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LONG-TERM OUTCOMES OF FIRST-ADMISSION PSYCHOSIS: A NATURALISTIC 21-YEAR FOLLOW-UP STUDY OF SYMPTOMATIC, FUNCTIONAL AND PERSONAL RECOVERY AND THEIR BASELINE PREDICTORS.

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ABSTRACT

This study was aimed at characterizing long-term outcomes of first-admission psychosis and examining their baseline predictors. Participants were assessed at baseline for 38 candidate predictors and re-assessed after a median follow-up of 21 years for symptomatic, functional and personal recovery. Associations between the predictors and the outcomes were examined using univariate and multivariate Cox regression models. At baseline, 623 subjects were assessed for eligibility, 510 met the inclusion/exclusion criteria and 243 were successfully followed-up (57.3% of the survivors). At follow-up, the percentages of subjects achieving symptomatic, functional and personal recovery were 51.9%, 52.7% and 51.9%, respectively; 74.2% met at least one recovery criterion and 32.5% met all three recovery criteria. Univariate analysis showed that outcomes were predicted by a broad range of variables, including sociodemographics, familial risk, early risk factors, premorbid functioning, triggering factors, illness-onset features, neurological abnormalities, deficit symptoms and early response to treatment. Many of the univariate predictors became non-significant when entered into a hierarchical multivariate model, indicating a substantial degree of interdependence. Each single outcome component was independently predicted by parental socioeconomic status, family history of schizophrenia spectrum disorders, early developmental delay, childhood adversity and mild drug use. Spontaneous dyskinesia/parkinsonism, neurological soft signs and completion of high school remained specific predictors of symptomatic, functional and personal outcomes, respectively. Predictors explained between 27.5% and 34.3% of the variance in the outcomes. In conclusion, our results indicate a strong potential for background and first-episode characteristics in predicting long-term outcomes of psychotic disorders, which may inform future intervention research.

Key words: first-episode psychosis, risk factors, prognosis, full remission**.**

INTRODUCTION

The prediction of the long-term outcome continues to represent an unmet need in psychotic disorders. Actually, the course and outcome of first-episode psychosis (FEP) is highly variable, ranging from full symptomatic and functional recovery to a chronic course and substantial psychosocial impairment. In a ground-breaking study, Strauss and Carpenter[1] pointed out that the outcome of psychotic disorders embodies a multidimensional and transdiagnostic construct with several areas of outcome dysfunction comprising interrelated and interdependent systems each affected partly by the other areas. Thus, the challenge for the clinician is how to predict the varied outcomes based on the subject's FEP characteristics and background risk factors and make the best treatment choices for individual patients.

After large-sample, long-term European outcome studies[2-4], many studies using a standardized methodology have examined the outcomes of psychotic disorders and eventually their baseline predictors, and some systematic reviews and meta-analyses have tried to summarize the varied results.[5-14] However, the lack of consistent definitions of outcomes and the heterogeneity of assessed populations hampers cross-study comparisons and limits the generalizability of findings. For instance, the term "long-term" is frequently (mis)used to describe follow-ups ranging from 1 year to 10 years, thus leading to confusion about what the term truly means. According to McGlashan[15], short-, medium-, and longer-term follow-up studies are defined as those with follow-up lengths of <10 years, 10-19 years, and ≥20 years, respectively. Although McGlashan's differentiation is to some extent arbitrary, we will adhere to it in the present study since there is substantial evidence for length of follow-up influencing outcome,[16, 17] and baseline predictors.[15-18]

To date, no single set of criteria for defining the varied outcomes of psychotic disorders has been determined. Recovery has been focused mainly on remission of symptoms and improvement of function. However, self-reported personal recovery[19] has been increasingly considered the third pillar of the recovery construct. Preliminary

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evidence indicates that symptomatic, functional and personal recovery are distinct, although to some extent, overlapping concepts.[20, 21] However, under a long-term perspective, the degree to which these concepts converge remains largely unknown as do their baseline predictors.[22] This is particularly true for personal recovery, since it is a relatively new concept not usually included in long-term follow-up studies. Indeed, we are aware of only one previous study examining the baseline predictors of personal recovery, in addition to symptomatic and functional recovery, after a mean follow-up of 20 years.[21] This study, however, examined only a few baseline predictors in 80 subjects with psychotic disorders, not all of whom were interviewed personally at follow-up.

Despite there being much research in this area, there is no agreed-upon set of predictors of long-term outcomes of FEP, mainly because of methodological differences across studies.[23] However, several reviews of the evidence[23-25] have revealed some relatively consistent predictors of symptomatic or functional outcomes, such as gender, parental socioeconomic status (P-SES), educational level, age at onset, type of onset, premorbid adjustment, the duration of untreated psychosis (DUP) and early treatment response. Regarding personal recovery, a recent meta-analysis concluded that associations with baseline variables remained largely inconclusive.[26]

Examining recovery as a multifaceted construct encompassing domains of symptomatology, functioning, and personal recovery is a critical conceptual shift for psychosis research,[21] which, together with the study of their baseline determinants, may provide a more holistic understanding of recovery from psychosis. The 2 main goals of our study were as follows: a) to characterize the long-term outcome of psychotic disorders regarding symptomatic, functional and personal recovery, and b) to examine the baseline predictors of each outcome domain.

METHODS

Study design and population

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This was a longitudinal and naturalistic study of subjects with epidemiologically defined first-admission psychosis. Eligible subjects were consecutively admitted to a psychiatric ward in Pamplona (Spain), serving a defined catchment area for approximately 200.000 inhabitants, between January 1990 and December 2008.

The baseline study cohort comprised subjects meeting the following inclusion criteria: a) being admitted for a FEP fulfilling the DSM-III-R or DSM-IV criteria for a functional psychotic disorder; b) being 15-65 years old; c) residing in the catchment area of the hospital; d) completing the inpatient treatment period and a 6-month assessment after discharge; e) having close relatives available to provide broad background information; and e) providing written informed consent. Exclusion criteria included: a) previous antipsychotic treatment for more than 2 months; b) a suspected or confirmed diagnosis of drug-induced psychosis; c) a history of serious medical or neurological disease; and d) mental disability as defined by an IQ less than 70. A detailed description of study's methodology has been described elsewhere.[27]

Between January 2018 and May 2021, we sought to trace and re-interview the subjects to assess the clinical course and different outcomes of psychotic illness. Tracing and re-contact procedures are described in the Supplementary Methods.

Assessment methodology and raters

The senior authors (VP or MJC) assessed participants at baseline. The follow-up field interviewers (LMI and EGJ) were clinical psychiatrists with more than 15 years of clinical expertise in assessing psychotic disorders using standardized rating scales. Field interviewers were blind to the baseline characteristics of each subject and their background information; they conducted face-to-face interviews with each subject, consulted clinical records and interviewed significant others. This multisource information was utilized to rate the clinical status of the subjects at follow-up and to characterize outcomes.

Baseline assessments

The main instrument for assessing background and FEP variables was the Comprehensive Assessment of Symptoms and History (CASH),[28, 29] and for some relevant variables not included in the CASH, specific assessment instruments were employed. The methods and instruments for the baseline assessments have been described in detail elsewhere[27] and are summarized in the Supplementary Methods. A major advantage of the CASH is that it provides broad descriptive coverage to make diagnoses using a variety of criteria, which is especially important because of the changing diagnostic systems over the study period. In this manner, we could diagnose all the subjects at baseline using the DSM-III-R[30] or DSM-IV[31] criteria and rediagnose them with the DSM-5[32] criteria using all information obtained with the CASH.

We selected 38 baseline candidate predictors that have been shown to be of relevance for the outcome of psychotic disorders.[23-25, 33] They were segmented according to their distance to the FEP into the following clusters: sociodemographics, family history, distal antecedents, intermediate antecedents, proximal antecedents/trigger factors, illness-onset features, FEP characteristics and early response to treatment.

Outcome measures and definition of recovery

Symptomatic recovery was defined according to the Remission in Schizophrenia Working Group (RSWG) criteria.[34] These criteria require a score of mild or less in the 8 SAPS and SANS symptom global ratings (item scores ≤2) for all items and a period of at least 6 months during which the aforementioned symptom severity must be maintained. Functional outcome was rated by means of the Social and Occupational Functioning Assessment Scale (SOFAS).[35] Functional recovery was defined as a SOFAS score ≥61 sustained over the last year.

The 15-item version of the Questionnaire about the Process of Recovery (QPR-15)[36] was used to assess personal recovery. The QPR is a validated and frequently used measure of personal recovery,[26] which was developed in collaboration with service users[37]. This instrument has been cited as the only current measure that maps directly on to the major processes of personal recovery, including the establishment of identity,

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finding meaning in life, taking responsibility for recovery, and having a sense of purpose and hope [38]. The QPR-15 is a self-rated scale where each item consists of a declarative statement with a five-point Likert scale that ranges from 0 ("strongly disagree") to 4 ("strongly agree"), where higher scores indicate recovery. Subjects were asked to complete the questionnaire considering their customary state over the last year. A cut-off score ≥45, corresponding to an average rating of "agree" responses, was used to define personal recovery. Complete recovery required that subjects simultaneously fulfilled the criteria for symptomatic, functional and personal recovery.

Statistical analysis

Chi-squared or t statistics were used to compare the followed and not followed subjects on baseline variables. Concordance among recovery outcomes was assessed using the κ statistic. We used Cox proportional hazards regression of the time to follow-up assessment to estimate the association between candidate predictors and the three outcome measures. We ensured that the proportional hazards assumption was met by examining hazard plots and checking that the hazard ratio (HR) between two groups remained constant over time.

We first conducted univariate Cox regression to estimate the association between each candidate predictor and each recovery component. For baseline predictors assessed at the same point and pertaining to the same conceptual domain (i.e., family history, index episode psychopathology), multivariate Cox regression was performed. Next, we applied hierarchical multivariate Cox regression to estimate the unique contribution of the univariate significant variables to each recovery component. We built a multivariate regression model by adding groups of predictors in successive steps, which were ordered according to time-frame criteria from step 1 (demographics) to step 8 (early response to treatment). Thus, the HRs resulting from the regression model were adjusted for the previous blocks of predictors. We report McFadden's pseudo R^2 for estimating the proportion of the variation in the predictors explained by each recovery domain.

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Lastly, we performed a sensitivity analysis for the univariate and multivariate associations of the predictors with the outcomes in the subpopulation of participants aged ≤35 at study entry. All statistical tests were deemed significant at the 5% level, and the Benjamini-Hochberg procedure was used for multiple comparison correction.

RESULTS

Core analytical sample

We initially interviewed 623 subjects who were admitted for FEP and were assessed for eligibility; 510 met the eligibility criteria and 243 subjects were successfully followed-up and made up the study sample (Figure 1). Participants represented 47.6% of the eligible subjects and 57.3% of the alive subjects and were followed for a mean of 20.9 years (SD=5.21) and a median of 21 years (interquartile range=18-24). The baseline demographic and clinical characteristics of the followed and non-followed subjects are presented in Table 1. The only difference between the groups was in age, which was significantly lower in the followed sample ($p<0.001$). This finding was explained by the higher mean age of the excluded subjects due to mortality (38.4, SD=14.2) or organic mental disorder/severe medical illness (40.0, SD=15.6) (Supplementary Table 1). The main sociodemographic and clinical features of the subjects at follow-up are presented in Supplementary Table 2.

Rates and concordance of recovery outcomes

The numbers (and percentages) of recovered subjects according to the symptomatic, functional and personal recovery criteria were 126 (51.9%), 128 (52.7%) and 126 (51.9%), respectively. A Venn diagram representing the associations among recovery domains is shown in Figure 2. One hundred seventy-two subjects (74.2%) met at least one recovery criterion, 108 subjects (44.4%) met both symptomatic and functional recovery criteria, and 79 (32.5%) were fully recovered. The κ of symptomatic recovery with functional and personal recovery was 0.68 and 0.39, respectively (both $p<0.001$); the κ between functional recovery and personal recovery was 0.39 ($p<0.001$).

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Univariate Cox regression analysis

The baseline characteristics of subjects with FEP by recovery status at follow-up are presented in Supplementary Table 3. Results from the univariate analysis revealed that of the 38 candidate predictors, 21 predicted symptomatic recovery, 19 predicted functional recovery and 15 predicted personal recovery (Table 2). More specifically, with the sole exception of psychopathological dimensions, at least one indicator from each predictor domain was significantly related to each recovery outcome. Common predictors of recovery domains included P-SES, completion of high school, family history of schizophrenia spectrum disorders (SSD), developmental delay, childhood adversity, premorbid adjustment, premorbid cognitive reserve, drug use, spontaneous dyskinesia/parkinsonism, neurological soft signs (NSS), deficit syndrome, a brief psychotic disorder diagnosis, and the two definitions of early treatment response. Additional common predictors of symptomatic and functional recovery were acute psychosocial stressors, mode of onset, duration of untreated continuous psychosis (DUCP) and a schizophrenia diagnosis. Age at illness onset was an additional common predictor of symptomatic and personal recovery. The only specific predictor of recovery outcomes was length of index admission and it was for symptomatic recovery (HR=0.83, 95% CI=0.73-0.94).

Hierarchical Multivariate Cox Regression Analysis

The final multivariate model revealed 9 independent predictors of symptomatic recovery, 8 independent predictors of functional recovery and 7 independent predictors of personal recovery (Table 3). Common predictors of each recovery component included P-SES, family history of SSD, developmental delay, childhood adversity and drug use. Additionally, common predictors of both symptomatic and functional recovery were acute psychosocial stressors (both HRs=1.15, $p<0.05$) and DUCP (HRs between 0.47 and 0.34, $p<0.01$). Age at illness onset independently predicted both symptomatic recovery (HR=1.04, 95% CI=1.02-1.06, $p<0.01$) and personal recovery (HR=1.03, 95% CI=1.02-1.05, $p<0.001$). Specific predictors of each recovery domain included spontaneous

dyskinesia/parkinsonism for symptomatic recovery (HR=0.87, 95% IC=0.79-0.95, p<0.01), NSS for functional recovery (HR=0.94, 95% CI=0.92-0.97, p<0.001) and completion of high school for personal recovery (HR=1.66, 95% IC=1.10-2.56, p<0.05). The multivariate model revealed that predictors explained 33.7%, 34.3% and 27.5% of the variance of symptomatic, functional and personal recovery, respectively.

Because of the counterintuitive association found between drug use and higher rates of recovery, we further explored this issue by taken into account levels of drug use. Unadjusted and adjusted HRs for the associations between levels of drug use and the outcomes consistently indicated that, compared to no drug use, only mild use was significantly related to remission across outcomes (Supplementary Table 4).

Sensitivity analysis

Compared to the total sample, univariate and multivariate analysis in participants aged ≤35 (n=193) showed that, overall, associations between the predictors and the outcomes were rather similar although with slightly reduced effect sizes. Major differences were that age at illness onset no longer predicted symptomatic and personal recovery, early treatment response no longer predicted personal recovery and manic symptoms emerged as a predictor of personal recovery (Supplementary Tables 5 and 6).

DISCUSSION

This study examined rates and baseline predictors of symptomatic, functional and personal recovery assessed on average 21 years after a FEP. To the best of our knowledge, this study represents the most complete analysis of baseline predictors of all 3 recovery domains assessed at long-term follow-up and makes clear advances from earlier observations in several ways. First, our study enhances the understanding of the prevalence and relationships of symptomatic, functional and personal recovery over a long-term follow-up. Second, a comprehensive and standardized assessment at baseline allowed us to examine a broad range of background and FEP candidate predictors of later recovery status, which made it possible to identify the common and specific determinants of each recovery domain. Third, we assessed for the first time

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some baseline predictors of long-term follow-up, such as childhood adversity, premorbid cognitive reserve, primary neurological abnormalities, DUCP, deficit symptoms and two measures of early response to treatment. Finally, outcomes were blindly assessed regarding baseline predictors. Taken together, these features add meaningfully to the existing literature on the baseline predictors of the long-term outcomes of psychotic disorders.

Key findings

Our results can be summarized by 5 main findings. First, 74% of the subjects met the criteria for at least one recovery domain, approximately 50% were recovered according to the specific outcomes, 44% met criteria for both symptomatic and personal recovery, and 32% could be considered fully recovered as they met all recovery domains criteria. These figures point out the relevance of considering different recovery domains when interpreting recovery rates.

Second, symptomatic and functional recovery had substantial concordance with each other, while these two domains had a fair concordance with personal recovery. Notwithstanding this, only a minority of participants were recovered according to a single domain, this suggesting that recovery in one domain can be supportive or protective of recovery in other domains.

Third, univariate analysis showed that a broad range of predictors were shared by the 3 recovery outcomes, including higher P-SES, higher educational level, lack of a family history of SSD, less developmental delay, less childhood adversity, better premorbid social and cognitive functioning, mild drug use, fewer primary neurological abnormalities, lack of deficit symptoms, a diagnosis of brief psychotic disorder and early treatment response.

Fourth, a number of significant univariate predictors became non-significant when entered into a hierarchical multivariate model, indicating a substantial degree of interdependence. Notwithstanding this, P-SES, family history of SSD, developmental delay, childhood adversity and mild drug use were all independent predictors of each

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recovery component. Spontaneous dyskinesia/parkinsonism, NSS and completion of high school remained specific predictors of symptomatic, functional and personal recovery, respectively. This association pattern indicates that background socioeconomic factors, familial liability to SSD and a deviance in normal psychological and neurological development are of major relevance in the outcomes of psychotic disorders.[39] Furthermore, the lack of an independent effect of diagnosis on the recovery outcomes suggests a transdiagnostic character of the predictors.

Five, compared with the existing literature on the predictors of long-term outcome of FEP, we outline the following novel findings: (a) for each outcome domain, a family history of SSD and childhood trauma were strong independent predictors of nonrecovery; (b) DUCP, but not DUP, was a predictor of symptomatic and functional nonrecovery; (c) deficit symptoms, but not negative symptoms, predicted nonrecovery across outcome domains in the univariate analysis; and (d) primary neurological abnormalities were predictors of nonrecovery across domains in univariate analysis and specific predictors of symptomatic or functional nonrecovery in multivariate analysis.

Comparison with the literature

Within the context of marked heterogeneity in outcome definitions, our estimate that approximately 50% of the subjects experienced symptomatic or functional recovery is in agreement with the findings from older longer-term studies[40] and most modern studies with medium- or long-term follow-ups.[9, 41, 42] Regarding personal recovery, our results confirm previous findings reporting a similar recovery rate over a long-term follow-up[21] and support the notion that personal recovery is related to, but conceptually distinct from, symptomatic and functional recovery.[20, 43]

Our findings extend previous evidence of P-SES as a strong outcome predictor in psychotic disorders.[23, 44-46] Growing up in a family with low socioeconomic status is linked to a broad array of developmental problems that may also act as mediators of poor outcomes[44, 47, 48] Furthermore, a low P-SES is associated with substantially worse

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cognitive and emotional development throughout the lifespan[49-51], which would explain the widespread influence of that variable across outcomes observed in this study.

The association between a family history of SSD and nonrecovery was striking and likely indicates complex and, to some extent, overlapping mechanisms across outcome domains that goes beyond genetic factors. Having a first-degree relative, and particularly a parent, with SSD leads to higher rates of neurodevelopmental deviance in the proband[52, 53] and has a sizeable impact on psychological and social development and well-being,[54] which could explain the negative impact of this variable across recovery domains.

Whereas previous studies of drug-naïve subjects with SSD have shown that spontaneous movement disorders are linked to several indicators of illness severity,[55-58] ours is the first long-term study demonstrating such a relationship. A meta-analysis of mostly short-term studies[59] suggested no clear influence of NSS on the course of schizophrenia, although two medium-term follow-up studies reported a relationship of NSS with a nonremitting illness course.[60,61] Our finding that spontaneous dyskinesia/parkinsonism and NSS were specific predictors of symptomatic and functional nonrecovery, respectively, adds to previous evidence indicating that these 2 neurological domains are differentially related to premorbid factors[62] and psychosocial functioning.[63]

We found that a later age at illness onset was related to symptomatic and personal recovery, while association with functioning bordering on significance in univariate analysis. This association was particularly strong for personal recovery, which may be explained by the fact that a later illness onset allows the subject to achieve a number of personal, vocational and social milestones before becoming ill. Moreover, subjects who develop the psychosis later may have a foundation of personal skills, such as enhanced resilience to cope with the illness,[21] thereby assisting the process of recovery.

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Relatively unanticipated findings included the association of mild drug use with recovery, and the lack of an association of DUP and negative symptoms with nonrecovery. Contrary to expectations,[64] we found that mild drug use predicted recovery across domains. The relationship between drug use and psychosis outcome, however, is highly dependent on factors such as the frequency and severity of drug use.[65] Indeed, when these variables are controlled for, mild or sporadic use has been related to a better outcome in one or more domains.[66-70] Furthermore, meta-analytic evidence of high-quality studies found that former substance users had significantly fewer symptoms at follow-up than nonusers.[71] These findings may be understood within the vulnerability-stress model,[72] where drug use may precipitate psychosis in vulnerable individuals in a similar manner to acute psychosocial stressors,[73] which have long been related to a more favourable prognosis.[74, 75]

Extensive literature, from mostly shorter longitudinal studies, indicates that DUP is related to worse prognosis with a modest effect.[76-78] However, recent synthesis of the evidence has reached contradictory findings in this regard,[9, 79] which may be not surprising because DUP is a rather heterogeneous concept. In the pretreatment stage of illness, psychosis may briefly develop, spontaneously subside and recur only many months or years later, or psychosis may be continuous from the onset and an indicator of illness severity that may be independent of delayed treatment. Furthermore, some evidence indicates that the relationship between DUP and poor outcome may represent an epiphenomenon[80-82] or a lead-time bias,[83] and it has been suggested duration of untreated unspecific symptoms, DUP and DUCP represent successive phases of increasing severity in the pretreatment period,[81] with DUCP being the most potent predictor of later poor outcomes.

Data from short[84] and medium-term studies[60, 85, 86] suggest that negative symptoms are related to poor outcomes. Such a relationship, however, appears to be a complex one, since negative symptoms may be transitory and secondary,[87] as illustrated by the finding that 47% of the variance of negative symptoms in FEP may be attributed

to covariation with positive and depressive symptoms.[88] Furthermore, this association tends to decrease over time.[16, 84] By contrast, the association between baseline deficit symptoms and nonrecovery across outcome domains in univariate analysis underscores the relevance of using trait rather than state indicators of negative symptoms to undercover associations with outcome.

Most previous studies using somewhat different set of predictors and follow-up periods (mostly in the medium-term range) have reported that predictors account for 20-30% of the variance in symptomatic and/or functional outcomes.[41,86,89-92] Most importantly, the predictive ability of baseline variables tends to decrease markedly over time;[93] thus, our finding that baseline predictors account for approximately one-third of the outcomes variance over a long-term follow-up adds meaningfully to the predictive ability of previous studies. As a final caveat, many of the outcome predictors identified in the present study are difficult to manage, mainly because they are premorbidly established conditions, which might help to explain the intriguing finding that the overall outcome of psychotic disorders has changed little over the past several decades,[6,13,94,95] despite important advances in pharmacological and psychosocial treatments.

Limitations

Generalizability of the results to epidemiologically incident samples is clearly limited by the selection of a population of first-admission psychosis. However, epidemiologically ascertained first-admission samples do not differ meaningfully from incident samples regarding clinical and outcome variables, with the notable exception of disruptive behavior, which has been consistently reported to be more frequent in first-admission subjects[96,97] and may represent a marker of illness severity; thus, our results may overestimate severity of clinical course. We had a 42.7% attrition rate of the alive subjects; although substantial, this rate is similar or slightly higher than those reported in other FEP studies with comparable methodology and follow-up length.[21,41,98] Our attrition analysis suggest that the nonparticipants were largely similar to the participants except for a higher age at study entry, which suggests that older people may have been

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underrepresented within this cohort. Personal recovery was lower predicted than the other outcomes, and it is possible that we missed some relevant predictors thereof. Personal recovery is conceptualized as an ongoing process that is particularly subject to fluctuations in concurrent social factors[43] and mood states[99, 100] and has been linked to trait-like factors such as resilience[21] and attachment style,[101] but none of these variables were assessed in the present study.

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Figure legends

Figure 1. Flow diagram of included and excluded subjects

Figure 2. Venn diagram representing relationships between symptomatic, functional and personal recovery

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Conflict of Interest

All the authors have no relevant conflicts of interest to report.

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Figure 1.

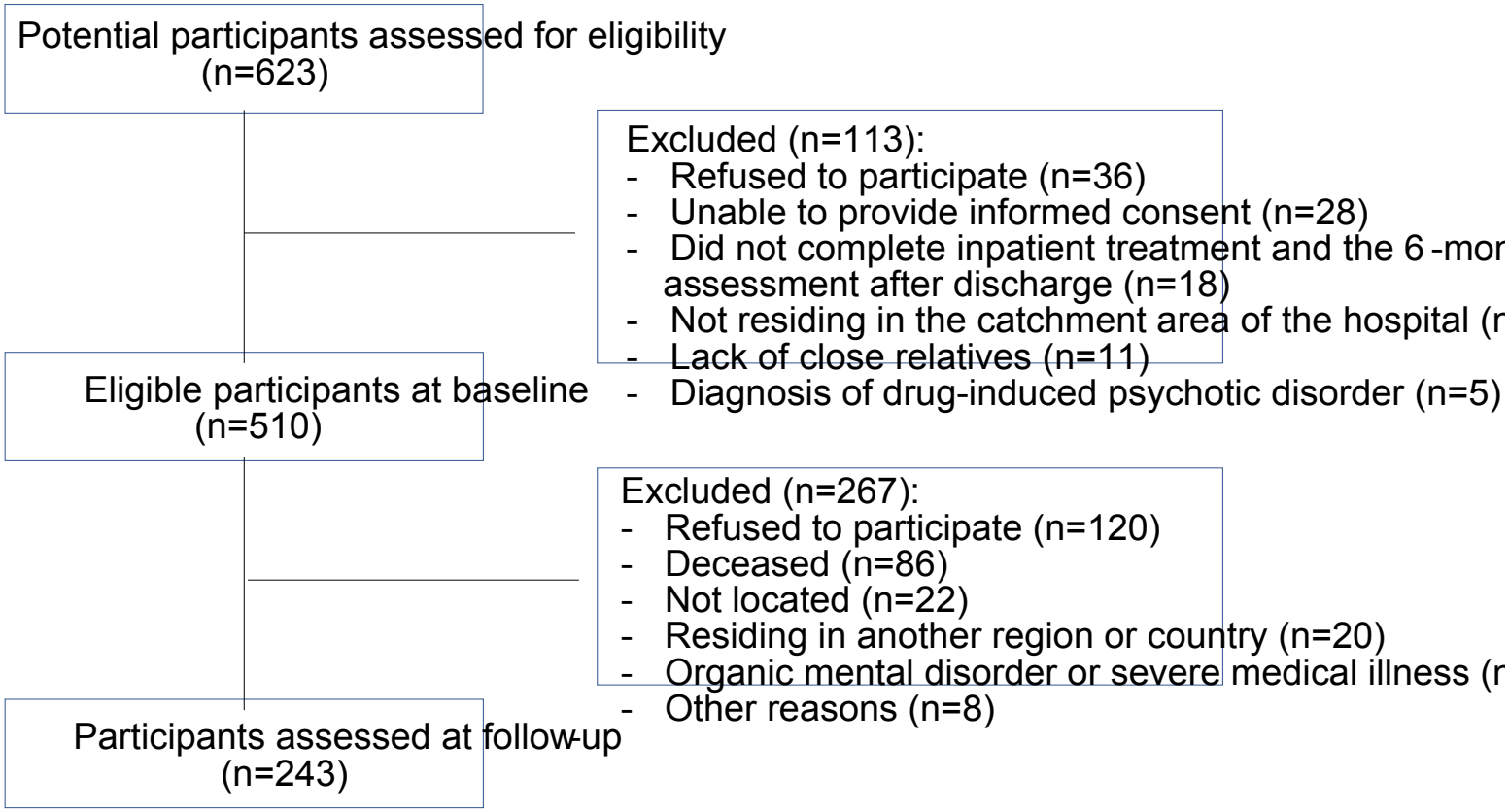

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Table 1. Baseline sociodemographic and clinical characteristics of cohort members assessed at follow-up (n=243) and those not assessed (n=267)

	Assessed	Not assessed	X^2 or $t_{(df)}$	p
Gender, female, n (%)				
Age, y	27.5 (9.83)	31.8 (12.6)	$4.197_{(508)}$	<0.001
Socioeconomic status score (1-5)	3.07 (0.72)	3.16 (0.67)	$1.475_{(508)}$	0.141
Married/cohabiting at illness onset, n (%)	73 (30.0)	94 (35.2)	$1.541_{(1)}$	0.214
Education, years	11.2 (3.37)	10.6 (3.43)	$1.865_{(508)}$	0.063
Premorbid adjustment total score	5.32 (4.23)	5.61 (3.78)	$0.837_{(508)}$	0.403
DUP, months	15.3 (35.2)	20.2 (44.5)	$1.388_{(498.8)}$	0.166
Drug use before admission, n (%)	81 (33.3)	100 (37.5)	$0.943_{(1)}$	0.331
Type of onset (1=acute, 4=chronic)	2.59 (1.23)	2.72 (1.19)	$1.21_{(508)}$	0.226
Compulsory admission, n (%)	76 (31.3)	87 (32.6)	$0.100_{(1)}$	0.752
Antipsychotic drug-naïve status, n (%)	194 (79.8)	199 (74.5)	$2.024_{(1)}$	0.155
Diagnosis, n (%):				
Schizophrenia	72 (29.6)	89 (33.3)	$2.262_{(7)}$	0.944
Schizophreniform disorder	40 (16.5)	39 (14.6)		
Brief psychotic disorder	41 (16.9)	40 (15.0)		
Delusional disorder	16 (6.6)	23 (8.6)		
Schizoaffective disorder	13 (5.3)	12 (4.5)		
Mania/bipolar disorder	20 (8.2)	23 (8.6)		
Major depressive disorder	29 (11.9)	30 (11.2)		
Psychotic disorder NOS	12 (4.9)	11 (4.1)		
Length of index admission, weeks	3.00 (1.78)	3.13 (2.02)	$0.771_{(508)}$	0.441
SAPS, global ratings total score	9.57 (4.09)	8.97 (4.07)	$1.662_{(508)}$	0.097
SANS, global ratings total score	4.96 (5.23)	5.49 (5.35)	$1.115_{(508)}$	0.265
CGI, Efficacy Index	1.56 (0.77)	1.66 (0.91)	$1.434_{(505.7)}$	0.152

DUP= Duration of untreated Psychosis; NOS= Not Otherwise Specified; SAPS= Scale for the Assessment of Positive Symptoms; SANS= Scale for the Assessment of Negative Symptoms; CGI= Clinical Global Impression.

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Figure 2.

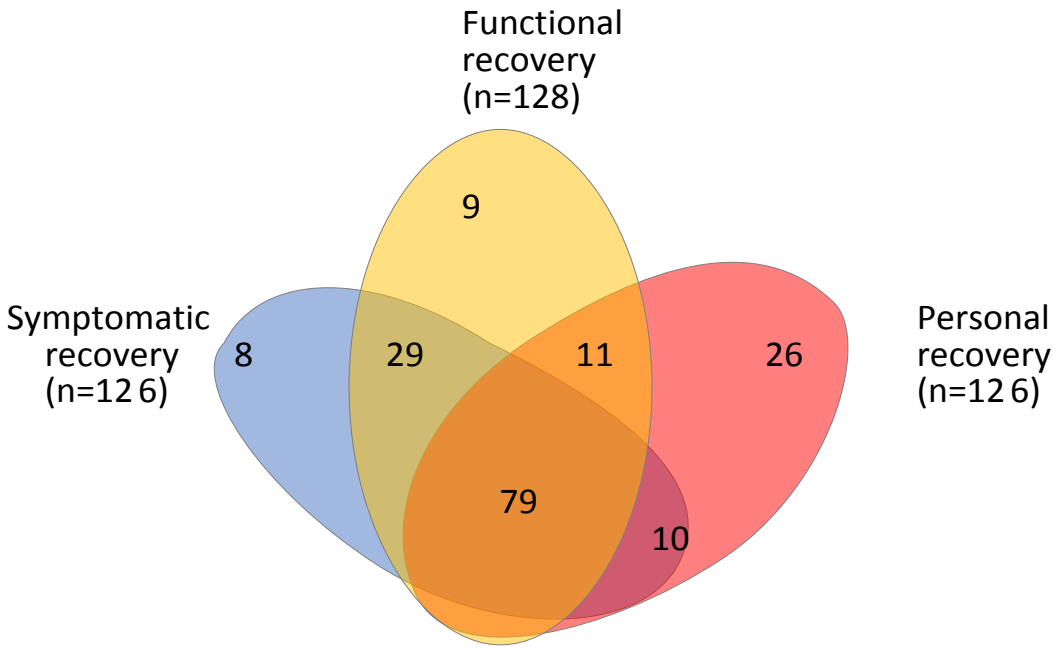

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Table 2. Univariate Cox regression analysis of baseline candidate predictors of symptomatic, functional and personal recovery

	Symptomatic recovery (n=126)	Functional recovery (n=128)	Personal recovery (n=126)
Sociodemographic factors			
Gender, female	1.06 (0.75-1.52)	0.96 (0.67-1.37)	1.13 (0.79-1.60)
Parental socioeconomic status	0.51 (0.39-0.66)[c]	0.48 (0.37-0.62)[c]	0.58 (0.45-0.76)[c]
High school	1.95 (1.37-2.68)[c]	2.29 (1.61-3.26)[c]	2.12 (1.49-3.01)[c]
Married/stable partner at illness onset	1.19 (0.82-1.73)	1.15 (0.79-1.67)	1.05 (0.72-1.53)
Winter birth	0.82 (0.57-1.17)	0.88 (0.62-1.26)	0.72 (0.50-1.03)
Urban environment during upbringing	1.24 (0.87-1.77)	1.28 (0.90-1.82)	1.19 (0.83-1.69)
Familial risk factors			
Family History of SSD	0.34 (0.19-0.60)[c]	0.36 (0.21-0.63)[b]	0.39 (0.23-.066)[b]
Family history of bipolar disorder	0.98 (0.53-1.84)	0.84 (0.44-1.62)	1.16 (0.67-2.07)
Family History of MDD	1.21 (0.75-1.97)	1.16 (0.72-1.89)	1.40 (0.88-2.34)
Distal antecedents			
Obstetric complications	0.56 (0.36-0.88)[a]	0.55 (0.35-0.86)[b]	0.61 (0.40-0.93)
Developmental delay at year 3	0.73 (0.62-0.86)[c]	0.65 (0.54-0.78)[c]	0.67 (0.56-0.80)[c]
Intermediate antecedents			
Childhood adversity	1.02 (1.01-1.03)[c]	1.02 (1.01-1.03)[c]	1.01 (1.01-1.02)[c]
Premorbid adjustment	0.90 (0.86-0.95)[c]	0.89 (0.84-0.94)[c]	0.93 (0.88-0.97)[b]
Premorbid cognitive reserve	1.04 (1.02-1.05)[c]	1.05 (1.03-1.07)[c]	1.04 (1.02-1.05)[b]
Proximal antecedents			
Drug use	1.13 (1.04-1.23)[b]	1.13 (1.04-1.22)[b]	1.15 (1.09-1.25)[c]
Acute psychosocial stressors	1.17 (1.05-1.31)[b]	1.19 (1.07-1.33)[c]	1.01 (0.95-1.14)
Illness-onset features			
Age at illness onset	1.02 (1.01-1.04)[b]	1.02 (1.00-1.04)	1.04 (1.02-1.06)[c]
Mode of onset	0.84 (0.73-0.97)[a]	0.84 (0.73-0.97)[b]	0.92 (0.79-1.06)
Duration of untreated psychosis	0.95 (0.75-1.21)	0.92 (0.73-1.17)	0.99 (0.78-1.26)
Duration of untreated continuous psychosis	0.59 (0.43-0.80)[b]	0.57 (0.42-0.77)[c]	0.74 (0.55-0.98)
First-episode characteristics			
Compulsory index admission	1.07 (0.73-1.55)	0.86 (0.59-1.27)	1.04 (0.72-1.52)
Length of index admission, weeks	0.83 (0.73-0.94)[b]	0.89 (0.79-1.00)	0.92 (0.82-1.02)
Spontaneous dyskinesia/parkinsonism	0.86 (0.80-0.92)[c]	0.87 (0.82-0.93)[c]	0.88 (0.83-0.94)[c]
Neurological soft signs	0.95 (0.93-0.97)[c]	0.94 (0.92-0.96)[c]	0.96 (0.94-0.98)[b]
Deficit syndrome	0.24 (0.10-0.54)[b]	0.27 (0.12-0.58)[b]	0.40 (0.21-0.77)[a]
Dimensions of psychopathology:			
Reality-distortion	1.08 (0.94-1.23)	1.07 (0.94-1.22)	1.62 (0.98-2.67)
Disorganization	1.01 (0.89-1.16)	1.00 (0.87-1.14)	1.05 (0.73-1.53)
Negative	0.88 (0.75-1.04)	0.92 (0.79-1.07)	0.64 (0.37-1.11)
Catatonia	0.93 (0.79-1.09)	0.96 (0.82-1.15)	0.49 (0.25-0.98)
Mania	1.09 (0.95-1.23)	1.07 (0.94-1.22)	1.24 (0.77-2.00)
Depression	1.08 (0.95-1.22)	1.94 (0.90-1.23)	0.78 (0.48-1.28)
DSM-5 diagnosis:			
Schizophrenia	0.58 (0.37-0.90)[a]	0.47 (0.29-0.76)[b]	0.78 (0.52-1.17)
Schizophreniform disorder	0.87 (0.54-1.39)	0.95 (0.60-1.50)	0.76 (0.47-1.25)
Brief psychotic disorder	1.80 (1.20-2.68)[b]	1.81 (1.22-2.70)[b]	1.64 (1.09-2.47)[a]
Mood disorder with psychotic symptoms	1.15 (0.76-1.73)	1.30 (0.88-1.93)	0.94 (0.61-1.46)
Other psychotic disorders	0.97 (0.59-1.61)	0.90 (0.54-1.51)	1.12 (0.69-1.81)
Early treatment response			
At discharge from index admission	2.06 (1.37-3.09)[c]	2.05 (1.37-3.07)[b]	1.64 (1.11-2.41)[a]
6 months after index admission	2.30 (1.42-3.79)[b]	2.66 (1.61-4.39)[c]	1.70 (1.10-2.61)[a]

[a] p<0.05; [b] p<0.01; [c] p<0.001

DSM-5, diagnostic and statistical manual, fifth edition; MDD, major depressive disorder; SSD, schizophrenia spectrum disorders.

Note: the level of measurement for each variable is shown in the Supplementary Table 2.

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Table 3. Hierarchical multivariate Cox regression analysis of baseline predictors of symptomatic, functional and personal recovery

	Symptomatic recovery (n=126)	Functional recovery (n=128)	Personal recovery (n=126)
Step 1 (demographics)			
Parental socioeconomic status	0.56 (0.41-0.76)[c]	0.57 (0.42-0.77)[c]	0.71 (0.52-0.96)[a]
High school	–	–	1.66 (1.10-2.56)[a]
Step 2 (familial risk)			
Family history of SSD	0.40 (0.23-0.70)[b]	0.46 (0.27-0.80)[b]	0.44 (0.26-0.75)[b]
Step 3 (early risk factors)			
Developmental delay at age 3	0.83 (0.70-0.98)[a]	0.74 (0.61-0.89)[b]	0.74 (0.62-0.89)[b]
Step 4 (intermediate risk factors)			
Childhood adversity	1.02 (1.01-1.04)[a]	1.03 (1.02-1.04)[a]	1.02 (1.01-1.04)[a]
Step 5 (proximal risk factors)			
Drug use	1.24 (1.13-1.37)[c]	1.25 (1.13-1.38)[c]	1.23 (1.11-1.35)[c]
Acute psychosocial stressors	1.15 (1.02-1.32)[a]	1.15 (1.01-1.31)[a]	–
Step 6 (illness onset features)			
Age at illness onset	1.04 (1.02-1.06)[b]	–	1.03 (1.02-1.05)[c]
Duration of untreated continuous psychosis	0.47 (0.27-0.81)[b]	0.34 (0.18-0.63)[b]	–
Step 7 (first-episode characteristics)			
Spontaneous dyskinesia/parkinsonism	0.87 (0.79-0.95)[b]	–	
Neurological soft signs	–	0.94 (0.92-0.97)[c]	–

[a]= p<0.05; [b]= p<0.01; [c]= p<0.001

SSD, schizophrenia spectrum disorders.

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Supplementary material

Supplementary Methods. (A)Tracing and recontact procedures for the follow-up. (B) Methodology and instruments used for assessing baseline variables.

Supplementary Table 1. Age at first admission by participants and non-participants at follow-up.

Supplementary Table 2. Baseline characteristics of the participants by recovery status at follow-up.

Supplementary Table 3. Sociodemographic and clinical features of the participants at follow-up.

Supplementary Table 4. Unadjusted and adjusted Hazards Ratios for the associations between levels of drug use and recovery outcomes.

Supplementary Table 5. Univariate Cox regression analysis of baseline candidate predictors by recovery domain in participants aged ≤35 at study entry(n=193).

Supplementary Table 6. Hierarchical multivariate Cox regression analysis of baseline candidate predictors by recovery domain in participants aged ≤35 at study entry (n=193).

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SUPPLEMENTARY METHODS

(A) Tracing and re-contact procedures for the follow-up

We began by identifying deceased subjects via electronic health records and the General Register Office. Then, we proceeded to locate the alive subjects by sending letters to their last known address inviting them to participate. Nonresponders were contacted by telephone if the number was available in the health records. Subjects who did not respond to the first contact attempt were sent another letter two months later. Finally, for those identified individuals who did not respond, we sought to make contact and invite them via their treating psychiatrist or general practitioner. If subjects expressed an interest in the study, they were invited to meet the field researchers to learn about and discuss participation.

(B) Methodology and instruments used for assessing baseline variables

Baseline variables were rated using multiple sources of information, including interviews with the participants, clinical records, first-degree relatives, significant others, and, if necessary, information provided by the primary physician.

Sociodemographic factors were assessed with the Comprehensive Assessment of Symptoms and History (CASH)[1] and included gender, civil status at illness onset, educational level (completion of high school), urbanicity during upbringing scored from 1 (rural area, < 5.000 inhabitants) to 3 (urban area, >100.000 inhabitants), and winter birth (December to March). Furthermore, parental socioeconomic status was assessed using the Hollingshead Index.[2]

The family history of schizophrenia spectrum disorders (SSD), bipolar disorder and major depressive disorder was assessed in the first-degree relatives of the subjects by means of the Family History-Research Diagnostic Criteria (FH-RDC),[3] which was administered at baseline and follow-up interviews. The combined information of the two

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interviews was used to rate the family history. SSD included all non-affective psychotic disorders plus schizotypal personality disorder.

Distal antecedents included obstetric complications assessed with the Lewis-Murray scale[4] and neurodevelopmental delay that was assessed according to Shapiro et al. scale.[5] The scale rates developmental milestones attainment at age 3, including sitting, standing, walking, talking words, talking sentences and urine/faces control. These 2 variables were rated using clinical records and information provided by the subjects' mother, which was available in the majority of the cases.

Intermediate antecedents comprised different premorbid events and functioning rated up to age 18. These included premorbid functioning, childhood adversity and, premorbid cognitive reserve.

The modified Gittelman-Klein scale (GKS), as included in the CASH, was used to rate premorbid psychosocial adjustment during childhood (ages 6-12) and adolescence (ages 13-18). For the present study, the GKS total score (childhood plus adolescence scores) was employed.

Childhood adversity was assessed by means of the Global Family Environment Scale (GFES),[6 7] which indexes the global quality of the environment in which the child was raised. The scale has shown good convergent validity with other adverse childhood experiences instruments.[8] Raters use a hypothetical continuum from 1 (e.g., severe abuse, deprivation) to 90 (e.g., stable and secure nurturing) and formulate a single score reflecting the lowest quality of family environment to which the child has been exposed. The GFES was not available at the beginning of the baseline recruitment period; thus, in 28% of the cases ratings were made using the rich available background information on this variable.

Premorbid cognitive reserve was estimated according to established proxy measures of premorbid intelligence, education and leisure activities[9,10]. Premorbid intelligence was assessed by means of the Word Accentuation Test (WAT), which is the Spanish equivalent of the National Adult Reading Test. We used the WAIS III full scale IQ

equivalence of the WAT scores as reported by Gomar et al.[11] to obtain the premorbid IQ scores. Educational level was assessed using the years of education completed beyond the compulsory education and the scholastic performance scale from the Cannon-Spoor scale.[12] Participation in leisure activities was rated according to the peer relationships and interests subscales from the GKS. Higher scores were arranged to denote better performance and a Principal Component Analysis was performed, which resulted in a single factor, to create a premorbid cognitive reserve score for each subject.[10]

Proximal antecedents were conceptualized as trigger factors occurring within the 6 months before illness onset. They included acute psychosocial stressors rated per DSM-III Axis IV,[13] and substance abuse or dependence as rated per CASH. Severity of drug abuse was also scored using the Addiction Severity Scale,[14] and the global rating severity score ranging 0-9 was used in the present study.

Illness-onset factors were assessed with the CASH and included age at illness onset, duration of untreated psychosis (DUP), duration of untreated continuous psychosis (DUCP) and mode of onset.

Age at onset was defined as the age at which the subject met DSM criterion A for schizophrenia.

DUP was defined as the months that elapsed between the appearance of the first psychotic symptom and the first antipsychotic treatment. DUCP was defined as the months that elapsed between the appearance of the first continuous psychotic symptom (i.e., present most of the days) and the first antipsychotic treatment.

Mode of onset was rated from 1 (acute, <1 month) to 4 (chronic, >6 months), indicating the time elapsed between the onset of any illness-related symptom and the development of the full psychotic syndrome.

First-episode characteristics included type of admission (compulsory vs. voluntary), the length of index admission (a proxy for initial illness severity) in weeks, cross-sectional

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psychopathology, deficit syndrome, primary neurological abnormalities and DSM-5 diagnosis.

Cross-sectional psychopathology was assessed using the current state section from the CASH, which includes 73 symptoms rated at their worst over the previous month on a 6-point scale. This instrument includes the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), 5 catatonic signs and a global severity rating for catatonia, 10 depressive symptoms and a global severity rating for depression, and 8 manic symptoms and a global rating for mania. For the present study, 6 syndromic global ratings assessed at admission were used: reality-distortion, disorganization, negative, catatonia, mania and depression, each rated on a 0 (absent) to 5 (severe) severity scale.

Primary and persistent negative symptoms and the deficit syndrome were rated using the Schedule for the Deficit Syndrome.[15]

Primary neurological abnormalities were assessed in those drug-naïve participants at index admission (n=194, 79.8% of the sample). We assessed spontaneous dyskinesia and parkinsonism using the Abnormal Involuntary Movement Scale[16] and the Simpson-Angus Rating Scale,[17] respectively, and a combined score of the two scales was used to rate spontaneous dyskinesia/parkinsonism. The Neurological Examination Schedule[18] was also administered to those drug-naïve participants who were able to collaborate (n=179, 73.7% of the sample).

Early treatment response was assessed at discharge from index admission and 6 months after discharge. At discharge, we administered the Clinical Global Impression Efficacy Index (CGI-EI) scale,[19] which rates the degree of symptomatic improvement from 1 (marked remission) to 4 (unchanged), and symptomatic remission was defined as scoring 1 in the CGI-EI scale. Subjects were reevaluated 6 months after discharge using the SAPS and SANS as included in the CASH, and the Remission in Schizophrenia Working Group criteria[20] were employed to define symptomatic remission.

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Supplementary Table 1. Age at first admission of participants and non-participants at follow-up

	Mean age	SD
Participants (n=243)	27.5	9.83
Nonparticipants:		
Refused to participate (n=120)	28.0	10.2
Dead (n=86)	38.4	14.2
Not located (n=22)	30.0	8.67
Residing in another region/country (n=20)	27.5	8.38
Organic mental disorder/severe medical illness (n=11)	40.0	15.4
Other causes (n=8) †	23.1	7.54

† Six subjects did not complete all the outcome measures and 2 subjects retired the consent to participate

Supplementary Table 2. Baseline characteristics of the participants by recovery status at follow-up.

	Symptomatic recovery		Functional recovery		Personal recovery	
	Yes (n=126)	No (n=127)	Yes (n=128)	No (n=115)	Yes (n=126)	No (n=117)
Sociodemographics						
Gender (female), n (%)	55 (43.7)	51 (43.6)	53 (41.4)	53 (46.1)	57 (45.2)	49 (41.9)
Married/stable partner at illness onset, n (%)	43 (34.1)	30 (25.6)	42 (32.8)	31 (27.0)	39 (31.0)	34 (29.0)
P-SES, mean (SD), range 1-5	2.91 (0.63)	3.23 (0.78)	2.88 (0.66)	3.27 (0.74)	2.98 (0.71)	3.15 (0.72)
High school, n (%)	65 (51.6)	44 (37.6)	77 (55.5)	38 (33.0)	67 (53.2)	42 (35.9)
Urban environment during upbringing, n (%)	59 (46.8)	53 (45.3)	61 (47.7)	51 (44.3)	57 (45.2)	55 (47.0)
Winter birth, n (%)	52 (41.3)	52 (44.4)	55 (43.0)	49 (42.6)	48 (38.1)	56 (47.9)
Family history:						
Schizophrenia spectrum disorders, n (%)	14 (11.1)	35 (29.9)	15 (11.7)	34 (29.6)	16 (12.7)	33 (28.2)
Bipolar disorder, n (%)	11 (8.7)	10 (8.5)	10 (7.8)	11 (9.6)	13 (10.3)	8 (6.8)
Major depressive disorder, n (%)	20 (15.9)	18 (15.4)	20 (15.6)	18 (17.5)	22 (17.5)	16 (13.7)
Distal antecedents						
Obstetric complications, mean (SD), range 0-2	0.13 (0.40)	0.33 (0.63)	0.13 (0.42)	0.34 (0.62)	0.14 (0.41)	0.32 (0.62)
Developmental delay, mean (SD), range 0-6	0.60 (1.00)	1.41 (1.64)	0.50 (0.89)	1.54 (1.65)	0.54 (0.88)	1.48 (1.68)
Intermediate antecedents						
Childhood adversity, mean (SD), range 4-97‡	78.3 (16.0)	60.9 (23.6)	78.2 (17.1)	60.8 (22.8)	75.2 (17.5)	64.2 (24.4)
Premorbid adjustment, mean (SD), range 0-20	3.77 (3.37)	6.98 (4.45)	3.59 (3.23)	7.23 (4.41)	4.14 (3.50)	6.58 (4.59)
Premorbid cognitive reserve, mean (SD), range 13-66‡	46.4 (10.6)	37.5 (11.5)	47.5 (9.62)	36.1 (11.4)	45.8 (10.9)	38.1 (11.7)
Proximal antecedents						
Drug abuse, mean (SD), range 0-9	1.41 (1.96)	1.09 (2.00)	1.40 (1.96)	1.10 (2.00)	1.49 (2.02)	1.01 (1.91)
Acute psychosocial stressors, mean (SD), range 1-7	2.33 (1.53)	1.70 (1.33)	2.37 (1.58)	1.64 (1.24)	1.98 (1.43)	2.07 (1.51)
Illness-onset factors						
Age at illness onset, mean (SD), range 15-60	26.8 (9.54)	25.0 (9.27)	26.4 (9.59)	25.4 (9.28)	27.7 (10.4)	24.1 (7.87)
Mode of onset, mean (SD), range=1-4	2.22 (1.15)	2.99 (1.18)	2.23 (1.41)	3.00 (1.20)	2.35 (1.23)	2.85 (1.17)
DUP, mean (SD), range -0.70-2.46*	0.31 (0.79)	0.62 (0.80)	0.29 (0.75)	0.64 (0.83)	0.33 (0.81)	0.60 (0.78)
DUCP, mean (SD), range -0.70-2.46*	0.02 (0.51)	0.54 (0.76)	0.01 (0.47)	0.56 (0.78)	0.09 (0.63)	0.45 (0.71)
First-episode characteristics						
Involuntary admission, n (%)	41 (32.5)	35 (29.9)	36 (28.1)	40 (34.8)	41 (32.5)	35 (29.9)
Length of index admission, mean (SD), range 1-16	2.57 (1.49)	3.46 (1.96)	2.76 (1.93)	3.30 (1.55)	2.79 (1.90)	3.22 (1.63)
SDP, mean (SD), range 0-20	1.50 (2.24)	4.27 (5.01)	1.65 (2.35)	3.98 (4.99)	1.70 (2.60)	3.85 (4.73)
Neurological soft signs, mean (SD), range 0-47	13.9 (9.06)	20.9 (9.53)	13.1 (8.42)	21.6 (9.45)	15.0 (9.11)	19.0 (10.32)
DSM-5 diagnosis:						
Schizophrenia, n (%)	24 (19.0)	48 (41.0)	21 (16.4)	51 (44.3)	31 (24.6)	41 (35.0)
Schizophreniform disorder, n (%)	21 (16.7)	19 (16.2)	23 (18.0)	17 (14.8)	19 (15.1)	21 (17.9)
Brief psychotic disorder, n (%)	32 (25.4)	9 (7.7)	33 (25.8)	8 (7.0)	30 (23.8)	11 (9.4)
Mood disorder with psychotic symptoms, n (%)	31 (24.6)	18 (15.4)	34 (26.6)	15 (13.0)	26 (20.6)	23 (19.7)
Other psychotic disorders, n (%)	18 (14.3)	23 (19.7)	17 (13.3)	24 (20.9)	20 (15.9)	21 (17.9)
Dimensions of psychopathology:						
Reality-distortion, mean (SD), range 0-5	3.72 (1.42)	3.68 (1.38)	3.69 (1.45)	3.72 (1.45)	3.82 (1.38)	3.58 (1.42)
Disorganization, mean (SD), range 0-5	2.37 (1.54)	2.35 (1.70)	2.32 (1.56)	2.40 (1.68)	2.34 (1.60)	2.38 (1.64)
Negative, mean (SD), range 0-5	0.95 (1.24)	1.56 (1.53)	1.05 (1.24)	1.47 (1.57)	0.94 (1.27)	1.58 (1.50)
Catatonia, mean (SD), range 0-5	0.71 (1.18)	0.96 (1.36)	0.77 (1.22)	0.90 (1.34)	0.62 (1.09)	1.06 (1.42)
Mania, mean (SD), range 0-5	1.11 (1.63)	0.62 (1.24)	1.04 (1.59)	0.69 (1.31)	1.17 (1.62)	0.55 (1.22)
Depression, mean (SD), range 0-5	1.24 (1.71)	1.19 (1.64)	1.32 (1.81)	1.10 (1.51)	0.98 (1.59)	1.46 (1.73)
Deficit syndrome, n (%)	6 (4.8)	33 (28.2)	7 (5.5)	32 (27.8)	10 (7.9)	29 (24.8)
Early treatment response:						
At discharge from index-admission, n (%)	95 (75.4)	51 (43.6)	96 (75.0)	50 (43.5)	88 (69.8)	58 (49.6)
Six-month after discharge, n (%)	106 (84.1)	65 (55.6)	110 (85.9)	61 (53.0)	100 (79.4)	71 (60.7)

For continuous variables, and unless otherwise specified (‡), higher values are indicative of more impairment

* Log-transformed scores

DSM-5; diagnostic and statistical manual, fifth edition; DUP, duration of untreated psychosis; DUCP, duration of untreated continuous psychosis; P-SES, parental socioeconomic status; SDP, spontaneous dyskinesia and parkinsonism.

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Supplementary Table 3. Sociodemographic and clinical features of the participants at follow-up

	N (%)	Mean (SD)
Civil status (single)	150 (61.7)	
Living:		
Own family	71 (29.2)	
Other family members	54 (22.2)	
Other persons	17 (7.0)	
Supported housing	37 (15.2)	
Employment (paid working)	80 (33)	
DSM-5 illness course:		
Full remission	73 (30.0)	
Partial remission	149 (61.3)	
Chronic/continuous	59 (24.3)	
Comorbid drug use:	121 (49.8)	
Lifetime DSM-5 diagnosis:		
Schizophrenia	113 (46.5)	
Major mood disorders	52 (21.4)	
Non-schizophrenia non-affective psychoses	78 (31.1)	
Psychiatric medication:		
Antipsychotics	182 (74.9)	
Mood stabilizers	72 (29.6)	
Antidepressants	81 (33.3)	
Anxiolytics/hypnotics	105 (43.2)	
None	41 (16.9)	
Age, years		48.5 (10.4)
No. of psychiatric admissions		5.85 (6.24)
GAF		64.0 (19.8)
SOFAS		62.8 (21.4)
SAPS, global ratings total score		2.86 (3.66)
SANS, global ratings total score		5.89 (4.96)
QPR-15, total score		43.0 (11.1)

DSM-5, diagnostic and statistical manual, fifth edition; GAF; global assessment of functioning scale; QPR, questionnaire about the process of recovery; SAPS, scale for the assessment of positive symptoms; SANS, scale for the assessment of negative symptoms; SOFAS, social and occupational functioning assessment scale.

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Supplementary Table 4. Unadjusted and adjusted Hazards Ratios for the associations between levels of drug use and recovery outcomes

	Symptomatic recovery (n=126)	Functional recovery (n=128)	Personal recovery (n=126)
Drug use (unadjusted):			
Absent	1	1	1
Mild	2.15 (1.45-3.20)[b]	2.13 (1.43-3.17)[b]	2.54 (1.72-3.76)[b]
Moderate	2.00 (0.96-4.16)	1.85 (0.88-3.83)	1.00 (0.36-2.77)
Severe	1.01 (0.42-3.01)	1.07 (0.39-3.17)	2.37 (1.14-4.93)
Drug use (adjusted by parental SES and subjects' educational level)			
Absent	1	1	1
Mild	1.82 (1.21-2.73)[a]	1.75 (1.17-2.64)[a]	2.24 (1.50-3.35)[b]
Moderate	1.86 (0.89-3.87)	1.69 (0.81-3.54)	0.93 (0.33-2.56)
Severe	1.22 (0.46-3.35)	1.20 (0.44-3.12)	2.58 (1.24-5.38)
Drug use (adjusted by parental SES, subjects' educational level and drug use at follow-up)			
Absent	1	1	1
Mild	1.78 (1.15-2.77)[a]	1.81 (1.17-2.82)[a]	2.29 (1.48-3.54)[b]
Moderate	1.80 (0.81-3.97)	1.81 (0.81-4.03)	0.97 (0.33-2.82)
Severe	1.19 (0.42-3.34)	1.25 (0.45-3.48)	2.65 (1.24-5.64)

The number (and percentage) of subjects with the different levels of drug abuse at baseline was as follows: absent 161 (66.3%), mild 57 (23.5%), moderate 15 (6.2%) and severe 10 (4.1%)

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Supplementary Table 5. Univariate Cox regression analysis of baseline candidate predictors by recovery domain in participants aged ≤35 at study entry (n=193)

	Symptomatic recovery (n=99)	Functional recovery (n=102)	Personal recovery (n=94)
Sociodemographic factors			
Gender, female, n (%)	0.88 (0.58-1.31)	0.75 (0.50-1.14)	0.90 (0.59-1.36)
Parental socioeconomic status	0.49 (0.36-0.66)[c]	0.43 (0.33-0.61)[c]	0.51 (0.37-0.70)[c]
High school	2.05 (1.37-3.06)[c]	2.38 (1.59-3.54)[c]	2.29 (1.52-3.47)[c]
Married/stable partner at illness onset	1.01 (0.64-1.60)	1.05 (0.66-1.65)	0.81 (0.49-1.34)
Winter birth	0.84 (0.56-1.26)	0.87 (0.59-1.30)	0.64 (0.42-0.99)
Urban environment during upbringing	1.21 (0.82-1.81)	1.36 (0.92-2.04)	1.27 (0.84-1.91)
Familial risk factors			
Family History of SSD	0.32 (0.17-0.63)[b]	0.37 (0.20-0.69)[b]	0.33 (0.17-.064)[b]
Family history of bipolar disorder	1.16 (0.61-2.18)	0.97 (0.50-1.86)	1.29 (0.70-2.39)
Family History of MDD	1.28 (0.73-2.23)	1.13 (0.64-1.99)	1.41 (0.81-2.46)
Distal risk factors			
Obstetric complications	0.58 (0.36-0.93)[a]	0.59 (0.38-0.93)[a]	0.60 (0.37-0.96)
Developmental delay at year 3	0.71 (0.60-0.86)[c]	0.66 (0.54-0.80)[c]	0.67 (0.55-0.82)[c]
Intermediate risk factors			
Childhood adversity	1.02 (1.01-1.03)[c]	1.02 (1.01-1.03)[c]	1.01 (1.01-1.02)[b]
Premorbid adjustment	0.90 (0.85-0.95)[c]	0.90 (0.85-0.95)[c]	0.91 (0.86-0.96)[b]
Premorbid cognitive reserve	1.04 (1.02-1.06)[c]	1.05 (1.03-1.06)[c]	1.04 (1.02-1.05)[c]
Proximal risk factors			
Drug use	1.15 (1.05-1.25)[b]	1.15 (1.05-1.25)[b]	1.18 (1.08-1.29)[c]
Acute psychosocial stressors	1.21 (1.07-1.38)[b]	1.20 (1.06-1.36)[b]	1.03 (0.89-1.19)
Illness-onset features			
Age at illness onset	**1.03 (0.99-1.07)**	1.02 (1.00-1.04)	**1.03 (0.98-1.07)**
Mode of onset	**0.84 (0.71-0.99)**	**0.88 (0.75-1.03)**	0.88 (0.74-1.04)
Duration of untreated psychosis	0.97 (0.73-1.28)	1.00 (0.76-1.31)	0.94 (0.70-1.25)
Duration of untreated continuous psychosis	0.60 (0.43-0.85)[b]	0.61 (0.44-0.86)[b]	0.68 (0.48-0.96)
First-episode characteristics			
Compulsory index admission	1.09 (0.72-1.66)	0.90 (0.59-1.38)	1.10 (0.71-1.68)
Length of index admission	0.85 (0.75-0.97)[a]	0.91 (0.80-1.03)	0.95 (0.84-1.07)
Spontaneous dyskinesia/parkinsonism	0.86 (0.79-0.92)[c]	0.87 (0.82-0.94)[c]	0.89 (0.83-0.95)[b]
Neurological soft signs	0.94 (0.92-0.97)[c]	0.94 (0.91-0.96)[c]	0.95 (0.93-0.98)[b]
Deficit syndrome	0.22 (0.09-0.55)[b]	0.30 (0.14-0.65)[b]	0.38 (0.18-0.78)[b]
Dimensions of psychopathology:			
Reality-distortion	1.10 (0.95-1.28)	1.10 (0.95-1.27)	1.11 (0.95-1.31)
Disorganization	1.03 (0.89-1.19)	1.01 (0.88-1.17)	0.95 (0.81-1.11)
Negative	0.88 (0.74-1.05)	0.92 (0.78-1.09)	0.99 (0.82-1.19)
Catatonia	0.94 (0.79-1.11)	0.97 (0.83-1.14)	0.86 (0.72-1.04)
Mania	1.09 (0.95-1.25)	1.08 (0.94-1.24)	**1.19 (1.04-1.36)[b]**
Depression	1.10 (0.95-1.25)	1.12 (0.97-1.28)	1.00 (0.86-1.17)
DSM-5 diagnosis:			
Schizophrenia	0.57 (0.35-0.93)[a]	0.53 (0.32-0.87)[a]	0.79 (0.50-1.25)
Schizophreniform disorder	0.89 (0.54-1.47)	0.86 (0.52-1.42)	0.76 (0.44-1.31)
Brief psychotic disorder	1.65 (1.04-2.63)[a]	1.75 (1.11-2.75)[a]	**1.54 (0.95-2.51)**
Mood disorder with psychotic symptoms	1.26 (0.70-1.81)	1.24 (0.78-1.97)	0.94 (0.61-1.46)
Other psychotic disorders	1.24 (0.71-2.16)	1.12 (0.63-1.98)	1.12 (0.69-1.81)
Early treatment response			
At discharge from index admission	1.88 (1.20-2.93)[b]	1.82 (1.18-2.81)[b]	**1.56 (1.01-2.41)**
6 months after index admission	2.02 (1.22-3.33)[b]	2.52 (1.35-3.74)[b]	**1.50 (0.93-2.40)**

In bold are presented the associations that differed from those in the total sample (n=243) in terms of statistical significance at p<0.05 level.

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Supplementary Table 6. Hierarchical multivariate Cox regression analysis of baseline candidate predictors by recovery domain in participants aged ≤35 at study entry (n=193)

	Symptomatic recovery (n=99)	Functional recovery (n=102)	Personal recovery (n=94)
Step 1 (demographics)			
Parental SES	0.58 (0.40-0.78)[c]	0.59 (0.41-0.78)[c]	0.62 (0.43-0.90)[a]
High school	–	–	1.70 (1.06-2.73)[a]
Step 2 (familial load)			
Family history of SSD	0.45 (0.22-0.73)[b]	0.46 (0.25-0.81)[b]	0.39 (0.20-0.75)[b]
Step 3 (early risk factors)			
Developmental delay at age 3	0.78 (0.68-0.98)[a]	0.70 (0.63-0.90)[b]	0.73 (0.63-0.88)[b]
Step 4 (intermediate risk factors)			
Childhood adversity	1.02 (1.01-1.04)[a]	1.03 (1.02-1.04)[a]	1.02 (1.01-1.04)[a]
Step 5 (proximal risk factors)			
Drug use	1.26 (1.12-1.39)[b]	1.25 (1.12-1.40)[b]	1.23 (1.10-1.37)[b]
Acute psychosocial stressors	1.25 (1.04-1.35)[a]	1.22 (1.02-1.33)[a]	–
Step 6 (illness onset features)			
Duration of untreated continuous psychosis	0.63 (0.41-0.87)[b]	0.64 (0.38-0.89)[b]	–
Step 7 (first-episode characteristics)			
Spontaneous dyskinesia/parkinsonism	0.89 (0.78-0.95)[b]	–	–
Neurological soft signs	–	0.95 (0.91-0.97)[b]	–

Notes: Age at illness onset no longer predicted symptomatic and personal recovery, since these variables were not included in the model because lack of significance in the univariate analysis. At Step 8 (early treatment response), no variable entered in the model.

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