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Original Article

Young people at ultra high risk for psychosis: a research update

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Abstract

Aim: Over the last fifteen years attempts have been made to prospectively identify individuals in the prodromal phase of schizophrenia and other psychotic disorders. The 'ultra high risk' approach, based on a combination of known trait and state risk factors, has been the main strategy used. The validation of the ultra high risk criteria led to a series of intervention studies in this population. The aim of this paper is to provide an overview of ultra high risk research.

Method: We review studies in this area, focusing on intervention research. Intervention studies have included the use of low dose antipsychotic medication, cognitive therapy, and omega-3 fatty acids.

Results: The evidence for specific intervention strategies for this population is moderate and requires replication with larger samples.

Conclusion: Recently, it has been proposed to include an adaption of the ultra high risk criteria in the next version of the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition). This has raised some controversy in the field. The authors conclude that it would be premature to include the Risk Syndrome in the Diagnostic and Statistical Manual of Mental Disorders at this stage.

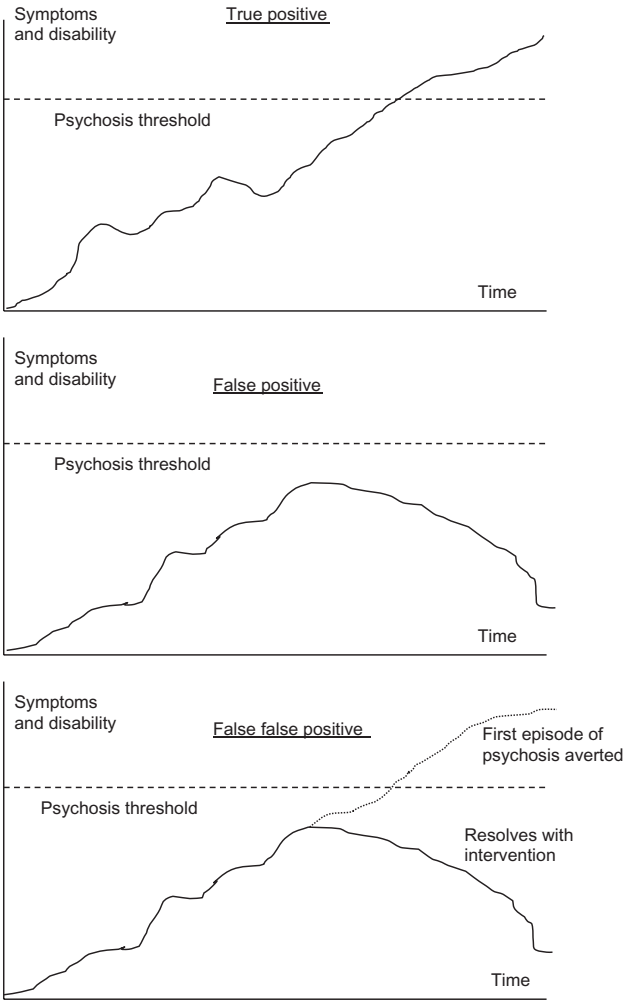
Key words: high risk, psychosis, schizophrenia.

Psychotic disorders such as schizophrenia are usually characterized by a prodromal period that precedes the onset of full-blown psychotic symptoms.[1–3] This phase is potentially a target for intervention. Treatment of the prodrome could prevent onset of fully-fledged disorder, or at least may ameliorate or delay the onset phase. However, a major challenge has been to prospectively identify the prodrome, particularly given the non-specific nature of prodromal symptoms.[4,5] Typical prodromal symptoms, such as sleep disturbance, lowered mood and anxiety,[6,7]could be the result of a number of conditions, such as major depression, substance abuse and physical illness, as well as a psychotic prodrome. Even attenuated or isolated psychotic symptoms may not necessarily progress to a frank psychotic disorder, as these are now known to be quite common in the general population.[8–11]

Thus, although some people with an apparent 'prodrome' do indeed progress to develop a psychotic disorder (the 'true positives'), many do not. 'False positives' are those who would have never developed a psychotic disorder. These 'false positives' need to be distinguished from those who would have developed a psychotic disorder but for some change in their circumstances, such as intervention, stress reduction or cessation of illicit drug use. We have called this latter group 'false false positives' (see Fig. 1). Theoretically, the 'false false positives' would share genotypes and endophenotypic markers with the 'true positives' while being phenotypically like the 'false positives'.

As can be gleaned from this discussion, the prodrome is a retrospective concept. A person presenting with sleep disturbance, lowered mood and even attenuated (subthreshold) psychotic symptoms may turn out to be a 'true positive', a 'false positive' or a 'false false positive'. The danger of using non-specific symptoms to identify the 'prodrome' is that many will be false positives. The challenge is therefore to develop criteria that are able to detect people with a high likelihood of developing psychosis, that

FIGURE 1. Diagrams illustrating true positive, false positive and false false positive cases.



is, to maximize the 'true positives' and minimize the 'false positives'. One strategy to achieve this aim has been the development of the ultra high risk (UHR) criteria. These criteria use a sequential screening approach or 'close-in strategy'[12] requiring combined multiple risk factors, with the effect of concentrating the level of risk in the selected group. This strategy prioritizes specificity over sensitivity, with the possibility that people genuinely at risk may not be identified. The UHR criteria use the risk factor of age (adolescence and young adulthood), given that this is the age range of highest incidence for psychosis.[13] Age is combined with clinical risk factors, such as functional decline and putatively prodromal symptoms, particularly those hypothesized to occur immediately before the onset of frank psychosis, such as attenuated and isolated psychotic symptoms. Additionally, presumed genetic risk combined with functional deterioration is a criterion. Detailed descriptions of the operationalized UHR criteria are provided elsewhere[14–16]; however, the original criteria required that a young person aged between 14 and 30 being referred for mental health difficulties met criteria for one or more of the following groups: (i) attenuated psychotic symptoms group (APS): have experienced sub-threshold, attenuated positive psychotic symptoms during the past year. (ii) brief limited intermittent psychotic symptoms group (BLIPS): have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and havespontaneously abated; or (iii) trait and state risk factor group: have a first-degree relative with a psychotic disorder or the identified client has a schizotypal personality disorder, and they have experienced a significant decrease in functioning during the previous year. The UHR criteria have been adapted and adopted around the world, and have been variably termed UHR,[15] 'clinical high risk' (CHR),[17] 'at risk mental state' (ARMS),[18,19] or 'prodromal' criteria.[20,21] They have been tested over the last 15 years, and have been found to predict onset of first episode psychosis at rates several hundred-fold above that of the general population.[15,16,20]

Another approach to overcoming the non-specific nature of prodromal symptoms is to use the German concept of 'basic symptoms',[22,23] subjectively experienced phenomena that are thought to be close to the underlying disturbance in schizophrenia. Certain basic symptoms have been found to be predictive of schizophrenia in a clinical sample,[24] and have led to the development of a checklist of nine symptoms suggestive of a schizophrenia prodrome: inability to divide attention, thought interference, thought pressure, thought blockages, disturbance of receptive speech, disturbance of expressive speech, disturbances of abstract thinking, unstable ideas of reference and captivation of attention by details of the visual field.[25] High risk criteria require the presence of at least two of these symptoms. In recent studies, these criteria have been combined with the UHR criteria to identify a high-risk group.[26,27]

Thus, this research has enabled identification of groups at high risk of schizophrenia and other psychotic disorders. Numerous clinical services have been established to provide care for UHR individuals and to serve as research platforms to further develop knowledge in the area. The PACE (Personal Assessment and Crisis Evaluation) clinic in Melbourne, Australia was the first clinic of this type in the world.[18]

The next wave of studies in this area has been to investigate interventions in this group. The main

aims of intervention in the pre-onset phase are (i) to prevent or delay transition to psychosis and (ii) to treat current problems, such as co-morbid depressive or anxiety symptoms or syndromes. A secondary aim is to ensure that should transition occur, the individual is already well engaged with treatment and thereby minimize the duration of untreated psychosis (DUP) and facilitate non-traumatic entry into an early intervention program.

Five intervention studies in this population have been published to date. The first was conducted in PACE and compared combined cognitive behaviour therapy (CT) and low-dose atypical antipsychotic medication with usual case management. The rate of transition to psychosis in the treatment group was significantly lower than in the control group after the 6-month treatment phase. However, at 12-month follow up, there was no difference in transition unless participants were fully compliant with the anti-psychotic medication.[28] Medium-term follow-up (mean of 3 years) showed no significant difference between treatment groups in terms of transition rate, level of symptomatology or functioning.[29]

The second study from New Haven, USA, compared 12 months of low-dose antipsychotic (olanzapine) with placebo.[30] There was a trend towards the treatment group showing a reduction in transition rate, although this did not reach statistical significance. This may have been due to under-powering of the study.

A third trial was conducted in Manchester, UK, in which subjects were randomized to receive CT for 6 months or monitoring of mental state. The group that received CT had a significantly lower rate of transition to full threshold disorder, and a significantly greater reduction in psychiatric symptoms at 12 months.[31] However, as in the PACE medium-term follow-up study, these significant differences were not maintained at 3-year follow-up.[32]

A fourth intervention trial in Vienna, Austria examined the effect of 12 weeks of omega-3 fatty acids (fish oil) in the UHR group.[33] At the end of the 12-week treatment phase, the intervention group had a significantly lower transition rate compared to the placebo control group. This significant effect persisted at 12-month follow-up, with the finding that 2 of 41 individuals (4.9%) in the treatment group had developed psychosis compared with 11 of 40 (27.5%) in the control group ($P = 0.007$). The treatment group also had significantly reduced positive symptoms ($P = 0.01$), negative symptoms ($P = 0.02$), and general symptoms ($P = 0.01$) and improved functioning ($P = 0.002$) compared with the placebo group.

Finally, an interim report on a fifth study from the PACE clinic has recently been published. This compared CT plus risperidone, CT plus placebo, and supportive therapy plus placebo.[34] There was a 12-month treatment phase and a 12-month follow-up phase; however, the interim paper reports only data after 6 months of follow-up. This study found no significant differences between the groups. This may have been because the transition rate in the control group (supportive therapy plus placebo) was much lower than expected – at the 6-month follow-up point only 7.1% of the control group (2 out of 28) had developed psychosis.

This low transition rate has in fact been observed at the PACE clinic over the last few years.[35] We have previously speculated on the possible reasons for this.[36] It seems that as the work of the PACE clinic has become well known, the formal and informal use of the UHR criteria has increased, and the period of time between onset of psychiatric symptoms and referral to PACE has decreased.[35] Thus, psychotic-like experiences (PLEs) are being detected earlier and possibly being detected when previously they may not have been. This could result in individuals being referred to PACE who may previously not have been referred and possibly earlier referrals. For those referred earlier, this means that onset of psychosis would be expected to occur later than 6 or even 12 months, or possibly prevented altogether. For those who would previously not have been detected and referred, it means that more false positives, who may never be at risk of psychosis, could be being referred. It is known that PLEs are common in the community and are often not associated with distress or help-seeking.[8–11,37,38] Thus, we could speculate that through increasing potential referrers' and the community's awareness about PLEs and their relationship to full-blown psychotic disorders, the work of the PACE Clinic may have inadvertently resulted in clinical attention being given to individuals who may not need it. Of course, it is not yet clear which individuals in the community with PLEs are genuinely at risk of psychosis and which could remain well despite their PLEs.

The lowered transition rate and possible change in referral practices highlights another important issue in UHR research. The predictive validity of UHR criteria depends on the sample to which they are applied. The UHR criteria will have low predictive power in samples with a low rate of transition to psychotic disorder, such as the general population.[36]Thus, although young help-seekers meeting these criteria are at greater risk of psychotic disorder than those who do not meet them, caution

TABLE 1. Proposed DSM-5 criteria for the attenuated psychotic symptoms syndrome

All six of the following:
(a) Characteristic symptoms: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency that it is not discounted or ignored.
  (i) Delusions
  (ii) Hallucinations
  (iii) Disordered communication
(b) Frequency/currency: symptom or symptoms meeting criteria A must be present in the past month and occur at an average frequency of at least once per week in the past month.
(c) Progression: symptoms meeting criteria A must have begun or worsened in the past year;
(d) Distress/disability/treatment seeking: symptoms meeting criterion A are sufficiently distressing and disabling to the patient and/or parent/guardian to lead them to seek help.
(e) Symptoms meeting criterion A are not better explained by any other DSM-5 diagnosis, including substance-related disorder.
(f) Clinical criteria for any DSM-5 frank psychotic disorder have never been met.

Source: http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=412.
DSM-5, Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition).

is needed in their management, since a high transition rate can no longer be assumed.

Finally, a controversial issue has been discussed online and in the literature recently: whether an adaptation of the UHR criteria should be included as a diagnosis in the next version of the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5). Different terms have been suggested for this new diagnosis, including 'psychosis risk syndrome', 'risk syndrome for first psychosis', and, most recently, the 'attenuated psychotic symptoms syndrome'([39, 40], see Table 1). The diagnosis would be a 'transitional' diagnosis in that it would be intended to be used for a limited period of time and be supplanted by other DSM diagnoses later, should their criteria be met. In this sense, it would be akin to 'mild cognitive impairment' as a prodromal risk syndrome for dementia.[41]

Some of the benefits of including the Risk Syndrome in DSM-V include: early intervention to prevent later psychosis; encouraging attention and resources to be directed to an important clinical population; highlighting epidemiological work that demonstrates that attenuated psychotic symptoms are prevalent in the general population, and may be associated with both current morbidity and risk for illness; and aligning psychiatry more closely with other fields of medicine that identify risk factors for the purposes of instituting preventative interventions.[42] Authors in favour of including the risk syndrome argue that a clinical need exists for these patients, as evidenced by the help-seeking status of individuals and families. Furthermore, individuals with this syndrome may not attract a satisfactory diagnosis under DSM-IV that adequately addresses their needs. Thus, they may have difficulty accessing care and receiving reimbursement under medical insurance schemes. DSM-IV does not account for these patients because the trait-like personality diagnoses, such as schizotypal personality disorder, do not fit the state-like and duration aspects of the risk syndrome criteria, and the symptoms are not severe enough to attract a full psychotic diagnosis. These cases may eventually meet criteria for other diagnoses, such as psychotic or mood disorders, or may simply recover and not attract a definitive diagnosis. Woods and colleagues[43] present data indicating that clinicians can select DSM-IV diagnoses for risk syndrome patients when required to do so for reimbursement purposes, but that the clinicians are not satisfied that these DSM-IV diagnoses accurately capture the clinical picture of the patients. Therefore, these authors argue that there is a gap in the current DSM for the Risk Syndrome that is not currently addressed by other diagnostic categories, and which allows for various outcomes in identified individuals.

A number of points have been made against including the risk syndrome in DSM-V. First, there is the issue of the potentially high number of 'false positives' diagnosed with the syndrome.[42,44] This high number of 'false positives' may be due to the inherent problem of 'false positives' in those identified as being 'at risk', compounded by the problem of misdiagnosis in 'non-expert' settings.[42] In addition, the base rate of psychosis may be lower in populations outside tertiary research settings, particularly in primary care and the general population, thus increasing the 'false positive' rate, as noted above.[44–47] This concern has led to the inclusion of the caveat that the attenuated psychotic symptoms must be associated with distress, disability and help-seeking. However, this addition is also problematic, as help-seeking is dependent on a number of non-illness factors, including availability of services and cultural and sub-cultural attitudes to seeking help.

While identifying false positives is not inherently problematic and may be acceptable in other areas of medicine (e.g. heart disease), these opponents of the inclusion of the risk syndrome argue that the risk–benefit ratio is not favourable with regards to the risk syndrome due to a number of unintended

consequences: the high risk of stigma (both by self and other) and discrimination, including from health insurance companies;[44,48] the possibility of exacerbating the already evident trend of treatment with antipsychotic medications for patients with attenuated psychotic symptoms in the absence of good evidence for this;[42,44,49,50] and the low benefits resulting from case identification given the lack of a clear evidence base for effective interventions.[42,46] It is also possible that the risk syndrome would suffer from the phenomenon of 'diagnostic creep' – that is the threshold for a diagnosis gradually shifting in response to clinical practice, political lobbying and other social forces.[44] An example of this would be a scenario of a clinician providing a patient with a diagnosis of risk syndrome in order to access treatment and gain insurance coverage, even though the patient technically falls just below the risk syndrome threshold. The 'creep' might also occur in the other direction, that is patients previously diagnosed with schizophreniform or delusional disorder may be given a diagnosis of risk syndrome instead. This problem, according to Ross,[50] might be particularly salient given the lack of a clear operational definition of 'attenuated' symptoms in the proposed criteria. He argues that the degree of 'attenuation' that is allowed before an individual is below threshold for the risk syndrome will result in low reliability in clinical settings.

CONCLUSION

The UHR criteria were introduced to identify young people with a high risk of imminent onset of psychotic disorder, that is as possibly being in the prodromal phase of illness. Early studies provided evidence for the validity and reliability of the criteria. However, there is a need for further refinement of risk factors to decrease the number of 'false positives' identified with this approach, particularly given the declining transition rate observed in recent years. Therefore, current evidence does not support the inclusion of the risk syndrome in DSM-5 at present.

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