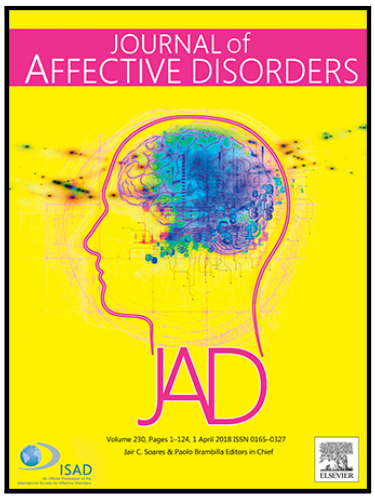
Accepted Manuscript



The efficacy of cognitive behavioural therapy in somatoform disorders and medically unexplained physical symptoms: A meta-analysis of randomized controlled trials

Jing Liu , Neeraj S. Gill , Andrew Teodorczuk , Zhan-jiang Li , Jing Sun

PII: S0165-0327(18)30696-7
DOI: https://doi.org/10.1016/j.jad.2018.10.114
Reference: JAD 10200

To appear in: *Journal of Affective Disorders*

Received date: 4 April 2018
Revised date: 19 October 2018
Accepted date: 19 October 2018

Please cite this article as: Jing Liu , Neeraj S. Gill , Andrew Teodorczuk , Zhan-jiang Li , Jing Sun , The efficacy of cognitive behavioural therapy in somatoform disorders and medically unexplained physical symptoms: A meta-analysis of randomized controlled trials, *Journal of Affective Disorders* (2018), doi: https://doi.org/10.1016/j.jad.2018.10.114

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Highlights:

- This study aimed to update the former meta-analyses, and give an overview of the evidence from RCTs that focused on the efficacy of CBT for patients with somatoform disorders and medically unexplained physical symptoms.
- It suggested that CBT is effective for somatoform disorders and MUPS by reducing physical symptoms, anxiety symptoms and depressive symptoms, improving physical functioning. The efficacy of CBT on alleviating somatic symptoms, anxiety and depressive symptoms were sustained on follow-up.
- The results of subgroup analysis indicated that CBT was particularly beneficial to reduce the somatic symptoms when the session duration was over 50 mins, group based, and applied affective and good interpersonal strategies.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

The efficacy of cognitive behavioural therapy in somatoform disorders and medically unexplained physical symptoms: A meta-analysis of randomized controlled trials

Jing Liu[a], Neeraj S Gill[c,d], Andrew Teodorczuk[c,e], Zhan-jiang Li[a]*, Jing Sun[b,c]*

Affiliations: [a]The Department of Clinical Psychology & National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China;
[b]Menzies Health Institute Queensland, Griffith University, Queensland, Australia, and
[c]School of Medicine, Griffith University, Queensland, Australia
[d]Gold Coast University Hospital, Southport, Queensland, Australia
[e]The Prince Charles Hospital, Brisbane, Queensland, Australia

Address correspondence to:

*Jing Sun, Menzies Health Institute Queensland and School of Medicine, Griffith University, Queensland, Australia Q4222. Email: j.sun@griffith.edu.au Phone: 6156780924

*Zhan-Jiang Li, Beijing Anding Hospital, Capital Medical University, No. 5 Ankang Hutong Deshengmen Wai, Xicheng District, 100088, Beijing, China. Email: lizhj8@ccmu.edu.cn Phone: 0086-10-58303004

Running head: Model of competency for qualified cognitive behaviour therapists

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The authors have no conflicts of interest to disclose.

Clinical Trial Registration: N/A

Abbreviations: CBT: cognitive behavioural therapy

Contributor's statements:

- Jing Liu: Conceptualized study, collected data, drafted the manuscript, and edited the manuscript.
- Z.J Li: Critically reviewed and revised the manuscript, and approved the final manuscript as submitted.
- Jing Sun: Conceptualized study, statistical analysis, critically reviewed, edited and revised the manuscript, and approved the final manuscript as submitted.
- Neeraj S Gill: Critically reviewed, edited and approved the final manuscript as submitted.
- Andrew Teodorczuk: Critically reviewed and approved the final manuscript as submitted.

ACCEPTED MANUSCRIPT

Abstract

Background: This systematic review and meta-analysis aimed to update and give an overview of the evidence from published literature that focused on the efficacy of cognitive behaviour therapy (CBT) in the management of somatoform disorders and medically unexplained physical symptoms (MUPS).

Methods: A comprehensive literature search was carried out through an electronic search of various databases on randomized controlled trials (RCTs). Primary outcome was the severity of somatic symptoms. Secondary outcomes were also measured based on severity of anxiety symptoms, severity of depressive symptoms, social functioning, physical functioning, doctor visits and the compliance with CBT, as well as follow-up visits. Effects were summarized by a random effects model using mean differences or odds ratio with 95% confidence intervals (CIs).

Results: A total of 15 RCTs comprising 1671 patients with somatoform disorders or MUPS were enrolled in our systematic review and meta-analysis. The main analysis revealed that CBT could alleviate somatic symptoms: -1.31 (95% CI: -2.23 to -0.39, $p = 0.005$); anxiety symptoms: -1.89 (95% CI: -2.91 to -0.86; $p < 0.001$); depressive symptoms: -1.93 (95% CI: -3.56 to -0.31; $p = 0.020$); improve physical functioning: 4.19 (95% CI: 1.90 to 6.49; $p < 0.001$). The efficacy of CBT on alleviating somatic symptoms, anxiety and depressive symptoms were sustained on follow-up. CBT may not be effective in reducing the number of doctor visits: -1.23 (95% CI: -2.97 to 0.51; $p = 0.166$); and improving social functioning: 3.27 (95% CI: -0.08 to 6.63; $p = 0.056$). The results of subgroup analysis indicated that CBT was particularly beneficial when the duration of session was more than 50 minutes to reduce

the severity of somatic symptoms from pre to post treatment time, when it was group based and applied affective and developed good interpersonal strategy during the treatment. Longer duration and frequency such as more than 10 sessions and 12 weeks treatments had significant effect on reduction of the comorbid symptoms including depression and anxiety, but they may underpin low level of compliance of CBT based treatments. *Conclusions:* CBT is effective for the treatment of somatoform disorders and MUPS by reducing physical symptoms, psychological distress and disability.

Declaration of interest

None.

Key words: somatoform disorders; medically unexplained physical symptoms; somatic symptom disorder; somatization disorder; interventions; CBT = cognitive behavioral therapy; MUPS = medically unexplained physical symptoms.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

1. Introduction

Somatoform disorders, as the precursor diagnostic classification of somatic symptom disorder, are characterized by a wide range of persistent somatic symptoms and impairment which are not attributable to any verifiable, conventionally defined diseases (1-4). The prevalence of somatoform disorders in the general population is approximately 6% (5). The key feature of somatoform disorders is the presence of "medically unexplained physical symptoms" (MUPS) which are common in all healthcare settings. There are as yet no agreed clinical or research diagnostic criteria for patients with "MUPS" (6), and they are divided into a large number of terminology-defined diagnostic concepts (7).

The Diagnostic and Statistical Manual of Mental Disorders (1, 2) and International Classification of Diseases (8) describe four somatoform diagnostic categories that include MUPS as their main indication (9). Despite this variability in terminology, all diagnostic concepts have in common that disabling conditions are characterized by multiple persistent physical complaints with no identifiable organic pathology, accompanied by decreased quality of life and social functioning, all of which place a heavy burden on the utilization of health resources (10).

Given that persistent somatic symptoms are difficult and costly to treat, multidisciplinary treatment has been proposed for somatoform disorders and MUPS in order to integrate "mental" and "physical" health care of these disorders (11). The most commonly used and investigated type of psychotherapy for somatoform disorders and MUPS is cognitive behavioural therapy (10, 12, 13). Cognitive behavioural model of somatoform

disorders and MUPS refers to a self-perpetuating cycle based on the interaction of multiple factors, including somatic (physical) aspects, cognitions (thoughts), behaviour, emotions and environment (14, 15). The treatment framework of CBT for somatoform disorders and MUPS incorporates patients' personal and environmental circumstances in the form of predisposing, precipitating and perpetuating factors. According to symptoms, the treatment focus on addressing and changing cognitions, information processing, behaviour, emotions, physical functioning, problem-solving, coping styles and social functioning in its broadest sense (9).

In the past decade, several reviews or meta-analysis have been conducted which demonstrate the efficacy of CBT for somatoform disorders and MUPS (9, 10, 16-20). However, certain reviews restricted the diagnostic types to somatisation and symptom syndromes (17), others did not include a meta-analysis (16, 19) and some reviews did not focus on CBT (9, 10, 21). This narrow research evidence base limits the adoption of CBT for management of somatoform disorders and MUPS in clinical setting (22, 23).

The current systematic review and meta-analysis aimed to update the former meta-analyses, and give an overview of the evidence from RCTs that focused on the efficacy of CBT for patients with somatoform disorders diagnosed according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Third or Fourth Edition* (DSM-III, DSM-IV or DSM-IV-TR) (1, 2, 4); or with somatic symptom disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (3); MUPS in adults, and persistent somatisation according to the Diagnostic Criteria for Psychosomatic

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Research (DCPR/DCPR-Revised) (24). The efficacy of CBT and their stability were analysed separately for different outcome variables.

2. Methods

2.1. Search strategy

The review protocol was registered at the PROSPERO International Prospective Register of Systematic Reviews (Registration ID= CRD42017074731 PROSPERO 2017 website: https://www.crd.york.ac.uk/prospero/#recordDetails).

A comprehensive literature search was carried out using electronic databases: Cochrane Library databases (up to date), MEDLINE through PubMed (1966 to date), EMBASE (1974 to date), and PsycINFO (1967 to date), Scopus, Chinese databases (WanFang, Chinese Biomedical and China Journal Net databases, and Griffith Research Online repository (grey literature) from inception to the final update in December 2017.

Searches were confined to literature using the following search terms: ‘somatic symptom disorder’, ‘medically unexplained symptoms’, ‘somatisation disorder’, ‘somatoform disorders’, ‘undifferentiated somatoform disorder’, ‘cognitive behaviour therapy’, ‘cognitive therapy’, ‘randomized controlled trials (RCTs)’ with Boolean operators AND and OR in abstract, key words or title, as follows:("cognitive behavi* therapy"[All Fields] OR "cognitive therapy"[All Fields]) AND ("somatization Disorder "[MeSHTerms] OR "medically unexplained symptoms "[MeSHTerms] OR "somatoform disorder"[MeSHTerms] OR "somatic symptom disorder "[All Fields]) AND ("randomized/randomised controlled trial” [All Fields]) (no restriction to publication period). The search terms were modified to suit the

search strategies for these databases. To ensure a comprehensive review, the literature search was supplemented by examination of the reference lists of the papers generated from the original searches.

2.2. Inclusion criteria

The criteria used to determine the inclusion of studies in the systematic review and meta-analysis was as follows:

1. Diagnosis fits one of the following conditions: 'somatic symptom disorder', 'medically unexplained physical symptoms', 'somatisation disorder', 'somatisation', 'persistent somatisation', 'somatoform disorder', 'undifferentiated somatoform disorder' 'functional somatic symptoms' as officially defined by DSM-III (4), DSM-IV (1), DSM-IV-TR (2), DSM-5 (3), or ICD-10 (8, 25), or DCPR/DCPR-Revised (24) or the criteria for one of the alternative somatoform disorders diagnoses proposed in the literature.
2. Participants were aged 18 years or older.
3. The intervention was CBT versus usual care, enhanced care or waiting list.
4. The study design involved RCTs.
5. If multiple studies were published on the same sample, the most recent one was included in the analysis.

2.3. Data extraction

We used a data collection form, piloted on one study in the review, to extract the first author, publication year, status of publication, study design, inclusion/exclusion criteria,

ACCEPTED MANUSCRIPT

study population, participant demographics, treatment form, frequency and duration of treatment, compliance with CBT, control conditions, outcome data, times of measurement and information for assessment of the risk of bias. The primary outcome was severity of somatic symptoms; secondary outcomes were severity of anxiety symptoms, severity of depressive symptoms, social functioning, physical functioning, doctor visits and the treatment compliance, as well as follow-up visits. Disagreements were resolved through discussion or consultation among the review authors until consensus was reached.

When necessary, the first author or corresponding authors of the studies were contacted to seek further information and acquire the necessary data. Seven authors were contacted for weight at the beginning and end of the study (26-32). Four authors replied with the weight gain (26, 27, 29, 31), and their values were included in the analysis.

2.4. Quality assessment

The methodological quality of each study was assessed using the Physiotherapy Evidence Database tool (33). This tool categorizes the quality of studies into three levels: high quality (≥ 8 points), moderate quality (4~7 points) and low quality (≤ 3 points). Parameters used to assess study quality include random allocation of subjects; concealed randomization; similarity of baseline information between groups; blinding to subjects, assessors and researchers; attrition rate; maintenance of group allocations; use of intention-to-treat analysis; use of variability measures; and use of between group comparison methods.

2.5. Statistical analysis

ACCEPTED MANUSCRIPT

All statistical analyses were conducted using Comprehensive Meta-Analysis software, Version 3.0, on Windows (http://www.meta-analysis.com). The efficacy of CBT on somatoform disorder and MUPS was described with the pooled mean differences method. Random effect in meta-analysis was performed to describe the overall mean differences. Pooled mean differences of outcome variables include severity of somatic symptoms, severity of anxiety symptoms, severity of depressive symptoms, social functioning, physical functioning, doctor visits; Odds ratio of outcome variables for treatment compliance was calculated that odds of treatment group compliance divided by odds of control group compliance to the program.. Confidence intervals (CIs) and *p* values were calculated for each of the outcome variables. The significance level was set at 0.05 (two sided). An I^2 test was used to assess sample heterogeneity.

Subgroup analyses were performed for somatic symptoms at post intervention and follow-up time, anxiety, depression and compliance at post intervention time. The pooled mean difference was calculated for each subgroup, and differences in mean differences between the subgroups (with a minimum of two studies) were examined for statistical significance using the Q statistic. Subgroup analyses were performed, including the treatment form (individual treatment versus group treatment), treatment course (<12 weeks versus ⩾12 weeks), sessions of treatment (<10 versus ⩾10), duration of per session (< 50 min versus ⩾ 50 min), manual-based treatment (yes versus no), specific treatment technique (important compared with not important).

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Modern CBT refers to a broad intervention approach that combines a variety of cognitive, behavioural, emotion-focused and body-directed techniques (14, 34, 35). We classified the treatment technique of CBT according to the Comprehensive Psychotherapeutic Interventions Rating Scale (36) and another previous study (13), including psychoeducation, behavioural strategies, cognitive strategies, affective strategies, interpersonal strategies, exposure, body-directed intervention, mindfulness and attention, and homework assignment. The intervention technique was rated as 'important' (explicitly mentioned as a core component), or 'not important' (not mentioned and definitely not a core component) (13, 36).

Publication bias was assessed using the Egger test. Sensitivity analyses were conducted to estimate the effect of CBT owing to a particular study or studies.

3. Results

3.1. Selection of studies

Initially, two assessors (JS, JL) independently scanned the titles and abstracts identified by the electronic literature searches to select potentially suitable papers. We found 358 abstracts after de-duplication, and then identified and discarded 219 publications and studies that obviously did not fulfil the inclusion criteria at this stage of the screening process. Finally, 139 articles were retrieved for further scrutiny. During the full-text assessment, two assessors independently scrutinized the full-text articles carefully, discussed disagreements and decided whether to keep the studies according to the definitive selection criteria. We recorded the selection process and reasons for exclusion of studies, and resolved disagreements by consensus—if necessary with the involvement of a third review author—in

ACCEPTED MANUSCRIPT

sufficient detail to complete a PRISMA flow diagram, and characteristics of included studies and characteristics of excluded studies tables. The process of identifying relevant articles for inclusion in the systematic review and meta-analysis is described in Fig. 1. This resulted in 15 studies being included in the systematic review and meta-analysis.

[Insert Fig. 1: PRISMA flow diagram]

Fig.1: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow chart representing the review process.

3.2. Participants

Full details of the included studies are shown in Table 1. The 15 included studies reported outcomes. Of 15 trials reviewed, three were performed in the United States (26, 28, 37), three in the Netherlands (38-40), two in Denmark (27, 32), two in Sweden (41, 42), one in Germany (43), two in Sri Lanka (29, 44), one in Scotland (45) and one in Spain (46). Only two studies were carried out in a low and middle income country (Sri Lanka) (29, 44).

3.3. Diagnostic criteria

Diagnostic criteria and inclusion criteria varied widely across studies. Twelve studies used standardized diagnostic interviews such as The Composite International Diagnostic Interview (CIDI), Structured Clinical Interview for DSM-IV (SCID), Mini-International Neuropsychiatric Interview (MINI), Schedules for Clinical Assessment in Neuropsychiatry (SCAN) and Present State Examination (PSE) to establish the diagnosis. Three studies used standardized questionnaires such as General Health Question-30 (GHQ-30) or Patient Health

ACCEPTED MANUSCRIPT

Questionnaire (PHQ-15). Three studies targeted somatoform disorders (28, 32, 43), three studies targeted somatisation disorder (26, 37, 41), five studies focused on medically unexplained physical symptoms (29, 39, 44, 45, 47), one study focused on somatisation disorder and functional somatic syndromes (27), one study focused on somatic symptom disorder and illness anxiety disorder (42), one study focused on abridged somatisation disorder (46), and one study focused on undifferentiated somatoform disorder or a chronic pain disorder (31).

The 15 included studies compared CBT with usual care or waiting list or structured care. The total number of randomized participants was 1671, and sample size of individual trials ranged from 32 to 172. In all included studies, the mean age of intervention group participants was 41.77 years, ranging from 34 (29) to 49.2 (45), and the mean age of control group participants was 42.56 years, ranging from 35.8 (29) to 51.7 (43).

3.4. Setting

Studies were carried out in primary, secondary or tertiary care settings. Eight studies recruited participants in primary care (26-29, 44-47), three studies recruited in secondary care (e.g. outpatient clinics) (39, 41, 43), one study recruited in primary care and secondary care (31), one study recruited in tertiary care settings (32), and two studies recruited via medical settings as well as the open population (e.g. through advertisements) (37, 42). Fourteen studies provided data for some of the outcomes, and one study did not provide any outcome data that were suitable for meta-analysis, because the authors only reported change scores (26).

[Insert Table 1: Characteristics of 15 randomized control trials included in the study]

3.5. Post- to pre-treatment effect of CBT

3.5.1. Effects on severity of somatic symptoms

Eleven studies with a total sample of 1623 participants measured the severity of somatic symptoms. The meta-analysis showed a significant reduction in the severity of somatic symptoms across 10 studies with reduction of symptom mean of -1.31 (95% CI: -2.23 to -0.39; $p = 0.005$). The heterogeneity was statistically significant ($I^2 = 86.46\%$, $p < 0.001$). The forest plot of the effect is presented in Fig. 2A.

A subgroup analysis (Table 3) found that CBT has statistically reduced somatic symptoms and it was more effective when it was group treatment (-4.43, 95% CI:-8.47 to -0.39; $p < 0.05$) compared with individual treatment (-1.00, 95% CI:-1.90 to -0.10; $p < 0.05$). CBT has statistically reduced somatic symptoms when treatment course was over 12 weeks (-2.28, 95% CI:-4.05 to -0.52; $p < 0.05$) compared to treatment with treatment course less than 12 weeks (-0.41, 95% CI:-1.43 to 0.61; $p > 0.05$). CBT has statistically reduced somatic symptoms when the duration of sessions was over 50 minutes (-1.48, 95% CI:-2.48 to -0.47; $p < 0.01$) compared with less than 50 minutes (-0.33, 95% CI:-2.37 to 1.71; $p > 0.05$). CBT has statistically reduced somatic symptoms and was more effective when it emphasized the body-directed technique (-1.70, 95% CI: -2.89 to -0.51; $p < 0.01$) than those did not emphasize it (-0.82, 95% CI:-1.60 to -0.03; $p < 0.05$). The effects of CBT on the reduction of somatic symptoms was significant when trials emphasized the affective technique (-3.95, 95% CI:-6.99 to -0.91; $p > 0.05$) compared to those that did not emphasize it (-0.54, 95% CI:-1.33

ACCEPTED MANUSCRIPT

to 0.24; $p > 0.05$). CBT has statistically reduced somatic symptoms when it emphasised the interpersonal technique (-18.78, 95% CI: -40.94 to 3.38) compared with trials without emphasising it (-0.64, 95% CI:-1.21 to -0.07), but it was statistically significant.

CBT has also significantly reduced severity of somatic symptoms with reduced pooled mean 0.87 (95% CI: -1.61 to -0.12; $p = 0.02$) across 10 studies during the follow-up period. The subgroup variables including more than 50 minutes duration of treatment sessions have explained CBT continued to have significantly reduced somatic symptoms, and the effects of the importance of detailed CBT strategies such as interpersonal strategies continued to be significant compared with no emphasise on interpersonal skills and group based treatment has significantly reduced somatic symptoms. The heterogeneity was statistically significant ($I^2 = 71.19\%$, $p = 0.001$). The forest plot of the effect is presented in Fig. 3A.

[Insert Figure 2: Forest Plots of post- to pre-treatment effect of CBT on somatic symptoms, anxiety symptoms, depression symptoms, social functioning, physical functioning and number of doctor visits]

[Insert Figure 3: Forest plots of the effects of CBT on somatic symptoms (follow-up), anxiety symptoms (follow-up), depression symptoms (follow-up), and treatment compliance]

[Insert Table 3: Subgroup analysis of the effect of CBT on somatic symptoms]

3.5.2. Anxiety symptom

ACCEPTED MANUSCRIPT

Nine studies with a total sample of 1076 participants measured the severity of anxiety symptoms. CBT has significantly reduced severity of anxiety symptoms with reduced pooled mean across nine studies of -1.89 (95% CI: -2.91 to -0.86; p <0.001). The heterogeneity was statistically significant (I^2 = 83.04%, p <0.001). The forest plot of the effect is presented in Figure. 2B.

A subgroup analysis (Table 4) found that CBT has reduced the severity of anxiety symptoms for both group based treatment (-1.67, 95% CI:-3.03 to -0.31; p < 0.05) and individual based treatment (-2.18, 95% CI:-4.39 to 0.04; p > 0.05) although the individual level based treatment is not statistically significant. CBT has significantly reduced anxiety symptoms when the number of treatment sessions was more than 10 times (-2.46, 95% CI:-3.60 to -1.32; p < 0.001) compared with treatment sessions less than 10 times (-0.54, 95% CI:-2.10 to 1.03; p > 0.05). CBT has also reduced anxiety symptom when treatment was manual based (-2.07, 95% CI:-3.32 to -0.83; p < 0.01) compared with those non-manual based treatment (-0.89, 95% CI:-3.15 to 1.38; p > 0.05).

CBT has significantly reduced anxiety symptom when treatment course was more than 12 weeks (-2.28, 95% CI:-3.36 to -1.20; p <0.001) compared with those less than 12 weeks (-0.49, 95% CI:-2.25 to 1.27; p >0.05). CBT has significantly reduced anxiety symptoms when it emphasised homework (-2.34, 95% CI:-4.01 to -0.67; p < 0.01) compared with those which did not emphasise it (-1.44, 95% CI:-2.79 to -0.08; p < 0.05). CBT has reduced anxiety symptoms when it emphasized affective technique (-2.45, 95% CI:-4.50 to

-0.40; $p < 0.05$) compared with when it did not emphasize it (-1.52, 95% CI:-2.88 to -0.17; $p > 0.05$).

CBT has significantly reduced severity of anxiety symptoms across seven studies during follow up period with reduced pooled mean difference of -2.92 (95% CI: -5.26 to -0.59, $p = 0.01$). The heterogeneity was statistically significant ($I^2 = 85.98\%$, $p < 0.001$). The forest plot of the effect is presented in Fig. 3C.

[Insert Table 4: Subgroup analysis of the effect of CBT on anxiety symptoms and depression symptoms]

3.5.3. Depression symptoms

Nine studies with a total sample of 1076 participants measured the severity of depressive symptoms operationalised in different ways. CBT has significantly reduced the severity of depressive symptoms across nine studies with reduced mean difference of -1.93 (95% CI: -3.56 to -0.31; $p = 0.020$).The heterogeneity was statistically significant ($I^2 = 59.93\%$, $p = 0.01$). The forest plot of the effect is presented in Fig. 2C.

A subgroup analysis (Table 4) found CBT has significantly reduced depressive symptoms when it was individual based treatment (-2.90, 95% CI:-4.55 to -1.26; $p < 0.01$) compared to group based treatment (-0.79, 95% CI:-2.31 to 0.73; $p > 0.05$). CBT also significantly reduced depressive symptoms when there were more than 10 sessions (-2.50, 95% CI:-3.91to -1.10; $p < 0.001$) compared with the studies with less than 10 sessions (-0.36, 95% CI:-2.30 to 1.59; $p > 0.05$). CBT has statistically and significantly reduced depressive symptom when the treatment time length greater than 12 weeks (-2.17, 95% CI:-3.64 to -0.69;

ACCEPTED MANUSCRIPT

$p < 0.01$) in comparison to a treatment time less than 12 weeks (-0.54, 95% CI:-3.28 to 2.19; $p > 0.05$). CBT has statistically reduced depressive symptoms when the trials were manual-based treatment (-2.15, 95% CI:-3.80 to -0.50; $p < 0.05$) compared with trials without manuals (-1.06, 95% CI:-3.53 to 1.42; $p > 0.05$). Moreover, CBT has significantly reduced depressive symptoms when trials did not emphasise homework (-2.04, 95% CI:-3.63 to -0.44; $p < 0.05$) compared with trials emphasising homework (-1.22, 95% CI:-3.84 to 1.41; $p > 0.05$). CBT has significantly reduced depressive symptoms when trials did not emphasise psychoeducation (-2.54, 95% CI:-4.25 to -0.83; $p < 0.01$) compared with trials emphasising it (-0.93, 95% CI:-2.76 to 0.91; $p > 0.05$).CBT has significantly reduced the depressive symptoms when trials emphasised affective technique (-3.24, 95% CI:-5.07 to -1.42; $p < 0.01$) compared with trials did not emphasize it (-0.88, 95% CI:-2.29 to 0.54; $p > 0.05$). Finally, CBT has significantly reduced depressive symptoms when trials emphasised interpersonal technique (-2.26, 95% CI:-4.28 to -0.25; $p < 0.05$) compared with trials did not emphasised it (-1.42, 95% CI:-3.29 to 0.44; $p > 0.05$).

CBT has significantly reduced the severity of depressive symptoms across seven studies during follow up period with mean difference of -2.73 (95% CI: -4.89 to -0.57, $p = 0.01$). The heterogeneity was statistically significant ($I^2 = 82.72\%$, $p < 0.001$). The forest plot of the effect is presented in Fig. 3B.

3.5.4. Social functioning

Five studies with a total sample of 617 participants measured social functioning. The pooled mean difference of social functioning for CBT across five studies was 3.27 (95% CI:

ACCEPTED MANUSCRIPT

-0.08 to 6.63; $p = 0.056$). The heterogeneity was statistically significant ($I^2 = 62.56$, $p = 0.03$). The forest plot of the effect is presented in Fig. 2D.

3.5.5. Physical functioning

Six studies with a total sample of 620 participants measured physical functioning. CBT has significantly improved physical functioning across six studies with pooled mean difference of 4.19 (95% CI: 1.90 to 6.49; $p < 0.001$). The heterogeneity was statistically significant ($I^2 = 0.00$, $p = 0.83$). The forest plot of the effect is presented in Fig. 2E.

3.5.6. Doctor visits

Four studies with a total sample of 352 participants measured healthcare use. The CBT has not increased number of doctor visits across four studies with mean difference of 0.60 (95% CI: 0.34 to 1.06; $p = 0.078$). The heterogeneity was not statistically significant ($I^2 = 40.39$, $p = 0.169$). The forest plot of the effect is presented in Fig. 2F.

3.6. Treatment Compliance

Participants in the CBT intervention group are less likely to comply to the treatment across 15 studies with reduced odds ratio of 0.54 (95% CI: 0.34 to 0.85; $p = 0.01$). The heterogeneity was statistically significant ($I^2 = 59.88\%$, $p = 0.002$). The forest plot of the odds ratio is presented in Fig. 3D. Compliance was calculated from data about the total number of randomized participants in the study groups and the total number of participants who received complete treatment at the end of treatment (also in the control group). We measured compliance by the complement of the proportion of trial participants who dropped out during the trial from either the experimental or the comparison group.

ACCEPTED MANUSCRIPT

A further subgroup analysis (Table 5) found that CBT group had better compliance when it was on individual based treatment (0.35, 95% CI: 0.19 to 0.65; $p < 0.01$) compared with group based treatment (0.82, 95% CI: 0.47 to 1.44; $p > 0.05$). The studies with more than 12 weeks duration (0.49, 95% CI:0.28 to 0.85; $p < 0.05$) had less treatment compliance of CBT than the treatment course with s < 12 weeks (0.66, 95% CI:0.26 to 1.70; $p > 0.05$) and it was statistically significant ($P_{between}$ =0.008). The studies with ⩾50 duration of sessions min (0.45, 95% CI:0.27 to 0.75; $p < 0.01$) had less compliance of CBT than the studies with < 50 min (1.01, 95% CI:0.41to 2.50; $p > 0.05$) and the difference between the two groups was statistically significant. The odds ratio of treatment compliance of CBT was poorer in studies emphasizing homework (0.43, 95% CI: 0.21 to 0.89; $p < 0.05$) than studies without emphasizing homework (0.62, 95% CI: 0.33 to 1.16; $p > 0.05$), and the difference between the two subgroups was significant (P=0.008). The odds ratio of treatment compliance of CBT was statistically poorer studies emphasizing psychoeducation (0.43, 95% CI: 0.21 to 0.87; $p < 0.05$) than studies did not emphasize it (0.63, 95% CI: 0.33 to 1.17; $p > 0.05$). The treatment compliance of CBT waspoorerin studies withoutemphasizing interpersonal technique (0.50, 95% CI: 0.28 to 0.89; $p <0.05$) than studiesemphasizing it (0.59, 95% CI: 0.25 to 1.39; $p > 0.05$). The treatment compliance of CBT was poorer when CBT emphasizing affective technique (0.50, 95% CI: 0.28 to 0.91; $p < 0.05$) than CBT studieswithout emphasizing it (0.57, 95% CI: 0.25 to 1.30; $p > 0.05$).Thetreatment compliance of CBT was higher whenCBT emphasizing body-directed technique (0.54, 95% CI: 0.30 to 0.97; $p < 0.05$) than CBT studies with out emphasizing it (0.49, 95% CI: 0.22 to

1.13; $p > 0.05$), and when it involved interpersonal strategies (0.59, 95%CI: 0.25 to 1.39) compared with studies without involvement of interpersonal strategies (0.50, 95%CI: 0.28 to 0.89)

[Insert Table 5: Subgroup analysis of the treatment compliance of CBT]

Both cumulative and one study removed method was used to assess sensitivity suggesting the removing one study at a time does not change the overall results for all outcome variables. Table 6 using Egger test suggests that there is minimal publication bias for all outcome variables except somatic symptoms.

[Insert Table 6: Egger's regression analysis on publication bias]

4. Discussion

In this paper we present the results of a meta-analysis of the efficacy of CBT for somatoform disorders and MUPS. The results based on this meta-analysis indicated that CBT was superior to the usual care or enhanced care or waiting list. It significantly reduced somatic symptoms, anxiety symptoms and depressive symptoms as well as improving physical functioning. The efficacy of CBT on somatic symptoms, anxiety symptoms, and depressive symptoms were maintained from three months to one year of follow up. The efficacy of CBT on improving social functioning and reducing doctor visits were not significant. Possible reasons could be complex aetiology of disability, in addition to the fact that improvement of social functioning needs to take considerable time, given the chronic nature of this disorder. Overall, the clinical efficacy of CBT was relatively modest and was most noticeable in terms of somatic symptoms, anxiety symptoms and depressive symptoms.

ACCEPTED MANUSCRIPT

This finding is congruent with previous studies suggesting that CBT has a beneficial effect on reducing the somatic symptoms, anxiety and depression (9, 10, 13, 20, 34, 35, 44).

In terms of understanding the effective components of CBT, subgroup analysis sheds further light on the issue. The key aspects of CBT included manual-based treatment and longer than 50 minutes per session were significantly reducing the symptoms of severity of somatic symptoms. Longer duration and frequency such as more than 10 sessions and 12 weeks treatments was required to reduce the comorbid symptoms including depression and anxiety This result is consistent with previous studies that suggested that negative cognitions, maladaptive behaviour and mood states need structured treatment plan and session time to be reframed and modified (13, 48).

Moreover, the results of the subgroup analysis demonstrated that group based treatment were effective in alleviating somatic symptoms, and individual based treatments were effective in improving depression and anxiety symptoms. A possible reason could be the study results in this field have been inconsistent as some studies indicated that there were no significant differences between individual CBT and group CBT relating to its effect on anxiety disorder (49) whereas other studies suggested that seriously ill patients get little benefit from group treatment and need more intensive individual treatment (7). Findings in our study suggest individual treatment could provide individualized and tailored treatment, which is more effective for depressive and anxiety symptoms than group treatment. On the other hand, group treatment could alleviate somatic symptoms through communication, social support among the group members, positive peer-modelling opportunities, normalization of

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

symptoms, and facilitating the reinforcement of the treatment process, all of which are lacking in individual treatment (50).

Subgroup analysis further identified the key technical components of CBT for somatoform disorder and MUPS. Body-directed techniques showed shows its superiority in alleviating somatic symptoms, but the effect may not sustain until follow-up. Previous studies suggested mindfulness could be considered the antipole of attention to and misinterpretation of somatic symptoms and rumination (27, 38). Further research is needed to replicate or expand these findings.

Affective strategies and interpersonal techniques showed possible advantage in alleviating somatic symptoms, depression and anxiety. It was consistent with another study indicated that interpersonal psychotherapy has positive effect on depression (51). Somatising behaviour was considered a form of interpersonal communication driven by insecure attachment, but has little clinical research on interpersonal psychotherapy for somatoform disorders and MUPS (52). However, the careful interpretation of the results is needed due to the lack of statistical power and high level of heterogeneity for the present study.

Contrary to our expectations, psychoeducation wasn't proved advantageous for somatoform disorders and MUPS. This results need to have careful explanation due to the limited data. Psycho-education is widely recognized and important technique in CBT, but we also noticed another study showed psycho-education didn't relieve psychological symptoms or improve mental health-related quality of life for patients with mental disorder (53). It needs to be further explored.

ACCEPTED MANUSCRIPT

CBT which emphasized homework didn't show it's superiority to the treatment without emphasizing homework for somatoform disorders and MUPS; the results are not consistent with previous meta-analysis which suggested that greater compliance with homework is related to improving treatment outcome (54). The possible reason was that we only assessed whether the treatment emphasize homework, but didn't assess the compliance with homework of participants.

CBT intervention is rather time-consuming and needs detailed techniques for busy clinical setting as showed in our subgroup analysis, this meta-analysis indicated that CBT had higher dropout rates and poorer compliance than usual care, waiting list or structured care when it required detailed CBT treatment strategies including longer treatment course, more frequent sessions, application of psychoeducation and affective strategies. However, when interpersonal level strategies and body directed strategies were applied, the compliance level was improved. Hence, it is not only important to evaluate the efficacy of CBT but also explore the features of CBT and the value of its interpersonal compassion component in real-world practice (10, 55).

This meta-analysis indicated high heterogeneity. The first and foremost reason is that there is no standardized procedure for CBT in somatoform disorders and MUPS and the studies are markedly different in the study design, treatment form, duration of treatment, number of sessions, duration of per session, intervention composition, and the type of therapist (20). Secondly, we need to consider variation in the diagnosis criteria in different diagnostic systems and comorbidity with other mental disorders. Thirdly, there are significant

ACCEPTED MANUSCRIPT

differences in the assessment tools of outcome measures, the time point of assessment and duration of follow up. The overall quality of evidence is relatively low due to a high risk of bias with lack of blinding of the participants, therapists, and outcome assessors.

We found minimal publication bias in the following outcome variables: anxiety, depressive symptoms, physical functioning, number of doctor visits, social functioning and treatment compliance. However there was significant publication bias for somatic symptoms at post intervention and follow up stage. Trim and fill method was used to identify the sources of bias. The efficacy of the CBT treatment remained significant after trim and fill method was used suggesting CBT is efficacious in the treatment of somatic symptoms.

4.1. Strengths and limitations of the study

We undertook a systematic review and meta-analysis on the efficacy of CBT for patients with somatic symptoms using a reasonable number of RCTs with a moderate to high quality study design and minimal publication bias. However, a few limitations in this meta-analysis should be taken into consideration. We searched databases in both English and Chinese, but only English-language based articles were found in the published literature. Grey literature was searched but no studies were found. Given that studies with positive findings were more likely to be published, this might have generated a "file-drawer effect" (55).

Second, there was high degree of heterogeneity due to various factors elaborated above. Third, the diagnostic criteria of somatoform disorder and MUPS present certain problems in clinical practice, such as low applicability, vague standards and overlapping

classifications (56) . In the ICD-10, DSM-III and DSM-IV, DSM-IV-TR diagnostic systems, medically unexplained physical symptoms were considered as the main indication of somatoform disorder (1, 2, 8), and the DSM-5 diagnosis system does not requires the somatic symptoms to be medically unexplained (3). Fourth, the use of concomitant medications was not reported in every study, so it is not clear whether the effects on the somatic symptoms were due to the CBT method or medication. Finally, in the subgroup analysis of treatment technique, due to the lack of detailed information and objective criteria for grouping, and the sample size of subgroup analysis was relatively small; therefore, the analysis results should be interpreted with cautions.

4.2. Implications

Arguably, the treatment of somatoform disorders and MUPS using CBT is in its relative infancy. Currently, CBT is effective for somatoform disorder and MUPS based on this meta-analysis.

The results of this meta-analysis suggest that optimal duration of effective CBT for somatoform disorders and MUPS should be more than 50 minutes per session. As the compliance level was low in most CBT studies due to the longer duration of the treatment and more than 10 times session, care needs to be taken when this approach is recommended to the general practice and busy clinics. Guidelines for the management of somatoform disorders and MUPS should consider the appropriate duration of treatment and length per session into the treatment process. Provision of long duration of CBT treatment by specialists

ACCEPTED MANUSCRIPT

should be referred by general practitioners in primary care clinics where most patients with somatoform disorders and MUPS make the first consultations.

As few clinical randomized controlled studies have compared CBT with other psychotherapy treatments for somatoform disorder (57, 58), future research should be conducted to include a large number of clinical experimental studies to compare the effects of CBT for somatoform disorder and MUPS with those of pharmacotherapy or other forms of psychotherapy.

5. Conclusion

In summary, the findings of this systematic review and meta-analysis suggest that CBT is efficacious for somatoform disorders and MUPS in reducing somatic symptoms, anxiety symptoms, depressive symptoms, and improving physical functioning. The effects of CBT on alleviating somatic symptoms, anxiety and depressive symptoms could sustain on follow-up.

Acknowledgements

The authors would like to acknowledge the following research authors who provided data, treatment manuals and related information: Athula Sumathipala, Lyonne N. L. Zonneveld, Javier Escobar, Kashner, T. Michael and Kurt Fritzsche.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Included studies

1. Allen LA, Woolfolk RL, Escobar JI, Gara MA, Hamer RM. Cognitive-behavioral therapy for somatization disorder: a randomized controlled trial. Arch Intern Med. 2006;166(14):1512-8.
2. Burton C, Weller D, Marsden W, Worth A, Sharpe M. A primary care Symptoms Clinic for patients with medically unexplained symptoms: pilot randomised trial. BMJ open. 2012;2:e000513.
3. Escobar JI, Gara MA, Diaz-Martinez AM, Interian A, Warman M, Allen LA, et al. Effectiveness of a time-limited cognitive behavior therapy type intervention among primary care patients with medically unexplained symptoms. Annals of family medicine. 2007;5(4):328-35.
4. Fjorback L, Arendt M, Ornbøl E, Walach H, Rehfeld E, Schröder A, et al. Mindfulness therapy for somatization disorder and functional somatic syndromes: randomized trial with one-year follow-up. Journal of psychosomatic research. 2013;74(1):31-40.
5. Hedman E, Axelsson E, Andersson E, Lekander M, Ljotsson B. Exposure-based cognitive-behavioural therapy via the internet and as bibliotherapy for somatic symptom disorder and illness anxiety disorder: randomised controlled trial. Br J Psychiatry. 2016;209(5):407-13.
6. Kashner TM, Rost K, Cohen B, Anderson M, Smith GR. Enhancing the health of somatization disorder patients. effectiveness of short-term group therapy. Psychosomatics. 1995;36::462-70.
7. Lidbeck J. Group therapy for somatization disorders in general practice: effectiveness of a short cognitive-behavioural treatment model. Acta Psychiatr Scand. 1997;96(1):14-24.
8. Martin A, Rauh E, Fichter M, Rief W. A one-session treatment for patients suffering from medically unexplained symptoms in primary care: a randomized clinical trial. Psychosomatics. 2007;48(4):294-303.
9. Moreno S, Gili M, Magallón R, Bauzá N, Roca M, Del Hoyo YL, et al. Effectiveness of group versus individual cognitive-behavioral therapy in patients with abridged somatization disorder: a randomized controlled trial. Psychosomatic medicine. 2013;75(6):600-8.
10. Ravesteijn (47) H, Grutters J, olde Hartman T, Lucassen P, Bor H, van Weel C, et al. Mindfulness-based cognitive therapy for patients with medically unexplained symptoms: a cost-effectiveness study. Journal of psychosomatic research. 2013;74(3):197-205.
11. Schroder A, Rehfeld E, Ornbol E, Sharpe M, Licht RW, Fink P. Cognitive-behavioural group treatment for a range of functional somatic syndromes: randomised trial. Br J Psychiatry. 2012;200(6):499-507.
12. Speckens AE, van Hemert AM, Spinhoven P, Hawton KE, Bolk JH, Rooijmans HG. Cognitive behavioural therapy for medically unexplained physical symptoms: a randomised controlled trial. BMJ (Clinical research ed). 1995;311(7016):1328-32

13. Sumathipala A, Hewege S, Hanwella R, Mann AH. Randomized controlled trial of cognitive behaviour therapy for repeated consultations for medically unexplained complaints: a feasibility study in Sri Lanka. Psychol Med. 2000;30(4):747-57.
14. Sumathipala A, Siribaddana S, Abeysingha MR, Silva P, Dewey M, Prince M, et al. Cognitive-behavioural therapy v. structured care for medically unexplained symptoms: randomised controlled trial. Br J Psychiatry. 2008;193(1):51-9.
15. Zonneveld LN, Rood YR, Timman R, Kooiman CG, Van't Spijker A, Busschbach JJ. Effective group training for patients with unexplained physical symptoms: a randomized controlled trial with a non-randomized one-year follow-up. PLoS One. 2012;7(8):e42629.

ACCEPTED MANUSCRIPT

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC: American Psychiatric Association; 2000.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA: American Psychiatric Publishing; 2013.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders, 3rd Edition. 3rd ed. Washington DC: American Psychiatric Association; 1980.
5. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. European Neuropsychopharmacology. 2011;21(9):655-79.
6. Greco M. The classification and nomenclature of 'medically unexplained symptoms': conflict, performativity and critique. Soc Sci Med. 2012;75(12):2362-9.
7. Schröder A, Sharpe M, Fink P. Medically unexplained symptom management. The Lancet Psychiatry. 2015;2(7):587-8.
8. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Geneva: World Health Organization; 1992.
9. van Dessel N, den Boeft M, van der Wouden JC, Kleinstauber M, Leone SS, Terluin B, et al. Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults. Cochrane Database Syst Rev. 2014(11):Cd011142.
10. Kleinstäuber M, Witthöft M, Hiller W. Efficacy of short-term psychotherapy for multiple medically unexplained physical symptoms: a meta-analysis. Clinical Psychology Review. 2011;31(1):146-60.
11. Creed F. Medically unexplained symptoms--blurring the line between "mental" and "physical" in somatoform disorders. J Psychosom Res. 2009;67(3):185-7.
12. Deary V, Chalder T, Sharpe M. The cognitive behavioural model of medically unexplained symptoms: a theoretical and empirical review. Clin Psychol Rev. 2007;27(7):781-97.
13. Koelen JA, Houtveen JH, Abbass A, Luyten P, Eurelings-Bontekoe EH, Van Broeckhuysen-Kloth SA, et al. Effectiveness of psychotherapy for severe somatoform disorder: meta-analysis. Br J Psychiatry. 2014;204(1):12-9.
14. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. Cognit Ther Res. 2012;36(5):427-40.
15. McMain S, Newman MG, Segal ZV, DeRubeis RJ. Cognitive behavioral therapy: current status and future research directions. Psychother Res. 2015;25(3):321-9.
16. Sumathipala A. What is the evidence for the efficacy of treatments for somatoform disorders? A critical review of previous intervention studies. Psychosom Med. 2007;69(9):889-900.

17. Kroenke K, Swindle R. Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials. Psychother Psychosom. 2000;69(4):205-15.
18. Nezu AM, Maguth Nezu C, Lombardo ER. Cognitive-behavior therapy for medically unexplained symptoms: a critical review of the treatment literature. Behav Ther. 2001;32(3):537-83.
19. Edwards TM, Stern A, Clarke DD, Ivbijaro G, Kasney LM. The treatment of patients with medically unexplained symptoms in primary care: a review of the literature. Ment Health Fam Med. 2010;7(4):209-21.
20. Menon V, Rajan TM, Kuppili PP, Sarkar S. Cognitive behavior therapy for medically unexplained symptoms: a systematic review and meta-analysis of published controlled trials. Indian J Psychol Med. 2017;39(4):399-406.
21. Kroenke K. Efficacy of treatment for somatoform disorders: A review of randomized controlled trials. Psychosomatic Medicine 2007;69:881–8.
22. Tazaki M, Landlaw K. Behavioural mechanisms and cognitive-behavioural interventions of somatoform disorders. Int Rev Psychiatry. 2006;18(1):67-73.
23. Looper KJ, Kirmayer LJ. Behavioral medicine approaches to somatoform disorders. J Consult Clin Psychol. 2002;70(3):810-27.
24. Fava GA, Cosci F, Sonino N. Current Psychosomatic Practice. Psychother Psychosom. 2017;86(1):13-30.
25. Janca A, Hiller W. ICD-10 checklists--a tool for clinicians' use of the ICD-10 classification of mental and behavioral disorders. Comprehensive psychiatry. 1996;37(3):180-7.
26. Kashner TM, Rost K, Cohen B, Anderson M, Smith GR. Enhancing the health of somatization disorder patients. Effectiveness of short-term group therapy. Psychosomatics. 1995;36::462–70.
27. Fjorback L, Arendt M, Ornbøl E, Walach H, Rehfeld E, Schröder A, et al. Mindfulness therapy for somatization disorder and functional somatic syndromes: randomized trial with one-year follow-up. Journal of psychosomatic research [Internet]. 2013; 74(1):[31-40 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/799/CN-00861799/frame.html.
28. Escobar JI, Gara MA, Diaz-Martinez AM, Interian A, Warman M, Allen LA, et al. Effectiveness of a time-limited cognitive behavior therapy type intervention among primary care patients with medically unexplained symptoms. Ann Fam Med. 2007;5(4):328-35.
29. Sumathipala A, Siribaddana S, Abeysingha M, Silva P, Dewey M, Prince M, et al. Cognitive-behavioural therapy v. structured care for medically unexplained symptoms: randomised controlled trial. British journal of psychiatry [Internet]. 2008; 193(1):[51-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/461/CN-00650461/frame.html.

30. Smith R, Lyles J, Gardiner J, Sirbu C, Hodges A, Collins C, et al. Primary care clinicians treat patients with medically unexplained symptoms: a randomized controlled trial. Journal of general internal medicine [Internet]. 2006; 21(7):[671-7 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/194/CN-00566194/frame.html.
31. Zonneveld L, Rood Y, Timman R, Kooiman C, Van't SA, Busschbach J. Effective group training for patients with unexplained physical symptoms: a randomized controlled trial with a non-randomized one-year follow-up. PloS one [Internet]. 2012; 7(8):[e42629 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/983/CN-00841983/frame.html

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413637/pdf/pone.0042629.pdf.
32. Schroder A, Rehfeld E, Ornbol E, Sharpe M, Licht RW, Fink P. Cognitive-behavioural group treatment for a range of functional somatic syndromes: randomised trial. Br J Psychiatry. 2012;200(6):499-507.
33. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol. 1998;51(12):1235-41.
34. Hofmann SG, Asmundson GJ, Beck AT. The science of cognitive therapy. Behav Ther. 2013;44(2):199-212.
35. Beck AT, Dozois DJ. Cognitive therapy: current status and future directions. Annu Rev Med. 2011;62:397-409.
36. Trijsburg RW, Frederiks GCFJ, Gorlee M, Klouwer E, den Hollander AM, Duivenvoorden HJ. Development of the Comprehensive Psychotherapeutic Interventions Rating Scale (CPIRS). Psychotherapy Research. 2002;12(3):287-317.
37. Allen LA, Woolfolk RL, Escobar JI, Gara MA, Hamer RM. Cognitive-behavioral therapy for somatization disorder: a randomized controlled trial. Arch Intern Med. 2006;166(14):1512-8.
38. Ravesteijn H, Grutters J, olde Hartman T, Lucassen P, Bor H, van Weel C, et al. Mindfulness-based cognitive therapy for patients with medically unexplained symptoms: a cost-effectiveness study. J Psychosom Res. 2013;74(3):197-205.
39. Speckens AE, van Hemert AM, Spinhoven P, Hawton KE, Bolk JH, Rooijmans HG. Cognitive behavioural therapy for medically unexplained physical symptoms: a randomised controlled trial. BMJ (Clinical research ed). 1995;311(7016):1328-32.
40. Zonneveld LN, Rood YR, Kooiman CG, Timman R, van't Spijker A, Busschbach JJ. Predicting the outcome of a cognitive-behavioral group training for patients with unexplained physical symptoms: a one-year follow-up study. BMC Public Health. 2012;12:848.
41. Lidbeck J. Group therapy for somatization disorders in general practice: effectiveness of a short cognitive-behavioural treatment model. Acta Psychiatr Scand. 1997;96(1):14-24.

ACCEPTED MANUSCRIPT

42. Hedman E, Axelsson E, Andersson E, Lekander M, Ljotsson B. Exposure-based cognitive-behavioural therapy via the internet and as bibliotherapy for somatic symptom disorder and illness anxiety disorder: randomised controlled trial. The British journal of psychiatry : the journal of mental science. 2016;209(5):407-13.
43. Martin A, Rauh E, Fichter M, Rief W. A one-session treatment for patients suffering from medically unexplained symptoms in primary care: a randomized clinical trial. Psychosomatics. 2007;48(4):294-303.
44. Sumathipala A, Hewege S, Hanwella R, Mann A. Randomized controlled trial of cognitive behaviour therapy for repeated consultations for medically unexplained complaints: a feasibility study in Sri Lanka. Psychological medicine [Internet]. 2000; 30(4):[747-57 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/052/CN-00316052/frame.html.
45. Burton C, Weller D, Marsden W, Worth A, Sharpe M. A primary care Symptoms Clinic for patients with medically unexplained symptoms: pilot randomised trial. BMJ Open. 2012;2:e000513.
46. Moreno S, Gili M, Magallón R, Bauzá N, Roca M, Del Hoyo YL, et al. Effectiveness of group versus individual cognitive-behavioral therapy in patients with abridged somatization disorder: a randomized controlled trial. Psychosomatic medicine. 2013;75(6):600-8.
47. Ravesteijn H, Lucassen P, Bor H, Weel C, Speckens A. Mindfulness-based cognitive therapy for patients with medically unexplained symptoms: a randomized controlled trial. Psychother Psychosom. 2013;82(5):299-310.
48. Christensen SS, Frostholm L, Ornbol E, Schroder A. Changes in illness perceptions mediated the effect of cognitive behavioural therapy in severe functional somatic syndromes. J Psychosom Res. 2015;78(4):363-70.
49. Wergeland GJ, Fjermestad KW, Marin CE, Haugland BS, Bjaastad JF, Oeding K, et al. An effectiveness study of individual vs. group cognitive behavioral therapy for anxiety disorders in youth. Behaviour research and therapy. 2014;57:1-12.
50. Wolgensinger L. Cognitive behavioral group therapy for anxiety: recent developments. Dialogues in Clinical Neuroscience. 2015;17(3):347-51.
51. Cuijpers P, Geraedts AS, van Oppen P, Andersson G, Markowitz JC, van Straten A. Interpersonal psychotherapy for depression: a meta-analysis. Am J Psychiatry. 2011;168(6):581-92.
52. Stuart S, Noyes R, Jr. Interpersonal psychotherapy for somatizing patients. Psychother Psychosom. 2006;75(4):209-19.
53. Pedersen P, Sogaard HJ, Labriola M, Nohr EA, Jensen C. Effectiveness of psychoeducation in reducing sickness absence and improving mental health in individuals at risk of having a mental disorder: a randomised controlled trial. BMC Public Health. 2015;15:763.

ACCEPTED MANUSCRIPT

54. Mausbach BT, Moore R, Roesch S, Cardenas V, Patterson TL. The Relationship Between Homework Compliance and Therapy Outcomes: An Updated Meta-Analysis. Cognitive therapy and research. 2010;34(5):429-38.
55. Shedler J. Where Is the Evidence for "Evidence-Based" Therapy? The Psychiatric clinics of North America. 2018;41(2):319-29.
56. Barsky AJ. Assessing the New DSM-5 Diagnosis of Somatic Symptom Disorder. Psychosomatic medicine. 2016;78(1):2-4.
57. Chavooshi B, Saberi M, Tavallaie SA, Sahraei H. Psychotherapy for medically unexplained pain: a randomized clinical trial comparing intensive short-term dynamic psychotherapy and cognitive-behavior therapy. Psychosomatics. 2017;58(5):506-18.
58. Schroder A, Heider J, Zaby A, Gollner R. Cognitive behavioral therapy versus progressive muscle relaxation training for multiple somatoform symptoms: results of a randomized controlled trial. Cognitive therapy and research. 2013;37(2):296-306.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Table1 Characteristics of included studies

Study(year**)**	Location	Sample size	Gender: female,	QS	Disorder	Diagnosis	Current comorbid DSM-IV axis I disorder	Intervention	Format	Manual	Number of sessions	Duration of session s	Duration of treatment	Therapist type	Compliance	Control group	Outcome measure	Follow up
Allen, 2006	USA	84	75(89%)	middle	SD	DSM-IV-TR SCID	54(64%)	CBT+PCI	individual	yes	10	50m	3m	experienced psychologist	90.70%	PCI	CGI-SD,SSD, SSS,SF-36	12m
Burton, 2012	Scotland	32	21(66%)	middle	MUS	PHQ-14 PHQ-15	22(69%)	Symptoms Clinic +TAU	individual	no	4	mean 30m	3m	experienced specialized GP	81.25%	TAU	SF-12,PHQ-14, PHQ-9,GAD-7	no
Escobar, 2007	USA	172	151(88%)	middle	SFD	ICD-10 CIDI	158(92%)	CBT + PCI	individual	yes	10	50m	3m	therapist received training	72.41%	TAU	CGI,MOS-10, HAM-D,HAM-A,VAS	6m
Fjorback,2013	Denmark	119	95(80%)	high	SD and FSS	DSM-IV and ICD-10 SCAN	53(45%)	Mindfulness therapy	group	yes	9	3.5h	3m	experienced psychiatrist	88.13%	EUC	SF-36,SCL-90, SCL-8,WI	12m
Hedman, 2016	Sweden	132	98(74%)	High	SSD or IAD	DSM-5 HPDI	77(58%)	Internet Exposure-based CBT	internet	yes	12	unclear	3m	internet and psychologist	96.88%	no active treatment	HAI,IAS,WI, ASI,BAI,SDS MADRS-S	6m
Kashner,1995	USA	70	59(84%)	middle	SD	DSM-III-R criteria	None reported	Group therapy +SPCL	group	unclear	8	2h	4m	master's level clinicians	45.45%	SPCL	RAND	8m
Lidbeck, 1997	Sweden	50	42(84%)	middle	SD	ICD-9 ICHPPC-2	None reported	CBT	group	yes	8	3h	3m	attending physician	96.97%	WLC	SPQ, IBQ, HAD, SDI, healthcare use	6m
Martin A,2007	German	140	105(75%)	high	SD/PD/HP/USD/CD/SD NOS	DSM-IV Structured diagnosis	82(59%)	CBT	group	yes	1	3-4h	1d	psychologists	84.29%	TAU	BSI-SOM,SOMS-7,WI,BSI-GSI,BDI	6m
Moreno, 2013	Spain	168	145(86%)	high	Abridged SD	DSM-IV and ICD-10	142(85%)	CBT	individual or group	yes	10	individual 1h; group 2h	3m	psychologists	Individual: 89.29%; group 90.63%	TAU	SOMS,HARS, HDRS	12m
Ravesteijn, 2013	Netherlands	125	87(70%)	high	SD/PD/HP	DSM-IV SCID	41(35%)	MBCT+EUC	group	yes	8	2.5h	8w	experienced mindfulness trainers	80.33%	EUC	EQ-5D,SF-36, PHQ,WI,healthcare use	9m
Schröder, 2012	Denmark	120	95(79%)	high	SFD	DSM-IV SCAN	40(33%)	STreSS	group	yes	9	3.5h	4m	psychiatrists	83.33%	EUC	SF-36,WI,SCL-90	12m
Speckens,1995	Netherlands	79	39(49%)	middle	MUS	DSM-III PSE	None reported	CBT	individual	no	6-16(mean 11.8)	1h	Max 6m	physician trained in CBT	87.18%	optimized medical care.	GHQ,HADS,IAS,WI,MCU	6m
Sumathipala,2000	Sri Lanka	68	48(71%)	high	MUS	SEMI, GHQ-30 BSI	None reported	CBT	individual	yes	6	30min	3m	research psychiatrist	70.59%	usual care	GHQ-30,MCU,BSI,patients satisfaction	3m

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Sumathipala,2008	Sri Lanka	150	118 (78 %)	middle	MUS	SEMI, GHQ-30, BSI	None reported	CBT	individual	yes	6	30min	Max 3m	hospital-based physicians	85.33%	structured care	GHQ-30,MCU,BSI,patients satisfaction	9m
Zonneveld, 2012	Netherlands	162	131 (81 %)	high	USD and CPD	DSM-IV SCID	67(41%)	CBT	group	yes	13	2h	13w	psychologist	77.38%	WLC	SF-36,SCL-90-R	12 m

ASI=Anxiety Sensitivity Index; BAI=Beck Anxiety Inventory; BDI=Beck Depression Inventory; BSI=Brief Symptom Inventory; CBT=cognitive-behavioral therapy; CGI-SD=Clinical Global Impression Scale anchored for Somatic Symptoms; CIDI= he Composite International Diagnostic Interview; DSM-III=the Diagnostic and Statistical Manual of Mental Disorders, the 3rd Edition; DSM-IV= the Diagnostic and Statistical Manual of Mental Disorders, the 4th Edition; DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders, the 4th Edition, Text Revision; DSM-5=the Diagnostic and Statistical Manual of Mental Disorders, the 5th Edition; EQ-5D=an instrument for measuring health-related quality of life (EuroQol-5D); EUC=Enhanced usual care; FSS=Functional somatic syndromes; GHQ-30=General Health Questionnaire; GSI=Global severity index; HAM-A=the Hamilton Anxiety Rating Scale; HAM-D=the 17-item Hamilton Depression Rating Scale; HADS=the Hospital Anxiety and Depression Scale; HAI=the 64-item Health Anxiety Inventory; HPDI= the Health Preoccupation Diagnostic Interview; IAD=Illness anxiety disorder; IAS=Illness attitude Scale; IBQ=the Illness Behavior Questionnaire; ICD-10=the 10th revision of the International Statistical Classification of Diseases and Related Health Problems; ICD-9=the 9th revision of the International Statistical Classification of Diseases and Related Health Problems; ICHPPC-2='The International Classification of Health Problems in Primary Care; IDCL=International Diagnostic Checklists for DSM-IV; IIP=Inventory of Interpersonal Problems; ADRS-S=Montgomery-Asberg Depression Rating Scale-Self-rated; MBCT=Mindfulness-based Cognitive Therapy; MCU=the number of medical consultations/health care utilizations; MUS=medically unexplained symptoms; MOS-10=the Medical Outcomes Study Scale's Short-Form Health Survey; NPRS =11-point numerical pain rating scale; PCI=psychiatric consultation intervention; PHQ=the Patient Health Questionnaire; PSE= Present state examination; QS=Quality assessment; RAND=Health status measures which assess five domains: physical functioning, general health, mental health, social functioning, and days in bed; SCAN=Schedules for Clinical Assessment in Neuropsychiatry; SCID= Clinical Interview for *DSM-IV* Axis I Disorders; SCL-90=Symptom Checklist; SD=Somatisation disorder; SDI=Sleep Disturbance Index; SDS=Sheehan Disability Scale; SEMI=the Short Explanatory Model Interview; SFD=Somatoform disorder; SF-12=the physical functioning subscale of the 12-Item Short-Form Health Survey; SF-36=36-item Medical Outcomes Study Short-Form General Health Survey; SOMS =Screening for Somatoform Disorders; SPCL=Standard psychiatric consultation letter; SPQ=the Social Problem Questionnaire; SSD=Somatic symptom disorder; SSS=Severity of Somatic Symptoms scale; STreSS=a new CBT-based intervention entitled "Specialized Treatment for Severe Bodily Distress Syndrome"; TAU=Treatment as usual; UPS=Unexplained physical symptoms; VAS=the severity of medically unexplained symptoms on a visual-analog scale; Visits=the number of patient-initiated visits to healthcare providers of their choice; WI=the whitely Index; WLC=Wait list control

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Table 2 Overview of therapeutic interventions of CBT

Author(year)	Treatment form	Treatment course	Duration of session	Sessions	Psycho-education	Behavioral strategies	Cognitive strategies	Affective strategies	Interpersonal strategies	Exposure	Body-directed strategies	Behavior experiment	Mindfulness and attention	Homework assignment
Allen, et al 2006	0	1	1	1	0	1	1	1	0	0	1	0	0	0
Burton, et al 2012	0	1	0	0	1	1	1	1	0	0	0	0	0	0
Escobar, et al 2007	0	1	1	1	0	1	1	1	1	0	1	0	0	0
Fjorback,et al 2013	1	1	1	0	0	1	1	1	0	0	1	0	1	1
Hedman, et al 2016	0	1	1	1	1	1	1	0	0	1	1	0	1	1
Kashner, et al 1995	1	1	1	0	0	1	0	1	1	0	0	0	0	0
Lidbeck, et al 1997	1	1	1	0	1	1	1	0	1	0	1	0	0	0
Martin A, et al 2007	1	0	1	0	1	1	1	0	0	0	1	0	0	0
Moreno, et al 2013(a)	0	1	1	1	0	1	1	1	1	0	1	0	0	0
Moreno, et al 2013(b)	1	1	1	1	0	1	1	1	1	0	1	0	0	0
Ravesteijn, et al 2013	1	0	1	0	1	1	1	0	0	0	1	0	1	1
Schröder, et al 2012	1	1	1	0	1	1	1	1	0	0	0	0	0	1
Speckens, et al 1995	0	1	1	1	0	0	1	0	0	0	0	1	0	0
Sumathipala, et al 2000	0	1	0	0	0	1	1	1	0	0	0	0	0	1
Sumathipala, et al 2008	0	0	0	0	1	1	1	0	0	0	0	0	0	1
Zonneveld, et al 2012	1	1	1	1	1	1	1	1	0	0	1	0	0	1

Treatment form: 0=individual treatment; 1=group treatment

Treatment course: 0=＜12week;1=≥12weeks

Duration of session: 0=＜50min;1=≥50min

Sessions: 0=＜10; 1=≥10

Psychoeducation= instructions about a theory of causal and maintaining mechanisms of the disorder

Behavioural strategies=modifying adverse and dysfunctional behavior

Cognitive strategies=creating insight into and changing patterns of thinking

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Affective strategies=emphasizing emotional awareness, i.e., identifying, controlling and expressing emotions
Interpersonal strategies=increasing a patient's (understanding of) maladaptive behavioral patterns in relating to other people
Exposure= systematic and prolonged contact with a feared stimulus or situation
Body-directed strategies= relaxation, respiratory or vocal exercises, massage, physical therapy, gymnastics, biofeedback, or acupuncture
Behavior experiment=planned activities to test out thoughts in action in everyday situations
Mindfulness and Attention=derived mostly from Buddhism that aim to increase awareness of mind states
Homework assignment=assign homework to patients as part of their treatment
Psycho-education; behavioral; cognitive; affective; interpersonal; exposure; body-directed; behavior experiment; mindfulness and attention; homework assignment: 0= 'not important' (not mentioned or definitely not a core component). 1='important' (explicitly mentioned as core component)

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Table 3 Subgroup analysis on the effect of CBT on severity of somatic symptoms

	Somatic symptoms: post- to pre-treatment effect							Somatic symptoms: follow-up to pre-treatment effects						
Subgroups	Studies, n	Participants, n	I^2(%)	Q-test	Mean difference	95% CI	$P_{between}$	Studies, ,n	Participants, n	I^2(%)	Q-test	Mean difference	95% CI	$P_{between}$
Treatment form							0.009 **							0.000**
Individual	6	657	54.89	11.08	-1.00	-1.90,-0.10*		6	657	0.00	2.32	-0.91	-1.34,-0.49**	
Group	4	539	94.42	45.62	-4.43	-8.47,-0.39*		3	377	86.39	14.70	-2.27	-5.86,1.32	
Treatment course							0.051							0.144
<12weeks	3	415	31.32	2.91	-0.41	-1.43,0.61		3	415	0.00	0.73	-0.12	-0.32,0.08	
⩾12weeks	7	781	88.01	50.05	-2.28	-4.05,-0.52*		6	619	67.89	15.57	-1.37	-2.66,-0.08*	
Duration of session							0.007 **							0.025*
<50 mins	2	218	0.00	0.56	-0.33	-2.37,1.71		2	218	0.00	0.15	-0.75	-3.07,1.57	
⩾50 mins	8	978	89.38	65.90	-1.48	-2.48,-0.47**		7	816	78.15	27.46	-0.90	-1.71,-0.08*	
Number of sessions							0.640							0.149
<10	4	483	0.00	2.97	-0.02	-0.22,0.19		4	483	0.00	0.74	-0.12	-0.32,0.08	
⩾10	6	713	89.88	49.39	-2.84	-4.83,-0.85**		5	551	74.06	15.42	-1.55	-3.00,-0.10*	
Body directed strategies							0.001**							0.011*
not important	3	297	0.00	0.82	-0.82	-1.60,-0.03*		3	737	0.00	0.15	-0.79	-1.74,0.16	
important	7	899	90.52	63.30	-1.70	-2.89,-0.51**		6	297	81.07	26.42	-0.97	-1.94,0.01	
Homework							0.003**							0.024*
not important	7	853	90.65	64.14	-1.47	-2.55,-0.39**		6	691	81.68	27.29	-0.94	-1.83,-0.05*	
important	3	343	0.00	1.30	-0.96	-2.41,0.48		3	343	0.00	0.15	-0.72	-2.27,0.82	
Psycho-education							0.011*							0.144
not important	6	619	89.00	45.45	-2.10	-4.04,-0.15*		6	619	67.89	15.67	-1.37	-2.66,-0.08*	
important	4	577	71.42	10.50	-1.32	-2.99,0.36		3	415	0.00	0.73	-0.12	-0.32,0.08	
Affective strategies							0.051							0.115
not important	4	494	55.72	6.78	-0.54	-1.33,0.24		4	494	0.00	2.32	-0.15	-0.35,0.06	
important	6	702	90.00	49.96	-3.95	-6.99,-0.91		5	540	74.17	15.48	-2.04	-4.28,0.20	
Interpersonal strategies							0.026*							0.031*
not important	7	808	67.80	18.63	-0.64	-1.21,-0.07*		6	646	42.69	8.73	-0.49	-0.94,-0.03*	
important	3	388	94.38	35.59	-18.78	-40.94,3.38		3	388	82.87	11.68	-7.90	-18.15,2.35	

*p< 0.05, **p<0.01, ***p< 0.001.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Table4 Subgroup analyses on the effect of CBT on severity of anxiety symptoms and depression symptoms

	Anxiety symptom: post- to pre-treatment effect							Depression symptom: post- to pre-treatment effect						
Subgroups	Studies, n	Participants, n	I^2(%)	Q-test	Mean difference	95% CI	$P_{between}$	Studies, n	Participants, n	I^2(%)	Q-test	Mean difference	95% CI	$P_{between}$
Treatment form							0.002**							0.002**
Individual	3	355	30.65	2.88	-2.18	-4.39,0.04		3	355	52.92	4.25	-2.90	-4.55,-1.26**	
Group	6	721	26.40	6.79	-1.67	-3.03,-0.31*		6	721	0.00	2.72	-0.79	-2.31,0.73	
Number of sessions							<0.001***							0.002**
<10	3	315	0.00	0.08	-0.54	-2.10,1.03		3	315	0.00	0.37	-0.36	-2.30,1.59	
⩾10	6	761	14.80	5.87	-2.46	-3.60,-1.32***		6	761	26.89	6.84	-2.50	-3.91,-1.10***	
Treatment course							<0.001**							0.007**
<12weeks	2	265	0.00	0.07	-0.49	-2.25,1.27		2	265	0.00	0.33	-0.54	-3.28,2.19	
⩾12weeks	7	811	11.58	6.79	-2.28	-3.36,-1.20***		7	811	30.55	8.64	-2.17	-3.64,-0.69**	
Manual available							0.001**							0.01*
no	2	129	0.00	0.02	-0.89	-3.15,1.38		2	129	0.00	0.63	-1.06	-3.53,1.42	
yes	7	947	31.39	8.75	-2.07	-3.32,-0.83**		7	947	34.35	9.14	-2.15	-3.80,-0.50*	
Homework strategies							0.001**							0.009**
not important	6	657	9.99	5.56	-1.44	-2.79,-0.08*		6	657	33.39	7.51	-2.04	-3.63,-0.44*	
important	3	419	25.65	2.69	-2.34	-4.01,-0.67**		3	419	14.91	2.35	-1.22	-3.84,1.41	
Psycho-education							0.002**							0.005**
not important	4	467	12.33	3.42	-2.44	-4.44,-0.43*		4	467	47.50	5.72	-2.54	-4.25,-0.83**	
important	5	609	32.69	5.94	-1.51	-2.89,-0.13*		5	609	0.00	2.68	-0.93	-2.76,0.91	
Affective strategies							0.002**							0.002**
not important	5	526	32.08	5.89	-1.52	-2.88,-0.17*		5	526	0.00	1.16	-0.88	-2.29,0.54	
important	4	550	13.01	3.45	-2.45	-4.50,-0.40*		4	550	42.26	5.20	-3.24	-5.07,-1.42**	
Interpersonal strategies							0.001**							0.009**
not important	5	638	32.25	5.90	-1.52	-2.79,-0.24*		5	638	0.00	2.51	-1.42	-3.29,0.44	
important	4	438	4.19	3.13	-2.63	-4.80,-0.45*		4	438	58.94	7.31	-2.26	-4.28,-0.25*	

*p< 0.05, **p<0.01, ***p< 0.001.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Table 5 Subgroup analysis on the treatment compliance

Treatment compliance of CBT							
Subgroups	Studies, n	Participants, n	I^2(%)	Q-test	Odds ratio	95% CI	$P_{between}$
Manual available							0.007**
no	4	231	25.26	4.01	0.21	0.06,0.75*	
yes	12	1488	35.97	17.18	0.63	0.40,0.99*	
Treatment form							0.006**
Individual	7	689	0.00	3.14	0.82	0.47,1.44	
Group	9	1030	50.73	16.24	0.35	0.19,0.65**	
Treatment course							0.008**
<12weeks	3	415	63.65	5.50	0.66	0.26,1.70	
⩾12weeks	13	1304	34.69	18.37	0.49	0.28,0.85*	
Duration of session							0.007**
<50 mins	3	250	0.00	1.59	1.01	0.41,2.50	
⩾50 mins	13	1469	38.87	19.63	0.45	0.27,0.75**	
Homework							0.008**
not important	9	843	8.91	8.78	0.62	0.33,1.16	
important	7	876	60.34	15.13	0.43	0.21,0.89*	
Psycho-education							0.008**
not important	8	808	37.81	11.26	0.63	0.33,1.17	
important	8	911	43.93	12.48	0.43	0.21,0.87*	
Affective strategies							0.008**
not important	6	676	23.21	6.51	0.57	0.25,1.30	
important	10	1043	49.75	17.91	0.50	0.28,0.91*	
Interpersonal strategies							0.008**
not important	11	1211	42.42	17.37	0.50	0.28,0.89*	
important	5	508	43.33	7.06	0.59	0.25,1.39	
Body directed strategies							0.008**
not important	6	519	66.03	14.72	0.49	0.22,1.13	
important	10	1200	8.19	9.80	0.54	0.30,0.97*	

*p< 0.05, **p<0.01, ***p< 0.001.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Table6. Egger's regression analysis on publication bias

Variables	*t*	95%CI	*P*
Somatic symptoms	3.73	-4.17, -0.98	0.01
Anxiety symptom	0.74	-6.03, 3.23	0.48
Depression symptom	0.07	-7.98, 8.41	0.95
Physical functioning	4.00	-2.09, 1.55	0.70
Doctor visit	1.61	-15.50, 7.07	0.25
Social functioning	2.09	-0.82, 3.99	0.13
Somatic symptom(follow up)	2.82	-2.94, -0.26	0.03
Treatment compliance	1.43	-4.52,0.92	0.17

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Supplementary Table 1 Quality assessment results of included studies

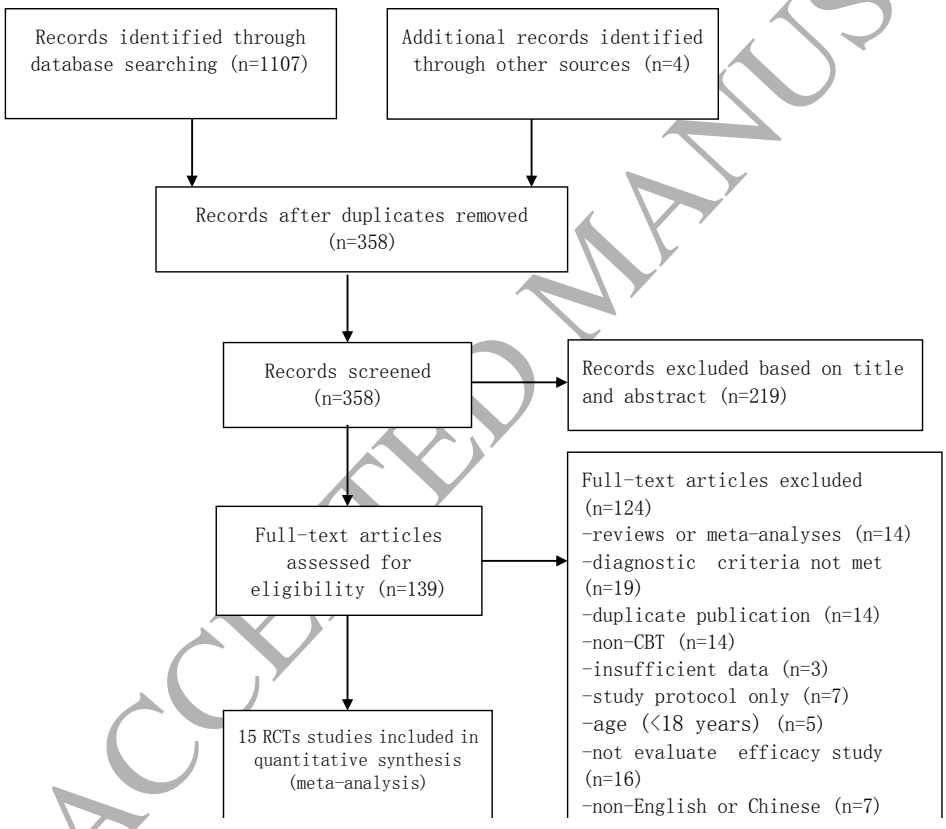
Trial	1.Inclusion Criteria	2. Random Allocation	3. Allocation Concealment	4. Similar at baseline	5. Blinding of subjects	6. Blinding of therapists	7. Blinding of assessors	8. key outcome measurement 85%	9. Intention to treat	10. between group comparison	11. measure of variability	TOTAL SCORE
Allen, 2006	1	1	?	1	0	0	0	1	1	1	1	7
Burton, 2012	1	1	1	1	0	0	0	0	0	1	1	6
Escobar, 2007	1	1	?	1	0	0	1	0	1	1	1	7
Fjorback, 2013	1	1	1	1	0	0	0	1	1	1	1	8
Hedman, 2016	1	1	1	1	1	0	0	1	1	1	1	8
Kashner,1995	1	1	?	1	0	0	0	0	0	1	1	5
Lidbeck, 1997	1	1	1	1	0	0	0	1	0	1	1	7
Martin, 2007	1	1	1	1	0	0	0	1	1	1	1	8
Moreno, 2013	1	1	1	1	0	0	?	1	1	1	1	9
Ravesteijn, 2013	1	1	1	1	0	0	0	1	1	1	1	8
Schröder, 2012	1	1	1	1	0	0	0	1	1	1	1	8
Speckens,1995	1	1	1	0	0	0	0	1	1	1	1	7
Sumathipala, 2000	1	1	1	1	0	0	?	1	1	1	1	8
Sumathipala, 2008	1	1	1	1	0	0	?	1	0	1	1	7
Zonneveld, 2012	1	1	1	1	0	0	?	1	1	1	1	8

(1='yes'; 0='no'; ?= 'unclear')

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Figure 1 PRISMA flow diagram



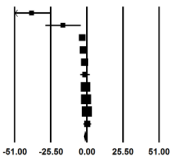
ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

A

Somatic symptoms: post- to pre-treatment effects

Study name	Difference in means	Lower limit	Upper limit	p-Value
Moreno, et al 2013b	-39.040	-51.831	-26.249	0.000
Moreno, et al 2013a	-16.860	-29.241	-4.479	0.008
Zonneveld, et al 2012	-3.270	-5.573	-0.967	0.005
Escobar, et al 2007	-2.370	-4.189	-0.551	0.011
Ravesteijn, et al 2013	-1.600	-3.650	0.450	0.126
Sumathipala, et al 2008	-1.300	-4.553	1.953	0.433
Speckens, et al 1995	-0.900	-1.752	-0.048	0.038
Allen, et al 2006	-0.570	-0.972	-0.168	0.005
Martin A, et al 2007	0.000	-0.206	0.206	1.000
Sumathipala, et al 2000	0.300	-2.324	2.924	0.823
	-1.311	-2.229	-0.394	0.005

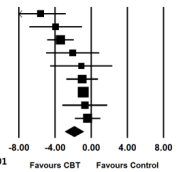


Pooled mean difference: -1.311(95%CI: -2.229 to -0.394),*p*=0.005

B

Anxiety symptoms: post- to pre-treatment effects

Study name	Difference in means	Lower limit	Upper limit	p-Value
Moreno, et al 2013a	-5.610	-8.377	-2.843	0.000
Moreno, et al 2013b	-3.940	-6.847	-1.033	0.008
Hedman, et al 2016	-3.400	-4.856	-1.944	0.000
Escobar, et al 2007	-2.050	-4.989	0.889	0.172
Ravesteijn, et al 2013	-1.100	-4.529	2.329	0.530
Speckens, et al 1995	-1.000	-2.729	0.729	0.257
Zonneveld, et al 2012	-0.880	-1.079	-0.681	0.000
Lidbeck, et al 1997	-0.700	-3.171	1.771	0.579
Martin A, et al 2007	-0.400	-1.792	0.992	0.573
	-1.887	-2.911	-0.863	0.000

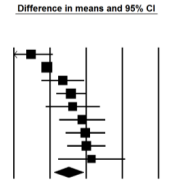


Pooled mean difference: -1.887(95%CI: -2.911 to -0.863),*p*<0.001

C

Depression symptoms: post- to pre-treatment effects

Study name	Difference in means	Lower limit	Upper limit	p-Value
Moreno, et al 2013a	-6.110	-8.521	-3.699	0.000
Zonneveld, et al 2012	-4.360	-4.671	-4.049	0.000
Escobar, et al 2007	-2.590	-4.945	-0.235	0.031
Speckens, et al 1995	-1.700	-3.308	-0.092	0.038
Martin A, et al 2007	-1.500	-4.493	1.493	0.326
Moreno, et al 2013b	-0.440	-2.973	2.093	0.733
Lidbeck, et al 1997	-0.100	-2.280	2.080	0.928
Ravesteijn, et al 2013	0.010	-2.096	2.116	0.993
Hedman, et al 2016	0.600	-3.095	4.295	0.750
	-1.935	-3.559	-0.311	0.020

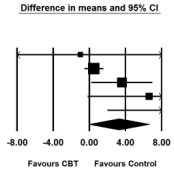


Pooled mean difference: -1.935(95%CI: -3.559 to -0.311), *p*=0.020

D

Soical functioning: post- to pre-treatment effects

Study name	Difference in means	Lower limit	Upper limit	p-Value
Fjorback,et al 2013	-1.000	-11.804	9.804	0.856
Speckens, et al 1995	0.500	-0.550	1.550	0.351
Hedman, et al 2016	3.600	0.233	6.967	0.036
Zonneveld, et al 2012	6.610	-0.188	13.408	0.057
Ravesteijn, et al 2013	11.000	2.030	19.970	0.016
	3.274	-0.079	6.627	0.056



Pooled mean difference: 3.274(95%CI: -0.079 to 6.627),*p*=0.056

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

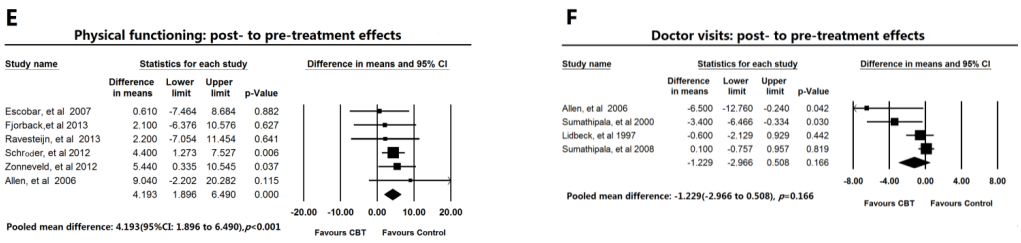


Fig.2 Forest plots of the effects of CBT on somatic symptoms (A), anxiety symptoms (B), depression symptoms (C), social functioning (D), physical functioning (E) , doctor visits (F).

ACCEPTED MANUSCRIPT

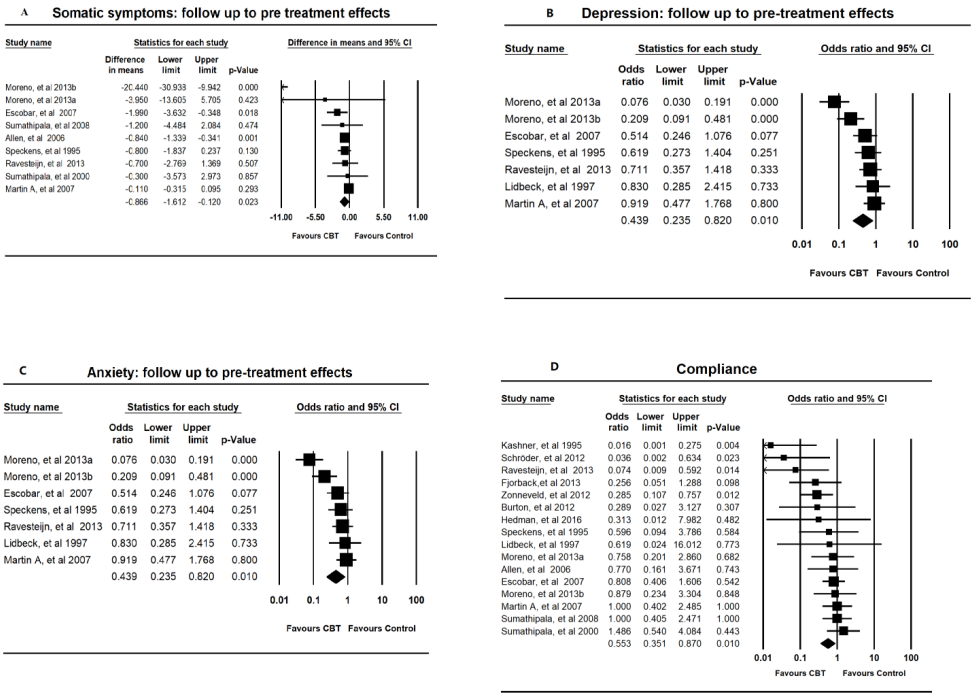


Figure.3 Forest plots of the effects of CBT on somatic symptoms（follow-up）(A), depression (B), anxiety symptoms（follow-up）(C), and compliance (D)