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The Critical Need for Help-Seeking Controls in Clinical High-Risk Research

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Abstract

Despite rapidly growing knowledge of the clinical high-risk (CHR) state for psychosis, the vast majority of case-control studies have relied on healthy volunteers as a reference point for drawing inferences about the CHR construct. Researchers have long recognized that results generated from this design are limited by significant interpretive concerns, yet little attention has been given to how these concerns affect the growing field of CHR research. We argue that overreliance on healthy controls in CHR research threatens the validity of inferences concerning group differences, hinders advances in understanding the development of psychosis, and limits clinical progress. We suggest that the combined use of healthy and help-seeking (i.e., psychiatric) controls is a necessary step for the next generation of CHR research. We then evaluate methods for help-seeking control studies, identify the available CHR studies that have used such designs, discuss select findings in this literature, and offer recommendations for research.

Keywords

clinical high-risk; psychosis; transdiagnostic; etiology; research design

Introduction

Hundreds of empirical reports have been published concerning those at clinical high-risk (CHR) for psychosis since the construct's inception two decades ago. Despite the exciting

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potential for scientific and clinical breakthroughs, a significant interpretive concern potentially limits the impact of this literature: The vast majority of CHR studies to date have relied on healthy controls as a reference point. Although common in psychopathology research, this strategy is problematic for studies of CHR states because the clinical characteristics of the average CHR participant are inherently complex and heterogeneous, most often involving non-CHR psychopathology in addition to psychosis-risk concerns. Despite this mixed clinical picture, group differences between CHR and healthy control groups in the literature are typically - and perhaps erroneously - attributed to risk status. It remains possible that the majority of findings to date are not related specifically to psychosis, but instead to nonspecific or co-occurring psychopathology among those at CHR. Fortunately, methodological approaches that take advantage of the broader help-seeking (i.e., psychiatric) population as comparison groups can help to resolve these interpretive issues, advancing the basic and translational understanding of CHR illness and the psychosis spectrum more broadly.

The thesis of this critical review is that (1) the field's reliance on healthy control designs threatens the validity of inferences that can be made about CHR illness and limits clinical progress, but that (2) the combined use of healthy and clinical, help-seeking control (HSC) groups represents a promising solution to this problem. We begin by briefly reviewing the principle of *threats to validity* in "case-control" research. Next, we discuss the significance of this principle to the present state of healthy control CHR research. We argue that (a) other diagnoses are highly prevalent and potentially even primary in CHR samples, but by design are absent from healthy samples; (b) many abnormalities observed among those at CHR closely parallel abnormalities that are common to these other diagnoses; (c) healthy control CHR designs are not ideal for paradigms informed by transdiagnostic models of psychopathology, such as the Research Domain Criteria (RDoC), the Hierarchical Taxonomy of Psychopathology (HiTOP), or by pluripotential frameworks for understanding the onset of mental illness; (d) reliance on healthy controls has limited capacity to enhance the specificity of psychosis prediction; and that (e) the comparison of CHR and healthy control groups has limited clinical utility. Concurrently, we describe how the addition of help-seeking control (HSC) groups to traditional CHR-control designs circumvents these threats and adds additional inferential benefits to CHR research by increasing the similarity of the groups on factors associated with psychopathology more generally, while preserving the uniqueness of clinical psychosis-risk to the CHR group - all while still allowing for contrasts against non-ill comparators. We then evaluate several methodological approaches to HSC designs, identify the available CHR studies that have used HSCs, and briefly discuss several. Finally, we discuss some implications of the models proposed here for experimental design, and conclude with recommendations for future research.

Threats to Validity in Case-Control Research

Threats to validity encompass the broad class of reasons why investigators can make incorrect inferences about research findings (Reichardt, 2000). In case-control designs (the research design most common in the CHR field), the characteristics of the control group exert a critical influence on the number, type, and degree of validity threats that affect the study, because the control group functions as a reference point from which inferences about

the clinical group are made (Shadish, Cook, & Campbell, 2002). Researchers for decades have voiced concerns about the threats to validity introduced by use of healthy controls in psychiatric research. In a seminal paper, Kendler (1990) demonstrated algebraically how exclusion of individuals with any psychiatric disorder from the control group results in extreme comparison of already-ill participants to never-ill, "supernormal" controls, inflating the effects of independent variables and muddling interpretability of study results. Similarly, Schwartz and colleagues have asserted that this practice violates principles of case-control research, because different entry criteria are applied to the two groups under study (Schwartz & Link, 1989; Schwartz & Susser, 2011). Others have shown empirically how choice of control group affects important conclusions made about clinical groups (e.g., inferences about brain structure in schizophrenia; Smith et al., 1988), and furthermore, researchers have concluded that the procedures by which controls are selected is most often either of poor quality or inadequately described, even among top psychiatric journals (Lee et al., 2007).

Despite the well documented limitations of relying on healthy participants as comparators, healthy controls continue to constitute sole comparison group in most CHR studies to date. We believe that the implications of this practice for CHR research have not been adequately addressed. The CHR field is now entering its third decade alongside the rising popularity of dimensional, transdiagnostic, and pluripotential models of developmental psychopathology (Krueger & Eaton, 2015; McGorry, Hartmann, Spooner, & Nelson, 2018), together highlighting the need for a more nuanced understanding of how psychosis develops. Although traditional healthy control designs have played a crucial role in putting the CHR construct "on the map" and will continue to provide essential clues about the pathophysiological basis of psychosis, it seems now is a good time to discuss the ways in which this convention has limited what we know about the CHR state and to discuss opportunities for addressing this important gap in the literature.

The Problem with Reliance on Healthy Control Designs in Clinical High-Risk Research

High rates of comorbidity in the CHR population.

CHR syndromes rarely present in the absence of other psychopathologies. An analysis of over 500 individuals at CHR found that 73% of participants met criteria for another DSM diagnosis at the time of identification (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014). These disorders tend to persist over time (Lin et al., 2015; Woods et al., 2017), and new onsets of psychiatric illness are also common (Kraan et al., 2017; Lin et al., 2015). In fact, baseline comorbidity, persistence of comorbid disorders, and emergence of non-psychotic diagnoses are more common in CHR individuals than either persistence of risk syndromes or transition to psychosis (Addington et al., 2011; Fusar-Poli, Schultze-Lutter, et al., 2016; Lin et al., 2015; Woods et al., 2017), raising questions about which pathophysiological mechanisms are primarily operating at the time of assessment. The striking prevalence of non-psychosis-spectrum psychopathology in CHR samples poses a significant interpretive problem for reliance on healthy control designs because the CHR and control groups *systematically differ* on a criterion that is highly likely to influence outcomes of interest in the same direction as CHR status: Other psychopathology. Group differences

could be due to psychosis-specific processes, to co-occurring mental health concerns in the CHR group, or to joint or interactive contributions of the two. Healthy control designs are inherently unable to disentangle these relative contributions.

In contrast to the healthy control design, a distinct advantage of HSC designs is that they are capable of accounting for the high rates of comorbidity among those at CHR. Because HSC groups are characterized by the presence of (non-CHR) psychopathology, group differences can more confidently be interpreted to be a unique function of a psychosis-spectrum process. In turn, more nuanced knowledge regarding the pathognomonic features of CHR illness can be attained, advancing the understanding of early psychosis and the broader psychosis spectrum.

Common illness processes across psychosis-risk syndromes and frequently co-occurring psychiatric disorders.

As would be expected given the high rates of other DSM diagnoses in the CHR population, many of the seemingly core deficits observed among those at CHR are seen in the very disorders with which CHR tends to co-occur, such as major depressive disorder (MDD), bipolar disorder, anxiety disorders, and posttraumatic stress disorder. For example, elevated resting cortisol (Chaumette et al., 2016) and inflammatory cytokines (Perkins et al., 2014), hippocampal atrophy (Fusar-Poli et al., 2013), impaired executive function (Bora & Murray, 2013), history of trauma exposure (Kraan, Velthorst, Smit, De Haan, & van der Gaag, 2015), and social impairment (Fusar-Poli et al., 2017) are all observed in individuals at CHR relative to healthy controls. These same abnormalities, however, are also observed among those with MDD relative to healthy controls (Danese et al., 2009; Kessler et al., 2003; Lee, Hermens, Porter, & Redoblado-Hodge, 2012; McGorry et al., 2014; Schmaal et al., 2016; Slavich & Irwin, 2014). The fact that these illness markers are observed in individuals with CHR but also those with MDD while approximately half of those at CHR present with a comorbid depressive disorder (e.g., Fusar-Poli et al., 2014; Kline et al., 2018) suggests that inferences drawn from the healthy control literature must be limited to the conclusion that the role of these factors in the CHR population may be *nonspecific*.

Due to the high rates of false positives for transition to psychosis in CHR research, crosssectional studies (the majority of CHR publications) are particularly affected by concerns of illness specificity. Prospective longitudinal research has increased potential to identify unique vulnerability markers due to its built-in clinical control group (i.e., the non-transitioned individuals). Other than CHR-specific symptom severity (e.g., unusual thought content), however, factors that predict transition to psychosis are also often nonspecific and shared by multiple disorders, including neuroendocrine abnormalities (Hankin et al., 2016; Hariri & Holmes, 2015; Walker et al., 2013), cortical thinning (Bora, Fornito, Yucel, & Pantelis, 2010; Cannon et al., 2015; Schmaal et al., 2017), stress exposure (Green et al., 2010; Trotman et al., 2014), and social impairment (Cannon et al., 2008; Kessler et al., 2003). Because many HSCs are likely to present with these abnormalities as well, their use in CHR research can help to reveal whether these processes impact psychosis-risk symptoms directly (supporting the hypothesis that these are “core features” of psychosis), or indirectly

(supporting alternative possibilities, e.g., that they potentiate psychosis-specific symptoms but actually reflect a more generalized or multidimensional illness process).

Limited compatibility with transdiagnostic and pluripotential models of psychopathology.

The arguments articulated above suggest that reliance on healthy controls as a means to elucidate the mechanisms of CHR illness is not entirely compatible with dimensional, transdiagnostic models of psychopathology, including the National Institute of Mental Health's (NIMH) RDoC for psychopathology research (Insel et al., 2010) or the HiTOP initiative (Kotov et al., 2017). A central observation driving these paradigms is that, as noted above, psychiatric disorders tend to be highly comorbid. As a result, researchers have expressed doubt that these multiple disorders are truly distinct clinical entities, and have instead proposed that these variable clinical manifestations possess at least some common etiological mechanisms (Caspi et al., 2014; Kotov et al., 2017; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017; Sanislow et al., 2010). Similar hypotheses lie at the heart of pluripotential models, which highlight the tendency of risk factors for psychopathology to portend a range of clinical outcomes (Hartmann, Nelson, Ratheesh, Treen, & McGorry, 2019; van Os & Reininghaus, 2016). If depression, anxiety, or common psychiatric symptoms are related to psychosis etiology (and are not simply "comorbidities" of the CHR syndrome), it is important to leverage research designs capable of capturing this complexity while isolating dimensions hypothesized to be central to the CHR state (e.g., positive symptoms, aberrant salience). The HSC strategy complements RDoC, HiTOP, and pluripotential conceptual frameworks in that many RDoC domains (e.g., negative affect, executive function) and HiTOP components (e.g., dysphoria, anhedonia) are likely to be affected in HSCs beyond what would be seen in healthy samples, both at the time of identification and over time. Thus, a HSC group is likely to occupy a unique interval on the distribution of scores on domains of interest, allowing, together with a healthy control group, for a more complete, nuanced picture of how these domains contribute to psychosis as a unique condition.

Limited capacity to enhance specificity of psychosis prediction.

In order to best predict who among those seeking help for mental health problems will develop a psychotic disorder, enrolling individuals who are initially suspected of being at risk but who subsequently score low on prediction measures is a necessity. Healthy controls do not serve as optimally informative comparators because they are by definition not seeking help for the problems the measure was designed to identify, and thus are clinically unrepresentative of the population for which the measure would be used (Youngstrom, Meyers, Youngstrom, Calabrese, & Findling, 2006). As a function of this status, healthy controls are likely to have very low scores on many prediction measures, distilling the overall sample composition and inflating the instrument's apparent specificity (Youngstrom, Genzlinger, Egerton, & Van Meter, 2015). This is of particular concern when attempting to develop prediction measures for people at CHR, because only some of the remarkably heterogeneous psychopathology among these individuals is likely to be related to psychosis. Unfortunately, although clinical scale development studies for CHR have been among those that have already demonstrated the value of clinical controls, these measures continue to have relatively low specificity in predicting transition to psychosis (Fusar-Poli et al., 2015)

or, in the case of self-report screening instruments, interview-defined CHR status (Kline & Schiffman, 2014). Descriptive and experimental studies of people at CHR and HSCs will help to refine the understanding of the nature of true psychosis-risk, and as a result will promote the development of more efficient, cost-effective, and outcome-specific prediction measures.

Limited clinical utility.

In addition to the theoretical implications, reliance strictly on healthy control groups also is limited in its potential to advance clinical practice (Kapur, Phillips, & Insel, 2012). Practically, it is unlikely that most diagnosticians will be challenged to distinguish between attenuated or prodromal symptoms of psychosis and a “squeaky clean” mental health presentation among consumers. Rather, distinguishing between psychiatric diagnoses, identifying the degree of risk for specific outcomes (e.g., substance abuse, relapse of mood episodes), and determining the most appropriate course of treatment are of major clinical concern. With healthy controls as the primary reference point in the literature, clinicians have little empirical guidance in understanding how the majority of these clinical challenges concern clients at CHR over and above clients with other mental health conditions.

Relative to work with healthy controls, CHR research with HSCs may have enhanced potential to inform treatment development. Many psychosocial interventions for those at CHR are adaptations of treatments designed for individuals with other mental health concerns (e.g., depression, bipolar disorder, schizophrenia; Thompson et al., 2015), suggesting that the majority of intervention approaches are currently nonspecific. If common mechanisms of psychopathology account for the observed benefits of interventions across disorders (including reductions in transition rates from CHR to psychosis; Hutton & Taylor, 2014), targeting these processes may continue to present the most successful option. It is likely, however, that elucidating psychosis-specific vulnerability mechanisms will help researchers and clinicians to refine or distill psychosocial and pharmacologic treatment options to more directly target the mechanisms driving psychosis progression (Mulder, Murray, & Rucklidge, 2017).

CHR-HSC research is also likely to inform transdiagnostic staging approaches to early intervention in psychosis. In its earliest forms, psychopathology is often characterized by a nonspecific mixture of distress, motivational disturbances, and psychosomatic manifestations, among other features, which over time may or may not progress to fully syndromal disorders (Cicchetti & Rogosch, 1996; van Os, 2013). As research aims to identify individuals even earlier in the development of psychosis, this clinical overlap will become even more relevant. Novel interventions tailored to individuals’ type and presumed stage of illness represent a promising direction for widely implementable prevention programs (McGorry et al., 2018). Such interventions, however, first require prospective studies of people with a range of early phenotypic expressions to characterize trajectories, identify pluripotent vs. specific risk mechanisms, and point to treatment targets (Lee, Lee, Kim, Choe, & Kwon, 2018). Whether the mechanisms underlying recovery in CHR are common or specific, direct comparison of these mechanisms across the populations in which

they are affected is critical to a more informed approach to early intervention (Kazdin, 2007).

Methodological Approaches to Case-Control Designs in Clinical High-Risk Research.

Several unique case-control designs can be used in CHR research, each coming with its own unique practical and inferential benefits and limitations. In some situations, a healthy control group alone may be sufficient to address the research question, such as first-in-kind studies in which researchers simply wish to determine if a construct functions abnormally (at all) in people at CHR, or situations in which the specificity of an effect is considered of relatively little importance and the absolute effect is of primary interest. There may also be cases when a HSC group adds considerable incremental value to a study in the absence of a healthy control group, such as when well-established norms on a particular measure are available and comparisons between clinical groups and a known population average can be made. As previously discussed, however, the ideal approach to many CHR-control studies is likely to include more than one control group, including a group of HSCs and a group of typically developing individuals. Results generated from studies using just one of these comparators are susceptible to invalid inferences of specificity (i.e., in the case of studies relying only on healthy controls), loss of valuable information about shared risk factors (i.e., in the case of studies relying only on HSCs), or other inferential limitations and threats. In contrast, multiple control groups allow investigators to test more complex and differentiated hypotheses about the construct of interest and to elucidate the amount of hidden bias that may be present in a two-group design (Shadish et al., 2002). As Meehl (1971) concluded when discussing the relative inferential merits of adjusting or not adjusting statistical models for the effects of covariates, “we know more if we have both [findings] to think about” (p. 147).

Help-seeking controls who respond to clinical high-risk recruitment but fail to meet diagnostic criteria.

A useful approach to CHR-HSC research involves assignment of HSC status to participants who are initially recruited for inclusion in a CHR group, but upon clinical interview, are found not to meet CHR criteria. A primary benefit of this design is that these participants are drawn from the same participant pool as CHR participants, increasing the likelihood of their similarity to those at CHR in ways related to psychosis. For example, these HSCs may be more likely to report transient but distressing psychosis-like experiences than individuals recruited through other means. This would lend itself well to studies of the broader psychosis spectrum while also allowing for stringent tests of the dichotomous CHR construct. As a result, the design may be appropriate for studies that wish to determine the clinical utility of screening tools, diagnostic interviews, or neurocognitive tests aiming to distinguish CHR participants from other similarly help-seeking youth.

Other than instrument development, however, this design may not be ideal for dichotomized, case-control CHR research in which maximal group differentiation is the goal, particularly in studies in which small but meaningful effects are expected relative to healthy controls.

Psychosis is believed to present along a continuum, and the distinction between psychotic experiences that meet CHR criteria and those that do not has been criticized as arbitrary (van Os & Guloksuz, 2017). The conceptual significance of any observed group differences in essence depends on the construct validity of binary CHR criteria. Importantly, individuals who respond to CHR recruitment but do not meet the criteria may also genuinely be at risk (e.g., at an earlier stage of illness, less willing to disclose symptoms). Ultimately, given their dimensional similarity and likely overlapping etiologic origins (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009), group comparisons using this HSC design may be limited in their statistical power.

Help-seeking controls who meet a specific set of diagnostic or research criteria.

A second approach to HSC research may be assigning HSC status to help-seeking participants who meet specific DSM or research criteria that are of theoretical interest to psychosis or are highly common in CHR/psychosis. In contrast to the HSC method discussed above, this approach has the advantage of generating a more clinically defined control group and more confidence in ruling out the contribution of specific pathologies to group differences. Research that aims to test highly specific hypotheses about CHR would therefore be ideal in this context. Individuals with depressive and anxiety disorders may represent particularly good candidates for this design, as would individuals with high levels of internalizing or negative symptomatology regardless of DSM diagnosis (Strauss & Cohen, 2017). Evidence suggests a critical interplay between affective symptoms and psychotic experiences, or an “affective pathway to psychosis” (Myin-Germeys & van Os, 2007). An important study recently found that childhood maltreatment predicted not only the onset of psychosis, but also the onset of depressive and anxiety disorders in a large cohort of youth at CHR (Kraan et al., 2017). These findings suggest that the pathways to psychotic and affective disorders share common developmental mechanisms, highlighting the need to better understand where these pathways diverge among those at CHR.

A potential disadvantage of this approach is that not all individuals at CHR have prominent comorbidities, so the groups would not necessarily be matched in this respect, regardless of the specific diagnostic group selected for HSC status (e.g., affective disorders, neurodevelopmental disorders). Additionally, although these HSC participants are likely to be drawn from a population far more similar to the CHR population, and using much more similar recruitment strategies than are healthy controls, it is possible that sampling differences may still influence findings derived from this approach.

Help-seeking controls with clinical risk syndromes for non-psychotic disorders.

A third approach to HSC research in CHR studies may be to include individuals with clinical risk syndromes for disorders other than psychosis. Similar to the CHR state for psychosis, subdiagnostic levels of depression or hypomania are strong predictors of mood disorders (Birmaher et al., 2018). Interestingly, however, mounting evidence indicates that diagnostic outcomes of these high-risk states do not necessarily correspond to the disorder for which the individual was initially considered at risk (Kaymaz et al., 2007; Lee et al., 2018; Woods et al., 2017). Clinical criteria have recently been developed to identify attenuated, high-risk syndromes for a range of diagnostic outcomes (Hartmann et al., 2017).

This HSC approach represents a powerful strategy for tracking the onset of psychosis as it relates to other serious psychopathologies, and as a result may be useful for researchers interested in poor outcome more broadly.

One challenge of this design is that most people with CHR for psychosis already have another fully syndromal disorder by the time they are identified (Fusar-Poli et al., 2014). Thus, the true stage of illness for these individuals is likely more advanced than those deemed to be at risk for these other (e.g., depressive/anxiety) disorders alone. A second limitation is that known clinical indicators of affective disorders are often present earlier in life than are indicators of psychosis (Birmaher et al., 2006), resulting in incomplete overlap of the windows for early identification, and potentially unequal age ranges across groups. Selecting participants only within an overlapping age interval (e.g., 15-25) is of course one solution, although this could result in samples that are unrepresentative of the populations they are intended to reflect (see Meehl, 1970). Given that depressive disorders often emerge several years earlier for girls than boys (Hankin et al., 1998), this practice could disproportionately exclude females from the benefits of early identification research. A third limitation is that clinical criteria for other risk syndromes are less established than for the psychosis-risk state, although this will likely change with continued attention to the area.

What Clinical High-Risk Studies Have Been Conducted Using Help-Seeking Controls?

Table 1 displays the CHR studies we could find that used a HSC group. The majority of studies concerned instrument development or demographic/clinical characteristics; very few examined neurocognitive or neurobiological constructs which, as we have argued here, we believe are ripe areas for research. A thorough discussion of the studies included in Table 1 is outside the scope of the present review, but below we highlight a few examples that we contend illustrate the potential of HSC designs to significantly advance the field. All of the studies discussed here share the common aim of bringing together clinical and basic information about CHR. The unique nature of each HSC group, however, shapes the meaning of the results, stimulating new questions, hypotheses, and ideas for the next generation of CHR research.

In an elegant study, Koutsouleris and colleagues (2018) recently found that clinical and regional grey matter volume measures could longitudinally predict social functioning outcome among individuals at CHR and same-age peers with recent-onset depression. Poor functioning at baseline was a transdiagnostic predictor of social outcome, but regional gray matter volume was differentially predictive for the clinical groups, with medial prefrontal reductions predicting poor outcome for the CHR group, and medial-temporal reductions predicting poor outcome for the depression group. These findings are consistent with the notion that while psychosocial functioning impairments may warn of future difficulties in any young person, the neural aberrations contributing to this broad construct likely differ across clinical populations. The study by Koutsouleris and colleagues provides important early evidence as to which aberrations might be of concern for those at CHR relative to peers with clinical depression.

In another study of gray matter volume, participants at CHR were parsed by the presence of a comorbid depressive or anxiety disorder and compared to individuals with MDD and healthy controls (Modinos et al., 2014). Participants with MDD and those with CHR plus comorbidities both had smaller volumes of the subgenual prefrontal and anterior cingulate cortices than participants with CHR alone. Critically, only when CHR participants had a comorbid depressive or anxiety disorder did grey matter volumes in this region differ from healthy controls; volumes of those with CHR only did not differ from volumes of typically developing participants. Thus, in this study volume reductions were associated with depressive and anxiety illness, not with CHR diagnosis. Given the high frequency of affective symptoms in the CHR population, a study examining these same measures in overall CHR and healthy groups alone would miss this nuanced picture, and observed volume reductions would likely be attributed to CHR status. Only by including an MDD group and taking comorbidities into account does this important issue become more fully illuminated.

An important study by Chaumette and colleagues (2016) examined basal cortisol levels among individuals at CHR, healthy controls, and a mixed clinical sample of HSCs. They reported new data in which CHR and HSC groups were compared on resting cortisol and followed over time. They subsequently meta-analyzed eight existing studies of basal cortisol levels among individuals at CHR relative to healthy controls. Consistent with a neural diathesis-stress model of psychosis (Walker & Diforio, 1997), their meta-analysis found reliably elevated resting cortisol in the pooled CHR group relative to typically developing peers. Despite these reliable differences, however, when the authors compared their newly-reported sample of people at CHR to their psychiatric control group, no differences in basal cortisol levels were observed. Nonetheless, longitudinal analysis of their sample indicated that higher baseline cortisol levels were associated with worsening attenuated psychosis over time (although the meta-analysis detected no effect of cortisol levels on transition to psychosis). Thus, although CHR status appears to be consistently associated with neuroendocrine abnormalities and may portend illness progression, the lack of differences between the CHR and mixed clinical groups raises questions about whether these abnormalities represent a unique psychosis-related mechanism or perhaps a shared “general” abnormality among any seriously distressed individual.

In another study, Carrión and colleagues (2018) found that relative to healthy controls, CHR and HSC participants (who sought CHR assessment but failed to meet the criteria) were equally impaired on nearly all neurocognitive domains assessed. Longitudinal analyses, however, indicated that CHR participants who eventually developed psychosis were substantially lower than HSCs at baseline on working memory and verbal learning, more closely reflecting the first episode psychosis group. From a HSC perspective, one implication of this study is that neurocognitive testing is not sufficient for distinguishing between individuals who do and do not meet CHR criteria following assessment, but could perhaps be combined with clinical measures to predict future psychosis.

The studies discussed above present a much more nuanced understanding of CHR psychopathology and risk for transition than could be discerned using only a healthy control group design. On one hand, CHR and non-CHR psychopathology seem to be associated with

common biopsychosocial features. On the other, close examination of these features over time may reveal differential patterns of development, highlighting specific risk factors, pointing toward illness mechanisms, and potentially informing clinical care. Studies such as these represent important steps in understanding poor functioning and clinical outcome among young people with emerging psychopathology of varied clinical nature.

Implications of Help-Seeking Control Methods for Experimental Design

Dealing with smaller between-group differences.

Effects representing differences between CHR and HSC groups will often be smaller than is typically seen when participants at CHR are compared to healthy controls alone. This is likely an inevitable consequence of the HSC models discussed here, but such a pattern of results is not itself a limitation of this approach as it can reveal important information about shared risk factors and mechanisms of psychopathology. Nonetheless, in the case of true but small differences between clinical groups, greater attention to effect sizes may help interpret findings from multi-group comparisons (Knutson & Heinz, 2015). Effect sizes provide important information about the magnitude of a relation between two or more variables, rather than simply the likelihood that the effect is not zero, as is the case with *p* values (Durlak, 2009). Larger samples, however, may also be needed to identify statistically significant differences between these groups at conventional probability thresholds. As research moves toward more regular use of HSC designs, the field may benefit from a systematic review of psychosis-relevant effect sizes across different psychiatric populations (e.g., as seen in McGorry et al., 2014), paired with statistical simulation to determine necessary sample sizes for detecting a putatively unique presentation in CHR. Such a review taking comorbidity into account would be especially useful.

Modeling group differences statistically.

In addition to issues related to effect sizes, inclusion of HSCs in CHR research may have implications for data analysis. Data-driven stratification approaches, such as cluster analysis and mixture modeling, may become especially useful in this context (Marquand, Wolfers, Mennes, Buitelaar, & Beckmann, 2016). Researchers have successfully used these “bottom-up” analytic strategies to empirically identify subgroups of individuals based on biological, neuropsychological, and social-cognitive measures among people with a range of psychotic and non-psychotic disorders (e.g., Clementz et al., 2015; Stefanik et al., 2018), and studies have used similar approaches to better understand the pathophysiology of CHR in relation to healthy controls (Dean, Walther, Bernard, & Mittal, 2018). Given that the majority of biopsychosocial constructs relevant to CHR research appear to share common and potentially specific features across disorders, the current challenges of identifying etiologically and clinically relevant subgroups may be addressed in part by applying data-driven stratification approaches to CHR-HSC samples. Importantly, these models also can enhance statistical power by reducing within-group heterogeneity (Milligan & Cooper, 1987).

Commonly-used statistical models (e.g., regression, ANOVA) estimating interactions between diagnosis (i.e., CHR, HSC, healthy control) and some key variable in predicting an

outcome have the potential to determine whether important constructs operate uniquely among individuals at CHR. The presence of a significant interaction between diagnosis and that key variable can suggest that a process (e.g., stress-induced dopamine release) is specific to psychosis vulnerability if simple slope analyses indicate a significant correlation between independent (e.g., experimental stress induction) and dependent variables (e.g., dopamine displacement during positron emission tomography) only for the CHR group; they would suggest a nonspecific effect of psychopathology if both the CHR and HSC groups showed this pattern with equal magnitude relative to a healthy control group. Numerous other patterns of results, of course, are also possible.

Defining and measuring constructs of interest.

It may be the case that a more detailed look into certain constructs is necessary to reveal qualitatively distinct patterns of scores or relations across CHR, HSC, and health control groups. Overall measures of social functioning, for example, may fail to capture the unique nature of social impairment among individuals with CHR versus MDD. Although both may present with socially isolative behavior (potentially of equal magnitude), depressed individuals may do so as a function of reduced motivation, whereas those at CHR may do so as a function of increasing suspiciousness. Carefully formulated hypotheses about the causal agents driving social isolation in these populations may lead researchers to examine specific subscales of a social functioning measure, to identify moderators of social functioning for these groups (e.g., suspiciousness), or even to develop new measures of this construct.

Interpreting more complex patterns of results.

As stated throughout this review, the numerous possible patterns of results generated from the multi-group designs encouraged here (i.e., CHR, healthy control, different types of HSCs) pose unique challenges and opportunities for interpreting research findings. In some cases, these results may challenge conceptualizations of psychosis pathogenesis, but as a result may also encourage the field to develop new hypotheses about psychosis and build a more integrative framework inclusive of models regarding non-CHR disorders. Figure 1 displays a few such patterns that we believe are likely to be identified in future CHR-HSC research. The figure depicts scenarios in which an effect is specific to CHR; is observed along a continuum of mental health problems; or is observed nonspecifically in groups with psychopathology. It also depicts a scenario in which effects thought to be a function of risk status are actually a function of co-occurring mental health problems (e.g., as in the study by Modinos and colleagues, 2014). The meaning of each hypothetical pattern will depend on the variables involved in the analysis, but each case will provide more information about attenuated psychosis and risk for progression than would the same study using only healthy controls.

General Recommendations and Conclusions

Provide more attention to the implications of control groups in clinical high-risk research.

We have argued that control groups serve as a reference point from which inferences about the CHR group are made. Given that the most appropriate control group(s) depends on the research question (among other considerations), we recommend that authors report their

rationale for selecting control groups, the sampling and recruitment strategies used for all groups, and the clinical characteristics (e.g., diagnoses) of all psychiatric controls. This is consistent with the guidelines put forth by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative, which offers a set of reporting standards for biomedical observational (including case-control) research (Von Elm et al., 2007). To promote a more thorough understanding of sample characteristics, we also recommend that researchers regularly report comorbidities of CHR participants. These practices will help to define the reference point(s) from which inferences about the CHR group are made, and would help readers hypothesize about the overarching populations from which participants were drawn.

Follow help-seeking controls longitudinally.

Longitudinal studies in which both CHR and HSC participants are followed provide important understanding of the trajectories of symptoms and other constructs associated with help-seeking (Woods et al., 2017). Cognitive deficits in mood disorders, for example, may have different longitudinal trajectories than in schizophrenia (Bora & Pantelis, 2015). We recommend that HSC participants are followed longitudinally to help disentangle which abnormalities covary with psychosis vulnerability over time vs. with other vulnerability states or psychopathology in general. Identifying state vs. trait vulnerability markers may be particularly important during adolescence, when many developmental changes are taking place (McGorry et al., 2018).

Give special attention to depressive and anxiety disorders.

Given that depressive and anxiety disorders are especially common in the CHR population (and with one another), share clinical and neurobiological features with CHR, and appear to be closely connected to the transdiagnostic expression of psychotic experiences, we recommend that special attention be given to understanding the role of these disorders in CHR. Some have suggested that CHR symptoms are secondary to depression and anxiety (van Os & Guloksuz, 2017), and we have argued elsewhere that risk syndromes should not always be considered the primary diagnosis among those meeting the criteria (Millman & Schiffman, 2018). HSC groups defined in part by the presence of these disorders or their suspected prodromal states are therefore essential for achieving this goal. Where HSCs are not available, we suggest researchers consider reporting their findings with depressive/anxiety symptoms as covariates, in situations where there is reason to believe that these symptoms may be closely related to the outcome of interest. Statistical alternatives, however, in our view are not a full replacement for design controls (Meehl, 1971; Miller & Chapman, 2001; Shadish et al., 2002).

Recruit help-seeking controls for neurobiological research.

Neurobiological research has begun to elucidate the abnormal illness processes associated with CHR states, but an understanding of how these processes operate uniquely among those at CHR is critical for refining models, identifying biomarkers, and planning interventions. We recommend that researchers strive toward this goal using HSC designs, which are aptly fit for the endeavor. We recommend that researchers put well-supported models of psychosis pathogenesis to the test, including dopamine, glutamate, neurodevelopmental, and diathesis-

stress models of psychosis by examining core constructs across CHR, HSC, and healthy control groups. Constructs or mechanisms for which there is evidence of cross-disorder impairment (e.g., stress and reward processes) as well as those which may be related specifically to psychotic disorder (e.g., motor abnormalities, presynaptic striatal dopamine synthesis) represent excellent candidates for such studies. Multiple control groups can be used to more strongly support causal inference and test competing hypotheses about the neurobiology of the psychosis spectrum, bringing together largely disparate literatures on these critical topics into powerful, unified protocols (D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013; Lahey et al., 2017).

Develop screens and interview-based diagnostic tools for clinical risk syndromes more broadly.

Mounting evidence indicates that the diagnostic outcomes of multiple clinical risk states (e.g., for psychosis, bipolar disorder) do not necessarily correspond to the disorder for which the individual was initially considered at risk (Kaymaz et al., 2007; Lee et al., 2018; Woods et al., 2017). We recommend that the field work toward developing and validating screening instruments and interview-based diagnostic tools designed to estimate risk beyond just one of these outcomes. This would represent a considerable advancement in developmental psychopathology research. Clinical interviews as well as brief, self-report screening instruments have been successful in distinguishing people with CHR or bipolar disorder from clinical controls (Fusar-Poli et al., 2015; Kline & Schiffman, 2014; Youngstrom et al., 2018), suggesting the potential for combined screens and interviews to provide even more clinically and scientifically useful information. Refining classification criteria, interview questions, and rating scales for existing tools may also help reduce within-sample heterogeneity and improve outcome specificity.

Recruit help-seeking controls for intervention research.

Early psychosocial intervention programs for individuals at CHR tend to share similar components with treatments designed for other disorders and, potentially, similar mechanisms of action (Thompson et al., 2015). Given the likely shared risk factors, illness processes, and treatment options for these groups, we recommend that individuals with varying risk syndromes be recruited alongside those at CHR for clinical intervention studies. In addition to their potential to elucidate common or differential mediators of treatment response across clinical groups, such programs (if validated) are more likely to be taken up by community providers than interventions specialized to treat low base-rate conditions, and as a result may be poised to make a significant public health impact. Flexible, staged, and modular interventions that match evidence-based treatment components to the stated needs of clients and families may represent a promising approach (Chorpita, Daleiden, & Weisz, 2005; McGorry, Hikie, Yung, Pantelis, & Jackson, 2006; Millman & Schiffman, 2018). Engagement, psychoeducation, and problem-solving skills, for example, may be beneficial for most or all individuals in putatively pluripotent risk states. Depending on the risk factors, active clinical concerns, and stated needs of the consumer, however, additional modules may be offered, such as CBT, family therapy, or social skills training. Modular interventions have been used successfully in youth already experiencing common mental disorders (Weisz et

al., 2012); we believe it be time to apply this model to those for whom serious, fully syndromal psychopathology is still yet to manifest.

A shift toward routine addition of HSCs to CHR-control research programs would not be without challenges. Recruitment of multiple control groups is associated with increased costs, new recruitment challenges, and the need for expertise in new clinical populations. To promote the clinical and scientific benefits of this design, it will be important for key institutions like funding agencies and scientific journal boards to adapt.. Despite these challenges, we believe that making clinically and etiologically meaningful comparisons that account for the multidimensional nature of the psychosis spectrum is a necessary next step in the field of CHR research. A better understanding of the specific and nonspecific features of CHR psychopathology will ultimately advance the field, leading to a greater positive impact for a range of people in need.

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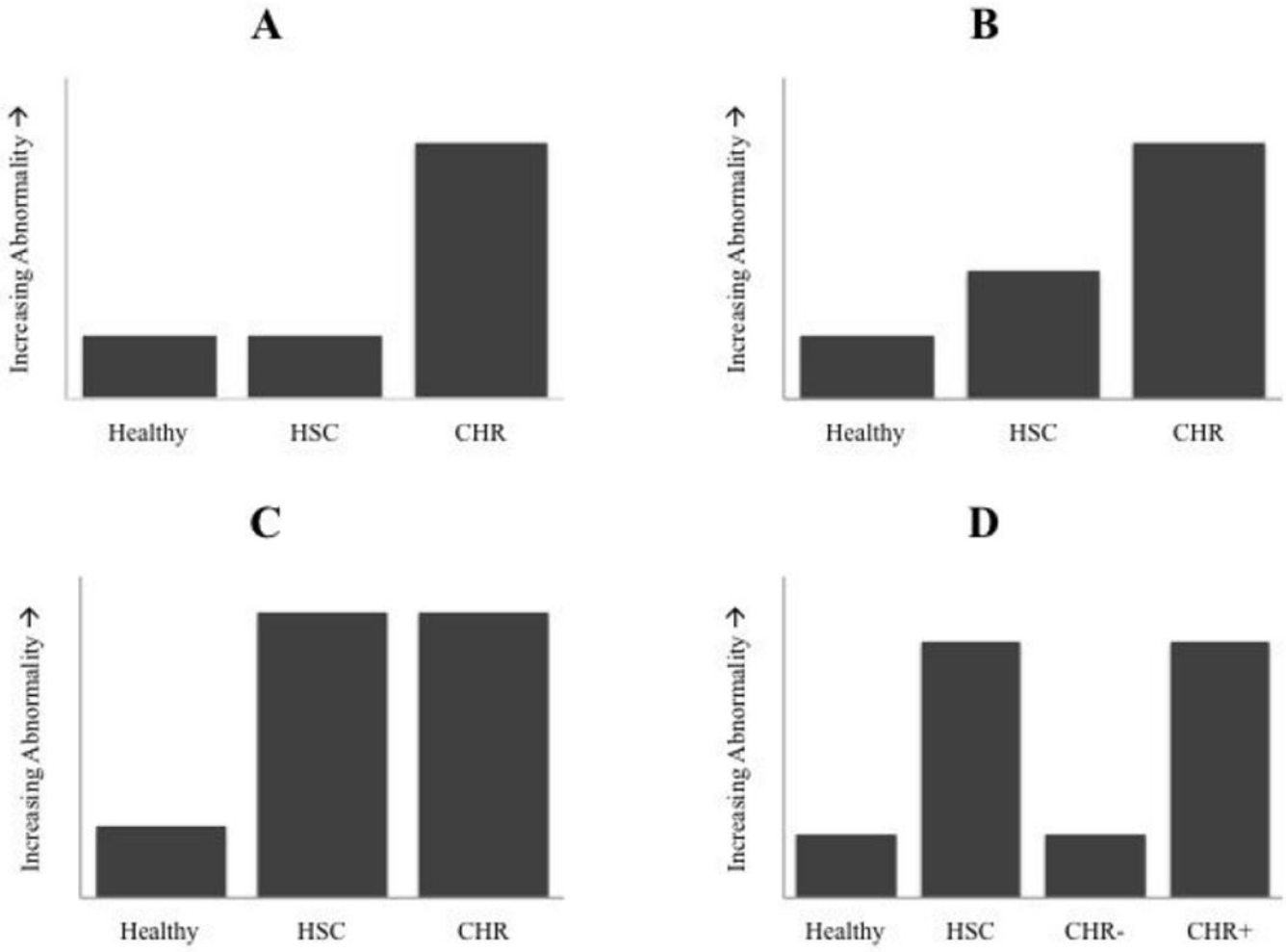

Figure 1.

Hypothetical patterns of results when comparing CHR, HSC, and healthy control participants on a construct of interest in a single study. **A**: Evidence an effect is specific to the CHR group. The CHR group has elevated scores relative to the HSC and healthy control groups, which themselves to not differ from one another. **B**: Evidence of a gradient effect across a spectrum of psychopathology. The healthy group has the lowest scores, the CHR group has the highest scores, and the HSC group has scores intermediate between these two. **C**: Evidence an effect is nonspecific. Both clinical groups score higher than the healthy group, and equally so. **D**: Evidence of an effect in CHR, but only due to comorbid disorder. In this scenario, the CHR group without comorbidities resembles the healthy control group, whereas the CHR group with comorbidities scores higher than these two groups, resembling HSCs. CHR, clinical high-risk; HSC, help-seeking control; CHR+, CHR with comorbidities; CHR-, CHR without comorbidities.

Table 1:

Clinical High-Risk Studies Using a Help-Seeking Control Group

Research Group	Study	Type of HSC[a]	Concept/Domain Studied
Austria	1. Mossaheb et al., 2012	1	Scale development
Calgary/UNC/Yale	2. Addington et al., 2012	1	Facial affect recognition
	3. Barbato et al., 2012	1	Metacognitive functioning
	4. Healey et al., 2013	1	Social cognition
	5. Healey et al., 2017	1	Clinical outcomes
	6. Tarbox-Berry et al., 2017	1	Clin/demog characteristics
Basel	7. Schulze et al., 2013	6	Cognitive functioning
	8. Studerus et al., 2018	7	Cognitive functioning
Bruderholz	9. Simon et al., 2012	1	Clinical outcome
C'JAAD	10. Chaumette et al., 2016	2	Resting cortisol
	11. Magaud et al., 2010	2	Cognitive functioning
	12. Magaud et al., 2014	2	Cognitive functioning
	13. Oppetit et al., 2016	2	Clin/demog characteristics
CMNNI	14. Spada et al., 2016	1	Clin/demog characteristics
DUPS	15. Niessen et al., 2010	1, 2, 5	Scale development
EDIE-NL	16. Ising et al., 2012	2	Scale development
EDIPPP	17. McFarlane et al., 2014	1	Clinical trial
	18. Carrión et al., 2018	1	Cognitive functioning
	19. Tso et al., 2017	1	Scale development
FETZ	20. Schultze-Lutter et al., 2014	1	Scale development
Hamburg	21. Lincoln et al., 2018	8	Psychosocial stress
Headspace	22. Carney et al., 2017	3	Substance use history
	23. Purcell et al., 2015	3	Clin/demog characteristics
Helsinki	24. Lindgren et al., 2010	3	Cognitive functioning
	25. Loewy et al., 2012	2	Scale development
Israel	26. Koren et al., 2013	3	Disturbances of self
JERI	27. Grano et al., 2011	1	Scale development
Liberiamo il Futuro	28. Cascio et al., 2016	2	Clin/demog characteristics
	29. Cascio et al., 2017	2	Scale development
	30. Comparelli et al., 2014	4	Clin/demog characteristics
	31. Kotzalidis et al., 2017	2	Scale development

Research Group	Study	Type of HSC[a]	Concept/Domain Studied
	32. Masillo et al., 2016	2	Interpersonal sensitivity
	33. Raballo et al., 2016	2	Disturbances of self
LYRIKS	34. Kraus et al., 2016	1	Latent inhibition
	35. Lee et al., 2013	1	Clin/demog characteristics
Multiple	36. Fusar-Poli et al., 2015a	1	Clinical outcomes
	37. Fusar-Poli et al., 2015b	1	Referral source, outcome
Multiple	38. Brody et al., 2017	3	Scale development
	39. Brody et al., 2018	1	Scale development
Multiple	40. Gerstenberg et al., 2015	5	Clin/demog characteristics
Multiple	41. Kindler et al., 2017	3	Resting cerebral blood flow
Multiple	42. Salinger et al., 2018	11	Family communication
NAPLS	43. Webb et al., 2015	1	Clinical outcomes
	44. Woods et al., 2009	1	Clin/demog characteristics
	45. Woods et al., 2017	1	Clinical outcomes
OASIS	46. Fusar-Poli et al., 2016	1	Scale development
	47. Fusar-Poli et al., 2017a	1	Referral source, outcome
	48. Fusar-Poli et al., 2017b	1	Clinical outcomes
	49. Fusar-Poli et al., 2017c	1	Referral source, outcome
	50. Modinos et al., 2014	6	Regional brain volumes
PACE	51. Purcell et al., 2015	1	Criminal involvement
	52. Yung et al., 2005	1	Scale development
	53. Yung et al., 2006	1	Scale development
	54. Yung et al., 2008	1	Scale development
PAS	55. Conrad et al., 2014	1	Clinical outcomes
	56. Conrad et al., 2017	1	Clin/demog characteristics
PRIME	57. Miller et al., 2002	1	Scale development
	58. Miller et al., 2003	1	Scale development
PROCAN	59. Addington et al., 2019	9, 10	Clin/demog characteristics
	60. Romanowska et al., 2018	9, 10	Cognitive functioning
PRONIA	61. Koutsouleris et al., 2018	6	Regional brain volumes, clinical outcomes
RODIN	62. Raballo et al., 2018		Disturbances of self
RAP	63. Lencz et al., 2004	2	Clin/demog characteristics
Shanghai Mental Health Center	64. Xu et al., 2016	2	Scale development

Research Group	Study	Type of HSC[a]	Concept/Domain Studied
	65. Zhang et al., 2014	2	Scale development
	66. Zhang et al., 2015	2	Clin/demog characteristics
Taiwan	67. Liu et al., 2011	1	Clinical outcome
	68. Liu et al., 2015	10, 12	Cognitive functioning
UCLA/UCSF	69. Loewy et al., 2005	1	Scale development
	70. Loewy et al., 2011	1	Scale development
United Kingdom	71. French et al., 2012	1	Scale development
	72. Taylor et al., 2013	1	Symptom distress
Tokyo	73. Kobayashi et al., 2008	2	Scale development
Turku	74. Ilonen et al., 2010	5	Cognitive functioning
	75. Heinimaa et al., 2003	2	Scale development
Youth FIRST / SFW	76. Bentley et al., 2016	2	Psychosocial stress
	77. Kline et al., 2012	2	Scale development
	78. Kline et al., 2013	2	Scale development
	79. Kline et al., 2014	2	Symptom distress
	80. Kline et al., 2015	2	Scale development
	81. Kline et al., 2016	2	Scale development
	82. Millman et al., 2016	2	Social cognition, stress
	83. Millman et al., 2017	2	Symptom severity, stress
	84. Thompson et al., 2015	2	Scale development
	85. Waltz et al., 2015	2	Reinforcement learning
	86. Wilson et al., 2016	2	Neighborhood crime

Note. Studies were excluded from the table if they did not determine CHR status from a standardized clinical interview (and instead used, e.g., a questionnaire), used community or epidemiological (versus help-seeking) ascertainment methods for CHR participants, did not make direct comparisons between CHR and HSC groups, or included non-CHR participants (e.g., those with full psychosis, genetic relatives not meeting CHR criteria) in the CHR sample. Other study inclusion/exclusion criteria (e.g., IQ, age) were not considered for inclusion in the table. Some studies included in the table also compared CHR participants to a psychotic disorders group and/or a healthy control group. Study samples tend to overlap within research groups.

[a]1 = responded to CHR recruitment, but failed to meet criteria; 2 = receiving any mental health care; 3 = receiving mental health care at specific outpatient clinics; 4 = generalized anxiety disorder; 5 = psychiatric inpatient unit; 6 = major depressive disorder; 7 = attention deficit/hyperactivity disorder; 8 = anxiety/depressive disorder; 9 = no symptoms, but psychiatric risk factors (e.g., family psychiatric history); 10 = nonspecific, mild/moderate symptoms of anxiety or depression; 11 = clinical risk syndrome for bipolar disorder; 12 = schizotypal personality disorder with symptoms less severe than the CHR group. CHR = clinical high-risk, HSC = help-seeking control, clin/demog = clinical/demographic, UNC = university of North Carolina, C'JAAD = adolescent and young adults assessment center, CMNNI = C. Mondino national neurological institute, DUPS = Dutch prediction of psychosis study, DEPP = detection of early psychosis project, EDIE-NL = Dutch early detection and intervention evaluation study, EDIPPP = Early detection and intervention for the detection of psychosis program, FETZ = Cologne early recognition and prevention center, JERI = Jorvi early psychosis recognition and intervention project; LYRIKS = longitudinal youth at risk study, NAPLS = North American prodromal longitudinal study, OASIS = outreach and support in south London, PACE = personal assessment and crisis evaluation center, PAS = psychological assistance service, PRIME = prevention through risk identification management and education, PROCAN = Canadian psychiatric risk and outcome study, PRONIA = personalized prognostic tools for early psychosis management, RAP = recognition and prevention program, RODIN = Rome early detection of psychosis in adolescence collaborative network, UCLA = university of California, Los Angeles, UCSF = university of California, San Francisco, Youth FIRST = youth-focused identification research and service team, SFW = strive for wellness.