## Staging of Major Depressive Disorder

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# How different are depressed patients with a first onset episode from those with recurrent episodes?
## A 2-year prospective study

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## ABSTRACT

**Objective** Recurrent depression is considered a more progressed from of major depressive disorder (MDD). It is therefore expected that patients with recurrent episodes have a different clinical presentation and worse prognosis as compared to those with a first episode. In a well-characterized sample we tested whether patients with first vs. recurrent episodes of depression differ in terms of clinical-, etiological and course characteristics.

**Methods** Patients (n=478) with a current recent onset MDD episode were selected from the baseline assessment of the Netherlands Study of Depression and Anxiety. Clinical (e.g. age at onset, symptom severity) and etiological (e.g. childhood trauma, life events, personality) characteristics, and 2-year course outcomes were compared between patients with first (n=278) and recurrent (at least 3 episodes; n=375) episodes.

**Results** Patients with a first episode experienced more recent life events. In contrast, patients with recurrent episodes had a younger age at onset and higher neuroticism and openness scores, and more often had first-degree relatives with depression. Patients with first-episode or recurrent episodes did not differ in 2-year course outcomes.

**Conclusions** In first episode depressed patients environmental triggers seem more important, while in recurrent episode patients the disorder seems linked to inherited liability factors. Characteristics distinguishing first episode from recurrent episode patients may provide important clues to specific treatment needs. Nevertheless, the 2-year course of patients with a first or recurrent episode did not differ, suggesting that the number of experienced episodes may not be a strong clinical indicator for a progressive course of the current episode.

## INTRODUCTION

Major depressive disorder (MDD) is a common disorder that has a highly heterogeneous natural course, varying from patients experiencing only one to recurrent and chronic episodes in life. Therefore, the first questions clinicians often ask their patients is whether they experience a first or a recurrent episode and how long they have been suffering from the current episode. Both recurrent and chronic MDD are considered more progressed forms of MDD. The distinction between first, recurrent and chronic MDD has been so well accepted that it is now part of the DSM-5[1] and even has become part of clinical staging algorithms.[2] In line with the thought that recurrent depression is a more progressed form of MDD, it is expected that recurrent cases have a well-defined clinical presentation, prognosis and treatment-requirement that is different and likely worse than that of persons with a first episode.



Over the past 30 years clinical and etiological characteristics have been compared between first versus recurrent episode MDD patients in several cross-sectional studies, providing mixed results. Among the more consistent findings are that recurrent episode patients have a younger age at onset[3–9] and more often a family history of depression[3–5,7,8], while first episode patients are more likely to have experienced recent life-events.[10–12] The evidence is conflicting for important characteristics such as severity of depressive symptoms[5,7,8,10,13–15], suicide attempts[4,6,8,16], comorbid psychiatric disorders[4,6,1]or personality traits[17]. Previous conflicting results may be partially due to methodological differences between the studies, such as specific recruitment settings[7,10,15,17,18], small sample sizes[12,14,17,18], or having examined a limited set of characteristics[14,15,17,18]. Moreover, an aspect not systematically controlled for in previous studies was the duration of the index episode, which may confound comparisons among first versus recurrent episodes. One study[19] did additionally stratify the comparison between first and recurrent episode patients by chronicity, defined as an index-episode >2 years. This study[19] found that compared to first-episode patients, recurrent episode patients had a younger age at onset, more often a family-history of depression and more somatic medical conditions, but did not differ in age, education, and severity of symptoms. Moreover, they found[19] that after one year first vs. recurrent patients did not differ in time to remission, or response, but that recurrent patients relapsed sooner. Other studies that examined the longitudinal course of depression suggest more severe symptoms in recurrent episode patients[20], but in general provided mixed results probably due to methodological differences, such as specific recruitment setting[21], or not controlling for duration of the index episode.[20–23] In summary, whether the presence/absence of prior MDD episodes is a true discriminator for a difference in clinical presentation and course of the current episode is as yet unresolved.

This large-scale study aims to examine the differences in clinical and etiological

characteristics and course outcomes among first and recurrent episode patients with a recent-onset MDD. Given the available evidence, we expected a stronger link to environmental stress-related factors (e.g. life-events) for first-episode patients, and a stronger link with inherited liability factors (e.g. family history, younger age at onset) for recurrent episode patients. Moreover, we expected that recurrent-episode patients had a worse course of their current episode over time. Findings from the present study may have important implications, demonstrating the utility of distinguishing between first and recurrent MDD patients presenting at clinical settings as a criteria to identify subgroups of patients with different features, clinical needs, and course prognosis.

## MATERIALS & METHODS

### Sample selection

We used data from the Netherlands Study of Depression and Anxiety (NESDA), an on-going longitudinal cohort study into the course of depressive and anxiety disorders. The methodology of NESDA has been extensively described elsewhere.[24] In summary, at baseline (2004-2006) 2981 adults between the age of 18 and 65 were recruited from community (19%), general practice (54%) and specialized mental health care (27%) to represent the entire developmental spectrum of both disorders. The assessment consisted e.g. of a psychiatric interview, several self-report questionnaires and a basic medical interview. The ethical review boards of contributing universities approved NESDA and all participants signed informed consent. DSM-IV MDD and dysthymia diagnoses were made with the Composite International Diagnostic Interview (CIDI) version 2.1.[25] Severity and presence of depressive symptoms in the week prior to interview were measured with the inventory of depressive symptoms (IDS, ≥14 is cut-off for symptoms present).[26] A current episode was defined as an MDD diagnoses present in the year prior to baseline interview with the patient still experiencing symptoms in the week prior to baseline. Recurrent was defined as having had at least 3 episodes (including the current episode) to increase the likelihood that it concerns true recurrent cases; as discussed in a paper on concept of depression recurrence, the more episodes a person experience in a relatively short time the more likely it is that it is caused by the same underlying disease.[27] Moreover by choosing those with at least 3 episodes we increase the contrast with those with a first episode. Chronicity was defined as the presence of a dysthymia disorder in the year prior to baseline and/or depressive symptoms present 100% of the ±1.5 years prior to the baseline interview. The presence of depressive symptoms was measured with the Life Chart.[28] The life-chart uses a calendar strategy; at baseline it asked about the number of months spent with depressive symptoms in the year of interview and in the four prior years. It also registered how burdensome those symptoms were (no/

minimal, mild, moderate, severe, very severe). The duration of symptoms was calculated as the number of months with at least mild burdened symptoms divided by the number of months assessed. We used information of ±1.5 years prior to the baseline to strictly define chronicity as symptoms present > than at least one year. Recent onset was defined as a current MDD diagnoses that was not chronic.

We selected 653 patients with a recent onset first MDD episode (n=278) or recurrent (≥3) MDD episode (n=375). First and recurrent MDD episode patients did not differ in gender, however the recurrent patients were slightly older (41.0 vs. 38.4 years) and slightly more educated (12.1 vs. 11.3 years) (see Table 1). Although, these differences were minimal, since we wanted to compare cases that only differed in their presence of prior episodes experienced, all our following analyses were corrected for age, gender and years of education attained. Two year follow-up data was available for 545 cases (83.5%). Compared to those without follow-up data (n=108), those with available follow-up data did not differ in age, gender, but were significantly more often recurrent patients (59.6% vs. 46.3%).



**Clinical presentation of first & recurrent episode patients.**

*Clinical characteristics.* Age at onset of the first depressive episode was ascertained via the CIDI. The severity of depressive, anxious, and avoidance symptoms in the week prior to baseline assessment was measured with the IDS[26], the Beck Anxiety Inventory (BAI)[29], and the Fear Questionnaire (FQ)[30] respectively. The presence of suicide ideation and whether a suicide was ever attempted were measured with the Beck Suicide Intent (BSI) Scale.[31] Comorbid presence of anxiety disorders (social phobia, panic disorder, agoraphobia, generalized anxiety disorder) in the year prior to interview was derived from the CIDI. Antidepressant used in the month prior to baseline, were registered according to the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification,[32] and included selective serotonin reuptake inhibitors (N06AB), tricyclic antidepressant (N06AA), and other antidepressant (N06A, not N06AA, not N06AB). Psychological treatment was considered received if it was given at least 3 times by a health-care professional, as measured with the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P).[33] Treatment was then dichotomized into none, or antidepressant and/or psychological treatment. Finally, disability (range 0-100%) was measured with the 36-item World Health Organization Disability Assessment Schedule II (WHODAS-II).[34] We included all subscales except for the 4-item work disability (total 32 items) to avoid missing answers due to MDD patients often not working.[35]

*Etiological characteristics.* Presence of a first-degree family member with depression was assessed with the family-tree method.[36] Childhood trauma (yes/no) was assessed with the structured inventory used in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) that asks about four types of abuse happened before the age of 16 (emotional

neglect, psychological abuse, physical abuse and sexual abuse).[37] The number of 12 possible negative life events (such as death or illness of a family member) experienced in the past year were counted and dichotomized to none and one or more.[38] Presence of chronic somatic diseases under treatment (including cardiovascular diseases, diabetes, lung disease, arthritis, cancer, intestinal problems, liver disease, epilepsy and thyroid gland disease) was self-reported. Five personality traits (Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness) were assessed with the NEO-Five- Factor Inventory.[39]

**Course outcomes of first & recurrent episode patients.**

We examined clinically relevant outcomes at 2-year follow-up. The CIDI was used to diagnose the presence of depressive and anxiety disorders. The life-chart[28] was used to examine the duration of symptoms, by listing each month since baseline that was spent with depressive symptoms and the burden of those symptoms. Symptoms were only taken into account when of at least mild severity.

Since all patients experienced depressive symptoms at baseline, (time to) remission was defined as the first follow-up month in which the participant did not experience MDD for three continuous months. This definition of remission is in line with previous NESDA/NEMESIS studies.[40,41] More precise, if the CIDI did not record an MDD diagnosis during follow-up, time to remission was set to 4 months (the first follow-up months in which the patient did not experience MDD for three months). If the CIDI did record an MDD diagnosis during follow-up, time to remission was set to the month after the first 3 months interval. Patients that did not reach remission during the 2-year follow-up were defined non-remitted.

A chronic episode was defined as lasting 2-year (presence of a CIDI diagnosis of MDD in the 6 months prior to the 2-year assessment in combination with symptoms for >= 85% of the follow-up time as measured with the life-chart). Duration of depressive symptoms, regardless of the presence of a CIDI MDD diagnosis, was measured with the life-chart. Duration was dichotomized at the median (29.2% of time), because of its highly skewed distribution. Both suicide attempt and comorbid anxiety were considered present if they had occurred anywhere during 2-year follow-up. Severity of depressive, anxious, or avoidance symptoms were examined with the IDS/BAI/FQ respectively. Disability was examined with 32 items (excluding work-disability) of the 36-item WHODAS-II.

**Statistical analyses**

Socio-demographics were compared across first- and recurrent episode patients groups using analyses of variance and Chi-Square analyses. Socio-demographic adjusted differences between first- and recurrent episode patients in clinical and etiological characteristics and follow-up outcomes were examined using analyses of co-variance for continuous variables, and binary logistic regression for categorical variables. Cohen's D and odds ratios derived

from analyses for continuous and categorical variables, respectively, were reported as effect-sizes of the group differences. Analyses were performed with SPSS version 22[42], significance level was set to 0.05, two-tailed.

## RESULTS

### Clinical presentation of first & recurrent episode patients.

Table 1 shows the socio-demographic, clinical and etiological characteristics of first-episode



**Table 1: socio-demographics, clinical and etiological characteristics of first MDD episode and recurrent MDD episode (n=653)**

| | | First MDD episode (n=278) | Recurrent MDD episode (n=375) | Effect size Cohen's D / OR | P-value |
|---|---|---|---|---|---|
| **Socio-demographics** | | | | | |
| Age, M (SD) | | 38.4 (12.8) | 41.0 (11.9) | -0.21 (-0.24 – -0.19) | .007 |
| Gender (female), % (n) | | 66.9 (186) | 70.7 (265) | 1.19 ( 0.85 – 1.67) | .304 |
| Years of Education, M (SD) | | 11.3 (11.3) | 12.1 (12.1) | -0.28 (-0.29 – -0.27) | .001 |
| **Clinical Characteristics*1** | | | | | **P-value*2** |
| Age at Onset (years), M (CI) | | 30.4 (29.2–31.6) | 23.9 (22.9–24.9) | 0.66 ( 0.64 – 0.68) | <.001 |
| Severity Depressive symptoms (IDS), M (CI) | | 31.5 (30.3–32.7) | 31.3 (30.3–32.3) | 0.01 ( 0.00 – 0.03) | .859 |
| Severity Anxiety symptoms (BAI), M (CI) | | 18.0 (16.8–19.2) | 17.1 (16.1–18.1) | 0.09 ( 0.07 – 0.10) | .277 |
| Severity Avoidance symptoms (FQ), M (CI) | | 32.8 (30.5–35.1) | 32.1 (30.1–34.1) | 0.04 ( 0.02 – 0.05) | .633 |
| Suicide Attempt (yes), % (n) | | 19.5 (54) | 16.8 (63) | 0.87 ( 0.58 – 1.32) | .523 |
| Suicide Ideation (yes), % (n) | | 17.6 (49) | 20.3 (76) | 1.22 ( 0.82 – 1.84) | .332 |
| Comorbid Anxiety, % (n) | | 66.5 (185) | 66.1 (248) | 1.00 ( 0.71 – 1.40) | .989 |
| Treatment (yes), % (n) | | 67.6 (188) | 51.5 (193) | 0.49 ( 0.36 – 0.69) | <.001 |
| Disability, M (CI) | | 31.5 (29.8–33.2) | 31.6 (30.1–33.0) | -0.01 (-0.02 – 0.01) | .932 |
| **Etiological Characteristics*** | | | | | **P-value*2** |
| Family history of MDD, % (n) | | 73.7 (205) | 80.2 (300) | 1.40 ( 0.96 – 2.04) | .079 |
| Childhood trauma, % (n) | | 55.0 (153) | 62.3 (233) | 1.25 ( 0.90 – 1.73) | .189 |
| Live Events-recent, % (n) | | 64.0 (178) | 51.2 (192) | 0.59 ( 0.43 – 0.82) | .002 |
| Chronic diseases under treatment, % (n) | | 48.6 (135) | 45.1 (169) | 0.79 ( 0.56 – 1.10) | .160 |
| Personality, M (CI) | Neuroticism | 41.4 (40.7–42.2) | 42.3 (41.6–42.9) | -0.14 (-0.15 – -0.12) | .087 |
| | Extraversion | 33.5 (32.7–34.2) | 34.2 (33.5–34.8) | -0.11 (-0.12 – -0.09) | .182 |
| | Openness | 37.2 (36.5–37.9) | 38.6 (38.0–39.2) | -0.24 (-0.26 – -0.23) | .002 |
| | Agreeableness | 42.3 (41.7–42.9) | 42.5 (42.0–43.0) | -0.04 (-0.06 – -0.03) | .598 |
| | Conscientiousness | 39.4 (38.7–40.2) | 39.5 (38.8–40.1) | -0.01 (-0.02 – 0.01) | .933 |

*1 Adjusted (age, gender and years of education) means and confidence intervals are shown for continuous variables.
*2 All p-values shown for clinical and etiological characteristics are from adjusted (age, gender and years of education) models.
Abbreviations: BAI=Beck Anxiety Inventory; CI=95% Confidence Interval; FQ=Fear Questionnaire; IDS=Inventory of Depressive Symptomatology; LT=Lifetime; M=mean; MDD=Major Depressive Disorder; n=number.
Some characteristics had missing data: Age at Onset 7 missing (5 first, 2 recurrent); Suicide attempt 2 missing (1 first, 1 recurrent); Disability 13 missing (6 first, 7 recurrent); Family history 1 missing (1 recurrent); Childhood trauma 1 missing (1 recurrent).

and recurrent-episode MDD patients. Compared to first-episode patients, recurrent MDD patients had a significantly younger age at onset, were more likely to report a family history of depression, experienced significantly less recent life events, and they scored higher on neuroticism and significantly higher on openness. Finally, compared to first-episode patients, recurrent episode patients received less often antidepressant and/or psychological treatment. They did not differ in any of their other clinical characteristics, such as severity of depressive/anxiety/avoidance symptoms, suicide attempts, and disability level; nor in any of their other etiological characteristics, such as childhood trauma.

**Course outcomes of first & recurrent episode patients.**

Table 2 shows the 2-year course comparisons between first- and recurrent MDD episode patients. They did not differ in any of the course measures, for example remission percentages, time to remission, chronic episodes, attempted suicides, and neither in severity or disability at 2-year follow-up. Results remained similar when analyses were adjusted for treatment status at baseline (data not shown).

**Table 2: 2 year follow-up outcome of first MDD episode and recurrent MDD episode (n=545)**

| | First MDD episode (n=220) | Recurrent MDD episode (n=325) | Effect size | P-value *[2] |
|---|---|---|---|---|
| Measures between baseline – 2-year follow-up | % (n) | % (n) | Odds Ratio | |
| Remitted | 77.3 (170) | 80.9 (263) | 1.21 (0.79 – 1.86) | .381 |
| Of those remitted, time to remission*[3] | 29.4 (50) | 27.8 (73) | 0.99 (0.64 – 1.53) | .968 |
| Chronic episode*[4] | 15.5 (34) | 14.8 (48) | 0.93 (0.57 – 1.52) | .776 |
| Duration*[5] | 50.0 (110) | 50.5 (164) | 1.01 (0.71 – 1.44) | .941 |
| Suicide attempt | 18.7 (41) | 16.3 (53) | 0.89 (0.56 – 1.42) | .618 |
| Comorbid anxiety | 48.6 (107) | 50.2 (163) | 1.12 (0.79 – 1.59) | .519 |
| Measures at 2-year follow-up | Mean (CI)*[1] | Mean (CI)*[1] | Cohen's D | |
| Severity of Depressive symptoms (IDS) | 21.4 (19.8 – 23.0) | 21.3 (20.0 – 22.6) | 0.01 (-0.01 – 0.03) | .926 |
| Severity of Anxiety symptoms (BAI) | 11.7 (10.5 – 12.9) | 11.8 (10.8 – 12.8) | -0.01 (-0.03 – 0.01) | .919 |
| Severity of Avoidance symptoms (FQ) | 24.6 (22.2 – 27.0) | 25.0 (23.0 – 27.0) | -0.02 (-0.04 – 0.00) | .810 |
| Disability | 22.0 (19.9 – 24.1) | 22.2 (20.5 – 24.0) | -0.02 (-0.04 – 0.01) | .854 |

*[1] Adjusted (age, gender and years of education) means and confidence intervals are shown for continuous variables.
*[2] All p-values shown are from adjusted (age, gender and years of education) models.
*[3] Time to remission = those that spend more than 4 months (median) to reach remission.
*[4] Chronic = MDD present in the 6 months prior to follow-up in combination with symptoms for >=85% of follow-up period.
*[5] Duration = those that spent more than 29% (median) of the follow-up period with depressive symptoms
Abbreviations: BAI = Beck Anxiety Inventory; CI=95% Confidence Interval; FQ=Fear Questionnaire; IDS=Inventory of Depressive Symptomatology; M=Mean; MDD=Major Depressive Disorder; n=number.
Some characteristics had missing data: IDS and BAI 21 missing (4 first, 17 recurrent), FQ 23 missing (6 first, 17 recurrent); WHODAS 23 missing (7 first, 16 recurrent)

## DISCUSSION

Using data from a large and well-characterized cohort we tested for differences in clinical and etiological characteristics and course outcomes between patients with a first- versus those with a recurrent MDD episode. We confirmed that the two groups had a distinct clinical presentation, with a stronger link to environmental stress-related factors among first-episode patients, which contrasts with a stronger link to inherited liability factors for recurrent-episode patients. Nevertheless, the two groups did not differ in disease course outcomes over the two-year follow-up.

The specific distinct clinical presentation, with a stronger link to environmental stress-related factors among first-episode patients and a stronger link to inherited liability factors for recurrent-episode patients, is comparable to those found in previous studies.[3–12] Especially, our profile of the recurrent episodes patients is comparable to the one found by the only prior study[19] that examined characteristic of recent onset first and recurrent episode patients.[19] They did not only found that recurrent patients had a younger age at onset and more family members with depression, but they also found that recurrent patients did not differ in severity of symptoms from first episode patients. We also found that recurrent episode patients scored higher on the Big-Five Openness trait as compared to first-episode patients. To our knowledge, prior studies have not compared the trait Openness between MDD recurrent versus first episode patients. Moreover, the specific distinct clinical/etiological profiles for the two groups are consistent with the theory of scar models of depression[43] describing the disease progression from first to recurrent episodes. According to these models the inception of the disorder is more strongly related to relevant environmental stressors, such as recent life events; then prior episodes lead to some form of (neurological and/or psychological) damage that creates liability for recurrent MDD, causing subsequent episodes to occur more spontaneously, without a direct (life-stress related) cause. Furthermore, Kendler et al suggested that not only prior episodes, but also genetic-risk (e.g. family history) can 'kindle' the brain for subsequent 'spontaneous' episodes.[44] The present findings highlighted indeed the importance of heredity related factors, such as family history, in patients with recurrent episodes. In addition, neuroticism, which is a well-known risk factor for depression onset[45–47], scored higher in recurrent episodes. Finally, a younger age at onset, which may also be a marker of increased heredity[48–50], was associated with recurrent risk. This profile for recurrent episodes is indeed suggestive of both an environmental (prior episodes) and a genetically driven (pre-kindling) of the brain. Stable liability models[51], however, postulate that vulnerability factors for depression exists prior to the first-onset of a depressive episode (e.g. genetic) and as long as the factor remains present after remission of the first episode, the persons remains susceptible to developing recurrent episodes of depression. The profile for recurrent episodes that we found thus also

fits with these stable liability models. To our knowledge, only two studies[52,53] have been done that followed patients from prior to onset of the first-episode till the development of recurrent episodes, therefore allowing for within person comparisons.[27] In line with our study, they found evidence for both models. This suggests that stable liability- and scar-models are not mutually exclusive, but that recurrent depression is a consequence of both genetic vulnerability (stable-liability) and prior episodes (scarring).

Contrary to the expectations, our findings did not show that the course of the current episode differed between first and recurrent-episode patients suggesting that the absence or presence of earlier MDD episodes may not be a strong clinical indicator for a progressive course of the current episode. Prior studies indicated that recurrent episode patients experience more severe[20,43] next to more frequent and spontaneous episodes; which are seen as signs of recurrent MDD being a progressive disorder (scar-models).[43] However, it has been recently proposed that results from previous studies may have been hampered by Slater's fallacy.[51] Slater's fallacy argues that differences between first and recurrent MDD patients appear to happen because highly recurrent individuals with consistently shorter intervals become a larger proportion of the remaining sample with each recurrence. E.g. previous studies did not separate between within-patients effects and between-patients effect. After correction for Slater's fallacy, the study showed that cycle-acceleration (recurrent cases have longer episodes with shorter well intervals) is not present in highly recurrent MDD patients.[51] Currently, our findings suggest that the absence or presence of earlier MDD episodes is a poor discriminator for a progressive course of the current episode. This is further supported by a study that found that the effect of antidepressants in acute depression is not dependent on the number of episodes previously experienced.[54]

As stated in the introduction, the distinction between first and recurrent episodes is so well accepted that has become part of clinical staging algorithms.[2,55] Clinical staging algorithms focus the diagnostics of depression to early recognition (e.g. prior to first episode) and aim to prevent progression to more severe stages of the disorder (e.g. recurrent and chronic episodes) via early treatment intervention. Our current findings suggest that the presence of prior MDD episodes is not a characteristic predictive of a worse course. Prior work of our group, showed instead that the other feature, the duration of the current episode seems to better predict those with a worse course.[56] Our prior research and other studies, moreover, suggest that characteristics currently only used to define some but not all clinical stages might be associated with a worse prognosis, e.g. severity of depressive symptoms[48,57,58], disability levels experienced.[59] Furthermore, the characteristics that we found to differ between first and recurrent depressive patients might be another indicator for characteristics that are associated with progression. Age at onset and family history have prior been associated with more chronic symptoms over time.[60–64] Patients that present with those characteristics could be at risk for further recurrent/chronic episodes and thus could

be the appropriate candidates for intensified treatment to prevent recurrences/chronicity to develop.

In the current paper we examined whether the distinction in first versus recurrent MDD episode patients is associated with clinical progression of the disease (e.g. recurrent episodes being associated with worse clinical presentation and episode prognosis). Progression, however, can also be measured in other ways. For instance, at a pathophysiology level it could be examined whether recurrent depression is associated with more dysregulation in biological mechanisms. The latter was examined by our research group, and no association was found between episode number and dysregulation in the hypothalamic-pituitary axis, inflammation, brain derived neurotrophic factor, or vitamin D levels.[65] Moreover, from a patient's perspective a recurrent episode is a vastly different experience than a single episode, and expectations and self-perspective may chance due to recurrences. For patients a recurrent episode is progression of disease, even if we cannot find progression at a clinical or pathophysiological level. The differences that we found in the clinical presentation of first- and recurrent episode patients, could be of relevance for both patient and clinician as they might indicate that in first-episode patients treatment needs to focus on the recent life-event experienced, and first-episode patients with a young age at onset of high family-risk are at risk for developing recurrent episode and in these patients intensified treatment to prevent recurrences might be indicated.

The strength of the current study is represented by the availability of a large and well-characterized sample that could be followed up for two years. This allowed us to specifically select patients with a recent-onset MDD while removing bias due to duration of symptoms, which is strongly associated with a worse clinical profile and course. A limitation of this study is that because it is an observational study we could not examine the differential response to treatment of the two groups. Our course outcomes, however, still did not show differences between the two groups after an additional adjusted for baseline treatment status in a sensitivity analyses.

In conclusion, in first episode patients environmental triggers seem important, while in recurrent episode MDD patients the disorder seems more linked to inherited liability factors. Characteristics distinguishing first episode from recurrent MDD patients may provide important indications for treatment/prevention needs. Nevertheless, the 2-year course of patients with a current first- or recurrent MDD episode did not differ, suggesting that the number of experienced episodes may not be a strong clinical indicator for a progressive course of the current episode.

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