Association of cannabis, cannabidiol and synthetic cannabinoid use with mental health in UK adolescents

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Relevance Statement

This paper adds to the literature on cannabis, synthetic cannabinoids and cannabidiol and adolescent mental health problems. We provide the first population-level description of associations between the use each of these cannabinoids and a significant increased risk of reporting probable depression, anxiety, conduct disorder and auditory hallucinations. Given the liberalisation of cannabis policy globally these results provide psychiatrists with evidence to have informed discussions with service users about these substances.

Abstract

Background Cannabis has been associated with poorer mental health, but little is known of the effect of synthetic cannabinoids or cannabidiol (CBD).

Aims To investigate associations of cannabis, synthetic cannabinoids and CBD with mental health in adolescence.

Methods We conducted a cross-sectional analysis with 13-to-14 year-old adolescents across England and Wales in 2019-2020. Multilevel logistic regression was used to examine the association between lifetime use of cannabis, synthetic cannabinoids and CBD with self-reported symptoms of probable depression, anxiety, conduct disorder and auditory hallucinations.

Results Of the 6672 adolescents who participated, 5.2% reported using of cannabis, 1.9% CBD, and 0.6% synthetic cannabinoids. After correction for multiple testing, adolescents who had used these substances were significantly more likely to report a probable depressive, anxiety or conduct disorder, as well as auditory hallucinations, than those who had not. Adjustment for socioeconomic disadvantage had little effect on associations, but weekly tobacco use resulted in marked attenuation of associations. The association between cannabis use with probable anxiety and depressive disorders was weaker in those who reported using CBD than those who had not. There was little evidence of an interaction between synthetic cannabinoids and CBD.

Conclusion To our knowledge, this study provides the first general population evidence that synthetic cannabinoids and CBD are associated with probable mental health disorders in adolescence. These associations require replication, ideally with prospective cohorts and stronger study designs.

Introduction

Globally, cannabis is the most widely used and internationally regulated illicit drug.[1] Cannabis use has been consistently associated with an increased risk of mental health disorders. The strongest evidence is found for psychosis,[2] with limited evidence for depression and anxiety.[3] Delta-9-tetrahydrocannabinol (THC) is the most researched psychoactive cannabinoid in herbal cannabis.[4] Experimental evidence suggests that the effects of THC on psychotomimetic symptoms, similar to those experienced with psychosis (e.g., hallucinations, delusions, paranoia), are dose-dependent.[5] Far fewer studies have researched the effects of other cannabinoids. There has been research suggesting cannabis of a higher potency, defined as the ratio of cannabidiol (CBD) to THC, is associated with an increased risk of psychosis and cannabis use disorder ,[6] and some evidence suggesting that CBD attenuates psychotomimetic effects of THC,[7] but little research into the effects of CBD in isolation. The limited experimental evidence on CBD suggests it may alleviate symptoms of psychosis and social anxiety.[8] There is a comparable paucity of population-level research into the effects of synthetic cannabinoids. While THC is a partial agonist with weak affinity for the CB1 receptor, synthetic cannabinoids are full agonists and generally have a higher affinity such that more potent effects might be expected. The limited case reports suggest synthetic cannabinoids can have profound acute effects in young people including anxiety, paranoia, hallucinations, breathlessness and tachycardia.[9]

Legal status of cannabis, CBD and synthetic cannabinoids

Cannabis use policy is liberalizing in several jurisdictions. The use of the herbal cannabis and associated derived products containing THC is, however, illegal in the majority of the world.[10] In contrast, synthetic cannabinoids often start as unregulated legal products, but after

a period either become controlled (e.g. the USA's Synthetic Drug Abuse Prevention Act of 2012)[11] or come under blanket acts that ban products with psychoactive effects (e.g. the UK's Psychoactive Substances Act).[12] In contrast, CBD is a legally marketed product in the United States and many European countries. In the United States in 2019, CBD was one of the top ten selling herbal supplements in mainstream stores, increasing revenue by 872% from 2018 with total US sales of close to $36 million[13], and is often advertised as a natural over-the-counter remedy for mental health problems[14].

Methodological limitations of previous research

Nearly all research to date has focussed on the association between cannabis and mental health, with very few studies on use of synthetic cannabinoids and CBD. Existing studies have also tended to be either small and thus likely lacking in statistical power, case reviews which might introduce sampling bias,[9] or based on cannabinoids administered in a lab which is unlikely to reflect how these drugs are used in the general population.[15] As far as we are aware, there have been no studies of the association between cannabis, synthetic cannabinoids and CBD with the risk of probable mental health disorders in a general adolescent population sample.

Aims

To address these limitations, we aimed to (a) describe the use of cannabis, synthetic cannabinoids and CBD among a population of UK adolescents; (b) examine associations between the use of cannabis, synthetic cannabinoids and CBD with symptoms from a range of mental health disorders; and (c) explore the extent to which CBD modifies the association between cannabis and synthetic cannabinoids with probable disorders.

Methods

Study Population

These data arise from baseline assessments within a randomised controlled trial in England and Wales between September 2019 and March 2020.[16] Schools were randomly sampled from the West of England and South Wales. Questionnaires were self-completed by year 9 students (aged 13-14) before random allocation. Fee-paying schools, schools for children only with learning difficulties, and pupil referral units were excluded. Paper questionnaires were completed by students in classrooms under exam conditions. Further details are available elsewhere.[16] Of 7077 eligible students, 6672 participated and completed the questionnaire (94.3% response). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures were approved by Cardiff University's School of Social Sciences Ethics Committee (SREC/3342). Written informed consent was obtained from all participants and a process of opt-out consent used with parents. This manuscript adheres to the STROBE reporting guidelines.[17]

Exposure

Participants were asked whether they have ever tried, "Cannabis (also called: marijuana, spliff, hash, skunk, grass, draw, dab, shatters)", "CBD products (also called: cannabidiol, CBD oil)" and, "Synthetic cannabinoids (these mimic the effect of cannabis; they are also called: spice, black mamba)". Images were provided of each type of cannabis reduce misclassification of use (questions shown in the Supplement). The images of cannabis were

taken from a previously validated measure of cannabis potency,[18] CBD a stock image, and

synthetic cannabinoid from the UK national drug education website: www.talktofrank.com.

Outcomes

Probable depressive disorder

Participants completed the 13-item Short Mood and Feelings Questionnaire which assesses

depressive symptoms over the past two weeks.[19] We applied the validated ≥ 12 cut-off point

to indicate a disorder.[19]

Probable anxiety disorder

Participants completed the seven-item Generalized Anxiety Disorder (GAD-7) scale which

assesses anxiety symptoms over the past two weeks.[20] We applied the validated ≥ 10 cut-off

point considered indicative of a disorder.[20]

Probable conduct disorder

The Oregon Adolescent Depression Project Conduct Disorder Screener was completed by

participants.[21] It has six items asking whether participants have engaged in the past week in

behaviours such as getting into fights. We applied the ≥ 9 cut-off point as indicative of

disorder.[21]

Auditory hallucinations

A binary measure for experience of an auditory hallucinations (0 = no hallucination, 1=

hallucination) was constructed from self-reported using questions from the World Health

Organization Composite International Diagnostic Interview.[22] Young people who reported a

hallucination were then asked about the distress caused by this experience (response options

ranging from not to very distressing) and frequency (not at all to nearly every day/ daily). To increase the diagnostic relevance, we recoded responses into very distressing versus the other categories of distress and also into nearly every day/daily versus the other frequency categories.

Covariates

Gender identity was self-reported and categorised as boy, girl or a gender minority (transboy; transgirl; non-binary (neither male or female); unsure / questioning; other; prefer not to say). Participants also reported their age, ethnicity, employment status of adults they lived with, free school meal entitlement, and weekly smoking status (at least one cigarette a week). To describe the characteristics of users and non-users of each cannabinoid we also assessed participants consumption of a whole alcoholic drink in the past 30 days and the frequency of cannabis use over the past 12 months (never; monthly or less; weekly or more).

Statistical Analysis

To describe the characteristics of young people who reported using each type of cannabis we compared the demographic characteristics, exposure to socioeconomic disadvantage, weekly smoking status and the use of alcohol in the past 30 days according to use with univariable multilevel logistic regression (students nested within schools). The association between each type of cannabis and mental health was analysed using univariable and multivariable multilevel logistic regression (students nested within schools). Two separate multivariable models were performed for the association between exposure to cannabis, synthetic cannabinoids, and CBD with each outcome to examine the potential confounding effects of: (1) adjusting for gender identity and socioeconomic disadvantage (comprising living with no adults in part- or full-time employment and entitlement to free school meals), and (2) after

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additional adjustment for weekly smoking status. Subgroup analyses were conducted in participants reporting an auditory hallucination into whether use of cannabis, synthetic cannabinoids and CBD were associated with being very distressed by hallucination(s) and hallucinating nearly every day or more. Interactions were then modelled between CBD and both cannabis and synthetic cannabinoids when examining their associations with probable disorders adjusting for gender identity, socioeconomic disadvantage, and weekly smoking status. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). To reduce the risk of generating spurious findings due to multiple testing, the threshold for significance was Bonferroni adjusted to P <0.001 (p=0.05/42). Sensitivity analyses were conducted after excluding participants with any missing data and using cannabis frequency as the exposure variable, and examined the percentage overlap in reported cannabis, CBD, synthetic cannabinoid and weekly smoking. Analyses were performed in Stata version 17.0 (Stata Corp).

Missing Data and Imputation

Missing data per variable ranged from 1.0 to 9.5%. Missing data in all variables (exposures, outcomes, and covariates) were addressed through multiple imputation using chained equations. Each model included all variables, including the following auxiliary variables: age, ethnicity, and alcohol consumption in the past 30 days. Estimates were obtained by pooling results across 20 imputed data sets using the Rubin rules, and assessment of Monte Carlo errors suggested this was a suitable number of imputations.[23]

Results

Of the 6672 participants, 5.2% (95% CI, 4.6-5.7%) reported use of cannabis, 1.9% (95% CI, 1.6-2.3%) CBD, and 0.6% (95% CI, 0.4-0.7%) synthetic cannabinoids (**Table 1**). Use of

cannabis was more common in participants who identified as a gender minority than boy (12.3 vs 5.1%) or girl (4.8%), were entitled to free school meals (9.6 vs 4.6%), lived with no employed adults (11.3 vs 4.8%), were weekly smokers (79.4 vs 4.0%) and those consuming alcohol in the past 30 days (12.0 vs 0.9%). Use of CBD was more common in those who were entitled to free school meals (3.9 vs 1.6%), lived with no employed adults (3.6 vs 1.8%), weekly smokers (33.3 vs 1.8%), and had consumed alcohol in the past 30 days (4.2 vs 0.5%). The characteristics of synthetic cannabinoid users were very similar to those for cannabis and CBD. There was a stepped association between CBD and cannabis use in the past 12 months (never: 0.8; monthly or less: 18.5; weekly or more: 49.2%) and reported synthetic cannabinoids use (never: 0.1; monthly or less: 4.7; weekly or more 26.7%) (**Table 1**).

The prevalence of probable depressive disorder was 22.7% (95% CI, 21.6-23.7), anxiety disorder 19.9% (95% CI, 18.8-20.9), conduct disorder 22.1% (95% CI, 21.1-23.1), and 17.7% (95% CI, 16.6-18.8) reported an auditory hallucination. There was a significant unadjusted association between the use of cannabis with probable depressive (OR, 3.28; 95% CI, 2.58-4.10), anxiety (2.94; 95% CI, 2.32-3.72), or conduct disorder (8.17; 95% CI, 6.35-10.51), and auditory hallucinations (3.10; 95% CI, 2.35-4.10) (**Table 2**). There was also a significant unadjusted association between the use of CBD with probable depressive (OR, 3.51; 95% CI, 2.40-5.12), anxiety (3.09; 95% CI, 2.11-4.53), or conduct disorder (8.21; 95% CI, 5.38-12.53), and auditory hallucination (4.65; 95% CI, 3.02-7.16). Those who reported using synthetic cannabinoids and reported symptoms consistent with a probable depressive (OR, 6.44; 95% CI, 3.07-13.52), anxiety (6.24; 95% CI, 3.05-12.79), or conduct disorder (29.52; 95% CI, 10.32-84.42), and auditory hallucinations (12.22; 95% CI, 4.29-34.84) than those had not. There was little evidence of attenuation of these association after adjustment for sociodemographic factors. Associations were markedly reduced after the addition of weekly

smoking, but participants using any of these cannabinoids remained more than 2-times as likely to report a probable disorder or an auditory hallucination compared to their peers who reported no use (**Table 2**).

Among students who reported a hallucination, there was an unadjusted association between the use of cannabis with being very distressed by the hallucination (OR, 2.66; 95% CI, 1.52-4.65). There was weaker evidence of an association for the use of CBD (1.83; 95% CI, 0.74-4.52) or synthetic cannabinoids (OR, 2.20; 95% CI, 0.58-8.33). There was evidence that hallucinating nearly every day was associated with use of CBD (2.15; 95% CI, 1.06-4.38) and synthetic cannabinoids (OR, 2.88; 95% CI, 0.94-8.83), but weaker evidence for cannabis use (Adjusted OR (AOR), 1.30; 95% CI, 0.71-2.37). Associations were again attenuated after adjusting for weekly smoking (**Table S1 in the Supplement**).

There was an interaction between cannabis and CBD use in associations with probable depressive and anxiety disorder. Evidence for an association between cannabis and probable depressive disorder was stronger in those who did not use CBD (AOR, 2.77; 95% CI, 2.05-3.75) than in those who did (AOR, 0.66; 0.26-1.70, *p for interaction*: 0.001). This pattern was also observed in the association between cannabis and probable anxiety disorders (AOR, 2.33; 95% CI, 1.71-3.18versus 0.83; 0.31-2.18, *p for interaction*: 0.001). To explore these interactions, we examined the frequency of cannabis use by CBD use. There was evidence that cannabis use was more frequent in CBD users (never: 40.9%, monthly: 32.7%, weekly: 26.4%) than non-users (never: 96.7%, monthly: 2.8%, weekly: 0.5%).

There was, however, little evidence of an interaction between cannabis and CBD use for symptoms of conduct disorders (*p for interaction*: 0.07), auditory hallucinations (*p for*

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interaction: 0.22), nor synthetic cannabinoid and CBD use in associations with probable

disorder (depressive: *p for interaction*: 0.48, anxiety: *p for interaction*: 0.27, conduct: *p for

interaction*: 0.99, auditory hallucination: *p for interaction*: 0.81).

Sensitivity analysis conducted in the datasets where there was no missing data, showed the

confidence intervals for estimates overlapped with those from the main results using imputed

data indicating there were no meaningful differences (**Table S2 and S3**). There was a

stepwise association between cannabis frequency and outcomes. Adjustment for weekly

smoking status attenuated these associations, particularly for those who used cannabis on a

weekly basis or more frequently (**Table S4)**. There was a greater overlap between weekly

smoking with cannabis than CBD or synthetic cannabinoid use (**Table S5**).

Discussion

Main findings

In a general population sample of 13–14-year-olds in the UK, individuals using cannabis,

synthetic cannabinoids and CBD (compared with those that did not) were more likely to

report symptoms consistent with a probable depressive, anxiety disorder, conduct disorder

and auditory hallucinations. There was some evidence that the strength of associations varied

by substance with the largest associations for synthetic cannabinoids although confidence

intervals for all overlapped. Adjusting for tobacco use attenuated associations, but evidence

of these associations was still present. These results are the first to provide a profile of young

adolescents who use CBD and synthetic cannabinoids, indicating that, as for cannabis, use is

more common among young people who live with parents with a relatively low income, are

unemployed, report being a weekly smoker, or have used alcohol in the past 30 days. Around

40% of the young people who had used CBD had never used cannabis whereas around half of

those using synthetic cannabinoids had used cannabis weekly or more often over the previous year. As far as we are aware, this is the first study to examine the link between using different cannabinoids and a range of mental health outcomes in adolescence.

Comparison with previous findings

To our knowledge the present study gives the first user profiles for both CBD and synthetic cannabinoid users in young adolescents. A survey of university students in the USA found that synthetic cannabinoid users did not differ greatly from cannabis users. [24] Synthetic cannabinoid users were slightly younger than abstainers and more likely to be of non-Hispanic white ethnicity. A household survey of German people aged over 14 found that having ever used CBD was associated with higher education level, urban living, tobacco and e-cigarette use.[25] We replicated the link for CBD and synthetic cannabinoid use with the use of cannabis and tobacco, but found use of all cannabinoids was associated with greater exposure to household socioeconomic deprivation.

Cannabis use was associated with all the mental health outcomes assessed. These findings support other reports of cannabis use in adolescents being a risk factor for developing mental illness in early adulthood.[3] We have characterised the attenuation after adjusting for weekly smoking as due to confounding as the majority of studies suggest the initiation of smoking tobacco tends to precede cannabis use.[25] Having said this, recent research indicates the age of tobacco smoking initiation has increased among US youth,[26] while the initiation age for cannabis has remained stable.[27] There is also data from the UK suggesting that cannabis use has increased over time among 11-16 year-olds while tobacco use stayed the same.[28] This suggests that for some young people it is possible that regular smoking developed secondary to cannabis use, and that this therefore acted as a mediator rather than a confounding factor, if

smoking increases the risk of these disorders. This could mean that this adjusted analysis might underestimate the real associations between cannabis use and mental health outcomes.

Synthetic cannabinoids had large (but imprecise) associations with mental health outcomes. We found fewer than 1% of students had used synthetic cannabinoids. We could not find any other estimates of synthetic cannabinoid prevalence in adolescence. One convenience sample of US undergraduates found 7.9% reported ever using synthetic cannabinoids and that use was associated with considering attending an emergency department for anxiety, depression and hallucinations.[24] Another US registry study of 107 adolescents presenting to emergency departments found synthetic cannabinoid use was associated with a higher occurrence of acute neuropsychiatric symptoms (e.g. coma, central nervous system depression) than cannabis, and effects were stronger where patients had used other drugs alongside cannabinoids.[29]

CBD was associated with an increased risk of probable depressive, anxiety and conduct disorder and auditory hallucinations. Randomised and non-randomised controlled trials administering CBD have found improvements in symptoms of psychosis and in patients with social anxiety.[8] One systematic review of 20 observational studies suggested that cannabis with a higher CBD to THC concentration may have less of an effect on psychosis and cannabis use disorder, than cannabis with a lower CBD to THC ratio.[6] Laboratory studies investigating the effect of CBD consumed prior to THC or cannabis have had mixed results. One study with adults found people who took CBD prior to being given THC were less likely to experience clinically significant psychotic symptoms or paranoia,[15] but others with adolescents have not replicated this effect of CBD.[30]

In the present study we found exploratory evidence of an interaction on a multiplicative scale between CBD use and cannabis use, such that the association between cannabis and both depression and anxiety was weaker in those who had also used CBD than those who had not. Whilst these findings are potentially consistent with CBD ameliorating the effects of cannabis on depression and anxiety, there are alternative explanations. It could be that CBD users use cannabis less frequently have had less cumulative use of cannabis, or select cannabis with a higher CBD:THC ratio, compared to those not using CBD. We found the frequency of cannabis use was higher in CBD users than non-users suggesting there is limited support for that explanation. For these reasons, and that we do not know whether individuals ever used CBD and cannabis at the same time, this finding has to be regarded as highly speculative.

Strengths and Limitations

One of the strengths of our study lies in the use of a large sample of adolescents as both CBD and synthetic cannabinoid have a relatively low prevalence. Another strength is the use of pictorial aids for the different types of cannabis to reduce the chance of misclassification, and multiple validated measures of probable disorders covering a range of symptoms previously linked with cannabis use.[3] We had a high response rate to our survey and a low amount of missing data for each variable. To account for the missing data, we used multiple imputation to maximize the plausibility of the missing at random assumption. Results were comparable when using the datasets with missing and imputed data, increasing confidence in the findings. Bias due to non-ignorable missing data cannot, however, be ruled out completely.

The cross-sectional design of the study means we cannot establish whether the associations reported are causal. Reverse causality is a tenable explanation for the associations reported where young people with existing mental health problems choose to use cannabis, synthetic

cannabinoids or CBD because they believe they will improve their symptoms. In the case of CBD, this may because CBD is advertised as a natural over the counter remedy for mental health problems.[14] We found an association between use of each cannabinoid with conduct disorder, but it is unclear what mechanism underpin this association. An alternative to a causal explanation is that these associations are brought about by confounding, whereby both cannabinoid use and probable mental health disorder share common antecedents such as exposure to adverse childhood experiences.[31] The questions on the use of three cannabinoids did not ask whether use was concurrent. This limits the inferences that can be drawn from the interactions showing CBD moderated the association between cannabis use with anxiety and depressive symptoms, particularly given the limitation around mechanistic understanding from most patterns of interaction.[32] It is possible that young people who used both cannabis and CBD had a lower profile of risk factors for mental disorder than those who solely used cannabis. We did not assess the frequency of CBD and synthetic cannabinoid use limiting inferences that could have been drawn on the extent of exposure. The exclusion of fee-paying schools would have reduced the variability in the assessment of socioeconomic disadvantage and potentially the confounding effect of socioeconomic disadvantage on associations.

Implications

Using data from a general population sample in the UK, we found the use of cannabis, synthetic cannabinoids and CBD was associated with an increased risk of three probable mental health disorders. General population studies are useful in estimating associations at the population level and can be crucial for informing policy makers and clinical service providers. There is a need for larger trials into the effectiveness and safety of CBD as a treatment for depression, anxiety and psychosis, and greater consideration of how CBD is marketed given the paucity of evidence of benefit to mental health. Our findings signal to

clinicians, educators and policy makers there is a need for education on the uncertainty in the evidence of benefit for CBD and additional research, ideally with longitudinal data into the link between synthetic cannabinoid use and probable mental health disorders in young people.

Acknowledgements

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Table 1. Association between type of cannabis and participant characteristics (n = 6672)

	Cannabis, %			Cannabidiol, %			Synthetic cannabinoids, %		
Characteristic	Never (n = 6326) [a]	Used (n = 346)	*P* Value [b]	Never (n = 6545)	Used (n = 127)	*P* Value [b]	Never (n = 6632)	Used (n = 40)	*P* Value [b]
Gender identity									
Boy	94.9	5.1		97.9	2.1		99.4	0.6	
Girl	95.2	4.8	0.56	98.3	1.7	0.22	99.5	0.5	0.85
Gender Minority [c]	87.7	12.3	<0.001	96.7	3.3	0.29	98.6	1.4	0.22
Ethnicity									
White	94.7	5.3		98.1	1.9		99.5	0.5	
Non-white	96.1	3.9	0.17	97.2	2.8	0.14	98.3	1.7	0.001
Entitled to free school meals									
Yes	90.5	9.5		96.1	3.9		98.6	1.3	
No	95.4	4.6	<0.001	98.4	1.6	<0.001	99.5	0.5	0.006
Don't know	94.5	5.5	0.33	97.6	2.4	0.10	99.4	0.6	0.76
Parent(s) unemployment									
Unemployed	88.7	11.3		96.4	3.6		98.5	1.4	
Employed	95.2	4.8	<0.001	98.2	1.8	0.02	99.5	0.5	0.03
Weekly smoking									
Not smoked	96.0	4.0		98.6	1.4		99.7	0.3	
Smoked	20.6	79.4	<0.001	66.7	33.3	<0.001	85.2	14.8	<0.001
Alcohol in past 30 days									
Not consumed	99.1	0.9		99.5	0.5		99.9	0.1	
Consumed	88.0	12.0	<0.001	95.7	4.2	<0.001	98.7	1.3	0.001
12-month frequency of cannabis [d]									
Not used		14.0		99.2	0.8		99.9	0.1	
Monthly or less		65.9		81.5	18.5	<0.001	95.3	4.7	<0.001
Weekly or more		20.0		50.8	49.2	<0.001	73.3	26.7	<0.001

[a] All numbers estimated from imputed proportions.
[b] Determined by logistic regression.
[c] Gender minority comprised: transboy; transgirl; non-binary (neither male or female); unsure / questioning; other.
[d] No observations on frequency for those who did not use.

Table 2. Odds ratio (95% confidence interval) for association between lifetime cannabis, cannabidiol and synthetic cannabinoid use with probable depressive disorder, generalised anxiety disorder, conduct disorder and auditory hallucinations (n = 6672)

Exposure variable	Probable depressive disorder		
	Unadjusted	Adjusted for sociodemographic factors [a]	Additionally adjusted for weekly smoking
Cannabis	3.25 (2.58, 4.10) ***	3.48 (2.72, 4.46) ***	2.73 (2.07, 3.60) ***
Cannabidiol	3.51 (2.40, 5.12) ***	4.06 (2.71, 6.07) ***	2.89 (1.87, 4.44) ***
Synthetic cannabinoids	6.44 (3.07, 13.52) ***	7.28 (3.36, 15.78) ***	4.18 (1.80, 9.71)
	Probable generalized anxiety disorder		
Cannabis	2.94 (2.32, 3.72) ***	3.00 (2.34, 3.85) ***	2.35 (1.76, 3.13) ***
Cannabidiol	3.09 (2.11, 4.53) ***	3.42 (2.29, 5.11) ***	2.42 (1.57, 3.76) ***
Synthetic cannabinoids	6.24 (3.05, 12.79) ***	6.80 (3.18, 14.54) ***	4.03 (1.78, 9.13)
	Probable conduct disorder		
Cannabis	8.17 (6.35, 10.51) ***	7.88 (6.11, 10.16) ***	5.60 (4.26, 7.35) ***
Cannabidiol	8.21 (5.38, 12.53) ***	7.85 (5.12, 12.02) ***	5.25 (3.31, 8.35) ***
Synthetic cannabinoids	29.52 (10.32, 84.42) ***	28.12 (9.78, 80.88) ***	16.47 (5.43, 49.97) ***
	Auditory hallucination [b]		
Cannabis	3.10 (2.35, 4.10) ***	2.84 (2.13, 3.79) ***	2.25 (1.62, 3.11) ***
Cannabidiol	4.65 (3.02, 7.16) ***	4.57 (2.94, 7.12) ***	3.44 (2.23, 5.55) ***
Synthetic cannabinoids	12.22 (4.29, 34.84) ***	11.00 (3.76, 32.19) ***	7.08 (2.30, 21.85) ***

[a] Sociodemographic factors comprised: gender identity, free school meal entitlement and living with an employed parent.
[b] Analytical n = 5105 as excludes students who responded that they preferred not to say or didn't know whether they had hallucinated.
Probable depressive disorder (Scoring ≥12 on Short mood and feelings questionnaire); Probable generalized anxiety disorder (Scoring ≥ 10 on Generalized Anxiety Disorder Scale); Probable conduct disorder (Scoring ≥ 9 on the Oregon Adolescent Depression Project Conduct Disorder Screener).

*** Statistically significant under a Bonferroni-corrected P <0.001 for 42 comparisons