

Early adolescent cannabis exposure and positive and negative dimensions of psychosis

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ABSTRACT

Aims To investigate the effect of exposure to cannabis early in adolescence on subclinical positive and negative symptoms of psychosis.

Design Cross-sectional survey in the context of an ongoing cohort study.

Setting Government-supported general population cohort study.

Participants A total of 3500 representative 19-year olds in Greece.

Measurements Subjects filled in the 40-item Community Assessment of Psychiatric Experiences, measuring subclinical positive (paranoia, hallucinations, grandiosity, first-rank symptoms) and negative psychosis dimensions and depression. Drug use was also reported on.

Findings Use of cannabis was associated positively with both positive and negative dimensions of psychosis, independent of each other, and of depression. An association between cannabis and depression disappeared after adjustment for the negative psychosis dimensions. First use of cannabis below age 16 years was associated with a much stronger effect than first use after age 15 years, independent of life-time frequency of use. The association between cannabis and psychosis was not influenced by the distress associated with the experiences, indicating that self-medication may be an unlikely explanation for the entire association between cannabis and psychosis.

Conclusions These results add credence to the hypothesis that cannabis contributes to the population level of expression of psychosis. In particular, exposure early in adolescence may increase the risk for the subclinical positive and negative dimensions of psychosis, but not for depression.

KEYWORDS Cannabis, CAPE, psychosis, schizophrenia.

INTRODUCTION

There is evidence that cannabis increases the risk for incident psychotic disorder and poorer prognosis in those with established psychotic disorder, independent of other drug use, premorbid personality traits and early prodromal psychotic states [1–6]. The more distal the use of cannabis in relation to the onset of the disorder, the more powerful the effect [4], with very high risks reported in individuals using in early adolescence [3]. Individuals with pre-existing vulnerability for psychosis may be more

susceptible to the psychosis-inducing effects of cannabis than those without [4,7].

In addition, evidence is accumulating [4,5,7–10] that cannabis has powerful effects on non-clinical positive psychotic experiences that are much more prevalent than DSM- or ICD-defined psychotic disorders but nevertheless show a degree of continuity with more severe states such as schizophrenia [11]. One study reported that cannabis use was also associated independently with the negative dimension of non-clinical psychosis, whereas another, much smaller, study reported a negative association with

introvertive anhedonia, which is also thought to tap into the negative psychosis dimension [12]. Neither study reported an association with the dimension of depression [7,12], whereas a large general population study reported a positive association between cannabis and states of anxiety/depression [13], but another study did not [14].

The fact that cannabis may cause non-clinical expression of psychosis is extremely important, as it suggests that cannabis is feeding the population risk of psychosis at the level of subtle alterations in mental states that may grow out to form the clinical dimensions of positive and negative psychotic symptoms. Given the still early and not yet entirely consistent findings with regard to the effect of cannabis on the non-clinical expression of psychosis, this issue was investigated further using the non-clinical dimensions of psychosis measured with the CAPE (Community Assessment of Psychic Experiences), used in the previous study by Verdoux and colleagues [7]). As an expansion to the previous paper, the CAPE positive psychosis dimension was divided in its clusters of hallucinations, paranoia, grandiosity and first-rank symptom experiences in order to test whether any effect of cannabis was specific for a particular cluster of positive experiences, in particular that of hallucinations versus delusional ideation [15,16]. In addition, the issue of the disproportionately increased risk for schizophrenia associated with cannabis use early in adolescence [3] was also applied to psychotic experiences in the non-clinical domain. Finally, the issue of reversed causality was addressed: distress associated with psychotic experiences results in use of cannabis to reduce distress. This was carried out by measuring not only psychotic experiences, but also the degree of distress associated with them.

METHODS

Sample

The Greek Birth Cohort is an ongoing longitudinal data collection based on the National Perinatal Survey, which was a prospective study of all the 11 048 births throughout Greece between 1 and 30 April 1983 [17]. The study sought and received approval, as required, from both the National Hellenic Research Foundation (NHRF) Institute of Biological Research and Biotechnology (IBRB) and the National Privacy Principles Board.

In the year 1990, when the children were aged 7 years, attempts were made to identify all children at primary schools throughout Greece in order to collect subject and parental postal questionnaires. All participants were assured of confidentiality and anonymity. Completed questionnaires of 6594 individuals and their

parents were merged successfully with corresponding data collected in 1983.

In the year 2001, attempts were made again to locate these adolescents, now aged 18 years, in order to collect subject and parental postal questionnaires once again. Questions were divided into the following sections: family friends and school, general and current health, questions about mood, life-style and hobbies, attitude, biological measurements, nutrition habits, other habits and behaviour. Parents filled in questions about socio-economic factors, family affairs and life-style. A total of 4675 postal adolescent/parent questionnaires were sent out. Individuals were assured that all procedures had been anonymized and that all information obtained was strictly confidential. Of the 4675 individuals, 3016 responded while 716 declined to collaborate. In a second round, another 484 completed questionnaires were collected, making a total of 3500 completed questionnaires at age 18 years.

We applied several tests (χ^2 and *t*-test) in order to evaluate the representativeness of this subsample of 3500, using the following variables: place of birth (urban, rural), birth weight, length at birth, father's occupation, mother's education, sex of the adolescent, marital status, maternal age and region of adolescent's residence. We found no significant differences in the distribution of all the above variables between this subsample and the remainder of the original 1983 sample as a whole (all $P > 0.05$). In particular, adolescents in the subsample and the remainder of the cohort were equally likely to have an urban background (66% and 65%). Although in the subsample there were more adolescents whose mothers had been married when the child was born (99% versus 97%) and less adolescents whose mother's marital status was unknown (0.05% versus 0.68%; $P < 0.0001$), the potential bias in this respect is minimal because of the high proportion of married mothers in both groups. It can be assumed, therefore, that no significant bias between the two samples was introduced.

Cannabis

At age 19 years, participants were asked the following questions: have you ever tried or used one of the substances below—where options used in this analysis were (i) 'cannabis' and (ii) 'ecstasy, heroin, cocaine, amphetamines, LSD or other similar drug'. This latter option (ii) was rated as one item, i.e. there were no ratings for these drugs separately and 'other similar drug' was not defined further. Subjects could indicate 'never', 'once', 'two to four times', 'five times or more', 'systematic use' (defined as daily or almost daily use). The cannabis item will hereafter be referred to as 'cannabis life-time frequency use'. In addition, subjects could indicate at what age they had

started use which was collapsed, guided by previous research [3], into two groups: 15 years or younger and older than 15 years.

Community assessment of psychic experiences

Adolescents filled in the 40-item CAPE [18,19], an instrument that captures variation in the positive and negative dimensions of non-clinical psychotic experiences, and additionally captures variation in depression. External criterion and discriminant validity of these dimensions has been demonstrated previously [7,18,19]. The 40-item CAPE is a self-report instrument and is mainly based on the 21-item 'Peters *et al.* Delusions Inventory' (PDI-21) [20]. The PDI was developed to measure delusional ideation in the general population on a dimensional scale. The PDI is derived from the Present State Examination [21]. Peters and co-workers (1999) toned down the PSE items, by adding 'as if' to the questions to ensure the acceptability of the scale in the general population. In addition, questions are styled in a 'Do you ever feel/think'-fashion in order to study continuous experiences during life-time. The PDI enquires first about the presence of a delusional ideation (measured with dichotomized answer categories: 'Yes' or 'No') and secondly the three dimensions of the delusional experience, namely distress, preoccupation and conviction (measured on a five-point ordinal scale from 1 to 5; 'not at all distressing'-'very distressing'; 'hardly ever think about it'-'think about it all the time'; 'don't believe it's true'-'believe it's absolutely true'). Some modifications and additions were implemented to the PDI to construct the CAPE [18]. First, items on religious delusions were omitted because of concerns that it might confuse religious subjects. Secondly, some items that subjects in previous studies had reported to be ambiguous were omitted or rephrased [22]. Thirdly, two items on auditory hallucinations were added. Fourthly, 14 negative and eight depressive symptom items were added to the PDI. The negative symptom items were derived from the SANS [23] and an instrument of subjective experience of negative symptoms, the SENS [24]. As it is difficult to discriminate between negative and depressive symptoms, items of depressive symptoms that are most specific for depression, i.e. cognitive symptoms of depression (e.g. sadness, pessimism, hopelessness, feeling a failure, feeling guilty) [25], were added to the PDI. Finally, the CAPE was reduced to two-dimensional scales. The first scale scores the frequency of the experience (measured on a four-point scale from 'never', 'sometimes', 'often' to 'nearly always', to avoid 'ticking the middle box' bias) and the second scale scores the degree of distress (measured on a four-point scale from 'not distressed', 'a bit distressed', 'quite distressed' to 'very distressed'). This reduction in

dimensions of the psychotic experience was introduced as previous research with the PDI-21 in a large general population sample (Verdoux *et al.* [22]) had shown that individuals failed to fill in consistently all the dimensional scales of each symptom.

Cape dimensions

The CAPE provides an overall score and a total score per dimension (negative, depressive, positive) by adding up the number of positive answers to the frequency question, and provides a distress score by adding up the scores of the distress questions. A conservative threshold was used by recoding a score of '2' (experiencing the item only 'sometimes' or feeling only 'a bit distressed') to '1'. In order to define a fine data-driven subdivision of clusters of positive experiences of psychosis, a principal component factor analysis followed by varimax rotation was conducted, which revealed four factors of paranoid (persecution, voodoo, references on TV and radio, conspiracy, getting odd looks, things having double meaning, things not what they seem to be), first-rank (thought echo, thought withdrawal, thought broadcasting, thought insertion, feeling controlled, devices influencing person, telepathy) hallucinatory (hearing voices or noises) and grandiose experiences (being special or important). Sum scores for these four clusters were obtained by adding the scores of the experiences in each cluster. The four clusters of the positive psychosis dimension were only modestly intercorrelated (mean Pearson's r : 0.31, range 0.19–0.47).

Analysis

Associations were expressed as regression coefficients of cannabis use in multiple regression models of continuous scores of positive, negative and depressive dimensions. Associations were adjusted for (i) other drugs used, (ii) other dimensions and (iii) sex and school grade obtained (score from 0 to 20, higher score indicating better grades). For example, in the regression of the negative dimension, associations were adjusted for the depressive and the four positive dimensions; each of the four positive dimensions was adjusted for the negative and the depressive dimensions. The effect of age of first use was examined adjusted for life-time frequency of use.

In order to examine confounding by life-time experience of distress associated with positive psychotic experiences, two separate analyses were conducted: (i) association between cannabis and positive psychosis dimensions excluding the group with positive psychotic experiences with no distress on any of the items (distress group) and (ii) association between cannabis and positive psychosis dimensions, excluding the group with positive

psychotic experiences with distress on at least one item (no distress group).

In order to examine whether effects of cannabis increased linearly with increasing life-time frequency of use, models with and without squared cannabis life-time frequency of use were compared by likelihood ratio test.

Interpretation of effect sizes

In order to facilitate interpretation of and compare effect sizes across dimensions in the multiple regression analyses, all regressions coefficients were expressed in standard deviation (SD) of the dependent variables ('B') units. Thus, if the effect size of 'cannabis life-time frequency use' on a positive dimension is 0.1, this means that those who used cannabis had an 0.1 SD higher score on this dimension with each increasing unit of the 'cannabis life-time frequency use' variable (units were: never, once, two to four times, five times or more, systematic use).

RESULTS

The sample consisted of 3500 adolescents, of which 45% were male. The frequency of cannabis life-time frequency use was 6% ($n=200$): never: 94.3% ($n=3300$), once: 2.0% ($n=70$), two to four times: 1.4% ($n=48$), five times or more: 1.5% ($n=51$), systematic use: 0.9% ($n=31$). Of the 200 cannabis users, 52 (26%) had reported first use before or at age 15 years. The frequency of other drugs was much lower at 1% ($n=32$). Girls were less likely to consume cannabis (boys' cannabis life-time frequency use: 8%, girls' cannabis life-time frequency use: 4%, $\chi^2=25.5$, d.f. = 1, $P<0.001$) and other drugs (boys' any use: 1.7%, girls' any use: 0.3%, $\chi^2=16.9$, d.f. = 1, $P<0.001$). Neither cannabis life-time frequency use nor frequency of use of other drugs was correlated with school grade (both: Pearson's $r=-0.03$).

The mean (SD) scores for the different dimensions were: paranoia: 0.20 (0.24); grandiosity: 0.20 (0.40), first-rank symptoms: 0.10 (0.17), hallucinations: 0.02 (0.15); depression: 1.9 (0.5) and negative: 1.8 (0.4). The proportion of individuals with at least one positive score on one of the psychosis items was paranoia: 65% ($n=2282$); first-rank symptoms: 36% ($n=1253$), grandiosity: 24% ($n=855$), hallucinations: 3% ($n=102$). The proportion of individuals who, given the presence of a psychotic symptom, did not report distress on any of the items was: paranoia: 17%; first-rank symptoms: 46%, grandiosity: 87%, hallucinations: 54%.

Cannabis and psychosis dimensions

Cannabis life-time frequency use was associated positively with all four clusters of the positive psychosis

dimension (Table 1). For hallucinations the effect of cannabis was non-linear, in that most of the difference appeared to be between systematic use versus all other categories (unadjusted standardized $B=1.38$, $P=0.000$; adjusted for other drug use, depressive and negative dimensions, sex and school grade: $B=0.86$, $P=0.000$), while for grandiosity most of the effect appeared to be apparent between non-use versus any use of cannabis (unadjusted standardized $B=0.44$, $P=0.000$; adjusted for other drug use, depressive and negative dimensions, sex and school grade: $B=0.34$, $P=0.000$). Associations were reduced but remained statistically significant after adjustment for the various confounders (Table 1).

There was a large difference in effect size between the two groups who had started before and after age 15 years, independent of cannabis life-time frequency use, such that the effect size of cannabis life-time frequency use was much larger in those who had started early in adolescence (Table 2).

In the unadjusted analyses, cannabis life-time frequency use was associated with both the depressive and negative dimensions. However, adjustment for the negative dimension nullified the effect of cannabis on the depression dimension, whereas the effect on the negative dimension when adjusting for the depressive dimension was reduced but remained statistically highly significant (Table 3). For the negative dimension there was also a large age of first use effect, independent of cannabis life-time frequency use (age first use = 15 years: $B=0.58$, $P=0.007$; age first use > 15 years: $B=0.19$, $P=0.23$).

The distribution of cannabis use of any life-time frequency in relation to distress in those with at least one positive score on one of the positive psychosis dimensions was as follows (in view of the earlier observed non-linearities for the cannabis effect on hallucinations—effect of extreme use; and grandiosity—effect of any use, the exposure systematic use versus any other use was used for hallucinations and the exposure non-use versus any use for grandiosity): hallucinations with distress: 11% ($n=5$), hallucinations without distress: 13% ($n=7$); grandiosity with distress: 9% ($n=10$), grandiosity without distress: 10% ($n=71$); paranoia with distress: 7% ($n=123$), paranoia without distress: 10% ($n=39$); first-rank symptoms with distress: 9% ($n=58$), first-rank symptoms without distress: 8% ($n=48$). Examination of the effect of cannabis life-time frequency use on positive psychosis after exclusion of, respectively, individuals with and without distress revealed that there was no difference between individuals with or without distress associated with their positive experiences of psychosis (Table 4).

Table 1 Associations between cannabis and psychosis, and effect of adjusting for various confounders.

Life-time frequency of cannabis use	Hallucinations			Paranoia			Grandiosity			First-rank		
	Mean value	B† (P-value)	Mean value	Mean value	B† (P-value)	Mean value	Mean value	B† (P-value)	Mean value	B† (P-value)	Mean value	B† (P-value)
	Never	0.02	0*	0.20	0.19	0*	0.09	0.19	0*	0.09	0*	0.19
Once	0.03	0.06 (0.61)	0.28	0.36	0.31 (0.009)	0.12	0.36	0.44 (0.000)	0.12	0.44 (0.000)	0.12	0.18 (0.13)
2–4 times	0.05	0.22 (0.13)	0.30	0.43	0.38 (0.009)	0.19	0.43	0.59 (0.000)	0.19	0.59 (0.000)	0.19	0.53 (0.000)
= 5 times	0.06	0.27 (0.058)	0.36	0.33	0.64 (0.000)	0.18	0.33	0.36 (0.010)	0.18	0.36 (0.010)	0.18	0.50 (0.000)
Systematic	0.23	1.39 (0.000)	0.44	0.34	0.96 (0.000)	0.19	0.34	0.37 (0.037)	0.19	0.37 (0.037)	0.19	0.55 (0.002)
Deviation from linearity††	$\chi^2 = 13.0$, d.f. = 1, P = 0.000			$\chi^2 = 0.00$, d.f. = 1, P = 0.94			$\chi^2 = 9.92$, d.f. = 1, P = 0.002			$\chi^2 = 1.36$, d.f. = 1, P = 0.24		
Regression coefficient: linear trend‡	–\$			0.23 (0.000)			–\$			0.17 (0.000)		
Regression coefficient: linear trend‡ adjusted**	–\$			0.09 (0.003)			–\$			0.06 (0.000)		

*Reference category. †Regression coefficient indicates change in positive psychotic dimension, in units of standard deviation, associated with one unit increase in cannabis life-time frequency use. ††Tests whether increase in positive symptom dimension with frequency in cannabis use deviates statistically from a straight line. ‡Regression coefficient 'B' indicates linear change in positive psychotic dimension, in units standard deviation, with each unit increase in cannabis life-time frequency use (five units). §Was calculated only if there was no evidence of non-linearity—for adjusted non-linear effects see text. **Adjusted for other drug use (ecstasy, cocaine, amphetamines, heroin, LSD or similar drug), depressive and negative dimensions, sex and school grade.

Table 2 Effect of cannabis age first use, controlling for life-time frequency of use.

Adjustment made	Effect of age of first cannabis use on continuous psychosis dimension, expressed as the regression coefficient, from multiple regression equations					
	Age first use†	Hallucinations	Paranoia	Grandiosity	Comparison	Comparison
	Mean value	B‡ (P-value)	B‡ (P-value)	B‡ (P-value)	young versus old§	young versus old§
Not adjusted for frequency use	Never use	0*	0*	0*	0*	0*
	≤ 15 years	1.16 (0.000)	0.91 (0.000)	0.86 (0.000)	F (1, 3489) = 40.3	F (1, 3489) = 10.1
	≥ 16 years	0.15 (0.076)	0.36 (0.000)	0.27 (0.001)	P < 0.0001	P = 0.0015
Adjusted for frequency use	Never use	0*	0*	0*	0*	0*
	≤ 15 years	0.74 (0.001)	0.56 (0.10)	0.74 (0.001)	F (1, 3488) = 40.0	F (1, 3488) = 11.8
	≥ 16 years	–0.18 (0.25)	0.09 (0.56)	0.18 (0.18)	P < 0.0001	P = 0.0045

*Reference category. †The effect of age of first cannabis use, expressed dichotomously as '≤ 15 years' or '≥ 16 years' on having positive psychotic experiences is shown relative to those who never used cannabis (the reference category). ‡Regression coefficient 'B' indicates mean change in positive psychotic dimension, in units of standard deviation associated with different categories of age at first use. §In the columns 'comparison young versus old' the effect sizes of the categories '≤ 15 years' and '≥ 16 years' are formally compared with each other: a statistically significant comparison indicates that the effect size of the '≥ 15 years' category is significantly greater than the '≤ 16 years' category by Wald test.

Table 3 Effect of cannabis life-time frequency use on depressive and negative dimensions.

Life-time frequency of cannabis use	Effect of cannabis life-time frequency use on continuous negative and depressive dimensions, expressed as the regression coefficient from multiple regression equations			
	Depressive dimension		Negative dimension	
	Mean value	B† (P-value)	Mean value	B† (P-value)
Never	1.85	0*	1.79	0*
Once	1.99	0.31 (0.009)	1.88	0.22 (0.071)
2–4 times	2.11	0.54 (0.000)	1.97	0.43 (0.003)
≥ 5 times	2.02	0.35 (0.012)	2.05	0.63 (0.000)
Systematic	2.00	0.33 (0.070)	2.05	0.64 (0.000)
Deviation from linearity‡	$\chi^2 = 6.47$, d.f. = 1, $P = 0.011$		$\chi^2 = 0.64$, d.f. = 1, $P = 0.42$	
Regression coefficient linear trend§ unadjusted	–			0.20 (0.000)
Regression coefficient linear trend§ adjusted 1¶	–			0.11 (0.000)
Regression coefficient linear trend§ adjusted 2¶	–			0.07 (0.004)

*Reference category. †Regression coefficient indicates change in symptom dimension, in units of standard deviation, associated with one unit increase in cannabis life-time frequency use. ‡Tests whether increase in symptom dimension with frequency in cannabis use deviates statistically from a straight line. §Regression coefficient 'B' indicates linear change in symptom dimension, in units of standard deviation, with each unit increase in cannabis life-time frequency use (five units); was only calculated if there was no evidence of non-linearity. ¶Adjusted-1: for paranoia, hallucinations, first-rank and grandiosity dimensions, sex, school grade and other drug use; adjusted-2: as in 1, but in addition adjusted for depressive dimension (in the model of negative dimension) and negative dimension (in the model of depressive dimension).

Table 4 Self-medication hypothesis: effects of cannabis as a function of distress associated with psychotic experiences.

	Effect of cannabis life-time frequency use on continuous psychosis dimension, expressed as the regression coefficient from multiple regression equations			
	Hallucinations* B† (P-value)	Paranoia B† (P-value)	Grandiosity* B† (P-value)	First-rank B† (P-value)
No distress group	1.30 (0.000)	0.45 (0.000)	0.41 (0.000)	0.21 (0.000)
Distress group	0.78 (0.000)	0.11 (0.000)	0.31 (0.001)	0.14 (0.000)

*In view of the earlier observed non-linearities for the cannabis effect on hallucinations (effect of extreme of use) and grandiosity (effect of any use), the exposure systematic use versus any other use was used for hallucinations and the exposure non-use versus any use for grandiosity. †Regression coefficient 'B' indicates change in symptom dimension, in units of standard deviation, associated with each unit increase in cannabis life-time frequency use (five units for paranoia and first-rank symptoms; two units for hallucinations and grandiosity).

DISCUSSION

The results of this population-based study suggest that cannabis is associated with the positive and negative experiences of psychosis, independent of each other and independent of depression. The association was, in line with previous work, specific for the positive and negative dimensions of psychosis and did not extend to the domain of depression [12,26].

The prevalence of cannabis use at 6% and other drugs use at 1% was low compared to other European countries, raising the question of possible under-reporting. However, European surveys have determined that cannabis use in Greece, at a prevalence of around 9% of use in high school students, is indeed less common than in other European countries, or at least was so at the time of

the survey [27,28]. We cannot exclude under-reporting related to the fact that both parents and adolescents were sent questionnaires at home, which could have resulted in adolescents under-reporting any drug habits for fear of their parents seeing their questionnaires before sending them off. However, such under-reporting resulting in false negatives, had it occurred, would have led to a bias towards the null rather than induce spurious findings, as it would have reduced case–control differences. Thus, the assumption of under-reporting and false negatives would confirm rather than negate the reported results, unless one assumes that cannabis-using adolescents with low levels of psychosis-proneness would be much more likely to under-report than cannabis-using adolescents with high levels of psychosis proneness. This is unlikely as, for example, for paranoid ideation associated with psychosis-

prone to the predicted relationship with under-reporting would be inverse.

Other limitations are that exposure measurement was not precise, in that quantity used could not be assessed, and the categories of cannabis life-time frequency use were not precise. For example, there is no way of knowing whether or not the difference between 'never' and 'two to four times' is the same as the difference between 'two to four times' and 'five times or more'. In addition, children were asked if they had ever during their lives used cannabis in any of these frequencies, not for how long they had persisted with this nor when they had last used. The effect of this is reduced accuracy of exposure measurement with more random error. It would not have resulted, however, in non-random error and spurious results. In addition, the way these frequencies were presented clearly indicate increasing levels of use, and it was this information that was retained and tested in the analyses.

It is possible that some adolescents were actually in a state of acute cannabis intoxication at the time of responding to the questionnaire, but this can only have been a minority and would in all likelihood have applied only to those in the category of most frequent use.

The study was cross-sectional, making it difficult to disentangle the direction of the effect. For example, cannabis may result in psychotic experiences but psychotic experiences may also result in the individual to use cannabis in order to reduce the experiences of psychosis. The CAPE does not measure age of onset of the experience, so that it may well precede cannabis use. Two elements in this study, however, suggest that the direction of causality is, at least in part, from cannabis to psychosis. First, a longitudinal variable reflecting age of first use, discriminated strongly between early and later cannabis users, independent of life-time frequency of use. The only conceivable way in which this finding could be spurious is to assume that individuals with high levels of psychotic experiences have systematically biased reports of earlier use and/or those with low levels of psychosis have systematically biased reports of later use. While this cannot be excluded it is unlikely, and is also not compatible with the fact that the association persisted after adjustment for life-time frequency of use. Another explanation is that the early users have more severe psychosis diathesis and therefore start using cannabis earlier as a means of self medication. A *post-hoc* analysis, however, comparing early and late users on severity of distress associated with each of the four psychosis dimensions, showed no large or significant differences for any of the dimensions ($P=0.58$ to $P=0.85$). This does not suggest more severe psychosis diathesis in early users, although it does not rule it out either. Secondly, individuals who in their lives had had more distress associated with their psychotic experiences

did not differ in their pattern of association between cannabis and psychosis compared to those without distress and, within the group of users, there was also no association between frequency of use and distress. This suggests that the hypothesized direction from psychotic experiences to cannabis on the basis of self-medication is unlikely to explain the entire association.

The use of multiple regression with a low prevalent outcome such as hallucinatory experiences (3%) may yield imprecise results. We therefore repeated the analyses using a binary measure of hallucinations and recalculated effect sizes using logistic regression, comparing systematic use versus all other categories of cannabis life-time use. This revealed the same pattern of non-linear results with a large and highly significant relative risk of auditory hallucinations in the highest cannabis life-time frequency category of systematic use (odds ratio = 6.7, $P=0.000$; adjusted OR = 4.3, $P=0.046$).

The fact that early use of cannabis increases the risk for not only clinical psychotic disorder [3] but also non-clinical psychotic experiences is informative. In a recently postulated framework linking the psychological and biological aspects of psychosis [29], it was suggested that a dysregulated, hyperdopaminergic state may lead to stimulus-independent release of dopamine which may take over the normal process of contextually driven salience attribution and leads to aberrant assignment of salience to external objects and internal representations. Hallucinations and delusions may consequently arise from cognitive explanations for these altered experiences. Furthermore, it has been suggested that in chronic schizophrenia progressively enhanced susceptibility to psychotic state and relapse occurs. Sensitization of the endogenous mesolimbic dopaminergic system, triggered by repeated stimulation with cannabis [30], may be the underlying mechanisms in this acquired susceptibility [31,32], to which individuals with liability to psychosis may be particularly sensitive [33]. Dopamine sensitization is dependent on developmental stage and is thought to begin in adolescence [34]. The higher rates of psychotic experiences seen in younger populations [35], as well as the apparent developmental effect of cannabis on onset of psychotic experiences fit well with the hypothesized onset of dopamine sensitization potential in adolescence. Our results suggest that hallucinations are less, and grandiosity is more sensitive to the hypothesized sensitizing effect of cannabis, while the other symptom domains are associated with cannabis in a dose-response fashion.

The fact that cannabis use was associated with both the positive and negative dimensions of psychotic experiences suggests a pleiotropic mechanism of one risk factor contributing to two outcomes, and resembles the pattern for other proxy environmental risk factors such as

urbanicity, that was also shown to simultaneously influence the positive and negative symptom domains of psychosis [36]. Although cannabis use was associated with depression, the association disappeared after adjustment for negative symptoms whereas the reverse did not hold. This may explain the fact that cannabis, in a previous population study, was shown to be associated with symptoms of depression [13] that are known to show a large degree of overlap with the negative symptomatology of psychosis [25]. Similarly, the replication of associations between cannabis and psychosis across the different and only weakly to moderately correlated clusters of psychotic experiences suggests a single underlying pathway with variable expression.

The findings, in conclusion, suggest that previous reports of an association between cannabis and schizophrenia should be interpreted in the light of cannabis feeding the population risk of psychosis at the level of subtle alterations in mental states that form the dimensions of positive and negative psychotic experiences. It has been argued that the absence of ecological correlations between population cannabis consumption and population administrative incidence rates for psychosis indicate that cannabis is not a sufficient cause for psychosis [37]. There is evidence, however, that administrative indices of psychosis are only a very biased, limited and unreliable reflection of the total population morbidity force of psychosis [11,22,38]. Given the fact that the effects of cannabis are detectable far beyond the conventional criteria for psychotic disorder, urgent further work is needed to establish to what degree cannabis can act as a sufficient cause for psychosis liability at the population level.

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