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Added value of Mindfulness-Based Cognitive Therapy for Depression: A Tree-based Qualitative Interaction Analysis

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ABSTRACT

Aim: To identify moderators of treatment effect for Mindfulness-Based Cognitive Therapy (MBCT) versus Treatment As Usual (TAU) in depressed patients.

Methods: An individual patient data-analysis was performed on three randomized-controlled trials, investigating the effect of MBCT + TAU versus TAU alone (N = 292). Patients were either in (partial) remission, currently depressed or had chronic, treatment-resistant depression. Outcomes were depressive symptoms and quality of life. The QUalitative INteraction Trees (QUINT) method was used to identify subgroups that benefited more from either condition.

Results: MBCT + TAU outperformed TAU in reducing depressive symptoms. For both conditions, the effect of baseline depressive symptoms on post-treatment depressive symptoms was curvilinear. QUINT analyses revealed that MBCT + TAU was more beneficial than TAU for patients with an earlier onset and higher rumination levels in terms of depressive symptom reduction and for patients with a lower quality of life in terms of improving quality of life.

Conclusions: The results suggest that MBCT might be more beneficial for those with earlier onset and higher levels of rumination and for patients with a lower quality of life. Sophisticated analytical techniques such as QUINT can be used in future research to improve personalized assignment of MBCT to patients. Long-term outcome could also be integrated in this.

1. Introduction

Major depressive disorder (MDD) is a common and severe psychiatric disorder and a leading cause of disease burden worldwide (World Health Organization, 2017). Aside from antidepressant medication, numerous psychological interventions have been developed for MDD among which Mindfulness-Based Cognitive Therapy (MBCT; Segal, Williams, & Teasdale, 2002).

Mindfulness is defined as the awareness that emerges by purposefully paying attention to the present experiences with a curious, open,

Abbreviations: IPD, Individual Patient Data; ITT, Intention-To-Treat; MBCT, Mindfulness-Based Cognitive Therapy; MBI(s), Mindfulness-Based Intervention(s); MDD, Major Depressive Disorder; PP, Per Protocol; RCT(s), Randomized-Controlled Trial(s); TAU, Treatment As Usual; QUINT, Qualitative INteraction Trees

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accepting, non-judgmental, and friendly attitude (Kabat-Zinn, 1994). MBCT consists of 8 weekly group sessions of 2.5 hrs and a silent day (Segal, Williams, & Teasdale, 2012). The intervention includes training in mindfulness skills and elements from cognitive therapy for depression (Beck, Rush, Shaw, & Emery, 1979). Originally, MBCT was designed to prevent relapse for recurrently depressed patients who are in (partial) remission, and it has been shown to be effective for this patient group (Kuyken et al., 2016).

Initially, MBCT was not considered suitable for patients with current depression because of the expectation that fully attending to the present moment might be especially difficult in the midst of depressive symptomatology. One might become preoccupied with negative thoughts and difficulties in concentration might impede effectiveness (Baer, Crane, Miller, & Kuyken, 2019; Segal et al., 2012; Strauss, Cavanagh, Oliver, & Pettman, 2014).

More recently, however, research about the effectiveness of Mindfulness-Based Interventions (MBIs) has started to include currently depressed patients, and results support the feasibility and effectiveness of MBCT in this population (Goldberg et al., 2018; Hedman-Lagerlof, Hedman-Lagerlof, & Ost, 2018; Lenz, Hall, & Smith, 2016; Strauss et al., 2014; Wang et al., 2018). Fewer studies have been conducted on the effectiveness of MBCT in patients with chronic or treatment-resistant depression. Some of these revealed that MBCT can be effective in this population too (Barnhofer et al., 2009; Cladder-Micus et al., 2018; Eisendrath et al., 2016; Kenny & Williams, 2007), whereas Michalak, Schultze, Heidenreich, and Schramm (2015) found that MBCT was not more effective than Treatment As Usual (TAU) in reducing depressive symptoms.

Considering the heterogeneity of patients with depression, an improved understanding of what patient characteristics moderate treatment effect could enable improved targeting of MBCT in this population (van der Velden et al., 2015). Several studies of MBCT aimed at preventing depressive relapse/recurrence in remitted patients have shown stronger treatment effects for those with increased vulnerability, including patients with three or more previous major depressive episodes, earlier onset of MDD (Ma & Teasdale, 2004; Teasdale et al., 2000), a history of early adversity (Kuyken et al., 2015; Williams et al., 2014) and more fluctuation in depressive symptoms (Segal et al., 2010). In an individual patient data (IPD) meta-analysis of all existing trials on preventing relapse/recurrence in recurrent depression ($N = 258$; Kuyken et al., 2016), only higher severity of depression at baseline was associated with a better treatment effect of MBCT.

In currently depressed patients, a few patient characteristics have been suggested to moderate the effect of MBCT. In terms of reduction of depressive symptoms, Lenz et al. (2016) found that older patients benefited more from MBCT. Another study indicated that female gender and low levels of acceptance (or non-judgment) are associated with greater changes in depressive symptoms over the course of MBCT (van Aalderen et al., 2012). With regard to chronically or treatment-resistant depressed patients, higher baseline levels of rumination appeared to predict a larger decrease in depressive symptoms after MBCT (Cladder-Micus et al., 2018).

Taken together, our current knowledge of moderators in the context of MBCT for depression is still limited and in need of more sophisticated examination. At first, most studies investigated homogeneous populations of depressive patients, limiting the range of depressive symptoms at baseline. Therefore, the current study conducted an IPD analysis based on three multicenter randomized-controlled trials (RCTs), including patients with recurrent depression either in (partial) remission and patients with current or chronic and treatment-resistant depression. Secondly, despite promising results of the effect of MBCT on quality of life (Cladder-Micus et al., 2018; Kuyken et al., 2008, 2015), most research into possible moderators has involved the effect of MBCT on risk of relapse and/or level of depressive symptoms. MDD has a huge impact on quality of life (World Health Organization, 2017) and the initial aim of MBCT is not to change or eliminate depressive symptoms, but rather to relate to them in a different way. Therefore, the current study includes both the level of depressive symptoms as the primary outcome and quality of life as the secondary outcome.

Another issue we would like to raise concerns the statistical approach to moderator analysis, which is in the context of differential treatment efficacy research often called treatment-subgroup analysis. In all aforementioned studies into the effect of MBCT, no distinction is made between quantitative treatment-subgroup interactions (or treatment-covariate interaction) or qualitative treatment-subgroup interactions. The latter type of interactions indicate that for one or more subgroup(s) of patients one treatment (e.g., MBCT) is better than another treatment (e.g., TAU), while for other subgroup(s) the reverse is true. In contrast, quantitative interactions indicate that one treatment is always better than the other but only the strength of the effect differs for subgroups of patients. For optimal treatment assignment in clinical practice, however, quantitative interactions imply that all patients would still be assigned to one and the same treatment. Therefore, to identify for which type of patients MBCT has added value and for which type of patients MBCT is not recommended, qualitative treatment-subgroup interactions are of utmost importance. In addition, most studies into possible moderators of treatment effect assume linear associations. This assumption is not in line with current thinking that the relationships between psychological and physical processes and outcome may run an inverted U-curve (non-monotonicity) trajectory (Grant & Schwartz, 2011). For example, it has been suggested that depressive symptoms might have an optimum level in which MBCT is effective, above or below this optimum level the effect might be minimal or undesirable effects might occur (Kuyken et al., 2016; van Dam et al., 2017). Furthermore, most studies only consider two-way interaction effects, while maybe, higher order interaction effects may play a role in explaining the variance in treatment efficacy. As a solution, the current study uses a tree-based method, QUalitative INteraction Trees (QUINT; Dusseldorp & van Mechelen, 2014), which focuses on identifying qualitative treatment-subgroup interactions, allows for nonlinear relationships and considers higher order interaction effects. The method identifies subgroups of patients in which one treatment is more beneficial than another. It is especially suited for situations with many potential moderating variables that might interact with the treatment variable without clear a priori hypotheses. The result of an analysis with QUINT is a binary tree from which treatment assignment criteria can be derived, relevant for clinical practice.

The current study sought to answer the following questions: (1) For which subgroup(s) is MBCT + TAU more beneficial than TAU alone?; (2) For which subgroup(s) is MBCT + TAU less beneficial than TAU alone? Based on previously discussed research, a non-linear association between baseline levels of depression severity and outcome is expected, more specifically, we expect that patients with moderate levels of depression benefit more from MBCT than those with relatively low or high values (allowing the possibility of worsening of symptoms for those with highest baseline values). The investigation of additional possible moderators is more exploratory of nature. Next to demographic characteristics (age, gender, educational level, employment, marital status), the following baseline clinical characteristics were investigated as possible moderating variables with the use of the QUINT method: number of prior depressive episodes, age of onset, medication use, mindfulness skills, and rumination.

2. Method

2.1. Design

Data have been drawn from three (multicenter) RCTs that were conducted in the Netherlands, investigating the effect of MBCT + TAU vs. TAU alone for patients with depression. The respective populations consisted of patients with recurrent depression in (partial) remission (RCT-1; Huijbers et al., 2015), patients either in remission or currently

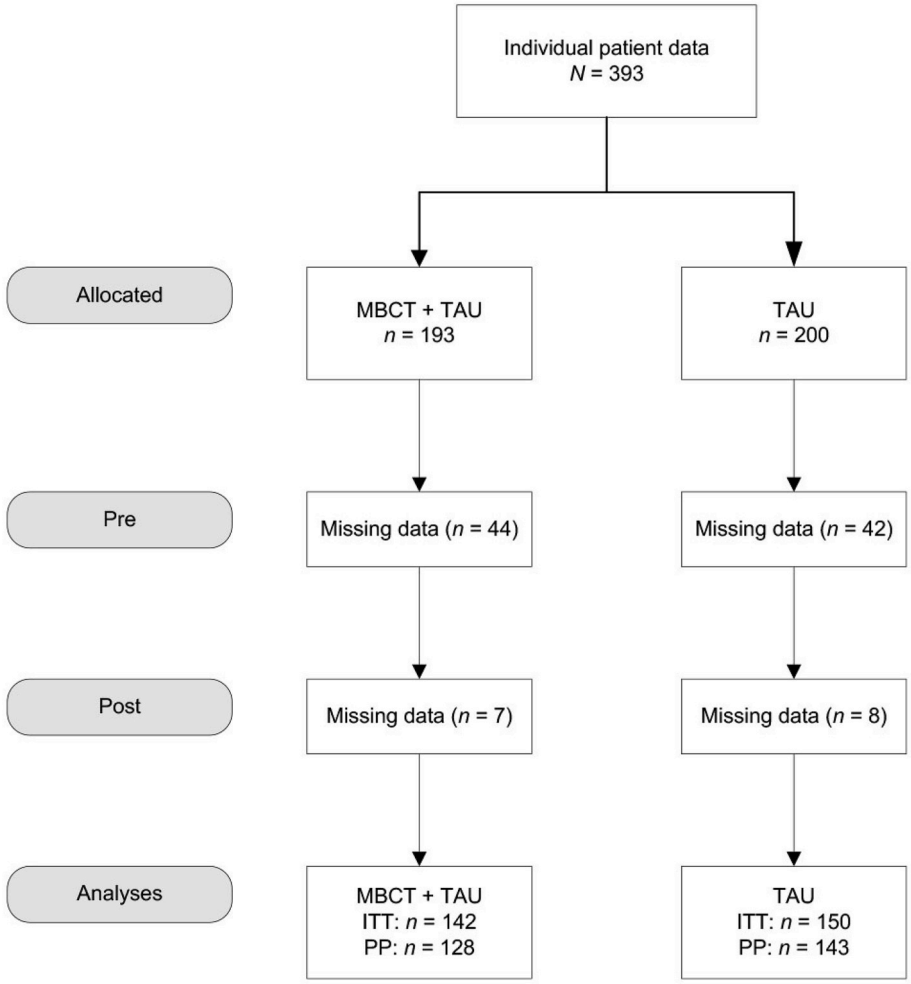

Fig. 1. Flow chart of the current study. Data were derived from three randomized controlled trials (RCTs) of which participants were assigned to Mindfulness-Based Cognitive Therapy (MBCT) as an add-on to Treatment As Usual (TAU) or TAU alone. In the analysis of the primary outcome, the sample size was $n = 292$ for intention to treat (ITT) and $n = 271$ per protocol (PP).

depressed (RCT-2; van Aalderen et al., 2012), and patients with chronic, treatment-resistant depression (RCT-3; Cladder-Micus et al., 2018). By including patients with a wide range of baseline depressive symptoms, the differential treatment effect of baseline depressive symptoms could be investigated more thoroughly. The RCTs were approved by the Medical Ethics Committee Arnhem-Nijmegen for all participating sites and/or the Medical Ethical Committee of local hospitals in Nijmegen, the Netherlands (RCT-1: nr. 2008/242, RCT-2: nr. 2005/284, RCT-3: nr. 2012/339). Written informed consent from all participants was obtained after complete description of the studies and before eligibility was assessed. Demographic and clinical characteristics were obtained at baseline. Primary and secondary outcome measures were assessed at baseline and after the MBCT + TAU or TAU period (8–12 weeks). Participants allocated to the TAU condition were offered participation in the MBCT after the intervention or study period. A full description of the methods and procedures can be found in the respective (protocol) papers (RCT-1: Huijbers et al., 2012; RCT-2: van Aalderen et al., 2012; RCT-3: Cladder-Micus et al., 2015). For the flow chart of the current study, see Fig. 1.

2.2. Participants

Participants were on average 48.05 years old ($SD = 11.70$), mainly female (68.4%), married or cohabiting (56.2%) and highly educated (50.4%). About half were unemployed (51.8%). Most participants had already experienced several prior depressive episodes ($M = 6.05$, $SD = 6.56$), and had experienced their first MDD at an average age of 25.65 years old ($SD = 12.14$). More than half of the participants used antidepressant medication (63.9%). A wide range of depressive symptoms was observed on the (converted) Hamilton Rating Scale for Depression (range: 0–37; for conversion see 2.5.1), with an average mean score of 12.43 ($SD = 8.08$). There were no baseline differences in demographic and clinical characteristics between participants allocated in the MBCT + TAU condition versus TAU alone, see Table 1.

2.3. Interventions

MBCT. The MBCT was largely based on the protocol by Segal et al. (2002) with some adaptations based on the most recent version of the MBCT protocol (Segal et al., 2012). The intervention consisted of 8 weekly sessions of 2.5 hrs and one day of silent practice of 6 hrs between the 5th and 7th session. It was delivered in groups of 8–15 participants. MBCT included both formal (e.g., the body scan, sitting meditation, mindful movement) and informal meditation exercises (e.g., bringing present-moment awareness to daily life activities). Cognitive-behavioural techniques included psycho-education, monitoring and scheduling of activities, identification of negative automatic thoughts, and devising a relapse prevention plan. Participants were encouraged to practice meditation at home for 45–60 min a day by using CDs or audio files. Participants of all three RCTs were enrolled in

Table 1
Baseline demographic and clinical characteristics of participants allocated to Mindfulness-Based Cognitive Therapy (MBCT) in addition to Treatment As Usual (TAU) versus TAU alone: means (SD) and frequencies (%).

Variable	MBCT + TAU (n = 193)	TAU (n = 200)	Statistics°
Age (in years)	48.05 (11.64)	48.05 (11.78)	$t(391) < -0.01$, $p = .99$
Gender			$\chi^2(1) = 0.04$, $p = .85$
Male	60 (31.1%)	64 (32.0%)	
Female	133 (68.9%)	136 (68.0%)	
Educational level			$\chi^2(2) = 4.00$, $p = .14$
Low	24 (12.5%)	30 (15.0%)	
Middle	52 (26.9%)	68 (34.0%)	
High	107 (55.4%)	91(45.5%)	
Marital Status			$\chi^2(2) = 0.14$, $p = .93$
Single	41 (21.2%)	45 (22.5%)	
Married/cohibiting	108 (56.0%)	113 (56.5%)	
Divorced/widowed	29 (15.0%)	28 (14.0%)	
Employment			$\chi^2(1) = 2.67$, $p = .10$
Yes	91 (47.1%)	80 (40.0%)	
No	82 (42.5%)	102 (51.0%)	
Age of onset	25.70 (11.98)	25.61 (12.32)	$t(363) = -0.07$, $p = .94$
Prior depressive episodes	6.29 (7.45)	5.81 (5.58)	$t(367) = -0.71$, $p = .48$
Medication use			$\chi^2(1) = 0.04$, $p = .84$
Yes	125 (64.8%)	126 (63.0%)	
No	52 (26.9%)	55 (27.5%)	
Depressive symptoms [a]	12.26 (7.91)	12.59 (8.26)	$t(390) = -0.39$, $p = .69$
Quality of life [b]	46.56 (16.50)	45.11 (17.98)	$t(346) = -0.79$, $p = .43$
Mindfulness [c]			
Observing	22.34 (5.78)	21.73 (5.79)	$t(377) = -1.03$, $p = .31$
Describing	25.53 (7.76)	25.36 (7.00)	$t(377) = -0.22$, $p = .83$
Non-judging	25.38 (6.91)	224.93 (7.19)	$t(377) = -0.63$, $p = .53$
Rumination [d]	12.37 (3.01)	12.61 (3.21)	$t(377) = -0.75$, $p = .46$

Note. MBCT = Mindfulness-Based Cognitive Therapy; TAU = Treatment As Usual.
Due to missing values the degrees of freedom differ between the analyses.
[a] (Transformed) Hamilton Rating Scale for Depression (HRSD-17; Hamilton, 1960; Rush et al., 2003; Trivedi et al., 2004).
[b] Psychological domain of the World Health Organization Quality of Life, short version (WHOQOL-BREF; The WHOQOL Group, 1996).
[c] Five Facets Mindfulness Questionnaire (FFMQ; Baer et al., 2006) or computed from the Kentucky Inventory of Mindfulness Skills with person mean imputation (KIMS; Baer et al., 2004).
[d] Brooding scale of the Ruminative Response Scale, extended version (RRS-NL-EXT; Raes et al., 2007) or computed from the Ruminative Response Scale (RRS-NL; Raes et al., 2003) with person mean imputation.

mixed groups comprising patients from the trials as well as regular (remitted) depressed patients. MBCT classes of all three RCTs were taught by experienced mindfulness teachers who all met the teaching criteria described in the MBCT good practice guidelines (UK Network of Mindfulness-Based Teachers, 2015). In addition to MBCT the participants received TAU, as a concurrent intervention.

TAU. Those who were in the TAU condition were encouraged to continue their baseline treatment for the study period. This could include maintenance of antidepressant medication, psychological treatment, support by a psychiatric nurse, or day-hospital treatment.

2.4. Measuring instruments

2.4.1. Primary outcome

Depressive symptoms. In RCT-1 depressive symptoms were assessed by the Hamilton Rating Scale for Depression (HRSD-17; Bech, Kastrup, & Rafaelsen, 1986; Hamilton, 1960). The HRSD-17 is a semi-structured 17-item interview designed to assess depressive symptoms over the previous week on a 0–52 score range. It has good psychometric properties (Bagby, Ryder, Schuller, & Marshall, 2004; Morriss, Leese, Chatwin, & Baldwin, 2008). In RCT-2 the Inventory of Depressive Symptomatology – Clinician rated (IDS-C30; Akkerhuis, 1997) was used. The IDS-C30 consists of 30 multiple choice 4-point Likert scale questions assessing depressive symptoms over the last 7 days. The IDS-C30 is scored by summing responses of 28 out of 30 items to obtain a total score ranging from 0 to 84 (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). The internal consistency and inter-rater reliability of the IDS-C30 have been shown to be adequate, also among individuals with current depression (αrange: .76 - .82; Rush et al., 1996; Trivedi et al., 2004). In RCT-3 depressive symptoms were measured with the self-report version of the IDS, which has shown good psychometric properties (IDS-SR; Rush et al., 1996). The HRSD-17, IDS-C and IDS-SR are sensitive to symptom change and highly correlated, indicating high concurrent validity (Geschwind, Peeters, Huibers, van Os, & Wichers, 2012; Rush et al., 1996, 2003; Trivedi et al., 2004).

2.4.2. Secondary outcome

Quality of life. In all three RCTs, perceived quality of life, rated on a 5-point Likert scale in relation to the past two weeks, was assessed using the self-report 26-item World Health Organization Quality of Life scale (WHOQOL-Bref; De Vries & Van Heck, 1996). This questionnaire represents four domains: Physical health, Psychological, Social relationships and Environment. The WHOQOL-Bref has good to excellent psychometric properties of reliability and has shown to be a cross-culturally valid assessment of quality of life (Skevington, Lotfy, & O'Connell, 2004). Psychometric properties tested in a sample of Dutch psychiatric outpatients were good (Trompenaars, Masthoff, Van Heck, Hodiamont, & De Vries, 2005).

2.4.3. Moderator variables

Mindfulness. In RCT-1, baseline mindfulness was measured with the Kentucky Inventory of Mindfulness (KIMS; Baer, Smith, & Allen, 2004). This is a 39-item, 5-point Likert scale, self-report questionnaire, developed to measure mindfulness skills in four domains: Observe (12 items), Describe (8 items), Act with Awareness (10 items), and Accept without Judgment (9 items). The KIMS has good psychometric properties (Baum et al., 2010). In RCT-2 and RCT-3 mindfulness skills were measured with the Five Facet Mindfulness Questionnaire (FFMQ; Baer,

Smith, Hopkins, Krietemeyer, & Toney, 2006). This instrument is based on a factor analytic study of five independently developed mindfulness questionnaires (one of which is the KIMS). The FFMQ is a 39-item, 5-point Likert scale, self-report questionnaire, which covers five domains: Observing (8 items), Describing (8 items), Acting with awareness (8 items), Non-judging of inner experience (8 items) and Non-reactivity to inner experience (7 items). The psychometric properties of the Dutch FFMQ are reliable (αrange: .73 - .91) and valid for use in adults with clinically relevant symptoms of depression (Bohlmeijer, ten Klooster, Fledderus, Veehof, & Baer, 2011).

Rumination. In RCT-2, rumination was measured with the Ruminative Response Scale (RRS-NL; Raes, Hermans, & Eelen, 2003). This questionnaire contains 22 4-point Likert scale items, describing responses to depressed mood that are self-focused, symptom-focused, and focused on the possible causes and consequences of dysphoric mood. In RCT-1 and RCT-3 the extended version was used (RRS-NL-EXT; Raes & Hermans, 2007). This questionnaire contains 26 4-point Likert scale items and has an adequate reliability and good validity (Raes et al., 2009). It enables a distinction between 'reflection' (5 items) and 'brooding' (5 items). The brooding subscale refers to a more maladaptive way of thinking about depression and contains items like "Why do I always react this way?" and "What am I doing to deserve this?" (Schoofs, Hermans, & Raes, 2010).

2.5. Data management

Inconsistencies in measuring instruments were handled as described below.

2.5.1. Primary outcome

Depressive symptoms. Per study, total scores on depressive symptoms (HRSD-17, IDS-C, or IDS-SR) were calculated when a patient scored at least 60% of the corresponding items. In case of missing values on the remaining 40% of the items, person mean imputation was applied. Subsequently, scores on the IDS-C and IDS-SR were converted into HRSD-17 values to obtain one measure for depressive symptoms across studies. We refer to this converted measure as HRSD-C. The converter table used can be found in the Inventory of Depressive Symptomatology manual (IDS-QIDS, 2019) and is based on previous psychometric research on these questionnaires in depressed patients by Rush et al. (2003) and Trivedi et al. (2004).

2.5.2. Secondary outcome

Quality of Life. The psychological domain of the WHOQOL-Bref was used, which covers the following themes: bodily image and appearance, negative and positive feelings, self-esteem, spiritual/religion/personal beliefs, thinking, learning, memory and concentration. Scores of the domain were calculated based on the WHOQOL-Bref Manual (The WHOQOL Group, 1996). This includes allowing missing data on 1 item and applying person mean imputation when necessary. We refer to this outcome as QOL-PSY.

2.5.3. Moderator variables

Gender (male/female), age (in years), age of onset (in years), number of prior depressive episodes and medication use at baseline (yes/no) were assessed in the same manner across all participants. For other categorical baseline characteristics the least number of categories used across the three studies was maintained: marital status was brought back to three categories (single/married or cohabiting/divorced or widowed), employment to two categories (yes/no), and level of education to three categories (low/middle/high; Centraal Bureau voor de Statistiek, 2017).

Mindfulness. The FFMQ was used as a starting point, because this instrument is developed more recently. Given the fact that the FFMQ includes the subscale 'Nonreactivity to inner experiences', which is not included in the KIMS, it was decided to not use the total score for mindfulness in the current study. Data on three of the remaining FFMQ subscales ('Observing', 'Describing', and 'Non-judging of inner experiences') were calculated when a patient scored at least 60% of the corresponding items. In case of missing values on the remaining 40% of the items, person mean imputation was applied. For patients who scored the items of the KIMS, the same rule was applied (using the overlapping items and treating the non-overlapping items as missing). Only 3 of the 10 items of the FFMQ subscale 'Acting with awareness' overlapped with the KIMS, therefore, this subscale was excluded from the analyses in the current study.

Rumination. The brooding scale of the RRS-NL-EXT (Raes & Hermans, 2007) was used to measure rumination in RCT-1 and RCT-3. This subscale contains 5 items. The RRS-NL (Raes et al., 2003), which was used in RCT-2, contains 3 of these 5 items and these were used to calculate the brooding subscale. Again, at least 60% of the brooding scale items (≥ 3 from 5) needed to be present per patient and when necessary, person mean imputation was applied.

2.6. Statistical analysis

Firstly, to compare whether the group of participants included in the analyses was different from the group not included, see Fig. 1, with regard to the baseline characteristics and outcome variables, chi-square tests and independent *t*-tests were performed. Secondly, to test the hypothesis whether MBCT added to TAU was especially beneficial for those with a moderate amount of depressive symptoms, a moderated curvilinear regression analysis was performed. Thirdly, to identify subgroups that differed in the treatment efficacy, QUINT was performed. Below, the details of the latter two analyses are explained.

2.6.1. Confirmatory moderated regression analysis

As outcome variable post-treatment HRSD-C was used. As predictor variables, the condition variable, baseline HRSD-C, and all other baseline characteristics were included. In addition, a quadratic term of baseline HRSD-C was added. Before computing the quadratic term, baseline HRSD-C was centred. Finally, in a second block, the product terms of condition with baseline HRSD-C and of condition with squared baseline HRSD-C were included in the regression analysis. A significant change in multiple R^2 indicates whether the curvilinear effect of baseline HRSD-C is different for the two conditions. If so, probing of the interaction terms was used to investigate at which level(s) of baseline HRSD-C the conditions differed. If not, the analysis was performed again without including the interaction terms, as recommended by Hayes (2018).

2.6.2. Exploratory moderator analysis by QUINT

QUINT is a nonparametric tree-based subgroup identification method, appropriate for data from randomized controlled trials involving two experimental conditions. The aim of QUINT is to induce subgroups of patients, defined in terms of baseline characteristics that are involved in qualitative treatment-subgroup interactions. The result of an analysis with QUINT is a binary tree from which treatment assignment criteria can be derived. Therefore, it is recommended that all moderator variables included in the analyses are measured at baseline. QUINT assumes that the outcome variable is measured at interval level and has no further a priori assumptions about the measurement levels of the moderator variables or about the distributions of the variables. Because of the data-driven nature of QUINT, it should be regarded as an exploratory and hypothesis generating method (Breiman, 2001). Examples of applications of QUINT can be found in the field of clinical psychology (Doove, van Deun, Dusseldorp, & van Mechelen, 2016), and social and organisational psychology (Formanoy et al., 2016).

Before the analysis, the user needs to choose among several options to fit the tree (Dusseldorp, Doove, & van Mechelen, 2016). To fit the tree, the effect size criterion or the difference in means criterion may be used. Because the scale of the primary outcome variable, the Hamilton

Table 2
Descriptive statistics in the leaves of the QUINT results for HRSD-C (Fig. 3) using the intention-to-treat sample. The mean values and standard deviations (SD) on improvement in HRSD-C are displayed. A higher score means more improvement.

	MBCT + TAU			TAU				95% *CI*		
	n	Mean	*SD*	*n*	Mean	*SD*	Dif.	*LB*	*UB*	*d*
Leaf 1	25	1.18	5.05	15	3.03	6.70	−1.85	−5.99	2.29	−0.32
Leaf 2	15	−0.13	2.55	15	−3.90	4.01	3.77**	1.24	6.30	1.12
Leaf 3	15	1.73	4.46	20	2.63	3.89	−0.89	−3.85	2.07	−0.22
Leaf 4	18	4.97	6.79	15	−0.17	4.84	5.14*	1.00	9.28	0.86
Leaf 5	30	4.57	5.43	36	−1.63	5.52	6.19***	3.49	8.89	1.13
Leaf 6	22	1.77	4.80	29	0.93	4.85	0.84	−1.90	3.58	0.17
Leaf 7	17	−1.35	4.04	20	1.03	5.55	−2.38	−5.59	0.83	−0.48

Note. Dif. = Difference in mean change scores (baseline HRSD-C minus post-treatment HRSD-C) between conditions; CI = Confidence Interval; LB = Lower Bound; UB = Upper Bound; *d* = Cohen's *d*.
*$p < .05$. **$p < .01$. ***$p < .001$.

scale, is interpretable (e.g., a 5-points difference between groups has clinical meaning, Leucht et al., 2013), we chose the difference in means criterion. To prune the tree, in order to avoid overfitting, we decided the number of bootstrap samples to be 200 as recommended by (Dusseldorp et al., 2016). Because our total sample size in the analysis was about 300, the absolute value of $d_{\min}$ (i.e., the minimum value of the effect size in one of the green leaves assigned to P1, and in one of the red leaves assigned to P2, see for example Fig. 3) was set at a higher value (0.40) than the default (0.30). In this way, the risk of finding spurious subgroups was reduced (i.e., the Type I error rate was acceptable; see Dusseldorp & van Mechelen, 2014). For the remaining options, the default values were used.

QUINT was performed separately for both outcome variables. For depressive symptoms, the change in HRSD-C was used as outcome, that is, the post-treatment HRSD was subtracted from baseline HRSD-C to assure that a higher score means more improvement (i.e., a higher decrease in HRSD-C from baseline to post-treatment). For quality of live, the change in QOL-PSY was computed by subtracting baseline QOL-PSY from post-treatment QOL-PSY. As possible moderators, all baseline characteristics and the baseline levels of outcome measure were included in the analysis.

In the leaves of the pruned tree that resulted from the QUINT analyses, we performed independent *t*-tests to inspect whether mean differences between the treatment groups were significant. It should be noted that the significance level of these *t*-tests is somewhat inflated, due to the data-induced subgroups.

2.6.3. Intention to treat and per protocol

In addition to intention to treat (ITT) analyses, per protocol (PP) analyses were performed. Consistent with trials to date (Kuyken et al., 2010; Teasdale et al., 2000), an adequate dose of MBCT was defined as participation in at least 4 MBCT sessions. This minimum of attended MBCT sessions was applied to participants who were randomized to MBCT + TAU. A restriction of 0 MBCT sessions was imposed on participants randomized to TAU alone. See Fig. 1 for the number of participants who adhered to the protocol in each condition.

2.6.4. Computational note

As significance level, we used a two-sided alpha level of .050. All analyses were performed in SPSS version 25 (IBM Corporation, 2017), except for the QUINT analyses. The latter were performed using the R package quint version 2.0 (Dusseldorp, Doove, van de Put, & van Mechelen, 2018) in the R software environment.

3. Results

Of the available 393 participants, 101 were excluded from the analyses due to missing values, see Fig. 1. The excluded participants did not differ significantly on any of the baseline characteristics and outcome variables from those participants that were included in further analyses. One hundred forty-two (74%) of the 193 participants in the MBCT + TAU condition remained in the analyses, compared to 150 (75%) of the 200 participants in the TAU condition. This difference was not significant ($\chi^2(1, N = 393) = 0.10$, $p = .75$). The average HRSD-C of the participants in the MBCT + TAU condition declined from 11.70 ($SD = 7.96$) at baseline to 9.62 ($SD = 7.57$) at post-treatment ($t(141) = -4.67$, $p < .001$). In contrast, the HRSD-C of the participants in the TAU condition stayed about the same, 12.87 ($SD = 8.53$) at baseline and 12.70 ($SD = 8.38$) at post-treatment ($t(149) = -0.39$, $p = 0.70$). The difference in change of HRSD-C between the conditions was significant ($t(290) = -3.03$, $p < .01$) indicating that overall MBCT + TAU was effective on depressive symptoms. The average QOL-PSY of the participants in the MBCT + TAU condition improved from 46.49 ($SD = 16.26$) at baseline to 53.47 ($SD = 16.18$) at post-treatment ($t(129) = 6.11$, $p < .001$). Also, the average QOL-PSY of the participants in the TAU condition improved from 45.20 ($SD = 18.25$) at baseline to 49.71 ($SD = 19.10$) at post-treatment ($t(131) = 3.87$, $p < .001$). The difference in increase of QOL-PSY between the conditions was not significant ($t(290) = 1.52$, $p = .13$), indicating that overall MBCT + TAU was not effective on quality of life.

3.1. Results confirmatory moderated regression analysis

The addition of the interaction terms of condition*baseline HRSD-C and condition*baseline HRSD-C^2 was not significant in the moderated curvilinear regression analysis of post-treatment HRSD-C ($\Delta R^2 = .003$, $F(2,272) = 1.24$, $p = .29$). This means that the linear and quadratic effect of baseline HRSD-C did not moderate the effect of condition on post-treatment HRSD-C. Therefore, the regression analysis was repeated without the interaction terms. The result showed that both the linear and quadratic effect of HRSD-C at baseline were significant (respectively, $b = 0.64$, $t(274) = 14.48$, $p < .01$, and $b = 0.01$, $t(274) = 2.82$, $p < .01$, see Table 2). This tells us that the curvilinear effect of baseline HRSD-C is present, but it is the same for both conditions. Especially patients with a mild to severe level of baseline HRSD-C (between 9 and 21) show a lower level of post-treatment HRSD-C, see Fig. 2. The effect of condition was significant ($b = -2.11$, $t(274) = -3.61$, $p < .01$), which means that on average the MBCT + TAU condition scored −2.11 lower on post-treatment HRSD-C adjusted for the effects of all other variables. None of the other baseline characteristics showed a significant effect on post-treatment HRSD-C.

3.2. Intention-to-treat results by QUINT

3.2.1. Primary outcome: depressive symptoms

The ITT analysis by QUINT resulted in a pruned tree with seven leaves, see Fig. 3. Each leaf indicates a subgroup of patients. In three of these leaves (leaves 2, 4 and 5) MBCT + TAU was effective compared

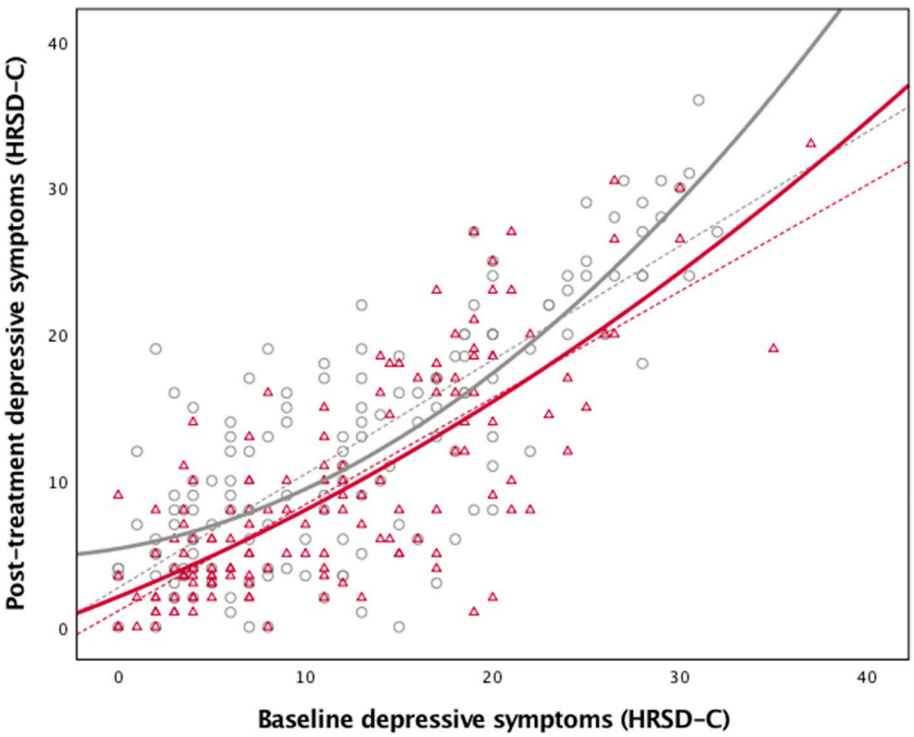

Fig. 2. Curvilinear effect of baseline depressive symptoms on post-treatment depressive symptoms, fitted separately for Mindfulness-Based Cognitive Therapy as an add-on to Treatment As Usual (MBCT + TAU, red solid line) and for TAU alone (grey solid line). As reference, the linear effects are displayed as dotted lines. The lines for MBCT + TAU are lower than those of TAU, suggesting a treatment main effect. The curves are about parallel, suggesting no interaction effect.

to TAU alone; these subgroups are shown in green. The difference between the conditions in mean improvement was significant in each of these subgroups, see Table 2. Furthermore, the corresponding effect sizes (Cohen's *d*) were high (i.e., > 0.80). QUINT also identified subgroups for which TAU alone was effective compared to MBCT + TAU; these are shown in red, see Fig. 3. However, in each of these subgroups the difference between the conditions in mean improvement was not significant, see Table 2.

The branches of the tree identify the characteristics of the patients in the subgroups. We focus here on the subgroups that showed a significant treatment outcome difference. Patients with a lower age of onset (≤30.5) and higher baseline levels of brooding at baseline (RRS-brooding > 14.5) who received MBCT + TAU showed a larger improvement in HRSD-C (6.2 points larger) than the same type of patients who received TAU alone (Leaf 5). In addition, patients with a "medium" age of onset (between 15 and 30), a lower level of brooding (≤14.5), and a higher level of depressive symptoms at baseline (HRSD-C > 12.5) who received MBCT + TAU showed a larger improvement in HRSD-C (5.1 points larger) than the same type of patients who received TAU alone (Leaf 4). Finally, patients with a medium age of onset (between 15 and 30), lower levels of both brooding (≤14.5), and depressive symptoms at baseline (HRSD-C < 4.5) showed less deterioration in HRDS-C after MBCT + TAU (−0.1 points) than after TAU alone (−3.9 points; Leaf 2, see Table 2).

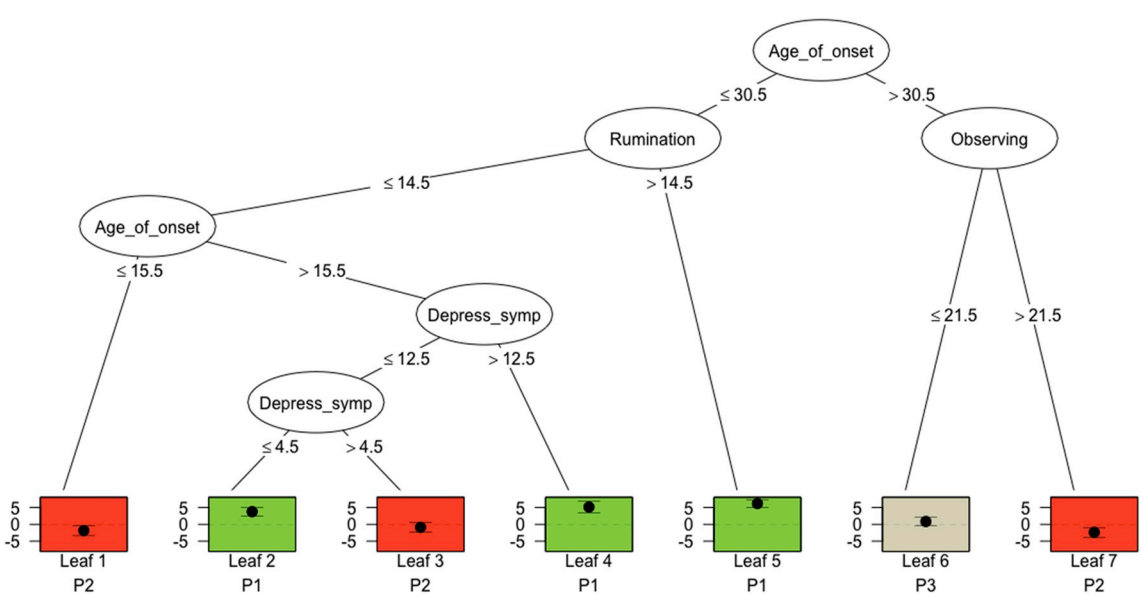

Fig. 3. Result of QUINT analysis with improvement in depressive symptoms (baseline HRSD-C minus post-treatment HRSD-C) as outcome using the intention-to-treat sample. In the green leaves (P1), MBCT + TAU is more beneficial than TAU alone; for the red leaves (P2) the reverse is true. In the grey leaves (P3), there is no difference between the interventions.

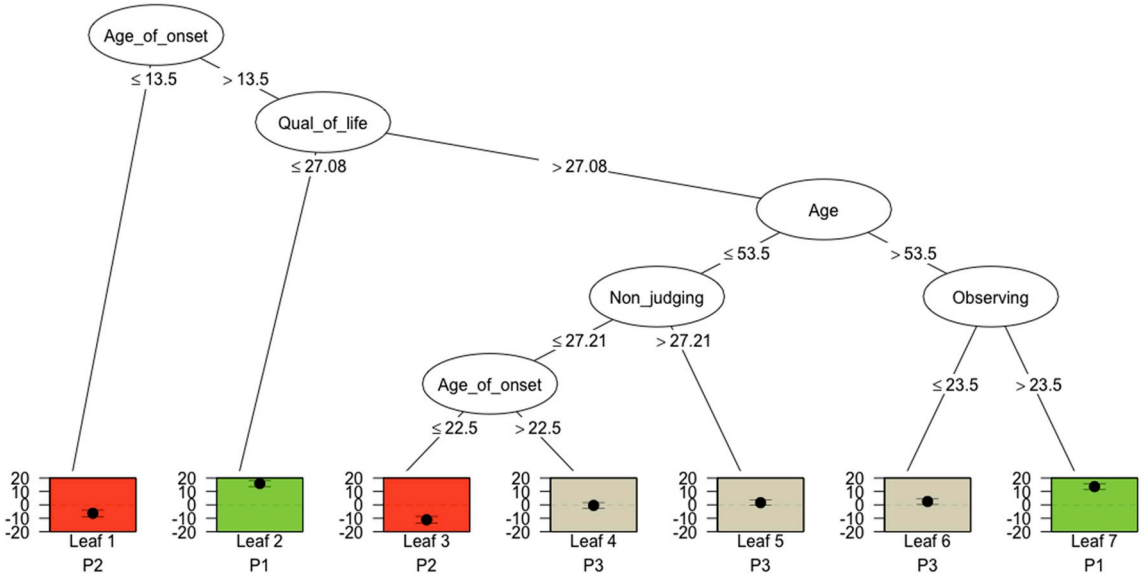

Fig. 4. Result of QUINT analysis with improvement in quality-of-life (post-treatment QOL-PSY minus baseline QOL-PSY) as outcome using the intention-to-treat sample. In the green leaves (P1), MBCT + TAU is more beneficial than TAU alone; for the red leaves (P2) the reverse is true. In the grey leaves (P3), there is no difference between the interventions.

3.2.2. Secondary outcome: psychological subscale of quality of life

The ITT QUINT analysis for QOL-PSY resulted in a pruned tree with seven subgroups, see Fig. 4. In two of these subgroups (leaves 2 and 7), MBCT + TAU was effective compared to TAU alone whereas in two subgroups the reverse was true: TAU alone was more effective than MBCT + TAU (leaves 1 and 3). In the subgroups of patients for whom MBCT + TAU was more beneficial, the difference in mean change score was significant, see Table 3. The corresponding effect sizes were high (> 0.80). One of the subgroups of patients for whom TAU alone was better than MBCT + TAU, showed a significant difference in mean change score (Leaf 3). The corresponding effect size was high (> |0.80|). In the remaining subgroups (Leaves 4, 5 and 6), there was no difference in response to the two interventions.

Patients with a lower baseline QOL-PSY (≤27.08) who received MBCT + TAU showed a larger improvement in QOL-PSY (15.9 points) than the same type of patients who received TAU alone (Leaf 2, Table 3). The characterization of the other two subgroups with a significant difference in treatment outcome (leaves 3 and 7) is more complex: they consist of combinations of splits on four different splitting variables (i.e., age of onset, baseline QOL-PSY, age, and either FFMQ-non-judging or FFMQ-observing).

3.3. Per-protocol results by QUINT

3.3.1. Primary outcome: depressive symptoms

The PP analysis by QUINT resulted in a pruned tree with six leaves (see Appendix A, Figure A1). The first, third and fourth split of this tree (i.e., on the variables age of onset, RRS-brooding, and again on age of onset) were exactly the same as in the ITT tree, see Fig. 3. In the subgroups of patients for whom MBCT + TAU was more beneficial (leaves 3 and 4, see Figure A1), the difference in mean change score was significant, see Table A1. In the other four subgroups the difference in mean change score between the conditions was not significant, see Table A1. The characteristics of the patients in Leaf 4 were the same as those in Leaf 5 of the ITT analysis: patients with an earlier onset (≤30.5) and a higher level of brooding at baseline (RRS-brooding > 14.5) who received MBCT + TAU showed a larger improvement in HRSD-C (6.5 points) than the same type of patients who received TAU alone.

3.3.2. Secondary outcome: psychological subscale of quality of life

The PP analysis by QUINT for the secondary outcome resulted in a pruned tree with six leaves, see Appendix A, Figure A2. The first and second split of this tree (i.e., on the variables baseline QOL-PSY and age) corresponded to the second and third split of the ITT tree, see Fig. 4. In the subgroups of patients for whom MBCT + TAU was more

Table 3
Descriptive statistics in the leaves of the QUINT results (Fig. 4) for QOL-PSY using the intention-to-treat sample. The mean values and standard deviations (SD) on improvement in QOL-PSY are displayed. A higher score means more improvement.

	MBCT + TAU			TAU				95% *CI*		
	n	Mean	*SD*	*n*	Mean	*SD*	Dif.	*LB*	*UB*	*d*
Leaf 1	18	4.54	14.56	17	10.83	13.72	−6.30	−16.02	3.43	−0.45
Leaf 2	16	19.53	17.66	22	3.60	7.96	15.93**	6.05	25.82	1.23
Leaf 3	19	4.65	10.59	13	15.77	15.89	−11.12*	−21.64	−0.60	−0.86
Leaf 4	20	5.63	9.77	18	6.02	12.48	−0.39	−7.86	7.07	−0.04
Leaf 5	21	4.96	12.26	25	3.33	9.39	1.63	−5.00	8.25	0.15
Leaf 6	19	3.95	10.80	22	1.44	15.30	2.51	−5.79	10.80	0.19
Leaf 7	18	7.18	10.09	15	−6.44	11.91	13.62**	5.65	21.59	1.24

Note. Dif. = Difference in mean change scores (post-treatment QOL-PSY minus baseline QOL-PSY) between conditions; CI = Confidence Interval; LB = Lower Bound; UB = Upper Bound; *d* = Cohen's *d*.
*$p < .05$. **$p < .01$.

beneficial (leaves 1 and 6; see Figure A2), the difference in mean change score was significant, see Table A2. Also, in the subgroup of patients for whom TAU alone was more beneficial (Leaf 3), the difference in mean change score was significant, see Table A2. The characteristics of the patients in Leaf 1 were the same as those in Leaf 2 of the ITT analysis: Patients with a lower baseline QOL-PSY (≤27.1) who received MBCT + TAU showed a larger improvement in QOL-PSY (17.5 points) than the same type of patients who received TAU alone (Table A2).

4. Discussion

The current study aimed to identify moderators of treatment effect for MBCT + TAU versus TAU alone, in patients with depression. An IPD analysis was performed (N = 292), including patients with recurrent depression in (partial) remission, currently depressed and chronically or treatment-resistant depressed. Overall efficacy results showed that MBCT + TAU outperformed TAU alone in decreasing depressive symptoms from baseline to post-treatment. Furthermore, all patients (irrespective of condition) with mild to severe baseline levels of depressive symptoms, showed a stronger decrease in depressive symptoms compared to patients with none to very mild or very severe baseline levels of depressive symptoms. Qualitative interaction sub-group analyses revealed that MBCT + TAU might be more beneficial than TAU alone for patients with earlier onset and higher baseline levels of rumination and for patients with a lower baseline quality of life.

4.1. Depression

Overall, MBCT + TAU outperformed TAU alone, which is in line with literature to date for recurrently depressed patients in (partial) remission (Kuyken et al., 2016), those who are currently depressed (Goldberg et al., 2018; Hedman-Lagerlof et al., 2018; Lenz et al., 2016), and patients with chronic or treatment-resistant depression (Barnhofer et al., 2009). To our knowledge, this is the first study that examined a possible curvilinear association of baseline depressive symptoms on post-treatment depressive symptoms. As expected, patients with very mild and very severe baseline depressive symptoms appeared to have a smaller reduction of depressive symptoms than patients with mild to severe levels of baseline depressive symptoms (inverted U-curve). This is in line with recent suggestions that psychological processes and outcome may run an inverted U-curve trajectory (Grant & Schwartz, 2011).

However, baseline depressive symptoms did not moderate the intervention effect. This contradicts the idea that adding MBCT to TAU could cause harm in patients with severe depression as lately has been proposed (van Dam et al., 2017). Although the current study included patients with a wide range of baseline depressive symptoms, it should be noted that extremely severe depressed patients (≥37 points on the HRSD), were not included in the current study. For this specific patient group, no statements can be made about whether MBCT for depression can be of added value or has a possible counterproductive effect. The current findings also seem to be in contrast with the results of the IPD meta-analysis by Kuyken et al. (2016), who found that severity of baseline depressive symptoms predicted a better response to MBCT in terms of prevention of relapse. In their study, only recurrently depressed patients (partial) in remission were included, restricting the range of baseline depression severity, which might be in line with the upward slope of the inverted U-curve (Britton, 2019). Besides, Kuyken et al. (2016) performed linear regression analyses including condition, baseline depressive symptoms and their interaction, while not allowing a possible non-linear trajectory of baseline depression severity which could have led to finding a spurious moderating effect (Lubinski & Humphreys, 1990).

Results from the Qualitative INteraction Trees (QUINT) analysis on depression outcome revealed that for several subgroups MBCT + TAU appeared to be more beneficial than TAU alone. Especially for those with an earlier onset (≤30.5 years) and higher baseline levels of rumination (> 14.5). This subgroup was found in both the ITT and PP analysis. This is in line with the theoretical underpinnings of MBCT. In MBCT, patients learn to recognize automatic activation of their habitual dysfunctional cognitive processes that lead to depression, e.g., rumination, and decentre and disengage from these dysfunctional processes. The underlying theoretical model is called the 'differential activation hypothesis' (Teasdale, 1988) which assumes that vulnerability to depression increases with each depressive episode, because previous patterns of negative thoughts become easier accessible when feeling low. In line with the current finding, Ma and Teasdale (2004) found in recurrently depressed patients in remission that patients with an earlier onset had stronger benefits of MBCT in terms of preventing depressive relapse/recurrence. However, this was not confirmed by the research by Kuyken et al. (2016).

The QUINT analysis did not reveal clear evidence of subgroups for whom TAU alone was more beneficial than additional MBCT. This points into the direction that, in general, the addition of MBCT to TAU does not lead to worsening of depressive symptoms. No clear moderating effects were found for age, gender, educational level and marital status, employment, number of prior depressive episodes, and medication use.

4.2. Quality of life

To our knowledge, this is the first study that investigated qualitative subgroup-treatment interactions with an increase in quality of life as outcome measure. Results from the QUINT analysis showed that for patients with relatively lower scores on quality of life at baseline (≤27.08), the addition of MBCT to TAU is more beneficial than TAU alone. This effect was found in both the ITT and PP analysis. In addition, MBCT + TAU was also more beneficial than TAU alone for patients with an age of onset of 13.5 years or older, relatively higher baseline quality of life (> 27.08), who were > 53.5 years old, and scored relatively high on the mindfulness skill 'Observing' (> 23.5). One very specific subgroup of patients was identified in which TAU seemed to outperform MBCT + TAU, namely patients with an age of onset during adolescence (between 13.5 and 22.5 years), with relatively higher baseline levels of quality of life (> 27.08), age of 53.5 years or younger, who score 27.21 or lower on the mindfulness skill 'Non-judging of inner experience'. This seems less practical to implement in clinical practice but nevertheless gives a clear direction of which variables to further investigate in future research. These results encourage similar research in different populations to further investigate age of onset, baseline quality of life, age, and separate facets of mindfulness as possible moderating variables in terms of treatment effect on quality of life in MBCT for depression. No moderating effects were found for gender, educational level, marital status, employment, number of prior depressive episodes, medication use, and baseline levels rumination.

4.3. Strengths

The analytical technique used in the current study is clearly an advantage to investigate which subgroups benefit more from which type of intervention, which is very important in optimizing treatment assignment. Being a data-driven subgroup identification method, there is a risk of overfitting the data (i.e., fitting a tree that is too large and in this way finding spurious subgroups). However, by applying a pruning procedure based on bias-corrected bootstrapping QUINT controls this risk (Lipkovich, Dmitrienko, & D'Agostino Sr., 2017). This procedure uses resampling with replacement of patients in the original sample and estimates the amount of optimism in the partitioning criterion using the bootstrap samples as training data and the original sample as test data. In this way, bootstrapping is combined with cross-validation, which is recommended as a model validation method not only in tree-based

models (LeBlanc & Crowley, 1993) but in any multivariable prognostic model (Harrell, Lee, & Mark, 1996). In addition, QUINT allows the user to control the Type I error rate by specifying the minimum value of the effect size in a leaf. QUINT yields output with possible treatment assignment criteria, which makes it highly suitable for generating hypotheses about which patient characteristics to consider in future research and which patient characteristics possibly matter for clinical practice. Second, the current study is highly ecologically valid, which contributes to the generalization to secondary and tertiary care in depressed patients. Data were derived from three multicenter RCTs with few exclusion criteria. In addition, patients were treated in routine clinical care where they received MBCT in mixed groups comprising both research participants and clinical patients. Third, the current study analyzed data from a wide range of depressed patients, from fully remitted to chronic and treatment-resistant depression. This led to a more adequately powered investigation of the possible moderating effect of baseline depressive symptoms on treatment outcome. Fourth, different facets of mindfulness were included as possible moderators for treatment outcome, which is in line with recent suggestions that each mindfulness skill might influence treatment outcome in its own way (Eisenlohr-Moul, Walsh, Charnigo, Lynam, & Baer, 2012).

4.4. Limitations

Of course, the current study is not without limitations. First, the three RCTs used different measurement instruments to assess depressive symptoms. The three resulting scales had to be converted to a common metric using a converter table. As a conversion table always introduces some error, we would ideally have used the same measurement instrument in each study. However, the converter table used is based on previous psychometric research on the same three scales in large samples (N = 596–946) in patients with depressive disorders (Rush et al., 2003; Trivedi et al., 2004). It was found that these scales were equally sensitive to symptom change indicating high concurrent validity. Second, it is important to acknowledge that the effects in the subgroups found by a data-driven method are overestimated (Lipkovich, Dmitrienko, & D'Agostino, 2017). Therefore, the current study used a particularly conservative approach by also performing independent t-tests within the subgroups to inspect whether mean differences between the treatment groups were significant. However, the significance level of such a test is somewhat inflated due to the data-induced subgroups. QUINT has a double bootstrapping method to obtain honest estimates for the effect sizes in the subgroups, but this procedure is yet restricted to the two extreme leaves only (Dusseldorp & van Mechelen, 2014, supplementary material). A better option for inference in the leaves of the tree would be to estimate confidence intervals around the treatment outcome difference using a bootstrap procedure such as Loh, He, and Man (2015) but this procedure still needs to be developed for QUINT. Third, a problem not specific to this study, is that most tree-based algorithms have the (slight) tendency to prefer variables with more possible split points (e.g., continuous variables and categorical variables with many categories; Hothorn, Hornik, & Zeileis, 2006). Even though it is likely that the categorical variables included in the current study did not moderate the intervention effect (i.e., gender, employment, medication use, educational level, and marital status), this cannot be ruled out entirely. Finally, due to missing data on at least one of the investigated variables, the analyses were finally conducted among 292 patients, while the recommended sample size for QUINT is higher ($N \geq 400$; Dusseldorp & van Mechelen, 2014). However, this problem was highly diminished by a priori adjustment of a control parameter used in the analysis (i.e., increasing the minimum required value of the effect size in a leaf $d_{\min}$).

4.5. Conclusions and implications

This study aimed to identify moderators of treatment effect for MBCT versus TAU in depressed patients by using the QUINT method. Particularly patients with an earlier onset and higher rumination levels and patients with a lower quality of life seemed to benefit more from the addition of MBCT to TAU than TAU alone. This is a first step to improve personalized assignment of MBCT for depressed patients. Before definite treatment assignment criteria can be formulated and implemented in clinical practice, the current findings should be replicated, treatment outcome of the leaf nodes of the trees should be estimated in an independent test dataset and, preferably, also long-term outcomes should be included in future research.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2019.103467.

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