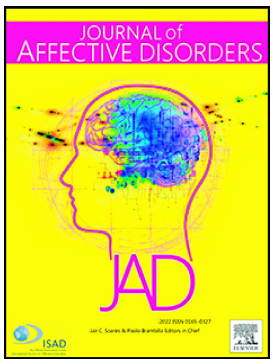

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Clinical High Risk State Of Major Depressive Episodes:

Assessment of prodromal phase, its occurrence, duration and symptom patterns by the instrument The DEpression Early Prediction-INventory (DEEP-IN).

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Abstract

Background: To decrease the incidence of major depressive episodes, indicated prevention that targets clinical high-risk individuals with first detectable signs that forecast mental disorder is a highly relevant topic of preventive psychiatry. Still little is known about the prodrome of MDE. The aim of the current study was to identify the occurrence of a clinical high-risk state of depression, its duration and symptom constellation.

Methods: Seventy-three patients with a diagnosed affective disorder in partial remission were assessed with our newly developed semi-structured extensive clinical instrument, the DEpression Early Prediction-INventory (DEEP-IN). Within DEEP-IN the course of prodromal symptoms was explored by using a life-chart method.

Results: The significant majority of patients (93.2%) reported a prodromal phase. The mean duration was 7.9 months (SD=12.5). Within the group with an identified prodromal phase, psychopathological (95.6%) as well as somatic symptoms (88.2%) were reported. Somatic symptoms showed a moderate-to-strong effect of sex with higher prevalence in females than in males (97.6% vs 73.1%; V=0.370). ~~Additionally, a small-to-moderate sex effect on duration of the prodrome with longer duration in males compared to females was found (10.7 vs. 6.1 months; r=0.205).~~

Limitations: This feasibility study had only a small sample size.

Conclusions: The majority of patients with affective disorders reported a clinical prodromal phase with both psychopathological and somatic symptoms that developed months before the onset of the depressive episode. The development of structured instruments for the assessment of depressive risk states is a promising approach for indicated prevention of depression in the future.

Introduction

Major depressive episodes (MDE) are a common and serious health condition, with 12-month prevalence rates of unipolar depression of 7.7% (6.9-8.6) and of bipolar disorders of 1.5% (1.1-2.0) as demonstrated by Jacobi et al (2014). Each year, over 700,000 people with depression die by suicide. In order to reduce the incidence of MDE and the associated high burden, early detection and prevention are of high priority for global health (WHO, 2022).

Peak of the first onset of affective disorders was reported to be around 20.5 years of age (Solmi et al., 2022). Despite functional impairment occurring in the early stages of the illness, MDE is often diagnosed with a significant delay (Sheehan et al., 2004; Cheung et al., 2017). This delay is largely caused by the lack of knowledge about the early diagnosis of the disease (Davidson et al., 1999, Cepoiu et al., 2008). Therefore, it is crucial to understand the prodrome in order to identify clear indications for early intervention in a preventive psychiatry. Currently, there is a lack of reliable instruments that comprehensively assess various dimensions associated with the prodrome of depression, including clinical and multimodal markers.

Significant progress has been made in predicting and preventing psychosis, incl. affective psychoses, over the last decades (Worthington et al., 2021). The approach of assessing clinical high-risk (CHR) states of psychosis can serve as a model for indicated prevention in psychiatry. The concept of indicated prevention involves targeting individuals who exhibit minimal but identifiable signs or symptoms of a mental, emotional, or behavioural disorder, as well as biological markers indicating a predisposition to such a disorder, even if they do not meet diagnostic criteria at the time of intervention (O'Connell et al., 2009). Important impulse for indicated prevention of mental disorders was earlier given by conceptual advancements in prevention research (Bell, 1992; Yung et al., 1996) and a paradigm shift from a deterministic prevention approach in somatic medicine oriented on well-defined cause–effect-relations towards a probabilistic approach based on risk factors (Gordon, 1983). Extending the concept of primary prevention, this new approach distinguishes between indicated, selective, and universal prevention, with the primary goal of reducing the occurrence of a disorder (Ruhrmann et al., 2010). This approach has gradually gained recognition and acceptance in both scientific and clinical settings since the 1990s. As an adaption to mental disorders, the definition of indicated prevention was broadened to enable the development of criteria that can include clinically significant signs and early symptoms of pathological mental changes, as long as the clinical picture does not meet diagnostic criteria for the manifest disorder (Mrazek and Haggerty, 1994).

As a first necessary step before the initiation of prospective studies with psychosis high-risk-individuals and inclusion of CHR states of psychosis into the research criteria of The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013) and European guidelines (NICE, 2014, DGPPN, 2019), extensive retrospective research has been conducted on the prodrome and risk states of psychosis (Ebel et al., 1989; Häfner et al., 1992, Yung et al., 1996; 1998; McGorry, 2002; Pantelis et al., 2003; Schultze-Lutter et al., 2007a, 2007b, 2008, 2009a, 2009b, 2010; Schmidt et al., 2014; Fusar-Poli et al., 2018;). Similar to psychosis, depression is supposed to arise from a complex interplay of social, psychological, and biological factors (Remes et al., 2021). While predominantly psychosis research faced challenges in operationalizing the prodromal or clinical high-risk state of the condition in the past (David, 2004; Huber, 1995;

Larsen et al., 2001), the complexity and heterogeneity of depression has been used as an argument against such operationalization. Nevertheless, recent studies on early detection of psychosis and the development of CHR of psychosis criteria with the support of advanced precision medicine techniques have shown that this complexity may in opposite offer opportunities to enhance individual-level prediction (Schultze-Lutter et al., 2015; Meisenzahl et al., 2020; Koutsouleris et al., 2021a, 2021b).

In the field of MDE, the concept of early recognition, in particular the development of appropriate clinical tools and early treatment still remains poorly addressed (Benasi et al., 2021). However, the identification of individuals at risk for MDE with appropriate clinical tools underlines the opportunity for future indicated prevention strategies in the field of affective disorders.

The still limited studies on the prodromal stage of MDE already point to a prodromal phase and a pronounced prodromal symptomatology before the onset of the overt MDE. The investigations of possible prodromal phases and their characteristics have been carried out with different methods, and it is a scientific field that is constantly evolving. The approaches of the individual research groups differ, whereby most researcher understandably pursued a retrospective approach. This retrospective approach consisted of examining patient records and/or conducting structured or semi-structured interviews, in which symptoms were queried. The period of time the interviewers investigated for a prodromal phase was chosen differently. The patient groups were composed in terms of their disease phases and frequently included patients with both unipolar and bipolar disorders (Fava et al., 2007, Benasi et al., 2021).

Regarding the definition of the prodromal phase in several previous studies, it was defined as a mild form of psychiatric symptoms of MDE, or assessed by unspecific symptoms – that, potentially depending on its stage (Otto et al., 2022), more or less differ from typical depressive symptoms of manifest depression. Molnar et al. (1988) considered the prodromal phase an early marker of MDE by referring to the **time interval between the onset of first signs and symptoms of mental distress, and the onset of the characteristic manifestations** of the fully developed illness. Pede et al. (2017) and Iacoviello et al. (2010) described the prodromal phase as the **period between the occurrence of at least one symptom, which must be consistently present until the acute phase,** and manifest depression. Similarly, Sohoo et al. (2012) asked patients and relatives about any symptoms antedating the onset of the full-blown episode **fixed by six months** or less, which were regarded as prodromal symptoms of the illness episode. The different definitions of the prodromal phase are presented by Benasi et al. (2021) in his recent review indicating a distinct prodromal phase before the onset of depression. In summary, regardless of the time period chosen, a prodromal phase was identified in the vast majority of patients in the studies to date (e.g. Fava et al., 1990; Sahoo et al., 2012; Pede et al., 2017).

The **duration of the prodromal phase** of MED varied greatly between the studies, from less than a month to several years (Benasi et al., 2021). Pede et al. (2017) found a mean prodromal phase duration of 115 days (range: 20-300 days). Sahoo et al. (2012) reported a prodromal phase of 42.7 days (range: 1-150 days). One prospective study presented the duration of the prodromal phase of 44.83 days (Iacoviello et al 2010). These differences are partly due to the above different definitions time spans and, thus, observation periods of the prodromal phase.

As regards the prodromal symptoms of MDE, the vast majority of studies have focused on psychopathological signs (Benasi et al., 2021). In their excellent review, Benasi et al. (2021) grouped the prodromal symptoms described in the studies into (1) cognitive (2) emotional (3) physical and (4) psychomotor signs. Of these, anxiety, tension, irritability and a remarkable number of physical symptoms, such as reduced energy, fatigue, sleep disturbances and somatic complains, were the most commonly reported signs (Benasi et al., 2021). In the overall view of the studies to date, also physical complaints as early signs of MDE were already described in the first studies in the sixties (Hopkinson 1965; Widmer & Codoret 1978; Codoret et al 1980; Wilson et al 1983; Fava et al 1990; Young et al 1991; Eaton et al. 1997; Perlis et al. 1997; Iacoviello et al 2013; Pede et al. 2017). Interestingly, a first study (Snipe et al., 2023) using Ecological Momentary Assessment showed a significant increase in repetitive negative thinking (worry, negative thoughts about the self) as the most sensitive early sign of recurrence.

In parallel to the clinical examination of the prodrome, overarching framework concepts on the development and course of psychiatric disorders are evolving. Especially a transdiagnostic staging model was introduced in the first consensus statement from an International Working Group on Transdiagnostic Clinical Staging in Youth Mental Health by Shah et al. (2020), based on the transdiagnostic concept developed by McGorry et al. (2006). Referring to this concept, Hetrick et al. (2008) described an earlier stage for affective disorders characterized by "mild, non-specific" or "subthreshold symptoms of anxiety or depression" with a decline in the Global Assessment of Functioning (GAF) score (<70) and neurocognitive changes associated with affective disorders as indicative of the prodromal phase, while Otto et al. (2022) suggested an earlier (stage 1a) and later (stage 1b) stage of progressing symptom severity. Fava and Tossini (2007) adapted the concept of a staging model specifically for depressive disorders, conducting an overview of studies on “early stage” of depression. The “first stage” of depression defined by Fava was a prodromal phase that showed mainly symptoms like anxiety, irritability, loss of interest and sleep disturbances (Fava and Tossini, 2007).

In the study presented here, first we used a retrospective approach with a new semi-structured interview, the DEpression Early Prediction-Inventory (DEEP-IN) questionnaire, in order to interview stabilised patients with affective disorders for a possible prodromal phase of MDE, its duration and its symptoms. Secondly, we aimed to examine any potential impact of sex on the duration and presentation of symptoms in the prodromal phase. Thirdly, we investigated whether specific patterns of prodromal symptoms were associated with specific sociodemographic and disease-related factors.

Methods

Study sample

Patients were consecutively recruited from the in- and outpatient units of the Department of Psychiatry and Psychotherapy at the Ludwig-Maximilian University in Munich according the inclusion and exclusion criteria by the trained clinician (E.M., V.S.). Patients between 18 and 65 years-of-age and with a past or current ICD-10 diagnosis of unipolar depressive disorder (F.32) or recurrent

depressive disorder (F33) or bipolar disorder (F31), who were in partial remission (BDI II <20) and had the ability to provide written informed consent, were invited to participate (Köllner and Schauenburg, 2012). Exclusion criteria were insufficient German language skills, comorbid diagnosis of an organic mental disorders (ICD-10: F0.xx), comorbid diagnosis of schizophrenia and delusional disorders (ICD-10: F2.xx), comorbid diagnosis of pervasive developmental disorders (ICD-10: F84), acute suicidality, medical history of craniocerebral trauma or unconsciousness ≥5 minutes and medical history of organic or neurological disease with impairment of brain function. Data of 73 patients were available for analyses. All patients were included in the study, after written informed consent. The study was approved by the Ethics Committee of the Ludwig-Maximilian University (EK524-15).

Assessments

The semi-structured clinical interview DEpression Early Prediction INventory (DEEP-IN), supported by the life-chart method (Honig et al., 2001; Supplementary Figure 1), was used to explore occurrence and frequency of the prodromal phase, its duration, signs and symptoms, and clinical course of the affective disorder. The design of DEEP-IN follows that of the Interview for the Retrospective Assessment of Onset of Schizophrenia (IRAOS) developed by Haefner et al. (1992). The comprehensive questionnaire was used to collect detailed information on the prodromal development of psychosis, its onset and early course. The duration of the interview was 90-120 minutes. The interview was divided into different sections, described below.

The first section of DEEP-IN contained sociodemographic information, including sex, age, marital status, education, occupation, income, nationality/migrant status, and native language.

The second section registers the complete medical history (number and begin of MDE, use of the health care system etc.). Additionally for the validation of the diagnosis and the course of the disease episodes, the patient's medical records and doctors' letters were examined. Moreover, current medication as well as information on physical illnesses and compliance were recorded.

In the third section, the investigation of possible prodromal symptoms of depression was conducted supported by the life-chart method according to Lyketsos et al. (1994) that was found to perform well in depressive patients (Honig et al., 2001). In a first step, trained clinicians (E.M., V.S.) recorded the number of previous MDEs, their onset and duration. Patients were asked to represent their course of disease graphically in a time-lifeline (onset: month/year; end: month/year; Supplementary Figure 1). The onset of the prodromal phase was defined as the time at which patients noticed first somatic or psychopathological symptoms as subjectively perceived initial impairments in their well-being. The end of the prodromal phase was defined as the time at which the diagnosis of the manifest affective disorder was made by a physician. To improve the validity of recall, the best remembered MDE by patients was identified as the 'index episode'. In patients with bipolar disorder, the selected 'index episode' was required to proceed the first (hypo) manic episode.

In the fourth section, the index episode was used to identify prodromal symptoms in patients. This was done by asking patients to describe the index period in more detail, using a second graphical time-lifeline. This graph allowed to capture the temporal span before the index episode. The exploration focussed on the first individually remembered changes of wellbeing, days, weeks. months or even years before the index MED.

At the beginning of the interview, the patient was asked to speak freely instead of initially presenting a list of symptoms. After the detailed clinical and in-depth exploration by the clinician, the symptoms were documented.

Statistical analysis

First, descriptive statistics of study variables were provided, and comparisons of the course of disease according to sociodemographic variables were performed. Second, means and standard deviation (SD) of the duration of prodromal phase in months by sex, course of disease and reported index episode were calculated. Third, a frequency analysis was performed for the evaluation of the prevalence of prodromal phase and prodromal symptoms. To this aim, psychopathological and somatic symptoms were dichotomized into presence and absence of symptom.

For group comparisons, t-tests for normally distributed interval data with Cohen's d as effect size measure, Mann-Whitney U test for ordinal or non-normally distributed continuous data with Rosenthal's r as effect size measure, and χ^2 tests for categorical variables with Cramer's V as effect size measure were calculated. Considering the small sample size, effect sizes were prioritised in the interpretation of comparative analyses because they are regarded as less effected by sample size (Sullivan and Feinn, 2013). Furthermore, because this feasibility study was only used to investigate possible fruitful targets for a subsequent larger study, because of the critiques on the P-value (e.g., Amrhein et al., 2019) and because of our sample size-related emphasis on effect sizes, we did not adjust for multiple testing. The statistical Package for the Social Sciences (IBM SPSS Statistics, version 28.0) was used for these data analyses.

A latent class analysis (LCA) was performed using package poLCA for R (Linzer and Lewis, 2011) to determine possible subgroups of reported prodromal symptoms. LCA is used to identify qualitatively different subgroups within populations (Nylund et al 2007), and is particularly appropriate for binary data, such as the presence or absence of symptoms. Following recent criteria for the final model selection (Weller et al 2020), the fit of various models with 2-6 classes was compared using two statistical information criteria (ICs) - Bayesian information criteria (BIC) and Akaike information criterion (AIC), in which lower values suggest better model fit (see Supplementary Table 2). Furthermore, theoretical interpretability was considered in the choice of the best solution (Muthén & Muthén, 2000; Nylund et al., 2007).

Finally, using R statistics, a multivariate logistic regression analysis was performed to investigate the association of demographic and disease-related factors with LCA classes of symptoms. The following variables were included in the analysis simultaneously: sex, age, educational level, marital status, living alone, children, net income, duration of prodromal phase, and index episode.

Results

Characteristics of the study sample

Thirty-three patients (45.2%) were inpatients and 40 patients (54.8%) were outpatients. Twenty patients (27.4%) reported their first MDE (ICD10 F32.x), 51 patients (69.9%) had recurrent MDEs (ICD10 F33.x) and two patients (2.74%) had a bipolar disorder with a current MDE (ICD 10 F31.x).

Table 1 shows the main characteristics of the study sample by disease course (first episode vs recurrent). The mean age was 39.3 years (SD = 10.45; range 20-63 years), median was 38 years (25^{th} and 75^{th} percentiles: 31 and 47), women were more frequent than men (63.0% vs 37.0) (*Table 1*). The majority of the patients were German native speakers, single, or separated or divorced (52.0%), childless (68.8%), had at least twelve years of schooling (74.0%), were currently employed (57.5%), and had a net income of 850 to 2,500 Euros per month. About half of the patients (49.3 %) lived alone. 42.2% of all treated patients received monotherapy with antidepressants (SNRI, SSRI, NDRI). 55.6% of patients received antidepressive therapy with an additional augmentation strategy by a second antidepressant (SNRI, SSRI, NDRI,NaSSA), or antipsychotics (Quetiapine, Olanzapine, Aripripazole) or mood stabiliser (lamotrigine, valproate, lithium). Comorbid somatic diseases were reported by 23.3% of all in the study included patients, 2.7% patients reported two somatic illnesses. Reported were illnesses as: thyroid diseases, chronic inflammatory diseases, allergy or asthma, musculoskeletal illnesses, rheumatic disease, diabetes, and heart valve insufficiency.

INSERT TABLE 1 HERE.

Occurrence and frequency of a prodromal phase

A prodromal phase was reported by 93.2% of patients (n = 68). This included 90.0 % of patients with a first manifestation (18 of 20 patients) and 94.3 % of patients with a recurrent depressive or bipolar disorder (50 of 53 patients). With regard to sex, 96.3% of males (26 of 27 male patients) and 91.3% of females (42 of 46 female patients) presented a prodromal phase.

In the group with recurrent depression, 11.3% had chosen the first depressive episode as the index episode, while 30.2% reported the second episode. Most patients (58.5%) best recalled a later depressive episode and had chosen this as the index episode.

Duration of the prodromal phase

The mean total duration of the prodromal phase of the index episode was 7.2 months (SD 12.5). There was only an indication of a small difference in duration between first-episode patients compared to recurrent disorders, with a longer duration prior to first episodes. The patient's choice of the index phase (first or later episode),

however, did not indicate an effect (*Table 2*). Sex had the most prominent, i.e., a small-to-moderate effect on the reported duration, with longer duration of the prodromal phase in males (10.75 months vs 6.11 months with Rosenthal's r=0.205), in particular in prodromes of a recurrent depressive episode (9.40 months vs 5.23 months with Rosenthal's r=0.212) (*Table 2*). Furthermore, age was unrelated to the duration of the prodrome (Kendall's tau = -0.087).

INSERT TABLE 2. HERE.

Characteristics of prodromal symptoms

The prevalence of reported somatic and psychopathological symptoms in total and by sex is presented in *Table 3*. The most frequent prodromal symptoms were sleep disturbances, followed by fears and worries, sadness, depressed mood, exhaustion, tiredness and appetite and weight changes. Of the 68 patients reporting a prodromal phase, 60 (88.2%) described somatic symptoms and 65 (95.6%) psychopathological symptoms. Sex had the strongest, albeit moderate effect on somatic symptoms, with female patients being significantly more likely to report somatic symptoms. The overall frequency of psychopathological symptoms did not differ between the sexes. On item level, a small effect of sex for headache and a nearly moderate effect for emotional lability was found; both showed consistently higher frequencies in females. Regarding the type of symptom occurring first in the prodrome of the index phase, 37 patients (54.4%) described a simultaneous occurrence of psychopathological and somatic prodromal symptoms. Only 26 patients (33.8%) reported solely psychopathological symptoms, and eight patients (11.8%) reported solely somatic prodromal symptoms as the first sign. A difference in the occurrence of psychopathological or somatic prodromal symptoms of only small effect size was detected in relation to the index phase (Chi-square=1.317, df=2, p=0.518, Cramer's V=0.139).

INSERT TABLE 3. HERE.

Latent class analysis of prodromal symptoms

All 27 prodromal symptoms listed in Table 3 were included in the LCA. The two-class solution with the best model fit (AIC=1426.798; BIC=544.432) was selected (Figure 1). *Class 1* (n=26; 38.2%) is characterised by higher likelihood of somatic complaints with fatigue and inflammation, low energy and anhedonia. Moreover, social withdrawal and the feeling of being overwhelmed were frequently reported (*Figure 1, Supplementary Table 1*). *Class 2* (n=42; 61.8%) was characterised by higher likelihood of psychopathological complaints including rumination, tension, emotional lability and restlessness. Sleep disturbances, poor appetite, headache and musculoskeletal complaints, fears and poor concentration did not differ significantly between the two classes (*Figure 1, Supplementary Table 1*).

INSERT FIGURE 1 HERE.

Comparisons of sociodemographic and disease-related factors between the two LCA classes revealed that patients in C*lass 2* (n=26; 38.23%) were more likely to be male, living alone and having a recurrent disorder with small and small-to-moderate effects (*Table 4*).

INSERT TABLE 4 HERE.

The logistic regression analysis revealed a significant model (AIC=103.96; McFadden=0.050; Nagelkerke=0.087). It indicated that living alone and financial difficulties were the most likely predictors of membership to the classes of prodromal symptoms, with patients with lower income and living alone being more likely members of class 2; yet, results were only at statistical trend level ($p<0.1$) (*Table 5*). Duration of the prodromal phase and course of disease were unlikely predictors of class membership (*Table 5*).

INSERT TABLE 5 HERE.

Discussion

The aim of the current study was to identify the occurrence and frequency of an initial prodromal phase of MDE, its duration and symptom constellation with the DEEP-INventory. Further, we explored sex differences in the prodromal phase presentation, and the presence of specific symptom patterns or classes.

The significant majority of patients (93.2%) reported a prodromal phase with mean duration of 7.9 months (SD=12.5). Both, psychopathological as well as somatic symptoms were reported. The most common prodromal symptoms were sleep disturbances. This was followed by fears and worries, sadness, depressed mood, exhaustion, tiredness and appetite as well as weight changes. There was a moderate sex effect in the duration of the prodromal phase with male patients showing a longer prodromal phase compared to female patients. Another small-to-moderate sex effect showed in somatic symptoms that were more prevalent in female than in male patients. Furthermore, two different prodromal patterns were detected: *Class 1* was characterised by higher likelihood of somatic complaints with fatigue and inflammation, low energy, anhedonia, social withdrawal and feeling of being overwhelmed. *Class 2* was characterised by higher likelihood of psychopathological complaints like rumination, tension, emotional lability and restlessness.

Occurrence, frequency and duration of the prodrome of major depressive episodes

Our findings of a high **prevalence** of a prodromal phase in our sample is within the prevalence range reported from previous studies (Benasi et al. 2021). However, the range of frequencies is relatively wide from 26% to 100%, and certainly related to the various chosen time periods and definitions of the prodromal phase. The lowest prevalence rates of prodromal phases of 26% and 29.5% were found in a study by Hopkinson (1963) and in the retrospective evaluation of possible prodromes in depression in a long-term population-based study from Eaton et al. (1997). Hopkinson (1963) described the prodromal phase using only medical records; while Eaton et al. (1997) defined the prodromal phase as a precursor period with mild depressive symptoms. Similar our findings are the results of Fava et al. (1990) and Pede et al. (2017) with an occurrence of 100%, who used a comprehensive clinical interview of remitted patients with major depression. Similarly, the study of

Sahoo et al. (2012) investigated the prodromal phase by a retrospective interview of prodromal symptoms and reported a prodrome in 93% of the patients.

In the current study a mean duration of the prodromal phase was of 7.2 months with a range up to several years (5.9 years). We would like to note that up to now only a few studies have systematically investigated the duration of the prodromal phase and that is a methodological challenge. To this aim, we had chosen the well-established life-chart method (Häfner et al. 1992; Honig et al., 2001) that assesses the individual duration retrospectively from the depressive index episode to the time point when the patient describes substantial mental or physical changes. The existing range of the duration of the prodromal phase of depression in literature is likely due to inclusion of different diagnostic groups and differences in the definition of the prodromal phase (Benasi et al., 2021).

Clinical picture of the prodrome of major depressive episodes

Both, psychopathological *and* somatic symptoms were reported by patients with an identified prodromal phase. Sleep disturbances were most frequent, followed by fears and worries.

Our psychopathological prodromal profile seems in line with the findings of another study (Benasi et al 2021). In particular, the frequent report of fears and worries in our study is in concordance with earlier reported generalized anxiety symptoms as a commonly reported prodrome (Benasi et al 2021). For example, Fava et al. (1990) identified generalized anxiety and irritability as the most common prodromal symptoms, and Pede et al. (2017) suggested that not classical depressive symptoms but other symptoms, such as irritability and insomnia, were core components of the prodrome.

Importantly, the majority of our patients (88%) spontaneously reported somatic prodromal symptoms. This finding underlines the importance of the exploration of somatic symptoms in the prodromal phase because of their possible prognostic value of transition into the manifest MDE. Somatic symptoms were already proposed to be coexistent with the well-known affective, behavioural, and cognitive symptoms of depression (Kapfhammer 2006) and may be proxy indicators for underlying pathophysiological processes (Aletemus et al 2014). Earlier, investigation of somatic symptoms before depression onset were mostly based on medical records (Cadoret et al 1980; Wilson et al 1983), focused on particular one or several somatic symptoms (Wilson et al. 1993; Perlis et al 1997) or investigated the special condition of postpartum depression (Chaudron et al 2001; Okun et al 2009; Okun et al 2011). The relevance of physical complaints was pointed out by a review of Kapfhammer (2006) who stated that, from a primary care perspective, this unmet diagnostic need is deplorable, as the main mode of presenting a depression is by reporting somatic symptoms. This somatic presentation, however, significantly contributes to low rates of recognition in primary care (Kapfhammer 2006). Yet, the vast majority of the work in the area of the prodromal phase of depression has focused mostly on psychopathological signs with little attention to the exploration of heterogenic somatic early signs (Benasi et al 2021). As our analysis supports that physical complaints can be important prodromal signs, physical complaints should be considered in scientific studies of the prodromal phase of depression in future.

Sex differences of the prodromal phase of depression

Our analyses revealed some potentially meaningful sex effects of moderate and small-to-moderate size. Firstly, male patients had a significantly longer prodromal phase, a result that should be urgently investigated in larger studies. There are no studies on this so far, so we will have to wait for further studies to carry out this comparative analysis. It is remarkable that male patients notice and name precisely the significant changes. The male patients thus have the same awareness for intrapsychic and physical processes as female patients and experiences this prodromal state over a significantly longer period of time.

Secondly, both groups showed predominantly somatic *and* psychopathological symptoms, but females reported significantly more physical signs in the prodromal phase, which is an interesting result. The fact that depression is diagnosed less often in male was partly attributed to the fact that they seek medical help less often than females (Möller-Leimkühler 2002). Conversely, it could be speculated that the higher incidence of somatic symptoms in women might bring them into contact with doctors more often, which might enhance an earlier diagnosis.

Latent class analysis of prodromal symptoms

The result of this preliminary study remarkably show two symptomatically different prodromal patterns. Class 1 pattern was characterised by higher likelihood of somatic complaints with fatigue and inflammation, low energy, anhedonia, social withdrawal and feeling of being overwhelmed while pattern of Class 2 was characterised by higher likelihood of psychopathological complaints including rumination, tension, emotional lability and restlessness.

The classification of depressive disorders is controversial (Joyce 2008; Gaebel et al., 2020). In the current diagnostic system, the model is unitarian and the earlier binary model was dropped primarily because no clear demarcation between two types of depression (melancholic and with neurotic/reactive) could be established (Kessing 2007). Longitudinal studies are needed to reveal, which symptom may be a precursor of possible subtypes of depression. From another perspective, the investigation of syndromal clusters already in the prodromal phase may help to identify possible later clinical subtypes. Interestingly, the predominantly physical complaints detected in our feasibility study seems to form a separate prodromal 'entity' in this feasibility study, and it remains to be studied, if they are indeed more related to the hypothesized early stage (1a) of the prodrome of MDE rather than to the later, more progressed stage (1b) that is assumed to consist of more depression-like symptoms and the emergence of functional decline (Otto et al., 2022).

Strength and limitations

To our knowledge, this is the first study evaluating the prodromal phase for depression and its duration by using a semi-structured comprehensive clinical interview, DEEP-IN, supported by the life-chart method and

including comprehensive exploration of somatic and psychopathological symptoms of the prodromal phase and evaluating sex differences.

As a limitation, these findings of this feasibility study are based on a small study sample. Further studies with larger case numbers are needed. In addition, retrospective elicitation of remembered prodromal symptoms always have a risk of recall bias. To reduce effects of memory problems, patients could choose the episode they remembered best as the index episode of a possible prodromal phase. This approach has been widely accepted as an important starting point in research on the prodrome of psychosis and has led to important results (Häfner 1998, Huber 1979, Janzarik 1988; Young et al. 1996).

Another limitation might be the inclusion of patients with bipolar disorders, as these might slightly differ in their prodrome of MDEs (Benasi et al., 2021). Yet, bipolar disorders frequently start with MDE (McIntyre et al., 2020), and prevention of the progression of a risk state for MDE might as well prevent both uni- and bipolar affective disorders.

Further, the missing adjustment for confounding variables might be perceived as potentially introducing bias; yet, the clearly heterogenous nature of the sample with respect to the course of the disorder and sociodemographic variables makes systematic bias seem unlikely.

Finally, for the retrospective nature of our study, we cannot completely rule out that the assessed prodromal periods partly included the very early phase of the manifest MDE, as an exact dating of the onset of the manifest MDE was not always possible. However, as the diagnosis of MDE can only be made in retrospect, i.e., after the persistence of diagnostically relevant symptoms for two weeks, a certain overlap of the prodrome or risk state, and the manifest episode within this period seems unavoidable.

Conclusions and Outlook

Our results show a high prevalence of a prodromal phase of MDE with a duration of several months that, alike in psychoses, offers the opportunity to intervene early in terms of an indicated prevention. In line with psychosis research, we suggest the term '**clinical high-risk of depression (CHR-D)**' for future use in prospective studies. For the first time, it was described that the duration of the prodromal phase differs between male and female patients, with a longer prodromal phase in males and, in addition, more physical prodromal symptoms in female patients. Both results should be urgently investigated in larger studies as they may affect preventive measures. Finally, future studies should examine syndromal stratifications of the prodrome detected in this investigation to capture possible subtypes of depression and/or different risk stages. The final goal is the development of valid, reliable as well as economical clinical and multimodal instruments (clinical interviews and self-rating questionnaires) for the early detection of MDE in various settings with special conceptual focus on the lifespan, including the transition phase of early adulthood as well as older age. This developmental perspective is already well advanced in the field of psychoses (Schultze-Lutter et al 2015, Koutsouleris et al. 2021) and encourages the transfer to the to the field of affective disorders.

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Individual author contributions

EM and FSL conceptualized and designed the study. EM and VS conducted the study. NW and EM conducted the analysis and drafted the manuscript. GSK, EG, UD, TH, GR, MR, LD, CT, CK, CKl and SR were involved in interpretation of data, discussion of the results, and in reviewing and editing of the manuscript. All authors revised it critically for important intellectual content and gave final approval of the version to be published.

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Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Eva Meisenzahl reports financial support was provided by Heinrich Heine University Düsseldorf. Eva Meisenzahl reports a relationship with Heinrich Heine University Düsseldorf that includes: employment. Board member of the journal of affective disorder

Table 1. Descriptive characteristic of the study sample (in total and by course of affective disorder, N=73 (%)).

Variables	**Total (N=73)**	**First episode N=20 (27.4%)**	**Recurrent * N=53 (72.6%)**	**χ^2(df)/F; *p***
Age, mean (SD)	39.38 (10.19)	36.85 (9.32)	40.36 (10.85)	T=-1.424; *p*=0.248
Sex, n (%)				
– Male	27 (37%)	7 (25.9%)	20 (74.1%)	χ^2(1)=0.047;
– Female	46 (63%)	13 (28.3%)	33 (71.7%)	*p*=0.829
First Language				
- German	64 (87.7%)	16 (80.0%)	48 (90.6%)	
- Other European	9 (12.3%)	4 (20%)	5 (9.4%)	χ^2(1)=1.500;
				p=0.201
Highest school education				
– Not completed school education	3 (4.1%)	-	3 (100%)	χ^2(2)=2.012; *p*=0.366
– Lower secondary education	16 (21.9%)	6 (37.5%)	10 (62.5%)	
– Higher secondary education	54 (74%)	14 (25.9%)	40 (74.1%)	
Marital status				
– Married	18 (24.6%)	7 (38.9%)	11 (61.1%)	χ^2(3)=5.522;
– Steady partnership	17 (23.3%)	7 (41.2%)	10 (58.8%)	*p*=0.137
– Single	29 (39.7%)	5 (17.2%)	24 (82.8%)	
– Divorced	9 (12.3%)	1 (11.1%)	8 (88.9%)	
Children				
– Yes	20 (27.4%)	6 (30.0%)	14 (70.0%)	χ^2(1)=0.388;
– No	44 (60.3%)	10 (22.7%)	34 (77.3%)	*p*=0.533
– n.n.	9 (12.3%)			
Living conditions				

– Living alone	26 (35.6%)	7 (26.9%)	19 (73.1%)	$\chi^2(2)=0.040$;
– Living with a family member	37 (50.7%)	10 (27.0%)	27 (73.0%)	$p=0.980$
– Living with other flat member	10 (13.7%)	3 (30.0%)	7 (70.0%)	
Employment status				
– Employed	42 (57.5%)	14 (33.3%)	28 (66.7%)	$\chi^2(7)=5.298$;
– Unemployed	13 (17.8%)	3 (15.0%)	10 (76.9%)	$p=0.624$
– Student	12 (16.4%)	3 (25%)	9 (75.0%)	
– Retired	6 (8.2%)	-	6 (100%)	
Net income in Euro				
– ≤450	8 (11.8%)	2 (25%)	6 (75.0%)	$\chi^2(5)=0.408$;
– 451-850	6 (8.8%)	1 (16.7%)	5 (83.3%)	$p=0.790$
– 851-1500	14 (20.6%)	6 (42.9%)	8 (57.1%)	
– 1501-2500	18 (26.5%)	4 (22.2%)	14 (77.8%)	
– 2501-3500	16 (23.5%)	4 (25.0%)	12 (75.0%)	
– > 3500	6 (8.8%)	2 (27.9%)	4 (66.7%)	
– N.n.	5 (7.8%)			
Explored index episode				
– 1	26 (35.6%)	20 (100%)	6 (11.3%)	$\chi^2(7)=49.797$;
– 2	16 (21.9%)	-	16 (30.2%)	$p=<0.001$
– 3	14 (19.2%)	-	14 (26.4%)	
– 4	8 (11.0%)	-	8 (15.1%)	
– 5	4 (5.5%)	-	4 (7.5%)	
– 6	3 (4.1%)	-	3 (5.7%)	
– 8	2 (2.7%)	-	2 (3.8%)	

* Includes 2 patients with a bipolar disorder with a current depressive episode (ICD 10: F31.x)

Table 2. Comparison of the duration of the prodromal phase of the index episode in months between sex, course of disorder and chosen index episode, N=68.

	Duration (Mean±SD)	**None-parametric statistics; effect size (r)˜**

Sex		U=433.00;
- Male	10.75±15.47	z=-1.451; p=0.147; r=0.205*
- Female	6.11±10.05	
Course of disorder		U = 390.500;
- First episode	9.58±17.26	z = -.842; p=0.400;
- Recurrent disorder	7.22±10.23	r = 0.102
Chosen index episode		U = 522.000;
- First episode	8.79±16.06	z = -.078; p = .938;
- Recurrent episode	7.38±10.22	r = 0.009.
First episode		U = 34.500;
- Male	15.17±27.63	z=-0.142; p =0.892;
- Female	7.58±10.53	r = 0.033
Recurrent episode		U = 226.000;
- Male	9.42±16.30	z =-1.498; p=0.134;
- Female	5.33±9.97	r = 0.212*

U - Mann-Whitney U test; Rosenthal's r: r=>0.1 (small effect), r=0.3 (moderate effect) and r=0.5 and above (large effect); *indicates at least small to moderate effect.

Table 3. Somatic (in white) and psychopathological symptoms (in grey) of prodromal phase (N=68), in total and by sex n (%).

Symptom, n (%)	Total N (%)	Males	Females	χ^2(df); *p; V*
Sleep disturbances	30 (44.1%)	11 (42.3%)	19 (45.2%)	$\chi^2(1)=0.056$; $p=0.813$; V=0.029
Fears and worries	20 (29.4 %)	10 (38.5%)	10 (23.8%)	$\chi^2(1)=1.661$; $p=0.198$; V=0.156
Sadness, depressed mood	19 (27.9 %)	9 (36.45%)	10 (23.8 %)	$\chi^2(1)=0.931$; $p=0.335$; V=0.117
Exhaustion, tiredness	17 (25.0 %)	7 (26.9%)	10 (23.8%)	$\chi^2(1)=0.083$; $p=0.773$; V=0.035
Appetite and weight changes	15 (22.1 %)	4 (15.4 %)	11 (26.2%)	$\chi^2(1)=1.091$; $p=0.296$; V=0.127
Lack of energy	14 (20.6 %)	5 (19.2%)	9 (21.4%)	$\chi^2(1)=0.047$; $p=0.828$; V=0.026
Irritability, tension	13 (19.1 %)	3 (11.5%)	10 (23.8%)	$\chi^2(1)=1.564$; $p=0.211$; V=0.197
Rumination	13 (19.1 %)	6 (23.1%)	7 (16.7%)	$\chi^2(1)=0.427$; $p=0.514$; V=0.079
Emotional lability	12 (17.6 %)	1 (3.8%)	11 (26.2%)	**$\chi^2(1)=5.517$; $p=0.019$; V=0.285'**
Somatic misperception	11 (16.2 %)	2 (7.7%)	9 (21.4%)	$\chi^2(1)=2.235$; $p=0.135$; V=0.181
Social withdraw	11 (16.2%)	4 (15.4%)	7 (16.7%)	$\chi^2(1)=0.019$; $p=0.889$; V=0.017
Headache	10 (14.7 %)	1 (3.8%)	9 (21.4%)	**$\chi^2(1)=3.958$; $p=0.047$; V=0.241'**
Concentration impairment	10 (14.7	5 (19.2%)	5 (11.9%)	$\chi^2(1)=0.687$; $p=0.407$;

	%)			V=0.101
Gastrointestinal complaints	9 (13.2 %)	2 (7.7%)	7 (16.7%)	$\chi^2(1)=1.126$; $p=0.289$; V=0.129
Cardiovascular complaints	8 (11.8 %)	1 (3.8%)	7 (16.7%)	$\chi^2(1)=2.543$; $p=0.111$; V=0.193
Nervousness, restlessness	7 (10.3 %)	2 (7.7%)	5 (11.9%)	$\chi^2(1)=0.309$; $p=0.579$; V=0.067
Being overwhelmed	7 (10.3 %)	4 (15.4%)	3 (7.1%)	$\chi^2(1)=1.181$; $p=0.277$; V=0.132
Anhedonia	7 (10.3 %)	3 (11.5%)	4 (9.5%)	$\chi^2(1)=0.071$; $p=0.790$; V=0.032
Musculoskeletal complaints	6 (8.8 %)	2 (7.7%)	4 (9.5%)	$\chi^2(1)=0.067$; $p=0.796$; V=0.031
Inflammation	5 (7.4 %)	1 (3.8%)	4 (9.5%)	$\chi^2(1)=0.760$; $p=0.383$; V=0.106
Increased feelings of anger	5 (7.4 %)	1 (3.8%)	4 (9.5%)	$\chi^2(1)=0.760$; $p=0.383$; V=0.106
Obsessive/overvalued thoughts	4 (5.9 %)	0	4 (9.5%)	$\chi^2(1)=2.631$; $p=0.105$; V=0.197
Low self-esteem/self-blame	4 (5.9%)	1 (3.8%)	3 (7.1%)	$\chi^2(1)=0.315$; $p=0.574$; V=0.068
Respiratory complaints	2 (2.9 %)	1 (3.8%)	1 (2.4%)	$\chi^2(1)=0.121$; $p=0.728$; V=0.042
Libido problems	2 (2.9 %)	1 (3.8%)	1 (2.4%)	$\chi^2(1)=0.121$; $p=0.728$; V=0.042
Jaw problems/teeth grinding	1 (1.5 %)	0	1 (2.4%)	$\chi^2(1)=0.628$; $p=0.428$; V=0.096

Psychopathological symptoms	65 (95.6%)	25 (96.5%)	40 (95.2%)	$\chi^2(1)=0.032$; $p=0.858$; V=0.022
Somatic symptoms	60 (88.2%)	19 (73.1%)	41 (97.6%)	**$\chi^2(1)=9.318$; $p=0.002$; V=0.370***
First prodromal symptom				
Somatic symptom	8 (11.8%)	5 (19.2%)	3 (7.1%)	**$\chi^2(2)=9.576$; $p=0.008$**
Psychopathological symptom	23 (33.8%)	13 (50.0%)	10 (23.8%)	**V=0.375***
Both somatic and psychopathological symptoms	37 (54.4%)	8 (30.8%)	29 (69.0%)	

*Significance level <0.005; ‘significance level <0.05;

Interpretation of effect size: V = 0.1’ – small, V = 0.3* – medium, V = 0.5- large.

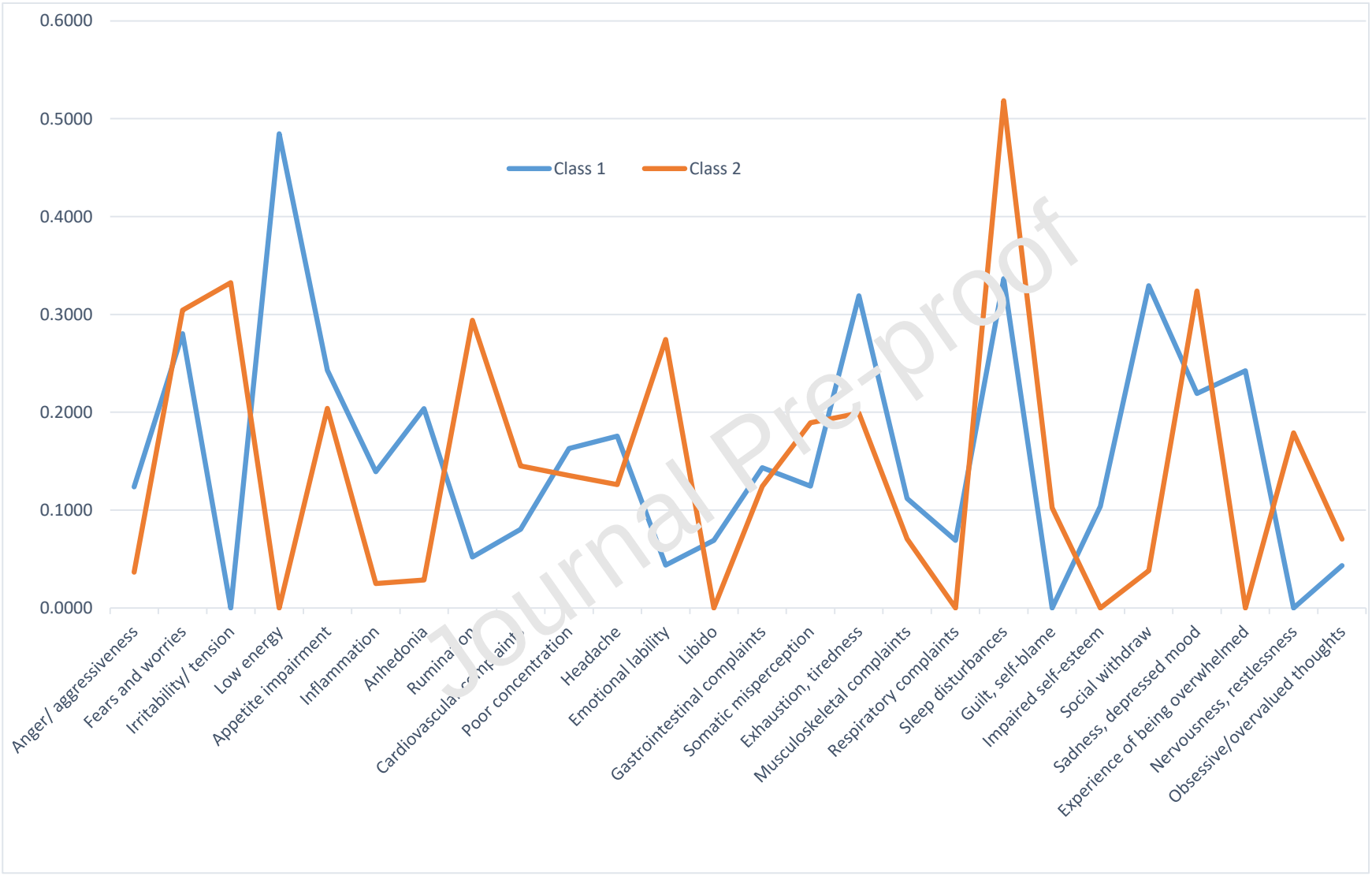

Figure 1. Prodromal symptoms - probability estimates of the two-class solution.

Table 4. Descriptive statistic, two classes of prodromal symptoms

Variables		**Class 1 (n=42)**	**Class 2 (n=26)**	**Statistics; effect size**
Age in years (mean; SD)		38.83±10.32	40.23±9.88	W=492.5; p=0.503
Sex				
– Male	26	14 (53.8%)	12 (46.2%)	$\chi^2(1)=0.641$,
– Female	42	28 (66.7%)	14 (33.3%)	p=0.423; V=0.128
Years of school education				
– =>Higher secondary education	51	32 (62.75%)	19 (37.25%)	$\chi^2(1)=0.083$,
– <Low secondary education	17	10 (58.82%)	7 (41.18%)	p=0.773; V=0.035
Marital status				
– Married / in relationship	32	21 (65.63%)	11 (34.38%)	$\chi^2(1)=0.135$,
– Single/Divorced	36	21 (65.63%)	15 (44.67%)	p=0.713; V=0.075
Children				
– No	49	29 (59.18%)	20 (40.82%)	$\chi^2(1)=0.181$,
– Yes	19	13 (68.42%)	6 (31.58%)	p=0.671; V=0.085
Living conditions				
– Living alone	23	11 (47.83%)	12 (51.17%)	$\chi^2(1)=2.037$,
– Living with a family, Shared apartment	45	31 (68.89%)	14 (31.11%)	p=0.153; V=0.205
Employment status				
– Employed	50	30 (60.0%)	20 (40.0%)	$\chi^2(1)=0.047$,
– Unemployed	18	12 (66.67%)	6 (33.33%)	p=0.829; V=0.060
Net income in categories (range 1 to 6**; mean ± SD)	63	3.84 [1.53]	3.6 [1.38]	W=528; p=0.461
Duration of prodromal phase	68	8.02 [13.29]	7.65 [11.35]	W=575.5; p=0.710

Index episode				
- First	24	17 (70.83%)	7 (29.17%)	$\chi^2(1)=0.766$,
- Recurrent	44	25 (56.82%)	19 (43.18%)	p=0.381; V=0.138
Course of disorder				
- First episode	18	13 (72.22%)	5 (27.78%)	$\chi^2(1)=0.611$,
- Recurrent disorder	50	29 (58%)	21 (42%)	p=0.434; V=0.129

* Includes 2 patients with a bipolar disorder with a current depressive episode (ICD 10: F31.x);

**Net income categories: 1-<=450€; 2-451-850€; 3-851-1500€; 4-1501-2500€; 5-2501-3500€; 6-> 3500 €.

Table 5. Multivariate regression analysis for two LTA classes of prodromal symptoms.

	OR [95%CI]	**Estimate**	**Std. Error**	**z-value**	***p***
Age	0.97 [0.90-1.05]	-0.03	0.04	-0.72	0.471
Female (ref. male)	2.50 [0.64-10.45]	0.92	0.70	1.30	0.193
No partner (ref. partnership/married)	1.99 [0.52-8.31]	0.69	0. 70	0.98	0.325
Low education (ref. higher school education)	0.91 [0.21-3.97]	-0.09	0.73	-0.12	0.904
Unemployed (ref. employed)	1.01 [0.24-4.51]	0.019	0.73	0.02	0.987
Living alone (ref. living with partner/family)	3.41 [0.91-14.25]	1.23	0.69	1.78	0.076*
Children (ref. no children)	1.27 [0.26-6.74]	0.24	0.81	0.29	0.768
Low net income (ref. higher income)	1.54 [0.97-2.60]	0.43	0.25	1.76	0.078*
Recurrent depression (ref. first episode)	0.90 [0.08-11.95]	-0.10	1.24	-0.08	0.932
Duration of prodromal phase	1.03 [0.98-1.10]	0.03	0.03	1.15	0.252
Index episode not the first episode (ref. first episode)	0.50 [0.04-4.65]	-0.69	1.16	-0.59	0.552

Highlights

- By the majority of patients with depression a clinically prodromal phase was identified, that develops months before the onset of depression.
- Both, psychopathological as well as somatic prodromal symptoms were reported.
- The development of structured instruments (like DEEP-IN) for the assessment of depressive prodromes is a promising approach for indicated prevention of depression in the future.
- with our approach we introduce the term of the 'clinical high-risk stage of depression (CHR-D)' that can be used uniformly in the future.