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The effectiveness of behavioural and cognitive behavioural therapies for insomnia on depressive and fatigue symptoms: a systematic review and network meta-analysis

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Running head: Treating daytime symptoms of insomnia.

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Conflict of interest

None to declare.

Summary

This review aimed to assess the impact of behavioural therapy for insomnia administered alone (BT-I) or in combination with cognitive techniques (cognitive-behavioural therapy for insomnia, CBT-I) on depressive and fatigue symptoms using network meta-analysis. PubMed, Scopus and Web of Science were searched from 1986 to May 2015. Studies were included if they incorporated sleep restriction, a core technique of BT-I treatment, and an adult insomnia sample, a control group and a standardised measure of depressive and/or fatigue symptoms. Face-to-face, group, self-help and internet therapies were all considered. Forty-seven studies were included in the meta-analysis. Eleven classes of treatment or control conditions were identified in the network. Cohen's *d* at 95% confidence interval (CI) was calculated to assess the effect sizes of each treatment class as compared with placebo. Results showed significant effects for individual face-to-face CBT-I on depressive (*d*= 0.34, 95% CI: 0.06 - 0.63) but not on fatigue symptoms, with high heterogeneity between studies. The source of heterogeneity was not identified even after including sex, age, comorbidity and risk of bias in sensitivity analyses. Findings highlight the need to reduce variability between study methodologies and suggest potential effects of individual face-to-face CBT-I on daytime symptoms.

Keywords: insomnia; depression; fatigue; CBT; network meta-analysis.

Abbreviations

BT-I= behavioural therapy for insomnia including sleep restriction strategy alone or in combination with other behavioural techniques

CBT-I= cognitive behavioural therapies for insomnia combining behavioural therapy, cognitive therapy, and psychoeducation for insomnia

CI= confidence interval

DF= degrees of freedom

PRISMA= preferred reported items for systematic reviews and meta-analysis

RCT= randomised controlled trial

SC= stimulus control

SR= sleep restriction

Glossary of terms

Network meta-analysis: statistical method that evaluates the effectiveness of multiple treatments simultaneously combining direct and indirect evidence of treatment differences within a structure called network.

Net graph: graphical tool which depicts the geometry of the network. It consists of nodes (representing treatments) and edges (representing direct comparisons between treatments).

Inconsistency: network meta-analysis assumes that direct and indirect evidence of treatment difference is consistent. Consistency means that indirect evidence of difference between any two treatments in the network do not differ from the direct evidence, i.e. the assumption that direct and indirect evidences are similar in factors that could affect the relative treatment effects.

Net heat plot: graphical tool to detect inconsistency in the network. The grey squares indicate the amount of contribution of the direct estimate in design (shown in the column) to the network (shown in the row). Colours are related to the degree of inconsistency between direct and indirect

evidence for the corresponding design. Blue colours indicate low level of inconsistency, while red colours indicate “hot spots” of high inconsistency.

Forest plot: graphical representation of meta-analysis results.

Heterogeneity: variability in the distribution of effect sizes of the studies included in a meta-analysis.

Sleep restriction: behavioural intervention for insomnia which consists of initially reducing time in bed with the aim of enhancing homeostatic sleep pressure. Time in bed is then adjusted on a weekly basis based on average sleep efficiency of the preceding week.

Stimulus control: behavioural intervention prescribing patients to use their bed only for sleeping, to go to bed only when they are sleepy, and not to use their bedroom for anything but sleep.

Cognitive therapy: cognitive interventions consisting of cognitive restructuring, problem solving and cognitive control techniques.

Sleep hygiene education: sleep-promoting behaviours such as avoiding naps, caffeine and/or alcohol intake and physical activity right before sleeping.

Relaxation therapy: behavioural interventions including progressive muscle relaxation and autogenic training aimed to decrease the levels of arousal.

Introduction

Daytime symptoms of insomnia, particularly depressive and fatigue symptoms, are often the reason insomnia patients seek help [1]. Nevertheless, neither frequency, duration, nor intensity criteria are available for these symptoms. The gold standard for psychological treatment of insomnia is behavioural intervention administered alone (BT-I) or in combination with cognitive techniques (cognitive-behavioural therapy for insomnia CBT-I)[2]. However, it is unclear to what extent BT-I and/or CBT-I is effective for depressive and fatigue symptoms. The aim of the present study was to address this gap in the literature by performing a systematic review and network meta-analysis on the effectiveness of BT-I and CBT-I on daytime depressive and fatigue symptoms.

Behavioural and cognitive behavioural therapies for insomnia

BT-I and CBT-I are, at present, the gold standard for psychological treatment of insomnia [2]. BT-I includes two main interventional strategies: sleep restriction (SR) and stimulus control (SC). Both strategies have been shown to be effective for insomnia even if delivered as standalone treatments [3].

BT-I is often delivered with cognitive interventions and/or sleep hygiene psychoeducation protocols [3]. BT-I and CBT-I can be administered face-to-face individually or in group settings, as well as through self-help using the internet or booklets.

Depressive symptoms in insomnia

Individuals with insomnia often complain of negative mood or subclinical depression (e.g. [4]). A meta-analysis of epidemiological longitudinal studies found that insomnia is a predictor of the onset of depressive disorder [5]. Thus, reducing subclinical depression reported by those with insomnia through sleep therapy may also have a potential preventive impact on the incidence of major depression [6].

Previous meta-analyses of randomised controlled trials (RCTs) of self-help [7-9] and group [10] CBT-I showed promising results on self-reported depressive symptoms. However, there are several limitations to previous meta-analyses. First, previous research has been limited to pairwise comparisons using traditional meta-analysis. Comparative effectiveness reviews usually include only one subset of all potential comparisons between the arms of a trial. Consequently, previous studies have not compared the effects of different therapeutic settings (e.g. face-to-face, group, self-help CBT-I). Second, to our knowledge, no meta-analysis investigating the efficacy of individual face-to face CBT-I for alleviating depressive symptoms has been conducted [11].

Fatigue symptoms in insomnia

Fatigue has been reported as one of the most frequent complaint of patients with insomnia [12]. Thus, there is a need to clarify the extent to which standard treatment for insomnia is effective in reducing fatigue, with a view to improving patients' quality of life. Recent RCTs suggest that treating insomnia with psychotherapy also reduces fatigue symptoms [13]. However, to the best of our knowledge, no meta-analysis assessing the efficacy of BT-I or CBT-I on fatigue symptoms has been conducted.

Network meta-analysis

Systematic reviews are important tools for summarising scientific evidence, particularly in clinical interventions, where the benefits and harms of the available treatments for a given medical condition need to be identified in order to adequately develop and implement evidence-based clinical guidelines and practice. In the past, meta-analyses were mostly based on pairwise comparisons investigating the effectiveness of one treatment against one control condition. In recent years, however, meta-analytic reviews have gradually evolved to evaluate the effectiveness of multiple treatments simultaneously [14]. This has led to the application of more sophisticated synthesis methods able to simultaneously compare the effectiveness of multiple treatments, generally referred to as network meta-analysis or mixed treatment comparison [15]. In the context of

evidence-based medicine, network meta-analysis aims to compare a number of available treatments for a given diagnosis by combining direct and indirect evidence on treatment effects based on a common comparator [16]. Network meta-analysis is a valid statistical method which allows for simultaneous analysis of both direct and indirect comparisons among multiple treatments across multiple studies. This method has advantages over pairwise meta-analysis, including: a) borrowing strength from indirect evidence to compare all treatments; b) estimating comparative effects that have not been investigated head-to-head in RCTs; c) comparing between different interventions for one condition which informs clinical practice [17,18].

To explain the conceptual underpinning of network meta-analysis, and specifically the meaning of direct and indirect evidence, suppose we compare two active treatments, A and B, and a control condition, C. Given direct evidence from studies regarding the difference of treatment effects for A and C and evidence regarding the difference of treatment effects for B and C from other studies, these studies also provide indirect evidence for treatments A and B. Therefore, the aim of network meta-analysis is to estimate the treatment differences and associated standard errors combining direct and indirect evidence [16]. With respect to pairwise meta-analyses, network meta-analyses allow for visualisation of a larger amount of evidence, and estimation of the relative effectiveness among all treatments, even if some comparisons are absent [19]. For this reason, network meta-analysis increases power and precision as compared to pairwise meta-analyses [20]. For network meta-analyses to be possible, important assumptions have to be met. It is assumed that direct and indirect evidence of treatment difference maintain transitivity, i.e., included trials are similar in factors that could affect the relative treatment effects. Furthermore, it is assumed homogeneity of the network, that is, the effects estimates of studies with similar designs (i.e. comparing the same interventions) are similar. Finally, consistency of the network is required, i.e. indirect evidence of difference between any two treatments in the network do not differ from the direct evidence. Inconsistency within treatments network is assessed through net heat plot [21], a graphical tool that represents changes in heterogeneity due to relaxing the consistency assumption for single designs in

a matrix visualisation. Although valid, the network approach is not free of limitations. For instance, Mills [22,23] highlighted how most networks have unbalanced designs, that is, many trials are present for some comparisons whereas there are few or none for other comparisons. Consequently, evidence may be of high quality for some treatments and comparisons but of low quality for others [22,23].

Study aim

Previous pairwise meta-analyses have primarily focussed on night-time symptoms of insomnia and only few have examined the effectiveness of CBT-I on daytime symptoms [7-10]. Therefore, the present review aimed to provide a qualitative and quantitative synthesis of the effectiveness of BT-I and CBT-I, defined by including at least SR, in reducing depressive and fatigue symptoms reported by patients with insomnia. A decision to focus on SR was made because it is a core evidence-based behavioural technique for the treatment of night-time symptoms of insomnia [24,25]. SR is the only psychological intervention for insomnia which has been systematically assessed for standardisation [24]. For this reason, and in order to minimize the risk of heterogeneity within the tested treatments, a decision was made to include all studies that include SR.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [14] (a table of contents of supplementary material is reported in Document S1, see PRISMA check-list in Document S2).

Literature search

To identify the papers for this review, we first considered all studies included in the systematic review on the implementation of SR for insomnia by Kyle et al. [24], where authors searched relevant BT-I and CBT-I trials including at least SR in PubMed, Scopus and Web of Science from 1986 to June 2014. Using this database, we updated the searches using the same search engines from June 2014

to May 2015. Search terms were: “cognitive therapy” or “cognitive behavior* therapy” and “insomnia” or “sleep initiation and maintenance disorder”. Further, we expanded our search through hand searching the references of the screened full-texts. The second author conducted the literature search. The first and the second authors independently screened titles and abstracts for the inclusion as well as full texts’ reference list. Final selection of articles was discussed by the first and last authors.

Inclusion and exclusion criteria

To be included, studies had to fulfil each of the following inclusion criteria: 1)RCTs ; 2) published in English; 3) incorporating at least SR or sleep compression in the treatment; 4) an adult insomnia sample; 5) a standardised measure of depressive and/or fatigue symptoms. Controlled studies consisting of CBT-I combined with other therapies (i.e. CBT-I and pharmacotherapy, CBT-I and mindfulness therapy) were excluded. To examine differences in the effectiveness of different therapeutic settings, studies using different types of CBT-I administration (individual therapy, group therapy, self-help therapy) were included. Unpublished studies were excluded.

Data extraction

For each selected study, socio-demographic, clinical and methodological variables were extracted. Risk of biases was assessed through a checklist derived from the integration of the quality assessment tool for quantitative studies [26] and the Cochrane Collaboration’s tool for assessing risk of bias [27] (see Document S3). Since the weight of the conclusions drawn from meta-analytic reviews largely depends on the validity of the findings of single studies included, it is essential to assess study quality [27]. The tool used in the present review assessed the following potential areas of bias:

1) *Selection bias*: evaluation of recruitment and randomisation methods;

2) *Blinding of outcome assessment*: evaluation of awareness of outcome assessors of intervention or exposure status of participants;
3) *Incomplete outcome data:* evaluation of withdrawals and dropouts. This item does not assess whether the risk of dropout is related to treatment.
4) *Other sources of bias*:
    a. *Confounders*: evaluation of important differences between groups prior to the intervention on confounding variables (e.g. race, sex, marital status, age, health status);
    b. *Data collection methods*: evaluation of validity and reliability of instruments.

The first and the second authors independently rated each study, and disagreements were resolved through consensus discussion. The final score identified whether a study was either at low, moderate or high risk of bias. After data extraction, treatments were grouped into six CBT-I classes and five control conditions:

1) *BT-I individual*: behavioural therapy for insomnia face-to-face in individual setting;
2) *BT-I group*: behavioural therapy for insomnia in group setting;
3) *BT-I self-help*: behavioural therapy for insomnia in self-help setting;
4) *CBT-I individual*: behavioural and cognitive therapy for insomnia face-to-face in individual setting;
5) *CBT-I group*: behavioural and cognitive therapy for insomnia in group setting;
6) *CBT-I self-help*: behavioural and cognitive therapy for insomnia in self-help setting including internet interventions, booklets with and without phone consultations, video and audiocassette instruction and classes;
7) *Pharmacological*: including not only sleep drugs or antidepressant, but any medication used as a treatment or control condition;
8) *Sleep hygiene*: including sleep hygiene education alone, which is associated with limited effectiveness [28];

9) *Placebo*: including both placebo pills and behavioural placebo such as self-monitoring of sleep with and without professional help and quasi-desensibilization placebo technique;
10) *Psychological*: including relaxation, mindfulness, tai chi, stress management, CBT for pain, CBT for depression;
11) *Waiting list*: including both waiting list and no intervention.

Pre- and post- treatment means and standard deviations of self-reported questionnaires of depression and/or fatigue, for both experimental and control groups were extracted by the first author to calculate effect sizes as standardised mean differences. When means and standard deviations were not reported in the articles, effects sizes were calculated from other indexes such as standard errors, root mean square deviations, quartiles and degrees of freedom (DF).

Statistical analyses

Effect sizes (Cohen's *d*) were estimated for groups' differences with respect to change from baseline. For each study, we used data from participants who completed post-treatment assessments. Meta-analytic calculations were performed using the statistical software package R (http://www.R-project.org/). We performed a frequentist network meta-analysis [29] using the R-package "netmeta" [30]. All classes of intervention were compared against placebo, considered a preferable reference condition [31]. A random-effects model was used because of the considerable heterogeneity between studies (e.g. different populations, settings, etc.). To test network heterogeneity, Cochran's *Q* and Higgins's I^2 were calculated. Cochran´s *Q* is computed as a weighted sum of squared differences between single study effects and the pooled effect across studies. Significant values indicate a high level of heterogeneity between effects that need to be further investigated. Higgins's I^2 assesses the variability in effect estimates that is due to between-study heterogeneity rather than due to chance. Low percentages of I^2 are indicative of low heterogeneity while percentages over 75% represent considerable levels of heterogeneity [32].

To assess the geometry of the network, the netgraph function of "net-meta" package was used. Additionally, net heat plots [21] have been used to detect "hot spots" of inconsistency among comparisons. The contribution of pooled direct evidence of each single design (shown in column) to each network estimate (shown in row) is represented by the area of the grey squares. The colours of the diagonal represent the intensity of inconsistency of the network, with red squares (hot spots) indicating greater inconsistency and blue squares indicating less inconsistency.

To investigate the source of heterogeneity, sensitivity analyses were conducted by selecting or excluding groups of studies depending on possible confounding variables. This allows for effect sizes of different treatments in specific groups of studies such as those with only comorbid insomnia or single sex samples to be compared. Possible sources of variance accounted for in the network were: self-help with or without professional contact, comorbidity, sex, age, and risk of bias.

Results

Database searching

Database searching yielded 1076 abstracts (Scopus n=629, PubMed n=258, Web of Science n=188). Of these, 48 studies were included in systematic review while 47 were entered in the meta-analysis. One study was excluded from the analysis because the CBT-I treatment was administered in two phases and modes: first in group format and then individually [33]. Therefore, it did not fit the treatment categories identified in this review. The aggregated sample size is as follows: 2448 insomnia patients who underwent CBT-I and 1869 controls. The study selection flowchart is reported in Figure 1. Excluded studies and reasons for exclusion are reported in Table S1.

Please insert figure 1 here.

Study characteristics

A summary of the included studies is reported in Table 1. Additional qualitative information is reported in Table S2. Risk of bias assessment data is reported in Table S3. The mean age of participants in the included studies was 51.9 years and mean percentage of females was 62.8. CBT-I was administered individually in 16 trials [34-49], in group in 10 trials [50-59] and through self-help in 17 trials [35,45,60-74]. BT-I was administered individually in two trials [75,76], in groups in two trials [77,78] and through self-help in two trials [79,80].

Thirty-nine studies measured depressive [34-48,50-53,55-64,66,67,69,71,72,74,75,77,79,80] while 22 studies measured fatigue [34,41,43-45,47,49,51,53-55,58,59,62,64,65,68,70,73,78,79] symptoms as outcome measures. The majority of studies (n=13: [34,35,37,38,40,46,50,57,58,62,67,69,80]) measured the presence and severity of depressive symptoms through the Beck depression inventory [81]. Nine studies [39,43,45,47,51,56,59,60,64] measured depressive symptoms using the hospital anxiety and depression scale [82], and 4 [36,41,52,71] using the profile of mood states [83]. Three studies [66,72,79] used the centre for epidemiologic studies-depression scale [84] and 1 the revised form of this questionnaire [44]. Two studies [74,77] used the geriatric depression scale [85], 1 study [63] used the depression anxiety stress scale [86] and 1 study [75] the Hamilton rating scale for depression [87].

With respect to fatigue, the majority of studies (n=11: [34,44,45,47,53,55,59,64,70,73]) assessed the presence and severity of symptoms using the multidimensional fatigue inventory [88] while 5 studies [49,58,62,68,78] used the fatigue severity scale [89]. Furthermore, 1 study [79] measured fatigue through the fatigue/inertia subscale of the profile of mood states [83], 1 [41] through the chronic respiratory disease questionnaire fatigue scale [90], 1 [54] through the Flinder fatigue scale [91], 1 [43] through the Piper fatigue scale [92], 1 [51] through the fatigue symptom inventory [93], 1 [76] through a subscale of an insomnia symptom questionnaire and 1 through a specific daytime fatigue scale [65].

Please insert Table 1 here.

Network meta-analysis results

Depressive symptoms

Considering depressive symptoms, the network was based on 57 pairwise comparisons. The net graph is shown in Figure 2. Original data with estimated effects, standard errors and adjusted standard errors for multi-arm trials are reported in Document S4.

Please insert Figure 2 here.

Comparing each class of treatment with placebo, results showed significant mean effects of CBT-I individual with an effect size of medium magnitude (d= 0.46, 95% CI: 0.19 - 0.73). No significant effects were found in relation to other treatments. Q and I^2 tests revealed high heterogeneity between studies (Q= 167.24, df= 38, p<0.0001; I^2= 77.3%) and net heat "hot spots" indicated inconsistency in the network as shown in Figure 3.

Please insert Figure 3 here.

The net heat graph suggests that the design that mostly contributed to this inconsistency involved the three edges: CBT-I individual-psychological-waiting list. Direct evidence for two of these (CBT-I individual-psychological and psychological-waiting list) was associated with only one study [44]. Thus, this study was excluded from the analyses performed. Significant effects remained for CBT-I individual (d= 0.43, 95% CI: 0.17 - 0.69), with a decreased, but significant level of heterogeneity (Q=

153.71, df= 36, p<0.0001, I^2= 76.6 %). Consequently, we considered the second design that mostly contributed to inconsistency, which consisted of the following edges: CBT-I individual-pharmacological-sleep hygiene. Thus, we excluded all edges including this design [36,38,45] from the analyses. Significant effects were found only for CBT-I individual (*d*= 0.41, 95% CI: 0.15 - 0.67), with a significant level of heterogeneity (*Q*= 112.89, df= 31, p<0.0001, I^2= 72.5%). By further excluding the third design contributing to the inconsistency in the network with the edge CBT-I individual-waiting list [37,39,42,45] we still observed significant effects for CBT-I individual (*d*= 0.34, 95% CI: 0.06 - 0.63). Levels of heterogeneity decreased although these remained significant (*Q*= 64.14, df= 22, p<0.0001, I^2= 65.7%). "Hotspots" of inconsistency were absent from the net heat plot as shown in Figure 4. A forest plot exploring this more consistent network is presented in Figure 5.

Please insert Figure 4 here.

Please insert Figure 5 here.

To investigate other potential sources of heterogeneity, further sensitivity analyses were conducted. First, analyses were performed considering the clinical characteristics of the studies' samples. Specifically, data analysis included only studies which excluded any form of psychiatric and/or medical condition (including other sleep disorders) co-occurring with insomnia. Twelve studies were deemed suitable for analysis [37,56,57,63,60,66,67,69,70,72,77,80]. Results indicated no significant effects on depressive symptoms for any treatment. However, studies included in this analysis either identified the presence of depression as part of their inclusion criteria, or obtained samples with low levels of pre-treatment depression. With respect to heterogeneity, *Q* value decreased while I^2 tests indicated considerable presence of heterogeneity (*Q*= 19.61, df= 4, p<0.0006, I^2= 79.6%).

Therefore, our analyses included only studies with comorbid insomnia samples, comprised of 28 studies [34-36,38-48,50-53,55,58,59,61,62,64,71,74,75,79]. Results indicated a significant effect for

CBT-I individual (*d*= 0.41, 95% CI: 0.11 - 0.71) with high levels of heterogeneity (*Q*= 97.52, df= 26, p<0.0001, I^2=73.3%). No significant effects were found relating to other treatments.

Second, we considered other possible sources of heterogeneity such as sex and age. Six studies had exclusively female samples [43,45,56,58,59,79]. Because studies were too few to perform a network meta-analysis, we indirectly evaluated the effect of this group of trials by excluding this group from the analyses. A significant mean effects for CBT-I individual of medium magnitude (*d*= 0.47, 95% CI: 0.17 - 0.76) was found. However, *Q* and I^2 tests revealed high levels of heterogeneity between the remaining studies (*Q*= 127.44, df= 29, p<0.0001, I^2= 77.2%).

Six studies [53,57,71,74,75,77] included exclusively elderly samples (i.e. age >60 years or defined as older adults sample in the title). Again there were too few studies to warrant a network meta-analysis; we indirectly evaluated the effect of this group of trials by excluding this group from the analyses. Results indicated significant effects of CBT-I individual (*d*= 0.45, 95% CI: 0.19 - 0.72). *Q* and I^2 tests revealed high levels of heterogeneity (*Q*=139.47, df= 33, p<0.0001, I^2= 76.3%).

To indirectly analyse the efficacy of self-help with or without professional contact, sensitivity analyses were conducted, excluding specific groups of studies. First, analyses were performed excluding studies which used self-help with contact [35,61,64,65,72,67]. A significant effect for CBT-I individual (*d*= 0.47, 95% CI: 0.19 - 0.75) with high heterogeneity (*Q*=147.58, df= 32, p<0.0001, I^2= 78.3%) was found. Second, analyses were performed excluding studies which used self-help therapy without professional contact [45,60,62,63,66,69,80]. Results indicated significant effects for CBT-I individual (*d*= 0.38, 95% CI: 0.07 - 0.70) with decreased but significant levels of heterogeneity (*Q*=112.19, df= 28, p<0.0001, I^2= 75%).

Finally, analyses were conducted excluding the study evaluated at high risk of bias [67]. Results indicate a significant effect for CBT-I individual of medium magnitude (*d*= 0.47, 95% CI: 0.20 - 0.73), with high heterogeneity maintained (*Q*= 162.86, df= 37, p<0.0001, I^2= 77.3%).

It was not possible explore the impact of depression instrument on heterogeneity due to a small number of studies. Nevertheless, it was possible to indirectly evaluate the effect of the Beck depression inventory, the most frequently used instrument, by excluding 13 studies using this scale [34,35,37,38,40,46,50,57,58,62,67,69,80] from the analysis. Results still indicated a significant effect of CBT-I Individual on depression (*d*= 0.65, 95% CI: 0.23 - 1.06), with high and significant levels of heterogeneity (*Q*= 115.37, df= 21 p< 0.0001, I^2= 81.8%). Forest plots for all analyses are reported in Document S5.

To further explore the possible contribution of depression instrument in determining high heterogeneity between studies, we estimated whether the instruments were unequally distributed over the three comparisons; CBT-I Individual vs BT-I Individual, CBT-I Group vs BT-I Group, CBT-I Self-help vs BT-I Self-help. Fisher's exact test revealed no association between comparisons (p=0.546).

Fatigue symptoms

Considering fatigue, the network was based on 32 pairwise comparisons. The net graph is shown in Figure 6. Original data with estimated effects, standard errors and adjusted standard errors for multi-arm trials are reported in Document S6.

Please insert Figure 6 here.

Comparing each treatment category with placebo, significant effects for CBT-I individual (*d*= 0.45, 95% CI: 0.07 - 0.83) were found. *Q* and I^2 tests revealed high heterogeneity between studies (*Q*= 72.23, df 17, p<0.0001; I^2= 76.5%) and net heat "hot spots" indicated inconsistency in the network as illustrated in Figure 7.

Please insert Figure 7 here.

Net heat graph data indicates that the design with greatest contribution to inconsistency involved the three edges CBT-I group-pharmacological-placebo. Direct evidence for this (CBT-I group-placebo and-waiting list) was drawn from two studies [51,58]. Thus, we excluded them from the analyses. Results showed significant effects for CBT-I individual (d= 0.39, 95% CI: 0.02 - 0.75), with Q and I^2 tests indicating reduced but significant heterogeneity among studies (Q= 48.96, df= 14, p<0.0001, I^2= 71.4%). The second design with greatest contribution to inconsistency, consisted of the following edges: CBT-I individual-psychological-waiting list. Consequently, we excluded all the edges defining this design [44,45] from the analyses. No significant effects across all treatments were found. Heterogeneity, although reduced, remained significant (Q= 36.63, df= 10, p<0.0001, I^2= 72.7%). Net heat plot showed no more "hot-spots" of inconsistency, as shown in Figure 8. Figure 9 shows the forest plot exploring this more consistent network.

Please insert Figure 8 here.

Please insert Figure 9 here.

To investigate other potential sources of heterogeneity, further sensitivity analyses were conducted. First, analyses accounted for clinical characteristics of the studies samples. Because studies which excluded any form of psychiatric and/or medical condition co-occurring with insomnia were too few to perform a network meta-analysis, we indirectly evaluate the effect of this group of trials by excluding them from the analyses [49,54,70,78]. Results indicated significant effects of CBT-I

individual (*d*= 0.43, 95% CI: 0.00 - 0.86). *Q* and I^2 tests indicated high levels of heterogeneity (*Q*= 65.48, df= 13, p<0.0001, I^2= 80.1%).

Furthermore, we considered other possible sources of heterogeneity including sex and age. Seven studies included exclusively female samples [43,45,55,58,59,70,79]. This did not warrant a network meta-analysis. We indirectly evaluated the effect of this group of trials by excluding it from the analyses. Results indicate significant effects of CBT-I individual (*d*= 0.66, 95% CI: 0.21 - 1.11). With respect to heterogeneity, *Q* value decreased but remained significant (*Q*= 31.11, df= 9, p<0.0002), and Higgins's test resulted in a considerable level of heterogeneity (I^2= 72%).

Eight studies included exclusively elderly samples (i.e. age >60 years or defined as older adults sample in the title [41,51,53,54,58,68,76,78]). The limited number of studies did not allow for a network meta-analysis, and the effect of this group of trials was evaluated indirectly through exclusion from the analyses. Results indicate significant effects of pharmacotherapy (*d*= 1.15, 95% CI: 0.23 – 2.07). *Q* and I^2 tests revealed high levels of heterogeneity (*Q*= 39.28, df= 10, p<0.0001, I^2=74.5%).

To indirectly analyse the efficacy of self-help with or without professional contact, sensitivity analyses were conducted excluding specific groups of studies. First, analyses were performed excluding studies which used self-help with professional contact [64,65,68]. Results revealed a significant effect for CBT-I individual (*d*= 0.46, 95% CI: 0.05 - 0.87), with high heterogeneity (*Q*=58.05, df= 14, p<0.0001, I^2= 75.9%). Second, analyses were performed excluding studies which used self-help therapy without professional contact [45,62,70,73]. Results indicated significant effect only for CBT-I individual (*d*= 0.48, 95% CI: 0.03 - 0.93) with significant but decreased levels of heterogeneity (*Q*= 58.52, df= 12, p<0.0001, I^2= 79.5%).

Furthermore, analyses were conducted excluding the study with a high risk of bias [78]. Accordingly, results revealed a significant effect of CBT-I individual of medium magnitude (*d*= 0.41, 95% CI: 0.00 - 0.82). Heterogeneity remained high (*Q*= 71.2, df= 16, p<0.0001, I^2= 77.5%).

It was not possible to perform the analysis on specific group of studies according to the fatigue measure used due to a small number of studies. Nevertheless, it was possible to indirectly evaluate the effect of the multidimensional fatigue inventory, the most frequently used instrument, by excluding 11 studies using this scale [34,44,45,47,53,55,59,64,70,73] from the analysis. Results indicated no significant effects for any treatments. Heterogeneity levels remained significant (Q= 39.18, df= 4 p< 0.0001, I^2= 86.7%). Forest plots for all analyses are reported in Document S7.

To further explore the role of the instrument in determining heterogeneity, we estimated whether the instruments were unequally distributed over the three comparisons: CBT-I Individual vs BT-I Individual, CBT-I Group vs BT-I Group, CBT-I Self-help vs BT-I Self-help. Fisher's exact test revealed no association between comparisons (p=0.571).

Discussion

The aim of the present systematic review and network meta-analysis was to synthesise the literature regarding the effectiveness of BT-I and CBT-I on depressive and fatigue symptoms. After excluding inconsistent designs within the network, results showed that only individual CBT-I was associated with greater improvement at post-treatment compared with placebo on depressive symptoms, but not on fatigue.

High heterogeneity between studies was found and markedly impacted our results. The source of heterogeneity could not be pinpointed despite investigating clinical and demographic variables, such as sex, age, comorbidity or risk of bias. With respect to outcome measures, we found that instruments were equally distributed across treatment types. Additionally, excluding studies that used the most frequently used scales, i.e., Beck depression inventory and the multidimensional fatigue inventory, did not substantially reduced heterogeneity. Thus, the choice of instrument did not notably contribute to heterogeneity. Nevertheless, the majority of the studies using the Beck

depression inventory [81] were associated with limited effectiveness [34,35,37,38,40,46,50,57,58,69,80].

These results demonstrate an excessive amount variance in study designs, populations, and procedures which limits the impact of the evidence. Thus, it is imperative that clinical research on insomnia treatment moves towards establishing consistent (e.g. identifying target populations, adequate treatment settings and including strategies) and methodologically robust evidence (e.g. increasing power, using adequate recruitment procedures). Furthermore, efforts should be made to encourage replication studies in the field despite the challenges linked with publishing such work.

Cognitive techniques embedded in treatment packages appear to contribute to treatment effectiveness. However, cognitive interventions within included studies were largely (n=29) [34-37,39-43,54-50,54-57,59,60,62,65,68-74] limited to the cognitive restructuring of dysfunctional beliefs and attitudes about sleep according to Morin's model [94]. Thus, future studies would benefit from including other techniques that may improve daytime symptoms such as paradoxical intention, cognitive control, emotion regulation training, behavioural activation and exercise.

Group or self-help therapy both with and without professional contact seem to have limited effects on symptoms. A growing body of evidence from RCTs on group and self-help CBT-I demonstrate positive effects on depressive symptoms [45,66,72]. A comparison of treatments using network meta-analysis demonstrate less promising results. Nevertheless, in our review, due to the limited number of comparisons we were unable to perform analyses differentiating between booklet-based treatments and internet-based treatment.

Individual CBT-I appears effective in reducing depressive symptoms and partially fatigue in those suffering from insomnia. These findings may corroborate the recently proposed hypothesis that CBT-I may have potential preventive properties for psychopathology, particularly for depression [6,11]. Sleep disturbances are widely spread in psychopathology [95] and insomnia is one of the most common mental disorders [2]. Yet, transdiagnostic models highlighted insomnia as a process

involved in the onset of several psychiatric disorders [96]. Accordingly, improving sleep and mood in patients with insomnia through CBT-I may have potential impact on the incidence of mental disorders and specifically on depression. The results of the present meta-analysis partially provide empirical support for this hypothesis. This may represent intriguing and challenging implications for insomnia therapy. However, it must be noted that most of the included samples in this review were without severe baseline levels of depression. Additionally, included studies were not designed to assess the effects of CBT-I in preventing depression. Finally, high heterogeneity further limits conclusions that can be drawn.

With respect to study limitations, it is important to note that this review focussed on studies integrating at least SR in the treatment and excluded trials using SC only. However, a more comprehensive picture of treatment efficacy can be obtained from focussing on SC. It is recommended that future meta-analyses consider the effects of the two core behavioural strategies. Nevertheless, in line with the emerging literature on the standardisation of SR therapy [24], we decided to contribute to the debate aggregating empirical evidence on the efficacy of CBT-I integrating SR.

A limitation of the present network meta-analysis is that a publication bias analysis was not possible. However, the conduct of publication bias analysis specifically in network meta-analysis is still yet to be established. Funnel plots, used in traditional meta-analysis to assess publication bias are not recommended for use in network meta-analysis where the direction of effects of small studies cannot be assumed [97]. This was the case for our study samples, composed of trials in which primary outcomes were sleep and insomnia severity while daytime symptoms of depression and fatigue were only secondary outcomes. Thus, there was minor risk of not publishing negative results.

A further limitation of the present review is that the literature search relied on three databases. A more comprehensive literature research involving other databases may have provided a greater number of studies for this meta-analysis. Furthermore, grey literature was excluded in our review

which might have prevented the inclusion of potentially eligible studies, consequently affecting our results.

Additionally, this review is limited to daytime depressive and fatigue symptoms, as these are two of the most common symptoms reported by patients [1,4,12]. However, future meta-analyses should consider other health-related variables such as quality of life and cognitive impairments.

In conclusion, CBT-I may have a positive impact on depressive and fatigue symptoms. However, the high variability between study methodologies and limited evidence regarding efficacy on fatigue symptoms, suggest that the review findings are interpreted with caution. Future research on insomnia would benefit from addressing these gaps in order to further strengthen the empirical evidence base on the effectiveness of CBT-I.

Practice points

1. The effectiveness of standard psychological treatments for insomnia on daytime depressive and fatigue symptoms remains poorly investigated.

2. Results from meta-analysis highlighted an overall high level of heterogeneity between studies that was only partially explained by clinical and demographic characteristics of the samples.

3. Findings suggest that CBT-I appears to positively impact daytime symptoms when administered individually.

Research agenda

1. Daytime symptoms of insomnia should be included as primary outcomes in future trials.

2. Studies should describe randomisation and blinding procedures in detail to decrease risk of bias.

3. Replication studies should be encouraged. Future randomised controlled trials should be conducted with larger samples to increase statistical power.

4. Settings and treatment strategies should be better operationalised and common experimental procedures should be shared.

5. Future randomised controlled trials should test the long-term effects of psychological therapies for insomnia on daytime symptoms.

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Figures Legend:

Figure 1: Search flow.

Figure 2: Network graph depression. BT-I= behavioural therapy for insomnia, CBT-I = cognitive behavioural therapy for insomnia.

Figure 3: Net heat plot of depressive. BT-I= behavioural therapy for insomnia, CBT-I = cognitive behavioural therapy for insomnia.

Figure 4: Net heat plot depression after sensitivity analyses. BT-I= behavioural therapy for insomnia, CBT-I = cognitive behavioural therapy for insomnia.

Figure 5: Forest plot depression after sensitivity analyses.
Number of studies: 29
Number of treatments: 11
Number of pairwise comparisons: 35
Heterogeneity tests: Q= 64.14, df= 22, p<0.0001,I^2= 65.7%
Legend: BT-I= behavioural therapy for insomnia, CBT-I= cognitive behavioural therapy for insomnia, CI= confidence intervals, DF= degrees of freedom.

Figure 6: Network graph fatigue. BT-I= behavioural therapy for insomnia, CBT-I = cognitive behavioural therapy for insomnia.

Figure 7: Net heat plot fatigue. BT-I= behavioural therapy for insomnia, CBT-I = cognitive behavioural therapy for insomnia.

Figure 8: Net heat plot fatigue after sensitivity analyses.BT-I= behavioural therapy for insomnia, CBT-I = cognitive behavioural therapy for insomnia.

Figure 9: Forest plot fatigue after sensitivity analyses.
Number of studies: 18
Number of treatments: 11
Number of pairwise comparisons: 22
Heterogeneity tests: Q= 36.63, df= 10, p<0.0001, I^2= 72.7%.
Legend: BT-I= behavioural therapy for insomnia, CBT-I= cognitive behavioural therapy for insomnia, CI= confidence intervals, DF= degrees of freedom.

Age CBT (means)
46.2
49.6
51.9
57
45
43.3
57.2
64.5
55.8
50.1
55.7
68.7
61
49
58.7
70.2
41.5
38.6
78
58.9
49.1
52
65
51.7
67.9
64
36.4
46.5
52.1
36.4
47.7
43.9
63
62.5
49
50.7
64.5
53.7
70.1
54.8
53.9
37.1
45.7
47
48.7
n.s
69.2

57.2727273

Age controls (means)
46.1
50.3
48.7
59
45
43.3
59.2
67.6
55.1
47.4
52.4
69.5
61
49
60.3
70.2
41.5
38.6
66.3
53.6
45.4
43
60
51.9
68
64
39.1
48.6
52.8
72.6
56.9
50.2
66.3
62.5
42
50.7
67.4
59.6
67.7
53.3
55.4
37.3
51.3
50.2
50.1
n.s
66.5

54.5555556

Sex CBT (%Female)
33.3
59.7
38.4
54
55
30
100
62.5
44
95.7
52.1
64.4
69
73.1
79
71.4
17-Jun
39.9
78
58.9
75.8
78.9
22-Feb
71.5
70.8
50
10
100
100
43
58.3
100
69.4
50
65.6
66.6
100
100
60.8
100
100
75.9
90
33.3
59.3
67.8
78.2

3894.59091
82.80%

Sex controls (%Female)
37.5
56.4
46.1
62.8
55
30
100
50
48
94.4
36.3
64
68
73.1
62
71.4
10-Jan
69
68.3
66.6
40
88.8
22-Feb
68
71.4
50
10
100
100
80
61.1
100
63.2
50
66.7
66.6
33.5
71.4
73.9
100
100
56.3
90
44.4
81.4
66.1
96.4

3717.6087
79%

Table 1. Study characteristics.

Study	Insomnia according to	Insomnia duration	Mental comorbidity	Physical comorbidity	Sleep comorbidity	Drug use	N CBT-I	N controls	Age CBT M (SD/range)	Age controls M (SD/range)	CBT-I % females	Controls % females	Risk of bias	Depression measure	Fatigue measure
Arnedt et al. 2011 [34]	ISI	NS	Alcohol dependence	Excluded	Excluded	Sleep	9	8	46.2 (8.9)	46.1 (12.0)	33.3	37.5	Low	BDI	MFI
Bjorvatn et al. 2011 [60]	BIS	NS	NS	NS	Excluded	Sleep and others	77	78	49.6 (14.5)	50.3 (13.2)	59.7	56.4	Moderate	HADS	—
Blom et al. 2015 [61]	AASM, DSM	NS	Major depression	NS	Excluded	Sleep and others	22	21	46.1 (13.6)	48.2 (11.0)	35	65	Low	MADRS-S	—
Chen et al. 2008 [49]	DSM	NS	Excluded	Excluded	Excluded	Sleep	13	13	51.9 (8.6)	48.7 (14.6)	38.4	46.1	Moderate	—	FSS
Chen et al. 2011 [62]	DSM	<1 year	Excluded	Hemodialysis	Excluded	NS	37	35	57 (9.0)	59 (11.0)	54	62.8	Low	BDI	FSS
Currie et al. 2000 [50]	DSM	>1 year	Mood disorders	Chronic pain	Excluded	Psychotropic and others	32	28	45 (8.0)	45 (8.0)	55	55	Moderate	BDI	—
*Currie et al. 2004 [35]**	DSM	NS	Alcohol dependence	NS	NS	Sleep and others	40	20	43.3 (10.9)	43.3 (10.9)	30	30	Moderate	BDI	—
Dirksen & Epstein 2008 [79]	DSM, ICSD	>1 year	NS	Breast cancer survivors	Excluded	Sleep and others	34	38	57.2 (9.9)	59.2 (10.7)	100	100	Moderate	CES-D	POMS/FI
Edinger et al. 1996 [76]	ISQ	< 1 year	NS	NS	PLMD	Excluded	8	8	64.5 (4.1)	67.6 (4.1)	62.5	50	Low	—	ISQ-DF
*Edinger et al. 2001 [80]**	DSM	>1 year	Partially excluded	Excluded	Excluded	Excluded	25	50	55.8 (12.1)	55.1 (11.5)	44	48	Low	BDI	—
*Edinger et al. 2005 [36]**	DSM	NS	Excluded	Pain	Excluded	Psychotropic and others	18	29	50.1 (6.9)	47.4 (9.0)	95.7	94.4	Low	POMS	—
Edinger et al. 2007 [37]	DSM	< 1 year	Excluded	Excluded	Excluded	Excluded	39	9	55.7 (10.2)	52.4 (7.3)	52.1	36.3	Moderate	BDI	—
Epstein et al. 2012 [77]	DSM	< 1 year	Excluded	Excluded	Excluded	Excluded	129	50	68.7 (7.7)	69.5 (8.3)	64.4	64	Moderate	GDS	—

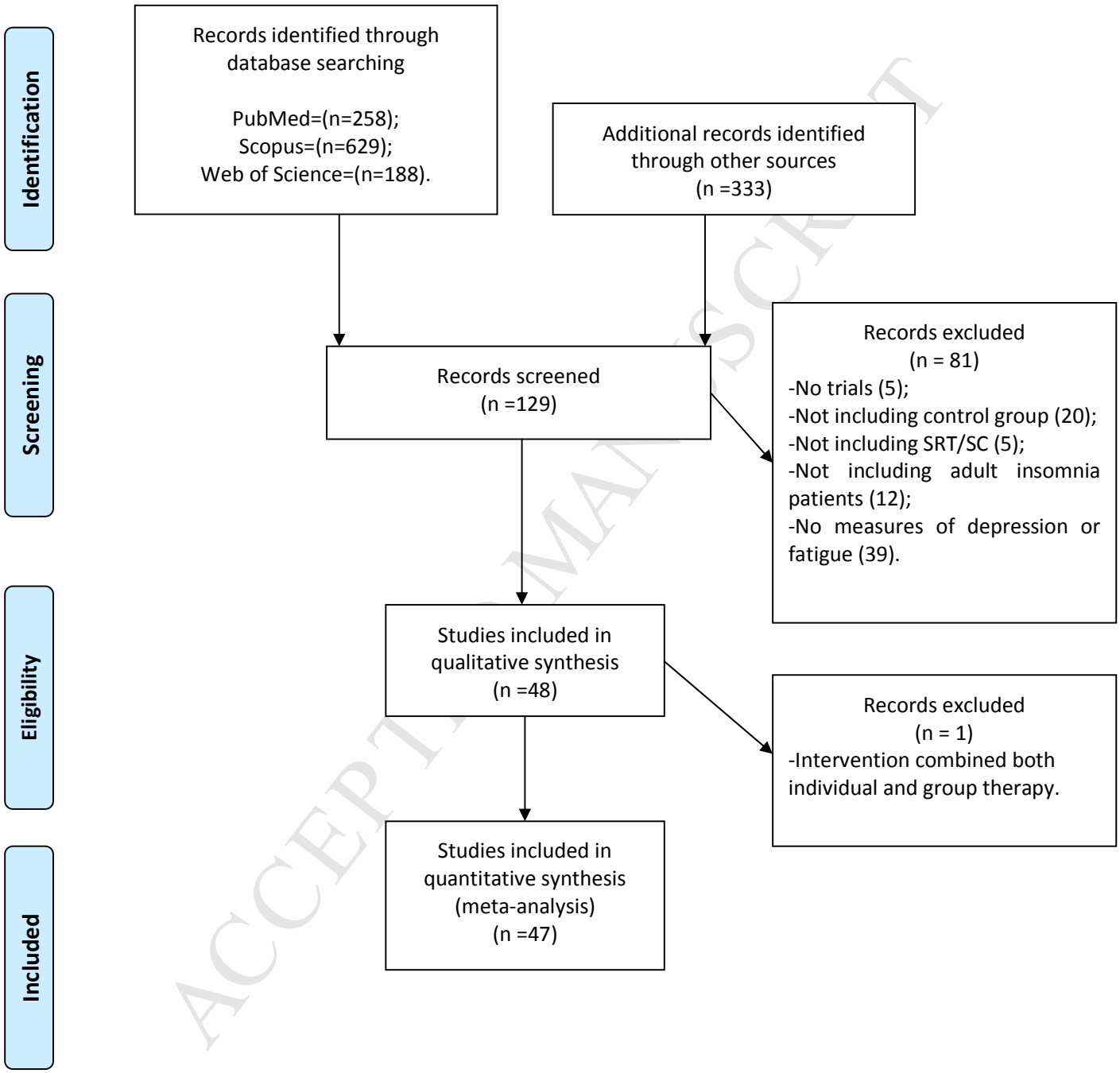
Espie et al. 2008 [51]	DSM	>1 year	Marginal depression	Cancer	Excluded	Sleep	100	50	60.5 (53.3-70)	58 (52-68)	69	68	Low	HADS	FSI
*Espie et al. 2014 [63]**	DSM	>1 year	Excluded	Excluded	Excluded	Sleep and others	55	109	49 (18-78)	49 (18-74)	73.1	73.1	Low	DASS	—
Garland et al. 2014 [52]	DSM	>1 year	Excluded	Cancer	Excluded	Psychotropic and others	40	32	58.7 (10.4)	60.3 (12.2)	79	62	Low	POMS	—
Germain et al. 2006 [75]	DSM	>1 year	Depression, anxiety	Arthritis, cancer, joint, cardiovascular and bladder diseases	Excluded	Sleep	17	18	70.2 (5.3)	70.2 (5.3)	71.4	71.4	Low	HAM-D	—
*Germain et al. 2012 [38]**	DSM	NS	PTSD	Excluded	Partially excluded	Other	17	33	40 (14.1)	41.5 (12.9)	17.6	10.1	Low	BDI	—
Ho et al. 2014 [64]	DSM	>1 year	Depression, GAD, panic and bipolar disorder	Respiratory disease, pain, cardiovascular disease, diabetes	Marginal	Other	207	105	38.6 (11.8)	39.9 (12.7)	39.9	69	Moderate	HADS	MFI
*Irwin et al. 2014 [53]**	DSM, ICSD	NS	Excluded	Cardiovascular disease	Excluded	Excluded	50	73	64.4 (6.1)	66.3 (7.4)	78	68.3	Low	IDS-C	MFSI
Jansson-Fröjmark et al. 2012 [39]	DSM	>1 year	Depression, GAD, social phobia	Hearing impairment	Excluded	Sleep	17	15	57.8 (6.6)	53.6 (10.4)	58.9	66.6	Moderate	HADS	—
Jernelöv et al. 2012 [65]	RDC	>1 year	Marginal depression and anxiety	Marginal allergic disease, pain, stress	RLS, snoring, bruxism	Sleep	89	44	49.1 (12.5)	45.4 (16.0)	75.8	40	Low	—	DTF
Jungquist et al. 2010 [40]	DSM	>1 years	NS	Chronic pain	Excluded	Other	19	9	52 (9.9)	43 (10.7)	78.9	88.8	Low	BDI	—
Kapella et al. 2011 [41]	SII, PSG	NS	Excluded	Chronic obstructive polumary disease	Excluded	Excluded	9	9	65 (9.0)	60 (10.0)	22.2	22.2	Moderate	POMS	CRQ-FS
Lancee et al. 2012 [66]	DSM	NS	Excluded	NS	Partially excluded	Sleep	417	200	51.7 (12.1)	51.9 (12.2)	71.5	68	Low	CES-D	—
*Lichstein et al. 2001 [78]**	ASDA	>1 year	Excluded	Excluded	Excluded	Excluded	24	50	67.9 (6.7)	68 (7.1)	70.8	71.4	High	—	FSS
Lovato et al. 2014 [54]	DSM	>1 year	Excluded	Excluded	Excluded	Excluded	89	32	64 (NS.)	64 (NS.)	50	50	Moderate	—	Flinder fatigue scale
Margolies et al. 2013 [42]	DSM	NS	PTSD	Excluded	Excluded	Sleep	15	12	36.4 (9.3)	39.1 (8.9)	10	10	Moderate	PHQ	—
Martinez et al. 2013 [55]	DSM	>1 year	Excluded	Fibromyalgia	Excluded	Other	30	29	46.5 (6.3)	48.6 (7.2)	100	100	Low	—	MFI

Matthews et al. 2014 [43]	DSM, ISI	NS	Excluded	Cancer	Excluded	Excluded	30	30	52.1 (6.8)	52.8 (7.7)	100	100	Low	HADS	PFS
McCurry et al. 1998 [33]	Jenkins scale	NS	NS	Excluded	Excluded	Excluded	21	15	66.4 (10.4)	72.6 (7.7)	43	80	Low	CES-D	—
Mimeault & Morin 1999 [67]	DSM, ASDA, ISI	>1 year	Partially excluded	Excluded	Excluded	Sleep	36	18	47.7 (10.8)	56.9 (13.4)	58.3	61.1	High	BDI	—
Miro´et al. 2011 [56]	DSM	>1 year	Partially excluded	Excluded	Excluded	Other	16	15	43.9 (6.0)	50.2 (6.1)	100	100	Low	HADS	—
Morgan et al. 2012 [68]	DSM	NS	NS	Chronic disease	Excluded	Sleep	98	95	67 (7.9)	66.3 (6.9)	69.4	63.2	Low	—	FSS
Morin et al. 2004 [57]	DSM	>1 year	Excluded	Excluded	Excluded	Benzodiazepine tapering	24	25	61.4 (6.4)	62.9 (4.7)	50	50	Moderate	BDI	—
Morin et al. 2005 [69]	DSM, ISI	>1 year	NS	NS	Excluded	Sleep	96	96	49 (15.3)	45.9 (14.2)	65.6	66.7	Low	BDI	—
*Pigeon et al. 2012 [44]**	DSM	NS	Excluded	Chronic pain	Excluded	NS	6	9	50.7 (8.3)	50.7 (8.3)	66.6	66.6	Moderate	CES-D	MFI
*Rios Romenets et al. 2013 [58]**	ISI	NS	NS	Parkinson´s disease	Partially excluded	Excluded	6	12	64.5 (16.3)	67.4 (10.5)	100	33.5	Moderate	BDI	Krupp fatigue scale
Ritterband et al. 2012 [70]	DSM	>1 year	Excluded	Excluded	NS	Excluded	14	14	53.7 (10.8)	59.6 (12.3)	100	71.4	Moderate	—	MFSI-SF
Rybarczyk et al. 2005 [71]	DSM	NS	Excluded	Osteoarthritis, coronary artery and pulmonary diseases	Excluded	Sleep and others	46	46	70.1 (9.1)	67.7 (7.9)	60.8	73.9	Low	POMS	—
Savard et al. 2005 [59]	DSM, ICSD	>1 year	Depression, GAD, adjustment disorders	Cancer and not specified other physical comorbidities	Excluded	Sleep	27	30	54.8 (7.0)	53.3 (7.7)	100	100	Low	HADS	MFI
*Savard et al. 2014 [45]**	ISI	>1 year	Anxiety, adjustment, mood disorders	Not specified other comorbidities	Excluded	Sleep	161	81	53.9 (8.8)	55.4 (8.8)	100	100	Low	HADS	MFI
Talbot et al. 2014 [46]	RDC	NS	PTSD, depression and other not specified	NS	Partially excluded	Psychotropic	29	16	37.1 (10.4)	37.3 (11)	75.9	56.3	Low	BDI	—
Tang et al. 2012 [47]	ISI	>1 year	Depression, social phobia, substance dependence, PTSD, GAD	Chronic pain	Excluded	Sleep and others	10	10	45.7 (9.3)	51.3 (7.9)	90	90	Moderate	HADS	MFI
Ulmer et al. 2011 [48]	ISI	NS	PTSD	NS	Excluded	Sleep and others	9	9	47 (9.4)	50.2 (11.6)	33.3	44.4	Moderate	PHQ	—

van Straten et al. 2013 [72]	DSM	>1 year	Partially excluded	NS	NS	Sleep	59	59	48.7 (13.8)	50.1 (11.9)	59.3	81.4	Moderate	CES-D	—
Vincent et al. 2009 [73]	RDC	NS	Depression, panic, social phobia, GAD, OCD	NS	Sleep apnea, plmd, RLS, parasomnia	Sleep	59	59	NS	NS	67.8	66.1	Low	—	MFI
Vitiello et al. 2009 [74]	DSM	>1 year	Partially excluded	Osteoarthritis	Partially excluded	Sleep and others	23	28	69.2 (8.9)	66.5 (7.7)	78.2	96.4	Moderate	GDS	—

Abbreviation: AASM= American academy of sleep medicine; ASDA= American sleep disorders association; BDI= Beck depression inventory; BIS= Berger insomnia scale; CBT= cognitive behavioral therapy; CBT-I= cognitive behavioral therapy for insomnia; CES-D= center for epidemiological studies depression scale; CRQ-FS= chronic respiratory disease questionnaire-fatigue scale; DASS= depression anxiety stress scale; DSM= Diagnostic and statistical manual of mental disorder; DTF= daytime fatigue scale; FSI= fatigue symptom inventory; FSS= fatigue severity scale; GAD= generalized anxiety disorder; GDS= geriatric depression scale; HADS= hospital anxiety and depression scale; HAM-D= Hamilton depression rating scale; ICSD= International classification of sleep disorders; IDS-C= inventory of depressive symptomatology; ISI= insomnia severty index; ISQ-DF= insomnia severity questionnaire-daytime fatigue scale; ISQ=insomnia severity questionnaire; MADRS-S= MontgomeryÅsberg depression rating scale; MFI= multidimensional fatigue inventory; MFSI= multidimensional fatigue symptom inventory; MFSI-SF= multidimensional fatigue symptom inventory-short form; NS= not specified; OCD= obsessive compulsive disorder; PFS= Piper fatigue scale; PHQ= patient health questionnaire; PLMD= periodic limb movement disorder; POMS= profile of mood states; POMS-FI= profile of mood states-fatigue inertia scale; PSG= polysomnography; PTSD= post-traumatic stress disorder; RDC= research diagnostic criteria; RLS= restless legs syndrome; SD= standard deviation; SII= sleep impairment index. Multi-arm studies are marked with *. For multi-arm studies pooled data is reported.

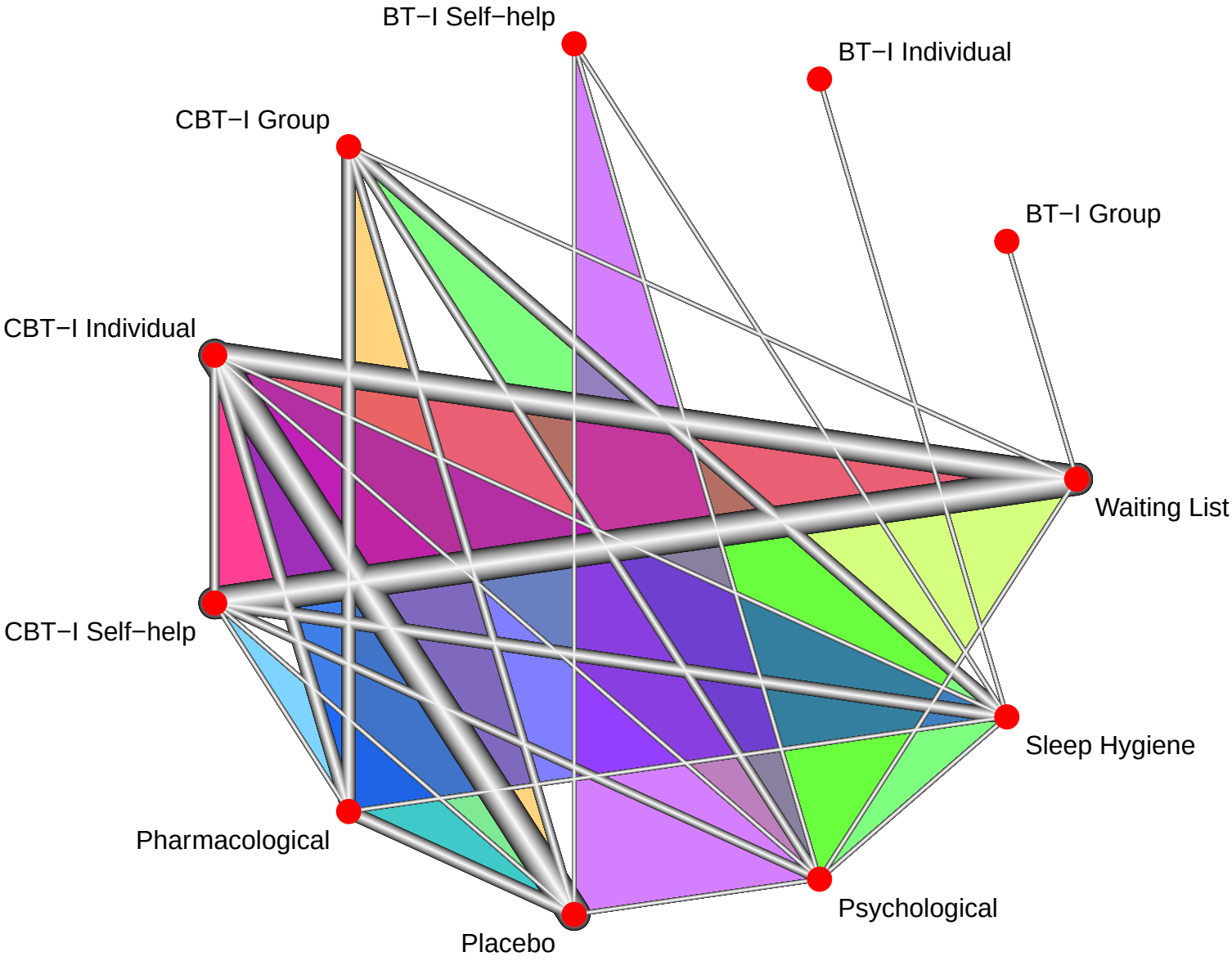
Figure 1. Search flow.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Depression



Line width: Weight of studies

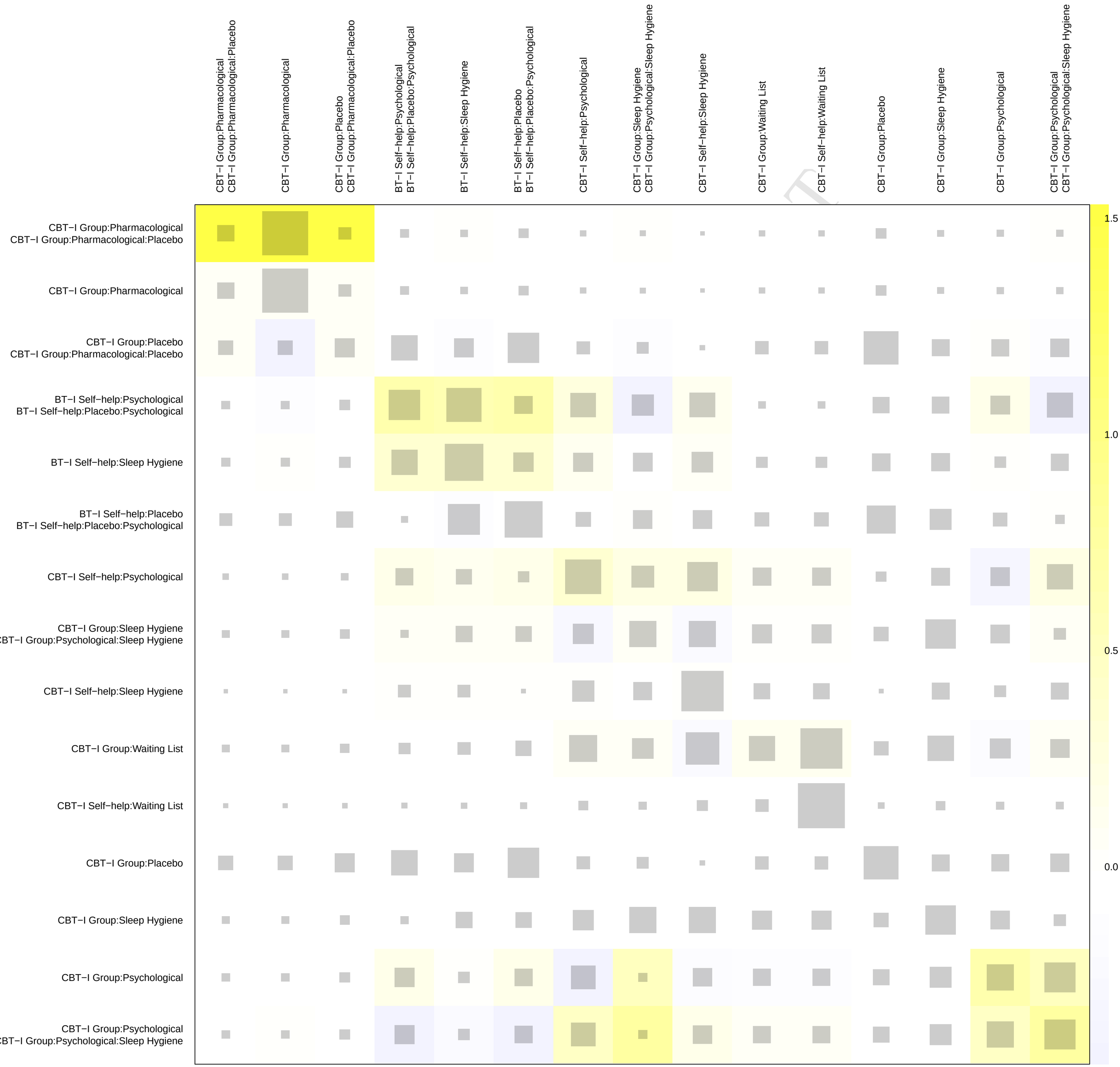
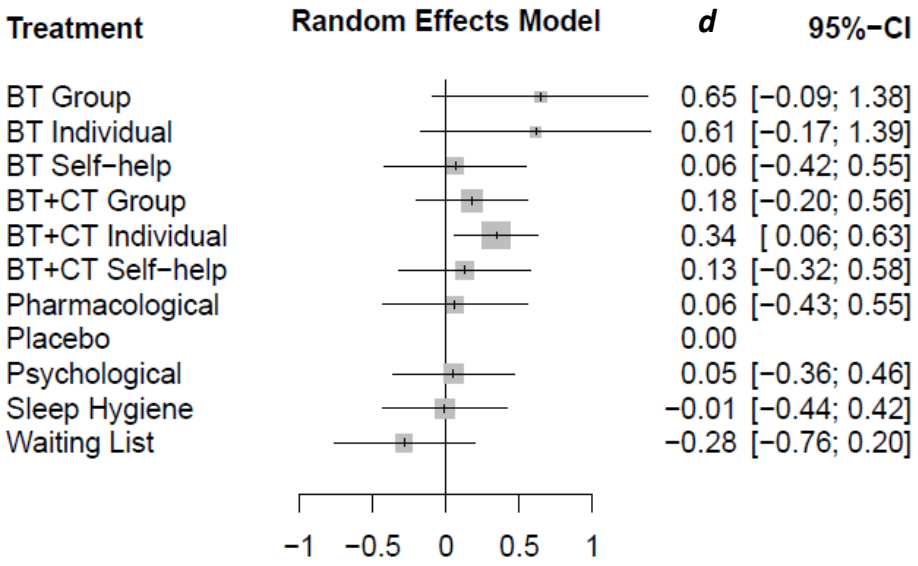
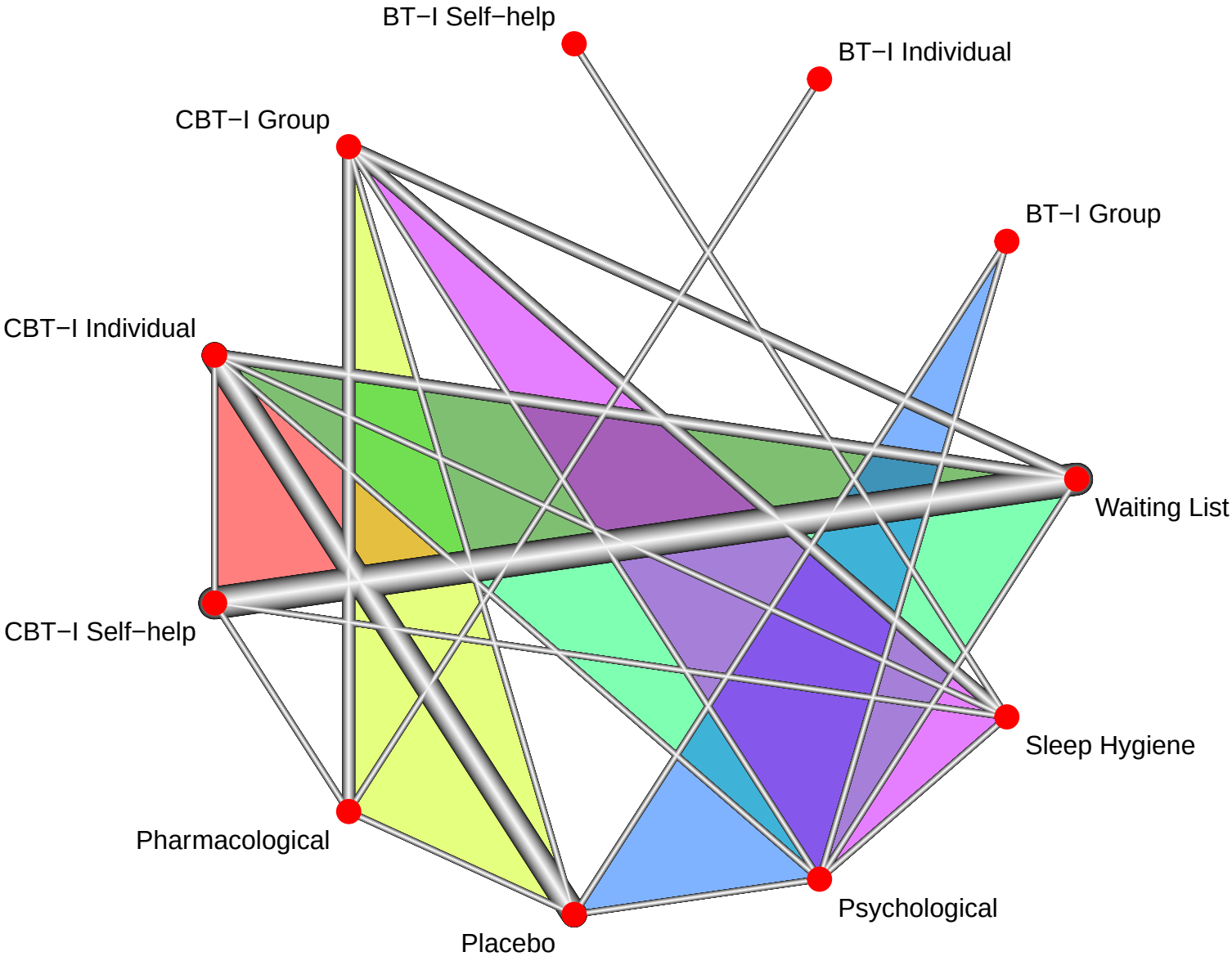


Figure 5. Forest plot depression after sensitivity analyses.



Fatigue



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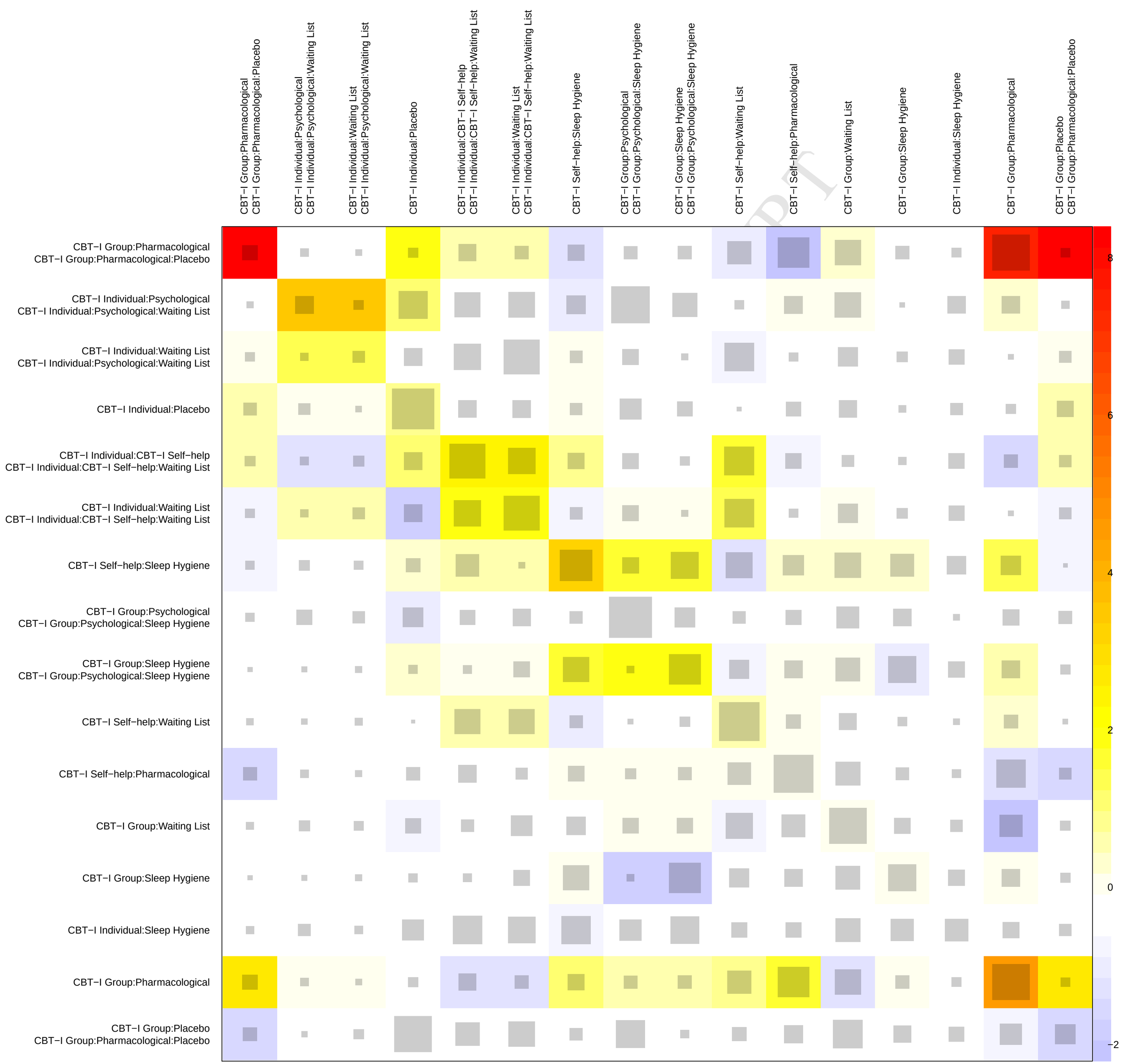

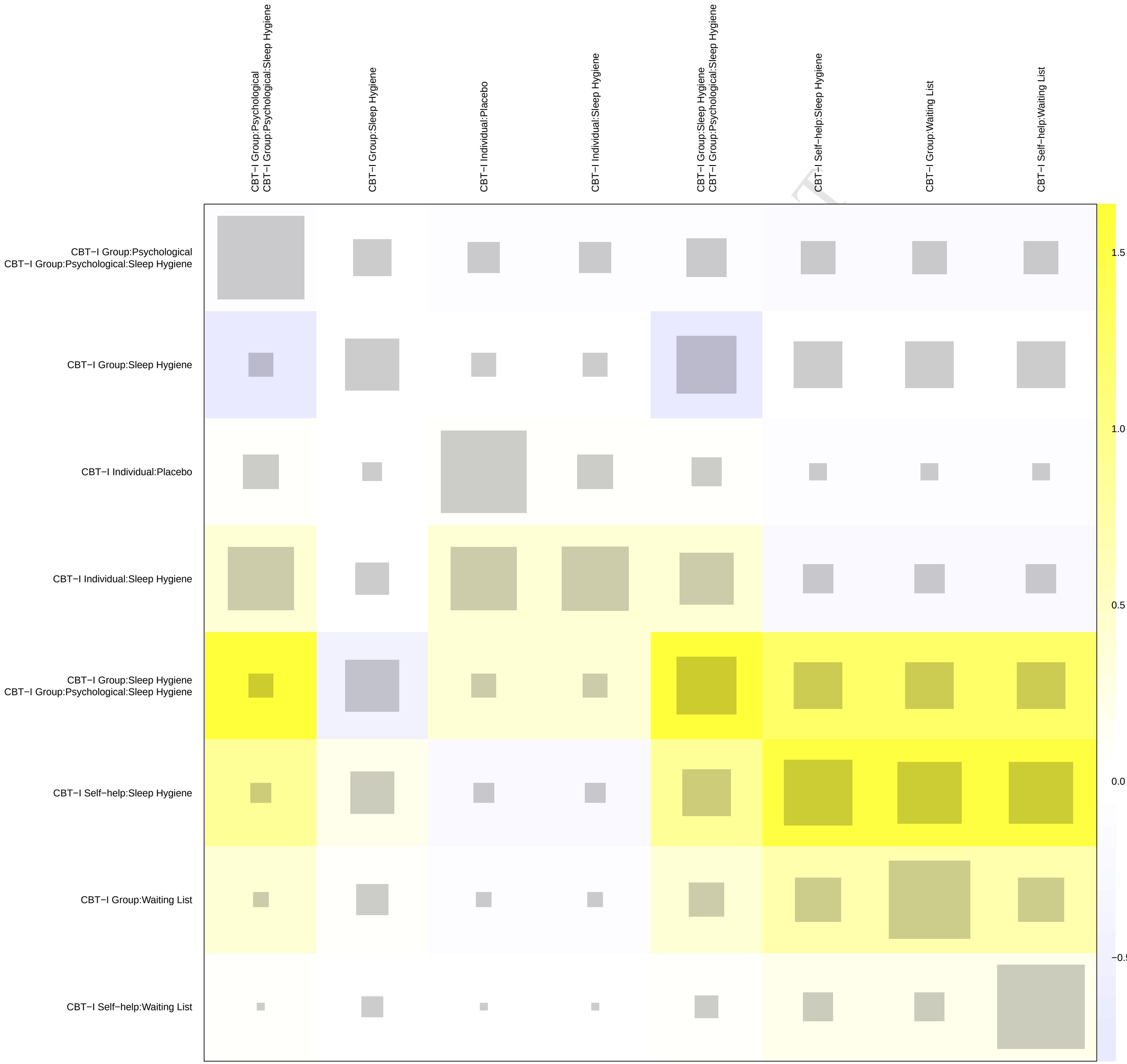

Figure 9. Forest plot fatigue after sensitivity analyses.