# Cannabinoids in Hair and Their Prospective Association with Mental and Physical Health Outcomes in Adolescents

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**Abstract**

**Background.** Cannabis is one of the most widely used drugs in early adolescence, a crucial time for development. Cannabinoids within the cannabis plant (e.g., delta-9-tetrahydrocannabinol [THC], and cannabidiol [CBD]) are suggested to have a range of health implications. These may differ by sex, given sex differences in the endocannabinoid system (ECS). Yet, how aspects of mental and physical health are related to cannabis use as measured by hair concentrations, both within early adolescence and across sexes, is so far inconclusive.

**Methods.** We analyzed hair toxicology data from three cannabinoid analytes (THC, CBD, and 11-nor-9-carboxy-THC [THCCOOH]) and multiple mental and physical health measures in 9-15 year-old youth (49% female) from the Adolescent Brain Cognitive Development (ABCD) Study (N=2,262). Two-part linear regression models were fit to assess the effects of cannabis constituent presence, concentrations, and THC concentrations + CBD presence on externalizing and internalizing symptoms, physical and strengthening exercise, asthma presence, and sleep duration. Secondary analyses fit the same models but stratified by sex.

**Results.** In the full sample, greater THC concentrations predicted more frequent strength exercise and physical exercise one year later; greater CBD concentrations predicted fewer internalizing symptoms and strength exercise days; and greater THCCOOH concentrations predicted shorter sleep duration. Among males, cannabinoids differentially predicted exercise days; greater THC and THCCOOH concentrations predicted shorter sleep duration; and greater CBD concentrations predicted longer sleep duration and fewer externalizing symptoms. Among females, greater THC and THCCOOH concentrations predicted strength exercise frequency; THCCOOH predicted asthma presence one year later; and THC concentrations predicted shorter sleep duration.

**Conclusion.** In a nationwide study of youth ages 9-15 years old, we found cannabinoid hair concentrations predict differences in health outcomes a year later, suggesting potential differential mechanisms for THC and CBD effects on health. Furthermore, sex-specific observations in these prospective associations emphasize the importance of considering sex assigned at birth when investigating correlates of cannabis use. Analysis of cannabinoid hair concentrations can reveal key links to mental health, physical activity, and sleep, aiding understanding of complex cannabis effects.

**Keyword(s):** cannabis, hair toxicology, adolescents, internalizing, externalizing, exercise, sleep

**Abbreviation(s):**

- THC = delta-9-tetrahydrocannabinol

- CBD = cannabidiol

- THCCOOH = 11-nor-9-carboxy-Δ9-tetrahydrocannabinol

1                                    **1. Introduction**

2              Early adolescence is a pivotal developmental period when youth may start experimenting

3    with cannabis use (Johnston et al., 2020) or experience onset of mental health problems (Solmi et

4    al., 2022). Prior literature indicates cannabis use may relate to mental and physical health

5    outcomes such as increased risk for symptoms of depression (Pacheco-Colón et al., 2019) and

6    anxiety (Xue et al., 2021), intensified asthma (Chatkin et al., 2019), sleep difficulties (Velzeboer

7    et al., 2022), and reduced engagement in physical activity (West et al., 2020). Given cannabis is

8    a plant consisting of over 100 different cannabinoid constituents (dos Santos et al., 2021; Rock &

9    Parker, 2021), specific cannabinoids (e.g. delta-9-tetrahydrocannabinol, or THC, and

10   cannabidiol, or CBD) may demonstrate distinct relationships with mental and physical health.

11   However, the relationships between cannabinoid constituents and health outcomes are

12   inconclusive, and examination of these associations in late childhood is lacking. Thus, to

13   promote optimal mental and physical health during early adolescence, understanding the

14   implications of cannabinoid constituents with health within a young population is important.

15             Two of the most widely researched cannabinoids are THC and CBD. THC is a partial

16   agonist of the endocannabinoid system (ECS), a neuromodulatory system responsible for

17   homeostatic functions. THC primarily binds to cannabinoid 1 (CB1) receptors (dos Santos et al.,

18   2021; Solowij et al., 2018) which are present across brain regions (Sim-Selley, 2003). THC is

19   responsible for the more euphoric and pleasurable effects of cannabis, in addition to potential

20   paranoia or anxiety (D'Souza et al., 2004; Fusar-Poli et al., 2009; Turna et al., 2017). CBD, on

21   the other hand, may antagonize effects of THC (McPartland et al., 2015) and demonstrates

22   therapeutic potential across a range of indications (Solowij et al., 2018).

23      There may also be sex-specific associations between cannabis and health consequences,

24      given functional and structural differences by sex in brain regions abundant in CB1 receptors

25      (McPherson et al., 2021). Males experience greater endocannabinoid density and binding in

26      earlier stages of life, whereas CB1 receptor binding in females increases across the lifespan,

27      contributing to sex-based neurodevelopmental trajectories (Crane et al., 2013). Consequently,

28      any sort of disturbance to the ECS, such as through the introduction of exogenous cannabinoids,

29      may result in sex-varied outcomes. However, there are few examinations of sex-specific

30      variation in cannabis-related health outcomes in youth, and existing studies in this realm yield

31      inconclusive findings (Hawes et al., 2019).

32      Investigations of cannabis use and health outcomes to date largely rely on self-report.

33      Though cost-effective and efficacious, self-report may yield inaccurate reporting of cannabis use

34      in youth (Wade et al., 2022, 2023). For example, youth may not disclose their use accurately, or

35      at all, because of desirability effects, privacy concerns, and inaccurate memory or knowledge

36      (Johnson, 2014; Williams & Nowatzki, 2005). While self-report provides important information

37      on frequency of use or cannabis product consumed, reports of specific cannabinoid constituents

38      within products used are not often obtainable. Even in cases of use of retail products in states

39      with legal recreational cannabis use, the labeled cannabinoid potency may be incorrect (Schwabe

40      et al., 2023). Thus, objective measures of cannabis use (e.g., plasma or hair toxicological

41      analysis) are beneficial as they yield information on specific cannabinoid content. Hair

42      toxicology identifies moderate to frequent cannabis use (Huestis et al., 2007; Taylor et al., 2017)

43      and detects different cannabinoid concentrations: the parent analytes (i.e. THC and CBD),

44      indicate exposure to cannabis, and THC's metabolite, 11-nor-9-carboxy-$\Delta$9-

45      tetrahydrocannabinol (THCCOOH), which indicates bio-verified cannabis consumption (Hill et

46  al., 2016). Further, hair cannabinoids offer a unique qualitative impression of frequency of

47  cannabis consumption, as concentrations positively correlate with self-reported use (Taylor et al.,

48  2017) and, in some instances, with cannabinoid potency (Kroon et al., 2024). Comparing hair

49  toxicology data to self-reported substance use reveals that self-report underestimates the

50  frequency of substance use in early adolescents (Wade et al., 2023) and, in young adults,

51  underreports exposure by 30% to 60% (Steinhoff et al., 2023). While self-report is frequently

52  employed and useful, hair cannabinoids reveal more robust brain-behavior relationships than

53  reliance on self-report alone (Wade et al., 2024), underscoring the potentially pivotal role of hair

54  cannabinoids as an objective measure of cannabis use in young cohorts.

55      Limited research utilizes hair toxicology in early adolescents. Studies using hair

56  toxicology data in individuals with cannabis use focus on neurocognition in adolescents and

57  adults (Morgan et al., 2012; Wade et al., 2024) and psychosis in adults (Curran et al., 2019;

58  Morgan et al., 2012; Morgan & Curran, 2008). Few studies investigate mental or physical health

59  outcomes in relation to cannabinoid hair concentrations. Specifically, Morgan et al. (2012)

60  reported higher THC concentrations in hair are associated with greater depression and anxiety in

61  adults, while Bouso et al. (2020) found cannabinoids in hair relates to somatization in cannabis

62  users with chronic diseases. However, to our knowledge, there are no studies examining how

63  cannabinoid hair concentrations relate to mental and physical health outcomes in youth.

64      The current study served as the first examination of prospective associations between

65  cannabinoid hair concentrations and risk for various mental and physical health outcomes in a

66  large sample of youth during late childhood and early adolescence. We leveraged data from

67  ~2,200 youth (ages 9-14) enrolled in the longitudinal, nationwide Adolescent Brain and

68  Cognitive Development (ABCD) Study™. Health outcomes investigated were based on data that

69    were available within the ABCD Study and fit the cannabis literature. Specifically, for mental

70    health, externalizing and internalizing symptoms were included (Sullivan et al., 2022), as

71    cannabis is associated with increased externalizing and internalizing symptoms (Girgis et al.

72    2020; Meier et al. 2020) (Griffith-Lendering et al., 2011). For physical health, asthma, sleep, and

73    exercise frequency were measured. Asthma symptoms are positively associated with cannabis

74    use (Chatkin et al., 2019). Sleep is associated with disrupted sleep quality (Cohen-Zion et al.,

75    2009; Maple et al., 2016). For physical activity, adults who use cannabis engage in *more* days of

76    exercise (French et al., 2021) than those who do not use cannabis.

77         To investigate cannabinoid constituents' impacts on health outcomes, cannabinoid hair

78    concentrations were used. First, we examined whether presence and concentrations of THC,

79    CBD, and THCCOOH in hair predict subsequent mental and physical health outcomes one year

80    later. Consistent with prior documented effects of THC and CBD, we hypothesized that higher

81    concentrations of THC and THCCOOH would predict poorer mental and physical health

82    outcomes, while CBD would demonstrate more beneficial associations. Second, considering

83    known sex-differentiated ECS functioning and in outcomes in individuals who use cannabis

84    (Crane et al., 2013), we explored sex-specific effects in these prospective associations.

85                                    **2. Methods**

86    **2.1 Participants**

87         Data were obtained from the Adolescent Brain and Cognitive Development (ABCD)

88    Study, a longitudinal study that collects annual data from youth at 21 study sites across the

89    United States (Volkow et al., 2018). From 2016 to 2018, participants aged 9-10 years old were

90    recruited from schools with few criteria for exclusion, resulting in a sample of 11,880 youth at

91    baseline. For detailed recruitment procedures, see Garavan et al. (2018). Nearly half (49%) of

92    these youth were female. Regarding race/ethnicity, 66% were White, 7% were Black, 20% were

93    non-White Hispanic, and 8% identified as a different category. The median household income

94    was $87,500. For the current study, we drew upon data from the ABCD 5.1 release (DOI:

95    10.15154/z563-zd24, Haist & Jernigan, 2023), consisting of data from baseline to the 4-year

96    follow-up[1]. Given our interest in examining relationships between cannabinoid constituents in

97    hair with health outcomes, we restricted the larger ABCD Study dataset to youth with data

98    available for hair toxicology and mental/physical health, resulting in a total sample size of 1,903

99    youth with $N = 2,262$ observations. Sample characteristics for this subsample, including

100   demographics and variables of interest, are presented in **Table 1**. Demographic characteristics of

101   our subsample and the entire ABCD Study dataset at baseline are presented in **Table S1**.

102   **2.2 Measures**

103   **2.2.1 Internalizing and Externalizing Symptoms.** At each annual follow-up visit (e.g. baseline,

104   1-year follow-up, 2-year follow-up, 3-year follow-up, 4-year follow-up), parents completed the

105   Child's Behavior Checklist (CBCL; Achenbach et al., 2001), an evaluation tool for youth's

106   dimensional functioning. Thirty-five items measured externalizing symptoms ("rule-breaking

107   behavior," "aggressive behavior") and 32 items measured internalizing symptoms ("somatic

108   complaints," "anxious/depressed," "withdrawn/depressed"). We used the age and gender-normed

109   *t*-scores of externalizing and internalizing symptoms for analysis.

110   **2.2.2 Exercise, Sleep, and Asthma.** *Exercise.* Youth responded to two items, reporting the

111   number of days they did two types of physical activity. One item asked about physical exercise

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[1] ABCD data is released annually with the data being frozen half-way through data collection of current annual follow-up. As such, only ~50% of the sample had data collected for the 4-year follow-up within the 5.1 release and does not indicate missing data. The total Ns for each follow-up and the corresponding N for this study are presented in Table 1.

112    ("During the past 7 days, on how many days were you physically active for a total of at least 60

113    minutes per day?"). The other item was about strengthening exercise ("On how many of the past

114    7 days did you do exercises to strengthen or tone your muscles, such as push-ups, sit-ups, or

115    weightlifting?"). The youth were administered each item at baseline assessment and then yearly

116    after the 2-year follow-up. *Asthma.* We measured the presence of asthma as a binary yes or no

117    response from the parent's report of their youth's medical history. *Sleep Duration.* To measure

118    sleep, we used scores of average nightly sleep duration in hours as calculated by the youth's

119    answers to the Munich Chronotype Questionnaire, a well-validated measure that assesses sleep

120    schedule (MCTQ-C; Zavada et al., 2005).

121    **2.2.3 Cannabinoid Concentrations in Hair.** THC, CBD, and THCCOOH concentrations were

122    measured using hair toxicology data. Each year, hair was collected from 70% of youth in the

123    study who assented to hair collection and had a hair length of ≥1 cm (Uban et al., 2018). Due to

124    budget limitations, hair was assayed for a subset of youth who were largely identified by an

125    algorithm grounded in prior literature to place importance on youth at most risk for substance use

126    based on empirically validated risk factors (Wade et al., 2022). There were two selection groups:

127    (1) high-risk participants (the vast majority of those selected) and (2) randomly selected low-risk

128    youth. The random selection method was conducted in youth who reported no substance use and

129    obtained low scores on the risk algorithm (Wade et al., 2023).

130           Chosen samples were sent to Psychemedics (Culver City, CA) and were trimmed to a

131    length of 3.6 cm (Wade et al., 2023), where they underwent a standardized assay protocol. All

132    samples were washed to mitigate the risk of false positives due to environmental substance

133    exposure (see Wade et al., 2023 or Section 1 in the Supplementary Material for description of

134    hair washing protocol). Hair was then enzymatically broken down and screened for drug classes

135    using FDA-cleared immunoassays (for THCCOOH, LOD = 5 pg/10 mg) or directly tested by

136    mass spectrometry (THC and CBD). Presumed positive THCCOOH results and parent

137    cannabinoids were validated and quantified through LC-MS/MS or GC-MS/MS analysis

138    (THCCOOH, LOD/LOQ = 0.02 pg/mg; THC and CBD = 5 pg/mg). Concentrations of THC,

139    CBD, and THCCOOH were provided.

140    **2.2.4 Covariates.** We included three covariates in our models: age, household income, and

141    pubertal development. Age was covaried since hair toxicology data was obtained from youth

142    from ages 9 - 15 years old. Household income was covaried, as socioeconomic status is related to

143    all domains of interest. Lastly, pubertal development was covaried because this age range also

144    encompasses the onset of puberty for most youth. Pubertal development was assessed using the

145    Pubertal Development Scale (PDS; Petersen et al., 1988), a measure summarizing the stage of

146    pubertal development (i.e., pre-puberty, early puberty, mid-puberty, late-puberty, post-puberty)

147    the youth was currently in with regard to the participant's sex at birth.

148    **2.3 Data Analytic Plan**

149         Data were analyzed using R version 4.3.2 (R Core Team, 2023). All analyses were

150    prospective and linear models were fitted using the *survey* package (Lumley & Gao, 2024). To

151    account for the clustering of observations within individuals, families, and sites over time, we

152    clustered standard errors on family ID, site ID, and participant ID. Models were run with parent

153    analytes (THC, CBD) and, separately, THCCOOH.

154         We fit prospective models with cannabis constituents in hair toxicology predicting mental

155    and physical health outcomes one year later. Each outcome was examined as a separate model

156    (five models total). Cannabinoid constituents were examined using a two-part representation

157    method (Hedeker et al., 2009, 2012) that entails (1) a dummy variable capturing the

158     presence/absence of the cannabinoid, specifically THC and CBD (1 = > 0pg/mg; 0 = 0 pg/mg),

159     then (2) a continuous variable capturing the concentrations of the cannabinoid when present.

160     This representation was chosen to test whether presence alone (i.e., binary) was predictive of the

161     outcome and test the cumulative effects of each parent analyte among those with concentrations

162     of the cannabis constituent (i.e., continuous). For instance, it may be that individuals with any

163     THC use (as a binary predictor) demonstrate one pattern of results, while a different relationship

164     is exhibited through a continuous measure of THC, which more sensitively captures the

165     influence of higher frequency use, use of high potency products, or biological processes leading

166     to prolonged retention of cannabinoids in the body and, subsequently, in hair longer (Vaiano et

167     al., 2023). Lastly, we created an interaction term that examined non-zero THC concentrations in

168     the presence of dummy-coded CBD to examine whether having measurable CBD concentrations

169     influenced the relationship between THC and outcome variables. In secondary analyses, we

170     fitted models from the prior step in sex-specific models (i.e., for males and females only)

171     consistent with the above methods.

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### 3. Results

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173     **3.1 Prospective Associations in Overall Sample**

174          **Table 2** shows all the estimated associations. Higher THC concentration significantly

175     predicted more days of physical exercise ($\beta = 2.98$, $p = 0.02$) and strengthening exercise ($\beta =$

176     $4.80$, $p = <0.001$). Independently, CBD concentration predicted fewer strengthening exercise

177     days ($\beta = -1.59$, $p = 0.002$) and lower internalizing CBCL scores ($\beta = -6.89$, $p = 0.03$). Among

178     individuals with CBD present, higher THC concentration significantly predicted fewer days of

179     strengthening exercise ($\beta = -4.16$, $p = 0.001$). Higher THCCOOH concentration predicted

180     decreased average nightly sleep duration ($\beta = -0.20$, $p = 0.02$).

181 **3.2 Prospective Associations in Males**

182       **Table S3** shows all estimated associations for male-specific models and **Table S2** shows

183 male-specific means and standard deviations for outcome variables. For physical health measures

184 in males, THC presence was negatively associated with physical exercise days in males ($\beta$ = -

185 0.54, p = 0.04) though THC concentration was positively associated with physical exercise days

186 ($\beta$ = 5.31, p < 0.001) and strength exercise days ($\beta$ = 5.81, p = 0.001). However, when males had

187 CBD present in their hair, THC concentration was negatively associated with physical exercise

188 days ($\beta$ = -4.87, p = 0.002) and with strength exercise days ($\beta$ = -5.11, p = 0.005).

189       For males, THC presence and THCCOOH concentration were significantly negatively

190 associated with hours of average nightly sleep duration (THC presence: $\beta$ = -0.44, p = 0.010;

191 THCCOOH concentration: $\beta$ = -0.23, p = 0.03), while CBD concentration was significantly

192 positively associated with hours of average nightly sleep duration ($\beta$ = 1.98, p = 0.03).

193       For mental health outcomes in males, there was a significant negative association

194 between CBD concentration and externalizing CBCL scores ($\beta$ = -9.59, p = 0.03). All other

195 terms (i.e. coefficients, interactions) in models were nonsignificant for males.

196 **3.3 Prospective Associations in Females**

197       **Table S4** shows all estimated associations for female-specific models and **Table S2**

198 shows female-specific means and standard deviations for outcome variables. For females, THC

199 presence was negatively associated with strength exercise days ($\beta$ = -0.70, p = 0.002).

200 THCCOOH concentration was positively associated with strength exercise days ($\beta$ = 1.79, p =

201 0.001), as was THC concentration ($\beta$ = 4.21, p < 0.001). However, in the presence of CBD, THC

202    concentration became negatively associated with strength exercise days for females ($\beta$ = -4.73, p

203    < 0.001).

204         In females, THC concentration was significantly negatively associated with hours of

205    average nightly sleep duration ($\beta$ = -3.07, p < 0.001) and in the presence of CBD, THC

206    concentration was significantly positively associated with average nightly sleep duration ($\beta$ =

207    3.74, p = 0.02).

208         Finally, for asthma presence, THCCOOH concentration was significantly negatively

209    associated with asthma presence in females ($\beta$ = -0.04, p = 0.02). All other terms (i.e., main

210    effects, interactions) in models were nonsignificant.

211                                            **4. Discussion**

212         In a nationwide sample of youth in early adolescence, we examined the prospective

213    associations between cannabinoid concentrations measured via hair toxicology and mental and

214    physical health outcomes one year later. THC concentration positively predicted the number of

215    physical exercise and strengthening exercise days. However, in the presence of CBD, THC

216    concentration was negatively associated with exercise. CBD concentration alone was associated

217    with fewer exercise days. Further, greater CBD concentration was related to lower internalizing

218    symptoms at the next annual visit. There was also a main, negative effect of THCCOOH

219    concentration and nightly sleep duration. When we conducted sex-stratified analyses to

220    investigate the potential sex-specific effects for males and females, they exhibited the same

221    pattern of results regarding strength exercise. However, for other health outcomes, we observed

222    sex-specific associations between cannabinoid concentrations and mental and physical health. In

223    females, cannabinoid analytes prospectively predicted relationships with sleep duration, and

224    asthma, while in males, analytes uniquely predicted externalizing symptoms, number of physical

225    exercise days, and sleep duration.

226    **4.1 Full Sample Associations and their Implications**

227         Regarding mental health outcomes models, higher CBD concentrations predicted fewer

228    internalizing symptoms. This was consistent with prior literature that suggested CBD

229    concentrations may modulate the depression and anxiety symptoms that are potentially

230    associated with cannabis use (Morgan et al., 2012; Niesink & van Laar, 2013; Solowij et al.,

231    2018; Xue et al., 2021). CBD also was proposed to have beneficial, therapeutic effects in

232    depression (García-Gutiérrez et al., 2020). Though we did not find a relationship between THC

233    concentrations and internalizing symptoms one year later, it may be that the influence of THC

234    operates more acutely.

235         The relationships between cannabinoid concentrations and physical health outcomes were

236    mixed by analyte and measurement method (i.e., binary presence variables or specific

237    cannabinoid concentrations). Presence alone, a binary indicator not considering concentrations,

238    of THC or CBD was not significantly associated with health outcomes. More frequent use or use

239    of higher potency products or individual factors, captured in continuous THC concentrations

240    (Vaiano et al., 2023) may more sensitively relate cannabinoid constituents in hair with health

241    outcomes. Among continuous cannabinoid measures, THC concentrations were positively

242    associated with the number of days of both physical exercise and strengthening exercise. Prior

243    research in adults revealed those who used cannabis were more likely to adhere to the World

244    Health Organization's physical activity guidelines (Vidot et al., 2017). Additionally, cannabis

245    consumption related to more physical activity when looking at frequent cannabis users (Ong et

246    al., 2021), and, consistent with our study, when measured in days of physical and strengthening

247    activities (French et al., 2021). Though there are potential physical (e.g., respiratory), mental

248    health, and cognitive concerns related to cannabis use in athletes (Huestis et al., 2011),

249    exogenous cannabinoids may replicate the positive effects of endocannabinoids released during

250    acute exercise (Gibson et al., 2024; YorkWilliams et al., 2019). Indeed, studies showed that

251    moderate to frequentcannabis use correlates with enhanced positive moods during exercise

252    (Gibson et al., 2024), heightened self-reported recovery (YorkWilliams et al., 2019), and greater

253    motivation to engage in activity (YorkWilliams et al., 2019). Interestingly, CBD concentrations

254    were negatively associated with strength exercise days. One potential reason for this negative

255    association could be related to exercise-induced muscle damage, as adult elite athletes use CBD

256    in response to injury (Burr et al., 2021), especially following strength training (Cochrane-

257    Snyman et al., 2021; Isenmann et al., 2021). Higher CBD concentrations could, therefore,

258    indicate youth were unable to engage in exercise due to injury and were using CBD in response

259    to injury, though this was not assessed here. Our study served as a novel documentation of the

260    association between cannabis use and exercise in youth. Given the prospective design of our

261    analyses, it was not possible to determine the exact role of THC and/or CBD in later physical

262    activity, warranting future investigation into the underlying mechanisms of this relationship in

263    young adolescents.

264         Regarding sleep, THCCOOH negatively predicted sleep duration one year later. Cannabis

265    use was linked to disturbed sleep quality (Burr et al., 2021), and limited evidence supports

266    cannabis' efficacy as a potential sleep remedy (Velzeboer et al., 2022). Our findings provided

267    further evidence that cannabis use, and here specifically THCCOOH concentrations, may put

268    individuals at increased risk for decreased duration of sleep.

269    **4.2 Sex-Specific Associations Between Hair Toxicology and Mental/Physical Health**

270        Exploratory sex-specific models identified differences in directionality by cannabinoid

271    concentrations across several measures. Sex-specific models were fitted to observe differences in

272    health outcomes given the unique trajectories of the ECS and cannabis-behavior associations by

273    sex (Crane et al., 2013; McPherson et al., 2021), with cannabis constituents assessed through hair

274    cannabinoid concentrations.

275        We limited our discussion of sex-specific associations to the relationships between the

276    continuous measures of cannabinoid concentrations with mental and physical health outcomes,

277    as binary cannabinoid presence was not independently related to outcomes in these models with

278    two exceptions. For males, THC presence was negatively associated with physical exercise,

279    while THC concentrations demonstrated a positive relationship. For females, the same pattern

280    was observed but for strengthening exercise. These results are not wholly unexpected as the two-

281    part regression model provides differential insight that wouldn't be obtained by treating THC or

282    CBD as unidimensional (i.e., only binary) (Dziak & Henry, 2017). Prior studies using this

283    modeling representation found coefficients with opposite signs for smoking status and frequency

284    of smoking on affect, suggesting negative outcomes were most prevalent in those with higher

285    frequency of use (Hedeker et al., 2009, 2012). Given the majority of null findings regarding THC

286    and CBD presence, our results suggest higher THC concentrations—a measure which combines

287    frequency of use or potency of products used, along with individual factors (Vaiano et al.,

288    2023)—may more sensitively identify relationships with health outcomes.

289        In males, CBD concentrations were significantly negatively associated with externalizing

290    CBCL scores. Cannabis usage, in general, was linked to increased externalizing symptoms

291    (Fergusson et al., 2002; Griffith-Lendering et al., 2011; Monshouwer et al., 2006). However, our

292    findings aligned with emerging research suggesting that CBD may have effects to the contrary.

293    CBD was proposed as a potential treatment for two facets of externalizing symptomatology:

294    substance use disorder (Chye et al., 2019; Navarrete et al., 2021), which includes cannabis use,

295    and behavior in autism spectrum disorder (Ma et al., 2022; Nezgovorova et al., 2021; Poleg et

296    al., 2019). The role of CBD in specifically modulating externalizing symptoms requires further

297    exploration.

298          Both male and female young adolescents demonstrated similar patterns between

299    cannabinoids and sleep duration. Overall, THC and THCCOOH were negatively related to sleep

300    duration. Yet CBD, by independent concentrations in males or the presence of CBD in

301    conjunction with THC in females, positively predicted nightly sleep duration. This could suggest

302    a distinct mechanism through which CBD may affect the relationship between THC and sleep

303    duration, possibly mitigating the negative effects of THC in isolation. As there are increasing

304    reports of CBD as a sleep remedy (Moltke & Hindocha, 2021), it is important to consider the

305    contents of cannabis in relation to its therapeutic or risk profile.

306          In terms of physical activity and asthma, males and females displayed similar

307    associations between THC concentrations and strength exercise, but different associations

308    between cannabinoid constituents and physical exercise or asthma. THC concentrations were

309    positively associated with strengthening exercises for both males and females, however, when

310    looking at individuals who also had CBD present, THC concentrations became negatively

311    associated with strengthening exercise for both sexes. Exercise is known to upregulate

312    endocannabinoid activity (Brellenthin & Koltyn, 2016), and thus exogenous cannabinoids may

313    interact and influence the relationship between exercise and the endocannabinoid system (ECS).

314    In terms of physical exercise, males' physical exercise was related to cannabinoid concentrations

315    while female's physical exercise was not. Conversely, THCCOOH concentrations were found to

316    put females at greater risk for asthma, while asthma presence in males was not related to any

317    cannabinoid concentrations. Given the unique trajectories of the ECS by sex, it will be important

318    to continue to monitor these youth longitudinally with repeated assessments of hair toxicology to

319    assess changes in cannabinoid concentrations and the corresponding impacts on physical health

320    outcomes.

321    **4.3 Strengths and Limitations**

322            Our study had many strengths. First, to overcome the many limitations of self-report for

323    studying the effects of cannabinoids, we used hair toxicology to objectively measure cannabis

324    constituent concentrations (Johnson, 2014; Wade et al., 2023; Williams & Nowatzki, 2005). Hair

325    toxicology data enabled us to examine specific major cannabinoid concentrations (i.e., CBD,

326    THC, and THCCOOH) in both binary (present/not present) and dose-dependent (continuous)

327    manners. Second, we examined prospective associations between cannabinoids in hair with

328    health outcomes one year later. Third, we were one of the few studies examining sex-specific

329    associations between hair cannabinoid concentrations and mental/physical health one year later.

330    Lastly, we examined all associations among youth during late childhood into early adolescence,

331    a developmental range not usually examined when studying the associations between hair

332    cannabinoid concentrations, cannabis use, and mental/physical health.

333            Our study also had limitations. First, hair toxicology detects moderate to frequent regular

334    use (Huestis et al., 2007; Taylor et al., 2017), not low infrequent cannabis use which most youth

335    in this age group engage in (Hawes et al., 2019; Sullivan et al., 2022). Thus, our results pertained

336    to the heaviest users, who are at greatest risk for negative outcomes. Relationships in occasional

337    or less frequent users may be different from moderate to heavy users. Second, hair toxicology as

338    a measure is reflective of a mixture of frequency of use, product potency, method of

339    consumption, and individual factors (Vaiano et al., 2023); it was not possible to determine

340    whether the mental and physical health outcomes are related to how often adolescents consume

341    cannabis or how much they are consuming at once. Third, there may be confounders of the

342    prospective associations between cannabinoids and physical and mental health, which limited

343    our ability to make causal statements. Future analysis of repeated hair samples in the ABCD

344    Study™ will allow us to examine change over time with corresponding mental and physical

345    health outcomes to delineate the directionality of associations and whether associations hold

346    across development.

## 5. Conclusion

348         In a nationwide sample of youth ages 9-15 years old, we found differences in health

349    outcomes varied as a function of both dose-dependent cannabinoid concentrations and presence

350    of cannabinoid analytes in hair measured one year prior. This suggested potential differential

351    mechanisms by which THC and CBD influence the ECS and downstream health outcomes.

352    Furthermore, the unique prospective associations of cannabis constituents based on sex

353    underscored the importance of looking at these mechanisms within the context of sex assigned at

354    birth. Given the complexity of characterizing the effects of cannabis use on mental/physical

355    health, leveraging cannabinoid analyte concentrations in hair can highlight important prospective

356    relationships with mental health, physical activity, and sleep measures.

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**Table 1**

*Sample Characteristics of Youth with Hair Toxicology Results*

| | Baseline | 1-Year Follow-Up | 2-Year Follow-Up | 3-Year Follow-Up | 4-Year Follow-Up | Range |
|---|---|---|---|---|---|---|
| N | 105 | 551 | 907 | 243 | 455 | |
| Female (%) | 49 | 47 | 47 | 52 | 53 | |
| Household Income | 114,142 (66,545) | 111,330 (62,316) | 106,230 (60,902) | 108,827 (61,517) | 113,602 (60,400) | 1,200 - 200,000 |
| Age | 10.0 (0.7) | 11.0 (0.6) | 12.0 (0.7) | 13.1 (0.6) | 14.2 (0.7) | 9.0 - 15.8 |
| **Race/Ethnicity (%)** | | | | | | |
| Asian | 0 | 1 | 2 | 2 | 1 | |
| Black | 7 | 5 | 4 | 2 | 1 | |
| Hispanic | 20 | 17 | 21 | 23 | 20 | |
| White | 66 | 63 | 63 | 62 | 65 | |
| Other | 8 | 13 | 10 | 12 | 12 | |
| **Hair Toxicology** | | | | | | |
| THC Concentrations (pg/mg) | 5.1 (19.4) | 1.5 (7.1) | 4.3 (43.8) | 13.8 (158.4) | 15.9 (111.9) | 0.0 - 2462.0 |
| CBD Concentrations (pg/mg) | 1.8 (16.8) | 0.7 (5.7) | 1.8 (16.5) | 4.4 (26.2) | 5.5 (34.3) | 0.0 - 508.0 |
| THCCOOH Concentrations (pg/10mg) | 0.0 (0.2) | 0.0 (0.2) | 0.1 (1.4) | 0.4 (2.6) | 1.9 (10.8) | 0.0 - 103.0 |
| **Mental Health/Physical Health Variables** | | | | | | |
| Physical Exercise (days) | 4.1 (2.3) | - | 3.9 (2.1) | 3.9 (2.1) | 3.4 (2.1) | 0.0 - 7.0 |
| Strength Exercise (days) | 3.6 (2.3) | - | 3.1 (2.1) | 3.4 (2.2) | 3.0 (2.0) | 1.0 - 8.0[a] |
| Asthma Presence (%) | 9 | 8 | 7 | 5 | 3 | |
| Sleep Duration (hours) | - | - | 9.0 (1.8) | 8.6 (2.1) | 8.3 (1.4) | 1.3 – 24.0 |
| Internalizing Symptoms (T-Score) | 50.7 (11.7) | 51.6 (11.4) | 51.1 (11.0) | 51.6 (10.3) | 51.2 (11.4) | 33.0 - 86.0 |
| Externalizing Symptoms (T-Score) | 50.0 (11.1) | 50.0 (11.2) | 48.8 (10.9) | 48.5 (9.5) | 46.9 (10.3) | 33.0 - 83.0 |

*Note.* Percentages presented for female, race/ethnicity, and asthma presence. Means and standard deviations presented for all other variables. Physical exercise and strength exercise was measured in days the youth engaged in that specific physical activity. Asthma presence was measured as a binary yes or no, thus the numbers indicate prevalence rates. Sleep duration is a calculation of how many hours of sleep the youth gets on average each night. CBCL internalizing and externalizing scores are age and gender normed T-scores of the youth's internalizing and externalizing symptoms.

[a] 1 means 0 days, 2 means 1 day, 3 means 2 days, etc.

**Table 2**

*Full Sample Cannabis Constituents in Hair Predicting Mental and Physical Health Outcomes One Year Later*

| | Outcomes | | | | | |
|---|---|---|---|---|---|---|
| | Strength Exercise Coef. (SE) | Physical Exercise Coef. (SE) | Sleep Duration Coef. (SE) | Asthma Presence Coef. (SE) | Int. Symptoms Coef. (SE) | Ext. Symptoms Coef. (SE) |
| THC Presence | -0.22 (0.20) $p = .25$ | -0.34 (0.20) $p = .08$ | -0.20 (0.15) $p = .17$ | -0.02 (0.02) $p = .30$ | 0.30 (1.00) $p = .77$ | 1.13 (0.97) $p = .24$ |
| THC Concentrations | **4.80 (1.30)** **$p < .001$** | **2.98 (1.32)** **$p = .02$** | -0.89 (0.97) $p = .36$ | 0.07 (0.13) $p = .62$ | -6.33 (3.78) $p = .09$ | 3.08 (4.08) $p = .45$ |
| CBD Presence | 0.10 (0.31) $p = .75$ | -0.07 (0.28) $p = .80$ | 0.13 (0.13) $p = .33$ | 0.00 (0.03) $p = .91$ | 0.18 (1.45) $p = .90$ | -0.34 (1.33) $p = .80$ |
| CBD Concentrations | **-1.59 (0.52)** **$p = .002$** | -0.08 (0.82) $p = .92$ | 0.78 (0.80) $p = .33$ | 0.02 (0.04) $p = .54$ | **-6.89 (3.25)** **$p = .03$** | -4.25 (2.43) $p = .08$ |
| THC Presence x CBD Presence | -0.04 (0.40) $p = .92$ | 0.23 (0.39) $p = .56$ | 0.24 (0.26) $p = .37$ | -0.00 (0.04) $p = .93$ | -0.37 (2.03) $p = .85$ | 1.06 (1.87) $p = .57$ |
| THC Concentrations x CBD Presence | **-4.16 (1.31)** **$p = .001$** | -2.62 (1.35) $p = .052$ | 0.46 (1.02) $p = .65$ | -0.07 (0.13) $p = .58$ | 7.50 (3.94) $p = .06$ | -2.43 (4.17) $p = .56$ |
| THCCOOH | 0.52 (0.31) $p = .10$ | 0.45 (0.22) $p = .046$ | **-0.20 (0.09)** **$p = .02$** | 0.00 (0.01) $p = .67$ | -0.37 (1.35) $p = .78$ | 0.31 (1.24) $p = .80$ |

*Note.* Rows contain predictors and columns represent outcomes. Int = Internalizing, Ext = Externalizing. Predictor and interaction terms: THC Presence, THC Concentrations, CBD Presence, CBD Concentrations, and THC Concentrations x CBD Presence were specified in one model. THCCOOH was analyzed in a separate model. The number of observations for models including THC and/or CBD ranged from 1419 to 1586. For THCCOOH, the number of observations ranged from 1105 to 1299. For models in which hair toxicology variables were predictors, THC and CBD Concentrations variables were rescaled via dividing raw values by 100 to ensure coefficients were interpretable.

**Table 3.**

*Cannabis Constituents in Hair Predicting Mental and Physical Health Outcomes One Year Later Among Males*

| | Outcomes | | | | | |
|---|---|---|---|---|---|---|
| | **Physical Exercise (days)** | **Strength Exercise (days)** | **Asthma Presence** | **Sleep Duration** | **Int. Symptoms** | **Ext. Symptoms** |
| THC Presence | **-0.54 (0.26)** **p = .04** | -0.14 (0.27) p = .59 | -0.02 (0.03) p = .38 | **-0.44 (0.17)** **p = .01** | 0.82 (1.36) p = .55 | 1.26 (1.33) p = .34 |
| CBD Presence | -0.33 (0.46) p = .47 | -0.68 (0.43) p = .11 | 0.01 (0.05) p = .77 | 0.21 (0.20) p = .29 | 1.14 (2.33) p = .62 | -1.08 (2.01) p = .59 |
| THC Concentrations | **5.31 (1.38)** **p = <.001** | **5.81 (1.76)** **p = .001** | 0.25 (0.29) p = .39 | 1.32 (1.03) p = .20 | -11.23 (8.17) p = .17 | 4.98 (7.81) p = .52 |
| CBD Concentrations | -0.48 (1.90) p = .80 | -1.94 (1.18) p = .10 | 0.03 (0.05) p = .55 | **1.98 (0.88)** **p = .03** | -11.91 (6.32) p = .06 | **-9.59 (4.50)** **p = .03** |
| THC Presence x CBD Presence | 0.66 (0.59) p = .27 | 0.62 (0.56) p = .27 | 0.00 (0.06) p = .98 | 0.44 (0.35) p = .21 | -2.23 (3.03) p = .46 | 1.41 (2.65) p = .59 |
| THC Concentrations x CBD Presence | **-4.87 (1.53)** **p = .002** | **-5.11 (1.80)** **p = .005** | -0.26 (0.29) p = .37 | -2.15 (1.07) p = .05 | 14.18 (8.46) p = .09 | -2.51 (7.99) p = .75 |
| THCCOOH Concentrations | 0.38 (0.22) p = .08 | 0.28 (0.27) p = .30 | 0.00 (0.01) p = .69 | **-0.23 (0.10)** **p = .03** | -0.44 (1.24) p = .72 | 0.46 (1.39) p = .74 |

*Note.* Rows contain predictors and columns represent outcomes. Int = Internalizing, Ext = Externalizing. Predictor and interaction terms: THC Presence, THC Concentrations, CBD Presence, CBD Concentrations, and THC Concentrations x CBD Presence were specified in one model. THCCOOH was analyzed in a separate model. Bolded values indicate significant associations. The number of observations ranged from 543 to 763 across the five outcomes. For models in which hair toxicology variables were predictors, THC and CBD Concentration variables were rescaled via dividing raw values by 100 to ensure coefficients were interpretable.

**Table 4.**

*Cannabis Constituents in Hair Predicting Mental and Physical Health Outcomes One Year Later Among Females*

| | Outcomes | | | | | |
|---|---|---|---|---|---|---|
| | **Physical Exercise (days)** | **Strength Exercise (days)** | **Asthma Presence** | **Sleep Duration** | **Int. Symptoms** | **Ext. Symptoms** |
| THC Presence | -0.29 (0.30) p = .33 | **-0.70 (0.22) p = .002** | -0.02 (0.02) p = .30 | 0.21 (0.25) p = .40 | -0.04 (1.48) p = .98 | 0.52 (1.44) p = .72 |
| CBD Presence | 0.13 (0.35) p = .72 | 0.65 (0.40) p = .10 | -0.00 (0.04) p = .95 | 0.10 (0.18) p = .58 | -0.52 (1.88) p = .78 | -0.00 (1.74) p = 1.00 |
| THC Concentrations | 0.80 (1.49) p = .59 | **4.21 (1.12) p = <.001** | -0.04 (0.05) p = .40 | **-3.07 (0.91) p = <.001** | -3.00 (4.29) p = .48 | 2.27 (4.42) p = .61 |
| CBD Concentrations | 0.45 (0.91) p = .62 | -0.59 (0.47) p = .21 | -0.02 (0.04) p = .54 | -0.21 (1.18) p = .86 | -4.68 (4.95) p = .35 | 2.56 (4.44) p = .56 |
| THC Presence x CBD Presence | -0.24 (0.52) p = .64 | -0.29 (0.51) p = .57 | -0.01 (0.05) p = .77 | -0.24 (0.41) p = .56 | 1.84 (2.91) p = .53 | 2.31 (2.90) p = .43 |
| THC Concentrations x CBD Presence | -0.39 (1.92) p = .84 | **-4.73 (1.24) p = <.001** | 0.10 (0.10) p = .31 | **3.74 (1.57) p = .02** | 1.80 (6.48) p = .78 | -11.59 (7.22) p = .11 |
| THCCOOH Concentrations | 0.16 (0.81) p = .84 | **1.79 (0.56) p = .001** | **-0.04 (0.01) p = .02** | 0.30 (0.47) p = .53 | 5.21 (2.89) p = .07 | -2.66 (5.04) p = .60 |

*Note.* Rows contain predictors and columns represent outcomes. Int = Internalizing, Ext = Externalizing. Predictor and interaction terms: THC Presence, THC Concentrations, CBD Presence, CBD Concentrations, and THC Concentrations x CBD Presence were specified in one model. THCCOOH was analyzed in a separate model. Bolded values indicate significant associations. The number of observations ranged from 468 to 656 across the five outcomes. For models in which hair toxicology variables were predictors, THC and CBD Concentration variables were rescaled via dividing raw values by 100 to ensure coefficients were interpretable.

**Supplementary Material**

This supplement includes 3 items:

- Section 1: Description of Hair Washing Protocol
- Table S1: Demographics for Subsample and Entire ABCD Study
- Table S2: Sex-Stratified Means and Standard Deviations for Hair Toxicology, Mental Health, and Physical Health Variables

**Section 1.**

Description of Hair Washing Protocol

Hair was first washed for 15 minutes with 2 mL of isopropanol per 12 mg hair, then washed three times for 30 minutes with phosphate buffer, and lastly washed twice for 60 minutes with phosphate buffer.

**Table S1.**

*Demographics for Subsample and Entire ABCD Study*

|  | **Current Study Subsample** | **Entire ABCD Study** |
|---|---|---|
| N | 1,903 | 11,868 |
| % Female | 49% | 49% |
| Household Income | 109,626 (61,518) | 104,601 (62,648) |
| Age | 12.3 (1.38) | 11.7 (1.49) |
| **Race/Ethnicity (%)** |  |  |
| White | 63% | 52% |
| Black | 4% | 15% |
| Asian | 2% | 2% |
| Non-White Hispanic | 20% | 20% |
| Other | 11% | 11% |
| **Cannabis Constituents in Hair Toxicology** |  |  |
| THC | 6.98 (77.7) | – |
| CBD | 2.56 (21.0) | – |
| THCCOOH | 0.56 (5.71) | – |
| **Mental/Physical Health** |  |  |
| Physical Exercise | 3.76 (2.14) | 3.65 (2.20) |
| Strength Exercise | 3.13 (2.11) | 3.04 (2.05) |
| Asthma Presence | 6% | 9.6% |
| Sleep Duration | 8.73 (1.79) | 8.99 (1.57) |
| Internalizing T-Score | 51.3 (11.1) | 48.1 (10.6) |
| Externalizing T-Score | 48.7 (10.8) | 44.8 (9.94) |

*Note.* The current substudy sample contains 1,903 youth with a total of 2,262 observations. Means and standard deviations are presented for all variables except for % female, race/ethnicity, and asthma presence which are percentages. Values for hair toxicology variables are not presented for the Entire ABCD Study as inclusion for the current study required the presence of those values.

**Table S2.**

*Sex-Stratified Means and Standard Deviations for Hair Toxicology, Mental Health, Physical Health Variables*

| Variable | Males M (SD) | Females M (SD) |
|---|---|---|
| **Physical Exercise** | 3.98 (2.17) | 3.53 (2.07) |
| **Strength Exercise** | 3.38 (2.21) | 2.88 (1.95) |
| **PE Class Days** | 2.47 (1.77) | 2.35 (1.80) |
| **Asthma Presence** | 7% | 5% |
| **Sleep Duration** | 8.83 (1.85) | 8.63 (1.73) |
| **CBCL Internalizing Scores** | 51.14 (11.22) | 51.42 (10.99) |
| **CBCL Externalizing Scores** | 48.99 (10.85) | 48.42 (10.64) |
| **THC Concentrations** | 8.1 (87.2) | 5.8 (66.2) |
| **CBD** | 2.3 (18.9) | 2.8 (23.1) |
| **THC Concentrations x CBD** | 983 (22474) | 1089 (31823) |
| **THCCOOH** | 0.48 (4.87) | 0.64 (6.48) |

*Note.* Means and standard deviations are presented for all variables except for Asthma Presence, a percentage.