A developmentally-stable pattern of premorbid schizoid-schizotypal features predicts psychotic transition from the clinical high-risk for psychosis state

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ABSTRACT

Background: Despite the extensive research performed on prediction of psychosis from a Clinical High Risk for Psychosis state (CHR-P), the positive predictive value of the CHR-P designation remains unsatisfactory and further models including additional clinical and biological variables are required. Existing studies indicate that schizotypy assessed at baseline in "at-risk" individuals may be considered a predictor of transition from CHR-P to psychosis. This approach, however, is burdened with bias resulting from a possible overlap between current psychopathology and schizotypal features. No studies so far have assessed schizotypy in CHR-P from a developmental perspective.

Aim: The aim of the study was to identify associations between a long-standing, parent-reported premorbid level of schizoid-schizotypal traits and the probability of psychotic transition in individuals with CHR-P.

Methods: The mothers of 107 individuals diagnosed as presenting CHR-P with the use of Comprehensive Assessment of At Risk Mental States12/2006 were interviewed with the Scale for the Assessment of Premorbid Schizoid-Schizotypal Traits (PSST).

Results: A high level of enduring schizotypy was found to be significantly associated with psychotic transition from CHR-P (HR: 1.78, 95% CI: 1.40–2.27, $p < 0.0001$), as indicated by the proportional hazards model, adjusted for age, sex and clinical covariates potentially related to the outcome. PSST items comprising negative schizotypy appeared to be the strongest predictors of transition.

Conclusions: The assessment of parent-reported, present early in the development premorbid schizoid-schizotypal traits, which can be easily performed in clinical settings, may be of value in estimating the probability of transition from an "at risk" state to psychotic disorder.

1. Introduction

Schizotypy is one of the well-known dimensions of psychosis-proneness. The concept of schizotypy derives from the observations of Kreapelin and Bleuler, who perceived schizophrenia as a developmental disorder and described latent forms of the illness in the relatives of schizophrenia patients [1,2]. Subsequently developed by Rado [3] and Meehl [4], the construct of schizotypy reflects a phenotypic expression of vulnerability to schizophrenia, which involves subtle but clinically-relevant abnormalities in thoughts, emotions, perception and interpersonal functioning. Schizotypy can also be conceptualised as a part of a normal personality, which may nevertheless constitute a background for the development of psychotic illness [5]. Corresponding to schizophrenia, schizotypy is described as a multidimensional construct, comprising positive (cognitive-perceptual), negative (interpersonal) and disorganized domains [6–8]. Some authors also distinguish a further dimension of behavioral symptoms, including impulsiveness, aggression and nonconforming behaviour, i.e. impulsive nonconformity [9–11].

Today schizophrenia is indeed considered a neurodevelopmental disorder [12,13]. Clinically, the pathological process may progress to full-blown illness through the development of subtle abnormalities in cognitive and social functioning and a distinct prepsychotic phase, currently known as clinical high risk for psychosis (CHR-P) [14].

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A considerable body of literature indicates that schizotypy may be considered a precursor to schizophrenia-spectrum disorder [15–18]. In this regard, schizotypal expression during childhood or adolescence may be understood as the presence of "early and broadly-defined mental risk states" associated with the future development of a psychotic disorder [19]. Surprisingly, little attention has been paid to schizotypy as a potential factor influencing the probability of transition from a strictly-defined "at risk" state (CHR-P) to psychosis. Some studies have found that schizotypal traits present at baseline assessment predict conversion from an "at risk state" to psychosis [20–25]. However, following a meta-analysis of literature material, Debbane et al. [26] conclude that little clinically-significant predictive value is presented by the positive dimension of schizotypy for the transition from CHR-P to psychosis. In fact, the negative dimension, especially physical anhedonia, appears to be a better predictive indicator of conversion [20,21,26,27], while other studies demonstrate no link between baseline schizotypy level and transition [28]. Any study in this field is subject to the potential bias resulting from the substantial degree of phenomenological overlap between CHR-P criteria and schizotypy, understood as an enduring pattern of abnormal social and cognitive functioning. This particularly regards the relationship between attenuated positive symptoms present in the CHR state and the positive dimensions of schizotypy, including magical thinking and unusual thought content. Therefore it is essential to differentiate between CHR-P symptoms which require *state* characteristic (operationalized by fulfilling "onset/worsening" criteria) and schizotypal *trait* manifestations which were stable during the past [26,29]. Indeed, various diagnostic approaches to "at risk" states, including require the criterion of onset (or substantial intensification of symptoms) to have been met within the previous 12 months [30–32]. In contrast, the identification of schizotypal features requires a pervasive pattern of deviant functioning which can be traced back at least to adolescence or early adulthood [30], or a pattern which has been present over a period of at least two years with no definite onset [33].

This distinction should be considered in studies aimed at better understanding the role of schizotypy in developmental trajectories resulting in schizophrenia-spectrum disorder among CHR-P individuals, as these individuals may represent an intermediate link between the clinically-latent potential pathological process and full-blown psychosis.

Existing studies assess the level of schizotypy in CHR-P individuals on the basis of self-administered questionnaires which concern the current status and the period covered by the memory of the examined person [20,21,25,27,28,34]. This approach can potentially be associated with a risk of bias deriving from the overlapping of schizotypal features and current psychopathology. No studies so far have assessed schizotypal traits of individuals "at-risk" for psychosis, observed by parents or caregivers from the early stages of their development.

The aim of the current study was to identify associations between a long-standing, developmentally-stable parent-reported premorbid level of schizotypy and the probability of psychotic transition in individuals with CHR-P.

2. Methods

2.1. Subjects and settings

The study included 107 individuals diagnosed as presenting CHR-P. All were participants of the Programme Of Recognition and Therapy (PORT): a clinical service dedicated to individuals "at risk" of developing psychotic disorder. The programme has been described in detail previously [35]. The inclusion criteria comprised meeting the criteria of CHR-P according to the CAARMS12/2006 (At Risk Mental State, ARMS) [32], and the availability of the parent (mother as first priority). The exclusion criteria were as follows: 1) the documented presence of a neurological disorder, 2) evidence of intellectual disability or 3) a

diagnosis of psychotic disorder established according to ICD-10 criteria, which is approved as the main classification in Poland [33,35].

The CHR-P state was identified with the use of the Polish version of the CAARMS [32,36]. According to the CAARMS guidelines, an "at risk" state can be diagnosed in the presence of at least one of the following: 1) attenuated psychotic symptoms (APS), 2) Brief Limited Intermittent Psychotic Symptoms (BLIPS - an episode of severe psychotic symptoms which resolved spontaneously within one week and occurred during the past 12 months) or 3) genetic risk plus mental state deterioration (GRD) [32]. The level of psychosocial functioning was evaluated with the Social Occupational Functioning Scale (SOFAS), which is an essential part of the CAARMS [32].

Demographic data was obtained with the use of a semi-structured interview. The level of intelligence, defined as Intelligence Quotient (IQ), was assessed as a part of neurocognitive evaluation of PORT participants [35] with Wechsler Intelligence Scales (for Children or for Adults), Polish versions [37,38].

The study was carried out in accordance with the latest version of the Declaration of Helsinki. The study protocol was accepted by the Medical University of Lodz Ethics Committee. Written informed consent was obtained from both the participants and the informants, these being the mothers of the participants.

All subjects included in the study were CHR-P individuals, consecutively referred to PORT between May 2010 and December 2017.

2.2. Assessment of premorbid schizoid-schizotypal traits

The level of premorbid schizoid-schizotypal traits was assessed at baseline through interviews with the mothers of the participants using a Polish version of the Scale for the Assessment of Premorbid Schizoid-Schizotypal Traits (PSST) by Foerster et al. [39,40]. The tool comprises seven items, each with a standardised entry question and a four-point (0–3) scale: maximum score is 21 points, with a higher score indicating greater impairment. The scale addresses negative- (sociability, demonstrative affect, social sensitivity/suspiciousness), positive- (ideas of reference/perceptual distortion) and disorganized schizotypy (speech disorganization), as well as antisocial behaviour carried out with a delinquent peer group or alone. The level of premorbid schizotypy is measured as the total PSST score, with a maximum score of 21. The surveyed mothers were instructed to consider enduring personality traits, stably present since childhood and not resulting from the current symptomatology.

2.3. Treatment

As the major therapeutic strategy in PORT is based on providing needs-based interventions, psychological for the first instance, CHR-P individuals did not receive any systematic treatment [35]. As far as pharmacological treatment is concerned, antidepressants and mood stabilizers were used to treat comorbid disorders. In rare cases, strictly defined in the International Clinical Practice Guidelines for Early Psychosis [41], antipsychotic medications were administered.

2.4. Outcome measures

The transition from CHR-P state to any form of psychotic disorder as a function of time was considered the study outcome. Baseline time was defined as the moment of entering the PORT programme. The transition was determined on the basis of CAARMS criteria for psychosis threshold [32]. To further validate the transition and to determine its diagnostic category, ICD-10 criteria were applied [33]. Participants were evaluated with CAARMS every three months, or more often, depending on their needs and the dynamics of symptoms. Consecutive follow-up assessments were performed by clinicians who were blinded to the baseline evaluation of schizoid-schizotypal traits.

2.5. Data analysis

As the parameters were found to have a non-normal distribution, descriptive statistics were given as median and 25th–75th percentile or absolute and relative frequencies, if not stated otherwise. The Kaplan-Meier method was used in survival analysis to estimate transition rates at various time points. The time-to-event models were developed using Cox proportional hazards regression with estimation of hazard ratio (HR) and 95% confidence intervals (CI). The associations between the variables were assessed using Spearman's rho. The false discovery rate (FDR) for the associations was controlled at the level of 0.05 with the Benjamini and Hochberg correction for testing multiple hypotheses. *p*-Values below 0.05 were considered statistically significant. The analysis was performed using STATISTICA 13.1 software (StatSoft, Tulsa, OK, USA).

3. Results

3.1. Clinical and demographic characteristics

The basic demographic and clinical data of CHR-P individuals participating in the study are shown in Table 1. The majority of the patients presented APS, and their psychosocial functioning, illustrated by a median SOFAS score of 50, was seriously impaired.

3.2. Transition to psychosis

The median follow-up period for the entire sample was 39 months (25th–75th percentile: 24–75 months) and the mean follow-up duration was 47 months ($\pm$31 months).

Twenty of the 107 CHR-P participants (18.7%) transitioned to psychosis during the observation period. The transition rates at subsequent time points estimated by the Kaplan-Meier method were as follows: 10.3% (95% CI: 4.5%–16.0%) after six months, 15.1% (95% CI: 8.3%–21.9%) after 12 months and 17.9% (95% CI: 10.6%–25.3%) after both 24 and 36 months. The median and mean time to transition were five months (25th–75th percentile: 3.5–10.5 months) and 9.1 months ($\pm$8.9 months), respectively.

3.3. Association between the level of premorbid schizoid-schizotypal traits and the transition to psychosis

The univariate Cox proportional hazards model indicated that premorbid schizotypy (measured as the PSST score) was a statistically significant predictor of transition from CHR-P to psychosis (HR: 1.66, 95% CI: 1.41–1.96, *p* < 0.0001). The effect was consistent after adjusting for covariates which were found to be potentially related to the outcome (univariate Cox regression analyses, *p* < 0.1): the Unusual Thought Content and Disorganized Speech items of CAARMS Positive Symptoms scores, the Alogia item of CAARMS Negative Symptoms score, the SOFAS score, and BLIPS subgroup of the CHR-P (HR: 1.78, 95% CI: 1.40–2.27, *p* < 0.0001). Hence, each additional score on the PSST scale (score range: 0–21) increases the risk of conversion by ca 78%. Proportional hazards assumption test for a Cox regression model fit was met for the above models (*p*-values for the dependent variable were: 0.11 and 0.71, respectively), indicating that premorbid schizotypy may be considered as a time-independent predictor of psychotic transition from CHR-P. The effect of premorbid schizotypy on the risk of transition is illustrated by Fig. 1. All nine study participants who achieved the highest recorded PSST total score (9 to 12) transitioned to psychosis within first 24 months from study entry, and none of the seven individuals who did not display any schizoid-schizotypal traits in their childhood or adulthood (PSST total score equal to zero) developed a psychotic disorder in the follow-up period.

Premorbid schizotypy was found not to be significantly associated with either positive or negative symptoms presented by CHR-P individuals or with the level of their psychosocial functioning: none of the tested significance of correlation coefficients survived the Benjamini and Hochberg correction for multiple comparisons (Table 2).

Table 3 presents the results regarding associations between particular items of premorbid schizoid-schizotypal traits scale and the conversion from CHR-P state to psychotic disorder. All analysed premorbid schizoid -schizotypal traits were found to be significantly associated with psychotic transition. However, high levels of premorbid negative schizotypy comprising social isolation, restricted affect and social anxiety/suspiciousness, appeared to be the strongest predictor of the future conversion to full-blown psychosis.

Table 1
Sociodemographic and clinical characteristics of the CHR-P sample (n = 107).

Variable	Median (25th–75th percentile) or n (frequency)
Sex	
Female	56 (52.3%)
Male	51 (47.7%)
Age [years]	18 (16–20)
Years of education	11 (9–12)
IQ	106 (97–112)
CAARMS positive symptoms	
Unusual thought content	3 (0–4)
Non-bizarre ideas	3 (0–4)
Perceptual abnormalities	0 (0–4)
Disorganized speech	2 (0–3)
CAARMS negative symptoms	
Alogia	2 (0–3)
Avolition/apathy	4 (2–5)
Anhedonia	4 (3–5)
SOFAS	50 (45–55)
CHR-P subgroup	
APS	72 (67.3%)
BLIPS	3 (2.8%)
GRD	16 (15.0%)
APS + GRD	15 (14.0%)
BLIPS + GRD	1 (0.9%)

APS - attenuated psychotic symptoms.
BLIPS - brief limited intermittent psychotic symptoms.
CAARMS - Comprehensive Assessment of At Risk Mental States.
CHR-P - clinical high risk for psychosis.
GRD - genetic risk and deterioration syndrome.
IQ - intelligence quotient
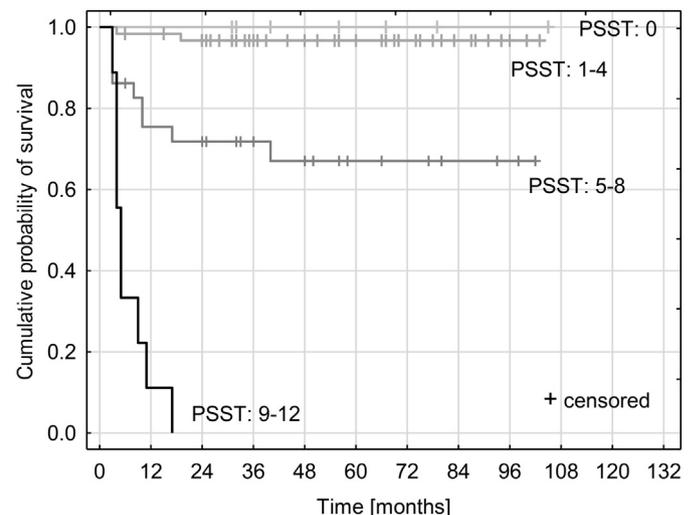SOFAS - Social and Occupational Functioning Assessment Scale.

Fig. 1. The risk of transition as a function of time for multiple Premorbid Schizoid Schizotypal Assessment (PSST) total scores. The scores were grouped to clarify the graphical presentation by dividing it into four classes: 0 (n = 7), 1–4 (n = 62), 5–8 (n = 29) and 9–12 (n = 9).

Table 2

Relationships of premorbid schizotypy, measured as Premorbid Schizoid Schizotypal Traits Scale (PSST) total score, with positive and negative comprehensive assessment of at risk state symptoms and with the level of psychosocial functioning. None of the associations were found to be statistically significant. The Benjamini and Hochberg corrected significance level was 0.0063.

Variable	Spearman's rho	p-Value
Unusual thought content	0.01	0.92
Non-bizarre ideas	0.04	0.68
Perceptual abnormalities	−0.03	0.77
Disorganized speech	0.11	0.27
Alogia	0.23	0.019
Avolition/Apathy	0.03	0.80
Anhedonia	0.07	0.50
SOFAS score	−0.22	0.024

SOFAS - Social and Occupational Functioning Assessment Scale.

As the PSST scale refers to a four-dimensional model of schizotypy, we adopted our data to this model and analysed the inter-correlations between PSST dimensions. The results indicate that from the four schizotypal dimensions, only three (negative, positive and disorganized) were significantly associated with each other, while antisocial schizotypy was not correlated with any other dimension (Table 4). After merging the associated subscales to a single latent variable, which was named "core schizotypy", a multivariate model was developed based on "core schizotypy" and "antisocial" dimensions. The model showed that both variables independently contribute to the risk of transition of psychosis (Table 5). This finding is indication of the possible contribution of antisocial schizotypal expression to psychotic conversion from CHR-P.

4. Discussion

The present study assesses the associations between the premorbid level of schizoid-schizotypal traits and the probability of psychotic transition from CHR-P.

Our findings suggest the presence of a strong relationship between the level of premorbid schizotypy and the risk of such transition. Premorbid schizoid-schizotypal traits should be considered an independent predictor of conversion, as indicated by the fact that the effect remained stable after adjustment for variables potentially associated with the outcome, and that the correlations between total PSST score and other clinical measures were insignificant. This is consistent with previous studies, even though they referred to current levels of schizotypal expression presented by CHR-P individuals [20–25]. Additionally, our findings confirm that, apart from "core schizotypy", the

Table 4

Inter-correlations between particular dimensions of schizotypy in Clinical High Risk for Psychosis sample.

SCHIZOTYPY DIMENSION	Positive	Disorganized	Behavioral (Antisocial)
Negative	0.41 $p<0.0001$	0.33 $p=0.0005$	-0.11 $p=0.27$
Positive		0.40 $p<0.0001$	0.02 $p=0.86$
Disorganized			0.14 $p=0.14$

The absolute value of Spearman's rho	Colour
<0.1	
≥0.1 and <0.2	
≥0.2 and <0.3	
≥0.3 and <0.4	
≥0.4	

antisocial aspects of schizotypal expression, not analysed in most studies, may constitute an independent factor increasing the probability of future psychotic transition. Lin et al. [34] indicate that Impulsive Nonconformity, i.e. the factor corresponding most closely with the antisocial behaviour items of the PSST, proved not to be a robust factor underlying schizotypy; however, this study again referred to current rather than premorbid psychopathological expression. Our present results are also in line with meta-analytical findings [26], and those from the recent studies [20,21,26,27] which indicate that it is not so much the broadly defined schizotypy as its negative dimension that can be considered a predictor of transition.

The major advantage of the present study is that it assesses schizotypy from a developmental perspective. Although the PSST scale used for the assessment of premorbid schizotypy levels is relatively

Table 3

Relationships between particular premorbid schizoid-schizotypal traits and the conversion from Clinical High Risk for Psychosis state to psychotic disorder.

Observed variable		Univariate Cox proportional hazards models for each observed variable		Adjusted[a] Cox proportional hazards models for each observed variable	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
1	Social isolation	3.36 (1.95–5.78)	<0.0001	3.09 (1.62–5.91)	0.0006
2	Demonstrative affect	3.04 (1.91–4.85)	<0.0001	2.98 (1.79–4.97)	<0.0001
3	Suspiciousness/sensitivity	3.34 (1.94–5.76)	<0.0001	3.13 (1.68–5.82)	0.0003
4	Thought content/beliefs/perception	2.33 (1.49–3.62)	0.0002	2.63 (1.43–4.84)	0.0019
5	Speech	2.65 (1.68–4.20)	<0.0001	2.34 (1.25–4.39)	0.0082
6	Antisocial behaviour (with peer group)	1.71 (1.01–2.90)	0.048	2.01 (1.11–3.62)	0.021
7	Antisocial behaviour (alone)	1.80 (1.02–3.16)	0.041	2.34 (1.17–4.67)	0.016

Proportional hazards assumption was met for all the Cox regression models reported in the Table.

[a] Adjusted for: sex, age, Unusual Thought Content, Disorganized Speech and Alogia (Comprehensive Assessments of At Risk Mental States items), Scale of Occupational and Social Functioning score, and Brief Limited Intermittent Psychotic Symptoms subgroup of Clinical High Risk for Psychosis.

Table 5

Multivariate Cox proportional hazards models for the associations between "core schizotypy" and "antisocial" dimension with the transition to psychosis.

Latent variable	Multivariate Cox proportional hazards model		Multivariate Cox proportional hazards model adjusted[a] for covariates	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Core schizotypy	1.66 (1.40–1.96)	<0.0001	1.76 (1.37–2.25)	<0.0001
Antisocial dimension	1.70 (1.19–2.42)	0.0037	2.01 (1.23–3.28)	0.0050

Core schizotypy comprised negative, positive and disorganized dimensions. Proportional hazards assumption was met for all components of the Cox regression models reported in the Table.

[a] Adjusted for: sex, age, Unusual Thought Content, Disorganized Speech and Alogia (Comprehensive Assessments of At Risk Mental States items), Scale of Occupational and Social Functioning score, and Brief Limited Intermittent Psychotic Symptoms subgroup of Clinical High Risk for Psychosis.

simple in comparison to extensive self-report questionnaires for evaluation of schizotypy [11,42–44], it also covers the major schizotypal traits. As it is based on parental reports, the scale clearly refers to long-term, stable patterns of personality features present from childhood; these typically did not directly prompt help-seeking behaviour by CHR-P individuals or their families, unless a significant exacerbation occurs in their intensity. Such approach help to minimalize the possible overlap between current symptomatology associated with CHR-P, or *state schizotypy*, and enduring schizotypal expression, or *trait schizotypy*. This overlap and the need for differentiation between *trait* versus *state* symptoms of schizotypy is regarded as the major methodological problem in studies of this kind [26]. However, some overlap in the present study cannot be excluded, especially if the difference was more quantitative than qualitative,

The obtained results are supported by the relatively long-time of follow-up (median 39 months) and the use of time-dependent analysis which is validated in the CHR-P literature and brings the findings closer to the real-world clinical experience [45].

As all the CHR-P individuals with psychotic transition developed schizophrenia, the results of the study may be considered as a valid assessment of premorbid schizotypy in the progression from CHR-P to schizophrenia, and not just to psychotic disorders in general.

Our present findings reflect the neurodevelopmental nature of schizophrenia [12,13]. Schizotypal traits observed from the early stages of life may be one of the clinical manifestations of the pathological process, resulting in the development of schizophrenia-spectrum disorder. Our present findings provide useful clinical information that the presence of a stable pattern of premorbid schizoid-schizotypal traits, especially from the negative domain, may indicate an increased probability of transition from an "at risk" state to schizophrenia. However, these observations should be regarded cautiously, as developmental psychopathology has highly variable outcomes (multifinality) [29,46], and the development of schizophrenia is a complex process with various developmental interactions engaged (equifinality) [29,47,48]. Additionally, it seems important to be aware that several interactions between particular dimensions of schizotypy occur during adolescence, increasing the risk of psychotic outcome [49,50]. Hence, the evaluation of premorbid schizoid- schizotypal expression, although informative for practising clinicians, should rather play a complementary role in estimating the probability of transition to psychosis in CHR-P individuals.

The major limitation of the study was the small sample size; however, the size was sufficient to achieve the statistical power necessary to demonstrate the main effect. In addition, the sampling method used to include the subjects to the study was a convenience non-probability method, which does not assure complete representativeness of the sample. However, since the recruitment strategies adopted in the PORT service are in line with the strategies used worldwide by other CHR-P services [51], and the level of risk enrichment in our sample (14%) is comparable to the meta-analytical mean (15%) [52], the sample may be considered representative of CHR-P services from different countries.

Moreover, it must be admitted that the CHR-P paradigm itself is controversial, with its key criticisms being that it offers limited value in detecting individuals "at risk for psychosis" in the general population, it

has insufficient prognostic accuracy in help-seeking populations and lacks diagnostic pluripotentiality [53–55]. Indeed, the actual transition rates in CHR-P samples are mostly determined by their risk enrichment during the recruitment phases [52,56].

The validity of the CHR-P paradigm as the prototypical state of risk for psychosis, as well as its narrow perspective, which is limited to positive psychotic symptoms, are also the subject of discussion [55,57,58]. Therefore, the need for a refined approach to CHR-P is postulated [54,59]. The development of individualized transdiagnostic risk calculators including multidimensional psychopathology offers potential for future research and clinical practice [60,61]. In this scenario, the search for key neurobiological markers indicative of development of psychosis from CHR-P may turn out to be a "dead end" topic for research in the field [54]. Even so, personality traits and cognitive dysfunctions are nevertheless included in proposed new assessment instruments [62]. Therefore, research in the field should be continued, possibly with larger samples. Larger studies could allow for multidimensional testing of the significance of schizotypy- among other clinical variables- clinical variables, including in promoting the risk of psychotic transition in CHR-P individuals. This may also clarify the role played by premorbid schizotypal expression in the development of particular subtypes of CHR-P (e.g. APS, VUL, BLIPS), and its association with transition risk in these subgroups. The potential significance of including schizotypy as a therapeutic goal within the prevention of schizophrenia would also be worth exploring. This, however, raises serious ethical dilemmas [63]. On the other hand, therapeutic interventions are postulated to be undertaken in the CHR-P state, as indicated prevention against developing psychotic disorder [59,64–66]. Since these interventions should be personalized, e.g. tailored to individual needs of "at risk" individuals [67], our present findings may offer some practical value: help-seeking "at risk" individuals who present an enduring pattern of schizoid-schizotypal traits should be closely monitored for the development of full-blown psychotic illness and offered specific therapeutic interventions.

To conclude, the results of the study highlight the potential need for including premorbid schizotypal expression as complementary information in estimating the probability of transition from CHR-P to psychotic illness.

Acknowledgment

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