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RESEARCH ARTICLE

Seeing the signs: Using the course of residual depressive symptomatology to predict patterns of relapse and recurrence of major depressive disorder

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Background: Major depressive disorder (MDD) is characterized by high relapse/recurrence rates. Predicting individual patients' relapse/recurrence risk has proven hard, possibly due to course heterogeneity among patients. This study aimed to (1) identify homogeneous data-driven subgroups with different patterns of relapse/recurrence and (2) identify associated predictors.

Methods: For a year, we collected weekly depressive symptom ratings in 213 primary care MDD patients. Latent class growth analyses (LCGA), based on symptom-severity during the 24 weeks after no longer fulfilling criteria for the initial major depressive episode (MDE), were used to identify groups with different patterns of relapse/recurrence. Associations of baseline predictors with these groups were investigated, as were the groups' associations with 3- and 11-year follow-up depression outcomes.

Results: LCGA showed that heterogeneity in relapse/recurrence after no longer fulfilling criteria for the initial MDE was best described by four classes: "quick symptom decline" (14.0%), "slow symptom decline" (23.3%), "steady residual symptoms" (38.7%), and "high residual symptoms" (24.1%). The latter two classes showed lower self-esteem at baseline, and more recurrences and higher severity at 3-year follow-up than the first two classes. Moreover, the high residual symptom class scored higher on neuroticism and lower on extraversion and self-esteem at baseline. Interestingly, the steady residual symptoms and high residual symptoms classes still showed higher severity of depressive symptoms after 11 years.

Conclusion: Some measures were associated with specific patterns of relapse/recurrence. Moreover, the data-driven relapse/recurrence groups were predictive of long-term outcomes, suggesting that patterns of residual symptoms could be of prognostic value in clinical practice.

KEYWORDS

coping, depression, measurement/psychometrics, mood disorders, primary care, resilience

1 | INTRODUCTION

Major depressive disorder (MDD) is the most common psychiatric disorder in primary care, with an estimated prevalence of 10% (Craven & Roger Bland, 2013; Üstün, 1994). At least 50% of MDD patients will experience more than one major depressive episode (MDE) (Burcusa & Iacono, 2007; Post, 1992), with recurrence going up to 80% in those with at least two episodes (Kupfer, Frank, & Wamhoff, 1996). An estimated 20% can eventually be considered chronic (Hölzel, Härter, Reese, & Kriston, 2011). Therefore, MDD constitutes a significant

burden for both patients and society (Ormel et al., 2008). Additionally, long-lasting depressive symptomatology has been associated with decreased quality of life and lower psychosocial functioning (Furukawa et al., 2001; Ormel, Oldehinkel, Brilman, & van den Brink, 1993; van Bijl & Ravelli, 2000).

Targeted interventions in those with increased risk of recurrence could be an effective way to reduce the risk of depression recurrence and chronicity and its associated burden and functional impairments. A review by Beshai, Dobson, Bockting, and Quigley (2011) shows, for example, that preventive cognitive behavioral therapy (CBT) works

best for patients who have had three or more episodes. However, in order to better tailor interventions, accurate prediction of recurrence and chronicity is needed first. Previous research has identified several possible predictors of MDD persistence and/or chronicity, including episode severity (van Beljouw, Verhaak, Cuijpers, van Marwijk, & Penninx, 2010), comorbid anxiety (Conradi, de Jonge, & Ormel, 2008b), and persisting residual symptoms after remission (Conradi et al., 2008b; Conradi, Ormel, & de Jonge, 2012; Judd et al., 1998, 2000; Kennedy & Paykel, 2004). However, these general predictors cannot be used to predict when and how often an individual patient will relapse. To address this question, other studies have investigated the predictors of the timing of relapse/recurrence of MDD. Previous studies among specialized- and primary-care patients found that a family history of MDD and a patient's number of previous MDEs predicted shorter time to recurrence after remission (Conradi et al., 2008b; Hardeveld et al., 2013). Mueller et al. (1999) found that recurrence over a period of 15 years was associated with a higher number of previous MDEs, female sex, a longer duration of the index episode, and never having been married. Importantly, these predictors only predicted relapse within the first 5 years after remission. In those who remained well for 5 years, recurrence could not be predicted. Patten et al. (2010) found family history and comorbidity to be predictive of recurrence, and also found other predictors such as negative cognitive style, pain, smoking, and stress. However, unlike Mueller et al. (1999), they did not find any association between female sex and recurrence. Together, these studies have shown that relapse/recurrence can be predicted but the results have not been consistent. Therefore, a priori identification of MDD patients at risk of recurrence and/or chronic (residual) symptoms has remained difficult.

One element that may impede success in predicting the course of MDD is that it is a very heterogeneous construct, meaning that two patients with an MDD diagnosis can be very different in terms of their symptomatology and overall clinical presentation. Consequently, these patients are also likely to show differences in their course trajectories. Indeed, Rhebergen, Lamers, Spijker, De Graaf, Beekman, and Penninx (2012) showed that formal DSM-diagnostic labels corresponded poorly (<50%) with course-trajectory groupings that had been identified previously using a bottom-up, data-driven approach. This means that within the group of MDD patients, many different course-trajectories are possible that do not necessarily align well with DSM-defined remission and/or recurrence. Second, MDD is a dichotomous or at the very least a categorical construct. When it comes to defining patients' course trajectories, this typically means that the disorder is either considered present or absent, with only some nuance added by using definitions such as partial versus full remission. More subtle, and possibly important depressive course-trajectory variations are hereby overlooked, for example, gradual build-up of symptomatology and persisting subclinical symptomatology are not taken into account, although residual symptomatology is known to be clinically relevant (Das-Munshi et al., 2008) and predictive of later adverse outcomes (Karsten et al., 2011). Underlining the importance of a dimensional approach parallel to a categorical one, Hosenfeld et al. (2015) showed that patients can have either gradual or sudden relapses in their course trajectory of depressive symptomatology. Identification

of subgroups with different course trajectories after remission based on repeated dimensional severity scores can be done by using a data-driven approach. Data-driven methods such as latent class growth analyses (LCGA) have been used previously to investigate course-trajectory heterogeneity in MDD patients (Ashman, Dawson, & Panagiotides, 2008; Colman, Ploubidis, Wadsworth, Jones, & Croudace, 2007; Rhebergen et al., 2012; Stoolmiller, Kim, & Capaldi, 2005; Wardenaar, Conradi, & Jonge, 2014; Wardenaar, Monden, Conradi, & de Jonge, 2015). Classes derived from these data-driven methods have also been used in prognostic research as outcomes (Rhebergen et al., 2012; Wardenaar, Conradi, Bos, & de Jonge, 2014) as well as predictors of long-term severity and functioning (Wardenaar et al., 2014). Together, these studies have shown that data-driven methods can provide very useful insight into the more subtle between-person course-trajectory variations in MDD patients.

The aim of the current study was to investigate predictors of patients' course trajectories after MDE criterion symptoms were no longer met (i.e., <5 criterion symptoms) using data-driven outcomes. To this end, primary care MDD patients' depressive symptomatology ratings for the 24 weeks after no longer fulfilling criteria for the index MDE were used in an LCGA to identify empirical patient subgroups with different patterns of residual symptomatology (and potentially subsequent relapse/recurrence). To evaluate the differences between these different symptomatology patterns, the associations of the relapse/recurrence subgroups with baseline demographic, clinical, and psychological factors were investigated. Additionally, to investigate the prognostic value of relapse/recurrence subgroup membership for long-term outcomes, assessments of depression severity and functioning at 3- and 11-year follow-up were compared between the subgroups.

2 | METHODS

2.1 | Participants and procedure

Data for the current study came from a randomized controlled trial (RCT) comparing three treatments for MDD and care as usual (CAU). The RCT took place between January 1998 and June 2003 (Conradi et al., 2007; Conradi, de Jonge, & Ormel, 2008a). All participants were primary care patients, recruited from 49 Dutch general practices and met criteria for a current, or recent (i.e. occurring in the past 12 weeks), MDE. After receiving study information, eligible patients provided written informed consent. Inclusion/exclusion criteria were checked using the lifetime composite international diagnostic interview (CIDI) (World Health Organization, 1997). Patients with a life-threatening somatic illness, psychotic and/or bipolar disorder, dementia, drug/alcohol dependency, and those already receiving psychotherapy were excluded from the study. For further details, see Conradi et al. (2007). Participants were followed up with 3-monthly CIDI-based depression measurements for a period of at least 2 years. Additionally, patients were followed up after 3 and 11 years.

At 3-year follow-up, 141 (52.8%) of the originally included 267 patients participated and at 11-year follow-up, 164 (61.4%) of the

TABLE 1 Baseline sample characteristics

Factor	Data Available for N	Sample
N	213	
<i>Sociodemographic characteristics</i>		
Gender, female n (%)	213	138 (64.8)
Age, mean (SD)	210	43.1 (11.5)
Employed, n (%)	210	129 (60.6)
Married, n (%)	210	137 (64.3)
Education, mean years (SD)	209	12.8 (3.5)
<i>Psychiatric characteristics</i>		
Beck depression inventory, mean (SD)	207	19.2 (9.0)
Number of previous episodes, median (IQR)	213	3 (2–6)
Age of onset/first depressive episode, mean (SD)	212	32.0 (13.0)
Antidepressant use, n (%)	213	159 (74.6)
Ever a suicide attempt, n (%)	212	21 (9.9)
<i>MOS-SF-36 score, median (IQR)</i>		
Social functioning	213	50.0 (25–62.5)
Physical functioning	213	83.1 (65–95)
Mental health	213	40.0 (28–48) ^a
Vitality	213	30.0 (15–40)
Emotional role functioning	213	0.0 (0–33.3)
Physical role functioning	213	0.0 (0–75)
Bodily pain	213	67.3 (44.9–94.9) ^a
General health perceptions	213	50.0 (40–65) ^a
<i>Comorbid disorders, n (%)</i>		
Dysthymia (n = 212)	212	4 (1.9)
Panic disorder (n = 198)	198	27 (12.8)
Agoraphobia (n = 212)	212	12 (5.7)
Social phobia (n = 212)	212	30 (14.2)
GAD (n = 212)	212	3 (1.4)
Any anxiety disorder (n = 212)	212	72 (34.0)
CAU	213	58 (27.2)
<i>Treatment arm, n (%)</i>		
CAU + PEP	213	86 (40.4)
CAU + PEP + psychiatric consultation	213	31 (14.6)
CAU + PEP + CBT	213	38 (17.8)
<i>Psychological characteristics</i>		
<i>NEO-FFI scales, mean (SD)</i>		
Neuroticism (n = 204)	204	41.8 (6.6)
Extraversion (n = 204)	204	33.2 (6.5)
Openness (n = 203)	203	35.9 (6.0)
Agreeableness (n = 203)	203	44.1 (5.6)
Conscientiousness (n = 204)	204	40.4 (7.0)
Mastery, mean (SD)	202	20.9 (4.2)
Loneliness scale, mean (SD) (n = 204)	204	25.6 (4.3)
Rosenberg self-esteem, mean (SD)	203	18.5 (8.6)

^aObserved population percentiles.

SD, standard deviation; IQR, interquartile range; GAD, generalized anxiety disorder; CAU, care as usual; PEP, psychoeducation program; CBT, cognitive behavioral therapy; NEO-FFI, neuroticism extraversion openness five factor inventory

patients participated. Those who did not fulfill criteria for a current depressive episode at the start of the study were excluded for the analyses described here ($n = 54$), resulting in a baseline sample of 213 patients (79.8%). Those that were not included were roughly the same age ($t = -0.52$, $P = .61$), not significantly different in terms of sex ($\chi^2 = 0.25$, $P = .64$), and had less (10.7) years of education than those that were included (13.3; $t = 2.03$, $P = .04$). Due to financial restrictions, the 3-year follow-up with the Beck Depression Inventory (BDI) and medical outcome study (MOS-SF-36) was conducted earlier in a subgroup of patients, resulting in a follow-up duration between 24 and 36 months (mean 33.2 months) (Wardenaar et al., 2014). Of the 213 included patients, 140 had a 3-year follow-up (65.7%). A total of 139 patients (64.6%) provided 11-year follow-up data. These had the same age ($t = -.9$; $P = .06$), were more often female ($\chi^2 = 6.3$; $P = .12$), and had the same number of years of education ($t = 0.9$; $P = .36$) as those without an 11-year follow-up ($n = 71$). All 213 patients remitted from their MDE during the first 3 years of follow-up. Randomness of missings on any measurement (baseline, 3 and 11-year follow-up) was also tested by comparing the included patients with the nonincluded or missing patients on all sociodemographic and psychiatric characteristics (see Supplementary Table 1). We did not find significant differences for any measures on either of the three time-points, besides a significantly higher percentage of males than females among those with missing values at 11-year follow-up ($\chi^2 = 14.14$, $P < .001$).

2.2 | Treatment conditions

All participants received CAU by their general practitioner according to national guidelines for treatment of depression (i.e., counseling, antidepressant medication, or referral to specialized care). Of the 213 participants that were included in the current study, 58 (27.2%) received CAU only, 86 (40.4%) received an additional psychoeducational program (CAU + PEP) (Conradi et al., 2007), 31 (14.6%) received 1 h of medication-related counseling by a psychiatrist as well as PEP (psychiatric consult [PC] + PEP), and 38 (17.8%) received 10–12 45-min sessions of CBT by a certified clinical psychologist prior to PEP (CBT + PEP).

2.3 | Measurements

2.3.1 | Depression ratings

At baseline, the CIDI was used to assess anxiety, depression, dysthymia, and bipolar disorder (Ter Smitten, Smeets, & Van den Brink, 1998; World Health Organization, 1997) as well as the number of previous depressive episodes. Every 3 months during the first 3 years of follow-up, an adapted version of the CIDI depression section was used to assess the weekly presence/absence of each of the nine individual DSM-IV criterion symptoms for MDD during the previous 12 weeks. To assist memory, the interviewer disclosed the results of the previous interview indicating the absence/presence of each of the nine symptoms at the end of the previous 3-month period. If symptoms were present at that time, participants were asked if they persisted or had changed during the past 3 months. If participants reported change, the interviewer asked how many weeks ago this had started. If no

symptoms were present at the start of the period, participants were asked if this had remained the same or if new symptoms had occurred during the past 3 months. If so, the interviewer asked how many weeks ago this occurred. Weekly depression and severity scores (range 0–9) were computed by summing the weekly CIDI symptom ratings. For the current analyses, each patient's 24 weekly depression scores after no longer fulfilling criteria for an MDE were selected and used to model the 6-month course trajectories of depressive symptomatology. The time point where patients no longer fulfilled criteria for an MDE varied from week 1 to week 49 after inclusion across patients.

2.3.2 | Clinical and psychological characteristics at baseline

BDI (Beck, Ward, & Mendelson, 1961) was administered at baseline and every 3 months thereafter during the first 3 years to measure depression severity.

Demographic information, medication use, health care use, and somatic health were assessed with the baseline interview. Additionally, self-report questionnaires investigating psychological characteristics were administered at baseline. The big five personality traits (neuroticism, extraversion, openness to experience, conscientiousness, and agreeableness) were measured using the neuroticism-extraversion-openness five-factor inventory (NEO-FFI) (Costa & McCrae, 1992). The mastery scale was administered to assess the respondent's locus-of-control (Pearlin & Schooler, 1978). The Rosenberg self-esteem scale (Rosenberg, 1965) and the Loneliness scale (de Jong-Gierveld & Kamphuis, 1985) were administered. Functioning on different domains was measured using the Short Form-36 from the Medical Outcome Study (MOS-SF-36) (Stewart, Hays, & Ware, 1988).

2.3.3 | Measures at follow-up

The BDI was administered at 3- and 11-year follow up, the MOS-SF-36 only at 3-year follow-up. The long-term recurrence rate of depression was measured using the lifetime CIDI, covering the number of depressive episodes between the 3- and 11-year follow-ups. We also calculated the number of symptom-free weeks from the weekly ratings of the CIDI during the first 3 years.

2.4 | Statistical analyses

2.4.1 | Latent class growth analyses

Data-driven subgroups of patients with different course trajectories during the 24 weeks after no longer fulfilling criteria for the index MDE were identified using LCGA. Models with increasing numbers of classes were estimated and compared using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), with the lowest value indicating the LCGA model that best described the data (Muthén, 2001; Muthén, Brown, Leuchter, & Hunter, 2008). The Bootstrapped Likelihood Ratio Test (BLRT) was calculated to formally test if adding a class to the model significantly improved model fit than a model with one less class. Additionally, to ensure usefulness of the resulting LCGA model, minimal class size (at least 20 members per class) was used as an additional criterion in the model-selection procedure. These analyses were carried out using robust maximum likelihood estimation in

TABLE 2 Latent class growth analysis on the 24 consecutive weekly severity scores after remission ($n = 213$)

Model	Df	AIC	BIC	BLRT	Smallest Class, n (%)
1 class	3	21,183	21,193	–	–
2 class	7	17,278	17,302	<0.001	81
3 class	11	16,454	16,491	<0.001	61
4 class	15	15,862	15,913	<0.001	30
5 class	19	15,508	15,572	<0.001	17
6 class	23	15,302	15,379	<0.001	7

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BLRT, bootstrapped likelihood ratio test.

Mplus 5.0 (Muthén & Muthén, 1998–2007). To avoid finding a solution at a local maximum, all models were run with 200 initial random starts and 40 final stage optimizations.

2.4.2 | Class comparisons

Categorical baseline predictors and long-term outcomes were compared across classes using χ^2 -tests or Fisher's exact tests if cell counts were lower than five. Continuous variables were compared across classes using analyses of variance or Kruskal–Wallis tests if the continuous variable was not normally distributed. P -values were corrected for multiple testing using the Bonferroni correction. Class comparisons were all done using SPSS 22.

3 | RESULTS

3.1 | Demographic and clinical characteristics at baseline

The baseline descriptive information is summarized in Table 1. Approximately two-thirds (64.8%) of the sample were female, the mean age was 43.1 years ($SD = 11.5$) and participants had a mean of 12.8 years of education ($SD = 3.5$). The majority was employed (60.6%) and about two-thirds were married (64.3%). All participants met criteria for an MDE as defined by the DSM-IV at intake, with a mean BDI score of 19.2, indicating moderate depression severity levels (Beck & Beamesderfer, 1974; Beck, Steer, & Carbin, 1988). At baseline, 58 of these participants fulfilled criteria for partial remission. During the 24 weeks used in the LCGA, 49 participants eventually fulfilled criteria for full remission.

The lifetime median number of previous episodes was three (IQR: 2–6). Of the sample, 74.6% used antidepressants at baseline and 9.9% had ever attempted suicide. Approximately one third had a comorbid anxiety disorder (panic disorder: 12.9%, agoraphobia: 5.7%, social phobia: 14.2%; GAD: 1.4%).

3.2 | Latent class growth analyses

Results for the LCGA are shown in Table 2. Because the AIC and BIC kept decreasing and the BLRT remained significant with each

FIGURE 1 Observed and estimated growth trajectories for each of the classes of the four-class model on the BDI in the 24 weeks following remission from the index episode. Class 1 = “quick symptom decline”; class 2 = “slow symptom decline”; class 3 = “steady residual symptoms”; class 4 = “slow symptom increase”

class addition, class size was also considered in choosing the optimal model (Marsh & Balla, 1994). Both the 5- and 6-class models contained classes with very few subjects ($n < 20$), making them of limited use for further class-comparison analyses. Therefore, the four-class model was selected for further consideration.

Inspection of the class-specific course trajectories in the four-class model (Fig. 1) showed that the first class had a trajectory characterized by declining residual symptoms until week 24 (“slow symptom decline”; $n = 49$, 23.3%). The second class showed persistent low symptom ratings over the whole 24-week period (“quick symptom decline”; $n = 30$, 14.0%). The third class showed persisting residual levels of symptomatology during the whole 24-week period (“steady residual symptoms”; $n = 84$, 38.7%). The fourth class showed a course trajectory of increasing symptomatology (“slow symptom increase”; $n = 50$, 24.1%).

3.3 | Baseline predictors of class membership

As shown in Table 3, the percentages of patients allocated to high-intensity (CBT + PEP or PC + PEP) treatment conditions did not differ across classes, indicating that treatment was not associated with course variations in residual symptomatology. The classes did not differ significantly on baseline sociodemographic and psychiatric characteristics either. On the baseline psychological measures, a few class-differences were found, with lower self-esteem scores in the “steady residual symptoms” and “slow symptom increase” classes ($F[3, 200] = 7.7$, $P < .001$) than in the other two classes. Moreover, the “slow symptom increase” class scored higher on neuroticism ($F[3, 198] = 7.2$, $P < .001$) and lower on extraversion ($F[3, 198] = 5.4$, $P = .001$) than the other classes.

TABLE 3 Comparison of baseline characteristics between latent classes

Factor	LCGA Classes				Test Statistic	P-value
	1 Slow Symptom Decline	2 Quick Symptom Decline	3 Steady Residual Symptoms	4 Slow Symptom Increase		
N	49	30	84	50		
<i>Sociodemographic characteristics</i>						
Gender, female n (%)	30 (61.2)	17 (56.7)	55 (65.5)	36 (72.0)	$\chi^2 = 2.3$	.513
Age, mean (SD)	42.5 (11.6)	42.0 (13.2)	44.1 (10.5)	42.6 (12.1)	$F = 0.4$	.773 ^b
Employed, n (%)	33 (67.3%)	14 (50.0%)	52 (61.9%)	30 (61.2%)	$\chi^2 = 2.3$	.517 ^b
Married, n (%)	31 (63.3%)	15 (53.6%)	61 (72.6%)	30 (61.2%)	$\chi^2 = 4.1$	.248 ^b
Education, mean years (SD)	13.3 (3.8)	12.4 (3.7)	13.1 (3.6)	12.3 (3.0)	$F = 0.8$	.472 ^c
<i>Psychiatric characteristics</i>						
Number of previous episodes, median (IQR)	2.0 (1–4)	2.5 (2–5)	3.0 (2–5)	14.0 (2–12.5)	K-W	.013 ^d
Antidepressant use, n (%)	36 (73.5%)	18 (60.0%)	69 (82.1%)	36 (72.0%)	$\chi^2 = 6.1$	.106
Age of onset of depression (CID-I)	34.0 (11.7)	31.6 (14.4)	33.9 (12.8)	27.2 (12.6)	$F = 3.4$	.019 ^d
Time to remission in weeks, mean (SD)	6.76 (6.7)	10.3 (11.9)	11.0 (9.7)	14.5 (12.4)	$F = 4.8$	.003
Ever a suicide attempt, n (%)	3 (6.3%)	3 (10.0%)	8 (9.5%)	7 (14.0%)	Fisher's exact test = 13.0	.037 ^d
<i>MOS-SF-36 score, median (IQR)</i>						
Social functioning	50 (25–62.5)	37.5 (25–62.5)	50 (25–62.5)	50 (25–62.5)	K-W	.990
Physical functioning	80 (62.5–90)	77.5 (63.8–95)	85 (70–95)	85 (70–95)	K-W	.188
Mental health	40 (32–48)	34 (24–48)	40 (25–52)	36 (32–48)	K-W	.346
Vitality	30 (25–45)	17.5 (10–31.3)	25 (15–40)	35 (20–45)	K-W	.031
Emotional role functioning	0 (0–33.3)	0 (0–33.3)	0 (0–33.3)	0 (0–33.3)	K-W	.940
Physical role functioning	12.5 (0–75)	0 (0–50)	25 (0–75)	25 (0–100)	K-W	.681
Bodily pain	67.35 (44.9–92.4)	56.12 (44.9–78.1)	67.35 (44.9–94.9)	77.55 (55.1–100)	K-W	.111
General health perceptions	60 (40–70)	50 (35–67.5)	50 (40–64)	50 (40–60)	K-W	.641
<i>Comorbid disorders, n (%)</i>						
Dysthymia	1 (2.1%)	1 (3.3%)	1 (1.2%)	1 (2.0%)	Fisher's exact test = 1.4	.898 ^d
Panic disorder	5 (10.9%)	3 (10.7%)	4 (5.1%)	2 (14.3%)	Fisher's exact test = 2.7	.483 ^e
Agoraphobia	2 (4.2%)	1 (3.3%)	3 (3.6%)	6 (12.0%)	Fisher's exact test = 4.0	.249 ^d
Social phobia	2 (4.2%)	2 (6.7%)	14 (16.7%)	12 (24.0%)	Fisher's exact test = 9.7	.019 ^d
GAD	0 (0.0%)	1 (3.3%)	1 (1.2%)	1 (2.0%)	Fisher's exact test = 2.1	.653 ^d
Any anxiety disorder	12 (25.0%)	8 (26.7%)	27 (32.1%)	25 (50.0%)	Fisher's exact test = 7.9	.047 ^d
High intensity treatment ^a , n (%)	15 (30.6%)	10 (33.3%)	23 (27.4%)	21 (42.0%)	$\chi^2 = 3.2$	.369

(Continues)

TABLE 3 (Continued)

Factor	LCGA Classes				Test Statistic	P-value
	1 Slow Symptom Decline	2 Quick Symptom Decline	3 Steady Residual Symptoms	4 Slow Symptom Increase		
Psychological characteristics						
Mastery, mean (SD)	22.1 (4.3)	21.3 (4.1)	20.9 (4.1)	19.5 (3.9)	F = 3.1	.029 ^f
Loneliness scale, mean (SD)	18.0 (9.2)	16.7 (8.6)	18.5 (8.3)	29.9 (8.4)	F = 0.8	.471 ^h
Rosenberg self-esteem, mean (SD)	27.5 (4.1)	26.9 (4.9)	25.1 (4.4)	23.7 (3.0)	F = 7.7	<.001 ^g
NEO-FFI, mean (SD)						
Neuroticism	39.9 (6.3)	39.8 (7.4)	41.6 (5.8)	45.3 (6.3)	F = 7.2	<.001 ^f
Extraversion	35.0 (6.6)	35.1 (6.2)	33.1 (6.3)	30.4 (5.9)	F = 5.4	.001 ^f
Openness	35.3 (6.3)	35.8 (5.9)	36.5 (6.2)	35.6 (6.2)	F = 0.4	.735 ^f
Agreeableness	44.9 (5.3)	44.6 (5.5)	43.9 (5.9)	43.3 (5.5)	F = 0.8	.495 ^f
Conscientiousness	41.4 (5.6)	40.1 (5.2)	41.3 (8.7)	38.2 (5.7)	F = 2.4	.068 ^f

^aHigh intensity treatment: CAU + PEP + cognitive behavioral therapy (CBT) and CAU + PEP + psychiatric counseling
^bn=210.
^cn=207.
^dn=212.
^en=198.
^fn=202.
^gn=204.
^hn=203.
P-value: significant after Bonferroni correction (0.05/46 tests, P < .0011).

TABLE 4 Comparison of long-term outcomes between LCGA classes using Kruskal–Wallis tests

Outcomes	Classes				P-value
	1 Slow Symptom Decline	2 Quick Symptom Decline	3 Steady Residual Symptoms	4 High Residual Symptoms	
N	28	21	56	35	
BDI					
3 years, median (IQR) ^a	2 (0–5)	3 (1.5–5.5)	7 (3–11.8) ^d	11 (7–15)	<.001
11 years, median (IQR) ^b	4 (1–7)	7 (1–9.3) ^d	8 (3–14)	11 (4.5–14) ^d	<.001
Symptom-free weeks (from target episode to 3 years FU), median (IQR) ^c	51 (14.5–90.5)	81.5 (48.3–101.8) ^d	14.5 (0–50.3) ^a	0 (0–13.5) ^d	<.001
Number of episodes between 3 years FU and 11 years FU, median (IQR)	0 (0–1)	1 (0–1.5)	1 (0–1.75)	2 (0.5–6.5)	<.001
MOS-SF36 score, median (IQR) ^c	n = 28	n = 20	n = 55	n = 35	
Social functioning	93.8 (78.1–100.0)	87.5 (81.3–100)	75 (62.5–87.5)	62.5 (37.5–87.5)	<.001
Physical functioning	95 (85.0–100.0)	92.5 (86.3–100)	95 (86.0–100)	75 (60–95)	.005
Mental health	80 (64–87)	76 (70–92)	68 (48–80)	64 (48–76)	.002
Vitality	70 (51.3–75)	60 (45–80)	55 (40–70)	40 (30–55)	<.001
Emotional role functioning	100 (100–100)	100 (100–100)	100 (33.3–100)	33.33 (33.3–100)	.002
Physical role functioning	100 (100–100)	100 (75–100)	100 (50–100)	75 (25–100)	.012
Bodily pain	100 (79.6–100)	100 (73.5–100)	89.90 (67.4–100)	77.55 (44.9–100)	.012
General health perceptions	77.5 (69.1–88.8)	75 (70–85)	65 (55–83.8)	55 (40–75)	<.001

^an=140.^bn=139.^cn=138.^dObserved population percentiles.

3.4 | Long-term outcome prediction

Comparisons of long-term outcomes between the LCGA classes are shown in Table 4. Three years after the start of the study, participants in the “steady residual symptoms” and “slow symptom increase” classes scored significantly higher on the BDI than the other two classes. This was still the case 11 years later. At 11-year follow-up, the median BDI score in the “quick symptom decline” group was four points higher than at 3-year follow-up. In the “slow symptom decline” group, the median BDI score was only two points higher at 11- than at 3-year follow-up. At 3-year follow-up, the “steady residual symptoms” and “slow symptom increase” classes showed significantly more recurrences of their depression than the other two classes “steady residual symptoms”: median 1 (IQR 0.1–175), “slow symptom increase”: median 2 (IQR: 0.5–6.5), “slow symptom decline”: median 0 (IQR: 0–1), “quick symptom decline”: median 1 (IQR: 0–1.5). Additionally, the “steady residual symptoms” and “slow symptom increase” classes showed significantly less symptom-free weeks since remission from the episode with which they entered the study. After 3 years, patients in the “slow symptom increase” class showed lower social functioning, vitality and general health perceptions on the MOS-SF-36 than the other classes. Moreover, patients in the “steady residual symptom” class scored significantly lower on social functioning and general health perceptions than those in the “slow symptom decline” class, who scored highest on these domains.

We performed post hoc analyses for the four-class LCGA solution based on the same sample minus the 58 patients who were in partial remission at baseline, finding a very similar four-class solution. When comparing these classes on both baseline and follow-up

measures, we found some differences with the results in the sample with 213 patients (see Supplementary Table 2); at baseline, we found higher vitality scores in the “slow symptom decrease” class than the “quick symptom decline” class. At 3-year follow-up, we found that the “high residual symptom class” scored higher on the BDI than the “slow symptom decline” and “quick symptom decline” classes and had significantly less symptom free weeks between the start of the study and the 3-year follow up than both the “slow” and “quick symptom decline” classes (both: $P < .001$). The “steady residual symptoms” class also had significantly less symptom free weeks than the “quick symptom decline” class ($P < .001$). Patients in the “high residual symptoms” class showed significantly lower social functioning than the “slow” and “quick symptom decline” classes as well as lower vitality than the “slow symptom decline” class. Moreover, the high residual symptoms class scored lower on general health perceptions than both the “slow” and “quick symptom decline” classes, all measured with the MOS-SF-36. The “steady residual symptoms” class scored significantly lower on the MOS-SF-36 mental health scale than the “slow symptom decline” class. We also found an overall difference between the groups on the emotional role functioning scale of the MOS-SF-36 ($H(3) = 19.03$, $P < .001$), but the subsequent pairwise differences were not significant after Bonferroni correction.

4 | DISCUSSION

Depression is often recurrent or even chronic, which is associated with poorer outcomes. It is therefore important to uncover useful

predictors to differentiate between the many possible patterns of relapse/recurrence that patients show after remission from an MDE. To optimally investigate these course trajectories, the current study used LCGA to identify data-driven subgroups of depressed primary care patients with different symptom patterns after no longer meeting MDE criteria. Using weekly symptom ratings for the first 24 weeks after this point, four classes were identified: “slow symptom decline”, “quick symptom decline”, “steady residual symptoms,” and “slow symptom increase”. Self-esteem scores were lower in the “steady residual symptoms” and “slow symptom increase” classes, and lower extraversion as well as higher neuroticism characterized the “slow symptom increase” class. The identified classes did predict outcomes at long-term follow-up at 3 as well as 11 years. At long-term follow-up, the “steady residual symptoms” and the “slow symptom increase” classes also showed higher depression severity (both at 3- and 11-year follow-up), lower functioning at 11 years in several domains (i.e., social functioning, vitality and mental health perceptions) and reported more recurrences and less symptom-free weeks during at 11 years than the “quick symptom decline” and “slow symptom decline” classes. Post hoc analyses excluding 58 patients in partial remission at baseline showed different results. Although the four-class solution from these analyses was largely similar to the original model, the smallest class had only 19 subjects and class differences showed other patterns. Since we performed many statistical tests and the sample had become quite small, these differences should be interpreted with care as they could reflect the effect of partially remitted cases, but also methodological factors. To prevent misinterpretation, we decided to report the results in the full sample as our main findings, while acknowledging that the presented post hoc analyses indicate that inclusion of patients in partial remission in the analyses does influence these results. This issue should ideally be resolved in a future study with a sufficiently large sample of nonremitted MDE patients.

The current findings have several implications. They show that it is possible to not only differentiate between the identified classes and predict their symptom patterns and possible consequent relapse/recurrence using certain cross-sectional baseline predictors (as was done by previous studies), but also that these patterns of mesolevel fluctuations can predict macrolevel (i.e., long-term, at 3 and 11-year follow-up, disorder-level) depression outcomes.

Previous studies found that several factors, including comorbidity, family history, the number of previous episodes, age of onset, and prior suicide attempt, were predictive of relapse and/or chronicity (Bukh, Andersen, & Kessing, 2016; Conradi et al., 2008b; Hardeveld et al., 2013; Mueller et al., 1999; Patten, 2010). The “slow symptom increase” class did have a higher number of previous episodes than the other classes, as well as an earlier age of onset, a higher incidence of previous suicide attempt and a lower mastery score than the “slow symptom decline” class. However, these differences did not remain significant after Bonferroni correction for multiple testing. Comorbidity and the number of previous episodes did not predict residual symptom pattern in the current study. One explanation for this discrepancy between significant predictors of recurrence in the current study versus previous studies may be that the current study used an outcome grouping based on symptom scales. This allows for identification of more subtle

differences between outcome groups than when defining recurrence based on a dichotomous diagnostic cut-off, as was done by previous studies (Hardeveld et al., 2013; Mueller et al., 1999; Patten, 2010). As such, our approach provides interesting insights into the different trajectories after episode resolution of an MDE, but also yielded subgroups that were not easily differentiated from each other using only baseline depression severity indicators. Interestingly, the only baseline predictors that were found to differentiate between classes were psychological characteristics (self-esteem and personality). This resembles results from the earlier study by Patten et al. (2010), in which a negative cognitive style was found to be associated with quicker recurrence. This could indicate that trait-like psychological characteristics play an important role in determining what happens after remission of an MDE. Indeed, several authors have suggested that lower psychological resilience makes individuals more vulnerable to the onset and/or recurrence of psychological problems (Arslan, 2016; Campbell-Sills, Cohan, & Stein, 2006; Gloria & Steinhardt, 2014; Schulz et al., 2014; Wingo et al., 2010). Vice versa, Campbell-Sills et al. (2006) showed that high resilience or the ability to adapt positively to adversity (Campbell-Sills et al., 2006; Connor & Davidson, 2003; Luthar & Cicchetti, 2000) was associated with less psychiatric symptoms.

Our finding that patterns of relapse/recurrence and residual symptoms just after episode resolution predict long-term depression and functional outcomes aligns with previous work in the same dataset that has shown general 1-year data-driven course trajectories of depressive symptoms to be predictive of long-term outcomes (Monden, Stegeman, Conradi, de Jonge, & Wardenaar, 2016; Wardenaar et al., 2014, 2015). Moreover, Judd, Schettler, Rush, Coryell, Fiedorowicz, and Solomon (2016) showed that patients with residual symptoms after the formal ending of their episode are worse off in the long-term than patients with minimal residual symptoms.

Besides a dichotomous distinction between presence and absence of residual symptoms, a refined profiling of MDD is warranted. Other studies, using the more fine-grained experience sampling method to monitor microchanges in affect, have also shown that patterns of affective responsiveness independently predicted later negative affective symptoms (Wichers et al., 2010) and treatment response (Höhn et al., 2013). Additionally, Geschwind, Nicolson, Peeters, van Os, Barge-Schaapveld, and Wichers (2011) showed that affective changes over a 1-week period were predictive of measures of antidepressant treatment response 6 weeks later.

The current and previous results suggest that (1) longitudinal, mesolevel measurements in patients can provide very useful information that is not captured by cross-sectional measurements and (2) not only macrolevel course characteristics of the depressive episode itself or longitudinal course trajectories but also relatively shorter depressive/affective symptom course trajectories can contain useful prognostic information.

The current study has several strengths, including the large number of weekly repeated measurements, the availability of long-term follow-up measurements and the broad range of measured baseline characteristics. Some limitations should however be noted. First, the high resolution of weekly symptom ratings was achieved by 3-monthly retrospective reports, which possibly induced bias. Second, the

sample was relatively small, limiting the choice of optimal class-solutions; the smallest classes in the 5- and 6-class solution had too few subjects ($n < 20$) to be useful in subsequent analyses. Additionally, the sample size was a limiting factor in interpreting post hoc analyses. Third, the predictors tested in the current study were all assessed once at baseline and not at the time point at which the episode ended. As a result, the time-lag between these measurements and the actual trajectories could be quite long. If predictors had been measured at the moment the episode ended, more predictors could potentially have been identified. However, this would answer a different research question, focusing more on the prediction of MDE rather than recurrence.

Future studies into the predictive value of specific symptom patterns could benefit from larger samples. Additionally, more in-depth investigations of the patterns of recurrence/chronicity and their predictors would be possible if a broader range of depression-related characteristics was assessed at repeated intervals and if predictors or potential mediators were repeatedly assessed as well.

The current study is the one of the first to attempt to unravel different patterns of depressive symptoms after remission. Although replication is needed, the current results are promising from a clinical perspective. As previous studies have shown, it is possible to measure changes in affect presenting over the course of several days or even just 1 day, and these changes have been shown to predict treatment response (Höhn et al., 2013; Wichers et al., 2010) and symptom development (Geschwind et al., 2011). Paying attention to symptom patterns after clinical criteria are no longer met, done by patients themselves using diary methods or by professionals in aftercare groups, could be a way to move forward in clinical practice.

In conclusion, the results of the current study suggest that besides cross-sectional baseline characteristics identified by previous studies, mesolevel depression characteristics such as patterns of symptom fluctuations can be used to predict the course of depression on a macrolevel (i.e., absence or presence of the disorder).

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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