Implementation of Early Intervention in Psychosis in Low- and Middle-Income Countries

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Dedication

This thesis is dedicated to

my kids, Adrian and Emilio, for being my constant source of joy and inspiration;

to my wife, Elisa, for her patience and unwavering support throughout this journey;

and to my mother, Isabel, for her guidance and endless encouragement that made this possible.

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Abstract

Introduction: Psychotic disorders are among the most serious mental health conditions, with a large proportion of affected individuals living in low- and middle-income countries (LMICs) where mental health resources are scarce. Early Intervention in Psychosis (EIP) programs have been shown to be effective and cost-effective in high-income countries (HICs), where they are widely implemented. In contrast, the implementation of EIP programs in LMICs has been limited to major urban centers in a few countries. The overall objective of this thesis was to generate evidence to inform resource-sensitive and contextually appropriate strategies for developing, adapting and implementing EIP approaches in LMICs by assessing existing capacities, examining implementation experiences,and exploring the perspectives of EIP implementers on scaling EIP in resource-limited contexts.

Methods: Four studies were conducted. Study I, a bibliometric analysis, mapped global scientific output and collaboration in EIP research using records from Scopus (1980-2022). Study II, a systematic review conducted in accordance with PRISMA guidelines, synthesized evidence on the treatment components and outcomes of EIP programs in LMICs. Study III, a case study guided by the Exploration, Preparation, Implementation and Sustainability framework, examined the implementation of EIP initiatives in Latin America and the Caribbean (LAC). Using semi-structured interviews, we engaged primary implementers of EIP initiatives to explore the processes involved in implementing such initiatives. Study IV, a quantitative analysis of national administrative health data from Peru (2018–2024), evaluated service utilization for psychosis in the context of mental health reform and the COVID-19 pandemic, comparing patterns with those for non-psychotic mental disorders and physical illnesses.

Results: Study I found that LMICs contribute minimally to global EIP research, with publications concentrated in a few countries, limited collaboration with HICs, and even less among LMICs. Study II (125 studies) found that programs and research projects providing multicomponent care for early psychosis remain limited to few LMICs and offer few psychosocial strategies. When present, multicomponent care proved effective and cost-effective compared to medication alone for first-episode psychosis. Study III revealed a diversity of EIP initiatives in the LAC region (clinical and research programs, studies, guidelines, a technical standard). Most were guided by foreign models, with little adaptation to social factors. Initiatives showed diverse paths: discontinued, vulnerable, or sustained. While participants valued EIP, they viewed national rollout as unfeasible, proposing alternative scaling strategies such as leveraging existing youth mental health and primary care infrastructure, task-shifting, and improving early psychosis literacy. Study IV found that during Peru's mental health reform, service utilization rose for non-psychotic mental disorders and physical illnesses but not for psychosis, with underserved regions benefiting less. Although COVID-19 reduced service use across diagnostic groups, its recovery was slower in psychosis than the other groups.

Conclusions: LMICs face low research capacity for EIP, limited availability of services for psychosis, and structural barriers in mental health systems that hinder adoption. Despite EIP improving outcomes in LMICs, current efforts remain fragmented and limited. Addressing these inequities requires targeted research funding for and equitable research collaborations with LMICs, scaling a broader set of context-specific strategies and embedding psychosis-specific priorities into health reform. Thus, advancing EIP in LMICs has significant potential for improving global outcomes for persons with psychosis and their families.

Résumé

Mise en œuvre d'une intervention précoce dans les cas de psychose dans les pays à revenu faible et intermédiaire

Résumé

Introduction : Les troubles psychotiques comptent parmi les troubles mentaux les plus graves, touchant de nombreuses personnes vivant dans des pays à revenu faible ou intermédiaire (PRFI) où les ressources en matière de santé mentale sont limitées. Les programmes d'intervention précoce pour la psychose (EIP) se sont révélés efficaces et rentables dans les pays à revenu élevé (PRE) et y sont largement implantés. En revanche, la mise en œuvre dans les PRFI a été limitée, souvent concentrée aux grands centres urbains de quelques pays. L'objectif général de cette thèse était de générer des données probantes pour éclairer des stratégies adaptées aux contextes, en évaluant capacités, expériences et perspectives de mise en œuvre et l'extension des programmes EIP en contexte de ressources limitées.

Méthodes : Quatre études ont été menées. L'étude I, une analyse bibliométrique, a cartographié la production scientifique mondiale et la collaboration dans le domaine de la recherche sur les EIP en utilisant les registres de Scopus(1980-2022). L'étude II, une revue systématique menée conformément aux lignes directrices PRISMA, a synthétisé les données sur les composantes thérapeutiques et les résultats des programmes EIP dans les PRFI. L'étude III, une étude de cas guidée par le cadre Exploration, Préparation, Mise en œuvre et Durabilité, a examiné la mise en œuvre des initiatives EIP en Amérique latine et dans les Caraïbes (ALC). Des entretiens semi-structurés avec les responsables ont exploré les processus de mise en œuvre. L'étude IV, une

analyse quantitative des données administratives nationales au Pérou (2018-2024), a évalué l'utilisation des services pour la psychose dans le contexte de la réforme de la santé mentale et de la pandémie de COVID-19, en comparant les tendances avec celles des troubles mentaux non psychotiques et des maladies physiques.

Résultats : L'étude I a montré la faible contribution des PRFI à la recherche mondiale sur l'EIP, concentrée dans quelques pays, avec peu de collaborations avec les PRE et encore moins entre PRFI. L'étude II (125 études) a révélé que les soins à composantes multiples pour la psychose précoce restent rares dans les PRFI et incluent peu de stratégies psychosociales. Lorsqu'ils sont mis en place, ils sont plus efficaces et rentables que la seule médication. L'étude III a mis en évidence une diversité d'initiatives en ALC (programmes cliniques, recherche, lignes directrices, normes techniques), souvent calquées sur des modèles étrangers et peu adaptées au contexte social. Leur trajectoire était hétérogène (interruption, vulnérabilité, poursuite). Les participants ont reconnu l'intérêt de ces initiatives mais jugé une mise en œuvre nationale irréaliste, proposant plutôt d'autres stratégies comme l'usage des infrastructures existantes de santé mentale pour les jeunes et de soins primaires, le transfert de tâches et le renforcement des connaissances sur la psychose précoce. L'étude IV a montré qu'au Pérou, la réforme a accru l'utilisation des services pour les troubles non psychotiques et maladies physiques, mais pas pour la psychose, avec un moindre bénéfice pour les régions mal desservies. La COVID-19 a réduit l'utilisation dans tous les groupes, mais la reprise a été plus lente pour la psychose.

Conclusions : Les PRFI font face à une faible capacité de recherche en EIP, une disponibilité limitée des services et des obstacles structurels qui freinent son adoption. Bien que l'EIP démontre son efficacité dans ces contextes, les efforts actuels demeurent fragmentés et limités.

Réduire ces inégalités exige recherche ciblée, collaborations équitables, stratégies adaptées et intégration des priorités liées à la psychose dans les réformes de santé. Promouvoir l'EIP dans les PRFI offre ainsi un potentiel majeur pour améliorer les résultats mondiaux des personnes atteintes de psychose et de leurs familles.

Acknowledgements

First and foremost, I extend my heartfelt gratitude to my supervisor, Dr. Srividya N. Iyer. I am truly grateful to her for the opportunity she gave me to explore other academic settings and grow both academically and personally. She has been an exceptional mentor, an inspiring leader, and a deeply trusted guide throughout this journey. Her unwavering support has profoundly shaped my academic development and personal growth, and I owe much of what I have accomplished to her. Her remarkable intellect, wisdom, and optimism were crucial in helping me navigate the challenges of this doctoral path and reach this milestone. Thank you for being an extraordinary role model and for instilling in me a lasting commitment to advancing mental health.

To the members of my advisory committee, Drs. Ridha Joober and Howard Margolese: over the years, your valuable insights, constructive feedback, and thoughtful support have been instrumental in shaping and enriching this work in countless ways. Your deep expertise in psychiatry and mental health research consistently challenged me to think critically and refine my ideas. Equally important, your steady encouragement and guidance were essential to the successful completion of my doctoral program. I am truly grateful for your generous commitment of time and for fostering an environment that encouraged academic rigor, intellectual curiosity, and personal growth in each of our meetings.

I feel truly privileged to have been part of the Youth Mental Health Collective. My deepest thanks go to Dr. Navdeep Kaur for her longstanding support and collaboration across the various projects I undertook during my doctoral program. I am also sincerely grateful to Drs. Aarati Taksal, Tovah Cowan, Salomé Xavier, Giuseppe D'Andrea, Kathleen MacDonald, and research assistants Nicole Pawliuk and Daniel Rabouin for the thoughtful suggestions and recommendations they generously

shared with me over the years. Their insights have meaningfully contributed to the development of my work and encouraged me to continuously refine my thinking and approach to early intervention in psychosis. Being part of this collective has been a constant source of intellectual stimulation, collegiality, and motivation throughout my doctoral journey. I am equally grateful to all past and present members of the Youth Mental Health Collective for fostering such a welcoming, supportive, and enriching academic environment.

During my time at the Douglas Institute, I had the pleasure of working alongside brilliant and kind fellow graduate students, whose camaraderie and intellectual exchange were a constant source of motivation and support. In particular, I would like to thank Sakiko Yamaguchi for her friendship, thoughtful conversations, and support. Her presence made this journey more meaningful—both academically and personally.

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Contribution of Original Knowledge

This thesis encompasses four original scientific studies, published or under review in peer-reviewed journals, for which I am the lead author. Taken together, they represent a unique and novel contribution to the scientific literature on the implementation of EIP in resource-limited settings. The use of diverse research methods, the variety of study contexts, and the range of outcomes evaluated provide a comprehensive overview of the research topic. Specific original contributions to the field include:

1. The first bibliometric study evaluating scientific output and collaboration in global EIP research. Despite the growing global interest in EIP, no prior study has systematically examined how scientific knowledge is produced across countries with different income levels. Using a meta-research approach, this study offers a novel perspective on the structure and collaboration patterns in global EIP scientific production. The findings show that although the number of EIP publications has increased over time, LMICs contribute a limited share of the output. Furthermore, most publications were produced by authors from a single HIC, with only a small proportion involving HIC–LMIC collaborations and even fewer LMIC–LMIC collaborations. Taken together, these findings indicated a limited research capacity for EIP in LMICs.

2. The second original contribution is a systematic review on the availability and efficacy of multi-component treatments for people in the early phases of psychosis in LMICs. While some LMICs have implemented EIP programs, little is known about the treatment components provided and their effectiveness. A previous systematic review addressed this topic only partially, focusing exclusively on English-language publications and low-income countries, thus limiting its scope. Our review addressed these gaps by including studies in all languages across the full range of

LMICs and providing a structured synthesis of implemented interventions and delivery contexts. Overall, the findings show that first-episode psychosis and clinical high-risk programs and studies in LMICs offer a limited range of psychosocial components; however, when multicomponent interventions (at least one intervention beyond medication and assessment) are offered to people with first-episode psychosis, they demonstrated both effectiveness and cost-effectiveness, pointing to the promise of EIP in LMICs.

3. The third study of this thesis is a case study that evaluated the implementation process of EIP initiatives in LAC and explored the perspectives of EIP implementers on the scaling-up of EIP in LMICs. This work represents an original contribution, as we interviewed primary implementers who had led diverse EIP initiatives across the LAC region. In doing so, this study addresses the limitations of previous research that relied solely on desk reviews or surveys to examine EIP implementation. Moreover, we adopted a broad approach by including various types of EIP initiatives, such as clinical programs, research projects, clinical guidelines, and public policies. This allowed us to examine the different trajectories of these initiatives across the phases of an implementation science framework and to identify implementers' view on the scaling-up of EIP.

4. Finally, we evaluated the setting of implementation of EIP by examining the utilization of health services for people with psychosis in a LMIC, Peru. We took advantage of the availability of a nationwide dataset to assess service utilization by people with psychosis and compared it to that of people with non-psychotic mental disorders and physical illnesses. In this way, the results are population-based and provide valuable epidemiological data on psychosis in an LMIC, a type of information that is scarce in the literature. The study is uniquely contextualized in the period from 2018 to 2024, which includes the development of the Peruvian Mental Health Reform and the

occurrence of the COVID-19 pandemic. The results demonstrate that accessing health services for people with psychosis remains challenging, after the pandemic and even in the context of ongoing mental health reform.

Contributions of Authors

This dissertation comprises seven chapters and four manuscripts. I, Ruben Valle, was responsible for the conception and writing of all components of this thesis. I am the first author of all four manuscripts included.

Manuscript I. How "Global" is Research in Early Intervention for Psychosis? A Bibliometric Analysis *(Published in: Asian Journal of Psychiatry, 2024.)*

I conceived this project in collaboration with my supervisor, Dr. Srividya N. Iyer, in response to significant gaps in knowledge regarding research capacity in EIP within LMICs. As a first step, we identified the need for a global bibliometric analysis to assess the existence and distribution of such capacity in these settings. I formulated the research questions, developed the search strategy in collaboration with Dr. Iyer, conducted the statistical analyses, and wrote the first draft of the manuscript. We also consulted Dr. Swaran Singh, a leading expert in the EIP field, whose insights informed the interpretation and discussion of the results. Dr. Alexandre Loch was invited to contribute to the discussion of the findings, drawing on his experience as a mental health researcher in an LMIC. All co-authors reviewed and approved the final manuscript. The specific contributions of each co-author are detailed below:

Ruben Valle conceptualized the study, carried out data collection, performed the analyses, interpreted the results, and drafted the manuscript.

Swaran Singh supported the interpretation of the results and provided critical feedback that strengthened the quality and clarity of the manuscript.

Alexandre Loch contributed to the interpretation of the findings and offered substantive feedback that enhanced the overall manuscript.

Srividya N. Iyer conceptualized the project, oversaw data collection and analysis, and provided detailed feedback throughout the writing process.

Manuscript II: Availability and Efficacy of Multicomponent Interventions for Early Psychosis in Low- and Middle-Income Countries: A Systematic Review (Under review, *eClinicalMedicine* (Published by The Lancet), 2025)

I developed this project in collaboration with Dr. Srividya N. Iyer, following the publication of our previous manuscript. Recognizing the need for a deeper understanding of the treatment components provided in EIP programs in LMICs and their efficacy in resource-limited settings, we determined that a systematic review was the most appropriate methodology to address this objective. Dr. Vijaya Raghavan, a psychiatrist working in an EIP program in India, contributed key methodological input for the study design and data analysis. Together with Nora Morrison, we conducted the data collection and carried out the data analysis. I drafted the manuscript, which was subsequently revised and edited by Dr. Iyer. All co-authors reviewed and approved the final manuscript. The specific contributions of each co-author are outlined below.

Ruben Valle formulated the project, developed the protocol, conducted data collection, performed data analysis, interpreted the results, and wrote the manuscript.

Vijaya Raghavan contributed to the development of the methodology, supported data analysis, and provided crucial feedback on the manuscript

Nora Morrison participated in data collection, contributed to data analysis, and assisted in drafting the initial version of the manuscript.

Srividya N. Iyer conceptualized the project, developed the methodology, oversaw data analysis, and offered substantive feedback that enhanced the manuscript.

Manuscript III: Implementation of Early Intervention in Psychosis Initiatives in Latin America and the Caribbean: A Case Study (Under review, *Implementation Research and Practice*, 2025)

I conceived this study in collaboration with my supervisor, Dr. Srividya N. Iyer, to understand the implementation process of EIP initiatives in resource-limited settings. We identified the need for a case study design to collect unpublished data directly from primary implementers of these initiatives and to address the limitations of previous studies that relied on electronic surveys or desk reviews for data collection. I designed the study, developed the interview guide in collaboration with Dr. Iyer, conducted the interviews, and wrote the first draft of the manuscript. Camila Velez contributed to data analysis and provided valuable input during the drafting of the manuscript. All co-authors reviewed, revised, and approved the final version. The specific contributions of each co-author are detailed below:

Ruben Valle formulated the research idea; developed the protocol, conducted data collection, performed the qualitative analysis, and wrote the manuscript.

Camila Velez conducted the qualitative data analysis and provided critical feedback that strengthened the quality and clarity of the manuscript.

Srividya N. Iyer conceptualized the project, developed the methodology, and oversaw data collection and analysis, and provided detailed feedback throughout the writing process.

Manuscript IV: Health Service Utilization by People with Psychosis in Peru in the Context of the Peruvian Mental Health Reform and the COVID-19 Pandemic (2018-2024) (Under review, *Schizophrenia Bulletin*, 2025)

This project was developed to understand the provision of mental health care for psychosis in LMICs. We considered it important to examine the settings where EIP initiatives are implemented in terms of their capacity to provide mental health care for psychosis. We took advantage of a nationwide database in Peru, which records all consultations conducted from 2018 to 2024. I designed the study with Dr. Srividya Iyer. I also downloaded the database, conducted the data analysis, and wrote the first draft of the manuscript. Drs. Juan Pablo Murillo and César Gutiérrez contributed to the interpretation and discussion of the findings, drawing on their extensive knowledge of public health in Peru. Peiyuan Huang provided support in analyzing complex longitudinal data. All co-authors reviewed and approved the final version. The specific contributions of each co-author are detailed below:

Ruben Valle developed the research idea, downloaded the databases, conducted the analysis, interpreted the results, and wrote the manuscript.

Juan P. Murillo supported the interpretation of the results and provided critical feedback that strengthened the quality and clarity of the manuscript from a public health perspective.

César Gutiérrez contributed to the interpretation of the findings and offered substantive feedback that enhanced the manuscript from an epidemiological perspective.

Peiyuan Huang provided support in the analysis of large, complex longitudinal data.

Srividya N. Iyer contributed to the conceptualization of the project, development of the methodology, oversight of the statistical analysis, and provided detailed feedback throughout the writing process.

A Note About Nomenclature

In global health, the classification of countries into categories such as High-Income Countries (HICs) vs. Low- and Middle-Income Countries (LMICs) is commonly used to delineate disparities in health resources and outcomes. The World Bank's classification serves as a commonly used framework for grouping nations, which uses Gross National Income per capita for dividing countries into four income groups: low income, lower-middle income, upper-middle income, and high income, with the first three groups often being grouped together as “low- and middle-Income countries”. As of 2024, approximately only 40% of countries were classified as HICs (1).

This nomenclature is used in this dissertation, while acknowledging its limitation. Various alternative classifications such as economically developed versus economically developing countries; Global North vs. Global South; and WEIRD (Western, Educated, Industrialized, Rich, and Democratic) vs. non-WEIRD countries also have limitations (2). Each label encompasses a diverse range of countries with varying levels of development and health infrastructure, making it broad and imprecise. As Khan et al. (2022) note, such classifications also often obscure more than they reveal, failing to account for internal inequalities within these groups and the complex historical and geopolitical factors that shape health disparities (2).

This dissertation generally uses the HICs vs LMICs classification as it is useful for describing broad patterns; wherever possible, it provides additional contextual information. The dissertation recognizes the power dynamics underpinning the differences imprecisely encompassed by these income-based classifications, as well as the inequities in global health research and policy.

Introduction

Around 80% of individuals with psychotic disorders live in LMICs, where limited access to care and substantial treatment gaps are common (3,4). Early World Health Organization (WHO) studies, such as the *International Pilot Study of Schizophrenia* conducted around 1970 (5–7), and the *Determinants of Outcomes of Severe Mental Disorders* conducted around 1980 (8,9), reported better outcomes in LMICs than in HICs, attributing this to socio-cultural factors. However, later scientific research questioned these findings, citing methodological issues such as high attrition, diagnostic variability, and inconsistent outcome definitions (10). Although epidemiological data on psychosis in LMICs is scarce (11), the available evidence indicates that psychosis is a prevalent and highly disabling condition in LMICs (12,13).

Mental health systems in LMICs face persistent structural, financial, and sociocultural barriers that limit service accessibility. They remain largely underdeveloped and chronically underfunded, with countries allocating about 2% of their total health budget to mental health (14), well below the recommended 5% for LMICs (15). Governments and health systems often concentrate services in major urban centers, leaving large regions without adequate coverage (16). Where services are available, they frequently provide only pharmacological treatment, with limited access to evidence-based psychosocial interventions (17,18). In addition, poverty, low mental health literacy, and widespread stigma further delay help-seeking and reduce engagement with care (15,19).

These barriers significantly hinder access to mental health care for individuals with mental disorders, particularly those with psychosis (20). For instance, studies examining the duration of untreated psychosis (DUP), defined as the time from symptom onset to the initiation of

antipsychotic treatment (21), have shown that people with psychosis experience substantial delays in initiating treatment (22). Although this delay is observed globally, people with psychosis in LMICs experience a DUP twice as long (average mean: 125.0 weeks) as their counterparts in HICs (average mean: 62.5 weeks) (23). This delay is not innocuous, as evidence from both LMICs and HICs shows a small, but consistent, association between long DUP and poorer general symptoms, more severe positive and negative symptoms, and lower likelihood of remission (24,25).

In HICs, the body of research demonstrating the negative impact of prolonged DUP on outcomes has been a key catalyst for the development of early intervention in psychosis (EIP) programs (21). These clinical services, based on a philosophy of hope and optimism (26), aim to promote recovery by providing comprehensive care to individuals in the early phases of psychotic disorders, integrating pharmacological, psychological, and psychosocial interventions (27,28). In addition, EIP programs often include family-focused components, such as family interventions, as well as strategies at the health system level (e.g., walk-in or direct access to services without referral; guaranteed response time benchmarks) to facilitate timely access to mental health services (28). Evidence shows that individuals receiving care through EIP programs experience better clinical and functional outcomes compared to those receiving treatment as usual (29,30).

Evidence supporting the effectiveness and cost-effectiveness of EIP programs has driven their implementation across many regions of the world, particularly in HICs (31). In these settings, EIP programs have often been incorporated into sustained mental health policy frameworks aimed at expanding access to quality care for individuals with psychosis (32). As a result, EIP has become the standard of care for individuals experiencing a first episode of psychosis (FEP) (30).

Conversely, the implementation of EIP programs in LMICs has been limited and fragmented (33). Globally, only a few LMICs have introduced EIP programs into their health systems, which have typically emerged as isolated initiatives based in single-site facilities, reaching only a small fraction of the population in need (34).

EIP is a Western model of care that often requires substantial resources. It may include trained multidisciplinary teams, access to psychological and psychosocial interventions, community-based services, and adequate infrastructure to support coordinated and continuous care (35). Consequently, experts have suggested that directly translating EIP programs from HICs to LMICs is often unfeasible (33,36). As an alternative, it has been proposed that only the key components of the intervention be implemented in LMICs (33). However, there is no consensus on which components are essential or how they should be delivered in resource-constrained settings. As a result, EIP implementation in most LMICs has remained stagnant, with limited progress in scaling up these programs (34).

Advancing the EIP paradigm in LMICs may require an approach that goes beyond the establishment of formal standalone programs. Such an approach must be informed by existing implementation experiences in LMICs, a deep understanding of local service contexts, and resource availability. This would enable the design of more scalable, feasible, and culturally relevant early intervention models that better address the needs of individuals with psychosis in these settings. This thesis explores these questions using multiple research methods and aims to generate contextually grounded knowledge on the implementation of EIP initiatives in LMICs, which may be instrumental in advancing the EIP paradigm globally.

Chapter 1. Literature Review

Section 1: Overview of Psychotic disorders

1.1 Definition

Currently, two major classification systems define and characterize psychotic disorders: The International Classification of Diseases, 11th Revision (ICD-11), developed by the World Health Organization (2018) (37), and the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), developed by the American Psychiatric Association (2013) (38). In general, both classification systems conceptualize psychotic disorders as affecting multiple functional domains, including affective, sensory, cognitive, motivational, and social functioning. Characteristic clinical symptoms include positive symptoms such as delusions, hallucinations, and disorganized behavior; and negative symptoms, such as blunted or flat affect, avolition, alogia, and psychomotor disturbances (37).

The term psychotic disorder refers to a syndrome encompassing several individual diagnoses. Some cases of psychosis can be attributed to a medical condition or to the effects of a substance on the central nervous system; in such cases, the diagnosis would be a psychotic disorder due to a medical condition or substance-induced psychotic disorder, respectively (37). However, psychotic disorders are most commonly associated with schizophrenia-spectrum disorders, or non-affective psychoses, where the main diagnosis is schizophrenia but may also include delusional disorder, schizoaffective disorder, and others. Another category includes psychotic disorders that occur with affective symptoms, called affective psychoses, which encompass conditions such as bipolar disorder or depressive disorders with psychotic features (37).

1.2 Etiology and risk factors

Psychotic disorders are thought to arise from the complex interplay of genetic predispositions and environmental exposures, which shape early brain development and modulate the capacity of biological systems to adapt to life experiences (39). Genetic susceptibility contributes substantially, with multiple loci implicated in neurodevelopmental processes, neurotransmitter regulation, and synaptic plasticity (40). Disruptions in dopamine signaling, glutamatergic function, and cortical–subcortical network connectivity are regarded as central mechanisms underlying the emergence of symptoms (39). However, these genetic alterations on their own account for only a modest increase in risk (41), highlighting the critical role of environmental and social factors, which have consistently been associated with increased vulnerability (42).

Several factors have been identified as increasing the likelihood of developing psychotic disorders across an individual's lifespan. Advanced paternal age (older than 55 years) is associated with a higher risk of psychosis in offspring (43,44). Male sex is associated with a greater risk of developing schizophrenia (45,46), particularly at an early age (47). Prenatal and perinatal complications, including problems during fetal development or complications at birth, have also been linked to an increased risk of psychosis (48). Moreover, exposure to childhood trauma, such as sexual abuse, physical abuse, maltreatment, and bullying (49), as well as social adversity such as low socioeconomic status in early life, unemployment and social isolation, may increase the risk of developing psychosis (50–53). Environmental factors, such as living in highly urban areas (54,55), having migrant status (56–58), as well as living in socially and materially deprived areas, also contribute to increased vulnerability (59). Use of psychoactive substances such as cannabis is associated with increased risk of schizophrenia (60).

1.3 Epidemiology

The prevalence and incidence of psychotic disorders vary widely between studies, depending on research methods and diagnostic criteria (61), as well as actual differences in incidence shaped by context (62). A systematic review with meta-analysis reported a pooled median point and 12-month prevalence of psychotic disorders of 3.89 (interquartile range [IQR]: 2.6)] and 4.03 (IQR: 1.77) per 1000 persons, respectively, while the median lifetime prevalence was 7.49 per 1000 persons (IQR: 6.29) (63).

In a population-based survey conducted in Finland, the lifetime prevalence of psychotic disorder was estimated to be 3.06% (2.66%-3.51%), with a prevalence of 1.94% (1.63%-2.29%) for non-affective psychosis, 0.59% (0.45%-0.77%) for affective psychosis, 0.21% (0.14%-0.32%) for psychosis due to medical conditions and 0.42% (0.30%-0.59%) for substance-induced psychosis. The lifetime prevalence of schizophrenia was 0.87% (0.68%-1.1%) (64).

In terms of incidence, a systematic review reported a pooled incidence of all psychotic disorders of 26.6 per 100,000 person-years (22.0-31.7). Moreover, men were more likely than women to have all types of psychotic disorders (rate ratio: 1.44 [1.27-1.62]) and non-affective psychotic disorders (rate ratio: 1.60 [1.44-1.77] (65). While generally following this pattern, findings from the INTREPID-II study indicated sex differences also vary by context, with women in some regions of India and Nigeria showing a higher likelihood of developing psychosis than men (62). A multisite incidence study in Europe reported an incidence of psychotic disorders of 21.4 per 100,000 person-years (95% confidence interval [CI]: 19.4-23.4 per 100,000 person-years), with an incidence of 16.9 (95%CI: 16.2-17.6) per 100,000 person-years for non-affective psychosis and 4.3 (95%CI: 3.9-4.6) per 100,000 person-years for affective psychosis. Moreover, an eight-fold

variation in the incidence of psychosis was observed across the six countries, ranging from 6.0 (95%CI: 3.5-8.6) to 46.1 (95%CI:37.3-55.0) per 100,000 person-years (66).

In LMICs, specifically, studies on incidence of psychosis have also reported heterogeneous estimates. In Taiwan, a population-based study using insurance registers between 1997 and 2001 reported an incidence of schizophrenia of 63.1 per 100,000 person-years (67). In China (Beijing), an incidence study conducted between 1974 and 1979 reported a rate of 11.0 per 100,000 person-years (68). In Sao Paulo, Brazil, a study carried out from 2002 to 2004 reported an incidence of all psychoses of 15.8 per 100,000 person-years (69). Finally, in Jamaica, a study estimated an incidence of schizophrenia of 23.6 per 100,000 person-years in 1992 (70). More recently, a 2023 systematic review and meta-analysis including 10 LMICs reported incidence rates ranged from 10.1 per 100,000 person-years (95% CI: 8.7–11.4) in Brazil to 42.0 (95% CI: 32.2–54.8) in India (11).

1.4 Global burden

Globally, psychotic disorders contribute significantly to the burden of disease for mental disorders. Mental disorders rank as the seventh leading cause of disability-adjusted life years (DALYs), with an age-standardized DALY rate of 1,426.5 (95% UI: 1,056.4–1,869.5) per 100,000 population for men and 1,703.3 (95% UI: 1,261.5–2,237.8) per 100,000 population for women (2019). Among mental disorders, psychotic disorders account for 12% of DALYs, surpassed only by depressive disorders (37.3%) and anxiety disorders (22.9%) (71). In 2019, mental disorders were the second leading cause of years lived with disability (YLD) worldwide. Among them, depressive and anxiety disorders ranked 2nd and 8th, respectively, while schizophrenia ranked 20th (71).

The global burden of psychosis disproportionately affects LMICs, where an estimated 80% of individuals with psychosis reside (4).For instance, a 2004 WHO report indicated that the prevalence of schizophrenia was higher in LMICs (13.1 million) than in HICs (2.2 million) (12), and that schizophrenia was the sixth leading cause of YLD in LMICs (accounting for 14.8 million YLDs; 2.8% of total YLDs), whereas it was not in the top 10 causes of YLDs for HICs (12). The 2016 Global Burden Disease study reinforced this finding, showing that schizophrenia had four times more YLDs in lower-and upper-middle income countries than in HICs (13). Globally, albeit with variation between contexts, people with psychotic disorders, especially schizophrenia, experience stigma and discrimination (experienced and anticipated) at levels higher than most other mental disorders (72,73). Such experiences can also have genders-specific patterns, for instance, in India with women with psychosis often face the burden of not being seen as marriageable or of broken marriages, with being married being a critical desirable social status (74,75).

1.5 Societal and economic burden

Psychotic disorders also generate profound socioeconomic consequences. For individuals with psychosis and their families, poverty often becomes a consequence, as the illness can disrupt education, employment, and income generation, leading to long-term financial instability (76). Households with members affected by psychotic disorders, particularly in LMICs, are at heightened risk of “catastrophic health expenditures”, as the cumulative costs of long-term treatment, medications, and ancillary care can constitute a substantial proportion of household income, often exacerbating economic vulnerability and poverty (77,78). At a societal level, schizophrenia imposes substantial costs, including direct healthcare expenditures and indirect

costs related to lost productivity, disability, and caregiving demands (79). These impacts are particularly pronounced in LMICs, where limited social protection systems exacerbate the economic burden on households and constrain broader societal resources (79). Evidence also shows that the economic toll extends across families, who experience enduring financial strain and substantial productivity loss (77).

1.6 Course

The development of a psychotic disorder is usually preceded by subtle alterations in thinking, perception, and decline in cognitive and social functioning, which is known as the prodromal phase (80). This phase typically begins in early adolescence and may precede the FEP by more than ten years (81). A recent review reported that about 78.3% of people with schizophrenia have this prodromal phase, while the remaining develop psychotic disorders without a clear prodrome (82). In this review, most of the available evidence came from HICs, with limited representation from LMICs (82); thus, these findings may not be generalizable to LMICs, where contextual factors may distinctly shape the onset of psychosis. A recent meta-analysis reported that 15% of people who were identified as being at clinical high risk developed a psychotic disorder within one year, while 25% made this transition within three years (81). Despite the disturbing symptoms of the prodromal phase, few people seek mental health care until psychotic symptoms become obvious and florid.

FEP usually begins in late adolescence or early adulthood, with 80% of cases occurring between the ages of 16 and 30 (83). However, important differences emerge when considering the country's income level. Findings from the INTREPID-II study, for example, showed that psychosis onset occurred earlier in Trinidad and Tobago (a HIC) compared to India and Nigeria (both LMICs)

(84). This critical stage in life coincides with a period of major developmental challenges including forming a stable identity, peer networks, academic achievement, vocational training, and intimate relationships (26). Thus, a FEP can affect social, educational, and vocational development of those affected, as well as result in significant functional decline, and reduced well-being and quality of life (26). It also causes considerable distress and social consequences for families (85). About 80% of people with FEP achieve positive symptom remission with antipsychotic medication (86,87). However, some experience relapses (88), owing to a combination of factors, including medication discontinuation (89), difficulties with health service access (90), and substance use in the first years after the diagnosis (91).

1.7 Prognosis

Once they emerge, psychotic disorders follow variable courses. While some individuals achieve full recovery and return to their premorbid level of functioning, others experience persistent mild symptoms with episodic exacerbations that require ongoing care. A third group develops a treatment-resistant form of illness, often marked by frequent relapses, significant functional impairment, persistent symptoms despite treatment, and a greater need for intensive mental health care (92). In general, individuals with psychosis have a life expectancy approximately 20 years shorter than that of the general population (93). Mortality among persons with psychosis has been raised as being particularly high and concerning in some low- and middle-income countries (94).Suicide is the leading cause of death in the early stages of the illness (95,96), while cardiovascular diseases become more prominent later in life, largely due to high rates of smoking, unhealthy lifestyles, weight gain from antipsychotic medications, and metabolic syndrome (97).

Notably, metabolic disturbances may already be present during the prodromal phase of psychotic disorders (98).

Traditionally, a sense of pessimism has shaped the prognosis of psychotic disorders, rooted in the early 19th century conceptualization of schizophrenia (26). Long-term disability was considered inevitable, and recovery was often seen as unlikely. This perspective contributed to reduced investment in the care of people with psychosis and reinforced stigma towards and social exclusion of people with this severe illness (27). However, the past decades have witnessed a shift in this perspective toward one that recognizes the potential for recovery, emphasizes early intervention, and promotes a more hopeful and person-centered approach to care (28). The EIP approach has emerged as a model of care demonstrating that better clinical and functional outcomes are achievable when intervention occurs early and individuals receive comprehensive, phase-specific support (28).

Section 2: Early Intervention in Psychosis

2.1 Conception of the EIP paradigm

Efforts to study the early stages of psychosis have been conducted during the 20th century. For instance, Klaus Conrad described “incipient schizophrenia” as a phenomenological progression unfolding in four phases: trema, apophany, anastrophe, and consolidation (99). Similarly, Gerd Huber conceptualized “basic symptoms” as subtle, self-experienced disturbances in perception, thought, speech, and related domains, which are considered early indicators of emerging psychosis (100,101). However, the modern concept of early-stage psychosis, as understood today, originated predominantly in Australia in the 1980s (102,103). Initially, the goal of this

Australian initiative was to observe people in the early stages of illness without the confounding factors present in multi-episode patients, in order to gain greater insight into its origins (27). It became evident, however, that people with FEP had distinct clinical needs, and that the management used for those with multiple episodes was inadequate for people with FEP.

The desire to improve outcomes in people in early stages of psychosis led to the launch of a unit for individuals with FEP at the Royal Park Hospital (Australia) in 1984 (27). Knowledge accumulated regarding the care of people with FEP during the 1980s led to the establishment of the Early Psychosis Prevention and Intervention Centre (EPPIC) at the hospital in 1991 (28), and around the same period, other EIP programs were launched in Canada, the UK (United Kingdom), Denmark, Norway, Singapore, and Hong Kong (31,104). EPPIC made significant changes to traditional forms of mental health care for psychosis. The program adopted an early detection and community-based model, with hospitalization as a backup, included a mobile early psychosis assessment and detection team, and introduced a recovery-oriented outpatient group program and case management (27). By that stage, the Personal Assessment and Crisis Evaluation clinic was also established at the hospital for identifying and treating people in the prodromal phase of psychosis (105). The development of the ultra-high-risk criteria allowed for greater clinical and scientific advances in these areas (106).

All efforts regarding the study of FEP and clinical high risk (CHR) for psychosis are largely grounded in the critical period hypothesis. This hypothesis posits that, “the early phase of psychosis may be viewed as a period during which it is possible to determine which path an individual is ultimately likely to follow,” and “this phase is also a major influence with implications for secondary prevention of the impairments and disabilities that accompany psychosis (107)”.

The occurrence of a neurotoxicity mechanism during this early phase, has been proposed to explain its harmful effects of the illness (108), Although this hypothesis remains unproven (109,110), a “social toxicity” mechanism, characterized by stigma, social isolation, and discrimination has been proposed to explain the adverse outcomes in psychosis (111).

2.2 Target population

The target population for EIP includes individuals in two distinct phases: those suspected to be in the prodromal phase of psychosis and those experiencing a FEP (26). The prodromal phase is defined as a subclinical stage that precedes the onset of full psychosis, characterized by attenuated or brief intermittent psychotic symptoms, functional decline, and behavioral or cognitive changes (26). Identification is typically conducted using structured instruments such as the Comprehensive Assessment of At-Risk Mental States (112), and the Structured Interview for Psychosis-Risk Syndromes (113).

FEP refers to the stage when a person experiences psychotic symptoms for the first time that meet diagnostic criteria for a psychotic disorder according to ICD-11 or DSM-5 (37,38). In the scientific literature, the FEP has been operationalized in one of three ways: initial contact with mental health services for psychosis; a set threshold for the duration of untreated psychosis, and a set threshold for the length of time the individual has been receiving antipsychotic medication (114).

2.3 Structure of EIP

EIP is a comprehensive and evidence-based approach aimed at identifying and treating psychotic symptoms in their early stages to reduce long-term adverse consequences and prevent relapses

(31). The intervention focuses on individuals with FEP and those at CHR (although CHR services are not always part of EIP services) and also involves the families and caregivers of service users. EIP programs provide pharmacological, psychological and psychosocial strategies to service users over 1-5 years, and include specific strategies at the health system and population levels (i.e. outreach, publicity or case identification efforts, easy access to health services) (115). The aim of the intervention is not only to improve clinical outcomes but to promote personal recovery that allows a full integration of the person in society (28).

EIP comprises the principles of *early detection* and *phase-specific treatment* (116). Early detection is defined as either the identification of people at CHR or people with FEP, with as short a delay post onset as possible (116). The goal here is to reduce DUP, simplify pathways to care and provide an engaging, soft landing into care, as opposed to through negative traumatic pathways like emergency rooms, police involvement, etc. Systematic reviews and meta-analyses have shown that DUP exerts a modest but significant impact on both clinical and functional outcomes (24,25). The "social toxicity" of DUP is now well acknowledged, with treatment delays often entail suffering for affected individuals and their families, interrupt vocational and romantic milestones, result in ruptures in family and peer relations causing loneliness (117,118). Most EIP services facilitate access by providing assessment and treatment with minimal delay after help is sought or within established wait time standards. Some EIP services also proactively promote early detection through community outreach, promoting psychosis awareness among healthcare providers and in educational settings or generally informing the public (119,120).

Phase-specific treatment is defined as the package of medical, psychological, psychosocial strategies that are specifically targeted to people in the early stages of psychosis (116). The

phase-specific nature of early psychosis treatment also involves tailoring interventions to the different stages of the illness, with strategies like psychosocial support and cognitive behavioral therapy (CBT) during the prodrome or clinical high-risk stage and then integrating medication and more intensive psychological treatments during the acute and recovery phases (121).

The provision of multiple components is essential, as each strategy impacts a specific outcome and people with psychosis often present with a range of needs (122). For instance, antipsychotic medication relieves or eliminates positive symptoms (123), case management can help ensure care coordination and service engagement (121), cognitive behavioral therapy often treats refractory positive symptoms and comorbid anxiety and depression (124), family interventions often reduce relapse rates and improve family communication and functioning (125), and vocational interventions may improve educational and employment-related functioning (126). Therefore, EIP strives to deliver a range of treatment components tailored to the specific needs of individuals with psychosis. Many EIP services restrict their services to youth, either between the ages of 18 and 30 years or 14 and 30-35 years. This has been questioned in the UK (127) where recent National Institute for Health and Care Excellence guidelines and the National Health Service (NHS) Long Term Plan now recommend the age range of 14-65 years for EIP services (128,129). In many jurisdictions in the world, like Australia, Denmark and Canada, EIP services do tend to exclusively serve adolescent and young adult populations. EIP also prioritizes being developmentally appropriate, often ensuring that care is provided in youth-friendly settings and focuses on age-appropriate goals like peer relations, educational or employment goals, etc.

2.4 Effectiveness of EIP care

a) *First-episode psychosis*

Randomized controlled trials have shown the effectiveness of EIP compared to treatment as usual for people with FEP in different countries. The OPUS trial in Denmark reported significant improvements in negative and psychotic symptoms, reduced comorbid substance use, and greater satisfaction with treatment over a two-year follow-up period (130). The Lambeth Early Onset trial in the UK reported better contact with services and fewer readmission to hospital after 18 months of follow-up (131). The Recovery After an Initial Schizophrenia Episode Early Treatment Program study (RAISE) in the United States of America (US) found that participants receiving coordinated specialty care had improved quality of life, greater engagement in work or education, and reduced symptom severity over a two-year follow-up compared to those receiving treatment as usual (132).

Two major systematic reviews with meta-analysis have synthesized the benefits of EIP compared to treatment as usual. The review by Correll, which included 10 randomized controlled trials, found that EIP was significantly superior to treatment as usual in improving all-cause treatment discontinuation, psychiatric hospitalization, involvement in school or work, among other variables of interest (29). Similarly, the review by Puntis, which included 4 trials, concluded that EIP reduced the likelihood of hospitalization, improved global functioning, and increased service engagement and patient satisfaction. Although some outcomes had moderate risk of bias, the evidence consistently favored EIP over standard care across multiple domains (30).

EIP is further supported by multiple economic evaluations indicating that it offers greater cost-effectiveness than treatment as usual. In the United Kingdom, McCrone reported that EIP did not lead to higher overall costs and was very likely to be a cost-effective alternative to standard care (133). In Australia, Mihalopoulos reported that 56% of people in the EPPIC cohort were in paid

employment over the previous two years, compared to 22% in the control group. The annual cost per EPPIC patient was A$3,445, while the cost per control patient was A$9,503 (134). In the US, Rosenheck found that coordinated specialty care led to improved quality of life, albeit with higher associated costs. Nevertheless, the clinical gains observed were considered sufficient to justify the additional spending (135). In a review of 14 studies, Shields found that health and social care interventions for people at CHR or with FEP were generally cost-effective despite higher initial investment; the benefits in terms of improved symptoms and quality of life were considered likely to outweigh the expenses (136).

Although EIP programs improved clinical and functional outcomes after two years, these effects were not sustained at five or ten years (137–139). Addressing this, randomized clinical trials have examined whether the positive effects observed in patients receiving EIP treatment could be maintained with prolonged intervention. A Canadian study showed that extending treatment to five years led to longer mean durations of remission of both positive and negative symptoms, along with other benefits, compared to regular care (140,141). In contrast, a Danish study found that prolonging EIP to five years had limited effects, which may be attributable to the high level of treatment received by control participants and the late initiation of specialized care (142). In Hong Kong, a randomized trial found that after two years of standard EIP, providing one additional year of specialized care significantly increased the likelihood of achieving functional remission compared to transfer to usual services, underscoring the benefits of prolonging intervention for FEP (143). A Cochrane review put together evidence from all three trials and concluded that while evidence for extending EIP for all other outcomes remains uncertain, extended EIP seems to have clear benefits with respect to reducing service disengagement rates (139).

b) Clinical high-risk for psychosis

Although to a lesser extent than in FEP, evidence supports the effectiveness of EIP for individuals at CHR. Within CHR programs, several strategies have been tested with the primary goal of preventing transition to a first episode of psychosis (i.e., supportive therapy, family therapy, antipsychotics). Among these, cognitive behavioral therapy has shown particular promise in reducing transition risk. Studies evaluating CBT alone (144), specifically designed for CHR populations (145), or integrated with other interventions such as group skill training, cognitive remediation and multifamily psychoeducation (146), have reported lower transition rates compared to controls conditions. However, other studies have found no significant benefit of CBT alone or in combination with antipsychotics in preventing transition to psychosis (147,148).

Two recent systematic reviews with meta-analyses have synthesized evidence on interventions for individuals at CHR. Devoe's review of 38 randomized controlled trials found that CBT significantly reduced transition risk at 12 and 18 months. However, the network meta-analysis, also included in the study, did not identify a single superior intervention among CBT, integrated psychological therapy, supportive therapy, family therapy, needs-based interventions, omega three, and antipsychotics, likely due to small sample sizes (149). Mei's review, which included 26 trials, also found that preventive interventions significantly reduced transitions at 12 months, with CBT showing sustained benefits at both 12 and 18 to 48 months. In contrast, antipsychotics and omega three did not demonstrate consistent effects (150).

Studies that have examined the economic impact of EIP for individuals at CHR suggest that intervention is cost-effective. Valmaggia evaluated a service for individuals at CHR in the UK and

found that although EIP was initially more expensive than treatment as usual at 12 months, it led to cost savings at 24 months (151). Ising, in a multicenter randomized controlled trial in the Netherlands, reported that the addition of CBT to standard care led to fewer transitions to psychosis and lower overall costs, with a favorable cost-effectiveness profile (152). Shields, in a systematic review, analyzed economic evaluations of CHR interventions and found that all four included studies showed a high probability, greater than 80% of being cost-effective, supporting the economic value of EIP in this population (136).

Over the years, observed conversion rates among individuals at CHR have declined, with recent cohorts showing transitions of approximately 25.7% within three years, a decrease from earlier reports of 31.1% (153). This decline may reflect broader referral patterns, earlier detection of less severe symptoms, and improved early intervention (153–156), but it also underscores that many individuals who later develop FEP are never captured by CHR services due to many reasons, including late help-seeking, seeking help in services other than CHR services, atypical symptom presentation and age factors (157). The lower conversion rates notwithstanding, there is a clear acknowledgement that most people presenting to CHR services often have high levels of distress, functional deficits and complex needs (158,159). Partly in response to these findings, there is growing interest in transdiagnostic or "broad" high-risk or youth mental health services that provide early support for a range of emerging mental health difficulties, including mood and anxiety disorders, rather than focusing narrowly on psychosis (160,161). Such approaches aim to mitigate functional decline and distress across transdiagnostic risk categories, recognizing that the impact of high-risk services may be limited if applied only to narrowly defined psychosis risk populations and the pluripotential trajectories from various high-risk states (e.g., those at CHR for

psychosis may go on to develop disorders other than psychotic disorders; youth who have hospitalizations for self-harm are at higher risk for developing psychosis later on, etc.) (162).

Section 3: Implementation of EIP programs

3.1 EIP programs in HICs

Based on the Australian experience from the 1980s, EIP services were also established in many HICs in the United Kingdom, Europe, North America and Asia from the 1990s onward (26). There are now hundreds of EIP programs of varying intensity and duration (26), which have been scaled up within each distinct healthcare system. EIP programs have been implemented at the national level in Australia (163), England, the Netherlands, Wales, Norway, Denmark (164,165), Singapore (166), and the United States, where this care model is considered the standard treatment for FEP (31). At a regional level in Canada, this model has been implemented in Quebec, Ontario, Alberta, British Columbia, Manitoba, New Foundland and Labrador and Nova Scotia, but services are still not consistently available in remote or rural areas (31). Some HICs have had difficulty adopting this service model which results in EIP services being offered by individual health organizations. This is the case of Spain and Italy where there are some research-based programs, mostly funded by research grants and some EIP services implemented within community mental health centers (31).

Implementation programs in HICs have been developed with strong economic and political support. In the UK, the Department of Health's Plan for the National Health Service stated that 50 EIP programs for young people with FEP aged 14–35 years would be established across England by 2004 (169). In Canada, Quebec's Ministry of Health and Social Services demonstrated its

commitment by developing EIP programs across all regions, including a recurring annual investment of $10 million dedicated to the implementation and maintenance of 15 new programs (170). The province now has 33 programs with coverage for about 88% of the population (170). In Australia, the Commonwealth Government allocated $248.6 million to establish nine EPPIC-model programs within designated headspace (171). These investments underscore the recognition in HICs that EIP is a critical component of the mental health system.

Additionally, EIP program implementation in HICs has been guided by clinical guidelines, implementation guides and fidelity scales. Several countries (or jurisdictions within countries in the case of countries with federated healthcare systems like Canada) have developed their own EIP guidelines which provide information on program operations (35,172,173). These guidelines outline the roles of team members, the core components of EIP services, and recommended assessment instruments. With a perspective on implementation, some countries have elaborated implementation guides that consider context-specific barriers and enablers (171) or have evaluated their implementation process using implementation frameworks (174). Once established, EIP programs are often monitored using fidelity scales or against benchmarks or standards (175–178). These tools assess how closely EIP programs adhere to the core principles and components of the EIP model and help determine whether services are delivered as intended and at the expected level of quality.

3.2 EIP programs in LMICs

In general, progress in implementing EIP services in LMICs has been slow and piecemeal (179–183). LMICs face different challenges that hinder the implementation of new mental health interventions. There has sometimes been a resistance to the decentralization of mental health

services in these settings; few health workers are trained in mental health care; it has been difficult to implement mental health care within primary-care settings; there is a limited attention to public health perspectives in mental health; and there is a shortage of funds allocated to mental health by governments (184). Therefore, evidence-based mental health interventions, including EIP programs, remain scarce in most LMICs (33). Still, researchers have designed ways to include EIP programs in settings with fewer resources because of the evidence supporting their benefits to patients (180). EIP programs have been implemented in LMICs across regions such as Asia (181), Central and Eastern Europe (182), Africa (186,187), and Latin America and the Caribbean (LAC) (179,180).

In Central and Eastern Europe, EIP programs have been implemented in three LMICs (Belarus, Serbia and Ukraine). These programs are mostly hospital-based, state-funded, healthcare sites for adolescents and young adults with no national plans for EIP development. The number of sites per country ranges from 1 to 3 in most countries (182). There is a striking lack of EIP programs in the African context (183). Although countries such as Nigeria (188,189), Malawi (186,187), and Uganda (190) have published studies conducted on FEP, to our knowledge, only one pilot EIP program exists in Malawi (Saint John of God community services)(187), and one EIP program in Ghana (191). Asian countries have made significant progress in EIP program development with the establishment of the Early Psychosis Declaration for Asia formulated by the Asian Network for Early Psychosis (192). Of note, this effort was championed by Singapore and Hong Kong, both of which are HICs (104,166). Beyond these two contexts, EIP programs have been implemented in specific parts of India and China (192,193). Indonesia and South Korea (an HIC) have conducted some research on FEP (194,195). In general, however, EIP is not widespread in Asia.

LAC has made some advances in EIP program implementation in recent years. A 2011 narrative review identified EIP programs only in Brazil and Mexico, primarily based in research institutions or universities (179). By 2020, a scoping review reported EIP programs in four countries: Brazil, Mexico, Chile and Argentina (180). However, closer examination revealed that the Argentinian initiative was not a formal program but rather a study involving people with FEP. These programs were concentrated in tertiary care settings, typically located in research centers in capital cities (180). A 2025 review indicated that the overall level of EIP programs in LAC remained largely unchanged (34). Although Bolivia proposed a pilot EIP program in the city of Santa Cruz (196), the project was never implemented. Thus, only three countries (Mexico, Brazil and Chile) have established some EIP programs in LAC according to published literature, thus far.

In addition, the implementation of EIP programs in LMICs has not been conducted systematically but has instead evolved over time in response to local population needs and available resources, and the initiative of a few local champions (197). Systematic implementation has been limited by the absence of clinical guidelines and the lack of fidelity monitoring. Moreover, most EIP programs have emerged as single-site projects with restricted local coverage (179), rather than under the aegis of public funds and policy commitment as commonly observed in many HICs (31).

Section 4. Addressing the Implementation of EIP in LMICs

4.1 Research capacity in EIP

Research has the potential to significantly improve mental health services in LMICs. Evidence generated through research is essential for identifying needs, designing culturally and contextually relevant and cost-effective strategies, and monitoring intervention implementation (198). In these

settings, such information is crucial for optimizing the limited mental health resources available (199). However, the research gap, defined as the difference between the research information that is needed to plan the best possible services in a given setting and what is currently available, is still large in LMICs (198). Addressing this challenge is critical to developing contextually appropriate and scalable interventions that meet the specific needs of LMIC populations.

However, conducting mental health research in LMICs remains difficult (198). Historically, mental health research has received little attention from health authorities, resulting in scarce dedicated public funding schemes (200). The shortage of trained researchers is compounded by brain drain, with skilled professionals often migrating to HICs in search of better opportunities (201,202). Low researcher salaries further hinder capacity building, and in many cases, policies prevent the use of research grants to supplement income (203). Within international collaborations, researchers frequently face implicit or explicit pressure to adopt Western models or agendas (204). Weak infrastructure further restricts access to laboratory facilities, technological resources, scientific journals, and robust data systems (203). Language barriers, particularly related to publishing in English-language journals, further limit dissemination (205).

These constraints have contributed to the low scientific output in mental health observed in LMICs, reflected in the limited number of publications in major databases. For instance, 94% of mental health research indexed in the Web of Science (formerly known as the ISI database) originates from HICs, with LMICs contributing only 6% (206). Similarly, 94% of psychiatric research published in six high-impact peer reviewed journals comes from North America and Western Europe, while just 6% originates from South America, Eastern Europe, Africa, and Asia (207,208). Although recent studies suggest growth in mental health and schizophrenia research

from LMICs (209–211), this increase seems to be insufficient to substantially reduce the global research gap seen in LMICs (209), as this growth is only addressed by some upper-middle income countries (Brazil and China) (210).

Much of the mental health research that exists in LMICs has focused on descriptive epidemiology—documenting prevalence, risk factors, and treatment gaps—rather than on intervention, implementation, or health systems research, leaving substantial gaps in knowledge on how to design and scale effective services (212–214). This imbalance has been repeatedly highlighted in global mental health priority-setting exercises, which emphasize the need for pragmatic trials, studies leveraging local health data, implementation studies, and systems-focused research to generate actionable evidence (215,216).

Given this context, scientific collaboration has been proposed as a strategy to strengthen research output (217). Evidence shows that collaboration increases both research productivity (218,219), and citation impact by improving access to resources and technology (220). While scientific collaboration can take many forms (221), these partnerships often involve institutions with different research capacities, enabling researchers in less resourced settings to access expertise, knowledge, and infrastructure from more advanced counterparts (204,222). Mutual trust, translation of findings into policy and practice, and the development of local research capacity should guide its rollout (223). Currently, several funding agencies promote collaboration by including it as a requirement in their funding schemes (218).

However, despite the potential benefits of scientific collaboration, HICs and LMICs partnerships remain relatively uncommon in practice. Between 2015 and 2022, only 2.7% of articles published

in the *Nature Index* included at least one author affiliated with an institution in the global North and one from the global South (North representing HICs and the South representing LMICs). Moreover, research indicates that 85% of international collaborations involving the US and UK are limited to one or two partners, typically from other high-income economies (224). In addition, some HICs-LMICs partnerships have sometimes been criticized for still reflecting a "semi-colonial" character, in which power asymmetries persist and local priorities may be sidelined (223,225).

In HICs, the development of EIP has been supported by a robust body of research on the early phases of psychosis. In contrast, the extent to which similar research informs EIP-related efforts in LAMICs remains unclear. Research not only generates knowledge but also fosters local capacity by building skills and training, representing valuable intangible capital (198). Although scientific collaboration is recognized as a key strategy to enhance research output and impact (218–220), the involvement of LMICs in collaborative EIP research has not yet been evaluated at a global level. Examining the scientific output of LAMICs and their patterns of collaboration with HICs could provide key insights into the current landscape of EIP research and identify opportunities to strengthen global research capacity in this field.

4.2. Configuration of EIP programs in LMICs

The design of EIP programs varies considerably across real-world settings. This variation often arises from the implementation setting (i.e., standalone programs or integrated into community mental health centers) (226), the organizational principles adopted (i.e., age range or definition of FEP), the availability of local resources, and the need to adapt strategies to the needs of the population. While a certain degree of adaptation is necessary to support the implementation and

sustainability of interventions in real-world contexts (227), extensive modifications may compromise the effectiveness (176). In response, EIP programs in HICs have developed clinical guidelines (35), implementation guidelines (172,228), and fidelity scales to guide service delivery and ensure that service users receive recommended components of EIP care (176).

A major source of variability in EIP program design lies in the range of treatment components offered. EIP programs usually offer a broad range of treatment components (228), which may include pharmacological, psychological, and psychosocial and nutritional strategies (229–231). The delivery of multiple strategies is both favorable and understandable, because each strategy has a different profile of effectiveness with respect to specific outcomes (122). For instance, while family intervention can reduce relapse and hospitalization rates (232), CBT is effective in reducing symptom severity (233). Moreover, offering different components helps address the diverse needs of individuals with psychosis and their families, including support for coping with life stressors, treatment for co-occurring physical or mental health conditions, and assistance with returning to work or school (234,235).

However, delivering all guideline-recommended components is challenging even in HICs. For example, a study of 31 US programs found that, out of 32 essential components, only 18 were implemented by more than 25 programs, with psychoeducation and outcomes tracking being most common, and outreach and inpatient coordination least frequent (236). Similarly, a fidelity assessment of 36 US programs reported only 2 (6%) with excellent fidelity, 25 (69%) with good fidelity, and 9 (25%) with fair fidelity (177). Other studies have also noted inclusion of non-recommended components, raising potential concerns about adherence to the EIP model (170).

This finding ultimately underscores the challenge of providing all EIP components in real-world settings.

EIP programs in LMICs have largely been modeled after those developed in HICs, aiming to incorporate the core principles and components of the EIP model. However, implementing mental health interventions, particularly complex multicomponent ones, in resource-limited settings is challenging due to the interplay of factors (214,237). These include limited financial resources, shortages of trained personnel, inadequate infrastructure, and broader difficulties in delivering comprehensive mental health care (17). For example, treatment for individuals with psychosis in LMICs often relies primarily on the provision of antipsychotic medication, with few people acceding to receiving comprehensive, multidisciplinary care (238,239). Given these constraints, it remains unclear which treatment components are delivered within EIP programs in LMICs.

In this vein, although the efficacy of treatment components offered in EIP programs has been well documented in HICs (29,30), their effectiveness in LMICs has not been systematically evaluated. In many LMICs, EIP programs have been introduced without embedded research frameworks to assess their outcomes or contextual relevance, often replicating models developed abroad (197). As a result, it remains unclear whether the clinical benefits observed in HICs are reproduced in settings where health system limitations and sociocultural factors may influence outcomes. Moreover, in the absence of robust evaluation mechanisms, it is difficult to determine which components of EIP are most effective or feasible within LMIC contexts. Addressing this evidence gap is essential to ensure that future investments are guided by data that are both contextually relevant and empirically grounded.

To date, only one systematic review has evaluated EIP for FEP in resource-limited settings, concluding that EIP can be implemented with adaptations for cultural and resource constraints. Although valuable, this review focused exclusively on English-language papers from low- and lower-middle-income countries (240), limiting the understanding of how EIP is configured across all LMICs. Without detailed information on delivered components and their effectiveness, it is difficult to assess alignment with best practices or to determine whether programs encompass all the core strategies of the intervention. Generating such evidence is essential to identify feasible, high-impact elements and guide the development of contextually appropriate care models.

4.3. Implementation of EIP initiatives in HICs

The implementation of EIP programs in HICs has varied widely across countries, reflecting differences in health system organization, resource availability, political commitment, and sociocultural contexts (32). In some settings, EIP programs have been established within tertiary psychiatric hospitals, whereas in others they have been embedded in community mental health centers (241). Likewise, while some programs have been supported through public government funding, others have relied on research funding (32,242). Certain initiatives have been implemented solely as clinical programs, whereas others have combined clinical care with research activities (32,242). These variations have shaped the scope and sustainability of services, underscoring the importance of understanding local processes and contextual factors that facilitate or hinder implementation.

In England, for example, the NHS was an early adopter of the EIP paradigm in the mid-1990s, with initial programs tested in the West Midlands (32). Advocacy campaigns and evidence from the West Midlands and Australia catalyzed substantial investment in EIP programs (32). In 2000, the

government's NHS Plan announced the implementation of 50 EIP programs to provide community-based treatment for young people and their families (32). However, the 2008 economic crisis led to public expenditure constraints, resulting in the dilution of some teams and the integration of others into general mental health services (31). By 2016, this decline had been reversed with the introduction of a new policy requiring that 50% of people with FEP start an EIP care package within two weeks of referral and extend EIP to individuals up to 65 years of age (243).

In Denmark, the OPUS trial was initially established in 1996 with support from the Ministry of Internal Affairs and Health through a special grant (244). The positive outcomes of the OPUS trial facilitated the integration of this research-based initiative into the general mental health system (31,130). This transition was further supported by the Danish Parliament, which created special grants for regional health authorities to implement EIP programs nationwide (244). As a result, the number of EIP programs increased tenfold, from two in 1998 to 20 in 2013, covering all five Danish regions. National guidelines also require that individuals suspected of having a psychotic disorder be evaluated within one month of referral (31). Despite these advances, the OPUS research team argues that current capacity remains insufficient to meet clinical needs and must be increased by at least 50% (244).

In the US, EIP development advanced through a series of research initiatives culminating in the RAISE program (245). In 2009, the National Institute of Mental Health funded two RAISE projects: *the Implementation and Evaluation Study*, aimed at developing dissemination tools (246); and the *Early Treatment Program*, which tested the NAVIGATE multi-component treatment model in 34 community mental health centers across 21 states (132). NAVIGATE demonstrated positive

clinical and functional outcomes, particularly among people with shorter DUP (132) and that it was possible to implement EIP (or what they called “coordinated specialty care”) could be implemented in real-world, community-based settings. Based on these findings, the federal government invested US$24.8 million in 2014 and 2015 to expand Coordinated Specialty Care programs nationwide, with funding doubled starting in 2016 (245). EIP programs in the US grew rapidly, increasing from 12 in 2008 to more than 160 a decade later (247).

In 2019, the National Institute of Mental Health launched EPINET (Early Psychosis Intervention Network), a national research initiative in the US, which comprises regional “hubs” of coordinated specialty care programs across multiple states joined into learning health systems, and a national data coordinating center to accelerate evidence generation, support continuous quality improvement, and enhance early psychosis services (248). EPINET has rapidly proliferated research, including multi-site studies and many publications, rapidly informed treatment guidelines; and generated publicly available tools, manuals, and reports to support early psychosis programs nationwide (248,249).

As observed, the implementation of EIP programs in real-world settings has followed diverse pathways in HICs. From conception to sustainability, implementers have used context-specific approaches adapted to their health systems, resources, and policies. Likewise, different strategies have been used to overcome the variety of obstacles impeding widespread implementation within healthcare systems. Sharing evidence from countries where implementation has achieved appropriate coverage, fidelity, and quality standards can generate ideas and strategies that may inspire or guide implementation in countries where EIP is less well developed or not developed at all.

The implementation process of EIP programs in HICs is well documented in the literature (31,32), albeit with fewer reports and studies using systematic implementation and implementation science frameworks (250). Such information about implementation is generally lacking for LMICs. Although some studies have addressed EIP implementation in LMICs, they have primarily mapped the existence of programs and described their functional characteristics (180). However, no study has examined in depth the formal implementation process of EIP programs in LMICs. Understanding this process in LMICs is essential to examine how programs adapt to local contexts, identify factors that facilitate or hinder their implementation, and determine strategies to enhance their sustainability. Moreover, such an analysis may help clarify the evolution, current status, and innovation of the EIP paradigm when implemented in resource-restricted settings.

4.4 Mental Health Care for Psychosis in LMICs

Despite the significant high incidence of psychotic disorders in LMICs (11), mental health care for psychosis remains largely limited (251). Globally, the median treatment gap for schizophrenia and other affective-psychotic disorders in LMICs is 69%, reaching 89% in low-income countries, 69% in lower-middle-income countries, and 63% in upper-middle-income countries (252). Similarly, service coverage for psychosis, defined as the proportion of affected individuals accessing mental health care, remains low, ranging from 10.9% in low-income countries to 21.5% in lower-middle-income and 29.2% in upper-middle-income countries (253). These figures highlight that a substantial proportion of people with psychosis in LMICs remain untreated.

A key factor contributing to the lack of access to mental health services in LMICs is the limited availability and unequal distribution of care. Mental health services are often concentrated in specialized psychiatric hospitals located in large urban centers, leaving many regions

underserved (16). Where services are available, they primarily rely on pharmacological treatment, with limited access to psychosocial interventions, such as psychotherapy, family support, or psychoeducation (238,239). In this context, the WHO has recommended integrating mental health into primary care and developing community-based services to decentralize care (254). However, few countries have effectively implemented these recommendations, and a large proportion of people continue to receive care through outdated service models (255).

This context is largely reflected in LAC, a region composed mainly of LMICs (around 60%) that has historically faced persistent challenges in providing mental health care (256). A key milestone in the region's mental health reform process was the Caracas Declaration, a regional conference on the restructuring of psychiatric care held in Caracas, Venezuela, in 1990 (257). During this event, participants highlighted that standalone psychiatric hospitals often violated human rights and contributed to chronicity, creating institutional settings that perpetuated patient submission and worsened mental states (258). In response, the declaration advocated for integrating mental health services into primary care, shifting from hospital-based to community-based approaches, and protecting the human rights of people with mental disabilities (256,257).

However, the implementation of the principles of the Caracas Declaration has been uneven across the region (258–260). Most LAC countries continue to rely on a mental health care model centered on psychiatric hospitals, which absorb the majority of national mental health budgets (261). Public investment in mental health remains disproportionately low compared to other health conditions with a similar burden of disease. Moreover, a significant portion of available resources is still allocated to maintaining hospital-based systems that often fail to provide adequate care (261). By 2010, only three countries, Brazil, Chile and Belize, in the region had

adopted a national community-based model of care, while others made partial progress aligned with the Caracas Declaration's principles (256). These efforts remain insufficient to overcome the substantial challenges LAC countries face in transforming their mental health systems (256).

Within this regional context, Peru, a LMIC in LAC, initiated a national mental health reform in 2012. In alignment with international recommendations (262–264), the reform aimed to shift from a hospital-based model to a community-based model by integrating mental health services into primary and secondary care settings (265). As part of this effort, new community mental health centers were established nationwide (266), with 288 centers and 94 halfway houses established by December 2024 (266). Psychological services have also been integrated into many primary care facilities, and psychiatric inpatient units have been implemented within general hospitals (265). Building on these principles, the reform has aimed to increase the accessibility of mental health services throughout the country, with particular emphasis on reaching underserved areas (263,264).

The Peruvian mental health reform represents a major step toward improving care for individuals with mental disorders. However, while service availability has expanded, it is essential to assess whether these efforts have translated into improved access for this population. In particular, it is important to analyze whether people with psychosis are now accessing health services more frequently after the reform. This population often faces unique challenges, including stigma, poor insight, cultural beliefs and other barriers that hinder their access to services (267). Indeed, studies have shown that people with psychosis experience lower access to health services compared to individuals with non-psychotic mental disorders and other health problems (268).

Evaluating these changes is crucial for understanding whether the reform has improved equitable access to mental health care for people with psychosis.

Chapter 2. Research Rationale, Approach, and Context

2.1 Research rationale

The EIP paradigm offers a promising approach to reducing the burden of psychotic disorders in LMICs and other resource-constrained settings. However, replicating models from HICs, particularly the implementation of standalone EIP programs, may be unfeasible in these settings which may have limited their broader dissemination. Although some experts have more recently suggested focusing on the core components of EIP (269), this approach has not yet been translated into structured implementation models, partly because these components remain ill-defined and difficult to isolate given the heterogeneous needs of individuals with psychosis. Advancing the EIP field in LMICs and resource-constrained settings therefore requires moving beyond replicating standalone programs to developing context-sensitive models aligned with available resources, mental health system structures, and cultural contexts.

2.2 Objectives

The overarching goal of this thesis is to generate evidence to inform contextually appropriate strategies for developing and adapting EIP approaches in LMICs and other resource-limited settings, by assessing existing capacities, examining implementation experiences, and exploring the perspectives of implementers on scaling, adapting and implementing EIP approaches in resource-limited contexts (Table 1). The specific objectives of this thesis are:

a) To assess research capacities relevant to EIP in LMICs.

b) To examine clinical, research, and programmatic experiences with implementing EIP or its elements in LMICs.

c) To explore the perspectives of EIP implementers in (LAC) on developing, implementing, scaling and adapting EIP approaches in resource-limited settings.

d) To analyze patterns of health service utilization among people with psychotic disorders in Peru as a foundation for understanding system readiness for EIP implementation in LMIC and resource-limited contexts.

2.3 Research Questions

To address these objectives, the following research questions will be explored:

a) What is the scientific output on EIP in LMICs, and what is the extent of international collaboration in this area?

b) What components are included in care for FEP and CHR in LMICs, and how effective are these components in these settings?

c) How have EIP initiatives been implemented in LAC, and what are implementers' perspectives on developing, implementing, adapting and scaling EIP approaches in these settings?

d) What are the patterns of health service utilization among people with psychotic disorders in Peru, an LMIC in LAC?

2.4 Approach

The research questions of this dissertation are addressed through four research manuscripts. We used a distinct methodological approach (synthesis methods, quantitative analysis, and qualitative analysis) to explore each question. These manuscripts are situated in different contexts, moving from a global perspective that consolidates existing knowledge to a more

localized focus on specific implementation settings. The research questions also targeted different outcomes, including research capacity, service delivery, implementation processes, and access to health services. Likewise, the units of analysis varied across studies, ranging from scientific publications to EIP initiatives and health service records. The combination of diverse research approaches, analytical methods, and outcome measures ensured a comprehensive and in-depth examination of the topic under study.

In the first manuscript, we conducted a bibliometric analysis to evaluate the research capacity of LMICs in the field of EIP by examining research output and patterns of scientific collaboration. Research on EIP in HICs has built technical and clinical capacity, guided service development, and generated robust evidence on both effectiveness and cost-effectiveness. By assessing the contributions of LMICs to EIP research, we used research output as a proxy for their existing research capacity (as well as the capacity of research to inform the development of EIP initiatives in resource-limited settings). Moreover, adopting a global scope enabled us to assess patterns of scientific collaboration between LMICs and HICs and determine whether such collaborations had been established and sustained in the field of EIP.

In the second manuscript, we conducted a systematic review to assess the availability of multicomponent care for FEP and CHR in LMICs and evaluate its effectiveness in these settings. EIP programs are grounded in the principles of early intervention and phase-specific comprehensive treatment (116). While engaging individuals at CHR or with FEP fulfills the early intervention principle, little is known about the capacity of EIP programs in LMICs to deliver comprehensive care. Historically, these countries have faced challenges in providing adequate treatment for mental disorders (184), raising concerns about their ability to offer all essential EIP

components. In the review, we documented guideline-based treatment components using standardized instruments, as well as cultural adaptations of these components and novel, locally driven treatment components. Because treatment in LMICs is often delivered within the context of research studies (179), we also explored the components provided in these research-based interventions (203). This study adopted a global perspective and used systematic review methods to synthesize data from research articles examining EIP care in LMICs.

In the third manuscript, we present a case study that explores the implementation of EIP initiatives in the LAC region and examines implementers' perspectives on developing, adopting, implementing and disseminating the EIP paradigm in their settings. Although some LMICs have successfully implemented EIP initiatives, little is known about their experiences during the implementation process. These lessons may inform considerations for other LMICs seeking to develop or adapt EIP approaches. To capture these experiences, we conducted semi-structured interviews with primary implementers of EIP initiatives in the LAC region, applying implementation science methods throughout data collection, analysis, and presentation of results. We selected this region because it includes a significant number of LMICs (270), and has been the site of several EIP implementation projects (34,179,180).

In the fourth manuscript, we examined service utilization among individuals with psychosis in an LMIC from LAC. Peru was selected because of the availability of detailed national administrative health data, which allows for a robust analysis of service utilization patterns. This database, compiled by an official Peruvian government office, includes information from all health sectors and levels of care nationwide from 2018 onwards. Importantly, Peru is undergoing a mental health reform aimed at decentralizing care through the establishment of community mental health

facilities. Studying this context provides valuable insights into how policy-level changes may influence access to care for individuals with psychosis in Peru and other LMIC contexts. Through this paper, we aimed to generate a broader understanding of the state of health service access for people with psychosis in resource-limited settings. Such an understanding has critical implications for informing efforts to improve access for people with psychosis, including in underserved areas, and for thinking through decisions about embedding EIP in tertiary care facilities in urban centers versus community mental health facilities that are often spread across the country in LMICs.

Table 1. Conceptual Framework of the Thesis

General thesis	***Implementation of Early Intervention in Psychosis in Low- and Middle-income countries***			
Geneal objective:	Identify efficient and contextually appropriate strategies for implementing the EIP paradigm in LMICs by analyzing research capacity, program configuration and effectiveness, implementation processes, and health service utilization.			
Study	**Study 1:** Research capacity on EIP in LMICs	**Study 2:** Configuration of EIP programs in LMICs	**Study 3:** Implementation of EIP initiatives	**Study 4:** Mental health care in LMICs
Context	Global	Global	Latin America and the Caribbean	One LMIC (Peru)
Specific objective	Determine the scientific output and the level of international collaboration on EIP in LMICs.	Determine the EIP components available in EIP programs in LMICs and evaluate their effectiveness in these settings.	Understand the implementation process of EIP initiatives in LMICs and evaluate implementers' perspectives on the dissemination of the EIP paradigm in these settings.	Evaluate health service utilization among people with psychotic disorders in Peru in the context of the mental health reform.
Design	Bibliometric study	Systematic review	Case study	Cross-sectional study
Outcomes:	Scientific output Scientific collaboration	EIP configuration Effectiveness	Implementation process Dissemination perspectives	Service utilization
Unit of analysis	Scientific publications	Scientific publications	EIP initiatives	Health records

Chapter 3

Manuscript I

How “global” is research in early intervention for psychosis? A bibliometric analysis

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How "global" is research in early intervention for psychosis?

A bibliometric analysis

Abstract

Introduction: Unlike high-income countries (HICs), there are few early intervention services for psychosis in low-and middle-income countries (LAMICs). In HICs, research spurred the growth of such services. Little is known about the state of EIP research in LAMICs, which we address by examining their research output and collaborations vis-à-vis that of HICs.

Methods: We conducted a search in Scopus database for early psychosis publications in scientific journals since 1980. Data from each record, including title, author affiliation, and date, were downloaded. For HIC-LAMIC collaborations, data on first, corresponding and last authors' affiliations, and funding were manually extracted. Descriptive statistics and social network analysis were conducted.

Results: Globally, early psychosis publications increased from 24 in 1980 to 1,297 in 2022. Of 16,942 included publications, 16.1% had LAMIC authors. 71.3% involved authors from a single country (regardless of income level). 21.9% were collaborations between HICs, 6.6% between HICs and LAMICs, and 0.2% among LAMICs. For research conducted in LAMICs and involved HIC-LAMIC collaborations, the first, last, and corresponding authors were LAMIC-based in 71.8%, 60.7%, and 63.0%, respectively. These positions were dominated (80%) by authors from four LAMICs. 29.4% of the HIC-LAMIC subset was funded solely by LAMIC funders, predominantly two LAMICs.

Conclusions: LAMICs are starkly underrepresented in the otherwise flourishing body of early psychosis research. They have far fewer collaborations and less funding than HICs. Closing these

gaps in LAMICs where most of the world's youth live is imperative to generate the local knowledge needed to strengthen early psychosis services that are known to improve outcomes.

How “global” is research in early intervention for psychosis?

A bibliometric analysis

1. Introduction

Over the past three decades, there has been growth in research and service reform focused on the early stages of psychosis, particularly first-episode psychosis and ultra-high risk (McGorry et al., 2008). Along with diagnostic criteria, first-episode psychosis has been defined in terms of a first treatment contact; no (or less than a pre-defined period) of prior antipsychotic treatment, and/or a pre-defined duration since onset of psychotic symptoms (Breitborde et al., 2009). Ultra-high-risk status is inferred from the presence of sub-threshold severity or duration of symptoms or family history of mental illness with/without declining functioning (Yung et al., 1998). Early intervention services for psychosis, comprising developmentally appropriate, phase-specific, high-quality, intensive, recovery-oriented care for two to three years, have proven superior to standard care in improving clinical and functional outcomes (Correll et al., 2018). Early intervention services are the standard of care in many high-income countries (HICs) (Csillag et al., 2016, 2018). In low- and middle-income countries (LAMICs), where 80%+ of people with psychosis live (World Bank, 2024), their implementation has been slow and fragmented (Brietzke et al., 2011) and their availability remains scanty (Maric et al., 2019). There are calls to implement early psychosis intervention more widely in LAMICs (Farooq et al., 2009).

Along with resource scarcity (Saraceno and Saxena, 2004), a dearth of research impedes the wide implementation of appropriate mental health interventions in LAMICs (Thornicroft et al., 2012; Loch et al., 2023). Knowledge from research is pivotal in planning, implementing and advocating for mental health services and policies (Razzouk et al., 2010), but mental health

research production and capacity are scarce in LAMICs (Larivière et al., 2013; Razzouk et al., 2010). Mental health research is underfunded everywhere but especially in LAMICs, which receive ≈2.4% of global mental health research funds (Woelbert et al., 2021). LAMICs also face a paucity of trained personnel and research leaders and unfavorable research environments (Saraceno and Saxena, 2004; Thornicroft et al., 2012).

The growth of early intervention in HICs has been underpinned by research on illness characteristics and course; treatments; outcomes and predictors; pathways to care; and the effectiveness and cost-efficiency of service models (Chen et al., 2019; Howes et al., 2021; Malla et al., 2017; Nordentoft et al., 2015; Rosenheck et al., 2016). Little is known about the state of early psychosis research in LAMICs. Very few studies have examined mental health research capacity in LAMICs (Maj, 2010; Mari et al., 2010), and none have focused on early psychosis. These studies examined the numbers of publications on particular mental health topics in LAMICs (Large et al., 2010). Exploring additional indicators of research capacity could help strengthen early psychosis services and research in LAMICs (Pulford et al., 2020). E.g., although collaborations help advance research and serve as metrics of research capacity (Pulford et al., 2020), no studies have assessed the extent and geographic scope of collaborations in early psychosis research.

This study assesses LAMICs' research capacity in early psychosis by analyzing their research output and collaborations and comparing these with corresponding figures for the field overall and among HICs.

There is growing interest in the equitability of North-South research collaborations, with some studies focusing on LAMIC representation in authorship (Dimitris et al., 2021; Pratt and Hyder, 2018). Our secondary aim was therefore to examine the affiliation (HIC vs LAMIC) of key authors and the funders of HIC-LAMIC collaborations in early psychosis research.

2. Methods

We conducted bibliometric analyses, including social network analysis, of early psychosis research publications after 1980, when literature on early intervention for psychosis began emerging (McGorry, 1993; McGorry et al., 2018; Nelson, 2008).

2.1. Search Strategy

We searched in the Scopus database using terms such as first-episode psychosis, ultra-high-risk and early intervention services for psychosis in the title, abstract and keyword sections (see supplement). Scopus was chosen because it registers authors' affiliations, which is necessary for network analysis.

The search was restricted to journal articles published from 1980 to 2022. We excluded conference papers, errata, retracted publications, records without data on authors' affiliations and those outside the early psychosis field. To compare early psychosis research output to that of the wider psychosis field, we searched for records on psychosis and schizophrenia-spectrum disorders more broadly. No language limitations were implemented. The search was performed on August 2, 2023.

2.2. Procedure

Data on the title, date and author affiliations of included papers were exported to Excel. Country names from authors' institutional affiliations were identified and standardized for each record. These countries were classified by income group and world regions using World Bank (2023) criteria. Multiple affiliations were considered, so records were assigned to more than one country, income group, or world region, when appropriate, e.g., records with authors from an LAMIC and an HIC were assigned to both categories.

For the subset of articles involving HIC-LAMIC collaborations, the funders and countries of the first, last, and corresponding authors were manually identified, considering multiple affiliations for each position. These countries, too, were classified by income group and world region.

2.3. Variables

Research output was the number of records published per country. Research collaboration was analyzed by country using the degree centrality measure, which determines the number of countries directly connected to each country (the number of nodes each network node is connected to). E.g., a country with a degree of 10 would have had publications involving authors from 10 other countries (one paper with authors from 10 countries or multiple papers with multiple authors representing 10 other countries) (Hou et al., 2008).

For studies involving HIC-LAMIC collaborations, we assessed the country of affiliation of the first, last, and corresponding authors separately for studies conducted in LAMICs, HICs and both settings. We defined HIC and LAMIC dominance as all three authorship positions being affiliated to HICs or LAMICs, respectively. Funding sources were categorized as LAMIC funders, HIC

funders, international organizations, private donors, pharmaceutical companies and no funding received.

2.4. Statistical Analysis

We analyzed research output, research collaborations, co-authorship patterns, and funding with descriptive statistics using STATA 14.2. Collaborative networks and degree estimations were visualized using Pajek v.3.0.2. In the graphic, thicker lines indicate more collaborative records between countries, while node size correlates with the numbers of records by country.

3. Results

We retrieved 17,659 early psychosis research records, of which 717 were excluded for not meeting the inclusion criteria on type of article (n=414), relevance to the topic (n=213), and incomplete data on authors' affiliation (n=90). The supplement contains a PRISMA-type flowchart and countrywide data on degree centrality, leading authorships and funding.

3.1. Research output

We included 16,942 records (91.9% in English). Publications on early psychosis rose from 24 in 1980 to 1,297 in 2022. Early psychosis research accounted for 0.9% of publications on schizophrenia-spectrum disorders in 1980, rising to 10.2% by 2022 (Figure 1a). HICs accounted for 90.5% of included records and LAMICs for 16.1% (low-income countries, LICs: 0.2%; lower middle-income countries, LMICs: 3.1%; and upper middle-income countries, UMICs: 13.1%) (Figure 1b). The regions with the highest early psychosis research output were Europe and Central Asia (54.2%), North America (35.4%), and East Asia and the Pacific (24.5%), followed by Latin

America and the Caribbean (3.4%), Middle East and North Africa (2.3%), South Asia (1.6%), and Sub-Saharan Africa (1.2%)

Authors hailed from 125 countries, representing 57.3% of the 218 countries and territories in the World Bank classification. These included 48.2% of LAMICs (11 of 27 LICs, 40.7%; 21 of 55 LMICs, 38.2%; and 24 of 55 UMICs, 61.8%), and 72.8% of HICs (59 of 81) (Figure 1c).

3.2. Research collaborations

The 125 countries that had early psychosis publications had an average degree centrality of 18 (i.e., published with authors from 18 other countries). LAMICs had an average degree of 10.2 (LICs: 2.1, LMICs: 11, UMICs: 12), and HICs an average degree of 27. North America, East Asia and the Pacific, and Europe and Central Asia had average degrees of 69, 27, and 26, respectively, while South Asia, Middle East and North Africa, Latin America and the Caribbean, and Sub-Saharan Africa had average degrees of 16, 10, 9, and 5, respectively.

12,087 records (71.3%) involved authors from single countries. The remainder (28.7%) represented collaborations, with 3,708 publications involving HIC-HIC collaborations (21.9%); 28 involving inter-LAMIC collaborations (0.2%); 1,119 involving HIC-LAMIC collaborations (6.6%) (Table 1).

Network analysis (Figure 2) showed that the core of the collaboration network comprised a few HICs with notable scientific output (large nodes), varied connections (high degree), and strong collaborations (thicker lines). Other HICs and the BRICS (Brazil, Russia, India, China, and South Africa) subgroup of LAMICs, exhibited scientific output but at a lower level with fewer

connections and lighter collaborations. The outer region includes most LMICs and LICs, and a few HICs, with limited publications and collaborations.

3.3. Co-authorship in HIC-LAMIC collaborations

In the 1,119 papers involving HIC-LAMIC collaboration, 152 first authors (13.6%), 93 last authors (8.3%), and 184 corresponding authors (16.4%) were affiliated with both HICs and LAMICs. 634 records (56.7%) pertained to studies in LAMICs; 233 (20.8%) in HICs; and 84 (7.5%) in both settings. The remaining records were unclassified (145 records, 13.0%; e.g., reviews, letters to editors) or included no information on study setting (23 records, 2.1%). For studies in LAMICs, 71.8% of first, 60.7% of last, and 63.0% of corresponding authors were from LAMICs. For studies done in HICs, 75.9% of first, 84.1% of last, and 83.1% of corresponding authors were from HICs. Studies conducted in both HICs and LAMICs, and unclassifiable studies, predominantly had first, last, and corresponding authors from HICs (Figures 3a-c).

Of the 1,119 publications involving HIC-LAMIC collaborations, LAMIC dominance occurred in 322 (28.8%) and HIC dominance in 298 records (26.6%). Their first authors came from 74 countries (41 LAMICs); last authors from 67 countries (32 LAMICs); and corresponding authors from 65 countries (31 LAMICs). 80% of articles with a LAMIC first, last or corresponding author were published by China, Brazil, South Africa, and India (Figure 4).

3.4. Funding of HIC-LAMIC collaborations

In the HIC-LAMIC subset, 145 records (12.9%) lacked funding details, 107 (9.6%) reported receiving no funding for research, and 867 (77.5%) disclosed funding sources (see Table 3). Research for 29.4% of these papers was funded solely by LAMIC funders. With non-LAMIC

funders (e.g., HICs, international organizations), LAMIC funders co-funded an additional 17.7% of HIC-LAMIC projects.

Research for 45.1% of the studies conducted in LAMICs (286/634) was funded exclusively by LAMIC funders. Alone and with other funders, HIC funders supported the research for 60.7% of HIC-dominant and 22.0% of LAMIC-dominant publications. LAMIC funders funded research for 11.1% and 79.2% of HIC- and LAMIC-dominant papers, respectively.

International organizations, global pharmaceutical companies, private donors, and funders from 30 HICs and 22 LAMICs supported research in 867/1,119 HIC-LAMIC publications. Among these, China funded research for 368 papers, Brazil for 78 papers, and both countries jointly for four papers. Their combined contribution represents 84% of the records (442/526) with some LAMIC funding.

4. Discussion

The significant growth in early psychosis research from 1980 to 2022 has been very uneven, with HICs exhibiting much higher scientific output than LICs. This aligns with the notion of the "10/90 gap" which posits that < 10% of research resources are in countries facing 90% of global health problems (Global Forum for Health Research and WHO, 1999, Razzouk et al., 2008). This gulf partly reflects the correlation between countries' economic wealth and output in global health research (Cash-Gibson et al., 2018; Dimitris et al., 2021). However, research output cannot be tied only to income levels. Not all HICs have high research productivity and capacity (e.g., the Gulf states). Conversely, LAMICs like China and Brazil have higher research outputs than some HICs (*Nature* editorial, 2021). Nonetheless, comparing early psychosis research outputs across

countries of different income levels can reveal associations between economic factors and service accessibility and quality. In LAMICs, for instance, durations of untreated psychosis are associated with gross domestic product purchasing power parity (Large et al., 2008).

Although collaboration is thought to enhance research capacity in LAMICs (da Silva et al., 2019), we found that just over a fourth of psychosis papers involved multi-country collaborations. Most early psychosis research involved single HICs with a fraction thereof representing inter-HIC collaborations, as in most research (Adams and Gurney, 2018). Little early psychosis research involves LAMIC-HIC collaborations and even less involves inter-LAMIC collaborations. LAMIC researchers, facing scarce local funding, may seek collaborations with HICs (rather than other LAMICs) to access more research enablers like funding, resources, capacity-building, research culture, and high-impact journal publications (fearing possibly higher rejection rates for LAMIC-only publications) (Patel and Kim, 2007). This is regrettable because inter-LAMIC collaborations can generate more locally relevant and transferable solutions; reduce global knowledge inequities; and help LAMIC researchers cooperate and advocate for more funding and better policies (*Nature* editorial, 2023).

Encouragingly, we did not find great imbalances in the authorship of papers from HIC-LAMIC collaborative early psychosis research conducted in LAMICs. For comparison, only 52.9% of papers on infectious diseases research done in Africa had an African first author and 33% of LAMIC-based RCTs in adolescent mental health research had a LAMIC-affiliated author (Hedt-Gauthier et al., 2019; Osborn et al., 2020). Four BRICS countries accounted for 80% of the LAMIC-affiliated first, last and corresponding authorships on collaborative publications. This aligns with BRICS countries' high output across mental health and other sciences (Larivière et al.,

2013; “Nature Index,” 2024). Overall, LAMIC researchers have few to no first, last or corresponding authorships in early psychosis research.

China and Brazil funded the research for four of the five publications involving LAMIC-funded HIC-LAMIC collaborations. This is consistent with these countries’ record of funding mental health research in LAMICs (Pollitt et al., 2016). It also underscores how limited funding is in other LAMICs. We also confirmed the influence of funding source on co-authorship patterns (Schneider and Maleka, 2018). Research funded by HIC and LMIC bodies respectively yielded HIC-dominated and LAMIC-dominated authorships. International organizations supported HIC-dominant and not LAMIC-dominant research, possibly because of being based in HICs or driven by HIC priorities. This trend is evident across mental health research (Woelbert et al., 2021).

4.1. Implications

Within the larger global health goal of strengthening LAMICs’ research capacity, emphasis must be placed on research into early interventions for serious mental illnesses, which is woefully scarce in LAMICs. This is imperative if early psychosis services and policies in LAMICs are to be guided by culturally and contextually relevant knowledge, rather than knowledge transposed from HICs (Singh et al., 2020).

Developing early psychosis research capacity in LAMICs requires sustained funding and policy commitment. We acknowledge that many LAMICs have limited means due to many historical factors (Charani et al., 2022; OECD Data, 2024). Still, LAMICs that can do so must invest more in mental health research to center the needs and priorities of their patients, practitioners, and policymakers and to mitigate power imbalances.

We also urge international funders to boost funding for mental health and early psychosis research and implement mechanisms to address global inequities in knowledge production, use, circulation, and leadership (e.g., by directly funding LAMIC researchers and projects).

Research capacity in LAMICs could benefit from more and stronger collaborations between HICs and LAMICs and among LAMICs. Well-known HIC-LAMIC collaborations that have supported early psychosis services development and research in LAMICs include the India-Canada partnership funded by the US National Institutes of Health (Iyer et al., 2010; Malla et al., 2020) and the Warwick-India-Canada project funded by the British National Institutes of Health Research (Singh et al., 2021). Research collaborations can also be promoted or coordinated by governments, funders and international organizations (Charani et al., 2022).

Beyond providing project-by-project funding, grants should advance capacity and leadership in LAMICs (e.g., by training LAMIC-based PhDs; supporting networks in and across LAMICs; helping sustain and scale up research endeavours/innovations, etc.) (da Silva et al., 2019). Enhancing local capacity may also help stem brain drain, which widens human resources gaps in LAMICs. Projects should follow equity-aligned global health research principles (CAGH, 2024; Collins, 2020) and avoid exacerbating epistemic injustices (e.g., involving LAMIC collaborators only in data collection and not conception; not valuing non-academic LAMIC partners; etc.) (Bhakuni and Abimbola, 2021). International associations also have a responsibility to highlight and reduce global health inequities. The World Psychiatry Association's early intervention LAMICs initiative is noteworthy (Singh et al., 2023).

4.2. Limitations

Our analysis potentially overlooked studies in non-Scopus-indexed journals. However, Scopus is widely used in bibliometric analyses, covers all world regions, and includes papers in some 40 non-English languages (Elseviere, 2024). Numbers for some types of collaborations might have been inflated by instances of researchers with institutional affiliations in more than one country.

Manually reviewing all included records was not feasible given the volume retrieved, but this is not required in standard bibliometric analyses. Still, we rigorously evaluated the subset of HIC-LAMIC collaboration records, manually extracting authorship and funding information. Country-level statistics may not disclose within-country disparities. In every LAMIC where early psychosis research is done, it is usually in one or a few institutions. Similar but smaller internal disparities also exist in HICs (Petersen, 2021; UK research & Innovation, 2021). Our paper is the first to map the state of early psychosis research in LAMICs and associated LAMIC-HIC inequities. The methodological constraints of bibliometric analyses precluded investigations of the structural and geopolitical determinants of these inequities. Nonetheless, this study is robust because of its well-developed search strategy, its extensive period of focus, and its use of multiple indicators and analyses.

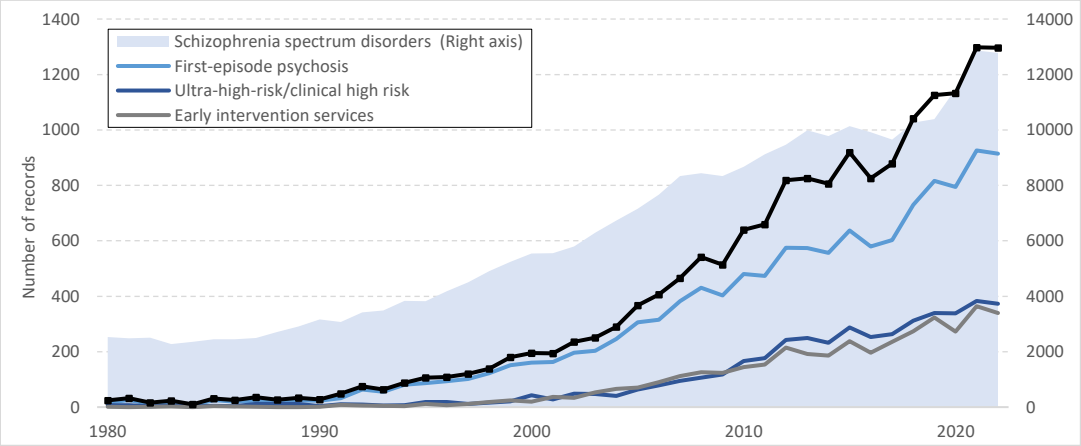
4.3. Conclusion

LAMICs have had a negligible share of worldwide early psychosis research, which has rapidly expanded since 1980. They also have far fewer collaborations in and far less funding for early psychosis research than HICs. Closing these gaps is imperative because it is in LAMICs that most of the world's people live; the bulk of global disease burden occurs; and mental health services

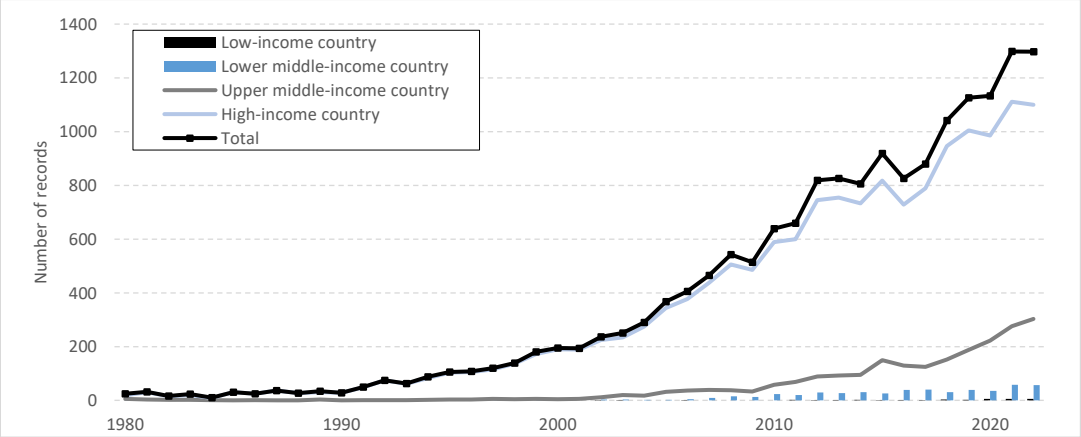
and resources are scarcest. More research in LAMICs is also needed to further strengthen with local knowledge the early intervention services that are known to improve psychosis outcomes.

More fundamentally, underfunded mental health services and research—realities even in HICs—reflect the low priority societies accord to mental health. Change in this regard cannot be driven solely by research. It requires social and political advocacy rooted in locally relevant knowledge.

a) Research areas



b) Income groups



c) Number of countries

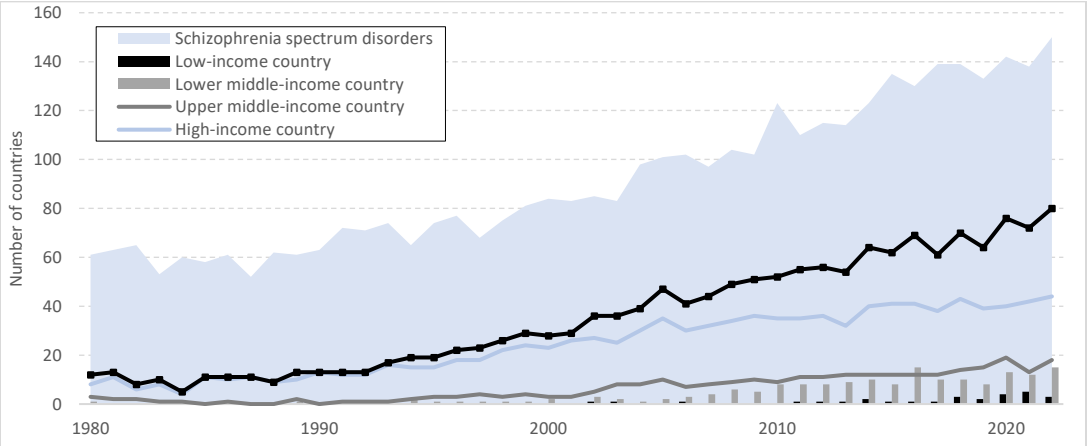


Fig. 1. Scientific output in early intervention in psychosis presented as: a) Number of records by research areas, b) Segmented by income groups, and c) the number of countries involved.

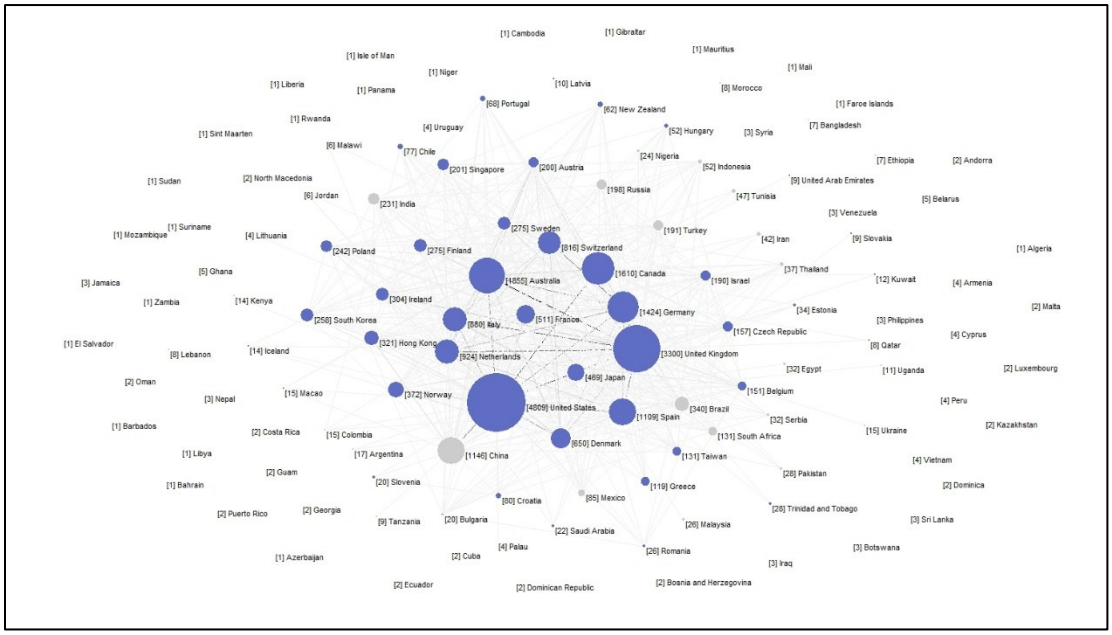
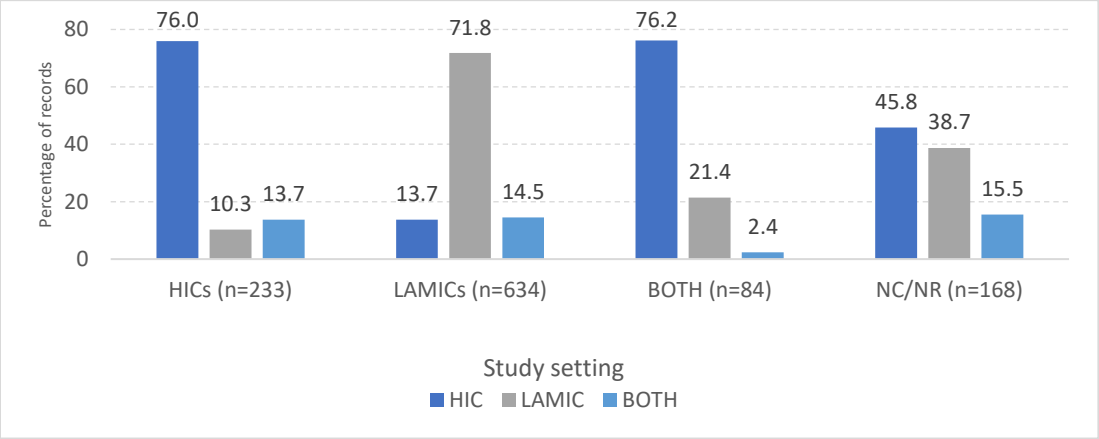


Fig. 2. Collaboration network in global early intervention in psychosis research by income groups of authors' country of affiliation (1980–2020). Color of nodes varies by country income groups (Gray: Low- and middle- income countries, and blue: high-income countries). Collaborations between two countries with more than two studies in common are shown.

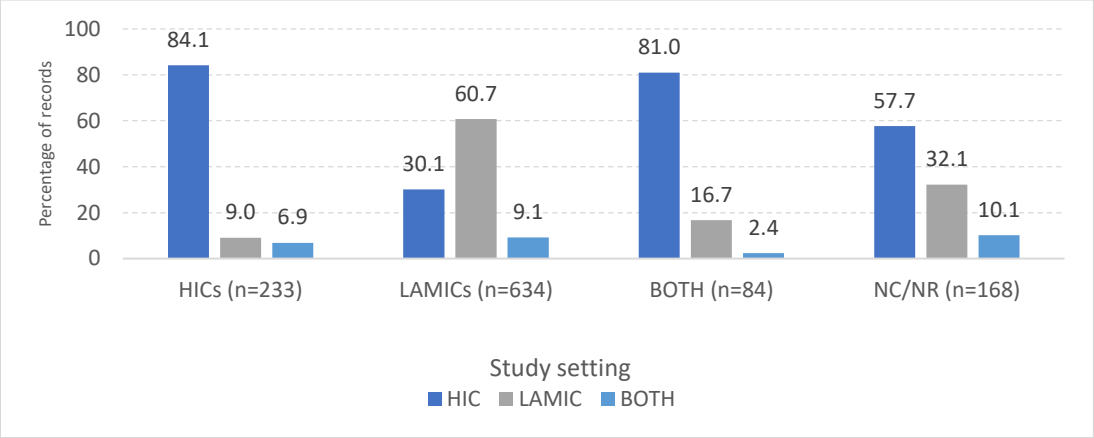
Table 1. Scientific collaboration by income group of authors' country of affiliation (n=16,942).

Authors affiliated with institutions from:	n	%
Only one country	*12,087*	*71.3*
HIC	10,507	62.0
UMIC	1,257	7.4
LMIC	305	1.8
LIC	18	0.1
Two or more countries (same country income group)	*3,719*	*22.0*
HICs	3,708	21.9
UMICs	9	0.1
LMICs	2	0.0
Two or more countries (between HIC and LAMICs)	*1,119*	*6.6*
HIC+UMIC	906	5.3
HIC+LMIC	171	1.0
HIC+LIC	5	0.0
HIC+UMIC+LMIC	28	0.2
HIC+UMIC+LIC	7	0.0
HIC+LMIC+LIC	2	0.0
Two or more countries (between LAMICs)	*17*	*0.1*
UMIC+LMIC	15	0.1
UMIC+LIC	1	0.0
LMIC+LIC	1	0.0

a) First authorship



b) Last authorship



c) Corresponding authorship*

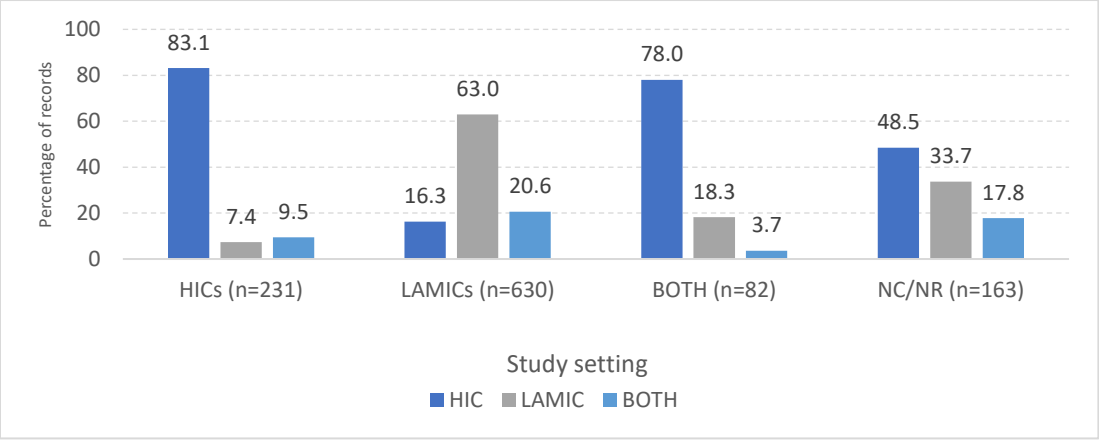


Fig. 3. Distribution of a) first, b) last, and c) corresponding authorship by study setting (n=1119). HIC: High-income country, LAMIC: Low- and middle-income country, NC: Not classified, NR: Not reported. *13 records did not report data on corresponding author.

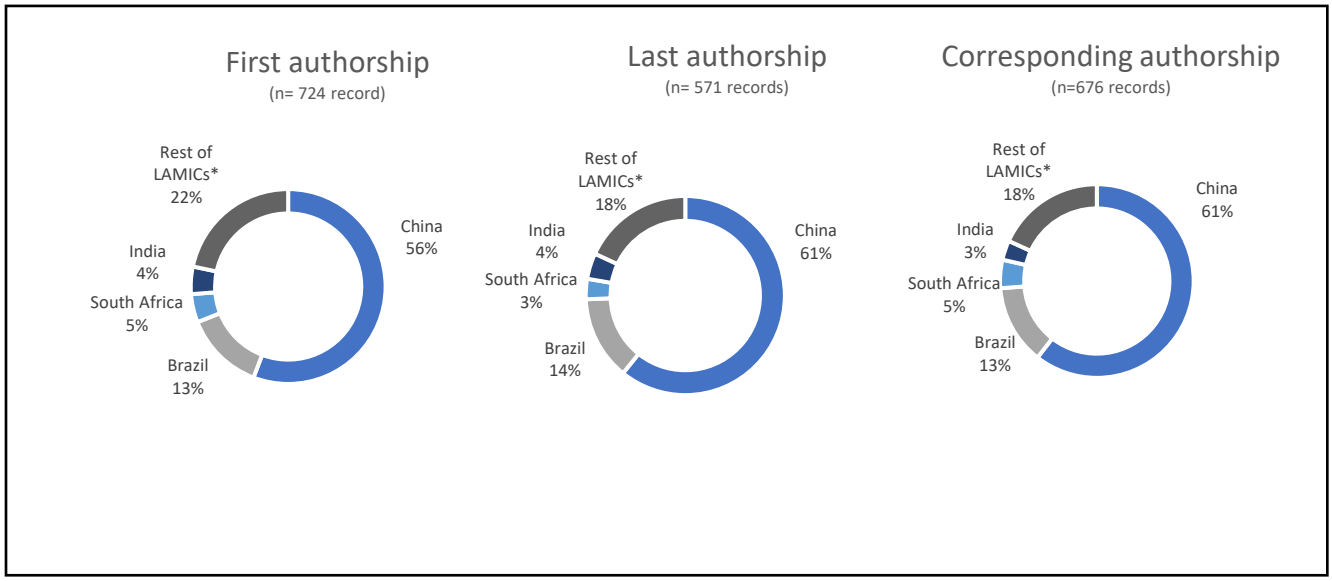


Fig. 4. LAMICs that most frequently held the first, last, and corresponding authorship positions in records from collaborations between HICs and LAMICs (1980–2022). *Includes 37, 28 and 27 LAMICs in the first, last and corresponding authorship positions, respectively.

Table 3. Funding agencies that support EIP records conducted between HICs and LAMICs (1980-2022).

Funding agencies	All records (N=1,119)		HIC dominance (N=298)		LAMIC dominance (N=322)	
	n	%	n	%	n	%
LAMIC	329	29.4*	5	1.7	190	59.0
HIC	229	20.5#	132	44.3	14	4.3
HIC+LAMIC	159	14.2@^	11	3.7	57	17.7
HIC+IO	31	2.8^	25	8.4	0	0.0
PH	28	2.5	10	3.4	3	0.9
IO	26	2.3	21	7.0	2	0.6
HIC+PH	14	1.3^	7	2.3	0	0.0
LAMIC+IO	14	1.3@	12	4.0	0	0.0
PD	8	0.7	6	2.0	0	0.0
LAMIC+PH	8	0.7@	0	0.0	4	1.2
HIC+LAMIC+IO	7	0.6@^	4	1.3	0	0.0
LAMIC+IO+PH	4	0.4@	0	0.0	4	1.2
IO+PH	3	0.3	2	0.7	0	0.0
HIC+LAMIC+PH	3	0.3@^	0	0.0	0	0.0
HIC+PD	1	0.1^	1	0.3	0	0.0
HIC+IO+PH	1	0.1^	0	0.0	0	0.0
HIC+LAMIC+IO+PH	1	0.1@^	0	0.0	0	0.0
HIC+LAMIC+IO+PH+PD	1	0.1@^	1	0.3	0	0.0
No funding	107	9.6	27	9.1	21	6.5
No information on funding	145	13.0	34	11.4	27	8.4

HIC: High-income country, LAMIC: Low- and middle-income country, IO: International organization, PH: Pharma company, PD: Private donor.
International organizations: European Union, New Partnership for Africa's Development, World Health Organization, etc.
* Included in calculating total for exclusively LAMIC-funded; # Included in calculating total for exclusively HIC-funded; @ Included in totals for some LAMIC funds received but not exclusively LAMIC-funded ^ Included in totals for some HIC funds received but not exclusively HIC-funded

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Bridge

Findings from Manuscript I revealed that only a small proportion of LMICs published EIP studies between 1980 and 2022. Similarly, only a limited share of scientific publications on EIP involved international collaborations with LMICs. Within LMICs, scientific production was largely concentrated in a few countries, particularly the BRICS (Brazil, Russia, India, China and South Africa), which also developed the most significant collaborations with HICs. In contrast, most LMICs had limited or no scientific production or collaborations in EIP. Although this study provided a global overview of EIP research capacity, it did not capture the details of work conducted within individual countries. For instance, it was not possible to determine the setting in which EIP programs were implemented, which treatment components were delivered, or what outcomes were achieved.

An in-depth examination of how EIP programs have been configured for people in the early phases of psychosis in LMICs therefore emerged as a clear next step. This approach allowed us to examine how the EIP paradigm and EIP principles have been translated into practice and to identify the treatment components provided for FEP and CHR in LMICs. Moreover, evaluating the effectiveness of these components in low-resource settings was necessary, as contextual factors could influence both their feasibility and impact. Anticipating that the number of EIP programs might be limited, we adopted a broader perspective and included all services or initiatives in which people at CHR or with FEP were treated. These insights were essential for understanding not only the presence of EIP programs but also the scope, structure, and potential of broadly conceptualized multicomponent care models to address and improve outcomes in the early stages of psychosis.

Accordingly, Manuscript II was designed to directly address the gaps identified in Manuscript I. It focused on a systematic review that gathered all research on multicomponent care for FEP and CHR conducted in LMICs and described the specific treatments provided. This review sought to determine which treatment components were offered and to assess their effectiveness in low-resource settings. Additional aspects evaluated included the extent to which guideline-based components were provided, the degree of cultural adaptation, and the length of follow-up. In conducting this systematic review, we aimed to build a more detailed understanding of the actual configuration of EIP programs and the extent to which comprehensive, multicomponent care has been implemented in these contexts.

Chapter 4

Manuscript II

Availability and efficacy of multicomponent interventions for early psychosis in low- and middle-income countries: A systematic review

(Submitted to *eClinicalMedicine:* published by The Lancet).

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Availability and efficacy of multicomponent interventions for early psychosis in low- and middle-income countries: A systematic review

Abstract

Background: Most individuals with psychosis live in low- and middle-income countries (LMICs) where treatment delays and gaps are common. Little is known about the types of interventions for first-episode psychosis (FEP) and clinical high-risk (CHR) for psychosis in LMICs and their efficacy. This systematic review aimed to identify treatment components delivered for FEP or CHR in LMICs and evaluate their effectiveness.

Methods: A systematic search of PsycINFO, Embase, and Medline was conducted from inception to May 2024. Records were included if they evaluated at least one more intervention beyond medication and assessment for FEP and beyond assessment for CHR, in LMICs with at least one follow-up. Included papers were classified as programs (offering FEP/CHR services) or research studies of intervention(s)/outcomes in FEP/CHR. Treatment components were categorized as guideline-based or additional. Effectiveness was assessed across 15 outcomes defined *a priori*. Study quality was evaluated using the Mixed Methods Appraisal Tool, and findings synthesized narratively. This study was pre-registered (PROSPERO-CRD42022308467).

Findings: Of 6046 screened records, 125 were included (Average:156 participants; range:10-1268). These comprised 10 programs and 30 studies for FEP in 16 countries (11.7% of LMICs), and 8 programs and 8 studies for CHR across 8 countries (5.8%). They delivered guideline-based and additional components; however, psychological and psychosocial components were scarce. For FEP, the addition of any psychological or psychosocial component was superior to medication

alone in improving outcomes. Patient psychoeducation and family interventions were the most frequently implemented components. For CHR, limited data prevented conclusions about the effectiveness of treatment components in LMICs.

Interpretation: Despite limited and moderate-quality evidence, findings suggest that early intervention can improve outcomes in FEP. However, coverage remains limited to few LMICs and even they struggle to provide comprehensive care. Further research is needed to strengthen, scale and culturally adapt such services.

Funding:Canadian Institutes of Health Research.

Key words: Psychotic disorders; Schizophrenia spectrum and other psychotic disorders, Developing countries, Psychosocial Intervention, Therapeutics, Global Health

Availability and efficacy of multicomponent interventions for early psychosis in low- and middle-income countries: A systematic review

(Research in context)

Evidence before this study: We searched Medline from database inception till January 1, 2022, using terms related to "systematic review", "network meta-analysis", "meta-analysis", "first-episode psychosis", "clinical-high risk for psychosis", and "early intervention in psychosis", without language restrictions. This search was repeated in April 2024. We found two systematic reviews with meta-analyses that reported that early intervention for psychosis (EIP) programs in high-income countries (HICs) are clinically effective. We also identified two systematic reviews reporting the cost-effectiveness of EIP in HICs. Only one systematic review examined EIP in the Global South (N=18 studies). It was restricted to low- and lower-middle-income countries and included only English-language records, which limited its comprehensiveness. To date, there has been no review of the full range of treatment components offered for first-episode psychosis (FEP) and clinical high-risk for psychosis (CHR), across low-and middle-income countries (LMIC), regardless of publication language. This gap is critical given that most individuals with psychosis live in LMICs, which face systemic barriers to mental healthcare delivery, including workforce shortages, limited financial resources, and inadequate infrastructure.

Added value of this study: This is the most comprehensive and inclusive systematic review of multicomponent interventions for FEP and CHR in LMICs (N=125 studies). By screening and identifying records across multiple languages and distinguishing structured EIP programs from one-off studies, we generated accurate counts for the field: 10 EIP programs and 30 studies for

FEP across 16 LMICs, and only 8 programs and 8 studies for CHR across 8 LMICs. Using validated fidelity and guideline frameworks, we classified treatment components; documented delivery settings and cultural adaptations; and assessed the effectiveness of both integrated (≥2 components besides medication) and single-component (besides medication) interventions. Our review establishes, albeit with moderate-quality evidence, that integrated and single-component interventions improve clinical and functional outcomes in FEP. Guideline-based psychological and psychosocial components remain inconsistently available across FEP and CHR programs and studies in LMICs. We also establish the scarcity of data on the effectiveness of interventions for CHR in LMICs, and identify challenges relating to implementation infrastructure, inclusion criteria, and service accessibility.

Implications of all the available evidence: Public funding for EIP services in HICs began growing with the emergence of the sort of evidence that we have now established the existence of in LMICs. Our review strengthens the impetus for the wider adoption and larger-scale study of EIP in LMICs, where it has the potential to improve the lives of the largest numbers of people with FEP. Our work helps build the case for governments in LMICs to confidently commit resources to expanding multicomponent EIP services for FEP based on the evidence for their effectiveness. But as they do so, governments and other global bodies must also invest in research and novel implementation strategies to address the gaps that we identified, including in the provision of psychological and psychosocial components, larger-scale implementation and evidence on population-level outcomes.

Availability and efficacy of multicomponent interventions for early psychosis in low- and middle-income countries: A systematic review

Introduction

Early intervention in psychosis (EIP) integrates pharmacological, psychosocial and psychological strategies to detect and treat people with first-episode psychosis (FEP) or at clinical high risk (CHR).[1] Grounded in optimism and the principle that early, comprehensive care is better than traditional, often delayed, and medication-focused treatment,[2] EIP has demonstrated superior clinical, functional, and quality-of-life benefits over standard care in randomized trials and meta-analyses,[3] with proven cost-effectiveness.[4] For CHR, although limited compared to that for FEP, evidence has shown that EIP can delay, prevent, or ameliorate transition to psychosis.[5]

The provision of multiple components is emphasized in EIP given the range of needs of people with psychosis and that different components target different outcomes.[6] EIP typically combines low-dose antipsychotic medication, consistent follow-up often through case management, psychoeducation, family interventions, cognitive-behavioral therapy and measures to reduce treatment delays and streamline care pathways. [1] Some programs incorporate peer support, digital tools, and population-level initiatives like public education and early detection campaigns.[1,6]

EIP programs originated in high-income countries (HICs), where evidence for their benefits, their integration into publicly funded healthcare systems, and support from health authorities drove their national or regional implementation as the standard of care for FEP.[7] In many HICs,

standards, fidelity scales, and clinical guidelines now support the quality and consistency of EIP.[8,9]

In low- and middle-income countries (LMICs), EIP remains nascent. EIP services—often limited to urban research centers—have usually been pioneered by individual clinicians or institutions rather than driven by policy.[10] Structural barriers, including workforce shortages, underfunding, and scarce facilities, impede mental healthcare service delivery and reform.[11] Care for schizophrenia and other psychotic disorders often consists primarily of antipsychotic medication with minimal psychosocial support.[12] Systematic quality measures (e.g., guidelines) and large-scale rollouts are rare.[13]

Little is known about the extent to which LMIC programs provide the multicomponent care recommended for early stages of psychosis, or whether components are adapted to local contexts. The one existing systematic review of EIP services in the Global South (n=18 studies from 6 countries) was based on articles written in English and from only low- and lower-middle-income countries (rather than the broader group of LMICs encompassing low-, lower-middle- and upper-middle-income settings).[14]

This review addresses these gaps by examining: (1) the availability and composition of multicomponent interventions for FEP and CHR in LMICs, and (2) their effectiveness. By including all LMIC income groups and publication languages; and studies of all interventions comprising more than one treatment component rather than self-labelled "EIP" programs, we provide the first comprehensive synthesis of early psychosis interventions in LMICs.

Methods

This systematic review followed PRISMA guidelines and was prospectively registered in PROSPERO (CRD42022308467).

Eligibility criteria

Records were included if: (1) participants were experiencing a FEP or were at CHR; (2) participants came from an LMIC(s);[15] (3) at least one additional EIP component was delivered, beyond clinical assessment and antipsychotic medication for FEP, or beyond clinical assessment for CHR (this defined multicomponent intervention for the two groups); (4) participants had at least one follow-up. Follow-up length was unrestricted to avoid excluding informative records. If a study had been conducted in both an LMIC and an HIC, it was included and only data from the LMIC was reported. Studies testing EIP components with family members of individuals with FEP or CHR were included. Records were excluded if they were a theoretical review/protocol/poster. No language restrictions were applied.

Key terms

FEP and CHR were defined as reported in the original studies. An EIP component refers to any psychopharmacological, psychological, psychosocial, or nutritional treatment offered to individuals with FEP or CHR. For FEP, records where the only additional components alongside antipsychotic medication and assessment were minocycline, melatonin, metformin, or bifidobacterium were excluded.[16–19]

EIP components for FEP were guideline-based if included in the 20-item FEP Services Fidelity Scale.[20] For CHR, components were guideline-based if listed in the Canadian Treatment Guideline

for Individuals at CHR of Psychosis (nine recommendations, Table S1), which was developed with rigor and shares similarities with international CHR guidelines.[21] Strategies not included in these references were categorized as "additional components" (e.g., yoga).

Information sources

In consultation with an EIP expert (SNI) and a university librarian, search terms were generated for prodromal psychosis, FEP, early intervention, and LMICs. The search strategy was applied to PsycINFO, EMBASE, and Medline via Ovid (Table S2, S3 and S4). Additional records were identified through hand-searching published reviews. The search was conducted on January 23, 2022, and updated on May, 2024.

Selection process

Two reviewers (RV, NM) independently screened titles, abstracts, and keywords using the software *Rayyan*. They then independently screened the full texts of potentially relevant articles. Disagreements were resolved by consensus or by author SNI, with experience in EIP service delivery and research in HICs and LMICs.

Data collection

A data extraction sheet was piloted on 10% of included records. Two reviewers (RV, NM) independently extracted data on participant demographics, study design, study setting, healthcare context, service characteristics, assessments, and findings. Authors were contacted for clarifications when necessary. Disagreements were resolved by discussion.

Data items

For FEP, we selected outcomes from the most cited systematic review on EIP outcomes as indicators of feasibility, acceptability, and effectiveness: 1) all-cause treatment discontinuation, 2) psychiatric hospitalization, 3) involvement in school or work, 4) total symptom improvement, 5) global functioning, 6) average number of psychiatric hospitalizations, 7) average bed days during treatment, 8) relapse, 9) remission, 10) recovery, 11) positive symptoms, 12) negative symptoms, 13) general psychopathology, 14) depressive symptoms, and 15) quality of life.[3] Other reported outcomes and cost-effectiveness were also extracted. For CHR, although conversion to psychosis was the main outcome, all reported outcomes were included given the anticipated small number of efficacy studies.[22] When multiple models were reported, the most fully adjusted was extracted.

Study risk of bias assessment

Two reviewers independently evaluated the quality of efficacy studies using the Mixed Methods Appraisal Tool.[23] This instrument is a valid and reliable tool to assess the quality of studies with different methodological designs (Table S5). Scores ranged from one (low) to five (high).

Synthesis methods

Records were categorized by population (FEP or CHR) and by EIP programs or studies. The term "EIP programs" was applied when authors identified the delivery of multicomponent interventions to be in specialized services designed to identify and treat individuals with FEP or at CHR.[24] The term "EIP studies" was applied when authors evaluated (1) a single component (besides medication and/or assessment); (2) integrated treatment (combined effect of ≥two components); or (3) participants' outcomes (e.g., quality of life), without identifying as an EIP program. Records from the same program/study were triangulated and unified under their brand

name or the name of the home research institution. Records that did not mention either name were categorized as 'Study' followed by the name of the study location. A narrative synthesis described (1) settings of programs/studies, (2) type of EIP component(s) provided, and (3) intervention effectiveness. A sensitivity analysis compared records with only guideline-based EIP components to those including any treatment components, analyzed by number of records.

The funders had no role in study design, data collection, analysis, interpretation, writing or submission.

Results

Of the 6,046 records identified, 125 met inclusion criteria. Main reasons for exclusion were not reporting treatment components, no follow-up, or populations other than FEP/CHR (Figure 1 and Table S6).

Study characteristics

Of the 125 records, 68 addressed FEP and 58 CHR, with one both. Among FEP records, 36 came from 10 FEP programs and 32 from 30 studies in 16 LMICs (11.7% of 137 LMICs). Programs were located in India,[25] Brazil,[26] Mexico,[27] Turkey,[28] and Malawi,[29] as single-site initiatives; only Russia reported national implementation (Table S7).[30] Of the 32 records (30 studies), four evaluated integrated treatment,[30–33] 17 evaluated a single EIP component,[34–36] 10 evaluated clinical outcomes,[37–39] and one was an economic evaluation (Table 1).[40] Three records were written in Spanish, Perish and Turkish, and the rest in English. Table S8 shows eligibility criteria for FEP programs and studies.

Among the 58 CHR records, 40 were from eight CHR programs and 18 from eight studies across eight LMICs (5.8% of the LAMICs). Programs were located in Brazil,[41] Mexico,[42] China,[43] Turkey,[44] and Tunisia,[45] all of which were in tertiary or university-based healthcare settings (Table S9). Of the 18 CHR records, four evaluated the efficacy of an intervention,[46–49] and 14 clinical outcomes (Table 2).[50–52] Eligibility criteria for CHR programs and studies are available in table S10.

Of the 125 records, 27 reported efficacy outcomes for FEP (five from FEP programs, 22 from studies). Of these, nine evaluated integrated treatment, 11 a single EIP component and seven exclusively a non-a priori outcome. Six records reported efficacy outcomes for CHR (two from CHR programs, four from studies). The quality scores of these 33 records ranged from one to five, with an overall average of 3.5 (Table S5).

Availability of EIP components

FEP programs (36 records) offered both guideline-based and additional components, averaging 10 components over 28 months. Beyond clinical assessments and antipsychotics, the most frequent guideline-based components were patient psychoeducation, and family education and support. Gaps included cognitive behavioral therapy (CBT) and psychosocial interventions, such as case management, educational support, and substance use treatment. Common additional components were non-CBT psychotherapy, multidisciplinary team and occupational therapy. Only two programs (India and Brazil) reported cultural adaptation. The Indian site emphasized family involvement in treatment and home-based cognitive retraining focused on household chores.[25] The Brazilian program mentioned culturally sensitive interventions without details (Table 3 and S11).[53]

FEP studies (32 records) included three randomized controlled trials of integrated treatment, all including family education and support.[31–33] One cohort study evaluated the effectiveness of antipsychotics along with assertive monitoring.[54] Seventeen records tested single EIP components (besides medication and clinical assessment),[55–57] mainly patient psychoeducation, and family education and support. One record was a cost-effectiveness study.[40] In ten records, participants regularly received various components,[37–39] and clinical outcomes were measured. On average, studies offered five components for 19 months. Cultural adaptation was present in three studies evaluating psychoeducation,[35,57,58] a family intervention,[55] and a local diagnostic system (Table 3 and S11).[59]

CHR programs (40 records) delivered both guideline-based and additional components, averaging seven components. All involved evaluation by a professional trained in CHR. Only two programs in Tunisia and one in Mexico offered most guideline-based components,[45,60,61] while the remaining did not report offering CBT or psychosocial interventions. Additional components included antipsychotic medication and omega-3 fatty acids. No program reported cultural adaptation. Two programs did not specify treatment length;[44,62] three did not limit the length of follow-up;[41,43,61] three reported an average of 14 months (Table 4 and S12).

CHR studies (18 records) assessed systemic therapy,[46] eye movement desensitization and reprocessing,[48] omega-3 fatty acids (with/without minocycline),[47] and mobile technology.[49] The remaining 14 followed CHR cohorts, while examining social, clinical, and biological outcomes,[51,63] establishing identification systems within schools,[64] and assessing predictors of conversion to psychosis.[50] On average, studies offered four components over 17 months. None reported cultural adaptation (Table 4 and S12).

Effectiveness of EIP components

Of 20 records on *a priori* outcomes, nine reported integrated treatment (Table 5). A Mexican trial showed 56.4% recovery in the intervention group, compared to 2.9% in the control group.[31] A Chinese trial reported lower treatment discontinuation in the intervention group (32.8%) than in the control group (46.8%).[33] Both outperformed antipsychotic medication alone on other outcomes. An Iranian trial found no differences between integrated treatment and antipsychotic medication.[32] Observational studies indicated higher symptom remission and lower unemployment rates with integrated treatment in Russia,[30] and greater improvements in negative symptoms and functioning in India than in Canada.[65,66] A South Africa/Nigeria cohort reported 82% treatment response with antipsychotics plus assertive monitoring.[54] Cost-effectiveness was shown in Brazil (EIP program) and China (study context).[40,67]

Eleven records evaluated single EIP components for the *a priori* outcomes (Table 6). Seven antipsychotics combined with case management yielded equivalent efficacy in improving symptoms and functioning.[68] CBT,[69] patient psychoeducation,[57,58] interpersonal psychotherapy,[70] and electroconvulsive therapy,[36] when added to antipsychotics, were superior to medication alone in improving psychotic symptoms, functioning, and other outcomes. Family psychoeducation and support, combined with antipsychotics, was more effective than medication alone in enhancing quality-of-life,[55] and medication adherence.[35,55] Cognitive training with treatment as usual (medication and psychoeducation) did not yield additional improvements in psychotic symptoms or functioning compared to treatment as usual.[34]

Nineteen records reported non-*a priori* outcomes, seven focused exclusively on them (Table S13 and S14).[25,71–76] These included medication adherence, insight, knowledge and stigma;

satisfaction; cognition; physical health indices like weight gain; expressed emotion, quality of life, psychological health, patient disengagement and family engagement.

Only three of six records evaluated conversion to psychosis. A Pakistani record reported higher transition (17.3%) with omega-3, either alone or combined with minocycline, compared with those not receiving omega-3 (10.4%).[47] Two Chinese records showed that antipsychotic treatment did not prevent psychosis onset.[43,77] Conversely, systemic therapy improved positive and depressive symptoms, social support, and self-esteem.[46] Eye movement desensitization and reprocessing significantly reduced post-traumatic stress scores and attenuated positive symptoms, and yielded higher remission compared to the waitlist group (60.7% vs. 31.0%).[48] Mobile technology also enhanced cognitive function, specifically attention/vigilance, in CHR.[49]

Four of the 125 records would have been excluded if only "guideline-based" components were considered, reducing FEP studies from 30 to 26. These included studies evaluating the long-term abilities of people with FEP to live and work independently;[78] cognitive training,[76] interpersonal group psychotherapy,[70] and electroconvulsive therapy.[36] Including them did not alter conclusions but highlighted additional components used in LMICs.

Discussion

We conducted the first comprehensive systematic review of the availability and effectiveness of treatment components for FEP and CHR in LMICs. Our analysis of studies from 20 countries, despite their heterogeneous study quality, allows the following conclusions: (1) multicomponent interventions are being implemented for both FEP and CHR in programs and studies; (2) psychological and psychosocial components remain scarce; (3) for FEP, multicomponent

interventions show clinical, functional and cost-effectiveness benefits; and (4) for CHR, evidence on the efficacy of treatment components is limited. Our review synthesizes progress and highlights gaps in implementing EIP in LMICs.

FEP programs in LMICs resembled those in HICs in the types of components provided. This is unsurprising, as EIP programs in LMICs have emulated those in HICs.[13] However, we cannot comment on the intensity or duration of each component as this was rarely reported. Programs often lacked guideline-based psychological and psychosocial components, including CBT, case management, supported employment, educational support, and substance use interventions, despite strong evidence for these from HICs.[79] Where CBT was mentioned, it was often unclear whether it was tailored for psychosis, as recommended,[8] or generic. Prior reports have also noted this scarcity of CBT and psychosocial components.[12,80] All reviewed programs offered additional components such as cognitive training, painting, non-CBT psychotherapy, occupational therapy and yoga. Some reflected local practices (e.g., yoga in India's SCARF program[81]); others lacked a clear rationale.

Our decision to include FEP studies proved valuable because only few efficacy studies had been conducted within FEP programs (5/27 records). Trials from Mexico and China and economic studies from China and Brazil showed that integrated treatment outperformed antipsychotics alone across outcomes and was cost-effective,[31,33] consistent with findings from HICs. A small Iranian trial found no differences, likely due to small sample size (N=20).[32] Similarly to HIC evidence,[82,83] our findings support CBT, patient psychoeducation, and family intervention for FEP in LMICs. While few HIC studies report on electroconvulsive therapy, evidence from LMICs

suggests that it may improve outcomes.[36] Our findings highlight the need to define core integrated treatment components for FEP in LMICs, while adapting to local preferences and resources.

Like FEP programs, CHR services in LMICs struggled to deliver several guideline-based treatment components and sustain treatment. Only half (4/8) offered CBT, despite it being recommended to reduce conversion risk[5] — a gap also reported globally.[84] Interventions to prevent functional deficits, a key predictor of conversion and disability,[85] were provided by just two programs. Of the six programs reporting duration, only three met the recommended three-year follow-up; the rest offered shorter monitoring, potentially missing cases who convert to psychosis later.[86] This limitation has also been noted of CHR programs in HICs.[84] Additional components included antipsychotics and omega-3 fatty acids, both controversial, as the former increases the likelihood of conversion to psychosis,[87] while the latter has mixed efficacy evidence.[5,88]

Efficacy evidence for CHR was scarce—only six records were identified, none assessing integrated treatment and only three examining conversion to psychosis. This reflects the challenges of conducting intervention studies on CHR in LMICs including limited funding, insufficient community involvement, and cultural obstacles, necessitating context-sensitive approaches to CHR research as suggested by LMIC researchers.[22]

HIC guidelines recommend multicomponent care for early psychosis.[8] In LMICs, however, while second-generation antipsychotics are widely used, psychological and psychosocial components remain inconsistently offered, even within formal EIP programs. This reflects systemic constraints, including workforce shortages, inadequate infrastructure, and limited budgets,[11] suggesting that the strict replication of HIC models may be unrealistic. Instead, LMICs may need

to adapt approaches like task-sharing, task-shifting, and mobile health, which have demonstrated benefits in other health areas in resource-limited settings.[89,90] This may help improve access to evidence-informed psychological and psychosocial treatments.

Furthermore, most of the research we reviewed focused on evaluating patient outcomes of interventions in tertiary care, with few studies addressing implementation outcomes, scale-up pathways, and integration into primary care systems.[91] Future research should also prioritize expanding EIP's reach by integrating services into existing health systems and ensuring cultural appropriateness.

Our review identified gaps in the implementation of the World Psychiatric Association's Expert International Advisory Panel's recommendations for EIP in LMICs.[92,93] Only one program (Russia) had national integration and public health activities.[30] Only two (Brazil and India) reported cultural adaptation.[25,53] Few used shared care or community engagement to facilitate help-seeking,[29] or provided workforce training.[45] Telepsychiatry and digital approaches were rare, limited to teleconsultation in Brazil,[26] and a hotline in Malawi,[29] as were coordinated networks such as Latin America's Andes Network.[94] Co-design, mental health awareness initiatives, and outreach to vulnerable populations (e.g., homeless, Indigenous) were notably absent.

For CHR, limited evidence, low conversion rates,[86] and recruitment and retention challenges raise concerns about feasibility and sustainability.[22] Similar debates exist in HICs, including that individuals accessing these programs do not represent the broader CHR population.[95] Recognition that psychosis can emerge from mood, anxiety, or other syndromes has led to

transdiagnostic youth mental health services[96,97]. Such models may be more appropriate in LMICs, yet our review found no such programs.

In terms of limitations, the review included only database-indexed records. Although we searched additional databases and contacted researchers, we did not search grey literature. We could review only as much detail on treatment components as was provided by authors, which was often scarce. Records from the same intervention were grouped, but some provided distinct data (e.g., different age limits); in such cases, all data were reported. Country income classifications may have changed since our search, but such shifts do not impact the health sector immediately and are therefore unlikely to affect our findings. Effect sizes could not be reported due to incomplete data. In some cases, initiatives combined clinical and research activities[98], making the distinction between programs and studies not straightforward. These were categorized as programs due to their specialization and sustained duration over time.

Some records were excluded for not describing treatment components but rather focusing on other aspects like care pathways. These include FEP studies in Jordan,[99] Malaysia,[100] Mauritius,[101] Morocco,[102] Sri Lanka,[103] Suriname,[104] Iran,[105] Nigeria; and Trinidad and Tobago,[106] and CHR studies in Kenya.[107] We also identified promising ongoing projects, including psychoeducation in Uganda,[108] and in Pakistan, culturally adapted CBT and family intervention,[109] and collaboration between traditional healers and clinicians.[110]

This review's strengths include the classification of interventions by delivery context (programs vs. studies). This avoided mislabeling short-term research as programs. We classified components as guideline-based or additional, allowing both the assessment of guideline

implementation and the documentation of innovative/culturally adapted strategies. We contacted many authors to clarify data, ensuring accuracy. Our review included all eligible records regardless of language, covering English, French, Spanish, Portuguese, Turkish, and Persian, thereby enhancing the breadth and diversity of the evidence.

Few LMICs have FEP programs and studies and even fewer target CHR. Guideline-based psychological and psychosocial components are seldom implemented, reflecting systemic resource constraints. Still, evidence from LMICs clearly shows that multicomponent care can improve recovery and quality of life for people with FEP. However, large-scale implementation and population-level impacts (e.g., coverage, mortality) remain underexplored. Innovative delivery methods may help expand access to early psychosis care, particularly its psychological and psychosocial components, in LMICs.

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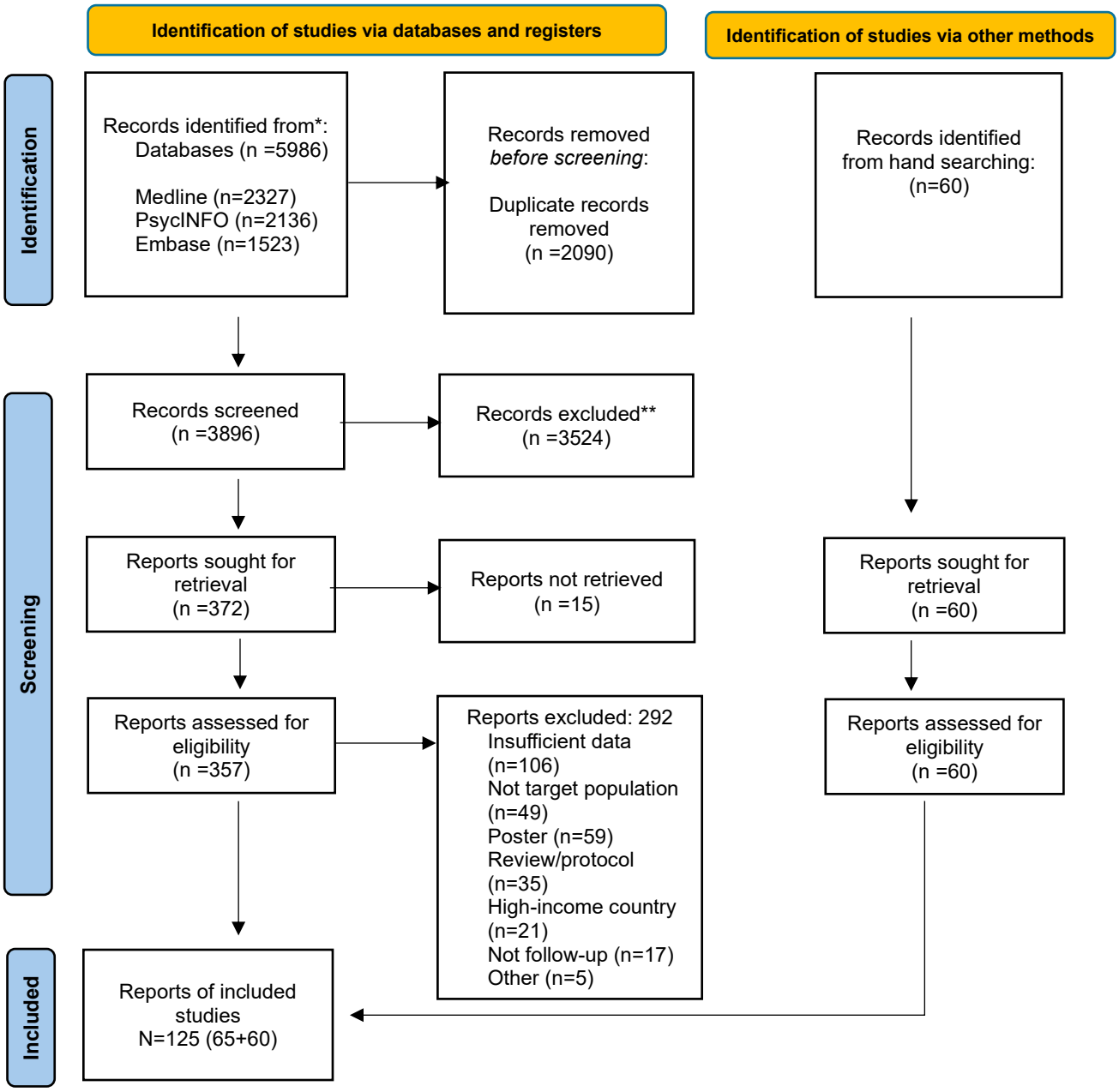

Figure 1. Flow diagram

Table 1. FEP interventions in LMICs

FEP intervention	Region	Country	Place(s)	N sites	N records
		FEP programs (n=10)			
Schizophrenia Research Foundation	SA	India	Chennai	1	20
All India Institute of Medical Sciences	SA	India	Chennai/New Delhi	2	1
Ribeirao Preto Early Intervention in Psy. P.	LAC	Brazil	Sao Paulo	1	2
Psy. Episode P. of the UNIFESP	LAC	Brazil	Sao Paulo	1	3
Early Psychosis Support Group	LAC	Brazil	Sao Paulo	1	2
Early Intervention Clinic in Psychosis*	LAC	Mexico	Mexico City	1	1
A. P. of Neuropsychiatric and Imaging Study*	LAC	Mexico	Mexico City	1	1
Moscow Research Institute of Psychiatry	ECA	Russia	Nationwide	>30	1
First-Episode Schizophrenia Follow-up Project	ECA	Turkey	Istanbul	1	1
Saint John of God Community Services	SSA	Malawi	Mzuzu	1	4
		FEP studies (n=30)			
Christian Medical College	SA	India	Vellore	1	2
NIMHANS in Bangalore[1]	SA	India	Bangalore	1	1
NIMHANS in Bangalore[2]	SA	India	Bangalore	1	1
NIMHANS in Bangalore[3]	SA	India	Bangalore	1	1
Silver Mind Hospital	SA	India	Mumbai	1	1
Central Institute in Psychiatry in Ranchi	SA	India	Ranchi	1	1
Medical College in Nepal	SA	Nepal	Chitwan	1	1
Study in Yogyakarta	EAP	Indonesia	Yogyakarta	4	1
Da Nang Psychiatric Hospital	EAP	Vietnam	Da Nang	1	1
Ten-site study in China	EAP	China	-	10	2
Study in Xuhui and HongKou	EAP	China	Shanghai	2	1
Study in Shanghai	EAP	China	Shanghai	6	1
Tongde Hospital	EAP	China	Zhejiang	1	1
Beijing Anding Hospital	EAP	China	Beijing	1	1
Suzhou Guangji Hospital	EAP	China	Jiangsu	1	1
Study in Jilin	EAP	China	Jilin	2	1
Study in China	EAP	China	-	2	1
Study in Shanghai and Changsha	EAP	China	Shanghai/Changsha	2	1
Second Xiangya Hospital	EAP	China	Changsha	1	1
Psychiatric Hospital in Thailand	EAP	Thailand	Northern Thailand	1	1
N. I. of Psychiatry Ramon de la Fuente Muñiz	LAC	Mexico	Mexico city	1	1
Nervous System Research Center	LAC	Colombia	Bogotá	1	1
Bolu Community Mental Health Center	ECA	Turkey	Bolu	1	1
University Hospital in Turkey	ECA	Turkey	-	1	1
Roozbeh Hospital	MENA	Iran	Tehran	1	1
University College Hospital in Nigeria	SSA	Nigeria	Ibadan	1	1
Federal Neuro-Psychiatric Hospital in Benin	SSA	Nigeria	Benin	1	1
Study in Ibadan and Cape Town	SSA	Nigeria/South Africa	Ibadan/Cape Town	2	1
Butabika National Referral Mental Hospital	SSA	Uganda	Kampala	1	1
Psychiatric Hospital in Cape Town	SSA	South Africa	Cape Town	1	1

Psy: Psychosis, A: Adolescent, P: Program, UNIFESP: Federal University of Sao Paulo, NIMHAN: National Institute of Mental Health and Neuroscience, N: National, I: Institute, SA: South Asia, LAC: Latin America and the Caribbean, ECA: Europe and Central Asia, SSA: Sub-Saharan Africa, MENA: Middle East and North Africa, EAP: East Asia and Pacific. 1,2,3 (superscripts): Different studies were conducted at the same site.
*Program for individuals at CHR and with FEP.

Table 2. CHR interventions in LMICs

CHR intervention	Region	Country	Place(s)	N sites	N records
CHR programs (n=8)					
Evaluation and Follow-up of Adolescent and Young Adults	LAC	Brazil	Sao Paulo	1	1
Recognition P. and Intervention in Risk Mental States	LAC	Brazil	Sao Paulo	1	5
Early Intervention Clinic in Psychosis*	LAC	Mexico	Mexico City	1	1
A. P. of Neuropsychiatric and Imaging Study*	LAC	Mexico	Mexico City	1	2
Shanghai at Risk for Psychosis Project**	EAP	China	Shanghai	1	23
Psychotic Disorders Research Program	ECA	Turkey	Istanbul	1	6
Clinical High-Risk Program in Tunisia	MENA	Tunisia	Tunis	1	1
Tunisian Early Intervention of Psychosis Project	MENA	Tunisia	Tunis	1	1
CHR studies (n=8)					
Subclinical Symptoms and Prodromal Psychosis Project	LAC	Brazil	Sao Paulo	1	8
Longitudinal Study in Early Detection of Psychosis	LAC	Mexico	Mexico City	1	2
Palau Early Psychosis Study	EAP	Palau	-	1	2
Study in Tongji University	EAP	China	Shanghai	1	1
Beijing Anding Hospital	EAP	China	Beijing	1	1
Suzhou Guangji Hospital¥	EAP	China	Suzhou/Shanghai	2	1
Study in Pakistan	SA	Pakistan	Lahore/Karachi/Rawalpindi	3	2
Study in Kenya	SSA	Kenya	Machakos	1	1

A: Adolescent, P: Program, LAC: Latin America and the Caribbean, ECA: Europe and Central Asia, MENA: Middle East and North Africa, EAP: East Asia and Pacific, SA: South Asia. SSA: Sub-Saharan Africa.
*Program for individuals at CHR and with FEP. ** Includes the Shanghai at risk for psychosis extended program. ¥ In collaboration with Shanghai mental health center.

Table 3. EIP components offered to individuals with FEP in LMICs

FEP interventions	Guideline-based components**														Additional component	Cultural adaptation	Duration (months)
	Clinical assessment	Psychiatric management	Antipsychotic medication	Patient psychoeducation	Family education and support	Cognitive behavioral therapy	Supporting health	Case management	Supported employment	Educational support	Active engagement and retention	Annual comprehensive assessment	Substance abuse treatment	Crisis intervention			
FEP programs (n=10)																	
Schizophrenia Research Foundation	■	■	■	■	■	■		■	■		■	■			■	■	24
All India Institute of Medical Sciences	■	■	■	■	■	■	■		■			■			■		12
Ribeirao Preto Early Intervention in Psy. P.	■	■	■	■	■		■					■	■		■		24
Psy. Episode P. of the UNIFESP	■	■	■	■	■									■	■	■	24
Early Psychosis Support Group	■	■	■	■	■				■	■		■			■		36
Early Intervention Clinic in Psychosis*	■	■	■	■		■									■		24
A. P. of Neuropsychiatric and Imaging Study*	■	■	■	■	■	■	■	■						■	■		Open
Moscow Research Institute of Psychiatry	■	■	■	■	■			■							■		-
First-Episode Schizophrenia Follow-up Project	■	■	■	■	■							■			■		58
Saint John of God Community Services	■	■	■								■				■		18
FEP studies (n=30)																	
Christian Medical College	■	■	■	■		■						■			■	■	60
NIMHANS in Bangalore[1]	■	■	■	■												■	12
NIMHANS in Bangalore[2]	■	■	■	■											■		6
NIMHANS in Bangalore[3]	■	■	■		■												3
Silver Mind Hospital	■	■	■												■		120
Central Institute in Psychiatry in Ranchi	■	■	■				■										1.5
Medical College in Nepal	■	■	■												■		12
Study in Yogyakarta	■	■	■	■	■											■	6
Da Nang Psychiatric Hospital	■	■	■	■	■											■	6
Ten-site study in China	■	■	■	■	■	■									■		12
Study in Xuhui and HongKou	■	■	■								■						24
Study in Shanghai	■	■	■	■	■												18
Tongde Hospital	■	■	■												■		1
Beijing Anding Hospital	■	■	■			■		■									12
Suzhou Guangji Hospital	■	■	■		■											■	18
Study in Jilin	■	■	■	■			■				■				■	■	18
Study in China	■	■	■	■											■	■	24
Study in Shanghai and Changsha	■	■	■	■													12
Second Xiangya Hospital	■	■	■				■										2
Psychiatric Hospital in Thailand	■	■	■				■								■		12
N. I. of Psychiatry Ramon de la Fuente Muñiz	■	■	■	■	■												12
Nervous System Research Center	■	■	■				■					■					60
Bolu Community Mental Health Center	■	■	■												■		6
University Hospital in Turkey	■	■	■		■												2.3
Roozbeh Hospital	■	■	■		■							■			■	■	24
University College Hospital in Nigeria	■	■	■			■								■	■		12
Federal Neuro-Psychiatric Hospital in Benin	■	■	■								■						6
Study in Ibadan and Cape Town	■	■	■	■			■				■						12
Butabika National Referral Mental Hospital	■	■	■	■	■												-
Psychiatric Hospital in Cape Town	■	■	■	■	■								■				24

Psy: Psychosis, A: Adolescent, P: Program, UNIFESP: Federal University of Sao Paulo, NIMHAN: National Institute of Mental Health and Neurosciences, N: National, I: Institute. 1,2,3 (superscripts): Different studies were conducted at the same site. *Program for individuals at CHR and with FEP. ** "Psychiatric management" was considered as part of "clinical evaluation" and "antipsychotic medication". White grey cell: Component not present. Light grey cell: Component present. Dark grey cell: Component evaluated in efficacious studies.

Table 4. EIP components offered to individuals at CHR in LMICs.

CHR intervention	Guideline-based components							Additional components	Cultural adaptation	Duration (months)
	Comprehensive clinical assessment	Assessment by a trained specialist	Cognitive behavioral therapy	Treatment of comorbid conditions	Prevent the development of functional deficits	Monitoring by a mental health provider	Monitoring for up to 3 years			
CHR programs (n=8)										
Evaluation and Follow-up of Adolescent and Young Adults										-
Recognition P. and Intervention in Risk Mental States										Open
Early Intervention Clinic in Psychosis*										24
A. P. of Neuropsychiatric and Imaging Study*										Open
Shanghai at Risk for Psychosis Project**										Open
Psychotic Disorders Research Program										-
Clinical High-Risk Program in Tunisia										6
Tunisian Early Intervention of Psychosis Project										12
CHR studies (n=8)										
Subclinical Symptoms and Prodromal Psychosis Project										30
Longitudinal Study in Early Detection of Psychosis										-
Palau Early Psychosis Study										48
Study in Tongji University										6
Beijing Anding Hospital										3
Suzhou Guangji Hospital¥										3
Study in Pakistan										12
Study in Kenya										20

A: Adolescent, P: Program.
*Program for individuals at CHR and with FEP. ** Includes the Shanghai At Risk for Psychosis extended program. ¥ In collaboration with Shanghai mental health center.
White grey cell: Component not present. Light grey cell: Component present. Dark grey cell: Component studied in efficacious studies.

Table 5. Effectiveness of integrated treatment for individuals with FEP in LMICs

FEP intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurements)	Findings	Statistical analysis	QS
			RCTs (n=3)			
N. I. of Psychiatry Ramon de la Fuente Muñiz (Valencia, 2012)	Single site RCT (12 months)	TAU + patient psychoeducation, family psychoeducation (n: 39) TAU: Antipsychotic medication (n: 34)	Functional recovery (Symptomatic and functional remission) Symptomatic remission (score ≤ 3 in 8 specified PANSS items for at least 6 months) Functional remission (GAF score ≥ 65) Psychotic symptoms (PANSS) **Positive symptoms** (PANSS) Negative symptoms (PANSS) G. psychopathology (PANSS) Functioning (GAF) Relapse (20% worsening on the PANSS score from baseline evaluation) Rehospitalization (Admission to a hospitalization unit) Medication compliance	Functional recovery: p<0.01 Intervention: 56.4% Comparator: 2.9% Symptomatic remission: p<0.01 Intervention: 94.9% Comparator: 58.8% Functional remission: p<0.01 Intervention: 56.4% Comparator: 3.6% Psychotic symptoms: p<0.01 Intervention $\Delta \bar{x}$: -46.7 Comparator $\Delta \bar{x}$: -26.1 Positive symptoms: nr [a] Intervention $\Delta \bar{x}$: -10.7 Comparator $\Delta \bar{x}$: -6.6 Negative symptoms: p<0.01 Intervention $\Delta \bar{x}$: -12.7 Comparator $\Delta \bar{x}$: -6.9 G. psychopathology: p<0.05 Intervention $\Delta \bar{x}$: -23.3 Comparator $\Delta \bar{x}$: -12.6 Functionality: p<0.01 Intervention $\Delta \bar{x}$: 23.8 Comparator $\Delta \bar{x}$: 1.9 Relapse: p<0.01 Intervention: 10.3% Comparator: 35.7% Rehospitalization: nr Intervention: 5.1% Comparator: 10.7% Medication compliance: p<0.01 Intervention: 85.0% Comparator: 67.6%	Analysis of quantitative outcomes with Anova-repeated measures (group x time interaction) Analysis of categorical outcomes with McNemar. [a] p-value not reported for interaction of group x time. Statistically significant for the main effect for time analysis only (p<0.001).	3
Ten-site study in China (Guo, 2010)	Multi-site RCT (12 months)	TAU + patient psychoeducation, family intervention, skills training, CBT (n: 635) TAU: Antipsychotic medication (n: 633)	*Primary outcomes:* Treatment discontinuation or change (Five specific criteria listed in the report) Relapse (Six specific criteria listed in the report) *Secondary outcomes:* **Psychotic symptoms** (PANSS) Functioning (GAS) Employment or accessed education (No definition) Quality of life (SF-36)	Treatment discontinuation or change: HR:0.6 (95%CI: 0.5-0.7) Intervention: 32.8% Comparator: 46.8% Relapse: HR:0.6 (95%CI: 0.4-0.7) Intervention: 14.6% Comparator: 22.5% Psychotic symptoms: F:0.4, p:0.81 Intervention $\Delta \bar{x}$: -9.9 Comparator $\Delta \bar{x}$: -8.9 Functioning: F:4.3, p:0.002 Intervention $\Delta \bar{x}$: 8.8 Comparator $\Delta \bar{x}$: 6.7 Employment or accessed education: x2:10.1, p:0.001 Intervention: 30.1% Comparator: 22.2% Quality of life: All p≤0.02 (4 out of 8 SF-36 domains)	Harzard ratio and 95%CI were calculated. • Mixed effects models for repeated-measures analysis (group x time interaction)	4
Roozbeh Hospital (Shahrivar, 2011)	Single site RCT (24 months)	TAU + family psychoeducation, and telephone follow-up (n: 20) TAU: Antipsychotic medication (n: 20)	**Positive symptoms** (PANSS) **Negative symptoms** (PANSS) **G. psychopathology** (PANSS) **Depressive symptoms** (HAM-D) **Functioning** (GAF, CGAS)	Positive symptoms: p: 0.610 Negative symptoms: p: 0.231 G. Psychopathology: p: 0.930 Depressive symptoms: p: 0.756 Functioning (GAF): p: 0.768 Functioning (CGAS): p: 0.958	Chi-square test Independent sample t-test.	1
			Observational studies (n=4)			

FEP intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurements)	Findings	Statistical analysis	QS
Moscow Research Institute of Psychiatry (Zayteseva, 2010)	Cohort-2 groups (60 months)	Atypical antipsychotics, psychoeducation, individualized family intervention, supportive therapy and case management (n: 114) Regular care-not specified (n: 119)	Relapse (No definition) Remission (No definition) Unemployment (No definition)	Remission Intervention: 46.5% Comparator: 36.7% Relapse rates [a] Intervention: x̄:0.2, sd: 0.5 Comparator: x̄:0.6, sd: 0.9 Unemployment Intervention: 17.7% Comparator: 47.1%	Do not specify the type of statistical analysis conducted [a] uninterpretable value	1
Schizophrenia Research Foundation (Malla, 2020)	Cohort: 2 groups (24 months)	Multicomponent intervention in LMIC (n=165) Same intervention in HIC (n=168)	Positive symptoms (Scales for the assessment of positive symptoms) Negative symptoms (Scale for the assessment of negative symptoms)	Positive symptoms: F: 44.1, p<0.001 LMIC Δ x̄: -16.8 HIC Δ x̄: -29.4 Negative symptoms: F: 7.4, p:0.002 LMIC Δ x̄: -17.4 HIC Δ x̄: - 11.9	Manova, adjusted for confounders (group x time interaction).	5
Schizophrenia Research Foundation (Iyer, 2010)	Cohort: 2 groups (12 months)	Multicomponent intervention in LMIC (n=61) Multicomponent intervention in HIC (n=88)	Psychotic symptoms (PANSS) **Positive symptoms** (PANSS) Negative symptoms (PANSS) **G. psychopathology** (PANSS) Functioning (SOFAS)	Psychotic symptoms: F:7.0, p:0.009 LMIC Δ x̄: -36.2 HIC Δ x̄: -25.7 Positive symptoms: F:1.6, p:0.21 LMIC Δ x̄: -9.9 HIC Δ x̄: -11.3 Negative symptoms: F:26.4, p<0.001 LMIC Δ x̄: -3.4 HIC Δ x̄: 4.6 G. psychopathology: F:2.8; p:0.09 LMIC Δ x̄: -14.6 HIC Δ x̄: -10.6 Functioning: F:12.9, p<0.001 LMIC Δ x̄: 35.6 HIC Δ x̄: 19.27	Ancova (group x time interaction)	5
Study in Ibadan and Cape Town (Chiliza, 2006)	Cohort: pre-post (12 months)	Depot antipsychotic + Assertive monitoring program (n, at 12-month= 149) (n, at baseline= 207)	Remission (≥50% PANSS total score improvement) Psychotic symptoms (PANSS) Positive symptoms (PANSS) Negative symptoms (PANSS) General psychopathology (PANSS) Functionality (SOFAS) Quality of life (World Health Organization quality of life scale) Depressive symptoms (Calgary depression scale for schizophrenia)	Treatment response: 170 of the 207 participants (82%). Psychotic symptoms: p<0.001 One-year: x̄: 42.5, sd:11.4 Baseline: x̄: 86.5, sd:19.2 Positive symptoms One-year: x̄: 8.8 , sd:3.0 Baseline: x̄: 22.3 , sd: 5.8 Negative symptoms One-year: x̄: 12.2 , sd: 4.7 Baseline: x̄: 23.2 , sd: 8.1 General psychopathology One-year: x̄: 21.5 , sd: 5.7 Baseline: x̄: 40.9 , sd:10.1 Functioning: p<0.001 One-year: x̄: 70.1, sd: 13.3 Baseline: x̄: 43.9, sd:11.9 Quality of life: p<0.001 One-year: x̄: 13.7, sd: 2.4 Baseline: x̄: 11.5, sd: 3.1 Depressive symptoms: p<0.001 One-year: x̄: 1.4, sd: 3.0 Baseline: x̄: 2.8, sd: 3.9	Wilcoxon signed rank two-tailed test	3
			Cost-effectiveness (n=2)			
Early Psychosis Support Group (Aceituno, 2024)	Cohort: 2 groups (12 months)	Clinical assessment + antipsychotic medication + patient psychoeducation, etc. (n= 317) Regular care: medication + psychosocial intervention (rarely implemented)	Cost-effectiveness	Multicomponent intervention: Mean costs (R$): 148,757.2 Mean effects (QALYs): 6.18 Regular care Mean costs (R$): 144,278.8 Mean effects (QALYs): 5.89 Incremental costs (R$): 4,478 Incremental effects (QALYs): 0.29 Incremental cost-effectiveness ratio: 15,495	Cost-effectiveness analysis by calculating the incremental cost-effectiveness ratio	4

FEP intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurements)	Findings	Statistical analysis	QS
Ten-site study in China (Zhang, 2014)	Multi-site RCT(12 months)	TAU + psychoeducation, family intervention, skills training, CBT (n= 580) TAU: Antipsychotic medication (n= 604)	Cost-effectiveness	Incremental costs (US$): 56.4 Incremental effects (QALYs): 0.031 Incremental cost-effectiveness ratio: 1,819.4	Cost-effectiveness analysis by calculating the incremental cost-effectiveness ratio	4

HIC: High-income country, LMIC: Low-and middle-income country, N: National, I: Institute, RCT: Randomized controlled trial, CBT: Cognitive-behavioral therapy, TAU: Treatment as usual, QALY: Quality-adjusted life-years, R$: Brazilian Real. US$: United Sates Dollar, G: General, HR: Hazard ratio, CI: Confidence interval, nr: Not reported. PANNS: Positive and negative syndrome scale, GAF: Global assessment of functioning scale, GAS: Global assessment scale, SF-36: Medical outcomes study 36-Item short form health survey, HAM-D: Hamilton depression rating scale, CGAS: Children global assessment scale. SOFAS: Social and occupational functioning assessment scale. QS: Quality Score with Mixed Methods Appraisal tool (Range:0-5), sd: standard deviation.
$\Delta \bar{x}$: Mean difference. Δ M: Median difference. Negative values represent improvements for psychotic (positive, negative and general psychopathology symptoms) and depressive symptoms. Positive values represent improvements in functioning and quality of life.
*Outcomes in bold indicate no statistical difference.

Table 6. Effectiveness of single-EIP components for individuals with FEP in LMICs.

FEP intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurement)	Findings	Statistical analysis	QS
			Essential components (n=8)			
Antipsychotic medication						
Study in Xuhui and HongKou (Zhang, 2016)	Cohort (pre-post) (24 months)	case management + Antipsychotic monotherapy: aripiprazole or clozapine or chlorpromazine or olanzapine or perphenazine or quetiapine or risperidone (n=312)	Psychotic symptoms (PANSS) Positive symptoms (PANSS) Negative symptoms (PANSS) Functioning (Personal and social performance scale) Medication adherence (Medication adherence rating scale)	Psychotic symptoms F:0.85, p:0.64 Positive symptoms F:0.97, p:0.49 Negative symptoms F:0.80, p:0.70 Functioning F:0.14, p:1.00 Medication adherence F:1.35, p:0.24	Mixed-effect models for repeated measures (group x time analysis).	5
CBT						
Beijing Anding Hospital (Liu, 2019)	A pilot RCT (12 months)	TAU + Brief CBT intervention (n=40) TAU: Antipsychotic medication + case management (n=40)	*Primary outcome* Relapse (rating of 6 or 7 on PANSS thought-disorder items, or 2 or more of these items rating 5 or above) **Hospitalization** (No definition) Psychotic symptoms[1] (PANSS) Psychotic symptoms[2] (PSYRATS) **Positive symptoms** (PANSS) **Negative symptoms** (PANSS) G. psychopathology (PANSS) *Secondary outcome* Functioning (Personal and social performance scale)	Relapse [a] Intervention: 10% Comparator: 32.5% Hospitalization: x^2: 3.53, p: 0.06 Intervention: 7.5% Comparator: 20% Psychotic symptoms[1]: F: 3.4, p: 0.04 Intervention Δ $\bar{x}$: -25.28 Comparator Δ $\bar{x}$: -17.07 Psychotic symptoms[2]: F: 1.945, p: 0.024 Intervention Δ M: -25.5 Comparator Δ M: -25.5 Positive symptoms [b]: F: 1.3, p: 0.265 Intervention Δ $\bar{x}$: -8.45 Comparator Δ $\bar{x}$: -6.65 Negative symptoms: F: 1.4, p: 0.23 Intervention Δ M: -4.0 Comparator Δ M: -4.5 G. psychopathology: F: 3.9, p: 0.027 Intervention Δ M: -10.5 Comparator Δ M: -10.5 Functioning: F: 3.1; p: 0.039 Intervention Δ $\bar{x}$: 22.85 Comparator Δ $\bar{x}$: 15.06	Chi-square test Anova-repeated measures (Group x time analysis) [a] Not reported statistical test results [b] Not significant for group x time analysis. There was a effect for group analysis (0.000).	5
Patient psychoeducation						
Study in Jilin (Chien, 2019)	Multi-site RCT(18 months)	TAU + Mindfulness-based psychoeducation program (n=60) TAU + standard psychoeducation (n=60) Comparator: TAU: Antipsychotic medication, supporting health, active engagement and retention (n=60)	*Primary outcome* Functioning (SLOF) *Secondary outcome* Duration of psychiatric re-hospitalization Average number of re-hospitalizations Psychotic symptoms (PANSS)	Functioning: F: 8.1, p<0.005 Intervention Δ $\bar{x}$: 53.8 Comparator Δ $\bar{x}$: 10 Average number of re-hospitalizations: F: 3.80, p: ns Intervention Δ $\bar{x}$: -0.6 Comparator Δ $\bar{x}$: 0.1 Duration of re-hospitalizations: F:6.82, p<0.001 Intervention Δ $\bar{x}$: -9.3 Comparator Δ $\bar{x}$: 2.7 Psychotic symptoms: F: 6.3, p<0.01 Intervention Δ $\bar{x}$: -35 Comparator Δ $\bar{x}$: 15 Positive symptoms: F: 7.5, p<0.01 Intervention Δ $\bar{x}$: -11.3 Comparator Δ $\bar{x}$: 5.8 Negative symptoms: F: 4.12, p<0.05 Intervention Δ $\bar{x}$: -5.7 Comparator Δ $\bar{x}$: 1.9	Manova (Group x time interaction)	5

FEP intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurement)	Findings	Statistical analysis	QS
Study in China (Chien, 2017)	Multi-site RCT (18 months)	TAU + Mindfulness-based psychoeducation group (n=114) TAU+ standard psychoeducation (n=114) Comparator: TAU: Antipsychotic medication, finance assistance, and psychological therapy. (n=114)	*Primary outcomes* Length of re-hospitalizations Average number of re-hospitalizations Remission (4-month simultaneous ratings of all individual items in PANSS as score ≤3) Psychotic symptoms (PANSS) *Secondary outcomes* Functioning (SLOF)	Length of re-hospitalizations: F:5.23; p<0.005 Intervention Δ $\bar{x}$: -9.1 Comparator Δ $\bar{x}$: 2.7 Average number of re-hospitalizations: F:3.78, p≥0.05 Intervention Δ $\bar{x}$: -1 Comparator Δ $\bar{x}$: -0.2 Remission: RR:2.0 (95%CI: 1.1-4.2) Intervention: 38.9% Comparator: 7.4% Psychotic symptoms: F:6.1; p<0.005 Intervention Δ $\bar{x}$: -16 Comparator Δ $\bar{x}$: 8.8 Positive symptoms: F:6.48; p<0.005 Intervention Δ $\bar{x}$: -8.1 Comparator Δ $\bar{x}$: 3.7 Negative symptoms: F:5.10; p<0.01 Intervention Δ $\bar{x}$:-0.9 Comparator Δ $\bar{x}$:2.4 Functioning: F: 6.40; p<0.005 Intervention Δ $\bar{x}$:59 Comparator Δ $\bar{x}$:-6.7	Manova (Group x time interaction)	4
Family psychoeducation						
Da Nang Psychiatric Hospital (Ngoc, 2016)	RCT (6 months)	TAU + family schizophrenia psychoeducation program (n=30) TAU: Antipsychotic medication (n=29)	Patient quality of life (QOL)	Patient quality of life: F: 4.32, p<0.05 Intervention Δ $\bar{x}$: 0.26 Comparator Δ $\bar{x}$: 0.06	Ancova [a] Higher score indicates higher non-compliance.	2
Study in Yogyakarta (Marchira, 2017)	RCT(6 months)	Brief psychoeducation program concerning schizophrenia(n=50 patients and their family members) TAU: Standard family education(n=50 patients and their family members)	Psychotic symptoms (Brief psychiatric rating scale) **Psychotic symptoms** (PANSS) **Relapse/ rehospitalization** (Compliance and relapse assessment)	Psychotic symptoms (BPRS): t: 2.064, p: 0.042 Intervention Δ $\bar{x}$: -35.52 Comparator Δ $\bar{x}$: -38.04 Psychotic symptoms (PANSS): t: 1.129, p: 0.262 Intervention Δ $\bar{x}$: -35.56 Comparator Δ $\bar{x}$: -36.92 Relapse/rehospitalization: x2: 2.367, p: 0.124 Intervention: 6% Comparator: 18%	Chi square Independent sample t-test (between intervention and control group in the last endpoint)	3
Study in Shanghai (Cai, 2015)	RCT (18 months)	TAU + family therapy focused on cognitive rehabilitation (social skills individualized training and family psychoeducation) (n=133) TAU: Antipsychotic medication (n=123)	**Psychotic symptoms** (PANSS) **Positive symptoms** (PANSS) **Negative symptoms** (PANSS) **G. psychopathology** (PANSS)	Psychotic symptoms: F: 3, p: 0.08 Intervention Δ $\bar{x}$: -4.44 Comparator Δ $\bar{x}$: -4.86 Positive symptoms: F: 1.59, p: 0.21 Intervention Δ $\bar{x}$: -1.09 Comparator Δ $\bar{x}$: -1.08 Negative symptoms: F: 1.10, p: 0.30 Intervention Δ $\bar{x}$: -1.48 Comparator Δ $\bar{x}$: -1.52 G. psychopathology: F: 3.71, p: 0.06 Intervention Δ $\bar{x}$: -1.87 Comparator Δ $\bar{x}$: -2.25	Ancova controlling for confounders	5

FEP intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurement)	Findings	Statistical analysis	QS
Suzhou Guangji Hospital (Zhang, 1994)	RCT (18 months)	TAU + Family intervention (group and individual counselling sessions) (n=42) TAU: Antipsychotic medication (n=41)	Hospital readmission Hospital-free period in readmitted patients **Psychotic symptoms** (Brief psychiatric rating scale) **Functioning** (Global assessment scale)	Hospital readmission: RR: 3.5 (95%CI: 1.6-7.6) x^2= 12.75, p<0.01 Intervention: 15.4% Comparator: 53.8% Hospital-free period in readmitted patients: t: 2.9, p<0.01 Intervention: 245 days, sd: 104 Comparator: 130 days, sd: 79 Psychotic symptoms: t: 0.67, p>0.05 Intervention Δ $\bar{x}$: -17.3 Comparator Δ $\bar{x}$: -17.0 Functioning: t: 1.08, p>0.05 Intervention Δ $\bar{x}$: 29.9 Comparator Δ $\bar{x}$: 30.4	The statistical analysis for these findings is not provided.	3
			Other components (n=3)			
Non-CBT psychotherapy						
Bolu Community Mental Health Center (Sukru, 2018)	Non-randomized controlled Study (6 months)	Antipsychotic medication+ Interpersonal psychotherapy group (n=20) Antipsychotic medication + Painting group (n=20) Antipsychotic medication + Waiting list group (n=20)	Functionality (Brief functioning assessment scale[a]) Psychotic symptoms (PANSS)	Functionality: (p<0.001) Psychotherapy group Δ$\bar{x}$: -23.3 Painting group Δ $\bar{x}$: -4.6 Waiting list Δ $\bar{x}$: -3.9 Psychotic symptoms: p<0.001 Psychotherapy group Δ M: -8.5 Painting group Δ M: 0 Waiting list Δ M: 2.5	General Linear Model Repeated ANOVA [a] The lower the score, the higher the functionality.	3
Cognitive training						
NIMHANS in Bangalore[2] (Hedge, 2012)	RCT(2 months)	TAU + cognitive training (n=22 patients and their family members) TAU: Antipsychotic medication + psychoeducation (n=23 patients and their family members)	**Psychotic symptoms** (PANSS) **Functionality** (WHODAS-II)	Psychotic symptoms and functioning: ns	Ancova (Group x treatment interaction) controlling for confounders.	1
Electroconvulsive therapy						
Medical College in Nepal (Adhikari, 2014)	Cohort (12 months)	Electroconvulsive therapy + Antipsychotic medication (n=12) Antipsychotic medication (n=33)	Psychotic symptoms (Brief psychiatric rating scale) Functionality (Global assessment of functioning scale)	Psychotic symptoms: p: 0.001 Intervention Δ $\bar{x}$: -61.9 Comparator Δ $\bar{x}$: -53.3 Functionality: p: 0.003 Intervention Δ $\bar{x}$: 76.0 Comparator Δ $\bar{x}$: 61.8	Statistical analysis does not specify a statistical test performed to evaluate outcomes.	3

N: National, I: Institute, NIMHAN: National Institute of Mental Health and Neuroscience, RCT: Randomized controlled trial, CBT: Cognitive-behavioral therapy, TAU: Treatment as usual, G: General, ns: not statistically significant, RR: Risk ratio, CI: Confidence interval, QS: Quality Score with Mixed Methods Appraisal tool (Range: 0-5). PANSS: Positive and negative syndrome scale, PSYRATS: Psychotic symptoms rating scale, SLOF: Specific level of functioning scale, QOL: Quality of life enjoyment and satisfaction questionnaire, WHODAS-II: World Health Organization Disability assessment schedule, second version. sd: standard deviation.

Δ $\bar{x}$: Mean difference. Δ M: Median difference. Negative values represent improvements for psychotic (positive, negative and general psychopathology symptoms) and depressive symptoms. Positive values represent improvements in functioning and quality of life.

*Outcomes in bold indicate no statistical difference.

Bridge

The previous manuscript provided rich and detailed information on the treatment components offered to people with FEP and CHR and on their effectiveness when implemented in LMICs. A key strength of that study was its ability to distinguish between implementation settings, showing that multicomponent interventions were delivered both within formal EIP programs and through research-based projects. Including the latter was essential, as we found a greater number of research-based projects than formal EIP programs, and these contributed valuable evidence on the effectiveness of treatment components. These findings underscore that many EIP initiatives in LMICs have been implemented outside formal standalone programs, an area that has received little attention in prior studies. This may be particularly important for LMICs, where the implementation of standalone EIP programs is often not feasible.

The next important step therefore was to explore and understand what types of EIP initiatives, beyond standalone programs, have been implemented in LMICs and how they were configured. To address this, we adopted a comprehensive approach and examined all initiatives aimed at meeting the needs of people in the early phases of psychosis in one region of the world, LAC. Based on the existing literature (Chapter 1, Sections 2 and 3), we anticipated that these initiatives could include clinical programs, research programs, clinical guidelines, and technical standards. We consider this among the first systematic attempts in the field of EIP to explore the value and relevance of initiatives other than standalone programs, which have received limited attention despite their potential to inform or advance the development of EIP in LMICs.

To conduct this work, we also sought to address the limitations of previous studies that have mapped EIP programs worldwide. First, unlike earlier studies that relied solely on synthesizing

published literature through desk reviews, we adopted a qualitative approach to obtain first-hand and detailed data on the implementation of EIP initiatives. Second, whereas previous studies collected information exclusively from national representatives of psychiatric associations, we gathered data through interviews with primary implementers of EIP initiatives. Third, we used a systematic implementation framework to examine implementation processes, pathways, challenges and facilitators, and how these are shaped by the local social, health and policy context(s). By following this approach, we aimed to enhance the rigor and trustworthiness of the study and to generate a more comprehensive understanding of how EIP approaches may be developed, implemented, adapted and scaled in within LAC, while also providing insights that may be relevant to other LMICs and resource-limited settings.

Chapter 5

Manuscript III

Implementation of Early Intervention in Psychosis Initiatives in Latin America and the Caribbean: A Case Study

(Submitted to *Implementation Research and Practice*)

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Implementation of Early Intervention in Psychosis Initiatives in Latin America and the Caribbean: A Case Study

Abstract

Background: Psychosis is a serious mental illness, with onset in adolescence and young adulthood. Few early intervention in psychosis (EIP) programs exist in the Global South, where most of the world's youth live. Addressing this gap requires understanding implementation contexts, pathways and challenges. This study examines EIP initiatives in Latin America and the Caribbean (LAC) and explores implementers' perspectives on scaling them.

Methods: A single-case study design was employed. Guided by the Exploration, Preparation, Implementation, and Sustainment (EPIS) framework, we conducted semi-structured interviews with EIP implementers across LAC and gathered policy documents. Data was coded and analyzed using thematic analysis.

Results: Twenty-five participants from 10 countries described 26 initiatives, including clinical and research programs, guidelines, and a technical standard. Themes were mapped onto EPIS phases. In Exploration, participants highlighted key motivators, the influence of collaborations with foreign researchers, contextual adversity (e.g., poverty, stigma), and the role of Indigenous cosmologies and religious traditions in shaping care pathways. In Preparation, they emphasized difficulties in culturally adapting models from high-income countries (HIC), limited staff awareness, and resource shortages. In Implementation, participants described how initiatives operated in local contexts (e.g., research programs offering care to address unmet needs), how they were generally well received by patients and staff, and the shortage of psychosocial

interventions. In sustainability, few initiatives persisted; participants pointed to dependence on international funding, limited policy support, capacity, and awareness. While EIP was valued, national dissemination of HIC-based programs was considered unfeasible.

Conclusions: EIP development in LAC has occurred amid structural and resource limitations affecting many LMICs. Implementers' proposals: task-shifting; simplified care packages; leveraging extant services; and enhancing early psychosis literacy— represent feasible strategies to support EIP across LAC. Recommendations for future research, including the involvement of service users and their families and the adaptation of implementation frameworks to context, are shared.

Keywords: Mental Health Services, Latin America, Implementation Science.

How Early Intervention in Psychosis Is Being Developed in Latin America and the Caribbean

(Plain language summary)

Psychosis is a serious mental illness that usually begins in teenage or early adulthood. It is characterized by hallucinations (seeing, hearing, or sensing things that are not there), delusions (beliefs held strongly despite contrary evidence), cognitive symptoms (e.g., trouble concentrating), and other changes like reduced motivation and social interaction. Research has shown that getting care soon after symptoms start and receiving psychosocial support, such as therapy or family psychoeducation, can help recovery. In high-income countries, early intervention for psychosis (EIP) programs have been introduced to offer people experiencing their first episode of psychosis quick, comprehensive care. However, in countries with fewer resources, such as in Latin America and the Caribbean (LAC), only a few EIP programs are available. Other initiatives, like research, guidelines, and public policies, have also been developed and play a key role in spreading EIP. We looked at how these initiatives were developed in LAC and explored strategies to make EIP widely available. We interviewed 25 people from 10 LAC countries who led 26 different EIP initiatives. We found that EIP programs in LAC countries faced the same difficulties that affect mental health care across the region, including limited funds and trained individuals, low mental health awareness and stigma. Many programs were copied from models in wealthier countries and were often difficult to implement without adaptation to local needs and cultures. Participants agreed that the EIP model is valuable but recognized that expanding it is challenging. They suggested practical, locally relevant strategies like training general health workers to provide care, simplifying care packages, and raising community awareness. Our study can help improve EIP services and policies for persons with psychosis and their families in LAC countries. It shows

why implementation research is needed to understand what helps and hinders the adoption of care models known to work.

Implementation of Early Intervention in Psychosis Initiatives in Latin America and the Caribbean: A Case Study

Introduction

Early Intervention in Psychosis (EIP) is a multicomponent service model for early stages of psychotic disorders, specifically, clinical high risk for psychosis (CHR) and first-episode psychosis (FEP) (McGorry, 1993; McGorry et al., 2008). Grounded in a philosophy of hope and optimism (McGorry, 2015), EIP promotes recovery through patient and family interventions (i.e., medication, cognitive-behavioral therapy, psychoeducation, etc.) (McGorry et al., 2008). Evidence from randomized clinical trials, systematic reviews, and meta-analyses shows that EIP leads to better clinical and functional outcomes in FEP compared to standard care (Correll et al., 2018; Craig et al., 2004; Petersen et al., 2005; Puntis et al., 2020). Cost-effectiveness analyses demonstrate benefits in high- and low-resource countries (Rosenheck et al., 2016; Zhang et al., 2014). For CHR, evidence suggests that EIP can reduce symptoms and potentially delay or prevent onset (Mei et al., 2021).

EIP programs are widely implemented in many high-income countries (HICs) (Csillag et al., 2018) as stand-alone services, but also through integrated services and hub-and-spoke models (Behan et al., 2017). Pathways to implementation have been diverse, including government policies and research projects (Malla & McGorry, 2019). The success of EIP in HICs has relied on leadership, sustained funding, supportive policies, and partnerships (Csillag et al., 2018). Complementary efforts, like research (Valle et al., 2024), guidelines (Addington et al.,

2017), and policies, have helped generate evidence, standardize care, and raise awareness about EIP (NHS England, 2023).

In Latin America and the Caribbean (LAC), where almost 60% of countries are low-and middle-income countries (LMICs) (World Bank, 2025), EIP implementation programs remain limited. Brazil established the first documented EIP program in 1999 (Chaves, 2007), but by 2011 only Brazil and Mexico had programs(Brietzke et al., 2011). A 2020 scoping review, added two Chilean facilities and a one-off Argentinian study training primary care staff to refer FEP cases (Aceituno et al., 2021). A 2025 narrative review reported no further expansion (van der Ven et al., 2025). Existing programs remain concentrated in research centers within tertiary care in metropolitan areas, thus reaching fewer people (Aceituno et al., 2021; Brietzke et al., 2011; van der Ven et al., 2025).

Previous work, mainly desk reviews of clinical programs (Aceituno et al., 2021; Brietzke et al., 2011; van der Ven et al., 2025), limits our understanding of contextual factors, implementation processes and challenges in provision and uptake. Non-clinical initiatives, like research and policies, remain overlooked despite their role in expanding EIP services (Farhang et al., 2022; Larach et al., 2022; Myles-Worsley et al., 2007). Replicating EIP programs from HICs in LAC is not feasible due to socio-cultural and resource differences, highlighting the need to examine the full spectrum of EIP initiatives and implementation pathways (Singh et al., 2020, 2023).

Addressing these gaps requires applying implementation science frameworks to analyze pathways, strategies, contexts, and stakeholder roles advancing EIP. This study's examines the

implementation processes of EIP initiatives in LAC and explores implementers' perspectives on disseminating EIP across the region.

Methods

Design

This qualitative study uses a single case design with embedded units (Yin, 2018). The single case is EIP implementation in LAC. The embedded units of analysis are country-level EIP initiatives. This design was chosen to generate an in-depth analysis of EIP implementation in LAC and each initiative's trajectory. The study was guided by the well-established (Krishnamoorthy et al., 2025; Zhao et al., 2023)Exploration, Preparation, Implementation, and Sustainment (EPIS) implementation framework (Aarons et al., 2011; Moullin et al., 2019, 2020). This framework is well aligned with the study's objectives as it examines outer, inner, bridging, and intervention contexts and different implementation phases: *Exploration (*assessing needs and deciding to adopt the intervention), *Preparation* (identifying barriers, facilitators, and adaptations), *Implementation* (launching the intervention and monitoring) and *Sustainment* (ensuring continued delivery). The study follows the Consolidated Criteria for Reporting Qualitative Research (Table S1) (Tong et al., 2007).

Definitions

An EIP initiative refers to a plan or process addressing FEP or at CHR, including:

- Clinical programs: healthcare services providing assessment, treatment, and follow-up.
- Research programs: multi-year initiatives generating knowledge around a theme.

- Clinical guidelines: evidence-based recommendations developed by experts for assessment, diagnosis and treatment.
- Technical standards: authoritative documents specifying procedures and minimum requirements for services.
- Individual studies: standalone projects addressing specific questions or evaluating care components.

Settings

LAC has 664 million inhabitants in 42 countries, with 24.5% aged 15-29 years (CEPAL, 2025), an age group at risk for psychosis (Shiers & Lester, 2004). By 2015, Brazil, Chile, Panama, and Peru had community-based mental health models (Minoletti et al., 2012; Toyama et al., 2017). In other countries, care remains centralized in city-based psychiatric hospitals (Pan American Health Organization, 2013). Schizophrenia affects 277.8 per 100,000 people in LAC (GBD 2019 Mental Disorders Collaborators, 2022). Estimated service coverage is only 26.7% (Jaeschke et al., 2021).

Participants

Eligible participants were clinicians, researchers, or policymakers involved in EIP implementation in LAC. Purposive sampling (Palinkas et al., 2015) was used to identify initial implementers via systematic reviews (Aceituno et al., 2021; Brietzke et al., 2011; van der Ven et al., 2025), conference abstracts (Crossley et al., 2019), and networking. We emailed participants to explain the study, obtain consent and schedule individual interviews. Snowball sampling

helped identify additional participants.

Sample size

Sample size was determined based on data saturation (Wutich et al., 2024) and inclusion of at least one implementer per initiative. The sample (Table S2) included 25 participants: 20 of the 22 initially identified implementers, two replacements (e.g., co-authors) and three identified through snowball sampling. Data saturation was reached by interview 22; three subsequent interviews were about initiatives that had not been covered.

Data collection

One-hour interviews were conducted via Zoom from August 2024-February 2025 in Spanish or English and video-recorded. We used a demographic questionnaire and an EPIS-based semi-structured interview guide (adaptable based on initiative), that were piloted with EIP coordinators in Canada and India. Participants were requested to share relevant policy documents.

Reflexivity

RV, a Peruvian male psychiatrist with training in epidemiology and a doctoral focus on EIP, conducted interviews. His professional background and cultural proximity may have facilitated rapport and trust with interviewees. CV, a Colombian female psychotherapist and doctoral student without prior EIP experience, offered an outsider perspective and approached the data with fresh eyes. SNI, an immigrant psychologist and experienced EIP researcher in Canada and LMICs, contributed expertise during analysis. We had no prior relationship with participants and remained attentive to how our identities shaped interactions and interpretation.

Data analysis

Recordings were transcribed in their original language. We used thematic analysis to identify, analyze, and report patterns within the data (Braun & Clarke, 2006). This involved familiarization with the data, generation of initial codes, identification and review of themes and subthemes, refinement and synthesis. RV and CV independently coded transcripts in ATLAS.ti (v25), met regularly and reached consensus through discussion, with input from SNI. Themes were mapped onto the EPIS framework and presented in Results with illustrative quotes from participants.

Rigor and trustworthiness (Stahl & King, 2020) were ensured through prolonged engagement, independent coding, data triangulation between interviews and four policy documents, and member checking with participants (in group presentations and individual communications).

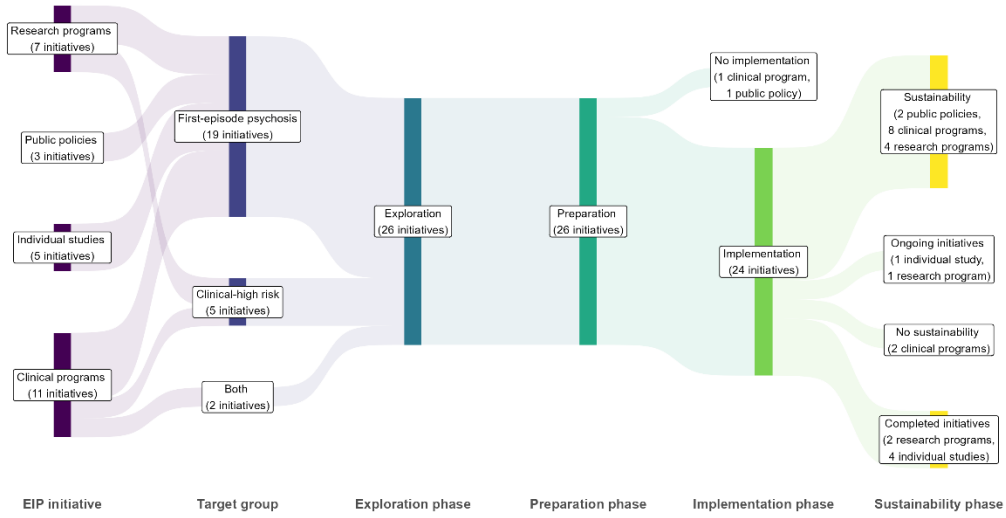
Results

EIP initiatives

Participants implemented 26 EIP initiatives across 10 countries, with one participant reporting on two (Table S3). These included 11 clinical programs, seven research programs, two clinical guidelines, one technical standard, and five individual studies. Most (19) initiatives focused on FEP, five on CHR, and two on both. All progressed through exploration and preparation; only some advanced to sustainability (Figure 1).

Figure 1

Implementation trajectories of EIP initiatives in Latin America and the Caribbean (n=26 EIP initiatives).



Note. Public policies include clinical guidelines and standards.

Exploration phase

Participants reflected on their motivations for implementing EIP and their local settings (Figure 2). Most initiatives were locally driven, motivated by participants' awareness of the impacts of untreated psychosis (suffering, employment/social losses, etc.) and unmet care needs among individuals and their families. Many became involved through international meetings, non-EIP psychosis work, and/or postgraduate/international training.

> *"The World Psychiatric Association offered training opportunities. I applied for a call to receive training at [organization in HIC], where they kindly showed me everything they*

were doing and allowed me to participate in their activities. This greatly inspired me to propose an early intervention program."

Clinicians were inspired by EIP's recovery orientation and by mentors. Researchers were drawn to generating local evidence for EIP in LAC, while policymakers aimed to implement best practices for people with psychosis. In a few cases, international researchers and funders initiated projects in collaboration with local leads, as required by funders.

"Our program, in contrast, emerged because a group at [foreign university], led by [researcher], a professor of psychiatric epidemiology with experience working in LAC, reached out to us and said it might be interesting to implement an adapted version of [EIP program] in [country], taking advantage of the [Health policy] to develop a program specifically for first-episode psychosis. So, we applied for an [foreign agency] grant. In that context, we adapted and evaluated [EIP program]."

Implementation contexts were widely seen as challenging. Mental health was not a governmental priority; recent well-intended regulations often failed due to limited resources and organizational capacity. Deinstitutionalization policies were rarely paired with services development and outdates pro-institutionalization policies persisted in some areas. Only one country, where a clinical guideline for first-episode schizophrenia is supported by universal access to health care coverage and strong primary care, was seen as supportive of case identification. Most described persistent structural barriers—shortages of personnel, infrastructure, funding, and psychosocial care—that left access limited, unequal, and often dependent on private services despite reforms and expanded insurance coverage.

"... what happens in [country], especially in cities without academic services or emergency psychiatric units, is that people with FEP experience a longer duration of untreated psychosis, because they don't have easy access to these facilities."

Participants also identified sociocultural factors shaping local understandings of mental illness, help-seeking and care pathways, such as low mental health literacy, stigma, supernatural beliefs, like *Aluxes (supernatural beings in Maya cosmology)*, and strong religious traditions like Catholicism, Kardecist spiritism and African religions. Families often consulted shamans, priests, or healers before formal services.

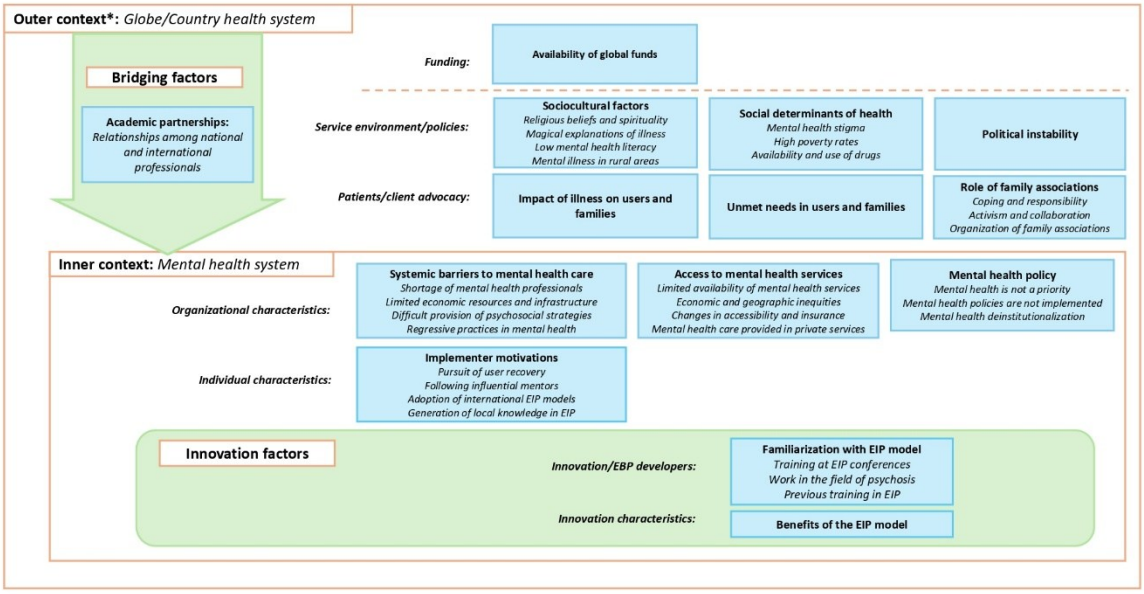
"So many religions in [country] involve spiritual contact with dead people, so it's not always easy to tell whether a patient's symptoms are due to psychosis or are part of their cultural background. This can interfere people from seeking psychiatric help, as they may first consult a priest or a medium associated with these religions."

Many participants identified adverse social determinants disproportionately affecting youths in LAC, including poverty, violence, and the availability of drugs. Political instability in some countries further disrupted health policy coordination. Within these challenging contexts, families played central, complex roles, sometimes seeking institutionalization due to pessimism about recovery, but more often acting as recovery allies and advocates working with government and health institutions to support individuals with mental health conditions. In rural areas, family support being in nature and working in the field (e.g., herding sheep) were identified as recovery-promoting.

"I tell you an anecdote about a young man who, before coming to our service, visited another psychiatric service. He was in his final years of secondary school when he started to suffer from psychosis. The doctor's message to the mother was: 'Madam, take him out of school, don't waste your money and your time, this boy, with difficulty in 10 years will be able to say his name'. She turned out to be a very brave mother and continued to seek treatment. Not only did she encourage him to continue in school, but she also encouraged the young man to enroll in university...This young man applied to law school, beating out a lot of people of his generation."

Figure 2

Themes and subthemes identified during the Exploration phase of EIP initiatives (n = 26).



Note. *The outer context comprises two dimensions, separated by the dashed orange line: global context and national health system.

Preparation phase

In the preparation phase, local actors developed EIP initiatives in clinical services, universities, and/or public agencies (Figure 3). Participants affiliated with health institutions created EIP programs that integrated clinical and research components; public agencies concentrated on developing policies; and university researchers led studies or contributed to guidelines. Except for public agencies developing policies, most relied on strong leadership, engaging decision-makers and building institutional relationships.

> *"They told me that there were psychiatrists who might be interested in this subject and then they passed me the details of the director of the schizophrenia clinic, and I made an appointment with him and his team…They helped me a lot to open doors… So, you meet one person, he gets involved in the project, and then you get to know someone else."*

Another key step was adapting EIP initiatives, as most were based on models from HICs, e.g., Australia or U.S.A., reflecting participants' training, work experience, or institutional ties. A common strategy was to preserve core evidence-based components, use local resources, and align with public health priorities. For instance, one participant emphasized strengthening family interventions, as youths in their context often live with their parents well into adulthood, reflecting the value of *familismo* (family unity, obligation, and interconnection) common in LAC. Cultural adaptation was often considered but applied unevenly due to perceived complexity. Common adaptations were translating tools, involving traditional healers, and incorporating cultural activities.

“I don't think people have a good definition of cultural adaptation. There are models, I know several, FRAME is one of them. ADAPT is another one that always includes that cultural element. But the cultural, I think is difficult, how to operate it….

Participants described institutional support as generally positive, though seldom accompanied by additional resources. Several initiatives received backing from professional associations and universities. Some required collaboration with health authorities, usually the Ministry of Health, which was mostly a positive process, with some exceptions. Funding varied: clinical and government programs used regular/existing resources, researchers relied on competitive grants, requiring repeated applications for sustenance.

“The initial program was based on research funds, with competitive research funds here in [country]. Until this year, science was done based on these competitive funds. From one of those research funds, this program was put together…because the clinic lent us the facilities, but the human resource to be able to evaluate and follow up these patients was what the funds mainly financed”.

External factors shaped the planning and design of EIP initiatives. In one country, EIP was backed by a clinical guideline for first-episode schizophrenia, and in a few others, clinical guidelines for psychosis included EIP, but most lacked formal policies. Participants noted the absence of dedicated services for early psychosis, making these initiatives pioneering efforts. Designing and integrating these programs was difficult due to scarce epidemiological data, low mental health literacy and limited capacity or interest among non-mental health professionals. Several noted that EIP was a new concept even for most mental health staff.

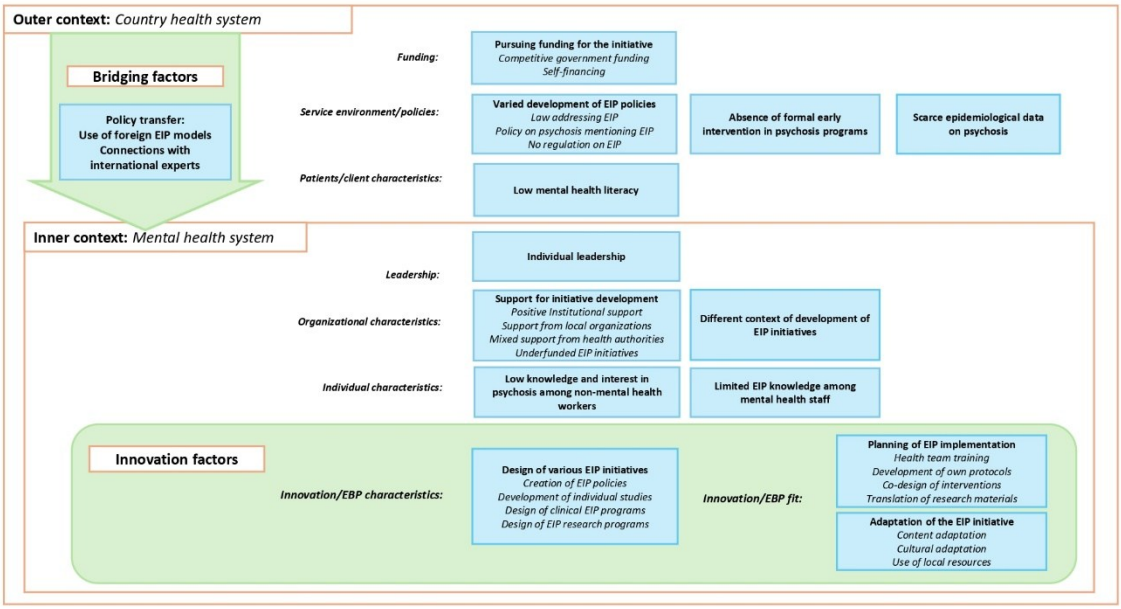
"When the training was done, it was seen that this [EIP] was something relatively new, even for psychiatrists... I understand, at least when I graduated and was an undergraduate, I finished in 2018, I remember that there was no talk of a first psychotic episode as such until that date."

Preparatory actions included staff training, developing care protocols from HICs' manuals, and translating materials. Policy initiatives often co-designed documents with user and family associations. Two initiatives had not been implemented at the time of interviews due to funding challenges, highlighting barriers to implementation.

"Yes, we presented it [EIP clinical program] to the hospital, presented it to the Ministry of Health, then to the [country] Society of Psychiatry. We even applied for a Canadian fund, but we didn't manage to get funding. We applied to two international calls for proposals and were unable to move forward due to lack of financial resources."

Figure 3

Themes and subthemes identified during the Preparation phase of EIP initiatives (n = 26).



Implementation phase

Participants described how EIP initiatives functioned in their settings, were received by users and providers, and the challenges faced (Figure 4). In the country with the clinical guideline for first-episode schizophrenia and strong primary care, the policy provided a strong foundation for further initiatives. Individual studies addressed specific goals without expanding into broader research agendas. Clinical programs focused on care delivery, but also engaged in research. Research programs prioritized scientific inquiry, but those in clinical settings offered care to address unmet needs. Most programs thus combined care and research to varying extents.

> "*We first initiated as a research program, so at the beginning we only had the assessments and the medical and then after the research assessments…[we began] to provide care, but*

we were all psychiatrists. So, I would say that things were evolving as patients were being enrolled in the research and we needed to provide some care for them."

Participants described their clinical and research EIP initiatives as well-received by users and families, who trusted implementers' clinical competence or institutional reputation. Enthusiasm sometimes declined due to limited family involvement, expectations for rapid recovery or rising substance use comorbidity, which demanded complex clinical management. While EIP models were generally accepted by mental health providers, some resistance to innovation and the perception that there is no difference between FEP and chronic stages were reported. Despite challenges, initiatives were seen as clinically important and building capacity. Research programs also enabled early detection and treatment of cases that might otherwise be missed.

"In our research, sometimes we did anti-psychotics for them. Sometimes we did antidepressants, sometimes we referred them to the psychologist for psychotherapy. Sometimes this was done for individual psychotherapy group therapy, and sometimes we just maintained surveillance on symptoms. So this was not structured, but was more on a as needed basis on an individual basis"

Across all initiatives, psychosocial interventions were deemed important but difficult to sustain due to resource and trained staffing shortages. Only one research program on psychosis epidemiology prioritized case identification over treatment but noted some psychosocial interventions offered within local services. Psychosocial interventions specialized for psychosis,

including cognitive-behavioral therapy, were rarely available. A participant reflected on these constraints:

> *"I think it [referring to fidelity scale for EIP] was developed by Donald Addington, and we realized half of what would be needed to be a first episode of psychosis proper program. But this is due to the lack of support…I think that we are not much better than we were at the beginning."*

Participants described clinical and research initiatives as often disconnected from the broader health system. Private sector programs served small groups; public programs had low coverage due to their stand-alone structure. In contrast, in the country with a clinical guideline for first-episode schizophrenia, the policy facilitated structured care through case notification, follow-up, and treatment. Programs in academic settings relied on researchers and trainees volunteering for assessments and therapy due to limited budgets.

> *"Depending on the resources that we had available, if we have someone, a psychologist, that would be a volunteer, then we could provide psychotherapy for [patients]. But so that's why it's hard for us to follow a specific model as we don't have people really hired specifically for this."*

The implementation phase revealed operational challenges. For CHR, these were under-resourced health systems, coordination challenges (e.g., limited referral pathways), and contextual factors like substance use complicating diagnosis. For FEP, defining onset was difficult when individuals arrived after long periods of untreated psychosis or unreliable antipsychotic use records. Some participants, therefore, preferred broader terms like "untreated psychosis" or

"early-onset psychosis." Retention of service users was a challenge, with many disengaging after initial symptom improvement. Programs often provided non-protocolized care based on resources and individual needs.

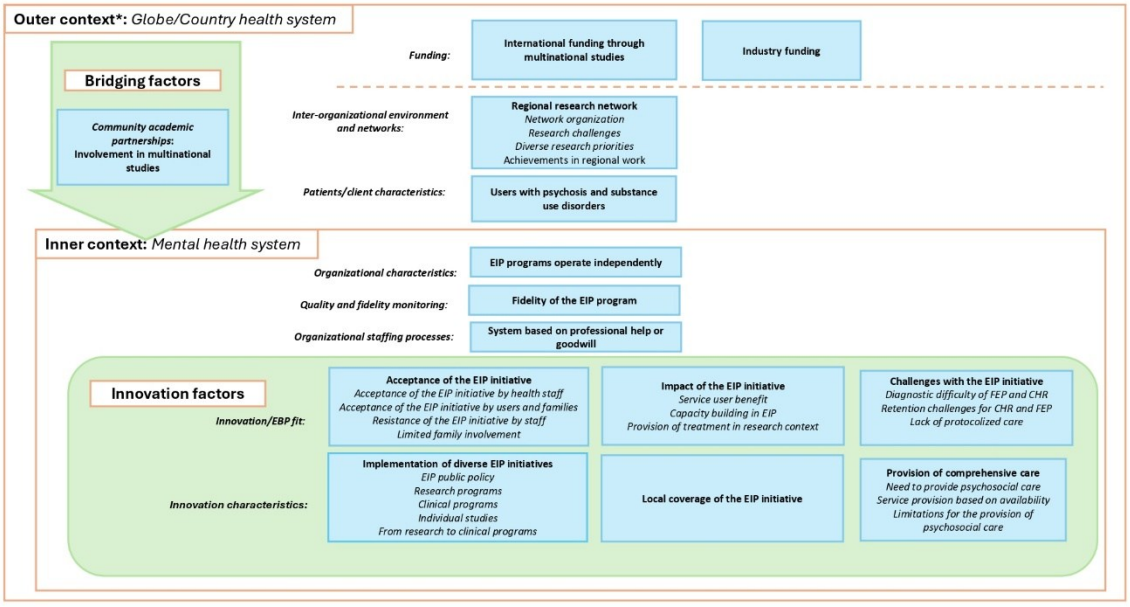
> *"We registered this participant as a patient here at the [institution], and we started treating the participants and there was no standard, it was more like on an individual basis."*

As clinical and research programs developed, some joined multicenter EIP studies, mainly contributing to participant recruitment, but gaining networks, research capacity, and funds. Some initiatives received industry support. One regional initiative was highlighted for unifying EIP efforts across LAC, setting research priorities and generating publications. Still, challenges included focusing solely on EIP, competing research priorities, and limited funding..

> *"Research in Latin America exists, there are funds. There are places that obviously have a greater offering; people from Brazil with FAPESP have good support; in Chile, ANID works; for example, COLCIENCIAS in Colombia also works. The Mexicans also works since they have the CONACYT. The problem is that generally all these funds are for intra-country financing. So, there's no way to harmonize projects together, and that's where we fall."*

Figure 4

Themes and subthemes identified during the Implementation phase of EIP initiatives (n = 26).



Note. *The outer context comprises two dimensions, separated by the dashed orange line: global context and national health system.

Sustainability phase

EIP initiatives' sustainability trajectories revealed implementation challenges. (Figure 5). The COVID-19 pandemic influenced their development and long-term viability, with a clinical program being discontinued due to administrative disruptions and service reorganization and another due to difficulties in identifying and retaining service users. *"[EIP clinical program] around 2022, we closed it because we didn't have so many volunteers. We didn't have so many patients. And we decided then to focus on the first-episode program"*

At interview, sustainable initiatives included two guidelines, eight clinical programs, and four research programs. The guideline in the strong primary care–based country was seen as essential for enabling and sustaining related initiatives, whereas a similar guideline was deemed unfeasible in another country due to limited resources and staffing. This contrast underscores that policy, without proper resource allocation, has limited impact. Some remained fragile with unstable funding and staffing. Others had benefited from institutional support and recognition (e.g., one initiative had been in place for 25 years), and had expanded regionally or used research to inform national policies. Both vulnerable and consolidated initiatives continuously sought resources.

> *"Funding is already gone, and we are looking for more funding. And the idea would be to, let's say, scale the screening process and make it a good cost benefit about screening process. This is one of the main goals, so that it turns sustainable."*

Large EIP research projects depended on international funding. One persisted but faced uncertain system integration once funding ended; another's continuation depended on new international funding; local resources were insufficient for large-scale research. The one regional research initiative had depended on international funding, as national grants were typically limited to country-specific projects. It continued through strong regional collaboration despite the loss of funding.

> *"Although we currently do not have funding, we maintain a collaboration. That is, we always have collaborations in Latin America with contacts and knowing that we can also apply for things together. So, we are applying with different countries; now more have*

joined us… we are going to do something with Uruguayans and Argentineans, without money, less resources, but we are able to keep the network alive."

Participants emphasized the need for sustained health sector action to support EIP initiatives, including reducing stigma; enhancing EIP training in academic programs; and improving mental health workers' knowledge of psychosis and competencies to integrate care into non-specialized settings. As EIP remains novel, participants recommended raising visibility through media, conferences, and policy-/decision-maker engagement.

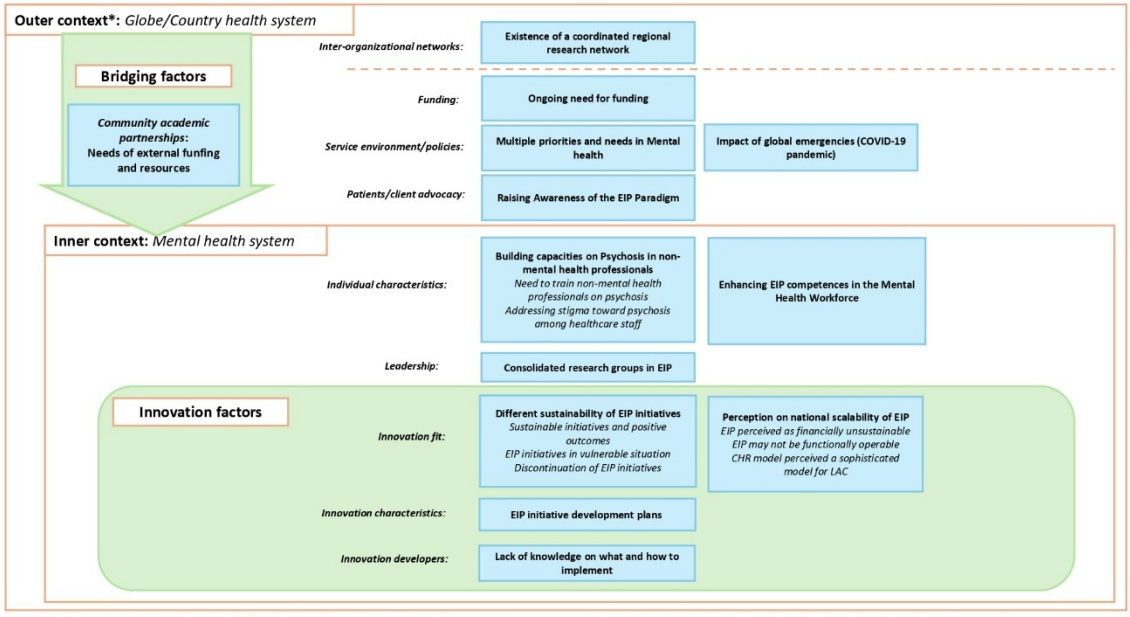
"Academia needs to be closer to those who are the public mental health organize the system. So I think academia needs to go outside the walls and try to influence mental health policies. Not only the training, because if we have the training, but we don't have the service and we don't have a protocol, but it's adopted the whole country, we'll do the same."

Participants valued EIP but held concerns about its nationwide expansion, particularly of HIC-like stand-alone clinical services, given their perceived high costs and implementation challenges in contexts with widely unmet mental health needs and limited services. They also justified this given the lack of guidance on implementing EIP in complex LAC contexts.

"The difficult part is sometimes being able to implement it, right? I mean, I think that, in theory, we know that we have to treat it early and provide the best possible treatment. What is complicated, and perhaps not so clear to me, is how we are going to implement it across the country. But I would think that the will, at least theoretically, exists."

Figure 5

Themes and subthemes identified during the Sustainability phase of EIP initiatives (n = 26).



Note. *The outer context comprises two dimensions, separated by the dashed orange line: global context and national health system.

Alternative approaches to scaling EIP

As nationwide implementation of existing EIP programs was considered unfeasible in LAC, participants proposed context-responsive dissemination models. Some suggested reserving CHR models for research, given limited resources and the need to prioritize FEP care.

> *"Perhaps the best position of the CHR model for LMIC is to focus on research fundamentally, but it's not possible in terms of wide implementation. It's not so cost effective to implement this kind of model across a country because there are other conditions that require also attention."*

Strengthening primary care or youth mental health services was proposed for identifying, managing, or referring CHR cases, as these are integrated into national systems and better positioned for early detection.

> *"I think it would be important to involve other institutions that work on mental health issues, which are not third level…that treat patients already with a diagnosis…for example, like a service that was implemented a few years ago, which is a hospital of emotions and treats young people, adolescents and young adults. So they offer psychological services and I think that working with them would be a very good option."*

Several participants recommended implementing FEP clinical programs in tertiary care settings, specialized institutions, or hospitals in major cities where services already exist, while also promoting early intervention in regional areas with limited services and trained staff.

> *"I think they can be done in all the major Latin American capitals, yes. I think they should and can be done. But also balancing it with the fact that in the regional cities there is a clear lack of psychiatrists, lack of development of services and awareness. So, it is not really feasible to be able to make an early intervention service that is more extensive, but probably rather to raise awareness of the issue and try to make an early recognition, a relatively benign intervention in more general services."*

Others proposed developing EPI protocols or care standards to guide service delivery across system levels, and staff training for implementation and sustainability.

"I would say that the two needs is to organize first episode protocol in the health system, [country name], using the existing network, and also to organize better the psychiatric emergence in the country."

Some recommended innovative delivery strategies, like task-shifting and simplified care packages, reflecting concerns about the feasibility of resource-intensive HIC models in low-resource settings.

"We would have to think of a compact version of that without losing the principles. If we cannot include interventions to prevent suicide or cognitive remediation. We can include other types of cheaper, more flexible interventions, which can be task-shifting, which can be provided here and which people have experience."

Discussion

Our findings highlight the contextual realities, structural barriers, and adaptive strategies shaping EIP initiatives across different implementation phases and levels of the social ecology in LAC. The EIP paradigm in LAC has been translated into diverse initiatives, driven by individual motivation, modelled after foreign programs, and constrained by local resources. While participants valued EIP, they cautioned against stand-alone EIP programs in LAC due to limited resources, instead proposing contextually grounded, resource-sensitive alternatives to ensure feasibility and effective scaling across LAC.

A broader approach to EIP in LMICs

It is well established that replicating models developed in HICs is often unfeasible in LMICs (Haycox, 2018; Singh et al., 2020). Some have proposed implementing only "key

ingredients" of these interventions (Singh et al., 2020). However, this assumes clearly defined core components that work across contexts, an assumption insufficiently defined. This proposal also overlooks the potential of alternative strategies in LAC and may partly explain stagnation of EIP implementation in many LMICs. Our findings underscore the value of diverse initiatives, whether standardizing practices, prioritizing specific populations, or addressing varied needs, thus calling for a more flexible conceptualization of EIP to advance it.

Beyond implementing programs, LMICs must foster complementary structures to enhance psychosis care. Unlike in HICs, guidelines, technical standards, and research (NHS England, 2023; Orygen, 2016) are largely absent in most LMICs (Haycox, 2018). Consequently, there is often no robust legal, educational, or evidence-based foundation to support the implementation of EIP programs in these settings. These structures are essential to support broader engagement in and sustainability of EIP, by leveraging local strengths, including strong primary care systems, community networks, and advocacy groups.

Context shaping EIP

Our results suggest that EIP programs in LAC have been shaped by the same structural conditions and resource limitations that define mental health care in LMICs: low policy and funding priority, scarce or fragile funding, and reliance on individual initiatives or external support. This is unlike HICs (e.g., U.K. Australia, Denmark, Singapore, Canada) (Bertulies-Esposito et al., 2022; Csillag et al., 2018; Hetrick et al., 2018; Lester et al., 2009; Verma et al., 2012), where strong political and financial commitment enabled widespread implementation and sustainability of EIP.

The provision of psychosocial interventions in LMICs is recognized as highly challenging due to limited resources (de Jesus et al., 2009; Patel & Thornicroft, 2009). EIP services in most LAC countries faced similar barriers. Although policies often stated that psychosocial care should be available nationwide, broader implementation was unfeasible due to a shortage of trained human resources or because services were concentrated in tertiary care. Although no formal fidelity evaluations were reported, care was generally described as non-protocolized/non-specialized and only partially aligned with international recommendations and local aspirations and needs.

International influences

Most EIP initiatives were conceptualized on foreign models, aided by guidelines, implementation manuals, and connections with implementers from HICs. This externally driven approach may have fostered an emulation of foreign practices and missed opportunities to incorporate contextual knowledge and culturally relevant practices. Systematic cultural and content adaptation was not formally pursued in any initiative. Only public policies showed some degree of co-design with service users. Instead, adaptations emerged pragmatically, based on implementers' experience and resources, a process also reported in other LMICs (Vaitheswaran et al., 2021).

Interestingly, in the cases with formal North–South collaboration and external funding, there was an emphasis on capacity building and cultural sensitivity through requests for local leadership and inclusion of local stakeholders and culturally sensitive practices. While such actions by funders should continue (Charani et al., 2022), they come with a risk of tokenistic practices (Kotze & Dymitrow, 2022). Dependence on foreign funding may also discourage local

investment; and external funds can be abruptly withdrawn due to shifting political or institutional priorities. Future efforts must therefore center LMIC agency and leadership in EIP (Valle et al., 2024).

Scaling EIP

This study has important implications for EIP implementation in LAC. In fragmented, under-resourced, urban-centered mental health systems, participants viewed scaling traditional EIP clinical program models as largely unfeasible and difficult to replicate from HICs. They called instead for flexible, context-specific strategies that integrate EIP into national agendas and align with existing capacities, while addressing structural inequities, strengthening the workforce, and promoting mental health literacy to reduce stigma and improve understanding of psychosis.

Participants' proposals for EIP dissemination were experienced-informed and appear feasible within low-resource environments, and could guide resource allocation, policy and workforce training. Strategies, like task sharing and task shifting, have already been successful in scaling mental health interventions in LMICs (Hoeft et al., 2018; Verhey et al., 2020). Regardless of the initiatives implemented, psychosis care must be included in universal health coverage frameworks to ensure that the population has access to services and financial protection against associated costs. The experience of LMICs like China and Brazil suggests that this measure can improve outcomes and reduce care gaps (Patel, 2016). Future EIP implementation must center the voices of people with lived experience and families, which is currently missing despite such involvement being a rights-based imperative that can enhance uptake, innovation and advocacy (Patel et al., 2018).

Limitations and strengths

This study focused on implementers' perspectives. Future work should integrate the perspectives of services users and families. Second, the implementers were predominantly men, which may have shaped findings around gendered influences on needs and implementation pathways. Third, some initiatives may have been overlooked, particularly of countries with low research capacity, although a wide definition for EIP initiatives and multiple identification strategies were used. Finally, by focusing on EIP actors, other locally grounded, potentially scalable approaches to psychosis care may have been missed. Despite these limitations, the richness and consistency of data across countries strengthen credibility of our findings.

This is the first qualitative study to comprehensively examine 26 EIP implementation initiatives across 10 countries in LAC, providing a comprehensive and evolving regional perspective. Implementation science remains limited in EIP and more generally in LMICs. Guided by the EPIS framework, our study makes important methodological contributions. Still, it did not fully capture factors like supernatural explanations of psychosis, poverty, and other social determinants. We suggest viewing implementation science frameworks as adaptable tools, echoing calls to add domains like resource constraints and system characteristics in LMIC implementation studies. (Vaitheswaran et al., 2021).

Conclusions

This study shows how the EIP paradigm has been translated into diverse, locally adapted initiatives across LAC, despite constraints, limited funding, and uneven political support. Some achieved progress and others struggled with sustainability. Findings underscore the need to move

beyond replicating HIC models toward a broader range of initiatives aligned with local priorities and capacities. Implementers' proposals—integrating EIP into youth mental health and primary care, promoting task-shifting, simplified care packages and early psychosis literacy—offer feasible strategies for scaling early psychosis care in resource-limited settings.

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Bridge

Results from manuscript III provided crucial insights into the broader implementation of the EIP paradigm in the LAC region. Collectively, primary implementers of EIP initiatives in LAC viewed the EIP paradigm as offering useful strategies to address the substantial burden of psychotic disorders in the region. However, they also considered exclusive reliance on standalone programs and HIC-based EIP implementation to be unfeasible, particularly given the limited availability of resources. Instead, they proposed alternative approaches focused on strengthening workforce training, simplified standardized care packages, leveraging existing primary, youth and tertiary health care systems, and increasing mental health literacy among both healthcare professionals and the general population. These strategies were seen as more scalable and sustainable, facilitating the integration of EIP approaches into existing general health systems.

In this study, a common view among EIP implementers was that mental health systems in LAC were often unable to adequately meet the needs of people with psychosis. These difficulties were evident in big cities and especially in remote or rural areas. This finding is consistent with the information presented in Chapter 2, Section 4, which highlighted the high treatment gap and low service coverage for psychosis in LMICs. Participants emphasized that although they were aware of government efforts to implement public health reform measures and allocate budgets to improve this situation, they perceived these efforts as insufficient to address the complex needs of people with psychosis, such as access to and sustained engagement in services, regular access to medication, rehabilitation centers, and opportunities for employment and education. Relatively few attempts have, however, been made to systematically investigate these concerns about service utilization patterns of persons with psychosis in LMICs, and more broadly, to

investigate whether and how reform efforts positively impact service utilization of people with psychosis.

Addressing this gap, we examined the status of mental health services for people with psychotic disorders in LMICs, using Peru as a case study. Peru, an LMIC in LAC, has traditionally struggled to provide nationwide mental health care due to the centralization of mental health services. However, over the last decade, the country underwent a mental health reform aimed at shifting care from tertiary to primary settings and increasing the availability of mental health services. We leveraged open-access, nationwide administrative databases to evaluate service utilization among people with psychosis. Although we examined only a single outcome (service utilization), the nationwide coverage and extended seven-year observation period ensured robust and reliable results. In the broader discussion for the entire dissertation, this evidence on patterns of health service utilization among people with psychosis in an LMIC is leveraged to provide insights into system readiness for EIP implementation.

Chapter 6

Manuscript IV

Health Service Utilization by People with Psychosis in Peru in the Context of the Peruvian Mental Health Reform and the COVID-19 Pandemic (2018-2024)

(Submitted to *Schizophrenia Bulletin)*

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Health Service Utilization by People with Psychosis in Peru in the Context of the Peruvian Mental Health Reform and the COVID-19 Pandemic (2018-2024)

Abstract:

Background and Hypothesis: Individuals with psychosis face persistent barriers to care. Peru's recent mental health reform expanded services nationwide but coincided with the COVID-19 pandemic. We hypothesized that service utilization among individuals with psychosis would increase between 2018 and 2024, particularly in underserved regions.

Study Design: We analyzed outpatient morbidity data from the Peruvian National Superintendence of Health (2018–2024). Service utilization was compared across three groups: psychosis, non-psychotic mental disorders, and physical illnesses. We examined changes in access (rate ratios, rate differences), the impact of the pandemic (interrupted time series), and decentralization trends (Poisson regression), separately for each disorder group.

Study Results: From 2018 to 2024, monthly service utilization per 100,000 declined for psychosis (28.2→19.2; rate ratio 0.68), rose for non-psychotic mental disorders (225.2→304.6; 1.35), and slightly fell for physical illnesses (12,688.1→12,370.4; 0.97). The pandemic caused an immediate drop, with rates falling to 37.9%, 37.0%, and 35.3% of expected levels for the three groups, followed by gradual monthly increases (psychosis 1.3%, non-psychotic mental disorders 2.6%, physical illnesses 2.2%). A shift from tertiary to primary and regional facilities was seen for both mental disorder groups, but greater utilization in underserved regions was observed only for non-psychotic disorders.

Conclusions: Despite nationwide expansion of mental health services, individuals with psychosis did not experience higher service use. The pandemic's impact was acute and enduring for this group. Findings underscore the need to examine reasons for this stagnation in service utilization and evaluate the acceptability and appropriateness of Peru's current service model for psychosis.

Keywords: Psychotic Disorders; Schizophrenia, Mental Health Services; Community Mental Health Services; Big Data, Peru (MeSH)

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Introduction

In low- and middle-income countries (LMICs), mental health systems struggle to address the needs for care of persons with psychosis, despite the high burden of disease.[1,2] Service coverage, the proportion of people with psychosis who contact a health service, ranges from 10.9% to 29.2%.[3] Many people remain untreated or inadequately treated, contributing to substantial burden.[4–6] Although many factors influence service utilization (e.g. stigma, financial constraints),[7,8] the limited availability of facilities is central in LMICs,[9,10] where care is largely provided in psychiatric hospitals in large cities.[11]

Peru, an LMIC in Latin America,[12] has experienced such challenges. In Lima, the capital city where the country's three psychiatric hospitals are located,[13] only 24.3% of people with mental disorders accessed services in 2002.[14] Access was even lower outside Lima: 10.1% in rural areas of the capital region,[15] 13.9% in the highlands and 14.3% in the jungle regions.[16,17] In 2012, only 15.6% of people with psychosis in metropolitan Lima received care in the past 12 months.[18] As a result of long-standing low service coverage, schizophrenia ranked 20th overall in disability-adjusted life years and 5th among individuals aged 15–44.[19] Services have historically been underdeveloped, marked by insufficient resources (0.27% of the health budget in 2011, vs. 5% recommended),[20,21] and inequitable distribution (98% of this budget went to the three psychiatric hospitals).[20]

To address these issues, Peru's Ministry of Health (MINSA) implemented mental health reform. In 2012, Congress approved Law N° 29889, guaranteeing universal access to treatment and social protection.[22,23] In 2013, universal health insurance included mental health care, followed by a results-based budget program of PEN 78 million (~US20 million) in 2015.[24,25] The Mental Health Law (N° 30947) in 2019 and its 2020 regulation further reinforced these efforts.[26,27] Collectively, these policies expanded access and facilitated the transition from hospital- to community-based care.[25] In practice, this led to the implementation of 288 community mental health centers since 2015,[28] alongside the integration of psychologists into primary care, and creation of hospitalization units and child and adolescent maltreatment modules in general hospitals.[29]

MINSA also enacted policies to strengthen services. In 2017, it launched a technical guideline on the organization of community mental health centers.[30] In 2020, another guideline set standardized care for psychosis, including medical appointments, family interventions, psychoeducation, and home visits.[31] In 2023, a second guideline set standards for continuity of care for severe mental disorders.[32]

The outbreak of COVID-19 coincided with the reform, with Peru recording its first case on March 8 2020.[33] The pandemic severely impacted the health system, and community mental health centers and other facilities suspended services on March 16, 2020.[34] This caused a sharp decline in care provision.[34,35] After a brief reorganization, services gradually resumed, primarily through telepsychiatry.[36] Despite preventive strategies, Peru was significantly impacted, recording the highest COVID-19 mortality rate worldwide.[37]

The extent to which reform increased service utilization by individuals with psychosis remains unknown. It is also unclear whether the transition from tertiary to primary care has occurred, or whether utilization increased in underserved areas, such as non-capital, low-income, or remote regions. The impact of COVID-19 on nationwide service use for psychosis is also unknown. Prior studies examined only all mental disorders,[34,35] or a sector of primary care.[34,38] This study aims to examine utilization of health services by people with psychosis throughout Peru between 2018 and 2024; evaluate the impact of the COVID-19 pandemic; and assess whether service utilization increased in underserved areas.

We hypothesized that: (a) service utilization by people with psychosis increased between 2018 and 2024, (b) in the COVID-19 period, there was an immediate decline in service utilization, followed by recovery to pre-pandemic levels, and (c) between 2018 and 2024, service utilization increased in primary and regional facilities (relative to tertiary and urban-centralized facilities) and in underserved areas. The study will compare service utilization of individuals with psychosis with that of persons with non-psychotic disorders and physical illnesses to examine whether trends are distinctive.[8]

Methods

This cross-sectional study involved an analysis of Peru's National Superintendence of Health (SUSALUD) outpatient morbidity database from 2018 to 2024, which includes nationwide healthcare data from all sectors. The database was downloaded in March 2025.[39]

Setting

Peru has a population of 34,038,457 inhabitants distributed in 24 departments and the constitutional province of Callao, further divided into provinces and districts.[40] The Andes run longitudinally through the country, demarcating three geographical regions: the coast, the highlands, and the rainforest, each characterized by unique environmental and climatic conditions. The Department of Lima, located on the coast, is home to 11,304,993 people (33.2% of the national population).[41] It also has the highest human development index in the country, reflecting notable achievements in health, education, and income.[42] Compared to cities in the highlands and rainforest, coastal cities have higher human development index levels.[43] Figure S1 shows a map of Peru illustrating the geographical distribution of community mental health centers and halfway houses.

Peru's health system

Peru has a segmented health system divided into public and private sectors[44,45] (Figure 1). In the public sector, MINSA oversees services in Lima, while regional governments oversee facilities elsewhere.[46] The public insurance, *Seguro Integral de Salud*, covers the cost of care within these sectors for people without any type of health insurance, reaching 64.5% of the population. The social security sector serves 22.6% of salaried workers and their dependents through its own facilities. Some provincial and district municipalities also offer low-cost health services. The Armed Forces and National Police provide care for their members and families through separate systems. In the private sector, care is delivered through clinics, accessed via private insurance or out-of-pocket payments. In 2024, 4.4% of the population was covered by private insurance or

affiliated with the health systems of the Armed Forces and National Police.[47] Mental health reform has been primarily addressed by the MINSA and regional government sectors.

Health facilities are classified into primary, secondary and tertiary levels. Primary care emphasizes health promotion, disease prevention, and common health needs. It has health posts and health centers, with health posts offering basic services, focusing primarily on health promotion and prevention. Specifically, it includes posts without physicians (I-1), posts with a physician (I-2), health centers with two physicians and other professionals (I-3), and centers with inpatient beds (I-4). Secondary care offers greater specialization and includes general hospitals (II-1), those with intensive care units (II-2), and specialized hospitals (II-E). Tertiary care provides the highest specialization, including comprehensive specialty hospitals (III-1), single-specialty hospitals with subspecialties (III-E), and institutions for research, innovation, and training (III-2).[48] Before the reform, mental health care was concentrated in tertiary facilities; the reform expanded services at the primary level through community mental health centers, which are I-3 and I-4 facilities[30] and also in secondary care, through the implementation of mental health inpatient units and day hospitals in general hospitals.[49]

Data sources

We used the SUSALUD database, where each entry contains information on the month and year of care, along with the department, province, and district, where the care was provided (including UBIGEO, i.e., the identifying code for each district). It also records the age and sex of the patients. Diagnoses are coded using the 10th version of the International Classification of Diseases (ICD-10). The total number of users seen by health services each month is reported. Since the data is recorded monthly, if the same person receives care in two different months, they are counted in

each month. Additional data sources used include population size projections for 2018-2024[40] and district-level monetary poverty data for 2018, both from the National Institute of Statistics and Information (*Instituto Nacional de Estadística e Informática*, INEI).[50]

Data selection

Diagnosis of psychosis included schizophrenia F20, schizotypal disorder F21, persistent delusional disorder F22, acute and transient psychotic disorder F23, induced delusional disorder F24, other non-organic psychotic disorder F28, and unspecified non-organic psychosis F29, schizoaffective disorder F25, mania with psychotic symptoms F30.2, bipolar affective disorder, current episode manic with psychotic symptoms F31.2, bipolar affective disorder, current episode severe depression with psychotic symptoms F31.5, severe depressive episode with psychotic symptoms F32.3, and recurrent depressive disorder, current episode severe with psychotic symptoms F33.3. Non-psychotic mental disorders included the F00 - F99 codes, excluding psychosis codes; and physical illnesses included any ICD-10 code without the F codes (some of these codes may include activities of health promotion or disease control).[51]

Dependent variables

Number of users seen per month in outpatient services during a given month by any health professional.[52] The indicator was independently assessed for people with psychosis, non-psychotic mental disorders and physical illnesses.

Covariates

Service user variables: Age was originally coded in five-year intervals. We categorized them into life stages: 0-9, 10-19, 20-34, 35-64, and ≥65 years.[53] Sex was retained in its original binary coding (men and women) in the SUSALUD database.

Health system variables: For level of care, we retained its original categories (primary, secondary, and tertiary care). For the health sector, the categories included MINSA, Regional government (encompassing provincial and district governments), and social security. The armed forces, national police, and private sector were grouped under the category "others" due to their lower coverage compared to the other sectors.

Geo-socioeconomic variables: Each health facility was assigned a category of monetary poverty, geographical region, and centralization level based on the district where it was located using the INEI classifications, and with UBIGEO (unique geographic location code) serving as the linking variable. Districts are allocated by SUSALUD into 28 levels of monetary poverty (using spending as an indicator of well-being), ranging from 1 (poorest) to 28 (richest). These levels were collapsed into four categories: extremely low income (1-7), low income (8-14), moderate income (15-21), and adequate income (22-28).[50] The natural region variable encompassed the three natural regions: coastal, highland, and rainforest.[54] The centralization variable included the categories: Lima province, which traditionally has a higher concentration of health facilities, followed by other capital provinces, with non-capital provinces with the least number of health services.

Statistical analysis

Statistical analyses were conducted using R version 4.3.0 and independently performed for each of the three diagnostic groups. To describe annual variation in health service utilization from 2018

to 2024 (Objective 1), we calculated the annual average of monthly rate per 100,000 inhabitants by averaging monthly user counts over each year, dividing by the population size, and multiplying by 100,000. Annual population estimates provided by the INEI were used as denominators.[41] These rates were age-standardized using the direct standardization method,[55] applying the World Health Organization's standard age distribution.[56] Rate differences and rate ratios between the year 2018 and 2014 were used to measure changes in the utilization of health services.

Addressing Objective 2, the impact of the COVID-19 pandemic on service utilization was assessed using interrupted time series analysis.[57] The breakpoint was set at March 2020,[33] defining a pre-COVID-19 period (January 2018 to February 2020) and COVID-19 period (April 2020 to December 2024). Preliminary regression models revealed significant temporal autocorrelation in the residuals, warranting the use of a time series approach. Accordingly, we fitted a series of ARIMA models with the logarithm of the monthly service utilization rate as the dependent variable, and two covariates: a post-pandemic time trend and a binary indicator for the post-COVID-19 period, while population size was included as an offset. An autoregressive structure of order 1 (AR(1)) was identified as the best fit. Model selection was based on the Akaike Information Criterion and the Bayesian Information Criterion.[58] The impact on service utilization was evaluated in terms of changes in level (an immediate shift following the onset of the pandemic and associated measures) and the post-pandemic slope (the change in trend over time between pre-COVID-19 and post-pandemic periods), while accounting for serial correlation in the residuals.

To examine whether service utilization varied over time by health system and geo-socioeconomic variables (Objective 3), we employed a Poisson regression model using Markov Chain Monte

Carlo methods.[59] The model estimated monthly service utilization rates per 100,000 inhabitants for both pre-pandemic (2018–2019) and post-pandemic (2022–2024) periods, with annual population size included as an offset. Observed monthly case counts were modeled as Poisson-distributed, and separately for the pre- and post-pandemic periods. Weakly informative Normal (0, 10) priors were specified for all fixed-effect parameters, including intercepts. Model fitting was conducted in JAGS (Just Another Gibbs Sampler) with four chains with 20,000 iterations each. The first 500 iterations were discarded as burn-in, and the remaining samples were thinned every 5 iterations.[60] The chains were judged to have converged appropriately. Marginal risk ratios were derived from the posterior distribution to compare changes in utilization between the two periods within each category of the covariates. Data from January 2020–December 2021 were excluded from the analysis, as the observed case counts were censored due to the closure or reduced capacity of many facilities during this period, leading to underreporting. This decision was based on the WHO's recommendation that achieving 70% COVID-19 vaccine coverage would enable the safe resumption of routine health services.[61] Peru reached this threshold in December 2021,[62] prompting MINSA to reopen most health facilities nationwide.[63] Previous studies have recognized this benchmark as indicative of the restoration of health services.[64]

Results

From 2018 to 2024, health facilities across Peru registered 114,343,160 entries in the SUSALUD database. Of these, 13,243,268 were repeated entries and 13,838 were missing; all of these were excluded from the analysis. The final sample included 105,086,054 entries, representing 91.9% of the original dataset.

Objective and Hypothesis 1: Utilization of health services

The annual average of monthly rates per 100,000 inhabitants of users seen with psychosis decreased from 28.2 in 2018 to 19.2 in 2024, representing a reduction of 26% (rate ratio: 0.74). In contrast, the rate for non-psychotic mental disorders increased from 225.2 in 2018 to 304.6 in 2024, reflecting a rise of 35% (rate ratio: 1.35). For physical illnesses, the rate went from 12,688.1 in 2018 to 12,370.4 in 2024, indicating a light reduction of 3% (rate ratio: 0.97). Age-standardized rates for psychosis, non-psychotic mental disorders, and physical illnesses remained consistent with the crude rates. Between 2018 and 2024, psychosis service utilization rates declined more among men than women, non-psychotic mental disorder service utilization rates increased more among women than men, and physical illness service utilization rates decreased in men but increased in women. Across age groups, psychosis service utilization rates declined consistently, while rates of service utilization for non-psychotic mental disorders increased in all age groups, with the highest increase for those between 10-19 years. Physical illness service utilization rates also rose across age groups, except among children aged 0–9 (Table 1 and Figure 2).

Objective and Hypothesis 2: Impact of the COVID-19 pandemic on health service utilization

The onset of the COVID-19 pandemic in March 2020 led to a sharp comparable decline in the monthly rate of service utilization across all diagnostic groups. Service utilization rates fell to 37.9% of expected levels for psychosis (95% CI: 29.0%–49.8%), 37.0% of expected levels for non-psychotic mental disorders (95% CI: 27.6%–49.6%), and 35.3% of expected levels for physical illnesses (95% CI: 28.2%–44.2%). Following these abrupt reductions, service utilization gradually recovered over the subsequent months. Specifically, the monthly rate of service utilization increased by 1.3% for psychosis (95% CI: 0.4%–2.2%), 2.6% for non-psychotic mental

disorders (95% CI: 1.8%–3.4%) and 2.2% for physical illnesses (95% CI: 1.6%–2.8%). Confidence intervals for these estimates partially overlap (Table 2 and Figure 3).

Objective and Hypothesis 3: Changes in service utilization according to health system and geo-socioeconomic variables

Health system variables

Model-based estimates indicated that, between the pre-and post-pandemic periods, the monthly service utilization rate for psychosis rose from 1.7 to 3.1 per 100,000 in primary care, while it declined from 19.0 to 10.4 per 100,000 in tertiary care. The proportion of primary relative to tertiary care utilization rose from 9% to 30%. For non-psychotic mental disorders, estimated service utilization increased in both primary (from 41.2 to 68.4 per 100,000) and secondary care (from 92.9 to 119.2 per 100,000), but declined in tertiary care (from 97.2 to 74.5 per 100,000). In this case, primary care rose from 42% to 92% of tertiary care levels. For physical illnesses, estimated utilization declined in both primary and tertiary care, but increased in secondary care (Table S1).

Between the pre- and post-pandemic periods, model estimates showed an increase in psychosis-related service utilization in facilities operated by regional governments (from 4.6 to 6.1 per 100,000 inhabitants), while a decline was observed in MINSA facilities (from 10.9 to 6.1 per 100,000). Whereas MINSA provided 135% more psychosis-related care than regional governments before the pandemic, this difference disappeared afterward. A similar shift occurred for non-psychotic mental disorders: estimated utilization increased in regional government facilities (from 75.4 to 101.4), while it declined in MINSA facilities (from 52.5 to

42.4), reducing MINSA's share relative to regional governments from 69% to 41%. In contrast, for physical illnesses, model estimates showed a decline in utilization in both MINSA and regional government facilities but increased in those operated by Social Security (Table S1). Percentual changes in service utilization between pre-and-post pandemic periods by level of care and health sector are shown in Figure S2.

Geo-socioeconomic variables

Based on model-derived estimates, service utilization for psychotic disorders increased more than threefold in very low-income areas (from 0.08 to 0.28 per 100,000), while it slightly declined in the highest-income areas (from 8.9 to 7.2). Nonetheless, large disparities persisted: very low-income districts accounted for only 0.09% of the cases seen in the highest-income areas before the pandemic, increasing modestly to 3.86% afterward. For non-psychotic mental disorders, model estimates indicated increases across all income levels; however, disparities remained. Before the pandemic, very low-income districts accounted for just 1.7% of the cases seen in the highest-income areas, rising to 3.3% in the post-pandemic period. For physical illnesses, service utilization declined in both very low-income and more affluent areas (Table S2).

Model estimates also showed that service utilization rates for psychosis declined on the coast (from 23.1 to 14.0 per 100,000), slightly increased in the highlands (from 3.9 to 4.9), and remained largely unchanged in the rainforest (from 0.9 to 0.8). The reduced ratios between the coast and highlands (from 6.0 to 2.8) and the coast and rainforest (from 26.8 to 17.3) are mainly attributable to the decline in cases seen on the coast. Service utilization for non-psychotic mental disorders increased across all three regions, with particularly notable gains in the highlands (from 59.6 to 75.8 per 100,000) and rainforest (from 11.4 to 17.8 per 100,000). For

physical illnesses, utilization increased in the highlands but declined on the coast and in the rainforest (Table S2).

In terms of level of centralization, model-derived rates of service utilization for psychotic disorders declined in Lima province (from 17.4 to 8.9 per 100,000), while it remained stable in other capital provinces (from 7.5 to 7.8) and in non-capital provinces (2.9 in both periods). For non-psychotic mental disorders, service utilization decreased in Lima (from 111.3 to 98.5) but increased in other capital provinces (from 81.7 to 113.7) and non-capital provinces (from 43.6 to 53.2). Before the pandemic, Lima's rate was 36.2% higher than that of other capitals; after COVID-19, it became 13.4% lower. Service utilization for physical illnesses declined across all three regions (Table S2). Percentual changes between pre-and-post pandemic periods by poverty level, geographical area, and centralization are shown in Figure S3.

Discussion

In the context of Peru's mental health reform and the COVID-19 pandemic, this study evaluated service utilization among people with psychosis from 2018-2024. Three findings stand out. First, contrary to expectations, utilization for psychotic disorders declined and remained below 2018 levels, despite increased use for non-psychotic disorders and return to 2018 levels for physical illnesses. Second, as hypothesized, utilization fell across all three conditions at the onset of COVID-19, but only rates for psychosis failed to return to baseline. Third, as hypothesized, primary care use expanded for psychotic and non-psychotic disorders. But utilization in underserved areas did not increase for psychotic disorders, but only for non-psychotic conditions. These findings suggest that people with psychosis face persistent barriers to care, with the

pandemic exacerbating gaps despite ongoing reform. This may reflect delayed implementation and/or effects of reform and structural barriers, rather than outright policy failure. Reform may take longer to benefit individuals with complex, intersecting needs/disadvantages, especially if unaccompanied by an adequate, appropriately-trained workforce.

Service utilization

The increase in service utilization for non-psychotic mental disorders can be attributed to reform-related new resources and policies,[29,31] as well as global trends in anxiety and depression among youth.[65,66] What is disconcerting is the divergence with psychosis, for which service utilization stagnated below 2018 levels through 2024, despite the reform targeting all mental health conditions and universal health insurance coverage.[26,27]

Disengagement from services is a likely explanation. Globally, about half of people with psychosis disengage from services, even specialized ones.[67–70] In Peru, service disengagement rates are unavailable. Epidemiological data show that 64% of those with psychosis did not recognize having a condition, and less than 20% reported receiving care in Lima in 2012, a setting with relatively high service availability.[18] Service utilization in underserved areas may be lower. This highlights a systemic gap in reaching and retaining individuals with psychosis.

Health system dimensions shape service access and engagement.[71] Through community health centers and free care, Peru's reform has likely addressed the dimensions of accessibility, availability, and affordability. However, whether the model ensures acceptability and appropriateness is unclear. In psychosis, engagement is influenced by stigma, insight, social

isolation, and cultural understandings of mental health, underscoring the need for services that align with the needs, lived experiences and contexts of patients and their families.[72]

COVID-19 pandemic's impact

Service utilization sharply declined with COVID-19 in 2020 across psychosis, non-psychotic mental disorders and physical illnesses, consistent with healthcare facilities' closures and movement restrictions rather than reduced needs. This is consistent with the 27% reduction in mental health visits in Mexico[73], but unlike high-income countries where rapid increases in teleconsultations corrected initial declines in visits.[74,75] Peru required significant time for rollout of teleconsultations,[36] highlighting disparities across systems in capacity to respond to emergencies.[35]

Although all three groups experienced similar initial declines, recovery of service utilization rates post COVID-19 differed, with people with psychosis having the lowest rates. This may be underpinned by exacerbation of pre-existing barriers,[76,77] poor digital access,[78] and/or a preference for face-to-face appointments.[38,79,80] Yet these factors alone cannot explain persistent reductions through 2024, especially after 70% COVID-19 vaccine coverage and regular/hybrid services around December 2021.[62]

Increased mortality among people with psychosis during COVID-19 may have reduced the number of service users. Peru experienced one of the highest mortality rates globally.[37] Research has consistently reported higher COVID-related deaths among those with psychosis compared to those with non-psychotic disorders and the general population, particularly those older and

males.[81–83] Aligned with this, in our data, fewer men and people over 35 accessed services in 2024.

Indirect impacts of COVID-19 on social determinants compounded disadvantages in LMICs like economic hardship, stigma, rights violations, economic hardship, and underfunded/poorly implemented services.[76] In Peru, the pandemic worsened poverty from 20.5% of the population in 2018 to 29% in 2023.[84] Poverty is strongly linked to vulnerability to mental illness,[85,86] and reduced service access.[87] These broader factors, amplified during the pandemic, may have contributed to the persistently low levels of service utilization among individuals with psychosis in the post-pandemic period.

Decentralization and geo-socioeconomic determinants

Our results reveal progress toward a major reform goal of shifting mental health care from tertiary to primary settings. This transition was enabled by political commitment, funding (87% of the mental health reform budget was allocated to this care level),[24] and rapid establishment of community mental health centers. Service utilization for mental disorders grew more in regional government facilities than in those operated by MINSA, highlighting much-desired progress in decentralization of healthcare outside Lima.[46] Meanwhile, social security facilities saw declines, likely due to a shift toward community centers that were perceived as more available and accessible.[88]

Over the study period, service utilization grew in historically underserved areas for non-psychotic mental disorders. By strengthening primary health care, reform may have improved equity[89,90] in access to services for individuals with these conditions, with respect to geographic (region and

centralization level) and economic conditions (poverty level). However, the impact was minimal for individuals with psychosis across these three geo-socioeconomic variables. Barriers to accessing care for psychosis, including intersecting disadvantages and limited mental health literacy, may be especially pronounced in poor and remote regions.[50] Also, elevated COVID-19 mortality in rural highlands and jungle regions[96] (with limited health service capacity) may have disproportionately affected people with severe mental disorders.

These results should be interpreted cautiously. Treating psychosis requires pharmacological and psychosocial interventions, as outlined by Peru guidelines.[91] Our analysis only evaluated number of service contacts, not adequacy or quality of treatment. This is particularly important for Peru, where evidence shows low rates of appropriate treatment for mental disorders,[92] and availability of psychotropic medications.[93] Likewise, our results precludes us from commenting on how the treatment gap changed after reform since prevalence estimates are not currently available.[1,2,94] Nonetheless, this gap may be widening as service utilization for psychosis has remained constant in 2023-24, despite the expected natural emergence of new cases.

Implications

Our findings suggest that people with psychosis in Peru may be disproportionately at higher risk of receiving inadequate or no treatment, with significant consequences for them, their families and systems. This calls for targeted strategies at multiple levels. There is a need to systematically improve and monitor service utilization and quality of care in psychosis, in alignment with MINSA-developed guidelines.[31,32,95] This includes ensuring psychotropic medication availability, psychosocial interventions, and community-based activities. It is also essential to assess the accessibility, acceptability and appropriateness of current care from the perspectives of patients,

their families, and healthcare providers. If shortcomings are identified, strategies, shown effective in identifying and engaging individuals with psychosis in other contexts could be adapted and integrated.[96,97]

At the public health level, it is crucial to examine the COVID-19 pandemic's impact on mortality among people with psychosis. Future studies with cohorts established using hospital records of patients with psychosis could clarify whether reduced utilization reflects disengagement, death or both. If elevated mortality is confirmed, future emergencies/crises should include protective measures targeting this population. More broadly, the pandemic exposed systemic fragility in addressing mental and physical illnesses. Preparedness planning for global health emergencies must prioritize timely, equitable, and sustained responses to mental health needs.

There is a pressing need to generate robust epidemiological data, including population-based estimates of psychosis prevalence and treatment coverage, to inform planning and resource allocation, and evaluate ongoing reform.

Limitations

Given the study's naturalistic approach, we cannot attribute changes solely to reform or the pandemic. Other factors, such as strikes, natural disasters or staff turnover, may have played a role. We assumed a constant mean rate per year, with fluctuations caused by external factors embedded within the variance term. Modelling with constant monthly rates was attempted, but model fit was not significantly improved. We exclusively analyzed outpatient care, which better reflects continuity and accessibility than inpatient data but misses crisis-oriented use. Future studies should address inpatient utilization. Our estimates may underrepresent primary care use

across all three diagnostic groups, as reporting from primary care facilities will be mandated from 2027.[98]

We lacked data on care modality (in-person vs. telemedicine) and service utilization for specific population groups (e.g., Indigenous peoples, 25.7% of population[99]). We cannot fully assess the quality of data reported to SUSALUD; however, it conducts ongoing review and corrective processes.

These limitations notwithstanding, to our knowledge, this is the first national study of service utilization for psychosis in Peru and one of the few in Latin America. Strengths include a large, nationally representative, population-based dataset spanning all health sectors; integration of multiple official data sources and rigorous methods. Database curation in collaboration with SUSALUD enhanced accuracy. Missing data were minimal and Missing Completely at Random, justifying their exclusion without introducing bias into the analysis.

Conclusions

Our study shows the feasibility and value of using population-based administrative data to track mental health service utilization in LMICs. Encouragingly, Peru's reform has expanded care for non-psychotic disorders, including in underserved areas. However, persistent underutilization of services by persons with psychosis highlights the need to address acceptability, appropriateness, and continuity of care for psychosis, particularly in underserved areas, and strengthen system preparedness for global crises.

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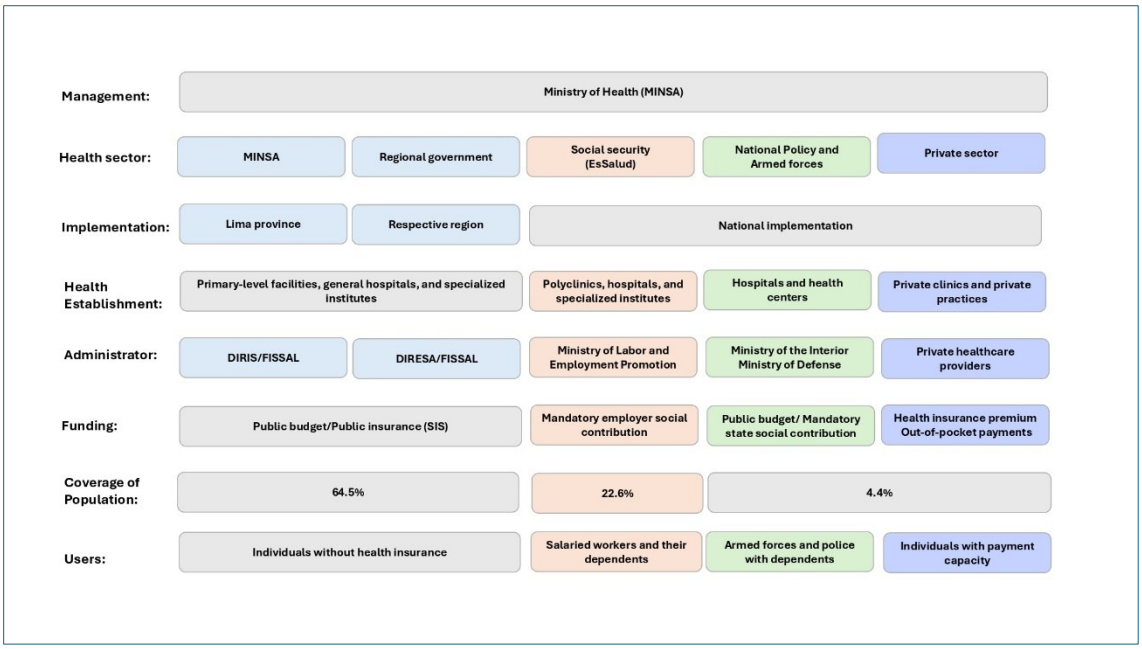

Figure 1. Organization of the Peruvian health system. Health establishments run by provincial and district municipalities are not represented due to their low number and limited coverage. MINSA: Ministry of Health, DIRIS: Integrated Health Network Directorates (Dirección de Redes Integradas de Salud), DIRESA: Regional Health Directorates (Direcciones Regionales de Salud), FISSAL: Solidarity Health Intangible Fund (Fondo Intangible Solidario de Salud).

Figure 2. Monthly rate and annual average of monthly rates of service utilization for psychosis, non-psychotic mental disorders, and physical illnesses in Peru, 2018–2024. The red dashed vertical line indicates the month when the COVID-19 pandemic began in Peru (March 2020). The red dashed horizontal lines represent the 2018 average monthly rate for each of the three diagnostic groups.

Figure 3. Impact of the COVID-19 pandemic on monthly rates of service utilization in health services in Peru, 2018–2024. Observed values represent the raw monthly service utilization rates. Fitted values correspond to the rates predicted by the AR(1) model, including both the fixed effects and the autoregressive component. The Expected rate reflects the predicted trend based on fixed effects only. The shaded area indicates the 95% confidence interval for the interpolated rates. The vertical dashed line marks the onset of the COVID-19 pandemic (March 2020).

Table 1. Annual average of monthly rates of service utilization for psychosis, non-psychotic mental disorders and physical illnesses, 2018–2024.

Indicators	Year							Rate difference	Rate ratio
	2018	2019	2020	2021	2022	2023	2024	(2024-2018)	(2024/2018)
					Psychosis				
Total population									
Average monthly users	8,908	8,821	4,936	6,178	6,919	6,541	6,551	-2,357.83^	0.74¥
Crude rate*	28.22	27.45	15.13	18.70	20.72	19.39	19.24	-8.98	0.68
Standardized rate*	28.21	27.10	14.77	18.11	20.01	18.70	18.47	-9.74	0.65
*Sex (crude rate)**									
Men	30.24	29.25	16.47	19.95	22.13	20.48	20.25	-10.00	0.67
Women	26.24	25.68	13.81	17.47	19.32	18.32	18.26	-7.98	0.70
*Age (crude rate)**									
0-9	0.18	0.25	0.12	0.19	0.17	0.17	0.19	0.01	1.05
10-19	10.90	9.19	4.55	5.63	8.91	8.91	8.33	-2.56	0.76
20-34	32.18	28.99	16.11	19.37	20.96	20.96	21.07	-11.11	0.65
35-64	47.47	47.15	25.99	31.70	30.84	30.84	30.15	-17.32	0.64
≥ 65	33.47	33.96	17.63	23.49	23.40	23.40	24.58	-8.90	0.73
					Non-psychotic mental disorders				
Total population									
Average monthly users	71,091	79,633	43,491	58,679	72,172	92,773	103,673	32,582.00^	1.46¥
Crude rate*	225.24	247.84	133.30	177.62	216.10	275.08	304.58	79.33	1.35
Standardized rate*	225.55	247.38	131.62	174.39	213.76	273.88	303.49	77.94	1.35
*Sex (crude rate)**									
Men	208.97	224.14	117.04	150.23	188.35	245.03	276.83	67.86	1.32
Women	241.23	271.16	149.32	204.61	243.44	304.65	331.85	90.63	1.38
*Age (crude rate)**									
0-9	259.20	282.94	107.89	140.50	342.12	342.12	410.01	150.81	1.58
10-19	204.57	218.89	96.15	134.34	309.07	309.07	351.48	146.90	1.72
20-34	144.97	150.66	92.87	120.84	184.83	184.83	201.75	56.78	1.39
35-64	208.78	224.81	138.46	181.57	221.17	221.17	230.66	21.87	1.10
≥ 65	494.68	596.64	336.57	452.03	523.26	523.26	563.02	68.34	1.14
					Physical illnesses				
Total population									
Average monthly users	4,004,635	3,883,577	1,869,482	2,265,870	2,915,407	3,763,878	4,210,704	206,069.33^	1.05¥
Crude rate*	12,688.10	12,086.55	5,730.05	6,858.94	8,729.63	11,160.22	12,370.43	-317.67	0.97
Standardized rate*	12,707.89	12,037.70	5,660.89	6,699.24	8,502.89	10,853.38	11,999.31	-708.57	0.94
*Sex (crude rate)**									
Men	10,574.02	9,727.86	4,695.51	5,421.05	6,767.19	8,663.18	9,673.97	-900.05	0.91
Women	14,765.43	14,408.12	6,749.21	8,275.48	10,662.06	13,617.33	15,021.77	256.34	1.02
*Age (crude rate)**									
0-9	19,853.70	16,068.16	6,892.83	6,387.81	11,880.12	11,880.12	12,922.12	-6,931.58	0.65
10-19.	7,580.27	7,410.40	3,025.78	3,057.54	6,436.99	6,436.99	7,800.49	220.22	1.03
20-34	8,004.20	7,217.22	3,809.20	4,884.38	7,133.86	7,133.86	8,051.37	47.17	1.01
35-64	11,866.29	11,968.72	5,934.16	7,717.38	11,765.94	11,765.94	12,727.41	861.12	1.07
≥ 65	24,927.23	27,298.48	12,856.34	16,178.09	25,219.39	25,219.39	27,550.72	2,623.49	1.11

* per 100,000 inhabitants, ^ Difference between the average monthly users in 2024 and 2018, ¥Ratio of average monthly users in 2024 to 2018.

Table 2. Interrupted time series analysis of the impact of the COVID-19 pandemic on monthly rates of service utilization in Peru's health services, 2018–2024.

Effect measures	Rate	Lower 95%CI	Upper 95%CI
	Psychosis		
Intercept	0.00030	0.00024	0.00039
Level change (March 2020)	0.37999	0.29005	0.49782
Trend change	1.01308	1.00439	1.02186
	Non-psychotic mental disorders		
Intercept	0.00249	0.00201	0.00309
Level change (March 2020)	0.36998	0.27617	0.49566
Trend change	1.02614	1.01792	1.03441
	Physical illnesses		
Intercept	0.12248	0.10563	0.14202
Level change (March 2020)	0.35300	0.28187	0.44207
Trend change	1.02235	1.01635	1.02838

An autoregressive structure of order 1 (AR1) was considered.
The intercept represents the monthly rate of service utilization at the beginning of the study period. The level change reflects the immediate impact of the COVID-19 pandemic on service utilization in the first month after March 2020. The trend change captures the sustained effect of the pandemic on monthly utilization rates over the subsequent period.

Chapter 7. Discussion

7.1 Overview of the main findings

Most people with psychotic disorders live in LMICs, where mental health resources are severely limited. The combination of high demand for care and limited availability of services has resulted in large treatment gaps for psychosis in LMICs (252). Addressing this problem requires innovative and contextually appropriate strategies that move beyond reliance on traditional hospital-based services. EIP has demonstrated effectiveness and cost-effectiveness in improving outcomes in both HICs and LMICs (135,271,272). However, translating these models to LMICs poses significant challenges due to resource constraints, so identifying sustainable approaches tailored to health system structures is essential. Collectively, the present dissertation aimed to generate evidence to guide contextually appropriate strategies for the development and adaptation of EIP approaches in LMICs and other resource-limited settings, by assessing capacities, previous experiences, and perspectives on dissemination. In this section, the overall results of this thesis will be discussed.

The first objective of this thesis was to determine research capacities related to EIP in LMICs. Overall, research capacity (Manuscript I), as measured by scientific output, mirrored the field of mental health research (206), with LMICs contributing relatively little to global output. Most EIP research in LMICs was concentrated in rapidly growing economies, BRICS, while the majority of other LMICs had produced little or no research on EIP. This highlights a scarcity of research evidence essential for identifying the needs of people with psychosis, designing appropriate services, and supporting the implementation of EIP models. Moreover, because research not only

generates knowledge but also builds professional skills and expertise (198), these findings point to a shortage of trained EIP professionals in LMICs.

Research capacity in LMICs, as reflected in scientific collaboration, showed that these countries participated in only a small proportion of collaborative EIP research (Manuscript I). Most collaborations involved partnerships with HICs and, to a lesser extent, with other LMICs. Notably, the LMICs with higher levels of collaboration were primarily the BRICS, whose researchers often held key authorship positions in collaborative publications. In contrast, LMICs outside the BRICS group rarely engaged in collaborative studies or held significant authorship roles. These findings indicate that scientific collaboration as a strategy for advancing EIP research in LMICs remains underdeveloped.

The second objective was to assess EIP initiatives implemented in LMICs. Our systematic review (Manuscript II) found that only a limited number of EIP programs have been established and that, in many cases, care is provided through research-based projects rather than formal health system initiatives. Both EIP programs and research-based projects for individuals at CHR and with FEP delivered a narrow range of evidence-based psychosocial components, focusing mainly on psychoeducation and family interventions. Still, in LMICs, multicomponent treatment for FEP demonstrated both effectiveness and cost-effectiveness. In the case of CHR, however, limited research prevented drawing firm conclusions about its effectiveness.

Our case study examined the implementation processes of EIP initiatives in LAC (Manuscript III). The findings revealed diverse trajectories: some initiatives were never implemented, others lacked sustainability, and a third group achieved sustainability over time. Most initiatives were

locally driven by champions, although some originated as part of collaborative global health efforts. Many were modeled closely on foreign EIP models, with minimal adaptation to local populations and little use of structured approaches for contextualization. Moreover, implementation took place within the same structural and resource limitations that constrain mental health systems in LMICs, often resulting in limited availability of psychosocial interventions.

The third objective explored the perspectives of implementers of EIP initiatives in the LAC region on the scaling up of the EIP paradigm (Manuscript III). Implementers in LAC recognized the value of the EIP paradigm in improving outcomes for people with psychosis. However, they also acknowledged that broad dissemination of EIP programs was not feasible under the current context in LAC. Instead, they proposed alternative strategies, such as implementing EIP programs within specialized mental health services, standardizing care through clinical guidelines or policy documents, increasing mental health literacy, building on strategies like task sharing that have worked to scale other mental health interventions in LMICs, serving those with CHR in extant primary or youth mental health settings, and limiting CHR detection to research purposes. These approaches present potential pathways for implementing EIP in contextually sensitive ways in LAC and other resource-restricted settings.

From a service delivery perspective (Manuscript IV), we observed a constant low rate of service utilization by people with psychotic disorders in Peru, an LMIC. This trend contrasted with the increased utilization of services for non-psychotic mental disorders and physical illnesses over the same study period. Notably, this low utilization of health services occurred during a mental health reform that expanded the offer of mental health services nationwide (263). Several factors,

including the appropriateness of services and the acute and long-term effects of the pandemic that coincided with the reform, may help explain this result. Nonetheless, our findings suggest that people with psychosis in LMICs, illustrated here through the case of Peru, continue to face both structural and individual barriers to care, even when the overall supply of mental health services increases. These patterns of health service utilization have implications for planning EIP implementation and more broadly, reform efforts to improve access among people with psychosis, in LMICs.

7.2 System foundations for EIP in LMICs

Together, these four manuscripts illustrate the existing capacities for EIP in LMICs, how the paradigm has been implemented in practice, and highlight alternative approaches that have received little attention to date. Based on this information, we analyzed four aspects of mental health systems in LMICs that are crucial for understanding and supporting the implementation of the EIP paradigm: a) funding EIP programs, b) development of policy documents and guidelines, c) generation of research-based evidence, and d) building mental health capacities.

a) Funding EIP programs in LMICs

A key challenge in implementing EIP programs in LMICs is securing sustainable funding. Globally, mental health services remain chronically underfunded. The median government spending on mental health is just 2% of total health budgets, unchanged since 2017 (273). In low-income countries, this figure is even more concerning, with some nations allocating less than 1% of their health budgets to mental health. While HICs may spend up to US$65 per person, low-income countries often spend as little as US$0.04 per person annually (273). This underfunding of mental

health across the globe, further exacerbated by disparities between countries in the proportion they allocate to mental health, needs to be urgently addressed if the needs of people with mental illness, across the globe, and particularly in LMICs, are to be met (273,274).

In the case of EIP, these programs are often perceived as costly, which can limit their scope even in HICs (32). Nevertheless, EIP interventions have consistently demonstrated cost-effectiveness both in HICs and LMICs, supporting their adoption (135,271,272). In HICs, broader implementation has been achieved when programs are publicly funded, as seen in Australia, the UK, Denmark, the US, and Norway. In contrast, EIP programs that rely primarily on research funding, such as those in Spain and Germany, or on charitable sources, such as Ireland's FEP program, have typically achieved only local coverage or restricted service provision (32). These examples highlight the importance of integrating the EIP paradigm into public health national agendas.

In LMICs, our work showed that the implementation of EIP clinical and research programs were primarily supported through public and international funding. Most clinical EIP programs did not require dedicated funding but were configured by reorganizing existing traditional services and making use of available resources. However, while some LMICs reorganized existing services to initiate EIP, scaling these models typically requires additional investment in human resources and infrastructure, which has rarely been secured. Research programs relied on competitive public funds, requiring implementers to apply regularly to secure their operation. Because these initiatives were not integrated into publicly funded healthcare systems, they remained small-scale and limited to single sites. In some cases, research programs were funded exclusively through international financial support. Although these efforts represented a significant contribution to

building knowledge and capacity on EIP, their sustainability was uncertain because they depended on the continued availability of international funding.

In LMICs, one approach to ensure that people with psychosis receive appropriate care is to incorporate psychosis into Universal Health Coverage (UHC) schemes. UHC, one of the United Nations Sustainable Development Goals, seeks to guarantee access to quality health services for all people worldwide without financial hardship (275). Many countries have adopted this policy, expanding coverage to include an increasing number of health conditions (276,277). The extent to which psychosis is currently integrated into UHC frameworks in LMICs remains unclear; however, its prioritization is often challenged by the condition's relatively low prevalence and mortality, which are metrics commonly used to guide health policy decisions (278). Given this, some authors argue that the social and economic impact of schizophrenia and the risk of human rights violations should also inform policy decisions (278). For example, the inclusion of schizophrenia in Chile's UHC framework was based not only on the burden of disease but also on people's preferences identified through qualitative methods (279,280)

Ensuring that psychosis care is included within UHC frameworks would guarantee that people with psychosis receive evidence-based care regardless of their economic status. It would also allow EIP to be financed as an integral component of essential health services rather than remaining isolated or research-driven initiatives. Incorporating psychosis care into UHC frameworks could further reduce within-country inequalities by ensuring that access to early intervention is available to everyone, not only to those who can afford to pay for health services. Embedding psychosis care within UHC would also help address global inequities, where access

to early intervention has become standard in many HICs but remains largely unavailable in LMICs (34).

b) Development of policy documents

Policy documentation may play a crucial role in supporting the development, standardization, and adoption of the EIP paradigm and EIP approaches in LMICs (32). These frameworks provide clear direction for service design, financing, workforce development, and clinical practices, ensuring that interventions are evidence-based and contextually relevant. By promoting standardized care pathways, clinical guidelines and technical standards can also help reduce unnecessary healthcare costs and improve efficiency. Countries with well-established EIP programs, such as Denmark, the US, the UK, Ireland, Italy, and Spain, have developed dedicated policy documents and clinical guidelines on EIP or incorporated specific chapters on EIP within their national schizophrenia guidelines (32).

Our studies show that clinical guidelines and technical standards on EIP are poorly developed in LMICs. In the LAC region, where we evaluated their availability, such documents remain scarce even in settings with active clinical and research programs. Two notable findings were that clinical and research programs were designed using international guidelines in the absence of local adaptation, a situation commonly observed in LMICs (281); and that when these documents were available, participants reported difficulties in meeting their recommendations due to a gap between guidelines and resources available (e.g., difficulty providing CBT because of a shortage of trained personnel). However, the presence of a health policy in Chile, accompanied by a solid primary care system that allowed its implementation, has been shown to yield positive effects on

the assessment, diagnosis, and treatment of psychosis at the population level (280,282). Although we did not assess the availability of these policy documents in LMICs from other regions, it is likely that these contexts face similar challenges with respect to policy development and implementation, including political instability, limited feasibility, bureaucratic constraints, and competing priorities.

A notable finding in our study was that participants recommended the creation of nationally applicable clinical guidelines or technical standards as a strategy to disseminate the EIP paradigm across the country. They considered this approach cost-effective, as it could regulate care through the standardization of practices and ensure consistency in service delivery. Although this strategy may be valuable and efficient, the creation of clinical guidelines in LMICs must overcome two long-standing problems commonly seen in these contexts. First, they must be adapted to the resources available or be accompanied by a clear funding commitment that aligns with the policy recommendation(s). (283). Second, they must incorporate the views and perspectives of diverse stakeholders (283). These stakeholders should explicitly include service users and families with a range of lived experiences of mental illness and services utilization and from diverse geo-sociocultural and economic backgrounds, ensuring that guidelines are feasible, culturally appropriate, and responsive to the needs of those directly affected. Furthermore, engaging community leaders, local policymakers, and civil society actors can further strengthen the relevance and uptake of guidelines. Importantly, such involvement of varied live experience perspectives has the potential for helping LMIC initiatives move beyond merely replicating or adapting guidelines from HICs to ensure true local applicability. It may even catalyze genuinely different strategies, interventions and services that can subsequently be evaluated.

Although the elaboration of policy documents requires considerable human, technical and financial resources, which are often scarce in LMICs (284,285), this process may currently be facilitated by using established frameworks. Tools such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the quality of evidence and strength of recommendations (286), and the Appraisal of Guidelines for Research and Evaluation (AGREE II) to evaluate the methodological rigor (287), provide structured approaches that can strengthen guideline development.

In particular, the AGREE-REX (Recommendation Excellence) is especially relevant, as it emphasizes clarity, applicability, and contextual relevance by incorporating domains that assess implementability and stakeholder representation (288). The use of frameworks like AGREE-REX may facilitate the development of guidelines that consider local health system context factors like service structure and workforce capacity; cultural factors such as gender norms, patient and family views about mental illnesses and their preferences for interventions, etc.; geographic factors like remoteness and rurality; and locally salient social determinants like violence, rates of youth unemployment, etc. to maximize real-world impact and ensure equitable access across diverse populations.

The translation of policy documents into practice depends on adequate dissemination, training, monitoring, and evaluation systems, which are often underdeveloped in LMICs; these additional considerations must be explicitly integrated into toolkits or implementation guidance booklets that often accompany policy statements.

Embedding EIP guidance within national policy frameworks and UHC could also help reduce inequities in access to early intervention and ensure that these guidelines have broader population impact. Policies should include explicit provisions for ongoing evaluation and adaptation of guidelines based on implementation outcomes and feedback from service users, families, and local communities. The need for such ongoing evaluation and adjustment is borne out by the analysis of service utilization of persons with psychotic disorders post-reform in Peru (Chapter 6).

c) Need for research-based information

The availability of reliable research-based information is fundamental for guiding mental health planning and decision-making. LMICs require data to design and implement efficient models of care delivery, identify patients' needs, and develop culturally adapted interventions. However, these countries face a long-standing substantial research gap. For instance, according to the WHO Atlas study, more than 24% of LMICs did not have any system for collecting and reporting mental health information, representing a major impediment to the development of mental health policies, plans, and services (289).

Our research shows that scientific output on EIP involving LMIC authors is scarce within the global EIP literature. At least in part related to this, critical topics in psychosis and EIP remain insufficiently studied. For instance, a systematic review reported information on DUP in only 18 out of 152 LMICs (11.8%) (23). Moreover, scientific publications resulting from collaborations between LMICs are substantially limited, further restricting research focused on priorities relevant to resource-constrained settings. There is therefore an urgent need to promote locally driven

studies to generate evidence that can guide service design and the development of clinical guidelines and policy documents. Such research should also explicitly engage service users, families, and communities with lived experience to ensure that findings are culturally relevant, feasible, and responsive to local needs, and local decision-/policy-makers so that effective and acceptable innovations and adaptations are more likely to be sustained, scaled and translated into policy.

The lack of mental health research information in LMICs, however, is a long-standing problem. The WHO has addressed this issue in a global context through a series of meetings such as Mental Health Research in Developing Countries (2003), initiatives like Research for Change (2004) (198), and studies that evaluated the status of mental health research in terms of published papers (290), research capacity and resources (201), and the priorities identified by researchers in LAC during the 2000s (291). Although some studies suggest that mental health research has increased in the last years (209,210), this increase may be driven primarily by those LMICs with emerging economies, and not by the majority of the other LMICs (210). Although research capacity varies across LMICs, broadly, structural barriers, including limited funding, a weak research culture, and inadequate compensation for conducting research (198) continue to hinder the development and sustainability of mental health research in LMICs. Ethical oversight, governance structures, and local institutional support are also essential for sustainable research capacity.

Despite these challenges, mental health professionals in LMICs can recognize that EIP research is both necessary and feasible and can be adaptable to local context. Creative and contextually relevant ideas are often more important drivers than technological or financial resources (292).

Several areas of EIP are relatively low cost yet highly relevant to clinical practice and service design. For example, identifying cases of FEP, measuring DUP, evaluating pathways to care, and assessing patients' needs, elements that grounded the development of the EIP field in HICs, do not necessarily require sophisticated infrastructure or major investment. In addition, the availability of administrative databases offers an opportunity to conduct research in these settings (293).

Based on our systematic review (Chapter 4) and case study (Chapter 5), some underrepresented research areas include the adaptation of psychosocial interventions and EIP strategies for local contexts; implementation studies of EIP models in LMICs; cost-effectiveness and policy evaluations; outcomes beyond symptom reduction such as social, vocational, and quality-of-life measures; co-design of service models, interventions and policies with service users, families and community stakeholders; and integration of social determinants into EIP models and services (e.g.; addressing poverty, stigma, violence, etc.). Research should also prioritize equity and inclusion, ensuring that findings are representative of underserved, rural, and marginalized populations within LMICs.

International funders play a critical role in strengthening research capacity in LMICs. However, such investments must be designed and implemented ethically, with funding mechanisms that support local leadership, equitable partnerships, capacity-building of early-career LMIC researchers, and sustainable development. Similarly, international collaborations can catalyze high-quality EIP research in LMICs when they are grounded in equity, mutual benefit, and shared decision-making. A good example is the longstanding research collaboration between the Schizophrenia Research Foundation in India and the Prevention and Early Intervention Program for

Psychoses in Montreal, Canada (294). Despite its origins in time-limited grants, the collaboration resulted in a sustained clinical-research program for FEP in Chennai, India, which is now a leader in the region and an exemplar for EIP programs in LMICs (295). The collaboration also resulted in multiple peer-reviewed publications, which have advanced both locally relevant knowledge about FEP and its treatment, as well as yielded insights about cross-cultural differences in course and outcomes (296,297).

Building on this, our case study identified other examples in which international funding supported large-scale research on early psychosis in the Global South. With funding from the UK, Trinidad and Tobago, Nigeria and India have established the INTREPID I, II and III studies to investigate the incidence, course and outcomes of untreated psychosis in diverse sociocultural contexts across the Global South (84,298,299); with funding from the US, Chile implemented OnTrack-Chile to adapt and scale the OnTrack-New York model within its national context (300); and with European funding, several countries in LAC configured the ANDES network to advance research on early psychosis in the region (301). These initiatives not only filled critical evidence gaps but also built lasting research infrastructures, enhanced training opportunities, and laid the groundwork for future regionally led EIP initiatives. Common to both these initiatives were local leadership, and a longer stream of funding than is typical for research projects that allowed for stability and capacity-building, which may be facilitating factors to replicate in the future, Fostering locally driven research initiatives in LMICs through local and international research funds can empower mental health professionals and generate evidence to strengthen psychosis care in these countries.

d) Mental health capacities

Most LMICs face challenges due to limited mental health resources to address the health needs of their populations. Schizophrenia affects more than 24 million people worldwide (302), most of whom live in LMICs (3). However, these countries have far fewer mental health professionals compared to HICs, with even greater disparities observed in low-income countries. For example, there are only 0.1 psychiatrists and 0.4 nurses per 100 000 population in low-income countries, compared with 8.6 psychiatrists and 29 nurses per 100 000 population in HICs (303). Similar gaps exist in the availability of psychologists, social workers, and other specialized mental health professionals (303), making it difficult to provide comprehensive and adequate mental health care in LMICs. These workforce gaps are even more exacerbated in the case of rural, remote and marginalized populations.

Findings from our research clearly illustrate this situation. Our systematic review showed that EIP programs and research initiatives in LMICs often lacked essential components of the EIP paradigm. Psychosocial interventions such as CBT, case management, and support for education and employment were reported in only a few of these initiatives. This finding was also confirmed in our case study, where primary implementers of EIP programs in LAC explicitly reported difficulties in delivering comprehensive care due to staff shortages. In these settings, most psychosocial interventions were provided by trainees or by staff who dedicated only part of their time to the program. This scenario demonstrated that providing comprehensive care in LMICs is challenging even within specialized services.

The global response to the scarcity of mental health professionals in LMICs has focused on innovating service delivery models. Various task-shifting and task-sharing strategies have been tested and implemented to address workforce shortages (304,305). Task shifting refers to the

provision of health services by non-specialist workers who, with appropriate training, support, and supervision, deliver evidence-based interventions (306). The terms task shifting and task sharing are often used interchangeably, although some researchers and reports use task sharing to emphasize the ongoing involvement of specialist providers alongside non-specialists in delivering care (307). The World Health Organization (2007) identifies four main types of task shifting. In Type 1, diagnostic and prescribing responsibilities are transferred from doctors and specialists to non-physician clinicians such as nurses or clinical officers—for example, in some LMICs, prescribing antipsychotic medications has been delegated to trained non-specialist clinicians. Type 2 involves nurses or midwives assuming clinical roles traditionally reserved for medical officers or clinical officers; for example, in mental health care, this has included nurses leading outpatient clinics or delivering structured psychosocial interventions. In Type 3, tasks performed by nurses and midwives are delegated to nursing assistants, aides, or community health workers; for instance, community health workers have been trained to deliver psychoeducation or medication adherence support for individuals with schizophrenia. Type 4 refers to the transfer of tasks from nurses or community health workers to expert patients, peers, or caregivers, as seen in peer-led support groups and caregiver-delivered interventions for psychosis (306). Evidence consistently shows that these approaches are effective and feasible in resource-limited settings (308), particularly for delivering psychological interventions such as CBT for common mental disorders and substance-use disorders (309). Evidence for task-shifting and task-sharing is comparatively limited for schizophrenia and psychotic disorders, but promising. These include uncontrolled studies in Ethiopia, Nepal, Uganda, Rwanda, Kenya, and India, which show increased access to care and improved clinical and functional outcomes for people with major

mental disorders, including psychosis (310–315). There have also been controlled trials in Ethiopia which showed that task-sharing with community workers was as effective and safe as specialist care for severe mental disorders (316), and in India, where community-worker driven community-based collaborative care resulted in greater improvements compared to specialist-driven care in facilities for persons with schizophrenia (317). Evidence from LAC (Chile) has shown that providing care for people with psychosis through task-shifting is both acceptable and feasible (318). Interestingly, in this study, task shifting happened through both community workers and peer workers. Although users generally saw peer support positively for its fostering of hope, self-efficacy, and social connectedness, the interviews also revealed the need to adapt peer support to fit cultural considerations (e.g., beliefs about hierarchies) (319). This study complements the evidence for the benefits of peer support for psychosis in LMICs, including a multi-country large trial of individual peer support and an RCT of group peer support (320,321). These studies, however, were not in early psychosis and were adjunctive to treatment as usual, unlike the Chile study where peer support was integral to the task-shifting strategy.

Furthermore, the use of telemedicine and other, accelerated by the COVID-19 pandemic, has further expanded access to care, especially for individuals facing geographical barriers (322). Information and communication technologies may be particularly useful in LMICs to bridge unmet needs gaps, especially in remote and rural regions. In many LMICs, vast segments of the population, including people with psychosis, have access to digital devices and the internet (323). Rigorous evidence for the acceptability and positive impacts of such technologies in psychosis in LMICs is still limited , but promising (324). In an uncontrolled study in a remote conflict-ridden region of India with no formal services, information and communication technologies were used

to train, supervise and support lay community workers, who provided care to persons with major mental disorders, with positive impacts (310,325). In China, an RCT showed that texting patients and their lay health supporters in a resource-poor community setting was more effective than a free-medicine program alone in improving medication adherence and reducing relapses and re-hospitalizations (326). mindLAMP, a digital platform for assessment, management, and monitoring of mental health conditions, including schizophrenia, was found to be acceptable by persons with schizophrenia and their families in India (as well as the US, the two sites in this study) and useful for generating real-time data on cognition and sleep (327,328).

The EIP paradigm, as a multicomponent intervention, might be challenging to implement in settings with a limited mental health workforce. To overcome these barriers, innovative approaches such as those mentioned above – task shifting, task sharing, peer support and technologies - must be further tested and scaled up (240). These approaches have thus far been strikingly under-utilized in EIP services in LMICs, due partly to a reliance on HIC models. A cluster randomized trial is currently evaluating task-shifting strategies for early detection that involve traditional and religious healers, and its results are expected to provide valuable insights into the use of this approach in LMICs (329).

For task shifting/task sharing to be successful and sustained, there is a need for adequate training, supervision, integration into local health systems, and attention to ethical oversight and culturally appropriate delivery; these will be important considerations in future research and programmatic EIP initiatives integrating task shifting/task sharing approaches. The Chile task shifting study, albeit not in EIP, highlights the importance of local adaptation and engaging service users and families in designing task-shifting strategies. Scaling technologies in LMICs will also

require attention to digital infrastructure, data governance, equitable access, and integration into existing pathways to mental health care. Leveraging these innovative approaches in LMICs to scale EIP will require combined attention to workforce capacity, supervision, digital infrastructure, cultural adaptation, health system integration and inclusion of underserved populations.

The use of approaches like task shifting and task sharing may result in an EIP model that moves away from a reliance on specialists or hyper-professionalized services. Such a model may also have relevance for low-resource settings in HICs, such as in remote Indigenous communities in Canada, that face very similar challenges as LMICs in terms of a dearth of formally trained mental health providers, thus promoting global South to global North knowledge exchange (330).

7.3 The way forward for EIP implementation in LMICs

a) Advocacy

The experience of several HICs shows that evidence alone is insufficient to secure the development and financing of EIP programs (31). Effective advocacy combined with the presence of champions has proven critical in raising awareness and generating investment in EIP (32). Experience indicates that decision-makers often respond to personal narratives from service users and their families who have benefited from and actively supported EIP programs (31). In England, for example, strong non-governmental organizations effectively engaged politicians, civil servants, clinicians, and the media in the late 1990s. The charity Rethink Mental Illness and its Getting Help Early campaign raised awareness with messages such as: "*When your car breaks down you can get help within 60 minutes; when your mind breaks down you may not get help for 18 months*"(32).

LMICs may adopt a similar approach to capture policymakers' attention and raise awareness of the importance of investing in EIP. Family involvement in the treatment of relatives has long been recognized as an asset in LMICs (296,331). In our case study, participants identified family members as proactive and supportive actors who often take the lead in seeking care, ensuring treatment adherence, and advocating for better services for their relatives. Fostering close connections with NGOs and community organizations, such as family associations of people with psychosis or other mental disorders, is also crucial to advance this initiative. Such collaboration, however, should extend beyond fundraising to include active participation in service design and implementation.

b) Changing the configuration of EIP initiatives

EIP programs in LMICs have often been modeled on those implemented in HICs. While this approach may have facilitated the adoption of key functional characteristics, it also risks limiting their adaptation to local needs and realities. Our results showed that the configuration of some EIP initiatives restricted access to people in need of treatment based on eligibility criteria. For example, some initiatives were designed with a youth focus, thereby excluding older individuals. Although suicide is a recognized cause of death among people with psychosis, some initiatives, particularly research projects, restricted access for individuals with suicide attempts or current suicidal thoughts. Likewise, comorbid psychiatric conditions such as major depression or anxiety disorders and physical illnesses, which are common among people with psychosis, were also grounds for exclusion in certain initiatives.

In line with international recommendations (33), we argue that EIP in LMICs must be designed with a broader perspective, ensuring that no person with psychosis is left untreated due to any attribute or additional condition. This broader approach would enhance equity in service provision and help address critiques that EIP has faced for concentrating resources solely on the early phases. These changes would be consistent with adaptations in the UK, where the age range for EIP programs was expanded to 65 years in recognition of the high number of cases appearing after the age of 35. This expansion also responds to the high co-occurrence of FEP with substance use in LMICs and the rapid epidemiological transition under way in LMICs, characterized by an increase in noncommunicable diseases (332), which may disproportionately affect people with psychosis. Furthermore, such a broader approach should also explicitly ensure equity across gender, socioeconomic status, rural/urban populations, and other marginalized groups.

While more research is needed to generate evidence from more rigorous controlled designs, and to evaluate what adaptations may be appropriate in which contexts or what populations, existing evidence does point to the potential value of adapting typical EIP service models for certain patient subgroups or settings, for example, with respect to duration and intensity/type of follow-up. In our systematic review, the EIP service in India reported sustained service engagement over two years for persons with FEP through primarily at-distance means of contact (e.g., phone, email) with the treatment team after the first three to four months of treatment (296). This was likely driven by the sample being young and living with their families who were involved in their treatment. This same approach of less intensive in-person treatment team outreach may not be

appropriate for other patient sub-groups, for example, with longer DUP, without family involvement, etc.

c) Broadening intervention pathways

Standalone EIP programs have been widely implemented in HICs to provide EIP care (32). However, this service model is difficult to replicate in certain contexts, such as rural or remote areas, even within HICs. This challenge has led to the development of alternative delivery models, such as hub-and-spoke systems and enhanced community mental health centers (226). For many years, LMICs have attempted to implement standalone EIP programs; as a result, only the most well-resourced centers in countries with strong mental health capacity have achieved some level of implementation. However, although these centers have achieved important research and clinical milestones, their coverage has remained restricted to a sector of the population over the years.

We posit that EIP can be implemented in LMICs beyond the traditional standalone program. Following implementers' perspectives, an integrative approach tailored to resource availability may be more appropriate. Such an approach could include: (a) implementing EIP programs within specialized mental health centers; (b) implementing innovative care delivery models, including task-sharing approaches; information and communication technologies; and hub-and-spoke or consultation-liaison models in partnership with specialist centers; to meet the needs of persons with FEP in rural or remote regions far from specialist centers; (c) incorporating the EIP paradigm into clinical guidelines and technical standards to standardize both clinical practice and psychiatry training; (d) restricting the CHR model to research settings until more evidence

emerges on effective pathways for people with this condition; and/or linking CHR models to existing youth or primary care services, depending on the context and local preferences; and (f) increasing EIP literacy among both the general population and health professionals. Overall, implementation of EIP initiatives must involve systematically co-designed and evaluated adaptations that consider local health system capacity and socio-cultural context, rather than direct replication of HIC models.

d) Integrating EIP into mental health system

Mental health systems in LMICs are characterized by marked heterogeneity in structure and coverage, often operating under severe constraints in workforce capacity, funding, and infrastructure. While in some countries service provision remains predominantly hospital-based, in others it has shifted toward community-based care, although often with variable coverage. Mental health care is typically delivered separately from general health services, with minimal involvement of non–mental health professionals in its provision. Referral pathways to mental health services remain largely informal, and cost and stigma constitute major barriers to accessing care for most people (333). These systemic limitations hinder the timely and appropriate delivery of mental health services to those in need.

In this context, the best approach to integrating EIP into mental health systems appears to be leveraging existing service structures rather than creating parallel, resource-intensive standalone programs. We argue that implementing the EIP paradigm through a broad and multi-strategic approach, as described above, represents a more feasible pathway for integration into the mental health system. This may involve embedding EIP within national policies, workforce training,

information-sharing mechanisms, and implementing stand-alone clinical programs in only those centers with higher resource capacity. Developing a comprehensive, resource-sensitive and collaborative framework for implementation in low-resource settings may help underpin this approach. Such a framework would include long-term funding strategies, robust monitoring and evaluation, data governance frameworks, ethical oversight, capacity-building and workforce development, and opportunities for local, regional and international research studies and collaborations.

7.4 Strength and limitations

a) Limitations

The overarching premise of this thesis, that it is valuable to implement EIP approaches in LMICs and other resource-limited settings, could itself be critiqued. Framing psychosis in LMICs primarily as a condition best addressed through EIP could be criticized for narrowing attention to individualized biomedical solutions and leaving less space for social, cultural, spiritual and political understandings of distress and psychosis-like experiences (334). An EIP focus can also be argued as inadvertently shifting priorities away from collective forms of care, cultural models of responding to psychosis-like experiences and structural interventions to addressing social determinants that increase vulnerability to psychosis, such as rapid urbanization, displacement, trauma associated with conflicts and humanitarian disasters (335). This premise may have stemmed from the positionality of the doctoral student leading this work and his supervisor, the former a psychiatrist and the latter a clinical psychologist with years of clinical and research experience in EIP, both based in an HIC university and psychiatric hospital with a stand-alone EIP service during the course of this doctoral work (121). Their clinical and scientific training (itself

shaped by a Euro-American lens) and experiences may have led them to value EIP. In humbly acknowledging this, they also recognize the need for multiple perspectives (different disciplines, different stances towards mental illness and how it should be viewed and addressed, different experiential standpoints) to influence the future of psychosis care and research in LMICs.

At the same time, it can also be argued that EIP, or more broadly multicomponent care, has demonstrated benefits in HIC and LMIC settings, including reductions in disability and improved functional outcomes (29,336). Timely, structured, hope-oriented care may play an important role in addressing the treatment gap in LMICs, where people with psychosis are often underserved and face numerous human rights violations and lost opportunities (3,334,337). The challenge, therefore, may not be whether to reject or accept EIP wholesale, but to critically and reflexively examine whether introducing EIP risks simply transposing foreign models that may cause harm and undermine local innovation and responses, or whether its principles can be locally appropriated and adapted to develop and strengthen contextually grounded responses that improve the lives of people with psychosis and their families.

This thesis also has other limitations that should be acknowledged. Although its overall focus is on the implementation of EIP initiatives in LMICs, two of the four studies concentrated on a specific region (LAC) or a single country (Peru). This focus allowed for an in-depth examination of factors relevant to EIP implementation within these contexts; however, it may have resulted in the omission of cultural and contextual factors specific to other LMICs. Evaluating all LMICs within a single thesis is challenging; therefore, it is essential for future studies to capture the diversity of experiences and contexts across regions.

While our study focuses on LMICs, a designation that helped frame our analysis and highlights countries with resource-constrained settings, this classification is not without limitations. Country income classifications can change over time (338), and during the period covered by our review, some countries shifted categories. Additionally, our case study adopted a regional perspective (focusing on LAC), which led to the inclusion of a few HICs. Nonetheless, these HICs shared many of the challenges observed in the region and in the case of Chile, may even serve as useful exemplars or champions for advancing EIP in the region. More broadly, the term "LMICs" oversimplifies the considerable diversity within and across countries in terms of resources, health systems, and sociocultural contexts, and does not fully capture the heterogeneity in experiences and capacities that shape early intervention implementation.

This research generated valuable strategies for integrating EIP into LMICs. Nevertheless, the dissertation did not evaluate in detail the processes by which these alternative strategies could be implemented and sustained in real-world settings, highlighting an important area for future research. Future studies should explore how these strategies can be embedded into mental health systems using implementation science frameworks and through methods that capture the direct experiences and perspectives of multiple stakeholders, such as conference meetings, consensus-building approaches (e.g., Delphi studies), and in-depth case studies.

This thesis was conducted from a comprehensive perspective, recognizing the importance of incorporating the voices of service users and their families. In the case study (Manuscript III), interviews were conducted with these groups to gather their views on the implementation of EIP in LAC. However, these interviews were ultimately excluded from the analysis, as participants reported having limited knowledge of EIP and their responses primarily referred to mental

disorders in general. Irrespective of this finding, it is our view that EIP initiatives implemented in LMICs should incorporate the perspectives of lived experience stakeholders. Our own set of studies would also have benefited from the involvement of service users with lived experience.

The identification of EIP efforts in the two global context studies (Manuscripts I and II) was based primarily on peer-reviewed publications. While this approach ensured the inclusion of well-documented initiatives, it may have excluded those without formal publications. We may have excluded promising initiatives reported in grey literature or implemented in practice but not formally published, which could limit the comprehensiveness of our findings. Insights from our case study (Manuscript III) demonstrated the existence of EIP initiatives that have not been described in peer-reviewed journals. These findings underscore the importance of combining literature-based searches with network-driven approaches to identify EIP initiatives in future implementation research.

That the doctoral student and his supervisor were both based in the same HIC context may have influenced their interpretations across all studies. Still, both the student and researcher are first-generation immigrants from LMICs who completed their initial training in mental health and gained work experience in Peru and India, respectively, and continue to actively collaborate with LMIC partners in these and other settings. Three of the four papers also included authors from LMICs, and the fourth—the case study—prioritized the voices of local implementers by adopting a qualitative approach and by sharing the results and their interpretation with the interviewees. The authors also engaged in reflexivity to identify how their past and present positions and contexts may have influenced the questions they asked and the conclusions they drew.

b) Strengths

Despite these limitations, this thesis also has several strengths that should be recognized. Although multiple publications have highlighted the importance of implementing the EIP paradigm in LMICs, few studies from these settings have specifically examined strategies for its implementation. This thesis addressed this gap in knowledge and generated evidence on a range of outcomes relevant to EIP in resource-limited countries. This knowledge is valuable not only for advancing the field of EIP but also for psychosis research more broadly, as studies on psychosis from LMICs remain scarce in scientific literature.

Another strength is that this thesis was guided by a pre-established framework for examining the implementation of EIP in LAC. This structured approach ensured that the four studies were conceptually aligned, non-overlapping, and mutually complementary. Each study addressed a distinct yet interconnected aspect of the research question, allowing the findings to be triangulated across different contexts. This triangulation not only enhanced the validity and robustness of the results but also provided a nuanced and comprehensive understanding of how such implementation can be achieved in practice.

The four studies that comprise this thesis employed different research methods, each contributing distinct and complementary information. This diversity of methodological approaches reflects the high level of rigor with which the research was conducted to generate overarching findings on EIP implementation in LMICs. It enabled the examination of the topic from multiple perspectives, capturing both macro-level patterns and in-depth contextual insights, and

ultimately produced a more comprehensive understanding of the processes that should guide the implementation of EIP in resource-limited settings.

7.5. Conclusion

To conclude, this thesis provides a comprehensive examination of the implementation of EIP in LMICs, addressing critical gaps in the literature and generating evidence that is contextually grounded but has global relevance. By integrating findings from four complementary studies, the research offers a nuanced understanding of the opportunities, challenges, and strategic pathways for developing, implementing, adapting and scaling the EIP paradigm in LMICs. The results highlight that while standalone EIP programs remain difficult to scale in many LMICs, alternative models, context-specific adaptations, and the integration of EIP principles into existing mental health structures represent viable approaches. Furthermore, the thesis underscores the importance of incorporating the perspectives of local stakeholders, applying implementation science frameworks, and building research capacity to ensure the successful and equitable delivery of early psychosis care. Taken together, these contributions offer a foundation for informed advocacy and policymaking, targeted investment, and future research aimed at closing the treatment gap for psychosis in LMICs.

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Appendices - Supplemental Materials for Manuscripts I-IV

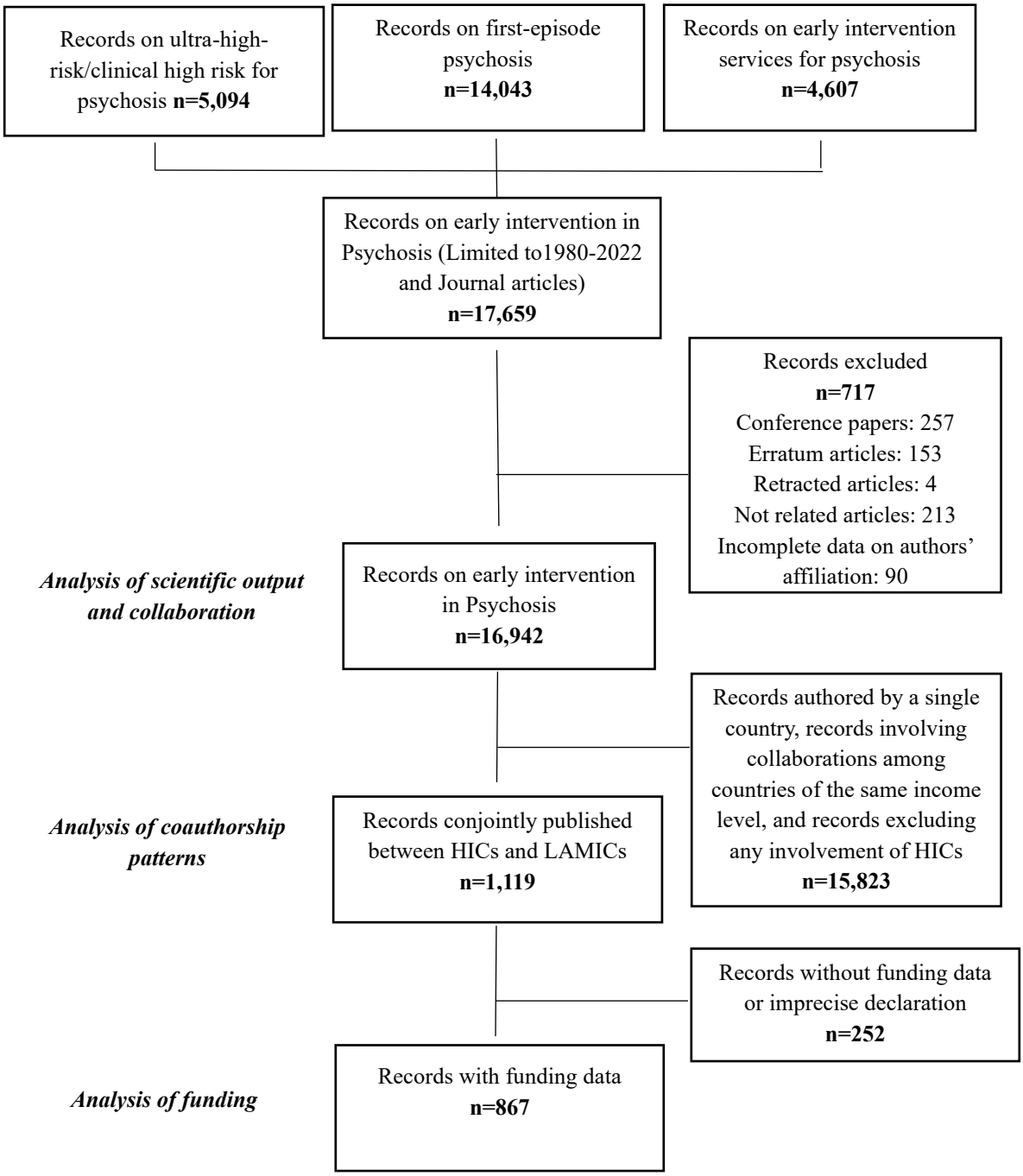
Supplemental material: Manuscript 1

Supplemental material: Manuscript 2

Supplemental material: Manuscript 3

Supplemental material: Manuscript 4

Supplemental material: Manuscript 1



Supplementary figure 1. Flowchart of the selected records.

Supplementary table 1. Search strategies

Ultra-high-risk/clinical high risk for psychosis (N=5,094)
(TITLE-ABS-KEY ("transition" OR "prodrom*" OR "ultrahigh risk" OR "ultra-high risk" OR "clinical high risk" OR "CHR" OR "UHR" OR "attenuat*" OR "high risk" OR "genetic high risk" OR "risk syndrome" OR "at risk mental state" OR "risk of progression") W/2 TITLE-ABS-KEY ("psychosis" OR "psychoses" OR "schizophrenia" OR "psychotic" OR "schizoaffective" OR "schizophreniform" OR "schizophrenic")) OR (TITLE-ABS-KEY ("Comprehensive Assessment of At Risk Mental States" OR "Structured Interview for Prodromal Syndromes"))
First episode psychosis (N=14,043)
(TITLE-ABS-KEY ((first OR early OR initial OR "recent") W/1 (episode OR onset OR intervention OR admission OR hospitalization OR breakdown OR stage OR phase OR detection OR break OR outbreak OR breakthrough OR attack OR event OR time OR presentation OR diagnosis OR course)) W/2 TITLE-ABS-KEY (psychosis OR psychoses OR schizophrenia OR psychotic OR schizoaffective OR schizophreniform OR schizophrenic)) OR (TITLE-ABS-KEY ("duration of untreated psychosis"))
Early intervention services for psychosis (N=4,607)
((TITLE-ABS-KEY (("early intervention") AND (psychosis OR psychoses OR schizophrenia OR psychotic OR schizoaffective OR schizophreniform OR schizophrenic) AND (service OR program* OR team* OR clinic OR intervention OR network))) OR (TITLE-ABS-KEY (("early psychosis" OR "first episode psychosis") W/1 (service OR program* OR team* OR clinic OR intervention OR network)))) OR (TITLE-ABS-KEY ("prevention and early intervention program for psychosis" OR "early psychosis prevention and intervention" OR "recovery after an initial schizophrenia episode" OR "coordinated specialty care" OR "early psychosis intervention program" OR "early assessment service for young people with early psychosis" OR "lambeth early onset" OR "parma early psychosis program"))
Early intervention in Psychosis (N=17,659)
((TITLE-ABS-KEY ((first OR early OR initial OR "recent") W/1 (episode OR onset OR intervention OR admission OR hospitalization OR breakdown OR stage OR phase OR detection OR break OR outbreak OR breakthrough OR attack OR event OR time OR presentation OR diagnosis OR course)) W/2 TITLE-ABS-KEY (psychosis OR psychoses OR schizophrenia OR psychotic OR schizoaffective OR schizophreniform OR schizophrenic)) OR (TITLE-ABS-KEY ("duration of untreated psychosis"))) OR ((TITLE-ABS-KEY ("transition" OR "prodrom*" OR "ultrahigh risk" OR "ultra-high risk" OR "clinical high risk" OR "chr" OR "uhr" OR "attenuat*" OR "high risk" OR "genetic high risk" OR "risk syndrome" OR "at risk mental state" OR "risk of progression") W/2 TITLE-ABS-KEY ("psychosis" OR "psychoses" OR "schizophrenia" OR "psychotic" OR "schizoaffective" OR "schizophreniform" OR "schizophrenic")) OR (TITLE-ABS-KEY ("comprehensive assessment of at risk mental states" OR "structured interview for prodromal syndromes"))) OR (((TITLE-ABS-KEY (("early intervention") AND (psychosis OR psychoses OR schizophrenia OR psychotic OR schizoaffective OR schizophreniform OR schizophrenic) AND (service OR program* OR team* OR clinic OR intervention OR network))) OR (TITLE-ABS-KEY (("early psychosis" OR "first episode psychosis") W/1 (service OR program* OR team* OR clinic OR intervention OR network)))) OR (TITLE-ABS-KEY ("prevention and early intervention program for psychosis" OR "early psychosis prevention and intervention" OR "recovery after an initial schizophrenia episode" OR "coordinated specialty care" OR "early psychosis intervention program" OR "early assessment service for young people with early psychosis" OR "lambeth early onset" OR "parma early psychosis program"))) AND PUBYEAR > 1979 AND PUBYEAR < 2023 AND (LIMIT-TO (SRCTYPE , "j"))
Schizophrenia spectrum disorders (N=269,128)
TITLE-ABS-KEY (psychosis OR psychoses OR schizophrenia OR psychotic OR schizoaffective OR schizophreniform OR schizophrenic) AND PUBYEAR > 1979 AND PUBYEAR < 2023 AND (LIMIT-TO (SRCTYPE , "j"))

Supplementary table 2. Data on number of records, degree and leading authorships and funding by country.

Rank	Country	Income	N records	Degree of centrality	First au.*	Last au.*	Cor. au.*	Funder
1	United States	HIC	4,809	81	154	188	181	219
2	United Kingdom	HIC	3,300	80	100	128	118	89
3	Australia	HIC	1,855	67	31	43	41	16
4	Canada	HIC	1,610	57	52	47	54	20
5	Germany	HIC	1,424	56	56	60	63	18
6	China	UMIC	1,146	52	404	347	409	368
7	Spain	HIC	1,109	62	30	27	30	28
8	Netherlands	HIC	924	55	23	29	23	7
9	Italy	HIC	880	57	14	13	12	4
10	Switzerland	HIC	816	52	27	31	24	22
11	Denmark	HIC	650	50	5	5	4	3
12	France	HIC	511	47	9	5	8	6
13	Japan	HIC	469	45	20	17	18	14
14	Norway	HIC	372	38	3	2	3	5
15	Brazil	UMIC	340	46	96	78	90	78
16	Hong Kong	HIC	321	38	20	12	21	25
17	Ireland	HIC	304	37	15	13	14	10
18	Finland	HIC	275	32	1	NA	2	2
19	Sweden	HIC	275	46	2	4	4	4
20	South Korea	HIC	258	38	10	11	11	10
21	Poland	HIC	242	44	2	2	3	NA
22	India	LMIC	231	41	33	24	22	12
23	Singapore	HIC	201	39	NA	2	1	NA
24	Austria	HIC	200	43	2	5	2	1
25	Russia	UMIC	198	39	16	15	15	11
26	Turkey	UMIC	191	35	20	14	21	5
27	Israel	HIC	190	39	3	4	3	NA
28	Czech Republic	HIC	157	44	5	1	6	4
29	Belgium	HIC	151	45	2	6	NA	1
30	South Africa	UMIC	131	38	34	19	32	14
31	Taiwan	HIC	131	42	4	3	4	2
32	Greece	HIC	119	27	2	2	2	1
33	Mexico	UMIC	85	25	22	13	18	21
34	Croatia	HIC	80	25	NA	NA	NA	NA
35	Chile	HIC	77	36	3	2	3	3
36	Portugal	HIC	68	29	3	2	2	4
37	New Zealand	HIC	62	32	1	NA	1	1
38	Hungary	HIC	52	32	NA	NA	NA	NA
39	Indonesia	LMIC	52	23	6	4	4	1
40	Tunisia	LMIC	47	23	7	6	7	4

Rank	Country	Income	N records	Degree of centrality	First au.*	Last au.*	Cor. au.*	Funder
41	Iran	LMIC	42	19	9	5	8	6
42	Thailand	UMIC	37	28	8	7	7	4
43	Estonia	HIC	34	24	1	6	4	8
44	Egypt	LMIC	32	8	8	4	5	NA
45	Serbia	UMIC	32	25	6	2	5	1
46	Pakistan	LMIC	28	19	8	4	7	NA
47	Trinidad and Tobago	HIC	28	8	NA	NA	NA	NA
48	Malaysia	UMIC	26	20	2	2	1	NA
49	Romania	HIC	26	17	NA	NA	NA	1
50	Nigeria	LMIC	24	5	NA	NA	NA	1
51	Saudi Arabia	HIC	22	23	3	1	2	1
52	Bulgaria	UMIC	20	22	3	4	5	NA
53	Slovenia	HIC	20	16	NA	1	NA	NA
54	Argentina	UMIC	17	20	5	1	1	NA
55	Colombia	UMIC	15	18	1	1	NA	1
56	Macao	HIC	15	16	NA	5	5	2
57	Ukraine	LMIC	15	14	2	NA	NA	NA
58	Iceland	HIC	14	10	1	1	NA	NA
59	Kenya	LMIC	14	9	2	6	2	1
60	Kuwait	HIC	12	7	1	2	1	NA
61	Uganda	LIC	11	11	2	NA	2	NA
62	Latvia	HIC	10	10	NA	NA	NA	NA
63	Slovakia	HIC	9	7	NA	NA	NA	NA
64	Tanzania	LMIC	9	5	1	NA	NA	NA
65	United Arab Emirates	HIC	9	6	1	1	2	NA
66	Lebanon	LMIC	8	11	4	1	3	1
67	Morocco	LMIC	8	19	1	1	1	NA
68	Qatar	HIC	8	8	NA	NA	NA	NA
69	Bangladesh	LMIC	7	9	2	1	1	NA
70	Ethiopia	LIC	7	2	2	1	1	NA
71	Jordan	UMIC	6	7	NA	1	NA	NA
72	Malawi	LIC	6	2	3	NA	NA	NA
73	Belarus	UMIC	5	2	2	NA	1	1
74	Ghana	LMIC	5	1	1	1	1	NA
75	Armenia	UMIC	4	1	1	1	1	NA
76	Cyprus	HIC	4	5	NA	NA	NA	NA
77	Lithuania	HIC	4	8	NA	NA	NA	NA
78	Palau	UMIC	4	1	NA	1	NA	NA
79	Peru	UMIC	4	5	1	NA	NA	1
80	Uruguay	HIC	4	4	NA	NA	NA	NA
81	Vietnam	LMIC	4	3	3	2	2	NA

Rank	Country	Income	N records	Degree of centrality	First au.*	Last au.*	Cor. au.*	Funder
82	Botswana	UMIC	3	5	1	NA	1	NA
83	Iraq	UMIC	3	0	NA	NA	NA	NA
84	Jamaica	UMIC	3	3	1	2	1	NA
85	Nepal	LMIC	3	3	1	NA	1	NA
86	Philippines	LMIC	3	14	NA	NA	NA	NA
87	Sri Lanka	LMIC	3	7	NA	1	NA	NA
88	Syria	LIC	3	0	NA	NA	NA	NA
89	Venezuela	UMIC	3	1	1	1	1	1
90	Andorra	HIC	2	1	NA	NA	NA	NA
91	Bosnia and Herzegovina	UMIC	2	0	NA	NA	NA	NA
92	Costa Rica	UMIC	2	1	1	NA	NA	NA
93	Cuba	UMIC	2	3	1	NA	NA	NA
94	Dominica	UMIC	2	3	NA	NA	NA	NA
95	Dominican Republic	UMIC	2	3	NA	NA	NA	NA
96	Ecuador	UMIC	2	2	NA	1	NA	NA
97	Georgia	UMIC	2	2	NA	NA	NA	1
98	Guam	HIC	2	4	NA	NA	NA	NA
99	Kazakhstan	UMIC	2	1	NA	NA	NA	NA
100	Luxembourg	HIC	2	4	NA	NA	NA	NA
101	Malta	HIC	2	2	NA	NA	NA	NA
102	North Macedonia	UMIC	2	1	NA	NA	NA	NA
103	Oman	HIC	2	1	NA	NA	NA	NA
104	Puerto Rico	HIC	2	3	NA	NA	NA	NA
105	Algeria	LMIC	1	0	NA	NA	NA	NA
106	Azerbaijan	UMIC	1	0	NA	NA	NA	NA
107	Bahrain	HIC	1	3	NA	1	1	NA
108	Barbados	HIC	1	0	NA	NA	NA	NA
109	Cambodia	LMIC	1	1	NA	NA	NA	NA
110	El Salvador	LMIC	1	0	NA	NA	NA	NA
111	Faroe Islands	HIC	1	2	NA	NA	NA	NA
112	Gibraltar	HIC	1	2	NA	NA	NA	NA
113	Isle of Man	HIC	1	1	NA	NA	NA	NA
114	Liberia	LIC	1	0	NA	NA	NA	NA
115	Libya	UMIC	1	0	NA	NA	NA	NA
116	Mali	LIC	1	1	NA	NA	NA	NA
117	Mauritius	UMIC	1	3	1	NA	NA	NA
118	Mozambique	LIC	1	3	NA	NA	NA	NA
119	Niger	LIC	1	0	NA	NA	NA	NA
120	Panama	HIC	1	1	NA	NA	NA	NA
121	Rwanda	LIC	1	2	NA	NA	NA	NA
122	Sint Maarten	HIC	1	2	NA	NA	NA	NA

Rank	Country	Income	N records	Degree of centrality	First au.*	Last au.*	Cor. au.*	Funder
123	Sudan	LIC	1	1	1	NA	NA	NA
124	Suriname	UMIC	1	1	NA	NA	NA	NA
125	Zambia	LIC	1	1	1	NA	NA	NA

N: Number, au: Author, NA: Not Applicable, Cor: Corresponding; Degree of centrality refers to the number of countries directly connected to each country.

Supplemental material: Manuscript 2

Table S1. List of guideline-based components

First-episode psychosis[1]	Clinical-high risk for psychosis[2]
1. Timely contact with referred individuals	1. Comprehensive assessment
2. Comprehensive clinical assessment	2. Assessment by a trained specialist
3. Comprehensive psychosocial needs assessment	3. Cognitive behavioral therapy
4. Family involvement in assessment	4. Treatment of comorbid conditions
5. Treatment/care plan after initial assessment	5. Interventions to prevent the development of functional deficits
6. Psychiatric management	6. Cognitive behavioral therapy plus pharmacological intervention (Adult CHR patients)
7. Case management/care coordination	7. Treatment monitoring by a mental health provider
8. Antipsychotic medication prescription	8. Staged intervention model (Adult CHR patients)
9. Antipsychotic dosing within recommendations for individuals with psychosis	9. Monitoring of symptoms and functioning up to three years after treatment
10. Clozapine for medication resistant symptoms	
11. Patient psychoeducation	
12. Family education and support	
13. Cognitive behavioral therapy	
14. Supporting health	
15. Annual comprehensive assessment	
16. Services for patients with substance use disorders	
17. Supported employment	
18. Supported education	
19. Active engagement and retention	
20. Crisis intervention	

1. Addington DE. First Episode Psychosis Services Fidelity Scale (FEPS-FS 1.0) and Manual. Calgary, Alberta: University of Calgary Press; 2021.
2. Addington J, Addington D, Abidi S, Raedler T, Remington G. Canadian Treatment Guidelines for Individuals at Clinical High Risk of Psychosis. Can J Psychiatry. 2017;62(9):656-61

Table S2: Search strategy in Medline

Step	Terms	N
1	exp Schizophrenia/	110444
2	exp Psychotic Disorders/	55595
3	(schizophrenia or schizophrenic).ti,ab,kf.	132554
4	(psychotic or psychosis).ti,ab,kf.	66116
5	1 or 2 or 3 or 4	213102
6	((first or early or initial or primary or recent) adj3 (episode* or onset or intervention* or admission* or hospitalization* or breakdown* or stage* or phase* or detection)).ti,ab,kf.	594195
7	duration of untreated psychosis.ti,ab,kf.	919
8	exp Early Medical Intervention/	3395
9	6 or 7 or 8	596320
10	5 and 9	16419
11	((Ultra* or transition or prodrom* or clinical high risk or at risk mental state or high risk) adj4 (schizophrenia or psychosis or psychoses or psychotic or schizophrenic)).ti,ab,kf.	3907
12	((Early intervention or program* or service) adj3 (schizophrenia or psychosis or psychoses or psychotic or schizophrenic)).ti,ab,kf.	1585
13	(afghanistan or albania or algeria or american samoa or angola or "antigua and barbuda" or antigua or barbuda or argentina or armenia or armenian or aruba or azerbaijan or bahrain or bangladesh or barbados or republic of belarus or belarus or byelarus or belorussia or byelorussian or belize or british honduras or benin or dahomey or bhutan or bolivia or "bosnia and herzegovina" or bosnia or herzegovina or botswana or bechuanaland or brazil or brasil or bulgaria or burkina faso or burkina fasso or upper volta or burundi or urundi or cabo verde or cape verde or cambodia or kampuchea or khmer republic or cameroon or cameron or cameroun or central african republic or ubangi shari or chad or chile or china or colombia or comoros or comoro islands or iles comores or mayotte or democratic republic of the congo or democratic republic congo or congo or zaire or costa rica or "cote d'ivoire" or "cote d' ivoire" or cote divoire or cote d ivoire or ivory coast or croatia or cuba or cyprus or czech republic or czechoslovakia or djibouti or french somaliland or dominica or dominican republic or ecuador or egypt or united arab republic or el salvador or equatorial guinea or spanish guinea or eritrea or estonia or eswatini or swaziland or ethiopia or fiji or gabon or gabonese republic or gambia or "georgia (republic)" or georgian or ghana or gold coast or gibraltar or greece or grenada or guam or guatemala or guinea or guinea bissau or guyana or british guiana or haiti or hispaniola or honduras or hungary or india or indonesia or timor or iran or iraq or isle of man or jamaica or jordan or kazakhstan or kazakh or kenya or "democratic people's republic of korea" or republic of korea or north korea or south korea or korea or kosovo or kyrgyzstan or kirghizia or kirgizstan or kyrgyz republic or kirghiz or laos or lao pdr or "lao people's democratic republic" or latvia or lebanon or lebanese republic or lesotho or basutoland or liberia or libya or libyan arab jamahiriya or lithuania or macau or macao or republic of north macedonia or macedonia or madagascar or malagasy republic or malawi or nyasaland or malaysia or malay federation or malaya federation or maldives or indian ocean islands or indian ocean or mali or malta or micronesia or federated states of micronesia or kiribati or marshall islands or nauru or northern mariana islands or palau or tuvalu or mauritania or mauritius or mexico or moldova or moldovian or mongolia or montenegro or "montenegro (republic)" or morocco or ifni or mozambique or portuguese east africa or myanmar or burma or namibia or nepal or netherlands antilles or nicaragua or niger or nigeria or oman or muscat or pakistan or panama or papua new guinea or new guinea	2160534

Step	Terms	N
	or paraguay or peru or philippines or philipines or phillipines or phillippines or poland or "polish people's republic" or portugal or portuguese republic or puerto rico or romania or russia or russian federation or ussr or soviet union or union of soviet socialist republics or rwanda or ruanda or samoa or pacific islands or polynesia or samoan islands or navigator island or navigator islands or "sao tome and principe" or saudi arabia or senegal or serbia or seychelles or sierra leone or slovakia or slovak republic or slovenia or melanesia or solomon island or solomon islands or norfolk island or norfolk islands or somalia or south africa or south sudan or sri lanka or ceylon or "saint kitts and nevis" or "st. kitts and nevis" or saint lucia or "st. lucia" or "saint vincent and the grenadines" or saint vincent or "st. vincent" or grenadines or sudan or suriname or surinam or dutch guiana or netherlands guiana or syria or syrian arab republic or tajikistan or tadjikistan or tadzhikistan or tadzhik or tanzania or tanganyika or thailand or siam or timor leste or east timor or togo or togolese republic or tonga or "trinidad and tobago" or trinidad or tobago or tunisia or "turkey (republic)" or turkey or turkmenistan or turkmen or uganda or ukraine or uruguay or uzbekistan or uzbek or vanuatu or new hebrides or venezuela or vietnam or viet nam or middle east or west bank or gaza or palestine or yemen or yugoslavia or zambia or zimbabwe or northern rhodesia or global south or africa south of the sahara or "sub saharan africa" or subsaharan africa or africa, central or central africa or africa, northern or north africa or northern africa or magreb or maghrib or sahara or africa, southern or southern africa or africa, eastern or east africa or eastern africa or africa, western or west africa or western africa or west indies or indian ocean islands or caribbean region or caribbean islands or caribbean or central america or latin america or "south and central america" or south america or asia, central or central asia or asia, northern or north asia or northern asia or asia, southeastern or southeastern asia or south eastern asia or southeast asia or south east asia or asia, western or western asia or europe, eastern or east europe or eastern europe or developing country or developing countries or developing nation? or developing population? or developing world or less developed countr* or less developed nation? or less developed population? or less developed world or lesser developed countr* or lesser developed nation? or lesser developed population? or lesser developed world or under developed countr* or under developed nation? or under developed population? or under developed world or underdeveloped countr* or underdeveloped nation? or underdeveloped population? or underdeveloped world or middle income countr* or middle income nation? or middle income population? or low income countr* or low income nation? or low income population? or lower income countr* or lower income nation? or lower income population? or underserved countr* or underserved nation? or underserved population? or underserved world or under served countr* or under served nation? or under served population? or under served world or deprived countr* or deprived nation? or deprived population? or deprived world or poor countr* or poor nation? or poor population? or poor world or poorer countr* or poorer nation? or poorer population? or poorer world or developing econom* or less developed econom* or lesser developed econom* or under developed econom* or underdeveloped econom* or middle income econom* or low income econom* or lower income econom* or low gdp or low gnp or low gross domestic or low gross national or lower gdp or lower gnp or lower gross domestic or lower gross national or lmic or lmics or third world or lami countr* or transitional countr* or emerging economies or emerging nation?).ti,ab,sh,kw.	
14	10 or 11 or 12	19297
15	13 and 14	2237

Table S3: Search strategy in PsycINFO

Step	Terms	N
1	exp Schizophrenia/	95129
2	exp Psychosis/	122710
3	(schizophrenia or schizophrenic).ti,ab,sh,mh.	131505
4	(psychotic or psychosis).ti,ab,sh,mh.	73441
5	1 or 2 or 3 or 4	178697
6	((first or early or initial or primary or recent) adj3 (episode* or onset or intervention* or admission* or hospitalization* or breakdown* or stage* or phase* or detection)).ti,ab,sh,mh.	99980
7	duration of untreated psychosis.ti,ab,sh,mh.	893
8	exp Early Intervention/	11699
9	6 or 7 or 8	104179
10	5 and 9	14968
11	((Ultra* or transition or prodrom* or clinical high risk or at risk mental state or high risk) adj4 (schizophrenia or psychosis or psychoses or psychotic or schizophrenic)).ti,ab,sh,mh.	3931
12	((Early intervention or program* or service) adj3 (schizophrenia or psychosis or psychoses or psychotic or schizophrenic)).ti,ab,sh,mh.	2716
13	(afghanistan or albania or algeria or american samoa or angola or "antigua and barbuda" or antigua or barbuda or argentina or armenia or armenian or aruba or azerbaijan or bahrain or bangladesh or barbados or republic of belarus or belarus or byelarus or belorussia or byelorussian or belize or british honduras or benin or dahomey or bhutan or bolivia or "bosnia and herzegovina" or bosnia or herzegovina or botswana or bechuanaland or brazil or brasil or bulgaria or burkina faso or burkina fasso or upper volta or burundi or urundi or cabo verde or cape verde or cambodia or kampuchea or khmer republic or cameroon or cameron or cameroun or central african republic or ubangi shari or chad or chile or china or colombia or comoros or comoro islands or iles comores or mayotte or democratic republic of the congo or democratic republic congo or congo or zaire or costa rica or "cote d'ivoire" or "cote d' ivoire" or cote divoire or cote d ivoire or ivory coast or croatia or cuba or cyprus or czech republic or czechoslovakia or djibouti or french somaliland or dominica or dominican republic or ecuador or egypt or united arab republic or el salvador or equatorial guinea or spanish guinea or eritrea or estonia or eswatini or swaziland or ethiopia or fiji or gabon or gabonese republic or gambia or "georgia (republic)" or georgian or ghana or gold coast or gibraltar or greece or grenada or guam or guatemala or guinea or guinea bissau or guyana or british guiana or haiti or hispaniola or honduras or hungary or india or indonesia or timor or iran or iraq or isle of man or jamaica or jordan or kazakhstan or kazakh or kenya or "democratic people's republic of korea" or republic of korea or north korea or south korea or korea or kosovo or kyrgyzstan or kirghizia or kirgizstan or kyrgyz republic or kirghiz or laos or lao pdr or "lao people's democratic republic" or latvia or lebanon or lebanese republic or lesotho or basutoland or liberia or libya or libyan arab jamahiriya or lithuania or macau or macao or republic of north macedonia or macedonia or madagascar or malagasy republic or malawi or nyasaland or malaysia or malay federation or malaya federation or maldives or indian ocean islands or indian ocean or mali or malta or micronesia or federated states of micronesia or kiribati or marshall islands or nauru or northern mariana islands or palau or tuvalu or mauritania or mauritius or mexico or moldova or moldovian or mongolia or montenegro or "montenegro (republic)" or morocco or ifni or mozambique or portuguese east africa or myanmar or burma or namibia or nepal or netherlands antilles or nicaragua or niger or nigeria or oman or muscat or pakistan or panama or papua new guinea or new	406021

Step	Terms	N
	guinea or paraguay or peru or philippines or philipines or phillipines or phillippines or poland or "polish people's republic" or portugal or portuguese republic or puerto rico or romania or russia or russian federation or ussr or soviet union or union of soviet socialist republics or rwanda or ruanda or samoa or pacific islands or polynesia or samoan islands or navigator island or navigator islands or "sao tome and principe" or saudi arabia or senegal or serbia or seychelles or sierra leone or slovakia or slovak republic or slovenia or melanesia or solomon island or solomon islands or norfolk island or norfolk islands or somalia or south africa or south sudan or sri lanka or ceylon or "saint kitts and nevis" or "st. kitts and nevis" or saint lucia or "st. lucia" or "saint vincent and the grenadines" or saint vincent or "st. vincent" or grenadines or sudan or suriname or surinam or dutch guiana or netherlands guiana or syria or syrian arab republic or tajikistan or tadjikistan or tadzhikistan or tadzhik or tanzania or tanganyika or thailand or siam or timor leste or east timor or togo or togolese republic or tonga or "trinidad and tobago" or trinidad or tobago or tunisia or "turkey (republic)" or turkey or turkmenistan or turkmen or uganda or ukraine or uruguay or uzbekistan or uzbek or vanuatu or new hebrides or venezuela or vietnam or viet nam or middle east or west bank or gaza or palestine or yemen or yugoslavia or zambia or zimbabwe or northern rhodesia or global south or africa south of the sahara or "sub saharan africa" or subsaharan africa or africa, central or central africa or africa, northern or north africa or northern africa or magreb or maghrib or sahara or africa, southern or southern africa or africa, eastern or east africa or eastern africa or africa, western or west africa or western africa or west indies or indian ocean islands or caribbean region or caribbean islands or caribbean or central america or latin america or "south and central america" or south america or asia, central or central asia or asia, northern or north asia or northern asia or asia, southeastern or southeastern asia or south eastern asia or southeast asia or south east asia or asia, western or western asia or europe, eastern or east europe or eastern europe or developing country or developing countries or developing nation? or developing population? or developing world or less developed countr* or less developed nation? or less developed population? or less developed world or lesser developed countr* or lesser developed nation? or lesser developed population? or lesser developed world or under developed countr* or under developed nation? or under developed population? or under developed world or underdeveloped countr* or underdeveloped nation? or underdeveloped population? or underdeveloped world or middle income countr* or middle income nation? or middle income population? or low income countr* or low income nation? or low income population? or lower income countr* or lower income nation? or lower income population? or underserved countr* or underserved nation? or underserved population? or underserved world or under served countr* or under served nation? or under served population? or under served world or deprived countr* or deprived nation? or deprived population? or deprived world or poor countr* or poor nation? or poor population? or poor world or poorer countr* or poorer nation? or poorer population? or poorer world or developing econom* or less developed econom* or lesser developed econom* or under developed econom* or underdeveloped econom* or middle income econom* or low income econom* or lower income econom* or low gdp or low gnp or low gross domestic or low gross national or lower gdp or lower gnp or lower gross domestic or lower gross national or lmic or lmics or third world or lami countr* or transitional countr* or emerging economies or emerging nation?).ti,ab,sh,mh,lo.	
14	10 or 11 or 12	18242
15	13 and 14	2136

Table S4: Search strategy in Embase

Step	Terms	N
1	exp schizophrenia/	207604
2	exp psychosis/	330732
3	(schizophrenia or schizophrenic).ti,ab,kf.	186261
4	(psychotic or psychosis).ti,ab,kf.	106245
5	1 or 2 or 3 or 4	365974
6	((first or early or initial or primary or recent) adj3 (episode* or onset or intervention* or admission* or hospitalization* or breakdown* or stage* or phase* or detection)).ti,ab,kf.	860857
7	duration of untreated psychosis.ti,ab,kf.	1569
8	exp early intervention/	28628
9	6 or 7 or 8	873185
10	5 and 9	2937
11	((Ultra* or transition or prodrom* or clinical high risk or at risk mental state or high risk) adj4 (schizophrenia or psychosis or psychoses or psychotic or schizophrenic)).ti,ab,kf.	6661
12	((Early intervention or program* or service) adj3 (schizophrenia or psychosis or psychoses or psychotic or schizophrenic)).ti,ab,kf.	2737
13	10 or 11 or 12	34045
14	(afghanistan or albania or algeria or american samoa or angola or "antigua and barbuda" or antigua or barbuda or argentina or armenia or armenian or aruba or azerbaijan or bahrain or bangladesh or barbados or republic of belarus or belarus or byelarus or belorussia or byelorussian or belize or british honduras or benin or dahomey or bhutan or bolivia or "bosnia and herzegovina" or bosnia or herzegovina or botswana or bechuanaland or brazil or brasil or bulgaria or burkina faso or burkina fasso or upper volta or burundi or urundi or cabo verde or cape verde or cambodia or kampuchea or khmer republic or cameroon or cameron or cameroun or central african republic or ubangi shari or chad or chile or china or colombia or comoros or comoro islands or iles comores or mayotte or democratic republic of the congo or democratic republic congo or congo or zaire or costa rica or "cote d'ivoire" or "cote d' ivoire" or cote divoire or cote d ivoire or ivory coast or croatia or cuba or cyprus or czech republic or czechoslovakia or djibouti or french somaliland or dominica or dominican republic or ecuador or egypt or united arab republic or el salvador or equatorial guinea or spanish guinea or eritrea or estonia or eswatini or swaziland or ethiopia or fiji or gabon or gabonese republic or gambia or "georgia (republic)" or georgian or ghana or gold coast or gibraltar or greece or grenada or guam or guatemala or guinea or guinea bissau or guyana or british guiana or haiti or hispaniola or honduras or hungary or india or indonesia or timor or iran or iraq or isle of man or jamaica or jordan or kazakhstan or kazakh or kenya or "democratic people's republic of korea" or republic of korea or north korea or south korea or korea or kosovo or kyrgyzstan or kirghizia or kirgizstan or kyrgyz republic or kirghiz or laos or lao pdr or "lao people's democratic republic" or latvia or lebanon or lebanese republic or lesotho or basutoland or liberia or libya or libyan arab jamahiriya or lithuania or macau or macao or republic of north macedonia or macedonia or madagascar or malagasy republic or malawi or nyasaland or malaysia or malay federation or malaya federation or maldives or indian ocean islands or indian ocean or mali or malta or micronesia or federated states of micronesia or kiribati or marshall islands or nauru or northern mariana islands or palau or tuvalu or mauritania or mauritius or mexico or moldova or moldovian or mongolia or montenegro or "montenegro (republic)" or morocco or ifni or mozambique or portuguese east africa or myanmar or burma or namibia or nepal or netherlands antilles or nicaragua or niger or nigeria or oman or muscat or pakistan or panama or papua new guinea or new guinea or paraguay or peru or philippines or philipines or phillipines or phillippines or poland or "polish people's	2612031

Step	Terms	N
	republic" or portugal or portuguese republic or puerto rico or romania or russia or russian federation or ussr or soviet union or union of soviet socialist republics or rwanda or ruanda or samoa or pacific islands or polynesia or samoan islands or navigator island or navigator islands or "sao tome and principe" or saudi arabia or senegal or serbia or seychelles or sierra leone or slovakia or slovak republic or slovenia or melanesia or solomon island or solomon islands or norfolk island or norfolk islands or somalia or south africa or south sudan or sri lanka or ceylon or "saint kitts and nevis" or "st. kitts and nevis" or saint lucia or "st. lucia" or "saint vincent and the grenadines" or saint vincent or "st. vincent" or grenadines or sudan or suriname or surinam or dutch guiana or netherlands guiana or syria or syrian arab republic or tajikistan or tadjikistan or tadzhikistan or tadzhik or tanzania or tanganyika or thailand or siam or timor leste or east timor or togo or togolese republic or tonga or "trinidad and tobago" or trinidad or tobago or tunisia or "turkey (republic)" or turkey or turkmenistan or turkmen or uganda or ukraine or uruguay or uzbekistan or uzbek or vanuatu or new hebrides or venezuela or vietnam or viet nam or middle east or west bank or gaza or palestine or yemen or yugoslavia or zambia or zimbabwe or northern rhodesia or global south or africa south of the sahara or "sub saharan africa" or subsaharan africa or africa, central or central africa or africa, northern or north africa or northern africa or magreb or maghrib or sahara or africa, southern or southern africa or africa, eastern or east africa or eastern africa or africa, western or west africa or western africa or west indies or indian ocean islands or caribbean region or caribbean islands or caribbean or central america or latin america or "south and central america" or south america or asia, central or central asia or asia, northern or north asia or northern asia or asia, southeastern or southeastern asia or south eastern asia or southeast asia or south east asia or asia, western or western asia or europe, eastern or east europe or eastern europe or developing country or developing countries or developing nation? or developing population? or developing world or less developed countr* or less developed nation? or less developed population? or less developed world or lesser developed countr* or lesser developed nation? or lesser developed population? or lesser developed world or under developed countr* or under developed nation? or under developed population? or under developed world or underdeveloped countr* or underdeveloped nation? or underdeveloped population? or underdeveloped world or middle income countr* or middle income nation? or middle income population? or low income countr* or low income nation? or low income population? or lower income countr* or lower income nation? or lower income population? or underserved countr* or underserved nation? or underserved population? or underserved world or under served countr* or under served nation? or under served population? or under served world or deprived countr* or deprived nation? or deprived population? or deprived world or poor countr* or poor nation? or poor population? or poor world or poorer countr* or poorer nation? or poorer population? or poorer world or developing econom* or less developed econom* or lesser developed econom* or under developed econom* or underdeveloped econom* or middle income econom* or low income econom* or lower income econom* or low gdp or low gnp or low gross domestic or low gross national or lower gdp or lower gnp or lower gross domestic or lower gross national or lmic or lmics or third world or lami countr* or transitional countr* or emerging economies or emerging nation?).ti,ab,sh,kw.	
15	13 and 14	1523

Table S5. Risk of bias among effectiveness records (n=32).

N	Title	Q1	Q2	Q3	Q4	Q5	Total
First-episode psychosis							
1	Comparison of clinical outcomes following 2 years of treatment of first-episode psychosis in urban early intervention services in Canada and India	Yes	Yes	Yes	Yes	Yes	*****
2	Effectiveness of a mindfulness-based psychoeducation group programme for early-stage schizophrenia: An 18-month randomised controlled trial	Yes	Yes	Yes	Yes	Yes	*****
3	Effectiveness of antipsychotic drugs for 24-month maintenance treatment in first-episode schizophrenia	Yes	Yes	Yes	Yes	Yes	*****
4	Effects of the family schizophrenia psychoeducation program for individuals with recent onset schizophrenia in Viet Nam	No	Yes	Yes	No	No	**
5	Effect of Antipsychotic Medication Alone vs Combined With Psychosocial Intervention on Outcomes of Early-Stage Schizophrenia	Ye	Yes	No	Yes	Yes	****
6	Effectiveness of the integrated long-term program of management of patients after first psychotic episode in 5-year follow-up	No	No	No	No	Yes	*
7	Targeting relapse prevention and positive symptom in first-episode schizophrenia using brief cognitive behavioral therapy: A pilot randomized controlled study	Yes	Yes	Yes	Yes	Yes	*****
8	The Efficacy of an Integrated Treatment in Comparison with Treatment as Usual in a Group of Children and Adolescents with First-Episode Psychosis during a Two -Year Follow-up	No	Yes	No	No	Can't tell	*
9	Brief interactive psychoeducation for caregivers of patients with early phase psychosis in Yogyakarta, Indonesia	No	Yes	Yes	No	Yes	***
10	Effect of Short Message Service Reminders on Clinic Attendance Among Outpatients With Psychosis at a Psychiatric Hospital in Nigeria	Yes	Yes	Yes	No	Yes	****
11	Combining depot antipsychotic with an assertive monitoring programme for treating first-episode schizophrenia in a resource-constrained setting	Yes	Yes	No	No	Yes	***
12	Cost-effectiveness analysis of psychosocial intervention for early stage schizophrenia in China: a randomized, one-year study	Ye	Yes	No	Yes	Yes	****
13	Comprehensive family therapy: an effective approach for cognitive rehabilitation in schizophrenia	Yes	Yes	Yes	Yes	Yes	*****
14	Preliminary findings from a study of first-episode psychosis in Montreal, Canada and Chennai, India: Comparison of outcomes	Yes	Yes	Yes	Yes	Yes	*****
15	Randomised-Control Trial of Family Intervention for 78 First-Episode Male Schizophrenic Patients An I8-Month Study in Suzhou, Jiangsu	Can't tell	Yes	Yes	Yes	Can't tell	***
16	The impact of a six-month interpersonal group psychotherapy on functionality of patients with schizophrenia in a community mental health center.	Yes	Can't tell	Can't tell	Yes	Yes	***
17	The Effects of Psychoeducation on the Expressed Emotion and Family Functioning of the Family Members in First-Episode Schizophrenia	Yes	Yes	Yes	No	Yes	****
18	A Pilot Study of iPad-Assisted Cognitive Training for Schizophrenia	Can't tell	Yes	Yes	No	Yes	***
19	Integrated Treatment to Achieve Functional Recovery for First-Episode Psychosis	Can't tell	No	Yes	Yes	Yes	***

N	Title	Q1	Q2	Q3	Q4	Q5	Total
First-episode psychosis							
20	Addition of home-based cognitive retraining to treatment as usual in first episode schizophrenia patients: a randomized controlled study.	Yes	No	No	No	Can't tell	*
21	Evaluating the efficacy of the Thai Health Improvement Profile intervention for preventing weight gain in people with early stage psychosis: A randomized controlled trial	Yes	No	No	Yes	Yes	***
22	Does group intervention have benefits on expressed emotion and social support in carers of persons with first episode psychosis?	No	Yes	Can't tell	Can't tell	Yes	**
23	Electroconvulsive Therapy in First Episode Schizophrenia – Experiences from Nepal	Yes	Yes	Can't tell	Can't tell	Yes	***
24	Metabolic syndrome in first episode schizophrenia — A randomized double-blind controlled, short-term prospective study	Yes	Yes	No	Yes	Yes	****
25	Cost-effectiveness of early intervention in psychosis in low- and middle-income countries: economic evaluation from São Paulo, Brazil	Yes	Yes	Can't tell	Yes	Yes	****
26	An international multi-site, randomized controlled trial of a mindfulness-based psychoeducation group programme for people with schizophrenia	Yes	Yes	Yes	No	Yes	****
27	Context and contact: a comparison of patient and family engagement with early intervention services for psychosis in India and Canada	Yes	Yes	No	Yes	Yes	****
Clinical High Risk for psychosis							
28	Further evidence that antipsychotic medication does not prevent long-term psychosis in higher-risk individuals	Yes	Yes	Yes	Yes	Yes	*****
29	Real-world effectiveness of antipsychotic treatment in psychosis prevention in a 3-year cohort of 517 individuals at clinical high risk from the SHARP (ShangHai At Risk for Psychosis)	Yes	Yes	No	Yes	Yes	****
30	Systemic Therapy for Youth at Clinical High Risk for Psychosis: A Pilot Study	No	Yes	Yes	Yes	Can't tell	***
31	A randomised double-blind placebo-controlled trial of minocycline and/or omega-3 fatty acids added to treatment as usual for at risk Mental States: The NAYAB study	No	Yes	Yes	Yes	Yes	****
32	Enhancing attention and memory of individuals at clinical high risk for psychosis with mHealth technology	No	No	No	Yes	Yes	**
33	EMDR versus waiting list in individuals at clinical high risk for psychosis with post-traumatic stress symptoms: A randomized controlled trial.	Yes	Yes	Can't tell	Yes	Yes	****

Table S6. Characteristics of the included records (n=125).

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
1	Ribeirao Preto Early Intervention in Psychosis Program	Correa-Oliveira (2021)	Early intervention in psychosis in emerging countries: Findings from a first-episode psychosis programme in the Ribeirao Preto catchment area, southeastern Brazil	Brazil	Cohort	FEP: 237
2	Schizophrenia Research Foundation	Iyer (2020)	Context and contact: a comparison of patient and family engagement with early intervention services for psychosis in India and Canada	India	Cohort	FEP: 168
3	Schizophrenia Research Foundation	Vaitheswaran (2021)	Implementation of first episode psychosis intervention in India – A case study in a low- and middle-income country	India	Case study	FEP: 15, Family: 12, Clinicians: 15
4	Butabika National Referral Mental Hospital	Mwesiga (2021)	Quality of individual and group level interventions for first-episode psychosis at the tertiary psychiatric hospital in Uganda	Uganda	Cross-sectional	FEP: 156
5	Ribeirao Preto Early Intervention in Psychosis Program	Silva (2020)	Family environment and depressive episode are associated with relapse after first-episode psychosis	Brazil	Cohort	FEP: 65, Family: 65
6	Saint John of God	Kaminga (2019)	Association between referral source and duration of untreated psychosis in pathways to care among first episode psychosis patients in Northern Malawi	Malawi	Cross-sectional	FEP: 140
7	Schizophrenia Research Foundation	Malla (2020)	Comparison of clinical outcomes following 2 years of treatment of first-episode psychosis in urban early intervention services in Canada and India	India	Cohort	FEP: 168
8	Study in Jilin	Chien (2019)	Effectiveness of a mindfulness-based psychoeducation group programme for early-stage schizophrenia: An 18-month randomised controlled trial	China/Hong kong	RCT	FEP: 180
9	Study in Xuhui and HongKou	Zhang (2016)	Effectiveness of antipsychotic drugs for 24-month maintenace treatment in first-episode schizophrenia	China	Cohort	FEP: 347
10	Da Nang Psychiatric Hospital	Ngoc (2016)	Effects of the family schizophrenia psychoeducation program for individuals with recent onset schizophrenia in Viet Nam	Vietnam	RCT	FEP: 59, Family: 59
11	Ten-site study in China	Guo (2010)	Effect of Antipsychotic Medication Alone vs Combined With Psychosocial Intervention on Outcomes of Early-Stage Schizophrenia	China	RCT	FEP: 1268
12	Moscow Research Institute of Psychiatry	Zaytseva (2010)	Effectiveness of the integrated long-term program of management of patients after first psychotic episode in 5-year follow-up	Russia	Cohort	FEP: 114, Control: 119

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
13	Beijing Anding Hospital	Liu (2019)	Targeting relapse prevention and positive symptom in first-episode schizophrenia using brief cognitive behavioral therapy: A pilot randomized controlled study	China	RCT	FEP: 80
14	Roozbeh Hospital	Shahrivar (2012)	The Efficacy of an Integrated Treatment in Comparison with Treatment as Usual in a Group of Children and Adolescents with First-Episode Psychosis during a Two -Year Follow-up	Iran	RCT	FEP: 40
15	Cohort in Colombia	Cano (2020)	Functionality During the First Five Years Afterthe Diagnosis of Schizophrenia. A Cohort Studyin a Colombian Population	Colombia	Cohort	FEP: 50
16	Clinical high-risk program in Tunisia	Ventura (2020)	Establishing a clinical high-risk program in Tunisia, North Africa: A pilot study in early detection and identification	Tunisia	Cohort	CHR: 10
17	Silver Mind Hospital	Srivastava (2009)	The abilities of improved schizophrenia patients to work and live independently in the community: a 10-year long-term outcome study from Mumbai, India	India	Cross-sectional	FEP: 200
18	Study in Yogyakarta	Marchira (2019)	Brief interactive psychoeducation for caregivers of patients with early phase psychosis in Yogyakarta, Indonesia	Indonesia	RCT	FEP: 100, Family: 100
19	Federal Neuro-Psychiatric Hospital in Benin	Thomas (2017)	Effect of Short Message Service Reminders on Clinic Attendance Among Outpatients With Psychosis at a Psychiatric Hospital in Nigeria	Nigeria	RCT	FEP: 192
20	Study in Ibadan and Cape Town	Chiliza (2016)	Combining depot antipsychotic with an assertive monitoring programme for treating first-episode schizophrenia in a resource-constrained setting	South Africa/ Nigeria	Cohort	FEP: 207
21	Ten-site study in China	Zhang (2014)	Cost-effectiveness analysis of psychosocial intervention for early stage schizophrenia in China: a randomized, one-year study	China	RCT	FEP: 1268
22	University College Hospital in Nigeria	Esan (2014)	Persistence in Treatment for One Year Among Patients in Nigeria With First-Episode Schizophrenia	Nigeria	Cohort	FEP: 216
23	Christian Medical College	Johnson (2014)	Predictors of disability: A 5-year cohort study of first-episode schizophrenia	India	Case-control	FEP: 131
24	Study in Shanghai	Cai (2015)	Comprehensive family therapy: an effective approach for cognitive rehabilitation in schizophrenia	China	RCT	FEP: 256

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
25	Schizophrenia Research Foundation	Rangaswamy (2012)	Intervention for first episode psychosis in India – The SCARF experience	India	Cohort	FEP: 47
26	Schizophrenia Research Foundation	Rangaswamy (2012)	Early Intervention for First-episode Psychosis in India	India	Cohort	FEP: 47
27	Schizophrenia Research Foundation	Iyer (2011)	An examination of patient-identified goals for treatment in a first-episode programme in Chennai, India	India	Cross-sectional	FEP: 68
28	Schizophrenia Research Foundation	Iyer (2010)	Preliminary findings from a study of first-episode psychosis in Montreal, Canada and Chennai, India: Comparison of outcomes	India	Cohort	FEP: 73
29	Suzhou Guangji Hospital	Zhang (1994)	Randomised-Control Trial of Family Intervention for 78 First-Episode Male Schizophrenic Patients An I8-Month Study in Suzhou, Jiangsu	China	RCT	FEP: 78
30	Bolu community Mental Health Center	Sukru (2018)	The impact of a six-month interpersonal group psychotherapy on functionality of patients with schizophrenia in a community mental health center.	Turkey	Non-randomized controlled Study	FEP: 60
31	University hospital in Turkey	Oksuz (2017)	The Effects of Psychoeducation on the Expressed Emotion and Family Functioning of the Family Members in First-Episode Schizophrenia	Turkey	Quasi-experimental	Family: 60
32	Early Intervention Clinic in Psychosis	Ramirez (2016)	Clínica de Intervención Temprana en Psicosis en el Hospital Psiquiátrico Fray Bernardino Álvarez	Mexico	Case series	FEP: 80
33	Tongde Hospital	Dang (2014)	A Pilot Study of iPad-Assisted Cognitive Training for Schizophrenia	China	RCT	FEP: 20
34	First-Episode Schizophrenia Follow-up Project	Ucok (2011)	Remission after first-episode schizophrenia: Results of a long-term follow-up	Turkey	Cohort	FEP: 93
35	National Insitute of Mental Health and Neuroscience[1]	Thirthalli (2011)	Prospective study of duration of untreated psychosis and outcome of never-treated patients with schizophrenia in India.	India	Cohort	FEP: 119
36	ShangHai at Risk for Psychosis research programme	Zhang (2018)	Using 'WeChat' online social networking in a real-world needs analysis of family members of youths at clinical high risk of psychosis	China	Cross-sectional	CHR: 108, Family: 171

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
37	Psychosis Episode Program of the UNIFESP	Cabral (2010)	Multi-family group intervention in a programme for patients with first-episode psychosis: a brazilian experience	Brazil	Cross-sectional	FEP: 46, Family: 65
38	Psychosis Episode Program of the UNIFESP	Chaves (2007)	First episode psychosis: a window of treatment opportunity?	Brazil	Case series	FEP: 45
39	Psychosis Episode Program of the UNIFESP	Eisenstadt, (2012)	Experience of recovery from a first-episode psychosis	Brazil	Qualitative study	FEP: 16
40	National Institute of Psychiatry Ramón de la Fuente Muñiz	Valencia (2012)	Integrated Treatment to Achieve Functional Recovery for First-Episode Psychosis	Mexico	RCT	FEP: 73
41	Schizophrenia Research Foundation	Raghavan (2017)	Social functioning in individuals with first episode psychosis: One-year follow-up study.	India	Cohort	FEP: 51
42	Christian Medical College	Johnson (2012)	Insight, psychopathology, explanatory models and outcome of schizophrenia in India: a prospective 5-year cohort study.	India	Cohort	FEP: 131
43	National Insitute of Mental Health and Neuroscience[2]	Hedge (2012)	Addition of home-based cognitive retraining to treatment as usual in first episode schizophrenia patients: a randomized controlled study.	India	RCT	FEP: 45
44	Schizophrenia Research Foundation	Raghavan (2019)	Medication adherence in first-episode psychosis and its association with psychopathology.	India	Cohort	FEP: 59
45	Schizophrenia Research Foundation	Iyer (2020)	ShareDisk: A novel visual tool to assess perceptions about who should be responsible for supporting persons with mental health problems.	India	Cross-sectional	FEP: 30, Family: 30, Clinicians: 15
46	Evaluation and follow-up of adolescents and young adults	Louza (2008)	An Early Psychosis Research program in Sao Paulo, Brazil. Organization and implementation	Brazil	Case series	CHR: 18
47	Study in China	Chien (2017)	An international multi-site, randomized controlled trial of a mindfulness-based psychoeducation group programme for people with schizophrenia	China/Hong kong/Taiwan	RCT	FEP: 342
48	Schizophrenia Research Foundation	Malla (2022)	An observational study of antipsychotic medication discontinuation in first-episode psychosis: clinical and functional outcomes.	India	Cohort	FEP: 124

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
49	Schizophrenia Research Foundation	Iyer (2022)	Show me you care: A patient- and family-reported measure of care experiences in early psychosis services.	India	Cohort	FEP: 29, Family: 27
50	Longitudinal study in early detection of psychosis	Nieto (2022)	Clinical and Functional Differences Between Mexican Youth at Clinical High Risk for Psychosis and With Familial High Risk	Mexico	Cross-sectional	CHR: 42
51	Early Psychosis Support Group	Cerqueira (2022)	Differences of affective and non-affective psychoses in early intervention services from Latin America.	Brazil and Chile	Cohort	FEP: 265
52	Schizophrenia Research Foundation	Iyer (2022)	Whose responsibility? Part 2 of 2: views of patients, families, and clinicians about responsibilities for addressing the needs of persons with mental health problems in Chennai, India and Montreal, Canada	India	Cohort	FEP: 250, Family: 228, Clinicians: 50
53	Schizophrenia Research Foundation	Iyer (2022)	Whose responsibility? Part 1 of 2: A scale to assess how stakeholders apportion responsibilities for addressing the needs of persons with mental health problems	India	Cohort	FEP: 26, Family: 28, Clinicians: 15
54	Schizophrenia Research Foundation	Iyer (2023)	Context and Expectations Matter: Social, Recreational, and Independent Functioning among Youth with Psychosis in Chennai, India and Montreal, Canada.	India	Cohort	FEP: 164
55	Study in Shangai and Changsha	Qi (2023)	Hippocampal Subfield Volumes Predict Disengagement from Maintenance Treatment in First Episode Schizophrenia.	China	RCT	FEP: 95
56	All India Institute of Medical Sciences	Singh (2023)	Pathways to care in first-episode psychosis in low-resource settings: Implications for policy and practice	India	Cross-sectional	FEP: 177
57	ShangHai at Risk for Psychosis research programme	Zhang (2022)	Individualized risk components guiding antipsychotic delivery in patients with a clinical high risk of psychosis: Application of a risk calculator.	China	Cohort	CHR: 208
58	Second Xiangya Hospital	Huang (2022)	PCSK9 mediates dyslipidemia induced by olanzapine treatment in schizophrenia patients.	China	Cohort	FEP: 41
59	ShangHai at Risk for Psychosis research programme	Zhang (2021)	Calculating individualized risk components using a mobile app-based risk calculator for clinical high risk of psychosis: findings from ShangHai At Risk for Psychosis (SHARP) program	China	Cohort	CHR: 400
60	Subclinical Symptoms and Prodromal Psychosis Project	Pereira (2021)	COX-2 pathway is upregulated in ultra-high risk individuals for psychosis	Brazil	Cross-sectional	CHR=67, Control: 55

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
61	ShangHai at Risk for Psychosis research programme	Zhang (2021)	Further evidence that antipsychotic medication does not prevent long-term psychosis in higher-risk individuals	China	Cohort	CHR: 300
62	Subclinical Symptoms and Prodromal Psychosis Project	Talib (2021)	Increased PLA(2) activity in individuals at ultra-high risk for psychosis	Brazil	Cross-sectional	CHR: 85, Control: 65
63	Subclinical Symptoms and Prodromal Psychosis Project	Nogueira (2021)	Influence of migration on the thought process of individuals at ultra-high risk for psychosis	Brazil	Cross-sectional	CHR: 42
64	Psychotic disorders research program	Uçok (2021)	Relationship of negative symptom severity with cognitive symptoms and functioning in subjects at ultra-high risk for psychosis	Turkey	Cross-sectional	CHR: 107
65	ShangHai at Risk for Psychosis research programme	Zhang (2021)	Subtypes of Clinical High Risk for Psychosis that Predict Antipsychotic Effectiveness in Long-Term Remission	China	Cohort	CHR: 289
66	Adolescent Program of Neuropsychiatric and Imaging Study	Kegeles (2020)	An imaging-based risk calculator for prediction of conversion to psychosis in clinical high-risk individuals using glutamate (1)H MRS	Mexico	Cohort	CHR: 19
67	ShangHai at Risk for Psychosis research programme	Collin (2020)	Brain functional connectivity data enhance prediction of clinical outcome in youth at risk for psychosis	China	Cohort	CHR: 137
68	Subclinical Symptoms and Prodromal Psychosis Project	Freitas (2020)	Childhood maltreatment in individuals at risk of psychosis: Results from the Brazilian SSAPP cohort	Brazil	Cross-sectional	CHR: 87, Control: 115
69	ShangHai at Risk for Psychosis research programme	Cui (2020)	Cognitive dysfunction in a psychotropic medication-naïve, clinical high-risk sample from the ShangHai-At-Risk-for-Psychosis (SHARP) study: Associations with clinical outcomes	China	Cohort	CHR: 57
70	Psychotic disorders research program	Togay (2020)	Lower prepulse inhibition in clinical high-risk groups but not in familial risk groups for psychosis compared with healthy controls	Turkey	Cross-sectional	CHR: 53, Control: 28
71	ShangHai at Risk for Psychosis research programme	Zhang (2020)	Poor functional recovery is better predicted than conversion in studies of outcomes of clinical high risk of psychosis: insight from SHARP	China	Cohort	CHR: 300
72	ShangHai at Risk for Psychosis research programme	Zhang (2020)	Real-world effectiveness of antipsychotic treatment in psychosis prevention in a 3-year cohort of 517 individuals at clinical high risk from the SHARP (ShangHai At Risk for Psychosis)	China	Cohort	CHR: 517

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
73	Subclinical Symptoms and Prodromal Psychosis Project	Ayoub (2020)	Relationship Between Symptomatic Dimensions and Global Functioning of Non-Help-Seeking Individuals at Risk for Psychosis	Brazil	Cross-sectional	CHR: 83, Control: 66
74	ShangHai at Risk for Psychosis research programme	Tang (2019)	Altered Cellular White Matter But Not Extracellular Free Water on Diffusion MRI in Individuals at Clinical High Risk for Psychosis	China	Cohort	CHR: 50, Control: 50
75	Subclinical Symptoms and Prodromal Psychosis Project	Loch (2019)	Hearing spirits? Religiosity in individuals at risk for psychosis-Results from the Brazilian SSAPP cohort	Brazil	Cross-sectional	CHR: 79, Control: 110
76	Recognition Program and Intervention in Risk Mental States	Zeni-Graiff (2019)	Peripheral levels of superoxide dismutase and glutathione peroxidase in youths in ultra-high risk for psychosis: a pilot study	Brazil	Cross-sectional	CHR: 13, Control: 29
77	ShangHai at Risk for Psychosis research programme	Li (2018)	A comparison of conversion rates, clinical profiles and predictors of outcomes in two independent samples of individuals at clinical high risk for psychosis in China	China	Cohort	CHR: 100
78	ShangHai at Risk for Psychosis research programme	Zhang (2018)	Duration of untreated prodromal symptoms in a Chinese sample at a high risk for psychosis: demographic, clinical, and outcome	China	Cohort	CHR: 391
79	ShangHai at Risk for Psychosis research programme	Zhang (2018)	Isolated hallucination is less predictive than thought disorder in psychosis: Insight from a longitudinal study in a clinical population at high risk for psychosis	China	Cohort	CHR: 511
80	Psychotic disorders research program	Soyata (2018)	Relationship of obsessive-compulsive symptoms to clinical variables and cognitive functions in individuals at ultra high risk for psychosis	Turkey	Cross-sectional	CHR: 84
81	Subclinical Symptoms and Prodromal Psychosis Project	Loch (2017)	Poverty, low education, and the expression of psychotic-like experiences in the general population of São Paulo, Brazil	Brazil	Cross-sectional	CHR: 30.8%
82	Recognition Program and Intervention in Risk Mental States	Maurya (2017)	Shorter leukocyte telomere length in patients at ultra high risk for psychosis	Brazil	Cross-sectional	CHR: 22, Control: 88
83	Tongji Hospital	Shi (2017)	Systemic Therapy for Youth at Clinical High Risk for Psychosis: A Pilot Study	China	RCT	CHR: 26
84	ShangHai at Risk for Psychosis research programme	Zhang (2017)	Two-year follow-up of a Chinese sample at clinical high risk for psychosis: timeline of symptoms, help-seeking and conversion	China	Cohort	CHR: 117

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
85	ShangHai at Risk for Psychosis research programme	Zhang (2016)	Faux pas recognition performance in a help-seeking population at clinical high risk of psychosis	China	Cohort	CHR: 50, Control: 52
86	Recognition Program and Intervention in Risk Mental States	Zeni-Graiff (2016)	Peripheral immuno-inflammatory abnormalities in ultra-high risk of developing psychosis	Brazil	Cross-sectional	CHR: 12, Control: 16
87	Recognition Program and Intervention in Risk Mental States	Zanini (2015)	Abnormalities in sleep patterns in individuals at risk for psychosis and bipolar disorder	Brazil	Cross-sectional	CHR: 20, Control: 22
88	Recognition Program and Intervention in Risk Mental States	Santoro (2015)	Gene expression analysis in blood of ultra-high risk subjects compared to first-episode of psychosis patients and controls	Brazil	Cross-sectional	CHR: 22, FEP: 66, Control: 67
89	Psychotic disorders research program	Üçok (2015)	History of childhood physical trauma is related to cognitive decline in individuals with ultra-high risk for psychosis	Turkey	Cross-sectional	CHR: 53
90	ShangHai at Risk for Psychosis research programme	Tang (2014)	Prolonged cortical silent period among drug-naive subjects at ultra-high risk of psychosis	China	Cross-sectional	CHR: 16, SQZ=17, Control: 28
91	Psychotic disorders research program	Üçok (2013)	Cognitive deficits in clinical and familial high risk groups for psychosis are common as in first episode schizophrenia	Turkey	Cross-sectional	CHR: 52, FEP: 53, Control: 30
92	Adolescent Program of Neuropsychiatric and Imaging Study	de la Fuente-Sandoval (2013)	Striatal glutamate and the conversion to psychosis: a prospective 1H-MRS imaging study	Mexico	Cohort	CHR: 19, Control: 26
93	Psychotic disorders research program	Sahin (2013)	The history of childhood trauma among individuals with ultra high risk for psychosis is as common as among patients with first-episode schizophrenia	Turkey	Cross-sectional	CHR: 41, FEP: 83, Control: 69
94	ShangHai at Risk for Psychosis research programme	Zhang (2018)	Progressive decline of cognition during the conversion from prodrome to psychosis with a characteristic pattern of the theory of mind compensated by neurocognition	China	Cohort	CHR: 83
95	Schizophrenia Research Foundation	Sicotte (2024)	Similar and different? A cross-cultural comparison of the prevalence, course of and factors associated with suicidal thoughts and behaviors in first-episode psychosis in Chennai, India and Montreal, Canada	India	Cohort	FEP: 168
96	Study in Pakistan	Qurashi (2023)	A randomised double-blind placebo-controlled trial of minocycline and/or omega-3 fatty acids added to treatment as usual for at risk Mental States: The NAYAB study	Pakistan	RCT	CHR: 326

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
97	Schizophrenia Research Foundation	Nair (2023)	Patient-reported outcome measures in early psychosis: Evaluating the psychometric properties of the single-item self-reported health and self-reported mental health measures in Chennai, India and Montreal, Canada	India	Cohort	FEP: 188
98	Tunisian early intervention of psychosis project	Fekih-Romdhane (2023)	Suicide risk among individuals at Ultra-High Risk (UHR) of psychosis in a developing North African country: A 12-month naturalistic prospective cohort study from the TRIP project	Tunisia	Cohort	CHR: 35, FEP: 33
99	Schizophrenia Research Foundation	Xavier (2023)	Trust of patients and families in mental healthcare providers and institutions: a cross-cultural study in Chennai, India, and Montreal, Canada	India	Cohort	FEP: 168, Family: 168
100	Psychiatric hospital in Thailand	Meepring (2023)	Evaluating the efficacy of the Thai Health Improvement Profile intervention for preventing weight gain in people with early stage psychosis: A randomized controlled trial	Thailand	RCT	FEP: 106
101	Schizophrenia Research Foundation	Iyer (2023)	Differential Trajectories of Delusional Content and Severity over 2 Years of Early Intervention for Psychosis: Comparison between Chennai, India, and Montreal, Canada	India	Cohort	FEP: 168
102	Schizophrenia Research Foundation	Mustafa (2023)	Subjective quality of life among first-episode psychosis patients in Chennai, India and Montreal, Canada	India	Cohort	FEP: 168
103	Beijing Anding Hospital	Zhao (2024)	EMDR versus waiting list in individuals at clinical high risk for psychosis with post-traumatic stress symptoms: A randomized controlled trial.	China	RCT	CHR: 57
104	Subclinical Symptoms and Prodromal Psychosis Project	D Medeiros (2024)	Cannabis use influences disorganized symptoms severity but not transition in a cohort of non-help-seeking individuals at-risk for psychosis from Sao Paulo, Brazil	Brazil and Chile	Cohort	CHR: 109, Control: 197
105	Study in Pakistan	Husain (2024)	Demographic and clinical correlates of suicidal ideation in individuals with at-risk mental state (ARMS): A study from Pakistan	Pakistan	Cross-sectional	CHR: 326
106	ShangHai at Risk for Psychosis research programme	Zhang (2023)	Duration of Untreated Prodromal Psychosis and Cognitive Impairments	China	Cohort	CHR: 506
107	Longitudinal study in early detection of psychosis	Nieto (2023)	The effect of stressful life events on the risk for psychosis: differences between Mexican at clinical and familial high risk	Mexico	Cross-sectional	CHR: 43, Control: 35
108	ShangHai at Risk for Psychosis research programme	Zhang (2023)	Duration of untreated prodromal psychosis among individuals with clinical high risk for psychosis.	China	Cohort	CHR: 704

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
109	ShangHai at Risk for Psychosis research programme	Zhang (2023)	Changes in inflammatory markers in clinical high risk of developing psychosis.	China	Cohort	CHR: 394, Control: 100
110	Psychiatric Hospital in Cape Town	Emsley (2023)	Antipsychotic treatment effects and structural MRI brain changes in schizophrenia.	South Africa	Cohort	FEP: 99, Control: 98
111	National Insitute of Mental Health and Neuroscience[3]	Sadath (2017)	Does group intervention have benefits on expressed emotion and social support in carers of persons with first episode psychosis?	India	Quasi-experimental	Family: 59
112	Medical College in Nepal	Adhikari (2014)	Electroconvulsive Therapy in First Episode Schizophrenia – Experiences from Nepal	Nepal	Cohort	FEP: 45
113	Central institute in psychiatry in Ranchi	Saddicha (2008)	Metabolic syndrome in first episode schizophrenia — A randomized double-blind controlled, short-term prospective study	India	RCT	FEP: 99
114	Early Psychosis Support Group	Aceituno (2024)	Cost-effectiveness of early intervention in psychosis in low- and middle-income countries: economic evaluation from São Paulo, Brazil	Brazil	Cohort	FEP: 357
115	The Palau Early Psychosis Study	Myles (2007)	The Palau Early Psychosis Study: Distribution of Cases by Level of Genetic Risk	Palau	Cohort	CHR: 300, Control: 104
116	The Palau Early Psychosis Study	Ngiralmau (2005)	Preventive intervention for early psychosis in adolescents-The Palau Youth At Risk Projects	Palau	Cohort	CHR: 299, Control: 94
117	Saint John of God	Chilale (2014)	Duration of Untreated Psychosis and Associated Factors in First Episode Psychosis in Mzuzu in Northern Malawi	Malawi	Cross-sectional	FEP: 140
118	Saint John of God	Kaminga (2018)	Effects of socio-demographic characteristics, premorbid functioning, and insight on duration of untreated psychosis in first-episode schizophrenia or schizophreniform disorder in Northern Malawi	Malawi	Cross-sectional	FEP: 110
119	Saint John of God	Kaminga (2018)	Rate of and time to symptomatic remission in first-episode psychosis in Northern Malawi A STROBE-compliant article	Malawi	Cohort	FEP: 126
120	ShangHai at Risk for Psychosis research programme	Li (2022)	Plasma metabolic alterations and potential biomarkers in individuals at clinical high risk for psychosis	China	Cohort	CHR: 90, Control: 86

N	Program/study	Author (year)	Title	Country	Study type	Study population: n
121	ShangHai at Risk for Psychosis research programme	Re (2021)	Baseline Cortical Thickness Reductions in Clinical High Risk for Psychosis: Brain Regions Associated with Conversion to Psychosis Versus Non-Conversion as Assessed at One-Year Follow-Up in the Shanghai-At-Risk-for-Psychosis (SHARP) Study	China	Cohort	CHR: 152, Control: 130
122	Guangji Hospital	Li (2021)	Enhancing attention and memory of individuals at clinical high risk for psychosis with mHealth technology	China	RCT	CHR: 80
123	Kenya cohort	Mamah (2016)	Characterizing psychosis risk traits in Africa: A longitudinal study of Kenyan adolescents	Kenya	Cohort	CHR: 277
124	ShangHai at Risk for Psychosis research programme	Zhang (2016)	Theory of Mind Impairments in Youth at Clinical High Risk of Psychosis	China	Cohort	CHR: 40, FEP: 62, Control: 42
125	Adolescent Program of Neuropsychiatric and Imaging Study	Reyes-Madrigal (2022)	Striatal glutamate, subcortical structure and clinical response to first-line treatment in first-episode psychosis patients	Mexico	Cohort	FEP: 48

FEP: First-episode psychosis, CHR: Clinical-high risk for psychosis, RCT: Randomized clinical trial, 1,2,3 (superschipts): Different studies were conducted at the same site. UNIFESP: Federal University of Sao Paulo.

Table S7. Setting of implementation of FEP interventions in LMICs.

FEP intervention	Income	Setting	Area	Country capital	Funding
	FEP programs (n=10)				
Schizophrenia Research Foundation	LM	NGO	Urban	No	Canada, USA
All India Institute of Medical Sciences	LM	Tertiary	Urban	No/Yes	UK
Ribeirao Preto Early Intervention in Psy. P.	UM	University	Urban	No	-
Psy. Episode P. of the UNIFESP	UM	University	Urban	No	-
Early Psychosis Support Group	UM	University	Urban	No	-
Early intervention clinic in psychosis*	UM	Tertiary	Urban	Yes	-
A. P. of Neuropsychiatric and Imaging Study*	UM	Tertiary	Urban	Yes	Mexico, USA
Moscow Research Institute of Psychiatry	UM	Health system	Urban	Yes	-
First-Episode Schizophrenia Follow-up Project	UM	University	Urban	Yes	-
Saint John of God Community Services	L	Community	-	No	-
	FEP studies (n=30)				
Christian Medical College	LM	Tertiary	Urban	No	India, UK
NIMHANS in Bangalore[1]	LM	Tertiary	Urban	No	No funding
NIMHANS in Bangalore[2]	LM	Tertiary	Urban	No	No funding
NIMHANS in Bangalore[3]	LM	Tertiary	Urban	No	-
Silver Mind Hospital	LM	NGO	Urban	No	India
Central institute in psychiatry in Ranchi	LM	Tertiary	Urban	No	No funding
Medical College in Nepal	LM	University	Urban	No	No funding
Study in Yogyakarta	LM	-	Urban	No	-
Da Nang Psychiatric Hospital	LM	-	Urban	No	USA
Ten-site study in China	UM	University	Urban	-	China
Study in Xuhui and HongKou	UM	Community	Urban	No	China
Study in Shanghai	UM	Tertiary	-	No	China
Tongde Hospital	UM	Tertiary	Urban	No	China
Beijing Anding Hospital	UM	Tertiary	Urban	Yes	China
Suzhou Guangji Hospital	UM	Tertiary	Urban	No	-
Study in Jilin	UM	-	-	No	HK
Study in China	UM	-	-	-	HK
Study in Shanghai and Changsha	UM	Tertiary	Urban	No	USA
Second Xiangya Hospital	UM	Tertiary	Urban	No	China
Psychiatric Hospital in Thailand	UM	Tertiary	Rural	-	Thailand
N. I. of Psychiatry Ramon de la Fuente Muñiz	UM	Tertiary	Urban	Yes	Mexico
Nervous System Research Center	UM	Private center	Urban	Yes	PI
Bolu Community Mental Health Center	UM	Community	Urban	No	-
University Hospital in Turkey	UM	University	Urban	-	-
Roozbeh Hospital	LM	-	-	Yes	-
University College Hospital in Nigeria	LM	University	Urban	No	-
Federal Neuro-Psychiatric Hospital in Benin	LM	-	-	No	-
Study in Ibadan and Cape Town	LM/UM	-	Urban	No/Yes	NEPAD, SA, PI
Butabika National Referral Mental Hospital	L	Tertiary	Urban	Yes	USA
Psychiatric Hospital in Cape Town	UM	University	-	Yes	NEPAD, SA, PI

Psy: Psychosis, A: Adolescent, P: Program, UNIFESP: Federal University of Sao Paulo, NIMHAN: National Institute of Mental Health and Neurosciences, N: National, I: Institute, NGO: Non-Governmental Organization, UK: United Kingdom, USA: United States of America, HK: Hong Kong, NEPAD: New Partnership for Africa's Development, SA: South Africa, PI: Pharma industry, L: Low-income country, LM: Lower middle-income country, UM: Upper middle-income country. 1,2,3 (superscripts): Different studies were conducted at the same site.
*Program for individuals at CHR and with FEP.

Table S8. Eligibility criteria in FEP interventions in LMICs.

FEP intervention	Inclusion criteria**			Exclusion criteria**	
	Diagnosis (Diagnostic system)	FEP definition	Age (years)	Physical disease	Neuro-psychiatric diseases
		FEP programs (n=10)			
Schizophrenia Research Foundation	Non-affective and affective psychosis (DSM-IV)	Duration of antipsychotic medication (< 1 month)	16-35	-	Mental retardation, neurological disorder and substance use disorder
All India Institute of Medical Sciences	Non-affective and affective psychosis (ICD-10)	First treatment contact	16-45	-	Mental retardation, neurological disorder and substance use disorder
Ribeirao Preto Early Intervention in Psy. P.	Non-affective, affective, and substance-induced psychosis (ICD-10)	Duration of psychosis (<5 years)	12-65.	-	-
Psy. Episode P. of the UNIFESP	Non-affective psychosis (DSM-IV)	Duration of antipsychotic medication (<3 months)	-	-	-
Early Psychosis Support Group	Non-affective, affective, and substance-induced psychosis (DSM-IV)	Duration of antipsychotic medication (first time)	16-40	-	Psychotic symptoms due to a general medical condition, intellectual disability, and acute intoxication.
Early intervention clinic in psychosis*	Non-affective and affective psychosis (ICD-10)	Duration of psychosis (<6 months)	17-35	-	-
A. P. of Neuropsychiatric and Imaging Study*	Non-affective psychosis (DSM-IV)	Duration of antipsychotic medication (first time)	-	Serious medical illness	Suicidal ideation, psychomotor agitation, neurologic illness, substance abuse, and traumatic brain injury
Moscow Research Institute of Psychiatry	Non-affective psychosis (ICD-10)	Duration of psychosis (<5 years)	-	-	-
First-Episode Schizophrenia Follow-up Project	Schizophrenia (DSM-IV)	Duration of antipsychotic medication (<15 days)	18-35	Serious medical illness	History of affective or non-affective psychosis
Saint John of God Community Services	Non-affective, affective, and substance-induced psychosis (DSM-IV)	Duration of antipsychotic medication (First time)	18-65	-	Organic brain syndrome, drug abuse disorder, and learning disability
		FEP studies (n=30)			
Christian Medical College	Schizophrenia (DSM-IV)	First treatment contact	-	-	Neurological, mood, and substance use disorders

FEP intervention	Inclusion criteria**			Exclusion criteria**	
	Diagnosis (Diagnostic system)	FEP definition	Age (years)	Physical disease	Neuro-psychiatric diseases
NIMHANS in Bangalore[1]	Non-affective psychosis (DSM-IV)	Duration of antipsychotic medication (first time)	-	-	Substance use disorders, organic brain disorder and mental retardation.
NIMHANS in Bangalore[2]	Schizophrenia(ICD-10)	Duration of psychosis (< 2 years)	-	Neurosurgical or neurological conditions	Mental retardation, electroconvulsive therapy in the past 6 months
NIMHANS in Bangalore[3]	Non-affective psychosis (-)	Duration of psychosis (< 5 years)	-	-	Affective psychosis
Silver Mind Hospital	Schizophrenia (DSM-IV)	-	-	Serious medical condition	Substance abuse, alcoholism and neurological disorder
Central institute in psychiatry in Ranchi	Schizophrenia (DSM-IV)	Duration of antipsychotic medication (first time)	-	Serious medical condition, history of diabetes or hypertension, family history of diabetes or hypertension	Psychiatric comorbidity, alcohol and substance abuse dependence.
Medical College in Nepal	Schizophrenia (ICD-10)	"Certain evidence that it was first episode schizophrenia"	-	Medical conditions that led to psychotic symptoms.	history of psychotic spectrum disorders, bipolar disorders, and alcohol and substance abuse.
Study in Yogyakarta	Non-affective psychosis (ICD-10)	Duration of psychosis (< 1 year)	-	-	Affective disorders with psychotic features
Da Nang Psychiatric Hospital	Schizophrenia (ICD-10)	Duration of psychosis (<3 years)	18-30	-	Suicidal ideation
Ten-site study in China	Non-affective psychosis (DSM-IV)	Duration of psychosis (<5 years)	16-50, 18-50	Serious medical condition	-
Study in Xuhui and HongKou	Schizophrenia (DSM-IV)	-	18-45	Physical disease	Psychiatric disorder other than schizophrenia
Study in Shanghai	Schizophrenia (DSM-IV)	Duration of psychosis (< 5 years)	18-60	Physical disease	Psychiatric disorder other than schizophrenia
Tongde Hospital	Schizophrenia (DSM-IV)	Duration of antipsychotic medication (first time)	-	Physical disease	Psychiatric disorder other than schizophrenia
Beijing Anding Hospital	Schizophrenia (DSM-IV)	Duration of psychosis (< 3 years)	16-45	Serious physical illness	Comorbid mental diagnosis
Suzhou Guangji Hospital	Schizophrenia (Chinese Medical Association's criteria for schizophrenia)	First treatment contact	-	Serious medical illness	-

FEP intervention	Inclusion criteria**			Exclusion criteria**	
	Diagnosis (Diagnostic system)	FEP definition	Age (years)	Physical disease	Neuro-psychiatric diseases
Study in Jilin	Non-affective psychosis (DSM-IV)	Duration of psychosis (<5 years)	18-60	-	Organic brain disorder, learning disability and mental instability.
Study in China	Non-affective psychosis(DSM-IV)	Duration of psychosis (<5 years)	18-64	-	Comorbid mental illness and learning disability
Study in Shanghai and Changsha	Non-affective psychosis (DSM-IV)	Duration of antipsychotic medication (<24 weeks)	15-40	Unstable medical illness	Major depression, suicidal ideation, and substance abuse (other than cannabis)
Second Xiangya Hospital	Schizophrenia (DSM-IV)	Duration of antipsychotic medication (first time)	18-50	Diabetes mellitus, cardiovascular diseases, cancer, pregnancy or lactating	Substance use disorder, intellectual disability, autism spectrum disorder, dementia or severe cognitive impairment
Psychiatric Hospital in Thailand	Non-affective and affective psychosis (NR)	Duration of psychosis (<5 years)	>=18	-	Learning disability, substance misuse disorders, or organic brain diseases.
N. I. of Psychiatry Ramon de la Fuente Muñiz	Non-affective and affective psychosis (DSM-IV)	-	16-50	-	Substance abuse
Nervous System Research Center	Schizophrenia (DSM-IV)	Duration of psychosis (<5 years)	18-35	-	Psychiatric comorbidity (except substance abuse/ dependence)
Bolu Community Mental Health Center	Schizophrenia (DSM-IV)	Duration of psychosis (<5 years)	-	-	Mental retardation, severe neurological disease and ongoing alcohol or substance abuse
University Hospital in Turkey	Schizophrenia (DSM-IV)	-	-	-	-
Roozbeh Hospital	Non-affective and affective psychosis (DSM-IV)	-	-	-	-
University College Hospital in Nigeria	Schizophrenia (ICD-10)	First treatment contact	18-65	-	-
Federal Neuro-Psychiatric Hospital in Benin	Affective and non-affective psychosis (Mini-International Neuropsychiatric Interview)	First treatment contact	18-64	-	-
Study in Ibadan and Cape Town	Non-affective psychosis (DSM-IV)	Duration of antipsychotic medication (< 1 month)	16-45	Serious medical condition	Mental retardation or current substance abuse
Butabika National Referral Mental Hospital	Non-affective and affective psychoses (-)	Duration of antipsychotic medication (First time)	18-60	Human immunodeficiency virus/acquired immunodeficiency syndrome and syphilis	Substance abuse
Psychiatric Hospital in Cape Town	Non-affective and affective psychosis (DSM-IV)	First treatment contact	16-45	A serious or unstable medical condition	Substance abuse or dependence, or substance induced psychotic disorder

FEP intervention	Inclusion criteria**			Exclusion criteria**	
	Diagnosis (Diagnostic system)	FEP definition	Age (years)	Physical disease	Neuro-psychiatric diseases

Psy: Psychosis, A: Adolescent, P: Program, UNIFESP: Federal University of Sao Paulo, NIMHAN: National Institute of Mental Health and Neurosciences, N: National, I: Institute, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICD-10: International Classification of Diseases, Tenth Revision; 1,2,3 (superscripts): Different studies were conducted at the same site.

*Program for individuals at CHR and with FEP, **Studies may include other inclusion or exclusion criteria.

Table S9. Setting of implementation of multicomponent interventions for individuals at CHR in LMICs.

CHR intervention	Income	Facility	Setting	Country capital	Funding
CHR programs (n=8)					
Evaluation and Follow-up of Adolescent and Young Adults	UM	University	Urban	No	-
Recognition P. and Intervention in Risk Mental States	UM	University	Urban	No	Brazil
Early Intervention Clinic in Psychosis*	UM	Tertiary	Urban	Yes	-
A. P. of Neuropsychiatric and Imaging Study*	UM	Tertiary	Urban	Yes	Mexico, USA
Shanghai at Risk for Psychosis Project**	UM	Tertiary	Urban	No	China, USA
Psychotic Disorders Research Program	UM	Tertiary	Urban	Yes	Turkey
Clinical High-Risk Program in Tunisia	LM	Tertiary	Urban	Yes	USA
Tunisian Early Intervention of Psychosis Project	LM	Tertiary	Urban	Yes	-
CHR studies (n=8)					
Subclinical Symptoms and Prodromal Psychosis Project	UM	University	Urban	No	Brazil
Longitudinal Study in Early Detection of Psychosis	UM	Tertiary	Urban	Yes	Mexico
Palau Early Psychosis Study	UM	Community	-	-	USA
Study in Tongji University	UM	University	Urban	No	China
Beijing Anding Hospital	UM	Tertiary	Urban	Yes	China
Suzhou Guangji Hospital¥	UM	Tertiary	Urban	No/No	USA
Study in Pakistan	LM	-	-	No	SMRI
Study in Kenya	LM	Community	Rural	No	USA

A: Adolescent, P: Program, USA: United States of America, SMRI: Stanley Medical Research Institute. LM: Lower middle-income country, UM: Upper middle-income country.
*Program for individuals at CHR and with FEP, ** Includes the Shanghai at Risk for Psychosis extended program, ¥ In collaboration with Shanghai mental health center.

Table S10. Eligibility criteria in CHR interventions in LMICs.

CHR intervention	Inclusion criteria***		Exclusion criteria***	
	Diagnosis	Age	Physical disease	Neuropsychiatric diseases
		CHR programs (n=8)		
Evaluation and Follow-up of Adolescent and Young Adults	Structured Interview of Psychosis-risk Syndromes	14-30	-	-
Recognition P. and Intervention in Risk Mental States	Comprehensive Assessment of At-Risk Mental States	14-26, 14-44	Acute or chronic medical condition	Suicide risk, subject with autism spectrum disorders, current substance use disorder, organic brain disease and diagnoses of bipolar or psychotic disorder.
Early Intervention Clinic in Psychosis*	Duration of attenuated psychotic symptoms (<6 months)	17-35	-	-
A. P. of Neuropsychiatric and Imaging Study*	Structured Interview of Psychosis-risk Syndromes	-	Medical illness	Current substance use, substance dependence, suicide risk, any mental disorders, neurological illness, and psychomotor agitation.
Shanghai at Risk for Psychosis Project**	Structured Interview of Psychosis-risk Syndromes	15-45, 14-35, 13-45	Severe somatic disease	Mental retardation, substance abuse, dementia, and clinical mental disorders
Psychotic Disorders Research Program	Comprehensive Assessment of At-Risk Mental States	18-35	Severe medical condition, and considerable head injury.	Mental retardation, history of psychosis, neurological illness and current alcohol and substance abuse.
Clinical High-Risk Program in Tunisia	Comprehensive Assessment of At-Risk Mental States	14-26	-	-
Tunisian Early Intervention of Psychosis Project	Comprehensive Assessment of At-Risk Mental States	16-35	Serious medical condition (neurological illness)	Intellectual disability, head injury and transitioning to psychosis during follow-up
		CHR studies (n=8)		
Subclinical Symptoms and Prodromal Psychosis Project	Structured Interview of Psychosis-risk Syndromes	18-30	-	Schizophrenia
Longitudinal Study in Early Detection of Psychosis	Comprehensive Assessment of At-Risk Mental States	13-40	Medical condition	Intellectual disability, head injury, neurological condition, organic psychosis, psychotic spectrum disorder
Palau Early Psychosis Study	Youth Psychosis At Risk Questionnaire	14-19	-	-
Study in Tongji University	Structured Interview of Psychosis-risk Syndromes	-	-	-
Beijing Anding Hospital	Structured Interview of Psychosis-risk Syndromes	18-35	-	Diagnosis of a psychotic disorder or brain injury
Suzhou Guangji Hospital¥	Structured Interview of Psychosis-risk Syndromes	14-45	Human immunodeficiency virus infection	Psychiatric treatment, mental retardation, psychoses, alcohol or drug dependence, central nervous system disorder, traumatic brain injury, visual or hearing impairment
Study in Pakistan	Structured Interview of Psychosis-risk Syndromes	16-35	Inflammatory conditions; hematologic, hepatic, renal, neurologic or other medical disorder	Psychotic illness, use of antipsychotics or mood stabilizers, organic brain diseases, learning disability and substance use disorders
Study in Kenya	Structured Interview of Psychosis-risk Syndromes, Washington Early recognition Center Affectivity and Psychosis Screen	14-20	-	Psychotic disorder

A: Adolescent, P: Program

*Program for individuals at CHR and with FEP. ** Includes the Shanghai at Risk for Psychosis extended program. ¥ In collaboration with Shanghai mental health center. ***The studies may include other inclusion or exclusion criteria.

Table S11. EIP components offered to individuals with FEP in LMICs.[***]

FEP intervention	Guideline-based components[**,¥]								Additional components[¥]	Cultural adaptation	Follow-up (months)
	Antipsychotic medication	Patient psychoeducation	Family education and support	CBT	Supporting health	Case management	Supported employment	Other			
					Programs (n=9)						
Schizophrenia Research Foundation	First and second gen.	Present	Family psychoeducation and individual family intervention	Present	-	Assertive case management	Present	Community outreach, annual comprehensive assessment, family involvement in assessment	Cognitive training, impatient care, yoga, multidisciplinary team	Psychosocial interventions were adapted to suit the Indian cultural setting	24
All India Institute of Medical Sciences	Present	Present	Family psychoeducation, counseling, and therapy	Present	Monitoring weight, glucose, lipids, etc.	-	Vocational therapy	Annual comprehensive assessment	Supportive therapy, occupational therapy	-	12
Ribeirao Preto Early Intervention in Psy. P.	First and second gen.	Weekly Psychoeducation group meeting	Family intervention based on systemic family therapy	-	Monitoring weight, glucose and lipids; lifestyle intervention.	-	-	Annual comprehensive assessment, substance abuse treatment,	Teleconsultation, occupational therapy, multidisciplinary team	Measurements were adapted and validated for Brazil	24
Psy. Episode P. of the UNIFESP	Present	Psychoeducation group	Psychoeducational multifamily intervention	-	-	-	-	-	Supportive therapy	Development of culturally sensitive interventions	24
Early Psychosis Support Group	Second gen.	Present	Systemic oriented interventions with family psychoeducation	-	-	-	Employment support	Educational support, annual comprehensive assessment	Psychological therapy (Not specified)	-	36
Early Intervention Clinic in Psychosis*	Second gen.	Present	-	Present	-	-	-	-	Supportive therapy, brief hospitalization, cognitive rehabilitation, multidisciplinary team, occupational therapy	-	24
A. P. of Neuropsychiatric and Imaging Study*	Second gen.	Present	Systemic family therapy	Present	Routine laboratory tests, Evaluation by other specialists	Present		-	Brain scan, telephone assistance, impatient care	-	Open

FEP intervention	Guideline-based components**,¥								Additional components¥	Cultural adaptation	Follow-up (months)
	Antipsychotic medication	**Patient psychoeducation**	**Family education and support**	**CBT**	**Supporting health**	**Case management**	**Supported employment**	**Other**			
Moscow Research Institute of Psychiatry	Second gen.	Problem solving techniques, social skills training	Individualized family intervention	-	-	Individualized case management	-	-	Supportive therapy, multidisciplinary team	-	-
First-Episode Schizophrenia Follow-up Project	First and second gen.	Present	Present	-	-	-	-	Annual comprehensive assessment	Group psychotherapy (non-CBT)	-	58
Saint John of God Community Services	First and second gen.	-	-	-	-	-	-	Outreach	Monitoring by telephone	-	18
					Studies (n=30)						
Christian Medical College	First and second gen.	Present	-	Present	-	-	-	Annual comprehensive assessment	Supportive therapy, occupational therapy	Use of the Tamil versions of the measurements	60
NIMHANS in Bangalore[1]	Present	Present	-	-	-	-	-	-	-	Measurement tools were modified to suit the Indian setting	12
NIMHANS in Bangalore[2]	Present	Present	Present	-	-	-	-	-	**Home-based cognitive training**	-	6
NIMHANS in Bangalore[3]	Present	-	**Family psychoeducation**	-	-	-	-	-	-	-	3
Silver Mind Hospital	Second gen.	-	-	-	-	-	-	-	Psychosocial rehabilitation program, multidisciplinary team	-	120
Central Institute in Psychiatry in Ranchi	**First and second gen**.	-	-	-	Monitoring of weight, glucose, lipids, etc.	-	-	-	-	-	1.5
Medical College in Nepal	Present	-	-	-	-	-	-	-	**Electroconvulsive therapy**	-	12
Study in Yogyakarta	Present	Psychoeducation concerning schizophrenia	**Psychoeducation concerning schizophrenia**	-	-	-	-	-	-	Psychoeducation program was culturally adapted	6

FEP intervention	Guideline-based components**,¥								Additional components¥	Cultural adaptation	Follow-up (months)
	Antipsychotic medication	Patient psychoeducation	Family education and support	CBT	Supporting health	Case management	Supported employment	Other			
Da Nang Psychiatric Hospital	Present	Present	**Family psychoeducation**	-	-	-	-	-	-	Cultural modifications to the program and involvement of family members	6
Ten-site study in China	First and second gen.	**Psychoeducation, skills training**	**Family intervention**	**Present**	-	-	-	-	**Skills training**	-	12
Study in Xuhui and HongKou	**First and second gen.**	-	-	-	-	**Present**	-	-	-	-	24
Study in Shanghai	Present	Social skills individualized training	**Family psychoeducation**	-	-	-	-	-	-	-	18
Tongde Hospital	Second gen.	-	-	-	-	-	-	-	**Cognitive training**	-	1
Beijing Anding Hospital	Present	-	-	**Brief CBT**	-	Case management (psychological health education and social support)	-	-	-	-	12
Suzhou Guangji Hospital	Present	-	**Family counselling**	-	-	-	-	-	-	Use of their own diagnostic system of mental disorders. Adaptations to measurement scales	18
Study in Jilin[1]	First and second gen.	**Psychoeducation group (Mindfulness-based)**	-	-	Referrals and treatments for specialized care	-	-	Home visits, psychosocial needs assessment	Psychological therapy (Not specified)	Intervention was adapted in Chinese psychotic patients, the scales were validated Chinese versions.	18
Study in China	First and second gen.	**Psychoeducation group (Mindfulness-based)**	-	-	-	-	-	-	Psychotherapy (Not specified), finance assistance	Intervention was adapted in Chinese psychotic patients, the scales were validated Chinese versions.	24
Study in Shanghai and Changsha	Second gen.	Present	-	-	-	-	-	-	-	-	12

FEP intervention	Guideline-based components**,¥								Additional components¥	Cultural adaptation	Follow-up (months)
	Antipsychotic medication	Patient psychoeducation	Family education and support	CBT	Supporting health	Case management	Supported employment	Other			
Second Xiangya Hospital	Second gen.	-	-	-	Anthropometric measurements (weight and height), physical examination, and lab tests.	-	-	-	-	-	2
Psychiatric Hospital in Thailand	Present	-	-	-	**Evaluation of physical Health, anthropometric measurements, lifestyle change intervention**	-	-	-	Brief non-specific counselling,	-	12
N. I. of Psychiatry Ramon de la Fuente Muñiz	Present	**Problem solving, improving communication skills**	**Family and social relations**	-	-	-	-	-	-	-	12
Nervous System Research Center	First and second gen.	-	-	-	Physical health indicators, comprehensive laboratory tests.	-	-	Annual comprehensive assessment	-	-	60
Bolu Community Mental Health Center	Present	-	-	-	-	-	-	-	**Interpersonal group psychotherapy**, Painting	-	6
University Hospital in Turkey	Present	-	**Family psychoeducation**	-	-	-	-	-	-	-	2.3
Roozbeh Hospital	Second gen.	-	**Family psychoeducation**	-	-	-	-	Annual comprehensive assessment	**Monitoring by telephone**	Use of Persian version of measurement tools	24
University College Hospital in Nigeria	First and second gen.	-	-	Present	-	-	-	-	Inpatient care, social skills training	-	12
Federal Neuro-Psychiatric Hospital in Benin	Present	-	-	-	-	-	-	**Short message service reminders**	-	-	6
Study in Ibadan and Cape Town	**First gen**.	Present	-	-	Measurement of weight, height and waist circumference	-	-	**Home visits**	-	-	12

FEP intervention	Guideline-based components**,¥								Additional components¥	Cultural adaptation	Follow-up (months)
	Antipsychotic medication	**Patient psychoeducation**	**Family education and support**	**CBT**	**Supporting health**	**Case management**	**Supported employment**	**Other**			
Butabika National Referral Mental Hospital	First and second gen.	Individual psychoeducation	Family group psychoeducation	-	-	-	-	-	-	-	-
Psychiatric Hospital in Cape Town	First gen.	Patient psychoeducation	Family psychoeducation, family therapy	-	-	-	-	Substance abuse treatment	-	-	24

Psy: Psychosis, A: Adolescent, P: Program, UNIFESP: Federal University of Sao Paulo, NIMHAN: National Institute of Mental Health and Neurosciences, N: National, I: Institute, CBT: Cognitive-behavioral therapy, Gen: Generation; 1,2,3 (superscripts): Different studies were conducted at the same site.

*Program for individuals at CHR and with FEP, **"Psychiatric management" was considered as part of "clinical evaluation" and "antipsychotic medication". *** "Present" is placed in the table when the service provides the component. If further information is available, it is described. ¥Components in bold indicated evaluated component.

Table S12. EIP components offered to individuals at CHR in LMICs

CHR intervention	Guideline-based components***,¥¥							Additional components¥¥	Cultural adaptation	Follow-up (months)
	Comprehensive assessment	Assessment by a specialist	CBT	Treatment of comorbidities	Prevention of functional deficits	Monitoring by a specialist	Monitoring for up to 3 years			
CHR programs (n=8)										
Evaluation and Follow-up of Adolescent and Young Adults	SIPS, SOPS	Staff trained to diagnose CHR	-	-	-	-	-	Active engagement	-	-
Recognition P. and Intervention in Risk Mental States	CAARMS	Present	Present	Present	-	Present	Present	-	-	Open
Early Intervention Clinic in Psychosis*	Present	Evaluation by psychiatrists	-	-	-	-	-	-	-	24
A. P. of Neuropsychiatric and Imaging Study*	SIPS	Employees receive standardized training to administer SIPS	Present	Present	-	Present	Present	Psychoeducation, Case management, Brain scan, Routine laboratory tests, Telephone assistance, Systemic family therapy, Evaluation by other specialists	-	Open
Shanghai at Risk for Psychosis Project**	SIPS	Evaluation by specialized staff	-	Use of antidepressants	-	Present	Present	Antipsychotic medication, Psychotherapy, Telephone monitoring	Use of the Chinese version of the SIPS	Open
Psychotic Disorders Research Program	CAARMS	Evaluation by a senior psychiatrist	-	Treatment with anti-depressants, Substance abuse program	-	-	-	Omega-3 fatty acids Use of antipsychotics	Use of the Turkish version of the scales	-
Clinical High-Risk Program in Tunisia	CAARMS	Evaluation by a assessment team	Present	Treatment with anxiolytics and anti-depressants	Cognitive remediation training	Present	-	Active engagement, supportive therapy, psychoeducation, and omega-3 fatty acids.	-	6
Tunisian Early Intervention of Psychosis Project	CAARMS	Extensive clinical assessment	Present	Treatment with anxiolytics and anti-depressants	Support for academic and vocational reintegration, cognitive remediation	Present	-	Use of antipsychotics, interventions with families, crisis management	Use of the Arabic version of the scales	12
CHR studies (n=8)										

CHR intervention	Guideline-based components***,¥¥							Additional components¥¥	Cultural adaptation	Follow-up (months)
	Comprehensive assessment	Assessment by a specialist	CBT	Treatment of comorbidities	Prevention of functional deficits	Monitoring by a specialist	Monitoring for up to 3 years			
Subclinical Symptoms and Prodromal Psychosis Project	PQ, BS, SIPS	Evaluation by experienced psychiatrists	-	-	-	Present	-	-	Use of the Portuguese version of the scales	30
Longitudinal Study in Early Detection of Psychosis	CAARMS	Evaluation by a Specialist	-	-	-	Present	-	-	Spanish version of the Scales	-
Palau Early Psychosis Study	Y-PARQ, K-SADS-PL	Evaluation by an experienced Palau clinician	-	-	-	-	Present	Active engagement	Adaptation of scales to reflect cultural norms in Palu	48
Study in Tongji University	PQ-16, SIPS	Evaluation by trained psychiatrists	-	-	-	-	-	**Systemic therapy, supportive therapy**	Use of the Chinese version of the PQ-16	6
Beijing Anding Hospital	SIPS	Evaluation by a researcher psychiatrist	-	Treatment with antidepressants and mood stabilizers	-	-	-	**Use of antipsychotics, Eye Movement Desensitization and Reprocessing Therapy**	-	3
Suzhou Guangji Hospital¥	SIPS, SOPS	Evaluation by a panel of clinicians	-	-	-	-	-	**Memory and attention in a real time application**	Use of the Chinese version of the SIPS and MATRICS	3
Study in Pakistan	PQ-16, CAAMRS	Evaluation by trained researchers	-	-	-	-	-	**Outreach, Omega-3 fatty acids**	-	12
Study in Kenya	WERCAP, SIPS	-	-	-	-	Multiple follow-up evaluations	-	Psychoeducation	Development of culturally-sensitive scales	20

A: Adolescent, P: Program, CBT: Cognitive-behavioral therapy, SIPS: Structured Interview for Psychosis, SOPS: Scale for the Assessment of Prodromal Symptoms, CAARMS: Comprehensive Assessment of At-Risk Mental States, PQ: Prodromal questionnaire, BS: Basic symptoms scale, Y-PARQ: Youth Psychosis At Risk Questionnaire, K-SAD-PL: Kiddie-Schedule of Affective Disorders and Schizophrenia, Present and Lifetime Version, WERCAP: Washington Early Recognition Center Affectivity and Psychosis Screen, MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia.
*Program for individuals at CHR and with FEP. ** Includes the Shanghai at Risk for Psychosis extended program. ¥ In collaboration with Shanghai mental health center. ***"Present" is placed in the table when the service provides the component. If further information is available, it is described. ¥¥ Components in bold indicated evaluated component

Table S13. Effectiveness of the multicomponent interventions for individuals with FEP in LMICs: Outcomes beyond the predefined list.

FEP intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurements)	Findings	Statistical analysis	QS
			RCTs (n=3)			
N. I. of Psychiatry Ramon de la Fuente Muñiz (Valencia, 2012)	Single site RCT (12 months)	TAU + patient psychoeducation, family psychoeducation (n=39) TAU: Antipsychotic medication (n=34)	Medication compliance (Taking ≥90% of the prescribed medication)	Medication compliance: p<0.01 Intervention: 85.0% Comparator: 67.6%	Chi-square test	3
Ten-site study in China (Guo, 2010)	Multi-site RCT (12 months)	TAU + patient psychoeducation, family intervention, skills training, CBT (n=635) TAU: Antipsychotic medication (n=633)	Medication adherence (No definition) Insight (Insight and treatment attitudes questionnaire)	Medication adherence: HR: 0.45 (95%CI: 0.25-0.79) Intervention: 2.8% Comparator: 5.7% Insight: F=25.9, p<0.01 Intervention Δ $\bar{x}$: 6.7 Comparator Δ $\bar{x}$: 3.2	Hazard ratio and 95%CI were calculated. Mixed effects models for repeated-measures analysis (group x time interaction)	4
Roozbeh Hospital (Shahrivar, 2011)	Single site RCT (24 months)	TAU + family psychoeducation, and telephone follow-up (n=20) TAU: Antipsychotic medication (n=20)	**Mania symptoms** (Young Mania Rating Scale) Rate and duration of recurrence	Mania symptoms: p= 0.219 Rate and duration of recurrence: nr [a]	Independent sample t-test [a] Not reported in the full text, the abstract only reports that the control and intervention groups differed on these variables.	1
			Observational studies (n=2)			
Schizophrenia Research Foundation (Iyer, 2020)	Cohort: 2 groups (24 months)	Multicomponent intervention in LMIC (Patients: n=165) (Family members: n=168) Multicomponent intervention in HIC (Patients: n=168) (Family members: n=156)	Patient engagement (Patient disengaged if they had no contact with training teams for three consecutive months) Family engagement (if the treating team had been in contact with them in contact or at distance)	Patient disengagement: x^2: 28.9, p<0.001 LMIC: 1% HIC: 19% Family disengagement (time of contact): t: -16.7, p<0.001. LMIC: x̄: 22.8 months, sd: 5.8 HIC: x̄: 11.4 months, sd: 7.8	Chi-square test T-test	4
Moscow Research Institute of Psychiatry (Zayteseva, 2010)	Cohort-2 groups(60 months)	Atypical antipsychotics, psychoeducation, individualized family intervention, supportive therapy and case management (n=114) Regular care-not specified (n=119)	Adherence to therapy (No definition) Stable social position (No definition)	Adherence to therapy Intervention: 48.0% Comparator: 12.0% Stable social position Intervention: 73.5% Comparator: 37.1%	Do not specify the type of statistical analysis conducted	1

HIC: High-income country, LMIC: Low-and middle-income country, N: National, I: Institute, RCT: Randomized controlled trial, CBT: Cognitive-behavioral therapy, TAU: Treatment as usual, G: General, HR: Hazard ratio, CI: Confidence interval, QS: Quality Score with Mixed Methods Appraisal tool (Range:0-5), sd: Standard deviation.

Δ $\bar{x}$: Mean difference. Positive values represent an improvement for insight.

*Outcomes in bold indicate no statistical difference.

Table S14. Effectiveness of individual EIP interventions for individuals with FEP in LMICs: Outcomes beyond the predefined list.

FEP Intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurement)	Findings	Statistical analysis	QS
			Essential components (n=12)			
Antipsychotic medication						
Central institute in psychiatry in Ranchi (Saddichha, 2008)	RCT (6 weeks)	Antipsychotic treatment (Haloperidol, n=31; olanzapine, n=35; or risperidone, n=33. Total, n=99) Control: Gender, age, exercise and diet matched healthy control group (n=51)	Metabolic syndrome (ATP IIIA, 3rd report of the Adult Treatment Panel; and IDF, International Diabetes Federation)	ATP IIIA metabolic syndrome: x^2:13.0, p: 0.005 Intervention: 10.1% Comparator: 2.0% IDF metabolic syndrome: x^2: 20.1, p<0.001 Intervention: 18.2% Comparator: 0%	Chi-Square test	4
CBT						
Beijing Anding Hospital (Liu, 2019)	Pilot RCT (12 months)	TAU + Brief CBT intervention (n=40) TAU: Antipsychotic medication + case management (n=40)	**Insight** (Schedule for assessing insight)	Insight: F: 0.814; p: 0.458 Intervention Δ $\bar{x}$: 3.92 Comparator Δ $\bar{x}$: 2.78	Anova-repeated measures (Group x time analysis	5
Supporting health						
Psychiatric hospital in Thailand (Meepring, 2023)	RCT (12 months)	TAU + Systemic health checks and personal health plan (n=53) TAU: Antipsychotic medication + psychosocial support (n=53)	Weight gain (prevention of ≥7% weight gain over 12-month) Obesity (Waist circumference Body mass index)	Weight gain: OR: 6.5 (95%CI: 1.9-22.7), p<0.004[a] Intervention: 15.7% Comparator: 53.6% Waist circumference: p<0.001[b] Intervention Δ $\bar{x}$: -2.67 cm. Comparator Δ $\bar{x}$: 5.9 cm. Body mass index: p: 0.003[b] Intervention Δ $\bar{x}$: -0.95 kg/m2 Comparator Δ $\bar{x}$: 1.51 kg/m^2	[a] Univariate logistic regression model [b] Generalized estimating equation (group x time interaction)	3
Patient psychoeducation						
Study in Jilin[1] (Chien, 2019)	Multi-site RCT (18 months)	TAU + Mindfulness-based psychoeducation program (n=60) C2: TAU + Psychoeducation (n=60) C1: TAU: Antipsychotic medication, supporting health, psychosocial needs assessment, psychological therapy. (n=60)	Insight (Insight and treatment attitudes questionnaire)	Insight: F: 9.25; p<0.005 Intervention Δ $\bar{x}$: 6.7 Comparator Δ $\bar{x}$: -0.1	Manova (Group x time interaction)	5
Study in China (Chien, 2017)	Multi-site RCT (18 months)	TAU + Mindfulness-based psychoeducation group (n=114) C2: TAU+ Psychoeducation (n=114) C1: TAU: Antipsychotic medication, supporting health, psychosocial needs assessment, psychological	Insight (Insight and treatment attitudes questionnaire)	Insight: F: 8.98; p<0.001 Intervention Δ $\bar{x}$: 8.6 Comparator Δ $\bar{x}$: -0.6	Manova (Group x time interaction)	4

FEP Intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurement)	Findings	Statistical analysis	QS
		therapy. (n=114)				
Family psychoeducation						
NIMHANS in Bangalore[3] (Sadath, 2017)	Quasi-experimental (3 months)	Family psychoeducation (n=31) Supportive therapy and psychoeducation (n=29)	**Expressed emotion** (Family questionnaire) **Social support** (Multidimensional scale of perceived social support)	Expressed emotion: F:1.807, p: 0.18 Intervention: nr Comparator: nr Social Support: F: 3.557, p: 0.064 Intervention: nr Comparator: nr	Anova-repeated measures	3
Da Nang Psychiatric Hospital (Ngoc, 2016)	RCT (6 months)	TAU + family schizophrenia psychoeducation program (n=30) TAU: Antipsychotic medication (n=29)	**Family quality of life** (Quality of life enjoyment and satisfaction questionnaire) Patient stigma towards schizophrenia (STSS) Family stigma towards schizophrenia (STSS) Medication non-compliance (Medication compliance inventory) Patient consumer satisfaction (Scale created) Family consumer satisfaction (Scale created)	Family quality of life: F: 3.87, p: 0.1 Intervention Δ $\bar{x}$: 0.77 Comparator Δ $\bar{x}$: 0.48 Patient stigma towards schizophrenia: F: 6.67, p<0.05 Intervention Δ $\bar{x}$: -0.5 Comparator Δ $\bar{x}$: -0.14 Family stigma towards schizophrenia: F: 9.36, p<0.001 Intervention Δ $\bar{x}$: -0.39 Comparator Δ $\bar{x}$: -0.20 Medication non-compliance: F: 7.65, p<0.01 Δ $\bar{x}$ (intervention-control): -30 Patient consumer satisfaction: F: 12.82, p<0.001 Δ $\bar{x}$ (intervention-control): 0.46 Family consumer satisfaction: F: 5.91, p<0.05 Δ $\bar{x}$ (intervention-control): 0.30	Ancova Anova	2
Study in Yogyakarta (Marchira, 2019)	RCT (6 months)	Brief psychoeducation program concerning schizophrenia (n=50 patients and their family members) TAU: Standard family education (n=50 patients and their family members)	Knowledge of psychosis (Knowledge of psychosis) Visits to health providers (Compliance and relapse assessment) Compliance (Compliance and relapse assessment)	Knowledge of psychosis: t: 11.75, p:0.0001 Intervention Δ $\bar{x}$: 4.3 Comparator Δ $\bar{x}$: -0.8 Visits to health provider: p: 0.003 Intervention: 100% Comparator: 82% Compliance: x^2: 28.41, p: 0.0001 Intervention: 66% Comparator: 12%	Chi square Independent sample t-test	3

FEP Intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurement)	Findings	Statistical analysis	QS
University hospital in Turkey (Öksüz, 2017)	Quasi-experimental (2.3 months)	Family psychoeducation (n=33 family members) Control (n=30 family members)	Expressed emotion (Expressed emotion scale) Family functioning (Family assessment device)	Expressed emotion Criticism/hostility: t: -8.5, p: 0.001 Intervention Δ $\bar{x}$: -5.5, p: 0.001 Comparator Δ $\bar{x}$: 1.93, p: 0.001 Over involvement-protecting-intervention: t: -7.3, p: 0.001 Intervention Δ $\bar{x}$: -4.46, p: 0.001 Comparator Δ $\bar{x}$: 0.96, p: 0.001 Family functioning [a]: t: -3.69, p: 0.001 Intervention Δ $\bar{x}$: -0.39, p: 0.001 Comparator Δ $\bar{x}$: -0.01, p: 0.211	Paired sample t-test [a] Data presented for the general functioning item only	4
Study in Shanghai (Cai, 2015)	RCT (18 months)	TAU + family therapy focused on cognitive rehabilitation (social skills individualized training and family psychoeducation) (n=133) TAU: Antipsychotic medication (n=123)	Cognition (Repeatable battery for the assessment of neuropsychological status)	Cognition [b]: F: 22.9, p<0.002[a] Intervention Δ $\bar{x}$: 27.96 Comparator Δ $\bar{x}$: 10.68	Independent sample t test [a]Ancova (Group x time interaction) controlling for confounders [b] Total score	5
Suzhou Guangji Hospital (Zhang, 1994)	RCT (18 months)	TAU + Family intervention (group and individual counselling sessions) (n=42) TAU: Antipsychotic medication (n=41)	Hospital-free period in readmitted patients	Hospital-free period in readmitted patients: t: 2.9, p<0.01 Intervention: 245 days, sd: 104 Comparator: 130 days, sd: 79	Statistical analysis lacks specification of the test used to evaluate outcomes.	3
Active engagement and retention						
Federal Neuro-Psychiatric Hospital in Benin (Thomas, 2017)	RCT (6 months)	TAU + SMS text reminders (n=95) TAU: Cards containing the appointment date (n=97)	Missed appointments (proportion of missed next appointments) *Other components (n=2)*	Missed next appointments: OR: 0.50, 95%CI: 0.3-0.9, p<0.03 Intervention: 47% Comparator: 62%	Binary logistic regression model (adjusted for confounders)	4
Cognitive training						
Tongde Hospital (Dang, 2014)	Pilot study-RCT (4 weeks)	TAU + Cognitive training (n=10) TAU: Antipsychotic medication (n=10)	Cognition (Wechsler memory scale-revised, Wechsler adult intelligence scale-revised, N-Back task)	Cognition Accuracy rate: Z=-3.27, p<0.01 Reaction time: Z=-2.98, p<0.01	Mann-Whitney U test	3
NIMHANS in Bangalore[2] (Hedge, 2012)	RCT (2 months)	TAU + cognitive training (n=22 patients and their family members) TAU: Antipsychotic medication + psychoeducation (n=23 patients and their family members)	Cognition (Neurological tests) **Family's psychological health** (General health questionnaire, GHQ-28) **Family distress** (Scale for assessment of family distress)	Cognition Divided attention: p<0.01 Planning: p<0.05 Concept formation: p<0.05 Set-shifting ability: p<0.05 Family's psychological health and family distress: ns	Ancova (Group x treatment interaction) controlling for confounders	1

FEP Intervention (First author, year)	Study type (Duration)	Intervention (n) Comparator (n)	Outcomes* (Measurement)	Findings	Statistical analysis	QS

N: National, I: Institute, NIMHAN: National Institute of Mental Health and Neuroscience, RCT: Randomized controlled trial, CBT: Cognitive-behavioral therapy, TAU: Treatment as usual, G: General. C: Comparator, ns: not significant, RR: Risk ratio, CI: Confidence interval, nr: not reported, SMS: Short message service, STSS: Stigma towards schizophrenia scale, sd: Standard deviation.
$\Delta \overline{x}$: Mean difference between endpoint and baseline values. Negative values represent improvements for expressed emotion. A positive mean difference represents an improvement for variables such as insight, quality of life, consumer satisfaction, and knowledge of psychosis.
QS: Quality Score with Mixed Methods Appraisal tool (Range:0-5).
*Outcomes in bold indicate no statistical difference.

Table S15. PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p. 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S2-4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 4,5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p. 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 5

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p. 10
Study characteristics	17	Cite each included study and present its characteristics.	Table S6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 5 & 6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p. 8
	23b	Discuss any limitations of the evidence included in the review.	p. 9

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	p. 9
	23d	Discuss implications of the results for practice, policy, and future research.	p. 9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 11
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p. 11
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	p. 11
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p. 11
Competing interests	26	Declare any competing interests of review authors.	p. 11
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Suppl. Mat

Supplemental material: Manuscript 3

Table S1

COREQ checklist

Item No	Guide Questions/Description	Page
Domain 1: Research team and reflexivity		
1. Interviewer/ facilitator	Which author/s conducted the interview or focus group?	6
2. Credentials	What were the researcher's credentials? E.g., PhD, MD	6
3. Occupation	What was their occupation at the time of the study?	6
4. Gender	Was the researcher male or female?	6
5. Experience and training	What experience or training did the researcher have?	6
6. Relationship established	Was a relationship established prior to study commencement?	6
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research?	6
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	6
Domain 2: study design		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	4
10. Sampling	How were participants selected? e.g., purposive, convenience, consecutive, snowball	6
11. Method of approach	How were participants approached? e.g., face-to-face, telephone, mail, email	6
12. Sample size	How many participants were in the study?	6
13. Non-participation Setting	How many people refused to participate or dropped out? Reasons?	6
14. Setting of data collection	Where was the data collected? e.g., home, clinic, workplace	6
15. Presence of nonparticipants	Was anyone else present besides the participants and researchers?	6
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Table S2
17. Interview guide	Were questions, prompts, and guides provided by the authors? Was it pilot tested?	6
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	-
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	6
20. Field notes	Were field notes made during and/or after the interview or focus group?	6
21. Duration	What was the duration of the interviews or focus group?	6
22. Data saturation	Was data saturation discussed?	6
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	7
Domain 3: analysis and findings		
24. Number of data coders	How many data coders coded the data?	7
25. Description of the coding tree	Did the authors provide a description of the coding tree?	-
26. Derivation of themes	Were themes identified in advance or derived from the data?	7
27. Software	What software, if applicable, was used to manage the data?	7
28. Participant checking Reporting	Did participants provide feedback on the findings?	7

Item No	Guide Questions/Description	Page
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g., participant number	8-18
30. Data and findings consistent	Was there consistency between the data presented and the findings?	19-22
31. Clarity of major themes	Were major themes clearly presented in the findings?	19-22
32. Clarity of minor themes	Is there a description of diverse cases or a discussion of minor themes?	8-18

Table S2

Sociodemographic variables of participants (n=25)

Variable	n
Age (mean; SD)	51.7; 10.4
Gender	
Male	21
Female	4
Highest completed degree	
MD	7
MD/MSc	5
MD/PhD	6
PhD	7
Field of study	
Psychiatry	20
Psychology	5
Primary work*	
Clinic	17
Research	12
Public health	6
Academia	3
Field of experience	
First episode psychosis	17
Clinical-high risk psychosis	4
Both	4
Experience in EIP*	
Research	19
Clinic	9
Service planning and development	5
Guideline development	2
Policy development	1
Worked in an EIP program	
Yes	10
No	15
Time working in mental health (Mean; SD)	24.4; 10.9
Time working in EIP (Mean; SD)	12.7;7.7
Heard about the IEPA	
Yes	20
No	5

Note: IEPA: International Early Psychosis Association, EIP: Early intervention in psychosis. *Multiple response

Table S3

Early intervention in psychosis initiatives by country (n=26).

Country	Income level	"Individual" EIP study	Research program	Clinical program	Clinical guideline	Technical standard	Total
Country 1	UMIC		1 initiative	5 initiatives			6
Country 2	HIC	1 initiative	1 initiative	2 initiatives	1 initiative		5
Country 3	UMIC	1 initiative	2 initiatives	2 initiatives			5
Country 4	HIC			2 initiatives			2
Country 5	HIC		1 initiative				1
Country 6	UMIC	2 initiatives					2
Country 7	LMIC			1 initiative			1
Country 8	UMIC	1 initiative					1
Country 9	UMIC				1 initiative	1 initiative	2
Country 10	HIC	1 initiative					1

Note: LMIC: Lower-middle income country, UMIC: Upper-middle income country, HIC: High-income country. EIP: Early intervention in psychosis.

Supplemental material: Manuscript 4

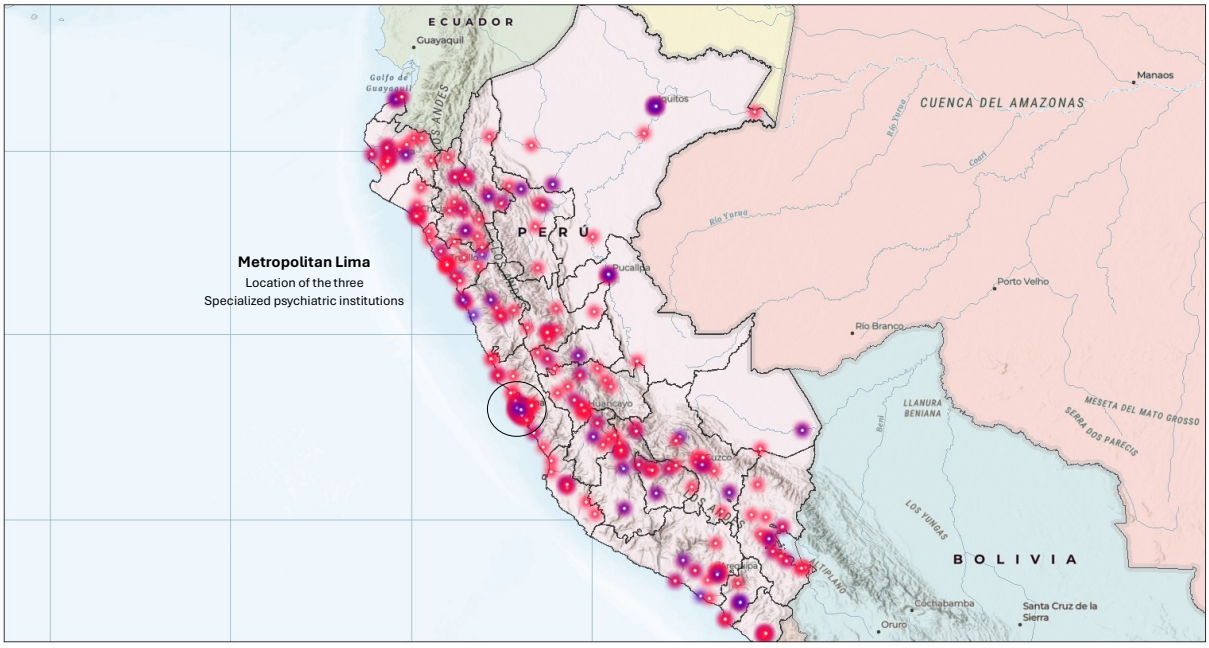


Figure S1. Geographic distribution of community mental health centers (red dots) and halfway houses (purple dots) across Peru (Total = 355). The map shows the location of these facilities across the country's three main geographical regions: coast, highlands ("*Los Andes*"), and rainforest, as well as within each department (outlined by solid black lines). The figure was created using the Geospatial System of Health Integrated Networks from the Ministry of Health of Peru, with data updated as of April 29, 2025, including 265 community mental health centers and 90 halfway houses. However, the total number of community mental health centers and halfway houses was 288 and 94 by January 5, 2025, respectively.

Table S1. Monthly rates of service utilization by health system variables

	Prepandemic period			Postpamdemic period		
	Rate*	Lower 95% CrI	Upper 95% CrI	Rate*	Lower 95% CrI	Upper 95% CrI
			Psychosis			
Level of care						
Primary	1.73	1.71	1.76	3.06	3.03	3.09
Secondary	6.94	6.88	7.00	6.18	6.14	6.23
Tertiary	19.01	18.91	19.11	10.36	10.30	10.41
Health sector						
Ministry of health	10.88	10.81	10.96	6.06	6.02	6.11
Regional Government	4.62	4.57	4.67	6.05	6.01	6.10
Social security	9.43	9.37	9.50	5.34	5.30	5.39
Others	2.90	2.86	2.94	2.32	2.29	2.34
			Non-psychotic mental disorders			
Level of care						
Primary	41.23	41.09	41.37	68.35	68.20	68.49
Secondary	92.92	92.69	93.13	119.20	119.01	119.39
Tertiary	97.16	96.94	97.38	74.56	74.40	74.71
Health sector						
Ministry of health	52.51	52.35	52.67	42.43	42.32	42.55
Regional Government	75.59	75.39	75.78	101.39	101.21	101.57
Social security	72.56	72.37	72.75	68.16	68.01	68.31
Others	35.98	35.85	36.11	53.55	53.42	53.68
			Physical illnesses			
Level of care						
Primary	5,377.08	5,375.46	5,378.69	4,163.04	4,162.20	4,164.29
Secondary	4,748.10	4,746.68	4,750.00	5,008.54	5,007.54	5,010.04
Tertiary	1,982.47	1,981.48	1,983.46	1,506.58	1,505.83	1,507.19
Health sector						
Ministry of health	834.81	834.14	835.47	656.88	656.42	657.34
Regional Government	5,338.50	5,336.90	5,340.10	3,597.88	3,596.80	3,598.96
Social security	3,505.89	3,504.84	3,507.29	3,742.09	3,740.97	3,743.21
Others	2,862.64	2,861.50	2,863.79	2,768.33	2,767.22	2,769.16

CrI: Credible interval. * per 100,000 inhabitants. Pre: Pre-pandemic period (2018-2019). Post: Post-pandemic period (2022-2024).

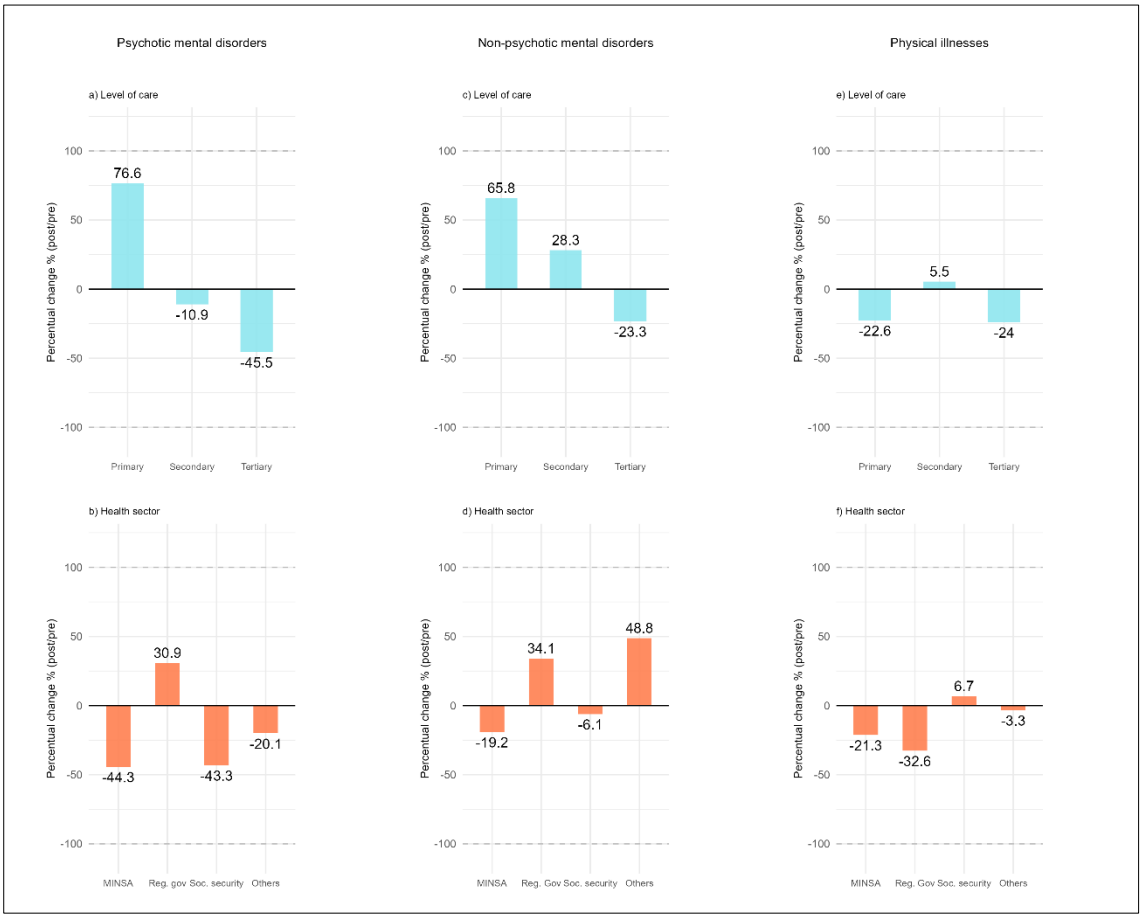


Figure S2. Percentual change in service utilization rates before and after COVID-19 by level of care and health sector. Positive values indicate increased utilization after the pandemic onset, while negative values indicate a reduction. Pre: Pre-pandemic period (2018-2019). Post: Post-pandemic period (2022-2024). Reg. gov: Regional government, Soc. Security: Social security. Others: Armed forces and private sector.

Table S2. Monthly rates of service utilization by socioeconomic variables

	Prepandemic period			Postpamdemic period		
	Rate*	Lower 95% CrI	Upper 95% CrI	Rate*	Lower 95% CrI	Upper 95% CrI
			Psychosis			
Monetary poverty level						
Very low income	0.08	0.08	0.09	0.28	0.27	0.29
Low income	1.19	1.17	1.22	1.55	1.53	1.57
Moderate income	17.66	17.57	17.76	10.74	10.69	10.80
Adequate income	8.90	8.83	8.96	7.21	7.16	7.25
Geographical region						
Coast	23.13	23.02	23.24	14.01	13.95	14.08
Highland	3.85	3.80	3.89	4.96	4.92	5.00
Rainforest	0.86	0.84	0.88	0.81	0.79	0.83
Centralization level						
Lima province	17.39	17.31	17.50	8.97	8.92	9.03
Capital province	7.51	7.45	7.57	7.88	7.83	7.93
Non-capital province	2.93	2.89	2.97	2.93	2.90	2.96
			Non-psychotic mental disorders			
Monetary poverty level						
Very low income	1.50	1.47	1.53	3.36	3.33	3.40
Low income	20.07	19.97	20.18	26.95	26.86	27.05
Moderate income	129.10	128.84	129.35	135.83	135.62	136.04
Adequate income	85.97	85.76	86.17	99.37	99.19	99.55
Geographical region						
Coast	165.50	165.34	165.84	171.91	171.74	172.09
Highland	59.62	59.44	59.80	75.79	75.64	75.94
Rainforest	11.43	11.35	11.50	17.83	17.76	17.90
Centralization level						
Lima province	111.29	111.04	111.52	98.48	98.31	98.66
Capital province	81.71	81.51	81.92	113.72	113.52	113.90
Non-capital province	43.64	43.49	43.79	53.34	53.21	53.47
			Physical illnesses			
Monetary poverty level						
Very low income	762.19	761.58	762.81	390.85	390.50	391.21
Low income	2171.34	2170.30	2172.38	1721.31	1720.57	1722.05
Moderate income	5402.25	5400.57	5403.92	5010.29	5009.04	5011.55
Adequate income	4048.86	4047.44	4050.27	3640.33	3639.24	3641.39
Geographical region						
Coast	6707.62	6707.62	6714.33	6167.20	6167.20	6167.20
Highland	5094.92	5094.92	5100.02	3619.17	3619.17	3622.79
Rainforest	578.82	578.25	579.40	976.52	975.55	976.52
Centralization level						
Lima province	4298.84	4297.55	4300.13	3647.15	3646.05	3648.24
Capital province	4153.47	4152.23	4155.13	3965.55	3964.36	3966.74
Non-capital province	3932.38	3930.81	3933.56	3152.34	3151.39	3153.28

CrI: Credible interval. * per 100,000 inhabitants. Pre: Pre-pandemic period (2018-2019). Post: Post-pandemic period (2022-2024).

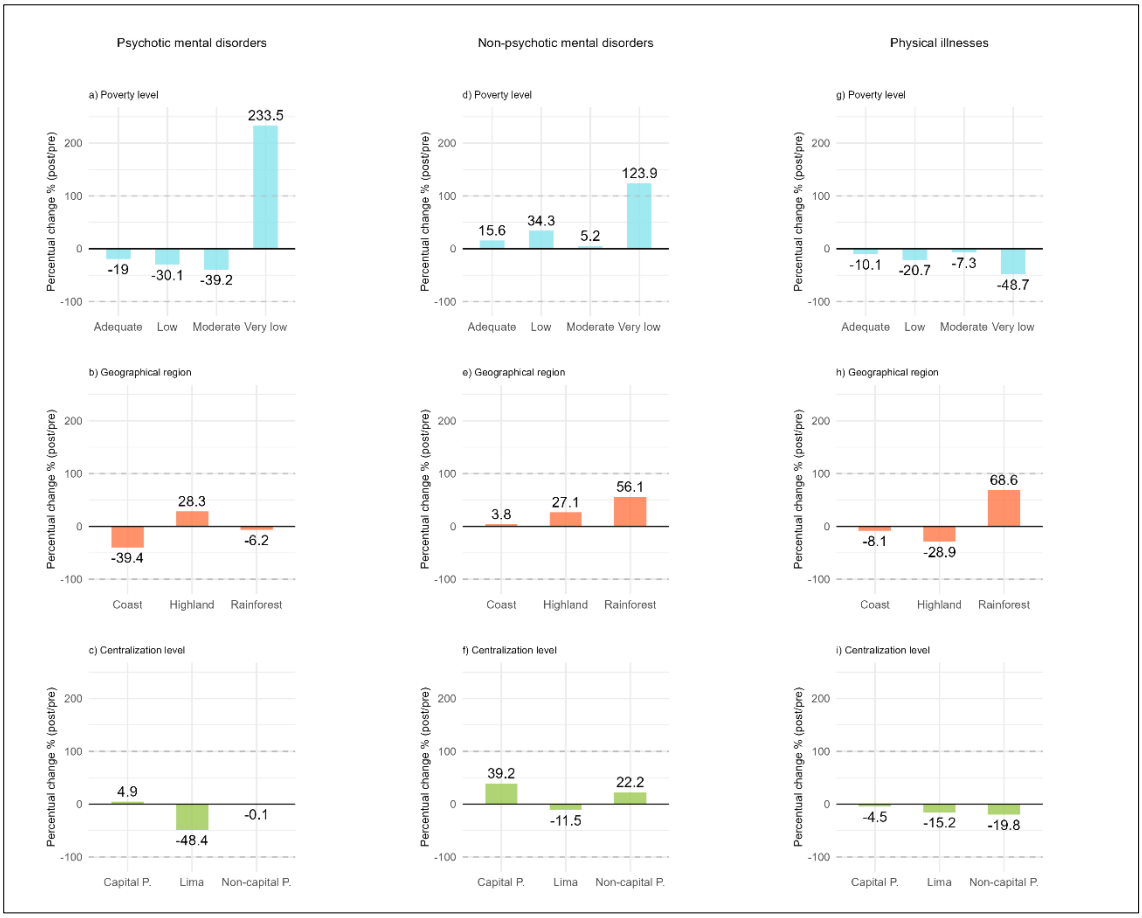


Figure S3. Percentual change in healthcare service utilization before and after the COVID-19 pandemic by poverty level, geographical region, and centralization level. Positive values indicate increased utilization after the pandemic onset, while negative values indicate a reduction. Pre: Pre-pandemic period (2018-2019). Post: Post-pandemic period (2022-2024).