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Rolle von subklinischen Negativsymptomen in der Psychoseprädiktion bei Kindern und Jugendlichen

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ZUSAMMENFASSUNG

Rolle von subklinischen Negativsymptomen in der Psychoseprädiktion bei Kindern und Jugendlichen

Bei Kindern und Jugendlichen wurde postuliert, dass subjektiv erlebte, abgeschwächte Negativsymptome (NS) am besten geeignet sind, um Patienten mit klinischem Hochrisiko für eine Psychose (CHR-P) von anderen Patienten zu unterscheiden und am stärksten für das Auftreten einer späteren Psychose prädiktiv sind. Um diese Annahme zu überprüfen, analysierten wir Daten von 8- bis 17-jährigen CHR-P-Patienten (n = 183) und stationären Patienten ohne klinischen Verdacht auf eine Psychose (n = 277). Die Analysen basierten auf Querschnittsdaten sowie naturalistischen Follow-up-Daten aus einer schweizerisch-deutschen Studie mit einer Beobachtungsdauer von zwei Jahren. Die CHR-P-Kriterien und weitere Symptome wurden mithilfe des Schizophrenia Proneness Instrument, Child & Youth Version, und des Structured Interview for Psychosis-Risk Syndromes erfasst. Zur Identifizierung von Clusterprofilen und der aussagekräftigsten Prädiktoren wurden paarweise Vergleiche, zweistufige Clusteranalysen und Cox-Regressionen durchgeführt.

In paarweisen Vergleichen unterschieden kognitive und perzeptive Basissymptome sowie abgeschwächte positive Symptome CHR-P-Patienten besser von Nicht-CHR-P-Patienten und Konverter von Nicht-Konvertern als die Negativsymptom-Subskalen „Adynamie“ und „Negative Symptome“. In der stabilen Zwei-Cluster-Lösung, die Patienten mit hohen (n = 338) bzw. niedrigen (n = 122) Werten auf allen Skalen umfasste, erwies sich „Adynamie“ als wichtigster Faktor (Bedeutung = 1,0). Der Cluster mit hohen Werten umfasste den größten Anteil der CHR-P-Patienten (86,9 %) und Konverter (84,6 %) und sagte die Entwicklung einer Psychose vorher. Die Cox-Modelle der Subskalen unterschieden sich hinsichtlich der ausgewählten Prädiktoren in Abhängigkeit von der analysierten Stichprobe (Gesamtstichprobe, CHR-P-Stichprobe und Stichprobe der Patienten mit Ultra-High-Risk-Status [UHR]). Der frühere Befund, dass „Negative Symptome“ bei UHR-Patienten ein Prädiktor der Konversion waren, konnte repliziert werden, wenn ausschließlich SIPS-Subskalen berücksichtigt wurden.

Unsere Ergebnisse stützen somit teilweise die Bedeutung subjektiv erlebter, abgeschwächter negativer Symptome für die Identifizierung von CHR-P-Patienten und die Vorhersage einer späteren Psychose. Sie deuten jedoch auch darauf hin, dass die Rolle negativer Symptome in hohem Maße von der Zusammensetzung der Stichprobe abhängt.

Schlüsselwörter: Klinisches Hochrisiko; Psychose; negative Symptome; Basissymptome, Kinder; Jugendliche

SUMMARY

Role of Subclinical and attenuated negative symptoms in the prediction of psychosis in children and adolescents

In children and adolescents, subjective and attenuated negative symptoms were hypothesized to best differentiate clinical-high risk for psychosis (CHR-P) from other patients, and to be most predictive of psychosis. To examine this, we analysed data from 8-17-year-old CHR-P patients (n=183) and inpatients not clinically suspected of developing psychosis (n=277) based on cross-sectional and two-year naturalistic follow-up data from a Swiss-German study. CHR-P criteria and other symptoms were assessed using the Schizophrenia Proneness Instrument, Child & Youth version, and the Structured Interview for Psychosis-Risk Syndromes. Pairwise comparisons, two-step cluster analyses and Cox regression models were applied to identify cluster profiles and the best predictors of psychosis.

In pairwise comparisons, cognitive and perceptive basic symptoms, and attenuated positive symptoms better distinguished CHR-P patients from non-CHR-P patients and converters from non-converters than the negative symptom subscales "Adynamia" and "Negative symptoms. In the stable two-cluster solution of patients scoring high (n=338) and low (n=122) on all scales, "Adynamia" was most important (importance=1.0) whereby the high-scorer cluster included most of CHR-P (86.9%) and converters (84.6%), and was predictive of psychosis. Cox models of subscales differed in the selected predictors depending on the analysed samples (total sample, CHR-P and ultra-high risk only (UHR)), whereby the earlier report of "Negative symptoms" predicting conversion in UHR was replicated when only SIPS subscales were considered.

While our findings partially support the significance of subjective and attenuated negative symptoms in CHR-P and psychosis prediction, they also suggest that the role of negative symptoms is highly dependent on sample composition.

Key words

Clinical high risk; psychoses; negative symptoms; basic symptoms, childhood; adolescence

LIST OF ABBREVIATIONS

AOS Adult-Onset Schizophrenia

APA American Psychiatric Association

APS Attenuated Psychotic Symptoms

BS Basic Symptoms

BLIPS Brief Limited Psychotic Symptoms

CAD Children and Adolescents

CARE Computer-assisted Risk Evaluation

CC Clinical Control Group

CHR Clinical High-Risk

CHR-P Clinical High-Risk for psychosis

COGDIS Cognitive Disturbances

COPER Cognitive-Perceptive basis symptoms

COS Childhood-Onset-Schizophrenia

DALYs Disability-Adjusted Life Years

DUI Duration of Untreated Illness

DUP Duration of Untreated Psychosis

DSM Diagnostic and Statistical Manual of Mental Disorders

DSM-5-TR Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision

EOS Early-Onset Schizophrenia

EOS/VEOS Early-Onset Schizophrenia and Very-Early-Onset-Schizophrenia

EPA European Psychiatric Association

ESCAP European Society for Child and Adolescent Psychiatry

EOP Early-Onset Psychosis

GAF Global Assessment of Functioning

ICD International Statistical Classification of Diseases and Related Health Problems

NS Negative Symptoms

PTSD Posttraumatic Stress Disorder

ROC Receiver Operating Characteristic

SIPS Structured Interview for Psychosis-risk Symptoms

SPI-A Schizophrenia Proneness Instrument, Adult Version

SPI-CY Schizophrenia Proneness Instrument, Child and Youth version

UHR Ultra-High Risk

VEOS Very Early-Onset Schizophrenia

WHO World Health Organisation

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1. INTRODUCTION

1.1. Psychosis and schizophrenia

Psychosis is a clinical syndrome characterized by a constellation of mental symptoms(Gaebel & Zielasek, 2015). Etymologically, it signifies an abnormal state of the mind (from Greek psykē meaning "mind" and -osis meaning "abnormal condition"). Early editions of the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM)(The Committee on Nomenclature and Statistics of the American Psychiatric Association, 1968) defined it as a ''gross impairment in reality testing'' or a ''loss of ego boundaries'' that significantly impairs the affected individual. More recent classifications (American Psychiatric Association, 2022) operationalized this concept by identifying its classic symptoms: delusions, hallucinations, disorganized thinking (manifested in speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms. According to Peters (Peters, 1977), consensus on its core symptoms is insufficient; defining psychosis requires the inclusion of more criteria like a profound absence of insight, communication impairment, a lack of comprehensibility of the manifestations of the disease and a significant social decline.

According to the International Classification of Diseases - 11th Revision (ICD-11)(World Health Organization, 2019), psychoses, in their primary form— i.e., independent of a medical or toxic aetiology—can be classified as schizophrenia, schizoaffective disorder, delusional disorder, and acute and transient psychotic disorder, among others. Its point prevalence is similar across countries and appears to be rising(Charlson et al., 2018).

Psychoses are a significant contributor to disability, with onset occurring as early as age 10 and lasting into adulthood (Gore et al., 2011). It is thus a disease of young people that represents enormous economic disadvantages for the affected population. The societal cost of psychosis is substantial but difficult to quantify precisely. In Western countries, direct costs for schizophrenia alone constitute up to 2.6% of total health expenditure, representing a significant portion (7–12%) of gross national income (Barbato, 1998). A systematic review performed by Gustavsson (Gustavsson et al., 2011) with European data from 2010 showed an estimated cost per person for psychotic disorders of €93,9 billion in only direct costs, medical and nonmedical. Indirect costs encompass productivity losses stemming from absenteeism or sick leave, presenteeism (reduced work productivity), unemployment, permanent disability, and early retirement, affecting patients, family members, or caregivers.

They are estimated to contribute to 50%–85% of the total costs associated with schizophrenia (Chong et al., 2016).

The initial manifestation of psychotic disorder symptoms typically occurs, on average, five years before diagnosis, extending thus deep into adolescence and childhood. These early signs are often underdiagnosed in daily clinical practice. Schizophrenia manifesting before age 18 is categorized as early-onset schizophrenia (EOS), with onset prior to age 13 defined as childhood-onset schizophrenia (COS) or Very Early-Onset Schizophrenia (VEOS) (Clemmensen et al., 2012; Driver et al., 2020).

The global burden of mental illness appears to be underestimated (Vigo et al., 2016). Schizophrenia alone ranged second place of the disease with the most daily adjusted life disability (DALYs) amongst 15–19-year-old adolescents, according to data from WHO's 2004 Global Burden of Disease study(Gore et al., 2011). The impairment associated with psychosis is so severe that only 15% of affected individuals are employed. The latter is largely attributed to negative symptoms (Anthony & Blanch, 1987; Nordstroem et al., 2017).

1.2. Negative symptoms of schizophrenia

Negative symptoms (NS) are present in 90 per cent of people with schizophrenia and include five phenomena, mainly assessed by observation: blunted affect (a decrease in the observed expression of emotion), alogia (reduced quantity of speech and its spontaneous elaboration), anhedonia (diminished capacity to experience pleasant emotions), asociality (reduction in motivation for social contacts) and avolition (reduced initiation and persistence of goal-directed activity) (Marder & Galderisi, 2017).

Negative symptoms have been crucially important in the psychopathology of schizophrenia for over 100 years. Eugen Bleuler described four group of symptoms, the so-called 4 As: blunted Affect (diminished emotional response to stimuli); loosening of Associations (by which he meant a disordered pattern of thought, inferring a cognitive deficit), Ambivalence (an apparent inability to make decisions, again suggesting a deficit of the integration and processing of incident and retrieved information) and Autism (a loss of awareness of external events, and a preoccupation with the self and one's own thoughts). For him these abnormalities were the main characteristic of schizophrenia (*Grundsymptome*) and positive symptoms were merely accessory (*akzessorische Symptome*) (Bleuler, 1911; McNally, 2009).

NS are particularly heterogeneous and can be divided into primary – due to schizophrenia - and secondary negative symptoms – i.e. due to positive, depressive, social deprivation, medication side effects and substance abuse -; as a whole, they are responsible for the most pronounced functional dysfunction associated with the disorder (Kirschner et al., 2017; Okada et al., 2021). The heterogeneity of the negative symptom dimension is regarded as a potential confounder in research and education, and an obstacle to proper management(Galderisi et al., 2017, 2018; Mucci et al., 2017).

NS significantly impair social functioning in schizophrenia and are linked to poorer outcomes like reduced quality of life and poor response to therapeutic interventions during adolescence(Galderisi et al., 2016; Nordstroem et al., 2017; Salazar De Pablo et al., 2023).

Efforts over the last two decades to enhance the conceptualization and assessment of NS have contributed to reducing their overlap with other schizophrenia dimensions and to identifying areas with unclear demarcations (Galderisi et al., 2018).

Significant developmental differences distinguish the clinical presentation of psychosis in minors from that in adults. These developmental factors are critical for early psychosis detection and may explain the longer duration of untreated psychosis (DUP) and lower conversion rates to manifest psychosis observed in minors (Baeza et al., 2024; Marshall et al., 2005; Penttilä et al., 2014; Schimmelmann et al., 2008; Schultze-Lutter, Michel, et al., 2015). A longer DUP is associated with severe negative symptoms (Boonstra et al., 2012).

1.3. Negative symptoms in children and adolescents

From a psychopathological perspective, patients with early-onset exhibit significantly more prodromal symptoms, with a higher frequency of thought disorders, avolition, and hallucinations compared to patients with adult-onset psychosis (AOP)(Baeza et al., 2024). A systematic review and meta-analysis by De la Higuera (de la Higuera-Gonzalez et al., 2025) showed lower memory performance in patients with EOS compared to adults.

Very Early Onset Schizophrenia (VEOS) is characterized by a higher prevalence of visual hallucinations, and significant comorbidities with neurodevelopmental disorders (Di Luzio et al., 2023), cognitive deficits, impaired attention and motor speed, difficulties in verbal learning, and a high prevalence of hallucinations (David et al., 2011; Kao & Liu, 2010; Tuulio-Henriksson et al., 2004). Armita et. al(Armita et al., 2025) reported mean IQ scores in patients with VEOS one to two standard deviations below normative data. Attentional deficits are evident, with longer reaction times, more omission/commission errors, and

slower processing speed than controls. Working memory and executive functions like planning and cognitive flexibility are also impaired.

Further disturbances can manifest across social, motor, and language domains, alongside cognitive and learning disabilities, which are present in up to 50% of cases. Notably, a study found that 27% of children-onset schizophrenia patients met the criteria for an autism spectrum disorder(Di Luzio et al., 2023).

This discrepancy between clinical presentations is traceable to peculiarities in brain maturation. Psychoses are considered as a brain development disorder with polygenic heredity. Negative symptoms seem to involve a unique pathophysiological mechanism. Beyond previously described developmental pathologies and atrophic changes, insufficient stimulation of frontal lobe D1 and D3 dopamine receptors appears to contribute to the negative symptoms and cognitive impairments characteristic of schizophrenia spectrum disorders(Cummings et al., 2025).

Brain development and maturation are markedly abnormal: Genetic vulnerability translates into aberrant synapse formation and higher complement protein levels that tag synapses for glial elimination. In parallel, environmental risk factors for schizophrenia may prime glia during early development, reactivating them later to facilitate aberrant synaptic pruning(Howes & Onwordi, 2023). Assuming the various cognitive and negative symptoms mentioned above are a consequence of manifest psychosis and its resulting irreversible cerebral neurobiological alterations, then attention should be directed towards prior states where these symptoms were not present, i.e. clinical high-risk (CHR) states.

A systematic review by Tor and colleagues (Tor et al., 2018) showed that children and adolescents at CHR for psychosis exhibit several baseline clinical characteristics. Most commonly, attenuated positive symptoms, such as perceptual abnormalities and suspiciousness, were observed. Comorbid conditions, including depressive and anxiety disorders, were also frequently reported. Compared to healthy controls, CHR samples showed significantly lower general intelligence and verbal intelligence quotient, but no significant structural brain changes. Another study made by Chung(Chung & Cannon, 2015) showed one-third to one-half of prodromal individuals show clear atrophic changes and enlarged lateral ventricles on brain imaging. This can result into positive, negative and cognitive symptoms.

These developmental aspects also play a crucial role in the early detection of psychosis (Armando et al., 2020; Schimmelmann et al., 2013; Schultze-Lutter et al., 2022), and may contribute to the observed lower conversion rates to manifest psychosis in minors at clinical high risk for psychosis. A potential explanation for this phenomenon is the higher prevalence and lower clinical relevance of symptoms used in CHR-P criteria in underage community subjects (Schimmelmann et al., 2015; Schultze-Lutter, Ruhrmann, et al., 2020; Schultze-Lutter, Schimmelmann, et al., 2020).

Another potential factor contributing to the age-related differences in transition rates may be the varying clinical significance for conversion of other symptom domains relevant to the diagnosis of psychoses, such as negative symptoms (NS) (Carrión et al., 2016; Lindgren et al., 2021; Paetzold et al., 2021; Piskulic et al., 2012; Salazar De Pablo et al., 2023; Schultze-Lutter, 2020). NS include five phenomena, mainly assessed by observations (Marder & Galderisi, 2017): blunted affect, alogia, anhedonia, asociality and avolition. Before NS become observable to others, they may be self-experienced as subtle disturbances in mental processes such as drive, volition, stress tolerance, emotional responsiveness and processes, in terms of so-called adynamic basic symptoms (BS) (Schultze-Lutter, 2020). Subjective and observable NS frequently precede the development of positive symptoms, and are associated with important social and role dysfunction (Carrión et al., 2016; Paetzold et al., 2021; Piskulic et al., 2012).

1.4. Subclinical and attenuated negative symptoms in the prediction of psychosis

In the domain of clinical prediction of psychosis, two influential models stand out: Huber and Gross's "basic symptoms" model, developed in Germany several decades ago, and Mc Gorry and colleagues' from the PACE clinic in Australia "ultra-high risk criteria for schizophrenia" model. There are five recognized and well-defined clinical high-risk (CHR) states. These include three Ultra-High-Risk (UHR) syndromes: attenuated psychotic symptoms (APS), brief, limited intermittent psychotic syndrome (BLIPS), and state-trait or the presence of one family member with psychosis or schizotypic personality and functional decline. The last two syndromes, following the German tradition of basic symptoms are the cognitive perceptive syndrome (COPER) and cognitive disturbances (COGDIS). For the purpose of this study, we will use the umbrella term "clinical high risk for psychosis" (CHR-P) to encompass both ultra-high risk (UHR) and basic-symptom (BS) criteria(Cornblatt et al., 2015; Schultze-Lutter, Michel, et al., 2015).

Gerd Huber regarded basic symptoms as the earliest perceivable signs of a developing psychosis and the most immediate psychopathological expression of the neurobiological correlates of the illness – hence the term 'basic'(Schultze-Lutter et al., 2012). Before NS are observable by others, they may be self-experienced as subtle disturbances in mental processes such as drive, volition, stress tolerance, emotional responsiveness and processes, in terms of so-called "adynamic" basic symptoms (BS)(Schultze-Lutter, 2020). Subjective and observable NS frequently precede the development of positive symptoms and are associated with important social and role dysfunction(Carrión et al., 2016; Paetzold et al., 2021; Piskulic et al., 2012).

This dynamic can be explained by the concept of coping mechanisms. Derived from research on stress (Selye, 1978) and different forms of stress processing, coping quickly gained status as a paradigm for many mental disorders, as people, not stressors, were recognized as active creators of their biographies as central figures (Braun-Scharm, 2000).

In the early stages of psychosis, problems often become noticeable to others only when a person's usual coping strategies stop working. As a result, basic symptoms (BS) begin to affect behavior. Others may then observe the person trying to cope—through avoidance, compensatory behaviours, or self-medication—as well as emotional reactions like anxiety, tension, confusion, or helplessness. These reactions can appear externally as negative symptoms, affective symptoms, or even suicidality (Schmidt et al., 2017).

According to Schultze-Lutter (Schultze-Lutter & Koch, 2010), basic symptoms can show up externally as functional deficits or negative symptoms (e.g., lack of motivation, reduced attention, reduced speech, anhedonia, social withdrawal, or blunted emotions), disorganized communication or behavior, and other changes in mood or emotional stability. For instance, social withdrawal may stem from reduced tolerance for social interaction, low energy or drive, or a diminished desire for social contact. It may also appear secondarily when the person struggles with speech perception or expression, or with reduced thought initiative, leading them to feel inadequate and avoid social situations.

In the same way, frequent and significant problems with speech or thinking can look like attention difficulties. These symptoms can trigger one another in a chain reaction. People may also develop coping habits—like spending far too much time studying—to manage these basic symptoms.

Other symptoms such as reduced drive, lower stress tolerance, mood changes, reduced emotional responsiveness, or intermittent depressive episodes can easily be mistaken for purely depressive symptoms.

The clinical significance of negative symptoms (NS) for psychosis conversion may vary by age, which likely contributes to observed variations in transition rates. Specifically, in the general community sample of children and adolescents (CAD), there is both a higher prevalence and a consequently lower clinical relevance for the symptoms typically used in CHR-P assessments, including attenuated positive symptoms (Schimmelmann et al., 2015).

Due to this high prevalence in truly prodromal and CHR-P states, attenuated NS have been proposed as an independent risk syndrome for psychosis onset, particularly in minors (Cornblatt et al., 2003; Piskulic et al., 2012). This is supported by studies that indicate a more important role for subjective and attenuated NS in underage compared to adult samples. For instance, in dimensional studies of BS (Schultze-Lutter et al., 2012; Schultze-Lutter, Steinmeyer, et al., 2008), the BS subsumed in the dimension "Adynamia" of the child and youth version of the SPI-CY (Schultze-Lutter & Koch, 2010) formed a central domain in minors, while in adults, the two cognitive dimensions of the adult version (SPI-A) (Schultze-Lutter et al., 2007) formed the centre. Moreover, more BS of the negative dimension were included in the SPI-CY, while in adults, these often did not correlate sufficiently with their own cluster and were therefore not included in the SPI-A (Schultze-Lutter, Steinmeyer, et al., 2008). Finally, in the SPI-CY pilot study on an underage sample (Fux et al., 2013), “Adynamia” discriminated best between CHR-P patients from patients not suspected to develop psychosis and healthy controls. This suggested that this subscale may play a unique role in the early detection in this age group. Furthermore, a three-year follow-up study identified age-specific prediction models for ultra-high risk (UHR) patients, distinguishing between underage and adult groups (Zhang et al., 2020). In minors, the “Negative symptoms” subscale of the “Structured Interview for Psychosis-Risk Syndromes” (SIPS) (Mcglashan et al., 2011) emerged as the strongest predictor of psychosis, whereas “Positive symptoms” best predicted conversion in adults. These findings suggest that adolescents and adults at clinical high risk may require age-specific strategies for early detection, with negative symptoms potentially being especially important for identifying risk in minors (Zhang et al., 2020).

Thus, taken together, these initial studies indicate that the reduction of subjective and attenuated NS might be given more attention in future early detection and intervention trials and that future studies should differentially investigate their role in CHR-P states.

Due to their high prevalence in truly prodromal and CHR-P states, attenuated NS have been proposed as an independent risk syndrome for psychosis onset, particularly in minors (Cornblatt et al., 2003; Marder & Galderisi, 2017; Paetzold et al., 2021; Piskulic et al., 2012). This is supported by studies that indicate a more important role for subjective and attenuated NS in underage compared to adult samples. For instance, in dimensional studies of BS (Schultze-Lutter et al., 2012; Schultze-Lutter, Ruhrmann, et al., 2008), the BS subsumed in the dimension "Adynamia" of the child and youth version of the “Schizophrenia Proneness Instrument” (SPI-CY) (Schultze-Lutter & Koch, 2010) formed a central domain in minors, while in adults, the two cognitive dimensions of the adult version (SPI-A) (Schultze-Lutter et al., 2007) formed the centre. Moreover, more BS of the negative dimension were included in the SPI-CY, while in adults, these often did not correlate sufficiently with their own cluster and were therefore not included in the SPI-A (Schultze-Lutter, Steinmeyer, et al., 2008). Finally, in the SPI-CY pilot study on an underage sample (Fux et al., 2013), “Adynamia” discriminated best between CHR-P patients from patients not suspected to develop psychosis and healthy controls. This suggested that this subscale may play a unique role in the early detection in this age group (Fux et al., 2013). Furthermore, a three-year follow-up study identified age-specific prediction models for ultra-high risk (UHR) patients, distinguishing between underage and adult groups (Zhang et al., 2020). In minors, the “Negative symptoms” subscale of the “Structured Interview for Psychosis-Risk Syndromes” (SIPS) (Mcglashan et al., 2011) emerged as the strongest predictor of psychosis, whereas “Positive symptoms” best predicted conversion in adults. These findings support the idea that underage and adult CHR patients may benefit from tailored approaches to early detection, with NS potentially playing a pivotal role in minors (Fux et al., 2013; Zhang et al., 2020). Thus, taken together, these initial studies indicate that the reduction of subjective and attenuated NS might be given more attention in future early detection and intervention trials and that future studies should differentially investigate their role in CHR-P states.

1.5. Aim of the study

In this first-time study of both subjective and attenuated NS assessed by the SPI-CY subscale "Adynamia" and the SIPS subscale “Negative symptoms” respectively, we differentially examined their role in 8- to 17-year-olds in separating the CHR-P state from other clinical

states and in predicting psychosis. In line with the SPI-CY pilot study by Fux et al. (Fux et al., 2013) and prediction study by Zhang et al. (Zhang et al., 2020), it was assumed that “Adynamia” and “Negative symptoms” would best distinguish CHR-P from other clinical states and would be most predictive of a conversion to psychosis.

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RESEARCH

Subclinical and attenuated negative symptoms in the prediction of psychosis in children and adolescents: sample composition matters

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Abstract

In children and adolescents, subjective and attenuated negative symptoms were hypothesized to best differentiate clinical-high risk for psychosis (CHR-P) from other conditions, and to be most predictive of psychosis. To examine this, we analysed data from 8-17-year-old CHR-P in-/outpatients (n = 183), and inpatients not clinically suspected of developing psychosis (n = 277) based on cross-sectional and two-year naturalistic follow-up data from a Swiss-German study. CHR-P criteria and other symptoms were assessed using the Schizophrenia Proneness Instrument, Child & Youth version, and the Structured Interview for Psychosis-Risk Syndromes. Pairwise comparisons, two-step cluster analyses and Cox regression models were applied to identify cluster profiles and the best predictors of psychosis. In pairwise comparisons, cognitive and perceptive basic symptoms, and attenuated positive symptoms better distinguished CHR-P patients from non-CHR-P patients and converters from non-converters than the negative symptom subscales "Adynamia" and "Negative symptoms. In the stable two-cluster solution of patients scoring high (n = 338) and low (n = 122) on all scales, "Adynamia" was most important (importance = 1.0) whereby the high-scorer cluster included most of CHR-P (86.9%) and converters (84.6%), and was predictive of psychosis. Cox models of subscales differed in the selected predictors depending on the analysed samples (total sample, CHR-P and ultra-high risk only (UHR)), whereby the earlier report of "Negative symptoms" predicting conversion in UHR was replicated when only SIPS subscales were considered. While our findings partially support the significance of subjective and attenuated negative symptoms in CHR-P and psychosis prediction, they also suggest that the role of negative symptoms is highly dependent on sample composition.

Keywords Clinical high risk · Psychoses · Negative symptoms · Basic symptoms · Childhood · Adolescence

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Introduction

Psychoses are a leading cause of disability starting from age 10 years, and continuing into adulthood [1]. However, notable developmental differences exist in the clinical presentation of psychosis between minors and adults [2–4]. These developmental aspects also play a crucial role in the early detection of psychosis [3, 5, 6], and may contribute to the observed lower conversion rates to manifest psychosis in minors at clinical high risk for psychosis (CHR-P; note: we use this as an umbrella term for both ultra-high risk (UHR) and basic-symptom criteria) [7, 8]. A potential explanation for this phenomenon is the higher prevalence and lower clinical relevance of symptoms used in CHR-P criteria in underage community subjects [9–11].

Another potential factor contributing to the age-related differences in transition rates may be the varying clinical significance for conversion of other symptom domains relevant to the diagnosis of psychoses, such as negative symptoms (NS) [12–17]. NS include five phenomena, mainly assessed by observations [18]: blunted affect, alogia, anhedonia, asociality and avolition. Before NS become observable to others, they may be self-experienced as subtle disturbances in mental processes such as drive, volition, stress tolerance, emotional responsiveness and processes, in terms of so-called *adynamic* basic symptoms (BS) [14]. Subjective and observable NS frequently precede the development of positive symptoms, and are associated with important social and role dysfunction [15–17].

Due to their high prevalence in truly prodromal and CHR-P states, attenuated NS have been proposed as an independent risk syndrome for psychosis onset, particularly in minors [16, 19]. This is supported by studies that indicate a more important role for subjective and attenuated NS in underage compared to adult samples. For instance, in dimensional studies of BS [20, 21], the BS subsumed in the dimension "Adynamia" of the child and youth version of the "Schizophrenia Proneness Instrument" (SPI-CY) [22] formed a central domain in minors, while in adults, the two cognitive dimensions of the adult version (SPI-A) [23] formed the centre. Moreover, more BS of the negative dimension were included in the SPI-CY, while in adults, these often did not correlate sufficiently with their own cluster and were therefore not included in the SPI-A [20]. Finally, in the SPI-CY pilot study on an underage sample [24], "Adynamia" discriminated best between CHR-P patients from patients not suspected to develop psychosis and healthy controls. This suggested that this subscale may play a unique role in the early detection in this age group [24]. Furthermore, a three-year follow-up study identified age-specific prediction models for ultra-high risk (UHR) patients, distinguishing between underage and adult groups [25]. In minors, the "Negative symptoms" subscale of the "Structured Interview for Psychosis-Risk Syndromes" (SIPS) [26] emerged as the strongest predictor of psychosis, whereas "Positive symptoms" best predicted conversion in adults. These findings support the idea that underage and adult CHR patients may benefit from tailored approaches to early detection, with NS potentially playing a pivotal role in minors [24, 25]. Thus, taken together, these initial studies indicate that the reduction of subjective and attenuated NS might be given more attention in future early detection and intervention trials and that future studies should differentially investigate their role in CHR-P states.

Aim of the study

In this first-time study of both subjective and attenuated NS assessed by the SPI-CY subscale "Adynamia" and the SIPS subscale "Negative symptoms", respectively (see sText 1 for details), we differentially examined their role in 8- to 17-year-olds in separating the CHR-P state from other clinical states and in predicting psychosis. In line with the SPI-CY pilot study by Fux et al. [24] and prediction study by Zhang et al. [25], it was assumed that "Adynamia" and "Negative symptoms" would best distinguish CHR-P from other clinical states and would be most predictive of a conversion to psychosis.

Methods

Sample

We used data from the German-Swiss naturalistic longitudinal "Bi-National Evaluation of At-Risk Symptoms in Children and Adolescents" (BEARS-Kid) study [27], which comprises a total of $N = 460$ with both a clinical control group (CC; $n = 277$) and a CHR-P group ($n = 183$). The BEARS-Kid study was conducted between 09/2013 and 02/2018 in the child and adolescent psychiatric departments of the universities of Bern, Zurich and Cologne. General inclusion criteria were age between 8 and 17 years, sufficient language skills in German, French or English, and IQ > 70. An additional inclusion criterion for the CHR-P group was the presence of any UHR or BS criteria. An additional inclusion criterion for the clinical controls was inpatient or day clinic treatment for any primary diagnoses that had been related to a higher frequency of psychosis in adulthood [28] (sFigure 1), i.e., anxiety (social phobia, specific phobia) and obsessive-compulsive disorder, eating disorders (anorexia and bulimia nervosa), and attention deficit and hyperactivity disorder (ADHD). Furthermore, Asperger's disorder was included as a primary diagnosis in childhood

and adolescence with a higher likelihood of psychosis in adulthood [29].

General exclusion criteria were mental symptoms being due to the direct physiological effect of a medical condition, and lifetime diagnosis of a psychotic disorder. An additional exclusion criterion for the CHR-P was CHR-P symptoms unequivocally being due to the direct physiological effect of a substance. An additional exclusion criterion for the CC was an ongoing antipsychotic treatment, clinical suspicion of an emerging psychosis or presence of any CHR-P criteria; in case of the latter, they were included into the CHR-P group. Furthermore, a third sample was recruited from the community that also contributed some subjects to the CHR-P group (sFigure 1). However, if these community subjects did not fulfil CHR-P criteria, they were not included in the present analyses (see sText 2 for additional details on recruitment).

Patients from CHR-P and CC groups were followed-up for 12 and 24 months for a transition to psychosis. Of the 460 patients, $n=137$ and $n=85$ CHR-patients, as well as $n=220$ and $n=173$ CC participated in the one-year and two-year follow-up (sFigure 1). Participants with no follow-up data ($n=83$; 18.0%) were conservatively categorized as "non-converters" for analytical purposes (see sText 3 for details).

The study was reviewed and approved by the ethical committees of the University of Bern (No. 174/10), the University of Zurich (No. 2010−0415/3), and the University of Cologne (No. 11–071). All participants, and their legal guardian, provided informed written consent prior to study enrolment.

Assessments

The BS criteria "Cognitive Disturbances" (COGDIS) and "Cognitive-Perceptive BS" (COPER) (sTable 1a) as well as other BS were assessed with the SPI-CY [21] that includes four subscales: "Adynamia", "Perceptual disturbances", "Neuroticism", and "Thought and motor disturbances". BS are rated according to their frequency in the past three months using scores ranging from '0' (absent) to '6' (daily). In addition, scores of '7' (trait feature and, consequently, not a basic symptom by definition), '8' (present, but frequency unknown), and '9' (questionable present) can be assigned. Following rating instructions of the SPI-CY [21], we recoded scores of '7' and '9' to '0' and '8' to '1', before calculating the sum scores of the subscales. To assess the three ultra-high risk (UHR) criteria, i.e., the Attenuated Psychosis Symptoms Syndrome (APSS), the Brief Intermittent Psychotic Symptoms Syndrome (BIPSS) and the Genetic Risk and Functional Decline syndrome (GRFD) (sTable 1b), and negative and other symptoms, we used the SIPS [11] that has four subscales: positive, negative, disorganization, and general symptoms. Items are syndromally rated according the quality of affirmed symptoms from '0' (absent) to '6' (severe and psychotic/extreme).

Interviews were conducted by clinical psychologists who had received an intensive three-month training, especially in the assessment of CHR-P symptoms/criteria and mental disorders, in order to achieve a ≥95% concordance rate with the trainers (F.S.-L. and C.M.). Weekly supervision of symptom ratings performed by the two trainers further ensured consistently excellent, valid and reliable data quality across centres.

Data analysis

Data analyses were performed using IBM SPSS Statistics version 29.0. Group differences in sociodemographic and clinical characteristics were examined using Mann-Whitney-U tests with Rosenthal's r as effect size for continuous variables and Chi²-tests with Cramer's V as effect size for categorical variables. In addition, receiver operating characteristic (ROC) analyses of the subscales were carried out for groups to explore their overall group-discriminative power.

A two-step cluster analysis procedure was used to identify profiles across the sample and subscales' importance to the cluster solution using a random order of cases. Because the solution of the two-step cluster analysis can be influenced by the order in which cases enter, the analysis was repeated in four different sorting of cases (groups, age, sex and educational level) to test for the solution's stability.

Cox regression analyses (stepwise Wald method for subscales and enter with bootstrapping for clusters) were used to explore the psychosis-predictive ability of the subscales and clusters in the UHR, the CHR-P and total sample.

Results

Sample characteristics

The CHR-P and CC group differed in age, nationality, level of education and the frequency of most mental disorders (Table 1). Patients with and without any follow-ups differed in their educational level in both groups. In the CHR-P group, patients with and without follow-up assessment showed differences in age, sex and nationality, but not in clinical characteristics (sTable 2, and 3). CHR-P patients scored higher across all subscales compared to CC, with moderate to high effect sizes (Table 2). These differences were reflected in areas under the curve ranging from moderate to excellent, with "Perception disturbances" showing

Table 1 Baseline characteristics of sample ($N=460$)

	CHR-*P* ($n=183$, 39.8%)	Clinical controls ($n=277$, 60.2%)	Total sample ($N=460$)	Statistics, effect size
Age, mean (SD), median	15.30 (2.07), 15.73	14.26 (2.54), 14.86	14.68 (2.41), 15.15	z=-4.484, $p<0.001$;r=-0.209
Sex, male, n (%)	69 (37.7%)	126 (45.5%)	195 (42.4%)	$\chi^2(1)=2.733$, $p=0.102$; V=0.077
Nationality, n (%)				$\chi^2(2)=8.719$, $p=0.013$; V=0.138
Switzerland	102 (55.7%)	153 (55.2%)	255 (55.4%)	
Germany	57 (31.1%)	108 (39.0%)	165 (35.9%)	
Other	24 (13.1%)	16 (5.8%)	40 (8.7%)	
Highest achieved/targeted school graduation, n (%)				$\chi^2(3)=13.305$, $p=0.004$; V=0.170
ISCED 0	2 (1.1%)	1 (0.4%)	3 (0.7%)	
ISCED 1	21 (11.5%)	69 (24.9%)	90 (19.6%)	
ISCED 2	89 (48.6%)	116 (41.9%)	205 (44.6%)	
ISCED 3	71 (38.8%)	91 (32.9%)	162 (35.2%)	
Clinical setting, n (%)				$\chi^2(1)=232.095$, $p<0.001$; V=0.710
Inpatient/day clinic	68 (37.2%)	277 (100%)	345 (75.0%)	
Outpatient	115 (62.8%)	0 (0.0%)	115 (25.0%)	
COGDIS, n (%)[a]	81 (44.3%)	0 (0.0%)	81 (17.6%)	$\chi^2(1)=148.810$, $p<0.001$; V=0.569
COPER, n (%)[a]	114 (62.3%)	0 (0.0%)	114 (24.8%)	$\chi^2(1)=229.412$, $p<0.001$; V=0.706
APSS, n (%)[a]	112 (61.2%)	0 (0.0%)	112 (24.3%)	$\chi^2(1)=224.091$, $p<0.001$; V=0.698
BIPSS, n (%)[a]	5 (2.7%)	0 (0.0%)	5 (1.1%)	$\chi^2(1)=7.651$, $p=0.010$; V=0.129
GRFD, n (%)	10 (5.5%)	0 (0.0%)	10 (2.2%)	$\chi^2(1)=15.437$, $p<0.001$; V=0.183
Any affective disorders, n (%)[a, b]	69 (37.7%)	43 (15.5%)	112 (24.3%)	$\chi^2(1)=29.435$, $p<0.001$; V=0.253
Any anxiety disorders, n (%)[a, b]	75 (41.0%)	72 (26.0%)	147 (32.0%)	$\chi^2(1)=11.389$, $p<0.001$; V=0.157
Any obsessive-compulsive disorders, n (%)[a, b]	15 (8.2%)	31 (11.2%)	46 (10.0%)	$\chi^2(1)=1.098$, $p=0.342$; V=0.049
Any eating disorders, n (%)[a, b]	16 (8.7%)	86 (31.0%)	102 (22.2%)	$\chi^2(1)=31.766$, $p<0.001$; V=0.263
Any somatoform disorders, n (%)[a, b]	3 (1.6%)	3 (1.1%)	6 (1.3%)	$\chi^2(1)=0.265$, $p=686$; V=0.024
Any substance misuse, n (%)[a, b,c]	15 (8.2%)	4 (1.4%)	19 (4.1%)	$\chi^2(1)=12.690$, $p<0.001$; V=0.166
Any trauma/stress-related disorders, n (%)[a, b]	13 (7.1%)	2 (0.7%)	15 (3.3%)	$\chi^2(1)=14.227$, $p<0.001$; V=0.176
Any developmental disorders, n (%)[a, b]	25 (13.7%)	122 (44.0%)	147 (32.0%)	$\chi^2(1)=46.780$, $p<0.001$; V=0.319
SOFAS, mean (SD), median	59.67 (12.08), 60.00	60.25 (11.10), 60.00	60.02 (11.49), 60.00	z=-0.864, $p=0.387$; r=-0.040
Conversion to psychosis, n (%)	12 (6.6%)	1 (0.4%)	13 (2.8%)	$\chi^2(1)=15.407$, $p<0.001$; V=0.183

[a] multiple CHR-P criteria and diagnosis possible

[b] assessed with the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-Kid)

ISCED: International Standard Classification of Education 2011; *CHR-P*: clinical high-risk for psychosis; *COGDIS*: Cognitive Disturbances; *COPER*: Cognitive-Perceptive basic symptoms; *APSS*: attenuated psychotic symptoms syndrome; *BIPSS*: brief intermittent psychotic symptoms syndrome; *GRFD*: genetic risk and functional decline; *SOFAS*: Social and Occupational Functioning Assessment Scale (0=lowest to 100=highest functioning)

[c] Please note: If CHR-P symptoms occurred clearly independently of substance effects, for example, by having occurred before the beginning of substance use or by having continued to occur in substance-free periods, they were considered as to not being exclusively the *direct* physiological effect of a substance, thus not meeting the respective exclusion criterion

good and "Positive symptoms" showing excellent discriminative performance (sTable 4).

Cluster analysis

All sortings resulted in the same stable two-cluster solution, separating high- from low-scorers across all subscales (Fig. 1). Silhouette measure of cohesion and separation was 0.5, indicating fair cluster quality. The ratio of largest-to-smallest cluster was 2.77. "Adynamia" was the most important subscale for clustering (Fig. 1).

Cluster 1 included a higher rate of CHR-P than of CC patients (Table 2). Furthermore compared to Cluster 2 patients, Cluster 1 patients were older, mostly female, had higher rates of substance use, affective, anxiety and stress-related disorders but lower rates of eating and developmental disorders, and poorer psychosocial functioning (sTable 5).

Table 2 Subscale means and cluster distribution of the two groups ($N=460$)

	CHR-*P* ($n=183$, 39.8%)	Clinical controls ($n=277$, 60.2%)	Statistics, effect size
SPI-CY subscales, mean (SD), median			
Adynamia	29.40 (20.11), 27.00	11.76 (13.19), 8.00	z=-9.643, $p<0.001$, r=-0.450
Perception disturbances	10.92 (12.34), 8.00	1.16 (2.60), 0.00	z=-12.997, $p<0.001$, r=-0.606
Neuroticism	9.58 (7.36), 9.00	4.53 (4.77), 3.00	z=-7.645, $p<0.001$, r=-0.356
Thought and motor disturbances	14.14 (12.63), 12.00	3.42 (4.99), 1.00	z=-10.636, $p<0.001$, r=-0.496
SIPS subscales, mean (SD), median			
Positive symptoms	8.38 (4.28), 8.00	2.19 (2.26), 1.00	z=-14.774, $p<0.001$, r=-0.689
Negative symptoms	9.87 (5.79), 10.00	5.30 (4.20), 5.00	z=-8.420, $p<0.001$, r=-0.393
Disorganization symptoms	3.87 (2.53), 3.00	2.13 (1.69), 2.00	z=-7.491, $p<0.001$, r=-0.349
General symptoms	8.27 (4.30), 9.00	4.56 (3.44), 4.00	z=-9.134, $p<0.001$, r=-0.426
Clusters			
Cluster 1, included, n (%)	106 (57.9%)	16 (5.8%)	$\chi^2(1)=153.772$, $p<0.001$; V=0.578

Prediction of psychosis

All but one converter ($n=13$, 2.8%) belonged to the CHR-P group (Table 1, sTable 6). Converters scored statistically significantly higher in all subscales except "Neuroticism" compared to non-converters, and were mostly part of Cluster 1 (Table 3). The Cox regression models on the subscales of SPI-CY and SIPS selected "Positive symptoms" and "Negative symptoms" in the total sample, "Disorganized symptoms" in the CHR-P sample, and "Negative symptoms" and, negatively, "Neuroticism" in the UHR sample. When only SIPS subscales were considered, only "Negative symptoms" were predictive in the UHR sample (Table 4). In the Cox regression models on the two clusters, Cluster 1 was a significant predictor in all samples, albeit with a large confidence interval (Table 4).

Discussion

Negative symptoms (NS) significantly impair social functioning in schizophrenia and are linked to poorer outcomes like greater cognitive impairments, reduced quality of life and poor response to therapeutic interventions during adolescence [13, 30–33]. However, despite this recognized importance, NS are understudied in their specific contribution to the clinical presentation and outcomes in children and adolescents at clinical high-risk for psychosis (CHR-P). Thus, the present study examined the potential of subjective and attenuated NS according to the SPI-CY "Adynamia" and SIPS "Negative Symptoms" subscales to differentiate youth at CHR-P from clinical controls (CC) and predict psychotic conversion. Based on the SPI-CY pilot study by Fux et al. [24] and prediction study by Zhang et al. [25], we had hypothesized that these scales would best distinguish CHR-P from other clinical states and predict psychosis. However, the observed results only partially confirmed previous reports that subjective and attenuated NS best discriminate underage CHR-P patients and are the most important predictors of conversion to psychosis, respectively.

Group discrimination by subjective negative symptoms

In contrast to the SPI-CY pilot study [24] (see sTable 7 for comparisons with our study), "Perception disturbances" and not "Adynamia" showed the largest group effect in our study. While both "Perception disturbances" and "Adynamia" had a median score that was four points higher than in the pilot study, the former had a larger and the latter a smaller effect size. Furthermore, the effect of "Adynamia" was also second to that of "Thought and motor disturbances", whose effect size was similar to that found in the pilot study. The effect of "Neuroticism" was similarly moderate in both studies and discriminated the groups least.

The fourteen BS relevant to COPER and COGDIS are part of "Perception disturbances" and "Thought and motor disturbances", whereby "Perception disturbances" is most relevant to COPER that includes four main items of this section compared to COGDIS that just includes one item. Because both studies have similar proportions of patients with COPER [24] (sTable 5), our higher median of "Perception disturbances" and relatedly the higher effect was not related to the proportion of COPER patients. Further, our larger proportion of COGDIS patients did not result in a larger median and effect of "Thought and motor disturbances" in our CHR-P. This indicates that the discriminatory effects of the two SPI-CY subscales that include criteria-relevant BS were not primarily related to the distribution of BS criteria.

Sociodemographic sample differences may explain the discrepancies in effect sizes for "Perception disturbances" and "Thought and motor disturbances" between our study and the pilot study [25]. Our sample was younger on average

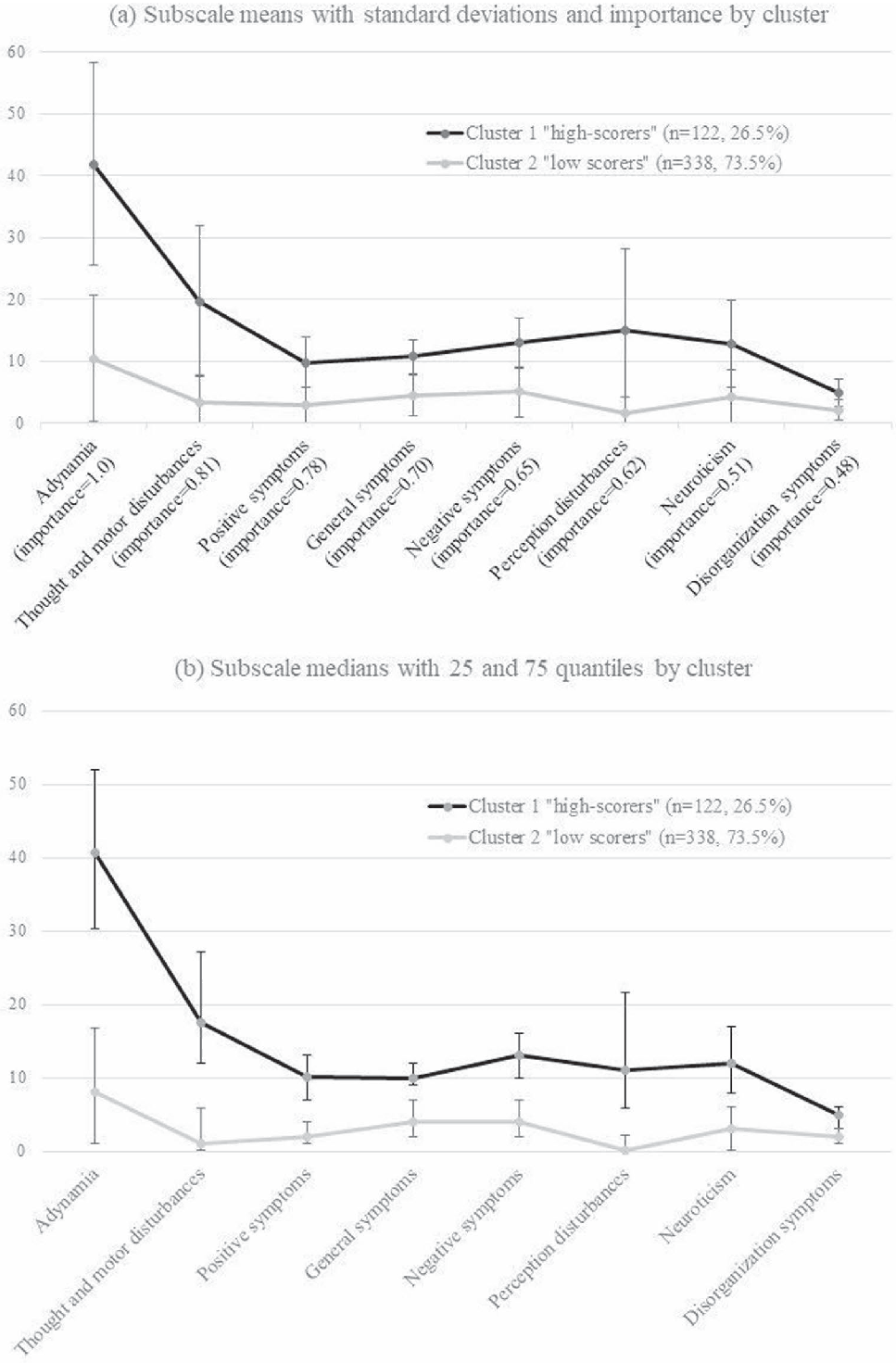


Fig. 1 The two-cluster solution; (**a**) means with standard deviations and importance, (**b**) medians with 25 and 75 quantiles

(by one year) and included more females (20% more in CHR-P and 10% more in CC) (sTable 7); both younger age and female sex were significantly associated with a higher prevalence of BS included in COGDIS and/or COPER in the community [11]. Thus, our higher proportion of females, particularly among CHR-P, as well as of younger patients might have increased the group effect of in "Perception disturbances" and "Thought and motor disturbances". While this view was partly supported by the median of "Perception disturbances" in the CHR-P group that was twice as high as in the pilot study, yet equal in the CC group, our medians for "Thought and motor disturbances" were lower. Thus, no

Table 3 Subscale means and cluster distribution of converters and non-converters ($N=460$)

	Non-converters ($n=447$, 97.2%)	Converters ($n=13$, 2.8%)	Statistics, effect size
SPI-CY subscales, mean (SD), median			
Adynamia	18.23 (18.05), 13.00	37.46 (22.44), 46.00	z=-3.063, $p=0.002$, r=-0.143
Perception disturbances	4.72 (8.91), 0.00	16.23 (15.73), 7.00	z=-3.970, $p<0.001$, r=-0.185
Neuroticism	6.46 (6.40), 6.00	9.23 (7.12), 8.00	z=-1.532, $p=0.126$, r=-0.071
Thought and motor disturbances	7.28 (9.94), 4.00	21.46 (12.79), 20.00	z=-4.277, $p<0.001$, r=-0.199
SIPS subscales, mean (SD), median s			
Positive symptoms	4.48 (4.31), 3.00	10.46 (4.35), 10.00	z=-4.275, $p<0.001$, r=-0.199
Negative symptoms	6.94 (5.23), 6.00	13.38 (6.73), 17.00	z=-3.414, $p<0.001$, r=-0.159
Disorganization symptoms	2.74 (2.14), 2.00	5.77 (3.37), 5.00	z=-3.505, $p<0.001$, r=-0.163
General Symptoms	5.90 (4.07), 6.00	10.77 (6.19), 12.00	z=-3.047, $p=0.002$, r=-0.142
Clusters			
Cluster 1, included, n (%)	111 (24.8%)	11 (84.6%)	$\chi^2(1)=23.168$, $p<0.001$; V=0.224

Table 4 Cox regression models of conversion to psychoses

	Beta	Standard error	Wald (df=1)	Significance	Exp(Beta)	95.0% Confidence interval (CI) of Exp(Beta)	
						lower	upper
Subscales, total sample[4]							
Positive symptoms	0.181	0.066	7.623	$p=0.006$	1.199	1.054	1.364
Negative symptoms	0.152	0.058	6.802	$p=0.009$	1.164	1.038	1.305
Clusters, total sample[5]							
Cluster 1 „high scorers“	3.098[1]	0.790	15.372	$p<0.001$	22.159	4.709	104.276
Subscales, CHR-P sample[6]							
Disorganization symptoms	0.317	0.099	10.329	$p=0.001$	1.373	1.132	1.666
Clusters, CHR-P sample[7]							
Cluster 1 „high scorers“	2.232[2]	1.052	4.504	$p=0.034$	9.317	1.186	73.186
Subscales, UHR sample[8]							
Negative symptoms	0.220	0.064	11.978	$p<0.001$	1.246	1.100	1.411
Neuroticism	-0.086	0.045	3.599	$p=0.058$	0.918	0.840	1.003
SIPS subscales, UHR sample[9]							
Negative symptoms	0.163	0.058	7.920	$p=0.005$	1.177	1.051	1.319
Clusters, UHR sample[10]							
Cluster 1 „high scorers“	3.712[3]	2.772	1.793	$p=0.181$	40.954	0.179	9380.630

[1] Bootstrap: $p<0.001$; 95% CI (Beta): 2.018, 6.633

[2] Bootstrap: $p=0.018$; 95% CI (Beta): 0.037, 4.210

[3] Bootstrap: $p<0.001$; 95% CI (Beta): 3.439, 4.072

[4] Model fit: $\chi^2(2)=37.252$, $p<0.001$

[5] Model fit: $\chi^2(1)=29.248$, $p<0.001$

[6] Model fit: $\chi^2(1)=10.790$, $p=0.001$

[7] Model fit: $\chi^2(1)=6.553$, $p=0.010$

[8] Model fit: $\chi^2(2)=13.598$, $p=0.001$

[9] Model fit: $\chi^2(1)=8.766$, $p=0.003$

[10] Model fit: $\chi^2(1)=5.441$, $p=0.020$

general influence of younger age and a higher proportion of girls in the sense of more or more severe perceptual and cognitive BS was observed in our sample.

However, age might have contributed indirectly to the median of “Thought and motor disturbances” in our CC group that included the highest rate of children, i.e., 8-12-year-olds. Five of the 19 items of this subscale cannot be assessed until the age of 13 years for developmental reasons [22] and score ‘0’ in children, thereby lowering its median. Thus, the higher number of children in our sample will have reduced the group effect of “Thought and motor disturbances” compared to the pilot group. Because of the relatively low number

8-12-year-olds, in particular in the CHR-P sample, that prevented targeted group comparison of the symptom profiles of only 8- to 12-year-old patients, larger, dedicated studies focusing on children are necessary to study very early, developmentally sensitive predictors of psychosis. So far, most paediatric CHR-P studies included 12-18- or 15-18-year-olds [34].

Despite larger group effects in "Perception disturbances" and "Thought and motor disturbances", "Adynamia" emerged as the most important feature distinguishing the two clusters of high- and low-scorers, while "Negative symptoms" ranked fifth. The smaller Cluster 1 included a good quarter of high-scoring patients, mostly CHR-P, who were also significantly more impaired in functioning than Cluster 2 patients. While the higher functional impairment might be related to higher rates of mental disorders in Cluster 1, particularly of affective, anxiety, substance use, and stress-related disorders, the same pattern of differences in distribution of mental disorders was found at baseline between CHR-P and CC; yet without any indication of a group difference in functioning. Thus, this finding may better align with the idea that negative symptoms – in this case subtle, subclinical and self-experienced forms such as adynamic BS [14] – are a key domain of the psychosis spectrum in minors and strongly associated with functional deficits [13].

Prediction of psychosis by subjective and attenuated negative symptoms

Supporting previous reports [16, 35], the subscale "Negative symptoms" was the sole predictor of conversion in our UHR sample when only SIPS subscales were considered as in Zhang et al. [25]. When all subscales were considered in the UHR sample, "Neuroticism" joined as a negative predictor, albeit one, only approaching significance. Some items of "Neuroticism" resemble borderline personality phenomena, such as irritability, increased emotional responsiveness and depersonalisation. Earlier studies had reported significant positive correlations of borderline symptoms with "Positive symptoms" but not with BS criteria or conversion to psychosis in UHR samples [36–38]. Thus, the slight negative psychosis-predictive value of "Neuroticism" might be mediated by the lower positive symptoms in the UHR patients.

In the total sample, "Negative symptoms" and "Positive symptoms" predicted conversion. This is in line with findings of Lindgren et al. [12] who compared the generalizability of 19 prediction models to clinical practice in an unselected adolescent psychiatric sample with a third fulfilling UHR criteria. Such a broader sample composition that also includes persons not meeting UHR criteria naturally results in a greater variance in "Positive symptoms" that defines the symptomatic UHR criteria. This resulted in a significant group effect with regard to conversion for "Positive symptoms" in our sample that was not found in the sample of Zhang et al. [25], although the means of "Positive symptoms" in our and Zhang's converters are identical. The mean of "Negative symptoms" in our converters however was slightly lower than that of Zhang et al. [25] and clearly lower in the non-converters. Nevertheless, the significant predictive contributions of "Negative symptoms" in our and Zhang's model were similarly low.

Interestingly, "Negative symptoms" had a lower group effect with regard to conversion than "Perception disturbances" and "Thought and motor disturbances" in group comparisons. Thus, the selection of "Negative symptoms" into the regression model indicates that there were too many redundancies between both "Perception disturbances" and "Thought and motor disturbances", and "Positive symptoms", in particular with regard to perception symptoms [39], that prevented the inclusion of these two BS-criteria-relevant subscales into the model in addition to "Positive symptoms". These high redundancies between the criteria-relevant subscales of SPI-CY and SIPS, however, support the alternative use of UHR and BS criteria, albeit the two approaches reflecting distinct psychopathology. Such a redundancy seemed to be low between "Negative symptoms" and "Positive symptoms", thus making NS a valuable addition in the early detection of psychosis in minors [12, 24, 25].

In the CHR-P sample, only the SIPS subscale "Disorganization symptoms" subscale, which notably not includes the positive item "disorganized communication", was predictive of psychosis. This sole selection is surprising in light of its rather small group effect with regard to both initial group assignment and conversion. Yet, disorganized symptoms had been included in several prediction models, though always in concert with other symptoms and always in concert with positive symptoms [40]. The non-selection of "Positive symptoms" into the model on our CHR-P sample might be related to the fact that, of the 12 converters, all had met COPER and/or COGDIS at baseline but only 9 had also met symptomatic UHR criteria. Thus, the selection of "Disorganization symptoms" might reflect the presence of severe and observable "Trouble with focus and attention", which is part of "Disorganization symptoms" and a result of severe cognitive BS but also the presence of more "Bizarre thinking" that dependent on the presence of unusual and delusion-like ideas. Though not related to conversion, "Disorganized symptoms" had also been related to cannabis use [41]; and indeed, substance use was more frequent in CHR-P converters (16.7%) compared to CHR-P non-converters (7.6%). This might have additionally contributed to our finding, but, just as single-item contributions, should be explored in more detail in future studies.

Regarding the cluster solution, unsurprisingly, the high-scorers' Cluster 1 – which consisted mostly of CHR-P

patients and all converters but the two with the longest time to conversion – was predictive of transition in Cox regression models, and, in pairwise comparisons, the cluster solution best distinguished converters from non-converters. Like the Cox regression solution, the cluster solution, which was primarily based on "Adynamia" and "Thought and motor disturbances", indicated a combination of subscales representing both the positive and negative symptom domain to be most important in underage patients.

Strengths and limitations

Key strengths of our study include the substantial sample size, the use of both UHR and BS criteria, the high control of data quality, and the inclusion of a CC group clinically unsuspected to develop psychosis but with primary diagnoses associated with increased risk for psychosis in adulthood and with symptom severity sufficient to require inpatient or at least day clinic treatment. While this high symptom severity might have biased the CC group towards higher symptom severity also on SPI-CY and SIPS, that this was not the case. Rather the CHR-P group comprising mostly outpatients showed the highest SIPS and SPI-CY subscale means overall, extending earlier reports from the same study that CHR-P criteria and symptoms are not merely a symptom severity marker or transdiagnostic phenomena [27]. Nevertheless, the small number of converters is a notable limitation, particularly given the recommended event-to-predictor ratio of 5:1 for reliable regression analyses [42].

Furthermore, our follow-up period of two years may have been too short, as psychoses with first prodromal symptoms before the age of 18 years show an extended prodrome [43]. At the same time, follow-up rates of 2 years are common in early detection studies, and most transitions happen in the first two years [8]. Another limitation is the dropout rate, which is significant in the CHR group, especially at the two-year follow-up. Nonetheless, dropouts and participants with follow-up data were largely similar, especially in clinical variables. While equating dropout with non-conversion likely reduced the discriminatory effects of subscales in pairwise comparisons, this limitation should have affected all subscales equally.

Conclusion

Subclinical and attenuated NS in minors are largely neglected both in research and clinical practice. While our findings partly support an important role of subjective and attenuated NS in CHR-P and conversion to psychosis, they do not support an overall outstanding role. Rather, the role of NS seems to largely depend on sample composition and, with regard to conversion, was most pronounced in UHR samples. Future studies should therefore focus on differentiating NS profiles specifically within these populations. Furthermore, most specific interventions in underage UHR samples focused on positive symptoms, with only three studies so far having also analysed the effect on NS [44]. Our results indicate that the reduction of NS should be given more attention in future intervention trials, in particular in underage UHR samples.

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Author contributions Drs. Schultze-Lutter and Schimmelmann designed the study; Drs. Walger, Franscini, Traber-Walker, Flückiger and Michel were involved in the acquisition of data; Mr. Cabrera, Mr. Osman and Dr. Schultze-Lutter analysed and interpreted the data for the work and drafted the first version of this work; all authors revised the article critically for important intellectual content, and agreed to the submitted version that follows the STROBE statement (sTable 8).

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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Supplementary material to "Subclinical and attenuated negative symptoms in the prediction of psychosis in children and adolescents: sample composition matters" by S. Cabrera et al.

sText 1. Description of attenuated and subjective negative symptoms as assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Schizophrenia Proneness Instrument, Child & Youth version (SPI-CY)

The SIPS negative symptom items include:

- social anhedonia, ranging from '1'=patient is lightly socially awkward or anxious but socially active to '6'=patient has no friends and prefers being alone.
- avolition, ranging from '1'=patient has maintained focus on goal-directed activities but less than what would be considered average to '6'= patient does not participate in virtually any goal-directed activities with prodding of others to do so being unsuccessful.
- expression of emotion, ranging from '1'=patient's emotional responsiveness is slightly delayed or blunted to '6'= patient has flat affect, monotone speech, and is unable to become involved with interviewer or maintain conversation despite active questioning by the interviewer
- experience of emotions and self, ranging from '1'=patient reports feeling distant from others and experiencing everyday feelings as muted to '6'=patient reports feeling profoundly changed and possibly alien to self, a feeling of no feelings
- ideational richness, ranging from '1'=some conversational awkwardness observable to '6'=patient is unable, at times, to follow any conversation no matter how simple and shows a verbal content and expression that is mostly limited to single words and yes/no responses.
- occupational functioning, ranging from '1'=more than average effort and focus required from the patient to maintain usual level of performance at work, school to '6'=patient failed or left school, left employment or was fired.

Basic symptoms have to be subjectively experienced by the young person as new and/or different from 'normal' troubles. These symptoms should have been absent, or only present at a significantly lower frequency, in what the young person considers his or her premorbid stage. Thus, a symptom is scored only when experienced by the young person as a disturbance, deficiency or complaint, irrespective of its appearance in behavior, gesture, miming or speech and when the possibility that it is an effect of drug use, especially of cannabis or ketamine, a side-effect of medication, a manifestation of a somatic illness or a by-product of a hypnagogic / hypnopompic state was excluded. The SPI-CY "Anhedonia" section includes the following symptoms:

- Reduced energy and vitality
- Reduced persistence and patience
- Reduced drive and initiative
- Impaired tolerance to physical and/or mental labor
- Impaired tolerance to unusual, unexpected or specific novel demands
- Impaired tolerance to certain social everyday situations
- Impaired tolerance to working under pressure of time or rapidly changing different demands
- Change in mood and emotional responsiveness
- Decrease in positive emotional responsiveness towards others
- Intermittent, recurrent depressive mood swings
- Disturbance in presenting oneself in terms of a disturbance in the ability to express oneself non-verbally.
- Increased emotional reactivity in response to everyday events
- Increased emotional reactivity in response to routine social interactions that affect the young person directly or indirectly
- Difficulties concentrating in terms of maintaining attention
- Forgetfulness, scatterbrainedness in terms of deficits in implicit (non-declarative), i.e., unconscious, unintentional memory
- Slowed-down thinking
- Lack of 'thought energy' or goal-directed thoughts

sText 2. Additional information on the recruitment of samples.

Clinical high-risk for psychosis (CHR-P) sample: The CHR-P sample was recruited at all three sites (Bern, Switzerland; Zurich, Switzerland; and Cologne, Germany), mainly from the clientele of established local early detection services. These services accepted both outpatients and inpatients who were clinically suspected of having psychosis and who were referred by (mental) health professionals, as well as individuals who approached the service themselves out of fear of developing psychosis.

Clinical control (CC) sample: The CC sample was also recruited at all three sites from the inpatients with the primary diagnoses relevant for inclusion but no clinical suspicion of emerging psychoses.

Community sample: The community sample was exclusively recruited in Bern, Switzerland. For the recruitment of a representative community sample, the Agency for Informatics and Organization of the Canton Bern randomly drew a sample (including addresses) stratified for age and sex from the population register of the city of Bern and its urban hinterland (approximately 200,000 residents). Subsequently, we searched directories and the Internet for telephone numbers. The availability of a working telephone number served as an eligibility criterion in this group. We established first contact by an information letter, personally addressing each potential participant and his/her parents. Next, we contacted parents and/or their children by phone, informed them in detail and asked them to give written informed consent and assent, respectively. In children below age 16.0 years, we contacted parents first.
N = 980 persons were drawn from the register, for n = 176 of them, we could not ascertain a working telephone number and n = 41 persons were drawn twice. Of the remaining n = 763 persons, n = 234 agreed to participate, yet one person later on withdrew consent. n = 353 did not agree, mainly for lack of interest (35.6%) or time (35.9%). Further, we excluded n = 52 persons because they had turned 18 years by the time contact was made (53.9%), had moved away from the greater Bern area (32.7%), or lacked the ability to participate in the study for language or physical health reasons (13.5%). With n = 124 persons, all attempts (at least 40) to reach them on the phone remained fruitless.
Thus, according to the standard definitions of the American Association for Public Opinion Research (2016), the contact rate was 82.7%, the cooperation rate was 39.9%, the refusal rate was 49.2%, and the response rate was 32.6%.

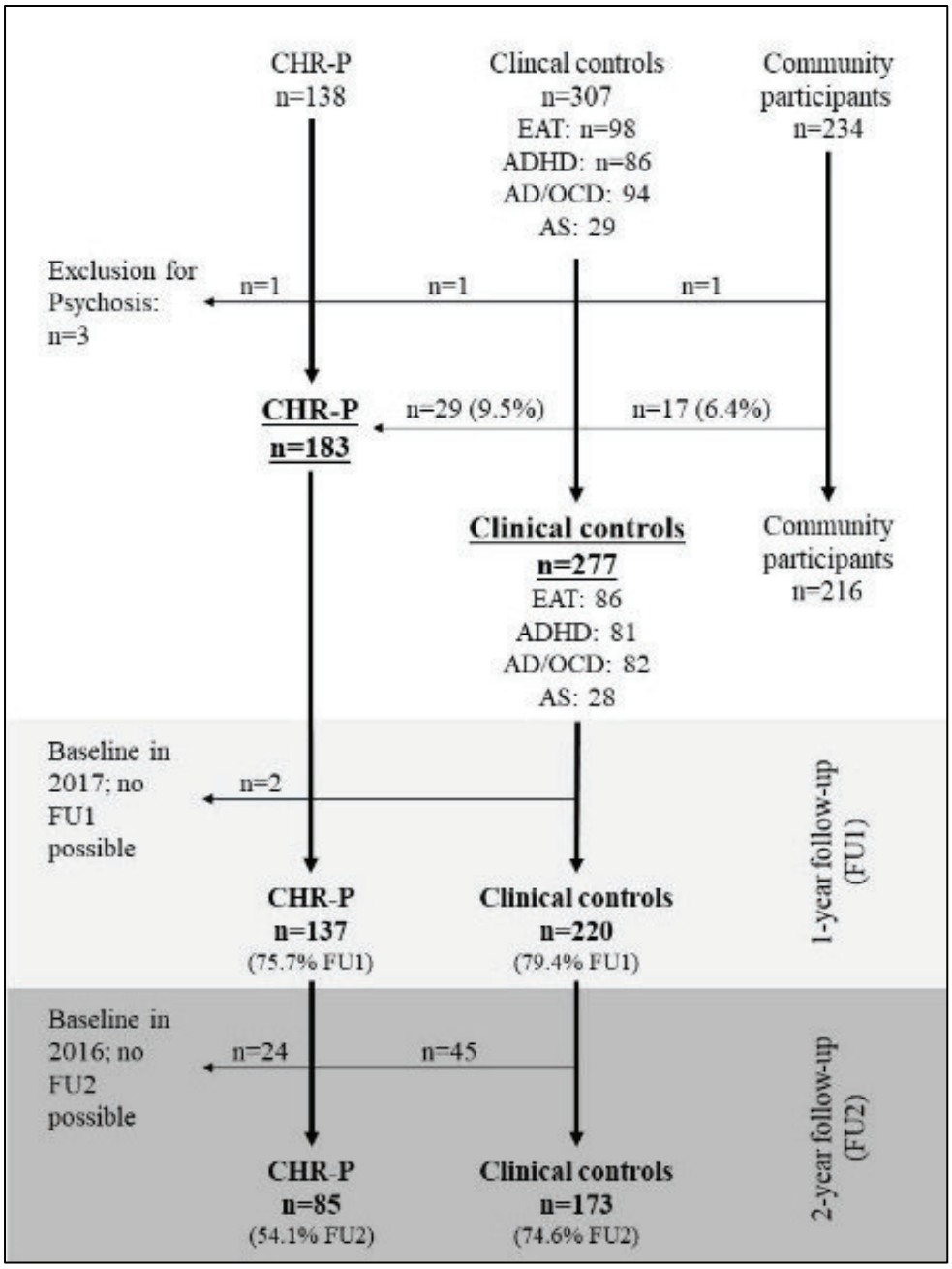
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sText 3. Reasons for rating patients lost-to-follow-up as non-converters.

The decision to rate patients with missing follow-up conservatively as non-converters was made for four reasons:

- At statistical level, we wanted to maintain sufficient power;
- Meta-analyses of conversion suggest a conversion rate in CHR-P around 20% within 2 years (for example: Schultze-Lutter et al., 2015; Fusar-Poli P et al., 2016; Salazar de Pablo et al., 2021), thus, for any CHR-P patient and even more for any CC inpatient (CHR-P negative patients have a conversion rate around 1%; see references above) who could not be followed up, a non-conversion was far more likely than a conversion.
- Because all three early detection services were part of a larger child and adolescent psychiatric university hospital serving the larger area of the Canton Bern, the city of Zurich and the city of Cologne, even lost-to-follow-up patients who had developed a first episode of psychosis would very likely have come to our attention.
- In all cases in which a follow-up could not be conducted with the patient but contact was made with a parent, it was reported that the mental health status of the patient had much increased and refusal was due to not wanting to look back and wanting to forget about the phase of mental ill health

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sFigure 1. Recruitment and follow-up of the analysed sample (N=460).

CHR-P: clinical high-risk for psychosis; EAT: eating disorders (Anorexia or Bulimia nervosa); ADHD: attention deficit/hyperactivity disorders; AD/OCD: anxiety (social or specific phobia) and obsessive-compulsive disorders; AS: Asperger's disorder

The primary diagnoses of the clinical control sample were chosen according to the prospective study of Rubino et al. (2009) that associated the following diagnoses in childhood and adolescence with a higher frequency of psychosis in adulthood: attention deficit/hyperactivity disorders, anxiety (social or specific phobia) and obstetric-compulsive disorders and eating disorders (Anorexia or Bulimia nervosa). This study did not include patients with Asperger's disorder; but as this condition was recognized as a condition with increased risk to develop psychosis in young adulthood (APA, 1994), we included this condition as a primary diagnosis in childhood and adolescence with a higher likelihood of psychosis in adulthood in addition.

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sTable 1: Criteria of a clinical high-risk for psychosis (CHR-P) according to the Schizophrenia Proneness Instrument, Child & Youth version (SPI-CY) and the Structured Interview for Psychosis-Risk Syndromes (SIPS)

1a. The basic symptom criteria "Cognitive Disturbances" (COGDIS) and "Cognitive-Perceptive BS" (COPER)

"Cognitive Disturbances" (COGDIS)
≥2 basic symptoms of at least weekly frequency (SPI ≥ '3') within past 3 months: ➢ inability to divide attention ➢ thought interference ➢ thought pressure ➢ thought blockages ➢ disturbance of receptive speech ➢ disturbance of expressive speech ➢ disturbance of abstract thinking ➢ unstable ideas of reference ➢ captivation of attention by details of the visual field
"Cognitive-Perceptive BS" (COPER)
≥1 basic symptom of at least weekly frequency (SPI ≥ '3') within past 3 months and first occurrence or significant increase in frequency at least 12 months ago: ➢ thought interference ➢ thought perseveration ➢ thought pressure ➢ thought blockages ➢ dist. of receptive speech ➢ decreased ability to discriminate between ideas and perception, fantasy and real memories ➢ unstable ideas of reference ➢ derealisation ➢ visual perception disturbances (14 subitems) ➢ acoustic perception disturbances (3 subitems)

1b. The ultra-high risk (UHR) criteria "Attenuated Psychosis Symptoms Syndrome" (APSS), "Brief Intermittent Psychotic Symptoms Syndrome" (BIPSS) and "Genetic Risk and Functional Decline" (GRFD)

"Attenuated Psychosis Symptoms Syndrome" (APSS)
≥1 positive symptom with a score of '3'-'5' that (I) is not better explained by another mental disorder, (II) has begun within the past year or do any currently rate one or more scale points higher compared to 12 months ago and (III) occurred at an average frequency of at least once per week in the past month: ➢ unusual thought content/delusional ideas ➢ suspiciousness/persecutory ideas ➢ grandiosity ➢ perceptual abnormalities/hallucinations ➢ disorganized communication
"Brief Intermittent Psychotic Symptoms Syndrome" (BIPSS)
≥1 positive symptom (see above) with a score of '6' that (I) is not better explained by another mental disorder, (II) has reached a psychotic level of intensity in the past three months, and (III) is currently present for at least several minutes per day at a frequency of at least once per month but less than 7 days.
Genetic Risk and Functional Decline" (GRFD)
The patient (I) meets criteria for Schizotypal Personality Disorder or has a first degree relative with a psychotic disorder and (II) is experiencing at least a 30% drop in GAF score over the last month as compared to 12 months ago.

sTable 2. Baseline characteristics of CHR-P patients with and without any follow-up (N=183).

	With follow-up (n=147, 80.3%)	**Without follow-up (n=36, 19.7%)**	**Statistics, effect size**
Age, mean (SD), median	15.06 (2.11), 15.45	16.29 (1.56), 16.35	z=-3.460, p<0.001; r=-0.256
Sex, male, n (%)	50 (34.0%)	19 (52.8%)	$\chi^2(1)=4.335$, p=0.037; V=0.154
Nationality, n (%)			$\chi^2(2)=11.191$, p=0.004; V=0.247
Switzerland	73 (49.7%)	29 (80.6%)	
Germany	52 (35.4%)	5 (13.9%)	
Other	22 (15.0%)	2 (5.6%)	
Highest achieved/targeted school graduation, n (%)			$\chi^2(3)=11.279$, p=0.010; V=0.248
ISCED 0	0	2 (5.6%)	
ISCED 1	20 (13.6%)	1 (2.8%)	
ISCED 2	70 (47.6%)	19 (52.8%)	
ISCED 3	57 (38.8%)	14 (38.8%)	
COGDIS, present, n (%)[a]	64 (43.5%)	17 (47.2%)	$\chi^2(1)=0.159$, p=0.690; V=0.029
COPER, present, n (%)[a]	88 (59.9%)	26 (72.2%)	$\chi^2(1)=1.880$, p=0.170; V=0.101
APSS, present, n (%)[a]	91 (61.9%)	21 (58.3%)	$\chi^2(1)=0.155$, p=0.693; V=0.029
BIPSS, present, n (%)[a]	4 (2.7%)	1 (2.8%)	$\chi^2(1)<0.001$, p=1.000; V=0.001
GRFD, present, n (%)	8 (5.4%)	2 (5.6%)	$\chi^2(1)=0.001$, p=1.000; V=0.002
Any affective disorders, present, n (%)[a,b]	58 (39.5%)	11 (30.6%)	$\chi^2(1)=0.975$, p=0.323; V=0.073
Any anxiety disorders, present, n (%)[a,b]	65 (44.2%)	10 (27.8%)	$\chi^2(1)=3.231$, p=0.072; V=0.133
Any obsessive-compulsive disorders, present, n (%)[a,b]	13 (8.8%)	2 (5.6%)	$\chi^2(1)=0.415$, p=0.519; V=0.048
Any eating disorders, present, n (%)[a,b]	13 (8.8%)	3 (8.3%)	$\chi^2(1)=0.009$, p=1.000; V=0.007
Any somatoform disorders, present, n (%)[a,b]	3 (2.0%)	0	$\chi^2(1)=0.747$, p=1.000; V=0.064
Any substance misuse, present, n (%)[a,b]	10 (6.8%)	5 (13.9%)	$\chi^2(1)=1.930$, p=0.165; V=0.103
Any trauma/stress-related disorders, present, n (%)[a,b]	11 (7.5%)	2 (5.6%)	$\chi^2(1)=0.163$, p=1.000; V=0.030
Any developmental disorders, present, n (%)[a,b]	20 (13.6%)	5 (13.9%)	$\chi^2(1)=0.002$, p=1.000; V=0.003
SOFAS, mean (SD), median	60.14 (12.62), 60.0	57.75 (9.50), 59.5	z=-0.832, p=0.410; r=-0.062
Adynamia, mean (SD), median	29.90 (20.81), 29.0	27.33 (17.07), 25.5	z=-0.615, p=0.539; r=-0.045
Perception disturbance, mean (SD), median **s**	11.80 (13.10), 8.0	7.33 (7.69), 6.0	z=-1.467, p=0.142; r=-0.108
Neuroticism, mean (SD), median	9.82 (7.41), 9.0	8.58 (7.15), 7.0	z=-0.936, p=0.349; r=-0.069
Thought and motor disturbances, mean (SD), median	14.37 (12.90), 13.0	13.19 (11.57), 12.0	z=-0.364, p=0.716; r=-0.027
Positive symptoms, mean (SD), median	8.53 (4.18), 9.0	7.75 (4.67), 7.0	z=-0.942, p=0.346; r=-0.070
Negative symptoms, mean (SD), median	9.49 (5.80), 10.0	11.42 (5.82), 10.0	z=-1.672, p=0.094; r=-0.124
Disorganization symptoms, mean (SD), median	3.92 (2.60), 4.0	3.69 (2.21), 3.0	z=-0.461, p=0.645; r=-0.034
General symptoms, mean (SD), median	8.46 (4.48), 9.0	7.53 (3.42), 8.0	z=-1.710, p=0.087; r=-0.126
Cluster 1, present, n (%)	89 (60.5%)	17 (47.2%)	$\chi^2(1)=2.106$, p=0.147; V=0.107

[a] multiple CHR-P criteria and diagnosis possible
[b] assessed with the Mini-International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I. Kid) (Sheehan, et al., 2010).
ISCED: International Standard Classification of Education 2011; CHR-P: clinical high-risk for psychosis; COGDIS: Cognitive Disturbances; COPER: Cognitive-Perceptive basic symptoms; APSS: attenuated psychotic symptoms syndrome; BIPSS: brief intermittent psychotic symptoms syndrome; GRFD: genetic risk and functional decline; SOFAS: Social and Occupational Functioning Assessment Scale (0=lowest to 100=highest functioning)

Reference: Sheehan DV, Sheehan KH, Shytle RD, et al. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiatry. 2010;71(3):313-26. doi: 10.4088/JCP.09m05305whi.

sTable 3. Baseline characteristics of clinical controls with and without any follow-up (N=277).

	With follow-up (n=230, 83.0%)	**Without follow-up (n=47, 17.0%)**	**Statistics, effect size**
Age, mean (SD), median	14.23 (2.59), 14.81	14.42 (2.30), 14.88	z=-0.236, p=0.814; r=-0.014
Sex, male, n (%)	107 (46.5%)	19 (40.4%)	$\chi^2(1)=0.585$, p=0.444; V=0.046
Nationality, n (%)			$\chi^2(2)=1.710$, p=0.425.; V=0.079
Switzerland	123 (53.5%)	30 (63.8%)	
Germany	93 (40.4%)	15 (31.9%)	
Other	14 (6.1%)	2 (4.3%)	
Highest achieved/targeted school graduation, n (%)			$\chi^2(3)=9.239$, p=0.026; V=0.183
ISCED 0	1 (0.4%)	0	
ISCED 1	61 (26.5%)	8 (17.0%)	
ISCED 2	87 (37.8%)	29 (61.7%)	
ISCED 3	81 (35.2%)	10 (21.3%)	
Any affective disorders, present, n (%)[a,b]	37 (16.1%)	6 (12.8%)	$\chi^2(1)=0.328$, p=0.567; V=0.034
Any anxiety disorders, present, n (%)[a,b]	60 (26.1%)	12 (25.5%)	$\chi^2(1)=0.006$, p=0.937; V=0.005
Any obsessive-compulsive disorders, present, n (%)[a,b]	29 (12.6%)	2 (4.3%)	$\chi^2(1)=2.740$, p=0.098; V=0.099
Any eating disorders, present, n (%)[a,b]	66 (28.7%)	20 (42.6%)	$\chi^2(1)=3.501$, p=0.061; V=0.112
Any somatoform disorders, present, n (%)[a,b]	3 (1.3%)	0	$\chi^2(1)=0.620$, p=0.431; V=0.047
Any substance misuse, present, n (%)[a,b]	3 (1.3%)	1 (2.1%)	$\chi^2(1)=0.186$, p=0.527; V=0.026
Any trauma/stress-related disorders, present, n (%)[a,b]	2 (0.9%)	0	$\chi^2(1)=0.412$, p=1.000; V=0.039
Any developmental disorders, present, n (%)[a,b]	103 (44.8%)	19 (40.4%)	$\chi^2(1)=0.301$, p=0.583; V=0.033
SOFAS, mean (SD), median	60.33 (10.80), 60.0	59.98 (12.60), 58.0	z=-0.522, p=0.601; r=-0.031
Adynamia, mean (SD), median	11.92 (13.61), 8.0	10.98 (11.01), 8.0	z=-0.024, p=0.981; r=-0.001
Perception disturbance, mean (SD), median **s**	1.20 (2.68), 0.0	0.96 (2.18), 0.0	z=-0.729, p=0.466; r=-0.044
Neuroticism, mean (SD), median	4.48 (4.85), 3.0	4.74 (4.42), 4.0	z=-0.683, p=0.495; r=-0.041
Thought and motor disturbances, mean (SD), median	3.54 (5.24), 0.5	2.83 (3.47), 1.0	z=-0.012, p=0.991; r=-0.001
Positive symptoms, mean (SD), median	2.30 (2.33), 1.0	1.68 (1.86), 1.0	z=-1.581, p=0.114; r=-0.095
Negative symptoms, mean (SD), median	5.13 (4.08), 4.5	6.13 (4.71), 5.0	z=-1.223, p=0.221; r=-0.073
Disorganization symptoms, mean (SD), median	2.13 (1.76), 2.0	2.13 (1.38), 2.0	z=-0.430, p=0.667; r=-0.026
General symptoms, mean (SD), median	4.43 (3.32), 4.0	5.19 (3.95), 5.0	z=-1.018, p=0.309; r=-0.061
Cluster 1, present, n (%)	14 (6.1%)	2 (4.3%)	$\chi^2(1)=0.241$, p=0.624; V=0.029

[a] multiple CHR-P criteria and diagnosis possible
[b] assessed with the Mini-International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I. Kid) (Sheehan, et al., 2010).
ISCED: International Standard Classification of Education 2011; SOFAS: Social and Occupational Functioning Assessment Scale (0=lowest to 100=highest functioning)

sTable 4: Discriminating patient groups: Receiver Operating Characteristic (ROC) analyses of subscales

	Area under the curve	Standard error	Asymptotic significance	95% Confidence interval lower	upper
Adynamia	0.765	0.024	p<0.001	0.719	0.811
Perception disturbances	0.835	0.021	p<0.001	0.795	0.876
Neuroticism	0.708	0.025	p<0.001	0.659	0.758
Thought and motor disturbances	0.786	0.023	p<0.001	0.741	0.831
Positive symptoms	0.904	0.014	p<0.001	0.876	0.932
Negative symptoms	0.731	0.025	p<0.001	0.683	0.780
Disorganization symptoms	0.703	0.025	p<0.001	0.653	0.753
General symptoms	0.751	0.024	p<0.001	0.703	0.799

Interpretation according to the review of de Hond et al. (2022): $0.7 \leq$ area under the curve (AUC) < 0.8 = moderate; $0.8 \leq$ AUC < 0.9 = good; $0.9 \leq$ AUC = excellent

Reference: de Hond AAH, Steyerberg EW, van Calster B. Interpreting area under the receiver operating characteristic curve. Lancet Digit Health. 2022 Dec;4(12):e853-e855. doi: 10.1016/S2589-7500(22)00188-1.

sTable 5. Baseline characteristics of clusters (N=460).

	Cluster 1 (n=122, 26.5%)	**Cluster 2 (n=338, 73.5%)**	**Statistics, effect size**
Age, mean (SD), median	15.83 (1.49), 15.84	14.26 (2.55), 14.87	z=-5.902, p<0.001; r=-0.275
Sex, male, n (%)	36 (29.5%)	159 (47.0%)	$\chi^2(1)$=11.284, p<0.001; V=0.157
Nationality, n (%)			$\chi^2(2)$=14.066, p<0.001.; V=0.175
Switzerland	51 (41.8%)	204 (60.4%)	
Germany	54 (44.3%)	111 (32.8%)	
Other	17 (13.9%)	23 (6.8%)	
Highest achieved/targeted school graduation, n (%)			$\chi^2(3)$=36.056, p<0.001; V=0.280
ISCED 0	0 (0.0%)	3 (0.9%)	
ISCED 1	2 (1.6%)	88 (26.0%)	
ISCED 2	64 (52.5%)	141 (41.7%)	
ISCED 3	56 (45.9%)	106 (31.4%)	
Clinical setting, n (%)			$\chi^2(1)$=79.262, p<0.001; V=0.415
Inpatient/day clinic	55 (45.1%)	290 (85.8%)	
Outpatient	67 (54.9%)	48 (14.2%)	
Any CHR-P criteria, present, n (%)	106 (86.9%)	77 (22.8%)	$\chi^2(1)$=153.772, p<0.001; V=0.578
COGDIS, present, n (%)[a]	65 (53.3%)	16 (4.7%)	$\chi^2(1)$=145.612, p<0.001; V=0.563
COPER, present, n (%)[a]	72 (59.0%)	42 (12.4%)	$\chi^2(1)$=104.387, p<0.001; V=0.476
APSS, present, n (%)[a]	78 (63.9%)	34 (10.1%)	$\chi^2(1)$=141.259, p<0.001; V=0.554
BIPSS, present, n (%)[a]	3 (2.5%)	2 (0.6%)	$\chi^2(1)$=2.907, p=0.119; V=0.079
GRFD, present, n (%)	3 (2.5%)	7 (2.1%)	$\chi^2(1)$=0.063, p=0.729; V=0.012
Any affective disorders, present, n (%)[a,b]	71 (58.2%)	41 (12.1%)	$\chi^2(1)$=103.278, p<0.001; V=0.474
Any anxiety disorders, present, n (%)[a,b]	59 (48.4%)	88 (26.0%)	$\chi^2(1)$=20.548, p<0.001; V=0.211
Any obsessive-compulsive disorders, present, n (%)[a,b]	12 (9.8%)	34 (10.1%)	$\chi^2(1)$=0.005, p=0.994; V=0.003
Any eating disorders, present, n (%)[a,b]	12 (9.8%)	90 (26.6%)	$\chi^2(1)$=14.646, p<0.001; V=0.178
Any somatoform disorders, present, n (%)[a,b]	2 (1.6%)	4 (1.2%)	$\chi^2(1)$=0.145, p=0.658; V=0.018
Any substance misuse, present, n (%)[a,b]	12 (9.8%)	7 (2.1%)	$\chi^2(1)$=13.650, p<0.001; V=0.172
Any trauma/stress-related disorders, present, n (%)[a,b]	9 (7.4%)	6 (1.8%)	$\chi^2(1)$=8.918, p=0.006; V=0.139
Any developmental disorders, present, n (%)[a,b]	18 (14.8%)	129 (38.2%)	$\chi^2(1)$=22.596, p<0.001; V=0.222
SOFAS, mean (SD), median	55.06 (0.09), 54.00	61.82 (11.75), 60.00	z=-5.648, p<0.001; r=-0.263

[a] multiple CHR-P criteria and diagnosis possible
[b] assessed with the Mini-International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I. Kid) (Sheehan, et al., 2010).
ISCED: International Standard Classification of Education 2011; CHR-P: clinical high-risk for psychosis; COGDIS: Cognitive Disturbances; COPER: Cognitive-Perceptive basic symptoms; APSS: attenuated psychotic symptoms syndrome; BIPSS: brief intermittent psychotic symptoms syndrome; GRFD: genetic risk and functional decline; SOFAS: Social and Occupational Functioning Assessment Scale (0=lowest to 100=highest functioning)

sTable 6: Overview of baseline characteristics and type of psychosis in converters (N=13)

	Age in yrs.	**Sex**	**Axis-I disorder**	**CHR-P criteria**	**Type of psychosis**	**Conversion time** in months	**Cluster**
1	15	Female	Developmental disorder	COPER, APSS	Delusional disorder	2.30	1
2	15	Female	None	COGDIS, APSS	Brief psychotic episode	3.45	1
3	15	Male	None	COGDIS, GRFD	Schizophrenia	4.14	1
4	17	Male	Substance misuse	COGDIS, APSS	Delusional disorder	4.63	1
5	16	Male	Affective disorder, anxiety disorder, developmental disorder	COGDIS, APSS	Schizophrenia	5.42	1
6	14	Female	Affective disorder, anxiety disorder, trauma/stress-related disorder	COGDIS, COPER, APSS	Major depression with psychotic symptoms	7.36	1
7	16	Male	Affective disorder, obsessive-compulsive disorder	COGDIS, COPER, APSS	Brief psychotic episode	10.58	1
8	16	Male	Anxiety disorder	COGDIS, COPER, APSS	Schizophrenia	12.00	1
9	15	Female	Affective disorder, substance misuse	COPER, APSS	Schizophrenia	12.00	1
10	17	Male	Affective disorder, developmental disorder	COGDIS	Major depression with psychotic symptoms	12.78	1
11	11	Male	Affective disorder, developmental disorder	COGDIS, APSS	Major depression with psychotic symptoms	26.51	1
12	17	Female	Anxiety disorder	COPER	Major depression with psychotic symptoms	29.73	2
13	13	Female	Developmental disorder	None	Schizoaffective disorder	38.11	2

COGDIS: Cognitive Disturbances; COPER: Cognitive-Perceptive basic symptoms; APSS: attenuated psychotic symptoms syndrome; GRFD: genetic risk and functional decline

sTable 7: Comparison between data of the SPI-CY pilot study by Fux et al. (2013) and the present study

	Pilot study		Present study	
	Effect sizes (Rosenthal's r)			
Adynamia	0.70		0.450	
Perception disturbances	0.41		0.606	
Neuroticism	0.37		0.356	
Thought and motor disturbances	0.53		0.496	
	Median subscale scores			
	CHR-P	***Clinical controls***	***CHR-P***	***Clinical controls***
Adynamia	23	8	27	8
Perception disturbances	4	0	8	0
Neuroticism	7	2	9	3
Thought and motor disturbances	13	3	12	1
	Discussed sociodemographic and clinical characteristics			
	CHR-P	***Clinical controls***	***CHR-P***	***Clinical controls***
COPER, present (%)	65%	-	62.3%	-
COGDIS, present (%)	26%	-	44.3%	-
Sex, male, present (%)	57%	55%	37.7%	45.5%
Age, mean (SD)	16.8 (1.6)	15.5 (2.3)	15.30 (2.07)	14.26 (2.54)

CHR-P: clinical high-risk for psychosis; COGDIS: Cognitive Disturbances; COPER: Cognitive-Perceptive basic symptoms

Reference: Fux L, Walger P, Schimmelmann BG, Schultze-Lutter F (2013). The Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY): practicability and discriminative validity. Schizophr Res. 146(1-3):69-78. doi: 10.1016/j.schres.2013.02.014.

sTable 8: STROBE Statement for cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5 Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5-6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	sFigure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	6, Table 1, sTables 1-2
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-7, Figure 1, Tables 2-4
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

3. DISCUSSION

The significance of negative symptoms (NS) is widely recognized; however, their precise impact on the clinical presentation and outcomes of children and adolescents (CAD) who are at clinical high-risk for psychosis (CHR-P) remains unclear. We aimed to assess, for the first time, both subjective and attenuated NS. Subjective NS, based on the BS concept, were assessed using the "Adynamia" subscale of the SPI-CY, whereas attenuated NS were assessed using the "Negative Symptoms" subscale of the SIPS. This approach allowed us to examine their role in differentiating the CHR-P state from other clinical states and the prediction of psychosis in a sample of 8- to 17-year-old minors.

Two important previous studies (Fux et al., 2013; Zhang et al., 2020) addressed a similar research question using different samples, as summarized in Table 1. Fux et al. (2013) included a Clinical High Risk for Psychosis (CHR-P) group consisting of inpatients and outpatients, a clinical control (CC) group of inpatients, and a non-clinical community sample recruited from schools in Cologne; however, their sample size was relatively small. Similar to our study, they assessed adolescents using both Ultra-High-Risk (UHR) and Basic Symptoms (BS) criteria. In contrast, Zhang et al. (2020) examined a larger sample comprising both adolescents and adults but relied exclusively on UHR criteria.

Our study extends this previous work by including a larger sample than that of Fux et al. Specifically, we recruited a CHR-P cohort from three CAD psychiatric departments, along with a clinical control group. Inclusion criteria for the CC group were an age between 8 and 17 years, current inpatient or day-clinic treatment, and the presence of a diagnosis associated with an increased risk of adult-onset psychosis.

Table 1: Comparison between samples of the Fux et al. (2013), Zhang et al. (2020) and the present study

	Fux et al. (2013)	**Zhang et al. (2020)**	**Present Study**
Sample	3 groups: In- and outpatients of 2 clinics At-Risk (CHR-P) and Clinical controls (CC), 1 nonclinical general population sample (GPS)	2 groups: CHR-P (adolescents <18 years and adults <45 years) from Shanghai Mental Health Center (SMHC)	2 Groups: CHR-P, Clinical control (CC) group
CHR-P definition	UHR and BS	UHR	UHR and BS
Age	8–18 years	Adults and adolescents <45 years	8-17 years
Male (%)	39 (61%)	244 (47,2%)	195 (42.4%)
Sample size	23 CHR-P, 22 CC, 19 GPS. N = 64	273 CHR-P adults, 244 CHR-P adolescents. N = 517	277 CC, CHR-P 183. N = 460

Reference: (Fux et al., 2013; Zhang et al., 2020)

Building on both studies, we hypothesized that "Adynamia" (SPI-CY) and "Negative symptoms" (SIPS) would effectively distinguish CHR-P individuals and predict psychosis onset. Our findings, nevertheless, only partially corroborated these prior studies, which had postulated subjective and attenuated NS as the most potent discriminators of underage CHR-P and the most robust predictors of conversion, respectively. In the upcoming sections, we will systematically analyse the causes of these differences.

3.1. Group discrimination by subjective negative symptoms

Contrary to the SPI-CY pilot study (Fux et al., 2013), "Perception disturbances" yielded the largest group effect in our study, not "Adynamia". While both "Perception disturbances" and "Adynamia" showed a four-point higher median score than in the pilot study, the former had a larger effect size (.606) than the latter (.450). "Adynamia's" effect was also surpassed by "Thought and motor disturbances" (.496) whose effect size mirrored that of the pilot study (.53). "Neuroticism" showed a similar, moderate effect in both studies and was the weakest discriminator.

The fourteen basis symptoms (BS) pertinent to COPER and COGDIS fall under the categories of "Perception disturbances" and "Thought and motor disturbances." Notably, "Perception disturbances" holds greater relevance for COPER, encompassing four primary items from this section, in contrast to COGDIS, which includes only one. Given that both studies exhibited similar proportions of patients with COPER (Fux et al., 2013), we can assert that our elevated median for "Perception disturbances" and the consequent greater effect were not attributable to the proportion of COPER patients. Furthermore, our larger proportion of COGDIS patients did not lead to an increased median or effect for "Thought and motor disturbances" within our CHR-P sample. This suggests that the discriminatory power of the two SPI-CY subscales, incorporating criteria-relevant BS, was not predominantly influenced by the distribution of these BS criteria.

Differences in sociodemographic characteristics between samples may account for the observed discrepancies in effect sizes for "Perception disturbances" and "Thought and motor disturbances" when comparing our study to the pilot study (Fux et al., 2013). Our cohort was, on average, one year younger and comprised a higher proportion of females (20% more in CHR-P and 10% more in CC). Both younger age and female sex have been significantly associated with a greater prevalence of basis symptoms (BS) included in COGDIS and/or COPER within the community (Schultze-Lutter, Schimmelmann, et al., 2020). Therefore,

our higher representation of female and younger patients, and consequently, the increased likelihood of reporting BS categorized under "Perception disturbances" and "Thought and motor disturbances," may have amplified the group effect observed for these two SPI-CY subscales.

While the median scores for the SPI-CY subscales were largely comparable between the studies, our CHR-P group exhibited a median for "Perception disturbances" that was twice as high as that in the pilot study. Conversely, the median for "Thought and motor disturbances" in our own clinical comparison (CC) group was only one-third as high. This observation suggests that younger age and a higher proportion of girls did not generally lead to higher medians in our sample as a whole. However, the comparatively higher proportion of younger children (aged 8-12 years) within our CC may indeed have contributed to their low median for "Thought and motor disturbances." This is because five of the 19 items in this subscale cannot be assessed until age 13 due to developmental considerations (see Table 2). Consequently, these items were rated as '0' for children, which lowered the medians in both our groups and slightly attenuated the group effect for "Thought and motor disturbances" compared to the pilot group. Due to the relatively small number of 8- to 12-year-olds, particularly in the CHR-P sample, a targeted group comparison of symptom profiles solely for 8- to 12-year-old patients could not be conducted. Therefore, larger, dedicated studies are required to investigate very early, developmentally sensitive predictors of psychosis, especially considering that most existing paediatric CHR-P studies have focused on adolescents aged 12-18 or 15-18 years (Lång et al., 2022).

Table 2. SPI-CY items, SPI-CY items assessed from age 13 onwards and their contribution to clinical high-risk for psychosis (CHR-P) criteria

Adynamia
➢ Reduced energy and vitality ➢ Reduced persistence and patience ➢ Reduced drive and initiative ➢ Intermittent, recurrent depressive mood swings ➢ Impaired tolerance to certain stressors ➢ Increased emotional reactivity in response to everyday events ➢ Change in mood and emotional responsiveness ➢ Disturbance in presenting oneself ➢ Decrease in positive emotional responsiveness towards others ➢ Increased emotional reactivity in response to routine social interactions ➢ Difficulties concentrating ➢ Forgetfulness, scatterbrainedness ➢ Slowed-down thinking ➢ **Lack of 'thought energy' or goal-directed thoughts (from age 13 onwards)**
Perception disturbances
➢ Decreased ability to discriminate between ideas and perception, fantasy and true memories ➢ Hypersensitivity to sounds and acoasms

➢ Unstable ideas of reference ➢ Visual perception disturbances ➢ Other acoustic perception disturbances ➢ Disturbance of the comprehension of visual or acoustic stimuli ➢ **Derealization (from age 13 onwards)** ➢ Body perception disturbances (cenesthesias)
Neuroticism
➢ Decreased need for social contacts ➢ Increased emotional reactivity in response to adversities of strangers ➢ Increased excitability and irritability ➢ Obsessive-compulsive phenomena ➢ Phobic phenomena ➢ **Autopsychic depersonalization (from age 13 onwards)** ➢ Unusual bodily sensations of pain in a distinct area ➢ Dysesthesias caused by touch or perceptions
Thought and Motor Disturbances
➢ **Increased indecisiveness with regard to choices between equal alternatives (from age 13 onwards)** ➢ Impaired social skills ➢ **Decreased spontaneity, increased self-reflection (from age 13 onwards)** ➢ Disturbances of immediate recall ➢ Difficulties to hold things in mind for less than an hour ➢ **Disturbance in retrieving knowledge from long-term memory (from age 13 onwards)** ➢ **Disturbances of abstract thinking (from age 13 onwards)** ➢ Inability to divide attention ➢ Thought interference ➢ Thought pressure ➢ Disturbances of expressive speech ➢ Disturbance of receptive speech ➢ Decreased capacity to discriminate between different kinds of emotions ➢ Thought perseveration ➢ **Thought blockages (from age 13 onwards)** ➢ Feeling overly distracted by stimuli ➢ Motor interference exceeding simple lack of coordination ➢ Motor blockages ➢ Loss of automatic skills ➢ Captivation of attention by details of the visual field

The basic symptom criteria "Cognitive Disturbances" (COGDIS) and "Cognitive-Perceptive BS" (COPER)

"Cognitive Disturbances" (COGDIS)
≥2 basic symptoms of at least weekly frequency (SPI ≥ '3') within past 3 months: ➢ inability to divide attention ➢ thought interference ➢ thought pressure ➢ thought blockages ➢ **disturbance of receptive speech (from age 13 onwards)** ➢ **disturbance of expressive speech (from age 13 onwards)** ➢ disturbance of abstract thinking ➢ unstable ideas of reference ➢ captivation of attention by details of the visual field
"Cognitive-Perceptive BS" (COPER)
≥1 basic symptom of at least weekly frequency (SPI ≥ '3') within past 3 months and first occurrence or significant increase in frequency at least 12 months ago: ➢ thought interference ➢ thought perseveration ➢ thought pressure ➢ thought blockages ➢ **disturbance of receptive speech (from age 13 onwards)** ➢ decreased ability to discriminate between ideas and perception, fantasy and real memories

- unstable ideas of reference
- derealisation
- visual perception disturbances (14 subitems)
- acoustic perception disturbances (3 subitems)

Bold print indicates items that only can be rated from age 13 onwards. (Fux et al., 2013; Schultze-Lutter & Koch, 2013)

Despite substantial group differences observed in "Perception disturbances" and "Thought and motor disturbances," "Adynamia" emerged as the most crucial feature differentiating the two clusters of high- and low-scorers. "Negative symptoms" ranked fifth in importance. The smaller Cluster 1, which encompassed approximately a quarter of the high-scoring patients, primarily consisted of individuals at clinical high risk for psychosis (CHR-P). Although the patient groups did not differ in overall functioning, the clusters themselves showed significant differences, with patients in Cluster 1 exhibiting greater impairment. This finding supports the notion that negative symptoms—particularly subtle, subclinical, and subjectively experienced forms such as adynamic basis symptoms (BS) (Schultze-Lutter, 2020) —represent a core domain of the psychosis spectrum in minors and are strongly correlated with functional deficits (Salazar De Pablo et al., 2023).

3.2. Prediction of psychosis by subjective and attenuated negative symptoms

In line with prior research (Piskulic et al., 2012; Schlosser et al., 2012), the "Negative symptoms" subscale was the only predictor of conversion in our Ultra-High Risk (UHR) sample when SIPS subscales were considered alone, as in Zhang et al. (Zhang et al., 2020). This was a key finding in our study. However, when all subscales were included, "Neuroticism" also became a predictor, albeit a negative one that only approached significance. Since "Neuroticism" includes items related to anxiety, obsessive-compulsive traits, and borderline phenomena (e.g., irritability, increased emotional responsiveness, depersonalization), this may indicate that negative symptoms are uniquely predictive of psychosis in underage UHR patients in the absence of these specific anxiety, obsessive-compulsive, and borderline conditions. Prior studies have reported significant positive correlations between borderline symptoms and "Positive symptoms," but not with BS criteria and "Positive symptoms" or conversion to psychosis in UHR samples (Martin et al., 2024; Paust et al., 2019; West et al., 2023). Thus, the weak negative psychosis-predictive value of "Neuroticism" could potentially be mediated by lower positive symptom levels in these UHR patients.

Within the total sample, “Negative symptoms” and “Positive symptoms” both served as predictors of conversion. This finding aligns with Lindgren et al.(Lindgren et al., 2021), who examined the generalizability of prediction models in a diverse adolescent psychiatric sample containing a UHR subgroup. The inclusion of UHR-negative individuals in our sample broadened the variance in “Positive symptoms,” a key symptomatic criterion for UHR. This broader sample composition thus yielded a significant group effect for “Positive symptoms” concerning conversion, a result not found in Zhang et al.’s(Zhang et al., 2020) study, despite comparable mean “Positive symptoms” in their converters. While the mean for “Negative symptoms” in our converters was slightly lower than that reported by Zhang et al. (Zhang et al., 2020), and considerably lower in non-converters, the significant predictive contributions of “Negative symptoms” in both our model and Zhang et al.’s were similarly modest.

Interestingly, while “Negative symptoms” demonstrated a lower group effect concerning conversion compared to “Perception disturbances” and “Thought and motor disturbances” in group comparisons, its selection into the regression model suggests substantial redundancy. This redundancy likely exists between “Perception disturbances” and “Thought and motor disturbances,” and also with “Positive symptoms,” particularly concerning perception disorders (Jimeno et al., 2022). These high overlaps prevented the simultaneous inclusion of “Perception disturbances” and “Thought and motor disturbances” into the model alongside “Positive symptoms.” Nevertheless, these substantial redundancies among the criteria-relevant subscales of the SPI-CY and SIPS support the complementary utility of both UHR and BS criteria, even though these two approaches represent distinct forms of psychopathology. In contrast, redundancy between Negative symptoms and Positive symptoms appeared to be low, making negative symptoms a valuable addition to early detection efforts in minors (Fux et al., 2013; Lindgren et al., 2021; Zhang et al., 2020).

Within the CHR-P sample, only the SIPS subscale “Disorganization symptoms” was predictive of psychosis. Notably, this subscale does not include the positive item “disorganized communication.” This sole selection is surprising, given its relatively small group effect for both initial group assignment and conversion. However, disorganized symptoms have been incorporated into several prediction models previously, always in conjunction with other symptoms and specifically with positive symptoms (Rosen et al., 2021). The exclusion of “Positive symptoms” from our CHR-P regression model might stem from the fact that all 12 converters met COPER and/or COGDIS criteria at baseline, but only

9 also met symptomatic UHR criteria. Therefore, the selection of "Disorganization symptoms" might reflect the presence of severe and observable "Trouble with focus and attention"—a component of "Disorganization symptoms" resulting from significant cognitive basis symptoms (BS)—as well as the presence of more "Bizarre thinking," characterized by unusual and delusion-like ideas. Although not directly related to conversion, "Disorganized symptoms" have been associated with cannabis or amphetamine use (de Medeiros et al., 2024). Indeed, substance use was more prevalent in CHR-P converters (16.7%) compared to CHR-P non-converters (7.6%), which might have further contributed to our findings. However, similar to single-item contributions, this requires more detailed exploration in future studies. It is worth noting that hebephrenic psychosis is more frequent among individuals with a history of drug abuse.

Unsurprisingly, the cluster solution demonstrated that Cluster 1, which largely consisted of CHR-P patients and included all converters save for the two with the longest conversion intervals, predicted transition in Cox regression models. Moreover, pairwise comparisons confirmed that the cluster solution provided the strongest distinction between converters and non-converters. Aligned with the Cox regression findings, the cluster solution, primarily based on "Adynamia" and "Thought and motor disturbances," indicated that a combination of subscales encompassing both positive and negative symptom domains is of greatest importance for underage patients.

3.3. Implications for early detection of psychosis

The European Psychiatric Association (EPA) has issued specific recommendations for early detection of psychosis (Schultze-Lutter, Michel, et al., 2015). Firstly, CHR criteria should be applied exclusively to individuals who are already experiencing distress due to mental problems and are actively seeking help (Recommendation 4), often because of depressive and anxiety disorders. In our study, 24.3% of the total sample received a diagnosis of an affective disorder and 32,0% any anxiety disorder. Like mentioned above, negative symptoms might be most predictive of psychosis in CAD-UHR patients without neuroticism traits like anxiety, obsessive-compulsive disorder, and borderline conditions. Running a standard diagnostic evaluation that encompasses SIPS and SPI-CY but also these mental disorders would be appropriate when evaluating CAD in early detection centres.

Given the overall insufficient evidence for the psychosis-predictive value of CHR-P in CAD —evidenced in our study by a transition rate of only 6.6% in CHR-P individuals—, the

diagnostic procedures being made, final diagnosis and prognosis should be communicated to both parents and CAD with utmost care, even when diagnostic criteria are fully met (Armando et al., 2020). This was also a concrete recommendation of the EPA guideline for early detection (Recommendation 5) (Schultze-Lutter, Michel, et al., 2015), particularly focused on children and young adolescents and aimed at preventing patient stigmatization. Furthermore, it is recommended to avoid over-pathologizing potentially transient and clinically irrelevant appearance of (subthreshold) positive psychotic symptoms when diagnosing and treating psychotic disorders and their clinical high-risk states in minors(Schultze-Lutter et al., 2022). The same principle should be applied to the presence of subthreshold negative symptoms in CAD.

Many of the CHR-P are based merely on positive symptoms and most current CHR-P diagnostic tools have been developed based on adult or young adult populations (Armando et al., 2020). Among these, the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY) (Fux et al., 2013) stands out as the only instrument specifically designed for basic symptoms in a child and adolescent population and can be applied from the age of 8. Another useful instrument, also for CAD, is the Prodromal Questionnaire—brief child version (Karcher et al., 2018) a self-report questionnaire validated on a population of 3,984 CAD (mean age 10.0 years; SE 0.01). As mentioned above, subclinical and attenuated negative symptoms seem to be more significant in cases of pure CHR-P according to our study, underscoring the need to identify distinct negative symptom profiles within these specific populations. More specific instruments for children could be useful toward this goal.

There are other reasons why NS are frequently neglected or overlooked during routine evaluations. In early-onset psychosis (EOP), both positive and negative symptoms can be particularly missed if parents and primary care providers attribute adolescents' symptoms to typical adolescent turmoil (Schimmelmann et al., 2007). Furthermore, comorbid conditions with high prevalence in CAD such as substance abuse, depression, and anxiety syndromes can mask the emergence of a psychotic disorder. To an untrained clinician, depressive symptoms and negative symptoms can appear similar (e.g., anhedonia or blunted affect), specially in CAD without past history of mental disorders. Adult psychiatry guidelines, such as those issued by the German Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde e. V. (DGPPN, Recommendation 111) (Deutsche Gesellschaft für Psychiatrie und Psychotherapie, 2025) and the North American APA guidelines for schizophrenia (Keepers et al., 2020), recommend directly extrapolating

diagnostic and treatment approaches from adults to adolescents. However, this approach risks neglecting negative symptoms and their clinical manifestations in younger populations.

Even with thorough training and the use of structured clinical tools like the SPI-CY, distinguishing these phenomena remains difficult, requiring both clinical experience and specific training for the clinician. Distinguishing emotional blunting from depressive anhedonia, apathy, and the mental indifference or amimia observed in parkinsonism is particularly difficult. Furthermore, apathoabulic disorders can easily be confused with depressive motor retardation, parkinsonian akinesia, and cognitive impairment. Disturbances in associative thinking may also be mistaken for depressive retardation, which is often accompanied by difficulties in concentration or bradypsychia, cognitive dysfunction, and impaired speech production characteristic of parkinsonism. Similarly, schizophrenic autism can be challenging to differentiate from social withdrawal seen in depression or the forced restriction of social contacts in parkinsonism. Even chronic substance abuse, such as with cannabis, is associated with the amotivational syndrome, which can clinically overlap with and mimic existing negative symptoms. The high rate of substance use among CHR-P converters (16.7%) compared to non-converters (7.6%) in our study indicates that drug abuse represents an additional risk factor that could alter the psychopathological presentation and outcome in CAD. Therefore, proper training and constant supervision in clinical settings and early detection centers might assist clinicians of alla ages in better differentiating CHR-P from other mental disorders.

As mentioned above, the higher proportion of 8–12-year-old children in our CC may account for their lower median "Thought and motor disturbances" score. Many symptoms from SPI-CY-Dimension A, "Adynamia", Dimension C "Neuroticism" and Dimension D "Thought and motor disturbances" can only be reliably measured from age 13 onward (Table 2): blunting of positive feelings toward others (including sympathy and appreciation of their worth) (A6), impairment in the ability to present oneself (A8), and a lack of "thought energy" or goal-directed thinking (A14); Autopsychic depersonalization (C6) and Increased indecisiveness with regard to choices between equal alternatives (D1), increased self-reflection (D2), Disturbance in retrieving knowledge from long-term memory (D6), Disturbances of abstract thinking (D7) and Thought blockages (D15). This is mainly because, according to Piaget, individuals typically reach the formal operational stage of cognitive development only around age 12 (Inhelder & Piaget, 2013). The role these developmental differences play when comparing our data with other studies remains unclear,

but it underscores the need for more comprehensive research focused exclusively on child populations.

3.4. Implications for prognostic prediction

Psychosis prediction models in adolescents based on positive and negative symptoms have not demonstrated consistent success (Lindgren et al., 2021). The analysis of individual symptom items in relation to their association with the transition to overt psychosis, as evidenced by our findings and prior research, holds significant potential for improving psychosis prediction. This includes also the potential contribution of subclinical and attenuated negative symptoms. Such an approach could enhance existing risk assessment tools, such as the diagnostic calculators developed for the large NAPLS-2 (Cannon et al., 2016) and PRONIA (Koutsouleris et al., 2021) cohort studies. The NAPLS-2 risk calculator, which incorporated a combination of clinical, neurocognitive, demographic, and psychosocial variables, determined that SIPS items P1 (Unusual Thought Content) and P2 (Suspiciousness), coupled with a decline in social functioning, neurocognitive deficits, age, and symptom progression, were significant predictors of psychosis transition. This cohort included 596 patients aged 12-34 (mean age 18.5, SD 4.3)(Addington et al., 2012), with its predictive algorithm limited a priori to eight predictors. Negative symptoms and their subclinical presentations were excluded.

Based on the PRONIA cohort (patients aged 15-40, mean age 23.8 years) (Koutsouleris et al., 2021), an algorithm was developed that utilizes artificial intelligence to leverage clinical, neuropsychological, and neuroimaging information for the individual prediction of psychosis transition and functional decline. This algorithm analysed indeed SIPS negative symptom items (social anhedonia, avolition, expression of emotions, experience of emotions and self, ideational richness, and occupational functioning), but notably excluded all SPI-CY items and SPI-A “Adynamia”.

A precisely designed algorithm that integrates CAD-relevant and subclinical/attenuated negative symptoms along with their available subscale items could complement existing models. This, in turn, would improve the predictability of psychosis and functional impairment.

3.5. Implications for therapy

Uncertain diagnoses often lead to inappropriate treatment. It is essential to distinguish primary negative symptoms—those considered an intrinsic feature of schizophrenia—from

secondary negative symptoms that arise from factors such as positive symptoms, comorbid depression, antipsychotic side effects, substance use, or social isolation. To provide appropriate therapy, diagnostic evaluations must adequately account for subclinical and attenuated negative symptoms to ensure they are accurately recognized.

Antipsychotic medication for CAD patients with CHR-P is not recommended. The EPA-Guideline for Early Intervention in CHR-P (Schmidt et al., 2015) endorses a pure psychotherapeutic approach (Recommendation 7). Nevertheless, the number of prescriptions of antipsychotics in CAD is worldwide constantly increasing (Aparasu & Bhatara, 2007; Vitiello et al., 2009), rising as rapidly as 62.8% over just a seven-year period (2011 to 2018) in Australia (Klau et al., 2022). This may be because primary negative symptoms can easily be mistaken for secondary negative symptoms (e.g., those caused by positive psychotic symptoms) or for depressive symptoms. Consequently, unnecessary treatment with sometimes high doses of antipsychotics is commonly observed in clinical settings. Many of these medications, due to their anticholinergic properties, can further aggravate negative symptoms. Amongst common side effects of antipsychotics, blunting of affect of positive and negative feelings can be difficult to differentiate from adynamic basic symptoms like reduced energy and vitality, drive and initiative, impaired tolerance to certain stressors or mood disorders. Research on this very topic is scarce and should be intensified.

If negative symptoms are not identified at an early stage, treatment may only begin once they emerge as part of a full-blown psychotic disorder. Unfortunately, evidence on the effectiveness of medication for manifest negative symptoms remains limited. The scarcity of research on negative symptoms in children and adolescents (CAD) is particularly concerning. A network meta-analysis by Pagsberg et al. (Pagsberg et al., 2017) showed that only aripiprazole, asenapine, risperidone, olanzapine and molindone were superior to placebo in improving negative symptoms in CAD. However, another network meta-analysis by Harvey et al. (Harvey et al., 2016) found that all eight interventions studied — aripiprazole, haloperidol, molindone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone— did not significantly reduce negative PANSS scores compared to placebo in minors.

Since these studies, new research has emerged: Lurasidone demonstrated significant improvement in negative symptoms in CAD patients with previously treated Early-Onset Psychosis (EOP) compared to placebo ($P = 0.017$) (Correll et al., 2022; Goldman et al., 2017); Blonanserin was evaluated in a 6-week multicenter, double-blind, randomized,

placebo-controlled study in minors (Saito et al., 2022), demonstrating good tolerability and a reduction in negative symptoms at the 16-mg/day dosage. In a randomized, double-blind, parallel-arm, placebo-controlled phase 3 trial (Ward et al., 2025), the PANSS negative subscale score exhibited a numerical improvement in the brexpiprazole group relative to a placebo group at week 6 ($p > 0.05$), also in CAD. Currently, lurasidone, molindone, blonanserin, and brexpiprazole are not available in Germany for a variety of reasons (Deutsche Gesellschaft für Psychiatrie und Psychotherapie, 2025), thereby restricting pharmacological treatment options and placing an additional burden on our patients.

The limited efficacy of antipsychotics in treating established negative symptoms of psychosis in minors is not well understood. A meta-analysis by Zhou and Cipriani (Zhou et al., 2020), focusing on antidepressants in adolescents, demonstrated that treatment approaches well-established in adults proved ineffective in adolescents. This pattern may also apply to psychosis. They postulated several possible explanations for these phenomena. Firstly, neurodevelopmental mechanisms, including significant changes in hormone levels and hormone receptors during adolescence, may amplify emotional responses to negative social stimuli through dysregulation of the hypothalamic-pituitary-adrenal axis. Secondly, the limited number of studies and smaller sample sizes in young patients with depression reduce the statistical power of individual comparisons, a challenge we also encountered in this study. Thirdly, differences in study designs between adults and children may lead to higher placebo response rates, thus obscuring positive treatment outcomes in childhood and adolescent depression. It is thus possible that established negative symptoms may not respond to standard therapies, and many novel pharmacological interventions are not available due to structural limitations in Germany. If this is the case, early detection and intervention remain critically important factors for improving the prognosis of psychosis in child and adolescent populations. It is also possible that responders and non-responders represent distinct phenotypes that have not yet been fully identified. Investigating these potential differences should be a priority for future research.

The higher risk of antipsychotic side effects in CAD and a high risk of distress related to these side effects interfering with development and daily living justifies the recommendation to use other, lower-risk treatment options first, such as supportive and family therapy(Schimmelmann et al., 2013), cognitive-behavioural therapy, social skills training, healthy lifestyle, sleep hygiene, stress reduction, and—if indicated—antidepressants or other targeted treatments of psychiatric syndromes or disorders.

Various studies have shown that early intervention in psychotic cases is less expensive (between 1/2 and 1/3 of the usual cost) compared to the usual public mental health services studied, and has better results across a wide spectrum of events, from vocational and social functioning to rehospitalization and relapse rates (Cullberg et al., 2006; Ibarrondo et al., 2024). Early, non-specific cognitive, behavioral, or social interventions could potentially trigger a protective cascade effect, which, considering the developmental status of individuals in the CHR stage (Poletti et al., 2019), may prove more effective and cost-efficient than specific clinical interventions.

3.6. Implications for university teaching and residency programs

A significant challenge exists in the awareness and training of the broader mental health network, which includes paediatricians, general physicians, school psychologists, and child and adolescent psychiatrists. Many may not be sufficiently equipped to appropriately and regularly assess psychotic symptomatology in adolescents. Mental health professionals excel at recognizing and treating positive schizophrenia symptoms but have less or not training at all in assessing and treating negative symptoms, which remain difficult to reliably measure(Galderisi et al., 2017). Similarly, clinical high-risk for psychosis (CHR-P) and its consistent clinical staging approach are not presently integrated as core subjects within most child and adolescent psychiatry training curricula (Armando et al., 2020). The International Working Group on Basic Symptoms, the European Society for Child and Adolescent Psychiatry (ESCAP) Research Academy, and the Computer-assisted Risk Evaluation (CARE)-Studie have made commendable efforts to provide training in psychiatric disorder assessment and treatment for children and adolescents (Guloksuz & Van Os, 2018; Kraemer, 2007), which take place regularly and should be continued.

3.7. Strengths and limitations

Key strengths of our study include the substantial sample size, the use of both UHR and BS criteria, the high control of data quality, and the inclusion of a CC group clinically unsuspected to develop psychosis but with primary diagnoses associated with increased risk for psychosis in adulthood. Nevertheless, the small number of converters is a notable limitation, particularly given the recommended event-to-predictor ratio of 5:1 for reliable regression analyses (Vittinghoff & McCulloch, 2007).

Furthermore, our follow-up period of two years may have been too short, as psychoses with first prodromal symptoms before the age of 18 years show an extended prodrome(Schultze-

Lutter, Rahman, et al., 2015). At the same time, follow-up rates of 2 years are common in early detection studies, and most transitions happen in the first two years(Schultze-Lutter, Michel, et al., 2015). Another limitation is the dropout rate, which is significant in the CHR group, especially at the two-year follow-up. Nonetheless, dropouts and participants with follow-up data were largely similar, especially in clinical variables. While equating dropout with non-conversion likely reduced the discriminatory effects of subscales in pairwise comparisons, this limitation should have affected all subscales equally.

3.8. Conclusions

Despite their potential clinical significance, subclinical and attenuated negative symptoms (NS) in minors have received limited attention in both research and clinical practice. Although our results partially support a role for subjective and attenuated NS in identifying youth at clinical high-risk for psychosis (CHR-P) and predicting conversion to psychosis, their overall impact was less pronounced than anticipated.

Our findings suggest that the importance of NS is highly influenced by sample composition, with the predictive value of NS for conversion to psychosis being most evident in ultra-high-risk (UHR) samples. Consequently, future research should prioritize the identification of distinct NS profiles within these specific populations. Furthermore, interventions targeting underage UHR individuals have predominantly focused on positive symptoms, in addition to a combination of genetic risk and functional level, with only a few studies (Frearson et al., 2024) also examining the impact on NS. Our findings underscore the need for future intervention trials to place greater emphasis on the reduction of NS, particularly within underage UHR samples.

A further finding of this study is the observed redundancy between the criteria-relevant subscales of the SPI-CY and SIPS assessments. While this redundancy highlights the distinct psychopathology reflected by the two approaches, it also supports the application both of UHR and basic symptom (BS) criteria.

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