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Factors associated with relapse and recurrence of major depressive disorder in patients starting mindfulness-based cognitive therapy

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Abstract

Background: Mindfulness-based cognitive therapy (MBCT) is effective for relapse prevention in major depressive disorder (MDD). It reduces cognitive reactivity (CR) and rumination, and enhances self-compassion and mindfulness. Although rumination and mindfulness after MBCT are associated with relapse, the association of CR, rumination, self-compassion, and mindfulness with relapse before initiation of MBCT has never been investigated.

Methods: Data were drawn from two randomized controlled trials, including a total of 282 remitted MDD participants (≥3 depressive episodes) who had been using maintenance antidepressant medication (mADM) for at least 6 months before baseline. All participants were offered MBCT while either their mADM was maintained or discontinued after MBCT. CR, rumination, self-compassion, and mindfulness were assessed at baseline by self-rated questionnaires and were used in Cox proportional hazards regression models to investigate their association with relapse.

Results: CR and mindfulness were associated with relapse, independent of residual symptoms, previous depressive episodes, and mADM-use. Higher CR and lower mindfulness increased the risk of relapse. Self-compassion was not associated with relapse. For rumination, a significant interaction with mADM-use was found. Rumination was associated with relapse in patients who discontinued their mADM, while this effect was absent if patients continued mADM.

Conclusions: These results show that CR, rumination, and mindfulness are associated with relapse in remitted MDD-patients before initiation of MBCT, independent of residual symptoms and previous depressive episodes. This information could improve decisions in treatment planning in remitted individuals with a history of depression.

Jessica M. de Klerk-Sluis and Marloes J. Huijbers shared the first authorship.

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KEYWORDS
antidepressants, depression, mindfulness/meditation

1 | INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric disorder affecting more than 350 million people worldwide (Marcus et al., 2012). MDD has the highest burden of psychiatric disorders in high-income countries and is expected to have the second-highest burden worldwide in 2030 (Mathers & Loncar, 2015; Sobocki et al., 2006). MDD is associated with a 50%–80% lifetime recurrence rate, therefore reduction of relapse risk is important.

Mindfulness-based cognitive therapy (MBCT) is an established intervention for patients with recurrent depression, combining elements of cognitive-behavioral therapy (CBT) and mindfulness-based stress reduction (Beck et al., 1979; Godfrin & Heeringen, 2010; Kabat-Zinn, 1990; Ma & Teasdale, 2004; Piet & Hougaard, 2011; Teasdale et al., 2000). MBCT is expected to reduce the engagement in repetitive negative thinking patterns of patients with recurrent depression, which already seem to occur during a mildly negative mood (Nolen-hoeksema, 1991). There is evidence that MBCT changes cognitive reactivity (CR), rumination, self-compassion, and mindfulness. There is growing evidence that these factors are indeed mediating the reduced relapse risk by MBCT (Cladder-Micus et al., 2018; Frostadottir & Dorjee, 2019; Gu et al., 2015; Van der Velden et al., 2015). CR is the vulnerability to indulge in patterns of negative thinking when experiencing (mild) dysphoric mood states (Figueroa et al., 2015; Segal et al., 2006; Van der Does, 2002). Rumination refers to repetitive and passive thoughts about one's negative feelings and symptoms (Nolen-hoeksema, 2000). Self-compassion is the capacity to respond kindly and compassionately to oneself when facing difficult situations (Neff, 2003). Mindfulness refers to the capacities of bringing one's deliberate attention to present moment experience with a kind, non-judging attitude (Baer et al., 2006).

Two important clinical factors associated with relapse are the number of previous episodes and the presence of residual symptoms (Hardeveld et al., 2010). In addition, CR measured by the self-rated Leiden Index of Depression Sensitivity (LEIDS; Van der Does, 2002) and its subscale 'rumination' were associated with relapse, in patients with ≥MDD-episodes (Elgersma et al., 2015; Figueroa et al., 2015; Moulds et al., 2008). Moreover, rumination and mindfulness after MBCT were associated with relapse after a 12-month follow-up (Michalak et al., 2008, 2011). Self-compassion also seems to be associated with depressive symptoms (López et al., 2018), but its association with relapse has not yet been investigated. Clinically, one would like to know how CR, rumination, self-compassion, and mindfulness are associated with future relapses of MDD-episodes in a patient group receiving MBCT.

Although maintenance antidepressant medication (mADM) significantly reduces the risk of relapse, this risk returns after stopping them (Geddes et al., 2003). Patients are often reluctant of long-term mADM usage, due to (fear of) side-effects or the perception that it would be difficult to discontinue ADM after long-term use (Sansone & Sansone, 2012). MBCT could be effective to reduce relapse risk after mADM discontinuation (Tickell et al., 2020). By investigating the effect of mADM discontinuation on the association of relapse with CR, rumination, self-compassion, and mindfulness clinicians could additionally indicate whether patients starting MBCT might be at higher risk when tapering their mADM.

Therefore, we aimed to examine whether baseline CR, rumination, self-compassion, and/or mindfulness are associated with future relapse/recurrence of MDD-episodes in a patient group receiving MBCT while either continuing or discontinuing their mADM.

2 | MATERIALS AND METHODS

2.1 | Design

We used data from two multicentre, randomized controlled trials (the MOMENT-study; Huijbers et al., 2012) approved by the CMO Arnhem-Nijmegen. The first trial consisted of patients who were randomly allocated to MBCT + mADM ($n = 121$) or MBCT + mADM discontinuation ($n = 128$), patients in the second trial were randomly allocated to MBCT + mADM ($n = 33$) or mADM alone ($n = 35$). For the current cohort study, we selected all participants allocated to MBCT, that is, those from the first trial (N = 249), plus the 33 patients allocated to MBCT + mADM from the second trial. All participants used mADM at the start of the trial and were offered eight weeks of MBCT. All participants gave written informed consent.

2.2 | Participants

Participants were recruited via 12 universities and secondary healthcare centers across the Netherlands. Dutch speaking participants (>18 years) with a history of ≥3 depressive episodes according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) were included; currently not meeting the criteria of a depressive episode assessed by the Structured Clinical Interview for DSM-IV (SCID); either in full (Inventory of Depressive Symptomology-Clinician (IDS-C) ≤ 11) or partial (IDS-C > 11) remission; and had been treated with mADM for ≥6 months. Exclusion criteria were: bipolar and/or primary psychotic disorder; clinically relevant neurological/somatic illness; current substance dependency; high dosage of benzodiazepines; electroconvulsive therapy in the past three months; previous MBCT and/or extensive meditation experience; and receiving frequent psychological treatment (more than once per 3 weeks).

2.3 | Procedures

The SCID-I (First et al., 1996) was performed by trained research assistants to assess the eligibility of participants. After randomization and baseline assessment, MBCT started within 2 months after randomization. Follow-up assessments took place after 3, 6, 9, 12, and 15 months.

2.4 | Interventions

2.4.1 | Mindfulness-based cognitive therapy

MBCT was based on the protocol developed by Segal et al. (2013) with a few alterations to intensify the original treatment. The treatment consisted of eight weekly 2.5-h group sessions and one day of silence practice during the second half of the course. Participants were encouraged to practice meditation each day for 45 min. For further detail see the MOMENT study protocol (Huijbers et al., 2012).

2.4.2 | Maintenance antidepressant medication

For all participants, mADM at the start of the study was reviewed by a study psychiatrist. For patients who were kept on mADM, psychiatrists maintained or reinstated an adequate dose of mADM and provided recommendations to manage side effects. Patients who were randomized to mADM discontinuation were seen by a study psychiatrist (3–12 visits). During the first MBCT week, patients were informed and prepared for mADM discontinuation. At Week 7, patients were asked to discontinue their mADM. For all common ADMs, a tapering scheme of 5 weeks was used and a specific withdrawal scheme for more exceptional treatments was determined from the shared opinion of the authors.

2.5 | Study measures

Relapse was determined at each follow-up assessment via a SCID-I-interview (First et al., 1996). Table S1 summarizes the questionnaires measured at baseline. In brief, residual symptoms were measured with the IDS-C (Rush et al., 1996). CR was measured with the LEIDS-Revised (LEIDS-R; Van der Does, 2002). Previously, the rumination subscale appeared to be better associated with relapse than the LEIDS-total (Figueroa et al., 2015). Therefore, the total LEIDS-R scores and the LEIDS-rumination scores were added in two separate analyses to investigate which is better associated with relapse in this patient group receiving MBCT. In addition to the LEIDS-subscale, rumination was also measured with the Ruminative Response Scale (RRS; Nolen-Hoeksema, 1991). The brooding subscale has been shown to be associated with depressive symptoms, while the reflection subscale was not (Schoofs et al., 2010). Therefore, we did two separate analyses; one with the RRS-total and one with the RRS-brooding subscale. Self-compassion was measured with the Self Compassion Scale (SCS; Neff, 2003) and Mindfulness with the Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2006).

2.6 | Statistical analysis

We used Cox proportional hazards regression models to examine the associations of baseline CR (LEIDS-R), rumination (RRS), self-compassion (SCS), and mindfulness (FFMQ) scores with time to first relapse (primary endpoint). Patients dropping out during follow-up or without a relapse within 15 months were considered censored. Well-established factors associated with relapse, that is, residual depressive symptoms at baseline (IDS-C) and number of previous depressive episodes (log-transformed), were a-priori included as covariates in all Cox-analyses (Hardeveld et al., 2010).

Because compliance to discontinuation and maintenance of mADM was variable, we added ADM discontinuation as time-dependent covariate to the model (i.e., using the timepoint during follow-up where the patient actually discontinued mADM).

First, for each factor of interest (i.e., LEIDS-R, RRS, SCS, and FFMQ), we applied a multivariate model including the factor of interest, IDS-score, number of previous depressive episodes, mADM-use, and the interaction of the factor of interest with mADM-use. The multivariate models were then pruned by stepwise eliminating the nonsignificant variables/interactions ($p \geq .050$) to obtain the most parsimonious model. We assessed the optimal association between these models with the Akaike Information Criterion (AIC). Second, we combined all significant factors of interest, assessed with the analysis above, in a multivariate model. Because our factors of interest are continuous variables, the hazard ratio (HR) indicates the change in the risk of relapse if the score of the questionnaire rises by one unit. To show the clinical significance of our factors of interest, we summarized relapse risks stratified for incremental levels of these factors, numbers of episodes, residual symptoms, and mADM-use in Supporting Information Risk Tables (using logistic regression models). Eighty-five participants dropped out or relapsed before finishing the first 3 months (i.e., the MBCT-period). We therefore performed a sensitivity analysis by using baseline scores in the group that completed the first three months.

3 | RESULTS

3.1 | Demographics and clinical characteristics

We included 282 participants. Twenty-two patients were excluded; 19 due to missing baseline scores, 1 due to an unknown ADM discontinuation date, and 1 because of a relapse 10 weeks before starting MBCT, leaving 260 patients for analysis. There were several significant differences in clinical characteristics between the two as received intervention groups (Table 1).

TABLE 1 Characteristics of patients with recurrent depression who were offered MBCT + mADM or MBCT with mADM discontinuation (as received), including patients from two trials and excluding those with missing baseline data, missing data on discontinuation, and one incorrectly randomized patient

	MBCT/ mADM (*n* = 183) *N* (%)	MBCT/ADM discontinuation (*n* = 77) *N* (%)	All subjects (*n* = 260) *N* (%)	*p*[a]
Female	117 (63.9)	59 (76.6)	176 (67.7)	**.046**
Educational level				.566
Low	12 (6.7)	8 (10.5)	20 (7.9)	
Middle	48 (27.0)	21 (27.6)	69 (27.2)	
High	118 (66.3)	47 (61.8)	165 (65.0)	
Marital status				.851
Single	45 (25.0)	17 (22.4)	62 (24.2)	
Married/cohabiting	106 (58.9)	45 (59.2)	151 (59.0)	
Divorced/widowed	29 (16.1)	14 (18.4)	43 (16.8)	
Employed	108 (59.0)	59 (76.6)	167 (64.2)	**.007**
Remission				**.040**
Full, IDS-C ≤ 11	91 (49.7)	49 (63.6)	140 (53.8)	
Partial, IDS-C > 11	92 (50.3)	28 (36.4)	120 (46.2)	
Type of mADM				.573
SSRI	135 (73.8)	60 (77.9)	195 (75.0)	
TCA	36 (19.7)	11 (14.3)	47 (18.1)	
Other	12 (6.6)	6 (7.8)	18 (6.9)	
Previous CBT treatment	112 (61.2)	39 (50.6)	151 (58.1)	.115
Suicide attempts	31 (16.9)	18 (23.4)	49 (18.8)	.226
Relapse	71 (38.8)	49 (63.6)	120 (46.2)	**.000**
	Mean (*SD*)	**Mean (*SD*)**	**Mean (*SD*)**	***p***[a]
Age	50.5 (11.3)	49.7 (10.9)	50.3 (11.1)	.605
IDS-C (baseline)[b]	12.0 (15.0)	9.0 (10.0)	10.0 (14.0)	.068
Nr. previous episodes[b]	5.0 (4.0)	4.0 (3.0)	4.0 (3.0)	.197
Age of MDD onset[b]	22.0 (14.0)	25.0 (16.0)	23.0 (15.0)	.187
LEIDS-R (baseline)	77.8 (14.1)	76.7 (16.8)	77.4 (14.9)	.647
LEIDS-R-Rumination (baseline)[b]	18.0 (6.0)	18.0 (6.0)	18.0 (6.0)	.470
RRS (baseline)	48.1 (10.4)	47.6 (12.9)	47.9 (11.2)	−695
RRS-Brooding (baseline)[b]	11.0 (4.0)	11.0 (5.0)	11.0 (4.0)	.543
SCS (baseline)	86.2 (14.7)	87.7 (14.5)	86.7 (14.6)	−491
FFMQ (baseline)	116.6 (16.6)	117.0 (15.2)	116.7 (16.2)	−874

Abbreviations: CBT, cognitive-behavioral therapy; FFMQ, Five Facet Mindfulness Questionnaire; IDS-C, Inventory of Depressive Symptomatology – Clinician rated; LEIDS-R, Leiden Index of Depression Sensitivity-Revised; mADM, maintenance antidepressant medication; MBCT, mindfulness-based cognitive therapy; MDD, major depressive disorder; RRS, Ruminative Response Scale; SCS, Self-Compassion Scale; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]Difference Event/Stop before finishing MBCT versus Event/Stop after finishing MBCT.

[b]Due to skewed distribution medians and 25%–75% interquartile range are reported and a nonparametric test (Mann–Whitney *U*) was used.

Patients in the MBCT/mADM-discontinuation group were more often female, employed, and in full remission compared to patients in the MBCT/mADM group (all $p \leq .046$), indicating that at the start of the study, participants in the MBCT/mADM-discontinuation group appeared more clinically stable than in the MBCT/mADM group. There were no significant differences in factors of interest between the two groups.

Eighty-five of 260 participants (32.7%) dropped out or relapsed before the 3-month measurement. As a group, patients who had a relapse or dropped out early were more often in partial (rather than full) remission, had a lower age and age of onset of MDD, scored higher on CR and rumination, and lower on mindfulness (all $p \leq .038$; Table S2). Thus, patients who dropped out or experienced a relapse before the 3-month measurement were more severely affected than patients who did not.

3.2 | Association with future relapse

Table 2 presents the most parsimonious models with CR, rumination, self-compassion, or mindfulness as factors of interest. Residual symptoms and (discontinuation of) mADM-use were associated with relapse in all models (all $p \leq .031$). After discontinuation of mADM, the relapse rate was 1.6–1.7 times greater compared to continuing mADM. The number of previous episodes was only associated with relapse in the self-compassion and mindfulness models ($p = .045$ and $p = .032$, respectively).

The significant association of relapse with CR, measured by LEIDS-R (HR = 1.019 [95% confidence interval (95% CI) = 1.007–1.030]), was independent of mADM-use (HR = 1.650 [1.073–2.538]) and did not change when mADM was used or not (i.e., no significant mADM-use*CR-interaction ($p = .177$)). Every 10-point increase in LEIDS-R resulted in approximately a 20.7% increase in relapse rate, with residual symptoms and mADM-use as independent factors associated with relapse in this model (Tables S3.1–S3.2).

For rumination measured by the LEIDS-R-subscale, we also found a significant association with relapse (HR = 1.068 [1.023–1.114]) although the AIC was slightly worse compared to the model with the full LEIDS-R. For rumination as measured by the RRS, we found an additional interaction between RRS-score and mADM-use ($p = .010$). This interaction indicated that rumination (RRS-scores) was especially associated with relapse in patients who discontinued mADM, while this effect was absent if patients continued mADM (Figure 1 and Tables S3.3–S3.4). When we confined the RRS-score to the brooding subscale, this interaction became nonsignificant, with higher AIC; that is, a worse model.

Mindfulness was significantly associated with relapse ($p = .020$). Every 10-point increase in FFMQ resulted in approximately a 14.0% decrease in risk of relapse (HR = 0.985 [0.973–0.998]). This was independent of residual symptoms, previous episodes, and mADM-use (Tables S3.5–S3.6). Self-compassion was not associated with relapse ($p = .229$).

Table S4 shows correlations between the variables of interest. Baseline LEIDS-R, RRS, SCS, and FFMQ were correlated. However, only the subscales relative to their full scale (LEIDS/RRS) and the SCS relative to FFMQ were highly correlated (>0.5). Finally, we included CR, RRS, and mindfulness scores in one model (Table 3). This model had the lowest AIC (1168.971). Only residual symptoms and mADM-use*RRS-interaction remained significant in this combined model ($p = .032$ and $p = .029$, respectively); CR, mindfulness, and mADM-use were no longer significantly associated with relapse ($p \geq .111$). When the subscale brooding was added instead of the total RRS-score (Table 3), the AIC of this model was higher compared to the model with the total RRS scale ($\Delta AIC = 3.046$). Moreover, the mADM-use*RRS-brooding-interaction was nonsignificant and discarded from the model. In the remaining model, thus without mADM-use*RRS-brooding-interaction, CR and mADM discontinuation became significantly associated with relapse ($p = .009$ and $p = .031$, respectively); all other variables were nonsignificant ($p \geq .073$).

3.3 | Sensitivity analyses

To examine how results were affected by 85 early dropouts/relapses (within 12 weeks), we repeated the analyses after the exclusion of these subjects using the baseline score (Table S5). After exclusion of the early dropouts/relapses, residual symptoms and medication discontinuation remained significantly associated with relapse ($p \leq .039$) while again rumination (RRS), and also the brooding subscale showed a significant interaction with medication discontinuation ($p \leq .024$; Table S5). The HRs of CR and FFMQ approached 1.0 more and lost significance.

4 | DISCUSSION

Our findings show that in a group of patients with recurrent MDD in remission, before starting MBCT, CR, and mindfulness were associated with relapse, in addition to residual symptoms and previous depressive episodes and independent of mADM-use. Rumination at baseline measured by the RRS was only associated with relapse if patients discontinued their medication: rumination was not associated with relapse in patients who continued their medication.

4.1 | Association of CR and rumination with relapse

We here demonstrate that CR measured by the LEIDS-R is a clinically relevant factor associated with relapse in MDD patients. Previously, Figueroa et al. (2015) reported that a 20-point increase in the score of the LEIDS (precursor of the LEIDS-R) resulted in a 10%–20% increase in relapse rate, also independent of residual symptoms and previous depressive episodes. Here, a 10-point increase in LEIDS-R increased relapse risk by approximately 20%. However, they also found a slightly higher association with the LEIDS-rumination subscale, which we could not replicate. Figueroa et al. (2015) used an older version of the LEIDS which could be a possible explanation for the differences in outcome. Given these opposing results for the rumination subscale, we are reluctant to support its superiority over the total LEIDS-R.

Interestingly, rumination measured by the RRS was significantly associated with relapse, but only when patients discontinued their mADM. This means that high levels of rumination in combination with discontinuing mADM could particularly mark vulnerability for relapse. As reported before, ADM discontinuation increased the risk of relapse,

TABLE 2 Models including cognitive reactivity, rumination, self-compassion, or mindfulness with mADM discontinuation as time-dependent covariate ($n = 260$)[a]

Model	HR	95% CI	*p*	AIC (BIC)[b]
1.1 Cognitive reactivity (LEIDS-R)				1185.211 (1199.438)
Cognitive reactivity (LEIDS-R)	1.019	1.007–1.030	.002	
Residual symptoms	1.019	1.002–1.036	.027	
Episodes in history[c]	1.676	0.789–3.561	.179	
mADM-use (mADM vs. mADM discontinuation)	1.650	1.073–2.538	.023	
1.2 Rumination (subscale LEIDS-R)				1195.444 (1209.687)
Rumination (subscale LEIDS-R)	1.068	1.023–1.114	.003	
Residual symptoms	1.021	1.004–1.038	.013	
Episodes in history[c]	1.934	0.942–3.974	.073	
mADM-use (mADM vs. mADM discontinuation)	1.669	1.086–2.567	.020	
2.1 Rumination (RRS)				1194.321 (1212.124)
Rumination (RRS)	1.006	0.987–1.026	.525	
Residual symptoms	1.026	1.009–1.043	.002	
Episodes in history[c]	1.736	0.842–3.580	.135	
mADM-use (mADM vs. mADM discontinuation)	0.152	0.022–1.063	.058	
Rumination (RRS)*mADM-use	1.052	1.012–1.093	.010	
2.2 Rumination (subscale brooding)				1203.004 (1217.247)
Rumination (subscale brooding)	1.036	0.977–1.098	.283	
Residual symptoms	1.024	1.007–1.041	.005	
Episodes in history[c]	1.924	0.943–3.928	.072	
mADM-use (mADM vs. mADM discontinuation)	1.659	1.074–2.563	.023	
3 Self-compassion (SCS)				1188.607 (1202.803)
Self-compassion (SCS)	0.992	0.980–1.005	.229	
Residual symptoms	1.023	1.006–1.040	.008	
Episodes in history[c]	2.070	1.018–4.211	.045	
mADM-use (mADM vs. mADM discontinuation)	1.630	1.057–2.514	.027	
4 Mindfulness (FFMQ)				1184.527 (1198.723)
Mindfulness (FFMQ)	0.985	0.973–0.998	.020	
Residual symptoms	1.019	1.002–1.036	.028	
Episodes in history[c]	2.181	1.071–4.443	.032	
mADM-use (mADM vs. mADM discontinuation)	1.608	1.044–2.478	.031	

Abbreviations: FFMQ, Five Facet Mindfulness Questionnaire; LEIDS-R, Leiden Index of Depression Sensitivity-Revised; mADM, maintenance Antidepressant Medication; RRS, Ruminative Response Scale; SCS, Self-Compassion Scale.

[a]Due to missing values for individual questionnaires the *N* is slightly different for different models.

[b]AIC was also calculated with an equal number of participants ($n = 256$) for each predictor which shows that rumination (RRS) had the lowest AIC (AIC = 1170.030) followed by cognitive reactivity (AIC = 1171.159).

[c]Due to a skewed distribution LOG transformation was used.

despite treatment with MBCT (Huijbers et al., 2016). Although it has been shown that ADM decreases rumination in depressed patients (Bieling et al., 2012), less is known about rumination in the context of discontinuing ADM. A possible explanation is that after discontinuation mADM, people who are prone to worry and rumination start to worry about a pending relapse. It has been reported that indeed, discontinuing ADM increases fear of relapse (Maund et al., 2019). However, ADM might also provide a more general protection against rumination.

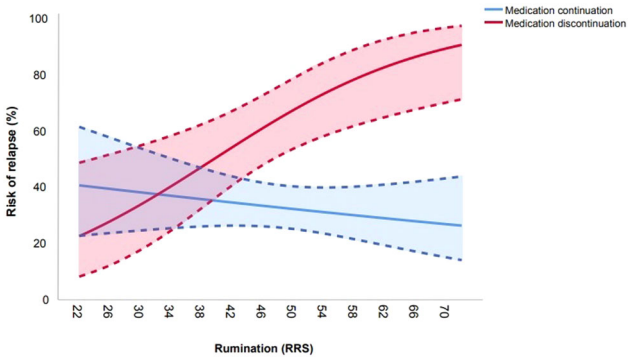

FIGURE 1 Graphical representation of interaction between rumination and antidepressant medication usage This graphical representation is based on a logistic regression model in which relapse anywhere within the 15-month follow-up was added as dependant variable. The median of residual symptoms (10) and episodes in history (4) of our sample where used for this representation. Odds ratios for independent variables included in the model were: IDS 1.034 (p = .017), episodes in history 3.019 (p = .050), mADM-usage 0.069 (p = .042), RRS 0.987 (p = .414), and RRS*mADM-usage interaction 1.087 (p = .003)

Therefore, although replication of this finding is crucial, the level of rumination might be an important factor to consider when patients wish to discontinue antidepressants.

The LEIDS-R rumination-subscale did not show this interaction, indicating that the RRS and LEIDS-R rumination-subscale might measure a different construct, as indicated by the instructions (Table S1), although proof thereof requires more eloquent analyses (Marchetti et al., 2016). Moulds et al. (2008) reported a correlation between RRS and LEIDS-R rumination-subscale (r = .51), similar to the correlation (r = .49) we found in our analysis. Moreover, the response style questionnaire (RSQ), a precursor of the RRS, did not show "absolute stability," which indicates how mean test scores in a group remain comparable over time (Bagby et al., 2004). A change in depression severity correlated positively with RSQ rumination scores. Absolute stability of the LEIDS-R has not been investigated.

In previous reports, higher scores on the RRS brooding-subscale were associated with an increase in depressive symptoms while the reflection-subscale did not, indicating that the brooding-subscale might be better associated with relapse compared to the RRS-total (Treynor et al., 2003). In contrast, our model with RRS-total was better than with RRS-brooding.

4.2 | Association of mindfulness and self-compassion with relapse

Mindfulness was significantly associated with relapse, independently of residual symptoms, previous episodes, and mADM-use. However, when CR and rumination were added to the model, mindfulness was not significantly associated with relapse. Petrocchi et al. (2016) reported that only the FFMQ-subscale "non-judgment" was significantly associated with depressive symptoms within 2 years. Interestingly, this relationship between nonjudgement and depressive symptoms was fully mediated by rumination. Therefore, the interaction of mindfulness with other factors of interest (e.g. CR, rumination, and self-compassion) warrants further investigation.

Self-compassion was not significantly associated with relapse. Recently the SCS was found to be significantly associated with depressive symptoms after one year (López et al., 2018). However, this association became nonsignificant after controlling for depressive symptoms at baseline. Secondary analyses pointed to an association between the subscale "isolation" and depressive symptoms independent of depressive symptoms at baseline, which we post hoc replicated in our sample (data available on request).

4.3 | Non-significance of CR, rumination, and mindfulness in the sensitivity analysis

Due to high dropout/relapse rates before the first follow-up measurement, we performed a sensitivity analysis with the patients who survived the first 12 weeks. CR and mindfulness were no longer associated with relapse in this analysis. The interaction between rumination and ADM discontinuation remained significant. Several explanations for these differences exist. First, the 32.7% dropouts/relapses substantially reduced power. Second, with the selection of subjects without an early relapse/dropout, a lower severity spectrum has been retained. As it, a priori, cannot be foreseen whether a patient will have an early or late relapse, we think that the results of our primary analysis have the best clinical validity.

4.4 | Limitations

Several limitations apply to our study. First, although patients were randomly assigned to the different treatment groups in the original RCTs, the randomized controlled feature was lost in the current study. In addition, many patients were non-adherent to the allocated condition. Nevertheless, the use of time-dependent covariate models instead of intention-to-treat models allowed us to estimate the effect of actual ADM discontinuation on relapse.

Second, due to the use of multiple models, there is an increased risk of type I errors (i.e., false positives). Even after a Bonferroni correction for the four main models, in which a $p \leq .0125$ would be considered significant, most of our main findings (e.g., association of LEIDS-R and RRS-interaction with relapse) remained significant. However, the association of FFMQ and mADM discontinuation with relapse would lose significance.

Third, besides residual symptoms and previous episodes, there are other well-known risk factors associated with relapse. Buckman et al. (2018) found that childhood maltreatment was also a strong risk factor for recurrence. Moreover, they also mentioned comorbid anxiety, rumination, neuroticism, and age of onset as risk factors. Adding more variables to a regression analysis increases the risk of overfitting, therefore only two risk factors were included in the analyses.

TABLE 3 Time-dependent Cox model with all significant factors of interest combined in one model ($n = 256$)

Model	HR	95% CI	*p*	AIC (BIC)
1.1 Model with RRS				1168.971 (1193.787)
Cognitive reactivity (LEIDS-R)	1.011	0.997–1.025	.135	
Rumination (RRS)	0.998	0.997–1.020	.877	
Mindfulness (FFMQ)	0.991	0.978–1.004	.158	
Residual symptoms (IDS)	1.019	1.002–1.037	.032	
Episodes in history[a]	1.692	0.789–3.629	.177	
mADM-use (mADM vs. mADM discontinuation)	0.190	0.025–1.467	.111	
Rumination*mADM-use	1.046	1.005–1.090	.029	
2.1 Model with RRS-brooding with interaction				1172.0.17 (1196.833)
Cognitive reactivity (LEIDS-R)	1.017	1.003–1.031	.016	
Brooding (RRS-subscale)	0.954	0.883–1.030	.226	
Mindfulness (FFMQ)	0.989	0.976–1.002	.102	
Residual symptoms (IDS)	1.017	1.000–1.035	.054	
Episodes in history[a]	1.915	0.891–4.114	.096	
mADM-use (mADM vs. mADM discontinuation)	0.575	0.121–2.732	.486	
Brooding*mADM-use	1.100	0.960–1.259	.169	
2.2 Model with RRS-brooding without interaction				1171.888 (1193.159)
Cognitive reactivity (LEIDS-R)	1.018	1.005–1.032	.009	
Brooding (RRS-subscale)	0.975	0.909–1.045	.468	
Minfulness (FFMQ)	0.988	0.975–1.001	.078	
Residual symptoms (IDS)	1.016	0.999–1.033	.073	
Episodes in history[a]	1.878	0.875–4.032	.106	
mADM-use (mADM vs. mADM discontinuation)	1.615	1.044–2.499	.031	

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; FFMQ, Five Facet Mindfulness Questionnaire; IDS, Inventory of Depressive Symptomatology; LEIDS-R, Leiden Index of Depression Sensitivity-Revised; mADM, maintenance Antidepressant Medication; RRS, Ruminative Response Scale.

[a]Due to a skewed distribution LOG transformation was used.

Fourth, we did not explore a differential effect of full or partial remission in relation to the associations of LEIDS-R, RRS, SCS, and FFMQ-scores with future relapse. In the future, these types of analyses should be tried in individual patient data meta-analyses (Breedvelt et al., 2021).

Finally, it is currently known that rapid cessation of ADM can lead to discontinuation symptoms (Horowitz & Taylor, 2019). Currently, ADM discontinuation is advised to use extended tapering schemes up to ten weeks or longer when patients have an increased risk of discontinuation symptoms (Ruhe et al., 2019). In our study, we used tapering schemes of 5 weeks which might have caused discontinuation symptoms mimicking relapse. Therefore, some patients with discontinuation symptoms in the ADM discontinuation group might have reported symptoms that were more related to discontinuation than to depressive relapse, with overestimated relapse rates as a result. Our study design could not disentangle discontinuation symptoms and relapse. Although more patients in the mADM discontinuation group relapsed, both groups showed similar relapse patterns over time. Median relapse of patients in the de mADM group was 24 weeks after initiating MBCT, while the median relapse of patients in the mADM discontinuation group was 20 weeks after initiating MBCT ($p = .956$). This suggests that the difference in relapse rate between groups cannot be completely attributed to discontinuation symptoms.

4.5 | Clinical implications and future research

Our study results showed that it is possible to give an indication of risk of relapse based on mADM usage/discontinuation, CR, rumination, and mindfulness in a patient group receiving MBCT. With more research, it might be possible to generate a relapse risk model and/or risk tables like in cardiovascular risk management that can support

clinicians in treatment planning (e.g., whether or not to discontinue mADM). Future research, preferably with an in individual patient meta-analytical evaluation, is needed to replicate our findings and quantify the effect of MBCT on the association between these factors with relapse. By adding data from other treatment modalities it would be possible to assess if the observed risk factors are specific to patients receiving MBCT or are also of importance in patients receiving other treatments. Moreover, a meta-analytical evaluation of all available risk factors, including childhood adversity, could give an even more accurate relapse risk assessment.

5 | CONCLUSION

We showed that in remitted patients with ≥3 previous episodes of MDD, CR and mindfulness before MBCT are independently associated with relapse/recurrence, in addition to residual symptoms and previous depressive episodes, and mADM-use. Moreover, the association of rumination at baseline with relapse/recurrence was only present when patients discontinued antidepressants.

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CONFLICTS OF INTEREST

Dr. M. J. Huijbers is employed by the Radboud Centre for Mindfulness and works as a mindfulness teacher. Dr. H. G. Ruhe received speaking fees from Janssen and Lundbeck.

DATA AVAILABILITY STATEMENT

The authors aim to make our data available for other researchers as much as possible, albeit with a restricted access policy. As data are currently not yet filed in a public repository, researchers interested in re-using our data are invited to contact the authors.

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