


Clinical high risk for psychosis provides new opportunities for schizophrenia intervention strategies

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To cite: Wang J, Stone WS. Clinical high risk for psychosis provides new opportunities for schizophrenia intervention strategies

General Psychiatry 2022;**35**:e100736. doi:10.1136/gpsych-2021-100736

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/gpsych-2021-100736>).

Received 02 April 2022
Accepted 15 April 2022



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Schizophrenia is a chronic lifelong illness that is associated with huge healthcare burdens for society and healthcare systems, and even more so for ill individuals and their families. It is characterised clinically by problems in multiple domains, including cognition, motivation, thinking, brain function, social functioning, and mood. Many of these difficulties precede the formal diagnosis of schizophrenia or a related disorder such as schizoaffective disorder. Psychosis usually develops in adolescence or early adulthood, after many of these clinical problems have already started, and eventually leads to the formal diagnosis of the illness.

Although helpful pharmacological treatments are available for schizophrenia, they do not fully ‘restore’ people to their previous states of health, and, as importantly, they do not treat all the problems created by the illness. Antipsychotic medications, for example, do not improve cognitive deficits or social dysfunction, which leaves many people unable to learn in school or work productively, even though their symptoms of psychosis (eg, auditory hallucinations, delusional thinking and paranoia) are likely reduced. For this reason, in addition to developing new treatments for schizophrenia, it is critically important to understand how the illness progresses and who is most likely to develop it to guide the development of therapeutic interventions that prevent it from occurring.

At this point, despite considerable gains in our knowledge about risk factors and mechanisms involved in the development of psychosis, we do not yet know enough to predict who will become ill. However, we know that many individuals experience a period of clinical high risk (CHR)

for psychosis (also called a prodrome for psychosis) that precedes the first psychotic episode. During this period, many patients start to experience symptoms that increase in frequency and intensity that then culminate, for some of them, in schizophrenia or other disorders involving psychosis. This high-risk period is also when many individuals and their families first notice something is wrong, leading them to seek help in institutions like the Shanghai Mental Health Center. Many of these individuals enrol in CHR studies to help understand further what is happening to them and to discover whether effective treatments are available. These CHR studies provide new opportunities to improve our understanding of schizophrenia and to develop new interventions to prevent psychosis.

Over the past 30 years, a growing number of research groups have moved the CHR field forward. Some of these have formed consortia, such as the North American Prodrome Longitudinal Study (NAPLS; centred in North America); the Personal Assessment and Crisis Evaluation (PACE; centred in Melbourne, Australia); PSYSCAN, a neuroimaging-based consortium centred in London; Personalised Prognostic Tools for Early Psychosis Management (PRONIA), a consortium centred in Munich; the Philadelphia Neurodevelopmental Cohort (PNC; centred in Philadelphia); the Outreach and Support in South London project (OASIS; centred in London); the Psychosis Risk Outcomes Network (ProNET; centred in North America but including European and Asian sites such as the Shanghai Mental Health Center) and PRESCIENT, also centred in Melbourne.

In addition to the consortia, individual sites also play critical roles in studying

CHR. Among these, the Shanghai-At-Risk-for-Psychosis (SHARP) study in Shanghai, China, is one of the largest single-site CHR studies in the world, which reduces heterogeneity due to site differences. SHARP subjects are also psychotropic medication naive at the time they enter the study. The SHARP research programme was launched about 10 years ago and has grown consistently in breadth of research and productivity.

In this issue, *General Psychiatry* has published several papers submitted by young researchers from the SHARP team, associated mainly with novel biomarkers or state-of-the-art research techniques employed in the study of CHR subjects.

Among these, the study by Zhu *et al*¹ examined eye movement abnormalities using eye-tracking paradigms. They investigated attentional biases involved in processing interpersonal communication and found biases towards pictures with intense interpersonal information value across different clinical phases in schizophrenia.

Functional near-infrared spectroscopy measures levels of oxygenated haemoglobin (Oxy-Hb) in cortical regions of interest. A study by Wei *et al*² observed significantly decreased levels of Oxy-Hb over the right superior temporal gyrus (STG) in CHR compared with healthy controls during a verbal fluency task and its significant correlation with performance on a working memory task in CHR. This interesting finding emphasises an important role of the (non-dominant) right STG in a verbal task in CHR subjects.

While electroencephalogram (EEG) has a long history in the study of psychosis, its signal-to-noise ratio is relatively low due to disturbances coming from the skull and scalp. The study by Hu *et al*³ applied a novel technique, magnetoencephalography (MEG), to record resting-state neural activities in CHR. Analysis of the resting-state MEG data in CHR subjects and controls showed a good signal-to-noise ratio of MEG. It also showed abnormal theta-band neural oscillations in the left occipital lobe and the left temporo-occipital junction and abnormal delta-band neural oscillations in the right dorsolateral prefrontal lobe for CHR. These data suggest that MEG may provide a promising approach to brain dysfunction in CHR.

In recent years, much attention has been paid to the association of metabolic deficits with psychosis. In this context, a study by Su *et al*⁴ reported a different pattern of association between brain white matter microstructure and plasma unsaturated fatty acids among CHR subjects compared with controls. A study by Gan *et al*⁵ reported an attenuated niacin-induced skin flush response in individuals with CHR for psychosis. Both studies provided new evidence suggesting metabolic deficits in CHR subjects. It should be noted that the blunt niacin-induced skin flush response has been reported among patients with schizophrenia with good specificity. This abnormality might be potentially useful for quick and convenient screening for CHR. In

light of this possibility, a study by Chen *et al*⁶ designed a new device and explored the feasibility of artificial intelligence-assisted niacin skin flush screening in CHR and first-episode psychosis.

After 30 years of largely passive observation, CHR researchers are also starting to turn their collective attention to interventions that might prevent or at least ameliorate the development of psychosis. At this point, interventions for CHR reflect a daunting challenge, but one that can no longer wait until we have answered all questions about how psychosis develops. Moreover, one of the few treatments available for CHR subjects, anti-psychotic medication, has yet to validate the hypothesis that it slows down or prevents conversion to psychosis. Moreover, many subjects are sensitive to the adverse side effects of these powerful drugs. Perhaps newer drugs with different mechanisms and side effect profiles are on the horizon. For example, some studies have indicated that deficits in oxidative and inflammatory systems are extensively involved in the pathogenesis of psychosis. Sulforaphane (SFN) is a dietary phytochemical extracted from cruciferous vegetables. A review by Zheng *et al*⁷ that focused on biological mechanisms of SFN in upregulating multiple antioxidants or reducing inflammatory responses included pilot evidence from current clinical trials suggesting that SFN might be a new treatment choice for CHR. An SFN trial for CHR is ongoing in Shanghai, with results expected in the near future.

The work presented here highlights staff efforts at the Shanghai Mental Health Center, the largest mental health center in China, with about one million outpatient visits each year. The prevalence of CHR among those initial mental health seekers within the age range of 15–45 years is 4.2%, showing the strong demand for mental health services for this population. This need drives our research activities to acquire new data, develop new techniques and explore new biomarkers. It is hoped that this special issue on CHR for psychosis will attract more attention, investigators and institutions to reach the critically important goal of preventing psychosis and reducing so much suffering.

Contributors JW wrote the draft; WSS reviewed and revised the draft.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

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Dr William S. Stone is an Associate Professor of Psychology at the Harvard Medical School (HMS), the Beth Israel Deaconess Medical Center (BIDMC) and the Massachusetts Mental Health Center (MMHC), all in Boston, Massachusetts. He is a clinical psychologist and board-certified clinical neuropsychologist and is the Director of the Fellowship in Clinical Neuropsychology at HMS, BIDMC and MMHC. Dr Stone is also the current Secretary of the American Psychopathological Association and the Director of the Psychosis Research Program at BIDMC and MMHC. His research focuses on the identification of cognitive, biological and cognitive risk factors and biomarkers for the development and persistence of psychiatric illness. Dr Stone is the principal investigator (PI) on several NIMH-funded research grants, including the Shanghai-At-Risk-for-Psychosis (SHARP) study at the Shanghai Mental Health Center, in which he has worked closely with Professor Jijun Wang for over 10 years.