HAVE WE GOT BETTER IN MAKING OUR SCHIZOPHRENIA PATIENTS BETTER?

EDITED BY: Anthony Ahmed, Jouko Miettunen and Erika Jääskeläinen
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HAVE WE GOT BETTER IN MAKING OUR SCHIZOPHRENIA PATIENTS BETTER?

Topic Editors:
Anthony Ahmed, Cornell University, United States
Jouko Miettunen, University of Oulu, Finland
Erika Jääskeläinen, University of Oulu, Finland

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EDITORIAL
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Editorial: Have We Got Better in Making Our Schizophrenia Patients Better?

Erika Jääskeläinen[1,2,3]*, *Jouko Miettunen*[1,2] and *Anthony O. Ahmed*[4]

[1] Center for Life Course Health Research, University of Oulu, Oulu, Finland, [2] Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland, [3] Department of Psychiatry, University Hospital of Oulu, Oulu, Finland, [4] Department of Psychiatry, Weill Cornell Medicine, Cornell University White Plains, New York, NY, United States

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Editorial on the Research Topic

Have We Got Better in Making Our Schizophrenia Patients Better?

Despite its heterogeneity in prognosis, schizophrenia is considered as a disorder with relatively poor outcomes. For some individuals, schizophrenia increases the risk for suicide, psychiatric and medical comorbidities, recurrent relapses, treatment resistance, and poor functioning. Remission and recovery are however well-documented, and ∼13.5% of individuals with schizophrenia experience good social and clinical recovery (1).

In this Research Topic, we wanted to find answer to the question *Have we got better in making our schizophrenia patients better?* This collection includes 12 articles on recovery and psychosocial interventions, early intervention and prevention services and cognition in psychoses.

In a study with hospitalized patients with schizophrenia or schizoaffective disorder, Chen et al. found that resilience and positive coping mediated the relationship between negative symptoms and functional disability. Their results suggest that resilience and positive coping are important treatment targets for attenuating the impact of negative symptoms. In a study by Chien et al., along with mindfulness based psychoeducation intervention, two facets of mindfulness, "observing" and "acting with awareness," were related to positive outcomes of recent onset psychosis. This study was first to show mechanism explaining the benefits of mindfulness skill on psychoses. Kim et al. identified an association between depression and functional mobility in schizophrenia. Improving functional mobility by treating depression may have considerable therapeutic value when aiming to functional recovery.

The last few decades have seen an increased interest in early interventions for patients with psychotic illnesses or those with clinical high risk for psychosis (CHR-P). Fusar-Poli et al. describe the Pan-London Network for Psychosis-Prevention (PNP), including four different early intervention teams, with heterogenous characteristics of the catchment areas and service users. Psychosis transition rate (30% in 4-year follow-up) in PNP suggests that the actual transition risk of clinical cohorts may not be declining, as opposed to research cohorts. Standalone teams were more established and successful than teams that share their resources with other mental health services. Fusar-Poli et al. paper highlights crucial operational issues which need careful consideration in the future planning of CHR-P services. Berze et al. present a study protocol of a 6 months early intervention program in Latvia—the Latvian Early Intervention Program—for first-episode patients in a low-resourced outpatient service.

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Ingrid Melle,
University of Oslo, Norway

***Correspondence:**
Erika Jääskeläinen
erika.jaaskelainen@oulu.fi

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The success of early intervention and prevention depends on efficient detection on individuals in need of assessment and care, and this depends on help-seeking behavior of the patients and families. Wong et al. made qualitative study on caregivers. They found that high level of right knowledge on schizophrenia and its treatment and low level of stigma related to better professional help-seeking behavior during first episode schizophrenia.

Cognitive deficits have been heavily studied in schizophrenia. To date, the majority of clinical trials of medications developed to address cognitive deficits in schizophrenia have been unsuccessful (2, 3). Three articles in the collection focused on cognition. In their review, Cotter et al. suggested that one of the reasons pharmacological trials of cognition have been unsuccessful may be because few studies have actually screened for patients with significant cognitive deficits and may have therefore included several cognitively "normal" patients. They found that only 11.5% of trials had included cognitive function as an eligibility criterion. Moreover, none examined the moderating effect of cognitive performance. Therefore, whether patients with more impaired cognition gain more from cognitive enhancing drugs remains an empirical question. Szczepanowski et al. showed that metacognitive accuracy in self-monitoring tasks in patients with schizophrenia can be improved by engaging a method of assessment that imposes a cost on overconfident judgments of incorrect responses. By implication, their study demonstrates that inducing an aversion to loss of desired incentives could increase metacognitive accuracy in self-monitoring task by decreasing over-confidence and perhaps other cognitive biases. Adamowicz et al. found that the dietary intervention addressing metabolic dysfunction improved cognitive performance whereas cognitive abilities remained unchanged in the non-dietary intervention group.

High rates of medication non-adherence and overall treatment disengagement remain a challenge in the care of people with psychotic illnesses. Studies have reported medication non-adherence rates that frequently exceed 30%, including rates as high as 50% in first-episode psychosis patients (4, 5). In this collection, Mucci et al. make the case about the importance of treatment alliance and the need to understand its nature and factors that may enhance or impede alliance in treatment. They present psychoeducation and shared-decision making as interventions that can foster alliance with patients and caregivers. Shared-decision making goes beyond psychoeducation as it involves a bidirectional exchange of information between two experts—the practitioner with knowledge of psychiatric care, and the patient with knowledge of their own history, preferences, and personal goals (6).

Like shared decision-making, motivational interviewing has been examined as an intervention to enhance treatment adherence. Motivational interviewing is a style of communication that targets patients' own decisional conflicts and ambivalence about improvement through "change talk" to enhance their commitment. Dobber et al. examined the active ingredients of motivational interviewing including clinician factors, client factors, and mechanisms of change. They wanted to identify what ingredients may trigger mechanisms of change. They found that clinician factors, in particular, reflection and questions about medication adherence that subsequently lead to change talk on the part of the patient triggered mechanisms of change. These variables, underscored in conjunction with other motivational interviewing principles including trust and empathy, allow meaningful conversations about the role of medication adherence in the patient's own self-identified values and long-term goals.

The goal in the treatment of schizophrenia is recovery. But what does it mean? Is it defined by the clinical, society, or the patient him/herself? Most of the studies on recovery in schizophrenia have focused on clinician's assessment of recovery. However, patients and advocates of the recovery movement that started about four decades ago have highlighted the importance of "personal recovery," the idea that people with schizophrenia can live a productive and satisfying life, despite the limitations of illness. The patient-based definition of personal recovery indicates a development of new meaning and purpose in one's life, due to growing beyond the catastrophic effects of mental illness (7).

In this collection Lee et al. describe the construct of post-traumatic growth (PTG) in psychosis. Drawing on personal experience, theoretical developments, and extant research, the authors argue that deeper insights into how mental health professionals can support their patients to achieve PTG could bring existing mental healthcare services to greater heights.

From a recovery-oriented perspective, a more appropriate question would be *Have we got better in helping our patients better?* Recovery is not about clinicians doing something (making better) for patients to make them recover clinically. Rather the role of the clinician is to deploy evidence-based interventions to the service of the patient's personal goals and aspirations. In this role, the clinician adopts a patient-centered approach to treatment, engages in information sharing for patients and families and shared decision-making, builds trust, and works to decrease stigma.

During last decades, several new options for psychosocial care and rehabilitation have been developed (8). We have gone far from the early times of solely institutional care or solely drug treatment. The patient-centered, recovery-oriented care has raised to be used in combination of evidence-based pharmacological and psychosocial treatment. We do believe that we clinicians and scientists have got better in helping our patients better.

AUTHOR CONTRIBUTIONS

EJ wrote the first draft of the manuscript. AA and JM provided critical revision and important intellectual contributions to the manuscript. All authors have read and approved the submitted version.

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MINI REVIEW
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The Use of Cognitive Screening in Pharmacotherapy Trials for Cognitive Impairment Associated With Schizophrenia

Jack Cotter[1]*, *Jennifer H. Barnett*[1,2] *and Kiri Granger*[1]

[1] *Cambridge Cognition, Cambridge, United Kingdom,* [2] *Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom*

There are currently no regulatory approved pharmacological treatments for cognitive impairment associated with schizophrenia (CIAS). One possibility is that trial methodology itself is hindering their development. Emerging evidence suggests that patients with schizophrenia may show limited benefit from pro-cognitive interventions if they already exhibit intact cognitive performance, relative to normative thresholds. The aim of this report was to examine the extent to which objectively assessed cognitive performance has been used as an eligibility and/or stratification criterion in CIAS pharmacotherapy trials. On 16th January 2019, we conducted a systematic search of studies listed on ClinicalTrials.gov to identify randomized, double-blind, placebo-controlled, add-on pharmacotherapy trials conducted in patients with a diagnosis of schizophrenia, in which a paper-and-pencil or computerized cognitive task (or battery) was specified as a primary outcome measure. Of the 87 trials that met our inclusion criteria, 10 (11.5%) required the presence of an objectively assessed cognitive deficit as part of their patient eligibility criteria. No studies reported stratifying patients according to the presence or degree of cognitive impairment they exhibited. These results suggest that the vast majority of CIAS trials may have been underpowered due to the inclusion of cognitively "normal" patients. Purposive screening for cognitive impairment could increase CIAS trial success.

Keywords: clinical trial, cognition, pharmacotherapy, psychosis, schizophrenia, trial methodology

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Edited by:
Anthony Ahmed,
Cornell University,
United States

Reviewed by:
Joseph Firth,
Western Sydney University,
Australia
Michael W. Best,
Queen's University,
Canada

***Correspondence:**
Jack Cotter
jack.cotter@camcog.com

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INTRODUCTION

Cognitive impairment is common in people with schizophrenia and is among the strongest predictors of functional disability in this patient group (1–3). Despite considerable efforts and some initially promising results, there are currently no regulatory approved pharmacological treatments for cognitive impairment associated with schizophrenia (CIAS) (4, 5). It remains unclear, however, whether this is truly due to these compounds being ineffective, or whether trial methodology itself has been a limiting factor in successfully demonstrating the efficacy of these agents.

Schizophrenia is a heterogeneous disorder associated with varying clinical and cognitive profiles (6). Though the majority of patients with schizophrenia exhibit some general cognitive dysfunction compared to antecedent expectations, such as premorbid intelligence (7, 8), there is evidence that approximately a quarter of patients display cognitive performance comparable to healthy controls (9–12). Recent evidence has indicated that these "normally" performing patients

are significantly less likely to exhibit changes in cognition when participating in CIAS trials (13, 14), suggesting that inclusion of these individuals may limit the scope to detect a pro-cognitive efficacy signal. Contemporary evidence has also reported that there is no association between cognitive performance and measures of social, vocational or everyday functioning in these cognitively "normal" patients (15), suggesting that other illness-related variables are the primary drivers of functional disability among these individuals. Given that cognition is thought to remain relatively stable following the first psychotic episode (11, 16), the rationale for including and administering an investigational medicinal product to this subset of "normally" performing patients is becoming increasingly unclear. Exclusion of these individuals, or at least identifying and ensuring equal stratification of these "normal" performers across trial arms during randomization, may provide additional power to observe pro-cognitive treatment effects, though it is currently unclear whether either of these approaches have been routinely adopted.

The aim of this report was to examine the extent to which objectively assessed cognitive performance has been used as an eligibility and/or stratification criterion in CIAS pharmacotherapy trials.

METHODS

On 16th January 2019, we conducted a systematic search of trials listed on ClinicalTrials.gov (since its inception) using the keyword "schizophrenia" (n = 2,978). Eligible studies were those recorded as randomized, double-blind, placebo-controlled, add-on pharmacotherapy trials conducted in patients with a diagnosis of schizophrenia, in which a paper-and-pencil or computerized cognitive task (or battery) was specified as a primary outcome measure. Phase 1 studies (which typically focus on drug safety), nutraceutical interventions (including pharmaceutical-grade dietary supplements) and single-dose studies (including crossover trials) were excluded. We cross-referenced study information listed on ClinicalTrials.gov with corresponding published literature where this could be identified. For all eligible trials, information was manually extracted (where provided) on: i) study details; ii) cognition-related study eligibility criteria; iii) cognition-related stratification procedures or sensitivity analyses.

RESULTS

Of the 87 trials that met our inclusion criteria, 10 (11.5%) explicitly reported requiring the presence of an objectively measured cognitive deficit as part of their patient eligibility criteria (**Table 1**; **Supplementary Table 1**). In contrast, six trials (6.9%) screened and excluded individuals with very high cognitive performance in an effort to avoid ceiling effects, while the majority of trials excluded those with (or at increased risk of) severe cognitive impairments that could potentially confound cognitive testing, such as low IQ, neurological or developmental disorders or a history of head trauma. A number of the included studies also stratified patients during randomization according to factors that could potentially influence treatment response, such as their sex, recruiting site, genetic profile, tobacco use, or inpatient/outpatient status. However, we found no studies reporting the stratification of patients according to the presence or degree of cognitive impairment exhibited at screening or baseline. Similarly, we identified only a single study that listed an intention to perform post-trial sensitivity analyses to establish whether any pro-cognitive effects were exclusive to those exhibiting cognitive impairment at baseline.

DISCUSSION

The vast majority of CIAS pharmacotherapy trials have not included formal eligibility criteria to ensure participants exhibit a cognitive deficit as part of their study screening procedures. While this is consistent with consensus guidelines that have previously recommended such an approach (4), the failure to develop any effective compounds, coupled with recent evidence suggesting that the inclusion of "normal" performers may limit the ability to detect pro-cognitive effects, has brought the rationale for this into question.

In the absence of purposive screening for cognitive impairment, an important next step is to clarify how many patients entering CIAS trials already perform within the limits of "normal" cognitive performance. Pooled cognitive data from 15 multi-site trials involving patients with schizophrenia (n = 2,616) has recently been published, including both composite and domain-specific baseline MATRICS Consensus Cognitive Battery (MCCB) T scores (17). These T scores are standardized to age and sex-matched normative data, and have an estimated mean of 50 and standard deviation of 10 in the general healthy population (18). While the individual patient-level data is unavailable, visual inspection of the associated histograms suggests MCCB scores from the pooled trial data were broadly normally distributed (17). This coupled with the published sample means and standard deviations allow inferences to be made regarding the proportion of patients that performed within different cut-offs of the healthy normative

TABLE 1 | Eligible CIAS pharmacotherapy trials that listed an objectively measured cognitive deficit among their patient inclusion criteria.

Trial phase (as listed on ClinicalTrials.gov)	Total	Phase 2	Phase 2/3	Phase 3	Phase 4	Not reported
Number of eligible trials identified	87	46	2	9	19	11
Number requiring objectively assessed cognitive deficit for patient inclusion (%)	10 (11.5%)	6 (13%)	0 (0%)	0 (0%)	3 (15.8%)	1 (9.1%)

mean. On this basis, it appears that a number of patients scored within the normative range across each of the cognitive domains, for example, approximately fifty percent of patients had a T score equal to or greater than 40 for the "problem solving" MCCB subscale. Though the trials included in these pooled analyses were not exclusively pro-cognitive pharmacotherapy trials, the patient eligibility criteria used across these studies reflected those typically used in CIAS trials. Further analyses of existing patient-level data would help to clarify what proportion of patients entering CIAS pharmacotherapy trials already exhibit cognitive performance comparable to healthy controls. This will be valuable in helping to guide decision making in future CIAS trial design.

For the purposes of demonstrating efficacy, pro-cognitive intervention trials should be powered to detect a "clinically meaningful" difference between treatment groups, typically equating to an effect size in the small-medium range (e.g., Cohen's $d \geq 0.3$). However, recent evidence has suggested that it is unlikely that one would expect to see gains in cognition this large in up to a quarter of patients who score similarly to healthy controls on cognitive tasks (9–13). This means that the poorer performing patients would need to exhibit substantially greater cognitive gains in order to meet the pre-specified average group-based level of improvement. Based on the results of our database search, it also indicates that the majority of CIAS trials have likely been underpowered to detect beneficial treatment effects.

An interesting parallel in schizophrenia-related clinical trial methodology can be drawn with the development of treatments for negative symptoms. Like cognitive impairment, these are a common and highly debilitating aspect of schizophrenia for which there are currently no regulatory approved treatments (19–21). However, at the time of writing, all ongoing phase 2 and 3 trials listed on ClinicalTrials.gov in which a negative symptom measure is specified as the primary outcome, require that patients exhibit at least a moderate level of related symptomatology at screening and at baseline in order to be eligible for inclusion.

While it is more commercially practical and appealing to develop a treatment aimed at all patients within a diagnostic category, the substantial development costs involved, ever-increasing unmet need for an effective CIAS treatment and growing movement towards precision psychiatry (matching the right drug to the right patient at the right time) may make cognitive screening in the context of CIAS trials a necessity. There is also an argument that exposing cognitively normal patients to these investigational drugs represents an unnecessary and unethical risk, particularly given that polypharmacy is already common among patients with schizophrenia (22). Cognitive screening has already been successfully adopted in a small number of CIAS trials and could be adapted for use in clinical practice (if necessary) using relatively simple and brief testing procedures as is routine in other indications, such as Alzheimer's disease.

Practical considerations include the need to determine a consensus on suitable measures and thresholds for establishing a relevant level of cognitive impairment among patients with schizophrenia. Trials identified in our search used a range of tools and criteria to identify "impaired" patients (**Supplementary Table 1**), though a threshold ≥ 1 standard deviation below the healthy normative mean on an objective cognitive task(s) would align with similar guidelines in other disease-areas, as well as recent studies investigating the impact of cognitive impairment on real-world functioning in schizophrenia (15, 23). There is also an argument that this should be based on the hypothesized mechanism of action of the study drug and the cognitive domains thought most likely to be enhanced. Whether to then exclude or stratify "normally" performing patients across study arms during randomization are also potentially important considerations in this field, while pre-planned subgroup analyses may provide a practical intermediate approach, particularly during early stages of drug development.

Though the focus of this article is on CIAS pharmacotherapy trials, cognitive screening in the context of pro-cognitive intervention studies is likely to have implications beyond schizophrenia. Cognitive dysfunction is an important target for therapeutic intervention across a range of psychiatric populations, though substantial heterogeneity is also evident in cognitive profiles within these diagnostic groups (24–26). *Post hoc* analyses of trials involving patients with mood disorders also suggest that individuals with an objectively assessed cognitive deficit at baseline are substantially more likely to exhibit a clinically relevant improvement post-treatment, relative to those with normal cognitive functioning (27). This has led to similar calls for the use of cognitive screening in clinical trials to ensure the inclusion of only those patients with a clinically relevant deficit (23).

For the purposes of this report, we used ClinicalTrials.gov to identify randomized, double-blind, placebo-controlled, add-on pharmacotherapy trials conducted in patients with a diagnosis of schizophrenia, in which a paper-and-pencil or computerized cognitive task (or battery) was specified as a primary outcome measure. These study designs are widely recognized as the "gold standard" for evidence generation and are recommended by the National Institute of Mental Health (NIMH) MATRICS panel for use in CIAS trials (28). While this may not have provided an exhaustive list of all CIAS trials that have been conducted, it does provide a useful snapshot of contemporary methodological practices in this field, particularly for major commercial studies. We attempted to identify corresponding published literature for all trials in an effort to verify details listed on ClinicalTrials.gov (further information was found for 41 (47.1%) of the included trials). We excluded Phase 1 trials, which typically focus on establishing the safety of a compound while looking at potential efficacy signals across a range of clinical and symptomatic measures, though screening for cognitive dysfunction among patients included in these early phase studies may also be useful when attempting to detect a hypothesized pro-cognitive effect of a novel compound.

In conclusion, this paper highlights that purposive screening for cognitive impairment among patients with schizophrenia could increase statistical power to detect pro-cognitive treatment effects in clinical trials. While the focus of this article has been on pharmacotherapy studies, this could also have implications for other forms of therapeutic interventions. Further *post hoc* analyses of completed trials could help to shed further light on this hypothesis and ultimately aid in the development of effective treatments for this area of significant unmet clinical need.

AUTHOR CONTRIBUTIONS

JC designed and performed the database search and drafted the manuscript. JB and KG critically reviewed and approved the manuscript prior to its submission for publication.

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Positive Coping and Resilience as Mediators Between Negative Symptoms and Disability Among Patients With Schizophrenia

Haotian Chen[1,2†], Jianfeng Xu[1†], Yue Mao[1], Lili Sun[2,3], Yujing Sun[2] and Yuqiu Zhou[2]*

[1] Nursing Department, The Second Affiliated Hospital Zhejiang University School of Medicine (SAHZU), Hangzhou, China, [2] School of Nursing, Harbin Medical University, Daqing, China, [3] Department of Senior Citizens Welfare, Beijing College of Social Administration, Beijing, China

Objective: This study proposes a schizophrenia disability model to describe the associations between negative symptoms and disability to test the possible mediating roles of positive coping and resilience and to compare the relative weights of the indirect effects of these two mediators in an integrated whole.

Methods: A total of 407 hospitalized Han Chinese patients diagnosed with stable schizophrenia or schizoaffective disorder were included. Patients were evaluated using the following scales: the Simplified Coping Style Questionnaire (SCQ) for positive coping, the Connor-Davidson Resilience Scale (CD-RISC) for resilience, the Positive and Negative Syndrome Scale (PANSS) for negative symptoms, and the World Health Organization Disability Assessment Schedule, Version II (WHO-DAS II) for the severity of disability. The schizophrenia disability distal mediation model was constructed using the structural modeling (SEM) approach. Bootstrapping procedures and the PRODCLIN program were used to examine the mediating roles of positive coping and resilience.

Results: The schizophrenia disability model was well-fitted to the observed data. Positive coping and resilience together with negative symptoms explained 66% of the variance in disability. Positive coping and resilience partly mediated the negative symptoms–disability relationship. The bootstrapped unstandardized indirect effect was 0.319, and the direct effect was 0.224. Positive coping also has a significant positive effect on resilience. In addition, the ratio of the specific indirect effect of positive coping to the total indirect effect (48%) is higher than that of resilience (30%).

Conclusion: Positive coping and resilience are two key causal mediators of the negative symptoms–disability relationship. Positive coping and resilience are important personal resources for patients with schizophrenia. We found that the indirect effect of positive coping was relatively more important than that of resilience. This result suggests that personalized treatments aimed at resilience and positive coping can effectively buffer the impact of negative symptoms for patients with schizophrenia and promote rehabilitation.

Keywords: resilience, coping skill, personal resources, psychosis, schizophrenia, disability

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***Correspondence:**
Yuqiu Zhou
hlxzyq@126.com

†These authors share first authorship

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INTRODUCTION

Schizophrenia is among the most disabling disorders worldwide. Patients with schizophrenia have a wide range of deficits in their everyday functioning (1). Only approximately 40% of patients may experience a considerable improvement in functioning from the onset of psychosis, and more than 80% of patients with schizophrenia experience permanent disability (2). Negative symptoms have been identified as the main drivers of disability in patients with schizophrenia and are significantly better predictors than all other symptom domains, such as psychotic symptoms (3, 4). Approximately two-thirds of patients who achieve symptomatic remission continue to experience persistent problems with functioning (5). Recovery in schizophrenia refers to not only remaining free of psychopathology but also regaining social and vocational functions and returning to the community. Recently, some studies have suggested that patients with a similar severity of psychopathology may have different functional outcomes because of differences in personal resources (6, 7). Therefore, identifying the role of personal resources in the disability process of patients with schizophrenia may be an important step in developing effective targeted interventions that may offer new ways to reduce the impact of negative symptoms on disability and promote rehabilitation.

In the last few years, resilience has been considered a crucial personal resource and a therapeutic factor in psychiatry. Resilience refers to the ability to regain or maintain mental health and to positively adapt to adversity and challenges (8, 9). Resilience must be considered a multidimensional and dynamic construct that helps individuals redesign the relationship between their family and social and external support systems rather than a unitary construct (10). Resilience can positively influence real-life functioning and is considered a protective factor that guarantees a good outcome for patients with psychosis (11). Highly resilient individuals demonstrate adaptive psychological and physiological responses and maintain psychobiological allostasis when experiencing adverse events, which are extremely common in schizophrenia (12). Two long-term follow-up studies have clarified the close relationship between resilience and positive outcomes in patients with schizophrenia. A 15-year long-term follow-up study conducted by Harrow and Jobe (13) found that protective factors, including greater resilience, a favorable personality, and attitudinal approaches, contribute to better outcomes in patients with schizophrenia. In addition, resilience and a good personality allow recovered patients to maintain a state of recovery after 20 years, even without medication (14). Zizolfi et al. (15) found that resilience factors may predict the severity of symptoms and the extent of psychosocial functioning and are considered an intervening variable between psychopathology and global functioning. Galderisi et al. (6) also found support for the hypothesis that resilience partially mediates the relationship between avolition and real-life functioning. In Mihali's et al. (16) resilience theory, the effects of resilience, which is conferred by environmental, genetic, and social factors, can preclude, reverse, or slow the progression of schizophrenia. However, it remains unclear how resilience protects patients from disability and whether resilience works by buffering damage from negative symptoms.

Coping is a complex interaction between the individual and the environment that can be distinguished into emotion-focused coping, problem-focused coping, and avoidance-focused coping. Generally, problem-focused coping is associated with better outcomes and is therefore described as positive coping (17). Patients with schizophrenia who have serious negative symptoms might be characterized as more dependent on passive, emotion-focused coping, such as neglecting the problem, than on problem-focused coping when they face adversities. Patients with more severe schizophrenia symptoms often have poor outcomes partly because of their reduced use of positive coping strategies (18). Boschi et al. (19) also documented that adaptive coping is the best means to promote better functional outcomes for patients with schizophrenia. In addition, the severity of psychiatric symptoms is inversely correlated with positive coping, which in turn is correlated with functional outcomes (7).

Although coping and resilience are similar and the terms are used interchangeably, there is growing consensus that resilience and coping are distinct but related constructs. Gooding et al. (10) qualitatively interviewed 23 schizophrenia patients who had expressed suicidal thoughts and behaviors and found that an active response can combat negative stressors and is an effective psychological mechanism to promote resilience. A study of 200 postdoctoral scholars from a large research institution revealed that positive coping serves as an important mediator of the relationship between positive emotions and resilience and that an increase in positive coping can build resilience (20). However, the issues of whether positive coping and resilience are distinct constructs, whether positive coping is linked to resilience in patients with schizophrenia patients, and how these characteristics work together in disability have not been thoroughly explored.

Previous studies have paid attention to only a single mediator and have neglected the existence of interactions among mediators. This gap hinders the ability to fully understand the mechanisms of these personal resources in buffering the influence of negative symptoms on disability and to promote more effective and efficient intervention measures. Given the theoretical and empirical evidence, we propose a schizophrenia disability model (**Figure 1**) to describe the associations among negative symptoms, positive coping, resilience, and disability to test the possible mediating role of positive coping and resilience and to compare the relative weights of the indirect effects of these two mediators as an integral whole. We hypothesize that negative symptoms will have direct effects on disability, as previous studies have demonstrated, and will have indirect effects on disability that are mediated by positive coping and resilience. We further hypothesize that positive coping also has a direct influence on resilience.

MATERIALS AND METHODS

Procedures and Participants

Participants were recruited from the Third People's Hospital of Daqing, which is a neurosis faculty hospital in the Heilongjiang province of China. Data were collected from March 2014 to March 2015. The participants were assessed to determine their coping style, resilience, and disability using interviewer-assisted and self-report methods. Psychiatric symptoms were assessed by two well-trained and experienced research psychiatrists who were not

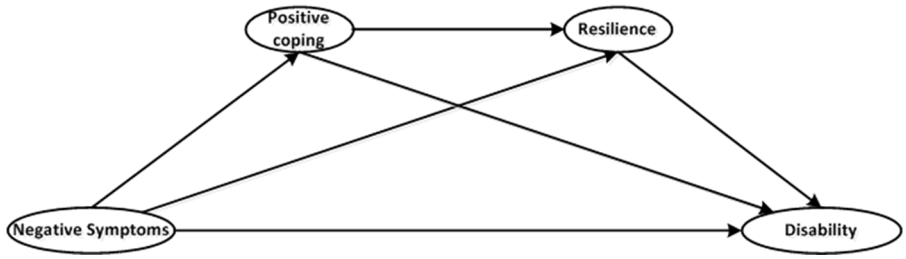

FIGURE 1 | Proposed schizophrenia disability distal mediation model.

involved in the patients' treatment and were blinded to all coping styles, resilience, and disability scores for the duration of the study. Patients with schizophrenia or schizoaffective disorder, as diagnosed by experienced research psychiatrists using the Structured Clinical Interview for the DSM-IV, were recruited after being referred by their clinicians. All patients were aged 18 years or above and signed a general written informed consent form. All patients were not taking antidepressants or mood stabilizers and had been in stable remission for at least 3 months. Participants were excluded if they were diagnosed with diseases known to affect neurocognition, such as Alzheimer's disease, if they had a history of substance abuse or dependence, such as alcohol drinking, in the 3 months preceding enrollment, or if they were undergoing treatments, such as modified electroconvulsive therapy (MECT), that made them unable to complete the assessments. All participants received a complete description of our study and provided written informed consent. Our study received approval from the medical ethics committee of Harbin Medical University (Daqing) and strictly followed the principles of the Declaration of Helsinki.

Measures

Positive Coping

The most widely used measures of coping style are the 66-item Ways of Coping Questionnaire (WCQ) (21) and the 30-item Coping Style Questionnaire (CSQ) (22). However, Chinese researchers have determined that these tools are not appropriate for Chinese populations because of the inconsistent factor analysis results. In our study, positive coping was assessed with the Simplified Coping Style Questionnaire (SCQ) developed by Xie (23). The SCQ is based on the WCQ and the characteristics of the Chinese population. It is a 20-item self-report questionnaire with two categories: positive coping styles (1–12 items, e.g., confiding in others) and negative coping styles (13–20 items, e.g., escaping troubles by taking a break). For the purpose of our study, the negative coping subscale was omitted, and only the positive coping subscale (SCQ-P) was used. The participants rated each item from 0 (never) to 3 (often) based on the frequency with which they used a given strategy when addressing a stressful situation or problem. A previous study reported that the positive coping scale had good reliability (24).

Resilience

Resilience was measured using the Connor-Davidson Resilience Scale (CD-RISC), which is a 25-item, 5-point Likert-type scale ranging from 0 (not true at all) to 4 (true all the time) (25). The participants rated each item based on how they felt over the previous month. The total score ranges from 0 to 100, with higher scores representing greater resilience. Given the possible differences in the factor structure of resilience in people with American and Chinese cultural backgrounds, we used the 3-factor structure (26), which is more meaningful to Chinese people than the 5-factor structure suggested by Connor and Davidson. The 3-factor structure comprises tenacity, strength, and optimism, all of which have adequate internal reliability (0.88, 0.80, and 0.60, respectively). The Chinese version of the CD-RISC also has good internal consistency (26).

Negative Symptoms

The Positive and Negative Syndrome Scale (PANSS) is currently the most widely used symptom measure in schizophrenia research settings. The PANSS instrument includes 30 items that were originally organized into three mutually exclusive subscales: positive symptoms (7 items), negative symptoms (7 items), and general psychopathology (16 items). Each symptom is rated on a 7-point scale from 1 (absent) to 7 (extreme). In the current study, we used the negative symptom scale of the PANSS to assess negative symptoms. We used analysis of variance (ANOVA) to examine interrater reliability, and psychiatrists with an intraclass correlation coefficient lower than 0.90 were excluded prior to the study. The remaining psychiatrists were trained, and reliability was retested at least once a month to maintain high interrater reliability.

Disability

We used the World Health Organization Disability Assessment Schedule, Version II (WHO-DAS II) to assess disability in patients with schizophrenia (27). The WHO-DAS II is a multidimensional instrument that provides a more accurate assessment of functional outcomes and disabilities in patients with schizophrenia compared with traditional instruments used to assess functioning (28). Because it is frequently difficult for hospitalized patients with schizophrenia to maintain employment, we selected the WHO-DAS II's alternate 32-item scoring, which omits four items in the life activities domain related to work situations. The 32-item WHO-DAS II consists of six domains: cognition (six items), mobility (five items), self-care (four items), getting along (five items), life activities (four items), and participation (eight items). The patients were asked to rate each item from 1 (none) to 5 (extreme/cannot do) based on how much difficulty they had

in the last month. The summary scores vary from 0 to 160 and are calculated by adding the ratings for each item, as described in the WHO-DAS manual (29). Higher scores reflect greater disability. It has previously been demonstrated that the Chinese version of the WHO-DAS II has good validity and reliability (30).

Statistical Analyses

Raw data for normality, outliers, and missing values were assessed prior to the analyses. We also used the raw data to calculate a variance–covariance matrix to avoid inaccurate standard errors, as described by Cudeck (31). Correlation analysis was performed using the Pearson correlation test.

According to the "two-step approach" recommended by Anderson and Gerbing (32), we evaluated the measurement model and the structural model sequentially. Confirmatory factor analysis (CFA) was performed first to test whether the observed variables accurately reflected each of the underlying latent variables and to test the convergent validity and discriminant validity of the measurement model.

Following the measurement model, we used structural equation modeling (SEM), which can model multiple latent variables simultaneously while considering the reliability of their indicators, to examine the antecedents and consequences of the four proposed latent variables (one exogenous: negative symptoms; and three endogenous: positive coping, resilience, and disability). The model fit was evaluated with five indicators: the normed chi-square (χ^2/df), the comparative fit index (CFI), the incremental fit index (IFI), the Tucker-Lewis Index (TFI), and the root mean-squared error of approximation (RMSEA). A good-fitting model requires the following standard indices: χ^2/df between 1 and 3 and IFI, TLI, and CFI greater than 0.90. In addition, the 90% confidence interval of the RMSEA should be under 0.08 (33–35).

Our schizophrenia disability distal mediation model consisted of three specific indirect effects. Positive coping and resilience served as a single mediator between negative symptoms and disability, respectively, in the first and second specific indirect effects. In the third specific indirect effect, both positive coping and resilience mediated the relationship between negative symptoms and disability. The total indirect effect, direct effect, and total effect between negative symptoms and disability were tested using bootstrapping procedures. Two thousand samples were requested for bootstrapping, and the bias-corrected confidence interval (CI) was set to 95%. Because all of the major SEM software packages can only estimate the total indirect effects and not specific indirect effects (36), the significance of each specific indirect effect in our distal mediation model was also tested using the PRODCLIN program (37). All statistical analyses were performed with SPSS version 22.0 and Amos version 24.0.

RESULTS

Demographic and Clinical Data

A total of 407 unrelated hospitalized patients with schizophrenia or schizoaffective disorder were recruited. All patients were Han Chinese with an average age of 39.3 (SD 10.6) years; 53.6% were male, and 31% were married. Their average total number of hospitalizations was 4.3 (SD 4.3), and their average course of schizophrenia was 11.7 (SD 9.9) years (for details, see **Table 1**). All of the included participants were receiving antipsychotic treatments (14% with a typical antipsychotic only, 78% with an atypical antipsychotic only, 8% mixed). The average PANSS total score was 61.8 (SD 14.4), the average CD-RISC score was 54.4 (SD 22.5), the average SCQ-P total score was 18.7 (SD 9.1), the average SAPS total score was 26.4 (SD 19), and the average WHO-DAS II total score was 66.9 (SD 19.6), as shown in **Table 1**.

Preliminary Analyses

No outliers or missing values were recorded in our raw data. All of the items had a normal distribution when tested for skewness and kurtosis. The results of the Pearson correlation test show significant correlations among all of the variables. Negative symptoms were negatively related to positive coping and resilience and were positively related to disability. Positive coping was negatively related to disability and was positively related to resilience. Resilience was negatively related to disability (for details, see **Table 2**). According to the sample size calculation tables provided by Fritz and Mackinnon (38) and our results from the structural model, the smallest path coefficients from exogenous variance to the mediator (r = -0.35) and the smallest path coefficients from the mediator to endogenous variance (r = -0.34) are the H level (the path coefficient of the H level is 0.26). A total of 148 participants for a bias-corrected bootstrap or 161 participants for the PRODCLIN program constitute a

TABLE 1 | Sociodemographic characteristics and the means and standard deviations (SDs) of clinical characteristics (n = 407).

Characteristics	Mean	SD
Demographics		
Age (years)	39.3	10.6
Male (%)	53.6	
Married (%)	31.0	
Duration of illness (years)	11.7	9.9
Number of hospitalizations	4.3	4.3
Symptoms (PANSS)	61.8	14.4
PANSS Positive Symptoms	12.9	5.4
PANSS Negative Symptoms	17.8	6.2
PANSS General Symptoms	31.1	10.7
Resilience (CD-RISC)	54.4	22.5
Tenacity	24.0	11.9
Strength	19.6	8.7
Optimism	5.9	3.4
Positive coping style (SCQ-P)	18.7	9.1
Disability (WHO-DAS II)	66.9	19.6
Cognition	10.9	4.3
Mobility	7.9	2.9
Self-care	6.8	3.0
Getting along	8.4	3.3
Life activities	7.2	3.1
Participation	18.8	6.7

SCQ-P, the positive coping subscale of the Simplified Coping Style Questionnaire; CD-RISC, the Connor-Davidson Resilience Scale; PANSS, The Positive and Negative Syndrome Scale; WHO-DAS II, the World Health Organization Disability Assessment Schedule, Version II.

TABLE 2 | Correlation analysis of study variables.

Variables	1	2	3	4
1. Negative symptoms	1			
2. Positive coping styles	-0.45***	1		
3. Resilience	-0.51**	0.62***	1	
4. Disability	0.56***	-0.68***	-0.64***	1

****p < 0.001; **p < 0.01.*

sufficient sample to achieve an empirical power of 0.8. Therefore, our sample size of 407 participants exceeded the required size.

Measurement Model

A good measurement of the latent variables is a necessary precondition for a causal relations analysis of the latent variables. Therefore, we first applied CFA to test the confidence of the relationship between the observed variables and the underlying latent variables. Items with factor loadings lower than 0.60, which indicates a lack of reliability (39), were discarded, as recommended by Hooper et al. (40). Three items for disability, two for positive coping, and two for resilience were excluded from further analyses (the factor loadings were between 0.43 and 0.52).

The construct convergent reliability and discriminant validity were measured. The composite reliability (CR) was between 0.84 and 0.98, and the average variance extracted (AVE) of the latent variables was between 0.55 and 0.63. All four constructs in our study had good convergent validity (39, 41). The AVE analysis showed that the AVE value of each latent variable was much larger than the square of Pearson's correlation coefficient for each pair of latent variables, which indicates that our study had good discriminant validity (41) (**Table 3**).

For disability, 29 items within six subdimensions remained after the unreliable items were discarded. We used the first-order and second-order CFA. To determine the fit with the data, we computed the target coefficient, which is the ratio of the chi-square of the first-order CFA to the chi-square of the second-order CFA, according to Marsh (42). The closer the target coefficient is to 1, the closer the second-order CFA is to the first-order CFA. The target coefficient of disability of 0.98 indicates that the second-order CFA explained 98% of the variation in the first-order CFA of disability. Therefore, the fitness index of the second-order CFA of disability was good. The measurement model for resilience consisted of three first-order factors that were identified. Although this model could not be distinguished in a statistical sense, all of the standardized second-order factor loadings were between 0.77 and 0.85, above the loading of 0.70 recommended by Hair et al. (39). Therefore, we used the second-order CFA of resilience and disability instead of the first-order CFA to make the model more precise.

TABLE 3 | Results of the average variance extracted (AVE) analysis and the composite reliability (CR) of the latent variables.

Variables	1	2	3	4	CR
1. Negative symptoms	0.55				0.98
2. Positive coping styles	0.20	0.59			0.93
3. Resilience	0.26	0.39	0.63		0.84
4. Disability	0.31	0.46	0.41	0.63	0.91

The shaded portion of the table is the AVE value, and the square of Pearson's correlation coefficient is shown below the AVE value.

Structural Model

Following the measurement model, a structural equation model of disability in schizophrenia was developed to test how well the proposed model fit the collected data. The results of the SEM for our distal mediation model are displayed in **Figure 2**. In the model, the exogenous variable of negative symptoms explained 24% of the variation in positive coping. For resilience, the model explained 59% of the variation in negative symptoms and positive coping. Finally, positive coping and resilience, together with negative symptoms, explained 66% of the variation in disability.

The bootstrapped unstandardized indirect effect was 0.319, with a 95% confidence interval between 0.317 and 0.481, and the direct effect was 0.224, with a 95% confidence interval between 0.112 and 0.330; zero was not included among the lower and upper bounds, indicating that the data are consistent with a partial mediation model (43). None of the asymmetric confidence intervals included a 0 value, indicating that all of the specific indirect effects were established (for details, see **Table 4**). The ratio of the indirect effect to the total effect was 0.63, indicating that positive coping and resilience accounted for approximately two-thirds of the effect of negative symptoms on disability. Among the three specific indirect effects, positive coping was the most vital mediator between negative symptoms and disability based on the ratios of the specific indirect effect to the total indirect effect: the mediation path with only positive coping (48%), the mediation path with only resilience (30%), and the mediation path with both positive coping and resilience (23%). The model was well-fitted to the observed data, with the following goodness-of-fit statistics: $\chi^2/df = 1.257$, CFI = 0.969, GFI = 0.844, IFI = 0.969, TLT = 0.968, and a 90% confidence interval for the RMSEA = 0.05; 0.06.

DISCUSSION

To the best of our knowledge, our research is the first to establish a mediation model to simultaneously specify the mediating effect of positive coping and resilience on the negative symptoms–disability relationship in patients with schizophrenia. The schizophrenia mediation model explained 66% of the variation in disability.

Our study confirmed that positive coping partly mediated the relationship between negative symptoms and disability in schizophrenia, in line with Meyer (44). We also confirmed that resilience can serve as another important mediator between negative symptoms and disability, which is consistent with the study by Galderisi et al. (6). Resilience reflects the ability to bounce back from stressful or traumatic life experiences rather than adapting passively to the context. The positive predictive role of resilience in functional outcomes and life satisfaction have been clarified in some study populations, such as adolescents, adults (45), and older geriatric patients with multiple comorbidities after orthopedic surgery (46). The identification and development of personal resources, such as resilience and positive coping, help patients with schizophrenia

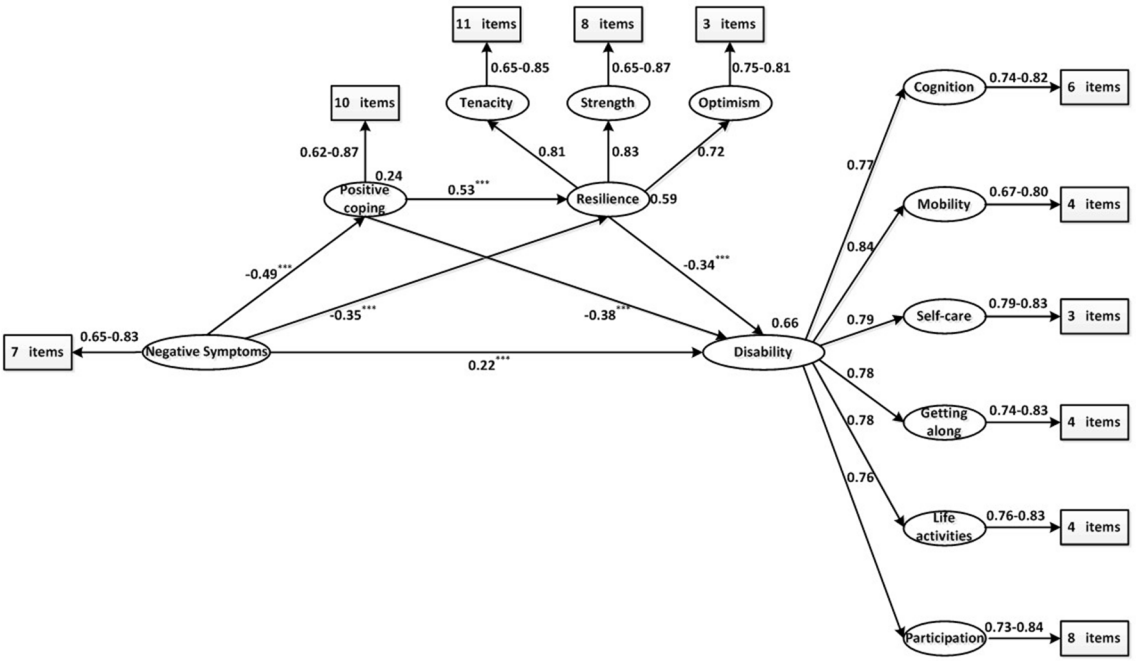

FIGURE 2 | Result of the proposed schizophrenia disability distal mediation model. The ellipses represent latent variables. The rectangles represent observed variables. All path coefficients are standardized. The squared multiple correlation (R^2) value for the dependent variable appears above the ellipses. *** $p < 0.001$.

TABLE 4 | Results of bootstrap and PRODCLIN testing.

Variance	Point estimates	Bootstrapping Bias-corrected 95%CI		Mackinnon PRODCLIN 95%CI		Ratio (%)*
		Lower	Upper	Lower	Upper	
Negative symptoms → Disability	Indirect effect 0.391	0.317	0.481	NS→PC→DI 0.079	0.227	47.6
				NS→RE→DI 0.04	0.168	30.4
	Direct effect 0.224	0.112	0.33	NS→PC→RE -0.426	-0.187	22.6
				PC→RE→DI -0.194	-0.056	

2,000 bootstrap samples.

NS, negative symptoms; PC, positive coping; RE, resilience; DI, disability; CI, confidence interval.

**The ratio of the specific indirect effect to the total indirect effect.*

obtain functional recovery, which is difficult to achieve by relying only on pharmacological therapy. However, another study found that resilience was only associated with social functioning and not with the severity of symptoms (7). In this study, psychiatric symptom severity scores were calculated as a composite score based on several items extracted from the positive symptoms, negative symptoms, and general symptoms subscales, which was included in the final SEM as an observed variable. This procedure may have masked specific predictor-mediator-outcome links (47). Another reason for the difference may have been transcultural differences in resilience (48). This possibility sheds light on the need for future studies to develop culture-specific psychosocial intervention programs to prevent schizophrenia-related disability.

The indirect effect of negative symptoms can also be passed on to disability sequentially through positive coping and resilience. These results may be interpreted as indicating that schizophrenia patients with severe negative symptoms are likely to feel unable to manage stress and are therefore more inclined to ignore their problems rather than using positive coping, which depends on attentional volition and adequate cognitive function (49). This deficit makes it more difficult for patients with schizophrenia to adapt to circumstances, to develop and maintain solid interpersonal relationships, or to

bounce back from a negative situation. Over time, patients become more isolated and unable to share family responsibilities or live on their own, and disability ultimately develops.

Although both coping and resilience are related to responses to stress, these concepts are distinct. Positive coping involves a set of skills, whereas resilience emphasizes the ability to adapt to and bounce back from extremely unfavorable circumstances. Moreover, the acceptable discriminant validity suggests that positive coping and resilience can be validly measured as different variables that are distinct from negative symptoms and disability, yet related to them. Therefore, positive coping and resilience not only coexist but are also significantly related. Distinguishing between positive coping and resilience may improve our understanding of these mediators, which in turn can enhance our understanding of the pathways of disability in schizophrenia.

Our findings have clinical implications. As any clinician knows, it is very difficult to treat the negative symptoms of antipsychotic medications. Antipsychotic treatment may produce an adverse effect on long-term outcomes by reducing patients' brain volume and cognitive function (50). According to our results, resilience and positive coping may play protective roles in the process of preventing disability. It may be possible to prevent the damage caused by negative symptoms for patients with schizophrenia by providing targeted interventions to increase positive coping and resilience. In our distal mediation model, positive coping was significantly positively related to resilience, indicating that positive coping may enhance resilience in patients with schizophrenia. Moreover, the ratio of the indirect effect of positive coping to the total indirect effect was 47.6%, higher than that of resilience (30.4%). The aforementioned causes indicate that positive coping should be adequately addressed in integrated interventions for schizophrenia and that treatment should sufficiently utilize the catalytic role of positive coping in resilience. However, this finding does not mean that interventions targeting resilience are not important for preventing disability in patients with schizophrenia. To optimize the protective effect of positive coping on disability in patients with schizophrenia, we also need to promote resilience, which is more proximal to the dependent variable disability. Overall, we suggest the need to integrate positive coping and resilience-targeted intervention into the schizophrenia health management model to sufficiently utilize patients' personal resources to prevent disability.

This study is not free of limitations. In this study, positive coping, resilience, and disability were assessed based on self-reports from patients with schizophrenia who had insight deficits to different degrees and may have underestimated their level of impairment (51). However, the validity of self-reported outcomes has been reported in some studies (51, 52). Moreover, some researchers have emphasized the importance of considering the self-reported outcomes of patients with schizophrenia in both research and treatment (53, 54). All of the patients had been hospitalized for at least 3 months before their inclusion in our study, and patients who could not complete all of the assessments for any reason were excluded. Therefore, it may not be possible to extrapolate our results to such patients. In addition, a study on resilience in older adults conducted by Callegari et al. (55) found that the level of resilience of older adults who lived in a nursing home, especially older adults suffering from psychiatric disorders, was significantly lower compared with those who lived at home. The results indicated that resilience skills and individual mental resources to face adversities in life may be reduced by institutionalization and psychiatric disease. Institutionalized hospitalization may cause the resilience of patients with psychiatric disorders to be weaker, which is not conducive to recovery. Therefore, to avoid institutionalization, adequate social support may be important when possible. Finally, we would like to acknowledge that the causality of the investigated variables cannot be confirmed because of the cross-sectional design of our study. It seems possible that deficits in positive coping may also have an adverse effect on negative symptoms. Patients with schizophrenia have difficulties using positive coping and usually cannot efficiently handle the stress of daily life, and there is no consensus regarding which coping strategies are most effective (56). Over time, patients become unable to tolerate stressful environments, which leads to an exacerbation of negative symptoms. Thus, we encourage future investigations to clarify the causal relationship between coping and negative symptoms using dynamic long-term studies.

To conclude, we clearly demonstrate that positive coping and resilience are two key causal mediators of the negative symptoms–disability relationship, and we provide new information regarding the complex relationship between negative symptoms and disability in schizophrenia. Furthermore, we found that the indirect effect of positive coping is relatively more important than that of resilience. Future clinical interventions to prevent schizophrenia-related disability can appropriately increase the proportion of interventions that target positive coping to optimize the buffering effect of positive coping and resilience.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript.

ETHICS STATEMENT

All the participants received a complete description of our study and provided written informed consent. Our study received approval from the ethics committee of Harbin Medical University (Daqing) and strictly followed the principles of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

HC, JX, YM, and YZ conceived and designed the experiments. HC, JX, YM, LS, and YS conducted the experiments and collected data. HC and JX analyzed the results. HC wrote the main manuscript text. All of the authors reviewed the manuscript.

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Pan-London Network for Psychosis-Prevention (PNP)

Paolo Fusar-Poli[1,2,3,4], Andrés Estradé[1,5], Tom J. Spencer[2,6], Susham Gupta[7], Silvia Murguia-Asensio[8], Savithasri Eranti[9], Kerry Wilding[10], Olivier Andlauer[7,11], Jonathan Buhagiar[7], Martin Smith[2], Sharon Fitzell[2], Victoria Sear[2], Adelaide Ademan[8], Andrea De Micheli[1,2] and Philip McGuire[4,6]*

[1] Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom, [2] OASIS Service, South-London and Maudsley NHS Foundation Trust, London, United Kingdom, [3] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [4] National Institute for Health Research, Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, London, United Kingdom, [5] Department of Clinical and Health Psychology, Catholic University, Montevideo, Uruguay, [6] Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [7] HEADS UP, East London NHS Foundation Trust, London, United Kingdom, [8] THEDS, East London NHS Foundation Trust, London, United Kingdom, [9] NEIS, East London NHS Foundation Trust, London, United Kingdom, [10] Luton and Bedfordshire Service for the Prevention of Psychosis, East London NHS Foundation Trust, London, United Kingdom, [11] Centre for Psychiatry, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

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Erika Jääskeläinen, University of Oulu, Finland

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***Correspondence:**
Paolo Fusar-Poli
paolo.fusar-poli@kcl.ac.uk

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Background: The empirical success of the Clinical High Risk for Psychosis (CHR-P) paradigm is determined by the concurrent integration of efficient detection of cases at-risk, accurate prognosis, and effective preventive treatment within specialized clinical services. The characteristics of the CHR-P services are relatively under-investigated.

Method: A Pan-London Network for psychosis prevention (PNP) was created across urban CHR-P services. These services were surveyed to collect the following: description of the service and catchment area, outreach, service users, interventions, and outcomes. The results were analyzed with descriptive statistics and Kaplan Meier failure function.

Results: The PNP included five CHR-P services across two NHS Trusts: Outreach and Support In South-London (OASIS) in Lambeth and Southwark, OASIS in Croydon and Lewisham, Tower Hamlets Early Detection Service (THEDS), City & Hackney At-Risk Mental State Service (HEADS UP) and Newham Early Intervention Service (NEIS). The PNP serves a total population of 2,318,515 Londoners (830,889; age, 16–35 years), with a yearly recruitment capacity of 220 CHR-P individuals (age, 22.55 years). Standalone teams (OASIS and THEDS) are more established and successful than teams that share their resources with other mental health services (HEADS UP, NEIS). Characteristics of the catchment areas, outreach and service users, differ across PNP services; all of them offer psychotherapy to prevent psychosis. The PNP is supporting several CHR-P translational research projects.

Conclusions: The PNP is the largest CHR-P clinical network in the UK; it represents a reference benchmark for implementing detection, prognosis, and care in the real-world clinical routine, as well as for translating research innovations into practice.

Keywords: psychosis, schizophrenia, risk, at risk mental state, structured interview for psychosis-risk syndromes, prevention

INTRODUCTION

Under standard care, outcomes of psychotic disorders are characterized by poor response to treatments, high chronicity and disability, low functional level, and high burden to families and society (1). Early interventions at the time of a first psychotic episode are associated with some important clinical benefits (2). However, these interventions are not particularly effective at preventing relapses (2) or reducing the duration of untreated psychosis (3). According to the definition of the World Health Organization, preventive strategies for mental disorders integrate the Gordon's classification of the prevention of physical illness (universal—targeted at the general public, selective—targeted at those with risk factors or indicated targeted at those with minimal signs or symptoms of mental disorders) and the classic public health classification (primary—seeking to prevent the onset of a mental disorder, secondary—seeking to lower the rate of established disorder, tertiary—seeking to reduce disability and relapses) (4).

Universal, selective, and indicated preventive interventions are "included within primary prevention in the public health classification" [page 17 in (4)].

Preventive strategies have entered clinical psychiatry through the Clinical High Risk paradigm for Psychosis [CHR-P hereafter (5)]. The conceptual and operational framework that characterizes the CHR-P paradigm has been reviewed elsewhere (6, 7). Briefly, young (typically 14–35 years) individuals presenting with attenuated symptoms of psychosis coupled with help-seeking behavior (8) and functional impairments (9) are assessed through validated psychometric assessment interviews (10). These interviews ascertain in the context of a clinical assessment (11), whether the individual is at-risk of developing psychosis. The increased risk is accounted for by the accumulation of specific risk factors for psychosis (12) and cumulates to about 20% of CHR-P developing the disorder at 2-year follow-up [from eTable 4 in Fusar-Poli et al. (13)]. The individuals who will eventually meet the CHR-P intake criteria will then be offered specialized care which involves needs-based intervention and preventive treatments [for a recent review of their efficacy, see the studies by David et al. (14, 15)]. These treatments have a threefold aim of reducing the presenting problems, reducing the risk of progression from a CHR-P stage to the first onset of the disorder, and reducing the duration of untreated psychosis in the case the disorder would occur (16, 17). In line with these arguments, interventions in CHR-P individuals are defined as indicated primary prevention of psychosis. The empirical success of the CHR-P paradigm is determined by the concurrent integration of three core components: i) efficient detection of cases at-risk, ii) accurate prognosis, and iii) effective preventive treatment (18, 19). On a real-world scenario, these three components are developed, integrated, and monitored by the specialized CHR-P clinics that operate in different health care systems worldwide. Despite their crucial relevance to the implementation of the CHR-P paradigm in clinical practice, research into CHR-P services is relatively scarce. For example, the characteristics of CHR-P services, their relationship with the specific catchment areas, the type of outreach implemented, the characteristics of the service users, the types of indicated primary prevention strategies adopted, and the outcomes are not fully addressed. This lack of knowledge limits the broader scalability of the CHR-P paradigm and the associated clinical guidelines. For example, in April 2016, NHS England implemented a new Access and Waiting Times-Standard for Early Intervention in psychosis (AWT EI Standard) to extend the prevention of psychosis across England. The Standard mandates an evidence-based nationwide detection and rapid treatment of CHR-P patients aged 14 to 35 years. Therefore, the NHS requires all suspected patients presenting to early intervention services in England to be assessed and interviewed for a potential state of CHR-P (10). Yet, the standard does not regulate how CHR-P services should be best configured to achieve this goal. Similar lifespan preventive approaches are under consideration for development in other countries worldwide (20).

The current study aims at overcoming these limitations. We present the new consortium of CHR-P services that are active across London in the detection of individuals at-risk, their assessment and prognosis and their clinical management. The main aim was to describe the characteristics of CHR-P services across London, local catchment areas, outreach implemented, service users, indicated primary prevention strategies and outcomes. This information was then used to appraise the potential and clinical impact of the consortium for advancing the care of CHR-P individuals.

METHODS

This manuscript originates from a reflective workshop on the progress, challenges, and future directions of CHR-P services in the London area, which was held on November 21, 2018, at the Institute of Psychiatry, Psychology, and Neurosciences (IoPPN) at King's College London. Senior representatives from a variety of CHR-P services attended the workshop. Following the conference, a proforma was created listing critical data to be collected for each CHR-P team, which included the following domains: i) description of the CHR-P service and catchment area, ii) outreach, iii description of service users, iv) interventions, and v) outcomes. When available, quantitative data were summarized in a descriptive table using mean and SD for continuous variables and frequencies for categorical variables. Furthermore, for each CHR-P service, we collected the initial sample size, the individual follow-up time, and the event (onset of psychosis). The current (2018) local population was estimated in each borough through the london.gov.uk website. We reported both total population and the 16- to 35-year age group, to better match the age range of the CHR-P patients. The local, as well as the national incidence of psychosis for the age range of 16 to 35 years, was estimated for each borough using PsyMaptic (http://www.psymaptic.org). The onset of psychosis was determined through the CHR-P instruments employed in each service. These data were then plotted and analyzed with a failure function (1-Kaplan Meier) and confidence intervals. The Kaplan Meier analysis was truncated when less than 10 individuals at-risk were available. The analyses were done in STATA.

RESULTS

OASIS Lambeth and Southwark (OASIS)

Service and Catchment Area Description

Outreach and Support In South-London (OASIS) was set up in 2001, and it is one of the oldest CHR-P services in the UK. The first 10 years of the service, along with its core characteristics have been presented in a previous publication (21). OASIS is part of the South London NHS Foundation Trust (SLaM) and provides early detection, assessment, and care for the boroughs of Lambeth (total population, 334,724; population age, 16–35 years; 133,543 in 2018 (22), **Figure 1**) and Southwark (total population, 322,302; population age, 16–35 years; 120,948 in 2018 (22), **Figure 1**). OASIS is a standalone service which is separated from the local first episode services.

Incidence of psychosis in Lambeth and Southwark is estimated at 71.9 and 69.6 cases per 100,000 person-years, respectively, which is higher than England national average of 34.9 cases (**Figure 2**).

OASIS is closely linked with the Institute of Psychiatry, Psychology, and Neuroscience at King's College London, and represents a successful integration of clinical research in the local NHS Trust.

The team is composed of two part-time consultant psychiatrists, a team leader, two clinical psychologists, an occupational therapist, a higher trainee psychiatrist, a part-time assistant psychologist, and a mental health nurse. In addition, there are several honorary visiting clinicians from all over the world who are supporting the clinical activities of the team. Inclusion criteria are being aged 14 to 35 years, having the general practitioner (GP) in the local borough, being help-seeking, and meeting the CHR-P criteria [determined with the Comprehensive Assessment of at Risk Mental States (CAARMS) 12/2006 (23)]. After inclusion OASIS provides care for 2-years. The caseload is approximately 80 patients per year.

Outreach

The success of OASIS is grounded on a long-standing and comprehensive outreach campaign with several local agencies. Details on the engagement activities of OASIS have been presented in previous publications (21, 24). GPs are the main source of referral to OASIS but referrals from self, caregivers or relatives, schools and colleges, social services or supported accommodations, community mental health services, inpatient mental health services, child and adolescent mental health services, early intervention for psychosis services, accident and emergency departments, police and criminal justice system, and physical health services are also allowed. More recently, a specific website has been launched to promote the clinical service (https://www.meandmymind.nhs.uk).

Service User Description

Over the past years, the OASIS has taken care of 419 patients meeting the CAARMS 12/2006 (23) CHR-P criteria. The vast majority of service users met the Attenuated Psychosis Symptom (APS) subgroup of the CHR-P (**Table 1**), but Brief and Limited Intermittent Psychotic Symptoms (BLIPS) were also well represented (19.59%). Service users are mostly white (48.55%) young (age, 22.84 years) males (54.65%) who are single (78.48%) and unemployed (57.87%) at the time of contact with the service (**Table 1**). The presence of comorbid substance use or other psychiatric conditions is not an *a priori* exclusion criterion for OASIS and has been detailed in previous publications (25).

Interventions and Outcomes

As previously detailed, of the initial sample collected since inception, 33% of OASIS patients are treated with cognitive behavioral therapy (CBT) only; 17% of subjects received antipsychotics in addition to CBT sessions (26). Another 17% of subjects were prescribed with antidepressants in addition to CBT

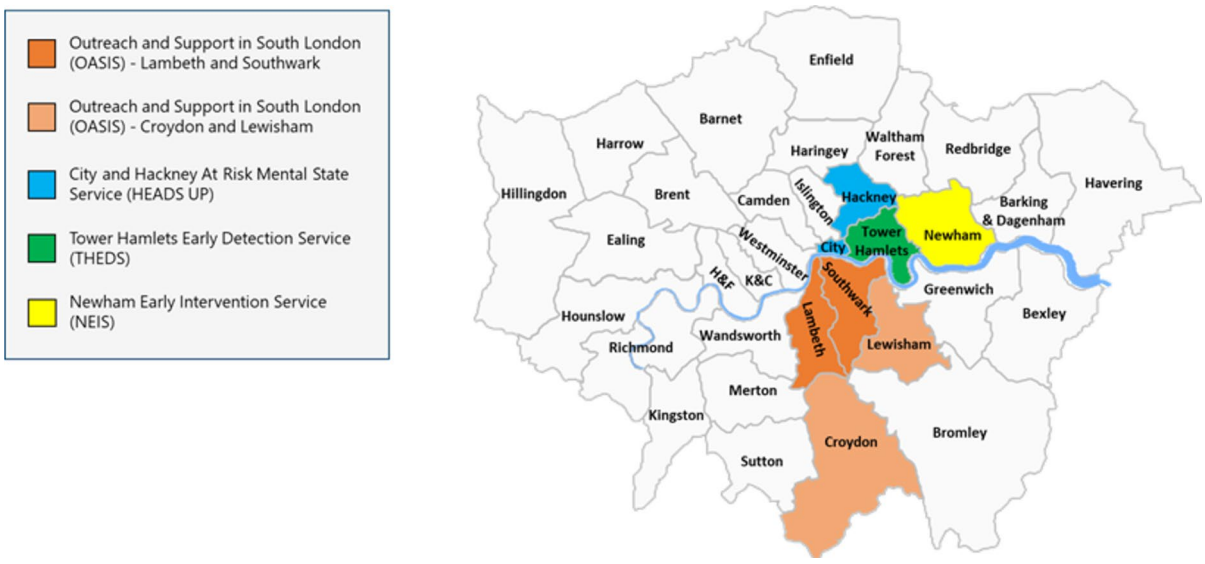

FIGURE 1 | Pan-London Network for Psychosis-Prevention (PNP). Luton and Bedfordshire services were not included. K&C, Kensington and Chelsea; H&F Hammersmith and Fulham.

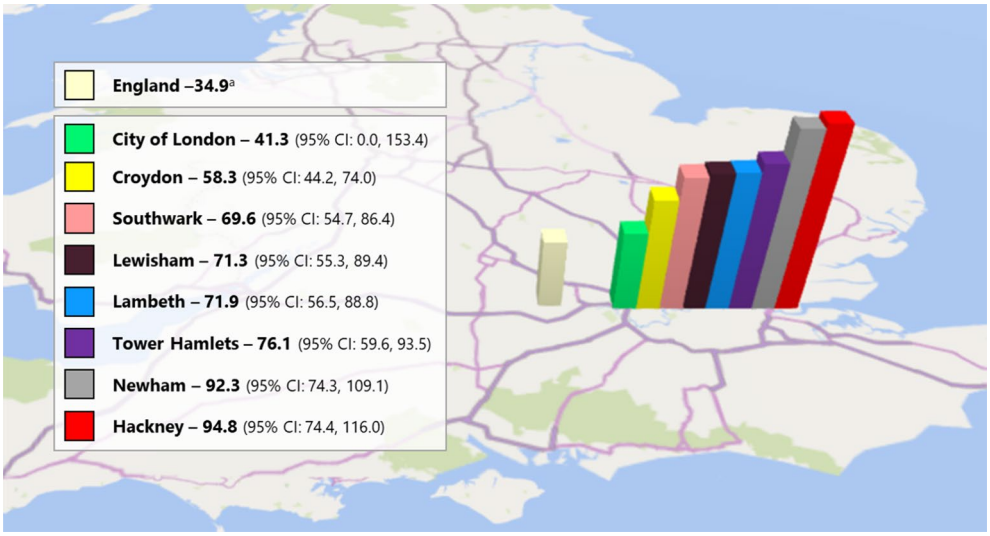

FIGURE 2 | Pan-London crude predicted incidence of psychosis per 100,000 person-year (16-35 years). [a]National average calculated from the PsyMaptic Psychosis LAD v1-0 xlsx file available at: http://www.psymaptic.org/prediction/psychosis-incidence-data/.

TABLE 1 | Sociodemographic characteristics of the PNP.

		OASIS Lambeth and Southwark	OASIS Croydon and Lewisham	THEDS	HEADS UP	NEIS
Sample size		419	159	104	31	36
CHR-P assessment		CAARMS	CAARMS	SIPS	CAARMS	CAARMS
Yearly caseload		80	55	50	25	10
Age mean (SD)		22.84 (4.93)	22.01 (4.76)	22.02 (4.02)	23.35 (4.88)	22.33 (3.66)
Age range		14-35	13-36	17-26	17-33	18-31
Gender						
	% males	54.65	57.14	69.23	58.06	69.44
	% females	45.35	42.86	30.77	41.94	30.56
Ethnicity						
	White	48.55	40.76	23.11	58.06	22.22
	Asian	6.04	10.19	59.24	9.68	52.78
	Black African	9.42	6.37	8.20	9.68	0
	Black Caribbean	6.76	6.37	1.56	9.68	0
	Black British	16.43	19.75	0	0	25.00
	Other	12.8	16.56	7.89	12.9	0
Employment						
	% unemployed	57.87	68.59	51.25	29.03	75.00
	% students or employed	42.13	31.41	48.75	70.97	25.00
Marital status						
	% married/with a partner	21.52	16.13	6.5	22.58	5.56
	% single	78.48	83.87	93.5	77.42	94.44
Any substance misuse						
	% yes	NA	NA	40.00	45.16	27.78
	% no	NA	NA	60.00	54.84	72.22
CHR-P subgroup						
	% APS	80	75.72	NA	51.61	55.56
	% BLIPS/BIPS	19.59	19.65	NA	32.26	25.00
	% GRD	0.41	4.62	NA	16.13	19.44

Additional 38 CHR-P individuals were detected in the Luton and Bedfordshire services; CAARMS, comprehensive assessment of at-risk mental states; SIPS, structured interview for psychosis-risk syndromes; APS, attenuated psychosis syndrome; BLIPS, brief and limited intermittent psychotic symptoms; BIPS, brief intermittent psychotic symptoms; GRD, genetic risk and deterioration syndrome; CHR-P, clinical high risk for psychosis.

and 20% were exposed to a combination of interventions. The CBT + antidepressant intervention was associated with a reduced risk of transition to psychosis, as compared with the CBT + antipsychotic intervention (hazards ratio = 0.129) (26). Among CHR-P who will not develop psychosis, 28.3% still reported APS and 45.3% remain functionally impaired at follow-up (GAF <60) (27). A substantial proportion of patients (56.8%) is affected by at least one comorbid disorder at follow-up (27). Among CHR-P patients who presented with some comorbid disorder at baseline, 61.5% had persistent or recurrent course (27). Incident comorbid disorders emerged in 45.4% of baseline CHR-P patients (27). There was no increased risk of developing incident mental disorders in OASIS patients meeting CHR-P criteria compared with control groups (28). Underage patients remain under the care of children and adolescent mental health teams, but OASIS provides specialized care.

OASIS Lewisham and Croydon (OASIS)

Service and Catchment Area Description

In 2014 to 2015, OASIS has expanded in two additional SLaM boroughs of Lewisham (total population, 310,324; population age, 16–35 years; 98,698 in 2018 (22), **Figure 1**) and Croydon (total population, 391,296; population age, 16–35 years; 101,336 in 2018 (22), **Figure 1**). Incidence of psychosis in Lewisham and Croydon is estimated at 71.3 and 58.3 cases per 100,000 person-years, respectively, which is higher than England national average of 34.9 cases (**Figure 2**).

The team is composed of two part-time consultant psychiatrists, a team leader, two clinical psychologists, a social worker, and a mental health nurse. Inclusion criteria, outreach, interventions, and outcomes have all been harmonized with OASIS Lambeth and Southwark and are presented in the section above. OASIS in Lewisham and Croydon is also a standalone service which is separated from the local first-episode services. The caseload is approximately 55 patients per year.

Service User Description

Over the past years, the OASIS has taken care of 159 patients meeting the CAARMS 12/2006 (23) CHR-P criteria. Most service users met the APS of the CHR-P intake criteria, but the BLIPS subgroup was also consistent (19.65%). Service users are mostly white (40.76%) young (age, 22.01 years) males (57.14%) who are single (83.87%) and unemployed (68.59%) at the time of contact with the service.

Tower Hamlets Early Detection Service (THEDS)

Service and Catchment Area Description

The THEDS was fully operating from January 2010. It is part of the East London NHS Foundation Trust (ELFT), and it provides mental health promotion, early detection, and support in the Borough of Tower Hamlets (total population, 317,203; population aged 16 to 35 years; 135,832 in 2018 (22), **Figure 1**). Tower Hamlets has the fourth youngest population in the UK (29). Incidence of psychosis in Tower Hamlet is estimated at 76.1 cases per 100,000 person-year, surpassing the England national average of 34.9 cases (**Figure 2**).

The team is composed of one team leader (nurse), a part-time senior practitioner, a part-time clinical psychologist, and one day of a consultant psychiatrist. THEDS is like OASIS, one of the few standalone services of this kind; nevertheless, it works closely with the Early Intervention Service and shares premises with them.

Inclusion criteria to THEDS are: 16 to 25 years, having the GP in the local borough, being help-seeking and meeting the CHR-P criteria [Structured Interview for Psychosis-risk Syndromes (SIPS) (30)]. After inclusion, THEDS offers 2 years of follow-up and support to service users and carers. The caseload fluctuates between 30 and 50 every given year.

Outreach

From the beginning, THEDS had a strong focus on outreach and mental health promotion. The team has established a close relationship with community-based services; it is present in the community and educational events, it meets with GPs regularly and trains front-line youth workers offering on-site presentations, consultation, and feedback over the phone. We also train new doctors and focus on changing policies around youth mental health in Tower Hamlets. THEDS has also developed a website (https://theds.elft.nhs.uk/) and is present in social media: facebook and twitter. We have included our young service users in their development. THEDS accepts referrals from GP (21%), secondary care (20%), primary care psychology (13%), third sector organizations (11%), self-referrals (14%), education (9%), and from carers. Every person that is assessed will receive a mental health promotion package and will be signposted or referred to the adequate service for them if they are not meeting CHR-P criteria.

Service User Description

About one third of the patients assessed met the CHR-P criteria. Most of them met the APS subgroup. Service users are mostly Asian (59.24%) young (age 22.02%) males (69.23%), single (93.5%) and unemployed (51.25%). Among service users, mood disorders are the most prevalent comorbid condition (56% of total comorbidities), followed by substance misuse (10%), and anxiety disorders (7%). Service users with CHR-P symptoms potentially secondary to other factors (e.g. substance use) are admitted to the service and offer a new assessment after 6 months (*extended assessment*). In the meantime, they are offered the same package of care as standard service users. Self-reported use of substances among the CHR-P population was 40%, cannabis is the most common substance used (28%). THEDS works closely with local substance misuse services and occupational services in the borough.

Interventions and Outcomes

THEDS offers 2 years of follow-up and mental state monitoring, casework and intervention. THEDS focuses on psychoeducation and psychosocial support. Every client is case worked, and support on job retention/seeking, education, and social needs is offered. THEDS also provides CBT (accepted by 65% of patients) and brief family interventions (accepted by 30% of patients) routinely. THEDS offers medical reviews and psychopharmacological treatment. Medication is mostly used to treat affective comorbidities. THEDS

may prescribe low-dose antipsychotics when the symptoms interfere with functionality.

City & Hackney At-Risk Mental State Service (HEADS UP)

Service and Catchment Area Description

The City & Hackney At-Risk Mental State Service (HEADS UP) has been in operation since 2015, initially, as a 1-year pilot which was then made permanent. It is part of the ELFT, providing early detection and support services in the City of London (total population 7,681; population aged 16–35 2,530 in 2018 (22), **Figure 1**) and Hackney boroughs [total population, 281,740; population age, 16–35 years; 105,945 in 2018 (22)]. Incidence of psychosis in the City is 41.3 and Hackney 94.8 cases per 100,000 person-year. Incidence of psychosis in Hackney is over twice the England national average of 34.9 cases and is one of the highest in the whole of the country (**Figure 2**).

The team is composed of one part-time team leader, one senior nurse practitioner, one part-time clinical psychologist, and two part-time consultant psychiatrists. HEADS UP is an embedded service, sharing human and financial resources with the local first episode early intervention service (EQUIP).

Inclusion criteria to HEADS UP are: 18 to 35 years of age, having the GP in the local boroughs, being help-seeking, and meeting CHR-P criteria [CAARMS 12/2006 (23)]. After inclusion, HEADS UP provides 2-year support to service users and carers. The caseload is capped at 25 service-users at any given time, with the intention to expand in the future.

Outreach

Outreach and service promotion is conducted *via* visits and training activities in GP offices and mental health services across ELFT. GPs are the primary source of referrals to HEADS UP (61%).

Service User Description

Between October 2015 and October 2017, 31 individuals had met criteria for CHR-P, mostly APS (50%) but the BLIPS subgroup is highly frequent (33%). Service users are mostly white (58.06%) young (age 23.4 years) males (58%), single (77%, **Table 1**). Most of them are either employed (45%) or in education (26%, **Table 1**). Any type of substance misuse is present in almost half (45%) of service users. Cannabis is the most common substance. The presence of comorbid substance use or other psychiatric conditions is not an *a priori* exclusion criteria for HEADS UP unless these conditions are assessed as the primary cause in the clinical presentation.

Interventions and Outcomes

All service users have a key worker providing psychosocial support and ongoing monitoring of the mental state. Most service users (77%) have received CBT-informed individual psychotherapy, and less frequently (19%), family therapy. Other psychosocial interventions include psychoeducation and practical support (education, housing, work). Medical reviews and psychopharmacological treatment are also offered. About half of service users receive psychopharmacological treatment, with antidepressants being the most commonly prescribed drugs. Only 1 of 31 service users has received low-dose antipsychotic medication.

Newham Early Intervention Service (NEIS)

Service and Catchment Area Description

The NEIS was established in 2008, with the aim of providing mental health services to young people at increased risk of psychosis and those who experience a first episode of psychosis. It is part of the ELFT and operates in the London borough of Newham (population, 353,245; population age, 16–35 years; 132,057 in 2018 (22), **Figure 1**). Incidence of psychosis in Newham is over twice the England national average of 34.9, with 92.3 cases per 100,000 person-year (**Figure 2**). An integrated model is in place at NEIS, and the CHR-P team shares financial and human resources with the first-episode team. The CHR-P team is not separate. The staff within the NEIS provides input to both first-episode psychosis patients and those at CHR-P. Inclusion criteria are: 18 to 35 years of age, having the GP in the local borough, meeting CHR-P criteria [CAARMS 12/2006 (23)], and being help-seeking. After inclusion, NEIS provides up to 3-year support to CHR-P service users. The caseload of CHR-P service-users is around 10 at any given time and is not capped.

Outreach

An assertive outreach strategy is conducted by the NEIS, mostly directed at GP training on CHR-P symptoms. Intentions to expand community outreach activities to incorporate third-party and education organizations are currently constrained by limited financial and human resources. Overall, engagement of CHR-P service users is better than that in the first-episode service although referral rates are lower.

Service User Description

Up to 36 individuals met CHR-P criteria, mostly the APS subgroup (55.56%). The BLIPS subgroup was also quite well represented (25%). Service users were mostly Asian (52.78%), unemployed (75%), single (94.44%), and of young (age 22.33) males (69.44%). About one third (27.78%) were presenting with any substance use. Comorbid conditions are not an exclusion criterion to be eligible for the service.

Interventions and Outcomes

CHR-P service users are offered medical and psychosocial support and ongoing mental state monitoring. Each service user has monthly sessions with a health care professional. In addition, available psychosocial interventions include CBT-informed individual psychotherapy, family therapy, and needs-based support. Low-dose antipsychotic medication is used in a small number of service users.

Risk of Psychosis Across the PNP Network

A total of 787 individuals at-risk for psychosis were followed up by the PNP (including 38 individuals from the Bedforshire and Luton service). The risk for psychosis onset was: 0.141 (95% CI, 0.117–0.169) at 1 year, 0.221 (95% CI, 0.189–0.258; 503 individuals still at-risk) at 2 years, 0.281 (95% CI, 0.242–0.325; 283 individuals still

at-risk) at 3 years, and 0.301 (95% CI, 0.259–0.347; 158 individuals still at-risk) at 4 years (**Figure 3**).

Translational Clinical Research in the PNP

There was consensus across PNP teams that improving the detection of individuals at-risk was the most challenging operational challenge to be overcome. A complementary strategy targeting secondary mental health care, primary care, and the community was discussed to improve the recruitment of CHR-P individuals. Accordingly, some PNP teams have set up new websites to facilitate detection of CHR-P individuals from the community. The PNP is also committed to supporting some research innovations that can improve detection of CHR-P individuals in secondary mental health care. These involve the use of transdiagnostic risk calculators to screen electronic health records and identify potential candidates for CHR-P assessment (19, 31, 32) as part of MRC-funded grant (MC_PC_16048). Other research innovations conducted in the PNP involve the development of personalized prediction algorithms (33) as part of large-scale international consortia (e.g., PSYSCAN, http://psyscan.eu) or experimental therapeutics studies in CHR-P individuals [e.g., intranasal oxytocin (34, 35)].

DISCUSSION

The PNP included five CHR-P services across two NHS Trusts: Outreach and Support In South-London (OASIS) in Lambeth and Southwark, OASIS in Croydon and Lewisham, Tower Hamlets Early Detection Service (THEDS), City & Hackney At-Risk Mental State Service (HEADS UP) and Newham Early Intervention Service (NEIS). The PNP serves a total population of 2,318,515 Londoners (830,889; age, 16–35 years), with a yearly recruitment capacity of 220 CHR-P individuals (age, 22.55 years). Standalone teams (OASIS and THEDS) are more established and successful than teams that share their resources with other mental health services (HEADS UP, NEIS). Characteristics of the catchment areas, outreach, and service users, differ across PNP services; all of them offer psychotherapy to prevent psychosis. The PNP is supporting several CHR-P translational research projects.

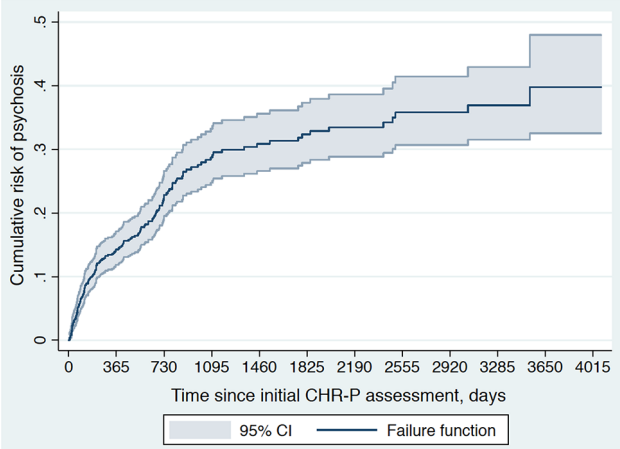

FIGURE 3 | Cumulative risk of psychosis onset (failure function) in 787 CHR-P individuals from the Pan-London Network for Psychosis-Prevention (PNP). There were 503 individuals at-risk at year 1, 283 individuals at-risk at year 2, 192 individuals at-risk at year 3, 158 individuals at-risk at year 4, 139 individuals at-risk at year 5, 113 individuals at-risk at year 6, 110 individuals at-risk at year 7, 72 individuals at-risk at year 8, 42 individuals at-risk at year 9, and 29 individuals at-risk at year 10. The function was truncated at 4081 days of follow-up when 10 individuals were still at-risk for psychosis.

This is the first network of CHR-P services to be established in the UK. It serves an extensive and diverse urban population of 2,318,515 Londoners (830,889; age, 16–35 years), which represent the largest catchment area for the recruitment of CHR-P individuals. Correspondingly, the sociodemographic characteristics of the young people meeting CHR-P criteria were highly heterogeneous across PNP's teams. First, the incidence of psychosis in the PNP was higher than in the rest of the country, likely reflecting the impact that the urban environment exerts on the onset of this disorder (36). Second, CHR-P patients under the care of the PNP were mostly unemployed males living alone. Third, non-white ethnic minorities were highly represented across users of CHR-P services. This is particularly important in light of the patterns of ethnic inequalities in pathways to psychiatric care, particularly affecting black groups (37), because it confirms that CHR-P services can provide easier access to care to ethnic minorities (16). The age limit of PNP service users ranged from 14 to 35 years, and the average age of CHR-P individuals was of 22.55 years. Therefore, the PNP teams have disregarded the recommendation of the Access and Waiting Time Standard, which has extended to the age 65 the acceptance criteria for the majority of early intervention in psychosis (and CHR-P) services in the UK (38). The Standard's recommendation is not supported by any psychometric validity because the CHR-P instruments have been validated in mostly in the age range of 14 to 35 years with possibilities to extend it to 8 to 40 years (7). There is not even epidemiological support for the Standard's recommendation: psychotic disorders, despite being relatively rare before the age of 14 years (39); peak in the age group of 15 to 35 years, and declines after the age of 35 years (36). Another recent appraisal of the standard confirmed that it is unclear how adopting the recommended extended age range and treating CHR-P cases could impact on the positive outcomes already associated with 14 to 35 years age range (40). A further independent survey of CHR-P services in the UK concluded that current provision for CHR-P in England does not match clinical guidelines (41). Fourth, concerning illicit substance misuse, only a minority of CHR-P individuals reported using them. The actual impact of illicit substance use, such as cannabis, on the risk of transitioning to psychosis from a CHR-P stage is not wholly clear (42). Fifth, with respect to other characteristics of the PNP service users, data were scattered and not always reported. Collecting real-world clinical data is not straightforward outside the research setting. This task could be facilitated by the availability of a standard data acquisition platform that incorporates the core CHR-P measures and that can be used in clinical routine; the proforma developed for this study can serve as the starting platform. The development of a core CHR-P measurements package to be consistently used Pan-London will be the subject of future PNP work. At the same time, the methods employed for this study, which represent the largest appraisal of CHR-P services in London, could be employed to conduct a national deep dive surveying the implementation

level, operational policies and challenges of CHR-P services in the UK. New national infrastructures, such as the National Institute of Health Research—Mental Health Translational Research Collaboration Early Psychosis Workstream (https://www.nihr.ac.uk/news/the-uks-leading-mental-health-experts-unite-to-solve-treatment-challenges/9193) could tackle this task.

In terms of outreach campaigns, there was high variability across PNP's teams. The problem of heterogeneous recruitment strategies for CHR-P patients and their profound impact on the level of risk enrichment that is eventually observed have been fully addressed in previous publications by our group [see Refs. (24, 43–46)]. Once the CHR-P individuals were recruited into the PNP, they were assessed with the CAARMS or with the SIPS. This operational approach diverges from the National Institute of Clinical Excellence (NICE) recommendations which suggest using the CAARMS only. However, there are no diagnostic or prognostic advantages of any psychometric interview over each other (10) (the SIPS has slightly superior sensitivity than the CAARMS (47). Furthermore, recent automatic packages allow the scores of the two interviews to be reciprocally converted (6). Therefore, current clinical guidelines should consider a more flexible approach to allow the implementation of the CHR-P paradigm. Another critical issue related to the presence of comorbid mental disorders, all the PNP teams allowed their concurrent presence in addition to CHR-P criteria, in line with established literature (25).

The PNP's clinical potentials cumulate in one of the largest real-world clinical cohort of CHR-P individuals worldwide, encompassing 787 individuals and a 4-year follow-up. In the PNP about one (30%) in three CHR-P individuals developed a psychotic disorder within 4 years. This value suggests that the actual transition risk of clinical cohorts, as opposed to research cohorts may not be declining. Such an effect could be to sampling biases, with more severe patients declining participation in research studies (48). The PNP's risk was observed in the context of naturalistic design with the potential confounding effect of preventive interventions such as CBT. However, the actual effect of preventive treatments for the reduction of the risk of psychosis onset is unclear (14). Clinical guidelines (e.g., NICE) are not updated to reflect the current status of knowledge, with respect to effective treatments for CHR-P patients. Of interest, there was a relatively high proportion of CHR-P individuals meeting the short-lived intake criterion (Brief and Limited Intermittent Psychotic Symptoms [BLIPS (49)], which may reflect the high incidence of psychosis in the PNP. Overall, the risk estimates of transition to psychosis can be used as a national benchmark for other future CHR-P studies in the UK. Notably, the PNP has an extensive recruitment capacity which cumulates to 220 individuals per year. This opens the door to the large-scale implementation of clinical research innovations in the London area, potentially impacting the lives of many young people. As noted above, the PNP has already implemented innovative approaches for improving the detection of CHR-P individuals in the community and secondary mental health care, to produce a personalized prediction of their outcomes and to test first-in-class experimental therapeutics. These studies have demonstrated the ability of the PNP to achieve an optimal integration of clinical and research aspects, which is pivotal to the successful translation of research innovations in clinical routine. Since the PNP leverages a universal healthcare system and NHS infrastructure, it offers competitive advantages compared to other international CHR-P infrastructures that are characterized by heterogeneous clinical scenarios.

A final important operational issue related to the configuration of CHR-P services in the PNP. OASIS and THEDS were standalone services, separated from the local early intervention services in terms of staffing resources and team leadership (they only shared the premises). Conversely, HEADS UP and NEIS were CHR-P services embedded within the local early intervention services, sharing staff, and team leadership. Standalone services appeared more successful than embedded services on several implementations, delivery and outcome measures. For example, **Table 1** clearly reports higher yearly caseloads for standalone teams compared with services that are embedded within first-episode services. This could be due to the fact that the CHR-P and first episode populations are different in terms of clinical needs. Although patients experiencing a first episode of psychosis typically are more acute and severe, CHR-P individuals require more subtle assessment and follow-up. Embedding CHR-P services within early intervention services may end up penalizing the less severe patients because the staff would tend to invest more time and effort in taking care of those more unwell. There was consensus across the PNP that standalone CHR-P services are more efficient than embedded CHR-P services in terms conducting the outreach, initial assessment, delivery or psychological therapies, and longitudinal follow-up. In line with these findings, the first appraisal of the Access and Awaiting Time Standard confirmed these operational issues and the importance of clear treatment pathways and targeted interventions that would need to develop and commission of distinct and standalone CHR-P services (40). Another independent UK survey has evidenced that only 42% to 50% of the CHR-P services that are embedded within early intervention services are in reality able to offer the NICE recommended treatments: CBT, family intervention, and training on CBT (41). Against the current clinical guidelines, 50% of embedded CHR-P services used antipsychotic treatments (41). Implementing dedicated CBT for CHR-P individuals in clinical routine is demanding in terms of staffing, training, and financial resources; this is hardly achieved in the context of first-episode teams that are already stretched with the provision of the same treatments for more severe and acute patients. Only standalone CHR-P services can ensure that sufficient time, financial resources, training, and clinical knowledge is devolved to the detection, prognostic assessment, and clinical care of CHR-P patients. This study concluded that this is because the majority of early intervention services in England did not receive allocated funding for the CHR-P population, and there are few standalone services specifically commissioned for these patients (41).

Limitations of this study included the lack of a common data acquisition dataset to record service-related data that could characterize CHR-P services. For example, the proportion of patients exposed to different types of preventive treatments was not consistently recorded across the different PNP services. The development of a standardized data acquisition system across CHR-P services will be the core objective of the next stages of the PNP. This could then be scaled up nationally and further benefit CHR-P services outside London.

In conclusion, this is the largest survey of CHR-P services in the UK, which focuses on a Pan-London area. The PNP represents the largest NHS collaboration across CHR-P services in the UK. The appraisal of the PNP can have some impact on the field. First, the extension of the CHR-P assessment to those older than 35 to 40 years is not justified. Rather, it may be possible to lower the age range to 12 years (50) to better capture young at-risk populations. Second, it is essential to develop a standard data acquisition platform and a package of measures to be recorded by CHR-P services in the UK to facilitate the appraisal of their success and the associated challenges. The next step would involve conducting a national survey. Third, NICE guidelines should be updated to allow the use of different CHR-P instruments and to recognize the challenges that are currently associated with the use of psychological therapies to prevent psychosis in this population. Fourth, the PNP represents a benchmark infrastructure to conduct translational research in the UK and could be considered for future national initiatives. Fifth, standalone CHR-P teams should be recommended by the national clinical guidelines, and their development should be supported by adequate funding. Overall, this study highlights crucial operational issues which will need careful consideration in the future planning of CHR-P services.

CONCLUSION

The PNP is the largest CHR-P clinical network in the UK; it represents a reference benchmark for implementing detection, prognosis, and care in the real-world clinical routine, as well as for translating research innovations into practice.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. There is no ethical permission for data sharing.

ETHICS STATEMENT

The study received ethical approval as an audit by the local NHS Trusts.

AUTHOR CONTRIBUTIONS

PF-P conceived the study. AE conducted it along with TS, SG, SM-A, SE, KW, OA, JB, MS, SF, VS, AA, PM and AM. PF-P provided ongoing supervision. PF-P drafted the first version of the manuscript and all authors contributed to the interpretation of findings.

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STUDY PROTOCOL
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Implementing the Latvian Early Intervention Program (LAT-EIP) for Patients With Schizophrenia Spectrum First-Episode Psychosis: Study Protocol

Liene Berze[1,2], Sandra Civcisa[2,3], Ilona Krone[4], Dmitrijs Kvartalovs[2,3], Sarmite Kikuste[2], Inna Sapele[2], Jelena Lazovika[2] and Elmars Rancans[3]*

[1] Department of Doctoral Studies, Riga Stradins University, Riga, Latvia, [2] Department of Mental Health Care, Daugavpils Psychoneurological Hospital, Daugavpils, Latvia, [3] Department of Psychiatry and Addiction Disorders, Riga Stradins University, Riga, Latvia, [4] CBT Department, Latvian Association of Cognitive Behavioral Therapy, Riga, Latvia

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***Correspondence:**
Liene Berze
lieneberze@gmail.com

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Background: Patients with first-episode psychosis are mainly young people in the active phase of their social and professional lives, and psychosis is a serious disruption of normal life with high risk of disability. Integrated biopsychosocial early intervention treatment is crucial for patients with first-time psychosis episode. The purpose of this trial is to adapt the first early intervention program for patients with first-time non-affective psychosis in Latvia, and to investigate whether it is possible to integrate this kind of treatment approach in the frame of existing services and whether it provides better outcomes for patients than existing services.

Design/Methods: The study has a nonrandomized controlled design in a real-life environment. Participants are all consecutive patients presenting in the psychiatric emergency room with first-time non-affective schizophrenia spectrum psychosis episode (ICD criteria F23, F20) from a catchment area of 262,541 inhabitants, with urban and rural regions. The Latvian Early Intervention Program is a 6-month program developed from existing treatment guidelines and recommendations and adapted to a low-resource environment, integrated in an existing outpatient unit. This study aimed to test the hypothesis that the patients who received intervention have milder symptoms, higher functioning, and better adherence to outpatient treatment. The study primary aims are: 1) to establish and examine in practice the adapted early intervention for patients with first schizophrenia spectrum psychosis; 2) compare clinical and functional outcomes (including occupation, housing, and social relationships) between intervention treatment and standard treatment; and 3) compare the number of rehospitalizations, adherence to outpatient treatment, and assigned disability. Secondary aims are: 1) to compare full recovery status in both treatment groups at 12 months follow-up and 2) to develop recommendations for establishing early intervention programs in limited resource settings.

Discussion/Conclusions: Across the world, there is wide inequality in the availably and accessibility to early intervention treatment. This study will increase our knowledge in early

intervention treatment approach and outcomes for patients with schizophrenia spectrum first psychosis episode in real-life working clinical practices. We hope to provide theoretical and practical aspects to develop strategies for early intervention service implementation in limited resource mental healthcare settings.

Keywords: psychosis, schizophrenia, intervention, treatment, outcomes

INTRODUCTION

Over the past three decades, evidence has increased that early intervention is an effective treatment approach and secondary prevention for patients with a first psychosis episode (1) and its importance as a treatment for the early phase of schizophrenia (2). The first episode of psychosis most often starts in late adolescence or early adulthood, in the phase of life of active personal growth in education and social aspects. Psychotic disorders are strongly associated with suffering for young adults and their families (3) and predict poor long-term outcomes in lifetime perspective with professional and social deterioration (4) if not adequately treated.

The first 2–3 years after the manifestation of the first episode of psychosis have been considered as a critical period or window of opportunity (5) for contemporary schizophrenia treatment. In the 5 years after the first episode of psychosis, the relapse rates reach 70–80% in patients receiving regular care or standard treatment (6), which could cause a decline in personal, social, and professional functioning (7) and increase direct and indirect costs of mental healthcare (8). Psychotic disorders, including schizophrenia, are among the most common reasons for mental disorder caused disability in Europe (3, 9), with consequently increased economic load and lost workforce. Therefore, it is crucial to offer intense and adequate treatment such as early intervention for this group of patients.

The first early intervention services started almost 30 years ago (1), when psychiatric practices were introduced with comprehensive, intense, and young people-friendly treatment. Patients with psychotic disorders who received early intervention reached higher rates of remission, lower rates of residual positive and negative symptoms, lower rates of relapse, and had less substance abuse and better overall functioning (10–13). Moreover, specialized early intervention services for first-episode schizophrenia spectrum patients are shown to be effective to increase medication adherence and lower admission and rehospitalization rates (14), higher social and vocational activities (15, 16), and decreasing stress and discomfort for patients' families (17).

The most highly functioning intervention teams are located in countries with developed mental healthcare systems (18). The most well-known early intervention services are in Australia (e.g., Early Psychosis Prevention and Intervention Centre (EEPIC), which is a part of the Orygen Youth Health Clinical Program) (19), the United Kingdom (e.g., LEO) (20), France (e.g., CJAA'D) (21), Denmark (OPUS) (22), the United States of America (23), Canada (13), and Scandinavian countries (TIPS) (24). A recent publication about European status in early intervention found that there were no significant differences between established intervention services and government expenditures in European countries, although countries with more psychiatrists and mental healthcare workers tended to have more established early intervention services (25). Nevertheless, there is lack of intervention services in Eastern Europe, mainly in the post-Soviet countries (26).

The authors were encouraged to adapt and start the first early intervention service in Latvia, which is a typical Eastern European country with one of the lowest levels of healthcare system funding in the European Union (EU) (27). A recent report of comparison of mental health of 30 European countries concluded that mental healthcare in Eastern Europe lacks integrated treatment; often, mental care is fragmented in separate hospital care and outpatient care and has an emphasis on institutions (28). In Latvia, there is no community treatment for patients with mental health disorders. In Latvia, the Ministry of Health is responsible for national health policy and the overall organization and functioning of the healthcare system—the state owns psychiatric hospitals, and Latvia currently has one of the highest rates of hospital beds in Europe (27), making psychiatric healthcare more hospital-based. The first initiative to shift from hospitals to outpatient care started in 2004 when Latvia joined the EU, and there was a dramatic decrease in the number of hospital beds. Almost 10 years later, the public health strategy was approved and had a strong influence on prevention and promoted intersectional approaches (29). The current health policy planning document, the Development Plan of Latvia for 2014–2020, continues these aims and highlights the importance of development on outpatient mental healthcare with planning long-term care for those with mental illness to provide not only medical care but also reintegration back into society (29). Psychiatric healthcare in Latvia is secondary care; if a patient has already been diagnosed with a psychiatric disorder, then their psychiatrist is a direct accessibility specialist. All psychiatric hospitals in Latvia are monoprofile and isolated from general hospitals. Four psychiatric hospitals in Latvia provide 24-h psychiatric emergency room services and are strictly organized by catchment area. Except for compulsory treatment or acute psychiatric states, including life threats to patients or others, all mental healthcare is voluntary based on patient preference and the patient is free to choose his or her outpatient psychiatrist or inpatient treatment facility. All psychiatric inpatient treatments and outpatient consultations with a psychiatrist (who has a contract with the government) are government-funded. Only in the capital Riga are outpatient mental healthcare centers separate from psychiatric hospitals; in the rest of Latvia, outpatient mental healthcare is administered by hospitals. Some centers offer

patients a multi-professional team involvement; it is optional for patients and no programs for specific treatment have been used. Traditionally, in Latvia, the standard treatment for patients with psychosis or schizophrenia includes consultations with psychiatrists (mostly pharmacological treatment) based on the patients' choices and subjective needs. In 2019, the Ministry of Health recognized the lack of integrated treatment in mental healthcare in Latvia and highlighted the problem and possible direction of action in the released strategy of improvement of mental healthcare accessibility for 2019–2020 (30). These facts indicate an opportunity for specialized treatment in practice, including case management and multidisciplinary teams for patients with first-time schizophrenia spectrum psychosis.

This study adapted the intervention program from existing guidelines and recommendations (31–34) without any funding. The program was implemented by reorganizing the existing resources in the outpatient center. To date, there are few "real-world" studies of regular mental healthcare systems with a sample of patients with first-episode psychosis.

The major objective of this study was to determine in routine Latvian outpatient settings whether the intervention treatment could be considered as more effective than standard treatment. To our knowledge, this is the first study on early intervention in the Baltic states; however, a single hospital initiative starting a separate psychosis ward (affective and non-affective) with a team of psychologists, psychiatrists, nurses, and modified case management after discharge in the Clinic of North Estonia Medical Centre Foundation (Tallinn, Estonia) has to be mentioned. We hope to fill the gap in theory and practice about the effectiveness and establishment of early intervention for patients with first-episode psychosis in limited resource settings.

HYPOTHESIS AND AIMS

The null hypothesis of this study is that patients who received intervention have milder clinical symptoms, higher functioning, increased employment, and better adherence to outpatient treatment. The study's primary aims are: 1) to establish and examine in practice the adapted early intervention for patients with first schizophrenia spectrum psychosis; 2) to compare clinical and functional outcomes (including occupation, housing, and social relationships) between intervention treatment and standard treatment; and 3) to compare the number of rehospitalizations, treatment adherence, and assigned disability. The secondary aims are: 1) to compare full recovery status in both treatment groups at 12 months follow-up and 2) to develop recommendations for establishing early intervention programs in limited resource settings.

METHODS

Design and Study Population

This study aimed to investigate the effectiveness and applicability of a "real-life" working early intervention program. Therefore, the research was conducted in routine clinical practice, and the subjects were consecutive patients with the first episode of psychosis (FEP) from Daugavpils Psychoneurological Hospital (DPNH) during the recruitment period. This study was designed as a nonrandomized quasi-experimental controlled trial comparing early intervention treatment *versus* standard care. The study was conducted in the second biggest psychiatric hospital of Latvia—Daugavpils Psychoneurological Hospital. The hospital is specialized and exclusively offers psychiatric treatment with 24-h psychiatric emergency care. The Daugavpils Psychoneurological Hospital has a catchment area of approximately 262,541 inhabitants in 19 municipalities (two governmental-level cities and rural areas—this region is called Latgale) (35). As the psychiatric emergency care in Latvia, including treatment of psychotic disorders, is strictly based on catchment area basis, the study patient sample is representative for evaluating the incidence of psychotic disorders for the defined catchment area. The research authors met and offered all consecutive patients with first-episode psychosis admitted to DPNH during 2016–2019 the opportunity to participate in the study. All patients received treatment in a DPNH acute psychiatric ward according to guidelines (36). During their treatment in the hospital, all potential participants could meet with the study investigators and, after providing written and informed consent, were invited to participate in the study. The size of the control group is 69 participants, all consecutive patients with first-episode schizophrenia spectrum psychosis who met the inclusion criteria during 2016–2017. The control group patients agreed to participate in two basal assessments at admission and at hospital discharge and follow-up assessment after 12 months. The intervention group patients agreed to the same assessments and were invited to participate in a 6-month outpatient early intervention program with additional interviews before and after intervention treatment. The primary endpoint of intervention treatment was considered a second psychosis episode with rehospitalization. After receiving standard or intervention treatment, participants were naturally followed up for 12 months. The expected sample size of the intervention group is 30–40 consecutive patients with first-time schizophrenia spectrum psychosis from the defined catchment area. The work with the intervention group is still ongoing. **Figure 1** shows an overview of the patient flowchart.

Eligibility Criteria

During the study period, the researchers examined the psychiatric emergency room register every 24 h for all first-time admissions to DPNH and identified from case records the patients diagnosed with non-affective schizophrenia spectrum psychosis by the emergency care psychiatrist. The study investigators then cross-checked the information with the treating psychiatrists and contacted patients in the DPNH inpatient units. Patients 18 and older were included if: 1) they had a diagnosis F20 or F23 as defined by the International Classification of Diseases, version 10 (37), by the research investigators (LB and IS); 2) this was the first psychosis episode in their lifetime; 3) they had read and signed an informed consent form; and 4) they were able and willing to participate in the study intervention treatment and

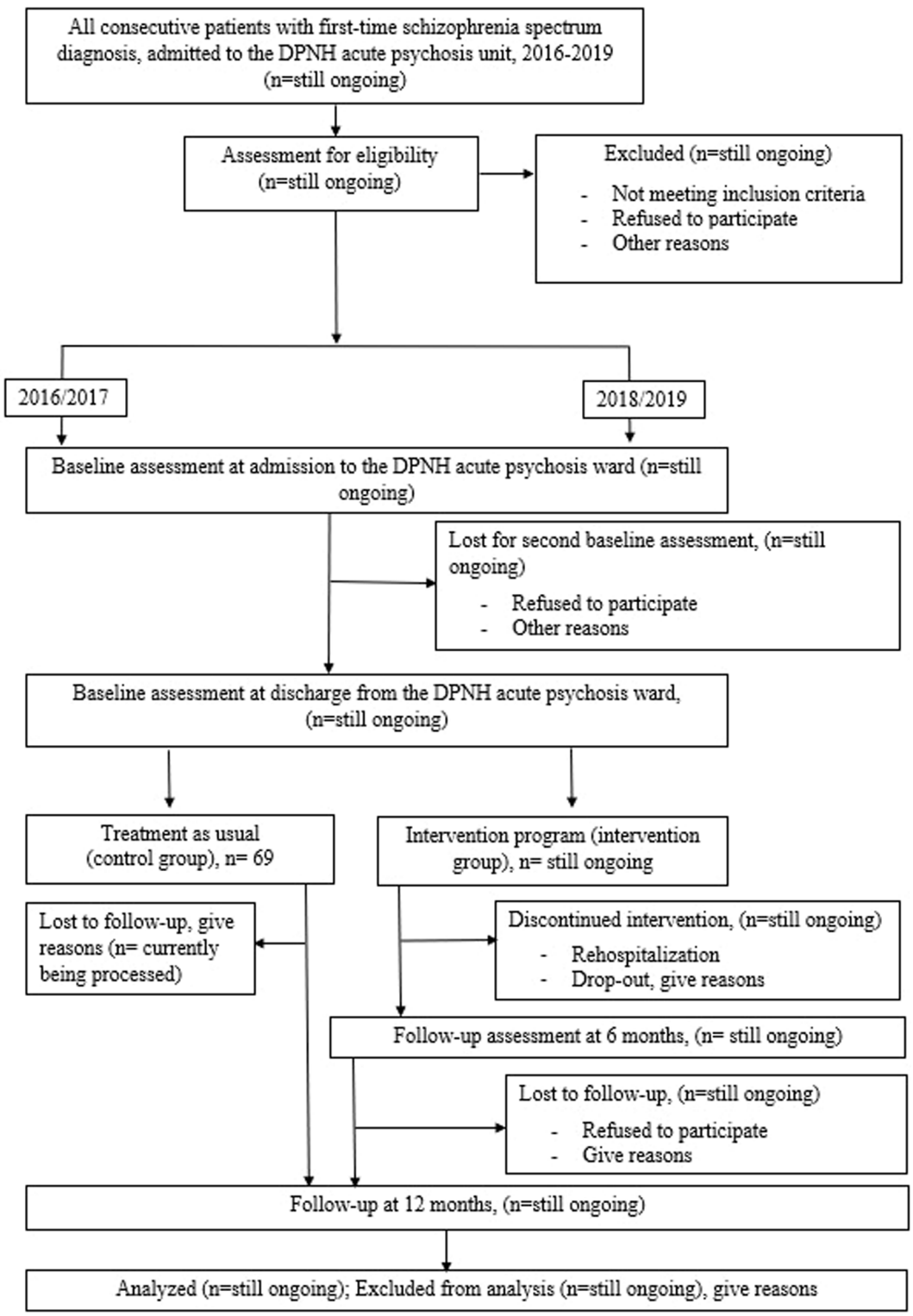

FIGURE 1 | Participant flowchart.

assessment. The inclusion and exclusion criteria were highly nondiscriminatory when applied to consecutive patients with FEP. Therefore, we also included patients with substance abuse, but excluded them if they had an addiction specialist-approved drug addiction or the psychosis was clearly substance-induced. Other exclusion criteria were as follows: 1) organic etiology of the presenting psychotic symptoms, for example, brain/head injuries; 2) exogenous etiology of presenting psychotic symptoms; 3) comorbidity with intellectual disabilities (IQ < 70) based on previous medical history; and 4) use of antipsychotic medication for more than 4 weeks.

Assessment Process and Instruments

All of the assessments in the study were applied by psychiatrists (LB and DK) with the supervision of a more experienced psychiatrist (IS). The kappa coefficient was used to evaluate the inter-rater reliability of the diagnosis and assessment procedure. The kappa values were interpreted as follows: excellent agreement (between 0.75 and 1.00), good agreement (between 0.60 and 0.74), fair agreement (between 0.40 and 0.59), and poor agreement (less than 0.40).

All of the participants were evaluated at the following time points: at the time of admission with FEP in a psychiatric ward (baseline = T_0), at the time of discharge (T_1), at follow-up assessment at 6 months (T_2), and at follow-up assessment at 12 months (T_3). In cases of withdrawal, one last assessment was performed at the final consultation (T_x) (**Table 1**).

All of the data were collected during face-to-face semi-structured clinical interviews and the expected time to complete all of the questionnaires and instruments was up to 60 min. In the baseline assessment, a semi-structured clinical interview contained three blocks: 1) sociodemographic data, 2) help-seeking behavior, and 3) clinical assessment with instruments. Additional information was derived from medical files, including clinical records from the attending psychiatrist, and used for cross-checking the information given by the patient. The provided information was checked by the closest family members or the patients' significant others.

Socio-Demographic Data

At the baseline, the following socio-demographic information were collected: age, sex, education level, relationship status (including being a parent), living arrangements (independently, with family, an/or with relatives), vocational status (employment: yes/no; studies: yes/no, additionally, time of employment or unemployment; the type of studies: full-time/part-time), family history of psychiatric disorders, comorbidities, and suicide attempts during lifetime.

Help-Seeking Behavior

To explore help-seeking behavior during the interview, we used a study author's conducted questionnaire that contained the following information: 1) help-seeking initiator (patient himself/herself, family members, friends/colleagues, medical workers, or other); 2) first contact with healthcare practitioners before admission to the psychiatric emergency room (general practitioner, psychiatrist, other, or none); and 3) how the patient was brought to the psychiatric emergency room (by himself/herself, by family members, by ambulance, or by ambulance with police escort).

Clinical Assessment With Instruments

To assess the different aspects of the patients' psychopathology, we used the following schedules and scales:

- The duration of untreated illness and the duration of untreated psychosis were evaluated using the Nottingham Onset Schedule-Duration of Untreated Psychosis version (NOS-DUP). The NOS-DUP is a short guided interview for recording several time points in the onset of psychosis. The NOS-DUP interview is designed to be administered by a clinician at the baseline evaluation. Onset is defined as the period between the first reported/observed changes in mental state/behavior to the development of psychotic symptoms (transition into psychosis). The NOS-DUP outlines several ways that the DUP can be defined. This study used the following definitions: 1) duration of untreated psychosis: duration from the first obvious psychotic symptoms to the start of anti-psychotic

TABLE 1 | Assessment tools used at each evaluation time point.

	T_0	T_1	T_2	T_3	T_x
	Admission to acute psychosis unit	**Discharge from acute psychosis unit**	**Follow-up at 6 months**	**Follow-up at 12 months**	**Before withdrawing**
Socio-demographic data	x		x	x	x
Help-seeking behavior schedule	x				
NOS-DUP	x				
SAPS	x	x	x	x	x
SANS	x	x	x	x	x
CDSS	x	x	x	x	x
SAI-E	x	x	x	x	x
GAF	x	x	x	x	x

NOS-DUP, Nottingham Onset Schedule-Duration of Untreated Psychosis Version; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; CDSS, Calgary Depression Scale for Schizophrenia; SAI-E, Schedule for the Assessment of Insight—Extended Version; GAF Global Assessment of Functioning.

treatment; and 2) duration of untreated illness: from the prodrome initiation to the start of anti-psychotic treatment. To conduct the NOS-DUP interview, the following structured and standardized steps were taken: the NOS-DUP was administered as near to the time of illness onset as possible after other schedules (covering history and mental state) have been administered, and the interview includes open-ended questions and standardized checklists (38). Similar to other studies, the admission day to the psychiatric hospital was considered the starting point for adequate treatment (39).

- The positive symptoms of the schizophrenia spectrum psychotic disorder were assessed with the Scale of the Assessment of Positive Symptoms (SAPS) (40) and the negative symptoms of the schizophrenia spectrum psychotic disorder were assessed with the Scale of the Assessment of Negative Symptoms (SANS) (41). The SAPS is a widely used assessment scale that includes four main domains of psychotic positive symptoms (schizophrenia spectrum): hallucinations, delusions, bizarre behavior, and positive formal thought disorder. The SANS is a widely used assessment scale that includes five main domains of psychotic negative symptoms (schizophrenia spectrum): affective flattening or blunting, alogia, avolition–apathy, anhedonia–asociality, and disturbed attention. Symptoms included in the SAPS and SANS were evaluated with a score from 0 (none) to 5 (severe). For the SAPS and SANS, we used the total score across all domains for a better comparison between these variables at admission and discharge (42).
- The Global Assessment of Functioning (GAF) was used to evaluate functioning (43). The scale has demonstrated good inter-rater reliability in those with psychosis (44). The GAF is a widely used scale measuring functioning during the previous month. It has 10 sections that provide a description of overall functioning based on the interviewer's opinion regarding the level of general activity and functioning of patients (severity). The evaluation step has 10 scores. The lower score of 1–10 is applied if there is a persistent inability to maintain even minimal personal hygiene and the person is in danger of severely hurting himself/herself or others, and the higher score of 91–100 is applied if there are no symptoms and the person has superior functioning.
- The Calgary Depression Scale for Schizophrenia (CDSS) scale was used for depressive symptom evaluation (45). The scale is designed to assess the symptoms of depression in patients with schizophrenia. The scale contains nine questions (scored from 0, absent, to 3, severe) asked by the interviewer. The scale has demonstrated good reliability and validity with a specificity of 77% and a sensitivity of 92% to diagnose depressive episodes starting with a score of 6 (45).
- The Scale for the Assessment of Insight (SAI) (46) was used to evaluate the patient's insight about their disorder, adherence to treatment, and medication use. It is a well-established measurement of insight in patients with psychiatric disorders and contains nine items: six items are scored 0–2 and three items are scored 0–4, for a scale rating range of 0–24 (higher scores represent good insight). The expanded version (SAI-E) contains three sub-items the interviewer uses to evaluate the patients' compliance with treatment based on one to seven previously asked questions (47).

Clinical Record Data

During the baseline and follow-up assessments, all available information was used from DPNH registers, medical records, and treating psychiatrists case notes to collect the following information: days spent in the hospital, emergency visits, outpatient visit contacts, number of readmissions (voluntary and involuntary), suicide attempts and suicide, disability status, and psychopharmacological treatment administered. Pharmacological treatment in the study sample is coded according to the Anatomical Therapeutic Chemical (ATC) classification index. This study evaluates only antipsychotic medication (ACT code N05A, excluding lithium) used in psychosis treatment, as this is the first-line treatment in most psychosis guidelines in Europe (32) and Latvia (36).

Outcome Measures

Primary Outcomes

The primary outcomes were assessed at baseline and at the 12-month follow-up comparing both treatment groups using the following instruments: 1) Clinical psychopathology was assessed using SAPS, SANS, CDSS, and SAI-E. The functional outcome was measured using GAF and vocational status (working or studying). The main measure was the difference between the total scores in both groups when comparing the baseline assessment and 12-month follow-up. Social functioning was explored in different social roles (interpersonal relationships, establishment of close personal relationships with a partner, and independent living from relatives) based on patients' answers during the clinical interview. 2) The number of rehospitalizations, days spent in hospital, and current disability status was counted using the DPNH register and all available medical records about the last 12-month period. Treatment adherence was measured by number of psychiatrist outpatient appointments during the last 12 months.

Secondary Outcomes

Secondary outcomes include full recovery status after FEP at 12 months follow-up in both groups. Full recovery is defined as a stable remission of both negative and positive symptoms (evaluated as 2 points or less in the SAPS and SANS global items), currently engaged in work or education, a GAF score over 60, and no psychiatric admissions to the hospital or disability during the last 12 months (48, 49). The recommendations of applicability of the early intervention program will be based on obtained study results and practical observations during the implementing process of Latvian Early Intervention Program (LAT-EIP) in real-life working everyday psychiatric practice.

Safety Assessments

Intervention is not expected to cause any adverse effects. The safety assessment will focus on adverse effects of psychopharmacological treatment and well-known adverse effects in patients with psychotic disorders: 1) suicide attempt or

suicide, 2) substance abuse, and 3) violence against self or others. In the assessment points, the researchers monitored the possible adverse incidents and immediately contacted the treating psychiatrists when any clinical worsening and suicidal risk were identified. In cases of patient death, the cause was attained from patient medical records.

Latvian Early Intervention Program

Theoretical Background of Intervention

This is the first time an early intervention program for patients with schizophrenia spectrum psychosis has been developed in Latvia (LAT-EIP). The study authors constructed the LAT-EIP in an *ad hoc* manner using the experience-based approaches described in research literature (14, 22, 23, 50, 51), well-known guidelines (31, 32, 52) and manuals and handbooks to adapt the program for Latvia's mental healthcare system. In the LAT-EIP development process, the study authors organized focus groups with expert researchers in psychiatry and psychology, clinicians working with FEP patients, and the administration of the hospital in order to identify the most relevant interventions to be included in the program The LAT-EIP structure and intervention elements are based on the Australian Clinical Guidelines for early psychosis (31). Strategies for managing organizational and financial aspects were found in the "Implementing Early Intervention in Psychosis: A Guide to Establishing Early Psychosis Services" by Jane Edwards and Patrick McGorry, 2006 (53). After developing a structure of the LAT-EIP with a description of the elements and piloting the LAT-EIP in a small sample of patients with FEP, the study authors conducted a real-life working version of the LAT-EIP protocol (**Table 2**), which was confirmed by local authorities (administration of DPNH) and the Ethics Committee of Riga Stradins University (no. 114/21.12.2017). The LAT-EIP consists of six main elements: 1) case management, 2) psychiatrist appointments, 3) family and individual psychoeducation, 4) techniques based on third-wave cognitive behavioral therapy (CBT) and social skills training, 5) consultations with vocational specialist, and 6) a nurse who will help with medication use and monitor the side effects. The LAT-EIP length is 6 months, which the authors consider the optimal time period, considering the patients' needs and providing multidisciplinary teamwork in limited resource settings. The LAT-EIP is developed to be easily tailored for individual patient needs. The study participants are encouraged to engage in all of the LAT-EIP interventions by the treating psychiatrist; nevertheless, the priority is the patient's opinion, and their voluntarily chosen activities are strongly respected.

Case Management

The case manager is involved in the patient care for 6 months to provide the coordination of the LAT-EIP realization in practice. The intervention plans are discussed between the patient, psychiatrist, and case manager to create the most acceptable plan for patients to visit the psychiatrist, psychologist, or vocational specialist. The case load is approximately 10 patients, and patients can reach their case manager every day from 0800 to 2000 via mobile phone (including weekends and holidays); if a message is sent after hours, the case manager will call back the next day. The contact with the case manager is provided via phone calls, messages, and face-to-face visits. The case manager's other tasks include establishing confidential and supportive contact with the patient and at least one family member or significant other, sending reminders about specialist appointments or rescheduling the visit if necessary, monitoring the patient's well-being and ensuring the availability of a psychiatrist within the next 48 h in case of sudden worsening of mental health status, and obtaining feedback about medication use and treatment compliance. A crisis plan was developed for each patient in which the first step is to contact the case manager or, if this is not possible, to provide help in a 24-h working psychiatric emergency room.

Psychiatrist Appointment

The psychiatrist is offering psychopharmacological treatment according to Latvian guidelines on schizophrenia treatment and management, including the management of a first-time psychosis episode (36). During team meetings, the psychiatrist plays a leading role by providing the best LAT-EIP option plan so that the patient can achieve his or her individual treatment goals.

Family Psychoeducation

To ensure better engagement with the treatment program, as one of the primary actions, the study authors emphasized the early involvement of family members. In this study, psychoeducation was applied as uni-family intervention. The definition we used is from the NICE guidelines in which psychoeducation is generally defined as information provided about a condition and its management (32). After the first contact with the

TABLE 2 | Structure of the LAT-EIP for patients with first-episode psychosis.

Intervention[a] (months)	Psychiatrist	Psychoeducation with family	Psychologist	Vocational specialist
1	1x/7 days1x/14 days	First session		
2	1x/14 days1x/21 days		2x/28 days	First consultation
3	1x/21 days1x/21 days	Second session	2x/28 days	Second consultation
4	1x/28 days	Third session	2x/28 days	Meeting at SEA
5	1x/28 days			
6	1x/28 days	Booster session (optional)	Booster session (optional)	

LAT-EIP, Latvian Early Intervention Program; SEA, State Employment Management.

[a]*All of the intervention times and places are tailored to the patient needs and specialist availability and coordinated by the case manager.*

patient, the psychoeducational family intervention was offered, and the team members always tried to contact at least one family member or emotionally close person and motivate them to participate in a psychoeducational session. This approach was primarily built on friendly, emphatic, optimistic, and open communication and collaboration.

Family psychoeducation included three 45-min sessions, and two booster sessions could be offered, if needed. The sessions were developed to help the family identify the psychotic disorder course, management, and prognosis and plan strategies for coping with future difficulties. Family psychoeducation was followed by two family psychosocial intervention manuals, Compton and Broussard's "The First Episode of Psychosis: A Guide for Patients and Their Families" (54) and Kuipers, Leff, and Lam's "Family Work with Schizophrenia: A Practical Guide" (55). Uni-family (including significant others by patient invitation) sessions are led by the treating psychiatrist with the case manager. The time and date of the sessions can be adapted to the family's needs and mental health professionals' availability.

The psychoeducation consists of three informative sessions (the booster session is optional) that cover the following: 1) information on the main clinical and epidemiological features of psychosis, including long-term outcomes, risk to children and impact on professional preferences, importance of adherence to therapy, pharmacological and non-pharmacological treatment options are discussed, and the possible side effects and benefits of treatment; 2) training on early warning signs, how to recognize them, and the importance of maintenance therapy as a prevention strategy for relapse (second psychosis), including non-pharmacological evidence-based psychosocial interventions; for each family, the crisis plan was discussed for psychiatric emergency situations, including substance abuse and suicidal behavior, and the social skills training with a main focus on strengthening problem-solving skills; and 3) the importance of the family's role in adherence to treatment and toward functional recovery and reintegration into employment and/or educational activities, the role of the family as emotional support during the development of social, professional, affective, and romantic relationships, taking into account that promoting patient independence is one of the main goals of treatment. In all of the sessions, the families are warmly encouraged to ask questions, discuss individual needs, and provide feedback at the end of the session. All of the details about the family education can be obtained from the authors.

Elements of Cognitive Behavioral Therapy and Social Skills Training

Structured CBT is not used in this study. Instead, the patients are offered need-based psychological interventions with elements of CBT in individual sessions with a certified clinical psychologist. The authors developed six sessions with one booster session for the psychological intervention based on third-wave CBT, including elements of acceptance, commitment therapy, and mindfulness (56). Additionally, specific individual social skills training was emphasized through CBT sessions. All of the sessions use a clear session structure and repetition and brief mindfulness exercises (57). There are possible adaptions for each patient; the individual approach is discussed during team meetings between the psychologist, psychiatrist, and patient. Each session length is approximately 30–40 min, and the frequency is tailored to the patient attending sessions twice or once per month. The psychological intervention focus is on personal value-based actions, acceptance of the psychotic experience, and developing non-judgmental attitudes toward the experience and the patient himself or herself (58). The important part of the work in the psychological intervention is anxiety, post-psychotic emotional symptom reduction, and the development of coping mechanisms, as well as social skills training (for example, developing problem-solving techniques) considering the individual patient needs. The psychological intervention is not supposed to be administered and evaluated separately, but is a part of the program and promotes adherence with the treatment plan, psychopharmacological treatment, and other specialists. **Table 3** shows the structure of the six sessions.

Consultations With Vocational Specialists

All of the participants who reach symptomatic remission are offered two consultations with vocational specialists in outpatient settings. The collaboration contract was signed between DPNH and the State Employment Agency (SEA). A vocational specialist ensured two consultations and a third scheduled meeting in the SEA office. During the first consultation, the client was asked about his or her preferences and his or her education and previous work experiences summarized, and consequently a client profile is created, including guided resume writing. In the second consultation, the possible options are offered in educational activities organized by SAE or job openings found by the vocational specialist. The client was encouraged to seek opportunities by himself/herself and ask for support and advice when it is needed for filling out applications or interviews. During the second interview, practical tasks were offered, such as job interview role-playing and self-presentation techniques. The third consultation in the SAE office included the contract and placement in educational courses offered by SAE and completely cost-free with cash benefits for attending the course and finishing it (provided by SAE). The vocational specialist was invited to the LAT-EIP team meeting at least once in 2 months, and after all of the consultations with clients (two to three individual consultations twice a month), the vocational specialist had a brief team meeting with the treating psychiatrist and case manager.

Withdrawal From Program

LAT-EIP philosophy is the early intervention program is patient-driven and tailored; therefore, the patient has the right during the program to refuse specific elements or interventions and continue to work with other interventions. If the patient was reluctant to be treated at all, the team remained in contact with the patient and the family to find a common focus for collaboration to motivate the patient to continue treatment. In this study, a dropout is defined as a situation when the patient stopped being reachable via mobile phone (quit answering phone calls and did not respond to messages), resulting in three missed appointments. If dropping out occurred, the team members tried to involve the patient and his or her family in one last

TABLE 3 | Overview of the adapted individual sessions with the clinical psychologists.

Session 1	• Introduction of structure and aims of psychological intervention • Establishment of honest and open therapeutic relationships • Introducing values-based actions • Mindful of body and breath exercises
Session 2	• Warm-up exercise • Introduction with the concept of acceptance of psychotic experience • Acknowledging the individual emotional difficulties and development of coping mechanisms • Mindfulness breathing exercise • Out-of-session planning activity exercise: value-based action plus mindfulness practice
Session 3	• Warm-up exercise • Mindfulness of body and stretching exercise • Review of out-of-session exercise • Identification of individual obstacles in value-based actions and developing coping strategies • Social skills training practice • Mindfulness breathing exercise • Out-of-session planning activity exercise: value-based action plus mindfulness practice
Session 4	• Warm-up exercise • Mindfulness eating exercise • Review of out-of-session exercise • Introduction to short vignettes that are comparable to patient's experiences • Strengthening the acceptance and commitment of personal experiences and values • Review of social skills training practice, introduction of alternative solutions • Mindfulness breathing exercise • Out-of-session planning activity exercise: value-based action plus mindfulness practice
Session 5	• Warm-up exercise • Mindfulness walking exercise • Review of out-of-session exercise • Review of learning and progress • Acknowledging individual strengths and weaknesses; developing strategies to overcome them • Mindfulness breathing exercise • Out-of-session planning activity exercise: value-based action plus mindfulness practice
Session 6	• Warm-up exercise • Mindfulness walking exercise • Review of out-of-session exercise • Review of learning and progress • Setting goals for value-based future actions • Refreshing coping mechanisms and social skills • Mindfulness breathing exercise • Wrapping-up exercise
Booster session	• Warm-up exercise • Review of learning and progress • Strengthening the coping mechanisms • Refreshing social skills exercises • Revising different mindfulness exercises • Wrapping-up exercise

meeting with the psychiatrist and case manager to ascertain the reasons for dropping out and to conduct a final assessment for the possible outcome evaluation. In the initial phase of the program, the participants were informed that they could refuse further treatment at any time during the program and they have the right to forbid the use of their medical records. To continue follow-up work after patient withdrawal, at the beginning of the study, the importance of using the data from medical records to obtain information for possible outcome measures was explained to the patients. A request to use patient data after withdrawal was included in the informed consent.

STATISTICAL ANALYSIS

The data were analyzed using IBM SPSS v.25. The Kolmogorov–Smirnov test was used to evaluate the normal distribution of continuous data. For normally distributed variables, the means (*M*) and standard deviation (SD) were applied for nonparametric numeric data: medians (Md) and interquartile ranges (IQR). Demographics and baseline characteristics were summarized and assessed for comparability between the intervention and control groups. Adjustment for baseline measures was used as this increased the statistical power and accounted for the regression to the mean (59). All of the continuous outcomes were analyzed as changes from the baseline with random intercepts for the participants and adjusted for the baseline measure. The study hypothesis was tested on the main effect for the group. For comparison between categorical variables, we used Pearson's chi-squared test or Fisher's exact test, with phi for the estimation of the effect size (weak effect: phi < 0.3, medium: 0.3–0.5, and large: >0.5). The paired samples *t* test was used to determine whether improvement over time occurred within both groups. To identify predictors and moderators related to the standard or intervention treatment outcomes, mixed regression methods were used. Univariate and multivariate logistic regression was used to find the association between the variables. The results were expressed in odds ratios (ORs) with a 95% confidence interval (CI). The Kaplan–Meier method was used to estimate the time to remission (in months) and remission rates. The log-rank test was used for statistical comparison between the two patient groups. The Cox proportional hazards regression was used to calculate the hazard ratios (HRs) to evaluate the influence of covariates for the adjusted analyses. The secondary outcomes were analyzed using relevant tests: the Mann–Whitney test, *U* tests, and the Kruskal–Wallis test with *r* as the effect size. We also explored Cohen's *d* and the effect size for the changes in positive and negative symptomology at the time of admission and discharge and compared between the groups. To describe the relationships, we used Spearman's two-tailed correlation coefficient analysis (r_s). In cases of nonexistent outcome measures (due to withdrawal, dropping out, or being lost to follow-up), the pattern of missing data and the assumption of missing data at random (MAR) was explored. The level of significance for all of the statistical analyses tasks was set at 0.05.

Ethics Statement

This study was approved by the Ethics Committee of Riga Stradins University, Riga, Latvia (no. 114/21.12.2017). Before signing informed consent, all of the patients were provided with written and verbal information on the study and given unlimited time to ask questions. All of the participants were informed both

verbally and in writing that they could withdraw from the study at any time without any consequences for their further treatment. The authors ensured that all of the specialists involved in this study were properly qualified in their professional field and fully informed about their study-related duties during the research process. This study was conducted in accordance with globally accepted standards of good clinical practice and in agreement with the Declaration of Helsinki and with national and local regulations.

DISCUSSION

This study investigated and practically examined the implementation of a first early psychosis program in an environment without community care by reorganization of existing resources. For many young people with psychosis, the introduction to mental services could be considered traumatic (14). Often, the first contact with a mental healthcare specialist is in a psychiatric emergency room and may include first-time admission in a psychiatric hospital in wards with disabled and chronic patients. The system in Latvia does not provide community care, assertive care, or individual case management for patients with psychiatric disorders, and it is left to the patient to voluntarily visit a psychiatrist by choice. It is crucial to use innovative approaches to assist stakeholders and policy makers in the development and spread of youth- and family-friendly early intervention services to ensure an optimistic first contact with services and minimize adverse effects such as unemployment, loss of life opportunities, and physical health comorbidities (60).

The literature documents disagreements on the type of early intervention model that is most appropriate for patients and applicable and feasible in real-world mental healthcare structures (61) and debates on obstacles when early intervention centers are established within the public Department of Mental Healthcare (62). In Latvia, healthcare expenditures are among the lowest compared to other countries; nevertheless, the situation in similar to other Eastern Europe countries with similar policy makers' attitudes toward mental healthcare (28). The goal of this study was to develop a working program for the early intervention team for routine outpatient mental healthcare practice without additional funding. During the research process, the authors not only explored the background and applicability of reorganizing existing structures and staff but also compared the two groups of patients with statistical approaches regarding which treatment option was better and more effective. There is evidence in the literature of the early intervention's superiority over standard treatment (63), but most studies are conducted in separate, funded institutions and projects that are almost impossible to replicate in real-world settings. The authors chose a model of early intervention team integration in a government-funded mental hospital, acknowledging that integration in already existing institutions has its advantages and disadvantages (64); nevertheless, it is one of the most realistic ways of implementing a new service in limited resource settings. When the authors started this study in Latvia, there were multidisciplinary teams working with patients with psychiatric disorders only in Riga, but there were no programs for specialized patient groups. There is an opinion in the literature that patients with psychosis are in a patient group with specific needs (14, 18) based on the fact that the LAT-EIP is the first specialized program for patients with psychosis in Latvia.

Although the LAT-EIP was developed following the best practice advice and experience from other countries, our program emphasizes the need for individualized approaches to patients, creative solutions for obtaining resources, and flexible administration and team members. Our core team specialists are a psychiatrist, a case manager, a psychologist, a nurse, and a vocational specialist, as previously described (14, 51, 64). The intervention program included empirical and scientific methods (65), psychiatrist appointments, case management, CBT-oriented psychological interventions, and vocational specialist consultations. As unemployment is a major problem among patients with psychotic disorders and is associated with poor social and economic inclusion as well as poorer life functioning (66), this study highlighted the need for the early involvement of vocational specialists via collaboration with the State Employment Agency.

To compare both treatment options, the standard treatment and intervention treatment, we selected assessment tools on the basis of their wide use in research trials (12, 51, 64) and therefore were able not only to evaluate the outcomes in our patient sample but also compare it to other studies. We aim to implement the early intervention model, which would be applicable to other limited resource settings in this region. At the end of this study, we plan to demonstrate the relevant statistics with the evaluation of the two treatment groups, the standard and intervention treatment, to confirm the hypothesis that the intervention is more effective than the standard treatment and could be implemented in the existing mental healthcare system. Practical observations will be included in the development of recommendations for mental healthcare specialists and policy makers to suggest the process of early intervention implementation in the available structures and institutions of the mental healthcare system in Latvia.

LIMITATIONS AND STRENGTHS

The strength of this study is that we were able to include a representative number of non-affective patients with first-time psychosis presenting to a secondary mental healthcare service in the defined region, which combines rural and urban areas. Nevertheless, the major strength of this study is the real-life approach that the LAT-EIP is being established in already existing organizational structures and it is possible to evaluate the intervention *versus* standard treatment effectiveness in a real-world patient sample. As this study was conducted in the second largest psychiatric hospital in Latvia and all five national psychiatric hospitals have similar administrative structures, the authors are confident that the LAT-EIP protocol could be considered as a pilot study representing the basis for implementation in any of the psychiatric hospitals in Latvia and possibly other Eastern European regions.

This study had several limitations that must be acknowledged. The first limitation is the study design; it was a nonrandomized

study, but a quasi-experimental study with the control group of all consecutive patients with first-episode psychosis were recruited before the intervention group. No reforms to the mental health system were conducted during the recruitment and intervention periods on the national level regarding psychiatric treatment options. However, the authors emphasize that this study has a real-life approach which allows making conclusions not only about patients but also on an administrative mental healthcare system level. The second limitation is that the sample size is one of five regions in Latvia and the incidence of patients with first-time psychosis in this region is comparable with the literature; the sample size could be considered small and could have an impact on the statistic power. It has to be taken into account that in the study were recruited all consecutive patients from one definite catchment area; the sample size covers the second biggest region of Latvia and is representative. Third, even though standard treatment and intervention treatment were ensured by different specialists, the evaluation was conducted by the same assessors, which may cause performance bias. In contrast, the effectiveness of the intervention could be biased by the short duration of the intervention treatment in this study; other studies have demonstrated the importance of extended interventions, confirming better effectiveness with prolonged early intervention in psychosis (67). Lastly, in this study, we did not include any cognitive testing which could affect clinical and functional outcomes. The authors strongly recommend adding these measurements when the early intervention will be expanding in the defined area and the protocol will be replicated. Therefore, it is necessary to implement early intervention programs in other mental health services in Latvia for a more valid and randomized methodology.

CONCLUSIONS AND FUTURE IMPLEMENTATION

The LAT-EIP study fills the gap in the current knowledge about implementing early intervention for patients with psychosis in specific non-community care mental healthcare systems with limited resource settings. By investigating the clinical and functional outcomes and effectiveness of the practical intervention protocol, we hope to develop recommendations for implementing feasible early interventions in Latvia for mental healthcare professionals, treatment providers, and policy makers. Implementing this study initiative in every psychiatric practice in Latvia should be a major benefit to individuals with first-time psychosis, their families, and society in general.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this manuscript are not publicly available. Requests to access the datasets should be directed to lieneberze@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Rigas Stradins University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ER and LB contributed to the study conception and design. LB, IK, IS, JL, and ER were involved in the development of the intervention program and created the study protocol. SK, IS, and JL were involved in the study organization, logistics, and implementation of the intervention program in outpatient settings. SC, LB, and DK were involved in the patient recruitment and data management. IS and JL are experts in psychiatry and IK is an expert in psychological interventions. LB coordinated the study and statistical counseling. LB wrote the first draft of the manuscript. ER, SC, IK, SK, IS, and JL provided critical revisions of the manuscript. All of the authors contributed to the manuscript revision and read and approved the final version.

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Factors Influencing Professional Help-Seeking Behavior During First Episode Psychosis in Schizophrenia: An Exploratory Study on Caregivers' Perspective

Daniel Teck Lung Wong[1], *Seng Fah Tong*[2], *Tuti Iryani Mohd Daud*[1], *Salina Abdul Aziz*[3] *and Marhani Midin*[1]*

[1] Department of Psychiatry and Mental Health, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia, [2] Department of Family Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia, [3] Department of Psychiatry and Mental Health, Hospital Kuala Lumpur, Kementerian Kesihatan, Kuala Lumpur, Malaysia

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Denmark

***Correspondence:**
Marhani Midin
marhani@ppukm.ukm.edu.my

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Schizophrenia is a severe mental illness that leads to significant productivity loss and is listed in the top 15 global burdens of disease. One important contributor to the high disease burden is duration of untreated psychosis (DUP) which can be shortened with promotion of professional help-seeking behavior. This study explored caregivers' perspective on factors influencing professional help-seeking behavior during first episode psychosis (FEP) in schizophrenia in Malaysia. The results of this study would inform the development of intervention strategies targeted at promoting professional help-seeking behavior in caregivers of individuals experiencing first episode psychosis (FEP). This is a thematic exploratory study which employed purposive sampling using focus group discussion (FGD). These interviews were audio recorded and transcribed verbatim. Basic thematic approach was used in analyzing the transcribed interviews. Two main themes identified were adequacy of knowledge and stigma. These two factors were found to co-influence each other. Stigma undermined the impact of knowledge on professional help-seeking; likewise, the reverse was also observed. Intervention strategies for promoting help-seeking behavior during FEP should simultaneously focus on improving knowledge about schizophrenia and reducing the stigma attached to it.

Keywords: schizophrenia, first episode psychosis, factor, help-seeking behavior, qualitative study, Malaysia

INTRODUCTION

Schizophrenia is one of the leading contributors to the high disease burden caused by mental, neurological and substance-use (MNS) disorders. It contributes to 16.8 million of disability-adjusted life year (DALY) (1) and remains one of the top 15 leading causes of disability worldwide (2). In Malaysia, productivity loss resulting from Schizophrenia amounts to USD 100 million a year (3). Despite the high burdens caused by the illness, research to improve its outcome is still inadequate. In

addressing the huge research gap in mental health, the Global Mental Health Initiative has identified priorities for research to improve the lives of people with mental illness worldwide (1). A total of 6 major goals encompassing 25 specific challenges has been listed (1). Goal B which is "Advance prevention and implementation of early interventions", targets at reducing the duration of untreated illness by developing culturally-sensitive early interventions (1).

Duration of untreated psychosis (DUP) is one of the factors contributing to the high disease burden in schizophrenia. Meta-analyses studies show a consistent correlation between long DUP and poor outcome (4, 5) Patients with schizophrenia who have a longer DUP prior to initial treatment have poorer symptom control and impaired long-term social functioning (6, 7), necessitating higher cost for their treatment and care. In Malaysia, mean DUP for schizophrenia is as long as 37.6 months (8), which is a huge concern in terms of the potential poor outcome and high burdens the illness brings to the individuals, families and the country.

The impact of DUP on illness outcome has led researchers to focus on first episode psychosis (FEP) in the last two decades. Many studies have been done to understand the barriers and facilitators of professional treatment-seeking that contribute to DUP and at the same time determine the pathways to care for people with FEP. Among the socio-demographic factors, education level has been found to be correlated with DUP while others such as age, gender, marital status, living situation and professional status had no evidence of association with DUP (7, 9–11). Cannabis use, which has a role in precipitating schizophrenia (12), was not found to influence DUP (9). Individual temperament and the availability of social support were found to play a role in DUP, whereby, good social support and low neuroticism helped to reduce DUP (13). Delayed treatment can also be due to under identification by general practitioners of some insidious features of the emerging psychosis (13).

Previous qualitative studies on pathways to care of patients with FEP indicated that that help-seeking behavior was affected by stigma, lack of symptom awareness, tendency to normalize psychotic symptoms, and lack of correct knowledge about treatment services (14–16). Support from significant others and availability of relevant information, on the other hand, were highlighted in those studies as important facilitating factors (14–17). For example, Cadario et al. found that many young people with FEP relied on others to access help (17) and Boydell et al. highlighted that help seeking as a social process that involved persuasive influence of significant others (15). Understanding this process of help-seeking behavior in FEP is crucial to inform development of relevant early interventions. In countries such as Australia, advancement the in understanding of many aspects FEP through research has contributed to the development of systematic delivery of evidence-based early interventions for this group of people (18, 19).

Research in FEP is far lagging behind in the Asian countries as compared to the western countries. Research findings from the western countries may not be applicable to the lower-resourced and culturally diverse Asian countries. Several studies done in India, both quantitative and qualitative, have investigated factors affecting help-seeking behavior in schizophrenia (20–22). These studies indicated the presence of unique cultural factors as determinants of help-seeking (21) which may be different in Malaysia with its unique multi-racial population. In Malaysia, studies done in this area have used checklists and interviewer directed questionnaires (23, 24) which may have missed some important details not covered by these quantitative data-collection tools. Qualitative method which encourages free-flow expression of experiences is a better option to explore the rich help-seeking-related information that have influenced care-givers' and patients' decisions to come forward to seek professional treatment.

We conducted a study to explore caregivers' perspective on factors influencing professional help-seeking behavior during FEP in schizophrenia patients as part of developing a comprehensive and appropriate educational tool to promote earlier psychiatric help-seeking behavior in Malaysia.

MATERIALS AND METHODS

Study Design and Setting

This study is a thematic exploratory study which employed a qualitative generic inductive approach using Caeli's generic principles (25). Such design allows better insight into the caregivers' perspectives on important information related to professional help-seeking behavior. The study was conducted from September 2018 till November 2018 on caregivers of schizophrenia patients at Universiti Kebangsaan Malaysia Medical Centre (UKMMC) in Kuala Lumpur, Malaysia. We have adopted COREQ Guidelines (26) in reporting.

Recruitment and Sampling

The study employed a purposive sampling method. A spectrum of participants was selected to represent different stages of recovery from schizophrenia, different educational levels and the major ethnicities in Malaysia. Purposive sampling is effective in identifying and selecting information-rich cases in settings with limited resources (27).

Inclusion criteria were family caregivers who were; 1) having a family member fulfilling diagnostic criteria of DSM-5 for Schizophrenia; 2) 18 years old or older; 3) being the main caregiver for the patient since the onset of the illness and; 4) able to converse in Malay or English language. Exclusion criteria were caregivers; 1) with concurrent life threatening medical condition or cognitive impairment and; 2) caregivers with the ill family member being in acute psychotic episode or facing life threatening medical condition or having dual diagnoses.

Data Collection and Data Analysis

Data collection was done via focus group discussion (FGD) consisting of an average of four participants. FGD sessions were initially co-conducted by first author and two senior co-researchers who are experienced in qualitative study and schizophrenia. All

facilitators were introduced to participants as doctors, either an academic psychiatrist, psychiatrist in training or academic family physician. We emphasized that FGD was a session where researchers attempt to understand caregivers' experiences in making their way to seek professional help during the time when their ill family members had FEP. Independent sessions were conducted by first author subsequently when his interview technique was deemed satisfactory.

FGD was chosen over In-Depth Interview (IDI) as caregivers were anticipated to be able to share their experiences in a closed group. Furthermore, FGD would help group members retrieve memories of their experiences when others share theirs and promote empowerment among participants to voice their needs for information related to help-seeking and treatment of this highly stigmatized illness.

FGDs were conducted by using semi-structured facilitator guide (**Table 1**). The topic guide consisted of open-ended questions with in-depth probing to allow a thorough understanding about the objectives in their own words to gain rich qualitative data. Duration of discussions ranged from 1 hour 10 minutes to 2.5 hours. All FGDs were audio-recorded with digital audio device and then transcribed verbatim.

Data were analyzed using thematic analysis after each data collection session to identify and generate major themes and sub-themes. We adopted basic descriptive thematic analysis suggested by Braun and Clarke (28). We aimed at providing overarching descriptive themes from the data collected and propose how these themes influence caregivers help-seeking behaviors during FEP in patients with schizophrenia. Transcripts were read first to gain an overall understanding. This was followed by initial coding and theme identification. Themes were constructed by comparing and contrasting the initial codes. Data analysis was done by the first author. To improve confirmability of data analysis, independent analysis was undertaken by two senior co-researchers with experience in qualitative study on two randomly chosen transcripts. In addition, analysis meetings were held with experienced co-researchers to discuss the coding framework, emerging themes and to interpret analysis. After each data analysis session, the questions for subsequent sessions were refined before proceeding with subsequent data collection. This research involved reading the data repeatedly to familiarize with the data and manually generating codes. The codes were reviewed, re-categorized and rearranged to clearly define a theme. Data analysis was done manually. QSR NVivo 12 Computer-Assisted Qualitative Data Analysis Software was used to ease organization of data.

The cycle of participant recruitment, data collection and analysis was continued until data saturation was achieved. Data saturation is reached when new data tend to be repeating of data already collected (29). Descriptive analytic report was generated from the themes in relation to the objectives.

TABLE 1 | Semi-structure interview guide.

Semi-structured Interview Guide
What information had stopped the caregivers from engaging psychiatric health care service?
What factors had discouraged them to seek professional (psychiatry) help?
What information had brought them to psychiatric health care
What factors had motivated them to seek professional (psychiatry) help

RESULTS

Socio-Demographic of Participants

A total of 18 (n = 18) primary caregivers of patients with schizophrenia who fulfilled the study criteria were interviewed in five focus group discussions (**Table 2**). They were aged between 33 to 69 years; 8 male and 10 female. Among them, 7

TABLE 2 | Socio-demographic data of participants (n = 18).

Focus group	Participant	Gender	Age (year)	Race	Duration of care (years)	Relationship with patient	Marital status	Employment
1	Par A	F	53	C	9	Mother	Married	E
	Par B	F	69	M	5	Mother	Married	UE
	Par C	M	63	M	9	Father	Widower	UE
	Par D	F	51	M	7	Mother	Married	UE
2	Par E	M	67	C	20	Father	Married	E
	Par F	M	44	C	20	Brother	Married	E
	Par G	F	54	M	6	Mother	Married	UE
	Par H	F	61	I	29	Sister	Married	Retired
3	Par I	M	40	C	8	Husband	Married	E
	Par J	F	58	M	20	Sister	Married	E
	Par K	F	62	C	20	Mother	Married	UE
	Par L	F	42	C	15	Sister	Divorced	E
	Par M	M	63	M	10	Father	Married	UE
4	Par N	M	53	M	9	Father	Married	E
	Par O	F	50	C	5	Mother	Married	UE
	Par P	M	52	C	5	Father	Married	E
5	Par Q	M	43	C	7	Husband	Married	E
	Par R	F	33	C	10	Sister	Married	E

Par, participant; M, Malay; C, Chinese; I, Indian; E, employed; UE, unemployed.

TABLE 3 | Factors influencing professional help-seeking during FEP.

Themes	Sub-themes
Adequacy of Knowledge	Knowledge on how schizophrenia could present itself
	Knowledge on effectiveness of psychiatric treatment for schizophrenia
	Attribution of schizophrenia symptoms to non-schizophrenic illness
	Attribution of cause of psychotic behaviour
	Knowledge on treatment setting
	Knowledge on resources to facilitate help-seeking
Stigma	Internal stigma
	External stigma

were Malay, 10 Chinese, and 1 Indian. Duration of care ranged from 5 to 20 years. The participants' relationship to the person with schizophrenia were either father (n = 5), mother (n = 6), spouse (n = 2), sister (n = 4) or brother (n = 1). Most of the participants (n = 16) were married, with 2 others either widowed or divorced. Ten were employed, 1 retired, and 7 unemployed.

Factors influencing help-seeking behavior during FEP are listed in **Table 3**.

Theme 1: Adequacy of Knowledge

Knowledge on How Schizophrenia Could Present Itself

Schizophrenia presented in a spectrum of different symptom variety and severity. Inadequate knowledge on the different types of presentation especially the subtle symptoms tended to delay caregivers' detection of FEP. Caregivers either overlooked or regarded it as normal variation of psychological experiences or responses to social stressors.

> "… I don't realize she has symptoms because ah … I, I thought after her big examination, she just wanted to relax, so she kept herself in the room…" (Participant C, 2018)
> "…he couldn't work, he told my dad he couldn't work. So, we thought that he was just giving excuses, being lazy" (Par L 2018)

Another participant shared inadequate knowledge on certain behavioral changes being symptoms of schizophrenia. This participant's son stopped playing badminton and suddenly went missing during training (patient was in badminton team of his school and was involved in an intensive training program at the onset of illness). The patient's subsequent behavior of being socially withdrawn and keeping himself in his room was seen by the caregiver as a normal adolescent behavior which had substantially delayed professional help-seeking behavior.

> "…I don't know whether it's because of pressure … he refused to play badminton and then went missing, suddenly missing from training. He was then found sitting in the hall at night. At that time, I didn't know that he was ill. I just didn't know about it. I thought that, 'Aiyoo, this must be a young man's attitude problem. So, it's okay if you (referring to his son) do not want anything' … so he did not come out (paused for 3 seconds) you know, for a year in the room…" (Participant E, 2018)

It was common among the caregivers that awareness about the mental illness only began when prominent aggressive behavior set in. One participant shared about his awareness that his wife was ill and needed treatment only when she demonstrated aggressive behavior.

> "So, ah, so how I end up to (to bring my wife) this hospital is ah, ah, it was in a private [sic] place, in a coffee shop, she behaved insanely, very serious, argue and she also try to damage people's ah, stuff lah that time. Then I know at that time that she must be having illness and not normal, not just the usual suspicious…" (Participant Q, 2018)

Besides aggressive behavior, prominent hallucinatory behavior and severe deterioration in functionality were other behavioral changes that triggered caregivers' awareness of the state of unwellness in the patients which prompted them to seek treatment. For example,

> "….form 3 beginning of the year okay, middle of the year, about June like that, he talking, he talk with the teacher first, he say hear the voice talking to him, then we thought, nothing one lah, normal one lah, sometime, heard people talking, heard people talking, like that also what. He talk to the teacher, teacher also listen what he says lah, come back he also, saw something there, we ask us come and see there got people talking there, talk about him, then we go and see, eh, nothing one, nothing one we also don't bother lah. We thought he was just being naughty. Then more and more, the thing is serious already until one day, around that PMR (Penilaian Menengah Rendah - form 3 public exam in Malaysia), ah PMR right, before the PMR got one exam one, oh he doesn't study, and in the exam he go and take out the book and find answer, answer the question. Then the teacher said, eh, something wrong already. So, during that time, we only started to realize he is unwell and need treatment." (Participant O, 2018)

Some caregivers could pick up behavioral changes as abnormal but had no idea they could be treated medically as they had never heard or seen anyone with a similar problem.

> "For me, not because I don't want to try, because I don't know about modern medication, this sort of abnormal behavior can be treated in the hospital, I don't have that knowledge … If I have the knowledge, I will come earlier, I can do both, I can go medical I can go traditional." (Participant C, 2018)
> "maybe the TV should play a role also. Instead of every now and then, educating people that Aedes mosquitoes has white stripes, they should also put and explain err how to recognize the symptoms of

> mental illness, if this person has such and such behavior for instance, don't leave it, ah help him, tell us what should be done, help him. because most of us don't know the symptoms of schizo, how to help if we don't what is schizo?" (Participant B, 2018)

Participants reported they would have brought the patients for treatment earlier if they knew the changes in the patients were symptoms of schizophrenia. This indicates knowledge about symptoms of schizophrenia would facilitate professional help-seeking behavior among caregivers of patients experiencing FEP.

> "Yes, yes definitely, if I am a doctor with knowledge, if I see my son having symptoms of schizophrenia, then I will definitely bring my son to hospital straight away … Because from 11 years old, sigh (paused for 2 seconds) if we know that is the symptom of schizophrenia, immediately we go… (Participant N, 2018)

If we knew the symptoms we would straight away go and see the doctor.
(Participant O, 2018)

Knowledge on Effectiveness of Psychiatric Treatment for Schizophrenia

Knowledge about the effectiveness of psychiatric treatment had motivated the caregivers to seek treatment for the patients under their care. Some obtained the information from personal experience of being a carer for another schizophrenia patient in the family. Meanwhile, others obtained such information from friends or people around them.

For instance, one participant gained her knowledge about the effectiveness of psychiatric treatment from her experience in caring for another family member with schizophrenia.

> "… my mother-in-law had this illness (schizophrenia) also, she was ill after she delivered my husband. My mother-in-law receive real treatment (psychiatric treatment) lah for her schizo … she recovered with treatment (psychiatric treatment)." (Participant G, 2018)

The same participant went on to equip herself through reading about schizophrenia before her daughter presented with symptoms of schizophrenia.

> "… I researched (reading articles related to schizophrenia) because my mother-in-law had it (schizophrenia)… before my daughter had it, I had, had, had already read about this mental illness (schizophrenia)…" (Participant G, 2018)

Another participant came to know about psychiatric treatment effectiveness from a friend.

> "Ya, ya, ya, because ah, my friend's father also had similar condition (Schizophrenia), he (friend) told that this must be because of that (Schizophrenia) lah. He say that his father is now okay after hospital treatment." (Participant E, 2018)

A few participants gained knowledge of psychiatric treatment benefits through the hard way after attempts with traditional treatments failed to improve the patient's condition which prompted them to switch to psychiatric treatment. Subsequently they opted to continue psychiatric care after they witnessed its effectiveness. For example, participant C brought his daughter for psychiatric treatment when she showed little improvement even after five years of religious therapy.

> "Well, I say okay, why don't give it a try, because we have done it (referring to religious therapy) for 5 years you see, without any improvement. So okay, I accept the advice why not? It's just a try. This is one of the efforts for us too, you know, bring her to treatment lah (referring to psychiatric treatment). Then it's okay. It's a good suggestion actually. Not, not many people know about this. That's why you can see there are still ah … a lot of untreated people…" (Participant C, 2018)

Attribution of Schizophrenia Symptoms to Non-Schizophrenic Illness

In some cases, caregivers knew that patients were unwell. However, wrong attribution of symptoms of schizophrenia by themselves or the primary care doctors had delayed the initial psychiatric treatment.

> "I have a friend who have a autistic son, err … Down syndrome. So I was thinking ah, I, I don't know err … what kind of mental illness my son is having. So my, my friend having a son, a Down syndrome, so I was thinking ah Darren is more or less like that, mental illness maybe another type, and I don't know what type, because at that time I'm a…. I don't do much reading about this mental illness, so I don't know much." (Participant A, 2018)

The same participant consulted a doctor who misled him by giving a wrong diagnosis.

> "I brought him to see a doctor in Pudu (pause 2 seconds) after taking some medication, the doctor was telling me that he was autistic." (Participant A, 2018)

Another participant who knew something was wrong with his son and was ready to accept treatment, was assured by a doctor that treatment was unnecessary and what his son needed was just rest.

> "Ah … I, I, I did bring him to see private. The private doctor says, because he is, ah … he is a … what we call … ah … too much of pressure. So, just ask him to relax." (Participant E, 2018)

Attribution of Cause of Psychotic Behavior

From this study, we found that different attributions of illness influenced the types of treatment sought. For example, one carer initially brought his ill family member for spiritual treatment as he believed the behavior changes in his son were caused by spiritual factors. Psychiatric treatment was not sought until he was enlightened by his friend who worked in a hospital on psychiatric illness being a potential explanation for these behavioral changes.

> "When he come back, we still think, it is ah something to do with ah, spiritual. So, we take him to the Ustad (religious teacher) for the treatment … And we have a relative, who happens to be a somebody in hospital … and he recommended to bring him to see the psychiatrist as he explained to us that my son may have psychiatric illness, so we met Dr Susan." (Participant N, 2018)

Participants who did not believe in traditional treatment were open to suggestion for medical treatment. For example:

> "I don't actually think about that lah (traditional method), I don't think so. It's because I enter into Uni and I am a so called 'science' student, herbs yes I believe is one of the cure, but that is not a long term solution and I study this before, I know this is because of the neurotransmitter, so, I don't think any herbs or spiritual treatment can actually improve it. So, when my uncle suggested to bring my brother to hospital for treatment, I agreed. (Participant R, 2018)

Knowledge on Treatment Setting

Caregivers became reluctant to bring patients for psychiatric treatment when they were misinformed about unfavorable psychiatric treatment setting.

> "… initially when the policeman advised me to send my son to general hospital, I refused. I thought that my child will be sent to Tanjung Rambutan (a mental institute in Malaysia), so I don't want … I am afraid because people there are naked and fight with each other, so I am worried and consider for so long … I got to know about it from media when I was so much younger, when I was in my twenties. I came across paper which talked about happening in Tanjung Rambutan for two, three days … so I thought that all psychiatric treatment are scary…" (Participant A, 2018)

Subsequently, caregivers were encouraged to bring the patients for treatment when they eventually found out that the psychiatric treatment setting could be conducive. A participant made a personal visit to a psychiatric clinic before deciding to bring his son for treatment.

> "Before I brought Darren here, I came to psychiatric GH (psychiatric clinic in general hospital) alone. I looked and walked around the clinic. I asked the patient, 'what happened during doctor's consultation? Any abuse going on?' I went on and spoke to [a] few patients and mothers, then I found out that the hospital environment is not bad … Yes. I really regretted, I should come earlier, it's such a great place, all the nurses, all the doctors they are so understanding…" (Participant A, 2018)

Knowledge on Resources to Facilitate Help-Seeking

Some caregivers were aware of mental illness as a potential explanation for the behavioral changes in the patients. They were aware of the availability of modern treatment; however they struggled to bring the patients to the hospital due to patients' refusal. They were informed that police can be involved only in the event of aggression. Therefore, they had to wait until aggression set in.

> "No, not try, we actually wanted to do that (bring patient to hospital) for a long time. But my brother refused to come to hospital, I even call the hospital ambulance myself, and ask and I even ask does anyone from hospital can do us a favor, send him to the hospital to get treatment? The hospital say they cannot force if patient refuses … Then they said if really don't want to come to treatment or what, you have to call police and ask the police to bring. So, the only way to get him I thought is the police. That's the only way I know. But police say if the patient is not aggressive, they also cannot do anything… 10 years, after 10 years he only get proper treatment." (Participant L, 2018)

Many caregivers were unaware of the availability of community psychiatric services that could facilitate access to psychiatric treatment.

Participant J

> "You aware of that (referring to community psychiatry service)? are you aware? I'm not aware."

Participant L

> "Oh, you are not aware? I am not aware of it too, but I call around and ask, I call and ask if they have a team to support my brother, my brother doesn't even want to go to the hospital … finally I got to know about community psychiatry service…" (Participant J & L, 2018)

Theme 2: Stigma

Stigma was found to be an important factor in influencing help-seeking behavior among the caregivers of

patients with schizophrenia in this study. A number of caregivers felt disgraced by the psychotic behavior of schizophrenia patients due to internalized prejudices related to mental illness.

> "I [was] ashamed to share with my friends, only some close ones. Initially I'm ashamed you know. I [was] ashamed to let people know … that my son is different, so … I only let 2 good friends know, the rest of my friends, I will never tell. And, because he always creates havoc for me ah, function I won't bring him, I will bring my other son. Because he really gives me … a lot of havoc. I am worried that my friend will look down upon me for not teaching my son properly." (Participant A, 2018)
>
> "… none of my husband's family knew about it (referring to her daughter who is diagnosed with schizophrenia). Ah, because (paused for 3 seconds) don't know lah … my husband also didn't allow me to, didn't allow me to share with his siblings. He felt shameful, worried that he will be look[ed] down by others." (Participant G, 2018)

Besides prejudices, some caregivers had internalized stereotypic beliefs about mental illness.

> "Family want to keep to themselves because *malu lah* (feeling shameful), something is wrong with the gene is it?" (Participant J, 2018)

Social stigma was another factor which had delayed professional help-seeking behavior in this study. Some caregivers perceived help-seeking as involving exposing the patients with schizophrenia to others, and that it would lead to disrespect and isolation from the local community.

> "Actually, in our community, accepting a mentally ill patient is indeed, indeed negative lah. We felt, we felt that as if we are marginalized. It is not exactly the feeling of being insulted but felt more or less like that. That's why as long as we can hide it (about one of the family members being mentally ill), we hide it…" (Participant M, 2018)

Relationship Between Adequacy of Knowledge and Level of Stigma

In this study, two main domains of factors that influenced professional help-seeking were identified: adequacy of knowledge and level of stigma. These two factors can be seen as a matrix of dynamic interplay between them in influencing professional help-seeking behavior, as illustrated in **Figure 1**. In this matrix, the dynamic interplay between adequacy of knowledge and level of stigma can be divided into four different quadrants, which is best illustrated through examples from the participants.

(Quadrant A) High Knowledge, Low Stigma (High Tendency in Seeking Professional Help)

The presence of adequate knowledge coupled with low level of stigma tends to facilitate professional help-seeking. Participant E, who did not have much stigma toward psychiatric treatment, brought his son to a hospital the moment he gained the knowledge about mental illness and availability of effective treatment.

> "… I did not prejudice psychiatrist. All types of doctors are the same, must consult doctor if there's an illness … Ya, ya, ya, because ah, my friend's father also had similar condition (Schizophrenia), he (friend) told that this must be because of that (Schizophrenia) lah. He say that his father is now okay after hospital treatment. Only then I knew that my son might be ill as well, so I immediately brought him (referring to son) to consult Psychiatrist in University Hospital…" (Participant E, 2018)

(Quadrant B) Low Knowledge, Low Stigma (Low Tendency in Seeking Professional Help)

Individuals tend not to seek professional help when knowledge about mental illness is lacking, even though level of stigma is low. The same participant in the previous example, i.e. Participant E, who did not have much stigma toward psychiatric treatment, experienced a substantial delay in seeking professional help for his son due to lack of knowledge about mental illness. He described himself as somebody who did not think negatively about psychiatrists at the onset of his son's illness.

> "…I don't know whether it's because of pressure or not … he refused to play badminton and then went missing, suddenly missing from training. He was then found sitting in the hall at night. At that time, I didn't know that he was ill. I just didn't know about it. I thought that, 'Aiyoo, this must be a young man's attitude problem. So, it's okay if you (referring to his son) do not want anything'. So, he did not come out (paused for 3 seconds) you know, for a year in the room … no, no, I did not prejudice psychiatrist. All types of doctors are the same, must consult doctor if there's an illness. I didn't know that he was already ill when he started to isolate himself…" (Participant E, 2018)

(Quadrant C) Low Knowledge, High Stigma (Low Tendency in Seeking Professional Help)

Lower tendency in seeking professional help is seen when an individual has inadequate knowledge and high stigma, as illustrated by participant A's experience. Participant A who lacked adequate knowledge about schizophrenia and psychiatric treatment was exposed to a media report on aggressive incidents occurring in a mental hospital. This negative image about mental

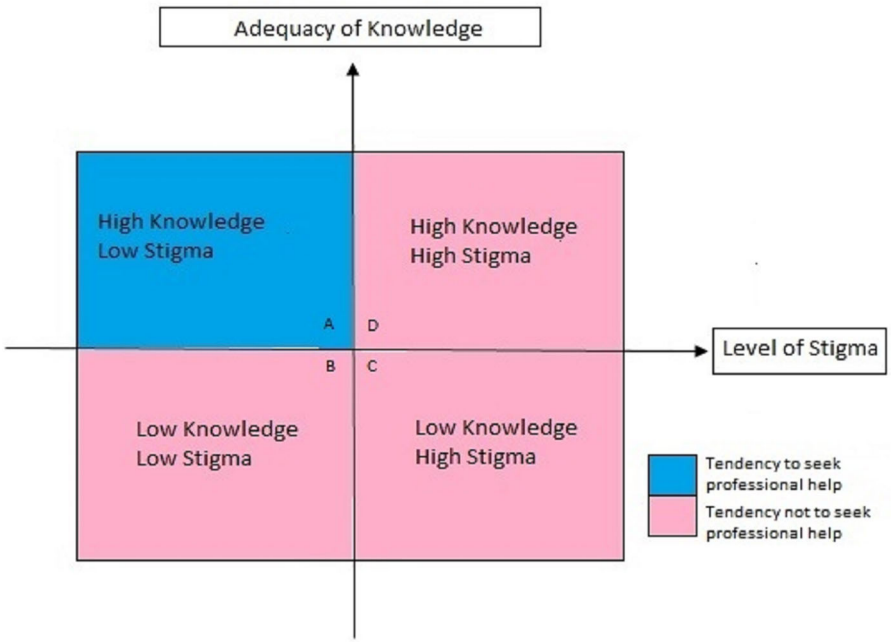

FIGURE 1 | Dynamic relationship of knowledge and stigma.

hospitals spread fast among the local community which shaped her view about psychiatric treatment. This biased information from the media (inadequate information), contributed to her stereotypic belief (stigma) about all psychiatric treatment settings being horrible and psychiatric patients being aggressive. She started to discriminate **(stigma)** psychiatric treatment since then.

> "As what I mentioned earlier on, I was twenty plus that time, I read from [the] newspaper about people in Tanjung Rambutan was hurt, can't remember exactly but is something about patients fighting in there. Scary-lah when I read the news, like like doctors just leave the patients alone-lah, patient fighting lah, naked lah, hitting lah, so scary. Many people also talk about it, very very hot topic that time. My friends that time also describe all the scary things to me … Ya, since then I always thought that psychiatric treatment is bad, is something more or less like that lah … I don't want psychiatric treatment, I worried that my son will be treated like that lah (referring to unfavorable psychiatric treatment)." (Participant A, 2018)

(Quadrant D) High Knowledge, High Stigma (Low Professional Help-Seeking Behavior)

High level of knowledge about schizophrenia is not equivalent to high tendency of seeking professional help if stigma level remains high. This dynamic interplay is illustrated through the experience of participant A. Participant A who had negative views toward psychiatric treatment since her early adulthood was very reluctant to seek psychiatric treatment when her son started to develop schizophrenia. She approached the police for help once when her son became aggressive and was informed by a police officer that her son was probably having mental illness and required psychiatric treatment. Increase in knowledge on mental illness in her did not facilitate professional help-seeking due to her remaining stereotypic belief about unfavorable psychiatric treatment in hospitals which led to a significant delay in seeking psychiatric treatment. Therefore, improvement in knowledge about treatment availability without reducing stigma is inadequate to promote help-seeking behavior.

> "…my friend has a son, a Down syndrome. So, I was thinking ah D (initial of son's name) is having something more or less like that." (Participant A, 2018).
>
> "The police are the one who advised me to bring my son to come to hospital. He said, '… please go to hospital, this is mental illness, it can be treated. There are other people who had similar conditions like this, but they are now well after treatment.'…" (Participant A, 2018)
>
> "… initially when the policeman advised me to send my son to general hospital, I refused. I thought that my child will be sent to Tanjung Rambutan (a mental institute in Malaysia), so I don't want … I am afraid because people there are naked and fight with each other, so I am worried and consider for so long … I got to know about it from media when I was so much younger, when I was in my twenties. I came across paper which talked about happening in Tanjung Rambutan for two, three days … so I thought that

> all psychiatric treatment are scary…" (Participant A, 2018)

She finally brought her son to hospital when her level of stigma reduced after seeing for herself that psychiatric treatment setting is not necessarily unpleasant.

> "Before I brought Darren here, I came to psychiatric GH (psychiatric clinic in general hospital) alone. I looked and walked around the clinic. I asked the patient, 'what happened during doctor's consultation? Any abuse going on?' I went on and spoke to [a] few patients and mothers, then I found out that the hospital environment is not bad … Yes. I really regretted, I should come earlier, it's such a great place, all the nurses, all the doctors they are so understanding…" (Participant A, 2018)

The two examples from the experiences of Participant A and E, illustrate the dynamic interplay of knowledge and stigma. Level of both factors changed over time when these participants went through different life experiences and were exposed to relevant information. An individual can be in different quadrant of the matrix at a different point in time and move to another quadrant at another time. From this study, it can be concluded that tendency to seek professional help is higher when an individual has high level of knowledge about schizophrenia and, at the same time, low level of stigma toward it.

DISCUSSION

In this study, factors influencing psychiatric help-seeking behavior during FEP among caregivers of patients with schizophrenia were explored *via* qualitative approach. A diverse set of factors that influenced decision to first psychiatric treatment were identified and can be broadly classified into adequacy of knowledge and level of stigma. This finding is consistent with findings from previous studies on factors influencing professional help-seeking behavior in schizophrenia during FEP (14–17, 20–22, 30). The study findings also shed some light on how these factors are closely linked and influence each other in determining professional help-seeking behavior.

In this study, various aspects of knowledge about schizophrenia was found to contribute to professional help-seeking behavior among caregivers of patients with schizophrenia during their FEP (from knowledge on symptoms to information about and how to seek treatment). In terms of knowledge on symptoms of schizophrenia, without adequate knowledge on how the illness might present itself, subtle symptoms tended to be overlooked and not recognized by caregivers in this study. Many caregivers normalized such subtle changes which eventually delayed professional help-seeking. These findings are not surprising and have been described in other studies (15, 16, 21). In a qualitative study looking at how people identify and respond to emerging psychosis, Judge et al. (16) found themes like normalization, giving explanation, withdrawal, avoiding help and coming to terms with psychosis which posed as barriers to help-seeking (16). On the other hand, obvious illness presentation such as aggressive and disorganized behavior had facilitated awareness of potential mental illness in some caregivers in this study, hence prompting professional help-seeking. This is consistent with findings from another local study using quantitative method (23).

Interestingly, we found that obvious symptoms did not necessarily motivate professional help-seeking behavior in caregivers. Caregivers in this current study experienced other barriers to professional help-seeking related to knowledge about schizophrenia. Firstly, attribution of cause of psychotic behavior was observed to play role as a barrier in help-seeking. Those who attributed psychotic behavior to magico-religious cause had opted for spiritual remedy over psychiatric treatment as their initial approach. This finding was also observed in other Asian studies (20, 23). Professional help-seeking behavior was hence delayed despite the caregivers having successfully identified the presentation of schizophrenia. In contrast, caregivers who attributed psychotic behavior to scientific causes were more open to suggestion for medical treatment. This finding suggests that cultural and religious factors can be important determinants of help-seeking in schizophrenia and therefore should be incorporated in the development of educational materials aimed to improve knowledge about schizophrenia.

Secondly, a few caregivers who were ready to seek medical treatment faced barriers at the general practitioner (GP) level in this study. In these cases, the GP offered inaccurate attribution of schizophrenia symptoms to non-schizophrenic illness such as ADHD or psychological stress, hence delaying psychiatric treatment. Under-diagnosis and misdiagnosis of specific mental disorders are common among GPs, and this could be improved when symptoms presented are clearly reflecting psychotic conditions and being raised explicitly to the GPs (31, 32). This gap of knowledge at different levels were closely linked and influenced each other but at the same time, they could be a standalone factor that affects professional help-seeking behavior. As the old saying goes, the eyes don't see what the mind don't know; it is important to address this deficit during development of intervention strategy to reduce DUP.

Thirdly, lack of knowledge about treatment efficacy, standards of treatment setting and the right process to seek help further added to delay in help-seeking at a psychiatric facility among caregivers in the current study. This current study highlighted the tendency for people to be misled by rumors or biased reporting in social media which contributes to the generation of stigma when accurate information is not made available. This finding supports evidence from the past on the development of negative views especially in young individuals which led to stigma arising from rumors or biased information about mental illness in the absence of accurate information (33–35).

In this current study, stigma was found to be an equally important contributor to delay in professional help-seeking

behavior in schizophrenia. Negative view on mental illness and its treatment coming from society is often internalized by the patients and their caregivers which hinder help-seeking for fear of being disgraced, disrespected, isolated and discriminated against. Stigma alone in the presence of right knowledge about mental illness was still a hindrance to professional help-seeking among the caregivers in this study. Stigma combined with inadequate knowledge was an even worse situation which lengthened the help-seeking process. Nevertheless, this relationship between knowledge, stigma and help-seeking is a dynamic process i.e. improving knowledge facilitates removal of stigma and encourages help-seeking. For example, stigma and avoidance of help-seeking in caregivers arising from unfavorable and inaccurate media reporting on psychiatric treatment setting improved when more accurate information was obtained. Inadequacy of the right knowledge being a large contributor to formation of stigma has been supported by many past studies (33, 36, 37). Improving reporting on mental illness and its treatment, especially in social media, thus should be recognized as an important intervention that could reduce stigma and facilitate professional help-seeking.

Cultural factors may also influence professional help-seeking in schizophrenia. High tolerance for behavioral abnormality and disability in Asian families often leads to symptoms being unrecognized (38). Misattribution of illness behaviors to typical adolescence, stress, lifestyle or supernatural causes, which was also observed in this current study, is another common cultural contribution to delay in help-seeking (39, 40). In Malaysia, beliefs about causes of schizophrenia vary. Although some attribute psychotic behavior to illness, many others believe that psychosis is a result of evil spirit, black magic, or spiritual related problem. This may arise from inaccurate understanding of religious stand on mental illness commonly conveyed by religious preachers and/or unconscious shifting of responsibility from another set of beliefs that mental illness is a sign of weakness and flaw. Schizophrenia may also be regarded as retribution for past wrongdoing of an individual (41). This does not only influence the choice of initial help sought but the stigma that follows might cause families to conceal the matter and delay help-seeking. Previous studies done in other countries have consistent results with this study (21, 42–44). Hence, addressing these cultural issues while developing intervention for promoting professional help-seeking behavior is important.

Findings from this current study could serve as important material for developing educational material about schizophrenia in developing countries such as Malaysia. In addition, the qualitative method employed in this study has an added advantage in capturing some of the patient or family-related factors that could be a limitation in quantitative study. Our initial objective was to include participants from patients with schizophrenia and their caregivers as study participants in order to gather richer and more complete data on seeking first psychiatric treatment. However, preliminary analysis of the result in the In-Depth Interviews (IDI) with up to 6 patients showed that all patients lost their reality testing during their acute episode at the onset of their illness and had to rely on family members totally to seek help. A patient recalled "I can't differentiate between real and hallucinatory voices when I was ill, the voices are the same" (Participant 1, 2018). Another patient recalled "I don't know doctor, my mind was so muddled up, I can't even recall now what happened at that time" (Participant 3, 2018). All the participants recalled that decision for initial treatment was not decided by themselves. Further IDI session was halted as it was learned at this stage that caregivers were the main determinant for the initial help-seeking decisions and actions. Caregivers play an important role in determining how promptly a patient is brought forward for psychiatric treatment in early psychosis (15).

The results of our study, however, should be interpreted with certain caveats. Caregivers from the rural areas were not represented in this study as the research was conducted in a centre for urban population. Therefore, the findings may not be generalized to the rural population. In this study, data collection on the patient group was terminated before saturation point was reached as all the participants in the first six interview session recalled that decision for initial treatment was not decided by themselves due to impaired reality testing and object relation. Though not specifically done for first episode psychosis, literature does describe that reality testing and object relation is impaired when a person undergoes acute phase of psychosis (45, 46). Hence, with the objective of promoting professional help-seeking behavior during first episode psychosis in mind, we found that it is more relevant to focus on caregivers rather than patients themselves when they are in the acute psychosis phase. However, this does not mean education for schizophrenia patients is less important as patient's reality testing and object relation improve when they are clinically stable. Psycho-education in both groups, the patients and their caregivers, does promote treatment adherence and relapse prevention.

CONCLUSION

Knowledge about and stigma attached to mental illness play an important role in professional help-seeking behavior among caregivers of people with schizophrenia. High level of right knowledge on schizophrenia and its treatment and low level of stigma attached to it better encourages professional help-seeking behavior. However, stigma can undermine the impact of knowledge if not addressed well. Intervention strategies for promoting help-seeking behavior among patients during FEP should simultaneously focus on improving both knowledge about schizophrenia and the stigma attached to it.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

This research study had obtained approval from Unitversiti Kebangsaan Malaysia Medical Centre Ethics Committee. Written informed consent was provided by all participants.

AUTHOR CONTRIBUTIONS

DW designed the research instruments, completed all data entry and data analysis, and wrote the manuscript as part of his master's research. MM is the principal supervisor of this project with co-supervision from ST, TM, and SA. DW, ST, and MM contributed to patients' recruitment, data collection, and interpretation of data. All authors were involved in the intellectual work for the article including generating research ideas, planning for the research, drawing up the manuscript, reading and approving the final manuscript.

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OPINION
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Beyond Recovery: Exploring Growth in the Aftermath of Psychosis

Ying Ying Lee[1*], *Swapna Verma*[2,3] *and Mythily Subramaniam*[1,4,5]

[1] Research Division, Institute of Mental Health, Singapore, Singapore, [2] Department of Psychosis, Institute of Mental Health, Singapore, Singapore, [3] Office of Education, Duke-National University of Singapore Medical School, Singapore, Singapore, [4] Neuroscience and Mental Health, Lee Kong Chian School of Medicine, Singapore, Singapore, [5] Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore

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INTRODUCTION

> "I'm unraveling," I said to my psychiatrist.
> "What do you mean? Tell me more," she inquired.
> "I feel … my personhood is falling apart … like a ribbon coming undone, unraveled," I replied.

Haltingly, I added that I was treading between reality and delusions. I felt like at any moment, I was going to be swept away by the torrential outpouring of psychotic thoughts in my mind. I couldn't stop crying.

All my efforts at rebuilding my life after my first psychotic episode were coming apart. I was in pieces again. What will become of my future? I shuddered at that thought.

That was 5 years ago.

After that second episode, I completed my doctoral thesis (1), defended my research to a panel of distinguished neuroscientists, and relocated home. After a 2-year stint as a peer support specialist at a tertiary psychiatric hospital (2), I joined its research department (3). My current research efforts endeavor to understand recovery and growth from first episode psychosis. Informed by my lived experience with schizophrenia, I am convinced that growth, in the aftermath of psychosis, is possible.

That growth happens in suffering is not a new idea. Friedrich Nietzsche's view on trauma—what does not kill us makes us stronger—is a well-known maxim. Most millennials in the English-speaking world would have grown up listening to Kelly Clarkson's hit song *Stronger (What doesn't kill you)*. Any entomologist will tell you that only butterflies that have struggled out of their cocoons can fly. Traumatic experiences, uncomfortable as they are, play a central role in subsequent growth and development of a living creature. Post-traumatic growth (PTG) is the scientific study of this curious phenomenon in humans. Coined by Tedeschi and Calhoun in the 1990s, PTG is defined as "[the] positive psychological changes experienced as a result of the struggle with highly challenging life circumstances" (4).

Post-Traumatic Growth Entails Three Levels of Positive Change

In a bid to measure the perceived positive outcomes experienced by people with traumatic experience, Tedeschi and Calhoun conducted an extensive literature review (5). They identified

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Erika Jääskeläinen, University of Oulu, Finland

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***Correspondence:**
Ying Ying Lee
ying_ying_lee@imh.com.sg

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three levels of positive changes experienced by people with traumatic experiences over time: intrapersonal changes, interpersonal changes, and suprapersonal changes.

Intrapersonal changes stem from a deeper understanding of one's limits and strengths (personal strength). Tedeschi and Calhoun described this positive change as being "more vulnerable, yet stronger" (6). That traumatic experiences could leave a person feeling the full extent of his or her fragility is not surprising. However, the paradox is the inner strength that one uncovers in the process of overcoming the obstacles tells of the hidden strengths and resources that he or she is previously unaware of.

Interpersonal changes come from stronger bonds with family and friends (relating to others). Crisis makes or breaks relationships. In times of trouble, a person may have friends or family members who abandon them. However, there may also be people who remain supportive of them. The disaster brought on by challenging life events prunes superficial connections and strengthens genuine relationships, resulting in a milieu filled with people who truly matter.

Suprapersonal changes are outward expressions of the intrapersonal and interpersonal changes. It goes beyond one's immediate personal life. It may involve a positive change in one's outlook in life and the development of one's spirituality (appreciation for life, new possibilities, and spirituality). This may include not taking life for granted, exploring new skills and interests in life, and having a more balanced view on spirituality and faith.

Based on these domains, the Post-Traumatic Growth Inventory (PTGI) was developed and validated in an initial sample population (5). Today, this inventory is used widely by researchers from different fields, on people with different kinds of trauma: survivors of natural disasters (7, 8), sexual abuse (9), cancer (10), suicide survivors (11), and even psychosis (12, 13). The five domains of PTGI include personal strength, new possibilities, relating to others, appreciation of life, and spiritual change (5). This growth happens only when the traumatic event causes significant psychological distress and nullifies the person's initial worldwide (i.e., the person's ideas and assumptions on the world were proven to be wrong) (4, 6).

Post-Traumatic Growth in Psychosis

Psychotic episodes are traumatic experiences. The symptoms of this illness—delusions, hallucinations, disorganized behaviors and more—can cause a lot of distress to its patients. In fact, many reported fear and anxiety during their episodes (14). A systematic review on post-traumatic experiences of persons with first episode psychosis estimated the pooled prevalence of post-traumatic stress disorder (PTSD) symptoms at 42%, and PTSD diagnosis at 30% (15). In Singapore, a study on patients recovering from first episode of psychosis estimated the prevalence of PTSD at 19.7% (16). Yet, two independent studies conducted in the UK and Canada suggested that post-traumatic distress may not be the sole outcome in the aftermath of psychotic episodes (12, 17).

The British team built a framework for PTG from the recovery narratives of persons with psychosis and other serious mental health issues (17). Six themes were generated from the semi-structured interviews with mental health patients: self-discovery, sense of self, life perspective, wellbeing, relationships, and spirituality. The authors concluded that growth was a part of the recovery narratives of persons with serious mental health issues. The Canadian team published a mixed methods study on PTG in persons with first episode psychosis (12). Their qualitative analysis showed that besides distress from psychosis, the participants also experienced positive changes such as a stronger sense of self, more balanced view of religiosity, and improvements in health and personality.

Readers familiar with Tedeschi's work would find the findings from the UK and Canada teams reminiscent of the five domains in PTGI. Even though every participant in the studies has his or her unique trauma story, the positive changes that result from their experiences fall into more or less consistent domains. The PTG framework developed by Tedeschi and colleagues in the 1990s holds true today and could be applied in the context of mental health research.

Conceptually, PTG has been contrasted with resilience by Tedeschi and colleague (4). Both PTG and resilience have some similarities, as both phenomena encompass the idea of thriving in adversity. However, they are conceptually different. Resilience has more to do with a person displaying positive adaptation *despite* significant trauma or adversity (18). PTG postulates that a person becomes psychologically stronger *because* of a significant trauma or adversity (4). Even though the outcomes of resilience and PTG (namely positive growth and adaptation) may appear to be identical, the processes in which these phenomena develop may be different. Researchers of resilience suggested that resilience is an innate characteristic (18), while PTG is a process that may be facilitated by healthcare workers (6). Hence, PTG and resilience are related, but distinct concepts.

To date, most published studies on PTG in psychosis are at the descriptive level. Even though they have laid a foundation for the presence of growth after psychosis, they have yet to explore the mechanism(s) behind its occurrence, and its relationship with related concepts such as resilience and recovery.

Beyond Survival

The American survivor culture has shaped therapy goals for many people with traumatic experiences to move from a victim mentality toward a survivor mentality (19). While the initial identification of the person as a victim, and then as a survivor, serve their respective purposes for help-seeking and for overcoming the immediate psychological damage, Dolan (19) noticed that staying in the survivor mode was not sufficient for her clients to thrive. A lot of them live against the backdrop of a mild depressive state, even if they managed to regain some semblance of life. At the same time, she encountered some clients with a history of abuse, yet leading meaningful and fulfilling life against all odds. When she interviewed them, she noticed that they do not refer to themselves as victims, or even survivors of their past. They seemed to have created new identities—free from their past, more toward to their authentic selves. She proposed that working beyond the survivor mentality, carving out a new sense of self, was the missing key for many of her clients (19). This involves growing beyond a traumatic past toward thriving.

Implications of Post-Traumatic Growth on Mental Healthcare

The implications of these growth findings are tremendous. It could change the way one thinks about the trajectory of serious mental illness and change how one treats these issues in the clinical setting. In the last decades, research on recovery from serious mental health issues grew exponentially (20–23). There is now a strong body of evidence that supports the notion of recovery from serious mental illness. That mental illness is not a one-way ticket into an abysmal depth of disability—but of recovery—is widely accepted by the community. However, the current understanding of the detriments brought on by mental illness, and the subsequent recovery, may be incomplete. Like Dolan's idea of victim-survivor-authentic self in trauma care, I would propose that there is more beyond recovery for persons with serious mental illness; that PTG is possible for them, because of the crisis that they went through during the condition. The seismic shift brought on by mental illness in a person's life may be viewed as a unique opportunity to re-evaluate one's strengths and weaknesses, to strengthen bonds with people who truly matter, and to connect with a purpose larger than oneself. Thus, a psychiatric condition could be a trigger for psychological growth. However, this growth does not happen by chance. To catalyze it, new dimensions have to be added to the roles of mental health professionals. Instead of limiting clinical work to rehabilitation and recovery, intentional efforts could also be made to capitalize the patients' traumatic experiences with mental illness and turn it into a growth opportunity.

The challenge remains for us to understand how growth may be facilitated after mental health conditions. Tedeschi and Calhoun proposed that cognitive rumination, coupled with appropriate self-disclosure and social support, produces a personal narrative shift in PTG (4). Janoff-Bulman (24) expounded on the importance of making sense of traumatic experiences in the development of PTG. There may be some hidden treasures waiting to be uncovered from the body of work on PTG that could be applied to mental healthcare practices.

Granted, not everyone who survives mental illness grows from the experience. It does not mean that PTG is reserved for the privileged few. In the context of mental healthcare, I believe that opportunities for growth need to be intentionally introduced into the recovery plans of persons with mental illness. To grow in the aftermath of a mental illness, a period of introspection, positive self-disclosure, and benefit finding needs to be injected into a person's life. Deeper insights into how exactly PTG develops after mental health conditions, and how mental health professionals can support their patients to achieve that, could bring existing mental healthcare services to greater heights.

Looking back, it is almost like the three psychotic episodes I have experienced were preparing me for the work that I do today. In many ways, I am expectant for the next 5 years. No longer do I shudder at the thought of my future, knowing that the psychological growth that ensued from my psychotic episodes has made me a stronger person.

AUTHOR CONTRIBUTIONS

YL conceptualized the manuscript and wrote the first draft. SV and MS gave intellectual inputs based on their clinical and research expertise on psychosis.

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ORIGINAL RESEARCH
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The Role of Five Facets of Mindfulness in a Mindfulness-Based Psychoeducation Intervention for People With Recent-Onset Psychosis on Mental and Psychosocial Health Outcomes

Wai Tong Chien[1], *Ka Ming Chow*[1], *Yuen Yu Chong*[1]*, *Daniel Bressington*[2], *Kai Chow Choi*[1] *and Carmen Wing Han Chan*[1]

[1] The Nethersole School of Nursing, The Chinese University of Hong Kong, Shatin, Hong Kong, [2] School of Nursing, The Hong Kong Polytechnic University, Kowloon, Hong Kong

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Edited by:
Erika Jääskeläinen,
University of Oulu, Finland

Reviewed by:
Michael W. Best,
University of Toronto Scarborough, Canada
Massimo Tusconi,
University of Cagliari, Italy

***Correspondence:**
Yuen Yu Chong
conniechong@cuhk.edu.hk

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Objective: This study aimed to examine how five facets of mindfulness may be associated with the changes in psychotic patients' health outcomes after participating in a mindfulness-based psychoeducation group (MBPEG) program.

Methods: Longitudinal follow-up data from two pragmatic randomized controlled trials of MBPEG for psychotic patients were used for this study. A total of 124 patients who completed the MBPEG program were included in this analysis. Patient outcomes (psychotic symptoms, functioning, insight into illness/treatment, subjective recovery) and five facets of mindfulness were assessed at baseline and six, 12 and 24 months post-intervention. Areas under the curve of individual outcomes in repeated-measures were computed using trapezoidal method, rescaled to the original possible range of the underlying variable and used for correlation and regression analyses.

Results: All mean scores of the five facets increased across time and were significantly correlated with the improvements in all patient outcomes (*p-values* ranged from $<$ 0.001 to $<$0.05), except "non-judging" facet and symptom severity. Regression analyses revealed that only "observing" and "acting with awareness" were significantly associated with positive changes across all outcomes (increase in adjusted R^2 ranged from 5.9% to 24.2%, $p < 0.001$).

Conclusions: Two facets of mindfulness, "observing" and "acting with awareness," were related to positive outcomes of psychotic patients after participating in the MBPEG. More efforts in addressing these two facets of mindfulness can be considered to increase the efficacy of mindfulness-based interventions in psychosis.

Keywords: five facets, mindfulness, psychosis, functioning, psychotic symptoms

INTRODUCTION

Mindfulness, with its roots in ancient Buddhist teaching, has been defined in a variety of ways so as to fit into the context of contemporary psychological science (1). Mindfulness is frequently described as a form of purposively and non-judgmentally paying attention (or being aware of) to unfolding moment-by-moment experiences with openness, curiosity, and acceptance (2–4). Practicing mindfulness is associated with a range of positive outcomes in diverse chronic and disabling conditions, including reduced stress and emotional distress, more positive thoughts and better quality of life (5–7). Mindfulness-based interventions, such as a combination of mindfulness training and psychoeducation program, have become increasingly popular in recent years, and they have been found to be more effective on improving psychological well-being, when compared to mindfulness and/or meditation training alone (8). There is a growing body of evidence from meta-analyses highlighting the significant effects of mindfulness-based interventions on psychological well-being and physical health outcomes of individuals diagnosed with cancer (9), chronic pain (10), psychiatric disorders (11), as well as healthy individuals (12). In a recent meta-analysis of ten randomized controlled trials (RCTs) of mindfulness- and acceptance-based interventions in adults with psychotic disorders, group format mindfulness-based interventions showed larger therapeutic effects (Hedge's $g = 0.46$, 95% CI: 0.18–0.75) than individual-based Acceptance and Commitment Therapy ($g = 0.08$, 95% CI: −0.23 to 0.38) (13).

While several trials have supported the effects of mindfulness-based interventions for psychotic patients (14–17), the mechanism that explains how mindfulness skills benefit psychotic patients has been underexplored. There is evidence that mindfulness-based interventions can improve mental health and well-being through reducing rumination and worry in adults with depressive symptoms, anxiety disorders and cancer (18). Other studies have also shown that changes in the levels of mindfulness in non-psychotic patients, such as those diagnosed with cancer or depression, are associated with perceived stress and other clinical outcomes, such as depression and anxiety (19, 20). However, it is currently not clear if increases in self-reported levels of different facets of mindfulness are associated with the changes in individual important clinical and psychosocial health outcomes of psychotic patients after undergoing mindfulness training and practices.

To investigate the mechanism by which the overall and/or components (facets) of mindfulness may produce benefits, there has been a growing interest in the assessment of mindfulness using validated self-reported questionnaires (21, 22). Among the commonly accepted self-reported measures, the Five Facet Mindfulness Questionnaire (FFMQ) (21) has been one of the most widely used and comprehensive measures of one's perceived levels of mindfulness in daily life (1). It consists of 39 items extracted and modified from five main mindfulness measures, including the Mindfulness Attention Awareness Scale (23), the Freiburg Mindfulness Inventory (24), the Kentucky of Mindfulness Skills (25), the Cognitive and Affective Mindfulness Scale—Revised (26), and the Southampton Mindfulness Questionnaire (27). The FFMQ has been validated (28) and found to include five facets of mindfulness, namely, "Observing" (noticing or attending to internal feelings and thoughts and external simulation); "Describing" (labeling feelings, thoughts and experiences with words); "Acting with awareness" (attending to what is happening in the present); "Non-judging of Inner Experience" (taking a non-evaluative stance toward internal thoughts and feelings); and "Non-reactivity to Inner Experience" (allowing emotions and thoughts to come and go, without being interfered by them). These five facets consolidate and reflect the five essential and most important aspects of mindfulness in current standardized approaches to mindfulness therapy, mainly Mindfulness-based Stress Reduction (MBSR) and Mindfulness-based Cognitive Therapy (MBCT).

Several previous studies on stress, depression and anxiety have examined the relationships between the overall and individual facets of mindfulness and a few health outcomes. Baer et al. (29) evaluated the effectiveness of an 8-week MBSR intervention and found that change in overall mindfulness skills during the first 3 weeks predicted change in perceived stress over the intervention period. In another study, an increase in mindfulness was found to fully mediate the relationships between meditation practices during the intervention and reductions in psychological symptoms and perceived stress (30). Cash and Whittingham (31) found that higher level of "non-judging" predicted lower levels of depression, anxiety and stress-related symptoms; whereas, higher level of "non-reactivity" predicted lower depressive symptoms. However, the aforementioned studies mainly targeted mood and stress-related conditions. There is a lack of investigation or understanding of the relationships between the changes in the five facets of mindfulness and other important health outcomes, such as psychosocial functioning, insight into illness/treatment and level of recovery in different severe mental illnesses.

In the context of contemporary psychological science, current methods of establishing construct validity of an instrument emphasize the importance of measuring each facet of a multifaceted construct via a unidimensional subscale (32). Hence, inconsistent with the Buddhist conceptions viewing mindfulness as a whole concept, mindfulness is often understood and measured in a multidimensional manner to cover different body-mind concepts, mainly including present-moment awareness, non-judging and non-reactivity (1). To better understand the nature and concepts of mindfulness and relationships between its dimensions/facets and level of patient functioning (1), it is interesting and important to know which facet(s) of mindfulness would show association(s) with individual health outcomes in psychotic patients. With this enhanced understanding, mindfulness-based interventions could be designed to address specific facets of mindfulness in order to maximize improvements in the targeted outcomes and optimize positive effects in specific patient groups.

This study aimed to examine whether and in what way the five facets of mindfulness were associated with the changes in the level of psychotic symptoms, subjective recovery, insight into illness/treatment, and functioning of patients with psychotic

disorders after participating in a six-month mindfulness-based psychoeducation group (MBPEG) program. These relationships would be examined in consideration with the main socio-demographics and clinical characteristics of the patients. We expected that, in general, improvements in the five facets of mindfulness would be associated with improvements in the aforementioned health outcomes of these psychotic patients after participating in the MBPEG program over a 24-month follow-up.

MATERIALS AND METHODS

Longitudinal follow-up outpatient data from two RCTs conducted between 2013 and 2016 (ClinicalTrials.gov registration: NCT01667601) for psychotic patients during their early stage of illness (within 5 years of onset) were used for data analyses of this study (15, 17). These RCTs examining the effects of a mindfulness-based psychoeducation group (MBPEG) program for people with psychotic disorders over a 24-month follow-up period have been described in our earlier published articles (15, 17). In this paper, we report the within-group effects of the MBPEG program for psychotic patients on their perceived abilities in performing five facets of mindfulness by pooling the data from two treatment (MBPEG) groups. These treatment groups consist of one mindfulness-based intervention group from each of the two RCTs; and these results have not been previously reported. This analysis does not include data from participants randomly allocated into the conventional psychoeducation and treatment-as-usual (TAU) groups in the two RCTs because they did not receive mindfulness training and therefore the five facets of mindfulness were not measured.

Participants

Patients were eligible for inclusion in the RCTs if they were aged between 18 and 64 years, diagnosed according to DSM-IV as psychosis (DSM-IV diagnostic code: 298.8, 297.1, 293.81, 293.82, or 297.3), schizophrenia, schizophreniform/schizoaffective disorders or other psychotic disorders (DSM-IV diagnostic code: 298.9) for <5 years by psychiatrists using the Structured Clinical Interview (33) as shown in their hospital records, and able to understand Mandarin/Cantonese. Participants were excluded if they were engaged in any mindfulness or other structured psychotherapeutic intervention(s) in the past year and diagnosed with co-morbidity of organic brain injury, learning disability or another mental disorder. A total of 124 patients (87%) who completed both the MBPEG program and 24-month follow-up assessments were included in the final data analysis. Sample size calculations were not conducted a-priori, but the sample size is considered as adequately powered for the two-block multiple regression analysis using the rule of thumb ($N > 50 + 8$ x number of independent variables) (34), hence being estimated to be not <114.

Procedures

Briefly, from the two studies, we recruited a total of 449 randomly selected adult patients with psychotic disorders from nine outpatient clinics of three geographical regions (Taiwan, mainland China and Hong Kong). After completing the baseline assessments, the patients were randomly allocated in a 1:1:1 ratio to one of three intervention groups (mindfulness-based psychoeducation group, MBPEG; conventional psychoeducation group, CPEG; and treatment-as-usual, TAU). Each patient underwent six months of intervention, with the follow-up assessments conducted at 1-week and 6-, 12-, and 24-months post-intervention. The primary outcomes were the Positive and Negative Syndrome Scale (PANSS) score and duration of re-hospitalizations. Secondary outcomes included the Questionnaire about the Process of Recovery (QPR) score, Insight and Treatment Attitude Questionnaire (ITAQ) score and Specific Level of Functioning Scale (SLOF). Only those patients in the MBPEG group completed the Five Facet Mindfulness Questionnaire (FFMQ) and subsequently were included in this study.

The MBPEG program was fully described in our published articles (15, 17). In short, the program consisted of 12 biweekly sessions (24 weeks), with 10–12 patients participating in each two-hour group session. Based on Kabat-Zinn's MBSR, the content of the MBPEG was modified and validated for use in Chinese psychotic patients (17). The program consisted of three phases. Phase one was conducted over six sessions involving three components ("Orientation and engagement;" "Focused awareness on bodily sensations, thoughts, feelings and symptoms;" and "Empowering self-control of symptoms and negative thoughts"). Phase two (three sessions) consisted of two psychoeducational components: knowledge of schizophrenia and illness management/problem solving. The final phase (three sessions) involved behavioral rehearsals of relapse prevention and discussion about community resources/planning for the future. During all group sessions, the patients were taught and supervised to practice body scan and other mindfulness exercises for enhancing attention and awareness of breath, bodily sensations, thoughts, and emotions, as well as mindful sitting and/or walking. In addition, they were encouraged and reminded to practice mindfulness regularly (not <20 min twice daily) as homework assignments. At the later stage, the patients were also encouraged to cultivate an accepting attitude and positive thoughts/responses to life problems, and to develop a "decentered" attitude on their thoughts and feelings.

Measures

Data collected at 0, 6, 12, and 24 months post-intervention were included in the analyses. Outcomes included the number of hospital admissions, the duration of hospital readmissions, the patients' symptoms (PANSS score), level of recovery perceived by patients (QPR score), insight into the illness/treatment (ITAQ score), level of functioning (SLOF score), and the five facets of mindfulness (FFMQ subscale scores).

Positive and Negative Syndrome Scale (PANSS)

The severity and impact of psychotic symptoms on behavior was assessed using the Positive and Negative Syndrome Scale (PANSS). The PANSS composes of 30 items across three subscales: positive symptoms (7 items, score range = 7–49), negative symptoms (7 items, score range = 7–49) and general psychopathology (16 items, score range = 16–112). Each item is

rated from 1 (absent) to 7 (extreme). The total score ranges from 30 to 210. Higher scores indicate more severe symptoms. The PANSS has demonstrated good to excellent interrater reliability [intra-class correlation (ICC) = 0.88], internal consistency (Cronbach's alphas = 0.87–0.93) and concurrent and predictive validity (35).

Questionnaire About the Process of Recovery (QPR)

The patient's level of recovery was assessed using the Questionnaire about the Process of Recovery (QPR) (36). The QPR was previously translated and validated for use in Hong Kong Chinese patients (37). The QPR consists of 22 items for three subscales (10 items for Self-empowerment, 6 items for Effective interpersonal relationships and 6 items for Rebuilding life). Each item is self-rated on a five-point Likert scale (from "0 = disagree strongly" to "4 = agree strongly"). The total score ranges from 0 to 88. Higher total scores suggest higher levels of satisfaction about the level/progress of recovery. The Chinese version has demonstrated very satisfactory internal consistency (Cronbach's alphas = 0.88–0.90), sensitivity to different symptom severity groups ($t = 5.34$, $p = 0.005$) and test-retest reliability (ICC = 0.87–0.92) in Chinese patients with psychosis (37).

Insight and Treatment Attitude Questionnaire (ITAQ)

The Insight and Treatment Attitude Questionnaire (ITAQ) (38) is an 11-item scale measuring patients' awareness of illness (5 questions) and attitudes toward medication/hospitalization/follow-up (6 questions). Items are rated on three-point Likert scale, ranging from 0 = "Not necessary to receive medication/treatment" to 2 = "Medication/treatment should be continued/required regularly." The total ITAQ scores (ranging from 0–33) can be categorized into three groups (poor insight = score of 0–7, fair insight = 8–14, good insight = 15 or above) (39). The ITAQ has been regularly used in patients with schizophrenia, and its validated Hong Kong Chinese version has shown good internal consistency (Cronbach's alphas = 0.85–0.88) and test-retest reliability(r = 0.80–0.86) (40).

Specific Level of Functioning Scale (SLOF)

Patient functioning was measured using the 43-item Specific Level of Functioning Scale (SLOF) (41). The SLOF items are self-rated on a five-point Likert scale (1 = poorest function to 5 = best function) and consist of three domains: physical functioning/personal care (12 items), social functioning (14 items), and community living skills (17 items). Higher scores suggest better functioning. The validated Chinese version has demonstrated satisfactory content validity, test-retest reliability (r = 0.76) and internal consistency (Cronbach's alphas = 0.88–0.96) in Hong Kong patients with schizophrenia (42).

Five Facet Mindfulness Questionnaire (FFMQ)

The FFMQ (21) is a 39-item self-completed questionnaire measuring the five facets of mindfulness: Observing (8 items), Describing (8 items), Acting with awareness (8 items), Non-judgmental (8 items), and Non-reactive (7 items). Participants rated the items on a five-point Likert scale (1 = never or very rarely true to 5 = very often or always true), each facet score ranges from 8 to 40, except for the non-reactive facet which ranges from 7 to 35. Higher scores indicate higher levels of mindfulness in terms of the scored facets. The Chinese version of the FFMQ has demonstrated acceptable internal consistency and test-retest reliability in Chinese people; and confirmatory factory factor analysis supported the five-factor model (28).

Data Analyses

Normality of continuous variables was assessed by skewness statistics and normal probability plots. Data were summarized and presented using appropriate descriptive statistics. Area under the curve (AUC) of each repeated outcome measure and each facet of mindfulness measured at 0, 6, 12, and 24 months were computed using trapezoidal method. The AUC of each variable was then rescaled to the original possible range of the underlying variable and used for inferential analysis. Repeated-measures of analysis of variance test (repeated-measures ANOVA) was performed to examine any significant within-group change for each outcome measure and each mindfulness facet score over time. Correlations between AUCs of the five facets of mindfulness and other outcomes were assessed using Pearson correlation coefficients. Univariate analyses were conducted to examine the association between each patient socio-demographic/clinical characteristics and each outcome including symptom severity (PANSS total score), recovery (QPR total score), insights to illness and treatment (ITAQ total score), and psychosocial functioning (SLOF total score). Those characteristics that were significantly associated with the outcomes in the univariate analyses were subsequently included as covariates in the two-block multiple regression models with the five mindfulness facets as the predictors. Specifically, for each outcome, those socio-demographic and clinical characteristics with $p < 0.05$ in univariate analyses were all entered in the first block. Next, all the five facets of mindfulness variables were subjected to a backward mode in block 2 until only the facets of mindfulness variables with $p < 0.05$ were retained. All statistical analyses were performed using IBM SPSS 24 (IBM Crop., Armonk, NY). All statistical tests involved were two-sided with the level of significance set at 0.05.

RESULTS

From the two RCTs (15, 17), a total of 150 participants with psychiatric disorders were randomly allocated to the six-month MBPEG program. Of these, 36 were from Chien et al. (17) and 114 were from Chien et al. (15). Twenty-six participants (17.3%) dropped out or withdrew from the study over 24 months follow-up, including 6 in Chien et al. (17) and 20 in Chien et al. (15). Hence, a total of 124 participants were included in our analysis. Reasons for attritions were due to having lost contact during intervention (n =15) or 1-week post-intervention (n = 4), withdrawal from the study/intervention due to loss of interest ($n = 4$) or absence from >4 intervention sessions ($n = 3$).

Table 1 presents the socio-demographic and clinical characteristics of the participants. Their mean age was 28.4 years ($SD = 7$), and 52% were male. The majority were single, divorced or widowed (59%), attained secondary school or

TABLE 1 | Baseline characteristics of the participants ($N = 124$).

	n	%
Age, *M* (*SD*)	28.4 (7.0)	
Sex		
Male	65	52.4
Female	59	47.6
Marital status		
Single/divorced/widowed	73	59.0
Married/cohabit	51	41.0
Educational level		
Secondary school or below	74	59.7
College or university or above	50	40.3
Employment status		
Full-time employed	39	31.5
Part-time employed	64	51.6
Unemployed/others	21	16.9
Type of housing		
Public	63	50.8
Private	30	24.2
Supported accommodation/hostel/others	31	25.0
Living condition		
Living with family/close friends	90	72.6
Living alone	22	17.7
Residential/supervised	12	9.7
Received any financial assistance		
No	46	37.1
Yes	78	62.9
Diagnosis		
Psychosis	54[a]	43.5
Schizophrenia	38	30.7
Schizophreniform disorder	16	12.9
Schizoaffective disorder	5	4.0
Other psychotic disorders	11[b]	8.9
Duration of illness (months), *M* (*SD*)	15.9 (5.5)	
Other chronic illness(es)[c]		
No	29	23.4
Yes, one diagnosis	49	39.5
Yes, two diagnoses	46	37.1
Dosage of oral anti-psychotics[d]		
Low	57	46.0
Moderate	53	42.7
High	14	11.3
Duration of using anti-psychotics (months), *M* (*SD*)	13.0 (5.0)	
Number of mental health services/ therapies currently received, *M* (*SD*)	3.2 (1.1)	
Current use of services in outpatient psychiatric departments		
No	6	4.8
Yes	118	95.2
Current use of services in day hospitals/centers		
No	94	75.8
Yes	30	24.2
Current use of substance		
No	83	66.9
Yes	41	33.1

M, mean; SD, standard deviation; n, number of subjects per category.

[a] Psychosis included: brief psychotic disorder (DSM-IV code: 298.8; n = 28); delusional disorder (DSM-IV code: 297.1; n = 8); psychotic disorder due to general medical conditions with delusions (DSM-IV code: 293.81; n = 7) and with hallucinations (DSM-IV code: 293.82; n = 9); shared psychotic disorder (297.3; n =2).

[b] Other psychotic disorders (DSM-IV code: 298.9).

[c] Other chronic illnesses included other chronic medical/physical illnesses, such as hypertension (n = 39), diabetic mellitus (n = 22), renal disease (n = 14), coronary heart disease (n = 10), and other cardiovascular diseases (n =24).

[d] "High dose" referred to a ratio of prescribed daily dose (PDD) to defined daily dose (DDD) >1.5, doses over 1 g/day in chlorpromazine equivalent or dosage exceeding the recommended British National Formulary limits in case of multiple anti-psychotics used (43). "Low dose" referred to an average dose of ≥0.5 and <1 DDD unit or <0.5 g/day of chlorpromazine equivalent; and "moderate dose" was defined as an average dose of 1–1.5 DDD unit or 0.5–1.0 g/day of chlorpromazine equivalent (44).

below education (60%), had a full- or part-time job (83%), were living in public housing flats (51%) with their families or close friends (73%), and had received financial assistance (63%). More than half of the participants were diagnosed with recent-onset psychosis or other psychotic disorders (52%) and less than one third were diagnosed with schizophrenia (31%). The mean duration of illness, the mean duration of using anti-psychotics and the number of mental health services or therapies received were 15.9 months ($SD = 5.5$), 13.0 months ($SD = 5.0$), and 3.2 times ($SD = 1.1$), respectively. The majority of the participants (77%) had one or more chronic medical/physical illnesses such as hypertension, diabetic mellitus, renal disease, coronary heart disease, and other cardiovascular diseases. Most participants had taken moderate or high dosages of oral anti-psychotics (54%), had outpatient department use (95%), but had not used any day hospital or center services (76%) or substances recently (67%).

Table 2 shows the levels of the symptom severity (PANSS total score), recovery (QPR total score), insights to illness and treatment (ITAQ total score), and psychosocial functioning (SLOF total score) as well as the FFMQ facet scores (Observing, Describing, Acting with Awareness, Non-Judging of Inner Experience, and Non-Reactivity to Inner Experience) across the four data collection time points (0, 6, 12, and 24 months). Furthermore, a summary measure based on area under the curve (AUC) of each variable measured over the 24-month period was computed using trapezoidal method to quantify the overall level of the variable of interest in that period. The AUC of each variable was then rescaled to the original possible range of the underlying variable for ease of comparison, which is also presented in **Table 2**. Repeated measures of ANOVA showed that all the scores showed significant linear trends across the time points at 0, 6, 12 and 24 months (all $p < 0.001$).

The relationships between the five facets of mindfulness and other outcomes were assessed by the Pearson correlation coefficients between their AUC values (**Table 3**). The mindfulness

TABLE 2 | Means, standard deviations, and possible ranges of outcomes and five facets of mindfulness across time.

Mean (*SD*)	Possible range	Baseline	6-months	12-months	24-months	AUC[a]
Outcomes						
PANSS total score	30–120	88.5 (9.3)	75.7 (10.4)	53.8 (13.7)	43.9 (14.7)	61.1 (11.6)
QPR total score	0–88	47.3 (3.9)	55.1 (3.9)	60.6 (3.6)	65.8 (3.8)	58.8 (3.3)
ITAQ total score	0–22	8.7 (3.0)	14.4 (2.6)	16.8 (1.7)	17.8 (1.6)	15.4 (1.5)
SLOF total score	43–215	121.3 (13.7)	143.5 (12.8)	161.8 (13.4)	182.6 (12.3)	157.4 (10.3)
Five facets of mindfulness						
FFMQ—Observing	8–40	12.5 (1.4)	16.0 (1.7)	18.9 (1.8)	23.1 (2.4)	18.4 (1.3)
FFMQ—Describing	8–40	12.6 (1.4)	16.1 (1.9)	19.3 (1.8)	24.1 (3.0)	18.8 (1.5)
FFMQ—Acting with awareness	8–40	11.9 (1.6)	15.3 (1.6)	18.6 (1.9)	23.2 (3.4)	18.1 (1.5)
FFMQ—Non-judging of inner experience	8–40	11.6 (1.6)	14.7 (1.8)	17.5 (1.6)	20.5 (2.4)	16.8 (1.4)
FFMQ—Non-reactivity to inner experience	7–35	12.1 (1.9)	15.8 (2.1)	17.5 (2.0)	20.6 (2.9)	17.2 (1.6)

AUC, Area Under the Curve; p, p-value; SD, standard deviation; FFMQ, Five Facet Mindfulness Questionnaire; ITAQ, Insight and Treatment Attitude Questionnaire; PANSS, Positive and Negative Syndrome Scale; QPR, Questionnaire about the Process of Recovery; SLOF, Specific Level of Functioning Scale.

[a]*The area under the curve of each variable spanned over the time from baseline to 24 months as estimated by trapezoidal method and rescaled to the original range of the underlying variable.*

TABLE 3 | Correlations between AUCs of the five facets of mindfulness and outcomes.

	Observing	Describing	Awareness	Non-judging	Non-reactivity
PANSS total score	−0.281**	−0.206*	−0.288**	−0.144	−0.295***
QPR total score	0.535***	0.509***	0.536***	0.282**	0.546***
ITAQ total score	0.607***	0.546***	0.536***	0.374***	0.537***
SLOF total score	0.554***	0.532***	0.516***	0.500***	0.356***

AUC, Area Under the Curve from baseline to 24-months post-intervention; ITAQ, Insight and Treatment Attitude Questionnaire; PANSS, Positive and Negative Syndrome Scale; QPR, Questionnaire about the Process of Recovery; SLOF, Specific Level of Functioning Scale.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

facets were significantly correlated with other outcomes (all *p*-values ranged from < 0.001 to <0.05), except the correlation between non-judging of inner experience and symptom severity (PANSS total score), which was insignificant (**Table 3**).

Table 4 presents the univariate analyses between patient characteristics and outcomes. Almost all patient characteristics assessed in this study were significantly associated with at least one outcome (all *p*-values ranged from < 0.001 to 0.043), except type of housing (all *p*-values ranged from 0.120 to 0.828), history of receiving financial assistance (all *p values* ranged from 0.190 to 0.832), current use of services in day hospitals/centers (all *p*-values ranged from 0.061 to 0.625). The variables with significant associations with each outcome (i.e., $p < 0.05$) were subsequently entered in a two-block multiple regression model for examining the associations between the five facets of mindfulness and the outcome of interest.

As shown in **Table 5**, variables related to patient characteristics accounted for at least 40% of variability of outcomes in block 1 (R^2 ranged from 0.40 to 0.50). The backward regression analyses in block 2 revealed that among the five facets of mindfulness, only "observing" was significantly associated with symptom severity (PANSS total score) (adjusted R^2 increase = 5.9%, $p < 0.001$). Likewise, the regression analysis with recovery (QPR total score) as the outcome found only "acting with awareness" was a significant predictor (adjusted R^2 increase = 16.4%, $p < 0.001$). Two facets of mindfulness, "observing" and "acting with awareness," were significantly associated with insight into illness and treatment (ITAQ total score) (adjusted R^2 increase = 19.1%, $p < 0.001$), while only "observing" was significantly associated with psychosocial functioning (SLOF total score) (adjusted R^2 increase = 24.2%, $p < 0.001$).

DISCUSSION

The present study aimed to examine the role of mindfulness in improving the health outcomes of psychotic patients who participated in a six-month mindfulness-based psychoeducation (MBPEG) program by using the data from our RCTs conducted in Taiwan, Hong Kong and Mainland China (15, 17). In order to achieve this aim we report the effects of the MBPEG program on the five facets of mindfulness, as well as the relationships between the changes of the five facets and the psychological health outcomes of psychotic patients.

There was a significant within-group effect of the MBPEG program on the five facets of mindfulness starting from post-intervention to 24-month post-intervention. This is in line with the current evidence from three meta-analyses showing that the scores of self-reported mindfulness measures can noticeably increase in response to mindfulness training received (12, 19, 45). In addition, the correlation matrix in this study showed that the positive changes in the five facets of mindfulness were significantly associated with the positive changes in most of the patient outcomes. This result is consistent with the findings of a recent systematic review, indicating the

TABLE 4 | Univariate association analyses between patient characteristics and outcomes.

Characteristics	PANSS total score[a]		QPR total score[a]		ITAQ total score[a]		SLOF total score[a]	
	Mean (*SD*)/*r*	*p*	Mean (*SD*)/*r*	*p*	Mean (*SD*)/*r*	*p*	Mean (*SD*)/*r*	*p*
Age (years)	0.105[b]	0.246	−0.401[b]	<0.001	−0.443[b]	<0.001	−0.308[b]	<0.001
Sex								
Male	61.4 (12.2)	0.784	59.1 (3.1)	0.410	15.6 (1.4)	0.117	159.3 (10.0)	0.032
Female	60.8 (11.1)		58.6 (3.6)		15.2 (1.7)		155.3 (10.4)	
Marital status								
Single /divorced/widowed	59.1 (11.6)	0.031	59.7 (3.2)	<0.001	15.8 (1.4)	<0.001	158.8 (9.2)	0.037
Married/cohabit	63.7 (11.4)		57.5 (3.1)		14.8 (1.6)		154.8 (11.3)	
Educational level								
Secondary school or below	61.3 (12.6)	0.871	58.4 (2.7)	0.092	15.1 (1.4)	0.017	155.3 (9.8)	0.007
College or university or above	60.9 (10.2)		59.5 (4.0)		15.8 (1.6)		160.4 (10.5)	
Employment status								
Full-time employed	62.5 (11.0)	0.007	59.9 (3.6)	0.001	16.0 (1.6)	0.012	159.2 (9.9)	0.383
Part-time employed	62.9 (9.7)		57.9 (3.2)		15.0 (1.6)		156.6 (11.1)	
Unemployed/others	53.0 (14.8)		59.8 (2.2)		15.5 (1.0)		156.1 (8.5)	
Type of housing								
Public	61.3 (11.5)	0.120	58.7 (3.4)	0.828	15.2 (1.6)	0.520	156.3 (11.1)	0.448
Private	64.1 (7.9)		58.8 (3.1)		15.6 (1.1)		158.2 (5.6)	
Supported accommodation/ hostel/other	57.9 (14.3)		59.2 (3.4)		15.5 (1.7)		158.8 (12.1)	
Living condition								
Living with family/close friends	61.6 (9.5)	<0.001	59.0 (3.4)	0.140	15.5 (1.5)	0.393	158.7 (8.8)	0.048
Living alone	68.2 (12.2)		57.8 (3.7)		15.0 (2.0)		154.3 (14.9)	
Residential/ supervised	44.4 (9.7)		59.6 (1.4)		15.5 (1.2)		152.7 (9.5)	
Received any financial assistance								
No	59.3 (10.8)	0.190	58.8 (3.4)	0.832	15.3 (1.5)	0.656	158.4 (9.4)	0.403
Yes	62.2 (12.0)		58.9 (3.3)		15.5 (1.6)		156.8 (10.9)	
Diagnosis								
Schizophrenia	60.4 (10.6)	0.013	59.2 (3.7)	0.058	15.6 (1.7)	0.061	158.6 (10.1)	0.178
Psychotic disorders	58.7 (15.2)		58.0 (2.5)		14.9 (1.2)		155.3 (11.4)	
Schizophreniform disorder/Schizoaffective disorder[c]	69.2 (5.7)		58.2 (1.9)		15.4 (1.0)		154.4 (9.1)	
Duration of illness (months)	−0.245[b]	0.006	−0.134[b]	0.139	−0.209[b]	0.020	−0.355[b]	<0.001
Other chronic illness(es)								
No	69.3 (10.6)	<0.001	57.6 (3.3)	0.043	15.2 (1.9)	0.190	158.5 (13.9)	0.101
Yes, one diagnosis	60.7 (8.3)		59.6 (3.0)		15.7 (1.3)		159.1 (9.1)	
Yes, two diagnoses	56.5 (12.7)		58.8 (3.5)		15.2 (1.6)		154.8 (8.5)	
Dosage of oral anti-psychotics								
Low	61.7 (12.4)	0.635	58.5 (3.5)	<0.001	15.2 (1.7)	<0.001	155.3 (12.6)	<0.001
Moderate	61.1 (12.3)		58.2 (2.7)		15.2 (1.2)		157.2 (7.3)	
High	59.0 (3.7)		62.6 (2.4)		17.2 (0.6)		166.6 (2.8)	
Duration of using anti-psychotics (months)	−0.197[b]	0.028	−0.078[b]	0.391	−0.135[b]	0.135	−0.268[b]	0.003
Number of mental health services/ therapies currently received	−0.067[b]	0.458	−0.109[b]	0.229	−0.111[b]	0.218	−0.107[b]	0.235
Current use of services in outpatient psychiatric departments								
No	69.2 (1.8)	<0.001	61.1 (2.2)	0.083	16.3 (0.7)	0.131	166.2 (6.0)	0.031
Yes	60.7 (11.8)		58.7 (3.3)		15.4 (1.6)		156.9 (10.3)	
Current use of services in day hospitals/centers								
No	60.0 (11.7)	0.061	58.7 (3.3)	0.497	15.4 (1.5)	0.625	156.9 (9.5)	0.361
Yes	64.6 (11.0)		59.2 (3.5)		15.5 (1.6)		158.9 (12.7)	

(Continued)

TABLE 4 | Continued

Characteristics	PANSS total score[a]		QPR total score[a]		ITAQ total score[a]		SLOF total score[a]	
	Mean (*SD*)/*r*	*p*	Mean (*SD*)/*r*	*p*	Mean (*SD*)/*r*	*p*	Mean (*SD*)/*r*	*p*
Current use of substance								
No	62.3 (8.3)	0.196	59.2 (3.6)	0.057	15.7 (1.6)	0.004	160.3 (8.7)	<0.001
Yes	58.7 (16.3)		58.1 (2.5)		14.9 (1.3)		151.4 (10.9)	

AUC, Area Under the Curve; SD, standard deviation; p, p-value; r, Pearson correlation coefficient; ITAQ, Insight and Treatment Attitude Questionnaire; PANSS, Positive and Negative Syndrome Scale; QPR, Questionnaire about the Process of Recovery; SLOF, Specific Level of Functioning Scale.

[a] *The area under the curve of each outcome spanned over the time from baseline to 24 months was used as dependent variable.*

[b] *Pearson correlation coefficient.*

[c] *Since the frequency of schizoaffective disorder is too small (n = 5), it was combined with the frequency of schizophreniform disorder (n = 16).*

TABLE 5 | Regression analyses to identify the facets of mindfulness independently and significantly associated with outcomes.

Independent variables	PANSS total score[a,b]			QPR total score[a,c]			ITAQ total score[a,d]			SLOF total score[a,e]		
	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*P*
Block 1												
Patient characteristics significantly associated with each underlying outcome in the univariate analyses as shown in **Table 4** were entered	$R^2 = 0.499$			$R^2 = 0.455$			$R^2 = 0.431$			$R^2 = 0.400$		
Block 2[f]												
Observing	−2.547	0.673	<.001	–	–	–	0.316	0.125	0.013	4.960	0.581	<.001
Describing	–	–	–	–	–	–	–	–	–	–	–	–
Acting with awareness	–	–	–	1.114	0.161	0.001	0.339	0.117	0.004	–	–	–
Non-judging of inner experience	–	–	–	–	–	–	–	–	–	–	–	–
Non-reactivity to inner experience	–	–	–	–	–	–	–	–	–	–	–	–
	Total $R^2 = 0.557$ ($\Delta R^2 = 0.058$, $p < 0.001$)			Total $R^2 = 0.619$ ($\Delta R^2 = 0.164$, $p < 0.001$)			Total $R^2 = 0.622$ ($\Delta R^2 = 0.191$, $p < 0.001$)			Total $R^2 = 0.642$ ($\Delta R^2 = 0.242$, $p < 0.001$)		

β, unstandardized beta-coefficient; SE, standard error; p, p-value; R^2, Multiple correlation squared; –, not retained in backward selection of the five independent variables; AUC, Area Under the Curve; ITAQ, Insight and Treatment Attitude Questionnaire; PANSS, Positive and Negative Syndrome Scale; QPR, Questionnaire about the Process of Recovery; SLOF, Specific Level of Functioning Scale.

[a] *The area under the curve of each outcome spanned over the time from baseline to 24 months was used as dependent variable.*

[b] *Marital status, employment status, living condition, diagnosis, duration of illness, number of other chronic illness(es), duration of using anti-psychotics, and use of services in outpatient psychiatric departments were included as covariates for the regression analysis.*

[c] *Age, marital status, employment status, number of other chronic illness(es), and dosage of oral anti-psychotics were included as covariates for the regression analysis.*

[d] *Age, marital status, educational level, employment status, duration of illness(es), dosage of oral anti-psychotics, and current use of substances were included as covariates for the regression analysis.*

[e] *Age, sex, marital status, educational level, living condition, duration of illness, dosage of oral anti-psychotics, duration of using anti-psychotics, outpatient department use, and current use of substance were included as covariates for the regression analysis.*

[f] *Backward selection of the five facets of mindfulness that significantly associated with each underlying outcome in Block 2.*

increased mindfulness after participating in mindfulness-based interventions can mediate or be associated with improvements of several psychological health outcomes in people with anxiety disorders and depression (46). The improvements of the five facets of mindfulness and psychotic symptoms following the MBPEG could be related to the therapeutic effects of the intervention on reducing psychotic symptoms through the enhanced mindfulness, particularly at the later stage, or vice versa. Another possible explanation could be that after participating in the MBPEG program, the psychotic patients could learn how to relate their aversive experiences (i.e., internal and external stimuli, such as distressing thoughts, feelings and bodily sensations) differently (19). Hence, there could be a chance that the psychotic patients acquired better mindfulness skills and embedded mindfulness practices into their daily activities over the 24-month follow-up, leading to better self-management of the illness and improved psychotic symptoms. Nevertheless, these proposed inter-relationships between the five facets of mindfulness, symptom severity and important health outcomes of these psychotic patients, the directions of their

changes, and the underlying reasons or mechanisms, deserve further research.

Among all four patient outcomes, psychosocial functioning was found to be the most responsive to the changes of the facets of mindfulness across time, as evidenced by the largest change of variance. Whereas psychotic symptoms were found to be the least responsive, with the smallest change of variance. These findings may highlight that although the general premise of mindfulness was delivered in the MBPEG program across all our trials, the specific mindfulness-based interventions were designed to improve the functional impacts of psychotic experiences, rather than to focus on reducing psychotic symptomology (47).

Patterns of the findings from the regression analyses show that among the five facets of mindfulness skills, only "observing" and "acting with awareness" are significantly associated with the improvements in health outcomes of psychotic patients after participating in the MBPEG program. Specifically, "observing" appeared to be the most influential facet, as it was associated with the improvements of three patient outcomes, including symptom reduction, insights into the illness and psychosocial functioning, after controlling for their clinical characteristics. Furthermore, "observing" was the only facet of mindfulness, which contributed the largest variance change in improved psychosocial functioning over 24-month post-intervention. In this study, the significant role of observing in improving patients' health outcomes could be due to the patients' increased ability of noticing or attending to present-moment experiences, which is a fundamental step for practicing mindfulness (48). Such practices may gradually increase attentional and behavioral control, ultimately leading to disruption of maladaptive thoughts and negative sensations (49). Indeed, a number of earlier studies have identified that an increase in "observing" (facet) is associated with or mediates the effects of mindfulness-based interventions in patients with post-traumatic stress disorders (50), diabetes (51), non-clinical samples with paranoia (52), depression and anxiety disorders (53), as well as psychological distress of breast-feeding mothers (54). However, it is still unclear if "observing" is the essential facet of mindfulness responsible for positive improvements in health outcomes across different conditions.

Although positive health outcomes have been found in psychotic patients after receiving mindfulness training (15, 17), there has been debate in the field that mindfulness may actually exacerbate symptoms of psychosis. This exacerbation is proposed to result from promoting awareness of internal states and other meditation-related adverse effects, such as meditation-induced psychosis, depersonalization, and mania (55). Of note, this evidence was mainly based on spontaneous reporting, case studies or observational studies, often in the absence of a control group (55). In line with the principle of mindfulness as suggested by Chadwick (2009), the MBPEG in our studies focused on "decentered awareness" in which psychotic patients could discover that much of their distress came from how they *reacted* to their psychotic experiences (distressing voices, images and thoughts), while mindfully observing and non-judgmentally accepting them could be alternative ways of *response*. Hence, as the patients' insight into their illness increased, they were more motivated to control their psychotic symptoms and became actively engaged with their treatment plans. In our studies (15, 17), the management strategies for potential risks were limited to excluding participants who were mentally unstable and those unable to provide informed consent, and no adverse events were found. Future research on the nature and scope of potential adverse events of mindfulness practice in psychotic patients should be considered in order to minimize potential risks and ascertain if specific types of patients are more susceptible to adverse effects.

Study Strengths, Limitations, and Recommendations for Future Research

This study has several methodological strengths, such as the size of combined samples from two studies, as well as inclusion of relatively long-term follow-up data. Nevertheless, a few limitations of this study should be noted. First, given that the patients who were randomly allocated to the conventional psychoeducation program or TAU only in our RCTs did not receive mindfulness training, their five facets of mindfulness were not measured. Therefore, we did not include these patients' data in the analysis. Although the findings of the RCTs had already proved that the significant changes in the patient outcomes were mainly contributed to, or explained by, the effects of the MBPEG program, the combined or synergic effects of the mindfulness training/practices and psychoeducation could not be identified and differentiated from the mindfulness training alone. In this report, we only conducted within-group analyses to examine the associations between the changes in the five facets of mindfulness and the health outcomes found to have significantly improved across time. We were unable to follow the criteria as suggested by Kazdin (56, 57) to assess whether changes in the facets of mindfulness mediated the effects of the MBPEG program on the patient outcomes, when compared with the conventional psychoeducation or TAU alone. As suggested by Baer (1), participants who did not receive explicit mindfulness training could report with "mild to moderate increases in mindfulness score" because people might sometimes self-cultivate some related skills such as awareness and willingness to experience thoughts and feelings. It is also possible that the facets of mindfulness could change under other cognitive and behavioral interventions. For future studies assessing treatment effects of a mindfulness-based intervention and exploring the mechanism of actions/changes, the comparison group(s) should also include the assessment of the levels of mindfulness.

Second, it could be possible that although the MBPEG program improved patient outcomes, the improvements may have occurred through a mechanism other than increased mindfulness *per se*. For example, psychotic patients who had received MBPEG training may also be motivated to change or improve other health-related behaviors such as adherence to anti-psychotics or psychiatric outpatient service. In addition, apart from mindfulness, decentering, rumination, worry, and self-compassion have been recently suggested as the mediators leading to improvements of mental health outcomes (46). Future research should attempt to measure these variables, so that triangulation of measures and sufficient study power can be provided to elicit more explanatory information about the underexplored mechanism of mindfulness-based interventions.

Third, the fidelity to mindfulness practices in both RCTs was assessed with a checklist as suggested by the NIH Behavior Change Consortium recommendations covering the following five components: design, training, delivery, receipt, and enactment (58). Nevertheless, we were unable to evaluate whether all facets of mindfulness were delivered equally in the MBPEG or some of the facets were delivered more than the others.

Lastly, while the 39-item FFMQ used in this study has demonstrated very satisfactory test-retest reliability and construct validity (59), there is a debate in literature about the insufficient construct validity in self-reporting measures of mindfulness (55). Indeed, there is a widespread acknowledgment that information based on self-reported measures of complex psychological characteristics, such as mindfulness, cognitions and emotions, are inadequate (60). The use of a multimodal approach, where neurobiological and behavioral assessments can be used to capture attentional capacity, may be helpful to mutually inform mindfulness and establish process models of mindfulness for future research (55).

CONCLUSION

The present study adds to existing research into mindfulness-based interventions for psychotic patients. We have shown that changes in two facets of mindfulness, "observing" and "acting with awareness," appear to have important roles in improving psychotic symptoms, progress of recovery, insight into illness/treatment, and psychosocial functioning in patients with psychotic disorders.

Study Implications

To date, mindfulness-based interventions usually adopt a range of distinct meditation techniques, such as body scan, walking meditation, and mindful breathing. However, to develop an effective intervention in a controlled trial, one logical step is to identify what specific facets of mindfulness are targeted by these meditation techniques, and then include the techniques that are the most effective on patient outcomes as the core components of the intervention. For example, body scan exercise is the most effective at cultivating "observing" and "observing" is the facet of mindfulness that was most strongly associated with positive health outcomes in psychotic patients. Therefore, focusing specifically on this exercise may improve the effectiveness of the mindfulness-based intervention. Considering cognitive changes in psychotic patients, more structured and focused approaches to mindfulness-based intervention, for instance, putting more efforts targeting at "observing" and "acting with awareness," may allow these patients to achieve better functioning and illness insight. Our findings set the foundation for future research on designing a tailored mindfulness-based intervention for psychotic patients and exploring the mechanism of changes in the five facets of mindfulness, thus potentially resulting in better health outcomes of these patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was granted ethical approvals by the Hospital Authority or Health Ministry governing the study clinics, and The University in Hong Kong (HSEARS20140218003). All study procedures complied with the ethical standards of the relevant institutional committees on human experimentation and the ethical standards laid down in the 1964 Declaration of Helsinki, and its later amendments. Written informed consent was obtained from all individual participants who were included in the study.

AUTHOR CONTRIBUTIONS

WC and DB: study design. WC: funding acquisition and study coordination and implementation. WC, KChow, YC, KChoi, and CC: data collection and analysis. WC, YC, KChoi, DB, and CC: drafting the manuscript. All authors approved the final version of the manuscript for submission.

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Active Ingredients and Mechanisms of Change in Motivational Interviewing for Medication Adherence. A Mixed Methods Study of Patient-Therapist Interaction in Patients With Schizophrenia

Jos Dobber[1], Corine Latour[1], Berno van Meijel[2,3,4], Gerben ter Riet[5], Emile Barkhof[6], Ron Peters[7], Wilma Scholte op Reimer[1,7] and Lieuwe de Haan[8]*

[1] ACHIEVE Centre of Applied Research, Faculty of Health, Amsterdam University of Applied Sciences, Amsterdam, Netherlands, [2] Research Group Mental Health Nursing, Inholland University of Applied Sciences, Amsterdam, Netherlands, [3] Department of Psychiatry, Amsterdam UMC (VUmc), Amsterdam Public Health Research Institute, Amsterdam, Netherlands, [4] Parnassia Academy, Parnassia Psychiatric Institute, The Hague, Netherlands, [5] Department of General Practice, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [6] GGZ Rivierduinen, Leiden, Netherlands, [7] Department of Cardiology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [8] Department of Psychiatry, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

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***Correspondence:**
Jos Dobber
j.t.p.dobber@hva.nl

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Background: Trials studying Motivational Interviewing (MI) to improve medication adherence in patients with schizophrenia showed mixed results. Moreover, it is unknown which active MI-ingredients are associated with mechanisms of change in patients with schizophrenia. To enhance the effect of MI for patients with schizophrenia, we studied MI's active ingredients and its working mechanisms.

Methods: First, based on MI literature, we developed a model of potential active ingredients and mechanisms of change of MI in patients with schizophrenia. We used this model in a qualitative multiple case study to analyze the application of the active ingredients and the occurrence of mechanisms of change. We studied the cases of fourteen patients with schizophrenia who participated in a study on the effect of MI on medication adherence. Second, we used the Generalized Sequential Querier (GSEQ 5.1) to perform a sequential analysis of the MI-conversations aiming to assess the transitional probabilities between therapist use of MI-techniques and subsequent patient reactions in terms of change talk and sustain talk.

Results: We found the therapist factor "a trusting relationship and empathy" important to enable sufficient depth in the conversation to allow for the opportunity of triggering mechanisms of change. The most important conversational techniques we observed that shape the hypothesized active ingredients are reflections and questions addressing medication adherent behavior or intentions, which approximately 70% of the time was

followed by "patient change talk". Surprisingly, sequential MI-consistent therapist behavior like "affirmation" and "emphasizing control" was only about 6% of the time followed by patient change talk. If the active ingredients were embedded in more comprehensive MI-strategies they had more impact on the mechanisms of change.

Conclusions: Mechanisms of change mostly occurred after an interaction of active ingredients contributed by both therapist and patient. Our model of active ingredients and mechanisms of change enabled us to see "MI at work" in the MI-sessions under study, and this model may help practitioners to shape their MI-strategies to a potentially more effective MI.

Keywords: motivational interviewing, schizophrenia, medication adherence, active ingredients, mechanisms of change

INTRODUCTION

Antipsychotic drug treatment is an effective intervention in patients with schizophrenia (1). However, non-adherence is a problem in approximately 42%–74% of the patients (2, 3). Motivational Interviewing (MI) may be an intervention to stimulate motivation for long-term medication adherence. However, studies on the use of MI to promote medication adherence in schizophrenia show mixed results (4–7), in contrast to the more consistent effects of MI on behavior change in many other disorders (8–11). These discrepancies may partially be explained by differences in MI-strategy, in particular by the application of active ingredients, leading to success or failure in subsequent activation of mechanisms of change in the patients (12). Furthermore, these ingredients and mechanisms of successful MI may be different for patients with schizophrenia (13).

MI is "a collaborative conversation style for strengthening a person's own motivation and commitment to change" [(14), p.29], it addresses the common problem of ambivalence about change. Patients may feel ambivalent about medication adherence, e.g., knowing it may help to prevent psychotic relapse and readmission, and at the same time experiencing burdensome side effects, such as sedation or weight gain. In MI, the therapist deliberately influences the patient's motivation for change, through eliciting change talk (pro change) and softening sustain talk (counter change). The therapist adopts an empathetic attitude, thus communicating the partnership with the patient. The intervention includes four overlapping processes: engaging (relation building), focusing (finding the patient's change goals), evoking (eliciting change talk: the patient's own motives for change), and planning (supporting the patient to create a small concrete plan to move on to actual change). (14).

Nock (15) described three classes of factors involved in psychological interventions to influence subsequent behavior change: clinician factors, client factors, and mechanisms of change (see **Table 1**). The clinician and client factors of interest are those that form the active ingredients of MI. In literature on MI-theory (12, 14, 16–18) and in research (19–23) there are several hypothesized active ingredients of MI in general, such as the clinician factor "discussing ambivalence" (17, 18), and the client factor "experiencing discrepancy" (19, 23). There are also some hypothesized mechanisms of change of MI, e.g. "arguing oneself into change" (14, 18). If we would know which active ingredients and which mechanisms of change determine the success of MI in patients with schizophrenia, then MI-therapists would be able to optimize their execution of MI.

In a previous study, we focused on the patient process in MI and we found three factors for successful MI in patients with schizophrenia: a trusting relationship between patient and therapist, the therapist's ability to adapt the MI-strategy to the patient's process, and relating the patient's values to long-term medication adherence (24). In the current study, we focus on therapist strategies to effectively employ MI, i.e., if and how the therapist applies active ingredients, and whether these stimulate mechanisms of change.

METHODS

Aim

The aim of this study is to explore which clinician factors are employed by MI-therapists, and whether these clinician factors activate client factors, and whether this triggers hypothetical mechanisms of change.

Study Population

The cases were the audiotaped and transcribed MI-sessions of 14 patients who participated in the intervention group of a Dutch

TABLE 1 | Factors involved in psychological interventions[a].

Clinician factors: what the clinician does in the treatment: behaviors, directives, characteristics.
Client factors: what the client does in treatment: behaviors, verbalizations, characteristics.
Mechanisms of change: the processes that emerge from the clinician and client factors that explain how these active ingredients lead to change.
Active ingredients: the specific ingredients in the intervention that cause the change.

[a]*Based on Nock (15).*

randomized controlled trial (RCT) on MI to promote medication adherence in patients with schizophrenia (4). All patients had recently experienced a psychotic relapse after nonadherence to treatment with antipsychotic medication. Some patients received inpatient psychiatric treatment during all MI-sessions. Other patients received inpatient psychiatric treatment at the start of the MI-intervention, and were dismissed from this treatment in the course of the intervention, and further received treatment from outpatient facilities. For other patients, the complete intervention was executed while receiving community mental health care. The mean age of the patients was 35.5 year (range: 23–48). Four patients were female. Two patients had primary education or less, ten patients had secondary education, and two patients had tertiary education or further education. The mean duration of their mental illness was 6.9 years (range: 1–23). The DSM IV diagnoses were schizophrenia (ten patients) or schizoaffective disorder (four patients).

With the patient's consent, the MI-sessions in the original RCT were audio-recorded. The five therapists (a psychiatrist, three community mental health nurses, and a psychologist) were not involved in the regular treatment of the patients. Before the study, the therapists had no previous experience in MI and they followed a 32-h training by a certified MI-trainer. All MI-therapists participated in monthly supervision on MI-fidelity.

Mixed Methods

We used mixed methods to study if and how MI-therapists apply clinician factors to activate client factors, and, through these, stimulate hypothetical mechanisms of change (after this: mechanisms of change).

First, to find potential active ingredients and mechanisms of change in MI, we performed a literature search in PsycInfo and in PubMed (search string 1: "motivational interviewing" and "active ingredients"; search string 2: "motivational interviewing" and "mechanism* of change") and in textbooks on MI (e.g., 14, 16). We also searched for relevant cross-references in the reference list in the selected articles.

Next, we performed a qualitative multiple case study (25) to explore clinician factors, client factors and mechanisms of change in the process of MI. This design contains three phases: single case analysis, cross-case analysis, cross-case synthesis (25). The single case analysis was an analysis of every case separately, guided by worksheets with questions on which the analysis focused. In the cross-case analysis, the findings from the separate cases were merged into clusters. In the cross-case synthesis, these clusters were translated in cross-case assertions, and the evidence for these assertions was reviewed.

In addition, we used sequential analysis (26) to find the probabilities that specific therapist use of MI-techniques, such as a reflection, is subsequently followed by patient change talk or patient sustain talk.

Data Collection and Analysis

To be included, cases had to have at least three audiotaped sessions. We excluded patients with severe psychotic symptoms which hindered effective communication and participation in the MI-sessions. Patients with moderate psychotic symptoms, who were able to effectively participate in the MI-sessions, were not excluded.

The audio recordings were transcribed and parsed in patient and therapist utterances in accordance with the coding manuals of the Motivational Interviewing Skill Code 2.1 (MISC 2.1) (27) and the Motivational Interviewing Sequential Code for Observing Process Exchanges (SCOPE) (28). We used MISC 2.1 Global Ratings (7-point scores) to score the therapist behavior on three dimensions (acceptance, empathy, MI-spirit), and to score the level of patient self-exploration. The SCOPE was used to sequentially code the patient and the therapist communication behavior in 20 codes for the therapist, and 10 codes for the patient language (**Table 2**) (29). Also, we computed five summary scores as suggested in the coding instruments, to assess the therapist fidelity to MI and thus the quality of the MI delivered. After a 37-h training, two coders coded all MI-sessions [for details, see Dobber et al. (24)]. A random selection of 10% (n = 7) of the sessions were re-coded by the same coder to verify intra-rater agreement, and another randomly selected 20% of the sessions (n=13) were double coded by the two coders independently, to compute the inter-rater agreement. For the global ratings, we considered a maximum of one-point difference on the 7-point scales as an agreement, and a difference of more than one point as a disagreement. So, we dichotomized the scores to "agreement" and "disagreement". For the intra-rater agreement, we found a Kappa of.77 for the behavior codes, and a Kappa of 1.0 for the global ratings. For the inter-rater agreement, the Kappa's were.71 and.84, respectively.

While performing the multiple case study analysis, the first author (JD) produced a detailed log on the findings and the decisions during the research process. Furthermore, in accordance with the method of multiple case study analysis (25), the analyst used worksheets to perform a systematic analysis and to register the findings, and composed detailed case reports. The worksheets concentrated on:

a. how clinician factors interacted with the client factors,
b. the hypothetical active ingredients, used by the MI-therapists,
c. clues for the stimulation of which mechanisms of change, and
d. how the MI-therapist applied the active ingredients within the four MI-processes (engaging, focusing, evoking, planning).

For the latter, we constructed a worksheet based on the targets of MI-consistency in the Motivational Interviewing Target Scheme 2.1 (MITS 2.1) (30, 31). In addition, based on the textbook by Berger and Villaume on MI for health care

TABLE 2 | Codes for therapist and patient verbal behavior.

	Codes
Therapist behavior	advise with permission, advise without permission, affirm, confront, direct, emphasize control, facilitate, feedback, filler, general information, opinion, permission seeking, question, raise concern, reflect, self-disclosure, structure, support, warn, not encodable
Patient behavior	ask, follow/neutral, commitment, desire, ability, need, reasons, taking steps, other, not encodable

Based on SCOPE (28).

professionals (32), we added the concept "sense making" (see **Table 3**). This concept refers to the phenomenon that patients develop their own ideas and beliefs about what is happening to them (for instance their illness) and how they should cope with what they perceive is happening to them. These beliefs explain the patient's stance towards therapy and consequently to using or not using medication. The therapist needs to understand this patient perspective to effectively apply the clinician factors and strengthen the patient's motivation for medication adherence [see also Berger and Villaume (32)]. Two investigators (BvM and CL) checked all these steps, and, for quality assurance of the research process, independently chose a subset of these materials and performed an inquiry audit. To check the reliability of the findings, another independent investigator double analyzed two cases. In case of disagreement we checked the original data to resolve the disagreement.

Finally, we used the Generalized Sequential Querier (GSEQ 5.1, software for analyzing sequential observational data) (26, 33) to perform a sequential analysis. Thus, through GSEQ 5.1, we computed the probability that a certain patient motivational statement (e.g., change talk), immediately followed any specified therapist verbal behavior (e.g., an open question querying the target behavior) within the MI-sessions. The p-values for the probabilities resulting from the sequential analysis, were not corrected for multiple analyses. Because of the low frequency of some verbal behavior codes, we combined these codes in broader categories on the basis of MI-theory (14, 16) and previous research (34, 35). For patient verbal behavior, we composed three categories: Change talk, Sustain talk, and Neutral. Apart from Reflections and Questions, we created three categories for the therapist verbal behavior: Sequential MI-consistent behavior, MI-inconsistent behavior, and Other.

TABLE 3 | Topics of a worksheet for the qualitative analysis of the cases.

Target	Description
1. Activity emphasis	The therapist chooses to perform the activity that, at any particular point of the conversation, contributes most to behavioral change.
2. Posture, empathy and collaboration	The therapist engages with the patient and demonstrates accurate understanding of the patient's perspectives and feelings, and works with the patient in a purposeful collaboration.
3. Independence	The therapist emphasizes the patient's control over his/her decisions and behavior, and encourages the patient to take responsibility for his/her decisions and behavior.
4. Evocation	The therapist elicits patient change talk and elaborates on this. Also, the therapist softens the patient's sustain talk.
5. Navigation	The therapist ensures that the conversation progresses in the direction of the change goal.
6. Contrasts	The therapist supports the patient to relate the target behavior to his/her values and life goals, and may develop discrepancy between values, goals and present behavior.
7. Structured brief tactics	The therapist performs optional MI-components as conversational strategies as short routes to facilitate the patient's process. Examples of these tactics are the use of "importance rulers", "confidence rulers", "a typical day", and the composition of a "change plan".
8. Information and advice	The therapist gives only information and advice after (implicit or explicit) permission of the patient, and in an effective way.
9. Sense making	The therapist actively tries to understand the patient's perspective on his/her health problems and the target behavior, and tries to influence the patient's sense making.

Topic 1 to 8: based on the MITS 2.1 (30).
Topic 9: based on Berger and Villaume 2013 (32, 33).

RESULTS

Development of the Model of Active Ingredients and Mechanisms of Change

The composition of the model is based on both the literature search and MI-textbooks [e.g., (14, 16)]. Our literature search yielded 89 articles, of which, based on title and abstract, the full text of 33 articles were retrieved. Of these, nine articles were excluded because of lack of relevance for determining potential active ingredients or mechanisms of change. As a result, we used 24 articles and four textbooks to compose our model of hypothesized active ingredients and hypothesized mechanisms of change (**Figure 1**).

Included Cases

There were 16 cases with three or more audiotaped MI-sessions. We excluded two cases with patients presenting with active psychotic symptoms during the MI-sessions, since this made practicing MI impossible. So, 14 cases, comprising 66 audiotaped MI-sessions were included. One therapist performed MI in five cases (28 sessions), one therapist performed MI in four cases (19 sessions), two therapists each performed MI in two cases (eight sessions per therapist), and one therapist performed MI in one case (three sessions).

Which Clinician Factors Are Present?

Overall, eight out of nine clinician factors (see **Figure 1**) were applied by the therapists. There was great diversity among the therapists in the number of clinician factors applied (**Table 4**). The most frequently used clinician factor was "eliciting change talk", without which the intervention would not be MI (12). Still, in two cases the interaction with the patients and the course of the sessions hindered the therapist to elicit change talk. There was some change talk, but in these sessions it was of such poor quality or artificially elicited (e.g. "You're sleeping well, aren't you, on these medications?"), that we did not consider it as a potential active ingredient. In the first case, the patient avoided serious conversations about medication adherence, and in the second case, a trusting relationship could not be established. This was apparent from superficial conversations with limited openness shown by the patient. A trusting relationship is fundamental to MI, and in this case the conversations, which were also strongly influenced by a language barrier, were dominated by mutual misunderstandings. Hence, though all therapists showed "empathy", not all therapists succeeded to always establish a 'trusting relationship' (**Table 4**).

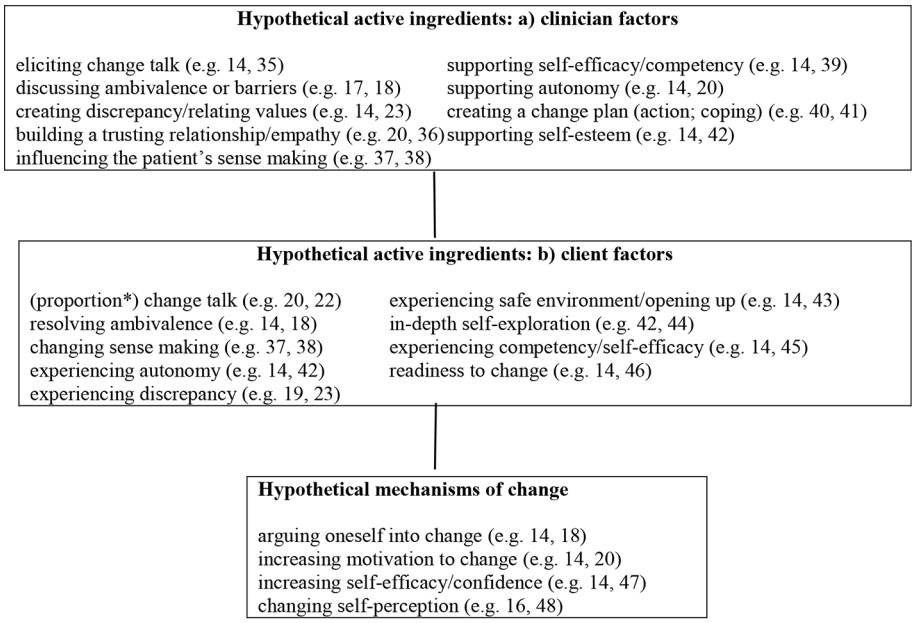

FIGURE 1 | Model of hypothetical active ingredients and mechanisms of change in MI for medications adherence in patients with schizophrenia. *Proportion change talk = frequency change talk/(total frequency change talk + sustain talk). For a brief explanation of each factor: see **Supplementary Material: File 1–3**. Numbers between brackets are references.

Which Client Factors Are Activated by the Clinician Factors?

Except for "readiness to change", we observed all client factors from our model (**Table 5**). Often, a clinician factor activated a variety of client factors, sometimes simultaneously. Discussing ambivalence, for instance, may activate "patient change talk", but can also activate the "patient experiencing discrepancy" and can lead to "resolving ambivalence". The application of a clinician factor however, does not always activate the targeted client factors. While "eliciting change talk" (almost) always led to "change talk", "supporting self-efficacy" activated only in 25% of the applications a client factor (**Table 5**, see **Box 1** for a successful and a less successful example).

TABLE 4 | Application of clinician factors.

Hypothetical clinician factors	Frequency	Number of therapists (n=5) who applied it	Number of clients (n=14) it was applied to
Eliciting change talk	61	5	12
Building a trusting relationship/empathy	*	4	10
Supporting self-esteem	10	4	6
Discussing ambivalence and/or barriers	7	3	3
Influencing the patient's sense making	6	3	4
Supporting self-efficacy/competency	16	3	4
Supporting autonomy	7	3	5
Creating discrepancy/relating values	9	3	4
Creating a change plan	0	0	0

*Mostly applied and maintained through all sessions.

Do Client Factors Lead to Mechanisms of Change?

Since mechanisms of change refer to processes within the patient's mind, it is not possible to observe these psychological processes from an outsider perspective. One can listen to the patient's change talk, and infer from the content and course of the patient change talk that he/she is arguing him or herself into change, but one cannot be certain this process is actually happening [see also Miller and Rollnick (18)]. So, when listening to motivational interviewing sessions, we needed to confine ourselves to, based on the content of patient speech, recognizing clues of a psychological process which might take place within the patient.

We recognized clues for mechanisms of change in sessions with six out of 14 patients. Clues for the mechanism of change "arguing oneself into change" were most prevalent, and the client

TABLE 5 | Clinician factors, client factors, mechanisms of change.

Clinician factors	Frequency	Client factors	freq	Hypothetical mechanisms of change	Frequency
Building a trusting relationship/Empathy	*	Experiencing safe environment/opening up	*		
		In-depth self-exploration	*		
Eliciting change talk	61	Change talk	60	Arguing oneself into change	12
		Sustain talk**	10		
		Experiencing competency/self-efficacy	1		
		Experiencing autonomy	1		
Supporting self-esteem	10	Experiencing competency/self-efficacy	1	Changing self-perception	1
		Experiencing autonomy	1	Increasing motivation to change	1
Discussing ambivalence and/or barriers	7	Experiencing discrepancy	1		
		Change talk	5	Arguing oneself into change	1
		Sustain talk**	2		
		Resolving ambivalence	2	Arguing oneself into change	1
Influencing the patient's sense making	6	Changing sense making	2	Arguing oneself into change	1
		Resolving ambivalence	1	Arguing oneself into change	1
Supporting self-efficacy/competency	16	Experiencing competency	3		
		Experiencing autonomy	1	Increasing motivation to change	1
Supporting autonomy	7	Experiencing autonomy	3	Increasing motivation *not* to change***	1
Creating discrepancy/relating values	9	Change talk	1		
		Changing sense making	2	Arguing oneself into change	2
		Experiencing discrepancy	1		
		Resolving ambivalence	1	Arguing oneself into change	1
		Experiencing autonomy	1	Increasing motivation to change	1

**Mostly applied and maintained through all sessions.*

***Sustain talk is a client factor in favor of nonadherence.*

****This patient did not feel ambivalent about his decision to stop the medication as soon as possible.*

BOX 1 | Examples of Supporting self-efficacy and patient reaction.

Therapist: "And you are good at that: fine-tuning your medication dose, you are able to do that yourself."

Patient: "Yes, I guess 10 years of experience made me some kind of an expert by experience."

(Case 5)

Comment: the patient experiences the therapist emphasizing his control over his medication as an affirmation of his competence.

Therapist: "So you do see which factors throw you off-balance and which, in contrast, keep you stable: your medication use, on which you have a clear vision of now, and alcohol-use which you want to, and can, control. And also, regularity in your life and daytime activities."

Patient: "Yes."

(Case 14)

Comment: the summarizing character of this supporting reflection seems to restrict the effect of the clinician factor 'Supporting self-efficacy'.

BOX 2 | Example of stimulation of a mechanism of change: arguing oneself into change.

Therapist: The medication taking in itself…

Patient: Is no problem.

T: You just think "that's how it is…"

P: Yes.

T: … or "I need it…"

P: Yes, you just accept it … To others, sometimes I tell them to stay on their medication. You know, sort of… (laughs) as if I have to advise them. It's just … to young people I sometimes say: you have to stay on medication, because they think 'I'm doing fine', you know, what they don't know … But one may have a chronic condition, and the other doesn't. But I have a chronic condition, so I know for the rest of my life I'll have to…

T: How do you see your condition? Sometimes, you experience psychosis, how would you call it? Some people would say schizophrenia, others…

C: With me, they say it's schizoaffective. (…)

T: Do you think you have an illness?

P: Yes. Yes, now, when I use my medication, I'm not ill, obviously. But if I don't use them then I'm ill. I can see that difference, yes.

(Case 1)

factor that mostly preceded it was "change talk" (**Table 5**, see **Box 2** for an example). However, this may paint a slightly distorted picture. While client factors are often activated by the immediately preceding clinician factors, the mechanisms of change are mostly the result of a much longer part of the session and preceded by a sequence of clinician factors and client factors.

The mechanism of change 'increasing motivation for change' seemed to occur in non-ambivalent patients who were arguing to strengthen their decision pro or against long-term medication adherence. The clue for "changing self-perception" was observed in a session in which the patient at first presented himself as "someone who *knows* that medication works". After therapist's reflection on *understanding* the importance of medication and the affirmation on the patient's *insight*, the patient expressed being "someone who *understands the utility* of medication", thus fostering a self-perception which may strengthen his medication adherence. We did not find clues for the stimulation of the mechanism of change "increasing self-efficacy/confidence".

How Does the MI-Therapist Apply Active Ingredients to Influence Mechanisms of Change?

Quantitative Analysis

The sequential analysis [in GSEQ 5.1 (26, 33)] over all 66 MI-sessions shows that the client factor "*Change talk*" is usually elicited by reflections directed at medication adherent behavior or intentions (Reflection+) and by questions directed at medication adherent behavior or intentions (Question+). *Sustain talk* is mainly elicited by reflections directed at medication non-adherent behavior or intentions (Reflection-). Surprisingly, sequential MI-consistent (sMI-consistent) therapist behavior like Affirmation and Emphasizing Control, was nine out of ten times followed by a neutral client statement, while we expected a higher proportion of change talk (**Table 6**). We performed a sensitivity analysis omitting the sessions of one patient in which a language barrier possibly hampered the MI-conversations. The sensitivity analysis revealed minor differences in some of the probabilities. In our opinion, this does not affect the interpretation of the analysis. In the **Supplementary Material, File 4**, we present the results of the sensitivity analysis.

Qualitative Analysis

Below, we describe the application of the active ingredients in the four MI-processes: engaging, focusing, evoking, and planning.

TABLE 6 | Conditional probabilities[ab].

Target (patient statements; n=6269) Given (therapist statements; n=6474)	Sustain talk[c]	Change talk[d]	Neutral[e]
Other[f]	.06	.07	.87
2-sided-question (±)[g]	.19	.36	.45
Question-	.58	.08*	.35
Question neutral	.01	.02	.96
Question+	.04	.69	.27
2-sided reflection (±)[g]	.24	.29	.47
Reflection-	.67	.05	.29
Reflection neutral	.01	.01	.98
Reflection+	.02	.74	.24
sMI-consistent[h]	.04*	.06	.90
MI-inconsistent[i]	.04*	.07*	.90

[a]*Probability of a certain type of patient statement given a particular type of therapist statement.*

[b]*All: $p \leq 0.01$, except *$0.01 < p < 0.05$.*

[c]*Sustain talk comprises desire to change, ability to change, reasons to change, need to change, commitment to change, taking steps to change, and other pro-change statements.*

[d]*Change talk comprises desire not to change, ability not to change, reasons not to change, need for status quo, commitment to status quo, taking steps to status quo, and other counter-change statements.*

[e]*Neutral comprises ask, follow/neutral, and not encodable patient statements.*

[f]*Other comprises facilitate, filler, self-disclosure, general information, raise concern, structure, advising with permission, not encodable.*

[g]*2-sided means questions or reflections addressing both change talk and sustain talk*

[h]*sMI-consistent, sequential MI-consistent, and comprises affirmation, emphasizing control, permission seeking, offering support.*

[i]*MI-inconsistent comprises confrontation, directing, warning, giving opinion, advising without permission.*

Note that row percentages add up to 100 (except for rounding).

Engaging

Though posture, empathy and collaboration remained important through all sessions, the clinician factor "trusting relationship", was built in the first session. Making an effort to understand the patient's perspective, showing empathy and interest in the patient and his/her story established rapport, which was maintained through all sessions. Moreover, therapists who understood how the patient made sense of his/her psychoses and of his/her antipsychotic medication treatment were able to use the clinician factor "influencing the patient's sense making" at a later moment in the evoking process of the MI-sessions (**Box 3**).

Focusing

In most sessions, the therapist managed to focus on the target behavior of medication adherence. However, therapists who were able to consistently select the conversational activity (e.g., active listening, goal setting, exploring ambivalence, providing information) which fit best to the patient's motivational process, used a higher variety of clinician factors to activate client factors.

Evoking

The quality of evocation of change talk varied between therapists, and for some therapists this variation also appeared within the sessions. Good quality "change talk" (in terms of depth, amount and strength) mostly occurred as a result of an MI-strategy in which the therapist navigated to support the patient to 'resolve his ambivalence', or to "develop discrepancy" (**Box 4**). However, the fine line between evocation of good quality change talk and lower quality change talk is easily crossed. Sometimes poor quality change talk was elicited, in particular when the therapist artificially sought to elicit change talk without embedding this in a more comprehensive MI-strategy (T: "Why is medication important for you according to your

BOX 3 | Influencing the patient's sense making.

This patient wants to have control over her life, but her life is negatively impacted every time she experiences a psychosis. She thinks that medication is helpful to recover from psychosis. However, during stable periods, she finds only a low dose of medication acceptable, or no medication at all. She prefers no medication because of the drugs' side effects and she feels more autonomous without medication.

Therapist: So, what I learn from you is that in your opinion medication may be a decisive factor to remain stable.

Patient: Yes, if it is not, that would be a problem, what else could I do then?

T: And you mentioned that if things go wrong, and you were off medication for a longer period of time, things seem to get worse.

P: Yes, it does.

T: Is that also a consideration?

P: It is, yes, it is. It may go well for say 3 months, but I've learned from the past that it ends up going wrong. So, medication should be used wisely, I should not experiment with it. Although I'm still a little bit troubled with the physical side effects for which I also need to see an internist, how many sorts of medication do I have to take to stay stable?

T: These long-term consequences are a concern for you…

P: They are.

T: …and at the same time it is obvious for you that medication protects you.

P: It is. (…) Apparently, I do need medication after all … I think.

(Case 14)

BOX 4 | Evoking change talk.

Patient: I stopped taking my medication because I thought … I feel fine … I'll quit taking them…

Therapist: I'm cured.

P: But that's what the medication does.

T: What does the medication do?

P: Make you feel better. So, if you feel fine, you should not stop taking medication but just continue … that's what the medication does.

T: You have experienced that, you learned from that.

P: I did. If I stop taking my medication that will make the chance of relapse much larger than when I do take my medication.

T: Did other persons tell you this, or do you feel … experience that this is how it works?

P: Yes, I've noticed that it works like this.

(Case 12)

BOX 5 | Arguing for medication adherence.

Patient: If I can take care of my own things, then I won't collect my medication at the clinic anymore, because previously I didn't go to the clinic for medication.

Therapist: Later, when you have a job, do you think that you'll need the medication and collect it somewhere else, or will you stop taking medication?

P: Yes, I'll stop taking medications. It is not a good thing to take medications for your whole life, but just for 3 years like I have done now. Previously I didn't take medication, and it's no good to be tired and fat. (…) If I have a job, no one can force me to take medications.

T: So, if you are not dependent anymore, there is no obligation for you to come to the clinic.

P: Yes.

T: Earlier you told me you don't think taking medication is a problem. And your mother thinks that it is very important for you to use medication.

P: Yes.

T: Will it cause big problems for you later?

P: No, when I have a home of my own, no one can say anything about that.

(Case 3)

physician, do you know?" P: "No, just for my illness." T: "Yes, for your illness. So it does help you.").

Since change talk plays a central role in MI (12, 14, 16) and as it is considered as an essential part of MI (12), it may be one of the most important client factors. To gain more insight in the pattern of change talk during the sessions, we added a visual overview of a MI-session (**Figure 2**), focused on occurrence of change talk and sustain talk, and the applied therapist techniques (for a visual overview of all 66 MI-sessions, see **Supplementary Material: File 5**).

"Developing discrepancy" is an important MI-strategy, especially with medication-adherence as target behavior, since many patients with medication-nonadherence in the recent history do not consider medication-use in the remission state as desirable or in line with their values and life goals. Values and life goals may provide, however, powerful motives to change the patient's perspective on long-term medication-adherence (24). Autonomy and independence are important values related to medication adherence, as pointed out by four patients, and these patients felt that the need for medication restricts their autonomy and independence. Only a few therapists addressed this topic to discuss if and how medication may contribute to autonomy and independence. Especially if patients expressed their intention to stop using medication in the near future, therapists tended to argue for medication-adherence instead of accepting the patient's perspective at that moment, thus taking over the responsibility and reducing the patient's independence (**Box 5**).

Some therapists used a decision balance (listing the pros and the cons of medication adherence), which was helpful when the therapist listened well to the patient and reflected his/her concerns, and when the therapist elaborated on the pro-side of medication use. However, often, the performance of a decision balance happened at the cost of much sustain talk. Giving information and advice is another technique that differentially could either support patient engagement and the patient's motivational process, or cause disengagement. Information and advice deepened the conversation if it was tailored to the patient process, or asked for by the patient. But otherwise, it could emphasize the therapist's expert role and threaten the patient's feeling of competence and autonomy, and a few times this caused some discord and patient disengagement.

Planning

In some sessions therapists and patients discussed potential barriers for prolonged medication adherence and relapse prevention. None of the patients, however, created a "change plan" or a relapse prevention plan.

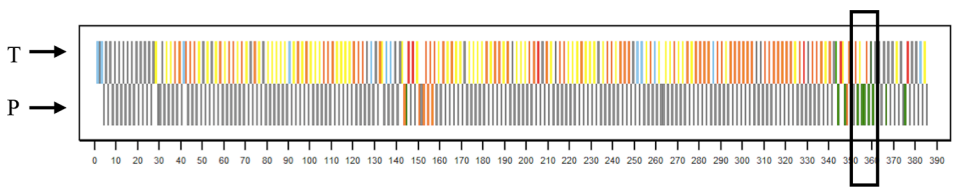

FIGURE 2 | Visual Visual overview of session 1, case 12. Overview of sequentially coded session. Colored bars therapist verbal behavior: dark green = question querying for change, or two-sided question; light green = reflection of change talk, or two-sided reflection; yellow = question querying counter-change, or question not directed at target behavior; orange = reflection of sustain talk, or reflection of neutral talk; blue = sequential MI-consistent techniques (affirm, emphasize control, permission seeking, support); red = MI-inconsistent techniques (confront, direct, warn, opinion, advice without permission); gray = other techniques. Colored bars patient verbal behavior: green = change talk; orange = sustain talk; gray = neutral. On the axis, the sequential utterance number is displayed. The line in the black rectangle shows the session part displayed in **Box 4**.

TABLE 7 | Therapist fidelity ratings.

Therapist	Global Therapist Ratings[a]	Reflection/ Question ratio[b]	Proportion open questions of all questions asked[c]	Proportion complex reflections of all reflections[d]	Proportion MI-consistent behavior[e]
1	+	+	−	++	+
2	+	−	−	++	+
3	−	+	−	++	+
4	+	−	+	++	+
5	+	−	−	++	+

Scores are means over all of the therapist's sessions.
-=not proficient; +=beginning proficiency; ++=competent [based on thresholds in manuals (27, 49)].
[a]Global Therapist Ratings. Scores based on mean ratings on three 7-point Global Rating scales (Acceptance, Empathy, MI-Spirit) (27). Threshold beginning proficiency: mean rating = 4.9 (49).
[b]Reflection/Question ratio. Ratio between reflections and questions (27). Threshold beginning proficiency if R:Q=1 (49).
[c]Proportion open questions of all (open and closed) questions (27). Threshold beginning proficiency if %OQ=50% (49).
[d]Proportion complex reflections of all (simple and complex) reflections (27). Threshold competency is %CR=50% (49).
[e]Proportion MI-consistent behavior of MI-consistent and MI-inconsistent behavior (27). Threshold beginning proficiency if %MICO=90% (49).

Therapist Fidelity

The quality of the MI delivered by the therapists also influenced the appearance and the potency of the active ingredients. As shown through the five summary scores of the MISC (27) and the SCOPE (28), the therapists performed MI at beginning proficiency level (**Table 7**). Overall, the therapists were good at verbalizing complex reflections, but were inclined to ask closed questions. One therapist focused mainly on factual information, and tended to pursue his own agenda, with limited effort to gain a deeper understanding of the patient's perspective and experiences.

DISCUSSION

This study was designed to study the mechanisms of MI for medication adherence in patients with schizophrenia. We unraveled the MI-intervention in active ingredients (clinician factors and client factors) and mechanisms of change, and we systematically studied the application of active ingredients and the appearance of clues for mechanisms of change in 66 MI-sessions with the target group. Our model helped us to see "MI at work". It offered a view on how therapists act to influence the patient's behavior, activating client factors, which may sometimes stimulate the occurrence of mechanisms of change: covert assumed psychological processes that are associated with a subsequent change in medication adherence [see also Miller and Rollnick (18)].

We found that whether the clinician factor activated one or more client factors depended on the specific clinician factor as well as whether or not the clinician factor was embedded in a broader MI-strategy. In a few sessions, the therapist was not able to apply such a strategy, and in these sessions therapists sometimes elicited change talk in an artificial way. This resulted in poor quality change talk, which never led to an active ingredient. These practices, however, occur in particular in newly starting MI-therapists at beginning proficiency.

We also detected indications for the appearance of three of the four mechanisms of change of our model: "arguing oneself into change", "increasing motivation to change", and "changing self-perception".

We did not observe the clinician factor "creating a change plan", the client factor "readiness to change", and the mechanism of change "increasing self-efficacy/confidence". The construction of a change plan was not included in the manual of the intervention (50) in the RCT (4) from which the MI-sessions originate. This may explain the absence of the factors "creating a change plan" and "readiness to change". It may also be an explanation for the absence of the mechanism of change "increasing self-efficacy/confidence". In four cases the therapists supported existing self-efficacy, but in none of the cases the therapist addressed the increase of self-efficacy in the context of creating a change plan for medication adherence.

Most of the present knowledge about active ingredients and mechanisms of change in MI originates from alcohol dependency research [e.g., (17, 19, 21, 22)]. Magill et al. (21) used mediation analysis to test a model with active ingredients, mechanisms of change and patient outcomes in a brief motivational interviewing intervention in heavy drinking underage young adults. Despite the differences between the studies in target populations, target behavior, and study design, two out of three of the MI-specific mechanisms of change of the model by Magill et al. (21), were also found in our study ("experiencing discrepancy", which we consider an active ingredient, and "increasing motivation for change"), but we did not find "increasing self-efficacy" in our sample.

In contrast to Magill et al. (21) our model differentiates between clinician factors and client factors, consistent the description by Nock (15). The influence of client factors in psychological interventions is recognizable in MI, since the mere act of "eliciting change talk" does not stimulate a mechanism of change. It depends on the client reaction (e.g. change talk in a certain depth, amount and strength) whether a mechanism of change is stimulated. Moreover, in our qualitative analysis we found that mechanisms of change mostly are a result of a MI-strategy adapted to the patient process, which comprised an interaction between therapist and patient during larger session parts, and included a variety of clinician factors and client factors. Also, while interaction between clinician factors and client factors seems to be a prerequisite for the appearance of a mechanism of change, many of these interactions did not result in a stimulation of a mechanism of change.

Kazdin and Nock (51) point out that knowing how or why psychological interventions work presumes knowledge about necessary and sufficient ingredients, effective and non-effective doses, and factors impeding change. Our study suggests that in particular the client factors are in fact a pool of factors from which, if properly activated by clinician factors, different combinations can form active ingredients that stimulate a mechanism of change.

However, a mechanism of change for a specific outcome is only a mechanism of change if it causes that specific outcome.

We did not study the relation between the mechanisms of change and medication adherence. Before studying such a relationship, we first needed to know what active ingredients are actually delivered in the intervention under study, and whether there are sufficient clues for the stimulation of mechanisms of change by the active ingredients. For causality, statistical mediation is required (15) in addition to the causal guidelines [e.g., (15, 51, 52)]: strong association, specificity, gradient/dose-response relationship, temporal relation, consistency, experiment, plausibility and coherence. Of these, we only showed temporality, and we had to accept the plausibility of the mechanisms of change from the theory of MI (14, 16).

Limitations and Strengths

A limitation of this study is the limited visibility or measurability of most of the client factors and mechanisms of change, and the subsequent interpretative character of the findings. Furthermore, we studied only a small sample of 14 patients. However, we believe that the sample was pragmatic and population-based, and in our opinion representative for schizophrenia patients with recurrent psychotic episodes, medication non-adherence, and frequent re-admission. In addition, due to the rigorous (systematic and transparent) method and the strict quality control measures, we believe the findings are credible and trustworthy.

Our tentative model is based on MI-theory and research literature, thereby reflecting the current state of the MI-knowledge on this subject. In spite of this, the hypothetical character of our model of active ingredients and mechanisms of change is still a limitation, and there may be other, possibly unknown, factors or mechanisms that are missing in the model (53, 54).

A strength of this study is the depth of analysis. We analyzed beyond the MI-measurement instruments [MISC (27), SCOPE (28), MITS (30)], and used both quantitative and qualitative research methods. This thorough analysis enabled us to study the interactions between ingredients and mechanisms. A better understanding of this is an important step in the development of knowledge on MI. With the results of this study, we add a building block to answer the question how and why MI works in general, and particularly how MI works in patients with schizophrenia with medication adherence as target behavior.

CONCLUSIONS

A large variation in the application of clinician factors enables the therapist to build a MI-strategy. The clinician factors activate the client factors, of which in our data 'change talk' was the most prevalent. It is plausible, however, that it is not about individual clinician factors activating individual client factors, but about a sufficient combination of factors. This combination acts as an active ingredient and can trigger a mechanism of change.

The most important conversational techniques that shape the clinician factors we observed are reflections and questions addressing medication adherent behavior or intentions, often followed by the client factor "change talk". "A trusting relationship and empathy" turned out to be an important clinician factor, that enabled both therapist and patient to attain sufficient depth in the conversation through which clinician factors and client factors allow for a fruitful interaction with opportunities to trigger mechanisms of change.

Our model enabled us to see "MI at work", and formed a basis for qualitatively studying MI. The model and our findings may help practitioners to improve the effectiveness of their MI-strategies to a more effective MI, in which active ingredients are intentionally employed to increase the probability of behavior change.

MI may be more effective if the therapist is informed about the active ingredients and the mechanisms of change. The current study provides possible ingredients of effective patient-therapist interactions triggering mechanisms of change. However, whether these mechanisms lead to better outcomes needs to be studied in further detail. A next step in research may be to study whether there are better outcomes for patients with MI-sessions in which one or more mechanisms of change appeared, compared to patients for whom no mechanisms of change were observed.

DATA AVAILABILITY STATEMENT

Parts of the dataset generated and analyzed for this study can be found in the Figshare repository: https://doi.org/10.21943/auas.9505436. Parts of the datasets generated and analyzed during the current study are not publicly available due to identifying patient information. Data may be available from the corresponding author upon request, but restrictions apply on the availability of these data in accordance with the ethical rules of the Medical Ethical Committee of the Amsterdam UMC.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the Amsterdam UMC, University of Amsterdam. The patients/participants provided their written informed consent to participate in this study. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JD, CL, BM, GR, EB, RP, WS, and LH contributed to the study design. JD and EB performed the data acquisition, JD, GR, and EB performed the data analysis. JD, GR, EB, and LH interpreted the data, and CL and BM checked the data-interpretation. JD, CL, BM, GR, EB, RP, WS, and LH participated in writing the manuscript. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00078/full#supplementary-material

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Metabolic Syndrome and Cognitive Functions in Schizophrenia—Implementation of Dietary Intervention

Katarzyna Adamowicz[1]*, *Aleksandra Mazur*[2], *Monika Mak*[1], *Jerzy Samochowiec*[1] and *Jolanta Kucharska-Mazur*[1]

[1] Department and Clinic of Psychiatry, Pomeranian Medical University, Szczecin, Poland, [2] Department of Social Sciences, Institute of Psychology, University of Gdańsk, Gdańsk, Poland

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Anthony Ahmed,
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***Correspondence:**
Katarzyna Adamowicz
groszewska.katarzyna@gmail.com

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Introduction: The co-existence of schizophrenia and metabolic syndrome is a widely described phenomenon that contributes to the worse functioning of patients in everyday life. A relatively new area of research is the relationship between metabolic syndrome (MS) and cognitive function in patients with schizophrenia. The aim of the study was to verify the relationship between the presence of metabolic syndrome and cognitive function of patients with schizophrenia and to assess the possibility of changing cognitive function by introducing appropriate dietary intervention.

Materials and Methods: The study involved 87 individuals diagnosed with schizophrenia according to ICD-10 criteria, aged 19 to 67 years (M = 41.67; SD = 11.87). Patients were in the remission phase of schizophrenia, all using antipsychotics for pharmacological treatment. From a group of 83 patients with schizophrenia and diagnosed metabolic syndrome (according to IDF criteria) 30 patients were randomly assigned to an experimental group—with dietary intervention, 29 patients—to group without dietary intervention, 24 patients with schizophrenia without metabolic syndrome was a comparison group. All groups were evaluated for cognitive function using Stroop Test, Trail Making Test (TMT), Verbal Fluency Test, Digit Span Backwards Test. In the experimental group a dietary intervention was applied, which was to provide the examined person with a 7-day dietary plan with reduced calorie content, in compliance with the Mediterranean diet.

Results: After the dietary intervention there was a significant improvement in the number of errors made in the third Stroop Test ($p < 0.001$), the time taken to complete the Point Linking Test was shortened (Test B; $p = 0.005$), there was an improvement in Verbal Fluency Test in "animals" category ($p = 0.006$) "sharp objects" category ($p = 0.009$), the number of repeated digits has increased in Digit Span Test in "forward" category ($p = 0.001$) and overall completion of the test ($p = 0.021$). In the group of patients with MS without dietary intervention, the results of cognitive tests remained mostly unchanged.

Conclusions: Change of eating habits may be a significant element of a holistic approach to the problems of treatment of schizophrenia.

Keywords: schizophrenia, metabolic syndrome, cognitive functions, Mediterranean diet, dietary intervention

INTRODUCTION

The coexistence of schizophrenia and metabolic syndrome is widely described in medical literature. Mental illness alone significantly impairs the functioning of the patient, and the occurrence of somatic disease further reduces the quality of life and functioning. It is also worth noting that about 50% of patients with mental disorders have at least one undiagnosed somatic disease (1). Therefore, it is worthwhile to address topics concerning the co-occurrence of mental disorders and somatic diseases.

In schizophrenia, cognitive dysfunctions (especially executive dysfunctions) are common. They usually appear already in childhood, most often they concern memory, visual-motor coordination and attention (2). Cognitive symptoms are an equally important element of the disorder as positive, negative and affective symptoms. Each of psychotic symptom clusters is associated with and may contribute to worsening of other symptoms clusters, worsening the patient's condition, in a similar manner to coexisting somatic diseases. As a result, the activity in specific areas of individual functioning is reduced (2–4).

A relatively new direction of research is the coexistence of metabolic syndrome and cognitive disorders in patients with schizophrenia. Meta-analysis of 18 studies confirms that the presence of MS (metabolic syndrome) or its components is associated with significantly worse cognitive function (5). Obesity is one of the components of MS, which causes a higher risk of developing neuropsychiatric disorders. On the other hand, patients with mental illnesses are more prone to unhealthy eating habits, and pharmacological treatment increases appetite, which may contribute to the development of obesity. The secretion of neuropeptide Y (NPY) is responsible for the appearance of the feeling of hunger. Studies show that when pharmacotherapy is included, an increase in concentration of leptin is observed, which entails incorrect NPY secretion and causes and increased need to consume food. Excessive supply of energy from food causes overweight and obesity to appear later on. A change in the production of hormones that regulate appetite can already be observed in the initial phase of psychotic disorders. It has also been shown that compared to people without schizophrenia, those diagnosed with schizophrenia have three times more visceral adipose tissue (6, 7). A meta-analysis of 48 studies showed that olanzapine is a drug that causes the greatest weight gain and increase in cholesterol. Large variations in weight gain are also observed when using clozapin. However, aripiprazole, risperidone or ziprasidone seem to be safer. When choosing the right neuroleptic, it is necessary to take into account not only its antipsychotic effect, but also its influence on the occurrence of metabolic side effects (8).

Both obesity and schizophrenia are associated with systemic inflammation. Obesity is often accompanied by neuroendocrine changes associated with the functioning of the hypothalamic–pituitary–adrenal axis. Moreover, obesity-related stress increases the risk of episodes of mood disorders, exacerbation of psychosis and deterioration of cognitive functions (9, 10). It has been noted that MS is a risk factor for the development of cognitive disorders, as obesity, hypertension and hyperglycemia are associated with inflammation of the nervous system, leading to cognitive impairment (11–13). Boyer et al. observed that patients with schizophrenia and concomitant MS have worse results in tests examining executive functions, attention and memory than patients with schizophrenia but without MS (14). It was also noted that a high BMI may contribute to a deterioration in memory, language functions, performance and even general intelligence (15). People with mental illnesses, with excessive fatty tissue content, perform worse in tests checking deferred memory, direct memory, and have reduced efficiency in abstract thinking (16). There were also connections between the occurrence of metabolic syndrome in adulthood and reduced cognitive function during adolescence, in people who were diagnosed with schizophrenia in adulthood. The study noted that poor school performance between the ages of 12 and 16 was linked to the emergence of MS in the future. This suggests that in addition to antipsychotics, the cognitive factor may be responsible for the risk of metabolic disorders later in life. Therefore, health education programs should be introduced during adolescence, especially for people with impaired cognitive function (17, 18).

Of course, the metabolic syndrome itself, without accompanying schizophrenia, may negatively affect cognitive functions. This was observed in middle-aged people with a diagnosis of MS, without mental illness, who, in comparison to their peers without MS, have greater problems in psychomotor efficiency and speed, creating concepts, decision making and intellectual functioning (19). Individuals with pathological obesity, in comparison to the group with BMI in normal range, obtain worse results in terms of operating memory and executive functions. They also show higher rigidity of thinking, which indicates the occurrence of cognitive dysfunctions related to prefrontal cortex function (20). The use of magnetic resonance imaging has shown that obese people have a smaller volume of white and grey matter in temporal and frontal structures compared to people with a normal body weight. The high adipocyte content in an obese person's body may amplify the cellular inflammatory response, which in turn damages brain tissue, especially oligodendrocytes, and, as a result, impairs cognitive functions (21–23).

On the other hand, actions aimed at improving the components of MS may improve cognitive efficiency (24).

Discovering further links between cognitive function and dietary behaviors, which have a significant influence on the development of MS, may contribute to understanding the mechanisms of obesity formation. The relationship between obesity and cognitive disorders may be bilateral. Loss of control over food intake is associated with changes in cognitive efficiency (25). Lips et al. found that fasting obese people show stronger functional communication between the brain areas responsible for cognitive control, motivation and reward system than people with normal body weight (26). Neural network connections in lean and obese individuals were also examined by means of functional magnetic resonance imaging. Functional integrity of resting network connections is different in both groups, especially in default mode network and frontal lobe network. This confirms that obesity affects brain function in areas responsible for nutrition regulation or reward system (27). These studies show that in planning the therapy for schizophrenia, both psychiatric and medical treatment, including dietary management, should be taken into account.

The aim of this study was to verify the relationship between the presence of metabolic syndrome and cognitive function of patients with schizophrenia and to assess the possibility of changing cognitive function by introducing appropriate dietary intervention. The following research hypotheses were posed:

1. Cognitive function of patients with schizophrenia and coexisting metabolic syndrome is reduced in comparison to patients with schizophrenia without metabolic syndrome.
2. The implementation of appropriate dietary intervention contributes to the improvement of cognitive function in patients with schizophrenia and coexisting metabolic syndrome.

The presented study is a part of a larger project concerning eating habits and metabolic syndrome in patients with schizophrenia. The study was approved by the Bioethics Committee of the Pomeranian Medical University in Szczecin (Resolution No. KB-0012/108/14).

MATERIALS AND METHODS

Participants

The study involved 87 patients with schizophrenia (F 20 according to ICD 10) in remission lasting at least 3 months at the time of giving consent to participate in the study, treated outpatient in the Department of Psychiatry of the Pomeranian Medical University in Szczecin. Four patients were excluded due to significant lack of data in the second measurement (lack of at least one test). Therefore, the analysis was carried out on 83 patients with F 20 diagnosis, aged from 19 to 67 years, of whom 59 (71.08%) met the diagnostic criteria of the metabolic syndrome.

Clinical Assessment

After obtaining written consent to participate in the study, each patient was examined by a specialist psychiatrist to verify the diagnosis of schizophrenia and to establish that the patient is in remission of the disease (using PANSS). The study also included an assessment of somatic status to exclude serious diseases that may affect cognitive functions (severe CNS damage, stroke, liver, kidney or heart failure, cancer, significant anemia, endocrine disorder, addiction to psychoactive substances excluding nicotinism). Patients who were diagnosed with these diseases were excluded from the study. The drugs used to treat the patients were olanzapine, clozapine, quetiapine and aripiprazole. Each patient has used at least one of these drugs. There were no statistically significant differences in pharmacological treatment, except for aripiprazole [$X2(2) = 15.574$; $p < 0.001$], 50% ($n = 12$) of patients without MS took this drug, while in the group with MS 23.3% ($n = 7$) and without dietary intervention 3.4% ($n = 1$).

Implements

Metabolic syndrome is associated with the coexistence of various risk factors that can cause cardiovascular disease and type 2 diabetes. There are no commonly accepted criteria for metabolic syndrome, but it is generally acknowledged to include abdominal obesity, glucose intolerance, hypertension and dyslipidemia. In order to determine the presence of metabolic syndrome according to IDF (International Diabetes Federation) criteria from 2005, anthropometric measurements, blood pressure measurement and laboratory tests were used (28). All patients had anthropometric measurements taken, which included measurements of height, body weight, hip circumference, waist circumference. Height was measured using a height gauge with an accuracy of ±0.1 cm with a fully upright posture, without shoes. Body weight was measured using an electronic scale with an accuracy of ±0.1 kg. In all patients the following blood levels were determined: total cholesterol, LDL, HDL, triglycerides and glucose. The obtained results were referenced to baseline values according to the recommendations of PTKK (Polish Society of Cardiology) and PTDL (Polish Society of Laboratory Diagnostics). A prerequisite was the occurrence of abdominal obesity (i.e. waist circumference of >94 cm in men and >80 cm in women), and any two of the following: raised triglycerides (> 150 mg/dl); reduced HDL cholesterol (< 40 mg/dl in men, < 50 mg/dl in women); raised blood pressure (> 130/85 mmHg); raised fasting plasma glucose (> 100 mg/dl) (29).

Four tests were used for assessment of cognitive function:

1. Stroop—used to check the reading speed, verbal operational memory and execution functions related to inhibiting the habitual response and the ability to switch to a new response criterion (30, 31),
2. Trail Making Test (TMT)—enables for the evaluation of visual-spatial operational memory, visual-motor coordination and psychomotor speed. Polish adaptation of the whole Halstead–Reiten battery under the supervision of Danuta Kądzielawa (32, 33),
3. Verbal Fluency—checks categorical verbal fluency (semantic) and phonemic fluency (literal) (34),
4. Digit Span Backwards—tests memory storage capabilities and numerical skills associated with the functioning of operational verbal memory (35).

After obtaining the above information, patients from the group with schizophrenia and MS were randomly assigned to the group with dietary intervention (MSwithDI) or without dietary intervention (MSw/oDI). The exact characteristics of the sample in terms of sociodemographic features and PANSS scale results, including the division of patients with MS into experimental and control groups, are presented in **Table 1**. The groups differed slightly in the distribution of the place of residence—among all participants of the study most individuals were from very large cities, but in the MSwithDI subgroup the advantage was slightly greater. ($p < 0.05$).

When planning dietary intervention, the Standards of Dietary Therapy of Simple Obesity in adults were used according to the recommendations of the Polish Dietetic Association issued in 2015 (36). The patient was given a 7-day menu. Two versions of dietary plans were prepared. In women, the calorific value of the proposed diet ranged from 1,500 to 1,700 kcal, while in men 2,000 to 2,200 kcal was estimated, with permitted minor deviations of 100 to 200 kcal, due to the fact that each time individual needs and preferences of the patient were considered concerning products that would be acceptable to them in the proposed dietary plan and minor modifications to the diet were made in accordance with them. This was done in order to make it easier for the patient to follow the proposed changes in their eating habits. In the proposed dietary plan, appropriate proportions of macro-elements were also established in relation to total dietary energy—protein 10–25%, carbohydrates 45–65%, fat 20–35% (37). The main assumptions of the prepared diet were as follows:

- reduction of the calorific value of the meal plan in relation to the total demand,
- complete elimination of sweets,
- the introduction of the desired culinary techniques,
- diversification of the existing diet,
- consumption of fruit and vegetables,
- introduction of products rich in desirable fatty acids, e.g. fish, avocados, etc,
- regularity of food consumption.

The prepared menus were based on the principles of the Mediterranean diet (38). The nutrition plan for patients was prepared with the use of the ALIANT computer program—a dietary calculator. Each day of the proposed diet included five meals per day, which were eaten at specific times after being agreed with the participant. The meal plan was used by patients for 3–4 months after receiving it, followed by a control visit, during which cognitive function was checked again by means of the above mentioned cognitive tests. After the same period, the cognitive performance of patients without dietary intervention was also checked, both without and with MS. Dietary compliance was monitored on the basis of statements made by the patients

TABLE 1 | Sociodemographic characteristics of groups studied, N(%) or M(SD).

Variables	Entire group, N = 83	MSwithDI, n = 30	MSw/oDI, n = 29	SH, n = 24	X^2/F	df	P
Age	41.06 (12.82)	44.33 (12.38)	41.66 (13.32)	36.25 (11.76)	2,846	2	0.066
Sex							
Female	53 (63.9%)	20 (66.7%)	16 (55.2%)	17 (70.8%)	1,556	2	0.459
Male	30 (36.1%)	10 (33.3%)	13 (44.8%)	7 (29.2%)			
Education					4,566	6	0.601
Primary	6 (7.2%)	1 (3.3%)	2 (6.9%)	3 (12.5%)			
Vocational	17 (20.5%)	6 (20.0%)	8 (27.6%)	3 (12.5%)			
Secondary	37 (44.6%)	13 (43.3%)	11 (37.9%)	13 (54.2%)			
Higher	23 (27.7%)	10 (33.3%)	8 (27.6%)	5 (20.8%)			
Place of residence							
Village	13 (15.7%)	4 (13.3%)	5 (17.2%)	4 (16.7%)	15,707	8	0.047
Town	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)			
City	7 (8.4%)	2 (6.7%)	1 (3.4%)	4 (16.7%)			
Large city	5 (6.0%)	0 (0.0%)	5 (17.2%)	0 (0.0%)			
Very large city	57 (68.7%)	24 (80.0%)	18 (62.1%)	15 (62.5%)			
Job market status							
Student	21 (25.3%)	7 (23.3%)	10 (34.5%)	4 (16.7%)	8,143	6	0.228
Employed	4 (4.8%)	0 (0.0%)	1 (3.4%)	3 (12,5%)			
Unemployed	12 (14.5%)	3 (10.0%)	5 (17.2%)	4 (16.7%)			
Retired/Pensioner	4 (55.4%)	20 (66.7%)	13 (44.8%)	13 (54.2%)			
Marital status							
Single	39 (47.0%)	11 (36.7%)	14 (48.3%)	14 (58.3%)	4,137	6	0.658
In a relationship	32 (38.6%)	13 (43.4%)	11 (37.9%)	8 (33.3%)			
Divorced	7 (8.4%)	3 (10.0%)	2 (6.9%)	2 (8.3%)			
Widow/Widower	5 (6.0%)	3 (10.0%)	2 (6.9%)	0 (0.0%)			
PANSS							
Positive	8.24 (1.83)	8.23 (1.41)	8.69 (2.49)	7.71 (1.12)	1,942	2	0.150
Negative	11.69 (4.04)	11.53 (3.95)	12.62 (4.39)	10.75 (3.59)	1,461	2	0.238
General	20.88 (4.75)	20.73 (4.09)	21.97 (5.28)	19.75 (4.74)	1,470	2	0.236

Source: own research.

themselves and objective interviews with their relatives, in the meantime, changes in anthropometric measurements were checked. Patients from both groups were also evaluated psychiatrically to assess whether the remission of schizophrenia persisted and whether their somatic status deteriorated. There was no change in treatment in patients throughout the study.

Statistics

Quantitative data analysis was performed with the use of a statistical software IBM SPSS Statistics v.25. Shapiro–Wilk test was used to assess the compliance of quantitative characteristics distribution with the normal distribution and Pearson's Chi-square test to assess differences in distributions of qualitative variables. The first of the research hypotheses was checked with two methods—to assess intergroup differences in quantitative test results, the analysis of variance using the ANOVA one-way method was used, with an additional correction by Brown–Forsyth, due to partial deviations from the normal distribution, for comparison. After the assessment of the homogeneity of variances using Levene's test, Tukey's HSD was used as a post-hoc test, provided that the variance was homogeneous and Dunnet's T3 when there was no homogeneity. To determine the differences in the number of errors made in the tests, the non-parametric equivalent of ANOVA, i.e. the Kruskal–Wallis Test, was used. The second hypothesis was verified with the Student's t test for two dependent groups, when the differences between the first and second measurement in quantitative results of cognitive tests were checked, as well as the non-parametric Wilcoxon test to assess the differences in the number of errors made. The significance index was calculated as $p < 0.05$ and $p < 0.1$ as an indicator of not fully significant statistical tendency.

RESULTS

All three groups (patients with schizophrenia without metabolic syndrome (SH), patients with schizophrenia and metabolic syndrome without dietary intervention (MSw/oDI), patients with schizophrenia and metabolic syndrome undergoing dietary intervention (MSwithDI) did not differ in the initial results of the cognitive function study ($p > 0.05$). **Table 2** contains information about the minimum, maximum and mean results obtained by patients and the significance of deviations of data distribution from normal distribution (marked with "*" symbols). Since the differences in the number of three compared subgroups were not statistically significant [$X2(2) = 0.707$; $p = 0.688$], a parametric method of variance analysis was used to assess the differences in the intensity of quantitative results.

In all cases the results of post-hoc tests were statistically insignificant ($p > 0.1$), no differences between the individual subgroups were shown using either Tukey's HSD test or Dunnet's T3 test (some of the compared groups showed heterogeneous variance of the selected measurements; in Levene's test $p < 0.05$).

In the Stroop Test and Trail Making Test, apart from the time and number of correct answers, the number of mistakes made by patients was also checked. Due to the small number of errors in all groups, these variables were more ordinal than quantitative in the sample and were therefore checked using the non-parametric Kruskal–Wallis test. Similarly, as in the case of time and efficiency of tasks, no significant differences in errors made were observed between patients from the three groups ($p > 0.05$).

The groups differed in average values of such MS components as waist circumference, body weight, BMI, HDL and TG ($p < 0.001$) and systolic pressure ($p < 0.01$), there were no differences in glucose and diastolic pressure. Post-hoc tests showed that these differences occurred only between MSwithDI and MSw/oDI groups and SH, almost in every case with $p < 0.01$ significance, the exception was systolic pressure, where in Tukey's HSD test with homogeneous variants the difference between SH and MSwithDI group was greater ($p = 0.003$) than between SH and MSw/oDI ($p = 0.043$).

Table 3 presents the results of comparing the effects of cognitive performance measurement in patients undergoing dietary intervention. Only in this subgroup the improvement of cognitive performance was observed. After a change in dietary behavior in patients with schizophrenia with concomitant metabolic syndrome, an improvement in Stroop Test time was observed in the 3rd attempt (3.38 s, $p < 0.05$) and a decrease in Point Merging Test time in the 2nd attempt (16.78 s, $p < 0.01$). Moreover, in the second measurement patients from this group showed higher verbal fluency, on average 2.10 more animal names ($p < 0.01$) and 1.07 more acute subjects ($p < 0.01$). The working memory was also improved, resulting in a greater number of digits repeated directly (on average by 0.8 words more; $p = 0.001$) and in total (on average by slightly more than one digit more; $p < 0.05$).

In comparison, after 3 months in the group with MS without dietary intervention the level of performance of every cognitive test remained at the same level (**Table 4**).

Furthermore, some differences were observed between measurements I and II of cognitive functions in SH group (patients with schizophrenia without MS). In the second measurement these patients achieved significantly worse results in the first attempt of the Point Merging Test—on average by 3.69 s ($p < 0.05$) they also mentioned 1.42 fewer animal names ($p < 0.05$) and 0.83 fewer acute objects ($p < 0.1$). There was also a weak tendency to extend the time of performing the Stroop Test in the 1st sample by 1.04 s on average. Detailed information about the results of cognitive function measurement in the initial measurement and after 3 months in patients without MS is presented in **Table 5**.

Changes between the first and second measurement were observed not only in the speed and effectiveness of the solved tasks, but also in the number of errors made in them. In the group of patients with dietary intervention in the second measurement the number of mistakes made in the Stroop Test

TABLE 2 | Results of cognitive function and results allowing for diagnosis of metabolic syndrome measurement before dietary intervention; min–max; M (SD).

Tools	Task	MSwithDI, n = 30	MSw/oDI, n = 29	SH, n = 24	One-way ANOVA		
					F	df	p
Stroop Test	**Trial 1—time [s]**	15.45–35.50; 22.46 (5.55)**	15.81–71.52; 24.80 (10.50)***	17.81–35.79; 22.84 (4.73)***	0.844	2	0.436
	Trial 2—time [s]	19.67–39.51; 28.64 (5.01)	17.20–86.83; 32.72 (13.70)***	21.62–59.31; 32.09 (9.22)***	1.416	2	0.251
	Trial 3—time [s]	34.61–67.24; 52. 36 (8.44)	28.77–137.42; 57.53 (19.84)***	36.69–103.71; 60.16 (18.63)**	1.578	2	0.215
Trail Making Test	**Test A [s]**	20.52–112.88; 47.47 (21.64)***	23.57–121.26; 46.52 (21.90)***	23.04–97.84; 45.89 (19.20)**	0.039	2	0.962
	Test B [s]	39.32–272.25; 108.67 (50.90)*	39.98–207.43; 94.60 (44.13)**	52.93–154.26; 97.11 (27.84)	0.947	2	0.393
Verbal Fluency Test	**Animals**	5.00–23.00; 15.00 (4.23)	3.00–27.00; 14.66 (5.49)	5.00–21.00; 14.67 (4.03)	0.052	2	0.949
	Objects starting with letter "K"	3.00–13.00; 8.07 (2.95)	0.00–17.00; 7.52 (4.21)	3.00–15.00; 7.42 (3.22)	0.283	2	0.755
	Sharp objects	1.00–4.00; 6.33 (3.12)*	1.00–13.00; 6.35 (2.47)	3.00–13.00; 6.92 (2.67)	0.373	2	0.690
Digit Span Test	**Forward**	3.00–8.00; 5.70 (1.21)*	3.00–13.00; 6.21 (2.14)**	4.00–9.00; 5.54 (1.53)***	1.184	2	0.312
	Backward	2.00–8.00; 4.40 (1.67)**	2.00–9.00; 4.45 (1.66)**	2.00–8.00; 4.42 (1.56)	0.007	2	0.993
	All	6.00–15.00; 10.10 (2.41)	6.00–22.00; 10.57 (3.24)***	4.00–17.00; 9.79 (2.93)	0.517	2	0.599
MS components	**Waist circumference**	94.00–148.00 113.77 (14.97)	93.00–160.00 110.63 (13.90)**	72.00–121.00 94.15 (12.40)	16.379	2	<0,001
	Body mass	73.00–147.70 101,24 (19,65)	67.00–129.00 93.00 (16.37)	44.00–112.00 76.98 (15.59)	14.377	2	<0,001
	BMI	27.14–48.88 35.09 (5.55)*	24.81–44.12 32.09 (4.86)*	19.56–39.68 27.74 (4.71)	15.160	2	<0,001
	Glucose	80.00–399.00 117.22 (62.33)***	61.50–231.00 109.09 (38.29)***	74.10–231.20 97.59 (29.88)***	1.336	2	0,270
	HDL	23.20–81.50 44.76 (14.63)*	21.70–69.44 39.66 (12.74)	35.00–74.80 56.77 (10.29)	13.612	2	<0,001
	TG	71.70–455.00 209.42 (86.75)**	68.30–653,40 246,09 (133.87)*	44.00–157.00 90.83 (29.69)	21.370	2	<0,001
	Systolic blood pressure	110.00–160.00 126.00 (12.25)***	110.00–140.00 123.33 (6.61)***	60.00–140.00 116.56 (14.06)***	5.883	2	0,005
	Diastolic blood pressure	50.00–100.00 74.17 (12.25)	60.00–90.00 76.17 (7.39)**	60.00–110.00 77.59 (9.24)***	0.879	2	0,420

*Source: own research; *p <0.05; **p <0.01; ***p <0.001.*

TABLE 3 | Comparison of results of cognitive function measurement before and after dietary intervention (MSwithDI group).

Tools	Task	Difference in mean values	Standard error in mean difference (SE)	95% confidence interval for mean difference (CI)		Student's t-test		
				Bottom limit	Upper limit	t	df	P
Stroop Test	**Trial 1—time [s]**	–0.01	0.72	–1.49	1.47	–0.010	29	0.992
	Trial 2—time [s]	0.70	1.02	–1.40	2.79	0.679	29	0.502
	Trial 3—time [s]	3.38	1.60	.11	6.66	2.113	29	0.043
Trail Making Test	**Test A [s]**	0.14	2.81	–5.62	5.90	0.049	29	0.961
	Test B [s]	16.78	5.46	5.61	27.94	3.072	29	0.005
Verbal Fluency Test	**Animals**	–2.10	0.70	–3.53	–.67	–2.999	29	0.006
	Objects starting with letter "K"	–0.47	0.44	–1.36	.43	–1.064	29	0.296
	Sharp objects	–1.07	0.38	–1.85	–.28	–2.782	29	0.009
Digit Span	**Forward**	–0.80	0.21	–1.23	–.37	–3.788	29	0.001
	Backward	–0.23	0.29	–0.83	0.36	–0.804	29	0.428
	All	–1.03	0.42	–1.90	–0.17	–2.448	29	0.021

Source: own research.

TABLE 4 | Comparison of cognitive function measurement results 3 months after the first measurement in patients with schizophrenia and co-occurring metabolic syndrome.

Tools	Task	Difference in mean values	Standard error in mean difference (SE)	95% confidence interval for mean difference (CI)		Student's t-test		
				Bottom limit	Upper limit	t	df	P
Stroop Test	**Trial 1—time [s]**	1.51	0.90	–0.34	3.37	1.675	28	0.105
	Trial 2—time [s]	1.31	0.86	–0.46	3.07	1.517	28	0.141
	Trial 3—time [s]	–.022	1.94	–4.20	3.75	–0.115	28	0.909
Trail Making Test	**Test A [s]**	–0.20	1.68	–3.63	3.24	–0.117	28	0.908
	Test B [s]	4.75	5.21	–5.93	15.42	0,911	28	0.370
Verbal Fluency Test	**Animals**	0.45	0.61	–0.79	1.69	0.741	28	0.465
	Objects starting with letter "K"	–0.24	0.50	–1.27	0.79	–0.480	28	0.635
	Sharp objects	–0.14	0.47	–1.11	0.83	–0.292	28	0.773
Digit Span	**Forward**	0.11	0.23	–0.37	0.57	0.451	28	0.655
	Backward	–0.35	0.21	–0.78	0.09	–1.625	28	0.115
	All	–0.31	0.33	–0.98	0.36	–0.952	28	0.349

Source: own research.

in the second sample (Z = −2.504; p = 0.012) and third sample (Z = −3.393; p = 0.001) decreased, although an increase in the correctness of task execution in the last sample was also observed in patients without MS (Z = −2.173; p = 0.030). In this group, the number of errors made during the Trail Making Test in the first attempt (Z = −2,000; p = 0.046) also improved, furthermore in this test, the number of errors made by the control group of patients with MS was also lower, and the improvement was made in the second attempt (Z = −2.328; p = 0.020). It cannot be excluded that some intergroup differences between the two measurements may be due to the learning effect.

Both groups of patients with MS did not differ significantly in the distribution of basic sociodemographic features such as gender, age and level of education, but it was checked whether the relationships between these variables and cognitive performance were similar in all groups. In the initial measurement, very similar relationships between these characteristics were observed both in patients with MS for whom a dietary intervention was planned and in the comparative group. It was shown, for example, that with age the number of errors in the Stroop Test increased in both groups (in task 2 rho = 0.363; p = 0.049 in MSwithDI, and a stronger correlation was observed in the MSw/oDI group: rho = 0.687; p < 0.001, in task 3 rho = 367; p = 0.046 and rho = 0.350; p = 0.058). The time of task execution also increased (e.g. in task three in MSwithDI group rho = 0.446; p = 0.013 and in MSw/oDI group rho = 0.491; p = 0.006). In the MSwithDI group a significant increase of Test B score with age was noted (rho = 0.532; p = 0.002), whereas in the MSw/oDI group this relation remained at the level of weak tendency (rho = 0.313; p = 0.092). In both groups the number of digits repeated backwards decreased with increasing age, although in the MSwithDI group the number of digits was higher (rho = −0.439; p = 0.006) than in MSw/oDI (rho = −0.338; p = 0.068). In both groups, however, there were no relationships between age and verbal fluence.

The level of education was almost equally significant in the number of mistakes made in the Stroop Test in the last task (rho = 0.446; p = 0.013 in the MSwithDI group and rho = 0.491; p = 0.006 in the group without intervention), and qualitatively a slightly different meaning for the time of the second task—although in the MSwithDI group fully significant (rho = −0.489; p = 0.006) and in the MSw/oDI group at the level of statistical tendency (rho = −0.352; p = 0.056). Similarly, a decrease in the performance quality of the Trail Making Test was observed, with a significant decrease in the MSwithDI group (rho = −0.558; p = 0.002) and a trend in the MSw/oDI group (rho = −0.343; p = 0.064), while in Test A only among patients undergoing dietary intervention (rho = −0.511; p = 0.004). In both groups verbal fluence in the "Objects starting with K" sample increased moderately as education increased (successively rho = 0.438; p = 0.015 in MSwithDI I rho = 0.518; p = 0.003 in MSw/oDI), although only in the non-interventional group weak correlation was also observed in the "animals" sample. In case of digit repetition, among patients from the MSwithDI group the number of digits increased slightly (but not statistically significant) with the increase in education (rho = 0.353; p = 0.056) and in MSw/oDI the number of words spoken backwards significantly increased (rho = 0.525; p = 0.003).

In the case of gender differences in the first measurement, occasional differences of minor importance were noticed. It turns out that only among patients from the MSw/oDI group in the measurement of verbal fluence in the "Animals" sample, men reached slightly more (but statistically insignificant) points than women (Z = −0.1856; p=0.063), moreover, in the digit repetition test in both groups men were able to repeat more digits backwards, while in the MSwithDI group this gender difference was fully significant (Z = −2.004; p = 0.045) and in MSw/oDI it was weaker—at tendency level (Z = −1.783; p = 0.075).

Analyzing the importance of sociodemographic variables in the view of results obtained in the second measurement—after a dietary intervention or after a 3-month interval—very similar results were obtained. This additional analysis suggests that just as the compared groups of patients with MS did not

TABLE 5 | Comparison of results of cognitive function measurement 3 months after the first measurement in patients with schizophrenia without metabolic syndrome.

Tools	Task	Difference in mean values	Standard error in mean difference (SE)	95% confidence interval for mean difference (CI)		Student's t-test		
				Bottom limit	Upper limit	t	df	p
Stroop Test	**Trial 1—time [s]**	–1.04	2.92	0.60	–2.27	–1.745	23	0.094
	Trial 2—time [s]	1.06	7.50	1.53	–2.11	0.693	23	0.495
	Trial 3—time [s]	–0.92	10.44	2.13	–5.33	–0.433	23	0.669
Trail Making Test	**Test A [s]**	3.69	8.38	1.71	0.16	2.159	23	0.041
	Test B [s]	–0.73	16.97	3.46	–7.90	–0.210	23	0.835
Verbal Fluency Test	**Animals**	1.42	2.84	0.58	0.22	2.442	23	0.023
	Objects starting with letter "K"	0.17	2.10	0.43	–0.72	0.389	23	0.701
	Sharp objects	0.83	2.06	0.42	–0.04	1.985	23	0.059
Digit Span	**Forward**	–0.25	1.11	0.23	–0.72	–1.100	23	0.283
	Backward	0.21	1.10	0.23	–0.26	0.926	23	0.364
	All	–0.21	1.84	0.38	–0.99	–0.554	23	0.585

Source: own research.

differ significantly in the overall distribution of the most important sociodemographic characteristics, the importance of these characteristics in shaping cognitive performance in both measurements was very similar. It can therefore be concluded that additional sociodemographic factors did not play a significant role in the picture of the phenomenon under study.

DISCUSSION

There are studies showing that metabolic syndrome, and especially obesity, is associated with the emergence of cognitive disorders in people with mental illness. Individuals with obesity as a major constituent of MS may show deficits in executive functions (worse decision making, problems with planning, inhibition of reaction, reduced elasticity in action) and decreased memory function, speed of reaction, language skills or concept development (39–41). However, this study did not demonstrate that the metabolic syndrome itself is a cause of cognitive decline, as there were no statistically significant differences in cognitive function between patient groups before the introduction of dietary intervention. Similar results were obtained in the CATIE study, where no links between the metabolic syndrome and cognitive disorders in schizophrenia were found (42). Also other research teams did not show any relationship between BMI and cognitive functions (43, 44). Perhaps the reason for the above discrepancies in the relationship between metabolic syndrome and cognitive disorders is the fact that the individual components of the syndrome may rather be related to specific disorders of these functions. A different cause may be found in varying degrees of education, age of patients, or duration of disease in different studies quoted above. For example, it is known that the early onset of schizophrenia may be associated with worse cognitive function (45). The gender of the respondents may also influence the results, as the studies show that women are more likely to suffer from negative consequences of metabolic disorders (46), including cognitive dysfunctions resulting from obesity (47).

The observed improvement in cognitive function tests after dietary intervention seems to be a very interesting result in the context of a holistic approach to the treatment of schizophrenia. We have long known that the management of this disease cannot be limited to pharmacological treatment only. Patients should be encouraged to try to change their lifestyle. The literature on the subject shows that the lifestyle of people with schizophrenia is one of the most important factors which determine the emergence of coexisting chronic diseases. Researchers observed significantly more frequent smoking, alcohol consumption and excessive amounts of food, while at the same time lower physical activity in patients with coexisting somatic diseases. Increased energy supply is the main dietary risk factor of developing coexisting diseases (48). The CHANGE study showed that people with schizophrenia spectrum had higher intakes of saturated fats, sugar and alcohol. However, the amount of fish, vegetables and fruit consumed was insufficient. From the studied group (n = 428) only 10.7% of people used healthy eating patterns (49, 50). Dietary mistakes made by patients with schizophrenia may result from their lack of knowledge and inability to obtain any support in changing eating habits. In this study, the majority of patients who received a nutrition plan tried to follow it. These patients willingly decided to reduce their body weight and improve their eating habits. It is very important to provide education on the influence of the drugs used, on metabolism. It should be pointed out how to avoid side effects in the form of weight gain after the applied pharmacological treatment. The patient should know that the healing process is not only a systematic intake of medication, but also a change in lifestyle.

Clinical studies also show that brain-derived neurotrophic factor (BDNF) is one of the biomarkers associated with cognitive function. There is a significant relationship between MS and decreased BDNF level, which affects the plasticity of synapses. A low-energy diet may contribute to an increase in BDNF (51, 52). The introduction of a diet with calorie reduction of about 500 kcal and compliance with the diet resulted in the reduction of the components of MS, which may have contributed to the reduction of systemic inflammation and increase in the level of BDNF factor, which in turn could have a positive effect on cognitive deficits in schizophrenic patients. The final decision whether this was the mechanism of cognitive

improvement will be the result of a study with the measurement of the level of BDNF during dietary intervention.

One of the elements used in the dietary plan was an increase in essential polyunsaturated fatty acids (PUFA). Many scientific studies point to the connection between the consumption of OMEGA-3 fatty acids and the treatment of mental disorders (53–56). More and more evidence suggests the occurrence of oxidative stress in schizophrenia, as the body is unable to balance the production of reactive oxygen species (ROS) and reactive nitrogen (RNS) produced from oxidative metabolism. Oxidative stress and impaired defense mechanisms may be associated with neurodevelopmental disorders, changes in brain structures, intensified negative symptoms or cognitive impairment (57). The supplementation of essential polyunsaturated fatty acids (PUFA) and alpha-tocopherol reduces the total glutathione concentration, whereas the administration of saturated fatty acids results in a significant decrease in gamma- and delta-tocopherol (58). MS is associated with chronic inflammation, and the supply of large amounts of saturated fatty acids from the diet contributes to an increase in the level of inflammation markers (59, 60). Lipid profile disturbances and obesity increase the risk of arterial atherosclerosis. Atherosclerosis may contribute to the occurrence of cognitive deficits. A significant disturbance of metabolic parameters may cause micro and macroscopic cerebrovascular changes, which may hinder the nervous system function and cause cognitive disorders in memory, executive functions or attention (61). There are also data on the effect of excessive fatty tissue on nervous tissue through neurochemical mediators, e.g. leptin (62). In this study, in patients with schizophrenia without metabolic syndrome, cognitive function deteriorated 3 months after the first visit, which may result from lack of nutritional awareness and persistence in their previous unhealthy eating habits, which negatively affected cognitive functions, causing their gradual deterioration. It is important to emphasize the importance of awareness of patients participating in the study, who subjectively assessed their eating habits as inadequate. At least some people with schizophrenia are aware that they lead an unhealthy lifestyle (63). Therefore, when working with patients, both psycho-education regarding proper nutrition and work on motivation to change their lifestyle should be undertaken. A small group of patients is a limitation of the study, but further work with a larger cohort is planned.

The lack of statistically significant differences between the MSwithDI and MSw/oDI groups speaks in favor of methodological correctness and the possibility to regard the group without intervention as a control for experimental measurement. On the other hand, the lack of differences between the two groups of patients with MS and the subgroup of patients with schizophrenia alone, suggests that the occurrence of metabolic syndrome does not have to be associated with a deterioration of cognitive performance in patients with schizophrenia.

The obtained results did not confirm the thesis that cognitive function in patients with schizophrenia and co-morbid metabolic syndrome is worse than in patients without metabolic syndrome. However, it was possible to demonstrate the importance of dietary intervention in the pursuit of cognitive function improvement. Understanding the relationship between diet and cognitive ability in schizophrenia may contribute to the development of therapeutic strategies that will not only avoid the development of MS, but also improve the level of functioning of people with schizophrenia. Change of eating habits may be a significant element of a holistic approach to the problems of treatment of schizophrenia.

LIMITATIONS

The project had a number of limitations that may have had the potential to obstruct the research procedure and the final results. The study was of a correlative nature, which did not allow to determine the cause–effect relationships, so it was not known what was the primary and secondary variable. Discussing eating habits and evaluating them subjectively may have sometimes been accompanied by a desire to present oneself in a favorable light. Attempts have been made to ensure that the person assessing cognitive function was not informed about the patients' affiliation to a given group, but it was not always possible to achieve this because of the differences in body weight between groups.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bioethics Committee of the Pomeranian Medical University in Szczecin (Resolution No. KB-0012/108/14). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KA: project design, data collection, database preparation, preparation of patients' nutritional plans, statistical calculations. AM: text editing, translation into a foreign language. MM: the choice of statistical tools. JS: verification of the content and approval of the final version of the manuscript. JK-M: project concept, project design, choice of statistical tools, critical content verification, choice of journal.

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Monetary Incentives Increase Metacognitive Confidence in Source Memory Performance in Patients With Schizophrenia

Remigiusz Szczepanowski[1]*, *Ewelina Cichoń*[2,3], *Aleksandra Helena Pasieczna*[4], *Łukasz Gawęda*[5] and *Joanna Rosińczuk*[6]

[1] Department of Public Health, Faculty of Health Sciences, Wroclaw Medical University, Wrocław, Poland, [2] Department of Psychology, WSB University in Torun, Torun, Poland, [3] Department of Psychology, Faculty of Education, University of Lower Silesia, Wrocław, Poland, [4] Department of Finance and Accounting, Kozminski University, Wrocław, Poland, [5] Institute of Psychology, Polish Academy of Sciences, Warsaw, Poland, [6] Department of Clinical Nursing, Faculty of Health Sciences, Wroclaw Medical University, Wrocław, Poland

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***Correspondence:**
Remigiusz Szczepanowski
remigiusz.szczepanowski@umed.wroc.pl

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Background: Contemporary psychiatric research focuses its attention on the patient's dysfunction of metacognition in relation to the basic cognitive processes of mental activity. The current study investigated dysfunctional metacognition in relation to self-monitoring of memory in patients diagnosed with schizophrenia. Dysfunctions in metacognition were examined by focusing on two types of metacognitive measures: post-decision wagering (PDW) scale and confidence ratings (CR) scale (CR).

Objectives: The research employed an action-memory task that required patients with schizophrenia (N = 39) and healthy controls (N = 50) to evaluate their metacognition by categorizing self-monitoring actions (imagined vs. performed actions) either with PDW or CR. It was hypothesized that metacognition in self-monitoring activity in patients diagnosed with schizophrenia is improved by imaginary monetary incentives.

Material and Methods: To test this hypothesis, participants were asked to memorize actions either performed or imagined during the first phase of the experiment. The second phase was to identify previous actions as performed, imagined or new, and then to express confidence using two measures of metacognition (CR or PDW scales) that were randomly allocated to participants.

Results: Our study showed reduced performance in the action memory task for patients with schizophrenia, although there were no group differences in confidence measures when assessing self-monitoring actions. In particular, irrespective of the diagnosis, no differences in confidence measures for correct responses were found in the case of the PDW and CR scales. We also observed that metacognitive judgements were more accurate for incorrect responses when both groups used monetary incentives to reveal their metacognition.

Conclusions: Our findings suggest that monetary incentives improve accuracy of metacognition among both patients and healthy controls. This accuracy-enhancing

effect of monetary incentives on metacognition was possibly a result of motivational processes, including aversion to loss. The paper discusses the potential application of PDW in therapeutic metacognitive training for patients with schizophrenia.

Keywords: metacognition, memory, schizophrenia, delusions, source memory task

INTRODUCTION

Recent clinical research has adopted a metacognitive approach to treating schizophrenia spectrum disorders (1, 2). The notion of "metacognition" *per se* describes cognitive processes that are linked with activation of "thinking about one's own thinking", by which individuals can reflect upon (monitor) their own internal mental states and apply their knowledge to evaluate and regulate (control) their own mental states (3). This theoretical approach claims that abnormality of higher-order processes and knowledge is responsible for dysfunctional regulation of the primary cognitive processes (i.e., memory and other cognitive functions) (3) and may lead to severe mental disorders. For the sake of brevity, abnormality of metacognition relates to impairments in control and monitoring and higher-order knowledge structures (e.g., beliefs) that together regulate storage and acquisition of information from different modalities. Given this theoretical view, clinicians may identify cognitive causes that lead to the formation and persistence of psychopathological symptoms in a variety of mental disorders, including psychotic disorders, schizophrenia, or anxiety disorders (1–6).

In fact, the dysfunctional operations that underlie metacognition are cognitive biases and include disturbances in accuracy of metacognition, impaired sense of confidence in responses, or dysfunctional cognitive strategies in regulating one's own behavior (4). A thorough description of abnormal metacognitive processes and knowledge structures is presented by Moritz and Woodward (7) [see also (4, 8)]. For example, in the case of the schizophrenia population, cognitive biases such as overconfidence are considered the basic driving mechanisms that perpetuate false judgments (2). In addition, several studies have also shown that inadequate confidence related to one's own experiences may preclude regulative mistrust in faulty decisions. In turn, this may lead to extreme beliefs and distortions in perceiving reality (e.g., in psychosis) (9) and prevent alternative explanations due to the holding of false information with strong conviction (knowledge corruption) (10). Several studies have shown that patients with schizophrenia are not only overconfident in false memories, but they are also underconfident in correct responses (10–13).

It is worth mentioning that the available theoretical concepts have advanced and refined the view on the abnormality of metacognition and the basic cognitive processes in schizophrenia. For instance, jumping to conclusions bias (JTC) or liberal acceptance bias may be useful in explaining this response pattern. Moritz and Woodward (14) suggested that patients with schizophrenia make memory decisions confidently and rapidly by relying more on the mere familiarity of information. This tendency promotes highly confident errors in patients and also, to some extent, less confidence in correct responses. On the other hand, healthy individuals apply more rigorous strategies based on the reluctance to fully accept answers based on partial evidence (7). Therefore, healthy control participants require rich cue information to ensure high confidence in their responses. This account suggests that if patients with schizophrenia adopted more vigilant strategies based on the detection of more cues (7), their confidence in errors might be reduced, and their confidence in correct responses might be enhanced.

From the experimental perspective, there are several measures of metacognition in which participants assess the accuracy of their first-order discriminations. Typically, confidence (CR) represents metacognitive judgments that describe a participant's confidence in how certain they are about processing a given stimulus or how accurate their own responses were in a given task (15). On the other hand, in a post-decision wagering (PDW) task, participants use economic categorization to reveal their metaknowledge about first-order cognitions (16). In particular, they are asked to discriminate an item (e.g., a memorized or seen object) and then wager first-order discrimination decisions. Importantly, participants are told that correct wagers are rewarded by imaginary or real earnings, while incorrect wagers are deducted from earnings. In this fashion, they start to believe that they are playing a sort of gambling game that can lead to losses (17). For instance, Clifford, Arabzadeh, and Harris (18, 19) demonstrated that the pay-off matrix of PDW can favor a particular gambling strategy, e.g., participants always tend to bet high. The response criterion of wagering can also be biased strongly by the loss aversion that is induced by monetary incentives (20). In fact, loss aversion may result in a precautionary strategy that often is based on low wager ratings even when participants are aware of the stimuli but are not fully confident in their first-order discriminations (21). Thus, the effect of loss aversion induced by monetary incentives seems to urge caution in the subjective assessment of patients' erroneous memories.

Indeed, our previous empirical study on a healthy population indicated that metacognitive judgments were more accurate when participants used the PDW scale rather than the confidence ratings (CR) scale in an action memory task (22). In this study, we required participants to perform or imagine physical actions and then distinguish performed and imagined memories. Finally, to reveal metacognitive judgments, participants rated their confidence in responses with CR (the numerical scale) or with imaginary monetary wagers (PDW) that engaged a more vigilant strategy based on loss aversion. Our previous research demonstrated that imaginary money resulted in more accurate metacognition because healthy participants who categorized their certainty with imaginary monetary wagers expressed lower confidence in self-monitoring errors (i.e., "misattributed imagined-as-performed" responses) than in responses expressed with the CR scale (22). Thus, monetary

incentives contributed to better metacognition accuracy in the case of misattribution errors (i.e., misattributed imagined-as-performed actions; misattributed performed-as-imagined actions). These findings, in turn, may suggest that metacognition driven by economical categorization may reduce overconfidence in faulty decisions and beliefs in patients with schizophrenia.

It is important to mention that basic cognitive activity such as source-monitoring (e.g., the ability to distinguish the origins of information, e.g., perceived and imagined memories presented in an action memory task) may be fundamental in establishing adequate cognitive functioning in the real world that leads to adaptive behavior and effective decision-making (23). In fact, an individual's capacity to discriminate the sources of mental experience serves as a theoretical background to explain reality distortions in a variety of mental disorders, such as hallucinations (9, 24, 25) or self-disturbances (24, 25). For instance, Gawęda and colleagues (9, 26) employed an analogical action memory paradigm to investigate self-monitoring processes in patients with schizophrenia. It was shown that patients diagnosed with schizophrenia committed more errors in the action memory task than healthy participants. Moreover, since the experimenters measured patients' metacognition with the CR scale, they observed that patients expressed overconfidence when they committed self-monitoring errors (9). Thus, the overconfidence related to self-monitoring errors observed in this study suggests that abnormality of metacognition may be involved in impairments in cognitive functioning in schizophrenia (9–14, 27).

Taken together, the above outcomes and premises raise an important question for psychiatry research as to whether metacognition based on monetary incentives (i.e., wagering with imaginary money) improves the accuracy of metacognition in individuals diagnosed with schizophrenia who perform self-monitoring of their own memory. To examine this claim, patients and healthy controls undertook rating tasks with two metacognition assessments (CRs vs. PDW) to evaluate performance in self-monitoring actions induced by an action memory paradigm. This experimental condition represents a typical metamemory paradigm that is intended to investigate subjective memory functioning and confidence (10, 26, 28). In fact, as opposed to healthy controls and non-schizophrenia psychiatric controls, several metamemory studies provide substantial evidence for the "*overconfidence effect*" because patients suffering from schizophrenia display robust overconfidence in memory errors and moderate effects of underconfidence in correct responses (26, 29, 30). Moreover, in order to investigate the relationships between confidence and psychosis in clinical populations, most of these memory studies use a conventional confidence rating scale that asks patients to reveal their confidence in their metamemory on this scale (9, 29, 31, 32). Yet, to the best of our knowledge no empirical study has used the PDW scale to investigate accuracy of metacognition in patients with schizophrenia. Determining whether patients with schizophrenia are accurately aware of their memory performance when stimulated with monetary incentives might be a real implication for psychological interventions. In the non-clinical population, judgments based on PDW when evaluating source monitoring performance were found to be more accurate than those based on the CR scale (22). In the present study, it was therefore expected that patients with schizophrenia would evaluate their subjective memory functioning with PDW more objectively, thus diminishing the presence of the "overconfidence effect".

MATERIAL AND METHODS

Participants

Eighty-nine individuals (50 healthy and 39 diagnosed as patients with schizophrenia; 10 inpatients, 29 outpatients) participated in this study. Patients fulfilled ICD-10 criteria for schizophrenia, as determined by an experienced psychiatrist at "Zielone Wzgórza" Social Welfare Home in Rościszów, Maria Med Center for Psychiatry and Psychology in Lubin, "Sudeckie Centrum Zdrowia" Non-public Healthcare Centre in Pieszyce, and Lower Silesian Mental Health Centre in Wrocław. Additionally, before testing, the psychiatrist's clinical diagnoses were confirmed by The Mini-International Neuropsychiatric Interview (33), which follows DSM-IV criteria. Exclusion criteria were alcohol and/or drug abuse or any form of documented or suspected neurological diseases. All patients were receiving atypical neuroleptic medication and were stable at the time of testing. **Table 1** presents the equivalents of mean daily antipsychotics doses to chlorpromazine (CPZ) that were calculated for each group of patients based on formulas relevant to defined daily doses (DDDs) presented by the World Health Organization's Collaborative Center for Drug Statistics Methodology (34). At the time of their participation, all of the schizophrenia participants were in treatment. Fifty healthy participants with a declared lack of life-time prevalence of any

TABLE 1 | Demographic characteristics of the group of patients with schizophrenia and healthy control.

Demographics		Healthy N = 50		Patients N = 39		Statistics
		CR	PDW	CR	PDW	
Gender	Males/females	8/17	5/20	10/9	15/5	$\chi2(3) = 15.729$, p = 0.001
		17	20	9	5	**Statistics**
		$\chi2(1) = 0.936$, p = 0.333		$\chi2(1) = 2.12$, p = 0.146		
Age		31.2 (7.94)	26.3 (7.73)	39.0 (16.49)	37.8 (11.40)	F = 16.767, p < 0.001
Years of sickness		–	–	14.0 (11.61)	17.1 (8.97)	$F = 0.739$, $p > 0.3$
In/outpatients[a]		–	–	48.28	50.0	$\chi2 = 0.01$, $p > 0.9$
CPZ equivalent dosage[b] (mg/day)		–	–	846.26 (1478.14)	807.29 (790.27)	$F = 0.01$, $p > 0.9$

[a]*percent of outpatients within sub-group;* [b]*dosage of the medication in chlorpromazine equivalent (34).*

mental disorders served as controls. Healthy controls were recruited from students of Psychology at SWPS University of Social Sciences and Humanities in Wroclaw. The students responded to the announcement about the study *via* the university's internal messaging system. The computer experiment was carried out in the laboratory room. Every participant took part in the study after informed consent was obtained. The study received the approval of the local ethical committees. The experiment was repeated three times. Two experiments were conducted on non-clinical populations (22, 35), and the third study on a clinical population of patients with schizophrenia was a part of an undergraduate research project in the Department of Psychology at the University of Lower Silesia (36).

We split the populations' samples according to the response mode (half of the participants were randomly assigned to the PDW scale and half to the CR scale) and expected group differences in that higher metacognition accuracy would be present for patients using economic-based categorization (PDW scale) as opposed to categorization based only on beliefs about one's own cognitions (CR scale).

Psychopathology Assessment of Schizophrenia

Psychopathology in patients was assessed with a semi-structured interview: Scale for the Assessment of Positive Symptoms (SAPS) (37) and Scale for the Assessment of Negative Symptoms (SANS) (38).

SANS includes 25 items related to negative symptoms. Raters assess each item using a 6-point Likert scale (from 0 to 5). Higher scores indicate higher symptom severity. The scale evaluates five domains: affective blunting, alogia, avolition/apathy, anhedonia/asociality, and attention (38–41). We assessed negative symptoms with the SANS scale by looking at these five subscales (39). The SAPS measures positive symptoms and allowed us to identify hallucinations, delusions, positive formal thought disorders and bizarre behavior (37). This scale consists of 34 items assessed on a 6-point scale (from 0 to 5). Items are categorized into four domains: hallucinations, delusions, bizarre behavior, and positive formal thought disorders (37, 41).

Thus, these two scales provide comprehensive measures of the symptoms of schizophrenia. It is important to note that SAPS and SANS scores were available for only 30 patients because nine patients took part in the action memory task but were then unavailable due to unpredicted discharge from the ward (see **Table 2**). There were no differences in SAPS, $F(1,28) = 0.36$; $p = .851$ and SANS scores $F(1,28) = 2.73$; $p = .109$ between patients with schizophrenia that were randomly assigned to PDW and CR conditions.

Action Memory Task

Participants undertook an action memory task that is commonly employed in studies of self-monitoring deficits in schizophrenia (9) and obsessive-compulsive disorder (42) populations. The procedure of this study consisted of two phases. In the learning phase, participants were asked to imagine or perform presented actions in accordance with verbal instructions displayed on a computer screen. Instructions set in a green frame had to be performed by the participants, whereas action instructions set in a red frame had to be imagined but not performed. Before the experiment, all participants were instructed that they would have to recall the presented actions and distinguish whether they had been imagined or performed by them. The participants performed a short practice trial to become familiar with the task requirements. In the main learning phase, we used 19 items for the participants to perform and 19 items to imagine. Each instruction with information about the action was displayed on the computer screen once for 10 s. In the second phase of this study, 38 verbal instructions of the learning-phase items were presented along with 20 new action instructions. The number of correct responses given by participants ranged from 0 to 58. The maximum number of possible false alarms was 20 (20 new items recognized as performed or imagined actions); the maximum number of possible forgotten actions was 38 (presented actions: imagined or performed recognized as new); the number of monitoring errors ranged from 0 to 38 because this was the sum

TABLE 2 | Psychopathological characteristics of the CR and PDW groups and group differences in SAPS and SANS scores among patients with schizophrenia.

		Schizophrenia (N = 30)*				
		CR (n = 14)		PDW (n = 16)		
SANS		**Mean**	**SD**	**Mean**	**SD**	
	Affective blunting	21.21	9.98	19.37	8.82	
	Alogia	11.50	6.31	12.50	5.97	
	Avolition-Apathy	8.00	5.22	10.31	5.86	
	Anhedonia-Asociality	12.79	7.81	12.56	4.52	
	Attentional Impairment	7.00	4.40	7.50	4.10	
	SANS total score	60.43	28.82	62.25	23.81	F(1,28) = 0.36, p = .851
SAPS						
	Hallucinations	9.29	9.19	13.94	11.94	
	Delusions	17.86	16.21	24.94	23.91	
	Bizarre behavior	6.36	4.89	9.81	6.18	
	Positive formal thought disorder	8.00	11.52	20.19	13.54	
	SAPS total score	41.50	38.82	68.87	50.11	F(1,28) = 2.73, p = .109

**SAPS and SANS scores were available for only 30 patients because nine patients took part in the action memory task but were then unavailable due to unpredicted discharge from the ward.*

of "imagined actions recognized as performed" (maximum of 19) and "performed actions remembered as imagined" (maximum of 19). Moreover, in order to prevent physical matching, the items were presented in different fonts and placed in different locations on the screen than those used for the earlier items. At the end of the experiment, participants were asked to respond to whether a given instruction was new or had been presented in the learning phase as a performed or imagined action; they were then required to express their metacognition in a self-monitoring activity based on CR or PDW, each of which was randomly assigned to the selected group.

Subjective Measures in Self-Monitoring

This experiment used two measures of metacognition that were randomized across participants. The participants were asked to rate their certainty in recognizing responses from the action memory task by choosing the numerical keys on the keyboard (from 1 to 6). The first scale was a CR scale with six levels expressed as such 1—Totally uncertain, 2—Quite uncertain, 3—Slightly uncertain, 4—Slightly certain, 5—Quite certain, and 6—Totally certain. The second scale was adapted from the PDW (15, 43, 44) task and consisted of asking participants to express their confidence as wagers in imagined money. No reward for the performance of the task was in fact awarded. Hence, wagers of 5, 10, 15, 20, 25, and 30 PLN (1 PLN is around 0.24 EUR) were used in this experiment (see **Figure 1**). Participants were informed that the study was a sort of gambling game with imaginary earnings. They were asked to wager an imaginary amount of money that they won when they made correct discriminations. When an answer was wrong, the participants were told that the wagered amount would be lost.

Statistical Analyses

The observed performance parameters were old/new recognition (imagined as imagined, performed as performed, new as new), false alarms (new as performed or imagined), forgotten (performed or imagined as new), and self-monitoring (imagined as performed, performed as imagined). Similarly, we calculated the metacognition accuracy on the basis of the confidence levels.

The participants' responses were collected, and in the next step we examined the influence of the diagnosis (healthy vs. unhealthy) and the type of metacognitive scale (CR vs. PDW) on performance in the action memory task. To do so, correct and incorrect item recognitions (old/new items) and correct and incorrect source-monitoring recognitions were calculated. The effects of these variables on metacognition accuracy were investigated by two-way analysis of covariance (two-way ANCOVA). The main effects of the diagnosis and metacognitive scale and the interaction effects on old/new item recognition and source-monitoring responses were then examined. Age was taken as a covariate in the ANCOVA analysis. All calculations were performed with SPSS software and a significance level of 0.05 was established. Our sample included 89 participants. For the purpose of this study, we calculated the required sample size using G*Power software (v3.1) beforehand. We simulated F tests for ANCOVA, including fixed effects, main effects, and interactions with the following assumptions: small effect size, α err prob = 0.05, power (1-β err prob) = 0.80, df = 1, Number of groups = 4, Number of covariates = 0. For these parameters, the simulation revealed that a total sample size of 73 participants was needed.

RESULTS

Sociodemographic Characteristics

Demographic and psychopathological characteristics are presented in **Table 1**. There were differences in age between the schizophrenia patients (M = 38.41, SD = 13.94) and the healthy controls (M = 28.74, SD = 8.14), $F(1, 87) = 16.767$, $p < 0.001$, partial $\eta^2 = 0.162$. The age variable was controlled for in the analysis. The group of patients included 25 males and 14 females, although the gender difference was not significant, $\chi2(1) = 3.10$, $p = 0.078$, as opposed to the healthy controls (13 males/37 females), $\chi2(1) = 11.52$, $p < 0.001$. In the group of patients, 10 males used the CR scale (9 females) and 15 males used the PDW scale (5 females). The gender association with the scale was not significant in the group of patients, $\chi2(1) = 2.12$, $p = 0.146$. In the control group, 8 males used the CR scale (17 females) and 5 males used the PDW scale (20 females). No significant gender association with type of scale was found in the group of healthy controls, $\chi2(1) = 0.936$, $p = .333$. The participants were assigned to four categories: 1) healthy controls using the CR scale; 2) healthy controls using the PDW scale; 3) patients using the CR scale; 4) patients using the PDW scale. There was a significant association between gender and participants' category, $\chi2(3) = 15.729$, $p = 0.001$.

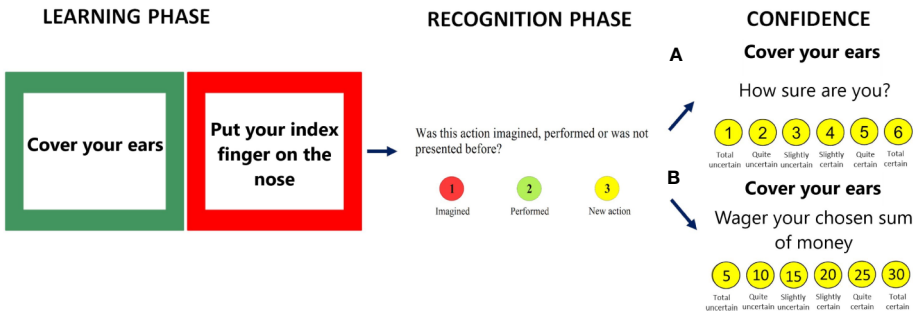

FIGURE 1 | The action memory task with confidence assessment: Demographic characteristics of the group of patients with schizophrenia and healthy control **(A)** CR scale or **(B)** PDW scale.

Performance: The Effect of Diagnosis (Patients With Schizophrenia vs. Healthy Controls) on Old/New Recognition and Self-Monitoring Errors

The results indicated that the main effect of diagnosis on performance was significant. In the case of old/new recognition, healthy participants demonstrated better performance than patients with schizophrenia, $F(1, 84) = 9.37$, $p = .003$; partial $\eta^2 = 0.10$. For the false alarms parameter (new items recognized as old), there was no difference between the healthy controls and the patient group, $F(1, 84) = 2.52$, $p = 0.116$; partial $\eta 2 = 0.03$. In the case of forgetting (old items recognized as new), there was no significant effect of diagnosis on performance, $F(1, 84) = 2.23$, $p = 0.139$; partial $\eta 2 = 0.03$.

For the self-monitoring (imagined actions recognized as performed) responses, we also observed that healthy participants (M = 2.36, SD = 1.88) recognized the information source better than the patients did (M = 4.28, SD = 3.68), $F(1, 85) = 10.08$, $p = .019$, and partial $\eta^2 = 0.064$. In addition, there was no group difference with regards to performed actions recognized as imagined, $F(1, 84) = 0.188$, $p = 0.666$; partial $\eta 2 = 0.002$. The results are presented in **Table 3**.

Performance: The Effect of Type of Scale (CR vs. PDW) on Old/New Recognition and Self-Monitoring Errors

In the next step of analysis, we examined the main effect of the type of metacognitive scale (CR or PDW) on performance. In the case of old/new recognition, we did not find any significant difference between the CR and PDW measures, $F(1, 84) = 0.001$, $p = 0.98$; partial $\eta 2 = 0.000$. For the false alarm responses, there was no significant effect of metaknowledge, $F(1, 84) = 0.43$, $p = 0.514$; partial $\eta 2 = 0.005$. In the case of forgetting, the difference between the CR and PDW groups was also not significant, $F(1, 84) = 0.11$, $p = 0.739$; partial $\eta 2 = 0.001$. For self-monitoring, in terms of both imagined actions recognized as performed $F(1, 84) = 0.251$, $p = 0.618$; partial $\eta 2 = 0.003$ and performed actions recognized as imagined, $F(1, 84) = 0.804$, $p = 0.373$; partial $\eta 2 = 0.009$, the difference between the CR and PDW groups was not significant (see **Table 4**).

Performance: The Interaction Effect of Diagnosis (Healthy vs. Patients With Schizophrenia) and Type of Scale (CR vs. PDW) on Old/New Recognition and Self-Monitoring Errors

The interaction effects between the mental disorder and the measures of confidence are presented in **Table 4**. There was no significant interaction effect for old/new recognition, $F(1, 84) = 0.057$, $p = 0.812$; partial $\eta 2 = 0.001$; false alarms, $F(1, 84) = 0.202$, $p = 0.655$; partial $\eta 2 = 0.002$; forgetting, $F(1, 84) = 0.041$, $p = 0.839$; partial $\eta 2 = 0.000$; or self-monitoring errors: performed recognized as imagined, $F(1,84) = 0.159$, $p = 0.691$; partial $\eta 2 = 0.002$; imagined recognized as performed, $F(1,84) = 0.017$, $p = 0.896$; partial $\eta 2 = 0.000$ (see **Table 5**).

Metacognition: The Effect of Diagnosis (Patients With Schizophrenia vs. Healthy Controls) on Confidence of Old/New Recognition and Self-Monitoring Errors

The following analyses were conducted to determine whether patients with schizophrenia differ from healthy controls in terms of confidence in given responses in the action memory task.

The results showed that there was no main effect of diagnosis on old/new confidence responses, $F(1, 84) = 0.053$, $p = 0.819$; partial $\eta 2 = 0.001$, and false alarms confidence, $F(1, 81) = 2.88$, $p = 0.094$; partial $\eta 2 = 0.034$. For the confidence responses in forgotten items there was no difference

TABLE 3 | The main effect of diagnosis (schizophrenia vs. healthy controls) on performance.

		Schizophrenia		Healthy participants		Statistics		
		M	SD	M	SD	*F*	p	partial η^2
The main effect of diagnosis	old/new hits	34.56	9.85	42.06	6.20	9.37	.003	0.10
	false alarms	5.72	5.78	4.40	2.00	2.52	.116	0.03
	forgotten	9.28	6.39	6.00	3.82	2.23	.139	0.03
	Self-monitoring errors							
	Imagined as performed	4.28	3.68	2.36	1.88	5.71	.019	0.06
	Performed as imagined	3.18	3.28	2.86	2.16	0.28	0.60	0.00

TABLE 4 | The main effect of type of scale (CR vs. PDW) on performance.

		CR group		PDW group		Statistics		
		M	SD	M	SD	*F*	*p*	partial η^2
The main effect of type of scale	Old/new hits	39.04	9.18	38.50	8.47	0.001	0.980	0.00
	False alarms	5.20	4.61	4.76	3.64	0.43	0.514	0.005
	Forgotten	7.50	5.29	7.38	5.43	0.11	0.739	0.001
	Self-monitoring errors							
	Imagined as performed	3.41	2.72	3.00	3.19	0.251	0.618	0.003
	Performed as imagined	2.75	2.74	3.24	2.66	0.804	0.373	0.009

TABLE 5 | The interaction effect of type of scale (CR vs. PDW) and diagnosis (patients with schizophrenia vs. healthy controls) on performance.

			Schizophrenia		Healthy group		Statistics		
			M	SD	M	SD	F	*p*	partial η^2
The interaction effect of diagnosis and scale	Old/new hits	CR	34.21	9.80	41.76	5.54	0.057	0.812	0.001
		PDW	34.90	10.13	42.36	6.89			
	False alarms	CR	6.21	6.54	4.44	2.14	0.202	0.655	0.002
		PDW	5.25	5.08	4.36	1.89			
	Forgotten	CR	9.32	6.65	6.12	3.53	0.041	0.839	0.000
		PDW	9.25	6.31	5.88	4.17			
	Self-monitoring errors								
	Imagined as performed	CR	4.42	3.42	2.64	1.75	0.017	0.896	0.000
		PDW	4.15	4.00	2.08	2.00			
	Performed as imagined	CR	2.79	3.61	2.72	1.90	0.159	0.691	0.002
		PDW	3.55	2.98	3.00	2.42			

between the healthy groups and the patient groups, $F(1, 83) = 3.50$, $p = 0.065$; partial $\eta^2 = 0.04$. The patients with schizophrenia did not differ in CR for imagined actions recognized as performed, $F(1, 74) = 0.007$, $p = 0.932$; partial $\eta 2 = 0.000$. There was a trend, but no statistical significance difference between groups in confidence in performed-as-imagined actions was present, $F(1, 69) = 3.85$, $p = 0.054$; partial $\eta 2 = 0.05$ (see **Table 6**). Note that patients with schizophrenia expressed higher confidence in misattributed performed-as-imagined actions ($M = 4.69$, $SD = 1.34$) than the healthy controls ($M = 4.20$, $SD = 1.23$).

Metacognition: The Effect of the Type of Scale (CR vs. PDW) on Confidence in Old/New Recognition and Self-Monitoring Errors

The results from the main effect of the usage of different metacognitive measures on confidence responses are presented in **Table 7**. There was no main effect of the metacognitive scale on confidence in old/new recognitions, $F(1, 84) = 2.91$, $p = 0.092$; partial $\eta 2 = 0.034$. In the case of confidence produced for false alarms, there was a significant difference between participants who used the CR and PDW scales, $F(1, 81) = 9.146$, $p = 0.003$; partial $\eta^2 = 0.101$. The results showed that lower confidence was used to assess false alarms when participants employed PDW ($M = 3.88$, $SD = 1.27$) than when they used the CR scale ($M = 4.60$, $SD = 0.98$). For confidence in forgotten items, there was also a significant difference between the CR and PDW groups, $F(1, 83) = 5.68$, $p = 0.019$; partial $\eta^2 = 0.064$. For forgotten actions, participants also assessed their confidence as lower when they categorized metacognition with PDW ($M = 4.17$, $SD = 1.35$) as opposed to CR ($M = 4.82$, $SD = 1.15$). It turned out that the main effect of metacognition measures was also significant for confidence in terms of self-monitoring errors. In particular, for performed actions that were recognized as imagined, participants produced more confident misrecognitions using CR scale (M = 4.84, SD = 1.06) as compared to the PDW scale (M = 3.98, SD = 1.36), F(1, 69) = 9.168, $p = 0.003$; partial $\eta^2 = 0.117$. In the case of imagined actions that were recognized as performed, participants also committed more confident misrecognitions using the CR scale

TABLE 6 | The main effect of diagnosis (patients' group vs. healthy controls) on confidence ratings.

		Schizophrenia		Healthy controls		Statistics		
	Confidence	M	SD	M	SD	F	p	partial η2
The main effect of diagnosis	Old/new hits	5.18	0.103	5.14	0.58	0.053	0.819	0.001
	False alarms	4.48	1.49	4.06	0.88	2.88	0.094	0.034
	Forgotten	4.85	1.32	4.21	1.21	3.50	0.065	0.04
	Self-monitoring errors							
	Imagined as performed	4.41	1.76	4.44	1.27	0.007	0.932	0.000
	Performed as imagined	4.69	1.34	4.20	1.23	3.85	0.054	0.05

TABLE 7 | The main effect of type of scale (CR vs. PDW) on confidence ratings.

		CR group		PDW group		Statistics		
	Confidence	M	SD	M	SD	F	*p*	partial η^2
The main effect of metacognition measure	Old/new hits	5.31	0.80	5.01	0.79	2.91	0.092	0.034
	False alarms	4.60	0.98	3.88	0.27	9.146	0.003	0.101
	Forgotten	4.82	1.15	4.17	1.35	5.68	0.019	0.064
	Self-monitoring errors							
	Imagined as performed	4.89	1.16	3.95	1.67	7.762	0.007	0.095
	Performed as imagined	4.84	1.06	3.98	1.36	9.168	0.003	0.117

($M = 4.89$, $SD = 1.16$) as compared to the PDW scale ($M = 3.95$, $SD = 1.67$), $F(1, 74) = 7.762$, $p = 0.007$; partial $\eta^2 = 0.095$.

Metacognition: The Interaction Effect of Diagnosis (Schizophrenia vs. Healthy Controls) and Type of Scale (CR vs. PDW) on Confidence in Old/New Recognition and Self-Monitoring Errors

In the final analysis, we investigated how both the diagnosis and the type of metacognitive scale affected confidence (see **Table 8**). Between both factors there were no significant interaction effects on confidence (see **Table 8**).

DISCUSSION

The present study investigated dysfunctional metacognition in self-monitoring of memory in patients diagnosed with schizophrenia. Dysfunctions in metacognition were assessed with either monetary incentives (PDW scale) and the conventional measure of confidence based on the CR scale. Our study demonstrated for the first time that accuracy of metacognition about correct responses and memory errors in source-monitoring performance in patients with schizophrenia and healthy controls improved due to imaginary wagering (PDW scale). For all groups of participants, more accurate confidence responses were revealed with monetary categorizations. This effect is of particular importance for clinical practice because the accuracy of metacognition in patients with schizophrenia improved when using the PDW as opposed to the CR scale. Our research therefore suggests that mistaken trust in self-monitoring actions may be reduced by engaging the wagering strategy that induced motivational processes and aversion to loss in patients with schizophrenia and healthy participants. The findings are in the line with previous research investigating metacognitive processes of control and monitoring in a general knowledge task with monetary incentive cues to encourage participants' accurate answers (45). Although schizophrenia patients had defective metacognition in this study, i.e., their subjective accuracy of correctness was impaired, their modulation of control (response criteria adjustments) was intact when a gambling strategy was involved that required them to bet a small amount of money on each response (45). Thus, this study suggests that patients with schizophrenia could improve their performance when encouraged to use monetary incentives (45). Similarly, our study shows that patients with schizophrenia can improve their metacognitive accuracy in self-monitoring tasks by engaging a gambling strategy to assess their confidence subjectively.

In addition, our research shows that patients with schizophrenia displayed lower performance than healthy subjects with respect to old/new recognition as well as self-monitoring responses. The patients with schizophrenia misremembered imagined actions as having been performed more often than healthy controls, but not *vice versa*. In fact, these results confirm observations from previous self-monitoring studies (9, 46) that indicated a specific cognitive bias pattern regarding self-monitoring errors in patients with schizophrenia who presented more misremembered imagined actions than were really performed, but not the reverse. This outcome may be explained by the hypothesis concerning *over-perceptualization* (47) that was proposed within the neuroanatomical model by Allen and colleagues [(47), see also (27)], which describes a network of brain areas and their respective contributions to the hallucinatory experience. The core of this model is hyperactivation of the secondary sensory cortex among patients while they are experiencing hallucinations. This account assumes that bottom-up dysfunctions through over-activation in the secondary and primary sensory cortices may lead to the experience of vivid perceptions in the absence of sensory stimuli (27, 47). The specific pattern of performance in patients with schizophrenia who more often misremembered imagined actions as having been performed may be explained to some extent by the account that demonstrates more vivid imagery in patients with schizophrenia (48).

Moreover, our study demonstrated that both the PDW and CR measures did not affect performance in the action memory task. The non-significant interaction effects from the ANCOVAs indicted that patients with schizophrenia achieved lower performance in self-monitoring regardless of the measure of metacognition. We also found that patients with schizophrenia showed a tendency ($p = 0.054$) to express over-confidence in self-monitoring errors (performed as imagined) for both metacognition-measurement scales. In fact, the overconfidence phenomenon for action self-monitoring errors has been found

TABLE 8 | The interaction effect of type of scale (CR vs. PDW) and diagnosis (Schizophrenia vs. Healthy controls) on confidence ratings.

			Schizophrenia		Healthy controls		Statistics		
			M	SD	M	SD	*F*	*p*	partial η^2
The interaction effect of diagnosis and scale	Old/new hits	CR	5.29	1.10	5.33	0.49	0.227	0.635	0.003
		PDW	5.07	0.98	4.95	0.62			
	False alarms	CR	4.95	1.20	4.37	0.73	0.309	0.580	0.004
		PDW	4.06	1.63	3.75	0.93			
	Forgotten	CR	5.19	1.19	4.54	1.05	0.004	0.953	0.000
		PDW	4.53	1.39	3.86	1.28			
	Self-monitoring errors								
	Imagined as performed	CR	4.78	1.42	4.97	0.97	0.415	0.521	0.006
		PDW	4.07	2.00	3.83	1.32			
	Performed as imagined	CR	5.13	1.27	4.68	0.91	0.066	0.798	0.001
		PDW	4.35	1.33	3.68	1.34			

in schizophrenia in several previous studies (11, 28, 32). Contrary to what was hypothesized, our results suggested a lack of impairment in metacognition among patients with schizophrenia. Thus, by using the metacognitive judgments of PDW or CR, patients with schizophrenia were found to evaluate source memory performance accurately, which suggests a dissociation between preserved metacognition and altered source-monitoring abilities. Interestingly, similar findings indicating preserved metacognitive functions which do not correspond to impaired memory performance were observed in patients with Alzheimer's disease (49), people with symptoms of amnesia (50), and in other metamemory studies in schizophrenia patients (51, 52). For example, Souchay et al. (51) examined metamemory and memory performance in patients with schizophrenia and control subjects by using a Feeling of Knowing (FOK)[1] task on episodic memory information. The results of Souchay et al. (44) clearly suggested a dissociation between impaired memory and preserved metacognitive ability to predict recognition performance accurately in patients with schizophrenia. Another study by Bacon at al. (52) investigated knowledge about one's own memory capability in patients with schizophrenia. Again, there was a clear dissociation between impaired semantic memory and accurate metacognition expressed with CR with regard to recollection processes in patients. However, another measure of metaknowledge based on FOK judgments that was dependent on information accessibility was significantly impaired in patients with schizophrenia. Our results confirm these findings, since preserved metacognitive ability in schizophrenia in relation to source-monitoring performance was about correctness of information from source-monitoring in the present study. This, in turn, might suggest that patients with schizophrenia (like healthy controls) are aware of source-monitoring performance when information processing is induced by a scale (PDW vs. CR).

Irrespective of the diagnosis categorization, our analysis indicated that accuracy of metacognition was better for PDW measure engaging the gambling strategy as compared to the conventional CR measure. In the case of using metacognitive judgments evoked by PDW scale, for both populations, we observed lower confidence expressed in all types of erroneous responses, such as false alarms, forgotten actions, and self-monitoring errors. Thus, patients presented enhanced metacognitive accuracy that was activated with the PDW scale. The demonstration of preserved metacognitive functions may have implications for the treatment of delusional convictions in patients with schizophrenia. Delusions are commonly defined as false beliefs that are maintained by patients with strong convictions (56). Since overconfidence is usually associated with delusional symptoms in schizophrenia (57), the reduction of such a bias may influence their treatment outcomes. Indeed, recent research on metacognitive intervention has indicated that the prognosis is good for the treatment of patients with schizophrenia who are aware of their memory function deficits (2, 58–60). Our study strongly suggests that monetary incentives may enhance the accuracy of metamemory in patients with schizophrenia and, therefore, may to some extent weaken their strong convictions in inaccurate inferences. Thus, taken together, the results of this study and our previous findings (22) indicate that encouraging patients' own assessments of performance with monetary incentives may be applicable to the treatment of metacognition in terms of reducing the severity of delusions in schizophrenia.

Several studies on metamemory in people with schizophrenia suggest that inaccurate metacognition arises from the fact that patients (similarly to healthy controls) are not aware of their deficits in some domains of everyday functioning or are not aware of their own skills and abilities (57, 61). It is well documented in experimental studies on motivation in the general population that monetary incentives are substantial ingredients of motivation that activate an individual's internalized drive to take action (62) and may increase metacognitive awareness and/or first-order discrimination (15). In the same vein, monetary incentives may act as stimuli for better first-order performance in people with schizophrenia by concurrently enhancing second-order discriminations, i.e., the accuracy of metacognition. On the other hand, from the cognitive perspective, post-wagering may be subjected to a variety of confounding factors (including loss aversion) (16) that result in a conservative wagering strategy that involves systematically using smaller wagers, even though participants are aware of the stimuli (17). Regardless of these conceptual issues, taking into account models of metacognitive regulation (63, 64) and phenomenology of delusional beliefs (57), the accuracy of preserved metamemory that is dissociated from source memory performance may still be increased and may have therapeutic effects in terms of weakening delusional inferences in schizophrenia.

Interestingly, from a cognitive perspective our results suggest that bottom-up processes involving primary structures of the brain related to basic performance (e.g., distinguishing the memory sources) are resistant to meta-knowledge manipulation. On the other hand, according to the neuroanatomical model, the psychotic experience is augmented by a weakening of top-down control driven by a variety of brain regions, e.g., the ventral anterior cingulate or the prefrontal, premotor and cerebellar cortices (45). Thus, maintenance of false experiences (e.g., hallucinations) may be caused by abnormality in control processes that do not provide effective regulation of these experiences at any given moment. According to the account presented in this study, metacognition cannot overcome errors on the primary level, although activation of metacognitive control may modify the false beliefs system when an individual uses more precise vigilant strategies to assess his/her basic performance.

[1] Feeling of knowing and the tip-of-the-tongue experience (53) induce the expectation in participants that the required information is available in memory, although it is currently inaccessible despite their efforts. Hence, these metacognitive feelings potentially motivate participants to search their memory further and use control strategies (54, 55).

Our study also has several limitations. First, whether we found the "overconfidence effect" in patients with schizophrenia may be debatable as statistical inferences relied on a p level of 0.054. Therefore, future replications on a larger sample are needed to increase the statistical power of our results. Second, we did not collect data relating to the educational level of patients in the demographic information. Although educational level could be a factor that may lead to poor memory functioning in schizophrenia population (64), some studies also indicate that less-educated healthy controls outperform patients with schizophrenia on memory tests (65), thus making the relations between schizophrenia and memory performance more confounded. Therefore, further studies should investigate the association between metamemory and source memory performance that would match comparison subjects in terms of age and education factors. It is also possible that the self-monitoring deficits observed in this study may be linked to particular symptoms of psychosis. For example, using a measure of the Positive and Negative Syndrome Scale (PANSS) (66), Gawęda et al. (9) observed correlations between imagined-actions-remembered-as-performed responses and hallucinations, and between these responses and general positive symptoms, but no correlation effect was observed in the severity of delusions [see also (67)]. Thus, in future studies the relationship between metacognitive processes induced by the PDW scale and the severity of symptoms in psychosis should be investigated. In fact, it is very interesting to take into account the prevalence of hallucinations and self-monitoring errors among healthy individuals and patients with psychiatric disorders other than schizophrenia (9, 68–70).

To sum up, as opposed to assessments of metacognition with the CR scale, patterns of metacognitive responses based on economic categorization resulted in better metacognition accuracy in both patients with schizophrenia and healthy controls. This has potential applications, most notably in that a single scale can be built to determine the metacognitive responses for healthy and schizophrenic groups without the need to develop specific scales for each group. Moreover, as expected, the diagnosis effect seems to affect performance in the task with practically no effect on measures of confidence.

As future research prospects, additional factors might need to be considered to fully understand the mechanism behind the accuracy of metacognition arising from the PDW scale. These factors might be linked to individual patient characteristics, such as medication type and dosage, or the time period since diagnosis. In particular, the reduction or discontinuation of treatment with antipsychotic drugs may significantly improve patients' cognitive functions (71). From the application perspective, the construction of "economic" feedback to treat metacognition in schizophrenia in order to distinguish between true and false memories might be considered. Thus, this study demonstrates promising implications of using imaginary monetary categorization in modern health-care programs for treating metacognition in psychiatric populations. The feasibility and efficacy of metacognitive therapy in patients with schizophrenia have been demonstrated in several empirical reports (2, 72–76). However, one also should be aware of a recent meta-analysis indicating that there is no convincing empirical evidence for the unambiguous efficacy of MCT (77), since group or individualized MCT interventions show small or small-to-medium effect sizes on average. These relatively poor outcomes of MCT in the reduction of positive symptoms (e.g., delusions) are explained partially by abnormal data gathering and reasoning biases in patients with schizophrenia, who often are under stress and driven by negative mood (77). Nevertheless, it seems reasonable to apply our findings concerning the effects of monetary incentives on metacognition in therapeutic practice to make attempts to reduce cognitive bias in the population of patients with schizophrenia. Future empirical research will be needed to address the potential benefits of activating gambling strategies based on motivation and aversion to loss in treating metacognition in psychiatric populations.

CONCLUSION

The main findings of our research can be summarized as follows. Firstly, patients diagnosed with schizophrenia showed poorer old/new recognition performance in the action memory task and, as opposed to healthy controls, they did not differ in false alarms and forgotten actions. Patients also committed more source memory errors because, as opposed to healthy controls, they were more likely to consider that imagined actions had been performed. Secondly, regardless of the group (patients with schizophrenia vs. healthy controls), evaluations of metacognition with the CR and PDW scales did not affect memory performance in the action memory task. Thirdly, compared to healthy controls, patients with schizophrenia showed a tendency to express higher confidence in self-monitoring errors (i.e., performed-as-imagined actions) when both measures of metacognition-measurement were employed, although the p-level of 0.054 implies that this effect might be debatable. Fourthly, there was no interaction effect between the type of metacognition measures (CR vs. PDW scale) and the diagnostic status of participants (patients with schizophrenia vs. healthy controls), thus indicating that both metacognition evaluation modes are the same for patients and healthy participants. This implies that patients and healthy participants are more likely to adjust their accuracy of metacognition when monetary incentives are at stake. In general, regardless of their diagnostic status, imaginary monetary loss induced by wagering diminishes participants' confidence in their incorrect responses (i.e., memory errors and source memory errors) as compared to explicit metacognitive confidence in memory performance.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Committee for Ethics in Empirical Studies with the Participation of People as Subjects of the SWPS University in Wroclaw. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RS: research concept and design, data analysis and interpretation, writing the article, critical revision of the article, and final approval of article. EC: research concept and design, collection and assembly of data, data analysis and interpretation, writing the article, and final approval of article. AP: data analysis and interpretation, writing the article, and final approval of article. ŁG: writing the article, critical revision of the article, and final approval of article. JR: writing the article, critical revision of the article, and final approval of article.

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Treating Schizophrenia: Open Conversations and Stronger Relationships Through Psychoeducation and Shared Decision-Making

Armida Mucci[1], *Wolfram Kawohl*[2], *Cristiana Maria*[3] *and Annette Wooller*[4]*

[1] Department of Psychiatry, University of Campania Luigi Vanvitelli, Naples, Italy, [2] Department of Psychiatry and Psychotherapy, PDAG, Brugg, University of Zurich, Zurich, Switzerland, [3] Communications EMEA, Janssen Pharmaceutica NV, Beerse, Belgium, [4] Medical Affairs EMEA, Janssen Pharmaceuticals, High Wycombe, United Kingdom

Integrated pharmacological and psychosocial treatments, such as psychoeducation (PE) and shared decision-making (SDM), have been shown to significantly improve outcomes for people living with schizophrenia (PLWS). Underpinning the success of these interventions is a strong therapeutic relationship between PLWS, their carers, and their healthcare team. While many recognize the value of this relationship, implementation of the interventions necessary to facilitate its construction remain low. In this article, we identify the barriers to developing productive therapeutic relationships and explain how PE and SDM, taking into account cultural difference, can improve adherence to treatment, strengthen therapeutic relationships, and ultimately equip patients to achieve better functional outcomes.

Keywords: psychoeducation, schizophrenia, carers, people living with schizophrenia, shared decision-making

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***Correspondence:**
Annette Wooller
awooller@its.jnj.com

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INTRODUCTION TO THE BIOPSYCHOSOCIAL MODEL IN SCHIZOPHRENIA AND THE IMPORTANCE OF PSYCHOEDUCATION

Schizophrenia is a complex disorder that is impacted by biological, social and psychological factors. Recent years have seen a shift towards how psychosocial factors, such as isolation, victimization, and substance abuse, can influence outcomes (1). The biopsychosocial model of schizophrenia considers the cause and course of schizophrenia as equally related to biological vulnerability interacting with social and psychological factors, e.g., isolation and low self-esteem, with recommended psychological interventions based on individual requirement (2, 3).

We believe that optimal outcomes for people living with schizophrenia (PLWS) arise when healthcare professionals (HCPs) consider both pharmacological and psychological interventions. This enables them to individualize each case and implement treatment plans tailored to their history, family, and cultural background. In clinical practice, pharmacological therapies are well understood and widely implemented however, psychosocial treatments are not. Therefore, we need to embed

psychosocial treatment into standard care for PLWS and improve the therapeutic alliance between PLWS, their carers, and their healthcare team (4).

This article aims to identify barriers to the achievement of strong therapeutic relationships and highlight the benefits of consistently implementing psychosocial treatments such as psychoeducation (PE), and shared decision-making (SDM).

PE involves providing accurate, relevant and up-to-date information to PLWS as well as to their carers and family (5). PE focuses on improving insight and giving practical support on managing the condition. SDM promotes collaboration between patients and clinicians, where information is shared and patients are supported to express and achieve informed preferences about their treatment (6).

This review article uses the biopsychosocial model to discuss the personalization of care for PLWS, focusing on the importance of knowledge and expertise in pharmacological and psychosocial aspects of schizophrenia and the importance of implementing an individualized approach that is sensitive to patients' history and cultural backgrounds. We believe that embedding PE and SDM into the interactions between PLWS and their healthcare teams will help improve therapeutic relationships and subsequently overall outcomes.

ESTABLISHING AND ADDRESSING A NEED FOR OPEN CONVERSATIONS AND STRONG RELATIONSHIPS

Clinicians should aim to build a strong therapeutic alliance between themselves, the patient and their primary carer(s). An alliance should be non-hierarchical, acknowledging the respective expertise of the individuals, with all members given respect and made to feel like partners with a common goal (7).

To construct a strong therapeutic alliance, open conversations, trust and respect play a fundamental role, with the ultimate goal being to establish a partnership to optimize patient outcomes. Strong therapeutic alliances have been shown to correlate with positive patient outcomes, notably symptom severity, hospitalizations, rates of drop-out from psychosocial treatment, and adherence to medication (8). This article discusses how various barriers specific to individual patients, such as social and cultural factors, influence the formation of strong therapeutic alliances.

RECOGNIZING THE ROLE OF CARERS

It is important to recognize all stakeholders involved in the care of PLWS; the role carers play should not be undervalued. Carers can relay important information about how the PLWS is coping, how the person is daily, and whether any change in wellness or behavior has occurred. It is important to note that carers may or may not be family members.

BARRIERS TO STRONG RELATIONSHIPS

There are numerous patient, carer, and clinician barriers that can impair the formation of relationships; these vary between cases and vary from misinterpretation of patient insight to appreciation of cultural background.

PATIENT BARRIERS TO STRONG RELATIONSHIPS

Insight

"Insight" describes the ability of PLWS to recognize that they have an illness and their ability to understand how their experiences relate to the illness (9). In our experience, insight exists on a continuum; patients often recognize some aspects of their symptomatology, but not others. For example, formal thought disorder and hallucinations are better recognized as pathological, while delusions are less so (10). Poor insight is a known feature of schizophrenia and has been linked to poorer perceived therapeutic alliance (8, 11, 12).

Impaired insight can hinder relationships, not least due to the negative effects this has on social interaction and perception of the actions of others (13). If a person does not believe that they have an illness, then any attempt to address it will be futile. Crucially, this can lead the person to distrust the help provided by carers and professionals. It is important to gauge the baseline level of insight to provide suitable individualized PE (14, 15). Although appreciation of insight prior to providing PE is beneficial, providing quality PE to all PLWS regardless of insight is beneficial. In PLWS, PE is one of the most consistently effective treatment modalities, with relapse rate reduction at 50%–60% over treatment as usual (5).

Stigma

Stigma describes a negative perception or judgement towards a person, which can lead to alienation and discrimination. For PLWS, stigmatization (from others and self) causes embarrassment, insecurity and stress. Stigma can lead to communication problems, including a reluctance to talk openly about their illness. Stigma changes how subjects perceive themselves—leading to feelings of incompetence and low self-esteem. Stigma correlates with poorer real-life functioning as measured by maintenance of close and extended social circles, productivity at work and independent living (16–18). PLWS often use social withdrawal as a mechanism for coping with stigma, which can have a negative impact on relationships and impede the desire to discuss and share during consultations.

Cultural context can affect family burden, stigma and the progression of schizophrenia. A predictor of poor course in schizophrenia is highly expressed emotion (EE), which varies widely across ethnic groups (19). Furthermore, differing levels of acceptance of schizophrenia and criticism towards PLWS exist between different cultural groups, e.g., Anglo-Americans tended to blame their affected relatives more than Latino Americans (20). Additionally, gender inequality is strongly affected by cultural factors and in certain regions, female PLWS may be devalued and submitted to excessive emotional stress, violence, isolation and denial of access to care (21). Cultural and gender-informed therapy should be offered to PLWS and their families. Therapists should be aware that PE, other psychological

therapies and the therapeutic alliance may be severely impacted by these factors. For example, a delay in seeking help may be associated with high levels of stigma in some cultures, e.g., Afro-Caribbean immigrants in the UK delayed access to care for PLWS, with an increase in the duration of untreated psychosis associated with a subsequent worsening of outcome (22).

HEALTHCARE SYSTEM/PSYCHIATRIST BARRIERS TO STRONG RELATIONSHIPS

Poor Provision of Information

Hesitancy from HCPs in sharing information with PLWS and their carers can have a negative impact on outcomes. In our experience, hesitancy occurs due to several factors including poor insight, insufficient training on PE technique, and the physician's fear of offending and disrupting the relationship with the patient. Sometimes even core pieces of information, such as the diagnosis of schizophrenia, are initially omitted, with vague terminology, e.g., "a disorder of the brain" used, which may be confusing, or even inaccurate (23, 24). Avoiding use of "schizophrenia" may prevent PLWS from seeking the treatment and support required and delay the opportunity to build a strong relationship (24).

Most people with severe mental illness have a high desire for information. This information is associated with variables, such as therapeutic relationship and symptom severity, which are amenable to change during treatment (25).

Poor communication of information extends to conversations about treatments. Some clinicians fear that informing PLWS about options like long-acting therapies too early may be viewed as suggesting that PLWS are untrustworthy, their condition is more severe, or that clinicians do not want to see them (26–28). In our experience, open discussion about the need for pharmacological treatment is fundamental and should always happen as early as possible. Discussions around drug options can be influenced by poor insight of PLWS, especially during the acute phase, and PLWS with persecutory ideas involving carers and staff, with no illness insight, may not be able to fully consent to treatments.

A poor understanding of cultural context may inhibit a HCP's ability to form an open, honest and transparent relationship with their patient. However, the integration of culturally-based treatment approaches with existing PE interventions are now available, or are being developed for PLWS from ethnic minority groups, including Hispanic, Latino, African, and Caribbean communities (29, 30). This is in accordance with the NICE Schizophrenia Guidelines, which state that "services should also ensure that all clinicians are skilled in working with people from diverse linguistic and ethnic backgrounds, and have a process by which they can assess cumulative inequalities through their routine clinical practice" (31).

Despite strong guideline recommendations of education for PLWS and carers, provision of PE remain low, with a minority of clinicians and nurses receiving relevant training (12, 31–34).

Lack of Patient-Centered Outcomes

PLWS generally value different outcomes to those considered by HCP's and this can create barriers in forming therapeutic relationships. While HCPs value outcomes are usually symptom relief or relapse prevention, PLWS may desire outcomes such as acceptance by their family or peers, or a return to school or work. These valued outcomes are not addressed in certain therapeutic settings, yet are invaluable in building strong therapeutic relationships. Discussing and setting patient-centered outcomes may build hope and help trust in the therapeutic relationship (35).

Outdated Attitudes

Sometimes, important aspects of personal life, like sexual activity and illicit drug use, are avoided in clinical discussions, which can create distrust. Avoiding discussions about sexual activity might suggest to PLWS that sexual disturbances due to treatment are being overlooked. Interestingly, patients are often willing to talk about these aspects when prompted (36).

Cultural factors directly impact relationships. Individual perceptions of schizophrenia and cultural context may affect the likelihood of the PLWS to seek help or be transparent about their experiences and their views of the role of their loved-ones in helping to fulfil the carer role (37).

PLWS and clinicians sometimes differ when defining treatment goals and outcomes. Patients often prioritize life goals and real-world problems, whereas clinicians usually place emphasis on symptoms, such as hallucinations (4). Patient-related outcomes should be valued and complement other outcome measures (38). A patient's job and housing situation should also be considered.

CARER BARRIERS TO STRONG RELATIONSHIPS

Carers' behaviors and attitudes can have significant effects on social functioning and treatment success. Often, stigma and a lack of understanding or acceptance from families may result in poor support for PLWS, which can impact their condition.

The influence of cultural context also extends to the carer. In some cultures, it may be considered humiliating and/or offensive to involve a relative younger than the patient, or a female peer in therapy discussions (37, 39).

EE can refer to positive or negative communication strategies used by a carer towards PLWS. The construct of EE includes five components: critical comments, emotional over-involvement, hostility, warmth, and positive remarks (40). The first three components are associated with poor outcomes while warmth and positive remarks are protective factors (41). Higher levels of negative EE correlate with poorer compliance and predicts poorer social functioning for PLWS (41, 42). The presence of these aspects is also influenced by the cultural context, for example, EE rates are higher in Western cultures (43).

SOCIOECONOMIC BARRIERS

Clinicians should be mindful of the socioeconomic and organizational barriers to maximizing their contact time with PLWS. These are typically beyond the control of individual clinicians, but awareness may help guide practice. In our experience, barriers that can reduce contact time include frequent changing of facilities and staff, high caseloads for clinicians, unstable living situations for PLWS, or unavailability of accessible transport to get to appointments. A broader availability of well-organized outpatient and outreach mobile services can improve early detection and the quality of the first therapeutic relationship that is crucial for treatment adherence. Studies have shown that early recognition and treatment improves outcomes for PLWS and reduces individual and societal costs (12, 44).

ADDRESSING THE BARRIERS TO ACHIEVE STRONGER RELATIONSHIPS

Greater Attention and Support for Carers

Studies have shown that having a family member or carer who provides informal support is associated with better treatment compliance (45, 46). Keeping carers closely involved in the treatment plan helps to open up other channels of communication for the clinician and PLWS.

It is important to make sure the patient-clinician-carer dynamic is positive; if this deteriorates, revisiting the roles of carers, when they should come to appointments, and whether changes are needed can help restore balance.

PE for Carers and PLWS

Benefits of PE for Carers and PLWS

PE is a useful tool for improving relationships within the care alliance. The clinical benefits of PE have been demonstrated in numerous studies and include positive impacts on clinical measures, e.g., relapse rates, relapse severity, and adherence (14, 47, 48). Regarding promoting strong therapeutic relationships, PE has been shown to improve patient insight, reduce self-stigma and improve social functioning (14, 49, 50). However, while improving insight is a key goal of PE, even patients with high levels of insight may still benefit (5).

PE also improves outcomes for the carers and family members of PLWS. Studies exploring family therapy approaches have shown that PE reduces carer stress and hostility towards other family members, while increasing warmth and reducing the perception of burden (51–53).

What Should PE Cover?

PE will inevitably include schizophrenia-specific information, such as how to recognize symptoms, the impact of the illness on real-life functioning and the importance of treatment for optimal outcomes. Clear and essential information should be provided, and basics of the vulnerability-stress model should be addressed to adequately present the need for treatment. Promoting healthy lifestyles, identifying causes of stress, and problem-solving and communication skills are equally important domains of PE (5).

A large part of the learning from a PE intervention will likely take place outside of the clinician consultation; the clinician plays a critical role in directing PLWS and their carers to reliable and easily-understandable sources of information, such as e-mental health interventions (54). Guidelines recommend that educational interventions, including those surrounding treatment options, are introduced as early as possible (31, 32).

Different PE approaches should be considered for PLWS and their carers. PLWS may benefit more from an approach that enhances problem-solving skills and promotes the identification and achievement of life goals. For carers, greater importance may be placed on the symptoms of schizophrenia, with a focus on promoting acceptance (51). Healthcare providers should consider how better access to PE can be provided in general to PLWS and carers (34). Importantly, all information should be accurate, fair and balanced, and, when possible, not influenced by preconceived attitudes and opinions of the clinician.

Shared Decision-Making and Patient Partnership

While clinicians are experts of the illness, PLWS, and carers are experts of themselves or experts by experience, and the contribution that each can bring to the decision-making process should be recognized and considered. Unfortunately, although there is strong support for SDM among PLWS and psychiatrists, evidence suggests that this does not routinely take place, often due to various different factors (55–57). Commonly-identified barriers to SDM include poor insight and lack of decisional capacity from the patient, societal and cultural expectations about psychiatric disorders, beliefs surrounding the effects of treatments, and financial and timing pressures which can limit options (35, 58).

There are a number of factors that can be incorporated into consultations to help facilitate SDM. These include honesty, trust, respect and politeness from all parties (7). Honesty is required from the clinician (e.g., regarding treatment options and potential side effects), but also from PLWS and carers (e.g., reporting symptoms or adherence) (7). In our view, a warm attitude from the treatment team, a manifest interest for the person and his/her opinions, and empathetic behavior towards distress caused by treatment or symptoms can help establish a correct and trustful therapeutic atmosphere even for PLWS with poor insight.

Open discussion of treatment options should happen as early as the patient is ready, with evidence suggesting that early introduction of both pharmacological and psychosocial treatments for schizophrenia can positively impact overall treatment success (27, 28, 32, 59), and positively impact SDM (32, 59).

In our view, following pharmacological treatment guidelines is the gold standard of treatment in schizophrenia in order to prevent hospitalization, relapse, and to promote community independent living which is imperative for patient recovery. When considering the recommended treatments, discussions should always include the pros and cons of different options, and the treating team should routinely consider whether the current treatment is optimal or

whether there might be better needs-oriented options. **Table 1** contains a list of questions, parameters and solutions that can be implemented to help uncover and address patients' needs and attitudes towards their current treatment. Everyone should be open to the idea of revisiting treatment discussions to find the best option for the patient. Therefore, we believe that the shared view of schizophrenia and its treatment that has to be reached in the therapeutic relationship should address biological vulnerability and the positive role antipsychotics have in treatment.

It is important to involve PLWS in treatment choices; you should openly discuss their attitudes towards drug or psychological treatment and allow their preferences to be stated without judgmental comments. Within this context, it is useful to frame pharmacological interventions as a way to reduce the distress related to symptoms and protect the patient against the stress-related development of these symptoms. A schizophrenia diagnosis should be discussed at the earliest opportunity, ideally when the team are confident of its veracity; if there is insufficient evidence, a provisional diagnosis should be communicated, explaining that further information is required for a definitive diagnosis.

Patients can be encouraged to take a more active role in their treatment by asking open-ended questions, taking time to consider their viewpoints, verifying their ability to understand information and instilling them with confidence about their involvement. PE and a strong patient partnership will often come hand in hand; more proactive and engaged patients are typically more informed regarding their treatment (7).

Formal PE Training for Clinicians

Psychiatrists should consider upskilling themselves and be aware of the benefits this could have for patient outcomes. Studies have shown that settings-based training programs can improve therapeutic relationships (60, 61).

Psychiatrists should be encouraged to access materials and courses that can further help them apply PE. Those who have more experience with PE should consider furthering their reach by advocating for widely available PE training within their countries, working closely with scientific professional societies to ensure that they produce more accessible opportunities for training, and promote awareness of the importance of PE within their healthcare communities.

DISCUSSION

There are several key components that are necessary to create a strong treatment plan for PLWS including; a strong therapeutic alliance, SDM, and PE. Each of these components build on the benefits of the others; for example, patients that are more educated regarding their condition are able to build stronger therapeutic relationships and engage in SDM. Likewise, patients that are more active decision-makers are more likely to seek out education and adhere to their treatment plans.

We believe that the role carers play in the treatment of PLWS requires wider recognition. Carers can have positive and negative

TABLE 1 | Example questions, parameters, and solutions to consider when assessing the success of a patient's treatment.

Questions for the patient regarding their wellbeing and treatment	Parameters to consider for reviewing the treatment plan	Side effect/emergent condition to address	Possible solution
How have you been feeling since your last appointment? What activities have you been doing since we last met? Do you have any questions you would like to ask?	N/A	General adherence	Encourage patient empowerment
Have you experienced any problems since your last visit? (e.g., fever, rash, fatigue, etc.)	Blood count, electrocardiogram	Common or rare drug side effects	Revise therapy taking into consideration drug interactions, intolerance, and common or rare side effects
Have you noticed an increase in appetite or weight? Has this been a problem for you?	Body weight, waist circumference, body mass index (BMI), glycaemia, serum lipid profile	Metabolic syndrome	Prescribe an antipsychotic with less of an impact on metabolism/weight
Have you noticed any irregularity in your menstrual cycle (females only), any discharge of milk from your breast or breast enlargement (either sex), a reduction of sexual drive, or other dysfunctions related to your sexual life?	Prolactin levels	Hyperprolactin-emia	Prescribe a different antipsychotic or prescribe an additional agent to lower prolactin
Have you felt demotivated or indifferent more than usual? Has anyone noticed that you are less active or expressive than usual? Do you feel sad most of the time?	N/A	Secondary negative symptoms due to extrapyramidal side effects or depression	Switch to a second generation antipsychotic or treat depression separately
Do you feel clumsy or slowed-down in your movements or unbalanced when standing? Do you notice a tremor when resting?	Muscle stiffness	Drug-induced parkinsonism	Switch to a second generation antipsychotic with low potential to induce parkinsonism; add an anticholinergic drug
Have you been able to take your medications regularly or did you need to be prompted? Would you prefer another schedule? Would you feel more comfortable if we simplified your schedule?	N/A	Adherence	If preferred by PLWS or deemed important by the doctor, a switch to a long-acting injectable antipsychotic should be considered

influences on outcomes for PLWS, which is why choosing the right person to support PLWS is imperative. As clinicians, we can help guide conversations about who is the patient's primary carer and how much they are involved, while considering any socio-economic and cultural factors, but decisions around this should ultimately belong to the patient. Having a supportive, reliable, and engaged carer should be a key ambition for all those involved in treating PLWS.

There is an inherent challenge to creating sustained engagement with PLWS, due to the nature of schizophrenia itself. Many of the associated symptoms, including lack of insight, delusions, and social withdrawal, directly impede relationships and the desire to participate in decisions, ultimately presenting as significant therapeutic barriers. These barriers should not be seen as insurmountable, but rather factors that can be improved with PE and a focus on strong partnerships. Henceforth, the importance of individual empowerment obtained with psychosocial interventions integrated with psychopharmacological strategies should be emphasized, as this has been shown to most effectively improve patient outcomes.

This paper provides a review of the importance of therapeutic relationships and PE in the schizophrenia setting and how PLWS, clinicians and their carers need to construct a shared view relating to treatment options to increase adherence and improve outcomes. Interventions including PE can have a broad positive impact on clinical and social outcomes. We believe that future treatment can be enhanced by placing a greater emphasis on social interventions, and promoting specific training for clinicians in how to conduct difficult conversations involving delicate subject matters such as drug use.

In conclusion, we need to ensure that PLWS, carers and clinicians are properly equipped with the knowledge and skills to provide reciprocal support, increase the flow of communication, and allow PLWS to take greater ownership of their illness and its treatment.

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Association of Depression With Functional Mobility in Schizophrenia

Jiheon Kim[1†], Ji-Hyeon Shin[2†], Jeh-Kwang Ryu[3], Jae Hoon Jung[1], Chan-Hyung Kim[4], Hwa-Bock Lee[5], Do Hoon Kim[1], Sang-Kyu Lee[1] and Daeyoung Roh[1]*

[1] Mind-Neuromodulation Laboratory and Department of Psychiatry, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, South Korea, [2] Department of Otolaryngology-Head and Neck Surgery, College of Medicine, The Catholic University of Korea, Uijeongbu, South Korea, [3] Department of Physical Education, College of Education, Dongguk University, Seoul, South Korea, [4] Department of Psychiatry, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea, [5] Gwangmyeong Mental Health Welfare Center, Gwangmyeong, South Korea

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***Correspondence:**
Daeyoung Roh
omydoc@naver.com

[†]*These authors have contributed equally to this work and share first authorship*

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Background: Functional immobility can cause functional disability in patients with schizophrenia and has been linked to prognosis and mortality. Although depression might be a barrier for physical activity engagement, scarce data are present on the relationship between depression and functional mobility (FM) in schizophrenia. Thus, we aimed to investigate the associations among FM, depression, and other clinical correlates in individuals with schizophrenia.

Methods: FM was evaluated by the pedometer-assessed daily steps and Timed Up-and-Go (TUG) test in the daily-living and clinical settings, respectively. Psychiatric symptoms were assessed using the Beck Depression Inventory, Brief Psychiatric Rating Scale (BPRS), and State-Trait Anxiety Inventory. Cognitive function was evaluated using the Sternberg Working Memory (SWM) Task. Multiple regression analyses were performed to identify predictive factors associated with FM, with adjustment for relevant covariates.

Results: Sixty patients were enrolled in this study. Depression was the most consistent explanatory variable for both pedometer ($\beta = -0.34$, $p = 0.011$) and TUG time ($\beta = 0.32$, $p = 0.018$). Additionally, SWM accuracy ($\beta = -0.29$, $p = 0.018$), BPRS-Withdrawal ($\beta = 0.19$, $p = 0.139$), and fasting blood sugar ($\beta = 0.34$, $p = 0.008$) were associated with TUG time. However, psychotic symptoms and anxiety were not associated with pedometer and TUG.

Conclusions: We identified an association between depression and FM after adjusting for other disorder-related correlates in schizophrenia. Since the intervention goal is functional recovery, improving FM by treating depression may have considerable therapeutic value.

Keywords: schizophrenia, depression, functional mobility, pedometer, Timed Up-and-Go test

INTRODUCTION

Although psychotic symptoms are a key feature of schizophrenia, the most costly problem in this condition is significant functional disability (1). One of the main causes of functional disability in patients with schizophrenia is impairment in functional mobility (FM) (2). FM is the ability to move from one place to another independently in the environment (3) and requires complex physical processes such as walking, transferring, and turning (4). Because FM enables functional living, including the ability to perform activities of daily living (3), it is necessary to focus on FM in schizophrenia.

Multiple factors may contribute to the FM impairments in patients with schizophrenia, including chronic medical conditions (e.g., diabetes, obesity), sedentary behavior, physical inactivity, or side effects of antipsychotic drugs (5–9). There is also evidence showing that FM predicts overall health decline and disability in activities of daily living (10). Based on these studies, FM can be directly linked to the prognosis and mortality of schizophrenia in the long term. Therefore, in addition to examining the various health factors that may affect FM, it is also important to explore other factors that may affect FM.

One such factor is psychiatric symptoms. A cross-sectional study focusing on psychiatric symptoms found that positive psychotic symptoms were not associated with everyday functioning in patients with schizophrenia (11). In addition, some researchers have shown that the relationship between positive symptoms and FM is not clear (5, 12). These findings imply that patients may experience persistent disability in multiple functional domains even after remission of psychotic symptoms (13). Therefore, it is necessary to examine the effects of other psychiatric symptoms, such as depression, on FM in patients with schizophrenia.

Depressive symptoms in schizophrenia are not only prevalent in the prodromal active and remission phases, but also are militating against long-term recovery (14). Depression results in perceived functional disability and increases the need to utilize healthcare services (15). Furthermore, depression has been found to predict FM limitations (16), and Hirvensalo et al. (17) proposed that depression and FM may progress simultaneously and partially share etiology. Such findings suggest that depression plays an important role in the FM impairments in schizophrenia.

Stubbs et al. (18) have suggested that depressive symptoms might be a barrier for engaging in vigorous physical activity; however, there is still a lack of data on the relationship between depression and FM in schizophrenia. A pedometer or accelerometer can objectively measure physical activity-related mobility without interfering with the normal patterns of life (19, 20). These measurements have previously been applied to assess the mobility level related to physical activity in individuals with mobility limitations (20, 21).

However, such mobility-related activity measurements are limited in their ability to assess the complex physical processes of FM. Therefore, the Timed Up-and-Go (TUG) test (22), a simple, practical, and widely used clinical performance-based test, is often employed to measure FM (4). The psychometric properties of the TUG test have high inter-rater and test-retest reliability (22). Despite its apparent simplicity, the TUG test has the advantage of reflecting multiple components of FM, and thus can help predict the overall functional level of the patient's daily life (4). To our knowledge, only one prior study has administered the TUG test to patients with schizophrenia (5). In that study, the FM measured by the TUG test was associated with negative symptoms and neurocognition in 46 older adults with schizophrenia, but depressive symptoms were not measured. As such, studies evaluating the relationship between FM, as assessed with the both a pedometer and the TUG test, and depression in schizophrenia are needed.

In the present study, we aimed to investigate the relationships among FM, depression, and other clinical correlates in individuals with schizophrenia. FM was assessed with both a pedometer and the TUG test. The clinical correlates included psychiatric symptoms (depression, anxiety, and psychotic symptoms), psychological variables (quality of life, self-esteem), cognitive function (working memory), and other related clinical factors (diabetes, obesity, and antipsychotic drugs). We hypothesized that lower FM would be associated with higher depressive symptoms, regardless of other clinical correlates, in patients with schizophrenia.

METHODS

Participants and Design

A cross-sectional design was used to examine the hypothesis. All procedures were approved by the Investigational Review Board of Severance Mental Health Hospital (IRB#: YJI130702). All participants provided written informed consent.

Patients aged 18 to 60 with a primary diagnosis of schizophrenia or schizoaffective disorder were recruited *via* posters placed in local hospitals with psychiatric units and community mental health centers, and *via* advertisements in local newspapers. Some patients were also referred by other local health professionals. Participants were included if they had a diagnosis of schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual for Mental Disorders, 4th Edition, Text Revision. Face-to-face diagnostic interviews were conducted by a psychiatric/mental health nurse and a board-certified psychiatrist who reviewed the history, symptoms, and psychosocial function of each patient using all available sources of information, in accordance with DSM-IV-TR criteria. All participants were required to be on a stable dose and dosing regimen of antipsychotics for at least 4 weeks prior to assessment. Participants were excluded if they had participated in any exercise program within 3 months of study onset or displayed evidence of significant cardiovascular, neuromuscular, endocrine, or other somatic/substance use disorders that would prevent safe participation. Five of the recruited participants failed to meet the initial eligibility criteria, and thus, a total of 60 patients were included in the final analysis.

Sociodemographic and Clinical Information

Evaluation of all variables for each participant was performed on the same day within 2 weeks from screening date. Sociodemographic information (age, sex, years of education, duration of illness) and

baseline clinical data (antipsychotic dosing, use of typical antipsychotics, fasting blood sugar [FBS], body mass index) were collected.

Antipsychotic Dosing

To yield antipsychotic dosing, the prescribed daily dose (PDD) in milligrams was divided by the defined daily dose (DDD) to calculate a PDD : DDD ratio. DDD is defined as the assumed average daily maintenance dose for a drug used for its main indication in adults (23).

Psychiatric Symptoms

Psychiatric symptoms were determined *via* interviews and self-report questionnaires. Outcome measures for psychiatric symptoms included the Beck Depression Inventory (BDI), Brief Psychiatric Rating Scale (BPRS), and State and Trait Anxiety Inventory (STAI).

Beck Depression Inventory (BDI)

The BDI was used to assess depressive symptoms (24). The BDI is a 21-item self-report inventory that asks participants to choose the one statement that best describes their feelings during the past 2 weeks.

Brief Psychiatric Rating Scale (BPRS)

The BPRS is an 18-item, semi-structured introductory interview that is completed by the interviewer (25). Each item is rated on a scale from 0 to 6. Scores between 15 and 30 indicate minor symptoms, while those above 30 indicate major symptoms. The BPRS has following five subscales: Thought (items - grandiosity, hallucinations, unusual thought content, and conceptual disorganization), Withdrawal (items - disorientation, blunted affect, emotional withdrawal, and motor retardation), Anxiety and Depression (items—somatic concern, anxiety, depression, and guilt), Paranoid (items—hostility, suspicion, and uncooperativeness), and Excitement (items—tension, excitement, and mannerisms and posturing) (26).

State-Trait Anxiety Inventory (STAI)

The STAI is a self-rated instrument that contains two 20-item subscales for the measurement of anxiety (27). One scale measures state anxiety, while the other measures trait anxiety.

Psychological Variables

Psychological variables included the Rosenberg Self-Esteem Scale (RSES) and World Health Organization Quality of Life Scale (QOL).

Rosenberg Self-Esteem Scale (RSES)

RSES is a 4-point scale consisting of 10 questions, 5 positive and 5 negative self-esteem. The higher the score, the higher the degree of positive self-esteem (28).

2.4.2 World Health Organization Quality of Life Scale Abbreviated Version (WHOQOL-BREF)

The World Health Quality Assessment Instrument-100 (29) was revised by Min et al. (30) to develop the Korean version of WHOQOL-BREF. This is composed of a total of 24 items on the 5-point scale and higher score means higher quality of life.

Cognitive Function

Sternberg Working Memory (SWM) Task

The classic Sternberg Working Memory (SWM) task (31) was administered using Inquisit 5.0.13.0 (Millisecond Software, LLC, Seattle, WA, USA). Each trial of the task consisted of a set of two to five white digits presented in a sequence (1200 ms each). A yellow probe digit appeared 2500 ms after the last digit (maintenance period), at which point participants were required to press an appropriate button indicating whether the digit had been present in the previously displayed sequence. Participants were provided with visual feedback regarding the accuracy of their responses. Task sessions were divided into equally distributed "in" (probe present in the memory sequence) and "out" (probe not present in the memory sequence) trials (120 trials in total, preceded by 15 training trials).

Functional Mobility

Pedometer

A pedometer is an inexpensive and easy-to-use device that measures real-time physical activity by counting an individual's steps during daily life (19). Typical physical activity, such as walking, reflects the level of daily FM well (20), and walking has been shown to improve various aspects of FM (20). In brief, as walking is the most primary mode of physical activity, counting steps with a pedometer is useful for quantifying the level of FM (20). In the present study, The Yamax digiwalker SW-200 (Yamax Corporation, Tokyo, Japan) were used one time for two consecutive days. In order not to interfere with the daily life of research participants, we did not have any restrictions except to wear a pedometer in the waist.

Timed Up and Go (TUG) Test

In contrast to the pedometer, which mainly measures FM during daily living, the TUG test is a performance-based FM test that requires an individual to perform complex physical activities in a clinical setting (4, 32). The TUG test includes turning, transfers from sitting, and walking, and requires more functional movement (4). This study used the TUG test described by Podsiadlo and Richardson (22). The participants were asked to perform the TUG test at their own pace in a well-lit environment. For the TUG test, the participants were seated and were allowed to use the arms of the chair to help them stand up. During the test, the participants were observed and timed during all the time they stood up from a seated position in an arm chair, walked 3 m, turned around, walked back to the chair, and then returned to a seated position.

Statistical Analysis

Descriptive analyses of the sociodemographic and clinical variables were performed. Quantitative variables are described as the mean ± standard deviation and qualitative variables as the number and percentage. Multiple regression analyses were used to identify predictive factors associated with FM, with

adjustments for relevant covariates. After performing the correlation analyses to identify the associated factors, separate multivariate stepwise analyses were conducted, with either the TUG test or pedometer variable as the dependent variable, for FM. All analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL). Statistical significance was set at $p < 0.05$.

RESULTS

Correlation Analysis

Table 1 shows the descriptive statistics and correlations between the clinical characteristics and FM. The Pearson correlation coefficients showed that the pedometer values was the mean number of steps per day, which were significantly positively correlated with the RSES ($p = 0.033$) and QOL ($p = 0.047$) scores, but significantly negatively correlated with the BPRS-Total ($p = 0.038$) and BDI ($p = 0.011$) scores. In addition, the TUG test times were significantly positively correlated with FBS ($p = 0.031$), as well as with the BPRS-Withdrawal ($p = 0.008$), BDI ($p = 0.010$), and Trait Anxiety Inventory ($p = 0.026$) scores; however, the TUG test times were significantly negatively correlated with the SWM correct rate ($p = 0.011$).

Multiple Regression Analysis

Multivariate analyses were applied to determine which variables were closely related to the pedometer values and TUG test times after adjusting for other clinical correlates. Significantly associated variables, as determined by the univariate analyses, were included as independent variables. Separate stepwise multiple regression analyses for the pedometer and TUG test variables provided the following models. As shown in **Table 2**, after excluding the BPRS-Total, RSES, and QOL scores, the only significant predictor of the pedometer value was the BDI score, which accounted for 12% of the variance. According to **Table 3**, in the first step, the SWM correct rate, FBS, and BDI score were significant predictors of changes in the TUG test times, accounting for 36% of the variance. In the second step, the introduction of the BPRS-Withdrawal score increased this to 39%.

DISCUSSION

Previous research examining the relationship between FM and depression in patients with schizophrenia utilized tests that measured mobility during activities of daily living (e.g.,

TABLE 1 | Clinical characteristics and their relationships with functional mobility in people with schizophrenia ($N = 60$).

	Mean (SD) or %	Correlation with pedometer, steps/day	Correlation with Timed Up-and-Go, time (s)
Age	38.88 (10.08)	–0.15	0.25
Sex (Male)	58.30%	–0.25	0.10
Years of education	14.07 (2.96)	0.05	–0.05
Duration of illness	14.68 (10.15)	–0.20	0.10
PDD : DDD ratio	2.17 (0.98)	0.00	0.08
Typical antipsychotics use	91.66%	0.09	–0.03
FBS	106.20 (36.39)	0.01	0.30*
BMI	27.44 (5.18)	0.06	0.06
BPRS-Total	42.26 (15.94)	–0.28*	0.26
BPRS-Thought	7.04 (3.59)	–0.19	0.20
BPRS-Withdrawal	9.17 (4.02)	–0.24	0.36**
BPRS-Anxiety and Depression	7.91 (3.47)	–0.26	0.02
BPRS-Paranoid	5.85 (2.95)	–0.19	0.14
BPRS-Excitement	4.33 (2.14)	–0.26	0.12
BDI	17.61 (11.01)	–0.34*	0.36**
STA	45.61 (9.39)	–0.06	0.20
TRA	48.63 (10.30)	–0.22	0.31*
RSES	21.48 (3.84)	0.29*	–0.22
QOL	45.61 (10.13)	0.27*	–0.26
SWM latency time	2570.64 (1808.62)	–0.13	0.13
SWM correct rate (sec)	0.63 (0.21)	0.16	–0.35*

PDD, prescribed daily dose; DDD, defined daily dose; FBS, fasting blood sugar; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale, BDI, Beck Depression Inventory; STA, State Anxiety Inventory; TRA, Trait Anxiety Inventory; RSES, Rosenberg Self-Esteem Scale; QOL, Quality of Life Scale; SWM, Sternberg Working Memory.

**Significant at $p < 0.05$ (Pearson correlation, two-tailed); **Significant at $p < 0.01$ (Pearson correlation, two-tailed).*

TABLE 2 | Multivariable stepwise regression of the pedometer values (steps/day) in people with schizophrenia.

	Explanatory variables	Standardized coefficient		P	R^2	F
		(ß)	t			
Step 1	BDI	–0.34	–2.63	0.011	0.12	6.91 ($p < 0.01$)
Excluded variables	BPRS-Total		–1.11	0.272		
	RSES		1.61	0.113		
	QOL		1.23	0.226		

BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; RSES, Rosenberg Self-Esteem Scale; QOL, Quality of Life Scale.

TABLE 3 | Multivariable stepwise regression of Timed Up-and-Go test times (sec) in people with schizophrenia.

	Explanatory Variable	Standardized Coefficient		p	R^2	F
		(ß)	t			
Step 1	BDI	0.40	3.28	0.002	0.36	8.80 ($p < 0.001$)
	FBS	0.39	3.26	0.002		
	SWM correct rate	–0.28	–2.36	0.023		
Step 2	BDI	0.32	2.46	0.018	0.39	7.34 ($p < 0.001$)
	FBS	0.34	2.79	0.008		
	SWM correct rate	–0.29	–2.50	0.018		
	BPRS-Withdrawal	0.19	1.51	0.139		

BDI, Beck Depression Inventory; FBS, fasting blood sugar; SWM, Sternberg Working Memory; BPRS, Brief Psychiatric Rating Scale.

pedometer, accelerometer, self-report questionnaire) (18). To our knowledge, the present study is the first to investigate the effects of depression on FM, not only during daily living with a pedometer, but also in the clinical setting using the TUG test. Additionally, we examined the effects of other disorder-related correlates on FM, including psychiatric symptoms, cognitive function, psychological status, and health-related variables. The results demonstrate that depression is the best explanatory variable for both the pedometer and TUG test values. Further, working memory and FBS were associated with the TUG test.

The present findings suggest that depression may have the most consistent influence on FM, regardless of how FM is measured, in individuals with schizophrenia. However, it is unclear what mechanisms may underlie the effects of depression on FM. Depression can affect FM owing to a combination of psychological, behavioral, and physiological factors. Patients with depressive schizophrenia are more likely to have low motivation, poor self-efficacy, psychomotor retardation, a sedentary lifestyle, and a low level of volition than are patients with non-depressive schizophrenia (17, 33, 34). Furthermore, these clinical features could result in poorer performance of up and go movements or make such patients hesitant to participate in physical activity (17). In particular, our findings of significant associations between the TUG test times and low RSES and QOL scores, which are closely related to depressive symptoms, suggest that a combination of diverse components in depression can aggravate FM. Indeed, depression was found in 34% of older people with manifest FM limitation, which suggest that both conditions may progress simultaneously (17). This shared etiology also may interfere with the functional adaptation in particular chronic schizophrenia (5, 14, 18). Nevertheless, subsequent studies are needed to reveal the complex mechanisms underlying their relationship.

Similarly, the neurological mechanisms of depression and FM in schizophrenia have not been elucidated. However, based on a study of mainly older adults, the volume of subcortical white matter hyperintensities (WMHs) increases as depressive symptoms increase, leading to FM and functional impairments (35). White matter lesions in individuals with depression are closely related to smaller caudate and putamen volumes, which can lead to impairments in movement regulation and psychomotor retardation, respectively (36, 37). Although the results are inconsistent across studies, there is some evidence supporting the presence of cerebral WMHs in patients with schizophrenia (38). Thus, patients with depressive schizophrenia can be assumed to have weighted FM limitations. In addition, WMHs in schizophrenia have been found to be associated with cognitive function (38), which may partially explain the relationship we observed between the SWM scores and TUG test times in this study.

One difference in our findings was that while the TUG test times were associated with cognition and depression, the pedometer values were only associated with depression. This is because the two measures differ in the process and the setting during the test. The pedometer is mainly used to measure mobility-related physical activity during daily living, thus motivation is an important factor (32). In contrast, the TUG test requires the rapid completion of complex physical maneuvers in an experimental setting (4). In this clinical performance-based FM test, the individual needs to process and memorize environmental information while simultaneously performing physical movements (39, 40). It also requires the planning and initiation of a series of actions (5, 39, 40). In fact, using the TUG test, Leutwyler et al. (5) showed that in patients with schizophrenia, slower processing speed, which represents cognitive dysfunction, affects FM impairments. Thus, the TUG test is a more complicated process when compared to pedometer, and in particular, the transferring and tuning components of the TUG test might tax cognition (4).

Focusing on FBS, it is well known that patients with schizophrenia are vulnerable to diabetes, impaired glucose tolerance, and metabolic syndrome (6), but the association of these factors with FM is unknown. A recent cohort study by Åström et al. (41) in the elderly demonstrated that individuals with impaired glucose regulation and diabetes show reduced FM. According to Åström et al. (41), insulin resistance can increase protein degradation and decrease protein synthesis in skeletal muscle, resulting in poor physical performance. This pathology further exacerbates glucose regulation because skeletal muscle is important for glucose uptake. In addition, hyperglycemia-induced changes in neuronal structure are most likely to contribute to the myelination of brain, and lead to reduction in neural transmission (42). Furthermore, Kumar (43) have shown diabetes is associated with greater total brain atrophy and poor motor function, independent of depression. Taken together, FBS should be considered as a significant health related factor that could affect FM in patient with schizophrenia.

Both TUG test and pedometer are valid and reliable for quantifying FM that are expected to be useful in individuals with schizophrenia (22). Since TUG test needs only a stopwatch and a chair and is easy to understand, it is ideal for patients with schizophrenia. Also, TUG test reflects complex cognitive function and physical performance, even with simplicity and cost-effectiveness (4). Thus it will be useful for intervention or evaluation to recover functional disability for the patients with schizophrenia (5). Because sedentary behavior or physical inactivity, which causes disability, are characteristics seen by patients with schizophrenia, it is necessary to accurately measure their FM in daily life. In this respect, the pedometer has the advantage of being able to overcome the limitations of subjective self-reports and can easily measure and record the mobility-related physical activity in real time (19).

To date, interventions for patients with schizophrenia have focused exclusively on psychotic symptoms such as hallucinations and delusions, with little attention being paid to depression. Considering that schizophrenia is one of the most disabling illnesses (1), a more realistic intervention goal would be for the patient to recover real-world functioning, thereby allowing for independent living and social adjustment. Our findings, at least in part, suggest the possibility that the direct treatment of patients' depressive symptoms may improve their functional ability and quality of life by increasing their level of FM. Collectively, our results support that alleviating depression will have considerable therapeutic value for patients with schizophrenia.

There are some limitations in this study. First, although the TUG test used in this study has been used to assess FM in various clinical populations, this test has not yet been standardized for patients with schizophrenia. Second, the structured diagnostic tools were not used, but diagnostic verification was double-checked by two psychiatric practitioners. In addition, 30-item Positive and Negative Syndrome Scale (PANSS), could have provided more adequate representation of negative symptoms than BPRS. Third, since the sample size of this study was small and mainly included patients with chronic schizophrenia, our findings may not be fully generalizable to all patients with schizophrenia. Fourth, as the study was cross-sectional, no causal relationships could be established. Physical difficulties, like FM limitations, may have made patients feel more depressed. Lastly, this study did not examine the mechanisms underlying depression and FM. Nevertheless, this study demonstrated for the first time that the depression experienced by patients with schizophrenia may impair FM in both the experimental and daily-living settings based on robust and practical tests, including the TUG and pedometer assessments. Follow-up studies should evaluate the biopsychosocial mechanisms of the link between depression and FM.

CONCLUSIONS

The present study demonstrated a strong association between depression and FM after considering other clinical correlates in individuals with schizophrenia. Depressive symptoms were correlated with FM in both the daily-living and clinical settings, as measured with a pedometer and the TUG test, respectively. Additionally, memory and FBS were found to be partially associated with the TUG test. Because patients' actual therapeutic goal is functional recovery, improving FM by treating depression has significant clinical implications. Further studies to elucidate the mechanisms underlying the relationship between depression and FM and appropriate intervention studies to alleviate depression are needed.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

All procedures were approved by the Investigational Review Board of Severance Mental Health Hospital (IRB#: YJI130702). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DR designed the study and structured this manuscript. J-KR wrote the protocol of exercise programs. JJ, C-HK, and DK managed the literature searches and analyses (including the statistical analysis). H-BL and S-KL contributed to the interpretation of the results. J-HS and JK wrote the first draft of the manuscript. J-HS and JK managed and contributed equally the entire this study process. All authors contributed to the article and approved the submitted version.

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