**The CannTeen Study: Cannabis use disorder, depression, anxiety, and psychotic-like symptoms
in adolescent and adult cannabis users and age-matched controls**

Disclaimer: This is preliminary scientific work that has not been peer reviewed.

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ABSTRACT

Background

Adolescence is characterised by psychological and neural development. Cannabis harms may be accentuated during adolescence. We hypothesised adolescents would be more vulnerable to cannabis-related mental health and addiction problems than adults.

Method

As part of the ‘CannTeen’ study, we conducted a cross-sectional analysis. There were 274 participants: adolescent users (n=76; 16-17 years old), and controls (n=63), and adult users (n=71; 26-29 years old), and controls (n=64). The users used cannabis 1-7 days/week and controls had 0-10 lifetime exposures to cannabis. We measured DSM-5 CUD, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Psychotomimetic States Inventory-adapted (PSI-a). Linear and logistic regressions with age-group, user-group, their interaction, and pre-defined covariates were conducted.

Results

After adjustment for covariates, adolescent users were more likely to have severe CUD than adult users (OR=3.474, 95% CI=1.501-8.036). Users reported greater psychotic-like symptoms than controls (b=6.004, 95% CI=1.211-10.796) and adolescents reported greater psychotic-like symptoms than adults (b=5.509, 95% CI=1.070-9.947). Depression and anxiety were not associated with user-group. No significant interactions between age-group and user-group were identified. Exploratory analyses suggested that users with severe CUD had greater depression and anxiety than users without.

Conclusions

Adolescent cannabis users are more likely than adult cannabis users to have severe CUD. Adolescent cannabis users have greater psychotic-like symptoms than adult cannabis users and adolescent controls, through an additive effect. There was no evidence of an amplified vulnerability to cannabis-related depression, anxiety, or psychotic-like symptoms in adolescence. However, poorer mental health was associated with the presence of severe CUD.

INTRODUCTION

Adolescence is considered to be a dynamic period that begins with puberty and ends when one achieves an independent role in society (Dumontheil, 2016). Brain structure, brain function, neurotransmitter systems (including the endocannabinoid system), cognitive function, and emotional processing continue to mature during adolescence (Blakemore and Choudhury, 2006; Galve-Roperh *et al.*, 2009; Smetana and Villalobos, 2009; Shaffer and Kipp, 2010). Mental health problems typically emerge during adolescence, with 50% beginning before age 18 and 75% by age 24 (Kessler *et al.*, 2005; Patel *et al.*, 2007; Paus, Keshavan and Giedd, 2008; Kielling *et al.*, 2011; Jones, 2013).

Cannabis is the third most commonly used controlled substance in the world, after alcohol and tobacco, with 3.9% of the world's population reporting use in the past year (UNODC, 2020). Cannabis is particularly popular in adolescents, with 28.0% of 15-16 year-olds in the United States (U.S.) (NIDA, 2020) and 19.3% of 15-year olds in England reporting use in the past year (NHS-Digital, 2018, 2019). In 2019, cannabis was the primary problem drug for 77% of young people (aged under 18) in England who received treatment for alcohol or illicit drug problems (NDTMS, 2019).

Concerns have been raised about the disruptive effect adolescent drug use can have during this crucial developmental stage in one's life (Lubman, Yücel and Hall, 2007; Levine *et al.*, 2017; Volkow *et al.*, 2018; Blest-Hopley *et al.*, 2020). Theoretically, adolescents endure substantially greater cannabis-induced harm than their adult counterparts because their brains are more malleable and vulnerable to the drug's impacts (Dow-Edwards and Silva, 2017).

Cannabis use carries a risk of addiction. Large, representative epidemiological studies in the U.S. from the 1990s and 2000s showed that roughly 9% of people who try cannabis transition to dependence at some point in their life (Anthony, Warner and Kessler, 1994; Lopez-Quintero *et al.*, 2011). However, a meta-analysis of studies from 2009 onwards found that among people who had tried cannabis, 22% developed a cannabis use disorder (CUD) (Leung *et al.*, 2020), while approximately 30% of last-year users in the U.S. have a CUD (Hasin *et al.*, 2015). Younger current age and age of first cannabis use (age-of-onset) reliably augments the risk of developing CUD (Von Sydow *et al.*, 2002; Wagner and Anthony, 2002; Chen, O'Brien and Anthony, 2005; Chen, Storr and Anthony, 2009; Ehlers *et al.*, 2010; Lopez-Quintero *et al.*, 2011; Wittchen *et al.*, 2011; Le Strat, Dubertret and Le Foll, 2015; Leung *et al.*, 2020). These studies tend to converge on an odds ratio of approximately three for risk of CUD in adolescents compared to adults. However, these studies typically failed to match or account for cannabis use frequency differences between adolescents and adults.

Multiple large-scale studies have found a small association between cannabis use and depression (Degenhardt, Hall and Lynskey, 2001, 2003; Horwood *et al.*, 2012). A meta-analysis of longitudinal studies found cannabis users had a higher likelihood of developing depression compared to controls (Odds Ratio (OR)=1.17) (Lev-Ran *et al.*, 2014) and another meta-analysis supported the link between cannabis use in adolescence and depression in early adulthood (OR=1.37) (Gobbi *et al.*, 2019). Some longitudinal studies have reported a greater vulnerability to depression in those with a younger age-of-onset (Horwood *et al.*, 2012; Schoeler *et al.*, 2018) and one systematic review concluded there was some evidence for an age-of-onset effect (Hosseini and Oremus, 2019). However, a non-linear association between age and contemporaneous depressive symptoms has been reported (Leadbeater, Ames and Linden-Carmichael, 2019). Moreover, a meta-analysis did not find a significant age-of-onset effect (Lev-Ran *et al.*, 2014). Hence, an age-specific vulnerability to cannabis-related depression is unclear. Moreover, the population cohort studies that contribute to these meta-analyses often include small numbers of frequent cannabis users and define frequent cannabis liberally, e.g. once per month (Pedersen, 2008; Schoeler *et al.*, 2018). Purposive sampling of frequent cannabis users is one way to address this.

Cross-sectional surveys have found higher levels of anxiety symptoms in people who frequently use cannabis compared to controls (Crippa *et al.*, 2009), with greater levels of cannabis use associated with greater severity of anxiety symptoms (Troisi *et al.*, 1998). A meta-analysis of longitudinal studies reported increased odds of developing any future anxiety condition with previous cannabis use (OR=1.25) (Xue *et al.*, 2020), but it also concluded that results varied considerably and more research is needed. Crucially, the evidence for a relationship between early age-of-onset and later symptoms of anxiety is inconclusive (Fergusson and Horwood, 1997; Gage *et al.*, 2015; Guttmanova *et al.*, 2017). Furthermore, the association between contemporaneous cannabis use and anxiety during adolescence and adulthood is unknown.

Longitudinal studies have consistently reported an association between cannabis use and an increased risk of psychosis and schizophrenia (Andréasson *et al.*, 1987; Van Os *et al.*, 2002; Zammit *et al.*, 2002; Moore *et al.*, 2007; Marconi *et al.*, 2016; Hjorthøj, Posselt and Nordentoft, 2021). Cannabis use during adolescence, compared to adulthood, has been associated with a greater risk of psychotic outcomes (Large *et al.*, 2011; Schimmelmann *et al.*, 2011; Dragt *et al.*, 2012; Galvez-Buccollini *et al.*, 2012; Manrique-Garcia *et al.*, 2012; Di Forti *et al.*, 2014). However, a large cross-sectional study found that in adolescents and young adults, current cannabis use was only associated with psychotic symptoms *after* age 22 and that there was no relationship with age-of-onset (Leadbeater, Ames and Linden-Carmichael, 2019). Positive associations have also consistently been reported between cannabis use and psychotic-like experiences or subclinical symptoms of psychosis (Arseneault *et al.*, 2002; Fergusson, Horwood and Swain-Campbell, 2003; Stefanis *et al.*, 2004; Henquet *et al.*, 2005; Miettunen

et al., 2008; Hides *et al.*, 2009; Kuepper *et al.*, 2011). Moreover, earlier age-of-onset has been linked with greater psychotic-like symptoms in later life in two studies (Stefanis *et al.*, 2004; Schubart *et al.*, 2011). These studies often failed to account for the greater duration of cannabis use in people with earlier onsets compared to later onsets (Schimmelmann *et al.*, 2011; Schubart *et al.*, 2011), which may bias results towards significant, negative associations between age-of-onset and poor mental health. Additionally, the relationship between current cannabis use and concurrent psychotic-like symptoms in adolescents and adults is unknown.

There are therefore some theoretical and empirical grounds to believe that earlier, adolescent use of cannabis may be particularly deleterious to mental health. However, there have been large variations in study design; disparate measures of cannabis use and mental health; and a plethora of discrepant findings regarding age-specific vulnerability. Few studies have compared the contemporary mental health of adolescents with adults, while adolescents are still under 18 years old. Furthermore, although many large epidemiological studies have the advantage of being representative, they often lack substantial numbers of frequent cannabis users; and include adolescent and adult-onset cannabis users with discrepant cannabis use frequencies.

Whether adolescent cannabis use, compared to adult use, genuinely heightens risk of poor mental health remains an unanswered question. In this study, we compared how current cannabis use is associated with presence of severe CUD, and the severity of depression, anxiety, and psychotic-like symptoms in adolescents and adults. Our cannabis-using groups were matched on current cannabis use frequency and our age-groups were matched on gender and current age. Adult users had not frequently used cannabis before age 18.

As registered on the Open Science Framework (OSF) (Lawn *et al.*, 2021), our hypotheses were:

1. Adolescent users will be more likely than adult users to have severe CUD.
2. Cannabis users will have higher levels of (a) depression, (b) anxiety, and (c) psychotic-like symptoms than controls.
3. There will be an interaction between user-group and age-group on (a) depression, (b) anxiety, and (c) psychotic-like symptoms, such that the difference between users and controls (where users > controls) will be greater in adolescents than adults.

For each hypothesis, we also predicted that the association would persist after adjusting for covariates. Additionally, we conducted exploratory, unregistered analyses investigating the relationship between severe CUD and mental health symptoms.

METHODS

Study design

This analysis uses cross-sectional, baseline data from the ‘CannTeen’ longitudinal project. The design has two between-subjects factors: age-group (adolescents and adults) and user-group (users and controls). The full study protocol (Lawn *et al.*, 2020) describes overall aims, participants, power analysis, data collection procedures, tasks, and timelines. Ethical approval was obtained from the University College London (UCL) ethics committee, project ID 5929/003. The study was conducted in line with the Declaration of Helsinki, and all participants provided written, informed consent.

Participants

The full sample comprises 274 participants: 76 adolescent users, 71 adult users, 63 adolescent controls, and 64 adult controls.

Participants were recruited using online advertisements on Facebook, Instagram, Gumtree, and Reddit; school assemblies in London and the surrounding area; in-person flyering; and word-of-mouth. We recruited participants in a targeted process, by advertising to specific age-groups. Potential participants were screened and selected based on their cannabis use and other criteria. Participants were compensated financially for their time.

For full eligibility criteria, see the supplementary materials. In brief, adolescents were aged 16-17 years and adults aged 26-29 years; users reported using cannabis between 1-7 days per week; adult users were excluded if they had used cannabis on a weekly or more frequent basis before the age of 18; and controls reported using either cannabis or tobacco at least once in their life, but with no more than 10 lifetime uses of cannabis. We recruited controls with limited cannabis or tobacco exposure, rather than people with no exposure, with the aim of more closely matching the controls and users on the opportunity to use drugs and associated unmeasurable confounds.

Exclusion criteria for all participants were: current daily use of psychotropic medication, current treatment for a mental health disorder including cannabis use disorder, a personal history of psychotic disorder, or use of any illicit drug except cannabis more than twice per month.

Measures

Psychotomimetic Scales Inventory – Adapted (PSI-a) (Mason *et al.*, 2008)

The PSI-a is a temporally adapted version of the original PSI, a 48-item self-report questionnaire assessing psychotic-like symptoms. Participants were asked questions about how they felt over ‘the last two weeks’, rather than ‘right now’. Each item is answered with ‘not at all’, ‘slightly’, ‘moderately’ or ‘strongly’ and scored from 0-3. Total scores range from 0 to 144. Higher scores indicate greater psychotic-like symptomatology.

Exposure variables

Age-group

Participants were either adults (aged 26-29 years; coded as 0) or adolescents (aged 16-17 years; coded as 1).

Cannabis use frequency

Using a timeline follow-back (Robinson *et al.*, 2014) method, we measured cannabis use frequency in days/week over the previous 12 weeks.

Outcome variables

Beck Depression Inventory-II (BDI) (Beck, Steer and Brown, 1996)

A 21-item self-report questionnaire. Each item is answered with ‘not at all’, ‘mildly’, ‘moderately’ or ‘severely’ and scored from 0 to 3, with total scores ranging from 0 to 63. Higher scores indicate greater levels of depression.

*Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988)*

A 21-item self-report questionnaire. Each item is scored from 0 to 3, with total scores ranging from 0 to 63. Higher scores indicate greater levels of anxiety.

*Psychotomimetic Scales Inventory – Adapted (PSI-a) (Mason *et al.*, 2008)*

The PSI-a is a temporally adapted version of the original PSI, a 48-item self-report questionnaire assessing psychotic-like symptoms. Participants were asked questions about how they felt over ‘the last two weeks’, rather than ‘right now’. Each item is answered with ‘not at all’, ‘slightly’, ‘moderately’ or ‘strongly’ and scored from 0-3. Total scores range from 0 to 144. Higher scores indicate greater psychotic-like symptomatology.

Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) Cannabis Use Disorder (CUD) (American Psychiatric Association, 2013) using the *Mini International Neuropsychiatric Interview (MINI)* (Sheehan *et al.*, 1998)

Severity of CUD was assessed using the MINI, in which 11 DSM-5 symptoms are assessed over the last 12 months. The presence of 0-1 symptoms is considered ‘none’, 2-3 symptoms is considered ‘mild’, 4-5 symptoms is considered ‘moderate’, and 6 or more symptoms is considered ‘severe’. We categorised users into having ‘severe CUD’ (coded as 1) or ‘not severe CUD’ (coded as 0).

Pre-defined covariates

We adjusted for gender, risk-taking, socioeconomic status (SES), problem alcohol use, tobacco use, and other illicit drug use. Risk-taking was measured using the total score from the risk-taking-18 (RT-18) questionnaire (De Haan *et al.*, 2011). Socioeconomic status (SES) was dichotomously measured using maternal education level, with categories of below undergraduate degree or undergraduate degree and above. Problematic alcohol use was measured using the total score from the alcohol use disorder identification test (AUDIT) (Babor *et al.*, 2001). Daily (non-cannabis) tobacco use was dichotomously measured using the timeline follow-back, with categories of daily (≥ 6.5 days per week) or non-daily (< 6.5 days per week) tobacco smoking. Other illicit drug use was dichotomously measured using the timeline follow-back, with categories of monthly (≥ 1 day per month) or less than monthly (< 1 day per month).

Procedure

As per the full protocol (Lawn *et al.*, 2020), participants were first screened and then potentially eligible participants were invited to a baseline session. At the start of the baseline session, inclusion and exclusion criteria and study-required abstinence (zero breathalyser reading; negative saliva drugs screen; self-reported alcohol and cannabis abstinence for 12 hours; self-reported other illicit drug use abstinence for 48 hours) were checked. Subsequently, participants completed the session including the measures described above.

Power

We powered the study to detect a cross-sectional group difference in cannabis use disorder between adolescent and adult cannabis users, as this is a robust finding with a quantified effect size (Chen, O’Brien and Anthony, 2005; Ehlers *et al.*, 2010; Le Strat, Dubertret and Le Foll, 2015) of odds ratio=3, equivalent to Cohen’s $d=0.6$ or Cohen’s $f=0.3$. With $\alpha=0.05$ and a desired power of 0.95, 148 users

were required, split evenly between adolescent and adult users. In fact, we recruited 147 users and a similar number of controls. Crucially, in terms of detecting age-group by user-group interactions, with our total sample size ($n=274$) and an assumed power of 0.8 we are powered to detect at least small interactions of size Cohen's $f \geq 0.17$.

Statistical analyses

Statistical tests were conducted on IBM SPSS Statistics Version 27. For pre-processing of data, assumptions of analyses, and details of missing data see the supplementary materials. We ran linear and logistic regression models in a blockwise manner, see Table S4. Models first included user-group, then age-group and user-group, then their interaction, and then we added pre-defined covariates to the best previous model (which was invariably the model with user-group and age-group as main effects, never the model with the interaction). We used an alpha value of 0.05. We ran post-hoc Bayesian t-tests to assess null findings for users vs. controls, and for adolescent users vs. adult users, with no adjustment for covariates. We assumed equal variances and used a Jeffreys default prior. Bayes factors (BF_{01}) ≥ 3 support the null hypothesis of no difference.

Exploratory, unregistered analyses were conducted to investigate relationships between severe CUD and BDI, BAI and PSI-a (see supplementary materials for full details).

RESULTS

Participant characteristics (Table 1)

All groups had a similar number of males and females. Adolescent users (3.7 days/week) and adult users (4.1 days/week) were matched on cannabis use frequency ($t_{145}=1.198$, $p=0.233$, $d=0.198$). The time since last cannabis use was similar for adolescent users (2.4 days) and adult users (2.5 days) ($t_{145}=0.118$, $p=0.906$, $d=0.019$). See Table 2 for data on cannabis use variables. Adolescent users (17.1 years) and adolescent controls (17.1 years) were matched on age ($t_{137}=0.224$, $p=0.823$, $d=0.038$), as were adult users (27.6 years) and adult controls (27.4 years) ($t_{145}=1.232$, $p=0.220$, $d=0.212$). See Table 1 and supplementary materials for differences in demographic variables.

Regressions

Descriptive statistics for outcome variables are presented in Table 3.

Severe cannabis use disorder (Table 4 and table S6)

Within users, adolescent status predicted likelihood of having severe CUD (OR=4.462, $p<0.001$, 95% CI: 2.106–9.454). This effect persisted after adjusting for covariates (OR=3.474, $p=0.004$, 95% CI: 1.501–8.036).

Depression (Table 4 and table S7)

Adolescent status predicted greater BDI score ($b=3.766$, $p<0.001$, 95% CI: 1.930–5.601). This effect persisted after adjusting for covariates ($b=3.915$, $p<0.001$, 95% CI: 1.994–5.836). User-group, and the user-group by age-group interaction, were not significantly related to BDI score.

Bayesian analyses did not support the null hypothesis that users and controls had similar BDI scores ($BF_{01}=1.846$) nor did they support the null hypothesis that adolescent users and adolescent controls had similar BDI scores ($BF_{01}=0.935$).

Anxiety (Table 4 and table S8)

Adolescent status predicted greater BAI ($b=4.627$, $p<0.001$, 95% CI: 2.642–6.612). This effect persisted after adjusting for covariates ($b=4.528$, $p<0.001$, 95% CI: 2.384–6.671). User-group, and the user-group by age-group interaction, were not significantly related to BAI.

Bayesian analyses supported the null hypothesis that users and controls had similar BAI scores ($BF_{01}=7.724$) and the null hypothesis that adolescent users and adolescent controls had similar BAI scores ($BF_{01}=4.401$).

Psychotic-like symptoms (Table 4 and table S9)

User-status predicted greater PSI-a ($b=7.121$, $p=0.001$, 95% CI: 3.033–11.465). Adolescent status predicted greater PSI-a ($b=7.254$, $p=0.001$, 95% CI: 3.130–11.378). These effects both persisted after adjusting for covariates (user-group: $b=6.004$, $p=0.014$, 95% CI: 1.211, 10.796; age-group: $b=5.509$, $p=0.015$, 95% CI: 1.070, 9.947). The user-group by age-group interaction was not significantly related to PSI-a.

Exploratory results (see supplementary materials)

After splitting the user groups into those with and without severe CUD and comparing (1) adult controls (2) adolescent controls, (3) adult users without severe CUD, (4) adolescent users without severe CUD, (5) adult users with severe CUD, (6) and adolescent users with CUD, there were strong linear effects of group in our outcome variables ($ps<0.001$). Qualitatively, adolescent users with severe CUD had the highest BDI, BAI and PSI-a mean scores (Figures S1, S2 and S3).

When conducting a 2x2 (age-group x CUD-status) ANOVA only in users, there were significant main effects of age-group on BDI ($F(1,143)=4.165$, $p=0.043$, $\eta^2_p=0.028$), BAI ($F(1,143)=4.299$, $p=0.040$, $\eta^2_p=0.029$), and PSI-a ($F(1,142)=4.273$, $p=0.041$, $\eta^2_p=0.029$) and significant main effects of CUD-status on BDI ($F(1,143)=11.236$, $p=0.001$, $\eta^2_p=0.073$), BAI ($F(1,143)=9.815$, $p=0.002$, $\eta^2_p=0.064$), and PSI-a ($F(1,142)=4.525$, $p=0.035$, $\eta^2_p=0.031$). However, all interactions were non-significant. Thus, being an adolescent and having severe CUD were additively associated with greater BDI, BAI and PSI-a. After adjusting for our pre-defined covariates and cannabis use frequency, the CUD-status main effect remained for BDI ($F(1,132)=9.382$, $p=0.003$, $\eta^2_p=0.066$) and BAI ($F(1,132)=7.414$, $p=0.007$, $\eta^2_p=0.053$), but the user-group effect for PSI-a and the age-group effects for all outcomes became non-significant.

DISCUSSION

This cross-sectional study compared presence of severe CUD and the severity of mental health symptoms in adolescent and adult cannabis users with gender- and age-matched controls. Adolescent users were significantly more likely to have severe CUD than adult users. Both cannabis user-status and adolescent-status were associated with greater psychotic-like symptoms, additively resulting in adolescent cannabis users having the greatest psychotic-like symptoms. User-status was not associated with depression or anxiety levels and there was Bayesian support for users and controls having similar anxiety levels. No significant interactions were found between user-group and age-group for depression, anxiety, or psychotic-like symptoms, indicating a lack of support for an adolescent-specific vulnerability to cannabis-related mental health problems. Exploratory analyses suggested that severe CUD predicted worse mental health symptoms, which resulted in adolescent users with severe CUD having the highest levels of depression, anxiety, and psychotic-like symptoms.

After adjustment for covariates, adolescents had a 3.5 times greater odds of having severe CUD than adults, with 50% of this group endorsing more than six symptoms. This effect size is similar to previous estimates of increased risk (Chen, Storr and Anthony, 2009; Ehlers *et al.*, 2010; Wittchen *et al.*, 2011; Le Strat, Dubertret and Le Foll, 2015), demonstrating the effect's replicability. CUD risk was greater in adolescents despite their shorter duration of cannabis use compared to adults. This is notable because previous studies have mainly tested associations between age-of-onset and addiction (and other outcome variables) in adults, where early age-of-onset is also associated with greater duration of cannabis use. Moreover, unlike many previous studies, our adolescent and adult user groups were matched on cannabis frequency, which therefore excludes this difference as a possible explanation. However, adolescent users reported using more cannabis per day of use (1.1g) than adults (0.6g), which may partially contribute to cannabis problems (Zeisser *et al.*, 2012; Tomko *et al.*, 2018; Callaghan, Sanches and Kish, 2020). On the other hand, this estimate may be inaccurate (Hindocha, Freeman and Curran, 2017; Hindocha, Norberg and Tomko, 2018) and further work carefully examining relationships between precise cannabis quantities, or better still standard units (Freeman and Lorenzetti, 2020), and addiction is needed.

We found null relationships between cannabis user-status and depression and anxiety, and no evidence for adolescent vulnerability. Furthermore, the absence of associations between cannabis use frequency and our measures of depression and anxiety in users (see supplementary materials) casts further doubt on the impact of cannabis use on subclinical levels of anxiety and depression. Previous research has suggested that cannabis use is associated with an augmented risk of depression and anxiety in adults (Degenhardt, Hall and Lynskey, 2001, 2003; Crippa *et al.*, 2009; Horwood *et al.*, 2012; Lev-Ran *et al.*, 2014; Guttmanova *et al.*, 2017) and associated with greater risks later in life for adolescents (Gobbi *et*

et al., 2019). Given the effect sizes of these relationships from meta-analyses are small (Chen, Cohen and Chen, 2010) (odds ratios of 1.17-1.62 for depression and 1.25 for anxiety), our sample was likely underpowered to detect differences in clinical anxiety and depression. This also reflects an important difference: our study used continuous self-report measures rather than interview-based clinical diagnoses.

Nevertheless, it is notable that in our sample of relatively frequent cannabis users, using at an average frequency of four days/week, there was no significant evidence of greater anxiety or depression in cannabis users aged 16-17 years compared to gender- and age-matched controls or cannabis-matched adults. Our study was powered to detect interactions with Cohen's $f \geq 0.17$. For anxiety, the null differences were supported by a Bayesian analysis. There has been inconsistent evidence of heightened cannabis-related vulnerability at younger ages for both disorders (Hayatbakhsh *et al.*, 2007; Horwood *et al.*, 2012; Lev-Ran *et al.*, 2014; Guttmanova *et al.*, 2017; Hosseini and Oremus, 2019; Leadbeater, Ames and Linden-Carmichael, 2019). In line with previous research, our study further suggests there is not sufficient evidence to claim that cannabis use during adolescence is associated with a greater risk of depression or anxiety compared to cannabis use in adulthood.

Previous research has consistently implicated cannabis in the development of clinical psychosis, psychotic-like, schizotypal, or subclinical symptoms (Arseneault *et al.*, 2002; Henquet *et al.*, 2005; Moore *et al.*, 2007; Miettunen *et al.*, 2008; Hides *et al.*, 2009; Kuepper *et al.*, 2011; Marconi *et al.*, 2016). Likewise, cannabis use was significantly associated with psychotic-like symptoms in our sample of adolescents and adults, a relationship that remained significant after adjusting for covariates. Although we did not measure clinical psychotic disorders, these findings indicate an important augmented risk, given the amplified chance of transition to psychosis with subclinical symptoms (Kuepper *et al.*, 2011; Kaymaz *et al.*, 2012). Adolescents overall had greater psychotic-like symptoms than adults, hence there was an additive effect, resulting in adolescent users showing the greatest severity. Indeed, adolescent users' mean PSI-a score was 75% higher than that of adult controls. However, age-group did not moderate the impact of user-group. Thus, there was no evidence of synergistic vulnerability.

Our exploratory analyses suggested that there was a consistent pattern in depression, anxiety and psychotic-like symptoms for those with and without severe CUD. Adolescent users with CUD consistently had the highest mean. Only adolescent users with severe CUD significantly differed from other groups and only they had greater odds of having at least mild anxiety or depression relative to the reference category, adult controls. When analysing users, adolescence and severe CUD were additively and significantly associated with mental health symptoms, explaining why adolescent users with severe CUD have the highest means. However, there were no significant interactions, so severe CUD did not

have a *greater* effect in adolescents than adults. Previous research has shown that dependent use of cannabis is particularly strongly associated with mental health problems (van der Pol *et al.*, 2013; Braidwood *et al.*, 2018), while non-dependent frequent use may not be (Braidwood *et al.*, 2018). Our exploratory findings add to these by demonstrating the relevance of CUD to mental health problems in adolescence, despite the fact that user-group differences were absent for anxiety and depression. This is important by virtue of adolescents' heightened risk of developing CUD and their greater likelihood of existing mental health problems. However, these results should be interpreted cautiously as they were exploratory, the sub-group sample sizes were small (see table S11), adjustment for covariates removed the significant effect of CUD-status on psychotic-like symptoms, and the study was not designed to compare users with and without CUD.

Strengths and limitations

Direct comparisons of adolescent and adult cannabis users are rare. One major strength of this study is its novel design in which four groups were compared: adolescent and adult cannabis users and controls, who were closely matched on cannabis use frequency, gender, and age. Controls had been exposed to limited cannabis or tobacco use, reducing unmeasured confounding differences with users. Adult cannabis users had never used cannabis frequently before age 18, ensuring adolescent development was not substantially impacted by cannabis. Recent abstinence from alcohol and other drugs was biochemically verified. Furthermore, we pre-registered our protocol and analyses, adjusted for pre-defined covariates, and objectively assessed abstinence from all drugs.

Due to the sampling methodology, the results cannot be interpreted as representative of the general population. However, this approach was necessary in order to target frequent cannabis users and select matched controls and maximise statistical power to test our hypotheses. This approach is common in observational cannabis research (Morgan *et al.*, 2012; van der Pol *et al.*, 2013), where baseline levels of illicit drug use are relatively low in the general population. Another limitation is the cross-sectional nature of the analysis. As some previous studies imply there may be a time-lagged effect of cannabis on mental health (Gobbi *et al.*, 2019), this could contribute to our null findings.

Inevitably, our adolescent users began using cannabis earlier than our adult users. Although we aimed to recruit similar adolescent and adult users; matched gender, age and cannabis frequency; compared demographics and adjusted for relevant covariates, it is still possible that people who initiate cannabis use early in life are qualitatively different from those who initiate cannabis use later in life in ways we did not account for. These pre-existing differences could have impacted our results. Crucially, however, age-of-onset in adult users was not associated with mental health symptomatology and the extant literature concerning these relationships is conspicuously equivocal (Lev-Ran *et al.*, 2014;

Guttmanova *et al.*, 2017). Moreover, arguably, we cannot disaggregate current age, age-of-onset, and duration of use. Triangulation of existing and future longitudinal research will allow conclusions about the impacts of these specific, closely related exposure variables to be drawn.

Conclusions

In sum, 16–17-year-olds were not at an interactively greater risk of cannabis-related mental health problems, compared to 26-29-year-olds. Researchers and policymakers should avoid sweeping generalisations that ‘adolescents are more vulnerable to the harmful effects of chronic cannabis use’. However, adolescents have an amplified risk of severe CUD relative to adults, which in combination with being young, augments symptoms of mental ill health. Cannabis harm reduction campaigns should therefore highlight the greater risk of addiction to cannabis during adolescence.

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Figure 1. Bar charts showing means, error bars representing 95% confidence intervals around the mean, and distribution of the data in adolescent controls (n=63) and users (n=76), and adult controls (n= 64) and users (n=71) for (a) Beck depression inventory (BDI) scores. Adolescents have greater BDI scores than adults (***p<0.001 adjusted and unadjusted), no difference between users and controls, and no interaction. (b) Beck Anxiety Inventory (BAI) scores. Adolescents have greater BAI scores than adults (***p<0.001 adjusted and unadjusted), no difference between users and controls, and no interaction. (c) Psychotomimetic Symptoms Inventory-adapted (PSI-a) scores. Adolescents have greater PSI-a scores than adults (**p=0.001 unadjusted, p=0.015 adjusted), and users have greater PSI-a scores than controls (**p=0.01 unadjusted, p=0.014 adjusted). (d) Percentage of adolescent and adult users with and without severe cannabis use disorder (CUD). Adolescents were more likely to have severe CUD than adults identified (***p<0.001 unadjusted, p=0.004 adjusted). In (a-c) controls are shown by black circles and dark grey bars; users are shown by green/grey crosses and light green/grey bars with diagonal stripes. In (d) the percentage of participants with severe CUD is shown by the black bar and the percentage of participants without severe CUD is shown by the grey bar.

● Control
 x User

Table 1. Summary of participant demographics. Sociodemographic and non-cannabis drug use variables for adolescent controls, adolescent users, adult controls, and adult users. Group differences are highlighted in the final column, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. SES (maternal education) has data missing for one adolescent user, one adolescent control, three adult users, and one adult control. Ethnicity has one adolescent user missing. Alcohol frequency and AUDIT scores include participants who have not consumed alcohol within the last 12 weeks and they are assigned zero. SES=socioeconomic status, RT-18=Risk-Taking 18, AUDIT=Alcohol use disorders identification test. For continuous data mean (SD) [median, minimum-maximum] is shown, for categorical data n (%) is shown.

	Adolescent control (n=63)	Adolescent user (n=76)	Adult control (n=64)	Adult user (n=71)	Group differences
Gender					
Male	31 (49.2%)	38 (50.0%)	31 (48.4%)	38 (53.5%)	
Female	32 (50.8%)	38 (50.0%)	33 (51.6%)	33 (46.5%)	
Age (years)	17.1 (0.5) [17.1, 16.1-18.0]	17.1 (0.6) [17.1, 16.2-18.0]	27.4 (1.0) [27.3, 26.0-30.0]	27.6 (1.2) [27.3, 26.0-30.0]	Adults > adolescents***
Ethnicity					
White	40 (63.5%)	51 (68.0%)	41 (64.1%)	45 (63.4%)	
Mixed	7 (11.1%)	15 (20.0%)	3 (4.7%)	8 (11.3%)	
Asian	10 (15.9%)	2 (2.7%)	15 (23.4%)	11 (15.5%)	
Black	2 (3.2%)	4 (5.3%)	2 (3.1%)	6 (8.5%)	
Other	2 (3.2%)	3 (4.0%)	2 (3.1%)	1 (1.4%)	
Prefer not to say	2 (3.2%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	
SES					
Mother's education below undergraduate degree	26 (41.9%)	31 (41.3%)	36 (57.1%)	37 (54.4%)	
Mother's education undergraduate degree or above	36 (58.1%)	44 (58.7%)	27 (42.9%)	31 (45.6%)	Adolescents > adults ***
RT-18	9.1 (4.1) [10.0, 0.0-17.0]	11.4 (3.1) [11.0, 3.0-18.0]	7.6 (4.1) [7.0, 0.0-16.0]	8.8 (3.9) [8.0, 3.0-17.0]	Users > controls*** & Adolescents > adults***

Alcohol, use frequency (days/week)		0.7 (0.7) [0.4, 0.0 – 3.7]	0.6 (0.6) [0.4, 0.0-3.3]	1.4 (1.0) [1.4, 0.0 - 5.3]	1.5 (1.4) [0.9, 0.0 – 6.8]	Adults > adolescents***
AUDIT		4.3 (3.5) [4.0, 0.0-13.0]	6.5 (4.6) [6.0, 0.0-18.0]	5.5 (4.2) [5.0, 0.0-22.0]	6.0 (4.3) [5.0, 0.0-18.0]	Users > controls **
Tobacco, daily use						
	No	61 (96.8%)	66 (86.8%)	62 (96.9%)	62 (87.3%)	
	Yes	2 (3.2%)	10 (13.2%)	2 (3.1%)	9 (12.7%)	Users > controls **
Other illicit drug use, monthly use						
	No	61 (96.8%)	31 (40.8%)	63 (98.4%)	53 (74.6%)	
	Yes	2 (3.2%)	45 (59.2%)	1 (1.6%)	18 (25.4%)	Users > controls*** & Adolescent users > adult users***

Table 2. Cannabis use variables for adolescent controls, adolescent users, adult controls, and adult users. Group differences are highlighted in the final column, *p<0.05, **p<0.01, ***p<0.001. Amount of cannabis used on a day of use has data missing for three adult users. For continuous data mean (SD) [median, minimum-maximum] is shown, for categorical data n (%) is shown.

	Adolescent control (n=63)	Adolescent user (n=76)	Adult control (n=64)	Adult user (n=71)	Group differences
Ever used cannabis (controls)					
No	8 (12.7%)	NA	2 (3.1%)	NA	
Yes	55 (87.3%)	NA	62 (96.9%)	NA	Adult controls > adolescent controls*
Cannabis, number of lifetime uses (controls)	3.4 (2.8) [2.0, 0.0-10.0]	NA	4.5 (3.1) [4.0, 0.0-10.0]	NA	Adults > adolescents*
Cannabis, time since last use (days) (users)	NA	2.4 (2.6) [1.6, 0.5 – 14.0]	NA	2.5 (4.6) [1.0, 0.5 – 35.0]	
Cannabis, age of first ever use (years) (users)	NA	14.6 (1.1) [14.7, 11.0 – 16.6]	NA	18.0 (2.9) [17.9, 13.0 – 25.0]	Adults > adolescents*
Cannabis, use frequency (days/week) (users)	NA	3.7 (1.9) [3.4, 0.8 – 6.9]	NA	4.1 (1.9) [3.8, 0.8 – 6.9]	
Cannabis, amount used on a day of use (grams) (users)	NA	1.1 (0.8) [1.0, 0.1 – 4.0]	NA	0.6 (0.7) [0.4, 0.03 – 3.5, n=68]	Adolescents > adults*

Table 3. Descriptive statistics for the four outcome variables. BDI=Beck depression inventory, BAI=Beck anxiety inventory, PSI-a=Psychotomimetic states inventory-adapted, DSM-5 CUD=Diagnostic and statistical manual of mental disorders-5 cannabis use disorder. Data is missing for one adolescent user for the PSI-a. Mean (SD) [median, minimum – maximum] are shown. **p<0.01, ***p<0.001.

	Adolescent control (n=63)	Adolescent user (n=76)	Adult control (n=64)	Adult user (n=71)	Group differences
BDI	9.90 (7.13) [10.00, 0.00-33.00]	12.71 (8.34) [11.00, 1.00-41.00]	7.30 (7.04) [5.00, 0.00-28.00]	7.94 (8.06) [6.00, 0.00-31.00]	Adolescents > adults***
BAI	11.37 (8.93) [10.00, 0.00-39.00]	13.13 (10.34) [10.50, 0.00-46.00]	7.86 (5.54) [8.00, 0.00-24.00]	7.54 (7.45) [5.00, 0.00-32.00]	Adolescents > adults***
PSI-a	23.05 (14.30) [21.00, 1.00-67.00]	32.71 (20.93) [29.00, 2.00-97.00, n=75]	18.53 (15.40) [16.00, 0.00-64.00]	23.07 (17.04) [18.00, 2.00-78.00]	Adolescents > adults** & Users > controls**
Severe DSM-5 CUD:					
No		38 (50.0%)		58 (81.7%)	
Yes		38 (50.0%)		13 (18.3%)	Adolescent user > adult user***

Table 4. Summary of regression results. Do the exposure variables (user-group and age-group, and their interaction) significantly predict the outcome variables? Severe CUD models were run only in users (n=147, adjusted models n=143). Depression, anxiety, and psychotic-like symptom models were run in the total sample (depression and anxiety: n=274, adjusted models n=268; psychotic-like symptoms: n=273, adjusted model n=267). Adjusted terms are from models including pre-defined covariates: gender, socioeconomic status (SES), risk taking (RT-18), daily smoking, alcohol use disorder identification test (AUDIT) and other drug use. The best models never included the interaction term, hence there are no adjusted interaction terms. CUD=cannabis use disorder; NA=not applicable; b=unstandardized beta; OR=odds ratio.

	Severe CUD (n=147)	Depression (n=274)	Anxiety (n=274)	Psychotic-like symptoms (n=273)
User-group	NA	No	No	Yes (b=7.121, p=0.001)
Age-group	Yes (OR=4.462, p<0.001)	Yes (b=3.766, p<0.001)	Yes (b=4.627, p<0.011)	Yes (b=3.130, p=0.001)
User-group X age-group	NA	No	No	No
Adjusted user-group	NA	No	No	Yes (b=6.004, p=0.014)
Adjusted age-group	Yes (OR=3.474, p=0.004)	Yes (b=3.915, p<0.001)	Yes (b=4.528, p<0.001)	Yes (b=5.509, p=0.015)

CannTeen: Cannabis use disorder, depression, anxiety, and psychotic-like symptoms in adolescent and adult cannabis users and age-matched controls

Disclaimer: This is preliminary scientific work that has not been peer reviewed.

Supplementary Materials

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Section 1: Background Information

Cannabis is particularly popular in adolescents, with 19.3% of 15 year-olds reported using cannabis in the past year, compared to 13.4% of 25-29 year olds and 7.3% of 30-34 year olds (NHS-Digital, 2018, 2019).

Cannabis is notably more popular amongst 15-year olds than other popular illicit drugs, including nitrous oxide (where 10.9% reported use in the last year), cocaine (4.2%) and ecstasy (3.9%) (NHS-Digital, 2018).

The second most common primary problem drug for <18s was alcohol, at 14% (NDTMS, 2019). From 2006 to 2019, there was a 40% increase in the number of young people receiving cannabis treatment, while there were falls of between 37-91% for cocaine, alcohol, amphetamine and opiates. Hence, cannabis is a particularly popular drug for adolescents in the UK and treatment demand for cannabis has increased in the past decade.

Section 2: Inclusion and Exclusion Criteria

Table S1. Inclusion and exclusion criteria for all participants, and specific criteria for each group. BMI=Body Mass Index

	Inclusion criteria	Exclusion criteria
All participants	<ul style="list-style-type: none"> • Able to come to UCL five times over the next year • Capacity to give informed consent • Normal or corrected-to-normal vision • Fluent in English 	<ul style="list-style-type: none"> • Any illicit drug use within 48 hours of the behavioural baseline session, verified with self-report and saliva testing • Any cannabis or alcohol use within 12 hours of the behavioural baseline session, verified with self-report and saliva/breathalyser testing. • Personal history of a diagnosed psychotic episode or disorder • Any one illicit drug taken >2 days/month (averaged over last 3 months) (except laughing gas) • Use of laughing gas >1 day/week (averaged over last 3 months) • Receiving treatment for any mental health condition, including cannabis dependence, in the last month • Unwilling to give blood samples or likely to faint on blood sampling • Current daily use of a medication which is commonly psychotropic • Any mental or physical health problem judged to be problematic for the study, by a medical doctor
Teenage cannabis users	<ul style="list-style-type: none"> • Aged 16-17 years • Cannabis use at a frequency of 1-7 days/week (averaged over last 3 months) 	<ul style="list-style-type: none"> • Age-adjusted BMI <2nd percentile or >99.6th percentile
Teenage controls	<ul style="list-style-type: none"> • Aged 16-17 years • Between 1 and 10 days of lifetime cannabis use <i>or</i> 0 days of lifetime cannabis use and at least 1 day of lifetime cigarette/roll-up use 	<ul style="list-style-type: none"> • Age-adjusted BMI <2nd percentile or >99.6th percentile • Cannabis use more than once in the last 3 months before behavioural baseline session • Cannabis use in the month prior to the behavioural baseline session
Adult cannabis users	<ul style="list-style-type: none"> • Aged 26-29 years • Cannabis use at a frequency of 1-7 days/week (averaged over last 3 months) 	<ul style="list-style-type: none"> • Before the age of 18, cannabis use at a frequency of once per week or more for a period of 3 months or more. • BMI <18.5 or BMI>34.9

Adult controls	<ul style="list-style-type: none">• Aged 26-29 years• Between 1 and 10 days of lifetime cannabis use <i>or</i> 0 days of lifetime cannabis use and at least 1 day of lifetime cigarette/roll-up use	<ul style="list-style-type: none">• Cannabis use more than once in the last 3 months before behavioural baseline session• Cannabis use in the month prior to the baseline session• BMI <18.5 or BMI>34.9
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Section 3: Measures and Statistical Analyses

3.1 Other measures

Instant saliva drugs tests (either Alere DDSV 703 or ALLTEST DSD-867MET/C) were administered to ensure that participants had not recently used cocaine, THC, opiates, amphetamine, methamphetamine, or benzodiazepine. Blood alcohol concentration (BAC) was measured using a breathalyser (Lion Alcometer 500) to ensure no alcohol had recently been consumed. A 12-week timeline follow-back (Robinson *et al.*, 2014) was completed to check recent abstinence and quantify frequency of cannabis, alcohol, tobacco and other illicit drug use.

3.3 Pre-defined covariates

Pre-defined covariates summary:

- Sex. Coded as: 0=female; 1=male
- Mother's educational level. Coded as 0=below undergraduate degree; 1=undergraduate degree or above
- RT-18 total score
- AUDIT total score
- Daily tobacco use. Coded as 0=non-daily; 1=daily.
- Frequency of other illicit drug use in days-per-month

3.4 Predictor and outcome variables

Predictor variables:

- Age-Group. Coded as: 0=adults; 1=teenagers
- User-Group. Coded as: 0=controls; 1=users
- Frequency of cannabis use, in days-per-week.

Outcome variables:

- BDI total score
- BAI total score
- PSI-a total score
- Severe CUD

3.5 Data Pre-processing

Missing questionnaire items were imputed using single-value substitution, where the number of missing items is <30% total items (Gmel, 2001; Hawthorne and Elliott, 2005; Shrive *et al.*, 2006). The missing items were replaced with the overall participant's mean response for that questionnaire, rounded to the nearest integer. Any questionnaires with >30% missing items were deleted entirely and treated as missing data.

Questionnaire totals were Winsorized, within each group, using Tukey's method, i.e. totals which were greater than three times the interquartile range away from the upper or lower quartile of the distribution were replaced with the nearest non-outlying datapoint. Impossible answers to any questions were deleted and treated as missing.

Note, this cross-sectional mental health and addiction data had previously been provisionally analysed for a masters dissertation and reported as a poster presentation (Lawn *et al.*, 2020). Our hypotheses remained the same throughout.

Table S2. Number of participants who had <30% data missing which was then imputed and number of participants where data was excluded due to number of missing items in a questionnaire >30%.

Variable	Participants with some missing data, <30%	Participants with fully missing data, >30%
PSI	16	1
BDI	4	0
BAI	12	0
RT	5	0
AUDIT	0	0
CUDIT	2	0
DSM-5 CUD	4	0

Table S3. Number of datapoints that were Winsorized using Tukey's method

Variable	Number of datapoints
BDI	3
BAI	0
PSI	0

3.6 Linear and Logistic Regression Models & Assumptions

First, we ran a logistic regression model only in users for severe CUD with age-group as the only predictor. Subsequently, we ran linear regression models in all participants for BDI, BAI, and PSI-a, in which user-group was entered in first block, then user-group and age-group in the second block, and their interaction in the third block. Then we added our pre-defined covariates to the best model for each outcome variable. This was always the model with both main effects, but not the interaction.

Additionally, we ran models in only users for BDI, BAI, PSI-a, and severe CUD with cannabis use frequency and age-group in the second block, and their interaction in their third block. Then we added our pre-defined covariates to the best model for each outcome variable. This was always the model with both main effects, but not the interaction. Within users, this tested the relationship between cannabis use frequency and our outcomes, as well as testing whether this relationship was moderated by age-group

Linear Regression models – assumptions

With all linear regression models, we checked for multicollinearity of predictors (using correlations and VIF values), normality of residuals (using visual inspection of histograms, Kolmogorov-Smirnov tests, skewness and kurtosis values), cases of influence (using Cook's distances), heteroscedasticity of variance and independence of errors, to ensure the models met assumptions.

For each linear regression model, we assessed R-square change values and interpreted the predictors' unstandardised betas and their 95% confidence intervals.

All assumptions were met for all models. Residuals in the models were visually inspected and were normal, homogeneity of variance of residuals was met, Durbin-Watson values were near 2, Cook's distances were very small (<0.1) and correlations between predictors were acceptably small.

Logistic Regression models - assumptions

With all logistic regression models we checked adequate presence of data in the yes/no categories for both groups, multicollinearity of predictors, and cases of influence to ensure the data meet assumptions.

We interpret odds ratios and 95% confidence intervals for the predictors. We consider $-2 \log$ likelihood and Nagelkerke R-square values of the models.

Table S4. Logistic and linear regression models in all participants. CUD=cannabis use disorder, BDI=Beck Depression Inventory, BAI=Beck Anxiety Inventory, PSI-a=Adapted psychotomimetic states inventory

Outcome variable	Model	Predictor variables
Severe CUD	Model 1a	Age-group
	Model 1b	Age-group and covariates
BDI	Model 2a	User-group
	Model 2b	User-group and age-group
	Model 2c	User-group, age-group and user-group by age-group interaction
	Model 2d	User-group, age-group (best model) and covariates
BAI	Model 3a	User-group
	Model 3b	User-group and age-group
	Model 3c	User-group, age-group and user-group by age-group interaction
	Model 3d	User-group, age-group (best model) and covariates
PSI-a	Model 4a	User-group
	Model 4b	User-group and age-group
	Model 4c	User-group, age-group and user-group by age-group interaction
	Model 4d	User-group, age-group (best model) and covariates

3.7 Exploratory statistical analyses

Clinical cut-offs

For BDI, a score of 14 or above was considered mild depression or above. For BAI, a score of 8 or above was considered mild anxiety or above.

We conducted logistic regression analyses to determine if user-group, age-group and their interaction predicted presence of mild depression or anxiety.

We did not conduct logistic regressions with PSI-a because this does not have a validated cut-off.

Correlations

We conducted Pearson correlations to test the interrelationships between BDI, BAI and PSI-a. We also conducted Pearson correlations to test associations between age-of-onset and BDI, BAI and PSI-a in only adult users.

Relationships between severe CUD and depression, anxiety, and psychotic-like symptoms

To test for associations between severe CUD and mental health symptoms, we split the participants into the following groups, with the following codes:

- Adult controls (1)
- Adolescent controls (2)
- Adult users without severe CUD (3)
- Adolescent users without severe CUD (4)
- Adult users with severe CUD (5)
- Adolescent users with severe CUD (6)

First, we ran one-way ANOVAs with a factor of group, with six levels as the groups above, and BDI, BAI and PSI-a as outcome variables. Although this approach loses the ability to detect interactions, it allows the comparison between control groups and user-groups with and without severe CUD. We investigated linear relationships between group and outcome variables. We conducted Bonferroni-corrected t-tests to investigate where differences lay between groups.

Second, we ran logistic regressions to investigate how these groups predicted presence of mild anxiety or depression, with adult controls as the reference category. We did not include PSI-a because this does not have a validated cut-off.

Third, only in users, we ran two-way ANOVAs with factors of age-group and CUD-status (severe CUD or not). This allowed us to statistically separate the impact of age-group and CUD-status and test their interaction, but only within users. Fourth, we included our pre-defined covariates and cannabis use frequency in ANCOVA models, to test if the effects were robust to adjustment, especially given participants with severe CUD have higher frequency of cannabis use.

Section 4. Participants

Significantly more adolescents were in the high SES category than adults ($\chi^2_1=5.345$, $p=0.021$), they used alcohol less frequently than adults ($F_{1,270}=44.114$, $p<0.001$, $\eta_p^2=0.140$), and they had higher RT-18 scores than adults ($F_{1,270}=21.077$, $p<0.001$, $\eta_p^2=0.072$)

Users had higher AUDIT score than controls ($F_{1,270}=7.099$, $p=0.008$, $\eta_p^2=0.026$), they were more likely to use tobacco on a daily basis than controls ($\chi^2_1=8.467$, $p=0.004$), they had higher RT-18 scores than controls ($F_{1,270}=14.847$, $p<0.001$, $\eta_p^2=0.052$), and were more likely to use other illicit drugs on a monthly basis than controls ($\chi^2_1=61.103$, $p<0.001$). Additionally, adolescent users were more likely to use other illicit drugs on a monthly basis than adult users ($\chi^2_1=17.183$, $p<0.001$).

For controls, adults had used cannabis slightly more times (4.5) in their life than adolescents (3.4) ($t_{125}=2.067$, $p=0.041$, $d=0.367$) and a greater proportion of adult controls had ever used cannabis than adolescent controls ($\chi^2_1=4.011$, $p=0.045$) (Table 2). For users, adolescents (14.6 years) first tried cannabis at an earlier age than adults (18.5 years) ($t_{144}=9.647$, $p<0.001$, $d=1.598$) and they reported using more cannabis (1.1g) on a day of use than adults (0.6g) ($t_{142}=3.623$, $p<0.001$, $d=0.605$).

Table S5. Lifetime drug use variables for adolescent controls, adolescent users, adult controls and adult users for ever (lifetime) use and use within the past 12 weeks: n (%). Use of e-cigarettes in past 12 months is missing for one adolescent user.

	Adolescent control	Adolescent user	Adult control	Adult user
Alcohol: ever used	61 (96.8%)	75 (98.7%)	64 (100.0%)	71 (100.0%)
Alcohol: used in past 12 weeks:	55 (87.3%)	71 (93.4%)	61 (95.3%)	67 (94.4%)
Tobacco (non-cannabis, i.e. cigarettes & roll-ups): ever used	49 (77.8%)	74 (97.4%)	58 (90.6%)	66 (93.0%)
Tobacco (non-cannabis, i.e. cigarettes & roll-ups): used in past 12 weeks:	18 (28.6%)	59 (77.6%)	18 (28.1%)	39 (54.9%)
Ecstasy: ever used	5 (7.9%)	54 (71.1%)	21 (32.8%)	52 (73.2%)
Ecstasy: used in past 12 weeks	1 (1.6%)	35 (46.1%)	2 (3.1%)	22 (31.0%)
Laughing gas: ever used	22 (34.9%)	66 (86.8%)	24 (37.5%)	43 (60.6%)
Laughing gas: used in past 12 weeks	4 (6.3%)	37 (48.7%)	1 (1.6%)	5 (7.0%)
E-cigarette: ever used	33 (52.4%)	50 (65.8%)	16 (25.0%)	36 (50.7%)
E-cigarette: used in past 12 weeks	10 (15.9%)	9 (12.0%)	3 (4.7%)	9 (12.7%)
Ketamine: ever used	7 (11.1%)	48 (63.2%)	10 (15.6%)	35 (49.3%)
Ketamine: used in past 12 weeks	4 (6.3%)	36 (47.4%)	1 (1.6%)	10 (14.1%)
LSD: ever used	1 (1.6%)	29 (38.2%)	3 (4.7%)	27 (38.0%)
LSD: used in past 12 weeks	0 (0.0%)	10 (13.2%)	0 (0.0%)	5 (7.0%)
Cocaine: ever used	1 (1.6%)	28 (36.8%)	18 (28.1%)	52 (73.2%)
Cocaine: used in past 12 weeks	1 (1.6%)	13 (17.1%)	6 (9.4%)	23 (32.4%)
Magic mushrooms: ever used	1 (1.6%)	16 (21.1%)	12 (18.8%)	39 (54.9%)
Magic mushrooms: used in past 12 weeks	0 (0.0%)	3 (3.9%)	3 (4.7%)	6 (8.5%)
Alprazolam ‘Xanax’: ever used	0 (0.0%)	23 (42.6%)	3 (5.0%)	10 (17.2%)
Alprazolam ‘Xanax’: used in past 12 weeks	0 (0.0%)	4 (7.5%)	0 (0.0%)	2 (3.4%)
Diazepam ‘Valium’: ever used	0 (0.0%)	13 (24.1%)	6 (10.0%)	12 (21.1%)
Diazepam ‘Valium’: used in past 12 weeks	0 (0.0%)	3 (5.7%)	1 (1.7%)	0 (0.0%)
Amphetamine: ever used	1 (1.6%)	13 (17.1%)	2 (3.1%)	21 (29.6%)
Amphetamine: used in past 12 weeks	0 (0.0%)	5 (6.6%)	0 (0.0%)	4 (5.6%)
Synthetic cannabinoids: ever used	0 (0.0%)	5 (6.6%)	2 (3.1%)	11 (15.5%)
Synthetic cannabinoids: used in past 12 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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THIS IS A PRELIMINARY SCIENTIFIC WORK THAT HAS NOT BEEN PEER REVIEWED

Methamphetamine: ever used	0 (0.0%)	0 (0.0%)	1 (1.6%)	2 (2.8%)
Methamphetamine: used in past 12 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Heroin: ever used	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)
Heroin: used in past 12 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Crack cocaine: ever used	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.8%)
Crack cocaine: used in past 12 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Section 5. Results from Logistic and Linear Regression Models

Table S6. Logistic regression models (model 1a and 1b) with outcome variable severe cannabis use disorder (CUD) and exposure variable age-group, in users. Model 1a includes age-group as a predictor (adolescents and adult) (n=147). Model 1b (n=143) includes age-group and predefined covariates (sex, socioeconomic status (SES), risk taking (RT-18), daily smoking, alcohol use disorder identification test (AUDIT) and other drug use). CI = confidence interval.

	-2 log likelihood	Nagelkerke R²	P for change in model	Predictor	Unstandardised beta	Standard error	Wald	p	Odds ratio	95% CI odds ratio: lower	95% CI odds ratio: upper	N
Model 1a	172.959	0.149	<0.001	Age-group	1.495	0.383	15.235	<0.001	4.462	2.106	9.454	147
Model 1b	164.725	0.183	0.470	Age-group	1.245	0.428	8.465	0.004	3.474	1.501	8.036	143
				Gender	0.090	0.388	0.053	0.817	1.094	0.511	2.342	
				SES	-0.442	0.391	1.279	0.258	0.643	0.299	1.383	
				RT-18	0.071	0.058	1.536	0.215	1.074	0.959	1.202	
				Daily Smoker	0.387	0.547	0.500	0.479	1.472	0.504	4.296	
				AUDIT	0.038	0.043	0.782	0.377	1.038	0.955	1.129	
				Other drug use	0.267	0.417	0.411	0.521	1.306	0.577	2.956	

Table S7. Linear regression models (2a, 2b and 2d) with outcome variable Beck Depression Inventory (BDI) and exposure variables user-group and age-group in all participants.

Model 2a includes user-group only (cannabis user and controls) (n=274); Model 2b includes user-group and age-group (adults and adolescents) (n=274). Model 2c includes user-group, age-group and their interaction (n=274). Model 2d (n=268) is an adjusted version of model 2b which includes covariates (gender, socioeconomic status (SES), risk taking (RT-18), daily smoker, alcohol use disorder identification test (AUDIT) score and other drug use) (n=268, due to missing data). CI=confidence interval.

	Change in R ² squared	P for change in model	df1, df2	Predictor	Unstandardised beta	Standard error	95% CI beta: lower	95% CI beta: upper	p	N
Model 2a	0.013	0.059	1, 272	User-Group	1.818	0.960	-0.073	3.708	0.059	274
Model 2b	0.056	<0.001	1, 271	User-Group	1.739	0.935	-0.101	3.579	0.064	274
				Age-Group	3.766	0.932	1.930	5.601	<0.001	
Model 2c	0.005	0.249	1, 270	User-Group	0.647	1.329	-1.969	3.263	0.627	274
				Age-Group	2.608	1.368	-0.086	5.301	0.058	
				User-Group X Age-Group	2.159	1.868	-1.519	5.837	0.249	
Model 2d (from 2b)	0.068	0.003	6, 259	User-Group	1.360	1.055	-0.717	3.437	0.198	268
				Age-Group	3.915	0.976	1.994	5.836	<0.001	
				Gender	-2.227	0.910	-4.019	-0.435	0.015	
				SES	-2.606	0.918	-4.414	-0.797	0.005	
				RT-18	0.260	0.125	0.013	0.507	0.039	
				Daily Smoker	-0.353	1.648	-3.598	2.891	0.830	
				AUDIT	0.062	0.112	-0.158	0.282	0.579	
				Other drug use	0.090	1.273	-2.416	2.597	0.943	

Table S8. Linear regression models (models 3a, 3b, 3c and 3d) with outcome variable Beck Anxiety Inventory (BAI) and exposure variables user-group and age-group, in all participants.

Model 3a includes user-group only (n=274); model 3b includes user-group and age-group as predictors (n=274); model 3c includes user-group, age-group and their interaction (n=274); and model 3d (n=268) is an adjusted version of 3b in which the covariates are also included (gender, socioeconomic status (SES), risk taking (RT-18), daily smoker, alcohol use disorder identification test (AUDIT) score and other drug use). CI=confidence interval.

	Change in R ² squared	P for change in model	df1, df2	Predictor	Unstandardised beta	Standard error	95% CI beta: lower	95% CI beta: upper	p	N
Model 3a	0.002	0.429	1, 272	User-Group	0.830	0.048	-1.231	2.892	0.429	274
Model 3b	0.072	<0.001	1, 271	User-Group	0.733	0.042	-1.257	2.723	0.469	274
				Age-Group	4.627	0.268	2.642	6.612	<0.001	
Model 3c	0.004	0.302	1, 270	User-Group	-0.324	1.438	-3.154	2.506	0.822	274
				Age-Group	3.506	1.480	0.592	6.420	0.019	
				User-Group X Age- Group	2.091	2.021	-1.889	6.070	0.302	
Model 3d (from 3b)	0.050	0.023	6, 259	User-Group	0.862	1.177	-1.456	3.179	0.465	268
				Age-Group	4.528	1.089	2.384	6.671	<0.001	
				Gender	-3.273	1.015	-5.272	-1.273	0.001	
				SES	-1.138	1.025	-3.156	0.880	0.268	
				RT-18	0.172	0.140	-0.103	0.448	0.220	
				Daily Smoker	-1.280	1.839	-4.901	2.341	0.487	
				AUDIT	0.118	0.125	-0.127	0.364	0.343	
				Other drug use	-0.340	1.420	-3.137	2.457	0.811	

Table S9. Linear regression models (4a, 4b and 4d) with outcome variable Psychotomimetic States Inventory-adapted (PSI-a) and exposure variables user-group and age-group in all participants.

Model 4a includes user-group only (n=273); model 4b includes user-group and age-group as predictors (n=273); model 4c includes user-group, age-group and their interaction (n=273); and model 3d (n=267) is an adjusted version of 3b in which the following covariates were included (gender, socioeconomic status (SES), risk taking (RT-18), daily smoker, alcohol use disorder identification test (AUDIT) score and other drug use). CI = confidence interval.

	Change in R ² squared	P for change in model	df1, df2	Predictor	Unstandardised beta	Standard error	95% CI beta: lower	95% CI beta: upper	p	N
Model 4a	0.041	0.001	1, 271	User-Group	7.249	2.141	3.033	11.465	0.001	273
Model 4b	0.041	0.001	1, 270	User-Group	7.121	2.100	2.987	11.255	0.001	273
				Age-Group	7.254	2.095	3.130	11.378	0.001	
Model 4c	0.005	0.223	1, 269	User-Group	4.539	2.979	-1.327	10.405	0.129	273
				Age-Group	4.516	3.068	-1.524	10.556	0.142	
				User-Group X Age- Group	5.120	4.196	-3.141	13.380	0.223	
Model 4d (from 4b)	0.060	0.007	6, 258	User-Group	6.004	2.434	1.211	10.796	0.014	267
				Age-Group	5.509	2.254	1.070	9.947	0.015	
				Gender	-3.996	2.095	-8.122	0.130	0.058	
				SES	-3.040	2.117	-7.209	1.129	0.152	
				RT-18	0.967	0.288	0.399	1.535	0.001	
				Daily Smoker	0.231	3.793	-7.238	7.701	0.951	
				AUDIT	-0.233	0.259	-0.742	0.276	0.369	
				Other drug use	1.035	2.940	-4.755	6.824	0.725	

5.1 Cannabis frequency results

In users, cannabis use frequency predicted likelihood of having severe CUD (OR=1.401, $p=0.001$, 95% CI: 1.158–1.695). This effect persisted after including age-group and the pre-defined covariates. However, the interaction between cannabis use frequency and age-group on likelihood of severe CUD was not significant.

Within users, cannabis use frequency did not significantly predict BDI, nor was there a significant interaction between cannabis use frequency and age-group on BDI. Within users, cannabis use frequency did not significantly predict BAI, nor was there a significant interaction between cannabis use frequency and age-group. Within users, cannabis use frequency did not significantly predict PSI-a, nor was there a significant interaction between cannabis use frequency and age-group on PSI-a.

Section 6. Exploratory results

6.1 Clinical thresholds for BDI and BAI

In line with the continuous data analyses in the main text, being an adolescent increased risk of at least mild depression relative to being an adult (OR=2.250, $p=0.006$, 95% CI: 1.265-4.000), while user-group had no significant relationship with risk of at least mild depression. There was no significant interaction between user-group and age-group.

Being an adolescent increased risk of at least mild anxiety relative to being an adult (OR=1.700, $p=0.030$, 95% CI: 1.053-1.391), while user-group had no significant relationship with risk of at least mild anxiety. There was no significant interaction between user-group and age-group.

Table S10. The number of participants (%) in each group with or without at least mild depression or anxiety. Mild depression is 14 or above on the BDI. Mild anxiety is 8 or above on the BAI.

		Adolescent control	Adolescent user	Adult control	Adult user
At least mild depression:					
	No	48 (76.2%)	47 (61.8%)	53 (82.8%)	59 (83.1%)
	Yes	15 (23.8%)	29 (38.2%)	11 (17.2%)	12 (17.9%)
At least mild anxiety:					
	No	27 (42.9%)	29 (38.2%)	30 (46.9%)	42 (59.2%)
	Yes	36 (57.1%)	47 (61.8%)	34 (53.1%)	29 (40.8%)

6.2 Relationship between severe CUD and depression, anxiety and psychotic-like symptoms

Table S11. Number of people in each CUD sub-group

	Adult control	Adolescent control	Adult user without severe CUD	Adult user with severe CUD	Adolescent user without severe CUD	Adolescent user with severe CUD
n	64	63	58	13	38	38

BDI

There was a main effect of group ($F(5, 268)=7.127$, $p<0.001$, $\eta^2_p=0.117$), with a strong linear relationship between group and BDI (contrast estimate=5.937, $p<0.001$).

After Bonferroni-correction for multiple comparisons, only adolescent users with severe CUD differed from any other group; they had significantly greater BDI scores than:

- adult users without severe CUD ($t(94)=5.204$, $p<0.001$, mean difference=8.201)
- adolescent controls ($t(99)=3.404$, $p=0.012$, mean difference=5.279)
- adult controls ($t(100)=5.098$, $p<0.001$, mean difference=7.887)
- and, marginally greater BDI scores than adolescent users without severe CUD ($t(74)=2.855$, $p=0.070$, mean difference = 4.947)

Qualitatively, the groups with the lowest BDI means were adult controls and adult users without severe CUD.

In terms of reaching mild depression, only being an adolescent user with severe CUD significantly increased one's odds relative to the reference category of adult controls (OR=4.818, 95% CI: 1.942-11.957).

When a 2x2 ANOVA was conducted only within users, there were main effects of age-group ($F(1,143)=4.165$, $p=0.043$, $\eta^2_p=0.028$) and CUD-status ($F(1,143)=11.236$, $p=0.001$, $\eta^2_p=0.073$), but no interaction between age-group and CUD-status ($F(1,143)=0.010$, $p=0.921$, $\eta^2_p<0.001$). The main effect of CUD-status ($F(1,132)=9.382$, $p=0.003$, $\eta^2_p=0.066$), but not the main effect of age-group, was robust to the inclusion of covariates, including cannabis use frequency.

Figure S1. Beck Depression Inventory (BDI) mean scores, with distributions of data and 95% CIs for adult controls, adolescent controls, adult users without severe CUD, adolescent users without severe CUD (sCUD), adult users with severe CUD and adolescent users with severe CUD. Post-hoc comparisons are Bonferroni-corrected. *** $p < 0.001$, * $p < 0.05$, # $p < 0.1$

BAI

There was a main effect of group ($F(5, 268)=7.000$, $p<0.001$, $\eta^2_p=0.116$), with a strong linear relationship between group and BDI (contrast estimate=5.479, $p<0.001$).

After Bonferroni-correction for multiple comparisons, adolescent users with severe CUD had greater BAI scores than:

- adult users without severe CUD ($t(94)=5.146$, $p<0.001$, mean difference=8.804)
- adult controls ($t(100)=4.331$, $p<0.001$, mean difference=7.272)

Also, adolescent users without severe CUD had marginally greater BAI scores than adults without severe CUD ($t(94)=2.808$, $p=0.080$, mean difference=4.804). And adolescent controls had greater BAI scores than adult users without severe CUD ($t(120)=3.376$, $p=0.013$, mean difference=5.037).

Qualitatively, the groups with the lowest BAI means were adult controls and adult users without severe CUD.

In terms of reaching mild anxiety, only being an adolescent user with severe CUD significantly increased one's odds relative to the reference category of adult controls (OR=2.843, 95% CI: 1.162-6.955).

When a 2x2 ANOVA was conducted only within users, there were main effects of age-group ($F(1,143)=4.299$, $p=0.040$, $\eta^2_p=0.029$) and CUD-status ($F(1,143)=9.815$, $p=0.002$, $\eta^2_p=0.064$), but no interaction between age-group and CUD-status ($F(1,143)=0.589$, $p=0.444$, $\eta^2_p=0.004$). The main effect of CUD-status ($F(1,132)=7.414$, $p=0.007$, $\eta^2_p=0.053$), but not the main effect of age-group, was robust to the inclusion of covariates, including cannabis use frequency.

Figure S2. Beck Anxiety Inventory (BAI) mean scores, with distributions of data and 95% CIs for adult controls, adolescent controls, adult users without severe CUD, adolescent users without severe CUD (sCUD), adult users with severe CUD and adolescent users with severe CUD. Post-hoc comparisons are Bonferroni-corrected. *** $p < 0.001$, * $p < 0.05$, # $p < 0.1$

PSI-a

There was a main effect of group ($F(5, 267)=6.454, p<0.001, \eta^2_p=0.108$), with a strong linear relationship between group and PSI (contrast estimate=13.890, $p<0.001$).

After Bonferroni-correction for multiple comparisons, adolescent users with severe CUD had greater PSI-a scores than:

- adult users without severe CUD ($t(93)=4.226, p<0.001$, mean difference=15.244)
- adolescent controls ($t(98)=3.944, p=0.002$, mean difference=14.006)
- adult controls ($t(99)=5.231, p<0.001$, mean difference=18.523).

Also, adolescent users without CUD had marginally greater PSI scores than adult controls ($t(120)=2.832, p=0.075$, mean difference=9.942).

Qualitatively, the groups with the lowest PSI means were adult controls, adolescent controls, and adult users without severe CUD. Adolescent users without severe CUD and adult users with severe CUD had qualitatively similar means.

When a 2x2 ANOVA was conducted only within users, there were main effects of age-group ($F(1,142)=4.273, p=0.041, \eta^2_p=0.029$) and CUD-status ($F(1,142)=4.525, p=0.035, \eta^2_p=0.031$), but no interaction between age-group and CUD-status ($F(1,142)=0.055, p=0.816, \eta^2_p<0.001$). Neither the main effect of CUD-status, nor the main effect of age-group, were robust to the inclusion of covariates, including cannabis use frequency.

Figure S3. Psychotomimetic states inventory-adapted (PSI-a) mean scores, with distributions of data and 95% CIs for adult controls, adolescent controls, adult users without severe CUD (sCUD), adolescent users without severe CUD, adult users with severe CUD and adolescent users with severe CUD. Post-hoc comparisons are Bonferroni-corrected. *** $p < 0.001$, ** $p < 0.001$, # $p < 0.1$

6.3 Correlations between age-of-onset and mental health symptoms in adult users

Within adult users, there were no significant correlations between age-of-onset and BDI ($r(69)=0.005$, $p=0.966$), BAI ($r(69)=0.051$, $p=0.671$) and PSI-a ($r(69)=0.006$, $p=0.963$). There was a negative trend association between age-of-onset and presence of severe CUD ($r(69)=-0.210$, $p=0.080$).

Section 7. Supplementary Discussion

CUD

The mechanisms behind the heightened adolescent vulnerability to CUD should be explicated in future research. Previously, differential impacts of other alcohol and drug use on cannabis dependence in adolescents and adults have been found (Von Sydow *et al.*, 2002), while the use of high-potency cannabis may be particularly deleterious in adolescents (Freeman and Winstock, 2015).

Overall adolescent effects

Apart from the relationship with CUD, our study does not support the theory that adolescence is a period in which the effects of cannabis use on mental health are more potent (Levine *et al.*, 2017). However, consistent with existing research, adolescents, were found to have significantly higher levels of depression, anxiety and psychosis-like symptoms than adults, regardless of user-status (Twenge *et al.*, 2019). In our study, adolescent status approximately doubled the odds of mild anxiety or depression.

Frequency of cannabis use

Also in opposition to our hypotheses, frequency of cannabis use was not significantly associated with severity of anxiety, depression or psychosis-like symptoms. This suggests that the impact of more frequent compared to less frequent cannabis use on mental health was not detectable in our sample of over 140 cannabis users. Larger, epidemiological studies have reported associations between cannabis use frequency and mental health outcomes (Troisi *et al.*, 1998; Henquet *et al.*, 2005; Kuepper *et al.*, 2011; Lev-Ran *et al.*, 2014; Marconi *et al.*, 2016); however these comparisons often involve much less frequent use, for instance weekly vs. monthly comparisons. Our use of controls who had limited exposure to cannabis or to tobacco should have reduced the impact of unmeasurable confounding variables. It is possible that previous associations between infrequent cannabis use and poor mental health are attributable to unknown confounds.

Further limitations and future research

Although our adult users all began frequent cannabis use (>1 day/week) after the age of 18, many first tried cannabis before the age of 18. Furthermore, adolescent users predictably first tried cannabis earlier than adult users. Crucially, however, age-of-onset was not associated with depression, anxiety, or psychotic-like symptoms in the adult users. Hence, we can likely exclude the possibility that any early initial use of cannabis contributed to the adult users' mental health symptoms. It is notable that some previous studies have found associations between mental health symptoms and an early age-of-onset in adult cannabis users (Stefanis *et al.*, 2004; Schubart *et al.*, 2011; Hosseini and Oremus, 2019), but we did not replicate this. In contrast, age-of-onset was marginally associated with the presence of severe CUD in adult users. A further limitation to consider is that we excluded participants receiving treatment for a mental health problem and those who had experienced psychosis. Adults are more likely than adolescents to receive treatment and to have already experienced psychosis. Thus our sample may be biased towards worse adolescent mental health, given problems are potentially more likely to be untreated (Sultan *et al.*, 2018) or prodromal and not yet fully expressed.

There are three critical, but inter-related, time periods that should be considered in relation to studies investigating age and drug use:

- current age
- age-of-onset
- duration of use

In our study, younger age (i.e. being an adolescent) is associated with a younger age-of-onset and a shorter duration of use. Whereas in most studies previously conducted on this topic, participants are of varying ages

and younger age-of-onset is associated with longer durations of use. This means it has often been difficult to disaggregate the impact of age-of-onset and duration of cannabis use. However, in our current study, one could argue that we are not able to disaggregate current age and age-of-onset; this might be relevant in the difference in rates of severe CUD between the adolescent and adult users. Moreover, our criteria allowed adult users to begin frequent cannabis use after age 18, which may still be considered ‘adolescence’. Hence, one could argue that some of our adult users began frequent cannabis use in late adolescence.

Although difficult to conduct, future studies could aim to include the following groups in order to parse out these potential differences:

- adolescent cannabis users
- adult cannabis users who initiated use at the same time as the adolescent cannabis users
- adult cannabis users who initiated use after a certain age (e.g. >18 or >21 years)
- adolescent controls
- adult controls

Furthermore, future studies may also wish to include groups of participants who began using cannabis in adolescence but stopped using at different points in life, to investigate if the consequences of adolescent and adult use are different, even following abstinence.

The impact of adolescent cannabis use may manifest itself more strongly later in life. Therefore, inclusion of adult users who initiated use as adolescents would be informative. However, our current aim was to investigate the association between current cannabis use and current depression and anxiety during adolescence and adulthood.

Our measurement of cannabis use frequency was likely to be accurate, because we conducted in-depth three-month timeline follow-back assessments (Robinson *et al.*, 2014). However, we did not include any measurements of cannabis potency, type or route of administration. Furthermore, our measurement of quantity of cannabis use is likely to be somewhat inaccurate (Hindocha, Norberg and Tomko, 2018).

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