IDENTIFYING INDIVIDUALS AT CLINICAL HIGH RISK OF PSYCHOSIS IN DIFFERENT CULTURES AND COUNTRIES

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Table of Contents

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EDITORIAL
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Editorial: Identifying Individuals at Clinical High Risk of Psychosis in Different Cultures and Countries

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Editorial on the Research Topic

Identifying Individuals at Clinical High Risk of Psychosis in Different Cultures and Countries

Identifying individuals at clinical high risk (CHR) for psychosis leverages a critical window of opportunity for prevention and early intervention. The characterization of effective detection and therapeutic strategies for this population represents one of the most unmet needs of contemporary psychiatry. The purpose of this Research Topic is to reflect on the similarities and differences in clinical, cognitive, biological, cultural and social aspects of CHR samples from different cultures and countries. This topic issue presents 3 perspectives, 1 study protocol, 4 reviews, and 4 original research articles which span the field of CHR research in different countries and offer insightful directions for future study and comprehensive practical suggestions in improving the efficacy in early intervention.

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PERSPECTIVES

All three perspective pieces speak to the degree to which current CHR methods are identifying and serving the actual target population. Schiffman et al., argue that the current "one-size-fits-all" approach of CHR identification does not fully reflect individual differences, particularly in context, ethnicity, race, culture, and development. They propose practical strategies for improving the accuracy of CHR identifications within and across different cultural settings. A culturally specific example, by Parabiaghi et al., describes the implementation of early detection and treatment of severe mental illness in youth across multiple regions of Italy. Promoting local community coalitions and an emphasis on accessibility, their broad preventive approach identified a group of 15–24 year olds enriched for CHR status. Finally, Kennedy et al., discuss what is needed from a public health perspective to extend systematic screening for early psychotic symptoms to general practice clinics.

PROTOCOL

Mahmood et al., describe a specific protocol to test a novel intervention in an underserved Latino CHR population in two different languages (Spanish and English) and countries (the United States and Mexico). This efficacy pilot is comparing Compensatory Cognitive Training (CCT) with recreational therapy (RT) to target cognitive and functional outcomes. Trials that extend the inclusiveness of the population served and real-life outcomes measured have important implications for the relevance of CHR efforts to public health.

REVIEWS

Improving the detection of CHR-P individuals is the topic of three reviews. Oliver et al. review the limitations of current structured interviews for identifying CHR and propose to address them with a Psychosis Polyrisk Score (PPS) prototype based on non-genetic risk factors, including social context. In a conceptual but non-systematic review furthering attention to sampling biases, Fusar-Poli et al., illustrate risk detection models targeting three different populations: secondary mental health care, primary care, and the community (general population). From their review of the evidence, the authors argue for the international advancement of CHR detection through complementary approaches. Transdiagnostic individualized risk calculators must be tested and implemented in primary and secondary care and digital and/or sequential screening in community samples. The final review on this topic extends the literature covered to include the prediction of outcomes in individuals identified using established structured interviews of CHR. Based on a meta-analysis of the largest sample of individualized data ($n = 1{,}676$), their model achieved only moderate prognostic value. They argue that the high level of heterogeneity in samples worldwide limits the clinical value of any one predictive model.

Finally, since the 0 to 25 years is a vulnerable developmental period during which children and young people experience many psychosocial and neurobiological changes, Fusar-Poli, on behalf of the Healthy London Partnership, reviews the evidence for established integrated and youth-friendly mental health services. In spite of the lack of robust controlled trials on their impact, early intervention for psychosis services may provide a paradigm to lead further reform.

ORIGINAL RESEARCH

Two original research studies investigate clinical and behavioral characteristics of early psychosis in culturally diverse samples. A study from the Korean Early Psychosis Cohort by Won et al., explores the characteristics and patterns of emotional recognition deficits in 495 patients with early psychosis. Their results show the correlation between symptom severity and the extent of emotional recognition deficits for different emotions. Examining the clinical characterization of schizotypy dimensions in a largely adolescent student sample ($n = 1{,}506$) from northern Spain, Fonseca-Pedrero et al., estimates a multidimensional psychosis liability network, a dynamic and complex system of risk and protective factors.

Two other studies target the biological correlates of CHR syndromes and symptoms. Liu et al., investigates the resting-state functional connectivity of the alpha rhythm measured by electroencephalography (EEG) to test a hypothesis of abnormal functional connectivity. Both early psychosis groups (first-episode schizophrenia and CHR) show an increased degree of connectivity compared with healthy controls, especially in the left occipital lobe area which is higher in the CHR group than in the first-episode schizophrenia group. Bonoldi et al., examine the relationship between basic self-disturbances and alterations in cortical midline structure volume measured by magnetic resonance imaging (MRI). They find that the higher level of basic self-disturbances in CHR individuals appear to be related to reductions in anterior cingulate volume.

Taken together, the high-quality contributions gathered in this Research Topic highlight both the promise and limitations of extant research for identifying, understanding, and helping CHR individuals across different cultures and countries. Several important and exciting efforts have been completed or are in progress, but much work still remains to be done. These articles provide international research collaborators with the key insights to further improve the tools and methods for identifying CHR individuals, and for developing effective interventions as well.

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TZ, JW, and KW have contributed intellectual content and have contributed to the actual writing of the editorial.

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Individual Differences and Psychosis-Risk Screening: Practical Suggestions to Improve the Scope and Quality of Early Identification

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Approaches to identifying individuals at clinical high-risk (CHR) for psychosis currently do not carefully weigh considerations around individual differences. Effective identification depends on awareness of factors beyond psychopathology as it is reflected in the current literature, such as sensitivity to idiographic circumstances and individual differences. The inability to address contextual factors when employing the status quo method of identification likely contributes to the unacceptably poor accuracy when identifying people at CHR. Individual differences related to factors such as culture, race, comorbidity, and development likely play an important role in accurate identification, and have the potential to improve the validity of approaches intended to identify this population. Tailored approaches to assessment based on an awareness of context, identity, setting, and preferences of clients are possible, and customizing assessment efforts accordingly may be useful for accurate identification of people at CHR. Highlighting the potential for the existing early identification paradigm to marginalize or misunderstand certain groups, we describe how effective identification and ethical diagnosis require sensitivity to individual differences writ large. We suggest that recognizing the importance of these factors advances a more inclusive and accurate approach to identification.

Keywords: individual differences, idiographic, clinical high risk, ultra high risk, prodromal psychosis, early identification, early intervention

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OVERVIEW

Research related to identifying people at clinical high-risk (CHR) for psychosis has seen exponential growth in the past decade, in part fueled by the building evidence that intervention during this phase can prevent, delay, and/or lessen the severity of future negative outcomes (1, 2). Significant gains in identification include increased accuracy using risk calculators based on large samples and advanced statistical approaches (3–5). Additionally, this body of work has revealed a clinically relevant vulnerability in those at CHR—associated with high rates of substance abuse, trauma exposure, cognitive impairments, and suicidal risk (6, 7)—irrespective of transition to first episode or full-threshold psychosis (8). Findings like these have likely generated a number of recognized and heretofore undiscovered benefits relating to earlier interventions, stronger therapeutic relationships, and shorter duration of untreated psychosis. To build on these

gains it is important to consider that while the current CHR assessment approach has relatively adequate positive predictive value in help-seeking individuals, it fails to capture a clinically meaningful percentage of individuals truly at risk for psychosis, and concurrently might over-pathologize individuals who are not at risk. Unfortunately, typical CHR interview practices such as those employed with the Structured Interview for Prodromal Syndromes (SIPS) (9) in North America, may in some cases not fully honor individual differences of those being evaluated for CHR.

In this *Perspective* commentary, we highlight several issues with this "one-size-fits-all" approach in relation to the ethnic and racial differences as well as culture, context and socio-economic status. This has a clear relevance for this special issue on identifying individuals at CHR in different cultures and countries, as we highlight how differences in factors such as race/ethnicity and culture can substantially impact clinician-ascribed diagnostic ratings, even within a single country—a point clearly aligning with the broader volume focusing on cross-cultural and international differences in CHR research. We also discuss how the status quo approach of interviews such as the SIPS' identification of Attenuated Psychosis Syndrome (APS) and related risk states can limit the incorporation of important information relating to comorbidity and developmental considerations, relevant concerns in the CHR population. After highlighting issues for each area, we will discuss suggestions for current research and intervention work, as well as outline a series of goals for future studies in this domain.

CULTURAL AND CONTEXTUAL COMPETENCE

Evidence suggests that immigrants, ethnic/racial minorities, and those raised in certain urban environments are at a heightened risk for developing psychosis-spectrum disorders (10, 11). It is possible that greater exposure to risk factors for psychosis, including trauma and discrimination associated with any minority identity (e.g., race, sexual identity, gender), lead to higher rates of psychosis symptoms and diagnoses (12). At the same time, it may be that contextual or environmental factors can lead to endorsing items—particularly those related to suspiciousness—on CHR assessment tools when the underlying mechanism is either distally connected or unrelated to psychosis (13, 14). Responses to discrimination, crime, and/or trauma may be causally, concurrently, concurrently that leads to causality, or illusorily linked to psychosis- risk symptoms (13, 14). Further, clinician biases can result in systematically ascribing psychosis-spectrum explanations for culturally distinct behaviors (15). For instance, some common themes in CHR interviews and screening tools probe for very normative behaviors in certain cultures (e.g., belief in superstitions, déjà vu, having special talents, religious convictions). In some cases, endorsement of these more normative prompts is associated with *better* functioning (16). All of these factors can lead to diagnostic confusion, false-positives, and ultimately large-scale health disparities for minority groups.

There are several possible routes to addressing these issues should they arise as consistent concerns in the field. First, it is useful to ensure that interview techniques are sensitive to cultural factors, which may require using structured interviews and potentially modifying existing measures and processes to explicitly probe for these relations. Assessments should allow time for clients to share their individual and cultural views around what are intended as CHR probes, such as their possible experiences of discrimination, social deprivation, and/or trauma related to their surrounding neighborhood context (15, 17). Additionally, screening tools used to indicate risk, and often trigger referrals, should be validated in different cultures and with different racial and minority groups; results should be considered accordingly prior to assuming psychopathology (16). Such analyses could drill down to scale, factor, or the item level. More broadly, designing validation studies to understand the role of other, often related, aspects of identity (e.g., SES, religion/spirituality, cultural identification, help-seeking response style, language differences) can create more individualized approaches to risk assessment. More explicitly infusing cultural competency into risk assessment training (e.g., the role of clinician bias, socially mediated stress as a dynamic factor when establishing risk), and perhaps even empirically measuring assessor's cultural competence may begin to create a more sensitive and possibly accurate workforce (18). These steps may help reduce the risk of misdiagnosis as well as enhance detection in those who may be more vulnerable for risk of a psychotic disorder.

COMORBIDITY

Comorbid psychopathology is another key individual difference requiring consideration. In many cases, "CHR symptoms" may more accurately reflect other, non-psychotic psychopathological processes. For example, symptoms of OCD such as recurring thoughts may in some cases resemble unusual thought content in CHR (e.g., "*Have you felt that you are not in control of your own ideas or thoughts?*"), despite being presumed as clinically "distinct." Additionally, use of psychoactive substances can elicit psychotic-like experiences that persist beyond acute intoxication and therefore be misinterpreted as risk symptoms despite resolving with sustained abstinence. Likewise, the persistent and preoccupying cognitive distortions associated with false perceptions of body image in eating disorders and body dysmorphic disorder can often resemble the delusional thinking and perceptual disturbances experienced in populations at clinical high risk for psychosis (19). Differentiating all of these experiences from "risk for psychosis" vis-a-vis CHR can present challenges, particularly because comorbid health conditions, experiences of adversity, and substance use are not only risk factors for CHR and psychosis, but can also mimic psychosis-risk and appear in conjunction with the CHR state, each of which has different clinical implications (20–23).

There are some practical solutions to addressing comorbidity in those at CHR, should additional research identify comorbidity as a concern for accurate identification of those at risk. Assessing

possible contributors to symptoms at the same depth as psychosis risk, in recognition of clinician bias to one's own specialty, can help address whether factors such as trauma, substance use, or eating disorders for instance are contributors, comorbidities, or unrelated to psychosis risk. In many cases, comorbidities can have accompanying psychotic symptoms, suggesting a need in some cases to expand the definition of psychosis in the context of CHR conceptualizations. Additionally, graduate training and continuing education programs providing psychodiagnostic training, periodic re-training, and assessment validity check-ins may limit misdiagnosis or possible assessor drift. Truly attending to these concerns may require more frequent and in-depth follow-up and an openness to new information that may run contrary to initial impressions—efforts that will hopefully provide a more accurate and individualized evaluation. Finally, it is important to recognize that comorbidity is the rule rather than the exception in individuals at CHR. Although CHR status does not appear to reliably predict other outcomes beyond psychosis (24), certainly the rich information regarding comorbidity will serve to strengthen predictive models and relatedly help to better characterize individual variation and thereby promote precision medicine. Notably, these conditions are clinically relevant in their own right, and should be carefully considered and treated in this manner.

DEVELOPMENT

A similar call for developmental considerations can also be made. For instance, pre-adolescents may endorse over valued beliefs (e.g., "*Do you daydream a lot or find yourself preoccupied with stories, fantasies, or ideas?*"), and adolescents may endorse ideas of reference (e.g., "*Have you had the sense that you are often the center of people's attention?*"), when such "symptoms" at face-value are often normative in these age groups (25, 26). Younger individuals might also interpret interview questions in ways that are different from the interviewer's intention or respond in all-or-nothing extremes on self-report measures (26–32). Longitudinal studies of self-reported psychotic-like experiences reveal a declining rate of endorsement with age, suggesting that these experiences may be part of typical developmental processes. Incorporating developmental awareness in our measures and among clinicians will likely increase accuracy of CHR detection (33, 34). For example, it is quite easy for CHR diagnosticians to confuse sensitivity to sound and belief in an invisible audience (experiences that become increasingly sensitive or salient in adolescence) with psychotic experiences (25, 35, 36). Measures of functioning are also likely particularly sensitive to stages of development as well; the functional expectations of adolescents and young adults vary dramatically from year to year.

There are also a number of practical suggestions to address issues around developmental variation in CHR research and treatment, should development be identified as a reliable confound to accurate identification. First, a developmentally-informed conceptualization of risk can be achieved by training clinicians on the unique developmental considerations of this age range, creating anchors within interview tools that reflect typical and atypical development, developing age-informed norms/cutoff scores, maintaining a sensitivity to response style biases, thoroughly probing endorsements to ensure a shared understanding of meaning, and committing to a longitudinal approach (clinically and through research). Second, investigators and clinicians alike can stay current on not only the literature (as we are regularly discovering new potential developmental confounds in this area), but also norms for adolescent behaviors [e.g., around social media use, social engagement patterns, and dating; (37, 38)] and recent trends in subculture identification and practice (a rapidly shifting area with many potential nuances that would likely confound accurate assessment and treatment). Further, investigators can be mindful not to treat the adolescent period as a unidimensional construct, but rather, understand that this is a dynamic span of time, beginning just at the end of late childhood and carrying many individuals into the mid to late 20's. The scope of "normative" behavior, as well as social and role functioning expectations will be much easier to assess with that consideration in mind, and to this point, it may be best to view different stages by the attainment of developmentally relevant landmarks, instead of age or year in school.

CONCLUSIONS

Prevention efforts in psychosis have never been more promising. True prevention will require the CHR concept to expand beyond specialty clinics, perhaps creating meaningful—but not insurmountable—hurdles between the current state of affairs and the aspirations of identifying the large proportion of people at CHR who are currently undetected, and avoiding labeling people as at-risk who are not. Systemic issues, such as increasing education; creating a culture of hope, prevention, and recovery; and reducing stigma so that more people are willing to seek help, are essential to this goal. Other systemic issues include addressing the bifurcation of mental health and education systems relevant to the risk age, engaging community partners beyond mental health specialists, and considering a more pluripotent approach to identification whereby outcomes are more broadly defined beyond the presence of psychosis. Within-field innovations are required as well, such as creating interview tools with increased accuracy and that require less training, and considering mechanisms when building risk models. To reach these goals, we will benefit from methods that require substantial investments, such as diagnostically-fluid prospective studies and studies that incorporate the voices of people at CHR and their families (e.g., participatory action research).

Complementing these initiatives are the promise of contextual and cultural adaptations. In the diagnosis of illnesses with threshold psychosis, for instance, when using the DSM-5 cultural formulation interview to re-evaluate diagnoses in an ethnically diverse sample initially diagnosed by community providers, Adeponle et al. (17) reported that 49% of individuals with initial diagnoses of psychosis were changed to non-psychotic disorders, while only 5% of initial non-psychotic disorders were re-diagnosed as having a psychotic disorder. In the emerging CHR field we argue a similar need to reach beyond nomothetic and normative perspectives, and to peer deeper to consider contextual and individualized approaches to identification and care.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Psychosis Polyrisk Score (PPS) for the Detection of Individuals At-Risk and the Prediction of Their Outcomes

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Primary prevention in individuals at Clinical High Risk for psychosis (CHR-P) can ameliorate the course of psychotic disorders. Further advancements of knowledge have been slowed by the standstill of the field, which is mostly attributed to its epidemiological weakness. The latter, in turn, underlies the limited identification power of at-risk individuals and the relatively modest ability of CHR-P interviews to rule-in a state of risk for psychosis. In the first part, this perspective review discusses these limitations and traces a new approach to overcome them. Theoretical concepts to support a Psychosis Polyrisk Score (PPS) integrating genetic and non-genetic risk and protective factors for psychosis are presented. The PPS hinges on recent findings indicating that risk enrichment in CHR-P samples is accounted for by the accumulation of non-genetic factors such as: parental and sociodemographic risk factors, perinatal risk factors, later risk factors, and antecedents. In the second part of this perspective review we present a prototype of a PPS encompassing core predictors beyond genetics. The PPS prototype may be piloted in the next generation of CHR-P research and combined with genetic information to refine the detection of individuals at-risk of psychosis and the prediction of their outcomes, and ultimately advance clinical research in this field.

Keywords: schizophrenia, clinical high risk, risk, psychosis, prediction, environment, polygenic risk, genetics

HIGHLIGHTS

- Research in individuals at Clinical High Risk for Psychosis is at a standstill.
- Limitations include low detection power and suboptimal prognostic accuracy.
- Psychosis Polyrisk Scores (PPS) have the potential to improve the detection of at-risk individuals.
- Psychosis Polyrisk Scores (PPS) have the potential to optimize the prediction of psychosis.

INTRODUCTION

Psychotic disorders such as schizophrenia are among the world's leading causes of disability from psychiatric disorders (1). Under standard care, outcomes of psychosis are relatively poor (2). The implementation of early intervention services for patients experiencing their first episode of illness may improve the course of the disorder (3). However, recent meta-analytical evidence indicates there is no robust evidence that these services can effectively prevent psychotic relapse (3) or reduce the duration of untreated psychosis (4). Thus, there are high expectations that primary prevention in individuals who have not yet experienced the disorder can ameliorate its course (5). In clinical practice, such a strategy has been limited to indicated prevention that is offered to individuals at Clinical High Risk for Psychosis [CHR-P (6)]. The definitions and description of specific CHR-P instruments have been fully presented in previous publications (7). In brief, the CHR-P state defines a condition of liability toward the development of incident psychotic disorders, but not of any other incident non-psychotic mental disorder (8, 9). CHR-P research has allowed the study of the factors that predate the onset of psychosis and experimental therapeutics to be trialed for the prevention of psychosis (e.g., omega-3 fatty acids (10, 11). However, its impact on improving the outcomes of psychotic disorders has been constrained by significant limitations. The present perspective review originates from a critical analysis of these limitations and confronts this in two sections. In the first part, it traces a new conceptual avenue for future research—tackling the above constraints by formulating the theoretical groundwork. In the second part, a practical prototype of a new prognostic tool is introduced to inform the future development of more efficient strategies to detect individuals at-risk for psychosis and the prediction of their outcomes.

METHODS

For the first part, a critical review of the past literature was conducted. Relevant articles were retrieved through international databases (PubMed, books, meetings, abstracts, electronic guidelines, and international conferences) and critically reviewed by the authors of the paper. Subsequently, results were presented after reaching a consensus and were summarized through illustrative tables and figures. This review is not following a systematic literature search, data extraction, or reporting approach, since its ultimate aim is to provide a conceptual perspective of the field. In the second part, we applied the concepts refined through the critical literature search to the field of psychosis prediction. We thus operationalize a Psychosis Polyrisk Score (PPS) and present it. Simulation analyses complemented our approach to provide some initial feasibility and prognostic values associated with the use of the PPS. Further details of the operationalization of the PPS and how simulation analyses were conducted can be seen in section "Psychosis Polyrisk Score (PPS) Prototype".

CONCEPTUAL REVIEW OF THE LIMITATIONS OF THE CLINICAL HIGH RISK STATE FOR PSYCHOSIS

The Epidemiological Weakness of the Clinical High Risk State for Psychosis

To illustrate the epidemiological weakness associated with the CHR-P paradigm we present data from our experience of detecting and providing clinical care to these individuals in South London (12). First, by using validated population-level prediction tools (e.g., www.psymaptic.org), we estimated the annualized incidence of psychotic disorders in the local general population (13). The recruitment of individuals who may be at CHR-P for psychosis is primarily based on unstructured selection and sampling strategies that are based on clinician's suspicion of psychosis risk (14) and on help-seeking behaviors (15). Therefore, the way these individuals are sampled will determine their level of accumulation of risk factors for psychosis. For example, when individuals undergoing a CHR-P assessment are recruited from mental health services, they accumulate several risk factors for the disorder (16) which increase their level of risk to 15% at 3-years, compared to the 0.43% 3-year risk in the local age-matched general population (12, 17) (**Figure 1**). This level of risk is also termed as "pre-test risk," because it is ascertained in the whole group of people undergoing a CHR-P assessment before the results of the assessment itself are known (19). Therefore, the level of risk of samples undergoing a CHR-P assessment does not reflect the level of risk of the general population, but it is substantially higher: from 0.43% at 3-year to 15% at 3-year (about 35-fold-higher). Once these individuals complete a CHR-P assessment, they will be predicted to have a certain post-test risk of developing psychosis or not. Thus, pre-test and post-test risks of psychosis index an individual's likelihood of developing psychosis before and after the results of the CHR-P assessment are known, respectively (19). It follows that the value of a test will depend on its ability to alter (increase or decrease) a pre-test probability of a target condition into a post-test probability that will influence a clinical management decision (20). When these individuals with a 15% pretest risk at 3-year are assessed (tested), those who will meet CHR-P criteria will have a 26% risk of developing psychosis at 3-year (1.7-fold increase) and those who will not meet the CHR-P criteria will have a 1.56% risk of developing psychosis at 3-year (10-fold decrease) (**Figure 2**). The relationship between the risk enrichment accounted by the recruitment step (pre-test) and diagnostic assessment step (post-test) (19) is illustrated in specific charts (Nomograms) that have been externally validated (23). It confirms that once individuals are recruited for undergoing a CHR-P assessment, there is only limited prognostic gain in meeting the CHR-P criteria (i.e., testing positive to the interview), while there is some prognostic gain in not meeting the CHR-P criteria (i.e., testing negative to the interview). In other words, the CHR-P tools are quite good at ruling out a state of psychosis risk but not very good at ruling it in; they can only be clinically meaningful when applied to samples that have been risk-enriched. When different CHR-P instruments (7) or

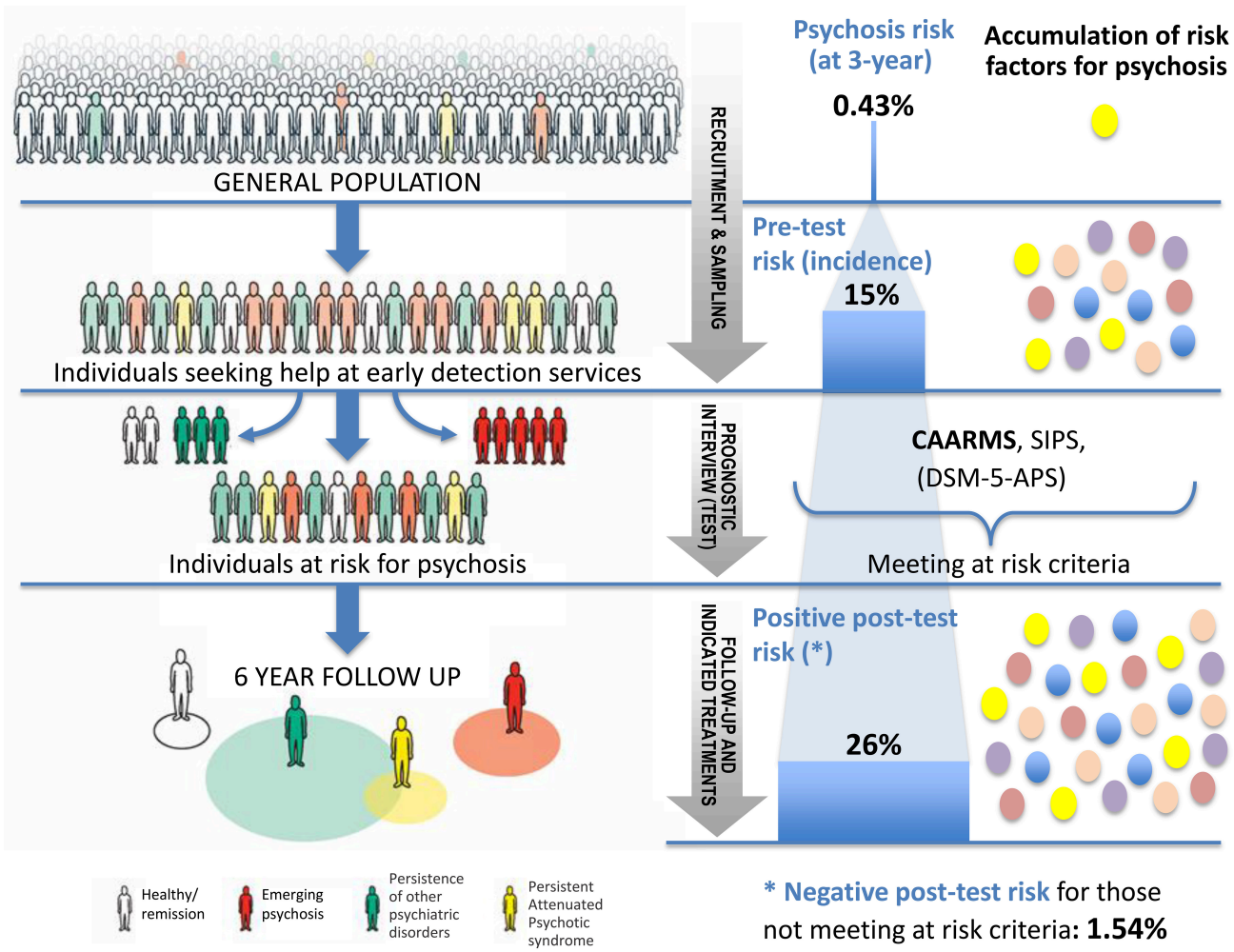

FIGURE 1 | Individuals seeking help at specialized psychosis early-detection clinics have a higher (pre-test) risk of developing psychosis [15% at 3 years (14)] than the general population (0.43% at 3 years) (17). Those who will meet the clinical high risk for psychosis (CHR-P) criteria at the prognostic interview (Comprehensive Assessment of At-risk Mental States [CAARMS]) will have only a modest increase in their (post-test) level of risk for psychosis (1.7-fold, from 15 to 26%). Those not meeting the CHR-P criteria (18) will have a substantial decrease in their (post-test) risk (10-fold, from 15 to 1.56%).

even the DSM-5 category of Attenuated Psychosis Syndrome, -which is not psychometric-based and therefore not strictly speaking a CHR-P instrument- are applied to these samples, they produce comparable prognostic performance (24, 25). As shown in **Figure 3**, the actual risk of developing psychosis in CHR-P samples is thus largely dependent on the way individuals are recruited for the assessment and on their pre-test risk enrichment (14, 17). The additional challenge is that recruitment strategies for individuals undergoing CHR-P assessment and therefore pre-test risk enrichment are highly heterogeneous, idiosyncratic and poorly standardizable (14). This results in a high variance of risk enrichment across samples undergoing CHR-P assessment [meta-analytical 48-months risk of psychosis 95%CIs 0.09–0.24 (14), **Figure 3**]. Therefore, CHR-P samples that undergo distinct psychosis risk enrichment pathways are hardly comparable as they are likely to have different profiles of risk factors (26, 27). These notions have both clinical and research implications. On a clinical level, the variable risk enrichment of CHR-P samples may amplify variations in patients' clinical needs and limit the provision of standard clinical care. On a research level, CHR-P samples with little risk enrichment or heterogeneous risk profiles may lead to negative findings in neurobiological studies (28) or even in preventative trials (29–31). Overall, because of these points, the key limitation of the CHR-P paradigm is currently that of substantial epidemiological weakness (27, 32).

Idiosyncratic Accumulation of Risk Factors in Individuals With a Clinical High Risk State for Psychosis

Risk factors contributing to the psychosis risk enrichment observed in CHR-P samples are not entirely known. A recent meta-analysis has summarized the available evidence across 54 putative risk factors investigated in CHR-P samples, in comparison to controls (16). Astoundingly, there are no existing studies on the association between genetic or epigenetic risk

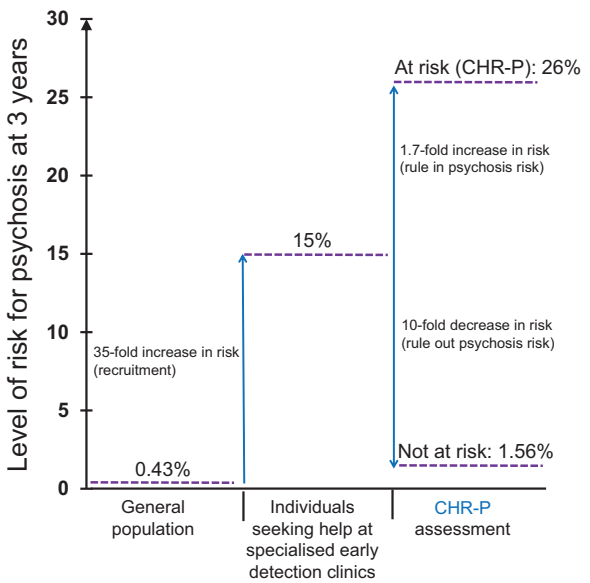

FIGURE 2 | Sampling procedure for individuals at clinical high risk for psychosis (CHR-P) (14). Idiosyncratic recruitment strategies that are characterized by heterogeneous sampling biases (convenience and judgmental sampling) result in the accumulation of various risk factors for psychosis and differential level of enrichment of psychosis risk. The figure is based on the data reported in Fusar-Poli et al. (17), Fusar-Poli (21), and Rutigliano et al. (22). CAARMS, Comprehensive Assessment of At Risk Mental States; SIPS, Structured Interviews for Psychosis-Risk Syndromes; DSM-5-APS, Diagnostic and Statistical Manual, 5th Edition, Attenuated Psychosis Syndrome. Adapted from: Fusar-Poli et al. (12).

factors and the CHR-P state. Although family history for psychosis is partially embedded in CHR-P criteria, its predictive significance within the CHR population is questionable. A recent collaborative meta-analysis has found that CHR-P individuals with a familial history of psychosis do not have an enhanced risk of developing psychosis within 4 years follow-up, compared to controls (33). Essentially, the above meta-analysis showed that CHR-P subjects are more likely to show obstetric complications, tobacco use, physical inactivity, childhood trauma, high perceived stress, childhood and adolescent low functioning, affective comorbidities, male gender, single status, unemployment, and low educational level as compared to controls (16). Overall, this study suggests that risk enrichment of CHR-P samples can be attributed to demographic and environmental risk factors like childhood trauma, adverse life events and affective dysfunction. The differential combination of risk/protective factors in each CHR-P individual is likely to account for the distinct clinical outcomes observed in these samples: psychosis onset, recovery, or disability (6).

Limited Detection Power

An additional problem is that the risk profiles observed in CHR-P individuals who will develop psychosis may not be representative of a prototypical first episode of psychosis. CHR-P individuals who later transition to psychosis represent only about 5% of first episode patients within secondary mental health care (34). This suggests there is limited detection power for at-risk cases and inefficient recruitment strategies (5). Such a limitation is substantial, undermining the significance of the entire paradigm. Although CHR-P interviews are particularly good at ruling out psychosis, only a minority of individuals are referred for a full CHR-P assessment. The alternative approach of using CHR-P instruments to screen all individuals accessing secondary mental health care is logistically untenable (5). These limitations of knowledge can be tackled through a refined approach for the detection of at-risk individuals and the prediction of psychosis. Recent studies have developed and externally validated individualized risk prediction tools that depend on few established risk factors for psychosis (34–36), with the ultimate goal of improving the detection of at-risk cases. This line of research can be further expanded through the integration of recent epidemiological research on genetic risk factors, demographic and environmental risk factors for psychosis.

Implications for Neuroscience and Behavioral Research

The above limitations have a profound impact on neurobiological research conducted in CHR-P samples. Idiosyncratic recruitment strategies lead to uncontrolled accumulation of risk and protective factors and increase the clinical heterogeneity of CHR-P samples (33). In turn, the high clinical heterogeneity has hampered the discovery of reliable and replicable biomarkers of psychosis risk (21). As summarized in **Figure 3**, CHR-P samples that had been largely recruited through the community (37) showed a dilution in pre-test risk (14) with a resulting lack of gray matter abnormalities, when compared to controls (28). Because of these issues, no reliable neuroimaging, electrophysiological or neurocognitive biomarker of psychosis risk has been validated for clinical use in CHR-P samples yet. Furthermore, the limited detection power of the current recruitment strategies adds concerns, undermining the assumption that the neurobiological alterations reported in CHR-P individuals would represent prototypical features preceding the onset of psychosis (3).

THE EXAMPLE OF POLYGENIC RISK SCORE

High heritability of psychotic disorders, such as schizophrenia, indicates a substantial impact of inherited genetic variants on risk. Although genetic variants can be common or extremely rare, nearly one-third of the genetic risk of schizophrenia is indexed by common alleles genotyped through arrays in genome-wide association studies (GWAS) (38). As each marker individually explains only a small proportion of the genetic variation, recent research has developed polygenic risk scores in order to examine disorder prediction by genetic variants "en masse," summarizing risk variants across many associated loci into quantitative scores (39). Such an approach requires robust a priori knowledge on the association between specific loci and psychosis as a first step (38). The polygenic risk score was therefore grounded on the GWAS meta-analysis conducted by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (38). This meta-analysis identified that despite the small effect sizes of single loci, the cumulative effect of thousands of schizophrenia-associated loci expressed a polygenic risk score

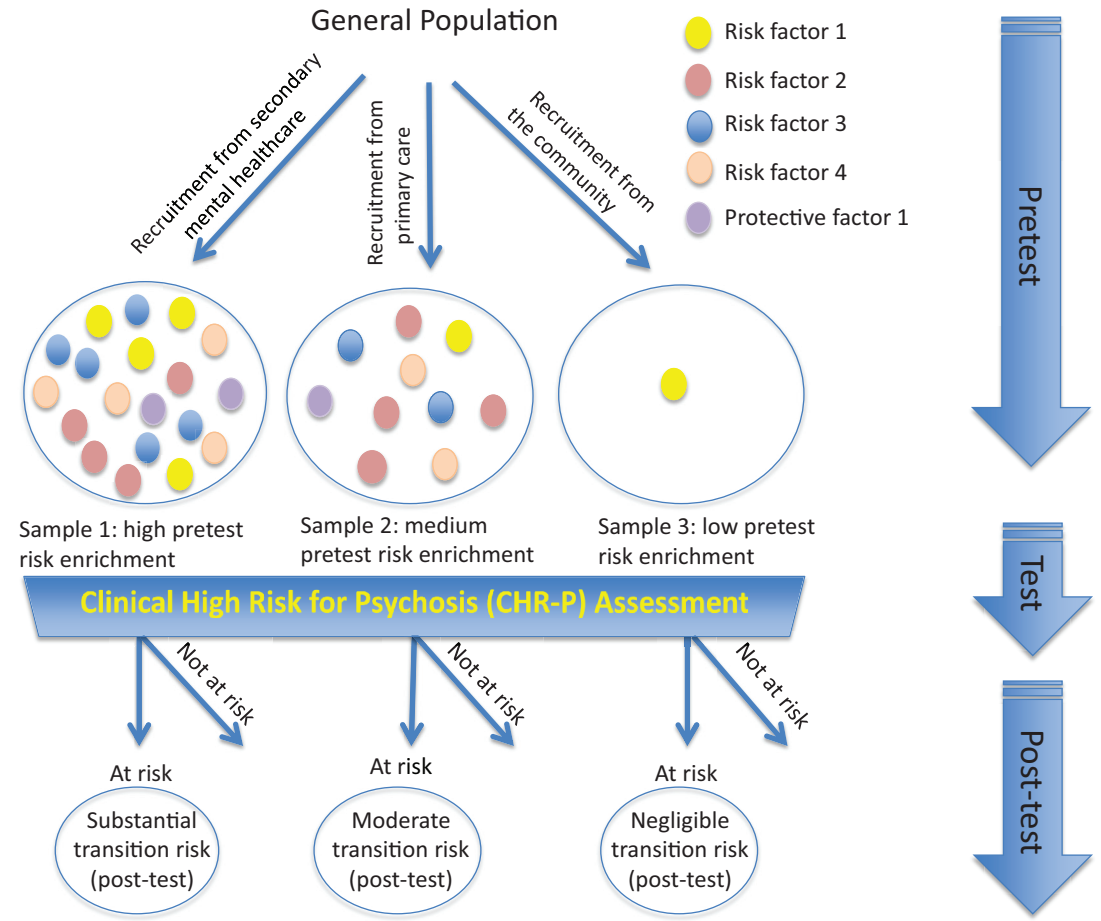

FIGURE 3 | Effect of sampling biases in the CHR-P paradigm. Idiosyncratic recruitment strategies lead to differential accumulation of risk factors for psychosis across samples undergoing CHR-P assessment. For example, recruiting from secondary mental health care (sample 1) is associated with high risk enrichment for psychosis (also termed "pretest" risk) compared to recruiting from the general practitioners (sample 2), while no or little psychosis-risk enrichment is observed if the sample is randomly selected from the general population (sample 3). Applying the CHR-P interviews to these samples discriminates between those at-risk for psychosis and those not at-risk (post-test risk). However, the actual (post-test) transition to psychosis that is observed at follow-up largely depends on the overall level of accumulation of risk factors for psychosis during the risk enrichment phase and only in minor part on the results (i.e., testing at-risk or not at-risk) of the CHR-P assessment itself.

explained up to 18% of variance between cases of schizophrenia and controls in GWAS studies and 7% of the variance on the underlying liability scale to schizophrenia in the general population (38). Polygenic risk scores have been used to predict case-control status at the time of a first episode psychosis, explaining nearly 9% of variance (39). However, as heritability of schizophrenia is 64% (95%CI: 62–68%) (40), a large proportion of the variance remains unaccounted. As the variance explained is too small for individual risk prediction, the use of polygenic risk scores in clinical routine is currently insufficient on its own (38, 41).

TOWARD A POLYRISK SCORE ENCOMPASSING NON-GENETIC RISK/PROTECTIVE FACTORS

Given the small proportion of variance explained, risk prediction needs to be boosted by supplementing the polygenic risk scores with additional information. The model that has received some empirical support indicates that the etiology of psychotic disorders like schizophrenia involves direct genetic and environmental effects, along with their interaction (42, 43). In reality, some of the most predictive factors, including family history of mental illness and socioeconomic status, include both a genetic and environmental component and hence a distinction between genetic and environmental factors may be spurious. We will, therefore, adopt a pragmatic approach and use the term non-genetic to define sociodemographic, social, parental, perinatal, later risk or protective factors, or antecedents -see below-. The use of a priori clinical knowledge is a robust method for developing a clinical prediction model [for a review on this see (44)].

Definition of Risk and Protective Factors for Psychosis

For descriptive purposes, in the current manuscript risk/protective factors for psychotic disorders are grouped

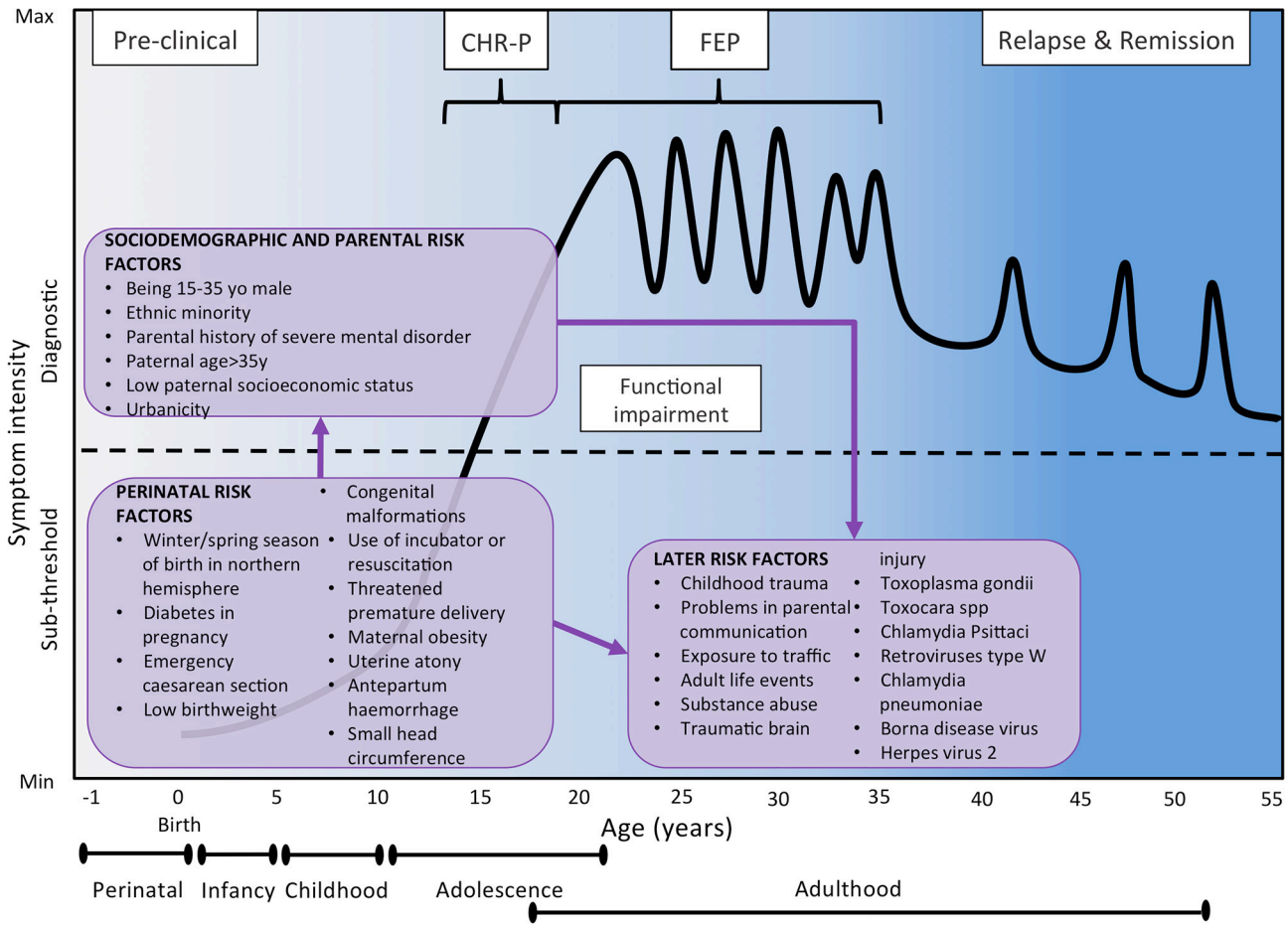

FIGURE 4 | Putative model of the onset and progression of psychosis in relation to non-purely genetic risk factors and developmental processes affected by the disorder. Sociodemographic and parental risk factors and perinatal risk factors have been implicated during the preclinical phase, usually observed from the birth to infancy, childhood and early adolescence. Additional later factors occurring during later adolescence and early adulthood can trigger the onset of attenuated psychotic symptoms, functional impairment and help-seeking behavior, which constitute the CHR-P stage. The diagnosis of psychosis, which operationally corresponds to the first episode of psychosis, is usually made during the adolescence or early adulthood, with a peak from 15 to 35 years (48). Once diagnosed, psychosis usually follows a fluctuating course punctuated by acute exacerbation of psychotic crises superimposed upon a background of poorly controlled negative, neurocognitive, and social cognitive symptoms. The pink boxes represent the risk factors for psychosis as identified by the umbrella review (48). There is no assumption that these risk factors are of causal nature or that they are independent of each other. Furthermore, certain risk factors may actually represent outcomes of earlier risk factors. Figure based on the data reported in Fusar-Poli et al. (16). FEP, First Episode Psychosis; CHR-P, Clinical High Risk for Psychosis.

across domains previously defined: sociodemographic and parental factors, perinatal factors, later factors, and antecedents (45–47). Demographic, parental, social, and perinatal risk factors are generally believed to exert their role during the early developmental phases that precede the onset of psychosis (see also **Figure 4**). On the contrary, later risk factors and antecedents are believed to modulate psychosis risk in the post perinatal period, from late childhood up to the phases that shortly precede the onset of a psychotic disorder. While later risk factors would indicate a passive exposure to socio-environmental factors, antecedents would index premorbid deviations in functioning and developmental milestones and active risk-modifying processes involved in psychosis onset (45–47). However, the boundaries of these categories may in fact overlap.

Evidence and Classification of Risk and Protective Factors for Psychosis

The inclusion of non-genetic factors in the development of polyrisk scores is not a conceptually novel approach, but it has been limited to date by the lack of established and robust a priori knowledge on the association of non-genetic factors and psychotic disorders. Such a limitation has been recently overcome by an umbrella review, which is a meta-analysis of meta-analyses or reviews, investigating several non-genetic risk/protective factors of psychosis that operate at an individual level. The umbrella review further classified these factors into convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), and non-significant (ns) evidence, according to a standardized classification already widely adopted in other branches of clinical medicine (48) to control for potential biases.

For instance, sensitivity analyses restricted to prospective studies assessed whether there was evidence for risk factor pre-existing before disorder onset, therefore controlling for reverse causation (48). By providing the required gold-standard *a priori* knowledge (44), the core results of this meta-analysis (**Figures 4**, **5A–E**) place the groundwork for the development of a comprehensive polyrisk score for psychosis prediction.

The Substantial Role of Sociodemographic Risk/Protective Factors

Most aetiopathogenic models for psychotic disorders have focused on genetic and environmental risk factors, while demographic factors have been investigated to a lesser degree, presumably in the light of the fact that these factors are not strictly modifiable. Nevertheless, the recent umbrella review found a main effect for male gender, a main effect for 15–35 years of age (48) and an association between psychotic disorders and being a male aged 15–40 year-old (48). Age older than 35 was found to be a protective factor (48). The additional risk factor that was consistently associated with psychosis was ethnicity, variously defined as being an ethnic minority or as having an immigrant status or through specific categories of ethnicity. For instance, being of a black Caribbean (OR 4.87, class I), black African (OR 4.72), Asian (OR 2.83) or mixed (OR 2.19) ethnicity in England or North African in Europe (OR 2.22) was associated with an increased liability to psychosis (48). These findings are of significant value for the development of polyrisk scores as they suggest that these factors should always be assessed and considered for the prediction of psychosis onset. In other branches of medicine, age and gender are consistently used in individualized risk scores for predicting cardiovascular diseases (QRISK) (49), diabetes (AUSDRISK) (50) or stroke (CHA2DS2-VASc score) (51). Recent confirmation of the clinical utility of demographic variables for predicting psychosis onset was shown by a recent study that included age, gender, age by gender, and ethnicity in an individualized risk estimation tool for predicting psychosis in secondary mental health care (34).

Parental and Perinatal Risk/Protective Factors

Psychotic syndromes are disorders of adapting to the environment (52), which include parental, perinatal, later risk factors, along with antecedents. The umbrella review identified that parental factors such as paternal age (>35 OR 1.22, >45 OR 2.36), low paternal socioeconomic status (OR 1.30) and parental history of severe mental disorder (OR 5.94) were all associated with psychosis (48). Polygenic studies controlling for the effect of parental risk factors found that parental socioeconomic status accounted for 45.8% (95%CI, 36.1–55.5) of cases with schizophrenia (53). Assuming social causation, this indicates that the impact of the environment is actually higher than the genetic factors. Similarly, a recent study indicated that polygenic risk scores can improve their predictive value, explaining 17.4% variance if used in cases with a family history of schizophrenia/psychoses (i.e., prediction by PRS including more genetic variants) (53). These findings concur with the need for integrating genetic and parental risk factors for psychosis in a polyrisk score. Some studies have already supplemented the polygenic score profile with information on family history for psychotic disorders (54). Other risk factors could be considered for the development of a polyrisk assessment including urbanicity (OR 2.19) (48). As this factor was robust and survived sensitivity analyses (class I), it should always be measured and considered in polyrisk assessment approaches (48). Finally, a series of perinatal risk factors were shown to be useful for the polyrisk score. The most robust of them was winter/spring season of birth in northern hemisphere (OR 1.04, class III) (48), followed by diabetes in pregnancy (OR 10.12), emergency cesarean section (OR 3.36), low birth weight (<2000 OR 2.46, <2500 OR 1.57), congenital malformations (OR 2.31), use of incubator or resuscitation (OR 2.12), threatened premature delivery (OR 2.05), maternal obesity (OR 1.99), uterine atony (OR 1.93), antepartum hemorrhage (0.163), and small head circumference (OR 1.41) (48). To the best of our knowledge, no studies have attempted to combine polygenic risk assessment with these risk factors, and this may prove to be a promising avenue of research.

Later Risk/Protective Factors

Later risk factors that have been associated with psychosis include a variety of environmental risk factors such childhood trauma (OR 2.87), problems in parental communication (OR 11.57), exposure to traffic (OR 5.55), adult life events (OR 5.34), substance abuse such as heavy cannabis (OR 5.17), benzene (OR 3.20) or tobacco (OR 2.19), and traumatic brain injury (OR 1.49) (48). Later risk factors also include a series of infective agents such as IgG Toxoplasma gondii (OR 1.82), Toxocara (OR 41.61), Chlamydia Psittaci (OR 29.05), retroviruses type W (OR 19.78), Chlamydia pneumoniae (OR 6.02), Borna disease virus (OR 1.94), and herpes virus 2 (OR 1.44) (48). Exposures to childhood trauma and Toxoplasma gondii were most robustly associated with increased risk of psychosis (class III), while the other later factors showed weak association (48).

Antecedents

There are numerous antecedent factors associated with psychosis. The risk factor with the most robust evidence was CHR-P status (OR 9.32, class I), followed by minor physical anomalies (OR 5.30), trait anhedonia (OR 4.41), olfactory identification ability (OR 0.19) and premorbid IQ (0.47) (all class II) (48). Childhood social withdrawal (OR 2.91) and non-right handedness (OR 1.58) were also associated with increased risk of psychosis with other antecedent factors showing weak association (48).

METHODOLOGICAL CONSIDERATIONS FOR THE DEVELOPMENT OF A PSYCHOSIS POLYRISK SCORE (PPS)

Specificity, Universality and Durability of Non-genetic Risk Factors

A crucial step toward the development of a PPS is to deconstruct and standardize the specificity of non-genetic risk factors. While polygenic risk scores build on variation in specific single nucleotides in exact positions in the genome, and thus are unambiguously defined at all ages for all individuals and thus across all studies, specificity of most non-genetic risk factors is not completely determined. For example, some of

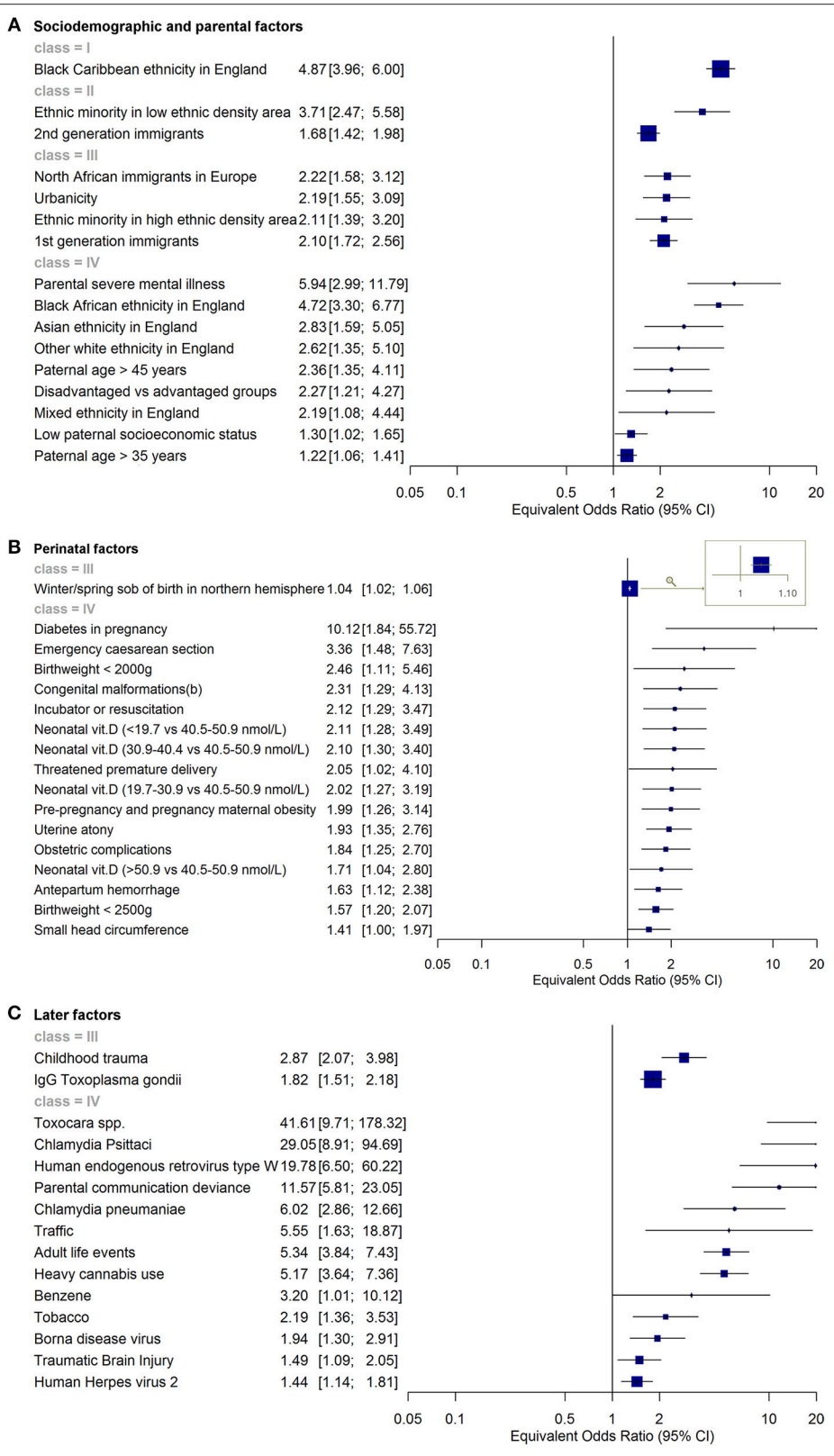

FIGURE 5 | Continued

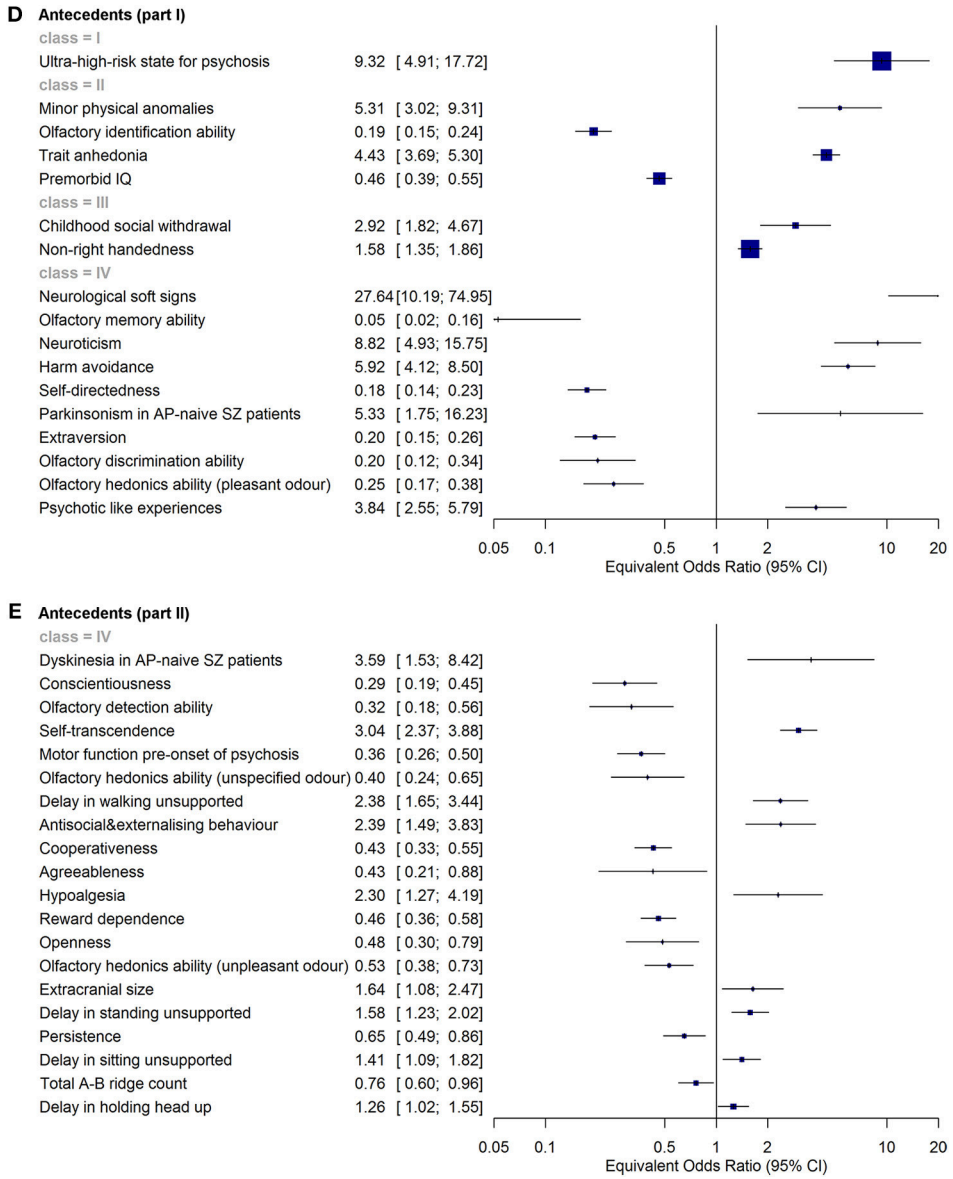

FIGURE 5 | (A–D) Umbrella review (meta-analysis of published meta-analyses or systematic reviews published up to January 31, 2017) investigating the level of evidence for an association of sociodemographic and parental **(A)**, perinatal **(B)**, later **(C)** risk/protective factors and antecedents **(D,E)** and psychotic disorders. Each of these factors operate at the individual level. Incidence rate ratio (IRR), odds ratio (OR), risk ratio (RR), greater than one or standardized mean difference (Hedges' g for continuous measures) greater than zero indicated that the factor was associated with an increased likelihood of psychotic disorders. IRR, OR, and RR lower than 1 or Hedges' g lower than zero indicated that the factor was associated with a reduced likelihood of psychotic disorders, i.e., it was protective. The level of evidence is further stratified according to established criteria in different classes: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), and non-significant (ns) evidence. The figures are based on the data from Radua et al. (48).

them may be ascertained through a multitude of instruments of questionable comparability. Others may require contextual specifiers (e.g., Black Caribbean Ethnicity in England), since their predictive validity may depend on their universality in different cultural scenarios. More on this point, other factors may be influenced by changes in the contextual environment (e.g., socioeconomic status) and therefore their durability over time periods may be questionable. An additional problem is that many factors are affected by both genetic and non-genetic influences; therefore the specific components of these risk factors should also be better elucidated. For instance, the effect of parental history of schizophrenia/psychoses is only partly mediated through the individual's genetic liability (54). The impact of shared environmental influences in the context of the parental history of severe mental illness on liability to schizophrenia amounts to nearly 11% (55). The umbrella review has adopted a pragmatic approach to partially mitigate the above concerns. First, it included several meta-analyses that were conducted

worldwide and that were representative of different contextual environments (universality). These studies were also published over two decades, minimizing the confounding role of time (durability). Finally, the umbrella review indicated that despite heterogeneous measurements (specificity) and spurious risk factors (encompassing genetic and non-genetic components), the factors analyzed were robustly associated with psychosis onset.

Assessment of Factors

The concurrent assessment of several demographic and environmental risk factors for psychosis listed in **Figures 5A–E** may appear logistically unviable in clinical practice. However, it would be facilitated by a sequential testing procedure (56). For instance, all demographic and parental risk/protective factors, as well as some environmental (urbanicity, winter/spring season of birth) and later risk factors (adult life events, tobacco use, cannabis use, childhood trauma, traffic) can be self-administered or automatically extracted from electronic medical records or from geolocating apps that capitalize on recent e-Health advancements. For the individuals whose predicted polyrisk of psychosis is over a certain threshold, a clinical comprehensive polyrisk assessment can be then performed in a sequential fashion (56). Such an assessment may involve more accurate testing to collect the remaining risk factors—blood sampling for assessing the exposure to infective agents as well as to estimate the polygenic risk, consultation of obstetric records or by interviewing the patients' relatives and clinical interviews.

Developmental Challenges of the PPS

The PPS can be subsequently developed for reproducing the methodology employed to get the polygenic risk score, based on an additive model for quantifying an individual's genetic loading for a disorder, as conferred by multiple risk alleles (57). From a statistical perspective, polygenic scores are weighted sums of the genotypes of a set of variants. To develop a PPS, the presence or absence of each of the above risk factor should be determined for each individual. The log of the odds ratio for each risk factor listed in **Figures 4**, **5A–E** can subsequently be multiplied by either 1 (risk factor deemed present in the individual) or 0 (risk factor deemed absent). These products can successively be added together and the sum divided by the total number of risk factors assessed (54). Validation of this approach through a prospective longitudinal study would be a key stage of the development of such a tool. Furthermore, since some of the factors are mutually exclusive or may be correlated some pruning may be required to reduce redundancy. An additional problem may be that missing values such as not knowing family history in adopted individuals should be considered and potentially imputed with statistical methods.

PSYCHOSIS POLYRISK SCORE (PPS) PROTOTYPE

In the second part of this review we will apply the concepts developed above to operationalize a PPS prototype.

Development and Operationalization of the PPS

To attain the most robust prognostic tool, the umbrella review factors were used. Factors with the greatest strength of evidence (class I–III) were initially considered for the PPS. Since our aim was to improve the detection of individuals at-risk for psychosis at scale, logistical considerations were of paramount importance. We thus applied a pragmatic filter to exclude factors that could not easily be measured at scale (such as Toxoplasma Gondii IgG). A total number of 13 class I–III factors that can be pragmatically measured were included in the prototype PPS assessment. To ensure accurate scoring, appropriate measurement and cut-offs for each factor is of great importance. Where possible, the same tools were selected to assess the presence of factors as used in their respective meta-analyses in the umbrella review (48). This was similarly true for cut-offs to preserve the validity of the Risk Ratios. The list of included factors, along with their definitions and the tentative cut-offs for defining each respective Risk Ratio can be seen in **Table 1**. While this may not be the most predictive set of factors in existence, one of the major characteristics of the PPS is that it is optimizable i.e., it can be refined by the inclusion of other predictors or by the fine tuning of the cut-offs to be used.

The PPS, similar to PRS, involves a weighted sum of exposure to risk and protective factors, using the relative risks associated with each factor [seen in (48)]. To construct the PPS we first estimated a raw score for each factor as the 10-base logarithm of its relative risk. For example, the estimated relative risk of psychosis in individuals living in urban settings is 2.2, and thus the raw score of the urbanity factor was $\log_{10}(2.2) = 0.34$. We

TABLE 1 | Operationalization of factors in the Psychosis Polyrisk Score (PPS).

Factor	Operationalization	Pilot cut-offs
Childhood trauma	Childhood trauma questionnaire	Moderate to severe
Ethnicity	Self-defined	Non-white ethnicity
Immigration	Self-defined	First- or second-generation
Premorbid IQ	National adult reading test	<93.6
Non-right handedness	Self-defined	Non-right handedness
Olfactory identification ability	University of Pennsylvania smell identification test	Mild microsmia
Clinical High Risk state for Psychosis	Prodromal questionnaire (16-item version)	>9
Urbanicity	Population density of local authority	Living in local administrative unit (LAU) where the majority of the population lives in an urban center of at least 50,000 inhabitants

then subtracted the population average of this raw score, so that individuals at-risk would have positive scores and the remaining individuals would have negative scores, with an average of zero. For example, given that ∼73.6% individuals live in urban settings (and thus 26.4% in rural settings with a raw score of 0), the population average of the urbanicity factor should be (73.6% × 0.34) + (26.4% × 0) = 0.25. We subtracted this average from the raw scores, i.e., the subtracted score was 0.34–0.25 = 0.09 for individuals in urban settings and 0–0.25 = −0.25 for individuals in rural settings. Further information about prevalence data used can be seen in **Table S1**. Finally, for the ease of use we multiplied the subtracted scores by 10 and rounded them to the nearest half integer. In the example, the final scores were 0.09 × 10 ≈ 1 for individuals in urban settings and −0.25 × 10 = −2.5 for individuals in rural settings. The final scoring of the PPS is reported in **Table 2**.

Furthermore, some adaptations were introduced to mitigate for conceptual dependency across some factors. Factors related to immigration had logical dependencies between them, i.e., immigrants cannot be both first-generation and second-generation, and North African immigrants are first- or second-generation immigrant. We combined these factors following this logic and assuming that the proportion and extra risk of North African immigrants is similar in first- and second-generation immigrants (58). Factors related to ethnicity had similar logical dependencies between them, i.e., black Caribbean is a non-white ethnicity, and individuals cannot be from a low ethnic density area, from a medium density area and from a high ethnic density area at the same time. We combined these factors again following this logic and assumed that the proportion and extra risk of black Caribbean individuals between non-white ethnicity individuals is similar in low, medium and high ethnic density areas.

TABLE 2 | Scoring system for the Psychosis Polyrisk Score (PPS).

Factor			PPS
Childhood trauma	Yes		4
	No		−0.5
Ethnicity	White		−2
	Black Caribbean	In low ethnic density area	6
		In medium ethnic density area	5.5
		In high ethnic density area	3.5
	Other	In low ethnic density area	3.5
		In medium ethnic density area	3
		In high ethnic density area	1
Immigration	Not immigrant		−0.5
	1st gen immigrant	From North Africa	3
		From other regions	2
	2nd gen immigrant	From North Africa	2.5
		From other regions	1.5
Premorbid IQ	<93.6		2
	>93.6		−1
Non-right handedness	Yes		2
	No		0
Olfactory identification ability	Yes		5.5
	No		−1.5
Clinical high risk state for psychosis	>9		8.5
	<9		−1.5
Urbanicity	Yes		1
	No		−2.5

*Please see **Table 1** for the operationalisation of these predictors.*

Simulating the PPS Scores in the Hypothetical General Population

As indicated in **Table 2**, an individual's potential PPS score ranges between−7.5 (least psychosis risk) and 32 (greatest psychosis risk). Utilizing prevalence data for each risk factor (**Table S1**), we ran 10,000,000 permutations to investigate the range and distribution of PPS scores in the general population. While this does require external longitudinal validation, this is the first attempt to do this in the field. As illustrated in **Figure 6**, the distribution is skewed to the left with 53.6% of individuals having a negative PPS score (RR <1), and a further 25.7% with PPS scores between 0 (RR = 1) and 5 (RR = 3). This leaves only 21.6% with RR >3, with only 1.8% having an RR >30.

COMBINATION OF THE PPS WITH POLYGENIC RISK SCORES: POTENTIALS AND CHALLENGES

Integrating the Genetic and Non-genetic Components

Consequently, the above-described PPS mostly includes non-genetic risk factors. Therefore, it can be integrated with the genetic risk score acquired in the same individuals. Integration of genetic and non-genetic information may benefit from considering gene by environment interactions. There is no consensus on the most effective model. The original GWAS meta-analysis found no epistatic or non-additive effects between the candidate loci (38) and other studies did not find interactions between polygenic risk score and environmental risk factors (53, 59). On the other hand, an interaction between polygenic risk score and demographic factors is demonstrated in individuals of African ancestry (poor prognostic accuracy) (39) or with a family history of psychosis (high prognostic accuracy) (60). Since the vast majority of potential interactions across genetic and non-genetic risk have not been tested yet (38), at present, an additive model that sums all known genetic and non-genetic risks is a pragmatic approximation. An additive approach combined with weighted summation to account for interactions has recently shown promise (61). A recent review of gene by environment interactions confirmed that

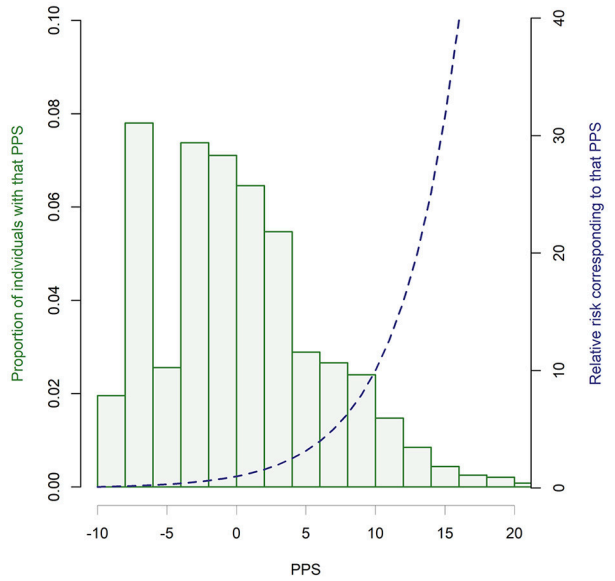

FIGURE 6 | Distribution of PPS scores in a hypothetical general population. Histogram bars indicate the proportion of individuals receiving each PPS score (in 0.5 increments) based on the prevalence of risk factors and 10,000,000 permutations. Blue dotted line illustrates the equivalent relative risk for PPS scores.

polymorphisms of catechol-O-methyltransferase (COMT), brain-derived neurotrophic factor (BDNF), and FK506-binding protein 5 (FKBP5) genes might interact with early life stress and cannabis abuse or dependence, influencing various outcomes of schizophrenia spectrum disorders (62). In the future, robust gene by environment interactions can be incorporated in the same way as other combinations of risk factors were already incorporated in the umbrella review. This would be facilitated by the proposed comprehensive approach that assesses several candidate risk factors and analyses them in a multivariate fashion. While this would be the ideal target for advancing the development of these integrated scores, with the evidence currently available to us, the most pragmatic approach would be an additive model.

Prognostic Modeling Challenges

The development and validation of a comprehensive genetic and non-genetic polyrisk score is faced by some prognostic modeling challenges. It is important to highlight that the association measures reported by the umbrella review were based on a univariate meta-analysis. Therefore, there is no assumption that the reported risk or protective factors are independent, and they could be mutually confounded. For instance, in the case of a parental history of severe mental disorder and paternal socioeconomic status the former could confound the impact of the latter, or conversely, low socioeconomic status may lead to certain mental disorders. In contrast, the polygenic risk score is based on genetic variations that are far apart in order to avoid linkage disequilibrium. Future studies are therefore requested to measure multiple exposures in the same individuals, to clarify the independence of each exposure. This should also be facilitated by data sharing policies across ongoing studies that would allow performing patient-data meta-analyses or umbrella reviews. Availability of advanced statistical learning methods (e.g., random forests, vector support machines, penalized linear regression methods) could also help to create risk prediction algorithms for complex multivariate situations in which multiple collinear risk factors are involved (63). A related problem is that the reported associative measures were all estimated in the same pool of meta-analyses. Although the sample size was the largest to date, and the evidence was subjected to established classification criteria, no strict external validation in an independent dataset was performed. As a result, PPS created on the basis of the measures reported in the umbrella review should be validated in independent datasets to test their actual prognostic performance (44).

CLINICAL POTENTIAL AND FUTURE RESEARCH

While the next decade of research will be requested to address the above challenges, the PPS approach holds promise for resolving the weaknesses of the CHR-P paradigm as well as to overcome knowledge in the etiology of psychotic disorders.

Clinical Staging and Dynamic Mapping of Developmental Risk Trajectories

The PPS approach combined with a polygenic risk score would allow researchers to control and replicate CHR-P risk enrichment in a controlled manner, while at the same time facilitating identification of at-risk cases on the basis of a determinate accumulation of risk factors. This would improve the detection of at-risk case and refine the prediction of psychosis. Furthermore, as illustrated in **Figure 7**, the PPS assessment accommodates a clinical staging framework for the development of psychosis, which has recently been reviewed elsewhere (3). For this aim, it will be important to draw a distinction between individually stable factors (genes, prenatal, and early childhood) that can be carried forward and developmental/state factors that will require reassessments over the life course. For instance, the PPS assessment can potentially be administered during the preclinical phase in non-clinical samples, such as screening programmes for schools or non-help-seeking youths in the community (time 1) for identifying at-risk groups and facilitate selective preventative focused interventions (3). Such an assessment can be followed by testing (56) in individuals who present with subtle symptoms of psychosis-like CHR-P features in the ones accessing secondary mental health services. Child and adolescent mental health services and early intervention services may be particularly suited for such an assessment (60) (**Figure 7**). The systematic incorporation of a temporal dimension (64) in the polyrisk assessment is consistent with a developmental framework for mental disorders that has recently been recommended for advancing etiological knowledge (65). Our group is currently piloting a beta version of the PPS after individuals are identified to be at-risk for psychosis by a validated transdiagnostic risk calculator (34–36).

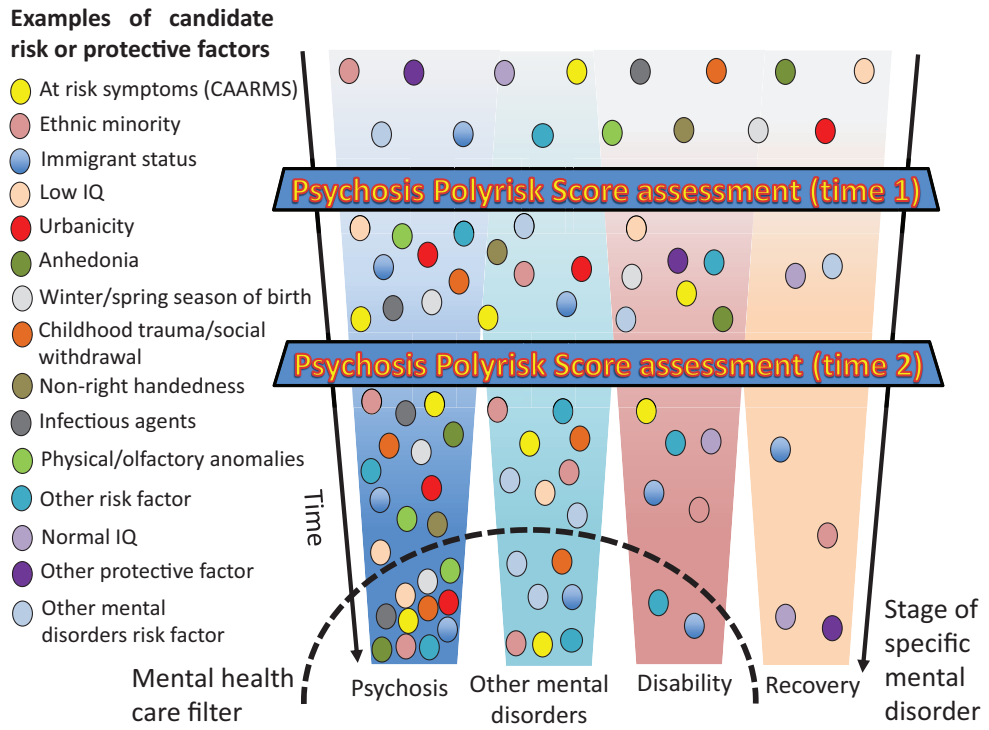

FIGURE 7 | Putative PPS assessment for the detection of at-risk individuals and the prediction of psychosis. Risk or protective factors that are diluted during the pre-clinical stages may accumulate as the individual progresses across different stages until they trigger signs or symptoms and functional impairment that are associated with help-seeking behavior and access to mental health care. In the later stages, specific aggregations of risk and protective factors may be associated with specific clinical outcomes.

Transdiagnostic Potential for the Prediction of Non-psychotic Mental Disorders

There is emerging evidence that the same risk factors may be associated with multiple types of disorders, beyond psychosis (pleiotropy). For instance, another recent umbrella review has indicated that childhood adversity, exposure to *Toxoplasma gondii* and a history of head injury are also linked to bipolar disorders (66). These findings do not eliminate the possibility that even if these risk factors are shared between bipolar disorder and psychosis, the loading and combination of factors that results in either of the two disorders may still be constituted of unique dimensions (65). While the risk factors themselves may be shared with other psychiatric disorders, the weighting of these factors will be different i.e., the same factor could have a differential impact on risk for different disorders. What is evident is that there is great potential for transdiagnostic research that focuses on broad and heterogeneous samples of mental disorders. Unfortunately, to date, transdiagnostic research has been poorly operationalized and has not provided robust evidence to improve the current classification system (67).

The Role of Biomarkers

In the current perspective, we selectively focused on genetic and non-genetic factors, while biomarkers were not primarily discussed. One of our aims was to improve the modest detection power of the CHR-P paradigm and the use of biomarkers would present specific challenges that would require a separate manuscript. For example, risk stratification models that include neuroimaging, electrophysiological, or peripheral biomarkers (68–70) have been mostly developed and validated within CHR-P samples (56). Therefore, these models could not be used to improve the detection of at-risk individuals. Furthermore, their broader use in the community or National Health Service scenarios is hampered by feasibility and economic caveats, because these models are logistically complex. Our group has recently demonstrated that risk stratification models encompassing neuroimaging, electrophysiological and peripheral biomarkers could rather be used in subsequent testing, in line with similar stepped risk enrichment assessments that are used in clinical medicine (56).

CONCLUSIONS

The combination of risk/protective factors encompassing genetic (PRS) and non-genetic information (PPS) holds promise for overcoming the epidemiological weakness of the CHR-P paradigm. The PPS conceptually and empirically developed here will facilitate future research in this field and hopefully advance our ability to detect individuals at-risk for psychosis and forecast their clinical outcomes.

ETHICS STATEMENT

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AUTHOR CONTRIBUTIONS

PF-P conceived the study under the supervision of RU. DO acquired the data. AR and JR coordinated the statistical analysis. PF-P and DO drafted the manuscript, and AR, JR, and RU made substantial contribution to the revision of the initial manuscript and interpretation of data.

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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.2019.00174/full#supplementary-material

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Basic Self-Disturbances Related to Reduced Anterior Cingulate Volume in Subjects at Ultra-High Risk for Psychosis

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Introduction: Alterations of the "pre-reflective" sense of first-person perspective (e.g., of the "basic self") are characteristic features of schizophrenic spectrum disorders and are significantly present in the prodromal phase of psychosis and in subjects at ultra-high risk for psychosis (UHR). Studies in healthy controls suggest that neurobiological substrate of the basic self involves cortical midline structures, such as the anterior and posterior cingulate cortices. Neuroimaging studies have identified neuroanatomical cortical midline structure abnormalities in schizophrenic spectrum disorders.

Objectives: i) To compare basic self-disturbances levels in UHR subjects and controls and ii) to assess the relationship between basic self-disturbances and alterations in cortical midline structures volume in UHR subjects.

Methods: Thirty-one UHR subjects (27 antipsychotic-naïve) and 16 healthy controls were assessed using the 57-item semistructured Examination of Anomalous Self-Experiences (EASE) interview. All subjects were scanned using magnetic resonance imaging (MRI) at 3 T, and gray matter volume was measured in *a priori* defined regions of interest (ROIs) in the cortical midline structures.

Results: EASE scores were much higher in UHR subjects than controls ($p < 0.001$). The UHR group had smaller anterior cingulate volume than controls ($p = 0.037$). There were no structural brain imaging alterations between UHR individuals with or without self-disturbances. Within the UHR sample, the subgroup with higher EASE scores had smaller anterior cingulate volumes than UHR subjects with lower EASE scores and controls

(p = 0.018). In the total sample, anterior cingulate volume was inversely correlated with the EASE score (R = 0.52, p < 0.016).

Conclusions: Basic self-disturbances in UHR subjects appear to be related to reductions in anterior cingulate volume.

Keywords: schizophrenia, ultra-high risk, psychosis, self-disturbances, magnetic resonance imaging, voxel-based morphometry

INTRODUCTION

The psychopathological construct of basic self-disturbances is based on the pre-conscious sense of self, termed "*basic self*," as opposed to conscious, reflective, and more elaborated levels of self-awareness (1, 2). This pre-reflective, implicit sense of self indexes a first-person perspective on the world (3). Abnormalities in basic self may result in alterations of the subjective sense of being a vital subject at the center of one's own experience (4). There is emerging evidence suggesting that *basic self-disturbances* are a key feature of the schizophrenic spectrum disorders (2) and that the presence of *basic self-disturbances* may distinguish schizophrenia from affective psychosis (5, 6) and other psychiatric disorders (6–9). *Basic self-disturbances* are nonpsychotic abnormalities of experience that could evolve in frank psychotic symptoms. For example, an altered sense of "ownership" of one's own experience can lead to thoughts being experienced as alien, eventually resulting in psychotic phenomena such as believing that one's thoughts come from an external source (thought insertion).

Basic self-disturbances have been reported in samples at genetic high risk for schizophrenia (10), at ultra-high risk (UHR) for psychosis (11), and in the prodromal phase of schizophrenia (12, 13). The UHR construct identifies subjects with an increased risk of developing psychotic disorders [20% at 2 years, see Table 4 in Ref. (14)] (15) but not of other nonpsychotic disorders (16). The vast majority (73%) of UHR subjects who develop psychosis will develop a schizophrenia spectrum psychosis (17). The increased risk that is observed in these individuals is mostly due to the accumulation of several risk factors for psychosis (18, 19) during the sampling and the recruitment of these individuals (20, 21). Recent evidence suggests that basic self-disturbances in UHR subjects are related to the risk of subsequently developing psychosis (particularly schizophrenic spectrum) (11).

Despite the large array of structural neuroimaging investigations in UHR individuals (22–26), the neurobiological substrate of *basic self-disturbances* is unknown, but some authors have suggested (27) that in healthy individuals, cortical midline structures, particularly anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and medial prefrontal cortex, represent the neural basis of the basic self (28).

In fact, a variety of brain regions are involved in self-referential processing requiring an active reflection on self (e.g., recognizing personality traits as belonging to self or others) (29). However, cortical midline structures are robustly activated in all self-referential tasks, regardless of the sensory mode within which the self-stimuli were presented (30). Therefore, they are postulated to be the basis of the pre-reflective (basic) self, which precedes and allows any more elaborated level of self-awareness.

A meta-analysis of functional imaging studies has identified three clusters within cortical midline structures (30), constantly recruited in self-related tasks in healthy volunteers, independent of the sensory modalities: 1) pre- and sub-genual ACC/ventromedial prefrontal cortex, 2) supra-genual ACC/dorsomedial prefrontal cortex, and 3) PCC. Collectively, these areas are implicated in the evaluation and representation (medial prefrontal cortex), monitoring (ACC), and integration of self-referential stimuli (PCC).

Both structural and functional neuroimaging studies of UHR subjects have reported alterations in cortical midline structures. Thus, magnetic resonance imaging (MRI) studies have described reductions in gray matter volume in UHR subjects in the ACC (31, 32), PCC and precuneus (33, 34), and medial frontal gyrus (31, 32). Functional MRI studies have reported alterations in activation in these regions in UHR subjects across a range of cognitive and emotional tasks (35–40). Furthermore, within UHR samples, alterations in the medial prefrontal cortex (31, 32, 41), ACC and PCC, and the precuneus (33) have been associated with the subsequent transition to psychosis. However, the extent to which alterations in cortical midline structure regions in UHR subjects relate to *basic self-disturbances* has not yet been investigated. Investigating these features can be important to improve the detection and the prediction of outcomes in UHR subjects at an individual level.

The present study was designed to address this issue. We used magnetic resonance imaging (MRI) to measure the volume of cortical midline structures regions in UHR subjects and healthy controls, and used the Examination of Anomalous Self-Experience (EASE) to assess *basic self-disturbances* in these subjects. We tested the following hypotheses: i) UHR subjects have higher levels of *basic self-disturbances* than controls; ii) UHR subjects have less gray matter volume than controls in the ACC, PCC, and medial prefrontal cortex; iii) within UHR subjects, the severity of *basic self-disturbances* is related to reductions in the volume of these regions.

MATERIALS AND METHODS

Subjects

Thirty-one participants meeting Comprehensive Assessment of the At Risk Mental State (CAARMS) 12/2006 (42) criteria for the At Risk Mental State (ARMS) were recruited from "Outreach and Support in South London, OASIS" (https://www.meandmymind.nhs.uk) in

South London and The Maudsley (43), "The West London Early Intervention service" (www.wlmht.nhs.uk/services/e/early_intervention_hf.html) in West London, and the "Cambridgeshire and Peterborough early intervention services, CAMEO" in Cambridge (http://www.cameo.nhs.uk), between November 2011 and March 2014. The neuroimaging study protocol was approved by the National Research Ethics Service Committee of London—Camberwell St Giles, United Kingdom, and all participants gave written informed consent. The UHR status was based on clinical assessment using the CAARMS (44) and a consensus meeting with the clinical team. An individual meets inclusion criteria for the ARMS if they present one or more of the following: 1) "attenuated" psychotic symptoms (APS); 2) frank psychotic symptoms that last less than 7 days and resolve spontaneously without treatment, i.e., brief limited intermittent psychotic symptoms (BLIPS); 3) a recent decline in function together with either schizotypal personality disorder or a first-degree relative with psychosis, i.e., genetic risk and functional deterioration (GRD). Four of the UHR participants were taking low-dose antipsychotic medications, while 27 were antipsychotic-naïve.

Healthy controls (HC) participants ($n = 16$) were recruited *via* advertisement in the local media. All subjects lived in the same geographical areas as clinical subjects; were matched for age, ethnicity, and premorbid IQ; and had an absence of personal or family history of psychiatric illness.

Participants for both groups were excluded if there was a history of neurological disorder or they met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for substance abuse.

Clinical Assessment

Assessment of Ultra-High Risk Symptoms

Severity of UHR symptoms was assessed using the following instruments: the Comprehensive Assessment of the At Risk Mental State (CAARMS 12/2006) (44), the Positive and Negative Symptom Scale (PANSS) (45), the Hamilton Depression Rating Scale (HAM-D) (46), and the Hamilton Anxiety Rating Scale (HAM-A) (47). Level of functioning was assessed using the Social and Occupation Functioning Assessment Scale (SOFAS) (48). Premorbid estimated IQ was assessed by using the National Adult Reading Test (NART) (49), and current IQ was assessed with the shortened version of the Wechsler Adult Intelligence Scale (WAIS-III) (50).

Assessment of Basic Self-Disturbances

Basic self-disturbances were investigated in both UHR and HC with the Examination of Anomalous Self-Experience (EASE) (51) by two psychiatrists (IB and LM), who attended a certified EASE training in Copenhagen. The two psychiatrists assessed a subset of the present sample independently, to standardize the procedure. The EASE is a semistructured interview that has shown a good to excellent internal consistency (Cronbach's α above 0.87) and an overall inter-rater correlation coefficient above 0.80 (52). It systematically explores the nonpsychotic abnormalities of experience articulating around the basic disturbance of self-awareness. The 57 items are grouped into five non-mutually exclusive domains: 1) cognition and stream of consciousness, 2) self-awareness and presence, 3) bodily experience, 4) demarcation/transitivism, and 5) existential reorientation. These items are then rated either dichotomously (present = 1 or absent = 0) (53) or continuously on a five-point severity and frequency scale (11). For the purpose of this study, the interview was rated continuously, and item subtypes were included in the scores.

Magnetic Resonance Imaging Scanning

For all participants, images were acquired at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London on a 3-T Signa HDx (General Electric, Milwaukee, WI). T1-weigthed scans were obtained using a volumetric three-dimensional Spoiled Gradient Recalled sequence (slice thickness = 1.2 mm, TE = 2.8 ms, TR = 6.98 ms, TI = 400 ms, flip angle = 11°, matrix = 256 × 256) producing 196 sagittal slices with an in-plane resolution of 1.0 × 1.0 mm.

Data Analysis

Clinical Measures

Differences in demographic and clinical variables between groups were examined using independent samples *t* tests for parametric and continuous data and a χ^2 test for categorical data using SPSS (version 19.0 for Mac; Statistical Package for the Social Sciences (SPSS) Inc., Chicago, Illinois). Mann–Whitney *U* test was used to assess differences in EASE scores between HC and UHR as EASE scores were not normally distributed.

Image Analysis

Between-groups differences in gray matter volume were assessed using voxel-based morphometry (VBM), as implemented in Statistical Parametric Mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm), running under MATLAB 8.2 (The MathWorks, Inc, Natick, MA). T1-weighted volumetric images were preprocessed using the DARTEL (54) SPM8 toolbox. This technique maximizes accuracy and sensitivity, as it creates a study-specific template and the segmentation of each individual image (55). VBM preprocessing was conducted as follows: 1) visually checking for scanner artifacts and gross anatomical abnormalities for each subject, 2) setting the image origin to the anterior commissure, 3) using the DARTEL toolbox to produce a high-dimensional normalization protocol, 4) checking for homogeneity across the sample, and 5) using standard smoothing (i.e., 8 mm). We also included a "modulation step" in the normalization to preserve the information about the absolute gray matter values (56). After this preprocessing, smoothed, modulated, normalized data were obtained and used for the statistical analysis.

We examined three *a priori* regions of interest (ROIs) in the ACC, PCC, and medial frontal gyrus. Using the SimpleROIBuilder toolbox (http://www.fil.ion.ucl.ac.uk/spm/ext/), we created a single mask that included the three preselected ROIs. Within the mask, statistical inferences were made at $p < 0.05$ and family-wise error (FWE) rate correction, using an analysis of covariance (ANCOVA) design to identify

significant differences in gray matter volume across UHR and HC, with age, gender, years of education, and total intracranial volume as covariates of no interest.

These ROIs were chosen, as they were the anatomical areas postulated by metanalytical literature to be the neurobiological underpinning of basic self (30).

For the correlation analysis, we used independent values, extracting the gray matter volume parameters from the peak coordinates of the three clusters 1) pre- and sub-genual ACC/ventromedial prefrontal cortex, 2) supra-genual ACC/dorsomedial prefrontal cortex, and 3) PCC derived from the metanalytical independent study (30), not to violate the assumption of independence (57).

Correlations Between Gray Matter Volume and Examination of Anomalous Self-Experiences Scores

To test our hypothesis that EASE scores are directly related to alterations in cortical midline structure volume, EASE scores were regressed onto the gray matter volume parameters in the peak cluster coordinates indicated in previous meta-analyses (30), after the coordinates have been converted from Talairach to Montreal Neurological Institute (MNI). Individual gray matter volume parameters from each of these peak coordinates within each cluster were extracted. Spearman's correlation was performed in SPSS between these values and EASE scores:

Cluster 1: Ventromedial prefrontal/pre- and sub-genual ACC ($x = -1.29$, $y = 54.1$, $z = -1.57$)

Cluster 2: Dorsomedial prefrontal/supra-genual ACC ($x = 0.38$, $y = 16.72$, $z = 48.56$)

Cluster 3: PCC/precuneus ($x = -1.84$, $y = -60.39$, $z = 36.38$)

Statistical inferences were made at $p < 0.05$ FWE corrected. A Bonferroni correction for multiple testing was also applied ($p < 0.05/3 = 0.016$), and sensitivity analyses were repeated in the subsample that was drug-naïve.

Gray Matter Differences Between Healthy Controls and UHR With High and Low Level of Self Disorders

To examine whether a high level of *basic self-disturbances* within the UHR group was associated with altered gray matter volume in cortical midline structures, one-way analysis of variance and *post hoc* test were performed to test the effect of group (UHR-High-EASE vs. UHR-low-EASE) on gray matter volume in each of the ROIs. Statistical threshold was set at $p < 0.05$, Bonferroni correction.

RESULTS

Sample Characteristics

Almost all UHR participants ($n = 28$) met ARMS criteria for APS alone, two met criteria for BLIPS alone, and one for GRD + APS. The two groups did not statistically differ for age, gender, or ethnicity, but HC had spent significantly more years in education, as compared to UHR subjects ($p = 0.013$, mean difference = 2.53 years) and significantly more of them were employed as compared to UHR individuals. As expected, UHR subjects had reduced levels of functioning relative to HC and higher levels of anxiety and depression. All UHR individuals were drug-naïve, with the exception of four individuals. The antipsychotics taken by four participants at the time of the study were as follows: quetiapine 50 mg OD (two participants), olanzapine 10 mg Once Daily (OD), and olanzapine 5 mg OD. Three of them belonged to the UHR with high self-disturbances, with one belonging to the UHR with low self-disturbance (the one taking olanzapine 5 mg). See **Table 1** for full statistical details. Over 2 years of follow-up, seven individuals developed a psychotic disorder (23%).

Assessment of Self-Disorders

The UHR group showed greater levels of *basic self-disturbances* compared to controls [overall continuous EASE score UHR 117.32 (68.6) vs. HC 6.5(8.2), Mann–Whitney U test $p < 0.00$] in all five EASE domains. The interview took an average of 134 min (SD = 40) in UHR and 58 min (SD = 10) in HC to complete, usually over one or two sessions. No subject failed to complete the interview. See **Table 1** for full statistical details.

When the two UHR groups (high levels of self-disturbances vs. low levels of self-disturbances) were compared in relation to HAM-A, HAM-D, Global Assessment of Functioning (GAF) disability, TOT PANSS, total (TOT) CAARMS, and relative four positive symptoms subscales, only differences between HAM-A (24.3 vs. 9.78, $p < 0.001$), HAM-D (24.4 vs. 8.62, $p < 0.001$), and Global Assessment of Functioning (GAF) disability (56 vs. 63, $p < 0.05$) were significant.

In order to investigate the effect of self-disturbances on cortical midline structure gray matter volume, the UHR group was divided into subgroups according to the median, as the scores were not normally distributed, resulting in subjects with higher EASE scores (≥median of EASE scores = 108, $n = 15$) and lower EASE scores (<median of EASE scores, $n = 16$). We then compared cortical midline structures volume in these subgroups and HC.

Between-Group Differences in Pre-Selected Regions of Interest (ROIs)

The UHR group has reduced gray matter volume relative to the control group in the ROI centered on the dorsal ACC (MNI coordinates $x = 0$, $y = 26$, and $z = 22$; $p = 0.037$ (FWE); $z = 3.76$; and cluster size = 332 voxels) (**Figure 1**). There were no significant group differences in the superior medial frontal or posterior cingulate ROIs.

Gray Matter Differences Between Healthy Controls and UHR With High EASE Scores and UHR With Low EASE Scores

One-way analysis of variance found a significant effect of group on gray matter volume ($p = 0.04$) in the dorsal anterior cingulate cortex (dorsal ACC). *Post hoc t* tests showed significant differences in the dorsal anterior cingulate only between HC and the UHR-high-EASE subgroup ($p = 0.018$), but not for HC vs. UHR-low-EASE ($p = 0.052$) or UHR-high-EASE vs. UHR-low-EASE ($p = 0.65$). See **Figures 2** and **3**.

TABLE 1 | Clinical and sociodemographic characteristics of the sample.

Categorical variables		***HC (%)***	***UHR (%)***	***χ^2 (DOF)***	***p***
Gender				3.0 (1)	0.81
	Male	5 (31.3)	18 (58.1)		
	Female	11 (68.8)	13 (40.9)		
Ethnicity				8.0 (3)	0.220
	White	12 (75)	17 (54.8)		
	Black	1 (6.3)	11 (35.5)		
	Asian	2 (12.5)	0 (0)		
	Other	1 (6.3)	2 (6.5)		
Employment				5 (1)	0.025*
	Unemployed	1 (6.3)	11 (35.5)		
	Employed or student	15 (93.8)	19 (61.3)		
UHR subgroup					
	APS	n.a.	29 (90.3)		n.a.
	BLIPS	n.a.	2 (6.5)		n.a.
	GRD	n.a.	1 (3.2)		n.a.
Continuous variables		***HC (SD)***	***UHR (SD)***	***F (DOF)***	***p***
Age		24.9 (3.3)	23.3 (4.3)	2.3 (45)	0.204
Years of education		16.2 (3.21)	12.8 (2.3)	2 (44)	0.01*
NART	tot 50	28.7 (7.6)	27.9	0.04 (42)	0.736
EASE					
	Overall	6.5 (8.2)	117.3 (68.6)	15.0 (45)	<0.001*
	Cognition and stream of consciousness	2.7 (5)	42.4 (23.2)	33.6 (45)	<0.001*
	Self-awareness and presence	1.8 (3.7)	49.5 (27.3)	15.6 (45)	<0.001*
	Bodily experiences	0.19 (0.75)	11.8 (12.8)	12.9 (45)	<0.001*
	Demarcation/transitivism	0 (0)	3.4 (5.3)	9.0 (45)	<0.001*
	Existential reorientation	1.50 (3.8)	10.9 (10)	20.6 (45)	<0.001*
SOFAS		92.4 (3.3)	60.0	14.4 (41)	<0.001
HAM-A		1.5 (1.7)	16.8 (10.7)	26.3 (36)	<0.001
HAM-D		0.2 (0.6)	15.8 (10)	22.4 (35)	<0.001
CAARMS	*Total symptoms*	n.a.	39.6 (24.0)	n.a.	n.a.
	Total positive symptoms	n.a.	11.39 (6.1)	n.a.	n.a.
	Total negative symptoms	n.a.	7.9 (6.1)	n.a.	n.a.
	Total cognitive symptoms	n.a.	3.4	n.a.	n.a.
PANSS	*Total symptoms*	n.a.	12.6	n.a.	n.a.

**Significant differences at p < 0.05 corrected for multiple comparisons. HC, healthy controls; UHR, ultra-high risk for psychosis; APS, attenuated psychotic symptoms; BLIPS, brief, limited intermittent psychotic symptom; GRD; genetic risk + functional deterioration; NART, National Adult Reading Test; EASE, Examination of Anomalous Self-Experience; SOFAS, Social and Occupation Functioning Assessment Scale; HAM-A, Hamilton Anxiety scale; HAM-D, Hamilton Depression Scale; PANSS, Positive and Negative Symptoms Scale; DOF, degrees of freedom; SD, standard deviation; n.a., not available; tot, total.*

Correlations Between Self-Disorders and Gray Matter Volume in Cortical Midline Structures

Spearman's rho correlation between continuous EASE scores and gray matter volume in the ventromedial prefrontal/pre- and sub-genual anterior cingulate cluster and in the dorsomedial prefrontal/supra-genual anterior cingulate cluster were significant ($p = 0.021$, -0.33 $r^2 = 0.141$, and $p < 0.001$, -0.553 $r^2 = 0.24$, respectively, see **Figure 4**). Outliers were detected *via* Cook's distance test. Four outliers were present in the correlation with the ventromedial prefrontal/pre- and sub-genual anterior cingulate cluster and one in the correlation with the dorsomedial prefrontal/supra-genual anterior cingulate cluster. Only the negative correlation between EASE score and the latter remained significant after the outlier had been removed ($r^2 = 0.269$, $p < 0.001$). Likewise, after Bonferroni correction for multiple comparisons, only the correlation in this cluster remained significant ($p < 0.016$).

No significant correlation was found between EASE scores and the volume of the posterior cingulate/precuneus cluster.

No correlations were found between CAARMS (total, positive, negative, cognitive, and general symptoms scores) or PANSS (total and positive symptoms) scores and the three gray matter volume clusters in the cortical midline structures.

HAM-A ($p < 0.001$), HAM-D ($p < 0.05$), and SOFAS ($p < 0.05$) correlate with the third cluster dorsomedial prefrontal/supra-genual ACC only.

Excluding those four participants who had received an antipsychotic medication, the correlation between self-disturbances and gray matter volume remains significant for the ventromedial prefrontal/pre- and sub-genual ACC and dorsomedial prefrontal/supra-genual ACC.

DISCUSSION

This is the first study to directly examine the association between basic self-disturbances and gray matter volume in a population of UHR subjects. Our first prediction was that UHR participants would have higher EASE scores than HC. This hypothesis was confirmed. These results replicate previous

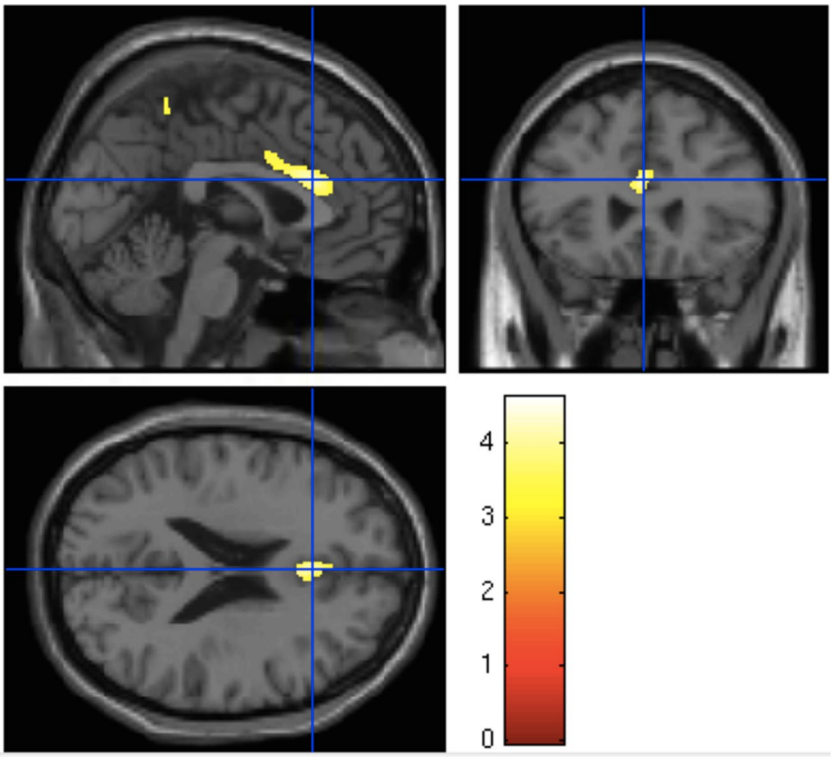

FIGURE 1 | Significant reduction of gray matter volume in the anterior cingulate gyrus in ultra-high risk for psychosis subjects relative to controls [$p = 0.037$; family-wise error (FWE)].

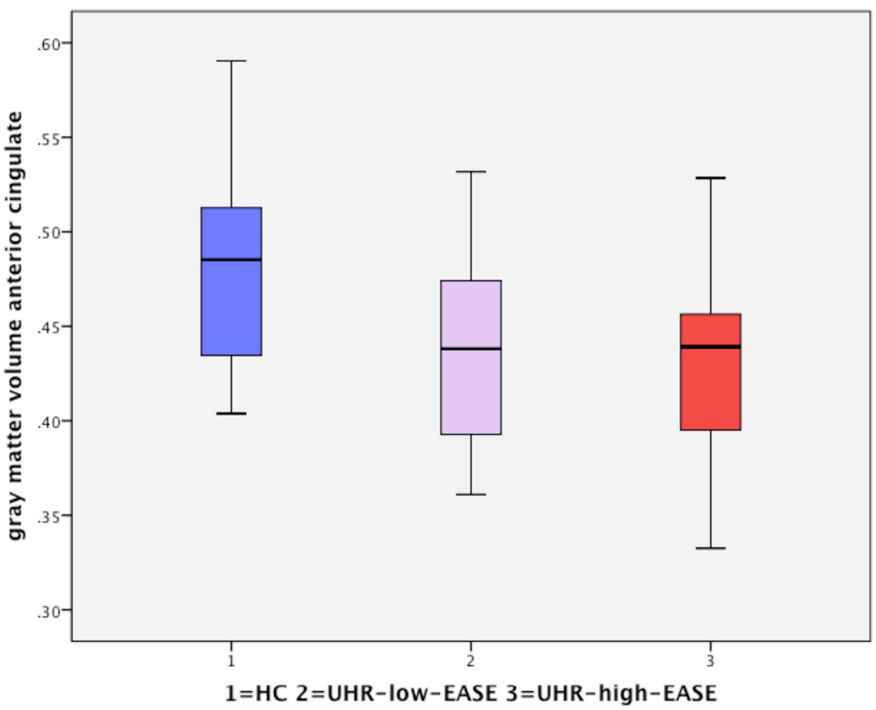

FIGURE 2 | Boxplot showing gray matter volume in the anterior cingulate in the three groups: HC (healthy controls), UHR-low-Examination of Anomalous Self-Experiences (EASE), and UHR-high-EASE. Values on the *y*-axis refer to mm^3 per voxel.

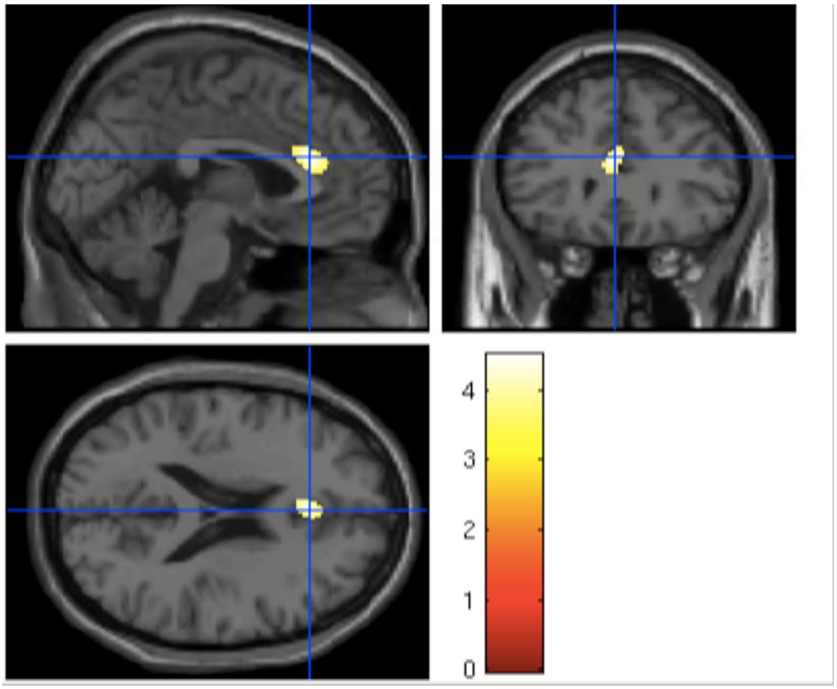

FIGURE 3 | Significant reduction in the anterior cingulate volume in UHR subjects with high EASE scores compared to HC.

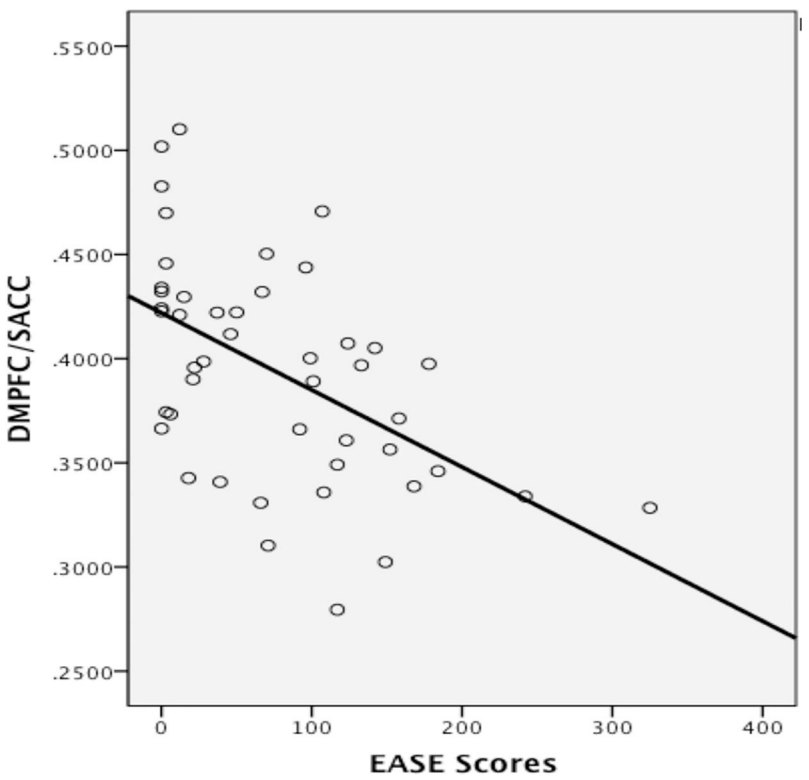

FIGURE 4 | Correlation between gray matter volume in the dorsomedial prefrontal (DMPFC)/supra-genual anterior cingulate cortex (ACC) cluster and levels of self-disturbances measured with the EASE. Values on the *y*-axis refer to mm^3 per voxel.

findings in two different UHR samples (11, 58), further confirming literature suggestions (10, 12, 13) that abnormalities of the basic self are nonpsychotic alterations of self-awareness that precede the onset of full blown psychosis and are core features of vulnerability to psychosis.

Our second prediction was that UHR subjects would show gray matter volume reductions relative to HC in the cortical midline structures regions that are implicated in self-referential processing. We found that UHR subjects had lower gray matter volume than HC in the ACC, one of the cortical midline structures. Previous MRI studies have reported structural alterations of ACC in UHR populations (31, 32, 34), but these have not been specifically related to basic self-disorders. A secondary analysis indicated that this reduction in ACC volume was influenced by the subgroup of UHR subjects with relatively higher level of self-disturbances, as measured with the EASE: ACC volume in UHR subjects with lower EASE scores was lower, but not significantly different to that in HC. Finally, a correlational analysis involving all the participants (UHR plus HC) revealed that ACC volume was inversely related to EASE score: the higher the level of self-disturbances, the lower the gray matter volume in the ACC.

Our main findings involved the dorsal part of the ACC, an area that has been implicated in mediating attention, cognitive/attentional control, conflict monitoring, response inhibition, and self-reflection (59–62). It also plays a role in the integration of rewarding environmental cues and behavioral responses, *via* its widespread projections to affective, cognitive, and motor cortices (63). The motivation of behavior in relation to reward relies on the attribution of salience to environmental stimuli. Salience models of psychosis propose that aberrant attribution of salience to irrelevant environmental stimuli underlies the development of positive psychotic symptoms (64). It has previously been suggested that dysfunctional salience processing may also contribute to emergence of basic self-disturbances (65, 66): the capacity to compare predicted and incoming stimuli would be altered, resulting in a violation of expectation. If such a prediction error does not fit the knowledge based on previous experience, a new inference occurs (67). These prediction errors make an event attention grabbing, i.e., more salient, which could result in basic self-disturbances such as a loss of "common sense" (i.e., a disruption of a person's "grasp" on the conceptual or perceptual field of awareness, loss of the implicit "grip" of the "rules of the game," of the ability to see things in the proper perspective), hyper-reflexivity (a tendency to constantly monitor one's own experience, normally tacit in the "background") (2, 68), and diminished self-presence (lack of vital contact, diminished sense of existence as a subject of awareness) (66, 69).

Sense of agency (e.g., while performing an action) would derive from the comparison of predicted (expected) and actual sensation: concordance signifies that the movement is one's own, while discrepancy suggests that the movement is externally generated. A similar process is thought to underlie sense of agency of mental content (cognitive–affective agency). The dorsal ACC and prefrontal cortex, *via* their interactions with motivational (ventral striatum) and limbic (amygdala) areas, are thought to play an important role in the sense of being a "cognitive-affective agent" (e.g., the agent and owner of mental content and affect) (70).

Different neurocognitive models of psychosis propose that symptoms such as auditory hallucinations and delusions of control may derive from misattribution of self-generated actions as externally generated as a consequence of a dysfunctional self-monitoring mechanism (71, 72).

In the motor domain, prediction of the sensory consequences of planned actions allows discrimination of self- and non-self-elicited sensation (73). Shergill et al. recently demonstrated that schizophrenia patients seem unable to predict the sensory consequences of their own actions (74). According to the conflict-monitoring model (75), an evaluative/regulative loop mediated by dorsal ACC (evaluative component) and PFC (regulatory component) would allow a self/nonself distinction between reafferent signals resulting from one's own cognitive control efforts (self) and exafferent signals about the level of conflict resulting from environmental sources (nonself) (70). Alterations in the dorsal ACC could therefore impair the self/nonself distinction and underlie basic self-disturbances such as loss of sense of agency and ownership of mental content (thoughts felt as alien, thought interference and insertion) and alteration of the first-person perspective, eventually resulting in psychotic passivity phenomena.

The results of the current study support the role of the ACC in the pathogeneses of basic self-disturbances.

A previous study in a UHR sample demonstrated that structural changes in the ACC appear before the onset of frank psychosis, can distinguish between UHR who will subsequently develop psychosis compared to those who will not, and seem relatively specific to UHR individuals who develop schizophrenia spectrum disorders, as opposed to affective psychoses (31). Volumetric changes in the ACC are also among the most robust neuroanatomical alterations in patients with established schizophrenia (76). This is in line with the notion that basic self-disturbances tend to segregate in the schizophrenic spectrum (6, 9) as opposed to affective psychosis (5) or borderline personality disorder (77).

The EASE interview targets nonpsychotic abnormalities of conscious experience that are not included in conventional psychopathological assessments of UHR symptoms, such as the CAARMS (44). Incorporating the EASE into the routine clinical assessment of UHR subjects may facilitate risk stratification and the provision of individualized interventions.

Our study has several limitations. The first one is the lack of follow-up neuroimaging data. Follow-up scan could inform on the longitudinal trajectory of the neuroanatomical alterations detected in our UHR subjects, while only functional and clinical outcome could shed light on the diagnostic and prognostic validity of our findings. Diagnostic and prognostic information can in turn support risk stratification and personalized focused interventions in early psychosis (78, 79).

The second limitation is the small sample size, which limits the validity of our results and the possibility to generalize them to the broader UHR population. Moreover, due to small numbers (two BLIPS and one GRD), we have been unable to stratify our findings across different UHR subgroups (APS, BLIPS, and GRD). These three groups have been found to be heterogeneous in terms of psychotic risk, with BLIPS having a significant higher

risk to develop psychosis as compared to APS and GRD, and GRD not showing an increased risk of developing psychosis in the short term (4 years) (14, 80, 81). In particular, the BLIPS group, which resembles the Acute and Transient Psychotic Disorder group defined by the International Classification of Diseases, tenth revision (ICD-10) (81), is characterized by specific unmet needs and poor longer-term outcomes, beyond the heightened risk of developing psychosis (82, 83).

This heterogeneity could confound both clinical and neuroanatomical findings. This can also be the cause for the lack of neuroanatomical differences between the UHR individuals with and without self-disturbances. It is thus possible that to detect these neuroanatomical effects, a larger sample would be needed. Third, in our study, we could not control for affective comorbidities, as in our sample, EASE scores positively correlated with levels of anxiety and depression. This is a potential limitation, as comorbid depression and anxiety disorders significantly contributed to gray matter volume reductions of the ACC in people at UHR of psychosis in a previous study (84).

Finally, these preliminary results need to be replicated in different larger samples and in longitudinal neuroimaging study designs.

CONCLUSIONS

The data from the present study suggest that high scores on the EASE in UHR subjects, which reflect subjective disorders of the self, are related to reductions in the volume of the ACC. These findings represent a first step forward toward the integration of subjective experiences of self and neurobiological alterations in the early phase of psychosis. Further studies integrating phenomenological, neurocognitive, and neurobiological aspects of basic self-disturbances are warranted to improve our understanding of the role of self-disorders in vulnerability to psychosis.

ETHICS STATEMENT

The study protocol was approved by the National Research Ethics Service Committee of London-Camberwell St Giles, United Kingdom, and all participants gave written informed consent.

AUTHOR CONTRIBUTIONS

IB conducted the study under the supervision of PA and drafted the version of the manuscript. LM contributed the administration of the EASE questionnaire. ST helped analyzing VBM data. MB help setting up the study and obtain ethics approval. MA, CS, BV were responsible for recruiting subjects for the study. MC, LV, MK, GM contributed to assessment of subjects and data analysis. JS, JP, PFP all contributed to the recruitment of subjects and set up of the study. PP and PFP critically revised the manuscript. OH, PA, PMG obtained the grant to set up the study and supervised the whole work and critically revised the manuscript. PFP and PMG substantially contributed to the ideation of the study.

All authors revised the manuscript, working together towards its final completion.

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Individualized Prediction of Transition to Psychosis in 1,676 Individuals at Clinical High Risk: Development and Validation of a Multivariable Prediction Model Based on Individual Patient Data Meta-Analysis

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Background: The Clinical High Risk state for Psychosis (CHR-P) has become the cornerstone of modern preventive psychiatry. The next stage of clinical advancements rests on the ability to formulate a more accurate prognostic estimate at the individual subject level. Individual Participant Data Meta-Analyses (IPD-MA) are robust evidence synthesis methods that can also offer powerful approaches to the development and validation of personalized prognostic models. The aim of the study was to develop and validate an individualized, clinically based prognostic model for forecasting transition to psychosis from a CHR-P stage.

Methods: A literature search was performed between January 30, 2016, and February 6, 2016, consulting PubMed, Psychinfo, Picarta, Embase, and ISI Web of Science, using search terms ("ultra high risk" OR "clinical high risk" OR "at risk mental state") AND [(conver* OR transition* OR onset OR emerg* OR develop*) AND psychosis] for both longitudinal and intervention CHR-P studies. Clinical knowledge was used to *a priori* select predictors: age, gender, CHR-P subgroup, the severity of attenuated positive psychotic symptoms, the severity of attenuated negative psychotic symptoms, and level of functioning at baseline. The model, thus, developed was validated with an extended form of internal validation.

Results: Fifteen of the 43 studies identified agreed to share IPD, for a total sample size of 1,676. There was a high level of heterogeneity between the CHR-P studies with regard to inclusion criteria, type of assessment instruments, transition criteria, preventive treatment offered. The internally validated prognostic performance of the model was higher than chance but only moderate [Harrell's C-statistic 0.655, 95% confidence interval (CIs), 0.627–0.682].

Conclusion: This is the first IPD-MA conducted in the largest samples of CHR-P ever collected to date. An individualized prognostic model based on clinical predictors available in clinical routine was developed and internally validated, reaching only moderate prognostic performance. Although personalized risk prediction is of great value in the clinical practice, future developments are essential, including the refinement of the prognostic model and its external validation. However, because of the current high diagnostic, prognostic, and therapeutic heterogeneity of CHR-P studies, IPD-MAs in this population may have an limited intrinsic power to deliver robust prognostic models.

Keywords: clinical high risk, psychosis, schizophrenia, individual patient data meta-analysis, prognosis, risk prediction

INTRODUCTION

Clinical research on early recognition and intervention of psychotic disorders has enormously expanded over the past two decades (1). There is converging evidence that individuals with an elevated risk for psychosis, commonly termed as at Clinical Risk for Psychosis [CHR-P; or as "ultra high risk" (UHR) or "at-risk mental state" (ARMS)], can be identified prior to the onset of a psychotic episode. CHR-P criteria are based by the presence of attenuated psychotic symptoms, brief and intermittent psychotic symptoms with spontaneous remission, or genetic risk for psychosis (2–4), usually combined with functional impairments and help-seeking behavior (5). CHR-P individuals accumulate several risk factors for psychosis (6) and have a meta-analytical risk of developing psychosis of 20% [95% confidence interval (95% CI) 17%–25%] at 2 years [for details, see Table 4 in Fusar-Poli et al. (7)] while they are not an increased risk for developing non-psychotic mental disorders (8). The level of risk for psychosis is highest in those with a short-lived psychotic episode, intermediate in those with attenuated positive psychotic symptoms and lowest in those at genetic risk (9). Overall, the meta-analytical prognostic performance of the CHR-P assessment

is excellent [area under the curve (AUC) of 0.9 at 38 months] (10) and comparable to that of prognostic models used in other branches of somatic medicine. Despite these achievements, to date, the formulation of a prognosis in CHR-P individuals has been limited to group-level predictions. In light of the recent emergence of precision medicine approaches, it is thus important to develop and validate prognostic models that can calculate a personalized risk rather than a group-level global risk estimate. Prognostic modeling combines multiple predictor variables with their relative weight to estimate the risk or probability that an outcome or specific event will occur in an individual patient (11) and is often used in medical sciences, such as cardiology or oncology [e.g., Refs. (12, 13)]. The calculated individual risks could then be utilized by the caregiver to inform treatment decisions.

More recently, prognostic models have entered clinical psychiatry [for a methodological review, see Fusar-Poli et al. (14)]. A systematic review has identified seven prognostic models for CHR-P populations, most of which suffer from methodological weaknesses, such as the use of suboptimal model building methods, small sample sizes, and the lack of internal or external validation (15). Several recommendations for building robust prognostic models in CHR-P populations were made, including the use of large sample sizes, appropriate events per variable ratios, the selection of *a priori* predictors on the basis of clinical knowledge or the use of automated selection features through machine-learning methods, and the essential need to present validated (internal and external) measures of prognostic performance (14). Some examples of robust prognostic subject-level models for CHR-P populations include the nothern american prodrome longitudinal study (NAPLS) risk calculator by Cannon et al. (16) [which has been externally validated (17)], the pretest risk enrichment stratification algorithm by Fusar-Poli et al. (18) (which has been externally validated), the transdiagnostic risk calculator by Fusar-Poli et al. (19) [which has been externally validated twice (20) and implemented in clinical routine (21)], and the functional outcome prognostic model by Koutsouleris et al. (22) (internally validated). Yet, the key create-limiting step toward implementation of prognostic models into CHR-P clinical routine is the availability of predictors. Biological and neurophysiological data require more expensive and intrusive assessment methods which are not always available in clinical practice, limiting the clinical utility of these models. Rather, neurobiological-based prognostic models can further refine the prediction of outcomes when used in a stepped sequential framework (23), after simpler prognostic models are applied.

We present here an innovative approach for developing risk prediction models for CHR-P individuals that are based on clinical predictors routinely collected as part of clinical practice. We developed a multivariable (i.e., including several predictors) risk estimation model through re-analyzing original individual raw data, requested from systemically sought research groups (24), through an individual patient data meta-analysis (IPD-MA). Prognostic models developed from an IPD-MA offer several unexplored advantages, such as large sample sizes, which are of core importance in the case of rare events, such as the transition to psychosis from CHR-P stage (25). Moreover, because an IPD-MA leverages the variation in the characteristics of the CHR-P included, it can potentially increase the generalizability of the prognostic model. Furthermore, a prognostic model derived from IPD-MA can statistically take into account the differences in prognostic parameters (such as intercepts and predictor-outcome associations) across the included original studies and can explore under which circumstances the prognostic model predicts optimally (26). Despite these potentials, no IPD-MA has ever been conducted in the CHR-P field.

The primary aim of the current study was to develop and validate an individualized, clinically based prognostic model for forecasting transition to psychosis from a CHR-P stage using predictors that were selected on the basis of *a priori* clinical knowledge and that were available in clinical routine.

METHODS

Search Strategies

A systematic search strategy was performed to identify relevant original studies. First, an electronic search was performed in PubMed, Psychinfo, Picarta, Embase, and ISI Web of Science. The search was conducted between January 30, 2016, and February 6, 2016. The following search terms were used: ("ultra high risk" OR "clinical high risk" OR "at risk mental state") AND [(conver* OR transition* OR onset OR emerg* OR develop*) AND psychosis]. Second, the reference lists of the included articles were manually checked for studies not identified by the computerized search.

Selection Criteria

Inclusion criteria were as follows:

(1) data reported in an original paper in a peer-reviewed journal;
(2) involved CHR-P subjects 14 to 40 years old, defined according to established international criteria (1);
(3) assessed attenuated positive and negative psychotic symptoms as well as level of functioning at baseline using standardized CHR-P measurements;
(4) reported transition status at follow-up (events);
(5) reported time to transition or time to last follow-up assessment.

Both longitudinal and intervention studies were included. In the case of studies investigating heterogeneous patient populations, only CHR-P individuals were selected for the analysis. Furthermore, CHR-P individuals who were not meeting the age criterion defined above were excluded from the analysis, as well as CHR-P patients who were already psychotic at baseline as documented in the corresponding articles.

To achieve a high standard of reporting, we adopted the Preferred Reporting Items for Systematic Reviews and Meta-analyses Guidelines-Individual Patient Data (PRISMA-IPD), (27) as well as the statement transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) (28). The meta-analysis was registered in the PROSPERO database for systematic reviews and meta-analysis (CRD42017071176).

Selection of Predictors

For developing and validating a prediction model, it is recommended to select prognostic variables *a priori* based on earlier research (28) and clinical knowledge (14). To develop a model that is readily applicable in clinical practice, the selected predictors were limited to those routinely assessed in CHR-P clinics and involved demographical and clinical predictors. The *a priori* selected predictors were age, gender, CHR-P subgroup (attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms, genetic risk, and deterioration syndrome), baseline severity of attenuated positive and negative psychotic symptoms, and level of functioning. The *a priori* clinical rationale for selecting these predictors is given below. The first predictor is age: in general, youth in their late teens and early 20s have the highest risk of developing psychosis (29) and a meta-analysis revealed that older CHR-P individuals had a significant higher risk for developing a psychotic episode (30). Another recent umbrella review found that those aged 15 to 35 years have a strong factor associated with an increased risk of psychosis (31). The same umbrella review found that gender, the second predictor in our model, has a clear association with an increased risk of psychosis (31). In fact, gender has already been used as predictor in other prognostic models developed for CHR-P populations (19). The third predictor was the severity of attenuated positive psychotic symptoms, such as delusions, unusual thought content, and suspicion, which are the most studied and established predictors in CHR-P field and already used by previous prognostic tools in this group (16). Furthermore, a recent meta-analysis of 33 studies, involving a total of 4,227 CHR-P individuals, showed different levels of the risk for psychosis onset, where persons with brief and limited intermittent psychotic symptoms had the highest risk of transition, followed by those with attenuated positive psychotic symptoms, and by those with genetic risk and deterioration syndrome who had the lowest risk (9). Therefore, the CHR-P subgroups were included as three independent predictors, recording whether or not the criteria of each distinctive risk group were met. Attenuated negative psychotic symptoms encompass social amotivation (apathy, anhedonia, asociality) and expressive deficits (alogia, diminished emotional expression) (32) and were selected as the seventh predictor. Attenuated negative psychotic symptoms were predictive of a subsequent psychotic disorder in CHR-P individuals (33, 34). The last predictor variable was the level of functioning at baseline: a meta-analysis in CHR-P individuals confirmed that functioning is a strong predictor of transition to psychosis (35).

Data Collection

Abstracts were screened independently by two reviewers (AM and NB or MP). Each article was assessed individually, and any disagreements resolved by discussion with a third reviewer. Subsequently, all corresponding authors of the eligible studies identified were contacted to request anonymized individual patient data and regarded as non-responders when no reaction was received after two reminder emails.

Data Extraction

From each individual patient, the following variables were included: gender, the baseline age of participant, CHR-P group, the severity of attenuated psychotic positive and negative symptoms, level of functioning, transition status at follow-up, and duration of the follow-up period. To get a better understanding of possible factors that may have influenced the performance of the prognostic model across the different studies, as well as to detect factors that may have contributed to the study heterogeneity, we also collected for each study additional data. These data are related to the inclusion period, inclusion strategies, inclusion and exclusion criteria, the psychometric criteria employed to define transition to psychosis and the type of CHR-P assessment instruments [for a comparative analysis of CHR-P assessment instruments, see Fusar-Poli et al. (36)], and the instruments applied to assess symptoms and functioning.

Data Storage

All data were anonymized by the researchers of the original studies and therefore not re-identifiable to an individual patient by the current investigators. All cleaned data sets were stored on a secured server in their original formats and converted to a master data set. Data were inspected on unusual outliers *via* range check of the all included variables.

Data Transformation

Studies vary in the CHR-P instruments assessing the severity of attenuate positive psychotic symptoms, attenuated negative psychotic symptoms, and functioning. Thus, to make it clinically applicable, only one measurement was selected in the model as the primary parameter. The selection of the assessment measure was defined *a priori* on the basis of clinical reasoning.

Missing Data

Missing data were imputed according to Multiple Imputations with Chained Equations (MICE) with 50 iterations sets. As recommended by White and Royston (37), the event indicator and Nelson-Aalen estimator of cumulative baseline hazard were included in the imputation model. Also, the study name of the original data was included as a dummy factor to account for potential between-study heterogeneity. Rubin's Rules were applied to combine the data from the imputation sets (38).

Risk of Bias Assessment in Individual Studies

The assessment of the methodological quality of each individual included study is an essential element in meta-analyses (27). The majority of the studies in this IPD-MA have a naturalistic observational design (N = 12). As such, we used the systematic review of Zeng et al. (39), which recommends the Newcastle-Ottawa Scale (NOS) (40), a nine-item scale categorized into three dimensions, namely, selection, comparability, and outcome. Quality assessment of naturalistic and observational studies in meta-analyses is problematic. In fact, the key components of

studies to be assessed on the MOOSE's recommendations were whether the outcome of interest was not present at the start of the study, the follow-up period of the study was long enough for the outcome to occur, and an adequate proportion of the subjects participated in the follow-up cohort (41). The minimal follow-up period in this IPD-MA was set at 12 months. Studies received a positive score for adequacy of follow-up cohort when they had a minimum follow-up rate of 50% to 80% in cohort studies or 80% in randomized controlled trials (RCTs) (42).

Primary Outcome

The primary outcome is the transition to psychosis (event) from a CHR-P stage. Transition to psychosis was defined according to the criteria of the Comprehensive Assessment of At Risk Mental State (CAARMS) (2), Structured Interview of Prodromal Symptoms/ Scale of Prodromal Symptoms (SIPS/SOPS) (3), Brief Psychiatric Rating Scale (BPRS) (43), Positive and Negative Syndrome Scale (PANSS) (44), or Structured Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (SCID-IV) (45). The CHR-P patient outcomes were recorded as transitioned to a psychosis, no transition, or lost to follow-up.

Data Analyses

Individuals with a complete follow-up assessment were compared with those lost to follow-up with an independent *t* test (continuous variables) or chi-square test (binary variables) for descriptive purposes. Collinearity of predictors was tested with the variance inflation factor (VIF) and estimated by the formula $1/(1 - R^2)$. An outcome of 4 or lower indicates a low indication of collinearity between the predictors (46).

A parametric survival model with a log-normal distribution for event times was computed (47). The evaluation of the model's performance and generalizability was done with an extended form of internal validation, because of the lack of true external validation data. Therefore, an internal–external cross validation (IECV) technique was applied, which maximized the data available for both model development as well as model validation (26). With the IECV, all studies (*M)* minus one study were used as a derivation set to develop a prediction model, and the remaining set is used for its external validation. This was repeated for each data set, leading to *M* scenarios to investigate consistent model performance, which was combined by applying Rubin's Rules (38). All discovered studies were utilized in the development and validation of the model. A *t* test calculated the significance of the final beta coefficients of the predictors.

The model performance was estimated by calculating its discrimination and calibration. Discrimination referred to the model's ability to separate CHR-P individuals who transitioned to psychosis versus those who did not transition. For each study, a bar graph with the frequency distribution of predicted survival of the survival groups was presented, for both 12 months as well as 24 months. For both 12 and 24 months, the bar graph showed 10 risk groups, which each represented an equal number of individuals. The distribution of the risk groups, which ranged from 0 (no chance of survival, i.e. transition to a psychosis) until 100 (100% chance of survival, so no transition to psychosis) was determined by the observed survival per study. A well-discriminating model shows a high overlap between the predicted survival and the observed survival in the different risk categories (48). Moreover, Harrell's C statistics with its 95% CI was calculated per study, which referred to the overall probability that the model estimates a higher risk for the CHR-P individual that does develop psychosis compared with a person that does not. Values of C-statistics higher than 0.5 (random prediction) and lower than 0.6 are considered "poor"; from 0.6 and 0.7 are considered "moderate"; from 0.7 to 0.8, "adequate"; from 0.8 to 0.9, "excellent"; and above 0.9, "outstanding," up to 1 (perfect prediction). The C-statistics of all individual studies was plotted in a forest plot, with the 95% CI indicating a possible statistical difference from random prediction. Furthermore, for each study, the calibration of the model was calculated, which referred to the agreement between the observed and the predicted outcomes (48) and was presented with its 95% CI for each individual article in a forest plot. The linear predictor is calculated according to the coefficients of the model and included as a covariate in a Cox model. The slope of the linear predictor is the calibration slope. The calibration plot can be viewed as a measure of fit of the prognostic model in the CHR-P population: when a study's 95% CI included the value of 1, it indicated a fit, whereas a 95% CI not containing a score of 1 implied a serious misfit of the model, suggesting that adjustments of the model's intercepts should be considered.

The CHR-P studies differed with regard to study design, inclusion period, recruitment strategies, inclusion and exclusion criteria, transition criteria, CHR-P assessment instruments, and treatments offered. These characteristics were expected to influence the effects of the prognostic model in this IPD-MA. In meta-analyses, heterogeneity is examined with the Q-statistic and I^2 Index (24). However, in studies that develop prediction models based on IPD-MA, the extent of heterogeneity is better quantified by studying the 95% prediction intervals (49).

All statistical analyses were conducted using R version 4.2.2 (50) and used the following packages: foreign, mice, micemd, Hmsic, VIM, jomo, flexsurv, metamisc, rms, and pec.

RESULTS

Studies and Participants

A total of 2,176 papers were identified by the literature search and 43 were deemed eligible for the IPD-MA. The corresponding authors of the 43 studies were contacted, of which 15 agreed to participate and shared all necessary individual patient data needed for the model (see **Figure 1**). Of the remaining authors, seven authors replied to work on the same subject, two were not able to share the essential data, and nineteen authors did not reply at all. These 28 studies related to a total of 2,815 CHR-P individuals (62.7% of CHR-P eligible subjects), of whom 475 transitioned to psychosis (16.9% of the eligible yet not included subjects). There is a selection bias in that the current IPD-MA included 1,676 CHR-P individuals, of whom 386 developed psychosis. This corresponded to 37.3% of all the CHR-P eligible participants.

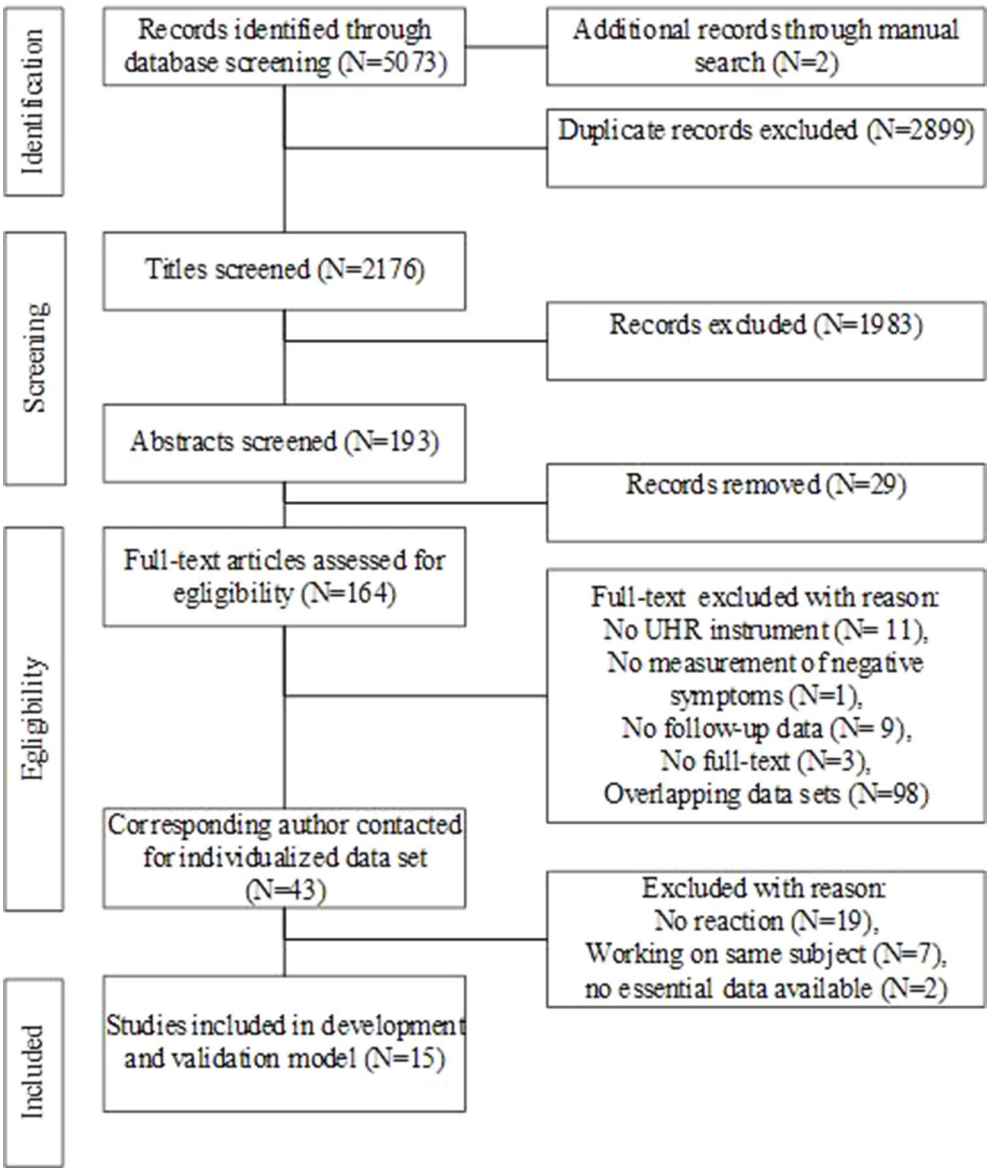

FIGURE 1 | Flow chart of the study.

The participating studies were Access, Detection And Psychosocial Treatment (ADAPT) (51), Clinic for Assessment of Youth at Risk (CAYR) (52), Dutch Prediction of Psychosis Study-Amsterdam (DUPS-A) (53), Early Detection and Intervention Evaluation-Netherlands (EDIE-NL) (54), Early Detection and Intervention-United Kingdom (EDIE-UK) (55), Früherkennung von Psychosen (FePsy) (56), Früherkennungs- und Therapiezentrum für psychische Krisen (FETZ) (57), Green Program for Recognition and Prevention of Early Psychosis (GRAPE) (58), Integrative Neuroimaging Studies in Schizophrenia Targeting for Early intervention and Prevention (IN-STEP) (59), Outreach and Support in South London (OASIS) (60), Personal Assessment and Crisis Evaluation (PACE) (61), Programme of Recognition and Therapy (PORT) (62), ROME (63), Sendai ARMS and First Episode clinic (SAFE) (64), and Dutch Prediction of Psychosis Study-Utrecht (DUPS-U) (65).

Furthermore, for each included study, we checked whether CHR-P individuals met the inclusion criteria. CHR-P individuals younger than 14 years were removed from the data set: ADAPT (N = 2), CAYR (N = 1), DUPS (N = 4), EDIE-NL (N = 1), PACE (N = 1), Rome (N = 19), and DUPS-U (N = 14), as well as participants older than 40 years: FePsy (N = 10) and IN-STEP (N = 1). Subjects with an elevated risk for psychosis but not meeting the established CHR criteria were excluded: FePsy (n = 30), FETZ (N = 30), INSTEP (N = 4), and DUPS-U (N = 4). Similarly, subjects who were already psychotic as reported in the corresponding article were filtered out: EDIE-NL [psychotic at inclusion (N = 4), history of psychosis (N = 1)]. Subjects' data

were censored to the primary study protocol-stated follow-up period: FePsy (N = 1) and CAYR (N = 4).

Because of these procedures, a final sample of 1,676 individuals fulfilled the inclusion criteria and was included in the IPD-MA. Key details of the included studies are summarized in **Table 1**, and a more comprehensive information on each study is included in **Supplement IV**.

An overview of the comparison of study characteristics is presented in **Table 2**. The CHR-P studies worldwide participated in the study, and majority of the studies took place in Europe (53–57, 60, 62, 63, 65). Three studies concerned an RCT (51, 54, 55), one study had a mixed design of both RCT and naturalistic observational design (61), whereas all the others had a naturalistic observational design. The earlier studies started including individuals in 1993 (61), whereas the later studies started including in 2013 (60). The inclusion period varied between 1 year (52) and 13 years (61). The smallest study contained 19 subjects (63), whereas the largest study contained over 400 individuals (61). Despite methodological differences, one inclusion criterion was shared by all studies, namely, meeting the clinical high-risk criteria of at least one of the high-risk groups [genetic risk and deterioration (GRD), attenuated psychotic symptoms (APS), or brief limited psychotic symptoms (BLIPS)]. Eleven studies had additional age criteria (52, 54, 55, 58–64), one study included only participants with a minimum of 9 years of education (58); and as additional criterion for another study, individuals should have no history of antipsychotic medication for over 16 weeks (59). There was a greater variety in the applied exclusion criteria, with only the EDIE-UK (55) study that did not exclude subjects in case of a known organic cause for the presentation of prodromal symptoms. Twelve studies excluded individuals with either a current or a lifetime psychotic condition (51, 54, 58, 60–68). Ten studies excluded individuals with lower intellectual capacities (51, 52, 54, 56, 57, 59, 60, 62, 64, 65), five studies excluded individuals in case of substance use or abuse (52, 59, 60, 63, 64). Current or a history of antipsychotic medication was an exclusion criterion in six studies. Two studies excluded individuals with insufficient competence of the primary language (54, 66). The presence of a pervasive developmental or autism spectrum disorder was an exclusion criterion in two studies (52, 59). In one study, a history of electroshock therapy (59), withdrawing their willingness to be followed by the service (60) or suicide risk due to personality disorder (64) was an exclusion criterion. In the final database, the mean follow-up time was of 32.37 months (SD, 31.59 months), and there were 386 (23.0%) transitions to psychosis (events). Therefore, the final event per variable ratio was 1:48, which is below the threshold recommended for building robust prognostic models (14).

Eight of 15 studies launched special information campaigns, either targeting only potential sources of participant referrals or the general public (51, 52, 55, 60, 62, 64, 66, 67). The campaigns differed in their elaborateness: from a website and folders to workshops, letters in newspapers, and advertisement on radio and television. All studies included individuals that were referred to them, but a few studies combined this with the option of self-referral (52, 62), referral by a close friend or family member (52) or screening in a help-seeking population (54). Six studies offered additional treatment, such as case management, cognitive

TABLE 1 | Overview of studies utilized for the development and validation of the prognostic prediction model.

Study	Country	Inclusion period	CHR	Positive psychotic symptoms	Negative psychotic symptoms	Functioning	Transition criteria	N (% m)	Age (M, SD)	Follow-up (months)	Transition status at last follow-up (n, %)
ADAPT	Can	2008–2010	SIPS/SOPS	SIPS/SOPS	SIPS/SOPS	GAF	SIPS/SOPS	49 (73.4%)	21.3 (3.9)	24	3 (6.1%)
CAYR*	Can	2005–2014	CAARMS	BPRS	SANS	GAF	CAARMS	176 (55.7%)	19.3 (4.0)	12	16 (9.0%)
DUPS-A	NLD	2002–2006	SIPS/SOPS	SIPS/SOPS	SIPS/SOPS	GAF	PANSS	69 (66.7%)	20.0 (3.7)	36	18 (26.1%)
EDIE-NL	NLD	2008–2012	CAARMS	CAARMS	CAARMS	SOFAS	CAARMS	195 (49.2%)	22.7 (5.4)	18	32 (16.4%)
EDIE-UK	UK	1999–2002	PANSS	PANSS	PANSS	GAF	PANSS	58 (68.9%)	22.2 (4.5)	36	13 (22.4%)
FePSY*	CH	2000–2015	BSIP	BPRS	SANS	GAF	BPRS	133 (31.8%)	24.2 (5.2)	12–78	38 (28.8%)
FETZ	D	1998–2003	SIPS/SOPS	SIPS/SOPS	SIPS/SOPS	SOFAS	BPRS	161 (63.3%)	25.3 (6.1)	12–72	72 (44.7%)
GRAPE	KOR	2007–2011	SIPS/SOPS	SAPS	SANS	QLS	SCID-I	60 (58.3%)	19.7 (3.3)	20,7	14 (23.3%)
INSTEP*	JPN	2008–2013	SIPS/SOPS	PANSS	PANSS	GAF	SIPS/SOPS	53 (56.6%)	24.0 (8.4)	36	6 (11.3%)
OASIS*	UK	2013–2016	CAARMS	CAARMS	CAARMS	GAF	CAARMS	51 (58.8%)	22.8 (5.2)	17,7	16 (31.4%)
PACE	AUS	1993–2006	CAARMS	BPRS	SANS	GAF	CAARMS	415 (48.2%)	19.4 (3.4)	12–168	114 (27.7%)
PORT*	POL	2010–2016	CAARMS	CAARMS	CAARMS	SOFAS	PANSS	107 (45.8%)	18.8 (3.5)	12–84	20 (18.7%)
Rome*	ITA	2012–2013	SIPS/SOPS	PANSS	PANSS	cGAS	SIPS/SOPS	19 (52.6%)	15.3 (1.3)	12–24	5 (26.3%)
SAFE	JPN	2004–2012	CAARMS	PANSS	PANSS	GAF	CAARMS	106 (62.3%)	20.0 (4.4)	28.8	14 (13.2%)
DUPS-U	NLD	2003–2006	SIPS/SOPS	SIPS/SOPS	SIPS/SOPS	mGAF	SIPS/SOPS	25 (40.0%)	16.6 (1.6)	60	7 (28%)

AUS, Australia; BPRS, Brief Psychotic Rating Scale; BSIP, Basel Screening Instrument for Psychosis; CAARMS, Comprehensive Assessment of At Risk Mental State; CAN, Canada; cGAS, children Global Assessment Scale; CH, Switzerland; DSM-IV, Diagnostical and Statistical Manual of mental disorders version IV; GAF, Global Assessment of Functioning scale; ITA, Italy; JPN, Japan; KOR, South Korea; m, male; M, mean; mGAF, modified Global Assessment of Functioning scale; NLD, the Netherlands; PANSS, Positive and Negative Syndrome Scale; POL, Poland; QLS, Quality of Life Scale; SANS, Scale for the Assessment of Negative Symptoms; SD, standard deviation; SIPS/SOPS, Structured Interview of Prodromal Symptoms/Scale of Prodromal Symptoms; CHR, Ultra High Risk; UK, United Kingdom.

**Data from the specified study, yet not identical to the data in the published paper, for instance, a subsample of the study or sample with a shortened or prolonged follow-up then reported in the original paper.*

TABLE 2 | Summary of study characteristics.

	N (studies)	% of studies	% of total sample
Continent:			
Europe	9	60.0	48.8
Australia	1	6.7	24.8
Northern America	2	13.3	13.4
Asia	3	20.0	13.1
Design:			
Naturalistic observational	11	73.3	82.0
RCT	3	20.0	18.1
Mixed	1	6.7	24.8
Start inclusion period:			
Before 2000	3	20.0	37.9
2000–2005	4	26.7	11.9
2005–2010	5	33.3	31.9
2010–	3	20.0	10.6
Inclusion period—duration:			
1 year	1	6.7	10.5
1–2 years	5	33.3	22.3
2–3 years	4	26.7	17.1
>3 years	5	33.3	48.6
Information campaigns			
Yes	8	53.3	50.0
No	7	46.7	50.0
Inclusion strategies			
Referral	12	80.0	71.4
Mixed	3	20.0	28.6
Inclusion criteria: in additional to CHR-group:			
Age at inclusion	10	66.7	74.1
A minimum of 9 years of education	1	6.7	3.6
No history of antipsychotic medication for over 16 weeks	1	6.7	3.2
Exclusion criteria:			
Organic cause for prodromal symptoms	14	93.3	96.7
Current or lifetime psychosis	12	80.0	82.9
Intellectual functioning	11	73.3	67.1
Substance use	5	33.3	24.2
Current or history of antipsychotic medication	6	40.0	53.8
Language requirements	2	13.3	19.5
Diagnosed with pervasive developmental disorder or autism spectrum	2	13.3	13.7
A history of electroshock therapy	1	6.7	3.0
Not help seeking individuals	1	6.7	3.0
Suicide risk due to personality disorder	1	6.7	6.3
Assessment of ultra high risk:			
SIPS/SOPS	7	46.7	26.1
CAARMS	6	40.0	63.1
PANSS	1	6.7	3.5
BSIP	1	6.7	7.9
Assessment of positive psychotic symptoms:			
BPRS	3	20.0	43.2
CAARMS	3	20.0	21.1
SIPS/SOPS	5	33.3	21.1
PANSS	3	20.0	13.9
SAPS	1	6.7	3.6
Assessment of negative psychotic symptoms:	4	26.7	46.8
SANS	4	26.7	13.6
PANSS	4	26.7	18.2
SIPS/SOPS	3	30.0	21.1
CAARMS			
Assessment of functioning:			
GAF	9	60.0	66.3
SOFAS	3	20.0	27.7
mGAF	1	6.7	1.5
cGAS	1	6.7	1.0
QLS	1	6.7	3.6
Transition criteria:			
CAARMS	5	46.7	56.3
SIPS/SOPS	4	26.7	8.7
PANSS	3	13.3	14.0
BPRS	2	13.3	17.5
SCID-I	1	6.7	3.6
Sample size:			
<50	3	20.0	5.6
50–100	5	33.3	17.4
100–150	3	20.0	20.6
150–200	3	20.0	31.8
>200	1	6.7	24.7
Transition rate:			
<10%	2	13.3	13.4
10–20%	4	26.6	27.6
20–30%	7	26.7	46.5
30–40%	1	6.7	3.0
>40%	1	6.7	9.6
Treatment:			
CBT (RCT)	3	20.0	18.1
Additional treatment	6	40.0	59.0
None	6	40.0	23.1

BPRS, Brief Psychotic Rating Scale; BSIP, Basel Screening Instrument for Psychosis; CAARMS, Comprehensive Assessment of At-Risk Mental State; CBT, Cognitive Behavioral Therapy; cGAS, children Global Assessment Scale; CHR, clinical high risk; GAF, Global Assessment of Functioning scale; mGAF, modified Global Assessment of Functioning scale; PANSS, Positive and Negative Syndrome Scale; QLS, Quality of Life Scale; RCT, Randomized Controlled Trial; SANS, Scale for the Assessment of Negative Symptoms; SCID-I, Structured Clinical Interview for DSM-IV; SIPS/SOPS, Structured Interview of Prodromal Symptoms/Scale of Prodromal Symptoms.

behavioral therapy, psychoeducation for the CHR individuals, as well as for family, medication, sport, and nutrition groups (52, 60–62, 66, 64). Information on specific treatments that were offered was only available for RCTs, and most studies did not keep detailed records of offered interventions.

With regard to the assessment of CHR-P, symptoms, and functioning, four instruments were applied to determine whether an individual met the CHR criteria, namely, PANSS (44), CAARMS (2), the Basel Screening Instrument for Psychosis (BSIP) (4), and the SIPS/SOPS (3). Positive psychotic symptoms were assessed with five different instruments: PANSS (44), CAARMS (2), BPRS (43), SIPS (69), and the Scale of Assessment of Positive Symptoms (SAPS) (70). Negative psychotic symptoms were measured with four scales:

PANSS (44), Scale of Assessment of negative symptoms (SANS) (71), CAARMS (2), and the SIPS (3). Functioning was assessed with five scales, namely, the Global Assessment of Functioning (GAF) (72), the Modified-Global Assessment of Functioning (m-GAF) (73), the Children Global Assessment Scale (cGAS) (74), the Social and Occupational Functioning Scale (SOFAS) (75), and the Quality of Life Scale (QLS) (76). Transition to psychosis was determined with four different transition criteria: CAARMS [five studies (52, 54, 60, 61, 64)], SIPS/SOPS [four studies (51, 59, 63, 65)], PANSS [three studies (53, 55, 62)], BPRS [two studies (56, 57)], and SCID-1 [one study (58)].

Quality Assessment of Individual CHR-P Studies

All CHR-P studies received the maximum score of 4 for assessing the study quality with the NOS (40): an adequate check that outcome is not present at the start of the study, an adequate duration of the follow-up period, and an adequate proportion of participants in the follow-up assessments (see **Supplements 1** and **2**). The three RCTs additionally received an extra point for blind assessments.

Data Cleaning and Preparation

Missing Data and Multiple Imputations

In the original sample, 78.6% had data on all variables. There were missing data with regard to attenuated negative psychotic symptoms (7.2%), functioning (6.6%), attenuated positive psychotic symptoms (4.8%), CHR-P group (4.2%), age (<0.1%), and sex (<0.1%). For the individuals, 3.8% were omitted from the analyses because of missing of follow-up data. There were no differences between CHR-P subjects with and without follow-up with regard to age, gender, type of CHR-P subgroup, attenuated negative psychotic symptoms, and functioning at baseline. Only the severity of attenuated positive psychotic symptoms at baseline was significantly higher for CHR-P individuals without follow-up ($t = -6.244$, $df = 1,563$, $p < .001$).

As noted above, the 15 included CHR-P studies had applied a variety in assessment instruments with regard to attenuated positive psychotic symptoms, attenuated negative psychotic symptoms, and functioning (see **Table 1**). All measurements were tested as the core parameters on the basis of the protocol, yet, although other instruments were applied in more individuals, attenuated negative psychotic symptoms—total score SIPS, attenuated positive psychotic symptoms—total score SIPS and GAF were selected because these had the best predictive performance. SIPS/SOPS is a frequently used instrument in the enclosed studies and is one of the golden standard measurements for positive and negative psychotic symptoms in CHR research (77). For functioning, the primary parameter is the frequently applied GAF (72). However, because the SIPS were only applied by 18.2% and the GAF by 66.3% of the individuals, there were missing data for 81.8% (attenuated positive and negative psychotic symptoms) and 33.7% (functioning). Multiple imputations were performed with 50 iteration sets. The data from the variables age, gender, GRD, APS, BLIPS, and functioning (GAF) were used to predict the missing SIPS-positive and -negative psychotic symptoms scores. The imputations diagnostics are presented in **Supplement III**.

Testing Collinearity

An overview of the estimated VIFs is presented in **Table 3**. Overall, the majority of the predictor variables showed a VIF close to 1, indicating low shared variance with the other variables. However, the three CHR-P subgroups showed a high level of collinearity. To investigate the influence of the collinearity, all three predictors were one-by-one subsequently omitted from the analysis, leading to a drop in VIF scores of below three, yet barely influencing the outcome of the produced model. Given our aim to develop a prognostic model in which all predictors are assessed for their relative contribution to risk, these predictors were retained in further analysis, in line with the methodological recommendations (14).

Development and Validation of the Prognostic Model

A parametric survival model with a log-normal distribution is fitted for event times (47): transition to psychosis from a CHR-P stage and time to transition. **Supplement V** displays the discriminative performance of the prognostic model in the individual studies at 12 and 24 months. **Figure 2** shows a forest plot with the 95% CI of the Harrell's C-statistics of the prognostic model per study and the overall C-statistics.

The C-statistic of the model was 0.655 with a 95% CI of 0.627 to 0.682 and (approximate) 95% prediction interval of 0.614 to

TABLE 3 | Predictor variables and accompanying VIF.

		Dependent							
		Gender	**Age**	**GRD**	**APS**	**BLIPS**	**Pos Sx**	**Neg Sx**	**Functioning**
Independent	Gender	—	1.029	1.028	1.028	1.028	1.028	1.005	1.028
	Age	1.021	—	1.022	1.022	1.020	1.012	1.016	1.022
	GRD	7.857	7.875	—	1.026	1.599	7.877	7.877	7.877
	APS	15.127	15.157	1.975	—	1.790	15.122	15.162	15.142
	BLIPS	9.848	9.848	2.004	1.165	—	9.851	9.870	9.855
	Positive Sx	1.415	1.404	1.419	1.415	1.416	—	1.208	1.418
	Negative Sx	1.833	1.867	1.879	1.879	1.879	1.599	—	1.339
	Functioning	1.586	1.589	1.590	1.588	1.587	1.589	1.133	—

APS, attenuated psychotic symptoms; BLIPS, brief limited psychotic symptoms; GRD, genetic risk and deterioration; Sx, symptoms; VIF, variance inflation factor.

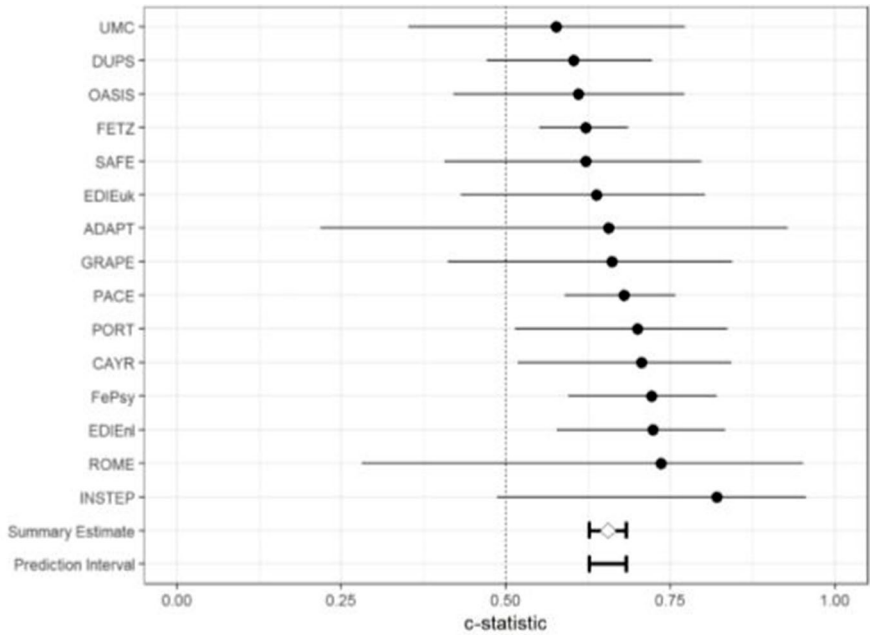

FIGURE 2 | Forest plot of the discriminative ability of the model in the individual studies and its 95% CI, assessed with the C-statistics.

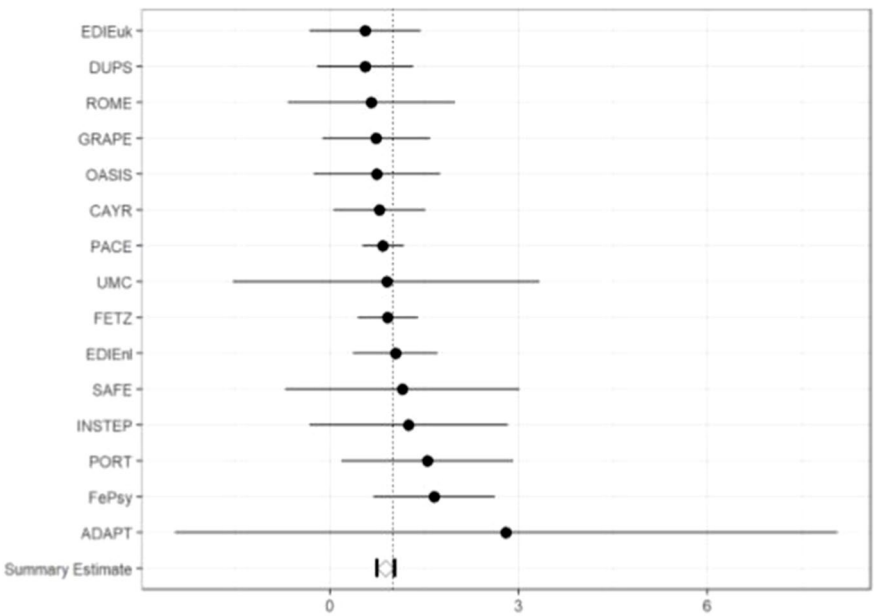

FIGURE 3 | Forest plot of the external validation of calibration slope and its 95% CI in the individual studies.

0.695. Inspection of the forest plot showed that the prognostic performance in the larger studies reached an adequate level, with C-statistics of around 0.700 and 95% CI between 0.54 and 0.87 (52, 54, 56, 57, 61, 62). This is also visible in the boxplots of the individual studies (see **Supplement V**): the proportion of predicted survival per risk group is relatively equal to the observed proportion, meaning that the model can adequately discriminate between CHR-P individuals with a higher versus lower risk of developing psychosis (one survival). Yet, smaller studies have lower discriminative adequacy: in the forest plot, the 95% CIs of these studies were broad and included 0.5, which indicated that the model did not discriminate better than chance.

The calibration slope of the model in the individual CHR-P studies, as well as overall calibration, is displayed in **Figure 3**.

The internal–external validation results for the calibration slope gives an overall estimate of 0.886 (95% CI, 0.745–1.022), which indicated that at 2 years, the predicted probabilities, on average, vary too much. Because the 95% CI includes 1, the overall calibration slope yields as non-significant. Calibration slopes of the individual studies not overlapping with 1 indicate no need for recalibration. Inspection of the forest plot showed that all studies overlapped with 1, which indicated that the prognostic model calibrates sufficiently well, and there are no direct indications that the parameters of the model should be adjusted with shrinkage methods.

Final Model

Table 4 presents the final model with its intercepts; all included predictors have a significant contribution to the prediction, as tested with an independent sample *t* test. The scale parameter is 2.119.

Prognostic Prediction for Individual CHR-P Patients

With a parametric survival model with a log-normal distribution for event times, a (cumulative) survival probability can be calculated for time (*t*) in CHR-P individual subjects, utilizing the linear predictor (5.777) and the earlier reported scale parameter (78).

The following formula that estimates the risk of psychosis (1 survival) for an individual patient derives from the model:

Risk of psychosis = 1 − (7.543 + 0.179 (sex = female) + −0.049 × (age)+.689 × (genetic risk and deterioration) + −0.370 × (attenuated psychotic symptoms = yes) + −0.738 × (brief limited intermittent psychotic symptoms = yes) + 0.006 × (functioning GAF) + −0.052 × (total score negative psychotic symptoms SIPS/SOPS) + −0.102 × (total score positive psychotic symptoms SIPS/SOPS)).

Case Study

Considering a 21-year-old female that meets the CHR-P criteria of brief intermittent psychotic symptoms, with baseline GAF score of 65, SIPS/SOPS attenuated negative psychotic symptoms total score of 13 and a SIPS/SOPS attenuated positive psychotic symptoms total score of 8, the predicted 2-year survival would be 0.835. This implies that her probability of developing psychosis within the first 2 years is 1 −.835 = .165, which is of about 16%.

Heterogeneity

The 95% prediction interval of the C-statistics (0.614–0.695) shows a moderate range, which indicates that there is substantial heterogeneity between the predictions of the model in the different studies. There is a larger amount of heterogeneity detectable with regard to the overall calibration slope which shows a rather large 95% CI of 0.745–1.022. This is supported by the large variety in operationalization of symptoms in the different assessment instruments, as well as variety in outcome criteria.

DISCUSSION

The aim of this study was to develop and validate a prognostic model based on clinical predictors that are available in clinical routine for forecasting the onset of a psychotic episode in CHR-P individuals, using an IPD-MA. The predictors were selected *a priori* as recommended by state-of-the-art prognosis guidelines. The predictors encompassed two demographical predictors (age, gender) and six clinical predictors collected at baseline (genetic risk and deterioration syndrome CHR-P subgroup, attenuated psychotic symptoms CHR-P subgroup, brief and limited intermittent psychotic symptoms CHR-P subgroup, severity of attenuated positive psychotic symptoms, severity of attenuated negative psychotic symptoms, level of functioning) predictors. The overall model achieved a C-index of .655, indicating a modest subject-level ability to differentiate between CHR-P individuals with a high-risk likelihood that develop psychosis from those at lower risk. The overall calibration slope indicated that the model can significantly distinguish CHR-P individuals who convert to psychosis versus those who do not. Most of the included predictors showed a significant contribution to the model, with the exception of CHR-P group membership (which was characterized by high collinearity). The removal of these variables from the model indicated that the influence of this collinearity on the final model was non-significant and minor in magnitude.

TABLE 4 | Variables and intercepts of the final model.

Variable	Intercept:	T	SE of Mean	Sign.	95% confidence interval	
					Lower	Upper
Intercept	7.543328648	51.792	.14565	<.001	7.251	7.836
Sex—female	0.179071582	13.247	.01352	<.001	0.152	0.206
Age	−0.048979637	−42.162	.00116	<.001	−0.051	−0.047
APS—yes	−0.369616434	−7.737	.04777	<.001	−0.466	−0.274
BLIPS—yes	−0.738429338	−15.950	.04630	<.001	−0.831	−0.645
Functioning: GAF score	0.006634737	4.059	.00163	<.001	0.003	0.010
Negative psychotic symptoms: SIPS/SOPS—total score	−0.054490819	−14.542	.00375	<.001	−0.062	−0.047
Positive psychotic symptoms: SIPS/SOPS—total score	−0.092850985	−16.356	.00574	<.001	−0.105	−0.082

APS, attenuated psychotic symptoms; BLIPS, Brief Limited Psychotic Symptoms; GRD, Genetic Risk and Deterioration; SE, Standard Error; Sign, significance level; SIPS/SOPS, Structured Interview of Prodromal Symptoms/Scale of Prodromal Symptoms.

This is the first IPD-MA and the largest clinical prediction modeling study conducted in the CHR-P field. Indeed, one of the main advantages of developing a prognostic model using an IPD-MA is the possibility of reaching large sample sizes, which enables the building of a more robust prediction model. Moreover, the model's generalizability can be strengthened by the inclusion of several large data sets from all over the world. Ensuring appropriate representativeness of CHR-P samples is pivotal to developing robust prognostic models because of the severe sampling biases that affect this population (18, 79, 80). Our approach was partially successful. On one side we demonstrated that our *a priori* selected predictors did produce a prognostic model that forecasted the onset of psychosis at the individual subject level with an accuracy superior to chance (0.655). From a methodological point of view this confirms that preselecting predictors on the basis of previous knowledge and using all of them in the prognostic model is a robust way for developing risk prediction algorithms. On the other side, the level of accuracy was only moderate. This could be due to the fact that our IPD-MA combined CHR-P studies employing different definitions of predictors and outcomes, and that there were some missing data (81). Furthermore, to ensure a prognostic model that could easily be applied in clinical practice, we decided to use only one instrument per predictor (e.g., the SIPS and not the CAARMS, PANSS, SAPS, or BPRS, and the GAF and not the SOFAS, mGAF, cGAS, or QLS). This was prespecified at the PROSPERO protocol level. This decision resulted in missing data, which has to be considered as missing not at random (MNAR). The problem was particularly severe because this led to a rather high level of missing data (81.8% for the attenuated positive/negative psychotic symptoms and 33.7% for the level of functioning). Although the missing data were handled with the recommended multiple imputation techniques (82), it did imbalance the final prognostic model. These choices counterweight the moderate prognostic accuracy of our model because they facilitate its theoretical implementability in clinical routine. Scalability of prognostic models is an essential criterion that should be fully considered beyond the level of prognostic accuracy. In fact, even prognostic models that have a suboptimal (but clearly higher than random prediction) level of prognostic performance can be clinically useful if they can enter clinical routine at scale. For example, a prediction model has recently been developed and validated using a patient data and machine learning to predict treatment outcome in depression: the overall performance of this model was of a very similar moderate prognostic performance (0.65) (83).

The next stage would be to refine and improve this model. The first option would be to consider using advanced machine-learning approaches. Yet, there is no strong evidence that these methods can deliver more robust and implementable prognostic models compared with *a priori*–defined statistical models. Interestingly, although the prognostic model described above leveraged machine learning methods, its overall prognostic performance was of a similar level than that of our current model (83). A recent systematic review conducted by methodologists showed no performance benefit of machine learning over logistic regression for clinical prediction models (84). However, it is possible that machine learning methods could demonstrate some clear advantages with the addition of multidimensional predictors encompassing neurobiological, genetic, and other modalities (14). The downside of multimodal approaches is that they tend to deliver more complex prognostic models at the expense of scalable implementability. This IPD-MA study also calls for more homogeneity in the CHR-P assessment instruments or at least more research in the development of converting formulas. This would have allowed minimizing missing and imputed data. For example, a between-assessment scale converter algorithm for symptom rating in schizophrenia has been developed by van Erp et al. (85), which enabled both researchers as clinicians to convert the scores of positive and negative psychotic symptoms assessed by the PANSS, SANS, and SAPS. Similarly, an automatic Phyton package called "convert" has been developed to convert CAARMS into SIPS scores and vice versa (36). The tool is freely available online at https://bitbucket.org/ioppn/convert. Unfortunately, we did not have the raw data on the specific CAARMS or SIPS (P1–P5) subscales to use this package, but we only had the overall severity of attenuated positive/negative psychotic symptoms across these two instruments. Beyond the diversity in the assessment instruments, there is another cause of suboptimal prognostic performance for our model, which is the baseline intrinsic difference in study populations. This is supported by the finding that there is substantial diversity in baseline risks and by the finding that our prognostic model had an adequate level of performance (C-statistic 0.7) in the subset of the largest CHR-P studies. These studies are likely to be those with the highest-risk enrichment and less affected by sampling biases which are particularly serious in the case of small CHR-P studies. A meta-analysis by Fusar-Poli et al. (86) demonstrated that these sampling biases are mostly due to the way CHR-P individuals are being recruited for undergoing the initial assessment. Specifically, recruiting CHR-P individuals mostly from the community would dilute the risk enrichment (and therefore the transition risk) compared with samples mostly recruited through the secondary mental health care system. This was also reflected by the type of outreach campaigns adopted by each CHR-P clinic. In comparison to CHR-P studies that targeted their outreach campaigns to health care referrers, CHR-P studies with outreach campaigns that were focused on the general public were associated with lower risk of psychosis. There was also a clear relation between the intensity of the campaign (amount of activities) and a diminished transition risk. In our IPD-MA, CHR-P studies differed strongly with regard to information campaigns, as well as sources of referrals, and this factor may have amplified sampling biases and reduced the prognostic performance of our model.

Another factor that could have modulated the prognostic accuracy of our model may have been the preventive treatments offered to the CHR-P individuals. An earlier meta-analysis (87) examined the preventive effects of antipsychotic medication, dietary supplements, integrated psychological treatments, and cognitive behavioral therapy on the transition to psychosis and reported an overall risk reduction pooled across all of these categories of 54% at 12 months and of 37% at 24 months.

However, the evidence remains inconclusive while a more recent network meta-analysis which included about 1,000 more CHR-P individuals found no evidence to favor specific preventive treatments compared with each other for the prevention of psychosis (88).

LIMITATIONS

One limitation of the current study is that it did not account for treatment effects. The majority of the included studies have a naturalistic, observational design, and as such are an adequate reflection of current clinical practice. Since subject-level data on preventive interventions were only available for RCTs (51, 54, 55), the effects of these treatments could not be entered into the model, and as such their effects could not be controlled for. However, as indicated above, the actual effectiveness of preventive treatments for CHR-P individuals is questionable. As such, it is unlikely that this factor would have impacted our findings substantially. Another limitation is that documented clinical predictors in transition risk could not be used in our model because these were not recorded in the majority of the studies. These predictors are for instance childhood adversities, cognitive biases, social cognition, verbal fluency, beliefs of social marginalization, subjective complaints about motor functioning, urbanicity, and poor premorbid social adjustment. The prediction model could be improved if future studies into risk assessment would measure these risk factors systematically. The main limitation of this IPD-MA was that we were only able to collect a minority of the available data. Because of the sampling biases discussed above, this represents a major barrier to generalizability. It is clear that future IPD-MAs in CHR-P populations face the difficult challenge of collecting all (at least 80%) of the potential studies identified. The additional limitation is that we had to disregard some data because of the high heterogeneity of the measurements. Future IPD-MA could benefit from the converting strategies across different scales that have been discussed above here.

CLINICAL IMPLICATIONS

Given the above caveats, implementing the current prediction model in clinical practice is not desirable. This does not imply that the model is overall redundant. Future refinement of the model in specific clinical circumstance can be considered. For example, future research can clarify the characteristics of the largest studies in which this model can perform better. An answer to this question is rather complex, since these studies vary greatly with regard to inclusion strategies, with studies accepting self-referrals or referrals by friend or family (52), studies that screened in help seeking populations (54), as well as specialized secondary care (57). The offered treatments varied from none (56) to studies with different treatment options (52, 61). Moreover, CAYR (52) shared data of a relatively short follow-up period of only 1 year and a transition rate of 9.0%, whereas FETZ (57) monitored their participants for up to 6 years and reported a transition rate of 44.7%.

FURTHER RESEARCH DIRECTIONS

One avenue for further research could be to investigate whether the prognostic quality of the current model can be optimized: even though a common reaction is to develop a new prediction model, the recommendation is to iteratively adjust the model by adding new data (89). The main reason for updating the available model is the opportunity for further improving the stability and generalizability of the model by considering additional predictors. Improving the stability of the current model would result in predicted outcomes less influenced by variation in input and enhance reliability. This updating can vary between simple recalibration (adjusting the intercept of the model) and an overall adjustment of the associations of the predictors with the outcome. The most obvious option for improvement could be found in the inclusion of data from research projects identified in the systematic search that have not shared their data so far. Yet, another possibility is that IPD-MA in CHR-P could never deliver robust prognostic models, because of the inherited heterogeneity of the underlying population, assessment measurements, and preventive treatments. Such a hypothesis may suggest that future prognostic research in the CHR-P field should rather focus on conducting new large-scale prospective cohort studies that are well characterized phenotypically.

CONCLUSION

This is the first IPD-MA in CHR-P individuals and the largest clinical prediction study ever conducted in these patients to date. There were 1,676 CHR-P individuals that have been used to develop and validate an individualized prognostic model based on clinical variables to forecast transition to psychosis. The model has a moderate to adequate prognostic accuracy, but there are potential options to improve its performance. At the same time, it is important to acknowledge that prognostic models based on IPD-MA may not be particularly effective in the CHR-P field. Harmonization in the CHR-P assessment instruments is a necessary step toward more homogenous databases that can support the development and validation of more robust prognostic models.

CONTRIBUTION TO THE FIELD

A psychotic disorder emerges mostly in adolescence and early adulthood and affects up to 4 in 100 individuals. The Clinical High Risk state for Psychosis (CHR-P) has become the cornerstone of modern preventive psychiatry. More recently, individualized prognostic models have been used to predict a transition to psychosis, but are typically not easily applicable in clinical practice, because required information to make a prediction requires specific equipment or training and is expensive.

In this study, we aimed to build a model to predict who will develop a psychosis based on information that is routinely collected in the clinical field. For the first time, data from CHR-P cohort studies worldwide were used to build this

model. In this study we show that our model can moderately predict whether an individual develops psychosis. Despite our positive results, it is also important to acknowledge some relevant limitations. Because of the large variety between the CHR-P studies prediction models based on IPD-MAs in this population may not be able to reach higher-performance measures. Harmonization of CHR-P assessments and therapeutic interventions may be the first step to facilitate future IPD-MAs in this field.

DATA AVAILABILITY STATEMENT

The data sets for this manuscript are not publicly available because individual patient data were provided by several research groups and are official property of the researchers who conducted the original cohort and intervention studies. They shared their data solely for the purpose of this study. Requests to access the datasets should be directed to the individual researchers of the participating studies.

AUTHOR CONTRIBUTIONS

The conception or design of the work was done by AM, NB, PF-P, and GP. Original study data were collected by JA, MP, DN, LH, AM, AR-R, ES, SR, FS-L, SA, SK, KK, BN, PM, SW, AL, AY, MK-A, MA, SV, MK, KM, SD, TZ, HI, MG, and PF-P. AM coordinated the data collection of the IPD-MA. Data analysis was done by Thomas Debray, whereby interpretation was performed by AM, HB, NB, PF-P, and GP. The drafting of the article was done by AM, HB, NB, and GP, and critical revisions were made by NB, SJ, Thomas Debray, PF-P, and GP. Final approval of the version to be published was given by AM, NB, HB, SJ, AA, JA, MP, DN, LH, AM, AR-R, ES, FS-L, SR, SA, SK, KK, BN, PM, AL, SW, AY, MK-A, MA, SV, MK, KM, SD, TZ, LW, HI, MG, FP-F, and GP.

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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.2019.00345/full#supplementary-material

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REVIEW
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Integrated Mental Health Services for the Developmental Period (0 to 25 Years): A Critical Review of the Evidence

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Background: The developmental period from 0 to 25 years is a vulnerable time during which children and young people experience many psychosocial and neurobiological changes and an increased incidence of mental illness. New clinical services for children and young people aged 0 to 25 years may represent a radical transformation of mental healthcare.

Method: Critical, non-systematic review of the PubMed literature up to 3rd January 2019.

Results: *Rationale*: the youngest age group has an increased risk of developing mental disorders and 75% of mental disorders begin by the age of 24 and prodromal features may start even earlier. Most of the risk factors for mental disorders exert their role before the age of 25, profound maturational brain changes occur from mid-childhood through puberty to the mid-20s, and mental disorders that persist in adulthood have poor long-term outcomes. The optimal window of opportunity to improve the outcomes of mental disorders is the prevention or early treatment in individuals aged 0 to 25 within a clinical staging model framework. *Unmet needs*: children and young people face barriers to primary and secondary care access, delays in receiving appropriate treatments, poor engagement, cracks between child and adult mental health services, poor involvement in the design of mental health services, and lack of evidence-based treatments. *Evidence*: the most established paradigm for reforming youth mental services focuses on people aged 12–25 who experienced early stages of psychosis. Future advancements may include early stages of depression and bipolar disorders. Broader youth mental health services have been implemented worldwide, but no single example constitutes best practice. These services seem to improve access, symptomatic and functional outcomes, and satisfaction of children and young people aged 12–25. However, there are no robust controlled trials demonstrating their impact. Very limited evidence is available for integrated mental health services that focus on people aged 0–12.

Conclusions: Children and young people aged 12–25 need youth-friendly mental health services that are sensitive to their unique stage of clinical, neurobiological,

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and psychosocial development. Early intervention for psychosis services may represent the starting platform to refine the next generation of integrated youth mental health services.

Keywords: mental health, youth, development, prevention, 0 to 25, model of care, mental health services

INTRODUCTION

At present, around one-fourth of the total population consist of youngsters in an age range between 10 and 24 years—the greatest proportion of this cohort in history (1, 2). When compared to their parents, the current generation faces increased complex difficulties for their well-being (3). For instance, the well-being of a great number of children and young people in human history is shaped by the exceptional worldwide forces (4). The future for this generation, and indeed for human beings, is set by population migrations, worldwide correspondences, financial challenges, and the sustainability of ecosystems (4). World Health Organization notes, "mental health disorders account for nearly half of the disease burden in the world's adolescents and young adults" (1), in view of these changes. Mental disorders will become one of the five most familiar ailment causing dismalness, mortality, and dysfunction among youths, by 2020 (5). These mental health problems inversely sway on their academic, professional, and social activities; quality of life; and significantly impact budgetary and societal expense. As a result, the need to search for effective treatment options for mental disorders is inevitable in children and young people (6). To achieve this aim, the UK Government's report on No Health Without Mental Health acknowledged and stressed the importance that only a lifelong approach will enable future mental health goals to be achieved (7). Correspondingly, the NHS England's report—Future in Mind—features the urgent need (by 2020) for a holistic approach, improved access for patients, support for the forefront staff, and adoption of innovative emotional wellness programs for youth that differ from the current tier system division between Child and Adolescent Mental Health Services (CAMHS) and Adult Mental Health Service (AMHS) (8). The Five-Year Foreign View for Mental Health that set the key NHS priorities for 2020–2021 further strengthened this vision (9). These incorporated the critical requirement for equality of regard between services of physical and mental health, the necessity for children and young people to get evidence-based interventions in mental health, and the need of training staff in children and adolescence mental health interventions (9). So as to help accomplish these targets, robust evidence-based information is required not just with the involvement of local and national leadership yet additionally through a driving force on multidisciplinary teams working over all sectors. This started with a local transformation plan for NHS England fusing local partners in the NHS, public health, social services, and youth education and justice sectors to enhance mental health for children and adolescents (10). The forthcoming NHS England Long Term Plan for Mental Health is expected to rely on the mental health of children and young people between the ages of 0–25 with a view to reduce the number of young people who experience a severe mental disorder. The development of a new model of care for children and young people between 0 and 25 years will be a fundamental transformative component to improving the experience, outcomes, and continuity of care. In preparation for this objective, Healthy London Partnership (https://www.healthylondon.org/) is working close by the London Children and Young People Health Transformation Board and the Mental Health Transformation Board to consider the chances and difficulties this would go with. Against this backdrop, the current report provides an initial critical review of the literature to establish mental health services targeting the developmental period. This period includes individuals aged 0–25 years and encompassing the following phases: the perinatal period (from 22 weeks of gestation to 7 days after birth, WHO); infancy (first year of life); childhood (1–10 years); adolescence [the period of time between the onset of puberty and the cessation of physical growth, usually between 10 and 19 years (11)]; and young adulthood (particularly from adolescence on a concept of fulfilment of mental and physical capacity, usually between 19 and 25 years) (12). The main purpose of this study is to critically review the rationale, unmet needs, and evidence for developing integrated mental health services for individuals of 0–25 years of age in order to inform the ongoing developments in this field.

METHOD

A critical review of the PubMed literature was undertaken up to 3rd January 2019. The articles included in this review were not selected on a systematic basis, and there is no assumption that the evidence reviewed is exhaustive. The articles were subsequently used in order to address three core subdomains that are essential to inform the development of mental health services for those belonging to the 0–25 age group: scientific rationale, unmet needs in children and young adults, and evidence for integrated mental health services for people aged 0–25.

SCIENTIFIC RATIONALE FOR INTEGRATED MENTAL HEALTH SERVICES FOR PEOPLE AGED 0 TO 25

This section will review the core evidence that builds the rationale for establishing mental health services for people aged 0–25.

Prevalence of Mental Disorder Across Ages

The WHO World Mental Health Survey epidemiological studies suggest that almost 50% (at least in the US) of the population will face a DSM-defined mental disorder over their life. A monotonic

increase in prevalence across all mental disorders occurs between the youngest (18–29 years of age) and the higher age group (30–44 years of age), before a decline in the older age group. The exceptions to this pattern are substance use and bipolar disorders. These studies also noted that the prevalence of mental disorders is always lowest in those aged more than 60 years, accordingly suggesting that the youngest ages have an increased risk of developing mental disorders.

Age of Onset of Mental Disorders

The vast majority of mental disorders have onset in childhood, adolescence, and young adulthood (**Figure 1**). About 50% of these disorders (as shown by the 50th percentile or median in **Table 1**) start by the age of 14 (**Table 1**) and 75% start by the age of 24, with later onsets for the most part ascribed to comorbid conditions (13). Moreover, more than 80% of those with mental disorders at the age of 26 had an earlier diagnosis of any mental disorder from the age of 11; in all, 74% had a diagnosis before accomplishing 18 years old and a half before the age of 15 (12). The median onset age tends to be earlier for anxiety disorders and impulse control disorders (11 years of age) in comparison with substance use disorders (20 years of age) and mood disorders (30 years, **Table 1**) (13). Correspondingly, 80% of lifetime attention deficit hyperactivity disorders start at the age of 4–11 years, whereas most of oppositional defiant disorders and conduct disorders start in the age range of 5–15 years (14). Half of all lifetime intermittent explosive disorders begin in childhood or adolescence. Similarly, the median age of the onset of depressive disorders typically lies in the early to mid-20s, although significant proportions of depressive cases have also been known to commence during adulthood and late adulthood (15). With respect to psychotic disorders, despite being relatively rare before the age of 14 (14), their risk peaks in the age group of 15–35 and declines after the age of 35 (16). Specifically, the abovementioned studies characterize the onset of a disorder as the start of characteristics that are part and contiguous to its first expression (12). Therefore, this figure is even more dramatic when attenuated, and mild symptoms characterizing clinical risk syndromes as opposed to established mental disorders are considered (see below). In fact, the age of onset of putative prodromal symptoms is generally even sooner than that of the onset of established mental disorders (17).

Developmental Pathophysiology of Mental Disorders

The model to have received the strongest empirical support for elucidating the pathophysiology of mental disorders implicates direct genetic and environmental effects alongside their interactions. For instance, as delineated in **Figure 2**, schizophrenia diagnosis corresponds to the first episode of psychosis. The diagnosis is usually made in young adults but can (although rarely) also happen in childhood, adolescence, or later in life. Generally, diagnosis of a first episode of psychosis is preceded by a clinical high-risk stage (17, 18) in which attenuated psychotic symptoms (19), functional impairment (20), and help-seeking behaviors (21), are evident. Schizophrenia, following the first episode, pursues a fluctuating course marked by the intensification of psychotic crises that are surrounded by negative psychotic symptoms, neurocognitive deficits, and alterations in social cognition. After their first episode, about 10–15% of patients recover, with a comparable extent showing an increasingly severe and unremitting form of the disorder. Beyond genetic inheritance, numerous environmental risk factors for the onset of psychosis have been implicated during the perinatal (first-wave) and adolescence (second-wave) period (16, 22). As portrayed in **Figure 2**, the majority of these risk factors exert their role before the age of

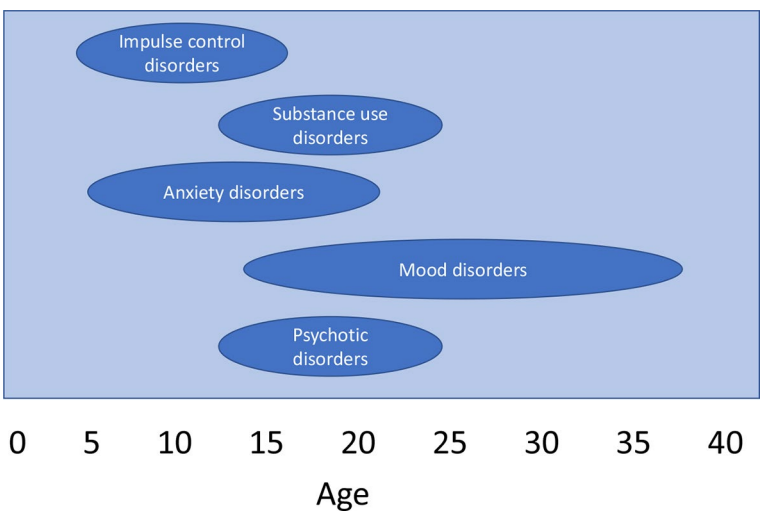

FIGURE 1 | Ranges of onset age for common psychiatric disorders. Data from the National Comorbidity Survey Replication study (13), a nationally representative epidemiological survey of mental disorders. The majority of those with a mental disorder have had the beginnings of the illness in childhood or adolescence. Some anxiety disorders such as phobias and separation anxiety and impulse-control disorders begin in childhood, while other anxiety disorders such as panic, generalized anxiety and post-traumatic stress disorder, substance disorders, and mood disorders begin later, with onsets rarely before early teens. Schizophrenia typically begins in late adolescence or the early 20s [adapted from Ref. (13)].

TABLE 1 | Ages at onset for five categories of mental health disorder [adapted from Ref. (12)].

		Age at which % of projected lifetime risk attained		
	Projected lifetime risk%	25%	50% (median)	75%
Anxiety disorders	32	6	11	21
Mood disorders	28	18	30	43
Impulse control disorder	25	7	11	15
Substance use disorders	16	18	20	27
Any disorder	51	7	14	24

25 years. Genetic and environmental factor impacts the epigenetic misprogramming of neurodevelopment (see below), amid this period. Importantly, some risk factors for psychosis, such as the perinatal risk factors, can impact the course of the disorder during the very early phases of the development. This lays the rationale for intervening at the time of birth (age 0) to impact the course of psychotic disorders. Finally, the model represented in **Figure 2** can be adapted to other mental disorders, some of which (e.g., autism spectrum disorders or attention deficit hyperactivity disorder) are intrinsically neurodevelopmental.

Neurobiological Changes During the Developmental Period

Neurobiological research shows that the human brain reflects this tides of risk factors and incident mental disorders during the developmental period of children and young people (12). Mental disorder pathophysiology is progressively understood to originate from abnormalities of maturational changes that regularly happen in the developing brain from the time of birth. Notably, these maturational changes are known to affect brain structure, brain activity, pruning and myelination processes, neural connectivity, and neurochemistry (23). Development of the neonatal brain from its ectodermal phase is a dramatic accomplishment of nature. Complex and predicated on different mechanisms, this period is particularly susceptible to neurodevelopmental disorders and

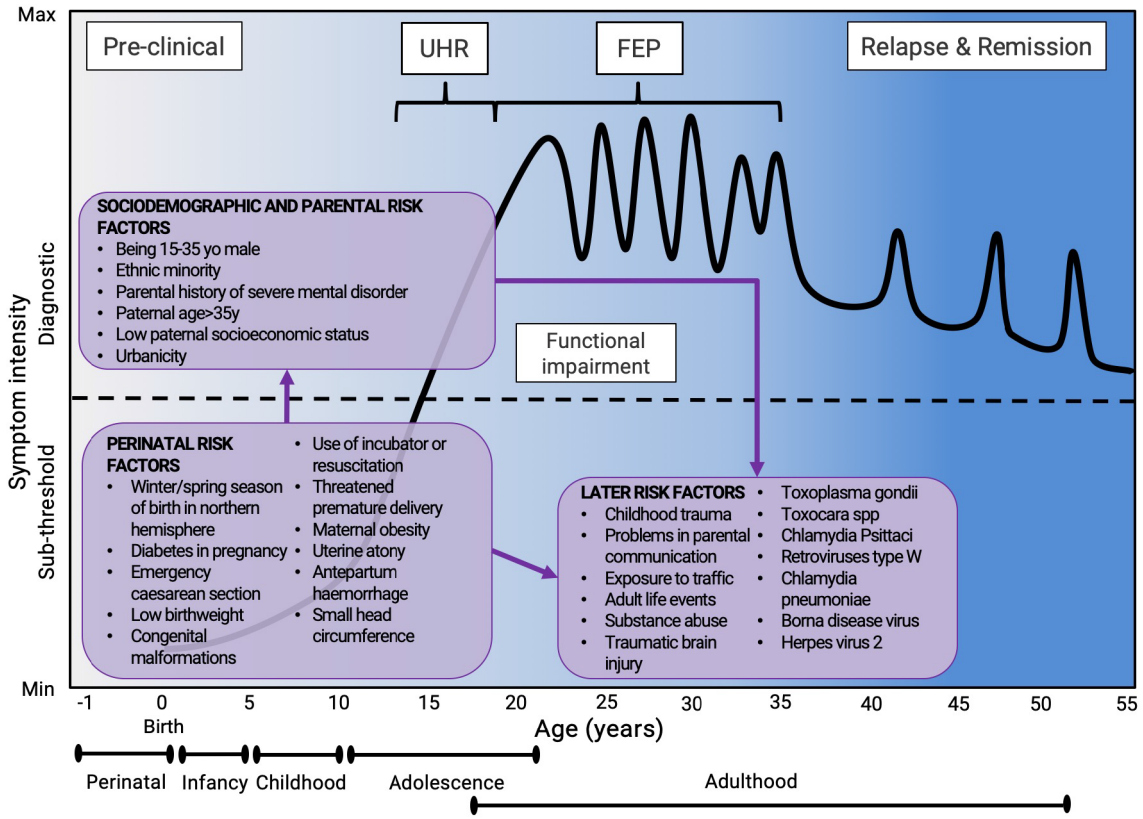

FIGURE 2 | Putative model of the onset and progression of psychosis in relation to non-purely genetic risk factors and developmental processes affected by the disorder. Sociodemographic and parental risk factors and perinatal risk factors have been implicated during the preclinical phase, usually observed from birth to infancy, childhood, and early adolescence. Additional later factors occurring during later adolescence and early adulthood can trigger the onset of attenuated psychotic symptoms, functional impairment, and help-seeking behavior, which constitute the CHR-P stage. The diagnosis of psychosis, which operationally corresponds to the first episode of psychosis, is usually made during the adolescence or early adulthood, with a peak from 15 to 35 years. Once diagnosed, psychosis usually follows a fluctuating course punctuated by acute exacerbation of psychotic crises superimposed upon a background of poorly controlled negative, neurocognitive, and social cognitive symptoms. The pink boxes represent the risk factors for psychosis (16). FEP, First Episode Psychosis; CHR-P, Clinical High Risk for Psychosis.

learning delays. The core processes that may be disrupted include the development of brain connectivity and programmed cell death, followed by fundamental cabling through myelination amid the first year (12). It takes as long as three decades to grow a mature human brain; much further development takes place during this period (12). In the meantime, there is a further phase of significant neurobiological and behavioral changes from mid-childhood through pubescence to mid-20s, especially in the connectivity balance between the brain areas (12). These maturational changes are normally useful, optimizing the brain for the challenges ahead but may at the same time increase the vulnerability to emerging mental disorders (23). Indeed, the risk of adult mental health disorders is the highest during this period. In addition, this maturation gap may also present a vulnerability window, which does not yet fully coordinate different brain mechanisms and systems (12).

The relationship between maturational changes and emerging psychopathology can be conceptualized as "moving parts get broken" (23), but this relationship is not a unitary concept; instead, it is specific to each type of mental disorder. For example, the course to and the progression of psychosis illustrated in **Figure 3** match the effects of risk factors for psychosis depicted in **Figure 2** and can be identified with three key stages in the "life" of the brain. In spite of being delineated consecutively, these three stages are interlinked, and there is no outright division. Also, each phase in psychosis is anomalous, with brain formation disruption and reorganization phases involved in causal pathophysiology. These two stages as well as brain maintenance encompass a range of mechanisms, which might be potentially targeted by preventive interventions. Similar neurodevelopmental models have been postulated for other mental disorders, including depression (24).

Overall, neurobiological research clearly indicates that the brain's developmental period represents the most important window of opportunities to impact the development of the brain and, as such, improve the outcomes of mental disorders. From the viewpoint of brain development, mental health services obviously require re-engineering to give a properly consistent and developmentally sensitive way to deal with children and young people during the two-decade venture from adolescence to adulthood (12).

The Course of Mental Disorders

It does not seem surprising that most adult mental disorders have a genesis in childhood, adolescence, or young adulthood, as developmental physiology and brain change occur during this period. We may then wonder what the longitudinal outcomes from these disorders are. Although certain incident disorders will resolve, it is obvious that many do persist, bringing lifelong disability and forcing substantial cost burden on society and the individual (12). The majority of mental health disorders associated with the personal burden that manifest at the age of 26 should be considered

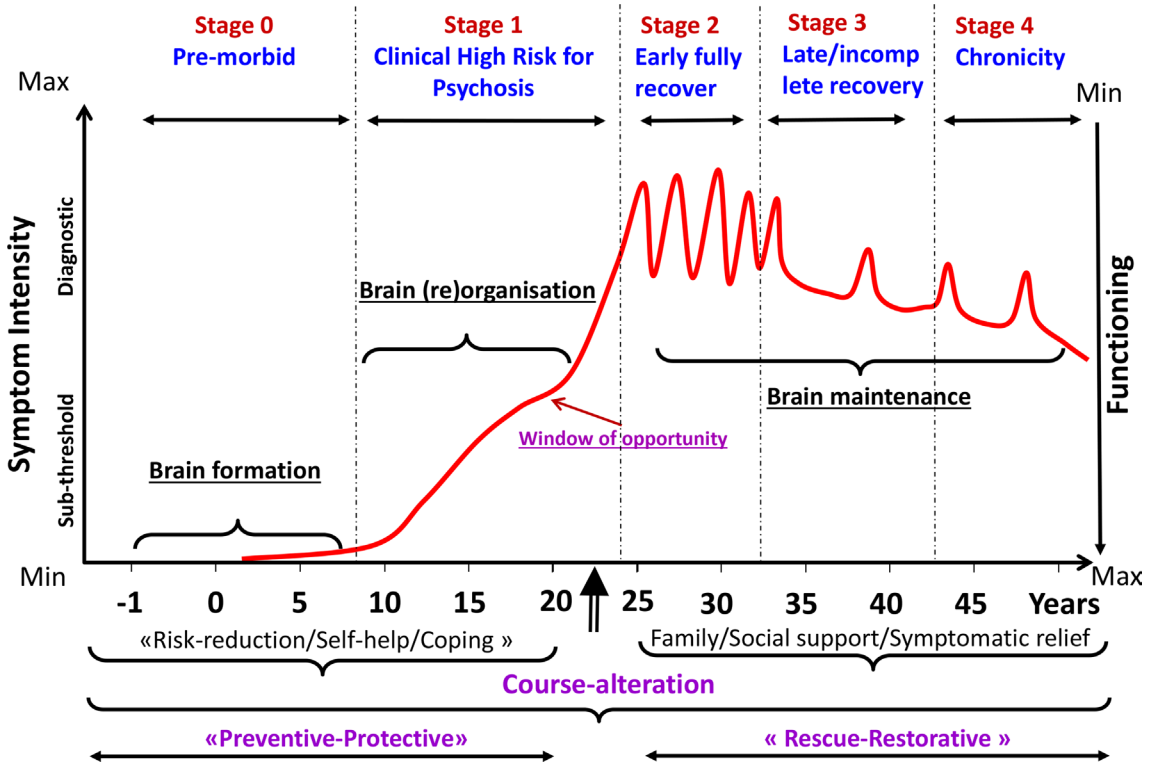

FIGURE 3 | Onset and progression of psychosis in relation to the developmental processes affected by the disorder [adapted from Ref. (25)]. During the premorbid and clinical high risk for psychosis neurodevelopmental phases, risk reduction strategies can exert the highest impact for course alteration. During the early fully recover/late incomplete recovery and chronicity phases, rescue and restorative strategies can have the highest impact on course alteration.

as extensions of adolescent disorders (16). Besides, in spite of the fact that the onset of the disorder at a very young age is commonly connected with a good response to treatment (12), these disorders accrue additional comorbidity once they persist into adulthood, especially if left untreated. Thus, their response to treatment becomes poorer in the later stages. For example, once psychotic disorders develop and become chronic, there are only limited treatment possibilities to improve their outcomes (26) (refer to the clinical staging model below). By and large, these discoveries recommend that it is fundamental to coordinate endeavors on early recognition and treatment targeting the developmental period that represents the most important window of opportunity to reduce the burdens and poor consequences of mental disorders. As illustrated in **Figure 3**, the most compelling "window of opportunity" to improve the outcomes of psychotic disorders is around the first episode of the disorder, to hinder it onset or stop early progression (25). According to these findings, the eradication of mental disorders presenting during the developmental period, through interventions aimed at prevention or early treatment in youths, would have a profound impact on reducing subsequent morbidity and chronicity (13).

Clinical Staging of Mental Disorders

Overall, the robust findings from modern epidemiology (prevalence and age of onset of mental disorders) and their compliance with the emerging pathophysiology, neurobiology, and course of the developmental period should represent a strong rationale for preventive and early intervention. Notably, the clinical staging model of mental disorders accommodates all these features to pragmatically facilitate preventive treatments and early interventions for youths. This clinical staging model was first proposed in psychiatry 25 years ago (in 1993) (27), before being subsequently adapted for psychotic disorders (28) (in 2006) to overcome the limitations of the standard ICD or DSM diagnostic systems. Clinical staging was put forward as a "simply more refined form of diagnosis" with two core fundamental assumptions: individuals experiencing an early phase of a disorder show a superior response to treatment and better prognosis, and the treatments offered during the early stages are more benign and effective (28). The main advantages of the clinical staging model are to accommodate the previously mentioned developmental findings, to facilitate preventive strategies to impede the progression to more advanced stages, or to facilitate the regression to an earlier stage and thus bolster better clinicopathological research (28).

For example, after about two decades of research into the clinical staging model in psychosis, its definition and impact have recently been reviewed (26). As summarized in **Figure 4**, stage 0 may allow primary selective prevention in asymptomatic subgroups. Meanwhile, stage 1 would allow primary selected prevention in patients who have an increased likelihood of developing psychosis

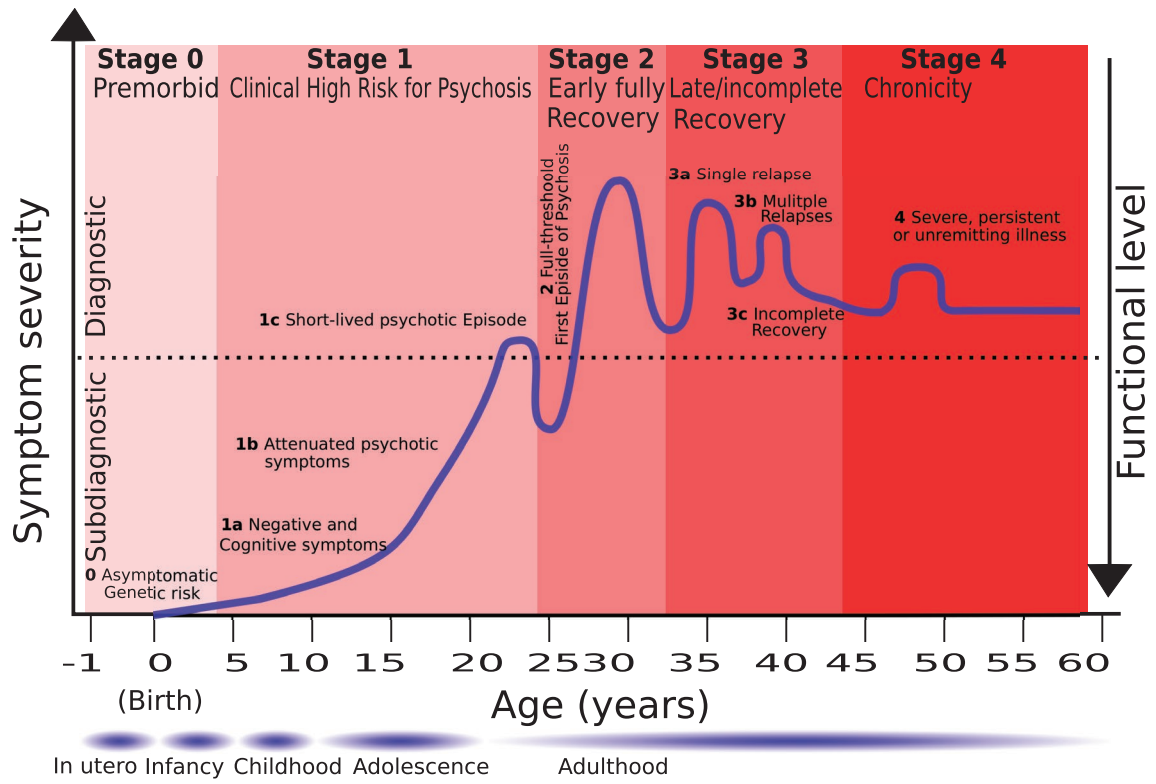

FIGURE 4 | Clinical staging of psychotic disorders. Unpublished figure courtesy of Paolo Fusar-Poli. The age bounds indicated are only descriptive. Stage 0 (premorbid) is followed by the clinical high-risk stage 1 for psychosis and then by stage 2 (early fully recover). Stage 3 describes a late/incomplete recovery and stage 4 is the chronic phase of psychotic disorders. Substages 1a–c and 3a–c are also indicated in the figure.

(i.e., those with negative and cognitive deficits: stage 1a; with attenuated psychotic symptoms: stage 1b; or with short-lived psychotic episodes: stage 1c) (26). At the time of the first episode of psychosis (stage 2), early intervention and secondary prevention strategies can minimize the duration of untreated psychosis, improve treatment response and adherence, reduce illicit substance abuse, and prevent relapses (26). Meanwhile, at the time of an incomplete recovery (stage 3, which includes single relapses: stage 3a; multiple relapses: stage 3b; and incomplete recovery: stage 3c), early intervention and tertiary prevention strategies can improve treatment resistance well-being and social skills, reduce the burden on the family, improve treatment outcomes of comorbid substance use, and prevent multiple relapses and disease progression (26). During the chronicity stage, i.e., stage 4, the key treatment focuses on maintenance treatment (26). Similar clinical staging models are also emerging for other mental disorders, such as bipolar disorders (29) or depressive disorders (30). Since clinical staging models for psychosis, bipolar disorders, or depressive disorders share some similarities, some authors have proposed an overall "transdiagnostic" clinical staging model that cuts across different diagnostic spectra (31, 32). However, the internal coherence of transdiagnostic approaches in psychiatry and their pragmatic advantages as compared to diagnostic-specific approaches to date have remained unclear [for a recent systematic review on transdiagnostic approaches in psychiatry, see Fusar-Poli et al. (33)].

In summation, the rationale for establishing mental health services for people aged 0–25 is premised on the following compelling pieces of evidence:

- The youngest age group has an increased risk of developing mental disorders;
- 75% of mental disorders begin by the age of 24;
- Putative prodromal features that precede mental disorders start even earlier;
- Most of the risk factors for mental disorders exert their role before the age of 25;
- Some risk factors exert their role during the perinatal period (age 0);
- Profound maturational brain changes occur from mid-childhood following puberty and finally mid-20s;
- Mental disorders can persist in adulthood with poor long-term outcomes;
- The most optimal window of opportunity to improve the outcomes of mental disorders is during the developmental period;
- Prevention or early treatment in individuals aged 0–25 may eradicate or at least improve the outcome of mental disorders during adulthood;
- The clinical staging model leverages the aforementioned points to allow early detection and intervention for young people with emerging mental disorders.

UNMET MENTAL HEALTH NEEDS IN CHILDREN AND ADOLESCENTS

This section will review to what extent current mental health services meet the scientific rationale detailed above in order to improve the mental health of individuals aged 0–25.

Barriers to Access

While 75% of psychiatric disorders, in general, develop before the age of 25, and the biggest burden of such disorders is on young people, the paradox is that they have the worst level of mental healthcare access throughout their entire lifespan (34). The gap between the prevalence of mental disorders in children and young people and treatment rates is therefore obvious, with only 25–35% of children and young people affected accessing treatment (6). Indeed, youngsters find it hard to access mental health services (8). The existing tier system for CAMHS is rigid and calls for children and young people to fit into the services, as opposed to services that respond to their needs (35). On the other hand, innovative healthcare options are needed in an increasingly modernized and digitalized world in order to promote and maintain engagement with children and young people, by involving them in service users groups, by transmitting practice news in social media, and by enlarging the utilization of digital healthcare innovation as a way to better connect with young people. A recent review demonstrated that the youngsters have uninformed and stigmatizing convictions about mental healthcare, mental health professionals, and access to care (36), which substantially curtail their abilities to look for help where they most need of it.

Delays to Initial Treatment

Analysis of service contact data from epidemiological studies investigations passes on a troubling story of disappointment, postponement, and lost opportunities (37, 38). The large majority of young individuals with lifelong mental disorders eventually reached mental health services, though more commonly for mood disorders than for anxiety, impulse controls, or substance use disorders (12). Treatment delay among those who in the long run made contact with mental healthcare ranged from 6 to 8 years for mood disorders (39). In this regard, a recent meta-analysis has identified a delay of 6 years between the onset of bipolar disorder and the initiation of a treatment (39). Delay to the initiation of treatment ranges from 9 to 23 years for anxiety disorders (12). Failure to establish initial contact with mental healthcare and delay in receiving treatment among those who finally made contact with services were associated either with early onset age or with sociodemographic characteristics such as being male, poorly educated, or black/minority ethnicity (12).

Poor Engagement With Mental Health Services

When youngsters gain access to mental health services, they experience consistent delays in receiving appropriate care. The situation is exacerbated by the fact that the retention rate for those who are eventually offered some treatment remains poor. According to a meta-analysis, a vast extent (up to 75%) of the treatments in children and young people leads to premature termination (dropout) (40). Both ethnic minority status and socioeconomic status have been established as risk factors for dropping out (41) and males are at particularly high risk of disengagement (42).

Barriers to Primary Care

General practitioners in primary care play a vital "gatekeeper" role to specialist mental healthcare for children and young people

(6, 43). Commonly, the average British kid consults their general practitioner at least once a year (6). Children and adolescents presenting to their general practitioners are twice as likely to develop a mental health problem (35). A survey made in 2016 across 302 general practitioners reported that 78% of general practitioners are seeing more children and adolescents with mental illness, and 61% are seeing more self-harming young people than they had 5 years ago (35). However, primary care professionals experience difficulties in both the recognition and management of mental health problems (6). For example, children and young people manifest symptoms of mental disorders differently from adults, may frequently present with physical symptoms, or may not be as forthcoming with their issues (6). Waiting times also tend to be longer, and 89% of general practitioners express concerns over exposing children and young people to risk while waiting for inputs from a specialist (35). These issues are additionally exacerbated by the fact that consultation time in primary care is ordinarily short. In the UK, for instance, patients talk to primary care practitioners about their mental health problems for just 9 min on average per consultation (6, 44). Primary care practitioners likewise face additional difficulties after having identified the presence of a psychological well-being issue. In fact, only a minority of children and young people are eventually able to access specialist mental health services (6, 45), typically those belonging to a majority ethnicity, with a higher parental perceived burden or greater symptom severity (6). Moreover, the individuals who do get referred onwards are frequently subject to significant delays in receiving specialist care, as observed above. A recent systematic review concluded that the paucity of specialist service providers for youths was the most highly endorsed barrier by primary care practitioners (6).

Falling Through the Cracks

Current mental health services have developed without the new clinical staging model knowledge that psychopathology and brain maturation sees no transition among adolescence and early adulthood (12). Therefore, access to mental health services has been driven by a historical paediatric–adult bifurcation in which CAMHS services are usually cut at the age of 18 (the transitional period) (34), when young people are the most liable to mental disorders and are at the greatest risk of decreased use of healthcare services (2). Indeed, only a minority of young people below the age of 18 can access these limited specialized services (34). Simultaneously, AMHS services are unable to take into account the needs of young people with emerging mental disorders (34). These services are developmentally inappropriate for young individuals since they center around older patients with more severe and persistent mental disorders and thus overlook the presence of less serious young adults (34). Young people with emerging mental illness or at-risk syndromes (discussed later) typically present with blurred and unspecific symptoms that do not fulfill the adult-type diagnostic criteria, which additionally limit their eligibility to receive AMHS care (46). Furthermore, an absence of clear linkage or pathway is often noted between CAMHS and AMHS. Inconsistencies in service provision and practice standards for continuity of care during the transitional period from CAMHS to AMHS also lead many youths to fall through cracks (47). The assumption that the transition from CAMHS to AMHS is easily possible for adolescents and their families—considering all of its concomitant complexities without embedded supports and coordination of care pathways—is misplaced (2). Research-based evidence from Australia, Canada, the UK, and the United States have confirmed that it is highly difficult to provide coordinated/integrated youth services during the transitional period (47). The transition is frequently portrayed by complexity because it associates with the peak of risk for the onset of mental disorders that requires a variety of community and vocational packages of care to meet the multifaceted needs of youths (47). For many governments and institutions all over the world, continuity of care for youths transitioning between CAMHS and AMHS who require mental healthcare has been identified as a top priority. These transitional health services are innately complex, and their organization and function can vary according to geographic, administration, types of delivery, financing, and service type. Within this complexity, an important element is the subjective experience of youths during the transitional period. Young people experience a deep emotional culture shift when transitioning from CAMHS to AMHS. Similarly, their carers may feel invisible and often in distress, with several of them reporting mental health problems arising from their experience of caring (9). At the same time, young people and their carers express important subjective views to direct the development and design of youth-friendly mental health services. Therefore, it seems imperative to incorporate the perspectives of young individuals into transitional service improvement (48). A final problem is the current division of training, which leads to different and often contrasting diagnostic and treatment approaches for CAMHS vs. AMHS clinicians, which may additionally enhance the cultural and pragmatic divide among the specialities and promote a silo approach to care (49). Collectively, the above system weaknesses create a barrier to children and young people receiving mental healthcare, resulting in missed opportunities for timely intervention.

To summarize, children and young people are currently encountering substantial unmet needs due to the following reasons:

- Barriers to access;
- Delays in receiving appropriate treatments;
- Poor engagement with mental health services;
- Up to 75% treatments leading to premature termination;
- Limitations to the gatekeeper role of primary care;
- Cracks between CAMHS and AMHS;
- Poor involvement in the design of mental health services;
- Lack of incorporation of scientific evidence into clinical care (clinical staging and early intervention during the developmental period).

EVIDENCE FOR MENTAL HEALTH SERVICES FOR PEOPLE AGED 0–25

This section will review different models of care and configurations of mental health services along with their impact on the unmet needs of those aged 0–25. More specifically, we pragmatically

define a "model of care" as an integrated youth-specific, stigma-free early intervention service that is developmentally appropriate (34). This endeavor aims to improve access to services and patient outcomes over the years most at risk for emerging mental illness, thereby obviating the need for a transition from CAMHS to AMHS services during this critical phase (34). This ideally implies the establishment of a youth mental health healthcare model that encompasses and interacts it, but is particular from healthcare systems for children and young people.

HIGH-ORDER PRINCIPLES GOVERNING THE DEVELOPMENT OF YOUTH-FRIENDLY HEALTH SERVICES

High-order principles have been published for the development of youth-friendly health services. These include the following: addressing inequities (including sex disparities) facilitating the regard, insurance, and satisfaction of human rights, as stipulated in internationally agreed human rights agreements such as the Millennium Development Goals and the UN Convention on the Rights of the Child (which likewise underpins the more explicit attributes of youth-friendly services, for example, youth participation and confidentiality). The characteristics of youth-friendly healthcare services have been fully described in the context of the WHO's guiding program development (**Box 1**).

Six groups of youth-friendly health services can be delineated. The first type is the health service that is specialized in children and adolescent care in a hospital setting. The second type is a similar specialized service but located in the community. The third type is school- or college-based and stakeholders connected with schools or universities. The fourth type is a community-based center that not only provides health services but also provides other services such as educational support. The fifth type of health services includes pharmacies and shops that sell health products but do not provide health services. The sixth type is based on outreach information on the provision of services. The point of contact for this type of service is in spots where children and young people assemble—work or in schools (3).

A large portion of these principles and configurations have been used and adapted so as to guide the advancement of youth-friendly mental health services.

Perinatal Mental Health Services

Perinatal mental health services have evolved over time. Initially, they were bound to a close interest in severe forms of postpartum psychosis (50), to encompass, during the most recent years, non-psychotic mental disorders (51), the broader mental health of women, and the neurodevelopmental course of the fetus and infant (52). For example, the identification and management of women affected with postnatal depression became an important public health target, with screening programs being developed in several countries (53). Usually, perinatal mental health services offer care from the time of conception until the end of the first postpartum year (54). The origin of perinatal psychiatry, as a medical speciality (1980), can be associated with the development of the first psychiatric units that allowed the joint admission of mothers and babies (mother and baby units) (54). These units have clear benefits because they maintain mothers and their babies in near proximity, thus alleviating the family burden and ameliorating maternal competence. These benefits, in turn, would support the development of the newborns (54). An associated relevant clinical issue has been the

BOX 1 | WHO framework for development of youth-friendly health services [from Ref. (3)].

An equitable point of delivery is one in which:

- Policies and procedures are in place that do not restrict the provision of health services on any terms and that address issues that might hinder the equitable provision and experience of care
- Healthcare providers and support staff treat all their patients with equal care and respect, regardless of status

An accessible point of delivery is one in which:

- Policies and procedures are in place that ensure health services are either free or affordable to all young people
- Point of delivery has convenient working hours and convenient location
- Young people are well informed about the range of health services available and how to obtain them
- Community members understand the benefits that young people will gain by obtaining health services, and support their provision
- Outreach workers, selected community members and young people themselves are involved in reaching out with health services to young people in the community

An acceptable point of delivery is one in which:

- Policies and procedures are in place that guarantee client confidentiality
- Healthcare providers
  - provide adequate information and support to enable each young person to make free and informed choices that are relevant to his or her individual needs
  - are motivated to work with young people
  - are non-judgmental, considerate, and easy to relate to
  - are able to devote adequate time to their patients
  - act in the best interests of their patients
- Support staff are motivated to work with young people and are non-judgmental, considerate, and easy to relate to the point of delivery:
  - ensures privacy (including discrete entrance)
  - ensures consultations occur in a short waiting time, with or without an appointment, and (where necessary) swift referral
  - lacks stigma
  - has an appealing and clean environment
  - has an environment that ensures physical safety
  - provides information with a variety of methods
- Young people are actively involved in the assessment and provision of health services

The appropriateness of health services for young people is best achieved if:

- The health services needed to fulfil the needs of all young people are provided either at the point of delivery or through referral linkages
- Healthcare providers deal adequately with presenting issue yet strive to go beyond it, to address other issues that affect health and development of adolescent patients

The effectiveness of health services for young people is best achieved if:

- Healthcare providers have required competencies
- Health service provision is guided by technically sound protocols and guidelines
- Points of service delivery have necessary equipment, supplies, and basic services to deliver health services

safety of prescribing antipsychotics, mood stabilizers (55), and other psychotropic molecules during pregnancy and for nursing mothers. Recognizing the advancements in perinatal psychiatry, some countries such as the UK and Switzerland have developed perinatal mental disorders, in order to improve mental health services for perinatal women and ensure adequate treatment (56). However, to date, perinatal mental health services have not been fully integrated into preventive approaches for the developmental period.

Primary Indicated Prevention of Psychosis in Those at Clinical High Risk

The building blocks for reforming youth mental services began with the management of young people who experienced early stages of psychosis (26). This model of care has been unequivocally successful in the UK as well as worldwide. It entails the primary indicated prevention of psychotic disorders in people at clinical high risk for psychosis—such as those meeting the At Risk Mental State criteria (57)—and early treatment of individuals presenting with a first episode of psychosis (26). Individuals who are at clinical high risk for psychosis are detected and evaluated with established psychometric tools that have been validated in the 8–40 age group, although the most frequent age range for this population, at least in the UK, is 14 to 35 (17). Subjects at clinical high risk for psychosis display subtle features and overall functional impairment (20). These problems impel them to seek help at specialized clinics (58). One of the largest and oldest of these clinics is the Outreach and Support in South-London (OASIS) clinic, at the Maudsley NHS Foundation Trust (58). **Box 2** illustrates the clinical care provided at the OASIS, which crucially involves the development of extensive collaborations between AMHS and CAMHS. Individuals at clinical high risk for psychosis are 20% likely to develop emerging psychotic disorders (but not other non-psychotic disorders (59, 60)) over a relatively short period of 2 years (61). While primary indicated prevention in people at high clinical risk can alter the course of psychosis and reduce the duration of untreated psychosis, secondary prevention in those people can ameliorate the severity of the first psychosis episode (26, 62). Furthermore, tertiary prevention of relapses or other adverse clinical outcomes/behaviors in patients experiencing a first episode of psychosis can improve their long-term outcomes (63–65).

The impact of primary indicated prevention in patients between 14 and 35 of age who are at clinical high risk for psychosis has been so relevant that NHS England implemented a new Access and Waiting Times-Standard for Early Intervention in psychosis (AWT EI Standard) in April 2016 to extend the prevention of psychosis across England. The Standard mandates an evidence-based nationwide detection and rapid treatment of patients at clinical high risk for psychosis aged 14–35. Therefore, the NHS requires all suspected patients presenting to early intervention services in England to be assessed and interviewed for a potential state of clinical high risk for psychosis (66). Early intervention services have grown to about 150 serving about 1000 people per month in England, and they are far more developed as compared to the rest of Europe. Early intervention services for people experiencing a first episode of the disorder are universal in England and are also available in other parts of the UK. While there are some stand-alone clinical high-risk services in the major cities, assessment and treatment of clinical high risk patients are

BOX 2 | Case study from the Outreach and Support in South-London (OASIS) service, which takes care of young individuals aged 14 to 35 who may be at risk of developing psychotic disorders. The clinical case is taken from Ref. (46).

Presentation

A 16-year-old boy was referred from the general practitioner to the local CAMHS owing to a drop in functioning and social withdrawal during the previous 6 months. The CAMHS then referred the patient to the OASIS, which managed to assess him within 5 working days. The patient began college 6 months prior but had found the workload difficult and failed his examinations. He had no family history of mental disorders, denied any current or past use of drugs, and reported no significant medical history. At the time of the OASIS assessment, he was well kempt, was quiet during his interview, and provided short answers. He reported that he no longer enjoyed his former interests and could not relate to people at college or to friends, but there were no clear signs of depressive disorders. No formal thought disorders were elicited. He was 80% convinced that random people looked and talked about him when he was out in public, but was able to question it. He stated that these people were probably commenting on the way he looked, but he did not believe these individuals meant him harm. He never acted on these thoughts. He also reported a vague feeling of perplexity and derealization. These experiences began when he started college and continued to occur every day for up to an hour at a time, causing significant distress. The Structured Clinical Interview for *DSM* did not reveal any mental disorder and, as such he would not be eligible to receive the care of local mental health services.

Diagnostic and prognostic formulation

Diagnostic designation: clinical high risk for psychosis (CHR), attenuated psychotic symptoms subgroup, determined using the Comprehensive Assessment of At-risk Mental States (CAARMS). Prognosis: the increased risk of developing psychosis is 26% at 3 years (95% CI, 23%–30%).

Clinical care

First, the OASIS shared with the CAMHS the result of the prognostic test. Over the past two decades, the OASIS has developed specific co-working agreements with the local CAMHS to optimize the care of children and young adults during their transitional period. These co-working agreements are particularly useful in avoiding crisis-driven connection between CAMHS and AMHS at points of heightened illness severity such as the transition from a CHR state to full-blown psychosis. At the same time, the result of the prognostic assessment was shared with the patient in the context of psychoeducational support offered by the OASIS. Informing patients about their risks is an essential component of preventive approaches in all branches of medicine. For example, individuals who meet CHR criteria accumulate several risk factors for psychosis, some of which may be potentially modifiable. The second clinical action of the OASIS was to recommend close clinical monitoring for adverse clinical outcomes during the ensuing 3 years, because this is the peak of risk. Finally, the patient was offered specific preventive interventions (indicated primary prevention) that were based on psychological therapies (cognitive behavioral therapy) and that are routinely provided by the OASIS, in line with the NICE recommendations. These treatments aim to improve the presenting symptoms and disability and to stop the progression to psychosis.

Outcome

When the patient turned 18, the OASIS took full clinical responsibility of him continuing the clinical monitoring and preventive interventions. At 3-year follow-up, the patient had not developed psychosis. He fully recovered from his initial problems, completed his college examinations, and was able to enjoy his social life. He expressed high satisfaction with the quality of care received by the OASIS.

confined to the remit of first episode services in the absence of a dedicated clinical high-risk team. The major cities in England will witness clinical high risk and first episode of psychosis services. Furthermore, several academic sites with diverse and complementary skills are conducting extensive research on clinical high-risk patients in the UK. For example, a new National Institute of Health Research-Mental Health Translational Research Centre (NIHR-MH TRC) has recently been established to facilitate clinical research in the UK. The NIHR-MH TRC includes a specific workstream on early psychosis, which will facilitate the early detection and intervention in individuals aged 15–35 who may be at risk of psychosis or experiencing a first episode of psychosis. Therefore, the UK has unparalleled central resources for early detection and treatment of individuals who are experiencing emerging serious mental disorders throughout the developmental period. This could serve as an ideal platform to further refine the development of youth mental health services for those aged 0 to 25. For example, the UK early intervention for psychosis platform could be broadened to incorporate early detection and intervention approaches for depression in young people aged 12–25 years old (67). In fact, when early interventions for depression are restricted exclusively to children and adolescents, they will miss much of the early symptoms of depression because the age of onset of this disorder—as reviewed above—overlaps with young adulthood (67). The upper limits of age eligibility, therefore, curtail continuous care. In addition to lessening the effect of depression, the provision of indicated primary prevention for depression is also known to ameliorate access to care (67). The UK early intervention for psychosis platform could additionally include early intervention in bipolar disorder, which is gaining momentum (68). New psychometric instruments have been developed in order to identify young people aged 14–35 who may be at risk of developing bipolar disorders (69) and preventive treatments are under development.

One-Stop Early Intervention Services: Headspace

Some integrated models of care have already leveraged the early psychosis field to broaden their horizons and target the wide mental health of children and young adults. The early intervention model of psychosis was broadened to include further diagnoses (e.g., mood disorders, eating, substance use, and personality disorders), following a campaign led by leaders in the mental health field in 2006. This was accomplished through the formation of Headspace in Australia (https://headspace.org.au) (34). Headspace is a governmental program providing stigma-free early intervention services configured in a "one-stop shop" location for people 12–25 years old with emerging mental disorders (34). The Headspace model of care is multidisciplinary, integrated, and delivered in a single setting that constitutes a soft entry point to mental healthcare. The Headspace model is centered on the needs of young people along with their families (70). Building up the Headspace program required the formation of a new mental health service to envelop four key domains: mental health, physical health, drug and alcohol interventions, and educational support (34). As mentioned above, young people's engagement is a central part of this healthcare model and helps to create a non-stigmatizing environment. This is achieved by ensuring the provision of Headspace services in an accessible setting, non-judgemental and young people-friendly (34). **Figure 5** summarizes the essential clinical components of Headspace. The success of Headspace is evidenced by the fact that it has grown from 10 centers to over 110 in 2018 (34). These centers are accessed by about 100,000 youngsters every year, and an extra 30,000 youngsters are accessing its online service platform through eheadspace (34). In the recent assessment, the authors have reported that a range of young people with high levels of psychological distress was able to access Headspace (34). Importantly, these young individuals included vulnerable groups (34). Headspace was likewise observed to be effective in diminishing suicidal ideation and self-harm, as well as in reducing the quantity of missing school or work days (34).

Other Youth Mental Health Services

The young mental health reform started in Australia has permeated to different zones of the world, including the UK, Ireland, Canada, USA, Europe, and Asia embracing unique, culturally sensitive models (70, 72). Some examples are given below and a systematic list of integrated services for young people (aged 10–30 years) along with their characteristics (year of setup, number of services, age range, targeted issues, position in care system, and number of young people accessing the service) is depicted in **Table 2**.

Ireland

The reform of youth mental health in Ireland led to the Jigsaw care model in 10 communities (https://www.jigsaw.ie). This model was derived from Headspace and similarly focuses on young people aged 12–25. Initial evidence has shown that it is an accessible and effective mental health service in the community.

UK

In the UK, the creation of the "Youthspace" in Birmingham, a youth-based mental health service (http://www.youthspace.me), resulted in the commissioning of an integrated care pathway: Forward Thinking Birmingham (https://www.forwardthinkingbirmingham.org.uk). This children and young people mental health partnership offers integrated working, prioritizing both individual choice and access through drop-in clinics. Forward Thinking Birmingham is different from other models in that it targets those in the age group of 0–25. Furthermore, it is also focused on promulgating good mental health, resilience, and emotional well-being through the provision of information, training, and consultation. This will be achieved through the voluntary community sector, family support, and providing information in a wide range of media in order to reach the population of Birmingham. However, no published evidence exists as of now on the impact of this model of care.

Other approaches in the UK have attempted to ameliorate the quality of mental health services for young people in primary care or in CAMHS.

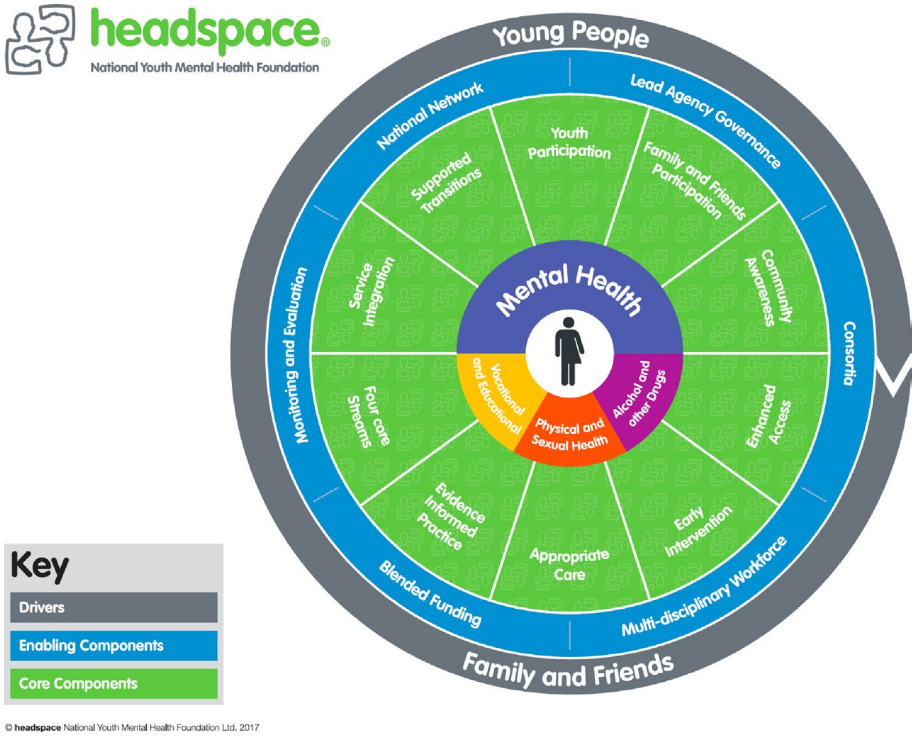

FIGURE 5 | The needs of young people and their families are the main drivers of the Headspace integrated mental health model for children and young adults. Headspace has 10 service components (youth participation, family and friends participation, community awareness, enhanced access, early intervention, appropriate care, evidence informed practice, four core streams, service integration, and supported transitions) and six enabling components (national network, lead agency governance, consortia, multidisciplinary workforce, blended funding, and monitoring and evaluation). Through implementation of these core components, Headspace aims to provide easy access to one-stop, youth-friendly mental health, physical and sexual health, alcohol and other drug, and vocational services for young people across Australia [from Ref. (71)].

The Well Center Model (www.thewellcentre.org) is a multi-disciplinary model for young workers, counsellors, and general practitioners. In order to provide holistic care that is family oriented, evidence-based, and culturally sensitive, primary care requires an incorporated, integrated and collaborative approach between general practitioner surgeries, secondary care, schools, third-sector organizations, justice systems, and social services.

The THRIVE model (http://www.implementingthrive.org/about-us/the-thrive-framework/) was created by a joint effort of the Anna Freud National Centre for Children and Families and the Tavistock and Portman NHS Foundation Trust. This model is an integrated, personalized, and need-driven approach to providing children, young people, and their families with mental health services. The focus is set on the prevention of mental disorders and the promotion of psychological well-being. Through a system of shared decision-making, children, young people, and their families can be empowered *via* active involvement in decisions about their care (73). Initial evidence proposes that the THRIVE approach can improve the mental health of children and young people.

Canada

Canada has joined the global youth mental health service movement with consolidated efforts from the Mental Health Commission of Canada, including various regional services interventions (e.g., YouthCan Impact in Ontario; Foundry in British Columbia). The special investment was recently made in the fields of service transformation research and evaluation, as shown in the ACCESS project for persons aged 12–25 (www.accessopenminds.ca) (74). Interestingly, the ACCESS project supports the view that any single model of service transformation for children and young people is not implementable over the geographic, political, and cultural diversity of this nation. Hence, the best way to overcome such obstacles is to steer test variations of a model of transformation customized to contextual scenarios before scaling it up or implementing a type of service that has been developed and imported from another country (74). The ACCESS approach encompasses different domains: promotion, prevention, intervention, and research and evaluation. ACCESS differs from Headspace since it doesn't propose the creation of a new system of care for young people. Rather, it proposes the radical creation of a transformed youth mental healthcare system that is embedded in the existing care system. The fundamental standards of this transformation should be introduced on reducing to the lacunae that are impeding access to timely and adequate care for young people (12–25 years of age) who are presenting with the whole range of mental health problems, as discussed above (74).

TABLE 2 | Evaluation studies on mental health programs for young people (aged 10–30 years) that include a mental health function and are integrated—in that they bring together or provide a range of physical health, mental health, and social service foci. Adapted from Ref. (71).

Your mental health services	Country	Number of services	Established	Age range	Target issues	Position in care system	People accessing the service
Jigsaw	Ireland	10	2008	12–25	Mental health	Primary care	8,000
Headspace	Australia	110	2006	12–25	Mental and physical health	Primary and secondary care	80,000
Maisons des Adolescents	France	104	2004	11–25	Mental and physical health	Primary and secondary care	310,000
Youth One Stop Shops	New Zealand	11	1994	10–25	Mental and physical health	Primary care	34,000
Foundry	Canada	11	2015	12–24	Mental and physical health	Primary and secondary care	912
Youth One Stop Shops	Ireland	4	2009	11–25	Mental and physical health	Primary care	NA
ACCESS Open Minds	Canada	Underway					
Integrated Collaborative Care Team	Canada	Underway					
Your Choice	New Zealand	1	2008	10–24	Mental health	Primary care	976
Community Health Assessment Team	Singapore	1	2009	16–30	Mental health	Between primary and secondary care	601
The Well Centre	UK	1	2011	13–20	Mental and physical health	Primary care	934
Youthspace	UK	1	2011	16–25	Mental health	Unclear	NA
The Junction	UK	1	2003	11–18	Mental health	Secondary care	494
Supporting Positive Opportunities with Teens	US	1	2008	13–24	Mental and physical health	Primary care	1,729
Adolescent Health Service	Israel	NA	1993	12–18	Mental and physical health	Primary care	838
Rural Clinic for Young People	Australia	1	2010	12–18	Mental and physical health	Primary care	4,350
KYDS Youth Development Service	Australia	1	2005	12–18	Mental health	Unclear	1,600
Youth Stop	Australia	1	2010	12–25	Mental health	Unclear	20

Outcomes

In a recent systematic review, 43 evaluation reports examine at least one aspect of the outcome of interest for integrated mental health services for children and young people:

- Access: most integrated services report attracting youngsters in the mid-older adolescent age range and traditionally underserved populations, including minorities. Levels of distress of young people accessing the services are defined and described variably across these evaluation reports. Presenting problems are commonly identified with mental health and psychosocial difficulties and less likely with physical health, educational, and vocational issues. Individual counselling is the most commonly described intervention following access to these services (75).
- Symptomatic and functional outcomes; clinical outcomes are reported for 7 out of 43 reports only (75) and mostly in pre–post study designs. In the Your Choice service study (**Table 2**), young people experienced critical decreases in symptoms and substance use as well as amelioration in functioning (75). In the Youth One Stop Shop service (**Table 2**), 58% of young people who presented with some difficulties experienced improvements in the short term. According to an evaluation of the Jigsaw service (**Table 2**), 62% of 17- to 25-year-olds displayed an improvement in their level of well-being and functioning. A study by Youthspace (**Table 2**) found that 58% of young people experienced an improvement in mental health and well-being. Comparative studies, such as the most recent evaluation of Headspace, found some promising results. For instance, over 20% of young people encountered a clinically significant or reliable decrease in trouble that was greater than a compared external group of young people who had not received any treatment (75). However, the effect size was observed to be quite small ($d = -0.11$) (75). The results are overwhelmingly positive when a survey design is used in the evaluation.
- Satisfaction, acceptability, and appropriateness (75). Whenever estimated, elevated levels of service users' satisfaction are commonly revealed. A common finding is that young people find (and value) that these services are accessible, acceptable, and appropriate:
  - Having a convenient location (access to easy transport was noted as being valuable);
  - Being youth-friendly (staff and environment) and welcoming;
  - Being staffed by youngsters;
  - Having timely appointments;
  - Being affordable;
  - Maintaining confidentiality and privacy;

- Having many incorporated services accessible in one spot, with non-mental-health-related signage;
- Delivering sheltered and appropriate interventions inside a positive and resilient- based framework (72).

To summarize, the evidence for mental health services for people aged 0 to 25 indicates that:

- High-order (WHO) standards overseeing the development of youth-friendly health services are available;
- The building blocks for reforming youth mental services began with the early intervention for psychosis in adolescents and young adults;
- The UK has unparalleled central resources for early detection and treatment of individuals aged 14–35 who are experiencing emerging serious mental disorders;
- Early interventions in bipolar, depressive, and other mental disorders may be feasible;
- The youth mental health reform started in Australia has penetrated to different territories of the world, including the UK, Ireland, Canada, USA, Europe, and Asia;
- There are different models of care spanning the establishment of a new system of care (Headspace) or the transformation of the care system (ACCESS);
- One-stop youth-friendly mental health services can improve access, symptomatic, and functional outcomes and satisfaction of the service users;
- The integration of physical and mental health in youths can have synergic benefits;
- Integrated mental health services mostly focused on adolescents and young adults (12–25).

CHALLENGES

Although there has been converging evidence that children and young people need integrated mental health services during the developmental period, there are still some challenges. First, in spite of significant efforts to develop holistic services and programs for youth-to-adult transitions, and also following nearly two decades of youth mental health research, there remains an absence of standards and models of care guiding research, service planning, and delivery for children and adolescents progressing from CAMHS to AMHS (47). No single example or model that can be considered to establish the best practice is provided (72). Second, the evidence of the effectiveness of integrated mental health models of care for children and young people remains modest. The types of evaluations described in the Outcome section vary in quality, but they are overall classified as Level IV evidence only, according to National Health and Medical Council levels of evidence (75): "evidence obtained from case series, either post-test or pre-test and post-test." No high-quality pragmatic randomized controlled trial has yet been published in the international scientific databases (76), not even for the most established models of care. However, some trials are underway, which demonstrates that it is feasible to run these types of studies in this field (75). Third, cost-effectiveness studies are similarly lacking. This may be particularly concerning given the fact that the reference model, Headspace, required substantive financial funding by the Australian government in order to establish brand new youth mental health services across the country. Besides, 40% of Headspace patients are excessively complicated or too unwell to profit by the program. Thusly, more specialized and intensive healthcare components should now be financed, gathered, and integrated horizontally with Headspace and other important pieces of the health and social system vertically (34). This would further increase the costs for upkeeping Headspace-like models of care. Until recently, there has been very little cross-national focus on how mental health services for children and youth are organized and financed (77). In the current financial climate and growing demand for mental health services among young individuals, it is important to understand international best practices that can improve service accessibility and reduce financial and organizational barriers to availing services at the patient level (77). In this scenario, the Canadian approach (ACCESS) focusing on transforming mental health, as opposed to creating brand new services, may be more feasible. This could be further facilitated by the existing national early detection and intervention services for psychosis within the UK. Notably, this platform is already demonstrating scalable impact for taking care (across CAMHS and AMHS) of both children and young adults aged 14 to 35. Fourth, an extra challenge is that suitable clinical and treatment response to the earliest signs of disorders in young people is yet to be completely clear. This lack of knowledge is problematic because the risk-to-benefit ratio of specialist early care is totally different in the wider subclinical, primary and secondary care population from that in the youth mental health services wherein these interventions have been developed. Treatment challenges have also been observed for the most established early intervention field for psychotic disorders (78). Fifth, the challenges mentioned above are even more pronounced for people below the age of 12, including those of perinatal, infancy, and early childhood age. In fact, the existing evidence for developing integrated mental health services for CAMHS and AMHS nearly focuses entirely on people between 12 and 25 years of age, with very few special exceptions that still require demonstration of feasibility and impact.

To summarize, the main challenges for mental health services for people aged 0–25 are:

- There are no standards and no single example can be considered to constitute best practice;
- The evidence of the effectiveness on mental health outcomes is modest; there are no RCTs;
- Cost-effectiveness studies are similarly lacking;
- Appropriate clinical and treatment response yet to be entirely clear;
- Very little evidence for individuals aged 0–12.

CONCLUSION

The focus of many emerging international health agendas is on the mental health of young people (2). An important strategy to enhance global health outcomes is to invest in identifying and addressing the mental health needs of vulnerable children and young people (79). There is a growing consensus that children and young people need youth-friendly mental health services that are sensitive to their unique stage of clinical, neurobiological,

and psychosocial development. Evidence has confirmed that the transitional phase from adolescence into young adulthood (12–25) represents a core window of opportunity for improving the outcomes of mental disorders. Conversely, there is only limited evidence that detection and intervention in the lower age (0–12) range is feasible and effective. The current configuration of mental health services split between CAMHS and AMHS is highly inefficient since it does not reflect state-of-the-art scientific evidence and produces barriers to access and treatment, and poor retention rates that impede early intervention approaches for those in need.

While different possible youth-friendly mental health models can be considered, there is a growing consensus that the focus should be kept on early detection and intervention models within the community that target both adolescent and young adults. The most successful early intervention paradigm that fully integrates adolescents and adult mental health services alike is the prevention and early treatment of psychosis. Over the past decade, the UK has implemented nationwide first-in-class early intervention services for psychosis. Therefore, it may be possible to leverage these UK early intervention templates in order to refine the next generation of youth-friendly mental health services that target the needs of adolescents and young people experiencing early stages of other mental disorders (e.g., depression, bipolar).

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The author designed the study, obtained financial support, and conducted the literature review, data extraction, and the interpretation of the findings.

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Distinct Differences in Emotional Recognition According to Severity of Psychotic Symptoms in Early-Stage Schizophrenia

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Patients with schizophrenia are characterized by deficits in their ability to identify facial expressions of emotion, which are associated with impaired social and occupational function. An understanding of the deficits of facial affect recognition (FAR) early in the course of the illness can improve early intervention efforts to ameliorate potential functional deterioration. This study aimed to investigate the characteristics and correlations between psychotic symptoms and FAR deficits in patients with early-stage schizophrenia using data from the Korean Early Psychosis Cohort Study. Patients with schizophrenia were divided into three groups: 1) severely and markedly ill (n = 112), 2) moderately ill (n = 96), and 3) mildly ill (n = 115). These groups were compared with age- and sex-matched healthy controls. The FAR test was developed using Korean emotional faces from the Korean Facial Expressions of Emotion database. Error rates, correct response times, and nonresponse rates of each subset were calculated. Several psychopathology assessments were also performed. There were significantly more deficits associated with the recognition of anger ($p < 0.01$), fear ($p < 0.01$), and contempt ($p < 0.01$) in the three patient groups than in the healthy control group. In the severely and markedly ill states, all emotions apart from surprise had impaired error rates ($p < 0.01$ for all analyses). The error rates for happiness, sadness, disgust, surprise, and neutral faces were not significantly different between mildly ill patients and healthy controls. All emotions, except for sadness, had significantly more delayed correct response times in all patient groups than in the healthy controls ($p < 0.01$ for all analyses). The severity of psychotic symptoms was positively correlated with the happiness and neutral error rates, and depression was

positively correlated with the happiness error rates. General social function was negatively correlated with the error rates for happiness, sadness, fear, disgust, and surprise. Overall, our results show that the severity of psychosis and clinical symptoms leads to distinct differences in certain emotions of patients with early-stage schizophrenia. It is considered that these specific emotional characteristics will help deepen our understanding of schizophrenia and contribute to early intervention and recovery of social function in patients with schizophrenia.

Keywords: schizophrenia, early stage, facial affect recognition, psychotic symptom, severity

INTRODUCTION

Schizophrenia is a chronic disorder that leads to disability in a number of clinical aspects, such as social functioning (1, 2). These disabilities are essential features and key diagnostic criteria of schizophrenia. Facial affect recognition (FAR) is a complex function involving the cortical and limbic systems and provides an indispensable source of information during face-to-face communication (3). Thus, a crucial component of successful personal interactions is to rapidly perceive facial expressions and correctly infer the internal states they convey. Facial expression misinterpretation in patients with schizophrenia generates a feeling of confusion, which triggers communication failure (4) and leads to more problems in interpersonal skills, work performance, social functioning, and independent living (5–7).

FAR has consistently been shown to be impaired in patients with schizophrenia. The impairment is present during the first episode (8), in patients with chronic schizophrenia (9), in prodromal states of psychosis (10), and in individuals at high familial risk for schizophrenia (11). Similar findings were reported for bipolar disorder (12). Thus, impairments in FAR may represent a possible endophenotype that is related to the genetic risk for and development of psychosis (13). FAR may also represent an enduring deficit and trait marker of psychosis (14).

There are often major changes in the psychosocial functioning of patients with schizophrenia within the first 3 years of onset even though the decline in function tends to plateau thereafter (15). Therefore, the first 3 years of this disorder have been described as a critical period that determines the recovery of social function, future course, and prognosis of the patient. In particular, research examining FAR deficits in people in the early stages of the illness is of critical importance. If these impairments are present early in life, they will hamper the acquisition of socially competent behaviors and ultimately alter the developmental trajectory of that individual. Patients with schizophrenia in the acute stages of the illness demonstrated a specific affect recognition deficit, but patients with chronic schizophrenia demonstrated a general face processing deficit (16, 17). Others have reported that these deficits are stable over time (14, 18). The pattern most frequently observed is that of intact recognition of positive expressions (i.e., happiness) and impaired recognition of negative expressions (i.e., anger, fear, sadness, and disgust) (19, 20). However, few studies have compared early-onset psychosis (schizophrenia) or first-episode psychosis (schizophrenia) with chronic psychosis. To date, there has only been one meta-analysis that evaluated early-onset psychosis, including schizophrenia (21). Studies that included patients with a heterogeneous diagnosis of early-onset psychosis were excluded from the analysis (21). Of the 12 studies that were analyzed in the meta-analysis, only eight included patients with schizophrenia, and of these, there were only three studies that used at least six types of specific emotions (8, 22, 23). The meta-analysis demonstrated that, in addition to general emotional recognition deficits in patients with early psychosis or first-episode psychosis, the severity of recognition deficits differed for specific emotions. Accordingly, when compared to healthy controls (HCs), large effect sizes appeared for disgust, fear, and surprise, and medium effect sizes appeared for sadness and happiness. However, there were no differences in the effect sizes for anger and neutral facial expressions. The fact that specific emotions showed differences in the extent of the recognition deficit suggested the possibility that deficits in classifying certain emotions may also be influenced by the severity of symptoms. However, all of the patients with schizophrenia in the aforementioned studies were in remission or stable, making it difficult to analyze whether symptom severity affected the extent of recognition deficits for certain emotions or whether there was any correlation between symptoms and emotional recognition deficits. In addition, the sample sizes were not very large (12–50 patients per study), which led to variation in the results depending on the characteristics of the tests and the patients.

In this study, we used data from the Korean Early Psychosis Cohort Study (KEPS) to examine if the severity of psychotic symptoms affects FAR deficits for specific emotions in patients with early-stage schizophrenia. We also analyzed possible correlations between these deficits and several psychopathologies.

MATERIALS AND METHODS

Study Design

This study analyzed data from the KEPS, which is a naturalistic long-term prospective cohort study of patients with first-episode psychosis who were recruited from the Korean population. There are currently 11 university hospitals and one national mental health hospital participating in the KEPS. The KEPS sample consists of patients with early psychosis aged 18–45 years. Patients were defined as having early psychosis when they had

received their first psychiatric treatment (outpatient or inpatient) within the last 2 years and is further divided into early stabilized patients (patients who received at least 4 consecutive weeks of antipsychotic medication with no change in dose within the last 2 months) and first-onset patients (patients who received less than 4 weeks of consecutive antipsychotic medication after the initial onset). All of the patients in the KEPS met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (2) criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, or other specified schizophrenia spectrum and psychotic disorders, including attenuated psychosis syndrome. Follow-up assessments were conducted at 2, 6, 9, and 12 months and then biannually through the third and fourth years. Early psychotic symptoms can be diagnosed as various disorders and can change with the clinical course of the illness, and diagnostic stability is regularly investigated using dimensional diagnosis of the DSM-5 and the Mini International Neuropsychiatric Interview (24), which is administered at baseline (registration) and 6 months, 1 year, and 2 years later. Our previously published paper provides details on the study design, methods, and subject inclusion/exclusion criteria for the KEPS (25).

For this study, we first collected data from 495 patients with early psychosis who were registered in the KEPS between January 2015 and July 2018. Patients were excluded for the following reasons: screening failure (28 patients), changed diagnosis (96 patients), no FAR test (40 patients), and incomplete data (eight patients). A total of 323 patients (134 male, 189 female) with schizophrenia or schizophreniform disorder were included for participation in the analysis. To evaluate the influence of symptom severity on FAR, we divided subjects into three groups based on their scores on the Positive and Negative Syndrome Scale (PANSS) (26, 27). Leucht et al. (28) compared the PANSS scores to ratings of the Clinical Global Impressions-Scale (CGI-S) (29). According to the CGI-S, mildly ill, moderately ill, markedly ill, and severely ill patients corresponded to PANSS total scores of 58, 75, 95, and 116, respectively. Based on these criteria, we divided patients into three groups: 1) the severely and markedly ill (SM) group (112 patients; 36 severely ill patients and 76 markedly ill patients), 2) the moderately ill (Mo) group (96 patients), and the mildly ill (Mi) group (115 patients). We used the information from 62 age- and sex-matched individuals (29 male, 33 female) for the HC group. HC data were stored at one research site from January 2013 to July 2018. Participants in the HC group did not have a personal or familial history of any DSM-IV axis I or II disorders (30) and were recruited through local advertisement. The Korean version of the Structured Clinical Interview for DSM-IV Axis I Disorders (31) was administered to all participants to confirm their diagnostic eligibility. Participants in the HC group had to be normo-thymic, which was defined as a score <8 on the Korean version of the Montgomery-Åsberg Depression Rating Scale (32) and a score <6 on the Korean version of the Young Mania Rating Scale (33). HC participants also had to be nonpsychotic, which was defined as a score ≤30 on the Brief Psychiatric Rating Scale (34). Additional exclusion criteria for the participants included head trauma, neurologic disorders, alcohol or substance abuse, mental retardation (intelligence quotient <70) as measured by the Wechsler Adult Intelligence Scale (35), and serious medical conditions. All subjects received an explanation of the research aims and the use of data and provided their written consent before participating. This study was approved by the Ethics Committee of the Chonbuk National University Hospital (approval number CUH-2014-11-002) and other participating hospitals.

Assessment Tools

Psychopathology

The severity of psychotic symptoms was assessed using the PANSS and CGI. The PANSS typically consists of positive, negative, and general psychopathology subscales; however, in this study, we used a classification and scoring system that was standardized in Korea (36) and based on the 5-factor model proposed by Lindenmayer et al. (37). The 5-factor model for the PANSS (Positive, Negative, Cognitive/Disorganization, Excitement, and Depression/Anxiety subscales) has been recently recommended rather than some of the original PANSS subscales (38). We also used the Calgary Depression Scale for Schizophrenia (CDSS) (39, 40) to assess depression and the Social and Occupational Functioning Assessment Scale (SOFAS) (2) to measure general social functioning.

Facial Affect Recognition

To assess FAR, we modified the facial affect labeling task (41) to develop the facial emotion recognition test. This is a forced-choice emotional identification task in which eight facial expressions (happiness, sadness, anger, fear, contempt, disgust, surprise, and neutral) are presented on a computer screen. Face stimuli were acquired from the valid and reliable photographs of the Korean Facial Expressions of Emotion (KOFEE) database (42), with an established set of photographs based on characteristic facial configurations by Ekamn and Friesen (43, 44). Out of 15 actors in total (seven males, eight females), four males and four females conveying all eight emotions with higher accuracy and shorter response time were selected for the actual test. Next, two male and two female actors with high accuracy were selected for the practice session (see **Supplement** for more information). Subjects were informed of the names of the eight specific emotions that would be shown and were instructed to indicate their response by using the mouse to press the button on the screen that corresponded to the emotion that was being conveyed. Subjects saw the face and responded as quickly as possible. The pictures were displayed randomly within one block (a total of 16 pictures of facial emotions with one male and one female face for each emotion). All subjects first participated in two practice blocks. After confirming that the subjects had thoroughly understood the procedure, the actual test was performed over four blocks (a total of 64 trials). The participants were allowed a short rest between blocks. Before, during, and after this task, the participants remained in a stable emotional state. Face stimuli appeared during 750 ms, and the intertrial interval was 4,500 ms (3,000 ms of reaction time plus 1,500 ms of feedback time).

Statistical Analysis

The primary outcomes of this study were accuracy and response time (mean correct response time) for each emotion. For accuracy, we calculated commission error rates (mean error rate) and omission error rates (mean nonresponse rate). The secondary outcomes were the correlation coefficients between recognition deficits for each emotion and several psychopathologies.

All analyses were conducted using SAS 9.4 (Copyright 2002–2012 by SAS Institute Inc., Cary, NC, USA). Values of $p < 0.05$ were regarded as significant. For the demographic and clinical data, we performed analysis of variance (ANOVA) to examine group differences for numerical data. Following the ANOVA, we used Tukey-Kramer's post-hoc correction to compare the groups. We used the chi-square test for categorical data. Analyses of covariance and Tukey-Kramer's post-hoc comparisons were performed to analyze the accuracy (error rate, nonresponse rate) and correct response time of the facial emotion recognition test results. The peak age for schizophrenia is 10–25 years in men and 25–35 years in women (45); therefore, it is considered that the difficulties in performing academic work after disease onset are caused by differences in education levels. Because of this difference, educational level was used as a covariate when analyzing the accuracy and response time. In patients, Pearson's correlations were performed to detect the relationship between psychopathology and performance on the facial emotion recognition test within patient groups. To compare the extent and patterns of emotional recognition deficits between the three patient groups and the HC group, we calculated the effect size for each emotion. Effect sizes (Cohen's d) were calculated based on the average standard deviation from the two means. A value of 0.2 indicated a small effect size, 0.5 indicated a medium effect size, and 0.8 indicated a large effect size (46).

RESULTS

Subject Disposition and Clinical Characteristics

The demographic characteristics and clinical features of patients are summarized in **Table 1**. There were no significant differences in mean age between the SM group (28.07 ± 8.15 years), Mo group (27.81 ± 8.34 years), Mi group (27.47 ± 7.39 years), and HC group (29.31 ± 5.31 years). There were also no significant differences among the groups regarding sex, marital status, or monthly income. However, education was significantly higher in the control group than in the patient groups ($\chi^2 = 23.01$, $p < 0.01$). The duration of untreated psychosis (DUP), the ratio of patients on antipsychotics at the time of registration, and mean

TABLE 1 | Demographic and clinical data of the subjects.

Variables	Severely and markedly ill state[a] (n = 112)	Moderately ill state[b] (n = 96)	Mildly ill state[c] (n = 115)	Healthy controls (n = 62)	F/χ^2	P	Post hoc*
Mean age	28.07 ± 8.15	27.81 ± 8.34	27.47 ± 7.39	29.31 ± 5.31	0.56	0.640	
Sex, male (n,%)	44, 39.27	44, 45.83	46, 40.00	29, 46.77	1.67	0.645†	
Education							
High school or less (n, %)	53, 47.32	36, 37.50	45, 39.13	7, 11.29	23.01	0.000†	
College or higher (n, %)	59, 52.68	60, 62.50	70, 60.87	55, 88.71			
Marital state							
Unmarried (n, %)	97, 86.61	79, 82.29	93, 80.87	44, 70.97	6.50	0.090†	
Married (n, %)	15, 13.39	17, 62.50	22, 19.13	18, 29.03			
Monthly income (%) (10,000 won)							
<150	23, 20.54	17, 17.90	16, 14.04	6, 9.68	5.29	0.508†	
150–350	55, 49.11	49, 51.58	56, 49.12	31, 50.00			
>350	34, 30.36	29, 30.53	42, 36.84	25, 40.32			
DUP (month)	15.27 ± 19.35	13.24 ± 29.97	15.16 ± 27.52		0.19	0.826	
Antipsychotics							
User ratio (n, %)	59, 52.82	48, 50.00	46, 40.00		4.04	0.133	
Mean dosage‡ (mg)	400.14 ± 245.78	348.96 ± 266.95	355.14 ± 262.33		0.55	0.576	
CGI-S	4.38 ± 1.04	3.62 ± 1.06	2.89 ± 1.06		57.35	0.000	a > b > c
PANSS							
Total	93.58 ± 17.91	66.86 ± 4.87	48.19 ± 7.48		426.14	0.000	a > b > c
Positive	13.35 ± 3.33	9.48 ± 2.23	6.78 ± 2.06		180.40	0.000	a > b > c
Negative	16.92 ± 4.68	12.51 ± 3.51	8.55 ± 2.55		146.65	0.000	a > b> c
Cognitive/Disorganization	19.92 ± 5.30	13.96 ± 3.43	10.32 ± 2.35		174.57	0.000	a > b > c
Excitement	15.47 ± 4.56	10.35 ± 2.81	7.17 ± 2.04		158.74	0.000	a > b > c
Depression/Anxiety	13.38 ± 4.03	10.36 ± 2.81	7.70 ± 2.39		91.75	0.000	a > b > c
CDSS	7.50 ± 5.63	5.45 ± 4.47	2.62 ± 2.47		36.69	0.000	a > b > c
SOFAS	49.61 ± 13.69	57.65 ± 9.41	62.81 ± 12.48		34.11	0.000	a < b < c

*p value was calculated using ANOVA. †p value was calculated using chi-square test. *Analysis of variance and Tukey-Kramer's post-hoc comparison were performed. n, number; DUP, duration of untreated psychosis; ‡chlorpromazine equivalents. CGI-S, Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; SOFAS, Social and Occupational Functioning Assessment Scale. [a]denoted a severely & markedly ill, [b]denoted a moderately ill, [c]denoted a mildly ill stage groups.*

antipsychotics dosage (converted to chlorpromazine equivalents) were not significantly different among the three patient groups.

The PANSS total scores and CGI-S scores, which are used to assess psychosis severity, in the SM group were significantly higher than were the scores in the Mo and Mi groups, and the scores in the Mo group were significantly higher than were the scores in the Mi group ($F = 426.14$, $p < 0.01$; $F = 57.35$, $p < 0.01$, respectively). The PANSS subscale scores, including the scores on the Positive, Negative, Cognitive/Disorganization, Excitement, and Depression/Anxiety subscales were also significantly different among the patient groups ($F = 180.40$, $p < 0.01$; $F = 146.65$, $p < 0.01$; $F = 174.57$, $p < 0.01$; $F = 158.74$, $p < 0.01$; $F = 91.75$, $p < 0.01$, respectively). The CDSS scores were significantly different among the three groups ($F = 36.69$, $p < 0.01$). The SOFAS scores were also significantly different among all three groups ($F = 34.11$, $p < 0.01$). For all analyses, the patients in the SM group had the highest scores, followed by the patients in the Mo group, and finally, the patients in the Mi group.

In the HC group, the scores on the Brief Psychiatric Rating Scale (19.33 ± 1.99), Korean version of the Young Mania Rating Scale (0.36 ± 0.78), and Korean version of the Montgomery-Åsberg Depression Rating Scale (1.61 ± 2.20) indicated that psychotic and mood symptoms were all within the normal range.

Primary Outcomes

Commission Error Rates

Commission error rates for each emotion are summarized in **Table 2**. Compared to the HC group, the SM group showed significantly higher error rates for all emotional faces except surprise; the Mo group showed significantly higher error rates for sadness, anger, fear, contempt, and disgust; and the Mi group showed significantly higher error rates for anger, fear, and contempt. Patients in the SM group showed significantly higher error rates for surprise than did the patients in the Mi group ($F = 4.64$, $p = 0.003$); however, there were no significant differences in the error rate for surprise between each patient group and the HC group.

The effect sizes for the FAR deficit relative to the HC group are summarized in **Table 3**. In the SM group, contempt and fear showed large effect sizes; anger, happiness, sadness, and neutral faces showed medium effect sizes; and disgust showed a small effect size. In the Mo group, contempt showed a large effect size; fear, anger, sadness, neutral, and happiness showed medium effect sizes; and disgust showed a small effect size. In the Mi group, contempt, anger, and fear showed medium effect sizes; neutral, happiness, and surprise showed small effect sizes.

TABLE 3 | The effect size (Cohen's *d*) of the error rates in the facial emotion recognition test: comparison of each patient group and healthy controls.

Variables	Severely and markedly ill state - Healthy controls	Moderately ill state - Healthy controls	Mildly ill state - Healthy controls
Happiness	-0.655	-0.462	-0.243
Sadness	-0.584	-0.493	-0.164
Anger	-0.734	-0.574	-0.665
Fear	-0.921	-0.674	-0.582
Contempt	-1.049	-0.809	-0.684
Disgust	-0.419	-0.438	-0.131
Surprise	-0.091	0.070	0.433
Neutral	-0.563	-0.486	-0.322

Omission Error Rates

The patients in the SM group showed significantly higher nonresponse rates for all emotional faces than did the patients in the HC group. The patients in the Mo group showed significantly higher nonresponse rates for fear, contempt, and disgust than did the patients in the HC group. The patients in the Mi group showed significantly higher nonresponse rates for fear than did the patients in the HC group (**Table 4**).

Response Time

Apart from sadness, all emotions showed slower correct response times in all patient groups compared to the HC group ($p < 0.01$ for all analyses). There were no significant differences in the correct response times for anger, fear, contempt, disgust, surprise, and neutral among the three patient groups. However, the correct response time for sadness was slower in the SM group than in the HC group (**Table 5**).

TABLE 2 | Commission error rates (percent of error trials) in the facial emotion recognition test: comparison of each patient group by disease severity in patients with schizophrenia and healthy controls.

Variables	Severely and markedly ill state[a] (n = 112)	Moderately ill state[b] (n = 96)	Mildly ill state[c] (n = 115)	Healthy controls[d] (n = 62)	F	*p*	Post hoc*
Happiness	0.09 ± 0.01	0.05 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	9.17	0.000	a > bcd
Sadness	0.26 ± 0.02	0.25 ± 0.02	0.18 ± 0.02	0.18 ± 0.03	4.04	0.008	ab > cd
Anger	0.43 ± 0.03	0.39 ± 0.03	0.40 ± 0.03	0.26 ± 0.04	4.87	0.003	abc > d
Fear	0.75 ± 0.02	0.69 ± 0.03	0.67 ± 0.02	0.53 ± 0.03	9.37	0.000	abc > d
Contempt	0.35 ± 0.03	0.27 ± 0.03	0.22 ± 0.03	0.09 ± 0.04	10.17	0.000	a > cd bc > d
Disgust	0.56 ± 0.03	0.57 ± 0.03	0.49 ± 0.03	0.46 ± 0.04	3.41	0.018	ab > d
Surprise	0.12 ± 0.01	0.09 ± 0.01	0.05 ± 0.01	0.11 ± 0.02	4.64	0.003	a > c
Neutral	0.09 ± 0.01	0.08 ± 0.02	0.06 ± 0.01	0.03 ± 0.02	2.79	0.040	a > d

*Estimated the marginal means over a balanced population. p value was the result of analysis of covariance (ANCOVA) adjusted for education. *Post-hoc comparisons using Tukey-Kramer's method following a significant ANCOVA. [a]denoted a severely & markedly ill, [b]denoted a moderately ill [c]denoted a midly ill states, [d]denoted a healthy control groups.*

TABLE 4 | Omission error rates (percent of nonresponse trials) in the facial emotion recognition test: comparison of each patient group and healthy controls.

Variables	Severely and markedly ill state[a] (n = 112)	Moderately ill state[b] (n = 96)	Mildly ill state[c] (n = 115)	Healthy controls[d] (n = 62)	F	*p*	Post hoc*
Happiness	0.049 ± 0.006	0.021 ± 0.007	0.010 ± 0.006	0.007 ± 0.009	7.94	0.000	a > bcd
Sadness	0.092 ± 0.011	0.056 ± 0.011	0.052 ± 0.010	0.014 ± 0.015	6.34	0.000	a > cd
Anger	0.115 ± 0.011	0.069 ± 0.012	0.048 ± 0.011	0.023 ± 0.015	9.58	0.000	a > cd
Fear	0.125 ± 0.013	0.069 ± 0.013	0.051 ± 0.012	0.010 ± 0.017	11.12	0.000	a > b > c > d
Contempt	0.107 ± 0.012	0.081 ± 0.013	0.030 ± 0.012	0.007 ± 0.016	11.40	0.000	ab > cd
Disgust	0.171 ± 0.016	0.108 ± 0.017	0.103 ± 0.015	0.010 ± 0.021	13.07	0.000	a > bcd bc > d
Surprise	0.059 ± 0.009	0.043 ± 0.009	0.015 ± 0.008	0.007 ± 0.012	6.67	0.000	a > cd
Neutral	0.069 ± 0.011	0.040 ± 0.011	0.020 ± 0.010	0.006 ± 0.014	5.47	0.000	a > cd

*Estimated marginal means over a balanced population. p value was the result of analysis of covariance (ANCOVA) adjusted for education. *Post-hoc comparisons using Tukey-Kramer's method following a significant ANCOVA. [a]denoted a severely & markedly ill, [b]denoted a moderately ill, [c]denoted a mildly ill states, [d]denoted a healthy control groups.*

TABLE 5 | Correct response time (mm second) in the facial emotion recognition test: comparison of each patient group and healthy controls.

Variables	Severely and markedly ill state[a] (n = 112)	Moderately ill state[b] (n = 96)	Mildly ill state[c] (n = 115)	Healthy controls[d] (n = 62)	F	*p*	Post hoc*
Happiness	1,679.42 ± 30.31	1,557.12 ± 26.02	1,541.61 ± 29.70	1,281.83 ± 41.37	19.62	0.000	a > bc > d
Sadness	2,107.11 ± 105.10	1,864.01 ± 113.90	1,875.64 ± 103.00	1,598.04 ± 143.57	2.75	0.042	a > d
Anger	2,063.41 ± 46.52	2,057.71 ± 48.95	2,061.61 ± 44.28	1,666.43 ± 59.98	11.83	0.000	abc > d
Fear	2,151.56 ± 56.20	2,133.59 ± 56.15	2,120.31 ± 51.64	1,808.94 ± 65.06	6.69	0.000	abc > d
Contempt	1,898.33 ± 47.76	1,804.43 ± 50.44	1,817.70 ± 44.61	1,386.99 ± 61.72	15.43	0.000	abc > d
Disgust	2,252.63 ± 52.73	2,284.44 ± 54.76	2,319.41 ± 49.33	1,986.41 ± 66.74	5.83	0.000	abc > d
Surprise	1,775.08 ± 33.59	1,703.97 ± 35.86	1,706.79 ± 32.78	1,464.84 ± 45.66	10.15	0.000	abc > d
Neutral	1,594.33 ± 32.29	1,572.17 ± 34.14	1,536.03 ± 31.20	1,216.79 ± 43.48	18.42	0.000	abc > d

*Estimated marginal means over a balanced population. p value was the result of analysis of covariance (ANCOVA) adjusted for education. *Post-hoc comparisons using Tukey-Kramer's method following a significant ANCOVA.[a]denoted a severely & markedly ill, [b]denoted a moderately ill, [c]denoted a mildly ill states, [d]denoted a healthy control groups.*

Secondary Outcomes

The PANSS total scores, which indicate the severity of psychosis, were positively correlated with the error rates for happiness ($r = 0.226$, $p < 0.01$), surprise ($r = 0.212$, $p < 0.01$), sadness ($r = 0.166$, $p < 0.01$), and contempt ($r = 0.128$, $p < 0.05$). The CGI-S scores, which also indicate the severity of psychosis, were positively correlated with the error rates for happiness ($r = 0.185$, $p < 0.01$) and surprise ($r = 0.158$, $p < 0.01$). Among the PANSS subscales, the Positive subscale score was positively correlated with the error rates for surprise ($r = 0.159$, $p < 0.01$) and happiness ($r = 0.118$, $p < 0.05$). The PANSS Negative subscale score was positively correlated with the error rates for surprise ($r = 0.253$, $p < 0.01$), happiness ($r = 0.243$, $p < 0.01$), sadness ($r = 0.179$, $p < 0.01$), contempt ($r = 0.122$, $p < 0.05$), and anger ($r = 0.118$, $p < 0.05$). The PANSS Cognitive/Disorganization subscale score was positively correlated with the error rates for happiness ($r = 0.247$, $p < 0.01$), sadness ($r = 0.168$, $p < 0.01$), contempt ($r = 0.157$, $p < 0.01$), surprise ($r = 0.177$, $p < 0.01$), neutral ($r = 0.136$, $p < 0.05$), and fear ($r = 0.111$, $p < 0.05$). The PANSS Excitement subscale score was positively correlated with the error rates for happiness ($r = 0.190$, $p < 0.01$), surprise ($r = 0.183$, $p < 0.01$), neutral ($r = 0.166$, $p < 0.05$), and contempt ($r = 0.134$, $p < 0.05$). The PANSS Depression/Anxiety subscale score was not significantly correlated with any emotion; however, there was a significant positive correlation between the CDSS score and the error rates for happiness ($r = 0.111$, $p < 0.05$). Finally, the SOFAS score was negatively correlated with the error rates for sadness ($r = -0.117$, $p < 0.01$), fear ($r = -0.151$, $p < 0.01$), happiness ($r = -0.125$, $p < 0.05$), surprise ($r = -0.117$, $p < 0.05$), and disgust ($r = -0.112$, $p < 0.05$) (**Table 6**).

DISCUSSION

We investigated the influence of symptom severity on FAR deficits for various emotions in patients with early-stage schizophrenia. To the best of our knowledge, this is the first study to examine, in detail, the relationship between psychotic symptoms and the characteristics of FAR deficits for specific emotions. Understanding the characteristics and patterns of emotional recognition deficits, which are known to be closely related to social function, is important for improving our understanding of symptoms in early-stage schizophrenia and plays an important role in disease prognosis and the recovery of social function.

There were no differences between the patients and controls in age, sex ratio, monthly income, or marital status, but the patient groups did show lower education levels than the HCs.

The PANSS total scores and CGI-S scores, which both evaluate the overall severity of psychosis, were mutually consistent and showed significant differences among the three patient groups. Using the PANSS 5-factor model established by Leucht et al. (28), the PANSS Positive, Negative, Cognitive/Disorganization, Excitement, and Depression/Anxiety subscales showed significant differences among the three patient groups. The CDSS and SOFAS also both showed significant differences among the three patient groups. For all analyses, patients in the SM group had the highest scores, followed by patients in the Mo group, and finally, patients in the Mi group. All of these findings suggest that all patients were appropriately classified by symptom severity and general functioning.

The three patient groups showed no differences in DUP or medication (chlorpromazine equivalent dose), indicating that there was little selection bias with regard to duration of disease or medication. Typically, it is believed that patients with more severe psychotic symptoms use higher dosages of antipsychotics; however, in this study, the dosage of antipsychotics was not different among the three patient groups. This is considered to be because only a few patients with severe symptoms were included, and even patients in the acute phase do not often use higher dosages of medication initially. Additionally, drug compliance was low; only half of the patients were using medication at the time of registration in the three groups.

In this study, the relationship between accuracy of emotional recognition and severity of psychotic symptoms for specific emotions can be explained as follows. The commission error rates for happiness, sadness, anger, fear, contempt, disgust, and neutral were significantly higher in the SM group than in the HC group. As the severity of symptoms decreased, the error rates for happiness and neutral faces improved, followed by the error rates for sadness and disgust. The error rates for anger, fear, and contempt were higher in the three patient groups than in the HC group. The error rates of surprise were not significantly different between the patient groups and the HC group. In the SM group, the effect sizes for contempt, fear, anger, happiness, sadness, neutral, and disgust were high. Additionally, contempt, fear, and anger consistently showed greater deficits across all levels of symptom severity. Happiness, sadness, disgust, and neutral recognition showed decreasing effect sizes with improved symptoms. There were no deficits in surprise recognition between patients in the three groups and patients in the HC group.

There have been prior studies of various emotions in stable, first-onset patients compared to HC groups. For instance, Edwards et al. (8) reported deficits in sadness and fear but not in happiness, anger, disgust, surprise, or neutral (contempt was not studied). Leung et al. (22) reported significant differences in surprise, fear, and disgust but not in anger, sadness, or happiness (contempt and neutral were not studied), whereas Comparelli et al. (23) reported differences in fear, disgust, anger, and sadness but not in happiness or surprise (contempt and neutral were not studied). Considering our results and those of prior studies, fear appears to demonstrate consistent recognition deficits across all studies, whereas happiness and neutral consistently demonstrate no deficits in patients in mild or stable condition. Anger, sadness, surprise, and disgust demonstrated inconsistent results (contempt cannot be compared across studies because it was only included in ours).

Lee et al. (47) performed a study of 55 Korean stable patients with chronic schizophrenia (mean age, 32.1 ± 8.1; years since first hospitalization 8.2 ± 5.9) using an FAR test with Korean faces and reported that the patients showed differences in sadness, fear, and anger recognition. However, there were no differences in the recognition of happiness, surprise, disgust, and neutral expressions (contempt was not studied). Even though this study was conducted with patients in chronic conditions, all results, except of those for sadness, are consistent with the results of our study. Studies comparing FAR deficits in first-episode and chronic-stage patients have reported that initial deficits are stable over time up to the chronic stage (14, 18, 22) and that deficits in the chronic phase are somewhat more generalized compared to the early stage (16, 17). The fact that our study and that of Lee et al. both showed similar FAR deficit patterns supports the theory that FAR deficits in first-episode patients are stable over time. Cross-cultural or cross-national differences in FAR deficits have been reported even in healthy individuals (48). Although the FAR deficits reported in patients with schizophrenia across all cultures share the same characteristics, it has been reported that there are differences in the FAR deficits for specific emotions (49). The fact that our results were closer to those of Lee et al. than to those from other cultures suggests that there are cultural differences in the recognition of specific emotions.

TABLE 6 | Correlations between psychopathology and error rates in the facial recognition test within the schizophrenia groups (n = 323).

Variables	PANSS Positive	PANSS Negative	PANSS Cognitive/ Disorganization	PANSS Excitement	PANSS Depression/ Anxiety	PANSS Total	CGI-S	CDSS	SOFAS
Happiness	0.118*	0.243†	0.247†	0.190†	0.099	0.226†	0.185†	0.111*	-0.125*
Sadness	0.105	0.179†	0.168†	0.103	0.089	0.165†	0.079	0.084	-0.200†
Anger	-0.018	0.118*	0.091	0.047	-0.023	0.064	-0.007	-0.016	-0.062
Fear	0.056	0.090	0.111*	0.080	-0.010	0.084	0.003	0.031	-0.151†
Contempt	0.093	0.122*	0.157†	0.134*	-0.010	0.128*	0.036	-0.031	-0.102
Disgust	0.065	0.091	0.085	0.088	0.034	0.085	0.076	-0.014	-0.112*
Surprise	0.159†	0.253†	0.177†	0.183†	0.066	0.212†	0.158†	0.034	-0.117*
Neutral	0.069	0.054	0.136*	0.166*	0.048	0.109	0.079	0.041	-0.087

$^{*}p < 0.05$, $^{\dagger}p < 0.01$. PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression-Severity; CDSS, Calgary Depression Scale for Schizophrenia; SOFAS, Social and Occupational Functioning Assessment Scale.

In an early study, Addington and Addington (9) found that improvements in positive and negative symptoms were not accompanied by improvements in face recognition in patients with schizophrenia. This suggests that face discrimination processing may be unrelated to disease severity. Subsequently, most studies have found a significant association between face recognition and negative symptoms but not positive symptoms (5, 50, 51). However, some of these studies also found a specific relationship between affect recognition and positive symptoms, such as bizarre behavior (52), thought disorder (53), and overall positive symptoms (54). Thus, investigations of the relationship between affect recognition and specific symptoms have yielded mixed findings, and a more detailed research has not yet been performed. Given the diverse severity of symptoms among our patient groups, we were in a suitable position to assess the symptoms and characteristics of each emotion. Among assessments of psychotic symptom severity, the PANSS total scores were positively correlated with the error rates for happiness, surprise, sadness, and contempt; the CGI-S scores were positively correlated with the error rates for happiness and surprise. This demonstrated that FAR deficits for expressions of happiness and surprise are associated with general psychotic symptoms. Among the PANSS subscales, the Positive subscale score was positively correlated with the error rates for surprise and happiness; the Negative subscale score was positively correlated with the error rates for surprise, happiness, sadness, contempt, and anger; the Cognitive/Disorganization subscale score was positively correlated with the error rates for happiness, sadness, contempt, surprise, neutral, and fear; and the Excitement subscale score was positively correlated with the error rates for happiness, surprise, neutral, and contempt. Depression in patients with schizophrenia was associated with higher error rates for happiness recognition. Finally, there were negative correlations between general social function and the error rates for sadness, fear, happiness, surprise, and disgust.

Few reports have evaluated omission rates; therefore, we cannot evaluate our findings in the context of previous results. In our study, the nonresponse rates for all emotional faces were significantly higher in the SM group than in the HC group. As the symptoms improved, the nonresponse rates for happiness also improved, followed by contempt, neutral, surprise, sadness, and anger. The nonresponse rates for fear and disgust were higher in the patient groups than in the HC group. All patients showed delayed responses to all emotions, except for sadness, regardless of the severity of psychotic symptoms. The results for response time and omission rate indicated that patients with schizophrenia experienced difficulties in emotional information processing, which provides evidence for the reliability of our results.

Overall, the relationship between emotional recognition and clinical symptoms for specific emotions in early-stage schizophrenia can be explained as follows. First, the accuracy of all emotions and response times were impaired (except for surprise) in patients who were severely and markedly ill. Second, the error rate for happiness was positively correlated with the PANSS total score and the CGI-S, CDSS, and SOFAS scores; therefore, we believe that happiness recognition is the state marker most closely related to general symptoms and social function. Third, the error rate for the neutral expression was positively correlated with the PANSS cognitive/disorganization and PANSS Excitement subscales, suggesting that this was the most sensitive state marker for initial improvement in the acute psychotic state. Fourth, anger, fear, and contempt recognition continued to show medium to large deficits even when symptoms improved, and response rates and omission rates both showed significant differences across all three patient groups. There was no correlation between the severity of psychotic symptoms (especially anger and fear), denoting that these are likely to be schizophrenia-specific trait markers that are scarcely affected by psychotic symptom severity. Fifth, the effect size for sadness, disgust, and surprise recognition indicated a mild or lower deficit in the recognition of these emotions. Therefore, patients with schizophrenia may be able to recognize these emotions well and show a somewhat appropriate response. Sixth, there were negative correlations between general social function and sadness, fear, happiness, surprise, and disgust. Depression in patients with schizophrenia was associated with impairments in happiness recognition.

This study had a few limitations. First, as this was a cross-sectional study rather than a longitudinal one, we were unable to identify differences in the same subjects according to the states of the illness. Moreover, the aim of this study was not to assess the impact of FAR deficits on longitudinal prognosis. However, the present results will contribute toward the understanding FAR deficits and clarify potential differences in its pathogenesis according to states of early-stage schizophrenia. Further studies are required to investigate these issues. Second, although we controlled for the level of education, cognitive function was not well-controlled because only discrete variables, such as intelligence, were used. Third, our emotion recognition task has some shortcomings, including a relatively low correction rate for fear and disgust in HCs (47% and 54%, respectively).

However, the major strength of our study is the large effect size of the planned comparisons between each clinical group and the HC group. Second, to our knowledge, this is the first study comparing the symptom severity of early-stage schizophrenia for each of the eight basic emotions. This study is a step toward the elucidation of emotion recognition impairment in schizophrenia. The understanding of the interactions between emotional recognition, social cognition, and social functioning in schizophrenia should be a goal for future research in the field of early intervention.

CONCLUSION

This study used data from the KEPS to examine the correlation between symptom severity and the extent of emotional recognition deficits for different emotions in patients with early-stage schizophrenia. We divided patients into three groups based on the severity of psychotic symptoms (SM, Mo, and Mi groups) and tested the recognition of facial expressions by Korean actors. The results showed deficits in all emotions apart from surprise in the SM group. There were deficits in the recognition of anger, fear, and contempt across all patient groups. There were no differences in the error rates for happiness, sadness, disgust, and surprise between the Mi and HC groups. The correct response times for all emotions, except for sadness, were significantly more delayed in patients in the three symptom groups than in the HC group. The severity of psychotic symptoms was positively correlated with happiness and

the neutral error rates, and depression was positively correlated with the happiness error rates. General social function showed negative correlations with the error rates for happiness, sadness, fear, disgust, and surprise. Our results are similar to those of a previous study that examined patients with chronic schizophrenia in Korea, suggesting that some emotional recognition deficits are stable over time and that there are cultural differences for certain emotions.

AUTHOR CONTRIBUTIONS

SW and Y-CC conceptualized the study. SW, S-WK, JJK, BJB, J-CY, KYL, S-HL, S-HK, SHK, EK and Y-CC performed the study and acquired data. SW and WKL conducted statistical analyses. SW and Y-CC analyzed and interpreted the data. SW drafted the manuscript. SW and Y-CC critically revised the manuscript. Y-CC received the grant. All authors approved the final 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.2019.00564/full#supplementary-material

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Occipital Alpha Connectivity During Resting-State Electroencephalography in Patients With Ultra-High Risk for Psychosis and Schizophrenia

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Schizophrenia patients always show cognitive impairment, which is proved to be related to hypo-connectivity or hyper-connectivity. Further, individuals with an ultra-high risk for psychosis also show abnormal functional connectivity-related cognitive impairment, especially in the alpha rhythm. Thus, the identification of functional networks is essential to our understanding of the disorder. We investigated the resting-state functional connectivity of the alpha rhythm measured by electroencephalography (EEG) to reveal the relation between functional network and clinical symptoms. The participants included 28 patients with first-episode schizophrenia (FES), 28 individuals with ultra-high risk for psychosis (UHR), and 28 healthy controls (HC). After the professional clinical symptoms evaluation, all the participants were instructed to keep eyes closed for 3-min resting-state EEG recording. The 3-min EEG data were segmented into artefact-free epochs (the length was 3 s), and the functional connectivity of the alpha phase was estimated using the phase lag index (PLI), which measures the phase differences of EEG signals. The FES and UHR groups displayed increased resting-state PLI connectivity compared with the HC group [$F(2,74) = 10.804$, $p < 0.001$]. Significant increases in the global efficiency, the local efficiency, and the path length were found in the FES and UHR groups compared with those of the HC group. FES and UHR showed an increased degree of connectivity compared with HC. The degree of the left occipital lobe area was higher in the UHR group than in the FES group. The hypothesis of disconnection is confirmed. Furthermore, differences between the UHR and FES group were found, which is valuable for producing clinical significance before the onset of schizophrenia.

Keywords: schizophrenia, ultra-high risk for psychosis, alpha rhythm, functional connectivity, occipital lobe

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INTRODUCTION

Schizophrenia (SZ) is a psychiatric disorder characterized by multiple symptoms, such as positive symptoms, negative symptoms, and cognitive symptoms (1). The neurocognitive deficits, such as verbal memory and vigilance, and social cognitive deficits, such as emotion expression and interpersonal relationships, seriously and continuously affect the normal lives of SZ patients (2–4). Researches on different stages of SZ are helpful to the early diagnosis and treatment of SZ. The stages include first-episode schizophrenia (FES), chronic SZ, and ultra-high risk for psychosis (UHR, also known as clinical high risk), depending on cognitive loss and morbidity (5, 6). Among them, UHR is considered the preclinical stage of SZ. Many studies have focused on UHR, with the aim of early detection and intervention to maximize the patient's functional performance and to preserve a life of the highest possible quality (7, 8). However, few studies compared the different brain activation patterns in FES with the patterns in UHR (9, 10).

Electroencephalography (EEG) is a non-invasive and low cost way to detect the brain activation patterns in severe mental illness (11, 12). In addition to having a low cost, EEG has a millisecond temporal resolution and the different oscillation frequencies of EEG are related to different brain functions. A review of resting-state studies revealed that SZ patients have shown the increase of absolute delta (0.5–4 Hz) and theta (4–8 Hz) power, and also the decrease of absolute alpha (8–13 Hz) power (13). The inconsistent results are reported on delta and theta band in two studies (14, 15). Compared to delta and theta band, the decrease of alpha band activity in resting state (eyes closed) is the dominant result in SZ researches (13, 16). The alpha activity is negatively correlated to positive symptoms of SZ patients (17, 18). Besides, the decreased alpha activity can be modulated by transcranial alternating current stimulation. Further, the increase of alpha activity is related to clinical improvement of auditory hallucinations (19). The alpha power is also influenced by verbal working memory task in SZ patients (20). Taken together, alpha band activity is a sensitive marker in the progress of SZ and more non-linear analyses are necessary.

Functional connectivity analysis is a popular non-linear analysis in recent years. Studies have shown that cognitive impairment in schizophrenia is related to hypo-connectivity or hyper-connectivity between brain regions, but the associated mechanism of these abnormalities is still controversial (21, 22). A large number of researches have revealed the abnormal functional connectivity in patients with SZ (21, 23). SZ is not the result of focal brain abnormalities but the result of pathological connections between brain regions. This view has been influential in SZ research (24). Stam and Straaten found insufficient neuronal network organization in patients with SZ (25). In addition to the abnormal changes in overall brain connectivity, local anomalies were also observed. Mp et al. (26) demonstrated very localized network changes in the frontal and temporal areas, maintaining global network properties. Functional connectivity studies on the early stage of SZ also reveal the abnormal cerebro-cerebellar functional connectivity in FES and UHR (27) and the abnormal frontal-occipital network in UHR (28). Compared to healthy controls and early illness SZ, UHR showed specific abnormal patterns in the functional connectivity between the superior frontal regions and calcarine cortex (29) and functional connectivity in the cerebello-thalamo-cortical circuitry across different tasks (30). In a word, high-risk individuals showed intermediate abnormal resting-state functional connectivity patterns measured by coherence between healthy controls and SZ, but the differences were not significant (31). Thus, the construction of functional connectivity and deep analysis of brain network topology need to be strengthened.

Phase synchronization is an effective method to construct the functional connectivity of EEG detection. EEG is ideal for building large functional connectivity networks and for the analysis of various frequencies, especially since it has good time resolution. However, there are certain drawbacks to using a phase synchronization to build a network (28). Volume conduction affects the construction of functional connectivity due to the distance between electrical potential and source generator. A strong false connection is generated because of the positional deviation between the effect of the recording signal (32). An alternative method is generated to measure functional connectivity to solve the problem of false connections using the phase lag index (PLI) (33). PLI has become an effective research indicator for several mental disorders (34). Studies of SZ using PLI to measure functional connectivity based on EEG at rest also have important applications in the field of disease research and engineering (35). SZ patients have obvious reduced functional connectivity strength measured by PLI in alpha band compared to healthy controls (19, 36). FES patients show the decrease of PLI in the low alpha band (8–10 Hz) in the resting state compared to healthy controls (37). Combined PLI with minimum spanning tree, researchers found the decentralized topology characterized by degree centrality in FES (38). Thus, PLI may be effective to construct the functional connectivity and reveal the different patterns in FES and UHR.

It is highly likely that the topological configuration of functional brain networks can be used to evaluate treatment effects, including those related to cognitive function, and, in some cases, can predict the risk of psychosis (16, 39). To construct functional brain network, the use of resting-state EEG avoids the experimental errors caused by participants' incompatibility and reduces the difficulty of detection (13). This article aims to study the abnormality of brain connections measured by EEG in the early stage of SZ to produce clinical significance before the onset of SZ. In this study, we hypothesize that FES and UHR show abnormal global functional connectivity patterns measured by PLI compared to healthy controls. Furthermore, the abnormal local functional connectivity will be revealed by degree centrality analysis.

MATERIALS AND METHODS

Participants and Data Acquisition

Sixty-nine participants, including 20 patients with FES, 21 UHR, and 28 healthy controls, were recruited in the present study. UHR participants were recruited according to the Criteria of Prodromal Symptoms from the Structured Interview for Prodromal

Syndromes (SIPS) (35). FES patients were diagnosed based on the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). Medical professions evaluated the psychiatric symptoms on the Positive and Negative Syndrome Scale (PANSS). The SIPS scale was used to assess the prodromal syndromes of SZ for participants without SZ. The Global Assessment of Functioning (GAF) and MATRICS Consensus Cognitive Battery (MCCB) were assessed in all subjects to evaluate functioning and cognition. In addition, the Calgary Depression Scale for Schizophrenia (CDSS) was used to rate participants' depressive symptoms. Demographic and clinical details are summarized in **Table 1**. This study was approved by the Ethics Committee of the Beijing Anding Hospital in accordance with the Declaration of Helsinki, and all participants were given informed written consent before the experiment.

EEG Acquisition and Processing

Participants were instructed to sit comfortably, stay awake, and keep eyes closed and calm in a quiet room during the 3-min EEG recording. One hundred twenty-eight electrodes were arranged, and the reference electrode was Cz during the recording. The arrangement of 128 electrodes was the same as in a previous study (40). The sampling rate was 1,000 Hz, and the electrode impedances were less than 5 kΩ during the recording. In order to further improve the signal noise ratio, a 0.1–100 Hz online bandpass filter and a 0.1–45 Hz offline bandpass filter were combined during the recording. Our data were pre-processed with MATLAB R2017a (Mathworks Inc., Natick, MA, United States) with the open source toolbox EEGLAB (Swartz Center for Computational Neuroscience, La Jolla, CA, United States). An independent component analysis was used to remove artefacts (e.g., eye artefacts, muscle artefacts, and electrocardiographic activity) from the data within all channels. For the selection of epoch length, previous studies have shown that 3–16 cycles (for alpha band, about 2 s) are sufficient for PLI analysis (41, 42). In each epoch, the first and last 75 ms need to be removed to avoid distortions caused by bandpass filtering (43). Under the above considerations and for convenience of calculations, pre-processed data were divided into 3-s epochs, totalling 50 epochs, to keep the data consistent. For each epoch, alpha (8–13 Hz) was isolated by bandpass filtering.

Network Construction

The network synchronization of alpha oscillations was investigated. For each subject, instantaneous phase measures were calculated for each epoch, source, and frequency band by the Hilbert transform. Phase locking was calculated for each EEG sensor pair and frequency with the PLI (33, 44).

$$\mathrm{PLI} = \left|\left\langle sign(\Delta\phi(t))\right\rangle\right| = \left|\frac{1}{M}\sum_{k=1}^{M} sign(\Delta\phi(t))\right|$$

$\Delta\phi$ describes the phase difference of two time series (3-s epochs) recorded from two electrodes and M is the number of epochs, and 50 epochs are obtained for each participant. Since 128 electrodes are applied in the present study, a 128-by-128 adjacency matrix is obtained for each participant, and the mean of the matrix is calculated for the following comparison.

Theoretical Analysis of the Network Topologies

A 128-by-128 functional network was constructed for each participant by PLI. To further evaluate the global and local

TABLE 1 | Demographic data.

	HC	UHR	FES	*P* value
N (sex ratio M/F)	28 (19/9)	21 (13/8)	28 (14/14)	p = 0.384[a]
Age (years)	24.14 ± 3.71	24.10 ± 6.56	25.86 ± 7.33	p = 0.876[b]
Education (years)	13.43 ± 3.72	13.76 ± 3.10	12.25 ± 3.30	p = 0.253[b]
IQ	111.91 ± 14.44	107.54 ± 11.41	96.32 ± 13.33	p < 0.001[b]
CDSST	0.14 ± 0.53	1.90 ± 2.41	1.21 ± 1.19	p < 0.001[b]
GAF	86.86 ± 8.99	57.14 ± 13.04	54.75 ± 11.84	p < 0.001[b]
MCCB	45.14 ± 5.91	39.24 ± 5.91	35.20 ± 5.95	p < 0.001[b]
PANSS				
Positive			23.21 ± 6.09	
Negative			20.75 ± 7.43	
General			41.54 ± 6.25	
Total			84.46 ± 13.02	
SIPS				
Positive	0.50 ± 1.53	9.24 ± 3.27		p = 0.001[c]
Negative	0.36 ± 1.10	9.52 ± 5.41		p < 0.001[c]
Disorganization	0.18 ± 0.67	4.57 ± 2.93		p < 0.001[c]
General	0.25 ± 0.65	5.62 ± 3.92		p < 0.001[c]
Total	1.29 ± 3.51	28.95 ± 9.68		p < 0.001[c]

FES, first-episode schizophrenia; UHR, ultra-high risk for psychosis; HC, healthy controls; GAF, global assessment of functioning; IQ, intelligence quotient; MCCB, MATRICS Consensus Cognitive Battery; PANSS, positive, negative, and general psychopathology scale scores; SIPS, Structured Interview for Prodromal Syndromes.

[a]χ^2 *test.*

[b]*One-way ANOVA. P < 0.05 was considered significant.*

[c]*Independent samples test.*

topological properties of the network, network parameters, including clustering coefficients, path length, small world, global efficiency, local efficiency, and degree, were calculated by GRETNA (45). Random effects are removed by generating a total of 100 random networks and comparing with the PLI network. In addition, the brain network parameters were calculated with sparsity ranging from 0.05 to 0.5 (the interval is 0.05). The area under the curve was regarded as the normalized brain network parameters to avoid the influence of sparsity threshold and to check for relative network organization. In addition, the degree analysis of the PLI network was performed as an extended EEG analysis to focus on the abnormal brain changes. Higher degree of one node indicated the more interactions in the network for this node or electrode in the present study. Thus, the degree may be a simple but effective measure to detect the abnormality of networks.

Statistical Analysis

Statistical analyses were performed on SPSS version 25.0 (SPSS, Inc., Chicago, IL, United States). Two-sample t tests and chi-squared tests were performed on the clinical and demographic data to test the significant differences ($p < 0.05$). Differences among three groups were analyzed *via* one-way ANOVA and *post hoc* unpaired t-tests (Bonferroni corrected). Relationship between the degree of the alpha band and clinical scales was evaluated by Pearson's correlations ($p < 0.05$) and Bonferroni correction due to the multiple tests. The region of interest (ROI) was defined by an appropriate ANOVA to evaluate the potential electrodes by group differences on degree centrality. The part of the variance test $p < 0.001$ was selected as the ROI, and the ROIs were divided into three areas according to the location.

RESULTS

Demographic Characteristics

Table 1 displays the relevant demographic and clinical information. There was no significant group effect on gender [χ^2 (2,74) = 1.912, p = 0.384], age [F(2,74) = 0.133, p = 0.876], or education [F(2,74) = 1.399, p = 0.253] among all three groups. The intelligence quotient (IQ) significantly differed among the three groups [F(2,74) = 8.999, $p < 0.001$]. The IQ of healthy controls and UHR participants showed no significant differences. The results of *post hoc* testing showed that FES participants had significantly lower IQ scores than healthy controls ($p < 0.001$, Bonferroni) or UHR participants (p = 0.032, Bonferroni). The tests that evaluate functioning and cognition, such as GAF [F(2,74) = 68.278, $p < 0.001$] and MCCB [F(2,74) = 18.881, $p < 0.001$], showed significant differences among the three groups. The results of *post hoc* testing showed that FES participants had significantly lower GAF than healthy controls ($p < 0.001$, Bonferroni) or UHR patients ($p < 0.001$, Bonferroni), while no differences were found between UHR and FES (p = 1.000, Bonferroni). In addition, the test that rates participants' depressive symptoms, CDSST, showed a significant difference among the groups [F(2,74) = 8.918, $p < 0.001$]. Several significant differences were found in the CDSST scores of the three groups (UHR vs. HC: $p < 0.001$; HC vs. FES: p = 0.25, Bonferroni). However, the difference between UHR and FES was not significant (p = 0.331, Bonferroni).

Global Network Analysis

The topographic analyses of the spatial distribution of the alpha frequency in all epochs averaged across the three groups are presented in **Figure 1A**.

The mean PLI was 0.312 ± 0.128 for the UHR group, 0.267 ± 0.09 for the FES group, and 0.183 ± 0.061 for the healthy controls. The group effect on PLI was significant across the three groups [F(2,74) = 10.804, $p < 0.001$]. The PLI network connection for healthy controls was significantly lower than that for the UHR and FES groups. Differences can be seen in the PLI distribution of UHR and FES, but the differences were not significant. PLI embodies the consistency of the brain network in the phase distribution. In UHR, the brain network presents a diffuse connection distribution. This connection anomaly is concentrated in some areas in FES. In HC, the brain network connections are regionalized and ordered connections.

Brain network parameters were analyzed to assess the group differences in brain network connectivity. Parameters were

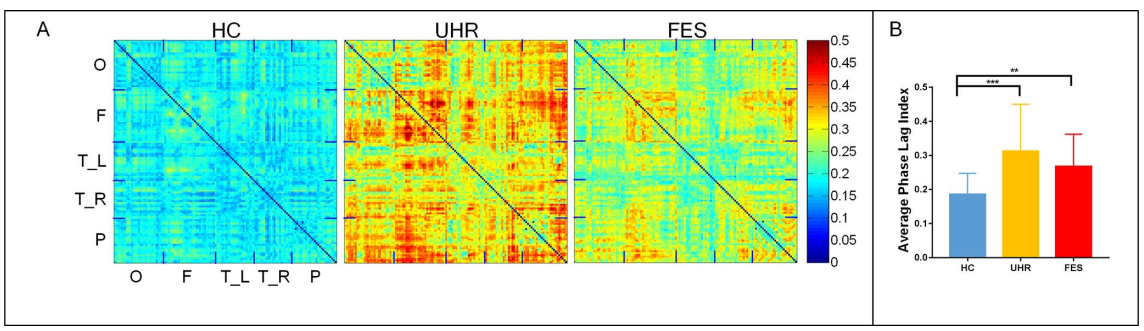

FIGURE 1 | First-episode schizophrenia (FES) and individuals with ultra-high risk for psychosis (UHR) showed an increased spontaneous eyes-closed alpha-band PLI relative to healthy controls (HC). No significant differences were observed for comparisons between the FES and UHR groups. **(A)** Differences can be seen in the PLI distribution of the three groups. The horizontal and vertical axes were electrodes, and the sequences of the electrodes were occipital network (O), frontal network (F), left (T_L) and right (T_R) temporal network, and parietal network (P). **(B)** Global PLI (average of 128 × 128 network) ANOVA results. *Post hoc* t-tests were corrected by Bonferroni. Significantly different results are indicated by asterisks (**: $p < 0.01$, ***: $p < 0.001$).

measured by the area under the curve below different sparsity threshold (from 0.05 to 0.5 with the interval of 0.05), such as clustering coefficient (Cp), path length (Lp), small-worldness (Sigma), global efficiency (Eg), local efficiency (Eloc), and degree centrality. All the group differences are shown in **Table 2**. The discriminative parameters among the groups are emphasized in bold fonts. There are significant interactions for the Eg [$p < 0.001$, $F(2,64) = 6.367$], Eloc [$p < 0.001$, $F(2,44) = 3.739$], and Lp [$p < 0.001$, $F(2,64) = 4.820$] values.

Degree Centrality Analysis

The distribution of degrees of centrality (area under the curve with the sparsity ranging from 0.05 to 0.5 with the interval of 0.05) is shown in **Figure 2**. The mean degree centrality was 8.18 ± 2.81 for the UHR group, 7.34 ± 2.16 for the FES group, and 4.64 ± 2.06 for the healthy controls. The group effect on degree centrality was significant across the three groups [$F(2,74) = 16.331$, $p < 0.001$]. The degree centrality for healthy controls was significantly lower than that for the UHR and FES groups. Differences could be seen in the degree distribution of UHR and FES, but the differences were not significant. UHR had a higher degree of connectivity in the subtemporal-occipital lobe. In addition, we examined the relation between the average global degrees and cognitive scales in all three groups. The analysis of behaviors showed significant results (MCCB: $r = -0.245$, $p = 0.041$; GAF: $r = -0.496$, $p < 0.001$). The degree centrality was negatively correlated with the cognitive scale (see **Figure 2C**). We also calculated the correlation within

TABLE 2 | Alpha network analysis.

	HC	UHR	FES	P value	Post hoc
Assortativity	−0.065 ± 0.058	−0.097 ± 0.059	−0.082 ± 0.061	0.186	
Hierarchy	0.01 ± 0.045	0.009 ± 0.061	0.003 ± 0.053	0.861	
Synchronization	0.013 ± 0.016	0.006 ± 0.008	0.01 ± 0.012	0.130	
Eg	0.084 ± 0.039	0.142 ± 0.037	0.13 ± 0.029	**< 0.001**	FES, UHR > HC
Eloc	0.088 ± 0.04	0.152 ± 0.044	0.14 ± 0.036	**< 0.001**	FES, UHR > HC
Cp	0.097 ± 0.018	0.105 ± 0.026	0.099 ± 0.022	0.439	
Lp	3.229 ± 1.618	1.573 ± 0.335	1.705 ± 0.361	**< 0.001**	FES, UHR < HC
Sigma	0.376 ± 0.044	0.352 ± 0.042	0.368 ± 0.043	0.163	

One-way ANOVA. P < 0.05 was considered significant.
The bolded text indicated the significant difference among groups.

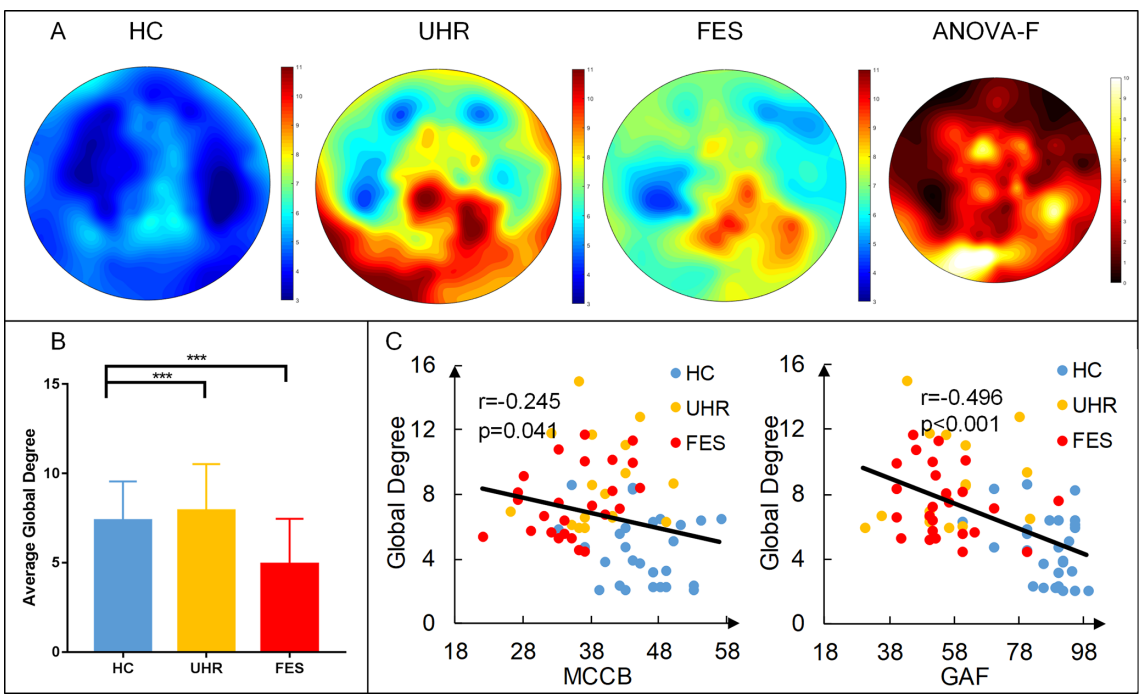

FIGURE 2 | First-episode schizophrenia (FES) and individuals with ultra-high risk for psychosis (UHR) showed an increased degree of connectivity (area under the curve with the sparsity ranging from 0.05 to 0.5 with the interval of 0.05) compared to healthy controls (HC). **(A)** Topography of the average degree of connectivity for the three groups. Rightmost map shows ANOVA results of the three groups. **(B)** Average global degree (average of 128 sites) ANOVA results. *Post hoc* t-tests were corrected by Bonferroni. Significantly different results are indicated by asterisks (***: $p < 0.001$). **(C)** Correlation of the average degree and cognitive scales. The result shows a negative correlation, which means that the higher the degree, the more damaged the cognitive situation.

one group (see **Supplementary Table 1**) and between two groups (see **Supplementary Figure 1**).

To better measure the difference in the degree centrality among the groups, a region of interest (ROI) analysis was applied to the differences among the whole brains of the three groups. The part of the variance test with significance ($p < 0.001$) was selected as the ROIs, and the ROIs were divided into three groups according to the location (**Figure 3**). The group effect on the degree centrality was significant across the three groups in ROI1 [$F(2,74) = 11.154$, $p < 0.001$], ROI2 [$F(2,74) = 13.662$, $p < 0.001$], and ROI3 [$F(2,74) = 15.004$, $p < 0.001$]. The degree centrality for healthy controls was significantly lower than that for the UHR and FES groups in all three ROIs. No significant differences were found between the UHR and FES groups in terms of ROI1 and ROI2, while the degree centrality of the FES group in ROI3 was significantly lower than that of the UHR group ($p = 0.014$, Bonferroni).

We examined the relation between the average degree of ROI, where we found statistically significant group differences and cognitive scales in all three groups. In ROI1, the linear regression analysis showed a statistically significant relation between the degrees and the cognitive scales (see **Figure 3C**). We found a statistically significant negative relation between the degree means and the cognitive scales ($r = -0.442$, $p < 0.001$). Negative relation between the cognitive scales and the degrees is also found in ROI2 ($r = -0.483$ $p < 0.001$) and ROI3 ($r = -0.334$, $p = 0.003$). We also calculated the correlation within one group (see **Supplementary Table 1**) and between two groups (see **Supplementary Figures 2** and **3**).

DISCUSSION

The present study described the abnormal brain disconnection in the FES and UHR groups compared with that in healthy controls. Furthermore, the association with clinical scales has been revealed to demonstrate the relationship between the functional connection results based on EEG and clinical manifestations. Our results showed the increase of functional connectivity mainly in superior parietal, right temporal, and left occipital brain regions. Furthermore, patients showed increased average degree and the degree was related to clinical scales. Differences between the FES and UHR groups have been found on the average degree in ROI3, which may be a potential biomarker of SZ.

Some scholars believe that alpha is related to non-task brain network activity (46), but some studies have shown that alpha-band brain activity is related to cognitive and memory representation, which reflects the performance of attention and semantic memory (47). Based upon these opinions, we believe that task-independent prohibition will help to allocate resources to the task-related areas necessary for optimal task execution. Therefore, we believe that the brain activity of the alpha band in the resting state can reflect the health of the brain to a certain extent. Moreover, several resting-state studies reported abnormalities in the alpha band in SZ (48–51). One of those studies reported a significant correlation between a measure of global network efficiency and cognitive ability in SZ (50).

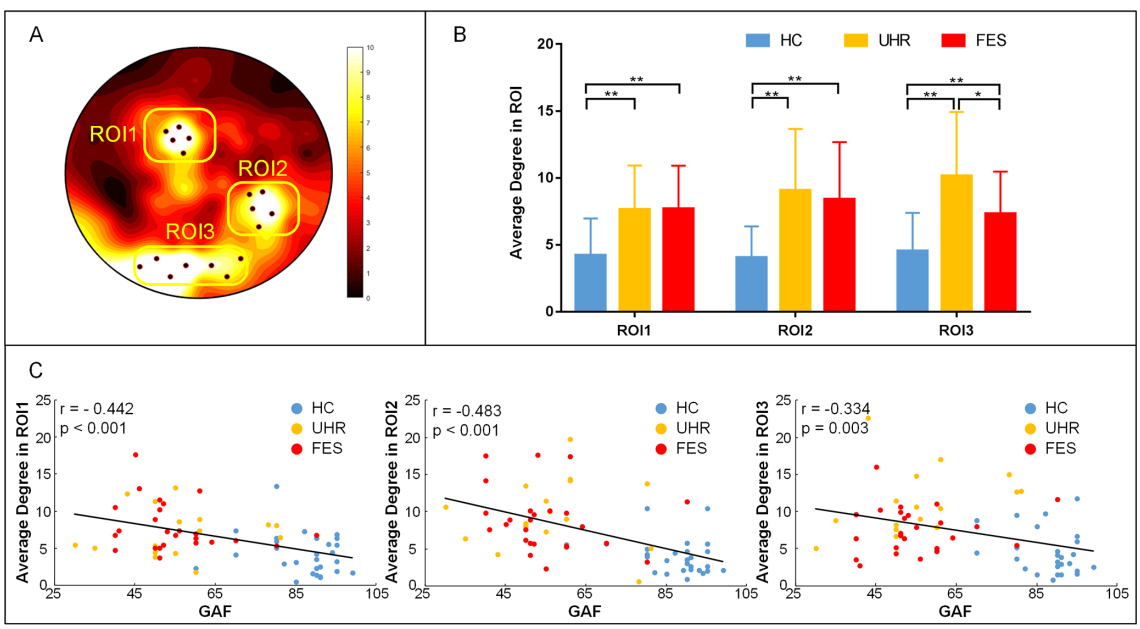

FIGURE 3 | ROI analysis results. **(A)** ROI (black dots) defined as the topography of ANOVA result. Sites whose $p < 0.001$ were considered. ROI1: superior parietal (electrode number: 12, 13, 19, 20, 24), ROI2: right temporal lobe areas (electrode number: 96, 97, 98, 101, 102), ROI3: occipital lobe areas for three groups (electrode number: 68, 69, 73, 74, 82, 88, 89). The arrangement of 128 electrodes was the same as in a previous study (40). **(B)** Average global degree (average of 128 sites) ANOVA results. *Post hoc* t-tests were corrected by Bonferroni. Significantly different results are indicated by asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$). **(C)** Correlation of the average degree and cognitive scales. The results show a negative correlation, which means that the higher the degree, the more damaged the cognitive situation.

Two different hypotheses about how abnormal connectivity affects patients are discussed in the field of SZ. For hyperconnectivity hypothesis, it assumed that synapses may fail to be eliminated in development. In contrast, that too many synapses are eliminated is what is believed by hyperconnectivity hypothesis. In this study, the network connection based on PLI was found to be significantly higher in the FES and UHR groups than in healthy controls, and excessive connectivity occurred in these patients. In previous studies, connection enhancements in schizophrenic patients have also been reported (52). The enhancement of local connectivity in the brain of the patient group may be due to impaired connections, which is a notion that was validated in previous studies. Synaptic plasticity may affect the process of connectivity construction. Functional connectivity between neurons may hardly survive from development due to the strength abnormality (53).

The global efficiency and local efficiency in the UHR and FES groups were significantly higher than those in the healthy controls. In addition, path length, which measures brain network connectivity integration, was decreased significantly in the patient group. This result is also reflected in previous studies. Lp for alpha activity was significantly higher in the FES group at rest (25). In summary, there is a problem with the functional integration of schizophrenic patients in brain network connections, which is consistent with previous studies. Further, our results indicate that the UHR group also has the problem of functional connectivity, which may be a more serious problem than that of the FES group.

To further analyze the connection abnormality of schizophrenia, the degree of centrality and ROI analysis were implemented. As mentioned in the above results, the degree of centrality was significantly higher in the FES and UHR groups than in healthy subjects, especially in the superior parietal, right temporal, and left occipital lobe areas. Previous studies have found the structural and functional abnormality of visual cortex in SZ patients by MRI, and the abnormality was related to clinical symptoms (54, 55). As for the abnormality in auditory cortex (56), the abnormality is mainly in the left temporal lobe (57, 58). Similar abnormality of the left temporal area in SZ is also found by PET (59). In the analysis of the degree centrality, the degree of the UHR group was significantly higher than that of the FES group in the occipital lobe areas. Previous studies have shown the abnormality of visual cortical processing in patients with SZ and UHR participants (60). SZ patients also showed other cortical processing dysfunctions (61). In the early stage of SZ, such as UHR participants, cognitive deficits are found (62).

We observed a statistically significant relation between the degree of network and cognitive scores in the three groups (see **Figures 2C**, **3C**). The degree of centrality in the ROI was negatively correlated with the score on the cognitive scale, indicating that the better the cognitive performance of the subject, the lower the degree of centrality. The relevant results in the present study suggest that the cognitive decline in schizophrenic patients is related to their network connectivity. This pattern of results suggests that as the abnormal nodes of the brain network increase, the cognitive ability of patients decreases. The direction of this relation indicates that some individuals with SZ might show a protracted developmental course of network topology.

Our results demonstrated that brain networks estimated at rest can also predict the stratified level of consciousness in patients and predict patient clinical outcomes. However, a current limitation of the EEG-based assessment proposed here stems from the expert intervention required for artefact removal, specifically for inspecting and identifying noisy data and independent components. There have been many recent methodological advances in automating this step (63–65), and in the future, we need more participants and follow-up study to validate our methods and hypothesis.

The current study has identified brain function network defects in patients with FES and clinically high-risk patients. The abnormal global and local functional networks are revealed in the different stages of SZ. The present methods on network construction and analysis, and the results of correlation between the central degree topological measurement and the clinical scales may be helpful in understanding the dysfunction syndrome of SZ.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Ethics Committee of the Beijing Anding Hospital with written informed consent from all participants. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Beijing Anding Hospital.

AUTHOR CONTRIBUTIONS

TL participated in experiments, assisted in data analysis, and wrote the paper. JZ analyzed the data and revised the paper. XD analyzed and interpreted the data and wrote the paper. ZL, XS, YT and RY helped with revised the paper and assisted in data analysis. JW provided a schematic of the principle. CW carried out scale evaluation and acquired the data. TY analyzed organized results 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.2019.00553/full#supplementary-material

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REVIEW
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Improving the Detection of Individuals at Clinical Risk for Psychosis in the Community, Primary and Secondary Care: An Integrated Evidence-Based Approach

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Background: The first rate-limiting step for improving outcomes of psychosis through preventive interventions in people at clinical high risk for psychosis (CHR-P) is the ability to accurately detect individuals who are at risk for the development of this disorder. Currently, this detection power is sub-optimal.

Methods: This is a conceptual and nonsystematic review of the literature, focusing on the work conducted by leading research teams in the field. The results will be structured in the following sections: understanding the CHR-P assessment, validity of the CHR-P as a universal risk state for psychosis, and improving the detection of at-risk individuals in secondary mental health care, in primary care, and in the community.

Results: CHR-P instruments can provide adequate prognostic accuracy for the prediction of psychosis provided that they are employed in samples who have undergone risk enrichment during recruitment. This substantially limits their detection power in real-world settings. Furthermore, there is initial evidence that not all cases of psychosis onset are preceded by a CHR-P stage. A transdiagnostic individualized risk calculator could be used to automatically screen secondary mental health care medical notes to detect those at risk of psychosis and refer them to standard CHR-P assessment. Similar risk estimation tools for use in primary care are under development and promise to boost the detection of patients at risk in this setting. To improve the detection of young people who may be at risk of psychosis in the community, it is necessary to adopt digital and/or sequential screening approaches. These solutions are based on recent scientific evidence and have potential for implementation internationally.

Conclusions: The best strategy to improve the detection of patients at risk for psychosis is to implement a clinical research program that integrates different but complementary detection approaches across community, primary, and secondary care. These solutions are based on recent scientific advancements in the development of risk estimation tools and e-health approaches and have the potential to be applied across different clinical settings.

Keywords: Clinical high risk, detection, e-health, prevention, psychosis, risk, schizophrenia

INTRODUCTION

Preventive strategies in young people at clinical high risk for psychosis [CHR-P (1)] can ameliorate the high personal, familial, societal, and clinical burden of psychotic disorders (2). CHR-P criteria, which include the ultra-high-risk state [e.g., at-risk mental state (3) or other psychosis-risk syndromes (4)] and/or basic symptoms (5), are detected by specialized clinical services (6) through established psychometric assessment tools (7), in the context of a clinical interview (8). These tools are internationally validated (7) and assess whether the individual is meeting at least one of the three ultra-high-risk subgroups: attenuated psychotic symptoms (~85% of cases), genetic risk and deterioration syndrome (5% of cases), or brief and limited intermittent psychotic symptoms (BLIPS, 10% of cases) (3, 9) subgroup. Individuals at CHR-P recruited from help-seeking clinical samples have a 20% probability of developing emerging psychotic disorders (but not other nonpsychotic disorders (10, 11)) over 2 years (12). This risk increases to 50% at 2 years for the BLIPS subgroup and to 89% at 5 years for the subset of BLIPS patients who present with seriously disorganizing and dangerous features (13). Overall, the real-world potential impact of the CHR-P paradigm for improving the outcomes of psychotic disorders will be determined by the successful and stepped integration of three key components (**Figure 1**): (i) efficient detection of individuals at risk for psychosis, (ii) accurate prognosis of outcomes, and (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 real-world ability to detect most individuals who are at risk for psychosis and will later develop it. Efficient detection of individuals at CHR-P has been a relatively neglected area of research in spite of the fact that inefficient detection impedes subsequent efforts. In fact, even the most accurate prognostic model and effective preventive treatment would exert a modest impact if they are only applied to a small proportion of those who later develop psychosis. The first challenge is that, to date, there has been an assumption that the CHR-P stage represents the prototypical prepsychotic stage for most individuals who will later go on to develop psychosis. However, in a thematic issue in Schizophrenia Bulletin titled "Dissecting the diagnostic pluripotentiality of the ultra high risk state for psychosis," (Volume 44, Issue 2, 2018) (15–18), a meta-analysis demonstrated that the onset of psychosis may also occur via previously identified nonpsychotic clinical risk syndromes (17). Separately, independent research groups have reported that first-episode psychosis (FEP) cases may occur without a prior identifiable period of subthreshold psychotic symptoms (19, 20). The second challenge is that even assuming that the CHR-P concept would be sufficient to detect the majority of individuals at risk, its real-world penetrance is undetermined. Emerging evidence suggests that current detection strategies for identifying individuals at CHR-P are highly inefficient. These strategies

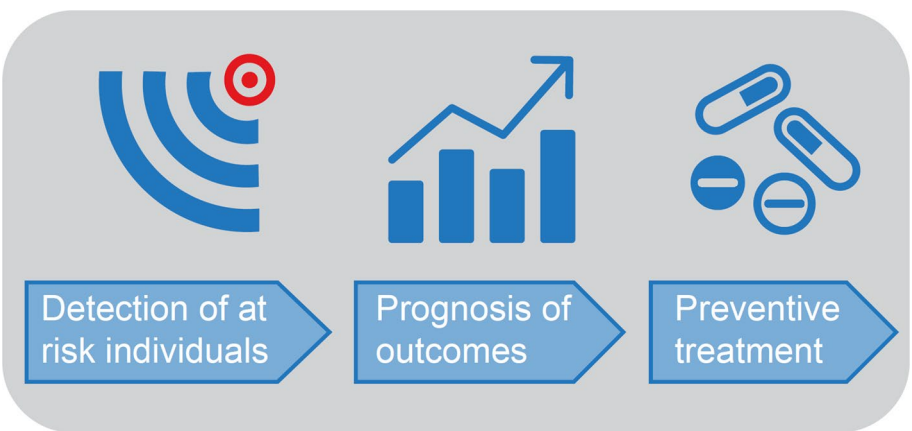

FIGURE 1 | Core clinical components for effective prevention of psychosis. The first rate-limiting step for improving outcomes of psychosis through preventive approaches is the ability to accurately detect individuals at risk for psychosis. Adapted from (14), Creative Commons Attribution License (CC BY).

are largely based on referrals to specialized CHR-P clinics (6), made on suspicion of psychosis risk. Only 5% of individuals who had presented with a first onset of nonorganic psychosis to the local NHS Trust had been detected by one local CHR-P service (21). Since the service had been fully established in the same Trust, there is a clear need to improve the detection of at-risk cases (22). To our best knowledge, there are no other original studies published to date reporting on the detection power of the CHR-P paradigm that could further validate or replicate these findings. Inefficient detection has important clinical implications. For example, although the NHS England's Access and Waiting Times-Standard for Early Intervention in psychosis (23) requires that CHR-P are detected nationwide and treated within 2 weeks, current detection strategies are inefficient. A first viable alternative may be to intensify the outreach campaigns currently adopted by CHR-P clinics. Converging evidence has demonstrated that such an approach conflicts with the intrinsic psychometric limitations of the CHR-P interviews, producing a diluted transition risk (24, 25) and unreliable prognostic accuracy. Another option may be to implement front-line youth mental health services such as the Headspace initiative (other youth mental health services are available worldwide; for a recent review, see (26)). Because of their one-stop-shop nature (26–28), youth-friendly services are expected to improve the attraction and detection of potential individuals who may be at risk of psychosis. Unfortunately, there are no original data reporting on the efficacy of detecting individuals at CHR-P through youth mental health services. Rough estimates indicate only a modest improvement of detection when adopting broad youth mental health services, with 12% of individuals with FEP being detected at the time of their CHR-P phase (29) (**Figure 2**). Therefore, at present, between 88% (Headspace model) and 95% [Outreach and Support in South London (OASIS) model] of individuals who will later develop psychosis remain undetected at the time of their CHR-P stage (see **Figure 2**).

In order to extend the preventive benefits of the CHR-P paradigm, more sophisticated and innovative approaches are urgently needed (30).

The current manuscript will review this issue in a comprehensive conceptual analysis of the current challenges and propose evidence-based ways for overcoming them. The detection program presented here integrates three separate approaches targeting different populations: secondary mental health care, primary care, and the community. The overarching methodology of this detection program leverages the recent advancements brought by clinical risk estimation tools (31) and digital approaches.

METHOD

This is a conceptual but nonsystematic review of the literature, which focuses on the areas of work conducted by our research teams. As such, the information included here largely reflects our conceptual opinion regarding the best path forward an improved detection of CHR-P individuals. We will first review the conceptual foundation of the CHR-P assessments, a necessary step to grasp their intrinsic limitations. Following this analysis, we will appraise the conceptual validity of the CHR-P stage as a universal and prototypical risk state for psychosis. Then, we will propose empirical ways for improving the detection of CHR-P

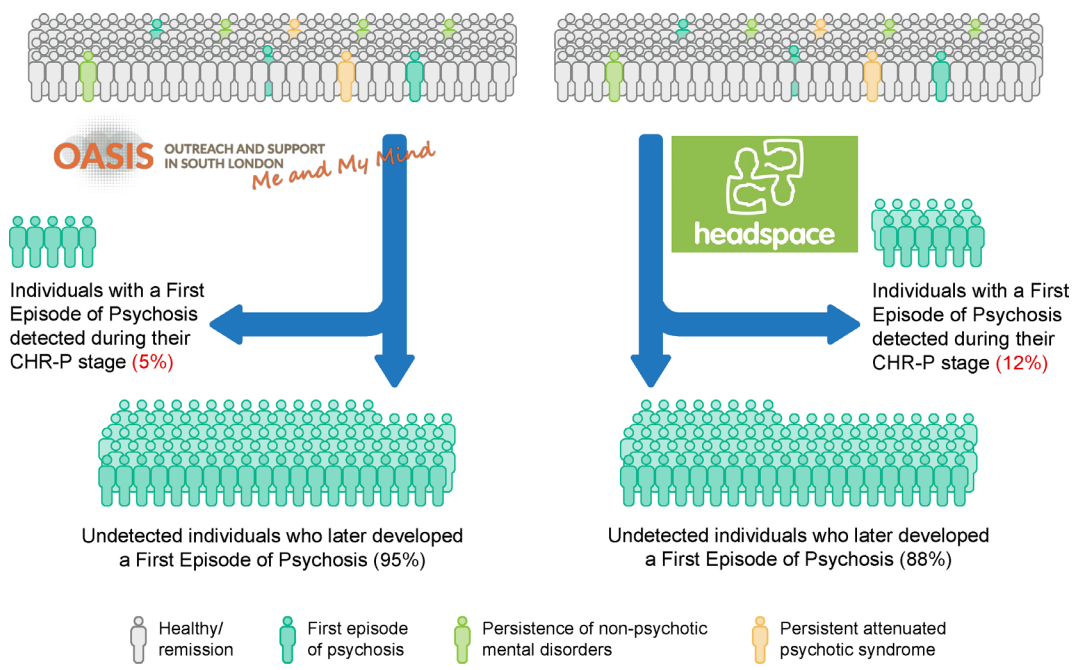

FIGURE 2 | Detection power of at-risk patients who will later develop a first-episode of psychosis under different preventive programs: OASIS and headspace. CHR-P: Clinical High Risk for Psychosis. New figure.

individuals. The results are structured in the following sections: understanding the CHR-P assessment, validity of the CHR-P as universal risk state for psychosis, improving the detection of at-risk individuals in secondary mental health care, improving the detection of psychosis in primary care, and improving the detection of psychosis in the community.

RESULTS

Understanding The CHR-P Assessment

CHR-P cohorts are not representative of the local general population because recruitment is affected by sampling biases. To exemplify this, in the general population of South London, the cumulative 3-year incidence of psychotic disorders is 0.43% (32) (**Figure 3**).

The recruitment of individuals for undergoing a CHR-P assessment is primarily based on unstructured and heterogeneous selection and sampling strategies based on the clinicians' suspicion of psychosis risk (33) and help-seeking behavior (37). These recruitment processes determine the extent to which individuals at CHR-P would accumulate several risk factors for psychosis (**Figure 3**) (22, 38); in turn, the accumulation of risk factors determines the level of functional impairment (39, 40) and associated attenuated psychotic symptoms (**Figure 4**) (8). Broadly speaking, individuals are generally recruited from secondary mental health care, primary care, or the community and represent different populations on the basis of clinical and functional characteristics. The current manuscript will be structured around strategies to detect these three different populations.

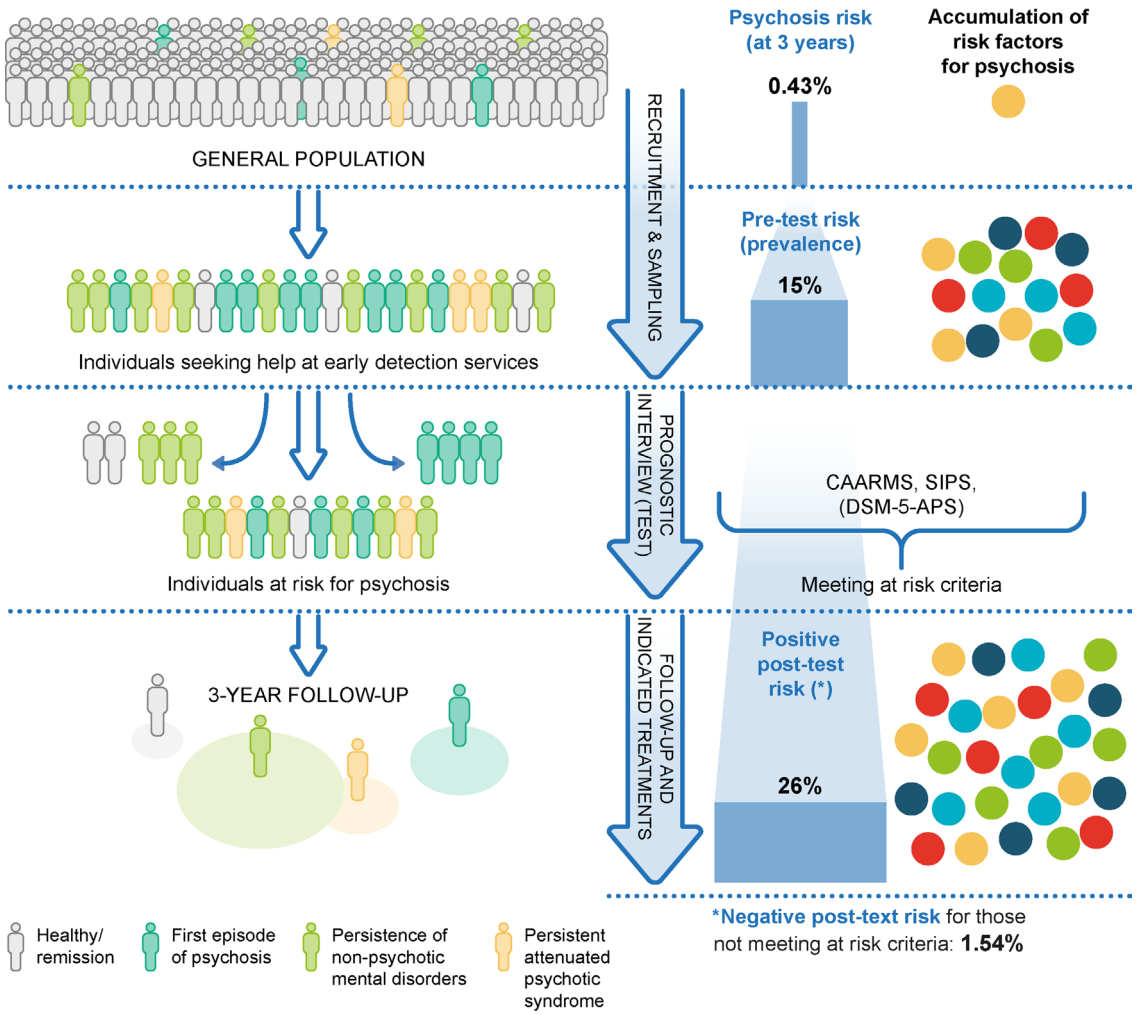

FIGURE 3 | Sampling procedure for individuals at clinical high risk for psychosis (CHR-P) (33). Idiosyncratic recruitment strategies that are characterized by heterogeneous sampling biases (convenience and judgmental sampling) result in accumulation of various risk factors for psychosis and differential level of enrichment of psychosis risk. The risk before the CHR-P assessment is completed is termed pretest risk or prevalence. The risk after the CHR-P assessment is completed is termed posttest risk (positive if CHR-P criteria are met and negative if CHR-P criteria are not met). The figure is based on the data reported in (32, 34, 35). CAARMS: Comprehensive Assessment of At-Risk Mental States; SIPS: Structured Interviews for Psychosis-Risk Syndromes; DSM-5-APS: Diagnostic and Statistical Manual, 5th Edition, Attenuated Psychosis Syndrome. Adapted from (36), Creative Commons Attribution License (CC BY).

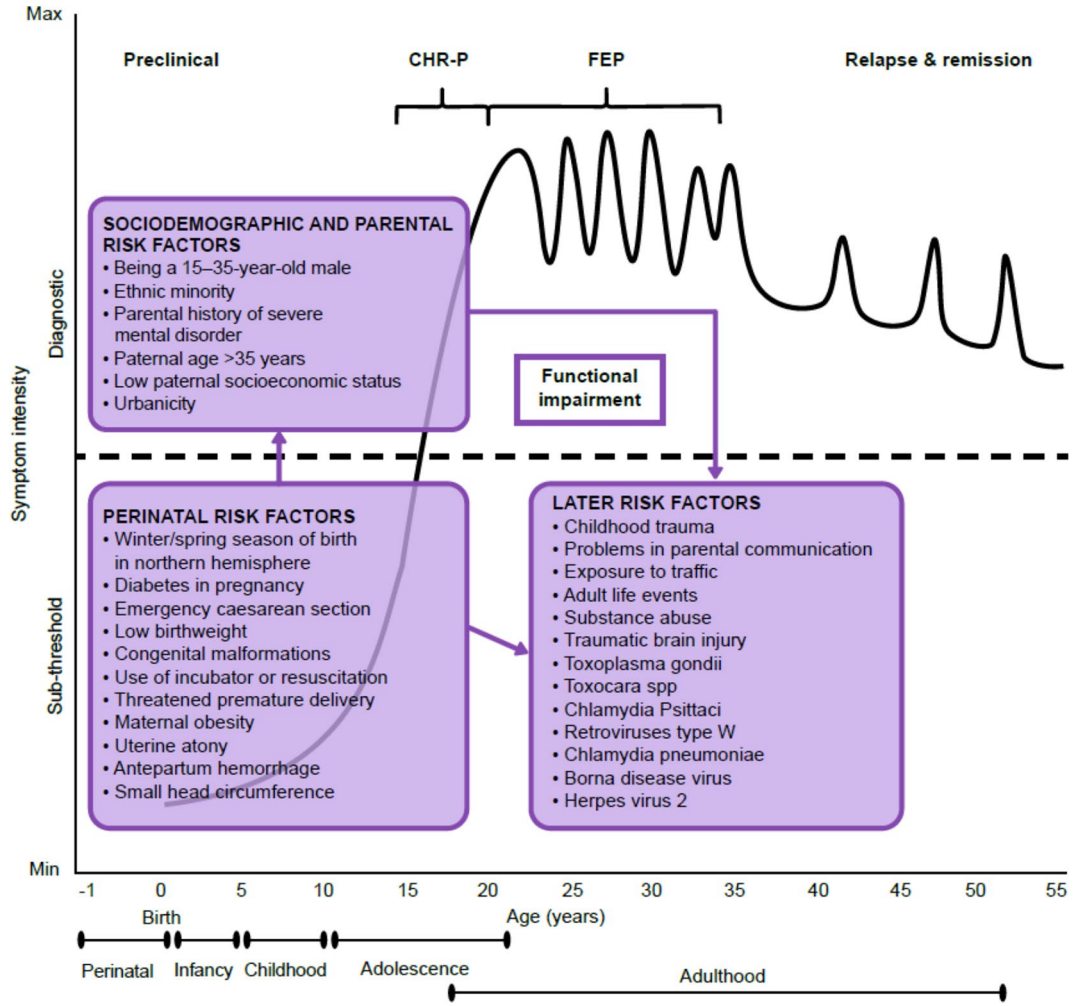

FIGURE 4 | Putative model of the onset and progression of psychosis in relation to nonpurely genetic risk factors and developmental processes affected by the disorder. Sociodemographic and parental and perinatal risk factors have been implicated during the preclinical phase, usually observed from the birth to infancy, childhood, and early adolescence. Additional later factors occurring during later adolescence and early adulthood can trigger the onset of attenuated psychotic symptoms, functional impairment, and help-seeking behavior, which constitute the CHR-P stage. The diagnosis of psychosis, which operationally corresponds to FEP, is usually made during the adolescence or early adulthood, with a peak at 15–35 years of age (38). Once diagnosed, psychosis usually follows a fluctuating course punctuated by acute exacerbation of psychotic crises superimposed upon a background of poorly controlled negative, neurocognitive, and social cognitive symptoms. The pink boxes represent the risk factors for psychosis as identified by a recent umbrella review (38). There is no assumption that these risk factors are of causal nature or that they are independent from each other. Furthermore, certain risk factors may actually represent outcomes of earlier risk factors. Figure based on the data reported in (22). CHR-P: clinical high risk for psychosis; FEP: first-episode psychosis. Adapted from (36), Creative Commons Attribution License (CC BY).

The type of recruitment strategies adopted will influence the level of risk of psychosis for these individuals. This level of risk is also defined as pretest risk (or prevalence) because it is ascertained in the whole group of people undergoing a CHR-P assessment before the results of the assessment itself are known (41). The relative increase in enrichment in this pretest risk, which is acquired through the recruitment step, is substantial (i.e., from 0.43 to 15%, ~35-fold higher). This pretest risk enrichment is also highly heterogeneous across different sites because it is unstandardized and not controlled for (32, 33, 42). For example, it is highest if recruitment targets secondary mental health care, intermediate if recruitment targets primary care, and lowest if it targets the nonhelp-seeking community (33). Clinical help-seeking samples who undergo pretest risk enrichment during the recruitment phase are then tested by specialized clinics (6). These clinics administer a comprehensive psychometric CHR-P assessment in the context of a clinical interview (43). Overall, a meta-analysis has confirmed that the prognostic accuracy of this CHR-P assessment is considered to be good (i.e., area under the curve at 38 months = 0.90, 95%CI 0.87–0.93) (7) and comparable to that of similar prognostic measurements employed in other areas of medicine (7). As illustrated in **Figure 3**, when help-seeking individuals presenting to a CHR-P service with a 15% pretest risk at 3 years are assessed (tested), those who meet CHR-P criteria will have a 26% risk of developing psychosis at 3 years (1.7-fold increase) and those who do not meet the

CHR-P criteria will have a 1.56% risk of developing psychosis at 3 years (10-fold decrease). However, these numbers indicate that the CHR-P tools can accurately predict the onset of psychosis (but not of other nonpsychotic mental disorders (11)) in samples who have been enriched in their risk for developing psychosis (7). If these tools are used to screen the general population, the pretest risk would be low, and even meeting CHR-P criteria would be associated with only a 5% risk of developing psychosis at ~3 years (24, 25). In other words, the overall accuracy of the CHR-P assessment is driven by a high power to rule out a state of risk for psychosis in samples that are risk enriched, but only a modest capacity to rule in a state of risk for psychosis (7).

These arguments clearly indicate that the CHR-P paradigm has the greatest utility when used to detect help-seeking populations that are accessing specialized clinical services (6). Intensifying outreach campaigns targeting the community would reduce the pretest risk and, in turn, dilute the prognostic accuracy of the CHR-P approach, thereby impeding effective preventive interventions. These considerations will be used to inform the detection approach proposed in the following sections.

Validity Of The CHR-P Paradigm As Universal Risk State For Psychosis

Most contemporary research on transitions from an at-risk state to FEP has been conducted with help-seeking individuals who are identified as being in CHR-P states. While this is undoubtedly valuable in its own right, there is emerging evidence that identification and intervention at the point of CHR-P currently detect only a small proportion of patients who eventually develop FEP (21). These findings dovetail with the sampling biases that characterize CHR-P studies (44) and, from a public health perspective, lead to the question of what proportion of FEP cases were in fact preceded by a CHR-P state.

The contemporary meta-analytical literature has revealed that reported risk of conversion from a CHR-P stage to FEP (29% at 2 years in 2012 (45)) has decreased internationally in recent years (20% at 2 years in 2016 (12)). However, this is not universal; for example, in South London, the risk of psychosis has remained stable over two decades (42). There is evidence suggesting that the decline in transition is linked to a change in recruitment strategies (42). Whatever the impact of recruitment strategies on the risk for psychosis onset, there is no evidence that the declining conversion rates in the most recent years have been matched by a similar change in the incidence of FEP (46–48). This implies that FEP cases passing through a CHR-P state are not being identified by existing CHR-P research and clinical infrastructures and/or that some individuals developed FEP without experiencing an identified preonset CHR-P state (19, 20). Congruent with this, it has been speculated that, in community samples, those who develop FEP may vary in their clinical backgrounds and outcomes to a greater extent than in those presenting to academic institutions (49).

First, the possibility that nonpsychotic risk syndromes could precede the first onset of psychosis has been demonstrated for some time and was recently summarized in a meta-analysis (17). Within prospective studies (n = 4, sample = 1,051), the pooled incidence of new psychotic disorders across these clinical risk syndromes was of 12.9 per 1,000 person-years. Within the same prospective studies, the incidence of common (nonpsychotic) disorders (n = 3, sample = 538) was of 43.5 per 1,000 person-years (95% CI: 30.9, 61.3) (17). The study concluded that nonpsychotic risk states may give rise to psychotic disorders, albeit at lower rates than in the CHR-P group (**Figure 5**).

Second, although the CHR-P state is not associated with an increased risk of developing new or emerging nonpsychotic mental disorders (10), at follow-up, many of them have other mental illnesses that were already present at baseline, in particular, depressive, anxiety, or substance-use disorders (50, 51). Since individuals at CHR-P often develop nonpsychotic disorders, it is also plausible that some individuals experiencing FEP had developed this without a prior CHR-P syndrome (i.e., without any past presence of subthreshold psychotic symptoms). Indeed, recently two retrospective cohort studies using different instruments each found a reasonably large subgroup of patients with FEP for whom there was no evidence of meeting prior CHR-P criteria for any identifiable length of time (19, 20). This cumulates to ~30% of the cases experiencing FEP (**Figure 6**).

Subsequent work has explored the longitudinal evolution of patients with FEP who did versus did not experience a preonset CHR-P stage. While there were no clinical or functional differences at baseline (entry to early intervention services) between patients with FEP with and without prior CHR-P states, such differences emerged after 1 year of early intervention services: those with preonset symptoms consistent with a CHR-P state had poorer psychotic symptom outcomes and global functioning (52). Furthermore, there is more frequent nonadherence to antipsychotic medication in the preonset/CHR-P state group (although without corresponding differences in insight) (53). Since this work involved retrospective assessments, it is possible that FEP cases without evidence of a preonset CHR-P phase exhibited a recall bias and that the true prevalence of symptoms consistent with a CHR-P state was substantially higher than measured. Nonetheless, it indicates that the CHR-P stage may not be the unique, universal clinical stage preceding the onset of psychosis. Therefore, to detect more individuals at risk for psychosis, it may be necessary to go beyond the CHR-P operationalization and to adopt a broader transdiagnostic approach (54) that cuts across psychopathological dimensions. For example, there is evidence that a first episode of schizophrenia-like psychosis can occur from depressive or bipolar disorders (22). This concept has informed the development of transdiagnostic risk calculators for this population, as detailed in the following section.

Improving The Detection Of Individuals At Risk In Secondary Mental Health Care

As noted in the introduction, most individuals accessing the mental health trust in South London who later developed psychosis were not detected at the time of their potential CHR-P stage. This happened in spite of the long-standing implementation of the local specialized CHR-P clinic, the OASIS (6) over the previous two decades, which was conducting an extensive outreach campaign. For example, the clinic uses a youth-friendly website to promote

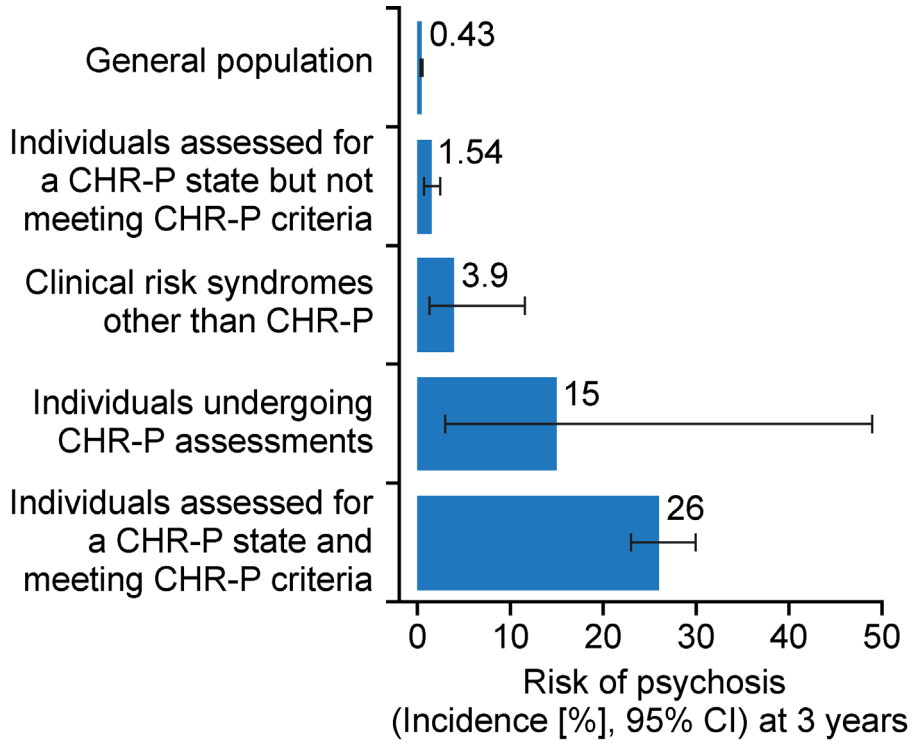

FIGURE 5 | Three-year risk of developing psychosis in different samples at risk. The incidence of psychotic disorders in the general population is significantly influenced by geographical, ethnical, environmental, and the diagnostic criteria of psychosis. However, it can be approximated at 0.43% at 3 years. Help-seeking samples that undergo a CHR-P assessment have a 15% risk of psychosis at 3 years. After the assessment is completed, those who do not meet the CHR-P criteria have a 1.54% risk of psychosis at 3 years, while those who meet the CHR-P criteria have a 26% risk at 3 years. Clinical risk syndromes other than psychosis have a 3.9% risk of psychosis at 3 years. New figure using data from (17, 36). CHR-P: Clinical High Risk for Psychosis.

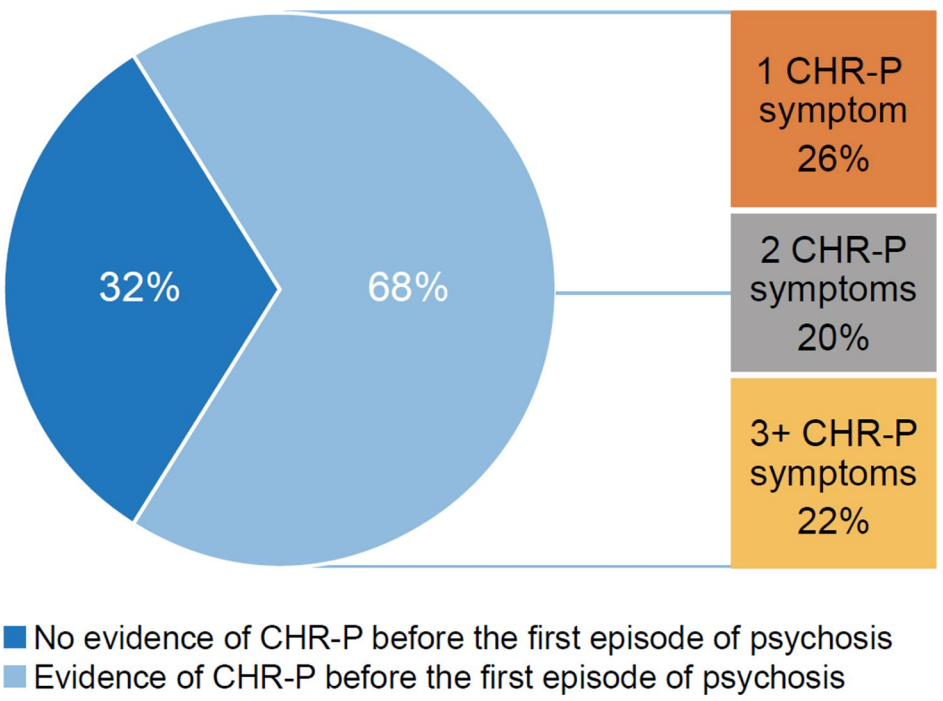

FIGURE 6 | Proportion of patients with first episode psychosis (FEP) who presented with subthreshold psychotic symptoms (consistent with a theoretical CHR-P stage) or not before developing FEP, retrospective analysis of medical records. CHR-P: clinical high risk for psychosis; FEP: first episode psychosis. New figure using data from (19).

help-seeking behavior and referrals (https://www.meandmymind.nhs.uk). As noted above, it is possible to estimate that up to two-thirds of these FEP cases developed their first onset of the disorder through a CHR-P like stage. As such, the majority of the individuals who developed psychosis would have been detected had these individuals been referred to the local CHR-P (OASIS) clinic. Importantly, all these young people were already under the care of a mental health team. As such, they clearly represent a window of missed opportunities for improving the detection of individuals at risk. Targeting this population would, therefore, be the most obvious first step towards improved detection of at-risk individuals. Within individuals in secondary mental health care, there is an incidence of psychosis of 3% at 6 years, which is higher than the risk of psychosis of 0.62 at 6 years in the local general population (22). The solution to this problem is not simple. One way would be to screen all patients accessing the local mental health trust using the existing CHR-P instruments. This option is logistically and financially unsustainable. The alternative may be to intensify outreach campaigns. However, as noted above (33), these are highly inefficient and dilute the pretest risk of psychosis and, consequently, the prognostic meaningfulness of meeting CHR-P criteria per se.

To overcome this substantial challenge, a clinically based, individualized, transdiagnostic risk calculator has been developed, which includes features that help improve the detection of individuals at risk for psychosis. First, this risk calculator has been externally validated twice: in South London and Maudsley NHS Trust and in Camden and Islington NHS Trust (14, 22, 55). External validation of prognostic models in psychiatry is infrequent (31). Second, this calculator could be applied to mental health trusts where there are no established CHR-P programs to detect patients at risk as in the Camden and Islington Mental Health Trust. Third, this calculator is low cost and simple to run because it uses 10th revision of the International Statistical Classification of Diseases and Related Health Problems index diagnoses (which is considered transdiagnostic because it allows several diagnostic spectra (54)), age, gender, age by gender, and ethnicity as key predictors, which have been selected on the basis of *a priori* clinical knowledge (31, 56). A recent version of the refined calculator that includes an advanced age predictor is also available (57). Fourth, the calculator is deliberately transdiagnostic and includes those meeting the CHR-P state as well as patients who might develop psychosis outside it, meaning that it can potentially detect the subgroup of patients who will go on to develop psychosis outside the CHR-P state. Fifth, the calculator can be automatized because it leverages electronic health records to screen secondary mental health care trusts. Therefore, it has great potential to be applied at scale, which is an essential prerequisite to improve the detection of patients at risk for psychosis. Sixth, the calculator is individualized, in that it provides prognostic outcomes at the individual subject level. This is a substantial advantage compared with the current CHR-P strategy, which is limited by group-level prediction, at risk or not at risk, with few exceptions such as the risk calculator by Cannon et al (58, 59). However, Cannon's risk calculator (58, 59) should be used only in individuals already meeting CHR-P criteria to predict their clinical outcomes; as such, Cannon's algorithm is not suited to improve the detection of individuals at risk in primary, secondary care, or in the community. Seventh, the transdiagnostic calculator can be further improved by the addition of more sophisticated predictors or by the stepped combination of sequential testing, which can improve prognostic accuracy in the CHR-P field (60).

This transdiagnostic risk calculator has been implemented in clinical care as part of an ongoing study funded by a Medical Research Council grant. Because external validation studies are rare, to our best knowledge, there are no other implementation studies of risk calculators for CHR-P patients. 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 (61). In fact, many more risk prediction models are published than are externally validated, and only a few of these are then implemented in the NHS (31). To achieve successful implementation, which is the true measure of a prediction model's utility, we carefully considered potential implementation challenges from the beginning of the model building 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 datasets that could be used for the external validation of existing models, a current gap in the implementation of risk prediction models in psychiatry. The implementation study protocol for this transdiagnostic risk calculator has just been published (14). As indicated in **Figure 7**, this pilot study comprises of two subsequent phases: an *in vitro* phase of 1 month and an *in vivo* phase of 11 months.

The *in vitro* phase does not involve patients or clinicians, and it 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. This pilot study is also the first to address the regulatory constraints that surround the automatic screening of electronic health-care records to detect patients at risk for psychosis [for a review, see (62)].

The study will be completed soon, and the results are expected over the next year. Should this study be successful, it will be followed by an effectiveness trial to test the real-world clinical and economic benefits of using this approach over standard care to detect patients at risk of psychosis in secondary mental health care. The complementary task would be to develop, validate, and implement risk calculators for the detection of patients at risk of psychosis in primary care, as highlighted in the following section.

Improving The Detection Of Individuals At Risk In Primary Care

In the UK, most people with psychosis enter specialist secondary care via referral from their primary care physician (63), and there

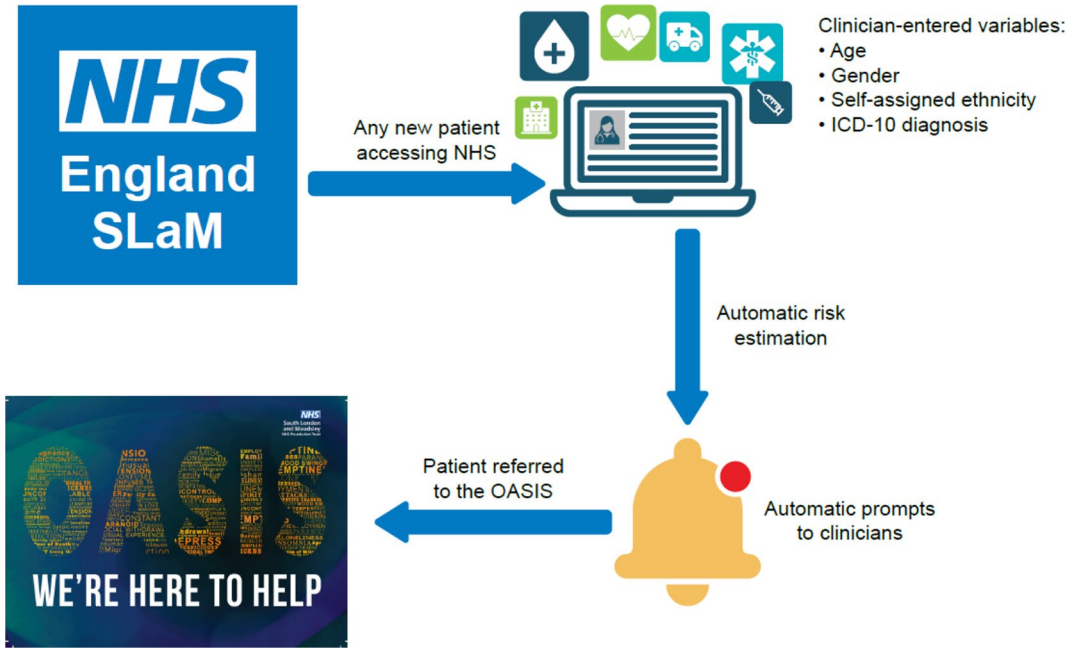

FIGURE 7 | Potential clinical use of the individualized, clinically based, transdiagnostic risk calculator in secondary mental health care. For any new patient accessing the local NHS Trust (South London and Maudsley, UK), clinicians will enter the predictors on the electronic case register, as part of their clinical routine. The calculator, embedded in the local electronic health record, would then use the predictors to estimate the individual risk of developing psychosis over time. This information would then be shared with clinicians through automated alerts, inform their decision making, and promote appropriate referrals to the local early detection clinic (OASIS). From (55), Creative Commons Attribution License (CC BY).

is some evidence that a shorter duration of untreated psychosis is associated with more primary care visits before diagnosis date (64). Primary care clinicians are therefore a vital part of the care pathway for people with psychosis, and it is consequently important that primary care clinicians can recognize a psychosis prodrome to expedite referral to specialist services for early treatment. Royal College of General Practitioners guidelines (65) stress the importance of detecting early signs and refer to some of the more common ones. There is evidence that the accuracy of psychosis diagnoses recorded on primary care electronic records is valid (66, 67), but there is also evidence that primary care physicians underidentify the more insidious symptoms (68). This is problematic because prodromal symptoms are frequently nonspecific and so may presage other health problems. In addition, most primary care physicians see very few new cases of psychosis per year and have little opportunity to increase personal experience in this area. There is also evidence (69) that there are barriers to referral for primary care when referring to specialist mental health services like CHR-P services. Therefore, there is a clear need for an accurate prognostic tool based in primary care. In line with the research program detailed above, it may be possible to use candidate predictors identified using clinical knowledge to develop and validate a prediction model based on primary care consultation data for nonpsychotic symptoms stored in electronic databases. Earlier studies (70) investigated the phases preceding psychosis, using a help-seeking general population sample from primary care consultation data collected before a diagnosis of psychosis and therefore unbiased by the presence of disorder. The sample used had a much larger number of cases ($n = 11{,}690$) than previous prospective studies. This method had the advantage of recording consultation events prospectively and should more accurately describe prodromal development. It was found that specific early behaviors and symptoms were strongly associated with a later diagnosis of psychosis, such as attention deficit hyperactivity-disorder-like problems, bizarre behavior, blunted affect, depressive-like problems, role functioning problems, social isolation, mania, obsessive–compulsive disorder-like problems, disordered personal hygiene, sleep disturbance, and suicidal behavior (including self-harm). The behaviors were cannabis use and cigarette smoking. The positive prognostic value of these behaviors and symptoms varied strongly with age and gender. There was also evidence of a pattern in consultation frequency per month for some of the prodromal behaviors and symptoms up to 5 years before diagnosis and evidence that people who are later diagnosed with psychosis are more frequent users of primary care services than those who do not develop psychosis. These findings can then be used to define candidate predictors for the development and validation of a psychosis detection and prediction model that can be used in primary care.

This research program is still ongoing, and the key methodological steps are summarized below. For the development and internal validation, we will conduct a population-based retrospective cohort study with a follow-up of ≥8 years. The Clinical Practice Research Datalink Gold (CPRD (71)) model will be used as a training dataset. CPRD Gold is a computerized database of anonymized longitudinal UK PC

records, which covers approximately 22 million patients who are representative of the general UK population regarding age, sex, and ethnicity (72). Validation studies (73) report that the quality and completeness of data are high. To ensure that the recording of outcomes is complete, the CPRD Gold dataset will be linked to the Hospital Episode Statistics (HES) database (74), which records secondary health-care events in the UK. All patients within CPRD without a coded diagnosis of a psychotic disorder before 2010, but who consult for any mental health problem (a diagnosis or symptoms) from January 1, 2010 until the date of most recent general practitioner (GP) practice data download. Each patient will be regarded as at risk of a psychosis diagnosis from the date of the first consultation for a mental health problem of any nature. The end date will be the earliest date out of either the date on which HES records confirm a diagnosis of psychosis, or the date of data download, or the date the individual leaves the general practice or dies, or the practice ceases to provide data for CPRD.

The candidate predictors identified from our previous work (70) are described above. The primary outcome is any coded diagnosis of a psychotic disorder from HES records. We estimate that a CPRD dataset of the records of 300,000 people will contain at least 695 psychosis diagnoses, which exceeds the recommended event-per-variable ratio for risk prediction models (31). We will use robust multivariable and modern estimation methods employing shrinkage (75) (including LASSO) for variable selection, to guard against overfitting, along with a clinical judgement. Model performance will be assessed with calibration and discrimination, using well-established statistical performance measures (76). Time-varying predictors such as consultations per month will be incorporated within a Cox model. Internal model validation will quantify the model's validity and the quality of predictors.

External validation will be conducted in the CPRD Aurum database linked to HES. GP practices included in CPRD Aurum only use EMIS primary care software for recording consultation data. Consequently, there is little or no overlap between the training and validation datasets. In internal model validation, calculations will be performed using bootstrap or cross-validation. In external validation, model performance measures will be calculated, and we will also report whether the prediction model is clinically useful using decision curve analysis to quantify the net benefit leading to an optimal decision threshold. Weighting of false versus true positive will be defined using clinician opinion (from the study team) and relevant literature (77). The final result will be a risk prediction algorithm—P risk (**Figure 8**).

Should this study be successful, it will lead to the next stage, which will be further external validation and pilot implementation of the P-risk algorithm in a live primary care setting. Following successful implementation, we would seek to test the effectiveness, cost effectiveness, and acceptability of P-risk using a randomized controlled trial design that would randomize a pop-up of the P-risk algorithm result to GPs and compare referral rates with GPs who do not receive the pop-up (see **Figure 8**).

Improving The Detection Of Individuals At Risk In The Community

An obvious avenue for extending the detection of emerging psychosis to the community is through electronic mental health approaches. A recent study by Birnbaum et al. (78) surveyed the use of internet and social media resources among patients with FEP. The majority of patients actively sought information regarding mental health issues online and had positive attitudes toward online interventions. Accordingly, these data provide support for the idea that wider identification of psychosis may benefit from digital detection strategies (79). This possibility was tested as part of the Youth-Mental Risk and Resilience Study (80), a cross-sectional study to identify neurobiological mechanisms and predictors of psychosis risk. Specifically, the study implemented an online-screening tool (http://www.your-study.org.uk), which consists of a web-based questionnaire (81) that utilizes the 16-item version of the Prodromal Questionnaire (PQ-16) (82) and a 9-items of perceptual and cognitive aberrations for the assessment of basic symptoms. Such an approach is essential to minimize the caveats discussed above. While it is not recommended to directly screen the general population through CHR-P assessment tools, this can become viable if the samples have undergone some previous risk enrichment before. Using the PQ-16 ahead of the CHR-P assessment tool fulfills these requirements. In line with this approach, participants were invited to the study website via email invitations, posters, and flyers to take part in a study on mental health problems (81). It is estimated that a population of 150,000–200,000 students were contacted. Cut-off criteria for further clinical assessments were 6 or more positively endorsed items on the PQ-16 based on previous data, suggesting a correct classification of CHR-P criteria based on Comprehensive Assessment of At-Risk Mental States (CAARMS) interviews with high sensitivity and specificity (82). For the perceptual and cognitive aberrations, a cut-off score of 3 or more positively endorsed items was selected (**Figure 9**).

Three thousand five hundred participants completed the questionnaire online over a 4-year period. Our previous analysis (81) had shown that ~50% participants fulfilled the PQ-16 cut-off criteria, while ~70% met criteria for the perceptual and cognitive aberrations. Approximately 20% of participants who met online cut-off criteria and were contacted attended clinical assessments to establish CHR-P criteria based on the positive scale of the CAARMS (3) as well as through items of the Schizophrenia Proneness Instrument (adult version). Approximately one-third of participants who met online cut-off criteria and who were interviewed met CHR-P criteria. Importantly, a subset of individuals (~5%) were also diagnosed with FEP and a substantial number of CHR-P participants had not received any intervention prior to the study. Receiver operating characteristic curve analysis revealed good to moderate sensitivity and specificity for predicting symptoms consistent with a CHR-P status based on online results for both CAARMS and Schizophrenia Proneness Instrument criteria (adult version) (sensitivity/specificity: PQ-16 = 82%/46%; perceptual and cognitive aberrations = 94%/12%) (81). To examine the possibility of improving the specificity of the online screening tool, we implemented a machine-learning

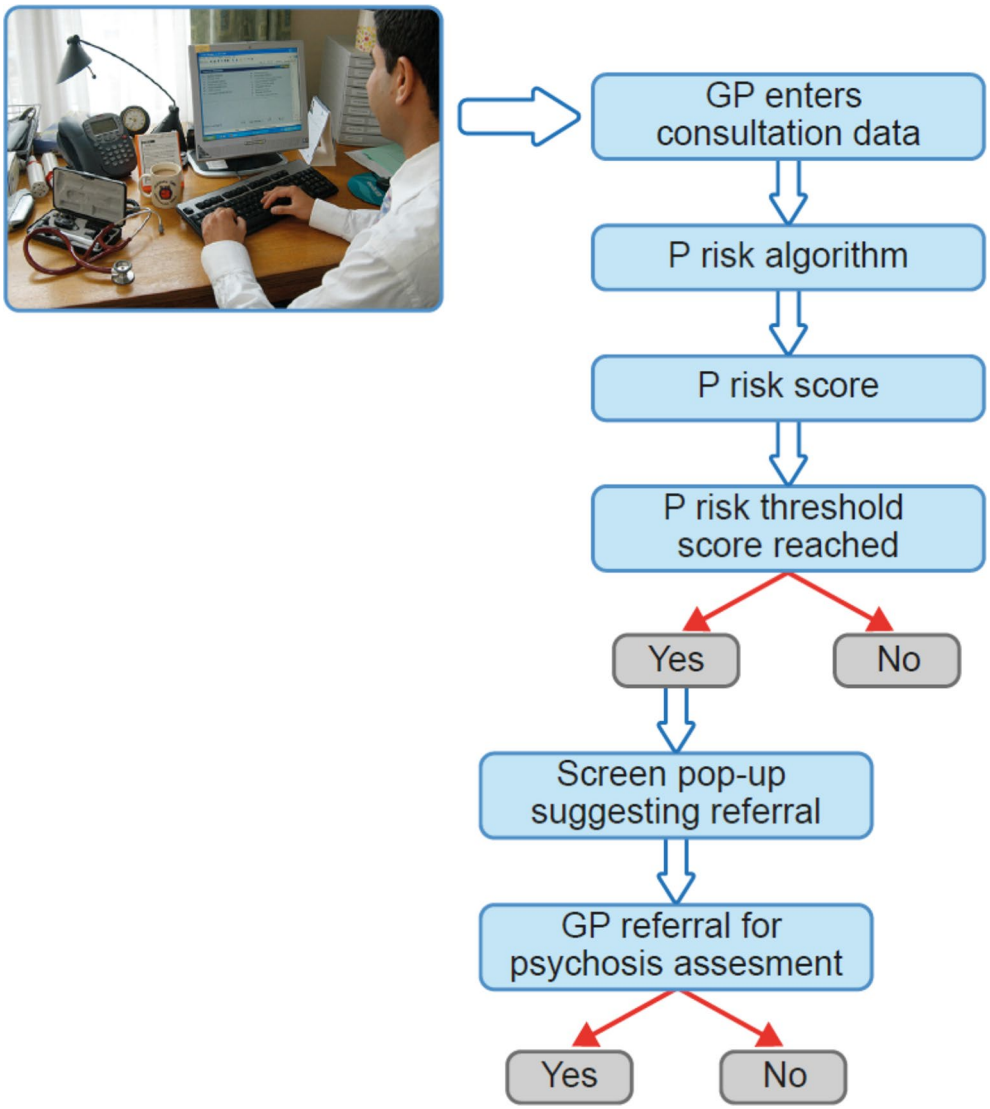

FIGURE 8 | P-risk psychosis risk prediction algorithm operating on primary care data systems. New figure.

approach that selected all 25 items from both the PQ-16 and the perceptual and cognitive aberrations in addition to demographical variables. Selection of a subset of 10 items from both PQ-16 and perceptual and cognitive aberrations that included familial risk lead to an improved specificity of 57% while only marginally affecting sensitivity (81%).

These data provide the first evidence for the feasibility of using a digital detection tool to identify emerging psychosis in the community. However, several refinements are needed to improve this approach, in particular in regard to the specificity/sensitivity of the screener. This can be achieved, for example, by adding known risk factors for the development of psychotic disorders (21, 55) that can be efficiently integrated into a web- or app-based screening. Some members of our team are currently working on this line as part of a recently funded Wellcome Trust grant. Specifically, the online assessment will be complemented by the sequential use of the recently developed Psychosis Polyrisk Score (PPS, **Figure 10**). The use of the PPS can be particularly suited to detect those individuals who may be at risk of developing psychosis outside the CHR-P stage, as indicated above.

Sequential Risk Assessment

The PPS leverages recent findings indicating that risk enrichment in CHR-P samples is accounted for by the accumulation of nongenetic factors such as parental and sociodemographic risk factors, perinatal risk factors, later risk factors, and antecedents (22). Examples of these risk factors are illustrated in **Figure 10**. The PPS additionally incorporates new meta-analytical evidence implicating specific risk factors that predict the onset of psychosis within CHR-P samples (83). The concurrent assessment of several demographic and environmental risk factors for psychosis may appear logistically unviable in clinical practice. However, it would be facilitated by a sequential testing

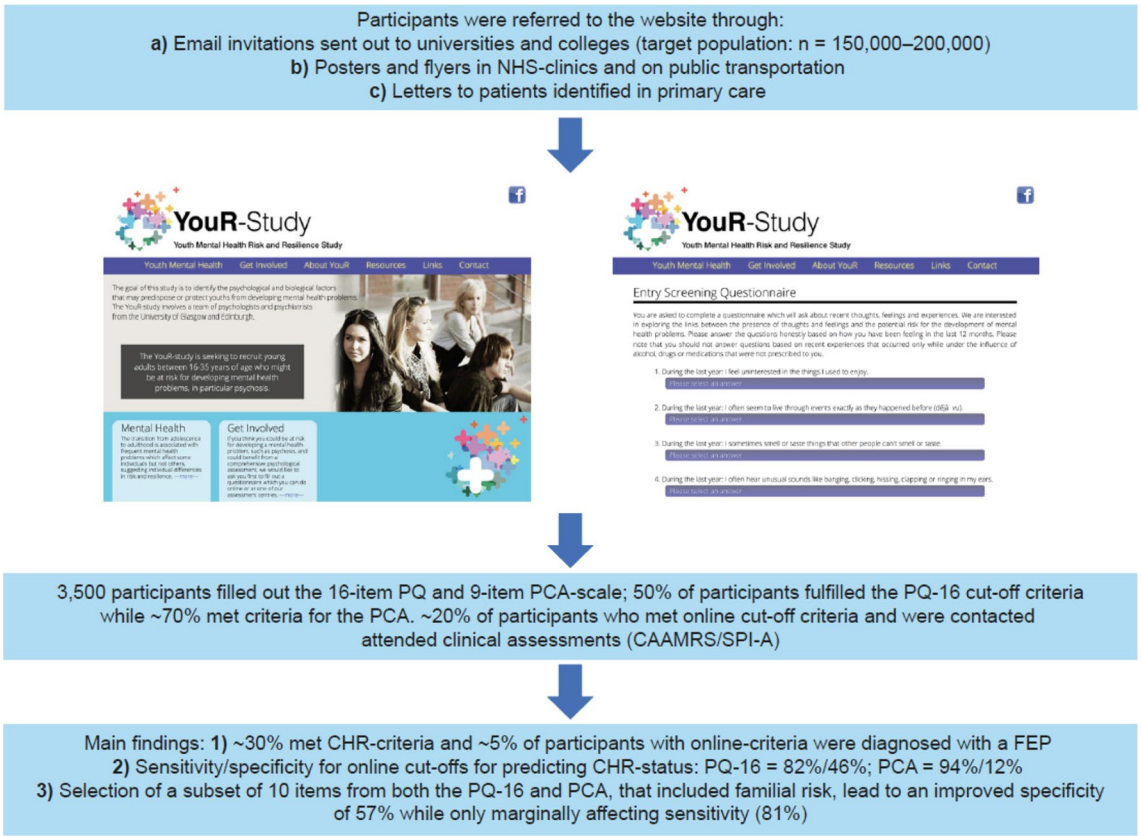

FIGURE 9 | e-Health strategy to improve the detection of individuals at CHR-P in the community. CAARMS: Comprehensive Assessment of At-Risk Mental States; CHR-P: clinical high risk for psychosis; FEP: first episode psychosis; PCA: Questionnaire of Perceptual and Cognitive Aberrations; PQ-16: 16-item version of the Prodromal Questionnaire; SPI-A: Schizophrenia Proneness Instrument. New figure.

procedure (60). For instance, all demographic and parental risk/protective factors, as well as some environmental (urbanicity, winter/spring season of birth) and later risk factors (adult life events, tobacco use, cannabis use, childhood trauma, traffic) can be self-administered or automatically extracted from electronic medical records or from geolocating applications that capitalize on recent e-health advancements (79). For the individuals whose predicted polyrisk of psychosis is over a certain threshold, a clinical comprehensive PPS assessment can be performed in a sequential fashion (60). Such an assessment may involve more accurate testing to collect the remaining risk factors: blood sampling to assess the exposure to infective agents and to estimate the polygenic risk, consulting obstetric records, or by interviewing the patients' relatives and clinical interviews. Such an approach would additionally allow incorporating a dynamic assessment framework, which may better reflect the fluctuating course of the disorder. In line with these arguments, the e-detection tool that will be developed by this program could also incorporate behavioral data obtained through mobile phones, which could add important dimensions to the characterization of cognitive and behavioral deficits of participants at CHR-P. There is consistent evidence that cognitive functions, such as processing speed, are a core dysfunction of emerging psychosis (84), which could be assessed through digital phenotyping (85). In this context, there is also data evidence that speech analysis can be used to identify emerging psychosis that could be potentially an additional domain for a digital phenotyping approach (86, 87).

Digital detection of emerging psychosis in the community also faces several challenges; the most important is the significant prevalence of subthreshold psychotic experiences in the general population (49, 88). There is a significant phenomenological and clinical difference between subthreshold psychotic symptoms that are self-reported by youths in the general populations as opposed to the symptoms disclosed by youths who are accessing CHR-P services and undergoing a clinical interview (for details, see (8)). As noted above (33), these differences are likely to be associated with different level of pretest risk enrichment and, as such, with differential prognostic outcomes. Accordingly, future studies are needed to understand the ethical implications and establish the long-term outcomes of CHR-P populations recruited from the community through the use of prescreening e-health methods. Nonetheless, while these are important challenges to overcome, in the modern digital world, it is likely that e-health approaches such as the one presented here will have an increasing role to play in the future for the detection of emerging psychosis. This could be particularly true if these approaches are combined with complementary strategies targeting secondary and primary care.

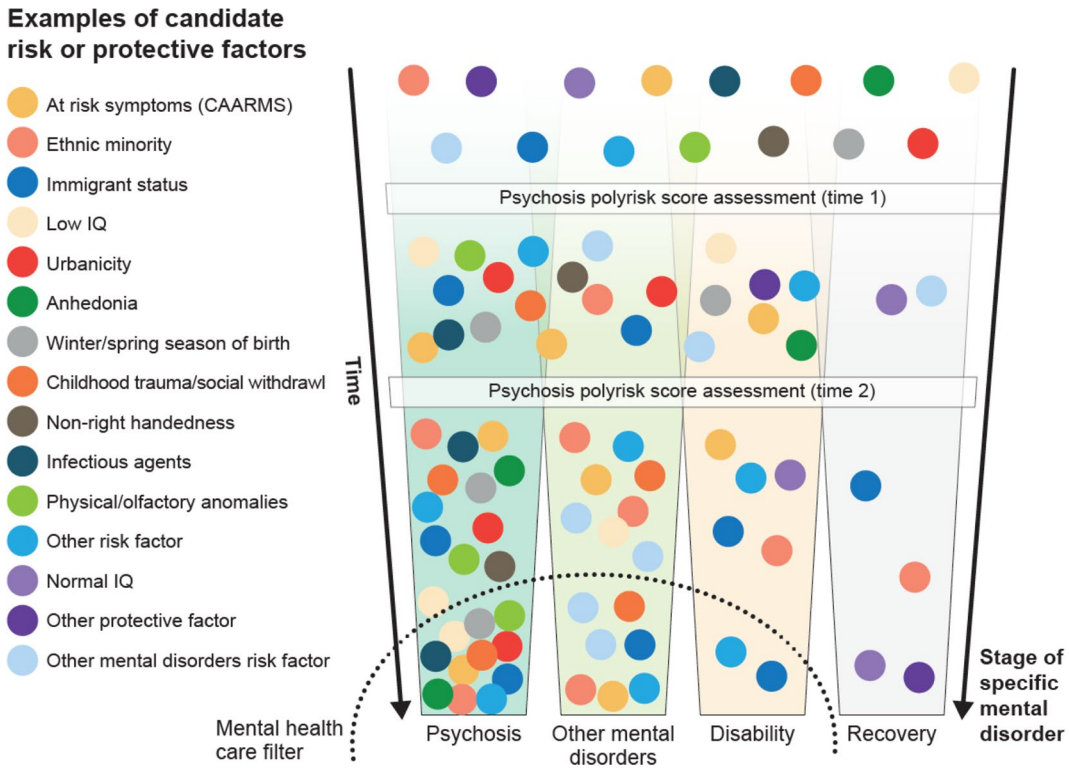

FIGURE 10 | Putative Psychosis Polyrisk Score (PPS) assessment for the detection of at-risk individuals and the prediction of psychosis. Risk or protective factors that have been selected through umbrella reviews (38) are diluted during the preclinical stages but may accumulate as the individual progresses across different stages, until they trigger signs or symptoms and functional impairment that are associated with help-seeking behavior and access to mental health care. In the later stages, specific aggregations of risk and protective factors may be associated with specific clinical outcomes. Adapted from (36), Creative Commons Attribution License (CC BY).

CONCLUSIONS

CHR-P instruments can provide reliable prognostic outcomes when they are employed in samples that have undergone risk enrichment during their recruitment. However, this enrichment substantially limits their detection power. Furthermore, there is evidence that psychosis onset may partially occur without a prior CHR-P stage and that nonpsychotic clinical risk states can precede FEP. To overcome these caveats, it is necessary to implement a clinical research program that integrates different but complementary detection approaches. A transdiagnostic individualized risk calculator could be used to automatically screen secondary mental health care to detect those at risk of psychosis and refer them to standard CHR-P assessment. Similar risk estimation tools for use in primary care are under development and promise to boost the detection of patients at risk in this setting. To improve the detection of young people who may be at risk of psychosis in the community, it is necessary to adopt e-health and sequential screening approaches that have been developed and are under refinement. These solutions are based on recent scientific evidence and can be potentially implemented into different contexts. Future research will test the cost effectiveness of these strategies, compared with current standards.

AUTHOR CONTRIBUTIONS

PF-P has conceived and led the study under the supervision of PU; PF-P, SS, JS, and PU wrote the initial draft of the manuscript, which was then collaboratively revised and approved by all authors.

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Integrated Programs for Early Recognition of Severe Mental Disorders: Recommendations From an Italian Multicenter Project

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The onset of mental disorders often occurs in adolescence or young adulthood, but the process of early diagnosis and access to timely effective and appropriate services can still be a challenge. The goal of this paper is to describe a pilot case of implementation of the ultra-high-risk (UHR) paradigm in six Italian departments of mental health employing an integrated approach to address clinical practice and service organization for youth in a broader preventive perspective. This approach entailed the integration of the UHR paradigm with a service provision model which prioritizes prevention and the promotion of local community coalitions to improve youth service accessibility. The multicenter Italian project "Integrated programs for recognition and early treatment of severe mental disorders in youths" funded by the National Centre for Disease Prevention and Control (CCM2013 Project) implemented in three Italian regions will be described. As a result of synergic actions targeting accessibility of young individuals to innovative youth mental health teams, a total of 376 subjects aged 15–24 years were recruited by integrated youth services within 12 months. Subjects have been screened by integrated multidisciplinary mental health youth teams employing standardized procedure and evidence-based clinical assessment instruments for at-risk mental states in young subjects [e.g., Comprehensive Assessment of At-Risk Mental States (CAARMS)]. Considering the three UHR categories included in CAARMS, the percentage of UHR subjects was 35% (n = 127) of the sample. In conclusion, future strategies to improve the organization of youth mental health services from a wider preventive perspective will be proposed.

Keywords: at-risk mental state, psychosis, ultra high risk, early intervention, transition, prevention strategies, community coalitions

CRITICAL ISSUES IN IMPLEMENTING THE "ULTRA-HIGH-RISK" AND THE "TRANSITION" PARADIGM IN ROUTINE CLINICAL PRACTICE

Over the last 25 years, a significant number of studies focused on the early detection and intervention for severe mental disorders. The onset of psychosis often occurs in adolescence or young adulthood, and the process of early diagnosis and access to timely effective interventions is still a challenge for mental health services. In the last decades, several clinical criteria have been identified with the aim to detect in youths the occurrence of a clinical high-risk state for psychosis as possible prodromal phase of psychotic disorders, including several labels as ultra-high-risk (UHR), clinical high risks (CHR), or at-risk mental states (ARMS) (1).

The UHR and transition paradigm involves specific criteria (extensively applied in numerous countries) to diagnose the UHR in help-seeking individuals (2–4). Inclusion requires the presence of one or more of the following: attenuated psychotic symptoms (APSs), brief limited intermittent psychotic episodes (BLIPs), trait vulnerability, schizotypal personality disorder plus a marked decline in psychosocial functioning [genetic risk and deterioration syndrome (GRD) and unspecified prodromal symptoms (UPSs)] (1).

The basic assumption for the UHR and transition paradigm is that it is possible to identify people who are at risk and in need of preventive interventions by applying a binary diagnostic category (psychosis risk vs. no psychosis risk) in young help-seeking individuals. In those subjects, the transition to psychotic disorders is clinically significant, with studies showing transition rates of 15–20% after the first year, and of 30% after 3 years (4). Consequently, according to the "Clinical Stage Model" (5), evidence-based interventions aimed at promoting the recovery process targeting a specific stage of the disorder (e.g., APSs) and to prevent the progression towards the following stages (e.g., first psychotic episode) should be provided (6–8).

Recently, alternative transdiagnostic perspectives have been presented (9–12). The concept of "at-risk mental states" can be conceived as a cue of wider and more general transdiagnostic psychological distress and vulnerability and psychotic experiences observed in youth as markers of the severity of multidimensional psychopathology rather than a binary psychosis risk criterion (9, 10). Epidemiological studies, in fact, showed that APSs as well as psychotic experiences are closely associated with non-psychotic disorders and/or sub-diagnostic non-psychotic psychopathology (13, 14).

An updated view for planning youth mental health services should embrace a wider perspective focusing the full range of person-specific psychopathology (9) in young subjects with emotional distress. Therefore, widening the concept of "at-risk mental state" with the aim of identifying risk and protective factors for youth mental health, and promoting access of young subjects to mental health services could be the line of action. Accordingly, beyond assessing the binary risk of psychosis, young individuals should be viewed as targets for wider secondary prevention strategies, also aimed at reducing stigma and improving access to innovative youth mental health services.

In Italy, adult and child–adolescent mental health services are strictly age-based and show a low level of integration. The activities of both services focus on patients outside the critical age range of 14–25. Child–adolescent mental services employ the majority of their resources on patients with neurodevelopment disorders and learning disabilities, whereas adult mental health services are much involved in the treatment and rehabilitation of severe and persistent mental disorders. In terms of prevention, a number of projects in the area of early detection and intervention of the psychosis onsets have been implemented in Italy (15, 16). From the national survey promoted by the *Associazione Italiana per la Prevenzione delle Psicosi* (16), the national diffusion of the model of Early Intervention in Psychosis can be estimated between 20% and 45%, with a higher diffusion in Northern and Central Italy than in Southern Italy and the Islands. However, all those projects are focused on early detection of psychosis and not on prodromal symptoms and UHR conditions in help-seeking youth.

Despite clear national and regional programmatic indications to improve primary and secondary prevention actions through the identification of at-risk conditions in youth (Mental Health Action Plan 2013–2020, Italian Ministry of Health), the development of multicentric standardized actions focused on UHR assessment as well as to services' accessibility is still not frequent within the mental health Italian system. Moreover, recent findings (17, 18) show that, in Italy, yearly treated prevalence was the lowest for people aged 18–24 and that accessibility to public mental health services should be increased for people below 30 years in order to improve early-psychosis outcome.

The aim of this paper is to describe a pilot case of implementation of youth mental health services within the Italian framework according to three key elements: 1) enhanced secondary prevention-oriented actions including the screening of at-risk mental states in young subjects through standardized procedures and instruments; 2) higher services' accessibility of young individuals with sub-threshold symptoms with specific attention to vulnerable or at-risk groups; and 3) the establishment of youth mental health teams with high level of integration between the adult and child–adolescence mental health services.

THE CCM2013 PROJECT: A PILOT IMPLEMENTATION OF THE HIGH-RISK PARADIGM WITHIN ITALIAN COMMUNITY SERVICES

Aims

The Italian project "Integrated programs for recognition and early treatment of severe mental disorders in youths" was funded by the National Centre for Disease Prevention and Control (CCM2013 Project). The project aimed at implementing the UHR paradigm in six departments of mental health in Italy (sited in Lombardy, Liguria, and Tuscany) developing an integrated approach to address clinical practice and service organization for youth in a broader preventive perspective. Specifically, the project's goal was

the integration of the traditional UHR paradigm with a service provision model which prioritizes prevention and the promotion of local community coalitions (19). Community coalitions are participatory models of intervention aimed at mobilizing people to promote community health in several domains, including mental health (20). Community prevention coalitions are formal, long-term collaborations composed of diverse non-institutional organizations (e.g., schools, ethnic and religious associations) aiming at developing effective prevention programs to promote adolescent health and well-being (21).

The CCM2013 Project intended to put into practice the national programmatic indications (Mental Health Action Plan 2013–2020, Italian Ministry of Health) to promote the accessibility to services and the preventive screening of young adults and adolescents. Its aims included to ensure effective evidence-based clinical assessment of ARMS in young subjects (15–24 years old) and to encourage youths' participation in different community organizations through the Community Coalition model (19). Moreover, it aimed at improving the integration between child–adolescent and adult mental health services through the creation of integrated and multidisciplinary youth mental health teams (22).

Implementation Actions

The implementation of the prevention-oriented model involved specific actions and organizational changes as follows. Multidisciplinary youth mental health teams integrating various child, adolescent, and adult mental health professionals were created (Integrated Youth Teams) thus promoting cooperation between services. All team members (psychiatrists, psychologists, social workers, etc.) were trained in the detection of risk for developing serious mental disorders. New locations have been identified and used in order to offer attractive and low-stigmatizing physical environments to young individuals accessing to the Integrated Youth Teams. Those locations were separated from the routine mental health service sites and hospitals, and possibly located near public areas visited by young individuals (e.g., parks, schools). Attractive signs with creative names indicating those sites were created. Locations were provided with modern non-medical furniture.

Local community coalitions were activated, aiming at promoting early referral to appropriate services and inclusive pathways for young people experiencing mental distress (20–22). Community coalitions involved different stakeholders (associations, schools, religious and ethnic organizations, family doctors and general practitioners, etc.) among which members of community coalitions' coordination boards were selected. The boards, after receiving specific training sessions on youth mental health, implemented local initiatives aimed at raising awareness on mental health and at reducing stigma in young individuals (e.g., information day inside schools and associations, art exhibitions focused on mental health in youth, online initiatives, etc.). Actions aimed at favoring accessibility for vulnerable youth groups were implemented, e.g., public events in cooperation with ethnic associations aimed at increase awareness on youth mental health. Local coalitions fostered the integration between youth mental health teams and community stakeholders in order to promote rapid and effective referral pathways.

During 12 months, help-seeking subjects aged 15–24 years have been recruited in six mental health departments within three Italian regions. Enrollment criteria for the UHR assessment have been designed in order to include as many young subjects as possible from the age of 15–24 presenting emotional distress and a wide range of psychological difficulties. Cutoff scores of the clinical assessment instruments were not required as inclusion criteria. Exclusion criteria for the UHR assessment were: age not included in the range 15–24 and the presence of mental retardation (IQ score less than 80).

Procedure and Instruments

Patients' referral to the project occurred through diversified ways: first, young subjects could be referred from the community coalition stakeholders (including family doctors and pediatricians); second, patients could be referred from other mental health services; third, they could have direct access to the project. Similarly, members of the community coalition boards could discuss referral cases during their meetings in order to identify adequate strategies to support young subjects and to help them contacting the Youth Integrated Teams. After obtaining informed consent, the assessment procedure started within maximum 3 working days.

Subjects have been assessed using a standardized procedure and clinical instruments validated to assess ARMS conditions. The following self-report questionnaires have been used: the Italian version of General Health Questionnaire-12 (GHQ-12), which is a 12-item self-report questionnaire used for identifying minor psychiatric disorders (23), and the Italian version of the Prodromal Questionnaire-16 (PQ-16), which includes 16 self-reported items screening for the risk of psychosis (24, 25). A psychotherapist and/or a psychiatrist (adequately trained to administer the CAARMS instrument) administered the Comprehensive Assessment of At-Risk Mental States (CAARMS) to assess at-risk mental states and prodromal conditions (26). Moreover, Global Assessment of Function (GAF) (27), Social and Occupational Functioning Assessment Scale (SOFAS) (28), and Health of Nation Outcome Scale (HoNOS) and Health of Nation Outcome Scale for Children and Adolscents (HoNOSCA) (29) were used as measures of the health and social functioning of patients.

The assessment regularly involved an integrated multidisciplinary team of mental health professionals, consisting in psychiatrists, psychologist–psychotherapists (with a minimum of 3 years of clinical practice experience and qualified on UHR assessment), social workers, and nurses. Subsequently, clinical meetings between the mental health professionals were routinely scheduled to identify UHR subjects and to define the type of intervention to recommend (e.g., cognitive–behavioral psychotherapy protocols, and/or pharmacological treatments, social skills training, etc.). However, the project's main focus was at the screening level of UHR conditions; in fact, the project's aims did not involve any monitoring of treatment outcome for empirical research purpose.

After the assessment, subjects could be referred to different patterns of care, from the Integrated Youth Team, to the activation of specific supportive interventions with the community coalition board or the routine clinical treatment at standard mental health services (e.g., young patients that not satisfied the UHR criteria).

Interventions were provided within maximum 2 weeks without any waiting list, according to the Clinical Stage Model (5) and prioritizing psychotic onsets.

Regarding the control quality of the organizational setup, the whole implementation process was monthly monitored by each center. Progresses were registered into the project monitoring forms and reported to the funding authorities each semester. Reports included information regarding actions implemented to promote the accessibility and attractiveness of locations, number and contents of Integrated Youth Team clinical review meetings, etc. In terms of quality control of the community coalitions' actions, projects' inspectors monitored through semestral reports and in-site visits the number and contents of community coalition board meetings, types and number of events organized, and procedures implemented to increase awareness and promote accessibility of vulnerable youth groups.

Each semester, monitoring visits were performed to verify and ensure that all the centers were implementing coordinated actions consistent with projects' aims. Continuous training and group supervision meetings (every 2 months) with youth mental health experts were organized in order to guarantee the quality of the clinical assessments.

Results

The proposed prevention-oriented clinical model was developed in all participating centers. This implied a change in the way young patients were identified and assessed. Moreover, through the promotion of local community coalitions, an innovation in the implementation of prevention-oriented programs was introduced. In fact, in all participating centers, local community coalitions were promoted. All community boards spontaneously performed at least one local action in the field of mental health promotion and/or mental health stigma prevention. They took an active role in connecting vulnerable youths with formal and informal help resources by activating and supporting their social networks and families.

The main results of this project consisted in the implementation of the actions described in the previous section. In order to provide a figure of the recruitment and UHR assessment phase, concise data will be presented. During the recruitment phase (from April 2015 to April 2016), 376 participants were referred. Twelve of them dropped out as they did not show up after first contact. Finally, 364 subjects were fully assessed. Participants were equally distributed in terms of gender (53% females). With respect to the age range (mean = 19.3; SD: ± 2.5), 29% of the patients (n = 105) were 15–17 years old, 48% (n = 175) were 18–21 years old, and 23% (n = 84) were 22–24 years old. Using the criteria defined by the CAARMS, 59% of the patients (n = 215) showed no vulnerability, 21% (n = 76) presented a degree of vulnerability (e.g., state/trait vulnerability, schizotypal personality disorder, −30% of SOFAS score), 13% (n = 47) showed Attenuated Psychotic Syndrome (APS), 1% (n = 4) were classified as Brief Limited Intermittent Psychotic Syndrome (BLIPS), and 6% (n = 22) were diagnosed with psychosis. Considering the three UHR categories included in CAARMS, the percentage of UHR subjects was 35% (n = 127) of the sample.

This sample of young people identified as UHR through the assessment implemented by the 2013 CCM Project was subsequently monitored by mental health service providing evidence-based interventions. The project did not plan modifications of the patterns of care of the local services. No follow-up evaluation of the recruited subjects was programmed, and no action to change psychological or pharmacological treatment or risk assessment was implemented. The local treatment guidelines and clinical experience were followed.

The absence of a control group to compare these data to previous results collected in the Italian mental health systems is a major limit of the present work. The project, however, aimed at implementing best available practices in the field of youth severe mental illness prevention by a strategical change in service provision. Institutional funding objectives did not include determining whether the implemented changes effectively improved the cohort outcome. This crucial question should be answered by further investigations. On the other hand, evidence of successful implementation of the model was simply the realization of the proposed actions ending in the recruitment and care of a relevant cohort of help-seeking youths.

FUTURE STRATEGIES

The prevention-oriented model with integrated community coalitions proved transferability to Italian services. In fact, the CCM2013 Project integrated in routine mental health services the high-risk paradigm with a public health perspective focused on a wider concept of youth mental health and secondary prevention through the application of the Community Coalition model (19).

According to this perspective, the preventive approach had been implemented at two levels. Inside the mental health services, specific actions to improve clinical assessment of young patients have been promoted. Outside the mental health services, local community coalitions have been developed to raise awareness of youth mental health, to reduce stigma, and to take responsibility for improving communities' ability to deal with the social problems related to youth mental illness (i.e., school dropout or early school-leaving, social withdrawal). Moreover, low-stigmatized and appropriate locations detached from the main adult mental health services as well as from the child services have been implemented to improve access and help-seeking behaviors in young general population.

The major limit of the CCM2013 Project resides in the lack of assessment of the efficacy of the implementation actions, without providing empirical evidence showing the increased mental health service accessibility for youth. Future research studies should include specific evaluation procedures and outcomes, as well as control groups to verify the efficacy of the integrated multicentric actions aimed at promoting service accessibility in young populations.

However, the above described perspective is in line with the principles of youth service transformation presented by Malla and colleagues (30), aimed at promoting early and simplified access to multidisciplinary services for young people presenting with a wide range of mental health problems. Similarities between Italian CCM2013 Project and other worldwide programs may be highlighted. An example is the Headspace Youth Psychiatry Program, implemented through different centers across Australia, aiming at widening the accessibility of young individuals from 12 to

25 years experiencing mental distress, involving multidisciplinary mental health teams and solid online support programs (31).

Further, the project's limitations should be acknowledged: first, the temporal stability of the organizational changes adopted and, in particular, of the integration of child–adolescent and adult mental health services; second, the transferability of the model to the whole Italian country, given the relevant regional differences in mental health policies and funding; and third, the project did not contemplate efforts to create strong online communication strategies.

Despite these limitations, some recommendations were further developed to improve youth mental health programs targeting young subjects with serious mental illness in Italy. Several actions can be advised: i) strengthen at a large scale the promotion of community coalitions to encourage the detection of signs and symptoms of mental distress and vulnerability in young subjects; ii) designing actions to facilitate accessibility and attractiveness to services to youth groups in general and with elevated risk for severe mental illness; and iii) creating established integrated child–adult mental health. Future directions should focus also on developing a user-friendly online platform and online support resources to improve youth's accessibility to mental health prevention strategies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

Local ethic committees' approval was not required as per the Italian legislation. The project was approved and funded by the National Centre for Disease Prevention and Control and supported by the Lombardy Region. The CCM2013 Project was an implementation project aimed at transferring best clinical practices into routine mental health care. Thus, patients' data were only gathered for clinical and not for research purposes. Specific written informed consent was obtained from each recruited subject or from his/her parents if under age.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Compensatory Cognitive Training for Latino Youth at Clinical High Risk for Psychosis: Study Protocol for a Randomized Controlled Trial

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Background: Early psychosocial interventions targeting cognitive and functional outcomes in individuals at clinical high risk for psychosis are a research priority. An even greater need is the identification of effective interventions in underserved populations. Compensatory Cognitive Training (CCT) is a psychosocial intervention with demonstrated efficacy in chronic schizophrenia and first episode psychosis, but remains to be evaluated in pre-illness phases. The aim of this study was to describe the development and implementation of an ongoing pilot randomized controlled trial investigating the efficacy of group-based, manualized CCT, as compared to recreational therapy (RT), for Latino participants at clinical high risk for psychosis (CHR) in both the United States and Mexico. It is hypothesized that, in comparison to those receiving RT, participants receiving CCT will show significant improvements in neurocognitive performance and functional capacity (co-primary outcomes) and self-rated functioning and clinical symptoms (secondary outcomes).

Methods: Latino CHR participants aged 12–30 years will be included in the study. Both CCT and RT will be delivered in either Spanish or English, depending on group preference. Additionally, all assessments will be administered in participants' preferred language. A comprehensive assessment of neurocognitive and functional performance and clinical symptomatology will be performed at baseline, mid-intervention (4 weeks, 8 weeks), post-intervention (12 weeks) and 3-month follow-up. The primary outcome measures are neurocognition and functional capacity, as assessed by the MATRICS (Measurement and Treatment Research in Cognition in Schizophrenia) Consensus Cognitive Battery and the University of California, San Diego Performance-Based Skills Assessment-Brief, respectively. Furthermore, secondary outcomes measures will be used to examine change in clinical symptoms and self-reported functioning in response to CCT versus RT.

Discussion: The evaluation of a novel treatment such as CCT in CHR youth will provide empirical support for a low risk, comprehensive cognitive intervention that could have important implications for public health if it improves neurocognition and functioning.

Keywords: cognition, attention, memory, executive functioning, rehabilitation, schizophrenia

INTRODUCTION

Recent efforts to extend medical prevention models to the field of schizophrenia have resulted in systematic, reliable identification of individuals who are at clinical high risk (CHR) for imminent onset of psychosis (i.e., putative prodromal psychosis) (1, 2). Compared to psychotic disorders, the symptoms of psychosis-risk syndrome are less severe and more transient. Symptoms are not longstanding trait-pathology, but rather present as a marked change in individual's mental state, evidenced through report from self and concerned others. Specific subtypes of the psychosis-risk syndrome are identified through formal structured clinical interview and are differentiated through individual risk factors. Broadly, risk factors for psychosis-risk syndrome include presence of: attenuated positive symptoms, negative symptoms, cognitive impairment or cognitive decline, decline in social, and/or role functioning, as well as family history of psychosis (3, 4). Diagnosis of a psychosis-risk syndrome requires that symptoms are associated with functional impairment and/or distress and of recent onset or worsening.

Findings from the North American Prodrome Longitudinal Study (NAPLS) have established that within the first 1–2 years after formal identification of being at CHR for psychosis, 20–40% of individuals go on to develop an acute psychotic illness (3, 5, 6). Despite advances in the early identification of individuals meeting CHR criteria, there is significant need for effective interventions that can be implemented early in the course of illness to improve symptoms and functional outcomes, especially considering that the strongest predictors of conversion to psychotic illness include modifiable risk factors such as prodromal symptom severity (as measured through structured interview), declines in social functioning, as well as verbal learning and memory deficits (6). Namely, there is a need for interventions that target the emerging neurocognitive (7–9), information processing (10–12), social, role, and global functioning deficits (13, 14) that characterize the prodromal period of illness. Not only are these early deficits disruptive to normal development and life trajectories, but they are also predictive of later conversion to psychotic illness (6, 15).

Antipsychotic medication, although effective in controlling positive symptoms, does not ameliorate cognitive deficits (16), nor has it shown any effects on conversion in randomized clinical trials (17, 18). Moreover, ethical concerns regarding exposing young people to psychotropic agents when less than half (~35%) are expected to convert to psychosis (19, 20) further support "staging" the prodromal period much like other medical illnesses (e.g., cancer, diabetes) and using less invasive treatments (psychosocial, education) for the early stages. Neurocognitive deficits are present across all identified stages of the CHR state and remain relatively stable, even during symptomatic remission upon illness onset (21). As such, an individualized, low risk treatment algorithm that focuses on neurocognition and functioning, in addition to the presenting subsyndromal psychotic symptoms, is a logical intervention strategy for this phase of the illness.

To date, there have been a limited number of randomized controlled trials analyzing the effectiveness of various psychosocial interventions in CHR, such as cognitive behavioral therapy (CBT), family focused therapy (FFT), or cognitive remediation (5, 22–24). Meta-analyses of psychosocial treatment effects on attenuated psychotic symptoms and negative symptoms yielded no statistically significant treatment effects for any intervention examined, although there were trends ($p = .07$) for CBT, FFT, and cognitive remediation (25, 26). Importantly, the existing RCTs use "transition to psychosis" as the primary outcome measure of treatment efficacy. However, the goal of psychosocial treatments may be reframed as improving cognitive, social, and functional impairments that are associated with poor prognosis in CHR, rather than preventing conversion to psychosis. In other words, for some individuals, "transition to psychosis" may be inevitable, but the degree of impairment associated with psychosis can be reduced if these individuals are provided skills to better cope with the cognitive and functional deficits associated with CHR.

In fact, cognitive deficits are a key determinant of functional outcomes in people with schizophrenia (27, 28) as well as individuals meeting CHR criteria (29, 30), irrespective of later development of a psychotic illness (15, 31, 32). Thus, there is a critical need for early interventions to improve cognitive impairment (and, therefore, everyday functioning) rather than focusing solely on symptomatic remission. Cognitive intervention trials (i.e., cognitive remediation or cognitive training) in individuals meeting CHR or early psychosis criteria remain limited and have produced mixed findings (33); although improvements in cognitive outcomes have been noted in some cognitive domains, these cognitive gains do not always generalize to improvements in community functioning. Although pro-cognitive interventions in pre- and early illness stages appear promising, preliminary evidence suggests that a compensatory strategy approach may best target areas of cognition typically impaired in early psychosis (34).

Compensatory Cognitive Training (CCT; (35–37), a strategy-based cognitive training approach, is one such psychosocial intervention that may hold promise as an efficacious treatment for CHR individuals. The most recent review and meta-analysis of cognitive remediation studies (35) found the largest effect sizes for compensatory strategy-based approaches in the context of psychiatric rehabilitation. In addition to improvements in

neurocognitive performance and functional outcomes, CCT has demonstrated a large effect size for negative symptoms (38, 39). CCT strategies teach participants how to bypass their deficits and directly address functional recovery through a focus on application of appropriate cognitive strategies in the real world. In essence, CCT provides an intervention that targets healthy neural circuitry to compensate for damaged circuit elements, or even protect this circuitry from future damage (40). The merits of CCT also exist in its format; it is manualized, group-based, low-tech, brief (38), and can easily be applied in the community in English or Spanish, making it a practical intervention for underserved populations.

Latino CHR individuals represent an underserved population in the United States. Latinos have become the largest minority group in the US (41); more than half (~54%) of California's elementary children are now of Latino origin (42). Despite the rising population of Latinos, disparities in mental health care continue to exist (43). Availability of and access to mental health resources is also limited in Mexico, with the Instituto Nacional de Neurología y Neurocirugía (INNN) serving as a local and national reference institution for the evaluation of CHR and early psychosis cases in Mexico City, a catchment area of over 20 million people. Latinos with CHR also present unique clinical challenges, presenting greater educational needs and exhibiting more severe negative symptoms predictive of conversion to psychosis (44).

Considering negative symptom severity is a predictor of long-term poor psychosocial functioning in schizophrenia (45) and CHR patients (30), and the lack of efficacy of any psychosocial or pharmacologic interventions in improving this symptom dimension in CHR patients (26), CCT's demonstrated efficacy for improving both cognition and negative symptom severity makes it a suitable intervention to evaluate within Latino CHR youth. As such, the aim of this paper is to describe the development and implementation of an ongoing pilot randomized controlled trial investigating the efficacy of CCT, as compared to recreational therapy (RT), for CHR Latino participants in both the United States and Mexico. We hypothesize that, in comparison to those receiving RT, participants receiving CCT will show significant improvements in neurocognitive performance and functional capacity (co-primary outcomes) and self-rated functioning and clinical symptoms (secondary outcomes).

DESIGN AND METHODS

We are currently conducting a dual center (University of California, San Diego [UCSD] and INNN) randomized controlled trial of CCT compared to RT for CHR Latino youth in the United States and Mexico. The study is registered as a clinical trial (Clinical Trials registration number: NCT02245607). Baseline assessment confirms CHR criteria, and participants are subsequently randomized in groups to receive group-based CCT or RT. Study procedures were approved by the University of California, San Diego Institutional Review Board and by the Ethics and Scientific Committees of INNN.

Participants

Projected enrollment is 120 CHR Latino youth (60 participants per site). In San Diego, participants are referred to the study by community health practitioners in San Diego who serve the Latino community, public schools in high Latino districts, County Mental Health, and the National Alliance on Mental Illness. In Mexico City, participants are recruited *via* the Neuropsychiatric Service, Early Psychosis Clinic, an advocacy group (Asociación de Familiares y Amigos de Personas con Esquizofrenia - AFAPE), and the Adolescent Study of Neuropsychiatric Assessment and Imaging (PIENSA) Program at INNN. Inclusion criteria are: 1) between the ages of 12 and 30; 2) meet CHR criteria per the Structured Interview for Prodromal Syndromes (SIPS); and 3) be of Latino descent. Specific to the Mexico City site, participants are eligible only if Spanish is their preferred language. Exclusionary criteria are: 1) current or lifetime psychotic disorder; 2) concomitant medical or neurological illness; 3) brain injury with loss of consciousness >30 min; 4) current substance abuse that interferes with group or assessment procedures or is judged to be causing subsyndromal psychotic symptoms (excluding nicotine); 5) IQ < 80; 6) high suicidal risk; and 7) Axis I disorder or substance use that better accounts for subsyndromal psychotic symptoms. Latino descent was identified through participant/family self-report. Only Spanish-speaking individuals were eligible for enrollment at the INNN site to reduce confounding factors associated with using two separate manuals presented in different languages for groups at that site. Psychotropic medication is permitted, including antipsychotics, antidepressants, and mood stabilizers. All cases are discussed in a weekly conference call between sites to reach consensus on inclusion/exclusion criteria and symptom and functional ratings. All participants over the age of 18 provide written informed consent; minors provide assent with written consent by a parent or legal guardian.

Treatment

Eligible participants are assigned to one of the two treatment conditions: CCT and RT. Both treatments are manualized, 12-week interventions. Via a randomization schedule developed by the study statistician, all eligible participants are randomized in groups (goal 4–6 per group) to receive 12 weeks of CCT or RT. Moreover, participants' age is factored in the randomization process to ensure that each intervention group only includes participants falling within a distinct age group (12–14, 15–17, and 18–30). This guideline was determined through direct communication with the National Institute of Mental Health (NIMH), given NIMH's concern for minors being co-enrolled and randomized into the same group with legal-aged adults.

Compensatory Cognitive Training

CCT is delivered in accordance with the manual and has been described extensively elsewhere (38). Briefly, participants in the CCT group receive weekly 90-min group CCT sessions for 12 weeks, which involve education regarding targeted skill areas as

well as modules of compensatory strategies targeting prospective memory, attention, learning/memory, and executive functioning. The CCT strategies are presented in an interactive, game-like format to maintain interest and reduce attrition. Homework assignments are designed to encourage additional practice outside treatment sessions. At the beginning of each session, previous homework assignments are reviewed or completed *in vivo* to ensure skill proficiency and execution. As the ongoing study is a feasibility trial, minor age-related modifications were made as necessary to ensure CCT was engaging and relevant to the specific needs of young Latinos with CHR (e.g., using Spanish names, focusing on school-related versus work-related examples).

English and Spanish versions are used in the study and employed based on the group's preferred language. The Spanish translation of the CCT manual (46), a collaborative effort between investigators at UCSD, INNN, and the University of Deusto, Bilbao, is applicable in both Spain and Latin America (translation performed by natives of Spain and Mexico). Translation back to English by translators unfamiliar with the manual was very successful and the final Spanish CCT manual required very little modification.

Recreational Therapy

RT was selected as a robust control condition, a group therapy intervention that provides the same frequency and amount of therapist and other group member contact as CCT, but does not provide any cognitive training. Participants assigned to the RT sessions participate in different recreational activities targeting their popular culture awareness, art, and physical activities. The 12 sessions of RT, also broken down into modules, consist of discussions on topics such as music, current events, art, and health. Reference materials were selected from current media (newspapers, magazines, and internet). Practice of RT skills is encouraged outside of session, but no formal homework assignments are given. At the beginning of each session, previous week's concepts are reviewed. The purpose of these sessions is to provide participants with access to information that would encourage social interactions and the addition of physical activity to their daily routine.

Assessments

Following enrollment/randomization, participants complete assessments at baseline, mid-intervention (4 weeks, 8 weeks), post-intervention (12 weeks) and 3-month follow-up, conducted by clinical raters and research assistants blind to group assignment (see **Table 1** for the Assessment Overview). Participants are compensated for their time per assessment and at each group session to offset the cost of transportation. Following baseline assessment, participants receive 12 weeks of their assigned intervention, delivered by bachelor's level or above therapists at each site. Therapists administer both treatments in an alternating schedule to avoid therapist effects in the design. The primary outcome measures are neurocognition and functional capacity, as assessed by the measures detailed below. Furthermore, secondary outcomes measures will be used to examine change in clinical symptoms and self-reported functioning in response to CCT versus RT.

Cognitive and Functional Assessment

Premorbid intellectual functioning is assessed *via* the Wechsler Adult Intelligence Scale (WAIS), Block Design and Vocabulary subtests. Participants are administered an expanded MATRICS (Measurement and Treatment Research in Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) in English or Spanish (47). The MCCB has excellent qualities, including psychometric properties for longitudinal studies, utility as a repeated measure, relevance to functional outcome, brevity, ease of use, and participant tolerability. These tests are administered according to published standardized procedures. As part of collaborative studies, the UCSD team has traveled to Mexico City and standardized administration of the neuropsychological battery. The battery includes the following domains: 1) Estimated IQ: Wechsler Adult Intelligence Scale Vocabulary and Block Design, 2) Learning & Memory: Hopkins Verbal Learning Test, Brief Visual Memory Test–R, 3) Processing Speed: Brief Assessment of Cognition in Schizophrenia: Symbol Coding, Category Fluency, Trail Making Part A, 4) Attention/Vigilance: Continuous Performance Task Identical Pairs, 5) Working Memory: WMS III Spatial Span, University of Maryland Letter-Number Span, and 6) Executive Functioning: Neuropsychological Assessment Battery Mazes, Wisconsin Card Sorting Test. A Global Cognitive Index will combine z scores of all cognitive domains per established methods (8). The University of California, San Diego Performance-Based Skills Assessment-Brief (UPSA-Brief) was selected to measure performance-based functional capacity (48), along with UPSA-Child and Adolescent version for adolescents. The Specific Levels of Functioning (SLOF) scale is used as a self-reported functioning measure because of its concordance with objective ability measures (49). In addition, the modified Global Assessment of Functioning (50) and the Social Adjustment Scale (51) are administered.

Clinical Assessment

CHR is assessed using the SIPS, with symptom ratings measured via the Scale of Prodromal Symptoms (SOPS) (1). To assure reliable diagnostic and clinical assessment across sites, a consensus diagnosis procedure was developed, including weekly clinical calls with certified Ph.D. or M.D. raters, all of whom were trained by Yale developers of the SIPS. Participants are also administered Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (52). Current and past psychosocial treatment, medication and hospitalization data are collected for all participants. Finally, the Alcohol/Drug Use Scale (AUS/DUS) is administered to measure current substance use (53).

During the final group session, all participants are given an exit interview in which they complete a small survey examining overall satisfaction with the intervention. Participants are asked to provide self-rated impressions of improvement in concentration, memory, attention, as well as conversational and task vigilance. These impressions are rated on a scale of 1

TABLE 1 | Assessment Overview.

	Time (Hour : Min)	Baseline	Week 4	Week 8	Week 12	Week 24
Clinical (Day 1)	**2:30**	**X**			**X**	**X**
Demographics	:15	**X**			**X**	**X**
SCID-I	1:00	**X**			**X**	**X**
SIPS/SOPS	1:00	**X**	**X**	**X**	**X**	**X**
AUS/DUS	:15	**X**	**X**	**X**	**X**	**X**
Functional (Day 1)	**1:35**	**X**			**X**	**X**
SAS-SR	:15	**X**			**X**	**X**
GAF	:05	**X**			**X**	**X**
SLoF	:30	**X**			**X**	**X**
UPSA	:45	**X**			**X**	**X**
Day 1 Total	***4:05***	**X**			**X**	**X**
Neurocognitive Battery (Day 2)	**2:15**	**X**			**X**	**X**
General Intelligence						
WAIS Vocabulary	:15	**X**			**X**	**X**
WAIS Block Design	:10	**X**			**X**	**X**
Verbal Learning						
HVLT	:05	**X**			**X**	**X**
BVMT	:05	**X**			**X**	**X**
Processing Speed						
BACS Symbol Coding	:05	**X**			**X**	**X**
Category Fluency	:05	**X**			**X**	**X**
Trails A	:05	**X**			**X**	**X**
Attention/Vigilance						
CPT-IP	:10	**X**			**X**	**X**
Working Memory						
WMS III Spatial Span	:10	**X**			**X**	**X**
LNS	:10	**X**			**X**	**X**
Executive Functioning						
NAB Mazes	:10	**X**			**X**	**X**
WCST	:10	**X**			**X**	**X**
Day 2 Total	***2:15***	**X**			**X**	**X**
Exit Interview	***:30***				**X**	
Total Assessment Time (H:M)		**6:20**	**1:15**	**1:15**	**6:50**	**6:20**

Structured Interview for Prodromal Syndromes (SIPS), Scale of Prodromal Symptoms (SOPS), Structured Clinical Interview for DSM-IV (SCID) Axis I, The Social Adjustment Scale – Self-Report (SAS-SR), Global Assessment of Functioning (GAF), Specific Level of Functioning (SLoF), The UCSD Performance-Based Skills Assessment (UPSA), Wechsler Adult Intelligence Scale (WAIS), Hopkins Verbal Learning Test (HVLT), Brief Visual Memory Test–R (BVMT), Brief Assessment of Cognition in Schizophrenia (BACS), Category Fluency, Trail Making Part A, Continuous Performance Task Identical Pairs (CPT-IP), Wechsler Memory Scale (WMS), Univ. of Maryland Letter-Number Span (LNS), Neuropsychological Assessment Battery (NAB) Mazes, Wisconsin Card Sorting Test (WCST).

(not at all helpful) to 10 (very helpful) referring to whether participants found the skills taught during group to be helpful in improving each respective domain of cognition. Participants are also given the opportunity to provide qualitative feedback regarding additional topics to be covered, topics to be removed, and feedback regarding difficulty attending group sessions, as well as any other suggestions to improve groups.

Design Considerations

Focusing on compensatory and environmental strategies, rather than drill and practice computer exercises, is consistent with empirical focus on improving functional skills among patients with schizophrenia (54, 55). In addition to attention, learning and memory, and executive functioning, the CCT intervention targets prospective memory ability (i.e., the ability to remember to do things in the future, such as complete homework assignments or attend a doctor's appointment). These CCT-targeted areas of cognition represent potentially modifiable cognitive domains with relevance for psychosocial functioning (27, 56, 57). Moreover, these domains represent areas of cognition also affected in the prodromal phase (9, 58) and predictive of later conversion to psychosis, thereby serving as key initial treatment targets. Prevention of further deterioration and preservation of cognitive abilities may be vital first steps to increase the effectiveness of other psychosocial treatments. Another strength of CCT is its exploitation of stronger cognitive functions in schizophrenia, such as imagery (59) and habit learning (60, 61), to bolster impaired abilities; for example, forming new habits in attention and problem-solving can lead to gains in performance efficiency *via* automatic processing and decreased cognitive demands. Increasing individuals' ability to remember appointments, sustain attention, encode important concepts, and think flexibly may well improve the success of concomitant treatments.

Therapist Training

Mental health providers at the bachelor's level or above deliver the treatment. Two San Diego site therapists, as well as one investigator and one study therapist at the Mexico City site, were formally trained on the CCT protocol by EWT at study initiation. The 2-day training included an introduction to the theoretical principles underpinning the treatment model, specific instructions on implementing each of the twelve CCT sessions, and review of RT sessions. Weekly individual supervision is ongoing throughout the trial between the study therapists and PIs.

Fidelity

Research recommendations by Perepletchikova and Kazdin (62) were implemented to maximize treatment manual adherence (e.g., use of checklists). All CCT and RT sessions are recorded to monitor fidelity; sessions are rated using items from the Cognitive Training Fidelity Scale (unpublished; available upon request from the authors). Therapist compliance was defined as 90% adherence to the items on the weekly checklist; subthreshold fidelity ratings will result in remedial training until these levels are achieved. To reduce the risk of treatment contamination, groups will be held at times and locations where subjects in different groups will not have the opportunity to meet in a waiting room. We will also ask subjects not to discuss their treatment with other subjects until after completion of the protocol. Monthly fidelity ratings will be fed back to therapists during supervision to improve fidelity. RT sessions will also be rated to ensure that RT groups do not receive training in CCT skills.

Data Analysis

The purpose of this pilot RCT is to examine feasibility and generate effect sizes to establish benchmarks for future studies, not to complete an adequately powered efficacy study. Power calculations based on Cohen method (63) and the method provided by Hedeker et al. for the Random Regression Model (64) indicated that with the proposed sample size, we will have a minimum 80% power to detect a medium to large effect across groups, consistent with the medium to large effects in prior studies.

A linear mixed model, with post-hoc procedures if indicated, will be used to analyze data in order to compare CCT versus RT in Latino CHR subjects in the United States and Mexico (co-primary outcomes: neurocognition [Global Cognitive Index and individual domain scores] and functional capacity; secondary outcomes: self-reported functioning and clinical symptom severity). Feasibility data such as recruitment rate, consent rate, reasons for not participating, reasons for dropping out, participants' satisfaction, and their suggestions to improve the study will be tabulated and will be analyzed descriptively.

Furthermore, predictors (moderators) of response to CCT versus RT, including age, baseline symptom severity, neurocognition, and comorbidity, will be explored. Moderators will be examined by building hierarchical linear models with potential moderator variables (e.g., baseline symptoms, neurocognition, functioning, age, and comorbidity) included in the model (65). The linear model to be used for both moderator and mediator analyses will compare CCT versus RT treatment groups. The independent variables are treatment group, moderator, and the treatment-moderator interaction. An interactive effect will mean that the effect of treatment on individual subjects depends on their value of moderator.

Finally, mediators of functional outcomes, including improvement in cognition and symptom severity, will be explored. Mediation analyses will use a similar linear mixed models approach. Two conditions must be met for mediation of the treatment effect: 1) correlation between the mediator and treatment; and 2) relationship between the mediator and outcome (65). First, we will test the effect of treatment group and the group × time interaction on the mediator (for example, improvement in cognition), and we expect a statistically significant group × time interaction. Second, we will test the effects of neurocognitive change (change score from baseline to mid-treatment) and the Global Cognitive Index change × group interaction on the outcome (UPSA) in the model that includes group and time, and we expect a statistically significant mediator × time or mediator × group × time interaction. The Global Cognitive Index change score from baseline to midway establishes temporal precedence of the mediator. We will also explore whether change in Global Cognitive Index and other variables mediates change in the other outcome variables (e.g., functioning). Finally, we will explore the relationships between specific measures (e.g., specific symptom factors) and functioning, number of sessions attended, as well as relationships between change in one domain and change in another (e.g., between change in symptoms, neurocognition, with change in functioning), when appropriate.

DISCUSSION

Developing psychosocial interventions to improve cognitive and functional outcomes in CHR participants is a research priority. In addition, the development of treatments that can be feasibly and acceptably delivered to diverse and underserved populations is greatly needed. CCT is a psychosocial intervention with demonstrated efficacy in first episode and chronic schizophrenia (35, 36), but remains to be evaluated in pre-illness phases.

Studies of cognitive training interventions in pre-psychotic illness remain limited. One study has demonstrated acceptability and feasibility of a compensatory-based approach (Cognitive Adaptive Training) in early illness phase (34); however, the small sample size (n = 5), individual format, and lengthy duration undermined its widespread application in real-world settings. Although preliminary evidence suggests computerized drill-and-practice as a feasible intervention with potential cognitive benefits for CHR (66), controlled studies are not yet published. The availability of CCT as a freely accessible, brief, manualized, group-based intervention provides a low-cost, scalable, and clinically relevant treatment with promise for widespread

uptake and implementation. CCT's utility is further boosted by its availability in both English and Spanish and because it can be delivered by bachelor and master's level clinicians. Furthermore, sample diversity in the ongoing trial is enhanced *via* recruitment from both US and Mexico, demonstrating attention to burgeoning national and international preventive efforts in psychosis research.

Several aspects of our study design could affect feasibility of participant recruitment and retention across sites, as well as generalizability. First, due to the nature of our established clinical services, groups are facilitated outpatient psychiatric service settings rather than primary care. In the United States, minority/immigrant individuals may be more likely to engage in mental health treatment through primary care settings as compared to specialty mental health settings (67, 68). Second, to increase socialization, we opted to offer clinic-based groups rather than home-based care. Some participants who prefer individual treatment or who cannot easily access transportation may be less likely to participate. The willingness of parents of minors to take time off work to facilitate their children's participation may also affect participation and retention. As such, future investigations may consider CCT delivery in real-world settings, or a telemedicine approach. To our knowledge, no studies to date have sought to investigate the feasibility of remote treatment delivery methods for CHR populations. Third, group randomization and stratification methods require that children, adolescents, and adults be separated into different groups. Thus, additional challenges are introduced in recruiting a sufficient number of individuals within the same age cohort to begin a group of at least 4–6 individuals. Finally, our results may not generalize to non-Latino CHR youth. Research on Latino youth indicate that prevalence rates of depressive symptomatology and alcohol use are significantly higher in Latino youth and these populations have inadequate access to mental health services (69). Thus, in addition to the considerations above, it is possible that CCT is differentially effective for this population given known mental health co-morbidities as well as access barriers.

Despite these potential limitations in study design, the introduction of cognitive training techniques at the INNN, the primary psychosis referral center in a city of over 20 million, is significant in that very few psychosocial treatments for schizophrenia are administered in Mexico. This work will clearly influence the treatment of psychotic illness in Latin America and the United States. This study will provide valuable information regarding the feasibility and efficacy of CCT to treat CHR Latino youth. UCSD's association with the North American Prodrome Longitudinal Studies (NAPLS) Consortium and the International Prodromal Research Network offers a platform for a larger scale treatment study should the proposed treatment prove promising. If found to be efficacious, CCT-associated improvements in cognitive and functional performance may well enhance success of concomitant treatments.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of California, San Diego Institutional Review Board Ethics and Scientific Committees of Instituto Nacional de Neurología y Neurocirugía (INNN). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

The Principal Investigators (CF-S, ET, and KC) were involved in designing and implementing the study. ZM and SK were primarily responsible for manuscript preparation. ET, KC, FR-M, and CF-S were involved in development, preparation, and distribution of the English and Spanish versions of the Compensatory Cognitive Training (CCT) manual. JW and FR-M served as group facilitators for the trial. Further, ET and FR-M served as clinical supervisors for CCT group facilitators. FR-M was involved in group facilitation and assessment procedures. All authors were involved in editing the manuscript and approved its final content.

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PERSPECTIVE
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A Public Health Perspective on Screening for Psychosis Within General Practice Clinics

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Screening for major mental illness in adolescents and young adults has lagged behind screening for physical illness for a myriad of reasons. Existing pediatric behavioral health screening tools screen primarily for disorders of attention, disruptive behaviors, depression, and anxiety. A few also screen for substance use and suicide risk. Although it is now possible to reliably identify young people at imminent risk for a psychotic disorder, arguably the most severe of mental illnesses, general practitioners (GP) rarely screen for psychotic symptoms or recognize when to refer patients for a specialized risk assessment. Research suggests that barriers such as inadequate knowledge or insufficient access to mental health resources can be overcome with intensive GP education and the integration of physical and mental health services. Under the lens of two public health models outlining the conditions under which disease screening is warranted, we examine additional evidence for and against population-based screening for psychosis in adolescents and young adults. We argue that systematic screening within general health settings awaits a developmentally well-normed screening tool that includes probes for psychosis, is written at a sufficiently low reading level, and has acceptable sensitivity and, in particular, specificity for detecting psychosis and psychosis risk in both adolescents and young adults. As integrated healthcare models expand around the globe and psychosis-risk assessments and treatments improve, a stratified screening and careful risk management protocol for GP settings could facilitate timely early intervention that effectively balances the benefit/risk ratio of employing such a screening tool at the population level.

Keywords: adolescents, prevention, primary care, clinical high risk, global mental health

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INTRODUCTION

Adolescence and early adulthood is the period of peak incidence for major mental illnesses (1). A large body of evidence now suggests that early intervention can reduce the duration of untreated illness and improve treatment outcomes for individuals in the initial stages of a major psychotic disorder (2). Improved detection of the early signs and symptoms emerging prior to or during this period has particular potential to improve long-term outcomes.

In spite of this evidence, even intervention in the first year or two following a first episode of psychosis (FEP) has proved challenging. Many of the initial symptoms of psychosis are not identified as such during the first months and years (2, 3). This is particularly troubling because the period preceding and including the first 5 years of illness is the window in which one third of suicides are completed, violent behavior may emerge, and impairments in neurocognition and functioning begin or worsen (2). As a result, a number of countries have developed early psychosis treatment programs for help-seeking youth. Yet, the fact remains that most youth who develop major psychotic disorders suffer for years before accurate diagnosis and treatment. Non-help-seeking but symptomatic youth are particularly at risk for delays in care (4, 5). If the promise of early intervention is to be realized, detection of emerging psychosis in this initial window must improve and reach those who need help but are afraid or uncertain how to seek it.

One of the major advances of the last three decades has been the identification of recognizable syndromes prodromal to schizophrenia-spectrum disorders (6–8). Because not all who have these syndromes transition to a psychotic disorder, syndromic individuals are broadly considered at "clinical high risk" (CHR). The majority of these youth have had psychotic-like symptoms for months to years prior to syndrome identification (9), and subtle, insidious, but not overtly psychotic symptoms for even longer (3, 10–12). A number of the earliest symptoms, such as insomnia, might be expected to prompt help-seeking from general practitioners (GP), who, if they have followed their patients over years, are well positioned to note gradual functional declines that might otherwise go unnoticed. For these reasons, one might expect GP to be the early frontier to psychosis detection.

HISTORY OF GLOBAL EFFORTS

Involving GP in the early detection of psychosis is not a new idea. Falloon and colleagues (13) in the United Kingdom (U.K.) conducted landmark studies of GP system interventions beginning in the early 1990's. In fact, they found that not only were GP a fruitful target for identifying emerging psychosis, but that formal screening in the context of GP services integrated with family and specialized mental health resources was associated with reduced incidence of schizophrenia in targeted communities (13). In this "Buckingham Project," GP and nurses were trained to inquire about specific and nonspecific risk factors such as insomnia, hallucinations, and grandiosity in all patients. A mental health professional was directly available to the GP office to facilitate a faster and more efficient pathway to care for positive screens. In Switzerland, Platz et al. (14), building on key components of Falloon's early work, found that intensive training focused on helping GP recognize insidious onset was associated with significantly improved knowledge and referral to specialized psychosis services. In fact, over half of referrals to this clinic contacted GP for help along their path to care, and 35% identified GP as their first point of contact. Particularly impressive, these referrals resulted largely from early help-seeking for insidious and nonspecific concerns rather than psychotic symptoms (15). In short, "sensitization" worked (16).

French and colleagues (17), in the U.K, tested a screening "checklist" designed to help GP evaluate help-seeking individuals. Unfortunately, it had poor specificity for detecting true psychosis risk, even in this population. Other U.K researchers, Perez and colleagues (18), compared the efficacy of low-intensity GP outreach (informational leaflets) against a high-intensity training and education campaign. Consistent with the model used in Buckingham, the intensive campaign that emphasized a more integrated relationship between physical and mental healthcare yielded more referrals and was a more clinically and cost-effective referral paradigm than traditional care (19). The relevance of GP practices to early intervention in psychosis has been indirectly exemplified by other literature. GP referral rates to specialized psychosis services were low in a Swiss study in which the training of GP and integration of physical and mental health services were absent (20). By contrast, a Canadian program using extensive community outreach found that 36% of help-seeking contacts prior to a FEP were with a GP (21). Furthermore, an impressive review of nearly 100,000 records of primary care visits in the UK confirmed the predictive value of non-specific concerns (suicidal ideation, obsessive-compulsive symptoms, and social isolation) with the development of a psychotic disorder within the subsequent 5 years, and identified a rise in medical visits for such complaints in the 3 months prior to a psychosis diagnosis (3). In a study of three regions of Norway, Bratlien and colleagues (4) found that self-reported eating disorder issues at ages 15 and 16, but not rates of health service use, were associated with higher rates of subsequent psychosis treatment. The potential role for GP in recognizing early and non-specific risk factors is clear, even if their role in the pathway to specialized services may vary across international boundaries (21, 22).

A PUBLIC HEALTH PERSPECTIVE ON SCREENING FOR PSYCHOSIS AMONG GENERAL PRACTITIONERS

In spite of the pioneering work noted above, delays to accurate diagnosis and treatment continue, particularly for earlier and insidious onsets (20). The potential for early detection within primary healthcare systems remains unrealized. For GP, limited knowledge and skills in recognizing the early signs of mental illness may be a critical barrier to early intervention. This barrier may be overcome by a key element of the Buckingham project: universal screening. The World Health Organization (WHO) has clear guidelines on where and when to implement screening, a number of which are clearly fulfilled for schizophrenia-spectrum disorders (**Table 1**; 23). The remaining WHO criteria pose important and serious challenges, which if taken on, will spawn necessary growth in the early intervention effort. Critical

TABLE 1 | World Health Organization Guidelines, Abbreviated (22).

WHO guidelines for disease screening tools
1. Condition must be an important health problem.
2. An accepted treatment should be available.
3. Facilities must be available for diagnosis and treatment.
4. There should be a stage of recognizable early symptoms.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from prodromal to declared disease, should be adequately understood.
8. There should be a policy on whom to treat.
9. The cost of case finding (including diagnosis) should be economically balanced in relation to possible overall costs of medical care.
10. Case finding should be ongoing and not just a single time effort.

steps must be taken before screening for psychosis can be wisely implemented.

The first four WHO criteria are easily met for schizophrenia and other psychotic-spectrum disorders. These disorders have an unquestionable impact on both individual and public health [criterion 1; (24, 25)]. There are well-established and generally acceptable, albeit imperfect, treatments available [criterion 2; (26–28)]. Similarly, most countries have established mental health systems and facilities for treating serious mental illness, even if access and quality may be inadequate [criterion 3; (29)]. GPs have different roles in early treatment-seeking and referrals to specialized care depending on individual health policies and systems (22, 30). Given proper training and connections to mental health resources, GPs may be some countries' main line of defense in spotting early psychosis (3, 21). The last 30 years have seen a major step forward in clarifying the early syndromes that precede psychotic disorders. Both retrospective and prospective studies have identified symptoms and biological markers characteristic of this prodromal stage and predictive of disease onset; risk calculators are continually being improved [criterion 4; (31, 32)]. Thus, we believe criterion 4 has been met, particularly for schizophrenia-spectrum disorders.

Criteria 5 and 6 call for a suitable test that is acceptable to the population in which it is performed. There are certainly established diagnostic criteria and structured interviews to diagnose psychotic-spectrum disorders [e.g., Structured Clinical Interview of Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), The Structured Clinical Interview for DSM-5 (SCID-5); (33)]. In addition, structured interviews are available to reliably identify youth with a 35% risk of imminent transition to a psychotic disorder (34). None of these are suitable and acceptable for use with a general population sample. They require substantial training and administration time. Self-report is likely to be the only cost-effective way to screen at the population level [(35); criterion 9)]. Several self-report screening tools have been developed, some with fairly good psychometric qualities (36, 37). However, most have been untested in general population, particularly adolescent samples, or have unacceptable rates of false positives relative to interview validation. Furthermore, in spite of data showing that age is a key factor in the frequency of psychotic-like experiences [e.g., (38)], there are almost no age-specific norms or thresholds for these screens. Self-report tools that have been tested in adolescent samples [e.g., the CAPE; (39)], are not written at an appropriate reading level for a general population sample of adolescents, despite the fact that this is the age range in which the incidence of psychotic disorders peaks (40). This is a substantial barrier as querying complex and abstract self-observations is inherently difficult to accomplish with simple language and short sentences. Efforts to prospectively probe early basic symptoms and self-disturbances have illustrated this challenge (41), yet refined questions continue to be tested (42). On a more encouraging note, the natural course and history of psychotic spectrum disorders is becoming ever clearer, in spite of the limited progress on specific causal mechanisms [criterion 7; (43)].

To satisfy criterion 8, there must be a policy on whom to treat. There is broad international consensus on the treatment of psychotic disorders, particularly within the first years of symptom onset (2). Although consensus on the treatment of CHR youth is still lacking largely due to clinical heterogeneity and challenges addressing early functional deficits (44), published guidelines do exist supporting specialized treatment in this stage of illness (32). Finally, criterion 10 indicates that screening must be ongoing. This remains an aspirational goal in the early detection of psychosis. Yet, if progress continues with screening tools and mental health service reform, it is not unrealistic to expect that youth, particularly those with known risk factors or changes in behavior or functioning, be screened on a repeated basis throughout the period of peak risk.

Aside from the WHO criteria, there is another model used to assess the appropriateness of screening called "The Balance Approach." This model suggests that the benefits of early detection should outweigh the risks of screening (45). It implores researchers to be conscientious of over-diagnosis, and to avoid measures that yield too many false positives. Prominent voices in the field of early intervention have argued against screening for psychosis at a population level, due primarily to concerns that transient or benign symptoms would be overpathologized [e.g., (46, 47)]. To address this important concern, any response to positive screens must begin with a general mental health-focused inquiry. In support of this approach is the fact that "false positive" psychosis screens are often "true positive" mental health screens. Perez et al.'s (18) research found that 68% of these individuals had other mental health conditions which required treatment. Systematic attention to balancing the risk of delayed identification with the risk of over-pathologizing needs to be central to any public screening effort. A stratified approach, ranging from a general mental health assessment to the skilled inquiry into the content, meaning-making, and distress associated with reported psychotic-like experiences, has potential to achieve this balance and protect low risk youth. Ideally, psychosis screening items would be embedded in general mental health screens.

NEXT STEPS

With the increasing integration of physical and mental health care and the growing evidence for early intervention, it is time to overcome the remaining barriers to psychosis screening in adolescents and young adults. Major mental illnesses are an

important health problem, for which too much of the care is provided in the chronic phases. Careful stratification of both risk and response could minimize harm to the majority of individuals at relatively low risk while maximizing the benefits to those at higher risk or with diagnosable psychotic disorders. GP clinics with integrated mental health services are ideal settings for ongoing screening and referral of these patients.

Toward this end, we identify the following steps:

1) A concerted effort is needed to improve and test self-report screening items for adolescents and young adults. We must collect normative data on the range and frequency of psychotic-spectrum experiences, including unusual thought content, hallucinations, disruptions of thought process and self-experience, and the rates of distress and/or impact associated with these experiences. A diverse adolescent and young adult general population sample will be essential. Building off of world-wide efforts with both self-report and interview questions of children and adolescents, items must be written at a pre-adolescent reading level (e.g., fifth grade for U.S. studies) but with as much specificity as possible.
   a. Cognitive interviewing, particularly of developmentally and culturally diverse adolescents, is recommended to assist with item wording and to identify the need for developmentally- and culturally-sensitive norms or screen versions (48).
   b. Longitudinal data and validation with specialized in-person assessment are needed to identify key self-report questions or sets of questions that might best identify youth at high risk for developing serious mental illness (psychotic and non-psychotic) in the early stages of symptom emergence.
   c. Thresholds will need to be defined indicating the appropriateness of a general mental health *versus* a psychosis-specific assessment. Individual risk calculators (31, 49) and resource availability may inform decisions regarding the appropriate level of treatment.
2) Pediatric GP and mental health organizations give rigorous consideration to the development and implementation of broad mental health screens that include probes of psychosis risk, and of guidelines for screening for and responding to psychotic symptoms. Psychosis-specific screening items should be selected based on careful analyses of age, gender, and sociodemographic norms and so as to maximize both sensitivity and specificity of detection (based on progress with step #1 above).
3) Mandated inclusion of material covering the developmental course of major mental illnesses (including risk factors and indicators, screening tools, and clinical management guidelines) in pediatric, family practice, and adult GP and mental health clinician training programs.
4) Large population studies of psychosis screening strategies within pediatric and young adult GP settings to identify best practices and to remove barriers to effective referral and timely assessment and treatment of positive screens. Refinement of clinical staging or stratified care models (50, 51) and expansion of general mental health and specialized care teams are both needed for broad feasibility and to avoid confounding positive GP screens with CHR status.

It is vital to emphasize that help-seeking behavior is not always the primary means of accessing psychosis-specific resources in this population. Research with first-time inpatients with psychosis suggests that roughly half of initial help-seeking is initiated by people other than the ill individual (5). General population screening is intended to enhance early detection of non-help-seeking youth, but it will be important for screening protocols to consider the inclusion of psychosis specific items in screening tools completed by caregivers, teachers, and others in a position to observe early risk indicators.

ARE WE READY TO SCREEN FOR PSYCHOSIS AMONG GENERAL PRACTITIONERS? FINAL THOUGHTS AND RECOMMENDATIONS

The international progress made in identifying individuals at CHR for psychosis and in early intervention in psychosis more broadly, has paved way for a transformation in the roles GP, particularly pediatric and young adult GP, can play in the global healthcare community. They have long been responsible for monitoring and intervening in the health trajectories of young people. Well-child visits provide an opportunity for disclosure and observation that is familiar and which may not carry the same stigma as mental healthcare visits. Policies for mental health screening and treatment may work best if they leverage GP visits to screen for psychosis. Unfortunately, we are not yet ready to screen for psychosis at the population level, particularly in the age range of peak symptom onset. A valid screening tool is needed as the foundation of such an effort, with screening thresholds linked to guidelines on assessment, referral, and intervention. This screening tool must facilitate a stratified approach to screening and subsequent care to maximize the benefit-risk ratio. Such a system would need to provide clear guidelines on graduated assessment and on who to treat and how, providing general care to those who have mild or non-specific risk factors and specialized psychosis resources only to those with specific psychosis risk indicators or established illness.

With both a screening tool and a clear policy, GP can be well positioned to apply their knowledge of patient trajectories to make appropriate referrals, improve rapid response to imminent risk and acute psychosis and support healthy development. In particular, GP have the potential to detect those who are not seeking help through mental health settings. Given their professional orientation toward prevention and early intervention, diagnostic accuracy, and capacity for recognizing syndromes, they are ideal partners in this public health effort.

From a public health perspective, screening has the potential to enhance detection and treatment of psychosis prior to the start of chronic illness. Long-term cost/benefit analysis for well-designed GP psychosis screening programs, including a stratified mental health response, will be an important area for

future research. The international work cited paves the way by demonstrating the feasibility and potential effectiveness of GP in this effort. Such innovation is essential to opening up new opportunities for the overall reduction of morbidity and potential prevention of major mental illness.

AUTHOR CONTRIBUTIONS

LK conducted the majority of literature review and took the lead in the manuscript organization and writing. KJ provided critical input, research and editing in relation to the public health perspective. JC assisted with the literature review and final manuscript preparation. KW conceived of the manuscript concept, oversaw the literature review and organization of the manuscript, and made a substantial contribution to the writing of the final draft.

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Beyond Clinical High-Risk State for Psychosis: The Network Structure of Multidimensional Psychosis Liability in Adolescents

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Objectives: The main goal of the present study was to analyze the network structure of schizotypy dimensions in a representative sample of adolescents from the general population. Moreover, the network structure between schizotypy, mental health difficulties, subjective well-being, bipolar-like experiences, suicide ideation and behavior, psychotic-like experiences, positive and negative affect, prosocial behavior, and IQ was analyzed.

Method: The study was conducted in a sample of 1,506 students selected by stratified random cluster sampling. The Oviedo Schizotypy Assessment Questionnaire, the Personal Wellbeing Index–School Children, the Paykel Suicide Scale, the Mood Disorder Questionnaire, the Strengths and Difficulties Questionnaire, the Prodromal Questionnaire–Brief, the Positive and Negative Affect Schedule for Children Shortened Version, and the Matrix Reasoning Test were used.

Results: The estimated schizotypy network was interconnected. The most central nodes in terms of standardized Expected Influence (EI) were 'unusual perceptual experiences' and 'paranoid ideation'. Predictability ranged from 8.7% ('physical anhedonia') to 52.7% ('unusual perceptual experiences'). The average predictability was 36.27%, implying that substantial variability remained unexplained. For the multidimensional psychosis liability network predictability values ranged from 9% (estimated IQ) to 74.90% ('psychotic-like experiences'). The average predictability was 43.46%. The results of the stability and accuracy analysis indicated that all networks were accurately estimated.

Conclusions: The present paper points to the value of conceptualizing psychosis liability as a dynamic complex system of interacting cognitive, emotional, behavioral, and affective characteristics. In addition, provide new insights into the nature of the relationships between schizotypy, as index of psychosis liability, and the role played by risk and protective factors.

Keywords: clinical high risk, schizotypal, schizotypy, network, complex dynamic system

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INTRODUCTION

The leitmotiv of psychosis high-risk paradigms [i.e., psychometric, genetic and Clinical High Risk (CHR)] is based on the ability to identify those individuals potentially at risk of developing psychosis in order to conduct prevention and prophylactic interventions (1, 2). Psychosis high risk approaches attempt to capturing early clinical (micro) phenotypes at early stages before care is needed and disability ensues. With these objectives in mind, proliferation of programs and centers specialized in early intervention in psychosis have emerged in the last twenty years (3–5). However, the "ultra-high risk" concept and "transition" paradigm have been questioned (6).

Psychosis high risk approaches assume (explicitly or implicitly) the idea of psychosis liability continuum (7). The construct that harbors the latent liability for schizophrenia and related manifestations is called schizotypy (8). At the phenotypic level, schizotypy can manifest itself, in a range variety of expressions, such us schizotypal traits, psychotic-like experiences, subclinical psychotic symptoms (i.e., CHR), frank psychotic symptoms, schizotypal personality disorder, or psychosis-spectrum disorders (2, 9). At population level, the non-clinical (or "soft") expression of psychosis phenotype may represent the behavioral manifestation of risk for psychosis (7, 10–12) and psychopathology. In fact, schizotypy probably represents the most clearly tractable risk factor for schizophrenia spectrum disorders (13). In its structure, schizotypy is a multidimensional construct, composed basically of three factors (Cognitive-Perceptual, Negative, and Disorganization), which is consistent with the factor structure found in patients with psychosis and CHR samples (14–16).

Modern approaches of psychosis promote a developmental, staging, and transdiagnostic approach which takes into account the different dimensions of risk, as well as protective factors, that influence liability to psychopathology (3, 6, 17, 18). In addition, clinical and subclinical psychosis phenotypes can be seen as complex dynamic systems of interacting cognitive, emotional, behavioral, social, and affective traits (19, 20). This viewpoint, named network model, represents a recent theoretical approach in the psycho(patho)logy arena, although it is not new in the scientific field (21–23). Basically, the network model is evolving as a response to the biomedical model, which is being disseminated by the leading nosological systems (e.g., DSM and ICD). Thus, new psychopathological and psychometric approaches, like network framework or chaos theory (24), might provide new insights in psychosis and mental health fields. In addition, a dynamic approach of psychopathology can complement and give new insight to a traditionally DSM categorical viewpoint.

From network approach, mental disorders, like psychosis, can be seen as emergent properties that arise from mutual interactions between mental states (or symptoms, signs, traits, etc.) (25–29).These findings can be considered within the network model of onset of psychotic disorders proposed by Linscott and van Os (30). The onset for the outcome of these mental health problems can be understood in part as: a) different psychotic-like experiences and schizotypal traits (e.g., psychosis proneness) that causally impact on each other over time (within phenotype domain), becoming persistent and leading then to clinical impairment, and b) many factors from multiple levels of analysis (e.g., trauma, cannabis, bullying, genetic background, brain function, etc.) that also causally impact on each other over time within and across - vertically and horizontally- domains in psychosis expression (31).

A wide variety of issues still remain to be resolved in psychosis research. It is necessary to gain a deeper understanding of the nature and structure of multidimensional psychosis liability beyond diagnostic systems (based on macrophenotypes) and in early stages of developmental disorders. At the same time, it would be interesting considering both risk (i.e. suicide ideation, emotional problems) and protective factors (i.e. well-being, positive affect) in the individual, as dynamic complex systems. Overall, these studies might be relevant in order to improve our knowledge about etiological mechanisms as well as early detection and intervention strategies in mental health. In addition, network model provides an informative way to describe the complex relationships between a set of key variables, focusing on the local interactions at the level of smaller units that compose the psychological problems, such as emotional and behaviors manifestations, and not at the disorder level. Based on this developmental, staging, non-clinical, and transdiagnostic approach, adolescence is a relevant developmental period where many changes at bio-psycho-social level take place. Therefore, it becomes a crucial stage to identify and intercept the unfolding of mental health problems. Moreover, if it is considered that almost 75% of all mental disorders begin in the first two decades of life and many of these individuals start with subclinical phenomena and/or report prodromal symptoms before to clinical outcome (32, 33).

To date, there has been no in-depth examination about the network structure of schizotypy and its relationship with cognitive, emotional, social, and behavioral indicators. Interestingly, no previous studies have analyzed the role of protective factors, such as personal well-being, prosocial behavior, or positive affect in psychosis liability network. Within this research framework, the main goals of the present study were: a) To analyze the network structure of schizotypy dimensions (within domain), as indirect indicator of psychosis liability in a representative sample of adolescents from the general population; and b) To estimate the network structure of schizotypy dimensions, mental health difficulties, subjective well-being, bipolar-like experiences, suicide ideation and behavior, psychotic-like experiences, positive and negative affect, prosocial behavior, and IQ (between domains).

METHODS

Participants

Stratified random cluster sampling was conducted at the classroom level, in an approximate population of 15,000 students selected from a region located in northern Spain. The students belonged to different public and concerted Educational

Centers of Compulsory Secondary Education and Vocational Training, as well as to different socio-economic levels. The layers were created as a function of the geographical zone and the educational stage.

The initial sample consisted of 1,881 students, eliminating those participants who presented a high score in the Oviedo Infrequency Response Scale (more than 3 points) (n = 104), an age older than 19 (n = 170) or did not complete the tests or the neurocognitive battery (n = 101). A total of 1506 students, 667 men (44.3%), belonging to 34 schools and 98 classrooms participated in the study. The mean age was 16.1 years (SD = 1.36), ranging from age 14 to 19 years.

Nationality distribution of the participants was as follows: 89.9% Spanish, 3.7% Latin American (Bolivia, Argentina, Colombia, and Ecuador), 2.4% Romanian, 1% Moroccan, 0.7% Portuguese, 0.7% Pakistani, and 2% other nationalities.

Instruments

The Oviedo Schizotypy Assessment Questionnaire-Revised (ESQUIZO-Qr) (34). The ESQUIZO-Qr is a self-report measure developed for the assessment of schizotypal traits in adolescents. It comprises a total of 62 items with Likert type response format in five categories (from 1 "totally disagree" to 5 "totally agree"). Its 10 subscales are derived empirically by means of factor analysis, which in turn are grouped into three general dimensions: Reality Distortion (e.g., Ideas of Reference, Magical Thinking, Unusual Perceptual Experiences, and Paranoid Ideation), Anhedonia (Physical Anhedonia and Social Anhedonia), and Social Disorganization (Odd Thinking and Speech, Odd Behavior, Lack of Close Friends, and Excessive Social Anxiety). In this revised version new items of Anhedonia dimension were added. Internal consistency levels for the subscales ranged from 0.62 to 0.90 and several sources of validity evidence with other psychopathology measures were gathered (34).

The Personal Wellbeing Index- School Children (PWI-SC) (35). The PWI-SC contains eight items of satisfaction, corresponding to different quality of life domains: standard of living, personal health, achievement in life, personal relationships, personal safety, feeling part of the community and future security. The PWI-SW has been validated in Spanish samples of adolescents (36). In the present study, the internal consistency, estimated with Cronbach's alpha, was 0.81.

The Paykel Suicide Scale (PSS) (37). The PSS is a self-report tool designed for the evaluation of suicidal ideation and behavior (lifetime prevalence). It consists of a total of 5 items with a dichotomous response system Yes/No (score, 1 and 0, respectively). The scores range from 0 to 5. The Spanish adaptation of the PSS has demonstrated adequate psychometric properties (38, 39). In the present study, the internal consistency, estimated with Cronbach's alpha, was 0.90.

The Mood Disorder Questionnaire (MDQ) (40). The MDQ consists of 13 yes/no items based on the DSM-IV criteria for bipolar disorder. A result is considered positive if the participant replies affirmatively to 7 or more items of the 13 proposed and if, in addition, the symptoms described occurred during the same time period (Criterion 2) and represented moderate or severe problems (Criterion 3). The Spanish version of the MDQ has demonstrated adequate psychometric properties (41). In the present study, the internal consistency, estimated with Cronbach's alpha, was 0.85.

The Strengths and Difficulties Questionnaire (SDQ) (42). The SDQ is a self-report tool that is widely used for the assessment of different emotional and behavioral problems related to mental health in adolescents. The SDQ is made up of a total of 25 statements distributed across five subscales: Emotional symptoms, Conduct problems, Hyperactivity, Peer problems, and Prosocial behavior. In this study we used a Likert-type response format with three options (0 = "Not true", 1 = "Somewhat true", 2 = "Certainly true"). The Spanish version of the SDQ was used (43) (see https://www.sdqinfo.com/a0.html). In the present study, internal consistency levels for the SDQ subscales ranged from 0.72 to 0.87.

The Prodromal Questionnaire–Brief (PQ-B) (44). The PQ-B is a psychosis-risk screening measure containing 21-items that are answered in a dichotomous response format (true/false). The PQ-B asks additional questions regarding frequency/severity of impairment and distress, rated on a Likert-type (1 "strongly disagree" to 5 "strongly agree"). The Spanish validation of the PQ-B has demonstrated adequate psychometric properties (45). In the present study, the internal consistency of PQ-B total score, estimated with Cronbach's alpha, was 0.89.

The 10-Item Positive and Negative Affect Schedule for Children Shortened Version (46). The PANAS-10, is a self-reported adjective checklist that contains two 5-item subscales designed to measure positive (i.e., joyful, cheerful, happy, lively, proud) and negative affect (i.e., miserable, mad, afraid, scared, sad). The PANAS-10 uses a Likert-type scale (ranging from 1, *very slightly or not at all*, to 5, *extremely or very much*). Evidences of internal consistency of the PANAS in Spanish population range from 0.86 to 0.90 for positive affect, and from 0.84 to 0.87 for negative affect (47). In the present study, internal consistency values for the PANAS ranged from 0.84 to 0.89.

The Penn Matrix Reasoning Test (PMRT) (48, 49). This is a task of the Penn Computerized Neurocognitive Battery-Child version developed to measure non-verbal reasoning within complex cognition domain. This task is composed by 20 items that can be considered as estimated IQ. The battery includes different neurobehavioral tasks adapted to youth samples that have demonstrated adequate psychometric properties (48, 49).

The Oviedo Infrequency Scale (INF-OV) (50). INF-OV was administered to the participants to detect those who responded in a random, pseudorandom or dishonest manner. The INF-OV instrument is a self-report composed of 12 items in a 5-point Likert- scale format (1 = completely disagree; 5 = completely agree). Students with more than three incorrect responses were eliminated from the present study.

Procedure

The research was approved by the Educational Government of La Rioja and the Ethical Committee of Clinical Research of La Rioja (CEICLAR). The self-reports and neurocognitive battery

were administered collectively through personal computers in groups of 10 to 30 students during normal school hours, and in a classroom specially prepared for this purpose. Administration took place under the supervision of researchers previously trained in a standard protocol. No incentive was provided for their participation. For participants under 18, parents were asked to provide a written informed consent in order for their child to participate in the study. Participants were informed about the confidentiality of their responses and the voluntary nature of the study.

Data Analyses

General Network Estimation

The details of network analysis were documented in-depth elsewhere (51, 52). Two networks were estimated. First, within schizotypy dimensions. Second, between schizotypy, mental health difficulties, subjective well-being, bipolar-like experiences, suicide behaviors, psychotic-like experiences, positive and negative affect, prosocial behavior, and estimated IQ.

A network consists of nodes (e.g., ESQUIZO-Qr domains) and edges (unknown statistical relationships between nodes that need to be estimated). For the domains, which were constructed by summing items per domain and then standardizing the resulting variable, we estimated a Gaussian Graphical Model (GGM) (53). This model resulted in conditional dependence relations which are akin to partial correlations: if two nodes are connected in the resulting graph *via* an edge, they are statistically related after controlling for all other variables in the network; if they are unconnected, they are conditionally independent. For the layout, the Fruchterman-Reingold algorithm was used, placing the strongly connected nodes closer to each other and the least connected nodes far apart (51).

Network Inference

Concordantly to previous studies examining network (54), we estimated two measures: Expected Influence (EI) and predictability.

a. EI is the sum of all edges of a node (55). We use EI instead of strength centrality (56), that has been used in prior works, because strength centrality uses the sum of absolute weights (i.e. negative edges are turned into positive edges before summing), which distorts the interpretation if negative edges are present.
b. Predictability is an absolute measure of interconnectedness: it provides us with the variance of each node that is explained by all its neighbors (57). Predictability can be understood as an upper bound of controllability: assuming that all undirected edges connected to a node point towards this node, predictability quantifies how much impact neighbors have on a focal node by intervening on them. In the figures, dark areas in the circle around nodes can be interpreted akin to R^2 (% of explained variance) (57).

Network Stability

To test network stability and accuracy, we used bootstrapping routines implemented in the R-package *bootnet* (58).

SPSS 22.0 (59), *R* (60), and FACTOR (61) were used for these analyses.

RESULTS

Network Structure of Schizotypy

The estimated schizotypy network was interconnected. Results are shown in **Figure 1**. Strong edges within Positive ('odd/magical beliefs', 'unusual perceptions', and 'ideas of reference'), Negative ('physical anhedonia' and 'social anhedonia'), and Disorganization domains ('no close friends', 'constricted affect', 'odd behavior', 'excessive social anxiety', and 'odd speech') were found.

Figure 2 depicts standardized EI values. The most central nodes in terms of standardized EI were 'unusual perceptual experiences' and 'paranoid ideation'. Predictability ranged from 8.7% ('physical anhedonia') to 52.7% ('unusual perceptual experiences'). The average predictability was 36.27%. The correlation between predictability and EI was 0.92.

Network Structure of Multidimensional Psychosis Liability

Figure 3 shows the estimated network for schizotypy dimensions and related psychopathological, affective, cognitive, and behavioral phenomena. First, strong and positive edges between nodes 'odd/magical beliefs', 'unusual perceptual experiences', 'ideas of reference', 'suspiciousness' and 'psychotic-like experiences' were found. Second, the majority connections between estimated IQ and other nodes are absent; this implies that these variables can be statistically independent when conditioning on all other nodes, or that there was not sufficient power to detect an edge between these nodes. Third, strong connections emerge among 'psychotic-like experiences' and 'bipolar-like experiences' nodes. Fourth, protective factors like 'prosocial behavior', 'positive affect', and 'subjective well-being' were positive associated. Especially, strong connections emerge among Node D17 (Positive affect) and Node D16 (personal well-being).

The most central nodes in terms of standardized EI were 'unusual perceptions', 'suspiciousness', and 'psychotic-like experiences' (both frequency and distress). Results are depicted in **Figure 4**. Interestingly, 'prosocial behavior', 'positive affect', and 'subjective well-being' were the least central domains. Predictability ranged from 9% (estimated IQ) to 74.90% ('psychotic-like experiences', both frequency and distress associated). The average predictability was 43.46%. The correlation between predictability and EI was 0.62.

Network Stability

The results of the stability and accuracy analysis (58) indicated that all networks were accurately estimated. Stability analyses

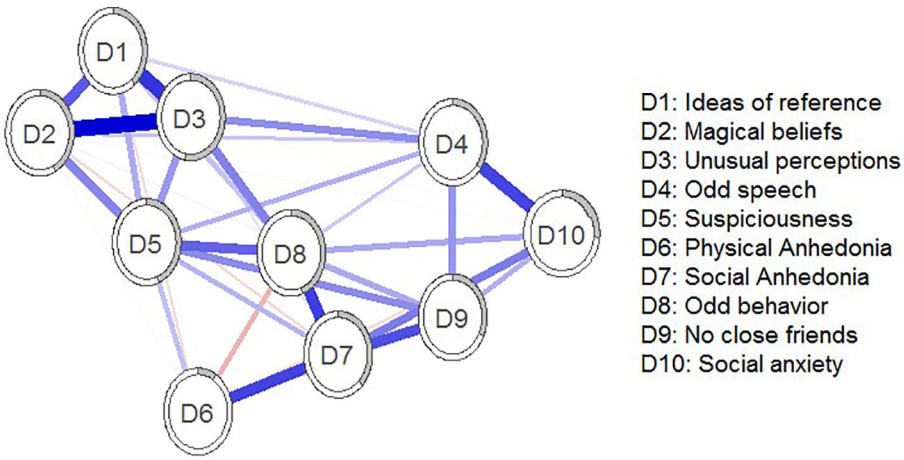

FIGURE 1 | Estimated schizotypy network. Blue edges represent positive associations; red edges represent negative associations. Thickness and saturation of edges indicate the strength of associations. The filled part of the circle around each node shows the predictability of each node, representing the variance of the nodes explained by all nodes with which it is connected.

revealed that the networks were accurately estimated, with moderate confidence intervals around the edge weights. The outputs for schizotypy network are presented in the online **Supplemental Materials**.

DISCUSSION

Here, we proposed to understand schizotypy, a multidimensional psychosis liability index, as a complex system of cognitive, emotional, and behavioral traits. To date, the network structure of schizotypy, as well as its links with other risk and protective indicators, have not been clearly delimited and analyzed. To the best of our knowledge, this is the first study to examine the empirical network structure of schizotypy during adolescence. In addition, no previous studies have examined the multidimensional psychosis liability with a large number of cognitive, affective, behavioral, and social indicators (e.g., mental health difficulties, subjective well-being, bipolar-like experiences, suicide ideation, psychotic-like experiences, positive and negative affect, and IQ). Thus, new approaches, such as network model, may provide new insights in the delimitation and conceptualization of psychosis liability, as well as psychopathology or mental health before clinical outcome and functional impairment. Furthermore, this novel conceptualization, as a complex system, is the first step in embracing the dynamic and complexity of early stages of psychopathology and emerging micro-phenotypes. In addition, this approach might help for the identification, prognosis, prevention, diagnosis, and prophylactic interventions.

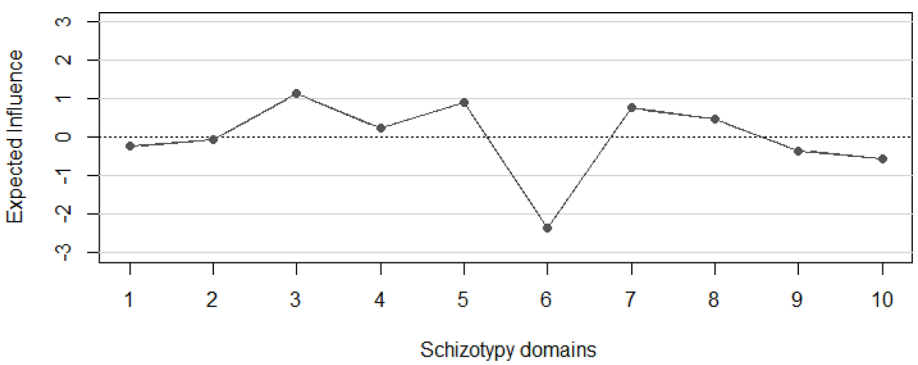

FIGURE 2 | Expected Influence of the domains of the estimated schizotypy network. 1 = Ideas of reference", 2 = "Magical beliefs", 3 = "Unusual perceptual experiences", 4 = "Odd speech", 5 = "Suspiciousness", 6 = "Physical Anhedonia", 7 = "Social Anhedonia", 8 = "Odd behavior", 9 = "No close friends", 10 = "Social anxiety".

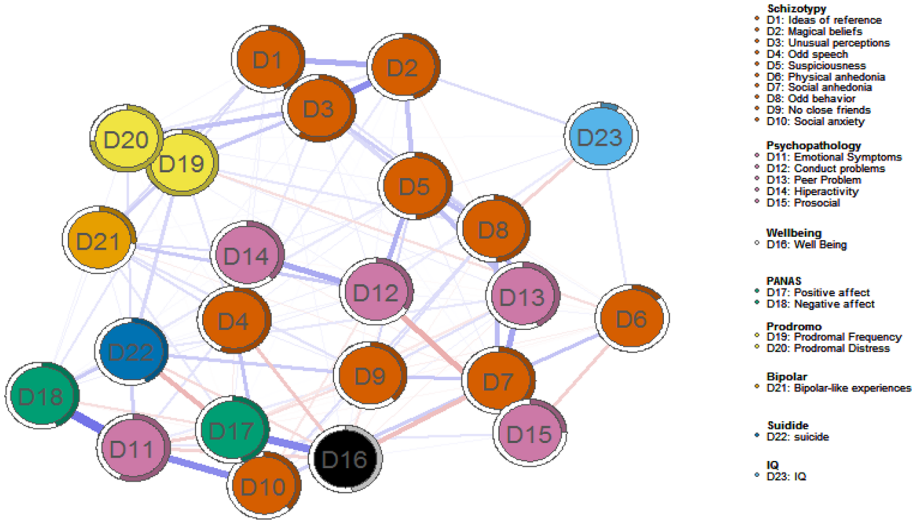

FIGURE 3 | Estimated multidimensional psychosis liability network. Blue edges represent positive associations; red edges represent negative associations. Thickness and saturation of edges indicate the strength of associations. The filled part of the circle around each node shows the predictability of each node, representing the variance of the nodes explained by all nodes with which it is connected.

The schizotypy domains were strongly interconnected. In particular, the relationship between nodes showed a three-cluster named Cognitive-Perceptual, Interpersonal (Negative), and Disorganized. The average predictability was 36.27%, implying that substantial variability remained unexplained. This network structure found was quite compatible with the three-dimensional model proposed schizotypy/schizotypal research (14, 62, 63). These results are also congruent with previous studies. Network models have also been used to analyze, amongst others, schizotypal personality traits in a multinational sample (54), psychotic like-experiences in cross-cultural study (64), and psychotic-like experiences in a large U.S.

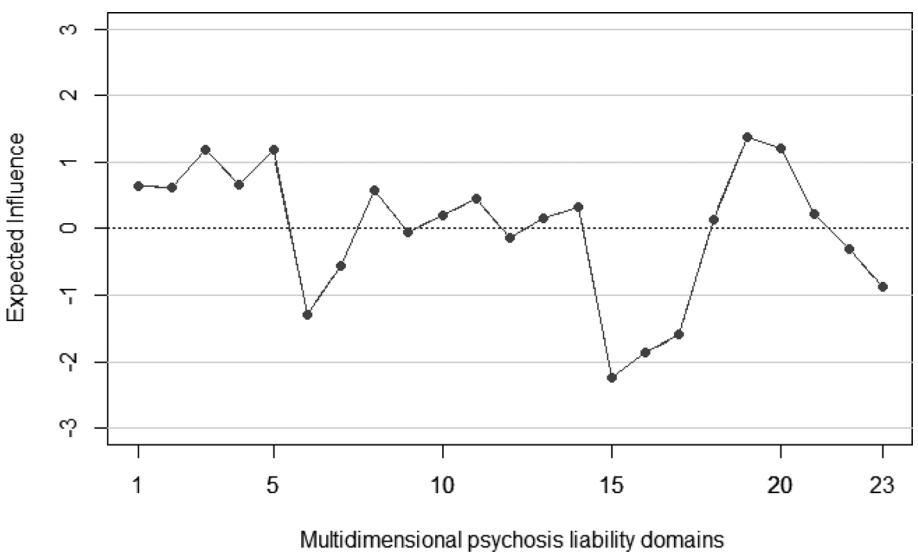

FIGURE 4 | Expected Influence of multidimensional psychosis liability network. 1 = "Ideas of reference", 2 = "Magical beliefs", 3 = "Unusual perceptions", 4 = "Odd speech", 5 = "Suspiciousness", 6 = "Physical anhedonia", 7 = "Social anhedonia", 8 = "Odd behavior", 9 = "No close friends", 10 = "Social anxiety", 11 = "Emotional Symptoms", 12 = "Conduct problems", 13 = "Peer Problem", 14 = "Hiperactivity", 15 = "Prosocial", 16 = "Well Being", 17 = "Positive affect", 18 = "Negative affect", 19 = "Prodromal Frequency", 20 = "Prodromal Distress", 21 = "Bipolar-like experiences", 22 = "Suicide behavior", 23 = "IQ".

sample (65). For instance, Fonseca-Pedrero et al., (54), using the Schizotypal Personality Questionnaire (66), indicated that schizotypal traits were strongly interconnected in the domain-level network. Predictability ranged from 31% (magical thinking) to 55% (restricted affect), with a mean of 43.7%. In another study, Murphy et al. (65) found that psychosis network revealed strong interconnectivity between psychotic-like experiences, where nodes indicating paranoia were among the most central in the estimated network. In addition, the viewpoint of psychosis phenotype, as a network system, is congruent with previous research that demonstrated how negative/disorganized symptoms predicted positive symptoms (67) or how hallucinations gave rise to delusions (68).

The network structure between schizotypy, mental health difficulties, subjective well-being, bipolar-like experiences, suicide ideation and behavior, psychotic-like experiences, positive and negative affect, prosocial behavior, and estimated IQ was analyzed. Variables showed relations both within and across domains, although within-domain associations were generally stronger. The network predictability values ranged from 9% (estimated IQ) to 74.90% ('psychotic-like experiences'), where the mean value of predictability was 43.46%. The psychosis-like experiences in terms of frequency and distress associated were the most central nodes in this estimated network. Also, suicide ideation and behavior were connected to negative affect and psychotic-like experiences. These results are consistent with previous studies conducted in other samples and with other measuring instruments (69–71). For instance, Zhang et al. (71) investigated the network structure between schizotypal traits and autistic traits, obsessive-compulsive traits, depressive symptoms, and anxiety symptoms in a college sample. They found that schizotypal features were highly overlap with depressive symptoms, however anxiety symptoms only connected with interpersonal traits. In addition, the network estimated showed high predictability, similar to the value yielded in the present study, where interpersonal traits had the highest expected influence. Interestingly, beyond to traditional psychopathology viewpoint, protective factors like prosocial behavior, positive affect, and subjective well-being were, on the one hand, more closely associated with each other than with other dimensions and, on the other hand, negative related with psychosis liability dimensions (e.g., 'ideas of reference', 'unusual perceptual experiences') and mental health difficulties (e.g., peer problems, emotional symptoms). To date, no previous studies have analyzed the psychosis liability network using both risk and protective factors. In this sense, it is plausible to argue that good subjective quality of life, positive emotions, or prosocial conduct might act as protective factors, leading to more resilient networks and becoming a less interconnected symptom network (22). This estimated network might be an example of the emerging psychopathology as a mixture picture of affective dysregulation, aberrant salience, cognitive impairments, and behavioral difficulties. Future studies should analyze the role of protective factors in psychosis extended phenotype as key elements to promoting well-being in young people, whether at risk or not.

Another relevant point in the present research is the role played by the estimated IQ in the multidimensional psychosis liability network. In the overall network, the associations between IQ and other nodes were generally low. Nonetheless, several issues have to be mentioned. First, IQ was measured by only a short task of complex reasoning (i.e., matrices test). Second, IQ was measured by an objective task while other indicators where measured by self-report tools. Third, adolescence is a developmental stage where executive and cognitive functions may develop at different pace. Fourth, the data were recollected both from different levels of analyses and measured with different tools. These facts might affect to the results found. However, we have to recognize that IQ (by extension cognitive abilities) is a key factor in the psychosis picture (both clinical and subclinical). Previous studies have demonstrated that people with psychosis have deficits in a wide variety of cognitive domains, in particular intelligence (72). In addition, such deficits are present in the premorbid stage and in the prodromal or at-risk mental phase, and predict the emergence of full-blown psychosis (73, 74). Therefore, to real understanding the psychosis liability it is relevant to gather information of IQ, because it is a multidimensional phenotype that requires cognitive, affective, psychophysiological, social, and behavioral variables. In addition, it is possible that accessing and analyzing data on multiple indicators, simultaneously, and from several levels of analyses, might accelerate the prediction of disease progression, as well as contribute to a better understanding of etiological mechanisms. To date, no previous studies have examined the network multidimensional structure of psychosis liability using IQ estimators. Thus, future studies in this line are still necessary.

These findings are congruent with the idea of transdiagnostic psychosis spectrum encompassing both non-affective and affective psychotic experiences (7) as well as with the psychosis proneness-persistence-impairment model (75). In particular, this model posits that the developmental expression of psychosis may become abnormally persistent and subsequently clinically relevant if there is a combination of other genetic, environmental, and psychological factors (7, 12). Thus, the presence of schizotypal traits or subclinical psychotic symptoms is not a necessary or sufficient condition for the later development of a psychotic disorder or other mental disorders (10, 12). Worth noting, the psychosis liability may interact synergistically or additively with genetic (e.g., unaffected family members of patients with psychosis), environmental (e.g., trauma, cannabis use), and/or psychological factors (e.g., affective dysregulation, avoidance coping). In addtion, this latent liability could causally impact on each other over time in a network of dynamic interactions, becoming abnormally persistent, help-seeking, and eventually give rise to transition to a psychotic spectrum disorder and impairment (12, 30, 7). For instance, Isvoranu et al. (76) demonstrated that psychosis symptom networks were more strongly connected for people

exposed to environmental risk factors (e.g., cannabis use, developmental trauma, urban environment), indicating that environmental exposure may lead to a more strongly connected network structure and less resilient symptom networks. As Lenzenweger (2) pointed out, mental disorders represent complex configural outcomes of multiple interacting systems that cannot be reduced to a mere collection of constituent parts.

Some limitations of this study should be acknowledged. First, adolescence is a developmental period in which brain, cognition, and personality are still consolidating. Second, in the present study, we only investigated the schizotypy through self-report screening measures. These measures have been associated with stigmatization and negative labeling. Third, it should be borne in mind that this study was of a cross-sectional nature, so we cannot make cause-effect inferences. Fourth, the results found in the present study needs longitudinal confirmation. Fifth, regarding the structure of the estimated network, a correct interpretation of it should not only focus on the visual inspection of its topography. A problem to avoid in the estimated networks, is precisely the over-interpretation on its visualization (77). This aspect refers especially to the design and placement of nodes in the graph, for example, when the nodes of the network are grouped in a cluster. However, it is relevant to know that the location of the node within a network is only one of the many equally 'correct' ways of placing the nodes in it, that is, with the same one showing the distribution of the nodes in the network. This network, in a new estimate, could be different. Also, the fact that a node is at the center of the network does not necessarily indicate that it is the most "central" node in it. We must be cautious when making a visual interpretation of the nodes and the analysis of their importance depending on the position in the estimated network. Therefore, for a better interpretation of the psychological network, and in order to avoid incorrect inferences, it is relevant to use other indicators as: predictability (78) or other statistical procedures (77). Finally, research in network analysis is currently in its infancy, and is not free of tentative limitations (e.g., generalizability and reproducibility of network estimation) (79, 80), so it is necessary to continue working on the construction of a solid and refutable scientific model and to incorporate new scientific evidence (22).

CONCLUSIONS

This study is the first to comprehensively examine the network structure of schizotypy, as an indicator of psychosis liability, using a large sample of adolescents. The results are consistent with the conceptual notion of schizotypy, understood as a complex network structure of cognitive, emotional, and behavioral traits. This study also offers a deeper understanding of the subclinical psychosis expression (psychosis liability) and its links with psychopathology, affective, personality, and cognitive domains. The understanding of the network structures of psychosis liability in general population may help to prevent psychotic-spectrum and mental health disorders. Finally, network analyses represent a data-driven approach allowing the investigation of the complex relationships of psychosis liability expressions and processes, including not only risk factors but also protective factors. Future studies should incorporate different scale levels of observation, like environmental and genetic variables, into network models.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The research was approved by the Educational Government of La Rioja and the Ethical Committee of Clinical Research of La Rioja (CEICLAR). For participants under 18, parents were asked to provide a written informed consent in order for their child to participate in the study. Participants were informed of the confidentiality of their responses and of the voluntary nature of the study.

AUTHOR CONTRIBUTIONS

EF-P designed the research and contributed with data analysis, and text writing. JO-S contributed with data analysis and text writing. FI contributed with text writing. JR-T contributed with text writing and helped in the design of the research. MD contributed with data analysis and text writing.

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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.2019.00967/full#supplementary-material

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