Schizophrenia Research 252 (2023) 317–325

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The trajectory of two negative symptom dimensions in first-episode psychosis and the role of cannabis use: A 10-year follow-up study

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ARTICLE INFO

Keywords:
Negative symptoms
Cannabis
Psychosis
Schizophrenia
Diminished expression
Apathy

ABSTRACT

Objective: To investigate the trajectories of diminished expression and apathy over 10 years. Further, to explore the effects of baseline- and persistent cannabis use on the development of diminished expression and apathy during follow-up, while controlling other potential sources and predictors of secondary negative symptoms.
Methods: 351 participants with a first episode of non-affective psychosis were examined at baseline and invited to follow-up at one year and 10 years. The trajectories of diminished expression and apathy were investigated using linear mixed models. Subsequently, cannabis use and other potential predictors and sources of secondary negative symptoms were added to the model to investigate the respective impact on their trajectories.
Results: The severity of both diminished expression and apathy decreased during the follow-up period after the first episode of psychosis, with the most improvement observed from baseline to 1-year follow-up. Cannabis use at baseline was associated with a long-lasting higher symptom load for diminished expression, but not apathy. Introducing persistent cannabis use to the model further strengthened the association with diminished expression.
Conclusion: Both cannabis use at baseline and persistent cannabis use after a first episode of psychosis were associated with more severe symptoms of diminished expression. Our results imply a causal relationship between cannabis use and diminished expression and suggest that measures to reduce cannabis use both before and after psychosis onset may reduce expressive negative symptoms.

1. Introduction

1.1. The link between cannabis use and negative symptoms

Cannabis use and negative symptoms are common in patients with psychosis (Galderisi et al., 2021b; Koskinen et al., 2010). Cannabis use is associated with earlier onset of psychosis and higher levels of positive symptoms, re-hospitalizations, and disability (Helle et al., 2016; Large et al., 2011; Ringen et al., 2016; Schoeler et al., 2016). Negative symptoms are associated with lower quality of life, functioning and remission rates (Galderisi et al., 2018; Marder and Galderisi, 2017). A recent meta-analysis suggests that stopping cannabis use leads to a reduction in negative symptoms (Sabe et al., 2020). The link between cannabis use and negative symptoms is, however, not yet clear, and treatment options for negative symptoms remain few (Galderisi et al., 2021a; Marder et al., 2011). The prevalence of annual cannabis users

Abbreviations: BIC, Bayesian Information Criterion; BNSS, The Brief Negative Symptoms Scale; CAINS, The Clinical Assessment Interview for Negative Symptoms; CBD, cannabidiol; CDSS, Calgary Depression Scale for Schizophrenia; DUP, duration of untreated psychosis; FEP, first episode psychosis; PANSS, The Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale; THC, tetra-hydro-cannabinol; TOP, Thematically Organized Psychosis study; UKU, The Udvalg for Klinisk Undersøgelse side-effect scale.

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https://doi.org/10.1016/j.schres.2023.01.024
Received 31 August 2022; Received in revised form 21 November 2022; Accepted 16 January 2023
Available online 25 January 2023

and the risk of developing cannabis dependence has increased globally in the last decade (World Drug Report, 2021). Increased cannabis use may lead to higher rates of cannabis-induced psychoses (Hjorthøj et al., 2021a) and later conversion to schizophrenia (Hjorthøj et al., 2021b), in addition to detrimental outcomes in patients with psychosis (Baandrup, 2022). Thus, more precise knowledge about the associations between cannabis use and negative symptoms is needed to evaluate the potential hazards of use in this group.

Negative symptoms comprise five subdomains: blunted affect and alogia (diminished expression), and avolition, asociality and anhedonia (experiential symptoms or apathy) (Kirkpatrick et al., 2006). Diminished expression and apathy are considered two distinguishable yet interrelated dimensions, with partly diverging underlying pathophysiologies (Bègue et al., 2020). They may develop as a consequence of the underlying psychotic disorder (primary negative symptoms), or as a result from other external factors (secondary negative symptoms), including depression or side-effects of antipsychotics. While primary negative symptoms remain a therapeutic challenge, secondary negative symptoms are more common (Lyne et al., 2015), and amendable by treating the underlying cause (Galderisi et al., 2021a).

Recent factor analytic studies suggest that the two dimensions of negative symptoms can be measured by the Positive and Negative Syndrome Scale (PANSS) (Demyttenaere et al., 2021; Jang et al., 2016; Khan et al., 2017; Liemburg et al., 2013; Lim et al., 2016; Stiekema et al., 2016). The original version of the PANSS, however, employs a unidimensional construct of negative symptoms. A recent meta-analysis found no differences between cannabis users and non-users using a unidimensional measure of negative symptoms (Sabe et al., 2020). However, using a two-dimensional measure and incorporating potential sources of secondary symptoms, we have recently shown that cannabis use was associated with diminished expression in first-episode psychosis (FEP) patients (Ihler et al., 2021).

1.2. Stability and trajectory of negative symptoms

There is a particular scarcity of studies on the longitudinal course of negative symptoms (Galderisi et al., 2021b), and previous findings concerning negative symptoms' long-term stability are contradictory. While these symptoms historically were hypothesized to be increasing over time (Kraepelin, 1919), more recent findings indicate improvements (Savill et al., 2015), but with a subpopulation with enduring negative symptoms (Carpenter et al., 1988). Tracking trajectories of individual negative symptoms (Abdin et al., 2017; Austin et al., 2015; Chang et al., 2018; Stiekema et al., 2018), and discerning between trajectories of primary and secondary negative symptoms (Mosolov and Yaltonskaya, 2022), could help disentangle these contradictory findings. Ten-year longitudinal studies of the trajectories of negative symptoms based on a unidimensional construct support the notion of an association between substance use in general and lack of improvement in negative symptoms (Austin et al., 2015; Weibell et al., 2017), as did a five-year follow-up focusing specifically on cannabis use (González-Pinto et al., 2009).

Studies based on a two-dimensional approach also identify group-level improvements and subgroups with different trajectories, including deteriorating or “non-responding” groups (Evensen et al., 2012; Stiekema et al., 2018). We have previously reported on the development of self-reported apathy over ten years (Lyngstad et al., 2020), and also found a general improvement over time. Longer duration of untreated psychosis (DUP), higher baseline apathy levels and more severe depressive symptoms predicted less improvement in apathy over time.

To our knowledge, there are, however, no studies on the association between cannabis use and the development of the two subdimensions of negative symptoms in the long term. Given our findings from the one-year follow-up study, using a unidimensional construct could mask significant associations. More knowledge could clarify any temporality between use patterns and symptoms' severity, shedding light on possible causal mechanisms and supporting the notion that treating cannabis use disorder is an indirect treatment approach for negative symptoms.

Accordingly, this study aims to:

- Characterize the trajectories of diminished expression and apathy over ten years in FEP.
- Investigate associations between cannabis use and trajectories of diminished expression and apathy, controlling for potential sources of secondary negative symptoms.
- Explore impacts of cannabis exposure at baseline and during the follow-up period separately to clarify the directionality of associations.

2. Material and methods

2.1. Study design

The current study is part of the ongoing Thematically Organized Psychosis (TOP) Study. Study protocol and inclusion criteria have been described in detail elsewhere (Ihler et al., 2021). In brief, participants aged 18–65 were recruited at first treatment contact and defined as FEP if the first adequate treatment for psychosis (further defined as hospitalization or using antipsychotic medication in prescribed doses for ≥12 weeks or symptom remission) did not exceed 12 months before inclusion into the study.

2.2. Sample

A total of 351 participants with a non-affective FEP (49.9 % Schizophrenia (n = 175), 8.5 % schizophreniform (n = 30), 9.1 % schizoaffective (n = 32) and 32.5 % psychosis not otherwise specified (n = 114)) were assessed at baseline. Of these, 155 participants met for the 1-year follow-up and 139 participants for the 10-year follow-up (see Fig. 2.2).

2.3. Clinical assessment

Demographic and clinical data were collected at baseline, one-year follow-up and 10-year follow-up. Diagnostic interviews were performed by trained clinical research personnel using the Structural Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995). Diagnostic reliability was assured by calibration based on training videos, as well as regular diagnostic consensus meetings with a senior clinical researcher (Ringen et al., 2008). An extensive interview regarding lifetime and current substance use was conducted at baseline and follow-up.

Positive and negative symptoms were assessed with the PANSS (Kay et al., 1987). Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993). Self-reported side-effects of antipsychotics were assessed with The Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale (Lingjærde et al., 1987). Premorbid social and academic functioning scores were based on the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982).

2.4. Definitions of key variables

2.4.1. Clinical data

Duration of untreated psychosis (DUP) was defined as the time from the first psychotic episode (the first weeks with a PANSS score ≥ 4 on one or more of the subitems P1, P3, P5, P6, or G9) until adequate treatment (Larsen et al., 2001).

Premorbid social and academic functioning was expressed by the sum score of PAS childhood and early adolescence for both domains. Participants with an age of onset <15 did not receive a PAS score (n =

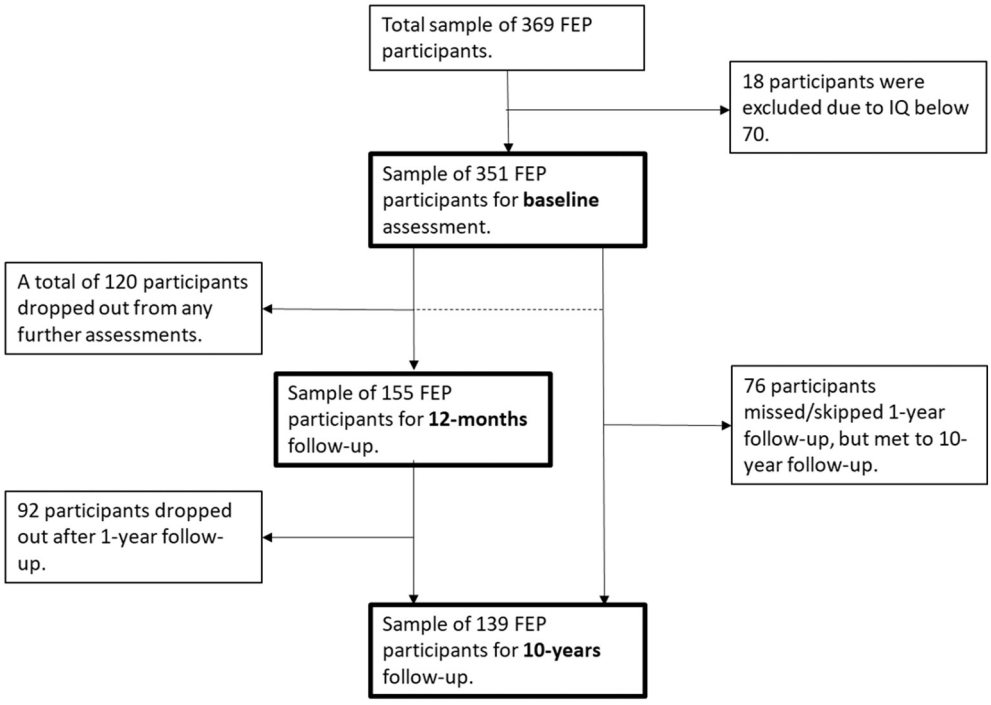

Fig. 2.2. Sample flow chart.
FEP: First Episode of Psychosis.

25).

Baseline diagnosis was dichotomized into schizophrenia vs. other diagnostic groups for the linear mixed models analyses.

Cannabis use was categorized into non-use, sporadic use, monthly use, weekly use and daily use based on reports of use in the last two weeks, six months, and two years before baseline- and ten-years-assessment, and the last two weeks and six months prior to one-year assessment. Current use of other illegal drugs (amphetamine, cocaine, opioids and hallucinogens) was operationalized as use (≥1× per month last six months) vs. non-use, nicotine use as average cigarettes per day and alcohol use as average units per week.

Use of antipsychotics was operationalized into regular use (per os or by injection) vs. sporadic use or non-use.

2.4.2. Symptom scores

Positive symptom scores were based on Wallwork's factor analysis (Wallwork et al., 2012). Negative symptoms were operationalized into two factors (apathy = N2, N4 and G16 and diminished expression = N1, N3, N6, and G7) based on prior validated factor analyses (Khan et al., 2017; Liemburg et al., 2013; Stiekema et al., 2016) and recent guidelines (Galderisi et al., 2021b).

Depressive symptoms were represented by the total raw score of the CDSS.

Relevant side-effects of antipsychotics were rated as present based on a UKU side-effect scale score of ≥2 on: 1.10 emotional indifference, 2.1 dystonia, 2.1 rigidity, and 2.3 hypokinesia/akinesia.

2.5. Statistical analyses

IBM SPSS package 27 was used for data analyses.

Independent samples *t*-test (parametric data), Mann-Whitney *U* test (non-parametric data), and chi-square test (categorical data) were applied to compare differences in clinical and sociodemographic variables between completers and non-completers of the study.

Correlation analyses (Spearman's rho) were applied to investigate correlations between the two negative symptom dimensions and sociodemographic and clinical data at baseline and follow-up. A scatter plot was used to inspect the association between the longitudinal development of diminished expression and apathy with the frequency of cannabis use.

Linear mixed model analyses were applied to model the trajectories of symptom development for the scores of diminished expression and apathy as the dependent continuous variable at three time points. The longitudinal development was described using a growth model, and the maximum likelihood was used to select the best fit. Time and quadratic time (time*time) were introduced as fixed factors to investigate linear and curvilinear functions. Intercept and slope were entered as random factors, with an autoregressive heterogeneous covariance structure. Only significant factors that improved model fit were kept for further analyses, using −2 Log Likelihood and Bayesian Information Criterion (BIC) to assess and compare the model fit.

Relevant early predictors and covariates of diminished expression and apathy development in FEP were chosen based on theoretical assumptions and previous research (Bègue et al., 2020; Ihler et al., 2021; Kirschner et al., 2017; Sabe et al., 2020), and investigated in the correlation matrix described above. Variables with significant ($p \leq 0.05$) bivariate associations to diminished expression and apathy were then introduced into the linear mixed model analyses stepwise, keeping only variables that significantly contributed to the model. Skewed variables (DUP, units of alcohol per week, daily cigarette intake) were log-transformed before being entered in the mixed model analyses. The academic PAS score was excluded due to intercorrelation with PAS social. Interaction effects with time, i.e. indications that the predictor's effect on the development of the dependent variable increased or decreased over time, were explored for all predictors and then removed from the final model if non-significant.

The last predictor to be included in the models was cannabis use. To increase interpretability, we made three dichotomized dummy variables representing increasing frequency of cannabis use (i.e., 1: ≥monthly use vs. ≤sporadic use, 2: ≥weekly use vs. ≤monthly use, 3: daily use vs. ≤weekly use), and started by adding the lowest frequency of use. If the expression was significant, we kept that variable, and if not, we added the next. For the first model (investigating baseline exposure), we only included baseline levels of cannabis use as a predictor. For the second

model (investigating the impact of persistent exposure), we included cannabis use as a time-varying predictor (i.e. values from baseline, one-year follow-up and 10-year follow-up).

The following formula describes the basic models:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta 1_{ij} + b1_{ij})*\text{time} + \beta 2_{ij}*\text{time}*\text{time} + \beta 3_{ij}*\text{predictor} + \beta 4_{ij}*\text{predictor}*\text{time} + \varepsilon ij.$$

Y_{ij} is the dependent continuous variable (diminished expression or apathy) in an individual i (=1…, 351) at year j (=1, … 10). $\beta_0 \ldots \beta_{4ij}$ are the estimates of the sample's means (i.e. fixed effects). The b_{0i} represents the specific random variation between individuals in baseline levels of the dependent variable (random intercept), and b_{1ij} represents the specific random variation between individuals in the slope of the dependent variable (random slope).

Based on observations of the raw data and the fit of the above-mentioned growth model, we further investigated the fit of a piecewise latent trajectory model (Flora, 2008), with a two-slope, piecewise discontinuous model of change. Time slope 1 represented growth between baseline and one year, and time slope 2 represented growth between one and 10 years.

Table 3.1
Demographic and descriptive data.

	Baseline	1 year	10 years
Number of participants (n/%)	351	155/44.2	139/39.6
Gender female (n/%)	125/35.6	56/36.1	59/42.4
Age (mean/median)	27.2/25	28.4/26	35.5/32
Premorbid functioning			
- PAS social (mean)	1.38 (SD 1.4)	–	–
- PAS academic (mean)	1.92 (SD 1.9)	–	–
DUP in weeks (mean/median)	144.9/52	–	–
Diagnosis (n/%)			
- Schizophrenia	175/49.9	79/51.0	67/48.2
- Schizophreniform disorder	30/8.5	18/11.6	12/8.6
- Schizoaffective disorder	32/9.1	9/5.8	18/12.9
- Psychosis NOS	114/32.5	49/31.6	42/30.2
Medical therapy			
- Regular users of antipsychotics (n/%)	290/82.6	110/73.8	84/62.2
Symptoms			
- Positive symptoms (mean)	10.6 (SD 4)	8.5 (SD 4.3)	8.0 (SD 4.2)
- Diminished expression (mean)	8.4 (SD 4.1)	7.3 (SD 5.7)	6.7 (SD 3.6)
- Apathy (mean)	7.6 (SD 3.2)	6.1 (SD 2.9)	5.8 (SD 2.9)
- Depressive symptoms (mean)	6.4 (SD 4.8)	4.0 (SD 3.7)	3.1 (SD 3.9)
- Reporting negative symptoms as side effects (UKU) (n/%)	66/23.1	15/11.5	
Substance use			
- Nicotine use daily (n/%)	190/54.4	83/55	65/46.8
- Alcohol units last 2 weeks (mean)	7.9 (SD 19.5)	9.2 (SD 17.9)	8.2 (SD 18.2)
- Any cannabis use last 2 years at baseline, and last 6 months at follow-up (n/%)	145/41.3	41/26.8	23/18.1
- Cannabis instances of use per month (mean)	12.4 (SD 38)	10.6 (SD 13.8)	6.9 (SD 12.1)
- Other drugs used last 6 months (n/%)	93/26.5	25/17.1	5/5.2

PAS: Premorbid Adjustment Scale, SD: Standard Deviation, DUP: Duration of Untreated Psychosis, NOS: Not Otherwise Specified, UKU: The Udvalg for Klinisk Undersøgelse side-effect scale.

3. Results

3.1. Demographic and descriptive data including cannabis use trajectories

Descriptive data are presented in Table 3.1. Fig. 3.1 displays the pattern of cannabis use and other drugs over the follow-up period. The monthly instances of cannabis use by diagnosis, the comparison between participants that dropped out of follow-up and those who retained, and the correlation matrix between the two negative symptom dimensions and variables of interest are presented in Supplementary Fig. 1, Supplementary Tables 1 and 2. There were more males and participants with schizoaffective disorder among study non-completers, but with no significant differences in symptom severity and substance use.

3.2. The trajectories of diminished expression and apathy

The native growth models (Fig. 3.2a and b), indicated that diminished expression and apathy decreased over the long-term follow-up period, as evidenced by a significant negative fixed effect of time (diminished expression: estimate = −0.159, $p < 0.001$, apathy: estimate = −1.523, $p < 0.001$). A positive quadratic effect of time was significant in the apathy model (estimate = 0.135, $p < 0.001$), indicating that the decrease in apathy decelerated over time. The quadratic effect was non-significant for diminished expression, indicating a stable level of change during the follow-up period. Levels of diminished expression and apathy varied significantly between individuals at baseline, as indicated by a significant random intercept ($p < 0.001$). The random slope and the covariance between the random intercept and slope were not significant. They also did not improve model fit, which suggested that the development of both dimensions did not significantly differ between individuals over time, representing an enduring effect of the baseline levels.

3.3. The trajectories of diminished expression and apathy with predictors and baseline cannabis use

For both diminished expression and apathy, the two-slope piecewise discontinuous growth models (Tables 3.3.1 and 3.3.2) outperformed the continuous models (presented in Supplementary Tables 3 and 4) after the inclusion of chosen predictors.

The two dimensions were both predicted by PAS social score, a diagnosis of schizophrenia, and side effects of antipsychotics, with indications of an enduring effect over the follow-up period. PAS social had a significant negative interaction with time for diminished expression, suggesting that the effect decreased over time.

Depressive symptoms and gender contributed significantly to the model of apathy, but not diminished expression, with an enduring effect over the follow-up period. Positive symptoms contributed differently to apathy and diminished expression. In the model for apathy, positive symptoms contributed directly to an enduring effect over time. Still, in the model for diminished expression, positive symptoms were only significant for the interaction term with time.

When adding information about cannabis use at baseline, this had a significant effect on diminished expression, but not apathy. There was also a trend-level positive interaction with the time slope between the baseline and the first year, and significant negative interaction with the time slope between one and ten years. This indicates that the effect of

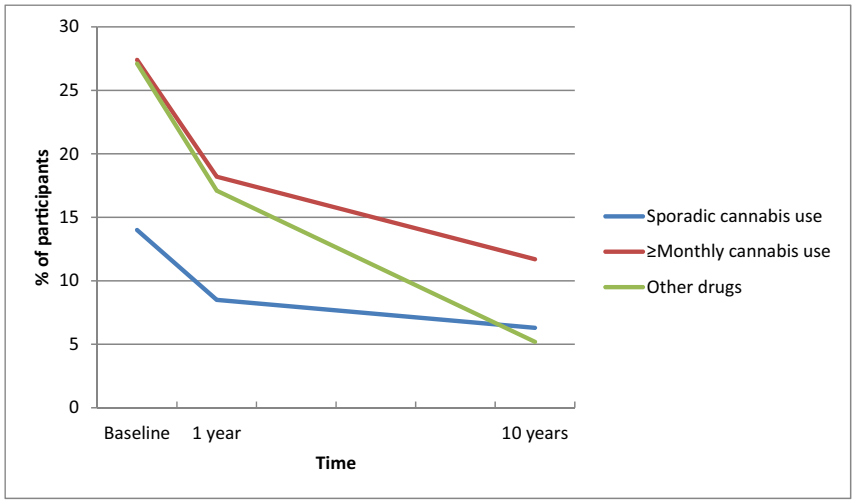

Fig. 3.1. Pattern of cannabis use and of other drugs in % of participants that report use.

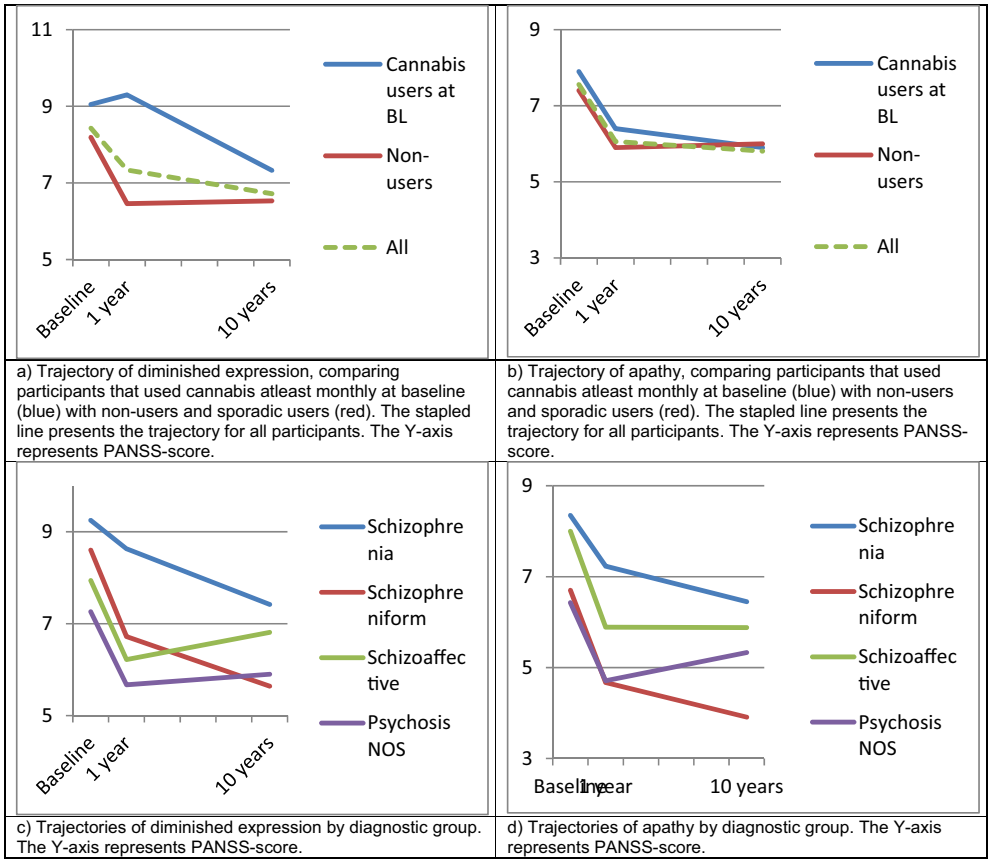

Fig. 3.2. Trajectories of diminished expression and apathy illustrating the role of cannabis use at baseline (a and b) and diagnosis (c and d). PANSS: The Positive and Negative Syndrome Scale.

baseline cannabis use on diminished expression was borderline increasing during the first year, and then decreasing between one and ten years of follow-up.

3.4. The trajectories of diminished expression and apathy with predictors and persistent cannabis use

Adding persistent weekly cannabis use contributed significantly to the model ($p = 0.026$) for diminished expression (Table 3.4.1). The two-slope piecewise growth model displayed a better fit than the continuous

Table 3.3.1
Two-slope piecewise discontinuous growth model for diminished expression with baseline cannabis use as predictor.

Parameter	Estimate	SE	t	p value	95 % Cl for t	
					Lower	Upper
Intercept	4.207	0.812	5.181	<0.001	2.609	5.804
Time slope 0–1 years	−1.137	0.557	−2.463	0.015	−2.473	−0.271
Time slope 1–10 years	−0.091	0.097	−0.942	0.347	−0.281	0.099
PAS social	0.529	0.179	2.954	0.003	0.176	0.882
PAS social * Time slope 1–10 y	−0.078	0.024	−3.207	0.002	−0.128	−0.030
Diagnosis of schizophrenia	1.287	0.448	2.871	0.004	0.404	2.169
UKU symptoms	2.305	0.521	4.422	<0.001	1.278	3.332
Regular use of antipsychotics	1.478	0.418	3.538	<0.001	0.657	2.300
Positive symptoms	−0.035	0.055	−0.632	0.528	−0.142	0.073
Positive symptoms * Time slope 1–10 y	0.026	0.009	2.888	0.004	0.084	0.044
Monthly cannabis use at BL	2.899	0.995	2.913	0.004	0.930	4.868
Monthly cannabis use at BL * Time slope 0–1 year	1.901	0.971	1.960	0.052	−0.018	3.821
Monthly cannabis use at BL * Time slope 1–10 years	−0.234	0.112	−2.088	0.038	−0.454	−0.013

ARh1: −2 Log Likelihood = 2609.79, BIC = 2720,61; BL: Baseline, UKU: The Udvalg for Klinisk Undersøgelse side-effect scale.

Table 3.3.2
Two-slope piecewise discontinuous growth model for apathy.

Parameter	Estimate	SE	t	p value	95 % Cl for t	
					Lower	Upper
Intercept	3.922	0.581	6.747	<0.001	2.778	5.066
Time slope 0–1 year	−1.380	0.364	−3.789	<0.001	−2.097	−0.663
Time slope 1–10	0.603	0.404	1.492	0.138	−0.197	1.402
Gender	−0.927	0.317	−2.925	0.004	−1.551	−0.302
PAS social	0.346	0.123	2.811	0.005	0.104	0.589
PAS social * Time slope 1–10 years	−0.394	0.200	−1.967	0.052	−0.790	0.002
Diagnosis of schizophrenia	1.080	0.308	3.506	<0.001	0.473	1.687
UKU symptoms	1.371	0.366	3.751	<0.001	0.651	2.091
Depressive symptoms	0.245	0.045	5.387	<0.001	0.156	0.335
Depressive symptoms * Time slope 0–1 year	0.147	0.054	2.724	0.007	0.041	0.254
Positive symptoms	0.160	0.034	4.727	<0.001	0.094	0.227

ARh1: −2 Log Likelihood = 2100.23, BIC = 2197,80; UKU: The Udvalg for Klinisk Undersøgelse side-effect scale.

linear growth model. The results of the latter are presented in Supplementary Table 5. Compared to the model with only baseline use as a predictor, weekly persistent cannabis use improved the overall model.

Adding persistent cannabis use to the apathy model was not significant and did not improve the model (not shown).

Table 3.4.1
Two-slope piecewise discontinuous growth model for diminished expression with persistent cannabis use as predictor.

Parameter	Estimate	SE	t	p value	95 % Cl for t	
					Lower	Upper
Intercept	5.019	0.768	6.537	<0.001	3.509	6.529
Time slope 0–1 year	−0.945	0.373	−2.514	0.012	−1.686	−0.205
Time slope 1–10 years	−0.096	0.118	−0.815	0.416	−0.330	0.137
PAS social	0.520	0.178	2.918	0.004	0.169	0.872
PAS social * Time slope 1–10 years	−0.082	0.025	−3.229	0.002	−0.132	−0.032
Diagnosis of schizophrenia	1.537	0.453	3.392	<0.001	0.644	2.429
UKU symptoms	2.451	0.526	4.658	<0.001	1.414	3.488
Regular use of antipsychotics	1.276	0.425	3.006	0.003	0.441	2.111
Positive symptoms	−0.044	0.055	−0.802	0.423	−0.153	0.064
Positive symptoms * Time slope 1–10 years	0.026	0.009	2.777	0.006	0.008	0.045
Persistent weekly cannabis use	1.281	0.573	2.233	0.026	0.153	2.409

ARh1: −2 Log Likelihood = 2528.87, BIC = 2626,83; UKU: The Udvalg for Klinisk Undersøgelse side-effect scale.

4. Discussion

In this 10-year prospective longitudinal study of negative symptoms in FEP, we found that both diminished expression and apathy decreased over time. The main new finding was that frequent cannabis use both at baseline and during follow-up had an enduring unfavorable effect on diminished expression over the follow-up period. Our findings support the notion that cannabis use could be causally linked to higher levels of diminished expression, and that reduction of cannabis use thus may reduce these symptoms.

4.1. The expected trajectory of negative symptoms

Negative symptoms respond poorly to currently available antipsychotics (Marder et al., 2011), and there are few treatment alternatives (Galderisi et al., 2021a). An important observation from the current study is that both diminished expression and apathy generally appear to improve over time after the first episode, in line with observations from other recent studies (Austin et al., 2015; Savill et al., 2015; Stiekema et al., 2018). When we modeled the trajectory of diminished expression and apathy, however, the level of diminished expression had a linear decline, while the level of apathy had a curvilinear decline. In the two-slope piecewise modeling, the decline was most prominent during the first year for both dimensions. The decelerated improvement of apathy after the first year was also observed by Lyngstad et al. (2020) using the Apathy Evaluation Scale self-report version (AES-S) in a partly overlapping sample to the current. The relatively rapid improvement during the first year, followed by stability, suggests that the early treated phase of FEP is critical for the course of the illness. It is also in line with the "critical period" hypothesis (Birchwood et al., 1998). Furthermore, the similarity between the trajectory measured by the AES-S self-report and PANSS apathy dimension supports their concurrent validity.

4.2. Cannabis use and negative symptoms

We found that cannabis use at baseline had a detrimental effect on diminished expression, but not apathy. The effect on diminished expression appeared to increase over the first year and then decrease

between years one and ten. Persistent weekly cannabis use further improved the predictive power of the model for diminished expression. This suggests that cannabis use during follow-up is an even stronger predictor of diminished expression severity than baseline use. Although the 10-year trajectory of diminished expression indicated an overall reduction of symptoms for both cannabis users and non-users, the symptom reduction was less evident in cannabis users during the critical first year of treatment. This was, however, not the case for apathy, which displayed the most rapid decline during the first year in both user groups.

The different associations between cannabis use and the two negative symptom dimensions warrant reflection. A possible explanation could be that the underlying neurobiological mechanisms of diminished expression and apathy respond differently to cannabis exposure. Cannabis may, for instance, exert more prominent effects on the motor aspects of emotion expression or primarily affect cognition and therefore accentuate expressive, rather than experiential, negative symptoms. However, when using the term "cannabis", we must acknowledge that the available substances contain several hundreds of different chemical compounds, including >120 cannabinoids (ElSohly et al., 2017). These may affect negative symptoms to varying degrees and in different directions on a compound-by-compound basis. Most previous research has focused on the effects of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), where it has been argued that CBD counteracts the effect of THC (Zuardi et al., 2006). A recent meta-analysis by Hindley et al. (2020), however, found that THC increases negative symptoms but found limited evidence for a beneficial effect of CBD. The specific relationship between different cannabinoids and the two negative symptom dimensions, however, was not explored due to the lack of available studies.

4.3. Secondary negative symptoms

In line with previous studies, we found that poor premorbid functioning, more severe positive symptoms, and reported side effects of antipsychotics were significantly predictive for more severe negative symptoms across both dimensions. Antipsychotics constitute a pillar stone in the medical treatment of psychotic disorders (Huhn et al., 2019), but may also induce secondary negative symptoms (Kirschner et al., 2017). The regular use of antipsychotics, however, only had a significant effect on diminished expression, which may represent the presence of extrapyramidal symptoms.

Male gender and depressive symptoms were on the other hand only predictive of apathy, not of diminished expression. This is in line with previous shorter-term studies (Faerden et al., 2010; Kirschner et al., 2017), and extends the finding of our previous study to the longer term (Ihler et al., 2021). The finding of several domain-specific sources or predictors further support to the notion of separate underlying neurobiological mechanisms, and emphasizes the need to investigate them separately.

4.4. Strengths and limitations

The main strengths of this study include the prospective longitudinal design with a well-characterized sample of FEP participants. The use of a validated and easily accessible measure of the two negative symptom dimensions, the collection and integration of a wide range of potential sources of secondary negative symptoms, and extensive information regarding patterns of cannabis use over time are also important strengths. The application of mixed models analyses allowed us to maximize statistical power, as this method is less sensitive to attrition.

There are also several limitations. First, the attrition rate is high and a potential cause of bias, since high levels of apathy could reduce the motivation and ability to participate in the follow-up assessments. Attrition is a common problem in recent prospective longitudinal studies, with reports of almost 90 % dropout over a one-year follow-up (Homman et al., 2021). However, based on 1) baseline comparisons of demographics, substance use and symptom severity between completers and non-completers (Supplementary Table 1), 2) the statistical approach with linear mixed models and maximum likelihood estimation, and 3) consistent results compared to previous research, it is unlikely that the obtained results are an artefact of selective retention. Second, even with three separate points for assessments, there is a substantial gap between one and ten years. Third, we used PANSS to measure negative symptoms. Although thoroughly validated and commonly used in research and clinics, more recent psychometric tools to assess negative symptoms, such as The Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) and The Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011), are considered superior. However, the inclusion on the study baseline started years before these were available and we thus would lack these data for the starting point of longer-term trajectories. Finally, cannabis use was based on self-report, rendering analyses unable to account for cannabinoid content. However, from police confiscation in Norway, we know that THC content in cannabis varies from 22 to 45 % (NDH).

4.5. Concluding remarks

In summary, we found that both diminished expression and apathy decreased over the 10-year follow-up period in FEP, with the most prominent improvements during the first year. Frequent cannabis use, both at baseline, and persistent use during the follow-up period, was linked to more severe diminished expression over the full period. Since we do not have any good treatment options for primary negative symptoms, the identification of amendable risk factors could give us new therapeutic targets, including interventions aimed at reduction or cessation of cannabis use as an integrated part of psychosis treatment.

Future studies should focus on dimension-specific measures of negative symptoms to advance our understanding of the phenomenon.

CRediT authorship contribution statement

All authors have at some point contributed in participant recruitment and assessment for data collection. HMI undertook the statistical analyses, with critical support from SHL and ESG, and wrote the first draft of the manuscript, under the supervision of TVL, IM and KLR. All authors critically revised methodology, analyses and manuscript through several steps of revision. TVL and IM have leading roles in the management and funding of the TOP study.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

Acknowledgements

First and foremost, we thank all the individuals that agreed to participate in this study. We also thank all staff members at NORMENT for their efforts in recruitment and operative work in the organization.

This study was supported by grants from the Research Council of Norway to NORMENT CoE (Grant #287714; and Grant #223273/F50, under the Centers of Excellence funding scheme), K.G. Jebsen (Grant #SKGJ-MED-008), and the South-Eastern Norway Regional Health Authority (Grant #2006233, #2006258, #2011085, #2014102, #2015088, and #2018093). We also benefited from the TSD p33 resource (#NS9666S). The funding bodies had no role in the analyses or

writing of the manuscript, or the decision to submit this work for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.01.024.

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