

Proportion and predictors of remission and recovery in first-episode psychosis: Systematic review and meta-analysis

Review/Meta-analyses

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Abstract

Background. To determine the proportion of patients in symptomatic remission and recovery following a first-episode of psychosis (FEP).

Methods. A multistep literature search using the Web of Science database, Cochrane Central Register of Reviews, Ovid/PsychINFO, and trial registries from database inception to November 5, 2020, was performed. Cohort studies and randomized control trials (RCT) investigating the proportion of remission and recovery following a FEP were included. Two independent researchers searched, following PRISMA and MOOSE guidelines and using a PROSPERO protocol. We performed meta-analyses regarding the proportion of remission/recovery (symptomatic plus functional outcomes). Heterogeneity was measured employing Q statistics and I^2 test. To identify potential predictors, meta-regression analyses were conducted, as well as qualitative reporting of studies included in a systematic review. Sensitivity analyses were performed regarding different times of follow-up and type of studies.

Results. One hundred articles (82 cohorts and 18 RCTs) were included in the meta-analysis. The pooled proportion of symptomatic remission was 54% (95%CI [30, 49–58]) over a mean follow-up period of 43.57 months (SD = 51.82) in 76 studies. After excluding RCT from the sample, the proportion of remission remained similar (55%). The pooled proportion of recovery was 32% (95%CI [27–36]) over a mean follow-up period of 71.85 months (SD = 73.54) in 40 studies. After excluding RCT from the sample, the recovery proportion remained the same. No significant effect of any sociodemographic or clinical predictor was found.

Conclusions. Half of the patients are in symptomatic remission around 4 years after the FEP, while about a third show recovery after 5.5 years.

Introduction

After the first-episode of psychosis (FEP), the disorder can display a severe cognitive and behavioral decline that worsens symptoms and poor functioning [1,2]. Outcomes are highly influenced by early interventions' timing and efficacy, which can improve symptoms and restore social and occupational functioning [3–5]. Accumulated evidence indicates that the early years after a FEP are critical for remission and recovery in psychosis [4,6]. Over the past decade, the criteria of The Remission Schizophrenia Working Group (RSWG) have been adopted as a common measure of symptomatic remission in clinical studies [7,9]. According to the RSWG, symptomatic remission is defined based on a fixed threshold for symptom severity (only mild or absent symptoms) and a time component (sustained for at least 6 months) [10].

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While symptomatic remission can lead to recovery [10,11], the latter is more broadly conceived. Contrary to remission, recovery still lacks an accepted and validated definition [12]. There is consensus that symptomatic remission should be one of the components to be included in a definition of recovery [13]. Additionally, a consensus initiative suggested that improvement in independent living and in social and occupational/educational functioning for more than 1 year are core defining features of recovery [12].

Given the clinical relevance of symptomatic remission and recovery in FEP, considerable research has also been undertaken to identify their predictors. In a previous meta-analysis on FEP patients, 109 potential predictors of clinical outcomes were analyzed [14]. While this study concluded that medication nonadherence, longer duration of untreated psychosis (DUP), and substance misuse were core risk factors of relapse [14], no remission or recovery predictors were analyzed in FEP. Another meta-analysis [15] showed that cognitive deficits, concurrent remission and both positive and negative symptoms were predictors of recovery in FEP. However, in this meta-analysis, recovery was broadly defined by global or social functioning measures, for example, Global Assessment of Functioning (GAF), while changes in the severity of symptoms were not incorporated [15].

To our knowledge, four meta-analyses [15–18] and three systematic reviews have investigated symptomatic remission and recovery in FEP or schizophrenia [19–21]. Overall, these studies are limited by a variety of outcome definitions used [20], are heterogeneous with regard to individuals included in the analysis (first-episode or multi-episode) [17], included both prospective and retrospective studies and searched the literature only until 2016 [16].

The current systematic review and meta-analysis address the gaps mentioned above. We included prospective studies until 2020 with first-episode psychosis spectrum disorder participants with standardized definition of remission/recovery. The first aim of this study was to assess pooled proportion of symptomatic remission and recovery in FEP. The second aim was to identify potential predictors of remission and recovery in FEP.

Methods

This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA, Supplementary Table S1) [22] and Meta-analysis for Observational Studies in Epidemiology (MOOSE) guidelines (Supplementary Table S2) [23], following EQUATOR Reporting Guidelines [24]. The study protocol was registered on PROSPERO (CRD42020182080).

Search strategy and selection criteria

A systematic literature search was performed by two independent researchers (A.C., A.R.) using the following search terms: “predictor*” “response” OR “outcome” OR “prognosis” OR “response” OR “remission” OR “recovery” AND “psychosis” OR “schizophrenia” OR “schizophreniform” OR “first-episode psychosis” OR “early psychosis” AND “cohort” OR “case-control” OR “RCT” OR “clinical trial.” A search was conducted in the Web of Science (which includes Web of Science Core Collection, BIOSIS Citation Index, KCI—Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index), the Cochrane Central Register of Controlled Trials, and Ovid/ PsychINFO databases, from inception until November 5, 2020. We further searched references from included studies and reviews that

were screened during the literature search. Abstracts identified were then screened, and after excluding those that were not eligible, the full-text of the remaining articles were retrieved for further inspection against the inclusion and exclusion criteria.

We included: (a) prospective studies with a minimum follow-up of at least 6 months to detect remission or recovery. According to a recent meta-analysis [5], we operationalized remission in the current study as: (a) stability of symptoms and/or, (b) minimum symptom severity for at least 6 months according to the RSWG remission criteria [10], and (c) study-defined (see Supplementary Table S4 for details); and recovery as: (a) symptom stability/minimum severity plus improved social, educational or vocational attainment, (b) study-defined (for details see Supplementary Table S4), (c) FEP patients (including nonaffective psychosis see below), and (d) peer-reviewed original studies published in English. FEP was defined as having the first contact with healthcare services (both inpatient and outpatient settings), or less than 5 years of disorder [6] and operationalized criteria established by a clinical standard classification (Diagnostic and Statistical Manual [DSM], International Classification Disease [ICD] or Research Diagnostic Criteria [RDC] [25]). When studies were reporting overlapping samples for the meta-analyses, the study with the longest follow-up period was included. If this was unclear, studies with the largest sample were included.

Data extraction

Three researchers (J.V.-S., G.M., and B.P.) independently extracted data from all included studies, and any discrepancies were resolved by consensus or by a third author (G.S.P.). The variables extracted included: first author and year of publication, country, setting, topic investigated, diagnostic classification method (DSM, ICD, and RDC), sample size, age, gender, length of study follow-up, DUP, study design, baseline presence of comorbidity, predictors of remission or recovery, the proportion of FEP patients exposed to anti-psychotic treatment at baseline, the severity of baseline positive/negative/general psychotic symptoms (mean scores and SD), criteria used to define remission and recovery, quality assessment (see below). We extracted the primary outcomes, defined as the proportions of individuals with FEP who met the criteria for remission or recovery (at each follow-up time point: 6–<12 months; $\geq 12 - < 24$ months; $\geq 24 - < 36$ months; and ≥ 36 months).

Risk of bias (quality assessment)

Risk of bias was assessed using a modified version of the Newcastle–Ottawa Scale for case-control studies (Supplementary Table S3) and cohorts. Studies were awarded a maximum of eight points on items related to representativeness, sample size, group definition, validity, outcomes and representativeness, exposure, outcomes, follow-up period and loss to follow-up for cohort studies. The risk of bias assessment was conducted independently by two researchers (J.V.-S., G.S.P.). In cases of disagreement, a consensus was reached through discussion and, when not possible, to obtain consensus, a third researcher (A.C.) was included in the process.

Strategy for data synthesis

Specific meta-analyses were: (a) proportion of remission and (b) recovery. Since heterogeneity was expected to be high, the random-effect model was employed [26]. Heterogeneity among studies was assessed using Q statistics, with the proportion of the total variability in effect size estimates evaluated using the I^2 index

(with an $I^2 > 50\%$ representing significant heterogeneity) [27]. Publication biases were assessed for the proportion of remission or recovery by inspecting funnel plots and assessing Egger's test [28]. Sensitivity analyses were performed to determinate the differences depending on whether the RSWG criteria were used to define remission or other broader definition was used; types of included studies (cohorts, case-control study, RCTs), and length of the follow-up period. In line with our hypotheses, we also performed (c) meta-regressions to estimate the association between potential predictors and remission and recovery proportions separately when data from at least 10 studies were available. The predictors included clinical variables (e.g., the severity of baseline positive/negative/general psychotic symptoms at baseline, DUP), sociodemographic variables (e.g., age and gender), percentage of FEP under antipsychotic treatment at baseline, length of follow-up, and NOS quality assessment. All analyses were conducted using STATA version 16 [29]. The significance level was set at a $p < 0.05$, two-sided.

We also provided a systematic narrative synthesis of the included studies around predictors of remission/recovery (supplementary results).

Results

Characteristics of the included studies

Of 7267 articles identified, 100 (RCTs $k = 18$, observational studies $k = 82$) studies were included in the meta-analysis ($n = 25375$ FEP individuals; Figure 1). The studies' sample size ranged from 16 to 2960; the mean age of included participants was 26.18 (SD = 3.93) years, and 67.8% of the sample was male in no overlapping samples. The characteristics of the included studies are detailed in Supplementary Tables S5 and S6.

Details of the operationalization criteria for remission and recovery are listed in Supplementary Tables S4 and S5. Most studies ($N = 43$, 57.33%) employed the RSWG criteria [10] to define remission: having mild or absent symptoms (symptom severity criteria) for at least 6 months (duration criteria). The remaining studies (42.66%) employed broader operational remission criteria to define significant symptomatic remission (24.14% of the studies using more than one instrument, see Supplementary Table S5) with no duration criteria.

Recovery was operationalized as symptomatic remission (16 studies [39.02%]) using the RSWG criteria, and 24 studies [60.97%] using broader remission criteria as described above) and significant improvement in functioning. Functional improvement involved the following domains: functioning status (19 studies, 46.34%), living independently (13 studies, 31.71%), working or studying (21 studies, 51.23%), and social interactions (9 studies, 21.95%).

Forty-two studies described predictors of remission (Supplementary Table S7) and 28 studies described predictors of recovery (Supplementary Table S8). The most studied predictors were sociodemographic and clinical variables.

Meta-analyses

Remission

We found 76 studies reporting on remission (RCTs $k = 15$, observational studies $k = 59$) (N FEP = 18528, Supplementary Table S5). The total remission proportion was 54% (95%CI [30, 49–58]; I^2 : 97.86%, $z = 21.63$; Supplementary Figure S1) with a mean follow-up

of 43.57 months (SD = 51.82; range = 6–240). Significant heterogeneity was found between studies (Supplementary Figure S3), but no significant publication bias (Egger's test $p = 0.79$).

Forty-two studies described predictors of remission (Supplementary Table S7). A systematic narrative synthesis of these studies is provided in supplementary results.

Recovery

We analyzed 40 articles with data reporting on recovery (RCTs $k = 5$, observational studies $k = 35$) (N FEP = 15064, Supplementary Table S6). A detailed description of the recovery definition used in these studies is shown in Supplementary Table S6. The total recovery proportion was 32% (95%CI [27–36]; $I^2 = 97.31\%$, $z = 13.17$; Supplementary Figure S2) with a mean follow-up of 71.85 months (SD = 73.54; range = 6–300). Publication bias for small studies was found (Egger's test $p = 0.02$; Supplementary Figure S4).

Twenty-eight studies described predictors of recovery (Supplementary Table S8). A systematic narrative synthesis of these studies is provided in supplementary results.

Sensitivity analyses

Sensitivity analyses were performed considering the duration of the follow-up period (Figure 2), the definition of remission (RSWG criteria [10] versus broader remission criteria), and the type of study (cohorts, case-controls, and RCT).

Sensitivity analysis on follow-up period showed that the remission proportion was slightly reduced with the longer duration of the follow-up (Figure 2). Depending on which remission criteria were applied, the proportion of remission varies (RSWG remission criteria: $k = 39$; 52% (95%CI [30,46–58]); broader remission criteria with no duration criteria: $k = 37$; 56% (95% CI [30,49–62]). After excluding 15 RCTs from the analysis, the remission proportion was 55%, 95%CI [30, 50–60] (I^2 : 97.93%, $z = 19.58$).

Regarding recovery, sensitivity analysis on follow-up period showed that the recovery proportion slightly increased the longer the duration of the follow-up (Figure 2). A sensitivity analysis of studies reporting recovery after ≥ 2 years and recovery at < 2 years were performed [30]. Six studies assessed recovery status after more than 2 years (38%; 95%CI [30, 19–56]), while 34 studies assessed recovery proportion in less than 2 years (30%; 95%CI [26–35]). After exclusion of RCT, the recovery proportion was similar to the pooled proportion (32%, 95%CI [27–37]).

Meta-regressions

The effect of different predictors of remission proportion is shown in Table 1. None of the predictors studied had a significant effect on remission. The meta-regression analyses showed that the proportion of patients in recovery was moderated by male sex ($\beta = 0.006$; 95%CI [0.0003,0.0117], $p = 0.04$, $R^2 = 10.71$) and by positive symptoms ($\beta = 0.0126$; 95%CI [0.0041,0.0207], $p = 0.002$, $R^2 = 57.22$; Table 2). These associations did not survive multiple comparison corrections ($p < 0.002$).

Quality assessment

The quality rating of the studies ranged from 2 to 7 (mean = 4.95; median = 5) on a modified version of the Newcastle–Ottawa scale (Supplementary Table S3).

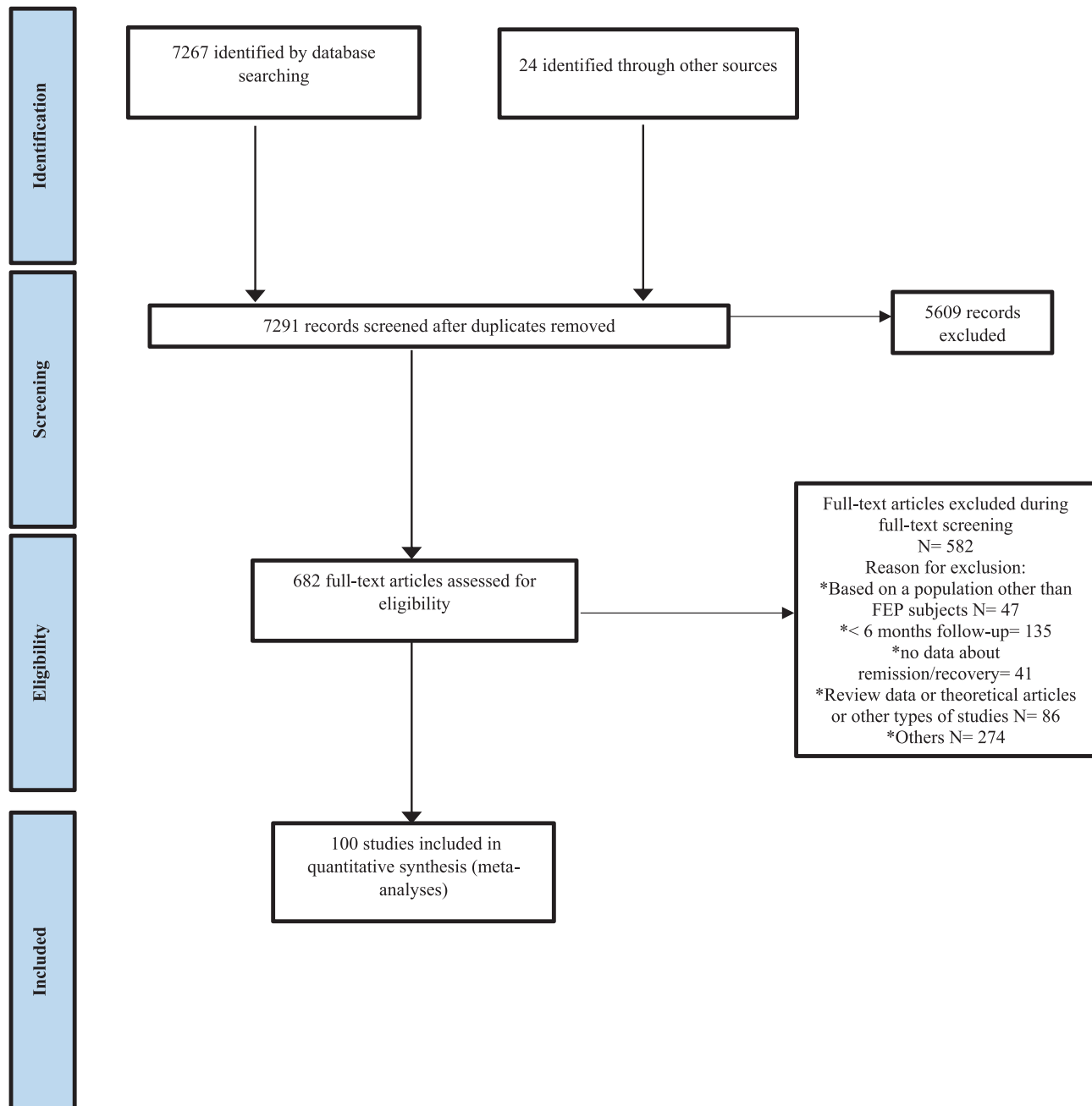


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart outlining the study selection process.

Discussion

To our knowledge, this is the largest systematic review of studies of remission and recovery in psychosis conducted to date. We found that more than half of the patients (54%) achieved remission 4 years after the first-episode, while around a third were in recovery after 5.5 years (32%). The most studied predictors of remission and recovery were clinical and sociodemographic variables.

Our results are consistent with those of a previous meta-analysis [16], although the proportion of remission and recovery is nominally lower (54 vs. 58% for remission and 32 vs. 38% for recovery). Another systematic review in FEP showed “good” outcomes for 42% of patients with psychosis and 31% of patients with

schizophrenia [20], while a more recent systematic review of remission identified a remission proportion of 40% (range 17–78%) in FEP patients [19].

The current study has several advantages compared to previous reviews: the inclusion of RCT studies, inclusion of only prospective designs, and all studies reporting measures of recovery were classified. Additionally, we included more studies using the RSWG remission criteria ($N = 43$ compared to $N = 25$) [16].

Without antipsychotic treatments, most FEP cases display frequent poor outcomes [4,31]. However, with antipsychotic treatment, one study showed that remission was achieved by 70% of FEP patients after 6 months [13], while another study showed that 74% were in remission after approximately 9 months [32]. This meta-analysis

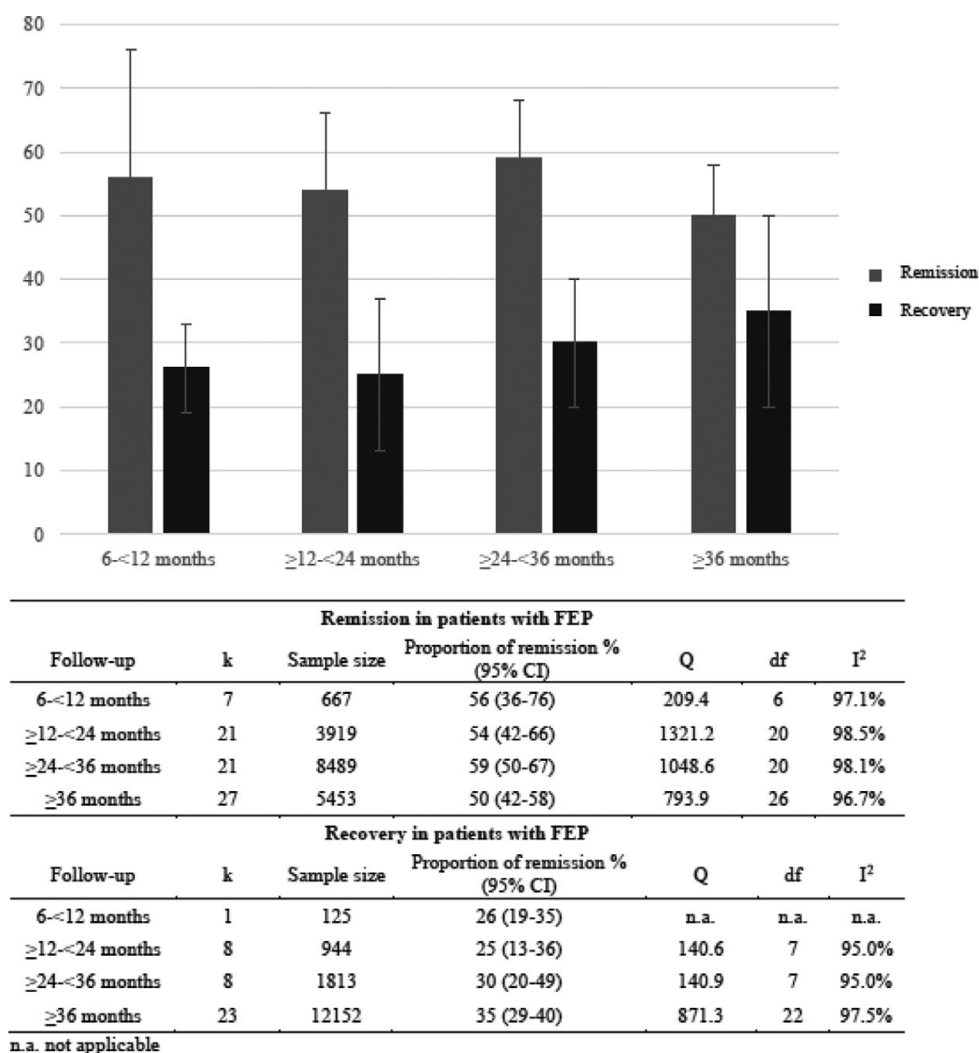


Figure 2. Meta-analytic symptomatic remission and recovery proportion in first-episode of psychosis (FEP) over time.

Table 1. Meta-regressions, effect of predictors on remission.

Name of predictor	N studies	β	95% CI	p	R ²
Follow-up (months)	76	-0.0004	[-0.0013, 0.0004]	0.270	0.24
NOS quality assessment	76	0.0179	[-0.0191, -0.0549]	0.343	<0.01
DUP median months	19	0.0004	[-0.0023, 0.0031]	0.767	<0.01
DUP mean months	29	-0.0031	[-0.0077, 0.0015]	0.189	2.81
Schizophrenia-spectrum diagnosis %	61	0.0004	[-0.0022, 0.0030]	0.763	<0.01
Sex male %	59	0.0013	[-0.0023, 0.005]	0.475	<0.01
Age	72	-0.0029	[-0.0138, 0.0079]	0.601	<0.01
Ethnicity Caucasian %	18	-0.0018	[-0.0058, 0.0022]	0.373	<0.01
Baseline positive symptoms PANSS	28	-0.0025	[-0.0155, 0.0105]	0.708	<0.01
Baseline negative symptoms PANSS	28	0.0042	[-0.0139, 0.0224]	0.645	<0.01
Functioning GAF	28	-0.0051	[-0.0119, 0.0016]	0.139	4.80
AP treatment baseline %	24	-0.0005	[-0.0027, -0.0018]	0.684	<0.01

Note: $p < 0.002$, after correction for multiple comparisons.

Abbreviations: DUP, duration of untreated psychosis; NOS, Newcastle-Ottawa Scale.

Table 2. Meta-regressions, effect of predictors on recovery.

Name of predictor	N studies	β	95% CI	<i>p</i>	R^2
Follow-up (months)	40	0.0004	[-0.0004, 0.0012]	0.297	0.51
NOS quality assessment	40	-0.0196	[-0.0802, 0.0410]	0.527	0.00
DUP median weeks	11	-0.001	[-0.0032, 0.0032]	0.368	0.00
DUP mean weeks	12	-0.0022	[-0.0101, 0.0057]	0.59	0.00
Schizophrenia-spectrum diagnosis %	21	-0.0025	[-0.0058, 0.0007]	0.130	7.75
Sex male %	31	0.006	[-0.0003, 0.0117]	0.040	10.71
Age	36	-0.0023	[-0.0173, 0.018]	0.768	0.00
Baseline positive symptoms PANSS	11	0.0126	[0.0041, 0.0207]	0.002	57.22
Baseline negative symptoms PANSS	12	-0.0037	[-0.0194, 0.012]	0.644	0.00
Functioning GAF	17	0.0014	[-0.0109, 0.0139]	0.817	0.00

Note: $p < 0.002$, after correction for multiple comparisons.

Abbreviations: DUP, duration of untreated psychosis; NOS, Newcastle-Ottawa Scale.

highlights that the remission proportion could be lower than previously reported.

As we expected, the remission proportion decreased over time (56–50%, Figure 2), as relapse after a FEP is common [33], while the recovery proportion increased (26–35%). This could partially be explained by the fact that recovery involved other social and functioning goals, which require more time to be achieved [34]. Although a high proportion of patients can achieve remission in the short-term [16], only a minority of them get the full recovery in the long-term [35].

The most recent systematic review and meta-analysis of recovery showed a pooled proportion of 38% in FEP patients [16], and an earlier systematic review and meta-analysis revealed that only 13.5% of patients with schizophrenia met the criteria for recovery [17]. While the most recent systematic review and meta-analysis completed the literature search in 2016, yielding 3021 studies [16], the current study provides a more comprehensive, up to date overview of the literature on remission and recovery (current search yielded 7267 studies).

After excluding RCTs from the analyses, we showed that the remission and recovery proportion rates remained the same. This is surprising given the sample biases generally attributed to RCTs [36] (e.g., RCTs usually include adherent participants with no drug abuse or suicidal ideation). Observational studies could be overrepresented in the meta-analysis. Besides, the cohort studies also used active treatments, including early intervention programs [37–39].

While we did not find any predictors associated with remission, two were associated with recovery, namely male sex and positive symptoms. Previous studies did not find gender differences in the prognosis of psychosis after a FEP [40,41]. The association between higher scores of positive symptoms and increased recovery proportion may be related to the intrinsic heterogeneity of FEP cohorts. However, it is important to note that both the association with male sex and positive symptoms did not survive multiple comparison corrections and need to be investigated in future studies to draw meaningful clinical conclusions. Different negative psychotic symptoms trajectories in FEP patients have been described [42]. Negative psychotic symptoms are generally linked to worse outcomes in FEP [43]. However, only a small proportion of FEP subjects present a high level of persistent negative symptoms [44];

therefore, this effect could be underestimated in large samples of FEP.

Although there is extensive literature [45–48] reporting that DUP is related to a worse prognosis in patients with psychosis, we did not find such an association. Several studies suggest that the relationship between DUP and prognosis is based on other factors [49,50], such as positive symptoms. In line with our findings, a recent systematic review investigating remission/recovery proportion also did not find a relationship between DUP and better outcomes in psychosis [16], which could also be related to some inaccuracy in defining or measuring DUP. However, a recent umbrella review described suggestive evidence for a relationship between longer DUP and lower chance of remission and poorer functioning [51], but this result could be affected by lead-time bias, and thus, DUP would not be an important predictor of the outcomes and it could be more an indicator of illness stage [52].

The proportion of recovery in FEP is dramatically low. As an extended concept of remission, recovery has attracted interest as a desirable outcome in psychosis. It usually comprises symptomatic remission as a basic condition and functional improvements in vocational perspectives, independent living and social functioning [34,53]. Thus, recovery is a more complex concept than remission [30,54]. Unlike symptomatic remission, recovery encompasses multiple aspects of the patient's life, including functioning and making it difficult to settle on a standard definition and develop reliable assessment criteria. Some clinicians think recovery can only be achieved when symptoms are mild or absent and remain that way for a prolonged time to not interfere with normal functioning in social activities and relationships [55]. Additionally, social and family circumstances, opportunities, and lifetime events contribute to extending the list of environmental factors that may influence recovery beyond clinical manifestations of schizophrenia [56,57]. The lack of a clear definition and assessment tools prevents from drawing strong conclusions regarding the feasibility of a therapeutic model based on the concept of recovery. However, empirical evidence on various therapeutic interventions suggests that many patients with schizophrenia can achieve recovery goals such as independent living and competitive employment and education in routine community settings [58]. Symptomatic recovery and functional recovery are different aspects that should be clearly differentiated to facilitate comparison between studies. Symptom

and functional illness trajectories are independent, with some studies reporting lower functional recovery rates than symptomatic recovery rates [59]. This might suggest that these outcomes are likely to be influenced by different predictor variables and thus needing to be treated by different interventions. Researchers have combined commonly used scales such as the Global Assessment Functioning (GAF) scale and other objective indicators of lifetime achievements [60,61]. Despite the lack of a well-defined concept of recovery, some authors identified a trend toward a common archetype of the definition and factors associated with recovery and its applicability in clinical practice and clinical research [62].

In most cases, symptomatic remission is a prerequisite for recovery [63–66], so it might not be surprising that the recovery proportion is lower than those for remission [10]. Although the RSWG criteria to operationalize remission are widely used [9, 67–70], some studies used criteria for symptoms severity without applying a duration criterion [71], while other studies have used other outcome measures (e.g., CGI-S) [72].

Limitations and strengths

This study includes a large sample of FEP and analyzed the proportion of remission and recovery. The main limitation of this study is the lack of operationalized definitions for recovery. Remission was operationalized in 2005 [10], and the majority of included studies used the RSWG criteria. However, there are other studies that applied broader remission criteria [63,73,74]. The definition of recovery is even more complicated. Some of the studies we examined used definitions that included functional remission [64,65] while others used much more exigent definitions, including having work and a relationship with a peer [14]. Some authors did not report the proportion of drop-out, the treatment used, premorbid adjustment, age of psychosis onset, or comorbidity in their samples which limited our set of different predictors being analyzed. In most studies, there was no information on the proportion of patients who met the remission or recovery criteria during the whole follow-up, limiting the final remission/recovery proportion. Moreover, psychosis is a long-term chronic disorder with negative outcomes frequently evolving over the whole lifetime [17]. A minor proportion of studies included a follow-up after 10 years which could impact remission/recovery rates and overestimate these rates for a subgroup of patients. Therefore, we conducted subgroup and meta-regression analyses to explore potential sources of heterogeneity. We showed that the main findings largely remained the same.

Conclusions

This is the most up to date meta-analysis of remission and recovery proportion, and predictors of both outcomes in people with FEP. We showed that around half of patients with FEP reached symptomatic remission after 4 years, and about a third were in recovery after 5.5 years. Remission and recovery rates in FEP subjects remain low, indicating that more than half of patients do not achieve remission, and two-thirds do not achieve recovery at long-term follow-up. The early intervention services should implement strategies to improve long-term outcomes and detect patients who can benefit more from intensive care.

Supplementary Materials. To view supplementary material for this article, please visit <http://dx.doi.org/10.1192/j.eurpsy.2021.2246>.

Data Availability Statement. The data that support the findings of this study are available from the corresponding author, A.C., upon request.

Author Contributions. Conceptualization: A.C., M.S., P.G., P.M., P.F.-P.; Data curation: A.C., A.R., J.V.-S., G.M., B.P., P.F.-P.; Formal analysis: A.C., J.V.-S., G.M., B.P., P.G., P.M., P.F.-P.; Investigation: A.C., J.V.-S., B.P.; Methodology: A.C., A.R., J.V.-S., G.M., C.A., P.G.; Supervision: C.A., M.S., P.M., P.F.-P.; Validation: G.M., C.A., M.S.; Writing—original draft: A.C., A.R., J.V.-S., G.M., B.P., P.G., P.M., P.F.-P.; Writing—review and editing: A.C., A.R., C.A., M.S., P.M., P.F.-P.

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References

- [1] Lieberman JA. Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. *Biol Psychiatry*. 1999;46:729–39.
- [2] DeLisi LE. The concept of progressive brain change in schizophrenia: implications for understanding schizophrenia. *Schizophr Bull*. 2008;34:312–21.
- [3] Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. *Schizophr Bull*. 2013;39:1363–72.
- [4] Fusar-Poli P, McGorry PD, Kane JM. Improving outcomes of first-episode psychosis: an overview. *World Psychiatry*. 2017;16:251–65.
- [5] Correll CU, Galling B, Pawar A, Krivko A, Bonetto C, Ruggeri M, et al. Comparison of early intervention services vs treatment as usual for early-phase psychosis: a systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry*. 2018;75:555–65.
- [6] Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl*. 1998;172:53–9.
- [7] Barrio P, Batalla A, Castellvi P, Hidalgo D, Garcia M, Ortiz A, et al. Effectiveness of long-acting injectable risperidone versus oral antipsychotics in the treatment of recent-onset schizophrenia: a case-control study. *Int Clin Psychopharmacol*. 2013;28:164–70.
- [8] Chang WC, Tang JYM, Hui CLM, Wong GHY, Chan SKW, Lee EHM, et al. The relationship of early premorbid adjustment with negative symptoms and cognitive functions in first-episode schizophrenia: a prospective three-year follow-up study. *Psychiatry Res*. 2013;209:353–60.
- [9] Kaminga AC, Dai W, Liu A, Myaba J, Banda R, Wen SW, et al. Rate of and time to symptomatic remission in first-episode psychosis in northern Malawi: a STROBE-compliant article. *Medicine (Baltimore)*. 2018;97:e13078.
- [10] Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatr*. 2005;162:441–9.
- [11] Dazzan P, Lappin JM, Heslin M, Donoghue K, Lomas B, Reininghaus U, et al. Symptom remission at 12-weeks strongly predicts long-term recovery from the first episode of psychosis. *Psychol Med*. 2020;50:1452–62.
- [12] Kane JA, Leucht S, Carpenter D, Docherty JP. Expert consensus guideline series - optimizing pharmacologic treatment of psychotic disorders - introduction: methods, commentary, and summary. *J Clin Psychiatry*. 2003;64:5–97.
- [13] Phahladira L, Luckhoff HK, Asmal L, Kilian S, Scheffler F, Plessis SD, et al. Early recovery in the first 24 months of treatment in first-episode schizophrenia-spectrum disorders. *NPJ Schizophr*. 2020;6:2.
- [14] Alvarez-Jimenez M, Priede A, Hetrick SE, Bendall S, Killackey E, Parker AG, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. *Schizophr Res*. 2012;139:116–28.
- [15] Santesteban-Echarri O, Paino M, Rice S, Gonzalez-Blanch C, McGorry P, Gleeson J, et al. Predictors of functional recovery in first-episode psychosis: a systematic review and meta-analysis of longitudinal studies. *Clin Psychol Rev*. 2017;58:59–75.

- [16] Lally J, Ajnakina O, Stubbs B, Cullinane M, Murphy KC, Gaughran F, et al. Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. *Br J Psychiatry*. 2017;211:350–8.
- [17] Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull*. 2013;39:1296–306.
- [18] Hegarty JD, Baldessarini RJ, Tohen M, Wateraux C, Oepen G. 100 years of schizophrenia - a metaanalysis of the outcome literature. *Am J Psychiatr*. 1994;151:1409–16.
- [19] AlAqeel B, Margolese HC. Remission in schizophrenia: critical and systematic review. *Harv Rev Psychiatry*. 2012;20:281–97.
- [20] Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med*. 2006;36:1349–62.
- [21] Warner R. Recovery from schizophrenia and the recovery model. *Curr Opin Psychiatry*. 2009;22:374–80.
- [22] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006–12.
- [23] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–12.
- [24] Altman DG, Simera I, Hoey J, Moher D, Schulz K. EQUATOR: reporting guidelines for health research. *Lancet*. 2008;371:1149–50.
- [25] Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978;35:773–82.
- [26] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–88.
- [27] Lipsey M, Wilson D. *Practical meta-analysis*; 2000.
- [28] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–34.
- [29] StataCorp. *Stata statistical software: release 16*. College Station, TX: StataCorp LLC; 2019.
- [30] Liberman RP, Kopelowicz A. Recovery from schizophrenia: a concept in search of research. *Psychiatr Serv*. 2005;56:735–42.
- [31] Fusar-Poli P, Cappucciati M, Bonoldi I, Hui LM, Rutigliano G, Stahl DR, et al. Prognosis of brief psychotic episodes: a meta-analysis. *JAMA Psychiatry*. 2016;73:211–20.
- [32] Lieberman J, Jody D, Geisler S, Alvir J, Loebel A, Szymanski S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. *Arch Gen Psychiatry*. 1993;50:369–76.
- [33] Berge D, Mane A, Salgado P, Cortizo R, Garnier C, Gomez L, et al. Predictors of relapse and functioning in first-episode psychosis: a two-year follow-up study. *Psychiatr Serv*. 2016;67:227–33.
- [34] Vita A, Barlati S. Recovery from schizophrenia: Is it possible?. *Curr Opin Psychiatry*. 2018;31:246–55.
- [35] Lappin JM, Heslin M, Lomas B, Jones PB, Doody GA, Reininghaus UA, et al. Early sustained recovery following first episode psychosis: evidence from the AESOP10 follow-up study. *Schizophr Res*. 2018;199:341–5.
- [36] Essock SM, Drake RE, Frank RG, McGuire TG. Randomized controlled trials in evidence-based mental health care: getting the right answer to the right question. *Schizophr Bull*. 2003;29:115–23.
- [37] Tempier R, Balbuena L, Lepnum M, Craig TKJ. Perceived emotional support in remission: results from an 18-month follow-up of patients with early episode psychosis. *Soc Psychiatry Psychiatr Epidemiol*. 2013;48:1897–904.
- [38] Mustafa S, Joober R, Lepage M, Iyer S, Shah J, Malla A. Predictors of ‘all-cause discontinuation’ of initial oral antipsychotic medication in first episode psychosis. *Schizophr Res*. 2018;201:287–93.
- [39] Wade D, Harrigan S, Edwards J, Burgess PM, Whelan G, McGorry PD. Substance misuse in first-episode psychosis: 15-month prospective follow-up study. *Br J Psychiatry*. 2006;189:229–34.
- [40] Segarra R, Ojeda N, Zabala A, Garcia J, Catalan A, Eguiluz JI, et al. Similarities in early course among men and women with a first episode of schizophrenia and schizophreniform disorder. *Eur Arch Psychiatry Clin Neurosci*. 2012;262:95–105.
- [41] Sommer IE, Tiihonen J, van Mourik A, Tanskanen A, Taipale H. The clinical course of schizophrenia in women and men—a nation-wide cohort study. *NPJ Schizophr*. 2020;6:12.
- [42] Gee B, Hodgekins J, Fowler D, Marshall M, Everard L, Lester H, et al. The course of negative symptom in first episode psychosis and the relationship with social recovery. *Schizophr Res*. 2016;174:165–71.
- [43] Wunderink L, van Bebber J, Sytema S, Boonstra N, Meijer RR, Wigman JTW. Negative symptoms predict high relapse rates and both predict less favorable functional outcome in first episode psychosis, independent of treatment strategy. *Schizophr Res*. 2020;216:192–9.
- [44] Hovington CL, Bodnar M, Joober R, Malla AK, Lepage M. Identifying persistent negative symptoms in first episode psychosis. *BMC Psychiatry*. 2012;12:224.
- [45] Penttilä M, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2014;205:88–94.
- [46] Farooq S, Large M, Nielsen O, Waheed W. The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: a systematic review and meta analysis. *Schizophr Res*. 2009;109:15–23.
- [47] Stentebjerg-Olesen M, Pagsberg AK, Fink-Jensen A, Correll CU, Jeppesen P. Clinical characteristics and predictors of outcome of schizophrenia-spectrum psychosis in children and adolescents: a systematic review. *J Child Adolesc Psychopharmacol*. 2016;26:410–27.
- [48] Drake RJ, Husain N, Marshall M, Lewis SW, Tomenson B, Chaudhry IB, et al. Effect of delaying treatment of first-episode psychosis on symptoms and social outcomes: a longitudinal analysis and modelling study. *Lancet Psychiatry*. 2020;7:602–10.
- [49] Ho BC, Andreasen NC. Long delays in seeking treatment for schizophrenia. *Lancet*. 2001;357:898–900.
- [50] Norman RM, Malla AK. Duration of untreated psychosis: a critical examination of the concept and its importance. *Psychol Med*. 2001;31:381–400.
- [51] Howes OD, Whitehurst T, Shatalina E, Townsend L, Onwordi EC, Mak TLA, et al. The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. *World Psychiatry*. 2021;20:75–95.
- [52] Jonas KG, Fochtmann LJ, Perlman G, Tian Y, Kane JM, Bromet EJ, et al. Lead-time bias confounds association between duration of untreated psychosis and illness course in schizophrenia. *Am J Psychiatry*. 2020;177:327–34.
- [53] Spellmann I, Schennach R, Seemueller F, Meyer S, Musil R, Jaeger M, et al. Validity of remission and recovery criteria for schizophrenia and major depression: comparison of the results of two one-year follow-up naturalistic studies. *Eur Arch Psychiatry Clin Neurosci*. 2017;267:303–13.
- [54] Corrigan PW. Recovery from schizophrenia and the role of evidence-based psychosocial interventions. *Expert Rev Neurother*. 2006;6:993–1004.
- [55] Lieberman RP. Recovery from schizophrenia: form follows functioning. *World Psychiatry*. 2012;11:161–2.
- [56] Lieberman RP, Kopelowicz A, Ventura J, Gutkind D. Operational criteria and factors related to recovery from schizophrenia. *Int Rev Psychiatry*. 2002;14:256–72.
- [57] Onken SJ, Craig CM, Ridgway P, Ralph RO, Cook JA. An analysis of the definitions and elements of recovery: a review of the literature. *Psychiatr Rehabil J*. 2007;31:9–22.
- [58] Bond GR, Drake RE, Becker DR. An update on randomized controlled trials of evidence-based supported employment. *Psychiatr Rehabil J*. 2008;31:280–90.
- [59] Ventura J, Subotnik KL, Guzik LH, Helleman GS, Gitlin MJ, Wood RC, et al. Remission and recovery during the first outpatient year of the early course of schizophrenia. *Schizophr Res*. 2011;132:18–23.
- [60] Torgalsbøen AK, Rund BR. Lessons learned from three studies of recovery from schizophrenia. *Int Rev Psychiatry*. 2002;14:312–7.
- [61] Giraud-Baro E, Dassa D, De Vathaire F, Garay RP, Obeid J. Schizophrenia-spectrum patients treated with long-acting injectable risperidone in real-life clinical settings: functional recovery in remitted versus stable, non-remitted patients (the EVerEST prospective observational cohort study). *BMC Psychiatry*. 2016;16:8.

- [62] Lahera G, Galvez JL, Sanchez P, Martinez-Roig M, Perez-Fuster JV, Garcia-Portilla P, et al. Functional recovery in patients with schizophrenia: recommendations from a panel of experts. *BMC Psychiatry*. 2018;18:176.
- [63] Ajnakina O, Trotta A, Di Forti M, Stilo SA, Kolliakou A, Gardner-Sood P, et al. Different types of childhood adversity and 5-year outcomes in a longitudinal cohort of first-episode psychosis patients. *Psychiatry Res*. 2018;269:199–206.
- [64] Austin SF, Mors O, Secher RG, Hjorthoj CR, Albert N, Bertelsen M, et al. Predictors of recovery in first episode psychosis: the OPUS cohort at 10 year follow-up. *Schizophr Res*. 2013;150:163–8.
- [65] Bertelsen M, Jeppesen P, Petersen L, Thorup A, Ohlenschlaeger J, Le Quach P, et al. Course of illness in a sample of 265 patients with first-episode psychosis - five-year follow-up of the Danish OPUS trial. *Schizophr Res*. 2009;107:173–8.
- [66] Harrow M, Grossman LS, Jobe TH, Herbener ES. Do patients with schizophrenia ever show periods of recovery? A 15-year multi-follow-up study. *Schizophr Bull*. 2005;31:723–34.
- [67] Klaerke LR, Baandrup L, Fagerlund B, Ebdrup BH, Pantelis C, Glenthøj BY, et al. Diagnostic stability and long-term symptomatic and functional outcomes in first-episode antipsychotic-naïve patients with schizophrenia. *Eur Psychiatry*. 2019;62:130–7.
- [68] Clausen L, Hjorthoj CR, Thorup A, Jeppesen P, Petersen L, Bertelsen M, et al. Change in cannabis use, clinical symptoms and social functioning among patients with first-episode psychosis: a 5-year follow-up study of patients in the OPUS trial. *Psychol Med*. 2014;44:117–26.
- [69] Crespo-Facorro B, Perez-Iglesias R, Mata I, Caseiro O, Martinez-Garcia O, Pardo G, et al. Relapse prevention and remission attainment in first-episode non-affective psychosis. A randomized, controlled 1-year follow-up comparison of haloperidol, risperidone and olanzapine. *J Psychiatr Res*. 2011;45:763–9.
- [70] Norman RM, Manchanda R, Windell D. The prognostic significance of early remission of positive symptoms in first treated psychosis. *Psychiatry Res*. 2014;218:44–7.
- [71] Emsley R, Rabinowitz J, Medori R, Early Psychosis Global Working Group. Remission in early psychosis: rates, predictors, and clinical and functional outcome correlates. *Schizophr Res*. 2007;89:129–39.
- [72] Lambert M, Schimmelmann BG, Naber D, Schacht A, Karow A, Wagner T, et al. Prediction of remission as a combination of symptomatic and functional remission and adequate subjective well-being in 2960 patients with schizophrenia. *J Clin Psychiatry*. 2006;67:1690–7.
- [73] Benoit A, Bodnar M, Malla AK, Joobar R, Bherer L, Lepage M. Changes in memory performance over a 12-month period in relation to achieving symptomatic remission after a first-episode psychosis. *Schizophr Res*. 2014;153:103–8.
- [74] Crumlish N, Whitty P, Clarke M, Browne S, Kamali M, Gervin M, et al. Beyond the critical period: longitudinal study of 8-year outcome in first-episode non-affective psychosis. *Br J Psychiatry*. 2009;194:18–24.