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REVIEW ARTICLE

Research in young people at ultra-high risk for psychosis: a review of the current evidence

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Background. The past 15 years have seen a growing interest in early intervention and detection of psychosis before the onset of the first episode. Recent proposals to include a psychosis risk syndrome (PRS) in DSM 5 have focused attention on the evidence base achieved to date in this field.

Aims. This article aims to (1) review the underlying principles of early identification and intervention during the pre-psychotic phase, (2) summarise the naturalistic follow-up studies conducted to date in this 'at-risk' population, (3) discuss the identified clinical risk factors for transition to psychosis, (4) summarise the interventional studies both psychological and pharmacological completed to date and (5) briefly discuss the controversy around the proposed inclusion of the PRS in DSM 5.

Methods. Electronic databases EmBase, MedLine and PsychInfo were searched using the keywords ultra-high risk/at-risk mental state/risk syndrome/pre-psychotic/prodrome/prodromal and psychosis/schizophrenia.

Results. The evidence suggests that it is possible to identify individuals who may be at risk of developing psychosis. Results from intervention studies, mostly involving second-generation antipsychotics and cognitive behavioural therapy, are currently insufficient to make treatment recommendations for this group. The emerging research with regard to possible neuroprotective factors such as omega fatty acids is promising, but will require replication in larger cohorts before it can be recommended.

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Key words: Pre-psychotic, prodrome, psychosis, schizophrenia, ultra-high risk.

Background

Despite research advances, schizophrenia remains one of the most debilitating chronic illnesses in medicine (Hegarty *et al*. 1994). Although course and severity vary, the illness is generally characterised by recurrent episodes, functional deterioration, residual negative symptoms and enduring cognitive impairment (Larsen *et al*. 1998; Clarke *et al*. 2006; Crumlish *et al*. 2009; Tandon *et al*. 2009). Findings that there may be greater treatment responsiveness in the first episode of psychosis (Bertelsen *et al*. 2008), that intervention early in the first episode may be associated with better prognostic outcomes (Henry *et al*. 2010), reports of progressive grey matter decline during the early illness phases and evidence that most people who develop a sustained psychotic disorder experience a significant period of sub-threshold symptoms, distress and functional decline long before they become frankly psychotic have impelled the development of early recognition programmes around the world (McGlashan & Johannessen, 1996; Yung & McGorry, 1996). This area of research is nascent and not without controversy. In particular, concerns have been raised about the ethics of intervening in a population that may or may not go on to develop mental illness.

Aims

This article aims to review the evidence to date on the 'ultra-high risk' (UHR) for psychosis population. This article is not a systematic review; however, it aims to:

- Review the underlying principles of early identification and intervention during the pre-psychotic/prodromal phase.
- Summarise the naturalistic follow-up studies conducted to date in this 'at-risk' population.
- Discuss the identified clinical risk factors for transition to psychosis.
- Summarise the interventional studies both psychological and pharmacological completed to date.
- Briefly review the controversy around the proposed inclusion of the psychosis risk syndrome (PRS) in DSM 5.

Methods

Electronic databases EmBase, MedLine and PsychInfo were searched using the key words ultra-high risk/at-risk mental state/risk syndrome/pre-psychotic/prodrome/prodromal and psychosis/schizophrenia.

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References of all identified studies were searched for further relevant studies.

Results

What is UHR?

Early intervention for psychosis services aims to detect emergent symptoms, reduce the duration of untreated psychosis and improve access to effective treatments. Early intervention for psychosis services differs from standard care in two ways: early detection and phase-specific treatment (phase-specific treatment is a pharmacological, psychological or social intervention adapted or developed for use specifically with people at an early stage of the illness) (Marshall & Rathbone, 2011). Early detection typically involves the early identification of people who are already psychotic, but who have not yet received adequate treatment. However, some early intervention services also endeavour to detect using standardised instruments people who display prodromal symptoms and as such are considered 'at risk' for developing psychosis (Schaffner & McGorry, 2001; Wyatt & Henter, 2001). These 'at-risk' people have not met the criteria for a psychotic disorder and their identification and any intervention offered aims to prevent or ameliorate an emerging psychotic illness.

The 'UHR' group, also referred to as the 'At Risk Mental State' (ARMS) group or the 'PRS', are defined as a group of help-seeking individuals identified using reliable measurement tools as being at high risk of developing a psychotic illness.

Some authors have raised concerns about the validity of the UHR concept and the potential harm associated with intervention during the 'prodromal phase'. Sub-threshold psychotic symptoms have a reported prevalence in the general population of around 5% (van Os *et al*. 2009), with higher rates of 7.5–23% being reported in children and adolescents (Kelleher *et al*. 2012*a*, 2012*b*). There is emerging evidence that sub-threshold psychotic symptoms may exist on a continuum with psychosis. This continuity is suggested by evidence that known risk factors for the development of schizophrenia such as urbanicity, social disadvantage and cannabis use are also associated with risk of sub-clinical psychotic symptoms in the general population transitioning to clinical psychosis (Binbay *et al*. 2011; Dominguez *et al*. 2011). Some authors have expressed concern about the risk of stigmatisation and psychological distress, especially for those false positives identified who were never going to develop a psychotic illness (Raven *et al*. 2012). A false-positive diagnosis of 'UHR' for psychosis could create unnecessary anxiety and demoralisation about prognosis. An even more serious risk is the potential for unnecessary use in this population of interventions, especially antipsychotics, which have potentially serious side-effects, including weight gain, diabetes, metabolic syndrome and neurological symptoms (Foley & Morley, 2011). Most involved in UHR research acknowledge the potential jeopardy associated with research and treatment of the UHR group and propose that it is only with high-quality research that clarity can be realised on these issues (Yung & Nelson, 2011). These concerns will be discussed in some more detail in the section on the proposed inclusion of a UHR syndrome in DSM 5.

Prodromal symptoms of psychosis have long been recognised (Meares, 1959; Bowers, 1965). The concept of being able to prevent the onset of schizophrenia and other psychotic illness by detecting and intervening at the prodromal phase has long been sought (Sullivan, 1927). Initial researchers in this area focused with little success on the early identification of florid psychotic symptoms. It was in the 1980s when a series of retrospective studies redirected attention to the fact that often more subtle, less florid signs of psychotic illness are present for days up to years before the onset of the first episode of frank psychotic illness (Hafner *et al*. 1995). This change in focus and the emerging data in the area facilitated the development of reliable measurement tools for the recognition of young people at 'UHR' of developing a psychotic illness.

Current research in this area began in Melbourne, Australia, with the work of Yung, McGorry and colleagues. In 1994, the Personal Assessment and Crisis Evaluation (PACE) clinic was established, aimed at identifying, monitoring and providing care for young help-seeking people described as being at high risk for developing psychosis. Yung and colleagues developed operationalised criteria: the UHR criteria, which aim to overcome the non-specific nature of prodromal symptoms using a 'close in' strategy (Philips *et al*. 2000). The features identified comprise a combination of state and trait factors (Box 1).

Using these UHR criteria, Yung and colleagues completed a number of studies to assess the validity of their UHR criteria (Yung *et al*. 2000). These studies found rates of transition to psychosis of 20–40% by 12-month follow-up. These rates are several thousand-fold over the expected incidence rate for first-episode psychosis in the general population. This occurred despite the provision of supportive counselling, case management and antidepressant medication if required. The peak time of risk for transition to psychosis was found to be within 4.5 months of entry to the clinic (Yung *et al*. 2004).

The PACE UHR criteria have since been adopted and adapted by a number of other settings around the world. UHR population-specific assessment tools have been developed. These tools now include the Comprehensive Assessment of At-Risk Mental States

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Box 1 Ultra-High Risk Criteria

PACE Clinic, Melbourne
Assessment tool: Comprehensive Assessment of At-Risk Mental States (CAARMS)

Person is referred for help to a clinical service and meets criteria for one or more of the following groups:

State-based criteria

a. **Attenuated Psychotic Symptom syndrome (APS):**
- One or more sub-thresholds, attenuated positive psychotic symptoms, e.g., unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/distortions, conceptual disorganisation.
- Held with either sub-threshold frequency or sub-threshold intensity; present for ⩾1 week within the past year and for ⩽5 weeks.

b. **Brief Limited Intermittent Psychotic Symptom syndrome (BLIPS)**
- Transient fully psychotic symptoms: symptoms in the realm of delusions, hallucinations, disorganisation.
- Duration of the episode <1 week.
- Spontaneous remission; symptoms occurred within 1 year but for not longer than 5 years.

Trait-based criteria

c. **The Genetic Risk and Deterioration Symptom syndrome (GRD)**
- First degree relative with a psychotic disorder

OR

- Personally meeting the *DSM-IV* criteria for schizotypal personality

AND

- Significant drop in functioning as defined by a GAF (global assessment of functioning) drop of 30% or more for at least 1 month over the past year.

PRIME Clinic, Yale
Assessment tool: Structured Interview for Psychotic Symptoms (SIPS)

Person is referred for help to a clinical service and meets criteria for one or more of the following groups:

State-based criteria

a. **Attenuated Positive Symptom Prodromal Syndrome (APSS):**
- One or more sub-threshold-positive symptoms, not fully psychotic in intensity: Unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/distortions, conceptual disorganisation.
- Currently present at a frequency of at least once per week in past month, onset or worsening in the past year.

b. **Brief Intermittent Psychosis Prodromal Syndrome (BIPS):**
- One or more fully psychotic symptoms:
- Present intermittently for at least several minutes/day at least once per month, *but less than* 1 hour/day, 4 days/week over 1 month.

Trait-based criteria

c. **Genetic Risk and Deterioration Prodromal Syndrome (GRD):**
- Has a first-degree relative with a psychotic disorder

OR

- Personally meeting criteria for schizotypal personality disorder

AND

- Precipitous decline in functioning rated on the General Assessment of Functioning (GAF) scale as a drop of at least 30% compared with 12 months ago.

PACE: Personal Assessment and Crisis Evaluation Clinic, Melbourne, Australia.
PRIME: Psychosis Prodrome Research Clinic, Yale, Connecticut, USA.
Underlined text indicates differences in SIPS criteria when compared with CAARMS.

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(CAARMS) (Yung *et al*. 2005) developed by Yung and colleagues and the Structured Interview for Prodromal Symptoms and the Scale of Prodromal Symptoms (SIPS/SOPS) developed by McGlashan and colleagues in Yale (see Box 1) (Miller *et al*. 2002).

The Bonn Scale for Assessment of Basic Symptoms (BSABS) has been proposed to identify an earlier phase of UHR [also known as Early Initial Prodromal State (EIPS)] (Gross *et al*. 1987). These 'basic symptoms' emerge from the German psychiatric literature and include disturbances of self-perception, stress tolerance, thought organisation and social and non-verbal interactions that are subjectively observed and not usually noticed by others (Schultze-Lutter, 2009). Klosterkotter *et al*. (2001) reported that 70% of 110 participants who had endorsed one or more items on the BSABS had developed schizophrenia at 9.6-year follow-up. However, other authors have questioned the generalisability of this sample, which was made up of people referred to a tertiary clinic on the grounds of possible emerging psychosis (Warner, 2002).

The basic symptoms concept has been operationalised by the 'Schizophrenia Proneness Instrument' Adult Version (SPI-A) (Schultze-Lutter *et al*. 2007), which allows for a frequency-based severity rating of basic symptoms.

The SIPS/SOPS has become the established instrument in North American studies, whereas the CAARMS has a prevailing influence in Australian and European studies. The SPI-A is used in some European centres and usually applied together with the SIPS/SOPS and, to a lesser degree, with the CAARMS in order to allow for the assessment of the PRS according to both approaches.

Both CAARMS and SIPS/SOPS are semi-structured interviews that measure positive, negative, disorganised and common symptoms. All interviews require training typically of postgraduate-level clinicians, although good to excellent inter-rater reliability has not been difficult to attain (Miller *et al*. 2002).

Why is identification of the UHR group important?

Research findings from the past 15 years have provided some evidence for identification, follow-up and intervention in the UHR group.

The findings include:

1. Identification of those at UHR of developing psychosis could facilitate prevention or amelioration of the psychosocial deficits that in most cases have their onset during the 'prodromal phase' and are treatment resistant in the wake of the first episode (McGorry *et al*. 2009).
2. A number of studies have shown that brain changes are already present in the UHR group compared with healthy controls, and additional progressive brain changes have been documented in UHR individuals who transition to psychosis compared with those who do not (Pantelis *et al*. 2003; Velakoulis *et al*. 2006; Fornito *et al*. 2008).
3. UHR individuals according to current prodromal criteria already suffer from a variety of social, psychological, neuropsychological and neurobiological problems and consequently are in need of psychological and/or psychiatric treatment (Bechdolf *et al*. 2005; Woodberry *et al*. 2010; Giuliano *et al*. 2012).
4. In this early phase of illness, neuroprotective intervention strategies with little if any side effects may be effective, e.g., ω-3 fatty acids (Amminger *et al*. 2010).
5. A preventative approach to psychosis might offer an opportunity to positively change the public perception of the predictability and treatability of psychoses, thereby reducing public stigmatisation and discrimination of those suffering from the disorder.
6. Early detection and intervention might prevent self-stigmatisation by increasing self-empowerment early and by preventing symptoms that might lead to stigmatisation and discrimination by others, e.g., odd and eccentric behaviour or significant psychosocial decline.

Naturalistic follow-up studies

Although no naturalistic follow-up studies of this population have been completed in Ireland, a good number of generally small studies have been completed across the world (Olsen & Rosenbaum, 2006). Two large multi-centred studies have also been completed in Europe (Ruhrmann *et al*. 2010) and North America (Cannon *et al*. 2008).

A number of methodological issues are associated with UHR studies, which makes them difficult to directly compare. The UHR studies vary in how they define UHR/ARMs/PRS, i.e., the study inclusion criteria. 'Transition to psychosis' has been the outcome of interest in UHR studies. However, the point at which an individual crosses the line from high risk or prodromal state to psychosis threshold is ill-defined (Yung *et al*. 2010). Furthermore, UHR studies are principally conducted in academic centres and therefore their findings may not be suitable for extrapolation to the general population.

A recent meta-analysis reported a consistent transition risk, independent of the psychometric instruments used, of 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years and 36% after 3 years of follow-up (Fusar-Poli *et al*. 2012). Significant moderators accounting for heterogeneity across studies and influencing the transition risk included the age of the

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participants, publication year, treatments received and diagnostic criteria used (Fusar-Poli *et al*. 2012).

A reduction in the transition rates has been reported more recently in the literature, from initially over 40% in 6 months to only 6.6% in 6 months and 12% in 1 year (Haroun *et al*. 2006).

The two largest studies conducted to date the European Prediction of Psychosis Study (EPOS) study in Europe, which included 245 patients, and the North American Prodrome Longitudinal Study (NAPLS) study in North America, which included 291 patients, reported transition rates of 19% and 26.8% at 18 months of follow-up, respectively (Cannon *et al*. 2008; Ruhrmann *et al*. 2010). However, at 30 months of follow-up NAPLS found that 40% had transitioned to psychosis (Woods *et al*. 2009). Although still considerable, clinically significant and validating the selection criteria for UHR, these rates are lower than those reported in the initial studies.

The reduction in transition rates has caused some concern among the research field and several potential reasons have been put forth for this trend (Yung *et al*. 2007). These include the provision of treatment to the UHR group, which may reduce transition rate. Treatment of UHR individuals often involves supportive therapy, cognitive therapy (CT) and medications only if indicated, e.g., an antidepressant if there is a comorbid depressive disorder. Antipsychotic prescribing is not routine in UHR centres; however, in NAPLS, in subjects not enrolled in clinical trials, 25% received antipsychotic medication and at least 13% in EPOS (Walker *et al*., 2009; Ruhrmann *et al*. 2010). As services become more established and staff experience of treating this cohort increases, the treatment effect could also be increasing. A related effect of UHR clinics becoming more established is that referrers become more vigilant and this could result in a 'lead-in' effect, in that patients tend to be identified in an earlier phase of the syndrome (Nelson, 2011, personal correspondence). This earlier recognition could result in enhanced prevention or could simply lead to a longer lag time to transition, i.e., the UHR populations being reported on in the literature could now differ from those of 5–10 years ago in that they are in an 'earlier' phase of the UHR syndrome and thus responding differently at least in the shorter term to identification and possibly treatment (Nelson, 2011, personal correspondence). As mentioned, the mean follow-up of the studies conducted to date is only 6–12 months, and thus it may be that longer periods of follow-up are required. Another possible consequence of this earlier 'diagnosis' of the UHR individuals is that more false positives are being included in the UHR sample. That is, the apparent UHR phenotype may have a number of different outcome trajectories, and that early detection increases the probability people never truly at risk of developing a psychotic disorder are being identified. Many individuals who at one stage meet UHR criteria diverge from the path leading to psychosis; some may have resolution of symptoms and difficulties, whereas others may develop non-psychotic disorders. Although these outcomes are seen in all UHR cohorts, it may be that these alternative pathways are more common earlier on. A number of medium- to long-term longitudinal follow-up studies of early UHR cohorts, e.g., PACE 400 (Nelson, 2011, personal correspondence), are currently underway and may assist in clarifying the longitudinal course of the UHR syndrome.

What predicts psychosis?

Yung *et al*. (2004) found significantly lower global assessment of functioning (GAF) scores (greater impairment), significantly longer delays accessing help and significantly higher levels of depression, measured with the Hamilton Rating Scale for Depression in the group that did transition. There were no significant differences between the groups on measures of anxiety, mania symptoms and negative symptom levels.

Schultze-Lutter *et al*. (2007) also reported that higher levels of depression at baseline were associated with transition as were higher levels of negative symptoms. The EPOS found in 124 patients that six baseline features predicted psychosis independently: schizotypal personality, SIPS positive scale score >16, bizarre thinking, sleep disturbance, greater social impairment and years of education. The NAPLS found in 291 patients that five baseline features predicted psychosis independently: genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, suspicion/paranoia, greater social impairment and a history of substance abuse (Cannon *et al*. 2008).

There has been considerable interest in the overlap and relationship between substance use, in particular cannabis use and psychosis, given that many of the symptoms experienced by people in the at-risk group parallel the effects of the use of substances. However, research findings have varied. Higher levels of cannabis use in the UHR population have been reported compared with controls. Cannabis use has been associated with lower levels of functioning within the UHR sample; however, although NAPLS reported substance misuse (not specifically cannabis use) as a clinical factor that predicted transition, a number of other studies have reported that cannabis use, misuse or dependence did not predict transition (Phillips *et al*. 2002; Auther *et al*. 2008).

Treatment options: interventional studies

A variety of interventions have been offered to those meeting criteria for being UHR. These interventions

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aim to reduce symptoms, as well as possibly delay or, even, fully prevent the onset of psychosis. However, as previously mentioned, there is methodological heterogeneity among these studies, thus making direct comparison difficult.

Psychosocial interventions

Supportive counselling and needs-based interventions are consistently used in UHR services and consist of assessment, education and empathetic but unstructured support (Yung *et al*. 2000). The aim of this approach is reducing stress and enhancing coping skills. Supportive counselling and needs-based intervention have only been evaluated against more elaborate interventions as a control condition in randomised control trials. However, this help-seeking UHR population usually have high levels of anxiety before presenting to UHR programmes (Yung *et al*. 2004). They frequently suspect that they have a psychotic illness as a result of the information they have gathered before presenting to services and the provision of supportive counselling with education and assistance with social and role functioning is considered a basic tenet in the provision of care for UHR patients.

Cognitive behavioural therapy (CBT)

Four randomised controlled trials (RCTs) have evaluated the effectiveness of CBT or CT as a treatment option for the UHR population (Morrison *et al*. 2004, 2007, 2012; Addington *et al*. 2011; Bechdolf *et al*. 2012). Details of the four CT/CBT trials are summarised in Table 1.

CBT was considered an acceptable and rational treatment for a number of reasons. CBT works with processes such as meta-cognitions and self-schemas, which are believed to be abnormal in people at risk of psychosis (Birchwood *et al*. 1989). Birchwood *et al*. (1989) showed that cognitive–behavioural monitoring of prodromal signs in clients with an existing diagnosis of psychosis enabled early intervention to prevent relapse or ameliorate mental state, and it has since been shown to significantly reduce relapse rates and hospital admissions in people at high risk of relapse (Gumley *et al*. 2003). CBT has proven efficacious in the treatment of both acute and chronic psychosis (Birchwood & Trower, 2006). Furthermore, most people in an ARMS show significant affective symptoms, for which CBT is an effective treatment. CBT with its use of collaborative problem identification and goal setting may also be a useful intervention for the false-positive group, who are seeking help for distressing symptoms but will not proceed to psychosis.

The CBT interventions used in all four trials used written manuals and were based on general principles of CBT. Key features of CBT for UHR individuals used in these trials included some of the basic tenets of CBT for psychosis; normalisation of experiences, de-catastrophising symptoms, generation and evaluation of alternative more reality-based interpretations, as well as testing them in behavioural experiments. In addition, CBT interventions included stress management, problem solving, coping and psycho-educational features.

Three of the four RCTs have demonstrated that treatment with CBT/CT is not associated with a reduced likelihood of developing psychosis in UHR patients. The studies vary in size ($n = 51$–288), duration of active treatment (6–24 months) and in the number of psychotherapy sessions (9 sessions in 6 months–60 sessions in 12 months). The largest trial by Morrison *et al*. (2007) ($n = 288$) is a multi-site RCT comparing CT and monitoring of mental state with monitoring of mental state alone found that CT plus monitoring did not significantly reduce transition to psychosis or symptom-related distress, but reduced the severity of psychotic symptoms in young people at high risk. However, the mean number of CT sessions received over the 6 months of active treatment were considerably lower than in previous studies [mean 9.11 (S.D. 6.69; range 0–26)] and the transition rates were considerably lower than expected in both groups, 6.9% for CT and 9.0% for monitoring, which raise concerns about how truly 'at risk' the participants in this study were.

Morrison *et al*.'s (2004) RCT demonstrated that CT significantly reduced the likelihood of transition to psychosis over 12 months; however, this reduction was not maintained at 36 months' follow-up (Morrison *et al*. 2007). The participant numbers in this study are small ($n = 58$) and the follow-up study at 3 years was very vulnerable to attrition with a loss to follow-up of 53% ($n = 33$). Bechdolf *et al*. (2012) in a multi-site RCT compared CBT with supportive counselling in 128 patients. CBT was provided for 12 months with an additional 12-month follow-up period. CBT significantly reduced the rate of transition to psychosis in the treatment group at 12 and 24 months. Addington and colleagues (2011) ($n = 51$) compared CBT with supportive counselling (Addington *et al*. 2011). Conversions to psychosis only occurred in the group who received supportive therapy, although the difference was not significant. Both groups improved in attenuated positive symptoms, depression and anxiety and neither improved in social functioning and negative symptoms. There were no differences between the two treatment groups.

Psychopharmacologic interventions

To date, five RCTs regarding psychopharmacologic interventions in the UHR state have been conducted (see Table 2). Four studies were double blind and one

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Table 1. *RCT of psychological interventions*

Study	Design	Inclusion criteria (instrument used)	*n*	Active Rx	Active Rx duration (months)	Mean dose/ schedule	Control	Follow-up off Rx (months)	Results
Morrison *et al.* (2004)	SBRCT	UHR criteria (CAARMS)	58	CBT	6	26 sessions/6 months	Monitoring	6	Reduced transition rate and symptoms in CBT group
Morrison *et al.* (2007)								36	No significant difference in transition rate, only difference at 36 months was in the prescription of antipsychotics
Addington *et al.* (2011)	SBRCT	Clinical high risk (structured interview for prodromal syndromes criteria)	51	CBT	6		Supportive counselling	18	No significant difference between two groups on transition rates
Bechdolf *et al.* (2012)	OLRCT	Early initial prodromal state (early recognition inventory)	128	Integrated psychological intervention	12	24 sessions/6 months	Supportive counselling	12 + 24	Integrated psychological intervention was superior to supportive counselling in preventing progression to psychosis at 12-month follow-up and at 24-month follow-up
Morrison *et al.* (2012)	SBRCT	UHR (CAARMS)	288	CT + mental state monitoring	6	9 sessions/6 months	Mental state monitoring	12–24	Cognitive therapy plus monitoring did not significantly reduce transition to psychosis or symptom-related distress but reduced the severity of psychotic symptoms in young people at high risk

RCT, Randomised controlled trial; SBRCT, single-blind randomised controlled trial; OLRCT, open-label randomised controlled trial; CAARMS, Comprehensive Assessment of At-Risk Mental States; UHR, ultra-high risk; CBT, cognitive behavioural therapy; CT, cognitive therapy.

Table 2. *RCT of pharmacotherapy*

Study	Inclusion criteria (instrument used)	Design	*n*	Active Rx	Active Rx duration (months)	Mean dose/ schedule	Control	Follow-up off Rx (months)	Results
McGorry *et al*. (2002)	UHR (CAARMS)	DBRCT	59	RIS + CBT	6	1.3 mg/day	Usual care	6	Reduced transition rate and reduced symptoms in RIS + CBT group
Philips *et al*. (2007)								30–40	No significant difference on transition rates
Woods *et al*. (2003)	Attenuated positive symptoms (structured interview for prodromal syndromes criteria)	DBRCT	60	OLZ + supportive family therapy	2	8 mg/day	Placebo + supportive family therapy	–	No significant difference in transition rates
McGlashan *et al*. (2006)					12			12	No significant difference in transition rates
Ruhrmann *et al*. (2007)	Late prodromal state (early recognition inventory)	OLRCT	114	Amisulpride	12	118 mg/day (50 mg–800 mg/day)	Needs focused intervention	–	Effects on transition rate not reported. Rx arm produced superior effects on all symptoms, and global functioning
Amminger *et al*. (2010)	UHR (CAARMS)	DBRPCT	81	Omega fatty acid	3	1.5 g/dl	Placebo	9	Reduced transition rate.
Yung *et al*. (2011)	UHR (CAARMS)	SBRPCT 3 arms	115	CBT + RIS *v*. CBT + placebo *v*. supportive psychotherapy + placebo	12–6 interim analysis	0.5–2 mg/day 1hour/1–2 weeks	Supportive psychotherapy + placebo	6-month interim analysis	No significant difference on transition rates

RCT, Randomised controlled trial; DBRCT, double-blind randomised controlled trial; OLRCT, open-label randomised controlled trial; SBRPCT, single-blind placebo controlled randomised controlled trial; DBRPCT, double-blind placebo controlled trial; CAARMS, Comprehensive Assessment of At-Risk Mental States; UHR, ultra-high risk; CBT, cognitive behavioural therapy; RIS, Risperidone; OLZ, Olanzapine.

single blind. Active treatments included low-dose antipsychotic medication: risperidone + CBT ($n = 59$) (McGorry *et al*. 2002), olanzapine ($n = 60$) (Woods *et al*. 2003), amisulpride ($n = 124$) (Ruhrmann *et al*. 2007), ethyl EPA (ω-3 fatty acids) ($n = 81$) (Amminger *et al*. 2010) and risperidone plus CBT or CBT in one three-arm study ($n = 115$) (Yung *et al*. 2011). Three studies were placebo controlled.

Of the five trials, two demonstrated significantly lower transition rates associated with psychopharmacological interventions. The omega fatty acids and the risperidone plus CBT studies were associated with significantly lower transition rates in the treatment arm. However, in the risperidone plus CBT group the reduction was not maintained in the at 30–40-month follow-up. Rather, patients who had been on treatment tended to catch up with the control condition once treatment was discontinued, whereas transition rates in patients who originally had been randomised to the control condition did not increase significantly over time. The amisulpride trial curiously does not report on transition rates, but does report on symptomatic and functional improvement in the treatment group. Only the ω-3 fatty acids study showed preservation of the low transition rate over the following 9 months. In this study, the transition rates of 2.6% *versus* 21.1% ($p < 0.05$) after the acute 2.5–3.5 months treatment with omega fatty acids *versus* placebo remained remarkably stable (4.6% *v*. 27.5%, $p < 0.05$) over the next 9 months post-treatment in both groups. A finding that the large multi-centre double-blind randomised placebo-controlled trial North America, EURope, Australia PROdrome (NEURAPRO) study is currently attempting to replicate.

The most recent Cochrane review published in June 2011 concluded that it is unclear whether treating UHR patients provides benefit and that further evidence is needed before recommendations on treatment in this cohort can be given (Marshall & Rathbone, 2011). Since this systematic review was conducted, a further four studies – three CBT RCT's (Birchwood *et al*. 1989; Gumley *et al*. 2003; Birchwood & Trower, 2006) and one RPCT – have been published (Woods *et al*. 2010). Of these studies, Birchwood *et al*. (1989) ($n = 128$) finds that CBT does reduce transition rates at 12 and 24 months; however, the other three studies fail to demonstrate a significant effect on transition rates of CBT (Gumley *et al*. 2003) ($n = 51$), CBT + monitoring of mental state (Birchwood & Trower, 2006) ($n = 288$) or Risperidone and CBT (Corcoran *et al*. 2010) ($n = 115$).

Ethical issues and DSM 5

The Psychosis Working Group for DSM 5, chaired by Prof. William Carpenter, was proposing the inclusion of a new diagnostic category 'Attenuated Psychotic Symptoms Syndrome' (APS) for DSM 5, which is expected to be released in May 2013. This proposal provoked considerable discussion and debate in the scientific community.

In the work towards a new classification system as part of DSM 5, dimensional and longitudinal aspects of psychiatric disorders are to be given more significance both in the definition and characterisation of psychiatric disorders (DSM Task Force, 2012). It is in this context that UHR research, which has at its core the dimensional measurement of psychopathology and the prospective evaluation of outcomes, was being considered for inclusion as part of the newly introduced risk syndromes section. However, although the move to a more dimensional approach for DSM 5 has been generally welcomed, opinions were divided on the inclusion of APS as a risk syndrome.

Those who favoured inclusion contended that (a) UHR patients are currently ill, (b) they are at high risk of deteriorating, (c) no DSM-IV diagnosis accurately captures their current illness or future risk, (d) the diagnosis has been made with reliability and validity in the research setting and (e) inclusion in DSM 5 would make UHR a more visible and a legitimate subject of research and increase its funding potential (Corcoran *et al*. 2010; Woods *et al*. 2010).

Those who opposed the inclusion of an 'at-risk' syndrome agreed that those meeting criteria for UHR are ill; however, the evidence base with regard to intervention in this population remains sparse. The inclusion of an 'at-risk' diagnosis in DSM 5 could increase the use of non-evidence-based interventions in this population (Yung *et al*. 2010). Those opposed to inclusion generally agreed that 'at-risk' patients are at risk for deterioration; however, the rising rate of false positives noted in the naturalistic follow-up studies (well above 50% in nearly all recent studies, as discussed above) is of grave concern and further work to improve accuracy of detection is required. Both sides agree that no DSM-IV diagnosis accurately captures an 'at-risk' individual's current illness or future risk (Woods *et al.* 2010) and also agree that the diagnosis of 'at risk' has been made with reasonable reliability and validity in the research setting. However, to date the diagnosis has been studied almost exclusively in academic centres and may not be generalisable to the community settings where the DSM 5 is routinely applied.

In the United States, in particular, large studies of pharmacological interventions are usually funded by pharmaceutical companies. However, these companies are reluctant to fund large studies unless they can use the results to promote their products. Food and Drug Administration (FDA) approval is required for companies to promote medication legally in the United States. Although there is no requirement for a

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disorder to be recorded in the DSM to receive an FDA indication, it is likely to facilitate the process. However, whether FDA approval or inclusion of an at risk for psychosis diagnosis in DSM 5 would have facilitated the study of relatively benign treatment options including psychotherapeutic options or less 'commercial' medications, e.g., omega fatty acids or serine was less certain.

In April 2012, it was announced that due to the nascency of the UHR research and the lack of substantive field trials, a PRS would not be included in the main text of DSM 5. However, 'Attenuated Psychotic Syndrome' will be included in Section III for conditions being recommended for further study (DSM Task force, 2012).

Conclusions

The evidence suggests that it is possible to identify individuals who may be at risk of developing psychosis. It may also be possible to reduce or delay the transition to psychosis and improve the severity of non-psychotic symptoms and distress. Results from intervention studies, mostly involving second-generation antipsychotics and CBT, are currently insufficient to make treatment recommendations for this 'at-risk' group. The emerging research with regard to possible neuroprotective factors like omega fatty acids is promising, but will require replication in larger cohorts before it can be recommended.

An area of particular concern for the UHR research field is the failing transition rates. The coming years are likely to see the emergence of substantial longitudinal data from some of the original UHR centres, e.g., PACE in Melbourne. Some of these data will hopefully address the ambiguity underlying the significance of falling transition rates and better define both the psychotic and non-psychotic outcomes within this population. In particular, the illness course of those who do transition to psychosis needs to be compared with patients who receive treatment from the onset of psychotic illness only.

Interventional research in the field appears to be moving away from antipsychotic medication and towards neuroprotective and low-risk pharmacologic and non-pharmacologic interventions. Data from the ongoing larger multi-centred interventional studies will hopefully offer clarification around the risks and benefits of UHR treatment strategies where the extent of potential harm needs to be carefully balanced against the risk of transition to psychosis.

References

Addington J, Epstein I, Liu L, French P, Boydell KM, Zipursky RB (2011). A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. *Schizophrenia Research* **125**, 54–61.

Amminger PG, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, Mackinnon A, McGorry PD, Berger GE (2010). Long chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomised placebo-controlled trial. *Archives of General Psychiatry* **67**, 146–154.

Auther AM *et al.* (2008). Presented at the 63rd Annual Meeting of the Society of Biological Psychiatry, Washington, DC, May 2008.

Bechdolf A, Pukrop R, Kohn D, Tschinkel S, Veith V, Schultze-Lutter F, Ruhrmann S, Geyer C, Pohlmann B, Klosterkotter J (2005). Subjective quality of life in subjects at risk of psychosis in Germany: concept and recruitment. *Schizophrenia Research* **79**, 137–143.

Bechdolf A, Wagner M, Ruhrmann S, Harrigan S, Putzfeld V, Pukrop R, Brockhaus-Dumke A, Berning J, Janssen B, Decker P, Bottlender R, Maurer K, Möller HJ, Gaebel W, Häfner H, Maier W, Klosterkötter J (2012). Preventing progression to first-episode psychosis in early initial prodromal states. *British Journal of Psychiatry* **200**, 22–29.

Bertelsen M, Jeppesen P, Petersen L, Thorup A, Øhlenschlaeger J, le Quach P, Christensen TØ, Krarup G, Jørgensen P, Nordentoft M (2008). Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Archives of General Psychiatry* **65**, 762–771.

Binbay T, Drukker M, Elbi H, Tanık FA, Özkinay F, Onay H, Zağli N, van Os J, Alptekin L (2011). Testing the psychosis continuum: differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophrenia Bulletin*. epub ahead of print (doi:10.1093/schbul/sbr003).

Birchwood M, Trower P (2006). The future of cognitive-behavioural therapy for psychosis: not a quasi-neuroleptic. *British Journal of Psychiatry* **188**, 107–108.

Birchwood M, Smith J, Macmillan F (1989). Cognitive therapy for the prevention of psychosis in people at ultra high risk for psychosis: randomised system using patients and families as observers. *Psychological Medicine* **19**, 649–656.

Bowers MB (1965). The onset of psychosis – a diary account. *Psychiatry* **28**, 346–358.

Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T, Heinssen R (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of General Psychiatry* **65**, 28–37.

Clarke M, Whitty P, Browne S, McTigue O, Kamali M, Gervin M, Kinsella A, Waddington JL, Larkin C, O'Callaghan E (2006). Untreated illness and outcome of psychosis. *British Journal of Psychiatry* **189**, 235–240.

Corcoran CM, First MB, Cornblatt B (2010). The psychosis risk syndrome and its proposed inclusion in the DSM-V: a risk–benefit analysis. *Schizophrenia Research* **120**, 16–22.

Crumlish N, Whitty P, Clarke M, Browne S, Kamali M, Gervin M *et al.* (2009). Beyond the critical period: longitudinal study of 8-year outcome in first-episode non-affective psychosis. *British Journal of Psychiatry* **194**, 18–24.

Dominguez MD, Wichers M, Lieb R, Wittchen HU, van Os J (2011). Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophrenia Bulletin* **37**, 84–93.

DSM Task Force (2012). American Psychiatric Association. (http://www.dsm5.org/about/Pages/DSMVOverview.aspx). Accessed 12 April 2012.

DSM Task Force (2012). American Pschiatric Association. (http://www.dsm5.org/proposedRevisions/Pages/proposedrevision.aspx?rid=412). Accessed 1 July 2012.

Foley D, Morley K (2011). Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. *Archives of General Psychiatry* **68**, 609–616.

Fornito A, Yung AR, Wood SJ, Phillips LJ, Nelson B, Cotton S, Velakoulis D, McGorry PD, Pantelis C, Yücel M (2008). Anatomic abnormalities of the anterior cingulate cortex before psychosis onset: an MRI study of ultra-high-risk individuals. *Biological Psychiatry* **64**, 758–765.

Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P (2012). Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of General Psychiatry* **69**, 220–229.

Giuliano AJ, Li H, Mesholam-Gately RI, Sorenson SM, Woodberry KA, Seidman LJ (2012). Neurocognition in the psychosis risk syndrome: a quantitative and qualitative review. *Current Pharmaceutical Design* **18**, 399–415.

Gross G, Huber G, Klosterkötter J, Linz M (1987). *BSABS, Bonner Skala für die Beurteilung von Basissymptomen, Bonn Scale for the Assessment of Basic Symptoms*. Springer: Berlin, Heidelberg, New York.

Gumley AI, O'Grady M, McNay L, Reilly J, Power K, Norrie J (2003). Early intervention for relapse in schizophrenia: results of a 12-month randomised controlled trial of cognitive behaviour therapy. *Psychological Medicine* **33**, 419–431.

Hafner H, Maurer K, Loffler W, Bustamante S, an der Heiden W, Riecher-Rossler A, Nowotny B (1995). Onset and early course of schizophrenia. In *Search for the Cause of Schizophrenia*, Vol. 3 (ed. H. G. W. Hafner), pp. 43–66. Springer-Verlag: Berlin.

Haroun N, Dunn L, Haroun A, Cadenhead KS (2006). Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. *Schizophrenia Bulletin* **32**, 166–178.

Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G (1994). One hundred years of schizophrenia: a meta analysis of the outcome literature. *American Journal of Psychiatry* **151**, 1409–1416.

Henry LP, Amminger GP, Harris MG, Yuen HP, Harrigan SM, Prosser AL *et al.* (2010). The EPPIC follow-up study of first-episode psychosis: longer-term clinical and functional outcome 7 years after index admission. *The Journal of Clinical Psychiatry* **71**, 716–728.

Kelleher I, Connor D, Clarke MC, Devlin N, Harley M, Cannon M (2012*a*). Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. *Psychological Medicine*. ePub ahead of print (doi:10.1017/S0033291711002960).

Kelleher I, Keeley H, Corcoran P, Lynch F, Fitzpatrick C, Devlin N, Molloy C, Roddy S, Clarke MC, Harley M, Arseneault L, Wasserman C, Carli V, Sarchiapone M, Hoven C, Wasserman D, Cannon M (2012*b*). Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *British Journal of Psychiatry*. ePub ahead of print (doi: 10.1192/bjp.bp.111.101543).

Klosterkotter J, Hellmich M, Steinmyer E (2001). Diagnosing schizophrenia in the initial prodromal phase. *Archives of General Psychiatry* **58**, 158–164.

Larsen TK, Johannssem JO, Opjordsmoen S (1998). First-episode schizophrenia with long duration of untreated psychosis. Pathways to care. *British Journal of Psychiatry* **172**, 45–52.

Marshall M, Rathbone J (2011). Early intervention for psychosis. *Cochrane Database of Systematic Reviews*, Issue 6. Art. No.: CD004718. (doi: 10.1002/14651858.CD004718.pub3).

McGlashan TH, Johannessen JO (1996). Early detection and intervention with schizophrenia: rationale. *Schizophrenia Bulletin* **22**, 201–222.

McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, Hawkins KA, Hoffman RE, Preda A, Epstein I, Addington D, Lindborg S, Trzaskoma Q, Tohen M, Breier A (2006). Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry* **163**, 790–799.

McGorry PD, Yung AR, Philips LJ, Yuen HP, Francey S, Cosgrave EM, Germano D, Bravin J, McDonald T, Blair A, Adlard S, Jackson H (2002). Randomised controlled trial of interventions designed to reduce the risk of progression to first episode psychosis in a clinical sample with sub-threshold symptoms. *Archives of General Psychiatry* **59**, 921–928.

McGorry PD, Nelson B, Amminger GP, Bechdolf A, Francey S, Berger G, Riecher-Rössler A, Klosterkötter J, Ruhrmann S, Schultze-Lutter F, Nordentoft M, Hickie I, McGuire P, Berk M, Chen EY, Keshavan MS, Yung AR (2009). Intervention in individuals at ultra high risk for psychosis: a review and future directions. *The Journal of Clinical Psychiatry* **70**, 1206–1212.

Meares A (1959). The diagnosis of pre-psychotic schizophrenia. *Lancet* **10**, 55–58.

Miller TJ, McGlashan TH, Rosen JL, Somjee L, Markovich PJ, Stein K, Woods SW (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry* **159**, 863–865.

Morrison AP, French P, Parker S (2007). Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. *Schizophrenia Bulletin* **33**, 682–687.

Morrison A, French P, Parker S, Roberts M, Stevens H, Bentall RP, Lewis SW (2007). Three-year follow-up of a

randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultra high risk. *Schizophrenia Bulletin* **33**, 682–687.

Morrison AP, French P, Walford L, Lewis SW, Kilcommons A, Green J, Parker S, Bentall RP (2004). Cognitive therapy for the prevention of psychosis in people at ultra high risk for psychosis: randomised control trial. *British Journal of Psychiatry* **185**, 291–297.

Morrison AP, French P, Stewart S, Birchwood M, Fowler D, Gumley AI, Jones PB, Bentall RP, Lewis SW, Murray GK, Patterson P, Brunet K, Conroy J, Parker S, Reilly T, Byrne R, Davies LM, Dunn G (2012). Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. *BMJ*, Apr 5;344:e2233. (DOI: 10.1136/bmj.e2233).

Olsen KA, Rosenbaum B (2006). Prospective investigations of the prodromal state of schizophrenia: review of studies. *Acta Psychiatrica Scandinavica* **113**, 247–272.

Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Philips LJ *et al.* (2003). Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* **25**, 281–288.

Philips LJ, Yung AR, McGorry PD (2000). Identification of young people at risk of psychosis: validation of Personal Assessment and Crisis Evaluation Clinic intake criteria. *Australian and New Zealand Journal of Psychiatry* **34**, 5164–5169.

Phillips LJ, Curry C, Yung AR, Yuen HP, Adlard S, McGorry PD (2002). Cannabis use is not associated with the development of psychosis in an 'ultra' high-risk group. *Australian and New Zealand Journal of Psychiatry* **36**, 800–806.

Phillips LJ, McGorry PD, Yuen HP, Ward J, Donovan K, Kelly D, Francey SM, Yung AR (2007). Medium term follow-up of a randomized controlled trial of interventions for young people at ultra high risk of psychosis. *Schizophrenia Research* **96**, 25–33.

Raven M, Stuart GW, Jureidini J (2012). 'Prodromal' diagnosis of psychosis: ethical problems in research and clinical practice. *Australian and New Zealand Journal of Psychiatry* **46**, 64–65.

Ruhrmann S, Bechdolf A, Kühn KU, Wagner M, Schultze-Lutter F, Janssen B, Maurer K, Häfner H, Gaebel W, Möller HJ, Maier W, Klosterkötter J (2007). Acute effects of treatment for prodromal symptoms for people putatively in a late initial prodromal state of psychosis. *British Journal of Psychiatry* **191**, S88–S95.

Ruhrmann S, Schultze-Lutter F, Salokangangas RK, Heinmaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heinz A, Morrison A, Lewis S, von Reventlow HG, Klosterkötter J (2010). Prediction of psychosis in adolescents and young adults at high risk; results from the prospective European prediction of psychosis study. *Archives of General Psychiatry* **67**, 241–251.

Schaffner K, McGorry PD (2001). Preventing severe mental illnesses – new prospects and ethical challenges. *Schizophrenia Research* **51**, 3–15.

Schultze-Lutter F (2009). Subjective symptoms of schizophrenia in research and the clinic: the basic symptoms concept. *Schizophrenia Bulletin* **35**, 5–8.

Schultze-Lutter F, Ruhrmann S, Picker H, Klosterkotter J (2007). The Schizophrenia Proneness Instrument (SPI-A) – a tool for the assessment of basic symptoms. *European Psychiatry* **21**, s27.

Schultze-Lutter F, Ruhrmann S, Hoyer C, Klosterkotter J, Leweke FM (2007). The initial prodrome of schizophrenia: different duration, different underlying deficits? *Comprehensive Psychiatry* **48**, 479–488.

Sullivan HS (1927). The onset of schizophrenia. *American Journal of Psychiatry* **151**, 135–139.

Tandon R, Nasrallah HA, Keshavan MS (2009). Schizophrenia, 'just the facts' 4. Clinical features and conceptualization. *Schizophrenia Research* **110**, 1–23.

van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine* **39**, 179–195.

Velakoulis D, Wood SJ, Wong MT, McGorry PD, Yung A, Phillips L, Smith D, Brewer W, Proffitt T, Desmond P, Pantelis C (2006). Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Archives of General Psychiatry* **63**, 139–149.

Walker EF, Cornblatt BA, Addington J, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Woods SW, Heinssen R (2009). The relation of antipsychotic and antidepressant medication with baseline symptoms and symptoms progression: a naturalistic study of the North American prodrome longitudinal sample. *Schizophrenia Research* **115**, 50–57.

Warner R (2002). Limitations of the Bonn Scale for the assessment of basic symptoms as a screening measure. *Archives of General Psychiatry* **59**, 470–471.

Woodberry KA, Seidman LJ, Giuliano AJ, Verdi MB, Cook WL, McFarlane WR (2010). Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. *Schizophrenia Research* **123**, 188–198.

Woods SW, Walsh BC, Saksa JR, McGlashan TH (2010). The case for including Attenuated Psychotic Symptoms Syndrome in DSM-5 as a psychosis risk syndrome. *Schizophrenia Research* **123**, 199–207.

Woods SW, Breier A, Zipursky RB, Perkins DO, Addington J, Miller TJ, Hawkins KA, Marquez E, Lindborg SR, Tohen M, McGlashan TH (2003). Randomised trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. *Biological Psychiatry* **54**, 453–464.

Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R *et al.* (2009). Validity of the prodromal risk syndrome for psychosis: findings from the North American Prodrome Longitudinal Study. *Schizophrenia Bulletin* **35**, 894–908.

Wyatt R, Henter I (2001). Rationale for the study of early intervention. *Schizophrenia Research* **51**, 69–76.

Yung AR, McGorry PD (1996). The prodromal phase of first episode psychosis: past and current conceptualisations. *Schizophrenia Bulletin* **22**, 353–370.

Yung AR, Nelson B (2011). Young people at ultra high risk for psychosis: a research update. *Early Intervention in Psychiatry* **5**, 52–57.

Yung AR, Philips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD (2000). Psychosis prediction: 12 month follow up of a high risk ('prodromal') group. *Schizophrenia Research* **60**, 21–32.

Yung AR, Philips LJ, Yuen HP, McGorry PD (2004). Risk factors for psychosis in an ultra high risk group: psychopathology and clinical features. *Schizophrenia Research* **67**, 131–142.

Yung AR, Phillips LJ, Yuen HP (2004). Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophrenia Research* **67**, 131–142.

Yung A, Nelson B, Thompson A, Wood SJ (2010). The psychosis threshold in ultra high risk (prodromal) research: is it valid? *Schizophrenia Research* **120**, 1–3.

Yung AR, Nelson B, Thompson AD, Wood SJ (2010). Should a 'Risk Syndrome for Psychosis' be included in the DSMV? *Schizophrenia Research* **120**, 7–15.

Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell-Olio M *et al.* (2005). Mapping the onset of psychosis: The Comprehensive Assessment of At Risk Mental States (CAARMS). *Australian and New Zealand Journal of Psychiatry* **39**, 964–971.

Yung AR, Yuen HP, Berger G, Francey S, Hung T, Nelson B *et al.* (2007). Declining transition rate in ultra high risk (prodromal) services: dilution or redirection of risk? *Schizophrenia Bulletin* **33**, 673–681.

Yung AR, Phillips LJ, Nelson B, Francey SM, PanYuen H, Simmons MB *et al.* (2011). Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. *Journal of Clinical Psychiatry* **72**, 430–440.

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