Is it still correct to differentiate between early and very early onset psychosis?

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ABSTRACT

Objective: It remains unclear whether very early onset psychosis (VEOP; ≤12 years of age) and early onset psychosis (EOP; onset 13–17 years of age) are homogeneous in their clinical presentation. We investigated the predictive value of age of psychosis onset for severity, functioning and demographic variation by: 1) comparing groups based on traditional cut-offs for age of psychosis onset, and 2) using receiver operating characteristic (ROC)-curve calculations, without a priori age of onset cut-offs.
Method: Participants were 88 (45 female, 43 male) children and adolescents with a recent onset of psychosis (age range = 6.7–17.5 years; $M = 13.74$, $SD = 2.37$).
Results: The VEOP group had significantly shorter duration of untreated illness and untreated psychosis, and lower functioning than the EOP group. The VEOP and EOP groups did not differ significantly on gender proportion, urbanicity, psychotic diagnosis, family history of psychotic disorder, psychotic, depressive and anxiety symptoms or IQ. When applying ROC-curves to the lowest three quartiles of positive psychotic symptoms scores, the optimal age-cut-off was 14.0 years (sensitivity = 0.62; specificity = 0.75). For the highest quartile of functioning scores, the optimal differentiating cut-off for age of psychosis onset was 14.7 years (sensitivity = 0.71; specificity = 0.70).
Conclusions: Larger samples of patients, assessed at presentation and followed-up, are necessary to clearly examine clinical presentation and outcome as a function of social and neural development to better understand if the differentiation between VEOP and EOP is justified. This will aid the development of predictive diagnostic tools, more accurate prognosis prediction, and age-tailored therapeutic interventions.

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1. Introduction

Schizophrenia is a heterogeneous clinical syndrome of unknown aetiology, comprising a number of psychopathological domains and patients vary considerably in which pathologies are manifest (Insel, 2010). In accordance with this definition, symptoms of schizophrenia are heterogeneous, even within the same age group (Carpenter and Buchanan, 1989). Besides the heterogeneity of the clinical presentation, some differences related to the age of onset (i.e. premorbid abnormalities, longer duration of untreated psychosis [DUP], poorer outcome) have been highlighted (Armando et al., 2015). Consequently, the need of age-specific research in the area of psychosocial treatments for

children and adolescents with schizophrenia has been argued (Tiffin and Welsh, 2013).

In accordance with this evidence, a distinction has traditionally been made between adult-onset psychosis (AOP; ≥18 years of age) and early onset psychosis (EOP; onset <18 years of age), which occurs in approximately one-third of all patients diagnosed with a psychotic disorder (Madaan et al., 2008). While this cut-off is arbitrary, there is evidence that psychotic illness which begins before the age of 18 tends to be more severe than AOP (Rabinowitz et al., 2006; Reichert et al., 2008; Kumra and Schulz, 2008; Díaz-Caneja et al., 2015). Compared to AOP, EOP is more strongly associated with premorbid social impairments, DUP (Hollis, 2003; Schimmelmann et al., 2007), a more severe clinical course (Werry et al., 1991; Eggers and Bunk, 1997), more severe premorbid neurodevelopmental abnormalities (Vourdas et al., 2003), greater genetic loading (Kumra and Schulz, 2008), and more severe negative symptoms (Pencer et al., 2005; Kao and Liu, 2010).

While the differences between AOP and EOP are well supported, there is still debate regarding whether EOP should be considered as a homogeneous entity. Most commonly, the cut-off of psychosis onset at or before 12 years of age is used; that is, EOP with onset between 13 and 17 years of age (sometimes referred to as adolescent onset psychosis) and very early onset psychoses (VEOP), with onset of illness at age 12 years or younger (often referred to as childhood onset schizophrenia). While many studies have investigated the clinical and neurocognitive features of VEOP specifically (see Kyriakopoulos and Frangou, 2007 for a review), very few have directly compared the clinical characteristics of EOP and VEOP. Those that have demonstrate the long-term outcome of individuals with VEOP appears to be worse than EOP. These individuals do more poorly at school and are less likely to have been employed than individuals with EOP (Biswas et al., 2006). They have a longer first hospital admission and subsequently have a greater number of days in hospital each year (Rabinowitz et al., 2006). There is also meta-analytic evidence that anti-psychotic medication initiated at a younger age is associated with an increased risk of side effects, particularly weight gain, higher discontinuation rates and leaving school early (Stafford et al., 2015). Evidence of neurocognitive variations according to age of psychosis onset is variable. Biswas and colleagues (Biswas et al., 2006) showed poorer cognitive function, namely IQ, memory and perceptuomotor skills, in individuals with VEOP compared to EOP. Conversely, Rhinewine et al. (2005) found no significant differences in the neurocognitive performance of VEOP and EOP groups, and no significant association between cognitive ability and age of psychosis onset.

In summary, there is still a lack of evidence of an 'age of psychosis onset effect' in youth <18 years of age. We lack the knowledge to determine whether psychoses with an onset before 18 years of age should be differentiated into VEOP and EOP, and if so, whether the traditional age cut-offs are clinically valid. A better understanding of this is important for the development of diagnostic criteria and age-specific therapeutic strategies. Indeed, the urgent need for studies investigating the role played by age of onset of psychosis on clinical presentation and response to therapeutic interventions has recently been highlighted (Schimmelmann and Schultze-Lutter, 2012; Schimmelmann et al., 2013; NICE, 2013).

To our knowledge, no study has investigated the clinical and demographic differences between young people with VEOP and EOP *at the time of psychosis onset*. In the current study, we examined psychoses with onset before the age of 18 years by: 1) examining differences at presentation between individuals with EOP and VEOP according to the traditional cut-offs for age of psychosis onset; and 2) by using receiver operating characteristic (ROC)-curves to determine if there was a clinically significant cut-off for the age of psychosis onset in the current sample.

2. Methods

2.1. Participants and procedure

Participants in this study were 88 (45 female, 43 male) children and adolescents consecutively admitted to the Child and Adolescent Neuropsychiatry Unit of the Clinical and Research Hospital Bambino Gesù of Rome with a recent onset of psychosis between 2012 and 2014. Patients had psychosis onset between ages 6.7 and 17.5 years ($M = 13.74$, $SD = 2.37$, median = 14.1) and had no previous drug treatment for psychosis (typical/atypical antipsychotics). Specific psychotic diagnoses are listed in Table 1. Exclusion criteria were past diagnosis of psychotic disorder, traumatic brain injury or known neurological disorder, verbal IQ < 70, and current drug or alcohol abuse. The participation rate was 95% of the consecutively admitted children/adolescents. Four patients (5%) were excluded because of the presence of an exclusion criteria (three due to verbal IQ < 70, one due to drug abuse). No eligible patient refused to participate. The study was approved by the Ethics Committee of the

Clinical and Research Hospital Bambino Gesù of Rome. Participants gave written informed assent and written informed consent was given by their parents/legal guardian.

2.2. Measures

Mental disorders were assessed using the Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Psychotic symptoms were indexed on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). This 30-item scale is used to assess the severity of positive and negative symptoms of psychosis, as well as general psychopathology. Both interviews were administered to the participants and their parent/guardian. All participants were screened for autism-spectrum disorder using the Autism Quotient Child (Auyeung et al., 2008) or Adolescent (Baron-Cohen et al., 2006) versions, completed by participants and their parent/guardian. In the case of positive screening, participants were assessed by a trained clinician on the Autism Diagnostic Observation Schedule-Generic (Lord et al., 2000). None met criteria for autism-spectrum disorder. Participants completed (via self-reported) the Multidimensional Anxiety Scale for Children (MASC) (March et al., 1997) to obtain an index of the severity of anxiety symptoms and the Children's Depression Inventory (CDI) (Kovacs, 1988) to obtain a global rating of depressive symptoms. Functioning was measured with the Childhood Global Assessment Scale (CGAS) (Shaffer et al., 1983). IQ was assessed with the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1991).

Duration of untreated illness (DUI) was defined as the delay between the onset of the first psychiatric disorder and the onset of criteria treatment, following the methodology used by Keshavan et al. (2003) DUP was defined as the delay between the onset of psychosis and the onset of criteria treatment, following the methodology used by Larsen et al. (2001).

We documented any first-degree relative with psychosis. Nine participants had no available information on family history (eight due to adoption). Living in an urban environment within the last three years was categorized according to a population of ≤100,000 or >100,001 (based on Dragt et al., 2011). Socio-demographic information were obtained from parents/guardians.

2.3. Statistical analyses

First, we divided and compared groups based on traditional cut-offs for age of psychosis onset: VEOP (onset of psychosis ≤ 12 years of age) and EOP (onset of psychosis 13–17 years of age). For group comparisons on categorical data, Chi-square was used. Independent Samples Mann–Whitney U was employed for group comparisons of continuous data. Effect sizes were calculated with Cohen's d for continuous variables and Cramer's phi for categorical data.

To investigate the predictive value of age of onset for psychotic symptom severity and functioning, without using the a priori cut-offs between EOP and VEOP, ROC-curves were calculated. Traditionally, ROC-curves are used to evaluate the ability of a test to detect a golden standard disorder/abnormality. Here, the curves were used in a slightly different context to evaluate the prognostic ability of age of onset at different age cut-offs. Thus, instead of evaluating whether, based on an a priori cut-off value, a test-score predicted an outcome with sufficient sensitivity (SENS) and/or specificity (SPEC), here optimal prediction of the outcome was used as a criterion to select the diagnostically most relevant age of onset cut-off. This approach was chosen because: (1) it allowed for the identification of an optimal age of onset cut-off (age with optimal SENS/SPEC), and; (2) it provided insight into the general prognostic value of age of onset for poor outcome.

In order to identify the factors associated with the poorest functioning and most severe symptoms using ROC analyses, the highest 25% of PANSS scores were compared to the lowest 75% of PANSS scores

Table 1
Sample characteristics.[*]

	Full sample			VEOP			EOP			Statistics	Effect size
	N	M	SD	N	M	SD	N	M	SD		Cohen's d
Clinical characteristics											
Age of psychosis onset (years)	88	13.75	2.37	29	10.97	1.58	59	15.11	1.20	p < 0.001	−3.10
DUI (weeks)	88	67.94	38.51	29	53.07	35.76	59	75.25	37.98	p = 0.005	−0.60
DUP (weeks)	88	29.33	19.39	29	22.45	14.97	59	32.71	20.50	p = 0.032	−0.54
PANSS Positive	88	24.45	6.30	29	25.10	6.50	59	24.14	6.23	p = 0.7	0.15
PANSS Negative	88	23.64	9.14	29	23.86	10.38	59	23.53	8.56	p > 0.9	0.04
PANSS general	88	40.23	12.20	29	41.00	13.41	59	39.85	11.66	p > 0.9	0.09
PANSS total	88	88.16	20.57	29	89.79	22.94	59	87.36	19.46	p = 0.9	0.12
CGAS	88	34.00	11.93	29	30.59	12.76	59	35.68	11.24	p = 0.048	−0.43
IQ	88	87.72	19.90	29	86.66	19.05	59	88.24	20.44	p = 0.4	−0.08
MASC anxiety scale	74	58.07	11.81	23	60.30	11.30	51	57.06	12.00	p = 0.2	0.28
CDI depression scale	75	20.81	9.69	23	22.30	8.82	52	20.15	10.06	p = 0.3	0.22
	N	%		N	%		N	%			Cramer's phi
Female gender	45	51.1		14	48.3		31	52.5		$\chi^2 = 0.14$, p = 0.7	0.04
Urbanicity > 100,000	55	62.5		18	62.1		37	62.7		$\chi^2 = 0.003$, p > 0.9	−0.006
Diagnosis											
Schizophrenia disorder	48	54.5		16	55.2		32	54.2		$\chi^2 = 2.21$, p = 0.14[*]	−0.009
Schizoaffective disorder	23	26.1		5	17.2		18	30.5			
Schizophreniform disorder	14	15.9		6	20.7		8	13.6			
Bipolar disorder with psychotic features	3	3.4		2	6.9		1	1.7			
Family history (FH)											
FH psychotic disorder	20	22.7		9	31.0		11	18.6		$\chi^2 = 0.007$, p > 0.9[**]	−0.17
FH non-psychotic bipolar disorder	11	12.5		4	13.8		7	11.9			
FH non-psychotic depressive disorder	8	9.1		2	6.9		6	10.2			
FH other psychiatric disorder	14	15.9		4	13.8		10	16.9			
FH unknown	9	10.2		4	13.7		5	8.5			
No FH	26	29.5		6	20.7		20	33.9			

Abbreviations: DUI, duration of untreated illness; DUP, duration of untreated psychosis; PANSS, positive and negative symptom scale; CGAS, Childhood Global Assessment Scale, IQ, Intelligence Quotient; MASC, Multidimensional Anxiety Scale for Children; CDI, Children's Depression Inventory; FH, family history.
  [*] Diagnosis of schizophrenia compared to any other psychotic disorder.
 [**] Family history of psychosis compared to having family history of non-psychotic psychiatric disorder or no family history of psychiatric disorder.

(positive, negative and total), and lowest 25% of CGAS scores were compared to the highest 75% of CGAS scores. After calculation of the ROC-curves, the non-parametric area under the curve (AUC) was investigated. If the AUC was significantly different from 0.5 (=chance level prediction), the curve's SENS and SPEC coordinates were inspected to find the age of psychosis onset cut-off with the most optimal SENS/SPEC balance, which was selected based on the highest J-statistic (SENS + SPEC-1) (Youden, 1950). Finally, SENS and SPEC were investigated for the traditional cut-off between VEOP and EOP. Finally, univariate data was reanalysed using the age cut-off shown to be most predictive in ROC analyses. All analyses were conducted with IBM SPSS (version 22).

3. Results

3.1. Sample characteristics

The characteristics of the sample are presented in Table 1. The distribution of age of psychosis onset is shown in Fig. 1. Twenty-nine participants (14 female) were in the VEOP group (mean age of psychosis onset = 10.97 years; SD = 1.58). Fifty-nine participants (31 female) were in the EOP group (mean age of psychosis onset = 15.11 years; SD = 1.20).

3.2. VEOP versus EOP

Psychotic diagnoses and family history of psychiatric illnesses for each group are presented in Table 1. There was no significant group difference between VEOP and EOP in terms of gender distribution (χ^2 = 0.14, p = 0.7, ϕ = 0.04), urban environment (χ^2 = 0.003, p > 0.9, ϕ = −0.006), diagnosis of schizophrenia as opposed to other psychotic disorders (χ^2 = 0.007, p > 0.9, ϕ = −0.009), or a family history of psychotic illness (χ^2 = 2.21, p = 0.14, ϕ = −0.17). The VEOP group showed a significantly shorter DUI (p = 0.005, d = −0.60) and DUP

(p = 0.03, d = −0.54) than the EOP group. They also had lower CGAS scores (p = 0.048, d = −0.43). In terms of symptoms, groups did not differ significantly on PANSS positive (p = 0.7, d = 0.15), negative (p > 0.9, d = 0.04), general (p > 0.9, d = 0.09) or total (p > 0.9, d = 0.12) subscales, MASC (p = 0.2, d = 0.28), or CDI (p = 0.3, d = 0.22) Similarly, IQ scores did not differ significantly between groups (p = 0.4, d = −0.08).

3.3. ROC-curves

To investigate whether older age of psychosis onset was predictive of lower psychotic symptom severity and better functioning without
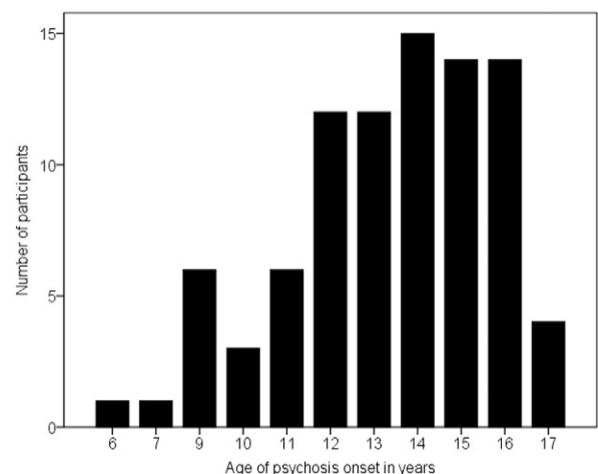

Fig. 1. Distribution of age of psychosis onset in the sample.

assuming an a priori cut-off, ROC-curves were calculated using age of onset (range: 6.7–17.5 years) as a predictor variable (see Fig. 2).

First, the AUCs for the ROCs with different outcomes were investigated to gain an overall insight of the prognostic value of age of onset for poor outcome. For the prediction of being in the lower three quartiles of PANSS total scores, the AUC was 0.63 and did not differ significantly from 0.5, indicating that total symptom severity could not be predicted above chance level by age of psychosis onset (95%CI: 0.49–0.78; p = 0.066). Being in the lower three quartiles of PANSS negative symptom scores was also not predicted above chance level by age of onset, as shown by a low AUC that did not differ significantly from 0.5 (AUC = 0.59; 95%CI: 0.46–0.72; p = 0.24). For the prediction of being in the lower three quartiles of PANSS positive symptom scores, the AUC was 0.69 (95%CI: 0.57–0.80; p = 0.012), showing that the age of onset was predictive of positive symptom severity. Inspection of the ROC-curve SENS/SPEC coordinates revealed that the optimal age-cut-off was 14.0 years. For this cut-off, the J-statistic was highest (J = 0.37), indicating an optimal combination of SENS (0.62) and SPEC (0.75). In the final ROC-analysis, predictive ability of age of onset for being in the upper quartile of CGAS scores was evaluated. Here, the AUC was 0.68 and this value was significantly higher than 0.5 (95%CI: 0.53–0.82; p = 0.015). This indicated that higher age of onset was predictive of better functioning. Inspection of the ROC-curve coordinates showed that optimal age of psychosis onset cut-off was 14.7 years: for this cut-off the J-statistic was highest (0.42) and the optimal combination of SENS (0.71) and SPEC (0.70) was observed. These results indicated that age of psychosis onset was generally predictive of positive symptomatology and functioning, and that setting the age of onset cut-off at <14.0 and <14.7, resulted in optimal prediction of, respectively more positive symptomatology and poorer functioning.

The observed optimal age cut-offs were higher than the cut-off traditionally used to differentiate between VEOP and EOP (age of onset ≤ 12). This age cut-off showed very high SENS but low SPEC in the current analyses: SENS = 0.81 and SPEC = 0.29 for low positive symptom severity and SENS = 0.81 and SPEC = 0.25 for high functioning.

3.4. Secondary analyses

To investigate the validity of the cut-off of 14–14.7 years of age, univariate analyses were rerun dividing groups based on age of psychosis onset < 15 (N = 56) or ≥15 years of age (N = 32). The younger group had significantly higher PANSS positive scale scores (p = 0.005; d = 0.70) and lower CGAS scores (p = 0.003, d = −0.65), as would be expected from ROC analyses results. They also had higher PANSS total symptom scores (p = 0.42, d = 0.48) and shorter DUI (p = 0.004, d = −0.59). There were no significant group differences on negative

Fig. 2. ROC curves.

(p = 0.16, Cohen's d = 0.35) or general (p = 0.4, d = 0.20) subscales, DUP (p = 0.3, d = −0.29), MASC (N = 47 and 27, p = 0.097, d = 0.34), CDI (N = 47 and 28, p = 0.8, d = 0.05) or IQ scores (p = 0.6, d = 0.27). In terms of demographic variables, there were no significant differences between the new groups in terms of gender distribution (χ^2 = 0.08, p = 0.8; ϕ = 0.03), urban environment (χ^2 = 3.35, p = 0.067; ϕ = −0.2), diagnosis of schizophrenia as opposed to other psychotic disorders (χ^2 = 0.04, p = 0.8; ϕ = −0.02), or a family history of psychotic illness (χ^2 = 1.58, p = 0.2; ϕ = −0.14).

4. Discussion

In this study, we investigated whether psychosis with onset before the age of 18 years old should be considered a homogenous entity by examining 88 participants aged 6.7 to 17.5 years at the time of psychosis onset. This was achieved by comparing groups defined by the traditional cut-offs for VEOP (onset ≤ 12 years) and EOP (onset 13–17 years), and subsequently exploring the data using ROC-curves to identify the age of onset cut-off with optimal predictive ability, without setting any a priori cut-off. Traditionally defined groups of VEOP and EOP could not be differentiated based on demographic factors, clinical symptoms (including psychotic, depressive or anxiety) or IQ. However, those with VEOP showed poorer functioning and shorter DUI and DUP. When data were explored using the ROC-analyses without a priori cut-offs, the optimal age of psychosis cut-offs to distinguish those with poor outcome from those with more favourable outcome were between 14 and 14.7 years, with lower levels of positive symptoms and better functioning being predicted by older age of onset. When used to predict poor outcomes, the cut-offs within this age range showed better SENS and SPEC than the traditional age cut-off of 12 years, which showed particularly poor specificity.

To the best of our knowledge, this is the first study to compare the clinical characteristics of EOP and VEOP at the time of diagnosis with psychotic disorder and statistically explore the validity of traditional age of onset cut-offs. Rabinowitz et al. (2006) used linked population-based registry data to empirically investigate the optimal cut-off for age of onset of schizophrenia for the long-term course of illness. They found that psychosis onset ≤ age 11 was associated with more days in hospital at first admission, and that psychosis onset ≤ age 12 was associated with greater number of days in hospital each year.

In our sample, the traditional age of psychosis onset cut-offs for VEOP and EOP were not particularly useful in clinically differentiating participants at presentation. The VEOP group did not show significantly higher levels of positive, negative or total symptoms, or depressive and anxiety symptoms. One explanation for the lack of group differences is that the CDI and MASC are self-report and younger children may have difficulty recognizing and describing their emotions. However, this was not the case with the PANSS, which is administered by clinicians. In fact, ROC-curves calculations suggested that the null findings may be attributed to the age of 12 years being an inaccurate cut-off for clinical significance of age of psychosis onset, at least for positive symptoms. We found that the optimal ages for differentiating the lowest three quartiles on the PANSS positive scores from the highest quartile was 14 years, with older age indicating less severe psychopathology. This is the same age cut-off used by Biswas et al. (2006), who showed higher levels of psychotic symptoms in their VEOP group. In our sample, age was not useful for differentiating the severity of total or negative symptoms.

Reanalysis of the data using the age of psychosis onset cut-off of <15 or 15–17 years old demonstrated larger effect sizes for the PANSS subscales, DUI, CGAS, and MASC than using the traditional age cut-off, although PANSS negative and general subscale scores and MASC did not differ significantly between these new groups. The increase in effect size demonstrates that a clinically-relevant difference may be present, at least for some symptoms, and that the current study may be underpowered to detect some differences. The findings provide tentative
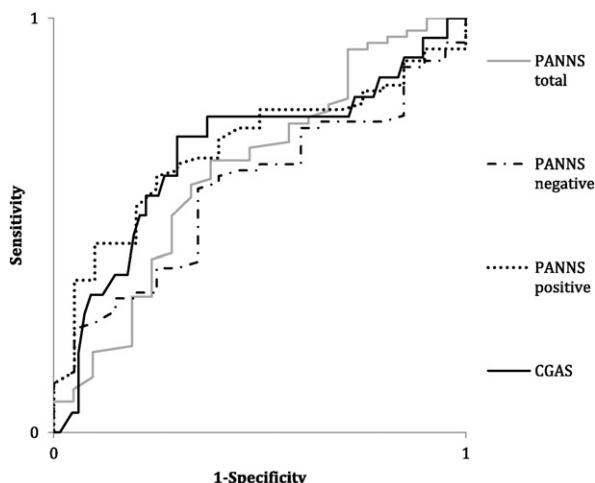
affirmation that the age of 15 years may be a more appropriate cut-off for detecting clinical differences in age of psychosis onset in children and adolescents, but more studies are needed to confirm this.

Better psychosocial functioning was associated with an older age of psychosis onset, evidenced in the group comparison and ROC-curve calculations. The EOP group showed CGAS scores which were on average six points higher than the VEOP group, a finding that was statistically significant. Additional ROC-curve calculations provided evidence that an age cut-off of 14.7 years was even more optimal, with relatively high sensitivity (71%) and specificity (70%) for the upper quartile of functioning. This cut-off was better than 12 years of age, which showed high sensitivity (81%), but very low specificity (25%) for CGAS scores.

More impaired psychosocial functioning in individuals with a younger age of psychosis onset is likely to reflect the impact of psychosis onset on the establishment of identity formation, social networks, and peer relationships, all of which are important developmental aspects of the transition into adolescence. Moreover, earlier disruption at school is likely to negatively affect academic performance and the behavioural experience of the school environment. Our ROC-curve analyses suggest that intervention for these psychosocial disruptions may be particularly important for those with onset of psychosis before approximately 14.7 years of age to improve long-term functional outcome.

In this study we also found that DUP and DUI were significantly shorter in the VEOP group than EOP. Previous literature suggests that psychosis onset before age 18 is associated with a more insidious onset than adult psychosis (Hollis, 2003; Schimmelmann et al., 2007). We propose that this may indeed be the case, but that in childhood (i.e. age 12 and earlier), parents are more vigilant and attentive to behavioural disorders or social difficulties, leading them to seek intervention earlier. This is in contrast to adolescence when young people typically develop a level of independence from their parents and it is more difficult to distinguish typical behavioural anomalies associated with being a teenager from early manifestations of psychotic condition. However, our data and this hypothesis are contradictory to a previous finding of more insidious onset of psychosis in VEOP compared psychosis onset at an older age (Russell, 1994). Given the well-established association between prolonged DUP and poor outcome, further research into the factors associated with DUP in children and adolescents is necessary.

There were a number of null findings from the comparison of VEOP and EOP. These included IQ, gender distribution, urbanicity, psychotic diagnosis and family history of psychosis. Similar to the findings of Rhinewine et al. (2005), our VEOP group did not have poorer IQ than the EOP group, whereas Biswas et al. (2006) found a significant difference between their childhood and adolescent groups on indices of IQ. This discrepancy is likely due to the fact that cognition was assessed an average of over 12 years after illness onset in the Biswas et al. (2006) sample, whereas our participants were assessed at illness onset and those reported by Rhinewine et al. (2005) had an average illness duration of 4 years. Given that the progression of cognitive changes in VEOP and EOP are largely unknown, deterioration in cognitive ability may occur in the years following diagnosis.

While there is evidence of a greater proportion of males (Russell, 1994) and a stronger genetic loading (Kumra and Schulz, 2008) in individuals who develop psychosis before the age of 18, to the best of our knowledge, no study has compared VEOP and EOP these demographic variables. Our findings suggest that in demographic and diagnostic respects, onset of psychosis before age 18 is somewhat homogenous. When univariate analyses were rerun by dividing the sample into psychosis onset < 15 years vs. onset 15–17 years), there were no significant group differences on demographic and diagnostic variables, providing further evidence of homogeneity in these respects in our sample.

The strengths of this study are a rare sample of individuals with a low prevalence disorder and no previous drug treatment for psychosis. The sample was recruited from a hospital considered to be the Italian point of reference for the assessment and treatment of VEOP/EOP and

is likely to be highly representative. This differs from many other VEOP/EOP samples, where referrals are often treatment-refractory patients from other medical centres. This study has several limitations. First, a sample size of 88 patients is not particularly large for ROC analyses, and we may have been underpowered to detect significant group difference. However, this sample size should be considered in light of the low prevalence of psychotic disorder in the age range investigated. Second, a full neurocognitive assessment was not conducted. Third, only a history of first-degree relatives was assessed. Second-degree relatives with psychosis may also infer increase genetic risk for the illness. Fourth, the cross-sectional design of the current study precluded the analysis of the possible role played by the age of onset on the longer clinical and functional outcome.

In summary, we found that the traditional cut-off for age of psychosis onset of ≤12 years for VEOP and 13–17 years for EOP were not particularly meaningful for describing the initial clinical presentation of this sample. ROC-curve calculations demonstrated that a more optimal age cut-off would fall between 14 and 14.7 years, particularly in terms of specificity for positive psychotic symptoms and functioning. We recognize that sensitivity of 62% and specificity of 75%, and sensitivity of 70% and specificity of 71% for positive symptoms and functioning respectively are not excellent prognostic values, particularly in light of the null findings for negative and general symptoms. However, our aim was not to determine the best prediction, but rather to gain insight into the clinical significance of the traditional age cut-offs for VEOP and EOP, and explore if there was a more appropriate cut-off. Our results suggest more investigation is required. There is a need for more in-depth studies into the developmental features of psychoses with an onset in childhood and adolescence. Future research should incorporate a comprehensive neurocognitive battery and neuroimaging to characterize the association between neurodevelopment and age of psychosis onset. Follow-up of this sample will allow us to investigate later outcome in relation to age of psychosis onset, and the associations between early presentation and outcome.

There is a temptation to apply adult models of schizophrenia and other psychoses to children and adolescents. A clearer understanding of the age-specific aspects of psychotic disorder will aid the development of predictive diagnostic tools, more accurate prognosis prediction, and more effective and age-tailored therapeutic interventions. Indeed, the question of whether or not to provide specific age-tailored therapeutic interventions in patients who develop schizophrenia before the age of 18 years is still under debate (Armando et al., 2015; Tiffin and Welsh, 2013). In accordance with the preliminary evidence emerging from our findings, we could speculate that the classical distinction between VEOP and EOP is not a useful tool. Psychosocial interventions to improve social and general functioning could be of particular usefulness under the age of 15 years old. The lack of relevant differences in terms of cognitive functioning, negative, depressive and anxiety symptoms, lead to a preliminary hypothesis that those symptoms and aspects of psychosis should be the target of any treatment, regardless the age of onset.

Authors and contributors

Dr. Armando designed this large First Episode Comparative Study. Dr. Pontillo, Dr. De Crescenzo, Dr. Mazzone collected the data. Dr. Lin, Dr. Wardenaar and Dr. Armando analysed and interpreted the data. Dr. Armando, Dr. Lin, Dr. Wardenaar and Dr. Vicari wrote the first draft of the manuscript. All contributed to and have approved the final manuscript.

Declaration of interests

The authors have no conflict of interest to declare related to the content of this study.

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