Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The Ultra-High-Risk for psychosis groups: Evidence to maintain the status quo

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ARTICLE INFO

Article history:
Received 20 April 2017
Received in revised form 31 August 2017
Accepted 3 September 2017
Available online xxxx

Keywords:
Ultra-High-Risk for psychosis
UHR
Transition
Long-term outcomes
Symptom severity

ABSTRACT

Individuals are considered Ultra-High-Risk (UHR) for psychosis if they meet a set of standardised criteria including presumed genetic vulnerability (Trait), or a recent history of Attenuated Psychotic Symptoms (APS) or Brief Limited Intermittent Psychotic Symptoms (BLIPS). Recent calls to revise these criteria have arisen from evidence that Trait, APS and BLIPS groups may transition to psychosis at different rates. Concurrently, it has become clear that the UHR status confers clinical risk beyond transition to psychosis. Specifically, most UHR individuals will not develop psychosis, but will experience high rates of non-psychotic disorders, persistent APS and poor long-term functional outcomes. Rather than focus on transition, the present study investigated whether UHR groups differ in their broader clinical risk profile by examining baseline clinical characteristics and long-term outcomes other than transition to psychosis. Four UHR groups were defined: Trait-only, APS-only, Trait + APS, and any BLIPS. Participants ($N = 702$) were recruited upon entry to early intervention services and followed-up over a period of up to 13 years (mean = 4.53, SD = 3.84). The groups evidenced similar symptom severity (SANS for negative symptoms, BPRS for positive and depression/anxiety symptoms) and psychosocial functioning (SOFAS, GAF, QLS) at baseline and follow-up as well as similar prevalence of non-psychotic disorders at follow-up. Our findings demonstrate that UHR groups evidence a similar clinical risk profile when we expand this beyond transition to psychosis, and consequently support maintaining the existing UHR criteria.

1. Introduction

It has been two decades since Yung and colleagues (Yung and McGorry, 1996a) introduced a set of standardised criteria to identify individuals at Ultra-High-Risk (UHR) of developing a psychotic disorder (also known as the At Risk Mental State or 'prodromal' phase of psychosis). Since this time, the UHR paradigm has provided a window into risk factors and aetiological mechanisms involved in psychosis onset and an opportunity to trial preventive interventions (van der Gaag et al., 2013). To be considered UHR, help-seeking individuals must be in the age range of highest risk for psychosis (late adolescence, early adulthood) and meet one or more of the following 3 criteria: 1) Attenuated Psychotic Symptoms (APS): sub-threshold positive psychotic symptoms during the past 12 months; 2) Brief Limited Intermittent Psychotic Symptoms (BLIPS): frank psychotic symptoms for less than one week which

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https://doi.org/10.1016/j.schres.2017.09.003
0920-9964/

resolve spontaneously; 3) Genetic vulnerability (Trait) – meet criteria for Schizotypal Personality Disorder or have a first-degree relative with a psychotic disorder. Each risk criteria must also be associated with a deterioration in functioning or chronic low functioning.[2]

Over the years, evidence has pointed to variability between groups defined by these UHR criteria in relation to risk of transitioning to a psychotic disorder (Fusar-Poli et al., 2015; Nelson et al., 2011, 2013). A history of BLIPS (regardless of APS or Trait risk) has consistently been linked to the highest risk of transitioning to a psychotic disorder (Fusar-Poli et al., 2015; Nelson et al., 2011, 2013). Presumed genetic vulnerability (Trait) with no history of APS or BLIPS (Trait-only) confers the lowest transition risk (Fusar-Poli et al., 2015; Nelson et al., 2011). An early study found that the combination of genetic vulnerability and APS (Trait + APS) was strongly predictive of transition to psychosis by twelve months (Yung et al., 2004). However, more recent evidence suggests similar risk trajectories for Trait + APS individuals and individuals who meet APS criteria alone (APS-only) (Fusar-Poli et al., 2015; Nelson et al., 2011).

Evidence of variability in transition risk has prompted some researchers to challenge the current composition of the UHR criteria. In a guidance paper for the European Psychiatric Association, Schultz-Lutter and colleagues recommended that having a first-degree relative with a psychotic illness should not be considered a clinical marker of risk for psychosis even in the presence of functional decline (Schultze-Lutter et al., 2015). Others have proposed that BLIPS should be treated as a separate clinical entity based on both higher transition risk and diagnostic overlap with DSM/ICD brief psychotic disorders (Fusar-Poli et al., 2015).

Concurrently, it has become increasingly evident that clinical implications of UHR status extend beyond risk of transition to psychosis. Most individuals who meet UHR criteria will not develop a psychotic disorder (Nelson et al., 2013; Simon et al., 2011) but will experience persistent Attenuated Psychotic Symptoms (de Wit et al., 2014; Simon et al., 2011), poor psychosocial functioning (Rutigliano et al., 2016a) and high rates of non-psychotic disorders (de Wit et al., 2014; Lin et al., 2015; Rutigliano et al., 2016b). Such findings have driven a reframing of UHR as a clinical state signifying pluripotent, transdiagnostic risk and the need for clinical care, rather than simply a marker of psychosis risk (McGorry et al., 2006; McGorry and Nelson, 2016; Yung et al., 2012).

In the current study we investigated possible differences between the UHR groups in clinical risk other than transition to psychosis. Specifically, we examined baseline clinical characteristics known to contribute to poor outcomes in UHR populations, including symptom severity (Fusar-Poli et al., 2013; Nelson et al., 2013; Seidman et al., 2010), psychosocial functioning (Nelson et al., 2013; Seidman et al., 2010), duration of symptoms prior to first contact with clinical services (Nelson et al., 2013) and the year that individuals entered clinical services (Nelson et al., 2013; Simon et al., 2014; Yung et al., 2007). We also examined long-term non-transition outcomes including symptom severity, psychosocial functioning and the prevalence of non-psychotic disorders. A large cohort ($N = 702$) of UHR individuals were recruited at entry to treatment early psychosis clinical service and re-assessed up to thirteen years later. For consistency with previous studies (Fusar-Poli et al., 2015; Nelson et al., 2011), we defined four combinations of UHR risk group: Trait-only, APS-only, Trait + APS, and any BLIPS (regardless of Trait or APS criteria). If the UHR groups defined here engender truly distinct psychopathological risk profiles, we would expect group differences to emerge in baseline characteristics and long-term non-transition outcomes.

[2] The requirement for deterioration in functioning has changed over the years (see Table 1 for a summary of the changes).

Methods

2.1. Participants and setting

The present sample ($N = 702$) were recruited between 1995 and 2013, across 10 research sites in Australia (Melbourne, Sydney), the Netherlands (Amsterdam), Germany (Jena), Switzerland (Basel, Zurich), Austria (Vienna), Denmark (Copenhagen), Singapore, and Hong Kong (Pok Fu Lam). Each site has an established early psychosis clinical service that conducts research with UHR clients. From 1995 to 2006 participants were recruited for UHR research studies at the Melbourne site only ($N = 398$). These included three intervention (Berger et al., 2012; McGorry et al., 2002; Yung et al., 2011) and four cohort studies (Phillips et al., 2009; Thompson et al., 2007; Yung et al., 2003; Yung and McGorry, 1996a, 1996b). This is the same group as previously reported in the PACE 400 long-term follow-up study (Nelson et al., 2013), excluding 18 participants for whom UHR risk group could not be determined. The sample (recruited to baseline studies between 1995 and 2006) were followed up between 2007 and 2008 (for full details see Nelson et al., 2013). The remaining 304 participants were recruited from 2010 to 2013 across the 10 research sites listed as part of a large multi-site intervention study (Neurapro; Markulev et al., 2015; McGorry et al., 2017).

Participants were required to meet criteria for at least one of the three UHR groups (APS, BLIPS or Trait risk). Criteria used to assess each are summarized in Table 1. As illustrated, over the years there have been changes in the requirement for functional deterioration across the three risk groups as well as in measures used to assess risk. Exclusion criteria were known history of a psychotic episode (treated or untreated); known organic cause of symptoms (e.g., epilepsy); or a lifetime antipsychotic dose equivalent to or >15 mg of haloperidol.

2.2. Measures

2.2.1. UHR status

Measures and methods used to assess UHR status from 1995 to 2013 are outlined in Table 1.

2.2.2. Symptoms and psychosocial functioning

The Brief Psychiatric Rating Scale (BPRS; Overall and Gorhum, 1962) was administered to assess positive symptoms (BPRS Psychosis subscale) and depression/anxiety (BPRS Depression and Anxiety subscale). Negative symptoms were assessed with the Schedule for the Assessment of Negative Symptoms (SANS; Andreasen, 1982). Psychosocial functioning was assessed with the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994), Social and Occupational Functioning Assessment Scale (SOFAS; American Psychiatric Association, 1994) and Quality of Life Scale (QLS; Heinrichs et al., 1984). SOFAS scores are reported for follow-up only as this measure was not administered at baseline prior to 2010. QLS and GAF were available at baseline and follow-up, but only for members of the PACE 400 subcohort.

2.2.3. Non-psychotic disorders

The presence of Axis I non-psychotic disorders at follow-up was determined with the Structured Clinical Interview for DSM-IV disorders (SCID-IV; First et al., 2002).

2.3. Procedures

Participants completed baseline assessments at entry to the clinical service. Follow-up interviews were conducted in 91.1% ($n = 277$) of the Neurapro cohort and 71.1% ($n = 283$) of the PACE 400 cohort. For PACE 400 participants, where face-to-face interviews were not possible assessments were conducted over the phone. Full details of follow-up procedures for the PACE 400 cohort are reported elsewhere (Nelson et

Please cite this article as: McHugh, M.J., et al., The Ultra-High-Risk for psychosis groups: Evidence to maintain the status quo, Schizophr. Res. (2017), https://doi.org/10.1016/j.schres.2017.09.003