Detection of bipolar disorder in the prodromal phase: a systematic review of assessment instruments.

Abstract

Background. Early detection of prodromal symptoms may contribute to improving the prognosis of patients with bipolar disorder (BD). The main objective of this systematic review is to present the different procedures for the identification of initial and relapse prodromes in these patients.

Methods. *PsycINFO, Web of Science and PubMed databases* were searched using a predetermined strategy, until January 4, 2022. Then, by means of a regulated process, studies that used a BD prodrome detection procedure, in English-language and all ages participants were selected. Quantitative and qualitative studies were assessed using a modified version of the Newcastle-Ottawa and by Critical Appraisals Skills Programme checklist, respectively.

Results. Forty-five studies were selected. Of these, 26 used procedures for identifying initial prodromes (n = 8,014) and 19 used procedures for detecting relapse prodromes (n = 1,136). The interview was the most used method in the detection of both types of prodromes (*k* = 30 papers, n = 4,068). It was variable in its degree of structure. Mobile applications and digital technologies are gaining importance in the detection of the relapse prodrome.

Limitations. A retrospective design in most papers, small samples sizes, existence of persistent subsyndromal symptoms and difficulty to identify the end of the prodrome and the onset of the disorder.

Conclusions. There is a wide variety of assessment instruments to detect prodromes in BD, among which the clinical interview is most frequently used. Future research should consider development of a brief tool to be applied in different formats to patients and family members.

Key words: bipolar disorder, prodrome, assessment tool, instrument, diagnoses, systematic review.

Detection of bipolar disorder in the prodromal phase: a systematic review of assessment instruments

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Conflict of interest

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Contributors

Ms. Laura Álvarez-Cadenas and Ms. Paula García-Vázquez conducted the systematic literature search, they were the principal reviewers for title/abstract and full text screening, create the tables and figures for data selection. They also took the lead in writing and editing the manuscript. Ms. Berta Ezquerra provided support to database search and data extraction from the studies. Mr. Bryan J. Stiles reviewed the redaction of the manuscript and provided suggestions regarding the subdivision of methods and discussion sections. Dr. Guillermo Lahera and Dr. Nelson Andrade-González provided guidance and supervision to principal reviewers during full text screening, both contribute to final redaction of the manuscript. Dr. Eduard Vieta contribute with additional citation searching and provided suggestions regarding the subdivision of the results section. All authors contributed to and have approved the final manuscript.

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Introduction

Bipolar disorder (BD) is a persistent and disruptive mood disorder associated with a high public health burden (Crump et al., 2013; Eaton et al., 2008; Kessler et al., 2007). The worldwide prevalence of BD is approximately 1-2%, regardless of ethnicity (Alloy et al., 2005; Craddock & Sklar, 2013) which would increase to 5% or more if hypomania were adequately detected (Angst, 2007; Angst & Cassano, 2005). Moreover, BD represents the fifth leading cause of disability in people aged 15-44 years (World Health Organization, 2011) and its epidemiological study is hampered by differences in the diagnostic criteria set out in the main classification manuals (e.g., DSM, ICD). However, to minimize these differences, BD type II, previously defined in the DSM-5 (American Psychiatric Association, 2013), has also been included in the ICD-11 (World Health Organization, 2018).

Over the last several decades, knowledge about the etiology of BD has increased considerably. Classical genetic epidemiological approaches in twin, family, and adoption studies have implicated family history of BD as a major predictor of the development of BD in offspring (O'Connell & Coombes, 2021). Furthermore, genome-wide association studies (GWASs) and genome-wide level polygenic risk score (PRS) analyses have identified specific genetic variants associated with BD (O'Connell & Coombes, 2021). Although some have posited that the etiology of BD is due to a complex interaction of genetic and environmental factors (Craddock & Sklar, 2013; Wray et al., 2014), few studies have investigated the transaction between genes and environment (GxE); within the available GxE literature, there are few replication studies and many GxE studies are constrained by small sample sizes (O'Connell & Coombes, 2021). However, these limitations do not necessarily contradict the importance of epigenetic mechanisms in the development of mental disorders (i.e., an alteration in genetic function subject to environmental influences with no modification or the DNA sequence) such as DNA methylation and histone acetylation (Lee et al., 2022). In addition, studies support the hypothesis that altered chronobiology would represent a central element of this disorder, which would play a causal and perpetuating role in BD (Salvatore et al., 2012) and would determine the sleep disturbances and circadian

rhythms, and the seasonal fluctuations in mood and behavior characteristic of BD patients (Geoffroy et al., 2013).

Early diagnosis and intervention are essential for improving the prognosis of BD patients (Berk et al., 2010). However, the average delay time for the diagnosis of this pathology is close to 10 years (Baldessarini et al., 2006). This delays the initiation of effective treatment, leading to an increase in the number of hospital admissions, the duration of these admissions, and in the risk of suicide (Baldessarini et al., 2006). Furthermore, these delays may produce, in some cases, neurological alterations that cast a shadow over long-term prognosis (Post et al., 1996). Some authors also argue that early intervention, in most cases, comes late (Vieta & Berk, 2022).

As a result, and in parallel to developments based on staging (Kupka & Hillegers, 2022), research on BD episode prodromes has increased (Correll et al., 2014a). In their 2019 statement, the International Society for Bipolar Disorders (ISBD) Task Force on Prodromes of Bipolar Disorder emphasized that accurate detection of prodromes in BD may be essential to predict the onset of first episodes, as well as the onset of future episodes of symptomatic relapse (Faedda et al., 2019). A prodrome is *"the period of disturbance which represents a deviation from a person's previous experience and behavior prior to the development of the florid features of a disorder"* (Conus et al., 2008, p. 556). The initial prodromes of BD type I includes the signs and symptoms that occur before the onset of the first episode of mania (and the corresponding diagnosis). The relapse prodrome, however, represents the signs and symptoms that signal to a patient that a subsequent episode of BD may be triggered (Conus et al., 2008). Prodromal symptoms of BD may include excessive energy, excessive talkativeness, racing thoughts, elated mood, decreased need for sleep, irritable mood, hyperactive behavior, or over-productive goal-directed behavior (Faedda et al., 2019). However, other non-specific psychopathological presentations such as emotional lability, substance use, psychotic features, depressive and anxiety symptoms, or impulsivity may occur in the period preceding the onset of BD, complicating diagnostic presentation with other related syndromes such as schizophrenia or major depressive disorder (MDD).

Assessment of prodromal symptoms has been important in many progressive, dangerous, and treatable diseases (Fava & Kellner, 1991). For BD, however, the low specificity of initial prodromes (Andrade-González et al., 2020; Conus et al., 2008; Skjelstad et al., 2010) makes prevention of a first episode of the disorder a real challenge. Regarding relapse prodromes, clinical guidelines recommend different procedures for identification (Malhi et al., 2015; National Institute for Health and Care Excellence, 2020) but their implementation in routine clinical practice lags behind (Merikangas et al., 2011), mainly due to the scarcity of economic resources (Kessler et al., 2007). In this sense, online procedures are cheaper, allow the detection of prodromes in general, and contribute to the implementation of action plans for the latter type of prodromes (Barnes et al., 2015; Bauer et al., 2016; Lauder et al., 2015; Murray et al., 2015).

Despite the established importance of early intervention in BD and a considerable increase in the development of tools for the detection of initial prodromes and relapses of BD episodes, there has not been a comprehensive review of the extant literature. To date, this is the first systematic review that details available tools for BD prodrome detection, both initial and relapse. This review will allow us to pool knowledge about these tools and provide a clearer picture that may aid clinicians and researchers in the selection of the most appropriate assessment instruments. Accordingly, the primary objective of this systematic review is to provide insight into the various methods of detecting initial prodromes and relapse episodes in BD. Secondary objectives are to determine the populations in which these assessment procedures are applied and to provide summary data on the psychometric properties of the main procedures used for initial and relapse prodrome identification.

Material and methods

We adhered to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA; Page et al., 2021) guidelines for this review.

Study selection criteria

Inclusion criteria for studies were as follows: (1) research that used a BD prodrome detection procedure, (2) English-language publications, and (3) participation of individuals of all ages. Exclusion criteria were: (1) review articles and meta-analyses, (2) instruments that did not detect BD-specific prodromes, (3) articles that included patients with other diagnoses in addition to BD (e.g., schizophrenia, schizoaffective disorders) and did not separate the results according to those diagnoses, and (4) work with patients who did not meet DSM or ICD criteria for a diagnosis of BD.

Search strategy

PsycInfo, Web of Science, and *PubMed databases* were searched until January 4, 2022. The search strategy in each of these databases was as follows: (*"Bipolar disorder" OR "Manic Depressive Illness"*) *AND* (*"Initial prodrome" OR "Relapse prodrome" OR "Prodrome" OR "Early warning sign"*) *AND* (*"Prodromes assessment tool" OR Instrument OR Measure OR Inventory OR Scale OR Questionnaire OR Interview*). A gray literature search was also performed, and the references of the selected articles were manually reviewed.

Study selection process

The first phase of our analysis, article identification, consisted of unifying the results of the searches performed in the three databases and the subsequent elimination of duplicate studies. Next, in the screening phase, we proceeded to read the titles and abstracts of the articles that potentially met the inclusion criteria. This process was carried out independently by the first two authors of this review (L.A.-C. and P. G.-V.) and their disagreements were resolved by a reasoned discussion. When there was no agreement, they agreed to review the questionable article in full text. In the eligibility phase, these same reviewers read all the articles shortlisted in the previous phase and the questionable articles. Their disagreements were resolved in a reasoned manner among them. When there was no agreement, another two authors of this review (G.L. and N.A.-

G.) finally decided whether the article met the inclusion criteria. Lastly, in the inclusion phase, the articles presented in this systematic review were finally selected.

Data extraction process for each study

The first two reviewers independently extracted the following information from each of the selected articles: study title, author(s), year of publication, country, sample size, participant characteristics, study design and methodology used, prodrome identification procedure, and study quality. Both reviewers independently assessed the risk of bias in the selected studies. Quantitative studies were assessed using a modified version of the Newcastle-Ottawa Scale (NOS; Rotenstein et al., 2016) adapted for this systematic review (Supplementary Table S1). Using the NOS, we assessed the representativeness and sample size of the study groups, the comparison between participants and nonparticipants, the prodrome assessment tools, and the quality of descriptive statistics. Selected quantitative studies were considered at low risk of bias (≥3 points) or high risk of bias (<3 points). Qualitative studies were assessed by means of the *Critical Appraisals Skills Programme* checklist (CASP, 2019).

Results

Forty-five studies met the inclusion criteria. The selection process of these studies is described in Figure 1. The main characteristics of the 26 studies that used initial prodrome identification procedures are presented in Table 1. A total of 8,014 persons participated in these studies. According to the available data, their weighted mean age was 18.91 years (k = 23). A quantitative methodology was used in 24 studies, a qualitative methodology in 1 study, and a quantitative and qualitative methodology in 1 study.

The main characteristics of the 19 studies that used relapse prodrome identification procedures are presented in Table 2. These studies involved 1,136 patients. According to the available data, their weighted mean age was 41.34 years (k = 16). A quantitative methodology was used in 18 studies and a quantitative and a qualitative methodology in 1 study.

Procedures for identification of initial prodromes

Twenty-six selected articles detect initial prodromes through different assessment tools. Figure 2 represents the percentage of use of each instrument.

Of the total articles about initial prodromes, 3 used the clinical interview as the only method of assessment of initial prodromes (Faedda et al., 2004; Özgürdal, et al., 2009; Skjelstad et al., 2012). In the case of Özgürdal and colleagues (2009), the *semi-structured* and *ad hoc elaborated interview* focused on mood swings. On the other hand, Benti and colleagues (2014) combined an *ad hoc semi-structured interview* with an *ad hoc self-report questionnaire*.

Sixteen studies used different types of instruments that were applied in a clinical interview format, alone or in combination with other prodrome screening instruments (Correll et al., 2014a; Duffy et al., 2007, 2010; Egeland et al., 2003, 2012; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Noto et al., 2015; Salazar de Pablo et al., 2020; Thompson et al., 2003; Tijssen et al., 2010; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021). Notable for its frequency of use in research is the *Bipolar Prodrome Symptom Scale* (BPSS), which was used as a semi-structured interview in 7 (Correll et al., 2014a; Noto et al., 2015; Salazar de Pablo et al., 2020; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021) of the 16 articles. The most employed BPSS format was retrospective (BPSS-R) and used in 4 (Noto et al., 2015; Zeschel et al., 2013, 2015; Zhao et al., 2021) of these 7 studies. The BPSS-R assesses the pattern of onset, duration, severity, and frequency of 39 symptoms and signs prior to the first episode of mania or depression. In 2 studies (Correll et al., 2014a; Salazar de Pablo et al., 2020) the prospective format (BPSS-P) was used. The BPSS-P is composed of 10 clinical manic items, 12 clinical depressive items, and 6 general symptoms. This tool was developed to assess and characterize lifetime prodromal mania, depression, and general symptoms, both in presence and severity. For its part, the last (Van Meter et al., 2019) of these 7 works applied two versions of the BPSS: the *Bipolar Prodrome Symptom Scale Full-Prospective* (BPSS-FP) and the *Bipolar Prodrome Symptom Scale - Abbreviated Screen for patients* (BPSS-AS-P). This latter version of the BPSS is based on the former (BPSS-FP) but is shorter and simpler

in format. Zeschel and colleagues (2013) combined the BPSS-R with an *ad-hoc semi-structured interview for mood swings*.

The second most frequently employed instrument in interview form was the *Kiddie-Schedule for Affective Disorders & Schizophrenia, Present and Life Version* (K-SADS-PL) aimed at early diagnosis of affective disorders. The K-SADS-PL is one of four versions of the *Schedule for Affective Disorders and Schizophrenia for School-aged Children* (K-SADS) which is used in school-aged children aged 6 to 18 years. The K-SADS-PL was used in 4 of the 16 studies mentioned above (Duffy et al., 2007, 2010; Hafeman et al., 2016; Hernandez et al., 2017). In the case of Hafeman and colleagues (2016), they selected only some subscales or items from this instrument, specifically *the K-SADS-PL Mania Rating Scale* and *depression items*. Additionally, in their study, Hafeman and colleagues (2016) included the *Child- Report Affective Lability* scale, derived from the *Children's Affective Lability Scale* (CALS). Hernandez and colleagues (2017), in addition to using the K-SADS in their article, included a survey developed from DSM-IV criteria to retrospectively assess the presence of BD symptoms.

Another instrument in interview format is the *Child and Adolescent Research Evaluation* (CARE) interview, used in 2 publications by the same authors (Egeland et al., 2003, 2012). The CARE includes three parts (A, B, and C): Part A collects information related to pregnancy and birth, Part B is composed of open-ended questions, and Part C is composed of 40 closed-ended questions.

Three studies (Findling et al., 2005; Thompson et al., 2003; Tijssen et al., 2010) used a variety of instruments in interview format. Findling and colleagues (2005) used the *Young Mania Rating Scale* (YMRS) and the *Children's Depression Rating Scale-Revised* (CDRS-R), both of which evaluate the presence and/or severity of manic and depressive symptoms. The YMRS consists of 11 items that are answered with 0-4 points, or 0-8 points depending on the item. The CDRS-R consists of 17 items that are answered with 1-5 points, or 1-7 points depending on the item (1 = *no difficulties*, 7= *severe difficulties*). Findling and colleagues (2005) also included an inventory within the prodrome assessment, the *Parent General Behavior Inventory* (P-GBI) composed of 73 items that assess parent-reported symptoms of mania and depression; parents answer according to a 4-point Likert scale (0 = *never or hardly ever*; to 3 = *very often or almost*

constantly). Thompson and colleagues (2003) used a clinical interview that incorporates items or questions from different instruments, including: the *Structured Clinical Interview for DSM-IV* (DSM-IV SCID), *Brief Psychiatric Rating Scale* (BPRS) and YMRS. Finally, Tijssen and colleagues (2010) used the computerized version of the *Munich-Composite International Diagnostic Interview* (CAPI version of DIA-X/M-CIDI) composed of 28 items measuring depressive symptoms and dysthymia and 11 items measuring mania symptoms. In this version, a clinician conducts an interview with the help of a computer and records the presence or absence of the symptom/item.

Of all the articles included in the systematic review on initial prodromes, the works of Bechdolf and colleagues (2014) and Hafeman and colleagues (2017) are unique for providing specific criteria that may predict development of BD based on the presence of these criteria in the prodromal phase. Bechdolf and colleagues (2014) developed the *Bipolar at-risk criteria (BAR-criteria)* to identify groups at increased risk of conversion to a first episode of mania/hypomania. Hafeman and colleagues (2017) proposed the *person-level risk calculator* as a predictive model of BD development; the clinician takes into consideration different variables and estimates the probability of occurrence of BD in a time interval.

Two papers (Fergus et al., 2003; Hirschfeld et al., 2003) of the 26 publications on early prodromes administered *ad-hoc* surveys exclusively.

Finally, we should point out that 2 early prodrome detection studies (Birmaher et al., 2013; Estey et al., 2014) used a scale as the only measuring instrument. Birmaher and colleagues (2013) used the *Children's Affective Lability Scale* (CALS), a 20-item tool completed by parents responding according to a 5-point scale (*never/rarely*; *1-3 times/month; 1-3 times/week; 4-6 times/week; and equal to or greater than 1 times/day*). Estey and colleagues (2014) applied the *Bipolar Scale of the Retrospective Coolidge Personality and Neuropsychological Inventory* (CPNI-R), which may be completed in either self- or observer-report (i.e., significant other) formats. Items are answered on a 4-point Likert scale (1 = *strongly false*, 2 = *more false than true*, 3 = *more true than false*, and 4 = *strongly true*). The *CPNI-R* has a 3-component structure, including a mania component, a depression component, and an emotional and behavioral lability component.

Table 3 presents information on the populations in which these screening procedures were used. In 20 of the 26 papers on early prodromes, different methods of prodrome screening were used in patients diagnosed with BD and/or other affective spectrum disorders (e.g., unipolar depression/major depressive disorder or mood disorder NOS) (Benti et al., 2014; Birmaher et al., 2013; Correll et al., 2014a; Estey et al., 2014; Faedda et al., 2004; Fergus et al., 2003; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Hirschfeld et al., 2003; Noto et al., 2015; Özgürdal et al., 2009; Salazar de Pablo et al., 2020; Skjelstad et al., 2012; Thompson et al., 2003; Tijssen et al., 2010; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021). The remaining 6 investigations (Bechdolf et al., 2014; Duffy et al., 2007, 2010; Egeland et al., 2003, 2012; Hafeman et al., 2017) recruited individuals at risk of developing BD as their primary sample.

Of the 20 articles conducted on patients with a diagnosis of BD and/or different affective spectrum disorders, 8 papers (Birmaher et al., 2013; Faedda et al., 2004; Fergus et al., 2003; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Salazar de Pablo et al., 2020; Van Meter et al., 2019) evaluated clinical diagnoses of BD in children and/or adolescents. In the case of Birmaher and colleagues (2013), Faedda and colleagues (2004), and Fergus and colleagues (2003), the informants were exclusively parents. In 4 studies (Correll et al., 2014a; Skjelstad et al., 2012; Thompson et al., 2003; Tijssen et al., 2010) the sample consisted of adolescents and adults with a clinical diagnosis of BD.

Seven papers (Benti et al., 2014; Estey et al., 2014; Hirschfeld et al., 2003; Noto et al., 2015; Özgürdal et al., 2009; Zeschel et al., 2013, 2015) evaluated BD in an exclusively adult population. In six of these studies (Benti et al., 2014; Hirschfeld et al., 2003; Noto et al., 2015; Özgürdal et al., 2009; Zeschel et al., 2013, 2015) the patient was the informant.

Finally, the study by Zhao and colleagues (2021), although conducted with a sample of patients with a diagnosis of BD, did not specify participant age or the main informant in the diagnostic evaluation.

Regarding the 6 investigations conducted on groups of people at risk of developing BD (Bechdolf et al., 2014; Duffy et al., 2007, 2010; Egeland et al., 2003,

2012; Hafeman et al., 2017), 3 studies (Egeland et al., 2003, 2012; Hafeman et al., 2017) sampled children and adolescents of a first-degree relative with BD (e.g., parents). In the studies by Egeland and colleagues (2003, 2012) the informants were solely the parents. Bechdolf and colleagues (2014) interviewed adolescents and young adults (15-24 years) who were analyzed for compliance with BAR- criteria. Finally, the work of Duffy and colleagues (2007, 2010) employed a heterogeneous sample in terms of age and included children, adolescents, and young adults (18- 25 years) at risk of developing BD.

Relapse prodrome identification procedures

Nineteen of the selected articles used different kinds of instruments for relapse prodrome detection in BD. Figure 3 represents the percentage of use of each instrument.

Of the total articles about relapse prodromes, 10 (Altman et al., 1992; Fletcher et al., 2013; Houston et al., 2007; Lam et al., 2001; Mander, 1990; Mantere et al., 2008; Molnar et al., 1988; Ryu et al., 2012; Sahoo et al., 2012; Smith & Tarrier, 1992) used clinical interviews or other instruments (e.g., BPRS, YMRS, CPSI) administered in a clinical interview format for detecting a relapse prodrome.

Four papers (Fletcher et al., 2013; Mander, 1990; Mantere et al., 2008; Molnar et al., 1988) employed clinical interviews. Fletcher and colleagues (2013) conducted a qualitative semi-structured interview covering various aspects of hypomania and depression from the prodromal phase to the onset of florid affective symptoms, documenting personal experiences and coping strategies prior to and during the recent episode. Mander (1990) conducted a weekly semi-structured interview of prodromal manic and depressive symptoms. Mantere and colleagues (2008) asked patients about the presence, type, and occurrence of their first prodromal symptoms and then subsequently categorized their responses according to DSM-IV criteria. Finally, Molnar and colleagues (1988) conducted a clinical interview about the duration of each patient's affective episode, the duration of their prodromal stage, and the symptoms they experienced.

Two papers (Ryu et al., 2012; Smith & Tarrier, 1992) employed symptom *checklists* applied in the form of an interview. Ryu and colleagues (2012) applied a 40-item checklist covering 15 symptoms of mania, 15 symptoms of depression, and 10

mixed-episode symptoms. For each item, the interviewer scored the absence (0) or presence (1) of a prodromal symptom; on this occasion, patients were interviewed about the prodromal phases of their last manic episode. Smith & Tarrier (1992) designed a checklist of 40 items (15 for mania, 15 for depression, and 10 for mixed episodes), extracted from the symptoms cited by Molnar and colleagues (1988), Birchwood and colleagues (1989), and from data collected during pilot interviews. The interview included questions about the prodromal period before their last manic episode and their last depressive episode. If symptoms occurred during the prodrome, they were rated as *mild (1) or strong (2).* If a symptom was not present, it was rated as *absent (0)*. In addition, the authors asked about other symptoms not included in the checklist, namely idiosyncratic experiences (a symptom unique to one subject).

Three of the articles reviewed (Altman et al., 1992; Houston et al., 2007; Lam et al., 2001) used different instruments in the form of clinical interviews. Altman and colleagues (1992) administered the expanded version of the *Brief Psychiatric Rating Scale* (BPRS-E). The BPRS-E is administered face-to-face and includes the 18 items of the original BPRS, plus 6 more items measuring affective and psychotic symptoms relevant to BD: *elated mood, motor hyperactivity, distractibility, suicidality, self-neglect, and bizarre behavior*. The items are answered according to a 7-point severity scale, with a score of 1 meaning that the patient is asymptomatic for that item. The BPRS also included a short version to be administered by telephone. This short version consisted of 10 items, which were considered as *"relapse scales"*: *depression, hostility, unusual thought content, hallucinations, conceptual disorganization, suicidality, self-neglect, bizarre behavior, elated mood, and motor hyperactivity*. Houston and colleagues (2007) chose to use the YMRS as an instrument to detect prodromes of mania relapse. This scale was completed by the clinician during the initial consultation in the form of a clinical interview and included subjective comments from the patient and observations by the interviewer. Finally, Lam and colleagues (2001) used the *Coping with Prodromal Symptoms Interview* (CPSI) in the form of a semi-structured interview to diagnose symptom relapse. Participants were asked about their experiences with prodromal symptoms in past episodes and how they coped with them.

The primary method used by Sahoo and colleagues (2012) for prodrome detection was an 83-item scale derived from the *Comprehensive Psychopathology*

Rating Scale, the *Young Mania Rating Scale*, the *Bech-Rafaelsen Mania Rating Scale*, the *Beck Depression Inventory* and *Paykel's Clinical Interview for Depression*. However, the authors also incorporated an unstructured interview to collect prodromal symptoms not reflected in the composite scale including *"idiosyncratic prodromal symptoms such as increased religiosity, taking decisions easily, reddening of eyes, being abusive, listening to loud music, recalling past events, and ideas of reference"* (Sahoo et al., 2012. p. 181). In their survey, Sahoo and colleagues (2012) provided a brief description of each item, and prodromal symptoms were classified as either present or absent.

The remaining 9 studies (Bauer et al., 2006; Fellendorf et al., 2021; Glenn et al., 2006; Goossens et al., 2010; Grünerbl et al., 2015; Keitner et al., 1996; Lobban et al., 2011; Perlman et al., 2006; Wong & Lam, 1999) used other formats (e.g., mobile apps, computerized tools) of relapse prodrome detection.

The *ChronoRecord* application, a computerized and validated version of the *ChronoSheet self-report*, was used in two studies (Bauer et al., 2006; Glenn et al., 2006) to detect the relapse prodrome in BD patients. This application allows the assessment of mood, medication intake, and sleep. Bauer and colleagues (2006) used a 100-unit visual analog scale between the extremes of mania and depression for the patient to indicate their mood. The patients provided a daily mood rating covering the previous 24 hours. Regarding the sleep recording, the patient's status alternated every hour, depending on whether the patient was awake, asleep, or on bed rest. In the case of Glenn and colleagues (2006), data from 60 days prior to symptom relapse were compared with data from at least one month of euthymia, in addition to comparing the 60 days prior to a manic relapse versus a depressive relapse.

In two articles (Fellendorf et al., 2021; Grünerbl et al., 2015) mobile apps were used for the detection of relapse prodrome. Fellendorf and colleagues (2021) employed the smartphone app *UP!* for a period of 6 months and collected data regarding sleep, physical activity, and social profile (e.g., app usage on a smartphone such as Facebook©, WhatsApp©, Skype©; and smartphone checks during the week and during weekends). Sleep-related information was obtained using the phone's accelerometer and light sensors. Furthermore, patients rated their mood with seven choices of emoticons

once a day at night. Physical activity behaviors and sleep periods were assessed using an *Axivity3* accelerometer, worn on the wrist of the non-dominant hand. Grünerbl and colleagues (2015) developed an Android smartphone app. Each patient was given a smartphone that ran the developed app and recorded all sensor data automatically at the end of the day. Data collection was based on the importance of different aspects of behavior: *social interaction, physical motion,* and *travel patterns*. *Social interaction* was assessed by two parameters: *phone call features* (e.g., number of phone calls, total length of calls, the average length of phone calls, a standard deviation of the length of phone calls, and number of unique numbers) and *sound features* (e.g., speech features such as average speaking length and speaking turn duration and voice features to detect the emotions from the voice). *Physical motion* and *travel patterns* were collected using sensors, GPS, and an accelerometer. Weighted fusion of only location and acceleration data provided very good results, but the addition of social interaction improved the overall accuracy of prodrome detection.

Three of the papers reviewed (Goossens et al., 2010; Keitner et al., 1996; Wong & Lam, 1999) employed open-ended questions. Goossens and colleagues (2010) asked two questions to explore prodromal symptoms: *"How can you tell if an episode of mania or depression is impending?"* and *"What is the first sign or behavior that you recognize in yourself that leads up to a manic or depressive episode?*". In the case of Keitner and colleagues (1996) patients were given an *ad hoc* open-ended self-report, in which prodromal and residual symptoms were assessed. The questions used were as follows: *"Please describe the behaviors you have experienced leading up to a manic or depressive episode. How can you tell that an episode is coming on?"* and *"Please describe any mood, thought, feeling, etc. That persists or lingers even when it appears to others that the episode is over. What is still not right?"*. Responses were classified into 6 domains: *mood symptoms, behavioral symptoms, cognitive symptoms, neurovegetative symptoms, social symptoms,* and *other symptoms*. Wong & Lam (1999) sent a postal survey, which included an open-ended question for the patient to describe the early warning signs of a manic episode, i.e., changes in the person's thinking, feeling, and behavior that may raise suspicion of relapse. The use of the open-ended question made it possible to describe the most idiosyncratic prodromes for each patient and subsequently categorize them.

One study (Lobban et al., 2011) used *an Early Warning Signs checklist for mania and depression* (EWS) as an instrument to detect prodrome of relapse within a two-part assessment. In the first part, the patient spontaneously reported his or her first prodromes and their frequency. In the second part, they used an EWS composed of 32 depression items and 31 mania items that classified them as absent, early, late, or complete. The checklist items were obtained from previous studies by Molnar and colleagues (1988); Smith & Tarrier (1992); Wong & Lam (1999) and Lam and colleagues (2001). The prodrome checklists were mailed to patients.

Finally, because of the importance of sleep disturbances as a prodrome in BD, Perlman and colleagues (2006) used the *Sleep Duration subscale* of the *Pittsburgh Sleep Quality Index* in the form of a self-report. Patients recorded the hours they slept during the past month and subsequently forwarded it by email to the investigators.

Regarding the populations to which these assessment procedures were applied, although all 19 studies were conducted with patients who had a diagnosis of BD according to DSM or ICD criteria. In 6 papers (Altman et al., 1992; Keitner et al., 1996; Lam et al., 2001; Perlman et al., 2006; Ryu et al., 2012; Sahoo et al., 2012) the sample consisted only of patients with type I BD, while one paper (Fletcher et al., 2013) was conducted only with patients with type II BD. Five of the studies (Keitner et al., 1996; Mander, 1990; Molnar et al., 1988; Ryu et al., 2012; Sahoo et al., 2012) involved a family member/caregiver as informants, in addition to the patient.

Psychometric properties of two prodrome identification procedures.

One of the most widely used prodrome screening instruments in adults and adolescents is the BPSS-P (Correll et al., 2014b). For the validation of the BPSS-P, Correll and colleagues (2014b) started with a total sample of 205 participants. Of these, 92 were patients at high risk of developing psychosis, 42 were subjects with neither psychiatric diagnosis nor a high risk of developing psychosis (control group) and 71 were patients with different diagnoses of affective spectrum disorders and psychotic spectrum disorders (e.g., BD-I, BD-II, BD NOS, cyclothymia, MDD, depressive disorder NOS, dysthymia, or mood disorder NOS, schizophrenia, schizoaffective disorder, schizophreniform disorder, or psychotic disorder NOS). The group of participants at high risk of developing psychosis and the control group (CG) had an age

range of 12-15 years; patients with different diagnoses of affective and psychotic spectrum disorders had an age range of 12-18 years. By biological sex, 40.5% were male in the CG whereas 57.5% were male between individuals with high risk of developing psychosis and individuals with a diagnosis of affective and/or psychotic spectrum disorders.

The BPSS-P is a semi-structured interview that assesses the occurrence and severity of prodromal symptoms and divides them into three sections: *Mania*, *Depression* and *General Symptom Index*. Each item is scored according to an ordinal scale (0 =*absent*; 1= *questionably present*; 2 = *mild*; 3 = *moderate*; 4 = *moderately severe*; 5 = *severe* and 6 = *extreme*). Symptom severity is evaluated for the month and year prior to the time of the interview.

To examine the psychometric properties of the BPSS-P, Correll and colleagues (2014b) employed the following measurement instruments: *Young Mania Rating Scale* (YMRS), *Montgomery-Asberg Depression Rating Scale* (MADRS), *Parent General Behavior Inventory-10-item Mania* (GBI-M-10) and *Cyclothymic-Hypersensitive Temperament* (CHT) questionnaire of the *Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Autoquestionnaire* (TEMPS-A).

Regarding the reliability in terms of internal consistency of the BPSS-P, Correll and colleagues (2014b) found acceptable to good reliability across the three sections of the instrument: *Mania* ($\alpha = 0.87$), *Depression* ($\alpha = 0.89$) and *General Symptom Index* ($\alpha = 0.74$). Inter-rater reliability (i.e., intraclass correlation or ICC) was also high for the BPSS-Total (ICC = 0.93), and for the different indices that compose it: BPSS-P *Mania Index* (ICC = 0.93); BPSS-P *Depression Index* (ICC = 0.98) and BPSS-P *General Index* (ICC = 0.98).

Regarding convergent validity, Correll and colleagues (2014b) found adequate values for the main Spearman's rank correlation coefficients. Namely, ρ values between the BPSS-P *Mania Index* and the YMRS, the GBI-M-10 and the CHT were 0.52, 0.54, and 0.56, respectively; ρ values between the BPSS-P *Depressive Index* and the MADRS and the CHT were 0.69 and 0.50, respectively; and ρ values between the *General Index* and the GBI-M-10 and the CHT were 0.56 and 0.55, respectively.

In terms of discriminant validity, the BPSS-P total scores were significantly different [F (5195) = 55.73; $p < 0.0001$] between diagnostic groups. Post-hoc analyses revealed that BPSS-P *Mania Index* scores were significantly higher in each of the following mood spectrum disorder groups when compared to the groups without an affective spectrum diagnosis and compared to the CG of participants without a psychiatric diagnosis: BD-I, BD-II, cyclothymia, BD NOS, and mood disorder NOS. In addition, patients diagnosed with BD-I, BD-II and/or cyclothymia had significantly higher BPSS-P *Total* scores than patients with depression spectrum disorders, patients with non-mood spectrum disorders, and CG individuals with no psychiatric diagnosis. Likewise, BPSS-P *Depression Index* scores were significantly higher [F (5,201) = 44.00; $p < 0.0001$] in patients with a diagnosis of depression spectrum disorder and in patients with BD-I, BD-II, cyclothymia, BD NOS, and mood disorder NOS when compared with scores in the group of patients with a diagnosis of non-mood spectrum disorder and with the CG of persons with no psychiatric diagnosis. Finally, BPSS-P *General Index* scores were also significantly different between the groups of patients with psychiatric diagnosis, [F (5,195) = 37.04; $p < 0.0001$] compared to the CG of persons without psychiatric diagnosis. However, no significant differences were found between each other in patients with psychiatric diagnoses, such as between patients with mood spectrum disorder and patients with non-mood spectrum disorder (Correll et al., 2014b).

Another instrument frequently used in the detection of prodrome is the K-SADS-PL. In their validation work, Kaufman and colleagues (1997) used 66 participants, 55 of whom were children and adolescents with a psychiatric diagnosis and 11 were children and adolescents without a diagnosis (CG). The age range of the entire sample was 7-17 years, 48% being boys.

The K-SADS-PL is a semi-structured interview composed of four parts: (1) an *Introductory Interview* which allows an interviewer to establish rapport and to collect demographic information, health information, presenting complaint, previous psychiatric treatments, information about the child's school functioning, hobbies and relationships with peer group and family; (2) a *Screening Interview* which covers 82-symptoms divided across 20 diagnostic areas that are evaluated by means of items ranging from 0 to 3 points (0 = *"no information is available"*; 1 = *"suggest the symptom*

is not present", 2 = *"indicate subthreshold levels of symptomatology"* and 3 = *"represent threshold criteria"*); (3) *Diagnostic supplements which* include (a) *Affective Disorders*; (b) *Psychotic Disorders*, (c) *Anxiety Disorders*, (d) *Behavioral Disorders*, and (e) *Substance Abuse, Eating and Tic Disorders;* (4) *Time Frame Coding Guidelines* which helps the clinician to score the symptoms in the child or adolescent's period of maximum severity (Kaufman et al., 1997).

To examine the psychometric properties of the K-SADS-PL, Kaufman and colleagues (1997) used the following measurement instruments: *Child Behavior Checklist* (CBCL), *Beck Depression Inventory* (BDI), *Children's Depression Inventory* (CDI), *Screen for Children Anxiety Related Emotional Disorders* (SCARED) and *Conners Abbreviated Questionnaire/Parent version.*

With regard to reliability in terms of temporal stability, Kaufman and colleagues (1997) found that the test-retest reliability coefficients ranged from excellent to good for most of the presenting diagnoses (MDD and *Any depression*, $\kappa = 0.90$; *Any bipolar disorder*, $\kappa = 1.00$; *Generalized anxiety disorder*, $\kappa = 0.78$; *Posttraumatic stress disorder*, $\kappa = 0.67$; *Any anxiety disorder*, $\kappa = 0.80$; ADHD, $\kappa = 0.63$; *Oppositional defiant disorder*, $\kappa = 0.74$) and for most of the *lifetime diagnoses* (MDD, *Any depression*, and *Any bipolar disorder*, $\kappa = 1.00$; *Depressive disorder* NOS, $\kappa = 0.86$; *Generalized anxiety disorder*, $\kappa = 0.78$; *Posttraumatic stress disorder* and *Any anxiety disorder*, $\kappa = 0.60$; ADHD, $\kappa = 0.55$; *Conduct disorder*, $\kappa = 0.83$ and *Oppositional defiant disorder*, $\kappa = 0.77$). Regarding the inter-judge or inter-rater reliability of the K-SADS-PL, Kaufman and colleagues (1997) found that the percentage of inter-judge agreement in assigning *present and lifetime diagnoses* was both 98% (range: 93% - 100%).

Regarding the concurrent validity of the K-SADS-PL; Kaufman and colleagues (1997) found that: (1) children who met the criteria for depressive disorders scored higher ($p < 0.01$) than other children on the *z*-scored transformed depression (calculated by combining BDI and CDI scores) and on the CBCL *Internalizing Scales* ($p < 0.001$); (2) children who met criteria for ADHD scored higher than other children on the *Conners Abbreviated Questionnaire/Parent version* ($p < 0.001$); (3) children who met criteria for *Any current anxiety disorder* scored higher than other children on the

SCARED ($p < 0.0001$) and *CBCL Internalizing Scales* ($p < 0.01$); and (4) children who met criteria for *Any current behavioral disorder* scored higher than other children on the CBCL *Externalizing Scale* ($p < 0.0001$).

Discussion

Interpretation of findings

This is the first systematic review that details the instruments used to identify the initial and relapse prodromes of BD. In addition, we identified the populations in which these instruments were used and the psychometric properties of two widely used instruments, the BPSS-P, and the K-SADS-PL.

Since the course of BD alternates phases of stability with symptomatic episodes, prodromes are sometimes difficult to distinguish from age-appropriate changes, mood changes, and even residual symptoms or unipolar episodes (Pfennig et al., 2020). Thus, the identification of tools that accurately detect prodromal processes or relapse in BD may help clinicians and researchers to make the best clinical decisions. Added to this, a delay in the treatment of the disorder (often debuting in adolescence or early adulthood) is associated with a worse prognosis, including greater symptom severity, fewer phases of euthymia, presence of rapid cycling, increased risk of suicide, and worse response to pharmacological treatment (Chen & Dilsaver, 1996; Kessing et al., 2014; Miller et al., 2014; Pfennig et al., 2020; Post et al., 2010; Verdolini et al., 2022). Therefore, it is important to know and use reliable and valid tools that enable early detection of prodromal symptoms of BD in different groups of people and to implement appropriate interventions at different stages of the disease (Vieta et al., 2018).

Fernández-Ballesteros (2013) classifies assessment instruments in psychology and psychopathology into 6 categories: observational techniques, objective techniques, self-report techniques, the interview, subjective techniques, and projective techniques. This classification may help situate the findings of the present systematic review. In the selected studies, the interview was the most frequently employed method in the detection of BD prodromes. Some papers used clinical interviews with varying degrees of structuring and, sometimes, *ad hoc* elaborated interviews (Benti et al., 2014; Faedda et al., 2004; Fletcher et al., 2013; Mander, 1990; Mantere et al., 2008; Molnar et al., 1988; Özgürdal, et al., 2009; Skjelstad et al., 2012). Furthermore, in several of the

included papers, the authors used different types of instruments (e.g., scales, questionnaires, symptom checklists) within a clinical interview format (Altman et al., 1992; Correll et al., 2014a; Duffy et al., 2007, 2010; Egeland et al., 2003, 2012; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Houston et al., 2007; Lam et al., 2001; Noto et al., 2015; Ryu et al., 2012; Sahoo et al., 2012; Salazar de Pablo et al., 2020; Smith & Tarrier, 1992; Thompson et al., 2003; Tijssen et al., 2010; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021).

The interview is a broad-spectrum assessment tool (Fernández-Ballesteros, 2013) that collects data from the subject being assessed but is also used to collect information about a third person from an interlocutor (Fernández-Ballesteros, 2013). An advantage of the interview as a general assessment tool is that it generates an immediate response from the individual. In addition, it allows the clinician to adapt his or her language to the educational level of the interviewed subject, rephrase the question if necessary, and observe the person's nonverbal behavior (Andrade-González et al., 2020). An advantage of the clinical interview aimed at detecting BD prodromes is that there is no *a priori* assumption about patients' prodromal symptoms so that the subject can report idiosyncratic symptoms (Lam & Wong, 2005) and the clinician can consider the differences between their patients' prodromal manifestations. However, a drawback of the interview is that it demands more resources and time on the part of the evaluator (Lam & Wong, 2005).

Other instruments such as symptom *checklists*, questionnaires, or inventories are less expensive than the interview, easier to administer, and may allow the subject to think about his or her answers. However, as far as BD prodrome detection is concerned, such instruments may have a drawback in that the patient may tend to indicate prodromes in an indiscriminate way (Andrade-González et al., 2020; Lam & Wong, 2005; Skjelstad et al., 2010).

In the present review, we found that new technologies were used in only one study for the detection of initial prodromes (Tijssen et al., 2010). However, for the detection of relapse prodromes, digital technology appears to be increasingly used (Bauer et al., 2006; Fellendorf et al., 2021; Glenn et al., 2006; Grünerbl et al., 2015). According to Monteith and colleagues (2016), the patient plays an active role in the data

collection (e.g., *ChronoRecord* by Bauer et al., 2006; Glenn et al., 2006) whereas other digital platforms rely on passive data collection methods like smart sensors (Fellendorf et al., 2021; Grünerbl et al., 2015). It should be noted that a Spanish research group is in the process of creating an app that may help BD patients self-monitor symptoms and access psychoeducation, although this digital application does not constitute, per se, a prodrome detection tool (Hidalgo-Mazzei et al., 2018). The contents of this app are based on a group psychological program previously developed, evaluated, and carried out by Colom and colleagues (2009).

Leopold and colleagues (2012) analyzed the early phases and *early symptoms* in the development of BD and developed an assessment instrument, a semi-structured interview called the *Early Phase Inventory for Bipolar Disorders* (EPIbipolar), that may help detect the frequent *early symptoms* of the disorder. These authors understand *early symptomatology* to include: (a) *changes in sleep and circadian rhythm*, (b) *changes in mood, mood swings/affective lability*; (c) *fearfulness/anxiety*; and (d) *dissociative symptoms*. Using the EPIbipolar interview, symptoms are assessed according to their frequency of occurrence and severity; *"those items thought to undergo dynamic changes in the early phase of bipolar disorders are described in terms of their temporal development"* (Leopold et al., 2012, p.1005). The assessed subjects are assigned to one of the following four final groups: *no risk at present*, *risk status*, *high risk status* and *ultra-high risk status* (Leopold et al., 2012) similar to the risk categories for BD development proposed by other authors (Howes et al., 2011; Skjelstad et al., 2010).

Regarding the secondary objectives of this review, the samples used in the selected papers consisted of patients with a diagnosis of BD and/or different affective spectrum disorders (Altman et al., 1992; Benti et al., 2014; Birmaher et al., 2013; Correll et al., 2014a; Estey et al., 2014; Faedda et al., 2004; Fergus et al., 2003; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Hirschfeld et al., 2003; Keitner et al., 1996; Lam et al., 2001; Noto et al., 2015; Özgürdal et al., 2009; Perlman et al., 2006; Ryu et al., 2012; Salazar de Pablo et al. et al., 2020; Sahoo et al., 2012; Skjelstad et al., 2012; Thompson et al, 2003; Tijssen et al., 2010; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021) and, to a lesser extent, by subjects at risk of developing BD (Bechdolf et al., 2014; Duffy et al., 2007, 2010; Egeland et al., 2003, 2012; Hafeman et al., 2017). Regarding the psychometric properties of two

instruments widely used in the reviewed studies, the BPSS-P and the K-SADS-PL are two reliable and valid measures, according to the results presented in the respective validation studies by Correll and colleagues (2014b) and Kaufman and colleagues (1997).

While the identification of relapse prodromes in BD has clear clinical implications, it may also serve as a guide for the choice of mood stabilizer prescribed, dose adjustment, or other clinical pharmacological decisions (i.e., drug substitution, combination, etc.). According to a recent systematic review (Kishi et al., 2021), most mood stabilizers reduced the recurrence or relapse rates of any mood episode. Lithium is recommended as the drug of choice for the treatment of adult patients with BD in the maintenance phase (Fountoulakis et al., 2017; Goodwin et al., 2016; Yatham et al., 2018), but very few patients maintain treatment long enough to establish remission; between 40-60% discontinue lithium after 5 to 7 years of treatment (Nilsson et al., 1989; Schumann et al., 1999), and around 13% become resistant to lithium after 10 years (Maj et al., 1996).

Limitations and strengths

The present systematic review has some limitations. First, 36% (n = 12) of the initial prodrome detection studies and 52.63% (n = 10) of the relapse prodrome detection studies employed a retrospective design. Although there are retrospective data showing that patients with BD can recognize relapse symptoms before the first episode occurs (Lam & Wong, 2005), conclusions drawn from retrospective data should be interpreted with caution due to potential recall bias. Second, sample sizes were variable but predominantly small, which limits the generalizability of the results. Third, the possibility of the existence of persistent subsyndromal symptoms, rather than genuine prodromes, which may not be related to new episodes, cannot be ruled out entirely. Finally, inherent in the detection of a prodrome, it is difficult to identify the end of the prodrome and the onset of the disorder.

An important ethical consideration concerns the evaluation of individuals at risk for BD (Fusar-Poli et al., 2022). Clinicians and researchers should consider the potential risks and benefits and the cost-benefit ratio from a public health perspective of early detection and intervention of any pathology (Burkhardt et al., 2021). Assessment and

intervention of individuals at putative risk of developing BD should be mindful of the normal fluctuations of a person's mood and behavioral patterns, the fact that not all individuals will develop the disorder, and the possible impact that interventions for BD (e.g., medication) may have on their daily functioning.

Future recommendations and conclusions

In conclusion, tools exist to detect initial and relapse prodromes of BD episodes. Since BD symptoms, as in other mental disorders, are dynamic and continuously evolving (Nelson et al., 2017), it will be necessary to confirm the predictive value and power of many of these procedures in studies that include larger samples of subjects and longer follow-up times. Although there are specific, reliable, and valid prodrome identification instruments available to clinicians and researchers such as the BPSS-P, future research should investigate the development of a brief tool that detects initial and relapse prodromes of BD using information gathered from interviews and self-reports and which can be applied to multiple stakeholders (e.g., patients, family members, and caregivers) either in-person or digitally (e.g., computer platforms or smartphones). This will require developing a set of items with excellent content validity, testing this tool in a multicenter study that provides a large sample of subjects, and providing adequate values for its reliability and validity. This tool may be a starting point to compare BD prodromes with those of other mental disorders and to evaluate differences across individuals of different age groups presenting with prodromal symptoms of BD.

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Introduction

Bipolar disorder (BD) is a persistent and disruptive mood disorder associated with a high public health burden (Crump et al., 2013; Eaton et al., 2008; Kessler et al., 2007). The worldwide prevalence of BD is approximately 1-2%, regardless of ethnicity (Alloy et al., 2005; Craddock & Sklar, 2013) which would increase to 5% or more if hypomania were adequately detected (Angst, 2007; Angst & Cassano, 2005). Moreover, BD represents the fifth leading cause of disability in people aged 15-44 years (World Health Organization, 2011) and its epidemiological study is hampered by differences in the diagnostic criteria set out in the main classification manuals (e.g., DSM, ICD). However, to minimize these differences, BD type II, previously defined in the DSM-5 (American Psychiatric Association, 2013), has also been included in the ICD-11 (World Health Organization, 2018).

Over the last several decades, knowledge about the etiology of BD has increased considerably. Classical genetic epidemiological approaches in twin, family, and adoption studies have implicated family history of BD as a major predictor of the development of BD in offspring (O'Connell & Coombes, 2021). Furthermore, genome-wide association studies (GWASs) and genome-wide level polygenic risk score (PRS) analyses have identified specific genetic variants associated with BD (O'Connell & Coombes, 2021). Although some have posited that the etiology of BD is due to a complex interaction of genetic and environmental factors (Craddock & Sklar, 2013; Wray et al., 2014), few studies have investigated the transaction between genes and environment (GxE); within the available GxE literature, there are few replication studies and many GxE studies are constrained by small sample sizes (O'Connell & Coombes, 2021). However, these limitations do not necessarily contradict the importance of epigenetic mechanisms in the development of mental disorders (i.e., an alteration in genetic function subject to environmental influences with no modification or the DNA sequence) such as DNA methylation and histone acetylation (Lee et al., 2022). In addition, studies support the hypothesis that altered chronobiology would represent a central element of this disorder, which would play a causal and perpetuating role in BD (Salvatore et al., 2012) and would determine the sleep disturbances and circadian

rhythms, and the seasonal fluctuations in mood and behavior characteristic of BD patients (Geoffroy et al., 2013).

Early diagnosis and intervention are essential for improving the prognosis of BD patients (Berk et al., 2010). However, the average delay time for the diagnosis of this pathology is close to 10 years (Baldessarini et al., 2006). This delays the initiation of effective treatment, leading to an increase in the number of hospital admissions, the duration of these admissions, and in the risk of suicide (Baldessarini et al., 2006). Furthermore, these delays may produce, in some cases, neurological alterations that cast a shadow over long-term prognosis (Post et al., 1996). Some authors also argue that early intervention, in most cases, comes late (Vieta & Berk, 2022).

As a result, and in parallel to developments based on staging (Kupka & Hillegers, 2022), research on BD episode prodromes has increased (Correll et al., 2014a). In their 2019 statement, the International Society for Bipolar Disorders (ISBD) Task Force on Prodromes of Bipolar Disorder emphasized that accurate detection of prodromes in BD may be essential to predict the onset of first episodes, as well as the onset of future episodes of symptomatic relapse (Faedda et al., 2019). A prodrome is *"the period of disturbance which represents a deviation from a person's previous experience and behavior prior to the development of the florid features of a disorder"* (Conus et al., 2008, p. 556). The initial prodromes of BD type I includes the signs and symptoms that occur before the onset of the first episode of mania (and the corresponding diagnosis). The relapse prodrome, however, represents the signs and symptoms that signal to a patient that a subsequent episode of BD may be triggered (Conus et al., 2008). Prodromal symptoms of BD may include excessive energy, excessive talkativeness, racing thoughts, elated mood, decreased need for sleep, irritable mood, hyperactive behavior, or over-productive goal-directed behavior (Faedda et al., 2019). However, other non-specific psychopathological presentations such as emotional lability, substance use, psychotic features, depressive and anxiety symptoms, or impulsivity may occur in the period preceding the onset of BD, complicating diagnostic presentation with other related syndromes such as schizophrenia or major depressive disorder (MDD).

Assessment of prodromal symptoms has been important in many progressive, dangerous, and treatable diseases (Fava & Kellner, 1991). For BD, however, the low specificity of initial prodromes (Andrade-González et al., 2020; Conus et al., 2008; Skjelstad et al., 2010) makes prevention of a first episode of the disorder a real challenge. Regarding relapse prodromes, clinical guidelines recommend different procedures for identification (Malhi et al., 2015; National Institute for Health and Care Excellence, 2020) but their implementation in routine clinical practice lags behind (Merikangas et al., 2011), mainly due to the scarcity of economic resources (Kessler et al., 2007). In this sense, online procedures are cheaper, allow the detection of prodromes in general, and contribute to the implementation of action plans for the latter type of prodromes (Barnes et al., 2015; Bauer et al., 2016; Lauder et al., 2015; Murray et al., 2015).

Despite the established importance of early intervention in BD and a considerable increase in the development of tools for the detection of initial prodromes and relapses of BD episodes, there has not been a comprehensive review of the extant literature. To date, this is the first systematic review that details available tools for BD prodrome detection, both initial and relapse. This review will allow us to pool knowledge about these tools and provide a clearer picture that may aid clinicians and researchers in the selection of the most appropriate assessment instruments. Accordingly, the primary objective of this systematic review is to provide insight into the various methods of detecting initial prodromes and relapse episodes in BD. Secondary objectives are to determine the populations in which these assessment procedures are applied and to provide summary data on the psychometric properties of the main procedures used for initial and relapse prodrome identification.

Material and methods

We adhered to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA; Page et al., 2021) guidelines for this review.

Study selection criteria

Inclusion criteria for studies were as follows: (1) research that used a BD prodrome detection procedure, (2) English-language publications, and (3) participation of individuals of all ages. Exclusion criteria were: (1) review articles and meta-analyses, (2) instruments that did not detect BD-specific prodromes, (3) articles that included patients with other diagnoses in addition to BD (e.g., schizophrenia, schizoaffective disorders) and did not separate the results according to those diagnoses, and (4) work with patients who did not meet DSM or ICD criteria for a diagnosis of BD.

Search strategy

PsycInfo, Web of Science, and *PubMed databases* were searched until January 4, 2022. The search strategy in each of these databases was as follows: (*"Bipolar disorder" OR "Manic Depressive Illness"*) *AND* (*"Initial prodrome" OR "Relapse prodrome" OR "Prodrome" OR "Early warning sign"*) *AND* (*"Prodromes assessment tool" OR Instrument OR Measure OR Inventory OR Scale OR Questionnaire OR Interview*). A gray literature search was also performed, and the references of the selected articles were manually reviewed.

Study selection process

The first phase of our analysis, article identification, consisted of unifying the results of the searches performed in the three databases and the subsequent elimination of duplicate studies. Next, in the screening phase, we proceeded to read the titles and abstracts of the articles that potentially met the inclusion criteria. This process was carried out independently by the first two authors of this review (L.A.-C. and P. G.-V.) and their disagreements were resolved by a reasoned discussion. When there was no agreement, they agreed to review the questionable article in full text. In the eligibility phase, these same reviewers read all the articles shortlisted in the previous phase and the questionable articles. Their disagreements were resolved in a reasoned manner among them. When there was no agreement, another two authors of this review (G.L. and N.A.-

G.) finally decided whether the article met the inclusion criteria. Lastly, in the inclusion phase, the articles presented in this systematic review were finally selected.

Data extraction process for each study

The first two reviewers independently extracted the following information from each of the selected articles: study title, author(s), year of publication, country, sample size, participant characteristics, study design and methodology used, prodrome identification procedure, and study quality. Both reviewers independently assessed the risk of bias in the selected studies. Quantitative studies were assessed using a modified version of the Newcastle-Ottawa Scale (NOS; Rotenstein et al., 2016) adapted for this systematic review (Supplementary Table S1). Using the NOS, we assessed the representativeness and sample size of the study groups, the comparison between participants and nonparticipants, the prodrome assessment tools, and the quality of descriptive statistics. Selected quantitative studies were considered at low risk of bias (≥3 points) or high risk of bias (<3 points). Qualitative studies were assessed by means of the *Critical Appraisals Skills Programme* checklist (CASP, 2019).

Results

Forty-five studies met the inclusion criteria. The selection process of these studies is described in Figure 1. The main characteristics of the 26 studies that used initial prodrome identification procedures are presented in Table 1. A total of 8,014 persons participated in these studies. According to the available data, their weighted mean age was 18.91 years (k = 23). A quantitative methodology was used in 24 studies, a qualitative methodology in 1 study, and a quantitative and qualitative methodology in 1 study.

The main characteristics of the 19 studies that used relapse prodrome identification procedures are presented in Table 2. These studies involved 1,136 patients. According to the available data, their weighted mean age was 41.34 years (k = 16). A quantitative methodology was used in 18 studies and a quantitative and a qualitative methodology in 1 study.

Procedures for identification of initial prodromes

Twenty-six selected articles detect initial prodromes through different assessment tools. Figure 2 represents the percentage of use of each instrument.

Of the total articles about initial prodromes, 3 used the clinical interview as the only method of assessment of initial prodromes (Faedda et al., 2004; Özgürdal, et al., 2009; Skjelstad et al., 2012). In the case of Özgürdal and colleagues (2009), the *semi-structured* and *ad hoc elaborated interview* focused on mood swings. On the other hand, Benti and colleagues (2014) combined an *ad hoc semi-structured interview* with an *ad hoc self-report questionnaire*.

Sixteen studies used different types of instruments that were applied in a clinical interview format, alone or in combination with other prodrome screening instruments (Correll et al., 2014a; Duffy et al., 2007, 2010; Egeland et al., 2003, 2012; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Noto et al., 2015; Salazar de Pablo et al., 2020; Thompson et al., 2003; Tijssen et al., 2010; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021). Notable for its frequency of use in research is the *Bipolar Prodrome Symptom Scale* (BPSS), which was used as a semi-structured interview in 7 (Correll et al., 2014a; Noto et al., 2015; Salazar de Pablo et al., 2020; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021) of the 16 articles. The most employed BPSS format was retrospective (BPSS-R) and used in 4 (Noto et al., 2015; Zeschel et al., 2013, 2015; Zhao et al., 2021) of these 7 studies. The BPSS-R assesses the pattern of onset, duration, severity, and frequency of 39 symptoms and signs prior to the first episode of mania or depression. In 2 studies (Correll et al., 2014a; Salazar de Pablo et al., 2020) the prospective format (BPSS-P) was used. The BPSS-P is composed of 10 clinical manic items, 12 clinical depressive items, and 6 general symptoms. This tool was developed to assess and characterize lifetime prodromal mania, depression, and general symptoms, both in presence and severity. For its part, the last (Van Meter et al., 2019) of these 7 works applied two versions of the BPSS: the *Bipolar Prodrome Symptom Scale Full-Prospective* (BPSS-FP) and the *Bipolar Prodrome Symptom Scale - Abbreviated Screen for patients* (BPSS-AS-P). This latter version of the BPSS is based on the former (BPSS-FP) but is shorter and simpler

in format. Zeschel and colleagues (2013) combined the BPSS-R with an *ad-hoc semi-structured interview for mood swings*.

The second most frequently employed instrument in interview form was the *Kiddie-Schedule for Affective Disorders & Schizophrenia, Present and Life Version* (K-SADS-PL) aimed at early diagnosis of affective disorders. The K-SADS-PL is one of four versions of the *Schedule for Affective Disorders and Schizophrenia for School-aged Children* (K-SADS) which is used in school-aged children aged 6 to 18 years. The K-SADS-PL was used in 4 of the 16 studies mentioned above (Duffy et al., 2007, 2010; Hafeman et al., 2016; Hernandez et al., 2017). In the case of Hafeman and colleagues (2016), they selected only some subscales or items from this instrument, specifically *the K-SADS-PL Mania Rating Scale* and *depression items*. Additionally, in their study, Hafeman and colleagues (2016) included the *Child- Report Affective Lability* scale, derived from the *Children's Affective Lability Scale* (CALS). Hernandez and colleagues (2017), in addition to using the K-SADS in their article, included a survey developed from DSM-IV criteria to retrospectively assess the presence of BD symptoms.

Another instrument in interview format is the *Child and Adolescent Research Evaluation* (CARE) interview, used in 2 publications by the same authors (Egeland et al., 2003, 2012). The CARE includes three parts (A, B, and C): Part A collects information related to pregnancy and birth, Part B is composed of open-ended questions, and Part C is composed of 40 closed-ended questions.

Three studies (Findling et al., 2005; Thompson et al., 2003; Tijssen et al., 2010) used a variety of instruments in interview format. Findling and colleagues (2005) used the *Young Mania Rating Scale* (YMRS) and the *Children's Depression Rating Scale-Revised* (CDRS-R), both of which evaluate the presence and/or severity of manic and depressive symptoms. The YMRS consists of 11 items that are answered with 0-4 points, or 0-8 points depending on the item. The CDRS-R consists of 17 items that are answered with 1-5 points, or 1-7 points depending on the item (1 = *no difficulties*, 7= *severe difficulties*). Findling and colleagues (2005) also included an inventory within the prodrome assessment, the *Parent General Behavior Inventory* (P-GBI) composed of 73 items that assess parent-reported symptoms of mania and depression; parents answer according to a 4-point Likert scale (0 = *never or hardly ever*; to 3 = *very often or almost*

constantly). Thompson and colleagues (2003) used a clinical interview that incorporates items or questions from different instruments, including: the *Structured Clinical Interview for DSM-IV* (DSM-IV SCID), *Brief Psychiatric Rating Scale* (BPRS) and YMRS. Finally, Tijssen and colleagues (2010) used the computerized version of the *Munich-Composite International Diagnostic Interview* (CAPI version of DIA-X/M-CIDI) composed of 28 items measuring depressive symptoms and dysthymia and 11 items measuring mania symptoms. In this version, a clinician conducts an interview with the help of a computer and records the presence or absence of the symptom/item.

Of all the articles included in the systematic review on initial prodromes, the works of Bechdolf and colleagues (2014) and Hafeman and colleagues (2017) are unique for providing specific criteria that may predict development of BD based on the presence of these criteria in the prodromal phase. Bechdolf and colleagues (2014) developed the *Bipolar at-risk criteria (BAR-criteria)* to identify groups at increased risk of conversion to a first episode of mania/hypomania. Hafeman and colleagues (2017) proposed the *person-level risk calculator* as a predictive model of BD development; the clinician takes into consideration different variables and estimates the probability of occurrence of BD in a time interval.

Two papers (Fergus et al., 2003; Hirschfeld et al., 2003) of the 26 publications on early prodromes administered *ad-hoc* surveys exclusively.

Finally, we should point out that 2 early prodrome detection studies (Birmaher et al., 2013; Estey et al., 2014) used a scale as the only measuring instrument. Birmaher and colleagues (2013) used the *Children's Affective Lability Scale* (CALS), a 20-item tool completed by parents responding according to a 5-point scale (*never/rarely*; *1-3 times/month; 1-3 times/week; 4-6 times/week; and equal to or greater than 1 times/day*). Estey and colleagues (2014) applied the *Bipolar Scale of the Retrospective Coolidge Personality and Neuropsychological Inventory* (CPNI-R), which may be completed in either self- or observer-report (i.e., significant other) formats. Items are answered on a 4-point Likert scale (1 = *strongly false*, 2 = *more false than true*, 3 = *more true than false*, and 4 = *strongly true*). The *CPNI-R* has a 3-component structure, including a mania component, a depression component, and an emotional and behavioral lability component.

Table 3 presents information on the populations in which these screening procedures were used. In 20 of the 26 papers on early prodromes, different methods of prodrome screening were used in patients diagnosed with BD and/or other affective spectrum disorders (e.g., unipolar depression/major depressive disorder or mood disorder NOS) (Benti et al., 2014; Birmaher et al., 2013; Correll et al., 2014a; Estey et al., 2014; Faedda et al., 2004; Fergus et al., 2003; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Hirschfeld et al., 2003; Noto et al., 2015; Özgürdal et al., 2009; Salazar de Pablo et al., 2020; Skjelstad et al., 2012; Thompson et al., 2003; Tijssen et al., 2010; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021). The remaining 6 investigations (Bechdolf et al., 2014; Duffy et al., 2007, 2010; Egeland et al., 2003, 2012; Hafeman et al., 2017) recruited individuals at risk of developing BD as their primary sample.

Of the 20 articles conducted on patients with a diagnosis of BD and/or different affective spectrum disorders, 8 papers (Birmaher et al., 2013; Faedda et al., 2004; Fergus et al., 2003; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Salazar de Pablo et al., 2020; Van Meter et al., 2019) evaluated clinical diagnoses of BD in children and/or adolescents. In the case of Birmaher and colleagues (2013), Faedda and colleagues (2004), and Fergus and colleagues (2003), the informants were exclusively parents. In 4 studies (Correll et al., 2014a; Skjelstad et al., 2012; Thompson et al., 2003; Tijssen et al., 2010) the sample consisted of adolescents and adults with a clinical diagnosis of BD.

Seven papers (Benti et al., 2014; Estey et al., 2014; Hirschfeld et al., 2003; Noto et al., 2015; Özgürdal et al., 2009; Zeschel et al., 2013, 2015) evaluated BD in an exclusively adult population. In six of these studies (Benti et al., 2014; Hirschfeld et al., 2003; Noto et al., 2015; Özgürdal et al., 2009; Zeschel et al., 2013, 2015) the patient was the informant.

Finally, the study by Zhao and colleagues (2021), although conducted with a sample of patients with a diagnosis of BD, did not specify participant age or the main informant in the diagnostic evaluation.

Regarding the 6 investigations conducted on groups of people at risk of developing BD (Bechdolf et al., 2014; Duffy et al., 2007, 2010; Egeland et al., 2003,

2012; Hafeman et al., 2017), 3 studies (Egeland et al., 2003, 2012; Hafeman et al., 2017) sampled children and adolescents of a first-degree relative with BD (e.g., parents). In the studies by Egeland and colleagues (2003, 2012) the informants were solely the parents. Bechdolf and colleagues (2014) interviewed adolescents and young adults (15-24 years) who were analyzed for compliance with BAR- criteria. Finally, the work of Duffy and colleagues (2007, 2010) employed a heterogeneous sample in terms of age and included children, adolescents, and young adults (18- 25 years) at risk of developing BD.

Relapse prodrome identification procedures

Nineteen of the selected articles used different kinds of instruments for relapse prodrome detection in BD. Figure 3 represents the percentage of use of each instrument.

Of the total articles about relapse prodromes, 10 (Altman et al., 1992; Fletcher et al., 2013; Houston et al., 2007; Lam et al., 2001; Mander, 1990; Mantere et al., 2008; Molnar et al., 1988; Ryu et al., 2012; Sahoo et al., 2012; Smith & Tarrier, 1992) used clinical interviews or other instruments (e.g., BPRS, YMRS, CPSI) administered in a clinical interview format for detecting a relapse prodrome.

Four papers (Fletcher et al., 2013; Mander, 1990; Mantere et al., 2008; Molnar et al., 1988) employed clinical interviews. Fletcher and colleagues (2013) conducted a qualitative semi-structured interview covering various aspects of hypomania and depression from the prodromal phase to the onset of florid affective symptoms, documenting personal experiences and coping strategies prior to and during the recent episode. Mander (1990) conducted a weekly semi-structured interview of prodromal manic and depressive symptoms. Mantere and colleagues (2008) asked patients about the presence, type, and occurrence of their first prodromal symptoms and then subsequently categorized their responses according to DSM-IV criteria. Finally, Molnar and colleagues (1988) conducted a clinical interview about the duration of each patient's affective episode, the duration of their prodromal stage, and the symptoms they experienced.

Two papers (Ryu et al., 2012; Smith & Tarrier, 1992) employed symptom *checklists* applied in the form of an interview. Ryu and colleagues (2012) applied a 40-item checklist covering 15 symptoms of mania, 15 symptoms of depression, and 10

mixed-episode symptoms. For each item, the interviewer scored the absence (0) or presence (1) of a prodromal symptom; on this occasion, patients were interviewed about the prodromal phases of their last manic episode. Smith & Tarrier (1992) designed a checklist of 40 items (15 for mania, 15 for depression, and 10 for mixed episodes), extracted from the symptoms cited by Molnar and colleagues (1988), Birchwood and colleagues (1989), and from data collected during pilot interviews. The interview included questions about the prodromal period before their last manic episode and their last depressive episode. If symptoms occurred during the prodrome, they were rated as *mild (1) or strong (2).* If a symptom was not present, it was rated as *absent (0)*. In addition, the authors asked about other symptoms not included in the checklist, namely idiosyncratic experiences (a symptom unique to one subject).

Three of the articles reviewed (Altman et al., 1992; Houston et al., 2007; Lam et al., 2001) used different instruments in the form of clinical interviews. Altman and colleagues (1992) administered the expanded version of the *Brief Psychiatric Rating Scale* (BPRS-E). The BPRS-E is administered face-to-face and includes the 18 items of the original BPRS, plus 6 more items measuring affective and psychotic symptoms relevant to BD: *elated mood, motor hyperactivity, distractibility, suicidality, self-neglect, and bizarre behavior*. The items are answered according to a 7-point severity scale, with a score of 1 meaning that the patient is asymptomatic for that item. The BPRS also included a short version to be administered by telephone. This short version consisted of 10 items, which were considered as *"relapse scales"*: *depression, hostility, unusual thought content, hallucinations, conceptual disorganization, suicidality, self-neglect, bizarre behavior, elated mood, and motor hyperactivity*. Houston and colleagues (2007) chose to use the YMRS as an instrument to detect prodromes of mania relapse. This scale was completed by the clinician during the initial consultation in the form of a clinical interview and included subjective comments from the patient and observations by the interviewer. Finally, Lam and colleagues (2001) used the *Coping with Prodromal Symptoms Interview* (CPSI) in the form of a semi-structured interview to diagnose symptom relapse. Participants were asked about their experiences with prodromal symptoms in past episodes and how they coped with them.

The primary method used by Sahoo and colleagues (2012) for prodrome detection was an 83-item scale derived from the *Comprehensive Psychopathology*

Rating Scale, the *Young Mania Rating Scale*, the *Bech-Rafaelsen Mania Rating Scale*, the *Beck Depression Inventory* and *Paykel's Clinical Interview for Depression*. However, the authors also incorporated an unstructured interview to collect prodromal symptoms not reflected in the composite scale including *"idiosyncratic prodromal symptoms such as increased religiosity, taking decisions easily, reddening of eyes, being abusive, listening to loud music, recalling past events, and ideas of reference"* (Sahoo et al., 2012. p. 181). In their survey, Sahoo and colleagues (2012) provided a brief description of each item, and prodromal symptoms were classified as either present or absent.

The remaining 9 studies (Bauer et al., 2006; Fellendorf et al., 2021; Glenn et al., 2006; Goossens et al., 2010; Grünerbl et al., 2015; Keitner et al., 1996; Lobban et al., 2011; Perlman et al., 2006; Wong & Lam, 1999) used other formats (e.g., mobile apps, computerized tools) of relapse prodrome detection.

The *ChronoRecord* application, a computerized and validated version of the *ChronoSheet self-report*, was used in two studies (Bauer et al., 2006; Glenn et al., 2006) to detect the relapse prodrome in BD patients. This application allows the assessment of mood, medication intake, and sleep. Bauer and colleagues (2006) used a 100-unit visual analog scale between the extremes of mania and depression for the patient to indicate their mood. The patients provided a daily mood rating covering the previous 24 hours. Regarding the sleep recording, the patient's status alternated every hour, depending on whether the patient was awake, asleep, or on bed rest. In the case of Glenn and colleagues (2006), data from 60 days prior to symptom relapse were compared with data from at least one month of euthymia, in addition to comparing the 60 days prior to a manic relapse versus a depressive relapse.

In two articles (Fellendorf et al., 2021; Grünerbl et al., 2015) mobile apps were used for the detection of relapse prodrome. Fellendorf and colleagues (2021) employed the smartphone app *UP!* for a period of 6 months and collected data regarding sleep, physical activity, and social profile (e.g., app usage on a smartphone such as Facebook©, WhatsApp©, Skype©; and smartphone checks during the week and during weekends). Sleep-related information was obtained using the phone's accelerometer and light sensors. Furthermore, patients rated their mood with seven choices of emoticons

once a day at night. Physical activity behaviors and sleep periods were assessed using an *Axivity3* accelerometer, worn on the wrist of the non-dominant hand. Grünerbl and colleagues (2015) developed an Android smartphone app. Each patient was given a smartphone that ran the developed app and recorded all sensor data automatically at the end of the day. Data collection was based on the importance of different aspects of behavior: *social interaction, physical motion,* and *travel patterns*. *Social interaction* was assessed by two parameters: *phone call features* (e.g., number of phone calls, total length of calls, the average length of phone calls, a standard deviation of the length of phone calls, and number of unique numbers) and *sound features* (e.g., speech features such as average speaking length and speaking turn duration and voice features to detect the emotions from the voice). *Physical motion* and *travel patterns* were collected using sensors, GPS, and an accelerometer. Weighted fusion of only location and acceleration data provided very good results, but the addition of social interaction improved the overall accuracy of prodrome detection.

Three of the papers reviewed (Goossens et al., 2010; Keitner et al., 1996; Wong & Lam, 1999) employed open-ended questions. Goossens and colleagues (2010) asked two questions to explore prodromal symptoms: *"How can you tell if an episode of mania or depression is impending?"* and *"What is the first sign or behavior that you recognize in yourself that leads up to a manic or depressive episode?*". In the case of Keitner and colleagues (1996) patients were given an *ad hoc* open-ended self-report, in which prodromal and residual symptoms were assessed. The questions used were as follows: *"Please describe the behaviors you have experienced leading up to a manic or depressive episode. How can you tell that an episode is coming on?"* and *"Please describe any mood, thought, feeling, etc. That persists or lingers even when it appears to others that the episode is over. What is still not right?"*. Responses were classified into 6 domains: *mood symptoms, behavioral symptoms, cognitive symptoms, neurovegetative symptoms, social symptoms,* and *other symptoms*. Wong & Lam (1999) sent a postal survey, which included an open-ended question for the patient to describe the early warning signs of a manic episode, i.e., changes in the person's thinking, feeling, and behavior that may raise suspicion of relapse. The use of the open-ended question made it possible to describe the most idiosyncratic prodromes for each patient and subsequently categorize them.

One study (Lobban et al., 2011) used *an Early Warning Signs checklist for mania and depression* (EWS) as an instrument to detect prodrome of relapse within a two-part assessment. In the first part, the patient spontaneously reported his or her first prodromes and their frequency. In the second part, they used an EWS composed of 32 depression items and 31 mania items that classified them as absent, early, late, or complete. The checklist items were obtained from previous studies by Molnar and colleagues (1988); Smith & Tarrier (1992); Wong & Lam (1999) and Lam and colleagues (2001). The prodrome checklists were mailed to patients.

Finally, because of the importance of sleep disturbances as a prodrome in BD, Perlman and colleagues (2006) used the *Sleep Duration subscale* of the *Pittsburgh Sleep Quality Index* in the form of a self-report. Patients recorded the hours they slept during the past month and subsequently forwarded it by email to the investigators.

Regarding the populations to which these assessment procedures were applied, although all 19 studies were conducted with patients who had a diagnosis of BD according to DSM or ICD criteria. In 6 papers (Altman et al., 1992; Keitner et al., 1996; Lam et al., 2001; Perlman et al., 2006; Ryu et al., 2012; Sahoo et al., 2012) the sample consisted only of patients with type I BD, while one paper (Fletcher et al., 2013) was conducted only with patients with type II BD. Five of the studies (Keitner et al., 1996; Mander, 1990; Molnar et al., 1988; Ryu et al., 2012; Sahoo et al., 2012) involved a family member/caregiver as informants, in addition to the patient.

Psychometric properties of two prodrome identification procedures.

One of the most widely used prodrome screening instruments in adults and adolescents is the BPSS-P (Correll et al., 2014b). For the validation of the BPSS-P, Correll and colleagues (2014b) started with a total sample of 205 participants. Of these, 92 were patients at high risk of developing psychosis, 42 were subjects with neither psychiatric diagnosis nor a high risk of developing psychosis (control group) and 71 were patients with different diagnoses of affective spectrum disorders and psychotic spectrum disorders (e.g., BD-I, BD-II, BD NOS, cyclothymia, MDD, depressive disorder NOS, dysthymia, or mood disorder NOS, schizophrenia, schizoaffective disorder, schizophreniform disorder, or psychotic disorder NOS). The group of participants at high risk of developing psychosis and the control group (CG) had an age

range of 12-15 years; patients with different diagnoses of affective and psychotic spectrum disorders had an age range of 12-18 years. By biological sex, 40.5% were male in the CG whereas 57.5% were male between individuals with high risk of developing psychosis and individuals with a diagnosis of affective and/or psychotic spectrum disorders.

The BPSS-P is a semi-structured interview that assesses the occurrence and severity of prodromal symptoms and divides them into three sections: *Mania*, *Depression* and *General Symptom Index*. Each item is scored according to an ordinal scale (0 =*absent*; 1= *questionably present*; 2 = *mild*; 3 = *moderate*; 4 = *moderately severe*; 5 = *severe* and 6 = *extreme*). Symptom severity is evaluated for the month and year prior to the time of the interview.

To examine the psychometric properties of the BPSS-P, Correll and colleagues (2014b) employed the following measurement instruments: *Young Mania Rating Scale* (YMRS), *Montgomery-Asberg Depression Rating Scale* (MADRS), *Parent General Behavior Inventory-10-item Mania* (GBI-M-10) and *Cyclothymic-Hypersensitive Temperament* (CHT) questionnaire of the *Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Autoquestionnaire* (TEMPS-A).

Regarding the reliability in terms of internal consistency of the BPSS-P, Correll and colleagues (2014b) found acceptable to good reliability across the three sections of the instrument: *Mania* ($\alpha = 0.87$), *Depression* ($\alpha = 0.89$) and *General Symptom Index* ($\alpha = 0.74$). Inter-rater reliability (i.e., intraclass correlation or ICC) was also high for the BPSS-Total (ICC = 0.93), and for the different indices that compose it: BPSS-P *Mania Index* (ICC = 0.93); BPSS-P *Depression Index* (ICC = 0.98) and BPSS-P *General Index* (ICC = 0.98).

Regarding convergent validity, Correll and colleagues (2014b) found adequate values for the main Spearman's rank correlation coefficients. Namely, ρ values between the BPSS-P *Mania Index* and the YMRS, the GBI-M-10 and the CHT were 0.52, 0.54, and 0.56, respectively; ρ values between the BPSS-P *Depressive Index* and the MADRS and the CHT were 0.69 and 0.50, respectively; and ρ values between the *General Index* and the GBI-M-10 and the CHT were 0.56 and 0.55, respectively.

In terms of discriminant validity, the BPSS-P total scores were significantly different [F (5195) = 55.73; $p < 0.0001$] between diagnostic groups. Post-hoc analyses revealed that BPSS-P *Mania Index* scores were significantly higher in each of the following mood spectrum disorder groups when compared to the groups without an affective spectrum diagnosis and compared to the CG of participants without a psychiatric diagnosis: BD-I, BD-II, cyclothymia, BD NOS, and mood disorder NOS. In addition, patients diagnosed with BD-I, BD-II and/or cyclothymia had significantly higher BPSS-P *Total* scores than patients with depression spectrum disorders, patients with non-mood spectrum disorders, and CG individuals with no psychiatric diagnosis. Likewise, BPSS-P *Depression Index* scores were significantly higher [F (5,201) = 44.00; $p < 0.0001$] in patients with a diagnosis of depression spectrum disorder and in patients with BD-I, BD-II, cyclothymia, BD NOS, and mood disorder NOS when compared with scores in the group of patients with a diagnosis of non-mood spectrum disorder and with the CG of persons with no psychiatric diagnosis. Finally, BPSS-P *General Index* scores were also significantly different between the groups of patients with psychiatric diagnosis, [F (5,195) = 37.04; $p < 0.0001$] compared to the CG of persons without psychiatric diagnosis. However, no significant differences were found between each other in patients with psychiatric diagnoses, such as between patients with mood spectrum disorder and patients with non-mood spectrum disorder (Correll et al., 2014b).

Another instrument frequently used in the detection of prodrome is the K-SADS-PL. In their validation work, Kaufman and colleagues (1997) used 66 participants, 55 of whom were children and adolescents with a psychiatric diagnosis and 11 were children and adolescents without a diagnosis (CG). The age range of the entire sample was 7-17 years, 48% being boys.

The K-SADS-PL is a semi-structured interview composed of four parts: (1) an *Introductory Interview* which allows an interviewer to establish rapport and to collect demographic information, health information, presenting complaint, previous psychiatric treatments, information about the child's school functioning, hobbies and relationships with peer group and family; (2) a *Screening Interview* which covers 82-symptoms divided across 20 diagnostic areas that are evaluated by means of items ranging from 0 to 3 points (0 = *"no information is available"*; 1 = *"suggest the symptom*

is not present", 2 = *"indicate subthreshold levels of symptomatology"* and 3 = *"represent threshold criteria"*); (3) *Diagnostic supplements which* include (a) *Affective Disorders*; (b) *Psychotic Disorders*, (c) *Anxiety Disorders*, (d) *Behavioral Disorders*, and (e) *Substance Abuse, Eating and Tic Disorders;* (4) *Time Frame Coding Guidelines* which helps the clinician to score the symptoms in the child or adolescent's period of maximum severity (Kaufman et al., 1997).

To examine the psychometric properties of the K-SADS-PL, Kaufman and colleagues (1997) used the following measurement instruments: *Child Behavior Checklist* (CBCL), *Beck Depression Inventory* (BDI), *Children's Depression Inventory* (CDI), *Screen for Children Anxiety Related Emotional Disorders* (SCARED) and *Conners Abbreviated Questionnaire/Parent version.*

With regard to reliability in terms of temporal stability, Kaufman and colleagues (1997) found that the test-retest reliability coefficients ranged from excellent to good for most of the presenting diagnoses (MDD and *Any depression*, $\kappa = 0.90$; *Any bipolar disorder*, $\kappa = 1.00$; *Generalized anxiety disorder*, $\kappa = 0.78$; *Posttraumatic stress disorder*, $\kappa = 0.67$; *Any anxiety disorder*, $\kappa = 0.80$; ADHD, $\kappa = 0.63$; *Oppositional defiant disorder*, $\kappa = 0.74$) and for most of the *lifetime diagnoses* (MDD, *Any depression*, and *Any bipolar disorder*, $\kappa = 1.00$; *Depressive disorder* NOS, $\kappa = 0.86$; *Generalized anxiety disorder*, $\kappa = 0.78$; *Posttraumatic stress disorder* and *Any anxiety disorder*, $\kappa = 0.60$; ADHD, $\kappa = 0.55$; *Conduct disorder*, $\kappa = 0.83$ and *Oppositional defiant disorder*, $\kappa = 0.77$). Regarding the inter-judge or inter-rater reliability of the K-SADS-PL, Kaufman and colleagues (1997) found that the percentage of inter-judge agreement in assigning *present and lifetime diagnoses* was both 98% (range: 93% - 100%).

Regarding the concurrent validity of the K-SADS-PL; Kaufman and colleagues (1997) found that: (1) children who met the criteria for depressive disorders scored higher ($p < 0.01$) than other children on the *z*-scored transformed depression (calculated by combining BDI and CDI scores) and on the CBCL *Internalizing Scales* ($p < 0.001$); (2) children who met criteria for ADHD scored higher than other children on the *Conners Abbreviated Questionnaire/Parent version* ($p < 0.001$); (3) children who met criteria for *Any current anxiety disorder* scored higher than other children on the

SCARED ($p < 0.0001$) and *CBCL Internalizing Scales* ($p < 0.01$); and (4) children who met criteria for *Any current behavioral disorder* scored higher than other children on the CBCL *Externalizing Scale* ($p < 0.0001$).

Discussion

Interpretation of findings

This is the first systematic review that details the instruments used to identify the initial and relapse prodromes of BD. In addition, we identified the populations in which these instruments were used and the psychometric properties of two widely used instruments, the BPSS-P, and the K-SADS-PL.

Since the course of BD alternates phases of stability with symptomatic episodes, prodromes are sometimes difficult to distinguish from age-appropriate changes, mood changes, and even residual symptoms or unipolar episodes (Pfennig et al., 2020). Thus, the identification of tools that accurately detect prodromal processes or relapse in BD may help clinicians and researchers to make the best clinical decisions. Added to this, a delay in the treatment of the disorder (often debuting in adolescence or early adulthood) is associated with a worse prognosis, including greater symptom severity, fewer phases of euthymia, presence of rapid cycling, increased risk of suicide, and worse response to pharmacological treatment (Chen & Dilsaver, 1996; Kessing et al., 2014; Miller et al., 2014; Pfennig et al., 2020; Post et al., 2010; Verdolini et al., 2022). Therefore, it is important to know and use reliable and valid tools that enable early detection of prodromal symptoms of BD in different groups of people and to implement appropriate interventions at different stages of the disease (Vieta et al., 2018).

Fernández-Ballesteros (2013) classifies assessment instruments in psychology and psychopathology into 6 categories: observational techniques, objective techniques, self-report techniques, the interview, subjective techniques, and projective techniques. This classification may help situate the findings of the present systematic review. In the selected studies, the interview was the most frequently employed method in the detection of BD prodromes. Some papers used clinical interviews with varying degrees of structuring and, sometimes, *ad hoc* elaborated interviews (Benti et al., 2014; Faedda et al., 2004; Fletcher et al., 2013; Mander, 1990; Mantere et al., 2008; Molnar et al., 1988; Özgürdal, et al., 2009; Skjelstad et al., 2012). Furthermore, in several of the

included papers, the authors used different types of instruments (e.g., scales, questionnaires, symptom checklists) within a clinical interview format (Altman et al., 1992; Correll et al., 2014a; Duffy et al., 2007, 2010; Egeland et al., 2003, 2012; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Houston et al., 2007; Lam et al., 2001; Noto et al., 2015; Ryu et al., 2012; Sahoo et al., 2012; Salazar de Pablo et al., 2020; Smith & Tarrier, 1992; Thompson et al., 2003; Tijssen et al., 2010; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021).

The interview is a broad-spectrum assessment tool (Fernández-Ballesteros, 2013) that collects data from the subject being assessed but is also used to collect information about a third person from an interlocutor (Fernández-Ballesteros, 2013). An advantage of the interview as a general assessment tool is that it generates an immediate response from the individual. In addition, it allows the clinician to adapt his or her language to the educational level of the interviewed subject, rephrase the question if necessary, and observe the person's nonverbal behavior (Andrade-González et al., 2020). An advantage of the clinical interview aimed at detecting BD prodromes is that there is no *a priori* assumption about patients' prodromal symptoms so that the subject can report idiosyncratic symptoms (Lam & Wong, 2005) and the clinician can consider the differences between their patients' prodromal manifestations. However, a drawback of the interview is that it demands more resources and time on the part of the evaluator (Lam & Wong, 2005).

Other instruments such as symptom *checklists*, questionnaires, or inventories are less expensive than the interview, easier to administer, and may allow the subject to think about his or her answers. However, as far as BD prodrome detection is concerned, such instruments may have a drawback in that the patient may tend to indicate prodromes in an indiscriminate way (Andrade-González et al., 2020; Lam & Wong, 2005; Skjelstad et al., 2010).

In the present review, we found that new technologies were used in only one study for the detection of initial prodromes (Tijssen et al., 2010). However, for the detection of relapse prodromes, digital technology appears to be increasingly used (Bauer et al., 2006; Fellendorf et al., 2021; Glenn et al., 2006; Grünerbl et al., 2015). According to Monteith and colleagues (2016), the patient plays an active role in the data

collection (e.g., *ChronoRecord* by Bauer et al., 2006; Glenn et al., 2006) whereas other digital platforms rely on passive data collection methods like smart sensors (Fellendorf et al., 2021; Grünerbl et al., 2015). It should be noted that a Spanish research group is in the process of creating an app that may help BD patients self-monitor symptoms and access psychoeducation, although this digital application does not constitute, per se, a prodrome detection tool (Hidalgo-Mazzei et al., 2018). The contents of this app are based on a group psychological program previously developed, evaluated, and carried out by Colom and colleagues (2009).

Leopold and colleagues (2012) analyzed the early phases and *early symptoms* in the development of BD and developed an assessment instrument, a semi-structured interview called the *Early Phase Inventory for Bipolar Disorders* (EPIbipolar), that may help detect the frequent *early symptoms* of the disorder. These authors understand *early symptomatology* to include: (a) *changes in sleep and circadian rhythm*, (b) *changes in mood, mood swings/affective lability*; (c) *fearfulness/anxiety*; and (d) *dissociative symptoms*. Using the EPIbipolar interview, symptoms are assessed according to their frequency of occurrence and severity; *"those items thought to undergo dynamic changes in the early phase of bipolar disorders are described in terms of their temporal development"* (Leopold et al., 2012, p.1005). The assessed subjects are assigned to one of the following four final groups: *no risk at present*, *risk status*, *high risk status* and *ultra-high risk status* (Leopold et al., 2012) similar to the risk categories for BD development proposed by other authors (Howes et al., 2011; Skjelstad et al., 2010).

Regarding the secondary objectives of this review, the samples used in the selected papers consisted of patients with a diagnosis of BD and/or different affective spectrum disorders (Altman et al., 1992; Benti et al., 2014; Birmaher et al., 2013; Correll et al., 2014a; Estey et al., 2014; Faedda et al., 2004; Fergus et al., 2003; Findling et al., 2005; Hafeman et al., 2016; Hernandez et al., 2017; Hirschfeld et al., 2003; Keitner et al., 1996; Lam et al., 2001; Noto et al., 2015; Özgürdal et al., 2009; Perlman et al., 2006; Ryu et al., 2012; Salazar de Pablo et al. et al., 2020; Sahoo et al., 2012; Skjelstad et al., 2012; Thompson et al, 2003; Tijssen et al., 2010; Van Meter et al., 2019; Zeschel et al., 2013, 2015; Zhao et al., 2021) and, to a lesser extent, by subjects at risk of developing BD (Bechdolf et al., 2014; Duffy et al., 2007, 2010; Egeland et al., 2003, 2012; Hafeman et al., 2017). Regarding the psychometric properties of two

instruments widely used in the reviewed studies, the BPSS-P and the K-SADS-PL are two reliable and valid measures, according to the results presented in the respective validation studies by Correll and colleagues (2014b) and Kaufman and colleagues (1997).

While the identification of relapse prodromes in BD has clear clinical implications, it may also serve as a guide for the choice of mood stabilizer prescribed, dose adjustment, or other clinical pharmacological decisions (i.e., drug substitution, combination, etc.). According to a recent systematic review (Kishi et al., 2021), most mood stabilizers reduced the recurrence or relapse rates of any mood episode. Lithium is recommended as the drug of choice for the treatment of adult patients with BD in the maintenance phase (Fountoulakis et al., 2017; Goodwin et al., 2016; Yatham et al., 2018), but very few patients maintain treatment long enough to establish remission; between 40-60% discontinue lithium after 5 to 7 years of treatment (Nilsson et al., 1989; Schumann et al., 1999), and around 13% become resistant to lithium after 10 years (Maj et al., 1996).

Limitations and strengths

The present systematic review has some limitations. First, 36% (n = 12) of the initial prodrome detection studies and 52.63% (n = 10) of the relapse prodrome detection studies employed a retrospective design. Although there are retrospective data showing that patients with BD can recognize relapse symptoms before the first episode occurs (Lam & Wong, 2005), conclusions drawn from retrospective data should be interpreted with caution due to potential recall bias. Second, sample sizes were variable but predominantly small, which limits the generalizability of the results. Third, the possibility of the existence of persistent subsyndromal symptoms, rather than genuine prodromes, which may not be related to new episodes, cannot be ruled out entirely. Finally, inherent in the detection of a prodrome, it is difficult to identify the end of the prodrome and the onset of the disorder.

An important ethical consideration concerns the evaluation of individuals at risk for BD (Fusar-Poli et al., 2022). Clinicians and researchers should consider the potential risks and benefits and the cost-benefit ratio from a public health perspective of early detection and intervention of any pathology (Burkhardt et al., 2021). Assessment and

intervention of individuals at putative risk of developing BD should be mindful of the normal fluctuations of a person's mood and behavioral patterns, the fact that not all individuals will develop the disorder, and the possible impact that interventions for BD (e.g., medication) may have on their daily functioning.

Future recommendations and conclusions

In conclusion, tools exist to detect initial and relapse prodromes of BD episodes. Since BD symptoms, as in other mental disorders, are dynamic and continuously evolving (Nelson et al., 2017), it will be necessary to confirm the predictive value and power of many of these procedures in studies that include larger samples of subjects and longer follow-up times. Although there are specific, reliable, and valid prodrome identification instruments available to clinicians and researchers such as the BPSS-P, future research should investigate the development of a brief tool that detects initial and relapse prodromes of BD using information gathered from interviews and self-reports and which can be applied to multiple stakeholders (e.g., patients, family members, and caregivers) either in-person or digitally (e.g., computer platforms or smartphones). This will require developing a set of items with excellent content validity, testing this tool in a multicenter study that provides a large sample of subjects, and providing adequate values for its reliability and validity. This tool may be a starting point to compare BD prodromes with those of other mental disorders and to evaluate differences across individuals of different age groups presenting with prodromal symptoms of BD.

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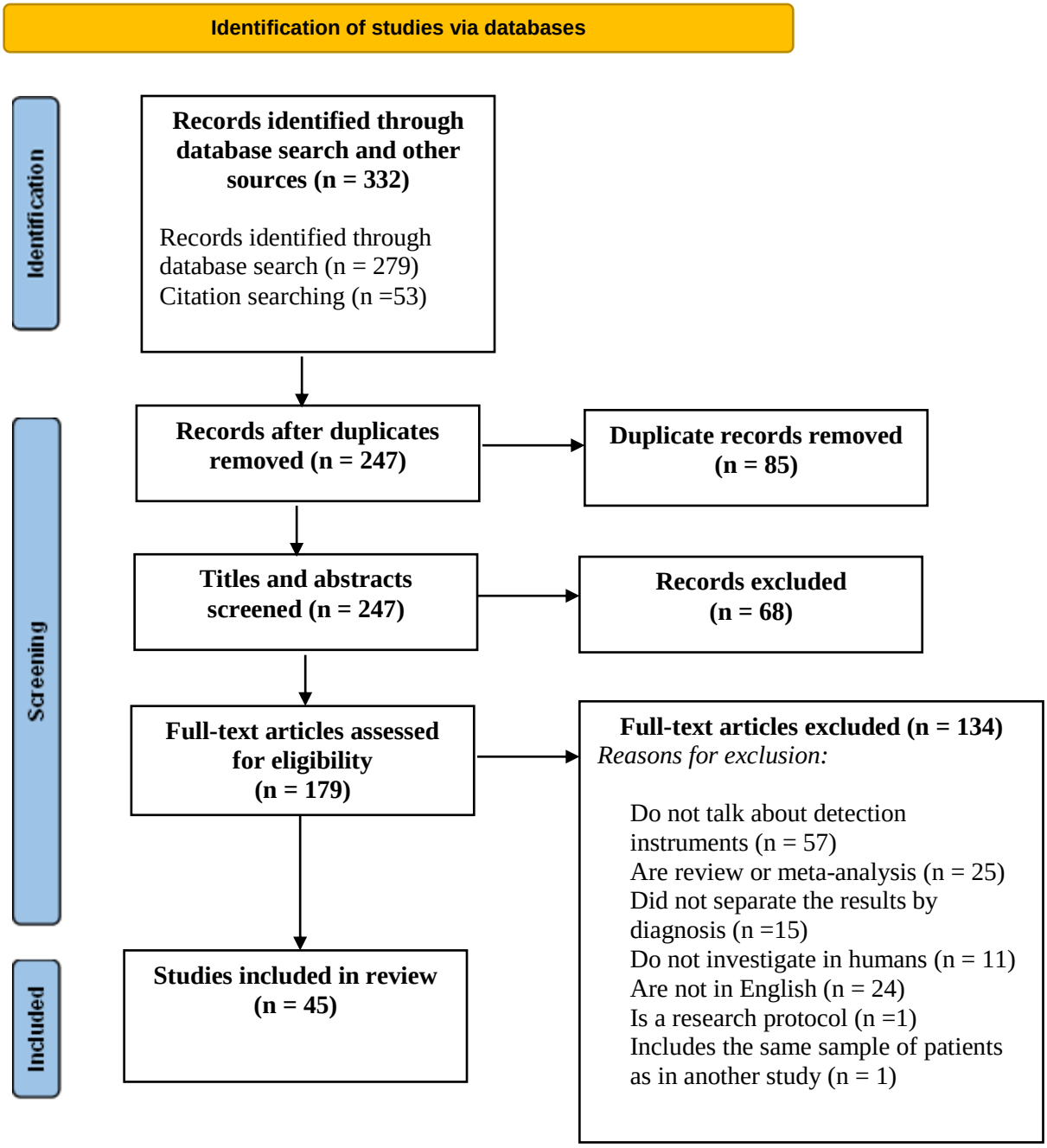

Figure 1. Flow Diagram of study selection – adapted from the diagram template provided by PRISMA (Page et al., 2021)

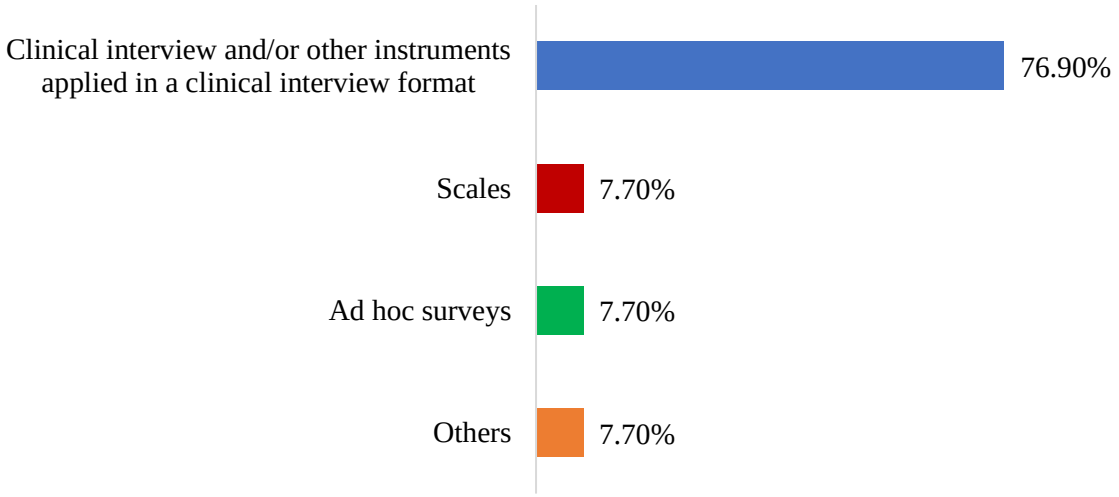

Figure 2. Initial prodrome assessment tools (percentage of use)

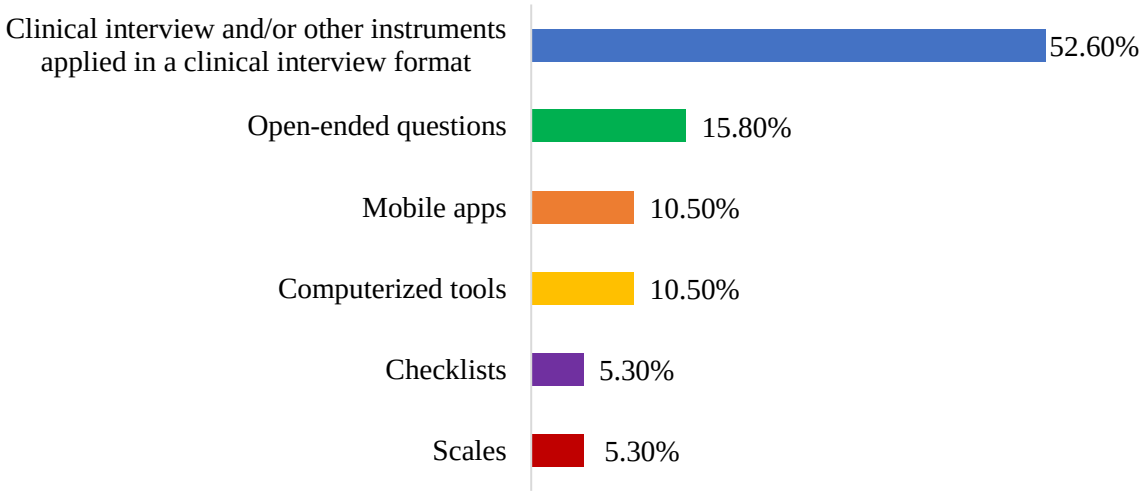

Figure 3. Relapse prodrome assessment tools (percentage of use)

Table 1. Initial prodromes. Characteristics of the selected studies

First author and year of publication	Country	Participants	*N*	Average age (SD)	Male (%)	BD I (%)	Design	Methodology	Prodrome identification procedure
Bechdolf et al. (2014)	Australia	BAR patients	35	19.20 (3.10)	17.10	0.00	P	Qn	BAR criteria
		Non-BAR patients	35	19.10 (2.70)	22.90	0.00			
Benti et al. (2014)	Australia	BD patients	19	n/a	16.00	†	R	Ql	Ad hoc semi-structured interview and ad hoc self-report questionnaire
		Unipolar depression patients	20	n/a	15.00	0.00			
Birmaher et al. (2013)	USA	BD offspring of parents with BD	41	13.80 (3.50)	41.50	26.80	P	Qn	CALS
		Non-BD offspring of parents with BD	257	12.80 (3.40)	52.10	0.00			
		Offspring of control parents	192	12.80 (3.30)	43.20	0.00			
		BD parents with BD offspring	38	37.60 (6.20)	5.30	60.50			
		BD parents with non-BD offspring	174	40.70 (7.20)	20.20	69.50			
		Control parents	117	42.20 (7.20)	23.90	0.00			
Correll et al. (2014a)	USA	Mood spectrum disorder patients	129	16.00 (1.90)	52.70	7.00	P	Qn	BPSS-P
		Non-mood spectrum disorder	34	16.00 (1.60)	76.50	0.00			
		Healthy controls	42	17.30 (2.40)	40.50	0.00			
		Caregivers	39	n/a	n/a	0.00			
Duffy et al. (2007)	Canada	Offspring of LiR	67	16.75 (5.65)	40.30	2.98	P	Qn	K-SADS-PL
		Offspring of LiNR	60	16.07 (5.06)	36.67	1.67			
		Offspring of normal control parent	61	14.44 (2.72)	42.62	0.00			

Duffy et al. (2010)	Canada	High risk offspring	207	16.50 (5.20)	41.00	3.86	P	Qn	K-SADS-PL
		Control offspring	87	14.70 (2.20)	41.00	0.00			
Egeland et al. (2003)	USA	Children with a BD parent	100	14.40 (8.10)[a]	100	0.00	P	Qn	CARE interview
				14.30 (7.10)[b]	0.00	0.00			
		Children with normal parents	110	14.40 (8.10)[a]	100	0.00			
				15.10 (7.10)[b]	0.00	0.00			
		Parents	28	n/a	50.00	50.00			
		Normal parents	26	n/a	50.00	0.00			
Egeland et al. (2012)	USA	Children with a BD parent	115	n/a	n/a	6.96	P	Qn	CARE interview
		Children with normal parents	106	n/a	n/a	0.94			
		Parents	30	n/a	50.00	50.00			
		Normal parents	24	n/a	50.00	0.00			
Estey et al. (2014)	USA	BD patients	30	29.60 (9.70)	26.67	30.00	R	Qn	Bipolar Scale of the CPNI-R
		Control group	30	28.10 (10.50)	26.67	0.00			
		Two groups of significant-others	60	46.00 (16.10)	10.00	n/a			
Faedda et al. (2004)	USA	BD patients	82	10.60 (3.60)	65.85	52.00	R[c]	Qn	Clinical interview
		Patients' parents	n/a	n/a	n/a	n/a			
Fergus et al. (2003)	USA	BD patients	78	13.70 (6.60)	50.00	†	R	Qn	Ad hoc parents' survey
		Non-BD patients	38	13.60 (6.90)	50.00	n/a			
		Healthy subjects	82	11.10 (7.10)	50.00	n/a			
		Parents	n/a	n/a	n/a	n/a			
Findling et al. (2005)	USA	BD patients	118	10.60 (3.20)	66.10	96.60	P	Qn	YMRS, CDRS-R, P-GBI
		Sub-syndromal BD patients	75	10.90 (3.10)	65.30	0.00			
		Non BD patients	207	11.80 (3.20)	57.00	0.00			
		Parents	756	n/a	47.49	16.80			
Hafeman et al. (2016)	USA	Offspring with bipolar spectrum	33	12.7 (2.70)	39.40	18.20	P	Qn	Child-Reported Affective Lability, K-SADS-PL Mania Rating Scale, and the depression items from the K-SADS-P
		At-Risk offspring	326	11.60 (3.60)	50.00	0.00			
		Community control	220	11.70 (3.40)	45.00	0.00			

		offspring							
		Bipolar parents with bipolar offspring	31	36.50 (5.90)	3.20	74.20			
		Bipolar parents without bipolar offspring	188	39.50 (7.50)	20.70	72.30			
		Community controls	127	41.00 (7.10)	22.80	0.00			
Hafeman et al. (2017)	USA	At risk offspring	412	12.00 (3.50)	51.00	2.18	P	Qn	Person-level risk calculator
Hernandez et al. (2017)	USA	BD patients	83	9.40 (3.86)	60.00	28.91	R	Qn	Retrospective ratings of symptoms from DSM-IV and K-SADS[d]
		Parents	83	n/a	n/a	n/a			
Hirschfeld et al. (2003)	USA	BD patients	600	n/a	34.00	†	R	Qn	Ad hoc self-report survey
Noto et al. (2015)	Brazil	BD patients	43	33.70 (6.80)	25.60	74.40	R	Qn	BPSS-R
Özgürdal et al. (2009)	Germany	BD patients	20	43.85 (9.38)	35.00	100	R	Qn[e]	Ad hoc semi-structured interview for mood swings
Salazar de Pablo et al. (2020)	USA	BD I patients	24	15.40 (1.40)	37.50	100	P	Qn	BPSS-P
		BD-NOS patients	29	15.90 (1.40)	34.50	0.00			
		MD-NOS patients	23	15.40 (1.40)	52.20	0.00			
Skjelstad et al. (2012)	Norway	BDII	15	26.70 (6.40)	26.67	0.00	R	Qn & Ql	Retrospective interviews of patients and family members.
		Family members	22	n/a	n/a	n/a			
Thompson et al. (2003)	Australia	BD patients	3	21 (4.00)	0.00	66.67	P	Qn	Clinical interviews incorporating DSM-IV SCID, BPRS and YMRS
Tijssen et al. (2010)	Germany	BD patients	1648	18.20 (3.30)	53.90	†	P	Qn	CAPI version of DIA–X/M–CIDI[f]
Van Meter et al. (2019)	USA	BSD	32	15.84 (1.30)	21.90	21.80	P	Qn	BPSS-AS-P and BPSS-FP
		Depressive disorder patients	81	15.60 (1.40)	26.20	0.00			
		No mood disorder	21	15.39 (1.60)	38.90	0.00			
Zeschel et al. (2013)	Germany	BD patients	42	35.10 (10.00)	40.50	64.30	R	Qn	BPSS-R and ad hoc semi-structured interview for mood swings
Zeschel et al. (2015)	Germany	BD patients I	24	35.71 (9.25)	33.30	100	R	Qn	BPSS-R
		BD patients II	15	36.67 (11.27)	53.30	0.00			

Zhao et al. (2021)	China	BD patients	120	26.50 (10.00)	65.00	76.67	R	Qn	BPSS-R

Note. *N* = total number of patients with bipolar disorder (BD) included in the study; SD, standard deviation; P = prospective; Qn = Quantitative data; BAR = Bipolar at-risk ; † = the study does not specify; BD I; R = retrospective; Ql = Qualitative data; CALS = Children's Affective Lability Scale ; BPSS-P = Bipolar Prodrome Symptom Scale-Prospective ; LiR = Lithium responder; K- SADS-PL = Kiddie-Schedule for Affective Disorders & Schizophrenia, Present & Lifetime Version; LiNR = Lithium non-responder; [a] = male; CARE = Children and Adolescent Research Evaluation ;[b] = female; CPNI-R = Coolidge Personality and Neuropsychological Inventory; [c] = partially retrospective study; CDRS-R= Children's Depression Rating Scale-Revised; YMRS = Young Mania Rating Scale; P-GBI = Parent General Behavior Inventory; [d] = Only 35 symptoms were selected; BPSS-R = Bipolar Prodrome Symptom Scale-Retrospective; [e] = The study also provides qualitative data; BD-NOS = Bipolar Disorder - Not Otherwise Specified; MD–NOS = Mood disorder - Not Otherwise Specified; DSM IV SCID = Structured Clinical Interview for DSM IV; BPRS = Brief Psychiatric Rating Scale; [f] = Interviews were conducted using the Computer-Assisted Personal Interview (CAPI) version of the Munich–Composite International Diagnostic Interview; BSD = Bipolar Spectrum Disorder; BPSS-AS-P = The Bipolar Prodrome Symptom Scale-Abbreviated Screen for Patients; BPSS-FP = The Bipolar Prodrome Symptom Interview and Scale-Full Prospective.

Table 2. Relapse prodromes. Characteristics of the selected studies

First author and year of publication	Country	*N*	Average age (SD)	Male (%)	BD I (%)	Design	Methodology	Prodrome identification procedure
Altman et al. (1992)	USA	19	24.00 (3.40)	57.89	100	P	Qn	BPRS and BPRS-E
Bauer et al. (2006)	Germany and USA	59	n/a	33.90	62.71	P	Qn	ChronoRecord
Fellendorf et al. (2021)	Austria	22	43.36 (10.89)	54.50	†	P	Qn	UP!
Fletcher et al. (2013)	Australia	13	40.50 (11.90)	46.20	0	R	Ql & Qn	Ad hoc semi-structured interview
Glenn et al. (2006)	Germany, Canada and USA	49	38.00 (11.70)	28.57	91.84	P	Qn	ChronoRecord
Goossens et al. (2010)	Netherlands	111	47.23 (12.06)	35.00	67.00	R	Qn	Two questions[a]
Grünerbl et al. (2015)	Austria	10	n/a	n/a	†	P	Qn	Android smartphone app
Houston et al. (2007)	USA	31	n/a	n/a	†	P	Qn	YMRS
Keitner et al. (1996)	USA	74	42.00 (12.00)	47.00	100	R	Qn	Ad hoc open-ended self-report[b]
Lam et al. (2001)	United Kingdom	40	43.70 (13.10)	42.50	100	P	Qn	CPSI
Lobban et al. (2011)	United Kingdom	96[c]	44.00 (10.40)	32.00	98.00	R	Qn	EWS checklists for mania and depression
Mander (1990)	Australia	8	54.60 (10.80)	50.00	†	P	Qn	Semistructured interview
Mantere et al. (2008)	Finland	191[d]	37.70 (12.10)	47.10	47.10	R	Qn	Unstructured interview
Molnar et al. (1988)	USA	20	37.65 (11.93)	45.00	†	R	Qn	Clinical interview
Perlman et al. (2006)	USA	54	43.72 (11.46)	46.00	100	P	Qn	The sleep duration subscale of the PSQI
Ryu et al. (2012)	South Korea	41	36.29 (12.06)	46.34	100	R	Qn	40-item symptom checklist
		42	36.10 (9.54)	45.24	100			
Sahoo et al. (2012)	India	30	33.80 (9.10)	70.00	100	R	Qn	Ad hoc scale of 83 items and unstructured interview
Smith and Tarrier (1992)	Australia	20	43.90 (15.90)	45.00	†	R	Qn	40-item symptom checklist and additional questions[e]
Wong and Lam (1999)	United Kingdom	206	44.00 (11.00)	40.00	†	R	Qn	One open-ended question

Note. N = total number of patients with bipolar disorder (BD) included in the study; P = prospective; Qn = Quantitative data; BPRS = Brief Psychiatric Rating Scale; BPRS-E = Brief Psychiatric Rating Scale Extended version; † = the study does not specify; BD I; R = retrospective; Ql = Qualitative data; [a] = "How can you tell if an episode of mania or depression is impending?" and "What is the first sign or behaviour that you recognise in yourself that leads up to a manic or depressive episode?"; YMRS = Young Mania Rating Scale; [b] = "Please describe the behaviors you have experienced leading up to a manic or depressive episode. How can you tell that an episode is coming on?"; CPSI = The Coping with Prodromal Symptoms Interview; [c] = Ninety-three patients completed the EWS (early warning signs) mania checklist and 89 patients completed the EWS depression checklist; EWS = Early Warning Signs; [d] = Nineteen patients were excluded from the data analysis; PSQI = Pittsburgh Sleep Quality Index; [e] = the additional questions were about symptoms not included in the checklist.

Table 3. Characteristics of the population that detects initial prodromes

	Age groups			Main informant			
At risk population	Child	Adolescents	Young adults	Child	Adolescents	Young adults	Parents
Bechdolf et al. (2014)		X	X			n/a	
Duffy et al. (2007)	X	X	X	X	X	X	X
Duffy et al. (2010)	X	X	X	X	X	X	X
Egeland et al. (2003)	X	X					X
Egeland et al. (2012)	X	X					X
Hafeman et al. (2017)	X	X		X	X		X
BD/Affective disorders patients	Child	Adolescents	Young adults or adults	Child	Adolescents	Young adults or adults	Parents/family members or caregivers
Benti et al. (2014)			X			X	
Birmaher et al. (2013)	X	X					X
Correll, et al. (2014a)		X	X		X	X	X
Estey et al. (2014)			X			X	X
Faedda et al. (2004)	X	X					X
Fergus et al. (2003)	X	X					X
Findling et al. (2005)	X	X		X	X		X
Hafeman et al. (2016)	X	X		X	X		X
Hernandez et al. (2017)	X	X		X	X		X
Hirschfeld et al. (2003)			X			X	
Noto et al. (2015)			X			X	
Özgürdal et al. (2009)			X			X	
Salazar de Pablo et al. (2020)		X			X		
Skjelstad et al. (2012)		X	X		X	X	X
Thompson et al. (2003)		X	X		X	X	
Tijssen et al. (2010)		X	X		X	X	
Van Meter et al. (2019)		X			X		
Zeschel et al. (2013)			X			X	
Zeschel et al. (2015)			X			X	
Zhao et al. (2021)		n/a				n/a	

Supplementary Table S1. Assessment of the risk bias of the studies selected in this systematic review

Newcastle-Ottawa risk of bias scores (based in Rotenstein et al., 2016) for forty quantitative studies						
First author	Sample representativeness	Sample size	Non-participants	Assessmennt of prodromal symptoms	Quality of descriptive statistics reporting	Total
Bechdolf et al. (2014)	1	1	1	1	1	5
Birmaher et al. (2013)	1	1	1	1	1	5
Correll et al. (2014a)	1	1	1	1	1	5
Duffy et al. (2007)	1	1	1	1	1	5
Duffy et al. (2010)	1	1	1	1	1	5
Egeland et al. (2003)	0	1	1	1	1	4
Egeland et al. (2012)	0	1	1	1	1	4
Estey et al. (2014)	1	1	0	1	1	4
Faedda et al. (2004)	0	1	0	0	1	2
Fergus et al. (2003)	1	1	1	0	1	4
Findling et al. (2005)	1	1	1	1	1	5
Hafeman et al. (2016)	1	1	1	1	1	5
Hafeman et al. (2017)	1	1	0	1	1	4
Hernandez et al. (2017)	0	1	1	0	1	3
Hirschfeld et al. (2003)	1	1	0	0	1	3
Noto et al. (2015)	0	1	0	1	1	3
Özgürdal et al. (2009)	1	0	0	1	1	3
Salazar de Pablo et al. (2020)	1	1	1	1	1	5
Thompson et al. (2003)	0	0	0	1	1	2
Tijssen et al. (2010)	1	1	0	1	1	4
Van Meter et al. (2019)	1	1	1	1	1	5
Zeschel et al. (2013)	1	1	1	1	1	5
Zeschel et al. (2015)	1	1	0	1	1	4
Zhao et al. (2021)	1	1	1	1	1	5

Altman et al. (1992)	0	0	0	1	1	2
Bauer et al. (2006)	1	1	0	1	1	4
Fellendorf et al. (2021)	0	0	1	1	1	3
Glenn et al. (2006)	1	1	0	1	1	4
Goossens et al. (2010)	1	1	0	0	1	3
Grünerbl et al. (2015)	0	0	0	1	1	2
Houston et al. (2007)	1	1	0	1	1	4
Keitner et al. (1996)	1	1	0	0	1	3
Lam et al. (2001)	1	1	0	1	1	4
Lobban et al. (2011)	1	1	0	1	1	4
Mander et al. (1990)	0	0	0	0	1	1
Mantere et al. (2008)	1	1	1	0	1	4
Molnar et al. (1988)	0	0	0	0	1	1
Perlman et al. (2006)	1	1	1	1	1	5
Ryu et al. (2012)	0	1	0	0	1	2
Sahoo et al. (2012)	0	1	1	0	1	3
Smith and Tarrier (1992)	1	0	0	0	1	2
Wong and Lam (1999)	1	1	0	0	1	3

Responses in the Critical Appraisals Skills Programme (CASP) checklist for three qualitative studies

First author	
Benti et al. (2014)	Yes = 6; Can't tell = 1; No = 2. Valuable research
Fletcher et al. (2013)	Yes = 7; Can't tell = 1; No = 1. Valuable research
Skjelstad et al. (2012)	Yes = 6; Can't tell = 1; No = 2. Valuable research