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Prodromal symptoms of a first manic episode: a qualitative study to the perspectives of patients with bipolar disorder and their caregivers'

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Abstract

Background Diagnosing bipolar disorder (BD) is challenging, and adequate treatment is of major importance to minimalize the consequences of the illness. Early recognition is one way to address this. Although in clinical research the prodromal phase of BD is gaining interest, the perspective of patients with BD and their caregivers on prodromal symptoms is still lacking. The aim of this study is to gain insights in prodromal symptoms of patients with BD and their caregivers before the onset of a first manic episode.

Methods A qualitative research method was used to investigate prodromal symptoms one year prior to a first manic episode. In-depth interviews were conducted with patients with BD type I and their caregivers. Only patients with a first manic episode in the previous five years were included.

Results The prodromal symptoms from patients' and caregivers' perspectives could be clustered into seven themes, with underlying subthemes: behavior (increased activity, destructive behavior, disinhibited behavior, inadequate behavior, changes in appearance), physical changes (changes in sleep, physical signals, differences in facial expression), communication (reciprocity, process, changes in use of social media), thought (process and content), cognition (changes in attention and concentration, forgetfulness), emotions (positive emotions, more intense emotions, mood swings), and personality (more pronounced manifestation of existing personality traits).

Conclusion Patients with bipolar I disorder and their caregivers described subsyndromal manic features one year prior to a first manic episode. In addition, they recognized mood lability, physical changes and more pronounced manifestation of existing personality traits. The results of this study confirm the presence of a prodromal phase. In clinical practice, monitoring of prodromal symptoms of BD can be useful in patients with depression, especially those with a familial risk of BD.

Keywords Bipolar disorder, Prodromal symptoms, Mania, Qualitative research, Patients' perspectives, Caregivers' perspective

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Background

Bipolar disorder (BD) is a complex and severe mood disorder, characterized by alternations of (hypo)mania, depression and euthymic phases, with a high risk of recurrence, and affecting more than 1% of the population worldwide (Grande et al. 2016). In the Netherlands, the estimated lifetime prevalence is 2.1% (ten Have et al. 2023). BD is associated with a decreased quality of life for both patients and their caregivers, functional and cognitive impairment even in euthymic phases, and increased risk of physical comorbidities and mortality (Bobo 2017; Grande et al. 2016; Granek et al. 2016; McIntyre et al. 2020; Vieta et al. 2018). In addition, each subsequent episode may shorten the interepisodic interval, increase the risk of recurrence, and decrease the effect of medication (Vieta et al. 2018). To minimize these consequences, timely diagnosis and adequate treatment are essential.

Diagnosing BD can be challenging. On average, it takes six to ten years after a first contact with a care provider until a patient is accurately diagnosed with BD (McIntyre et al. 2020). This gap can partly be explained by the heterogeneous course and characteristics of the disorder. First, in a majority of individuals the disorder starts with depressive episodes, only later in time followed by the occurrence of a first (hypo)manic episode (McIntyre et al. 2020). This inevitably results in an initial diagnosis of major depressive disorder. Second, patients more often present with and report depressive symptoms rather than (hypo)manic symptoms (Phillips and Kupfer 2013; Regeer et al. 2015), resulting in underrecognition of (hypo)mania (Grande et al. 2016). A third obstacle in timely diagnostics is the masking of BD symptoms by comorbid disorders (Berk et al. 2006). In our previous studies on patients' perspectives on challenges of living with bipolar disorder and on research needs, untimely diagnosis was a major issue (Maassen et al. 2018a, b; Maassen et al. 2018b). In order to overcome the gap between the onset of the disorder and making the correct diagnosis, research is focusing on early recognition.

Current clinical staging models of BD recognize phases of mild and non-specific mood symptoms prior to the first manic episode, whether or not in combination with a positive family history of BD (Berk et al. 2017; Duffy et al. 2019; Kapczinski et al. 2014; Kupka et al. 2021). Increased knowledge of these early phases could be beneficial for making a timely diagnosis of BD. Current research to these prodromal symptoms of BD occurs from different perspectives: (1) offspring studies (e.g.Birmaher et al. 2010; Mesman et al. 2013); (2) clinical studies (e.g.Bechdolf et al. 2010; Bechdolf et al. 2014; Horwitz et al. 2010); and (3) population studies (e.g.Beekman et al. 2023; Regeer et al. 2006). The Dutch Bipolar Offspring study found that 13% of the offspring of a patient with BD developed BD, and that a (mild) depression is a predictor for BD later in life (Mesman et al. 2013). In a clinical study, Bechdolf et al. (2010; 2014) validated a profile of the *'bipolar-at-risk'* criteria (BAR-criteria). This profile includes adolescents in the age of 15–25 years, meeting at least one of following criteria in the last 12 months: (1) subsyndromal manic symptoms; (2) depression with cyclothymic symptoms; or (3) depressions and a first degree family member with BD. They found that, among help-seeking adolescents, 14.3% of adolescents meeting these BAR-criteria later developed BD, in comparison with none of those who did not meet these criteria. Several risk calculators for BD have been investigated. Hafeman et al. (2017) developed a model including measures of mood and anxiety symptoms, general psychosocial functioning, age at mood disorder onset in the bipolar parent, and age at each visit of the child. This model could predict with a 76% certainty who would develop BD in the next 5 years. The Course and Outcome of Bipolar Youth (COBY) study and the Longitudinal Assessment of Manic Symptoms (LAMS) study further validated this model (Birmaher et al. 2018; van Meter et al. 2021). In NEMESIS-1, a Dutch population study investigating the presence, onset, course, and consequences of psychiatric disorders, it was found that the occurrence of isolated manic symptoms are predictive for the development of either depression (17.9%) or mania (7.1%) (Regeer et al. 2006).

These studies all show that mood symptoms occur prior to the first manic episode and suggest that identifying people at risk for the development of BD is possible. However, most of these studies focus on children or adolescents, while in the course of BD three phases of life are recognized in which the onset occurs: early onset (age 17.3 (45%), mid onset (age 26.0 (35%) and late-onset (age 41.9 (20%) (Bolton et al. 2021).

In current research on early recognition the perspective of patients with BD on the prodromal symptoms is missing. In order to enrich the scientific basis of prodromal symptoms of BD, this in-depth qualitative study focuses on the perspective of both patients with BD and their caregivers. We aim to answer the following research question: what are prodromal symptoms of a first manic episodes from the perspectives of patients with bipolar disorder and their caregivers?

Methods

We used a qualitative research method to generate narratives, feelings, and beliefs, and to elaborate on topics to deepen the understanding of patients' perspectives. (Gray 2014; Green and Thorogood 2009).

Data collection

To explore the perspectives of patients and their caregivers, semi-structured interviews were conducted. These

interviews were based on a preliminary guide, comprising two parts: (1) creating a timeline of a patient's life, including important life events, which was used as a tool to order all information that followed in the interview; and (2) identifying prodromal symptoms one year prior to the first manic episode. In this part we asked for changes in behavior, thoughts, feelings, and physical sensations prior to that manic episode. In addition, we asked for a description of the patient's personality. The interviews took 45–60 min, were audiotaped, and transcribed verbatim. A summary of the interviews was sent to the participants for a member check. After the interviews, the participants were asked to complete two questionnaires: (1) the Questionnaire for Bipolar Disorder (QBP-NL), part B, for demographic information and information on medical history (Leverich et al. 2001); and (2) Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Rush et al. 2003). The interviewer completed the Young Mania Rating Scale (YMRS) to rate possible manic symptoms at the time of the interview (Young et al. 1978). In addition, clinicians treating these patients were asked to complete two questionnaires to confirm the diagnosis: (1) QBP-NL, part A (Leverich et al. 2001); and (2) the Bipolarity Index (Aiken et al. 2015).

The inclusion criteria for patients were (1) being diagnosed with bipolar I disorder; (2) a first manic episode in the previous 5 years; and (3) aged 18 years or older. The inclusion criteria for caregivers were (1) aged 18 years or older; and (2) involvement with the patient prior to the first manic episode. Exclusion criteria were a severe mood episode at the time of the interview for patients and insufficient command of the Dutch language and lack of an informed consent statement for both patients and caregivers. Participants were recruited at a Dutch outpatient clinic specialized in bipolar disorder. Clinicians recruited patients by inviting them after providing information about the study. In addition, flyers were distributed to every patient coming in for an appointment with their health care professional. Participants were included until data saturation was reached.

Table 1 Patients characteristics ($n=15$)

Patient Characteristics	Value
Mean age, years (range)	35.8 (20–58)
Gender, males n (%)	8 (53)
Mean years of diagnosis, years (range)	2.2 (0–5)
Mean age first depression, years (range)	27.9 (14–56)
Mean age first mania, years (range)	30.5 (16–57)
YMRS	0
QIDS-SR	8
Mean total score Bipolarity Index (range)	69.7 (55–85)

Definition of prodromal symptoms

For the purpose of this study, prodromal symptoms were defined as symptoms or signs in the time one year prior to a first manic episode while not yet meeting the criteria for a (hypo)manic episode. DSM-5 criteria for a (hypo)manic episode were used to distinguish between a prodrome and a syndromal (hypo)manic episode. The timeline created in the interview was used as a tool to determine the moment in time in which the prodromal symptoms occurred to be able to distinguish between a (hypo)manic episode and (a cluster of) prodromes.

Data analysis

Data were analyzed using a framework for thematic analysis by Braun and Clarke (2006) to identify, analyze, and report themes in qualitative data. First, we familiarized ourselves with the data by carefully reading the transcripts. Second, open coding was used to generate all prodromal symptoms, by coding quotes that reflected a prodromal symptom. Third, the initial codes were clustered into themes, which were subsequently named. All interviews were independently analyzed by two investigators/clinicians (ER and EM). Differences were discussed to reach consensus.

Two clinicians (ER and EM) analyzed the data and independently judged if the symptoms or signals could be defined as prodrome or if a cluster of symptoms met the threshold of a (hypo)manic episode. When in doubt, this was discussed to reach consensus.

Ethical considerations

According to the Medical Ethical Committee of VU University Medical Center, Amsterdam, the Netherlands, the Medical Research Involving Human Subjects Act does not apply to this study. All participants gave written consent regarding the aim of and their contribution to the study and approved of audiotaping and its use for analysis and scientific information. Participation was on a voluntary bases and they could withdraw at any time. Anonymity was ensured. This study was approved by the Altrecht Research Committee.

Results

The results are described in two parts. The first part describes the characteristics of the participants, the second presents the prodromes of a first manic episode from the perspectives of patients and their caregivers. Seven key themes emerged from the data: behavior, physical changes, communication, thought (process and content), cognition, emotions, and personality traits.

Participants characteristics

In total 15 patients and 14 caregivers participated in this study (Tables 1 and 2). The mean age of the participating

Table 2 Caregivers characteristics ($n = 14$)

Caregivers Characteristics		Value
Gender, males n (%)		5 (40%)
Relation to patient	Parent, n (%)	5 (36%)
	Partner, n (%)	8 (57%)
	Friend, n (%)	1 (7%)

patients was 35.8 (20–58), of whom 53% were men. Patients had no symptoms of a (hypo)manic episode during the interviews (score of 0 on the YMRS) and the QIDS-SR showed an average score of a mild depression. The Bipolarity Index showed a mean score of 69.7. The majority of the caregivers were partners (57%), others were parents (36%) or a friend (7%).

Prodromes

Behavior

Patients and their caregivers both recognized *increased activity* in the period prior to the first manic episode. This was expressed in an increase in social contacts by renewing old contacts or by making more appointments with a wide variety of people; an increase of work productivity and spending more time at work; getting completely absorbed by certain tasks; doing many things at the same time; and searching for more external stimuli, for example by listening to more music. As one patient said:

> *I had a hard time relaxing. An evening on the couch was really a lost evening: sitting there, on the couch, watching TV with my roommates. I was thinking: let's go do something, this is boring, let's go guys!*

Furthermore, both patients and caregivers noticed an increase of *destructive behavior*. For patients this entailed an increase in smoking and drinking alcohol and coffee, a change towards an unhealthy diet, and being more sexually active. Caregivers additionally noticed a problematic change in emails and telephone texts, such as the use of swear words or an inappropriate expression of love.

Patient and their caregivers noticed an increase of *disinhibited behavior*, for example slamming the doors or, according to caregivers, in spending more money. Patients also mentioned changes in behavior clustered as '*inadequate' behavior*. These changes entailed chaotic and impulsive behavior, resulting in not getting any work done.

In addition, caregivers noticed *changes in appearance*, for example change of clothing. To illustrate:

> *Flowers in her hair. She had those plastic flowers and she wore a flower in her hair to work every day. She felt very sexy and attractive and yes, a little over the top.*

Physical changes

Patients and caregivers mentioned physical changes prior to a first manic episode. Both recognized *changes in sleep*, in particular a shorter or lighter sleep pattern, problems with falling asleep, and a shift in circadian rhythm. Patients added a decreased need for sleep. Both patients and caregivers recognized that patients had more energy and were less fatigued. In contrast, one patients mentioned an increase of fatigue.

In addition, participants reported *physical signals*, for example physical restlessness, such as shaking and tingling, weight loss, and dietary changes.

Moreover, caregivers thought a *difference in facial expression*, a faraway look, and wide eyes were remarkable.

> *"And yes, I could tell from his eyes. [.] Yes you have to know someone really well to see it. But I saw it in his facial expression, and yes a more faraway look".*

Communication

Patients and their caregivers mentioned changes in communication prior to the first manic episode. These changes could be clustered in (1) reciprocity; (2) process; and (3) changes in use of social media. *Reciprocity* entailed not listening, being absent-minded in conversations, not paying full attention to the conversation, and not being in tune with the others. As explained by a patient:

> *Or that you could just tell something that you think 'wow, that is pretty intense what you are telling right now' but you just tell it and go on with the next topic, okay wow!*

Many participants addressed that patients started more conflicts. These conflicts were further specified by caregivers, who noticed that patients were more contemptuous and manipulative and would not listen to reason. Some patients mentioned that they became more witty and made more jokes. In *the process* of communication participants noticed that patients were talkative, talked faster, and could not get to the point. A caregiver:

> *'And that you wanted to tell, tell, tell, talk, talk, talk and that you couldn't figure it out and that we didn't know what to do with you.'*

Furthermore, an increase in *social media use*, for example sending more text messages or posting more on Facebook, was seen prior to the first manic episode.

That I am extreme with texting and that I send texts in the middle of the night and that it doesn't cross my mind to leave other people alone.

Thought

A variety of signs reflecting *the thought process* were recognized by both patients and caregivers. These signs included having many thoughts, flight of ideas, loose associations, and a chaotic way of thinking. In addition, some patients experienced that their minds were full of thoughts.

Seeing a lot of connections that other people do not see. Very creative in that sense.
Yes I noticed that (....) I created an excel file with everything I needed to bring with me, because there was just too much chaos in my head.

Moreover, participants addressed changes in the *thought content*. Patients mentioned more self-awareness and increased self-esteem, but also insecurity and indecisiveness. Caregivers mainly mentioned an increased self-esteem, a strong belief in their own ideas, and self-centeredness.

Yes, I got the feeling that I could handle more, while I am naturally insecure.

Cognition

Patients experienced changes in attention and concentration prior to their first mania. They noticed an increase, or the opposite, a decrease in focus. In addition, patients mentioned an increased distractibility and forgetfulness. Apart from hyperfocus, caregivers barely mentioned changes in attention and concentration.

Yes, I didn't really know what I was doing. I forgot a lot of things. Yes that was in the manic episode itself, but also prior that that. That really took a while.

Emotions

Changes in emotions could be categorized in: (1) positive emotions; (2) more intense emotions; and (3) mood swings. *Positive emotions* include feeling good, increased happiness, being more enthusiastic, and enjoying life more fully. Some caregivers noticed that patients felt more sexy and attractive. One patient illustrated:

Yes at a certain moment I became more cheerful. Everything made me happy, work and just everything.

In addition, both patients and caregivers noticed *more intense emotions*, such as hypersensitivity and irritability, but also mood lability. Explained by a caregiver:

What was it again, with the Tour de France. That was when I thought: [name], act normal! Because Tom Dumoulin was almost winning but then a certain Australian men won and Tom Dumoulin became second and he [the patient] started crying. I really thought: [name], it is just sports.

Furthermore, both patients and caregivers noticed *mood swings* or depressed symptoms prior to the first manic episode.

What I noticed was that every now and then I felt more down, and some time later it went a little bit better. Not so down that you could speak of a depression, absolutely not, but I noticed that sometimes I felt a little bit under the weather for a week or so. I noticed that I sometimes had these feelings.

Personality traits

The last theme of prodromes preceding the first manic episodes describes the more pronounced manifestation of existing personality traits. This could for example entail the increase of creativity in a creative person, increased perfectionism in someone who is known to be a perfectionist, or the increase in enthusiasm in someone who is an enthusiast person. As a patient described it:

"Yes, I am a extravert person. And that became more extreme, but normally I am like that as well".

Discussion

Timely diagnosis and treatment of BD is important in order to minimize the negative consequences of the illness, and research that is focusing on prodromal symptoms is needed to support this. The current study adds to insights in bipolar prodromes by studying early signals of the first manic episodes from the perspective of patients with BD and their caregivers. We found considerable overlap between the described prodromal patterns by the patients and their caregivers, but differences within the themes could be recognized as well. Overall, patients mentioned the internally noticeable signals more often, such as decrease of attention and concentration, chaotic thoughts, decreased need for sleep, and physical sensations such tingling or restlessness. Caregivers focused on the signals that are externally visible, such as changes in behavior, appearance, facial expression, and text messages. In addition, patients mentioned positive changes

(for example in mood, focus, and communication), which were not described by caregivers.

Many of the prodromal symptoms derived from this study overlap with symptoms of a manic episode. Still, at the moment these prodromal symptoms were experienced, they did not meet the criteria for a (hypo)manic episode according to the DSM-5 and can therefore be described as subsyndromal manic symptoms. This finding corresponds with a report from the International Society of Bipolar Disorders Task force (Faedda et al. 2019). In their systematic review to clarify the clinical features preceding the onset of BD they conclude that 'retrospective and prospective information about a symptomatic prodrome to developing syndromal mania, is marked particularly by attenuated hypomanic features' (Faedda et al. 2019, p. 16). These are the so called homotypical risk factors, i.e. phenomenological expressions overlapping with the symptomatology of BD, such as increased energy (87%), excessive talkativeness (60%), racing thoughts (59%), elated mood (59%), decreased need for sleep (57%), irritable mood (54%), hyperactive behavior (50%), and over-productive goal-directed behavior (50%). Furthermore, they found that mood lability and mood swings are a core feature of the clinical prodrome of (hypo)mania. All these prodromal symptoms were also found and further refined in our study. In the theme 'behavioral changes', we did not only found increased activity, but an increase of destructive behavior and disinhibited behavior. Decreased need for sleep, as found by Faedda et al. (2019), was clustered within our key theme 'physical change'. This was further enriched with changes in sleep such as shorter or lighter sleep pattern, problems with falling asleep, and a shift in circadian rhythm. Furthermore, this theme entails physical changes, an aspect not described as part of the homotypical risk factors. In addition to excessive talkativeness, we found changes in reciprocity in the process of communication. In our study, racing thoughts was clustered within the theme 'thoughts'. Our findings further specified the changes in thoughts with changes in thought content, such as increased self-esteem, but also insecurity or indecisiveness. In our study, the aspects of mood lability and mood swings were further refined with the experience of more positive emotions, more intense emotions such as hypersensitivity and irritability, and more intense crying. This mood lability was also found in another qualitative study on the early experiences of people with BD compared to people with unipolar depression (UPD). In this study the authors found that people with BD experience 'up and down' moods prior to the age of 24 years and prior to the first mood episode (depression or mania) (Benti et al. 2013). In addition to the overlap in findings, the current study adds new prodromal features: a more pronounced manifestation of pre-existing personality traits, and cognitive changes, such as changes in attention and concentration.

The implications for clinical practice of formulating a prodrome for BD that can contribute to a timely diagnosis, is to be able to start early interventions. Since a vast majority of the patients who develop BD experience one or more depressive episodes as index episode (Grande et al. 2016), the results of our study could be used in patients currently in treatment for unipolar depression to monitor potential early signals of BD and start early intervention. This is especially applicable for individuals with a familiar risk for BD. The question is whether an early interventions could contribute to preventing a transition from depressive to bipolar disorder. Another question is whether early interventions can minimize the consequences when developing BD. There is still little evidence of the effectiveness of early interventions. A systematic review by Perich and Mitchell (2019) explored if early psychological interventions could contribute to reduce current psychiatric symptoms and prevent the development of new symptoms in individuals under the age of 30 with a family history of BD. They concluded that young people with psychiatric symptoms improved, with improved time to relapse and reduced symptoms of anxiety, depression, and (hypo)mania after receiving family focused therapy, Interpersonal and Social Rhythm Therapy, or Mindfulness-based Cognitive Therapy for Children. However, further research is needed to determine which symptoms should be the focus of treatment and which population would benefit most (Perich and Mitchell 2019). A second study by Leopold et al. (2020), investigated whether group CBT can improve affective symptoms and functional deficits in young people with a positive family history for (schizo)affective disorders, subthreshold bipolar symptoms, and reduction of psychosocial functioning. They found an improvement of affective symptomatology and psychosocial functioning in both the CBT group and the control group, concluding that group sessions as such are beneficial but additional research is needed to determine the effective psychotherapeutic component. A third study, by Farr et al. (2024), examined the patients' experiences of early intervention in psychosis services for people diagnosed with bipolar disorder, following first episode psychotic mania. They found that this early intervention enabled patients to 'understand wat had happened, gain insight into their perspective, develop agency, reconsider the future and feel safe' and provided an opportunity to talk about the experience. These findings suggest that early intervention after a first manic psychotic episode is beneficial according to patients. Another approach to early intervention would be to focus on psycho-education, life style, and coping styles. The results of the study by Duval et al. (2022) on patients' perspectives of the effect of a

group-based therapeutic patient education program for bipolar disorder indicate that 'therapeutic group education programs can be beneficial for people with bipolar disorder at any point during their experience of the disorder'. Kemner et al. (2015) found that a passive coping style increased the risk of mood episode onset, and enhanced the effect of a life event on the onset of a mood episode. This suggests a positive effect of focusing on coping styles as early intervention. In conclusion, these studies show that early interventions could contribute to minimize psychiatric symptomatology in persons at risk for BD and that further research is needed.

Strengths, limitations, and future research

Our study has several strengths. First, to the best of our knowledge, it is the first study that investigates prodromal symptoms preceding a first manic episode from the perspective of patients with BD and their caregivers. This adds new information to the existing scientific base. Second, including both patients and their caregivers provided us with the possibility to compare these experienced prodromal symptoms. Third, the chosen qualitative methodology provides the possibility to explore in depth and further refine prodromal symptoms. Our study also has some limitations. First, because of the retrospective character of the study, there is a risk for recall bias. This recall bias entails the difficulties in remembering early symptoms accurately, but could also entail difficulties with differentiating between prodromal symptoms and early symptoms of the first manic episode or manic episodes in general. This problem is partly intercepted by (1) the design of the interview, starting with the creation of the patient's timeline, to be able to check if the mentioned early symptoms indeed apply to the period prior to the first manic episode, and (2) the inclusion of both patients and their caregivers which gives the ability to compare the period in life being referenced to and supports the triangulation of data. Second, due to the explorative and qualitative nature of this study with a small sample size, the findings of this study must be validated in a larger group of patients and caregivers in order to be able to generalize the findings. Therefore, future research could focus on validating these results by means of quantitative research methods to study whether these prodromal signs are recognized among a larger group and if other prodromal presentations are reported. Subsequently, a follow-up study could be set-up to study the transition rate of depressive to bipolar disorder among patients treated for a (unipolar) depression and experiencing prodromal features as we found in our study.

Conclusion

Our study contributes to the research of prodromal presentations of BD from the perspective of patients with BD and their caregivers. Prior to the first manic episode subsyndromal (hypo)manic features were described, as well as mood lability, physical changes, and a more pronounced manifestation of pre-existing personality traits. There is considerable overlap between prodromal patterns experienced by patients and noticed by their caregivers. Patients mainly report prodromal signs that are internally noticeable, whereas caregivers contributed by adding externally noticeable changes. These findings strengthen the notion that individuals at risk for developing bipolar disorder can be timely identified and taken care of.

Author contributions

E.M. wrote the main manuscript. E.M., B.R., R.K. and E.R. contributed to the design of the study. E.M. and L.M. contributed to the data collection. E.M., L.M. and E.R. Contributed to the analyses of the data. All authors reviewed the manuscript. All authors read and approved the final manuscript.

Data availability

Our qualitative data consists of interview transcripts, securely stored in a research map in de computer system of Altrecht Institute for mental health care . These transcripts including analysis codes are available upon request.

Declarations

Competing interests

The authors declare no competing interests.

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