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Trajectories of adolescent psychotic-like experiences and early cannabis exposure: Results from a Finnish Birth Cohort Study

Alexander Denissoff[a,b,*], Antti Mustonen[c,d], Jouko Miettunen[e,f], Anni-Emilia Alakokkare[a,e], Juha Veijola[e], James G. Scott[g,h,i], Musa B. Sami[j,k], Solja Niemelä[a,b]

[a] University of Turku, Faculty of Medicine, Department of Psychiatry, Turku, Finland
[b] Addiction Psychiatry Unit, Department of Psychiatry, Turku University Hospital, Turku, Finland
[c] Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[d] Department of Psychiatry, Seinäjoki Central Hospital, Seinäjoki, Finland
[e] Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland
[f] Center for Life Course Health Research, University of Oulu, Oulu, Finland
[g] QIMR Berghofer Medical Research Institute, Herston, Qld, Australia
[h] Metro North Mental Health Service, Herston, Qld, Australia
[i] Queensland Centre for Mental Health Research, Wacol, Qld, Australia
[j] Institute of Mental Health, University of Nottingham, Nottingham, UK
[k] Nottinghamshire Healthcare Trust, Nottingham, UK

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ABSTRACT

Background: Longitudinal studies examining the effect of cannabis exposure (CE) on the prognosis of adolescents with psychotic-like experiences (PLEs) are scarce. We examined trajectories of mental health in adolescents with PLEs and cannabis exposure.

Methods: The Northern Finland Birth Cohort 1986 ($n = 6552$) with linkage to nationwide register data was used. Information on lifetime cannabis exposure was collected when participants were aged 15/16. Register-based outcome data on diagnoses made in clinical practice were obtained until age 33. Logistic regression was used to study the association of PLE/CE patterns and subsequent psychiatric disorders. The group with neither PLEs nor CE was utilized as the reference group. Parental psychiatric disorders, family structure, sex, frequent alcohol intoxications, daily smoking and illicit substance use other than cannabis were adjusted for.

Results: In all, 6552 subjects (49.2 % males) were included in analysis. PLEs with cannabis exposure were associated with any psychiatric disorder (OR = 2.59; 95 % CI 1.82–3.68), psychotic disorders (OR = 3.86; 95 % CI 1.83–8.11), mood disorders (OR 4.07; 95 % CI 2.74–6.04), depressive disorders (OR = 4.35; 95 % CI 2.93–6.48), anxiety disorders (OR = 2.06; 95 % CI 1.34–3.17) and substance use disorders (OR = 2.26; 95 % CI 1.13–4.50) compared to reference group. Effect sizes were greater for group with both PLEs and cannabis use than for group with PLEs only.

Conclusions: Early-onset cannabis use is an adverse prognostic marker for adolescents with PLEs after extensive confounder control including other substance use.

1. Introduction

Cannabis use is an established risk factor for psychosis (Campeny et al., 2020; Hasan et al., 2020; Mustonen et al., 2018; Sideli et al., 2020) and is highly prevalent among individuals at ultra-high risk for psychosis (Carney et al., 2017). Cannabis exposure in adolescence has also been associated with psychotic-like experiences (PLEs) (Bechtold et al., 2016; Miettunen et al., 2008; Schubart et al., 2011). Research indicates that PLEs are prevalent in the general population (Linscott and Van Os, 2013) and have prognostic significance for risk of onset of psychotic disorders even in non-help seeking populations (Connell et al., 2016; Dominguez et al., 2011; Fisher et al., 2013; Kaymaz et al., 2012; Poulton et al., 2000; Welham et al., 2009). Therefore, understanding the outcomes of cannabis-exposed adolescents with PLEs is of paramount

* Corresponding author at: Turku University Central Hospital, Addiction Psychiatry Unit, Kiinamyllynkatu 4-8, PL 52, 20521 Turku, Finland.
E-mail address: aldeni@utu.fi (A. Denissoff).

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importance, as adolescence is a time when the brain is most vulnerable and the risk of future mental disorders arising from cannabis use is greatest at this developmental phase (Bloomfield et al., 2019; Levine et al., 2017). Furthermore, it is reasonable to hypothesize that PLE-experiencing adolescents exposed to cannabis may be particularly vulnerable to cannabis-related harms even beyond transitioning to psychosis.

Research indicates that PLEs are associated with other mental health outcomes such as any non-psychotic psychiatric disorder and suicide attempts (Connell et al., 2016; Healy et al., 2019), depression (Yung et al., 2007), progression of mental disorders (Iorfino et al., 2019), functioning (Kelleher et al., 2015), and prolonged service use (Lindgren et al., 2019). Moreover, in the recent study by Kırlı et al. multiple prognostic factors of PLEs in adolescence and adulthood were studied with respect to any DSM-IV disorder as well as psychotic and non-psychotic disorders (Klrll et al., 2019). In this study, cannabis use was adjusted for in the multivariable analyses conducted but not studied as an exposure variable.

The Northern Finland Birth Cohort (NFBC) 1986 is a prospective general population-based study where rich phenotypic data are linked to national healthcare and medication registers for clinician rated ICD-10 diagnoses (University of Oulu: Northern Finland Birth Cohort, 1986). This study includes data on frequent alcohol intoxications, daily smoking, use of illicit substances, familial factors and baseline and parental psychiatric diagnoses made in clinical practice. Thus, it enables the examination of the psychiatric sequalae of adolescent psychotic-like experiences with cannabis exposure in a robust analytical framework.

The aim of our study is to examine broadly the mental health trajectories of individuals with psychotic-like experiences and exposure to cannabis at age 15/16 years during an 18-year follow-up period until adulthood. The association of cannabis use, baseline PLEs and subsequent psychotic disorders with 15 year follow-up has been reported in a previous study using NFBC1986 data by Mustonen et al. (Mustonen et al., 2018). In that study, as a preliminary finding, we have reported that the cumulative incidence of psychotic disorder might be significantly higher among subjects with PLEs and cannabis exposure.

Here, we extend the follow-up time from the national health care register until age of 33 years and include also non-psychotic outcomes such as mood and anxiety disorders as well as substance use disorders (SUDs) made in clinical practice. Furthermore, instead of examining the association of cannabis use with subsequent psychiatric disorders and controlling for baseline psychotic symptoms, cohort participants are stratified to four groups according to their PLE and cannabis exposure status: 1) without PLEs and cannabis exposure, 2) with PLEs and without cannabis exposure, 3) without PLEs and with cannabis exposure, and 4) with PLEs and cannabis exposure. As far as we are aware, this is the first birth-cohort study focusing on the trajectories of adolescents with PLEs and early cannabis exposure and discriminating between psychotic and non-psychotic outcomes.

2. Methods

2.1. Participants and data-collection

The Northern Finland Birth Cohort 1986 is an ongoing follow-up study including 99 % of all births in the two northernmost provinces in Finland between July 1st 1985 and June 30th 1986. The original sample included 9432 live born children. A follow-up study was conducted in 2001–2002 when study members were aged 15–16 years. Initially, self-report postal questionnaires with questions concerning health and wellbeing were sent to the adolescents ($n = 9215$), of which 7344 (80.0 %) were returned. Thereafter, all the participants were invited to a clinical study where they completed self-report questionnaires including questions on substance use (University of Oulu: Northern Finland Birth Cohort, 1986). Participants who provided informed consent, answered questions on cannabis use and psychotic-like experiences were included in the present study. Participants were included in the sample if they had answered to at least 10 of the 12 items in the PROD-screen questionnaire. The final sample totaled 6552 individuals (69.5 % of original sample) (Fig. 1). The 15–16 -year follow-up study was approved by the Ethics committee of the Northern Ostrobothnia Hospital District in Finland (15 January 2018). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013.

2.2. Exposure variables: psychotic experiences and cannabis use

Data on PLEs and lifetime adolescent cannabis use were collected during the clinical study when participants were aged 15–16 years. The participants were asked about the occurrence of psychotic-like experiences during the previous 6 months (no/yes) using the PROD-screen (Heinimaa et al., 2003). The PROD-questionnaire has 12 specific items (no/yes) rating, for example feelings that something strange or inexplicable is taking place within oneself or in the environment, feelings that one is being followed or influenced in some special way, experience of thoughts running wild or difficulty in controlling the speed of thoughts. In this study, the presence or absence of PLEs was defined in the main analyses by using the established PROD cutoff score of at least 3 points. When screening for at-risk patients in clinical practice, a cutoff of 3 points is used by convention (Mustonen et al., 2018). However, as the aim of this study was to assess PLEs as experienced in the wider non-prodromal population, separate analyses were also conducted utilizing a lower threshold of at least 2 points. Importantly the construct validity of the PROD-screen has been assessed also utilizing this threshold (Heinimaa et al., 2003).

Cannabis exposure was ascertained by asking 'Have you ever used marihuana or hashish?' with options 'never, once, 2–4 times, 5 times or more, or I use regularly'. In this study, lifetime cannabis exposure was examined as the dichotomized (no/yes). The study subjects were stratified into four groups according to PLE and cannabis exposure (CE) status: PLE/CE +/+, PLE/CE +/−, PLE/CE −/+, PLE/CE −/−.

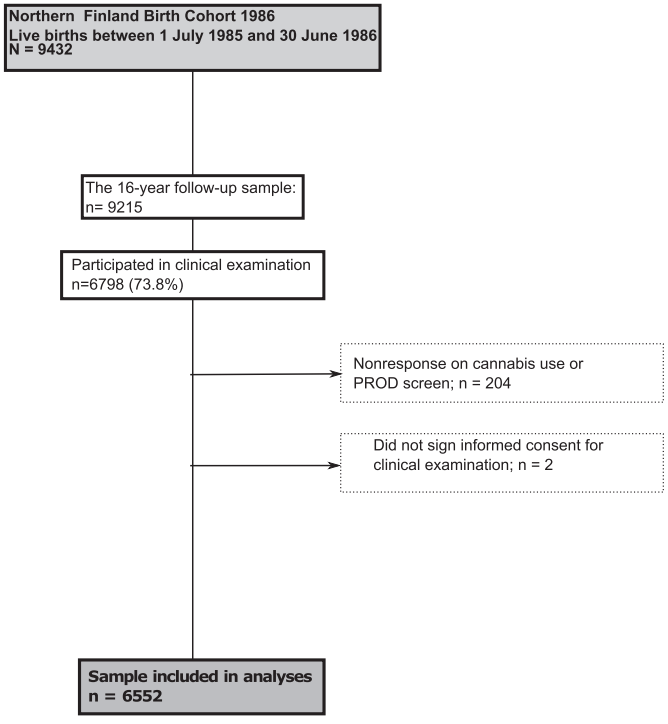

Fig. 1. The Northern Finland Birth Cohort 1986.

2.3. Outcome variables: any psychiatric disorder, psychosis, mood disorders, depressive disorders, anxiety disorders and substance use disorder

Data on diagnostic ICD-10 codes related to any psychiatric disorder (F00-F69, F80-F99) psychosis (F20-F25, F28, F29, F30.2, F31.2, F31.5, F32.3, F33.3), mood disorder (F30-F39), depression (F32, F33, F34.1, F38.10), anxiety disorder (F40–44) and substance use disorder (F1x.1–2) were collected cumulatively until the end of 2018, when participants were aged 33 years. Data on these diagnostic codes were obtained from the Care Register for Health Care 2001–2018, the Register of Primary Health Care Visits 2011–2018, the medication reimbursement register of the Social Insurance Institution of Finland 2001–2005 and the disability pensions of the Finnish Center for Pensions 2001–2016. The Care Register contains information on patients discharged from inpatient care, and since 1998 also on specialized outpatient care. The Register of Primary Health Care Visits includes all outpatient primary health care delivered in Finland. Detailed information concerning these registers is provided in previous studies (Filatova et al., 2017; Haukka, 2009; Miettunen et al., 2011).

2.4. Alcohol use, daily smoking, and other illicit substance use

Data on lifetime illicit substance use, daily smoking and frequent alcohol intoxications were collected at age 15–16 years using a questionnaire during the clinical study. The participants were asked: 'Have you used ecstasy, heroin, cocaine, amphetamine, LSD or other similar intoxicating drugs?' A person was categorized to the 'yes'-group if person had used any of these substances at least once. Information on regular cigarette smoking was collected from postal questionnaires: adolescents were asked if they currently smoked cigarettes daily (at least 1 cigarette/day, no/yes). Participants were considered smokers if they were smoking cigarettes daily. Frequent alcohol intoxications were questioned as 'Have you been drunk during the past year? (0, 1–2, 3–5, 6–9, 10–19, 20–39 or 40 times or more)', and this was categorized as 'Have you been drunk 10 times or more during the past year? - (no/yes)'.

2.5. Parental psychiatric disorders and family structure

Data on lifetime parental psychiatric diagnoses were obtained from the nationwide Registers of Health Care during the years 1972–2018 (includes inpatient care and visits to specialized outpatient health care since 1998, and primary health care since 2011), and Finnish Center for Pensions until 2016. The variable was classified dichotomously as whether either parent had been diagnosed with an ICD-10 psychiatric disorder.

Information on structure of the family were collected by combining data from parents at birth and from the clinical study in 2001–2002. Family structure was defined dichotomously as (a) both parents living with the participant continuously and (b) other families.

2.6. Statistical analyses

We used cross tabulation and χ^2 test to assess the relationship of PLE/CE-status and subsequent psychiatric disorders.

We applied logistic regression analysis with odds ratios (OR) and 95 % confidence intervals (CI) to compare the prognoses of the PLE/CE +/+ and PLE/CE +/− groups using the PLE/CE −/− group as the reference group. The outcomes of interest were any psychiatric disorder, any psychotic disorder, any mood disorder, depressive disorder, anxiety disorder and substance use disorder. Due to small subsample size, those presenting with cannabis use without PLEs at baseline (i.e., the PLE/CE −/+ group; $n = 170$, 2.6 %) were not included in these analyses. The models are as follows: Model 1: sex and family structure. Model 2: sex, family structure and parental psychiatric disorder Model 3: sex, family structure, parental psychiatric disorder, use of illicit drugs other than cannabis, daily smoking, and frequent alcohol intoxications.

Furthermore, the aforementioned logistic regression analyses were also conducted utilizing a lower PROD-threshold of at least 2 points as an indicator of presence of psychotic-like experiences. With the exposure variable thus defined, Aalen-Johansen cumulative incidence curves were computed for each outcome for all groups, including the PLE/CE −/+ group. Lastly, sensitivity analyses were carried out with both PROD screen cutoffs using the previous modeling with a sample from which individuals with a baseline psychiatric disorder of the participant ($n = 255$) were excluded.

Previous attrition analyses of this sample have shown that fewer males (64 % v. 71 %; $p < 0.001$), individuals living in urban areas (66 % v. 71 %, $p < 0.001$) and individuals with parental psychiatric disorder (58 % v. 69 %, $p < 0.001$) participated in the 15–16 year follow up study (Miettunen et al., 2014). Furthermore, descriptive statistics on the effects of nonresponse on sample characteristics indicate, that the participants included in the final model (Model 3) did not differ substantially from the whole (Crude model) sample in terms of any covariate included (see Online supplement Table 5) or proportions of outcomes by PLE/CE status class (see Online supplement Table 6).

Statistical analyses were performed using SPSS statistical software (IBM SPSS Statistics, version 25; IBM Co., Armonk, New York, USA) except for Aalen – Johansen cumulative incidence curves that were computed using the R programming environment (R version 3.6.0, R foundation for statistical computing, Vienna, Austria).

3. Results

The covariates and their relation to psychotic-like experience (PLE) and cannabis exposure (CE) status are presented in Table 1. The sample totalled 6552 individuals and was stratified as follows: In all, 30.5 % (2000/6552, 37.8 % male) presented with PLEs defined as a score of 3 or more items on the PROD-screen. Of these participants 10.3 % (205/2000, 36.6 % male) reported lifetime cannabis use. The reference group, i.e., participants with neither CE nor PLEs at baseline constituted 66.9 % (4382/6552, 54.2 % male) of the sample. Of the whole sample 5.7 % (375/6552, 44 % male) presented with early cannabis exposure.

255 participants (3.9 %) presented with a psychiatric diagnosis at baseline (i.e., had been diagnosed before the age of 16). The prevalence of baseline psychiatric disorders was 7.3 % (15/205) for those with PLEs and cannabis exposure, 5.3 % (96/1795) for those with PLEs only and 3.1 % (135/4382) for those with neither risk factor.

By the end of the follow-up 24.4 % (1601/6552) of the whole sample had been diagnosed with any psychiatric disorder, 2.4 % (154/6552) with a psychotic disorder, 10.7 % (702/6552) with any mood disorder, 10.2 % (669/6552) with depression, 11.6 % (758/6552) with anxiety disorder and 2.9 % (190/6552) with substance use disorder. The outcome data stratified according to PLE/CE status are summarized in Table 2. For all mental health outcomes, a greater proportion of those in the PLE/CE +/+ than in the PLE/CE +/− group had been diagnosed.

The results of the logistic regression models are presented in Table 3. In the fully adjusted model, individuals with psychotic experiences and cannabis exposure (PLE/CE +/+) were at increased risk of any psychiatric disorder (OR 2.59; 95 % CI 1.82–3.68), psychotic disorders (OR 3.86; 95 % CI 1.83–8.11), mood disorders (OR 4.07; 95 % CI 2.74–6.04), depressive disorders (OR 4.35; 95 % CI 2.93–6.48), anxiety disorders (OR 2.06; 95 % CI 1.34–3.17) and substance use disorders (OR = 2.26; 95 % CI 1.13–4.50) compared to the reference group (PLE/CE −/−). The odds ratios of the PLE/CE +/− group were uniformly smaller than for the PLE/CE +/+ group, with the association with substance use disorder found to be nonsignificant even in crude analysis.

The results of the sensitivity analyses conducted by excluding the subjects diagnosed with a psychiatric disorder before the age of 15/16 ($n = 255$) are summarized in the Online supplement Table 1. Individuals with PLE/CE +/+ were at greater risk than the PLE/CE +/− group for all subsequent outcomes. The results of the multivariable analyses

Table 1
Association of covariates and PLE/CE[a] status in Northern Finland Birth Cohort 1986.

	Total n = 6552		*PLE/CE+/+ n = 205*		*PLE/CE−/+ n = 170*		*PLE/CE+/− n = 1795*		*PLE/CE−/− n = 4382*		*p*-Value[b]
Sex	6552										
Male	3221	49.2 %	75	36.6 %	90	52.9 %	681	37.9 %	2375	54.2 %	<0.001
Female	3331	50.8 %	130	63.5 %	80	47.1 %	1114	62.1 %	2007	45.8 %	
Family structure	5595										
Family with two parents	4419	79.0 %	114	67.1 %	94	66.7 %	1213	77.6 %	2998	80.6 %	<0.001
Other	1176	21.0 %	56	32.9 %	47	33.3 %	351	22.4 %	722	19.4 %	
Daily smoking	6050										
No	5290	87.4 %	101	54.9 %	73	46.2 %	1494	88.4 %	3622	90.9 %	<0.001
Yes	760	12.6 %	83	45.1 %	85	53.8 %	196	11.6 %	396	9.1 %	
Other illicit drug use	6525										
No	6490	99.5 %	187	91.2 %	159	94.1 %	1783	99.7 %	4361	100 %	<0.001
Yes	35	0.5 %	18	8.8 %	10	5.9 %	6	0.3 %	1	0 %	
Alcohol intoxication 10 ≥ times past year	6390										
No	5203	81.4 %	65	32.2 %	7	33.9 %	1431	81.1 %	3650	85.8 %	<0.001
Yes	1187	18.6 %	137	67.8 %	111	66.1 %	333	18.9 %	606	14.2 %	
Parental psychiatric disorder	6552										
No	4152	63.4 %	120	58.5 %	105	61.8 %	1104	61.5 %	2823	64.4 %	0.07
Yes	2400	36.6 %	85	41.5 %	65	38.2 %	691	38.5 %	1559	35.6 %	

[a] PLE (psychotic like experience) and CE (cannabis use).
[b] Chi-squared test.

Table 2
Distribution of outcomes by PLE/CE[a] status in Northern Finland Birth Cohort 1986.

	Total n = 6552		*PLE/CE +/+ n = 205*		*PLE/CE −/+ n = 170*		*PLE/CE +/− n = 1795*		*PLE/CE −/− n = 4382*		*p*-Value[b]
Any psychiatric disorder											
No	4951	75.6 %	109	53.2 %	119	70.0 %	1263	70.4 %	3460	79.0 %	<0.001
Yes	1601	24.4 %	96	46.8 %	51	30.0 %	532	29.6 %	922	21.0 %	
Psychotic disorders											
No	6398	97.6 %	189	92.2 %	165	97.1 %	1730	96.4 %	4314	98.4 %	<0.001
Yes	154	2.4 %	16	7.8 %	5	2.9 %	65	3.6 %	68	1.6 %	
Mood disorders											
No	5850	89.3 %	141	68.8 %	143	84.1 %	1538	85.7 %	4028	91.9 %	<0.001
Yes	702	10.7 %	64	31.2 %	27	15.9 %	257	14.3 %	354	8.1 %	
Depressive disorders											
No	5883	89.8 %	143	69.8 %	144	84.7 %	1547	86.2 %	4049	92.4 %	<0.001
Yes	669	10.2 %	62	30.2 %	26	15.3 %	248	13.8 %	333	7.6 %	
Anxiety disorders											
No	5794	88.4 %	156	76.1 %	142	83.5 %	1549	86.3 %	3947	90.1 %	<0.001
Yes	758	11.6 %	49	23.9 %	28	16.5 %	246	13.7 %	435	9.9 %	
Substance use disorders											
No	6362	97.1 %	184	89.76 %	156	91.8 %	1743	97.1 %	4279	97.6 %	<0.001
Yes	190	2.9 %	21	10.24 %	14	8.2 %	52	2.9 %	103	2.4 %	

[a] PLE (psychotic like experience) and CE (cannabis use).
[b] Chi-squared test.

utilizing a PROD cutoff of at least 2 points were similar to those utilizing the conventional PROD 3 point cutoff (see Online supplement Table 4). Aalen-Johansen curves for cumulative incidences of psychiatric disorders by PLE/CE status with the PROD-screen 2p cutoff are presented in Fig. 2.

4. Discussion

In this large birth cohort study with an 18-year follow-up, we found that adolescents with psychotic-like experiences (PLEs) both with and without lifetime cannabis exposure (CE) were at an increased risk for a range of psychiatric disorders compared to adolescents with neither risk factor. These findings remained statistically significant after adjusting for sex, baseline and parental psychiatric disorders, frequent alcohol intoxications, daily smoking and use of illicit drugs other than cannabis. To our knowledge, this is the first general population-based study assessing the trajectories of psychotic-like experiences and cannabis exposure at a young age with respect to psychotic as well as non-psychotic outcomes.

Using those with neither PLEs nor CEs as the reference group in our analyses, we found that the odds ratios of the group with PLEs but unexposed to cannabis were uniformly smaller than for those with exposure to both PLEs and cannabis for each outcome. As we aimed to study prognosis rather than to infer causality, we did not statistically estimate the additional risk of subsequent psychiatric disorders conferred by cannabis exposure to PLE-experiencing adolescents. Even so, cannabis use has been associated with conversion from a range of at-risk states to respective adverse outcomes, e.g., from non-suicidal self-injury to suicide attempt (Mars et al., 2019) and from clinically high risk states to psychosis (Valmaggia et al., 2014) and bipolar disorder (Ratheesh et al.,

Table 3
Odds ratios of outcomes by PLE/CE[a] status.

	Crude; $n = 6382$		Model 1; $n = 5454$		Model 2; n = 5454		Model 3; $n = 5091$	
	OR	95 %CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Any psychiatric disorder								
PLE/CE −/− (reference)	1	–	1	–	1	–	1	–
PLE/CE +/+	3.31	2.49–4.39	3.02	2.20–4.13	3.01	2.19–4.14	2.59	1.82–3.68
PLE/CE +/−	1.58	1.40–1.79	1.51	1.32–1.73	1.50	1.31–1.73	1.48	1.29–1.71
Any psychosis								
PLE/CE −/− (reference)	1	–	1	–	1	–	1	–
PLE/CE +/+	5.37	3.06–9.44	5.46	2.91–10.25	5.31	2.82–10.01	3.86	1.83–8.11
PLE/CE +/−	2.38	1.69–3.36	2.52	1.74–3.67	2.49	1.71–3.62	2.41	1.61–3.62
Any mood disorder								
PLE/CE −/− (reference)	1	–	1	–	1	–	1	–
PLE/CE +/+	5.17	3.77–7.08	4.56	3.21–6.47	4.59	3.22–6.53	4.07	2.74–6.04
PLE/CE +/−	1.90	1.60–2.26	1.74	1.44–2.10	1.73	1.43–2.10	1.68	1.38–2.05
Any depression								
PLE/CE −/− (reference)	1	–	1	–	1	–	1	–
PLE/CE +/+	5.27	3.84–7.25	4.76	3.34–6.78	4.78	3.35–6.83	4.35	2.93–6.48
PLE/CE +/−	1.95	1.64–2.32	1.79	1.48–2.17	1.78	1.47–2.16	1.75	1.43–2.14
Anxiety disorder								
PLE/CE −/− (reference)	1	–	1	–	1	–	1	–
PLE/CE +/+	2.85	2.04–3.99	2.51	1.72–3.65	2.50	1.71–3.64	2.06	1.34–3.17
PLE/CE +/−	1.44	1.22–1.70	1.32	1.09–1.58	1.30	1.08–1.57	1.28	1.05–1.55
Substance use disorder								
PLE/CE −/− (reference)	1	–	1	–	1	–	1	–
PLE/CE +/+	4.74	2.90–7.75	4.69	2.59–8.49	4.60	2.53–8.37	2.26	1.13–4.50
PLE/CE +/−	1.24	0.88–1.74	1.43	0.97–2.10	1.40	0.95–2.06	1.37	0.90–2.07

Model 1: sex, family structure.
Model 2: sex, family structure, parental psychiatric disorder.
Model 3: sex, family structure, parental psychiatric disorder, frequent alcohol intoxications, daily smoking, other illicit substance use.
[a]) Psychotic-like experiences (PLE) and Cannabis exposure (CE).

2015). Thus, it is plausible that cannabis use may impair the prognosis of PLE-experiencing adolescents.

The association between cannabis use and psychotic disorders was examined in a previous study by Mustonen et al. using the NFBC1986 data (Mustonen et al., 2018). In that study, cannabis use of 5 times or more was associated with any psychotic disorder until age 30 years even after adjusting for baseline PLEs, sociodemographic factors, and other substance use. Also, cumulative incidences of psychotic disorders were reported with the sample stratified according to baseline PLEs and cannabis exposure. However, in the present study with longer follow-up and using cut-offs of both three and two points in the PROD-screen, the sample was stratified by PLE/CE status also for multivariable analyses.

Moreover, we found PLE-experiencing adolescents to be at a greater risk for both any psychiatric disorder and mood and anxiety disorders regardless of cannabis exposure status. The few previous studies addressing the prognosis of PLE-experiencing adolescents beyond conversion to psychosis are heterogeneous in terms of exposure and outcome variables as well as covariates controlled for: In the study by Dhossche et al., self-reported hallucinations in adolescence were associated with any DSM-IV diagnosis, depressive disorders and substance use disorders during follow up (Dhossche et al., 2002). However, this study did not adjust for substance use. Kırlı et al. analyzed multiple prognostic factors of PLEs in adolescence and adulthood with any DSM-IV diagnosis and psychotic/non-psychotic disorders at follow-up as the main outcomes (Klrll et al., 2019). Cannabis use was included as a covariate in their multivariable models but not studied as an exposure variable.

Regarding SUD, statistical significance was retained in the PLE/CE +/+ group in the fully adjusted model, whereas in the PLE/CE +/− group a significant association was not observed even in crude analysis. Dhossche and Cederlöf (Cederlöf et al., 2017; Dhossche et al., 2002) reported a statistically significant association between PLEs and subsequent SUD. However, it should be noted that the former study did not control for substance use at baseline and the latter reported only crude effect size estimates. Also, we found that daily smoking, frequent alcohol intoxications and exposure to other illicit drugs were several fold more common in the group with both PLEs and cannabis exposure than in the group presenting with PLEs only. This finding is in line with previous research indicating the prevalence of polysubstance use in adolescence (Halladay et al., 2020). Thus, it can be concluded that adolescents experiencing PLEs and presenting with alcohol intoxications or cigarette smoking should be especially screened for concomitant cannabis exposure.

The strengths of the study are as follows: To our knowledge, no other large scale general population studies with prospective data have examined the effect of cannabis use on the prognosis of adolescents experiencing PLEs with respect to both psychotic and nonpsychotic outcomes. Further, our 18-year follow-up time is comparable to the longest prospective studies examining the prognosis of PLEs in adolescence (Connell et al., 2016; Fisher et al., 2013). Several substance use-related covariates were also controlled for, as polysubstance use among adolescent cannabis use is common (Halladay et al., 2020) introducing a significant potential source of confounding. Importantly, parental psychiatric disorders were controlled for which is to be regarded as a strength, as genetic diathesis contributes significantly to the risk of several mental disorders. The NFBC1986 birth cohort provides data on a large community sample with high ethnic and genetic homogeneity. Additionally, there is almost complete participant retention among

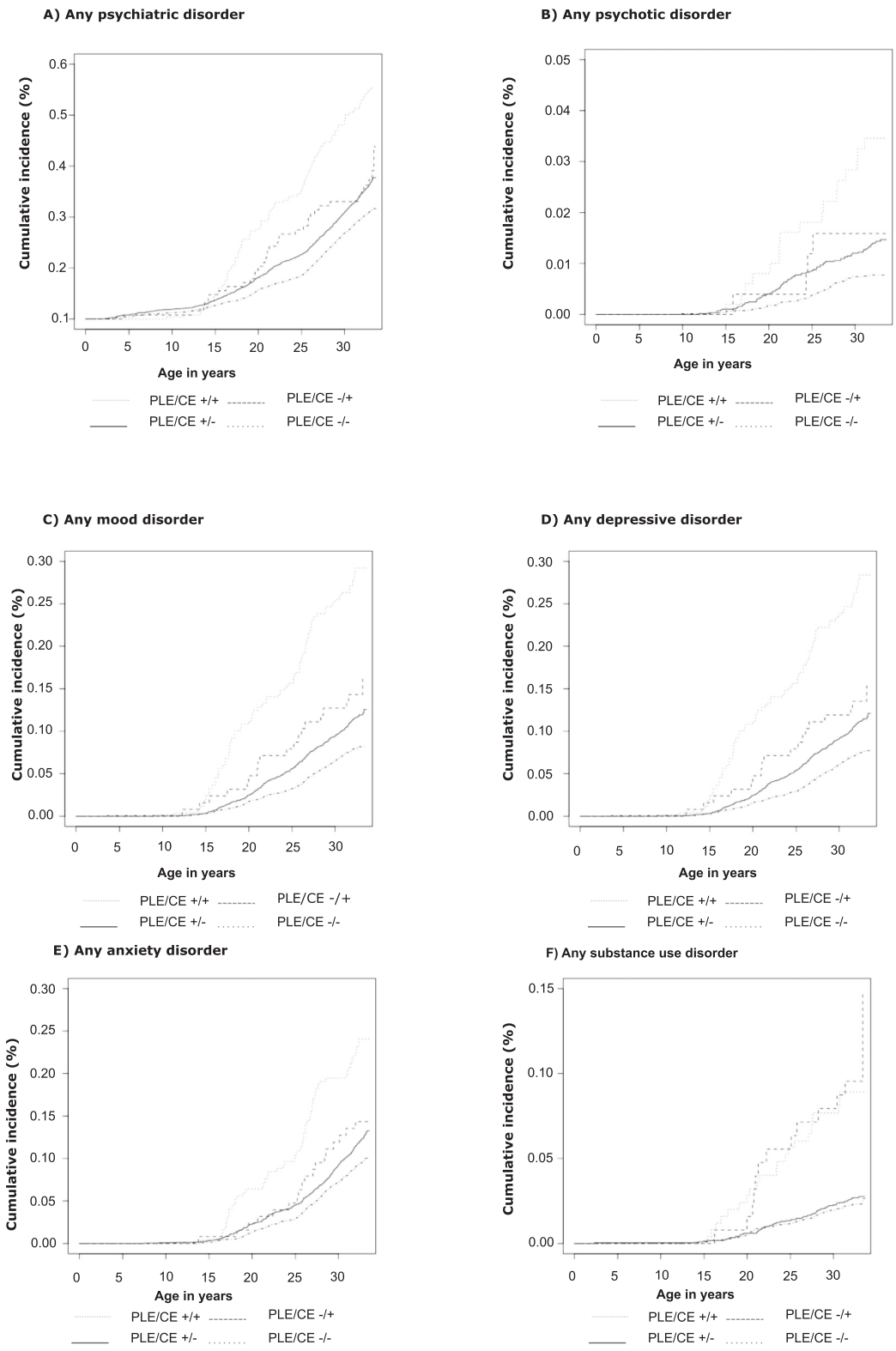

Fig. 2. Aalen-Johansen Cumulative Incidence curves for outcomes studied by PLE/CE status. A) Any psychiatric disorder, B) Any psychotic disorder, C) Any mood disorder, D) Depressive disorder, E) Anxiety disorder, F) Substance use disorder.

those with information on PLEs and cannabis exposure at age 15/16 years, as only a very small proportion of cohort members deceased or emigrated during the follow-up. Lastly, the analyses were also conducted utilizing a lower PROD screen threshold, and these results point to cannabis exposure to be an adverse prognostic marker even for those adolescents with a burden of PLEs not achieving the established PROD cutoff.

However, there are also limitations. Unfortunately, power issues prevented us from using a multi-class cannabis variable. Cannabis exposure may vary from one episode of cannabis experimentation to heavy use, and it is not biologically plausible that a single exposure would lead to a psychiatric disorder years later. Moreover, information

on lifetime cannabis use at age 15–16 years was collected using self-reports and in one time point, which may result in an underestimation of true association. However, focusing on early-onset exposure at age 15/16 years is crucial, as there is evidence that the age of initiation of cannabis use is associated with increased risk of other adverse sequelae such as psychosis (Arseneault et al., 2002; Marconi et al., 2016; Stefanis et al., 2013). Also, only 5.7 % reported using any cannabis at age 15/16 years introducing power issues and increasing the likelihood of type II error. In the ESPAD survey conducted in 2003, the lifetime prevalence of cannabis use at the age of 15/16 in Finland was 11 %, which suggests that underreporting might be an issue with our data (European Monitoring Centre fo Drugs and Drug Addiction (EMCDDA), 2003). However, this source of bias is more likely to weaken the associations observed rather than to inflate them. Of note is the fact that a substantial number (30.5 % 2000/6552) of study participants were detected as having PLEs defined as a PROD score of at least 3 points, which may raise questions concerning the validity of this instrument to detect PLEs. However, PLEs are common in adolescence (Yung et al., 2009) and considerable prevalence figures for baseline PLEs have been reported in previous prospective studies (Bechtold et al., 2016; Dominguez et al., 2011). In addition, self-report measures are known to be less specific than interview-based ratings for psychotic symptoms (Granö et al., 2011; Horwood et al., 2008), and may thus provide higher rates for PLEs. Furthermore, while PLEs were only assessed at one time point, previous longitudinal studies have shown that those adolescents who experience PLEs at more than one point in time are at increased risk of future mental disorders (Connell et al., 2016; Dominguez et al., 2011). Also, discerning predictive values of individual items, combinations of items and total numbers of items reported on the PROD-screen was beyond the scope of the study. In the same vein, not having information on the frequency or intensity of and distress caused by PLEs is also to be regarded as a limitation. As we studied hypotheses pertaining to prognosis rather than causality, we did not exclude those with psychiatric disorders at baseline from our main analyses. However, the results did not markedly change in the sensitivity analyses in which those with psychiatric disorders at baseline were excluded. The cumulative incidence of substance use disorder was low in our study as compared to population based survey findings (Suvisaari et al., 2009), reflecting underreporting of substance use disorders in Finnish health-care-based registers (Mäkelä et al., 2020). This may weaken the generalizability of our findings on PLEs, cannabis use and subsequent SUD. Also, power issues introduced by the low number of participants in the PLE/CE +/+ group precluded from examining dose response between cannabis use and the outcomes studied. Lastly, the differential attrition described in the Methods section might have introduced selection bias. However, when using register-based data as outcomes, attrition is minimal, thus enhancing the generalizability of the results.

5. Conclusions

Early-onset cannabis use is associated with an increased risk of adverse mental health outcomes for adolescents with PLEs even after extensive confounder control, i.e. parental psychiatric disorders, family structure, sex, frequent alcohol intoxications, daily smoking and illicit substance use other than cannabis. Although further research is needed examining the temporal relationship between PLEs and cannabis use in adolescents, cannabis use intensity and persistence of psychotic- like experiences, the findings of this study suggest that adolescents with PLEs and CE may be a particularly high-risk group for future mental disorders.

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Contribution

AD, AM, SN, AEA had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AD, AM, SN developed conception and design of the work. AD, AM, SN, AEA, JM, JS, MS, JV performed data analysis and interpretation and wrote the first manuscript draft. AD, AM, SN, AEA, JM, JS, MS, JV supervised conception and design of the work and provided critical revision of the article. All authors contributed approval of the final version of the manuscript.

Role of funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of competing interest

The authors have no conflicts of interest to report. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Appendix A. Supplementary data

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