PSYCHOSIS AND PERSONALITY DISORDERS: DO WE NEED EARLY DIAGNOSIS FOR SUCCESSFUL TREATMENT?

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PSYCHOSIS AND PERSONALITY DISORDERS: DO WE NEED EARLY DIAGNOSIS FOR SUCCESSFUL TREATMENT?

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EDITORIAL
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Editorial: Psychosis and Personality Disorders: Do We Need Early Diagnosis for Successful Treatment?

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Keywords: psychotic disorders, personality disorders, early onset, predictive factors, outcome

Editorial on the Research Topic

Psychosis and Personality Disorders: Do We Need Early Diagnosis for Successful Treatment?

Early diagnosis is one of the most relevant issues of modern clinical psychiatry. Several investigations pointed out the need to detect the prodromal signs and symptoms of psychiatric diseases to define specific monitoring and early interventions strategies. In particular, the lack of diagnosis and treatment in the early periods of disorders that present their onset in adolescence or young adulthood, such as schizophrenia spectrum disorders (SSDs) and severe personality disorders (PDs), deals with a high level of disability and a worse illness course.

Many patients who suffer from psychosis at the first contact with medical care present multiple risk factors to develop psychosis, such as positive family history for psychosis, pregnancy, or birth complications, early traumatic events, substance use, and mental disorders predisposing to the onset of psychosis. A careful search for detection of these factors would be important to prevent significant negative consequences in terms of psychosocial functioning.

In a similar way, although severe PDs, in particular borderline personality disorder (BPD), are known to have their onset in young age, their diagnosis and treatment are usually delayed. It is of fundamental importance to identify clinical conditions that can evolve in BPD, such as disruptive behaviour and disturbances in attention and emotional regulation, conduct disorders, oppositional defiant disorder, attention deficit-hyperactivity disorder, and substance use.

In the past decades, there was a lively debate to establish whether pharmacotherapy in the prodromal phases of psychiatric disorders is efficacious and ethically acceptable, but final conclusions have not been drawn. On the contrary, it is commonly accepted that specific psychosocial interventions that involve patients' family members produce positive results in terms of reduction of symptoms, comprehension of disorders and improvement of coping skills. These results can be particularly useful if we consider that, already during the first phases of monitoring and treatment, the risk of service disengagement and medication non-adherence is high and should be carefully faced.

The Editorial is aimed to make clear what are the main topics addressed by the articles of this Special Issue on early onset of psychosis and personality disorders. Many authors focused their contributions on identification of young individuals at high clinical risk for psychosis (CHR-P). In particular, Montemagni et al. reviewed studies that proposed or examined a model of transition to psychosis of subjects with high clinical risk. Authors found that only few studies performed an internal validation of models and only biological and neurocognitive models received validation. So, the validation process of predictive models is still at the initial stage. To promote further research on

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CHR-P state in children and adolescents, Molteni et al. proposed a longitudinal protocol study with the aim to measure transition to psychosis or other psychiatric disorders after 2 years and to investigate the predictive value of specific clinical, neuropsychological, and neuroimaging factors on prognosis. A core issue of studies of young individuals at risk for psychosis is to improve the ability to detect these subjects at an early phase, before the onset of a first psychotic episode. In order to obtain this goal, Fusar-Poli et al. developed a clinically based, transdiagnostic risk calculator and performed a study to support the implementation of this tool in the real-world clinical practice.

A relevant question concerning early detection and treatment of schizophrenia spectrum disorders (SSP) is why successfully treated patients still present social functioning impairment. Armando et al. suggested that functional impairment derives from arrested development of social cognition during adolescence and early adulthood, particularly of reflective thinking processes defined as mentalization.

Other contributions included in this Special Issue addressed questions concerning prediction and early detection of personality disorder. Bozzatello et al. examined literature studies in order to identify factors (precocious environmental factors, temperament and personality traits, early psychopathological features, and neuroimaging factors) that are related to high risk of early onset borderline personality disorder. Boldrini et al. investigated the relationship between personality disorders and CHR state. Authors found that personality disorders were present in almost 40% of CHR patients and the most common were schizotypal and borderline personality disorder. However, the studies investigating the effects of baseline personality diagnoses on transition to psychotic disorders obtained insufficient and contradictory results. Other two contributions examined the relationship of personality disorder with psychosis. In particular, Cavelti et al. compared cognitive, emotional, and behavioral responses to verbal hallucinations in youth with BPD versus schizophrenia spectrum disorders (SZ). Results replicated in BPD young patients the link between negative appraisal of voices and depression that has already been indicated in patients with SZ. Schultze-Lutter et al. considered the historical and phenomenological link of schizophrenia spectrum personality disorders, in particular schizotypal personality disorder (SPD) and psychotic disorders. This link was reassessed on the basis of recent evidence and authors concluded that SPD and psychotic disorders are not simply states of different severity on one common but on qualitatively different dimensions. The negative dimension would be predictive of SPD, the positive of psychosis. So, the assessment of multiple schizotypy dimensions would be an essential step for early differential diagnosis.

Other authors considered issues related to pharmacotherapy and psychosocial interventions for schizophrenia. Ringen et al. investigated clinical predictors of antipsychotic dose reduction or discontinuation in the first year of treatment in schizophrenia versus bipolar disorder. As treatment guidelines recommend to avoid dose reduction or discontinuation of antipsychotics in the first year, identification and differentiation of predictors between affective and non-affective psychoses is of central importance for clinical practice. Authors found a dose reduction in the first year in both first treatment groups across diagnoses, but predictors were different in the two groups (weight increase was a predictor in schizophrenia, baseline severity of symptoms predicted dose reduction in bipolar disorder). Deste et al. considered in their contribution the effects of a psychosocial intervention, cognitive remediation, in patients with schizophrenia, in order to verify whether cognitive deficits are more sensitive to remediation in early than in chronic schizophrenia. Results indicated a greater improvement of clinical and functional measures in early course patients compared with chronic patients, while no difference between groups was found in the neurocognitive parameters.

Another relevant issue concerning outcome of patients with first-episode psychosis was addressed in the article proposed by Weibell et al. These authors evaluated the long-term association between substance use and cognitive functioning in a large sample of first-episode psychotic patients. What is the effect of early substance use cessation on cognitive trajectories of these subjects? Patients who stopped using substances in the first 2 years improved on some cognitive measures, especially motor speed and verbal learning indices, while control groups did not.

In summary, this Special Issue presents a series of valuable contributions that deal with recent evidence on risk factors, early detection, and clinical and functional outcome of young patients with psychosis and personality disorders. In some cases, data are promising and can help the clinicians to improve their ability to detect subjects with high clinical risk and to obtain an early diagnosis with positive effects on outcome. More often, available evidence is insufficient, and further studies are required. So, this field of psychiatric research is certainly one that deserves significant efforts to confirm initial findings and can produce new knowledge with relevant implications for clinical practice.

AUTHOR CONTRIBUTIONS

All authors contributed to prepare the Editorial.

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PROTOCOLS
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Real World Implementation of a Transdiagnostic Risk Calculator for the Automatic Detection of Individuals at Risk of Psychosis in Clinical Routine: Study Protocol

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Background: Primary indicated prevention in individuals at-risk for psychosis has the potential to improve the outcomes of this disorder. The ability to detect the majority of at-risk individuals is the main barrier toward extending benefits for the lives of many adolescents and young adults. Current detection strategies are highly inefficient. Only 5% (standalone specialized early detection services) to 12% (youth mental health services) of individuals who will develop a first psychotic disorder can be detected at the time of their at-risk stage. To overcome these challenges a pragmatic, clinically-based, individualized, transdiagnostic risk calculator has been developed to detect individuals at-risk of psychosis in secondary mental health care at scale. This calculator has been externally validated and has demonstrated good prognostic performance. However, it is not known whether it can be used in the real world clinical routine. For example, clinicians may not be willing to adhere to the recommendations made by the transdiagnostic risk calculator. Implementation studies are needed to address pragmatic challenges relating to the real world use of the transdiagnostic risk calculator. The aim of the current study is to provide *in-vitro* and *in-vivo* feasibility data to support the implementation of the transdiagnostic risk calculator in clinical routine.

Method: This is a study which comprises of two subsequent phases: an *in-vitro* phase of 1 month and an *in-vivo* phase of 11 months. The *in-vitro* phase aims at developing and integrating the transdiagnostic risk calculator in the local electronic health register (primary outcome). The *in-vivo* phase aims at addressing the clinicians' adherence to the recommendations made by the transdiagnostic risk calculator (primary outcome)

and other secondary feasibility parameters that are necessary to estimate the resources needed for its implementation.

Discussion: This is the first implementation study for risk prediction models in individuals at-risk for psychosis. Ultimately, successful implementation is the true measure of a prediction model's utility. Therefore, the overall translational deliverable of the current study would be to extend the benefits of primary indicated prevention and improve outcomes of first episode psychosis. This may produce significant social benefits for many adolescents and young adults and their families.

Keywords: psychosis, schizophrenia, risk, transdiagnostic, prevention

INTRODUCTION

Outcomes of psychotic disorders are associated with high personal, familial, societal, and clinical burden (1). There is thus an urgent clinical and societal need for improving outcomes of psychosis (1). The past two decades of clinical research have opened new opportunities for ameliorating outcomes of psychosis by intervening during its early clinical stages (1), in individuals at Clinical High Risk for psychosis [CHR-P (2)] - such as those meeting the At Risk Mental State criteria (3) or other similar criteria (4)-. This type of intervention is termed as "primary indicated prevention." CHR-P individuals display subtle symptoms and overall functional impairment (5) that are due to the accumulation of several risk factors for psychosis (6, 7). In the wake of these issues (8), they seek help at specialized CHR-P clinics (9), where they receive a comprehensive psychometric assessment in the context of a clinical interview (10). Overall, the prognostic performance of this assessment is considered to be good [except for their use as screening tools in the general population (11, 12)] and comparable to that of similar prognostic measurements that are employed in organic medicine (13). Under those circumstances, CHR-P individuals have a 20% [see eTable 4 in (14)] probability of developing emerging psychotic disorders [but not other non-psychotic disorders (15, 16)] over a relatively short period of 2 years. Primary indicated prevention in CHR-P individuals has the unique potential to alter the course of psychosis and reduce the duration of untreated psychosis, although there is some uncertainty with respect to the true effectiveness of available treatments (17–21). An additional potential advantage is that secondary prevention in CHR-P who will develop the disorder can reduce the duration of untreated psychosis and ameliorate the severity of the disorder (1, 22). As summarized in **Figure 1**, the potential real world impact of the CHR-P paradigm for improving the outcomes of psychotic disorders is determined by the successful and stepped integration of the following key components:

(i) Efficient detection of individuals at-risk for psychosis;
(ii) Accurate prognosis of outcomes;
(iii) Effective preventive treatment.

As illustrated in **Figure 1**, the first rate-limiting step for improving outcomes of psychosis through the CHR-P paradigm is the detection of individuals who are at risk for psychosis. In fact, even the most accurate prognostic tool and the most effective preventive treatment would have little impact on improving the outcomes of psychosis without proper scalability to the vast majority of the at-risk population. Our lab (the Early Psychosis: Intervention and Clinical-detection, EPIC) has investigated the effectiveness of current detection strategies for identifying CHR-P individuals for the first time. These strategies are largely based on referrals to specialized CHR-P clinics (9) that are made on suspicion of psychosis-risk (23). Our local National Health Service (NHS) Trust, The South London And the Maudsley (SLaM), in partnership with King's College London and King's Health Partners, hosts one of the largest clinical services for CHR-P individuals worldwide: the Outreach And Support In South London (OASIS) (24). Established in 2001, the OASIS has emerged as a reference point for psychosis prevention in the UK and worldwide (24). The OASIS is detecting CHR-P individuals from the community, primary care, and secondary care through an extensive and ongoing outreach campaign, which has been fully established over the past years. Despite this outreach, we have found that OASIS' detection strategies are highly inefficient because only 5% of individuals diagnosed with a first episode of non-organic ICD-10 psychosis in SLaM had been detected at their CHR-P stage. This finding has clear-cut clinical implications. For example, NHS England, in April 2016 has implemented a new Access and Waiting Times-Standard for Early Intervention in psychosis, which requires that CHR-P are detected nationwide and treated rapidly (25, 26). Although it is now an NHS requirement that all suspected CHR-P patients who present to NHS Trusts are assessed and interviewed for a psychosis-risk state (13), such an approach is likely to miss the vast majority of those at risk. No alternatives are on the horizon. Intensifying the inefficient outreach campaigns currently adopted by CHR-P clinics is not viable because these campaigns are idiosyncratic and unstandardized (23, 27, 28), leading to a diluted transition risk and unreliable prognosis (11, 12). Front-line youth mental health services such as the Headspace initiative -as opposed to specialized CHR-P clinics such as the OASIS- are also expected to detect more at-risk individuals. Unfortunately, even youth mental health services can detect only 12% of first episode cases at the time of their CHR-P stage (29). It is thus clear that to extend the benefits of the CHR-P paradigm some innovative approaches are urgently needed (30).

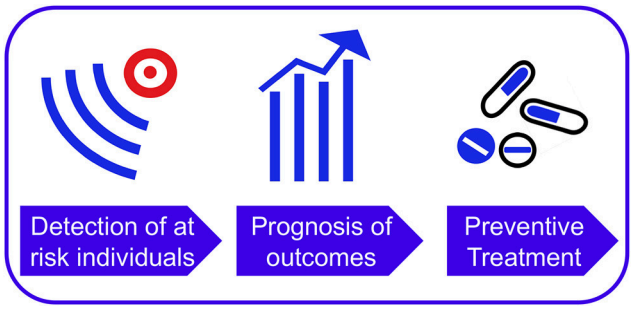

FIGURE 1 | Core clinical and research components for effective prevention of psychosis.

To overcome these issues, we have developed a pragmatic, clinically-based, individualized, transdiagnostic risk calculator for the detection of individuals at risk of psychosis in secondary mental health care at scale (24). In a subsequent step, the calculator has been externally validated, demonstrating good prognostic accuracy (24). Yet, a good model's (external) performance is necessary but not sufficient to ensure a clinical use of a risk calculator. Implementation studies are first needed to address pragmatic challenges relating to the use of a risk calculator in clinical routine (31). These challenges may suggest adaptations to the original models to allow its usability in the real world. Ultimately, successful implementation is the true measure of a prediction model's utility (32). For example, the transdiagnostic risk calculator was developed on retrospective cohort data (24). As such, it is not known whether it can be used prospectively in the real world of NHS Trusts. Data that are necessary to run the calculator (age, gender, age by gender, ethnicity, and ICD-10 index diagnosis) may not be available or not accessible. Furthermore, clinicians' adherence to the recommendations made by the transdiagnostic risk calculator is unknown. This represents the critical barrier toward its scalability in clinical routine. We describe here the protocol for the implementation study of this transdiagnostic risk calculator in the NHS. To our best knowledge, this will be the first implementation study of a risk calculator for clinical routine in the CHR-P field.

The overall translational deliverable of the current study would be to extend the benefits of primary indicated prevention and improve outcomes of first episode psychosis. This, in turn, may produce significant social benefits and cost-saving to many adolescents and young adults, their families and the NHS.

METHODS

This is a feasibility study which will evaluate essential real world parameters associated with the implementation of an electronic, clinically-based, individualized, transdiagnostic risk calculator for the detection of individuals at risk and the prediction of psychosis in secondary mental health care. Obtaining these figures is a necessary step in order to accurately estimate the resources (e.g., staffing) needed for the routine clinical use of the calculator. There are two phases in this study: an initial *in-vitro* (1 month) testing which does not involve patients contact and a second *in-vivo* piloting (11 months, total study duration 12 months), which involves recruitment of SLaM patients. Before we present the study design, we will briefly summarize the core characteristics of the transdiagnostic risk calculator.

Clinically-Based, Individualized, Transdiagnostic Risk Calculator for the Automatic Detection of Individuals at Risk of Psychosis in Secondary Mental Health Care

In a previous meta-analysis, we showed that secondary mental health care is the most frequent source of referrals to CHR-P services such as the OASIS (23). We additionally confirmed that the recruitment of individuals for CHR-P assessment through secondary mental health services is associated with the highest probability of developing psychosis (27). In fact, these individuals are more likely to have accumulated several risk factors for psychosis such as affective comorbidities, substance abuse and social deprivation (6). These findings are concurrent to the European Psychiatric Association guidelines, which recommend that CHR-P assessment should only be offered to individuals who are "already distressed by mental problems and seeking help for them" (33). The transdiagnostic risk calculator presented here is therefore in line with the clinical guidelines in the field.

Our calculator was developed and externally validated in a large clinical dataset of non-psychotic patients affected with non-organic mental disorders ($n = 91{,}199$), in the National Institute of Health Research (NIHR) Maudsley Biomedical Research Centre (BRC) Case Register. This register is electronic, because SLaM is paper-free, and all clinicians record their activity electronically on the Patient Journey System (PJS), as part of their clinical routine. PJS is a comprehensive record of all clinical information recorded throughout patients' journeys through SLaM NHS Trust services, including demographic and contact information, dates and other details of referrals and transfers, detailed clinical assessments, care plans and medication, clinical activity, and reviews. Anonymised information from PJS is subsequently used to create the Clinical Record Interactive Search (CRIS). CRIS allows researchers to search from PJS records. The details of the CRIS and the local electronic health record have been published previously (34–36). Therefore, this calculator leverages the potentials of e-Health innovations. The original study followed state-of-the-art guidelines for model development and validation (37). Thus, the external validation was done through a geographical split of the initial database in a derivation (Lambeth and Southwark SLaM boroughs, $n = 33{,}820$) and validation (Lewisham and Croydon SLaM boroughs, $n = 54{,}716$). The calculator showed good prognostic accuracy in the external validation, in terms of overall performance ($R^2 = 0.72$), discrimination (Harrell's $C = 0.79$) and calibration (calibration slope $= 0.96$) (24). Our calculator is based on simple sociodemographic variables (age, gender, ethnicity, age by gender interaction and ICD-10 index

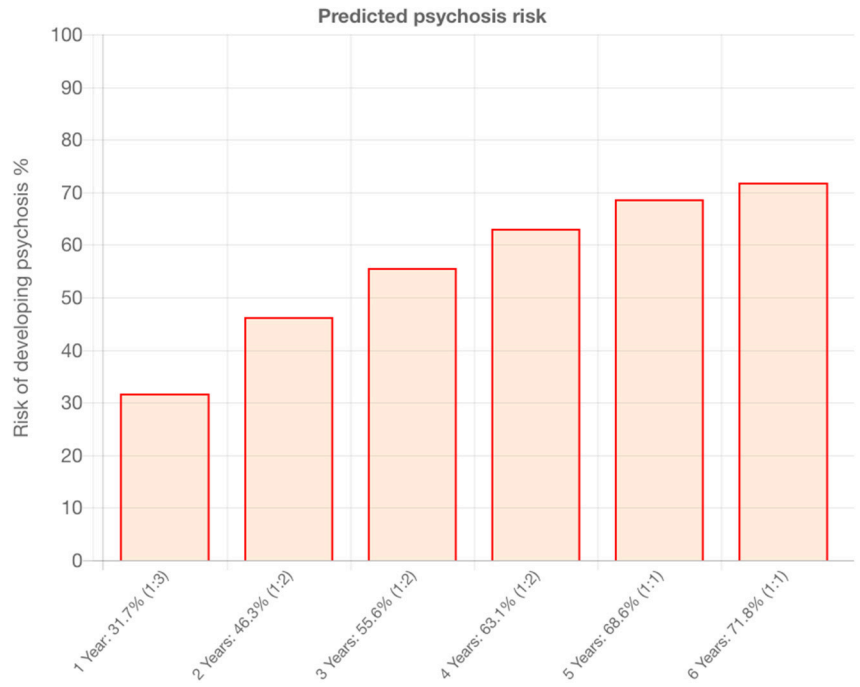

FIGURE 2 | Example of outcomes produced by the transdiagnostic risk calculator that is under implementation in the current study.

diagnosis) that can be easily accessed in clinical practice. It has been termed as "transdiagnostic" because it leverages several ICD-10 index diagnoses, and it can detect risk of psychosis across all diagnostic spectra (i.e., acute and transient psychotic disorders, substance abuse disorders, bipolar mood disorders, non-bipolar mood disorders, anxiety disorders, personality disorders, developmental disorders, childhood/adolescence onset disorders, physiological syndromes and mental retardation). This also represents one of the broadest transdiagnostic studies in psychiatry overall (38). The selection of predictors that were available in the local electronic health records was deliberately done with the view of facilitating its implementation in clinical routine at scale, which is an essential prerequisite to improve the detection of individuals at risk of psychosis. The predictors were preselected on the basis of a priori meta-analytical knowledge (39), a method which is recommended to develop robust prognostic models (31). In fact, the calculator is characterized by a significant clinical utility (net benefits) within a 1–50% range of threshold probability (individuals risk of developing psychosis by 5 years) (24). Such a range of predicted risk for psychosis is clinically meaningful since it is unlikely that a calculator would be needed to guide clinical practice for individuals with higher or lower predicted risks. The transdiagnostic risk calculator has also been implemented online (www.psychosis-risk.net) (24). This would allow its use in NHS Trusts that do not routinely employ electronic health records. An example of the output that is provided by the transdiagnostic risk calculator is appended in **Figure 2**. The core characteristics of the transdiagnostic risk calculator are appended in **Table 1**.

TABLE 1 | Core characteristics of the transdiagnostic risk calculator.

Robust	It includes predictors that have been selected through a priori clinical knowledge
Pragmatic	It is agnostic with respect to etiopathology of psychosis
Cheap	It leverages predictors that are routinely collected by clinicians
Automatized	It can accommodate electronic health records as well as the manual entry of predictors
e-Health	It has been implemented online
Scalable	It can be used to screen large electronic health records
Optimisable	It can be further refined by the inclusion of other predictors

Design

In-vitro Phase

The initial phase will have the transdiagnostic risk calculator integrated into the local electronic health register (step 0, **Figure 3**). This will involve several activities such as developing the prototype, addressing *in-vitro* feasibility problems associated with its implementation in SLaM clinical practice, and conducting clinician engagement work prior to initiating the *in-vivo* piloting. The team has already started initial work to prepare the implementation of the calculator. Firstly, we have approached the local NHS Trust IT facility (SL@M Connect) to discuss governance issues for using clinical material from the local NHS Trust. SL@M Connect has endorsed our study and will support it. Secondly, we have conducted data quality checks with the CRIS team to ensure that the resources needed are in place. Thirdly we have started the *in-vitro* phase by extracting preliminary data and running our calculator. We have also collaborated with the

Center for Translational Informatics in order to fully implement the calculator in the local electronic health register. Anonymised data will be used during this phase to develop a prototype of the tool that can be automatised within the local electronic health register. Qualitative data will be collected to identify pragmatic barriers associated with the use of the transdiagnostic risk calculator. This will be collected through organizing two workshops, each composed of five SLaM clinicians. This phase would also tune the pilot threshold probability to be used in the next phase and address implementation challenges that have emerged from the *in-vitro* phase. This phase will be developed in collaboration with SLaM IT Connect and with the Center for Translational Informatics at the Institute of Psychiatry, Psychology, and Neuroscience. Approval for the *in-vitro* study was granted by the Oxfordshire Research Ethics Committee C. Because the data set is made up of de-identified data, informed consent is not required. Furthermore, during this phase we will try to complete a further external validation of the transdiagnostic risk calculator in an independent NHS Trust in the UK which is using CRIS. This is seen as an essential step to address the transportability of our transdiagnostic risk calculator across different clinical scenarios.

The *in-vitro* phase will last 1 month.

In-vivo Phase

This phase will consist of a prospective feasibility study to test the real world usability of the transdiagnostic risk calculator to detect individuals at risk of psychosis at scale in clinical routine.

During this phase, a prototype will be made freely available to clinicians working in secondary mental health teams. In practice, clinicians will not be required to enter any new variables because all the predictors are already available as part of the standard clinical practice. In the first step (see step 1, Flow chart), the research team will screen potential patients meeting our study criteria using de-anonymised electronic health register data (CRIS). The data for these patients will be accessed by the study team to screen potential participants with the transdiagnostic risk calculator. The electronic health register will also be used to identify the responsible clinician for any individuals who are at risk as determined by the pre-defined threshold (established during the *in-vitro* phase).

The research team will then contact the responsible clinician through manual alerts (e.g., emails) and phone contact, recommending the patient be referred for a refined psychosis assessment. If an individual does not reach the threshold, the calculator will recommend no further assessment and standard care will be offered as usual. If possible, these alerts will be automatised during the study. During the second step (step 2, Flow Chart), the responsible clinicians will then decide whether to initiate the referral or not. A crucial outcome to be investigated will be the impact of different types of alerts on the clinicians' adherence on the use of the transdiagnostic risk calculator. If the individual is not referred for further assessment, standard care will be offered as usual. In the case the participant is referred for further assessment, the clinician will ask the patient if they consent to their details being given to the research team. If they do, the individual will be contacted by the research team and the procedure for collecting informed consent will be initiated.

If the patient agrees to participate in the study, they will then be invited to undergo a refined assessment (step 3, Flow Chart), which includes the standard CHR-P assessment. Specifically, we will use the combined Comprehensive Assessment for At Risk Mental States (CAARMS, version 12/2006) (3) and Structured Interview for Prodromal-Risk Syndromes, version 5.0 (SIPS) (40), clinician-rated and iPad version, that have been developed in our department as part of previous ongoing studies.

At the end of this assessment, the researchers would communicate the results to the responsible clinicians (step 4, Flow Chart). In case the individuals would meet the standard intake criteria for a state of risk for psychosis (i.e., a CHR-P state), they would be referred to the local Clinical High Risk service [the OASIS (9)] for standard care as recommended by the NICE (41). If the individuals do not meet the intake criteria for a CHR-P state, the referrer will be informed, and standard care provided accordingly. Overall, there will be no change in the current standard care for any participants. This prototype will be piloted in all local secondary mental health services present in the borough of Lambeth, Lewisham, Croydon and Southwark.

Participants will be reimbursed for their participation in the study at an hourly rate of £10. For patients under the age of 16, their time will be reimbursed with Amazon gift vouchers, again to the value of an hourly rate of £10 per hour. **Table 2** lists the study procedures.

The *in-vivo* phase will last 11 months.

Follow-Up

Individuals who are selected through the transdiagnostic risk calculator, referred by their clinicians for a psychosis-risk assessment and who accept it will be invited again to a face-to-face clinical follow-up at 6 months. This will consist of the same measures acquired at baseline.

Statistics

Sample Size

This is a feasibility study to investigate key implementation parameters for an electronic risk calculator. As such the study is neither designed nor powered to validate new tools or test specific hypotheses.

The primary outcome of the *in-vitro* phase is the development and integration of the transdiagnostic risk calculator in the local electronic health register. As such, no power calculation is made for the *in-vitro* primary outcome.

They key rate-limiting barrier toward a scalable use of the transdiagnostic risk calculator in the broader clinical scenario is the clinicians' adherence to the recommendations made by the calculator itself. Therefore, the primary outcome of the *in-vivo* phase of this study is the adherence of clinicians to the use of the calculator, defined by the proportion of clinicians who have responded to the prompts sent on the recommendation of the electronic risk calculator from SLaM secondary mental health care. The sample size calculation is therefore made for this primary outcome. In line with the NIHR guidance, our main outcomes are feasibility parameters,

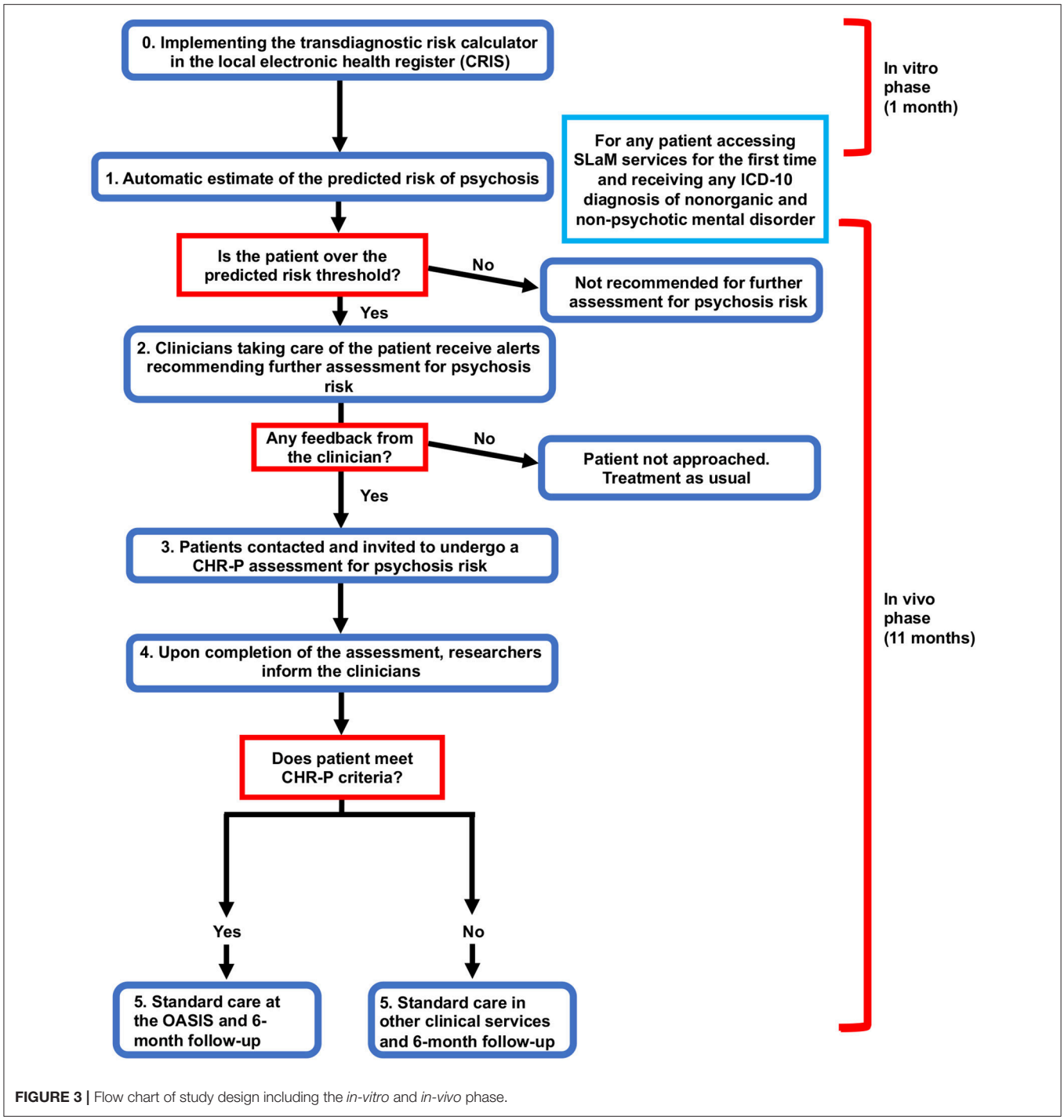

FIGURE 3 | Flow chart of study design including the *in-vitro* and *in-vivo* phase.

and sample size calculation is made for the expected level of precision (45). Assuming a predicted psychosis threshold of 5–10% (at 2 years), on the basis of the previous study (24), we expect to detect at least 120 at-risk individuals per 11 months recruitment in SLaM. Conservatively assuming that only half of SLaM clinicians would eventually respond to the alerts generated by the calculator, the anticipated sample size would allow us to have an acceptable (42) maximum margin of error of 0.1 (i.e., 95%confidence interval (CI) ±0.1) for adherence rates of clinicians >60%. The secondary outcomes of the *in-vivo* phase will measure other key feasibility parameters that are necessary to implement the calculator in the wider clinical routine: impact of different types of alerts on the clinicians' adherence to the recommendations made by the transdiagnostic risk calculator; raw number of referrals initiated from secondary mental health care clinicians for an

TABLE 2 | Study procedures for individuals detected by the transdiagnostic risk calculator and referred by clinicians for an assessment for psychosis-risk.

		Baseline		Follow-up
	Screening Visit	Day 1	Day 2 (2 weeks+- 3 days)	6 months +- 2 weeks
Patient information and informed consent	X			
CHR-P assessment		X	X	X

assessment of psychosis-risk; qualitative reasons for any lack of clinicians' adherence.

Analysis

This is a feasibility study and it is not planned to test any statistical hypotheses with regard to any of the endpoints in a confirmatory sense. For the exploratory evaluation of our hypotheses, a two-sided 95% CI of adjusted treatment differences will be computed. However, the CIs will have to be interpreted in the perspective of the exploratory character of study, i.e., as an interval estimate for effects under these conditions. All statistical analyses will be performed using STATA version 14 (43).

Participants

Inclusion Criteria

- Subject receiving any first ICD-10 diagnosis of non-psychotic mental disorder (including Acute and Transient Psychotic Disorders) at SLaM (borough of Lambeth) between April 1st 2018 and March 28th 2018;
- Aged $\geq$14;
- Subject with a good understanding of spoken and written English.

Exclusion Criteria

- Present or past diagnosis of any ICD-10 psychotic disorder [excluding Acute and Transient Psychotic Disorders (44)];
- Any evidence of organic condition that may be responsible for psychotic symptoms.

Withdrawal of Subjects

If an individual decides to take part in the study, they will still be free to withdraw at any time, without giving a reason. Their decision will not affect the standard of care they receive from any medical services at any time. Identifiable data already collected with consent would be retained and used in the study. No further data would be collected but the individual would be approached at follow-up.

Outcomes

In-vitro Phase

- Primary outcome: to develop and integrate an automated transdiagnostic risk calculator into the local electronic health register;
- Secondary outcome: to externally validate the transdiagnostic risk calculator in an independent NHS Trust in the UK;

In-vivo Phase

- Primary outcome: adherence of clinicians to the use of the transdiagnostic risk calculator (proportion of clinicians who have responded to the prompts sent on the recommendation of the transdiagnostic risk calculator).
- Secondary outcome: impact of different types of alerts on the clinicians' adherence to the recommendations made by the transdiagnostic risk calculator.
- Secondary outcome: raw number of referrals initiated from secondary mental health care clinicians for an assessment of psychosis-risk.
- Secondary outcome: qualitative reasons for any lack of clinicians' adherence.

Data Management

Type of Study

This is not a randomized clinical trial but instead a prospective cohort study. The *in-vitro* stage utilizes de-anonymised data from the local electronic case register, while the second uses a case-control design (prospective cohort study in SLaM).

Types of Data

The main experimental outcomes are quantitative and include the raw number of at risk cases detected by the calculator, the raw number of referrals made by clinicians, the raw number of individuals meeting CHR-P criteria, the raw number of individuals developing any ICD-10 psychotic disorder over time. Qualitative data will also be acquired from workshops conducted with SLaM clinicians during the *in-vitro* phase and from SLaM clinicians contacted during the *in-vivo* phase (in case of lack of adherence).

Format and Scale of Data

Data will be stored in standard formats using standard software for the field allowing easy sharing with other scientists as well as maintaining long-term validity.

Data Access

Data will only be accessed by the research team. Physical data will be stored in a locked drawer at OASIS with access restricted to the research team. Information collected from participants during the clinical investigation will be treated confidentially. The researchers will collect data and transfer it without recording the patient's name or date of birth but coded with a subject identification code. Therefore, data is not directly traceable to individual subjects. A subject identification code links the data to the individual subject. The code will be safeguarded by the responsible investigator at the site; the key to this code (subject identification code list) will be kept at the site, with limited access by study team members only.

Data Security

Privacy laws and regulations will be adhered to during all procedures related to this study. The collection and processing of participants' personal information will be limited to what

is necessary to ensure the study's scientific practicability and to assess the research questions. Information collected from participants during this clinical investigation will be treated confidentially.

The researchers collecting the data for this study will work under the direct supervision of the consultant psychiatrist of the OASIS team (Paolo Fusar-Poli) and who will ensure there is no breach of confidentiality.

Once recruited to the research, the participants will be allocated a participant ID number which will be attached to all research documentation along with their initials and date of participation. Any documentation, which would allow the identification of personal data, will be collected under the participant ID and will only be accessible by the researchers. All information collected during the study will be stored in a secure location at OASIS within a locked drawer only accessible by the researcher and the OASIS team. All data collected from the baseline assessment will be anonymised using participant ID and stored on a secure, encrypted, password-protected server. iPads will be based on existing technologies developed at King's College London and are in use for other research projects at the Department of Psychosis Studies.

Research data will be stored for a minimum of 5 years following the completion of the study. We intend to make use of the King's College London (KCL) Research Data Management system where data can be stored long-term.

Ethics and Regulatory Approval

The Chief Investigator of this study undertakes to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

If the research is approved the Chief Investigator undertakes to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval. The Chief Investigator undertakes to notify review bodies of substantial amendments to the protocol or the terms of the approved applications and to seek a favorable opinion from the main Research Ethics Committee (REC) before implementing the amendment. The Chief Investigator undertakes to submit annual progress reports setting out the progress of the research, as required by review bodies.

The CI will ensure that REC Favorable Opinion, Health Research Authority (HRA) approval, and SLaM Confirmation of Capacity and Capability will be in place before recruiting from SLaM. Should it be necessary to add research sites at a later stage, the sponsor will be approached to review an amendment for submission to the HRA, and Confirmation of Capacity and Capability will be obtained from the new NHS sites before starting recruitment from research sites.

Consent Procedures in Minors

For potential participants who are under the age of 16 years old at the start of the study, informed consent should be provided by their legal representatives/parents, in line with the Declaration of Helsinki and International Conference on Harmonization-Good Clinical Practice (ICH-GCP). Their consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor. Whenever appropriate, the minor should participate in the informed consent process together with the parents. If the minor is deemed to be able to give assent to decisions about participation in research, the researcher will obtain this assent in addition to the consent of the legal representatives/parents. If the minor's assent is not obtained, it is recommended that this is documented with justification in the consent form which is signed by the legal representatives/parents and investigator. The minor's assent is not sufficient to allow participation in the study; informed consent of the legal representatives/parents is required. Consent from legal representatives/parents and assent from the minor should be sought at the same time. In any case, the minor will receive information according to its capacity of understanding regarding the study and its risks and benefits from staff with experience in minors. The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation will be followed; in such case, the minor can be withdrawn from the study at any time.

In case a minor reaches adulthood (age of 16) during the study, the researcher is obliged to obtain informed consent from this participant as soon as possible. Informed consent from legal representative/parents is no longer required, although it is recognized that an adolescent is still vulnerable and may require additional discussions and explanations.

In case the above-described procedures are not in line with any applicable local law or regulation, any deviations need to be discussed and agreed upon with the sponsor, as well as clearly documented.

If a minor or incapacitated subject does not want to participate, they will not be included in the study. This is also explicitly stated in the information letter.

Management of Disclosures and Distress

The content of the assessments can potentially lead to patients feeling distressed or disclosing sensitive information. There are guidelines in place for managing these incidents. If this occurs, the researcher will contact the patient's consultant or team manager to inform them. The responsible clinician will then offer the patient an assessment and treatment plan. For issues where the consequences are more imminent, the Accident & Emergency department at King's College Hospital will be contacted and appropriate treatment and support will be offered.

Quality Assurance, Data Handling, Publication Policy, and Finance

Names and contact details of participants will be kept on separate databases from experimental data, with anonymous subject codes referencing between the two. Data will be kept in accordance with study ethical approval, research governance and the Data Protection Regulation Act (2018). We will encourage access to the anonymised raw data by external collaborators within this framework, in accordance with the international policy on data preservation and sharing, while maintaining strict confidentiality for study participants. Encrypted data will be saved for long-term storage and sharing within the KCL infrastructure.

The Institute of Psychiatrym Psychology and Neuroscience (IoPPN) has a dedicated communications office which disseminates research findings via the media (press releases, expert comment proactive placing) and communications vehicles such as the King's website, and those of partner organisations such as SLaM NHS Foundation trust and other King's Health Partners.

The study has been externally reviewed and approved for funding by King's Health Partners.

DISCUSSION

We have presented an innovative implementation study protocol, applying a pragmatic, clinically-based, individualized, transdiagnostic, risk calculator to the NHS. To our best knowledge, this is the first implementation study of a risk calculator for clinical routine in the CHR-P field. Implementation studies are as scarce as essential (31). The proliferation of risk models in the CHR-P field as well as in psychiatry has occurred largely without appropriate attention to implementation challenges, resulting in many models that have little or no clinical impact (32). In fact, many more risk prediction models are published than are externally validated, and only a tiny minority of these is then implemented in the NHS (31). To achieve successful implementation, which is the true measure of a prediction model's utility, we considered that the end from the beginning of the model development process. Because our aim was to improve the detection of individuals at risk of psychosis, it was necessary to screen a large NHS Trust at scale. To achieve this goal, we selected predictors that were already collected by clinicians as part of their clinical routine. Furthermore, the requirement of simple variables for implementation increases the number of data sets that could be used for the external validation of existing models, a current gap in the implementation of risk prediction models in psychiatry. Because of these considerations, we believe that the study protocol here described can advance knowledge and foster translational precision psychiatry research. We hope that the pragmatic and operational nature of this protocol will guide future researchers, funders and ethics committees toward the development of implementation studies for psychiatric populations. We recommend this protocol as a starting point to guide future implementation studies for risk prediction models in populations at risk for psychosis.

We believe that the protocol described here can contribute to the development of solid risk prediction models that can be implemented in clinical routine.

STUDY STATUS

The study status is ongoing, and recruitment for the *in-vivo* phase commenced on 1 August 2018. The study has been approved by National Research Ethics Service (NRES) East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (Ref: 18/EE/0066).

AUTHOR CONTRIBUTIONS

PF-P designed the study and the grant applications in liaison with all of the other co-investigators. DO wrote the protocol, information sheets, ethical applications. DO and GS will acquire and analyse the data. PF-P drafted this manuscript. All authors read and approved the final manuscript.

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frontiers in Psychiatry

ORIGINAL RESEARCH
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Effectiveness of Cognitive Remediation in Early Versus Chronic Schizophrenia: A Preliminary Report

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Background: Many evidences have demonstrated the effectiveness of cognitive remediation on cognition and functioning in patients with schizophrenia. Some researchers speculate that cognitive deficits are more amenable to remediation during earlier phases of illness than in chronicity. Therefore, cognitive rehabilitation should be used as an early intervention, seeking to produce durable functional changes in the early course of schizophrenia. Although there is strong evidence that cognitive remediation is effective in adult schizophrenia, there is little evidence about its efficacy and long-term generalized effectiveness in the early course of the disease. In this paper, we intended to investigate the possibility that cognitive remediation may produce more beneficial effects when applied in the early phase of the illness compared to chronic patients.

Materials and methods: Data were gathered from a database used for a previous study performed by our group, in which 56 patients with schizophrenia received a cognitive remediation intervention. In a *post hoc* analysis, patients with a duration of illness shorter than 5 years were defined as "early course" patients, while patients with a duration of illness longer than 5 years were defined as "chronic." Clinical, neuropsychological, and functional outcome variables were assessed at baseline and after treatment.

Result: Of the 56 patients included in the study, 11 were "early course" and 45 were "chronic." Both the early course group and the chronic group showed significant improvements in all the clinical, neurocognitive, and functional parameters analyzed. A significantly greater improvement in early course patients compared with chronic patients emerged in clinical and functional measures. No differential change was observed between early course patients and chronic patients in the cognitive composite score.

Conclusion: Our study confirms the effectiveness of cognitive remediation in improving clinical, cognitive, and functional parameters in patients with schizophrenia, both in patients in the early course and in chronic patients. However, patients in the early course showed a differential, greater change in clinical and functional parameters compared to chronic patients. Although this study has some limitations, it confirms the effectiveness of cognitive remediation interventions, particularly if applied in the early course of the illness.

Keywords: schizophrenia, early course, cognitive remediation, social function, effectiveness

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INTRODUCTION

Cognitive impairment represents a core feature of schizophrenia (1, 2), and its heavy impact on functional outcome has been widely demonstrated (3, 4). In recent years, several cognitive remediation (CR) interventions have been developed and have been used in integrated treatment approaches in patients with schizophrenia. The effectiveness of these treatments in the improvement of cognition and social functions is now well established (5, 6). However, many issues are still debated, such as the role of specific patients' characteristics in influencing the possibility to fully benefit from the effects of cognitive rehabilitation (7–11). Among those characteristics, younger age and shorter duration of illness have been identified as predictors of the effectiveness of CR in schizophrenia. In a review by our group (12), we found preliminary positive, yet not conclusive results. In fact, although in some studies age has been found not to be related to cognitive improvement (6, 13, 14), and in others mixed results emerged (15), a number of evidences confirmed the higher possibility of younger patients to achieve cognitive improvement after CR, with patients over the age of 40 showing a poorer response to CR, compared to patients under 40 (8, 11, 16–18). Furthermore, stage of illness, a variable closely related to age, might affect cognitive improvement after CR. In a study by Corbera et al. (11), the early-stage [25 years or younger; mean duration of illness (DOI) = 3.4 years] and early-chronic [26–39 years; mean DOI = 7.6 years] patients receiving CR showed larger improvements in working memory, compared to the late-chronic group (40 years and over; mean DOI = 18.2 years). In Bowie et al. (19), early course patients (less than 5 years from the psychotic onset) showed greater improvements in processing speed and executive functions, compared to chronic patients (more than 15 years of illness) after CR. Authors concluded that duration of illness was inversely associated with improvement in cognition after a CR intervention. The aim of this paper was to compare the effects of CR interventions in patients with schizophrenia in the early course of illness and in chronic patients, with the hypothesis of greater CR benefits in patients with a shorter duration of illness.

METHODS

Participants

Data for the present study were collected from a database originally composed for a previous study, conducted at the University Department of Mental Health of the Spedali Civili Hospital of Brescia, Italy (20), in which 84 patients with a diagnosis of schizophrenia The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were followed naturalistically for 6 months and were randomized to a CR intervention or treatment as usual. Patients with a diagnosis of substance use disorder and mental retardation [full scale IQ lower than 70 at the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (21)] or with positive symptomatology or impulsivity severity that needed hospitalization or major drug changes were excluded from the study. Patients with an age from 18 to 50 years were allowed to enter the study. Out of the 56 patients randomized to a CR intervention, 30 patients were treated with a computer-assisted CR intervention (CACR) [see Ref. (20)], and 26 received the first two sub-programs of the integrated psychological treatment (IPT). The CACR is an individualized computer-based procedure for CR, targeting cognitive functions through both domain-specific and non-domain-specific tasks. Domain-specific exercises are meant to target distinct cognitive functions among those reported to be impaired in schizophrenia patients (verbal memory, attention/vigilance, processing speed, working memory, and executive functions), while non-domain-specific tasks engage several cognitive functions at the same time. For the present study, the Cogpack software (Marker Software®) was used.

The IPT, on the other hand, is a manualized therapy program for schizophrenia patients, combining neuro- and social-cognitive remediation with psychosocial rehabilitation strategies; indeed, it is organized as a group approach (22). For the present study, groups of 8 to 10 patients were formed, and the cognitive subprograms of the IPT were administered each time by two trained mental health professionals.

Both IPT groups and CACR patients attended 45-min therapy sessions twice a week, for 24 weeks. For the same time, and following the same time schedule, the 28 patients randomized to treatment as usual received noncognitive specific rehabilitation, such as occupational therapy, art therapy, and physical training. However, for this study, only the 56 participants randomized to CR (i.e., the 30 patients who received CACR and the 26 who received IPT) were included in the analyses. All the patients went on receiving usual care provided by a multidisciplinary psychiatric team, including maintenance treatment with antipsychotics and rehabilitative interventions. Rehabilitation strategies (aiming at promoting the patients' functional recovery) were individually tailored depending on clinical demands and patients' attitudes and were delivered in a uniform way between groups (20).

Maintenance treatment was adiministered on a flexible dose schedule; the majority of patients (N = 41) received second-generation antipsychotics, while 15 patients were treated with first-generation drugs. Antipsychotics mean daily doses were reported using chlorpromazine equivalents, calculated for each patient using the method proposed by Woods (23). Use of benzodiazepines and anticholinergics was permitted when needed. Patients were assessed at study entry, and after treatments. They were assessed with measures of clinical severity, social functioning, and neuropsychological performance tests. The demographic characteristics of the sample are shown in **Table 1**.

Assessment

Clinical, neuropsychological, and functional assessment took place at baseline (t0) and at endpoint (6 months of follow-up), after the CR interventions.

Psychopathological assessment was performed using the Clinical Global Impression—Severity (CGI-S) scale (24) and the Positive and Negative Syndrome Scale (PANSS) (25). These scales were completed by the treating psychiatrists (not informed on

which kind of CR their patients were receiving) in the psychiatric outpatients units.

As for the neurocognitive evaluation, the raters were trained professionals, external to the treatment groups and blinded to the subjects' allocation. Before study entry, the patients were screened making use of the WAIS-R, adopted as an inclusion criterion measure (full scale IQ ≥70). Then, the included subjects underwent an exhaustive neuropsychological assessment at baseline and after 24 weeks. The following instruments were selected among those usually applied in neurocognitive evaluation of schizophrenia patients, representing a reasonable balance between comprehensiveness and ease of use (20, 26): Trail Making Test Part A (TMT-A), Trail Making Test Part B (TMT-B) (27), Wisconsin Card Sorting Test (WCST) (28), Self-Ordered Pointing Task (SOPT) (29), and California Verbal Learning Test (CVLT) (30).

Specific domains of cognitive functioning were then combined using the following four cognitive constructs: 1) processing speed: TMT-A; 2) working memory: TMT-B and SOPT, number of errors; 3) verbal memory: mean number of correct responses at immediate free recall, short- and long-delay free recall and short- and long-delay cued recall, CVLT; and 4) executive functions: TMT-B minus TMT-A (used as a flexibility index) (31), and mean percentage of perseverative and total errors, WCST. A global cognitive index was also derived by taking the average value of the other composite scores. When a neurocognitive test was not available, the relative composite score was considered as a missing value, and global cognitive score was not calculated (see the section Statistical Analysis). Z scores for each neuropsychological test were either derived using the Italian normative data for TMT and WCST (32) or control data published in previous studies for SOPT (26), or obtained in healthy subjects (N = 109) recruited by our group for CVLT.

The Z scores for each cognitive construct were calculated by taking the average of the Z scores of the specific corresponding tests (see 20). Finally, psychosocial functioning outcome measures were assessed by the referring multidisciplinary rehabilitative team, who usually took care of the patients and provided their standard rehabilitative interventions in the outpatient settings. This team did not include any personnel involved in the administration of the experimental CR programs and was also blinded to the patients' allocation. Evaluations were completed with team consensus, and every professional involved in the study was trained in the use of the rating instruments. The functional outcome measures used were the Global Assessment of Functioning (GAF) scale (33) and the Health of the Nation Outcome Scale (HoNOS) (34, 35).

Statistical Analysis

The analyses were performed only in the group of patients who received a CR intervention (N = 56). To test the hypothesis that patients in the early course of the illness could take more advantage from CR compared to chronic patients, participants were divided into two groups, based on the duration of illness. Patients with a duration of illness shorter than 5 years were defined as "early course," while patients with a duration of illness longer than 5 years were defined as "chronic."

This cutoff of 5 years was chosen according to literature on early course definition in schizophrenia and CR in early course patients with schizophrenia (19, 36).

Duration of illness was calculated starting from the first psychotic episode. Data regarding duration of illness were acquired by patients themselves, relatives, medical records, and health care professionals, involved in the routine care of the patients.

Demographic variables at baseline were compared between groups (early course and chronic) using t tests and chi-squared tests as appropriate. Clinical, neurocognitive, and psychosocial functioning variables at baseline were also compared between groups using t tests.

Within-group changes of clinical, neurocognitive, and functional variables were analyzed using pared samples t tests. Clinical, neurocognitive, and functional changes were compared between the two groups using repeated-measures analysis of variance, covaried by baseline. p values < 0.05 (two-tailed) were considered significant. Statistical analyses were conducted using SPSS 14.0 software.

RESULTS

Of the 56 patients included in the study, 11 were in their first 5 years of illness and thus were defined as "early course," while the other 45 were defined as "chronic," having a duration of illness longer than 5 years. Early course patients had a lower mean age, had a shorter mean duration of illness, and received a lower antipsychotic (chlorpromazine equivalents) mean daily dose. No differences between intervention (IPT and CACR) distribution, type of antipsychotics distribution (first- and second-generation antipsychotics), sex distribution, mean school years, and WAIS-R FSIQ emerged between early course and chronic patients (**Table 1**). A higher score at the PANSS negative and general psychopathology subscales and at the PANSS total score emerged in the early course group compared to chronic patients (**Table 2**). No baseline differences in any other clinical (CGI-S, PANSS positive subscale), neurocognitive, and psychosocial functioning variables emerged between groups. Significant ($p < 0.05$) within-groups improvements in all the clinical, neurocognitive, and functional parameters analyzed using the paired samples t tests emerged in both the early course group and the chronic group. A significantly greater improvement in early course patients compared with chronic patients emerged for CGI-S, PANSS total score, PANSS positive subscale, PANSS negative subscale, PANSS general psychopathology subscale, GAF, and HoNOS total score. No differential change was observed between early course patients and chronic patients in the Global Cognitive Composite Score.

DISCUSSION

This study confirms the effectiveness of CR in improving clinical, cognitive, and functional parameters in patients with

TABLE 1 | Demographic variables of the sample.

	Total	Early course	Chronic	p (t-test, chi-squared)
N	56	11	45	
M:F	40:16	9:2	31:14	0.395
IPT:CACR	26:30	5:6	21:24	0.942
Typicals:Atypicals	10:46	1:10	9:36	0.397
Chlorpromazine Equivalents	634±387	409±111	689±411	<0.001
Age	37.00±10.30	23.82±4.53	40.22±8.60	<0.001
Duration of illness (years)	14.87±9.68	2.50±1.39	17.89±8.32	<0.001
School Years	10.45±2.91	10.91±2.54	10.33±3.01	0.562
WAIS-R FSIQ	86.30±12.71	88.00±13.08	85.89±12.73	0.626

Early course, patients with a duration of illness (DOI) < 5 years; Chronic, patients with a duration of illness (DOI) > 5 years; WAIS-R FSIQ, Wechsler Adult Intelligence Scale—Revised, Full Scale Intelligence Quotient; IPT, integrated psychological therapy; CACR, computer-assisted cognitive remediation. Typicals and atypicals refer to first-generation and second-generation antipsychotics, respectively.

TABLE 2 | Between-group comparisons of change of clinical, neurocognitive, and psychosocial functioning variables.

	T0	T1	Repeated-measures ANCOVA (covaried by baseline) time × group interaction p	Effect size (partial eta squared)
CGI-S (early course)	5.09 ± 0.53	3.50 ± 0.70	0.002	0.172
CGI-S (chronic)	4.76 ± 0.74	3.98 ± 0.83		
PANSS Pos (early course)	19.45 ± 5.42	11.90 ± 3.34	0.028	0.092
PANSS Pos (chronic)	18.87 ± 5.25	13.65 ± 3.37		
PANSS Neg (early course)	31.36 ± 6.80*	18.60 ± 8.05	0.007	0.137
PANSS Neg (chronic)	23.78 ± 7.61	18.23 ± 4.83		
PANSS Gen (early course)	51.45 ± 10.44*	31.90 ± 8.81	<0.001	0.225
PANSS Gen (chronic)	44.20 ± 8.44	35.07 ± 7.73		
PANSS Tot (early course)	102.27 ± 17.90*	62.40 ± 17.99	0.001	0.190
PANSS Tot (chronic)	86.84 ± 15.63	66.95 ± 12.29		
GAF (early course)	41.09 ± 9.42	56.10 ± 8.43	0.006	0.138
GAF (chronic)	47.91 ± 10.53	55.14 ± 8.92		
HoNOS (early course)	19.55 ± 4.92	7.80 ± 5.63	0.010	0.127
HoNOS (chronic)	17.80 ± 5.39	10.91 ± 5.96		
Global cognition (early course)	−0.70 ± 0.79	−0.32 ± 0.92	0.648	0.004
Global cognition (chronic)	−1.21 ± 0.93	−0.63 ± 0.93		
Processing speed (early course)	0.10 ± 0.47	0.29 ± 0.66	0.871	0.001
Processing speed (chronic)	−0.36 ± 1.27	0.02 ± 0.80		
Working memory (early course)	−0.54 ± 1.11	−0.39 ± 1.16	0.693	0.003
Working memory (chronic)	−1.24 ± 1.05	−0.69 ± 1.07		
Verbal memory (early course)	−1.96 ± 1.31	−1.17 ± 1.68	0.570	0.006
Verbal memory (chronic)	−2.58 ± 1.46	−1.43 ± 1.68		
Executive functions (early course)	−0.40 ± 0.84	−0.02 ± 0.69	0.134	0.045
Executive functions (chronic)	−0.67 ± 0.94	−0.45 ± 0.95		

Early course, patients with a duration of illness (DOI) < 5 years; Chronic, patients with a duration of illness (DOI) > 5 years.
**Baseline between groups difference, t test, p < 0.05.*

schizophrenia. This effectiveness is demonstrated in patients in the early course of the illness as well as in chronic patients. However, patients in the early course showed a differential, greater change in clinical and functional parameters compared to chronic patients. In fact, it is possible that the group in the early course of the illness may benefit from the advantage of a younger age, with this parameter being a well-known predictor of functional improvement after CR (8). However, although both early course and chronic patients improved in global cognitive performance, no between-groups differences emerged in the change of such parameter. Even if this result confirms the possibility for patients with schizophrenia to benefit from CR both in the early phase of the illness and in later stages, it is not in line with previous evidences, reporting greater cognitive improvements in patients with a shorter duration of illness compared to chronic patients after CR (11, 19) and, more in general, with studies that suggest that psychosocial improvements after CR may be mediated by cognitive improvements (20).

Furthermore, the baseline greater severity of negative and general psychopathology observed in the early course group

compared to chronic patients, a factor found to be associated to less marked cognitive improvements after CR (18), could have represented a potentially limiting factor in detecting between-groups differences in cognitive change after CR. Conversely, the lower antipsychotic mean daily dose that emerged in the early course group, a factor that has been found to be associated to greater cognitive and psychosocial functioning amelioration after CR (8), in this case should not be considered as an indirect proxy of symptoms severity and suggests a more specific role of the antipsychotic treatments in psychosocial functioning improvement after CR, a hypothesis that should be better analyzed in future studies.

This study has several limitations: first, the small sample size could have limited the statistical power of the analyses and the possibility to perform further, potentially interesting analyses, such as the comparison between type of intervention (IPT and CACR) in early course and chronic patients; second, the possibility to generalize the results may be restricted by the specific sample recruited for the study, including patients followed in the Italian psychiatric rehabilitation services; third, the original study was not explicitly designed with the purpose of comparing the differences of the effects of CR between patients with schizophrenia in their early course of illness and chronic patients; fourth, being an exploratory study, a correction for multiple comparisons was not used, in order to avoid the possibility of missing potentially interesting results, to be further analyzed in future studies; fifth, the cutoff for early course patients, although not one of the strictest among those proposed in literature (36), did not allow the identification of two groups of identical size, thus further limiting the statistical approach. Nevertheless, in a recent review about the diverse definition of the early course of schizophrenia, the authors suggested that disease duration of <5 years encompasses the previous definition of the critical period for early intervention (36).

Despite these limitations, the results of the study clearly suggest that benefits from CR may be better when these interventions are applied in patients with schizophrenia at their early stages of the illness. These results, if confirmed by further studies, specifically designed for this purpose, point towards the perspective of earlier interventions in psychosis, with the possibility to also use non-pharmacologic evidence-based treatments that may also be potentially useful not only in the early course of schizophrenia but also in patients defined at risk of psychosis (12).

ETHICS STATEMENT

Written informed consent to treatment was obtained from all participants after the nature of the intervention procedures had been fully explained. The project was approved by the Board for Innovation in Psychiatry of the Health Authority of the Lombardia Region, Italy. The work has been carried out in accordance with the Code of Ethics of the World Medical Association.

AUTHOR CONTRIBUTIONS

AV designed the project, and reviewed and discussed the data and statistical analyses and the final version of the paper. GD administered and scored neuropsychological tests, prepared the database, participated in the analyses, and wrote the paper. SB and PC followed patients in the rehabilitative interventions. AG, PV, and CT participated in the discussion of the data and manuscript. All authors contributed to and approved the final manuscript.

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Preliminary Evidence for the Cognitive Model of Auditory Verbal Hallucinations in Youth With Borderline Personality Disorder

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Objectives: This is the first study to explore cognitive, emotional, and behavioral responses to voices in youth with borderline personality disorder (BPD) compared with those with schizophrenia spectrum disorder (SZ), and to examine if negative appraisals of voices predict depression and anxiety across the groups.

Methods: The sample comprised 43 outpatients, aged 15–25 years, who reported auditory verbal hallucinations (AVH) and were diagnosed with either *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) BPD or SZ. Data were collected using the Psychotic Symptom Rating Scales, the revised Beliefs About Voices Questionnaire, the Voice Rank Scale, and the Depression Anxiety Stress Scale.

Results: Youth with BPD did not differ from youth with SZ in beliefs about the benevolence or malevolence of voices. Youth with BPD appraised their voices as more omnipotent and of higher social rank in relation to themselves, compared with youth with SZ. In both diagnostic groups, beliefs about malevolence and omnipotence of voices were correlated with more resistance toward voices, and beliefs about benevolence with more engagement with voices. In addition, perceiving the voices as being of higher social rank than oneself and negative voice content were both independent predictors of depression, irrespective of diagnostic group. In contrast, negative appraisals of voices did not predict anxiety after adjusting for negative voice content.

Conclusions: This study replicated the link between negative appraisals of voices and depression that has been found in adults with SZ in a mixed diagnostic youth sample. It, thus, provides preliminary evidence that the cognitive model of AVH can be applied to understanding and treating voices in youth with BPD.

Keywords: borderline personality disorder, schizophrenia, psychosis, auditory hallucinations, beliefs about voices, distress, depression, anxiety

INTRODUCTION

Increasing evidence suggests that auditory verbal hallucinations (AVH) are common and highly distressing in adults with borderline personality disorder (BPD) (1–6). Although the cognitive model of AVH (7, 8) has informed the development of psychological treatments, such as cognitive behavioral therapy (CBT) for patients with schizophrenia, few studies have examined the usefulness of this model for the understanding and treatment of voices in BPD. None have done this in young patients early in the course of BPD. This study aimed to explore the cognitive model of AVH in youth (aged 15–25 years) with BPD. This age group coincides with the peak period of clinical onset for both BPD (9) and psychotic disorders (10).

Auditory hallucinations have been defined as "auditory experiences that occur in the absence of a corresponding external stimulation and which resemble a veridical perception" (11). If the auditory experiences involve the perception of spoken language, they are referred to as AVH or voices, which is their most common form (12). While AVH are most common in patients with psychotic disorders (40%–80%), there is increasing evidence that they also occur in healthy individuals (10%–20%) and in patients with nonpsychotic mental disorders, including BPD (20%–50%) (3, 11, 13, 14).

Not all individuals reporting AVH seem to be perturbed or impaired by these symptoms. Therefore, the determinants of distress and dysfunction associated with AVH need to be elucidated. Studies comparing AVH in clinical and nonclinical samples have revealed two clear, differentiating factors: voice content and voice appraisal. Patients (i.e., people who seek help for their distressing voices, irrespective of diagnosis) more often report negative voice content (e.g., negative comments, verbal abuse, personal insults, commands to harm oneself or others) and negative appraisals of voices (e.g., as malevolent, powerful, dominant, intrusive, controllable). Consequently, they are more likely to engage in maladaptive coping strategies (e.g., safety behaviors, compliance, resistance, ignorance, distance) than nonpatients (12, 15, 16). This suggests that factors other than the mere presence of the symptom lead to distress (e.g., any negative affect, such as depression, anxiety, or voice-related distress), dysfunction, and need for care. This is consistent with a "continuum hypothesis" of AVH, suggesting that voice-hearing occurs in the general population, as well as in clinical samples, with the latter group reporting higher levels of distress and need for care (15). Studies examining the differences between the two groups found that it is not the presence of AVH *per se*, but rather the negative voice content and the negative appraisals of voices that determine the level of distress and need for care [e.g., Ref. (16)].

Chadwick and Birchwood (7, 8) observed that, in patients with schizophrenia, beliefs about voices often involve the person making inferences beyond what is manifest in voice content alone. Consequently, the cognitive model of AVH asserts that the way an individual cognitively appraises their voices is the primary determinant of emotional and behavioral responses to the experience (7, 8). In support of this, *cognitive appraisals* of voices in terms of malevolent intention, power, and social rank have been associated with more resistance to (in contrast to engagement with) and higher levels of voice-related distress, anxiety, and depression among voice-hearers with schizophrenia and related disorders, irrespective of *form* (e.g., frequency, duration, location, loudness) or *content* of voices (17–23). Mawson et al. (24) reviewed the literature regarding the cognitive model of AVH and concluded that the relationship between appraisals of malevolence (i.e., intent of voices to harm) and supremacy of voices (i.e., omnipotence, social power, and rank of voices compared to voice-hearer) with distress received the most empirical support. The clinical implication is that making *cognitive appraisals* of voices the target of psychological interventions, rather than the *form* or *content* of voices, might assist reduction of distress and problematic coping behaviors in individuals with AVH.

Recent evidence indicates that AVH in adults with BPD are phenomenologically similar to those in schizophrenia, elicit high levels of distress, depression, and anxiety, and are associated with more psychiatric comorbidity, suicidal plans and attempts, and hospitalizations (2–3, 4, 6, 25–27). Limited evidence exists regarding whether the cognitive, emotional, and behavioral responses to voices in patients with BPD are similar or different to those in patients with schizophrenia. Hepworth et al. (28) reported that adults with BPD did not differ from those with schizophrenia in beliefs about malevolence and omnipotence of voices, or in behavioral resistance and engagement, but showed more emotional resistance toward and less emotional engagement with voices. In another study of adults with BPD, beliefs about malevolence and social rank of voices were correlated with distress, and beliefs about omnipotence of voices were also correlated with distress, along with the number of hospitalizations within 2 years postbaseline, and the number of days until hospitalization (29). These two studies explored cognitive appraisals of voices in adults with longstanding BPD [mean age was 33.70 years (28) and 39 years (29), respectively]. To date, no attention has been given to young people, even though adolescence and early adulthood represent a sensitive period for the development, detection, and early treatment of symptoms associated with both BPD and psychotic disorders, such as AVH (9, 10). Information about the cognitive, emotional, and behavioral responses to voices across the lifespan might inform clinical practice regarding whether a transdiagnostic, symptom-focused treatment approach is appropriate.

In a recent study, our group explored AVH in a sample of outpatient youth (15 to 25 years of age) with BPD and found that they were similar to those in youth with schizophrenia spectrum disorder (SZ) with regard to physical (frequency, duration, location, loudness), cognitive (beliefs regarding origin of voices, disruption to life, controllability), and emotional (negative content, distress) characteristics (30). Using this same sample, the current study aimed to investigate whether beliefs, emotions, and behaviors associated with AVH in youth with BPD are similar to or different from those in youth with schizophrenia spectrum disorder (exploratory aim 1). Based on the literature in adult patients, we hypothesized that youth with BPD will show higher levels of emotional resistance toward voices, depression, and anxiety compared to youth with schizophrenia spectrum disorder (Hypothesis 1). We also examined whether the assumptions of the cognitive model of AVH might apply, regardless of diagnostic group (BPD or SZ) (exploratory aim 2). Based on the literature in adult patients, the following hypotheses

were tested: Beliefs about malevolence and omnipotence of voices will be related to resistance toward voices, while beliefs about benevolence of voices will be related to engagement with voices, irrespective of diagnosis (Hypothesis 2). Negative appraisals of voices (in terms of malevolence, omnipotence, and high social rank) will predict high levels of depression and anxiety, after adjusting for the impact of form and content of voices, irrespective of diagnosis (Hypothesis 3).

MATERIALS AND METHODS

Participants

Forty-three help-seeking youth, aged 15–25 years, with AVH, who were diagnosed with either BPD (BPD+AVH; n = 23) or schizophrenia spectrum disorder (SZ) (SZ+AVH, n = 20) according to the *Diagnostic and Statistical Manual of Mental Disorders*, *5th Edition* (DSM-5) (31) and were fluent in English, participated in the study. They constituted a subsample of a study that has been reported elsewhere (30). Two participants from the original SZ+AVH group (n = 22) did not complete the questionnaires, and were thus excluded from these analyses. AVH were defined as present according to the threshold set in the Comprehensive Assessment of At Risk Mental States (CAARMS) (32) for more than 1 week within the past 3 months. Threshold AVH are defined in the CAARMS as an intensity rating of 5 or higher and a frequency rating of 4 or higher on the Perceptual Abnormalities subscale. This corresponds to hearing voices i) at least three times a week for more than an hour per occasion; or ii) daily for any duration per occasion.

The BPD+AVH group included youth with a DSM-5 BPD diagnosis and CAARMS threshold AVH. Participants were excluded from this group if they were diagnosed with a DSM-5 delusional disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance/medication-induced psychotic disorder, psychotic disorder due to another medical condition, catatonia, or bipolar I disorder.

The SZ+AVH group included youth with a DSM-5 brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder and CAARMS threshold AVH. Exclusion criteria for this group were a DSM-5 delusional disorder, substance/medication-induced psychotic disorder, psychotic disorder due to another medical condition, catatonia, or bipolar I disorder, or having more than two DSM-5 BPD criteria.

Procedure

Participants were recruited between June 2016 and February 2018 from Orygen Youth Health, the state government-funded specialist mental health service for 15–25 year olds living in northwestern and western metropolitan Melbourne, Australia. The service includes specialist early intervention programs for psychosis (33) and for BPD (34). In accordance with the Declaration of Helsinki, written informed consent was obtained from all participants, and additionally from a parent or guardian for those under 18 years old. Participants were interviewed by a clinical psychologist-researcher or by graduate research assistants who were specifically trained in the application of the measures. Participants were reimbursed for time and expenses. The study was approved by the Melbourne Health Human Research Ethics Committee (MHREC2016.086).

Measures

Participants were assessed using the positive symptom scales of the CAARMS, a semistructured interview conducted to determine the presence, type, frequency, and severity of subthreshold and threshold psychotic symptoms (32). The Perceptual Abnormalities subscale was used to assess AVH as described above. The modules A–D (affective and psychotic disorders) of the Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV) (35) and the BPD section of the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD) (36) were administered to establish diagnostic status.

After establishing eligibility for the study, a series of interviews and questionnaires, as described below, were administered and demographic data were collected. Residential postcode was used to determine socioeconomic status according to an Australian index of socioeconomic disadvantage (37). The tertiles of the rank (i.e., low, middle, and high socioeconomic status) were used for analyses.

General psychosocial functioning was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS) (38), which ranges from 1 (persistent instability to maintain minimal personal hygiene, unable to function without harming self or others or without considerable external support) to 100 (superior functioning in a wide range of activities).

Phenomenological characteristics of AVH were assessed using the Auditory Hallucinations subscale of the Psychotic Symptom Rating Scales (PSYRATS-AH) (39). It consists of 11 items, rated on a five-point scale (0–4). The items assessing form (i.e., frequency, duration, location, and loudness) and content (i.e., amount of negative voice content, and degree of negative voice content) were used for the current analyses.

The 21-item version of the Depression Anxiety Stress Scale (DASS-21) (40) was administered to assess distress over the past week. For the current analyses, only the depression and anxiety subscales were used. The depression subscale measures symptoms typically associated with dysphoric mood (e.g., sadness or worthlessness), while the anxiety subscale measures symptoms of physical arousal, panic attacks, and fear (e.g., trembling or faintness). The items are rated on a four-point Likert scale (0 = did not apply to me at all, to 3 = applied to me very much, or most of the time). The Cronbach's alpha scores in the current study were 0.94 and 0.87 for depression and anxiety, respectively, indicating excellent internal consistency. The depression and anxiety subscales of the DASS-21 were used as outcome variables in this study measuring amount and intensity of distress instead of the PSYRATS-AH items because a) the DASS-21 subscales are continuous in contrast to the four-point Likert scale of the PSYRATS items, and b) previous research found that nearly two-thirds of voice-hearers diagnosed with schizophrenia experience at least moderate depression (17) and that AVH is associated with increased levels of depression and anxiety in adults with BPD, too (27).

Cognitive, emotional, and behavioral responses to voices were explored using the revised Beliefs About Voices Questionnaire

(BAVQ-R) (18). It consists of 35 items rated on a four-point Likert scale (0 = disagree to 3 = strongly agree). There are five subscales, three relating to beliefs about voices (i.e., malevolence, benevolence, and omnipotence) and two relating to emotional and behavior responses to voices (i.e., engagement and resistance). The beliefs subscales each consists of six items. The resistance subscale includes five items on emotion and four on behavior, while the engagement subscale includes four items on emotion and four on behavior. Cronbach's alpha scores for the subscales in the current study ranged between 0.72 and 0.89, indicating adequate internal consistency.

The Voice Rank Scale (VRS) (18, 41) uses a semantic differential adapted from the Social Comparison Scale to measure the individual's rank relative to the dominant voice. The scale consists of 11 items with scores ranging from 1 to 10 (e.g., Incompetent 1 2 3….8 9 10 Component). A low sum score indicates that the individual experiences him-/herself as of lower social rank compared to the voice. Internal consistency of the scale in the current study was good, with Cronbach's alpha = 0.87.

Statistical Analyses

Statistical analyses were performed using IBM Statistical package for the social sciences (SPSS) Statistics for Windows, version 22.0 (42). Missing value analyses revealed one missing value in the DASS-21 and the VRS each, as well as three missing values in the BAVQ-R. These missing values were completely at random as indicated by nonsignificant Little's Missing completely at random (MCAR) tests, and were replaced by expectation maximization methods (43).

Demographic characteristics were compared between the two groups using chi-square tests (education status, employment status), Fisher's exact tests if expected cell counts of categorical variables were less than five (gender, relationship status, main financial support, socioeconomic status), Mann–Whitney *U* test (SOFAS), and *t*-test for independent samples (age).

In order to examine whether beliefs, emotions, and behaviors associated with AVH in youth with BPD differed from those in youth with SZ and AVH (exploratory aim 1 and Hypothesis 1), group comparisons were performed using the Mann–Whitney *U* test for the BAVQ-R subscales and the DASS-21 subscales, as well as the *t*-test for independent samples for the VRS. Group comparisons of the PSYRATS-AH items have been reported elsewhere (30).

In order to examine whether the assumptions of the cognitive model of AVH apply, regardless of BPD or SZ diagnosis (exploratory aim 2), correlation and regression analyses were conducted. In order to test Hypothesis 2, Spearman's correlations between the BAVQ-R subscales were conducted on the whole sample. The correlational analyses were then repeated for the BPD+AVH group and the SZ+AVH group separately, and correlation coefficients between the groups were compared using Fisher's *Z* test adapted for Spearman's rho in accordance to Sheskin (44).

In order to test Hypothesis 3, Spearman's correlations were first conducted between potential confounders (gender, age), the PSYRATS-AH items (frequency, duration, loudness, location, amount of negative voice content, degree of negative voice content), the BAVQ-R beliefs about voices subscales (malevolence, benevolence, omnipotence), the VRS, and the DASS-21 depression and anxiety subscales on the whole sample. The correlation analyses were then repeated for the BPD+AVH group and the SZ+AVH group separately, and correlation coefficients between the groups were compared using Fisher's *Z* test for Spearman's rho (44). Those variables that were identified as holding a significant correlation with depression or anxiety were used as predictor variables in the subsequent regression analyses. Two hierarchical linear regression analyses were then conducted for depression and anxiety separately. In each analysis, the demographic variables and the PSYRATS-AH items were entered as predictor variables in the first step, and the BAVQ-R subscales and VRS in the second step. Lastly, we conducted a moderation analysis to test if group (BPD+AVH, SZ+AVH) moderated the effects of cognitive appraisals of voices on distress, using SPSS PROCESS macro version 3.00 (45). PROCESS uses ordinary least squares regression to estimate the regression coefficients, and bootstrapping methods for the confidence intervals, yielding results that are less affected by sample size. For each regression analysis, the assumptions of linearity and multicollinearity, as well as of independence, normality, and homoscedasticity of residuals, were checked.

Nonparametric tests were used if variables were not normally distributed across groups, normality could not be achieved through transformation, and/or outliers were detected by visual inspection of box plots. To provide an estimate of the size of observed effects that is independent of sample size and measure used (46), effect sizes (d, θ, r, R^2, and rs^2) were computed. θ = U/mn is the generalized Mann–Whitney effect size measure that ranges from 0 to 1, taking the value 0.5 on the null hypothesis (identically distributed) and 0 or 1 if there is no overlap between the two samples (47). Newcombe (48) provided an Excel spreadsheet, which was used to calculate θ and its confidence intervals. Theta values in the range 0.4–0.6 were considered as small, in the ranges 0.61–0.8 and 0.2–0.39 as moderate, and in the ranges 0.81–1 and 0–1.9 as large. The sizes of *d* and r were interpreted according to Cohen (49).

RESULTS

Participant Characteristics

The demographic characteristics of participants are presented in **Table 1**. Participants in the BPD+AVH group did not significantly differ from participants in the SZ+AVH group with regard to demographic characteristics, except that participants of the former group were significantly more often female, younger, and enrolled in education.

SZ+AVH group participants were diagnosed with the following psychotic disorders: 1 (5.0%) with brief psychotic disorder, 5 (25.0%) with schizophreniform disorder, 3 (15.0%) with schizoaffective disorder, and 11 (55.0%) with schizophrenia. A comprehensive characterization of the groups in terms of psychotic symptoms is reported elsewhere (30). In short, AVH, as assessed by the PSYRATS-AH items, in the BPD+AVH group were found to be phenomenologically indistinguishable from those in the SZ+AVH group (see **Table S1**).

TABLE 1 | Participant demographics.

	BPD+AVH (*n* = 23)	SZ+AVH (*n* = 20)	Group differences	
	M (SD)/*n*(%)	M (SD)/*n*(%)	Test statistic	*p*
Gender				.001**
Male	1 (4.3)	10 (50.0)		
Female	22 (95.7)	10 (50.0)		
Age (years)	18.13 (2.30)	20.00 (3.15)	$t(41) = 2.24$	.030*
Romantic relationship	8 (34.8)	4 (20.0)		.327
In education	17 (73.9)	8 (40.0)	$X^2(1) = 5.06$	.033*
Employed	8 (34.8)	7 (35.0)	$X^2(1) = 0.00$	1.00
Main financial support			$X^2 = 0.45$	.853
Employment	4 (17.4)	5 (25.0)		
Acquaintances	10 (43.5)	8 (40.0)		
Government benefits	9 (39.1)	7 (35.0)		
Socioeconomic status			$X^2 = 1.86$	.395
Low	10 (43.5)	5 (25.0)		
Middle	9 (39.1)	9 (45.0)		
High	4 (17.4)	6 (30.0)		
Psychosocial functioning	52.74 (12.16)	54.30 (8.52)	$U = 223.00$	.864

*AVH, auditory verbal hallucinations; BPD, borderline personality disorder; SOFAS, Social and Occupational Functioning Assessment Scale; SZ, schizophrenia spectrum disorder. Significant at: *p < .05; **p < .01.*

Cognitive, Emotional, and Behavioral Responses to Voices and Depression and Anxiety in Youth With Borderline Personality Disorder Compared With Those With Schizophrenia Spectrum Disorder (Exploratory Aim 1, Hypothesis 1)

Table 2 presents the results of the group comparisons of the BAVQ-R subscales, the VRS, and the DASS-21 depression and anxiety subscales. Participants in the BPD+AVH group significantly more often appraised their voices as omnipotent, of higher social rank than themselves, and reported more symptoms of depression and anxiety, than did participants in the SZ+AVH group. The effect sizes for these group differences were medium to large. There were no statistically significant group differences in beliefs about malevolence and benevolence of voices, or in emotional or behavioral responses to voices (i.e., resistance, engagement), and these effect sizes were small to medium.

Relationship Between Negative Appraisals of Voices and Emotional and Behavioral Responses to Voices in Youth With Borderline Personality Disorder Compared With Those With Schizophrenia Spectrum Disorder (Exploratory Aim 2, Hypothesis 2)

Table 3 shows the correlations between the BAVQ-R subscales assessing beliefs about voices and the subscales assessing emotional and behavioral responses to voices for the whole sample. Malevolence and omnipotence were moderately to strongly correlated with more emotional resistance. In addition,

TABLE 2 | Group differences in cognitive, emotional, and behavioral responses to voices, depression, and anxiety.

	BPD+AVH (*n* = 23)			SZ+AVH (*n* = 20)			Group differences		
	M (SD)	Mnd	MR	M (SD)	Mnd	MR	Test statistic	*p*	ES and (95%) CI
BAVQ-R Malevolence	11.06 (5.24)	11.00	24.87	8.90 (4.42)	8.00	18.92	$U = 291.50$	.133	$\theta = 0.63$ (0.46, 0.78)
BAVQ-R Benevolence	4.26 (4.85)	2.00	21.67	4.55 (4.83)	3.00	22.38	$U = 222.50$	.852	$\theta = 0.48$ (0.32, 0.65)
BAVQ-R Omnipotence	12.85 (4.11)	13.00	26.15	10.35 (3.42)	11.00	17.22	$U = 325.50$	.019*	$\theta = 0.71$ (0.53, 0.83)
BAVQ-R Emotional resistance	9.11 (2.75)	9.00	24.85	7.90 (2.97)	8.00	18.95	$U = 291.00$	.133	$\theta = 0.63$ (0.46, 0.77)
BAVQ-R Behavioral resistance	9.83 (4.10)	10.00	22.07	10.05 (2.70)	10.50	21.92	$U = 231.50$	.971	$\theta = 0.50$ (0.34, 0.67)
BAVQ-R Emotional engagement	2.35 (3.11)	1.00	20.24	3.40 (3.50)	3.00	24.02	$U = 189.50$	.308	$\theta = 0.41$ (0.26, 0.58)
BAVQ-R Behavioral engagement	2.30 (2.98)	1.00	20.46	3.20 (3.41)	2.00	23.78	$U = 194.50$	.377	$\theta = 0.42$ (0.27, 0.59)
Voice Rank Scale	36.50 (15.03)	N/A	N/A	49.45 (15.92)	N/A	N/A	$t(41) = 2.74$	.009**	$d = 0.84$ (0.21, 1.46)
DASS-21 Depression	15.26 (4.97)	16.00	28.48	7.60 (6.44)	6.50	14.55	$U = 379.00$	.000***	$\theta = 0.82$ (0.66, 0.91)
DASS-21 Anxiety	13.74 (4.84)	13.00	29.24	6.70 (4.24)	6.50	13.68	$U = 396.50$	.000***	$\theta = 0.86$ (0.71, 0.94)

*BAVQ-R, revised Beliefs About Voices Questionnaire; DASS-21, Depression Anxiety Stress Scales; N/A, not applicable. Significant at: *p < .05; **p < .01; ***p < .001.*

TABLE 3 | Relationships between beliefs about voices and emotional and behavioral responses to them (n = 43).

	BAVQ-R Emotional resistance			BAVQ-R Behavioral resistance			BAVQ-R Emotional engagement			BAVQ-R Behavioral engagement		
	r_s	p	95% CI	r_s	p	95% CI	r_s	p	95% CI	r_s	p	95% CI
BAVQ-R Malevolence	.61	.000***	0.38, 0.77	.26	.092	−0.04, 0.52	−.36	.019*	−0.60, −0.07	−.25	.106	−0.51, 0.05
BAVQ-R Benevolence	−.40	.008**	−0.63, −0.11	−.19	.228	−0.46, 0.12	.79	.000***	0.64, 0.88	.72	.000***	0.54, 0.84
BAVQ-R Omnipotence	.45	.003**	0.17, 0.66	.44	.003**	0.16, 0.65	−.19	.216	−0.46, 0.12	−.09	.561	−0.38, 0.22

*BAVQ-R, revised Beliefs About Voices Questionnaire. Significant at: *p < .05; **p < .01; ***p < .001.*

malevolence was moderately correlated with less emotional engagement, and omnipotence with more behavioral resistance. In contrast, benevolence was moderately correlated with less emotional resistance, and strongly correlated with more emotional and behavioral engagement.

A comparison of correlations between the BPD+AVH group and the SZ+AVH group revealed a significant group difference in the correlation between malevolence and emotional engagement (p = .014) only. The relationship between these two variables was large and significant in the SZ+AVH group (r_s = −.71, p < .000, 95% CI [−0.88, −0.39]), and negligible and not significant in the BPD+AVH group (r_s = −.04, p = .843, 95% CI [−0.47, 0.41]).

Relationship Between Negative Appraisals of Voices and Depression and Anxiety in Youth With Borderline Personality Disorder Compared to Those With Schizophrenia Spectrum Disorder (Exploratory Aim 2, Hypothesis 3)

As seen in **Table 4**, depression was moderately to strongly correlated with being female, a higher amount and degree of negative voice content, and more negative appraisals of voices in terms of malevolence, omnipotence, and social rank. Anxiety was moderately correlated with the degree of negative voice content and negative appraisals of voices (malevolence, omnipotence, voice social rank). The comparison of the correlations between the BPD+AVH group and the SZ+AVH group revealed no significant differences (p > .05).

The results of the hierarchical regression analyses examining whether the addition of negative appraisals of voices improved the prediction of depression and anxiety, over and above gender and/or voice content, are summarized in **Table 5**. The estimated proportion of variance explained by gender and/or negative voice content alone was 40% for depression and 11% for anxiety. Entering negative appraisals of voices in the second step explained significant additional variance for depression only. The estimated proportion of variance explained by negative appraisals of voices was 19% for depression and 7% for anxiety. In the final model, depression was significantly predicted by the degree of negative voice content and perceived social rank of voices, which explained 16% and 11% of variance, respectively.

Finally, three moderation analyses were conducted first for depression as the dependent variable and then repeated for anxiety as the dependent variable, in order to examine if the effect of malevolence, omnipotence, or perceived social rank of

TABLE 4 | Relationship between demographic variables, voice form and content, and cognitive appraisals of voices with depression and anxiety (n = 43).

	DASS-21 Depression			DASS-21 Anxiety		
	r_s	p	95% CI	r_s	p	95% CI
Gender	.36	.018*	0.07, 0.60	.29	.061	−0.01, 0.54
Age	−.23	.140	−0.50, 0.08	−.09	.548	−0.38, 0.22
PSYRATS-AH frequency	.07	.662	−0.24, 0.36	−.12	.462	−0.41, 0.19
PSYRATS-AH duration	.28	.070	−0.02, 0.54	.05	.752	−0.25, 0.35
PSYRATS-AH location	−.07	.653	−0.36, 0.24	−.15	.325	−0.43, 0.16
PSYRATS-AH loudness	.20	.205	−0.11, 0.47	.23	.141	−0.08, 0.49
PSYRATS-AH amount of negative voice content	.37	.014*	0.08, 0.60	.23	.143	−0.08, 0.49
PSYRATS-AH degree of negative voice content	.66	.000***	0.45, 0.80	.34	.025*	0.05, 0.58
BAVQ-R Malevolence	.52	.000***	0.26, 0.71	.35	.021*	0.06, 0.59
BAVQ-R Benevolence	−.22	.159	−0.49, 0.09	.01	.97	−0.29, 0.31
BAVQ-R Omnipotence	.41	.007**	0.13, 0.63	.40	.008**	0.11, 0.63
VRS	−.49	.001**	−0.69, −0.22	−.34	.025*	−0.58, −0.05

*BAVQ-R, revised Beliefs About Voices Questionnaire; DASS, Depression Anxiety Stress Scale; PSYRATS-AH, Psychotic Symptom Rating Scales Auditory Hallucinations; VRS, Voice Rank Scale. Significant at: *p < .05; **p < .01; ***p < .001.*

TABLE 5 | Hierarchical regression analyses predicting depression and anxiety in youth with AVH who were either diagnosed with BPD or SZ (n = 43).

	B	β	t	rs^2	R_a^2	95% CI	F	ΔR^2	ΔF
DASS-21 Depression									
Step 1					.40	0.13, 0.59	10.45***	.45	10.45***
Sex	3.64	.23	1.92	.05					
PSYRATS-AH Amount of negative voice content	–0.37	–.06	–0.38	.00					
PSYRATS-AH Degree of negative voice content	4.34	.62	3.75**	.20					
Step 2					.59	0.32, 0.74	11.18***	.21	7.05**
Sex	2.36	.15	1.39	.02					
PSYRATS-AH Amount of negative voice content	–1.16	–.20	–1.35	.02					
PSYRATS-AH Degree of negative voice content	4.13.20	.59	0.41***	.16					
BAVQ-R Malevolence	18.31	.23	1.65	.03					
BAVQ-R Omnipotence	–0.04	–.02	–0.15	.00					
VRS	–0.16	–.38	–3.36**	.11					
DASS-21 Anxiety									
Step 1					.11	0.0, 0.33	6.27*	.13	6.27*
PSYRATS-AH Degree of negative voice content	2.14	.36	2.51*	.13					
Step 2					.18	0.0, 0.38	3.32*	.13	2.16
PSYRATS-AH Degree of negative voice content	1.48	.25	1.69	.06					
BAVQ-R Malevolence	0.10	.08	0.46	.00					
BAVQ-R Omnipotence	0.25	.17	0.97	.02					
VRS	–0.08	–.24	–1.59	.05					

*BAVQ-R, revised Beliefs About Voices Questionnaire; DASS, Depression Anxiety Stress Scale; PSYRATS-AH, Psychotic Symptom Rating Scales Auditory Hallucinations; VRS, Voice Rank Scale. Significant at: *p < .05; **p < .01; ***p < .001.*

voices on depression or anxiety differed according to diagnostic group (BPD+AVH versus SZ+AVH). None of the interaction effects of malevolence (β = −.49, p = .097, 95% CI [−1.08, 0.09]), omnipotence (β = −.47, p = .219, 95% CI [−1.24, 0.29]), or perceived social rank of voices (β = .17, p = .110, 95% CI [−0.04, 0.38]) with group on depression was significant. Similarly, no significant interaction effects for malevolence (β = −.11, p = .737, 95% CI [−0.78, 0.56]), omnipotence (β = −.44, p = .278, 95% CI [−0.37, 1.24]), or perceived social rank of voices (β = .05, p = .638, 95% CI [−0.17, 0.27]) with group on anxiety was found. These results indicate that the associations between negative appraisals of voices and depression or anxiety did not differ according to diagnostic group.

DISCUSSION

This study tested the cognitive model of AVH (7, 8) in youth voice-hearers with BPD or SZ. Overall, the results indicate that the cognitive model of AVH is applicable to the understanding and treatment of voices in youth, regardless of BPD or SZ diagnosis.

Concerning the first exploratory aim, this study found that youth with BPD showed similar beliefs about the benevolence or malevolence of voices, and similar emotional or behavioral responses to voices as youth with SZ. However, youth with BPD appraised their voices as being more omnipotent and of higher social rank than themselves. While the BAVQ-R subscale scores and the Voice Rank Scale scores in the current sample of youth with BPD are broadly comparable to those found in two studies of adults with BPD (28, 29), the current findings also differ in two aspects. First, contrary to the first hypothesis, the finding that adults with BPD and SZ differ in their specific emotional responses to voices, with more emotional resistance and less emotional engagement in the BPD group (28), was not replicated in the current youth sample. Instead, youth with BPD reported higher levels of depression and anxiety than those with SZ. These divergent findings might occur because young voice-hearers do not differ in their initial specific emotional response to voices, and that differences emerge over time as a result of the individual experience of hearing voices (e.g., the individual's appraisal of voices as malevolent and powerful, and ability to cope with the voices). However, the most likely explanation for the nonsignificant group differences regarding emotional responses to voices in the current study was insufficient statistical power to reliably detect such differences, as both the effect sizes and the sample size were small (50). Indeed, the achieved power to detect a significant group difference with α = .05 was 53% for emotional resistance and 34% for emotional engagement. Second, the finding that appraisals of supremacy of voices (i.e., omnipotence, social rank of voices compared with oneself) were more prominent in youth with BPD than in those with SZ is novel. In patients with SZ, appraisals of supremacy of voices have been found to mirror schema of social power and rank, and together they have been strongly linked to voice-related distress and depression (17, 41). Given that disturbances in the self-concept and interpersonal relationships are key features of BPD (51), it would be interesting to investigate if the appraisals of supremacy of voices found to be prominent among youth with BPD are influenced by negative schema of self and others.

In support of the second hypothesis, the findings show that, in youth with AVH, beliefs about malevolence and omnipotence of voices were correlated with more emotional resistance toward voices, while beliefs about benevolence of voices were associated with more emotional and behavioral engagement with voices. The correlations were similar across diagnostic groups (BPD versus SZ). These findings replicate findings from studies of adults with SZ and AVH, reporting that malevolence and omnipotence were

related to resistance, and benevolence to engagement (18, 21–22, 23, 52).

The third hypothesis tested the assumption that it is the way individuals *appraise* their voices, rather than the *form* or *content* of voices, that determines the level of distress experienced by the voice-hearer (7, 8). In partial support of this, frequency, duration, location, and loudness of voices reported in the combined youth sample were weakly (and not significantly) correlated with depression and anxiety, while negative voice content and negative appraisals of voices (i.e., malevolence, omnipotence, high social rank) were moderately to strongly correlated with depression and anxiety. Further, the negative appraisals of voices explained additional variance in depression, over and above the amount explained by negative voice content. However, negative appraisals of voices did not predict anxiety after controlling for negative voice content. Diagnostic group (BPD versus SZ) did not influence the findings. These findings are partially consistent with studies in adults with SZ and AVH reporting that negative appraisals of voices predict both depression and anxiety (18, 22, 23), or depression only (21). A potential explanation for the nonsignificant finding regarding anxiety in the current study is that appraisals of supremacy of voices (i.e., beliefs about power and social rank) render voice-hearers specifically vulnerable for symptoms of depression. Those who perceive their voices as powerful and of higher social rank than themselves might be more likely to experience themselves as powerless, helpless, entrapped, and defeated, and to subordinate themselves to their voices, a state of mind that resembles depression (17, 41). Consistent with this, findings from the current study show that a) negative appraisals of voices were important predictors of depression, but not of anxiety, and b) perceived social rank of voices was a more important predictor of depression than beliefs about malevolence of voices. Finally, the current findings in the combined youth sample replicate the finding that negative voice content influences negative beliefs about voices (23, 53, 54) and voice-related distress (55, 56) in adults with SZ. This suggests that *both voice content and beliefs about voices*—as well as their potential interplay—should be considered as determinants of distress in voice-hearers in research and treatment.

Taken together, the current study provides preliminary evidence that the cognitive model can be applied to the understanding of AVH in youth, regardless of diagnosis of BPD or SZ. This provisional conclusion needs further examination due to the following limitations of the study. First, the sample size was small, which reduced the power of the study to reliably detect group differences (50). For instance, the achieved power to detect incremental changes in R^2 by adding the interaction terms group×VRS, group×malevolence, and group×omnipotence to the regression analyses predicting depression were 43%, 46%, and 28%, respectively. Thus, it cannot be concluded that the nonsignificant findings reflect a true absence of a moderator effect by diagnostic group, or if this arose from a lack of power in this study. Second, the BPD+AVH group included significantly more females than the SZ+AVH group. The sex difference between the groups reflects typical presentation rates in clinical settings, as BPD is more frequently diagnosed in female patients (57), whereas psychotic disorders are more frequently diagnosed in male patients (58). However, we cannot rule out that the results of the current study were influenced by the sex difference between the diagnostic groups. Third, negative appraisals of voices and negative voice content were focused upon as determinants of depression and anxiety in youth with AVH, and did not consider other possible predictors, such as childhood trauma (56), experiential avoidance (59), psychological flexibility and nonjudgmental acceptance (21), meta-cognitive beliefs (60), attachment style (19, 61), interpersonal schema (17, 41), and dissociation (62). Fourth, recently, Strauss et al. (63) reported an alternative factor structure for the BAVQ-R, suggesting that malevolence and omnipotence form a combined factor ("persecutory beliefs"), as do items assessing emotional and behavioral response to voices. Future studies investing cognitive, emotional, and behavioral responses to voices in individuals with BPD should consider using these alternative BAVQ-R subscales. Fifth, depression and anxiety were focused upon as outcome variables in the current study. Recent evidence indicates that AVH in BPD is associated with more suicidal plans and attempts (26), and nonsuicidal self-harm (30). Future research is needed to investigate whether negative appraisals of voices and negative voice content are also predictors of these outcome variables. Finally, due to the cross-sectional design of the study, causal conclusions cannot be drawn regarding the relationship between cognitive appraisals of voices and negative voice content on the one hand, and depression and anxiety on the other.

Clinically, the results of the current study indicate that AVH in youth with BPD should not be marginalized with terms such as "pseudo-hallucinations," "quasi-psychotic," or "psychotic-like" symptoms (64, 65), as they are associated with negative appraisals of voices and high levels of depression and anxiety. Instead, when youth with BPD disclose hearing voices, clinicians should intervene early through appropriate diagnosis and treatment. However, clinicians might wonder how best to treat AVH in youth with BPD, as there are no clinical guidelines available. For patients with SZ, antipsychotic medication is the treatment of first choice, often in conjunction with psychological interventions (66, 67). However, no randomized-controlled trial (RCT) has tested whether conventional pharmacotherapy for AVH in SZ is applicable to AVH in BPD (68). To address this important question, our group is conducting the first RCT on aripiprazole in youth with BPD and AVH (69). With regard to psychological interventions, the results of the current study indicate that changing appraisals of supremacy of voices, along with negative voice content, could lead to a reduction in depression among youth voice-hearers, including those with BPD. As it is difficult to change the emotional content of voices directly, cognitive behavioral therapy (CBT) traditionally attempts to achieve a reduction in distress by working on the hearer's beliefs about the meaning of the voices, through methods such as cognitive restructuring, behavioral experiments designed to test alternative explanations, and the development of more adaptive coping strategies (67). In addition, new therapy approaches within the CBT framework have been developed to specifically address voice content (66), such as cognitive therapy for command hallucinations (70), competitive memory training for humiliating voices (71), and compassionate mind training for critical voices (72). However, although CBT and

related interventions have been demonstrated to be effective in treating AVH in SZ (66, 67, 73), to the authors' knowledge, no RCT to date has investigated its efficacy on voice-hearing in BPD. Thus, while accumulating evidence indicates that individuals with BPD and AVH could benefit from CBT-related interventions (28, 29), future studies are needed to investigate their efficacy in this group.

To conclude, youth with BPD and AVH might hold even more negative beliefs about voices, particularly with regard to supremacy of voices, than those with SZ, and these beliefs are closely linked to depression. Appraisals of voices should be assessed in youth with distressing voices regardless of diagnosis, as they provide an important target for interventions.

ETHICS STATEMENT

In accordance with the Declaration of Helsinki, written informed consent was obtained from all participants, and additionally from a parent or guardian for those under 18 years. The study was approved by the Melbourne Health Human Research Ethics Committee (MHREC2016.086).

AUTHOR CONTRIBUTIONS

MC, KT, and AC designed the study. MC and JB collected the data. MC, CH, and HJ analyzed the data and wrote the first draft. All authors contributed to and approved the latest version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00292/full#supplementary-material

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A Mentalization-Informed Staging Approach to Clinical High Risk for Psychosis

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The practice of diagnosis is fundamentally designed to orient treatment. In the case of early diagnosis for schizophrenia spectrum disorders (SSP) risk, the empirical base for such a practice is still young, and many clinical questions arise in the everyday clinical application of risk algorithms and ensuing therapeutic options. One of the key questions that we will focus on is the following: in cases of SSP where symptoms are successfully treated, why does residual social functioning impairment remain the most serious obstacle to remission and reinsertion in society? We will present the evidence suggesting that the roots of residual social functioning impairment may, in many cases, come from thwarted or arrested development in the specialization of social cognition during adolescence and early adulthood. We will review the evidence suggesting that both during the premorbid phase and clinical high-risk phase, attenuated psychotic symptoms may impede the maturation of key social cognitive processes, particularly the suite of reflective thinking processes coming under the term of mentalization. From this evidence base, we will adapt the staging model of SSP progression in function of our mentalization-informed model, tailored to provide a coherent framework of care addressing the key clinical needs at every stage of psychosis progression.

Keywords: schizophrenia, treatment, early intervention, mentalizing, social functioning

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BACKGROUND

In its short history, the topic of early diagnosis for clinical high-risk states to develop psychosis (CHR-P) has stirred both hope and controversy. Early diagnosis aiming to shorten the duration of untreated psychosis (DUP) proved valuable to improve outcome along the clinical course of schizophrenia spectrum disorders (SSP) (1). Powered by research on DUP, attempts to characterize the psychological risk states preceding psychosis were received with both enthusiasm and opposition. While an early diagnosis of prodromal states could justify indicated preventive treatment, intense debate and vigorous opposition appeared fuelled by concerns for the validity of the risk constructs, fear for diagnosing false positives and for the effects of labelling (2). Today, expert consensus puts forward validated tools to clinically assess CHR-P states preceding the onset of SSP (3); the clinical practice of these tools and the initiation of early treatment is currently exerted with caution (4). In this article, we wish to reframe the questions surrounding early diagnosis and early treatment to the following question: which type of clinical care is needed at different stages of the progression of psychosis? A central empirical finding will guide our discussion on this question: regardless of symptomatic remission in SSP, residual social

functioning impairment remains the most serious obstacle to full recovery and reinsertion in society. We will present the evidence suggesting that the roots of residual social functioning impairment may, in many cases, come from thwarted or arrested development in the specialization of social cognition during adolescence and early adulthood. We will review the evidence that many factors along the preclinical phase of psychosis may impede the maturation of key social cognitive processes, particularly the suite of reflective thinking processes coming under the term of mentalization. From this evidence base, we will revise the staging model of psychosis progression, and outline our mentalization-informed approached tailored to provide a coherent framework of care addressing the key clinical needs at every stage of psychosis progression.

WHY EARLY DIAGNOSIS?

In the past quarter of a century, research on the risk of developing schizophrenia spectrum and other SSPs [Diagnostic and Statistical Manual of Mental Disorders (DSM-5)] has dramatically transformed our clinical and scientific approach to what Eugene Bleuler referred to as the « schizophrenias » (5). In concert with emerging findings in developmental neuroscience, these disorders, which we regroup under the rubric of SSP, are now conceptualized as neurodevelopmental in origin (6). Importantly, expert agreement situates the development of SSP along four distinct periods: the premorbid phase, the clinical high-risk states, the first episode of psychosis, and the trajectories following the first diagnosis (7). The asymptomatic premorbid period during childhood and adolescence can be characterized by non-specific impairments in cognition (8), infra-clinical manifestations of trait risk such as negative and positive schizotypy or subtle cognitive disorganization (9–11), as well as slight social cognitive impairments (12, 13). The pathogenesis can evolve from the premorbid phase to a subclinical stage of risk symptoms preceding the actual onset of the disorder. These risk symptoms represent CHR-P states, which are reliably diagnosed through the use of validated instruments such as the CAARMS (Comprehensive Assessment of At-Risk Mental-States) (14), the SIPS (Structured Interview for Prodromal States) (15), and the SPI-CY/SPI-A for basic symptoms (Schizophrenia Proneness Instrument—Child and Youth version or Adult version) (16). Questions of diagnosis and early treatment are most controversial during this phase (17), when rates of CHR-P individuals not developing SSP can be high (18), diagnostic procedures focusing on different types of manifestations (19), notwithstanding that clinically speaking, the recognition of the psychotic nature of the risk may be difficult to perceive for the young person and her/his family.

Once a diagnosis of psychotic disorder is established, the treatment guidelines are clear (20), and potential issues with these guidelines lie beyond the scope of this article. Hence, the most debated issue of early diagnosis and treatment lies within the CHR-P period, and as we will suggest, can be extended to questions surrounding early prevention strategies in the premorbid phase. The diagnosis of CHR-P states, while widely practised and accepted by experts in the field, still fosters debate (21). While a categorical diagnosis of Attenuated Psychosis Syndrome (which correspond broadly to the CHR-P state) has been recently added in the section 3 of the DSM-5 (22), concerns for over-diagnosis are currently being researched (23), and conceptual debates confronting categorical versus continuum views of psychosis remain vigorous (2, 24).

The question of early treatment is closely linked to that of early diagnosis for a simple reason: ideally, a diagnosis should indicate clear treatment rationale and options. Yet in the present state of scientific advancement, research for treatment in CHR is only nascent (25). Additional issues originate from the point of view of public health: in many countries, health care systems will allocate resources to patients on the condition of a recognized medical diagnosis. In such instances, economic and political forces can both push for and/or pull away from the recognition of a condition (26). As it stands before the turn of the decade in 2020, the diagnosis of CHR (DSM-5) is still under observation, and as we have briefly summarized, a number of issues residing outside of the purely diagnostic debate still remain. While the question of early diagnosis is still open, an increasing number of studies point to two complementary pieces of evidence: 1) individuals diagnosed with a CHR-P state, but that do not transition to psychosis, still require clinical attention (27) and have worst outcome compared to those who didn't experienced a CHR-P (28); 2) longitudinal research does not overwhelmingly support the notion of *transition to psychosis* as a key predictor of functional outcome (29). This poses the questions of the clinical needs of individuals with sub-threshold psychotic symptoms and comorbid disorders, and furthermore, which kind of treatment would be adapted to their clinical profiles.

THE RATIONALE FOR EARLY TREATMENT

One of the issues reaching beyond diagnosis relates to the question of whether treatments can be offered to people before the onset of psychosis, and if so, what should be the main measure of outcome to judge their efficacy?

A recent meta-analysis of psychological and psychopharmacological randomized-control trials (RCTs) for individuals meeting the established criteria for CHR-P states a clear and structured perspective on the studies performed over the past 10 years (4), also pointing to areas of potential amelioration in both research and clinical work with CHR-P. The meta-analysis focuses on the conversion rate to psychotic disorder as the principal outcome of their analysis, and further considers functional improvements as a key outcome to studies with these populations. Schmidt et al. find evidence that early intervention provides significant benefits to individuals at CHR-P in terms of either significantly preventing or delaying the emergence of a psychotic disorder. This result has been supported by more recent meta-analyses on early treatment with CHR-P (30).

Interestingly, however, the available meta-analyses examining early treatment during CHR-P find no treatment superiority effects when comparing psychological vs neuroleptic medication, nor any superiority effect within the different psychological treatments under study (4, 25, 30). The variety of types of treatment, at this stage, is moderate. In addition to

psychopharmacological trials, RCTs have been performed for nutritional supplements, cognitive behavioural treatment, multi-family psychoeducation, and combined interventions with additional social skills training. Despite the important differences in methodology, no superiority effect was found for treatment type; this is consistent with recent reports on the "Dodo bird effect" in psychotherapy, using a variety of therapy models, for a variety of different psychiatric conditions (31). Perhaps most intriguing is the lack of superiority to control conditions with regards to functional improvements. Indeed, while specialized early treatment methods significantly decrease the transition rate to SSP, functional outcomes are roughly equivalent to those obtained through control conditions. It appears, therefore, that room for improvement in early treatment for psychosis is most apparent in the area of functional outcomes.

CONCERN FOR FUNCTIONAL OUTCOMES AND THE RELEVANCE OF A DEVELOPMENTAL MODEL

In many different domains of mental health treatment, a discrepancy can be observed between, on the one hand, an individual's symptomatic improvement with treatment, and on the other hand, the same individual's stability or worsening of adaptive functioning. In SSP, the functional outcome or global functioning beyond symptom severity represents the sum of several different but correlated domains, such as cognitive, role and social functioning. Further, several studies suggest that impairments in social functioning create the most disability in SSP. Conversely, the "symptom-disability gap" observed over the course of treatment is often portrayed in the treatment of SSP (32). This gap is not unique to SSP, it can also be observed in other conditions, for example attention deficit hyperactivity disorder (ADHD) (33). The symptom-disability gap creates a clinical puzzle: how can interventions that attenuate symptoms fail to produce positive cross-over effects into functional improvements? Treatment for individuals with the full diagnosis of schizophrenia have provided the clearest examples of the symptom-disability gap: indeed, it is estimated that social functional impairments characterize more than half of patients with treatment (34). While symptoms appear to respond to medication, patients often fail to benefit from improvements in their daily-living conditions.

In SSP, the issue of intact impairment of social functioning regardless of treatment also seems to apply to treatment for earlier stages of the disease, notably treatment for youth at CHR. In a recent meta-analysis of early interventions for youths at CHR for psychosis, Devoe et al. specifically examine the effect of preventive treatment on social functioning (35). The meta-analysis included 19 trials encompassing 1,513 patients meeting diagnostic criteria for CHR-P. Neither cognitive behavioural trials, nor omega-3 trials and cognitive remediation trials significantly improved social functioning in youth at CHR-P. The authors remark on the need to adapt early interventions to the domains of functioning, namely social functioning, that require support in the early stages of psychopathological progression to psychosis.

As we have argued elsewhere (36, 37), targeting social cognition in early interventions constitutes a challenging ambition, especially in the case of youths at CHR-P. Firstly, decades of research on socio-emotional development during adolescence and early adulthood suggest that a number of different processes interact to promote growth and socially adaptive behaviour. In parallel, cerebral maturation during the same age period will sculpt the morphological brain areas, contribute to the specialization of skills needed to function at high levels of social complexity, and fuel the integration of complex neuro-functional networks that will sustain continued maturation of social functioning skills (38, 39). Critically, within this same period of adolescence and early adulthood, youths in the premorbid stage can already show signs of subtle impairments on a range of skills sustaining social cognition, that is, the set of skills that enable to perceive, analyse, interpret and select adaptive behaviours in interpersonal and social contexts (40, 41). This set of skills can be subsumed under the construct of *mentalization*, that is, the suite of social cognitive imaginative activity enabling the interpretation of behaviour in terms of intentional mental states (42). Mentalization confers the possibility of imagining the intentions, emotions, motivations, and beliefs behind others' actions, as well as behaviours of oneself that are more complex to understand or justify. It is crucial for social understanding and adaptation and, in evolutionary terms, it is thought to have evolved out of the need for human collaboration and competition (43). Thinking about mental states underlying individual actions can provide the necessary tools for anticipating behaviour, understanding relationship patterns, and adapting to different types of social environments (44). Recent neuroscientific research has shown how adolescence constitutes a key developmental window for the integration of the neuro-functional networks that articulate the processes to sustain accurate mentalizing (44–46).

In a similar line of thought, but focusing on the origin of social cognitive impairments in clinical samples, current research points out that the relationship between impaired social cognition and psychosis does not originate from secondary deficits associated with chronic psychosis, nor does it constitute a consequence of first episode psychosis, because impairments in social cognition are already apparent during the stage of CHR-P (47), and can be found to be predictive of conversion to psychosis, notwithstanding that more subtle impairments have been associated to the premorbid phase (48–50). In parallel, several reports have suggested subtle early impairments in a number of different social cognitive processes contributing to mentalizing. From the point of view of neurodevelopment, aberrant maturation of the right superior frontal, middle frontal, and medial orbitofrontal predict conversion to psychosis in CHR-P (51); these regions are best known to sustain mentalizing (52). Behavioural evidence of developing mentalizing skills in youths suggest, first, that in 11–12 year olds who report auditory verbal associations (a symptom of positive schizotypy), present faulty inferences of others' mental states in the form of hypermentalizing (12, 13), that is, providing mentalistic assumptions clearly beyond the available evidence. Second, a number of studies reports impaired mentalizing in youths showing either trait risk, such as high schizotypy scores (53, 54), or state risk, such as CHR-P

(55, 56). In a recent study on 632 CHR-P participants aged 12–35, evidence for reduced theory of mind (mentalizing the mind of others) could be evidenced as of 17 years of age (57), suggesting that adolescents and young adults with CHR-P can experience significant difficulties in understanding phenomena such as sarcasm and lies, which require specialized mentalizing skills that mature during adolescent development.

The nature of the relationship between impairments in social cognition and manifestations of psychosis from the premorbid to the clinical stages of expression still remains unclear. If the developmental process of social cognition is independent from the pathogenesis process of psychosis, then impaired social cognition may simply reflect the impact of pathogenesis at every stage in association to neurodevelopment (49). If impaired social cognition interacts with pathogenesis, as hypothesized by several authors including Paul H. Meehl's theory of schizotypy (58, 59), then the best explanatory model would be one of the interacting processes leading to psychopathological outcome.

Another hypothesis, complementary to the first two, which stands on the idea of a synergy between psychotic symptoms and lack of social cognition, has recently been put forward by our group: we may conjecture that progressing psychotic pathogenesis impacts the very development of social cognitive processes, and vice versa (37). Indeed, the expression of negative schizotypy such as in physical and social anhedonia, social anxiety and social withdrawal may each impact the very opportunities of interpersonal and social interactions during adolescence and young adulthood. Anhedonia affects the motivational system responsible for triggering anticipated interest in interpersonal exchange, and impedes the allowance of cognitive resources to understand how minds work and how they influence behaviour. Social anxiety will affect the behavioural predisposition to seek out interpersonal and social exchange by fostering social avoidance. Finally, social withdrawal may affect the establishment and maintenance of close interpersonal relationships, a context in which significant interpersonal and social understanding can be experienced and deepened. Thus, many of the key manifestations in distal risk for psychosis (60) already affect the creation of the psychological tools to seek, participate in, and understand the interpersonal social world.

In the opposite but complementary direction, the development of mentalizing seems to confer a protective role in those individuals at risk of developing psychosis. In a longitudinal study among children experiencing auditory hallucinations at ages 7–8 and/or 12–13, Bartels-Velthuis et al. found that the development of delusional ideation secondary to abnormal perceptual experiences (AVH) was reduced when participants demonstrated strong mentalizing skills (61), hinting to the protective nature of strong mentalizing skills early in development. Furthermore, robust mentalizing may also reduce the distress caused by psychotic symptoms, as suggested recently by Peters et al. (62). In this original study comparing non-schizophrenic but persistent voice hearers to voice-hearers with schizophrenia and to non voice-hearing controls, the study investigated which kind of features might reliably distinguish between these three groups. While testing for a variety of clinical, socio-demographical and psychological characteristics, the study, which enrolled almost 100 participants in each group, found that the only psychological process distinguishing persistent but non-schizophrenic voice hearers from both controls and voice-hearers with schizophrenia was mindfulness, as measured by the Southampton Mindfulness Questionnaire (SMQ) (63). Indeed, the non-clinical voice-hearers reported higher mindful responding to internal thoughts and images in comparison to clinical voice-hearers, but what is more surprising is their increased mindfulness skills in comparison to controls. Mindfulness is directly linked to mentalizing one's own thought content, and cultivating a relationship of curiosity and acceptance with the production of one's mind (64). This study underlines that mentalizing others, as measured in ToM tasks, is not the only dimension of mentalizing that is key to resilience processes. Indeed, as we have suggested elsewhere, mentalizing oneself may be especially important in relation to risks for psychosis, because individuals on the clinical continuum of psychosis experience disturbing stimuli that is self-generated (self-criticism, paranoia, thought disorganisation, or disturbing sensory or perceptual experiences for example) that do not temporally respond to contingent and upsetting emotional stimulation by others, more typical in emotional arousal observed for borderline personality disorders (36, 37). As suggested by these reports and others [for a review, see Ref. (37)], both self and other mentalizing may thus constitute potent protective factors in the face of risk for psychosis. These different strands of evidence also underline the utility of the concept of mentalization, which unifies different psychological constructs related to thinking about mental states into a coherent framework articulated to a therapy model (65, 66).

Indeed among the therapeutic models adapted to focus on the early impairments in social cognition, Mentalization-Based Therapy (MBT) constitutes an integrative intervention first developed to address psychotherapeutic treatment for Borderline Personality Disorder (BPD), and more recently successfully adapted to psychological treatment for the most severe psychopathologies in adolescents and adults (67, 68). The model aims to increase the client's capacity to mentalize, that is, to identify mental states in oneself and others, and reflectively assess their contributions to patterns of dysregulated behaviour, emotional reactions, or maladaptive thought patterns. Three main reasons would sustain the pertinence of such a model for psychosis along its different stages of clinical evolution. First, recent studies on MBT adapted for patients with non-affective SSPs have shown feasibility and promising results (69, 70). Furthermore, MBT has proven to be effective in adolescent conditions which typically present sub-clinical psychotic symptoms (68). As such, the same model of therapy is applicable to the range of clinical manifestations along the continuum of psychosis expression. Randomized controlled trials (RCTs) conducted with patients suffering from borderline personality disorder have shown its therapeutic effect on interpersonal relationships and emotion regulation processes (71–73). More recently, MBT has been successfully adapted to a range of disorders (74), and interestingly, an increasing number of reports relate successful attempts to adapt MBT for CHR-P (36, 37) and SSP (75–77). In line with this preliminary evidence, we next sketch out a mentalization-informed

staging approach to psychosis, from the premorbid to the full diagnostic conditions.

A MENTALIZATION-INFORMED STAGING APPROACH TO PSYCHOSIS

Broadly speaking, the clinical staging model is a trans-diagnostic heuristic approach aimed at understanding the neurobiological and environmental processes underpinning the onset and course of a disorder. Clinical staging, through integrating stage and timing with evolution of clinical phenotype, also allows interventions to be tested from a preventive standpoint in reducing the risk of progression and persistence of illness. The idea of a clinical staging approach for psychosis as a progressively intensive intervention model aimed at prevent/delay the transition to psychosis in CHR-P subjects has been firstly developed by McGorry and colleagues more than 10 years ago (78). This model was originally focused on preventing the progression of psychotic symptomatology through different levels of intervention (starting from psychosocial interventions up to antipsychotic medications), in accordance with the severity of the symptomatology. Even if the most recent developments of the clinical staging model for psychosis (79) have broadened the outcomes of interest moving from symptoms to functioning, the proposed interventions are more focused on treating symptoms instead of intervening directly on psychological processes that sustain resilience, such as mentalization.

In accordance and as a consequence of the hypothesis that we formulated in the previous section, we propose a revised staging model, which is more focused on treating the progressive delay/impairment in social cognition (social functioning) alongside the monitoring of potentially progressing psychotic (and others) symptoms. As showed in **Table 1**, together with the clinical progression of the psychotic symptomatology from stage 0 (subtle, subjective, non clinical pre-psychotic experiences such as psychotic-like experiences (PLEs), anomalous self experiences (ASE), basic symptoms (BS), NSS) to stage III (chronic psychosis), we propose a model of progressive impairments mentalizing skills which filtrates in parallel (in synergy) to progressing symptomatology. This progression starts by slightly affecting interpersonal, academic and social functioning, may increase by perturbing the ability to interpret social interactions (further affecting interpersonal, academic, and social functioning), and can lead to an arrest in the development of mentalizing competences, with ensuing consequences much later in the outcome of trajectories with psychosis.

In **Table 2**, we attempt to provide an overview of a coherent and progressive MBT intervention model (MBT CHR-P) aimed at sustaining the development and safeguarding against impairments in mentalizing abilities in patients putatively at-risk for psychosis, at each stage of the clinical progression (**Table 1**). Broadly speaking, this intervention model is based on the 5 principles of the clinical staging model for CHR-P. Firstly, a staged approach to treatment is offered, with low intensity and least specialized interventions used initially, and "stronger,"

TABLE 1 | Clinical staging model of psychosis with focus on progressive social disfunctions (deficits of social understanding).

Stage	Clinical description	Persistence	Pervasiveness	Social functioning
Stage 0	Psychotic like experiences, basic symptoms, anomalous self experiences, soft neurological signs, cognitive and negative symptoms.	Pre-morbid	Non specific problems with subtle impairments in social cognition	Affects school functioning and social integration with peers (physical and social anhedonia, reduced peer contact, social anxiety)
Stage Ia	Attenuated psychotic symptoms, negative, neurocognitive and social cognitive symptoms, depressed mood and other psychological and behavioural abnormalities.	Duration of attenuated symptoms is limited, ability to discriminate between ideas and perception, fantasy partially preserved	Possibly axis 1 clinical disorders, like mood or anxiety disorders	Affects school functioning more severely (difficulties concentrating, peer contact, social anxiety)
Stage Ib	Brief self-limiting psychotic symptoms, negative, neurocognitive and social cognitive symptoms, depressed mood and other psychological and behavioural abnormalities.	Duration of psychotic symptoms is limited, loss of ability to discriminate between ideas and perception, fantasy (during brief symptoms episodes)	Possibly axis 1 clinical disorders, like mood or anxiety disorders	Imminent developmental arrest (abscence from school, social withdrawal); more significant polarizations in mentalizing, affecting interpretation of social interatcions, problems arise at different life areas (school, peers, home)
Stage II	First episode of psychosis (FEP)	First episode of full-blown psychosis. Long term loss of ability to differentiate between reality and thoughts	Possibly axis 1 clinical disorders, like mood or anxiety disorders	Severe impact on social functioning and school functioning; severe arrest in development and severe impairments in mentalizing
Stage III	Chronic psychosis	Chronic duration of total illness, progressive decline in cognitive and social functioning	Co-morbidity as a rule	Severe and chronic impairment in social and professional functioning; no or limited recovery

TABLE 2 | Possible mentalizing interventions according to the clinical stage.

Stage	Interventions	Timing/Setting	Targets/Goals
Stage 0	School and family-based prevention	'mental' or 'emotional' education in primary prevention large scale campaigns	Providing psychoeducation about mentalization, the linkage between arousal, anxiety, reduction of cognitive performance and mentalization.
Stage Ia	MBT-A; MBT-F psycho-education	Short intervention, including psycho-education, skills strenghtening in adolescent groups and/or family therapy	More focused psychoeducation about the linkage between arousal, loss of mentalization and the development of psychotic symptoms. Patients are told about the key aspects of MBT, including the meaning of mentalizing and its sensitivity to arousal
Stage Ib	As for 1a Medications targeted to treat comorbid disorders (eg. anxiety, depression) Take into account low doses of antipsychotics in accordance to severity of BLIPS	More intensive intervention including individual work, combined with intervention at multiple levels (school, family,…)	Starting from stage Ib the intervention is progressively focused on 1) the patient's state of mind as central to the rehabilitation of the capacity for social understanding; 2) the emphasis on the role of affect in disruptions of the ability to mentalize; and 3) the importance given to understanding the links between the quality of mentalization and specific Interpersonal/ attachment contexts. Five problem areas are developed and routinely reviewed with the patient, including: commitment to treatment, psychiatric symptoms, social interaction/relationships, destructive behavior, and community functioning
Stage II	As for Ib MBT-G for psychosis Antipsychotics	Long and intensive intervention	
Stage III	As for II AMBIT	Very long intervention with an explicit focus on case management and an outreaching approach	

MBT-A, Mentalization-Based Therapy Adolescents; MBT-F, Mentalization-Based Therapy Family; MBT-G, Mentalization-Based Therapy for Groups; AMBIT, Adaptive Mentalization-Based Integrative Treatment. AMBIT is a manualised mentalization based approach aimed at working with hard to reach people at risk of a wide range of life adversities. It uses mentalization as an organising framework for integrating a range of specific techniques and practices derived from different evidence based modalities of intervention. Integration is principally achieved through a focus on delivery of multiple modalities through a single worker, and mentalization-based practices developed to enhance team and network functioning.

more intensive interventions, reserved for those who do not respond to the earlier stages of intervention. In line with this approach and with the original clinical staging model for CHR-P, medications are considered as a possible intervention only starting from stage Ib. Moreover, there is still a lack of evidence concerning the efficacy of medications such antipsychotics or other molecules (eg. Omega-3 fatty acids; NAC) to prevent/ delay transition to psychosis (80). Secondly, this strategy should address the problem of the low transition rate to psychosis (2). Indeed, this strategy is primarily addressed at improving mentalizing abilities and consequently the clinical and social functioning needs instead of mainly avoiding transition to psychosis. Nevertheless, this latter remains one of the targets of the model. Thirdly, this model is based on the hypothesis that the efficacy of therapeutic interventions that strengthen resilience (such as MBT) is closely correlated to the timing of the intervention. In this sense, the developmental phase (i.e. age, psychological maturity) as well as the stage of the disorder must be taken into account to decide the type of intervention. Fourthly, the model seeks to enhance compliance by addressing the therapeutic objectives of the patient themselves in the treatment formulation, which do not necessarily include attenuated psychotic manifestations, but issue such as patient-reported sources of distress such as anxiety and social functioning (81). In line with the fourth principle, this staged approach addresses ethical concerns, namely the potential stigma, the "false positive" issue, and a perceived relative lack of predictive power, by adapting the intervention to key clinical targets at every stage.

We further attempt to integrate notions of primary and indicated selective prevention within the MBT-informed care plan. Referring again to **Table 2**, interventions for stage 0, a stage characterized by less severe and less specific clinical phenotypes, are tailored on the primary prevention that aims the education sector (82). In this early phase, interventions are provided at school and family levels and are aimed at sustaining the development of mentalizing skills and fostering a mentalizing environment which has a number of transversal benefits, such as reducing bullying and violence in schools (83, 84), and therefore may be relevant to legislators that would be less sensitive to a psychosis-targeted primary prevention program. The focus at this stage is really to enrich the traditional pedagogical stance with some mentalizing knowledge, and certain current schools-based experiments focus on integrating a mentalizing perspective within the educational context (85).

Moving along in **Table 2**, Stage Ia and Ib provide a progressively more intensive and specific intervention based on the MBT-adolescents (MBT-A) and MBT-family (MBT-F) model, along a selective prevention principle (36). MBT-A program and MBT-F are manualized, psychodynamic psychotherapy programs with roots in attachment theory [for descriptions of the interventions, see Refs. (68, 86, 87)]. During stage Ia, this intervention will be mostly provided for short periods and in a group setting. It involves weekly individual MBT-A sessions and monthly mentalization-based family therapy. During stage Ib, the MBT-A program will become more intensive and mostly structured on individual setting. In stage II and III, progressively more specific MBT intervention for SSP, such as MBT-G [see Ref. (69)] for psychosis and Adaptive Mentalization Based Integrative Treatment (AMBIT) (67, 88), which guides multidisciplinary teams working with hard to reach clinical cases using case manager models of care.

Overall, the mentalization-based approach to clinical staging of psychosis provides a coherent theoretical and clinical framework. This framework affords two key advantages: it provides a clinical intervention that is suited for both the psychotic related symptoms, but also the other psychiatric comorbidity issue that ultimately influence the severity of clinical outcome. Second, it provides a framework for training professionals that is applicable to a range of professionals who are susceptible to intervene at different stages of the progression of psychosis, from educators to general practitioners, as well as case managers, psychiatric nurses, psychologists and psychiatrists. The MBT model is based on the past 20 years of empirical research in child, adolescent and adult clinical interventions (89, 90). With regard to early diagnosis and treatment, the mentalization-informed model of staging we present here is specifically designed to promote development and prevent impairments in the key social cognitive processes before the onset of psychosis, in order to respond to the clinical needs of individuals "at-risk," and further to attempt to ameliorate the poor long-term outcome of social functioning should individuals evolve towards a diagnosed psychotic disorder. Nevertheless, at this stage, the proposed MBT intervention based on the clinical staging model still needs to be tested and evaluated in clinical settings. Indeed, while there are some preliminary reports on the efficacy of MBT in FEP and in SSD (69, 91), there is still a lack of evidence concerning the ability of this intervention to reduce the transition to psychosis and ameliorate social functioning in patient at CHR-P (36).

Consequently, the usefulness of MBT in these early stages should be tested empirically with pilot randomized single-blind superiority trials comparing the efficacy of the MBT model with TAU in CHR-P adolescent population on several targets. Indeed, such trials should test firstly the 1) acceptability and attrition rate of the MBT model. Secondly, the efficacy of MBT in improving 2) mentalization abilities and 3) social functioning in CHR-P patients indipendently to transition to psychosis should confirmed. Thirdly, the efficacy of MBT in reducing 3) severity of psychotic symptoms and 4) transition to psychosis rates should be investigated. As a fourth step, the presence of biological substrates of the effect of MBT such as stress hormones and brain function (f-MRI) should be investigated in order to confirm the validity and the specificity of the MBT model.

CONCLUSION

In providing a mentalization-informed framework for the staging of CHR-P and transition to psychosis, we attempt to target a key problem in the treatment of SSP, namely, the symptom-disability gap in outcomes of treatment where individuals still suffer from poor social functioning. We argue that the roots of residual social functioning impairment may, in many cases, come from thwarted or arrested development in the specialization of social cognition during adolescence and early adulthood. Our approach is also pragmatic, and sensitive to the cases of "non-conversion" to psychosis, for which important clinical care is still needed. Much of the clinical practice in developmental psychopathology is performed under conditions of uncertainty as to the symptomatic evolution and clinical outcome of individuals seeking help. Further clinical research that integrate the principles of good practice in the respect of empirical evidence will further sculpt the tools and methods of early diagnosis and intervention, to provide the most adapted care plan sustaining the development of the individual while attempting to divert the negative impact of psychosis progression on the interpersonal and social functioning domains, which today represent the key obstacles to therapeutic success with psychosis.

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All three authors contributed to writing the manuscript.

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Comorbid Personality Disorders in Individuals With an At-Risk Mental State for Psychosis: A Meta-Analytic Review

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Increasing evidence shows that personality pathology is common among patients at clinical high risk (CHR) for psychosis. Despite the important impact that this comorbidity might have on presenting high-risk psychopathology, psychological functioning, and transition to full psychotic disorders, the relationship between personality syndromes and CHR state has received relatively little empirical attention. The present meta-analytic review aimed at 1) estimating the prevalence rates of personality disorders (PDs) in CHR individuals and 2) examining the potential role of PDs in predicting transition from CHR state to a full-blown psychotic disorder. The systematic search of the empirical literature identified 17 relevant studies, including a total of 1,868 CHR individuals. Three distinct meta-analyses were performed to provide prevalence estimates of PDs in the CHR population. The first and more comprehensive meta-analysis focused on any comorbid PD (at least one diagnosis), the second one focused on schizotypal personality disorder (SPD), and the last one focused on borderline personality disorder (BPD). Moreover, a narrative review was presented to define the predictive role of personality disorders in promoting more severe outcomes in CHR patients. The findings showed that the prevalence rate of personality disorders in CHR patients was 39.4% (95% CI [26.5%–52.3%]). More specifically, 13.4% (95% CI [8.2%–18.5%]) and 11.9% (95% CI [0.73%–16.6%]) of this clinical population presented with SPD and BPD, respectively. Finally, the studies examining the effects of baseline personality diagnoses on conversion to psychotic disorders showed contradictory and insufficient results concerning the potential significant impact of SPD. Conversely, no effect of BPD was found. This meta-analytic review indicated that the CHR population includes a large subgroup with serious personality pathology, that may present with attenuated psychotic symptoms conjointly with distinct and very heterogeneous personality features. These findings support the need for improved understanding of both core psychological characteristics of CHR patients and differentiating aspects of personality that could have relevant clinical implications in promoting individualized preventive interventions and enhancing treatment effectiveness.

Keywords: personality disorders, ultra high risk (UHR), clinical high risk (CHR), high risk (HR), early detection and prevention

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INTRODUCTION

Very early detection and intervention in the course of illness are considered the crucial goals for realizing meaningful improvements in the outcome of schizophrenia spectrum disorders. Much research and many clinical works over the last 20 years have explored the possibility of intervention before the onset of the full psychotic disorder, in order to preempt negative clinical outcomes. These efforts focused on the pre-psychotic or "prodromal" stages of illness, which have been defined as the period of time characterized by increasing changes in thinking, feeling, and behaving from a person's premorbid mental state and level of functioning up to the appearance of psychotic features (1, 2). To promote early intervention, it is critical to prospectively assess the psychosis liability (i.e., detecting the true risk of developing a psychotic illness in specific help-seeking populations in an accurate manner).

Two sets of operational criteria for diagnosing the clinical high risk (CHR) state have been developed and tested: The Ultra-High Risk (UHR) and the Basic Symptom (BS) criteria. The UHR state has been operationalized by the presence of one or more of the following: 1) attenuated psychotic symptoms (APS), 2) brief limited intermittent psychotic symptoms (BLIPS), or 3) trait vulnerability plus a marked decline in psychosocial functioning (Genetic Risk and Deterioration Syndrome, GRD) [for a review, see Ref. (3)]. On the other hand, BSs have been conceptualized as the most immediate symptomatic expression of neurobiological aberrations, underlying the development of schizophrenia spectrum disorders (4). These symptoms could be described in terms of subjective subclinical disturbances in different domains (i.e., perception, thought processing, language, and attention) that are phenomenologically distinct from classical psychotic symptoms, by reason of their self-experienced nature and fully preserved insight and reality testing (5, 6).

Reliable and valid instruments have been developed and refined to identify the UHR (7, 8) and the BS groups (9). CHR subjects who met UHR or BS criteria or a combination of both showed a transition rate to a full-flagged psychotic disorder ranging from 18% after 6 months, 22% after 1 year, and 29% after 2 years to 36% after 3 years (10). Despite the promising predictive validity of these criteria, the rates of "false positives" and the most recent concerns of lower transition rates [for a deeper discussion, see Ref. (11)] have prompted researchers to identify additional clinical conditions and/or manifestations, in order to improve prediction and reduce the rate of converters.

It has been argued that premorbid personality disorders (PDs) may represent a noteworthy and relevant "vulnerability marker" or risk factor for psychotic disorders, especially within neurodevelopmental processes in adolescence and young adulthood (12). Due to the heterotypic continuity in mental disorders' development, as well as putative shared genetic or early developmental etiological factors, emerging dysfunctional personality patterns might promote a range of severe clinical pictures and possibly end in first-episode schizophrenia or another full-blown psychotic disorder (13–16). More generally, the relationship between personality and psychotic disorders can be explained by at least three explanatory models (17). First, personality and psychopathology may have a *pathoplastic* relationship, whereby the former modifies the phenotypic expression of the latter—and conversely. Second, the putative presence of common etiological and genetic factors may hesitate in a *spectrum* relationship, whereby personality and psychotic disorders fail to act as distinct entities—as in the case of schizotypal personality disorder (SPD) and schizophrenia (18–19). And third, personality and psychotic disorders may have a *causal* (etiological and possibly bidirectional) relationship, whereby individual patterns of thinking, feeling, behaving, and relating to others hesitate or contribute to the onset of a mental disorder, just as a severe or chronic psychotic disorder can itself contribute to important changes in personality[1]. Considering the clinical heterogeneity of CHR populations (22), as well as the lack of prognostic specificity of attenuated psychotic symptoms (23), exploring personality pathology in CHR individuals may aid in elucidating the etiopathogenetic pathways contributing to the onset of psychotic disorders.

Moreover, irrespective of their relationships with psychosis, personality pathology represents a very important threat and negative factor for positive therapy outcomes, considering its predominant role in how patients respond to treatment. Thus, the need to focus on personality characteristics in CHR individuals seems apparent: carefully understanding the patients' patterns of thinking, feeling, coping, interpersonal functioning, experiencing of self and others, in which mental health problems are rooted, can be very useful for making more accurate diagnostic formulations, as well as for providing a road map for the implementation of preventive treatment strategies and intervention programs in this specific population.

Nevertheless, to the best of our knowledge, no meta-analytic review of empirical studies on comorbid personality syndromes in CHR individuals was conducted. The present study aimed at 1) estimating the prevalence rates of PDs in individuals at CHR of first-episode psychosis and 2) examining the potential role of personality pathology in predicting transition to full-flagged psychotic disorders.

METHODS

The main research hypothesis and the study protocol were decided *a priori*. The present meta-analytic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (24).

Search Strategy

We performed a multi-step literature search using the following keywords: (high AND risk [MeSH Terms] AND psychotic disorders [MeSH Terms] OR psychosis OR risk [MeSH Terms] AND psychotic disorders [MeSH Terms] OR psychosis OR early diagnosis [MeSH Terms] AND psychotic disorders [MeSH Terms] OR psychosis OR prodrom* AND psychotic disorders

[1] This explanatory model seems particularly relevant on the basis of recent research investigating psychotic psychopathology through the lens of network theory, as applied to mental disorders (20, 21).

[MeSH Terms] OR psychosis) AND (personality [MeSH Terms] OR personality disorders [MeSH Terms]).

First, we conducted a systematic literature search in MEDLINE, PubMed, Scopus, Web of Science, and PsychINFO databases, including all the articles published until September 2018, in the English language. Second, the reference lists of the articles included in the review were manually checked for any studies not identified by the computerized literature search. The abstracts from the articles identified through this process were then screened, and the full texts were retrieved for further examination in relation to the inclusion and exclusion criteria (as detailed below). The database search, study selection, and data extraction were carried out by two authors (the first and the second) independently. Disagreements were solved through consensus discussions among all the authors.

Eligibility Criteria

Studies were considered eligible for inclusion in this review when they fulfilled the following criteria: 1) published as an original paper in a peer-reviewed journal; 2) involved CHR individuals as defined according to established international criteria and by validated assessments [e.g., Comprehensive Assessment of At Risk Mental State (CAARMS) (8); Structured Interview for Psychosis-Risk Syndrome (SIPS) (25)]; 3) evaluated comorbid PDs at baseline and/or reported the proportion of personality pathology in high-risk subjects with longitudinal transition to psychosis; and 4) evaluated PDs with reliable and validated instruments [e.g., Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM–IV) (26) Axis II Personality Disorders (SCID-II) (27)] . When two or more studies were from the same center, we contacted the authors to determine whether overlap existed in the respective samples; overlapping samples were excluded. When the proportion of comorbid personality diagnoses was not indicated in a retrieved article, we contacted the corresponding author to collect the additional data. Finally, when a study conveyed insufficient information to determine whether the selection criteria had been met, it was excluded from the review.

Recorded Variables

The variables for each article included in the meta-analytic review were year of publication, sex and mean age of participants, inclusion criteria for the CHR state, psychometric instruments used to assess the psychosis risk, psychometric instruments used to assess PDs, prevalence rates of PDs in CHR individuals, duration of follow-up, criteria used to define transition to psychosis, and transition risk at different time points (%).

Quality Assessment

To conduct the quality assessment of the studies included in this meta-analytic review, we adapted the Newcastle–Ottawa Scale (NOS) that has been adopted in recent meta-analyses [e.g., Ref. (28)]. This scale allows us to allocate a maximum of nine stars for the highest quality. Each study was independently assessed by the first and second authors to ensure interrater reliability. All authors double-checked and resolved inconsistency and disagreements on quality scoring.

Statistical Analysis

The meta-analysis was performed using Comprehensive Meta-Analysis (CMA) software version 2 (Biostat, Inc) (29). CMA software allows for the meta-analysis of proportions using the number of events and the total sample. The effect sizes were weighted according to the inverse of their variances and their calculation was based on a random-effects model (30, 31). The effect size represented the proportion of current PD (at least one diagnosis), SPD, and borderline personality disorder (BPD) in subjects with a baseline high-risk state for psychosis. It has not been possible to measure other proportions because the number of studies that had evaluated PDs other than SPD and BPD at baseline was too small for a meta-analysis (<4).

RESULTS

Retrieved Studies

The identification, selection, screening, and inclusion or exclusion of studies is extensively described in the flow chart (see **Figure 1**), in which reasons for article rejection are clearly indicated. The initial database search produced 2,945 records, and an additional 47 records were identified through the other sources previously described. After duplicates were removed, the first and second authors independently screened all titles and abstracts from the initial search to individuate the studies that were eligible for full-text retrieval. We excluded 2,468 records because they did not meet the inclusion criteria, with an interrater agreement of 89%. The remaining 248 articles were retrieved for full- text screening, and 231 were excluded for not meeting the inclusion criteria, with an interrater agreement of 84%. Uncertainties relating to an article's final inclusion in the review (n = 23) were resolved by the independent judgment of the other authors.

Seventeen studies were included in the final review and then qualitatively and meta-analytically synthesized.

Study Characteristics

Table 1 shows the descriptive characteristics of the 17 included studies. All studies were published in English between 2001 and 2018, with CHR sample sizes ranging from 21 to 377 (M = 117.56; SD = 95.99; Mdn = 99.50). In summary, there were two main forms of diagnostic criteria used to define CHR features in help-seeking patients, the UHR and BS. The UHR state was independently assessed with the CAARMS (8) and the SIPS (7). In most of the studies included (K = 15), PDs were assessed administering clinical interviews based on DSM-IV diagnostic criteria [e.g., Structured Clinical Interview for DSM-IV (SCID-II), Structured Interview for DSM-IV Personality (SIDP-IV) (51), or Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV) (52)]. Otherwise, self-report measures were administered (K = 2). These instruments for assessing personality are based on a set of dimensional traits, and a PD diagnosis is assigned when one or more traits are clinically relevant (in other words, the scores obtained on specific scales must be greater than certain threshold values or cut-off). The cross-sectional design was the most commonly adopted (K = 7). In the studies where cross-sectional design was used, CHR subjects were compared with healthy volunteers (K = 1; 45), patients from a

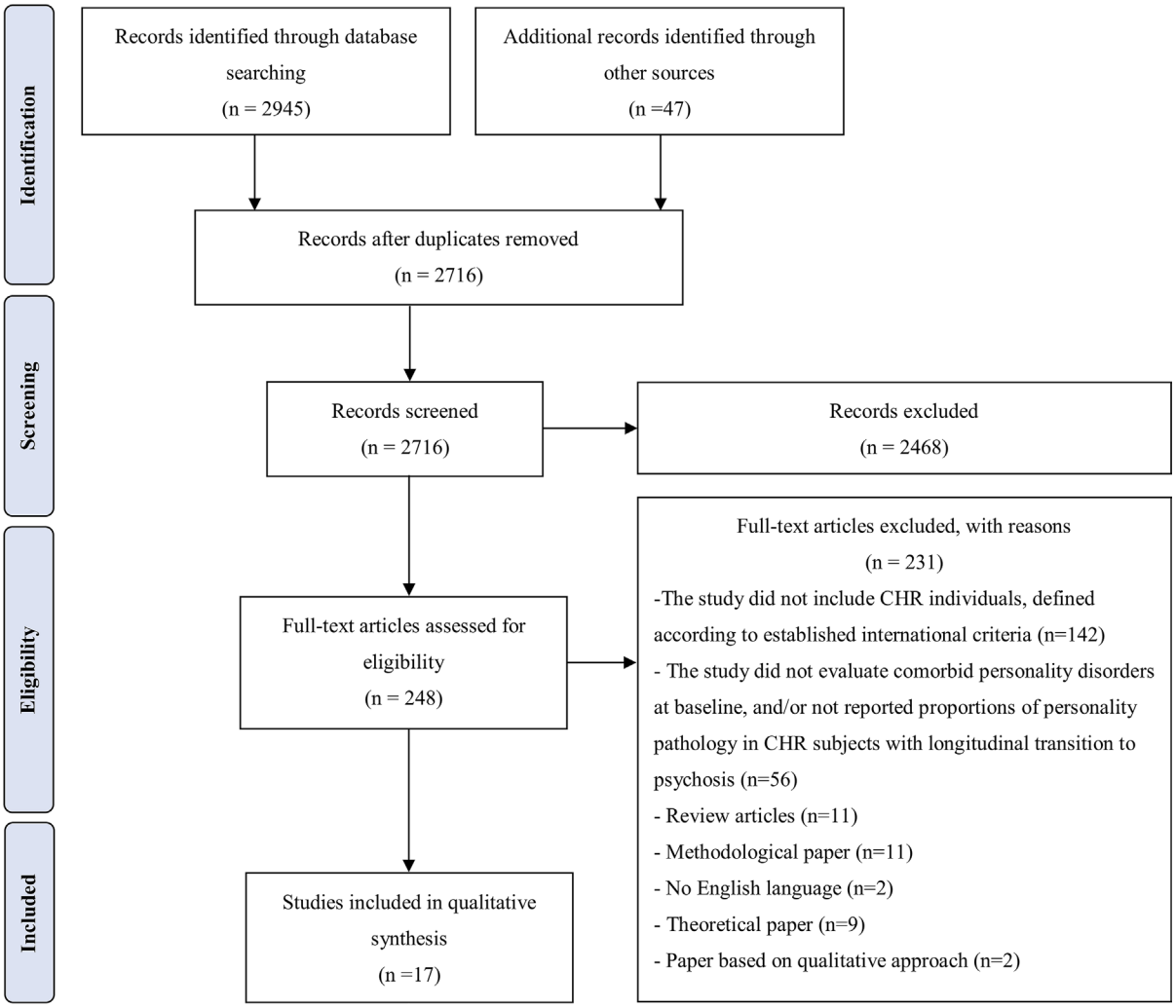

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flowchart [see Ref. (20)].

clinical population without a high-risk for psychosis (K = 4; 36, 39, 41, 46), healty volunteers and first-episode psychosis patients (K = 1; 48), or were assessed in terms of sociodemographic and clinical characteristics (K = 1; 38). Of the two case–control studies, the groups were CHR-treated patients who subsequently transitioned to full-threshold psychotic disorder (converters), and "controls" were patients who did not meet criteria for psychotic disorder in a follow-up period—ranging from 12 to 24 months. Of the studies that used a longitudinal design (K = 7), the follow-up length ranged from 6 months to 9.6 years. Psychosis transition was defined according to "standard" criteria [from the two major psychiatric diagnostic guidelines, DSM and International Classification of Diseases (ICD)] or criteria from the main UHR clinical assessment instruments (53).

Overall Quality Assessment

The quality assessment showed good interrater agreement (81.5%), with nine studies receiving high quality scores (≥8 NOS stars) and others receiving medium evaluation (5 ≤ NOS stars ≤ 7). A table explaining the calculation of the quality score for each study is available in **Supplementary Material**. Seven authors were contacted in order to clarify information relating to the quality criteria: one replied with relevant information, two did not reply, and in the remaining four cases, the email bounced back.

Study Findings

Personality Disorders in CHR Individuals

Seventeen empirical investigations meeting the inclusion criteria of the present study were considered to evaluate the prevalence rate of PDs in individuals at CHR for psychosis. Personality pathology was mostly assessed according to the DSM-IV Axis II diagnostic category criteria (26). Three meta-analyses focused on the prevalence of PDs (at least one diagnosis) (Meta-Analytic Results on Prevalence Rate of Any Personality Disorder), SPD (Meta-Analytic Results on Prevalence Rate of SPD), and BPD (Meta-Analytic Results on Prevalence Rate of BPD), respectively, in subjects with a baseline high risk state for psychosis.

TABLE 1 | Study characteristics.

Study	Research center	HR sample	HR definition	Personality assessment instrument	Personality variable	Study Design	Notes
Bechdolf et al. (32)	9 early detection and intervention centres, Germany	*N* = 156 F = 50, M = 106 Age M = 23.86 years (SD = 4.89)	SIPS; SPI-A	Structured Clinical Interview for DSM-IV (SCID-II)	DSM-IV personality disorders	Longitudinal randomized controlled trial (RCT)	
Cannon et al. (33)	NAPLS	*N* = 364 F = 124, M = 240 Age M = 18.3 years (SD = 9.75	SIPS	SIPS defined schizotypal personality disorder (presence of only at least one year required)	Schizotypal personality disorder	Longitudinal	Same sample of Woods et al. (34)
Falkenberg et al. (35)	OASIS, UK	*N* = 221 F = 104, M = 117 Age M = 22.6 years (SD = 4.7)	CAARMS; SPI-A	Structured Clinical Interview for DSM-IV (SCID-II)	DSM-IV personality disorders	Longitudinal	
Gerstenberg et al. (36)	Switzerland	*N* = 21 F = 11, M = 10 Age M = 15.00 years (SD = 1.4)	SIPS	Structured Interview for DSM-IV Personality (SIDP-IV)	DSM-IV personality disorders	Cross-sectional	Psychiatrically hospitalized adolescents with nonpsychotic disorders
Klosterkötter et al. (37)	CER, Germany	*N* = 110 F = 51, M = 59 Age M = 28.8 years (SD = 9.75)	BSABS	PSE9	DSM-III personality disorders	Longitudinal	
Kotlicka-Antczak et al. (38)	Center clinical hospital of Lodz, Poland	*N* = 99 F = 54, M = 45 Age M = 19 years (SD = 3.56)	CAARMS	Structured Clinical Interview for DSM-IV (SCID-II)	DSM-IV personality disorders	Cross-sectional	
Lee et al. (39)	Clinic FORYOU, Korea	*N* = 63 F = 25, M = 38 Age M = 19.7 years (SD = 3.5)	SIPS	Structured Clinical Interview for DSM-IV (SCID-II)	Schizotypal personality disorder	Cross-sectional	
Lencz et al. (40)	RAP, New York	*N* = 42 F = 17, M = 25 Age M = 16.4 years (SD = 2.3)	SIPS	Structured Interview for DSM-IV Personality (SIDP-IV)	DSM-IV personality disorders	Cross-sectional	
Lim et al. (41)	Seoul Youth Clinic, Korea	*N* = 129 F = NR, M = NR Age M = 20.74 years (SD = 3.2)	SIPS	Structured Clinical Interview for DSM-IV (SCID-II)	DSM-IV personality disorders	Longitudinal	
Rosen et al. (42)	PRIME, USA	*N* = 29 F = 15, M = 14 Age M = 18.4 years (SD = 4.8)	SIPS	Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV)	DSM-IV personality disorders	Cross-sectional	
Ruhrmann et al. (43)	EPOS project, Europe	*N* = 245 F = 108, M = 137 Age M = 23.0 years (SD = 5.2)	SIPS; BSABS-P	SIPS defined schizotypal personality disorder (presence of only at least one year required)	Schizotypal personality disorder	Longitudinal	
Ryan et al. (44)	PACE, Australia	*N* = 131 F = 83, M = 48 Age M = range from 15 to 24	CAARMS	Structured Clinical Interview for DSM-IV (SCID-II)	Borderline personality disorder	Longitudinal	
Schultze-Lutter et al. (45)	Cologne early detection and intervention service, FETZ, Germany	*N* = 100 F = 24, M = 76 Age M = 24 years (SD = 6)	SPI-A	Self-report version of the Aachener Merkmalsliste für Persönlichkeitsstörungen (SAMPS)	Personality traits and disorders	Case control study (converters vs. non-converters)	
Sevilla-Llewellyn-Jones et al. (46)	CAMEO Early Intervention in Psychosis Service, UK	*N* = 40 F = 21, M = 19 Age M = 21.65 years (SD = 2.64)	CAARMS	Millon Multiaxial Inventory, version III (MCMI-III)	Personality traits	Cross-sectional	
Spada et al. (47)	Italy	*N* = 22 F = 10, M = 12 Age M = 16.1 years (SD = 1.02)	CAARMS	Structured Clinical Interview for DSM-IV (SCID-II)	DSM-IV personality disorders	Cross-sectional	

TABLE 1 | Continued

Study	Research center	HR sample	HR definition	Personality assessment instrument	Personality variable	Study Design	Notes
Thompson et al. (48)	PACE, Australia	*N* = 96 F = 52, M = 44 Age M = 18.3 years (SD = 2.7)	CAARMS	Structured Clinical Interview for DSM-IV (SCID-II)	Borderline personality disorder	Case–control study	
Woods et al. (34)	NAPLS, USA	*N* = 377 F = 143, M = 234 Age M = 18.2 years (SD = NR)	SIPS	Structured Interview for DSM-IV Personality Disorders, Diagnostic Interview for DSM-IV Personality Disorders, or SCID-IV Axis II personality Disorders	DSM-IV personality disorders	Case–control study (converters vs non-converters)	

SIPS, Structured Interview for Prodromal Symptoms; CAARMS, comprehensive assessment of at-risk mental states; BSABS, Bonn Scale for the Assessment of Basic Symptoms; BSABS-P, Bonn Scale for the Assessment of Basic Symptoms: Prediction List (49); SPI-A, Schizophrenia Proneness Instrument-Adult Version; SPI-CY, Schizophrenia. Proneness Instrument Child-Youth; NAPLS, North American Prodromal Longitudinal Study; PACE, Personal Assessment and Crisis Evaluation Clinic; EPOS, European Prediction of Psychosis Study; RAP, Zucker Hillside Recognition and Prevention Program; CER, Cologne Early Recognition; PRIME, Prevention through Risk Identification; PSE9, Present State Examination, Ninth Version (50).

It is noteworthy that some studies included in these meta-analyses (*K* = 6) (32, 34, 37, 40, 42, 45) also reported data for other distinct concurrent personality syndromes. However, the paucity and heterogeneity of such empirical data did not allow us to perform additional meta-analytic estimations. In general, paranoid, schizoid, antisocial, and avoidant PDs were the most common syndromes, with prevalence rates ranging from 6% to 12%, 3% to 12%, 1% to 14%, and 10% to 26%, respectively. Conversely, the prevalence rates of histrionic, narcissistic, obsessive-compulsive, and dependent PDs were weaker (less than 5%).

Moreover, some studies (*K* = 2) (45, 46) used self-report instruments to assess PDs, whereas other studies employed clinical interviews (*K* = 15). It was not possible to compare these studies and to evaluate the influence of PD assessment method as a potential moderator variable due to the limited number of empirical investigations based on self-report evaluation. However, the results seem to indicate a potential impact of assessment method on the prevalence rate of PDs in all meta-analytical estimations [see, in particular, Ref. (46)].

Meta-Analytic Results on Prevalence Rate of Any Personality Disorder

From our database, 12 samples were included in the first meta-analytical estimate, relating to a total of 1,346 CHR subjects [male 53.3%; mean age 20.36 (SD = 3.93)]. These subjects were assessed at baseline for any PDs. All studies included in this meta-analytical estimation reported prevalence data for all PDs. The meta-analysis found that comorbid baseline PDs (at least one diagnosis) were present in 39.4% of high-risk subjects (95% CI [26.5%–52.3%]; **Figure 2**).

Meta-Analytic Results on Prevalence Rate of SPD

Eleven samples were included in the second meta-analytical estimate, relating to a total of 1,313 CHR subjects [male 54.84%; mean age 20.95 (SD = 3.71)]. These subjects were assessed at baseline for SPD. The first and second meta-analysis differ in four studies: two (39, 43); reported data of SPD but did not specify prevalence rates of other PDs, whereas the other two (36, 38) provided data for other PDs without clarifying the prevalence rate for SPD. Moreover, one study (33) was excluded because it reported data from the same sample as Woods and colleagues (Woods and colleagues 2009). The results showed that comorbid SPD was present in 13.4% of high-risk subjects (95% CI [8.2%–18.5%]; **Figure 2**).

Meta-Analytic Results on Prevalence Rate of BPD

Eleven samples were included in the third meta-analytical estimate, relating to a total of 1,124 CHR subjects [male 57.6%; mean age 20.03 (SD = 4.30)]. These subjects were assessed at baseline for BPD. The first and third meta-analysis differ in five studies: two of them (44, 48) provided data of BPD but did not specify prevalence rates of other PDs, whereas the other three (38, 41, 44) reported data for other PDs without clarifying the prevalence rate for BPD. Comorbid BPD was present in 11.9% of high-risk subjects (95% CI [0.73%–16.6%]; **Figure 2**).

Personality Disorders as Potential Predictors of Transition to Psychosis

Eight studies included in this systematic review were considered, in order to examine the impact of comorbid personality pathology on transition to full-flagged psychotic disorders (see **Table 2**). Overall, taking into account only the longitudinal studies (*K* = 6) and excluding case-control ones (*K* = 2), it is important to note that 341 of a total of 1,019 UHR subjects developed a psychotic episode (33.4%).

Two studies have investigated the presence of baseline comorbid PDs in predicting conversion to psychosis. Schultze-Lutter and colleagues (45) found that only schizoid features—in particular the "lack of close friends or confidants other than first-degree relatives" and "emotional detachment observed by others"—are able to significantly influence the subsequent development of psychosis despite the magnitude of this effect being quite weak. Contrary to their expectations, SPD was infrequent in CHR patients and did not predict conversion. Sevilla-Llewellyn Jones and colleagues (45) also examined the

Study name	Outcome	Rate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lencz et al. 2004	PD	0,690	0,128	0,016	0,439	0,942	5,385	0,000
Lim et al. 2018	PD	0,287	0,047	0,002	0,194	0,379	6,083	0,000
Rosen et al. 2006	PD	0,483	0,129	0,017	0,230	0,736	3,742	0,000
Schultze-Lutter et al. 2012	PD	0,460	0,068	0,005	0,327	0,593	6,782	0,000
Sevilla-Llewellyn-Jones et al. 2018	PD	0,750	0,137	0,019	0,482	1,018	5,477	0,000
Woods et al. 2009	PD	0,438	0,038	0,001	0,362	0,513	11,402	0,000
Kotlicka-Antczak et al. 2018	PD	0,283	0,053	0,003	0,178	0,388	5,292	0,000
Gerstenberg et al. 2015	PD	0,571	0,165	0,027	0,248	0,895	3,464	0,001
Spada et al. 2016	PD	0,091	0,064	0,004	-0,035	0,217	1,414	0,157
Klosterkotter et al 2001	PD	0,400	0,060	0,004	0,282	0,518	6,633	0,000
Bechdolf et al., 2011	PD	0,456	0,055	0,003	0,348	0,565	8,246	0,000
Falkenberg et al., 2015	PD	0,066	0,018	0,000	0,031	0,101	3,742	0,000
Any personality disorder		0,394	0,066	0,004	0,265	0,523	5,988	0,000
Lencz et al. 2004	SPD	0,190	0,067	0,005	0,058	0,322	2,828	0,005
Lim et al. 2018	SPD	0,116	0,030	0,001	0,057	0,175	3,873	0,000
Rosen et al. 2006	SPD	0,207	0,084	0,007	0,041	0,372	2,449	0,014
Ruhrmann et al. 2010	SPD	0,135	0,023	0,001	0,089	0,181	5,745	0,000
Schultze-Lutter et al. 2012	SPD	0,070	0,026	0,001	0,018	0,122	2,646	0,008
Sevilla-Llewellyn-Jones et al. 2018	SPD	0,275	0,083	0,007	0,112	0,438	3,317	0,001
Woods et al. 2009	SPD	0,266	0,030	0,001	0,207	0,325	8,888	0,000
Spada et al. 2016	SPD	0,022	0,031	0,001	-0,039	0,084	0,707	0,480
Klosterkotter et al 2001	SPD	0,209	0,044	0,002	0,124	0,295	4,796	0,000
Bechdolf et al., 2011	SPD	0,040	0,016	0,000	0,008	0,072	2,449	0,014
Lee et al., 2017	SPD	0,079	0,035	0,001	0,010	0,149	2,236	0,025
Schizotypal personality disorder		0,134	0,026	0,001	0,082	0,185	5,088	0,000
Lencz et al. 2004	BPD	0,024	0,024	0,001	-0,023	0,070	1,000	0,317
Rosen et al. 2006	BPD	0,172	0,077	0,006	0,021	0,324	2,236	0,025
Ryan et al. 2015	BPD	0,252	0,044	0,002	0,166	0,338	5,745	0,000
Schultze-Lutter et al. 2012	BPD	0,210	0,046	0,002	0,120	0,300	4,583	0,000
Sevilla-Llewellyn-Jones et al. 2018	BPD	0,350	0,094	0,009	0,167	0,533	3,742	0,000
Thompson et al. 2012	BPD	0,146	0,039	0,002	0,069	0,222	3,742	0,000
Woods et al. 2009	BPD	0,064	0,015	0,000	0,035	0,093	4,359	0,000
Gerstenberg et al. 2015	BPD	0,429	0,143	0,020	0,149	0,709	3,000	0,003
Spada et al. 2016	BPD	0,091	0,064	0,004	-0,035	0,217	1,414	0,157
Klosterkotter et al 2001	BPD	0,027	0,016	0,000	-0,004	0,058	1,732	0,083
Bechdolf et al., 2011	BPD	0,040	0,016	0,000	0,008	0,072	2,449	0,014
Borderline personality disorder		0,119	0,024	0,001	0,073	0,166	5,061	0,000

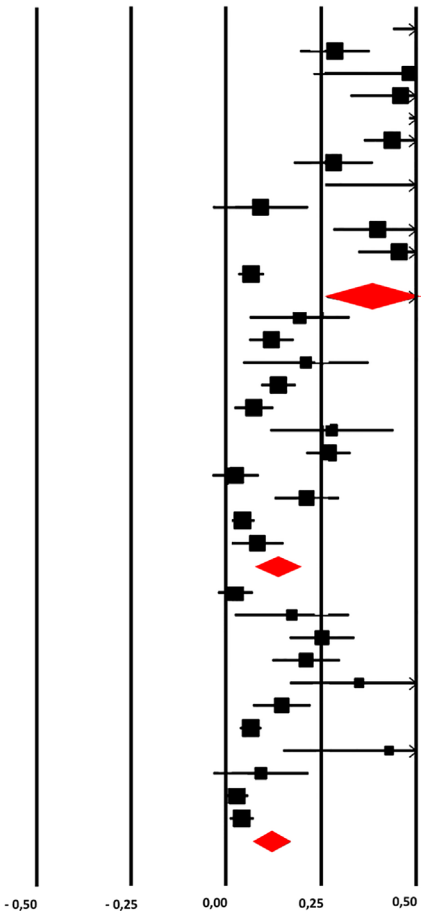

FIGURE 2 | The findings showed that the prevalence rate of comorbid personality diagnoses in clinical-high-risk (CHR) patients was 39.4% [95% CI (26.5%–52.3%)]. More specifically, 13.4% [95% CI (8.2%–18.5%)] and 11.9% [95% CI (0.73%–16.6%)] of this clinical population presented with the schizotypal personality disorder (SPD) and borderline personality disorder (BPD), respectively.

relationship between clinically significant personality traits and transitions to first-episode psychosis; however, the low transition rate in their sample precluded the possibility of testing the predictive power of overall personality traits.

Five studies based on different methodologies have longitudinally examined the role of SPD in developing a first episode of psychosis and provided inconsistent and mixed results. For example, SPD was the sole personality diagnosis related to conversion in the Cologne Early Recognition study (37). Moreover, schizotypal personality syndrome as defined by SIPS—that is, requiring a minimum presence of one year without changes in symptom severity—was one of six significant predictors of psychosis in the European Prediction of Psychosis Study (EPOS) (43). On the contrary, there was no evidence for a potential predictive effect of SPD in the North American Prodrome Longitudinal Study (NAPLS) (33). Notably, important differences between these studies can be traced, especially with regards to follow-up lengths and/or the mean age of samples. In particular, a significant psychosis-predictive role of SPD was found in samples with a greater mean age (e.g., 23 years) (43) and a longer follow-up period (e.g., 10 years) (37), suggesting that SPD can be considered as a distal trait risk factor that more significantly exerts its influence in the longer-term prognosis of CHR patients. Nevertheless, these inconclusive results do not allow us to establish whether the presence of SPD represents a more powerful predictor of transition to full psychotic disorder.

Three studies examined the potential predictive value of BPD for transition to psychosis in CHR sample. Schultze-Lutter and colleagues (45) and Ryan and colleagues (44) found that BPD did not predict the onset of psychotic disorder in CHR individuals. Moreover, Ryan and colleagues compared three groups of patients: "UHR only," "UHR and likely borderline personality pathology," and "UHR and borderline personality pathology," showing no differences in the level of unusual thought content, non-bizarre ideas, perceptual abnormalities, or disorganized speech. These results seem to suggest that borderline personality features in CHR patients did not influence the clinical expression of attenuated psychotic symptoms; however, this lack of

TABLE 2 | Study findings on the impact of comorbid personality disorders (PDs) on transition to psychosis.

Study	Study design	Follow-up	Outcome measure(s)/ transition	Personality assessment instrument	Rates of transition%	Predictor analyses	Main findings
Cannon et al. (33)	Longitudinal	2.5 years of follow-up	Transition to psychosis was assessed by SIPS.	SIPS defined schizotypal personality disorder (presence of only at least 1 year required)	35%	Kaplan–Meier survival analysis and Cox proportional hazard models.	SPDdid not predict conversion to psychotic disorders.
Klosterkötter et al. (37)	Longitudinal	9.6 years of follow-up	Psychosis diagnoses was rated according to DSM-IV criteria.	PSE9	49.4% (N = 160)	Logistic analyses	Irrespective of the presence of CHR criteria, only schizotypal personality disorder of all baseline diagnoses was significantly related to the subsequent development of schizophrenia (*n* = 79) in the total sample.
Lim et al. (41)	Longitudinal	8 years of follow-up divided in two groups (a group from 2005 to 2009 and a group from 2009 to 2013)	Transition to psychosis was defined as having psychotic level symptoms based on the SIPS for more than 4 days per week	Structured Clinical Interview for DSM-IV (SCID-II)	In the 2005–2009 group, the transition rates at 2 and 3 years were 25.3% and 31.1%, respectively. In the 2009–2013 group, the transition rates at 2 and 3 years were 4.4% and 25.7%, respectively.	Kaplan–Meier survival analysis and Cox proportional hazard models	Early referral and axis II comorbidities other than SPD were associated with the declining transition rate.
Ruhrmann et al. (43)	Longitudinal	18 months of follow-up	Transition to psychosis was assessed by SIPS. The diagnostic category of transition was determined by applying *DSM-IV* criteria for psychotic disorders and affective disorders with psychotic features.	SIPS defined SPD (presence of only at least one year required)	19%	Kaplan–Meier survival analysis and Cox proportional hazard models	SIPS-defined schizotypal personality disorder was one of six predictors of psychosis included in the predictor model
Ryan et al. (44)	Longitudinal	6–12 months of treatment.	Transition to psychosis was assessed by applying DSM-IV-TR criteria for psychotic disorders.	Structured Clinical Interview for DSM-IV (SCID-II)	13.9%	Direct logistic regression analysis	A quarter (25.2%) of UHR patients (*N* = 180) present with concurrent borderline personality features.
Schultze-Lutter et al. (45)	Case–control study [converters (*N* = 50) vs. non-converters (N = 50)]	1 year follow-up	Transition to psychosis in non-converters sample was assessed by applying DSM-IV criteria for psychotic disorders.	Self-report version of the Aachener Merkmalsliste für Persönlichkeitsstörungen (SAMPS)	/	Stepwise binary logistic regression analyses (no longitudinal) case-control (converters vs non-converters)	Unexpectedly, SPD was infrequent and did not predict conversion. Only schizoid subscale score was a significant though weak predictor of conversion; in particular items "lack of close friends or confidants other than first-degree relatives" and "emotional detachment observed by others".

TABLE 2 | Continued

Study	Study design	Follow-up	Outcome measure(s)/ transition	Personality assessment instrument	Rates of transition%	Predictor analyses	Main findings
Sevilla-Llewellyn-Jones et al. (45)	Longitudinal	3 years of follow-up	The severity of psychotic symptoms was assessed by Positive and Negative Syndromes Scale (PANSS) (54)	Millon Multiaxial Inventory, version III (MCMI-III)	5%	Logistic regression analyses	The low transition rate observed in the sample precluded the possibility of testing the predictive power of maladaptive personality traits.
Thompson et al., (47)	Case–control study [converters (n = 48) vs non-converters (n = 48)]	24 months of follow-up	Psychosis diagnosis following transition was rated from the clinical files using the operational criteria in studies of psychotic illness (OPCRIT) computer algorithm.	Structured Clinical Interview for DSM-IV (SCID-II)	/	A combination of parametric and non-parametric analyses of variance	Co-occurring borderline personality disorder or borderline features does not appear to strongly influence the risk of short-term transition to psychosis or the risk of developing a non-affective psychotic disorder in UHR population.

SIPS, Structured Interview for Prodromal Symptoms; PSE9, Present State Examination, Ninth Version.

significant effect could also reflect an important limitation in the study related to potential biases in personality assessment procedures. In fact, borderline pathology was evaluated using a screening tool and employing self-report measures that may be problematic in the context of personality assessment [e.g., Refs. (55, 56)]. One additional study assessed borderline features administering a clinical interview and showed no statistically significant difference in the rate of transition to psychotic disorder in CHR patients with and without baseline full-threshold BPD (48).

Interestingly, baseline borderline pathology was not related to the onset of any particular type of psychotic disorder in the follow-up, rejecting the hypothesis that UHR patients with BPD features would be more likely to develop nonschizophrenia spectrum diagnoses or briefer psychotic episodes, which would be reflected in diagnoses, such as psychosis not otherwise specified (NOS) and brief reactive psychosis. Overall, despite several limitations [e.g. the use of self-report instruments (44, 45) and the small sample size (48)], the results from these three studies suggest that BPD does not increase the risk of transition and does not have a pathoplastic effect, neither with respect to the current clinical presentation nor with respect to the prognosis in CHR samples. Nevertheless, due to the paucity of studies on this topic, caution is required in drawing conclusions.

DISCUSSION

This is the first meta-analytic review focused on personality syndromes in patients at-risk for psychosis. Notably, this study sought to answer some specific questions: a) Is comorbid personality pathology prevalent among CHR individuals? b) Are some specific PDs more common than others? c) Is the risk of conversion to psychosis greater in CHR populations with comorbid PDs? Adopting strict inclusion criteria (specifically using appropriate and internationally shared definitions of UHR, as well as valid and reliable instruments for their detection), a total of 17 studies with 1,828 patients were included in this meta-analytic review (see **Table 1**).

Previous reviews and meta-analyses pointed out the huge variability of mental disorders in CHR individuals and high prevalence rates for many psychopathological syndromes or conditions [e.g., Ref. (57)]. In particular, comorbid depression and anxiety disorders have been identified as frequently marking the onset of the initial prodromes of psychosis (3). Conversely, the empirical literature regarding PDs and at-risk mental states is still limited and is not exhaustive. Despite the paucity and heterogeneity of existing research, this meta-analytic review has attempted to increase knowledge in the field. Specifically, the first aim of the study was to provide the prevalence rates of personality syndromes in the CHR population by performing three meta-analytic estimations. Second, the study aimed at exploring the potential impact of personality pathology in transition to psychosis.

Prevalence Rate of PDs in CHR Individuals

Overall, the results showed that the prevalence of PDs is surprisingly high, with a baseline comorbidity present in

39.4% of CHR individuals. These data indicated that the CHR population includes a large subgroup with serious personality pathology, and 13.4% and 11.9% of CHR patients have comorbid SPD and BPD, respectively (**Figure 2**). These prevalence rates in CHR individuals are four times greater than those in the general population (58) and, for the most part, equivalent or superior to rates estimated in previous meta-analyses on other concurrent comorbid diagnoses (e.g., 40.7% for depressive disorders and 15.3% for anxiety disorders) (3).

Prevalence Rate of SPD in CHR Individuals

The results of the second meta-analysis showed that SPD is common in high-risk patients. It is not surprising, as schizotypy is considered to be an indicator of being prone to psychosis and, therefore, a precursor to schizophrenia-spectrum disorders (19). Moreover, the widely used UHR criteria partially refer to the positive symptoms of schizotypy and SPD, such as unusual thought contents or magical thinking. However, it is necessary to clarify that SPD and CHR represent two specific and clearly delineated syndromes: While SPD is an enduring and persistent personality pattern, that requires signs and symptoms in at least five out of nine areas of psychological functioning and may sometimes precipitate the development of psychotic symptoms in a gradual manner, CHR conditions do not present stability during the past, meet fewer SPD symptoms, and show a dramatic progression of psychotic diseases (19). Clear delineation of the two syndromes also allows them to co-occur. For example, in Woods and colleagues' (34) sample, 26% of prodromal patients met SPD criteria, whereas 67% of patients with an SPD diagnosis met prodrome criteria.

From a clinical standpoint, our results suggest the relevance of specific aspects of psychological functioning in CHR individuals with comorbid SPD diagnosis. These patients not only present with positive symptoms of schizotypy but also present with severe impairments in various personality domains. Beyond eccentric and idiosyncratic reasoning processes or unconventional beliefs, as well as perceptual distortions and an overall oddity in behavior and appearance, schizotypal patients show severe relational deficits marked by acute discomfort and reduced capacity for close relationships, affective flattening, and mental functioning impairment, characterized by difficulties in mentalizing processes and maladaptive metacognitions [e.g., Refs. (19, 59)]. These psychological characteristics may require the specific clinical attention of mental health professionals, as the treatment goal for CHR individuals should not be just preventing conversion to psychosis but also ameliorating the wider range of problems that members of this clinical population currently present (60).

Prevalence Rate of BPD in CHR Individuals

The results of our last meta-analytic estimation revealed the association between BPD and at-risk mental states. Some studies included in this meta-analysis were specifically focused on BPD, also due to the historically complex diagnostic boundaries between borderline pathology and psychosis (61, 62).

Overall, some considerations regarding the high prevalence of BPD in CHR patients need to be addressed. First, BPD is typically associated with psychosis-like symptoms, such as transient paranoid ideation or severe dissociation (63). These symptoms are often trauma- and stress-related, unlikely predictive of a subsequent psychotic disorder (64) and differ from shizophrenia symptoms from a phenomenological standpoint (65). As a result, several borderline patients presenting with transient- and stress-related psychotic symptoms might be diagnosed as being at high risk for developing psychosis, generating false positives. Improving clinicians' ability to distinguish between these different groups of patients would be meaningful and very useful for promoting clear case formulations and patient-tailored treatments [e.g., Ref. (48)].

Second, the comorbidity between BPD and CHR conditions could be influenced by other clinical variables. Substance abuse, for instance, is a recurrent clinical complication of borderline patients and is an important risk factor for the development of psychotic symptoms and disorders (66). Finally, the influence of putative, shared etiological factors between BPD and schizophrenia liability is notable. In particular, childhood traumatic experiences have been empirically associated with borderline pathology [e.g., Ref. (67)] and CHR status [e.g., Ref. (68)]. Emotional dysregulation and increased sensitivity to stress may be considered an endophenotype of psychosis, reflecting underlying gene–environment interactions associated with the impact of early trauma and stressful life events in vulnerable individuals (69). Consistent with this perspective, attenuated psychotic symptoms in CHR states could reflect core emotional dysregulation processes that would also account for their high comorbidity with anxiety and depressive diagnoses [see Refs. (3, 70, 71)]. In line with this possible explanation, it is important to highlight that borderline patients show, in general, severe emotional instability and are consequently vulnerable to experiencing overwhelming effects, including intense depression and anxiety. Considering all these relevant issues, the findings support potential interactions among emotional dysregulation, negative affectivity, and specific vulnerability for psychosis [e.g., Refs. (71–74)]. Further research is required to better clarify the complex processes underlying these associations.

Impact of PDs in Transition to Psychosis

The second aim of this study was to investigate the predictive role of personality syndromes in the onset of psychotic disorders. The lack of clear evidence did not allow us to define specific disorders that are systematically associated with transition to full-blow psychotic disorders. The studies included in this review revealed contradictory and non-exhaustive findings about the potential significant impact of SPD, as well as no meaningful effect of BPD (see **Table 2**). However, how global characteristics of schizotypal personality are related to conversion to psychosis in high-risk individuals remains unclear. A possible explanation for these mixed results might be attributable to the different follow-up lengths and/or the mean age of different samples. From a clinical standpoint, attenuated psychotic symptoms might appear as a clinical manifestation or an exacerbation of schizotypy features,

such as abnormal perceptual experiences, unusual beliefs, and transient quasi-psychotic episodes with intense illusions, auditory or other hallucinations, and delusion-like ideas (19). This perspective seems consistent with the current dimensional approach of schizophrenia-spectrum disorders (63), which assumes a distribution of schizotypal characteristics in the general population ranging from the adaptive and normal expression of schizotypy, *via* clinically significant expressions in terms of SPD diagnosis, to the most extreme psychotic expressions (18, 19, 75, 76). Moreover, schizotypy is associated with an increased risk of developing psychotic disorders in the general population; this predictive value, however, is only statistically significant over 10- to 50-year intervals (77–79) (Kwapil et al., 1998). Therefore, it appears that SPD [which is considered a clinical indicator of the latent, wider, and high order construct of schizotypy; see, e.g., Ref. (80–82)] may be more useful as a distal risk marker, detecting a more gradual progression of illness than prodrome criteria. Thus, it might fail to carry substantial clinical meaning in terms of its ability to discriminate between non-converters and converters in CHR samples. This is especially relevant among younger individuals, because more time would be required to enter the age of maximum risk for first-episode psychosis (34). Actually, among our retrieved studies, a significant psychosis-predictive role of SPD has been found in samples with a greater mean age (e.g., 23 years old) (43) and a longer follow-up period (e.g., 10 years) (37).

Overall, these results have clinical implications on current organization, validity and usefulness of UHR criteria. Along with genetic familiarity and a marked decline in psychosocial functioning, the SPD diagnosis in currently considered as an indicator of a trait vulnerability for psychosis proneness. The combination of these abovementioned risk criteria characterizes the Genetic Risk and Deterioration Syndrome (GRD), that forms a specific category of UHR syndrome [for a review, see Ref. (3)]. Despite the fact that further evidences are needed, our results on the predictive value of SPD on transition to psychosis call into question the validity of SPD as a trait risk for transition to psychotic disorders in CHR population. Interestingly, our findings are also consistent with recent meta-analytical evidence, which revealed that GRD subgroup has no higher risk of psychosis than patients that do not fulfill UHR criteria, irrespective of the length of follow-up (10).

It is important to note that the eligibility criteria of this meta-analytic review allowed us to collect studies on SPD, but not schizotypy construct dimensions. While a number of studies have focused on specific dimensions of the schizotypy construct, as well as their role in predicting psychosis transition in the CHR population, the review of such studies was not consistent with the aims of this meta-analytic review. Indeed, the schizotypy construct should be properly differentiated from SPD (80). SPD is considered a schizophrenia endophenotype on the psychosis continuum (63) and as mentioned above, a clinical indicator of the higher order latent construct of schizotypy, which can in turn be linked to a wider range of clinical and subclinical manifestations (80–82). Moreover, from the assessment standpoint, the various measures used to evaluate SPD and schizotypy are quite different. In fact, psychometric measures of schizotypy only partially overlap with SPD assessment procedures (19). For example, the negative dimensions of the Wisconsin Shizotypy Scales (physical and social anhedonia) and the interpersonal factor of the Schizotypal Personality Questionnaire (relating to social anxiety, no close friends, and flattened affect) evaluate overlapping but substantially different constructs (83). A recent review highlighted the putative predictive value of schizotypy on transition to psychosis, but it remains unclear how schizotypy features may be addressed in research on high-risk samples (19).

However, comorbid PDs diagnoses, rather than increasing the risk of conversion to psychosis, may contribute to explaining the current severe distress and disability of high-risk individuals. Currently, preventive clinical interventions usually focus on the "transition to psychosis" as the primary outcome, while the symptoms, the level of psychological functioning, and the level of distress are rarely included among treatment outcome measures. As pointed out above, it would be very useful to provide treatments for CHR individuals to promote their psychosocial well-being aside from preventing the conversion to psychotic disorders.

The comorbidity of PDs in high-risk patients might suggest putative explanations for negative outcomes of non-converters observed in longitudinal studies (84–86). Interestingly, non-converters might not have a favorable treatment outcome: one study showed that in 34–82% non-converters, attenuated psychotic symptoms persisted over 1–3 years (84); 40% had poor social or role outcomes after 3 years (86); and 75% were diagnosed with anxiety, affective, or substance use disorder after 1 year (85). It is important to consider that personality syndromes are enduring and persistent maladaptive patterns, able to incluence individual response to treatments, and, moreover, that personality changes may mediate clinically meaningful improvements in symptoms and overall psychological functioning (87, 89). PDs often require more intensive and long-term psychotherapy treatment to achieve successful outcomes (89), and their high prevalence in CHR individuals may explain the lack of evidence supporting that any specific intervention is particularly effective over others in preventing transition to psychosis (90).

Study Limitations

The present meta-analytic review has some limitations that should be addressed. First, the paucity of studies did not permit us to perform meta-analytic estimations of the prevalence rates for all PDs; nor did it enable us to precisely establish the psychosis-predictive role of other personality variables. Moreover, it was not possible for us to test the influence of potential moderators, such as the assessment method (self-report versus clinical interview) used to evaluate personality pathology. The impact of personality assessment procedures should be considered in future research, especially considering that self-evaluation in CHR individuals might suffer from a lack of insight and self-awareness, defensive processes, or social desirability biases [e.g., Ref. (91); see also Ref. (59)]. Second, the high variability of the reviewed studies, with respect to the assessment measures, procedures, and methods used to evaluate transition to psychosis, as well as the lengths of follow-up periods in longitudinal research designs, require conclusions to be drawn cautiously.

Clinical Implications

In conclusion, this meta-analytic review's findings seem to highlight that CHR individuals may present very different personality characteristics, from the social withdrawal and affective flattening that mark schizotypal patients to the interpersonal instability and emotional dysregulation, typically shown by borderline patients. This heterogeneity could reflect the presence of distinct personality constellations that could differ in adaptive functioning, etiological variables, patterns of comorbidity, treatment response, and therapeutic interventions. Future research focused on empirically derived personality subtyping in CHR individuals and enhancing knowledge on the role that personality plays in treatment effectiveness could be promising (92). Moreover, our findings have two important clinical implications: a) treatment of UHR individuals should be integrated into interventions that are focused on maladaptive personality patterns that may moderate therapy outcomes, and b) the need to address personality features may require rethinking basic parameters of manualized treatments for at-risk mental states tested in RCTs. Surprisingly, to date, no study has addressed the effect and implication of PD diagnoses on the clinical management and treatment of CHR individuals. Psychological interventions tailored on maladaptive personality traits and disorders may provide another avenue by which to achieve symptom and functional recovery in people suffering from high-risk mental states.

AUTHOR CONTRIBUTIONS

Each author of the present manuscript has participated sufficiently in the work to take public responsibility for the content. TB and AT have identified, selected, and reviewed the retrieved articles. AC has performed the statistical analyses. MP, SV, and VL have supervised the work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00429/full#supplementary-material

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Corrigendum: Comorbid Personality Disorders in Individuals With an At-Risk Mental State for Psychosis: A Meta-Analytic Review

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A Corrigendum on

Comorbid Personality Disorders in Individuals with an At-Risk Mental State for Psychosis: A Meta-Analytic Review

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In the original article, there was a mistake in **Figure 2** as published. Although the correct statistical values were reported both in the legend of **Figure 2** and in the text of the manuscript, some incorrect values were reported in **Figure 2** due to a copy and paste error. In addition, the wrong years were listed is some of the study names. The corrected **Figure 2** appears below.

The authors apologize for these errors and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

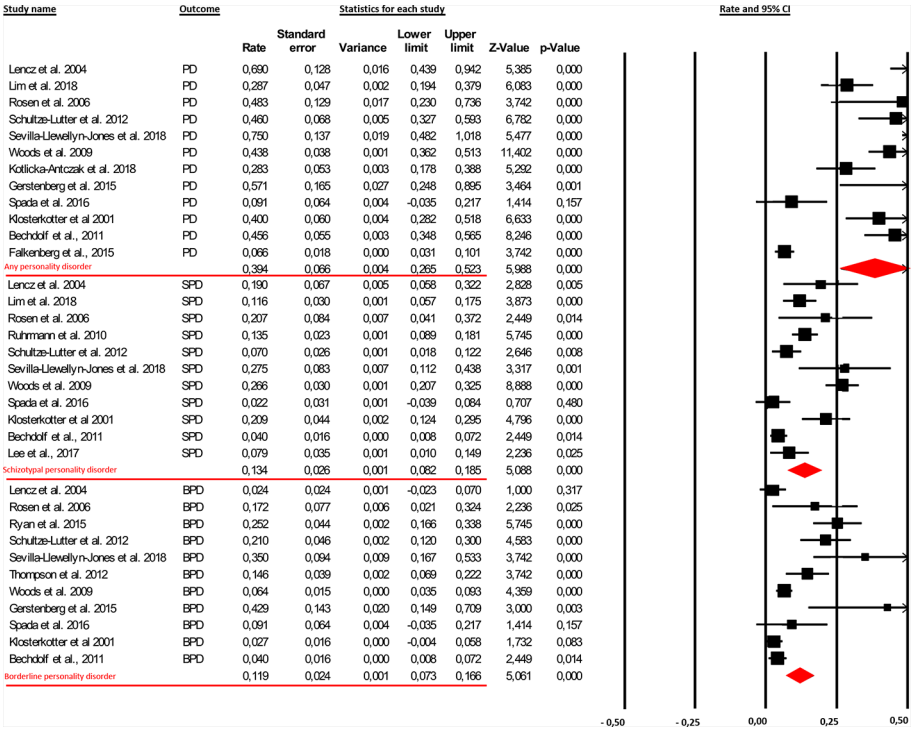

FIGURE 2 | The findings showed that the prevalence rate of comorbid personality diagnoses in clinical-high-risk (CHR) patients was 39.4% [95% CI (26.5%–52.3%)]. More specifically, 13.4% [95% CI (8.2%–18.5%)] and 11.9% [95% CI (0.73%–16.6%)] of this clinical population presented with the schizotypal personality disorder (SPD) and borderline personality disorder (BPD), respectively.

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Psychosis and Schizophrenia-Spectrum Personality Disorders Require Early Detection on Different Symptom Dimensions

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Psychotic disorders and schizophrenia-spectrum personality disorders (PD) with psychotic/psychotic-like symptoms are considerably linked both historically and phenomenologically. In particular with regard to schizotypal and schizotypal personality disorder (SPD), this is evidenced by their placement in a joint diagnostic category of non-affective psychoses in the International Classification of Diseases 10th Revision, (CD-10) and, half-heartedly, the fifth edition of Diagnostic and Statistical Manual of Mental Disorders, (DSM-5). Historically, this close link resulted from observations of peculiarities that resembled subthreshold features of psychosis in the (premorbid) personality of schizophrenia patients and their biological relatives. These personality organizations were therefore called "borderline (schizophrenia)" in the first half of the 20th century. In the 1970s, they were renamed to "schizotypal" and separated from psychotic disorders on axis-I and from other PD on axis-II, including modern borderline PD, in the DSM. The phenomenological and historical overlap, however, has led to the common assumption that the main difference between psychotic disorders and SPD in particular was mainly one of severity or trajectory, with SPD representing a latent form of schizophrenia and/or a precursor of psychosis. Thus, psychosis proneness and schizotypy are often assessed using SPD questionnaires. In this perspective-piece, we revisit these assumptions in light of recent evidence. We conclude that schizotypy, SPD (and other schizophrenia-spectrum PD) and psychotic disorder are not merely states of different severity on one common but on qualitatively different dimensions, with the negative dimension being predictive of SPD and the positive of psychosis. Consequently, in light of the merits of early diagnosis, the differential early detection of incipient psychosis and schizophrenia-spectrum PD should be guided by the assessment of different schizotypy dimensions.

Keywords: psychosis, schizotypy, schizotypal personality disorder, prediction, positive dimension, negative dimension, disorganized dimension

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The group of psychotic disorders mainly includes non-affective (i.e., schizophrenia and schizophrenia-spectrum psychoses) and affective psychoses (i.e., mania, bipolar disorders, and depression) whose common features are positive psychotic symptoms (i.e., delusions and hallucinations) (1). Personality disorders (PD) with positive and negative psychotic-like features are assumed to be closely related to

the schizophrenia spectrum; these are paranoid PD, schizoid PD, and schizotypal PD (SPD).

Despite their low lifetime prevalence of about 2% (1, 2), psychoses cause tremendous costs, burden, and disability, already in children and adolescents (3–5). Because a long duration of nontreatment of psychosis and its prodrome negatively impacts outcome (6), research on an early detection and intervention in psychosis prior to the first episode increasingly gained momentum since the 1990s. By now, clinical high-risk (CHR) criteria have already been suggested for transfer into clinical practice, e.g., within the framework of the guidance project of the European Psychiatric Association (7, 8).

The prevention of schizophrenia-spectrum PD is less clear. In the United States, the lifetime prevalence of schizophrenia-spectrum PD was 9% in adults of age ≥20; with SPD 3.9%, paranoid PD 4.3%, and schizoid PD 3.1% (9). Lower rates were reported from Norway (10) (paranoid, 2.4%; schizoid, 1.7%; SPD, 0.6%) and Germany (11) (paranoid, 1.8%; schizoid, 0.4%; SPD, 0.7%) with a higher SPD prevalence in relatives of schizophrenia patients (2.1%) (12). Little is known about the costs and burden of schizophrenia-spectrum PD beyond their assumed role of increasing risk for schizophrenia, as they are frequently not assessed in studies of societal impact of mental disorder (4, 5). Similarly, little research has specifically targeted their early detection and prevention beyond being a by-product of, e.g., research on early detection of psychosis (13).

PERSONALITY TRAITS AND DISORDERS, AND PSYCHOSIS

Psychoses and schizophrenia-spectrum PD, particularly SPD, are linked historically, phenomenologically, and through shared genetic and (neuro-)biological factors (14). This link is mirrored by SPD's placement within the ICD section for schizophrenia and related disorders and its mentioning as a related disorder in the schizophrenia section of DSM-5 (15, 16). Because SPD and schizotypy—as well as other terms often used in this context such as psychotic-like experiences (17)—are not synonymous (18); in the following, we will strictly distinguish between these terms and elucidate their conceptual differences later in the manuscript (see also **Table 1**).

Historical Links

Although SPD as a diagnostic entity was not formulated until 1979 (24), historically, its close link to schizophrenia-spectrum psychoses was earlier established by observations on two levels (25):

- *the familial level:* observations of peculiarities resembling subthreshold features of psychosis in the (premorbid) personality of patients with schizophrenia and their biological relatives, and
- *the clinical level:* observations of patients with attenuated forms of Bleuler's fundamental symptoms of schizophrenia without positive psychotic symptoms or severe personality deterioration.

Thus, these personality organizations were commonly called "*borderline* or *latent* schizophrenia" in the first half of the 20th century; with focus on their pathological and dysfunctional aspects (including its function as a risk indicator for psychosis), the difference between manifest psychotic disorders and their latent forms (particularly SPD) has commonly been (mis-) assumed to be one of severity or trajectory.

Both Kraepelin (26) and E. Bleuler (27) had frequently observed signs of *latent schizophrenia* in relatives of schizophrenia patients that they regarded as "essentially the same as the principle malady" (p. 234) (26) and "qualitatively identical with those of the patients themselves so that the disease appears to be only a quantitative increase of the anomalies seen in parents and siblings" (p. 238) (27). Thus, latent schizophrenia was seen as a mild expression of illness, usually not leading to help-seeking. Their and subsequent descriptions of the abnormal personality of relatives of schizophrenia patients mostly pointed towards the following core characteristics: being eccentric-odd, irritable-unreasonable, socially withdrawn, suspicious, superstitious, nervous, and hypersensitive, exhibiting an aloof and cold demeanor, functioning poorly, and speaking oddly (25).

Emphasizing the clinical link, clinical descriptions of patients emerged since the 1940s, who—though having neither familial risk nor frank schizophrenia—exhibited substantial schizophrenia-like symptoms (25). In 1953, Rado (28) coined the term *schizotype* (a contraction of "schizophrenic phenotype"; engendered by a schizophrenic genotype) to describe non-psychotic but schizophrenia-like individuals (with lifelong risk for psychotic decompensation). He assumed two major abnormalities, severe anhedonia and a distorted awareness of one's body, from which other abnormalities would result, including a propensity for cognitive disorganization and deviant, dependent social relationships.

Building up on Rado's ideas, Meehl (29, 30) used the term *schizotypy* to describe trait-like manifestations of *schizotaxia*, an integrative neural defect caused by a dominant *schizogene*. Relating to Bleuler (27), the core behavioral schizotypy traits were assumed to be cognitive slippage, interpersonal aversiveness (including suspiciousness and expectation of rejection due to a negative self-image of being unlovable), ambivalence, and anhedonia, with psychosis-like features merely as accessory phenomena (18, 25). In Meehl's model, all carriers of the schizogene are schizotaxics (i.e., a true taxon of ill individuals) and—depending on environmental influences—present with graded manifestations of schizotypy, including schizophrenia as its most severe form. Consequently, *schizotaxia* (as a neural defect) and *schizotypy* (as its manifestation) equal schizophrenia-liability, while—even under the poorest environmental circumstances—a non-schizotaxic cannot become a *schizotype* or a patient with schizophrenia.

While the early schizotypy approach is aimed at commonalities with schizophrenia, the DSM-III taskforce (24) targeted the differentiation between what was to become SPD and other disorders, when formulating criteria for schizophrenia-spectrum PD. Broadly in line with this first definition, SPD is still described in DSM-5 as follows:

> "a pervasive pattern of social and interpersonal deficits, including reduced capacity for close relationships; cognitive or perceptual distortions; and eccentricities of behavior, usually beginning by early adulthood but in some cases first becoming apparent in childhood and adolescence" (p. 89) (15).

Thus, unsurprisingly, SPD assessments based on this disorder-oriented view, formulate items conflating schizotypy with aspects of clinical relevance and distress (31).

Current Perspective

Beginning with notions by Kretschmer (32) and Eysenck (33), the current understanding of schizotypy was heavily influenced by the European school of temperament and is subtly but decisively distinct from Meehl's model (18). Proneness for psychosis was no longer believed to be a gradation of illness exclusive to a discrete subgroup of the general population but to be lying on a continuum graded throughout all people, with extreme expressions manifesting as disorders. Additionally, due to Schneider's influential emphasis on positive symptoms (34), research on general temperaments included schizophrenia liability rather in terms of proneness for unusual perceptual experiences and magical/paranormal thinking than for Bleuler's fundamental symptoms [e.g., Tellegen's "Absorption" (35) or Cloninger's "Self-Transcendence" (36)] (18).

Thus, building up further on Claridge's work (37), schizotypy is currently not perceived as a single likely pathological dimension but as a multi-dimensional construct that is *per se* neither pathological nor equal to schizophrenia liability. Instead, at least two dimensions (positive and negative) are assumed, and it is the clustering or co-occurrence of elevated levels of them in an individual that leads to taxon-like entities like schizophrenia, SPD, or CHR (18, 38, 39). Accordingly, factor analyses of both schizotypy and SPD measures suggest that schizotypy is best understood as consisting of the same three dimensions as found in schizophrenia: a positive, a negative, and a disorganized dimension (40–42), although their conceptualization differs greatly (**Table 1**) (31, 43). Commonly and especially in the discussion of a continuum hypothesis of psychosis (44), most emphasis is put on the positive dimension, although Claridge's fully dimensional model considers this dimension the one that is least (inherently) associated with schizophrenia liability.

Benign Schizotypy and "Happy" Schizotypes

Thus, in contrast to the disorder-based view of schizotypy, the temperament-based models allow for the existence of benign aspects inherent to unidimensional schizotypy that, only in excess, may become pathological. This is especially true for positive schizotypy, expressing, e.g., as spiritual experiences, feelings of interconnectedness with others and/or the environment, and personal enlightenment.

The supposition that positive schizotypy and disease proneness constitute different dimensions has been argued for (implicitly but convincingly) by Claridge and colleagues (37, 45–47) who regard the difference between mentally healthy—or even "happy" (p. 255) (46)—schizotypes and schizophrenia-spectrum patients not as one of *quantity* or severity of psychosis proneness but as one of *quality* of phenomena (**Table 1**) (18). These qualitative differences are due to influences of other dimensions that are linked to negative and disorganized schizotypy (18, 38, 48, 49). Being distinct from continuously distributed schizotypy, schizophrenia is, thus, regarded as a breakdown process and endpoint on a second graded continuum that starts from SPD, making it (and other disorders) taxon-like clusters of several (individually continuous) dimensions (18).

A recent review of studies on benign schizotypy (47) concluded that high positive schizotypy in itself seems more likely to be beneficial, i.e., associated with personal wellbeing, flexible and unconventional thinking (including creativity), and favorable personality traits and psychological features (e.g., openness to experience, fantasy proneness, and spirituality). In contrast to the continuum hypothesis of psychosis focusing on positive schizotypy and in line with findings on prediction of psychoses (see below), high negative schizotypy and/or high disorganized schizotypy emerged as factors relevant to psychopathological functioning and mental ill-health (47). Lately, the view on the positive dimension was detailed by a study of the effect of schizotypy on well-being (50). Next to the different negative effects of negative and disorganized SPD features on all aspects of well-being, only the positive features suspiciousness (commonly only part of SPD but not of schizotypy assessments; **Table 1**) and ideas of reference were significantly associated with negative affect and poor environmental mastery and with poor autonomy, respectively. Other positive features, i.e., odd beliefs/magical thinking and unusual perceptual experiences, were either significantly associated with happiness, positive affect, good environmental mastery, and good personal growth, or not related to any of these outcomes (50). Notably, physical anhedonia—which is part of the negative schizotypy dimension but not of SPD—was not assessed.

EARLY DETECTION OF PSYCHOTIC DISORDERS

In clinical samples, the early detection of psychoses mainly follows an indicated preventive approach. Currently, a CHR state is alternatively defined by two complementary approaches (8, 51): The ultra-high risk (UHR) approach, developed to identify persons with high likelihood of transition to psychosis within the next 12 months, and the basic symptom approach, developed to detect beginning psychosis as early as possible.

The UHR criteria include the brief intermittent psychotic symptoms, the attenuated psychotic symptoms, and the "trait-state" or "genetic risk and functional decline" criterion (52, 53). The latter criterion defines the risk trait by either a first-degree family member with psychosis or by an SPD in the index patient, and the state by a functional decline. However, in clinical samples, the trait-state criterion by itself did not significantly raise risk of conversion to psychosis in recent meta-analyses (8, 54). The attenuated psychotic symptoms criterion accounts

TABLE 1 | Current operationalizations of schizotypy, schizotypal disorder according to ICD-10, SPD and other schizophrenia-spectrum PD according to DSM-5, clinical high risk (CHR) of psychosis and psychosis (15, 19–23).

	Schizotypy	Schizotypal disorder	Schizoid (s) and paranoid (p) PD	SPD	CHR [a]	Psychosis
General characteristic	*Enduring personality trait, not per se considered as pathological character*	*Evolution and chronic course (alike that of a PD) with fluctuations of intensity and no definite onset (trait-state character)*	*An enduring pattern of inner experience and behavior (trait) that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment*		*Full or at least some insight into their abnormal nature; defined onset or worsening, not part of the premorbid personality (state)*	*Defined onset, state (positive symptoms with no insight into their abnormal nature)*
Positive factor	• Beliefs that are regarded as invalid and magical by conventional standards, but might well be shared by certain subgroups, e.g. certain esoteric or spiritual beliefs; • Distortions in the perception of one's body and/or environmental stimuli; • Sensory hypersensitivity	• Odd beliefs or magical thinking, influencing behavior and inconsistent with subcultural norms; • Suspiciousness or paranoid ideas; • Unusual perceptual experiences including somatosensory (bodily) or other illusions, depersonalization or derealization; • Occasional transient quasi-psychotic episodes with intense illusions, auditory or other hallucinations, and delusion-like ideas, usually occurring without external provocation;	• Suspects, without sufficient basis, that others are exploit-ting, harming, or deceiving him/her (p); • Is preoccupied with unjustified doubts about the loyalty or trustworthiness of friends/associates (p); • Is reluctant to confide in others because of un-warranted fear that the information will be used maliciously against him/her (p); • Reads hidden demeaning or threatening meanings into benign remarks or events (p); • Perceives attacks on his/her character or reputation that are not apparent to others and is quick to react angrily or to counterattack (p); • Has recurrent suspicions, without justification, regarding fidelity of spouse/sexual partner (p)	• Ideas of reference (excluding delusions of reference); • Odd beliefs or magical thinking that influences behavior and is inconsistent with subcultural norms (e.g., superstitious-ness, belief in clairvoyance, telepathy, or "sixth sense": in children and adolescents, bizarre fantasies or preoccupations); • Suspiciousness or paranoid ideation; • Unusual perceptual experiences, including bodily illusions.	• P1 unusual thought content/delusional ideas; • P2 suspiciousness/persecutory ideas; • P3 grandiose ideas; • P4 perceptual abnormalities/hallucinations; • P5 disorganized communication • Unstable ideas of reference • Derealization; • Decreased ability to discriminate between ideas and perceptions/memories; • Visual/acoustic perception disturbances immediately recognized as a problem with sensory or mental processes	• Delusions; i.e., firm beliefs held with full conviction that are untrue as well as contrary to a person's educational and cultural background • Hallucinations; i.e., perceptions experienced without an external stimulus
Negative factor	• Diminished pleasure or discomfort in social or interpersonal situations; • Deficits to experience pleasure in different sensory domains or discomfort from sensory stimulation; • reduction in psychomotor drive; • Flattened affect or reduction in emotional expressiveness; • reduction in verbal expressiveness	• Constricted affect (the individual appears cold and aloof); • Poor rapport with others and a tendency to social withdrawal	• Neither desires nor enjoys close relationships, including being part of a family (s); • Almost always chooses solitary activities (s); • Has little, if any, interest in having sexual experiences with another person (s); • Takes pleasure in few, if any, activities (s); • Lacks close friends or confidants other than first-degree relatives (s); • Appears indifferent to the praise or criticism of others. • Shows emotional coldness, detachment, or flattened affectivity (s)	• Lack of close friends or confidants other than first-degree relatives • Excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self • Constricted affect.	*Not part of CHR criteria:* • N1 social withdrawal; • N2 avolition; • N3 expression of emotion; • N4 experience of emotion and self; • N6 occupational functioning; • D3 trouble with focus and attention. • Multiple self-experienced impairments in drive, stress tolerance, affect, emotional responsiveness, desire for social contact, social skills, attention concentration, and memory	• Anhedonia (in social and other activities/situations); • Avolition; • Affective flattening; • Reduced intensity of emotional response; • Attentional impairment; • Alogia

TABLE 1 | Continued

	Schizotypy	Schizotypal disorder	Schizoid (s) and paranoid (p) PD	SPD	CHR [a]	Psychosis
Disorganized factor	• Speech deficits due to disorganized, confused thinking that do not cause grave problems in other people's understanding of the person; • Simultaneous experience of divergent emotions	• Vague, circumstantial, metaphorical, overelaborate, or stereotyped thinking, manifested by odd speech or in other ways, without gross incoherence; • Behavior or appearance that is odd, eccentric, or peculiar; • Inappropriate affect		• Odd thinking and speech (vague, circumstantial, metaphorical, overelaborate, or stereotyped). • Behavior or appearance that is odd, eccentric, or peculiar. • Inappropriate affect	*Not part of CHR criteria:* • D1 odd behavior and appearance; • D2 bizarre thinking; • D4 impairment in personal hygiene • N5 ideational richness	• Formal thought disorder/disorganized speech that severely hinders other people's understanding of the person; • Disorganized or bizarre behavior; • Incongruous affect
Cognitive factor [b]					• Thought interference; • Thought blockage; • Thought pressure; • Thought perseveration; • Disturbances of abstract thinking; • Disturbance of receptive; • Disturbance of expressive speech; • Inability to divide attention; • Captivation of attention	
Others		• Obsessive ruminations without inner resistance, often with dysmorphophobic, sexual or aggressive content	• Persistently bears grudges (i.e., is unforgiving of insults, injuries, or slights) (p)			
Features/ symptoms needed for diagnosis	Not applicable, no mental disorder	3 or more, each present for at least 2 years	4 or more	5 or more	1 or more (APS, BIPS, COPER criteria) 2 or more (COGDIS criterion)	Dependent on type of psychotic disorder

[a] *According to the Structured Interview for Psychosis-Risk Syndromes for the assessment of ultra-high risk (UHR) criteria (identified by a prefix of capital letter plus number; 23); Schizophrenia Proneness Instrument Adult/Child & Youth version for the assessment of basic symptom criteria (no prefix) (21, 22).*

[b] *According to the notion of an independent (fourth) "impaired cognition"-dimension in psychosis that, however, is commonly defined by objective neurocognitive impairments (15, 19, 20).*

APS, attenuated psychotic symptoms; BIPS, brief intermittent psychotic symptoms; COPER, basic symptom criterion "cognitive-perceptive basic symptoms"; COGDIS, basic symptom criterion "cognitive disturbances".

for the vast majority of CHR patients. Attenuated psychotic symptoms are mainly defined by sub-threshold psychotic-like experiences (as earlier defined on a clinical continuum by the Chapmans) (55) and by positive features of SPD (13). Nevertheless, attenuated psychotic symptoms differ from corresponding trait-like features of SPD (and paranoid PD) by their obligate recent onset or worsening (**Table 1**); i.e., by capturing early state-like signs of an emerging disorder that allow the initiation of an indicated prevention (13, 56). The trait-state distinction between positive schizotypy and APS was recently supported in a study showing significant changes in APS but not positive schizotypy over 1 year (57).

The basic symptom criteria include "cognitive disturbances" and the "cognitive-perceptive basic symptoms" (58, 59). Of these, the latter lacked sufficient meta-analytical evidence to be already recommended for clinical practice (7). Contrary to the trait character of schizotypy and SPD, basic symptoms decidedly have state character, as, by definition, they differ from what patients consider to be their "normal" mental self (57, 59, 60). Basic symptoms are conceptualized as the earliest primary psychopathological correlates of the neurophysiological disturbances of information processing underlying the development of attenuated and frank psychotic symptoms, which develop based on and partly in reaction to basic symptoms (61, 62). Thus, independently of any thought content or perception, basic symptoms are disturbances in mental processes themselves, thereby clearly differing from more content-related positive features of schizotypy and SPD, and attenuated and brief limited psychotic symptoms (**Table 1**) (60–62).

Studies of personality dimensions, schizotypy, PDs, and SPD, in CHR samples indicate the following:

- CHR patients, compared to CHR-negative patients, are more often high scorers on all four higher-order personality dimensions simultaneously, i.e. emotional dysfunction, inhibitedness, dissocial behavior, and compulsivity (63), rather than exhibiting a distinct "psychosis profile," e.g., of high neuroticism, low extraversion, and medium agreeableness and conscientiousness (64).
- Studies using positive and negative schizotypy assessments, such as the four Wisconsin Schizotypy Scales (65, 66), suggest that pronounced physical anhedonia enhances risk for psychosis, though likely only in the presence of CHR states (67, 68); moreover, physical anhedonia also predicted presence of UHR but not of basic symptom criteria (67).
- Studies using SPD assessments, such as the Schizotypal Personality Questionnaire (66, 69), in CHR patients indicated that SPD, particularly (paranoid) ideas of reference and lack of close friends, predicted psychosis (13) and that SPD assessment might help to identify CHR patients, especially those meeting the trait-state UHR criterion (70).
- When other PD were simultaneously considered, schizoid rather than schizotypal personality traits predicted conversion to psychosis in CHR patient, mainly by deficits in social interaction (that are also partly included in schizotypy assessments of social anhedonia) but not by indifference and emotional coldness (56).

Furthermore, in clinical samples defined by schizotypal disorder, schizoid PD or SPD, up to 48% developed psychosis, which was best predicted by unusual or paranoid ideas and social isolation (13). A similar pattern of predictors was found in non-clinical genetic-risk and community samples, in which positive schizotypy and SPD assessments of unusual and paranoid ideas and unusual perceptual experiences were main predictors of psychoses, whereby social or physical anhedonia and social withdrawal further improved prediction of psychosis—but even more of schizophrenia-spectrum disorders—in some studies (13, 71). Thus, schizotypy and SDP features seem to detect psychosis early; yet, the psychosis-predictive power of single assessments seems to depend on the examined population and, likely, on the interplay between positive and negative dimensions (49). Additionally, the inherent conflation of schizotypy features with distress found in inventories based on Meehl and the SPD conceptualization must be kept in mind (31).

Furthermore, it must be observed that little is known about the role of the disorganized dimension that has hardly been studied. Thus, some effects might be misattributed to the positive and negative schizotypy dimension, as recently shown for the earlier likely misattributed association of negative affective with positive schizotypy that is better explained by one with disorganized schizotypy (72, 73).

EARLY DETECTION OF SEVERE SCHIZOPHRENIA-SPECTRUM PERSONALITY DISORDER

Although schizotypal disorder and SPD have been studied for their propensity to predict psychosis in several studies (13), few studies have examined their predictors. An early study followed children clinically diagnosed as "schizoid" over a mean course of 18 years, whereby "schizoid" was defined by solitude, impaired empathy/emotional detachment, mental rigidity, hypersensitivity with a tendency to paranoid ideas, and odd communication (74). At follow-up, three quarters had developed SPD and 8% psychosis; only 13% had clearly recovered from their schizoid symptoms (75). Moderate stability of the three SPD dimensions across adolescence, i.e., from age 11 to age16, along with a clear indication of their heritability (h^2 = 38–57%) (76) at each assessment time has also been reported (77). Variance in SPD assessment scores at 16 years could be decomposed in 36% stable genetic, 3% stable environmental, 42% time-specific genetic, and 19% time-specific environmental influences, with the positive dimension score being explained by genetic variance only at age 11 years. SPD usually begins by early adulthood, and only rarely in childhood and adolescence (15). Furthermore, an increase in schizotypy and SPD severity across adolescence with a subsequent decrease in adulthood was repeatedly reported (78, 79). Thus, particularly when in concert with a parental schizophrenia-spectrum disorder, pronounced persistent or increasing schizotypy features (49) might currently be the best predictors of adult SPD in youth, especially when of the negative socially impaired and the positive paranoid-suspicious kind.

Other clinical (e.g., heightened anxiety levels), environmental (e.g., childhood adversity and trauma), genetic (e.g., Val allele of the Val[158]Met COMT polymorphism), neurobiological (e.g., various brain abnormalities in frontal, temporal, striatal, and parahippocampal regions), social-cognitive (e.g., poor emotion recognition), and neuropsychological (e.g., jumping-to-conclusion) risk factors of SPD resemble those described for schizophrenia (80, 81), thus not displaying a unique pattern that could be used for its prediction specifically.

CONCLUSIONS

We conclude that schizotypy, SPD (and likely other schizophrenia-spectrum PD), and psychotic disorder are rather manifestations of discrete profiles (i.e., qualitatively distinct taxon-like clusters) of schizotypy or SPD dimensions than merely states of different severity on only one dimension. In doing so, positive schizotypy features—other than the distressing SPD feature of paranoid ideas of reference and suspiciousness—do not appear to be pathognomonic by themselves. This is in contrast to continuum models of psychosis that mainly rely on positive features and assume a progression from positive schizotypy and SPD traits *via* psychotic-like experiences and attenuated psychotic symptoms to psychotic positive symptoms and, finally, schizophrenia (44). Pathological personality processes rather seem to require an interaction of the positive dimension with the negative and/or disorganized dimension, at which, of the positive features, trait-like distressing paranoid ideas of reference and suspiciousness, which are unique to the positive SPD dimension, seem to be most relevant and a starting point on the suggested SPD-psychosis continuum that is distinct from the potentially benign positive schizotypy dimension. The SPD-psychosis continuum, however, likely also involves state-like subclinical positive symptoms such as UHR symptoms that are predictive of psychosis. In doing so, the trait or state character of the positive features might be crucial for the development of SPD or psychosis in late adolescence or young adulthood.

In light of the merits of early diagnosis, a differential early detection of incipient psychotic disorders and schizophrenia-spectrum PD, guided by a comprehensive assessment of all relevant schizotypy-SPD-psychosis dimensions, is necessary—also in light of calls for dimensional diagnostic systems (82), yet requires more research into their differential prediction.

AUTHOR CONTRIBUTIONS

FS-L was responsible for the conception of the work and drafted the first versions of this work. PG and IN revised it critically for important intellectual contents. All authors provided approval for publication of the content.

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Early Substance Use Cessation Improves Cognition—10 Years Outcome in First-Episode Psychosis Patients

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Background: Cognitive impairment may be a risk factor for, as well as a consequence of, psychosis. Non-remitting symptoms, premorbid functioning, level of education, and socioeconomic background are known correlates. A possible confounder of these associations is substance use, which is common among patients with psychosis and linked to worse clinical outcomes. Studies however show mixed results for the effect of substance use on cognitive outcomes. In this study, the long-term associations of substance use with cognition in a representative sample of first-episode psychosis patients were examined.

Methods: The sample consisted of 195 patients. They were assessed for symptom levels, function, and neurocognition at 1, 2, 5, and 10 years after first treatment. Test scores were grouped into factor analysis-based indices: motor speed, verbal learning, visuomotor processing, verbal fluency, and executive functioning. A standardized composite score of all tests was also used. Patients were divided into four groups based on substance-use patterns during the first 2 years of treatment: persistent users, episodic users, stop-users, and nonusers. Data were analyzed using linear mixed effects modeling.

Results: Gender, premorbid academic functioning, and previous education were the strongest predictors of cognitive trajectories. However, on motor speed and verbal learning indices, patients who stopped using substances within the first 2 years of follow-up improved over time, whereas the other groups did not. For verbal fluency, the longitudinal course was parallel for all four groups, while patients who stopped using substances demonstrated superior performances compared with nonusers.

Persistent users demonstrated impaired visuomotor processing speed compared with nonusers. Within the stop- and episodic use groups, patients with narrow schizophrenia diagnoses performed worse compared with patients with other diagnoses on verbal learning and on the overall composite neurocognitive index.

Discussion: This study is one of very few long-term studies on cognitive impairments in first-episode psychosis focusing explicitly on substance use. Early cessation of substance use was associated with less cognitive impairment and some improvement over time on some cognitive measures, indicating a milder illness course and superior cognitive reserves to draw from in recovering from psychosis.

Keywords: psychosis, substance use, cognition, neurocognition, first-episode psychosis

INTRODUCTION

Cognitive impairment is a core feature of schizophrenia. It is observed in the majority of patients (1, 2), often present before the onset of psychosis and is also prevalent in non-affected relatives (3, 4). It is associated with negative symptoms such as apathy and flat affect (5, 6), and several studies have shown an association with poorer clinical and functional outcomes (7). Previous studies report deficits in both processing speed and episodic memory (8), as well as working memory, executive functions (9), and attention (10). One meta-analysis (11) showed moderate to large effect sizes across all cognitive domains, with impairments being more pronounced in older and more chronic patients. Correlates of cognitive impairments include premorbid intellectual functioning, level of education, social functioning, and socioeconomic status (12–14). It has also been suggested that the prevalent long-term use of antipsychotic medication in schizophrenia spectrum disorders could compromise cognitive functioning (15, 16). However, studies with short follow-up intervals have also found indications of cognitive improvement associated with the use of antipsychotics (17–19).

A possible confounder in the relationship between cognitive impairments and outcome is substance use, which is common in patients with psychosis. Reported prevalence rates of concurrent substance use converge on 50%, significantly higher than rates in the general population (20–22). Experimental studies have shown that tetrahydrocannabinol transiently induces psychotic symptoms in a dose-dependent manner and cognitive impairment in healthy individuals (23). Cannabis use is also consistently associated with more cognitive impairments in studies of schizophrenia (24); however, there are some contradictory findings. Several cross-sectional studies have found superior performance in visual memory, working memory, and executive functioning (25–30), attention (31), and, in overall, cognitive task performance in substance-using compared with the performance in non-using patients (12, 13, 32). Long-term longitudinal studies of cognition in psychosis are scarce, and very few extend beyond a 5-year follow-up (33–42). Overall findings indicate stable impairment over time. Studies focusing explicitly on the role of substance use appear to be lacking.

Several studies have reported that continued substance use leads to poorer outcomes than those who stop substances early on in their course of treatment (43, 44). Cessation of use is associated with improvements in symptoms, depression, and functioning (45–47). To our knowledge, no studies have focused on substance-use cessation and the effect on cognition in first-episode psychosis (FEP) patients.

The early Treatment and Intervention in Psychosis (TIPS) study is a prospective, longitudinal study that originally sets out to investigate the relationship between duration of untreated psychosis (DUP) and outcome in FEP patients. It includes a very rich database of the development of significant clinical characteristics from the first week of treatment. We have previously shown that substance users who stopped using during the first 2 years of treatment show a different illness trajectory than those who continue using or stopped using at a later point in time (47). Substance users had better social premorbid functioning than nonusers (NUs) (48). Cognition, in general, appeared to be stable over the first 10 years in treatment (39) in our sample, also with regard to clinical subsamples (39) and using improved statistical methods (49). Improved verbal memory and learning at 1- and 2-year follow-up was associated with fewer relapses during the first year of treatment (50), and follow-up analyses of subsamples suggested that patients who relapsed during the first year of treatment had different cognitive trajectories over the 10-year period (39).

The aim of the current study is to examine the long-term (10-year) associations between substance use and cognition as well as the effect of early substance-use discontinuation in the TIPS sample. Based on our extensive data material, we will also take into account potential predictive or confounding factors such as premorbid functioning, clinical symptoms, and diagnostic groups (narrow versus broad schizophrenia spectrum).

MATERIAL AND METHODS

Study Design

The TIPS study is a prospective, longitudinal follow-up of a large, clinical epidemiological cohort recruited consecutively over 4 years from four Scandinavian health care sectors during 1997–2000. These include two sectors in Rogaland County, Norway, the Ullevål sector in Oslo County, Norway, and a sector from Roskilde County, Denmark. The combined estimated population at the start

of the study period was 665,000 inhabitants. Health care services were catchment area based and publicly funded in all sectors. The areas were similar sociodemographically (e.g. urbanicity, mean educational and income levels, and opportunities for employment) (51). Patients from all areas were treated according to a 2-year standard treatment protocol that included antipsychotic medication, supportive psychotherapy, and multi-family psycho-education.

Participants

The sample consisted of FEP patients with *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition schizophrenia, schizophreniform disorder or schizoaffective disorder ("narrow schizophrenia spectrum"), delusional disorder, mood disorder with mood-incongruent psychotic features, brief psychotic disorder, or psychosis not otherwise specified ("broad schizophrenia spectrum") (51, 52). Participants had to reside in one of the participating sites and were 15–65 years of age in Rogaland or 18–65 years in Oslo/Roskilde and within the normal range of intellectual capacity (Wechsler Adult Intelligence Scale—Revised-based IQ estimate >70). Participants were included between 1997 and 2001 (baseline) and followed up at 1-, 2-, 5-, and 10 years. Twenty-three percent of those who were eligible declined participation. Within the group of 301 who consented to participate, the current sample consists of those who completed cognitive testing at baseline (n = 218) who had data for substance-use grouping (n = 195). There were no statistically significant differences in symptom levels, age, gender, premorbid functioning, or diagnostic distribution between those who did and those who did not complete testing at baseline. A total of 87% completed at least two neuropsychological tests, and 22% completed all five follow-ups. There were 138, 137, 82, and 85 participants who completed neurocognitive testing at each follow-up point. Dropout analyses did not show any statistical differences with regard to diagnoses, gender, duration of untreated psychosis (DUP), substance use, symptom levels, premorbid functioning, or age at 1-, 2-, 5-, or 10-year follow-up. However, 5- and 10-year follow-up dropouts had higher excitative symptom component scores at baseline. Also, participants who dropped out in the course of the study had better scores on the trail making tests (visuomotor processing) compared with those who only completed one test (t = 3.7; df: 44.4; p < .001).

Assessments

The Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (severe combined immunodeficiency) (53) was used for diagnostic purposes. All included patients were assessed using the global assessment of functioning (GAF) split into symptom and function scores (54). Demographic data, including family history of mental illness, was collected for all study-eligible patients. DUP was measured as weeks from the emergence of positive psychotic symptoms to the start of adequate treatment, defined as structured treatment with antipsychotic medication or the admission to psychiatric wards for psychosis. A few non-admitted patients started outpatient psychotherapy structured and directed toward psychosis but did not want medication initially. For these patients, start of psychotherapy was regarded as the start of adequate treatment. Symptom levels were measured by the positive and negative syndrome scale (PANSS) (53), scored on five symptom domains: positive, negative, cognitive, depressive, and excitative symptoms (55). Items constituting these components are as follows: positive component items P1 delusions, P3 hallucinatory behavior, P5 grandiosity, P6 suspiciousness, and general scale item G9 unusual thought content; negative component N1 blunted affect; N2 emotional withdrawal; N3 poor rapport; N4 passive withdrawal; and general scale items G7 motor retardation, G13 disturbance of volition, and G16 active social withdrawal; cognitive component items P2 conceptual disorganization, N5 difficulty in abstract thinking, N6 lack of spontaneity and flow of conversation and general scale items G10 disorientation, G11 poor attention and G15 preoccupation; depressive component general scale items G1 somatic concern, G2 anxiety, G3 guilt feelings, G4 tension and G6 depression; and excitative component items P4 excitement, P7 hostility, and general scale items G8 uncooperativeness and G14 poor impulse control. Onset of FEP positive symptoms was defined as a PANSS score of 4 or higher on any of the PANSS positive component items; not previously receiving adequate treatment for psychosis defined as antipsychotic medication of 3.5 haloperidol equivalents for 12 weeks or until remission of psychotic symptoms. Remission was defined as subthreshold symptoms for at least 7 days, whereas relapse involved reappearance of positive symptoms (items 1, 3, 5, 6, or general scale item 9) for at least 7 days. Stable remission was defined as no relapse in the first year after admission (53–55).

Premorbid functioning was measured by the premorbid adjustment scale (56), covering two areas of functioning—school adaptation and socialization—described through initial childhood level and subsequent change (57). Scores ranged from 1 through 6 with higher scores indicating more impairment. A premorbid adjustment scale change score was calculated as the difference between childhood scores and the last score available, to indicate decline or improvement over time (56, 57).

Length of treatment was split into number of weeks of antipsychotic medication and the number of weeks of psychosocial treatments measured as the sum of weeks with uninterrupted psychosocial treatments with a frequency of once every fortnight or more for the first 5 years or once a month between 5 and 10 years.

Neurocognitive Measures

Neurocognitive tests were administered by clinical psychologists trained in standardized assessments or by research assistants supervised by a senior psychologist.

The five domains of neurocognitive functioning were:

Verbal Learning and Delayed Recall (VL/VL index): The California verbal learning test (CVLT) was used to assess this domain, and the revised version of CVLT was used at 10-year follow-up (58). The number of words and trials were identical to the original version used at previous assessments, while scores were obtained for total immediate recall (the mean sum of trials 1–5), errors (the mean sum of trials 1–5), delayed free recall,

and perseverative responses. Combining raw scores obtained from these two test versions in the same analysis was justified as equivalency in total learning, and long-delay free recall raw scores is reported in healthy individuals (58).

Motor Speed (MS/MS index): The finger tapping test with both hands was used, and the mean score for both the dominant and nondominant hand was calculated.

Visuomotor Processing [trail making (TM) index]: Trail making (A and B) was used, with the scores representing total time for completion of both parts A and B.

Executive Function index: Executive Function index was assessed by the Wisconsin card sorting test, PC version (59). The scores were "categories completed," "perseveration," "trials to first category," and "failure to maintain sets."

Verbal Fluency index was assessed by the controlled oral word association task (60), where the sum mean scores for F-words, A-words, and S-words were used. At baseline, this domain also included measures from the digit span (with distractor) and continuous performance tests (number of hits) (61), but these were not repeated at 10-year follow-up.

For all tests, a *z* score was calculated based on mean scores at baseline. Except for finger tapping, indices were moderately correlated. The four indices (CVLT, TM, Wisconsin card sorting test, and controlled oral word association task) were therefore added together and averaged to form a composite index.

All cognitive ratings were done blind to the substance-use group affiliation of the participants. Reliability of GAF, DUP, and diagnosis was found satisfactory throughout the study. The results of the reliability assessments have been reported previously (62, 63).

Measurement and Classification of Substance Use

Substance and alcohol use was measured by the alcohol and drug use scale (64) using a scale from 1 to 5 (1 = no use; 2 = use without impairment; 3 = abuse; 4 = dependence; 5 = dependence with institutionalization). All commonly used illegal psychoactive substances were included in the assessment. We did not include tobacco, caffeine, or alcohol in our definition of substance use, as these follow different treatment paths and sequelae.

Patients were dichotomized into users or not users, where "use" was defined as any score >1. Abstinence is a culturally relevant concept in Norway, where substance use is largely restricted to subgroups, with any use being considered harmful. Patients were assessed concerning pattern of substance use at all follow-up points. At 5-year follow-up, we also did a retrospective assessment of substance use at 3 and 4 years based on patient information and medical charts. Patients' substance use changed most during the first 2 years after inclusion; thus, this interval was chosen for grouping. This interval is consistent with prior studies (65–68).

For analyses, we grouped patients into a) nonusers (NUs), i.e. patients who had never used, b) stop-users (SUs), c) episodic users (EUs), and d) persistent users (PUs). Patients who had only "no-use" measurements during the first 2 years of follow-up were defined as nonusers (NUs). Patients who had used at baseline and then not use for at least two consecutive measurements, i.e. at 1 and 2 years of follow-up, were defined as stop-users (SUs). Persistent users (PUs) used at all follow-up points, and episodic users (EUs) had various other substance-use patterns. This four-group solution was chosen based on recent studies that have shown that around half of substance-using patients who stop using appear to have less severe symptoms than those who continue (45). Merging previous substance users with NUs does not aid in understanding the impact of ceasing substance use on patient trajectories or prognosis.

Statistics

Statistical analyses were carried out using SPSS version 22.0 (69) and R version 3.4.3 (70).

Differences between groups at baseline were described using frequencies and percentages for categorical variables and means and standard deviations or medians and ranges for continuous variables. Comparisons between groups were made using chi-squared tests for categorical data and student t-tests for independent samples for continuous data. All tests were two-tailed.

To investigate the effect of substance abuse on performance over time, linear mixed effects models were used. The model uses maximum likelihood estimation to manage dropout to a certain degree. This is based on the assumption of dropout at random, that is, the probability of dropout is independent of future but may be dependent on previous history, which may be reasonable in this situation. Separate models were estimated, each with one of the cognitive index scores as the dependent variable and substance-use group as categorical predictor. Covariates were based on baseline differences: age, gender, years of education, and premorbid academic adjustment (**Table 1**). Furthermore, based on the literature, diagnostic category (narrow schizophrenia spectrum disorder or not) and DUP (log transformed due to skewed distribution) were included. Interaction between time and group was included in order to investigate whether change in neuropsychological test scores developed differently in the different groups. Furthermore, the interaction between narrow schizophrenia spectrum diagnoses and group was examined to determine whether narrow schizophrenia diagnoses are associated with different effects on the neuropsychological tests in the substance-use groups. The large data set justifies the number of parameters in the models. Random intercept and AR (1) was used to achieve a satisfactory model for correlation between longitudinal measurements within individuals. The executive function and TM indices were severely skewed to the left. In order to achieve a robust analysis, these data were log transformed after inverting the scale and adding a constant to assure positive values only.

TABLE 1 | Baseline characteristics at study inclusion and at 10 years of first-episode psychosis patients across patterns of substance abuse.

***N* = 195**	**No (NU) *N* = 106**		**Stop (SU) *N* = 26**		**Episodic (EU) *N* = 33**		**Persistent (PU) *N* = 30**		**Analysis**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**Chi²**	**df**
Male*	48	45	20	77	20	61	23	77	15.1	3
Diagnosis at inclusion										
Schizophrenia spectrum	71	67	18	69	26	79	21	70		6
Affective	20	19	2	8	3	9	3	10		6
Other"	15	14	6	23	4	12	6	20		
	Median	Range	Median	Range	Median	Range	Median	Range	F	Df***
DUP (weeks)**	8	0–520	9	0–416	17	0–468	16	1–555	1.6	191
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	Df***
Age****	30.8	10.3	27.5	8.3	21.9	4.0	22.5	4.3	13.2	191
Premorbid adjustment, last score										
Social	1.8	1.5	1.5	1.2	1.9	1.3	1.9	1.6	0.4	191
Academic*****	2.2	1.4	2.3	1.3	2.5	1.2	3.0	1.4	2.8	191
PANSS and GAF baseline										
Positive	15.3	4.4	16.1	4.9	14.7	3.6	15.2	4.7	0.4	190
Negative	20.2	9.8	20.4	8.1	22.3	9.2	21.3	7.5	0.4	189
GAF function.007 (SU/PU.01)	31.6	10.4	27.8	9.2	33.3	10.5	8.6	1.6	4.2	189
PANSS and GAF at 10 years										
Positive comp (NU/PU.035), (SU/PU.018)	8.5	4.1	7.2	3.3	10.2	4.5	11.6	5.5	4.6	130
Negative	15.9	7.2	14.6	6.3	17.9	6.9	19.5	9.6	1.9	130
GAF function 001 (SU/EU.002) SU/PU.036)	52.2	14.3	62.7	12.0	44.3	14.0	49.0	17.2	5.5	130

**p < .002; "Other diagnoses: delusional disorder (n = 7), brief psychotic disorder (n = 3), organic psychosis (n = 1), psychosis NOS (n = 10); **Reported values are median values, while analysis of variance was done with log transformed DUP values; ***All between-group degrees of freedom (df) = 3. Df reported in table concerns within-group df; ****Post hoc comparisons Scheffe test, pairwise comparisons NU&EU, NU&PU p < .001; *****p < .05; ǂPost hoc comparisons Scheffe test.*

RESULTS

Table 1 outlines the demographic and clinical characteristics of the sample. Substance users (all) at baseline were more likely to be male than NUs, had poorer premorbid academic functioning, and shorter length of education. NUs were significantly older at presentation than EUs, and PUs ($p = 0.001$ in both groups), but not SUs. No differences in terms of diagnostic distribution or DUP were found between groups. There were no differences in positive or negative symptoms on the PANSS or in GAF function scores between groups. Not outlined in the table; there were no group differences for family history.

The positive PANSS component scores differed among groups at all follow-up points post-baseline, with PUs exhibiting significantly higher symptom levels. The duration of use of antipsychotics or psychotherapy over the 10-year period did not differ between users and NUs. There were differences in time spent in hospital, both on a yearly basis ($p < 0.048$) and cumulatively ($p = 0.048$). In addition, substance users spent more time in psychosis, both per year (CU > NU $p = 0.011$; PU > SU $p = 0.024$) and cumulatively (CU > NU $p = 0.011$; PU > SU $p = 0.024$). Mean values and 95% CI for the neurocognitive indices shown over time in the groups are provided in the **Supplementary Material**.

Motor Speed

There were no group differences at baseline for motor speed (**Table 2**). LME modeling showed that development over time was significantly different between groups. SUs performed better over time ($t = 2.20$; df 433; $p = 0.03$) compared with all groups.

TABLE 2 | Standardized neuropsychological test scores at baseline in first-episode psychosis patients across patterns of substance abuse.

***N* = 195**	**No (NU) *N* = 106**		**Stop (SU) *N* = 26**		**Episodic (EU) *N* = 33**		**Persistent (PU) *N* = 30**		**Analysis**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**p**	**Df within**
Neuropsychological index scores											
Verbal learning	.17	1.1	.01	.82	-.08	.94	–.25	.95	1.4	.241	184
Verbal fluency	.03	.96	–.06	1.1	.16	.80	.14	.97	.37	.773	187
Executive function	–.43	.89	.12	.87	.06	.74	–.04	1.0	.29	.831	184
Motor speed	–.13	.96	.10	1.1	.14	1.1	.32	.89	1.9	.132	188
Trail Making	–.07	1.2	–.13	.79	–.12	.98	.42	.67	2.0	.113	183
Composite score	.01	.64	–.05	.69	.01	.49	.07	.61	.19	.906	191

Females had lower scores over time and at baseline (t = −7.07; df 208; p = 0.001).

Executive Function

There were no significant group differences for executive functioning.

Verbal Learning

All four groups perform poorer with time on verbal learning. SUs had higher scores across all follow-up points (t = 2.00; df 211; p = 0.05). Poorer premorbid function was associated with lower scores (t = −2.57; df 211; p = 0.01). Women performed significantly better than men at all follow-up points (t = 4.95; df 211; p = 0.001). Patients with narrow schizophrenia diagnoses in the SUs (t = −2.03; df 211; p = 0.04) and EUs (t = −2.76; df 211; p = 0.006) performed poorer than NUs.

Visuomotor Processing

The PUs scored significantly poorer than NUs across all time points on visuomotor processing (t = −2.37; df 207; p = 0.020). Performance levels were predicted by education where shorter length (t = −3.58; df 207; p = 0.001) and poorer premorbid adjustment predicted lower scores. Higher age was also a predictor of poorer scores (t = 4.63; df 207; p = 0.001).

Verbal Fluency

The SUs scored significantly higher than the NUs on verbal fluency, although change over time was parallel (t = 2.21; df 210; p = 0.03). There was a significant improvement over time in all groups. Longer education (t = 2.23; df 210; p = 0.03), better premorbid functioning (t = −2.75; df 210; p = 0.006), and female gender (t = 2.68; df 210; p = 0.008) were associated with better scores.

Composite Score

There was no significant change over time and no significant group differences in overall performances. The composite score was significantly associated with longer education (t = 2.73; df 213; p = 0.006), better premorbid functioning (t = −3.98; df 213; p = 0.001), female gender (t = 2.29; df 213; p = 0.022), and lower age (t = −2.24; df 213; p = 0.026). Within the SUs (t = −2.32; df 213; p = 0.022) and EUs (t = −2.34; df 213; p = 0.021), the narrow schizophrenia group performed poorer.

In summary, patients who stopped using substances had higher motor speed, better verbal learning, and better verbal fluency. Persistent users performed significantly worse on visuomotor processing, while participants who had never used substances had significantly better visuomotor processing and poorer verbal fluency. For EUs and SUs, patients with narrow schizophrenia diagnoses performed significantly poorer overall.

DISCUSSION

This study is one of the firsts to focus on cognition, substance use, and substance-use discontinuation in a sample of FEP patients. Our study is longitudinal and includes a large and representative sample. The main finding was that those who stop using substances early have superior cognitive functioning on several measures compared with those who continue using, either persistently or episodically. Those who stop using within the first 2 years of receiving treatment do as well as, or better than, NUs.

Better performance on cognitive functioning indices were associated with better premorbid academic functioning and more years of education as well as female gender. Persistent and EUs had poorer premorbid academic functioning and were more likely to be male. However, both male gender and poor premorbid adjustment represent poor prognostic factors in psychosis. Thus, it may be challenging to disentangle the effect of poor premorbid adjustment from substance use.

For instance, the trail making test and verbal fluency both have a strong component of mental control. Trail making part B relies heavily on set-shifting ability, and verbal fluency, whereas the F-A-S measure of verbal fluency relies on efficient search skills and, hence, also mental control. Both these tests were associated with premorbid educational attainment, academic adjustment, and substance use. Furthermore, mental control is an ability that is often compromised in patients with more severe psychotic illnesses. Improvement and superior performances in those who stop using substances and worse performances in those who continue to use may therefore contribute to a growing evidence base suggesting a milder illness process in SUs. It has indeed been suggested from other studies that substance users may have better cognitive functioning than NUs and follow a different path to illness, with a separate starting point and trajectory toward psychosis. The finding that verbal fluency was impaired in those who never used substances aligns well with this: verbal fluency has repeatedly been shown to be a robust and central impairment in schizophrenia and other psychoses. Having developed psychosis in the absence of the risk factor substance use may thus be indicative of a more severe or even more endogenous illness process.

Previous findings from this and other studies (45, 66, 71) show that patients who stop using have better clinical and functional outcomes than both EUs and PUs. One may speculate that these patients lack some vulnerabilities present in other groups and that perhaps psychosis may even have been avoided in the absence of substance use.

Susceptibility to psychosis is considered familial to a certain degree, and some family studies have found deficits in verbal learning and motor speed (72, 73) in unaffected relatives. We did not find any significant difference in the rate of positive family history of mental illness in first-degree relatives between groups or diagnostic categories. In summary, our findings appear to underscore the importance of substance use as an independent risk factor and, more malleable than familial risk, trauma, and other known factors. The possibility of substantial harm reduction with early discontinuation is an important message to clinicians and provides hope for patients who struggle with addiction and psychosis.

A longitudinal study such as ours holds several methodological limitations. Retest effects in cognitive testing are one of these. However, the spacing over a 10-year period with long intervals between testing reduces training effects. Since CVLT is the most likely candidate for training effects, we also used a parallel version at the 10-year follow-up.

The rate of dropout is high, although we have compensated for this by using linear mixed model analyses that account for missing data by calculating estimates.

Our main limitation concerns the lack of means for controlling patient's claims of substance-use cessation. This information could have provided valuable information in terms of further understanding the relationship between substance use and cognitive outcomes. Although urine toxicology screenings could have strengthened our findings, such sampling is considered intrusive by some and might have reduced the representability of our sample and increased attrition. Furthermore, these measures of sampling have limited validity and only for a narrow number of substances. We were aware of the possibility of underreporting, and therefore, assessments adopted a non-judgmental approach. Our impression was that details provided by patients was consistent with all other sources of information used in the project such as co-lateral information and patient files.

Longitudinal studies of FEP are useful in that they include baseline measures of neurocognitive performance thus minimizing the confounding effects of chronicity. Our study consists of a large representative cohort with patients followed up over a longer period than most other longitudinal FEP studies and with five repeated assessments of the cognitive domains.

The present study demonstrated differences in motor speed and verbal indices in patients who discontinued substance use early on in their course of treatment. This, as well as previous published results indicating that SUs reach levels as good as or better than NUs, conveys a powerful message to clinicians. Focusing on substance use early is crucial in order to maximize the likelihood of good outcomes.

ETHICS STATEMENT

The study was carried out in accordance with the recommendations and has been approved by the Regional Committee for Research Ethics Health Region 2 (#S95189) and the Regional Committee for Research Ethics Health Region East (#1.2007.2177). Data inspectorate license: #96/3017-2, #2003/2052. The Regional Committee for science ethics region Sjælland: #1-01-83-0002-07. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Regional Commitees for Research ethics (see above).

AUTHOR CONTRIBUTIONS

SF, JJ, TL, IJ, PV, SO, IM, BR, ES, and UH took part in designing the study. TL, IJ, IM, SF, ES, UH, and WH collected the data. MW, WH, and BA performed the analyses. MW wrote the first draft of the manuscript with support from WH, JJ, as well as HS, KB, JR and JB. All authors critically reviewed the paper and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00495/full#supplementary-material

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ORIGINAL RESEARCH
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Predictors for Antipsychotic Dosage Change in the First Year of Treatment in Schizophrenia Spectrum and Bipolar Disorders

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Background: Use of antipsychotic medication is central in the treatment of psychotic disorders. However, there is limited knowledge about prescription practice of antipsychotics in the critical early phase of these disorders. Clinical guidelines recommend low dosages, but no discontinuation of antipsychotic medication during the first year of treatment in first episode patients. The main aim of this study was to identify clinical predictors for dosage change or discontinuation of antipsychotics during this period.

Methods: A total of 426 antipsychotic-using patients with schizophrenia spectrum or bipolar disorder, including both a first treatment sample and a sample of patients with previous treated episodes ("multi-episode" sample) from the same diagnostic groups, underwent thorough clinical and sociodemographic assessment at study baseline and after 1 year. Prescribed dosage levels at baseline and follow-up and change in dosage or discontinuation of antipsychotics from baseline to follow-up were compared between groups, controlling for possible confounders.

Results: We found reduced dosages over the first year in both first treatment groups across diagnoses, but not in multi-episode groups. Weight increase predicted dosage reduction in the schizophrenia group, while the level of psychotic symptoms at baseline predicted dosage reduction in the bipolar group. We found higher baseline levels of antipsychotic use in the schizophrenia group than in the bipolar group.

Conclusion: We found indications of a trans-diagnostic reduction of prescribed dosages of antipsychotics over the first year in treatment, but with different predictors for this reduction in the two diagnostic groups. The findings increase the understanding of drivers of early medication change in psychotic disorder.

Keywords: antipsychotics, schizophrenia, bipolar disorder, prescription, dosage

BACKGROUND

Psychopharmacological agents are one of the main treatment approaches in clinical psychiatry. Antipsychotics ("neuroleptics") were introduced for the treatment of schizophrenia in 1956, and have persisted as the cornerstone of treatment for schizophrenia and related psychotic disorders (1, 2). They also effectively reduce the psychotic symptoms of affective psychoses in manic or depressive episodes (3), and some are approved as mood stabilizers in bipolar disorder (4, 5). There is however growing controversy around the use of antipsychotics (6, 7), including criticism of inadequate side effect management (8–11).

Prospective studies show beneficial effects of earlier adequate treatment in psychotic disorders, and treatments given in the early phases of illness seem to be of particular importance for short- and long-term outcome (12–14). Studies also indicate that first-treatment patients are more sensitive to lower dosages of antipsychotics than multi-episode patients, both in their responses to and in their experiences of adverse effects (15). Use of unnecessarily high dosages may lead to adverse effects and negative opinions about antipsychotics, with long-term consequences for treatment compliance. New treatment guidelines recommend the use of monotherapy and low dosages for the first psychotic episode and subsequent maintenance therapy for schizophrenia spectrum disorders (2, 11, 16). Discontinuing antipsychotic treatment in the first year of treatment is not recommended. In clinical practice, the choice of which antipsychotic to use and the dosage to administer is highly individualized (17–19). Factors which may affect the choice of individual treatment include diagnosis, current symptomatology, insight into the illness, known side effects of the drug in question, degree of functional loss, as well as perceived adherence to medical advice (20, 21). There are no specific recommendations for antipsychotic treatment of patients with bipolar disorder.

The efficacy of current antipsychotics is dependent on their effects on the dopamine neurotransmitter system in the central nervous system. Since drug uptake, first-pass metabolism and passage over the blood–brain barrier are highly individual there is no fixed dose–response (22, 23), and antipsychotic treatments typically have an aspect of trial and error (24). This carries risks, both for the use of ineffective dosages over too long periods of time, and for the use of too high dosages causing unnecessary side effects. An increase in knowledge to guide the choice of first treatment in psychotic disorder is thus warranted. Identifying predictors of discontinuation or change in dosages of antipsychotics during the first year of treatment can help to better understand the mechanisms behind the individual decision-making processes. Such insight may be important in guiding the complex task of finding the optimal treatment.

The current study is based on a 1-year follow-up of comprehensively characterized patients with schizophrenia and bipolar disorder, including both first-treatment and multi-episode patients from the same catchment areas, and thus using the same treatment services. These services give treatment based on guidelines that recommend low dosages of antipsychotics for first-treatment schizophrenia for 2 years, but with no particular advice for the dosages and length of maintenance treatment in first-treatment bipolar disorder. The study had the following aims:

1. Are there differences in the use of antipsychotics, between first-treatment and multi- episode patients in patients with schizophrenia spectrum and bipolar disorder at study baseline?
2. What dosage changes or discontinuation rates of antipsychotic medication are there over the subsequent year? Do these predictors differ between patients with schizophrenia spectrum and bipolar disorder, or between first-treatment and multi- episode patients?
3. What are the predictors of changes in the dosages or discontinuation of antipsychotics, and are there different predictors between patients with schizophrenia spectrum and bipolar disorder, and between first-treatment and multi-episode patients?

MATERIALS AND METHODS

The current study is a component of the TOP (Thematically Organized Psychosis research) Study, which is approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Recruitment was done from 2003 until 2017 from major hospitals in the Oslo area, Norway. The TOP study comprises several smaller sub-studies. All first treatment patients are included in prospective cohorts with planned follow-up studies. Multi-episode patients were part of smaller follow-up studies, based on the focus of ongoing projects. The reasons for multi-episode patients to participate, or not to participate, in follow-up studies were thus administrative (based in project design and funding) with no identified selection bias involved. There were no significant differences in baseline demographic and clinical characteristics between multi-episode patients participating or not participating in follow-ups. For a more detailed description, see Faerden et al. (25), Hellvin et al. (26), and Kvitland et al. (27).

Inclusion criteria at baseline: age 17 to 67 years and meeting the DSM-IV criteria for a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder NOS, delusional disorder or bipolar I, II or NOS disorder. Exclusion criteria were: presence of a diagnosis of a developmental disorder, IQ < 70 or acquired brain damage (head injury with hospitalization), and lack of fluency in a Scandinavian language. There were no exclusion criteria based on course of illness, history of treatment or substance use. Patients were recruited consecutively from in- and outpatient psychiatric units in the collaborating hospitals. There were no other treatment organizations serving these areas, allowing for a high degree of representation for participating patients. For details, see Ringen et al. (28). Each patient was referred to the project by their treating clinician, after an initial evaluation of their eligibility and ability to give informed consent. Emphasis was put on recruiting all patients regardless of the level of adherence to their respective treatment programs. All patients gave written informed consent to participation and for follow-up. The assessments were

conducted by trained clinicians working as research fellows (MDs or clinical psychologists). The recruitment teams were primarily based in the outpatient clinics, where patients are transferred for treatment after the acute illness phases. The study thus mainly includes patients who were symptomatically stable at the point of baseline assessments.

Assessments of Diagnosis, Onset of Illness, Treatment History and Sociodemographics at First Assessment; Creating of Groups

Diagnosis, onset of illness and treatment history at baseline were established using the Structural Clinical Instrument of Diagnosis for DSM-IV axis I disorders (SCID – I), modules A–E, with the aid of medical charts (29). All interviewers completed a training course in SCID assessment based on the training program at the University of California Los Angeles (30) and participated in regular diagnostic consensus meetings led by a clinically well-experienced professor of psychiatry. To evaluate reliability of actual study interviews, a stratified random sample was drawn, consisting of cases from every assessment staff member. Anonymous vignettes describing symptoms and development of the illness were then rated by two experts blind to the study ratings. For the 28 vignettes evaluated, the overall agreement for the nine DSM-IV diagnostic categories was 82% and the overall Kappa 0.77 (95% CI: 0.60–0.94).

The duration of untreated illness (DUI) was defined as the time (in weeks) from the onset of the first SCID verified illness episode to the start of use of adequate medication. For Bipolar disorder specifically, DUI was defined as time from first affective episode (regardless of polarity), to the start of adequate treatment, defined as either antipsychotic or mood-stabilizing medication for mania or mixed episodes (in appropriate dosages for minimum 6 weeks) according to available treatment guidelines for BD I (31).

Data was collected on marital status, occupational status, and educational level. Four groups were defined: "First treatment patients" were defined based on treatment history as patients receiving their first adequate treatment of the disorder in question within the last 12 months. "Schizophrenia spectrum" (SS) included schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder NOS and delusional disorder and was further divided into "First Treatment Schizophrenia Spectrum" and "Multi-episode Schizophrenia Spectrum" based on treatment history. "Bipolar disorder" (BD) included bipolar disorder I, II and NOS and was divided into "First Treatment Bipolar Disorder" and "Multi-episode Bipolar Disorder."

Assessment of Medication, Functioning, Symptoms and Socio-Demographical Characteristics at First Assessment (Baseline) and 12 Months Follow-Up

All patients were assessed at first recruitment ("Baseline") and 12 months later. At both time points, information on type and dosage of all antipsychotic medication was collected. Defined daily doses (DDD) were defined according to the WHO criteria (32, 33). For comparison of DDDs and Chlorpromazine equivalents, see **Table 1**. The ratios of currently prescribed daily dosage of an antipsychotic (PDD) and the corresponding DDD (PDD/DDD) were calculated for each prescribed antipsychotic. The sum of all PDD/DDD ratios for each participant was used as an estimate of current load of antipsychotics across different types of drugs. "PDD/DDD change" was created by subtracting PDD/DDD at 12 months follow-up from PDD/DDD at baseline (including cases not using antipsychotics, i.e., PDD/DDD = 0, at follow-up). The *Udvalg for Kliniske Undersøgelser* (UKU) side effect rating scale (34) was used to measure type and severity of side effects. All items in the UKU scale were scored from 0 to 3, where 0 indicated no side-effect, and scores 1–3 indicated presence of side-effect with increasing severity.

Insight was measured by the Birchwood Insight scale (36) items 2 and 8, and low levels of insight were defined as a score of 3 or higher. Level of physical activity was assessed by the clinicians as "light," "medium," or "heavy." Patients were interviewed about substance use prior to first assessment and in the follow-up period based on a common semi-structured interview form and from section "E" of the SCID (29). Current global functioning and symptoms were assessed by the Global Assessment of Functioning Scale (GAF), using the split version of GAF, with separate scores for symptoms and functioning (37). Current psychotic symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) (38). Current depressive symptoms were measured with the Inventory of Depressive Symptoms – Clinician rated (IDS-C) (39), and current manic symptoms were rated with the Young Mania Rating Scale (YMRS) (40). The Alcohol Use Disorders Identification Test (AUDIT) (41) was used to identify problematic alcohol use.

The inter-rater reliability of the symptom assessments in the TOP study have been shown to be good with an Intraclass Coefficient (ICC) (42) of 0.82 for PANSS positive symptoms and 0.86 for GAF (28).

TABLE 1 | Prescribed antipsychotics and comparison of defined daily dose and chlorpromazine equivalents.

	Defined daily dose Dose (mg/day)	CPZ eqv* Dose (mg/day)
Chlorpromazine	300.0	100.0
Haloperidol	8.0	1.6
Perphenazine	30.0	6.8
Zuclopenthixol	30.0	*na*
Amisulpride	400.0	*na*
Aripiprazole	15.0	8.0
Paliperidone	6.0	*na*
Olanzapine	10.0	5.3
Quetiapine	400.0	175.5
Risperidone	5.0	1.2
Ziprasidone	80.0	62.6
Clozapine	300.0	138.8

**Chlorpromazine equivalents, linear equations (35). na, not available.*

Statistics

All analyses were performed using the Statistical Package for the Social Sciences (SPSS version 25.0, SPSS Inc., Chicago, IL, USA). Differences between categorical variables were analyzed using chi square tests. Differences between normally distributed continuous variables were analyzed using univariate analyses of variance with *post hoc* Bonferroni corrections and paired t-tests as appropriate. Significance level was set to 0.05, two-tailed.

A two-way between-groups analysis of variance was conducted to explore the impact of diagnostic group (schizophrenia spectrum or bipolar disorder spectrum) and treatment group (first treatment or multi-episode) on change in dosage of antipsychotics. To identify predictors for change in dosages of antipsychotics from first treatment we performed a series of follow-up multivariate analyses for each group. We here used multiple linear regression analyses for normally distributed dependent variables, with independents entered hierarchically in several blocks. Age and sex were selected as priori independent variables, in addition to baseline measures regarded as plausible predictive factors for inducing change, including measures of common side-effects, insight and reported compliance. Additional putative predictors were added based on findings of significant bivariate associations to changes in dosage of antipsychotic medication in the current sample. The assumption of a linear relationship was evaluated based on examinations of residual plots for each analysis, and on examination of influential observations based on leverages and Cox distances. The final model with the best fits is presented in the paper.

RESULTS

A total of 426 patients were included in the current study, with assessments both at baseline and follow-up. Their demographic and clinical characteristics at baseline are described in **Table 2**. Out of these, 136 patients did not use antipsychotics at baseline (First Treatment Schizophrenia Spectrum: 40 (21% within the diagnostic group); First Treatment Bipolar Disorder: 47 (47% within the diagnostic group); Multi-episode Schizophrenia Spectrum: 10 (15% within the diagnostic group); Multi-episode Bipolar Disorder: 39 (57% within the diagnostic group)). Eight patients did not have reliable information for antipsychotic use at follow-up. For the 286 patients with information on dosage of antipsychotics at baseline, the schizophrenia spectrum patients

TABLE 2 | Demographic and clinical characteristics of groups at first assessment.

	Multi-episode schizophrenia spectrum (N = 69)			Multi-episode bipolar disorder (N = 69)			First treatment schizophrenia spectrum (N = 187)			First treatment Bipolar disorder (N = 101)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Age, years	69	33.2	1.2	69	35.4	11.8	187	26.9	7.5	101	3.3	9.7
Premorbid functioning	66	0.3	0.2	68	0.2	0.2	181	0.23	0.18	101	0.18	0.16
Education, years	69	13.0	2.6	68	14.4	3.3	187	13.1	2.9	101	14.6	2.7
DUI, weeks	9	121.2	132.3	6	21.5	4.0	185	119.1	199.4	54	43.1	134.3
Age at onset*, years	67	27.0	9.4	31	28.5	11.3	182	23.8	7.3	66	27.0	8.8
Age at first medication*, years	61	28.2	9.5	31	3.7	12.2	166	25.7	7.0	56	29.3	9.6
Number of suicide attempts	69	1.0	2.8	69	0.6	1.4	183	0.5	1.5	100	0.5	1.6
BMI, kg/m^2	67	26.4	5.0	69	25.8	4.3	181	24.6	4.3	98	24.9	4.2
Audit	20	3.5	5.9	16	0.7	1.9	177	5.8	9.5	87	3.4	6.4
Audit	17	7.2	7.0	10	5.9	4.6	172	7.2	7.2	83	8.9	6.8
GAF-Symptoms	69	45.0	12.0	69	57.6	9.9	187	43.0	12.3	101	57.9	11.5
GAF-Functioning	69	47.2	11.5	69	55.9	11.0	187	45.2	12.8	101	54.2	11.9
PANSS positive symptoms	69	14.4	5.6	69	9.5	2.8	187	15.1	4.9	101	9.9	3.6
PANSS negative symptoms	69	15.6	6.3	69	1.7	3.7	187	14.9	6.0	101	1.0	3.1
PANSS general symptoms	69	31.8	9.9	69	26.5	5.5	186	32.1	7.0	101	25.9	5.3
IDS depressive symptoms	65	18.3	13.0	66	15.2	1.5	106	17.1	12.7	95	16.8	11.5
YMRS manic symptoms	67	4.9	4.6	69	2.9	3.6	165	5.7	4.9	101	3.8	5.3
Side effects of medication	55	11.3	7.8	61	9.0	5.8	148	12.8	9.5	78	15.3	11.3
	n	%		n	%		n	%		n	%	
Male	41	59.4		31	44.9		115	61.5		41	40.6	
European (Caucasian)	57	82.6		60	87.0		132	70.6		85	84.2	
Never married and single	49	71.0		39	56.5		141	75.4.		57	56.4	
Daily tobacco use	45	65.2		36	52.2		89	47.6		51	50.5	
5+ cups of coffee daily	35	50.7		19	27.5		32	17.1		28	27.8	
Cannabis use past 14 days	7	10.1		2	2.9		23	12.4		11	10.9	
Medium/high physical activity	16	40.0		17	39.5		49	33.3		36	43.3	
BIS: No need for medication	40	60.6		38	56.7		63	40.1		50	51.5	
BIS: Low insight in illness	40	60.6		45	67.2		64	40.8		64	66.0	

**Of symptoms. SD, standard deviation; DUI, duration of untreated illness; BMI, body mass index; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; IDS, Inventory of Depressive Symptoms; YMRS, Young Mania Rating Scale; BIS, Birchwood Insight Scale.*

used significantly higher dosages of antipsychotics than bipolar disorder patients (**Table 3**). There were no significant differences between first-episode and multi-episode groups.

Use of antipsychotics and discontinuation rates for the different groups at baseline and follow-up are shown in **Table 4**. Of the 290 patients using antipsychotics at baseline, we had information on use of antipsychotics at follow-up for 282, of these 50 (18%) discontinued use. The difference in discontinuation rates between First Treatment Schizophrenia Spectrum and First Treatment Bipolar Disorder was statistically significant ($x^2 = 4.6$, $p = 0.032$). Thirteen (68%) of those discontinuing antipsychotics in the First Treatment Bipolar Disorder group had however changed to mood stabilizers at follow-up.

There was a statistically significant reduction in antipsychotic dosage for both the First Treatment Schizophrenia Spectrum group and the First Treatment Bipolar Disorder group. There were no significant changes in antipsychotic use in the two multi-episode illness groups (**Figure 1**). A two-way between-groups analysis of variance with change in PDD/DDD ratios as dependent variable showed a statistically significant main effect for treatment group (first-treatment versus multi-episode) ($F = 4.66$, $p = 0.032$), however with a small effect size ($\eta^2 0.02$). There was no significant main effect for diagnostic group and no significant interaction effects.

Bivariate analyses showed the following group-wise significant associations with change in dosage of antipsychotics measured as PDD/DDD ratio: First Treatment Schizophrenia Spectrum: Age (+), PDD/DDD for all antipsychotics at baseline (−), UKU weight gain (−), UKU investigators' assessment of global side effect load (−) and level of physical activity (−); First Treatment Bipolar Disorder: PDD/DDD for all antipsychotics at baseline (−), UKU hypokinesia (−), GAF-F (+), and PANSS-P scores (−). Since there were no changes for multi-episode patients, we did not do follow-up analyses for these groups.

Final combined models for the multivariate linear regressions analyses are presented in **Supplementary Tables 1A, B**. In First Treatment Schizophrenia Spectrum, a reduction in antipsychotic PDD/DDD ratio was significantly associated, with a small effect size, with baseline weight increase as a side effect of medication, as judged by the person conducting the assessment. In First Treatment Bipolar Disorder, a reduction in antipsychotic PDD/DDD ratio was significantly associated, with a small to medium effect size, with baseline higher levels of positive psychotic symptoms as measured by the PANSS.

The logistic regression analysis with discontinuation as the dependent variable showed significant contributions to the risk of discontinuation from higher GAF-F and alcohol use (AUDIT scores) at baseline in First Treatment Schizophrenia Spectrum, and from increased age in First Treatment Bipolar Disorder, significant odds ratios were in the range from 1.06 to 1.11 (**Supplementary Tables 2A, B**).

TABLE 3 | Total dosage of prescribed antipsychotics per defined daily dose (PDD/DDD) of all antipsychotics in use at baseline. N = 286 with information on PDD/DDD at baseline.

	n	Mean	SD	*Post hoc**
First treatment schizophrenia spectrum	147	1.32	0.85	vs FTBD: 0.011, vs MEBD: 0.001
First treatment bipolar disorder	53	0.92	0.65	
Multi episode schizophrenia spectrum	56	1.42	0.89	vs FTBD: 0.007, vs MEBD: 0.001
Multi episode bipolar disorder	30	0.69	0.45	

**ANOVA with Bonferroni correction. S.D., Standard Deviation; FTBD, First Treatment Bipolar Disorder; MEBD, Multi Episode Bipolar Disorder.*

DISCUSSION

As expected, and in line with current clinical recommendations (43, 44), we found that patients with schizophrenia spectrum disorders used higher dosages of antipsychotics compared to patients with bipolar disorders in both first-treatment and multi-episode groups. Contrary to clinical recommendations, we did not find that first-treatment patients used lower dosages at baseline as compared to multi-episode patients in both diagnostic groups. However, both first treatment groups showed significant reductions in dosages of antipsychotics over the first year of treatment, while both multi-episode groups did not show significant change.

In First Treatment Schizophrenia Spectrum, weight gain at baseline was a statistically significant predictor of dosage reduction over the first year of treatment. Although the effect size was modest, the association between weight gain and dosage reduction may be taken as an indication of awareness of the risks associated with obesity in this patient group, an aspect which is receiving increasing focus in clinical guidelines (2, 45).

TABLE 4 | Use of antipsychotic at baseline and follow-up.

	Full sample, N = 426		Use of AP at baseline and information on use of AP at follow-up for the same patient, n = 282
	Use of AP at baseline, n (%)	Use of AP at follow-up, n (%)	Discontinuation of AP, n (%)
First treatment schizophrenia spectrum	147 (78.6)	133 (74.3)	24 (16.8)
First treatment bipolar disorder	54 (53.5)	46 (49.5)	19 (36.5)
Multi-episode schizophrenia spectrum	59 (85.5)	58 (86.6)	2 (3.5)
Multi-episode bipolar disorder	30 (43.5)	28 (40.6)	5 (16.7)

AP, antipsychotic.

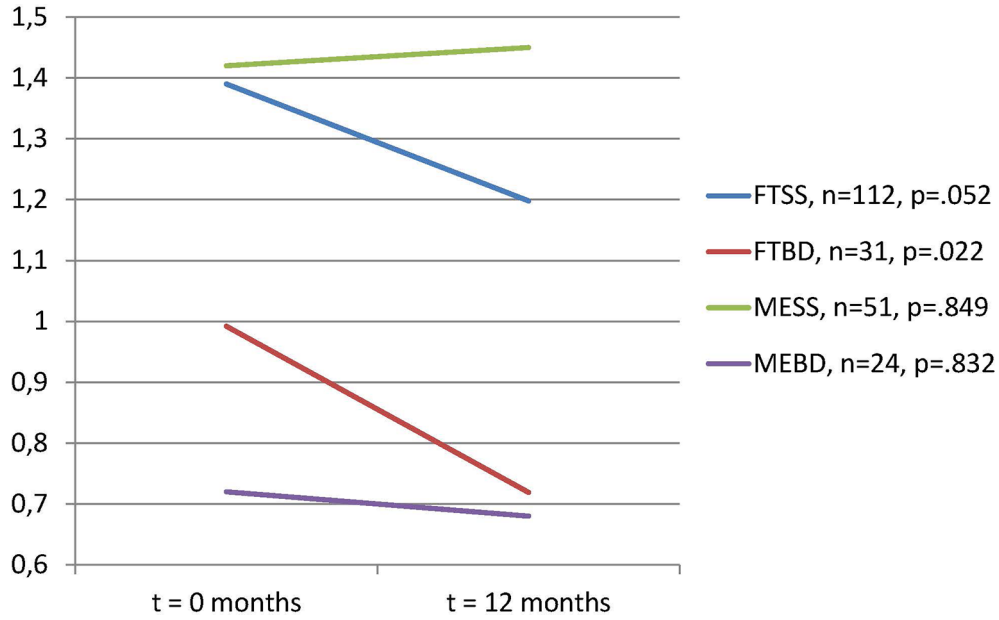

FIGURE 1 | Total dosage of prescribed antipsychotics per defined daily dose (PDD/DDD) of all antipsychotics in use, paired samples of subjects with dosages >0 at t = 0. Paired t-tests. N = 218 with information on PDD/DDD and use at both time points.

In the First Treatment Bipolar Disorder group, the baseline level of positive psychotic symptoms predicted dosage reduction of antipsychotics, although with a small to moderate effect size. The higher dosages of antipsychotics in the First Treatment Bipolar Disorder compared to the Multi-episode Bipolar Disorder group at baseline could thus partly be explained by the first treatment patients being closer in time to an acute phase with high symptom levels. Antipsychotics are recommended for the acute phase of mania (44), and the high dosages observed could be a transient response to treatment needs in this phase and thus in line with main guidelines (1, 2, 5). Taken together, our findings point to diagnostic-specific associations with dosage reductions in first treatment patients.

The discontinuation rates found in the First Treatment Schizophrenia Spectrum group are in line with previous findings (46). We found that high levels of functioning and problematic use of alcohol at baseline significantly predicted discontinuation in this group. These findings are clinically meaningful, as alcohol abuse has been shown to affect adherence to medical advice (45). To the best of our knowledge, there are no previous reports of discontinuations rates of antipsychotics in First Treatment Bipolar Disorder. The rate in this group is higher than that observed in the other three groups, again indicating that the medication at baseline is a transient response to acute mania. In the First Treatment Bipolar Disorder group we found that increased age was a significant predictor of discontinuation of antipsychotics. Increased age is usually associated with improved adherence to treatment; however, in this case the patients discontinued antipsychotic treatment and changed to other psychopharmacological agents. A possible explanation could be that clinicians felt more confident of their diagnosis of BD in the older patients and thus were more prone to change to mood stabilizing medication for secondary prevention.

In this context, we should note that adherence to prescribed medication is a major challenge for first episode patients (47, 48). In addition, previous studies have found that physicians' adherence to guidelines is adequate in the initial phase of treatment but reduces over time (49). The recommendation of low dosages for first-treatment phases also pertains to the acute phases of illness, and previous studies indicate that lower acute phase dosages is an achievable goal (50). Our findings may thus indicate that early dosage practices are more driven by acute phase symptoms than by guideline recommendations. Relapse prevention dosages are however in line with recommendations, with a particular emphasis on risk associated with obesity in First Treatment Schizophrenia Spectrum. In First Treatment Bipolar Disorder, antipsychotics appear to be used mainly as an acute phase treatment and not as relapse prevention.

The main strength of the current study is the well characterized and relatively large prospective sample of first-treatment patients with, both schizophrenia- and bipolar spectrum disorders followed over the early treatment phase. The catchment area based and consecutive sampling procedure, including both in-and outpatient treatment services, gives the sample a high degree of representation. The study also has some limitations. Although our cohorts of first treatment patients are large compared to other studies of bipolar disorders, some of the subgroups were relatively small which may increase the risk of type II errors. The study also used cross-sectional assessments at two time points, and there were thus restricted possibilities for a temporal sequencing of events in the follow-up period.

In conclusion, a statistically significant reduction in dosages over the first 12 months of treatment was associated with early medication-related weight increase in first treatment schizophrenia, and with higher levels of psychotic symptoms at baseline in first treatment

bipolar disorder. Our findings thus document potentially clinically meaningful diagnostic differences in patterns of prescription and adaptive prescription changes in the early treatment phases of psychotic disorders, and add to the understanding of what drives early antipsychotic dosage change. We did not find indications of lower dosages of antipsychotics at baseline in first-treatment patients compared to multi-episode patients across diagnostic groups. Further, our findings emphasize the risks for discontinuation associated with all types of substance abuse, including alcohol. There is a need for more specific treatment recommendations for the use of antipsychotics in the early treated phases of bipolar disorder. Further studies should preferably investigate motivations for medication change for the physicians, in addition to patients.

ETHICS STATEMENT

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by The Regional Committee on Research Ethics of South Eastern Norway.

AUTHOR CONTRIBUTIONS

PR and IM contributed to the conception and design of the study, performed the statistical analysis, and wrote the first draft of the manuscript. PR organized the database. ER, TV, OA, and NS wrote sections of the manuscript. All authors contributed to manuscript revision, and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00649/full#supplementary-material

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REVIEW
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Early Detection and Outcome in Borderline Personality Disorder

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Borderline personality disorder (BPD) is a severe and heterogeneous mental disorder that is known to have the onset in young age, often in adolescence. For this reason, it is of fundamental importance to identify clinical conditions of childhood and adolescence that present a high risk to evolve in BPD. Investigations indicate that early borderline pathology (before 19 years) predict long-term deficits in functioning, and a higher percentage of these patients continue to present some BPD symptoms up to 20 years. There is a general accordance among investigators that good competence in both childhood and early adulthood is the main predictive factor of excellent recovery in BPD patients. Some authors suggest that specific childhood personality traits can to be considered precursors of adult BPD, as well as some clinical conditions: disruptive behaviours, disturbance in attention and emotional regulation, conduct disorders, substance use disorders, and attention-deficit-hyperactivity disorder. Unfortunately, diagnosis and treatment of BPD is usually delayed, also because some clinicians are reluctant to diagnose BPD in younger individuals. Instead, the early identification of BPD symptoms have important clinical implications in terms of precocious intervention programs, and guarantees that young people with personality disorders obtain appropriate treatments. This review is aimed to collect the current evidences on early risk and protective factors in young people that may predict BPD onset, course, and outcome.

Keywords: borderline personality disorder, prodromal factors, early symptoms, childhood, adolescence, outcome

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INTRODUCTION

Borderline personality disorder (BPD) is a severe and heterogeneous mental disturbance connoted by a pattern of identity diffusion, interpersonal disturbances, and chronic instability, with episodes of severe affective and impulsive dyscontrol (1). Personality disorders (PD) do not suddenly emerge in the adulthood; in fact, prodromal signs and processes that confer vulnerability to later personality pathology are already present in young age, often in adolescence (2–5). In adolescents, epidemiological data reported a point prevalence around 0.9%, but studies in this age group are still scarce (6). Cumulative prevalence rates of BPD in youths are respectively 1.4% and 3.2% at 16 years and at 22 years. In mental health setting, the diagnosis of BPD in adolescence reach a prevalence of 11% in psychiatric outpatients and up to 50% in inpatients (2, 6–8). Investigations indicate that early borderline pathology (before 19 years) predicts long-term deficits in functioning, and a higher percentage of these patients continue to present some BPD symptoms up to 20 years. (9) A considerable proportion of these individuals continue to suffer from borderline symptoms up to 20 years (10).

For this reason, clinical conditions of childhood and adolescence that present a high risk to evolve in BPD should be carefully monitored. Unfortunately, diagnosis and treatment of BPD is

usually delayed as some symptoms are underestimated and clinician have hesitation to diagnose BPD in younger individuals. Stigma, the incompleteness of personality development in this age group, and similarities between physiological adolescent upheaval and BPD symptoms are the main reasons for this reluctance (11). Indeed, early identification of BPD symptoms may promote early intervention programs that should guarantee appropriate treatments in young people. Some retrospective studies in adult patients (12, 13) showed that the mean age of first psychiatric contact was 17 to 18 years and that the common failure in the diagnosis at first presentation resulted in losing the opportunity to set up early interventions. Several factors, including precocious environmental factors, child and adolescent temperamental characteristics, early psychopathological features, and neurobiological correlates were identified as predictors of early BPD onset. Although the importance of an early diagnosis to improve long-term outcome of the disorder is widely accepted, this issue is not extensively studied and many questions still remain open. In order to improve our knowledge on risk factors in young people that may predict early BPD onset, course, and outcome, we conducted a review to collect and summarize the available evidence in literature.

METHODS

In October 2018, an electronic search on PubMed about early prodromal factors and precursors of BPD without any filter or MESH restriction was performed, using the following search string: "borderline personality disorder" AND "early symptoms" OR "borderline personality disorder" AND "precursors" OR "borderline personality disorder" AND "prodromal factors" OR "borderline personality disorder" AND "childhood" OR "borderline personality disorder" AND "adolescence" OR "borderline personality disorder" AND "early symptoms" AND "outcome." This string ensured a high sensitive search for the published works indexed in PubMed. A limitation of this review is that PubMed was the only database used to search the articles. Overlapping studies were excluded. We included the following types of publications: controlled trials, observational studies, longitudinal and prospective studies, cohort studies, and reviews from January 2000 until November 2018. Publications must concern early factors that predict BPD in young age as the main topic. We excluded publications written in a language other than English.

RESULTS

The search described in the previous section provided 2,193 records, and among them 1,788 overlapping studies were excluded. Total records included in the review were 405. Eligibility status for articles was determined in the following way: 1) all studies were screened on the basis of title and abstract; 2) papers that have passed the initial screening were reviewed on the basis of a careful examination of the full manuscript content. Three hundred and four were excluded because they did not fit the objective of the review, 19 because were not written in English, 3 for the lack of the complete manuscript. Thus, this review included 79 records, including 7 reviews, 51 longitudinal/prospective studies, 3 retrospective studies, 1 observational study, 1 commentary/expert article, and 16 controlled trials.

BPD symptoms and diagnosis were assessed with the following evaluation instrument: in the majority of cases for adult was used the official tool of DSM (Structured Clinical Interview for DSM-IV Axis II Personality Disorders SCID-II, and for DSM-5 Personality Disorders SCID-PD). Specifically for children and adolescents, most of the studies adopted the Borderline Personality Features Scale for Children (BPFS-C) (14) including a newly developed parent report version of the measure (BPFS-P) (15).

Number of studies participants ranged between 40 and 6,050. Seven studies included only females; one study included only males; 3 studies did not report the gender percentage; the remaining studies had an equal distribution of males and females. The vast majority of patients in the reviewed articles was Caucasian and this is a limitation both in terms of clinical and socio-cultural limitations. Duration of the longitudinal/prospective studies presented a wide range between 1 and 30 years. Ninety percent of studies enrolled participants from the community (40% of these were "high-risk" subjects on the basis of the presence of relevant risk factors, i.e. economic disadvantages), 10% from the clinical settings. Drop-out rates were acceptable, with a retention ranged between 43% and 96%. Majority of studies had a retention ≥70%.

The selection process and a schematic representation of the results are represented in the literature search flowchart (**Figure 1**).

DISCUSSION

Precocious Environmental Factors

Several studies have identified a broad range of environmental factors that are related to subsequent risk for BPD, including socio-economic status, family psychopathology, parent-child relationship, and maltreatments or other traumatic events. In recent years, a growing number of investigations has been focused on the powerful role of social influences, particularly bullying and rejection by peer groups.

Family-Related Factors and Early BPD

Only two longitudinal studies specifically investigated the association between socioeconomic status (low income, low educational level, and low status occupation) and early onset of BPD. In the study performed by Cohen and collaborators (16) the authors examined the effects of familial socioeconomic status on the severity of schizotypal and borderline personality disorders symptoms in a general population of 608 children and adolescents living in urban, suburban, and rural residence. These subjects were longitudinally studied between ages 10 and 36. The authors concluded that lower socioeconomic status predicted BPD symptoms and the effect of magnitude remained stable over time. The same results were found in the second study with a similar design and objective in a large community sample of 766 children (17).

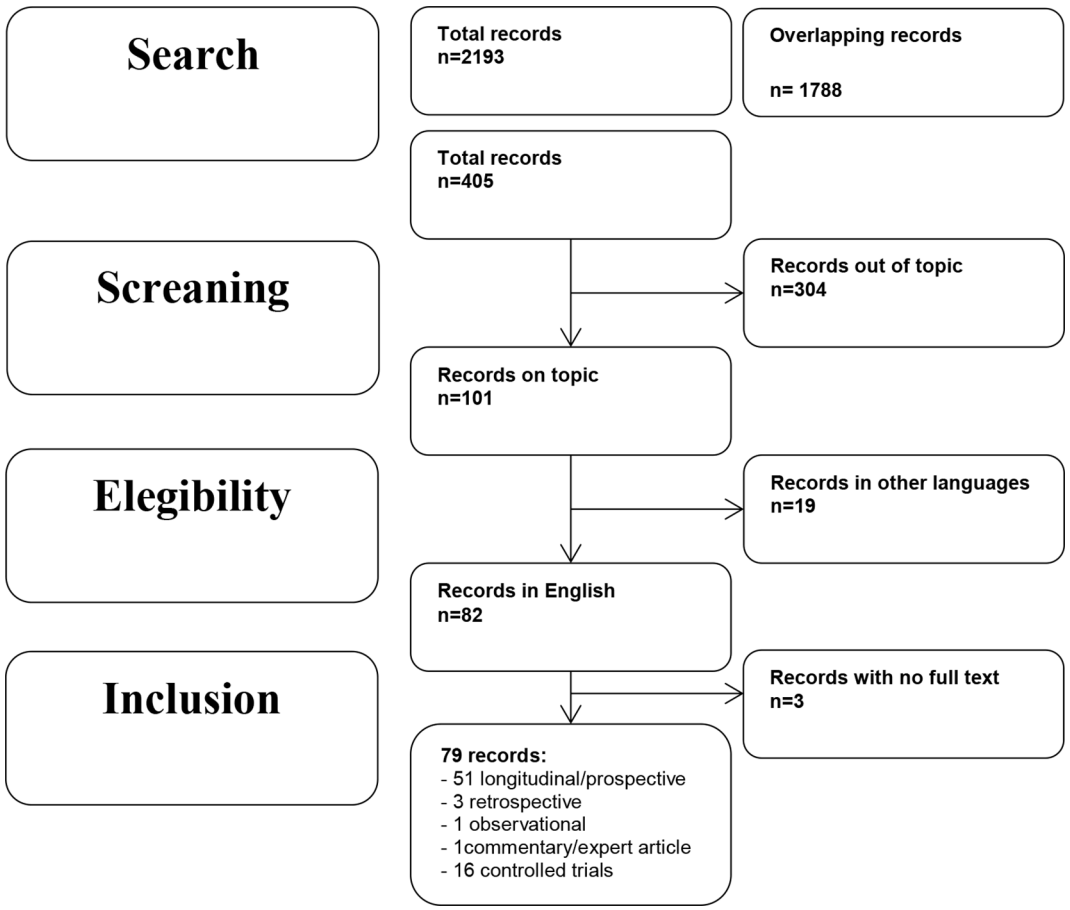

FIGURE 1 | Literature search flowchart.

Other investigations evaluated the impact of family environment including economic adversities and parents' psychopathology on precocious onset of BPD. Four studies were aimed to verify the association with poverty and maladaptive behaviours, such as hitting, shouting, hostility, and parent conflicts, on early BPD. One study was conducted in a large sample of 6,050 mothers and their children recruited in the community (18), while three investigations were performed in samples (ranged between 113 to 2,282 participants) of high-risk subjects (19–21). Winsper and colleagues (18) observed mothers and children for 12 years and found that family adversities and maladaptive parental behaviours predicted increased risk for BPD in very young age (11 years). Stepp and colleagues (19–21) showed that poverty condition that required public assistance may predict BPD symptoms during adolescence.

Theories on the role of parents' psychopathology, in particular maternal BPD, as putative precursor to BPD in children and adolescents (22, 23), have found empirical support from three longitudinal studies (24–26) and one controlled study (27). Barnow and colleagues (24) and Reinelt and collaborators (26) studied a large community sample (respectively, 286 and 295 subjects) during 5 years, while Stepp and colleagues' study (25) included a sample of 816 subjects from the community who were observed for 16 years. Results were consistent in identifying maternal BPD as predictor of BPD onset in adolescence (15 years) (24, 26) and early adulthood (24 years) (25). Mahan and colleagues (27) evaluated the association between maternal BPD, maternal psychological control, and onset of BPD in adolescence. The authors sampled 28 mothers with a diagnosis of BPD, 28 control comparisons, and their adolescent offspring. All subjects were assessed for borderline features. Maternal psychological control was found positively associated with borderline features of mothers and with affective instability of offspring with an increased risk for adolescents of developing BPD themselves.

The impact of other maternal psychopathological dimensions on BPD onset in adolescents was evaluated. In a study conducted in a high-risk sample of 700 youths that were studied from mid-adolescence to young adulthood, authors observed that maternal externalizing disorder and offspring internalizing disorder were significant associated with BPD risk (28). Study performed by Winsper and colleagues (9) showed that maternal anxiety and depression during pregnancy predict early BPD in sons/daughters. In a similar way, depressive symptoms and antisocial personality disorder (ASPD) in caregivers predicted the onset of BPD in adolescence (14–17 years) in a sample of 2,212 high-risk subjects (20). Actually, this relation was significant in bivariate analyses, but not in final analyses of Stepp's study.

Other three longitudinal studies aimed to evaluate the effects of maternal ego integration and impulsivity, medical problems, and interpersonal disturbances in producing early BPD symptoms in children/adolescents did not find any significant association (17, 29, 30).

As regards relationship between parents and children, studies obtained controversial findings. Among seven investigations, four reported a significant association between dysfunctional parent-child relationship and development of precocious BPD symptoms. Stepp and colleagues (25) evaluated in a 16-year follow-up study whether cohesion, discord, and support in relationships had an impact on BPD onset in 816 subjects from the community. The authors found that mother-child discord predicted BPD at 30 years. In accordance with the environment-genes interactions theory, Hammen and collaborators (31) observed a significant association between low relationship quality and BPD onset at 20 years in 385 subjects who had a particular genotype for the oxytocin receptor gene (AA/AG). Higher level of role confusion and disoriented behaviours in parent-young adult interaction seems to predict early borderline symptoms, in particular self-injuries and suicidality in late adolescence (32). Moreover, in a naturalistic study on the effects of inadequate parent-child boundaries, relationships centered on guilt induction, psychological control, and triangulation (children who mediated parental marital conflict) were found associated with children's BPD features in 301 adolescents with severe behavioural and emotional disorders (33). Divergent findings were reported by two studies that did not show any significant association between parent-child relationship and onset of BPD in young age (30, 34).

Trauma-Related Factors and Early BPD

The role of early traumatic events and maltreatments in the onset, course, and pathogenesis of BPD was extensively examined by several studies. The World Health Organization categorized maltreatment into physical neglect, emotional neglect, emotional abuse, physical abuse, and sexual abuse (35). Children who are abused and/or neglected show deficits of functioning in several mental areas that are associated with BPD symptoms (36–40). Among 15 investigations on this topic, 5 did not report a significant correlation between maltreatment/trauma and BPD symptoms in childhood and adolescence. On the contrary, in 10 longitudinal studies with a duration ranged between 8 and 30 years in large community samples of children and adolescents (ranging between 113 and 2,764 participants) a significant relation was reported between early BPD onset and emotional and physical neglect and verbal abuse (30, 41–43); cumulative traumas (15); emotional abuse (44); physical abuse (15, 30, 45); sexual abuse (15, 20, 30, 44). Lyons-Ruth et al. (46) also stated that "abuse experiences could not account for the independent effect of early maternal withdrawal on borderline symptoms." It is required that both abuse and these features of early caregiver–child interaction are present and produce their effects. Experiences of child abuse and neglect reciprocally interact with genes expressions influencing the emergence and timing of normal developmental processes and predicting child or adolescent borderline personality (47). Cicchetti and colleagues evaluated expression of the oxytocin receptor (OXTR) and the FK506 binding protein 5 (FKBP5) gene polymorphisms among 1,051 maltreated and non-maltreated children. Findings underlined the importance of the interaction between the genetic variants associated and maltreatment experiences in increasing the risk for early borderline symptomatology. Moreover, these associations were different between females and males (48). Females were more at risk for borderline symptoms when they add minor alleles of the two candidate genes. In contrast, males presented an increased for borderline symptoms when they presented major alleles. It is noticeable that the maltreatment-gene-gender interaction for females is consistent with a diathesis-stress model. In contrast, a different picture can be identified in males: frequent crossover interactions suggested a differential sensitivity to environment model.

In more recent years, particular attention was paid to the role of social group interactions, in particular peer relationships, in the development of psychiatric symptoms in childhood and adolescence. Dysfunctional relationships with peer may contribute to or promote the onset of BPD (2, 49). Being bullied during childhood predicted high risk to develop BPD not only in adulthood (2) but also in early adolescence (50–54). Five longitudinal studies specifically investigated this topic. Wolke and collaborators (50) participated in a 12-year prospective study that recruited 6,050 mothers and offspring enrolled in the Avon Longitudinal of Parents and Children (ALSPAC) study. Findings showed that chronic exposure to peer victimization during childhood can be considered a risk factor for the development of BPD symptoms in childhood (12 years). Among the same subjects of ALSPAC, Lereya and collaborators (51) evaluated the effect of exposure to bully between 7 and 10 years of age in 4,810 children and adolescents. Authors concluded that being bullied during childhood increased the risk of self-injuries in late adolescence, particularly if there is a concomitant exposure to an adverse family environment. ALSPAC data was also used by Winsper and colleagues (52) to assess the relationships between childhood disregulated behaviours, environmental factors (including bully victimization), and presence of BPD symptoms at 11 years. Bully victimization significantly predicted BPD, depressive and psychotic symptoms in children who had disregulated behaviours. Similar findings were obtained by data from 875 participants to the McMaster Teen Study (53), in which the association between early BPD development and chronic bullying involvement was confirmed in children with a reactive temperament. Antila et al. (54) verified the association of bullying behaviour in adolescence and PDs in early adulthood with particular attention to gender differences in 508 inpatient adolescents. They concluded that female, but not male, victims of bullying had a fourfold increased risk to develop PD, including BPD, in young age.

In summary, among precocious environmental factors, the most strong associations with the early onset of BPD are represented by verbal, physical, sexual abuses, maternal withdrawal/neglect in childhood, and chronic exposure to peer bully victimization during infancy. In addition, a smaller number of studies in a wide sample of patients monitored for many years showed that maternal psychopathology (BPD and

depression), economic adversities, and maladaptive parental behaviours promoted the early development of BPD in the offspring. It remains open and understudied how genetic factors may interact with the environmental factors in promoting precocious BPD symptoms. Results are displayed in **Table 1**.

Child and Adolescent Temperament and Personality Factors

The investigation of intrapsychic factors, including temperamental characteristics and personality trait profiles in childhood and adolescence, is fundamental to recognize predictors of BPD at an early phase. Researchers identified several personality traits in children or adolescents, including affective instability, negative affectivity, negative emotionality, inappropriate anger, poor emotional control, impulsivity, and aggression, that could prepare to borderline pathology [e.g., Refs. (45, 55–57)]. Few studies evaluated the relation of childhood personality traits to BPD in adulthood (30, 44, 58). Fifteen investigations examined the relationship between temperament or personality features associated with early BPD symptoms. Only one study (30) did not find any significant association in the final analyses.

Two studies adopted the Cloninger's model to evaluate the association between temperamental patterns in childhood or adolescence and onset of BPD (59, 60). In the first study (59) temperamental characteristics were retrospectively collected in 180 depressed adult patients with personality disorders. Although it is hard to distinguish temperamental dimensions in personality of adult patients, authors found that high harm avoidance and novelty seeking (in combination with childhood experiences and adolescent psychopathology) can be considered predictive of early BPD. In line with this investigation, Kaess et al. (60) observed in a controlled study comparing 33 BPD adolescents, 35 clinical controls, and 31 healthy subjects that high harm avoidance and novelty seeking but low reward dependence represent a biological vulnerability for developing BPD.

Across other temperamental traits, aggressive behaviors in childhood and early adolescence was associated to onset of BPD. Crick and collaborators (55) investigated different subtypes of aggression in a prospective study that recruited 400 children and found that relational aggression, but not physical aggression, emerged as a significant predictor for BPD features. This result was confirmed by Underwood (61) in a prospective study with the same objective. Similarly, Cramer et al. (62) performed a longitudinal study, in which childhood personality traits were assessed at age 11 in 100 subjects and provided evidence that aggression and impulsivity are two predictive traits for BPD traits at 23 years. Vaillancourt and colleagues (57) prospectively found in 484 children and adolescents that aggression predicted the diagnosis of BPD at 14 years with some gender differences: relational aggression was the predominant predictor in boys, while physical aggression was the strongest predictor in girls.

Negative emotionality, in terms of negative affectivity and poor emotional control, is another important precocious factor associated to BPD onset. Lenzenweger and collaborators (22) conducted a community 3-year study with 250 adolescents/young adults, aimed to evaluate whether negative emotionality and other dimensions such as affiliation, constraint, and agency might impact on early onset of BPD. Findings showed that negative emotionality and low constraint predicted BPD at 19 years, and lower agency predicted increasing of BPD during time. Tragesser and collaborators (63) in a high-risk population of 353 subjects of 18 years reported a significant association of negative affectivity and impulsivity in childhood with BPD at 20 years. Similar findings were obtained by Stepp and collaborators in two following investigations (19, 20) with a larger sample ranged between 2,212 and 2,282 children/adolescents. They confirmed the role of negative affectivity and impulsivity in predicting BPD, even at 14 years (19), and highlighted the importance of higher activity and lower sociability in childhood as precursors of the disorder. As concerns negative emotionality, the result was replicated in two following studies (5, 64) with similar design and number of participants. In addition, Hallquist and colleagues (64) found that low self-control may predict BPD at 14 years and a worsening self-control increased BPD symptoms during the time.

Low self-control, impulsivity, and affective instability are three tightly connected dimensions that in very young age can be considered predictors for developing borderline pathology. Several investigations have assessed the influence of these constructs in childhood on later BPD symptoms. Tragesser and colleagues (65) reported that affective instability and impulsivity predicted BPD onset at 20 years. Gratz et al. (66) highlighted, in a sample of 263 children (9–13 years), the importance of interrelationship among these two relevant personality traits (affective instability and impulsivity) with low self- and emotion regulation, and with childhood borderline personality symptoms. Lower self-control and higher level of impulsivity were also identified as predictors of a diagnosis of BPD at 12 years in a 7 years twins study conducted in 1,116 children (around 5 years old) (45).

Only one study investigated the impact of anger, as temperamental trait, in childhood on BPD in adolescence/adulthood. Crawford and colleagues (17) showed a significant association between anger/tantrum dimension and BPD symptoms in 766 children who were followed for 20 years.

Five studies explored the interaction between child/adolescent personality traits and environmental or neurobiological factors in development of precocious BPD. Four investigations examined the effect of the relationships between temperamental characteristics and childhood maltreatment on the onset of BPD. Jovev et al. (43) studied the interaction between emotional control and affiliation traits, parental maltreatment and BPD in 245 children aged between 11 and 13 years. They observed that specific early temperamental features, particularly low emotional control, interact with familial maltreatment in promoting BPD symptoms across early to middle adolescence. On the other hand, parental abuse could have a moderating role in the presence of low affiliation. Martin-Blanco and colleagues (67) found in 130 subjects with early BPD that neuroticism-anxiety, aggression-hostility dimensions, and emotional abuse were independent risk factors associated with BPD. Two studies of the same year performed by Sharp et al. (68) and Stepp et al. (21) with different sample amplitude and duration, respectively, followed 730

adolescents for 1 year and 113 adolescents studied for 13 years and reported that the effect of lower self-control in promoting early onset of BPD was mediated by harsh familial discipline (68), and the impact of negative affectivity on early BPD was moderated by family adversities (21).

One study evaluated in 153 healthy adolescents the interaction of a temperamental risk factor and a neurobiological risk factor in predicting the emergence of BPD during early adolescence (69). Authors examined several temperamental factors and volumetric measures of hippocampal asymmetry. Results showed that subjects were more likely to have BPD symptoms in presence of high affiliation, low effortful control, and rightward hippocampal asymmetry.

In summary, temperamental traits in childhood, including relational aggression, impulsivity, low emotional control, and negative affectivity, are robust predictors of early onset of BPD. Some evidences support the role of the interaction between temperamental features (low emotional control, negative affectivity, and low affiliation) and familial environment (parental maltreatment, harsh discipline, and familial adversities) in developing BPD.

Early Psychopathological Features and Diagnosis

Available evidences highlighted that internalizing and externalizing psychopathology is often present before the onset of BPD in adolescents. Externalizing pathology includes conduct disturbances, oppositional defiant disorder, attention-deficit/hyperactivity symptoms, impulsive-aggressive behaviours, self-injuries, and substance use disorder; while internalizing pathology mainly involves depression and anxiety, but also dissociation and suicidality. In addition, obsessive–compulsive disorder, separation anxiety disorder, and social phobia were frequently observed in adolescent populations (2, 11, 70, 71). Some authors suggested that internalizing and externalizing disorders emerge in pre-adolescence as anxiety and depressive symptoms in females, and ADHD, conduct problems in males. These disorders may form a platform on which develops personality pathology during adolescence (72, 73). In the context of predisposing biological vulnerabilities and interacting stressful life events, these antecedent disorders represent a predisposing condition that, if untreated, may contribute to the onset of personality pathology during adolescence (73).

Seventeen investigations explored the psychopathological conditions predicting BPD in youths. Three of them did not find any significant association. One study investigated the effect of interaction of negative emotionality and internalizing psychopathology on early onset of BPD (25). Conway and collaborators (28) combined risk factors into a more comprehensive developmental model of borderline pathology in a community sample of 815 youths (15 years of age) at high risk for psychopathology due to maternal depression. In fact, they examined the effects between several environmental stressors, including occurrence of acute stressors and chronic stressors across individual, family, peer, and academic contexts, and personal characteristics to give a contribution to the hypothesis that BPD results from the complex interaction between pathogenic environments and individual vulnerabilities. Results showed that only adolescent internalizing psychopathology and trait of negative affectivity continued to predict borderline pathology after controlling for the presence of other risk factors. Krabbendam and colleagues (74) identified dissociation (internalizing symptom) significantly associated with onset of BPD at 20 years in a prospective study in which 184 adolescents were followed for 6 years. Self-injuries, another symptom related to internalizing psychopathology, was found predictive of early BPD in one investigation performed in 77 adolescent psychiatric inpatients and 50 young detainees (75). Sharp and colleagues (68) in a 1-year study including 730 adolescents (16 years) found that anxiety and depression (internalizing symptoms) predicted BPD at 17 years. Depression recurred as predictor of early BPD in other three studies (25, 76, 77) in samples including respectively 158, 524, and 816 subjects aged between 14 and 17 years. Studies lasted from 8 to 16 years of follow-up. In these investigations were identified as predictors of early BPD substance use disorder (25, 76, 78) and attention deficit hyperactivity disorder (ADHD) (77). It is noticeable that both internalizing and externalizing disorders are implicated in promoting BPD in young patients. Belsky and collaborators (45), Bornovalova and colleagues (78), and Bo and Kongerslev (79) confirmed the role of both internalizing and externalizing psychopathological conditions to predict early BPD. In particular, Bo and Kongerslev (79) compared 46 children and adolescents with BPD and 62 children and adolescents with other clinical conditions. Findings showed that high level of psychopathology (internalizing and externalizing), poor mentalizing abilities, and attachment problems were strictly associated to BPD in adolescents compared with psychiatric disorders other than BPD. In addition, Bornalova et al. (78) reported that higher number of BPD traits predicted earlier onset and faster worsening of substance use symptoms and that substance use slows the reduction of BPD traits in youths.

Some studies showed a significant association between externalizing pathologies and early onset of BPD. Miller and colleagues (80) observed a significant relationship between ADHD in childhood and BPD at 18 years in a 10 years follow-up study including 181 children. Two following studies (71, 81) confirmed this association and also identified the oppositional defiant disorder in childhood as predictor of BPD respectively at 24 and 14 years. Similar findings were observed by Stepp and colleagues (20) that found a significant relationship of adolescent opposite defiant disorder and conduct disorder with BPD onset at age ranged between 14 and 17 years.

In the study performed by Wolke et al. (50) and described in the previous section, it was found that any Axis I diagnosis predicted BPD at very young age of 12 years. A recent controlled study performed by Thompson et al. (82) evaluated the prevalence of psychotic-like symptoms in 171 subjects of 15–18 years with BPD features. The authors found that adolescents with full-threshold BPD presented more confusion, paranoid ideation, visual hallucinations, and odd thoughts than adolescents with sub-threshold BPD symptoms and adolescents with no BPD symptoms.

In summary, among early psychopathological factors, both internalizing and externalizing disorders in childhood and adolescence are involved in producing early BPD in adult. In particular, the most robust associations are represented by depression, substance use disorder, ADHD, and oppositional defiant disorder. As the precise role of each of these potential etiological factors in determining risk for BPD is still unclear and there is a degree of overlap between them, their interaction with environmental stress has to be carefully considered. An additional hypothesis to explain the overlap of internalizing and externalizing disorders is that BPD pathology expresses itself in early stages of the disorder mainly with externalizing behaviours, although features of internalizing disorders are also present. When BPD adolescents grow up behavioral manifestations of externalizing disorders diminish in favour of a stronger expression of internalizing pathology (83). Result are displayed in **Table 2**.

Neuroimaging and Early BPD

To date, no functional brain imaging studies have been published in adolescent populations with BPD. Neuroimaging studies of these subjects only focused on structural abnormalities, including both changes in grey and white matter.

It is interesting to evaluate the neurobiological underpinnings of younger populations with BPD symptoms at their beginnings in order to minimize the burden of confounders: some factors, such as prolonged duration of illness, pharmacotherapy, and recurring traumas, could themselves produce changes of brain structures (84, 85).

Orbitofrontal cortex (OFC) was found reduced in volume by two studies which compared BPD to control groups (84, 86). By means of region of interest (ROI) methodology, Chanen et al. (84) found that 20 BPD patients of 15–19 years showed a right-sided loss of OFC grey matter, reversing the normal (right > left) asymmetry of brain area volume, in comparison to 20 control subjects. In the study performed by Brunner et al. (86) using voxel-based morphometry (VBM) techniques, 20 BPD patients of 14–18 years displayed a significant shrinking of the left OFC and bilateral dorsolateral prefrontal cortex (DLPFC) compared with a group of 20 healthy controls. Authors found no differences between BPD group and 20 patients with other mental disorders. Using the same cohort of patients but varying imaging technics (diffusion tensor imaging, DTI), Maier-Hein et al. (87) found that the bilateral fornices of BPD group had lower myelination and their white matter bundles were less organized when compared to clinical and healthy controls. Thalamus and hippocampus, as well as the heteromodal association cortex, showed white matter disrupted connections in BPD patients. Such findings led the authors to argue that adolescents with BPD lack a normally functioning network involved in emotion processing. Reanalyzing the same data by means of another software, Richter et al. (85) found that BPD patients' right amygdala was smaller than healthy (but not clinical) controls' right amygdala. In the same study the authors demonstrated that hippocampal volume of BPD patients was the smaller in comparison to both control groups. In the same sample, Walterfang et al. (88) showed that BPD patients had the same dimension of corpus callosum as healthy controls.

Two studies reported a volume reduction of anterior cingulate cortex (ACC) (89, 90) in adolescents with BPD. In the study performed by Whittle et al. (89) a shrinking in left AC cortex volume (across limbic and paralimbic regions) was found in 15 female patients (mean age 17,39) with BPD compared to 15 controls (mean age 19,65). Goodman et al. (90) found that 13 BPD/major depressive disorder (MDD) patients (mean age 15,8) had smaller relative volume in a part of the ACC, Brodmann area 24, in comparison to healthy subjects (mean age 16,2).

A study performed by Jovev et al. (43) has already been cited in a previous paragraph (see child and adolescent temperament and personality factors). The most important finding of the study is the moderator role of atypical rightward hippocampal asymmetry in the relationship between temperament traits and BPD symptoms in adolescents aged between 11 and 13 years. High scores in both affiliation and atypical rightward hippocampal asymmetry were good predictors of BPD symptoms in boys. For girls, low effortful control was linked to strong BPD symptoms in the presence of atypical rightward hippocampal asymmetry. It is noticeable that abnormalities of hippocampus are involved in memory processes and in emotional response to memories (emotional regulation and emotional recognition).

In a Diffusion Tensor Imaging (DTI) study, New et al. (91) observed bilateral tract specific decreased fractional anisotropy (FA) in the inferior longitudinal fasciculus (fibre bundle connecting the temporal lobe and occipital lobe) in 14 BPD adolescents in comparison to 13 controls. Moreover, a lower FA in the uncinate and occipitofrontal fasciculi (the white matter tracts connecting parts of the limbic system to the OFC among other frontal regions) was found at follow-up analysis in BPD adolescents.

Mainly in accordance with adult findings, studies discussed above showed structural anomalies both in grey and white matter of frontolimbic areas that are deeply involved in emotion regulation and impulse control. Even if no functional studies on BPD adolescents have been carried out yet, white matter alterations are compatible with functional findings in adults (92) displaying disruption in frontolimbic system connectivity. Result are displayed in **Table 3**.

Effect of Early Detection on Course and Outcome of BPD

Detecting personality abnormalities in childhood and adolescence is a challenge for clinicians and is crucial to increase our knowledge of personality psychopathology in adulthood. Several investigations suggested that generally BPD symptoms have their onset in adolescence, reach a peak in early adulthood, and then decline during the course of life (83, 93). The decrease of BPD symptoms might be attributed to declining levels of impulsivity and dyscontrolled behaviors, while the persistence of a subsyndromal BPD is probably due to enduring negative affects (94). Other studies indicated that 20% of youths had an increase of PD symptoms over the decade from mid-adolescence to early adulthood (95). Only a few studies specifically investigated the effect of early onset on outcome and whether early factors may influence the trajectories of later BPD. In a 2-years follow-up

TABLE 1 | Summary of studies on precocious environmental factors.

Family related	Study design	Patients (n)/ recruitment age	Trial duration	Outcomes
Cohen et al. (16)	Longitudinal study; Community population	680; 9–18 years	22 years	Lower SES predicted BPD symptoms and effect magnitude remained stable over time
Crawford et al. (17)	Longitudinal study; Community population	766; At birth	20 years	Lower SES predicted BPD symptoms
Winsper et al. (18)	Longitudinal study; Community population	6050; At birth	12 years	Family adversity predicted BPD symptoms
Stepp et al. (19)	Longitudinal study; Community high-risk	2282 girls; 14–19 years	14 years	Receipt of public assistance predicted BPD symptoms across adolescence
Stepp et al. (19, 20)	Longitudinal study; Community high-risk	2212 girls; 14–17 years	4 years	Receipt of public assistance predicted BPD symptoms; Caregiver ASPD and depression predicted BPD (*bivariate analyses only*)
Stepp et al. (21)	Longitudinal study; Community high-risk	113 girls; 5 years	10–13 years	Family adversity predicted increases in BPD symptoms
Barnow et al. (24)	Longitudinal study; Community population	286; 10 years	5 years	Maternal BPD predicted offspring BPD symptoms at 15 years old.
Reinelt et al. (26)	Longitudinal study; Community population	295; 10 years	5 years	Maternal BPD symptoms predicted offspring BPD symptoms at 15 years old and this association was mediated by maladaptive parenting style/behavior
Stepp et al. (25)	Longitudinal study; Community population	816; 14–18 years	16 years	Maternal BPD and paternal substance use predicted offspring BPD symptoms at 24. Mother-child discord predicted BPD symptoms
Mahan et al. (27)	Controlled trial; Community population	28 BPD mothers; 28 ctrl mothers; adolescent sons (14–18 years)		Maternal psychological control positively associated with all mothers' BPD features and with adolescent affective instability with an increased risk for adolescents of developing BPD themselves
Conway et al. (28)	Longitudinal study; Community high-risk	700; 15 years	5 years	Maternal externalizing disorders and offspring internalizing disorders predicted BPD symptoms
Winsper et al. (99)	Longitudinal study; Community population	6050; At birth	12 years	Maternal anxiety and depression during pregnancy predicted BPD symptoms
Hammen et al. (31)	Longitudinal study; Community High Risk	385; 15 years	5 years	Relationship quality & oxytocin receptor genotype interacted to predict BPD symptoms: relationship quality predicted BPD symptoms for those with AA/AG genotype, not GG genotype
Lyons-Ruth et al. (32)	Longitudinal study; Community population	120; 20 years	21 years	Role confusion and disoriented behaviours in parent-young adult interaction predicted early BPD symptoms
Vanwoerden et al. (33)	Naturalistic study; community inpatients	301; 12–17 years		Relationships centered on guilt induction, psychological control and triangulation predicted BPD symptoms
Trauma-related factors	**Study design**	**Patients (n)/ recruitment age**	**Trial duration**	**Outcomes**
Johnson et al. (41)	Longitudinal study; Community population	738; <18 years	17 years	Supervision neglect predicted BPD symptoms
Johnson et al. (42)	Longitudinal study; Community population	793; 5 years	17 years	Verbal abuse predicted BPD symptoms
Carlson et al. (30)	Longitudinal study; Community high-risk	162;	28 years	Physical and sexual abuse predicted BPD symptoms
Jovev et al. (43)	Longitudinal study; Community population	245; 11–13 years	2 years	Abuse associated with BPD symptoms for children with low Affiliation
Cohen et al. (16)	Longitudinal study; Community population	680; 9–18 years	22 years	Cumulative trauma (physical and sexual abuse & other traumas) predicted BPD symptoms.
Bornovalova et al. (44)	Longitudinal study; Community population	2764;	7–13 years	Abuse (physical, sexual, emotional) predicted BPD symptoms
Belsky et al. (45)	Longitudinal study; Community population	1116; 5 years	7 years	Physical abuse predicted BPD symptoms
Stepp et al. (21)	Longitudinal study; Community high-risk	113; 16 years	3 years	Sexual abuse predicted BPD symptoms
Lyons-Ruth et al. (46)	Longitudinal study; Community high-risk	56; At birth	21 years	Concomitance of childhood abuse and maternal withdrawal predicted BPD symptoms
Wolke et al. (50)	Longitudinal study; Community population (ALSPAC)	6050; at birth	12 years	Chronic exposure to peer victimization predicted BPD symptoms
Lereya et al. (51)	Longitudinal study; Community population (ALSPAC)	4810; at birth	18 years	Bullying exposure increased risk of self-harm by exacerbating the effects of exposure to an adverse family environment
Winsper et al. (52)	Longitudinal study; Community population (ALSPAC)	4826; at birth	14 years	Bully victimisation predicted BPD, depression, and psychotic symptoms

(Continued)

TABLE 1 | Continued

Trauma-related factors	Study design	Patients (n)/ recruitment age	Trial duration	Outcomes
Haltigan and Vaillancourt (53)	Longitudinal study; Community population (McMaster Teen Study)	875; 10 years	6 years	Association between early BPD development and chronic bullying involvement in children with a reactive temperament
Antila et al. (54)	Longitudinal study; Clinical inpatients	508; 13–17 years	12 years	Increased (fourfold) risk for bullied female to develop PD, mostly BPD

ALSPAC, Avon Longitudinal Study of Parents and Children; ASPD, antisocial personality disorder; BPD, borderline personality disorder; ctrl, control; PD, personality disorder; SES, socioeconomic status.

study Gunderson et al. (96) found that an early history of abuse and neglect is associated with a poor prognosis in 160 adults with BPD. Among factors related to a poor long-term outcome, younger age at first treatment plays an important role together with affective instability, length of prior hospitalization, antisocial behaviors, comorbid substance use disorder, history of family psychiatric diseases, and dysfunctional relationship with parents (97, 98). Available studies indicated that long-term (until 20 years) functioning does not reach a satisfactory level, even when BPD achieve the clinical remission (99). In particular, BPD in childhood and adolescence predicted a long-lasting impairment in relational, occupational, and economic domains, as resulted by investigation performed by Winograd and collaborators (100) in 748 subjects prospectively followed for 20 years. These findings are consistent with those obtained in the investigation published by Crawford and colleagues (101). The authors highlighted that poor functional outcome persists for many years in adolescents who presented borderline features, including risk for substance use, depressive symptoms, interpersonal dysfunctions, and poor quality of life. Furthermore, Biskin and colleagues (102) in a 4-years prospective study found that woman who received a diagnosis of BPD in adolescence (49 patients) were less likely to have a stable occupation in comparison with other psychiatric disorders. Haltigan and Vaillancourt (53) evaluated the associations of childhood risk factors and trajectories during 4 years of later BPD features in a 875 community-based sample. Authors identified three distinct trajectories on the basis of symptoms and severity of course of BPD: low or stable, intermediate or stable, and elevated or rising. Attention-deficit hyperactivity disorder (ADHD) and somatization symptoms reported by child predicted elevated or rising trajectory, whereas anxiety reported by parent and ADHD symptoms reported by child predicted intermediate or stable trajectory. Presence of somatization symptoms reported by child was the only factor to differentiate the intermediate or stable and elevated or rising trajectory groups and may predict histrionic traits and hypochondria in later BPD. Moreover, young subjects with a reactive temperament who experienced chronic bullying by peers were more likely to be in a rising/elevated BPD features trajectory group. In a recent long-term follow-up study, Zanarini and colleagues (98) examined two levels of positive outcome at 20 years: "good and excellent recovery" achieved by BPD patients in comparison with other personality disorders (controls). Results showed that controls reached superior rates of both "good and excellent recovery" than BPD patients and that high competence in both childhood and adulthood was the main predictor of excellent recovery. Predictors associated with competence were higher IQ, good childhood work competence, and temperamental features including neuroticism and agreeableness. In particular, pattern of lower neuroticism and higher agreeableness can be interpreted as protective temperamental factors in childhood that allow them to develop a stable and cohesive personality (98, 103, 104).

CONCLUSIONS

On the basis of the results discussed in the previous paragraphs, adolescence represents a sensitive and vulnerable phase for the development of BPD (83). In order to identify and monitor high-risk population from premorbid manifestations it is important to characterize and detect main associated risk factors for early BPD (99, 105). Despite strong evidence supporting the benefits of early identification of BPD and the recommendations of treatment guidelines for BPD (10, 106), fear of stigmatization still constitutes a barrier to early diagnosis in clinical practice (2, 8). Different processes may contribute to the early onset of this personality disorder and several precocious risk factors are involved. Among family-related environmental factors, low socioeconomic status of family, economic adversities, and maladaptive behaviors in parents are three robust independent prospective risk factors for early BPD (16–21). Another significant precursor to BPD in childhood and adolescence is maternal psychopathology. The most significant result concerns the association between maternal BPD and offspring early BPD (24–26). The association between other maternal psychopathological conditions such as externalizing disorder history (28) and anxiety (9) with early BPD onset is still understudied. As concerns the relationships between parents and children, investigations obtained controversial results. Anyway, some kind of dysfunctional parent-child relationship was identified as a potential predictor of early BPD: discord between mother and child, significant role confusion, and disoriented behaviors in parents, inadequate parent-child boundaries, psychological control by parents, and low relationships quality in individuals with a particular genotype for the oxytocin receptor gene (25, 31–34). Among trauma-related environmental factors, verbal abuse, emotional abuse, physical abuse, sexual abuse, and emotional and physical neglect were identified as potential risk factors for young BPD (16, 21, 30, 41, 42, 44, 45, 48). Particular attention was paid to chronic exposure

TABLE 2 | Summary of studies on child and adolescent temperament and personality factors and early psychopathological features.

Temperament and personality factors	Study design	Patients (n)/ recruitment age	Trial duration	Outcomes
Joyce et al. (59)	Retrospective study; Clinical outpatients	180 depressed		High NS and HA (in combination with childhood experiences and adolescent psychopathology) predictive of early BPD
Kaess et al. (60)	Controlled trial; Clinical patients and community population	33 BPD, 35 CC, 15 31 HC; 13-19 years		High NS and HA and low RD biological vulnerability for developing BPD
Crick et al. (55)	Longitudinal study; Community population	400	1 year	Relational aggression predicted BPD symptoms
Underwood et al. (61)	Longitudinal study; Community population	255; 9 years	5 years	High social aggression in female predicted BPD symptoms
Cramer et al. (62)	Longitudinal study; Community population	100; 11 years	12 years	Impulsivity and aggression predicted BPD symptoms
Vaillancourt et al. (57)	Longitudinal study; Community population	484; 10 years	4 years	Aggression (relational in boys, physical in girls) predicted BPD symptoms
Lenzenweger et al. (22)	Longitudinal study; Community population	250;	3 years	Negative emotionality and low constraint predicted BPD at 19 years, and lower agency predicted increasing of BPD
Tragesser et al. (63)	Longitudinal study; Community high risk	353 years; 18 years	2 years	Negative affectivity and impulsivity predicted BPD symptoms
Stepp et al. (19)	Longitudinal study; Community high-risk	2282 girls; 14–19 years	14 years	Higher activity and lower sociability predicted increases in BPD symptoms, higher shyness predicted decreases in BPD symptoms
Stepp et al. (20)	Longitudinal study; Community high-risk	2212 girls; 14–17 years	4 years	Negative affectivity and impulsivity predicted BPD symptoms
Hallquist et al. (64)	Longitudinal study; Community high-risk	2228 girls; 5–8 years	10 years	Poor self-control predicted BPD symptoms at 14 ys and a worsening self-control increased BPD symptoms during time
Tragesser et al. (65)	Longitudinal study; Community high-risk	350; 18 years	2 years	Affective instability and impulsivity predicted BPD symptoms at 20 ys
Gratz et al. (66)	Retrospective study; Community population	263; 9–13 years		Significant interrelationship among affective instability and disinhibition, self- and emotion regulation deficits, and childhood borderline personality symptoms
Belsky et al. (45)	Longitudinal study; Community population	1116; 5 years	7 years	Lower self-control and higher impulsivity predicted BPD dx at 12 ys
Crawford et al. (17)	Longitudinal study; Community population	766; At birth	20 years	Anger/tantrums predicted BPD symptoms
Jovev et al. (43)	Longitudinal study; Community population	245; 11–13 years	3 years	Low emotional control robust predictor in developing BPD symptoms; parental abuse moderating role in the presence of low affiliation
Martin-Blanco et al. (67)	Retrospective study; Clinical inpatients	130		Neuroticism-anxiety and aggression-hostility dimensions, as well as emotional abuse, independently associated with BPD
Sharp et al. (68)	Longitudinal study; Community population	730; 16 years	1 year	Lower self-control predicted BPD symptoms via harsh familial discipline
Stepp et al. 2015	Longitudinal study; Community high-risk	113 girls; 5 years	10–13 years	Higher levels of negative affectivity and family adversity predicted BPD symptoms
Jovev et al. (69)	Controlled trial; Community high-risk	153; 11–13 years		BPD symptoms associated to high affiliation, low effortful control and rightward hippocampal asymmetry (differences between genders)
Early psychopathological features	**Study design**	**Patients (n)/ recruitment age**	**Trial duration**	**Outcomes**
Conway et al. (28)	Longitudinal study; Community high-risk	700; 15 years	5 years	Adolescent internalizing psychopathology and trait of negative affectivity predicted BPD symptoms
Krabbendam et al. (74)	Longitudinal study; Clinical incarcerated	184 girls; 16 years	3–6 years	Dissociation predicted BPD diagnosis at 20 ys
Koenig et al. (75)	Controlled trial; Clinical inpatients and incarcerated	77 inpatients; 16,6 mean age 50 detainees; 17,7		Self-injuries predicted BPD symptoms
Sharp et al., (68)	Longitudinal study; Community population	730; 16 years	1 year	Anxiety and depression predicted BPD symptoms at 17 ys
Ramklint et al. (76)	Longitudinal study; Clinical inpatiens	158; 15 ys mean age	16 years	MDD and substance use disorder predicted adult BPD diagnosis
Thatcher et al. (77)	Longitudinal study; Community population and clinical outpatients	355 CC; 169 HC; 16 ys mean age	8–12 years	MDD and ADHD predicted 'severe' BPD symptoms

(Continued)

TABLE 2 | Continued.

Early psychopathological features	Study design	Patients (n)/ recruitment age	Trial duration	Outcomes
Stepp et al. (25)	Longitudinal study; Community population	816; 14–18 years	16 years	Depression, substance use and suicidality predicted BPD symptoms
Belsky et al. (45)	Longitudinal study; Community population	1116; 5 years	7 years	Internalizing and externalizing conditions predicted early BPD
Bornovalova et al. (78)	Longitudinal study; Community population	1763 twins; 11–17 years	10 years	Higher levels of BPD traits contribute to earlier onset of substance use. Substance use slows the normative decline of BPD traits in youths
Bo and Kongerslev (79)	Controlled trial; Clinical outpatients	46 BPD; 62 CC; 13–18 years		High level of psychopathology, poor mentalizing abilities, and attachment problems were strictly associated to BPD compared to adolescents with psychiatric disorders other than BPD
Miller et al. (80)	Longitudinal study; Clinical outpatients	96 ADHD; 85 CC; 7–11 years	10 years	Childhood ADHD predicted BPD at 18 ys
Burke et al. (107)	Longitudinal study; Clinical outpatients	142 boys; 7–22 years	12–18 years	Oppositional-defiant disorder and ADHD symptoms through adolescence predicted BPD symptoms at 24 ys
Stepp et al. (81)	Longitudinal study; Community high-risk	1233 girls; 5–13 years	6–9 years	Oppositional-defiant disorder and ADHD symptoms predicted BPD symptoms at 14 ys
Stepp et al. (20)	Longitudinal study; Community high-risk	2212 girls; 14–17 years	4 years	Conduct disorder and oppositional-defiant disorder symptoms predicted BPD symptoms
Wolke et al. (50)	Longitudinal study; Community population (ALSPAC)	6050; at birth	12 years	Any Axis I diagnosis predicted BPD at 12 ys
Thompson et al. (82)	Controlled trial; Clinical outpatients	171; 15–18 years		Adolescents with full-threshold BPD reported more confusion, paranoia, visual hallucinations , and strange thoughts than the other two subgroups

ADHD, attention deficit hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; BPD, borderline personality disorder; CC, clinical controls; dx, diagnosis; fts, features; HA, harm avoidance; HC, healthy controls; MDD, major depressive disorder; NS, novelty seeking; RD, reward dependence; ys, years.

to peer victimization (49–54, 60). Some authors highlighted the importance of gene-environment interaction in development of BPD. In fact, subjects with particular genotypes have a greater risk to develop BPD in presence of predisposing environment conditions (48).

With regard to child and adolescent-related factors, a number of studies identified as main predictors of BPD at an early stage the following temperamental traits: aggressiveness (in particular relational aggression) (55, 57, 61, 62), impulsivity, affective instability, negative affectivity (5, 19, 22, 45, 63–65), and low emotional control by interaction with maltreatments (21, 43, 68).

Several psychopathological conditions in childhood and adolescence that potentially predict BPD were examined. Results showed that both internalizing (depression, anxiety, dissociation, self-harming) and externalizing (substance use disorder, ADHD, opposite defiant disorder, conduct disorder) disorders are involved in promoting BPD onset in young people (25, 44, 45, 74–81).

Extensive overlap with internalizing and externalizing psychopathology in adolescence and early adulthood can produce noticeable difficulties in the diagnosis of BPD. The new alternative model of personality disorders proposed by *DSM-5* could contribute to address these difficulties as it combines the traditional categorical approach with a dimensional traits model that is likely more sensitive to specific traits of early onset BPD. Of course this is only a hypothesis that needs to be confirmed by data.

Findings from neuroimaging studies allow us to verify that in adolescents with BPD are already present some abnormalities that we can find in adulthood. Available studies investigated only the structural aspects, as functional brain imaging studies have not been conducted in adolescents to our knowledge. The most important abnormalities concern fronto-limbic structures. In particular, the reduction of volume of OFC (84, 86), ACC (89, 90), and hippocampal asymmetry (43) were found in early BPD compared with controls. Also in white matter, some specific alterations were observed: inferior longitudinal fasciculus and the fornix showed a diminished fractional anisotropy in BPD adolescents compared with controls. These findings suggested that abnormalities in specific white matter pathways involved in emotion regulation could indicate that a wider network of emotion processing is dysfunctional in adolescents with BPD (2).

Evidence collected on the impact of early BPD onset on later functioning of patients are generally in accordance to retain that BPD in childhood and adolescence predict a severe impairment of interpersonal and occupational functioning (99, 100), as well as younger age at first treatment, affective instability, antisocial behaviors, substance abuse, and dysfunctional relationships with parents (96–98). Furthermore, poor functional outcome persists up to 20 years into the future in individuals who presented BPD in adolescence (101). Some precocious protective factors related to childhood competence, such as higher IQ, good childhood work history, higher agreeableness, and lower neuroticism, were also identified (98, 103).

In conclusion, specific BPD features emerge in childhood and adolescence. Recognizing these precocious predictors

TABLE 3 | Summary of studies on neuroimaging and effect of early detection on course and outcome of BPD.

Neuroimaging	Study design	Patients (n)/ recruitment age	Trial duration	Outcomes
Chanen et al. (84)	Controlled trial; Clinical outpatients and community population	20 BPD; 20 HC; 15–19 years		Reversal of the normal (right > left) asymmetry of OFC grey matter volume in BPD pts compared with HC
Richter et al. (85)	Controlled trial; Clinical outpatients and community population	20 BPD pts; 20 CC; 20 HC; 14–18 years		Right amygdala, right and left hippocampi smaller in BPD pts compared to healthy (but not clinical) controls
Brunner et al. (86)	Controlled trial; Clinical outpatients and community population	20 BPD pts; 20 CC; 20 HC; 14–18 years		Left OFC and bilateral DLPFC smaller in BPD pts compared with HC, but not CC
Maier-Hein et al. (87)	Controlled trial; Clinical outpatients and community population	20 BPD pts; 20 CC; 20 HC; 14–18 years		Lower fractional anisotropy in the bilateral fornices of BPD group compared to CC and HC
Walterfang et al. (88)	Controlled trial; Clinical outpatients and community population	20 BPD; 20 HC; 15–19 years		No differences in corpus callosum size between BPD group and HCs
Whittle et al. (89)	Controlled trial; Clinical outpatients and community population	15 BPD girls; 15 HC girls; 15–19 years		Left ACC volume smaller in BPD pts compared to HC
Goodman et al. (90)	Controlled trial; Clinical outpatients and community population	13 BPD; 13 HC; 15,8 ys mean age		BPD/MDD patients had smaller BA 24 volume. Smaller BA 24 volume was associated with BPD (but not depressive) symptoms
Jovev et al. (69)	Controlled trial; Community high-risk and community population	153 11–13 years		BPD symptoms associated to high affiliation, low effortful control and rightward hippocampal asymmetry (differences between genders)
New et al. (91)	Controlled trial; Clinical outpatients and community population	14 BPD pts; 13 HC 15,8 ys mean age		Lower fractional anisotropy in the inferior longitudinal fasciculus, uncinate, and occipitofrontal fasciculi
Early detection effects	**Study design**	**Patients (n)/ recruitment age**	**Trial duration**	**Outcomes**
Gunderson et al. (96)	Longitudinal study; Clinical outpatients	160 BPD pts; 18–45 years	2 years	Early history of abuse and neglect is associated with a poor prognosis
Winograd et al. (100)	Longitudinal study; Community population	748; 9–18 years	20 years	BPD in childhood and adolescence predictive of enduring impairment in interpersonal, occupational, and financial domains of functioning
Crawford et al. (101)	Longitudinal study; Community population	629; 13,8 ys mean age	20 years	Persistent poor functional outcome in BPD features adolescents, including increased risk for substance use and mood disorders, interpersonal dysfunctions, and poor quality of life
Biskin et al. (102)	Longitudinal study	49 girls; 19,6 ys mean age	4 years	Non-remitters BPD pts more likely to be unemployed and to have a current episode of major depressive disorder, lifetime substance use disorder, self-reported childhood sexual abuse, and being unemployed
Haltigan and Vaillancourt (53)	Longitudinal study; Community population	875; 10 years	4 years	Child-reported ADHD and somatization symptoms predicted elevated or rising trajectory, whereas parent-reported anxiety symptoms predicted intermediate or stable trajectory
Zanarini et al. (98)	Longitudinal controlled study; Community population	290 BPD pts; 72 Axis II pts	20 years	Axis II pts reached higher rates of both good and excellent recovery than BPD pts. Competence in both childhood and adulthood was the best predictor of attaining an excellent recovery

ACC, anterior cingulate cortex; ADHD attention deficit hyperactivity disorder; BA, Brodmann area; BPD, borderline personality disorder; CC, clinical controls; DLPFC, dorsolateral prefrontal cortex; HC healthy controls; OFC, orbitofrontal cortex; MDD, major depressive disorder; pts, patients; ys, years.

may have significant clinical implications. Early onset of this complex and serious personality disorder is associated with high risk of negative outcome and long-term poor psychosocial functioning. Precocious identification of BPD symptoms and accurate investigation of protective and risk factors is fundamental to promote prompt and adequate intervention programs and to improve the natural life-course trajectory of the disorder.

A Preliminary Model of Risk Factors in BPD

We tried to support the work of clinicians in this field by providing a synthetic summary of findings collected in the different clusters of risk factors. So, it should be easier to identify more common and significant associations in the clusters of environmental precocious factors, child and adolescent temperament and personality factors, early psychopathological features, and neuroimaging factors.

A further step that can be useful for clinicians to detect early clinical conditions and to implement preventive interventions consists in the proposal of a hypothetic model that represents a high-risk condition for the onset of BPD. This model is a combination of more important and common factors identified in literature and is supported by the idea that their interactive effects are stronger and more relevant than the separate effects of single factors. A reasonable hypothesis on the basis of available data is that high-risk subjects are characterized by a series of predisposing factors. The first factor to consider is a positive history of early traumatic experiences. According to the more common findings in literature, early trauma can be represented by conditions of abuse or neglect in childhood or adolescence, or can be the consequence of persistent abnormalities in familial behaviors and relationships due to severe mother psychopathology. The effects of traumatic experiences are substantially increased when they do not occur as isolated events, but when the dysfunctional familial environment that produces traumas interacts with the child's innate temperamental features. In this case, authors have identified a significant role for three temperamental traits: impulsive aggression, inadequate emotional control, and negative affectivity. Another relevant factor that can combine its effects with the previously reported environmental and temperamental dysfunctions to enhance the risk of early onset BPD is the occurrence in childhood/adolescence of precocious internalizing and externalizing psychiatric disorders. Particular attention has been received by depression, ADHD, and substance use disorder, that all represent psychopathological conditions with a frequent onset in early age, but a long-lasting association with symptoms of BPD in adulthood. We can suggest that some of these disorders are not independent comorbidities, but must be conceptualized as precocious expressions of BPD pathology. A few studies indicated that studies of neuroimaging can contribute to identify which brain structures are altered in subjects with risk factors for early onset BPD. For example, structural abnormalities of fronto-limbic areas have been related to impulsive and emotional dysregulation. If these changes of brain structures are specific enough, they will contribute to identify biological markers or neural signatures, a primary goal in psychiatric and brain imaging research. Of course, it must be noticed that we present here only a hypothetical model with the main purpose to stimulate the interest of researchers and the debate among experts. The indicators of a high-risk condition for early onset of BPD, and particularly the effects of their coexistence and interaction in the proposed model, must be furtherly investigated and confirmed in specific studies. One of the more challenging issues at the present state of our knowledge is to make clear which of the factors proposed in this model have a primary role in the pathogenesis of BPD and which intervene only at a later time to augment and trigger the effects of primary factors.

An important contribution to understand the complex effects of temperamental traits, traumatic experiences, and environmental dysfunctions on the neurobiology of young BPD patients could derive from studies of functional changes in brain areas during administration of specific stimuli (108). For example, studies of autobiographical memories in such populations could be of great value to investigate the effects of life events and traumatic experiences on the function of fronto-limbic brain structures involved in the construction of identity.

AUTHOR CONTRIBUTIONS

PB and SB equally contributed to summarizing the literature data and writing the review. MB collected literature data and organized the tables. PR contributed to writing and supervising the review.

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Predictors of Outcomes in Adolescents With Clinical High Risk for Psychosis, Other Psychiatric Symptoms, and Psychosis: A Longitudinal Protocol Study

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In children and adolescents, schizophrenia is one of the ten main causes of disability-adjusted life years. The identification of people at Clinical High Risk of developing Psychosis (CHR-P) is one of the most promising strategies to improve outcomes. However, in children and adolescents research on the CHR-P state is still in its infancy and the clinical validity of at-risk criteria appears understudied in this population. Furthermore, only few studies have evaluated the psychopathological, neuropsychological, neuroimaging characteristics and, especially, long-term outcomes of adolescents at high risk. We present here the protocol of an innovative longitudinal cohort study of adolescents aged 12-17. The sample will consist of patients admitted to a third level neuropsychiatric unit, belonging to one of the following three subgroups: 1) adolescents with established Diagnostic and Statistical Manual of Mental Disorder–Fifth Edition psychosis, 2) adolescents with CHR-P, and 3) adolescents with psychiatric symptoms other than established psychosis or CHR-P. The primary aim of our study is to evaluate the 2-year prognosis across the three groups. We will measure transition to psychosis (or the stability of the diagnosis of psychosis in the psychotic group), the risk of development of other psychiatric disorders, as well as socio-occupational functioning at outcome. The secondary aim will be to explore the effect of specific predictors (clinical, neuropsychological and neuroimaging factors) on the prognosis. At baseline, 1-year and 2-year follow-up participants will be assessed using standardized semi-structured interviews and instruments. Psychopathological and functioning variables, as well as neuropsychological domains will be compared across the three subgroups. Moreover, at baseline and 2-year follow-up all recruited patients will undergo a 3-Tesla magnetic resonance imaging examination and diffusion tensor imaging parameters will be analyzed. We believe that this study will advance our ability to predict outcomes in underage CHR-P samples. In particular, our data will enable a better

understanding of the clinical significance of CHR-P in adolescents, and shed new light on prognostic factors that can be used to refine the prediction of clinical outcomes and the implementation of preventive interventions.

Keywords: attenuated psychosis syndrome, adolescence, transition, functioning, prognosis, ARMS, young people, psychosis

INTRODUCTION

During adolescence, the assessment of psychiatric symptoms and disorders is challenging. During this neurodevelopmental period, youth go through a period of body and psychic transformation and experience profound psychosocial and neurobiological changes (1). Several authors have underlined the difficulty in discriminating between normal behaviors and psychiatric symptoms (2). Normative adolescent experiences (e.g. imaginary audience and personal fable) can make the clinical picture blurred and lead to false positive psychiatric diagnoses, especially if non-validated diagnostic tools are administered and/or the assessment is done by professionals that are not adequately trained (3). In recent years, efforts have been devoted to develop diagnostic instruments and interviews that could help clinicians in differentiating between normal adolescent behaviors and psychiatric symptoms in this age range (4–6).

This is especially important as current research shows that 50% of mental disorders begin prior to 14 years of age and 75% have their onset by the age of 24 (7). Furthermore, retrospective studies highlighted that the vast majority of youth receiving a psychiatric diagnosis had already been diagnosed of at least one mental disorder by the age of 11 (8).

These findings support the need of specifically addressing to this neurodevelopmental period.

In children and adolescents, psychotic disorders are among the ten main causes of disability adjusted life years (9). One of the most promising strategies to improve outcomes for these disorders is to detect symptoms of the emerging disorder in patients at Clinical High Risk for Psychosis (CHR-P hereafter) (10, 11).

Over the last 3 decades, specific psychometric instruments have been developed and validated internationally to detect CHR-P individuals [for a meta-analysis of their prognostic accuracy see (12)]. In adult samples it has been shown that these criteria associated with a 20% 2-year risk of developing psychosis [see eTable 4 in (13)] with the majority of patients who transition going to develop schizophrenia spectrum disorders (14). The level of risk is highest in those meeting the Brief and Limited Intermittent Psychotic symptoms subgroup of the CHR-P criteria (15) and peaks within the first two years (16). CHR-P individuals have an increased probability of developing psychosis that can be related to several environmental risk factors (17, 18). Although there are different psychometric interviews available to identify CHR-P individuals (19), overall they show a comparable prognostic accuracy which is also similar to that of other instruments used in preventive medicine (12).

Beyond the risk of developing psychosis, several other studies have investigated the level of functioning and/or quality of life in CHR-P subjects (20–22) with controversial results. A recent meta-analysis found that CHR-P people have large impairment in functioning and worse quality of life than the healthy control group, similar to those observed in other coded psychiatric disorder (such as bipolar disorder). Moreover, only a small to moderate better functioning and similar quality of life compared with the psychosis group was highlighted (23).

In a recent study (24), the authors identified a factor structure composed of social-cognitive bias, reflective self (self-esteem, resilience, physical anhedonia and social anhedonia), neurocognition and pre-reflective self (magical ideation, perceptual aberration and basic symptoms) factors. These factors were not only different between recent-onset patients with schizophrenia, ultra-high risk for psychosis and healthy controls, but were also associated with baseline quality of life both in CHR-P individuals and psychotic patients.

Overall, the CHR-P field has attracted lot of interest to the point that clinically based operational criteria of attenuated psychosis syndrome (APS) have been introduced in the section III as well as in the main text (page 122) of the Diagnostic and Statistical Manual of Mental Disorder–Fifth Edition (DSM-5) (25–27). The prognostic accuracy of the APS category appears similar to that of CHR-P psychometric instruments, at least in individuals seeking help at specialized early detection clinics (28). Yet, the applicability and prognostic accuracy of the APS in adolescents is mostly undetermined (29, 30). Several studies (31–33) agreed that transition risk to psychosis in adolescents is lower than that in adults, suggesting that the APS could be

Abbreviations: AD, Axial Diffusivity; AF, Arcuate Fasciculus; APS, Attenuated Psychosis Syndrome; BVN 12-18, Batteria di Valutazione Neuropsicologica per l'Adolescenza (Neuropsychological Evaluation Battery for Adolescence); CAARMS, Comprehensive Assessment of At Risk Mental States; CBCL, Child Behavior Checklist; CGAS, Children's Global Assessment Scale; GF:R, Global Functioning: Role scale; GF:S, Global Functioning: Social scale; CGI-S, Clinical Global Impression-Severity; CHR-P, Clinical High Risk of developing Psychosis; DSM-5, Diagnostic and Statistical Manual of Mental Disorder–Fifth Edition; DTI, Diffusion Tensor Imaging; DWI, Diffusion-Weighted Images; EuroQoL scale, instrument for measuring quality of life; FA, Fractional Anisotropy; FACES-IV, Family Adaptability and Cohesion Evaluation Scales; FSL, FMRIB Software Library; FWE, Family-Wise Error; HARDI, High Angular Resolution Diffusion-Weighted Imaging; IFOF, inferior frontal-occipital fasciculus; ILF, inferior longitudinal fasciculus; IPAT, Integrated Parallel Acquisition Technique Acceleration Factor; IQ, intelligence quotient; KSADS-P, Kiddie-schedule for Affective Disorder and Schizophrenia; MD, Mean Diffusivity; MNI, Montreal Neurological Institute; MRI, Magnetic Resonance Imaging; RD, Radial Diffusivity; SCID-I and II, Structured Clinical Interview for DSM-IV axis I and II; SE-EPI, Single-Shot Spin-Echo Echo-Planar Imaging; SLF, Superior Longitudinal Fasciculus; SOFAS, Social and Occupational Functioning Assessment Scale; TBSS, Tract-based spatial statistics; UF, Uncinate Fasciculus; WISC-IV, Wechsler Intelligence Scale for Children; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WM, white matter; YSR, Youth Self Report.

less specific in youth (34). A recent study has confirmed that age has an effect on conversion rate to psychosis with lower rates in children and adolescents (35). On another hand, children and adolescents APS appear to display a higher range of psychiatric symptoms and disorders and to have a higher risk of future psychiatric hospitalizations as well as lower functioning (36, 37).

Candidate prognostic factors to refine the prediction of clinical outcome may include cognitive and neuropsychological factors (38, 39). Available meta-analyses (40, 41) showed that CHR-P people performed significantly worse in verbal learning, visual learning and speed of processing, which also differentiated between CHR-P subjects that converted to psychosis and the ones that did not transition. However, the prognostic relevance of the factors in underage populations is not known.

For example, in a study conducted in a small sample of CHR-P adolescents the only parameter who differentiate those who converted to psychosis from the ones that do not at 6-years follow up was baseline low IQ (42).

Recently, Lam et al. (43) found that cognitive dimensions are not only important in identifying youth that later convert to psychosis but account also for longitudinal changes in social and occupational functioning.

Other potential prognostic factors may be based on neuroimaging markers (14, 44, 45).

White matter abnormalities have been identified in schizophrenia. It has been hypothesized that the presence of an aberrant cortical network and functional connectivity could play a key etiopathogenetic role in the disorder (46).

To date, only a few studies have been conducted in CHR-P subjects where the integrity of white matter has been analyzed by using diffusion tensor imaging (DTI) technique (47).

In a sample of 68 adolescents (33 CHR-P and 35 healthy controls) a significant reduction of fractional anisotropy of superior cerebellar peduncles was found (48).

Other studies used resting state MRI scans and found alteration in the default mode (49) and salience networks connectivity (50) in CHR-P youth as compared to healthy controls.

The study protocol described here aims at filling these gaps in knowledge, with a longitudinal, broad risk approach, driven by the increasing need to refine the ability to predict different clinical outcomes in this population (51).

AIMS

The primary aim of this study is to evaluate the 2-year prognosis in adolescent patients through three diagnostics groups: 1) with established DSM5 psychosis, 2) with CHR-P, and 3) with other psychiatric disorders other than psychosis or CHR-P. Stability of diagnosis will be evaluated in the patients who already have psychosis at baseline.

Transition to psychosis will be evaluated according to the CAARMS criteria. In more detail, the psychosis threshold will be considered crossed if the score in the Unusual Thought Content, Non-Bizarre Ideas, and Disorganized Speech will be as high as 6 in the global rating scale and the score in the Perceptual Abnormalities will be at least equal to 5 in the global rating scale. Patients will enter the psychosis group only if these symptoms are present for more than 1 week and their frequency is equal or higher than: 3–6 times a week for more than one hour per occasion or daily.

Socio-occupational functioning will be evaluated by means of the Social and Occupational Functioning Assessment Scale (SOFAS) (52).

Development of other psychiatric conditions will be confirmed according to DSM-5 criteria.

The secondary aim is to study the effect of different prognostic factors (clinical factors, including family history, obstetric complications and drug use, neuropsychological and neuroimaging variables) influencing the clinical outcome.

METHODS AND ANALYSIS

Study Design and Population

We propose a longitudinal cohort study. The study will last 5 years in total with a recruitment period of 3 years, and each subject included will be assessed three times in a 2-year time span (baseline, 1-year and 2-year follow-up).

The study will be carried out in a third level center (Mondino Foundation, IRCCS, Pavia, Italy). The Mondino Foundation is a very well known National Specialist third level center that receives referrals in the field of child and adolescent neuropsychiatry from all over Italy (and in particular from the Lombardy region and the district of Pavia).

The sample will consist of adolescent patients aged 12–17 years, consecutively admitted to the inpatient or outpatient psychiatric units. Patients who already had a diagnosis of psychotic disorder (prior to assessment), established cognitive impairment (IQ < 70), neurological disorders, head injuries, or any other medical condition that could justify their psychiatric symptoms will be excluded.

Written informed assent and consent will be asked to both participants and their legal guardians, respectively.

Procedure

Each adolescent patient admitted to the psychiatric inpatient and outpatient units not presenting any of the exclusion criteria will be asked to take part in the study. The study procedure will be thoroughly explained by a trained psychologist to both patients and their legal guardian, and a written consent will be obtained. Patients will be free to ask additional questions and take their time in order to decide whether to take part or not in the study. Once patients and their caregivers consent to the study, the baseline assessment will take place.

Baseline and Follow-Up Assessments

Baseline

At baseline sociodemographic information and previous medical and psychiatric history (previous psychiatric symptoms or diagnoses, medical/pharmacological or psychotherapy

treatment) as well as socio-economic status [Four-Factor Index of Social Status, (53)] will be collected.

Patients will undergo an extensive diagnostic assessment that will include clinical interviews, semi-structured clinical interviews [CAARMS (54, 55); (Structured Clinical Interview for DSM-IV axis I and II, i.e. SCID-I and II (56–58), Kiddie-schedule for Affective Disorder and Schizophrenia, i.e. K-SADS-PL (59, 60)), and self-administered questionnaires administered to both parents and patients (Child Behavior Checklist, i.e. CBCL) (61, 62) and Youth Self Report, i.e. YSR (63)].

Based on this extensive clinical assessment, subjects will be divided into three subgroups: 1) adolescents with psychosis according to CAARMS criteria, 2) youth with other psychiatric symptoms that do not meet CHR-P or psychosis criteria, and 3) youth with other psychiatric symptoms that do not meet CHR-P criteria. The presence of psychiatric comorbidities will be recorded according to the DSM-5.

Self-administered questionnaires focusing on quality of life, distress, and family functioning will be completed by both guardians and parents. The clinician will complete specific scales describing the socio-occupational functioning and severity of the patient.

A thorough neuropsychological examination will be performed focusing on several cognitive domains: IQ, attention, reasoning and problem solving, verbal working memory, non-verbal working memory, verbal learning, and processing speed.

All the tests and questionnaires used are translated and validated into Italian.

A neuroimaging exam will complete the baseline examination. Patients will undergo a 3.0 Tesla magnetic resonance imaging (MRI) scan including a diffusion weighted sequence for DTI analysis (see MRI acquisition and processing section).

Follow-Up Assessments

Participants will be reassessed at 1-year and 2-year follow-up. Psychopathological, neuropsychological and functioning measures will be collected in the three subgroups. The same assessment as described in the baseline section will be carried out.

Neuroimaging exam will be performed at 2-year follow-up only.

As this is a naturalistic longitudinal study, the research team will not interfere on the patient's care and treatment, which will consist of treatments as usual (psychosocial, pharmacological and psychotherapy).

Clinical Variables and Instruments

In the present study, the validated Italian version of the (CAARMS) (55) will be used to determine whether enrolled subjects met research criteria for CHR-P.

The CAARMS is a semi-structured interview designed to assess prodromal psychopathology for people at high clinical risk for psychosis. The CAARMS has a total of 27 items, which are clustered in seven subscales, of which the first one is used to identify the CHR-P criteria, as detailed elsewhere (34).

This instrument has been shown to possess good to excellent concurrent, discriminant and predictive validity and excellent inter-rater reliability (54). CAARMS interview will be administered only to patients.

In order to further validate the information obtained by the patient and to assess the presence of comorbidity and other DSM-5 Axis I, Kiddie-Schedule for Affective Disorder and Schizophrenia, i.e. K-SADS-PL (59, 60), interviews will be conducted with both patient and parents separately. Structured Clinical Interview for DSM-IV axis II, i.e. SCID II (57, 58), will be administered to participants in order to verify the presence of personality disorders.

In addition, in order to gain the patient's and caregivers' perspectives on emerging problem behaviors, quality of life, perceived distress and family functioning, participants and legal guardians will be asked to fill in the following self-administered questionnaires: Child Behavior Checklist, i.e. CBCL (61) and Youth Self Report, i.e. YSR (63); EuroQoL scale (64, 65); Perceived Stress Scale (66, 67); and Family Adaptability and Cohesion Evaluation Scales (FACES-IV) (68, 69).

All clinical measures will be administered by trained psychologist or neuropsychiatrist and collected both at baseline, 1- and 2-year follow-up.

Functioning Variables and Instruments

As one of the aims of this study is to evaluate the long-term prognosis and outcome also in terms of functioning, the level of functioning will be evaluated using the Children's Global Assessment Scale, i.e. CGAS (70) and the Social and Occupational Functioning Assessment Scale, i.e. SOFAS (52) as well as specific scales for role functioning [Global Functioning: Role scale, i.e. GF:R (71) and social functioning (Global Functioning: Social scale, i.e. GF:S (72, 73)]. We will also use the Clinical Global Impression-Severity (CGI-S) scale (74) to assess overall severity of illness as assessed by clinicians.

These measures will be collected both at baseline, 1-year and 2-year follow-up.

Neuropsychological Domains and Instruments/Tests

In this study we aim at evaluating the longitudinal profiles of cognition in adolescents with CHR-P, compared with adolescents with psychosis and youth with other psychiatric symptoms that do not meet CHR-P criteria and to examine the possible role of specific cognitive deficits as predictors of outcome in this population. For this purpose, a trained psychologist will administer at baseline, 1-year follow-up, and 2-year follow-up the following extensive neuropsychological assessment focusing on several cognitive domains.

In particular the following cognitive domains will be explored:

- Intelligence quotient: Wechsler scales (WISC-IV and WAIS-R) (75, 76)
- Reasoning and problem Solving: Elithorn Perceptual Maze Test [BVN 12-18, Batteria di Valutazione Neuropsicologica per l'Adolescenza (77)]
- Abstract reasoning and flexibility (executive function): Wisconsin Card Sorting Test (78)
- Verbal working memory: Letter-Number Sequencing Subtest of the Wechsler Scales (75, 76)
- Non verbal working memory: Corsi Block Task (79)
- Selective auditory and visual attention: BVN 12-18 (77)

- Planning and attention (executive functions, visual learning): Rey–Osterrieth complex figure test (80)
- Verbal learning: Hopkins verbal learning test (81)
- Processing Speed: Coding-Digit Symbol subtest of the Wechsler Scales and Category Fluency of the BVN 12-18 (77)

The whole assessment usually takes approximately 2h.

MRI Acquisition and Image Processing

Subjects will be examined on a Siemens Skyra 3 T MR scanner, equipped with a sixteen-channel head coil. The MRI protocol will include a high-resolution 3D T1-weighted sequence (MPRAGE: 160 sagittal slices, with 1mm thickness; TR/TE = 2300/2.98 ms; TI = 900 ms; flip angle = 9°, voxel size 1 mm^3 isotropic). A high angular resolution diffusion-weighted imaging (HARDI) dataset will be acquired as well, using a single-shot spin-echo echo-planar imaging (SE-EPI) sequence [66 contiguous axial slices acquired in an interleaved order, in-plane resolution = 2.2 mm^2, slice thickness = 2.2mm, TR/TE = 8300/92 ms, flip angle = 90°, 64 non-collinear diffusion sensitization directions at b = 2000 s/mm^2, 1 at b = 0, and an integrated parallel acquisition technique acceleration factor (IPAT) of 2].

Image preprocessing will be performed through the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/). For each subject, skull stripping will be applied to both the T1-weighted and the diffusion-weighted images (DWIs) using FSL's brain extraction tool. For the DWI dataset, eddy current distortions and motion artifacts will be corrected by registering each diffusion-sensitized volume to the b0 volume with an affine transformation. After tensor diagonalization, whole-brain maps of the four main voxelwise quantitative WM metrics will be obtained [mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD)]. The T1-weighted images will be first registered (rigid body alignment) to the b0 volume of the DWI dataset and then to the Montreal Neurological Institute (MNI) standard stereotactic atlas using FSL's linear and nonlinear registration tool. DTI-derived voxelwise maps will be finally warped to the MNI space by applying the transform estimated for the coregistered T1 image.

Voxel-wise TBSS analysis will be performed using the default parameters in the FSL (82). A mean FA image will be created and thinned to create a mean FA skeleton that represents the centers of all tracts common to both the entire group and the chosen subgroups (see subjects' section). Each subject's aligned DTI-derived maps will be then projected onto this skeleton, allowing voxel-wise between-group comparisons. Comparisons will be tested using a two-sample t-test adjusting for the subject's age and sex; correction for multiple comparisons will be applied [family-wise error (FWE), thresholded at p = 0.05.]

Tractography will also be performed to identify the main white matter bundles, including the corticospinal tracts, forceps major and minor, the superior longitudinal fasciculus (SLF), the arcuate fasciculus (AF), the inferior frontal-occipital fasciculus (IFOF), the uncinate fasciculus (UF), the inferior longitudinal fasciculus (ILF). Average FA, AD, and RD will be evaluated along the entire reconstructed tracts.

Data Analysis Plan

Sample Size

Given the results of a preliminary feasibility study done by our group (83), we expect to recruit 60 patients per year. We assume that approximately 20% of them will belong to the psychosis group, while the other 80% will be equally distributed in the other two groups.

As the recruitment period will last 3 years, the total sample will consist of 180 subjects of which 40 suffering from psychosis at baseline. On the basis of our preliminary data we expect a Hazard Ratio of developing psychosis in the CHR-P versus youth with other psychiatric symptoms not meeting CHR-P criteria not lower than 2.

Power

Using this Hazard Ratio, a power calculation indicates that a sample size of 180 subjects will be needed to detect a statistically significant difference with over 95% power.

Planned Statistical Analysis

Kaplan-Meyer survival analysis will be performed to calculate time-dependent cumulative probability to develop psychosis in the two non-psychotic groups.

Log-rank test will be performed to evaluate statistic significance of the raw risk.

Multivariate Cox regression model would be used to investigate the independent contribution to the probability to develop psychosis of the two diagnostic categories, controlling for all potentially confounding variables. The same model will be adopted to differentiate between confounding variables and variables independently contributing to the prognosis.

To calculate the probability to develop psychosis at 1 year and at 2 year in the different diagnostic groups, Markov chain will be performed.

DTI quantitative WM metrics (MD, FA, AD, and RD) for each patient at baseline and 2-year follow-up will be analyzed through Matlab software. Independent sample t-tests will be used to determine if there is a significant longitudinal difference in the three groups.

Ethics and Dissemination

The study protocol was reviewed and approved by the ethics committee of the Institute and all subjects will provide written informed consent in accordance with the Declaration of Helsinki.

DISCUSSION

As described above, research on high-risk state, especially APS, is still in its infancy in childhood and adolescents.

The results of our projects will be important in addressing the urgent need for studies in this area as well as criticism against the inclusion of APS diagnosis in DSM-5.

An innovative and important aspect of our study is its longitudinal design. To our knowledge, no previous study has ever evaluated the long-term outcome and clinical course of CHR-P in children and adolescents. Moreover, we have adopted

the experimental approach to addresses the concept of a broader risk (84): prognosis encompass not only transition to psychosis, but the development of other DSM-5 diagnoses as well as evaluation of functioning in adolescents at risk.

Characterizing CHR-P subjects and identifying predictors of different clinical and functioning pathways, course and long-term outcomes represent a crucial step to enable risk stratification and personalized, risk-adapted treatment.

In particular, our data will enable a better understanding of the clinical significance of CHR-P and APS diagnosis in this age group. We will also evaluate the stability over time of CHR-P diagnosis and characterize its clinical course and socio-demographic, clinical, neuroimaging, and functioning correlates.

Overall, our data will raise knowledge in this research field by better characterizing clinically and functionally adolescents fulfilling CHR-P criteria. Moreover, it will provide information about CHR-P adolescent patients' specific needs and, thus, it will allow clinicians and researchers to plan more appropriate treatment options and evidence-based interventions.

AUTHOR CONTRIBUTIONS

SM, MP, IB, and UB wrote the manuscript. MM, GS, FF, CZ, AP, and EF revised it critically. SM, EF, AP, MM, and UB contributed to study design and critical evaluation of the protocol. EF and MM are currently involved in data collection. All the authors approved the final manuscript and agreed to be accountable for all the aspects of the study.

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REVIEW
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Models Predicting Psychosis in Patients With High Clinical Risk: A Systematic Review

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Objective: The present study reviews predictive models used to improve prediction of psychosis onset in individuals at clinical high risk for psychosis (CHR), using clinical, biological, neurocognitive, environmental, and combinations of predictors.

Methods: A systematic literature search on PubMed was carried out (from 1998 through 2019) to find all studies that developed or validated a model predicting the transition to psychosis in CHR subjects.

Results: We found 1,406 records. Thirty-eight of them met the inclusion criteria; 11 studies using clinical predictive models, seven studies using biological models, five studies using neurocognitive models, five studies using environmental models, and 18 studies using combinations of predictive models across different domains. While the highest positive predictive value (PPV) in clinical, biological, neurocognitive, and combined predictive models were relatively high (all above 83), the highest PPV across environmental predictive models was modest (63%). Moreover, none of the combined models showed a superiority when compared with more parsimonious models (using only neurocognitive, clinical, biological, or environmental factors).

Conclusions: The use of predictive models may allow high prognostic accuracy for psychosis prediction in CHR individuals. However, only ten studies had performed an internal validation of their models. Among the models with the highest PPVs, only the biological and neurocognitive but not the combined models underwent validation. Further validation of predicted models is needed to ensure external validity.

Keywords: clinical high risk for psychosis (CHR), attenuated psychotic symptoms (APS), brief and limited intermittent psychotic symptoms (BLIPS), genetic risk and deterioration syndrome (GRD), predictive model

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INTRODUCTION

Psychotic disorders are some of the most serious mental disorders considering the individual and the social impact (1, 2). They represented the 11th cause of disability in the world in 2013 (3). The delay between the diagnosis and the treatment ranges from 1 to 3 years (4) and results in worsening clinical outcomes (5). Therefore, the clinical focus has increasingly shifted to the early detection and treatment with the aim to either attenuate, postpone and globally avoid the transition to psychosis (6), or enhance clinical and functional outcomes of psychosis over time (7, 8). Psychosis does not

appear directly in its full-blown form in adults but it gradually develops over time: often the first manifestations already take place in adolescents (9, 10). For most of the patients suffering from schizophrenia and psychotic disorders, the onset of the disease is anticipated by different symptoms: slight changes in belief, thought, and perception that represent mild forms of delusions, formal thought disorder, and hallucinations, respectively (11).

The clinical staging model has been created to catch these progressive changes, with progressively increasing levels of severity over time (12, 13). This model describes psychopathology in a continuum of different subsequent stages. It comprises five different stages, from stage 0 to stage 4, starting from the lowest level of increased risk of mental illness to progressively higher stages of severity, leading to separated but overlapping pathologies at the highest levels (14, 15). Stage 0 includes subjects at increased risk without any kind of symptoms; stage 1 refers to individuals at clinical high risk for psychosis (CHR); stage 2 coincides with the acute phase or crisis, featured by full-blown psychotic symptoms (the full-threshold first episode psychosis), after which an early recovery phase or post- acute phase in the 6–12 months after the onset of the disease occurs; stage 3 encompasses individuals with either persistent illness or recurrent episodes after the first one (12, 13, 16) and stage 4 holds subjects with chronic disease.

This psychopathological model allows to stage this pathology so that different types of interventions, depending on the stage of illness, can be developed. The psychopathology would be more susceptible to intervention strategies in the first phases of the disease and more crystallized and resistant to therapies in the last phases (15).

The CHR criteria include: attenuated psychotic symptoms (APS), representing mild positive symptoms; brief and limited intermittent psychotic symptoms (BLIPS), characterized by transient, non-serious psychotic symptoms lasting part of the day, and lasted for a maximum period of one week after which spontaneously went to remission; and genetic risk and deterioration syndrome (GRD), including patients with family history of psychosis or schizotypal personality disorder, with additional decline in functioning (17).

Frequently, research in the area of psychiatry has as principal focus the transition from CHR to First Episode Psychosis. Help-seeking subjects meeting CHR criteria, regardless of the scale used, have an increased risk to develop psychotic disorders (18), within a period of time that can be considered quite short. According to a meta-analysis storing data from 27 studies including a number of 2,502 patients, 18% of them developed First Episode Psychosis at by 6 months, 22% by 1 year, 29% by 2 years, and 36% by 3 years from initial assessment (19), with about 73% of these developing a schizophrenia spectrum disorder (20).

Overall, compared to the general population, CHR subjects have a 2-year relative risk (RR) to develop psychosis of 460% as compared to general population (29%/0.063%) (21). However, extracting from the overall high-risk entity, its three principal subgroups, patients with BLIPS were at greater risk for developing psychosis (39% vs 19% after 24 months), than patients in the APS and GRD subgroups (22), while the GRD subgroup shows only a slight transition risks of 5% after three years of follow-up (22).

Since most of the studies conducted a follow-up period of not more than 3 years, after this period the transition rate to psychosis is not completely clear. However, most conversions occur during the first year following the evaluation and the conversion rate decreases significantly thereafter, suggesting that the CHR criteria are sensitive to an imminent risk of the onset of full psychosis (23). However, the CHR criteria alone seem to be insufficient in predicting the imminence of the first episode psychosis, given that from 2/3 to 4/5 cases identified through these instruments do not turn into psychosis within a period of 2 years (24). Thus, the aim is to propose a prognostic model that more effectively picks out those individuals who are more likely to switch from ultra-high risk to a first-episode psychosis (FEP) within a given period of time, to adapt treatments to what subjects really need.

Nevertheless, there is not a model of prediction of the transition to psychosis that has been utilized in clinical practice. One explanation can be that psychotic disorders are heterogeneous in phenomenology, pathophysiology, and etiology (25): it means that CHR samples are composed of different and largely heterogeneous subgroups (26). Another reason can be found in the poor quality of the statistical methods used in the studies involved in developing a transition model from CHR stage to full-blown psychosis. A recent review on 91 studies highlighted several shortcomings of this kind of research: poor methods and reporting, no internal or external cross-validation, small sample sizes, and strategies to create these models not well done. Therefore, most of these models probably have overoptimistic and not realistic predictive accuracy (27).

The present study reviews models predicting transition to psychosis, developed to enhance prediction of illness onset in CHR subjects, extending results of a previous study of prognostic accuracy parameters of predictive modeling studies using clinical, biological, neurocognitive, environmental, and combinations of predictors (28).

METHODS

Literature Search

On January 31, 2019, an electronic search on PubMed was carried out (from 1998 through 2019), using the following search terms: "at risk mental state," "psychosis risk," "prodrome," "prodromal psychosis," "high risk," "clinical high risk psychosis", "attenuated psychotic symptoms", "APS", "brief and limited intermittent psychotic symptoms", "BLIPS", "brief intermittent psychosis syndrome", "BIPS", "genetic risk and deterioration syndrome", "GRD", "psychosis prediction," "psychosis onset," "predictive model". The research was restricted to those articles published from 1998 onward,

because this is the year in which the first prospective studies with subjects meeting validated CHR criteria have been published (29).

This qualitative review was executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard, including evaluation of bias (confounding, overlapping data, publication bias) (30). (**Figure 1**).

Studies were selected in a two-step procedure. First of all, all references retrieved from the databases were screened based on their titles and abstracts. Subsequently, the articles that were potentially eligible were further evaluated based on their full texts. All references within the included studies and those of any previous pertinent reviews were carefully reviewed to identify additional relevant studies. Discrepancies were resolved by mutual discussions. Consensus was then obtained, resulting in a final set of articles that have been reviewed and summarized.

Inclusion/Exclusion Criteria

As depicted in **Figure 1**, these are the inclusion criteria for the studies in the present review: (a) original articles, to be published in English; (b) presence of CHR subjects [i.e., APS or GRD or BLIPS or brief intermittent psychosis syndrome (BIPS)] according to international standard criteria (6); (c) inclusion of clinical, biological, neurocognitive, environmental, or combinations of predictors to separate CHR individuals who later developed psychosis from those who did not; (d) inclusion of rigorous predictive models, algorithms, or learning systems that predicted later transition to psychosis from variables obtained at baseline, like regression (logistic, Cox proportional hazard model, least absolute shrinkage, and selection operator), support vector machines, or greedy algorithms (31–34).

The following were the exclusion criteria: (a) abstracts, pilot datasets, reviews, articles not written in English; (b) not rigorous statistic methods (i.e., use of mean differences or chi square tests); (c) articles with overlapping datasets using the same

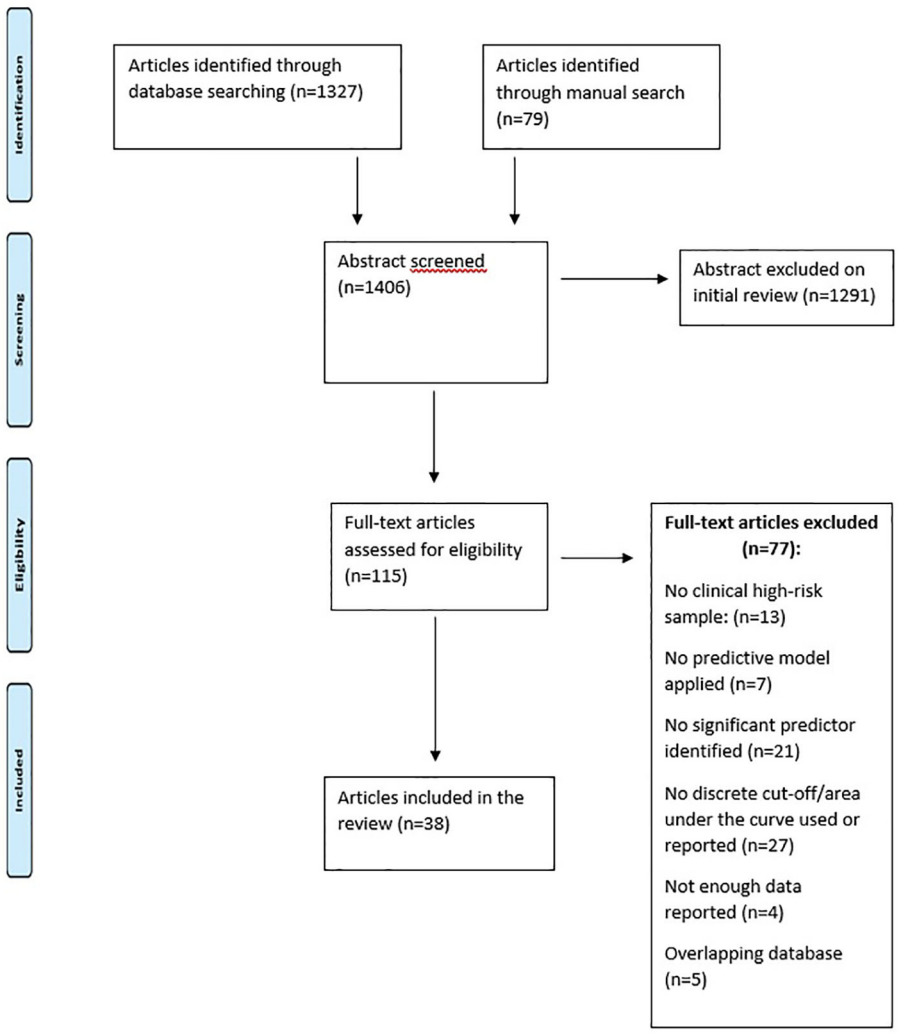

FIGURE 1 | PRISMA flow chart.

predictor. Particularly, when several articles were published using the same population sample, we have chosen the studies reporting the largest sample and most recent data set.

Recorded Variables

Two investigators (CM, NB) independently realized the extrapolation of data. Several variables have been extracted from the evaluated articles: author, year of publication, demographic characteristics of the CHR sample, predictor domain (clinical, biological, neurocognitive, environmental, combinations), cut-off of predictive variables, type of validation, diagnostic instrument used to define CHR group, administration of antipsychotics, follow-up time, predictive model, and prognostic accuracy data (sensibility SE, specificity SP, positive predictive value PPV, negative predictive value NPV). Moreover, we checked the missing data with all the corresponding authors to record all the information we needed.

RESULTS

Selection of Studies

Search

Figure 1 describes the details of what has been searched in literature and the reasons why some articles were excluded. The electronic and manual search described in the previous section provided 1,406 records.

Thirty-eight of these studies met the inclusion criteria: 11 studies made use of clinical predictive models, seven studies used biological models, five studies made use of neurocognitive models, five studies used environmental models, and 18 studies made use of combinations of predictive models across different domains. The results are schematically described in **Table 1**.

For all these studies, validation was evaluated. Some models have internal validation, that means test model in new data, random from underlying population. Other studies have external validation, that means test model in new data, different from development population. Some models have apparent validation, that gives an optimistic estimate of model performance. Some studies have a cross-validation: it means to test the model's ability to predict new data that was not used in estimating it, in order to flag problems like overfitting or selection bias (6) and to give an insight on how the model will generalize to an independent dataset. However, some models do not show any validation.

Clinical Predictive Models

The 11 studies that have tested the clinical predictive models are described in **Tables 1** and **2**. The clinical parameters included specific positive [odd belief: (35); auditory hallucinations: (35, 45); unusual thought content: (36); illogical thinking: (39); suspiciousness: (36, 42, 43); bizarre thinking: (44); delusions: (45); formal thought disorders: (45); disorganized communication: (40, 41); positive symptoms: (41)], negative [anhedonia/asociality: (35, 43); blunted affect: (35); alogia: (43)] and basic symptoms (41), social and global functioning (35–37, 44), and the Strauss and Carpenter Prognostic Scale (SCPS) (38). In details, we found that the best clinical predictors recognized were schizotypal personality characteristics (35), formal thought disorders (39), specific items of the SCPS assessing quality of useful work and social relations, positive symptoms and subjective distress (38), disorganized communication (particularly, subthreshold thought disorder) both at baseline and as a trajectory of high persistent disorganized communication (40), and early adolescent social dysfunction (43), with baseline prodromal symptoms of disorganized communication, social anhedonia, suspiciousness, and diminished ideational richness that mediate the association with transition to psychosis. We found that several studies presented an increased predictive power when more variables were evaluated together. Particularly, a prediction model was developed and included positive symptoms, bizarre thinking, sleep disturbances, a schizotypal disorder, level of functioning in the past year, and years of education (44). Another study, using the median score of the global assessment of functioning scale (GAF) and the QLS scale, identified a "high" and "low" group (comprising of subjects functioning above or below median at both baseline and follow-up) and a "deterioration" group and "improving" group; Chi-square analyses showed that the low and deteriorating functioning groups were the most likely to develop FEP (45). Otherwise, Cannon et colleagues (36) found that five features contributed uniquely to the prediction of psychosis: a genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, higher levels of suspicion/paranoia, greater social impairment, and a history of substance abuse. Predictive power was increased when prediction algorithms combining two or three of these variables were generated. Other studies have highlighted several different factors associated with transition to psychosis. A study (37) has identified five factors: year of entry into the clinic, duration of symptoms before clinic entry, baseline functioning, negative symptoms, and disorders of thought content. Another study (41) has recognized low IQ, the severity of attenuated positive symptoms, and particularly disorganized symptoms that were identified as highly predictive of functional outcome. A study (42) has identified, as the best transition predictors, selected APS (suspiciousness), negative symptoms (anhedonia/asociality), and cognitive deficits (reduced speed of information processing).

The highest PPV of 88.3% was obtained using a model that included measures of delusions, hallucinations or formal thought disorder (45). This model reached a SE of 97.3%, SP of 86.5%, and NPV of 96.8%. The worst PPV (24%) was produced by combining the following items of the SCPS for transition to a first psychotic episode in subjects clinically at high risk (CHR) of psychosis: most usual quality of useful work in the past year, quality of social relations, presence of thought disorder, delusions or hallucinations in the past year, and reported severity of subjective distress in past month, a predictive model that revealed an SE value of 76%, SP of 57%, and NPV of 93% (38).

Validation was not obtained in any clinical predictive model.

TABLE 1 | Articles Reporting Predictive Models of Transition to Psychotic Disorder in CHR Subjects.

Articles	Type of CHR diagnostic instrument used	Sample of the CHR subjects (NT/T)	Antipsychotics (patients treated)	Follow-up (months)
Mason et al. (35)	APSS, BPRS, SAPS, SANS	37/37	No	26
Cannon et al. (36)	SIPS	209/82	Yes	30
Nelson et al. (37)	CAARMS, BPRS	197/114	No	60
Nieman et al. (38)	SIPS, BSABS-P	207/37	Yes	18
Bearden et al. (39)	SIPS	33/21	Yes	12
DeVylder et al. (40)	SIPS	74/26	Yes	30
Ziermans et al. (41)	SIPS, BSABS-P	33/10	Yes	72
Riecher-Rössler et al. (42)	BSIP, BPRS, SANS	32/21	No	64
Tarbox et al. (43)	SIPS	192/78	n/a	30
Ruhrmann et al. (44)	SIPS, BSABS-P	146/37	Yes	18
Velthorst et al. (45)	SIPS	119/28	No	24
van Tricht et al. (46)	SIPS	91/22	Yes	18
Perkins et al. (47)	SIPS	40/32	Yes	24
Van Tricht et al. (48)	SIPS, PANSS, PAS	43/18	16*	36
Ramyead et al. (49)	BSIP	35/18	No	36
Koutsouleris et al. (50)	BSIP, BPRS	21/16	4	84
Koutsouleris et al. (51)	BSABS	18/15	No	18
Koutsouleris et al. (52)	BPRS, SANS, PANSS	33/33	No	52
Hoffman et al. (53)	SIPS	19/9	No	24
Koutsouleris et al. (54)	CAARMS, BSABS-P	20/15	No	48
Pukrop et al. (55)	SIPS, BSABS-P	39/44	No	36
Fusar-Poli et al. (56)	CAARMS	129/23	Yes	24
Dragt et al. (57)	SIPS and BSABS-P	53/19	Yes	36
Buchy et al. (58)	SIPS	141/29	No	48
Nieman et al. (59)	SIPS, BSABS-P	43/18	Yes	36
Lencez et al. (60)	SIPS	21/12	No	32
Cornblatt et al. (61)	SIPS	77/15	Yes	36
Michel et al. (62)	SIPS, SPI-A	53/44	Yes	24
Chan et al. (63)	CAARMS	58/18	No	24
Corcoran et al. (64)	SIPS, SOPS	42/7	n/a	24
Gschwandtner et al. (65)	BSIP, BPRS	30/12	No	72
Mittal. et al. (66)	SIPS	66/24	13	24
Rüsch et al. (67)	SIPS	159/13	33	12
Thompson et al. (68)	CAARMS	63/41	No	28
Zimmermann et al. (69)	BPRS, SANS	15/13	4	48
Ruhrmann et al. (44)	BSABS-P, SIPS	208/37	55	18
Yung et al. (70)	CASH, BPRS	68/36	No	12
Yung et al. (71)	CASH, BPRS	29/20	No	12

APSS, the assessment of prodromal and schizotypal symptoms; BPRS, Brief Psychiatric Rating Scale; BSABS-P, The Bonn Scale for the assessment of basic symptoms- prediction list; BSIP, Basel Screening Instrument for Psychosis; CAARMS, comprehensive assessment of at risk mental states; CASH, comprehensive assessment of symptoms and history; CHR, clinical high risk; ERIraos, early recognition inventory based on the retrospective assessment of the onset of schizophrenia; HR, high risk; n/a not available; NT, nontransition; PANSS, Positive and Negative Symptoms Scale; PAS, premorbid assessment scale; PSE, present state examination; SANS; Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessment of Positive Symptoms; SD, standard deviation; SIPS, structured interview for prodromal syndromes; SOPS, Scale of Prodromal Symptoms; SPI-A, Schizophrenia Proneness Instrument, Adult version; T:transition.aData are shown for the CHR subjects with a known outcome (n=183). The total group included 245 subjects.
**16 subjects treated: 9 of them nontransition and 7 transition to psychosis.*

Biological Predictive Models

Seven studies have evaluated the prognostic accuracy of biological predictive models (**Table 2**). These studies have taken into consideration the MRI based biomarkers (50, 52), multivariate neuroanatomical pattern (51), electrophysiological indicators [quantitative EEG: (46, 49); ERP: event-related potentials: (48)], and blood analyses (47). In details, two studies took into consideration quantitative EEG (46, 49). Van Tricht and colleagues (46) determined quantitative EEG (QEEG) spectral power and alpha peak frequencies (APF), founding that power in theta and delta ranges and occipital–parietal APF contribute to the short-term prediction of psychosis and enable a further stratification of risk in CHR samples. Ramyead et al. (49) assessed the individualized prediction of psychosis by detecting specific patterns of beta and gamma oscillations using machine-learning algorithms, determining that transition to psychosis could be predicted from current-source density (CSD). This study found that left superior temporal gyrus, the left inferior parietal lobule, and the precuneus most strongly contributed to the prediction of psychosis, suggesting that CSD measurements extracted from clinical resting state EEG can be useful to improve the prediction to psychosis. A study (47) took into consideration blood biomarkers, measuring expression of plasma analytes reflecting inflammation, oxidative stress, hormones, and metabolism. A "greedy algorithm" selected analytes that best distinguished individuals with clinical high-

TABLE 2 | Prognostic Accuracy Parameters of the Predictive Models Included in the Systematic Review.

Articles	Predictor area	Predictive model	Validation	Predictive variables (Cut-off and/or AUC)	SE (%)	SP (%)	PPV (%)	NPV (%)
Mason et al. (35)	Clinical	Logistic regression	No	Odd belief (SPD ≥ 1), marked impairment in role functioning (APSS ≥ mild), auditory hallucinations (SAPS ≥ 2), anhedonia/asociality (SANS ≥ 2), blunted affect (APSS ≥ mild)	84	86	86	84
Cannon et al. (36)	Clinical	Cox proportional hazard model	No	Unusual thought content (SIPS > 3)	56	62	48	/
				Suspicion/paranoia (SIPS > 2)	79	37	43	/
				Social functioning (SIPS < 7)	80	43	46	/
				Psychosis in first-degree relatives with functional decline (GAF and SIPS)	66	59	52	/
Nelson et al. (37)	Clinical	Cox proportional hazard model	No	Global functioning (GAF < 44), duration symptoms (CAARMS > 738 d)	45	88	72	69
Nieman et al. (38)	Clinical	Cox proportional hazard model	No	SCPS < 49	76	57	24	93
Bearden et al. (39)	Clinical	Logistic regression	No	Illogical thinking score (K-FTDS)	69	71	/	/
DeVylder et al. (40)	Clinical	Cox proportional hazard model	No	Disorganized communication (SIPS > 2, AUC in the 2 through 4 range: 0.64)	81	38	33	85
				Disorganized communication (SIPS > 3, AUC in the 2 through 4 range: 0.64)[b]	62	62	36	82
				Disorganized communication score (SIPS > 4, AUC in the 2 through 4 range: 0.64)	31	81	36	77
Ziermans et al. (41)	Clinical	Logistic regression	No	Positive symptoms (SIPS > 11.5, AUC: 0.80)	40	85	44	/
				Cognitive deficits ≥ 19 (BSABS-P ≥ 19, AUC: 0.79)	67	87	60	91
Riecher-Rössler et al. (42)	Clinical	Logistic regression	No	Suspiciousness (BPRS:0.41, AUC: 0.72)	70	72	61	79
Tarbox et al. (43)	Clinical	Cox proportional hazard model	No	Alogia, anhedonia-asociality (SANS:0.33, AUC: 0.78)	79	68	/	/
				Suspiciousness (SIPS > 3)	53	76	51	75
Ruhrmann et al. (44)	Clinical	Cox proportional hazard model	No	Disorganized communication (SIPS > 1)	72	46	40	76
				Social anhedonia (SIPS >2)	69	58	46	80
				Positive symptoms (SIPS>16), bizarre thinking (SIPS > 2), schizotypal personality disorder (SIPS), highest functioning score in the past year (GAF-M score), sleep disturbances (SIPS>2), years of education, AUC: 0.81	42	98	83	87
Velthorst et al. (45)	Clinical	Logistic regression	Apparent	PANSS, with a score of 4 or more on delusions, hallucinations or formal thought disorder'; having a score of 6 on any of the items of the SIPS-Positive Symptoms subscales for more than 7 d. LCFA to the 19 items of the SIPS.	97.3	86.5	88.3	96.8
Van Tricht et al. (46)	Biological	Cox proportional hazard model	No	Quantitative EEG: occipital-parietal individual alpha peak frequency, frontal delta and theta power.	46	87	56	87
Perkins et al. (47)	Biological	Greedy algorithm	Internal	Blood biomarker: interleukin-1B, GH, KIT ligand, interleukin-8, matrix metalloproteinase-7, interleukin-7, resistin, chemokine [c-c motif] ligand8, immunoglobulin E, coagulation factor VII, TSH, malondialdehyde-modified low-density lipoprotein, apolipoproteinD, uromodulin and cortisol (AUC: 0.88)	60	90	72	84
Van Tricht et al. (48)	Biological	Cox proportional hazard model	No	ERP: P300 (Amplitude < 14.7 microvolt)	83	79	/	/
Ramyead et al. (49)	Biological	LASSO	Internal	Quantitative EEG: lagged phase synchronization, current-source density (AUC: 0.78)	58	83	/	/
Koutsouleris et al. (50)	Biological	Binary SVM with radial	Internal with nested repeated 10-	MRI-based biomarkers (The neuroanatomical decision functions underlying these results particularly involved the prefrontal perisylvian and subcortical brain structures)	81.0	87.5	77.8	89.5

(Continued)

TABLE 2 | Continued

Articles	Predictor area	Predictive model	Validation	Predictive variables (Cut-off and/or AUC)	SE (%)	SP (%)	PPV (%)	NPV (%)
		basis function	fold cross-validation					
Koutsouleris et al. (51)	Biological	Binary SVM with radial basis function	Internal with 5-fold cross-validation	Multivariate neuroanatomical pattern classification performed on the structural magnetic resonance imaging data	83	80	83	80
Koutsouleris et al. (52)	Biological	SVM	Internal	Gray matter volume reduction (dorsomedial, ventromedial, and orbitofrontal areas extending to the cingulate and right intra- and perisylvian structures	76	85	83	78
Hoffman et al. (53)	Neurocognitive	Cox proportional hazard model	No	Length of speech illusion (babble task ≥ 4)	89	90	80	94
Koutsouleris et al. (54)	Neurocognitive	SVM	Internal	Verbal and executive functioning (MWT-B, DST, TMT-B, RAVLT-DR, and RAVLT-Ret)	75	80	83	71
Riecher-Rössler et al. (43)	Neurocognitive	Logistic regression	No	Verbal IQ and attention (MWT/TAP Go/NoGo false alarm: 0.38, AUC: 0.62)	80	59	57	83
Pukrop et al. (55)	Neurocognitive	Logistic regression	No	Verbal memory–delayed recall (Auditory Verbal Learning Test), verbal IQ (Multiple Choice Vocabulary Test), verbal memory–immediate recall (Auditory Verbal Learning Test) and processing speed (DST)	75	79	80	74
Ziermans et al. (41)	Neurocognitive	Logistic regression	No	IQ (Wechsler Intelligence Scales < 86.5, AUC: 0.77)	40	97	80	84
Fusar-Poli et al. (56)	Environmental	Log-rank test	No	Unemployment ("yes/no" assessed with unstandardized questionnaire)	57	61	20	89
Dragt et al. (57)	Environmental	Cox proportional hazard model	No	Urbanicity (BDF, ≤100 000 inhabitants), impaired social-sexual aspects, age 12–15 (PAS), impaired social-personal adjustment, general (PAS)	63	88	63	88
Tarbox et al. (43)	Environmental	Cox proportional hazard	No	Early adolescent social maladjustment (PAS > 2)	50	71	46	72
Buchy et al. (58)	Environmental	Cox proportional hazard	No	Alcohol use ("yes/no" AUS/DUS)	69	81	26	90
Cannon et al. (36)	Environmental	Cox proportional hazard model	No	Abuse of alcohol, hypnotics, cannabis, amphetamines, opiates, cocaine, hallucinogens ("yes/no" as assessed by the Structured Clinical Interview for DSM-IV or the Schedule for Affective Disorders and Schizophrenia for School-Age Children)	29	83	43	/
Ziermans et al. (41)	Combination	Logistic regression	No	Positive symptoms (SIPS > 11.5) and IQ (Wechsler Intelligence Scales ≤ 86.5) (AUC: 0.82)	50	91	63	86
Riecher-Rössler et al. (42)	Combination	Logistic regression	Internal	Suspiciousness (BPRS), anhedonia-asociality (SANS) and attention (TAP Go/NoGo false alarm) (cut-off: 0.41, AUC: 0.87)	83	79	71	86
Nieman et al. (59)	Combination	Cox proportional hazard model	Internal	P300 amplitude (ERP), social-personal adjustment (PAS) (AUC: 0.86)	78	88	74	90
Lencz et al. (60)	Combination	Logistic regression	No	Verbal memory (Wechsler Memory Scale) and positive symptoms (SIPS) (AUC: 0.43)	82	79	69	88
Tarbox et al. (43)	Combination	Cox proportional hazard model	No	Early adolescent social maladjustment (PAS > 2), suspiciousness (SIPS > 3)	28	92	59	70
				Early adolescent social maladjustment (PAS > 2), disorganized communication (SIPS > 1)	42	82	51	72
				Early adolescent social maladjustment (PAS > 2), social anhedonia (SIPS > 2)	43	78	49	72
				Early adolescent social maladjustment (PAS > 2), ideational richness (SIPS > 0)	32	85	50	70
Cornblatt et al. (61)	Combination	Cox proportional hazard model	No	Disorganized communication (SIPS > 2), suspiciousness (SIPS = 5), verbal memory deficit 2 SD below normal, declining social functioning (Global Functioning: Social scale) (AUC: 0.92)	60	97	82	93

(Continued)

TABLE 2 | Continued

Articles	Predictor area	Predictive model	Validation	Predictive variables (Cut-off and/or AUC)	SE (%)	SP (%)	PPV (%)	NPV (%)
Cannon et al. (36)	Combination	Cox proportional hazard model	No	Psychosis in first-degree relatives with functional decline (SIPS and GAF), unusual thought content (SIPS > 3), social functioning (SIPS < 7)	30	90	81	/
Michel et al. (62)	Combination	Cox proportional hazard	Internal	UHR criteria (SIPS), DST deficit t-score < 40, COGDIS criteria (BSABS-P)	57	66	58	65
Chan et al. (63)	Combination	LASSO	10-fold cross validation	22-Analyte panel, CAARMS-positive subscale (AUC:0.90)	89	79	57	96
Corcoran et al. (64)	Combination	Logistic regression	Apparent	Facial emotion discrimination (EMODIFF), Facial emotion recognition (ER40), Negative symptoms (AUC:0.99)	86	98	86	98
Gschwandtner et al. (65)	Combination	Logistic regression model	No	EEG and general psychopathology (SANS and BPRS) (AUC=0.81)	82	73	/	/
Mittal et al. (66)	Combination	Linear discriminant analysis	Internal with leave one out cross-validation	Movement abnormalities (Dyskinesia Identification System: Condensed User), functional domains (WAIS-III, WISC-III), Neurocognition (FSIQ, vocabulary, matrix reasoning, block design, Logical memory I, Logical Memory II	76.0	60	86.3	43
Rusch et al. (67)	Combination	Logistic regression and cox proportional hazard model	Apparent	Positive and Negative symptoms (PANSS), perceived stigma-related harm (validated 8-item self-report measure based on Lazarus and Folkman's (1984) conceptualization of stress appraisal processes; using the median of as a cut off)	58	98	/	/
Thompson et al. (68)	Combination	Cox proportional hazard model	Apparent	Genetic risk with functional decline; high unusual thought content score (>3 on the SIPS); high suspicion/paranoia score (>2 on the SIPS); low social functioning (<7 on the Social Functioning Scale) and history of substance abuse.	37.3	87.2	65.4	68.2
Zimmermann et al. (69)	Combination	Logistic regression	Apparent	Negative symptom scale (SANS) and EEG spectral data (EEG power in seven bands: delta, theta, alpha1, alpha2, beta1, beta2, beta3)	92	87	86	93
Ruhrmann et al. (44)	Combination	Cox proportion hazard model	Apparent	SIPS-Positive score, bizarre thinking, sleep disturbances, schizotypal personality disorder (according to SIPS) highest GAF-M score in the past year, and years of education (AUC: 80.8)	41.7	97.9	83.3	87.0
Yung et al. (70)	Combination	Cox proportional hazard model	Apparent	Belonging to both the Trait and Attenuated Groups, Duration>5 years, SANS attention>2, GAF<40	60.0	92.6	80.8	81.8
Yung et al. (71)	Combination	Cox proportional hazard model	Apparent	Duration of symptoms > 900 d, GAF score < 51, BPRS total > 15, BPRS psychotic subscale > 2, SANS attention score > 1 and HRSD > 18	86	91	80	94

CAARMS, Comprehensive Assessment of At-Risk Mental State; LCFA, Latent Class Factor Analysis; NPV, negative predictive value; PPV, positive predictive value; SE, sensibility; SP, specificity.

Adapted by Schmidt et al. (28).

APSS, the assessment of prodromal and schizotypal symptoms; AUC, area under the curve; AUS/DUS, The Alcohol and Drug Use Scale; BDF, basic data form; BPRS, Brief Psychiatric Rating Scale; BSABS-P, The Bonn Scale for the assessment of basic symptoms-prediction list; CAARMS, comprehensive assessment of at risk mental states; CODGIS, cognitive disturbances; DST, digit symbol test; EEG, electroencephalogram; ERP, event-related potentials; GAF: global assessment of functioning; HRSD, Hamilton Rating; Scale for Depression; K-FTDS, Kiddie-Formal Thought Disorder Scale; LASSO, least absolute shrinkage and selection operator; MWT, Mehrfachwahl- Wortschatz test; NPV, negative predictive value; PAS, Premorbid Adjustment Scale; PPV, predictive positive value; RAVLT-DR, Rey Auditory Verbal Learning-delayed recall;

RAVLT-Ret, Rey Auditory Verbal Learning-retention; SANS, Scale for Assessment of Negative Symptoms; SCPS, Strauss and Carpenter Prognostic Scale, score; SD, standard deviation; SE, sensitivity; SFS, social functioning scale; SP, specificity; SPD, Schizotypal Personality Disorder subscale of the International Personality Disorder Examination; SIPS, structured interview for prodromal syndromes; SVM, support vector machine; TAP, Testbatterie zur Aufmerksamkeitsprüfung; TMT, trail-making test; WISC-III, Wechsler Intelligence Scales for Children 3rd ed. for participants ages 11 to 15; WAIS-III, Wechsler Adult Intelligence Scales, 3rd ed; FSIQ, Full Scale Intelligence Quotient; HRSD, Hamilton Rating Scale for Depression.

[a]*Cut-off scores for determining sensitivity, specificity, and accuracy values were derived from the receiver operating characteristic curve.*

[b]*The Youden Index (maximal value for sensitivity + specificity – 1) was 0.24 with the optimal cut point of a score of 3 for baseline disorganized communication.*

[c]*This model included 58 (of 61) CHR subjects.*

risk symptoms who developed psychosis. The classifier included 15 analytes (selected from 117). These results support the hypothesis that inflammation, oxidative stress, and dysregulation of hypothalamic-pituitary axes may be prominent in the earliest stages of psychosis and could lead to develop a multiplex blood assay with a potential for high clinical utility. A study (48) analyzed abnormalities on neuroimaging and neuropsychological examinations before the onset of a first psychotic episode, founding that reduced P3 amplitudes (a scalp-recorded late ERP, occurring approximately 300 ms after an attended unusual or task-relevant stimulus.) were identified as the best predictor for subsequent psychosis in the UHR group. The P3 reduction was related to increased social anhedonia and withdrawal and a lower global assessment of social functioning and social personal adjustment. Different studies (50, 52) concentrated their efforts in individuate MRI biomarkers: the

first study (50) found that the neuroanatomical decision functions underlying these results particularly involved the prefrontal perisylvian and subcortical brain structures and the second (52) found that the predictor's decision function involved grey matter volume alterations in prefrontal, perisylvian, and subcortical structures, supporting the idea of the existence of a cross-center neuroanatomical signature of emerging psychosis enabling individualized risk staging across different high-risk populations. Finally, another study (51) developed a multivariate neuroanatomical pattern classification on the structural magnetic resonance imaging data of individuals, in order to help predicting transition to psychosis.

The highest PPV of 83% was reached using the predictive variable of the grey matter volumes (grey matter volume alterations in prefrontal, perisylvian, and subcortical structures), with a SE of 76%, SP of 85%, and NPV of 78% (52). This review has been internally validated. However, the study sample was 66 subjects, constituting a rather small sample. Globally, five of these studies (47, 49–52) were cross validated and two were not (46, 48).

The worst PPV (77.8%) resulted from a predictive model including MRI-based biomarkers. This predictive model yielded an SE of 81%, SP of 87.5%, and NPV of 89.5% (50).

Neurocognitive Predictive Models

Five studies have analyzed the prognostic accuracy of cognitive predictive models (**Table 2**). These studies have provided measurements of IQ (41, 42, 55), verbal memory (54, 55), attention (42), speech perception (53), executive functioning (54), and processing speed (54, 55).

One of the studies (41) showed that low IQ was the single neurocognitive parameter that discriminated patients at ultra-high risk converted to psychosis from individuals who did not. The severity of attenuated positive symptoms was the only significant predictor of a transition to psychosis and disorganized symptoms were highly predictive of functional outcome.

Another study (42) showed that best transition predictors were selected APS (suspiciousness), negative symptoms (anhedonia/asociality), and cognitive deficits (reduced speed of information processing). Prediction of transitions could be enhanced by a stronger weighting of certain early symptoms and by inserting neurocognitive tests into a stepwise risk assessment. Therefore, this study uses neurocognition in addition to clinical parameters for predicting transition to psychosis. Hoffman and colleagues (53) highlighted that elevated LSI (length of speech illusion) scores indicated increased risk of transition to psychotic disorders when individual participating to the study were not taking olanzapine. A further study (54) has demonstrated that patients at risk of transition to psychosis could be identified on an individual basis by evaluating neurocognitive test batteries using multivariate pattern recognition. In another study (55) several cognitive domains were identified as indicators of vulnerability to psychosis. In addition, the results of the article suggest that subtle deficits in verbal abilities (working and long-term memory, executive and intellectual functions) and decreased speed of processing may help to predict transition to psychosis.

Considering verbal and executive functioning in the predictive model (neuropsychological functions were assessed with a cross-domain neuropsychological test battery comprising nine standardized tests that evaluated premorbid verbal IQ, processing speed, working memory, verbal learning and memory, executive functions, and verbal fluency), the highest PPV of 83% could be obtained with a value of SE equal to 75%, SP equal to 80%, and NPV equal to 71% (54). This model is the only one that has been validated in this domain, with an internal validation. However, the sample of the study is quite small, resulting in 35 subjects. The worst PPV of 57% was achieved by using a model including verbal IQ and attention (42). This model yielded an SE of 80%, SP of 59%, and NPV of 83% (42).

Environmental Predictive Models

The prognostic accuracy of environmental predictive models was evaluated in five papers (**Table 2**). These models have taken into consideration substance abuse (36, 58), unemployment (56), urbanity (57), social-sexual aspects (57), and social maladjustments (43, 57).

Two studies analyzed substance abuse (36, 58). Buchy et al. (58) and demonstrated that low use of alcohol contributed to the prediction of psychosis. This study has also highlighted that prediction algorithms including associations of additional baseline variables known to be associated with psychotic transition increase predictive power compared with substance use alone. Cannon et al. (36) found that different features contributed to the prediction of psychosis, including clinical features and a history of substance abuse (alcohol, hypnotics, cannabis, amphetamines, opiates, cocaine, hallucinogens): predictive power was enhanced when prediction algorithms combining two or three of these variables were developed. Tarbox et al. (43) identified that early adolescent social maladjustment and baseline suspiciousness together demonstrated moderate positive predictive power (59%) and high specificity (92.1%) in predicting transition to psychosis. A study (57) has identified urbanicity, social–sexual aspects, and social–personal adjustment as predictors of transition to psychosis.

Another study (56) showed that unemployment at the first contact with the prodromal service may be a risk factor for the development of a psychotic episode.

The best predictive model was obtained in a study conducted on 72 subjects, with values of PPV, SE, SP, and NPV of 63%, 63%, 88%, and 88%, respectively (57). Measures of urbanity, social-sexual aspects, and social and personal adjustment were significant predictors ($P < .001$). The worst PPV of 26% was achieved by using a model evaluating alcohol use ("yes/no"). This model yielded an SE of 69%, SP of 81%, and NPV of 90% (58).

There are no predicting models evaluating environmental factors that have been validated.

Combinations of Predictive Models

Eighteen studies (36, 41–44, 59–71) have evaluated prognostic accuracy combining different predictive models across domains (**Table 2**).

Some of these studies concentrated their efforts in develop predictive models combining symptomatology and neurophysiology (59, 65, 69). The first study (59) combined different predictive models, suggesting that predicting transition to psychosis could be improved with a model including premorbid adjustment and information-processing variables (specifically parietal P300 amplitude) in a multistep algorithm combining risk detection and stratification. A second study (65) demonstrated that patients who develop psychosis showed significantly more pathological EEG abnormalities than subjects who did not, located more frequently in temporal or frontotemporal regions of the brain. The specificity of the prediction of psychosis could be increased from 59 to 73% by considering EEG pathology in addition to psychopathology alone. Zimmermann and colleagues (69) have shown that SANS score in combination with EEG power in four bands (delta, theta, beta1, and beta2 bands), respectively, predicted transition significantly in 13 individuals with later transition to psychosis.

Other research studied predictive models focusing on symptomatology and functioning (44, 61, 68, 70, 71). A prediction model was developed including positive symptoms, bizarre thinking, sleep disturbances, a schizotypal disorder, level of functioning in the past year, and years of education (44). Another study (61) developed a final predictor model, with a positive predictive validity of 81.8%, consisted of four variables: disorganized communication, suspiciousness, verbal memory deficits, and decline in social functioning during follow-up. A study (68) found three variables associated with transition to psychosis: high unusual thought content scores; low functioning; and having genetic risk with functional decline. Using a combination of two out of three of these features, the predictive validity of determining whether an individual develops psychosis was improved, although using this method the probability of a person not developing psychotic disorder is still quite high at 35%. A study (70) yielded a method of psychosis prediction at 12 months, identifying the following as predictors: poor functioning, long duration of symptoms, high levels of depression, and reduced attention. A combination of family history of psychosis, a recent significant decrease in functioning and recent experience of subthreshold psychotic symptoms was also predictive of psychosis. A study (71) developed a strategy for predicting transition to psychosis, within a relatively brief follow-up period (12 months), combining some highly significant predictors of psychosis: long duration of prodromal symptoms, poor functioning at intake, low-grade psychotic symptoms, depression, and disorganization. A study (67) has developed a predictive model focusing on individuals functioning and stigma. Specifically, this study (67) showed that more perceived stigma stress at baseline predicted transition to schizophrenia after adjusting for age, gender, symptoms (positive and negative symptoms), and functioning. Other studies concentrate on cognitive deficits and symptomatology (41, 42, 60, 62, 66). Another study (41) has identified low IQ, the severity of attenuated positive symptoms, and particularly disorganized symptoms as highly predictive of functional outcome. A study (42) has identified as the best transition predictors, selected APS (suspiciousness), negative symptoms (anhedonia/asociality), and cognitive deficits (reduced speed of information processing). A study (60) demonstrated that prodromal patients (with APS) who later developed psychosis had significantly lower verbal memory scores at baseline, suggesting that verbal memory deficits can represent an important risk marker of transition to psychosis, possibly indicating the presence of a prefrontal-hippocampal neurodevelopmental abnormality. A study (62) found that the combination of a processing speed deficit (digit symbol test) and at-risk criteria (APS plus subjective cognitive disturbances) provides an optimized stratified risk assessment to develop psychosis. A research (66) has studied movement abnormalities and cognitive deficits demonstrating that elevated dyskinetic movements in the upper-body region were correlated with deficits in domains of verbal comprehension, perceptual organization, and both immediate and delayed auditory memory. Further, discriminant function analyses indicated that baseline movement abnormalities and neurocognitive deficits significantly classified subjects at risk to develop psychosis (72.3%). Results support a common cortico-striato-pallido-thalamic circuit irregularity, underlying both movement abnormalities and cognitive deficits in individuals at high risk for psychosis.

Another study focused on maladjustment of individuals at high-risk to develop psychosis. Tarbox et al. (43) identified that early adolescent social maladjustment and baseline suspiciousness together demonstrated moderate positive predictive power (59%) and high specificity (92.1%) in predicting transition to psychosis. It uses also as predictor of transition to psychosis the early adolescent social dysfunction. Other research was carried out in the field of substance abuse. Particularly, Cannon et al. (36) found that different features contributed to the prediction of psychosis, including clinical features and a history of substance abuse (alcohol, hypnotics, cannabis, amphetamines, opiates, cocaine, hallucinogens): predictive power was enhanced when prediction algorithms combining two or three of these variables were developed. Another interesting field that has been faced was about predictive models combining biology and symptomatology. In details, a study (63) developed a combined molecular/symptom-based test. The authors described the development of a serum biomarker test for the identification of individuals at risk of transition to psychosis based on multiplex immunoassay profiling analysis of 957 serum samples, identifying and validating an optimal panel of 26 biomarkers that best discriminated patients and controls. The performance increased further incorporating the CAARMS (Comprehensive Assessment of At-Risk Mental State) positive subscale symptom scores into the model. Finally, attention was laid on emotion recognition. Specifically, a study (64) showed how deficits in

emotion recognition significantly identify subjects who develop psychosis. The authors, moreover, demonstrate that the best classification model for schizophrenia onset included both face emotion processing (facial emotion discrimination and recognition) and negative symptoms. The highest PPV (86.3%) was obtained in a study (66) that took into consideration movement abnormalities, functional domains and neurocognition, with values of SE of 76%, SP of 60%, and NPV of 43%.

The worst PPV of 49% was achieved using early adolescent social maladjustment and baseline suspiciousness together as the predictive variables, which produced an SE of 43%, SP of 78%, and NPV of 72% (43).

DISCUSSION

Although the field of risk prediction in mental health lags behind other areas of medicine, some promising studies have been conducted to begin to ascertain the operative combinations of risk factors for a number of psychiatric disorders (72). These models must be successfully replicated and validated in multiple samples, external to the one used for the model development phase. This often takes many years to be achieved. The use of risk prediction models must be thoroughly evidence based, with research demonstrating that the model is reliable and applicable to the intended populations of individuals (73).

The prediction and prevention of psychotic disorders should include a two-step approach: one step aimed at the identification of individuals in CHR phase, the other aimed to further stratify risk so that "indicated preventive interventions" can be given to patients in the highest risk stratum in an even more targeted and intensive way.

The present review wants to extend the results of a recent review of Schmidt et al. (28). Our review evaluated a total of 38 studies, encompassing clinical, biological, neurocognitive, environmental, or combinations of predictive models from various domains.

Four main findings should be highlighted.

First, while the highest PPVs in clinical (35), biological (51, 52), neurocognitive (54), and combined (66) predictive models were quite high (all above 83), the highest PPV in environmental predictive models was relatively low (63%) (57). This data could be due to the heterogeneity in the environmental factors included in the studies. Moreover, the examined environmental factors were mostly those that have been related with psychotic disorders, particularly substance abuse, urbanicity, and social maladjustment, so that it is possible that their specificity in detecting transition risk to psychosis of CHR is relatively poor, as outlined by a recent meta-analysis (21).

Moreover, regarding the neurocognition, while many previous studies have suggested that it is an important factor in predicting transition to psychosis, there is significant heterogeneity regarding the specific domains implicated: measurements of IQ, verbal memory, attention, speech perception, executive functioning, and processing speed (74, 75).

Second, none of the combined models showed a superiority when compared with more parsimonious models (using only neurocognitive, clinical, biological, or environmental factors). Thus, based on this data, it could be inferred that a strong PPV can be reached making use of psychopathological or neurocognitive data alone, therefore this approach should be preferred to, i.e., extensive neuroimaging batteries. However, a study (28) estimating the theoretical PPV of a sequential three-stage testing (that contained various combinations of three models predicting transition to psychosis, eg, electroencephalography/clinical, images taken from MRI, and blood indicators) following the initial CHR assessment, has shown that the highest value of PPV was obtained when using in sequence a combined model (clinical + EEG) and two biological models (structural MRI and blood indicators). Particularly, PPV reached a value of 98% for subjects with three positive tests, 71–82% for subjects with two positive complementary tests, 12%–21% for subjects with one positive complementary test, and 1% for subjects without any positive tests. This study could indicate that testing in sequence CHR individuals with models of prediction psychosis onset across multiple domains could substantially enhance psychosis prediction after the initial CHR assessment. Thus, multistage sequential testing enables individual risk stratification of CHR subjects to be made and improve prediction of transition to psychosis. Third, it should be highlighted that only a few studies have tried to replicate directly each other's risk algorithms. Consequently, most published predictive performance estimates are likely to be considerably overoptimistic. Only ten studies have used a strict prognostic accuracy method matching appropriate predictive models provided of internal validation. Some of the studies presented an "apparent validation", obtained on sample used to develop model, leading to strongly overoptimistic results. The majority part of the studies lacked sufficient details to precisely apply the model in a new dataset and this can be partly explained by the fact that there are no models externally validated.

In order to create rigorous risk prediction models, validation is one of the most important elements. A useful prediction model should give accurate estimates of risk, that can be used from the physicians to help them in clinical management and decision making. Moreover, this model should have a core role in predict individuals' outcome and cost-effectiveness of care. There is a substantial difference between models with internal and external validation. When new individuals were subjected to predictive model provided of internally validation, the performance is was lower than the one observed in the sample used to develop the model (76).

Fourth, our review found that poor conduct and reporting were quite common in both predictor finding and model developed studies. The results of our review highlight that one of the biggest limitations is that most of the studies were based on small sample sizes and number of events (particularly patients with transitions to psychosis) relative to the number of evaluated predictor variables. Small number of evaluated predictor variables ratios enhance the risk of overestimating the performance of the model, if it is developed and assessed in the same sample. When sample sizes are small, as is it frequently occurs in the field of prediction of psychosis research, their performance advantage resulting from the increased ability to capture the true underlying relationship

between predictors and response might not be high enough to compensate for the increased risk to overestimate.

Prediction in psychiatry needs to be considered a core aspect for testing hypotheses regarding clinically relevant issues (77). However, there are different problems that have to be faced before develop risk prediction models in psychiatry: one of them is the lack of availability of biological markers of illness; another is the idea that a particular discrimination value (e.g., an AUC threshold of 0.80) is required before clinical adoption. Indeed, in most prediction algorithms, including those regarding the Framingham risk score (FRS), the AUC often ranges from 0.75 to 0.80 (78).

Nevertheless, it's clear that a risk prediction model is useful only if early and preventive intervention are available and effective to prevent individual at high risk in developing disease. The use of validated risk prediction algorithms, despite being available, has delayed in primary care (79). If effective predictive models were designed, all the efforts should be done to make them useful and suitable for clinicians. In fact, quantification of validated prediction model impact in clinical care should be the target to be reached for implementation of these models. Though, impact studies are even less frequently performed than validation studies, as it can be elicited from literature (80).

The research about risk prediction models should progress together with the development of preventive interventions, i.e., long-chain ω-3 polyunsaturated fatty acids (PUFAs). Although ω-3 PUFAs treatment is attractive for prevention from a pathophysiologic perspective, preventive efficacy of ω-3 PUFAs for psychosis had been demonstrated in one single-site randomized, double-blind, placebo controlled trial which has compared ω-3 PUFAs with placebo (81), and later confirmed in a naturalistic, long-term follow-up (82). However, two large replication trials, the NEURAPRO trial (83) and the NAPLS-2 trial (84), did not confirm the hypothesis that ω-3PUFAs may be helpful to prevent psychosis in CHR individuals. The authors have hypothesized that such discrepancies might be explained by different overall transition rates, and by a ceiling effect due to concomitant antidepressant treatment. Other trials are currently underway to this end (Placebo-controlled Trial in Subjects at Ultra-high Risk for Psychosis With Omega-3 Fatty Acids in Europe, PURPOSE, NCT02597439). The efficacy of ω-3PUFAs in subgroups of patients should also be investigated—for example, in those with aberrant membrane fatty acid levels or inflammatory markers

However, until now, recent meta-analyses have not found robust evidence to favor specific preventive interventions, as confirmed by a recent umbrella review (85), i.e. a review of seven meta-analyses in the field of preventive interventions for psychosis in CHR individuals.

Several methodological limitations of our systematic, qualitative review must be acknowledged. First, we excluded articles published in languages other than English. Second, given the relative scarcity of research on this topic to date, and the variability across studies, we were not able to conduct a quantitative systematic review or meta-analysis. Meta-analytic results would be useful to provide important information regarding common predictors and the predictive power of existing models, but these are infeasible at present given the very limited state of research in this neglected area of clinical psychiatry. Third, combining the three CHR subgroups, populations may confound predictors and have an impact on the overall conversion rates (86) and, therefore, contribute to inconsistencies across sites. As an example, if compared with individuals at genetic high risk, people with intermittent psychosis are more severely impaired and develop more frequently acute psychosis (86). Therefore, extrapolating from the whole high-risk category its three fundamental subgroups, it is likely that more accurate predictors may be detected (61).

In conclusion, our systematic review revealed that poor methods and reporting are very common in prediction of psychosis research. In line with what has been reported above, measures of discrimination and calibration of risk prediction models have been reasonable. Most of the studies are based on small samples, did not perform internal or external cross-validation, and used poor model development strategies, and this is the reason why most published models are probably overestimated and their reported predictive accuracy is likely to be overoptimistic. Therefore, the science of risk prediction models in psychiatry is at the beginning, and this is clearly evident looking at the numerous limitations that these studies revealed. However, research on validation must be done. To make these models useful in clinical practice, predictors must be easily available and assessable, and people at high risk must have access to preventive intervention, that could be considered effective and with a minimal risk of side effects. As such, further research must be conducted to create and improve efficient but also focused preventive interventions. As for psychotic disorders, research is growing up, especially toward the direction of the risk prediction and risk stratification. The research must go forward and our goal must be to make effective prediction and prevention possible.

AUTHOR CONTRIBUTIONS

CM and NB contributed to summarize the literature data and to write the review. NB collected literature data and organized the tables. PB, SB, and PR contributed to writing and supervising the review.

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