- Mirtazapine
- Nortriptyline
- Paroxetine
- Problem solving group
- Problem solving individual
- Sertraline
- Supervised high intensity exercise group
- Supervised high intensity exercise group + sertraline
- Supervised low intensity exercise group + sertraline
- Trazodone
- Venlafaxine

There is some evidence to suggest that Waitlist has a decreased odds of remission compared to Pill placebo.

The classes for which there is evidence of an increased odds of remission compared to Placebo are the following (supplement B5, Figure 5.6 in appendix 5):

- Cognitive and cognitive behavioural therapies individual + AD
- Cognitive and cognitive behavioural therapies individual + placebo
- Exercise group + AD
- Long-term psychodynamic psychotherapy individual
- Long-term psychodynamic psychotherapy individual + AD

- Mirtazapine
- SNRIs
- SSRIs
- TCAs
- Trazodone

For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Long-term psychodynamic psychotherapy individual + AD was the highest rank class at 1st (95% CrI 1st to 4th) (Table 128). The only intervention in this class, Long-term psychodynamic psychotherapy individual + fluoxetine, was the highest ranked intervention at 1st (95% CrI 1st to 3rd) (Excel file in supplement B6: *"Depression NMA more severe REMIScompleters.xlsx"*, *"Ranks"* worksheet). The lowest ranked class was Waitlist, with a posterior median rank of 30th (95% CrI 25th to 31st).

Table 128. Posterior mean and median rank and 95% credible intervals by class. Remission in Completers.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Long-term psychodynamic psychotherapy individual + AD	1.647	1 (1, 4)
Long-term psychodynamic psychotherapies individual	3.215	2 (1, 13)
Problem solving group	4.942	3 (1, 24)
Cognitive and cognitive behavioural therapies individual + AD	9.357	9 (4, 20)
Short-term psychodynamic psychotherapies individual	10.62	9 (3, 28)
Light therapy + AD	10.62	8 (3, 29)
Exercise group + AD	11.1	10 (4, 25)
Self-help	12.27	10 (3, 28)
Counselling individual + AD	13.42	11 (3, 30)
TCAs	13.67	13 (8, 22)
Problem solving individual	13.98	12 (2, 31)
Light therapy	14.32	12 (2, 31)
Interpersonal psychotherapy (IPT) individual	15.07	13 (3, 31)
Self-help with support	15.62	15 (4, 29)
SNRIs	16.06	16 (11, 21)
Acupuncture + AD	17.29	17 (4, 31)
Cognitive and cognitive behavioural therapies individual	17.55	17 (4, 30)
Acupuncture	17.55	17 (4, 30)
Behavioural therapies individual	17.66	18 (4, 31)
Exercise group	17.88	18 (3, 31)
Mirtazapine	18.43	18 (13, 24)
Trazodone	19.57	20 (14, 25)
SSRIs	20.21	20 (15, 25)
Counselling individual	20.22	23 (4, 31)
Cognitive and cognitive behavioural therapies group	20.64	23 (4, 31)
TAU	21.06	22 (10, 29)
Sham acupuncture	21.71	24 (5, 31)

Exercise individual + AD	22.28	24 (6, 31)
Exercise individual	22.92	24 (7, 31)
Placebo	25.54	26 (21, 29)
Waitlist	29.54	30 (25, 31)

Outcome: Remission in those randomised

A further analysis of remission was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients who were randomised. After excluding rials with zero events in all arms or with the number events equal to the denominator in all arms, 202 trials of 64 interventions and 38 classes were included in the analysis for this outcome (Table 129,

Figure 97, Figure 98).

No meaningful differences were observed in posterior mean residual deviance, though DIC was slightly lower in the random effects consistency model, and between-study heterogeneity slightly lower in the inconsistency model (supplement B5, Table 3.11 in appendix 3). The prediction of several individual studies was worse in the consistency model, suggesting some evidence of inconsistency. These studies investigated Behavioural activation (BA) individual, CBT individual (15 sessions or over), Sertraline, Impiramine and Venafalxine (Figure 99).

Reported results are based on the random-effects NMA model, assuming consistency. There was moderate between trial heterogeneity observed for this outcome $\left(\tau_{study} = 0.27\ (95\%\ \text{CrI}\ 0.20\ \text{to}\ 0.34)\right)$. Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.7 & 5.8 in appendix 5).

Table 129. Interventions, classes and number of patients (N) included in Remission in those randomised analysis.

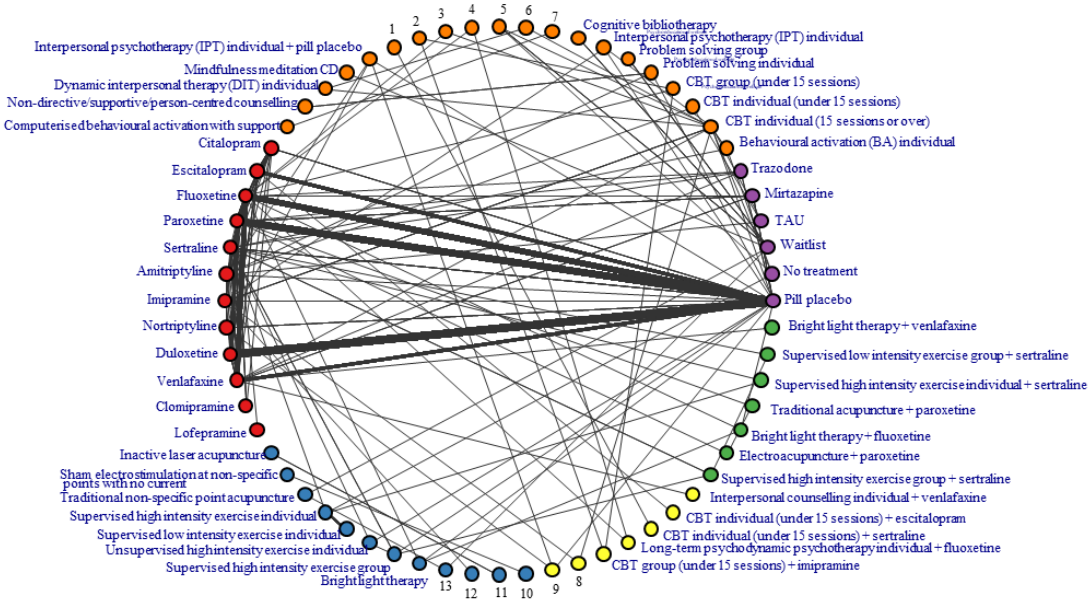
	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	8376	Placebo	1	8376	
2	No treatment	353	No treatment	2	353	
3	Waitlist	338	Waitlist	3	338	
4	TAU	60	TAU	4	60	
5	Mirtazapine	726	Mirtazapine	5	726	
6	Trazodone	742	Trazodone	6	742	
7	Behavioural activation (BA) individual	354	Behavioural therapies individual	7	354	1
8	CBT individual (15 sessions or over)	421	Cognitive and cognitive behavioural therapies individual	8	451	1
9	CBT individual (under 15 sessions)	30				
10	CBT group (under 15 sessions)	65	Cognitive and cognitive behavioural therapies group	9	65	1
11	Problem solving individual	232	Problem solving individual	10	232	1
12	Problem solving group	58	Problem solving group	11	58	1
13	Non-directive/supportive/person-centred counselling	124	Counselling individual	12	124	1
14	Interpersonal psychotherapy (IPT) individual	63	Interpersonal psychotherapy (IPT) individual	13	63	1
15	Cognitive bibliotherapy	156	Self-help	14	349	1
16	Mindfulness meditation CD	39				
17	Psychoeducational website	154				
18	Cognitive bibliotherapy with support	54	Self-help with support	15	416	1
19	Computerised-CBT (CCBT) with support	203				

20	Computerised behavioural activation with support	159				
21	Long-term psychodynamic psychotherapy individual	90	Long-term psychodynamic psychotherapies individual	16	90	1
22	Dynamic interpersonal therapy (DIT) individual	73	Short-term psychodynamic psychotherapies individual	17	129	1
23	Short-term psychodynamic psychotherapy individual	56				
24	Short-term psychodynamic psychotherapy group	24	Short-term psychodynamic psychotherapies group	18	24	1
25	CBT individual (under 15 sessions) + pill placebo	39	Cognitive and cognitive behavioural therapies individual + placebo	19	39	1
26	Interpersonal psychotherapy (IPT) individual + pill placebo	48	Interpersonal psychotherapy (IPT) individual + placebo	20	48	1
27	Citalopram	1676	SSRIs	21	15203	2
28	Escitalopram	3818				
29	Fluoxetine	3981				
30	Paroxetine	4571				
31	Sertraline	1157				
32	Amitriptyline	666	TCAs	22	1747	3
33	Clomipramine	184				
34	Imipramine	562				
35	Lofepramine	68				
36	Nortriptyline	267				
37	Duloxetine	5472	SNRIs	23	8727	2
38	Venlafaxine	3255				
39	Inactive laser acupuncture	36	Sham acupuncture	24	117	1
40	Sham electrostimulation at non-specific points with no current	29				
41	Traditional non-specific point acupuncture	52				
42	Electroacupuncture	28	Acupuncture	25	122	1
43	Laser acupuncture	41				
44	Traditional acupuncture	53				
45	Supervised high intensity exercise individual	177	Exercise individual	26	336	4
46	Supervised low intensity exercise individual	106				
47	Unsupervised high intensity exercise individual	53				
48	Supervised high intensity exercise group	104	Exercise group	27	104	1
49	Yoga group	15	Yoga group	28	15	1

50	Bright light therapy	32	Light therapy	29	32	1
51	CBT individual (15 sessions or over) + imipramine	25	Cognitive and cognitive behavioural therapies individual + AD	30	117	1
52	CBT individual (under 15 sessions) + escitalopram	52				
53	CBT individual (under 15 sessions) + sertraline	40				
54	CBT group (under 15 sessions) + imipramine	34	Cognitive and cognitive behavioural therapies group + AD	31	34	1
55	Long-term psychodynamic psychotherapy individual + fluoxetine	91	Long-term psychodynamic psychotherapy individual + AD	32	91	1
56	Interpersonal psychotherapy (IPT) individual + nortriptyline	16	Interpersonal psychotherapy (IPT) individual + AD	33	16	1
57	Interpersonal counselling individual + venlafaxine	13	Counselling individual + AD	34	13	1
58	Supervised high intensity exercise individual + sertraline	55	Exercise individual + AD	35	55	1
59	Supervised high intensity exercise group + sertraline	97	Exercise group + AD	36	134	1
60	Supervised low intensity exercise group + sertraline	37				
61	Electroacupuncture + paroxetine	58	Acupuncture + AD	37	112	1
62	Traditional acupuncture + paroxetine	54				
63	Bright light therapy + fluoxetine	29	Light therapy + AD	38	54	1
64	Bright light therapy + venlafaxine	25				

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 97. Network diagram of every study included in analysis by intervention. Remission in those randomised.



1 CBT individual (under 15 sessions) + pill placebo; 2 Short-term psychodynamic therapy group; 3 Short term psychodynamic psychotherapy individual; 4 Long-term psychodynamic psychotherapy individual; 5 Computerised CBT (CCBT) with support; 6 Cognitive bibliotherapy with support; 7 Psychoeducational website; 8 CBT individual (15 sessions or over) + imipramine; 9 Interpersonal psychotherapy (IPT) individual + nortriptyline; 10 Electroacupuncture; 11 Laser acupuncture; 12 Yoga therapy; 13 Traditional acupuncture

Without the use of a class network the following interventions would be disconnected from the rest of the network and would have to be excluded from the analysis: Psychoeducational website, CBT individual (under 15 sessions) + pill placebo, Inactive laser acupuncture, Sham electrostimulation at non-specific points with no current, Computerised behavioural activation with support, CBT individual (under 15 sessions) + sertraline, Laser acupuncture, and Electroacupuncture

Figure 98. Network diagram of every study included in analysis by class. Remission in those randomised.

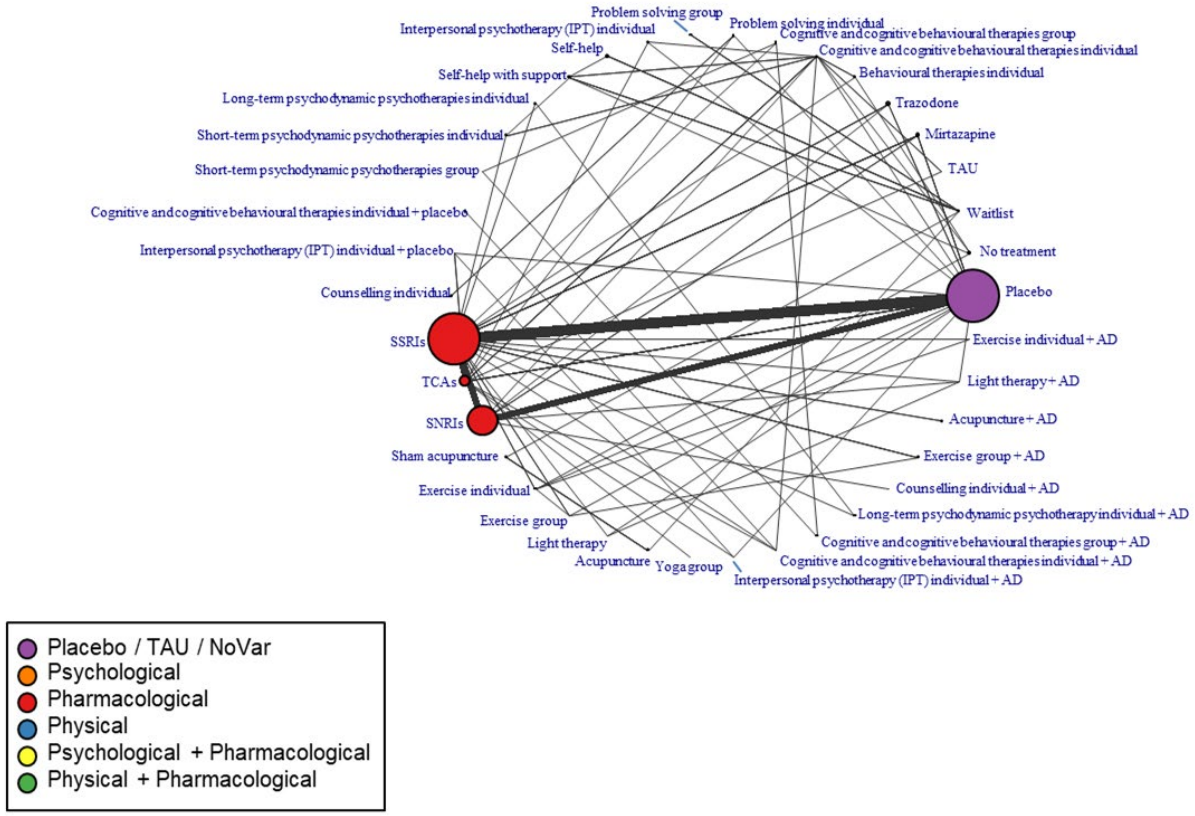
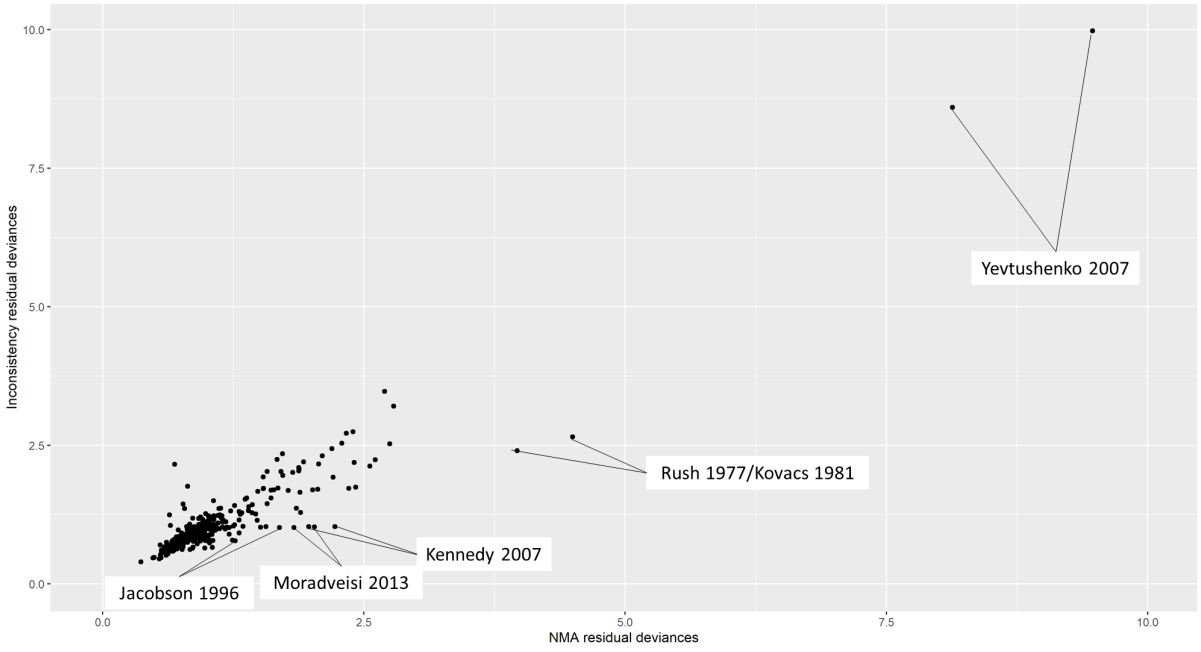


Figure 99. Deviance plot. Remission in those randomised.



There is evidence of increased odds of remission compared to Pill placebo for the following interventions (supplement B5, Figure 5.7 in appendix 5):

- Amitriptyline
- Behavioural activation (BA) individual

- Bright light therapy
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + impramine
- Citalopram
- Clomipramine
- Cognitive bibliography
- Duloxetine
- Dynamic interpersonal therapy (DIT) individual
- Escitalopram
- Fluoxetine
- Imipramine
- Interpersonal psychotherapy (IPT) individual
- Interpersonal psychotherapy (IPT) individual + nortriptyline
- Lofepramine
- Long-term psychodynamic psychotherapy individual
- Long-term psychodynamic psychotherapy individual + fluoxetine
- Mirtazapine
- Nortriptyline
- Paroxetine
- Problem solving group
- Problem solving individual
- Sertraline
- Supervised high intensity exercise group + sertraline
- Supervised low intensity exercise group + sertraline
- Trazodone
- Venlafaxine

Only one intervention, Short-term psychodynamic psychotherapy group, showed decreased odds of remission compared to Pill placebo.

The classes for which evidence suggests an increased odds of remission compared to Pill placebo are the following (supplement B5, Figure 5.8 in appendix 5):

- Long-term psychodynamic psychotherapy individual + AD
- Long-term psychodynamic psychotherapy individual
- Mirtazapine
- SNRIs
- SSRIs
- TCAs
- Trazodone

Short-term psychodynamic psychotherapy group, which contained only a single intervention of the same name, showed decreased odds of remission compared to Pill placebo. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Long-term psychodynamic psychotherapies individual was the highest ranked class at 2nd (95% CrI 1st to 17th) (Table 130). The highest ranked intervention, Long-term psychodynamic psychotherapy individual, was the only intervention in this class, with a posterior median rank of 2nd (95%CrI 1st to 9th) (Excel file in supplement B6: *"Depression NMA more severe REMISitt.xlsx"*, *"Ranks"* worksheet). The lowest ranked class is Short-term psychodynamic psychotherapies group at 35th (95% CrI 28th to 35th), and the lowest ranked intervention, also named Short-term psychodynamic psychotherapies group, was the only intervention in this class.

Table 130. Posterior mean and median rank and 95% credible intervals by class. Remission in those randomised.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Long-term psychodynamic psychotherapies individual	3.87	2 (1, 17)
Long-term psychodynamic psychotherapy individual + AD	5.54	3 (1, 24)
Problem solving group	8.18	5 (1, 31)
Light therapy + AD	10.09	8 (2, 28)
Interpersonal psychotherapy (IPT) individual + AD	11	8 (1, 32)
Self-help	11.28	9 (2, 29)
Short-term psychodynamic psychotherapies individual	12.5	11 (2, 30)
Exercise group + AD	13.42	12 (3, 30)
Interpersonal psychotherapy (IPT) individual	13.48	11 (2, 32)
Behavioural therapies individual	13.84	12 (2, 32)
Problem solving individual	13.96	12 (2, 33)
Cognitive and cognitive behavioural therapies individual + AD	14.17	13 (3, 31)
Light therapy	14.77	12 (2, 33)
Counselling individual + AD	16.43	14 (1, 34)
TCAs	17.28	17 (9, 27)
Acupuncture	18.64	18 (2, 33)
SNRIs	18.76	19 (12, 25)
Cognitive and cognitive behavioural therapies individual	18.84	18 (5, 32)
TAU	19.14	19 (8, 31)
Mirtazapine	19.15	19 (12, 26)
Acupuncture + AD	19.19	19 (4, 33)
Self-help with support	19.56	20 (5, 32)
Exercise group	20.59	22 (4, 34)
SSRIs	21.81	22 (16, 27)
Exercise individual + AD	22.13	24 (4, 34)
Cognitive and cognitive behavioural therapies group	22.3	25 (4, 34)
Counselling individual	22.35	25 (4, 34)
Yoga group	22.36	26 (3, 35)
Sham acupuncture	22.55	26 (4, 34)
Exercise individual	22.69	24 (6, 33)
Cognitive and cognitive behavioural therapies group + AD	22.9	26 (3, 34)
Trazodone	23.11	23 (16, 29)

Placebo	27.78	28 (23, 32)
Waitlist	32.01	33 (25, 35)
Short-term psychodynamic psychotherapies group	34.32	35 (28, 35)

Outcome: Response in completers

The response analysis was first carried out only in those who completed treatment, using WinBUGS code given in supplement B5, appendix 1. After excluding trials with zero events in all arms or with the number events equal to the denominator in all arms, 250 trials reported response. Out of the remaining studies in the dataset, 21 reported change from baseline in completers (but not response) and 56 reported baseline and final scores in completers (but not response or change from baseline). This meant that 327 trials of 87 interventions and 44 classes were included in the analysis for this outcome (Table 131,

Figure 100,

Figure 101).

Posterior mean residual deviances, DIC and between-study heterogeneity were all lower in the random-effects NMA consistency model than in the inconsistency model (supplement B5, Table 3.12 in appendix 3). Prediction of data points were largely similar in both models, although for one study (Moradveisi 2013) the fit was substantially poorer in the consistency model, due to one arm in which the number of responders was equal to the number of completers (Figure 102).

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The bias parameter for comparisons with active versus control or counselling interventions was estimated to be 0.86 (95%CrI 0.33, 1.42). This indicated that smaller studies were likely to be biased in favour of active interventions versus control or counselling interventions. The posterior mean residual deviance, DIC and between study heterogeneity were substantially reduced compared to the base-case consistency model (supplement B5, Table 3.12 in appendix 3). Reported results are therefore based on the bias-adjusted random-effects NMA model. Results from the bias-adjusted model and from the base-case unadjusted model can be found in Excel files in supplement B6 ("*Depression NMA more severe RESPcompleters bias-adjusted.xlsx"* and *"Depression NMA more severe RESPcompleters base-case.xlsx"*, respectively).

Moderate between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.60\ (95\%\ CrI\ 0.52\ to\ 0.68)$). Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.9 & 5.10 in appendix 5).

Table 131. Interventions, classes and number of patients (N) included in Response in completers analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	9333	Placebo	1	9333	
2	Attention placebo	25	Attention placebo	2	25	
3	No treatment	266	No treatment	3	266	
4	Waitlist	371	Waitlist	4	371	
5	TAU	64	TAU	5	64	
6	Mirtazapine	1845	Mirtazapine	6	1845	
7	Trazodone	1003	Trazodone	7	1003	
8	Behavioural activation (BA) individual	310	Behavioural therapies individual	8	320	1
9	Behavioural therapy (Lewinsohn 1976) individual	10				
10	CBT individual (15 sessions or over)	348	Cognitive and cognitive behavioural therapies individual	9	507	1
11	CBT individual (under 15 sessions)	141				
12	Third-wave cognitive therapy individual	18				
13	CBT group (under 15 sessions)	64	Cognitive and cognitive behavioural therapies group	10	64	1
14	Problem solving individual	123	Problem solving individual	11	123	1
15	Problem solving group	47	Problem solving group	12	47	1

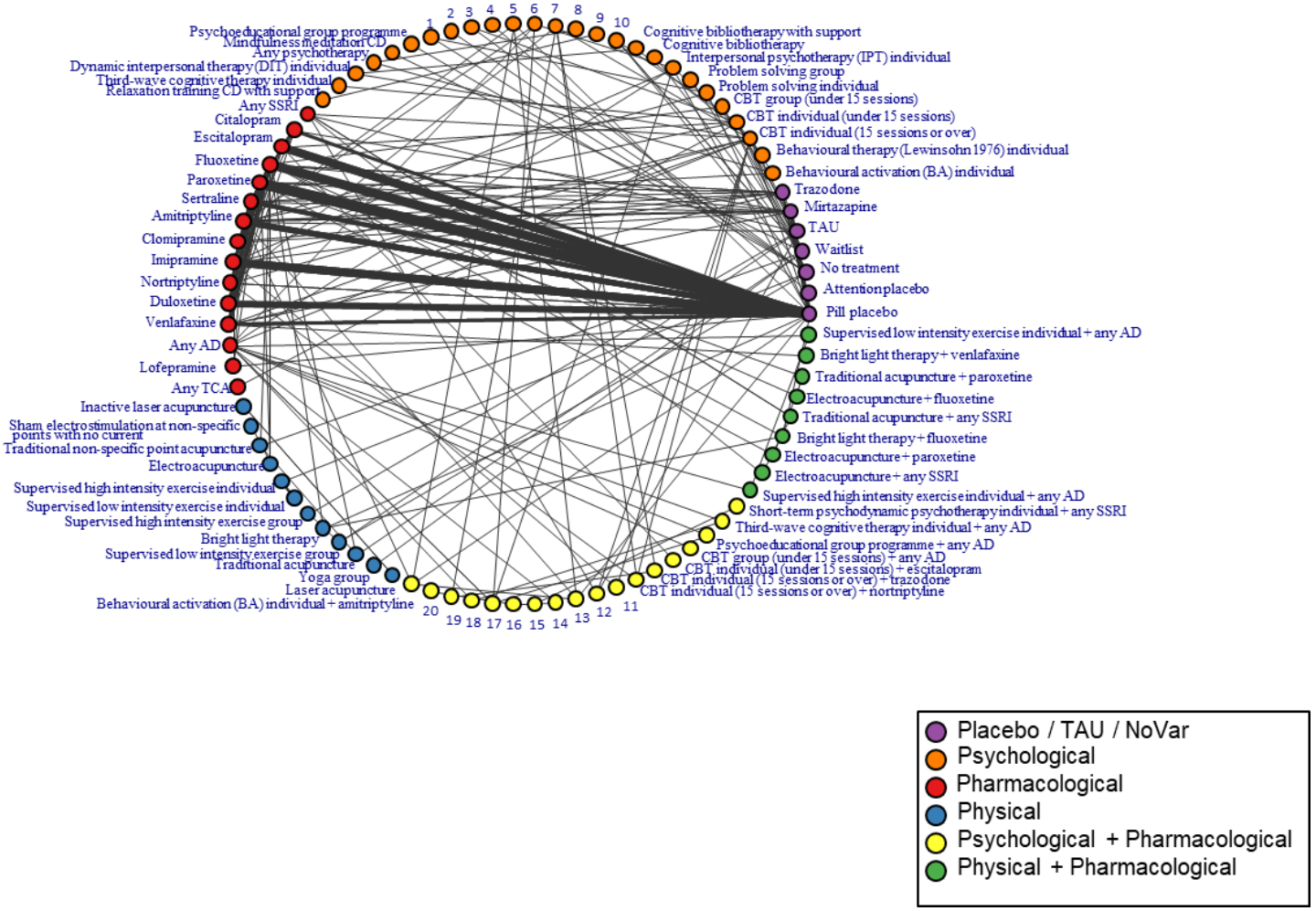
16	Non-directive/supportive/person-centred counselling	216	Counselling individual	13	216	1
17	Interpersonal psychotherapy (IPT) individual	132	Interpersonal psychotherapy (IPT) individual	14	132	1
18	Psychoeducational group programme	44	Psychoeducation group	15	44	1
19	Cognitive bibliotherapy	147	Self-help	16	231	2
20	Computerised-CBT (CCBT)	23				
21	Computerised attentional bias modification	26				
22	Mindfulness meditation CD	35				
23	Cognitive bibliotherapy with support	38	Self-help with support	17	189	3
24	Computerised-CBT (CCBT) with support	114				
25	Mindfulness meditation CD with support	19				
26	Relaxation training CD with support	18				
27	Dynamic interpersonal therapy (DIT) individual	59	Short-term psychodynamic psychotherapies individual	18	75	1
28	Short-term psychodynamic psychotherapy individual	16				
29	Music therapy group	12	Music therapy group	19	12	1
30	Any psychotherapy	27	Any psychotherapy	20	27	1
31	CBT individual (15 sessions or over) + pill placebo	26	Cognitive and cognitive behavioural therapies individual + placebo	21	26	1
32	Interpersonal psychotherapy (IPT) individual + pill placebo	69	Interpersonal psychotherapy (IPT) individual + placebo	22	69	1
33	Progressive muscle relaxation individual + pill placebo	11	Relaxation individual + placebo	23	11	1
34	Any SSRI	201	SSRIs	24	16720	4
35	Citalopram	1762				
36	Escitalopram	3396				
37	Fluoxetine	4804				
38	Paroxetine	4291				
39	Sertraline	2266				
40	Amitriptyline	2222	TCAs	25	4233	4
41	Any TCA	21				
42	Clomipramine	297				
43	Imipramine	1247				
44	Lofepramine	188				
45	Nortriptyline	258				
46	Duloxetine	3700	SNRIs	26	6569	4
47	Venlafaxine	2869				
48	Any AD	286	Any AD	27	286	4

49	Inactive laser acupuncture	33	Sham acupuncture	28	188	1
50	Sham electrostimulation at non-specific points with no current	22				
51	Traditional non-specific point acupuncture	133				
52	Electroacupuncture	83	Acupuncture	29	249	1
53	Laser acupuncture	36				
54	Traditional acupuncture	130				
55	Supervised high intensity exercise individual	47	Exercise individual	30	88	3
56	Supervised low intensity exercise individual	41				
57	Supervised high intensity exercise group	18	Exercise group	31	55	3
58	Supervised low intensity exercise group	37				
59	Yoga group	20	Yoga group	32	20	1
60	Bright light therapy	28	Light therapy	33	28	1
61	Behavioural activation (BA) individual + amitriptyline	12	Behavioural therapies individual + AD	34	22	5
62	Behavioural activation (BA) individual + any AD	10				
63	CBT individual (15 sessions or over) + amitriptyline	10	Cognitive and cognitive behavioural therapies individual + AD	35	157	5
64	CBT individual (15 sessions or over) + any AD	10				
65	CBT individual (15 sessions or over) + any SSRI	43				
66	CBT individual (15 sessions or over) + imipramine	16				
67	CBT individual (15 sessions or over) + nortriptyline	18				
68	CBT individual (15 sessions or over) + trazodone	10				
69	CBT individual (under 15 sessions) + escitalopram	40				
70	Third-wave cognitive therapy individual + any AD	10				
71	CBT group (under 15 sessions) + any AD	43	Cognitive and cognitive behavioural therapies group + AD	36	43	5
72	Interpersonal psychotherapy (IPT) individual + any AD	87	Interpersonal psychotherapy (IPT) individual + AD	37	87	5
73	Non-directive/supportive/person-centred counselling + any AD	55	Counselling individual + AD	38	71	5
74	Non-directive/supportive/person-centred counselling + any SSRI	16				

75	Short-term psychodynamic psychotherapy individual + any AD	152	Short-term psychodynamic psychotherapies individual + AD	39	168	5
76	Short-term psychodynamic psychotherapy individual + any SSRI	16				
77	Psychoeducational group programme + any AD	27	Psychoeducation group + AD	40	27	5
78	Progressive muscle relaxation individual + amitriptyline	10	Relaxation individual + AD	41	10	5
79	Supervised high intensity exercise individual + any AD	13	Exercise individual + AD	42	22	5
80	Supervised low intensity exercise individual + any AD	9				
81	Electroacupuncture + any SSRI	138	Acupuncture + AD	43	519	1
82	Electroacupuncture + fluoxetine	46				
83	Electroacupuncture + paroxetine	49				
84	Traditional acupuncture + any SSRI	185				
85	Traditional acupuncture + paroxetine	101				
86	Bright light therapy + fluoxetine	27	Light therapy + AD	44	52	1
87	Bright light therapy + venlafaxine	25				

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 100. Network diagram of every study included in analysis by intervention. Response in completers.



1 Non-directive/supportive/ person-centred counselling; 2 Music therapy group; 3 Computerised CBT (CCBT); 4 Computerised attentional bias modification; 5 Progressive muscle relaxation individual +pill placebo; 6 Interpersonal psychotherapy (IPT) individual +pill placebo; 7 CBT individual (15 sessions or over) + pill placebo; 8 Short-term psychodynamic psychotherapy individual; 9 Mindfulness meditation CD with support; 10 Computerised-CBT (CCBT) with support; 11 CBT individual (15 sessions or over) + imipramine; 12 CBT individual (15 sessions or over) + any SSRI; 13 Progressive muscle relaxation individual + amitriptyline; 14 Short-term psychodynamic psychotherapy individual + any AD; 15 Non-directive/supportive/ person-centred counselling + any SSRI; 16 Non-directive/supportive/ person-centred counselling + any AD; 17 Interpersonal psychotherapy (IPT) individual + any AD; 18 CBT individual (15 sessions or over) + any AD; 19 CBT individual (15 sessions or over) + amitriptyline; 20 Behavioural activation (BA) individual + any AD
Without the use of a class network the following interventions would be disconnected from the rest of the network and would have to be excluded from the analysis: Attention placebo, Mindfulness meditation CD with support, Inactive laser acupuncture, Non-directive/supportive/person-centred counselling + any SSRI, Computerised attentional bias modification, Relaxation training CD with support, Laser acupuncture, and Short-term psychodynamic psychotherapy individual + any SSRI

Figure 101. Network diagram of every study included in analysis by class. Response in completers.

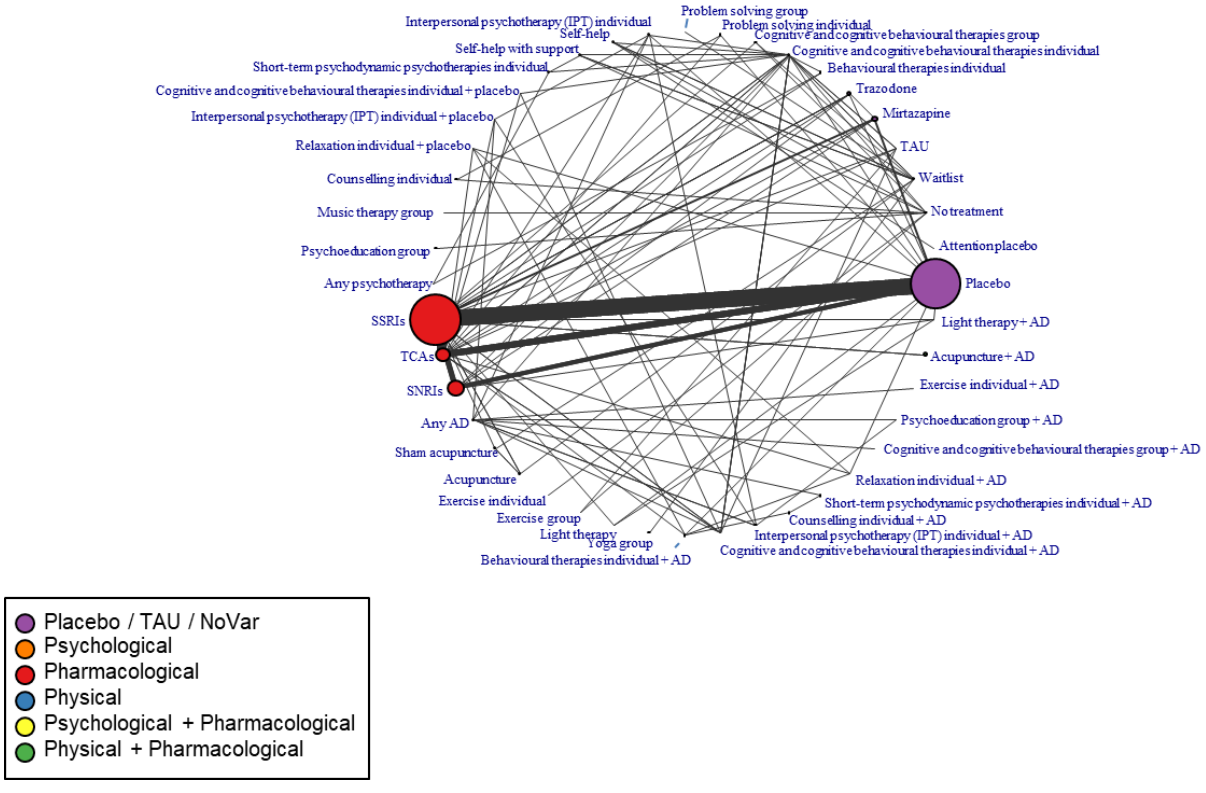
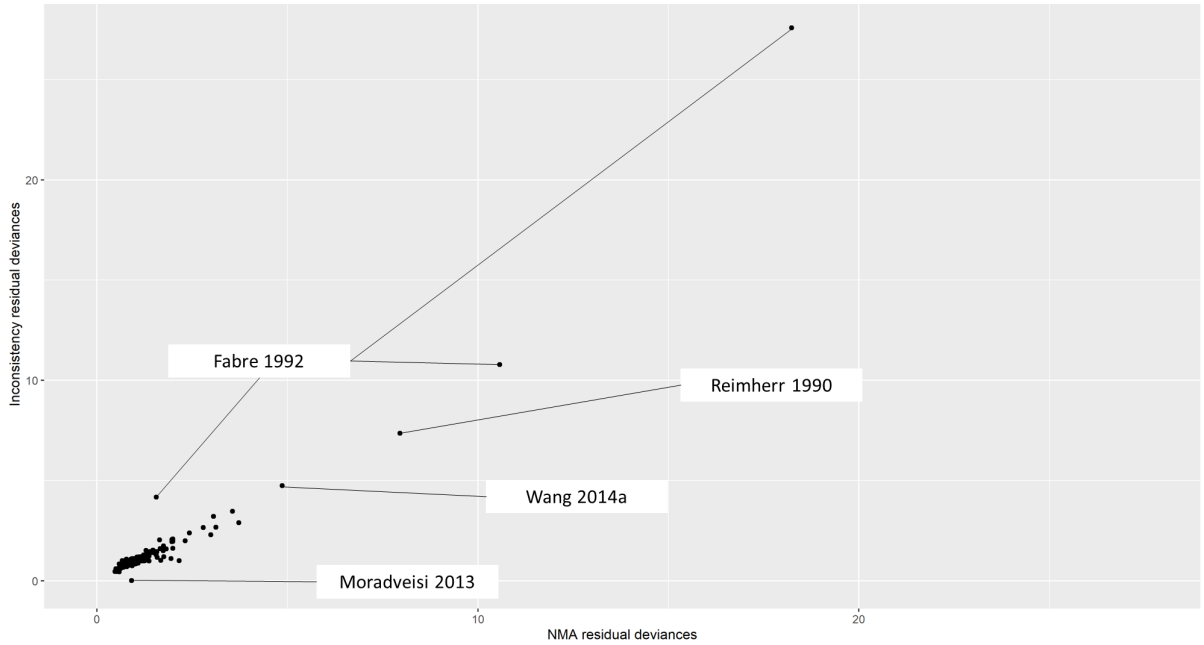


Figure 102. Deviance plot. Response in completers.



There is evidence suggesting the interventions with an increased odds of response compared to Pill placebo are the following (supplement B5, Figure 5.9 in appendix 5):

- Amitriptyline
- Any SSRI
- Any TCA

- Behavioural therapy (Lewinsohn 1976) individual
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + amitriptyline
- CBT individual (15 sessions or over) + any AD
- CBT individual (15 sessions or over) + any SSRI
- CBT individual (15 sessions or over) + impramine
- CBT individual (15 sessions or over) + nortriptyline
- CBT individual (15 sessions or over) + trazodone
- CBT individual (under 15 sessions)
- CBT individual (under 15 sessions) + escitalopram
- Citalopram
- Clomipramine
- Cognitive bibliography
- Duloxetine
- Electroacupuncture + any SSRI
- Electroacupuncture + fluoxetine
- Electroacupuncture + paroxetine
- Escitalopram
- Fluoxetine
- Imipramine
- Lofepramine
- Mirtazapine
- Non-directive/supportive/person-centred counselling
- Nortriptyline
- Paroxetine
- Problem solving group
- Problem solving individual
- Sertraline
- Third-wave cognitive therapy individual + any AD
- Traditional acupuncture + any SSRI
- Traditional acupuncture + paroxetine
- Trazodone
- Venlafaxine

There is evidence to suggest Waitlist has a decreased odds of response compared to Pill placebo.

The classes for which there is evidence of an increased odds of response compared to Pill placebo are the following (supplement B5, Figure 5.10 in appendix 5):

- Acupuncture + AD
- Cognitive and cognitive behavioural therapies individual + AD
- Mirtazapine
- Problem solving group

- SNRIs
- SSRIs
- TCAs
- Trazodone

Waitlist is the only class for which there is evidence of decreased odds of response compared to Pill placebo. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Problem solving group is the highest ranked class at 2nd (95% CrI 1st to 17th), though Acupuncture + AD (6th; 95% CrI 2nd to 15th) and Cognitive and cognitive behavioural therapies individual + AD (7th; 95% CrI 2nd to 15th) also rank highly (Table 132). The highest ranked intervention is Traditional acupuncture + any SSRI, with a posterior median rank of 3rd (95% CrI 1st to 10th) (Excel file in supplement B6: *"Depression NMA more severe RESPcompleters bias-adjusted.xlsx"*, *"Ranks"* worksheet). The lowest ranked class is Waitlist, with a posterior median rank of 36th (95% CrI 30th to 38th). The lowest ranked active class is Counselling individual + AD with a posterior median rank of 33rd (95% CrI 6th to 38th).

Table 132. Posterior mean and median rank and 95% credible intervals by class. Response in completers.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Problem solving group	3.8	2 (1, 17)
Acupuncture + AD	6.4	6 (2, 15)
Cognitive and cognitive behavioural therapies individual + AD	7.2	7 (2, 15)
Exercise individual + AD	9.3	5 (1, 34)
Problem solving individual	11.2	9 (1, 33)
Light therapy + AD	12	10 (2, 31)
Yoga group	12.1	9 (1, 35)
Psychoeducation group	14.2	12 (1, 35)
Behavioural therapies individual	14.3	13 (3, 32)
Cognitive and cognitive behavioural therapies group + AD	15.3	13 (1, 36)
Short-term psychodynamic psychotherapies individual	15.9	14 (2, 35)
Counselling individual	15.9	14 (2, 36)
Exercise group	17.6	16 (2, 36)
Cognitive and cognitive behavioural therapies individual	17.7	17 (6, 32)
Exercise individual	18	16 (1, 38)
TAU	18	17 (8, 31)
TCAs	19.3	19 (13, 26)
Light therapy	19.7	19 (3, 37)
SNRIs	19.8	20 (13, 27)
Relaxation individual + AD	19.9	19 (1, 38)
Self-help	20.1	20 (2, 37)
Interpersonal psychotherapy (IPT) individual + AD	20.6	21 (3, 37)
Mirtazapine	20.8	21 (13, 28)
Behavioural therapies individual + AD	22.5	25 (3, 38)
Cognitive and cognitive behavioural therapies group	23	25 (4, 37)

SSRIs	23.1	23 (16, 29)
Attention placebo	23.3	28 (1, 38)
Acupuncture	23.7	25 (8, 36)
Interpersonal psychotherapy (IPT) individual	23.7	25 (5, 37)
Music therapy group	24.2	27 (3, 38)
Trazodone	24.8	25 (17, 32)
Short-term psychodynamic psychotherapies individual + AD	25.3	29 (4, 38)
Psychoeducation group + AD	25.6	28 (4, 38)
Self-help with support	28	30 (9, 38)
Counselling individual + AD	29.3	33 (6, 38)
Placebo	29.9	30 (24, 35)
Sham acupuncture	30.1	32 (13, 38)
Waitlist	35.4	36 (30, 38)

Outcome: Response in those randomised

A further response analysis was first carried out only in all patients who were randomised, using WinBUGS code given in supplement B5, appendix 1. After excluding trials with zero events or with the number events equal to the denominator in all arms, 280 trials reported response. Out of the remaining studies, 31 reported change from baseline in completers (but not response) and 53 reported baseline and final scores in completers (but not response or change from baseline). This meant that 364 trials of 83 interventions and 43 classes were included in the analysis for this outcome (Table 133,

Figure 103, Figure 104).

Lower posterior mean residual deviance and between study heterogeneity in the inconsistency model suggested evidence of inconsistency (supplement B5, Table 3.13 in appendix 3). The inconsistency model notably predicted the data in one study (Sahranavard 2018) much better than the consistency model, further adding evidence of inconsistency (Figure 105). This study compared Waitlist, Dialectical behavioural therapy (DBT) individual and CBT group (under 15 sessions).

Reported results are based on the random-effects NMA model, assuming consistency but should be interpreted with caution due to the identification of potential inconsistency. Relative to the size of the intervention effect estimates, moderate between trial heterogeneity was observed for this outcome $\left(\tau_{study} = 0.26\ (95\%\ \text{CrI}\ 0.21\ \text{to}\ 0.31)\right)$. Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.11 & 5.12 in appendix 5).

Table 133. Interventions, classes and number of patients (N) included in Response in those randomised analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	15384	Placebo	1	15384	
2	Attention placebo	36	Attention placebo	2	36	
3	No treatment	441	No treatment	3	441	
4	Waitlist	349	Waitlist	4	349	
5	TAU	176	TAU	5	176	
6	Mirtazapine	2629	Mirtazapine	6	2629	
7	Trazodone	1181	Trazodone	7	1181	
8	Behavioural activation (BA) individual	368	Behavioural therapies individual	8	368	1
9	CBT individual (15 sessions or over)	470	Cognitive and cognitive behavioural therapies individual	9	779	1
10	CBT individual (under 15 sessions)	260				
11	Dialectical behavioural therapy (DBT) individual	10				
12	Third-wave cognitive therapy individual	39				
13	CBT group (under 15 sessions)	155	Cognitive and cognitive behavioural therapies group	10	155	1
14	Problem solving individual	338	Problem solving individual	11	338	1
15	Non-directive/supportive/person-centred counselling	421	Counselling individual	12	421	1
16	Interpersonal psychotherapy (IPT) individual	61	Interpersonal psychotherapy (IPT) individual	13	61	1
17	Cognitive bibliotherapy	32	Self-help	14	168	2
18	Computerised-CBT (CCBT)	97				
19	Mindfulness meditation CD	39				
20	Cognitive bibliotherapy with support	66	Self-help with support	15	274	1

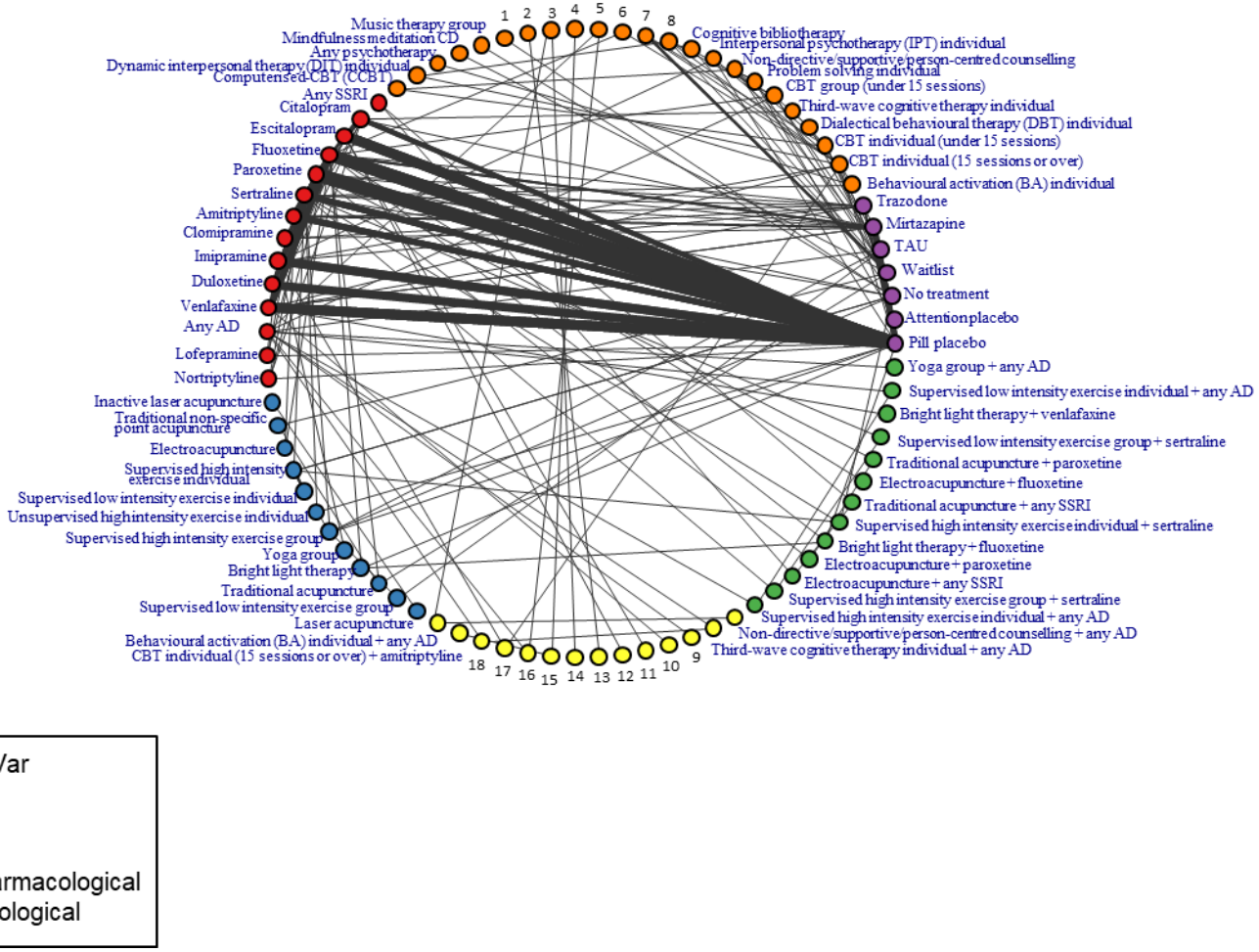
21	Computerised-CBT (CCBT) with support	208				
22	Dynamic interpersonal therapy (DIT) individual	73	Short-term psychodynamic psychotherapies individual	16	217	1
23	Short-term psychodynamic psychotherapy individual	144				
24	Music therapy group	12	Music therapy group	17	12	1
25	Mindfulness-based cognitive therapy (MBCT) group	15	Mindfulness or meditation group	18	15	1
26	Peer support group	39	Peer support group	19	39	1
27	Any psychotherapy	22	Any psychotherapy	20	22	1
28	CBT individual (15 sessions or over) + pill placebo	14	Cognitive and cognitive behavioural therapies individual + placebo	21	58	1
29	CBT individual (under 15 sessions) + pill placebo	44				
30	Non-directive/supportive/person-centred counselling + pill placebo	26	Counselling individual + placebo	22	26	1
31	Any SSRI	156	SSRIs	23	26961	3
32	Citalopram	3242				
33	Escitalopram	5863				
34	Fluoxetine	7732				
35	Paroxetine	6661				
36	Sertraline	3307				
37	Amitriptyline	2519	TCAs	24	5437	4
38	Clomipramine	414				
39	Imipramine	2061				
40	Lofepramine	242				
41	Nortriptyline	201				
42	Duloxetine	5472	SNRIs	25	10469	3
43	Venlafaxine	4997				
44	Any AD	188	Any AD	26	188	5
45	Inactive laser acupuncture	22	Sham acupuncture	27	74	6
46	Traditional non-specific point acupuncture	52				
47	Electroacupuncture	77	Acupuncture	28	217	6
48	Laser acupuncture	25				
49	Traditional acupuncture	115				
50	Supervised high intensity exercise individual	114	Exercise individual	29	273	7
51	Supervised low intensity exercise individual	106				
52	Unsupervised high intensity exercise individual	53				
53	Supervised high intensity exercise group	106	Exercise group	30	126	1

54	Supervised low intensity exercise group	20				
55	Yoga group	45	Yoga group	31	45	1
56	Bright light therapy	32	Light therapy	32	32	6
57	Behavioural activation (BA) individual + any AD	10	Behavioural therapies individual + AD	33	10	8
58	CBT individual (15 sessions or over) + amitriptyline	12	Cognitive and cognitive behavioural therapies individual + AD	34	158	8
59	CBT individual (15 sessions or over) + any AD	10				
60	CBT individual (15 sessions or over) + imipramine	25				
61	CBT individual (15 sessions or over) + trazodone	11				
62	CBT individual (under 15 sessions) + escitalopram	52				
63	CBT individual (under 15 sessions) + sertraline	38				
64	Third-wave cognitive therapy individual + any AD	10				
65	CBT group (under 15 sessions) + any AD	20	Cognitive and cognitive behavioural therapies group + AD	35	20	8
66	Interpersonal counselling individual + venlafaxine	12	Counselling individual + AD	36	52	8
67	Non-directive/supportive/person-centred counselling + any AD	15				
68	Non-directive/supportive/person-centred counselling + fluoxetine	25				
69	Cognitive bibliotherapy + escitalopram	79	Self-help + AD	37	79	8
70	Peer support group + any AD	42	Peer support group + AD	38	42	8
71	Supervised high intensity exercise individual + any AD	14	Exercise individual + AD	39	40	8
72	Supervised high intensity exercise individual + sertraline	15				
73	Supervised low intensity exercise individual + any AD	11				
74	Supervised high intensity exercise group + sertraline	42	Exercise group + AD	40	79	8
75	Supervised low intensity exercise group + sertraline	37				
76	Yoga group + any AD	15	Yoga group + AD	41	15	8
77	Electroacupuncture + any SSRI	160	Acupuncture + AD	42	553	9
78	Electroacupuncture + fluoxetine	48				
79	Electroacupuncture + paroxetine	80				

80	Traditional acupuncture + any SSRI	161				
81	Traditional acupuncture + paroxetine	104				
82	Bright light therapy + fluoxetine	29	Light therapy + AD	43	54	6
83	Bright light therapy + venlafaxine	25				

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 103. Network diagram of every study included in analysis by intervention. Response in those randomised.



1 Minfulness-based cognitive therapy (MBCT) group; 2 Non-directive/supportive/person-centred counselling + pill placebo; 3 CBT individual (under 15 sessions) + pill placebo; 4 CBT individual (15 sessions or over) + pill placebo; 5 Peer support; 6 Short-term psychodynamic therapy individual; 7 Computerised-CBT (CCBT) with support; 8 Cognitive

bibliotherapy with support; 9 CBT group (under 15 sessions) + any AD; 10 Interpersonal counselling individual + venlafaxine; 11 Cognitive bibliotherapy + escitalopram; 12 CBT individual (under 15 sessions) + citalopram; 13 Non-directive/supportive/person-centred counselling + fluoxetine; 14 CBT individual (under 15 sessions) + sertraline; 15 Peer support group + any AD; 16 CBT individual (15 sessions or over) + trazodone; 17 CBT individual (15 sessions or over) + imipramine; 18 CBT individual (15 sessions or over) + any AD

Without the use of a class network the following interventions would be disconnected from the rest of the network and would have to be excluded from the analysis: CBT individual (15 sessions or over) + pill placebo, CBT individual (under 15 sessions) + pill placebo, Non-directive/supportive/person-centred counselling + pill placebo, Any SSRI, Inactive laser acupuncture, Behavioural activation (BA) individual + any AD, CBT individual (15 sessions or over) + amitriptyline, Electroacupuncture + any SSRI, CBT individual (15 sessions or over) + trazodone, CBT individual (under 15 sessions) + sertraline, Non-directive/supportive/person-centred counselling + fluoxetine, Traditional acupuncture + any SSRI, Laser acupuncture, and Non-directive/supportive/person-centred counselling + any AD

Figure 104. Network diagram of every study included in analysis by class. Response in those randomised.

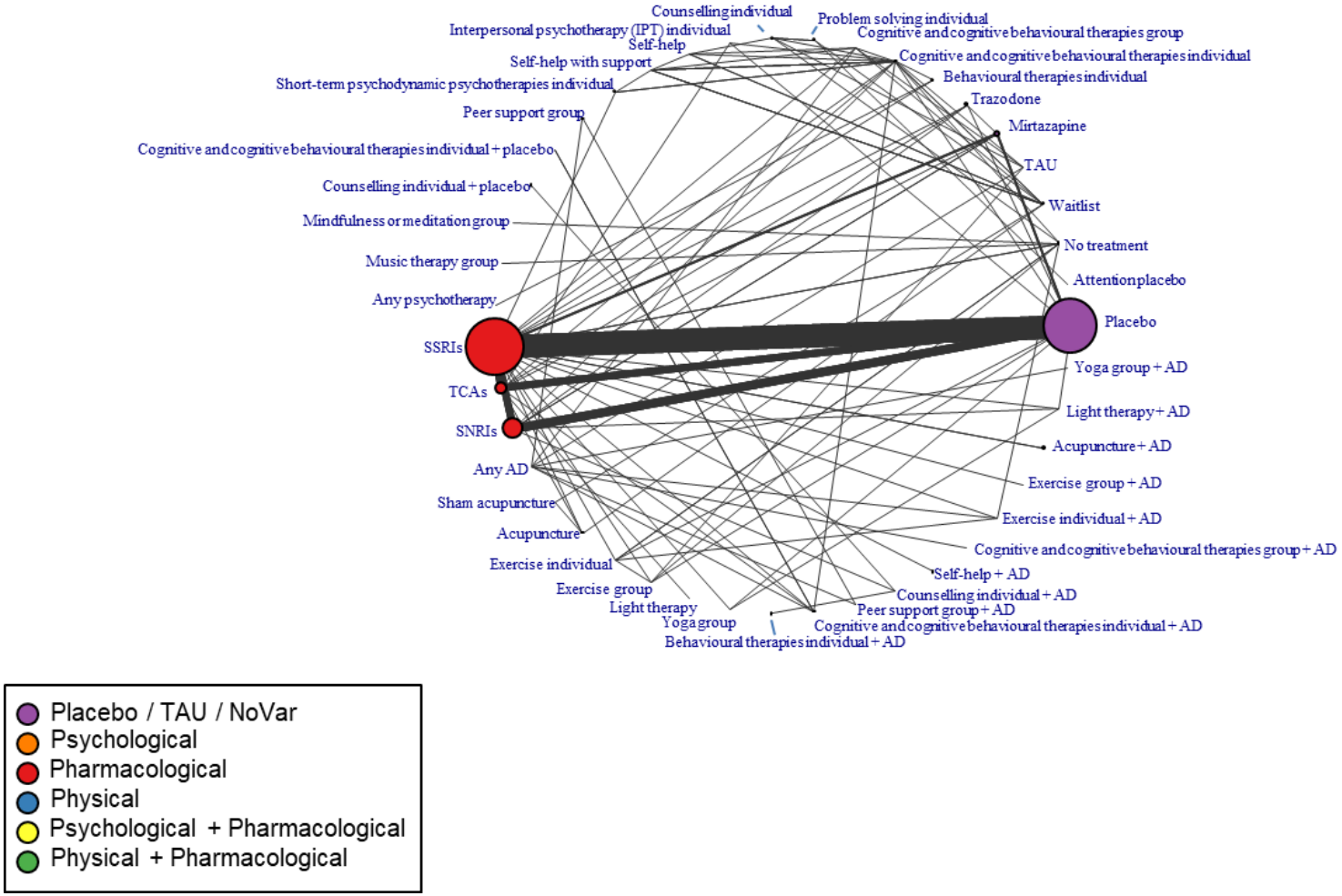
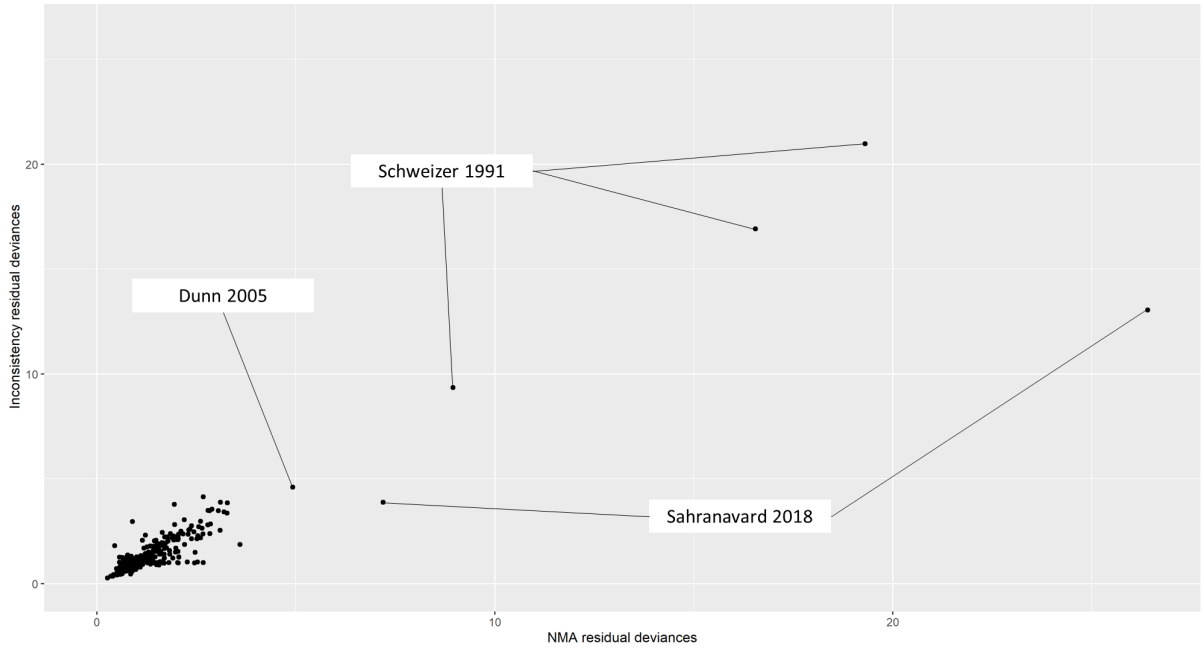


Figure 105. Deviance plot. Response in those randomised.



Interventions for which evidence suggests an increased odds of response compared to Pill placebo are the following (supplement B5, Figure 5.11 in appendix 5):

- Amitriptyline
- Any AD
- Any SSRI
- Behavioural activation (BA) individual
- Bright light therapy
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT group (under 15 sessions)
- CBT group (under 15 sessions) + any AD
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + any AD
- CBT individual (15 sessions or over) + imipramine
- CBT individual (15 sessions or over) + trazodone
- CBT individual (under 15 sessions)
- Citalopram
- Clomipramine
- Cognitive bibliotherapy
- Cognitive bibliotherapy with support
- Computerised-CBT (CCBT)
- Computerised-CBT (CCBT) with support
- Dynamic interpersonal therapy (DIT) individual
- Electroacupuncture + any SSRI
- Electroacupuncture + fluoxetine
- Electroacupuncture + paroxetine

- Escitalopram
- Fluoxetine
- Imipramine
- Interpersonal psychotherapy (IPT) individual
- Lofepramine
- Mindfulness medication CD
- Mindfulness-based cognitive therapy (MBCT) group
- Mirtazapine
- Non-directive/supportive/person-centred counselling
- Nortriptyline
- Paroxetine
- Peer support group
- Peer support group + any AD
- Problem solving individual
- Sertraline
- Short-term psychodynamic psychotherapy individual
- Supervised high intensity exercise group
- Supervised high intensity exercise group + sertraline
- Supervised high intensity exercise individual
- Supervised high intensity exercise individual + any AD
- Supervised high intensity exercise individual + sertraline
- Supervised low intensity exercise individual + any AD
- Third-wave cognitive therapy individual
- Third-wave cognitive therapy individual + any AD
- Traditional acupuncture + any SSRI
- Traditional acupuncture + paroxetine
- Trazodone
- Unsupervised high intensity individual
- Venlafaxine
- Yoga group + any AD

There is evidence suggesting Waitlist is the only intervention and class with a decreased odds in response compared to Pill placebo.

The classes for which there is evidence of an increased odds of response compared to Placebo are the following (supplement B5, Figure 5.12 in appendix 5):

- Acupuncture + AD
- Any AD
- Cognitive and cognitive behavioural therapies individual
- Cognitive and cognitive behavioural therapies individual + AD
- Exercise individual + AD
- Mindfulness or meditation group
- Mirtazapine
- Peer support group
- SNRIs

- SSRIs
- TCAs
- Trazodone
- Yoga group + AD

For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Mindfulness or meditation group is the highest ranked class at 1st (95% CrI 1st to 4th) (Table 134). The highest ranked intervention is Mindfulness-based cognitive therapy (MBCT) group with a posterior median rank of 1st (95% CrI 1st to 3rd) (Excel file in supplement B6: *"Depression NMA more severe RESPitt.xlsx"*, *"Ranks"* worksheet). The lowest ranked class and intervention is Waitlist, with a median class rank of 36th (95% CrI 33rd to 38th). The lowest ranked active class is Trazodone at 29th (95% CrI 24th to 33rd) (Table 134).

Table 134. Posterior mean and median rank and 95% credible intervals by class. Response in those randomised.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Mindfulness or meditation group	1.48	1 (1, 4)
Yoga group + AD	6.91	4 (1, 32)
Exercise individual + AD	8.25	7 (2, 25)
Cognitive and cognitive behavioural therapies individual + AD	8.39	7 (2, 21)
Peer support group	9.03	7 (2, 29)
Peer support group + AD	9.64	7 (1, 35)
Exercise group + AD	10.21	8 (2, 33)
Cognitive and cognitive behavioural therapies group + AD	10.36	7 (2, 36)
Behavioural therapies individual + AD	12.55	6 (1, 38)
Cognitive and cognitive behavioural therapies individual	13.92	14 (6, 24)
Light therapy + AD	14.44	12 (3, 36)
Behavioural therapies individual	14.87	13 (4, 35)
Self-help	15.07	14 (4, 34)
Short-term psychodynamic psychotherapies individual	16.16	15 (5, 32)
Acupuncture + AD	16.29	16 (10, 23)
Self-help with support	17.34	17 (6, 33)
Counselling individual + AD	17.97	15 (3, 38)
Interpersonal psychotherapy (IPT) individual	18.9	18 (5, 36)
Problem solving individual	19.43	18 (5, 36)
Light therapy	20.52	19 (2, 38)
Music therapy group	21.57	21 (5, 38)
Counselling individual	22.14	22 (6, 37)
Self-help + AD	22.42	22 (3, 38)
Mirtazapine	22.98	23 (18, 28)
Yoga group	23.32	24 (5, 38)
TCAs	23.45	23 (18, 29)
SNRIs	24.03	24 (19, 29)
Cognitive and cognitive behavioural therapies group	24.44	25 (7, 37)

Acupuncture	24.51	26 (6, 38)
Exercise individual	24.77	25 (10, 37)
Exercise group	25.93	27 (11, 37)
SSRIs	26.53	27 (22, 31)
Trazodone	28.71	29 (24, 33)
Sham acupuncture	30.33	34 (7, 38)
TAU	30.9	31 (23, 36)
Placebo	32.04	32 (28, 36)
Attention placebo	35.03	36 (27, 38)
Waitlist	36.17	36 (33, 38)

Outcome: SMD

This analysis was carried out on all patients randomized where possible, using WinBUGS code given in supplement B5, appendix 1. However, if trials only reported the number of completers then these were also included. After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 146 trials reported CFB. Out of the remaining studies 172 reported baseline and follow-up scores (but not CFB) and 34 reported response (but not CFB or baseline and follow-up). This meant that 352 trials of 99 interventions and 50 classes were included in the analysis for this outcome (Table 135,

Figure 106, Figure 107). One study (Leinonen 2007), comparing Escitalopram versus Short-term psychodynamic psychotherapy individual + any AD, was excluded because it was causing convergence issues in the model.

The model was a reasonable fit to the data, with the exception of two very poorly fitting studies (Schweitzer 1991 and Sahranavard 2018). Schweitzer 1991 compared different regimens of venlafaxine, which may explain the poor fit for this study. Between-study heterogeneity and posterior mean residual deviance were slightly lower in the inconsistency model than in the random effects consistency model (supplement B5, Table 3.14 in appendix 3). The inconsistency model notably predicted the data in three studies much better than the consistency model, further adding evidence of inconsistency (

Figure 108).

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The posterior mean residual deviance, DIC and between study heterogeneity was substantially reduced compared to the base-case consistency model (supplement B5, Table 3.14 in appendix 3), and the bias parameter was negative (-2.57; 95%CrI -3.65 to -1.51), indicating that smaller studies tended to favour active interventions versus inactive controls or counselling. Reported results are therefore based on the bias-adjusted random-effects NMA model. Results from the bias-adjusted model and from the base-case unadjusted model can be found in Excel files in supplement B6 ("*Depression NMA more severe SMD bias-adjusted.xlsx"* and *"Depression NMA more severe SMD base-case.xlsx"*, respectively).

Moderate between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.19\ (95\%\ CrI\ 0.15\ to\ 0.23)$). Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.13 & 5.14 in appendix 5).

Table 135. Interventions, classes and number of patients (N) included in SMD analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	12554	Placebo	1	12554	
2	Attention placebo	61	Attention placebo	2	61	
3	No treatment	504	No treatment	3	504	
4	Waitlist	526	Waitlist	4	526	
5	TAU	220	TAU	5	220	
6	Mirtazapine	1884	Mirtazapine	6	1884	
7	Trazodone	1072	Trazodone	7	1072	
8	Behavioural activation (BA) individual	368	Behavioural therapies individual	8	378	1
9	Behavioural therapy (Lewinsohn 1976) individual	10				
10	CBT individual (15 sessions or over)	626	Cognitive and cognitive behavioural therapies individual	9	1044	1
11	CBT individual (under 15 sessions)	369				
12	Dialectical behavioural therapy (DBT) individual	10				
13	Third-wave cognitive therapy individual	39				
14	CBT group (under 15 sessions)	165	Cognitive and cognitive behavioural therapies group	10	165	1
15	Problem solving individual	367	Problem solving individual	11	367	1
16	Problem solving group	47	Problem solving group	12	47	1
17	Non-directive/supportive/person-centred counselling	404	Counselling individual	13	404	1
18	Interpersonal psychotherapy (IPT) individual	146	Interpersonal psychotherapy (IPT) individual	14	146	1

19	Psychoeducational group programme	44	Psychoeducation group	15	44	1
20	Cognitive bibliotherapy	159	Self-help	16	344	2
21	Computerised-CBT (CCBT)	120				
22	Computerised attentional bias modification	26				
23	Mindfulness meditation CD	39				
24	Cognitive bibliotherapy with support	66	Self-help with support	17	267	3
25	Computerised-CBT (CCBT) with support	164				
26	Mindfulness meditation CD with support	19				
27	Relaxation training CD with support	18				
28	Dynamic interpersonal therapy (DIT) individual	73	Short-term psychodynamic psychotherapies individual	18	233	1
29	Short-term psychodynamic psychotherapy individual	160				
30	Music therapy group	12	Music therapy group	19	12	1
31	Mindfulness-based cognitive therapy (MBCT) group	15	Mindfulness or meditation group	20	15	1
32	Peer support group	39	Peer support group	21	39	1
33	Any psychotherapy	37	Any psychotherapy	22	37	1
34	CBT individual (15 sessions or over) + pill placebo	17	Cognitive and cognitive behavioural therapies individual + placebo	23	61	1
35	CBT individual (under 15 sessions) + pill placebo	44				
36	Interpersonal psychotherapy (IPT) individual + pill placebo	69	Interpersonal psychotherapy (IPT) individual + placebo	24	69	1
37	Non-directive/supportive/person-centred counselling + pill placebo	26	Counselling individual + placebo	25	26	1
38	Progressive muscle relaxation individual + pill placebo	11	Relaxation individual + placebo	26	11	1
39	Any SSRI	207	SSRIs	27	22018	4
40	Citalopram	2195				
41	Escitalopram	4930				
42	Fluoxetine	6031				
43	Paroxetine	5861				
44	Sertraline	2794				
45	Amitriptyline	2462	TCAs	28	4524	5
46	Any TCA	21				
47	Clomipramine	345				
48	Imipramine	1306				

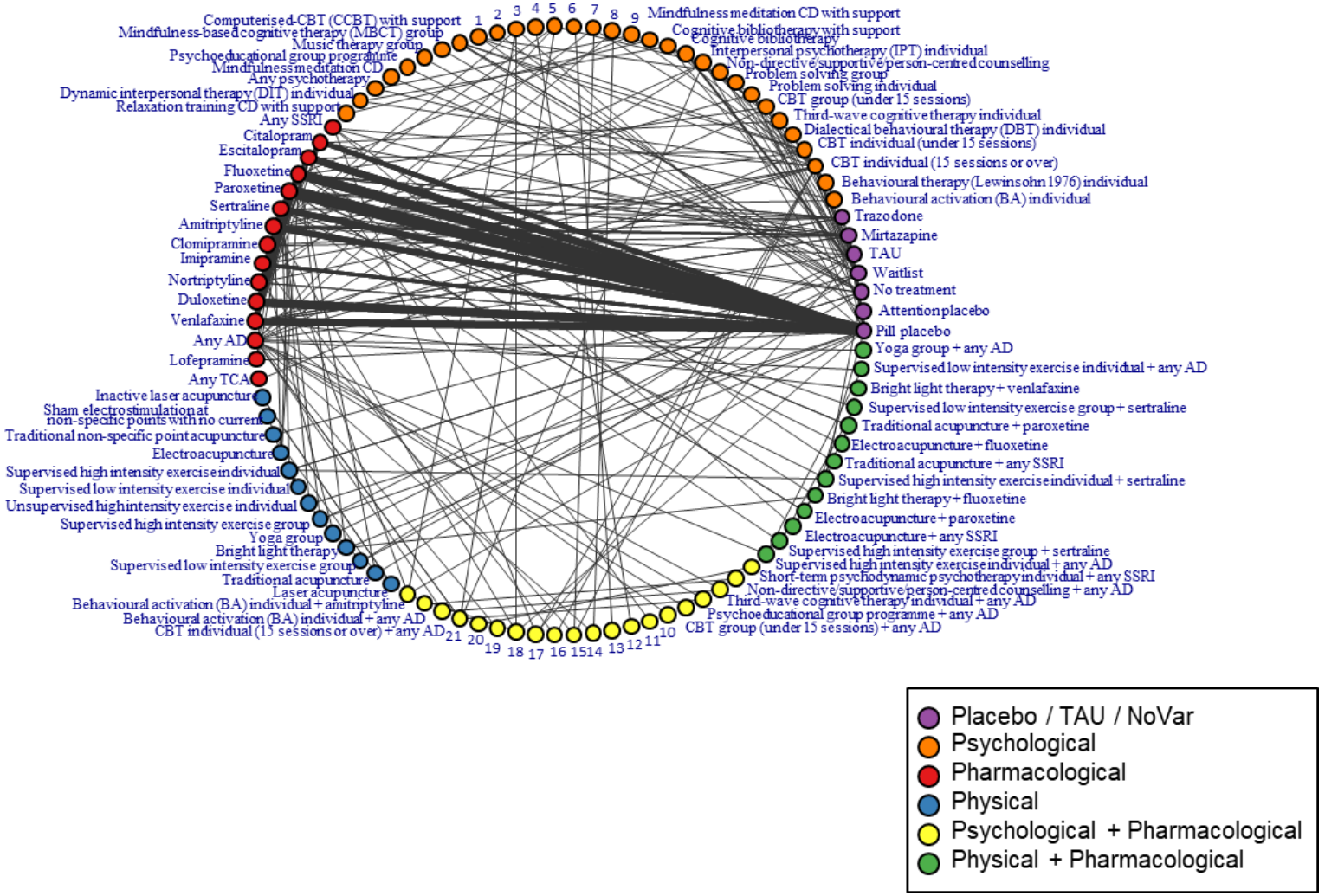
49	Lofepramine	145				
50	Nortriptyline	245				
51	Duloxetine	5269	SNRIs	29	9538	4
52	Venlafaxine	4269				
53	Any AD	452	Any AD	30	452	6
54	Inactive laser acupuncture	34	Sham acupuncture	31	108	1
55	Sham electrostimulation at non-specific points with no current	22				
56	Traditional non-specific point acupuncture	52				
57	Electroacupuncture	110	Acupuncture	32	264	1
58	Laser acupuncture	39				
59	Traditional acupuncture	115				
60	Supervised high intensity exercise individual	128	Exercise individual	33	298	7
61	Supervised low intensity exercise individual	117				
62	Unsupervised high intensity exercise individual	53				
63	Supervised high intensity exercise group	69	Exercise group	34	106	3
64	Supervised low intensity exercise group	37				
65	Yoga group	65	Yoga group	35	65	1
66	Bright light therapy	32	Light therapy	36	32	1
67	Behavioural activation (BA) individual + amitriptyline	12	Behavioural therapies individual + AD	37	22	8
68	Behavioural activation (BA) individual + any AD	10				
69	CBT individual (15 sessions or over) + any AD	10	Cognitive and cognitive behavioural therapies individual + AD	38	192	8
70	CBT individual (15 sessions or over) + any SSRI	43				
71	CBT individual (15 sessions or over) + imipramine	25				
72	CBT individual (15 sessions or over) + nortriptyline	18				
73	CBT individual (under 15 sessions) + escitalopram	48				
74	CBT individual (under 15 sessions) + sertraline	38				
75	Third-wave cognitive therapy individual + any AD	10				
76	CBT group (under 15 sessions) + any AD	63	Cognitive and cognitive behavioural therapies group + AD	39	63	8

77	Interpersonal counselling individual + venlafaxine	12	Interpersonal psychotherapy (IPT) individual + AD	40	99	8
78	Interpersonal psychotherapy (IPT) individual + any AD	87				
79	Non-directive/supportive/person-centred counselling + any AD	15	Counselling individual + AD	41	57	8
80	Non-directive/supportive/person-centred counselling + any SSRI	17				
81	Non-directive/supportive/person-centred counselling + fluoxetine	25				
82	Short-term psychodynamic psychotherapy individual + any AD	113	Short-term psychodynamic psychotherapies individual + AD	42	131	8
83	Short-term psychodynamic psychotherapy individual + any SSRI	18				
84	Psychoeducational group programme + any AD	27	Psychoeducation group + AD	43	27	8
85	Peer support group + any AD	42	Peer support group + AD	44	42	8
86	Progressive muscle relaxation individual + amitriptyline	10	Relaxation individual + AD	45	10	8
87	Supervised high intensity exercise individual + any AD	14	Exercise individual + AD	46	40	8
88	Supervised high intensity exercise individual + sertraline	15				
89	Supervised low intensity exercise individual + any AD	11				
90	Supervised high intensity exercise group + sertraline	42	Exercise group + AD	47	79	8
91	Supervised low intensity exercise group + sertraline	37				
92	Yoga group + any AD	15	Yoga group + AD	48	15	8
93	Electroacupuncture + any SSRI	160	Acupuncture + AD	49	584	9
94	Electroacupuncture + fluoxetine	46				
95	Electroacupuncture + paroxetine	71				
96	Traditional acupuncture + any SSRI	206				

97	Traditional acupuncture + paroxetine	101				
98	Bright light therapy + fluoxetine	29	Light therapy + AD	50	54	1
99	Bright light therapy + venlafaxine	25		50		

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 106. Network diagram of every study included in analysis by intervention. SMD.



1 Computerised-CBT (C-CBT); 2 Computerised attentional bias modification; 3 Progressive muscle relaxation individual + pill placebo; 4 Non-directive/supportive/person-centred counselling + pill placebo; 5 Interpersonal psychotherapy (IPT) individual + pill placebo; 6 CBT individual (under 15 sessions) + pill placebo; 7 CBT individual (15 sessions or over) + pill placebo; 8 Peer support group; 9 Short-term psychodynamic psychotherapy individual; 10 Interpersonal counselling individual + venlafaxine; 11 CBT individual (under 15 sessions) + escitalopram; 12 Non-directive/supportive/person-centred counselling + fluoxetine; 13 CBT individual (under 15 sessions) + sertraline; 14 Peer support group + any AD; 15 CBT individual (15 sessions or over) + nortriptyline; 16 CBT individual (15 sessions or over) + imipramine; 17 CBT individual (15 sessions or over) + any SSRI; 18 Progressive muscle relaxation therapy + amitriptyline; 19 Short-term psychodynamic psychotherapy individual + any AD; 20 Non-directive/supportive/person-centred counselling + any SSRI; 21 Interpersonal psychotherapy (IPT) individual + any AD
Without the use of a class network the following interventions would be disconnected from the rest of the network and would have to be excluded from the analysis: Mindfulness meditation CD with support, CBT individual (under 15 sessions) + pill placebo, Non-directive/supportive/person-centred counselling + pill placebo, Inactive laser acupuncture, Behavioural activation (BA) individual + any AD, Non-directive/supportive/person-centred counselling + any SSRI, Relaxation training CD with support, CBT individual (under 15 sessions) + sertraline, Non-directive/supportive/person-centred counselling + fluoxetine, Laser acupuncture, Non-directive/supportive/person-centred counselling + any AD, and Short-term psychodynamic psychotherapy individual + any SSRI

Figure 107. Network diagram of every study included in analysis by class. SMD.

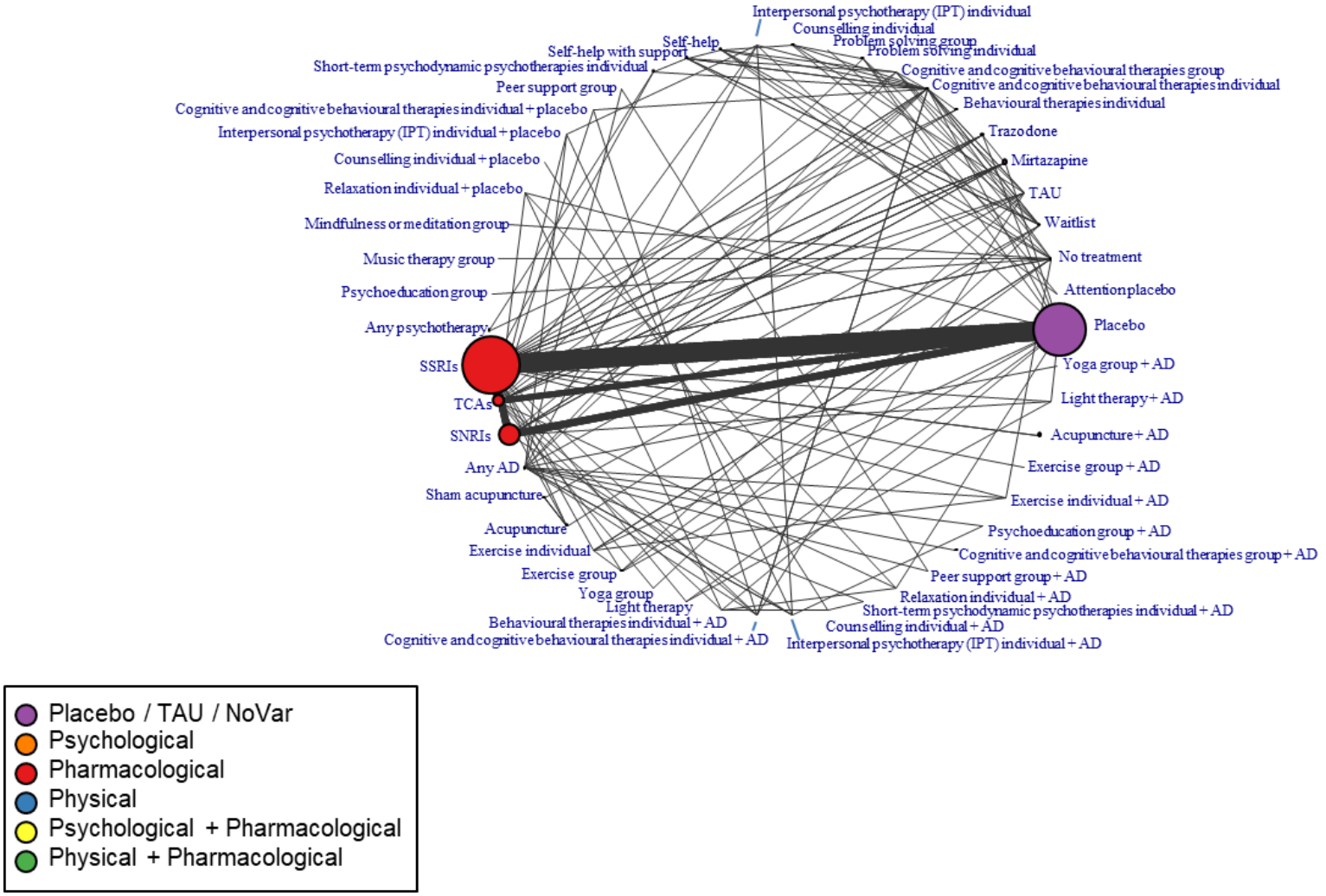
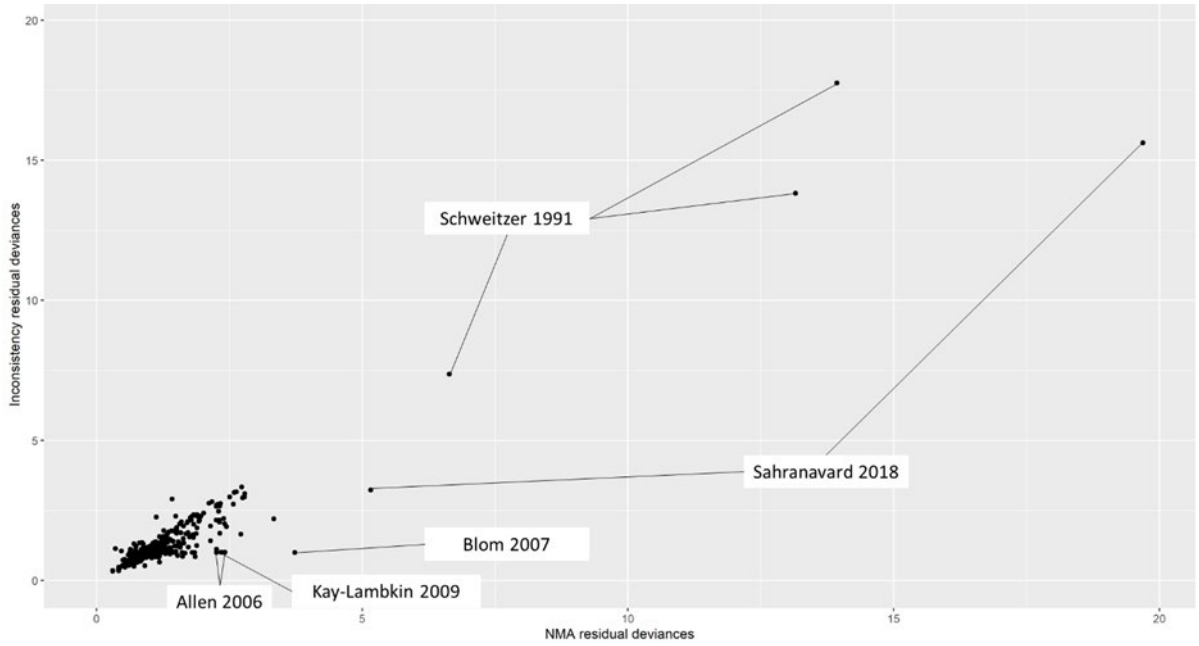


Figure 108. Deviance plot. SMD.



There is evidence that the following interventions have a lower standardized mean difference in depression compared to Pill placebo (supplement B5, Figure 5.13 in appendix 5):

- Amitriptyline
- Any AD
- Any SSRI
- Behavioural activation (BA) individual
- Behavioural therapy (Lewinsohn 1976) individual
- Bright light therapy
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT group (under 15 sessions) + any AD
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + any AD
- CBT individual (15 sessions or over) + any SSRI
- CBT individual (15 sessions or over) + imipramine
- CBT individual (under 15 sessions)
- CBT individual (under 15 sessions) + escitalopram
- CBT individual (under 15 sessions) + sertraline
- Citalopram
- Clomipramine
- Cognitive bibliotherapy
- Computerised-CBT (CCBT)
- Computerised-CBT (CCBT) with support
- Dialectical behavioural therapy (DBT) individual
- Duloxetine
- Dynamic interpersonal therapy (DIT) individual

- Electroacupuncture
- Electroacupuncture + any SSRI
- Electroacupuncture + fluoxetine
- Electroacupuncture + paroxetine
- Escitalopram
- Fluoxetine
- Imipramine
- Interpersonal psychotherapy (IPT) individual
- Interpersonal psychotherapy (IPT) individual + any AD
- Lofepramine
- Mindfulness meditation CD
- Mindfulness-based cognitive therapy (MBCT) group
- Mirtazapine
- Non-directive/supportive/person-centred counselling
- Paroxetine
- Peer support group
- Peer support group + any AD
- Problem solving group
- Problem solving individual
- Psychoeducational group programme
- Sertraline
- Short-term psychodynamic psychotherapy individual
- Supervised high intensity exercise group + sertraline
- Supervised high intensity exercise individual + any AD
- Supervised low intensity exercise group + sertraline
- Third-wave cognitive therapy individual
- Third-wave cognitive therapy individual + any AD
- Traditional acupuncture
- Traditional acupuncture + any SSRI
- Traditional acupuncture + paroxetine
- Venlafaxine
- Yoga group
- Yoga group + any AD

The only class/intervention for which there was some evidence of having a higher standardized mean difference than Pill placebo was Waitlist.

The following classes have a lower standardized mean difference compared to Pill placebo (supplement B5, Figure 5.14 in appendix 5):

- Acupuncture + AD
- Any AD
- Behavioural therapies individual
- Cognitive and cognitive behavioural therapies individual
- Cognitive and cognitive behavioural therapies individual + AD
- Exercise group + AD

- Light therapy + AD
- Mindfulness or meditation group
- Mirtazapine
- Peer support group
- Problem solving group
- Problem solving individual
- Psychoeducation group
- SNRIs
- SSRIs
- TAU
- TCAs
- Yoga group
- Yoga group + AD

For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Mindfulness or meditation group is the highest ranked class at 1st (95% CrI 1st to 4th) (Table 136). The highest ranked intervention, Mindfulness-based cognitive therapy (MBCT) group, belongs to this class with a posterior median rank of 1st (95% CrI 1st to 3rd) (Excel file in supplement B6: *"Depression NMA more severe SMD bias-adjusted.xlsx"*, *"Ranks"* worksheet). The lowest ranked class and intervention is Waitlist, with a posterior median class rank of 39th (95% CrI 31st to 43rd). The lowest ranked active class and intervention is Trazodone, with a posterior median class rank of 34th (95% CrI 27th to 40th).

Table 136. Posterior mean and median rank and 95% credible intervals by class. SMD.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Mindfulness or meditation group	1.41	1 (1, 4)
Problem solving group	3.76	3 (1, 12)
Yoga group + AD	7.82	4 (1, 38)
Peer support group	9.83	8 (3, 30)
Peer support group + AD	10.42	7 (2, 39)
Exercise group + AD	10.63	8 (2, 37)
Cognitive and cognitive behavioural therapies individual + AD	11.09	10 (4, 24)
Cognitive and cognitive behavioural therapies group + AD	12.86	9 (2, 40)
Psychoeducation group	14.18	12 (3, 36)
Yoga group	14.26	12 (3, 39)
Self-help	14.99	13 (3, 41)
Behavioural therapies individual	15.97	15 (5, 33)
Exercise individual + AD	15.98	13 (3, 40)
Light therapy + AD	16.07	15 (5, 34)
Problem solving individual	16.22	15 (5, 36)
Acupuncture + AD	16.88	17 (9, 26)
Cognitive and cognitive behavioural therapies individual	17.28	17 (8, 27)
Counselling individual	19.96	19 (7, 39)

Light therapy	20.89	20 (6, 40)
Self-help with support	21.32	20 (6, 41)
Interpersonal psychotherapy (IPT) individual + AD	21.32	20 (4, 42)
Short-term psychodynamic psychotherapies individual	22.08	22 (8, 38)
Interpersonal psychotherapy (IPT) individual	25.01	24 (8, 41)
Acupuncture	26.35	26 (12, 39)
Short-term psychodynamic psychotherapies individual + AD	26.51	29 (3, 43)
Psychoeducation group + AD	26.59	28 (4, 43)
Mirtazapine	27.04	27 (20, 34)
Behavioural therapies individual + AD	28.06	35 (2, 43)
SNRIs	28.07	28 (22, 34)
Sham acupuncture	28.47	29 (12, 41)
TAU	28.96	29 (19, 38)
Relaxation individual + AD	29.23	38 (2, 43)
TCAs	29.34	29 (21, 37)
Music therapy group	29.54	34 (5, 43)
Cognitive and cognitive behavioural therapies group	29.59	31 (11, 42)
Exercise group	30.6	32 (10, 42)
SSRIs	31.21	31 (25, 37)
Exercise individual	31.75	34 (9, 43)
Counselling individual + AD	32.21	40 (4, 43)
Attention placebo	32.27	34 (15, 42)
Trazodone	34.14	34 (27, 40)
Placebo	37	37 (32, 41)
Waitlist	38.83	39 (31, 43)

Assumptions and limitations

- We assumed that our methods for converting baseline and final and response data to CFB would give reliable estimates of CFB. These equations are based on a mathematical relationship with the assumption of normality of the underlying continuous data. As mentioned in the methods section we checked these assumptions by looking at the observed data for studies reporting all outcomes and found good agreement, however this may not apply to the other studies.
- Similarly we assumed that the method we used to convert SMD to response gave reliable estimates of response. This method is well known and recommended by the Cochrane Collaboration, although it is an approximation and may perform poorly at $-5 \geq \ln(OR) \geq 5$ (Chinn 2000).
- For the SMD analysis we needed to make an assumption about the relationship between the standard deviation at baseline and standard deviation at follow-up. Based on an analysis of studies which reported both, we assumed that these were equal.
- We assumed the existence of class effects and modelled the data in this way. For classes with only one or two interventions we needed to make some assumptions about the variance of those classes. However, this did allow for fitting a more flexible model than could otherwise be achieved by fitting fewer class variances. The assumptions we made are highlighted in the report and informed by clinical opinion from members of the guideline committee.
- We assumed additivity of TAU efficacy when given in combination with other treatments. This meant that if TAU was given with other treatments in all arms in a study, we assumed

that the relative effects of the different treatments in each arm would be the same as in a similar study in which TAU was not given in any arms. We assessed the impact of this by fitting a model that assumed a multiplicative effect and found no difference in model fit (see below under '*Post-hoc sensitivity analyses*').

- For estimating the indirect evidence contributions from inconsistency models we assumed that the posterior distributions of relative effects were normally distributed. Whilst they were generally approximately normal, deviations from normality in some cases may have affected our findings regarding which comparisons had significant discrepancies between direct and indirect evidence.

Sensitivity analyses: prespecified

A key assumption in NMA is that of transitivity – i.e. that the balance of effect modifiers (factors that influence the treatment effect) is similar across all trials in the network. In order to explore the validity of this assumption, pre-specified sensitivity analyses were conducted. We also further explored this key assumption using several additional sensitivity analyses that were conducted post-hoc (see 'Sensitivity analyses: post-hoc' below).

In this section we present forest plots comparing relative effects versus a common reference treatment for several prespecified sensitivity analyses.

Table 137 shows the number of RCTs included in the NMAs on the SMD outcome that were rated as low, unclear or high risk of bias for different domains of the RoB tool, for both less and more severe depression.

Table 137. Number of RCTs according to risk of bias ratings for each domain in the NMAs on the SMD outcome for less and more severe depression

Domain	Less severe depression			More severe depression		
	Risk rating			Risk rating		
	Low	Unclear	High	Low	Unclear	High
Allocation Method	52	51	24	77	235	39
Allocation Concealment	48	76	3	70	281	0
Blinding (Participants)	6	14	107	232	12	107
Blinding (Care Adminstrator)	8	9	110	229	11	111
Performance	6	12	109	229	15	107
Detection	13	113	1	61	270	20
Attrition	79	30	18	239	93	19
Selective Reporting	22	78	27	62	123	166

For many domains, there were insufficient studies to analyse a low risk of bias subgroup. We conducted post-hoc sensitivity analyses in the subgroups of studies rated as low risk for attrition (see 'Sensitivity analyses: post-hoc').

Boxplots of risk of bias domains by the number of participants randomised per study arm are shown for less severe depression (Figure 109) and more severe depression (Figure 110). These show that smaller studies are at higher risk of bias across almost all domains in both less and more severe depression.

Figure 109. Boxplots showing the number of participants randomised per study arm by risk of bias rating for each risk of bias domain in less severe depression

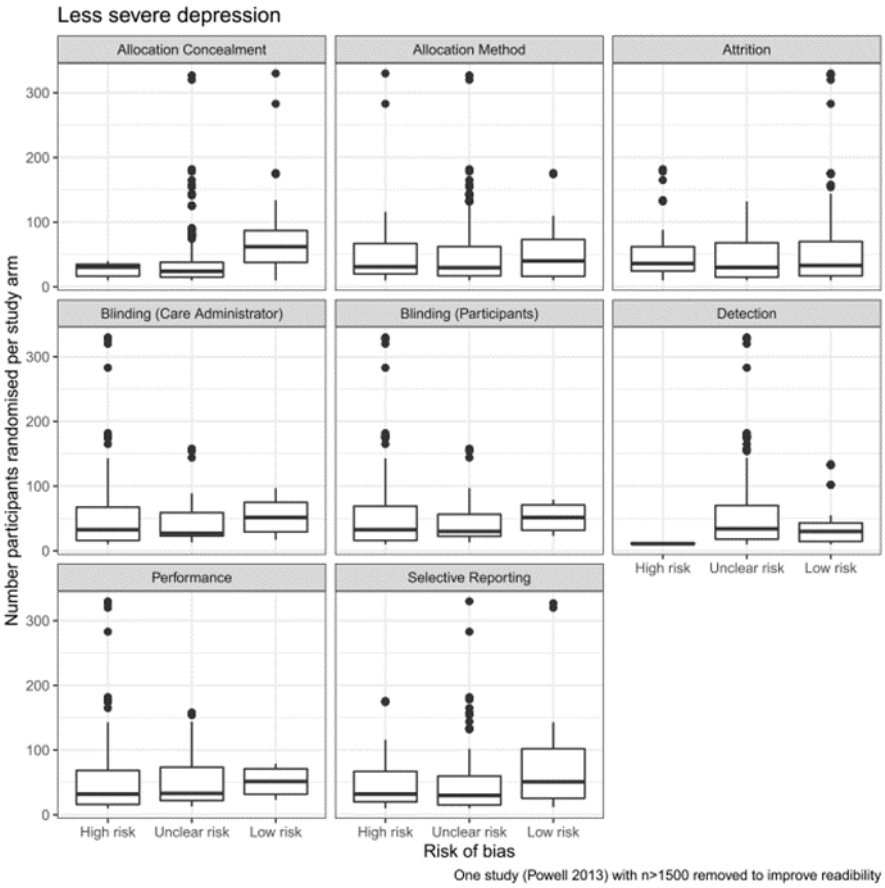
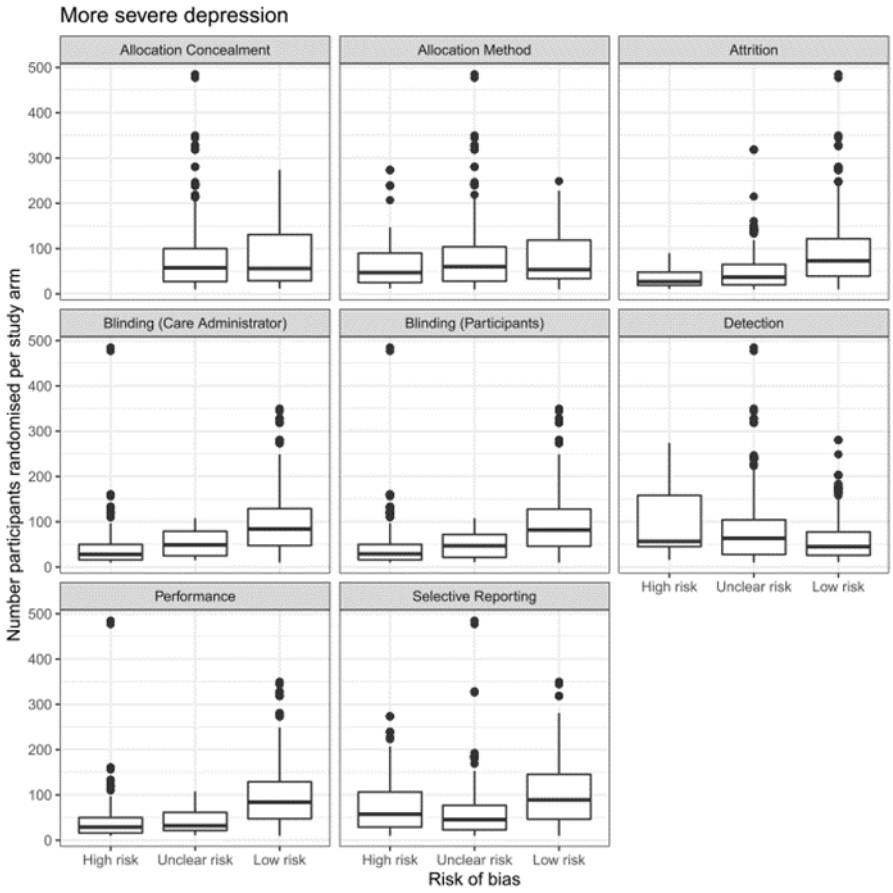


Figure 110. Boxplots showing the number of participants randomised per study arm by risk of bias rating for each risk of bias domain in more severe depression

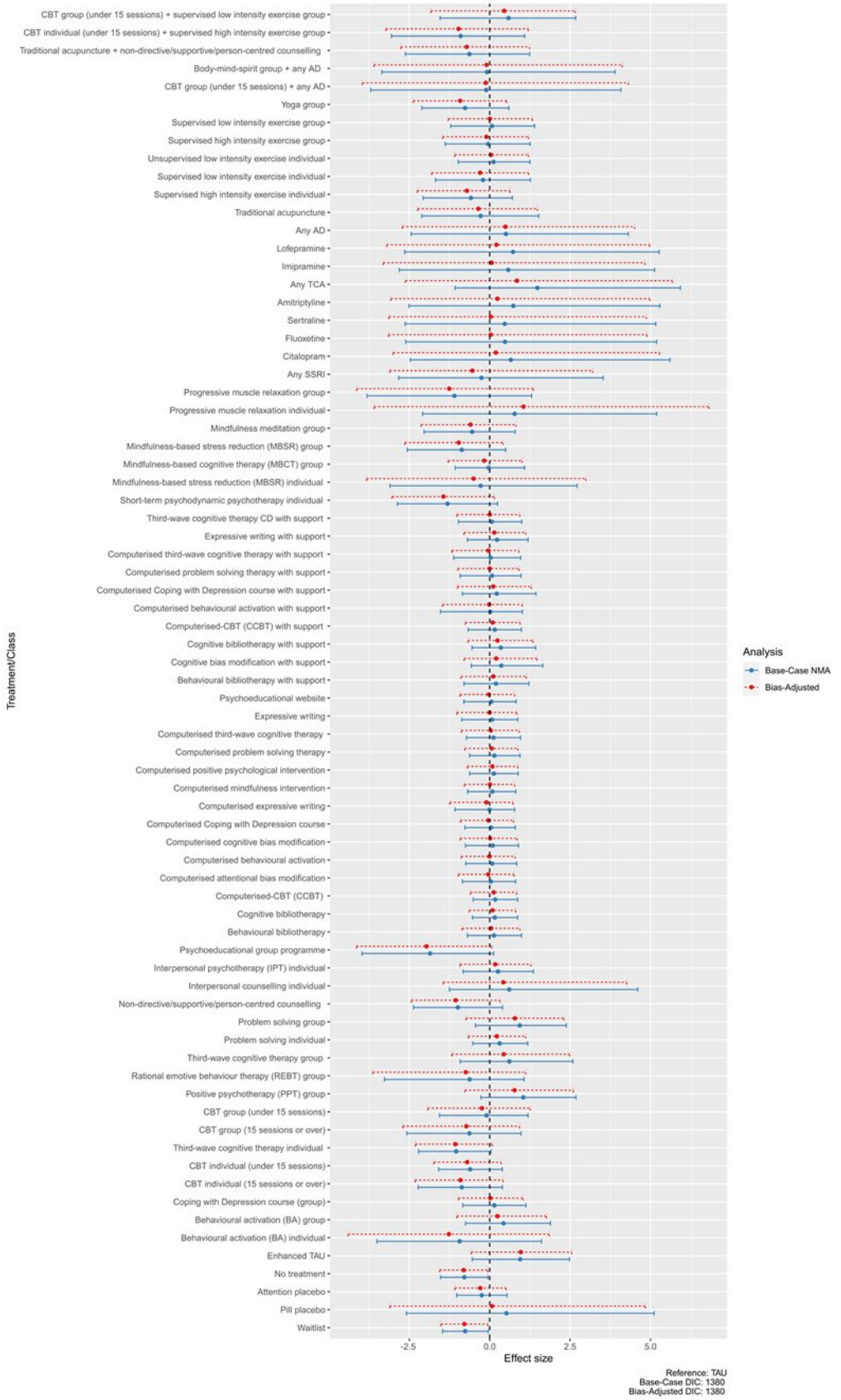


Less severe depression – Discontinuation (for any reason)

Results were similar between base-case and bias-adjusted NMA models, with only very minimal changes in relative effects compared to TAU for most interventions, and minimal reductions in efficacy for pharmacological interventions (Lofepramine, Imipramine, Any TCA, Amitriptyline, Sertraline, Fluoxetine, Citalopram, Pill placebo) and classes (TCAs, SSRIs, Placebo) (Figure 111 and Figure 112). 95%CrIs for relative effects were slightly wider in the bias-adjusted model, and this effect was typically greater for treatments / classes for which there was high uncertainty.

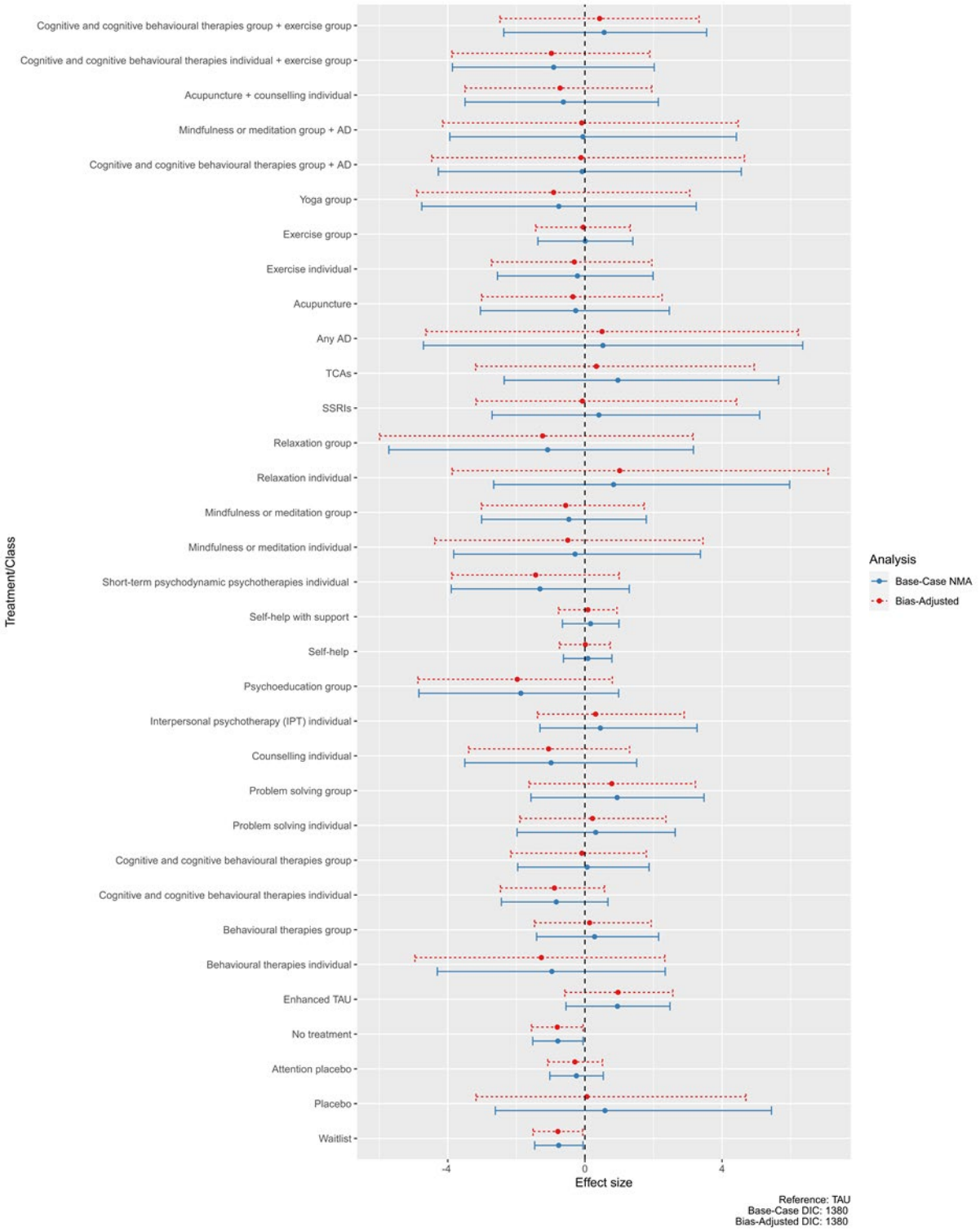
Although the between study heterogeneity was slightly lower in the bias-adjusted model (supplement B5, Table 3.1 in appendix 3; Figure 72), the DIC remained the same as in the base-case consistency model. For this reason, results are reported for the base-case model.

Figure 111: Log-odds ratios and 95% credible intervals for discontinuation due to any reason in less severe depression for each intervention versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Figure 112: Log-odds ratios and 95% credible intervals for discontinuation due to any reason in less severe depression for each class versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

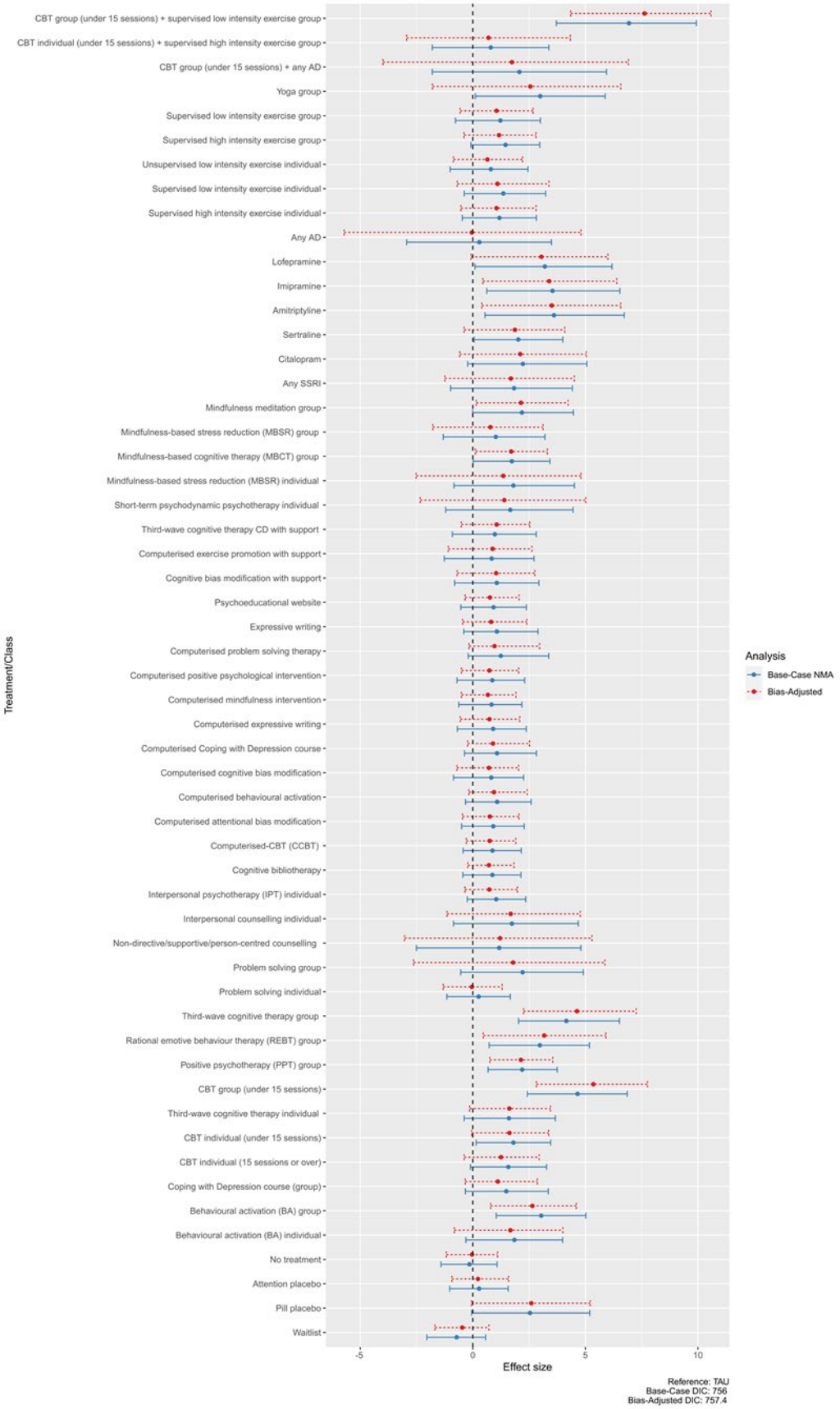
Less severe depression – Response in completers

Results were similar between base-case and bias-adjusted NMA models, with only very minimal changes in relative effects compared to TAU for most interventions that was generally towards zero (i.e. a smaller effect) in the bias-adjusted model compared to the base-case. There was an increase in efficacy versus TAU in the bias-adjusted model

compared to the base-case model in CBT group (under 15 sessions) and CBT group (under 15 sessions) + supervised low intensity exercise group, though this change was less noticeable at the class level (Figure 113 and Figure 114).

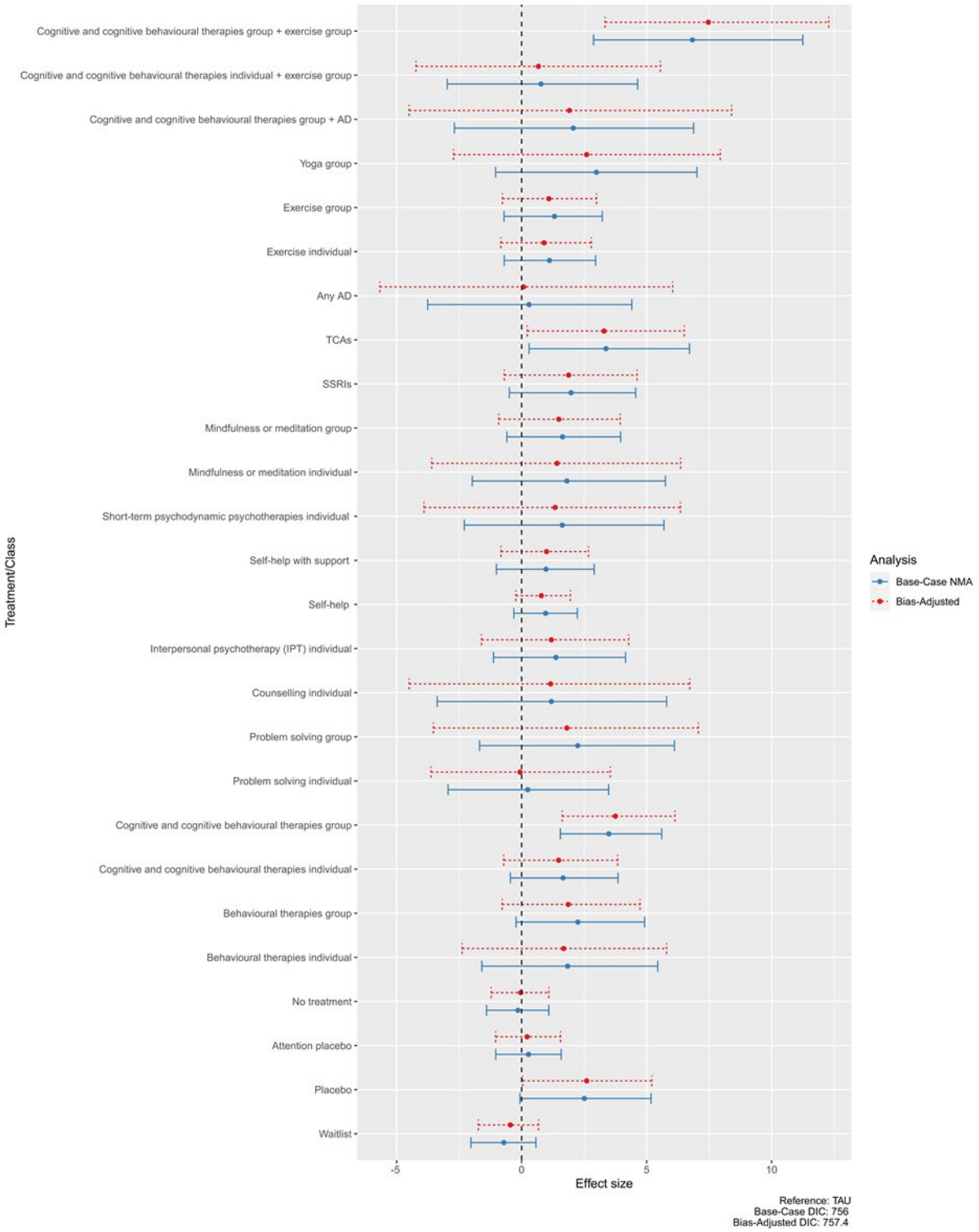
Although the DIC between the models, the between study heterogeneity was substantially reduced (supplement B5, Table 3.5 in appendix 3) in the bias-adjusted random-effects NMA model, and the prediction of data points improved. Reported results are therefore based on the bias-adjusted random-effects NMA model.

Figure 113: Log-odds ratios and 95% credible intervals for response in completers in less severe depression for each intervention versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Figure 114: Log-odds ratios and 95% credible intervals for response in completers in less severe depression for each class versus TAU.

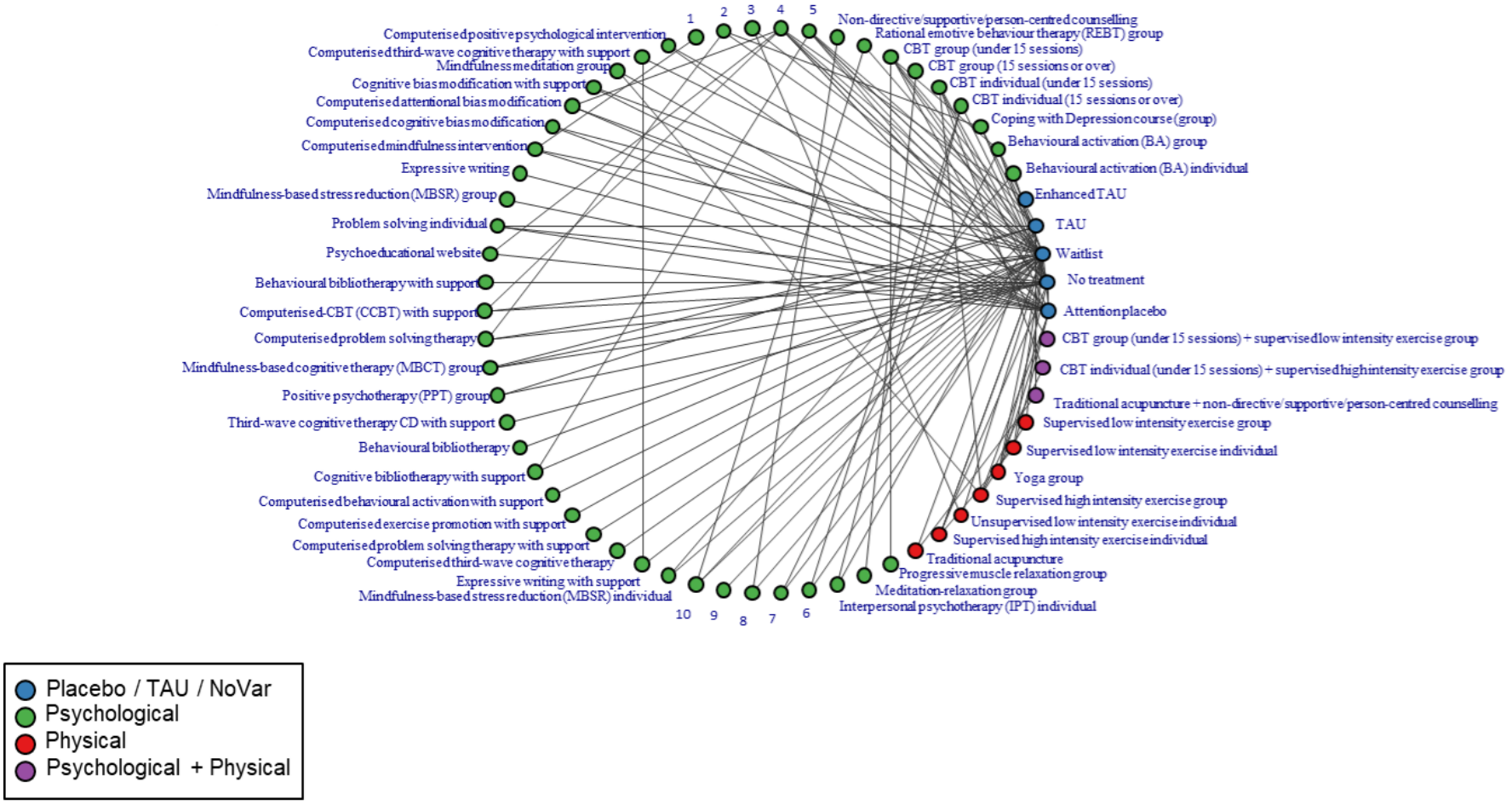


Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Less severe depression – SMD

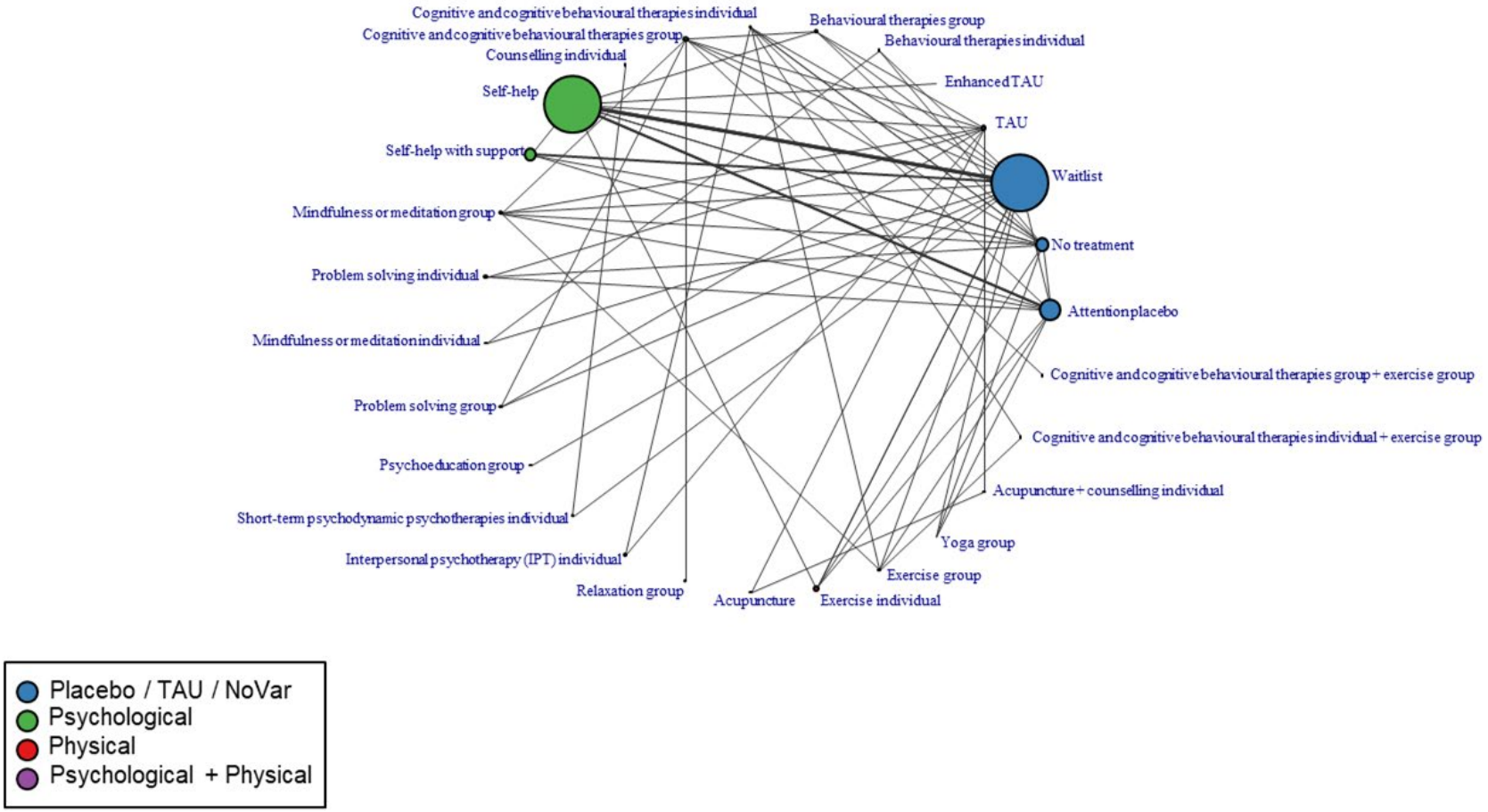
The network diagrams for the analysis of studies that included non-pharmacological interventions only are shown in Figure 115 and Figure 116.

Figure 115. Network diagram of every study included in analysis by intervention. SMD for non-pharmacological interventions.



1 Computerised expressive writing; 2 Computerised Coping with Depression Course; 3 Computerised behavioural activation; 4 Computerised-CBT (CCBT); 5 Cognitive bibliotherapy; 6 Third-wave cognitive therapy individual; 7 Third-wave cognitive therapy group; 8 Short-term psychodynamic psychotherapy individual; 9 Psychoeducational group programme; 10 Problem solving group

Figure 116. Network diagram of every study included in analysis by class. SMD for non-pharmacological interventions.



Compared to results from the base-case NMA model, estimates for most interventions versus TAU from the non-pharmacological interventions only NMA were very similar. However, the efficacy versus TAU was lower in the non-pharmacological interventions-only NMA for Supervised high intensity exercise group, Supervised low intensity exercise individual and Supervised high intensity exercise individual (Figure 117). At the class level, although posterior medians were similar in the two models, 95%CrIs for most classes were slightly wider in non-pharmacological interventions-only NMA, reflecting the reduction in information in the network with which to estimate class effects and variances (Figure 118). For Exercise group and Exercise individual 95%CrIs were substantially narrower than in the base-case NMA.

There were some differences between results from the bias-adjusted NMA and base-case NMA models, though these typically varied in direction. This led to less clear evidence of efficacy versus TAU for the following interventions in the bias-adjusted model compared to the base-case model (Figure 117):

- Behavioural activation (BA) individual
- CBT individual (under 15 sessions)
- Rational emotive behavioural therapy (REBT) group
- Interpersonal psychotherapy (IPT) individual
- Meditation-relaxation group
- Supervised high intensity exercise group
- Yoga group

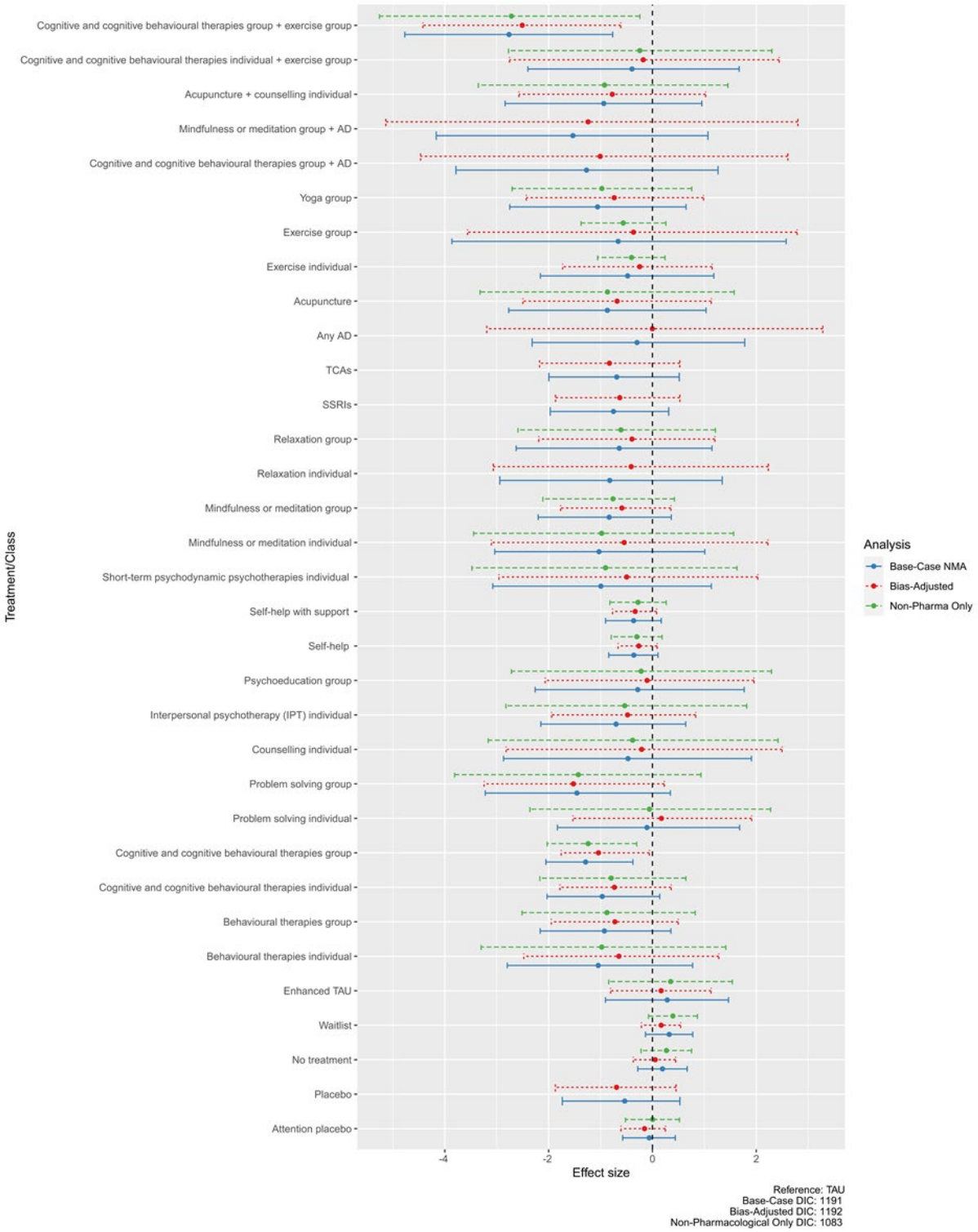
Differences in estimates between the bias-adjusted and base-case models were smaller for classes and are unlikely to have changed any conclusions regarding any class's efficacy versus TAU (Figure 118).

Between study heterogeneity and posterior mean residual deviance were lower in the bias-adjusted model than in the base-case model (supplement B5, Table 3.7 in appendix 3). Reported results were therefore based on the bias-adjusted random-effects NMA model, assuming consistency.

Figure 117: Standardised Mean Differences and 95% credible intervals for symptom severity in less severe depression for each intervention versus TAU.

Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, bias-adjusted results by a short-dashed red line, and non-pharmacological interventions only NMA results by a long-dashed green line.

Figure 118: Standardised Mean Differences and 95% credible intervals for symptom severity in less severe depression for each class versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, bias-adjusted results by a short-dashed red line, and non-pharmacological interventions only NMA results by a long-dashed green line.

More severe depression – Discontinuation (for any reason)

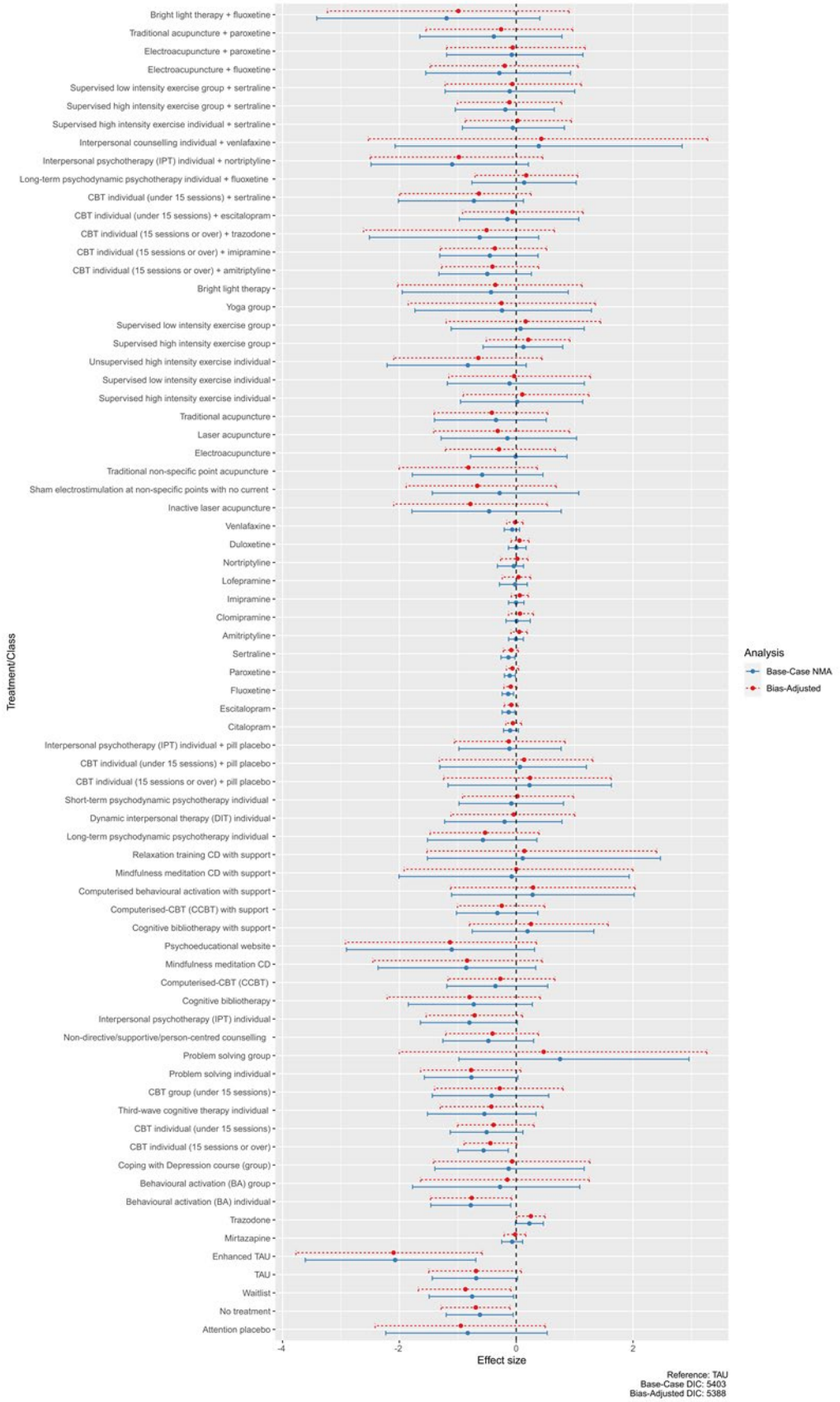
There were some differences between results from the bias-adjusted NMA and base-case NMA models, though these typically varied in direction. 95%CrIs were slightly wider for all estimates in the bias-adjusted model. In particular, estimates differed substantially for sham

and active acupuncture (Inactive laser acupuncture, Sham electrostimulation at non-specific points with no current, Traditional non-specific point acupuncture, Electroacupuncture, Laser acupuncture) versus TAU between the base-case and bias-adjusted models, due to small studies informing these interventions (Figure 119).

Differences between the models were smaller for classes, though 95%CrIs were also slightly wider for all estimates in the bias-adjusted model (Figure 120).

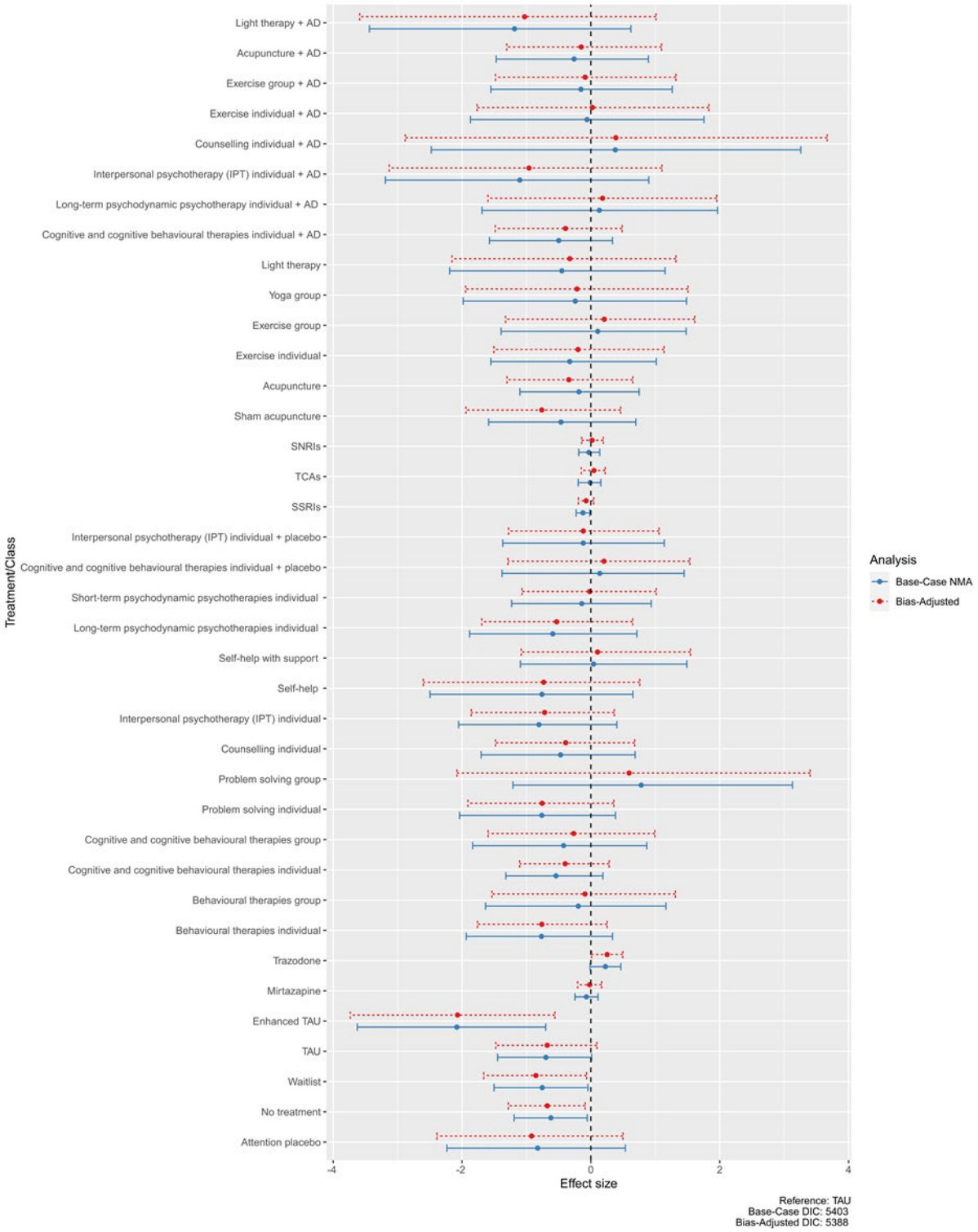
The between study heterogeneity was slightly reduced and the DIC was lower than in the base-case consistency model (supplement B5, Table 3.8 in appendix 3). For this reason, results are reported for the base-case model.

Figure 119: Log-odds ratios and 95% credible intervals for discontinuation due to any reason in more severe depression for each intervention versus Pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Figure 120: Log-odds ratios and 95% credible intervals for discontinuation due to any reason in more severe depression for each class versus Pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

More severe depression – Response in completers

There were some clear differences between results from the bias-adjusted NMA and base-case NMA models. Intervention estimates from the bias-adjusted model indicated lower response versus TAU than in the base-case model, leading to less clear evidence of efficacy

versus TAU for the following interventions in the bias-adjusted compared to the base-case model (Figure 121):

- Behavioural activation (BA) individual
- Behavioural therapy (Lewinsohn 1976) individual
- CBT individual (under 15 sessions)
- Third-wave cognitive therapy individual
- Dynamic interpersonal therapy (DIT) individual
- CBT individual (15 sessions or over) + pill placebo
- Any AD
- Yoga group
- CBT group (under 15 sessions) + Any AD

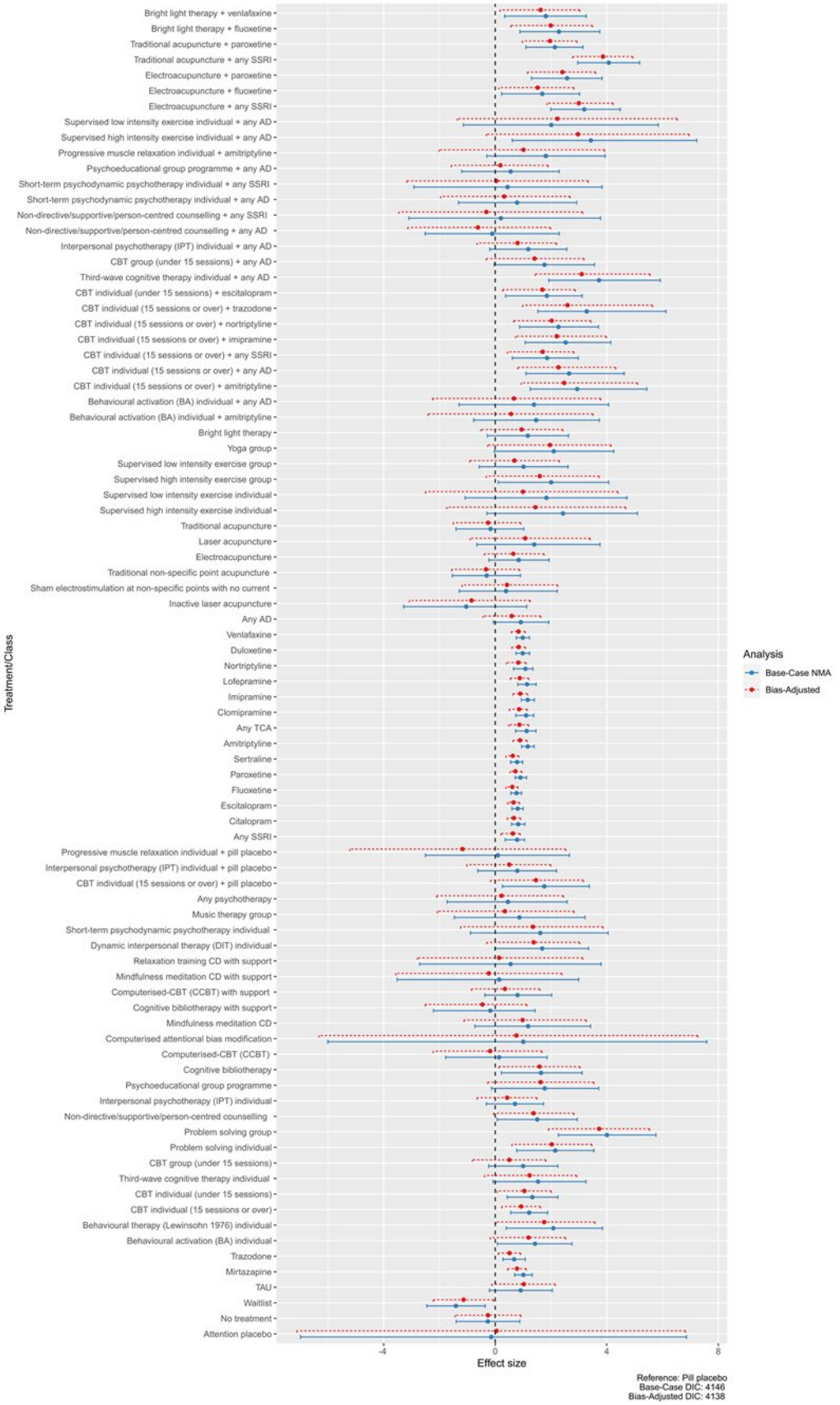
There were also very large reductions in efficacy versus TAU for the following interventions:

- Progressive muscle relaxation individual + amitriptyline
- Behavioural activation (BA) + any AD
- Behavioural activation (BA) + amitriptyline
- Supervised low intensity exercise individual
- Supervised high intensity exercise individual

Differences between the models were smaller for classes, though 95%CrIs were also slightly wider for all estimates in the bias-adjusted model (Figure 122Figure 120).

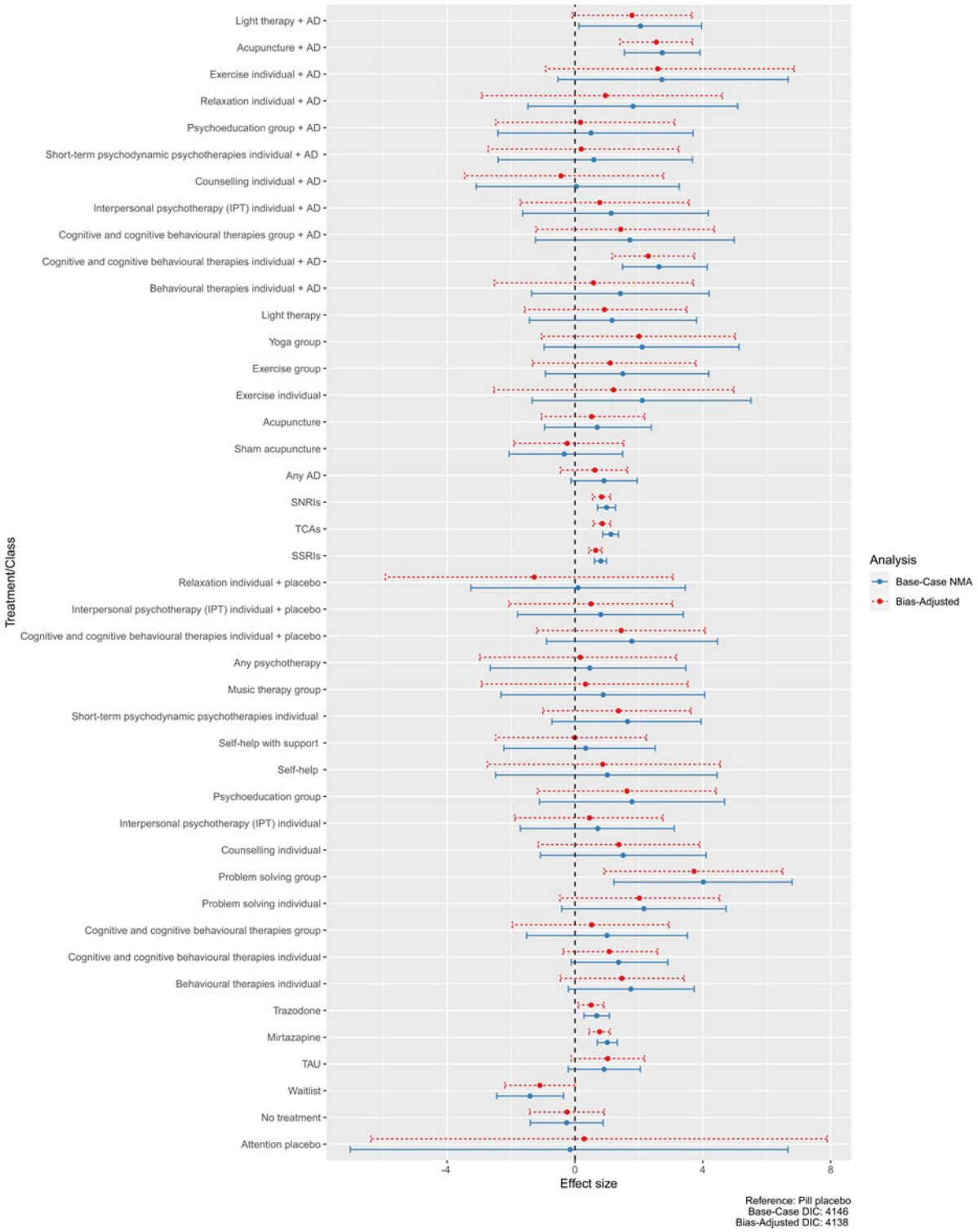
The posterior mean residual deviance, DIC and between study heterogeneity was substantially reduced compared to the base-case consistency model (supplement B5, Table 3.12 in appendix 3). Reported results are therefore based on the bias-adjusted random-effects NMA model.

Figure 121: Log-odds ratios and 95% credible intervals for response in completers in more severe depression for each intervention versus Pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Figure 122: Log-odds ratios and 95% credible intervals for response in completers in more severe depression for each class versus Pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

More severe depression – SMD

The network diagrams for the analysis of studies that included non-pharmacological interventions only are shown in Figure 123 and Figure 124.

Figure 123. Network diagram of every study included in analysis by intervention. SMD for non-pharmacological interventions.

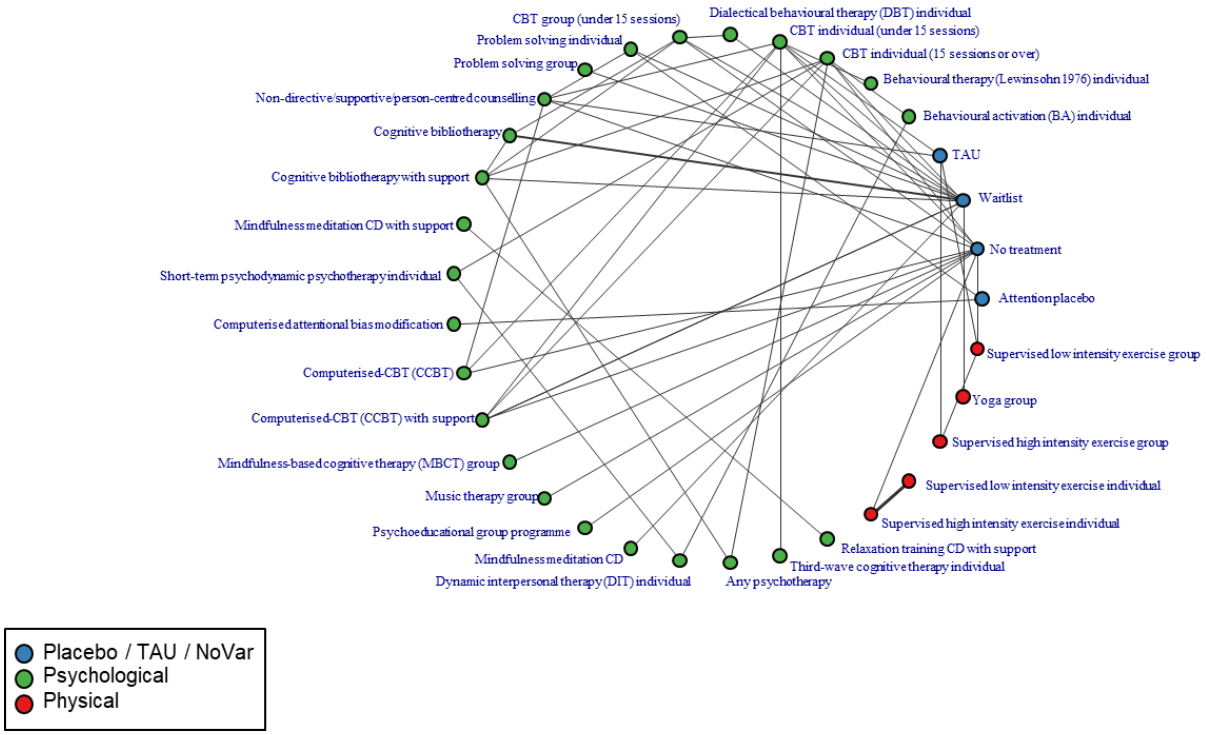
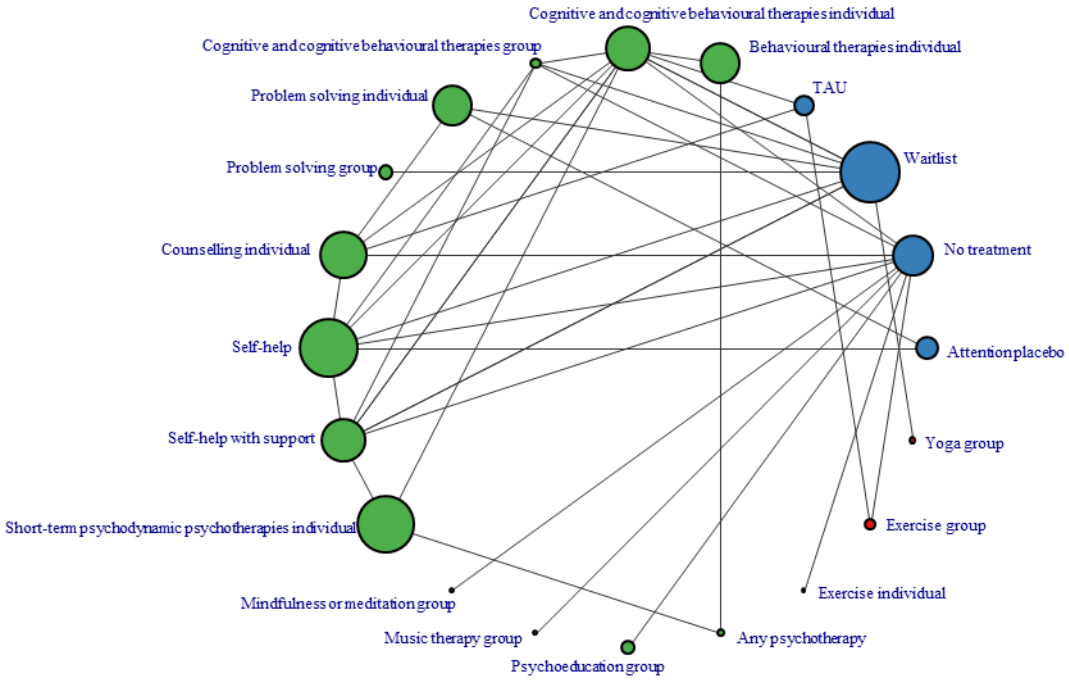


Figure 124. Network diagram of every study included in analysis by class. SMD for non-pharmacological interventions.



There were some significant differences in results between the base-case NMA model and the non-pharmacological interventions-only NMA. For all interventions and classes, 95%CrIs

were narrower in the base-case model. However, for the following interventions there were also substantial differences in the posterior medians of relative effects versus TAU, with a reduction in SMD versus TAU in the non-pharmacological interventions-only NMA compared to the base-case NMA (Figure 125):

- Attention placebo
- Behavioural activation (BA) individual
- CBT individual (15 sessions or over)
- Third-wave cognitive therapy
- CBT group (under 15 sessions)
- Computerised attentional bias modification
- Mindfulness medication CD
- Short-term psychodynamic psychotherapy individual
- Any psychotherapy
- Supervised high intensity exercise individual
- Supervised low intensity exercise individual

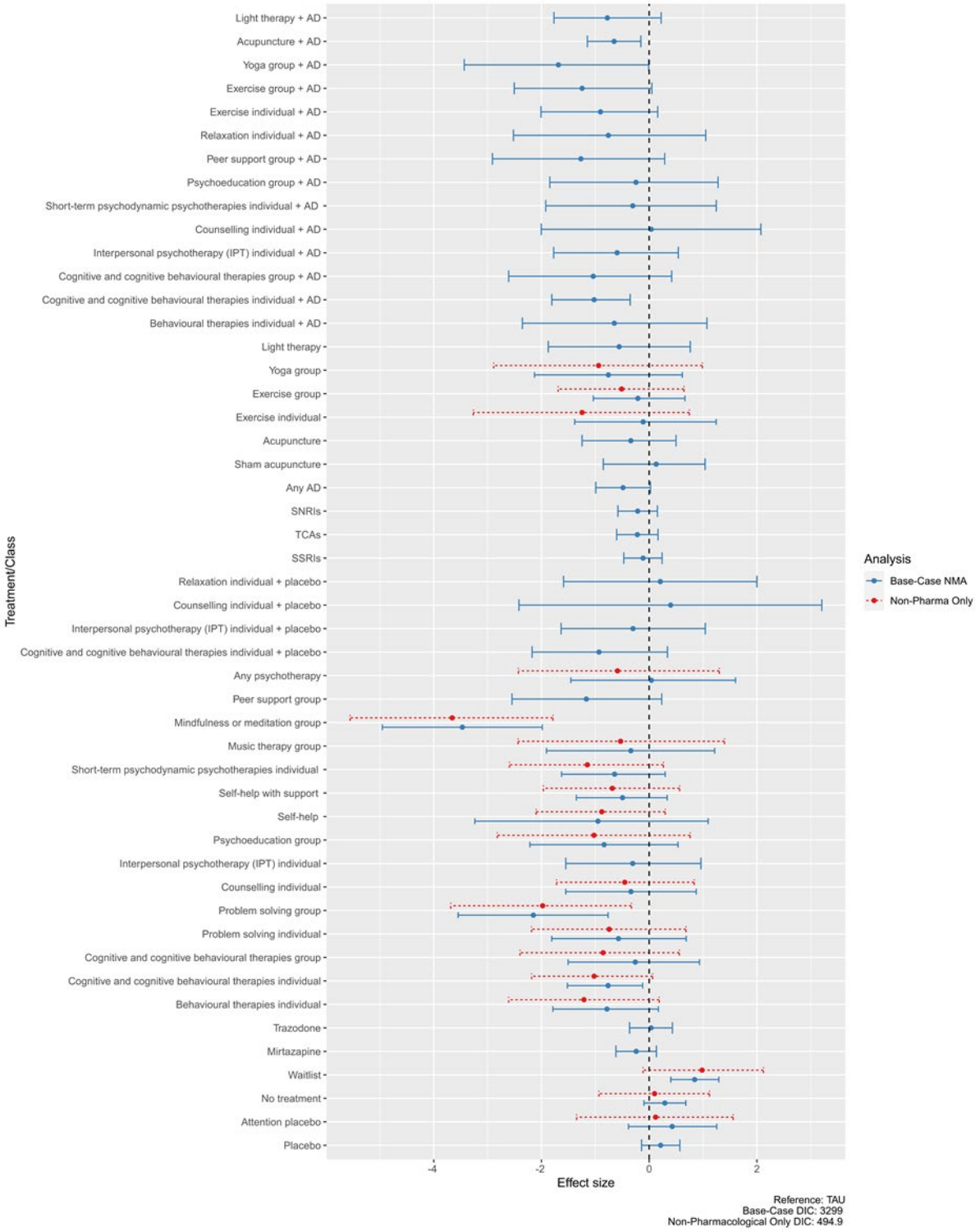
For the following classes there were substantial differences in relative effects versus TAU, with a reduction in SMD versus TAU in the non-pharmacological interventions-only NMA compared to the base-case NMA (Figure 126):

- Attention placebo
- Behavioural therapies individual
- Cognitive and cognitive behavioural therapies group
- Short-term psychodynamic psychotherapies individual
- Any psychotherapy
- Exercise individual

Figure 125: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each intervention versus TAU.

Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, non-pharmacological interventions-only results by a short-dashed red line.

Figure 126: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each class versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, non-pharmacological interventions-only results by a short-dashed red line.

There were also some substantial differences between results from the bias-adjusted NMA and base-case NMA models, with relative effects from the bias-adjusted model typically indicating less efficacy versus TAU than those from the base-case model. This led to less clear evidence of efficacy versus TAU for the following interventions in the bias-adjusted model compared to the base-case model (Figure 127):

- Behavioural activation (BA) individual

- Behavioural therapy (Lewinsohn 1976) individual
- CBT individual (15 sessions or over)
- CBT individual (under 15 sessions)
- Dialectical behavioural therapy (DBT) individual
- Dynamic interpersonal therapy (DIT) individual
- CBT individual (15 sessions or over) + pill placebo
- CBT individual (15 sessions or over) + any SSRI
- CBT individual (15 sessions or over) + imipramine
- CBT individual (under 15 sessions) + sertraline
- Interpersonal psychotherapy (IPT) individual + any AD
- Supervised high intensity exercise individual + any AD
- Supervised low intensity exercise group + sertraline
- Electroacupuncture + any SSRI
- Electroacupuncture + fluoxetine
- Traditional acupuncture + any SSRI
- Traditional acupuncture + paroxetine
- Bright light therapy + fluoxetine

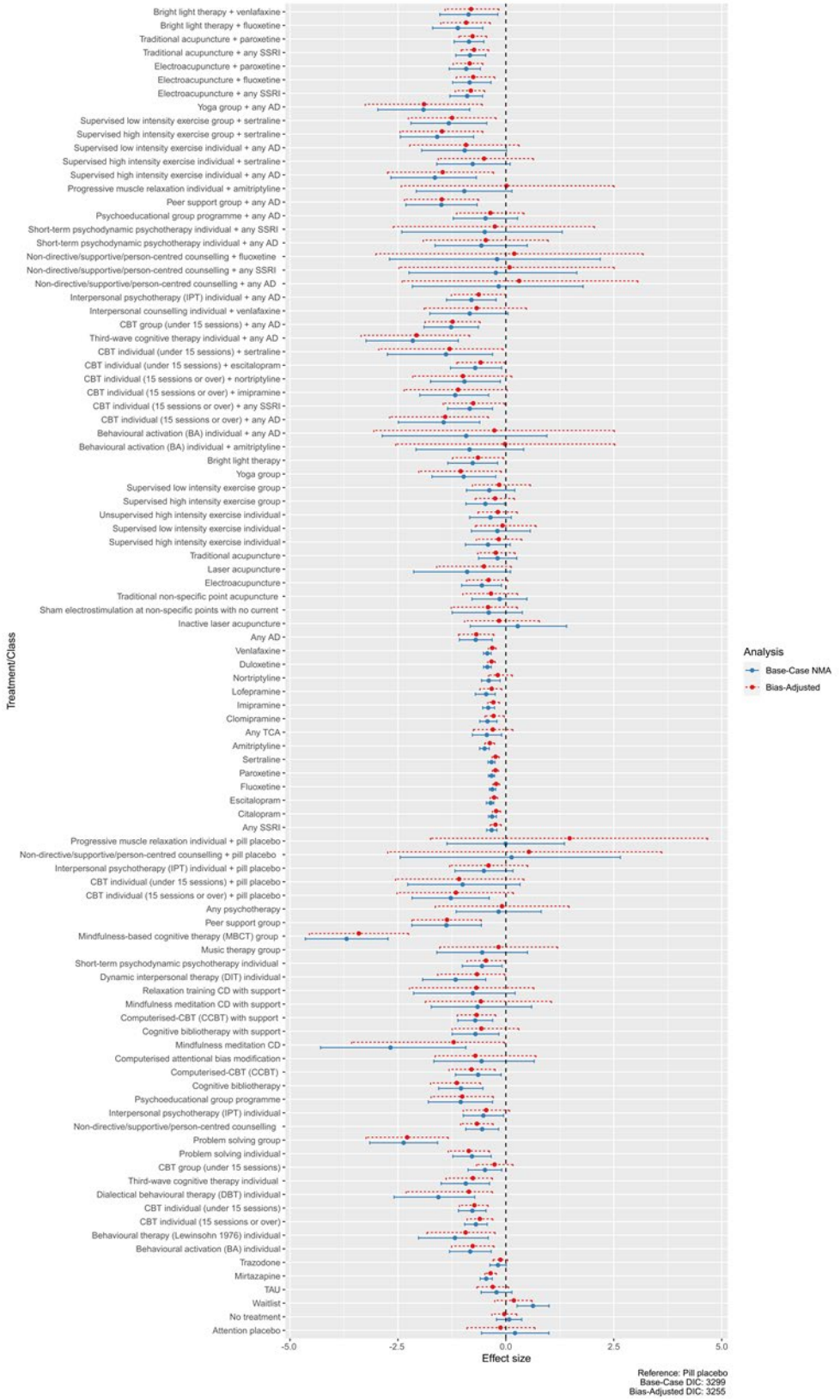
Although differences in estimates between the bias-adjusted and base-case models were smaller for classes, the change led to less clear evidence of efficacy versus TAU for the following classes in the bias-adjusted model compared to the base-case model (Figure 128):

- Cognitive and cognitive behavioural therapies individual
- Any AD
- Exercise group + AD
- Yoga group + AD

However, the direction of change in relative effects between the two models was less consistent for classes than for interventions.

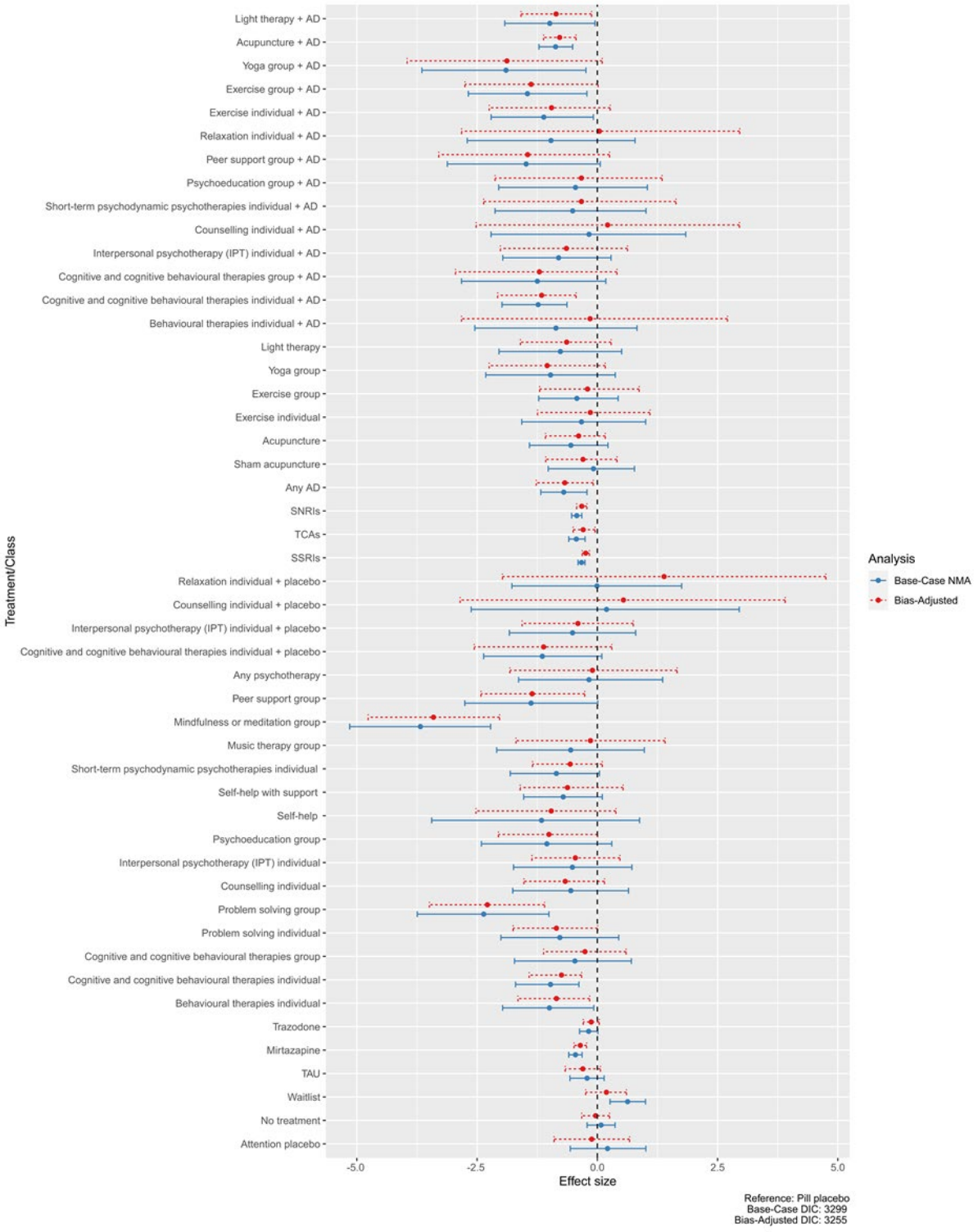
The posterior mean residual deviance, DIC and between study heterogeneity was substantially reduced compared to the base-case consistency model (supplement B5, Table 3.14 in Appendix 3). Reported results are therefore based on the bias-adjusted random-effects NMA model.

Figure 127: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each intervention versus pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, and bias-adjusted results by a short-dashed red line.

Figure 128: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each class versus pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, and bias-adjusted results by a short-dashed red line.

Sensitivity analyses: post-hoc

In addition to the pre-specified sensitivity analysis several post-hoc sensitivity analyses were performed to explore aspects of the data and modelling process that may have impacted results. They are reported here narratively.

In addition to investigating small study effects using bias-adjusted models (see under '*Pre-specified sensitivity analyses*'), the impact of excluding studies with <15 participants in any arm, and studies with >5 points contribution to the residual deviance was examined in analyses of response in randomised participants in both less severe and more severe depression. Although in both analyses the random effects NMA model was a better fit for this data and heterogeneity was considerably lower, there were no substantial changes in treatment efficacy. Several interventions and classes were excluded as these were only informed by very small studies.

To investigate the additivity assumption of interventions administered in combination with TAU, a separate model was fitted to the analysis of SMD in more severe depression that relaxed this assumption. The model included an interaction term for studies in which TAU was given in all study arms, which allowed for a multiplicative effect of an intervention when given in combination with TAU. Although the posterior distribution for the interaction term was non-zero (0.47; 95%CrI: 0.16, 0.79), neither the DIC (3359 in the interaction model compared to 3362 in the base-case model) nor the between-study SD (0.26 in the interaction model compared to 0.26 in the base-case model) was meaningfully different, suggesting that the assumption of additivity was reasonable.

Although we reported the results of prespecified bias-adjusted sensitivity analyses that were intended to investigate the impact of small study effects likely to be related to risk of bias (see 'Sensitivity analyses: prespecified'), we also investigated performing subgroup analyses including only studies rated as "low risk" for different risk of bias domains.

For many domains, there were insufficient studies to analyse a low risk of bias subgroup. We conducted post-hoc sensitivity analyses in the subgroups of studies rated as low risk for attrition. Results for SMD in both less severe depression (Figure 129) and more severe depression (Figure 130) showed that results were very similar to those from the an NMA of the overall network. This suggested that bias from Attrition was unlikely to be an effect modifier in either analysis.

Figure 129. Standardised Mean Differences and 95% credible intervals on the SMD outcome in less severe depression for each class versus TAU from low risk of bias (attrition) subgroup and the overall network (base-case NMA).

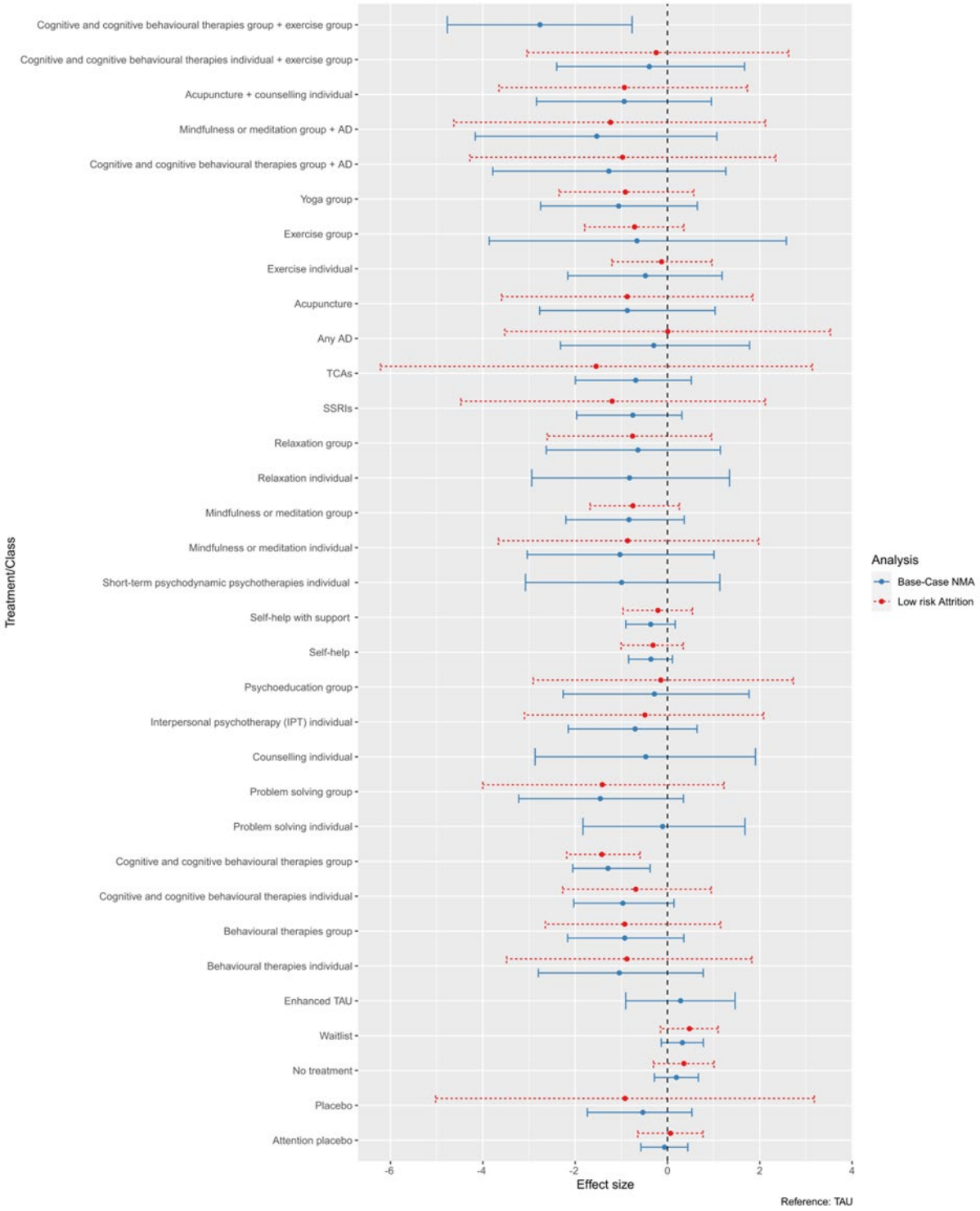
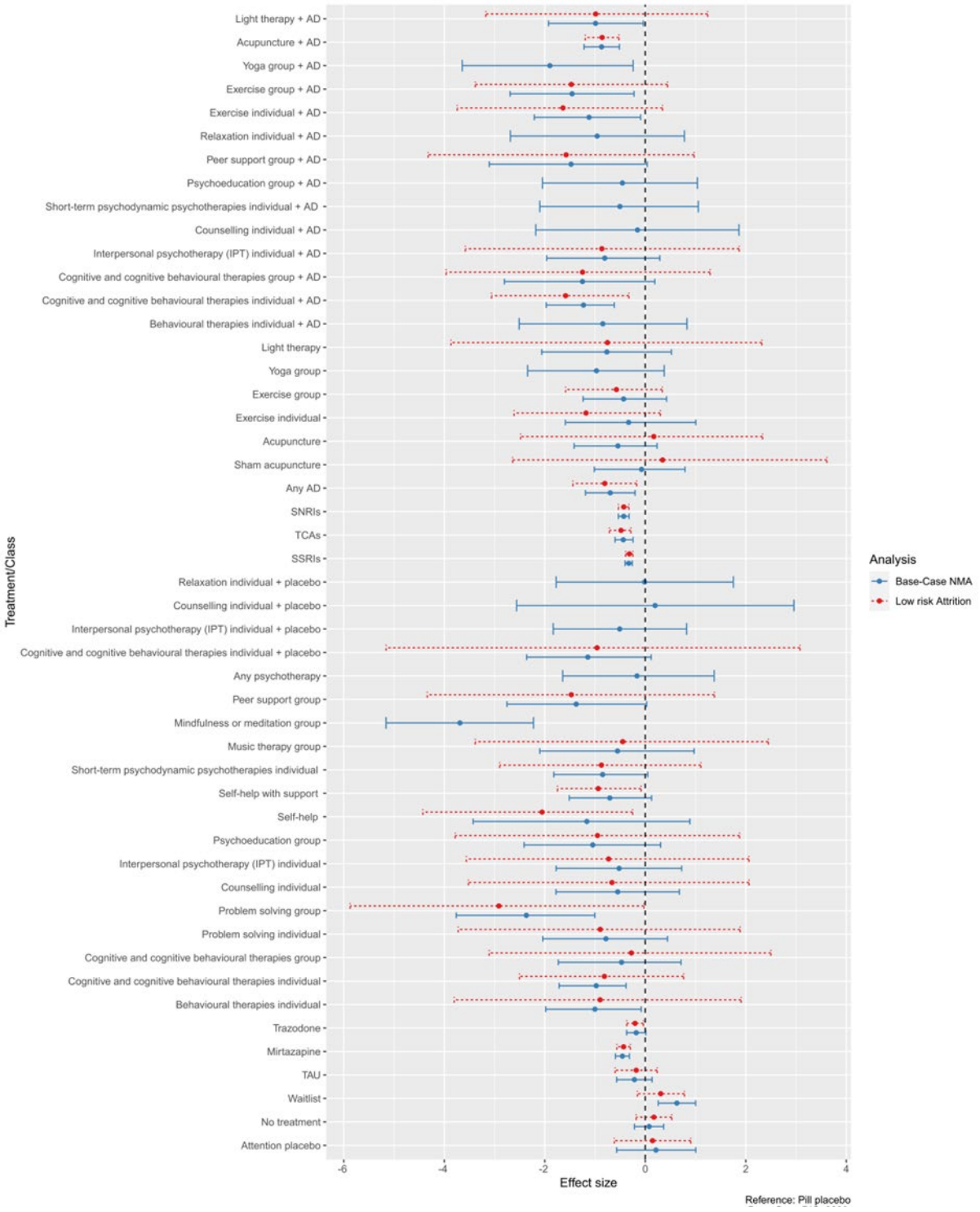


Figure 130. Standardised Mean Differences and 95% credible intervals on the SMD outcome in more severe depression for each class versus pill placebo from low risk of bias (attrition) subgroup and the overall network (base-case NMA).



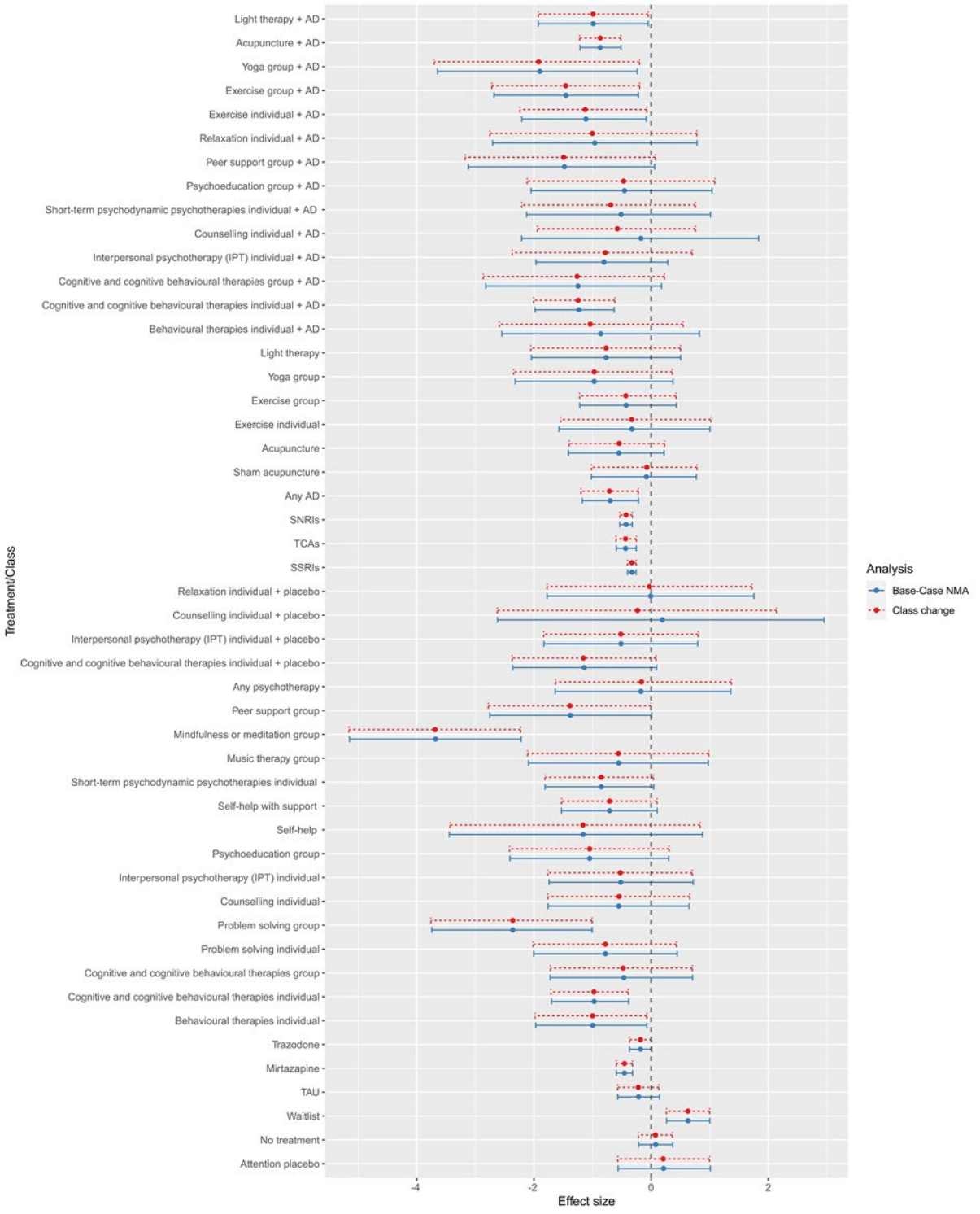
For Blinding (participants), Blinding (care administrator) and Performance, studies at low risk of bias are almost exclusively pharmacological studies, and the analysis is therefore equivalent to performing a subgroup analysis of pharmacological studies only. Given that we performed a prespecified sensitivity analysis of non-pharmacological studies only and found there was no meaningful impact on results, we would be unlikely to detect any differences that might arise from a subgroup of pharmacological only (equivalent to low risk of bias for Blinding or Performance).

Following the completion of the base-case analyses, it was identified that Interpersonal counselling + AD had been included in the class of Counselling + AD, when it was agreed by the Committee that it should be included in the class of Interpersonal psychotherapy (IPT) individual + AD. Although the class coding has been corrected for the main results presented for SMD in more severe depression, a sensitivity analysis was run to examine the impacts of this by fitting a model in which Interpersonal counselling + AD was included in the class of Counselling + AD. This led to (Figure 131):

- Substantially narrower 95%CrI for Counselling individual + AD versus Pill placebo, with a lower posterior median SMD (favouring Counselling individual + AD)
- Wider 95%CrI for Interpersonal psychotherapy (IPT) individual + AD versus Pill placebo, though the posterior median remained similar
- Substantially narrower 95%CrI for Counselling individual + Placebo versus Pill placebo, with a lower posterior median SMD (favouring Couselling individual + Placebo).

The changes would not have impacted conclusions and therefore the decision was taken to report the sensitivity analysis and retain the original (incorrect) class coding for all other outcomes.

Figure 131: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each class versus Pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results, in which Interpersonal counselling + AD was included in the class of Interpersonal counselling + AD, are indicated by a solid blue line. Results from the class change model, in which Interpersonal counselling + AD was included in the class of Counselling individual + AD, are indicated by a short-dashed red line.