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The Development and Internal Evaluation of a Predictive Model to Identify for Whom Mindfulness-Based Cognitive Therapy Offers Superior Relapse Prevention for Recurrent Depression Versus Maintenance Antidepressant Medication

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Abstract

Depression is highly recurrent, even following successful pharmacological and/or psychological intervention. We aimed to develop clinical prediction models to inform adults with recurrent depression choosing between antidepressant medication (ADM) maintenance or switching to mindfulness-based cognitive therapy (MBCT). Using previously published data ($N = 424$), we constructed prognostic models using elastic-net regression that combined demographic, clinical, and psychological factors to predict relapse at 24 months under ADM or MBCT. Only the ADM model (discrimination performance: area under the curve [AUC] = .68) predicted relapse better than baseline depression severity (AUC = .54; one-tailed DeLong's test: $z = 2.8$, $p = .003$). Individuals with the poorest ADM prognoses who switched to MBCT had better outcomes compared with individuals who maintained ADM (48% vs. 70% relapse, respectively; superior survival times, $z = -2.7$, $p = .008$). For individuals with moderate to good ADM prognoses, both treatments resulted in similar likelihood of relapse. If replicated, the results suggest that predictive modeling can inform clinical decision-making around relapse prevention in recurrent depression.

Keywords

antidepressant medication, depression, mindfulness-based cognitive therapy, precision medicine, relapse prevention

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Globally, depression is now the leading cause of life years lived with disability (Patel et al., 2016, 2018). In many cases, the course of depression is recurrent over the life span (Kessler & Bromet, 2013), even following successful acute-phase interventions (Cuijpers et al., 2013). Successful prevention of the return of depression is therefore key to alleviating the individual and societal burden of depressive disorders. Antidepressant medication (ADM) following successful treatment is currently the predominant preventive intervention targeted at depressive relapse.[1] Multiple agencies, including the UK National Institute for Health and Care Excellence (NICE), the British Association for Pharmacology (Cleare et al., 2015), and the American Psychiatric Association, recommend both prescription of ADM and mindfulness-based cognitive therapy (MBCT) after remission if a person is deemed at high risk of relapse because of multiple previous episodes or high residual symptoms (Gelenberg et al., 2010; NICE, 2009). An international review of 13 sets of ADM guidelines revealed that recommendations for the duration of such continuation or maintenance[2] treatment in people deemed at high risk ranged from 1 year to lifelong or indefinite (Piek et al., 2010). Unsurprisingly, therefore, longer term use of ADMs is high and rising (Mojtabai & Olfson, 2014; Organisation for Economic Co-operation and Development, 2013), which accounts for the recorded increase in person-years on ADMs from 0.73 in 1995 to 4.94 in 2012 reported in the United Kingdom (McCrea et al., 2016). The antidepressant benefits of longer term ADM use are tempered by diverse physical and emotional side effects in the majority of patients (Bet et al., 2013; Cartwright et al., 2016), tachyphylaxis and other loss-of-response phenomena (Bosman et al., 2018; Fornaro et al., 2019; Kinrys et al., 2019), and user surveys indicating a desire for evidence-based psychosocial interventions as an alternative to ADMs for all aspects of depression management (Dorow et al., 2018; McHugh et al., 2013; Schweizer et al., 2010).

One such alternative is MBCT, an 8-week, group-based program that has emerged as a leading evidence-based psychological intervention for relapse prevention in recurrent depression (Kuyken et al., 2016). In a multicenter definitive randomized controlled trial (RCT; $N = 424$)—the PREVENT trial (Kuyken, Byford, et al., 2010; Kuyken et al., 2014)—we evaluated MBCT combined with support to taper or discontinue ADM against maintenance of a clinical dose of ADM for 2 years in patients (age ≥ 18 years) with recurrent depression (at least three previous episodes) who were in partial or full remission on ADM.[3] The trial showed no significant differences in relapse over 2 years between the MBCT and ADM groups (hazard ratio [HR] = 0.89, 95% confidence interval [CI] = [0.67, 1.18]; $p = .43$; relapse rate: 44% MBCT vs. 47% ADM; Kuyken et al., 2015a), a finding corroborated by an individual patient data meta-analysis of 1,258 patients from nine RCTs (Kuyken et al., 2016). Recent meta-analytic work has confirmed and expanded these findings: A network meta-analysis by McCartney et al. (2021) provided additional evidence that MBCT is superior to control conditions in terms of rate of relapse (MBCT vs. treatment as usual) or time to relapse (MBCT vs. treatment as usual or placebo), and a meta-analysis by Breedvelt and colleagues (2021) added evidence of the superiority of combination psychological prevention and continuation ADM over continuation ADM alone.

Given the association between depressive relapse and negative long-term outcomes, helping individuals select the optimal intervention for relapse prevention (from among the available options) is of high importance. Treatment guidelines stipulate that patient preferences should inform treatment selection through a process of shared decision-making (Weston, 2001), and there is some evidence that treatment outcomes are superior for preferred versus nonpreferred treatments (Kwan et al., 2010; Shay & Lafata, 2015; Windle et al., 2019). A critical component of effective shared decision-making is ensuring that comparative evidence for different interventions in the context of the patient's own clinical profile—what works for whom—is available at the point of care delivery (Winston et al., 2018). This information can come in a variety of different forms, including decision aids (Stacey et al., 2017) or more quantitative outcomes from clinical-prediction models (Bonnett et al., 2019). Recent methodological and empirical advances in "precision medicine" (F. S. Collins & Varmus, 2015) have generated prediction models that provide indices to identify which patients might expect improved clinical outcomes following different acute treatments for depression (Chekroud et al., 2021; Cohen & DeRubeis, 2018; Cohen et al., 2021; Perlis, 2013). A variety of factors are known to predict risk of depressive relapse (Buckman et al., 2018), but clinical prediction models in this area are lacking. Moriarty and colleagues' (2021) systematic review of prognostic models for predicting depressive relapse identified 10 unique prognostic models, but the studies' high bias and models' poor predictive performance suggest that further work is needed.

The participants in PREVENT were assessed at trial baseline on a broad range of psychosocial variables that putatively have a bearing on treatment outcome (Kuyken et al., 2015a). Here, we focus on identifying patient characteristics and constructing prognostic models that could putatively guide the treatment choice between continuing ADM versus MBCT with support to taper or discontinue antidepressant treatment for the prevention of depressive relapse.

Method

For a checklist corresponding to the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) guidelines (G. S. Collins et al., 2015), see the Supplemental Material available online.

Data set description

The full PREVENT sample comprised 424 individuals randomly assigned (1:1) to ADM or MBCT. Participants with more than 20% missing data on predictor variables (n = 15), no data beyond baseline (n = 17), or not in receipt of a dose of MBCT deemed sufficient (at least four sessions; following the PREVENT trial protocol: Kuyken et al., 2010, 2015a) for evaluation of MBCT as an intervention alternative (n = 25) were excluded from the primary analyses. This led to a sample of 367 participants for the primary analyses. For the data exclusion pipeline, see Figure S1 in SM1 in the Supplemental Material. Sensitivity analyses were performed to probe the impact of removing the 25 who were excluded because of inadequate MBCT dose. The results for this larger sample (n = 392) are included in SM2 in the Supplemental Material. Descriptive data for the predictor variables at baseline are provided in the SM3 in the Supplemental Material, as are comparisons of the two treatment groups (ADM vs. MBCT; see Table S1 in the Supplemental Material) and the excluded versus included samples (see Table S2 in the Supplemental Material). These comparisons indicated that there was a significantly greater proportion of women in the ADM group and that ADM participants reported more comorbid diagnoses, had a lower probability that their most recent episode of depression was chronic (≥ 24 months in duration), and were younger, at baseline, compared with the MBCT group (see Table S1 in the Supplemental Material). Relative to the analysis sample, excluded participants were, on average, 4 years younger, had 0.3 more comorbid diagnoses, and reported lower scores on the Dispositional Positive Emotions Scale Curiosity subscale, Self-Compassion Scale Isolation subscale, and the Five-Facets Mindfulness Questionnaire Describe subscale (see Table S2 in the Supplemental Material).

Predictor variables

The PREVENT study included a wide range of 53 potential demographic, clinical, and psychological predictor variables (Table 1). The demographic and clinical predictors were selected because they are available in clinical practice, and indeed, many are commonly included as part of routine diagnostic procedures. Psychological predictors included standardized self-report measures of potential mechanisms of treatment efficacy (including mindfulness, self- and other-compassion, and repetitive thinking).

Missing predictor variable data at baseline were imputed using the full (N = 424) sample via the *missForest* (Version 1.4; Stekhoven & Bühlmann, 2012) package for the R software environment (Version 3.5.1; R Core Team, 2018), which implements a random-forest-based nonparametric imputation approach. Random-forest-based imputation compared favorably in several evaluations of different imputation approaches (Hong & Lynn, 2020; Shah et al., 2014; Stekhoven & Bühlmann, 2012; Waljee et al., 2013).

For the 53 potential predictors assessed at baseline in the PREVENT data, following imputation, continuous variables were z-scored, and dichotomous variables were set to −0.5 and 0.5. No outcome data were included in the imputation of the missing baseline data. Note that the education variable was imputed as an ordered categorical variable and then was converted into a continuous (numeric) variable for the remainder of the analyses.

Statistical approach to treatment selection

An in-depth discussion of how data can be used to create and evaluate treatment recommendations can be found in a recent review of treatment selection (Cohen & DeRubeis, 2018). The core concept is that statistical models are constructed and used to generate predictions for an individual in two (or more) treatments, and then those predictions are used to determine which treatment to recommend (Cohen et al., 2019). Much of the work in this space (e.g., the Personalized Advantage Index approach; DeRubeis et al., 2014) has been based on the proportional-interaction model. Luedtke and colleagues (2019) highlighted potential problems with the use of this approach in the small RCT samples that are often available, including the fact that implicit estimation and testing of interaction effects (vs. main effects) requires larger samples. Their simulation work suggested that sample sizes of at least 300 per condition are required for adequate statistical power to detect clinically significant improvements in response associated with model-based treatment selection. Other approaches that have been demonstrated rely solely on prognostic models (e.g., Lorenzo-Luaces et al., 2017; Wiltsey Stirman et al., 2021). For a discussion and contrasting of these different approaches, see Cohen et al. (2021). Following the approach proposed by Kessler et al. (2017) and demonstrated by Deisenhofer and colleagues (2018), we constructed separate prognostic

Table 1. Predictors Included in the Variable-Selection Analysis

Variable	Description
Demographic	
Age	Age at baseline in years
Gender	Binary variable, reflecting self-identified gender: female or male (variable was made dichotomous because most individuals identified as one or other gender)
Education	Level of education attained, in which 0 = no educational qualification, 1 = O levels or GCSEs, 2 = AS and A levels (UK Advanced Level), 3 = vocational training/qualification, 4 = university bachelor's degree, 5 = university master's degree, and 6 = university professional training/PhD
Relationship status	Binary variable: no (single/divorced/widowed) versus yes (married/civil partnership/cohabiting)
Employment status	Binary variable: unemployed versus full- or part-time
Clinical	
Clinician-rated depressive symptoms	The total score on the GRID-Hamilton Rating Scale for Depression (GRID-HAMD; Williams et al., 2008) was used as an index of clinician-rated depressive symptoms. The GRID-HAMD is a scale that offers explicit standardized scoring guideline for the clinician-rated assessment of depression. The scale consists of 17 items assessing symptoms of depression that are rated on a scale from 0 (*not present*) to 4 (*severe*).
Self-reported depressive symptoms	The total score of the Beck Depression Inventory–II (Beck et al., 1996) was used to assess self-reported symptoms of depression. The 21-item scale requires participants to endorse symptom levels ranging from 0 (*not present*) to 3 (*severe*).
Age of depression onset	Age at first depressive episode
Chronicity	Binary variable indicating whether the duration was ≥ 24 months
Previous psychological treatment	Binary variable indicating whether the participant had received a previous psychological treatment
Previous suicide attempt	Binary variable indicating whether the participant had previously attempted suicide or not
Family history of depression	Binary variable indicating whether the participant reported a family history of mood disorders or not
Comorbidity	Number of comorbid diagnoses
Psychological	
Validated questionnaires[a]	
Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2006)	The FFMQ measures five facets of mindfulness: (a) Observe – observing internal and external experiences (eight items); (b) Describe – describing internal experiences/states verbally (eight items); (c) Aware – acting with awareness (eight items), (d) Non-Judging – a nonjudgmental stance toward one's thoughts and feelings (eight items), and (e) Non-Reactivity – allowing thoughts and feelings to come and go (seven items). Individuals rated the extent to which they experienced these states ranging from 1 (*never or very rarely true*) to 5 (*very often or always true*).
Self-Compassion Scale (SCS; Neff, 2003)	The SCS consists of six self-compassion subscale factors: Self-Kindness (five items), Self-Judgment (five items), Common Humanity (four items), Isolation (four items), Mindfulness (four items), and Over-Identification (four items). We additionally included a bespoke subscale that assesses compassion for others. Ratings are provided on a scale ranging from 1 (*almost never*) to 5 (*almost always*).
Dispositional Positive Emotion Scale (DPES; Shiota et al., 2006)	We included the following DPES subscales: Joy (six items), Contentment (five items), Love (six items), Compassion (five items), and Awe (six items). We additionally included a bespoke subscale that assesses Curiosity for internal and external experiences. Ratings were provided ranging from 1 (*strongly disagree*) to 5 (*strongly agree*).
Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski et al., 2001)	The CERQ is a 36-item questionnaire assessing individuals' propensity to employ four maladaptive (Catastrophizing, Rumination, Other-Blame, and Self-Blame) and five adaptive (Acceptance, Positive Refocusing, Positive Reappraisal, Putting into Perspective, and Refocus on Planning) emotion-regulation strategies when they were confronted with negative events. Item ratings ranged from 1 (*almost never*) to 5 (*almost always*).

(continued)

Table 1. *(continued)*

Variable	Description
Cambridge-Exeter Repetitive Thought Scale (CERTS; Barnard et al., 2007)	The CERTS assesses individuals' dispositional tendency for Brooding (Section 1), the temporal course of their brooding thinking (Section 2), dispositional tendency for repetitive thinking in general (Section 3), difficulties disengaging from repetitive thinking (Section 4), and attitudes toward repetitive thinking (Section 5). For Sections 1 through 4, responses were provided with respect to eight scenarios: (a) feeling sad, (b) feeling happy, (c) feeling angry, (d) feeling anxious, (e) being with others, (f) being alone, (g) experiencing a set-back, and (h) making progress. In Sections 1, three to five items were given ratings ranging from 1 (*almost never*) to 5 (*almost always*), and in Section 2, items were rated from *only moments* to *what seems like hours*.
Measure of Parental Style (MOPS; Parker et al., 1997)	The MOPS was administered to assess levels of parental abuse experienced as a child. Participants indicate to what extent 15 statements about their mother and father (30 items total) were true for the first 16 years of their lives. Participants rated the statements from 0 (*not at all true*) to 3 (*extremely true*). A median split was used to categorize participants as high or low (see Kuyken et al., 2015).
General Self-Efficacy Scale (GSE; Schwarzer & Jerusalem, 1995)	The GSE is a 10-item scale that assessed individuals' sense of self-efficacy over the past 2-week period. Participants answered the scale on items from 1 (*definitely disagree*) to 5 (*definitely agree*).
Bespoke measures	
Stigmatization and normalization (SN)	SN was a bespoke seven-item questionnaire asking individuals to indicate how often they experienced stigmatization because of their depression. Items were rated on a scale from 1 (*almost never*) to 5 (*almost always*).
Warning signs (WS)	WS was a bespoke six-item questionnaire assessing individuals' ability to recognize warning signs of depression. Responses ranged from 1 (*almost never*) to 5 (*almost always*).
Relationship satisfaction (RS)	RS was assessed with a bespoke questionnaire that individuals were asked to complete thinking of the most important relationship in their lives. The scale's seven items assess relationship satisfaction on a scale ranging from 1 (*almost never*) to 5 (*almost always*).
Preference for mindfulness-based cognitive therapy (MBCT)	Item assessing participants' sentiment about being assigned to MBCT (Question: "How do you feel about the possibility of being in an MBCT group"), rated on a Likert scale from 1 (*not positive at all*) to 5 (*extremely positive*).
Preference for antidepressant medication (ADM)	Item assessing participants' sentiment about being assigned to ADM (Question: "How do you feel about remaining on your ADMs"), rated on a Likert scale from 1 (*not positive at all*) to 5 (*extremely positive*).
Preference for therapy type	Item assessing participants' preferred treatment option (Question: "Do you have a preference for a group"), rated on a Likert scale from 1 to 5 (1 = *MBCT*, 3 = *no preference*, 5 = *continue on ADM*).

Note: Individuals were asked to complete all measures with respect to the previous 2 weeks. The scaling was standardized to facilitate interpretation from factor analyses and similar computations planned for the trial. The labels of the original scales were maintained. GCSE = General Certificate of Secondary Education.

[a]These scales were scored on a 5-point Likert scale irrespective of their original scoring range.

algorithms for each of our two treatment conditions (MBCT and ADM). For each patient, a "factual prediction"—how well they were expected do in their actual treatment arm on the basis of their scores on the variables selected for that treatment's prognostic model—was generated, as was a "counterfactual prediction"—how well they would hypothetically have done in the alternative treatment arm on the basis of their scores on the predictors that were included in the prognostic model for the alternative treatment arm.

In this approach, the predictive performance of each of the two separate treatment arm algorithms could be independently evaluated (see below for information about cross-validation) by comparing the factual predictions with the observed outcomes. If both algorithms yielded inaccurate factual predictions, this would have revealed that the data, or the modeling procedures that were implemented, did not provide a useful signal for prediction purposes. If both models yielded accurate factual predictions, the computed difference between the sets of predictions for MBCT and ADM could have served as an index for each patient that indicated which of the two treatments would be optimal (Cohen & DeRubeis, 2018). Finally, if only one of the models (e.g.,

Tx-A) yielded accurate factual predictions, that model on its own could be evaluated for its potential utility for guiding treatment decisions. Patients could be arrayed according to their predicted outcome in the condition with the reliable prognostic model (Tx-A). In the absence of reliable information about expected response to the other treatment (Tx-B) and the assumption that the two treatments yielded similar outcomes on average, participants with poor prognoses in Tx-A could be reasonably advised to try Tx-B, whereas a sensible recommendation for those with good prognoses in Tx-A would be Tx-A. Thus, the expectation in this scenario would be that differential response would be observed across the spectrum of Tx-A prognoses.

We applied this approach to the PREVENT data, and below we outline the steps of variable selection, cross-validation, and assessment of model fit involved in building and evaluating the prognostic algorithms for MBCT and ADM. Although analyses revealed the MBCT model to have poor predictive performance (as indicated by low area under the curve [AUC]), the ADM model evidenced good predictive performance and was superior to a benchmark model constructed using only baseline depression severity. Consequently, we generated and evaluated the treatment-selection indices using the ADM prognostic model only. This allowed us to ask the question of whether there were differential outcomes for participants who received MBCT versus ADM in patients predicted to do well, moderately, or poorly if they continued with ADM. The details regarding the model building and evaluation for the poorly fitting MBCT model are described in detail in SM4 in the Supplemental Material.

Cross-validation. When using cross-validation in the context of predictive model evaluation, it is essential to protect against "double-dipping" (Hastie et al., 2009). For example, it is critical that the predictions that are evaluated are generated from models that are constructed (in terms of variable selection, hyperparameter tuning, and weight setting) without the use of data from individuals for whom the predictions are being made.

We performed 10-fold cross-validation (Hastie et al., 2009), which involved splitting both the ADM and MBCT samples into 10 subgroups, balanced on outcomes (Fig. 1, Step 1). Each of the 10 ADM subgroups was then held out (Fig. 1, Step 2), and a prediction model was constructed using the remaining nine ADM subgroups as the training sample (Fig. 1, Steps 3–6). That model was then applied to the 10th ADM group to generate factual predictions of expected response in ADM (Fig. 1, Step 7[a]) and was also applied to the entire MBCT sample to generate counterfactual predictions of their expected response if they had received ADM (Fig. 1, Step 7[b]). The protections needed differ when generating factual and counterfactual prediction for each treatment arm. When predicting ADM outcomes for the MBCT sample, no cross-validation is needed because the ADM model was constructed without the MBCT individuals and thus can be applied to these individuals without concern over double-dipping.

This process was repeated nine more times for each of the other nine ADM subgroups (Fig. 1, Step 8), which resulted in the generation of a single "protected" factual prediction for each of the individuals in the ADM condition. The 10 protected counterfactual predictions (one from each of the 10 ADM models) for each of the individuals in the MBCT condition were averaged to create an ensemble counterfactual prediction of how patients who received MBCT would have been expected to fare had they received ADM (Fig. 1, Step 9[b]). The analogous process was then performed for the MBCT group, which resulted in each individual in MBCT receiving a single factual prediction of their outcomes in MBCT and patients in the ADM condition receiving ensemble counterfactuals for their expected outcomes had they received MBCT (see Fig. S3 in the Supplemental Material).

Finally, to provide a benchmark to help in the evaluation of these multivariable prediction models, we used the same cross-validation strategy, again in both groups, to generate predictions from "severity only" models (constructed using logistic regression), in which the only predictor available to the models was baseline symptom severity on the clinician-assessed Hamilton Rating Scale for Depression (HAMD; Hamilton, 1967; see Fig. S2 in the Supplemental Material), assessed using the 17-item GRID-HAMD (Williams et al., 2008).[4] Outcome for all models was relapse, which was assessed retrospectively via the Structured Clinical Interview for DSM-IV (First et al., 1995) at five time points across the 24-month study period (1 month after acute intervention, and then 9, 12, 18, and 24 months after randomization; Kuyken et al., 2015a). See Figure 1 for a schematic summarizing the analytic pipeline.

Modeling via elastic-net regularized regression. Multivariable prognostic models were constructed using elastic-net regularized regression (ENRR; Zou & Hastie, 2005; see Fig. 1, Step 6). ENRR allows for the estimation of the predictive utility of a large number of variables, and its use has been demonstrated and extensively discussed in several previous predictive modeling efforts (Buckman et al., 2021; Chekroud et al., 2016, 2017; Cohen et al., 2020; Iniesta et al., 2016; Kim et al., 2019; Pearson et al., 2018; Webb et al., 2020). ENRR combines the

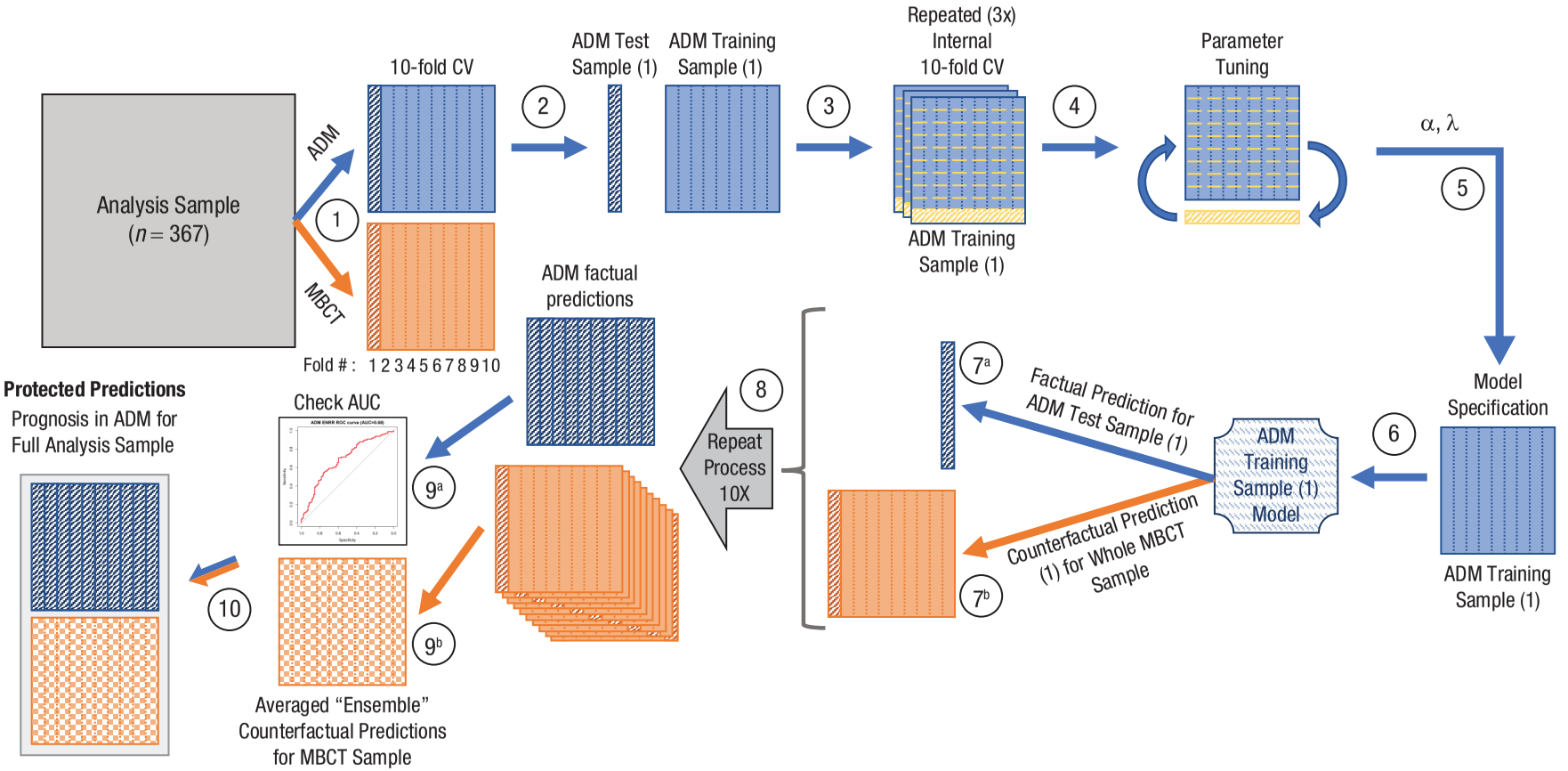

Fig. 1. Schematic of cross-validation procedure for producing antidepressant medication (ADM) predictions for the full analysis sample. Ten key steps in the procedure are indicated by circled numbers. Step 1 (10-fold cross-validation [CV]): The main analysis sample was separated into ADM and mindfulness-based cognitive therapy (MBCT) samples, each of which was then split into 10 subgroups, balanced on outcomes. Step 2: The ADM sample was separated into its first train-test samples, and the first of the 10 subgroups was held out as ADM test sample (1); the other nine subgroups constituted ADM training sample (1). Steps 3 and 4: ADM training sample (1) was then itself split into 10 subgroups, and parameter tuning was performed using internal 10-fold CV; this entire process was repeated three times using different random permutations of the internal 10-fold CV of ADM training sample (1). Step 5 (hyperparameter optimization): The optimal alpha (α) and lambda (λ) were selected and used in Step 6 (model specification), in which elastic-net regularized regression (ENRR) was applied to the entire ADM training sample (1) to derive the ADM training sample (1) Model. Step 7[a]: This model was then used to generate factual predictions for the held-out ADM test sample (1) and to generate counterfactual predictions (Step 7[b]) for the entire MBCT sample. Step 8: Steps 2 through 7 were then repeated nine more times to complete the 10-fold CV. Step 9[a]: The resulting set of (protected) factual predictions for the entire ADM sample (likelihood of relapse in ADM) were then evaluated using the area under the receiver operating characteristic curve. Step 9[b]: The set of 10 (protected) counterfactual predictions for each individual in the MBCT sample (likelihood of relapse if they had received ADM) were averaged, which resulted in a set of averaged "ensemble" counterfactual predictions for the MBCT sample. Step 10: The ADM and MBCT samples and their ADM predictions were then recombined, which resulted in protected prognoses under ADM for the full analysis sample.

L_1 (LASSO penalty) and L_2 (ridge regression penalty) penalization, which provides a hybrid of least absolute shrinkage and selection operator (LASSO) and ridge regression that thus addresses issues of correlated predictors and overfitting by shrinking coefficients of correlated predictors toward each other and by removing uninformative predictors from the model (Hastie et al., 2009). ENRR was implemented using the R package *glmnet* (Version 2.0-16; Friedman et al., 2010). Hyperparameter optimization (Fig. 1, Steps 3–5) was performed within each training sample using nested cross-validation. To reduce a source of potential bias (risk of overfitting because of information leakage from the test cases; Pearson et al., 2018) that can arise when a grid search is performed for hyperparameter setting in the context of cross-validation, we used three tuning loops (as suggested by a reviewer), 10-fold cross-validation (Friedman et al., 2010; Zou & Hastie, 2005, p. 310), and a small set of α values (.01, .5, .99) as implemented in the R package *beset* (Version 0.0.0.9409; Shumake, 2022) and described in Pearson et al. (2018) and McNamara et al. (2021). These three α values represent heavy weighting of the ridge penalty (α = .01), heavy weighting of the LASSO penalty (α = .99), or equal weighting (α = .5). The λ path of 100 possible values was generated using the *glmnet* package's default calculation equation for λ path. In addition, the regularization parameter λ was selected using the one-standard-error rule, which helps to avoid overfitting and elevated Type I error (James et al., 2013; Waldmann et al., 2013). All analyses were performed in the R software environment (R Core Team, 2018); for additional information about packages used, see SM5 in the Supplemental Material.

Evaluating the models. Primary evaluation of model performance was performed via receiver-operating-characteristic (ROC) curves, which delineate the relative sensitivity (true-positive rate) and specificity (false-positive rate) of a model's predictions at different thresholds. The area under the ROC curve (AUC) was used to quantify each model's discrimination; AUCs of 0.5 indicate no or "chance" discrimination, and AUCs of 1 indicate perfect discrimination. In this context, because we are evaluating the outcome, "Did a relapse occur?" (yes/no), the AUC is equivalent to the concordance or c-statistic (Steyerberg et al., 2010). Another important aspect of model performance to evaluate is calibration (Van Calster et al., 2019); following recommendations based on sample size, we present only "weak calibration," assessed via the calibration intercept and slope, with target values of 0 for the intercept (in which negative and positive values suggest overestimation and underestimation, respectively) and 1 for the slope (in which slopes > 1 indicate predictions that are too conservative and slopes < 1 indicate those that are too extreme).

We computed AUCs for the ENRR models' factual predictions for patients in each treatment arm (ADM and MBCT; see Step 9[a] of both Fig. 1 and Fig. S3 in the Supplemental Material). We also computed the AUC for each treatment arm for the depression-severity-at-baseline-only logistic regression models (HAMD) as a benchmark to compare against the more complex multivariable models. Within each treatment arm, we then compared these two AUCs using a one-tailed DeLong test for correlated ROC curves (DeLong et al., 1988) under the hypothesis that the multivariable models would outperform the benchmark models.

Evaluating prognostic utility. As noted in the results and described in detail in SM4 in the Supplemental Material, the internally cross-validated evaluation of the MBCT model's factual predictions found that they were near chance and that they failed to noticeably outperform the HAMD model. We therefore focused our evaluation of prognostic utility on the ADM model alone under the rationale that in the absence of trustworthy information about MBCT prognosis, it would be rational to evaluate whether individuals who are predicted to have a high risk of relapse if they maintain ADM might have a better (relative) predicted outcome with a switch to MBCT. Likewise, we wanted to examine whether patients predicted to have good prognoses with ADM might be better advised to maintain the treatment regimen they are already following (i.e., ADM).

To evaluate the overall utility of the predictions generated by the ADM prognostic model in guiding treatment selection, we used two tertiles to divide the sample into three groups (Altman & Bland, 1994) on the basis of risk of relapse in ADM (good ADM prognosis, moderate ADM prognosis, and poor ADM prognosis). Sample sizes and descriptive statistics for the ADM prognoses (i.e., means, standard deviations, and ranges) for three groups, broken down by treatment received, are available in Table S3 in the Supplemental Material. Predictive utility of the ADM prognostic index was then evaluated by examining the time to relapse (in a survival analysis using Cox regression) and overall relapse rates over the 2-year follow-up. The independent variables were treatment condition (ADM, MBCT), ADM prognosis (both as a continuous variable and in categorical form: good, moderate, poor), and their interaction. For any significant interactions, the effects of treatment group were analyzed within each of the three prognostic categories.

Results

Model predicting relapse in the ADM treatment arm

Using observed depressive relapse (yes/no) over 24 months to evaluate the factual predictions in the ADM model that had been made without the use of each patient's own data, we found that the AUC for the ADM ENRR model was 0.68 (Fig. 2a), which was significantly better (one-tailed DeLong test: $z = 2.80$, $p = .003$) than that of the ADM HAMD comparison model (AUC = 0.54; see Fig. S4 in the Supplemental Material). The ADM ENRR model had a calibration intercept of −0.02 (in the direction of overestimation of relapse) and a calibration slope of 1.49 (which suggests overly conservative predictions at both ends of the risk spectrum). In contrast, the MBCT model (AUC = 0.54) did not outperform the HAMD comparison model (AUC = 0.52; $z = 0.37$, $p = .35$), a detailed description of which is available in Figure S5 in the Supplemental Material. Additional information regarding calibration for all models is available in SM4 in the Supplemental Material.

The specific variables that were retained and their associated coefficient weightings varied across the 10 ADM ENRR models that were generated. The key results of these models are summarized in Table 2. An expanded version of this table describing all 53 variables that were considered is provided in Table S4 in the Supplemental Material, and the analogous information for the 10 MBCT models is available in Table S5 in the Supplemental Material.

Five baseline variables (from our set of 53) were retained as predictors of relapse across all 10 ADM ENRR models generated during the 10-fold CV procedure: level of child abuse, depression chronicity, and three subscales of the Dispositional Positive Emotions Scale (Shiota et al., 2006): Contentment, Joy, and Love. Higher levels of these positive emotions were associated with lower risk of relapse in ADM, whereas a history of child abuse was associated with increased risk of relapse. In the ADM models, having one's most recent episode of depression be chronic (duration ≥ 24 months) was associated with reduced risk of relapse relative to people whose most recent episode was not. Two subscales of the Cambridge-Exeter Repetitive Thought Scale (Barnard et al., 2007) were retained in nine of the 10 models: Both Negative Rumination and Unresolution were associated with elevated risk of relapse in ADM. History of suicide attempt or attempts and number of comorbidities were both retained in eight of the 10 models and were associated with increased risk of relapse. Additional variables retained in more than 50% of the models are summarized in Table 2 and Table S4 in the Supplemental Material.

Prognostic utility

We first verified that the outcome data for our analysis sample were comparable with that of the total PREVENT sample (Kuyken et al., 2015a). As in the full sample, survival times ($z = -1.02$; $p = .31$, HR [MBCT relative to ADM] = 0.86; 95% CI = [0.64, 1.15]) and relapse rates (MBCT = 47.1%, ADM = 50.3%) during the 24-month follow-up period in our analysis sample did not differ significantly between the two treatment conditions. In the survival analysis, in which we examined time to relapse with main effects for treatment and continuous ADM prognosis, there was a significant main effect of continuous ADM prognosis ($z = 4.615$; $p < .001$). We next compared observed outcomes across the two treatment conditions for individuals according to their ADM prognoses (i.e., good, moderate, poor; Fig. 2b).

The survival curves did not differ across treatments for individuals with good ADM prognoses (HR reflecting increased risk of relapse for those in MBCT vs. ADM = 1.34; 95% CI = [0.73, 2.45]; $p = .35$). The same was true for individuals with moderate ADM prognoses (HR = 1.19; 95% CI = [0.73, 1.96]; $p = .48$). In contrast, individuals with poor ADM prognoses had significantly reduced relapse risk (HR = 0.52; 95% CI = [0.32, 0.84]; $p = .008$) if they switched to MBCT instead of staying on ADM.

When comparing rates of participants who had actually relapsed by the end of the 2-year follow-up period, the same pattern emerged (Fig. 2c). There was a significant main effect of ADM prognosis on observed relapse rates, $\chi^2(2) = 16.16$, $p < .001$. As expected, the individuals with good ADM prognoses showed the lowest rates of relapse (35%), the group with moderate prognoses showed an intermediate relapse rate (51%), and the group with the poor prognoses showed the highest rate of relapse (60%). Relapse rates were low for individuals with good ADM prognoses regardless of which treatment they received (ADM = 31%, MBCT = 38%). Relapse rates did not differ significantly as a function of treatment assignment for this group, $\chi^2(1) = 0.45$, $p = .50$, or for those with moderate ADM prognoses (ADM = 47%, MBCT = 56%): $\chi^2(1) = 0.71$, $p = .40$. However, for individuals with poor ADM prognoses, relapse rates were significantly worse for participants who received ADM (70%) compared with participants who received MBCT (48%): $\chi^2(1) = 4.86$, $p = .03$. Finally, results from the sensitivity analyses that repeated the above analyses in a sample that included the 25 MBCT

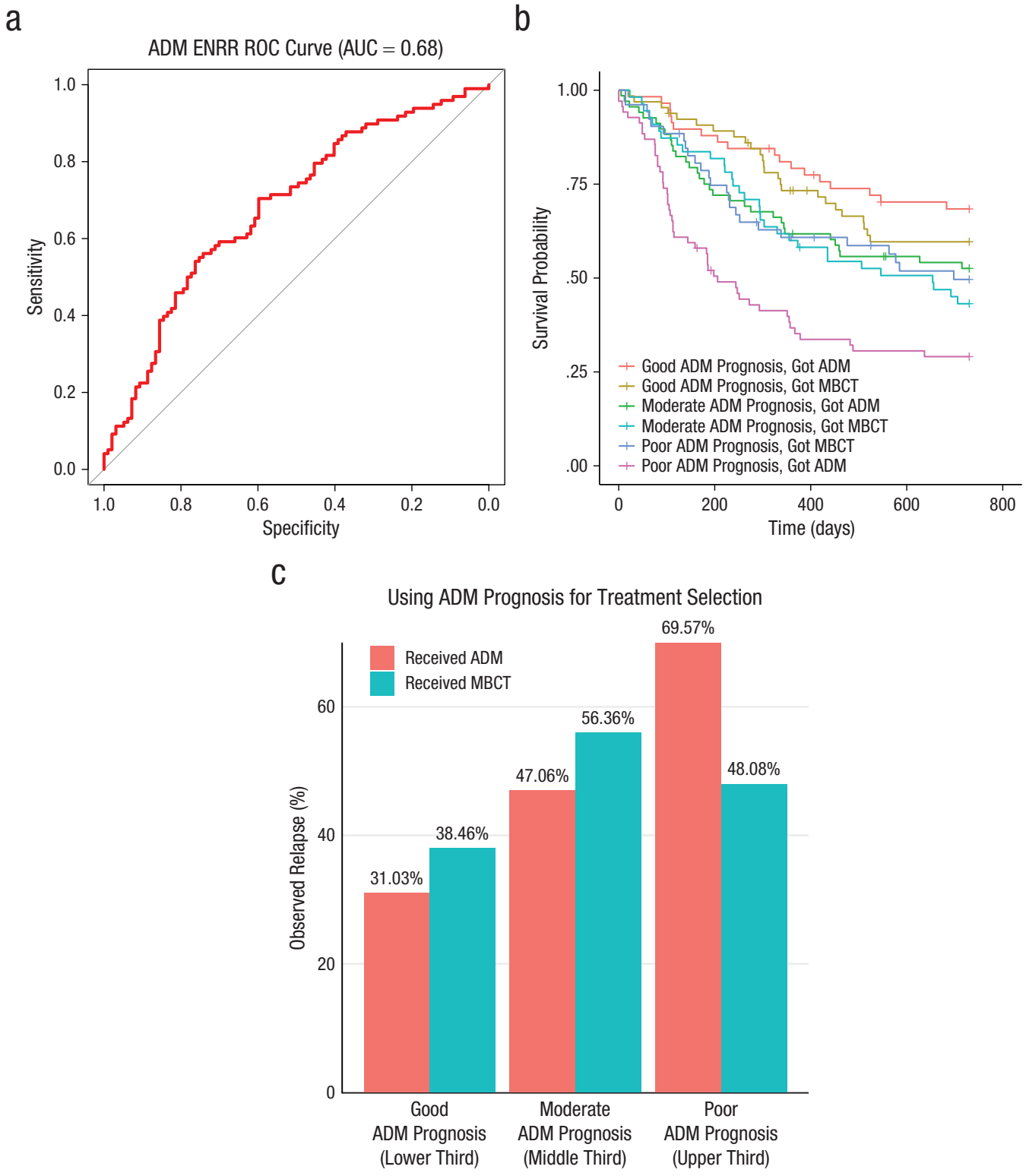

Fig. 2. Probability of relapse in the ADM model. The graph in (a) shows the area under the receiver-operating-characteristic (ROC) curve (AUC), which delineates the relative sensitivity (true-positive rate) and specificity (false-positive rate) of the prognostic multivariable antidepressant medication (ADM) elastic-net model. The AUC (red line) is plotted against the straight gray line, which represents the threshold at which the model has no predictive utility. The gray line indicates the likelihood that someone above and below that threshold on the prognostic index has an equal likelihood of relapse. That is, the larger (farther away from the gray line) the AUC, the greater a model's predictive utility. The graph in (b) plots the predicted survival curves for time (measured in days) to depressive relapse over the 2-year follow-up period for each ADM-prognosis group (poor, moderate, good) as a function of the treatment they received (mindfulness-based cognitive therapy [MBCT] or ADM). The graph in (c) shows the observed relapse rates over the 2-year follow-up as a function of the ADM relapse risk, separately by treatment received.

Table 2. Predictor Weightings for the ADM Prognostic Models Across 10-Fold Cross-Validation

Variable	No. of times selected	*M*	*SD*	Min	Max
MOPS level of parental abuse (low/high)[a]	10	0.34	0.16	0.03	0.57
Previous depressive episode chronicity[a,b]	10	−0.33	0.17	−0.60	−0.02
DPES Contentment	10	−0.08	0.06	−0.20	−0.01
DPES Joy	10	−0.05	0.038	−0.12	−0.003
DPES Love	10	−0.07	0.04	−0.14	−0.01
CERTS Negative Rumination	9	0.05	0.03	0	0.10
CERTS Unresolution	9	0.07	0.06	0	0.15
Previous suicide attempt[a]	8	0.10	0.09	0	0.26
Comorbidities	8	0.03	0.03	0	0.07
FFMQ Aware	8	−0.04	0.04	−0.11	0
CERQ Acceptance	8	0.04	0.05	0	0.14
GSE Self-Efficacy	7	−0.03	0.03	−0.08	0
Age of depression onset	6	−0.03	0.03	−0.08	0

Note: The table reports regression coefficients for the predictors in the ADM elastic-net prognostic models that were retained more than 50% of the time across the 10-fold cross-validation. In the model, all continuous variables entered were *z*-scored ($M = 0$, $SD = 1$), and dichotomous variables were set to −0.5 and +0.5. No. of times selected = number of times the variable was selected across the 10 cross-validations; min, max = minimum and maximum for variable's coefficient value (includes zeros for when variable was not retained); ADM = antidepressant medication; MOPS = Measure of Parental Style (Parker et al., 1997); DPES = Dispositional Positive Emotion Scale (Shiota et al., 2006); CERTS = Cambridge-Exeter Repetitive Thought Scale (Barnard et al., 2007); FFMQ = Five Facet Mindfulness Questionnaire (Baer et al., 2006); CERQ = Cognitive Emotion Regulation Questionnaire (Garnefski et al., 2001); GSE = General Self-Efficacy Scale (Schwarzer & Jerusalem, 1995).
[a]Dichotomous variables (set to −0.5 and +0.5). [b]Chronicity (no/yes) based on duration of previous depressive episode of 24 months or more.

participants who had been excluded for not having attended at least four sessions of MBCT aligned with the results from the primary analysis sample (see SM2 in the Supplemental Material).

Discussion

Clinical depression is a heterogeneous condition, which often runs a relapsing-and-remitting course across the life span and for which no single treatment has been shown to be effective for all patients (Fried, 2017; Fried & Nesse, 2015). A precision-medicine approach to depressive relapse prevention has potential utility in facilitating clinical choices between maintenance pharmacotherapy regimens and preventive psychosocial interventions such as MBCT.

We described a prognostic model that was developed using baseline data (demographic, clinical, and readily available psychological measures) from individuals who were randomly assigned to receive maintenance ADM following a successful course of acute treatment with ADM in an RCT comparing maintenance ADM with MBCT for relapse prevention. This ADM model (for a discussion of the predictors included in the model, see SM6 in the Supplemental Material), which predicts depressive relapse across a 24-month follow-up period, performed comparably with algorithms predicting acute remission response to antidepressants (Chekroud et al., 2016, 2017; Iniesta et al., 2016). We then generated ADM prognoses for the entire RCT sample (including participants randomly assigned to receive MBCT) to investigate whether the information from the ADM predictions might be helpful in deciding between staying on antidepressants or switching to preventive psychotherapy (MBCT). We observed a large difference in relapse rates for patients with poor ADM prognoses: 70% relapse in ADM versus 48% relapse in MBCT. In other words, patients with poor prognoses on ADM do not seem to simply be clinical nonresponders, but, rather, they may be individuals for whom MBCT represents a clinically beneficial alternative. Interpreted clinically, the findings suggest that if people present with a history of depression but do not report other risk factors, such as early abuse, anhedonia, rumination, and early onset, then ADM works well. However, our model suggests that when these other risk factors are present, it is worth considering MBCT because outcomes may be enhanced. This is consistent with other articles (Kuyken et al., 2016; Ma & Teasdale, 2004) that have suggested that for such individuals, there is more "grist for the MBCT mill" and possibly more motivation to engage in an active intervention such as MBCT (or indeed cognitive-behavioral therapy).

The survival model's estimate of a 48% reduction in risk of relapse across the 24-month follow-up period (HR = 0.52) for patients with poor ADM prognoses who received MBCT versus ADM would suggest, if replicated, that such patients should pursue MBCT. The potential impact of the absolute observed difference in relapse rates (22%) for patients in the poor-ADM-prognosis subgroup who received ADM versus MBCT, however, is tempered by the fact that these individuals accounted for only one third of the sample. Yet the potential clinical utility of these findings may not necessarily be limited to this subgroup: Given the low relapse rates and lack of difference between treatments for patients with good ADM prognoses (31% ADM vs. 38% MBCT), such patients could be encouraged to select which relapse prevention strategy to pursue according to other factors. Clinically, our data indicate that treatment selection for depressive relapse prevention in individuals with recurrent depression who have a moderate to good ADM prognoses could be guided by factors such as patient preference, cost, and resource availability. Although resource availability may be a limiting factor, cost–benefit analyses have shown noninferiority of MBCT (Kuyken et al., 2015b), and some have even favored MBCT over ADM (Pahlevan et al., 2020). For individuals with poor prognoses on ADM, however, our data indicate that MBCT alongside tapering or cessation of medication to prevent relapse potentially confers a better clinical outcome and should be offered as an alternative to ADM. Recent systematic reviews and individual-participant meta-analyses suggest that combination relapse prevention, in which both medication continuation and preventive psychotherapy are provided, is superior to monotherapy and thus should also be considered for patients at higher risk for relapse.

Our study has a number of potential limitations. With the present data, we are unable to disaggregate the effects of MBCT from the tapering or discontinuation of ADM because they were both part of the MBCT protocol. We are also unable to comment on whether the effects are specific to MBCT or whether any effective alternative psychosocial intervention would offer potentially similar benefits for individuals with poor prognoses on maintenance ADM.

The utility of any model depends on its ability to generalize. The present algorithm was subjected to internal validation during variable selection and model building. The imputation of missing baseline data was not included in the cross-validation, but given the low number of missing data points, it is unlikely that this was a substantial source of bias. Previous work suggests that penalization and shrinkage methods may not provide as much protection as is assumed and that such methods (including ENRR) can produce unreliable clinical prediction models when sample sizes are small (Riley et al., 2021). Despite the internal cross-validation, we were not able to externally validate the model on a wholly independent sample because comparable sufficiently large trials evaluating the same preventive interventions with the same or a similar set of baseline measures are not currently available. This reflects the current state of precision medicine research (Cohen & DeRubeis, 2018), in which predictive models are too rarely subjected to proper external validation (Salazar de Pablo et al., 2021). Further external validation of the model[5] and these results, when suitable data become available, will be an important next step before the translation of the current findings into firm treatment recommendations. Although we were fortunate to receive extensive reviewer feedback that allowed us to enhance our analytic approach, the many researcher degrees of freedom that remain represent potential threats to generalizability that merit caution and are worthy of further study.

Ideally, both the ADM and MBCT models would have been sufficiently robust to actively compare the two predictive indices to elucidate what works best for whom. However, our computed MBCT model did not perform above chance and was no better than a prediction model built solely on baseline depression severity scores. This lack of robust prediction within the MBCT model accords with the replicated finding that very few demographic, clinical, or psychological variables over and above baseline symptom severity appear to predict outcome to MBCT (Kuyken et al., 2016; Kuyken, Watkins, et al., 2010), which testifies to the intervention's broad suitability. Second, in the present study, MBCT was combined with support for medication tapering or discontinuation, and it may be that the mixture of these two different intervention components (and possible associated effects of medication withdrawal) obscured any clear relations in the MBCT arm with the predictor variables included here.

The current findings represent a significant first step in the application of precision medicine to inform patient and clinician choice around optimal interventions for depressive relapse prevention. Additional work is needed to further validate the model reported here in wholly independent, yet-to-be-collected, large samples. The eventual success of this and similar personalized-medicine approaches to mental-health care will depend on the acquisition and dissemination of large-scale clinical data sets, which will allow for the development and validation of predictive models (Chekroud et al., 2017, 2021). The utility of these models must then be evaluated in prospective clinical trials (Delgadillo & Lutz, 2020), which have begun to emerge with promising results (e.g., Delgadillo et al., 2022; Lutz et al., 2022).

Transparency

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Author Contributions

T. Dalgleish and S. Schweizer should be regarded as joint senior authors. Z. D. Cohen, T. Dalgleish, and S. Schweizer conceived of the secondary analyses. Z. D. Cohen analyzed the data. Z. D. Cohen, T. Dalgleish, and S. Schweizer wrote the manuscript. All coauthors commented on the final version of the manuscript. All of the coauthors approved the final manuscript for submission.

Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Notes

1. We note that a recent systematic review of 56 studies and almost 40,000 subjects by De Zwart and colleagues (2019) reexamined the distinction between relapse and recurrence established by Frank et al. (1991) and concluded that "the idea that a recurrence of depressive symptoms shortly after their initial remission constitutes a 'relapse' of the previous episode, whereas their later recurrence is the first sign of an entirely new episode, is a model that lacks empirical support" (De Zwart et al., 2019, p. 544). Therefore, in this article, we use the term "relapse" to describe a return of depressive symptoms meeting criteria from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (as assessed via Structured Clinical Interview for DSM-IV), regardless of when during the 24-month follow-up it occurred.
2. Although the terms "continuation" and "maintenance" are often used interchangeably in the literature, they are sometimes used more specifically (e.g., DeRubeis et al., 2019) to differentiate treatment following remission and up to recovery (continuation) from treatment past the point of recovery (maintenance). Here, we align with the trial's main outcome article (Kuyken et al., 2015a) and use "maintenance" to describe all medication use during the study.
3. We note that in the PREVENT trial's main outcome article (Kuyken et al., 2015a), "MBCT-TS" was used as the abbreviation for mindfulness-based cognitive therapy with support to taper or discontinue antidepressant treatment and that "m-ADM" was used as the abbreviation for maintenance antidepressant medication, but here these two conditions are simply abbreviated as MBCT and ADM, respectively.
4. From here forward, when we reference the "HAMD" (Hamilton Rating Scale for Depression) models (either for ADM or MBCT), we mean the simple "severity only" logistic regression comparison models that include only baseline HAMD, whereas when we reference the "ADM model" or the "MBCT model," we mean the multivariable prognostic models constructed with elastic-net regularized regression.
5. See SM7 in the Supplemental Material for further details regarding a model constructed using the full ADM analysis sample that could be subjected to external validation in future efforts.

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Supplemental Material

The development and internal evaluation of a predictive model to identify for whom Mindfulness-Based Cognitive Therapy (MBCT) offers superior relapse prevention for recurrent depression versus maintenance antidepressant medication

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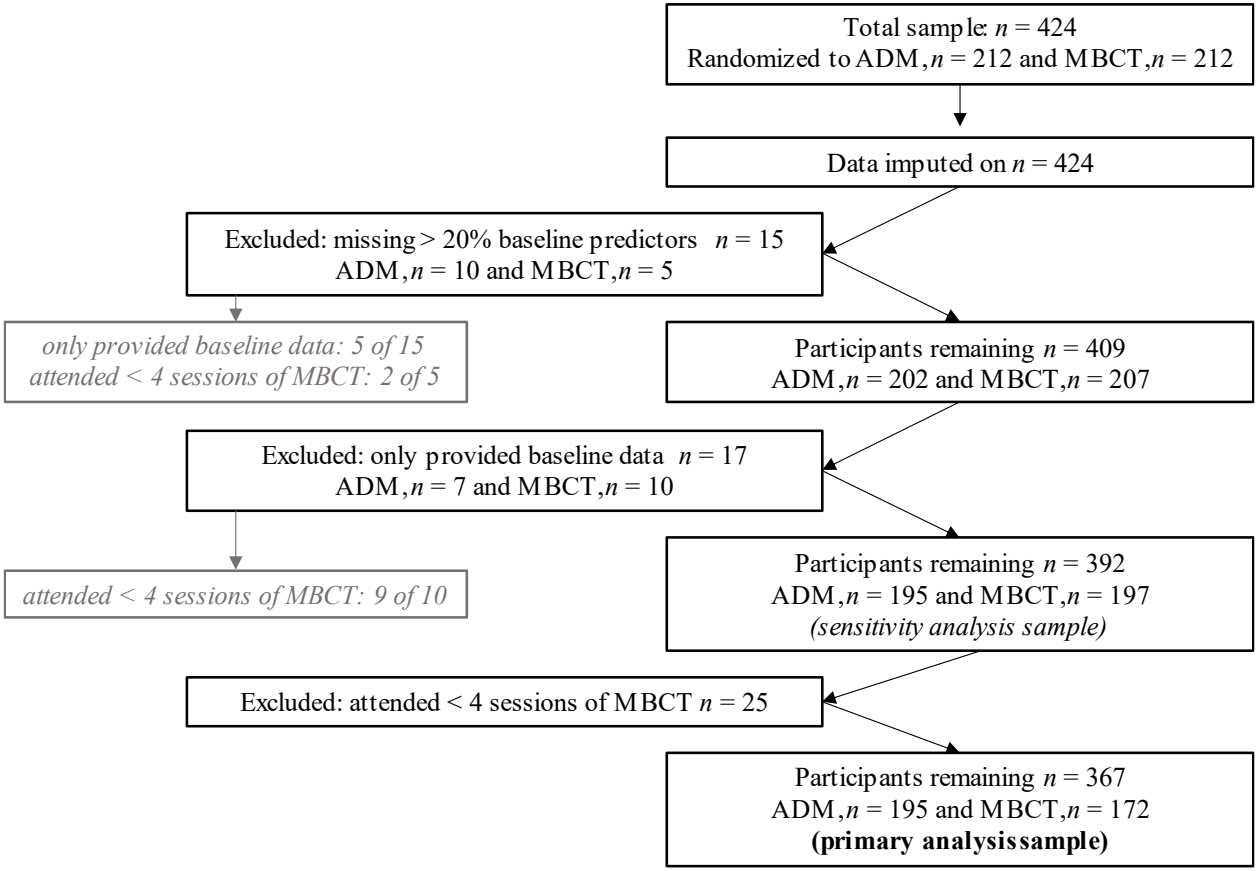
SM1 – Participant Exclusion

Figure S1

Pipeline for Participant Exclusion ~ Data Exclusion Pipeline



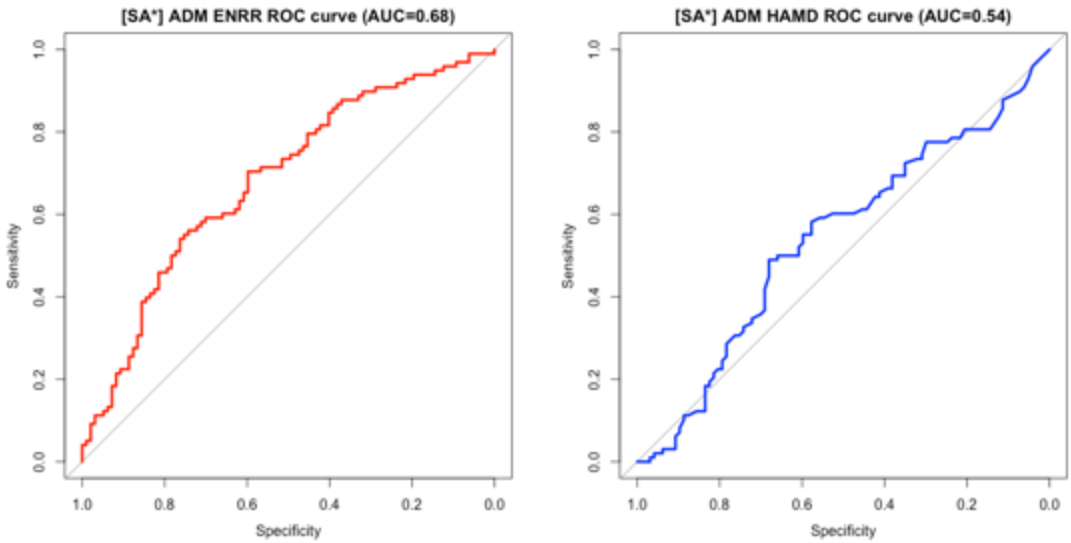
Note. MBCT = Mindfulness-Based Cognitive Therapy; ADM = Antidepressant medication

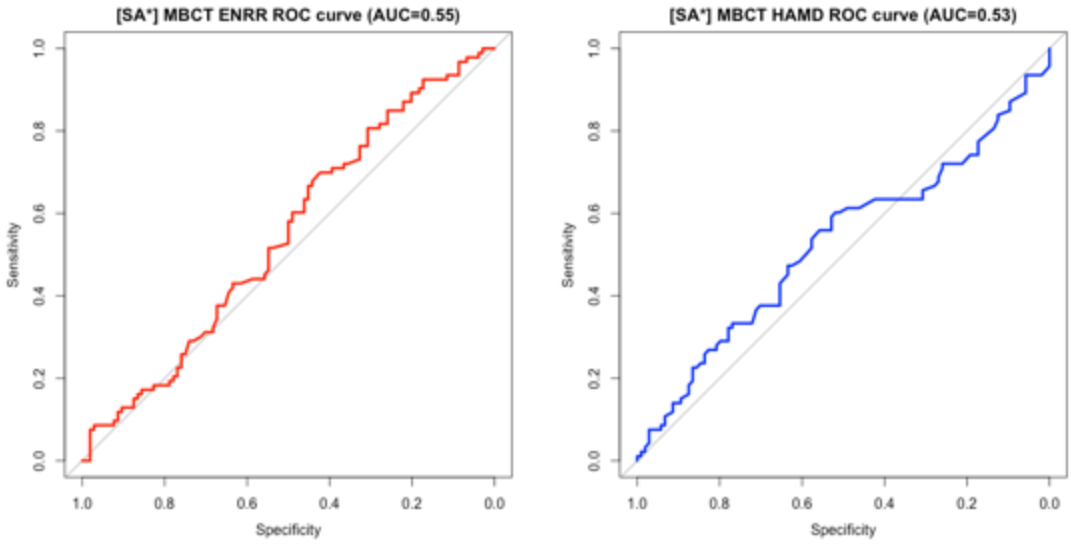
SM2 - Sensitivity Analyses

Because we did not end up using the MBCT prediction model in our treatment selection analyses, all analyses were repeated including the 25 MBCT participants that were initially excluded from the main analyses based on lack of treatment dose (completing fewer than four MBCT sessions). Consistent with the main analyses, the ADM AUC continued to offer significantly greater predictive utility relative to the HAMD-only model AUC, $z = 2.80$, $p = .003$. This was still not the case for the MBCT model, where there remained no significant difference in AUCs relative to the HAMD-only model, $z = 0.34$, $p = .37$ (Figure S2).

Figure S2

Receiver Operating Characteristic (ROC) Curves for Probability of Relapse within the ADM and MBCT Groups for the Sensitivity Analyses





Note. The panels show the Area Under receiver operating characteristic (ROC) Curves (AUC) for the prediction models. The curves delineate the relative sensitivity (true positive rate) and specificity (false positive rate) of the prediction models. The left panels (in red) show the AUCs for multi-variable elastic net (ENRR) models predicting the rate of relapse over 24 months in ADM (top) and MBCT (bottom). The right panels (in blue) shows the AUCs for the comparison models using baseline Hamilton Rating Scale for Depression (HAMD) as the only predictor across the two treatment arms, again for ADM (top) and MBCT (bottom). The AUCs are plotted against the straight grey line, which represents the threshold at which the model has no predictive utility. The grey line delineates the likelihood that someone above and below that threshold on the prognostic index has an equal likelihood of relapse. That is, the larger (further away from the grey line) the AUC the greater a model's predictive utility. SA* = Sensitivity Analysis.

In the survival analysis examining time-to-relapse with main effects for treatment and continuous ADM prognosis for the sensitivity sample, as in the main analysis sample, there was a significant main effect of continuous ADM prognosis ($z = 4.237$; $p < .001$). We next compared observed outcomes across the two treatment conditions for individuals

according to their ADM-prognosis. As in the main analysis sample, the predicted survival curves did not differ across treatments for those with good ADM prognoses (hazard ratio reflecting increased risk of relapse for those in MBCT vs. ADM = 1.27; 95%CI, 0.70 to 2.31; p = .43), or for those with moderate ADM prognoses (hazard ratio = 1.11; 95%CI, 0.69 to 1.79; p = .66). In contrast to those with good and poor prognoses, again aligning with the main analysis sample results, those with poor ADM prognoses had significantly reduced relapse risk (hazard ratio = 0.59; 95%CI, 0.38 to 0.93; p = .023) if they switched to MBCT instead of staying on ADM.

As with the survival sensitivity analyses, the results of the sensitivity analyses of numbers relapsed by the end of follow up rates were aligned with the main analyses. There was the expected significant main effect of prognostic sub-group on numbers relapsed, X^2 (2) = 17.98, $P < .001$. Investigating numbers relapsed across each prognostic sub-group, again revealed no significant effects in the sub-groups with moderate, X^2 (1) = 0.41, $P = .52$ and good X^2 (1) = 0.28, $P = .60$, ADM-prognoses. The 18% difference in numbers relapsed by the end of follow-up (51% MBCT vs. 69% ADM) in the poor ADM-prognosis group for the sensitivity analysis sample was smaller than the 22% difference observed in the main analysis sample, and was no longer significant (X^2 (1) = 3.60, $P = .052$).[*]

[*] As humorously but depressingly illustrated by Matthew Hankin's famous blog post (link below) summarizing more than 500 unique phrases that have been used in peer-reviewed journal articles to inaccurately describe non-significant results, incorrectly describing "marginally significant" (i.e., non-significant) results is a problem in the scientific literature (Olsson-Collentine et al., 2019). In the effort to contribute science's self-correction, we must thank Reviewer #2 for correcting our embarrassing misstep of describing one of our results as "trending towards significance" in our initial submission, and error which we have corrected and will never again commit.

https://mchankins.wordpress.com/2013/04/21/still-not-significant-2/

SM3 - Descriptive data for predictor variables at baseline

ADM vs MBCT Sample

Descriptive data for the predictor variables, prior to imputation, at baseline in the analysis sample (*N*=367) broken down by treatment group (ADM vs MBCT) is provided in Table S1, along with group comparisons. There was a significantly greater proportion of women in the ADM group (82% vs 69%), and ADM participants, on average, were 2.5 years younger, reported 0.2 more comorbid diagnoses, and had a lower probability that their most recent episode of depression was chronic (>24 months in duration), at baseline, compared to the MBCT group (19% vs 31%, respectively; see Table S1 for more details).

Table S1

Predictor Variables at Baseline in the Primary Analysis Sample, Broken Down by Treatment Group

Predictor	ADM (*N* = 195)	MBCT (*N* = 172)	Continuous: Mean difference (t-stat) Categorical: χ^2	*P* Value
Demographic characteristics				
Age (years)			**1.99**	**.048**
Mean (*sd*)	48.77 (12.69)	51.30 (11.56)		
Range	20-79	24-78		
Female (%)	160 (82)	118 (69)	**8.28**	**.004**
Education†			–1.47††	.14††
No educational qualification	10 (5)	10 (6)		
O levels or GCSEs	38 (20)	24 (14)		
AS and A levels (UK Advanced Level)	26 (13)	15 (9)		
Vocational training/qualification	64 (33)	56 (33)		
University Bachelor's degree	32 (17)	44 (26)		
University Master's degree	9 (5)	9 (5)		
University professional training/PhD	14 (7)	12 (7)		
Relationship			0.33	.57
No (Single/Divorced/Widowed)	67 (34)	65 (38)		
Yes (Married/Civil partnership/Cohabiting)	128 (66)	107 (62)		
Employed* (unemployed vs. full- or part-time)	119 (61)	98 (57)	0.46	.50
Clinical characteristics				
Clinician-rated depressive symptoms (HAMD)			0.31	.75
Mean (*sd*)	4.62 (4.31)	4.76 (4.27)		
Range	0-20	0-19		

Self-reported depressive symptoms (BDI-II)			–0.76	.45
Mean (*sd*)	14.39 (10.08)	13.59 (10.24)		
Range	0-42	0-48		
Age of onset			–0.20	.84
Mean (*sd*)	25.16 (12.30)	24.91 (11.82)		
Range	6-65	5-67		
Chronicity (previous depressive episode ≥ 24months)	38 (19)	53 (31)	**5.69**	**.02**
Previous psychological treatment	98 (52)	84 (49)	0.17	.68
Previous suicide attempt	49 (25)	33 (19)	1.53	.22
Family history of depression	90 (50)	85 (53)	0.13	.72
Number of comorbid diagnoses			**–2.59**	**.01**
Mean (*sd*)	0.68 (0.94)	0.44 (0.77)		
Range	0-5	0-3		
Psychological mechanisms				
Five-Facets Mindfulness Questionnaire (FFMQ)				
Observe			0.19	.85
M (*sd*)	24.11 (5.63)	24.23 (5.69)		
Range	11-37	8-39		
Describe			0.38	.71
M (*sd*)	26.08 (7.14)	26.35 (6.62)		
Range	8-40	10-40		
Aware			0.34	.73
M (*sd*)	24.01 (5.28)	24.20 (5.62)		
Range	10-40	10-39		
Non-Judging			0.16	.87
M (*sd*)	24.87 (6.35)	24.98 (6.93)		
Range	10-40	8-39		
Non-Reactivity			1.58	.11
M (*sd*)	19.29 (4.59)	20.10 (5.24)		

Range	10-31	7-35		
Self-Compassion Scale (SCS)				
Self-Kindness			0.01	.99
M (*sd*)	12.57 (3.96)	12.58 (4.35)		
Range	5-25	5-25		
Self-Judgement			0.39	.69
M (*sd*)	11.77 (3.91)	11.93 (4.02)		
Range	5-25	5-24		
Common Humanity			–0.50	.62
M (*sd*)	11.79 (3.81)	11.58 (3.85)		
Range	4-20	4-20		
Isolation			–0.49	.63
M (*sd*)	9.58 (3.32)	9.40 (3.48)		
Range	4-20	4-20		
Mindfulness			–0.03	.98
M (*sd*)	11.79 (3.14)	11.78 (3.39)		
Range	4-20	4-20		
Over-Identification			0.42	.67
M (*sd*)	9.22 (3.11)	9.37 (3.43)		
Range	4-19	4-20		
Compassion for others			0.65	.51
M (*sd*)	27.15 (3.32)	27.38 (3.36)		
Range	16-33	11-33		
Dispositional Positive Emotions Scale (DPES)				
Joy			–1.07	.29
M (*sd*)	17.23 (4.34)	16.74 (4.38)		
Range	6-30	6-28		
Contentment			–0.29	.77
M (*sd*)	14.18 (3.93)	14.05 (4.15)		
Range	5-25	5-25		

Love			–0.62	.53
M (*sd*)	19.22 (4.66)	18.92 (4.23)		
Range	6-30	9-29		
Compassion			–0.63	.53
M (*sd*)	21.36 (3.00)	21.16 (3.22)		
Range	12-25	13-25		
Awe			1.13	.26
M (*sd*)	19.25 (4.45)	19.786 (4.09)		
Range	8-30	9-30		
Curiosity			1.10	.27
M (*sd*)	14.39 (3.20)	14.76 (3.19)		
Range	4-20	5-20		
Cognitive Emotion Regulation Questionnaire (CERQ)				
Catastrophizing			1.35	.18
M (*sd*)	8.54 (2.95)	8.99 (3.39)		
Range	4-18	4-18		
Rumination			0.44	.66
M (*sd*)	12.04 (3.55)	12.20 (3.42)		
Range	4-20	5-20		
Other-blame			1.20	.23
M (*sd*)	7.41 (2.46)	7.75 (3.00)		
Range	4-20	4-18		
Self-blame			0.91	.36
M (*sd*)	10.72 (3.39)	11.05 (3.64)		
Range	4-20	4-20		
Acceptance			–0.08	.94
M (*sd*)	11.76 (3.02)	11.74 (3.03)		
Range	6-20	5-19		
Positive Refocusing			–1.52	.13
M (*sd*)	8.10 (3.16)	7.59 (3.26)		

Range	4-18	4-18		
Positive Reappraisal			0.54	.59
M (*sd*)	10.05 (3.78)	10.28 (4.25)		
Range	4-20	4-20		
Putting into Perspective			–0.31	.76
M (*sd*)	10.95 (3.41)	10.83 (3.89)		
Range	4-20	4-20		
Refocus on Planning			0.63	.53
M (*sd*)	10.64 (3.32)	10.87 (3.71)		
Range	4-20	4-20		
Cambridge-Exeter Repetitive Thought Scale (CERTS)				
Negative Rumination			0.56	.58
M (*sd*)	73.18 (15.37)	74.08 (15.10)		
Range	23-100	20-100		
Positive Rumination			1.40	.16
M (*sd*)	22.43 (5.84)	23.28 (5.71)		
Range	8-40	8-38		
Constructive Rumination			1.38	.17
M (*sd*)	10.91 (3.04)	11.35 (3.09)		
Range	4-20	4-20		
Unresolution			0.01	.99
M (*sd*)	12.31 (2.70)	12.31 (2.97)		
Range	4-19	4-20		
Moving On			–0.79	.43
M (*sd*)	7.83 (1.76)	7.68 (1.74)		
Range	3-13	4-12		
Other				
Level of parental abuse (MOPS)			0.47	.49
Low	93 (48)	90 (52)		
High	100 (52)	82 (48)		

Self-Efficacy (GSE)			–0.05	.96
Mean (*sd*)	32.31 (7.77)	32.27 (8.18)		
Range	13-50	10-50		
Stigmatisation (SN)			–0.39	.70
Mean (*sd*)	20.88 (6.38)	20.60 (7.15)		
Range	7-35	7-35		
Recognizing warning signs (WS)			1.25	.21
Mean (*sd*)	18.26 (5.83)	19.01 (5.55)		
Range	6-30	6-30		
Relationship Satisfaction (RS)			0.88	.38
Mean (*sd*)	26.50 (6.71)	27.11 (6.28)		
Range	7-35	9-35		
Preference for MBCT			–0.46	.64
	4.51 (0.67)	4.48 (0.72)		
	2-5	1-5		
Preference for ADM			0.50	.61
	3.10 (1.10)	3.16 (1.09)		
	1-5	1-5		
Preference for Therapy Type			–0.83	.41
	1.80 (1.07)	1.70 (1.07)		
	1-5	1-5		

Note. HAMD = Hamilton Depression Rating Scale (Hamilton, 1967), assessed using the 17-item GRID-HAMD (Williams et al., 2008); BDI-II = Beck Depression Inventory Version-II (Beck et al., 1996); MOPS = Measure of Parenting Style (Parker et al., 1997); GSE = General Self-Efficacy Scale (Schwarzer et al., 1995); SN = Stigmatization and Normalization (bespoke questions); WS = Warning signs (bespoke questions); RS= Relationship satisfaction (bespoke questions). † Education, which was assessed and imputed as an ordered categorical variable, was transformed into a continuous variable following imputation as follows: 0 = No educational qualification, 1 = O levels or GCSEs, 2 = AS and A

levels, 3 = Vocational training, 4 = University Bachelor's degree, 5 = University Master degree, 6 = University professional training. †† The reported group difference test comparing excluded vs. included for Education is for the numeric version of the variable via a mean difference test (Two Sample Student's t-Test). * Employed was defined as a categorical variable where Yes (employed=1) was defined as full- or part-time employed, and No (unemployed=0) also included the following categories: retired, voluntary working, housewife, househusband, homemaker, full time mum/dad, student, "not applicable", at home, and carer for family member. Individuals were asked to complete all measures (except for the MOPS) with respect to the previous two weeks. All scales except for the HAMD, BDI-II, and MOPS were scored on a 5-point Likert scale irrespective of their original scoring range. The scaling was standardized to facilitate interpretation from factor analyses and similar computations planned for the trial. The labels of the original scales were maintained. Further details on the psychological predictor variables are presented in Table 1.

Excluded vs Included (Analysis) Sample

Descriptive data for the predictor variables, prior to imputation, at baseline for the excluded and included (i.e., main analysis) samples, are provided in Table S2, along with group comparisons and information on missingness. Relative to the analysis sample, excluded participants were, on average, four years younger, had 0.3 more comorbid diagnoses, and reported lower scores on the Dispositional Positive Emotions Scale Curiosity subscale, Self-Compassion Scale Isolation subscale, and the Five-Facets Mindfulness Questionnaire Describe subscale.

Table S2

Predictor Variables at Baseline

Predictor	Excluded (*n* = 57)	Included (*n* = 367)	Continuous: Mean difference (t-stat) Categorical: χ^2	*P* Value
Demographic				
Age (years)			**2.23**	**.03**
Mean (*sd*)	46.07 (12.42)	49.96 (12.22)		
Range	22-73	20-79		
Female	47 (82)	278 (76)	0.89	.34
Education†	[a]	[b]	0.68††	.50††
No educational qualification	0 (0)	20 (6)		
O levels or GCSEs	19 (37)	62 (17)		
AS and A levels (UK Advanced Level)	1 (2)	41 (11)		
Vocational training/qualification	14 (27)	120 (33)		
University Bachelor's degree	13 (25)	76 (21)		
University Master's degree	2 (4)	18 (5)		
University professional training/Phd	3 (6)	26 (7)		
Relationship	[c]		1.46	.23
No (Single/Divorced/Widowed)	25 (45)	132 (36)		
Yes (Married/Civil Partnership/Cohabiting)	30 (55)	235 (64)		
Employed* (unemployed vs. full- or part-time)	24 (44)[d]	217 (59)	3.57	.06
Clinical characteristics				
Clinician-rated depressive symptoms (HAMD)			–0.15	.88
Mean (*sd*)	4.77 (4.61)	4.68 (4.29)		
Range	0-19	0-20		
Self-reported depressive symptoms (BDI-II)			–0.49	.62
Mean (*sd*)	14.78 (10.05)[e]	14.01 (10.15)		
Range	0-37	0-48		

Age of depression onset			1.49	.14
Mean (*sd*)	22.53 (10.41)	25.04 (12.06)[f]		
Range	4-50	5-67		
Chronicity (previous depressive episode ≥24 months)	11 (19)	91 (25)	0.54	.46
Previous psychological treatment	29 (55)[g]	182 (50)	0.21	.65
Previous suicide attempt	19 (35)[e]	82 (22)	3.58	.06
Family history of depression	24 (51) [h]	175 (51)[i]	9.68e-30	1.00
Number of comorbid diagnoses			**–2.28**	**.02**
Mean (*sd*)	0.86 (1.06)	0.57 (0.87)		
Range	0-4	0-5		
Psychological Mechanisms				
Five-Facets Mindfulness Questionnaire (FFMQ)	[j]	[k]		
Observe			1.07	.29
M (sd)	23.20 (5.60)	24.17 (5.65)		
Range	11-39	8-39		
Describe			**2.10**	**.04**
M (sd)	23.93 (5.67)	26.20 (6.90)		
Range	10-36	8-40		
Aware			0.90	.37
M (sd)	23.32 (5.24)	24.10 (5.44)		
Range	15-37	10-37		
Non-Judging			–0.49	.62
M (sd)	25.45 (6.79)	24.92 (6.62)		
Range	12-39	8-40		
Non-Reactivity			0.82	.42
M (sd)	19.05 (4.02)	19.67 (4.92)		
Range	11-29	7-35		
Self-Compassion Scale (SCS)	[g]	[b]		
Self-Kindness			0.50	.62
M (sd)	12.24 (3.89)	12.58 (4.14)		
Range	5-20	5-25		

Self-Judgement			0.68	.50
M (sd)	11.40 (4.03)	11.84 (3.96)		
Range	5-25	5-25		
Common Humanity			0.66	.51
M (sd)	11.29 (3.44)	11.69 (3.83)		
Range	5-19	4-20		
Isolation			**2.23**	**.03**
M (sd)	8.29 (2.72)	9.50 (3.39)		
Range	4-15	4-20		
Mindfulness			0.31	.76
M (sd)	11.62 (3.37)	11.78 (3.25)		
Range	4-18	4-20		
Over-Identification			–0.03	.97
M (sd)	9.31 (2.86)	9.29 (3.26)		
Range	4-20	4-20		
Compassion for others			0.21	.83
M (sd)	27.14 (3.26)	27.26 (3.34)		
Range	19-34	11-33		
Dispositional Positive Emotions Scale (DPES)	[g]	[k]		
Joy			–0.37	.71
M (sd)	17.26 (3.64)	17.00 (4.36)		
Range	9-24	6-30		
Contentment			0.07	.94
M (sd)	14.07 (3.64)	14.12 (4.03)		
Range	7-23	5-25		
Love			0.84	.40
M (sd)	18.48 (3.77)	19.08 (4.46)		
Range	9-27	6-30		
Compassion			–0.27	.79
M (sd)	21.40 (3.86)	21.27 (3.10)		
Range	5-25	12-25		

Awe			1.76	.08
M (sd)	18.26 (4.18)	19.50 (4.29)		
Range	6-28	8-30		
Curiosity			**2.12**	**.04**
M (sd)	13.48 (2.83)	14.57 (3.19)		
Range	6-20	4-20		
Cognitive Emotion Regulation Questionnaire (CERQ)	[g]	[f]		
Catastrophizing			–0.72	.47
M (sd)	9.12 (2.77)	8.75 (3.17)		
Range	5-15	4-18		
Rumination			1.00	.32
M (sd)	11.55 (3.47)	12.12 (3.49)		
Range	6-20	4-20		
Other-blame			0.37	.71
M (sd)	7.40 (2.60)	7.57 (2.73)		
Range	4-14	4-15		
Self-blame			–0.70	.49
M (sd)	11.29 (4.45)	10.87 (3.51)		
Range	4-20	4-20		
Acceptance			–0.72	.47
M (sd)	12.12 (3.91)	11.75 (3.02)		
Range	6-20	5-20		
Positive Refocusing			0.29	.77
M (sd)	7.71 (2.26)	7.86 (3.22)		
Range	4-14	4-15		
Positive Reappraisal			0.54	.59
M (sd)	9.81 (3.55)	10.16 (4.01)		
Range	4-19	4-20		
Putting into Perspective			–0.23	.82
M (sd)	11.02 (2.62)	10.89 (3.64)		
Range	5-18	4-20		

Refocus on Planning			0.86	.39
M (sd)	10.26 (3.16)	10.75 (3.51)		
Range	5-18	4-20		
Cambridge-Exeter Repetitive Thought Scale (CERTS)	[l]			
Negative Rumination		[m]	0.98	.33
M (sd)	71.23 (13.15)	73.61 (15.23)		
Range	29-91	20-100		
Positive Rumination		[m]	0.32	.75
M (sd)	22.53 (6.10)	22.83 (5.79)		
Range	8-34	8-40		
Constructive Rumination		[n]	0.86	.39
M (sd)	10.70 (2.86)	11.12 (3.07)		
Range	5-19	4-20		
Unresolution		[k]	–1.17	.24
M (sd)	12.84 (2.37)	12.31 (2.83)		
Range	6-17	4-20		
Moving on		[n]	–1.93	.055
M (sd)	8.30 (1.66)	7.76 (1.75)		
Range	5-13	3-13		
Other				
Level of parental abuse (MOPS)	[e]	[k]	0.25	.62
Low	27 (55)	183 (50)		
High	22 (45)	182 (50)		
Self-Efficacy (GSE)			1.24	.22
Mean (*sd*)	30.76 (6.95)[o]	32.29 (7.96)[k]		
Range	16-50	10-50		
Perceived Stigmatisation (SN)			–0.99	.32
Mean (*sd*)	21.83 (6.67)[g]	20.75 (6.74)[c]		
Range	7-34	7-35		
Recognizing Warning Signs (WS)			–0.56	.58
Mean (*sd*)	19.12 (4.24)[g]	18.61 (5.70)[f]		

Range	12-28	6-30		
Relationship Satisfaction (RS)			–0.95	.34
Mean (*sd*)	27.79 (6.29)[c]	26.78 (6.51)		
Range	12-35	7-35		
Preference for MBCT			1.08	.28
Mean (*sd*)	4.38 (0.87)[c]	4.49 (0.69)[n]		
Range	2-5	1-5		
Preference for ADM			0.11	.91
Mean (*sd*)	3.11 (1.10)[c]	3.13 (1.09)[n]		
Range	1-5	1-5		
Preference for Therapy Type			–1.83	.07
Mean (*sd*)	2.04 (1.10)[c]	1.75 (1.07)[n]		
Range	1-5	1-5		

Note. Data are n (%) unless otherwise specified. Missing cases resulted in the following *n* for the following variables. [a] *n* = 52; [b] *n* = 363; [c] *n* = 55; [d] *n* = 54; [e] *n* = 49; [f] *n* = 366; [g] *n* =42; [h] *n* =47; [i] *n* = 340; [j] *n* = 44; [k] *n* = 365; [l] *n* = 43; [m] *n* = 362; [n] *n* = 364; [o] *n* = 45. HAMD = Hamilton Depression Rating Scale (Hamilton, 1967), assessed using the 17-item GRID-HAMD (Williams et al., 2008); BDI-II = Beck Depression Inventory Version II (Beck et al., 1996); MOPS = Measure of Parenting Style (Parker et al., 1997); GSE = General Self-efficacy Scale (Schwarzer et al., 1995); SN = Stigmatization and Normalization (bespoke questions); WS = Warning signs (bespoke questions); RS= Relationship satisfaction (bespoke questions). [†] Education, which was assessed and imputed as an ordered categorical variable, was transformed into a continuous variable following imputation as follows: 0 = No educational qualification, 1 = O levels or GCSEs, 2 = AS and A levels, 3 = Vocational training, 4 = University Bachelor's degree, 5 = University Master degree, 6 = University professional training. [††] The reported group difference test comparing excluded vs. included for Education is for the numeric version of the variable via a mean difference test (Two Sample

Student's t-Test). * Employed was defined as a categorical variable where Yes (employed) was defined as full- or part-time employed, and No (unemployed) also included the following categories: retired, voluntary working, housewife, househusband, homemaker, full time mum/dad, student, "not applicable", at home, and carer for family member. Preference questions were: "How do you feel about the possibility of being in an MBCT group" and "How do you feel about remaining on your ADMs", both scored on a 5-point Likert scale with anchors of 1 = not positive at all and 5 = extremely positive, and "Do you have a preference for a group", also scored on a 5-point Likert scale with anchors of 1 = MBCT, 3 = no pref, and 5 = continue on ADM.

SM4 - Model Construction

Cross-validation

Most treatment selection work in mental health has suffered from two potential limitations related to the sample sizes usually available in randomized controlled trials (Lorenzo-Luaces et al., 2020) and a lack of separate test/validation samples (Cohen et al., 2021). First, questions regarding a model's generalizability beyond the sample in which it was built (or population from which the sample was drawn) are not easily addressed without a held-out sample in which the model can be evaluated. In an ideal world, every predictive model would be evaluated in a completely separate test sample. Here, this was not possible, as no other study comparing ADM to MBCT has measured a comparably inclusive set of potential predictors as used in our analyses. Thus, although the variable selection approach and weight setting approach we employed was designed to improve generalizability and reliability (c.f., Riley et al., 2021), the extent to which our final model would generalize to a new population is unknown.

The second issue with most analytic efforts that rely on small RCT samples (in which held-out test samples are not practical) is the risk of overconfidence due to "double-dipping", which arises when a model is evaluated within the same sample in which it was constructed (Fiedler, 2011; Hastie et al., 2009). When a truly separate sample is unavailable, one approach to avoid double-dipping is to perform split-halves analysis, in which the sample is split into two halves, one of which is used to create the model, while the other is completely held out to evaluate the model. Given our small sample, a split-halves approach was not feasible. To maximize the sample size available for model creation while simultaneously ensuring that data from the individual for whom predictions were being generated did not contribute to the predictive model, we therefore

employed K-fold cross-validation (specifically, 10-fold), as described in the main manuscript.

Figure S3

Schematic of Cross-validation Procedure for Producing MBCT Predictions for the Full Analysis Sample

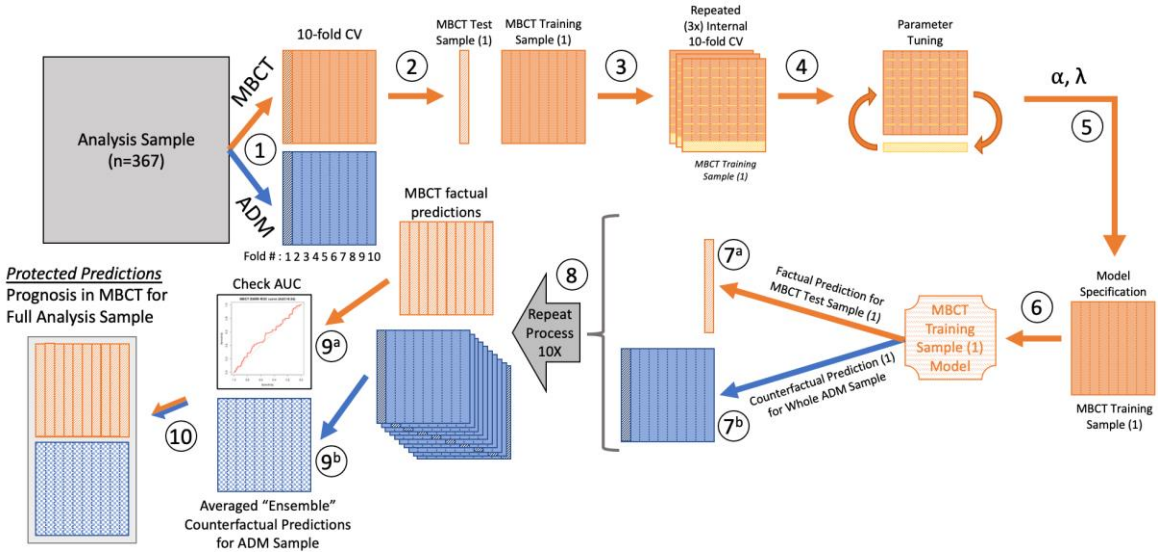
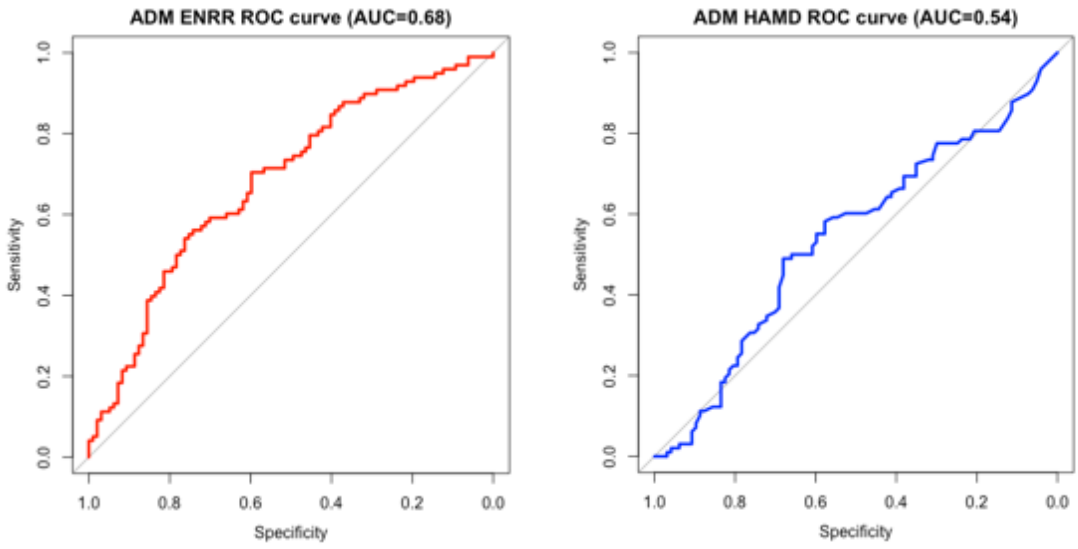


Figure S3: Step 1 (10-fold cross-validation [CV]): The main analysis sample was separated into MBCT and ADM samples, which were then split into ten sub-groups, balanced on outcomes. Step 2: The MBCT sample was separated into its first train-test samples, with the first of the ten sub-groups held out as MBCT Test Sample (1), and the other nine sub-groups comprising MBCT Training Sample (1). Steps 3 and 4: MBCT Training Sample (1) was then itself split into ten sub-groups, and parameter tuning was performed using internal 10-fold cross-validation; this entire process was repeated 3 times using different random permutations of the internal 10-fold CV of MBCT Training Sample (1). Step 5 (hyperparameter optimization): The optimal alpha (α) and lambda (λ) were selected and used in Step 6 (Model Specification), in which Elastic Net Regularized Regression (ENRR) was applied to the entire MBCT Training Sample (1) to derive MBCT Training Sample (1) Model. Step 7^a: This model was then used to generate factual predictions for held-out MBCT Test Sample (1), and to generate counterfactual predictions (Step 7^b) for the entire ADM Sample. Step 8: Steps 2-7 were then repeated nine more times to complete the 10-fold CV. Step 9^a: The resulting set of (protected) factual predictions for the entire MBCT sample (likelihood of relapse in MBCT) were then evaluated using the Area Under the Receiver Operating Characteristic Curve (AUC). Step 9^b: The set of ten (protected) counterfactual predictions for each individual in the ADM sample (likelihood of relapse if they had received MBCT) were averaged, resulting in a set of Averaged "Ensemble" Counterfactual Predictions for the ADM sample. Step 10: The MBCT and ADM samples and their MBCT predictions were then re-combined, resulting in protected Prognoses in MBCT for the Full Analysis Sample.

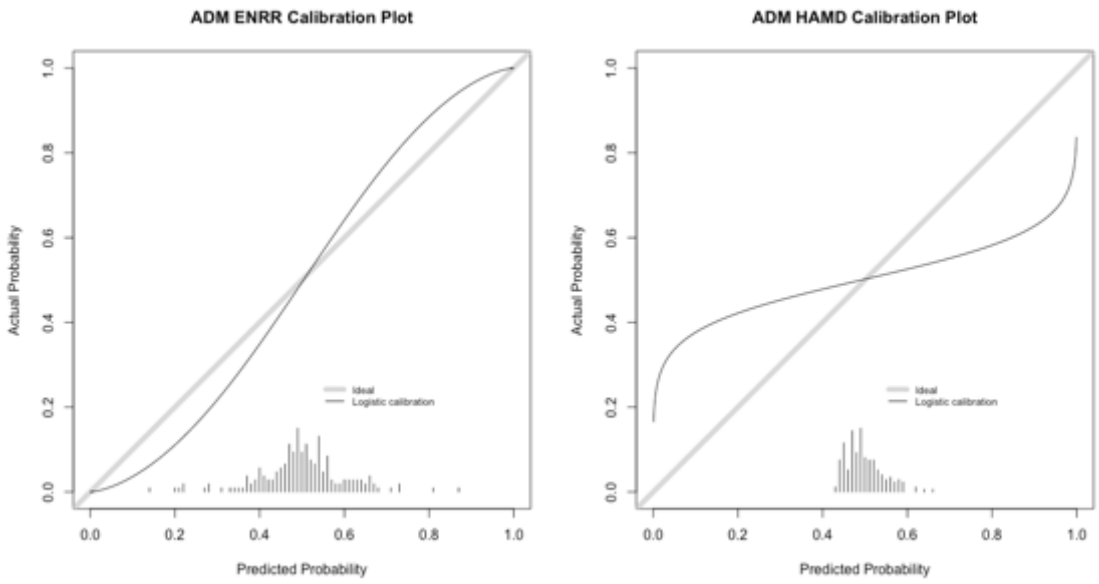
Modeling ADM Prognosis

Figure S4

Area Under the Receiver Operating Characteristic (ROC) Curve (AUC) for ADM Prognostic Models



Note. Figure S4 demonstrates the Area Under the Receiver Operating Characteristic (ROC) Curve (AUC), which delineates the relative sensitivity (true positive rate) and specificity (false positive rate) of the prognostic multivariable ADM elastic net (ENRR) model (left, in red) and the baseline comparison ADM Hamilton Depression Scale (HAMD) model (right, in blue). The AUC (red or blue line) is plotted against the straight grey line, which represents the threshold at which the model has no predictive utility. The grey line delineates the likelihood of someone above and below that threshold on the prognostic index has an equal likelihood of relapse. That is, the larger (further away from the grey line) the AUC the greater a model's predictive utility.



ADM ENRR Calibration Plot: Intercept = –0.02; Slope = 1.49

ADM HAMD Calibration Plot: Intercept = 0.01; Slope = 0.23

We used two tertiles to divide the sample into three groups (based on risk of relapse in ADM) that we labelled: good ADM prognosis, moderate ADM prognosis, and poor ADM prognosis. Sample sizes and descriptive statistics (i.e., means, standard deviations, and ranges) for the ADM prognoses for three groups, broken down by treatment received, are described in Table S3.

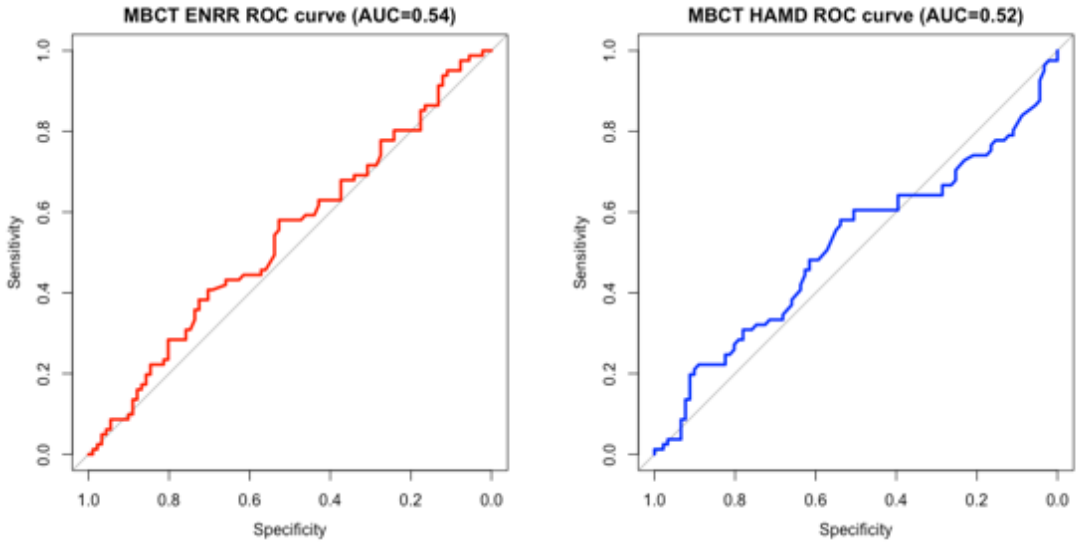
Modeling MBCT Prognosis

Using observed depressive relapse (yes/no) over 24 months to evaluate the factual predictions in the MBCT model that had been made without the use of each patient's own data, the AUC for the MBCT elastic net model was 0.54 (Figure S5). The AUC for the MBCT HAMD comparison model was 0.52. A one-tailed DeLong test failed to reject the null hypothesis that the true difference in AUC between the elastic model and the HAMD model was equal to zero (z=0.37, p=.35), which indicates that the MBCT ENRR model's

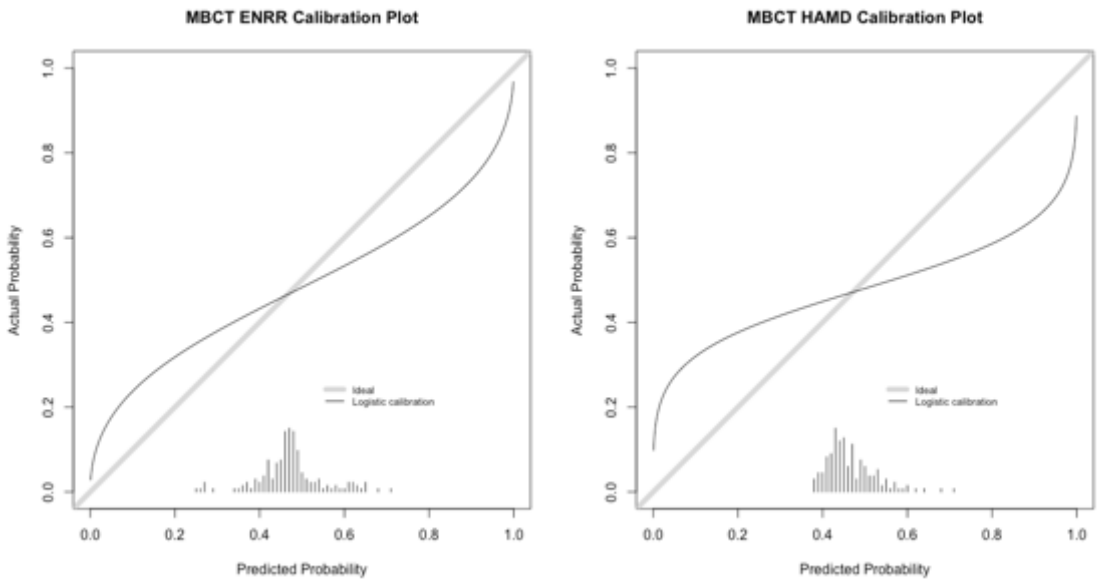
performance was not superior to the MBCT HAMD model. Figure S4 depicts these two ROC curves.

Figure S5

Area Under the Receiver Operating Characteristic (ROC) Curve (AUC) for MBCT Prognostic Models



Note. Figure S5 presents the Area Under the Receiver Operating Characteristic (ROC) Curve (AUC), which delineates the relative sensitivity (true positive rate) and specificity (false positive rate) of the prognostic multivariable MBCT elastic net (ENRR) model (left, in red) and the baseline comparison MBCT Hamilton Depression Scale (HAMD) model (right, in blue). The AUC (red or blue line) is plotted against the straight grey line, which represents the threshold at which the model has no predictive utility. The grey line delineates the likelihood of someone above and below that threshold on the prognostic index has an equal likelihood of relapse. That is, the larger (further away from the grey line) the AUC the greater a model's predictive utility.



MBCT ENRR Calibration Plot: Intercept = –0.07; Slope = 0.50

MBCT HAMD Calibration Plot: Intercept = –0.08; Slope = –0.31

Table S3

Prognoses from ADM Elastic Net (ENRR) Models Summarized by Subgroups

Prognosis type	*n*	*M*	*SD*	min	max
Good	123	0.404	0.059	0.197	0.473
Good (got ADM)	61	0.407	0.068	0.197	0.472
Good (got MBCT)	62	0.401	0.049	0.294	0.473
Moderate	123	0.501	0.016	0.473	0.530
Moderate (got ADM)	67	0.501	0.016	0.475	0.530
Moderate (got MBCT)	56	0.502	0.015	0.473	0.527
Poor	121	0.591	0.052	0.531	0.772
Poor (got ADM)	67	0.594	0.057	0.531	0.772
Poor (got MBCT)	54	0.589	0.045	0.532	0.703

Note. Good = Participants who have a good prognosis across the 24-month follow-up (i.e., low likelihood of relapse) as indicated by their baseline scores on the variables included in the predictive model; Moderate = Participants who have a moderate prognosis across the 24-month follow-up (i.e., moderate likelihood of relapse) as indicated by their baseline scores on the variables included in the predictive model; Poor = Participants who have a poor prognosis across the 24-month follow-up (i.e., high likelihood of relapse) as indicated by their baseline scores on the variables included in the predictive model; got MBCT = refers to participants who were randomized to the Mindfulness-Based Cognitive Therapy group; got ADM = refers to participants who were randomized to the maintenance of antidepressant medication condition.

Variable Selection Results

Tables S4 and S5 describe, for all 53 variables that were considered, the number of times each variable was retained across the 10 ADM and MBCT (respectively) elastic net models, along with the mean, SD, and range of the associated coefficients. the specific variables that were retained and their associated coefficient weightings varied that were generated.

Table S4

Variable Coefficient Summary for 10-fold Cross-validation of ADM Elastic Net Models

Variable Name	Variable	# times selected	*M*	*SD*	Min	Max
AbuseHL	Level of Parenting Abuse (MOPS)	10	0.34	0.16	0.03	0.57
Chronic	Chronicity	10	-0.33	0.17	-0.60	-0.02
DPES_contentment_pre	DPES Contentment	10	-0.08	0.06	-0.20	-0.01
DPES_joy_pre	DPES Joy	10	-0.05	0.04	-0.12	-0.003
DPES_love_pre	DPES Love	10	-0.07	0.04	-0.14	-0.008
CERTS_negrumin_pre	CERTS Negative Rumination	9	0.05	0.03	0	0.10

CERTS_unresolution_pre	CERTS Unresolution	9	0.07	0.06	0	0.15
CERQ_acceptance_pre	CERQ Acceptance	8	0.04	0.05	0	0.14
Comorbidities	Number of comorbid diagnoses	8	0.03	0.03	0	0.07
FFMQ_actaware_pre	FFMQ Aware	8	-0.04	0.04	-0.11	0
Suicide	Suicide	8	0.10	0.09	0	0.26
BLGSS_TOTAL	Self-Efficacy (GSE)	7	-0.03	0.03	-0.08	0
BLSCIDAgeOnset	Age of depression onset	6	-0.03	0.03	-0.08	0
Age	Age	4	-0.003	0.008	-0.02	0
BDI_TotalB	BDI-II	2	0.001	0.003	0	0.01
Employed	Employed	2	0.01	0.03	0	0.08
SCS_isolation_pre	SCS Isolation	2	-0.01	0.03	-0.11	0
SCS_selfjudge_pre	SCS Self-Judgement	2	-0.01	0.02	-0.05	0
BLSN_TOTAL	Perceived Stigmatisation (SN)	1	0.001	0.002	0	0.01
CERQ_selfblame_pre	CERQ Self-blame	1	0.0002	0.001	0	0.002
CERTS_moveon_pre	CERTS Moving on	1	-0.0001	0.0003	-0.001	0

DPES_awe_pre	DPES Awe	1	-0.0001	0.0004	-0.001	0
DPESb_curiosity_pre	DPES Curiosity	1	0.003	0.01	0	0.03
Fam_hist	Family history of depression	1	0.0001	0.0004	0	0.001
FFMQ_describe_pre	FFMQ Describe	1	-0.0003	0.001	-0.003	0
Gender	Gender	1	0.0005	0.001	0	0.01
Prior_TX	Previous psychological treatment	1	0.004	0.01	0	0.04
SCS_overident_pre	SCS Over-Identification	1	-0.0001	0.0003	-0.001	0
BLRelationships_TOTAL	Relationship Satisfaction (RS)	0	-	-	-	-
BLWS_TOTAL	Recognizing Warning Signs (WS)	0	-	-	-	-
CERQ_catastroph_pre	CERQ Catastrophizing	0	-	-	-	-
CERQ_otherblame_pre	CERQ Other-blame	0	-	-	-	-
CERQ_perspective_pre	CERQ Putting into Perspective	0	-	-	-	-
CERQ_planning_pre	CERQ Refocus on Planning	0	-	-	-	-
CERQ_reapprais_pre	CERQ Positive Reappraisal	0	-	-	-	-
CERQ_refocus_pre	CERQ Positive Refocusing	0	-	-	-	-

CERQ_rumination_pre	CERQ Rumination	0	-	-	-	-
CERTS_constructive_pre	CERTS Constructive Rumination	0	-	-	-	-
CERTS_posrumin_pre	CERTS Positive Rumination	0	-	-	-	-
DPES_compassion_pre	DPES Compassion	0	-	-	-	-
Education	Education	0	-	-	-	-
FFMQ_nonjudge_pre	FFMQ Non-Judging	0	-	-	-	-
FFMQ_nonreact_pre	FFMQ Non-Reactivity	0	-	-	-	-
FFMQ_observe_pre	FFMQ Observe	0	-	-	-	-
HAMD_BL	GRID-HAMD	0	-	-	-	-
PrefADM	Preference for Antidepressant Medication	0	-	-	-	-
PrefCog	Preference for Cognitive Therapy	0	-	-	-	-
PrefWhich	Preference for Therapy Type	0	-	-	-	-
Relationship	Relationship	0	-	-	-	-
SCS_humanity_pre	SCS Common Humanity	0	-	-	-	-

SCS_mindfulness_pre	SCS Mindfulness	0	-	-	-	-
SCS_selfkindness_pre	SCS Self-Kindness	0	-	-	-	-
SCSb_compassionothers_pre	SCS Compassion for others	0	-	-	-	-

Note. Table S4 reports model variable regression coefficient summaries for the ADM prognostic model across the 10-fold cross-validation. Times Selected = Number of times (out of 10) the variable was retained by elastic net regression across the 10-fold cross-validation procedure; Min, Max = minimum, and maximum for variable's coefficient value (includes zeros for when variable was not retained); MOPS = Measure of Parenting Style (Parker et al., 1997); GSE = General Self-Efficacy Scale (Schwarzer et al., 1995); CERQ = Cognitive Emotion Regulation Questionnaire (Garnefski et al., 2001); DPES = Dispositional Positive Emotions Scale (Shiota et al., 2006); CERTS = Cambridge-Exeter Repetitive Thought Scale (Barnard et al., 2007); SCS = Self-Compassion Scale (Neff, 2003); GRID-HAMD = GRID Hamilton Depression Rating Scale (Williams et al., 2008); BDI-II = Beck Depression Inventory Version II (Beck et al., 1996); FFMQ = Five Facet Mindfulness Questionnaire (Baer, 2003). All variables included are described in Table 1.

Table S5

Variable Coefficient Summary for 10-fold Cross-validation of MBCT Elastic Net Models

Variable Name	Variable	# times selected	*M*	*SD*	min	max

SCSb_compassionothers_pre	SCS Compassion for others	10	0.17	0.12	0.05	0.36
Age	Age	7	-0.11	0.11	-0.30	0
DPES_contentment_pre	DPES Contentment	6	-0.06	0.08	-0.22	0
BLSCIDAgeOnset	Age of depression onset	5	-0.01	0.02	-0.05	0
CERTS_posrumin_pre	CERTS Positive Rumination	5	-0.04	0.05	-0.14	0
Suicide	Suicide	5	0.05	0.08	0	0.20
Comorbidities	Number of comorbid diagnoses	4	0.04	0.05	0	0.16
FFMQ_describe_pre	FFMQ Describe	4	0.06	0.08	0	0.17
SCS_humanity_pre	SCS Common Humanity	4	-0.05	0.07	-0.19	0
BLRelationships_TOTAL	Relationship Satisfaction (RS)	3	-0.01	0.01	-0.04	0
HAMD_BL	HAMD	3	0.02	0.05	0	0.13
SCS_isolation_pre	SCS Isolation	3	0.03	0.04	0	0.12
CERQ_planning_pre	CERQ Refocus on Planning	2	0.02	0.03	0	0.08
CERTS_constructive_pre	CERTS Constructive Rumination	2	-0.02	0.04	-0.10	0
Chronic	Chronicity	2	-0.02	0.04	-0.13	0

CERQ_acceptance_pre	CERQ Acceptance	1	0.004	0.01	0	0.04
DPES_joy_pre	DPES Joy	1	-0.002	0.01	-0.02	0
PrefCog	Preference for Cognitive Therapy	1	0.003	0.01	0	0.03
Relationship	Relationship	1	-0.01	0.02	-0.07	0
SCS_mindfulness_pre	SCS Mindfulness	1	-0.004	0.01	-0.04	0
AbuseHL	Level of Parenting Abuse (MOPS)	0	-	-	-	-
BDI_TotalB	BDI-II	0	-	-	-	-
BLGSS_TOTAL	Self-Efficacy (GSE)	0	-	-	-	-
BLSN_TOTAL	Perceived Stigmatisation (SN)	0	-	-	-	-
BLWS_TOTAL	Recognizing Warning Signs (WS)	0	-	-	-	-
CERQ_catastroph_pre	CERQ Catastrophizing	0	-	-	-	-
CERQ_otherblame_pre	CERQ Other-blame	0	-	-	-	-
CERQ_perspective_pre	CERQ Putting into Perspective	0	-	-	-	-
CERQ_reapprais_pre	CERQ Positive Reappraisal	0	-	-	-	-
CERQ_refocus_pre	CERQ Positive Refocusing	0	-	-	-	-

CERQ_rumination_pre	CERQ Rumination	0	-	-	-	-
CERQ_selfblame_pre	CERQ Self-blame	0	-	-	-	-
CERTS_moveon_pre	CERTS Moving on	0	-	-	-	-
CERTS_negrumin_pre	CERTS Negative Rumination	0	-	-	-	-
CERTS_unresolution_pre	CERTS Unresolution	0	-	-	-	-
DPES_awe_pre	DPES Awe	0	-	-	-	-
DPES_compassion_pre	DPES Compassion	0	-	-	-	-
DPES_love_pre	DPES Love	0	-	-	-	-
DPESb_curiosity_pre	DPES Curiosity	0	-	-	-	-
Education	Education	0	-	-	-	-
Employed	Employed	0	-	-	-	-
Fam_hist	Family history of depression	0	-	-	-	-
FFMQ_actaware_pre	FFMQ Aware	0	-	-	-	-
FFMQ_nonjudge_pre	FFMQ Non-Judging	0	-	-	-	-
FFMQ_nonreact_pre	FFMQ Non-Reactivity	0	-	-	-	-

FFMQ_observe_pre	FFMQ Observe	0	-	-	-	-
Gender	Gender	0	-	-	-	-
PrefADM	Preference for Antidepressant Medication	0	-	-	-	-
PrefWhich	Preference for Therapy Type	0	-	-	-	-
Prior_TX	Previous psychological treatment	0	-	-	-	-
SCS_overident_pre	SCS Over-Identification	0	-	-	-	-
SCS_selfjudge_pre	SCS Self-Judgement	0	-	-	-	-
SCS_selfkindness_pre	SCS Self-Kindness	0	-	-	-	-

Note. Table S5 reports model variable regression coefficient summaries for the MBCT (S5) prognostic model across the 10-fold cross-validation. # times selected = Number of times (out of 10) the variable was retained by elastic net regression across the 10-fold cross-validation procedure; Min, Max = minimum, and maximum for variable's coefficient value (includes zeros for when variable was not retained); MOPS = Measure of Parenting Style (Parker et al., 1997); GSE = General Self-Efficacy Scale (Schwarzer et al., 1995); CERQ = Cognitive Emotion Regulation Questionnaire (Garnefski et al., 2001); DPES = Dispositional Positive Emotions Scale (Shiota et al., 2006); CERTS = Cambridge-Exeter Repetitive Thought Scale (Barnard et al., 2007); SCS = Self-Compassion Scale (Neff, 2003); GRID-HAMD = GRID Hamilton Depression

Rating Scale (Williams et al., 2008); BDI-II = Beck Depression Inventory Version II (Beck et al., 1996); FFMQ = Five Facet Mindfulness Questionnaire (Baer, 2003). All variables included are described in Table 1.

SM5 - R Packages

Citations and version information for the software used in data pre-processing, imputation, analyses and visualization are provided below:

- All analyses were performed in **R version 3.5.1**.

R Core Team. (2013). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. http://www.R-project.org

Packages [version #]

- missForest [1.4]

Stekhoven, D.J. and Buehlmann, P. (2012), *MissForest - nonparametric missing value imputation for mixed-type data*. Bioinformatics, 28(1) 2012, 112-118, doi: 10.1093/bioinformatics/btr597

- glmnet [2.0-16]

Friedman, J., Hastie, T. and Tibshirani, R. (2008) *Regularization Paths for Generalized Linear Models via Coordinate Descent*. Journal of Statistical Software, Vol. 33(1), 1-22 Feb 2010. https://web.stanford.edu/~hastie/Papers/glmnet.pdf and http://www.jstatsoft.org/v33/i01/

- caret [6.0-80]

Kuhn, M. (2008). *Building Predictive Models in R Using the caret Package*. Journal of Statistical Software, 28(5). https://doi.org/10.18637/jss.v028.i05

- pROC [1.13.0]

Xavier Robin, Natacha Turck, Alexandre Hainard, *et al.* (2011) *pROC: an open-source package for R and S+ to analyze and compare ROC curves*. BMC Bioinformatics, **7**, 77. DOI: 10.1186/1471-2105-12-77.

- ggplot2 [3.3.0]

Wickham H (2016). *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York. ISBN 978-3-319-24277-4, https://ggplot2.tidyverse.org.

- rms [5.1-4]

Harrell, F. E. (2020). *rms: R functions for biostatistical/epidemiologic modeling, testing, estimation, validation, graphics, prediction, and typesetting by storing enhanced model design attributes in the fit*. https://hbiostat.org/R/rms

- survival [3.1-11]

Therneau, T., Grambsch, P., *Modeling Survival Data: Extending the Cox Model*. Springer-Verlag, 2000. https://github.com/therneau/survival

- survminer [0.4.3]

A Kassambara, M Kosinski, & P Biecek. (2017). *survminer: Drawing Survival Curves using'ggplot2'*. https://rpkgs.datanovia.com/survminer/index.html

- RcmdrPlugin.survival [2.5-1]

John Fox, Marilia Sa Carvalho (2012). *The RcmdrPlugin.survival Package: Extending the R Commander Interface to Survival Analysis*. Journal of Statistical Software, 49(7), 1-32.

SM6 - Discussion of Model Components

Several clinical factors were consistently retained in the ADM prognostic models, including as chronicity of depression and history of an abusive childhood, and to a lesser extent disorder comorbidity, history of suicide attempts, and age of depression onset. A number of psychological prediction factors were also consistently retained, and while these psychological factors were initially included in the PREVENT trial as putative predictors of MBCT outcomes, it is useful to consider their role in predicting ADM response. We note, however, that such discussion must always be accompanied by suitable caution concerning interpreting the role of any given *individual* predictor within a multivariable model.

The variable selection-derived finding that history of an abusive childhood was associated with increased risk of relapse in ADM is in line with the original analyses (Kuyken et al., 2015) and previous findings (Williams et al., 2014), which suggests that MBCT may more directly target consequences of high levels of child abuse (e.g., rumination) than ADM (Earley et al., 2014; Kimbrough et al., 2010).

Interestingly greater chronicity of individuals' depression (indexed by the most recent depressive episode lasting for 24 months or more) was associated with lower rates of relapse on ADM. Considering that individuals needed to have remitted on ADM to be included in the PREVENT trial, individuals with a more chronic presentation may have remitted once ADM type and dosage were optimized. Titration of optimal medication dosage and type can be a lengthy process. However, this is purely speculative and

arguably applies just as much individuals whose most recent episode was not classified as chronic.

Higher levels of positive emotions on three of the Dispositional Positive Emotions Scale's subscales (Contentment, Joy, and Love) were associated with lower risk of relapse in ADM. The capacity to experience these positive emotions may be associated with a normalization of abnormal neural responses to positive stimuli in the reward circuitry (Fischer et al., 2021) as well as in the brain circuitry involved in affective processing more generally (Ma, 2015) following ADM treatment.

Elevated scores on the Negative Rumination and Unresolution subscales of the Cambridge-Exeter Repetitive Thought Scale were associated with elevated risk of relapse in 9 of the 10 ADM models. MBCT is known to reduce ruminative thinking (Hölzel et al., 2011; Segal et al., 2013; van der Velden et al., 2015) (though high baseline rumination has been associated with higher dropout from MBCT (Crane & Williams, 2010; Williams et al., 2014)) and post intervention levels of depressive rumination are associated with subsequent relapse (Hölzel et al., 2011; Michalak et al., 2011). Ineffective ruminative thinking (i.e., high on Unresolution) may be insufficiently addressed by pharmacological relapse prevention but instead benefit from the rumination reducing effects of MBCT.

Higher scores on the CERQ-acceptance subscale were associated with greater risk of relapse in 8 of the 10 ADM models, which fits with the psychometric explorations of the CERQ-acceptance subscale in populations with depressive symptoms (Lei et al., 2014; McKinnon et al., 2020). That is, the CERQ-acceptance subscale has been proposed to capture a construct akin to hopelessness in those experiencing recurrent depressive episodes (McKinnon et al., 2020). Although this may appear counter intuitive based on the subscale's name, it has been argued that the subscale (including items such as "cannot change anything about it" and "learn to live with it"), taps into ideas of hopelessness

(Abela, 2001) and arguably learned helplessness (Maier & Seligman, 2016) in depression, rather than content acceptance of the self (McKinnon et al., 2020; Öst, 2014). MBCT is specifically designed to foster acceptance but from a neutral rather than pessimistic perspective and may therefore be particularly benefit individuals with high levels of depressogenic acceptance at baseline.

A higher number of comorbid diagnoses was associated with greater risk of relapse in 8 of 10 ADM models. The finding may be accounted for by the transdiagnostic properties of MBCT. Mindfulness-based interventions have been proposed to target general neurocognitive and affective processes that are shared across disorders (Greeson et al., 2014), such as cognitive flexibility (Shapero et al., 2018; Zou et al., 2020), emotion regulation (Desrosiers et al., 2013; Roemer et al., 2015) and distress tolerance (Brake et al., 2016). In support of its transdiagnostic reach, MBCT has been shown to lead to significant and sustained improvement in mental health problems across a wide range of disorders (Geurts et al., 2021). Consequently individuals who reported higher levels of comorbidity in the PREVENT trial then may have benefited more from being randomized to MBCT versus ADM compared to those with no or fewer comorbid disorders.

Higher scores on the Awareness subscale of the FFMQ at baseline were associated with reduced risk of relapse in 8 of 10 ADM models. Fostering awareness of ones thoughts and feelings is central to mindfulness practice. Individuals who already demonstrated high levels of awareness at baseline may therefore benefit relatively less from mindfulness-based interventions.

A history of attempted suicide was associated with greater risk of relapse in 8 of 10 ADM models. This finding may be accounted for by the benefits that mindfulness-based interventions confer on suicidal ideation and behavior (Forkmann et al., 2014; Williams et al., 2006). Improved distress regulation and reduction of worry have been

proposed as mechanisms through which mindfulness reduces suicidal ideation (Chesin et al., 2016; Forkmann et al., 2014). Moreover, meta-analytic evidence shows that compared to psychological interventions, antidepressant treatment of depression is less effective in reducing suicidal ideation (Boschloo et al., 2019). Together these findings suggest that individuals were at an increased risk of relapse in the ADM condition because MBCT maybe relatively more effective at targeting suicidal ideation compared to ADM.

Higher self-efficacy was associated with reduced risk of relapse in 7 of 10 ADM models. Previous work has shown self-efficacy to be a reliable indicator of individuals' intention to continue ADM treatment. Greater self-efficacy then may have been particularly advantageous in the PREVENT ADM group given the trial's relatively long-term continuation period. Finally, earlier age of depression onset was associated with increased risk of relapse in 6 of 10 ADM models. While the literature on the effectiveness of ADM across age of onset is mixed, the current finding suggests that MBCT may be more effective in targeting more entrenched depression.

SM7 – Table S7. ADM Model from Full ADM Analysis Sample

Variable	Final Model Beta
Intercept	–0.10
Level of Parenting Abuse (MOPS)	0.46
Chronicity	–0.49
DPES Contentment	–0.11
DPES Joy	–0.10
DPES Love	–0.08
CERTS Negative Rumination	0.07
CERTS Unresolution	0.11
CERQ Acceptance	0.10
Number of comorbid diagnoses	0.06
FFMQ Aware	–0.06
Suicide	0.21
Self-Efficacy (GSE)	–0.05
Age of depression onset	–0.05
Age	–0.02

Note. Table S7 reports model variable regression coefficient summaries for an ADM prognostic model constructed via elastic net regression using the full ADM analysis sample (N=195). MOPS = Measure of Parenting Style (Parker et al., 1997); DPES = Dispositional Positive Emotions Scale (Shiota et al., 2006); CERTS = Cambridge-Exeter Repetitive Thought Scale (Barnard et al., 2007); CERQ = Cognitive Emotion Regulation Questionnaire (Garnefski et al., 2001); FFMQ = Five Facet Mindfulness Questionnaire (Baer, 2003); GSE = General Self-Efficacy Scale (Schwarzer et al., 1995). Note, this

model was not used in any analyses for this study, but could be subjected to external validation in future efforts.

Supplementary references

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Baer, R. A. (2003). Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clinical Psychology: Science and Practice*, *10*(2), 125–143.

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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	4
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	7
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	8
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	8
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	6
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	20
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Table 1
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	D;V	Explain how the study size was arrived at.	8, Figure S1
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	16
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	16, Figure 1
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	17-20, 23, Figure 1
	10c	V	For validation, describe how the predictions were calculated.	
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	24-25
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	25
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Figure S1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Tables S1 & S2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	throughout
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table S7
	15b	D	Explain how to the use the prediction model.	
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	25-26, 28-29
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	32-34
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	31-34
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	34-35
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	8
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	2-3

TRIPOD Checklist: Prediction Model Development and Validation

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.