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COMMENTARY

Resurrection of the Follow-Back Method to Study the Transdiagnostic Origins of Psychosis
Comment on: "Timing, Distribution, and Relationship Between Nonpsychotic and Subthreshold Psychotic Symptoms Prior to Emergence of a First Episode of Psychosis", by Cupo et al.

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There has been a major drive in research trying to understand the onset of psychosis. Clinical-high risk (CHR) studies focus on opportunistic help-seeking samples with non-psychotic disorders and a degree of psychosis admixture of variable outcome, but it is unlikely that these represent the population incidence of psychotic disorders. Longitudinal cohort studies of representative samples in the general population have focused on development and outcome of attenuated psychotic symptoms, but typically have low power to detect transition to clinical psychotic disorder. In this issue of Schizophrenia Bulletin, Cupo and colleagues resurrect a time-honored method to examine psychosis onset: the epidemiological follow-back study, modernizing it to fit the research framework of the early intervention era. The authors set out to investigate the hypothesis that psychotic disorder represents the poorest outcome fraction of initially non-psychotic, common mental disorders and present compelling findings, unifying previous opportunistic CHR and representative cohort-based work.

Key words: psychosis/schizophrenia/transition/onset/affective symptoms

There is a major interest in advancing the research on predictive modeling of psychosis, similar to other areas of medicine such as cardiovascular medicine, oncology, and dementia care. This type of activity makes eminent sense, given that in the general population around a fifth of healthy people will be diagnosed with an illness requiring immediate attention one year later and, vice versa, around a sixth of chronically or critically ill people will become healthy a year later. Finding ways to understand and predict important health transitions, and the factors causally impacting on these, represents a growing part of health expenditure at the interface of clinical medicine and public health.

In some areas of health care, such as cardiovascular medicine, reliable risk prediction based on actuarial projection models forms part of clinical practice.[1] This type of work was developed on the basis of large prospective cohort studies in general populations, followed for many years in order to study the incidence and risk factors of disease, and its associated pathophysiology.

Psychosis research has been slow to develop strong links with public health approaches.[2] One reason is that the incidence of psychosis spectrum disorder is low and the latency long. Much of the risk contributing to adult mental ill-health is developmental. To conduct decades-long cohort studies to study the relationship between developmental risk and the onset of adult psychopathology is impractical and expensive. Although some impressive work has been carried out in, for example, the UK MRC birth cohort studies, the New Zealand Dunedin cohort study, the Israeli draft board studies, and the Scandinavian birth cohort studies, there is an urgent need for data on the ontogenesis and prediction in the psychosis spectrum.

In order to bypass the problem of low incidence and long latency inherent in population-based approaches to psychosis, high-risk approaches have been piloted, resulting in a burgeoning literature on prognostic prediction in so-called "ultra-high-risk" or "clinical high-risk" samples. The results of these, however, cannot be translated to psychosis incidence in the general population—and clinical practice—as they are based on non-epidemiological opportunity sampling of selected help-seeking individuals with a nonpsychotic disorder, yielding sample-specific results that are neither representative[3] nor generalizable.[4] Indeed, "transitions" in these individuals largely arise as a function of risk enrichment strategies embedded in specific sampling procedures,[5] further limiting their use as a model of the onset of psychosis in the general population.

Parallel to the high-risk research endeavors, a number of prospective population-based cohort studies, focusing on risk factors for mental health outcomes, including psychotic disorder, have been carried out. For example, the German EDSP and the Dutch NEMESIS-2 studies managed to follow representative cohorts of around respectively 3000 and 6600 individuals over a period of approximately 10 years, conducting four extensive structured interviews over that period. While these cohort studies yield interesting findings, analyses typically focus on the outcome of subclinical psychotic experiences, not clinical psychosis.[6] Although rare "transitions" to full psychotic disorder can be used to study real population-based transitions,[7] these analyses are often hampered by low power and difficulties accurately pinpointing transitions given low frequency of interviews over the follow-up period.

Despite the limitations of high-risk and population-based approaches of psychosis prediction, a consistent finding is the importance of the nonpsychotic psychopathology. The actual emergence of psychosis is not an isolated "onset" of a specific phenotype, but rather is an indicator of increasing severity/complexity of an underlying process of mixed psychopathology, particularly affective dysregulation.[8] These findings echo the increasing awareness that genetic and environmental risk and the clinical manifestation of early psychopathology, including psychosis, to large degree is "transdiagnostic." The broader, trans-psychopathological approach has conceptual and statistical advantages over a more narrow focus on psychosis in population-based research and can be indexed accurately in the clinical characterization framework.[9]

The question rises, however, how the trans-psychopathological study of the onset of psychosis can dive deeper into these issues whilst overcoming the limitations of both high-risk and population-based approaches. In this issue of *Schizophrenia Bulletin*, Cupo and colleagues[10] resurrect a time-honored method addressing this issue: the epidemiological follow-back study. The authors use intensive follow-back methodology to study the onset of psychosis in an epidemiologically representative incidence sample (n = 430), similar to the seminal work of Heinz Häfner in Germany, but modernizing it to fit the research framework of the current early intervention era. The authors thus introduce a much required innovative approach that can shed light on many unresolved issues and misunderstandings that are currently clouding the field.

The authors set out to investigate the hypothesis that psychotic disorder represents the poorest outcome fraction of initially nonpsychotic, common mental disorders. They expected that individuals experiencing a first-episode psychotic disorder would represent those with the most complex nonpsychotic syndromes, indexed as the number of pre-onset symptoms identified. Their follow-back paradigm allowed them to examine the hypothesis that initial subthreshold psychotic symptoms would follow nonpsychotic symptoms temporally, and that nonpsychotic symptoms would be more frequent and complex in those with subthreshold psychotic symptoms, as well as that more nonpsychotic symptoms would be predictive of more subthreshold psychotic symptoms.

Their results confirmed these hypotheses, thus for the first time shedding light on how the complexity and severity of nonpsychotic states may assist in the "transition" to admixture with subthreshold psychosis, thus initiating a prognostic separation from initial less severe and less complex nonpsychotic states. The authors thus suggest that what we commonly consider the onset of a "psychotic disorder" may in fact represent an outcome of a prior nonpsychotic state.

In resurrecting the follow-back methodology, the authors do psychiatric research a world of good. At a relatively low cost, they deliver data that are representative, well-powered statistically, and clinically highly relevant, shedding insight into the onset of psychosis in ways that ultra-high-risk and population-based approaches cannot. Standardizing follow-back procedures in clinical practice allows for pooling of data and even more fine-grained analyses, including moderators of the early course of nonpsychotic psychopathology on its way to psychosis admixture and relatively poor prognosis.

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