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Twelve-month psychosis-predictive value of the ultra-high risk criteria in children and adolescents

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ABSTRACT

Objective: The validity of current ultra-high risk (UHR) criteria is under-examined in help-seeking minors, particularly, in children below the age of 12 years. Thus, the present study investigated predictors of one-year outcome in children and adolescents (CAD) with UHR status.
Method: Thirty-five children and adolescents (age 9–17 years) meeting UHR criteria according to the Structured Interview for Psychosis-Risk Syndromes were followed-up for 12 months. Regression analyses were employed to detect baseline predictors of conversion to psychosis and of outcome of non-converters (remission and persistence of UHR versus conversion).
Results: At one-year follow-up, 20% of patients had developed schizophrenia, 25.7% had remitted from their UHR status that, consequently, had persisted in 54.3%. No patient had fully remitted from mental disorders, even if UHR status was not maintained. Conversion was best predicted by any transient psychotic symptom and a disorganized communication score. No prediction model for outcome beyond conversion was identified.
Conclusions: Our findings provide the first evidence for the predictive utility of UHR criteria in CAD in terms of brief intermittent psychotic symptoms (BIPS) when accompanied by signs of cognitive impairment, i.e. disorganized communication. However, because attenuated psychotic symptoms (APS) related to thought content and perception were indicative of non-conversion at 1-year follow-up, their use in early detection of psychosis in CAD needs further study. Overall, the need for more in-depth studies into developmental peculiarities in the early detection and treatment of psychoses with an onset of illness in childhood and early adolescence was further highlighted.

1. Introduction

Psychoses are one of the most severe disorders in children and adolescents (CAD) (Gore et al., 2011). Their poor outcome generally correlates positively with the durations of untreated psychosis (DUP) and illness (DUI) (Marshall et al., 2005). Outcome is even worse in early-onset psychosis (EOP), with the first episode starting before the age of 18 years (Rabinowitz et al., 2006).

1.1. Early-onset psychoses

Compared with adult-onset psychosis (AOP), the poorer outcome of EOP might not be intrinsic, but due to a significantly longer DUP (Schimmelmann et al., 2007, 2008). Furthermore, clinically, EOP often presents slightly differently compared with AOP (Gochman et al., 2011; Tiffin and Welsh, 2013). Thus, the challenges of early detection and treatment of first signs of the emerging disorder may be different in EOP and also in AOP with an illness onset in childhood and early adolescence compared with AOP that has an onset in late adolescence and adulthood (Schimmelmann and Schultze-Lutter, 2012; Schimmelmann et al., 2013a, 2013b).

1.2. Early detection of psychosis in children and adolescents

Two approaches for an early detection of psychoses currently prevail: the "ultra-high risk" (UHR) (Yung et al., 1998), mainly relying on attenuated psychotic symptoms (APS) and the "basic symptoms" (Schultze-Lutter et al., 2012). The alternative UHR criteria, which comprise the attenuated psychotic symptom (APS) criterion, the brief intermittent psychotic symptom (BIPS) criterion, and the genetic risk and

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functional decline (GRFD) criterion, were originally developed with the explicit aim of detecting an imminent risk for psychoses, i.e., persons at risk for developing a first-episode within the next 12 months (Schultze-Lutter et al., 2015). In contrast to the UHR criteria, the criteria based on basic symptoms, i.e., the cognitive-perceptive basic symptoms, (COPER) criterion and the cognitive disturbances (COGDIS) criterion (Schultze-Lutter et al., 2012), were developed to detect the risk for psychosis as early as possible in the development of the illness, ideally before functional impairments have appeared (Schultze-Lutter et al., 2015).

A recent meta-analysis showed pooled conversion rates in UHR samples that increased from 9.6% at 6 months to 37.0% at >4-year follow-up, with significantly lower conversion rates in 12- to 18-year-olds (Schultze-Lutter et al., 2015). Lower conversion rates in CAD might not be surprising as current risk criteria were developed and validated in predominately adult samples (age ≥ 16 years; Schultze-Lutter et al., 2015; Yung et al., 1998).

CAD studies reporting high prevalence of (attenuated) psychotic symptoms (hallucinations) in the general population further indicated age-related peculiarities of UHR symptoms (Schimmelmann et al., 2013a, 2013b). These seem to decrease throughout adolescence (Kelleher et al., 2012b; Brandizzi et al., 2014; Schimmelmann et al., 2015) and remit spontaneously in about three quarters of CAD (Bartels-Velthuis et al., 2011).

Thus, it was recently argued that the validity of current risk criteria needs to be examined in and possibly adapted to CAD populations (National Institute for Health and Clinical Excellence NICE, 2013; Schimmelmann and Schultze-Lutter, 2012; Schimmelmann et al., 2013a; Schultze-Lutter et al., 2012, 2015).

1.3. Aims of the study

To address this need, we investigated predictors of 1-year outcome in CAD at increased risk of psychosis in terms of both predictors of conversion to psychosis and of outcome of non-converters (remission and persistence of UHR criteria versus conversion).

2. Methods

2.1. Participants

The sample consisted of 35 patients (aged 9–17-years, n = 7 (20%) each age 9–11 and 16–17) with suspected EOP at the Child and Adolescent Neuropsychiatry Unit of the Children Hospital Bambino Gesù in Rome from 2012 to 2013 (Table 1). Inclusion criterion was the presence of any UHR criterion (Yung et al., 1998): APS, brief intermittent psychotic symptoms (BIPS) and/or genetic risk plus functional deterioration (GRFD). Exclusion criteria were: past or present psychosis, traumatic brain injury or any known neurological disorder, and current drug or alcohol abuse. A history of drug use was permitted if symptoms had also been present in drug-free periods. Participants were followed-up for 12 months.

The study was approved by the Ethics Committee of the Children Hospital Bambino Gesù. All participants provided written informed assent and their parents/legal guardians, written informed consent.

2.2. Assessments

UHR criteria and negative, disorganization, and general symptoms were assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS; McGlashan, 2001). It was also used to assess past or present psychosis at baseline and follow-up, defined by the presence of any positive symptom rated '6' that is seriously disorganizing or dangerous and/or persists for more than 7 days. The type of psychosis was diagnosed using DSM-IV (American Psychiatric Association, 1994).

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); alcohol and drug use using sections J and L of the Composite International Diagnostic Interview (CIDI; McGlashan, 2001). Functioning was rated globally on the Childhood Global Assessment Scale (CGAS; Shaffer et al., 1983) and differentially on the Global Functioning: Social (GF:Social; Auther et al., 2006) and the Global Functioning: Role (GF:Role; Niendam et al., 2006) scales. Baseline verbal IQ was assessed with the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991).

Table 1
Sociodemographic and clinical characteristics of ultra-high risk (UHR) patients at baseline (n = 35).

Age: mean (sd); Mdn (range)	13.8 (2.1); 13.8 (9–17)
Sex, male: n (%)	18 (51.4)
1st- or 2nd-degree relative with psychosis: n (%)	4 (11.4)
Verbal IQ: mean (sd); Mdn (range)	87.2 (17.3); 91 (53–129)
Education (in years): mean (sd); Mdn (range)	8.4 (2.2); 8 (3–12)
Urbanicity level, more than 2500 citizens: n (%)	25 (71.4)
Duration of mental problems (in months): mean (sd); Mdn (range)	28.1 (28.2); 12 (2–120)
SIPS sum scores: mean (sd); Mdn (range)	
Total SIPS	43.1 (14.6); 42 (12–80)
Positive subscale (SIPS-P sum)	12.2 (5.2); 13 (0–24)
Negative subscale (SIPS-N sum)	14.5 (6.4); 16 (1–29)
Disorganization subscale (SIPS-D sum)	6.5 (3.5); 6 (1–14)
General psychopathology subscale (SIPS-G sum)	9.9 (4.3); 10 (1–18)
UHR criterion: n (%)	
Any attenuated psychotic symptom (APS)	29 (82.9)
By unusual thought content/delusional ideas (P1 = |3–5|)	20 (57.1)
By suspiciousness/persecutory ideas (P2 = |3–5|)	27 (77.1)
By grandiosity (P3 = |3–5|)	5 (14.3)
By perceptual abnormalities/hallucinations (P4 = |3–5|)	18 (51.4)
By disorganized communication (P5 = |3–5|)	13 (37.1)
Any brief intermittent psychotic symptom (BIPS)	5 (14.3)
By unusual thought content/delusional ideas (P1 = 6)	1 (2.9)
By suspiciousness/persecutory ideas (P2 = 6)	1 (2.9)
By grandiosity (P3 = 6)	0
By perceptual abnormalities/hallucinations (P4 = 6)	3 (8.6)
By disorganized communication (P5 = 6)	0
Any genetic risk plus functional decline (GRFD)	4 (11.4)
By 1st-degree relative with psychosis	3 (8.5)
By schizotypal personality disorder according to SIPS	1 (2.9)
Main axis-I DSM-IV disorder by K-SADS-PL: n (%)	
Any depressive disorder	18 (51.4)
Any behavioral disorder	7 (20.0)
Any anxiety disorder	2 (5.7)
Any obsessive–compulsive disorder	5 (14.3)
Any other disorder	3 (8.6)
C-GAS: mean (sd); Mdn (range)	48.6 (4.3); 50 (37–55)
GF:Role: mean (sd); Mdn (range)	4.0 (0.7); 4 (3–5)
GF:Social: mean (sd); Mdn (range)	4.1 (0.6); 4 (3–5)
Cannabis use: n (%)	
Never	34 (97.2)
Last (regular) use >1 month ago	1 (2.9)
Current psychopharmacological medication: n (%)	
Any antidepressant	1 (2.9)
Any benzodiazepine	1 (2.9)
Any antipsychotic	0

SIPS: Structured Interview for Psychosis-Risk Syndromes (McGlashan, 2001); *C-GAS*: Childhood Global Assessment Scale (Shaffer et al., 1983); *GF:Role*: Global Functioning: Role (Niendam et al., 2006); *GF:Social*: Global Functioning: Social (Auther et al., 2006); *K-SADS-PL*: Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (Kaufman et al., 1997).

2.3. Data analyses

Using SPSS 21, predictors of psychosis-conversion were assessed by logistic regression analyses; predictors of UHR status remission and persistence versus conversion by ordinal logistic regression analyses. Predictors were sociodemographic characteristics (age, gender, education,

urbanicity, family history of mental disorders) and clinical parameters (main diagnosis, IQ, social and role functioning, duration of mental problems, type of UHR criterion, SIPS positive item scores, single APS and BIPS, SIPS subscale sum scores). For descriptive purposes, notwithstanding the recommended 5:1 relation of number of events to number of predictors (Vittinghoff and McCulloch, 2007), potential predictors showing at least a trend-level result of $p < 0.10$ were entered into multivariate stepwise logistic and ordinal regression analyses to detect the best, non-redundant predictor(s) of outcomes. Furthermore, the presence and size of potential age effects on outcome and the presence of BIPS and APS were examined by $k \times l\ \chi^2$ test and Cramer's V across 2 age groupings (AG1: 9–11, 12–14 and 15–17 years, and AG2: 9–15 and 16–17 years).

3. Results

3.1. One-year outcome

Within 1 year, 7 (20.0%) patients developed an EOP (schizophrenia), while 9 (25.7%) remitted from UHR status, which persisted in 19 (54.3%) patients. No significant differences across age groups revealed (AG1: $\chi^2_{(4)} = 1.38$, $p = 0.848$; AG2: $\chi^2_{(2)} = 1.06$, $p = 0.588$), indicating a small age effect on outcome (AG1: $V = 0.140$; AG2: $V = 0.174$). Furthermore, neither in general nor on item-level did BIPS or APS reveal any significant age group difference at baseline, and a moderate effect only revealed for APS in general in AG1 with APS being most frequent in 8–11-year-olds ($V = 304$), and for P2-BIPS in AG2 with transient paranoid delusions being most frequent in 16–17-year-olds ($V = 343$).

Most non-converters retained their baseline diagnosis, only one received a different diagnosis. Thus, none fully remitted from mental disorders, even if UHR status was not maintained. However, only non-converters who remitted from UHR status significantly improved on both GF:Role and GF:Social (Wilcoxon tests: $Z = -2.333$, $p = 0.020$), while non-converters who maintained UHR status also maintained poor functioning.

3.2. Predictors of conversion to psychosis

In univariate logistic regression analyses, the presence of any BIPS and the SIPS-P5 score ("disorganized communication") became significant, while trend-level results were detected for the absence of any APS, and the presence of APS-level SIPS-P5 and BIPS-level SIPS-P4 ("perceptual abnormalities/hallucinations"). None of the socio-demographic variables was a significant predictor of either conversion to psychosis or remission from UHR status (Table 2).

When entered into the multivariate stepwise model, only any BIPS ($\beta = 2.560$, $\chi^2_{(1)} = 4.321$, $p = 0.052$; $\text{Exp}(\beta) = 12.937$; 95%CI = 0.980/170.729) and the SIPS-P5 score ($\beta = 0.740$, $\chi^2_{(1)} = 4.321$, $p = 0.041$; $\text{Exp}(\beta) = 2.096$; 95%CI = 1.029/4.269) were selected into the model by both forward and backward methods (Omnibus goodness-of-fit test: $\chi^2_{(2)} = 10.557$, $p = 0.005$).

3.3. Predictors of non-psychotic outcome

In univariate ordinal regression analyses with conversion as poorest outcome and, consequently, as reference value, the absence of APS-level SIPS-P1 ("unusual thought content/delusional ideas") and a lower SIPS-

Table 2
Results of univariate logistic regression analyses of effect of potential baseline predictors on conversion to psychosis.

Covariates (potential baseline predictors)	β	SE	Wald (df)	p	Exp(β)	Lower 95%-CI	Upper 95%-CI
Age (in years)	0.057	0.205	0.078 (1)	.781	1.059	0.708	1.583
Main diagnosis ("other" as reference)			0.703 (4)	.951			
Main diagnosis (anxiety)	21.203	23,205.5	<0.001 (1)	.999	>1000	0.000	–
Main diagnosis (depressive)	19.950	23,205.5	<0.001 (1)	.999	>1000	0.000	–
Main diagnosis (behavioral)	20.287	23,205.5	<0.001 (1)	.999	>1000	0.000	–
Main diagnosis (obsessive-compulsive)	<0.001	29,352.8	0.000 (1)	1.0	1.000	0.000	–
Urbanicity level[a]	−0.206	0.246	0.700 (1)	.403	0.814	0.502	1.318
Education × age	0.002	0.009	0.051 (1)	.822	1.002	0.984	1.020
Education (in years)	0.053	0.197	0.074 (1)	.786	1.055	0.717	1.551
Verbal IQ	−0.042	0.028	2.236 (1)	.135	0.959	0.907	1.013
Sex (female)	1.204	0.920	1.714 (1)	.190	3.333	0.550	20.217
Family member with psychosis (any)	−19.971	20,096.5	<0.001 (1)	.999	<0.001	0.000	–
GF:Role	−0.972	0.704	1.905 (1)	.167	0.378	0.095	1.504
GF:Social	−0.811	0.738	1.208 (1)	.272	0.444	0.105	1.887
Duration of mental problems (in months)	−0.055	0.037	2.118 (1)	.146	0.947	0.880	1.019
Any BIPS (present)	**2.277**	**1.059**	**4.623 (1)**	**.032**	**9.750**	**1.223**	**77.724**
BIPS by P1 (present)	−19.853	40,193.0	<0.001 (1)	1.0	<0.001	0.000	–
BIPS by P2 (present)	22.743	40,193.0	<0.001 (1)	1.0	>1000	.000	–
BIPS by P3 (present)	Not reported						
BIPS by P4 (present)	**2.380**	**1.318**	**3.260 (1)**	**.071**	**10.800**	**0.816**	**142.981**
BIPS by P5 (present)	Not reported						
Any APS (present)	**−1.833**	**0.978**	**3.510 (1)**	**.061**	**0.160**	**0.024**	**1.088**
APS by P1 (present)	20.584	10,377.8	<0.001 (1)	.998	>1000	0.000	–
APS by P2 (present)	0.383	0.955	0.161 (1)	.688	1.467	0.226	9.534
APS by P3 (present)	<0.001	1.208	<0.001 (1)	1.0	1.0	0.094	10.664
APS by P4 (present)	−0.431	0.853	0.255 (1)	.613	0.650	0.122	3.457
APS by P5 (present)	**1.833**	**0.935**	**3.838 (1)**	**.050**	**6.250**	**0.999**	**39.094**
Any GRD (present)	−19.930	23,205.4	<0.001 (1)	.999	<0.001	0.000	–
SIPS P1 score	0.334	0.286	1.362 (1)	.243	1.397	0.797	2.447
SIPS P2 score	0.438	0.417	1.105 (1)	.293	1.550	0.685	3.507
SIPS P3 score	−0.377	0.426	0.784 (1)	.376	0.686	0.297	1.581
SIPS P4 score	0.278	0.280	0.984 (1)	.321	1.320	0.763	2.285
SIPS P5 score	**0.674**	**0.308**	**4.800 (1)**	**.028**	**1.963**	**1.074**	**3.588**
SIPS-P sum score	0.143	0.094	2.284 (1)	.131	1.153	0.958	1.388
SIPS-N sum score	0.036	0.069	0.271 (1)	.603	1.036	0.906	1.186
SIPS-D sum score	0.150	0.125	1.453 (1)	.228	1.162	0.910	1.484
SIPS-G sum score	−1.626	1.102	2.177 (1)	.140	1.024	0.842	1.245

Predictors that are significant at least at a statistical trend level ($p < .10$) are given in bold.
[a] In 5 ascending levels from 1 = "less than 500 citizens" to 5 = "more than 2500 citizens".

P5 score were related to better outcome, while an association between better outcome and the absence of any BIPS, of BIPS-level SIPS-P4 and of APS-level SIPS-P5, a lower SIPS-P sum score and the presence of any APS was indicated at a trend-level (Table 3). None of these became significant, not even on trend-level, in multivariate analyses (Goodness-of-fit: $\chi^2_{(7)} = 12.805$, $p = 0.077$) (Table 4).

4. Discussion

Addressing the need to examine the validity of UHR criteria in and possibly adapt them to CAD (National Institute for Health and Clinical Excellence NICE, 2013; Schimmelmann et al., 2013a, 2013b, Schimmelmann et al., 2015; Schultze-Lutter et al., 2015), we examined the 1-year outcome in 35 CAD meeting UHR criteria, thereby including children below the age of 12 for the first time. We found a fifth of patients developing psychosis; schizophrenia in all cases. UHR status persisted in the majority (54.3%); only a quarter remitted from it within 12 months. However, none had remitted from mental problems.

4.1. Conversion to psychosis at one-year follow-up

A recent meta-analysis (Schultze-Lutter et al., 2015) reported lower pooled conversion rates at 1-year follow-up in CAD UHR samples (9.5%) compared to adult (18.0%) or even mixed age UHR samples with a majority of adolescents (20.9%). In light of this, our 20.0% conversion rate seems rather high for a CAD sample.

However, conversion was related to the presence of any BIPS, predominately hallucinations and more pronounced, yet still attenuated disorganized communication. Though BIPS are usually rare in UHR samples, they were related to the significantly highest pooled conversion rate of all 3 UHR criteria in the recent meta-analysis (Schultze-Lutter et al., 2015). Thus, their presence – 14.3% in our sample and 40.0% in control intervention group in Amminger et al. (2010) – might explain the high 1-year conversion rates of 20.0% and 27.5%, respectively, in these 2 CAD samples. Accordingly, in adolescent samples with lower conversion rates (3.3–9.7%), BIPS were absent (Cornblatt et al., 2007; Lindgren et al., 2014; Welsh and Tiffin, 2014) or only reported by 5.6% (Ziermans et al., 2011). Thus, a higher rate of BIPS might be related to a higher conversion rate in CAD.

An association between psychotic symptoms and subsequent psychosis was also reported by the Dunedin birth cohort study (Poulton et al., 2000): in the initial absence of a psychotic disorder, psychotic symptoms at age 11 predicted development of schizophreniform disorders until the age of 26. Yet, two other studies (Bartels-Velthuis et al., 2011; Hlastala and McClellan, 2005) with shorter follow-ups of 5 and 2 years, respectively, reported high remission rates of psychotic symptoms and no conversion to psychosis in CAD. The 5-year follow-up study (Bartels-Velthuis et al., 2011) investigated the course of auditory hallucinations in a community sample of 7–8-year-old children. The 2-year follow-up study (Hlastala and McClellan, 2005) examined the course of atypical psychotic symptoms in 7–18-year-old non-psychotic psychiatric patients. Consequently, the applicability of subthreshold or atypical psychotic symptoms for early detection of psychosis in CAD was challenged (Hlastala and McClellan, 2005). A feature distinguishing atypical psychotic and psychotic symptoms in patients with psychosis was lack of accompanying disorganized communication (Hlastala and McClellan, 2005). This agrees with our finding of a higher rating on 'disorganized communication' being an additional predictor of

Table 3
Results of the univariate ordinal regression analyses of effects of potential predictors on outcome (conversion as reference value).

Covariates (potential baseline predictors)	Estimate	SE	Wald (df)	p	Lower 95%-CI	Upper 95%-CI
Age (in years)	0.036	0.156	0.054 (1)	.816	−0.269	0.341
Main diagnosis ("other" as reference)						
Main diagnosis (anxiety)	2.363	1.818	1.689 (1)	.194	−1.200	5.926
Main diagnosis (depressive)	0.737	1.212	0.370 (1)	.370	−1.638	3.113
Main diagnosis (behavioral)	1.344	1.358	0.980 (1)	.322	−1.318	4007
Main diagnosis (obsessive–compulsive)	−0.207	1.410	0.022 (1)	.883	−2.970	2556
Urbanicity level[a]	0.127	0.204	0.384 (1)	.536	−0.274	0.527
Education × age	0.002	0.007	0.078 (1)	.780	−0.012	0.016
Education (in years)	0.045	0.149	0.091 (1)	.753	−0.247	0.337
Verbal IQ	−0.024	0.020	1.526 (1)	.217	−0.063	0.014
Sex (female)	1.002	0.681	2.166 (1)	.141	−0.332	2336
Family member with psychosis (none)	−0.191	1.020	0.035 (1)	.851	−2.191	1.809
GF:Role	−0.343	0.500	0.471(1)	.493	−1.323	0.637
GF:Social	−0.160	0.538	0.089(1)	.766	−1.216	0.895
Duration of mental problems (in months)	−0.019	0.012	2.276(1)	.131	−0.043	0.006
Any BIPS (absent)	**−1.822**	**0.989**	**3.398 (1)**	**.065**	**−3.760**	**0.115**
BIPS by P1 (absent)	Not calculated for unexpected singularities					
BIPS by P2 (absent)	Not calculated for unexpected singularities					
BIPS by P3 (absent)	Not reported					
BIPS by P4 (absent)	**−2.449**	**1.314**	**3.475 (1)**	**.062**	**−5.023**	**0.126**
BIPS by P5 (absent)	Not reported					
Any APS (absent)	**1.503**	**0.904**	**2762(1)**	**.097**	**−0.270**	**3.276**
APS by P1 (absent)	**−1.905**	**0.775**	**6.046 (1)**	**.014**	**−3.424**	**−0.387**
APS by P2 (absent)	0.668	0.784	0.726 (1)	.394	−0.869	2.204
APS by P3 (absent)	−0.789	0.939	0.706 (1)	.401	−2.629	1.051
APS by P4 (absent)	−0.024	0.649	0.001 (1)	.970	−1.296	1.248
APS by P5 (absent)	**−1.417**	**0.734**	**3.724 (1)**	**.054**	**−2.856**	**0.022**
Any GRD (absent)	−0.183	1.160	0.025(1)	.875	−2.456	2.090
SIPS P1 score	0.322	0.209	2369(1)	.124	−0088	0,731
SIPS P2 score	0.124	0.275	0.204(1)	.652	−0.414	0.662
SIPS P3 score	0.189	0.252	0.562(1)	.453	−.306	0.684
SIPS P4 score	0.303	0.203	2.235(1)	.135	−0.094	0.700
SIPS P5 score	**0.423**	**0.206**	**4.210(1)**	**.040**	**0.019**	**0.828**
SIPS-P sum score	**0.131**	**0.069**	**3.577(1)**	**.059**	**−0.005**	**0.267**
SIPS-N sum score	0.005	0.051	0.008(1)	.929	−0,096	0,105
SIPS-D sum score	0.101	0.095	1.127(1)	.288	−0.085	0.287
SIPS-G sum score	0.016	0.077	0.044(1)	.834	−0.134	0.166

Predictors that are significant at least at a statistical trend level ($p < .10$) are given in bold.
[a] In 5 ascending levels from 1 = "less than 500 citizens" to 5 = "more than 2500 citizens".

Table 4
Result of the multivariate ordinal regression analysis of effect of potential predictors on outcome (conversion as reference value).

Covariates, factors	Estimate	SE	Wald (df)	p	Lower 95%-CI	Upper 95%-CI
SIPS-P5 score	0.174	0.484	0.129 (1)	.720	−0.775	1.123
SIPS-P sum score	−0.023	0.117	0.039 (1)	.843	−0.253	0.206
No BIPS (any BIPS = 0)	1.306	2.873	0.207 (1)	.649	−4.325	6.936
No APS (any APS = 0)	1.682	2.374	0.502 (1)	.479	−2.971	6.335
No SIPS-P1 APS (P1-APS = 0)	−1.593	1.023	2.425 (1)	.119	−3.598	0.412
No SIPS-P4 B.P. (P4-BIPS = 0)	−1.938	1.986	0.952 (1)	.329	−5.830	1.954
No SIPS-P5 APS (P5-APS = 0)	−0.870	1.606	0.294 (1)	.588	−4.017	2.277

conversion; it might be this co-occurrence that procured the psychosis-predictive value of BIPS in our sample. Indeed, only the 3 BIPS patients with a rating of 'disorganized communication' ≥2 (i.e., speech that is slightly vague, muddled, overelaborated, or stereotyped) converted, while those with a lower rating did not. Yet, the comparability of our results with those of these 3 studies is limited by the fact that these studies did not use current UHR instruments for the distinction between APS and BIPS and did not assess BIPS criteria (i.e., the respective onset and frequency requirements). Thus, CAD with psychotic symptoms in these samples most likely only partly represent CAD with BIPS of UHR samples.

Recently, 'disorganized speech' was the only positive item distinguishing converters (13.2%, mainly within 1 year) from non-converters in a 14–35-year-old UHR sample with a 2.4-year-follow-up (Katsura et al., 2014). Furthermore, 'disorganized communication' was the sole predictor of psychosis in a UHR sample (12–30-year-olds) with a 26% conversion rate at 2.5-year follow-up, and suggested as a potential endophenotype or stable trait marker for schizophrenia risk (DeVylder et al., 2014). A relationship between communication deviances and 2-year conversion (38.9%) was also revealed in speech analyses of mixed-age UHR patients (17 ± 4 years), using audio recordings and transcripts (Bearden et al., 2011). This study indicated the presence of an impaired use of reasoning (illogical thinking) and development of the topic (poverty of content of speech) when formulating and organizing thoughts and an under-utilization of linguistic devices necessary for cohesive communication prior to the onset of psychosis.

4.2. Attenuated psychotic symptoms and development of psychosis

Interestingly, the absence of any APS – though not selected into the final predictor model of conversion – was also suggestive of subsequent conversion in univariate analyses, and, relatedly, the presence of any APS was suggestive of better outcome in univariate analyses. The majority of APS in our sample had occurred for 'suspiciousness/persecutory ideas' (77.1%) followed by 'unusual thought content/delusional ideas' (57.1%) and 'perceptual aberrations/hallucinations' (51.4%).

Earlier studies on an adolescent UHR (Cornblatt et al., 2007) and a mixed-age help-seeking sample (Yung et al., 2006) had also reported 'suspiciousness/persecutory ideas' as the most frequent clinician-assessed APS, and the factor 'Conceptual Disorganization and Suspiciousness' was most frequent in questionnaire-studies (Armando et al., 2010, 2012, 2013; Brandizzi et al., 2014). Persecutory APS, however, had remitted in a considerable proportion of adolescents over the 2–88-month follow-up period irrespective of type of medication (Cornblatt et al., 2007). Hence, it was concluded that seemingly pathological suspiciousness and paranoid ideas of reference (e.g., adolescents' typical report of feeling watched and negatively evaluated by peers) might be more prevalent and less predictive of psychosis in adolescents than in adults (Cornblatt et al., 2007). This is supported by epidemiological data of 8–40-year-olds that indicated an increase in the clinical significance of unusual thought contents, including persecutory ideas, in terms of functional impairment with advancing age (Schimmelmann et al., 2015).

Other community-studies on adolescent UHR patients (Meyer et al., 2005) and CAD (Kelleher et al., 2012a, 2012b) reported a preponderance of perceptual APS, potentially decreasing throughout adolescence (Kelleher et al., 2012b). In a recent cross-sectional community study of APS, an age-effect on prevalence revealed solely for 'perceptual aberrations/hallucinations' (Schimmelmann et al., 2015). Perceptive APS showed a significant shift in prevalence from early to late adolescence, i.e., around age 16, and were more frequent in 8–15-year-olds compared to 16–40-year-olds. An increased association between APS and psychiatric morbidity across adolescence as suggested by Kelleher et al. (2012b) was not confirmed (Schimmelmann et al., 2015). A higher prevalence of the self-reported factor 'Perceptual Abnormalities' in 11–12-year-olds compared to 17–18-year-olds and lack of an association between self-reported attenuated psychotic-like experiences and psychiatric morbidity was also reported from a help-seeking CAD sample (Brandizzi et al., 2014).

Thus, alike BIPS, more research into the differentiation of atypical (i.e., not psychosis-predictive) and psychosis-related APS in larger CAD samples and with longer follow-ups is necessary. Longer follow-ups will be required to distinguish an actually lesser predictive value of APS from effects of a more insidious development of psychosis and a potential extended lag-time-to-conversion in CAD as suggested by Cornblatt et al. (2007).

4.3. Predictors of remission of an UHR state

Our UHR state overall remission rate of 25.7% (i.e., of 32.1% in non-converters) was slightly lower than the average overall remission rate of 35.4% (i.e., of 46% in non-converters) reported in a recent meta-analysis of mainly mixed-age samples with an average 2-year follow-up (Simon et al., 2013). However in line with Huber's notion of outpost syndromes (Schultze-Lutter, 2009), symptom fluctuations with only temporary remissions were also observed for UHR criteria (Lee et al., 2014; Woods et al., 2014), so that remission – alike non-conversion – at 1-year follow-up must be regarded as an intermediate outcome.

Neither socio-demographic nor clinical variables were found to predict remission; in line with de Wit et al. (2014) who also reported that baseline socio-demographic characteristics and clinical symptoms did not distinguish between remitters and non-remitters at 6-year follow-up of 44 UHR adolescents. Thereby, the most substantial reduction in positive symptoms occurred within the first 2 years, while improvements in general, mood and anxiety symptoms occurred at a later stage. This might explain why most non-converters – even if remitted from UHR status – still suffered from mental, mainly affective and anxiety disorders, in particular at short-term follow-ups (Addington et al., 2011; de Wit et al., 2014; Haroun et al., 2006; Lemos-Giráldez et al., 2009; Lin et al., 2014).

However, while all non-converters of our study continued suffering from a mental disorder without significant improvement in overall functioning, remitters from UHR status improved in both role and social functioning. This is partly in line with the only small 6-year improvement in global functioning of 33 adolescent non-converters whose UHR status at follow-up was not reported (Ziermans et al., 2014). Yet, a 3-year follow-up study of 77 adolescent non-converters reported good role and social functioning outcomes (defined by a score of '7' or higher on GF:Role or GF:Social) in at least two thirds that were significantly related to better baseline functioning (Carrión et al., 2013), and,

consequently, did not necessarily indicate significant functional improvement. Thus, functioning in adolescents might be more persistently affected than in older UHR samples, as improvement in non-converting mixed adult-adolescent samples within 3–6 years were significant, particularly within the first year (Lemos-Giráldez et al., 2009; Velthorst et al., 2011, 2013). The factors contributing to a lesser functional impairment that might also be related to a longer DUI still need to be examined.

5. Strengths and limitations

Our sample differs from other adolescent UHR samples in several aspects: (1) Being recruited at a hospital that is an Italian point of reference for the assessment and treatment of psychosis in CAD participants had been referred rather on the suspicion of a first episode of EOP than on that of a still developing psychosis as is usual when referring to an early detection service. Thus, similar to early UHR samples, our sample likely represents a more severe spectrum of the UHR state with high rates of BIPS and conversion and is not affected by a risk-dilution effect described for more recent samples (Yung et al., 2007), in particular for samples recruited from the community rather than – unlike our sample – from mental health services (Fusar-Poli et al., 2015). This sample bias can be considered both a strength and limitation of the study. (2) Only 5.6% of our sample had received any psychopharmacological treatment at baseline; this rate was much lower than the 41–49% medication rate reported by other adolescent UHR samples (Amminger et al., 2010; Carrión et al., 2013; Lindgren et al., 2014; Ziermans et al., 2011) allowing the observation of a more natural course. As any treatment seems to delay or prevent psychosis onset (van der Gaag et al., 2013), this low medication rate might have further contributed to both the high rate of BIPS and conversions. (3) A certain strength is the absence of any refusals to participate or drop-outs, while (4) the small sample size is a certain limitation similar to previous studies (Amminger et al., 2010; Fux et al., 2013; Lindgren et al., 2014; Welsh and Tiffin, 2014) which prevented a more detailed analysis of clinical outcomes. However, our analyses uniquely distinguished between APS- and BIPS-level risk symptoms, thereby giving new indications towards possible developmental peculiarities of UHR states in CAD.

6. Conclusions

Our findings provide first evidence for the predictive utility of UHR criteria in CAD in terms of BIPS when accompanied by signs of cognitive impairment, i.e., disorganized communication. Yet, as APS related to both thought content and perception were rather indicative of non-conversion at 1-year follow-up, their use in early detection of psychosis in CAD needs further study. Overall, the need for more in-depth studies into developmental peculiarities in the early detection and treatment of psychoses with an onset of illness in childhood and early adolescence was again highlighted. For this, it seems necessary to distinguish the predictive utility of risk phenomena (e.g. disorganized communication and unusual thought content/delusional ideas) and their severity category (e.g. APS and BIPS).

Conflicts of interest

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

Role of funding source

None.

Contributors

Dr. Armando designed this large First Episode Outcome Study. Dr. Pontillo, Dr. Decrescenzo, Dr. Mazzone, Dr. Monducci, Dr. Lo Cascio, Dr. Santonastaso and Dr. Pucciarini collected the data. Dr. Armando and Dr. Schultze-Lutter analyzed and interpreted the data. Dr. Armando, Dr. Schultze-Lutter, Dr. Vicari and Dr. Schimmelmann wrote the first draft of the manuscript. All contributed to and have approved the final manuscript.

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