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Daedelow, L.S.; Berning, M.; Hardon, A.; Murray, H.; Oei, N.Y.L.; Wiers, R.W.; ERANID Consortium; IMAGEN Consortium

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Laura S. Daedelow [a,*], Tobias Banaschewski [b], Moritz Berning [c], Arun L.W. Bokde [d], Rüdiger Brühl [e], Erin Burke Quinlan [f], H. Valerie Curran [g], Sylvane Desrivières [f], Herta Flor [h,i], Antoine Grigis [j], Hugh Garavan [k], Anita Hardon [c], Jakob Kaminski [a], Jean-Luc Martinot [l], Marie-Laure Paillère Martinot [m], Eric Artiges [n], Hayley Murray [c], Frauke Nees [b,h,o], Nicole Y.L. Oei [p,q,r], Dimitri Papadopoulos Orfanos [j], Tomáš Paus [s], Luise Poustka [t], Sarah Hohmann [b], Sabina Millenet [b], Annika Rosenthal [a], Juliane H. Fröhner [u], Michael N. Smolka [u], Henrik Walter [a], Robert Whelan [v], Reinout W. Wiers [w], Gunter Schumann [f,x], Andreas Heinz [a], ERANID Consortium and IMAGEN Consortium

[a] Department of Psychiatry and Psychotherapy CCM, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
[b] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, 68159 Mannheim, Germany
[c] Amsterdam Institute for Social Science Research, University of Amsterdam, Amsterdam, the Netherlands
[d] Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
[e] Physikalisch-Technische Bundesanstalt (PTB), Braunschweig and Berlin, Germany
[f] Centre for Population Neuroscience and Precision Medicine (PONS), Institute of Psychiatry, Psychology & Neuroscience, SGDP Centre, King's College London, United Kingdom
[g] Clinical Psychopharmacology Unit, University College London, London, United Kingdom
[h] Institute of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, Mannheim, Germany
[i] Department of Psychology, School of Social Sciences, University of Mannheim, 68131 Mannheim, Germany
[j] NeuroSpin, CEA, Université Paris-Saclay, F-91191 Gif-sur-Yvette, France
[k] Departments of Psychiatry and Psychology, University of Vermont, 05405 Burlington, VT, USA
[l] Institut National de la Santé et de la Recherche Médicale, INSERM U A10 "Trajectoires développementales en psychiatrie"; Université Paris-Saclay, Ecole Normale supérieure Paris-Saclay, CNRS, Centre Borelli, Gif-sur-Yvette, France
[m] Institut National de la Santé et de la Recherche Médicale, INSERM U A10 "Trajectoires développementales en psychiatrie"; Université Paris-Saclay, Ecole Normale supérieure Paris-Saclay, CNRS, Centre Borelli; and AP-HP.Sorbonne Université, Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Paris, France
[n] Institut National de la Santé et de la Recherche Médicale, INSERM U A10 "Trajectoires développementales en psychiatrie"; Université Paris-Saclay, Ecole Normale supérieure Paris-Saclay, CNRS, Centre Borelli; and Psychiatry Department 91G16, Orsay Hospital, France
[o] Institute of Medical Psychology and Medical Sociology, University Medical Center Schleswig Holstein, Kiel University, Kiel, Germany
[p] Research Priority Area (RPA) Yield, University of Amsterdam, Amsterdam, the Netherlands
[q] Developmental Psychology (Addiction Development and Psychopathology ADAPT-lab), University of Amsterdam, Amsterdam, the Netherlands
[r] Amsterdam Brain and Cognition (ABC), University of Amsterdam, Amsterdam, the Netherlands
[s] Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Departments of Psychology and Psychiatry, University of Toronto, Toronto, Ontario M6A 2E1, Canada
[t] Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, von-Siebold-Str. 5, 37075 Göttingen, Germany
[u] Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany
[v] School of Psychology, Global Brain Health Institute, Trinity College Dublin, Ireland
[w] Department of Developmental Psychology, Adapt Lab, Research Priority Area Yield, University of Amsterdam, Nieuwe Achtergracht 129-B, 1018 WS Amsterdam, the Netherlands
[x] PONS Research Group, Dept of Psychiatry and Psychotherapy, Campus Charite Mitte, Humboldt University, Berlin and Leibniz Institute for Neurobiology, Magdeburg, Germany, and Institute for Science and Technology of Brain-inspired Intelligence (ISTBI), Fudan University, Shanghai, PR China

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ABSTRACT

Objective: To assess changes in cannabis use in young adults as a function of psychotic-like experiences.
Method: Participants were initially recruited at age 14 in high schools for the longitudinal IMAGEN study. All measures presented here were assessed at follow-ups at age 19 and at age 22, respectively. Perceived stress was only assessed once at age 22. Ever users of cannabis ($N = 552$) gave qualitative and quantitative information on cannabis use and psychotic-like experiences using the Community Assessment of Psychic Experiences (CAPE). Of those, nearly all $n = 549$ reported to have experienced at least one psychotic experience of any form at age 19.
Results: Mean cannabis use increased from age 19 to 22 and age of first use of cannabis was positively associated with a change in cannabis use between the two time points. Change in cannabis use was not significantly

Abbreviations: PLEs, psychotic-like experiences; CAPE, Community Assessment of Psychic Experiences.

* Corresponding author at: Department of Psychiatry and Psychotherapy, Charité Campus Mitte, Charitéplatz 1, 10117 Berlin, Germany.
E-mail address: laura.daedelow@charite.de (L.S. Daedelow).

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Age of first use
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Cannabis discontinuation hypothesis

associated with psychotic-like experiences at age 19 or 22. In exploratory analysis, we observed a positive association between perceived stress and the experience of psychotic experiences at age 22.
Conclusion: Age of first use of cannabis influenced trajectories of young cannabis users with later onset leading to higher increase, whereas the frequency of psychotic-like experiences was not associated with a change in cannabis use. The observed association between perceived stress and psychotic-like experiences at age 22 emphasizes the importance of stress experiences in developing psychosis independent of cannabis use.

1. Introduction

Cannabis is the most used illicit drug in Europe, with estimates that 24.7 million adults have used the drug in the last year (EMCDDA, 2019). Cannabis use across adolescence is reported to increase and reach its peak in young adulthood (Patton et al., 2007; Tucker et al., 2019). Herbal cannabis and its extracts contain numerous cannabinoids, most notably tetrahydrocannabinol (THC) and cannabidiol (CBD). Evidence has linked cannabis consumption to psychosis (Moore et al., 2007), specifically THC, which is known for its psychoactive effect and can cause intoxicating effects (Morgan and Curran, 2008). The potency of THC in cannabis has risen in herbal and in resin cannabis (EMCDDA, 2019). The increased levels of THC may put users at a higher risk for developing psychosis (Di Forti et al., 2019).

Longitudinal studies show that regular cannabis use is associated with an increased risk for schizophrenia and for reporting psychotic symptoms (Hall and Degenhardt, 2008). More frequent cannabis use is independently associated with more frequent or intense symptoms on three psychotic dimensions: positive, negative and depressive (Bernardini et al., 2018; Schubart et al., 2011a; Skinner et al., 2011; Verdoux et al., 2003). The negative dimension refers to one of the key symptom domains of schizophrenia, with negative symptoms including anhedonia or apathy (Selten et al., 1998), whereas the depressive dimension partly overlaps with negative symptoms, but additionally covers more cognitive symptoms of depression (e.g. sadness, pessimism, feeling guilty) that discriminate between depression and negative symptoms (Kibel et al., 1993; Stefanis et al., 2002; Stefanis et al., 2004). According to meta-analyses, psychotic experiences and cannabis intake show a dose-response relationship (Marconi et al., 2016; Ragazzi et al., 2018), which suggests that psychosis and psychotic-like experiences (PLEs) share the same risk factors, thus supporting an association between cannabis use and PLEs.

Not only is continuous cannabis consumption related to psychosis, but also the age of first use is predictive of frequency and intensity of psychotic symptoms (Konings et al., 2008; Ragazzi et al., 2018; Schubart et al., 2011b; Skinner et al., 2011). Such an association is also reported for negative psychotic symptoms, but to a lesser degree (Schubart et al., 2011b). Together, these findings support the hypothesis that the impact of cannabis use is age dependent and stronger for positive psychotic symptoms.

Although the association between cannabis consumption and PLEs is well documented, its causality and directionality are still intensely debated (Degenhardt et al., 2018; DeVylder et al., 2018; Hall and Degenhardt, 2008; Murray and Hall, 2020). Different theories are discussed: First, the psychosis risk might be primarily caused by familial risk for schizophrenia and only appears to be triggered by cannabis consumption. For example, Proal et al. (2014) showed that both cannabis using and non-using relatives of patients with psychosis showed increased familial risk for psychotic-like symptoms compared with their respective non-psychotic control samples. Secondly, co-occurring genetic or environmental risk factors including stress exposure could contribute to both cannabis use and PLEs in adolescents (Shakoor et al., 2015; Arranz et al., 2018). Thirdly, cannabis use disorder also could directly affect the risk for PLEs (Nesvåg et al., 2017). Fourthly, cannabis could be used as self-medication in face of subclinical symptoms of psychosis to reduce distress (Mané et al., 2015).

It has been reported that a decrease in cannabis use in $n = 705$ young adults aged 18–27 years was associated with a decrease in psychotic experiences, while increased consumption was linked to positive symptoms at follow-up (Van Gastel et al., 2014). This association between changes in cannabis use and changes in the frequency of PLEs does not prove a causal relationship, but strongly suggests a bidirectional association and a reduction of PLEs after the cessation of cannabis use. Interestingly, the "cannabis discontinuation hypothesis" suggests that in young adolescents, aversive effects of cannabis use including the manifestation of psychotic symptoms may trigger a reduction in cannabis consumption by self-selection, i.e. a self-imposed protection from the risk of developing enduring psychotic disorders (Sami et al., 2019; Van Gastel et al., 2012). Moreover, cessation of cannabis consumption was predicted by more aversive subjective experiences with cannabis and by no increase in the first three years after first use (Seidel et al., 2019), which could partly be mediated by aversive psychotic experiences. Hence, in the present study we sought to investigate the association of change in cannabis use over a period of 3 years with the occurrence of PLEs in a non-clinical sample of young adults, controlling for potentially confounding factors including age of first use of cannabis, other illicit drug use and socio-economic status.

1.1. Anecdotal evidence from qualitative interviews for hypothesis generation

Qualitative interviews in our study were conducted within the scope of the interdisciplinary research project ERANID, which focuses on use of illicit drugs including cannabis (ERANID, 2015). For the purpose of hypothesis generation, interviews were conducted additionally to quantitative data using a mixed-method approach. Detailed information on the ethnographic methods can be found in Section 2.1. One topic that emerged in several interviews was the cessation of cannabis consumption after the experience of psychotic experiences, as suggested by the so-called cannabis discontinuation hypothesis (Sami et al., 2019). For exemplification, we here provide a quote of one participant (age 22):

> "I think that definitely a motivation for stopping was every time I got reasonably high, I would start to have paranoid thoughts, not in a psychotic way like, people were watching me or whatever […]. So, yeah, I kind of had enough of that. Taking a break has stopped that so I think that was a good decision."

1.2. Hypotheses

We tested the hypothesis that (1) cannabis use at age 19 is predictive of cannabis use at age 22; (2) early age of first use of cannabis is predictive of increase in cannabis use from 19 to 22; (3) total occurrence of distressful PLEs at age 19 as well as frequency and distress of positive PLEs are associated with reductions in cannabis use between age 19 and 22; and (4) current cannabis use at age 19 or 22 is associated with current PLEs at these time points. Furthermore, we explored the association of stress effects at age 22 with PLEs and cannabis use.

2. Methods

2.1. Sample

The sample was drawn from the longitudinal European IMAGEN cohort (Schumann et al., 2010). The IMAGEN study consists of a community sample recruited at the age of 14 ($N = 2214$) from 8 sites across Europe. Follow up 1 (FU1) was conducted at age 16 ($N = 1700$). Here we used data from the second follow up at age 19 (FU2; $N = 1515$) and the third follow up (FU3; $N = 1360$) at age 22. In the current study, we included all participants who had reported to have used cannabis at least once in their life at the age of 19 (for assessment see 2.2.2.). Recruitment strategies and inclusion criteria can be found elsewhere (Schumann et al., 2010). The anecdotal evidence provided above was obtained in a subsample ($N = 42$) of the IMAGEN cohort within the scope of the research project Imagen Pathways funded by ERANID (ERANID, 2015). Here, ethnographic interviews on the experience of illicit drug use were conducted at age 22, transcribed by independent assistants, and reoccurring topics in relation to cannabis use were extracted by ethnographic researchers.

All study participants were provided with a description of the study and written informed consent was obtained before participation. The research protocol was approved by local Ethics Committees and adhered to the Declaration of Helsinki.

2.2. Measures

2.2.1. Psychotic-like experiences (PLEs)

2.2.1.1. Community Assessment of Psychic Experiences (CAPE). PLEs were assessed using the CAPE (Stefanis et al., 2002), a self-report questionnaire consisting of 42 items, which has been found to be a reliable and valid instrument for evaluating the presence of lifetime psychotic-like symptoms in the general population in various languages (Mark and Toulopoulou, 2016, 2017; Mossaheb et al., 2012; Schlier et al., 2015; Vermeiden et al., 2019). The CAPE measures 1) frequency and 2) associated distress of psychotic experiences on three symptom dimensions: positive (*Pos*), negative (*Neg*) and depressive (*Dep*) (Konings et al., 2006; Stefanis et al., 2002). PLEs were not queried explicitly in relation to cannabis consumption, hence the CAPE score reflects PLEs induced by cannabis use as well as non-cannabis related PLEs across lifespan. The frequency scale answers comprise the options: never (0); sometimes (1); often (2); and nearly always (3); whereas the distress scale answer options are: not distressed (0); sometimes (1); often (2); and nearly always (3). Items scores were re-coded (range: 1 to 4) and added up to a total score (CAPE*Total*) and to the sum scores for the positive dimension, i.e. the frequency of positive symptoms and the distress associated with them (CAPE - positive frequency: CAPE*PosFreq*; CAPE - positive distress: CAPE*PosDis*). Sum scores were weighted with number of answered items to account for partial non-responders resulting in a value ranging from 1 to 4. In our analysis, the total score and the weighted sum scores were used as continuous measures.

2.2.2. Cannabis use

2.2.2.1. European School Survey Project on Alcohol and Drugs (ESPAD). The ESPAD (Hibell et al., 1997) was used to measure the frequency of cannabis use in the past year at age 19 and age 22 respectively in an online design by asking the question: "On how many occasions OVER THE LAST 12 MONTHS have you used marijuana (grass, pot) or hashish (hash, hash oil)?". Answers were scored between 0 and 6 according to their use frequencies: never (0); once or twice (1); 3–5 times (2); 6–9 times (3); 10–19 times (4); 20–39 times (5); 40 times or more (6). Additionally, age of first use of cannabis was asked at age 19 using the question: "When did you first try marijuana (grass, pot) or hashish (hash, hash oil)?"

The difference in frequency of cannabis use assessed at FU2 versus FU3 was calculated by subtracting frequency at age 22 from frequency at age 19. The difference in frequency of cannabis use was used as main outcome variables in our analysis.

2.2.3. Stress measures

2.2.3.1. Perceived Stress Scale. The Perceived Stress Scale (PSS) is a self-report scale measuring perceived stress with 10 items (Cohen et al., 1994). The degree to which situations are perceived as unpredictable, uncontrollable and overloaded is assessed using a 5-point Likert scale ranging from never (0), almost never (1), sometimes (2), fairly often (3), very often (4). Total scores range from 0 to 40, with higher scores indicating greater perceived stress.

2.2.4. Covariates

Additional parameters of drug use were assessed at FU2 and FU3 and used as covariates. Apart from gender, age of first use of cannabis (if applicable), the use of other illicit drugs (ever vs. never), nicotine dependence, parental socio-economic status (SES) and psychiatric disorders were introduced as covariate in our analysis (for details of assessment see supplements). Additionally, recruitment site was introduced as covariate in our analysis. As number of inhabitants is related to urbanicity, which has been associated with psychotic-like experiences in children (Karcher et al., 2020) and considered to be a general risk factor for psychosis in adults in developed countries (Heinz et al., 2013), we ranked the recruitment sites in the order of inhabitants of the respective city to account for possible differences in urbanicity.

2.3. Data analysis

The analyses were carried out with the statistical package for the social sciences (SPSS 20.0). Descriptive statistics for the predictor (CAPE*Total*, CAPE*PosFreq* and CAPE*PosDis*), main outcome variables (cannabis use, change in cannabis use) and all covariates (gender identification, recruitment site, age of first use, other illicit drug use, nicotine dependence, SES, and diagnosis of any psychiatric disorders) were estimated as means and standard deviations (*SD*) for continuous variables and as frequencies for all other variables (Table 1). Listwise exclusion was applied for missing values and a quality check was applied for cannabis use: participants who stated never to have used at age 22, while they indicated cannabis use at age 19, were removed from the original sample of 562 participants ($N = 10$). First exploratory analyses including *t*-tests for continuous variables and $\chi 2$ test for categorical variables were conducted to compare the 3 groups of change in use (decrease, unchanged, increase) (Table 2).

Regressions (ordinal and linear) were carried out according to our hypotheses with either cannabis use or the change in cannabis use as the outcome measure and, respectively, cannabis use, age of first use, CAPE*Total*, CAPE*PosFreq* and CAPE*PosDis* score as predictors. The predictor variables were tested a priori to verify there was no violation of the assumption of no multicollinearity (see T1 in supplements). We first investigated model (I) correcting for gender identification and site. In model (II), the other covariates were additionally included. Post-hoc analyses were performed with the changes in cannabis use and the frequency and distress scores of the positive subscales as outcome variables.

3. Results

3.1. Sample characteristics

Of the 1434 subjects who participated in FU2 and FU3 the IMAGEN study, 562 subjects indicated ever use of cannabis at age 19 and

Table 1
Sample characteristics of total study sample ($n = 552$) by gender identification at age 19 and age 22.

Characteristics	Total sample		*N* available for analyses	*p*-Value[a,b]
N	552			
Gender identification	Female	Male	Female/male	
	258	294		
Parental socio-economic status (SES)* ($M \pm SD$)	5.94 ± 0.90	5.86 ± 0.93	215/244	.382
Ethnicity*			258/294	.351
Central European	236	270		
Black or mixed Black	8	5		
Asian or mixed Asian	7	13		
Other or mixed other	7	6		
Recruitment site (*N*)			258/294	.534
London	36	38		
Paris	45	43		
Berlin	29	22		
Hamburg	33	47		
Dresden	21	31		
Dublin	25	38		
Nottingham	40	44		
Mannheim	29	31		
Age of onset of cannabis use* ($M \pm SD$)	15.94 ± 1.59	15.84 ± 1.71	143/217	.583
				p-Value[a,c]
Total frequency of PLEs (CAPE*Total*)				.000
Age 19 ($M \pm SD$)	64.83 ± 12.41	62.12 ± 11.74	258/294	
Age 22 ($M \pm SD$)	62.26 ± 11.03	60.21 ± 11.19	254/289	
Frequency of positive PLEs (CAPE*PosFreq*)				.000
Age 19 ($M \pm SD$)	1.32 ± 0.24	1.32 ± 0.25	258/294	
Age 22 ($M \pm SD$)	1.25 ± 0.22	1.26 ± 0.22	254/289	
Distress of positive PLEs (CAPE*PosDis*)				.000
Age 19 ($M \pm SD$)	1.79 ± 0.48	1.59 ± 0.50	246/286	
Age 22 ($M \pm SD$)	2.73 ± 0.49	2.50 ± 0.45	230/272	
Cannabis use within last 12 month*				.000
Age 19 (*yes*/*no*)	192/66	233/61	258/294	
Age 22 (*yes*/*no*)	153/105	225/69	258/294	
Other illicit drug use ever*				.000
Age 19 (*yes*/*no*)	89/169	110/184	258/294	
Age 22 (*yes*/*no*)	140/118	185/109	258/294	
Nicotine dependence*				.030
Age 19 ($M \pm SD$)	0.57 ± 1.38	0.70 ± 1.40	258/294	
Age 22 ($M \pm SD$)	0.39 ± 1.13	0.64 ± 1.42	258/294	
Any disorder (clinical rating, DSM-IV)*				.000
Age 19 (*yes*/*no*)	68/175	30/245	243/275	
Age 22 (*yes*/*no*)	61/134	40/163	195/203	

Annotations: N = sample size; M = mean; SD = standard deviation; f = female; m = male; *details of assessment can be found in supplements; [a]according to one-way ANOVA or $\chi 2$ tests to test for possible differences in [b]gender groups or [c]between age 19 and age 22 for the total sample.

provided data for both follow up time points. After inconsistency checks for cannabis use (see 2.3.), 552 subjects who used cannabis at least once were included in our analysis (221 from UK, 88 from France and 243 from Germany). Of those, nearly all ($n = 549$) reported to have experienced at least one psychotic experience of any form at age 19. Average age at FU2 was 19.08 years ($SD = 0.78$), ranging from 17 to 21 years. Average age at FU3 was 22.59 years ($SD = 0.69$) ranging from 20 to 25 years. The average time span between two timepoints was 3.51 years ($SD = 0.74$) (Table 1).

3.2. Changes in cannabis consumption over time

In this sample of 552 ever users of cannabis, 37.9% of all participants reduced their cannabis use between age 19 and age 22, about a third showed no change (33.5%), and 28.4% increased their cannabis use over the course of 3 years. More participants reported no use of cannabis within the past year at age 22 (31.5%) than at age 19 (23%). Change in cannabis use was normally distributed (Fig. 1) and sample characteristics stratified for three groups (decrease, unchanged, increase) are shown in Table 2.

In line with our hypothesis, cannabis use at age 19 in the ordinal logistic regression analysis was found to predict cannabis use at age 22 in model (I) ($\beta = 0.536$, $SD = 0.042$; Wald $\chi 2(1) = 160.050$, $p < .001$) with an estimated odds ratio of 1.7-fold (95% CI, 1.573 to 1.857) for every unit increase of cannabis use at age 19. Also, gender was found to contribute to the model as covariate ($\beta = 0.643$, $SD = 0.163$; Wald $\chi 2(1) = 15.52$, $p < .001$) with an estimated odds ratio of nearly 1.9-fold (95% *CI*, 1.382 to 2.621) for male gender identification. In model (II) age of first use and other illicit drug use also showed a significant association (see T2 in supplements).

3.3. Age of first use and change in cannabis use

Testing whether early age of onset is predictive of an increase in cannabis use from age 19 to age 22 in model (I), we found that age of first use was predictive for the observed change in cannabis consumption, with later age increasing the odds for an increase in consumption ($\beta = 0.180$, $SD = 0.057$; Wald $\chi 2(1) = 9.92$, $p = .002$). The estimated odds ratio favored a positive relationship of 1.2-fold (95% CI, 1.070 to 1.340) for every year later the first use occurred (Fig. 2). Thus, our hypothesis was not confirmed that early age of onset is predictive of a later increase in cannabis use, with results even pointing in a different direction. In model (II), other illicit drug use, nicotine dependence score, SES and psychiatric diagnosis were introduced as covariates, of which other illicit drug use ever significantly contributed to the increase of cannabis use from age 19 to 22 (Table 3).

3.4. Association between PLEs at age 19 and change in cannabis use between age 19 and 22

We did not find PLEs at age 19 to be predictive of the change in cannabis use from age 19 and 22 in model (I) using gender and site as covariates (Table 4). Also, no significant association was found for any of the CAPE subscales: CAPE*Total*; CAPE*PosFreq*; CAPE*PosDis*. Applying model (II) with age of first use of cannabis, other illicit drug use ever, smoking and SES did not change the predictive value of PLEs (Table 4).

We also explored whether PLEs at age 22 are significantly associated with changes in cannabis use from age 19 to 22, and again observed no significant association, neither in model (I) nor in model (II) (see T3 in supplements).

3.5. Association between current PLEs and current cannabis use at age 19 or 22

We tested whether current cannabis use at age 19 or 22 is associated with current PLEs at age 19 or 22, respectively. In model (I), an association at age 19 was not confirmed, whereas at age 22, we found frequency of cannabis use to be associated with the CAPE*Total* score ($\beta = 0.700$, $SD = 0.212$; Wald $\chi 2(1) = 10.812$, $p = .001$) at age 22 in model (I). When including the covariates in the analysis (model II), only psychiatric diagnoses and SES were significantly associated with the CAPE*Total* score (Table 5).

Table 2
Sample characteristics of total sample (n = 552) stratified by change in cannabis use between age 19 and age 22: decrease, unchanged or increase.

	Group: change in cannabis use from age 19 to 22						*p*-Value [a]	
	Decrease		Unchanged		Increase			
N	209		185		158			
Gender identification (*female/male*)	110/99		81/104		67/81		.093	
Timepoint of assessment	*Age 19*	*Age 22*	*Age 19*	*Age 22*	*Age 19*	*Age 22*	*Age 19*	*Age 22*
Total frequency of PLEs (CAPE*Total*) (*M* ± *SD*)	63.90 ± 12.83	60.50 ± 10.48	63.39 ± 12.13	62.97 ± 12.53	62.69 ± 11.16	59.66 ± 11.46	.638	.021
Frequency of positive PLEs (CAPE*PosFreq*) (*M* ± *SD*)	1.33 ± 0.24	1.23 ± 0.19	1.32 ± 0.26	1.28 ± 0.25	1.31 ± 0.23	1.24 ± 0.23	.811	.077
Distress of positive PLEs (CAPE*PosDis*) (*M* ± *SD*)	1.75 ± 0.52	2.64 ± 0.52	1.63 ± 0.47	2.59 ± 0.47	1.65 ± 0.50	2.56 ± 0.47	.054	.294
Age of onset of cannabis use* (*M* ± *SD*)	15.78 ± 1.61	15.61 ± 1.75	15.14 ± 1.42	15.11 ± 1.64	16.31 ± 1.43	16.36 ± 1.65	.000	.000
Cannabis use within last 12 month* (*yes/no*)	209/0	95/114	125/60	125/60	91/67	158/0	.000	.000
Other illicit drug use ever* (*yes/no*)	88/121	88/121	72/113	79/106	39/119	88/60	.002	.002
Nicotine dependence* (*M* ± *SD*)	0.69 ± 1.49	0.49 ± 1.23	0.70 ± 1.37	0.56 ± 1.33	0.51 ± 1.29	0.51 ± 1.27	.356	.885
Socio-economic status* (*M* ± *SD*)	5.94 ± 0.86	-[b]	5.91 ± 1.00	-[b]	5.82 ± 0.89	-[b]	.530	-[b]
Any disorder (clinical rating, DSM-IV)* (*yes/no*)	41/158	39/106	35/138	38/98	7/56	22/124	.373	.348

Annotations: *N* = sample size; *M* = mean; *SD* = standard deviation; *details of assessment can be found in supplements; [a]according to one-way ANOVA or $\chi 2$ tests to test for possible differences between groups; [b]parental socio-economic status was assessed at age 14 and used for our analyses.

3.6. Association between perceived stress and PLEs and between perceived stress and cannabis use

In exploratory analyses, we observed a positive correlation for perceived stress at age 22 and the CAPE*Total* score ($r(539) = 0.48$, $p < .001$), the CAPE*PosFreq* scale ($r(539) = 0.305$, $p < .001$) and the CAPE*PosDis* scale ($r(539) = 0.308$, $p < .001$), respectively (Fig. 3). For perceived stress and current cannabis use at age 22, no significant association was found ($r_\tau = -0.026$, $p = .428$).

4. Discussion

In this longitudinal study in 552 subjects from the general population, we investigated whether cannabis use and its change between age 19 and 22 are associated with PLEs, and we explored whether perceived stress is associated with cannabis use or PLEs. We observed that cannabis use at age 19 was positively associated with cannabis use three years later (age 22). Surprisingly, later first use of cannabis was associated with an increase in cannabis use between age 19 and 22. Regarding the "cannabis discontinuation hypothesis" (Sami et al., 2019; van Gastel et al., 2014), we could not confirm that (distressful) PLEs predict subsequent reductions in cannabis use. Instead, we observed that frequency of cannabis use was positively associated with PLEs at age 22, however, this finding was no longer significant after including presence of psychiatric diagnoses as a covariate. In our exploratory analysis, we observed perceived stress to be associated with PLEs at age 22, but not with cannabis use.

Regarding our first results, observing that cannabis use at age 19 is associated with cannabis use 3 years later is a plausible finding, which confirms previous study results (Chen et al., 1997; Jones et al., 2016; Patton et al., 2007). The frequency of cannabis use tends to increase in puberty, and on average still continues increasing between age 19 and 22 (Melchior et al., 2008), which was also found in our sample. From age 19 on, different trajectories can be observed in our data, including no change of use as well as increases or decreases in cannabis use. Surprisingly, in our sample the age of first use of cannabis was positively correlated with change in cannabis use from age 19 to 22, indicating that those who initiated use at age 15 and later were more likely to increase their use between age 19 and 22 than those who started earlier. While we hypothesized a straightforward association of early first use with higher frequency in cannabis use, some studies indeed suggest more complex trajectories of cannabis use across adolescence and

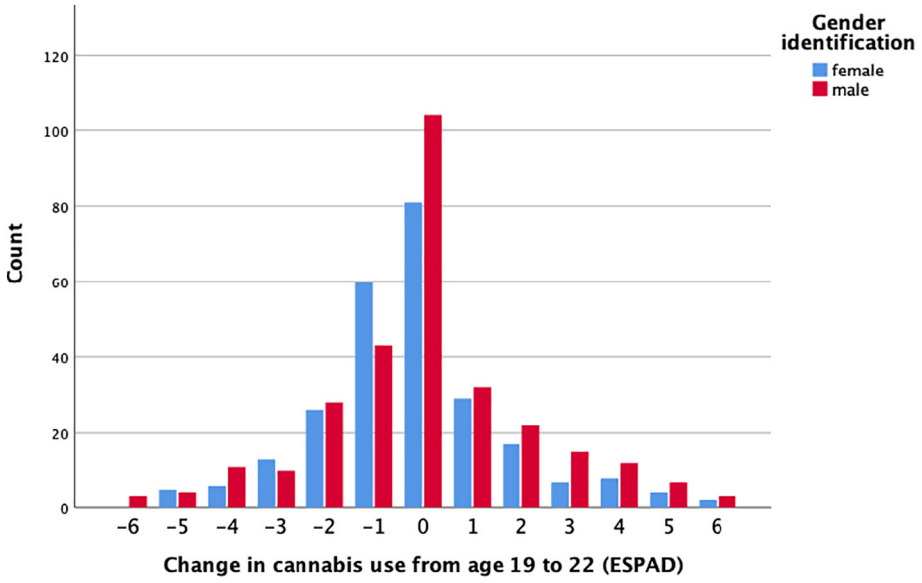

Fig. 1. Changes in cannabis use (for last 12 month) from age 19 to age 22 stratified for gender identification. Differences according to ESPAD categories: never (0); once or twice (1); 3-5 times (2); 6-9 times (3); 10-19 times (4); 20-39 times (5); 40 times or more (6).

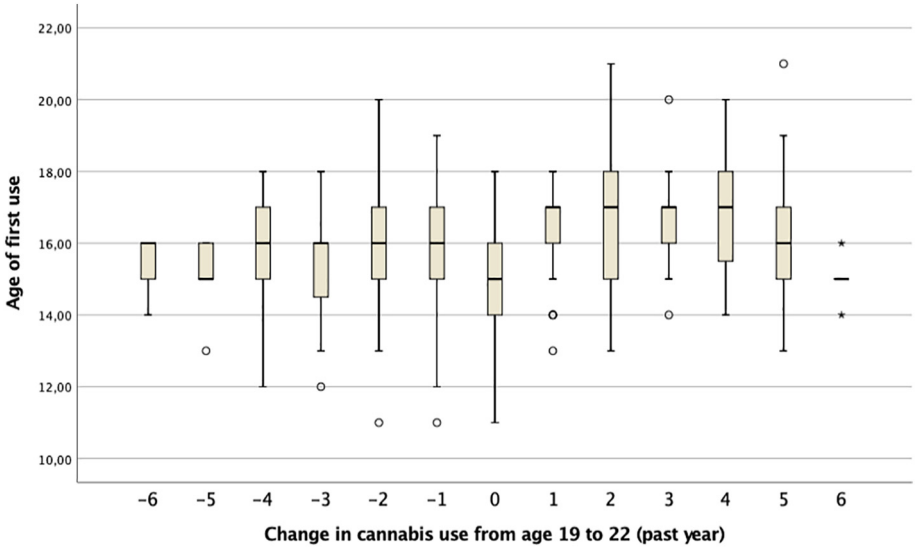

Fig. 2. Boxplot for changes in cannabis use within past year and age of first use of cannabis.

early adulthood (Scholes-Balog et al., 2016; Taylor et al., 2017). According to Scholes-Balog et al. (2016), early-onset cannabis users often start before the age of 15 and usually show persistent use throughout adolescence (1/month), whereas late-onset users usually start after age 15 and tend to use cannabis less often (3–5/year). In our sample, first users at age 15 decreased their use between 19 and 22, which does not support the hypothesis of a rather persistent use of "early-onset" users. Late-onset users in our study increased their use during early adulthood, which raises the concern of persisting harmful use. Given that our sample was followed up 3 times since the age of 14 (Schumann et al., 2010), it is possible that our results partly reflect a selection bias inherent to the longitudinal study design. Dropouts in longitudinal studies are more likely to use substances and tend to report higher mean use of substances at baseline than non-dropouts (Snow et al., 1992), which could affect our final sample at age 22 and contribute to an underestimation of use. Unlike hypothesized (Mullin et al., 2012; Van Gastel et al., 2014), we did not find an association between PLEs at age 19 (or 22) and the change in cannabis use during this observation period. Therefore, the "cannabis discontinuation hypothesis" (Sami et al., 2019; Van Gastel et al., 2012) was not confirmed.

Regarding current cannabis use predicting PLEs at the same time point, the occurrence of other psychiatric diagnoses explained the

Table 3
Ordinal regression coefficients (β) and *p*-values for the association between age of first use of cannabis and changes in cannabis use between age 19 and 22 (differences of ESPAD scores) for model (I) and models (II).

Model	Variable	Association with changes in cannabis use	
		β	*p*-Value
Model (I)	Age of first use of cannabis	*0.180*	*.002*
	Male gender identification	0.268	.165
	Recruitment site	−0.456 to 0.19	.05 to .93
Model (II)	Age of first use of cannabis	*0.195*	*.011*
	Male gender identification	0.254	.323
	Recruitment site	−0.391 to 0.617	.179 to .684
	Other illicit drug use ever	*0.719*	*.023*
	Nicotine dependence	−0.073	.400
	Socio-economic status	−0.159	.207
	Any disorder (clinical rating, DSM-IV)	0.290	.309

Annotations: For model (II), associations between all factors and change in cannabis use are also displayed. βs with a *p*-value below 0.05 are shown in italic.

Table 4
Ordinal regression coefficients (β) and *p*-values for the association between CAPE scores at age 19 (CAPE*Total*; CAPE*PosFreq*; CAPE*PosDis*) and changes in cannabis use (differences of ESPAD scores) for model (I) and models (II).

Model	Variable	Association with changes in cannabis use	
		β	*p*-Value
Predictor: CAPE*Total*			
Model (I)	CAPE*Total*	−0.003	.668
	Male gender identification	0.264	.086
	Recruitment site	−0.475 to 0.285	.10 to .638
Model (II)	CAPE*Total*	−0.001	.910
	Male gender identification	0.187	.417
	Recruitment site	−0.874 to 0.188	.038 to .664
	Age of first use of cannabis	0.141	.054
	Other illicit drug use ever	*−0.551*	*.024*
	Nicotine dependence	0.024	.740
	Socio-economic status	−0.121	.290
	Any disorder (clinical rating, DSM-IV)	−0.042	.897
Predictor: CAPE*PosFreq*			
Model (I)	CAPE*PosFreq*	−0.122	.686
	Male gender identification	0.271	.075
	Recruitment site	−0.407 to 0.391	.203 to .737
Model (II)	CAPE*PosFreq*	−0.239	.595
	Male gender identification	0.193	.403
	Recruitment site	−0.871 to 0.177	.039 to .682
	Age of first use of cannabis	0.140	.055
	Other illicit drug use ever	*−0.540*	*.027*
	Nicotine dependence	0.025	.730
	Socio-economic status	−0.124	.277
	Any disorder (clinical rating, DSM-IV)	−0.012	.968
Predictor: CAPE*PosDis*			
Model (I)	CAPE*PosDis*	−0.257	.101
	Male gender identification	0.173	.275
	Recruitment site	−0.410 to 0.343	.153 to .269
Model (II)	CAPE*PosDis*	−0.292	.199
	Male gender identification	−0.015	.948
	Recruitment site	−0.841 to 0.141	.049 to .747
	Age of first use of cannabis	0.143	.059
	Other illicit drug use ever	*−0.546*	*.032*
	Nicotine dependence	0.029	.691
	Socio-economic status	−0.129	.267
	Any disorder (clinical rating, DSM-IV)	−0.045	.881

Annotations: For model (II), associations between all factors and change in cannabis use are also displayed. βs with a *p*-value below 0.05 are shown in italic.

Table 5
Regression coefficients (β) and *p*-values for the association between CAPE*Total*; and current cannabis use for model (I) and models (II) at age 19 and age 22 respectively.

Model	Variable	Association with CAPE*Total*	
		β	*p*-Value
Predictor: cannabis use at age 19			
Model (I)	Cannabis use at age 19	0.422	.079
	Male gender identification	*−3.133*	*.002*
	Recruitment site	−0.2.490 to 0.820	.231 to .689
Model (II)	Cannabis use at age 19	0.055	.887
	Male gender identification	−0.779	.576
	Recruitment site	−4.467 to 0.342	.011 to .951
	Age of first use of cannabis	−0.503	.256
	Other illicit drug use ever	1.040	.501
	Nicotine dependence	0.351	.426
	Socio-economic status	0.467	.509
	Any disorder (clinical rating, DSM-IV)	*13.931*	*.000*
Predictor: cannabis use at age 22			
Model (I)	Cannabis use at age 22	*0.700*	*.001*
	Male gender identification	*−2.728*	*.006*
	Recruitment site	0.228–5.241	.009 to .910
Model (II)	Cannabis use at age 22	0.092	.774
	Male gender identification	−1.085	.439
	Recruitment site	−3.013 to 4.781	.042 to .267
	Age of first use of cannabis	−0.275	.502
	Other illicit drug use ever	2.248	.194
	Nicotine dependence	*0.968*	*.047*
	Socio-economic status	*−1.383*	*.048*
	Any disorder (clinical rating, DSM-IV)	*13.237*	*.000*

Annotations: For model (II), associations between all factors and change is cannabis use are also displayed. βs with a *p*-value below 0.05 are shown in italic.

occurrence of PLEs better than cannabis use (or male gender) at both time points. This may reflect the genetic overlap between several mental disorders (Witt et al., 2017) or common environmental factors contributing to both cannabis use disorder and other mental disorders (Heinz et al., 2013; Van Os et al., 2010). Also, the fact that we did not observe an association may be due to the rather low clinical load of our sample. Our PLE score was rather low compared with Barragan et al. (2011) ($M = 68.3$, $SD = 13.4$) and this restricted variance may limit significant associations with individual differences in cannabis use.

Finally, the frequency of PLEs was significantly and positively associated with perceived stress. It has been hypothesized that stress exposure contributes to the manifestation of psychotic experiences (Heinz et al., 2020) or that perceived stress levels indicate an increased vulnerability for severe mental disorders (Fusar-Poli et al., 2017). However, our data are only correlational, and the directionality of this interaction needs to be examined in longitudinal studies. On the other hand, we did not find a significant association between perceived stress and cannabis use, rendering it rather unlikely that cannabis was used as self-medication to reduce stress by a majority of the sample (Mané et al., 2015).

4.1. Limitations

The major limitation of this study is that selective drop-outs may have occurred during the observation period. This could reduce power to detect effect of increased cannabis use on PLEs. Also, the fact that consumption data were gathered by self-report via online assessment could possibly lead to either over- or underreporting of illegal drug consumption including cannabis use. However, recent studies have shown that web-based questionnaires are a suitable instrument for scientific research and potential biases regarding drug use are unlikely to be systematic (Martin-Willett et al., 2020; Meyerson and Tryon, 2003; Vleeschouwer et al., 2014). Another potential limitation is that the CAPE questionnaire assesses some PLEs that can be hard to distinguish from acute intoxication effects of cannabis. There is, however, some evidence that high CAPE scores associated with acute cannabis intoxication also reflect psychosis proneness (Genetic Risk and Outcome in Psychosis (GROUP) investigators, 2011).

5. Conclusion

Altogether, we observed a general increase in cannabis use across early adulthood and a positive correlation with (late) age of first use, supporting the notion of diverse trajectories in cannabis use in the general population (Bourque et al., 2017; Patton et al., 2007). We did not find an association between PLEs and subsequent cannabis use, thus not confirming the hypothesis that distressful or other PLEs induce a decline in cannabis use (Van Gastel et al., 2014). Interestingly, perceived stress at age 22 was associated with PLEs (but not with cannabis consumption), emphasizing the importance of perceived stress for psychosis risk (Fusar-Poli et al., 2017). These findings suggest to further explore stress effects on the manifestation of PLEs and vice versa.

CRediT authorship contribution statement

Laura S. Daedelow was involved in the conceptualization of the study, collecting and analyzing the data, interpreting the data and drafting the paper.

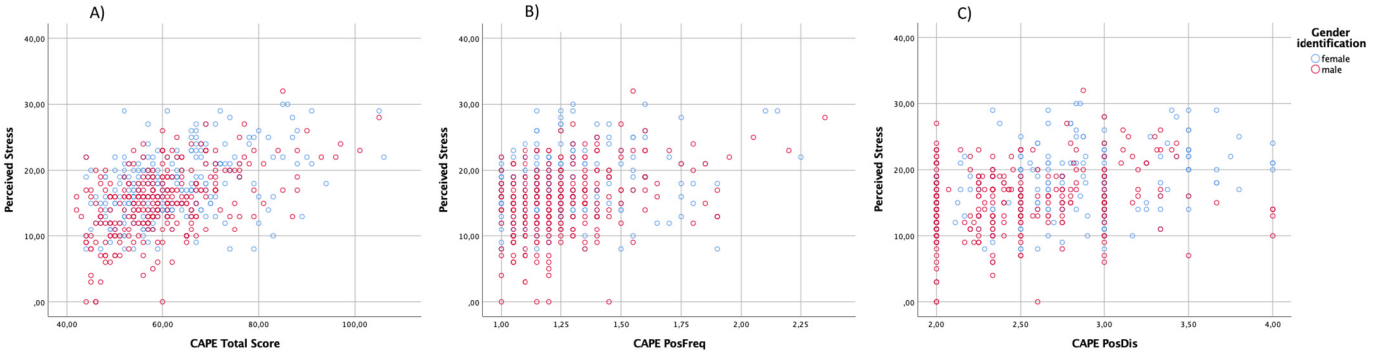

Fig. 3. Scatterplot for association of perceived stress (assessed by PSS) and PLEs at age 22 respectively: A) CAPE*Total* Score B) CAPE*PosFreq*: Frequency of positive dimension C) CAPE*PosDis*: Distress of positive dimension.

Andreas Heinz was involved in the design of the study, interpretation of the data, revision of the draft and supervision of the project.

Annika Rosenthal, Moritz Berning and Hayley Murray were involved in collecting the data and in a critical revision after the draft.

Anita Hardon, Nicole Y.L. Oei and Reinout W. Wiers were involved in the conceptualization of the study, in the supervision of the ERANID project and in a critical revision after the draft.

Tobias Banaschewski, Arun L.W. Bokde, Rüdiger Brühl, Erin Burke Quinlan, H. Valerie Curran, Sylvane Desrivières, Herta Flor, Antoine Grigis, Hugh Garavan, Jakob Kaminski, Jean-Luc Martinot, Marie-Laure Paillère Martinot, Eric Artiges, Frauke Nees, Dimitri Papadopoulos Orfanos, Tomáš Paus, Luise Poustka, Sarah Hohmann, Sabina Millenet, Juliane H. Fröhner, Michael N. Smolka, Henrik Walter, Robert Whelan, Gunter Schumann were involved in the design of the IMAGEN study and a critical revision after the draft.

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Declaration of competing interest

Dr. Banaschewski served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Shire. He received conference support or speaker's fee by Lilly, Medice, Novartis and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships. The other authors report no biomedical financial interests or potential conflicts of interest.

References

Arranz, S., Monferrer, N., Algora, M.J., Cabezas, A., Sole, M., Vilella, E., Labad, J., Sanchez-Gistau, V., 2018. The relationship between the level of exposure to stress factors and cannabis in recent onset psychosis. Schizophr. Res. 201, 352–359.

Barragan, M., Laurens, K.R., Navarro, J.B., Obiols, J.E., 2011. Psychotic-like experiences and depressive symptoms in a community sample of adolescents. European Psychiatry 26, 396–401.

Bernardini, F., Gobbicchi, C., Attademo, L., Puchalski, S., Trezzi, R., Moretti, P., Tortorella, A., Loas, G., 2018. Cannabis use, psychotic like experiences and aberrant salience in a sample of Belgian students. J. Nerv. Ment. Dis. 206, 493–500.

Bourque, J., Afzali, M.H., O'Leary-Barrett, M., Conrod, P., 2017. Cannabis use and psychotic-like experiences trajectories during early adolescence: the coevolution and potential mediators. J. Child Psychol. Psychiatry 58, 1360–1369. https://doi.org/10.1111/jcpp.12765.

Chen, K., Kandel, D.B., Davies, M., 1997. Relationships between frequency and quantity of marijuana use and last year proxy dependence among adolescents and adults in the United States. Drug Alcohol Depend. 46, 53–67. doi:10.1016/S0376-8716(97)00047-1.

Cohen, S., Kamarck, T., Mermelstein, R., 1994. Perceived stress scale. Meas. Stress A Guid. Heal. Soc. Sci. 10.

Degenhardt, L., Saha, S., Lim, C.C.W., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Andrade, L.H., Bromet, E.J., Bruffaerts, R., Caldas-de-Almeida, J.M., 2018. The associations between psychotic experiences and substance use and substance use disorders: findings from the World Health Organization World Mental Health surveys. Addiction 113, 924–934.

DeVylder, J.E., Oh, H.Y., Kelleher, I., 2018. Commentary on Degenhardt et al. (2018): cause or consequence? Disentangling the relationship between psychosis and substance use. Addiction 113, 935–936.

Di Forti, M., Quattrone, D., Freeman, T.P., Tripoli, G., Gayer-Anderson, C., Quigley, H., Rodriguez, V., Jongsma, H.E., Ferraro, L., La Cascia, C., 2019. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry 6, 427–436.

ERANID, 2015. A Strategic Research Agenda for Europe in the Field of Illicit Drugs.

European Monitoring Centre for Drugs and Drug Addiction (EMCDD), 2019. European Drug Report, European Union Publications Office. doi:https://doi.org/10.1097/JSM.0b013e31802b4fda.

Fusar-Poli, P., Tantardini, M., De Simone, S., Ramella-Cravaro, V., Oliver, D., Kingdon, J., Kotlicka-Antczak, M., Valmaggia, L., Lee, J., Millan, M.J., Galderisi, S., Balottin, U., Ricca, V., McGuire, P., 2017. Deconstructing vulnerability for psychosis: meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. Eur. Psychiatry 40, 65–75. doi:10.1016/j.eurpsy.2016.09.003.

Hall, W., Degenhardt, L., 2008. Cannabis use and the risk of developing a psychotic disorder. World Psychiatry 7, 68.

Heinz, A., Deserno, L., Reininghaus, U., 2013. Urbanicity, social adversity and psychosis. World Psychiatry 12, 187–197.

Heinz, A., Zhao, X., Liu, S., 2020. Implications of the association of social exclusion with mental health. JAMA Psychiatry 77, 113–114. https://doi.org/10.1001/jamapsychiatry.2019.3009.

Hibell, B., Andersson, B., Bjarnason, T., Kokkevi, A., Morgan, M., Narusk, A., Ahlström, S., 1997. The 1995 ESPAD Report. Alcohol and Other Drug Use Among Students in 26 European Countries.

Jones, C.B., Hill, M.L., Pardini, D.A., Meier, M.H., 2016. Prevalence and correlates of vaping cannabis in a sample of young adults. Psychol. Addict. Behav. https://doi.org/10.1037/adb0000217.

Karcher, N. R., Shiffman, J. E., Barch, D. M. 2020. Environmental risk factors and psychotic-like symptoms in children aged 9–11. J. Am. Acad. Child Psy. S0890-8567.

Kibel, D.A., Laffont, I., Liddle, P.F., 1993. The composition of the negative syndrome of chronic schizophrenia. Br. J. Psychiatry 162, 744–750.

Konings, M., Bak, M., Hanssen, M., Van Os, J., Krabbendam, L., 2006. Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. Acta Psychiatr. Scand. 114, 55–61.

Konings, M., Henquet, C., Maharajh, H.D., Hutchinson, G., Van Os, J., 2008. Early exposure to cannabis and risk for psychosis in young adolescents in Trinidad. Acta Psychiatr. Scand. 118, 209–213.

Mané, A., Fernández-Expósito, M., Bergé, D., Gómez-Pérez, L., Sabaté, A., Toll, A., Diaz, L., Diez-Aja, C., Perez, V., 2015. Relationship between cannabis and psychosis: reasons for use and associated clinical variables. Psychiatry Res. 229, 70–74.

Marconi, A., Di Forti, M., Lewis, C.M., Murray, R.M., Vassos, E., 2016. Meta-analysis of the association between the level of cannabis use and risk of psychosis. Schizophr. Bull. 42, 1262–1269.

Mark, W., Toulopoulou, T., 2016. Psychometric properties of "community assessment of psychic experiences": review and meta-analyses. Schizophr. Bull. 42, 34–44. https://doi.org/10.1093/schbul/sbv088.

Mark, W., Toulopoulou, T., 2017. Validation of the Chinese version of Community Assessment of Psychic Experiences (CAPE) in an adolescent general population. Asian J. Psychiatr. 26, 58–65.

Martin-Willett, R., Helmuth, T., Abraha, M., Bryan, A.D., Hitchcock, L., Lee, K., Bidwell, L.C., 2020. Validation of a multisubstance online timeline followback assessment. Brain Behav. 10, e01486. https://doi.org/10.1002/brb3.1486.

Melchior, M., Chastang, J.-F., Goldberg, P., Fombonne, E., 2008. High prevalence rates of tobacco, alcohol and drug use in adolescents and young adults in France:

results from the GAZEL Youth study. Addict. Behav. 33, 122–133. doi:10.1016/j.addbeh.2007.09.009.
Meyerson, P., Tryon, W.W., 2003. Validating internet research: a test of the psychometric equivalence of Internet and in-person samples. Behav. Res. Methods, Instruments. Comput. 35, 614–620. https://doi.org/10.3758/BF03195541.
Moore, T.H.M., Zammit, S., Lingford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., Lewis, G., 2007. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 370, 319–328.
Morgan, C.J.A., Curran, H.V., 2008. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br. J. Psychiatry 192, 306–307.
Mossaheb, N., Becker, J., Schaefer, M.R., Klier, C.M., Schloegelhofer, M., Papageorgiou, K., Amminger, G.P., 2012. The Community Assessment of Psychic Experience (CAPE) questionnaire as a screening-instrument in the detection of individuals at ultra-high risk for psychosis. Schizophr. Res. 141, 210–214.
Mullin, K., Gupta, P., Compton, M.T., Nielssen, O., Harris, A., Large, M., 2012. Does giving up substance use work for patients with psychosis? A systematic meta-analysis. Aust. New Zeal. J. Psychiatry 46, 826–839. https://doi.org/10.1177/0004867412440192.
Murray, R.M., Hall, W., 2020. Will legalization and commercialization of cannabis use increase the incidence and prevalence of psychosis? JAMA Psychiatry
Nesvåg, R., Reichborn-Kjennerud, T., Gillespie, N.A., Knudsen, G.P., Bramness, J.G., Kendler, K.S., Ystrom, E., 2017. Genetic and environmental contributions to the association between cannabis use and psychotic-like experiences in young adult twins. Schizophr. Bull. 43, 644–653.
Patton, G.C., Coffey, C., Lynskey, M.T., Reid, S., Hemphill, S., Carlin, J.B., Hall, W., 2007. Trajectories of adolescent alcohol and cannabis use into young adulthood. Addiction 102, 607–615.
Proal, A.C., Fleming, J., Galvez-Buccollini, J.A., DeLisi, L.E., 2014. A controlled family study of cannabis users with and without psychosis. Schizophr. Res. 152, 283–288.
Ragazzi, T.C.C., Shuhama, R., Menezes, P.R., Del-Ben, C.M., 2018. Cannabis use as a risk factor for psychotic-like experiences: a systematic review of non-clinical populations evaluated with the community assessment of psychic experiences. Early Interv. Psychiatry 12, 1013–1023.
Sami, M., Notley, C., Kouimtsidis, C., Lynskey, M., Bhattacharyya, S., 2019. Psychotic-like experiences with cannabis use predict cannabis cessation and desire to quit: a cannabis discontinuation hypothesis. Psychol. Med. 49, 103–112.
Schlier, B., Jaya, E.S., Moritz, S., Lincoln, T.M., 2015. The community assessment of psychic experiences measures nine clusters of psychosis-like experiences: a validation of the German version of the CAPE. Schizophr. Res. 169, 274–279.
Scholes-Balog, K.E., Hemphill, S.A., Evans-Whipp, T.J., Toumbourou, J.W., Patton, G.C., 2016. Developmental trajectories of adolescent cannabis use and their relationship to young adult social and behavioural adjustment: a longitudinal study of Australian youth. Addict. Behav. 53, 11–18. https://doi.org/10.1016/j.addbeh.2015.09.008.
Schubart, C.D., Sommer, I.E.C., van Gastel, W.A., Goetgebuer, R.L., Kahn, R.S., Boks, M.P.M., 2011a. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophr. Res. 130, 216–221.
Schubart, C.D., Van Gastel, W.A., Breetvelt, E.J., Beetz, S.L., Ophoff, R.A., Sommer, I.E.C., Kahn, R.S., Boks, M.P.M., 2011b. Cannabis use at a young age is associated with psychotic experiences. Psychol. Med. 41, 1301–1310.
Schumann, G., Loth, E., Banaschewski, T., Barbot, A., Barker, G., Büchel, C., Conrod, P.J., Dalley, J.W., Flor, H., Gallinat, J., 2010. The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Mol. Psychiatry 15, 1128–1139.
Seidel, A.-K., Pedersen, A., Hanewinkel, R., Morgenstern, M., 2019. Cessation of cannabis use: a retrospective cohort study. Psychiatry Res. 279, 40–46.
Selten, J.P., Gernaat, H.B., Nolen, W.A., Wiersma, D., van den Bosch, R.J., 1998. Experience of negative symptoms: comparison of schizophrenic patients to patients with a depressive disorder and to normal subjects. Am. J. Psychiat. 155, 350–354.
Shakoor, S., Zavos, H.M.S., McGuire, P., Cardno, A.G., Freeman, D., Ronald, A., 2015. Psychotic experiences are linked to cannabis use in adolescents in the community because of common underlying environmental risk factors. Psychiatry Res. 227, 144–151.
Skinner, R., Conlon, L., Gibbons, D., McDonald, C., 2011. Cannabis use and non-clinical dimensions of psychosis in university students presenting to primary care. Acta Psychiatr. Scand. 123, 21–27.
Snow, D.L., Tebes, J.K., Arthur, M.W., 1992. Panel attrition and external validity in adolescent substance use research. J. Consult. Clin. Psych. 60, 804.
Stefanis, N.C., Hanssen, M., Smirnis, N.K., Avramopoulos, D.A., Evdokimidis, I.K., Stefanis, C.N., Verdoux, H., Van Os, J., 2002. Evidence that three dimensions of psychosis have a distribution in the general population. Psychol. Med. 32, 347–358.
Stefanis, N.C., Delespaul, P., Henquet, C., Bakoula, C., Stefanis, C.N., Van Os, J., 2004. Early adolescent cannabis exposure and positive and negative dimensions of psychosis. Addiction 99, 1333–1341.
Taylor, M., Collin, S.M., Munafò, M.R., MacLeod, J., Hickman, M., Heron, J., 2017. Patterns of cannabis use during adolescence and their association with harmful substance use behaviour: findings from a UK birth cohort. J. Epidemiol. Community Health 71, 764 LP – 770. doi:https://doi.org/10.1136/jech-2016-208503.
Tucker, J.S., Rodriguez, A., Dunbar, M.S., Pedersen, E.R., Davis, J.P., Shih, R.A., D'Amico, E.J., 2019. Cannabis and tobacco use and co-use: trajectories and correlates from early adolescence to emerging adulthood. Drug Alcohol Depend. 204, 107499.
Van Gastel, W.A., Wigman, J.T.W., Monshouwer, K., Kahn, R.S., van Os, J., Boks, M.P.M., Vollebergh, W.A.M., 2012. Cannabis use and subclinical positive psychotic experiences in early adolescence: findings from a Dutch survey. Addiction 107, 381–387.
Van Gastel, W.A., Vreeker, A., Schubart, C.D., MacCabe, J.H., Kahn, R.S., Boks, M.P.M., 2014. Change in cannabis use in the general population: a longitudinal study on the impact on psychotic experiences. Schizophr. Res. 157, 266–270.
Van Os, J., Kenis, G., Rutten, B.P., 2010. The environment and schizophrenia. Nature 468, 203–212.
Verdoux, H., Gindre, C., Sorbara, F., Tournier, M., Swendsen, J.D., 2003. Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. Psychol. Med. 33, 23–32.
Vermeiden, M., Janssens, M., Thewissen, V., Akinsola, E., Peeters, S., Reijnders, J., Jacobs, N., van Os, J., Lataster, J., 2019. Cultural differences in positive psychotic experiences assessed with the Community Assessment of Psychic Experiences-42 (CAPE-42): a comparison of student populations in the Netherlands, Nigeria and Norway. BMC Psychiatry 19, 244.
Vleeschouwer, M., Schubart, C.D., Henquet, C., Myin-Germeys, I., van Gastel, W.A., Hillegers, M.H.J., van Os, J.J., Boks, M.P.M., Derks, E.M., 2014. Does assessment type matter? A measurement invariance analysis of online and paper and pencil assessment of the Community Assessment of Psychic Experiences (CAPE). PLoS One 9, e84011. https://doi.org/10.1371/journal.pone.0084011.
Witt, S.H., Streit, F., Jungkunz, M., Frank, J., Awasthi, S., Reinbold, C.S., Treutlein, J., Degenhardt, F., Forstner, A.J., Heilmann-Heimbach, S., Dietl, L., Schwarze, C.E., Schendel, D., Strohmaier, J., Abdellaoui, A., Adolfsson, R., Air, T.M., Akil, H., Alda, M., Alliey-Rodriguez, N., Andreassen, O.A., Babadjanova, G., Bass, N.J., Bauer, M., Baune, B.T., Bellivier, F., Bergen, S., Bethell, A., Biernacka, J.M., Blackwood, D.H.R., Boks, M.P., Boomsma, D.I., Børglum, A.D., Borrmann-Hassenbach, M., Brennan, P., Budde, M., Buttenschøn, H.N., Byrne, E.M., Cervantes, P., Clarke, T.-K., Craddock, N., Cruceanu, C., Curtis, D., Czerski, P.M., Dannlowski, U., Davis, T., de Geus, E.J.C., Di Florio, A., Djurovic, S., Domenici, E., Edenberg, H.J., Etain, B., Fischer, S.B., Forty, L., Fraser, C., Frye, M.A., Fullerton, J.M., Gade, K., Gershon, E.S., Giegling, I., Gordon, S.D., Gordon-Smith, K., Grabe, H.J., Green, E.K., Greenwood, T.A., Grigoroiu-Serbanescu, M., Guzman-Parra, J., Hall, L.S., Hamshere, M., Hauser, J., Hautzinger, M., Heilbronner, U., Herms, S., Hitturlingappa, S., Hoffmann, P., Holmans, P., Hottenga, J.-J., Jamain, S., Jones, I., Jones, L.A., Juréus, A., Kahn, R.S., Kammerer-Ciernioch, J., Kirov, G., Kittel-Schneider, S., Kloiber, S., Knott, S.V., Kogevinas, M., Landén, M., Leber, M., Leboyer, M., Li, Q.S., Lissowska, J., Lucae, S., Martin, N.G., Mayoral-Cleries, F., McElroy, S.L., McIntosh, A.M., McKay, J.D., McQuillin, A., Medland, S.E., Middeldorp, C.M., Milaneschi, Y., Mitchell, P.B., Montgomery, G.W., Morken, G., Mors, O., Mühleisen, T.W., Müller-Myhsok, B., Myers, R.M., Nievergelt, C.M., Nurnberger, J.I., O'Donovan, M.C., Loohuis, L.M.O., Ophoff, R., Oruc, L., Owen, M.J., Paciga, S.A., Penninx, B.W.J.H., Perry, A., Pfennig, A., Potash, J.B., Preisig, M., Reif, A., Rivas, F., Rouleau, G.A., Schofield, P.R., Schulze, T.G., Schwarz, M., Scott, L., Sinnamon, G.C.B., Stahl, E.A., Strauss, J., Turecki, G., Van der Auwera, S., Vedder, H., Vincent, J.B., Willemsen, G., Witt, C.C., Wray, N.R., Xi, H.S., Tadic, A., Dahmen, N., Schott, B.H., Cichon, S., Nöthen, M.M., Ripke, S., Mobascher, A., Rujescu, D., Lieb, K., Roepke, S., Schmahl, C., Bohus, M., Rietschel, M., Consortium, B.D.W.G. of the P.G., Consortium, M.D.D.W.G. of the P.G., Consortium, S.W.G. of the P.G, 2017. Genome-wide association study of borderline personality disorder reveals genetic overlap with bipolar disorder, major depression and schizophrenia. Transl. Psychiatry 7, e1155. https://doi.org/10.1038/tp.2017.115.