Mindfulness-based cognitive therapy for preventing recurrence of depression: a systematic review and meta-analysis

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Abstract

Background: Mindfulness-based cognitive therapy (MBCT) has been increasingly applied to clinical management of relapse of depression. However, the uncertainties of MBCT versus active-control conditions (ACCs) in reducing relapse rate in subjects with recurrent depression exist. This systematic review and meta-analysis intend to compare the effects of MBCT versus ACCs in reducing relapse of depressive disorder.

Methods: Electronic search of relevant literatures was performed on major medical databases. Randomized controlled trials evaluating MBCT versus ACCs for recurrent depressive disorder among adults were included. Risk of bias evaluation, meta-analysis, trial sequential analysis and evidence rating of all extracted information were conducted by two independent reviewers.

Results: Six trials with 1061 participants were deemed eligible for meta-analysis. Low risk of bias was found across the 6 studies and no heterogeneity was found among them. There was no significant difference between MBCT and ACCs in reducing relapse rate in patients with recurrent depressive disorder. The pooled sample size did not meet the inquired information size of trial sequential analysis which indicated that the result may be false negative. A total of 25 adverse events were formally recorded, but none were attributed to intervention. The quality of evidence was moderate due to the inadequate pooled sample size.

Conclusions: There was no significant difference between MBCT and ACCs in reducing relapse rate in patients with recurrent depressive disorder based on the available evidence. Future research will be needed to obtain a more explicit conclusion.

Background

Depressive disorder, one of the most common mental disorders, is characterized by depressed mood, loss of interest and enjoyment, decreased energy, and feelings of guilt or low self-worth[1, 2]. Globally, over 300 million people are believed to suffer from depression, equivalent to 4.4% of the world's population[3]. An observation of 245 404 participants from 60 countries in all regions of the world found depression produced the greatest decrement in health compared with other chronic diseases[4]. The depressive disorder is also usually highly recurrent[5], with at least 50% of patients had one or more relapses after the first episode of depression[6]. The risk of depressive relapse would reach to 80%-90% after two or more episodes of depression[5, 7], which burdens not only sufferers, but also their family and the society[8, 9]. As the second leading cause of Years Lived with Disability (YLD)[10], depressive disorder had led to a global total of YLDs over 50 million in 2015[3]. Given the heavy burden of depressive disorder, prevention of relapse of depression is absolutely essential[11].

Currently, the primary care and maintenance antidepressant medication (mADM) are most common strategies to prevent recurrence of depressive disorder[12]. However, numerous barriers hinder the effective management of recurrent depression in primary care[13], and mADM is always associated with poor adherence[14, 15] and unpleasant side effects[16, 17]. Given these limitations, many psychologists and patients prefer psychosocial interventions which provide safe protection against relapse of depression [18, 19].

Mindfulness-based cognitive therapy (MBCT) is a group-based intervention designed to cultivate intentional and non-judgmental observation of present moment experiences[20]. It integrates elements of cognitive behavioral therapy with training in mindfulness meditation, which has been applied to clinical management of relapse of depression[21]. Based on current evidence, systematic reviews and meta-analyses have shown that MBCT is superior to usual care or placebo in reducing relapse of depressive disorder[22–25]. Although MBCT has been shown to be effective, it is not clear how MBCT compares with other approaches to prevent depressive relapse—most notably, mADM[26]. MacKenzie[27] reviewed current studies of MBCT in patients with depression found that there were discrepancies in outcomes for the effectiveness of MBCT compared to active-control conditions (ACCs), including mADM and cognitive therapy(CT). In light of the above evidence and the uncertainties of MBCT versus ACCs in reducing relapse rate in subjects with recurrent depression, we conducted this systematic review and meta-analysis to extend prior studies in order to come up with a solid conclusion for clinical practice.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement[28], a detailed guideline which help us improve the reporting quality of systematic reviews and meta-analyses. The full PRISMA checklist and flow diagram were presented in Supplementary file 1. To ensure the methodological quality of this study, A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2[29] was taken as a reference.

Database and search

PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge infrastructure (CNKI), Technology Periodical Database (VIP), WanFang Data and China Biology Medicine (CBM) were searched from inception to December 2019, using a combination of relevant keywords and subject terms. The following key terms were searched: MCBT, depressive disorder, relapse, recurrent depression, randomized controlled trial (RCT). The full searching strategy was shown in Supplementary file 2. The grey literature and articles identified in reference lists were additionally searched to avoid missing eligible RCTs.

Studies selection

The following inclusion criteria were used to identify potential studies:

1. RCTs of MCBT versus ACCs for preventing relapse of depression;
2. Participants aged 18 years or older;

3. Participants diagnosed as having recurrent major depressive disorder in full or partial remission according to a formal diagnostic classification system (such as DSM-IV[30] or ICD-10[31]);
4. Studies published in English or Chinese.

The following exclusion criteria were used to filter studies for meta-analysis:

1. Intervention combined MCBT with other methods;
2. Studies did not report relapse rate.

Two reviewers (JZ, DLZ) independently screened potential studies based on title and abstract and assessed the full-texts according to prespecified inclusion criteria. Disagreements were resolved by discussion or consultation with an experienced reviewer (JL).

Data extraction

Two reviewers (HJL, LHS) independently extracted data using a predefined data extraction template. Following items were extracted: first author, title, journal, year of publication, country, sample size, age, gender, previous episode, age of first onset, protocol of intervention (duration, frequency, etc.), design, method of randomization, allocation concealment, blinding method, outcome, adverse events (AEs) etc. Any discrepancies were resolved by the third reviewer (RJJ).

Risk of bias

Assessment of risk of bias was conducted in accordance with Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook). Studies were independently assessed by two reviewers (YXL, YJH) with the following items: random sequence generation, allocation concealment, blind subjects and therapists, blind assessors, incomplete outcome data, selective outcome reporting and other bias. The risk of bias was categorized as low (meet all criteria)/unclear (trials with insufficient information to judge)/high risk (meet none of the criteria) of bias. Any discrepancies were resolved by the third reviewer (HLZ).

Data analysis

The Review Manager V5.3 software was utilized to calculate relative risk (RR) with 95% confidence intervals (CI) comparing relapse rate of patients with recurrent depressive disorder. The heterogeneity was assessed using the I^2 statistics. Statistical heterogeneity was checked using the χ^2 test, and the extent of inconsistency was assessed by the I^2 statistic. Fixed-effects model (FEM) was used if the heterogeneity of outcomes across studies was small ($I^2 < 50\%$), otherwise the random-effect model (REM) was used ($I^2 \geq 50\%$) to calculate the parameters. If possible, we planned to conduct subgroup analyses or sensitivity analyses for different interventions, diagnostic criteria, age groups to evaluate the robustness of the outcomes.

In a single trial, interim analyses increase the risk of type-1 error. To avoid this error, monitoring boundaries can be applied to decide whether a single trial could be stopped early because of the P sufficiently small value[32]. Because there is no reason why the standards for a meta-analysis should be less rigorous than those for a single trial, analogous monitoring boundaries can be used, which called trial sequential monitoring boundaries. Trial sequential analysis provides the necessary sample size for our meta-analysis and boundaries that determine whether the evidence in our meta-analysis is reliable and conclusive[33, 34]. We performed a trial sequential analysis to maintain an overall 5% risk of type-1 error and calculate the required sample size.

We intended to carry out Begg's Test and Egger's test with STATA for publication bias assessment if more than 10 studies reported the same outcome and assess the quality of evidence with the Grading of Recommendations Assessment, Development and Evaluation system (GRADE) pro and the Guideline Development Tool (https://gdt.gradepro.org/). Two qualified reviewers (JL and DLZ, certificated by GRADE center in LanZhou, China) independently rated quality of evidence for each outcome as high, moderate, low, or very low level according to the GRADE handbook [35].

Results

A total of 280 potential trials were identified. After duplications removed, 247 papers were screened by title and abstracts, and 32 papers were retrieved for full-text review. Of these, 6 trials[36–41] were identified eligible and were included in meta-analysis (excluded studies with reasons were listed in Supplementary file 3). Figure 1 shows the progress of selection.

Characteristics of included studies

The included trials were conducted in the UK(n = 3), Canada(n = 2), and the USA(n = 1), between 2008 to 2018. One trial conducted a follow-up of 8 months, while the other 5 trials had over 1 year of follow-up, of which 1 study[41] conducted a 26-month follow-up[39]. A total of 1061 participates were recruited, with the size of individual trials ranged from 54 to 424. Of these participants, about 70% were female. Most trials recruited participants with history of at least 3 depressive episodes according to DSM-IV[42], although 3 studies[38, 39, 41] included participants with more than 1 or 2 episodes. All trials defined relapse of depression as a return of symptoms meeting the criteria for major depression on Module A of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID) [43]. In the intervention groups, 4 studies[36–40] chose MBCT for treatment, while 2 trials[37, 41] used MBCT with discontinuation of antidepressant medication. During the discontinuation, patients were asked and recommended to withdraw gradually from their antidepressants over a period of 4–5 weeks. The program of MBCT was based on the protocol by Segal, Williams & Teasdale[44], across 8 weekly group meetings of 2 ~ 2.5 hours duration with or without a retreat day held between 6th and 7th session. The control groups 6 studies used ACCs. ACCs including mADM [37, 40, 41] and program comprised most of elements of MBCT except mindfulness meditation[36, 38, 39]. In mADM group, patients were monitored and treated by their physicians with an adequate dose of antidepressants, and recommendations were provided to manage side-effects. Key characteristics of included trials are shown in Table 1.

Table 1
Study characteristics

Author, year, country	Sample	Age Mean (SD)	Female(%)	Previous episodes Mean (SD)	Age of first onset Mean (SD)	Intervention (frequency,duration)	Intervention(n/drop outs/analysis)	Control
Kuyken 2008 UK	Participants with three or more previous episodes of depression with mADM over the last 6 months and were in full or partial remission. (N = 123)	49.16(11.17)	76	6.39(2.96)	26.22(12.14)	MBCT (8, weekly, 2 h)	(61/2/61)	mADM
Segal 2010 Canada	Participants with 2 previous episodes of depression. (N = 54)	45.32(10.40)	61	4.70(2.40)	31.80(11.75)	Discontinuation + MBCT (8, weekly,2 h with a retreat day held between sessions 6 and 7)	(26/5/26)	mADM
Williams 2014 UK	Patients with at least 3 episodes of major depression and remission for the previous 8 weeks. (N = 274)	43.82(12.17)	72	≥ 5:77%	21.26 (10.93)	MBCT (8, weekly, 2 h)	(108/9/99)	CPE progra
Kuyken 2015 UK	Patients with diagnosis of recurrent major depressive disorder in full or partial remission and three or more previous major depressive episodes. (N = 424)	49.50(12.50)	77	6:53.3%;≥6:46.7%	24.9(12.42)	MBCT (8, weekly, 2·25 h) + taper or discontinue antidepressant treatment	(212/46/212)	mADM
Frab 2018 Canada	Patients were absence of a diagnosis of depression, with 1 previous episode. (N = 166)	40.63(11.77)	67	3.86(2.33)	22.43(10.66)	MBCT (8, weekly, 2 h)	(82/33/82)	CT

N, number; MBCT, mindfulness-based cognitive therapy; mADM, maintenance antidepressant medication; NR, no report; CPE, cognitive psychological educati condition.

AE, adverse event; SAE, serious adverse event

Author, year, country	Sample	Age Mean (SD)	Female(%)	Previous episodes Mean (SD)	Age of first onset Mean (SD)	Intervention (frequency,duration)	Intervention(n/drop outs/analysis)	Control
Shallcross 2018 USA	Patients with minimum of 1 prior episode of depression, current remission from depression for at least 1 month. (N = 92)	34.90(11.40)	76	≥ 3:95%	16.10(7.00)	MBCT (8, weekly, 2.5 h)	(46/24/46)	ACC was based on th validated a manualized Health Enhanceme Program

N, number; MBCT, mindfulness-based cognitive therapy; mADM, maintenance antidepressant medication; NR, no report; CPE, cognitive psychological educati condition.

AE, adverse event; SAE, serious adverse event

Risk of bias assessment

The Cochrane Collaboration Risk of Bias Tool[45] was used to assess risk of bias across studies. Of the 6 included studies, all described the details of random sequence generation by computer software[37–41] or a dynamic type of treatment allocation[36, 46] and all trials conducted proper allocation concealment. Research assessors were blinded to treatment allocation in five trials[36, 37, 39–41], while 1 trial did not report the blinding method[38]. All studies reported drop-outs and 2[40, 41] with reasons, and all trials carried out the intention-to-treat analysis. In selective reporting, all studies were registered advanced and 1 study[37] published a prior-protocol, while 1[39] failed to provide a registration number.(Fig. 2, Fig. 3)

Relapse rate of MBCT versus. ACCs

This is a dichotomous outcome and defined as the proportion of participants who had a return of symptoms meeting the SCID. All the included studies reported the relapse rate after intervention and follow-up. The pooled results showed that there was no statistical difference between the MBCT group and the ACCs group in reducing relapse of depressive disorder (RR = 0.90, 95% CI 0.79 to 1.03, P = 0.13). There was no heterogeneity (χ^2 = 0.97, P = 0.97, I^2 = 0%) across these studies. Subgroup analysis was carried out based on different controls. No significant difference of relapse rate was found between patients received MBCT versus program comprised most of elements of MBCT except mindfulness meditation (RR = 0.80, 95% CI 0.60 to 1.08, P = 0.15) and MBCT versus mAMD (RR = 0.93, 95% CI 0.79 to 1.08, P = 0.13). No heterogeneity was found in both subgroup analyses (I^2 = 0%). (Fig. 4)

Trail sequential analysis

To determine the required sample size of MBCT versus ACCs in reducing relapse rate in recurrent depressive patients, we assumed a 46.15% relapse rate in control group and a relative risk reduction of 10% based on our meta-analysis. The cumulative Z-curve for trials with low bias risk did not cross any of the boundaries, which showed that we need a sample of 3622 to detect a plausible effect of MBCT on relapse rate (with 80% power and α = 0.05). (Fig. 5)

Safety assessment

Three studies reported AEs during experiments. Kuyken[40] found no AEs through the oversight of the Trial Steering Committee in the study of 2008. Williams[36] reported 15 SAEs to the research team, 5 arising from MBCT group and 10 from control group. Of these, only 1 was adjudged to be a serious adverse reaction potentially arising from a trial treatment. In the 2015 study, Kuyken[37] reported a total of 10 SAE, 4 of which resulted in the death of the participant, and the Trial Steering and Data Monitoring Committees concluded that there was no reason to believe that any of the SAEs were related to either the intervention or the trial.

Publication bias

As less than 10 studies were included, the Begg's Test and Egger's test would have no valuable reference.

Evidence rating

The assessment of evidence would offer a clear, precise illustration of decision-making progress with the GRADE tool. The quality of evidence was moderate. The reason for downgrading was that the sample size was lower than the optimal information size. The outcome from the meta-analysis was presented in Table 2.

Table 2
Grade evidence profile of MBCT versus ACCs

Certainty assessment							№ of patients		Effect		Certai
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MBCT	ACC	Relative (95% CI)	Absolute (95% CI)	
relapse rate (follow up: range 8 months to 26 months)											
6	randomised trials	not serious	not serious	not serious	serious [a]	none	219/528 (41.5%)	246/533 (46.5%)	OR 0.90 (0.79 to 1.03)	46 fewer per 1,000 (from 97 fewer to 14 more)	⨁⨁◯ MODE

CI, Confidence interval; OR, Odds ratio

a. The pooled (cumulative) sample size was lower than the optimal information size (OIS) and/or the total enrollment was less than 300 (dichotomous data)

Discussion

Summary of findings

We obtained 6 RCTs with a total of 1061 participants examining the effect of MBCT to prevent the occurrence of depressive episode. Low risk of bias was found across the 6 studies and no heterogeneity was found among them. Present study indicated that there was no significant difference between MBCT and ACCs in reducing relapse rate in patients with recurrent depressive disorder. The trail sequential analysis indicated that we still need a cumulative sample of 2561 to detect a plausible effect of MBCT on relapse rate. The result may be false negative. A total of 25 AEs was formally recorded in 3 of 7 studies, but none were attributed to intervention. The quality of evidence was moderate due to the inadequate pooled sample size.

Comparison with other views

Previous studies suggested that MBCT showed beneficial effects compared with TAU. MBCT was found superior than TAU in lowering the rate of depressive relapse[47], depressive and comorbid symptoms, and increasing the quality of life[40, 41] in recurrent depression patients. Moreover, MBCT has also been compared with ACCs in prevention of depressive relapse. However, the results were controversial. In a 2014 trial[48], Meadows et al found that MBCT combined with depression-relapse active monitoring was superior to ACCs in reducing depressive relapse over a 2-year follow-up. Shallcross et al compared MBCT with ACCs in 2015, the results were found that MBCT did not differ from the ACCs on rate of depression relapse, symptom reduction, and life satisfaction[49]. A recent meta-analysis indicated that MBCT was more effective in reducing rumination with a depressive disorder than ACCs[50]. The inconsistencies between these studied were probably owing to small sample size, poor quality of methodology and lack of long-term follow-up.

In comparison, our work especially focused on the effect of MBCT compared with ACCs. We narrowed the inclusion criteria to studies in which MBCT was the sole intervention and ACCs was the control. In addition, we assessed the strength of the available evidence through trial sequential analysis. This method adapted from interim monitoring boundaries in single RCT applied to cumulative meta-analysis[33, 34], which supported our finding and call for more data for a firm evidence. Furthermore, the GRADE system was applied in our study to help us evaluate the outcome, which not only facilitated a better understanding but also implied an improvement for further research.

Implication for future study

With an increasing proportional contribution to the Burden of Disease, major depressive disorder as a major public health problem even becomes a heavy burden in countries with well-developed mental health-care services[51]. To reduce depressive relapse, MBCT was developed and has gained increasing reliability and popularity among patients with recurrent depression. A systematic review reviewed 23 clinical trials of MBCT for recurrent depression to evaluate mechanisms of change[52]. The study showed that outcomes of MBCT was associated with or predicted by changes in mindfulness, rumination, worry, self-compassion, decentering, and/or meta-awareness. Despite of the theoretical predicted variables, additional psychological, neural and genetic factors were also been mentioned to be potential mechanisms which are worthy for further investigation.

Strength and Limitations

This is the first systematic review and meta-analysis focused on MBCT versus ACCs in reducing recurrent depression. We conducted this review in accordance with PRISMA checklist, and we also referred to AMSTAR 2 to ensure the methodological quality. GRADE system and trail sequential analysis were performed in this study to support our findings. In addition, several limitations in our review should be mentioned. Firstly, we only included 6 trials for meta-analysis. We believe the evidence will be more rigorous that researchers carry out more trials in the future. Secondly, the follow-up period of included studies ranged from 8 to 26 months. We did not analyze the difference of depression relapse rate between short-, medium- or long-term follow-up due to the diverse time of follow-up. Thirdly, we only searched for Chinese and English articles so that inclusion bias was unavoidable.

Conclusions

In our systematic review, we have showed that there was no significant difference between MBCT and ACCs in reducing relapse rate in patients with recurrent depressive disorder based on the available evidence. However, the pooled sample size does not meet the required information size, which indicated that there may be a false negative result. Future research will be needed to obtain a more explicit conclusion.

Abbreviations

MBCT: Mindfulness-based cognitive therapy, ACC: active-control condition, YLD: Years Lived with Disability, mADM: maintenance antidepressant medication, CT: cognitive therapy, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis, AMSTAR: A MeaSurement Tool to Assess systematic Reviews, CENTRAL: Cochrane Central Register of Controlled Trials, CNKI: China National Knowledge infrastructure, VIP: Technology Periodical Database, CBM: China Biology Medicine, RCT: randomized controlled trial, AE: adverse event, RR: relative risk, CI: confidence interval, GRADE: Grading of Recommendations Assessment, Development and Evaluation system, SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders,

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

This is an evidence synthesis study, all data is available from included primary studies, or can be circulated from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YGZ, JL and RJJ contributed to the study design. JZ and DLZ conducted literature search and screening. XBL and LHS conducted literature review and data extraction. YXL, YJH and HLZ conducted assessment of risk of bias and data analysis. YXL and JZ interpreted the data and drafted the manuscript. JL, YGL and QQL critically revised the manuscript. All authors contributed to the paper and revised it into its final version.

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Figures

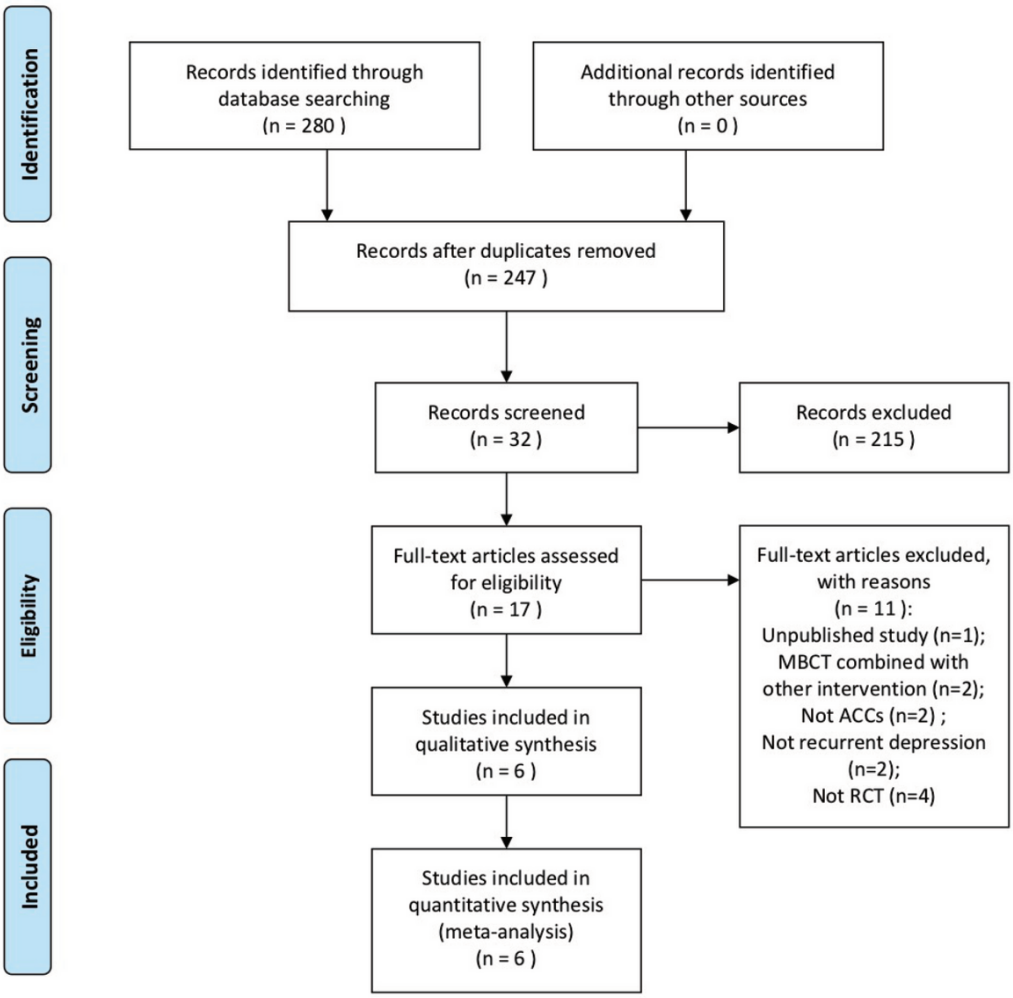

Figure 1

PRISMA flowchart of trial flow

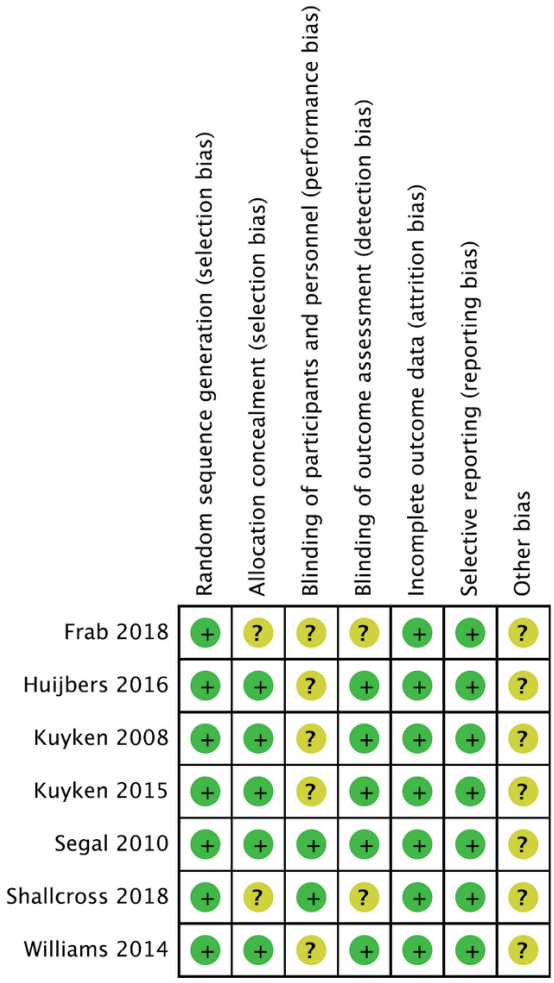

Figure 2

Summary of risk of bias

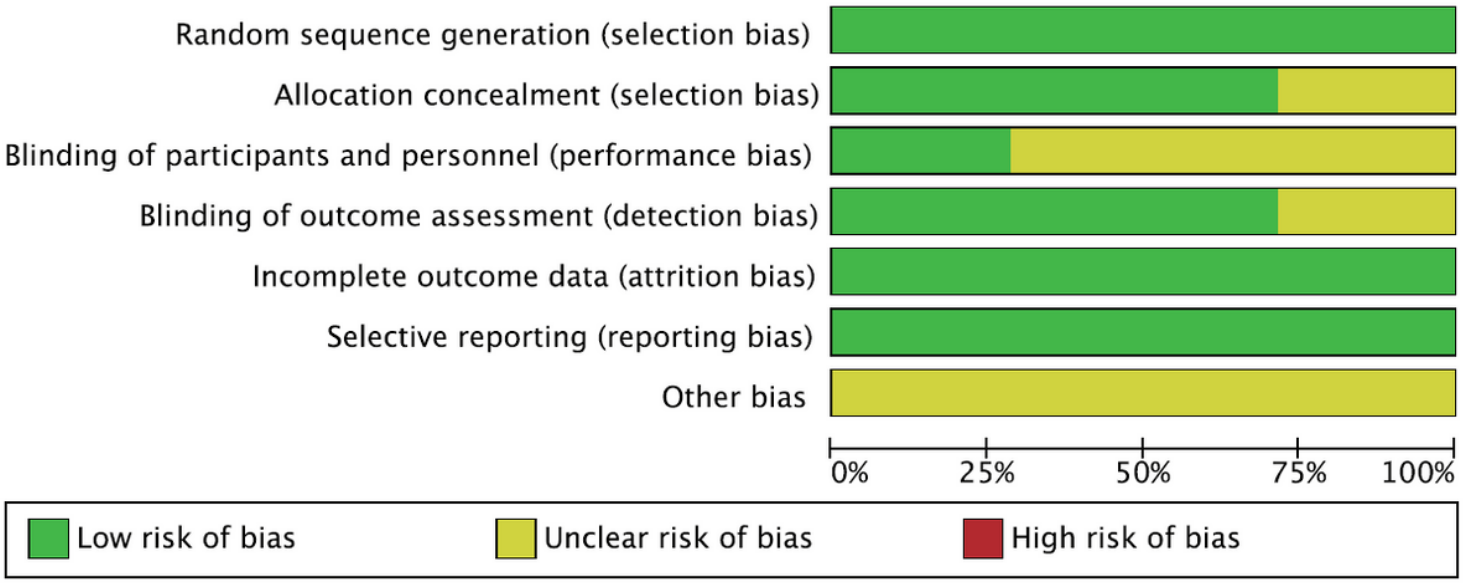

Figure 3

Graph of risk of bias

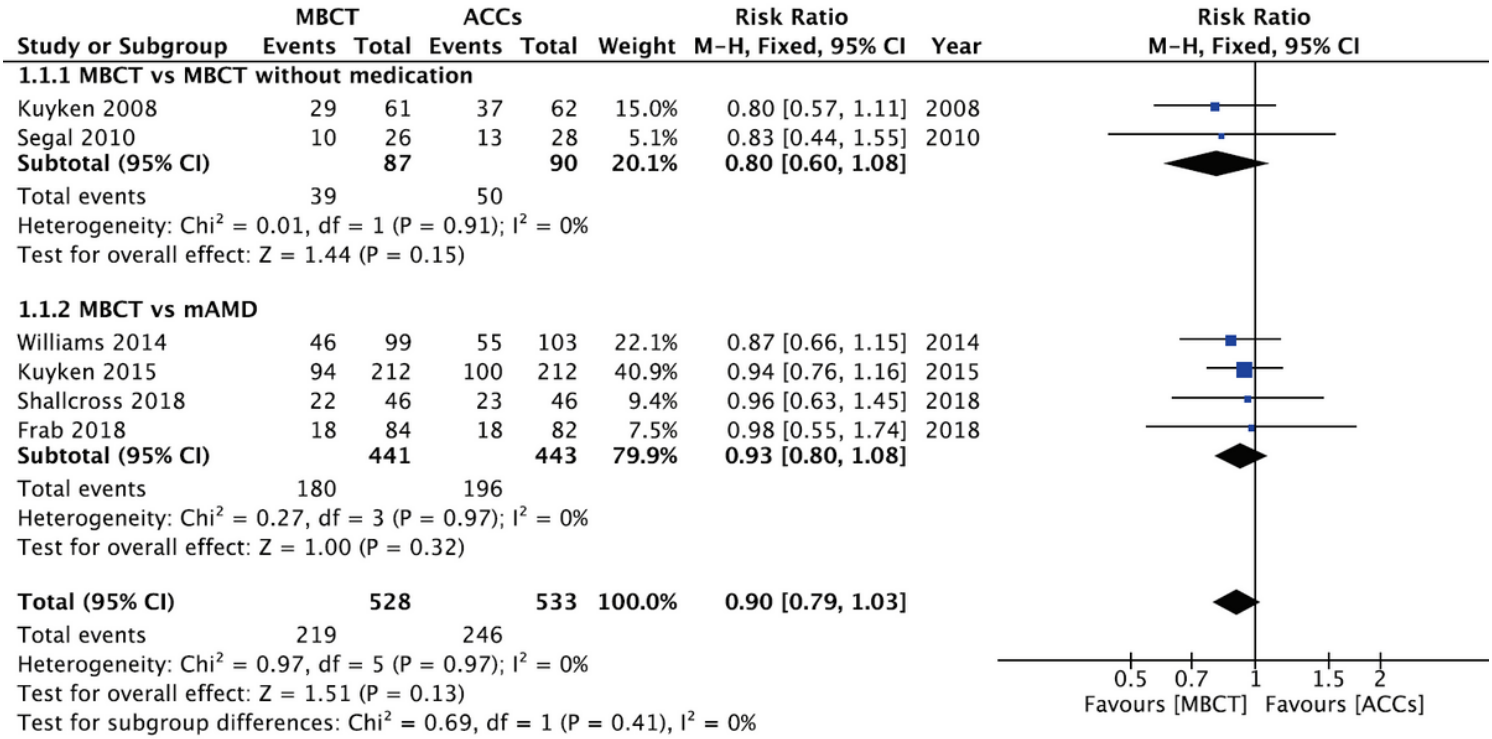

Figure 4

The pooled outcomes of depressive relapse rate in MBCT versus ACCs.

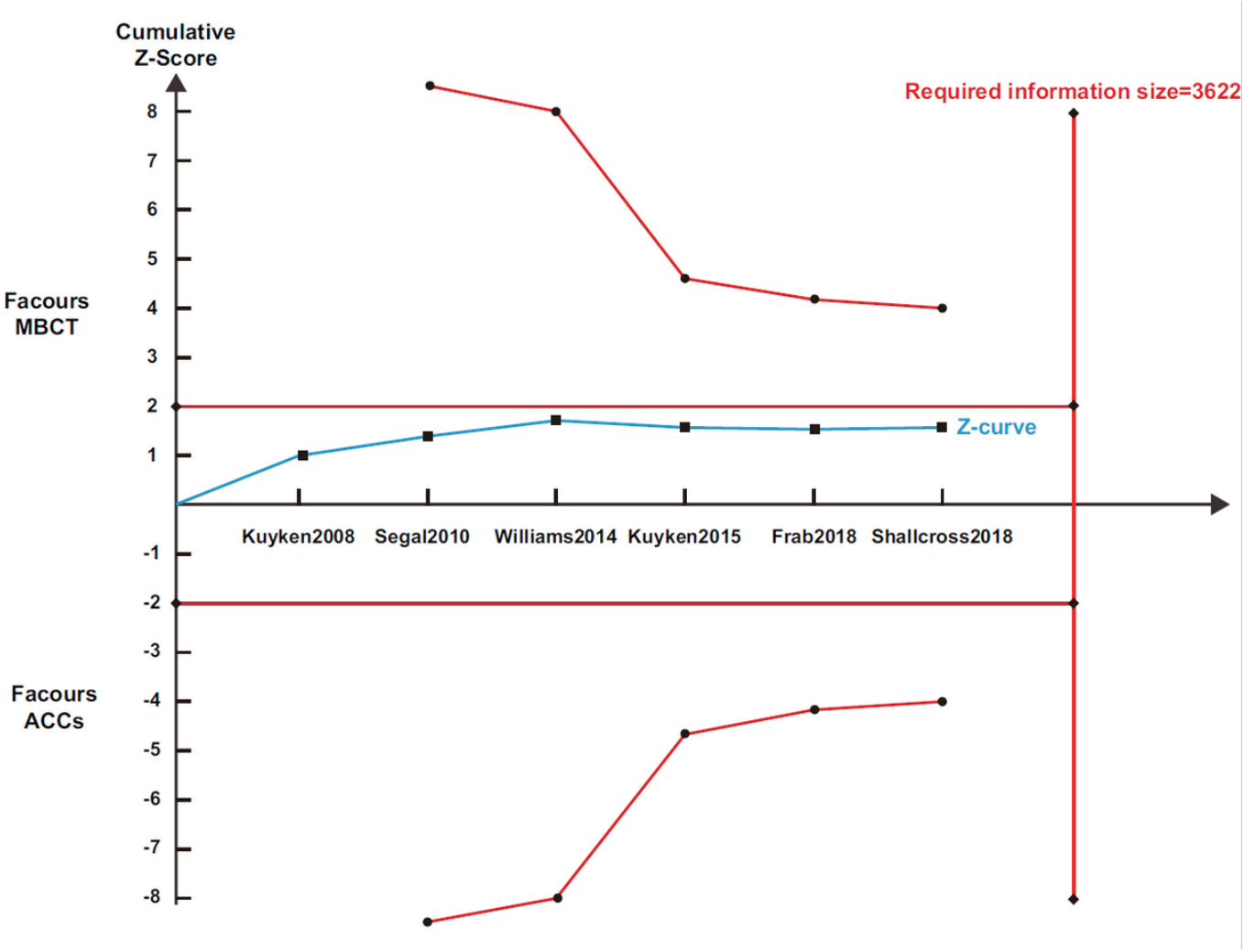

Figure 5

Results of trail sequential analysis

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfile3.docx
- Supplementaryfile1.pdf
- Supplementaryfile2.docx