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CORRELATES, TRANSITION RATE AND FUNCTIONAL OUTCOME OF CHILDREN AND ADOLESCENTS WITH ATTENUATED PSYCHOTIC SYMPTOMS: FINDINGS FROM A LONGITUDINAL STUDY

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1. INTRODUCTION

Despite advances in pharmacological and psychotherapeutic interventions over the last decades, psychotic disorders, especially in the schizophrenia spectrum, continue to be among the most severe disorders in medicine, with only a small proportion of patients achieving recovery and improvements in social, cognitive and socio-occupational functioning are still limited and suboptimal (Jääskeläinen et al. 2013; Kahn et al. 2015; Wittchen et al. 2011a).

Moreover, they are associated with considerable burden to patients and their families due to stigma and discrimination (Allerby et al. 2015; Rössler et al. 2005) as well as direct and indirect health care costs (Olesen et al. 2012). A recent meta-analysis has shown that schizophrenia also has a substantial effect on life expectancy with a weighted average of 14.5 years of potential life lost (Hjorthøj et al. 2017).

In children and adolescents, schizophrenia is one of the ten main causes of disability-adjusted life years (DALYs) in 10 to 14-year-old boys and 15 to 19-year-old girls (Gore et al. 2011). It has been estimated that around 10-15% of all psychotic disorders have their onset prior to 18 years of age (early-onset psychoses, EOP) and 1-3% have their onset before the age of 13 (very-early onset psychoses, VEOP) (Schimmelmann et al. 2013a; Wittchen et al. 2011b). Despite their relatively low prevalence, devastating consequences such as long-term neuropsychological deficits as well as huge impairments in psychosocial functioning leading to poor outcomes have been extensively reported (Jepsen et al. 2010; Stentebjerg-Olesen et al. 2016).

Although the core symptoms described in adult-onset schizophrenia may also be present in children and adolescents, EOP represents a more severe form of the disorder, showing a slow and insidious onset, more negative symptoms, high rates of comorbidity, fewer systematic or persecutory delusions and hallucinations occurring in different modalities (Ballageer et al. 2005; Driver et al. 2013; Schaeffer and Ross 2002). Furthermore, young people appear to be less prone to seek help and psychotic symptoms could be initially misinterpret or neglected as adolescent crisis by caregivers (Schimmelmann and Schultze-Lutter 2012). Thus, there are additional challenges faced in dealing with EOP and VEOP resulting in more difficulties in identification, longer duration of untreated illness and, overall, poorer outcomes (Clemmensen et al. 2012; Díaz-Caneja et al. 2015).

1.1 Shifting from secondary to primary indicated prevention: the concept of a clinical high-risk (CHR) state for psychosis

In addition to previous considerations, several studies in first-episode psychotic (FEP) patients have shown that the duration of untreated psychosis (DUP), or rather the period between the onset of first frank psychotic symptoms and the establishment of an indicated treatment, is associated with poorer clinical and functional outcomes, including more severe positive and negative symptoms, cognitive impairments, weak social cognition and lesser likelihood of remission (Altamura et al. 2015; Boonstra et al. 2012). These findings have further corroborated the importance of early identification and intervention in psychosis and supported the

setting of specialized early intervention and first-episode services worldwide (Bertelsen et al. 2008; Cocchi et al. 2018; Fusar-Poli et al. 2017a; Ruggeri et al. 2015; Srihari et al. 2015). Compared to treatment as usual, early intervention services appear to be superior and show significant improvement. In a recent meta-analysis comparing the effectiveness of early intervention services versus treatment as usual in patients with first-episode or early phase psychosis, the authors found that patients treated in these specialized services displayed lower hospitalization risk, treatment discontinuation and relapse rate and a greater improvement in both total, positive and negative symptoms and global functioning (Correll et al. 2018). However, to date there is lack of evidence of the effectiveness of current available interventions in reducing DUP in first-episode patients (Oliver et al. 2018).

Alongside reducing DUP by providing efficient and specialized treatment as early as the manifest disorder appears (secondary prevention) (Fraguas et al. 2014; Penttilä et al. 2014), one of the most promising strategies to improve outcomes in psychosis is to detect early signs of the emerging disorder before full-blown psychotic symptoms occur. Indeed, retrospective studies indicate that the onset of full psychosis is commonly preceded by a prodromal phase lasting up to several years (Häfner et al. 1999; Schultze-Lutter et al. 2010). This prodromal period is characterized by the gradual emergence of nonspecific psychiatric symptoms such as reduced concentration, decreased drive and motivation, sleep disturbances, anxiety, social withdrawal, suspiciousness, deterioration in role functioning and irritability ("early" prodromal phase) as well as less severe manifestations of the illness, e.g. attenuated (subthreshold) positive psychotic symptoms ("late" prodromal phase) (Cornblatt et al. 2003; Yung and McGorry 1996).

Of note, patients who present to specialized intervention services in their prodromal phase, before developing psychosis, are less likely, after the onset of psychosis, to be hospitalized and to be admitted compulsory (Fusar-Poli et al. 2016c) and have a much shorter DUP (11.2 days versus 366.5 in first-episode psychosis (FEP) services) (Valmaggia et al. 2015). Unfortunately, in a recent study only 5.19% of the total cases of first-episode psychotic patients accessing secondary mental health services had been intercepted and had had access to care in CHR services well-established in the local national health system (Fusar-Poli et al. 2017b).

Over the last three decades, efforts to prospectively detect and treat psychosis in the prodromal phase have greatly progressed. At the same time, in line with the shifting toward predictive and preventive approaches, the concept of prodrome, derived from medical terminology and implying a subsequent inevitable illness onset has been reconceptualized and the construct of "clinical high risk" (CHR) state for psychosis has been introduced, underlying that several different pathways (progression to psychosis, persistence, resolution or onset of a different disorder) could follow this specific state (Correll et al. 2010; McGorry et al. 2018). To an indicated prevention, or rather prevention directed to CHR persons that are already suffering from first complaints and impairments of the disease and who are actively seeking help, two specific sets of criteria have been developed: the ultra-high risk (UHR) criteria including attenuated psychotic syndrome (APS), brief limited intermittent psychotic symptoms (BLIPS) and a combination of genetic risk and functional decline (GRFD) and the basic symptoms (BS) based on subtle self-perceived cognitive and perceptive disturbances that, although not specific for psychotic disorders, occur during the prodromal state and seem to constitute a

fundamental core of the psychotic disorder as they appear to be present in all stages of the disease (Fusar-Poli et al. 2013b; Schultze-Lutter et al. 2010; Schultze-Lutter and Theodoridou 2017). While UHR criteria were originally designed to identify subjects at imminent risk of developing psychosis (Late At-Risk Psychosis State), the aim of BS criteria was to detect them in the earliest phase of the illness, ideally even before the onset of functional decline (Early At-Risk Psychosis State) (Schultze-Lutter and Theodoridou 2017). The findings of a recent meta-analysis demonstrated that, although there are different psychometric interviews available to identify CHR individuals (Fusar-Poli et al. 2016b), overall they show a prognostic accuracy which is also similar to that of other instruments used in preventive medicine (Fusar-Poli et al. 2015a). Indeed, in adult and mixed-age samples both UHR and BS criteria are associated with pooled 1-3 year conversion rates to psychosis ranging from 15% to 29% for UHR and from 14% to 50% for BS criteria (Fusar-Poli P et al. 2012; Schultze-Lutter et al. 2015b), with the majority of patients (73%) transitioning to schizophrenia (Fusar-Poli et al. 2013a). Thus, CHR individuals have an increased probability of developing psychosis that can be related to several environmental risk factors (Fusar-Poli et al. 2017d; Radua et al. 2018). The risk of transitioning is maximal in the first 24 months after presentation (Kempton et al. 2015) and appear to be specific for the development of psychotic disorders but not for incident non-psychotic disorders (Fusar-Poli et al. 2017c; Webb et al. 2015; Woods et al. 2018). However, recently a decline in transition rates has been reported and the risk of developing psychosis was shown to vary with follow-up time, recruitment strategies and sample characteristics (Fusar-Poli et al. 2014b; Hartmann et al. 2016; Simon et al. 2014). In fact, intensive outreach campaigns targeting the general population determining a higher proportion of self-referrals are associated with the inclusion of a higher number of false positive patients, diluting the pre-test risk for psychosis and resulting in a global decline of transition risks (dilution effect) and possible exposure of false-positive individuals to unnecessary treatments (Fusar-Poli et al. 2016d; Hartmann et al. 2016). These findings underscore that, according to current scientific knowledge, CHR criteria should clinically be applied only in patients that are "already distressed by mental problems and seeking help for them" (see recommendation 4 of the European Psychiatric Association) (Schultze-Lutter et al. 2015b). A second possible explanation is that the improved awareness of CHR paradigm among mental health professionals could result in referral to CHR centers of subjects in an earlier phase of the disorder with the need of longer follow-ups before we can exclude that they will develop psychosis (lead-time bias) (Wiltink et al. 2015). Indeed, in the long-term follow-up study of 416 CHR subjects recruited at The Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne, the authors found that, although the transition risk peaks in the first two years after referral, patients continue to display a high risk up to 10 years after entry into the clinic (Nelson et al. 2013). It could also be likely that early identification and the prompt start of a focused treatment may prevent or delay psychosis onset (Yung et al. 2007). Unfortunately, recent meta-analyses did not find evidence of the superiority of any specific intervention over the others in preventing psychosis onset nor in improving attenuated positive psychotic symptoms (Davies et al. 2018b, 2018a). The authors posit that these negative findings could be related to the heterogeneity of CHR samples (Davies et al. 2018a). In fact, it has been demonstrated that subjects belonging to BLIPS subgroup have higher rates of conversion to psychosis (39% vs 19% and 3% in the APS and GRFD

group respectively at 24 months) and a lower risk of developing non-psychotic disorders when compared both to APS and GRFD subgroups (Fusar-Poli et al. 2016a, 2017c). Thus, individuals meeting BLIPS criteria appear to display distinct characteristics and clinical outcomes; it is unclear whether it is still reliable to include the BLIPS in the CHR group or it warrants its own diagnosis as an established psychotic disorder as it overlaps with the diagnostic DSM category of brief psychotic disorder (Winton-Brown et al. 2011). Based on these results, it has been suggested that, in order to boost current efforts to identify reliable prognostic factors and markers for clinical practice, it would be useful to deconstruct the CHR paradigm, to stratify research findings across the 3 subgroups, and to introduce new clinical staging models (Carrión et al. 2017; Fusar-Poli 2017).

Beyond transition risk: clinical, cognitive and functional characteristics of CHR subjects

Persistence of attenuated psychotic symptoms

Approximately two-thirds of CHR subjects do not transit to psychosis (Addington et al. 2011). Several studies in age-mixed samples have examined the outcomes for non-converters (Addington et al. 2011; Lin et al. 2015). A high proportion of individuals at risk who do not develop psychosis continue to display attenuated psychotic symptoms at 1 year (23-54% according to different studies) (Armando et al. 2015; Haroun et al. 2006; Simon et al. 2013), 2 year (35-40%) (Addington et al. 2011; Ziermans et al. 2011) and 3 year (25-50%) follow-ups (Lemos-Giráldez et al. 2009; Velthorst et al. 2011). Overall, despite non-developing psychosis, the majority of CHR subjects remain symptomatic.

Attenuated negative symptoms

Anhedonia, alogia, asociality, apathy and blunted affect appear to be present in each stage of psychosis, including psychosis prodrome (Sauvé et al. 2019). In the North American Prodrome Longitudinal Study (NAPLS), the presence of at least one moderate to severe negative symptom was reported in 82% and 54% of CHR subjects at baseline and 1 year follow-up, respectively. Experiential negative symptoms (anhedonia, amotivation and asociality) were the most frequently endorsed (Piskulic et al. 2012).

It could be argued that this high prevalence could be due to the high prevalence rates in the CHR group of comorbid affective disorders, confounding the assessment of negative symptoms (Fusar-Poli et al. 2014b). However, in another study, when the prevalence of negative symptoms and primary negative symptoms (negative symptoms in the absence of depression) was evaluated, primary negative symptoms were still present in 32.7% of patients at baseline and a similar prevalence was found at all time-points for a period of 12 months (Azar et al. 2018).

Longitudinal studies found that attenuated negative symptoms in CHR subjects predict psychosis onset (Nelson et al. 2013; Piskulic et al. 2012) and poorer role and social functioning (Fulford et al. 2013; Meyer et al. 2014). Indeed, in the Prodrome Assessment, Research and Treatment program, negative symptoms severity was the only predictor of social functioning, above and beyond affective disorders and cognitive factors (Schlosser et al. 2015).

Moreover, the prevalence of attenuated negative symptoms in the CHR group appear to be stable over long-term (up to 10-years) follow-ups (An der Heiden et al. 2016; Dominguez et al. 2010). Interestingly, a recent study, evaluating the prevalence of negative symptoms across different phases of the psychosis continuum, found that the prevalence of amotivation, alogia, asociality and blunted affect decreases between CHR and FEP stages (Sauvé et al. 2019). It may be that attenuated negative symptoms constitute a core feature of vulnerability in CHR youth representing a key target for early intervention.

Comorbidity

Already at baseline, up to 70-80% of CHR subjects presents with at least 1 comorbid, above-threshold, axis I disorder (Salokangas et al. 2012a). A meta-analysis conducted with 1683 CHR individuals found that, at baseline, the prevalence rates of depressive and anxiety disorders were 40% and 15% respectively (Fusar-Poli et al. 2014b). Even though depressive disorders are the most prevalent comorbid diagnoses, obsessive compulsive, bipolar and eating disorders also show high prevalence rates (Hui et al. 2013; Lim et al. 2015; Madsen et al. 2018; McAusland et al. 2017). Comorbidity in CHR is not limited to axis-I disorders. In fact, prevalence rates of any personality disorder (especially schizotypal and borderline personality disorder) in CHR patients are four-times higher than those in the general population (Boldrini et al. 2019). Interestingly, none of the mental disorders listed above appear to predict the transition to psychosis (Albert et al. 2018; Boldrini et al. 2019; Fusar-Poli et al. 2014b), but, when present at baseline, non-psychotic disorders persist over time in half of the CHR group (Lin et al. 2015). In addition, even those who did not display comorbid disorders at baseline in over a third of cases develop an incidental mental disorder during the follow-up period. Female gender, higher level of negative symptoms and not meeting BLIPS criteria were associated with higher probability of persistent, recurrent or incidental non-psychotic disorders (Lin et al. 2015).

The evidence that highly prevalent multidimensional psychopathology in CHR subjects does not correlate to higher risk of transitioning to psychosis lead some authors to question the validity of the CHR and "transition" paradigm. These authors underline the need in help-seeking youth not to focus the attention only on attenuated psychotic symptoms as markers of an incipient psychotic disorder, but to move towards a multidimensional approach where the full-range of the psychopathology is taken into account (van Os and Guloksuz 2017). In accordance with recommendation 5 of the European Psychiatric Association guidance, all the interventions in CHR subjects should target "current individual needs and other mental disorders present (comorbidities), in particular depression and anxiety, according to their respective treatment guidelines" (Schmidt et al. 2015). Thus, clinicians dealing with CHR youth need to carefully look for the presence of other mental disorders that, when present, constitute one of the focus of the intervention and treatment plan.

Global functioning and quality of life

CHR youth are functionally impaired and have a significantly lower global functioning and quality of life compared to healthy subjects (Addington et al. 2008; Hui et al. 2013; Velthorst et al. 2010). In a recent study,

poor social networks, few close friends, difficult relationships with family members, high levels of isolation and solitude were observed in CHR youth (Robustelli et al. 2017). In this context, the results of the 2015 meta-analysis by Fusar-Poli et al. are meaningful. The authors found that the CHR group displayed a functional level close to that of psychotic patients and similar to that observed in other psychiatric disorders, such as major depressive disorders and social phobia (Fusar-Poli et al. 2015b). Of note, the functional impairment in CHR patients does not seem to be solely secondary to the presence of comorbidities. In fact, in the European Prediction of Psychosis (EPOS) study, when the impact of both at-risk symptoms and depressive psychopathology on global functioning was evaluated, only positive and negative attenuated psychotic symptoms, and not depressive ones, were retained in the model (Ruhrmann et al. 2010b).

Several studies have highlighted that, beyond CHR criteria, social functioning plays a key role in predicting transition to psychosis (Addington et al. 2017). It has been shown that, compared to at-risk youth, the 2-year transition risk of subjects experiencing psychotic-like symptoms, but with good functioning, is very low (approximately 1.2%) (Kaymaz et al. 2012).

However, functional impairment in CHR subjects appear to be stable over time and independent from at-risk symptoms (Cornblatt et al. 2012). Poor social functioning is persistent at follow-ups in at least half of those who do not develop psychosis (Addington et al. 2011). These data suggest that, besides possible prediction of psychosis, baseline functional impairment may be associated with long-term disability in the CHR sample.

Starting from the above considerations, various authors have supported that research in this area should focus not only on transition to psychosis, but also on other important outcomes, such as the long-term functioning level (Brandizzi et al. 2015; Niendam et al. 2009).

Several factors, in adult or age-mixed samples, have been identified as possible predictors of functional outcomes in CHR individuals. Among baseline clinical variables, besides poor functioning, working status and the presence of negative symptoms, affective disorders, motor disturbances, as well as positive, disorganized and basic symptoms have been found to be variously associated to poor long-term functional impairment (Brandizzi et al. 2015; Carrión et al. 2013; Lee et al. 2017; Schlosser et al. 2015).

Poorer functional outcomes could be also predicted by specific neurocognitive domains. According to longitudinal studies, the following domains appear to be associated with poor global functioning: verbal learning, fluency and memory, attention and processing speed (Lin et al. 2011). The importance of processing speed and verbal fluency as predictors of global and role functioning has been underlined by a recent study by Bolt et al. (2019) .

Overall, these findings underline that CHR subjects, independent of their risk of transitioning to psychosis, are in need of care and therapeutic interventions should target social disability and functional impairment. This is relevant and in line with the proposed model of "pluripotent risk syndrome" where CHR patients are not only at higher risk of developing psychosis but also other mental disorders that have their onset from initial non-specific symptoms and lead to functional deterioration (Fusar-Poli et al. 2014c; Yung et al. 2012).

Perceived distress

One of the core characteristics of CHR paradigm is that the symptoms should be sufficiently disabling to the subject to prompt help-seeking behaviour (Fusar-Poli and Yung 2012). Although CHR criteria are based on the presence of attenuated psychotic or basic symptoms and a high proportion of CHR subjects reported them to be distressing, affective symptoms (depression and anxiety) and impairment in role and social functioning are the main self-perceived causes of distress and the main reported reasons to seek help (Falkenberg et al. 2015; Rapado-Castro et al. 2015). Even if one study found that the clinical distress related to APS symptoms, anxiety and substance abuse predicted transition to psychosis (Rapado-Castro et al. 2015), this association was not replicated by subsequent studies (Falkenberg et al. 2015; Power et al. 2016). However, subjective complaints at presentation were linked to significantly poorer longitudinal psychosocial functioning (Falkenberg et al. 2015). As APS and basic symptoms do not appear to be solely nor the main cause of distress for CHR subjects, assessment at presentation, monitoring and treatment should evaluate and target the individual needs, including sources of distress.

Suicidality

Elevated prevalence of suicide, suicide attempts and self-harm have been described in patients diagnosed with psychotic disorders, especially in the early phases of the disorder (Nordentoft et al. 2011; Palmer et al. 2005). High rates of suicidal ideation (68%) and attempts (18%), lifetime self-injurious behaviours (49%) are also present in the CHR population with comorbidities (especially substance use and affective disorders), with positive family psychiatric history, previous suicide attempts, childhood adversities and trauma (particularly if followed by the onset of depressiveness) predicting suicidal risk (Grivel et al. 2018; Schmidt et al. 2017; Taylor et al. 2015). Baseline suicidal ideation, although not associated with transition to psychosis, appears to be related to suicidal behaviour at follow-ups (Grivel et al. 2018). Interestingly, in an adolescent psychiatric sample, CHR status was related to higher current suicidality, but not to long-term intentional self-injurious behaviour that was best predicted by decreased expression of emotions (Lindgren et al. 2017). However, suicidal thinking should be regularly monitored as on ongoing risk in CHR patients.

Neurocognitive profiles

Cognitive deficits are core characteristics of schizophrenia (van Os and Kapur 2009) and a recent longitudinal birth cohort study has highlighted that specific neurodevelopmental periods (specifically childhood and adolescence) are associated with the timing and course of distinct cognitive domains (Mollon et al. 2018).

In a recent study, a factor structure composed of neurocognition, alongside with social-cognitive bias, reflective self (self-esteem, resilience, physical anhedonia and social anhedonia) and pre-reflective self (magical thinking, perceptual aberration and basic symptoms) differentiated between recent-onset patients with schizophrenia, CHR and healthy controls and was also associated with baseline quality of life both in CHR individuals and psychotic patients (Kim et al. 2019).

Indeed, CHR subjects present moderate cognitive impairment. Their cognitive functioning is significantly poorer than that of healthy controls, similar to individuals with a family history of schizophrenia, but less

severe than first-episode and schizophrenic patients (Bora et al. 2014; Fusar-Poli et al. 2012a; Simon et al. 2012). Several cognitive domains are affected in CHR youth (Velthorst et al. 2019). In a critical review of the literature, verbal and visual episodic memory, attention and processing speed differentiated the CHR group from healthy controls with medium to substantial effect sizes. On the contrary, results were conflicting on verbal and visual memory and executive functioning (Mam-Lam-Fook et al. 2017). Processing speed has attracted special attention. Indeed, this appear to be the cognitive domain where the most consistent results as well as the most significant differences between CHR subjects and healthy controls have been found (Carrión et al. 2011; Kelleher et al. 2013b, 2013a). Moreover, it distinguishes CHR to subjects with BS only and subjects at risk for other disorders, such as bipolar disorders (Metzler et al. 2014).

Several studies have evaluated the predictive value of cognitive domains, both in term of transition to psychosis and functional outcomes, with heterogeneous results (Lam et al. 2018). According to the results of three meta-analyses the following domains appear to predict psychosis transition: verbal and visual learning, speed of processing, verbal fluency and language, executive functions and attention as well as visuo-spatial memory and reasoning (Fusar-Poli et al. 2012a; Giuliano et al. 2012; Hauser et al. 2017a). Of note, Hauser at al. underlined a significant overlap in the cognitive performances of individuals that transition and those who do not develop psychosis; diminishing their usefulness in risk stratification (Hauser et al. 2017a).

As already described above, the importance of processing speed and verbal fluency as predictors of global and role functioning has been underlined by a recent study by Bolt et al (2019).

The course and prognostic relevance of neurocognitive factors in underage CHR populations is not established. In a study conducted in a small sample of CHR adolescents the only parameter that differentiated those who converted to psychosis from the ones that did not at 6-years follow-up was baseline low IQ (Ziermans et al. 2014).

The lack of consensus across studies underlines the need of further longitudinal studies investigating the different paths of cognitive changes in the UHR state, especially in children and adolescent samples.

The introduction of Attenuated Psychosis Syndrome in the Diagnostic and Statistical Manual, fifth edition (DSM-5): an open debate

The importance of research in persons at high risk has been increasingly recognized to such an extent that Attenuated Psychosis Syndrome has been introduced in section III ("Emerging Measures and Models") of the Diagnostic and Statistical Manual of Mental Disorder, fifth Edition (DSM-5) (American Psychiatric Association et al. 2013) as a condition for further studies. Additionally, DSM-5-APS is coded under "Other Specified Schizophrenia spectrum and Other Psychotic Disorder" in section II (American Psychiatric Association et al. 2013). The diagnosis was originally formulated as a risk syndrome (psychosis risk syndrome) (Carpenter 2009), but was subsequently reformulated as a disorder or rather a self-contained syndrome requiring diagnosis and clinical care (Tsuang et al. 2013).

Woods et al. (2010) advocated in their original proposal for DSM-5-APS that: the majority of subjects meeting

CHR criteria are usually included on the basis of attenuated psychotic symptoms criteria (Fusar-Poli et al. 2013c), that these persons are already symptomatic and suffer from functional disturbances and cognitive impairment for those they seek help (Ruhrmann et al. 2010a) and they are at a high risk of getting worse and/or developing psychosis (Carrión et al. 2013; Fusar-Poli et al. 2015b).

The DSM-5-APS construct specifically requires patient distress and disability, which has not explicitly been part of high-risk criteria. People meeting the DSM-5-APS diagnosis do in fact fulfill the broad definition of mental disorder in the DSM-5: "a clinically significant behavioral and psychological syndrome or pattern…that is associated with present distress or disability". Thus, clinical attention care is clearly justified regardless of the justification of reduction of risk or prevention (Yung et al. 2012).

In a recent study, DSM-5-APS criteria have shown an acceptable prognostic accuracy (AUC 0.76 at 2 years) comparable to that of the Comprehensive Assessment of At Risk Mental States (CAARMS), one of the most widely used tools to identify CHR subjects (Fusar-Poli et al. 2018a). Subjects meeting the DSM-5-APS criteria have a 5-fold higher transition to psychosis risk compared to individuals not fulfilling the criteria.

Despite all these considerations, the introduction of DSM-5-APS diagnosis has been hotly debated (Carpenter 2014, 2015; Fusar-Poli et al. 2014a; Nelson 2014).

Some concerns raised during the debate need to be addressed with special attention in children and adolescents, where research on the high risk state is still in its infancy (Schimmelmann et al. 2013b).

In particular, criticism about pathologization of non-ill behaviors and experiences has been voiced. In fact, during adolescence, the assessment of psychiatric symptoms and disorders is challenging. During this neurodevelopmental period, youths go through a period of body and psychic transformation and experience profound psychosocial and neurobiological changes (Paus et al. 2008). Several authors have underlined the difficulty in discriminating between normal behaviors and psychiatric symptoms (Welsh and Tiffin 2013). Normative adolescent experiences (e.g. imaginary audience and personal fable) can make the clinical picture blurred and lead to false positive psychotic diagnoses, especially if non-validated diagnostic tools are administered and/or the assessment is done by professionals that are not adequately trained (Carol and Mittal 2015). Community studies of children and adolescents found high prevalence rates of psychotic symptoms, especially hallucinations, with a spontaneous remission in about three quarters of cases (Bartels-Velthuis et al. 2016). Additionally, a systematic review and meta-analysis of population-based studies reporting prevalence rates of psychotic symptoms confirmed that psychotic experiences are common in childhood and adolescence with a median prevalence of 17% among 9- to 12-year-olds and 7.5% among 13- to 18-year-olds (Kelleher et al. 2012a). However, when considering only psychotic symptoms that had begun or worsened in the past year and had been present at least once per week for the previous month (frequency and onset/worsening criteria of DSM-5-APS), the prevalence rate decreased by 66% to 7.7% in the younger sample. In addition, the risk syndrome group reported being distressed by their symptoms and showed a higher prevalence of non-psychotic Axis-I psychiatric diagnoses and poorer global functioning compared with controls (Kelleher et al. 2012b). Moreover, in another study comparing a sample of help-seeking adolescents with a sample from the general population, the authors found that approximately 25% of the adolescents in the general population that

displayed auditory hallucinations were in need of clinical care, not necessarily due to hallucinations severity but also for other internalizing and externalizing symptoms (Maijer et al. 2019).

In another recent population-based study aimed at evaluating the prevalence and clinical significance of ultra-high-risk for psychosis symptoms and criteria in a sample of individuals aged 8-40 years (of whom less than a quarter children and adolescents), only 1.3% of participants met criteria for CHR (9% for APS) and, again, APS diagnosis was associated with more frequent current DSM-IV axis I disorders and/or functional impairment (Schimmelmann et al. 2015).

Data about the frequency and clinical significance of CHR criteria in clinical samples and especially in adolescents are lacking (Tor et al. 2018). Earlier studies showed lower transition rates, ranging from a short-term transition risk of 3% to a cumulative 2-year transition risk of 21%, (Armando et al. 2015; Lindgren et al. 2014; Pelizza et al. 2018; Poletti et al. 2019; Welsh and Tiffin 2014; Ziermans et al. 2011) and/or longer transition times compared to adults (Cornblatt et al. 2007). Conversely, a study by our group found a 1-year cumulative transition rate of 26.7%, comparable to those observed in adult or age-mixed samples (Spada et al. 2016). Furthermore, attenuated psychotic symptoms in 108 adolescents newly referred to mental health services were associated with severe psychopathology, including multiple comorbidities, poor functioning as well as suicidal behavior compared to patients in the same clinic who did not have psychotic experiences (Kelleher et al. 2014). The finding of an elevated prevalence of suicidality in CHR adolescents has recently been replicated in a study conducted in 112 help-seeking youth, where the authors found that around 68% of UHR subjects reported suicidal thinking and approximately 18% had a positive history for suicide attempt (Pelizza et al. 2019b).

Several studies also highlighted that, although at follow-up the majority of adolescents had remitted from their at-risk status, they were still meeting criteria for a wide range of psychiatric disorders and/or that the presence of attenuated psychotic symptoms at baseline was predictive of psychiatric hospitalization and persistent psychiatric service use (de Wit et al. 2014; Lindgren et al. 2014, 2019). Also self-rated quality of life, especially the subjective perception of the neurocognitive and social functioning related to school environment, appear to be worse in CHR adolescents compared to healthy controls in the same age-range (Nitka et al. 2016).

Subsequently, some commentaries expressed concern about stigma and potentially harming treatment strategies, such as an increased use of antipsychotics in young treatment-naïve subjects reporting attenuated positive symptoms (Arango 2011; Yung et al. 2012). However, a small sample of adolescents with at-risk "label" claimed they felt validated and relieved by receiving a diagnosis and reported few if any feared negative changes in their interactions with family and friends (Welsh and Tiffin 2012, 2015). Importantly, an APS coded diagnosis will facilitate the development of evidence-based treatments, including psychological interventions and could therefore reduce inappropriate antipsychotic use (Schmidt et al. 2015; Yung et al. 2012).

Notably, the main criticism against APS's inclusion in section II of DSM-5 as a coded diagnosis was not based on any of the above issues but pointed to limited and inconclusive data regarding the reliability of APS in clinical practice (Yung et al. 2012). Thus, the need for further studies also in clinical settings is unquestionable.

This is especially true for children and adolescents given the paucity of data on the immediate clinico-pathological significance of APS, as well as longitudinal outcomes, in clinical samples in this age group as the limited available data refers to research-based clinics or population-based samples. To our knowledge, only one study specifically focused on characteristics of APS in adolescent inpatients finding a high prevalence and complex entanglement of DSM-5-APS status with a broad range of psychiatric symptoms and disorders (Gerstenberg et al. 2015) .

Aims of the study

Starting from the above considerations and, according to the urgent need of further studies in underage CHR populations, the aims of the present study were:

1) to compare the baseline clinical, psychopathological and socio-occupational functioning profile of APS adolescents, adolescents suffering from early onset psychosis (EOP) and adolescents with psychiatric disorders other than APS and EOP (non-APS). Thus, with the objective to exploratory investigate whether APS adolescents displayed a peculiar and distinct profile compared to the other 2 groups

2) to calculate the cumulative transition rate to psychosis of APS adolescents at follow-ups

3) to investigate predictors of conversion to psychosis in APS adolescents

4) to evaluate socio-occupational functioning at 12-month and last visit follow-ups in APS patients

5) to study the effect of potential clinical prognostic factors in influencing functional outcome (socio-occupational functioning) at follow-up in APS adolescents

In line with several authors' suggestion to deconstruct the CHR paradigm (Carrión et al. 2017; Fusar-Poli 2017), and taking into consideration the debate about the introduction of DSM-5-APS diagnosis with concerns especially in children and adolescents, in this study we specifically focused on APS adolescents.

2. METHODS

Setting

Adolescents consecutively admitted to the Child and Adolescent Neuropsychiatric inpatient and outpatient units of the third level center IRCCS Mondino Foundation (Pavia, Italy) between October 2012 and July 2019, were enrolled in this study. The C. Mondino National Neurological Institute is a very well-known tertiary care center that receives referrals in the field of child and adolescent psychiatry from all over Italy, particularly from the Lombardia region and the district of Pavia.

The study protocol was reviewed and approved by the ethics committee of the Mondino Foundation and has been carried out in accordance with the Declaration of Helsinki.

Sample

In this longitudinal cohort study, with a naturalistic design, the sample consisted of 243 help-seeking subjects aged 12-18 years consecutively admitted to the Mondino Foundation Child and Adolescent Neuropsychiatric

inpatient and outpatient units.

Exclusion criteria were: history of any psychotic disorder (prior to research assessment) according to the Diagnostic and Statistical Manual of Mental Disorders, 5 Edition (DSM-5) (American Psychiatric Association et al. 2013), established cognitive impairment (IQ<70), head injuries or any other medical/neurological condition that could justify their psychiatric symptoms and current substance dependence or substance induced mental disorders.

Each adolescent patient admitted to the psychiatric inpatient and outpatient units not presenting any of the exclusion criteria was asked to take part in the study. The study procedure was thoroughly explained by a trainee in child and adolescent neuropsychiatry/ trained psychologist to both patients and their legal guardian and a written consent was obtained. Patients were free to ask additional questions and take their time in order to decide whether to take part or not in the study. Once patients and their caregivers consented to the study, the baseline assessment took place.

Procedures and measures

Baseline assessment

Demographic, family history of psychiatric disorders, past psychiatric illness and treatment information were collected from parent/legal guardians implemented with clinical notes. Socio-economic status (SES) was assessed using the Four-Factor Index of Social Status (Cirino et al. 2002).

All semi-structured interviews and cognitive testing were administered by experienced and extensively trained medical doctors or psychologist that received an intensive 3-month training prior to the start of the study as well as ongoing supervision. All the tests, clinical interviews and questionnaires used are translated and validated in Italian.

Clinical measures

Upon research admission, patients underwent an extensive diagnostic assessment that included clinical interviews, semi-structured clinical interviews (Structured Clinical Interview for DSM-IV axis I and II, i.e. SCID-I and II (First et al. 1996, 1997, 2017a, 2017b), Kiddie-schedule for Affective Disorder and Schizophrenia, i.e. K-SADS-PL (Kaufman et al. 1997, 2019) and self-administered questionnaires administered to both parents and patients (Child Behavior Checklist, i.e. CBCL (Achenbach 1991a; D'Orlando et al. 2010) and Youth Self Report, i.e. YSR (Achenbach 1991b)).

DSM-5 diagnoses were based on a combination of SCID-I and II and K-SADS-PL results. According to DSM-5 criteria, a primary or comorbid diagnosis of personality disorder was only applied when distinctive features had been present for more than 1 year.

In the present study, the validated Italian version of the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Fusar-Poli et al. 2012b) was used in order to evaluate the presence of attenuated or full-blown psychotic symptoms. The CAARMS is a semi-structured interview designed to assess prodromal psychopathology for people at high clinical risk for psychosis. The CAARMS has a total of 27 items, which

are clustered in seven subscales: Positive Symptoms, Cognitive Change-Attention and Concentration, Emotional Disturbances, Negative Symptoms, Behavioral Change, Motor/Physical Changes and General Psychopathology. Subscales are intended to provide a thorough understanding of the young person's psychopathology. Scores for each subscale range from 0 ("never-absent") to 6 ("extreme"). CAARMS has been shown to possess good to excellent concurrent, discriminant and predictive validity and excellent inter-rater reliability (Yung et al. 2005). CAARMS interview was administered only to patients.

Based on this extensive clinical assessment, subjects were divided into three groups: 1. adolescents with psychosis according to CAARMS criteria (EOP), 2. adolescents with APS as evaluated by CAARMS interview (APS) and 3. youths with other psychiatric disorders that do not meet APS or psychosis criteria (non-APS).

As the primary focus of this study was Attenuated Psychosis Syndrome, patients meeting BLIPS criteria at the baseline CAARMS assessment were excluded from the final total baseline sample and further analysis. However, only 3 patients evaluated at baseline out of 246 initially enrolled belonged to this category. The final sample consisted of 31 EOP, 110 APS and 102 non-APS adolescent patients.

The presence of psychiatric comorbidities was recorded according to the DSM-5 criteria. In addition, in order to further validate the information obtained by the patient, K-SADS-PL interviews were conducted with both patient and parents separately.

In this sample, all APS participants also met DSM-5-APS criteria as defined in sections II and III of DSM-5(American Psychiatric Association et al. 2013).

Functioning

The level of functioning was evaluated using the Children's Global Assessment Scale, i.e. CGAS (Shaffer et al. 1983) and the Social and Occupational Functioning Assessment Scale, i.e. SOFAS (Goldman et al. 1992). The SOFAS is a global rating of socio-occupational functioning ranging from 0 to 100, with lower scores representing lower functioning. In order to take into account the possible differences in social and role functioning that a patient might present, specific scales for role functioning (Global Functioning: Role scale, i.e. GF:R (Niendam et al. 2006) and social functioning (Global Functioning: Social scale, i.e. GF:S (Auther et al. 2006; Lo Cascio et al. 2017) were also administered. GF:S and GF:R scales' scores range from 0 to 10, where 0 corresponds to extremely poor functioning and 10 to excellent functioning. The GF:S scale focuses on the level and quality of social contacts, relationships and conflicts with peer, age-appropriate intimate relationships and involvement with family members, while the GF:R scale assesses the level independence or support needed by the individual in one's specific role (i.e. school or work) as well the subject's overall performance.

We also used Clinical Global Impression-Severity (CGI-S) scale (Guy 1976) to assess overall severity of illness as assessed by clinicians.

Additional Psychopathological Scales

Starting from December 2017, the research protocol was further implemented and additional

psychopathological scales were administered to patients (14 EOP, 37 APS and 36 non-APS) enrolled after that date. The protocol extension was approved by the local ethical committee. In particular, self-administered questionnaires focusing on quality of life (EuroQoL scale (Balestroni and Bertolotti 2012; EuroQol Group 1990)), distress (Perceived Stress Scale, PSS (Cohen et al. 1983; Concerto et al. 2017)) and family functioning (Family Adaptability and Cohesion Evaluation Scales, FACES-IV (Olson 2011; Visani et al. 2014)) were completed by both guardians and patients.

The EuroQol scale is a Visual Analogue scale (EQ VAS), which represents the respondent's self-rated health, with the score 0 marked as 'the worst health you can imagine' and the score 100 marked as 'the best health you can imagine'.

The PSS is a well-known instrument that measures the subjective perception of stress; it consisted of 10 multiple-choice items, which evaluate how unpredictable, uncontrollable and overwhelming the respondents have found their life during the course of the previous month. The respondent must assign to each question a score ranging from 0 to 4. A final score higher than 25 is considered indicative of a clinically relevant level of stress.

The FACES is a self-administered questionnaire developed to study family dynamics and to identify critical areas that could benefit from a psychotherapeutic intervention. The FACES consist of 62 items: 42 inspect family cohesion and adaptability, 10 evaluate communication and 10 examine satisfaction; a score from 1 to 5 is assigned to each item. Higher scores correspond to higher levels of the evaluated category.

Neurocognition

IQ was estimated for all patients with The Wechsler scales (Wechsler 1997, 2006, 2012) or Raven's progressive matrices (Raven 2000).

After the protocol's implementation, patients enrolled from December 2017 performed a comprehensive neurocognitive assessment.

The following tests exploring several cognitive domains were administered:

Executive functions:

Reasoning and problem Solving: Elithorn Perceptual Maze Test (BVN 12-18, Batteria di Valutazione Neuropsicologica per l'Adolescenza (Gugliotta et al. 2009))

Abstract reasoning and flexibility: Wisconsin Card Sorting Test (WCST (Nelson 1976))

Planning and attention: Rey–Osterrieth complex figure test (Caffarra et al. 2002)

Attention:

Selective auditory and visual attention: BVN 12-18 (Gugliotta et al. 2009)

Working Memory:

Verbal Working memory: Letter-Number sequencing subtest of the Wechsler Scales, Digit Span Forward and Backward of the BVN 12-18 (Gugliotta et al. 2009)

Non Verbal Working memory: Corsi Block Task, Selective auditory and visual attention: BVN 12-18 (Gugliotta et al. 2009)

Processing Speed:

Coding-Digit Symbol subtest of the Wechsler Scales and Verbal Fluency Tests of the BVN 12-18 (Gugliotta et al. 2009)

Treatment and follow-up

After the baseline assessment, according to their psychopathology and symptoms, patients were address to one or more of the following treatments: active monitoring, supportive psychotherapy and pharmacological treatment. Monitoring consisted of regular clinical visits with a neuropsychiatrist with a schedule that depended on the patient's individual needs. Due to the naturalistic nature of the study, the research team did not intervene in the treatment's decision; however, with the consent of the patient and his/her caregivers, information about the results of both baseline and follow-up assessments could be shared with the patient's clinical team.

All APS patients recruited until march 2019 were followed up for a median period of 33 months (range 4-81 months) and baseline measures were repeated (every 12 months). Transition to psychosis was defined according to the CAARMS criteria (Fusar-Poli and Van Os 2013). All cases meeting criteria for transition were discussed in consensus conference supervised by a senior clinician.

Data about transition to psychosis and SOFAS at last follow-up visit were available for 103 APS patients (7 patients were lost at follow-ups). Moreover, information about the possible transition to psychosis and SOFAS at follow-up was gathered also for 94 non-APS patients (8 patients were lost at follow-ups) by means of a semi-structured telephone interview or from medical records and chart reviews.

Statistical analysis

Descriptive analyses included median and first and third quartiles and mean values and standard deviation (SD), as appropriate, for continuous variables, and absolute and relative frequencies for categorical variables.

Baseline analysis

As preliminary analysis, we used hypothesis tests to determine for which variables a statistical significance difference existed between the three groups (APS, non-APS and EOP): Kruskal Wallis was used for numerical variables and Chi Square test for categorical variables, if $p<0.05$ a post hoc analysis was performed (Dunn test and Fisher test respectively). To reduce the chance of type I error due to multiple testing, Bonferroni correction was applied to all post-hoc analyses.

Variables for those a statistical significant difference at univariate analyses was found as well as factors deemed relevant based on current literature or clinical judgment were included in an ordinal logistic regression to understand which of them most influenced the belonging to the three groups.

A stepwise selection process was also performed to select the best subset of variables that could predict group membership.

Follow up analyses

As preliminary analyses, we used hypothesis tests to determine for which variables a statistical significance difference existed between APS patients that converted to psychosis and APS patients that did not transition:

Kruskal Wallis was used for numerical variables and Chi Square test for categorical variables.

Variables that remained significant in the univariate analyses as well as other variables deemed of clinical relevance were entered in a multivariable logistic regression analysis to explore their influence on transition.

In order to take into consideration the different duration of follow-ups and patients that dropped out at different time points, a Kaplan-Meier Survival Analysis was performed in order to study to assess rates of transition at 1,2,3 and 4 years.

To identify predictors of APS adolescents' socio-occupational functioning at last follow-up visit, a linear regression analysis was performed entering the variables deemed of clinical relevance based on current literature.

Data were analyzed using R (R core Team 2013); all tests were two-sided, with alpha set at 0.05.

3. RESULTS

Cross-sectional analysis

Socio-demographic characteristics

Between October 2012 and July 2019, 243 help-seeking adolescents (median (min, max) age 15.4 (12.0, 17.9), 62.6% female, 81.5% white Italian), consecutively admitted to the Child and Adolescent Neuropsychiatric inpatient and outpatient units of the third level center IRCCS Mondino Foundation (Pavia, Italy) were included in this study.

The majority of adolescents were referred to the research team by child and adolescent psychiatrists working in the inpatient unit (207/243, 85.2%), a minority by the Institute outpatient unit (33/243, 13.6%) and private practitioners (3/243, 1.2%).

The sample included 102 non-APS, 110 APS and 31 EOP adolescent patients.

Of note, although not statistically different between the three groups (p=0.26), positive psychiatric family history was present in a high proportion of patients (61.3%), with a high percentage of EOP (51.6%), APS (59.1%) and non-APS (66.7%) adolescents having at least one first or second-degree family member suffering from a psychiatric disorder, especially mood and anxiety disorders.

Age, sex, ethnicity, adoption status, family intactness and socio-economic status did not differ between the three groups.

Complete socio-demographic characteristics are listed in Table 1.

Table 1. Socio-demographic characteristics in the total sample, psychiatric control (non-APS), attenuated psychosis (APS) and early-onset psychosis (EOP) adolescent patients

Characteristic	Total (N=243)	Non-APS (N=102)	APS (N=110)	EOP (N=31)	p-value
Age, median (min, max), y	15.4 (12.0, 17.9)	15.3 (12.1,17.9)	15.5 (12.0, 17.9)	14.5 (12.0,17.8)	0.28
Sex, female, n (%)	152 (62.6)	67 (65.7)	69 (62.7)	16 (51.6)	0.37
Ethnicity, n (%)					0.60

Italian	198 (81.5)	82 (80.4)	88 (80.0)	28 (90.3)	
Northern African	7 (2.9)	3 (2.9)	3 (2.7)	1 (3.2)	
Hispanic	7 (2.9)	2 (1.9)	5 (4.5)	0 (0)	
Albanian	8 (3.3)	4 (3.9)	4 (3.6)	0 (0)	
Eastern European	11 (4.5)	3 (2.9)	7 (7.4)	1 (3.2)	
Other	12 (4.9)	8 (7.8)	3 (2.7)	1 (2.3)	
Socio-economic status, median (IQR25, 75)	29.25 (20.0, 39.0)	27 (18.5, 37.5)	31.0 (21.0, 41.0)	27.0 (18.5, 37.0)	0.57
Adopted, n (%)	15 (6.17)	6 (5.8)	7 (6.3)	2 (6.5)	0.98
Separated-divorced family, n (%)	91 (37.5)	35 (34.3)	42 (38.2)	14 (45.2)	0.54
Family history, n (%)					
None	94 (38.7)	34 (33.3)	45 (40.9)	15 (48.4)	0.26
Psychosis	19 (7.8)	6 (5.9)	7 (6.1)	6 (19.3)	0.08
first degree	5 (2.0)	1 (1)	3 (2.7)	1 (3.2)	
second degree	14 (5.8)	5 (4.9)	4 (3.7)	5 (16.1)	
Depression	73 (30.1)	32 (31.4)	32 (29.1)	9 (29.0)	0.94
first degree	40 (16.5)	17 (16.7)	19 (17.3)	4 (12.9)	
second degree	33 (13.6)	15 (14.7)	13 (11.8)	5 (16.1)	
Anxiety	47 (19.4)	21 (20.6)	18 (16.4)	8 (25.8)	0.55
first degree	24 (9.9)	10 (9.8)	11 (10.0)	3 (9.7)	
second degree	23 (9.5)	11 (10.8)	7 (6.4)	5 (16.1)	
Substance abuse	21 (9.0)	11 (10.8)	10 (9.1)	1 (3.2)	0.68
first degree	19 (7.8)	10 (9.8)	8 (7.3)	1 (3.2)	
second degree	3 (1.2)	1 (1.0)	2 (1.8)	0 (0)	
Disruptive disorder	11 (4.6)	4 (3.9)	5 (4.5)	2 (6.5)	0.19
first degree	7 (2.9)	3 (2.9)	4 (3.6)	0 (0.0)	
second degree	4 (1.7)	1 (1)	1 (0.9)	2 (6.5)	
Eating disorder	11 (4.6)	6 (5.8)	4 (3.6)	2 (3.2)	0.84
first degree	6 (2.5)	3 (2.9)	2 (1.8)	1 (3.2)	
second degree	5 (2.1)	3 (2.9)	2 (1.8)	0 (2.3)	
Other	40 (16.4)	12 (11.7)	23 (20.9)	5 (16.1)	0.12
first degree	21 (8.6)	9 (8.8)	11 (10.0)	1 (3.2)	
second degree	19 (7.8)	3 (2.9)	12 (10.9)	4 (12.9)	

Treatment characteristics

84 participants (34.6%, 15 EOP, 43 APS and 26 non-APS) were already on psychotropic medications at baseline. Most received antidepressants (19.8%, 5 EOP, 26 APS and 17 non-APS), followed by benzodiazepines (16.5%, 7 EOP, 21 APS and 12 non-APS).

Significantly more EOP than both other groups, were receiving antipsychotic medications at baseline (p=0.0008). Duration of psychotropic treatment prior study entry was greater in both EOP and APS group compared to non-APS (p=0.0088).

The three groups showed no differences in terms of psychotherapeutic treatment and duration of psychotherapy prior admission to the study (table 2).

Table 2. Treatment characteristics at the time of assessment in the total sample, psychiatric control (non-APS), attenuated psychosis (APS) and early-onset psychosis (EOP) adolescent patients

Characteristic	Total (N=243)	Non-APS (N=102)	APS (N=110)	EOP (N=31)	p-value	Post-hoc adjusted p-values		
						Non-APS vs APS	Non-APS vs EOP	APS vs EOP
Psychotropic drugs, yes, n (%)	84 (34.6)	26 (25.5)	43 (39.1)	15 (48.4)	0.075			
Number of psychotropic drugs, median (min, max)	0.0 (0.0,4.0)	0.0 (0.0,4.0)	0.0 (0.0,4.0)	0.0 (0.0,3.0)	0.11			
Specific psychotropic drugs, n, (%)								

Antipsychotics	17 (7)	3 (2.9)	7 (6.4)	7 (22.6)	**0.0008**	n.s	**0.0044**	**0.043**
Antidepressants	48 (19.8)	17 (16.7)	26 (23.6)	5 (16.1)	0.38			
Benzodiazepines	40 (16.5)	12 (11.8)	21 (19.1)	7 (22.5)	0.22			
Mood stabilizers	8 (3.3)	2 (1.9)	4 (3.6)	2 (6.5)	0.45			
Duration psychotropic treatment prior admission, days, median (IQR 25, 75)	0.0 (0.0,30.0)	0.0 (0.0,0.0)	0.0 (0.0,30.0)	0.0 (0.0,60.0)	**0.0088**	**0.036**	**0.033**	n.s.
Psychotherapy at admission, yes, n (%)	115 (47.3)	40 (39.2)	59 (53.6)	16 (51.6)	0.096			
Psychotherapy duration prior admission, months, median (IQR 25, 75)	0.0 (0.0,11.0)	0.0 (0.0,8.0)	2.0 (0.0, 12.0)	2.0 (0.0,13.0)	0.11			

Diagnostic characteristics

The number of DSM-5 diagnoses was significantly higher (p<0.0001) and a number of diagnoses ≥3 (p<0.0001) was more frequently reported in the APS compared to both EOP and non-APS groups. Between the three groups no significance difference was observed in the duration of psychiatric symptoms, or rather the time frame between the onset of psychiatric symptoms as reported by patients and parents and the current admission (p=0.53).

In the total sample, depressive disorders were the most frequent axis I DSM-5 diagnoses (42%), mainly major depressive disorder (20.2%), followed by anxiety disorders (30.5%), mostly generalized anxiety disorder (14%), eating disorders (16.5%), disruptive, impulse-control and conduct disorders (12.4%), and bipolar disorders (11.5%).

Personality disorders were also frequent (30.5%), with borderline personality disorder (14.8%) most common. All of the patients having a primary or comorbid diagnosis of personality disorder had presented distinctive features for more than 1 year. Of note, 76% of them were older than 15 years.

APS adolescents showed a significant higher prevalence of depressive disorders (p<0.0001), mainly driven by major depressive disorder, and personality disorders (p<0.0001) than non-APS and EOP youth.

A difference in anxiety disorders was only found between APS and EOP patients (p=0.0036), with anxiety disorders more prevalent in the first group. On the contrary bipolar disorders (p=0.0059) and obsessive disorders (p=0.0085) were significantly more diagnosed at baseline in APS than non-APS patients.

Other diagnostic characteristics are presented in Table 3.

Table 3. Clinical characteristics in the total sample, psychiatric control (non-APS), attenuated psychosis (APS) and early-onset psychosis (EOP) adolescent patients

Characteristic	**Total (N=243)**	**Non-APS (N=102)**	**APS (N=110)**	**EOP (N=31)**	**p-value**	**Post-hoc adjusted p-values**		
						Non-APS vs APS	**Non-APS vs EOP**	**APS vs EOP**
Number of DSM-5 diagnoses,mean±SD	1.38±0.8	1.5±0.7	2.3±0.8	1.0±0.0	**<0.0001**	**<0.0001**	**0.0005**	**<0.0001**
Number of diagnoses≥3, n (%)	40 (16.5)	6 (5.9)	34 (30.9)	0 (0)	**<0.0001**	**0.000**	n.s.	**0.0002**
Months since psychiatric symptoms onset, months, median (IQR25,75)	14.0 (9.0,24.0)	14.0 (9.0, 24.0)	14 (10.0, 24.0)	18.0 (12.0, 26.5)	0.53			

Presence of negative symptoms, n (%)	161 (66.3)	51 (50)	81 (74.3)	29 (93.5)	**<0.0001**	**0.001**	**<0.0001**	0.07
Primary and comorbid DSM5 diagnoses, n (%)								
Depressive disorders	102 (42)	42 (41.2)	60 (54.5)	0 (0)	**<0.0001**	**0.0028**	**0.0003**	**<0.0001**
Major depressive disorder	49 (20.2)	13(12.7)	36 (32.7)	0 (0)				
Other specified depressive disorder	42 (17.3)	20 (19.6)	22 (20)	0 (0)				
Persistent depressive disorder	11 (4.5)	9 (8.8)	2 (1.8)	0 (0)				
Anxiety disorders	74 (30.5)	30 (29.4)	44 (40)	0 (0)	**0.028**	n.s.	n.s.	**0.0036**
Generalized anxiety disorder	34 (14)	12 (11.8)	22 (20)	0 (0)				
Social anxiety disorder	13 (5.4)	5 (4.9)	8 (7.3)	0 (0)				
Other specified anxiety disorder	17 (7)	9 (8.8)	8 (7.3)	0 (0)				
Separation anxiety disorder	3 (1.2)	1 (1.2)	2 (1.8)	0 (0)				
Panic disorder	7 (2.9)	3 (2.9)	4 (3.6)	0 (0)				
Personality disorders	74 (30.5)	21 (20.6)	53 (48.2)	0 (0)	**<0.0001**	**0.0003**	n.s.	**<0.0001**
Borderline	36 (14.8)	9 (8.9)	27 (24.5)	0 (0)				
Others (avoidant, dependent, narcissistic, schizotypal, other specified)	38 (15.6)	12 (11.8)	26 (23.6)	0 (0)				
Disruptive, impulse-control and conduct disorders	30 (12.4)	15 (14.7)	15 (13.6)	0 (0)	0.080			
Eating disorders	40 (16.5)	21 (20.6)	19 (17.3)	0 (0)	0.075			
Anorexia nervosa	31 (12.8)	15 (14.7)	16 (14.5)	0 (0)				
Others (bulimia/binge-eating)	9 (3.7)	6 (5.9)	3 (2.7)	0 (0)				
Bipolar disorders	28 (11.5)	8 (7.5)	20 (18.2)	0 (0)	**0.0017**	**0.0059**	n.s.	n.s.
Bipolar I or II	15 (6.2)	1 (1.0)	14 (12.7)	0 (0)				
Other specified bipolar disorders	13 (5.4)	7 (6.9)	6 (5.5)	0 (0)				
Conversion disorder	17 (7)	8 (7.8)	9 (8.2)	0 (0)	0.26			
Obsessive compulsive and related disorders	14 (5.8)	2 (2.0)	12 (11)	0 (0)	**0.0086**	**0.0085**	n.s	n.s
Others (ADHD, tics, PTSD, substance related disorders)	20 (8.2)	6 (5.9)	14 (12.7)	0 (0)	0.41			

Illness severity and functioning

There were significant between-group differences in CGI-Severity scores.

CGI-severity scale resulted in a median (IQ25,75) illness severity score, in the total sample, of 4.0 (3.5, 5.0) (moderately ill); the value was significantly higher in APS adolescents (5.0 (4.0, 5.0), i.e. markedly ill) compared to non-APS (3.0 (3.0,4.0), i.e. mildly ill) (p<0.0001). EOP displayed higher scores than both APS (p=0.006) and non-APS adolescents (p<0.0001) .

Significant differences between the three groups were also found for all functioning scales evaluated (current SOFAS, GF:S, GF:R and current, highest and lowest previous year CGAS) (*p-values*<0.0001). APS presented a significant worse functioning compared to non-APS (p<0.0001), but significantly better than EOP (with the only exception of the lowest CGAS in the previous year where the difference between EOP and APS was not significant, p=0.52).

Table 4. Illness severity and functioning in the total sample, psychiatric control (non-APS), attenuated psychosis (APS) and early-onset psychosis (EOP) adolescent patients

Characteristic median (IQR25, 75)	**Total (N=243)**	**Non-APS (N=102)**	**APS (N=110)**	**EOP (N=31)**	**p-value**	**Post-hoc adjusted p-values**		
						Non-APS vs APS	**Non-APS vs EOP**	**APS vs EOP**

Clinical Global Impression-Severity (CGI-S)	4.0 (3.0, 5.0)	3.0 (3.0, 4.0)	5.0 (4.0, 5.0)	6.0 (5.0, 6.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.006**
Current SOFAS	51.0 (44.5,60.0)	60.5 (55.0,70.0)	50.0 (41.0,55.0)	40.0 (31.0,50.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.044**
Current role functioning (GF:R)	6.0 (4.0, 7.0)	7.0 (6.0,8.0)	5.0 (4.0,6.0)	4.0 (2.5,5.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.0013**
Current social functioning (GF:S)	5.0 (4.0,6.0)	7.0 (6.0,7.0)	4.0 (4.0,5.0)	3.0 (3.0,5.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.009**
Global assessment functioning (CGAS)	51.0 (420, 60.0)	60.0 (55.0,70.0)	50 (41.0,51.0)	35.0(30.0,47.50)	**<0.0001**	**<0.0001**	**<0.0001**	**0.02**
Highest of past year	60.0 (51.0,70.0)	70.0 (60.0,80.0)	55.0 (50.25,61.75)	50.0 (44.0,55.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.02**
Lowest of past year	45.0 (40.0,55.0)	55.0 (50.0,61.0)	41.0 (35.0,45.0)	35.0 (25.0,45.0)	**<0.0001**	**<0.0001**	**<0.0001**	**n.s.**

Multivariable ordinal logistic regression analysis: socio-demographic and clinical variables that most influence group membership

In order to identify the variables that among the other socio-demographic and clinical variables most influence group membership a multivariable ordinal regression analysis was performed.

The following variables remained significant in the model: age, sex, ethnicity, family history of psychiatric disorder, diagnosis of depressive disorders and eating disorders, CGI-severity and global functioning: social role scale.

Being older (p=0.0116), female (p=0.024) and having a diagnosis of eating disorders (p=0.041) were associated with a higher chance of being in the non-APS and APS groups than in the EOP group. Having a diagnosis of depressive disorder (major depressive disorder p=0.0024, other specified depressive disorder p=0.0254 and persistent depressive disorder p=0.0004) was related to a higher probability of being in the APS group than in the two other groups, while not having a positive family history of any psychiatric disorder (p=0.0006), being more clinically severe (p=0.0015) and having a lower social functioning (p=0.0012) were associated to being in the APS and EOP group (table 5).

Table 5. Multivariable ordinal logistic regression analysis: socio-demographic and clinical variables that most influence group membership

Variables	Estimate	Standard error	Z-value	P-value
Age	-0.36762	0.1461	-2.5247	**0.0116**
Female sex	1.059	0.46619	2.2541	**0.024**
Ethnicity: African	-0.02934	1.2538	-0.0234	0.98
Ethnicity: Hispanic	-1.6373	1.2425	-1.3177	0.1875
Ethnicity: Albanian	2.1130	1.2705	1.6632	0.10
Ethnicity: eastern Europe	-0.5756	0.86856	-0.6569	0.51
Ethnicity: other minorities	-2.1091	1.0220	-2.0637	**0.039**
Negative psychiatric family history	1.5117	0.43822	3.4496	**0.0006**
First degree family psychiatric psychotic history	-1.5055	1.8616	-0.8087	0.41
Presence of negative symptoms	-0.41828	0.48545	-0.8616	0.39
Major depressive disorder	-1.8457	0.6746	-3.0383	**0.0024**
Other specified depressive disorder	-1.2575	-0.56273	-2.2347	**0.0254**
Persistent depressive disorder	-4.9275	1.3952	-3.5318	**0.0004**
Generalized anxiety disorder	-0.60687	-0.56448	1.0751	0.28
Separation anxiety disorder	-0.3811	1.5591	0.2444	0.8070
Panic disorder	-0.64800	1.2466	-0.5198	0.6032
Other specified anxiety disorder	-0.11592	-0.76727	0.1511	0.88

Social anxiety disorder	-0.20708	-0.899	-0.2303	0.81
Obsessive compulsive and related disorders	0.67463	-0.80816	0.8348	0.40
Borderline personality disorder	-0.61008	-0.60912	-1.0016	0.3165
Other personality disorders	-0.047943	0.55851	0.0858	0.93
Bipolar I or II disorder	-0.14567	0.76436	-0.1906	0.85
Other specified bipolar disorders	-0.89512	0.88799	-1.0080	0.31
Anorexia nervosa	-1.2999	-0.63602	-2.0438	**0.041**
Months since psychiatric symptoms onset	0.00167	0.00935	0.1782	0.86
Duration psychotropic treatment prior study entry	-0.000642	0.00132	-0.0486	0.96
Psychotherapy duration prior study entry	0.01167	0.018077	0.6457	0.52
CGI-severity scale	1.1822	0.37140	3.1830	**0.0015**
GF:S	-0.79411	0.24442	-3.2489	**0.0012**
GF-R	-0.1261	-0.19533	-0.6456	0.52
SOFAS	-0.02567	0.03228	-0.7593	0.4264

CAARMS subscales and symptoms

The severity and frequency of symptoms as measured by CAARMS are reported in Table 6.

Between-groups differences were found for all CAARMS items, expect for "subjective complaints of impaired autonomic functioning" ("motor/physical changes" subscale) and "mania" ("general psychopathology" subscale).

As expected, in all CAARMS "Positive Symptoms" subscales (i.e. unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganized speech), EOP had higher scores than both the other two groups (*p-values*<0.0001). The APS group's scores were higher than those in non-APS subjects, but lower than those in EOP adolescents.

In the APS-group, the most intense and frequent positive symptoms experienced were perceptual abnormalities (3.0 (3.0, 4.0), reported by 77% of APS subjects) and non-bizarre ideas (3.0 (2.0, 4.0), reported by 61%). Disorganized speech was the least severe and frequent positive symptom endorsed (2.0 (0.0, 3.0), 37%).

Significant differences with regard to the CAARMS "Negative Symptoms" subscales' scores were also found. Frequency and severity of "alogia" were highest in the EOP group compared to both APS and non-APS adolescents (p<0.0001). However, APS subjects had significantly higher alogia's scores than non-APS (p<0.0001).

"Avolition/apathy" (p=0.0016) and "anhedonia" (p=0.0034) scores were significantly higher in EOP and APS compared to non-APS adolescents, while no significant differences regarding those items was found between EOP and APS.

A trend similar to that observed for "apathy" and "anhedonia" (EOP>non-APS, APS>non-APS, EOP≠APS) was also found for other 5 Huber's basic symptoms as assessed by the CAARMS (i.e. "subjective experience of cognitive change", "subjective emotional disturbances", "subjective complaints of motor functioning", "subjective complaints of impaired bodily sensation" and "impaired tolerance to normal stress"). For all these items, although the scores were slightly higher in the EOP group compared to APS adolescents, the differences were not statistically significant.

Among "behavioral change" subscale's items, the only statistical difference between the APS and EOP group was found for "aggressive/dangerous behavior" (EOP>APS, p=0.019). Non-APS scores were significantly

lower than both those of APS and EOP in the "social isolation" (p<0.0001), "impaired role functioning" (p<0.0001) and "disorganized behavior" (p<0.0001).

Non-APS patients presented also significantly lower scores than both the two other groups in the "suicidality/self-harm" (p=0.0003), "anxiety" (p<0.0001) and "dissociative symptoms" (p<0.0001) items belonging to the CAARMS "general psychopathological" subscale. Furthermore, APS individuals had significantly higher CAARMS "depression" (p=0.0005), "mood lability" (p=0.0005), "obsessive-compulsive symptoms" (p=0.018) than non-APS participants.

Table 6. Severity and frequency of symptoms as assessed by the CAARMS in the total sample, psychiatric control (non-APS), attenuated psychosis (APS) and early-onset psychosis (EOP) adolescent patients

Characteristic, median (IQR25, 75)	**Total (N=243)**	**Non-APS (N=102)**	**APS (N=110)**	**EOP (N=31)**	**p-value**	**Post-hoc adjusted p-values**		
						Non-APS vs APS	**Non-APS vs EOP**	**APS vs EOP**
Positive symptoms								
Unusual thought content								
Severity	2.0 (0.0,3.0)	0.0 (0.0,1.0)	2.0 (1.0,4.0)	5.0 (4.0,6.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.0002**
Frequency	2.0 (0.0,4.0)	0.0 (0.0,1.0)	3.0 (2.0,4.0)	5.0 (4.0,5,0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.0006**
Level of distress	0.0 (0.0, 60.0)	0.0 (0.0,0.0)	40.0 (0.0,80.0)	75.0 (50.0,92.50)	**<0.0001**	**<0.0001**	**<0.0001**	**0.035**
Non-bizarre ideas								
Severity	2.0 (0.0,3.0)	0.5 (0.0,2.0)	3.0 (2.0,4.0)	5.0 (4.0,6.0)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Frequency	3.0 (0.0,4.0)	0.0 (0.0,3.0)	3.0 (2.0,4.75)	5.0 (4.0, 5.5)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Level of distress	40 (0.0, 80.0)	0.0 (0.0,47.5)	60.0 (0.0,85.0)	80.0 (67.5,95.5)	**<0.0001**	**<0.0001**	**<0.0001**	**0.01**
Perceptual abnormalities								
Severity	3.0 (1.0,4.0)	0.5 (0.0,2.0)	3.0 (3.0,4.0)	5.0 (4.0,5.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.0012**
Frequency	2.0 (0.25,4.0)	0.5 (0.0,2.0)	3.0 (2.0,4.0)	4.0 (3.0,4.0)	**<0.0001**	**<0.0001**	**<0.0001**	**n.s.**
Level of distress	7.5 (0.0,70.0)	0.0 (0.0,0.0)	50.0 (0.0,80.0)	80.0 (22.5, 100.0)	**<0.0001**	**<0.0001**	**<0.0001**	**n.s.**
Disorganized speech								
Severity	2.0 (0.0,3.0)	0.0 (0.0,2.0)	2.0 (0.0,3.0)	3.0 (2.5,4.5)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Frequency	2.0 (0.0,4.0)	0.0 (0.0,2.0)	3.0 (1.0,4.0)	4.0 (3.0,6.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.009**
Level of distress	0.0 (0.0,50.0)	0.0 (0.0,0.0)	50.0 (0.0,55.0)	50.0 (15.0,80.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.015**
Cognitive change- attention/concentration								
Subjective experience (Huber's basic symptom)								
Severity	2.0 (1.0,3.0)	1.0 (0.0,2.0)	3.0 (2.0,3.0)	3.0 (2.0,4.0)	**<0.0001**	**<0.0001**	**<0.0001**	n.s.
Frequency	3.0 (1.0,4.0)	2.0 (0.0,3.0)	3.0 (2.0,4.0)	4.0 (3.0,5.0)	**<0.0001**	**<0.0001**	**<0.0001**	n.s
Observed cognitive change								
Severity	0.0 (0.0,2.0)	0.0 (0.0,1.0)	0.0 (0.0,2.0)	2.0 (0.5,3.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.0012**
Emotional disturbances								
Subjective emotional disturbance (Huber's basic symptom)								
Severity	2.0 (0.0,3.0)	0.5 (0.0,2.0)	3.0 (0.0,4.0)	3.0 (2.0, 4.0)	**<0.0001**	**<0.0001**	**<0.0001**	n.s.
Frequency	3.0 (0.0,4.0)	0.0 (0.0,3.0)	3.0 (0.0,4.0)	4.0 (3.0,5.0)	**<0.0001**	**0.0015**	**0.0002**	n.s.
Observed blunted affect								
Severity	2.0 (0.0,3.0)	0.0 (0.0,3.0)	2.0 (0.0,3.0)	3.0 (2.0,3.0)	**0.0006**	n.s.	**0.0003**	**0.020**
Frequency	2.0 (0.0,3.0)	0.0 (0.0,3.0)	2.0 (0.0,3.0)	3.0 (3.0,5.0)	**0.0001**	n.s.	**<0.0001**	**0.002**
Observed inappropriate affect								
Severity	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,1.0)	1.0 (0.0,3.0)	**<0.0001**	**0.0066**	**<0.0001**	**0.0054**
Frequency	0.0 (0.0,1.0)	0.0 (0.0,0.0)	0.0 (0.0,3.0)	3.0 (0.0, 3.0)	**<0.0001**	**0.0033**	**<0.0001**	**0.0077**
Negative symptoms								
Alogia								
Severity	1.0 (0.0,2.0)	0.0 (0.0,1.0)	2.0 (0.0,3.0)	3.0 (1.5,4.0)	**<0.0001**	**<0.0001**	**<0.0001**	**0.0035**
Frequency	2.0 (0.0.3.0)	0.0 (0.0,3.0)	3.0 (0.0,4.0)	3.0 (2.0,5.0)	**<0.0001**	**0.0038**	**<0.0001**	**0.020**
Avolition/Apathy (Huber's basic symptom)								
Severity	3.0 (2.0,4.0)	2.0 (1.0,3.0)	3.0 (2.0,4.0)	4.0 (2.5,5.0)	**0.0016**	n.s	**0.0016**	n.s
Frequency	3.0 (2.0,5.0)	3.0 (0.25,4.0)	3.5 (2.0,5.0)	5.0 (3.0,5.0)	**0.0009**	**0.05**	**0.0012**	n.s.
Anhedonia								
Severity	2.0 (0.0,4.0)	0.0 (0.0,3.0)	2.0 (0.0,4.0)	3.0 (0.0,4.5)	**0.0034**	**0.014**	**0.020**	n.s
Frequency	3.0 (0.0,4.0)	0.0 (0.0,3.0)	3.0 (0.0,5.0)	3.0 (0.0,5.0)	**0.0045**	**0.0083**	n.s.	n.s.

Behavioral change								
Social isolation								
Severity	3.0 (0.0,4.0)	2.0 (0.0,3.0)	3.0 (2.0,4.0)	4.0 (3.0,5.0)	**<0.0001**	**<0.0001**	**<0.0001**	0.06
Frequency	3.0 (0.0,4.0)	2.0 (0.0,4.0)	3.5 (0.0,5.0)	4.0 (4.0,5.5)	**<0.0001**	**<0.0001**	**<0.0001**	0.07
Impaired role function								
Severity	3.0 (0.0,4.0)	3.0 (0.0,3.0)	3.5 (2.0,5.0)	4.0 (3.5,5.0)	**<0.0001**	**0.0006**	**<0.0001**	n.s.
Frequency	3.0 (0.0,5.0)	3.0 (0.0,4.0)	4.0 (3.0,5.0)	4.0 (3.5,5.5)	**<0.0001**	**0.0012**	**<0.0001**	n.s.
Disorganized/odd/stigmatizing behavior								
Severity	0.0 (0.0,2.0)	0.0 (0.0,0.0)	0.0 (0.0,3.0)	2.0 (0.0,4.0)	**<0.0001**	**0.0044**	**0.0002**	n.s.
Frequency	0.0 (0.0,3.0)	0.0 (0.0,0.0)	0.0 (0.0,3.0)	0.0 (0.0,5.0)	**0.0002**	**0.0065**	**0.0007**	n.s.
Aggressive/dangerous behavior								
Severity	3.0 (2.0,4.0)	2.5 (1.3,3.0)	3.0 (2.0,4.0)	4.0 (3.0,5.0)	**0.001**	n.s.	**0.0006**	**0.019**
Frequency	3.0 (2.0,4.0)	3.0 (1.0,4.0)	3.0 (2.0,4.0)	3.0 (3.0,5.0)	**0.031**	n.s.	**0.029**	n.s.
Motor/physical changes								
Subjective complaints of impaired motor functioning (Huber's basic symptom)								
Severity	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,1.0)	0.0 (0.0,2.0)	**<0.0001**	**0.0003**	**0.0025**	n.s.
Frequency	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,3.0)	0.0 (0.0,3.0)	**<0.0001**	**0.0002**	**0.0008**	n.s.
Informant reported or observed changes in motor functioning								
Severity	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,2.0)	**<0.0001**	**0.015**	**<0.0001**	0.052
Subjective complaints of impaired bodily sensation (Huber's basic symptom)								
Severity	0.0 (0.0,2.0)	0.0 (0.0,0.0)	0.0 (0.0,2.0)	0.0 (0.0,4.0)	**0.00012**	**0.0030**	**0.0007**	n.s.
Frequency	0.0 (0.0,3.0)	0.0 (0.0,0.0)	0.0 (0.0,3.0)	1.0 (0.0,3.5)	**0.00016**	**0.0021**	**0.0016**	n.s.
Subjective complaints of impaired autonomic functioning (Huber's basic symptom)								
Severity	2.0 (0.0,3.0)	2.0 (0.0,3.0)	2.0 (0.0,3.0)	2.0 (0.0,3.0)	0.52			
Frequency	2.0 (0.0,3.0)	2.0 (0.0,3.0)	3.0 (0.0,4.0)	3.0 (0.0,3.5)	0.29			
General psychopathology								
Mania								
Severity	0.0 (0.0,1.0)	0.0 (00,0.0)	0.0 (0.0,2.0)	0.0 (0.0,0.5)	0.32			
Frequency	0.0 (0.0,1.0)	0.0 (0.0,0.0)	0.0 (0.0,2.0)	0.0 (0.0,0.0)	0.16			
Depression								
Severity	3.0 (2.0,4.0)	3.0 (2.0,3.0)	3.0 (3.0,4.0)	3.0 (2.5,4.0)	**0.0007**	**0.0005**	n.s.	n.s.
Frequency	4.0 (3.0,5.0)	3.0 (2.0,5.0)	4.0 (3.0,5.0)	4.0 (3.0,5.0)	**0.0080**	**0.0067**	n.s.	n.s.
Suicidality and self –harm								
Severity	2.0 (0.0,3.0)	0.0 (0.0,3.0)	3.0 (0.0,4.0)	3.0 (0.0,4.0)	**0.00027**	**0.0008**	**0.011**	n.s.
Frequency	1.0 (0.0,3.0)	0.0 (0.0,2.75)	2.0 (0.0,4.0)	3.0 (0.5,3.0)	**0.00011**	**0.00048**	**0.0039**	n.s.
Mood swings/lability								
Severity	2.0 (0.0,3.0)	0.0 (0.0,2.0)	2.0 (0.0,3.0)	1.0 (0.0,3.0)	**0.00080**	**0.00051**	n.s.	n.s.
Frequency	2.0 (0.0,3.0)	0.0 (0.0,3.0)	3.0 (0.0,4.0)	2.0 (0.0,3.0)	**0.011**	**0.0091**	n.s.	n.s.
Anxiety								
Severity	3.0 (1.0,4.0)	3.0 (0.0,3.0)	4.0 (2.0,4.0)	4.0 (3.0,4.5)	**<0.0001**	**0.00036**	**0.0024**	n.s.
Frequency	3.0 (2.0,4.0)	3.0 (0.0,4.0)	4.0 (2.0,5.0)	4.0 (3.0,5.0)	**<0.0001**	**0.0025**	**0.00069**	n.s.
OCD symptoms								
Severity	0.0 (0.0,2.0)	0.0 (0.0,2.0)	1.0 (0.0,2.0)	0.0 (0.0,3.0)	**0.018**	**0.018**	n.s.	n.s.
Frequency	0.0 (0.0,3.0)	0.0 (0.0,3.0)	0.0 (0.0,3.0)	0.0 (0.0,3.5)	**0.041**	**0.046**	n.s.	n.s.
Dissociative symptoms								
Severity	0.0 (0.0,2.0)	0.0 (0.0,0.0)	0.0 (0.0,3.0)	2.0 (0.0,4.0)	**<0.0001**	**0.0013**	**<0.0001**	n.s.
Frequency	0.0 (0.0,2.0)	0.0 (0.0,0.0)	0.0 (0.0,3.0)	2.0 (0.0,3.0)	**<0.0001**	**0.0004**	**<0.0001**	n.s.
Impaired tolerance to normal stress (Huber's basic symptom)								
Severity	3.0 (0.0,4.0)	0.5 (0.0,3.0)	3.0 (0.0,4.0)	4.0 (1.0,5.0)	**<0.0001**	**0.0022**	**0.00014**	n.s.
Frequency	3.0 (0.0,4.0)	1.0 (0.0,3.0)	3.0 (0.0,4.0)	4.0 (1.5,5.0)	**0.00089**	**0.025**	**0.0020**	n.s.

Multivariable ordinal logistic regression analysis: CAARMS subscales that most influence group membership

As we sought to identify CAARMS specific symptoms items significantly influencing group membership, positive symptom items were excluded from the model as these items, according to the CAARMS criteria, are used to define the 3 groups.

In order to identify the variables that among the other CAARMS subscales most influence group membership a multivariable ordinal regression analysis was performed.

The following variables remained significant in the model: "Subjective experience of cognitive change" (p=0.010), "alogia" (p=0.041), "disorganized/odd/stigmatizing behavior" (p=0.026), "subjective complaints of

impaired bodily sensation" (p=0.009), "suicidality and self –harm" (p=0.018). Having higher scores in these scales was associated to a higher chance of belonging to APS than non-APS group (Table 7).

Table 7. Multivariable ordinal logistic regression analysis: CAARMS subscales that most influence group membership

Variables	Estimate	Standard error	Z-value	P-value
Subjective experience of cognitive change	0.3663	0.1462	2.5733	**0.01001**
Observed cognitive change	0.2421	0.1423	1.7014	0.0899
Subjective emotional disturbance	0.0403	0.1091	0.3695	0.7117
Observed blunted affect	0.1185	0.1183	1.0014	0.3166
Observed inappropriate affect	0.0453	0.1343	0.3372	0.7359
Alogia	0.3005	0.1472	2.0412	**0.04123**
Avolition/apathy	-0.1042	0.1162	-0.8969	0.3698
Anhedonia	-0.0074	0.0975	-0.0762	0.9392
Disorganized/odd/stigmatizing behavior	0.2399	0.1076	2.2305	**0.0257**
Aggressive/dangerous behavior	0.0018	0.0997	0.0180	0.986
Subjective complaints of impaired motor functioning	-0.1686	0.1734	-0.9722	0.3309
Informant reported or observed changes in motor functioning	0.0479	0.1990	0.2406	0.8099
Subjective complaints of impaired bodily sensation	0.2804	0.1074	2.6101	**0.009**
Subjective complaints of impaired autonomic functioning	-0.039	0.0924	-0.4246	0.6712
Suicidality and self –harm	0.2007	0.0849	2.3632	**0.01812**
Impaired tolerance to normal stress	0.1479	0.0814	1.8163	0.07

Additional Psychopathological Scales

Between group-differences were found also in self-rated scales assessing behavioral problems filled in by both parents and patients. Indeed, a statistical significant difference emerged in the Internalizing score of CBCL filled in by both caregivers (mothers p=0.0079, fathers p=0.032) and YSR filled in by the patients with APS patients displaying scores significantly more severe than non-APS patients. The same trend was also observed for the Total scores of the CBCL (mothers p=0.0063) and YSR (p<0.0001). Moreover, mothers of APS adolescents reported higher scores in the subscales describing their child withdrawn (p=0.041), social problems (p=0.0079) and thought problems (p=0.0024) compared to mothers of non-APS patients. Of note, APS subjects compared to non-APS reported higher scores in all YSR subscales, expect for aggressive behavior.

Significant differences emerged also between EOP and non-APS individuals (mother's CBCL anxious/depressed (p=0.018), social (p=0.0082) and thought problems (p=0.013), YSR withdrawn (p=0.022), anxious/depressed (p=0.0042) and thought problems (p=0.001)), while no differences were observed in any of the CBCL and YSR's items between APS and EOP.

In addition, APS patients reported higher levels of perceived stress than non-APS subjects (p=0.0077), while EOP expressed lower quality of life as evaluated through the EUROQoL scale than non-APS individuals (p=0.017) (no significant differences were observed between the EOP and APS group).

No between-group differences were observed for both mother's and father's FACES scores with the exception of the over-involvement scale were APS fathers reported a higher level of over-involvement in their families compared to non-APS (p=0.019).

All the results are shown in Table 8.

Table 8. CBCL, YSR, PSS, EUROQoL and FACES scores in the total sample, psychiatric control (non-APS), attenuated psychosis (APS) and early-onset psychosis (EOP) adolescent patients

Characteristic median (IQR25, 75)	**Total (N=243)**	**Non-APS (N=102)**	**APS (N=110)**	**EOP (N=31)**	**p-value**	**Post-hoc adjusted p-values**		
						Non-APS vs APS	**Non-APS vs EOP**	**APS vs EOP**
Child Behavior Checklist mother, T scores, median (IQR25, 75)								
Total Problems	66 (61,72)	65 (60,70)	68 (62.3,73)	68.5 (64,72)	**0.0063**	**0.0076**	n.s.	n.s.
Internalizing Problems	70 (64,75)	69 (59,72)	71 (66.3,76)	70 (69,78.3)	**0.0079**	**0.017**	n.s.	n.s.
Externalizing Problems	61 (54.5,68)	59 (53,66.5)	63 (56,69)	61 (54.8,68)	0.14			
Subscales								
Anxious/depressed	68 (62,76)	67 (57,73)	70 (62.3,78)	76 (66,86)	**0.0085**	n.s.	**0.018**	n.s.
Withdrawn	69 (60,78)	68 (57,74)	70 (63,81)	69.5 (66,75)	**0.045**	**0.041**	n.s.	n.s.
Somatic complaints	67 (58,74)	65 (57.5,72)	70 (59,74)	67.5 (58, 72)	0.06			
Social problems	63 (54,69)	61 (51,65)	64 (57.3,69.8)	67 (61,70)	**0.0012**	**0.0079**	**0.0082**	n.s.
Thought problems	67 (59,73)	63 (56,70)	67 (60,74.8)	69 (66,75.5)	**0.0024**	**0.013**	**0.013**	n.s.
Attention problems	61 (55,67)	61 (54,65)	61.5 (56,69.8)	62 (59,68)	0.06			
Rule-breaking behavior	60 (51, 65)	57 (51,64)	60 (52,67)	61 (52.5,64)	0.14			
Aggressive behavior	61 (54, 68.5)	59 (52,65.5)	63 (55,69.8)	61 (55.3,65.8)	0.11			
Child Behavior Checklist father, T scores, median (IQR25, 75)								
Total Problems	63.5 (56,70)	58.5 (52,67.8)	65 (60,70)	65.5 (59.8,70)	0.08			
Internalizing Problems	68.5 (59,73)	61 (55,72.8)	70 (64.3,73)	70 (65.5,72.8)	**0.032**	**0.035**	n.s.	n.s.
Externalizing Problems	59 (51, 65.8)	54.5(49.3,64.8)	59.5 (53,66)	59.5 (51.8,61.8)	0.39			
Subscales								
Anxious/depressed	65 (57,72)	59 (55,67.8)	67 (57.8,72)	69 (66.3,76.5)	0.06			
Withdrawn	66 (57,74)	60 (54,73)	68 (63,74)	69 (63.8,76.8)	0.07			
Somatic complaints	61 (56,68)	60 (54,68)	62 (58,70)	60 (58,66.3)	0.31			
Social problems	58 (51,67)	56 (51,63.8)	58 (51,68.5)	64 (61,70)	0.06			
Thought problems	64 (55,69)	59 (52,67)	66.5 (56.8,70)	67 (61,72.3)	0.07	0.06	n.s.	n.s.
Attention problems	56 (53, 65)	56 (52,61)	57 (54,66)	60 (54.3,64)	0.10			
Rule-breaking behavior	54 (51,62)	54 (51,62)	57 (52,63)	54.5 (52.5, 60.8)	0.27			
Aggressive behavior	58 (52,65)	56 (51,64)	60 (54,66)	56.5 (52,61)	0.29			
Youth Self Report, T scores, median (IQR25, 75)								
Total Problems	64 (54,70.8)	59 (54.3,65)	67 (61,74)	68 (62,73.5)	**<0.0001**	**<0.0001**	**0.008**	n.s.
Internalizing Problems	66 (59,75)	63 (55,68.8)	71 (62.8,78)	73 (61.5,78)	**<0.0001**	**<0.0001**	**0.006**	n.s.
Externalizing Problems	57 (51,66)	56.5 (48,64.8)	59 (52,68)	58 (49,62.5)	0.11			
Subscales								
Anxious/depressed	66(57.5,77.5)	64 (52,70)	69 (62,81)	75 (64.5,81.5)	**<0.0001**	**0.0001**	**0.0042**	n.s
Withdrawn	64 (58,73)	61 (54.3, 68.8)	66 (60,82)	70 (60.5,73.5)	**0.0008**	**0.0019**	**0.022**	n.s.
Somatic complaints	64 (54,69)	57 (52,66)	66 (57.8,69)	65 (57,69.8)	**0.0006**	**0.0006**	n.s.	n.s.
Social problems	61 (52, 70)	55 (51,63.8)	64 (57,73)	63 (56,68)	**<0.0001**	**<0.0001**	n.s.	n.s.
Thought problems	61 (54,67)	56 (51,61)	64 (58,73)	66 (58,74)	**<0.0001**	**<0.0001**	**0.001**	n.s.
Attention problems	60 (53, 68.8)	57 (52,63)	63 (57,73)	60 (52,73)	**0.0023**	**0.0015**	n.s.	n.s.
Rule-breaking behavior	54 (50,65)	52 (50,60.8)	59 (51,67)	53 (51,59.3)	**0.019**	**0.023**	n.s.	n.s.
Aggressive behavior	58 (52,67)	57 (51,65)	59 (54,68)	59 (51,62.8)	0.08			
Perceived Stress Scale (PSS), median (IQR 25,75)								
Patient	24 (20,31)	22 (19,26)	26 (23,32)	29 (20,35)	**0.0053**	**0.0077**	n.s.	n.s.
Mother	20 (15,26)	17 (14,24)	24 (16,27)	21(16,28)	0.33			
Father	17 (13,23)	16.5 (13,23)	17 (11,23)	16 (13.5,19)	0.96			
EUROQoL, median (IQR 25,75)								
Patient	60 (40,73)	65 (45,85)	58 (40,70)	30 (15,60)	**0.018**	n.s.	**0.017**	n.s.
Mother	70 (50,80)	70 (64,86)	60 (48,80)	55 (45,70)	0.07			
Father	70 (60,90)	70 (60,90)	75 (53,90)	65 (55,75)	0.53			
Family Adaptability and Cohesion Evaluation Scale (FACES) mother, percentiles, median (IQR25,75)								
Cohesion	40 (30,70)	40 (30,70)	40 (29,52)	53 (34,63)	0.51			
Adaptability	50 (25,70)	50 (30,75)	45 (25,70)	55 (38,70)	0.48			
Disengagement	60 (30,80)	55 (30,75)	60 (40,82)	55 (9,72)	0.15			
Over-involvement	50 (30,70)	40 (25,60)	55 (30,71)	45 (26,71)	0.37			
Rigidity	40 (20,70)	40 (20,60)	45 (20,70)	70 (50,76)	0.09			
Disorganization	60 (40,80)	50 (40,70)	73 (49,83)	60 (44,80)	0.07			
Communication	35 (29,40)	34 (31,40)	34.5 (29,39)	36 (29,39)	0.88			
Satisfaction	32 (27,38)	32 (28,38)	32 (26,36)	32.5 (25,38)	0.88			
Family Adaptability and Cohesion Evaluation Scale (FACES) father, percentiles, median (IQR25,75)								
Cohesion	40 (28.70)	55 (27,75)	40 (28,65)	45 (36,66)	0.91			
Adaptability	45 (28.70)	43 (25,60)	45 (30,65)	55 (31,81)	0.65			
Disengagement	45 (30,70)	48 (22.5,60)	40 (30,78)	40 (19.5,75)	0.88			

Over-involvement	50 (28,70)	35 (20,60)	70 (43,85)	45 (30,60)	**0.022**	**0.019**	n.s.	n.s.
Rigidity	40 (25,60)	32.5 (25,50)	50 (25,70)	60 (43,74)	0.06			
Disorganization	60 (30,83)	50 (30,83)	70 (43,83)	38 (23,78)	0.37			
Communication	35 (30,40)	35.5 (30,40)	32 (29.5,38)	37 (28,41)	0.59			
Satisfaction	32 (27,39)	33 (29.3,40)	31 (26,34)	32.5 (30,39)	0.29			

Neurocognitive characteristics

Among the different neurocognitive domains examined, between-group differences were found in the Total IQ (p=0.0008), Perceptual Reasoning Index (PRI) (p=0.028), Working Memory Index (WMI) (p=0.028) and its subscale Letter-Number Sequencing (p=0.033), Processing Speed Index (PSI) (p<0.0001), and its subscales Coding (p=0.017) and Symbol Search (p=0.0033), Rey-Osterrieth Complex Figure Test (copy) (p=0.020), Digit Span Forward and Backward (BVN 12-18) (p=0.031), Semantic (p=0.034) and Phonemic (p=0.043) Verbal Fluency (BVN 12-18), Elithorn Perceptual Maze Test (BVN 12-18) (p=0.037) and Wisconsin Card Sorting Test (BVN 12-18) (p=0.032). The domains of executive function, Working Memory and Processing Speed were all significantly more affected in EOP patient than non-APS patients in all the neurocognitive tests described, while no significant difference was found between APS and non-APS adolescents. Better scores were obtained by APS patients when compared to EOP in the total intelligence quotient (p=0.0011), perceptual reasoning (p=0.042), working memory index (p=0.0058) and processing speed index (p=0.01) and its subscale symbol search (p=0.016) (Table 9).

Entering all the cognitive variables examined in a multivariable regression analysis, Elithorn Perceptual Maze Test's score was the only variable that significantly influenced group membership (p=0.0062) with lowest scores in this test increasing the risk of being in the EOP group.

Table 9. Neurocognitive characteristics in the total sample, psychiatric control (non-APS), attenuated psychosis (APS) and early-onset psychosis (EOP) adolescent patients

Characteristic median (IQR25, 75)	**Total (N=243)**	**Non-APS (N=102)**	**APS (N=110)**	**EOP (N=31)**	**p-value**	**Post-hoc adjusted p-values**		
						Non-APS vs APS	**Non-APS vs EOP**	**APS vs EOP**
General Intelligence (Wechsler scales)								
Full-scale IQ (FSIQ)	97 (87,110)	101 (87,112)	98 (90,110)	88(76,97.5)	**0.0008**	n.s.	**0.0011**	**0.0011**
Verbal Comprehension (VCI)	104 (92,114)	104 (93,116)	104 (92,114)	95 (82.5,108.5)	0.13			
Perceptual Reasoning (PRI)	104 (93.3,111)	104 (95,113)	104 (95.5,112)	94 (82.3,105.5)	**0.028**	n.s.	**0.031**	**0.042**
Working Memory (WMI)	94 (84, 103)	94 (86,106)	94 (85.8,103)	85 (79.3,88)	**0.0054**	n.s.	**0.0091**	**0.0058**
Processing Speed (PSI)	96 (85,106)	103 (88,112)	97 (86, 106)	82 (74.5,88.8)	**<0.0001**	n.s.	**<0.0001**	**0.001**
Subscales								
Block design (PRI)	10 (8,12)	10 (7,12)	10 (8,12)	11 (10,11)	0.85			
Similarities (VCI)	11 (9,12.5)	11 (10,13)	11 (9,12.5)	11 (9,12)	0.91			
Digit span (WMI)	9 (7,11)	9 (7,11)	9 (8,11)	6.5 (5.3,9.5)	0.08			
Matrix Reasoning (PRI)	11 (8.5,12.5)	11 (9,13)	11 (8,12)	10 (7.3,11.8)	0.24			
Coding (PSI)	9 (7,11)	10 (7,12)	9.5 (7,11)	8 (5,8.8)	**0.017**	n.s.	**0.013**	n.s.
Vocabulary (VCI)	11 (9,13)	11 (9,13)	11 (9,12.3)	10 (8.3,11)	0.65			
Arithmetic (WMI)	9.5 (8,12)	11 (8,13)	8 (7,11)	9.5 (5.8,10)	0.06			
Letter-number sequencing (WMI)	8 (7,11)	9 (7,11)	8 (7,11)	8 (5,8.3)	**0.033**	n.s.	**0.027**	n.s.
Picture concepts (PRI)	10 (8.3,12)	10 (9,12)	10 (8.5,12)	9 (6.3,10)	0.062			
Comprehension (VCI)	11 (8,12.8)	11 (8.8,13)	11 (8,13)	9 (8,11)	0.28			
Symbol Search (PSI)	10 (8,11.5)	11 (8,13)	10 (9,11)	7 (6,9.5)	**0.0033**	n.s.	**0.0024**	**0.016**
Rey-Osterrieth Complex Figure Test, percentiles*								
Copy	68 (24,90)	75 (50,90)	75 (24.5,90)	21 (5.25,63.8)	**0.020**	n.s.	**0.016**	n.s.

Recall	52 (21.3, 81)	52 (25,82)	62.5 (21.9,86.3)	27.5 (7.0,46.3)	0.06			
Batteria di Valutazione Neuropsicologica per l'età evolutiva – 12-18 (BVN 12-18), T scores*								
Denominazione lessicale (expressive language)	94 (81.6,101.3)	96.7 (85.3,106.5)	91.2 (81.9,97.3)	85.5 (75,99.8)	0.10			
Memoria di cifre in avanti (Digit span forward)	88.5 (84.2,106.4)	95.6 (85.8,107)	90.7 (84.2,107)	85.8 (81,88.5)	**0.031**	n.s.	**0.027**	n.s.
Memoria di cifre indietro (Digit span backward)	94.2 (83,107.3)	95.5 (93.8,109.4)	94.2 (83,104)	82 (81,93.8)	**0.011**	n.s.	**0.0085**	n.s.
Corsi block-tapping test	93.5 (87,111)	105.5 (92.7,111)	93.4 (81.6,110.5)	93.4 (70.4,110.7)	0.27			
Auditory selective attention test	92.5 (68.8,104)	95 (77,105)	89 (77,99)	75 (40,99)	0.28			
Visual selective attention test	107 (98,116)	111 (103,120)	105 (98,116)	98 (90,111)	0.06			
Semantic verbal fluency test	94.6 (81.2,105)	98 (82.2,109)	93 (84.4,105.7)	81.5 (70.2,96.4)	**0.034**	n.s.	**0.037**	n.s.
Phonemic verbal fluency test	99.4 (85.3, 114)	102.6 (87,117)	99.4 (91.4,109.5)	81.7 (71.9,101)	**0.043**	n.s.	**0.045**	n.s.
Elithorn Perceptual Maze Test	100.6 (80,114)	114 (97,114)	99.4 (76,114)	80 (60.5,101)	**0.037**	n.s.	**0.033**	n.s.
Wisconsin Card Sorting Test, percentiles*								
Number of right answers	70 (28,86)	80 (48,86)	74 (25,87)	37 (7,54)	**0.032**	n.s.	**0.026**	n.s.
Number of repetitive answers	85 (47.96)	85 (50,95)	90 (62,99)	62 (38,87)	0.26			
Number of perseverative errors	82.5 (59.5,99)	82.5 (71.3,95)	87 (58,99)	75 (55,93)	0.66			

*data systematically collected only for patients enrolled after December 2017 (14 EOP, 37 APS and 36 non-APS)

Multivariable ordinal regression analysis: model that best predicted group membership

In order to select the variables that best predicted group membership we applied a step-wise selection procedure to the multivariable regression model.

Based on current literature and on the results of the previous regression analyses, the following variables were initially entered into the model: age, sex, ethnicity, family history of any psychiatric disorder, presence of negative symptoms, number of diagnoses, diagnosis of depressive, personality and eating disorders, duration of psychiatric symptoms, duration of psychotropic and psychotherapeutic treatment prior study entry, total IQ, CGI-severity scale, Global functioning: Social scale, Global Functioning: Role Scale, current SOFAS. Also CAARMS' items "Subjective experience of cognitive change", "Observed cognitive change", "Subjective emotional disturbance", "Observed blunted affect", "Observed inappropriate affect", "Alogia", "Avolition/apathy", "Anhedonia", "Disorganized/odd/stigmatizing behavior", "Aggressive/dangerous behavior", "Subjective complaints of impaired motor functioning", "Informant reported or observed changes in motor functioning", "Subjective complaints of impaired bodily sensation", "Subjective complaints of impaired autonomic functioning", "Suicidality and self-harm" and "Impaired tolerance to normal stress" were entered into the analysis.

Age (p=0.0048), family history of any psychiatric disorder (p=0.0002), major depressive (p=0.0060) and persistent depressive disorder (p=0.0006), CGI-severity scale (p<0.0001), global functioning-social scale (p<0.0001) and CAARMS items "subjective experience of cognitive change" (p=0.0029), "Subjective complaints of impaired bodily sensation" (p=0.030), significantly predicted group membership in our sample. Other variables, i.e. "other specified depressive disorders", duration of psychotherapeutic intervention prior study entry, CAARMS' items "Observed blunted affect", "Anhedonia" and "Subjective complaints of impaired motor functioning" remained into the final model, approached, but did not reach statistical significance (Table 10). Although not statistically significant, these variables were kept into the model as they

contributed to the overall prediction ability of the model itself.

Being older, not having a psychiatric family history, having a depression disorders (major depressive disorders or persistent depressive disorder), being more clinically severe and displaying a lower social functioning associated with a higher chance of being in the APS group than in the non-APS group.

Table 10. Multivariable ordinal regression analysis: model that best predicted group membership

Variables	Estimate	Standard error	Z-value	P-value
Age	-0.3852	0.1367	-2.8185	**0.0048**
Female gender	0.6132	0.4137	1.4819	0.1383
Negative psychiatric family history	1.6322	0.4380	3.7263	**0.00019**
Major depressive disorder	-1.4368	0.5229	-2.7480	**0.0060**
Other specified depressive disorder	-0.9562	0.5092	-1.8778	0.0604
Persistent depressive disorder	-4.3601	1.2755	-3.4182	**0.00063**
Psychotherapy duration prior study entry	0.0244	0.0145	1.6828	0.0924
Subjective experience of cognitive change	0.6313	0.1743	3.6220	**0.00029**
Observed cognitive change	0.2718	0.1664	1.6335	0.1024
Observed blunted affect	0.2992	0.1576	1.8983	0.057
Anhedonia	-0.2012	0.1185	-1.6983	0.090
Subjective complaints of impaired motor functioning	-0.3232	0.1895	-1.7058	0.0880
Subjective complaints of impaired bodily sensation	0.3186	0.1467	2.1710	**0.0299**
CGI-severity scale	1.3400	0.2965	4.5185	**<0.0001**
GF:S	-0.8792	0.2169	-4.0535	**<0.0001**

Longitudinal analysis

As described in the methods section, APS patients recruited until march 2019 were followed up for a median period of 33 months (range 4-81 months). 7 patients (6.4%) were lost at follow-ups, so follow-up data were available only for 103 APS patients.

Based on the clinical judgment of patients' needs, APS patients were offered intensive clinical follow-up assessment (active monitoring) and focused interventions consisting of psychotropic drugs (antipsychotic, antidepressant, mood stabilizers, benzodiazepine) and/or psychotherapy. In detail, all patients were actively monitored and had been prescribed (or invited to continue with) psychotherapy. However, 25 APS adolescents (24.3%) did not start any psychotherapeutic treatment (refusal by the patient was the main reason). For those patients who did start psychotherapy, the treatment lasted on average 19 months (SD=19 months).

At least one psychotropic medication was prescribed to 64 (62.1%) APS participants (antipsychotics n=45, 43.7%, antidepressants n=33, 32.0%, mood stabilizers n= 15, 14.6% and benzodiazepines n=8, 7.8%).

Comparing clinical management of APS with non-APS adolescents, a higher proportion of APS patients had been started on psychotropic medications (62% *vs* 34%, p=0.0002) and this difference was driven by antipsychotics' prescription (43.7% *vs* 13.8%, p<0.0001), while no difference was found in the proportion of APS and non-APS patients prescribed other medications or attending psychotherapy sessions.

Transition rate

During the whole research study period, 21 out of 103 APS patients (20.4%) transitioned to psychosis (APS-T). In detail, 11 APS adolescents transitioned during the first year, 4 during the second, 5 during the third and

1 during the fourth year of follow-up. Of the 82 patients that did not transition, 12 had a follow-up period of less than 1 year, 70 had a follow-up period of at least 1 year, 52 of at least 24-months, 30 of at least 36-months and 17 longer than 4 years.

APS patients that converted to psychosis had a mean number of days to conversion from baseline equal to 423.7 days (SD= 343.5); the mean age at transition was 16.9 years (SD=1.8).

Using a Kaplan-Meyer survival analysis, the cumulative proportion of psychosis transition was 13% (SE=3.9%), 17% (SE=4.7%), 24.2% (SE=6.6%) and 26.8% (SE=7.4%) at 1,2,3 and 4-year follow-ups, respectively.

Of note, one of the patients in the non-APS group developed psychosis during the follow-up period, without displaying attenuated or brief psychotic symptoms in the prodromal period. Interestingly, this patient was characterized by high levels of negative symptoms and had a transition time (time elapsing between the baseline assessment and conversion) equal to 631 days.

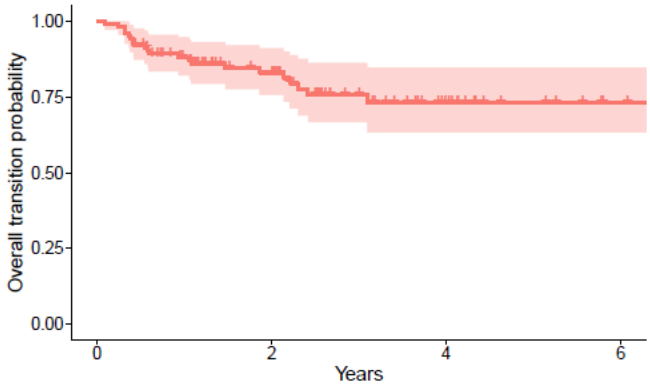

Fig 1. Survival function of APS adolescents (n=103)

Comparison of converter and non-converter APS adolescents

Comparing the baseline socio-demographic, clinical and functioning characteristics of the APS subjects that transitioned to psychosis (APS-T) and non-converters (APS-NT) we found that: APS converters more frequently were adopted (19% *vs* 3.7%, p= 0.04), had a family history of substance abuse (24% *vs* 6.1%, p=0.0073) and conduct disorders (14.3% *vs* 2.4%, p=0.02), had a diagnosis of disruptive, impulse-control and conduct disorder (33.3% *vs* 9.6%, p= 0.02), had been exposed to psychotropic medication prior study entry (61.9% *vs* 34.1%, p=0.04).

Only CAARMS' subscales "avolition/apathy" and "anhedonia" significantly differed between APS-T and APS-NT subjects, with the latter showing significantly lower scores in those two items (average "avolition/apathy" score: 4.0±1.5 *vs* 3.0±2.0, p=0.009, average "anhedonia" score: 2.9±1.9 *vs* 1.9±1.9, p=0.04).

Among neurocognitive variables we compared only Wechsler's scale Total IQ, Indexes and Subscales as the results of the other neurocognitive tests were available only for a minority of patients that developed psychosis.

At baseline APS-T showed significantly worse Total IQ (average Total IQ scores: 92±17.1 *vs* 102.2±15.6, $p=0.02$) and Processing Speed Index scores (88.8±17.7 *vs* 98.4±15.5, $p=0.03$).

Moreover, APS-T already at baseline displayed a significantly lower global (SOFAS average score 42.7±9.3 *vs* 48.5±9.3, $p=0.0092$) and social functioning (GF:S average score 4.1±0.9 *vs* 4.8±1.2, $p=0.015$) and were significantly more severe (CGI-S average score 5.6±0.7 *vs* 4.7±0.8, $p<0.0001$) than APS-NT adolescents.

Of note, APS-T continued to present a significantly lower functioning at 12-months and last follow-up visit (average SOFAS score at 12-months: 37.6±7.0 *vs* 55.2±9.6, $p<0.0001$; average SOFAS at last follow-up visit: 36.3±7.2 *vs* 55.6±12.0, $p<0.0001$).

During the follow-up period, compared to APS-NT, a higher proportion of APS-T was prescribed psychotropic medications (100% *vs* 52.4%, $p<0.001$), specifically antipsychotics (85.7% *vs* 33%, $p<0.001$) and antidepressants (62% *vs* 24.3%, $p=0.0024$) and the duration of both psychotropic and psychotherapy treatment were longer (average duration of psychotropic treatment expressed in months 35±22 *vs* 11±16.3, $p<0.0001$, average duration of psychotherapy treatment 28.9±23.5 *vs* 16.5±16.9, $p=0.037$).

No other significant differences between APS-T and APS-NT were found.

Entering the variables that remained significant in the univariate analyses as well as other variables deemed of clinical relevance in a multivariable regression analysis, none of the variables was significantly associated to transition to psychosis.

Socio-occupational functioning at follow-ups

Although a slight improvement in the socio-occupational functioning in APS patients was observed at follow-ups, at 12 months and last visit follow-ups APS patients overall continued to display a significant impairment in socio-occupational functioning that persisted over time (baseline SOFAS average score 47.3±9.6, average 12-months follow-up 51.7±13.7, average last-visit follow-up SOFAS 51.6±11.5).

As stated above, the dysfunction was higher in APS adolescents that transitioned to psychosis whose functioning significantly deteriorated over time (baseline SOFAS average score 42.7±9.3, 12-months follow up 37.6±7.0, average last-visit follow-up SOFAS 36.3±7.2, $p=0.031$)

Also APS patients that did not convert continued to experience a moderate impairment in their functioning, but they did improve over time (baseline SOFAS average score 48.5±9.3, 12-months follow up average score 55.2±9.6, average last-visit follow-up SOFAS score 55.6±12.0, $p<0.0001$).

One of the aims of our study was to attempt to identify predictors of APS adolescents' socio-occupational functioning at last follow-up visit. To take into account the potential confounding effect of conversion status, this variable was entered into the model as a covariate.

Table 11 shows the final logistic regression model.

Besides conversion status (p=0.04), a higher SOFAS (p=0.0026) and better social functioning (p=0.016) at baseline, not having a baseline diagnosis of anxiety disorders (generalized anxiety disorder, p=0.005 and panic disorder, p=0.003), a longer duration of psychiatric symptoms (p=0.006), a higher total IQ (p=0.02), a lower scores in "Subjective complaints of impaired autonomic functioning" (p=0.02) and a higher score in

CAARMS' "Mania" (p=0.01) items significantly predicted socio-occupational functioning at follow-up.

Table 11. Results of logistic regression analysis of effect of potential predictors on functional outcome (SOFAS at last follow-up visit as a reference value)

Variables	Estimate	Standard error	Z-value	P-value
Age at baseline	0.9992	1.667	0.600	0.56
Length of follow-up	1.873	1.305	1.435	0.17
Female gender	0.7083	3.707	0.191	0.85
Ethnicity: African	13.7941	11.123	1.240	0.23
Ethnicity: Hispanic	-2.3314	8.089	-0.288	0.78
Ethnicity: Albanian	10.956	7.341	1.493	0.15
Ethnicity: eastern Europe	3.2969	7.510	0.439	0.67
Negative psychiatric family history	3.5358	2.774	1.275	0.22
First degree family psychiatric psychotic history	-5.7846	10.202	-0.567	0.58
Presence of negative symptoms	-1.1254	5.007	-0.225	0.82
Number of diagnoses at baseline	4.1546	2.620	1.585	0.13
Major depressive disorder	-0.2935	4.055	-0.072	0.94
Other specified depressive disorder	0.6812	3.748	0.182	0.86
Persistent depressive disorder	5.9621	14.419	0.413	0.68
Generalized anxiety disorder	-15.284	4.838	-3.159	**0.0047**
Separation anxiety disorder	11.716	9.921	1.181	0.25
Panic disorder	-40.054	11.805	-3.393	**0.0027**
Other specified anxiety disorder	-9.1393	5.7144	-1.599	0.12
Social anxiety disorder	0.7394	6.9373	0.107	0.92
Obsessive compulsive and related disorders	-0.8285	5.071	-0.163	0.87
Borderline personality disorder	-5.3897	5.0141	-1.075	0.30
Other personality disorders	-6.5283	4.5015	-1.450	0.16
Bipolar I or II disorder	-9.6359	5.5222	-1.745	0.096
Other specified bipolar disorders	-3.1607	6.537	-0.484	0.63
Anorexia nervosa	-1.706	5.162	-0.331	0.74
Months since psychiatric symptoms onset	0.1937	0.064	3.030	**0.0064**
Total IQ	0.2383	0.096	2.476	**0.022**
CGI-severity scale	1.4821	2.859	0.518	0.61
GF:S	3.810	1.4554	2.618	**0.016**
GF-R	-2.399	1.3185	-1.820	0.083
SOFAS	0.7868	0.2305	3.414	**0.0026**
Transition to psychosis (yes)	-10.120	4.522	-2.238	**0.0361**
Psychotropic treatment during follow-up (yes)	-5.7717	5.6421	-1.023	0.32
Duration of psychotropic treatment during follow-up	-0.2398	0.1463	-1.639	0.12
CAARMS items				
Unusual thought content	-1.061	1.362	-0.780	0.44
Level of distress associated to unusual thought content	0.1110	0.0586	1.896	0.072
Non-bizarre ideas	-2.2831	1.1562	-1.975	0.062
Level of distress associated to non-bizarre ideas	-0.0098	0.0497	-0.197	0.85
Perceptual abnormalities	1.900	1.2145	1.564	0.13
Level of distress associated to perceptual abnormalities	-0.077	0.045	-1.726	0.099
Disorganized speech	-0.050	0.0382	1.316	0.21
Level of distress associated to disorganized speech	-0.0102	0.046	-0.220	0.83
Subjective experience of cognitive change	-1.944	1.4670	-1.325	0.20
Observed cognitive change	-0.801	1.431	-0.560	0.58
Subjective emotional disturbance	0.242	1.5237	0.159	0.88
Observed blunted affect	-2.341	1.3197	-1.774	0.091
Observed inappropriate affect	-0.4867	1.5277	-0.321	0.75
Alogia	-0.1766	1.6140	-0.109	0.91
Avolition/apathy	2.1412	1.1823	1.811	0.084
Anhedonia	-0.8608	1.2336	-0.698	0.49
Aggressive/dangerous behavior	0.0275	1.4452	0.019	0.98
Subjective complaints of impaired motor functioning	1.2749	1.4478	0.881	0.39

Subjective complaints of impaired bodily sensation	0.7115	1.0648	0.668	0.51
Subjective complaints of impaired autonomic functioning	-2.6345	1.066	-2.471	**0.022**
Mania	3.3704	1.203	2.802	**0.011**
Depression	-1.1395	1.4467	-0.788	0.4397
Anxiety	-0.2387	1.2336	-0.193	0.85
Suicidality and self –harm	0.761	0.9697	0.785	0.44
Impaired tolerance to normal stress	0.6427	0.878	0.732	0.47

4. DISCUSSION

In light of the indisputable need for more studies assessing the clinico-pathological significance as well as longitudinal outcomes of APS in clinical samples, especially in children and adolescents, the present longitudinal study aimed to describe the clinical, psychopathological profile and the functioning level of APS adolescents as well as to investigate longitudinal outcomes in terms of transition rates to psychosis and socio-occupational functioning at follow-ups. Given that the identification of prognostic factors is a key step in enabling risk-stratification and personalized risk-adapted treatment, we also attempted to identify predictors of both transition to psychosis and socio-occupational functioning in this underage group.

Considering all adolescent patients admitted to the Child and Adolescent Neuropsychiatric inpatient and outpatient units that underwent our baseline assessment between October 2012 and July 2019, we found an overall APS prevalence of 45.3%. This data is intermediate between that reported in the NAPLS study when considering all help-seeking mixed-age individuals (50.4%) (Addington et al. 2007) and the lower prevalence of 31.7% in unselected adolescent psychiatric outpatients (Lindgren et al. 2014). A similar prevalence was also found in a previous study by our group (Spada et al. 2016) as well as other studies conducted in children and adolescent populations (Poletti et al. 2019). Overall, these findings highlight the presence of a high prevalence of APS when patients are carefully assessed by trained medical doctors or psychologists with the use of standardized interviews specifically designed to evaluate prodromal psychopathology.

APS sample baseline clinical, psychopathological and functioning characteristics

At baseline, poor socio-occupational functioning, especially social functioning, as well as clinical severity as assessed by clinicians were significantly associated with APS status. Indeed, even though APS adolescents displayed a lower level of impairment and were less clinically severe than EOP patients, they were significantly more impaired and severe than non-APS subjects. Our results underscore that subjects fulfilling APS criteria have a marked impairment in functioning, consistent with previous studies in selected at risk populations, outpatients and general population (Kelleher et al. 2012b, 2014; Schultze-Lutter et al. 2014b; Velthorst et al. 2010). Thus, irrespective of their longitudinal outcome and their risk of transitioning to psychosis, support and care in APS patients seems strongly justifiable and therapeutic interventions should specifically address social disability and functional impairment.

Surprisingly if we consider the results of the previous study by Gerstenberg et al. (2015), in our sample both clinical severity and social functioning significantly differentiated APS from non-APS adolescents and were among the variables that best predicted being in the APS rather than in the non-APS group. In children and

adolescents, social isolation is often reported as one of the symptoms preceding the onset of psychosis (D'Angelo et al. 2019; Lencz et al. 2004) and, among the symptoms evaluated by the Child and Youth Version of the Schizophrenia Proneness Instruments (SPI-CY), "decreased need for social contacts" is one of the items that best differentiated between CHR adolescents and clinical controls (Fux et al. 2013).

Besides the scores in the Global Functioning: Social scale, deficit in social functioning was also confirmed in our sample by the results of the CAARMS' item "social isolation" that significantly differed between the three groups, with APS and EOP displaying significantly higher scores than non-APS adolescents.

Overall, our findings are in line with a recent meta-analysis that indicated that high risk state is characterized by marked impairment in functioning, with a functional level closer to that reported in people with psychosis, similar to that observed in some psychiatric disorders, such as major depressive disorder and social phobia and lower than that observed in others, such as bipolar disorder (Fusar-Poli et al. 2015b).

Moreover, although suicidality and self-harm were only assessed in our study through the specific item of the CAARMS, APS adolescents reported a higher level of suicidality compared to non-APS, while no difference was found between APS and EOP subjects. This finding is consistent with previous studies both in adult and adolescent samples (Grivel et al. 2018; Kelleher et al. 2014; Lindgren et al. 2017; Pelizza et al. 2019b; Schmidt et al. 2017; Taylor et al. 2015), further stresses the clinical severity of the APS status and underlines the need of regularly monitoring suicidality as an ongoing risk in these patients.

Furthermore, already at baseline APS adolescents had a level of perceived stress higher than non-APS and similar to that of EOP subjects and, similarly of EOP, had been exposed to psychotropic medications prior study entry for a longer period. These data confirm that APS adolescents are sufficiently disabled by their symptoms to seek for help or to require medical attention (Fusar-Poli and Yung 2012), which are core characteristics of the at-risk criteria.

Of interest, in our sample adolescents who fulfilled APS criteria also had significantly more severe scores in both the parent completed CBCL and self-administered YSR than non-APS adolescents, while no differences were observed in any of the CBCL and YSR's items between APS and EOP. This result is in line with an earlier study where, assessing the prevalence and course of auditory hallucinations in a sample of children, 12 and 13 years of age, young adolescents who disclosed psychotic symptoms were found 3-5 times more likely to score in the clinico-pathological range of the CBCL total score (Bartels-Velthuis et al. 2011). Similarly, Meyer et al. (2005) observed that 94% and 63% of at-risk adolescents scored within the clinically significant range for Internalizing Problems and Externalizing Problems, respectively. In our sample, mothers of APS adolescents reported higher scores in the subscales describing their child being "Withdrawn", having "Social problems" and "Thought problems" compared to mothers of non-APS patients. In line with that, in another study, Simeonova et al. (2014) evaluating the validity of the CBCL as a screening tool to identify at-risk youth found that two individual CBCL rating scales, "Withdrawn/Depressed" and "Thought Problems", discriminated between them and neuropsychiatric controls. Our data further support previous evidence that most APS adolescents are viewed by their parents as suffering from significant behavioral problems. Not surprisingly, besides Total score, the Internalized score of YSR and caregivers' CBCL significantly

differentiated APS from non-APS adolescents. Indeed, affective symptoms, i.e. depression and/or anxiety, were the most frequently reported reasons to seek help at a specialized early intervention service ("Outreach and Support in South London") (Falkenberg et al. 2015).

One of the main findings of our cross-sectional analyses is that the APS group displayed a higher number of comorbid disorders compared to the EOP and non-APS and, interestingly, was not related to a single diagnosis or group of diagnoses, but to a wide range of disorders.

In line with the results of population-based studies and clinic-based research conducted in children and adolescents (Armando et al. 2015; Gerstenberg et al. 2015; Kelleher et al. 2012b, 2014; Lindgren et al. 2019; Meyer et al. 2005; Schultze-Lutter et al. 2014b; Welsh and Tiffin 2014), the finding of a higher number of comorbid disorders confirms previous evidence of an association between APS status and other mental disorders in adult and mixed-age samples (Albert et al. 2018; Fusar-Poli et al. 2014b; Salokangas et al. 2012a). Indeed, in our sample 30.9% of APS patients had more than two DSM-5 diagnoses. Similarly, Kelleher et al. (2014) found in 108 adolescents newly referred to mental health outpatient services that 46% of young people who reported psychotic experiences (hallucinations or delusions in an attenuated form) had three or more diagnoses compared with 19% of young people without psychotic experiences. In addition, approximately 41% of at-risk subjects displayed two or more psychiatric diagnoses in a recent study comparing 91 at-risk youth younger than 18 years recruited in Child and Adolescent Psychiatry and Psychology departments at Hospital Clinics (Dolz et al. 2019).

Of note, in our study several axis-I and II disorders resulted associated with APS status.

In our APS sample depressive disorders, mainly major depressive and other specified depressive disorders, were the most frequent diagnoses at baseline, followed by anxiety disorders, mostly generalized anxiety disorder. Furthermore, depressive disorders were among the variables that best predicted belonging to the APS rather than non-APS and EOP groups at the multivariable analysis. The association of major depressive and other specified depressive disorders as well as anxiety disorders is consistent with a recent meta-analysis that found a high prevalence of comorbid depression (41%) and anxiety (15%) (Fusar-Poli et al. 2014b) as well as with the results of the NAPLS study where lifetime MDD rates were shown to be higher in high-risk patients compared to help-seeking subjects not fulfilling at-risk criteria (Woods et al. 2009).

Furthermore, retrospective studies in first-episode psychotic patients indicated that affective disturbance is frequently described as one of the initial symptoms in the "early" prodromal phase (Häfner et al. 1999).

The high prevalence of depression and anxiety in addition to attenuated psychotic symptoms, led to the hypothesis that these symptoms could be phenomenologically connected and reflect core emotional dysregulation processes and delusional mood in prodromal psychosis (Mishara 2010).

The high prevalence of personality disorders in our APS adolescent patients, is very similar to that reported in the Prevention through Risk Identification, Management and Education (PRIME) study and NAPLS (Rosen et al. 2006; Woods et al. 2009) and consistent with recent findings that prevalence rates of any personality disorder in CHR patients are four-times higher than those in the general population (Boldrini et al. 2019). Contrary to Gerstenberg et al. (2015), in our study personality disorders overall and not borderline personality

disorder specifically were associated with APS status. Our data support the lack of a specific personality profile in high risk subjects in line with negative findings in an age-mixed sample (Schultze-Lutter et al. 2015a).

In our sample, obsessive-compulsive and bipolar disorders were also significantly more prevalent in APS adolescents compared to non-APS.

The presence of prior obsessive-compulsive disorder (OCD) is associated with an increased risk of developing schizophrenia (Meier et al. 2014) and its prevalence in patients at clinical high risk exceeds that in the general population and is associated with positive and depressive symptoms and suicidal ideation (DeVylder et al. 2012; Fontenelle et al. 2011; Sterk et al. 2011). However, little is known about the significance of at risk symptoms in children and adolescents with obsessive compulsive disorders. One previous study in APS adolescent patients did not find a significant correlation between APS status and OCD (Gerstenberg et al. 2015), while a recent research found a high prevalence of at-risk symptoms (43.1%) in adolescents with obsessive-compulsive disorders and OCD patients fulfilling CHR criteria reported worse functioning (Averna et al. 2018). In our sample OCD was significantly more frequent in APS than non-APS, supporting the idea of a continuum between the two disorders. However, our finding was based on a small proportion of patients (11% of the sample) and further replication studies are needed.

Hypomanic and manic symptoms are less frequently reported in help-seeking individuals, nevertheless in our sample bipolar disorders were present in a higher prevalence in patients fulfilling APS criteria. Interestingly, in the EPOS study, alongside somatoform disorders, bipolar disorders were the fourth most common diagnoses following anxiety and depression and were significantly associated with transition to psychosis (Salokangas et al. 2012a). Thus, it is possible that during the prodromal phase patients experience a state of emotional disturbances and affective lability that does not manifest only with depressed mood but also with hypomanic and manic symptoms. Furthermore, in adolescents, the high risk state for psychosis may be indistinguishable from the bipolar prodrome (Olvet et al. 2010). Since depression and hypomania can be precursors of both non affective psychotic disorders and bipolar disorders, in these patients careful monitoring is needed and treatment options should be thoroughly weighted (Hauser and Correll 2013).

Overall, APS diagnosis in children and adolescents may be superimposed on other spectra, such as mood, anxiety and personality disorders, with the results that the global picture could appear even more blurred than in adults.

A broad variety of non-psychotic symptoms, as assessed by the CAARMS, were significantly more frequent and severe in APS adolescents than non-APS and, for some of them, the APS group shared similarities in severity with the EOP group.

As expected, APS adolescents reported intermediate scores between non-APS and EOP patients in all positive psychotic symptoms. Consistent with earlier studies on adolescents conducted in research settings (Armando et al. 2015; Cornblatt et al. 2007; Meyer et al. 2005; Welsh and Tiffin 2014), the most severe, frequent and distressing positive symptoms in our sample were perceptual abnormalities and non-bizarre ideas (mainly suspiciousness), while disorganized speech was the least intense and distressing.

In addition to diagnostic items, between group significant differences emerged in the severity and frequency

of a wide range of non-psychotic symptoms belonging to different CAARMS subscales. Regarding the general psychopathology subscales, higher intensity and frequency in the depression, mood swings, anxiety and OCD symptom items mirror previous findings on the high prevalence of comorbidity with mood, anxiety and OCD disorders in our APS adolescent patients.

Of note, although the CAARMS scale was not specifically designed to assess basic symptoms, among non-psychotic symptoms, except for subjective complaints of impaired autonomic functioning, in univariate analyses all Huber's basic symptoms assessed by the CAARMS (i.e. cognitive change-subjective experience, subjective emotional disturbance, subjective complaints of impaired motor functioning, subjective complaints of impaired bodily sensation, avolition/apathy, impaired tolerance to normal stress) significantly discriminated between APS and non-APS adolescents and the APS group displayed a level of severity that did not significantly differ from that of EOP subjects.

Our results, linking basic symptoms to APS status, confirmed earlier studies of first-episode psychotic adolescents who reported subtle subjectively experienced cognitive and perception disturbances preceding the onset of full-blown psychosis (Meng et al. 2009; Szily and Kéri 2009). Good discriminative validity of basic symptom criteria in children and adolescents as assessed using specifically developed instruments, such as Schizophrenia Proneness Instrument, Child and Youth Version (SPI-CY), has been demonstrated (Fux et al. 2013). The authors advocated that combining the UHR and BS criteria could be extremely useful especially in children and adolescents in which differentiating between aspect of normal behavior or behaviors linked to non-psychotic disorders and emerging psychosis can be at times very difficult. Furthermore, the presence of both BS and APS increased predictive power for conversion to psychosis in mixed-age samples (Schultze-Lutter et al. 2014a).

Moreover, in multivariable analysis, among all non-psychotic symptoms, only greater cognitive change-subjective experience and subjective complaints of impaired bodily sensation significantly predicted being in the APS rather than in the non-APS status. Our data support the fundamental role of cognitive disturbances discriminating between schizophrenia spectrum disorders and other psychiatric disorders. In fact, in an earlier study, comparing basic symptoms in adolescents first admitted for early onset psychosis and non-psychotic psychiatric disorders, the best two items discriminating between the two groups were "thought interference" and "difficulty in concentrating" (Meng et al. 2009). Overall, anomalous self-experience, such as cenesthesic changes and unusual cognitive experiences, are known to be prevalent during the prodromal stage of help-seeking adolescents, they constitute a potential risk dimension and remain prominent during the course of schizophrenia (Koren et al. 2013; Lo Cascio et al. 2016; Pienkos et al. 2019).

The results of our study confirm that APS adolescents present high levels of negative symptoms (alogia, anhedonia and avolition/apathy), similar to those observed in EOP adolescents. These findings are in line with a previous study in CHR children and adolescents where the authors found a negative symptomatology profile in CHR patients overlapping with that of FEP patients (Poletti et al. 2019). In our sample, in fact, the level of anhedonia and abulia did not differ between EOP and APS patients and both groups had significantly higher scores than non-APS patients. The presence of negative symptoms, especially experiential (amotivation,

asociality and anhedonia) is often endorsed in the phase preceding psychosis onset (Jhung et al. 2016; Piskulic et al. 2012) and, according to the clinical staging model, they seem to characterize the earliest phase of the prodromal stage (Carrión et al. 2016; McGorry et al. 2006). Interestingly, as stated above, a recent study, found that the prevalence of amotivation, alogia, asociality and blunted affect decreases between CHR and FEP stages (Sauvé et al. 2019). It may be that attenuated negative symptoms constitute a core feature of vulnerability in CHR youth representing a key target for early intervention. Although in need of replication, our findings support the hypothesis that, in adolescent patients, negative symptoms are clinically significant markers of the APS status. Of note, in a recent study conducted in a CHR adolescent population, severe deficits of the ability to feel pleasure and to participate in pleasing activities were found; anhedonia associated with more severe impairment in functioning and worse quality of life (Pelizza et al. 2019a).

The presence of a high prevalence of comorbid disorders as well as non-psychotic symptoms in APS adolescents, besides underlining the clinical complexity of the APS status, further highlights the need in help-seeking youth not to focus the attention only on attenuated psychotic symptoms as markers of psychosis risk, but to move towards a multidimensional approach where the full-range of the psychopathology is taken into account (van Os and Guloksuz 2017). This is relevant and in line with the proposed model of "pluripotent risk syndrome" where APS patients, especially in adolescence, are not only at higher risk of developing psychosis but also other mental disorders that have their onset from initial non-specific symptoms and lead to functional deterioration (Fusar-Poli et al. 2014c; Tor et al. 2018; Yung et al. 2012). Thus, clinicians dealing with APS youth need to carefully look for the presence of other mental disorders and non-psychotic symptoms that, when present, constitute one of the main targets of the intervention and treatment plan (Schmidt et al. 2015).

In a subset of patients, we attempted to compare the neurocognitive profile of EOP, APS and non-APS adolescent patients. While discussing our findings, it is important to take into account that they were derived from a small sample and should be considered with caution. In line with previous literature, we did find significant between group differences in several cognitive domains (executive function, working memory and processing speed) (Mollon et al. 2018; van Os and Kapur 2009). However, this difference was mainly driven by EOP patients that displayed significantly more severe deficits than non-APS subjects. Even if APS and non-APS adolescents did not significantly differ in any of the tests administered, a worsening trend was observed between the two groups with lower scores in APS adolescents (especially in the Total IQ, Processing Speed and its subscales Coding and Symbol Search, expressive language, digit span forward and backward, visual and auditory selective attention test, Elithorn Perceptual Maze Test).

Of interest, even though APS subjects did not appear to be significantly more impaired than non-APS individuals at the objective neurocognitive assessment, APS patients reported significantly higher scores at the CAARMS subscale "subjective experience of cognitive change" describing subjectively perceived, subclinical abnormalities in concentration, memory and attention. We can hypothesize that our APS patients were in an early phase of their at-risk state where, even if subjective cognitive changes were already ongoing, their level was not as prominent to be detected by objective measures. Moreover, in our study we compared APS patients with clinical controls, or rather adolescents suffering from mental disorders other than APS or psychosis. It is

thus possible that we did not identify a specific neurocognitive profile in APS as patients in the control group could as well present deficits in several cognitive domains due to their underlying psychiatric condition (Castaneda et al. 2008; Cortese et al. 2015; Elias et al. 2017).

Overall, although in need of replication, our baseline results show that APS adolescent patients suffer from a variety of comorbidities and non-psychotic symptoms and are markedly impaired compared to non-psychotic adolescent not fulfilling APS criteria. This finding is relevant to address criticism over the possible pathologization of non-ill behaviors in children and adolescents that has been raised against the inclusion of APS diagnosis in DSM-5.
Confirming previous results in adults, our data further stress that APS adolescents are truly in need of care.

Transition rate

In the present study, using a survival analysis, the cumulative proportion of psychosis transition in the APS group was 13%, 17%, 24.2% and 26.8% at 1,2,3 and 4-year follow-ups, respectively; the mean number of days to conversion from baseline equalled to 423.7 days and the mean age at transition was 16.9 years.
In children and adolescents, as stated in the introduction, transition rates appear to be lower than in adults (Tor et al. 2018) were both UHR and BS criteria are associated with pooled 1-3 year conversion rates to psychosis ranging from 15% to 29% for UHR and from 14% to 50% for BS criteria (Fusar-Poli P et al. 2012; Schultze-Lutter et al. 2015b). In the underage population, the results are highly heterogeneous among different studies, with transition rates ranging from a short-term transition risk of 3% to a cumulative 2-year transition risk of 21%, (Armando et al. 2015; Lindgren et al. 2014; Pelizza et al. 2018; Poletti et al. 2019; Welsh and Tiffin 2014; Ziermans et al. 2011) and/or longer transition times compared to adults (Cornblatt et al. 2007). These mixed results could be explained by differences in recruitment strategies as well as other methodological issues, such as differences in the management and treatment offered during the follow-up phase (Fusar-Poli et al. 2016d).
Our results appear in line with the previous work of Ziermans where the authors found, in a sample of 57 CHR adolescents, a cumulative 2-year transition rate of 15.6%, a mean number of days to transition from baseline equals to 315.5 days and a mean age at transition of 16.9 years (Ziermans et al. 2011). Another study from the same group reported that 23.3% of CHR adolescents converted to psychosis at a 6-year follow-up (Ziermans et al. 2014). Moreover, in the follow-up study conducted in the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne in 311 youth aged 15 to 30 years, the estimated transition rates were 16.5%, 20.4%, 24.9% and 27.6% at 1,2,3 and 4 years from baseline assessment (Nelson et al. 2013). Conversely, our current results contrast with the finding of a cumulative 1-year transition risk of 26.7% in our previous work (Spada et al. 2016). However, recently a decline in transition rates has been reported in adult and age-mixed samples (Fusar-Poli et al. 2018b; Hartmann et al. 2016). As our patients where mainly referred by child and adolescent psychiatrists working in the inpatient and outpatient units of the same hospital where the research took place, it is possible that, after the setup pilot period of our service to which the patients included in the

first paper belonged, the referring child and adolescent psychiatrists became more familiar to the service and to the research team and started referring more patients to it, including false-positive patients (dilution effect) (Fusar-Poli et al. 2016d) or subjects in an earlier phase of the disorder (lead-time bias) (Wiltink et al. 2015).

In line with previous literature in adults (Kempton et al. 2015), in our sample the risk of transitioning was maximal in the first 24 months after study entry (15/21 APS patients transitioned during the first two years, 71.4%). However, although reduced, there was an ongoing rate of transition after the second year of follow-up and 5 patients developed psychosis during the third and 1 during the fourth year of follow-up. These results are consistent with previous researches that showed that at-risk patients continue to display a high risk and can transition to psychosis up to 10 years after initial assessment (Nelson et al. 2013). Thus, also and especially in adolescents, it seems important to monitor these patients and follow them up for at least two years and, hopefully, for a longer period.

It is important to observe that a high percentage of APS patients received at least one psychotropic medication (62.1%) during the follow-up period, although the majority of APS (56.3%) took medications combined with psychological interventions. Moreover, significantly more APS adolescents were started on psychotropic medications than non-APS participants and this difference was driven by antipsychotics' prescription that was present in 43.7% of APS adolescents. Of note, 34 APS adolescents exposed to antipsychotics did not develop psychosis at follow-ups. This data could elicit two different observations: it could be that antipsychotic medications were effective in delaying or preventing the psychosis onset, but, on the other hand, it could also imply that antipsychotic medications were administered to "false positive" subjects that would never develop psychosis exposing them to the potential worrisome side effects of these medications (Vitiello et al. 2009). Moreover, in our sample 11 APS patients transitioned to psychosis even though they were prescribed antipsychotic medications.

To date, only limited and sparse evidence suggest the use of antipsychotics in at-risk subjects and clinical trials evaluating the potential therapeutic effect of these drugs in preventing psychosis were limited by short duration and small sample size (Liu and Demjaha 2013). Moreover, recent meta-analyses did not find evidence of the superiority of any specific intervention over the others in preventing psychosis onset nor in improving attenuated positive psychotic symptoms (Davies et al. 2018b, 2018a) and antipsychotic medication do not appear more effective in reducing transition risk than less harmful interventions (McGlashan et al. 2006; McGorry et al. 2013; Morrison et al. 2004) .

In accordance with several national and international guidelines (Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology 2011; Schmidt et al. 2015) and current knowledge, in at-risk patients, especially in children and adolescents, antipsychotics should not be used as a first line treatment and considered only when psychological interventions have not been effective, they should be prescribed at a low dose and only for short-term periods.

Several factors significantly differentiated APS patients that developed psychosis to adolescents that did not transition.

In our adolescent sample having a lower global and social functioning at baseline was associated with

transitioning to psychosis at follow-ups. This finding is consistent with previous literature in adults that identifies baseline functioning as a robust predictor of later transition to psychosis (Addington et al. 2017; McLaughlin et al. 2016; Nelson et al. 2013).

Indeed, in a recent meta-analysis, including 10 studies conducted mainly in adult samples, high-risk subjects that later developed psychosis had poorer functioning at baseline (Fusar-Poli et al. 2015b). Moreover, the 2-year transition risk of adult subjects experiencing psychotic-like symptoms, but with good functioning, is very low (approximately 1.2%) (Kaymaz et al. 2012). Although in need of replication, our data support the hypothesis that also in underage populations, a decline in global and especially social functioning at baseline could be a risk factor for transitioning to psychosis, thus, representing a key target for early intervention in APS patients. Indeed, it appears essential not to focus only on symptoms, but also on functioning levels and to develop psychological and social intervention aimed at improving social functioning that, besides being beneficial per se, could reduce the risk of conversion (Nelson et al. 2013).

Among all symptoms evaluated in our APS adolescent sample, only negative symptoms "avolition/apathy" and "anhedonia" significantly differed between the transition and the non-transition group, with the latter showing significantly less severe scores in those two items. The finding of an association between negative symptoms and transition is not new in adult populations; in fact several longitudinal studies in age-mixed CHR samples showed that attenuated negative symptoms robustly predict psychosis onset (Brucato et al. 2017; Nelson et al. 2013; Piskulic et al. 2012). It may be that attenuated negative symptoms constitute a core feature of vulnerability in CHR youth representing another key objective for early intervention and this could be especially true for children and adolescents where the onset of negative symptoms is much earlier than attenuated positive symptoms and they are associated with long-term social deficits (Carrión et al. 2016).

Also, being adopted and having a positive family history of substance abuse and conduct disorders were associated in our APS adolescent sample to later transition to psychosis. As shown also by a recent meta-analysis CHR individuals have an increased probability of developing psychosis that can be related to several environmental risk factors (Fusar-Poli et al. 2017d). To our knowledge, no previous work has highlighted the association of adoption status to higher risk of developing psychosis, while positive family history of psychosis as well as other nonpsychotic psychiatric disorders distinguished at-risk subjects from healthy controls and help-seeking subjects not fulfilling at-risk criteria (Woods et al. 2009). However, our results need to be considered cautiously as only 7 APS patients (6.3%) were adopted, 10 (9.1%) had a family of substance abuse and 5 (4.5%) of conduct disorders and further replication studies are needed.

As stated in the introduction, candidate prognostic factors to refine the prediction of clinical outcome may include cognitive and neuropsychological factors (Palmer et al. 2009). Notwithstanding, the course and prognostic relevance of neurocognitive factors in underage CHR populations is not well established. Our results, highlighting the association of a lower IQ and transition to psychosis, are consistent with a study conducted in a small sample of CHR adolescents where the only neurocognitive parameter that differentiated those who converted to psychosis from the ones that did not at 6-year follow-up was baseline low IQ (Ziermans et al. 2014). However, in our adolescent population also scores in the Processing Speed Index were

significantly worse in APS patients that converted to psychosis. Deficits in the processing speed domain were found to be predictors of conversion in meta-analyses conducted in age-mixed samples (Fusar-Poli et al. 2012a; Hauser et al. 2017a). As stated in the introduction, this cognitive domain has attracted special attention. Some authors have hypothesized that it could represent the core of schizophrenia cognitive impairment in agreement with the "disconnection" hypothesis of schizophrenia that postulates that full-blown symptoms manifest when a focal dysfunction has a substantial adverse effect on the whole brain network (Bullmore et al. 1997; Kelleher et al. 2013b). While, in fact, other neurocognitive functions are linked with prefrontal and temporal lobe cerebral regions, processing speed is considered to be "system" based depending on a process of integration and coordination between brain networks. Indeed, studies applying the digital tractography imaging technique showed an aberrant functional connectivity between whole brain neural systems in patients with deficits in speed of processing (Turken et al. 2008) .

Overall, our findings, although in need of replication, suggest that APS adolescents that enter early intervention services with lower global and social functioning, high levels of negative symptoms and lower scores in the total IQ and speed of processing should be carefully monitored as they seem to present a higher risk of developing psychosis. If confirmed these results could indicate that these variables constitute promising candidate for improving risk prediction and could be considered in future revisions of the at-risk criteria, especially in children and adolescents where current criteria appear less predictive than in adult samples.

Functional outcome

Of interest, in the present study we did not only investigate conversion to psychosis, but we also evaluated functional outcome in terms of socio-occupational functioning at follow-up as a clinically meaningful outcome measure. Assessing longitudinal functional outcomes, besides the risk of transition, seems especially important in underage populations given the concerns about the use of at-risk criteria in this age range where several authors have highlighted that these symptoms appear to be more common and transient than in adults and could, more often, represent normative experiences (Bartels-Velthuis et al. 2016; Schimmelmann et al. 2013b). Notably, in this study, although a slight improvement in the socio-occupational functioning in APS adolescent patients was observed at follow-ups, at 12 months and last visit follow-ups APS adolescents overall continued to display a significant impairment in socio-occupational functioning that persisted over time. Moreover, even if the dysfunction was higher in APS adolescent that transitioned to psychosis, also APS subjects that did not convert continued to experience a moderate impairment in their functioning that, although improving significantly from a statistical point of view, was still in the range of a "moderate difficulties in social or occupational functioning" with only a moderate change from a clinical point of view.

Our findings are in line with literature in age-mixed and adult samples. In fact, previous studies have highlighted that functional impairment in at-risk subjects appear to be stable over time and poor social functioning is persistent at follow-ups in at least half of those who do not develop psychosis (Cornblatt et al. 2012) (Addington et al. 2011). Similar to the work of Addington et al. (2011), we found a moderate improvement in non-converters, nevertheless their functioning level was still moderately impaired and 43 out

of 82 (52.4%) non-converters continued to display poor functioning (SOFAS score lower than 60).

Our results underscore the need, also and especially in adolescents, not to focus only on transition risk, as APS adolescents appear to be both at risk of conversion to psychosis and functional disability persistent over time. Thus, preventive interventions should not only target emerging psychosis, but also improving APS social and global functional impairment.

As a main objective of early intervention research is to understand potential prognostic factors associated with poor outcomes, one of the aims of our study was to attempt to identify predictors of APS adolescents' socio-occupational functioning at follow-up.

Besides conversion status, other baseline variables were significantly associated with later socio-occupational functioning.

In our study, having a better socio-occupational and especially social functioning at the time of study entry significantly predicted having a better socio-occupational functioning at follow-ups. In several studies, both in subjects suffering from chronic schizophrenia and first-episode psychosis (Barajas et al. 2013; Fenton and McGlashan 1987), premorbid functioning was one of the most robust predictors of later functional outcome (Chang et al. 2013). More recently, studies in age-mixed samples have confirmed this strong association also in at-risk patients (Brandizzi et al. 2015; Carrión et al. 2013). Given that social competencies deficits, withdrawal and social decline emerge, already in adolescence, during the earliest phases of the at-risk stage, sometimes long before the onset of the full-blown disorder (Cornblatt et al. 2003; Hans et al. 2000) and appear to be linked with such a disabling outcome, it is essential to carefully assess, monitor changes in functioning in APS adolescents and tackle them as soon as possible.

Deficits in premorbid childhood IQ long before the onset of full blown schizophrenia have been extensively documented in adults (Woodberry et al. 2008). In our sample, besides being associated with later transition to psychosis, in contrast with the long-term follow-up study by Ziermans et al (2014), low total IQ was also predictive of poor socio-occupational functioning at follow-up. In young patients, cognitive impairments, leading to a generalized slowdown in the understanding and reaction to new information as well as deficits in encoding and recall facts and previous knowledge, may prove to be particularly debilitating, leading to difficulties in social interaction and possible isolation as well as greater effort in keeping up with school and academic tasks (Carrión et al. 2011). Given that, to date, only a subset of patients had undergone the extensive neurocognitive assessment, we could not thoroughly investigate the relationship between specific cognitive domains and socio-occupational functioning at follow-up. However, our result of an association between baseline Total IQ and later global functioning supports the need, also in children and adolescents, to look for specific neurocognitive predictors of long-term functional outcome.

Another interesting finding of our study is the association in APS adolescents of baseline anxiety disorders with poor socio-occupational functioning at follow-up.

In FEP patients, the co-occurrence and the severity of anxiety constitute an important factor in determining clinical non-remission and anxiety has been linked to social functional deficits as well as self-reported social functioning and increased relapse rate (Cacciotti-Saija et al. 2018; Montreuil et al. 2013).

In at-risk individuals anxiety disorders are often present as comorbid diagnoses and anxiety symptoms are frequently reported as main subjective reasons to seek help (Fusar-Poli et al. 2014b). Furthermore, CHR subjects often considered these symptoms even more disabling that attenuated psychotic symptoms (Falkenberg et al. 2015).

In a recent study, 51% of 756 CHR individuals had an anxiety disorder, with higher and more severe levels of anxiety compared to controls; anxiety appeared to be linked to attenuated psychotic symptoms especially suspiciousness (Lim et al. 2015; McAusland et al. 2017) . High levels of anxiety have also been reported in at-risk adolescent samples (Tor et al. 2018). Based on the results of previous studies, anxiety does not seem to be associated with a higher risk of transitioning to psychosis. However, the results of our study, although in need of replication, suggest a potential role of anxiety in determining APS adolescents lower functional outcome (socio-occupational functioning). Recently specific interventions to reduce the level of anxiety have been implemented in at-risk subjects with promising results (McAusland and Addington 2018); they could be useful adjunctive treatment not only with the aim of reducing the distress associated to anxiety itself but also of improving the overall baseline and long-term socio-occupational functioning.

4.1 LIMITATIONS

One of the main limitations of this study is represented by the heterogeneous character of the sample in terms of treatments (active monitoring, use of psychotropic medication or psychotherapy). These treatments could have had a significant effect on transition rate to psychosis as well on socio-occupational functioning at follow-ups, as seen in previous studies (van der Gaag et al. 2013).

Moreover, we did not exclude patients that had been treated with antipsychotics prior study entry. However, only a small proportion of adolescents had been exposed to these medications (6% APS; 3% non-APS), there was no significant difference between the percentage of non-APS and APS patients that were exposed to antipsychotics and the reasons for prescription were not linked to psychotic symptomatology, but rather to aggressive behavior or mood instability. While this could have affected the results, the naturalistic design and inclusion of patients that were consecutively admitted to inpatient and outpatient units increase the generalizability of the results.

Moreover, as we included patients recruited at a third-level center, it is possible that our subjects were more severe and clinically impaired than that recruited from the community or mental health services (Fusar-Poli et al. 2016d), thus, representing a more severe spectrum of the APS status.

Results about neurocognitive variables need to be carefully evaluated as they were derived from a small sample size.

Furthermore, as already stated, some of the symptoms (basic symptoms and suicidality) were not assessed using instruments specifically designed for their assessment. However, besides determining whether an individual meets criteria for “at risk mental state” one of the main aims of the CAARMS is to map a wide range of psychopathology and functioning factors.

Finally, although no formal inter-rater reliability testing was performed, a major strength of the current study

is the use, in children and adolescents, of an extensive standardized diagnostic assessment that included clinical interviews, semi-structured clinical interviews (SCID-I and II (First et al. 1996, 1997), K-SADS-PL (Kaufman et al. 1997) and self-administered questionnaires administered to both parents and patients (CBCL (Achenbach 1991a) and YSR (Achenbach 1991b)) that was conducted by highly trained medical doctors.
Despite these limitations, it is worth noting that longitudinal studies, in particular with a follow-up longer than 2 years, are rare in this age range and usually conducted with smaller sample size.

4.2 CONCLUSIONS

Although in need of replication and despite the shortcomings described above, our findings support the validity and clinical relevance of the identification of APS in children and adolescents. Indeed, in our sample APS adolescents suffer from a variety of comorbidities and non-psychotic symptoms, present higher suicidality and are markedly impaired compared to non-psychotic adolescents not fulfilling APS criteria. Moreover, they show a cumulative transition risk to psychosis of 26.8% at 4 years that, although being lower to that found in adult samples, is still comparable to that of other conditions in preventive medicine, such as clinical isolated syndromes in multiple sclerosis (Beck et al. 2004; Thrower 2007). Of note, in line with previous literature in adults (Kempton et al. 2015), in our sample, APS adolescents continue to display a high risk and can transition to psychosis up to several years after initial assessment. Thus, also and especially in adolescents, it seems important to monitor these patients and follow them up for at least two years and, hopefully, for a longer period. Moreover, besides the risk of transitioning, at 12 months and last visit follow-ups APS adolescents overall continued to display a significant impairment in socio-occupational functioning that persisted over time.
However, unlike in other conditions treated in preventive medicine, the identification of robust predictors of outcome is still in its infancy in at-risk children and adolescents.
Characterizing at-risk subjects and identifying predictors of different clinical and functioning pathways, course and long-term outcomes represents a crucial step to enable risk stratification and personalized, risk-adapted treatment. In our study, social-occupational functioning as well as Total IQ and Processing Speed Index seem promising prognostic factors both of conversion to psychosis and long-term functioning. Future studies, in large children and adolescent samples, besides replicating these findings, will have to explore other potential prognostic factors, such as neuroimaging markers (Borgwardt et al. 2011; Fusar-Poli et al. 2012c). In line with this, our group has just set up a research protocol, that will expand the previous one, where also MRI acquisition and image processing will be conducted in APS patients. Studies focusing on neuroimaging markers could also shed light on the physiopathological process underlying APS status.
Overall, confirming previous results in adults, our data further show that APS adolescents are truly in need of care and treatment that should not only be focused on potential transition to psychosis, but also on global and especially social functioning as well as current mental state and problems. Our data also highlighted an alarming high antipsychotics prescription rate in APS adolescents. As stated by the European Psychiatric Association (EPA) guidelines, a stage-intervention model should be applied with psychological interventions

being offered as first choice, implemented with pharmacotherapy only in case they have proven ineffective, at the lowest dosage and for the shortest period of time (Schmidt et al. 2015). In APS children and adolescents a multidimensional treatment plan including careful monitoring for a potential progression, psychological interventions aiming at improving functioning and interventions targeting co-morbid mental disorders and symptoms is strongly recommended.

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