BMJ Open

Shanghai Community-Based Schizophrenia Cohort (SCS): a protocol for establishing a longitudinal cohort and research database of patients with schizophrenia receiving community-based mental health treatment

Youwei Zhu,1,2 Siyuan He,1 Yanli Liu,1 Chunmei Chen,1 Xiaolei Ge,1 Weibo Zhang,1,2,3 Yi Zhu,1 Qing Zhou,4 Yihua Jiang,5 Yanping Zhang,6 Weiyun Xu,7 Na Wang,8 Jun Cai,1,9 Bin Xie10

ABSTRACT

Introduction Drivers for remission, relapse and violence-related behaviour among patients with schizophrenia are the most complicated issue.

Methods and analysis This study aims to recruit a longitudinal cohort of patients with schizophrenia. Two suburban districts and two urban districts were randomly selected according to health service facilities, population, geographical region and socioeconomic status. Individuals (>18 years old) who received a diagnosis of schizophrenia following the International Classification of Diseases (10th edition) criteria within the past 3 years will be invited as participants. Assessments will be carried out in local community health centres. Data will be used to (1) establish a community-based schizophrenia cohort and biobank, (2) prospectively determine the course of multidimensional functional outcomes of patients with schizophrenia who are receiving community-based mental health treatment, and (3) map the trajectories of patients with schizophrenia and prospectively determine the course of multidimensional outcomes based on the differential impact of potentially modifiable moderators.

Ethics and dissemination The study has been reviewed and approved by the Human Research Ethics Committee of Shanghai Mental Health Center (2021-67). Results of the study will be disseminated through peer-reviewed journals. If effective, related educational materials will be released to the public.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This ongoing, large-scale community-based cohort study is one of the first studies to comprehensively investigate the health profiles and prognosis of community-dwelling patients with schizophrenia in China.

⇒ The use of multidimensional outcomes and health profiles provides an opportunity to investigate predictors of relapse and recurrence and to establish a community-based prognostic model that could facilitate the development of new mental health services.

⇒ The short follow-up duration (3 years) may limit the generalisability of the findings.

⇒ This study will only recruit patients receiving community-based mental health treatment, which may limit the generalisability of the findings.

INTRODUCTION

Schizophrenia is a devastating, complex, severe mental disorder that affects approximately 1% of the global population.1 It is characterised by several complex positive and negative symptom clusters and subcluster and cognitive impairment—positive symptoms, also known as psychosis or the psychotic syndrome, common positive symptoms including delusions, hallucinations, behaviour disorder and formal thought disorders such as speech that are difficult to follow or even to the point of incomprehensibility.3 Positive symptoms are often the main reason the patient presents to the clinician.4 While negative symptoms mainly consist of a lack of volition, reduced speech output, diminished expression, anhedonia and asociality,5 6 Schizophrenia leads to a tremendous public health burden worldwide, and its incidence is increasing annually.4 Since 2016, it has become the most disabling disorder worldwide, accounting for 7.4% of disability-adjusted life years and nearly 13.4 million years of life lived with disability.7 The life
expectancy of patients with schizophrenia is approximately 15 years shorter than that of the general population. In many countries, the social cost of this disease has even exceeded $20 000 per patient. In China, the weighted lifetime prevalence and 12-month prevalence of schizophrenia are 0.6%, and the weighted 12-month prevalence of schizophrenia has reached 1.4% for people aged between 18 and 34 years. The disease imposes a serious financial burden and considerable socioeconomic loss in this age group.

Schizophrenia is a longstanding mental disorder; therefore, the long-term outcomes of patients have received an increasing amount of attention. Interventions to treat relapse and prevent violence have already been implemented among patients. However, relapse is still common among this population. It is the occurrence of at least one positive symptom or two negative symptoms after a period of remission. These symptoms often include the reappearance or development of auditory hallucinations, delusions and thought disorder for positive symptoms, while anhedonia, asociality, flattening of affect and demotivation for negative symptoms. One systematic review of longitudinal studies estimated that the pooled prevalence rates of relapse of positive symptoms were 28% and 54% at the 1-year and 3-year follow-ups, respectively. 24% of patients relapse at 7–12 months despite receiving drug treatment, although this percentage is much lower than that of patients who are not receiving drug treatment. Generally, continual relapse is positively correlated with detrimental long-term outcomes and irreversible progression of brain integrity. There is also a subgroup of patients with a heightened risk of violent and aggressive behaviours. Compared with the general population, patients with schizophrenia have more than a fourfold greater risk of exhibiting aggressive behaviours and even committing violent crimes. The 1-year prevalence of violent episodes in patients with schizophrenia who are receiving stable treatment has reached 21.8%. In addition, a multicentre retrospective study showed that vocational function and household income are predictors of relapse, but these two risk factors were not regarded as predictors of relapse in our studies conducted in developed countries. Additionally, the models that have been used for predicting relapse are relatively simplistic, and little attention has been devoted to community-based patients. To advance our understanding of the pathophysiology of schizophrenia and to progress towards disease-modifying treatments and relapse prevention, it is essential to investigate schizophrenia relapse as broadly as possible in community-dwelling patients. Here, we report a cohort study of community-dwelling individuals with the aim of identifying markers for improved mental health management among patients with schizophrenia who exhibit relapse or aggressive behaviours.

Shanghai is one of the largest and most urbanised cities in China. In 2021, the life expectancy of residents reached 84.11 years (81.76 years for males and 86.56 years for females). Urbanisation and changes in lifestyle may have affected the mental health of these populations. According to the 2021 Shanghai Statistical Yearbook, the mental illness death rate was 8.83 per 100 000 individuals, which was the seventh highest among all causes of death (https://tjj.sh.gov.cn/tjnj/20220309/0e01088a76754b448de6d608c42dad0f.html). Long-term community-based medication is crucial for preventing mental illness. In 2001, Shanghai enacted China’s first local regulation on mental health, namely, the ‘Shanghai Mental Health Regulations’, followed by the ‘Shanghai Mental Health System Construction and Development Plan (2020–2030)’ and ‘the Shanghai Community-based Health Management Regulations for Severe Mental Disorders Service Management (2019 edition)’. These efforts all promoted the development of community-based mental health in Shanghai. From 2001 to 2020, community-based mental health services developed rapidly in Shanghai. Patients had the highest regular management rate and stable rate, with a much lower Gini coefficient in China than in other countries. The prevalence of schizophrenia in China has more than doubled since 2010, with particularly high rates observed in the most developed areas of modern China; moreover, the prevalence of schizophrenia is still increasing. As the most populous and developed city, Shanghai provides an opportunity for studying the nature and magnitude of mental illness. Shanghai is a suitable research site for exploring the possible factors affecting the prognoses of patients receiving community-based mental health treatment in China. In addition, this community-based cohort study will provide guidance for optimising the mental health management system and for developing mental health policies.

Objectives of the study and conceptual framework
Schizophrenia is a chronic recurrent mental disorder with a high relapse rate. The purpose of this longitudinal study was to establish a cohort of patients with schizophrenia who were clinically stable, compliant with their
medication and adherent to community-based appointments. The aims of this follow-up study are as follows: 1. To study the process and prognoses of schizophrenia among current stabilised patients. 2. To map the clinical trajectories and explore the predictive effects of biological, psychosocial, imaging and other indicators on patient recurrence and other events among community-dwelling patients. 3. To create a progression and prognosis database of community-based patients with schizophrenia, thus providing a working foundation and sample resources for subsequent related mechanistic research, drug research and intervention research. 4. To establish a biobank of new cases to monitor the occurrence of disease recurrence, violent behaviours and other outcome events during the whole life cycle.

Standardised multidimensional and longitudinal assessments will be routinely carried out among first-episode and multiphase patients with schizophrenia who are receiving community-based mental health treatment in Shanghai. Key illness outcomes, including antipsychotic medication use, psychotic symptoms, social function, occupational function, physical health, stress events, aggressive violent behaviours, self-harm and suicidal-related behaviours, will be continuously measured and tracked over time.

METHODS AND ANALYSIS

Study setting and design
This study is an ongoing, community-based, naturalistic longitudinal cohort study that examines potential differences in relapse risk factors, development, cognition and behaviour in community-dwelling patients with schizophrenia. The study was designed and will be conducted by the Shanghai Mental Health Center, Xu Hui Mental Health Center, Hong Kou Mental Health Center, Jinhua Mental Health Center and Min Hang Mental Health Center in Shanghai, China. Eligible patients were informed of the study and encouraged to participate. Informed consent forms were obtained from the patients and their guardians before enrolment in the study. The ethics committee at the Shanghai Mental Health Center approved this study protocol.

Study population and eligibility criteria
Patients with schizophrenia older than 18 years will be encouraged to participate in this cohort study. The eligibility criteria are as follows: (1) received either an outpatient or inpatient diagnosis of schizophrenia in accordance with the International Classification of Diseases (10th edition) (ICD-10) criteria within the past 3 years; (2) aged between 18 and 65 years; (3) IQ >70 as measured by the short form of the Wechsler Adults Intelligence Scale-IV; and (4) clinically stable and provided informed consent. According to previous studies, a current clinically stable state was defined as no exacerbation of psychotic symptoms or less than a 50% change in the dose of any primary psychotropic medication for the previous 3 months. The exclusion criteria will be as follows: (1) history of head injury and/or a neurological condition; (2) a history of head trauma with loss of consciousness; (3) pregnancy; (4) history of illicit drug abuse; (5) low level of proficiency with the Chinese language and lacked cooperativeness with the assessment; and (6) not living in Shanghai or planning to leave and settle down in other cities within 6 months.

Recruitment and enrolment process
The recruitment of eligible subjects started in January 2022. Recruitment and enrolment are scheduled to occur at local community healthcare centres. Enrolment and follow-up are conducted simultaneously. Enrolment will be completed when the sample size meets the requirements of our cohort study. The full cohort is anticipated to be complete when all patients complete the 3-year follow-up. Two trained psychiatrists or general practitioners will refer potential candidates to the principal investigator of the project and arrange a first prerecruitment interview in the nearest community healthcare centres. Detailed information on the project will be provided to the candidate and their guardian. Those who meet the study criteria and agree to participate will be invited to complete the demographic data questionnaire. All participants will be encouraged to continue their medication during the whole study period.

Outcome measures
Clinical efficacy is a commonly used outcome variable for schizophrenia prognosis and is usually defined as a clinically meaningful percentage of reduction in symptoms. Rating scales such as the Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome Scale can also be useful for measuring clinical efficacy. Previous studies have revealed that a cut-off of at least a 25% reduction in the BPRS score from baseline roughly indicates minimal improvement according to Clinical Global Impressions. Based on the above criteria, in this cohort study, the primary outcome measure is clinical efficacy, which is defined as a 25% decrease in the BPRS score compared with the last assessment.

The secondary outcomes include relapse, violent attacks, suicide, suicide attempts, suicide ideation, cognitive function, social function, disease burden and quality of life. Risk behaviours such as violent attacks, suicide, suicide attempts and suicidal ideation will be evaluated and assessed by general practitioners from community health centres. Additionally, suicide will be judged by general practitioners based on diagnostic criteria according to the ICD-10.

In our study, relapse is defined using three operational evaluation criteria based on previous study results: (1) change in antipsychotic medication use due to exacerbation of psychotic symptoms; (2) increased frequency of outpatient mental health services or rehospitalisation; and (3) patient needs intensive supervision because
of self-harm, violent behaviours, suicidal/homicidal ideation or related behaviours. Relapse outcome information will be collected through family member reports and clinical evaluations by general practitioners in the community every 3 months. Patients who meet any of the aforementioned conditions will be considered to have experienced relapse.

Data collection procedures

After providing informed consent, two standardised baseline clinical assessments are scheduled. Each enrolled participant will be invited to receive free assessments at the local community health centre. Although there are no direct monetary benefits for each participant, individuals will receive their assessment report after each assessment.

During the first interview, information regarding sociodemographic characteristics, family medical history of mental illness, medical history, employment status, living arrangement, family and social support, and financial status is collected by two trained mental health professionals. The standard 18-item version of the BPRS will be administered for the assessment of psychopathology symptoms every 6 months during the follow-up period. The Patient Health Questionnaire-9, Generalized Anxiety Disorder-7 and Life Event Scale (LES) will be administered to assess psychological status. The LES evaluates 48 common life events in China regarding family, occupational, academic and social communication domains. A higher LES score indicates greater psychological stress. The LES was designed specifically for Chinese people and has good inter-rater reliability and internal consistency. These three assessments will also be administered at baseline and every 6 months.

In the second interview, participants will be interviewed by a trained psychiatrist, and the following instruments will be administered: the Montreal Cognitive Assessment, the Perceived Social Support Scale (PSSS), the Social Disability Screening Schedule, the Modified Overt Aggression Scale, the Pittsburgh Sleep Quality Index and the WHO Quality of Life Instruments. The second interview will also be conducted every 6 months. Multimodal MRI can be used to reveal structural and functional changes in the brain. Structural and resting-state MRI data will be obtained with a Siemens 3T Primsa scanner at the Neuroimaging Core at the Shanghai Mental Health Center.

All the assessments will be administered at baseline and at the 12-month, 24-month and 36-month follow-ups except for the health history and the PSSS, which will only be assessed at baseline. Considering the workload of each subject, follow-up assessments will be scheduled in 2 days. In addition, this study specifically focuses on patient relapse-related outcomes, recurrence-related outcomes and prognosis-related events, such as an increased frequency of outpatient mental health services, rehospitalisation, relapse, violent behaviours, dangerous behaviours, and suicide-related and self-harm-related behaviours. Patients will be scheduled for follow-up every 3 months. These outcomes are assessed and evaluated by general practitioners in community health service centres.

To elucidate potential blood biomarkers of diseasespecific alterations in patients with schizophrenia, peripheral blood samples will be collected at baseline, at the 1-year follow-up, at the 2-year follow-up and at the 3-year follow-up. At baseline, 7 mL of blood will be collected for proteomic and genomic studies, while at 12-month, 24-month and 36-month follow-ups, only 5 mL of peripheral blood will be collected for proteomic analyses. Risk behaviour assessments will be carried out every 3 months after recruitment. The data will be collected via telephone or face-to-face interviews according to self-reports or caregiver reports. In our study, risk behaviours include aggressive behaviours, stressful events, traumatic events, alcohol and nicotine usage, psychotic symptom recurrence, adverse reactions related to antipsychotic medication, physical disease and employment. Physical examination for weight, height, waist and hip circumference evolution, blood pressure, blood sugar, blood routine, glycosylated haemoglobin, blood lipid level and ECG tests were conducted every 6 months during follow-up. In addition, long-term follow-up will be continued if desired by the subjects, even after the 3-year follow-up. An overview of the assessments is shown in figure 1.

Sample size calculation

There are multiple prognostic outcomes of schizophrenia, including remission, relapse, psychotic symptom-related violent behaviour, self-injury and suicide. We assumed that suicide has the lowest incidence and applied this to calculate the sample size; the formula is as follows:

\[ n = \left( \frac{z_{\alpha} \sqrt{pq} + z_{\beta} \sqrt{p_0 q_0 + p_1 q_1}}{p_2 - p_3} \right)^2 \]

According to contemporary studies, the suicide rate \( p_0 \) is set as 5%. The other related parameters are set as \( \alpha = 0.05, \beta = 0.1, Z_{\alpha} = 1.96 \) and \( Z_{\beta} = 1.28 \).

Considering the need for subgroup analysis and the 20% loss to follow-up, as we increased the total sample size to 1000, a total of 1200 patients needed to be included according to a 20% loss to follow-up. This 3-year cohort study aimed to recruit at least 1200 community-dwelling patients with schizophrenia.

Data storage and analysis plan

Each participant will be assigned a unique identification number. The corresponding data will be entered into the electronic case report form platform and maintained anonymously on password-locked computers and mobile hard disks.

During the assessment, all the questionnaires will be checked by two independent personnel to minimise missing data. If more than 10% of the items are missed or have obvious logical errors, the questionnaire will be considered invalid. In these cases, we will reinvite patients to complete the questionnaire or recruit new patients. In the data imputation stage, data will be imputed and...
cross-checked by two independent professionals. During the analysis stage, a multiple imputation model will be applied to handle missing outcome data. Potential predictors with more than 50% missing data will be discarded from the prediction model analysis.

All the statistical analyses will be performed in line with the objective as formulated above. In general, demographic data, clinical assessments, psychological status assessment and physical examination variables will be presented as the mean±SD or median. Relationships between relapse, psychosocial and demographic variables will be analysed using multiple regression and structural equation models. Mixture models will be used to identify subgroups of participants based on their psychosocial, physical and mental health characteristics. Multivariate analysis by linear or logistic regression will be performed to identify independent predictors of primary and secondary outcome measures. Mixed models, repeated analysis of variance, Cox regression and latent class growth analysis will be applied in the longitudinal data analyses. Relapse HRs will be estimated using proportional hazard regression. Finally, based on the Transparent Reporting for Individual Prognosis or Diagnosis guidelines, a relapse prediction model will be developed using regression analysis and machine learning approaches. α=0.05 (two tailed) was set as the statistical significance level. Statistical analyses will be performed using IBM SPSS Statistics V.21 or R software.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this community-based cohort study.

Findings to date

As of 31 December 2023, we have recruited 660 participants. Baseline face-to-face interviews and clinical examinations have been conducted with all 660 participants. A total of 534 participants have completed the first follow-up assessments. The mean age of the recruited participants was 47.04±15.07 years. A total of 329 participants were female, and 264 participants were male. The average age at diagnosis was 41.33±15.58 years.

DISCUSSION

Here, we introduce the protocol for a cohort study to predict relapse and violence among patients with schizophrenia. This is the first community-based prospective cohort study examining multiple vulnerability and resiliency factors associated with the rehabilitation of patients with schizophrenia. This cohort study aims to recruit 1200 patients with clinically stable schizophrenia who are receiving community-based rehabilitation and mental health treatment. Comprehensive demographic, biological, clinical, psychological and social function data will be collected during the 3-year follow-up. Meaningful associations between outcomes and assessment measures will provide valuable information on mental health services for community-dwelling patients with schizophrenia. The

Figure 1  Overview of the cohort study process and data collection procedure. ICD-10, International Classification of Diseases (10th edition); WAIS-IV, Wechsler Adults Intelligence Scale.
results will also help to identify patients at risk of relapse and violence and might facilitate the development of interventions targeted at improving health services for these patients.

In China, when a patient’s condition stabilises after inpatient or outpatient treatment, he or she is referred to a community health service centre for further community-based mental health and rehabilitation services. These services mainly included antipsychotic maintenance treatment, behaviour therapy, social skills training, vocational rehabilitation, health education, physical examination and regular follow-up services. A mental health service team is responsible for these aforementioned services. The team members include general practitioners, psychiatric nurses, psychological therapists and rehabilitation therapists. If a patient relapses, team members refer the patient to the hospital. Currently, nearly 90% of patients with schizophrenia live and receive community mental health treatment in their communities, and a robust method of measuring disease progression among community-based patients is imperative for advancing the development of disease-modifying treatments. In addition, given the clinical and possible aetiological heterogeneity of psychotic symptoms, accurate markers of disease relapse could advance our understanding of disease mechanisms and lead to the implementation of patient-modifying interventions, especially for high-risk violent patients.

Our community-based cohort fulfils these needs and takes advantage of the linkage between hospital-based and community-based mental health services, which could have great implications for the development of high-quality mental health services, especially for community-dwelling patients.

Author affiliations
1Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China
2Shanghai Institute of Infectious Disease and Biosecurity, Fudan University, Shanghai, People’s Republic of China
3Mental Health Branch, China Hospital Development Institute, Shanghai Jiao Tong University, Shanghai, People’s Republic of China
4Shanghai Xu Hui Mental Health Center, Shanghai, China
5Shanghai Min Hang Mental Health Center, Shanghai, China
6Shanghai Jin Shan Mental Health Center, Shanghai, China
7Shanghai Hong Kuo Mental Health Center, Shanghai, China
8Fudan University, Shanghai, Xuhui District, China
9Shanghai Key Laboratory of Psychotic Disorders, Shanghai, China
10Forensic Psychiatry, Shanghai Jiao Tong University School of Medicine Affiliated Shanghai Mental Health Center, Shanghai, China

Acknowledgements The authors would like to thank the psychiatrists, general practitioners from community health service centres, and social workers who participated and helped recruit and follow up patients during the study. We wish the patients speedy recovery.

Contributors YQZ and SH are responsible for the writing and editing of the original paper; in addition, they contributed equally to this paper. YL and SH are in charge of data quality control and data cleaning. YL also helped write and edit the revised paper. QZ, YJ, YQZ and WX are in charge of designing the subjects’ recruitment and data collection plan. CC, YQZ and XG contributed to the data quality control plan. English language editing and data analysis were carried out mainly by NW and WZ. JC and BX contributed to the conception and design of this study.

Funding Health Industry Clinical Research Project of the Shanghai Municipal Health Commission (2020040362); Shanghai New Star Young Medical Talents Training Program; the Science and Technology Commission of Shanghai Municipality Research Project (19411950800); Project of the Key Discipline Construction, Shanghai 3-Year Public Health Action Plan (GWJ-10.1:KX18, GWJ-11.2-XD25); Key Project of ‘Medical and Industrial Cross-Research Foundation’ of Shanghai Jiao Tong University in 2024 (HG2024ZD04); Project of Science and Technology Committee of Xuhui District (Shh01202040); key discipline construction project of public health in Minhang District (MGWKX05); Project of Science and Technology Committee of Minhang District (2020MH0009); Medical project of Hongkong District Science and Technology Committee (2201-04, 2023XKR098) and the fourth cycle ‘Excellent Young Talents’ training programme of Jinshan District Health Commission (JSYQ201915).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Youwei Zhu http://orcid.org/0000-0001-7891-3297

REFERENCES
5 Holder SD, Wayhs A. Schizophrenia. Am Fam Physician 2014;90:775–82.


26 Zhao M, Ma N, Wang X, et al. Community-based management and treatment services for psychosis - China, 2019


