The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: A systematic review and meta-analysis

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A B S T R A C T

Background: Mindfulness-based cognitive therapy (MBCT) is a group-based clinical intervention program designed to reduce relapse or recurrence of major depressive disorder (MDD) by means of systematic training in mindfulness meditation combined with cognitive-behavioral methods.
Objective: By means of a meta-analysis to evaluate the effect of MBCT for prevention of relapse or recurrence among patients with recurrent MDD in remission.
Method: Electronic databases were searched and researchers were contacted for further relevant studies. Studies were coded for quality. Meta-analyses were performed by means of the Cochrane Collaboration Review Manager 5.1.
Results: Six randomized controlled trials with a total of 593 participants were included in the meta-analysis. MBCT significantly reduced the risk of relapse/recurrence with a risk ratio of 0.66 for MBCT compared to treatment as usual or placebo controls, corresponding to a relative risk reduction of 34%. In a pre-planned subgroup analysis the relative risk reduction was 43% for participants with three or more previous episodes, while no risk reduction was found for participants with only two episodes. In two studies, MBCT was at least as effective as maintenance antidepressant medication.
Conclusion: Results of this meta-analysis indicate that MBCT is an effective intervention for relapse prevention in patients with recurrent MDD in remission, at least in case of three or more previous MDD episodes.

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Contents

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1. Introduction

Originating from ancient eastern meditation and yoga traditions, mindfulness is generally described as a particular way of paying attention characterized by intentional and non-judgmental observation of present moment experiences, including bodily sensations, feelings, thoughts, and external stimuli from the environment (e.g. Baer, 2003; Grossman, Niemann, Schmidt, & Walach, 2004; Kabat-Zinn, 1994). Mindfulness-training, assumed to cultivate this capacity of awareness, has been adapted into clinical intervention programs including mindfulness-based stress reduction (MBSR) (Kabat-Zinn, 1990), and mindfulness-based cognitive therapy (MBCT) (Segal, Williams, & Teasdale, 2002). MBCT is an 8-session group intervention program with 8–15 participants designed for prevention of relapse or recurrence among patients with major depressive disorder (MDD) in remission.

MDD is a common mental disorder with a lifetime prevalence rate of about 20% (Kessler et al., 2005), and it is associated with a high degree of subjective distress and psychosocial disability (Judd et al., 2000). According to a recent report by the World Health Organization (WHO), MDD is currently the leading cause of disease burden, as measured by disability-adjusted life years (DALYs), in the United States of America and other middle- and high-income countries (WHO, 2008). Furthermore MDD is expected to be the leading cause of disease burden worldwide by the year 2030 (Ibid.). While the outlook for a first episode of MDD is rather good with spontaneous remission in most cases, the prognosis in the long run will often be poor with very high relapse or recurrence rates (50–90%); especially in case of prior depressive episodes (Judd, 1997; Mueller et al., 1999). With each new MDD episode the risk of worsening the course of the disease increases (Kessing, Hansen, Andersen, & Angst, 2004), and about 20% develops into chronic MDD with symptoms persisting for more than two years (Keller & Boland, 1998). Therefore, development of effective prevention interventions for MDD is a high priority enterprise within mental health.

The underlying model of MBCT specifies that previously depressed persons are characterized by greater cognitive vulnerability to states of low mood, as even mild dysphoric states may reactivate patterns of negative, ruminative thinking similar to those of previous episodes, causing the configuration of depression to be re-established (Segal, Williams, Teasdale, & Gemar, 1996; Teasdale, 1988; Teasdale, Segal, & Williams, 1995). MBCT may be assumed to work by targeting rumination and emotional avoidance, both considered to be maintaining processes across mood and anxiety disorders (e.g. Barlow, Allen, & Choate, 2004; Harvey, Watkins, Mansell, & Shafran, 2004; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996).

It has been claimed (e.g., Teasdale, Segal, & Williams, 2003) that MBCT particularly benefits patients with three or more MDD episodes, since such patients are especially prone to engage in ruminative thinking. In fact, two randomized controlled trials (RCTs) (Ma & Teasdale, 2004; Teasdale et al., 2000), both of which stratified participants prior to randomization by number of episodes (2 versus 3 or more), found that MBCT only lowered risk of relapse in case of three or more MDD episodes.

MBCT integrates elements of cognitive behavioral therapy for depression (CBT) (Beck, Rush, Shaw, & Emery, 1979) with training in mindfulness meditation (Kabat-Zinn, 1990). The aim of MBCT is to teach patients to become more aware of and relate differently to their thoughts, feelings, and bodily sensations. Through the practice of mindfulness exercises, such as the body scan, simple yoga exercises, and prolonged periods of sitting meditation, patients are taught to 'turn towards' and accept intense bodily sensations and emotional discomfort, and they are provided with cognitive skills that allow them to recognize the automatic activation of habitual dysfunctional cognitive processes, such as depression-related rumination, to detach or "decentre" from the content of negative thoughts, and to disengage

from these processes by redirecting attention to experiences as they flux and change moment by moment.

Since the protocol release in 2002, MBCT has been adapted to different psychological disorders and conditions, and empirical research on the effectiveness of MBCT has expanded greatly. There is preliminary evidence of the effect of MBCT on pre-post symptoms of depression in people with fully or partially remitted depression (Britton, Haynes, Fridel, & Bootzin, 2010; Crane et al., 2008; Kingston, Dooley, Bates, Lawlor, & Malone, 2007); currently symptomatic depression (Barnhofer et al., 2009; Eisendrath et al., 2008; Kenny & Williams, 2007; Manicavasgar, Parker, & Perich, 2011; Mathew, Hayley, Kenny, & Denson, 2010); bipolar disorder (Miklowitz et al., 2009; Williams et al., 2008); social phobia (Piet, Hougaard, Hecksher, & Rosenberg, 2010); and generalized anxiety disorder (Craigie, Rees, Marsh, & Nathan, 2008; Evans et al., 2008). In a recent meta-analysis of mindfulness-based therapy, including MBSR and MBCT for different medical and psychological disorders, Hofmann, Sawyer, Witt, and Oh (2010) found a large pre-post effect size (Hedges's $g = 0.85$) of MBCT for symptoms of depression. Additionally, studies have found that MBCT reduces overgeneral autobiographical memory, which has been associated with depression and a number of detrimental effects on functioning (Heeren, Van Broeck, & Philippot, 2009; Williams, Teasdale, Segal, & Soulsby, 2000).

Research investigating potential mechanisms of action in MBCT is in its infancy. Recent studies suggest that the effect of MBCT may be facilitated or mediated by improved meta-awareness (Hargus, Crane, Barnhofer, & Williams, 2010; Teasdale et al., 2002); increased mindfulness and self-compassion (Kuyken et al., 2010); decreased rumination (Shahar, Britton, Sbarra, Figueredo, & Bootzin, 2010); reduced cognitive reactivity (Raes, Dewulf, Van Heeringen, & Williams, 2009); and a balanced pattern of emotion related brain activation (Barnhofer et al., 2007). Two studies on recovered recurrently depressed patients, respectively found increased mindfulness and reduced rumination during MBCT, and showed that post treatment levels of mindfulness and rumination significantly predicted MDD relapse over a 12 month follow-up period, even after controlling for residual depressive symptoms and number of previous episodes (Michalak, Heidenreich, Meibert, & Schulte, 2008; Michalak, Hölz, & Teismann, 2010).

Coelho, Canter, and Ernst (2007) conducted the first narrative review of controlled clinical trials of MBCT for participants with a history of depression. They identified two studies focussing on MBCT as a preventive treatment for recurrent MDD, and tentatively concluded that the program had an additive benefit to usual care for patients with three or more previous episodes of depression. Chiesa and Serretti (2011) recently reviewed 16 controlled studies of MBCT for different psychiatric disorders, including four studies on MBCT for MDD relapse prevention, thus further consolidating the tentative conclusions of Coelho et al. (2007).

While former research broadly has reviewed the effect of MBCT for different disorders, this article reports the first formally adequate meta-analytic evaluation, following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA); (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009), of the effectiveness of MBCT for relapse prevention among patients with recurrent MDD in remission.

The aim of this study was by means of a meta-analysis to evaluate the effect of MBCT for prevention of relapse or recurrence among patients with recurrent MDD in remission; both for different control conditions, and for subgroups of patients ($<$ or ≥ 3 MDD episodes).

2. Method

The study was conducted in accordance with the PRISMA statement, which provides a detailed guideline of preferred reporting style for systematic reviews and meta-analyses (Liberati et al., 2009; Moher et al., 2009).

2.1. Inclusion criteria

Studies were included in the meta-analysis according to the following a priori criteria for eligibility:

Type of studies: RCTs of MBCT for prevention of relapse in recurrent MDD in remission, reported in English language, and published or accepted for publication in peer-reviewed journals. *Type of participants:* Participants aged 18 years or above, diagnosed with recurrent MDD in remission according to a formal diagnostic classification system.

Type of interventions: MBCT conducted according to the manual by Segal et al. (2002).

Type of outcome measures: Number of participants meeting the diagnostic criteria for a new MDD episode over the follow-up study period.

2.2. Identification of studies

Electronic databases (EMBASE, PubMed, PsycINFO, Web of Science, Scopus, and the Cochrane Controlled Trials Register) were searched to locate studies from the first available year to November 2010, using keywords ([(mindfulness-based cognitive therapy) OR (mindfulness based cognitive therapy) OR (MBCT)] AND depress*). In addition, reference lists of selected articles and other reviews were inspected, and leading researchers in the field of MBCT were contacted to identify further relevant studies. Initially, duplicates were removed from the total number of identified records. Abstracts from the remaining records were then screened to retrieve full-text articles for assessment of eligibility. Finally, studies fulfilling inclusion criteria were selected for meta-analytic evaluation. The retrieval process was checked by both authors.

2.3. Data collection

A data extraction sheet was developed, and the following data from included studies were extracted by the first author, and checked by the second: 1) participant characteristics (including age, sex, remission period, baseline depression score, number of prior episodes, age of first onset, history of antidepressant medication); 2) group characteristics (including intervention, comparison condition, number of group participants and dropouts, use of non-study treatments for depression within groups); and 3) MDD relapse/recurrence outcome (including number of relapse/recurrence between groups, diagnostic classification system, length of follow-up period).

2.3.1. Methodological quality of studies

The methodological quality of study reports was assessed by the two authors using a table adopted from Coelho et al. (2007) on nine criteria (see Table 2), including the following revised Jadad criteria (Jadad et al., 1996): a) the study was described as randomized, b) the randomization procedure was described and appropriate, i.e., study participants were randomly allocated independent of the investigators by methods "allowing each participant to have the same chance of receiving each intervention" (Jadad et al., 1996, p. 9), c) blind outcome assessments were reported (blindness of participants and therapists, as required by the original Jadad criteria, are not possible), d) number and reasons of withdrawals and dropouts were provided for each group. One point was assigned for each of the four fulfilled criteria, constituting a maximum Jadad score of 4 points. Disagreements between the two raters (in two cases) were resolved by discussion.

2.4. Statistical analysis

Computed effect sizes (ESs) were relative risk ratios (RRs) for relapse/recurrence between groups over total follow-up periods, presented with confidence intervals (CI). ESs were calculated from intention-to-treat (ITT) data, or from complete cases data, if appropriate ITT data were not available, using the following formula: $RR = \frac{MBCTrelapse / MBCTtotal}{Controlrelapse / Controlrelapse}$. ITT data was considered "appropriate" if adequate statistical methods, such as censoring, were used to handle drop out/missing data. ESs were weighted by the inverse standard error of the studies, thus taking precision or number of participants into account. The relative risk reduction was calculated as $100\% \times (1 - RR)$.

Statistical analyses were conducted using the computer software program *Review Manager 5.1* (RevMan), provided by The Cochrane Collaboration (Review Manager, 2011). Additional analyses, including meta-regression and tests of publication bias, which could not be performed within the RevMan program, were conducted by use of the software program Comprehensive Meta-analysis, Version 2 (CMA) (Borenstein, Hedges, Higgins, & Rothstein, 2005).

All analyses were performed within the inverse variance random effects model (DerSimonian & Laird, 1986). In this model ES parameters for individual studies are treated as if they were a random sample from a larger population, thus allowing for generalization beyond the observed studies (Hedges & Vevea, 1998). For the purpose of establishing whether the results of studies were consistent, tests of heterogeneity were included using Q and I^2 statistics. Q statistics calculates the probability value for heterogeneity of studies (significant heterogeneity is indicated by a p-value ≤ 0.05). The I^2 estimates the amount of variance in a pooled ES that can be accounted for by heterogeneity in the sample of studies (Higgins, Thompson, Deeks, & Altman, 2003). An I^2 value of 0% indicates no observed heterogeneity, while values of 25%, 50%, and 75% are considered low, moderate, and high.

Fail-Safe N statistics and a funnel plot of individual study ESs were used for detecting potential biases in the publication of study results. A funnel plot is a graphic illustration of ESs from individual studies in relation to a measure of study size or precision. In general, estimates of ESs have more precision the larger the study, and therefore ESs derived from smaller studies are likely to scatter more widely at the bottom of the graph. In the absence of bias, the plot should resemble an inverted funnel with ESs from individual studies symmetrically distributed in relation to the overall mean ES (Sterne, Egger, & Moher, 2008). If many small studies show large ESs (with individual risk ratios below the overall mean, and the funnel plot skewed to the left) it may indicate bias, since small studies with insignificant results are more likely not to be published (the file-drawer problem). In addition to the visual graph, we included a formal test of funnel plot asymmetry provided by Egger, Smith, Schneider, and Minder (1997), to examine whether the association between the overall estimated intervention effect and a measure of study size, such as the standard error of the intervention effect, was significantly greater than what could be expected by chance alone. The funnel plot Trim and Fill method by Duval and Tweedie (2000) was used to further test and (if needed) adjust for possible bias in the overall ES by taking into account ESs from the estimated number of missing studies. *Fail-Safe N* statistics was included to provide an estimate for the number of unpublished or unretrieved equal sample size studies with no intervention effect, needed to reduce the overall estimated ES to a non-significant level ($p > 0.05$) (Rosenthal & Rubin, 1988).

Separate meta-analyses were performed for: a) MBCT versus controls, including treatment as usual (TAU), and placebo + clinical management (PLA); and b) MBCT versus maintenance antidepressant medication (m-ADM). Pre-specified subgroup analyses of participants with < or ≥3 MDD episodes were carried out. Possible predictors of treatment outcome, publication year, sample size, and study quality, were explored by use of meta-regression analyses.

3. Results

3.1. Trial flow

The flow of information from identification to inclusion of studies is summarized in Fig. 1 using the PRISMA flow diagram (Moher et al., 2009). Our search strategy identified 666 publications. Duplicates were removed, and abstracts from the remaining 317 publications were screened. Initially reviews, qualitative studies, case studies, dissertation abstracts, study protocols, and non-English articles were excluded ($N = 171$) (in this article, N refers to number of studies; n to number of participants). The remaining 146 articles were selected for further screening, and exclusion was carried out for the following reasons: a) no MBCT intervention ($N = 98$) or b) did not deal with MBCT for prevention of relapse in recurrent major depressive disorder ($N = 40$). Eight full text articles on studies investigating the effect of MBCT on MDD relapse were retrieved and assessed for eligibility. Two full text articles (Michalak et al., 2008, 2010) were excluded because they did not use a randomized controlled design. Finally 6 studies, fulfilling the inclusion criteria, were selected for meta-analytic evaluation.

3.2. Characteristics of studies

Table 1 summarizes the characteristics of the six included studies investigating MBCT for prevention of relapse or recurrence in recurrent MDD. Study sample sizes ranged from 60 to 145 with a total of 593 randomized participants, 74% were women (range 63–81%), and the mean age was 46 (range of means 43–49). The mean baseline depression score was 4.9 for the Hamilton Depression Rating Scale, 17-item version (Hamilton, 1960), and 14.3 for the Beck Depression Inventory, 1st or 2nd version (Beck et al., 1996, 1961).

Participants in the studies had experienced either two or more ($N = 2$), or three or more ($N = 4$) previous episodes of MDD, with the mean/median number of prior episodes = 5.6 ($N = 2$)/3.4 ($N = 3$). The mean age of first onset of MDD was 28.3 years. Participants had a history of medical treatment for depression in 96% of all cases. In half of the studies ($N = 3$) participants were free of antidepressant medication (ADM) for at least 3 months prior to baseline assessment, one study allowed baseline use of ADM, and two studies included participants, who had been receiving m-ADM for at least the preceding 6 months. Four studies compared MBCT (+ TAU; henceforth just MBCT) to TAU, one compared MBCT to m-ADM, and one three-arm-trial compared MBCT, m-ADM, and PLA. Follow-up periods (from pre-treatment to final assessment) were 14 months ($N = 4$), 15 months ($N = 1$), and 18 months ($N = 1$). All studies reported relapse/recurrence in the form of a new MDD episode according to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition revised (DSM-III-R), or 4th edition, (DSM-IV) (American Psychiatric Association, 1987, 1994).

The methodological quality of MBCT trial reports, including the revised Jadad criteria, is reported in Table 2. The studies achieved Jadad scores in the range of 2 to 4 points ($M = 3.00$, $SD = 0.63$).

3.3. Quantitative data synthesis

3.3.1. MBCT versus controls

Risk ratios for five studies comparing MBCT to controls (TAU or PLA) are shown in Fig. 2. The sample included relapse data on 408 participants. Risk ratios varied from 0.44 to 0.93 with an overall mean of 0.66 (95% CI [0.53, 0.82], $z = 3.81$, $p = 0.0001$), corresponding to a relative risk reduction of 34% in favor of MBCT. The relapse rate for MBCT participants ($n = 200$) was 38%, compared to 58% for controls ($n = 208$). There was no evidence of heterogeneity between the
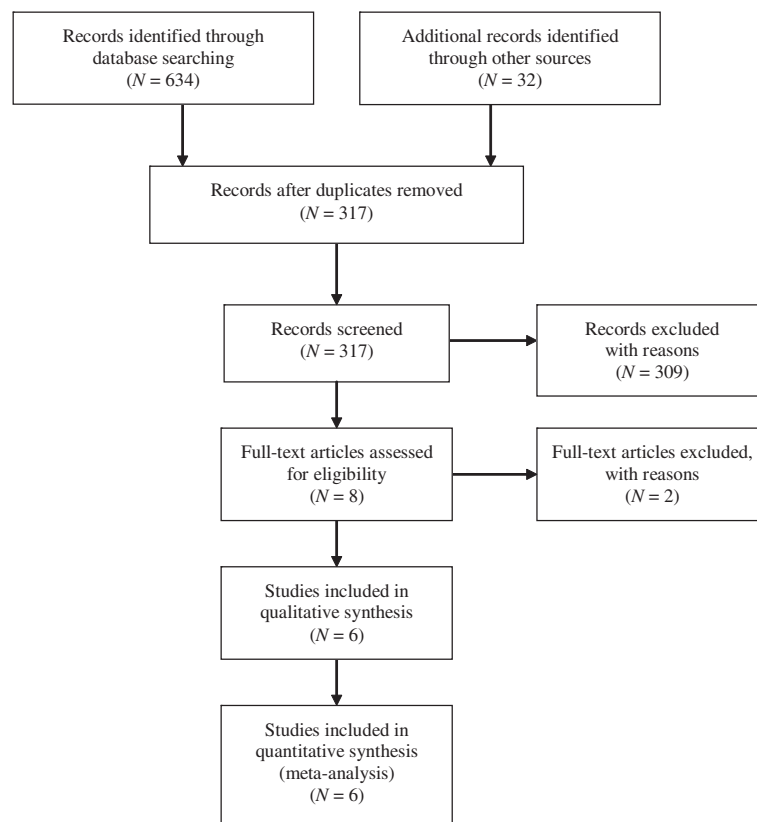

Fig. 1. Flow of information from identification to inclusion of studies.

Table 1
Characteristics of studies.

Study	n*	Participants	Percent women	Mean age	Mean baseline depression score	Previous Episodes; M or Mdn	Mean age of first onset	History of antidepressant medication (%)	Groups (n/protocol dropouts/included in meta-analysis)	Non-study medical/psychosocial treatments for depression during follow-up period (%)	Follow-up period
Bondolfi et al. (2010)	60	Recurrent MDD in remission for at least three months with three or more prior episodes; MADRS score ≤13 (≈ HAM-D≤10) at baseline; free of ADM for the preceding 3 months	72	47[a]	MADRS = 3.5[a] BDI-II = 8.0[a]	4.0[a]	25[a]	100	MBCT (31/4/27) TAU (29/1/28)	36/46[b] 31/55[b]	14 months
Godfrin and van Heeringen (2010)	106	Recurrent MDD in remission for at least two months with three or more prior episodes; HAM-D score<14 at baseline; current ADM allowed	81	46	HAM-D = 6.9 BDI-II = 20.0	NR	30	77	MBCT (52/18/40) TAU (54/12/47)	73/27[c], 64/28[d] 61/13[c] 62/13[d]	14 months
Kuyken et al. (2008)	123	Recurrent MDD in remission from recent episode with three or more prior episodes; on m-ADM for at least the preceding 6 months	77	49	HAM-D = 5.7 BDI-II = 19.3	6.4	26	100	MBCT (61/9/61) m-ADM (62/10/62)	25/NR[e] NR/NR	15 months
Ma and Teasdale (2004)	75	Recurrent MDD in remission for at least three months with two or more prior episodes; HAM-D score<10 at baseline; free of ADM for the preceding 3 months	76	45	HAM-D = 5.7 BDI = 14.3	3.0[a]	31	100	MBCT (37/6/36) TAU (38/1/37)	19/19[b] 35/22[b]	14 months
Segal et al. (2010)	84	Recurrent MDD in remission for at least seven months with three or more prior episodes; HAM-D score during remission ≤7 with occasional elevated scores between 8 and 14; on m-ADM for at least the preceding 7 months	63	44	HAM-D = 2.8	4.7	31	100	MBCT (26/5/26) m-ADM (28/7/28) PLA (30/6/30)	NR/NR[f] NR/NR[f] NR/NR[f]	18 months
Teasdale et al. (2000)	145	Recurrent MDD in remission for at least 3 months with two or more episodes; HAM-D score<10 at baseline; free of ADM for the preceding 3 month	76	43	HAM-D = 3.5 BDI = 10.0	3.3[a]	27	100	MBCT (76/14/71) TAU (69/3/66)	45/49[b] 40/34[b]	14 months

Note. ITT = intention-to-treat; MDD = major depressive disorder; MADRS = Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979); HAM-D = Hamilton Depression Rating Scale (Hamilton, 1960); ADM = antidepressant medication; BDI-II = Beck Depression Inventory-II (Beck et al., 1996); MBCT = mindfulness-based cognitive therapy; TAU = treatment as usual; m-ADM = maintenance antidepressant medication; BDI = Beck Depression Inventory (Beck et al., 1961); and PLA = pill placebo + clinical management.
[a] Median.
[b] Once or more at any time during the follow-up period.
[c] Baseline assessment.
[d] Final follow-up assessment.
[e] 6-month follow-up assessment.
[f] Although numbers were not reported, patients who assessed non-study treatments for depression without a documented relapse were treated as censored observations in the data analysis.
* Number of randomized participants.

Table 2
Methodological quality of MBCT trial reports.

Authors (date)	Was the trial randomized?	Was the randomization procedure described and was it appropriate?	Was the treatment allocation concealed?	Were groups similar at baseline on prognostic indicators?	Were blind outcome assessments conducted?	Was the number of withdrawals/dropouts in each group mentioned?	In addition to stating the number of withdrawals/dropouts, were reasons given for each group?	Was an analysis conducted on the intention-to-treat sample?	Was a power calculation described?	Jadad score (revised, maximum score = 4)
Bondolfi et al. (2010)	**Yes**	**Yes**	Yes	Yes	**Yes**	Yes	**No**	Yes[a]	Yes	3
Godfrin and van Heeringen (2010)	**Yes**	**Yes**	Yes	Yes	**No**	Yes	**No**	No	Yes	2
Kuyken et al. (2008)	**Yes**	**Yes**	Not clear	Yes	**Yes**	Yes	**Yes**	Yes	No	4
Ma and Teasdale (2004)	**Yes**	**Yes**	Yes	Yes	**Yes**	Yes	**No**	No[b]	No	3
Segal et al. (2010)	**Yes**	**Yes**	Yes	Yes	**Yes**	Yes	**No**	Yes	No	3
Teasdale et al. (2000)	**Yes**	**Yes**	Yes	Yes	**Yes**	Yes	**No**	No[b]	Yes	3

Note. Columns in bold constitute the revised Jadad Scale.
[a] ITT data was inappropriate, as patients with incomplete follow-up data were treated as survivors.
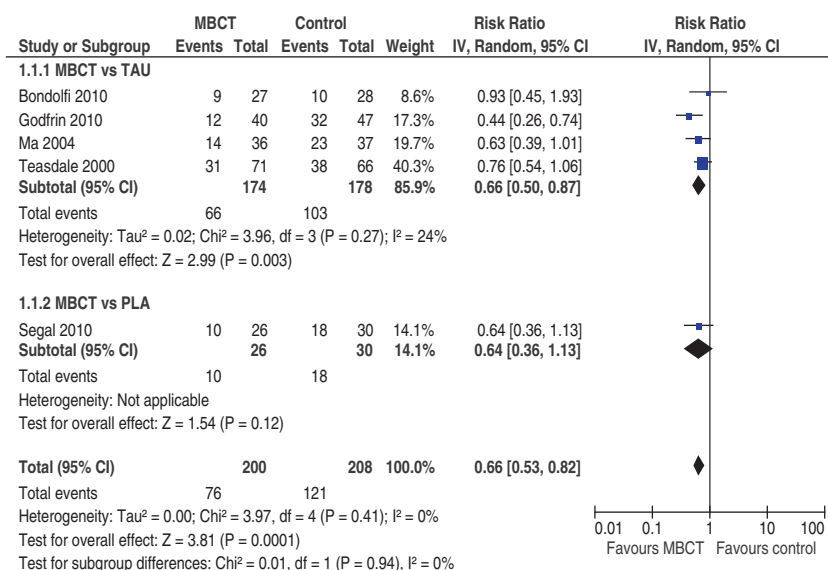[b] Almost all cases (97%, 94%) included in the analyses.

Fig. 2. Comparison of risk of relapse between MBCT and controls, including ES statistics. Note. MBCT = mindfulness-based cognitive therapy; CI = confidence interval; TAU = treatment as usual; and PLA = placebo. Figure explanation: The first left-sided column shows included studies categorized into two subgroups according to use of different control conditions. The next columns indicate number of relapses (events) and total number of participants within MBCT and controls. The column "Weight" shows the weight ascribed to each individual study, taking into account the study sample size and precision of result (see text for an explanation). The column "Risk Ratio" shows the relative risk of relapse between MBCT and controls together with the confidence interval. A risk ratio below 1 favors MBCT, while a risk ratio above 1 favors the control group. The final column is a forest plot of the risk ratios. The length of the horizontal lines for each risk ratio within the forest plot indicates the interval of confidence, while the size of the squares indicates the size of the study sample. The bottom row of the figure shows the overall results.

studies ($I^2 = 0\%$, p = 0.41). The Fail Safe N analysis indicated that 14 missing equal sample size studies with no effect of MBCT compared to controls (i.e., a risk ratio of 1.0), would be needed to reduce the overall risk of relapse ES to a non-significant level (p>0.05). Fig. 3 shows a plot of ESs in relation to the ES standard error. Eggers regression test showed no evidence of asymmetry in the ES funnel plot (t = 0.220, df = 3, p = 0.42), and the Trim and Fill method indicated that no missing studies (falling to the right of the overall mean ES) were needed to make the plot symmetric.

3.3.2. Number of prior episodes

Three studies comparing MBCT to controls in the form of TAU or PLA (Bondolfi et al., 2010; Godfrin & van Heeringen, 2010; Segal
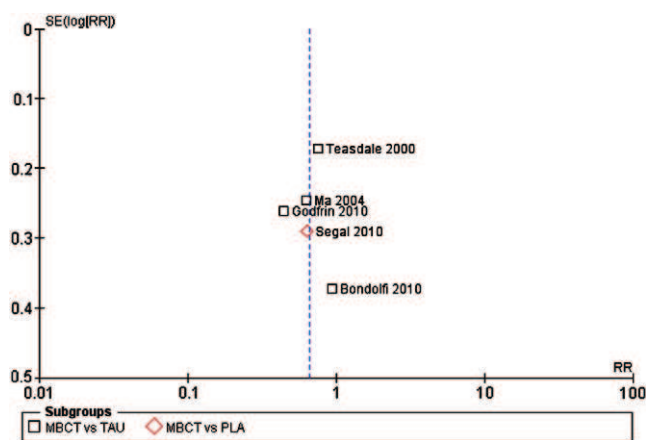

Fig. 3. Funnel plot of standard error by ESs for relative risk of relapse between MBCT and controls. Note. SE = standard error; RR = risk ratio; MBCT = mindfulness-based cognitive therapy; TAU = treatment as usual; and PLA = placebo. The funnel plot indicates absence of publication bias when individual study effect sizes (risk ratios) are relatively symmetrically distributed around the overall mean effect size, which is marked by the broken vertical line in the middle of the figure.

et al., 2010) only included participants with three or more previous MDD episodes, while two studies (Ma & Teasdale, 2004; Teasdale et al., 2000) had stratified prior to randomization on this variable, and separately analyzed relapse rates for this subgroup of patients. Risk ratios for MBCT and controls in these five studies reporting relapse data on participants with three or more prior episodes varied from 0.44 to 0.93 with an overall mean of 0.57 (95% CI [0.45, 0.72]), corresponding to a relative risk reduction of 43% in favor of MBCT (see Fig. 4). This overall mean ES was highly significant (z = 4.83, p<0.00001), and there was no evidence of heterogeneity between the studies ($I^2 = 0\%$, p = 0.46). Relapse rates for this particular subgroup of patients were 36% and 63% for MBCT (n = 176) and controls (n = 182), respectively. The Fail Safe N for risk of relapse in participants with three or more previous episodes was 23, indicating that 23 missing studies with a risk ratio of 1.0 were needed to bring the observed mean ES to a non-significant level (p>0.05). There was no evidence of funnel plot asymmetry using Eggers regression test (t = 0.59, df = 3, p = 0.30), or the Trim and Fill method.

Two studies (Ma & Teasdale, 2004; Teasdale et al., 2000) provided relapse data for a subgroup of participants with only two previous episodes of depression (n = 50). The overall risk ratio of 0.51 (95% CI [0.25, 1.05]) for relapse in this subgroup of patients showed a trend towards significance (z = 1.82; p = 0.07) favoring TAU compared to MBCT. Relapse rates were 27% for TAU participants, compared to 54% for MBCT participants.

3.3.3. MBCT versus m-ADM

Two studies compared MBCT to m-ADM. In the study by Kuyken et al. (2008), 123 participants in primary care with at least 3 MDD episodes on ADM for the previous 6 months in full or partial remission were randomized to either MBCT + ADM tapering, or m-ADM administered by the general practitioner in line with standard clinical practice and the British National Formulary. 75% of participants in the MBCT group had completely discontinued their ADM at 6 month follow-up. The three-arm-study by Segal et al. (2010) included arms of MBCT + ADM tapering (n = 26) and m-ADM (n = 30). Participants

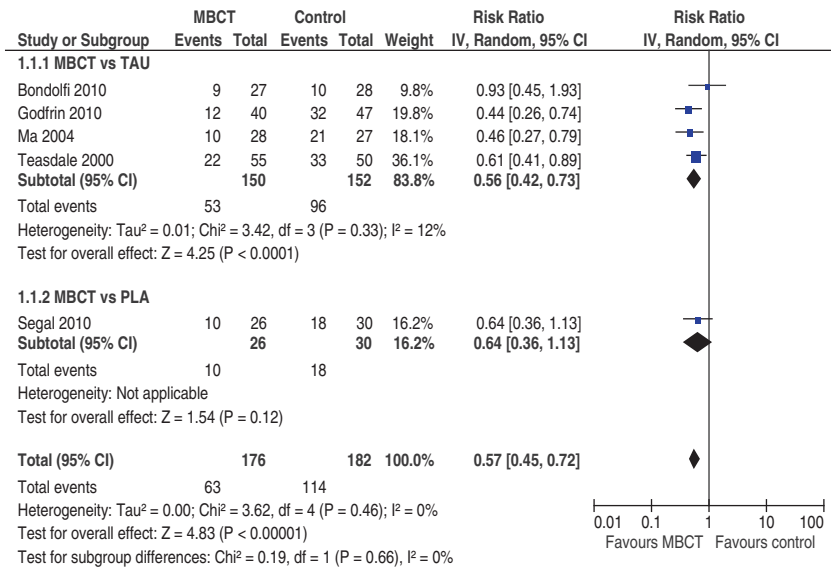| | MBCT | | Control | | | Risk Ratio | Risk Ratio |
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 MBCT vs TAU							
Bondolfi 2010	9	27	10	28	9.8%	0.93 [0.45, 1.93]	
Godfrin 2010	12	40	32	47	19.8%	0.44 [0.26, 0.74]	
Ma 2004	10	28	21	27	18.1%	0.46 [0.27, 0.79]	
Teasdale 2000	22	55	33	50	36.1%	0.61 [0.41, 0.89]	
Subtotal (95% CI)		**150**		**152**	**83.8%**	**0.56 [0.42, 0.73]**	
Total events	53		96				
Heterogeneity: Tau² = 0.01; Chi² = 3.42, df = 3 (P = 0.33); I² = 12%							
Test for overall effect: Z = 4.25 (P < 0.0001)							
1.1.2 MBCT vs PLA							
Segal 2010	10	26	18	30	16.2%	0.64 [0.36, 1.13]	
Subtotal (95% CI)		**26**		**30**	**16.2%**	**0.64 [0.36, 1.13]**	
Total events	10		18				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.54 (P = 0.12)							
Total (95% CI)		**176**		**182**	**100.0%**	**0.57 [0.45, 0.72]**	
Total events	63		114				
Heterogeneity: Tau² = 0.00; Chi² = 3.62, df = 4 (P = 0.46); I² = 0%							
Test for overall effect: Z = 4.83 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%							

Favours MBCT　Favours control

Fig. 4. Comparison of risk of relapse between MBCT and controls for participants with three or more previous episodes of major depression, including ES statistics. For figure explanation, see caption for Figure 2.

with at least 3 MDD episodes had been on ADM (primarily venlafaxine) with remission for at least seven months prior to randomization. ADM was administered according to a protocol by study psychiatrists with the same drug at the maximum tolerated effective dose in the study period. ADM in the MBCT condition was tapered gradually via reduced pill count during a 4-week period.

The combined relative risk ratio for MBCT versus m-ADM in the two studies was 0.80 (95% CI [0.60, 1.08], z = 1.45, p = 0.15), corresponding to a non-significant MBCT risk reduction of 20%, with no evidence of heterogeneity between the studies (I² = 0%, p = 0.91; see Fig. 5).

3.3.4. Regression analyses

Using risk of relapse ESs (the logarithm of risk ratios) as the dependent variable in meta-regression analyses of studies comparing MBCT to controls (shown in Fig. 2), no evidence of ES moderation was found by either publication year (B = − 0.024, SE = 0.024, p = 0.31), sample size (B = 0.002, SE = 0.003, p = 0.57), or study quality (B = 0.144, SE = 0.260, p = 0.58). These analyses were underpowered and results should be interpreted with caution.

4. Discussion

The overall risk ratio for relapse or recurrence in MBCT versus control groups (TAU or PLA) of 0.66 in this meta-analysis is highly significant, indicating that MBCT (added to TAU) is an effective intervention for relapse prevention in recurrent MDD in remission. The ES corresponds to a relative risk reduction of 34%, with relapse rates of 38% and 58% for MBCT and controls, respectively. As can be seen from Table 2, the studies are generally of a high methodological

quality with a mean revised Jadad score of 3 out of max 4. There was no evidence of heterogeneity between individual studies, and no evidence of publication bias according to tests of funnel plot asymmetry. Fourteen missing studies of comparable sample size with an ES of zero would be needed to nullify the result. Therefore, the overall result of this meta-analysis should be considered credible.

A very substantial difference was found for the subgroup of participants with three or more previous episodes of MDD, in that the relapse rate for MBCT here was 36%, compared to 63% for control conditions (TAU or PLA), corresponding to a relative risk reduction of 43%.

On the other hand, it should be noted that the result for participants with only two prior episodes of MDD (n = 50) tendentially showed a lower risk of relapse for TAU compared to MBCT (relative risk reduction = 49%; p = 0.07). The tendentially higher relapse rate among MBCT treated patients with only two episodes is a rather paradoxical finding, since MBCT has been found generally to benefit depressed patients (Chiesa & Serretti, 2011; Hofmann et al., 2010), and since patients with three or more episodes formerly must have been patients with only two episodes. Teasdale et al. (2000) and Ma and Teasdale (2004) found that patients with two episodes reported later first episode onset, and Ma and Teasdale (2004) also found that such patients also reported less childhood adversity. They suggest that patients with only two episodes in their studies were derived from a less vulnerable population, less likely to suffer from dysphoria-activated depressive rumination that may be considered a primary target of MBCT. Indeed, Ma and Teasdale (2004) found that relapse was more often associated with significant life events in patients with only two prior episodes compared to patients with three or more episodes. They argue that MBCT may be ineffective for reducing relapse/recurrence provoked by stressful life events.
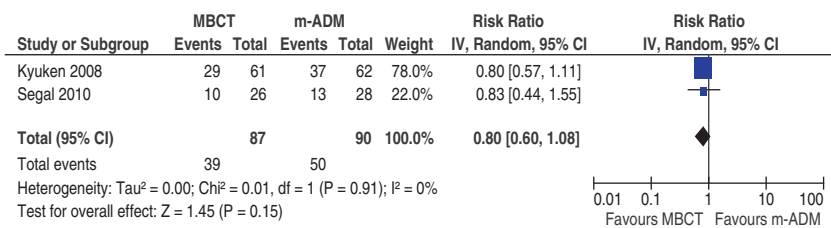

| | MBCT | | m-ADM | | | Risk Ratio | Risk Ratio |
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Kyuken 2008	29	61	37	62	78.0%	0.80 [0.57, 1.11]	
Segal 2010	10	26	13	28	22.0%	0.83 [0.44, 1.55]	
Total (95% CI)		**87**		**90**	**100.0%**	**0.80 [0.60, 1.08]**	
Total events	39		50				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%							
Test for overall effect: Z = 1.45 (P = 0.15)							

Favours MBCT　Favours m-ADM

Fig. 5. Comparison of risk of relapse between MBCT and m-ADM, including ES statistics. Note. MBCT = Mindfulness-based cognitive therapy; and m-ADM = maintenance antidepressant medication. For further figure explanation, see caption for Fig. 2.

The non-significant higher relapse among MBCT participants with only two prior episodes could, of course, be a chance event. It should be noted, however that Segal et al. (2010) also found that MBCT did not reduce relapse risks compared to PLA for a subgroup of participants; namely those characterized by a stable remission period following three or more MDD episodes. Like number of depressive episodes, unstable remission has been found to be a negative prognostic variable in MDD (Nierenberg et al., 2010). Therefore, the possibility should be considered that MBCT may not be so helpful for remitted MDD patients with a lesser degree of risk of relapse.

Although more studies are needed for firm conclusions, results from the quantitative data synthesis of two studies suggest that MBCT is at least comparable to m-ADM for effective relapse prevention of recurrent MDD with three or more episodes. If tenable, this conclusion is of high practical importance, since m-ADM is generally recommended for such cases, and many patients will prefer a psychological alternative with no adverse medical side-effects. It is further worth noting that one of these studies found that MBCT was more effective than m-ADM for reducing residual depressive symptoms and improving quality of life (Kuyken et al., 2008).

MBCT is apparently a cost-efficient strategy for relapse prevention. Two studies (Ma & Teasdale, 2004; Teasdale et al., 2000) respectively reported that MBCT on average required less than 3 and 5 therapist contact hours per patient. The one study with actual cost-effectiveness calculations (Kuyken et al., 2008) found estimated annual per-patient total costs for the first 15 months of $2767 and $2340 for the MBCT and m-ADM conditions respectively (difference not significant). The incremental cost-effectiveness ratio for MBCT was estimated to be $962 per prevented relapse/recurrence, and $50 per depression-free day. MBCT was less expensive than m-ADM for the last three of the 15 months, perhaps indicating a more favorable cost-effectiveness of MBCT in the long run. Since MBCT can be delivered in groups with up to 15 participants, it is, anyhow, a low cost psychological intervention.

The present meta-analysis has several limitations. No formal protocol was developed before the review was carried out, although the study was highly focused, with pre-specified aims, inclusion criteria and methods of analysis. The search strategy only included studies published or accepted for publication. It is, however, unlikely that major accomplished studies are not published or close to publishing, due to the area's high degree of current interest. There is still a relatively small number of RCTs, thus limiting the value of sub-group analyses, and only two studies comparing MBCT with m-ADM. The studies do not allow for conclusions about the specific effects of MBCT, since there are no studies with psychological placebo or componential control. Only one study of the cost-effectiveness of MBCT was located.

In conclusion, this meta-analysis supports use of MBCT as a low cost intervention for relapse prevention in recurrent MDD in remission, at least in case of three or more previous episodes. Future research should investigate the differential effects of MBCT for patients with low and high risk of relapse; due to the few data on patients with only two prior episodes, it may be premature to exclude such patient, as has been done in most recent studies. More rigorous designs to investigate specific effects and change mechanisms of MBCT should also be considered.

Acknowledgments

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