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Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse

Kuyken, W

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Efficacy and moderators of mindfulness-based cognitive therapy (MBCT) in prevention of depressive relapse: An individual patient data meta-analysis from randomized trials

Willem Kuyken[1] PhD, Fiona Warren[2] PhD, Rod S Taylor[2] PhD, Ben Whalley[3] PhD, Catherine Crane[1] PhD, Guido Bondolfi[4] MD PhD, Rachel Hayes PhD[5], Marloes Huijbers[6] MSc, Helen Ma[1] PhD, Susanne Schweizer PhD[7], Zindel Segal[8] PhD, Anne Speckens[6], MD, John D. Teasdale[9] PhD, Kees Van Heeringen[10] PhD, Mark Williams[1] PhD, Sarah Byford[11] PhD, Richard Byng[12] PhD, Tim Dalgleish[13] PhD

1 Department of Psychiatry, University of Oxford, Prince of Wales International Centre, Warneford Hospital, Oxford OX3 7JX, UK

2 Institute of Health Research, Primary Care Research Group, Exeter Medical School, Smeall Building, St Luke's Campus, Magdalen Road, Exeter, EX1 2LU, UK

3 School of Psychology, Faculty of Health & Human Sciences, University of Plymouth, Drake Circus, Plymouth, PL4 8AA, UK

4 Department of Psychiatry, University Medical Centre, University of Geneva, CH-1211 Geneva 4, Switzerland

5 Institute of Health Research, Child Health Group, Exeter Medical School, Smeall Building, St Luke's Campus, Magdalen Road, Exeter, EX1 2LU, UK

6 Department of Psychiatry, Radboudumc, Nijmegen, The Netherlands

7 Medical Research Council Cognition and Brain Sciences Unit, Cambridge, UK

8 Department of Psychology, University of Toronto Scarborough, 1265 Military Trail, Toronto, Ontario, M1C 1A4, Canada

9 Cambridge, Cambridgeshire, UK

10 University Department of Psychiatry, University Hospital, De Pintelaan 185, 9000 Gent, Belgium.

11 King's Health Economics, King's College London, Box P024, De Crespigny Park, London SE5 8AF, UK

12 Plymouth University Peninsula School of Medicine, John Bull Building, Research Way, Plymouth, PL6 8BU, UK

13 Medical Research Council Cognition and Brain Sciences Unit, Cambridge, UK and Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

Corresponding author:

Willem Kuyken, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK

Tel: +44 (0)1865 613139

E-mail: willem.kuyken@psych.ox.ac.uk

Abstract

Importance: Relapse prevention in recurrent depression is a significant public health problem and antidepressants are the current first-line treatment approach. Identifying an equally efficacious non-pharmacological intervention would be an important development.

Objective: To conduct an individual patient data meta-analysis examining the efficacy of Mindfulness Based Cognitive Therapy (MBCT) compared with usual care and other active treatments, including antidepressants.

Data Sources: Studies reported in the English language, and published or accepted for publication in peer-reviewed journals identified from EMBASE, PubMed/Medline, PsycINFO, Web of Science, Scopus, and the Cochrane Controlled Trials Register from the first available year to 22 November 2014.

Study Selection: Randomized trials of manualized MBCT for relapse prevention in recurrent depression in full or partial remission that compared MBCT with at least one non-MBCT treatment, including usual care.

Data Extraction and Synthesis: Individual patient data were obtained for nine out of ten randomized trials, comprising 1329 participants, with data available for 1258 (95%). The main outcome measure was time (weeks) to depressive relapse over a 60 week follow-up period. Data were pooled using two-stage and one-stage meta-analysis methods, and fixed and random effect(s) models.

Results: Using a two-stage random effects approach, patients receiving MBCT had a reduced risk of depressive relapse within a 60-week follow-up period (hazard ratio: 0.69, 95% confidence interval 0.58 to 0.82), compared with those who did not receive MBCT. Furthermore, comparisons with active treatments suggest a reduced risk of depressive relapse within a 60-week follow-up period (hazard ratio: 0.79, 95%

confidence interval 0.64 to 0.97). Using a one-stage approach, socio-demographic (i.e. age, gender, education and relationship status) and psychiatric (i.e. age of onset and number of previous episodes of depression) variables showed no statistically significant interaction with MBCT treatment. However, there was some evidence to suggest that greater severity of depressive symptoms prior to treatment was associated with a larger effect of MBCT compared with other treatments.

Conclusions and Relevance: MBCT appears efficacious as a treatment for relapse prevention for those who suffer recurrent depression, particularly those with more pronounced residual symptoms. Recommendations are made concerning how future trials can address remaining uncertainties and improve the rigor of the field.

Introduction

Although progress has been made in the treatment of many psychiatric conditions, recurrent depression continues to cause significant disability and suffering, as well as costs to society (1, 2). Interventions that prevent depressive relapse among people at high risk of recurrent episodes have significant potential to reduce disease burden (3). Mindfulness-based cognitive therapy (MBCT) is one such intervention. MBCT teaches people with a history of depression psychological skills that target cognitive mechanisms implicated in depressive relapse (4) by combining systematic mindfulness training with elements from cognitive therapy. A systematic review and meta-analysis (5) of six randomized controlled trials (*n*=593 patients) suggested that MBCT significantly reduces rates of depressive relapse compared with usual care or placebo, corresponding to 34% relative risk reduction (risk ratio 0.66, 95% confidence interval (CI) 0.53-0.82).

While we have a growing body of evidence pointing to MBCT's efficacy in preventing depressive relapse, we do not know if MBCT is differentially efficacious for sub-groups of people known to be at greater or lesser risk for depressive relapse/recurrence (6, 7).

Here we present an analysis of individual patient data (IPD) compiled from nine published randomized trials of MBCT identified through a systematic literature search. Unlike meta-analysis of aggregate data at the trial level, IPD analysis permits investigation of patient-level characteristics that may be potential moderators of MBCT's treatment effect (8). We examined MBCT's efficacy compared with usual care or active treatment comparison groups, for patients from a range of socio-demographic and psychiatric backgrounds, participating in studies conducted in a

number of different countries in Europe and North America, taking into account differential periods of follow-up across studies.

Methods

The study was conducted in accordance with the PRISMA statement for systematic reviews and meta-analyses and the good practice guidelines of the Cochrane collaboration IPD methods group (9, 10).

Study identification and data extraction

We searched for relevant publications from November 2010 (the searching end date of the previous meta-analysis (5)) to November 2014 (Figure 1) using the same a priori criteria for study inclusion as the previous review, as follows:

- Study design: randomized trials of MBCT for prevention of relapse in recurrent major depressive disorder currently in remission, reported in the English language, and published or accepted for publication in peer-reviewed journals.
- Participants: participants aged 18 years or above, diagnosed with recurrent major depressive disorder in full or partial remission according to a formal diagnostic classification system. Major depressive disorder was defined as a diagnosis based on the DSM-III, III-R, IV or IV-TR or International Classification of Diseases (ICD-10).
- Intervention group: MBCT delivered according to the treatment manual (11).
- Control group: At least one non-MBCT treatment, including usual care.
- Outcome measures: number of participants meeting the diagnostic criteria for a new major depressive episode over the follow-up study period according to accepted clinical diagnostic criteria such as the ICD-10 or DSM-IV TR.

Studies were identified from searches of titles, abstracts and keywords of electronic databases (EMBASE, PubMed/Medline, PsycINFO, Web of Science, Scopus, and the Cochrane Controlled Trials Register) using the search terms (mindfulness-based cognitive therapy) OR (mindfulness based cognitive therapy) OR (MBCT) AND depress*). No language or other limitations were imposed at this stage. We also checked reference lists of relevant studies and reviews for additional references to potentially relevant studies. The procedure is summarized in Figure 1 (narrative text and an example of a full search string are provided in online appendix Table B).

IPD were obtained from the authors of nine of the ten trials meeting the inclusion criteria and collated into one dataset (n = 1329). Overall IPD integrity was found to be high. The trials are summarized in Table 1 and data extraction and cleaning is elaborated in the online appendix (Table C). Of the nine relevant trials, two had three arms and seven had two arms. One trial included a pill placebo arm (14); this small arm (n=30) was excluded from all analyses. The other three-arm trial (18) had two non-MBCT arms, one treatment as usual (TAU) and the other TAU plus cognitive psychological education (CPE). For the analyses of MBCT vs. non-MBCT the two non-MBCT arms were combined; for the analyses of MBCT vs. an active comparator, the TAU arm was excluded. We used the Cochrane risk of bias assessment tool (19). While the risk of bias was generally low across all trials for most criteria (Online appendix Table A), 2/9 trials did not blind assessors (15) (20), and one of these also had incomplete outcome data (15).

Primary Outcome

The primary outcome was relapse to depression within 60 weeks of follow-up, collected through a structured clinical diagnostic interview (21). For studies with

follow-up beyond 60 weeks, follow-up was censored at 60 weeks. From the nine trials available, participants with data for relapse status and time-to-relapse measured in weeks (if relapse occurred; otherwise time to end of follow-up was used) were included in all analyses. We also report adverse events.

Moderator variables: Socio-demographic and psychiatric status variables

We pre-defined several socio-demographic characteristics as potential moderators of the effect of MBCT, i.e., gender, age, education, relationship status, ethnicity, socioeconomic status and employment status. These variables were standardized across the nine trials using available data to map the participant to the standardized category (online appendix Table C).

Psychiatric status variables included in the moderator analyses were: severity of depression symptoms at baseline (measured with the BDI-II or IDS), baseline mindfulness measured on one of several scales, age of onset of depression and number of previous major depressive episodes.

Statistical methods

All statistical analyses were conducted according to participants' randomized allocation in the primary studies. Only complete case data were included for all trials in the main analyses. In the event of substantive missing data (>10%) for an individual trial, a sensitivity analysis was performed using imputed data based on two scenarios, one maximally favoring the intervention group, and the other maximally favoring the control group for the two stage meta-analysis comparing MBCT with non-MBCT only. All analyses were performed using Stata v.14.

Question 1: Does MBCT reduce depressive relapse/recurrence compared with control conditions?

Meta-analyses of time-to-event data were used to evaluate the effect of MBCT compared with non-MBCT on the primary outcome. Both two-stage and one-stage meta-analysis methods were used (22). Two-stage methods involved calculating a hazard ratio (HR) for depressive relapse (MBCT vs. non-MBCT) for each study individually (23, 24), using Cox proportional hazard models, and then combining these HRs in a meta-analysis. Heterogeneity was assessed within the two-stage models using the I^2 statistic (25). A 95% CI for the I^2 statistic was calculated using the test-based method (26). Both fixed and random effect(s) models were applied (27). Meta-analyses were performed on three pairwise comparisons: MBCT vs. all non-MBCT treatments, MBCT vs. active treatments (ADM or CPE), and MBCT vs. ADM only.

For the one-stage meta-analyses, both fixed and random effect(s) models were applied to the same three pairwise comparisons. Fixed effect models used the Cox proportional hazards model, yielding a hazard ratio, with individual study as a stratum, allowing the baseline hazard to vary across studies (28); where the proportional hazards assumption was unsupported, the addition of MBCT status interacting with log(time) was added to the model (and to all subsequent models) to allow the effect of MBCT status on risk of relapse to vary during the follow-up period. Random effects one-stage models used the Stata command stmixed (29), included a study level random effect on MBCT status, and applied a flexible parametric survival model (30).

Question 2 – Are any of the socio-demographic or depression-related covariates associated with time to depressive relapse? Are MBCT's effects on these outcomes moderated by demographic or depression-related variables?

For our primary outcome of depressive relapse, the use of one-stage meta-analysis models facilitated inclusion of our socio-demographic and depression-related covariates to investigate moderation (31). The choice of whether to use a fixed effect or random effects approach would be informed by the degree of between-studies heterogeneity evident from the two-stage and one-stage models comparing MBCT with non-MBCT; in the event of very low heterogeneity, a fixed effect model would be used. A series of multivariable models were performed, initially including only the MBCT status of the participant and one additional covariate (the interaction between MBCT and log(time) would be included if appropriate). As a further check, all covariates were included in one overall model, to establish which were significantly associated with depressive relapse in the presence of all other covariates. Individual covariates that were found to be statistically significant (at the $p<0.10$ threshold) in a model including MBCT status only, or in a model with all covariates combined, were then included in a further model. Covariates that did not achieve significance at the $p<0.05$ level were removed individually from this model until the most parsimonious model had been ascertained. Each covariate within this model was individually investigated for interaction with MBCT status (i.e. each model included only one interaction term) and any that were not found to be a significant predictor of time-to-relapse were individually included in the model with all other significant predictors to investigate potential interaction with MBCT status. In addition, moderation effects between each MBCT status and each individual covariate were investigated in a series of models including only MBCT status, the specified covariate, and their interaction.

Results

Description of primary studies

The nine included studies are described fully in the original trial reports and are summarized here in Table 1. We defined loss to follow-up as being lack of data on relapse status after 60 weeks (or closest available time) of follow-up. Of the 1329 randomized participants from the nine trials with available IPD, data on relapse status and time to relapse (or end of follow-up with no relapse) were available for 1258 participants (95%). Within individual studies, the proportion of participants lost to follow-up ranged from 0% to 18% (Table 1). Of 596 participants who received MBCT, 229 (38%) had a depressive relapse within 60 weeks' follow-up; this compared with 327/662 participants (49%) who did not receive MBCT.

Question 1 – Does MBCT reduce depressive relapse compared with the control condition?

Due to clinical heterogeneity across the nine studies, the results of random effects models are reported, although due to very low between study heterogeneity of treatment effect, the results of equivalent fixed effect analyses were very similar. Comparing MBCT with all non-MBCT treatments, the HR was 0.69 (95% CI 0.58 to 0.82), with an I^2 of 1.7% (Figure 2a.); the 95% CI for I^2 was 0% to 20%. The funnel plot associated with this analysis indicates some asymmetry, with an absence of smaller studies that themselves showed an increased risk of relapse with MBCT treatment (online appendix Figure A). The associated Egger's test produced a *p*-value of 0.182, although we recognise the limited power of this test with only nine studies. A sensitivity analysis whereby missing outcome data from Godfrin (15) were imputed favoring the MBCT group produced an HR of 0.63 (95% CI 0.49 to 0.82); using imputed data that favored the non-MBCT group produced an HR of 0.74 (95% CI 0.63 to 0.88). An equivalent analysis comparing MBCT with all active treatments, using data from five studies (14, 18, 20, 32, 33), produced an HR of 0.79 (95% CI

0.64 to 0.97, I^2 0%; Figure 2b). Comparing MBCT with ADM treatment using data from four studies (14, 18, 20, 32, 33), the HR was 0.77 (95% CI 0.60 to 0.98; I^2 0%, Figure 2c). For the latter two meta-analyses, the I^2 value was 0%, in both cases the lower boundary of the 95% CI was 0%, and the upper boundary 43% and 65% respectively.

An unadjusted one-stage fixed effect meta-analysis comparing MBCT vs. non-MBCT treatment (1248 patients, 554 depressive relapses within 60 weeks) yielded an HR of 0.69 with a 95% CI 0.58 to 0.82 (Table 2, Model A). However, there was evidence to indicate that the proportional hazards assumption was not valid (online appendix Figure B shows the log-log plots comparing the MBCT and non-MBCT groups for each of the nine included studies). Due to the lack of proportional hazards, the interaction between MBCT status and log(time) was added, allowing the effects of MBCT to vary with log(time). This model (Table 2, Model B) yielded an HR for MBCT of 0.34 (95% CI 0.19 to 0.60), and for the interaction of MBCT with log(time) of 1.28 (95% CI 1.06 to 1.55), indicating a reduction in the preventative effect of MBCT on depressive relapse as time progressed during the follow-up period.

Comparing MBCT with active treatments only (five studies with 892 participants and 385 relapses), the HR from the one-stage fixed effect model was 0.78 (95% CI 0.64 to 0.96; Table 2, Model C), very similar to that of the two-stage random effects model (in this analysis, there was little evidence to indicate lack of proportional hazards). The equivalent analysis comparing MBCT with ADM treatment (four studies, 637 participants and 266 relapses) produced an HR of 0.77 (95% CI 0.60 to 0.98; Table 2, Model D), identical to the results of the two-stage random effects model, again with little evidence to support lack of proportional hazards.

The one-stage random effects model (using a flexible parametric model with 2 degrees of freedom) comparing MBCT with all non-MBCT treatments resulted in an HR of 0.68 (95% CI 0.58 to 0.81; Table 2, Model E), with a between study standard deviation (SD) of 0.0008. Adding the interaction between MBCT status and the restricted cubic splines derived from the previous model produced a hazard ratio comparing MBCT with non-MBCT of 0.63 (95% CI 0.53 to 0.76; Table 2, Model F) with a between study SD of 0.0007; the global p-value for the interaction between MBCT status and each restricted cubic spline was 0.04 (consistent with a significant time-varying effect of MBCT status observed in the fixed effect model). Equivalent analyses comparing MBCT with all active treatments, or MBCT with ADM, with or without a time-varying effect on MBCT status failed to converge, almost certainly due to very low between study heterogeneity..

Question 2 – Are MBCT's effects on outcome moderated by demographic and psychiatric status variables?

In view of the low between study heterogeneity, fixed effect one-stage models were used for the moderation analyses. Individually, five socio-demographic and psychiatric variables were found to be significantly associated with risk of relapse within 60 weeks (p-value <0.1): baseline depression z-score, baseline mindfulness z-score, age of onset, number of previous episodes, and marital status. (With the exception of marital status all of these covariates were also significantly associated with time to relapse when included in a model with MBCT status and its interaction with log(time), and all other covariates.) When included in a model with MBCT status and MBCT status varying with log(time), only four remained statistically significant: baseline depression z-score, baseline mindfulness z-score, age of onset, and number of previous episodes. However, on including all four predictors in a model with

MBCT and its interaction with log(time), the effect of baseline mindfulness became non-significant at the $p<0.05$ level. Thus, the significant predictors of depressive relapse were baseline depression z-score, age of onset, and number of previous episodes. When including the interaction with MBCT and each predictor in turn into this model, only baseline depression z-score had a significant interaction with MBCT status (Table 2, Model G; Figure 3), whereby patients with a higher baseline depression z-score received greater benefit from MBCT therapy compared with all non-MBCT treatments. Of the remaining covariates, only baseline mindfulness z-score had a significant interaction with MBCT status, both in a model with no other covariates and in a model with all other significant covariates. However, these interactions became non-significant when the interaction between MBCT status and baseline depression z-score was added to the model. No other covariates were found to have a significant interaction with MBCT status, either in a model including the respective covariate, MBCT status, their interaction, and MBCT status varying with log(time), or in that model plus all significant covariates.

Discussion

Summary of Results

Replicating previous work, we found clear evidence that MBCT significantly reduces the risk of depressive relapse/recurrence over 60 weeks compared with usual care. Extending previous work, we found that compared with the current mainstay approach, maintenance antidepressants, MBCT reduces the risk of depressive relapse/recurrence. We further showed that there is no support for MBCT having differential effects for patients based on their gender, age, education or relationship status, suggesting the intervention's generalizability across these characteristics. Different research groups conducted the nine RCTs, employing different clinicians,

across a range of European and North American countries. The lack of between study heterogeneity in effects on time to depressive relapse suggests that the effects of MBCT are similar in these different contexts.

MBCT was developed for patients in remission, but at high risk for depressive relapse/recurrence. Our analyses suggest that the treatment effect of MBCT on risk of depressive relapse/recurrence is larger in participants with higher levels of depression symptoms at baseline compared with non-MBCT conditions, suggesting that MBCT may be particularly helpful to those who still have significant depressive symptoms. This is consistent with several recent trials that suggest MBCT may be more effective for people whose depressive symptoms fluctuate (14) and/or who report a history of early adversity (18, 32). Adverse events were formally recorded in 6/9 studies but none were attributed to MBCT.

Strengths and limitations of the study

To address the questions of whether treatment effects are influenced by individual patient characteristics a study needs to be adequately powered and use appropriate statistical approaches. Within the constraints of the constituent studies our IPD approach provided an opportunity to answer these questions; risk of bias was low, suggesting confidence in these findings. Combining a series of modest sized trials, with effects in the predicted direction but missing significance individually, yields a significant combined estimate of effect.

We did observe some asymmetry in the funnel plot with an absence of smaller studies that themselves showed an increased risk of relapse with MBCT treatment. It is possible that there are unpublished studies that we are not aware of and we would welcome investigators of any such studies to bring them to our attention so that their data can be included in future updates. The unavailability of the Meadows study data

represents an impediment to IPD, transparency and external scrutiny. Funding bodies, ethics committees and sponsors should work to a consensus position. Finally, allegiance effects can influence effect sizes in psychological therapy trials (34), and the constituent trials were largely conducted by proponents of MBCT. Therefore, we included a risk of bias table (Online Supplement).

There were a number of limitations resulting from availability of data within the constituent studies. For example, we were not able to obtain information about important potential moderators such as ethnicity and employment. Trials also vary in the way data are collected. For example, age of first onset of depression was collected in some trials by simple self-report and in others through standardized structured clinical interview. Number of prior episodes was also gathered inconsistently. Adverse events were not systematically recorded/reported. As with all meta-analyses, there may be trials published in other languages or unpublished trials we were not able to access. Moderator analyses were not formally powered, exploratory, and relatively large in number, increasing the risk of Type I errors. Future studies should plan and power for moderator analyses.

Implications for practice and directions for future research

While previous research has shown MBCT's superiority compared with usual care (5), this study provides important new evidence that MBCT is also effective compared with other active treatments, and that its effects are not restricted to particular groups defined by age, educational level, marital status or gender. A recent meta-analysis of the effectiveness of all psychological interventions to prevent recurrence compared with usual care and antidepressants, suggests that MBCT's protective effects are comparable to those for cognitive therapy (vs usual care RR=0.68, 95% CI = 0.54,0.87; vs ADM RR=.079, 95% CI=0.61, 1,02) and

interpersonal therapy (vs usual care RR=0.41, 95% CI=0.27,0.63; vs ADM RR=.083, 95% CI=0.50, 1,38) (35). However, MBCT addresses a particular clinical problem, namely teaching skills to stay well to people currently well but at high risk of depressive relapse. There is a reduction in protective effects over time. The finding that MBCT may be most indicated for patients with higher levels of depressive symptoms adds to an emerging consensus that the greater the risk for depressive relapse/recurrence, the more benefit MBCT confers. Patients with lower baseline scores appeared to receive less benefit but were not disadvantaged by MBCT.

We recommend that future trials: consider an active control group, use comparable primary and secondary outcomes (Structured Clinical Interview for DSM for depressive relapse); use longer follow-ups; report treatment fidelity; collect key background variables (e.g. ethnicity, employment); take care to ensure generalizability; conduct cost-effectiveness analyses; put in place ethical and data management procedures that enable data sharing; consider mechanisms of action and; systematically record and report adverse events.

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Authorship: WK, FW, RST, BW and TD were responsible for the original proposal, securing resourcing for the study and drafting the original protocol. All authors (except SS & RH) contributed to refinement of the protocol. TD and SS conducted the database searches. FW carried out the data cleaning and analyses (under the supervision of RT), drafted the results and contributed to the interpretation of the data. GB, HM, CC, RH, AS, KVH, ZS, JT and JW were either corresponding authors and/or chief investigators of the constituent trials. WK, FW, TD and CC drafted the manuscript. WK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors revised the manuscript for important intellectual content and approved the final manuscript.

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FIGURES

Figure 1. PRISMA flow diagram from record identification to study inclusion.

Figure 2. Forest plot of 2-stage meta-analysis of aggregate data on hazard ratio scale comparing (a) risk of relapse of depression in participants receiving MBCT compared with participants not receiving MBCT; (b) risk of relapse of depression in participants receiving MBCT compared with participants not receiving MBCT, but receiving an alternative active therapy to prevent relapse/recurrence; and (c) risk of relapse of depression in participants receiving MBCT compared with participants not receiving MBCT, but receiving antidepressant medication.

Figure 3. Predictive margins for relative hazard for relapse of depression comparing participants receiving MBCT with those not receiving MBCT, at baseline depression z-scores, derived from a model including MBCT status, the interaction between MBCT status and log (time), baseline depression z-score, the interaction between MBCT status and baseline depression z-score, age of onset of depression, and number of past episodes of depression (five or more/four or fewer).

Online appendix *Figure A.* Funnel plot for random effects two-stage meta-analysis of MBCT vs non-MBCT.

Online appendix *Figure B.* Log-log plots comparing MBCT with non-MBCT for each of the nine included primary studies

TABLES

Table 1. Description of the nine primary studies of MBCT versus non-MBCT treatment.

Study	**Study population and country**	**Arms: *n* randomized**	**Patients with primary outcome data (60-week relapse status and time-to-relapse); n (% total *n* randomized), combining non-MBCT arms Total % missing**	**Person-weeks contributed to unadjusted analyses**	**Patients with final BDI[a] (closest available to 60 weeks; primary outcome data available)**	**Baseline BDI[a, b]; mean (SD), n**	**Mindfulness measure used**	**Patients with pre- and post-treatment mindfulness score (with primary outcome data available)**	**Serious Adverse Events (SAE)/Serious Adverse Reactions (SAR)**
Teasdale 2000	Community adults, with history of depression, currently in full remission, not on ADM at assessment UK, Canada	TAU: 69 MBCT: 76	Non-MBCT: 66 (96) MBCT: 70 (92) Total % missing: 6	Non-MBCT: 2363 MBCT: 3093	Non-MBCT: 65 MBCT: 65	11.4 (7.9), 132	Experiences questionnaire (36)	Non-MBCT: 12 MBCT: 14	Not formally recorded
Ma 2004	Community adults, with history of depression, currently in full remission, not on ADM at assessment UK	TAU: 38 MBCT: 37	Non-MBCT: 37 (97) MBCT: 36 (97) Total % missing: 3	Non-MBCT: 1237 MBCT: 1770	Non-MBCT: 33 MBCT: 34	13.9 (8.4), 73	Experiences questionnaire (36)	Non-MBCT: 31 MBCT: 32	Not formally recorded

Study	Study population and country	Arms: *n* randomized	Patients with primary outcome data (60-week relapse status and time-to-relapse); n (% total *n* randomized), combining non-MBCT arms Total % missing	Person-weeks contributed to unadjusted analyses	Patients with final BDI[a] (closest available to 60 weeks; primary outcome data available)	Baseline BDI[a, b]; mean (SD), n	Mindfulness measure used	Patients with pre- and post-treatment mindfulness score (with primary outcome data available)	Serious Adverse Events (SAE)/Serious Adverse Reactions (SAR)
Kuyken 2008	Community adults, with history of three or more episodes of depression, currently in remission, on ADM UK	ADM: 62 MBCT: 61	Non-MBCT: 62 (100) MBCT: 61 (100) Total % missing: 0	Non-MBCT: 2271 MBCT: 2592	Non-MBCT: 58 MBCT: 59	19.3 (11.9), 123	KIMS (37)	Non-MBCT: 58 MBCT: 55	No SARs, in either arm.
Bondolfi 2010	Community adults, with history of three or more episodes of depression, currently in remission, not on ADM at assessment Switzerland	TAU: 29 MBCT: 31	Non-MBCT: 29 (100) MBCT: 31 (100) Total % missing: 0	Non-MBCT: 1205 MBCT: 1386	Non-MBCT: 26 MBCT: 26	9.9 (9.0), 60	MAAS (38)	Non-MBCT: 29 MBCT: 28	Not formally recorded, author communication that none were recorded.
Godfrin 2010	Community adults, with	TAU: 54 MBCT: 52	Non-MBCT: 47 (87) MBCT: 40 (77)	Non-MBCT: 1690	Non-MBCT: 40	19.9 (12.2), 86	MAAS (38)	Non-MBCT: 47	Not formally recorded

Study	Study population and country	Arms: *n* randomized	Patients with primary outcome data (60-week relapse status and time-to-relapse); n (% total *n* randomized), combining non-MBCT arms Total % missing	Person-weeks contributed to unadjusted analyses	Patients with final BDI[a] (closest available to 60 weeks; primary outcome data available)	Baseline BDI[a, b]; mean (SD), n	Mindfulness measure used	Patients with pre- and post-treatment mindfulness score (with primary outcome data available)	Serious Adverse Events (SAE)/Serious Adverse Reactions (SAR)
	history of at least 3 episodes of depression, currently in remission. Included patients on and off ADM at assessment. Belgium		Total % missing: 18	MBCT: 1964	MBCT: 35			MBCT: 37	
Segal[c] 2010	At point of randomization to MBCT, community adults, with history of depression, currently in full remission after 8 months of	Maintenance ADM: 28 MBCT+Discontinue ADM: 26	Non-MBCT: 28 (100) MBCT: 26 (100) Total % missing: 0	Non-MBCT: 1002 MBCT: 1007	Non-MBCT: 7 MBCT: 11	4.0 (3.9), 51	MAAS (38)	Non-MBCT: 10 MBCT: 15	1 SAE in acute phase (ADM arm) and in the follow up phase 0 SAE in both arms of the trial.

Study	Study population and country	Arms: *n* randomized	Patients with primary outcome data (60-week relapse status and time-to-relapse); n (% total *n* randomized), combining non-MBCT arms Total % missing	Person-weeks contributed to unadjusted analyses	Patients with final BDI[a] (closest available to 60 weeks; primary outcome data available)	Baseline BDI[a, b]; mean (SD), n	Mindfulness measure used	Patients with pre- and post-treatment mindfulness score (with primary outcome data available)	Serious Adverse Events (SAE)/Serious Adverse Reactions (SAR)
	algorithm-informed ADM in an earlier study phase Canada								
Huijbers (2015)	Community adults, with history of three episodes of depression, currently in remission, on ADM Netherlands	Maintenance ADM: 35 MBCT+ADM: 33	Maintenance ADM: 35 (100) MBCT+ADM: 33 (100) Total % missing: 0	Non-MBCT: 1342 MBCT: 1433	Non-MBCT: 28 MBCT: 28	12.1 (9.6), 68	FFMQ (39)	Non-MBCT: 27 MBCT: 26	No SARs, in either arm
Kuyken (2015)	Community adults, with history of three episodes of depression, currently in	Maintenance ADM: 212 MBCT+discontinue ADM: 212	Maintenance ADM: 202 (95) MBCT+discontinue ADM: 200 (94) Total % missing: 5	Non-MBCT: 8882 MBCT: 9471	Non-MBCT: 157 MBCT: 167	14.1 (10.2), 396	FFMQ (40)	Non-MBCT: 169 MBCT: 173	10 SAEs (5 MBCT; 5 ADM, of which none judged SAR)

Study	Study population and country	Arms: *n* randomized	Patients with primary outcome data (60-week relapse status and time-to-relapse); n (% total *n* randomized), combining non-MBCT arms Total % missing	Person-weeks contributed to unadjusted analyses	Patients with final BDI[a] (closest available to 60 weeks; primary outcome data available)	Baseline BDI[a, b]; mean (SD), n	Mindfulness measure used	Patients with pre- and post-treatment mindfulness score (with primary outcome data available)	Serious Adverse Events (SAE)/Serious Adverse Reactions (SAR)
	remission, on ADM UK								
Williams (2014)	Community adults, with history of at least 3 episodes of depression, currently in remission, on ADM UK	TAU: 56 CPE: 110 MBCT: 108	TAU: 53 (95) CPE: 103 (94) MBCT: 99 (92) Total % missing: 7	Non-MBCT: 6022 MBCT: 4199	Non-MBCT: 135 MBCT: 88	8.0 (7.8), 255	FFMQ (40)	Non-MBCT: 138 MBCT: 87	15 SAEs (5 MBCT; 10 CPE, of which 1 in CPE condition judged SAR).

[a]Huijbers used IDS-C. [b]Includes all participants irrespective of trial arm. [c]Placebo arm excluded. ADM: antidepressant medication. CPE: cognitive psychological education. FFMQ: Five Facet Mindfulness Questionnaire. KIMS: Kentucky Inventory of Mindfulness Scale. MAAS: Mindful Attention Awareness Scale. MBCT: mindfulness based cognitive therapy. TAU: treatment as usual.

Table 2. Cox proportional hazards regression models and flexible parametric survival models.

Covariate	HR (95% CI)	*p*-value
Model A[a]. N participants: 1248. N depressive relapses: 554.		
MBCT status (reference: non-MBCT)	0.69 (0.58 to 0.82)	<0.001
Model B[a]. N participants: 1248. N depressive relapses: 554.		
MBCT status (reference: non-MBCT)	0.34 (0.19 to 0.60)	<0.001
MBCT by log(time[b])	1.28 (1.06 to 1.55)	0.010
Model C[a]. N participants: 892. N depressive relapses: 385.		
MBCT status (reference: active treatments) MBCT	0.78 (0.64 to 0.96)	0.02
Model D[a]. N participants: 637. N depressive relapses: 266.		
MBCT status (reference: anti-depressant medication)	0.77 (0.60 to 0.98)	0.03
Model E[c]: N participants: 1248. N depressive relapses: 554. Between study standard deviation: 0.0008.		
MBCT status (reference: non-MBCT)	0.68 (0.58 to 0.81)	<0.001
Model F[d]: N participants: 1248. N depressive relapses: 554. Between study standard deviation: 0.0007.		
MBCT status (reference: non-MBCT)	0.63 (0.53 to 0.76)	<0.001
Model G[a,e] . N participants: 1105. N depressive relapses: 481.		
MBCT status (reference: non-MBCT) MBCT	0.31 (0.16 to 0.57)	<0.001
MBCT by log(time[a])	1.34 (1.09 to 1.64)	0.006
Baseline depression z-score	1.49 (1.33 to 1.67)	<0.001
MBCT status x baseline depression z-score	0.81 (0.67 to 0.96)	0.018

[a]Cox proportional hazards regression model stratified by individual study. [b]Time measured in weeks. [c]Flexible parametric model with 2 degrees of freedom, random treatment effects. [d]As Model E with inclusion of interaction between MBCT status and restricted cubic splines to account for time-varying effect of MBCT; global *p*-value for interaction between MBCT status and restricted cubic splines 0.04. [e]Model adjusted for age of onset of depression and number of past episodes of depression (five or more/four or fewer).

Figure 1

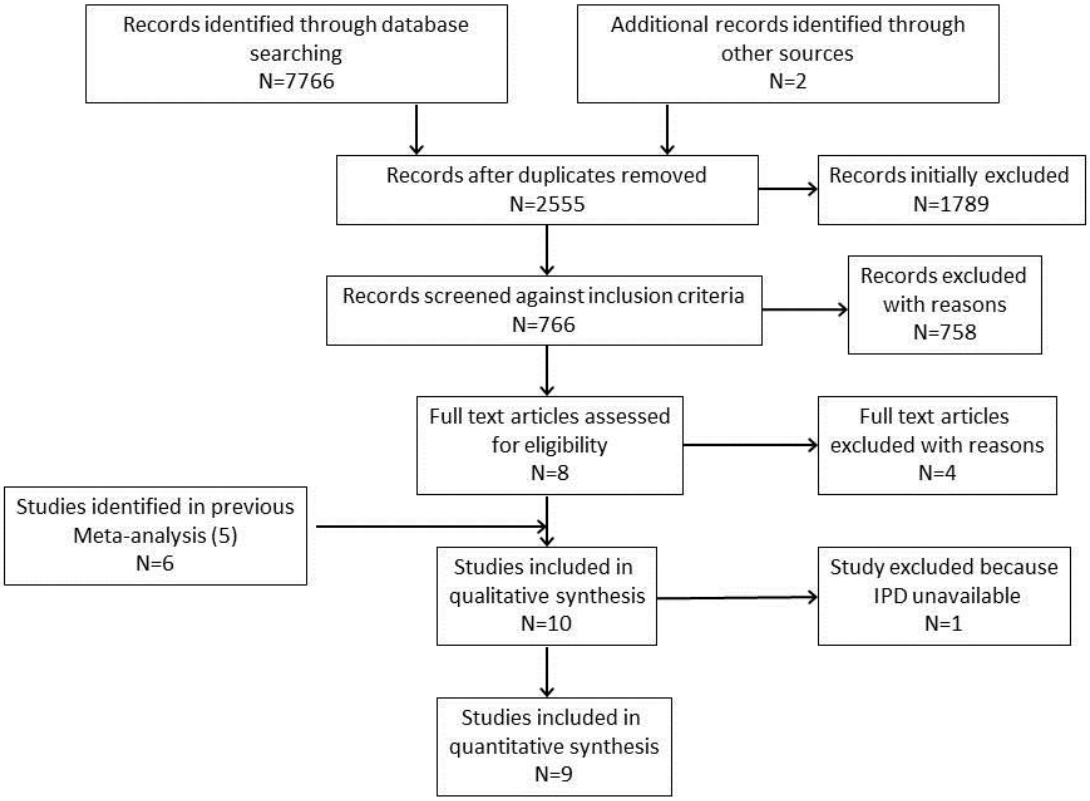
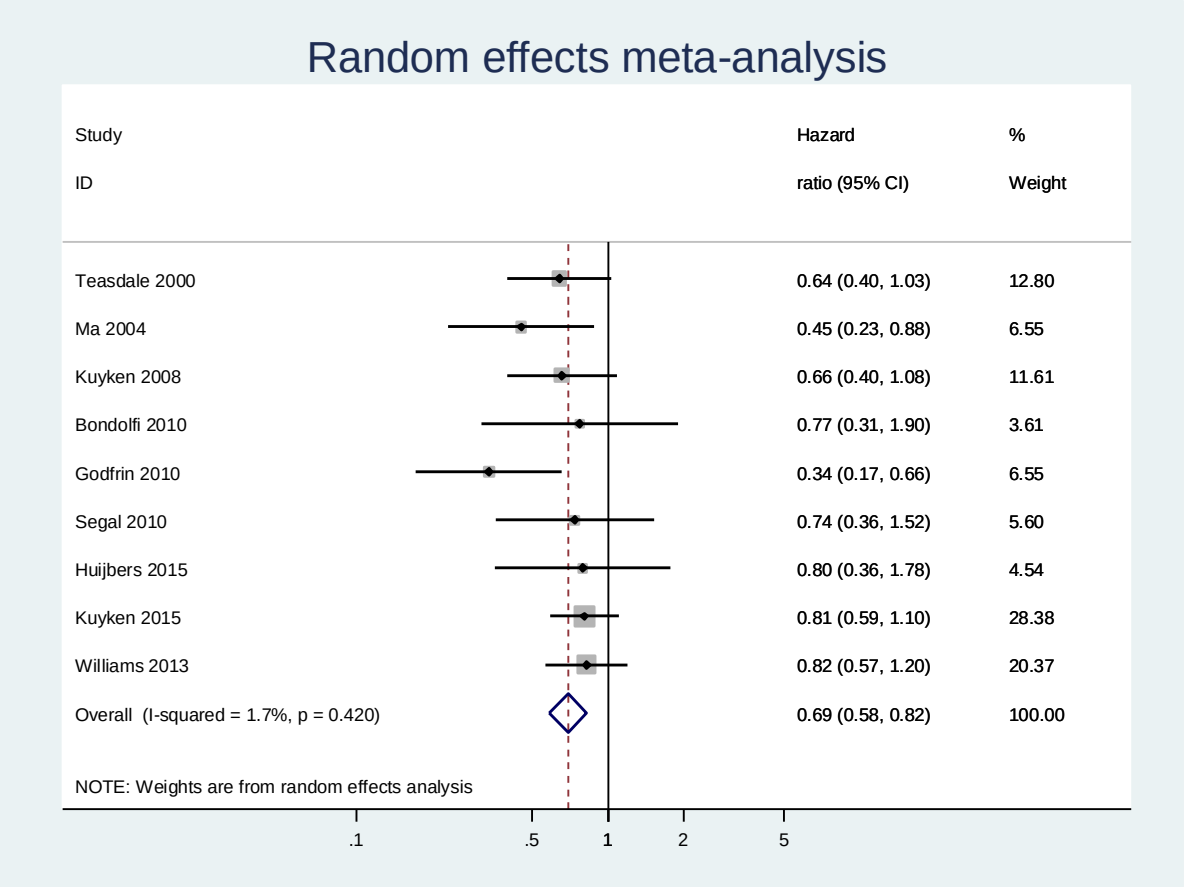
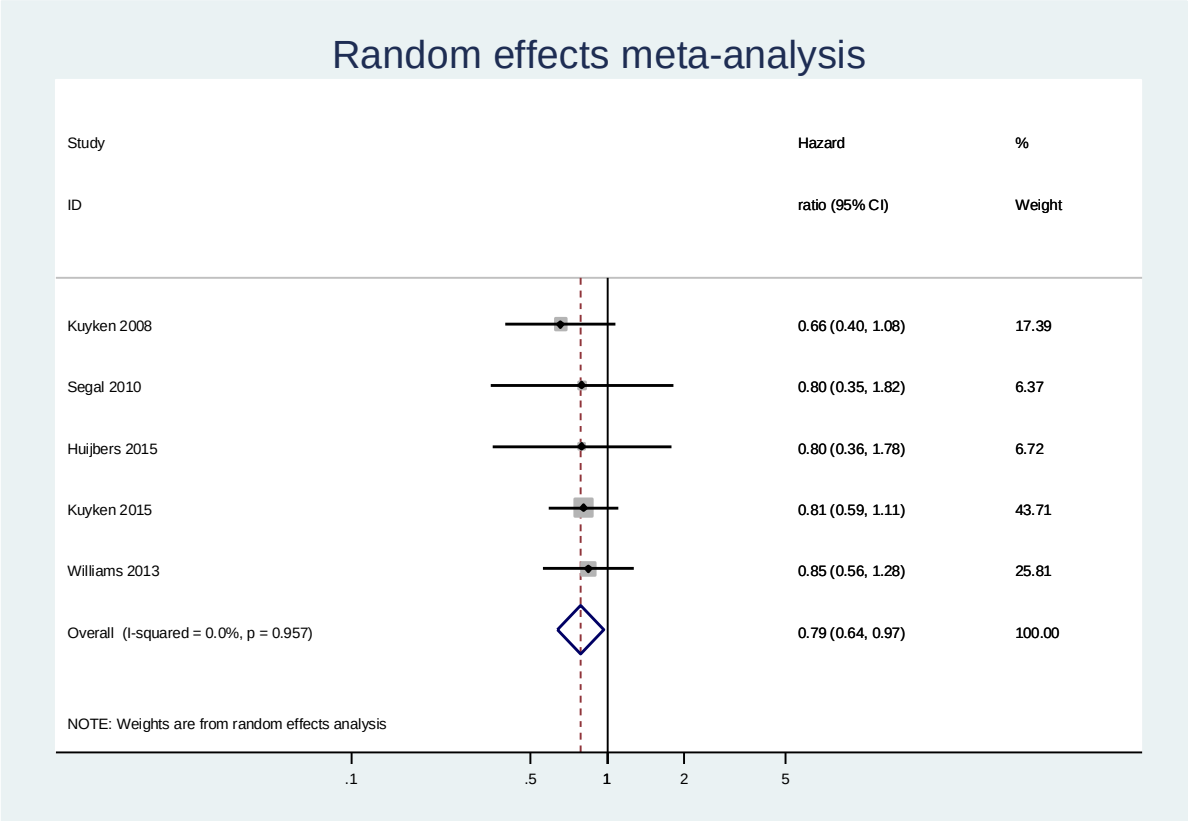


Figure 1. PRISMA flow diagram from record identification to study inclusion.

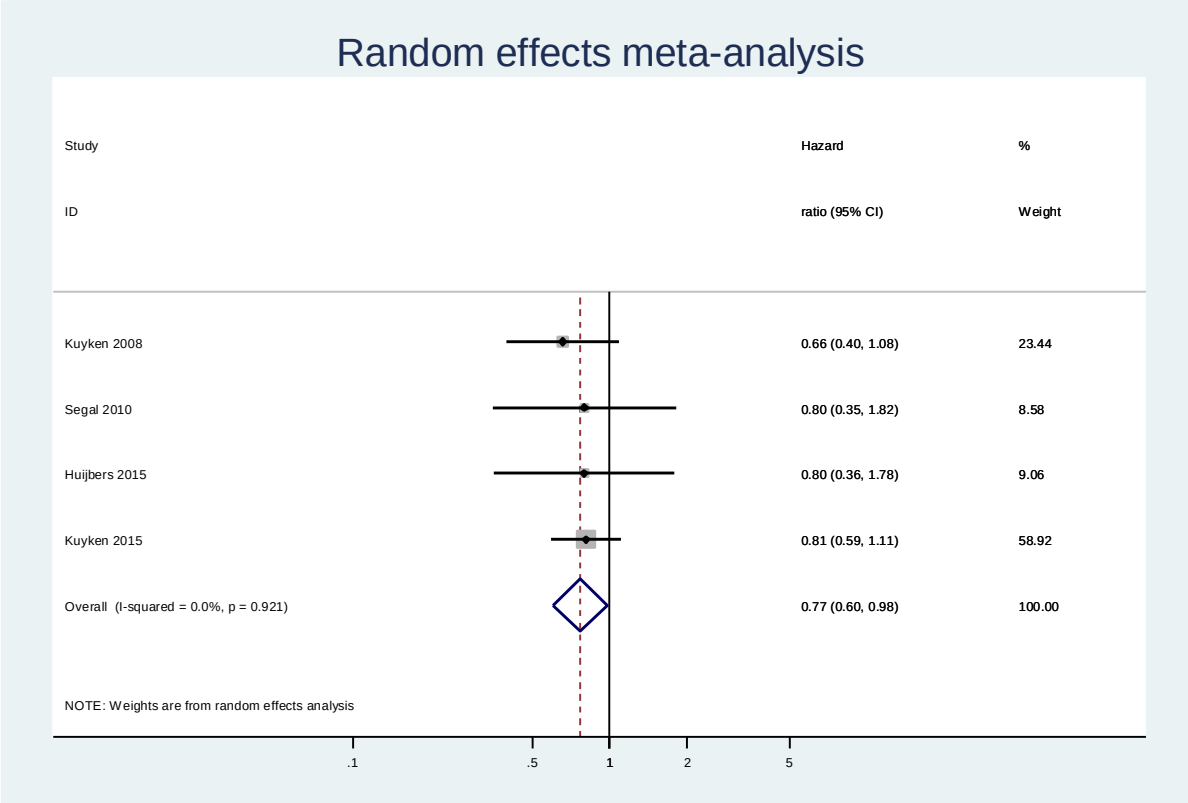
Figure 2



a) Forest plot of 2-stage meta-analysis of time to relapse of depression comparing MBCT with no MBCT.



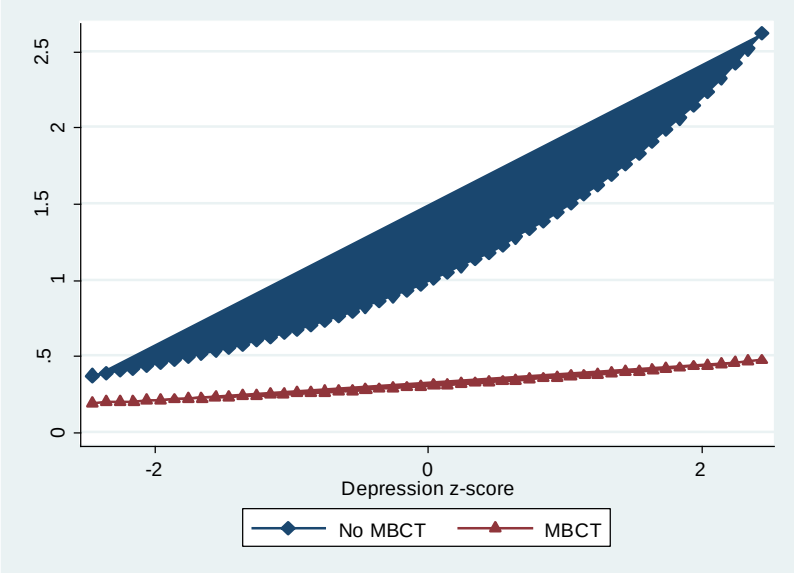
b) Forest plot of 2-stage meta-analysis of time to relapse of depression comparing MBCT with any active treatment.



c) Forest plot of 2-stage meta-analysis of time to relapse of depression comparing MBCT with anti-depressant medication.

MBCT: mindfulness based cognitive therapy.

Figure 3. Predictive margins for relative hazard for relapse of depression comparing participants receiving MBCT with those not receiving MBCT, at baseline depression z-scores, derived from a model including MBCT status, MBCT status interacted with log (time), baseline depression z-score, interaction between MBCT status and baseline depression z-score, age of onset of depression, and number of past episodes of depression (five or more/four or fewer).



Online Appendices
Table A. Cochrane Collaboration tool for assessment of risk of bias

Cochrane Collaboration tool for assessment of risk of bias

Primary study	**Domain**	**Description**	**Review authors' judgement**
Teasdale 2000	Sequence generation	Participants were randomized within site based on two baseline variables with reference to a random number table or by using a computer to generate random numbers.	Low risk
	Allocation concealment	Randomization performed by central independent allocator remote from treatment sites, which randomly assigned participants to treatment allocation and conveyed allocations back to treatment sites.	Low risk
	Blinding of participants, personnel and outcome assessors	Participants could not be blinded due to nature of intervention. Assessments of outcome were made by assessors blinded to treatment condition; however, occasional unblinding did occur. To mitigate this, interviews to assess outcomes were audiotaped and evaluated by an independent research psychiatrist who was blind to allocation and with any information that would reveal allocation excluded .	Moderate risk

	Incomplete outcome data	9/145 (6%) participants had missing primary outcome data.	Low risk
	Selective outcome reporting	Only one outcome (time to relapse of depression) was included in our review, which was reported in the paper.	Low risk
	Other sources of bias	No additional sources of bias identified.	Low risk
Ma 2004	Sequence generation	Randomization was stratified based on two baseline binary variables with reference to a random number table or by using a computer to generate random numbers.	Low risk
	Allocation concealment	Randomization was performed by a statistician who was not part of the research team.	Low risk
	Blinding of participants, personnel and outcome assessors	Participants could not be blinded due to nature of interventions. Assessments of outcome were performed by a clinical psychologist blind to allocation. Interviews were audiotaped and evaluated by an independent blind research psychiatrist, with any information that may prejudice blindness removed from the tapes.	Moderate risk
	Incomplete outcome data	2/75 (3%) participants had missing primary outcome data.	Low risk.

	Selective outcome reporting	Only one outcome (time to relapse of depression) was included in our review, which was reported in the paper.	Low risk
	Other sources of bias	No additional sources of bias identified.	Low risk
Kuyken 2008	Sequence generation	Block randomization (block size 4) to the two groups was performed by an independent statistician using computer-generated quasi-random numbers. Randomization was stratified using one baseline variable.	Low risk
	Allocation concealment	Randomization was performed by an independent statistician	Low risk
	Blinding of participants, personnel and outcome assessors	Participants could not be blinded due to nature of interventions. Participants were assessed by research staff who were blind to treatment allocation; however, occasional unblinding did occur. To mitigate this, interviews to assess outcomes were audiotaped and evaluated by an independent research psychiatrist who was blind to allocation and with any information that would reveal allocation excluded .	Moderate Risk[c]
	Incomplete outcome data	0/123 (0%) participants had missing outcome data.	Low risk

	Selective outcome reporting	Only one outcome (time to relapse of depression) was included in our review, which was reported in the paper.	Low risk
	Other sources of bias	No additional sources of bias identified.	Low risk
Bondolfi 2010	Sequence generation	Randomization was performed using a stratified block randomization procedure based on three stratification factors. This included shuffling envelopes and random envelope selection within each stratum.	High risk
	Allocation concealment	Randomization was performed using a stratified block randomization procedure based on three stratification factors. It proceeded through shuffling envelopes and random selection within each stratum by someone independent oft he trial team.	Low risk
	Blinding of participants, personnel and outcome assessors	Participants could not be blinded due to the nature of the interventions. Participants were instructed not to inform the research team about group assignment to ensure that blind outcome assessment could be performed. When a person was	Low Risk

		unblinded inadvertently (very rare occasions 3 participants), the audiotaped evaluation (rating scales, etc) was re-evaluated by an independent evaluator. The rating of the relapses were systematically evaluated by an independent evaluator.	
	Incomplete outcome data	0/60 (0%) participants had missing outcome data.	Low risk
	Selective outcome reporting	Only one outcome (time to relapse of depression) was included in our review, which was reported in the paper.	Low risk
	Other sources of bias	No additional sources of bias identified.	Low risk
Godfrin 2010	Sequence generation	Participants were allocated to their intervention using a computer generated randomization procedure.	Low risk
	Allocation concealment	The sequence of allocation to the study groups was concealed until assignment. Participants were informed of their allocation by the study coordinator.	Low risk
	Blinding of participants, personnel and outcome assessors	Participants could not be blinded due to the nature of the interventions. Participants were assessed by a	High Risk

		psychologist who was not blind to treatment allocation.	
	Incomplete outcome data	19/106 (18%) participants had missing outcome data.	High risk
	Selective outcome reporting	Only one outcome (time to relapse of depression) was included in our review, which was reported in the paper.	Low risk
	Other sources of bias	No additional sources of bias identified.	Low risk
Segal 2010	Sequence generation	Block randomization was performed using computer generated quasi-random numbers.	Low risk
	Allocation concealment	Randomization was performed by an independent statistician. Allocation was communicated to the coordinator once patient eligibility was confirmed.	Low risk
	Blinding of participants, personnel and outcome assessors	Participants could not be blinded due to the nature of the interventions. Participants were assessed by clinical evaluators blind to treatment allocation. There was no third party independent re-rating of interviews.	Moderate risk[c]
	Incomplete outcome data	0/54 (0%) participants had missing outcome data.	Low risk
	Selective outcome reporting	Only one outcome (time to relapse of depression) was included in our	Low risk

		review, which was reported in the paper.	
	Other sources of bias	No additional sources of bias identified.	Low risk.
Huijbers 2015 (MOMENT1)	Sequence generation	Randomization was performed using a website based application, with minimisation on five factors.	Low risk
	Allocation concealment	Randomization was performed by an independent statistician. Allocation was communicated to participants by research assistants after eligibility confirmed.	Low risk
	Blinding of participants, personnel and outcome assessors	Participants could not be blinded due to nature of interventions. Research assistants performing outcome assessments were not blinded to intervention. A sample of assessment interviews was assessed by blind raters and inter-rater agreement found to be high.	High risk[c]
	Incomplete outcome data	0/68 participants had missing outcome data.	Low risk
	Selective outcome reporting	Only one outcome (time to relapse of depression) was included in our review, which was reported in the paper.	Low risk
	Other sources of bias	No additional sources of bias identified.	Low risk

Kuyken 2015 (PREVENT)	Sequence generation	Participants were allocated using a computer generated quasi random number sequence stratified by two factors.	Low risk
	Allocation concealment	Allocation was undertaken using a password protected website maintained by a Clinical Trials Unit, independent of the trial. Participants were informed of the outcome of randomisation via a letter sent from the trial administrator.	Low risk
	Blinding of participants, personnel and outcome assessors	Participants could not be blinded due to nature of the interventions. Research assessors remained blind to treatment allocation for the duration of the follow-up period. If an assessor knowingly became unblinded, which occurred in only a very small proportion of cases, an alternative assessor was used for subsequent assessments [a]	Moderate Risk[c]
	Incomplete outcome data	22/424 (5%) participants has missing outcome data.	Low risk
	Selective outcome reporting	Only one outcome (time to relapse of depression) was included in our review, which was reported in the paper.	Low risk

	Other sources of bias	No additional sources of bias identified.	Low risk
Williams 2013 (SWAD)	Sequence generation	Randomization was performed using dynamic allocation (retaining a stochastic component in each allocation) with stratification by four variables.	Low risk
	Allocation concealment	Randomization was conducted by email contact with the independent randomizing organization. Participants were informed of their allocation by letter, email or telephone.	Low risk
	Blinding of participants, personnel and outcome assessors	Participants could not be blinded due to nature of interventions. Assessors were blinded to intervention allocation. Assessor blindedness was checked after every assessment session. If an assessor knowingly became unblinded, which occurred in only a very small proportion of cases, an alternative assessor was used for subsequent assessments[b].	Moderate risk[c]
	Incomplete outcome data	19/274 (7%) participants had missing outcome data.	Low risk
	Selective outcome reporting	Only one outcome (time to relapse of depression) was included in our	Low risk

		review, which was reported in the paper.	
	Other sources of bias	No additional sources of bias identified.	Low risk

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[a]The fidelity of this masking was moderate with assessors correctly guessing allocation for 56% of assessments. However inter-rated agreement for the subset of diagnostic interviews that were re-rated by an independent rater indicated an agreement rate of 89.9% (additional information obtained from authors)

[b]A sample of all assessment interviews was re-rated by an independent psychiatrist and inter-rater agreement was found to be high at 87% (additional information obtained from authors).

[c]Although a small proportion of assessments are likely to have been carried out by assessors who were able to guess random allocation we estimate that the overall risk associated with this is low to moderate, and do not consider it likely that the outcome was substantially influenced by any lack of blinding. This conclusion is drawn particularly in view of the fact that studies which conducted independent third party blind rating of interviews (SWAD, PREVENT) found high levels of agreement with original assessor ratings. Indeed inter-rater agreement was also high in MOMENT 1 which did not employ blind assessors. However we conservatively list the risk associated with blinding in these studies as moderate (high in the case of MOMENT 1) to reflect the fact that complete blinding of outcome assessments was not possible. We have categorised Bondolfi et al (2010) as low risk on blinding because all three interviews in which unblinding occurred were re-rated independently.

Table B. Full search string used to identify relevant papers in PubMed/Medline search

Selection of publications to explain PRIMSA diagram in Figure 1 in more detail.	The search strategy identified 7768 publications. Duplicates were removed, and abstracts from the remaining 2555 publications were screened. Reviews, qualitative studies, case studies, dissertation abstracts, study protocols, and non-English articles were excluded (N=1789). (In this article, N refers to number of studies; n to number of participants). The remaining 766 articles were selected for further screening, and exclusion was carried out for the following reasons: a) no MBCT intervention (N=617) or b) did not use with MBCT for prevention of relapse in recurrent major depressive disorder (N=122), or c) did not use a randomized controlled design (N = 19). Eight full text articles on studies investigating the effect of MBCT on MDD relapse were retrieved and assessed for eligibility. One full text article was excluded (12) because it was a follow-up analysis of an included study (13). Three full-text articles duplicated articles identified in the previous meta-analysis (13-15). The six studies identified in the previous meta-analysis (5) along with the four new identified studies, fulfilling the inclusion criteria, were therefore finally selected for synthesis.
PubMed/Medline Search String	((((("2010/11/1"[Date - Publication] : "2014/11/30"[Date - Publication])) AND MBCT[Title/Abstract]) AND depress*[Title/Abstract])) OR ((((("2010/11/1"[Date - Publication] : "2014/11/30"[Date - Publication])) AND mindfulness based cognitive therapy[Title/Abstract]) AND depress*[Title/Abstract])) OR ((((("2010/11/1"[Date - Publication] : "2014/11/30"[Date - Publication])) AND mindfulness-based cognitive therapy[Title/Abstract]) AND depress*[Title/Abstract])

Table C. Elaboration of the IPD data extraction, checking and management

Data extraction and checking	One study comprised two related trials, only one of which met our inclusion criteria (Huijbers). Two important dimensions on which the trials differed were their inclusion criteria with respect to antidepressant medication and their comparator group. We were unable to obtain IPD or aggregate data from one trial (Meadows trial), which compared MBCT with a psychotherapy control and included 203 participants, due to legal/ethical constraints raised by the corresponding author. Each individual trial dataset was checked to ensure that the number of participants by arm corresponded with the primary reference. Data queries were resolved by communication with the trial authors. Some minor inconsistencies between the original papers and our results were observed. We checked the raw numbers of relapses reported for each paper against the datasets we were given. Checking the HRs against the 2-stage MA was not always feasible. 1) Teasdale: this data set has extra data not included in their paper (ie so the raw numbers of relapses differ from those reported). Also, they report separate HRs for patients with 3+/<3 past episodes, to emphasise a moderator effect, namely that patients with 3+ episodes benefit from MBCT but not those with <3. 2) Ma: takes same approach as Teasdale. They report an HR for patients with 3+ episodes which we can replicate with their data (no HR for patients with <3 episodes is reported). Also, the raw numbers of relapses by treatment group reported in the paper match our dataset. They report a planned HR for the interaction between MBCT status and number of episodes, which also replicates with our data. 3) Kuyken: reports HR for 15 months rather than 60 weeks, but the 15 month HR is very similar to that resulting from 2-stage MA. The raw numbers of relapses by arm are the same in the paper as in our dataset. 4) Bondolfi: reports only non-significant p-values for their Cox regression model, which is consistent with 2-stage MA. The raw numbers of relapses by group are consistent with our IPD. 5) Godfrin: reports a Cox model with adjustment for HRSD and BDI as well as treatment group. We get slightly different results: Godfrin hazard ratio 0.23 (95% CI: 0.09 to 0.63), vs 0.33 (0.17 to 0.65). The raw data for number of relapses by group corresponded with the paper, although the

	Godfrin paper was not clear on the details of modelling used to derive the reported HRs. We assume that our data as received are correct. 6) Segal: results are reported separately for stable remitters and unstable remitters. For unstable remitters they get an HR of 0.26 (95% confidence interval [CI], 0.09-0.79) for MBCT vs placebo (we get 0.27 (0.09; 0.80)) and 0.24 (95% CI, 0.07-0.89) for ADM vs placebo (we get 0.28 (0.08; 1.02)), so similar. For stable remitters they say that both MBCT and ADM were had a non-significant HR vs placebo. The raw figures for relapses by group correspond to placebo. 7) Huijbers MOMENT1: results are reported over a 15 month FU period as opposed to 60 weeks. Their reported HR can be replicated from their data and the raw numbers of relapses by group also match. 8) Kuyken: the HR reported is 24 months not 60 weeks (but 60 weeks HR is similar). 9) Williams: they report an HR for MBCT vs CPE and MBCT vs TAU, which can replicated virtually identically from our data (minor discrepancies in their reported MBCT vs CPE and ours probably due to them using days to relapse which we converted to weeks.).
Coding of moderator variables	Education level was separated into three categories: no qualifications, qualifications below degree level, and degree or higher. Relationship status was subdivided into three categories: married/cohabiting, single, and divorced/separated/widowed. Data on social class, ethnicity, and employment status were inconsistently collected across primary studies and these factors were not included in analyses. Two trials suggested that number of previous episodes (fewer than three episodes versus three episodes or more) was a moderator (6, 7) and all subsequent trials therefore only included patients with three or more episodes. To enable adequate numbers in each category we used fewer than five episodes versus five episodes or more to dichotomize this variable. One trial only included <5/5+ (6). If appropriate data were not available, then the variable was coded as missing for that participant.

Figure A Funnel plot for random effects meta-analysis of MBCT vs no MBCT.

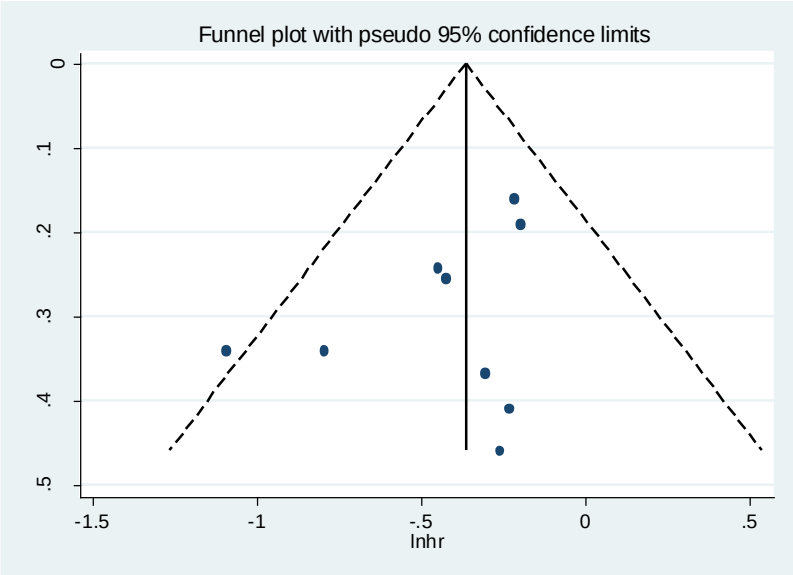

Figure B Log-log plots comparing MBCT with no MBCT for each of the nine included primary studies.