

# Clinical profile, conversion rate, and suicidal thinking and behaviour in children and adolescents at ultra-high risk for psychosis: a theoretical perspective

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## ABSTRACT

Over the past years there has been substantial growing interest in the prodromes of psychosis to identify individuals at risk for psychosis prior to their first psychotic episode. Researchers have proposed criteria to detect young adults at Ultra-High Risk (UHR) for psychosis, and these criteria have also been applied to children and adolescents, though few clinical studies have examined this population. This theoretical perspective presents some of the crucial issues in the assessment and treatment of UHR children and adolescents: the presence of a specific clinical profile (*i.e.*, different to that of healthy controls and UHR young adults), the predictive value of UHR criteria, and the presence and clinical significance of suicidal thinking and behaviour. In UHR children and adolescents, like UHR young adults, the presence of Attenuated Psychotic Symptoms (APS) is the most frequently reported inclusion criterion at baseline, with a prevalence of approximately 89–100%. In addition, there are frequently non-psychotic comorbid diagnoses of depressive and anxiety disorders. In contrast to the UHR adult population, UHR children and adolescents demonstrate a lower conversion rate to frank psychosis, most likely due to their high rate of APS. Finally, UHR adolescents report a high prevalence of suicidal ideation and self-injurious behaviour (67.5%), as well as a significantly greater frequency of attempted suicide, relative to adolescents with frank psychosis. On this basis, UHR children and adolescents report a clinical complexity that should be carefully monitored and considered for specific and targeted therapeutic interventions to be planned and developed.

**Key words:** Ultra High Risk; psychosis; children and adolescents; suicidality.

## Introduction

Over the past 25 years, the scientific literature has demonstrated increased clinical efforts to identify and in-

tervene in the prodromal phase of the first psychotic episode (McGorry, Hickie, Yung, Pantelis, & Jackson, 2006; Pelizza et al., 2018; Tor et al., 2018, Lingiardi & Boldrini, 2019). Yung and McGorry (1996) proposed a set of standardized criteria to identify individuals at Ultra-High Risk (UHR) of developing a psychotic disorder (*i.e.*, those demonstrating an at-risk mental state). These criteria distinguish between: i) Attenuated Psychotic Symptoms (APS), which are sub-threshold positive symptoms; ii) Brief Limited Intermittent Psychotic Symptoms (BLIPS), which are transient psychotic symptoms that spontaneously remit within 1 week; and iii) Genetic Risk And Functioning Deterioration syndrome (GRFD), which is a trait/state risk condition involving a family history of psychosis (within first-degree relatives) and a schizotypal personality disorder associated with poor functioning that is manifested and sustained for  $\leq 1$  month (Yung et al., 2005; Table 1). In general, individuals who present any of these three risk conditions may develop frank psychosis.

A meta-analysis conducted by Fusar-Poli et al. (2012) estimated a transition risk of 18% at the 6-month follow-up, 22% at the 1-year follow-up, 29% at the 2-year follow-up, and 36% at the 3-year follow-up, independent of the psychometric instruments used. Fusar Poli et al. (2016) later proposed that the three UHR subgroups differ according to their level of risk: those with BLIPS have a higher transition risk than those with APS, who have a

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higher transition risk than those with GRFD. Despite the wide availability of validation studies for UHR criteria in adult samples, empirical evidence on the clinical significance and prognostic value of UHR criteria in children and early adolescents is not clear (Schimmelmann, Walger, & Schultze-Lutter, 2013; Tiffin & Welsh, 2013). For example, in the BEARS-Kid Study, Schimmelmann, Michel, Martz-Irgartinger, Linder and Schultze-Lutter (2015) examined UHR symptoms and criteria in a sample of individuals from a general population aged 8–40 years. The findings showed a strong age effect at around 16 years: compared to older participants, subjects aged 8–15 years reported more perceptively attenuated psychotic symptoms, equal to unusual perceptual experiences and attenuated hallucinations. In this study, perceptively attenuated psychotic symptoms were found to be less related to functional impairment, irrespective of age. Conversely, non-perceptively attenuated psychotic symptoms including unusual thought content/delusional ideas, were found to relate to low functioning, although this relationship was weaker in participants younger than 16 years. Based on these results, Schimmelmann et al. (2015) concluded that, as interest in the early detection of psychosis in younger age groups is increasing, it is necessary to clarify the validity and clinical significance of UHR symptoms and criteria in children and adolescents.

Starting from this background, the present theoretical perspective discusses some key issues in the identification and management of UHR children and adolescents. In particular, we first focus on the clinical characterization of UHR children and adolescents in comparison to adult samples and healthy controls; second, we address the predictive value of UHR criteria in this age group; finally, we illustrate the few studies that have investigated suicidal thinking and behaviour in UHR children and adolescents.

## Is it Possible to Characterize a Specific Clinical Profile for UHR Children and Adolescents?

Studies on the characterization and identification of UHR populations have focused mostly on the young adult population (Boldrini et al., 2019). Indeed, samples of UHR children and adolescents are lacking and few studies have provided detailed baseline descriptions of these samples compared to healthy controls. Tor et al. (2018), in a systematic review of the literature, proposed that UHR children and adolescents have several clinical symptoms at baseline, with most attenuated positive symptom inclusion criteria observed; these subjects report mostly perceptual abnormalities and suspiciousness, and present non-psychotic comorbid conditions such as depressive and anxiety disorders. Finally, UHR children and adolescents show lower general intelligence and no structural brain differences compared with controls. In a more recent study, Dolz et al. (2019) replicated the results of Tor et al. (2018) by comparing a sample of UHR children and adolescents ( $N=91$ , mean age:  $15.5\pm 1.5$  years) with a healthy control group ( $N=45$ , mean age:  $15.1\pm 1.7$  years), with respect to socio-demographic, neurodevelopmental, and clinical characteristics. The results showed that, at baseline, 79.1% of the UHR sample ( $N=72$ ) reported APS, with the most common positive symptoms being suspiciousness and delusional ideas. Additionally, the UHR sample presented more psychiatric comorbidities associated with UHR (65.9%), including a prevalent diagnosis of depressive disorder (60%). Finally, 49.5% of the UHR children and adolescents had a first- or second-degree psychotic relative who met a significant number of the UHR criteria. According to the socio-demographic variables, the UHR group had significantly lower socio-economic status, premorbid academic performance, and global functioning relative to the healthy control group.

**Table 1. Ultra-High-Risk Criteria.** (Nelson, Yuen, & Yung, 2011)

Group 1: Attenuated positive psychotic symptoms	<ul style="list-style-type: none"> <li>- Presence of at least one of the following symptoms: ideas of reference, odd beliefs or magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech, odd behaviour, and appearance</li> <li>- Frequency of symptoms: at least several times a week</li> <li>- Recency of symptoms: present within the last year</li> <li>- Duration of symptoms: present for at least 1 week and no longer than 5 years</li> </ul>
Group 2: Brief limited intermittent psychotic symptoms	<ul style="list-style-type: none"> <li>- Transient psychotic symptoms. Presence of at least one of the following: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, odd thinking, or speech</li> <li>- Duration of episode: less than 1 week</li> <li>- Frequency of symptoms: at least several times per week</li> <li>- Symptoms resolve spontaneously</li> <li>- Recency of symptoms: must have occurred within the last year</li> </ul>
Group 3: Trait and state risk factors	<ul style="list-style-type: none"> <li>- Schizotypal personality disorder in the identified individual, or a first-degree relative with a psychotic disorder</li> <li>- Significant decline in mental state or functioning, maintained for at least 1 month and not longer than 5 years</li> <li>- This decline in functioning must have occurred within the past year</li> </ul>

While Tor et al.'s (2018) comparison of UHR children and adolescents with healthy controls is useful, it did not seek to uncover differences between UHR children and UHR adolescents, to provide insight into potential age-related clinical characteristics. On this subject, Ribolsi et al. (2017) investigated age differences in a sample of 94 UHR children and adolescents (45 females, 49 males). Participants were divided into two groups: early (46 participants, aged 9–14 years) and later (48 participants, aged 15–18 years). The results indicated that the latter group showed lower levels of depressive symptoms and better social and role functioning than the early group. Otherwise, the groups were homogeneous with respect to comorbid diagnoses. More specifically, the majority of the sample reported a unipolar mood disorder ( $N=44$ ), while other participants reported schizotypal personality disorder ( $N=16$ ), an anxiety disorder ( $N=20$ ), obsessive-compulsive disorder ( $N=24$ ), and/or behavioral disorder ( $N=12$ ). Ribolsi et al. (2017) concluded that while the UHR clinical condition in the older age group was associated with less functional impairment, age was not associated with psychotic symptoms.

More recent investigations have focused on the domain of negative symptoms, which are a core clinical feature of both psychotic disorders and the UHR condition. Indeed, relative to attenuated positive symptoms, the prevalence of negative symptoms is high in UHR young adults (Velthorst et al., 2009), with social isolation being the most frequently reported (Lencz, Smith, Auther, Correll, & Cornblatt, 2004). Additionally, Lam et al. (2015) and Piskulic et al. (2012) proposed that negative symptoms were related to functional impairment in UHR young adults, and that the severity of negative symptoms at baseline predicted conversion to psychosis. Finally, McHugh et al. (2018) showed that the severity of negative symptoms was similar at baseline and follow-up in all three UHR groups (*i.e.*, APS, BLIPS, GRFD). However, these studies were all conducted on UHR young adults and adults, and only the recent study of Poletti et al. (2019) investigated samples composed of only UHR children and adolescents. Poletti et al. (2019) examined the negative symptomatology profile of 51 UHR adolescents compared to 33 FEP (first episode psychosis) adolescents (aged 13–18 years), according to the Comprehensive Assessment of At-Risk Mental State (CAARMS; Raballo, Semrov, Bonner, & Simmons, 2013) and the Positive and Negative Syndrome Scale (PANSS; Pelizza et al., 2018). The results demonstrated that the UHR sample reported a similar severity of negative symptomatology (*e.g.*, social isolation) as the FEP group. These results support the findings of previous studies (Velthorst et al., 2010; Hafner et al., 2004) revealing a high level of negative symptomatology and significant impairment in global functioning (relating to, *e.g.*, academic performance and social relationships) in both FEP and UHR young adults. The results also suggest that

the presence of negative symptoms could be an important variable in the early prodromal state in adolescence, as well as in adulthood.

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### Are UHR Criteria Predictive of the Transition to Psychosis in Children and Adolescents?

Rate transition to frank psychosis is significant for the predictive value of UHR criteria in children and adolescents. In one of the first studies conducted on UHR adolescents (aged 12–18 years), Ziermans et al. (2014) investigated the neurocognitive and clinical predictors of the transition to psychosis and functional outcome in a clinical sample of 43 UHR adolescents (mean age:  $15.2\pm 2.2$  years) compared to 44 controls (mean age:  $15.4\pm 1.3$  years). At the 6-year follow-up, 10 UHR subjects had converted to psychosis. Comparing this converted UHR group with the non-converted UHR group ( $N=33$ ) on clinical variables, the results demonstrated that, similar to the pattern demonstrated by UHR adults, presence of attenuated positive symptoms at baseline was a strong predictor of adolescents' conversion to psychosis, while presence of disorganized symptoms at baseline predicted a lower functional outcome. With respect to neurocognitive predictors, the UHR sample reported a lower IQ compared to the control group at baseline. Ziermans et al. (2014) proposed that IQ could be the unique neurocognitive parameter that predicts conversion to psychosis at a young age.

Subsequent studies (Schultze-Lutter et al., 2015; Armando et al., 2015) examined the predictive value of UHR criteria and their associated transition rates in children and adolescents. In a meta-analysis, Schultze-Lutter et al. (2015) reported lower conversion rates at 1-year follow-up in a sample of UHR children and adolescents (9.5%) compared to a sample of UHR adults (18%). Investigating the predictive factor for conversion to frank psychosis at 1-year follow-up, Armando et al. (2015) examined 35 UHR children and adolescents (aged 9–17 years) using the Structured Interview for Prodromal Syndromes (SIPS/SOPS; McGlashan, 2008). The results showed that, after 1 year, 20% had developed schizophrenia, 25.7% had remitted from their UHR status, and 54.3% had retained their UHR status. Conversion to frank psychosis was best predicted at baseline by the presence of BLIPS and disorganized communication symptoms. The authors held that, since BLIPS are usually rare in UHR samples, they demonstrated a significantly higher conversion rate than other UHR criteria (Schultze-Lutter et al., 2015). In fact, their presence in 14.3% of the sample might explain the high 1-year conversion rate of 20%. Indeed, in a previous study with UHR adolescent samples, which found lower conversion rates (3.3–9.7%), BLIPS were absent (Cornblatt et al., 2007; Lindgren et al., 2014; Welsh & Tiffin, 2014) or only reported by 5.6% of the sample (Ziermans, Schothorst, Sprong, & van Engeland, 2011). Some



of these studies (Welsh & Tiffin, 2014; Ziermans et al., 2011) also showed conversion rates of 7–21% at 2-year follow-up.

Finally, in Armando et al. (2015), age was not a significant predictor of transition. Considering other predictive factors for the conversion to frank psychosis, the literature shows that up to 70–80% of UHR adolescents and young adults have at least one non-psychotic comorbid diagnosis (Fusar Poli et al., 2012; Salokangas et al., 2012). For example, Fusar Poli, Nelson, Valmaggia, Yung and McGuire (2014) found a prevalence of 40.7% for depressive disorders and 15.3% for anxiety disorders in a UHR sample. However, despite the high prevalence of non-psychotic comorbid disorders associated to UHR state, these comorbidities do not seem to increase the risk of transition. In fact, Albert, Tomassi, Maina, and Tosato (2018), in a systematic review of studies conducted with UHR young adults, confirmed that UHR patients with non-psychotic comorbid disorders are not at greater risk of conversion to psychosis than those without non-psychotic comorbid disorders.

Similarly, as mentioned above, Armando et al. (2015) showed that, in a sample of UHR children and adolescents (aged 9–17 years), non-psychotic comorbid disorders (e.g., anxiety, depressive, behavioural, or obsessive-compulsive disorders) were not predictive of the transition to psychosis after 1 year.

Interesting, in a more recent study (Poletti et al., 2019), transition to psychosis was not only evaluated in accordance with the criteria for frank psychosis, according to a gold-standard psychosis assessment instrument (e.g. CAARMS, PANSS), but also in terms of the presence of a functional transition (i.e., deterioration of global functioning and cognitive ability that requires intense, even pharmacological, treatment). Such functional deterioration is more frequent during the first year, while the general peak of the transition seems to occur within the first 2 years (Fusar Poli et al., 2016; Tor et al., 2018). Based on this data, Poletti et al. (2019) developed a follow-up study to characterize the clinical profile and functioning of 112 distinct help-seeking subgroups of UHR adolescents (aged 13–18 years) and to monitor the cumulative transition rate from UHR to FEP at a 2-year follow-up. Approximately 7% of the UHR children ( $N=51$ ) met the criteria for frank psychosis at 1 year; at 2 years from the first diagnosis of UHR, the proportion increased to 13%. When considering also functional transition (linked to the introduction of antipsychotic medication), the conversion at 1 year was 29.4%, while at 2 years no functional transition was detected. The authors concluded that the cumulative psychosis transition (i.e., meeting the criteria for both UHR and functional deterioration) was approximately 33% at 1 year and 37% at 2 years. Of note, at baseline, the UHR group ( $N=51$ ) and the FEP group ( $N=33$ ) demonstrated similar levels of functional impairment (Poletti et al., 2019).

## Are Suicidal Thinking and Behaviour Present in the Clinical Picture of UHR Children and Adolescents?

Suicide risk is clinically relevant to FEP, and the literature associates psychotic experiences with increased longitudinal rates of suicidal thoughts and behaviour (Bromet et al., 2017). Pompili et al. (2011) and Bang et al. (2017) showed that suicide risk in the early phases of schizophrenia (FEP and UHR subjects) is higher than that of the general population. Despite this evidence, suicide risk in UHR individuals has received scant empirical attention.

On this topic, Taylor, Hutton and Wood (2015) conducted a systematic review and meta-analysis involving mixed samples (aged 8–40 years) of UHR individuals to evaluate prevalence, risk factors, predictors, and correlates of suicidality and self-injury. The results showed that the UHR patients exhibited more prevalent suicidal ideation than healthy controls. In particular, 66.08% of the UHR patients reported a “recent suicidal ideation” over a 2-week period, but a lower prevalence (30%) over a 1-week period. “Lifetime suicidal ideation” was prevalent in 66.25% of the UHR patients. With respect to self-injurious behavior, the differences were less clear. The prevalence of self-harm in the UHR patients was 41.72%. Moreover, the UHR patients recorded half of the cases of self-injury and more than half of the reports of recent and lifetime suicidal ideation. Finally, between 6.67–28% of the UHR patients reported a suicide attempt.

Non-psychotic comorbid disorders (e.g., obsessive-compulsive, depressive, and substance use disorders) and a family history of psychiatric disorder have been identified as factors associated with suicide risk in the UHR clinical population. Interestingly, Taylor et al. (2015) concluded that the rates of suicidality and self-harm detected in UHR samples are similar to those observed in FEP samples (Upthegrove et al., 2010; Challis, Nielssen, Harris, & Large, 2013). Furthermore, the authors proposed that the high levels of suicidality in UHR populations might precede the onset of frank psychosis. While UHR individuals may be protected from some of the events associated with FEP, such as an increase in psychotic symptoms and distressing treatment experiences (e.g. hospitalization), they may try to give meaning to their unusual experiences, fears of stigma, and comorbid difficulties (Byrne & Morrison, 2010; Fusar-Poli et al., 2014). Recently, Pelizza et al. (2019) examined the prevalence of suicidal ideation and suicide attempts in 40 UHR adolescents (aged 13–18 years), compared to FEP ( $N=32$ ) and non-UHR ( $N=40$ ) adolescents. In the study, the presence of suicidal ideation was calculated across a 2-year follow-up period, considering the incidence of suicide attempts and completed suicides. The results showed that 67.5% of the UHR adolescents had engaged in suicidal ideation, and 18.5% had done so to a severe degree. Furthermore,

attempted suicide before recruitment was higher in the UHR group than the non-UHR/FEP groups (17.5% vs. 2.5%).

In the UHR group, ideation severity was stable at the 1-year follow-up and decreased at the 2-year follow-up. No death by suicide was reported in the follow-up period. Overall, these studies (Taylor et al., 2015; Pelizza et al., 2019) confirm the high prevalence of suicidal ideation among UHR adolescents and the risk of self-injurious thinking and behavior in this clinical population.

Finally, in Table 2 we summarize the main points of the comparison between UHR children and adolescents and UHR young adults.

## Conclusions

Studies on the clinical significance and prognostic value of UHR criteria have predominantly focused on adults and older adolescents, with little consideration of the possible specific clinical characteristics and special needs of children and younger adolescents. Despite this, based on the present analysis of the recent literature, some conclusions can be drawn. Concerning the clinical profile, APS comprise the most frequently reported inclusion criterion in UHR children and adolescents at baseline, with a prevalence of approximately 89–100%. The most common positive symptoms include perceptual abnormalities and suspiciousness, and the most prevalent non-psychotic comorbid diagnoses are depressive and anxiety disorders. As this clinical baseline picture for UHR children and adolescents is similar to that of the adult population (Fusar

Poli et al., 2014, Fusar Poli et al., 2016), these two groups may be similar at baseline. However, differences may emerge over time, as UHR children and adolescents have been shown to have conversion rates of 17–20% at 1-year follow-up (Armando et al., 2015) and 7–21% at 2-year follow-up (Welsh & Tiffin, 2014; Ziermans et al., 2011); in contrast, adult conversion rates have been found to be 22% at 1-year follow-up and 29% at 2-year follow-up. These differences, according to Tor et al. (2018), could be explained by the instability of psychotic-like symptoms in the general population (Werbeloff et al., 2012) and the high rates of attenuated psychotic symptoms in children and adolescents (Schimmelmann et al., 2015; Kelleher et al., 2012), which could give rise to a significant number of false positives and a lower rate of transition in UHR samples. Based on these data, the European Psychiatric Association (EPA) guidance (Schultze-Lutter et al., 2015; Schmidt et al., 2015) on early UHR detection and intervention proposes that UHR criteria “should only be used and communicated with outmost care in children and young adolescents” (Schultze-Lutter et al., 2015). According to this recommendation, Poletti et al. (2019) proposed that the UHR state in children could imply an imminent higher risk for not only full-blown psychosis, but also other clinical and behavioral complexity, including suicidal thinking and behavior. Indeed, approximately 67.5% of UHR adolescents have been found to engage in suicidal ideation; risk factors for this include a family history of psychiatric disorder and the presence of a non-psychotic comorbid disorder (*e.g.* depressive disorder) (Taylor et al., 2015, Pelizza et al., 2019).

**Table 2. Clinical characteristics of children and adolescents at Ultra High Risk for psychosis compared to UHR young adults.**

### Clinical profile

- At baseline, clinical picture for UHR children and adolescents is like that of the UHR young adult population (Fusar Poli et al., 2016, Fusar Poli et al., 2014)
- In UHR children and adolescents, like UHR young adults, the presence of Attenuated Psychotic Symptoms (APS) is the most frequently reported inclusion criterion at baseline, with a prevalence of approximately 89–100% (Fusar Poli et al., 2016, Fusar Poli et al., 2014)
- UHR children and adolescents presented high prevalence of negative symptoms related to a significant impairment in global functioning, like UHR adults (Poletti et al., 2019; Velthorst et al., 2010; Hafner et al., 2004)

### Conversion rate

- Lower conversion rates in UHR children and adolescents (9.5%) compared to UHR young adults (18%) at 1-year follow-up (Schultze-Lutter et al., 2015)
- Similar to UHR young adults, presence of attenuated positive symptoms at baseline was a strong predictor of conversion to psychosis in UHR children and adolescents (Ziermans et al., 2014)
- Non-psychotic comorbidity was not a significant predictor of transition, both in UHR children and adolescents than in UHR adults (Albert, Tomassi, Maina, & Tosato, 2018; Armando et al., 2015)

### Suicidality thinking and behaviour

- 67.5% of the UHR adolescents had engaged in suicidal ideation and 18.5% had done so to a severe degree (Poletti et al., 2019)
- High prevalence of suicidal ideation and risk of self-injurious thinking and behaviour are similar among UHR adolescents and UHR young adults (Taylor et al., 2015)
- High levels of suicidality in UHR adolescents and young adults might precede the onset of frank psychosis (Taylor et al., 2015)

Considering these results, we propose that the baseline characteristics of UHR children and adolescents indicate that this clinical group has a specific pattern of neurodevelopmental impairment and clinical complexity that requires help. Indeed, several studies (Poletti et al., 2019; Doltz et al., 2019) have reported that, in addition to attenuated positive symptoms, UHR children and adolescents exhibit several negative symptoms (especially social anhedonia) and significant functional impairment. For these patients, worse global and academic functioning will likely present in the first year (Doltz et al., 2019), similar to the profile of FEP children and adolescents. In addition, regarding their neuropsychological profile, UHR adolescents have been found to achieve lower scores in general intelligence compared to healthy controls (Ziermans et al., 2011). We therefore conclude that all these clinical variables should be taken into account in the assessment of children and adolescents for UHR criteria. In fact, these variables may be associated with other conditions, such as traumatic or stressful life events (Trotman et al., 2014) or severe psychiatric disorders (e.g. psychosis), which are unrelated to normal brain maturation (Doltz et al., 2019). Thus, the goal for clinicians and researchers should be to validate instruments to identify these clinical characteristics in children and adolescents and to plan age-specific interventions. For example, it must be considered that a younger presentation of the UHR clinical condition could be associated with greater functional impairment and more psychiatric complications (e.g. depressive symptoms). Moreover, the EPA (Schmidt et al., 2015) recommends that UHR children and adolescents be assessed, monitored, and treated with an integrated treatment plan that includes psychosocial and pharmacological interventions.

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