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Exploring the relationship between recency and frequency of cannabis use and diminished expression and apathy as two dimensions of negative symptoms in first episode psychosis. A one-year follow-up study

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ABSTRACT

The association between cannabis use and negative symptoms remains unclear because of inconsistent results in existing studies. In this study we aimed to investigate the association between different aspects of cannabis use and 1) diminished expression and 2) apathy as a two-dimensional model of negative symptoms in a sample of 460 participants with first-episode psychosis. Data were collected on relevant clinical and demographic factors including diagnostics and habits of drug use at baseline, with a follow-up assessment after 12-months. We found an association between the frequency of cannabis use two years prior to baseline and the severity of diminished expression and apathy at baseline, while only the association to diminished expression held after controlling for potential clinical and demographic confounders. Frequency of cannabis use at baseline also had a significant effect on the development of diminished expression over the 12-month follow-up period. In conclusion, this study suggests that the frequency of cannabis use contributes to the severity of diminished expression at baseline, and to the progression of diminished expression after 12-months follow-up. Our findings also imply a dose-response relationship between frequency of use and severity of symptoms and add evidence to an association between cannabis use and negative symptoms.

1. Introduction

The association between cannabis use and negative symptoms in psychosis remains unclear. One in four patients with schizophrenia have a comorbid cannabis use disorder (Koskinen et al., 2010), and cannabis use is associated with earlier onset of psychosis (Large et al., 2011), higher relapse rates, longer hospital admissions, and more severe positive symptoms (Schoeler et al., 2016). In addition, the relative content of tetra-hydro-cannabinol (THC) – the main psychoactive ingredient in cannabis – is increasing in available drugs, from 3% or less to 16% in England (Hardwick and King, 2008), 20% in Holland (Pijlman et al., 2005), 15% in Australia (Swift et al., 2013), and 30% in Norway (NDH, N. D. o. H, 2021). As the prevalence of cannabis use is high in schizophrenia, and the potency of cannabis is on the rise, it is of vital importance to further investigate this relationship, to take appropriate measures to reduce negative symptoms.

Negative symptoms impact patients' functioning and quality of life (Stiekema et al., 2018) – and we still lack effective treatments (Marder et al., 2011). Recent research has depicted negative symptoms as two partly interrelated dimensions, commonly denoted as 1) diminished expression (blunted affect and alogia) and 2) apathy (avolition, asociality and anhedonia) (Bègue et al., 2020; Kirkpatrick et al., 2006; Marder and Galderisi, 2017). The two dimensions are interrelated, but also show diverging associations to external validators such as

Abbreviations: AAO, age at onset; CDSS, Calgary depression scale for schizophrenia; DDD, defined daily dose; DUP, duration of untreated psychosis; FEP, first episode psychosis; PANSS, the positive and negative syndrome scale; PAS, premorbid adjustment scale; SCID-1, structured clinical interview for DSM-IV axis I disorders; SCZ, schizophrenia spectrum disorders; THC, tetra-hydro-connabinol; TOP, thematically organized psychosis study.

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premorbid functioning, duration of untreated psychosis (DUP) and functional outcome, and are thus hypothesized to have partly separate neurobiological underpinnings (Bègue et al., 2020; Marder and Galderisi, 2017; Strauss et al., 2013). Consequently, patients may primarily be affected by symptoms from one of the two negative symptom dimensions. Moreover, negative symptoms may also be secondary to other factors, e.g. depression, social deprivation, positive symptoms or pharmacological effects of antipsychotics or illicit drugs (Kirschner et al., 2017). These factors may in turn affect the two dimensions differently (Stiekema et al., 2016).

Previous studies investigating the association between cannabis use and negative symptoms have shown mixed results. Cannabis consists of more than hundred cannabinoids (ElSohly et al., 2017) that interact with the endocannabinoid system. Disturbances in the endocannabinoid system have been implicated in schizophrenia spectrum disorders (SCZ) (Dean et al., 2001), and exogenous cannabis may lead to a dysregulation of this system (Leweke et al., 2007). Thus, an association between cannabis use and more severe negative symptoms is biologically plausible. Reports that THC can induce symptoms resembling negative symptoms when given in laboratory settings (Hindley et al., 2020), adds further experimental evidence in support of this hypothesis. And from clinical settings, the observed amotivational syndrome in chronic cannabis users (Johns, 2001; Pacheco-Colon et al., 2018; Rovai et al., 2013) favours an association between cannabis use and more severe negative symptoms.

In contrast, several clinical studies indicate that cannabis-users have less severe negative symptoms than non-users in SCZ populations (Potvin et al., 2006; Quattrone et al., 2020; Salyers and Mueser, 2001; Talamo et al., 2006). This apparent paradox has led to many alternative explanations. The more controversial is the self-medication hypothesis, suggesting that cannabis is used to relieve psychotic symptoms, including negative symptoms (Mane et al., 2015). This is contradicted by the recent meta-analysis by Hindley et al. (Hindley et al., 2020), which reports induction of negative symptoms by cannabis use. A more plausible explanation is that cannabis users with SCZ constitute a subgroup that differs from non-users in that they have a higher premorbid functioning and lower baseline levels of negative symptoms (Ferraro et al., 2019). This illustrates that apparent differences in negative symptoms between users and non-users may be confounded by demographic and other clinical factors.

A large body of previous clinical studies also report that they find no associations between cannabis use and negative symptoms (Large et al., 2014; Sabe et al., 2020). The most recent meta-analysis by Sabe et al. (Sabe et al., 2020) found no significant difference in negative symptom severity between cannabis users and non-users. However, cannabis-users who had recently abstained from cannabis use, had significantly less severe negative symptoms compared to continued users and non-users, suggesting that stopping cannabis use may have a beneficial effect on negative symptoms. The authors also pointed out several methodological shortcomings in the existing literature. First, there are limited studies on the association between cannabis use and the different dimensions of negative symptoms. Second, there is a lack of identifying and integrating potential confounders affecting their relationship, such as premorbid functioning, and sources of secondary negative symptoms, such as depression and use of antipsychotic drugs. And third, variable reporting of the amount of cannabis use rendered the meta-analysis unable to evaluate dose-dependent effects. Detailed information on the frequency and recency of cannabis use may both elucidate putative dose-response relationships and distinguish acute toxic effects from long-term effects.

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is widely used to assess negative symptoms. The PANSS measures the negative symptoms through seven subitems, with a common unidimensional sum score. This approach fails to reflect our current dimensional understanding of negative symptoms. Factor analytic studies from large samples of participants have resulted in a suggested two-factor model of negative symptoms in PANSS (Liemburg et al., 2013). This two-factor model of PANSS is not identical to the original theoretical two-dimensional model (Kirkpatrick et al., 2006), however, a recent validation study has confirmed its ability to distinguish the two dimensions on a clinical, behavioural and neural level (Kaliuzhna et al., 2020).

Patients with a First Episode Psychosis (FEP) have a shorter duration of illness and a shorter treatment history. Subsequently, the relationship between negative symptoms and cannabis use in FEP will therefore be less affected by confounders. Hence, in this study, we aim to explore the relationship between cannabis use and negative symptoms in FEP using Liemburg et al.'s two-factor model of negative symptoms to address the following research questions:

- Are there differences in the severity of diminished expression and apathy in FEP cannabis users compared to non-users? Is there a dose-response relationship between the frequency of cannabis use and symptom severity for either dimension?
- Does cannabis use contribute to the severity of diminished expression and apathy, after controlling for relevant confounders?
- Does cannabis use at baseline independently predict the development of negative symptoms during the first year of treatment?

We hypothesized that: 1) cannabis use shows different associations with the two dimensions of negative symptoms, with a dose-response relationship between frequency of cannabis use and symptom severity, 2) cannabis use has an independent effect on negative symptom severity also after controlling for relevant confounders, and 3) cannabis use at baseline influences the progression of negative symptoms after one year of treatment.

2. Methods

2.1. Sample

The current study is part of the ongoing Thematically Organized Psychosis (TOP) Study. This is a multi-center study in the Oslo and Innlandet catchment area, and participants are recruited from inpatient and outpatient mental health care. Participants are considered FEP if they never have received adequate treatment for psychosis (defined as hospitalization due to psychosis or using antipsychotic medication at an adequate dosage for a minimum of 12 weeks or until symptom remission). Since acute psychosis may render some FEP unable to give informed consent at start of treatment, they were allowed to enter the study within the first 12 months of treatment. Inclusion criteria are: age 18–65 years; meeting DSM-IV criteria (Bell, 1994) for schizophrenia spectrum disorders (schizophrenia, schizophreniform disorder, schizoaffective disorder, and other psychosis including delusional disorder and psychosis "not otherwise specified"); speaking and understanding a Scandinavian language and being able to give a written, informed consent to participation. Exclusion criteria are IQ below 70, a history of moderate or severe head injury, or somatic illness or neurological disorder that could influence psychotic- or negative symptoms.

A sample of 460 participants with a FEP and classified as a SCZ (schizophrenia = 243, schizophreniform = 39, schizoaffective = 42, other psychosis = 136) were assessed at baseline. Out of these, 181 participants were re-assessed at 12 months follow-up. A substantial proportion of the sample was not planned for follow-up due to inclusion in other sub-projects ($n = 175$), while the remaining reasons for dropout included not wanting to participate or not being available. For study flow, see Fig. 1.

2.2. Clinical assessment

Demographic and clinical data were collected at baseline. Diagnostic interviews were done by trained clinical research personnel using the

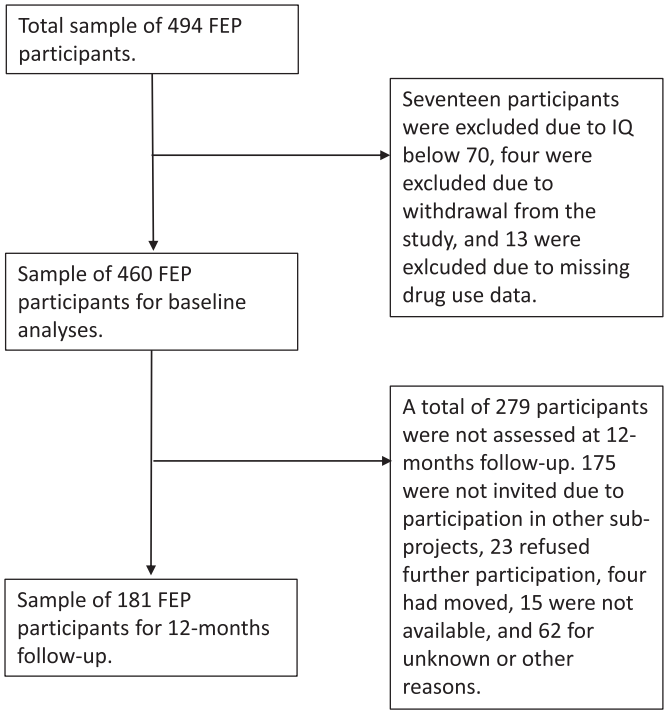

Fig. 1. Flow-chart.

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1995) including the modules for affective and psychotic disorders, and substance abuse/dependence. Diagnostic reliability was assured by calibration based on training videos, as well as regular diagnostic consensus meetings with a senior clinical researcher. Participants underwent an extensive interview regarding lifetime and current drug use, including cannabis use in different periods. Frequency of use was collected in a format counting instances of illicit drug use the last two weeks, last six months and last two years. In addition, a dichotomic variable indicating the use (yes/no) of cannabis was applied. A composite variable combining instances of use for all drugs and a positive answer on cannabis use was utilized as a proxy for frequency of cannabis use. Alcohol use was assessed by recording consumed units the last two weeks, last six months and last two years prior to baseline. Tobacco use was assessed by recording average daily cigarette intake. The level of psychotic symptoms was measured with the PANSS (Kay et al., 1987). Negative symptoms were divided into the two-factor model (Liemburg et al., 2013), and positive symptoms defined as the positive factor suggested by Wallwork et al. (2012). The Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) was used to assess level of depressive symptoms. The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) was used to assess premorbid social and academic functioning in childhood and early adolescence. Duration of untreated psychosis (DUP) was defined as the time from the first psychotic episode until first adequate treatment, and was operationalized as the number of weeks with a PANSS score ≥ 4 on subitem P1, P3, P5, P6 or G9 (Larsen et al., 2001). Information regarding current antipsychotic medication was collected and dose equivalents were calculated according to the Defined Daily Dose of the World Health Organization (WHO, 1996).

2.3. Statistical analyses

SPSS package 26 was used to carry out the statistical analyses. Skewed data were log-transformed before applying parametric tests.

2.3.1. Baseline

Independent samples *t*-tests (for normally distributed data) and Mann-Whitney *U* tests (for non-normally distributed data) were used to test for differences between cannabis users and non-users in demographical and clinical variables, including the two-factor model of negative symptoms. The chi-squared test was used for categorical data.

Spearman's rank correlation analysis was used to investigate putative correlations between frequency of cannabis use and severity of diminished expression and apathy.

Possible confounders based on theoretical assumptions and prior studies (Bègue et al., 2020; Kirschner et al., 2017; Sabe et al., 2020) were investigated in a correlation matrix to assess for their multicollinearity (rho>0.4) and revise singularity (Supplementary Table 1). Variables displaying no significant correlation ($p > .05$) to diminished expression and/or apathy were not included in the relevant multivariate analyses (this included alcohol use and DDD of antipsychotics). The PAS score from childhood and early adolescence was highly correlated (rho>0.7), and the sum score of both variables was therefore used as the measure for premorbid functioning. Before setting up the multiple regression model, skewed data variables, including diminished expression, apathy, DUP and frequency of cannabis use were log-transformed.

Hierarchical multiple regression analyses were applied to investigate the impact of frequency of use on the two domains of negative symptom severity, while controlling for possible confounding factors. The negative symptom scores of the two dimensions were plotted as dependant variables in each regression. Variables were only included in the regression model if they were significantly correlated to the dependant variable (average daily cigarette intake for diminished expression and DUP for apathy), with the exception of basic demographic variables (age and gender) and depressive symptoms, which were included in both models. The final models was thus as follows: Age and gender were entered at Step 1; premorbid functioning (PAS) and DUP (only in the apathy-model) at step 2; positive symptoms and depressive symptoms at step 3; the use of any other illicit drugs the last two years (dichotomic variable) and average daily cigarette intake (only in the diminished expression-model) at step 4; and finally, frequency of cannabis use at step 5. The diagnosis of cannabis misuse or dependency was tested in step 5 in an alternative model. Analyses of residuals were performed to assess for the assumptions of normality, linearity, homoscedasticity and independence. Variance inflation factor was assessed to ensure no multicollinearity in the final model (<1.6).

2.3.2. Longitudinal data

Participants at follow-up were first compared to the dropout group for demographic and clinical variables at baseline (Supplementary Table 2). There were no significant differences between the dropout and the followed-up sample.

Differences in mean scores of the two negative symptom-dimensions at follow-up compared to baseline were investigated with paired-sample *t*-tests for the whole group. Independent t-tests were used to investigate differences in the symptom score at 12-months between cannabis users and non-users. Between-group differences in continued users, non-users and abstained users were investigated with ANOVA.

Multiple hierarchical regression analyses were applied to investigate the contribution of frequency of cannabis use two years before baseline on the negative symptom-dimensions at follow-up. We controlled for possible confounding factors as described above, with the addition of the cross-sectional symptom score of the respective dimension at baseline, and a dummy-variable considering continued cannabis use against non-use and abstained use.

All the abovementioned analyses were also performed on a subpopulation consisting of participants with a diagnosis of schizophrenia or schizophreniform disorder only.

3. Results

3.1. Descriptive characteristics

A total of 88 participants (19.1%) got a diagnosis of cannabis misuse or dependency. In the complete sample of $N = 460$ at baseline 42.6% ($n = 196$) reported cannabis use during the last two years, 29.6% ($n = 136$) the last six months, and 8.7% ($n = 40$) the last two weeks. Cannabis users (defined as any use of cannabis the last two years) were significantly younger, more likely to be male, had an earlier age of onset of psychosis, more severe diminished expression, and had a higher consumption of other illicit drugs, cigarettes and alcohol compared to non-users (Table 1).

At 12-months follow-up, of the $N = 181$ who completed the study, 25.5% ($n = 46$) reported cannabis use the last six months and 12.7% ($n = 23$) the last two weeks. Eighty % ($n = 37$) of those who reported cannabis use at 12-months follow-up had also used cannabis at baseline.

3.2. Negative symptoms and cannabis use at baseline

Participants who reported cannabis use the last two years prior to baseline assessment had significantly higher levels of diminished expression, but not of apathy (Table 2). However, when adjusting for differences in age, sex, age at onset of psychosis, positive symptoms and the use of cigarettes, alcohol and other illicit drugs the difference was no longer statistically significant ($p = .149$).

3.3. Negative symptoms and frequency of cannabis use at baseline

Correlation analyses in exposed individuals (including only individuals that had reported cannabis use in the three different time frames) showed a significant positive correlation between the frequency of use the last two years and both dimensions of negative symptoms (Table 3). Bivariate correlation analyses for the whole sample (including non-users) showed only a significant correlation between frequency of use the last two years and diminished expression (rho = 0.142, $p = .004$).

Multiple hierarchical regression analyses showed that the frequency of cannabis use, still had an independent contribution to the severity of diminished expression. The models explained 13.4% of the variance in diminished expression, and 17.9% of the variance in apathy (Table 4).

In an alternative model we found that a diagnosis of cannabis misuse or dependency also contributed significantly to diminished expression, but not to apathy (Supplementary File 4).

3.4. Negative symptoms and frequency of cannabis use at 12-months follow-up

At follow up, mean negative symptom scores were significantly lower for both dimensions: diminished expression was reduced from 11.2 (SD 4.7) to 10.1 (SD 4.1) ($p = .001$) and apathy from 7.2 (SD 3.1) to 6.0 (SD 2.9) ($p < .001$). We found no significant differences between current cannabis users and non-users with respect to the mean score of the two negative symptom dimensions at 12-month follow up ($p = .563$ for diminished expression, $p = .822$ for apathy). When comparing between-group differences for continued users ($n = 41$), non-users ($n = 100$) and abstainers ($n = 40$), we found no significant differences between the groups (ANOVA: diminished expression: $p = .201$, and apathy: $p = .824$).

The results showed that the frequency of use over the last two years prior to baseline assessment was significantly associated with the severity of diminished expression at 12-months follow-up, but not with the level of apathy (Table 5). Continued cannabis use at follow-up did not contribute significantly to either dimension.

Supplementary File 3 provides the results of all analyses carried out on a sub-population of participants with a diagnosis of schizophrenia and schizophreniform disorder only.

Table 1
Sociodemographic information at baseline with participants divided into groups based on use of cannabis the last 2 years.

	No cannabis use last 2 years ($n = 264$)	Cannabis use last 2 years ($n = 196$)	
Age (mean/median)	28.6/26 (SD 9.3)	24.7/24 (SD 5.2)	$p < .001$
Sex (% females)	45.8 ($n = 121$)	24.0 ($n = 47$)	$p < .001$
DUP (mean/median weeks)	148.4/54 (SD 230)	110.1/35 (SD 178.7)	$p = .064$
AAO of psychotic symptoms (mean)	24.9 (SD 9.1)	21.9 (SD 5.4)	$p < .001$
PAS childhood	0.24 (SD 0.19)	0.26 (SD 0.19)	$p = .479$
PAS early adolescence	0.28 (SD 0.18)	0.28 (SD 0.17)	$p = .808$
Positive symptoms (mean)	10.3 (SD 4.1)	10.8 (SD 4.1)	$p = .184$
Diminished expression (mean)	11.1 (SD 4.9)	12.3 (SD 5.0)	$p = .005$
Apathy (mean)	7.2 (SD 3.2)	7.5 (SD 3.3)	$p = .392$
Depressive symptoms (mean)	6.15 (SD 4.7)	5.52 (SD 4.8)	$p = .163$
DDD Antipsychotic	115 (SD 169) (58 missing)	100 (SD 160) (51 missing)	$p = .426$
Use of other illicit drugs last two years (%)	6.4	50	$p < .001$
Daily cigarette use (mean/median)	4.9/0 (SD 8.8)	7.6/5 (SD 7.8)	$p = .001$
Alcohol units used last two weeks (mean/median)	4.5/0 (SD 15)	10.1/2 (SD 19.4)	$p < .001$

SD: Standard deviation, DUP: Duration of untreated psychosis, AAO: Age at onset, PAS: Premorbid adjustment scale, DDD: Defined daily dose.

Table 2
t-Tests comparing mean score on the two domains of negative symptoms between users and non-users at BL. Bold entries highlight statistically significant findings.

		Cannabis users	Non-users	T-test
Use last 2 weeks	Diminished expression	12.65 (SD = 4.34, n = 40)	11.53 (SD = 5.06, $n = 417$)	$p = .069$
	Apathy	7.75 (SD = 2.98, n = 40)	7.27 (SD = 3.28, $n = 418$)	$p = .222$
Use last 6 months	Diminished expression	12.24 (SD = 4.98, n = 136)	11.37 (SD = 4.99, $n = 321$)	$p = .060$
	Apathy	7.49 (SD = 3.39, n = 136)	7.22 (SD = 3.20, $n = 322$)	$p = .504$
Use last 2 years	**Diminished expression**	**12.31 (SD = 5.0, $n = 195$)**	**11.14 (SD = 5.0, $n = 262$)**	**$p = .005$***
	Apathy	7.48 (SD = 3.34, n = 195)	7.18 (SD = 3.19, $n = 263$)	$p = .392$

* Eta squared = 0.0134, small effect size,

Table 3
Bivariate Spearman's rank correlation for cannabis-users (non-users excluded):

Baseline		Frequency of cannabis use last 2 weeks ($n = 40$)	Frequency of cannabis use last 6 months ($n = 136$)	Frequency of cannabis use last 2 years ($n = 196$)
Diminished expression	Correlation coeff.	−0.262	0.170	**0.211**
	Significance	0.123	0.075	**0.008**
Apathy	Correlation coeff.	−0.197	0.182	**0.212**
	Significance	0.250	0.055	**0.008**

Table 4
Summary of the final model in hierarchical regression for diminished expression and apathy at baseline.

		Diminished expression			Apathy		
		B (95% CI)	SE (B)	β (95% CI)	B (95% CI)	SE (B)	β (95% CI)
1	Age	−0.004 (−0.006, −0.002)	0.001	**−0.183** ** **(−0.279, −0.088)**	−0.003 (−0.009, 0.002)	0.003	−0.057 (−0.153, 0.038)
	Sex	−0.026 (−0.063, 0.011)	0.019	−0.071 (−0.170, 0.028)	−0.137 (−0.231, −0.043)	0.048	**−0.141** * **(−0.237, −0.045)**
2	PAS childhood and early adolescence	0.103 (0.052, 0.155)	0.026	**0.196** ** **(0.099, 0.296)**	0.236 (0.103, 0.369)	0.068	**0.172** ** **(0.075, 0.270)**
	DUP	–	–	–	0.018 (−0.041, 0.077)	0.030	0.032 (−0.073, 0.137)
3	Positive symptoms	0.005 (0.001, 0.010)	0.002	**0.120** * **(0.023, 0.218)**	0.024 (0.012, 0.035)	0.006	**0.206** ** **(0.105, 308)**
	Depressive symptoms	−0.002 (−0.006, 0.002)	0.002	−0.052 (−0.154, 0.051)	0.015 (0.005, 0.025)	0.005	**0.147** * **(0.046, 0.246)**
4	Use of other drugs last two years	−0.046 (−0.094, 0.002)	0.024	−0.111 (−0.227, 0.005)	−0.079 (−0.201, 0.042)	0.062	−0.073 (−0.186, 0.039)
	Average daily cigarette intake	0.001 (−0.001, 0.003)	0.001	0.057 (−0.040, 0.155)	–	–	–
5	Frequency of cannabis use last two years	0.010 (0.001, 0.019)	0.005	**0.130** * **(0.029, 0.250)**	0.019 (−0.004, 0.042)	0.012	0.095 (0.020, 0.210)
Model 5 performance		$R^2 = 0.134$ F Change = 4.622 Sig.F Change = 0.032			$R^2 = 0.179$ F Change = 2.620 Sig.F Change = 0.106		

PAS: Premorbid adjustment scale, DUP: Duration of untreated psychosis.
* $p \leq .05$.
** $p \leq .01$.

Table 5
Summary of the final model in hierarchical regression for diminished expression and apathy at 12-months follow-up.

	Independent variables from baseline	Diminished expression at 12-month follow-up			Apathy at 12-month follow-up		
		B (95% CI)	SE (B)	β (95% CI)	B (95% CI)	SE (B)	β (95% CI)
1	Age	0.003 (−0.003, 0.009)	0.003	0.068 (−0.064, 0.199)	0.009 (0.001, 0.016)	0.004	**0.155** * **(0.025, 0.287)**
	Sex	−0.086 (−0.190, 0.021)	0.053	−0.109 (−0.242, 0.026)	−0.127 (−0.255, 0.000)	0.065	−0.133 (−0.265, 0.000)
2	PAS	0.044 (−0.105, 0.193)	0.076	0.040 (−0.096, 0.176)	0.216 (0.034, 0.399)	0.092	**0.160** * **(0.025, 0.295)**
	DUP	–	–	–	0.063 (−0.016, 0.143)	0.040	0.114 (−0.030, 0.258)
3	Positive symptoms	−0.002 (−0.014, 0.011)	0.006	−0.017 (−0.150, 0.116)	−0.009 (−0.025, 0.007)	0.008	−0.078 (−0.220, 0.063)
	Depressive symptoms	0.004 (−0.007, 0.015)	0.006	0.049 (−0.091, 0.187)	0.004 (−0.010, 0.018)	0.007	0.041 (−0.098, 0.178)
	Baseline value of the respective NS dimension	1.060 (0.777, 1.343)	0.143	**0.508** ** **(0.370, 0.640)**	0.466 (0.331, 0.600)	0.068	**0.472** ** **(0.335, 608)**
4	Use of other drugs last two years	−0.165 (−0.302, −0.028)	0.069	**−0.190** * **(−0.347, −0.032)**	−0.020 (−0.184, 0.145)	0.083	−0.018 (−0.172, 0.136)
	Average daily cigarette intake	<0.001 (−0.006, 0.005)	0.003	−0.011 (−0.143, 0.121)	–	–	–
5	Frequency of cannabis use last two years on BL	0.041 (0.013, 0.069)	0.014	**0.254** ** **(0.081, 0.426)**	0.010 (−0.024, 0.043)	0.017	0.048 (−0.120, 0.217)
	Continued cannabis use at follow-up vs. non-use and abstainers	0.032 (−0.151, 0.216)	0.093	0.025 (−0.115, 0.164)	−0.026 (−0.248, 0.195)	0.112	−0.016 (−0.153, 0.121)
Model 5 performance		$R^2 = 0.356$ F Change = 4.435 Sig.F Change = 0.013			$R^2 = 0.374$ F Change = 0.268 Sig.F Change = 0.766		

PAS: Premorbid adjustment scale, DUP: Duration of untreated psychosis, NS: Negative symptoms.
* $p \leq .05$.
** $p \leq .01$.

4. Discussion

To the best of our knowledge, this study is the first to investigate the frequency of cannabis use in relation to the two dimensions of negative symptoms. The main finding is that the frequency of cannabis use was primarily associated with increased severity of diminished expression at baseline and contributed to the development of diminished expression during follow-up. Frequency of cannabis use did not display the same effect on baseline levels and 12-months development of apathy.

The most recent meta-analysis did not find any differences between users and non-users using a unidimensional measure of negative symptoms (Sabe et al., 2020). We hypothesized that by replacing the unidimensional measure with two more refined and empirically established sub-dimensions, we could explore more specific aspects of the associations to cannabis use. After correcting for differences in age, sex, positive symptoms, and use of other drugs, we did not find any differences in diminished expression or apathy between users and non-users in the whole sample. However, analyses in a sub-population of participants with a diagnosis of schizophrenia and schizophreniform disorder only, showed that diminished expression was significantly higher in cannabis users. This could suggest that individuals with a diagnosis of schizophrenia or schizophreniform disorder are more vulnerable to the effects of cannabis use, than participants in the other diagnostic categories. It has been suggested that patients with schizophrenia are more vulnerable to the effects of cannabis (and especially THC), compared to non-clinical populations (D'Souza et al., 2005).

By further exploring the recency and frequency of cannabis use, we found an association between frequency of use during the last two years

prior to baseline assessment and negative symptom severity within both dimensions of negative symptoms. In extension of this, we investigated the role of other potential sources of secondary negative symptoms in addition to putative confounders in relation to the two dimensions of negative symptoms. Our findings suggest that younger age, poor premorbid adjustment, more positive symptoms, and higher frequency of cannabis use were associated with more severe diminished expression. Male sex, poor premorbid adjustment, positive symptoms and depressive symptoms were associated with more severe apathy. While in line with previous studies (Faerden et al., 2010; Kirschner et al., 2017), it is important to note the different patterns of association related to the two dimensions. Younger age and frequency of cannabis use were only associated with diminished expression, while male sex and depressive symptoms were only associated with apathy. A recent review on the pathophysiology of the two dimensions suggests that diminished expression is linked to deficits in emotion expression and perception (Bègue et al., 2020). A developing brain subject to chronic cannabis-exposure may to a greater extent affect these underlying mechanisms, and hence result in increased severity of diminished expression.

Apathy, on the other hand, is linked to reward expectancy and cost-benefit-computation (and accordingly different underlying neural processes). It is possible that these mechanisms have other determinants, and therefore present as associations to male sex and depressive symptoms. A previous study by Strauss et al. (2013) also found male sex to be linked to the apathy-dimension. And depression shares many features with the apathy-dimension of negative symptoms, such as anhedonia. Especially anticipatory anhedonia is affected in schizophrenia (Marder and Galderisi, 2017), but is also found as a feature in depression (Barch et al., 2016), and may therefore contribute to drive this association.

The frequency of cannabis use at baseline was also associated with the severity of diminished expression after 12 months. Our interpretation is that higher frequency of cannabis use before baseline predicts less improvement in symptom severity over the first year of treatment. In contrast to Sabe et al.'s (2020) findings of less severe negative symptoms in recent cannabis abstainers, we found no difference in symptom severity in either dimension when comparing abstainers to continued-users and non-users. And continued use did not contribute to symptom severity at 12-month follow-up. A possible explanation for this is the abstaining groups' heterogeneity with regards to amount of intake, i.e. that both heavy and more recreational users are included in the abstainer group, with consequences for the effect of abstaining. In our sample, the "abstainer"-group was too small to do further sub-categorization. We could, however, speculate that abstaining from heavy continued use (as opposed to recreational use) would have beneficial effects on the development of negative symptoms.

The use of other illicit drugs (i.e. other than cannabis) was associated with a lower severity of diminished expression after 12-months. Illicit drugs are as a group considered a potential source of secondary negative symptoms (Kirkpatrick, 2014; Kirschner et al., 2017). However, both the effect of different classes of drugs, and the severity of substance misuse will vary significantly. We consider it unlikely that the intake of drugs of abuse protect against or reduce negative symptoms. Rather, it may suggest that individuals with a heterogenous intake of illicit drugs constitute a subgroup with lower levels of primary negative symptoms.

The main strength of this study is the use of a validated two-dimensional model of negative symptoms in a large sample of FEP participants. This enabled us to counteract some of the limitations found in previous studies, and provides a more differentiated investigation of negative symptoms in line with the current theoretical understanding of its phenomenology. We also used a more differentiated measure of cannabis use, encompassing the frequency and recency of use and thus enabling study of potential dose-response effects. The sample size and the inclusion of relevant clinical and sociodemographic characteristics enabled statistical control for potential confounding group differences associated with both cannabis use and negative symptoms.

There are also important limitations. First, the chemical composition of cannabis may vary significantly, especially with regards to the THC content. We could not correct for this in the analyses. From police confiscate in Norway, THC content has been estimated to vary from 30 to 45% (NDH, 2021). In line with this, the assessment of "instances of use" as a proxy for the amount of cannabis used is no measure of the actual amount of cannabis consumption, or the effect of other illicit drugs that may have been used simultaneously. Second, it is widely accepted that side-effects of antipsychotics, such as sedation and extrapyramidal symptoms, may constitute sources of secondary negative symptoms (Kirschner et al., 2017). Clinical measures of these were not included in the analyses. Different antipsychotics display different side-effect profiles (Huhn et al., 2019), and this variation is not fully captured by the measure of DDD. It may be that the dose dependent effects are less relevant than the receptor profile of the different antipsychotics. Since this is a naturalistic study, the treating clinicians may also have adjusted the dose or changed medication to reduce side-effects. The absence of an association in our data does not contradict antipsychotics' potential to cause secondary negative symptoms. Finally, there was a substantial loss to follow-up. However, there were no significant differences between the drop-outs and those who completed follow-up.

5. Conclusion

Understanding the relationship between frequency of cannabis use and negative symptom severity is important, as our current alternatives in treating negative symptoms are limited. Our findings indicate a dose-response relationship between frequency of cannabis use and diminished expression. It adds further evidence to the notion that cannabis use can constitute a source for secondary negative symptoms, and suggests that the association is more pronounced in relation to diminished expression, as compared to apathy. This may be an expression of their different underlying pathophysiologies (Bègue et al., 2020).

Due to the dose-response relationship, reduction in frequency of use may have beneficial effects on the severity of diminished expression and the development in severity over the first year of treatment. As negative symptoms adversely influence patients' functioning and quality of life (Stiekema et al., 2018), the effects of reducing cannabis intake may also extend beyond reducing negative symptoms. A proactive stance towards reduction of cannabis use should therefore be prioritized in FEP treatment. A systematic division between facilities that offer specialized addiction treatment and FEP treatment may counteract optimal combinations of treatment-approaches, and our findings advocate for a better integration.

In line with current efforts to achieve precision psychiatry, assessing the different dimensions of negative symptoms separately may help clinicians to have a more differentiated assessment of patients' problems, and allow for more targeted interventions. The use of dimensional measures for negative symptoms should be a priority for future studies, to increase our understanding of these phenomena.

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Contributors

HMI undertook the statistical analyses and wrote the first draft of the manuscript, under the supervision of KLR. TVL, SHL and IM critically revised the analyses and manuscript. TVL and IM have leading roles in the management and funding of the TOP study.

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Declaration of competing interest

All authors declare that they have no conflicts of interest.

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