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Premorbid characteristics of patients with DSM-IV psychotic disorders

Line Widing [a,*,1], Carmen Simonsen [a,b], Camilla B. Flaaten [a], Beathe Haatveit [a], Ruth Kristine Vik [a], Kristin F. Wold [a], Gina Åsbø [a], Torill Ueland [a,c], Ingrid Melle [a]

[a] NORMENT, Norwegian Centre for Mental Disorders Research, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[b] Early Intervention in Psychosis Advisory Unit for South East Norway, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[c] Department of Psychology, University of Oslo, Oslo, Norway

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ABSTRACT

Introduction: Psychotic disorder not otherwise specified (PNOS) is considered part of the psychosis spectrum, together with schizophrenia spectrum disorders (SSD) and psychotic bipolar spectrum disorders (PBD). The atypical clinical presentations of PNOS conditions may lead to uncertainty regarding treatment choices and expected outcomes. PNOS is understudied, and little is known about patients' premorbid characteristics including premorbid adjustment, prevalence of early cannabis use and childhood trauma. Knowledge about early illness phases can increase our understanding of this diagnostic group.

Methods: We included 1099 participants from the Norwegian TOP-study; 688 with narrow SSD diagnoses (schizophrenia, schizoaffective disorder, schizophreniform disorder), 274 with PBD (psychotic bipolar 1 and bipolar NOS) and 137 with PNOS diagnosed with the SCID-I for DSM-IV. Participants were assessed with the Premorbid Adjustment Scale (PAS) divided into the areas of premorbid academic and social functioning. We obtained information on age at first exposure to cannabis and use of cannabis before the age of 16. The participants also provided information regarding early traumatic experiences using the Childhood Trauma Questionnaire (CTQ).

Results: Participants with PNOS and SSD had poorer premorbid academic functioning than those with PBD ($F_{2, 1029} = 7.81$, $p < 0.001$, ${}_p\eta^2 = 0.015$). Premorbid social adjustment was significantly worse in the SSD group compared to the PBD group ($F_{2, 1024} = 3.10$, $p = 0.045$, ${}_p\eta^2 = 0.006$), with PNOS in the middle position. Significantly more of the participants with PNOS (17.5%) and SSD (11.5%) used cannabis before the age of 16 compared with PBD (5.3%, Wald $\chi^2 = 6.86$, $p = 0.03$). There were no significant differences between the three groups regarding mean CTQ scores or in the proportion of participants who had experienced at least one type of childhood adversity.

Conclusions: Participants with PNOS appear as more similar to participants with SSD than to those with PBD regarding early premorbid adjustment and early cannabis use. The results indicate that many conditions classified as PNOS have functional impairments and problematic substance use from an early age. The prevalence of childhood adversities are high in all three groups.

1. Introduction

Schizophrenia spectrum disorders (SSD) and psychotic bipolar spectrum disorders (PBD) are disorders with significant overlaps in etiologies and clinical presentations [1–3]. The conceptualization of both SSD and PBD as part of a larger psychosis spectrum is increasingly replacing the earlier notion of two discrete diagnostic entities [4,5]. While still not fully understood, their etiologies is seen as parts of a complex interplay between polygenic predispositions and a range of environmental risk factors [6–8].

Abbreviations: PNOS, Psychotic disorder not otherwise specified; SZ, schizophrenia; SSD, schizophrenia spectrum disorders; PBD, psychotic bipolar I and NOS disorders; SIPD, substance-induced psychotic disorder; PNOS-SIPD, PNOS where SIPD could not be ruled out; PNOS-other, all other PNOS outside of PNOS-SIPD..

* Corresponding author.
E-mail address: l.h.widing@studmed.uio.no (L. Widing).
[1] **Postal address:** Oslo University Hospital HF, Division of Mental Health and Addiction, Psychosis Research Unit/TOP, Ullevål Hospital, building 49, P.O. Box 4956 Nydalen, N-0424 Oslo, Norway.

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The DSM-IV assigns the diagnosis "Psychotic disorder not otherwise specified (PNOS)" to psychotic syndromes that either do not meet all the criteria for a more specific psychotic disorder, or where inadequate or contradictory information temporarily preclude more specific diagnoses [9]. The latter criterion includes syndromes with uncertainty between a primary psychotic disorder (PPD) and a substance-induced psychotic disorder (SIPD), a common comorbidity also in ascertained PPDs. The more recent DSM-5 assigns the diagnosis "Other specified schizophrenia spectrum and other psychotic disorder" to psychotic syndromes that do not meet the full criteria for a specific disorder, and "Unspecified schizophrenia spectrum and other psychotic disorder" to the group defined by uncertain information [10]. The DSM-IV category and the two DSM-5 categories are otherwise conceptually overlapping. The lack of more specific criteria for the PNOS diagnostic category however leads to the formation of a clinically heterogeneous group [11], which makes research studies challenging. While 7–12% of first episode patients are diagnosed as PNOS [12–14], patients with this diagnosis is often not included in research studies. PNOS is thus highly understudied compared to other psychotic disorders.

In a recent study of the current sample, we found that the participants with PNOS were intermediate between participants with SSD and PBD regarding current symptom severity and functional impairment [11]. We also found that difficulties ruling out SIPD was the diagnostic basis for almost 30% of the PNOS cases. In line with this, this subgroup (hereafter referred to as PNOS-SIPD) had a particularly high prevalence of current substance use compared to all other diagnostic groups, including other PNOS subgroups [11].

The rare longitudinal studies of PNOS show that about one third will receive a SSD diagnosis at a later stage, while about one third will retain their PNOS diagnosis in the long term [15]. It is thus likely that the diagnosis PNOS partly captures early manifestations of SSD, but also conditions that simply do not fit any of the specific psychotic diagnostic categories. There is however limited information regarding illness development and clinical prognosis. For instance, should patients in the PNOS-SIPD subgroup be treated as an early case of a SSD or as a time-limited SIPD? Examining early illness development may here help to clarify differences within the psychosis spectrum [16]. However, most studies that have examined premorbid- and early illness factors have either examined first-episode psychosis sample as one group across all diagnosis [17–19], or focused on differences between SSD and PBD [20,21] excluding PNOS. There is thus a specific lack of knowledge about the early illness phases of the PNOS group.

Findings of impaired premorbid functioning and early cognitive deficits in people who develop SSD, have led to the understanding of SSDs as neurodevelopmental disorders [22,23]. Current knowledge suggests that SSDs often develop in parallel with the maturation of the cerebral cortex, and are caused by a combination of genetic and environmental effects on brain development [24]. Developmental pathologies preceding the onset of psychotic symptoms are also associated with PBD, but these tend to be less severe and less common than in SSD [20]. Only a few studies have investigated premorbid functioning in people with PNOS [12,25].

The most used measure of premorbid functioning is the Premorbid Adjustment Scale (PAS) [26]. The PAS covers social and academic adjustment for the premorbid periods of childhood, early adolescence, late adolescence and adulthood, with scores assigned for time-periods preceding the onset of the disorder [18]. Poor premorbid functioning in childhood has been linked to both lower level of global functioning at illness onset and poor outcome [27,28]. Korver-Nieberg et al. compared adult participants with PNOS and a narrow schizophrenia diagnosis (SZ) using the PAS [12]. They found no differences in premorbid adjustment in childhood and early adolescence, but poorer functioning in late adolescence in the SZ group. In another study comparing adolescents with PNOS, SZ and PBD, McClellan et al. found a trend for poorer premorbid academic performance in PNOS compared to PBD, and indications that adolescents with PNOS were intermediate between the other two groups in terms of premorbid social functioning [25]. However, these differences were not statistically significant, possibly due to small samples and ensuing lack of statistical power.

Cannabis is the drug most commonly used by adolescents [29] and also a well-documented risk factor for psychotic disorders [30–33]. In addition to the use of high-potency cannabis [33], early cannabis use, i.e. use in adolescence, seems to be a particularly potent risk factor [34,35]. Substance abuse is on the other hand also a common comorbid factor in PPDs. Distinguishing SIPD from PPDs with concurrent substance abuse thus poses a significant diagnostic challenge. Since the inability to exclude SIPD is a frequent reason for the diagnosis of PNOS [9] it is thus relevant to investigate early substance use, to explore if the problematic use exhibited after onset is long-standing or relatively current.

As the syndromes categorized as PNOS present with atypical or subsyndromal symptoms, some authors have suggested that these conditions may represent other types of psychopathologies that are misdiagnosed as psychosis [25]. This is of relevance, since psychotic symptoms also occur in several other conditions [36–38] including trauma-related disorders [39,40] where auditory misperceptions are prevalent [41]. The prevalence of childhood trauma is on the other hand high among people with PPDs [42,43]. A study of adolescents with PNOS [25] reported particularly high levels of childhood trauma, and raised the question of whether the more uncharacteristic syndromes in this group can be seen as trauma correlates. This has not been investigated in adult PNOS samples.

Taken together, a more comprehensive knowledge about the premorbid- and early illness phases of PNOS and PNOS subgroups will increase our understanding of the syndromes covered by the diagnosis and help disentangle the relationships to other psychotic disorders and common comorbidities. We thus pose the following research questions:

- Do participants with PNOS differ from those with SSD and PBD in terms of premorbid adjustment?
- Do participants with PNOS more often start to use cannabis at an early age (< 16 years) compared to those with SSD and PBD? Does this in particular apply to participants with PNOS-SIPD?
- Are experiences of childhood trauma more common in participants with PNOS than in participants with SSD and PBD?

2. Methods

2.1. Subjects

The present study is part of the ongoing Thematically Organized Psychosis Research study (TOP) at the Norwegian Center for Mental Disorders (NORMENT) in Oslo. We included participants aged 18–65 years with DSM-IV SSD diagnoses (narrow schizophrenia spectrum; schizophrenia, schizoaffective disorder and schizophreniform disorder), PBD (psychotic bipolar I and NOS) and PNOS. The participants were recruited consecutively from 2002 until 2018 from psychiatric inpatient and outpatient units at the major hospitals in Oslo, covering a catchment area of approximately 485,000 inhabitants and about 88% of the total population of Oslo. The participants consisted of both people with first-episode psychosis and people who had experienced several episodes. Participants with comorbid substance use disorders were included. Participants who met the criteria for a SIPD were excluded, as this is not considered a PPD. For the same reason, we did not include participants with subthreshold psychotic symptoms (Attenuated Psychotic Syndrome). Other exclusion criteria were IQ below 70, severe brain damage or not speaking a Scandinavian language.

A total of 1099 participants were included. The diagnostic distribution was as follows (n (%)): schizophrenia 513 (46.7%), schizoaffective disorder 123 (11.2%), schizophreniform disorder 52 (4.7%), bipolar type I 255 (23.2%), bipolar disorder NOS 19 (1.7%) and PNOS 137 (12.5%).

The study was conducted in accordance with the Helsinki declaration of ethics in medical research and approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All participants gave written informed consent prior to assessment.

2.2. Clinical assessment

The clinical assessment was carried out by doctors and psychologists specifically trained for the study protocol, and diagnostic evaluations were made in consultation with specialists in psychiatry and clinical psychology at NORMENT. The diagnosis was determined using the Structured Clinical Interview for DSM-IV Axis I disorders, modules A-E (SCID-I) [44], supplemented by information from the participants' clinical records. A full illness history was obtained, as well as information about education, substance use and migration status. Most of the participants also completed Alcohol Use Disorder Identification Test (AUDIT) [45] and Drug Use Disorders Identification Test (DUDIT) [46] to measure the amount and pattern of alcohol and drug use over the past 12 months. Both tests are self-report instruments, used to identify problematic use of alcohol (AUDIT) and problems with illegal drugs and/or prescription drugs (DUDIT). As clinical cut-off for problematic use, a score of 8 for men and 6 for women was used for AUDIT [47], and a score of 6 for men and 2 for DUDIT [46].

The structured assessment was carried out in 2–3 sessions spaced out over several days.

2.3. Premorbid adjustment

We measured premorbid adjustment with the Premorbid Adjustment Scale [26], which is a clinician-rated 7-point scale (0–6) that assesses social and academic performance in different age groups. The premorbid phase is defined as the time from birth to 6 months before the onset of psychosis and is divided into 4 age periods: childhood (age 0–11), early adolescence (age 12–15), adolescence (16–18) and adulthood (age 19+). The PAS scores were further divided into premorbid academic and social function, as these are relatively independent dimensions of premorbid functioning [18]. High PAS scores indicate poor academic and social adjustment. PAS scores are only valid for periods that precede the onset of the disorder. Thus, patients with onsets before the age of 11 will not be given any PAS scores at all while patients with onsets between the ages of 12–15 will only have valid childhood PAS scores; etc. In this study, we calculated the childhood subscale scores (0–11 years) for patients with onsets after the age of 11, the last valid PAS score based on the age at onset of the first episode and the change from the childhood score to the last valid score. The childhood score was used in the statistical analyses.

2.4. Cannabis use

We used a structured questionnaire designed for the TOP-study to investigate substance use. We obtained information on age at first exposure to cannabis and level of cannabis use (daily, weekly, monthly, or rarely/never) at different ages including the age of 12–15 years. The variable "Cannabis use before the age of 16" was based on a score of monthly, weekly, or daily use of cannabis versus rarely/never use at the age of 12–15 years. "Frequent cannabis use before age of 16" was defined as weekly or daily cannabis use during this age period. This definition of frequent cannabis use has been used in previous studies, in which frequent premorbid cannabis use was associated with higher symptom levels [48], later problematic substance use and poorer functional outcome [49]. Those who had only tried cannabis once or a few times were categorized in the same group as those who had not used cannabis at all.

2.5. Childhood trauma

The investigation of childhood trauma was added to the study at a later stage. A subsample of 607 participants, recruited in the later part of the inclusion period, provided information about traumatic events in childhood using the Norwegian version of the Childhood Trauma Questionnaire-Short Form (CTQ-SF) [50]. This is a 28-item self-report questionnaire, which yields scores on five subscales of trauma: emotional abuse (EA), physical abuse (PA), sexual abuse (SA), physical neglect (PN) and emotional neglect (EN). Each subscale was measured by ranking 5 items on a 5-point Likert scale, from 1 (never true) to 5 (very often true). The five subscales are summarized to the total CTQ score, which has a minimum score of 25 and a maximum score of 125. In this study, we dichotomized the CTQ subscale scores into "no-or-low trauma" versus "moderate-severe trauma." The dichotomization was done based on cut-off scores recommended by Bernstein and Fink: EA - 13, PA - 10, SA - 8, EN - 15, PN – 10 [50]. For the analyses, we used total CTQ and the proportion of participants who had experienced at least one type of childhood trauma, i.e., who scored above the cut-off of at least one subscale.

2.6. Statistical analyses

The Social Science Statistics Package (SPSS) for Windows, version 27, was used for statistical analyses. The threshold for statistical significance was set at $p<0.05$. For participants lacking summary scores for the PAS or the CTQ due to lack of one (PAS) or one-to– two (CTQ) item scores, we imputed missing item scores based on the following algorithms: For participants lacking one CTQ item we calculated the missing item as the mean of the other items within the subscale in question (i.e. for a participant lacking an item from the EN score we calculated the missing item as the mean of the other EN item scores). For participants lacking a PAS childhood item score we first performed a multiple linear regression analysis for the best prediction fit, and then calculated the score based on the regression equation.

Group differences in demographic variables were examined with Chi-Square tests for categorical variables and Analyses of variance (ANOVAs) for continuous variables using general linear models. For continuous variables with unequal variances, Welch's ANOVAs were used. Statistically significant results were interpreted using Bonferroni (ANOVA) and Games-Howell (Welch ANOVA) post hoc tests. Standardized residuals were used as post-hoc tests for categorical variables. Residuals less than −2 or greater than 2 were interpreted as statistically significantly different at the 0.05 level from expected count for that category.

As the groups had different gender and age compositions, we adjusted for these covariates in analyses of the outcome variables. We here performed Analyses of covariance (ANCOVAs) for continuous variables using general linear models. Non-normally distributed variables (CTQ and Age at first exposure to cannabis) were log transformed prior to inclusion in the ANCOVAs. For the final models, residual plots were used to assess the assumptions of a general linear model. In the results section, we use the age- and gender-adjusted means and significance levels. For the categorical outcome variables, we used logistic regression analyses, adjusting for differences in age and gender. We report effect sizes as partial eta squared ($_p\eta^2$) for the ANOVA/ANCOVAs and odds ratios (OR) and Nagelkerke's R for the logistic regressions.

Due to the PNOS-SIPD group's particularly high prevalence of substance use [11], we conducted follow-up analyses of research questions with PNOS participants divided into two separate groups; i.e. PNOS-SIPD versus other PNOS subgroups (PNOS-other). When examining categorical variables with binary logistic regression, we compared the PNOS-SIPD group versus the three other diagnostic groups combined (PBD, PNOS-other and SSD). In addition, we performed follow-up analyses in which we examined premorbid academic and social functioning in the participants with early cannabis use versus the other participants.

We used ANCOVA for these analyzes, adjusting for age and gender.

3. Results

3.1. Demographics

Demographic and clinical data are presented in Table 1. The PNOS group was significantly younger than the two other diagnostic groups. The SSD and the PNOS group included more males and had lower levels of education compared to the PBD group. The proportions of immigrants (first and second generation) were equal among the three groups. Significantly more of the participants with PNOS had a substance use disorder, a score above cut-off on DUDIT and had more often used cannabis recently, compared to participants with SSD and PBD.

3.2. Premorbid adjustment in childhood

A total of 21 participants (1.9%) had an onset of illness before the age of eleven and thus no valid PAS scores. As shown in Table 2, the groups differed significantly in terms of premorbid academic adjustment ($F_{2, 1029} = 7.81$, $p < 0.001$, ${}_p\eta^2 = 0.015$) and premorbid social adjustment ($F_{2, 1024} = 3.10$, $p = 0.045$, ${}_p\eta^2 = 0.006$) in childhood, however with small effects. Post hoc analyses revealed that premorbid academic adjustment was significantly poorer in participants with PNOS and SSD compared to PBD. Premorbid social adjustment differed significantly only between participants with SSD and PBD, with PNOS in a middle position.

We performed follow-up analyses with the PNOS group divided into the subgroups of PNOS-SIPD and PNOS-others. We still found significant group differences in premorbid academic- ($F_{3, 1025} = 6.05$ $p < 0.001$, ${}_p\eta^2 = 0.017$) and social adjustment ($F_{3, 1023} = 3.85$, $p = 0.009$, ${}_p\eta^2 = 0.011$). However, the post hoc analyses showed a statistically significant difference in premorbid academic adjustment only between SSD and PBD, with PNOS-SIPD scores at the level of SSD (supplementary table 1 and fig. 1).

3.3. Cannabis use

Data regarding cannabis use are presented in Table 2. There were no statistically significant differences between the three groups in terms of age at first exposure to cannabis. There was however a significant difference between the three groups concerning cannabis use at age 12–15 years, also after adjusting for differences in age and gender (Wald $\chi^2 = 6.86$, $p = 0.032$, Nagelkerke R^2:0.06). More of the participants with PNOS and SSD used cannabis before the age of 16, compared to participants with PBD (PNOS vs PBD: OR 3.02 (1.31–6.90), SSD vs PBD, OR 2.04 (1.01–4.12)). There were however no significant differences between the three groups regarding proportion of participants with frequent use of cannabis (daily or weekly) before the age of 16.

In the follow-up analyses dividing the participants with PNOS into PNOS-SIPD and PNOS-other we found lower age at first exposure of cannabis ($F_{3, 537} = 3.07$, $p = 0.028$, ${}_p\eta^2 = 0.017$), a higher proportion of cannabis use before the age of 16 years (Wald $\chi^2 = 12.81$, $p < 0.001$, Nagelkerke R^2:0.08) and more frequent cannabis use before the age of 16 years in the PNOS-SIPD group (Wald $\chi^2 = 8.03$, $p = 0.005$, Nagelkerke R^2: 0.055) compared to other groups. It was four times more likely that the PNOS-SIPD had used cannabis before the age of 16 (OR 4.08 (1.89–8.79)) and more than three times more likelihood of frequent cannabis use (OR 3.62 (1.49–8.82)) compared to the other diagnostic groups (PBD, PNOS-other and SSD combined) (supplementary table 1).

The follow-up analyses examining premorbid functioning in those with early cannabis use versus all other participants showed poorer academic functioning in childhood in the early cannabis users ($F_{1, 713} = 6.64$, $p = 0.01$, ${}_p\eta^2 = 0.009$). There were no differences regarding premorbid social adjustment (supplementary table 2).

3.4. Childhood trauma

As shown in Table 2, there were no statistically significant differences in mean CTQ scores or in proportion of participants who had experienced at least one type of childhood adversity between the diagnostic groups. A total of 44.9% of participants in the PBD group, 48.5% in the PNOS group and 50.4% in the SSD group reported at least one type of childhood trauma.

4. Discussion

In this study, we examined premorbid characteristics of a large sample of participants with psychotic disorders, i.e. PNOS, SSD and PBD. Our main findings were that participants with PNOS were more similar to participants with SSD than participants with PBD regarding premorbid adjustment and early cannabis use, while childhood adversities were equally prevalent in all patient groups. Follow-up analyses indicated that participants in the PNOS-SIPD group had a statistically higher proportion of early and frequent cannabis use than both SSD, PBD and other PNOS participants.

Our findings regarding childhood premorbid adjustment in participants with PNOS are in line with the findings of Korver-Nieberg et al.

Table 1
Demographics.

	1. PBD	2. PNOS	3. SSD	ANOVA/ Chi-square analysis*			
	($n = 274$)	($n = 137$)	($n = 688$)	F/ χ^{2*}	Df	p	post hoc
Gender, female, n (%)*	155 (56.6)	54 (39.4)	279 (40.6)	21.9*	2	**<0.001**	PNOS, SSD < PBD
Age, years: mean (SD)	34.1 (12.3)	27.6 (8.4)	29.9 (9.6)	20.80	2, 343	**<0.001**	PNOS<SSD < PBD
Education, years: mean (SD)	14.5 (2.9)	13.2 (2.8)	12.8 (2.8)	34.23	2, 1209	**<0.001**	PNOS, SSD < PBD
Migration:	$n = 208$	$n = 101$	$n = 579$				
1. generation, n (%)*	39 (18.8)	20 (19.8)	137 (23.7)	2.49*	2	0.288	n.s.
2. generation, n (%)*	22 (10.7)	11 (11.0)	64 (12.5)	0.55*	2	0.761	n.s.
Substance use:							
Current substance use disorder, n (%)*	28 (10.2)	35 (25.5)	114 (16.6)	16.18*	2	**<0.001**	PBD < SSD < PNOS
Previous substance use disorder, n (%)*	27 (9.9)	11 (8.0)	67 (9.8)	0.43*	2	0.807	n.s.
AUDIT score above cut-off, n (%)*	85 (43.1)	58 (51.3)	173 (34.5)	12.85*	2	**0.002**	SSD < PNOS
DUDIT score above cut-off, n (%)*	38 (18.4)	50 (43.9)	140 (28.1)	23.85*	2	**<0.001**	PBD < SSD < PNOS
Lifetime cannabis use, n (%)*	65 (32.8)	61 (51.7)	238 (45.9)	13.56*	2	**0.001**	PBD < PNOS,SSD
Duration lifetime cannabis use, years: mean (SD)	8.93 (7.73)	8.85 (5.68)	8.42 (6.52)	0.19	2, 304	0.830	n.s.
Current cannabis use (past 2 weeks), n (%)*	24 (8.8)	21 (15.6)	48 (7.2)	9.97*	2	**0.007**	PBD,SSD < PNOS

PBD, psychotic bipolar disorder; PNOS, psychotic disorder not otherwise specified; SSD, schizophrenia spectrum disorder; n.s., non-significant. *Denotes test statistics from chi-square analysis.

Table 2
Premorbid characteristics.

	1. PBD	2. PNOS	3. SSD	ANCOVA / logistic regression analysis*				
	n = 274	n = 137	n = 688	F/ Wald χ^{2*}	Df	p	$_p\eta^2$/ OR*	post hoc
Premorbid Adjustment Scale:	n = 274	*n* = 133	*n* = 671					
Academic, mean (SE)	1.24 (0.09)	1.56 (0.12)	1.58 (0.08)	7.81	21,029	**<0.001**	0.015	PBD < PNOS,SSD
Social, mean (SE)	0.97 (0.10)	1.13 (0.14)	1.21 (0.06)	3.10	2, 1024	**0.045**	0.006	PBD < SSD
Childhood Trauma Scale:	*n* = 186	*n* = 69	*n* = 352					
Total CTQ score, mean (SE)	39.5 (1.03)	40.7 (1.05)	41.4 (1.03)	1.17	2557	0.310		n.s.
Experienced at least one type of childhood adversity, n (%)*	83 (44.9)	33 (48.5)	176 (50.4)	1.50*	2	0.47		n.s.
Early cannabis use:	*n* = 189	*n* = 103	*n* = 486					
Age first exposure, mean (SE)	19.6 (1.02)	18.8 (1.03)	19.5 (1.02)	1.14	2, 538	0.321		n.s.
Cannabis use before the age of 16, n (%)*	10 (5.1)	18 (17.5)	56 (11.5)	6.86*	2	**0.032**	PNOSvsPBD: 3.02 SSDvsPBD: 2.04	PBD < PNOS, SSD
Frequent cannabis use before 16, n (%)*	7 (3.7)	10 (9.7)	37 (7.6)	3.04*	2	0.219		n.s.

PBD, psychotic bipolar disorder; PNOS, psychotic disorder not otherwise specified; SSD, schizophrenia spectrum disorder; n.s., non-significant. Means and p-values after adjusting for age and gender. *Denotes test statistics from binary logistic regression analysis.

[12]. In our sample, the difference in premorbid functioning was more pronounced in the academic domain, and there were indications that the PNOS-SIPD group contributed most to this finding, even if the effect sizes were small. This may indicate that the participants in the PNOS-SIPD group are afflicted by more long-standing psychopathological difficulties resembling SSD participants and are not acute psychotic symptoms triggered by current substance intoxication or withdrawal. As shown previously, approximately 2/3 of the participants in the PNOS-SIPD group consisted of participants meeting the A-criteria for SSD [11] i.e. are exhibiting severe psychopathology.

To our knowledge, this is the first study examining premorbid cannabis use in people with PNOS. The high proportion of early and frequent cannabis use seen in participants with PNOS-SIPD points to very long-standing substance use histories in some of these participants and could be taken to imply a substance-induced basis for the clinical disorder. It could also be presumed that their psychotic symptoms will cease once the substance use is reduced. In that case, one might expect that these are psychotic disorders with a better prognosis, and that the focus of treatment should be on their substance abuse. However, in a previous study of a subsample of the current including all diagnostic groups, we found that patients with early and frequent onset of cannabis use had higher polygenic risk scores for schizophrenia across diagnoses [51]. Additionally, it has been reported that approximately 25% of patients diagnosed with SIPD later transitions to SZ [52], and that patients with SIPD who convert to a primary psychotic disorder have poorer premorbid functioning than those who do not [53]. It is thus possible that both poor premorbid functioning and early cannabis use is predictive of a later SSD diagnosis in patients with PNOS. To investigate this, however, more longitudinal studies are needed. It is also important to keep in mind that disorders classified as SIPD do not necessarily have a better outcome than PPDs [54,55]. Together with the current findings of poor premorbid adjustment in the PNOS-SIPD group, this has implications for their clinical management. These patients should thus be offered comprehensive and long-term treatment in line with patients with SSD, even if ongoing substance use prevent completion of all SSD diagnostic criteria.

The relationship between premorbid functioning, cannabis use and psychotic disorders is however complex [56]. Several studies have found an association between cannabis use and impaired premorbid academic adjustment in psychotic disorders [57–60]. Regarding social functioning, some studies find similar premorbid social adjustment in cannabis users and non-users with PPD [59,60], while others find better premorbid social adjustment in cannabis users [57,58]. A proposed mechanism behind the latter finding is that better social functioning contributes to early exposure to substances [61]. Similarly, there are indications that people with psychotic disorders and occasional cannabis use have higher IQ than never-users [58], and that people with SZ and concomitant cocaine dependence have better executive functioning than those without such comorbidity [62]. However, others have found an association between poor social adjustment and a more rapid escalation to daily use of and a higher cumulative dose of cannabis [63]. Our findings do not indicate that the PNOS-SIPD group with their particularly high prevalence of early cannabis use represents a subgroup with better premorbid adjustment.

Symptomatic overlap combined with heterogeneity within PPD makes the investigation of differences between diagnostic groups difficult. This may be particularly challenging in the examination of PNOS, where the diagnosis itself is a consequence of not fitting more specific diagnostic criteria and where diagnostic instability is expected [11]. The similarities between PNOS and SSD in terms of premorbid factors can be interpreted as representing a closer relationship to SSD than PBD. While this may simply reflect that a significant proportion of those assigned a PNOS diagnosis are early manifestations of conditions later classified as SSD, it has clear implications for clinical practice in the treatment of first episode patients with PNOS.

We did not find support for the notion that trauma exposure is more often associated with atypical psychotic illness presentations and a diagnosis of PNOS, rather than with SSD and PBD. However, it is worth noting that, in line with other studies [42,64], nearly 50% of the participants in *all* diagnostic groups had been exposed to at least one type of trauma over the cut-off for moderate-severe levels. This emphasizes that disorders across the psychosis spectrum are complex conditions where the differential diagnostic assessment between psychotic disorders and trauma disorders can be challenging in clinical practice. The importance of childhood trauma for the development of psychotic disorders should be recognized by acknowledging that these conditions are often "trauma-related" disorders in- and of themselves [42].

There may be several reasons why we did not replicate the findings of McClellan et al. when they examined the same issue in adolescents with early onset psychosis [25]. The PNOS diagnosis may capture different conditions in adolescence and adulthood. In accordance with this, Correll et al. found that approximately 40% of adolescents with PNOS were diagnosed as such due to mono-symptomatic hallucinations and with only a few (approx. 8%) meeting the A-criteria for SSD [65]. As

reported earlier, in the current sample of adults we found that only 13% of PNOS patients were assigned the diagnosis due to mono-symptomatic hallucinations while the proportion of participants who met the A-criteria for SZ was 30% [11]. Several additional factors make the diagnosis of psychotic disorders more challenging in adolescents [66,67]. The prevalence of psychotic symptoms such as hearing voices is especially high in children and adolescents, even in non-clinical populations [68]. The symptoms appear to be even less specific to psychotic disorder than in adults and are mainly predictors of mental illness in general rather than parts of a psychotic disorder [69]. These studies also suggest that psychotic symptoms in children and adolescents are increasingly predictive of psychotic psychopathology with increasing age and persistence [5,69]. It can thus be hypothesized that a PNOS diagnosis in adolescence is not always indicative of a PPD. In line with this, several (but not all) studies of adolescents with PNOS find that few of these conditions progress to SSD compared to studies of adults [70–73].

4.1. Strengths and limitations

The main strengths of the paper are the large sample and the broad assessment battery covering both clinical and premorbid characteristics in a rarely investigated group.

Even if the general sample is very large and one of the largest PNOS studies to date, the size of the PNOS group could potentially still be too small to have adequate statistical power. The sample size was however large enough to identify group differences with small effect sizes. In addition, PNOS is a very heterogeneous group, where a proportion of the conditions are probably early stages of narrow SSD and PBD. This is a limitation when it comes to interpreting the results. Only a subsample of participants provided information on childhood trauma using the CTQ. However, the limited nominal differences in trauma prevalence between the diagnostic group does not imply that the lack of statistically significant differences is due to limited statistical power. The CTQ do not cover all types of traumas such as bullying or parental loss. The assessment of all premorbid characteristics was retrospective with risks of recall bias.

5. Conclusion

Our findings indicate that participants with PNOS do not differ significantly from participants with SSD in terms of premorbid adjustment, early cannabis use and childhood trauma. The findings emphasize that conditions classified as PNOS are not mild transient disorders, but conditions with long-term dysfunction, often complicated by substance abuse. The poor premorbid function in the PNOS-SIPD group may indicate that this is a group of PNOS patients with a particularly high risk of a serious outcome and a later SSD diagnosis. Future research should investigate whether premorbid factors such as childhood adjustment and early cannabis use can be used to predict the course of illness in patients with a PNOS diagnosis.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2022.152310.

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