Prediction of Recurrence in Recurrent Depression: A 5.5-Year Prospective Study

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Objective: Depression is a disease with high recurrence rates. Identifying predictors of recurrence and their relative importance in patients with recurrent depression is important for a better understanding of the course of this disease. This type of knowledge can be used to optimize and tailor preventive strategies of recurrence. In this study, we examined predictors of recurrence over a 5.5-year follow-up period and quantified to which extent these predictors explained observed variation in recurrence.

Method: Data from 172 remitted recurrently depressed patients over a 5.5-year follow-up period were used. Recurrence was assessed with the Structured Clinical Interview for *DSM-IV*. Illness-, stress-, and coping-related factors were examined as predictors of recurrence. Multiple Cox regression analysis was used, and explained variation was assessed to quantify the relative importance of the predictors. Patients were recruited between February 2000 and September 2000.

Results: Number of previous episodes and residual symptoms explained each 15% of the variation in recurrence, indicating a medium effect size. The final multivariate prediction model included: a higher number of previous episodes, more residual symptoms, and lower levels of positive refocusing (explained variation 29%, indicating a strong effect size).

Conclusion: In our multivariate prediction model, the number of previous episodes, residual symptoms, and a specific coping style were predictors of recurrence over a 5.5-year follow-up period in remitted recurrently depressed patients. Preventive therapies should focus on these factors. Although a substantial part of variation in recurrence (29%) was explained by these predictors, most of it remains unexplained. Consequently, recurrence remains a difficult to predict and only partially understood phenomenon.

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Major depressive disorder is a disease with a high recurrence rate. Identifying predictors for recurrence in patients with recurrent depression is important for a better understanding of the course of this disease. This type of knowledge might contribute to optimizing and tailoring of specific prevention strategies for recurrence. To improve the clinical relevance of predictors of recurrence, it is not only relevant to know which variables do predict recurrence but also to quantify their relative importance in terms of explained variation. We followed 172 recurrently depressed patients within a clinical trial comparing treatment as usual (TAU) with preventive cognitive therapy (CT).[1,2] Just like mindfulness-based CT and well-being therapy, this type of CT can prevent recurrence in recurrent depression, especially in patients with a high number of previous episodes.[1–11]

Previously, we reported predictors of time to recurrence over a 2-year follow-up period.[12] In this article, we will extend the follow-up period to 5.5 years. For the 2-year follow-up period, we found that a higher number of previous episodes, a higher level of residual depressive symptoms, and more daily hassles predicted recurrence.[12] We also found that factors related to coping style could predict recurrence, ie, a higher level of dysfunctional attitudes, an avoidant way of dealing with problems, as well as a lower level of coping by refocusing on positive matters, such as thinking of other, pleasant matters instead of the actual event. Of note, the effect of the latter 2 predictors was modified by the number of previous episodes, resulting in a diminishing influence as the number of previous episodes increased. Furthermore, we found little impact of socio-demographic variables on time to recurrence.[1]

As far as we know, there are no studies that reported predictors of recurrence and a multivariate prediction model in combination with a quantification of their relative importance in terms of explained variations for time to recurrence in remitted patients suffering from recurrent depression. In the current study, we therefore examined 172 patients with recurrent depression, who were in remission at study entry, over a 5.5-year follow-up period, using structured interviews[13] based on *DSM-IV*. The study had 4 aims: (1) to determine predictors of time to recurrence over a 5.5-year follow-up period, (2) to quantify the explained variation of these predictors, (3) to find the most parsimonious set of predictors of time to recurrence (with a Cox regression model) during this 5.5-year follow-up period, and (4) to quantify the explained variation of the multivariate model.

For Clinical Use

- Depression is a disease with high recurrence rates.
- It is important for a better understanding of the course of depression to identify predictors of recurrence.
- A high number of previous episodes, more residual symptoms, and lower levels of the capability to refocus positively have been found to be predictors for recurrence.
- Preventive therapies for recurrence should focus on modifiable coping strategies and residual symptoms.

METHOD

Participants

Patients were recruited between February 2000 and September 2000. All respondents participated in a clinical trial of patients with recurrent depression, in remission at the start of the study, in which the effect of TAU on recurrence was compared to TAU with additional preventive CT.[1] To be eligible, subjects had to meet the following criteria: (1) at least 2 separate major depressive episodes in the last 5 years, as defined according to *DSM-IV*[14] and assessed by the Structured Clinical Interview for *DSM-IV* (SCID-I)[13] by trained evaluators; (2) current remission status, according to *DSM-IV* criteria, for longer than 10 weeks and no longer than 2 years ago; and (3) a Hamilton Depression Rating Scale (HDRS)[11,15] score of < 10. For this study, the exclusion criteria were current mania or hypomania or a history of bipolar illness, any psychotic disorder (current and previous), organic brain damage, alcohol or drug misuse, predominant anxiety disorder, recent electroconvulsive therapy, recent CT or receiving CT at the start of the study, and/or current psychotherapy with a frequency of more than 2 times a month. There was no restriction in using pharmacotherapy. Participants were recruited at psychiatric centers and through media announcement. They completed telephonic screening (n > 1000) and diagnostic interviews (n = 321) and provided informed consent to enter the study (n = 187). The research protocol was approved by the institutional ethics review committees.

Procedure

Participants were screened on inclusion and exclusion criteria via the telephone version of the SCID-I. The κ value for interrater agreement between the interviewers (psychologist/research assistants), based on audiotaped interviews, for inclusion or exclusion, was 0.77, which is indicative of good/excellent agreement.

Participants meeting the inclusion criteria were randomly allocated to (1) TAU, which involved "naturalistic" care, ie, standard care (including no treatment at all) as typically provided by the referring agencies, with no restriction on the use of pharmacotherapy during the period from entry through follow-up; or (2) TAU + 8 weekly 2-hour sessions of group CT.

Randomization was performed using random permuted blocks and was stratified by study location and type of aftercare (ie, family doctor, mental health center, no aftercare). Consecutively numbered, sealed envelopes contained computer-generated cards with concealed assignment codes. This procedure was organized and administered by an independent research associate.

Study Measures

Primary outcome measure. Recurrence was assessed with the SCID-I.[13] Using this instrument, current and past depressive episodes were assessed at baseline and at 5 follow-up measurements at 3, 12, 24, 36, and 66 months after baseline. Cox regression analyses revealed no confounding effect of the duration of the last episode before remission on the relation between predictors and time to recurrence. Although, conceptually, one might distinguish between a recurrence (the appearance of a new episode of major depressive disorder, which can, by definition, only occur in a period of recovery, ie, a remission period > 6 months) or a relapse (defined as the early return of depressive symptoms following an apparent remission within 4–6 months), this distinction is still arbitrary. For that reason, we do not make a distinction between relapse and recurrence and, to improve readability, refer to both as recurrence.

To maintain the blindness of assessors to treatment condition, we instructed participants not to reveal their treatment condition to the interviewers (psychologist/research assistants). All interviews were audiotaped. Two independent experienced psychiatrists who were blind to treatment condition evaluated the participants meeting the *DSM-IV* criteria for major depression. In case of disagreement, the ratings of the psychiatrists were used for further analyses. The κ values for interrater agreement between the interviewers and psychiatrist on categorization of a recurrence versus no recurrence over the follow-up period ranged from .94 to .96, indicating high agreement.

Predictor Variables

The following potential predictor variables were assessed at baseline, ie, at entry of the study: demographic characteristics (sex, marital status, age, education level), historical illness-related characteristics (age at onset, severity of last depression, duration of last episode, duration of remission since last episode, percentage of time illness free since first episode, familial psychiatric disease), antidepressant use at study entry, recent illness-related characteristics (level of residual depressive symptoms), coping, and stress (daily hassles, life events).

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Residual depressive symptoms. Participants' baseline level of depressive symptomatology was assessed with the 17-item HDRS.[15] The HDRS, administered by psychologist/research assistants who were blind to treatment condition, is a widely used semistructured clinical interview that covers a range of affective, behavioral, and biologic symptoms and has acceptable psychometric properties.[16] Scores can range from 0 to 52. Our 4 interviewers (psychologist/research assistants) second rated 17 interviews. The intraclass correlation was 0.94, indicating high agreement. The 21-item self-report Beck Depression Inventory[17] was used to assess baseline depression symptomatology in the past week. Beck Depression Inventory scores can range from 0 to 63. The 90-item Symptom Checklist (SCL-90)[18] was used to assess the total baseline level of psychopathology in the past week. In this study, the total score (the sum-score of all 90 items) is reported.

Coping. We examined behavioral and cognitive coping. Information on behavioral coping with problems was obtained at baseline by using 2 subscales of the Utrecht Coping List[19]; ie, avoidant coping (8 items), characterized by an avoidant way of dealing with problems, and active approach of problems (7 items). Participants were asked how they reacted in general to the mentioned items (eg, avoid difficult situations). The Utrecht Coping List has good psychometric properties.[20]

Information on cognitive coping was obtained with the self report Cognitive Emotion Regulation Questionnaire,[21] containing 36 items with 9 subscales such as rumination, self-blame, and refocus on other positive matters. Participants were asked how they think in general when confronted with stressful events (eg, I think about how I can change the situation). The subscale, positive refocusing, refers to thinking of other, pleasant matters instead of the actual event (eg, I think of nicer things than what I have experienced).

Dysfunctional attitudes. These were assessed at baseline with the Dutch adaptation of the Dysfunctional Attitude Scale (DAS).[22] The DAS is a 40-item scale that assesses excessive and rigid beliefs, hypothesized by Beck[23] to be vulnerability factors for depression. Participants rate their agreement with each belief on a 7-point scale ranging from "totally agree" to "totally disagree." Scores range from 40 to 280, with higher scores indicating greater levels of dysfunctional attitudes. Form A of the DAS was used, which has been shown to have good psychometric properties.[24]

Stress. Daily hassles were assessed at baseline with the 114-item Everyday Problem Checklist (EPCL).[25] The items of the EPCL refer to stressors of daily living, particularly those in the domains of work, parenthood, relationship, and household activities. The EPCL assesses the frequency of daily hassles over the past 2 months and has good psychometric properties.[25]

The experience of negative life events was measured at baseline with a 15-item checklist that covered adulthood (from the age of 16 to the start of the study). This checklist is based on the Negative Life Events Questionnaire.[26] Events can involve the participant or significant others. In previous studies,[26–28] the predictive validity of the Negative Life Events Questionnaire proved to be good, as the number of negative life events predicted severity of depressive symptoms.

Statistical Analysis

The effect on recurrence for all predictors mentioned was assessed with Cox regression. Here we took into account the fact that half of our sample received CT. The effect of this intervention depended upon the number of previous depressive episodes.[1,2] We did this by assessing for each predictor whether the intervention moderated the relation between the predictor and recurrence (ie, whether the effect of the predictor on recurrence differed between patients that received CT and patients that did not receive CT).

To define the univariate effect of a specific predictor on recurrence, we used a 2-step procedure. In the first step, we tested, by a 3-way predictor by treatment by number of previous episodes interaction term, and a 2-way treatment by number of previous episodes interaction term, for each predictor whether its effect on recurrence was modified by treatment condition and whether the strength or direction of this modification depended upon the number of previous depressive episodes. In the second step, we assessed, by a predictor by number of previous episodes interaction term, whether the effect of a predictor was modified by this number of episodes. Depending upon the results of the first step, these analyses were performed either in the total sample (n = 172) or (in case of a significant interaction with treatment condition) only in the TAU group (n = 84). In both cases, the treatment factor would not be incorporated in the statistical model, in the first case because treatment had no effect on this relation and in the latter case because we restricted ourselves to one treatment condition (the control group).

To account for chance capitalization because of multiple testing, which affects type I error, we used a relative conservative α level of .01 for all main effects tests. However, given the relatively lower power of test for interaction compared to tests for main effects, we used an α level of .06 for all tests for interaction to guard against type II error. Because the distribution of number of previous episodes was skewed and the minimum number of previous episodes was 2, we used the following transformation $PE = \ln(p-1)$, with p the actual number of previous episodes and PE the transformed variable used in the analysis.

Combined effect. To assess the combined effect of predictors on time to recurrence, we used a method proposed by Hosmer and Lemeshow.[29] All variables univariately related to time to recurrence (using a lenient *P* value threshold of < .20) were entered in a multiple Cox regression, using a stepwise procedure with backward elimination with entry and removal criteria set at .01 for the main effects and .05 for the interaction effects. Relative risks (RRs), 95% confidence intervals, and the amount of explained variation (Nagelkerke R^2) were calculated.

Explained variation. The relative importance of the predictor for recurrence is quantified in its explained variation.

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For logistic regression and Cox regression, several explained variation measures are proposed. However, especially for Cox regression, there is still not a single, simple, easy to interpret pseudo R^2 measure available.[29,30] A main problem is the sensitivity of existing measures to censoring. However, in our sample with only 20% censoring, this effect is expected to be small. Hosmer and Lemeshow[29] propose the Cox-Snell R^2 as the easiest and best one to use. However, this measure has a maximum value that is smaller than 1. This problem is corrected by Nagelkerke. For this reason Nagelkerke R^2 will be used in this article as the measure of explained variation. All analyses were performed using SPSS for Windows version 16 (SPSS, Inc, Chicago, Illinois).

RESULTS

Sample Characteristics

The baseline sample comprised 187 participants, of which 15 participants (9 from CT; 6 from TAU) were excluded because they dropped out of the study immediately after randomization. Dropouts (n = 15) were younger than completers (N = 172), $t_{170} = -2.25$, $P = .026$ (mean age = 38.9 years, SD = 10.6 vs mean = 44.7 years, SD = 9.5), but comparable on all other characteristics. Demographic and clinical characteristics of TAU (n = 84) and CT (n = 88) patients are summarized in Table 1. Both groups were comparable on each of the characteristics except that, compared to TAU patients, a larger proportion of CT patients experienced negative life events before their 16th year of age (CT: 84/88 experienced negative life events vs TAU: 70/84; $\chi^2_1 = 6.74$, N = 172, $P = .009$). To examine whether this confounded the relation between the potential predictors and recurrence, the effect parameters in the model with and without negative childhood life events were compared. No confounding effect of childhood life events was found.

Table 1. Baseline Demographic and Clinical Characteristics of Remitted Recurrently Depressed Subjects

Characteristic	Completer Group (N = 172)
Sex, female, %	73
White, %	98
Age, mean ± SD, y	44.7 ± 9.5
Years of education (range, 8–18), mean ± SD	14.2 ± 2.5
Marital status, %	
Single	24
Married/cohabiting	58
Divorced/widowed	18
Type of current treatment, %	
Family doctor	29
Psychiatric help	31
No treatment	40
Antidepressant medication, %	51
HDRS score, mean ± SD	3.8 ± 2.8
Previous episodes	
Median ± IQR	4.0 ± 3.8
> 2 previous episodes, %	82
Age at first onset, mean ± SD, y	28.5 ± 12.5
Coping, mean ± SD	
Dysfunctional attitudes (DAS-A)	124.6 ± 33.5
Avoidant coping strategy (UCL)	17.1 ± 3.9
Refocus on positive matters (CERQ)	8.7 ± 3.3

Abbreviations: CERQ = Cognitive Emotion Regulation Questionnaire, DAS-A = form A of the Dutch adaptation of the Dysfunctional Attitude Scale, HDRS = Hamilton Depression Rating Scale, IQR = interquartile range, UCL = Utrecht Coping List.

Recurrence

In the total sample (N = 172), 135 participants (79%) were diagnosed with at least 1 new depressive episode over the 5.5-year follow-up period.

Predictors of Time to Recurrence

In Table 2, we present the results of the Cox regression analyses for all potential predictors that were related to time to recurrence, using a threshold of $P < .20$. As described in the statistical analysis section, effects that are modified by treatment condition are presented only for the control group. When the predictor by the number of previous episodes interaction is statistically significant, results for the main effect of the number of previous episodes and its interaction with the predictor in question are also presented.

Univariate predictors of recurrence are defined as those potential predictors with a univariate P value < .01 or, in case of effect modification by number of previous depressive episodes, a univariate P value < .06 for the predictor by number of previous episodes interaction term. Univariate predictors are presented in italic. The explained variation by these predictors varies between 3% (duration of last depression) and 15% (number of previous episodes and SCL-90 total score).

To assess whether the explained variation could be improved by a combination of predictors, we entered all potential predictors with a univariate P value < .20 (ie, all variables in Table 2) in a multiple Cox regression model. Backward elimination with $P < .01$ for main effects and $P < .05$ for interaction terms resulted in a model comprising the number of previous episodes, the SCL-90 total score, and coping by refocusing on positive matters as predictors of recurrence. The latter was modified by number of previous episodes (Table 3). Patients with a higher SCL-90 total score at baseline had an increased risk of recurrence.

Table 4 presents RRs for all the univariate predictors and predictors comprising the multivariate prediction model. Predictors with RRs smaller than 1 indicate protective factors, ie, relatively longer time to recurrence; those with RRs exceeding 1 indicate risk predictors, ie, a relatively shorter time to recurrence. In case of effect modification by the number of previous episodes the RR depends on this number. To visualize this interaction effect, the RRs for patients with respectively 2 and 8 previous episodes are presented.

The number of previous episodes, daily hassles, residual symptoms (as measured by the HDRS, Beck Depression Inventory, and SCL-90), and DAS score are all positively related to recurrence risk. The effect on recurrence of avoidant coping, duration of last depressive episode, refocusing on positive matters, and marital status depends on the number of previous episodes. In general, an increase in the number of previous episodes from 2 to 8 diminishes the effect of these predictors (the RR gets closer to 1). The effect of duration of

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Table 2. Predictors of Time to Recurrence Over 5.5 Years (N = 172)[a]

Predictor[b]	β	SE(β)	*P*	Explained Variation[c]	Multiple Regression Model
Residual depressive symptomatology (HDRS)	0.096	0.029	.001	0.06	…
Residual depressive symptomatology (BDI)	0.507	0.141	.000	0.08	…
Residual symptoms (SCL-90)[d]	1.805	0.322	.000	0.15	+
Duration of last depression[d]	0.526	0.362	.146	0.03	…
No. of episodes	0.513	0.174	.003		
Predictor × episodes	−0.448	0.207	.030		
No. of previous episodes[d,e]	0.525	0.137	.000	0.15	+
Age at onset[e]	−0.022	0.010	.031	0.06	…
Avoidant coping (UCL)[d,e]	0.163	0.055	.003	0.10	…
No. of episodes	0.596	0.153	.000		
Predictor × episodes	−0.070	0.030	.021		
Positive refocusing (CERQ)[d]	−0.140	0.046	.003	0.06	+
No. of episodes	0.166	0.094	.078		
Predictor × episodes	0.058	0.030	.055		
Acceptance (CERQ)	−0.034	0.024	.153	0.01	…
Self blame (CERQ)[e]	0.154	0.064	.016	0.07	…
No. of episodes	0.550	0.149	< .001		
Predictor × episodes	−0.084	0.041	.039		
Rumination (CERQ)	0.062	0.026	.016	0.03	…
Catastrophizing (CERQ)[e]	0.080	0.042	.056	0.05	…
Other blame (CERQ)	0.044	0.030	.139	0.01	…
Dysfunctional attitudes (DAS-A)[d]	0.009	0.002	.000	0.07	…
Daily hassles (EPCL)[e]	0.514	0.185	.005	0.09	…
Marital status (single/widowed/divorced vs married/cohabitating)[d]	1.103	0.296	.000	0.09	…
No. of episodes	0.365	0.122	.003		
Predictor × episodes	−0.417	0.197	.035		
Age	−0.017	−0.010	.081	0.02	…
Education[e]	−0.455	0.249	.068	0.04	…

[a]Cox regression analysis; reference values for predictors are: duration of last episode = 0 (ie, ≤ 2 months); number of previous episodes (transformed as PE = ln[ndeps − 1], where ndeps equals the raw number) = 0 (ie, 2 previous episodes); ln(EPCL score) = 0 (ie, EPCL score = 1); marital status = 0 (married/cohabitating); HDRS = 0 (ie, HDRS score = 0); ln(BDI + 1) = 0 (ie, BDI score = 0); and ln(SCL-90) = 0 (ie, SCL-90 = 1), education (low). Other continuous variables were centered around their mean, ie, the mean score is subtracted from the raw scores: avoidant coping (raw score − 16), positive refocusing (raw score − 8), and DAS-A (raw score − 119). Only predictors with a univariate *P* value < .20 are presented. Predictors that did not fulfill this criterion were severity of last depression, duration of remission of last episode, percentage of time illness-free since first episode, other types of emotional coping, familial psychiatric disease, and life events between 16th year and the start of the study.
[b]Univariate predictors are presented in italics.
[c]Nagelkerke R^2.
[d]Significant predictor by number of previous episodes interaction.
[e]Results pertain to control group data only (n = 84), because of a significant modification by treatment interaction.
Abbreviations: BDI = Beck Depression Inventory, CERQ = Cognitive Emotion Regulation Questionnaire, DAS-A = form A of the Dutch adaptation of the Dysfunctional Attitude Scale, EPCL = Everyday Problem Checklist, HDRS = Hamilton Depression Rating Scale, ln = natural logarithm, PE = number of previous episodes, SCL-90 = Symptom Checklist-90, SE(β) = standard error of the β estimate, UCL = Utrecht Coping List.
Symbols: … = variable did not reach the inclusion threshold in the stepwise procedure (a univariate *P* value < .20) and consequently was not incorporated in the stepwise model, + = predictor is part of the multivariate prediction model.

Table 3. Results of Multiple Cox Regression Analysis (n = 84)[a]

Predictor	RR	*P*	95% CI for Exp(B)
Positive refocusing (CERQ)[b]	0.890	.086	0.779–1.017
No. of previous episodes[c]	1.528	.006	1.130–2.065
Residual symptoms (SCL-90)[d]	3.609	.008	1.402–9.293
No. of previous episodes[c] × positive refocusing[b]	1.117	.021	1.017–1.226

[a]Cox regression analysis, reference values for predictors are: number of previous episodes (transformed as PE = ln[ndeps − 1], ie, number of previous episodes = 1, ln(SCL-90) = 0, ie, SCL-90 = 1.
[b]Centered around mean (8).
[c]ln(raw score − 1).
[d]ln(raw score).
Abbreviations: CERQ = Cognitive Emotion Regulation Questionnaire, CI = confidence interval, exp = exponent, ln = natural logarithm, PE = number of previous episodes, RR = relative risk, SCL-90 = Symptom Checklist-90.

the last depressive episode, however, changes its direction within this range of previous episodes. For patients with 2 previous episodes, a longer duration of the last episode increases the probability for recurrence. In patients with 8 previous episodes, a longer duration of the last episode decreases the probability for recurrence.

DISCUSSION

This is the first prospective study that both univariately and multivariately examined predictors of time to recurrence over 5.5 years, as well as their explained variations for time to recurrence in a large and well defined cohort of remitted patients with recurrent depression. In summary, we found that earlier time to recurrence was univariately predicted by a higher number of previous episodes before the start of the study, more residual depressive symptoms, and a higher level of dysfunctional attitudes at the start of the study, and more daily hassles. The percentage of explained variation by these predictors varied between 6% (baseline residual depressive symptoms: HDRS score) and 15% (baseline level of psychopathology: SCL-90 total score).

In addition, we identified several predictors with an effect on recurrence that was modified by the number of previous depressive episodes. A longer duration of the last depressive episode before the start of the study mainly predicted a shorter time to recurrence in patients with a relatively low number of previous depressive episodes. This effect diminished with an increasing number of previous episodes. Furthermore, a higher level of dealing with problems in an avoidant way; a lower level of coping by refocusing on positive matters; and being single, widowed, or divorced mainly predicted a shorter time to recurrence.

The most parsimonious multivariate model (stepwise multiple Cox regression analyses with backward elimination) comprised the following predictors—a higher number of previous episodes, a higher level of residual symptoms, and a lower level of coping by refocusing on positive matters—and one interaction term (number of previous episodes × positive refocusing), accounting for 29% of the variation in time to recurrence.

The predictors we found in univariate analyses were the same as those identified over a 2-year follow-up period.[12] These

Table 4. Univariate Predictors for Time to Recurrence Over 5.5 Years[a]

Predictor	RR	SE	90% CI[b]	Previous Episodes
Avoidant coping (UCL)[c,d,e]	1.177	0.0550	1.076–1.288	2
	1.027	0.0349	0.970–1.088	8
Duration last depressive episode[f,g]	1.692	0.3620	0.9346–3.064	2
	0.708	0.2198	0.4935–1.015	8
Positive refocusing (CERQ)[c,d,g]	0.869	0.0460	0.8062–0.9375	2
	0.973	0.0353	0.9184–1.031	8
No. of previous episodes[e,h]	1.690	0.1370	1.350–2.116	…
Daily hassles (EPCL)[e,i]	1.672	0.1850	1.234–2.265	…
Marital status[g,j]	3.013	0.2960	1.854–4.896	2
	1.339	0.2370	0.9168–1.954	8
Residual depressive symptomatology (HDRS)[c]	1.101	0.0290	1.022–1.186 (99% CI)	…
Residual depressive symptomatology (BDI)[c,i]	1.660	0.1410	1.156–2.385 (99% CI)	…
Residual symptoms (SCL-90)[c]	6.080	0.3220	2.658–13.91 (99% CI)	…
Dysfunctional attitudes (DAS)[c,d]	1.009	0.0020	1.004–1.014 (99% CI)	…

[a]Cox regression analysis.
[b]90% Confidence intervals (CIs) are reported, unless otherwise specified (99%). Limits of the 90% CI for RR are given by $e^{\beta predictor \pm 1.645 \times SE[(ln(RR)|PE])}$. Limits for the 99% CI for RR are given by $e^{\beta predictor \pm 2.567 \times SE[(ln(RR)|PE])}$.
[c]Continuous scores.
[d]Centered around mean; UCL avoidant(17), CERQ(8), DAS(119).
[e]Only control group data (n = 84) used because of a significant modification by treatment interaction.
[f]Categorized: 2 months or less versus 3 (ref category) versus 3 months or more.
[g]Values are given for 2 and 8 episodes. Formulas used to assess CI for specific number of episodes (eg, PE) are: $(SE[(ln(RR)|PE]) = \sqrt{[((SE(\beta_{predictor})]^2 + [(SE(\beta_{interaction})]^2 \times PE^2 + 2COV(\beta_{predictor}\beta_{(interaction)} \times PE)]$. 90% $CI_{ln(RR|PE)} = e^{\beta predictor \pm 1.64 \times SE[(ln(RR)|PE])}$, with PE = ln (number of depressive episodes – 1). βs can be found in Table 2.
[h]ln(raw score – 1).
[i]ln(raw score + 1).
[j]Dichotomized: single/widowed/divorced versus married/cohabitation.
Abbreviations: BDI = Beck Depression Inventory, CERQ = Cognitive Emotion Regulation Questionnaire, DAS = Dysfunctional Attitude Scale, EPCL = Everyday Problem Checklist, exp = exponent, HDRS = Hamilton Depression Rating Scale, ln = natural logarithm, PE = number of previous episodes, RR = relative risk, SCL-90 = Symptom Checklist-90, UCL = Utrecht Coping List.
Symbol: … = not modified by number of previous episodes.

variables continued to be predictors over 5.5 years in this recurrent depressive sample. As reported in our 2-year analyses, we again found little impact of other illness-related features, except for the number of previous episodes. The predictors in our multivariate model are in accordance with findings in several previous studies (for a review, see Burcusa and Iacono[31]). Residual depressive symptoms and the number of previous episodes were predictors of recurrence in several former studies.[12,32–36]

Coping-related factors have also been associated with depressive symptoms and recurrence in several studies.[32,37–41] Other aspects of coping are the beliefs of patients or dysfunctional attitudes. Teasdale and colleagues[42] studied the extremity of the attitudes by focusing on the frequency of extreme response categories on the DAS-approval subscale. They found that the frequency of extreme response categories of this subscale was correlated positively with negative therapy outcome. In a more recent study, Petersen[43] examined whether the extent of change in extreme responses differed significantly between patients who received cognitive-behavioral therapy in combination with antidepressants versus patients who solely received antidepressants during the continuation treatment phase. Petersen found that patients in the medication only group showed a significant increase in the number of extreme responses on the DAS-approval subscale over the course of the continuation phase versus no significant increase in patients receiving cognitive-behavioral therapy in addition to medication in this period. These findings indicate that not only focusing on this type of coping, ie, dysfunctional attitudes, is important, but attention should also be paid to the way people process depression related material.[42] Yet, the specific coping style "refocusing on positive matters" has not been described as a predictor of recurrence before.

To understand our finding that a lower level of coping by refocusing on positive matters predicted recurrence, we might utilize a theory on the working mechanism of CT. In short, in this theory, as stated by Brewin,[44] CT does not directly modify negative information in the patient's memory but assumingly targets on creating more positive competitor representations to win the retrieval competition. Analogous to this, we hypothesize that the coping style "refocusing on positive matters" creates more positive competitor representations, which can prevent recurrence of depression. Furthermore, effective preventive psychological interventions with cognitive elements, such as preventive CT, mindfulness-based CT, and well-being-therapy, might all share the promotion of more helpful coping strategies.[1,3–9] The focus on coping strategies (eg, endure refocusing on positive matters and diminish avoidant coping) might be an essential ingredient in psychological preventive strategies.

The strongest univariate predictors we found are the number of previous episodes and residual symptoms, which each explained 15% of variation in recurrence, indicating a "medium" effect in terms of effect sizes.[45] Both are well-known predictors of recurrence, but in terms of clinical relevance they are not too impressive in predicting recurrence. Using a multiple Cox regression model, the predictors explained a substantial part of the variation (29%). This is a "strong" effect in terms of effect sizes[45] and considerably better than the best single predictor. However, from a clinical point of view this is still moderate, even though we examined the most promising predictors of recurrence.

Not included factors, like genetic, neurobiological, and endophenotypic factors play a role in recurrence too. The heritability of major depressive disorder is likely to be in the range of 31%–42% (for a review, see Sullivan et al[46]). Yet, these above mentioned factors were not part of our analyses. Additionally, sample sizes were too small to examine all potential interactions, like the interaction between avoidant

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coping with daily hassles and life events and dysfunctional attitudes, as stated by Holahan et al.[47]

Strengths and Limitations

Our study has some major strengths. It comprises a representative cohort, including exclusively patients with at least 2 previous episodes, and was followed prospectively for 5.5 years with structured interviews based on *DSM-IV*. Furthermore, we included patients with recurrent depression remitted on medication and/or psychological therapy or no treatment at all, without restrictions on medication status at entry to the study. As such, this study was designed to maximize external validity, which suggests good generalizability of the findings. Finally, we calculated explained variations of the predictors of recurrence.

However, some limitations should also be noted. First, the relatively small sample size reduces power to detect weaker associations between recurrence and prediction factors and potential interactions between these factors. Although we used an α level of .05 for interaction with treatment condition (N = 172) to account for a lower power, we cannot completely rule out that CT did not influence the relation between the predictor and recurrence in case of nonsignificant interaction terms with treatment condition.

Furthermore, this study is restricted to patients with 2 or more previous depressive episodes, and comprises almost exclusively white patients. We do not know whether our results can be generalized to patients with less previous episodes and to other ethnic groups. Another limitation concerns the retrospective nature of the information on the number of previous episodes before the start of the study as collected with a structured interview, although major predictors seemed relatively little impaired based on retrospective recall.[48] One more limitation concerns the (well validated) self-report measures, which are subject to social desirability, and therefore further research is needed with interview based stress and coping measures.

Finally, the Cox regression analyses in this article took right censoring into account. However, the inclusion criteria pertaining to the duration of the remission of the last depressive episode before study entry also introduced left truncation. This might have biased the predictor estimates. Yet, since the duration of the left truncation was not related to recurrence ($P = .992$) and the mean hazard scores were comparable for different categories of left truncation duration ($P = .510$), this bias is probably small or not existent. For this reason, we refrained from more complicated statistical analyses and used the standard Cox regression analysis.

CONCLUSION

In our final prediction model, we found that the number of previous episodes, coping style, and residual depressive symptoms were predictive of recurrence in remitted recurrently depressed patients in a 5.5-year follow-up study and that these predictors were rather stable over time. Although the final prediction model explained a substantial part of the variation (29%) in recurrence, most of it remained unexplained. This suggests that prediction of recurrence is a complex and multivariate phenomenon yet not completely understood. In ending, focus on enhancement of coping-related factors and reduction of residual depressive symptoms by specific psychological interventions might be essential in preventing future recurrences of this highly recurrent disease.

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