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

3
4
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6
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53 The authors have no conflicts of interest to report.

54 **ABSTRACT**

55

56 *Background*

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

60 *Method*

61 As part of the ‘CannTeen’ study, we conducted a cross-sectional analysis. There were 274 participants:
62 adolescent users (n=76; 16-17 years old) and controls (n=63), and adult users (n=71; 26-29 years old)
63 and controls (n=64). Amongst users, cannabis use frequency ranged from 1-7 days/week, while controls
64 had 0-10 lifetime exposures to cannabis. We measured DSM-5 Cannabis Use Disorder (CUD), Beck
65 Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Psychotomimetic States Inventory-
66 adapted (PSI-a).

67 *Results*

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

74 *Conclusions*

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

80 INTRODUCTION

81

82 Adolescence is considered to be a dynamic period that begins with puberty and ends when one achieves
83 an independent role in society (Dumontheil, 2016). Brain structure, brain function, neurotransmitter
84 systems (including the endocannabinoid system), cognitive function, and emotional processing
85 continue to mature during adolescence (Blakemore & Choudhury, 2006; Galve-Roperh et al., 2009;
86 Giedd et al., 1999; Shaffer & Kipp, 2010; Smetana & Villalobos, 2009). Mental health problems
87 typically emerge during adolescence, with 50% beginning before age 18 and 75% by age 24 (Jones,
88 2013; Kessler et al., 2005; Kieling et al., 2011; Patel et al., 2007; Paus et al., 2008). No agreed-upon
89 age range constitutes ‘adolescence’, but definitions are usually 10-19 years or 10-24 years (Sawyer et
90 al., 2018).

91

92 Cannabis is the third most commonly used recreational psychoactive substance in the world, after
93 alcohol and tobacco, with 3.9% of the world’s population reporting use in the past year (UNODC,
94 2020). Cannabis is particularly popular in adolescents, with 28.0% of 15-16 year-olds in the United
95 States (U.S.) (NIDA, 2020) and 19.3% of 15-year olds in England reporting use in the past year (NHS-
96 Digital, 2018, 2019). In 2019, cannabis was the primary problem drug for 77% of young people (aged
97 under 18) in England who received treatment for alcohol or illicit drug problems (NDTMS, 2019).

98

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

104

105 Cannabis use carries a risk of addiction. Results from large, representative epidemiological studies in
106 the U.S. from the 1990s and 2000s showed that roughly 9% of people who try cannabis transition to
107 dependence at some point in their life (Anthony et al., 1994; Lopez-Quintero et al., 2011). However,
108 Leung *et al* (2020) conducted a meta-analysis of studies from 2009 onwards and found that among
109 people who had tried cannabis, 22% developed a cannabis use disorder (CUD) (Leung et al., 2020),
110 while approximately 30% of last-year users in the U.S. have a CUD (Hasin et al., 2015). Younger
111 current age and age of first cannabis use (age-of-onset) reliably augments the risk of developing CUD
112 (Chen et al., 2005, 2009; Ehlers et al., 2010; Le Strat et al., 2015; Leung et al., 2020; Lopez-
113 Quintero et al., 2011; Von Sydow et al., 2002; Wagner & Anthony, 2002; Wittchen et al.,
114 2011). These studies tend to converge on an odds ratio of approximately three for risk of CUD in
115 adolescents compared to adults. However, these studies typically failed to match or account for cannabis

116 use frequency differences between adolescents and adults, which is strongly related to addiction
117 severity (Freeman & Winstock, 2015).

118
119 Results from multiple large-scale studies indicate that there is a small association between cannabis use
120 and depression (Degenhardt et al., 2001, 2003; Horwood et al., 2012). A meta-analysis of longitudinal
121 studies found cannabis users had a higher likelihood of developing depression compared to controls
122 (Odds Ratio (OR)=1.17) (Lev-Ran et al., 2014) and another meta-analysis supported the link between
123 cannabis use in adolescence and depression in early adulthood (OR=1.37) (Gobbi et al., 2019). Some
124 longitudinal studies have reported a greater vulnerability to depression in those with a younger age-of-
125 onset (Horwood et al., 2012; Schoeler et al., 2018) and one systematic review concluded there was some
126 evidence that a younger age-of-onset was linked to depression (Hosseini & Oremus, 2019). However,
127 a non-linear association between age and contemporaneous depressive symptoms has been reported
128 (Leadbeater et al., 2019). Moreover, a meta-analysis did not find a significant age-of-onset effect (Lev-
129 Ran et al., 2014). Hence, an age-specific vulnerability to cannabis-related depression is unclear.
130 Moreover, the population cohort studies that contribute to these meta-analyses often include small
131 numbers of frequent cannabis users and define frequent cannabis liberally, e.g. once per month
132 (Pedersen, 2008; Schoeler et al., 2018). Purposive sampling of frequent cannabis users is one way to
133 address this.

134
135 In a cross-sectional survey, Crippa et al (2009) found higher levels of anxiety symptoms in people who
136 frequently use cannabis compared to controls (Crippa et al., 2009), While Troisi et al (1998) found
137 greater levels of cannabis use was associated with greater severity of anxiety symptoms (Troisi et al.,
138 1998). In a meta-analysis of longitudinal studies, Xue et al (2020) reported that, overall, cannabis use
139 increased odds of developing any future anxiety condition (OR=1.25) (Xue et al., 2020). However, Xue
140 et al (2020) concluded that results varied considerably, which may be due to differences in cannabis
141 exposure and analytical differences. Crucially, the evidence for a relationship between early age-of-
142 onset and later symptoms of anxiety is inconclusive (Fergusson & Horwood, 1997; Gage et al.,
143 2015; Guttmanova et al., 2017). Furthermore, the association between contemporaneous cannabis
144 use and anxiety during adolescence and adulthood has not been researched.

145
146 Longitudinal studies have consistently reported an association between cannabis use and an increased
147 risk of psychosis and schizophrenia (Andréasson et al., 1987; Hjorthøj et al., 2021; Marconi et al., 2016;
148 Moore et al., 2007; Van Os et al., 2002; Zammit et al., 2002). Cannabis use during adolescence,
149 compared to adulthood, has been associated with a greater risk of psychotic outcomes (Di Forti et al.,
150 2014; Dragt et al., 2012; Galvez-Buccollini et al., 2012; Large et al., 2011; Manrique-Garcia et al.,
151 2012; Schimmelmann et al., 2011). However, a large cross-sectional study found that in adolescents

152 and young adults, current cannabis use was only associated with psychotic symptoms *after* age 22 and
153 that there was no relationship with age-of-onset (Leadbeater et al., 2019). Positive associations have
154 also consistently been reported between cannabis use and psychotic-like experiences or subclinical
155 symptoms of psychosis (Arseneault et al., 2002; Fergusson et al., 2003; Henquet et al., 2005; Hides et
156 al., 2009; Kuepper et al., 2011; Miettunen et al., 2008; Stefanis et al., 2004). Moreover, earlier age-of-
157 onset has been linked with greater psychotic-like symptoms in later life in two studies (Schubart et al.,
158 2011; Stefanis et al., 2004) and cannabis use during adolescent has been associated with psychotic-like
159 symptoms one or two years afterwards (Bourque et al., 2018)

160 Additionally, the relationship between current cannabis use and concurrent psychotic-like symptoms in
161 adolescents and adults is unknown.

162

163 As reviewed above, there are theoretical and empirical grounds for suggesting that earlier, adolescent
164 use of cannabis may be particularly deleterious to mental health. However, there remain large variations
165 in study design, disparate measures of cannabis use and mental health and a plethora of discrepant
166 findings regarding age-specific vulnerability. Few studies have compared the contemporary mental
167 health of adolescents with adults, while adolescents are still under 18 years old. Whether adolescent
168 cannabis use, compared to adult use, genuinely heightens risk of poor mental health remains an
169 unanswered question. In this study, we therefore compared how current cannabis use may be associated
170 with presence of severe CUD, and the severity of subclinical depression, anxiety, and psychotic-like
171 symptoms in adolescents and adults. Our cannabis-using groups were matched on current cannabis use
172 frequency and our age-groups were matched on gender and age. Adult users had not frequently used
173 cannabis before age 18.

174

175 As registered on the Open Science Framework (OSF) (Lawn et al., 2021), and on the basis of evidence
176 reviewed here, our hypotheses were:

177

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

184

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

188

189 **METHODS**

190

191 **Study design**

192

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

199

200 **Participants**

201

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

204

205 Participants were recruited using online advertisements on Facebook, Instagram, Gumtree, and Reddit;
206 school assemblies in London and the surrounding area; in-person flyering; and word-of-mouth. We
207 recruited participants in a targeted process, by advertising to specific age-groups. Potential participants
208 were screened and selected based on their cannabis use and other criteria. Participants were
209 compensated financially for their time (£240 for completing all sessions with payments split across five
210 separate sessions over a 12 month period).

211

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

219

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

223

224 **Measures**

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

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

231

232 *Exposure variables*

233

234 *Age-group*

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

237

238 *Cannabis use frequency*

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

241

242 *Outcome variables*

243

244 *Beck Depression Inventory-II (BDI)* (Beck et al., 1996)

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

248

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

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

252

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

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

259

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

263 Severity of CUD was assessed using the MINI, in which 11 DSM-5 symptoms are assessed over the
264 last 12 months. The presence of 0-1 symptoms is considered ‘none’, 2-3 symptoms is considered ‘mild’,
265 4-5 symptoms is considered ‘moderate’, and 6 or more symptoms is considered ‘severe’. We
266 categorised users into having ‘severe CUD’ (coded as 1) or ‘not severe CUD’ (coded as 0).

267

268 *Pre-defined covariates*

269

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

280

281

282 **Procedure**

283

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

290

291 **Power**

292

293 We powered the study to detect a cross-sectional group difference in cannabis use disorder between
294 adolescent and adult cannabis users, as this is a robust finding with a quantified effect size (Chen et al.,
295 2005; Ehlers et al., 2010; Le Strat et al., 2015) of odds ratio=3, equivalent to Cohen’s $d=0.6$ or Cohen’s
296 $f=0.3$. With $\alpha=0.05$ and a desired power of 0.95, 148 users were required, split evenly between
297 adolescent and adult users. Crucially, in terms of detecting age-group by user-group interactions, with
298 our total sample size ($n=274$) and an assumed power of 0.8 we are powered to detect at least small-

299 medium interactions of size Cohen's $f \geq 0.17$ (Cohen's f effect size around 0.1 are considered small; f
300 effect size around 0.25 is considered medium; and f effect size around 0.4 is considered large).

301

302

303 **Statistical analyses**

304

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

314

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

317 **RESULTS**

318

319 **Participant characteristics (Table 1)**

320

321 All groups had a similar number of males and females. Adolescent users (3.7 days/week) and adult
322 users (4.1 days/week) were matched on cannabis use frequency ($t_{145}=1.198$, $p=0.233$, $d=0.198$). The
323 time since last cannabis use did not differ between adolescent users (2.4 days) and adult users (2.5 days)
324 ($t_{145}=0.118$, $p=0.906$, $d=0.019$). Furthermore, a similar number of adolescent users ($n=69$, 90.8%) and
325 adult users ($n=59$, 83.1%) used strong herbal cannabis as their most common type of cannabis, and
326 these distributions did not differ significantly ($\chi^2_3=3.866$, $p=0.276$). However, adolescents reported
327 using more cannabis (1.1g) on a day of use than adults (0.6g) ($t_{142}=3.623$, $p<0.001$, $d=0.605$). See Table
328 2 for data on cannabis use variables. Adolescent users (17.1 years) and adolescent controls (17.1 years)
329 were matched on age ($t_{137}=0.224$, $p=0.823$, $d=0.038$), as were adult users (27.6 years) and adult controls
330 (27.4 years) ($t_{145}=1.232$, $p=0.220$, $d=0.212$). See Table 1 and supplementary materials for differences
331 in demographic variables.

332

333 **Regressions**

334

335 Descriptive statistics for outcome variables are presented in Table 3.

336

337 *Severe cannabis use disorder (Table 4 and Table S6)*

338

339 Within users, adolescent status predicted likelihood of having severe CUD (OR=4.462, $p<0.001$, 95%
340 CI: 2.106–9.454) (Table 4). This effect persisted after adjusting for covariates (OR=3.474, $p=0.004$,
341 95% CI: 1.501-8.036).

342

343 *Depression (Table 4 and Table S7)*

344

345 Adolescent status predicted greater BDI score ($b=3.766$, $p<0.001$, 95% CI: 1.930–5.601) (Table 4).
346 This effect persisted after adjusting for covariates ($b=3.915$, $p<0.001$, 95% CI: 1.994-5.836). User-
347 group, and the user-group by age-group interaction, were not significantly related to BDI score.

348

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

352

353 *Anxiety (Table 4 and Table S8)*

354

355 Adolescent status predicted greater BAI ($b=4.627$, $p<0.001$, 95% CI: 2.642–6.612) (Table 4). This
356 effect persisted after adjusting for covariates ($b=4.528$, $p<0.001$, 95% CI: 2.384–6.671). User-group,
357 and the user-group by age-group interaction, were not significantly related to BAI.

358

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

362

363 *Psychotic-like symptoms (Table 4 and table S9)*

364

365 User-status predicted greater PSI-a ($b=7.121$, $p=0.001$, 95% CI: 3.033–11.465). Adolescent status
366 predicted greater PSI-a ($b=7.254$, $p=0.001$, 95% CI: 3.130–11.378) (Table 4). These effects both
367 persisted after adjusting for covariates (user-group: $b=6.004$, $p=0.014$, 95% CI: 1.211, 10.796; age-
368 group: $b=5.509$, $p=0.015$, 95% CI: 1.070, 9.947). The user-group by age-group interaction was not
369 significantly related to PSI-a.

370

371 *Exploratory results (see supplementary materials)*

372

373 The patterns of our results described above were mirrored when considering the relationships between
374 age-group, user-group and clinical categorical outcomes of ‘at least mild depression’ and ‘at least mild
375 anxiety’. Adolescent-status increased the risk (depression OR=2.25; anxiety OR=1.70), but user-status
376 did not.

377

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

383

384 When conducting a 2x2 (age-group x CUD-status) ANOVA only in users, there were significant main
385 effects of age-group on BDI ($F(1,143)=4.165$, $p=0.043$, $\eta^2_p=0.028$), BAI ($F(1,143)=4.299$, $p=0.040$, η^2_p
386 $=0.029$), and PSI-a ($F(1,142)=4.273$, $p=0.041$, $\eta^2_p=0.029$) and significant main effects of CUD-status
387 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-
388 a ($F(1,142)=4.525$, $p=0.035$, $\eta^2_p=0.031$). However, all interactions were non-significant. Thus, being
389 an adolescent and having severe CUD were additively associated with greater BDI, BAI and PSI-a.
390 After adjusting for our pre-defined covariates and cannabis use frequency, the CUD-status main effect

391 remained for BDI ($F(1,132)=9.382$, $p=0.003$, $\eta^2_p=0.066$) and BAI ($F(1,132)=7.414$, $p=0.007$, η^2_p
392 $=0.053$), but the user-group effect for PSI-a and the age-group effects for all outcomes became non-
393 significant.

394

395

396

397

398 **DISCUSSION**

399

400 This cross-sectional study compared presence of severe CUD and the severity of mental health
401 symptoms in adolescent and adult cannabis users with gender- and age-matched controls. Adolescent
402 users were significantly more likely to have severe CUD than adult users. Both cannabis user-status
403 and adolescent-status were associated with greater psychotic-like symptoms, additively resulting in
404 adolescent cannabis users having the greatest psychotic-like symptoms. User-status was not associated
405 with subclinical depression or anxiety levels and there was Bayesian support for users and controls
406 having similar anxiety levels. No significant interactions were found between user-group and age-group
407 for subclinical depression, anxiety, or psychotic-like symptoms, suggesting that adolescents do not
408 have a greater vulnerability to cannabis-related mental health problems in comparison to adults.
409 However our exploratory analyses suggested that severe CUD predicted worse mental health symptoms,
410 which resulted in adolescent users with severe CUD having the highest levels of depression, anxiety,
411 and psychotic-like symptoms.

412

413 After adjustment for covariates, adolescents had a 3.5 times greater odds of having severe CUD than
414 adults, with 50% of this group endorsing more than six CUD symptoms. This effect size is similar to
415 previous estimates of increased risk (Chen et al., 2009; Ehlers et al., 2010; Le Strat et al., 2015; Wittchen
416 et al., 2011), demonstrating the effect's replicability. CUD risk was greater in adolescents despite their
417 shorter duration of cannabis use compared to adults. This is notable because previous studies have
418 mainly tested associations between age-of-onset and addiction (and other outcome variables) in adults,
419 where early age-of-onset is also associated with greater duration of cannabis use. Moreover, unlike
420 many previous studies, our adolescent and adult user groups were matched on cannabis frequency,
421 which therefore excludes this difference as a possible explanation. Furthermore, a similar proportion of
422 adolescents (91%) and adults (83%) used strong herbal cannabis as their usual type, and the THC
423 concentration in both groups' strong herbal cannabis was the same (21%). However, adolescent users
424 reported using more cannabis per day of use (1.1g) than adults (0.6g), which may partially contribute
425 to cannabis problems (Callaghan et al., 2020; Tomko et al., 2018; Zeisser et al., 2012). On the other
426 hand, this estimate may be inaccurate (Hindocha et al., 2017, 2018), especially because UK cannabis
427 users buy their cannabis illegally, so the weight purchased may not be known, and estimating the
428 quantity put into a joint (or other method) is difficult. Further work carefully examining relationships
429 between precise cannabis and cannabinoid quantities, or better still, standard THC units (Freeman &
430 Lorenzetti, 2020), and addiction is needed.

431

432 We speculate that adolescents may be more sensitive to the development of CUD than adults for a
433 number of reasons, including: greater disruption of interpersonal relationships, e.g. with parents or
434 teachers; a hyper plastic brain and a developing endocannabinoid system (Meyer et al., 2018); a more

435 malleable social life and evolving sense of identity which can quickly shift towards cannabis use
436 (Hammersley et al., 2001); potentially subtle differences in acute effects of cannabis (Mokrysz et al.,
437 2016; Murray et al., 2022); a greater desire to binge on cannabis (Borissova et al., *in press*); and a drive
438 towards social attunement (Cousijn et al., 2018). However, research into the different profiles of
439 adolescent and adult CUD, and the neuropsychopharmacological predictors of CUD onset in
440 adolescents is needed.

441

442 We found null relationships between cannabis user-status and subclinical depression and anxiety levels,
443 and no evidence of adolescent vulnerability. Furthermore, the absence of associations between cannabis
444 use frequency and our measures of depression and anxiety in users (see supplementary materials) casts
445 further doubt on the impact of cannabis use on levels of anxiety and depression. We also found null
446 relationships between user-status and the presence of clinically relevant anxiety or depression. Previous
447 research has suggested that cannabis use is associated with an augmented risk of depression and anxiety
448 in adults (Crippa et al., 2009; Degenhardt et al., 2001, 2003; Guttmanova et al., 2017; Horwood et al.,
449 2012; Lev-Ran et al., 2014) and associated with greater risks later in life for adolescents (Gobbi et al.,
450 2019). Given that the effect sizes of these relationships from meta-analyses are small (Chen et al., 2010)
451 (odds ratios of 1.17-1.62 for depression and 1.25 for anxiety), and base rate of clinical anxiety or
452 depression is not high, our sample may have been underpowered to detect differences in clinical anxiety
453 and depression.

454

455 Nevertheless, it is notable that in our sample of relatively frequent cannabis users, using at an average
456 frequency of four days/week, there was no significant evidence of greater subclinical anxiety or
457 depression levels in cannabis users aged 16-17 years compared to gender- and age-matched controls or
458 cannabis-matched adults. Our study was powered to detect interactions with Cohen's $f \geq 0.17$. For
459 anxiety, the null differences were supported by a Bayesian analysis. There has been inconsistent
460 evidence of heightened cannabis-related vulnerability at younger ages for both disorders (Guttmanova
461 et al., 2017; Hayatbakhsh et al., 2007; Horwood et al., 2012; Hosseini & Oremus, 2019; Leadbeater et
462 al., 2019; Lev-Ran et al., 2014). In line with previous research, our study further suggests there is not
463 sufficient evidence to claim that cannabis use during adolescence is associated with a greater risk of
464 higher levels of depression or anxiety compared to cannabis use in adulthood. We should await further
465 longitudinal analyses and studies with clinical diagnoses to corroborate these findings.

466

467 Previous research has consistently implicated cannabis in the development of clinical psychosis,
468 psychotic-like, schizotypal, and subclinical symptoms (Arseneault et al., 2002; Henquet et al., 2005;
469 Hides et al., 2009; Kuepper et al., 2011; Marconi et al., 2016; Miettunen et al., 2008; Moore et al.,
470 2007), including psychotic-like symptoms during adolescence (Bourque et al., 2018). Likewise,
471 cannabis use was significantly associated with psychotic-like symptoms in our sample of adolescents

472 and adults, a relationship that remained significant after adjusting for covariates. Although we did not
473 measure clinical psychotic disorders, these findings indicate an important augmented risk, given the
474 amplified chance of transition to psychosis with subclinical symptoms (Kaymaz et al., 2012; Kuepper
475 et al., 2011). Adolescents overall had greater psychotic-like symptoms than adults, hence there was an
476 additive effect, resulting in adolescent users showing the greatest severity. Indeed, adolescent users'
477 mean PSI-a score was 75% higher than that of adult controls. However, age-group did not moderate the
478 impact of user-group. Thus, there was no evidence of synergistic vulnerability.

479
480 Our exploratory analyses suggested that there was a consistent pattern in depression, anxiety and
481 psychotic-like symptoms for those with and without severe CUD. Adolescent users with CUD
482 consistently had the highest mean across these three outcomes. Only adolescent users with severe CUD
483 significantly differed from other groups and only they had greater odds of having at least mild anxiety
484 or depression relative to the reference category, adult controls. When analysing users, adolescence and
485 severe CUD were additively and significantly associated with mental health symptoms, explaining why
486 adolescent users with severe CUD have the highest means. However, there were no significant
487 interactions, so severe CUD did not have a *greater* effect in adolescents than adults. Previous research
488 has shown that dependent use of cannabis is particularly strongly associated with mental health
489 problems (Braidwood et al., 2018; van der Pol et al., 2013), while non-dependent frequent use may not
490 be (Braidwood et al., 2018). Our exploratory findings add to these by demonstrating the relevance of
491 CUD to mental health problems in adolescence, despite the fact that user-group differences were absent
492 for anxiety and depression. This is important by virtue of adolescents' heightened risk of developing
493 CUD and their greater likelihood of existing mental health problems. However, these results should be
494 interpreted cautiously as they were exploratory, the sub-group sample sizes were small (see table S11),
495 adjustment for covariates removed the significant effect of CUD-status on psychotic-like symptoms,
496 and the study was not designed to compare users with and without CUD.

497 498 *Strengths and limitations*

499
500 Direct comparisons of adolescent and adult cannabis users are rare. One major strength of this study is
501 its novel design in which four groups were compared: adolescent and adult cannabis users and age- and
502 gender-matched controls. Crucially our adolescent and adult users were matched on cannabis use
503 frequency and the proportions of each group who typically use strong herbal cannabis (i.e. skunk) were
504 similar. Controls had been exposed to limited cannabis or tobacco use, reducing unmeasured
505 confounding differences with users. Adult cannabis users had never used cannabis frequently before
506 age 18, ensuring adolescent development was not substantially impacted by cannabis. Recent
507 abstinence from alcohol and other drugs was biochemically verified. Furthermore, we pre-registered
508 our protocol and analyses and adjusted for pre-defined covariates.

509

510 Due to the sampling methodology, the results cannot be interpreted as representative of the general
511 population. However, this approach was necessary in order to target frequent cannabis users and select
512 matched controls and maximise statistical power to test our hypotheses. This approach is common in
513 observational cannabis research (Morgan et al., 2012; van der Pol et al., 2013), where baseline levels
514 of illicit drug use are relatively low in the general population. Another limitation is the cross-sectional
515 nature of the analysis. As some previous studies imply there may be a time-lagged effect of cannabis
516 on mental health (Gobbi et al., 2019), this could contribute to our null findings. A further limitation is
517 that we did not conduct DSM clinical interviews for diagnoses of mental disorders; larger
518 epidemiological studies are needed to probe these relationships.

519

520 Inevitably, our adolescent users began using cannabis earlier than our adult users. Although we aimed
521 to recruit similar adolescent and adult users via matched gender, age and cannabis frequency, compared
522 demographics and adjusted for relevant covariates, it is still possible that people who initiate cannabis
523 use early in life are qualitatively different from those who initiate cannabis use later in life in ways we
524 did not account for. These pre-existing differences could have impacted our results. Crucially, however,
525 age-of-onset in adult users was not associated with mental health symptomatology and the extant
526 literature concerning these relationships is conspicuously mixed (Guttmanova et al., 2017; Lev-Ran
527 et al., 2014). Moreover, arguably, we cannot disaggregate current age, age-of-onset, and duration of
528 use. Triangulation of existing and future longitudinal research will allow conclusions about the impacts
529 of these specific, closely related exposure variables to be drawn. We have therefore followed up our
530 participants on four further testing occasions every 3 months over one year to provide a snapshot of a
531 developmental profile; these results will be provided in the future.

532

533 *Conclusions*

534

535 In sum, 16–17-year-olds were not at an interactively greater risk of cannabis-related mental health
536 problems, compared to 26-29-year-olds. This suggests that adolescents might not be more vulnerable
537 to cannabis harms than adults. More longitudinal research using the same is needed to further test this
538 suggestion. However, adolescents have an amplified risk of severe CUD relative to adults, which in
539 combination with being young, augments symptoms of mental ill health. Cannabis harm reduction
540 campaigns should therefore highlight the greater risk of addiction to cannabis during adolescence.

541

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547

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560

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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 (**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.

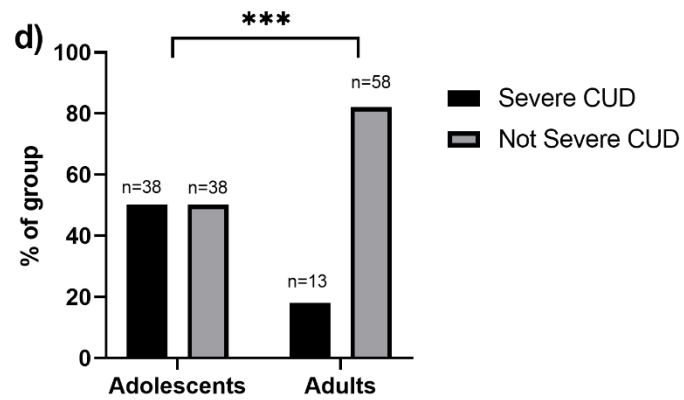
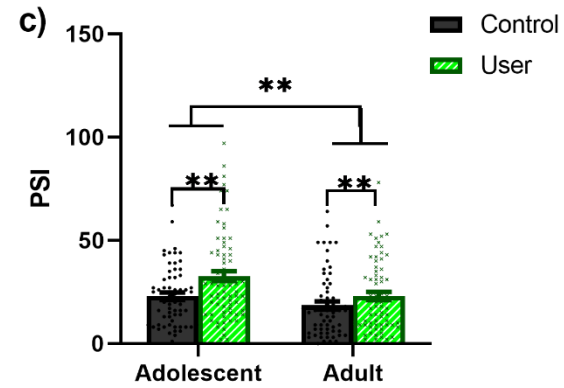
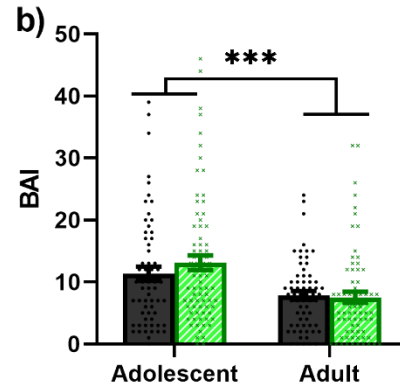
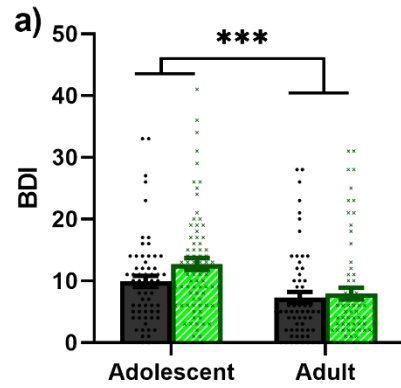


Table 1. Summary of participant demographics. Sociodemographic and non-cannabis drug use variables for adolescent controls, adolescent users, adult controls, and adult users. Group differences are highlighted in the final column, *p<0.05, **p<0.01, ***p<0.001. SES (maternal education) has data missing 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 (0.5) [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	0.7 (0.8) [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***

frequency (days/week)						
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. CUDIT-R=cannabis use disorder identification test revised. 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	Adult users > adolescent users*
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]	Adult users > adolescent users*
Cannabis, use frequency (days/week) (users)	NA	3.7 (2.0) [3.4, 0.8 – 6.9]	NA	4.1 (1.9) [3.8, 0.8 – 6.9]	
CUDIT-R	NA	15.4 (5.6) [5.0-27.0]	NA	11.9 (4.8) [3.0-26.0]	Adolescent users > adult users***
Number of users who most commonly use strong herbal cannabis (i.e. ‘skunk’)	NA	69 (90.8%)	NA	59 (83.1%)	
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]	Adolescent users > adult users*

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. 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]	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 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)