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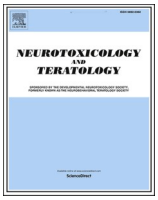

Cannabinoids in hair and their prospective association with mental and physical health outcomes in adolescents

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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 ($N = 2262$). 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. Finally, to further characterize these relationships, we conducted two exploratory analyses: we assessed health variables prospectively and concurrently predicting cannabinoid concentrations. False discovery rate corrections were employed for all analyses.
Results: In the full sample, greater THC concentrations predicted more frequent strength exercise one year later; greater CBD concentrations predicted fewer 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. Among females, greater THC and THCCOOH concentrations predicted strength exercise frequency, and THC concentrations predicted shorter sleep duration. In exploratory models, asthma presence predicted THCCOOH concentration one year later. Concurrently, THC concentration alone and in the presence of CBD predicted both sleep duration and lower exercise days, while THCCOOH concentration predicted lower exercise days, less asthma presence, as well as greater internalizing and externalizing symptoms.
Conclusion: In a nationwide study of youth ages 9–15 years old, we found cannabinoid hair concentrations predicted 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.

Abbreviations: THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol; THCCOOH, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol.

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1. Introduction

Early adolescence is a pivotal developmental period when youth may start experimenting with cannabis use (Johnston et al., 2020) or experience onset of mental health problems (Solmi et al., 2022). National surveys indicate 11.3 % of youth aged 14–15 reported using cannabis within the past year (National Survey on Drug Use and Health 2023, 2024), however limited research has queried use in earlier ages (e.g., 9–13) and data that do exist show <1–1 % of youth 9–13 report past-year cannabis use (Sullivan et al., 2022). Prior literature indicates cannabis use may relate to mental and physical health outcomes such as increased risk for symptoms of depression (Pacheco-Colón et al., 2019) and anxiety (Xue et al., 2021), intensified asthma (Chatkin et al., 2019), sleep difficulties (Velzeboer et al., 2022), and reduced engagement in physical activity (West et al., 2020). Given cannabis is a plant consisting of over 100 different cannabinoid constituents (dos Santos et al., 2021; Rock and Parker, 2021), specific cannabinoids (e.g. delta-9-tetrahydrocannabinol, or THC, and cannabidiol, or CBD) may demonstrate distinct relationships with mental and physical health. However, the relationships between cannabinoid constituents and health outcomes are inconclusive, and examination of these associations in late childhood is lacking. Thus, to promote optimal mental and physical health during early adolescence, understanding the implications of cannabinoid constituents with health within a young population is important.

Two of the most widely researched cannabinoids are THC and CBD. THC is a partial agonist of the endocannabinoid system (ECS), a neuromodulatory system responsible for homeostatic functions. THC primarily binds to cannabinoid 1 (CB1) receptors (dos Santos et al., 2021; Solowij et al., 2018) which are present across brain regions (Sim-Selley, 2003). THC is responsible for the more euphoric and pleasurable effects of cannabis, in addition to potential paranoia or anxiety (D'Souza et al., 2004; Fusar-Poli et al., 2009; Turna et al., 2017). CBD, on the other hand, may antagonize effects of THC (McPartland et al., 2015) and demonstrates therapeutic potential across a range of indications (Solowij et al., 2018).

There may also be sex-specific associations between cannabis and health consequences, given functional and structural differences by sex in brain regions abundant in CB1 receptors (McPherson et al., 2021). Males experience greater endocannabinoid density and binding in earlier stages of life, whereas CB1 receptor binding in females increases across the lifespan, contributing to sex-specific neurodevelopmental trajectories (Crane et al., 2013). Consequently, any sort of disturbance to the ECS, such as through the introduction of exogenous cannabinoids, may result in outcomes that differ based on sex. However, there are few examinations of sex-specific variation in cannabis-related health outcomes in youth, and existing studies in this realm yield inconclusive findings (Hawes et al., 2019).

Investigations of cannabis use and health outcomes to date largely rely on self-report. Though cost-effective and efficacious, self-report may yield inaccurate reporting of cannabis use in youth (Wade et al., 2022, 2023). For example, youth may not disclose their use accurately, or at all, because of desirability effects, privacy concerns, and inaccurate memory or knowledge (Johnson, 2014; Williams and Nowatzki, 2005). While self-report provides important information on frequency of use or cannabis product consumed, reports of specific cannabinoid constituents within products used are not often obtainable. Even in cases of use of retail products in states with legal recreational cannabis use, the labeled cannabinoid potency may be incorrect (Schwabe et al., 2023). Thus, objective measures of cannabis use (e.g., plasma or hair toxicological analysis) are beneficial as they yield information on specific cannabinoid content. Hair toxicology identifies moderate to frequent cannabis use (Huestis et al., 2007; Taylor et al., 2017) and detects different cannabinoid concentrations: the parent analytes (i.e. THC and CBD), indicate exposure to cannabis, and THC's metabolite, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH), which indicates bio-verified cannabis consumption (Hill et al., 2016). Further, hair cannabinoids offer a unique qualitative impression of frequency of cannabis consumption, as concentrations positively correlate with self-reported use (Taylor et al., 2017) and, in some instances, with cannabinoid potency (Kroon et al., 2024). Comparing hair toxicology data to self-reported substance use reveals that self-report underestimates the frequency of substance use in early adolescents (Wade et al., 2023) and, in young adults, underreports of use range from 30 % to 60 % (Steinhoff et al., 2023) reveal more robust brain-behavior relationships than reliance on self-report alone (Wade et al., 2024), underscoring the potentially pivotal role of hair cannabinoids as an objective measure of cannabis use in young cohorts.

Limited research utilizes hair toxicology in early adolescents. Studies using hair toxicology data in individuals with cannabis use focus on neurocognition in adolescents and adults (Morgan et al., 2012; Wade et al., 2024) and psychosis in adults (Curran et al., 2019; Morgan et al., 2012; Morgan and Curran, 2008). Few studies investigate mental or physical health outcomes in relation to cannabinoid hair concentrations. Specifically, Morgan et al. (2012) reported higher THC concentrations in hair are associated with greater depression and anxiety in adults, while Bouso et al. (2020) found cannabinoids in hair relate to somatization in cannabis users with chronic diseases. However, to our knowledge, there are no studies examining how cannabinoid hair concentrations relate to mental and physical health outcomes in youth.

The current study served as the first examination of prospective associations between cannabinoid hair concentrations and risk for various mental and physical health outcomes in a large sample of youth during late childhood and early adolescence. We leveraged data from ~2200 youth (ages 9–14) enrolled in the longitudinal, nationwide Adolescent Brain and Cognitive Development (ABCD) Study™. Health outcomes investigated were based on data that were available within the ABCD Study and fit the cannabis literature. Specifically, for mental health, externalizing and internalizing symptoms were included (Sullivan et al., 2022), as cannabis is associated with increased externalizing and internalizing symptoms (Girgis et al., 2020; Griffith-Lendering et al., 2011; Meier et al., 2020). For physical health, asthma, sleep, and exercise frequency were measured. Asthma symptoms are positively associated with cannabis use (Chatkin et al., 2019). Cannabis use is associated with disrupted sleep quality (Cohen-Zion et al., 2009; Maple et al., 2016). For physical activity, adults who use cannabis engage in *more* days of exercise (French et al., 2021) than those who do not use cannabis.

To investigate cannabinoid constituents' impacts on health outcomes, cannabinoid hair concentrations were used. Our initial analyses were two-fold. First, we examined whether presence and concentrations of THC, CBD, and THCCOOH in hair predict subsequent mental and physical health outcomes one year later. Consistent with prior documented effects of THC and CBD, we hypothesized that higher concentrations of THC and THCCOOH would predict poorer mental and physical health outcomes, while CBD would demonstrate more beneficial associations. Second, considering known sex-differentiated ECS functioning and in outcomes in individuals who use cannabis (Crane et al., 2013), we investigated sex-specific effects in these prospective associations. We then conducted two exploratory analyses to better contextualize our initial results. To consider the possibility of reverse association directionality, we looked at whether our mental/physical health variables predicted cannabinoid concentrations one year later. We also examined concurrent associations between mental/physical health variables and cannabinoid concentrations.

2. Methods

2.1. Participants

Data were obtained from the Adolescent Brain Cognitive Development (ABCD) Study, a longitudinal study that collects annual data from

youth at 21 study sites across the United States (Volkow et al., 2018). From 2016 to 2018, participants aged 9–10 years old were recruited from schools with few criteria for exclusion, resulting in a sample of 11,880 youth at baseline. For detailed recruitment procedures, see Garavan et al. (2018). For the current study, we drew upon data from the ABCD 5.1 release (DOI: 10.15154/z563-zd24, Haist and Jernigan, 2023), consisting of data from baseline to the 4-year follow-up.[2] Given our interest in examining relationships between cannabinoid constituents in hair with health outcomes, we restricted the larger ABCD Study dataset to youth with data available for hair toxicology and mental/physical health, resulting in a total sample size of 1903 youth with $N = 2262$ observations.

2.2. Measures

2.2.1. Internalizing and externalizing symptoms

At each annual follow-up visit (e.g. baseline, 1-year follow-up, 2-year follow-up, 3-year follow-up, 4-year follow-up), parents completed the Child's Behavior Checklist (CBCL; Achenbach and Rescorla, 2001), an evaluation tool for youth's dimensional functioning. Thirty-five items measured externalizing symptoms ("rule-breaking behavior," "aggressive behavior") and 32 items measured internalizing symptoms ("somatic complaints," "anxious/depressed," "withdrawn/depressed"). We used the age and gender-normed *t*-scores of externalizing and internalizing symptoms for analysis.

2.2.2. Exercise, sleep, and asthma

Exercise. Youth responded to two items, reporting the number of days they did two types of physical activity. One item asked about physical exercise ("During the past 7 days, on how many days were you physically active for a total of at least 60 minutes per day?"). The other item was about strengthening exercise ("On how many of the past 7 days did you do exercises to strengthen or tone your muscles, such as push-ups, sit-ups, or weightlifting?"). The youth were administered each item at baseline assessment and then yearly after and including the 2-year follow-up. ***Asthma.*** We measured the presence of asthma as a binary yes or no response from the parent's report of their youth's medical history. At baseline, parents were asked whether a doctor had "ever diagnosed" their child with asthma and at every annual follow-up, parents were asked, "since we last saw you, has your child been to a doctor for asthma?" ***Sleep Duration.*** To measure sleep, we used scores of average nightly sleep duration in hours as calculated by the youth's answers to the Munich Chronotype Questionnaire, a well-validated measure that assesses sleep schedule (MCTQ-C; Zavada et al., 2005).

2.2.3. Cannabinoid concentrations in hair

THC, CBD, and THCCOOH concentrations were measured using hair toxicology data. Each year, hair was collected from youth who assented to hair collection and had a hair length of ≥1 cm (Uban et al., 2018). Hair was collected from 70 % of youth in the study; the remaining 30 % either had hair styles that would be adversely impacted by sample collection or declined to contribute a sample. Due to budget limitations, hair was assayed for a subset of youth who were largely identified by an algorithm grounded in prior literature to place importance on youth at most risk for substance use based on empirically validated risk factors (Wade et al., 2022). Examples of risk factors include lifetime substance use, intention to use cannabis soon, curiosity about using cannabis, any biological relative with history of drug use disorder. For a full list of factors, see Supplemental Section 2. There were two selection groups: (1) high-risk participants (the vast majority of those selected) and (2) randomly selected low-risk youth. The random selection method was conducted in youth who reported no substance use and obtained low scores on the risk algorithm (Wade et al., 2023).

Chosen samples were sent to Psychemedics (Culver City, CA) and were trimmed to a length of 3.9 cm (Wade et al., 2023), where they underwent a standardized assay protocol. All samples were washed to mitigate the risk of false positives due to environmental substance exposure (see Wade et al., 2023 or Section 1 in the Supplementary Material for description of hair washing protocol). Hair was then enzymatically broken down and screened for drug classes using FDA-cleared immunoassays (for THCCOOH, LOD = 5 pg/10 mg) or directly tested by mass spectrometry (THC and CBD), which detects different cannabinoid concentrations through measurement of each constituent's peak area at its specific retention time and after comparison to known concentrations of reference standards. Presumed positive THCCOOH results and parent cannabinoids were validated and quantified through LC-MS/MS or GC–MS/MS analysis (THCCOOH, LOD/LOQ = 0.02 pg/mg; THC and CBD = 5 pg/mg). Concentrations of THC, CBD, and THCCOOH were provided.

2.2.4. Covariates

We included three covariates in our models: age, household income, and pubertal development. Age was covaried since hair toxicology data was obtained from youth ages 9–15 years-old. Household income was covaried, as socioeconomic status is related to all domains of interest. Lastly, pubertal development was covaried because this age range also encompasses the onset of puberty for most youth. Pubertal development was assessed using the Pubertal Development Scale (PDS; Petersen et al., 1988), completed by youth, a measure summarizing the stage of pubertal development (i.e., pre-puberty, early puberty, mid-puberty, late-puberty, post-puberty) the youth was currently in with regard to the participant's sex at birth.

2.3. Data analytic plan

Data were analyzed using R version 4.2.1 (R Core Team, 2023). All analyses were prospective and linear models were fitted using the *survey* package (Lumley and Gao, 2024). To account for the clustering of observations within individuals, families, and sites over time, we clustered standard errors on family ID, site ID, and participant ID. Models were run with parent analytes (THC, CBD) and, separately, THCCOOH.

For our primary analyses, we fit prospective models with cannabis constituents in hair toxicology predicting mental and physical health outcomes measured one-year after the hair toxicology collection. As such, our regression models included two time points for each youth: the hair toxicology predictor at the first time point, and the health outcome at the second time point. Only 318 youth had repeated measures of hair toxicology, thus, given the low power, we did not conduct any repeated measures analyses. Each outcome was examined as a separate model (five models total). Cannabinoid constituents were examined using a two-part representation method (Hedeker et al., 2009, 2012) that entails (1) a dummy variable capturing the presence/absence of the cannabinoid, specifically THC and CBD (1 > 0 pg/mg; 0 = 0 pg/mg), then (2) a continuous variable capturing the concentrations of the cannabinoid when present. This representation was chosen to test whether presence alone (i.e., binary) was predictive of the outcome and test the cumulative effects of each parent analyte among those with concentrations of the cannabis constituent (i.e., continuous). For instance, it may be that individuals with any THC use (as a binary predictor) demonstrate one pattern of results, while a different relationship is exhibited through a continuous measure of THC, which more sensitively captures the influence of higher frequency use, use of high potency products, or biological processes leading to prolonged retention of cannabinoids in the body and, subsequently, in hair (Vaiano et al., 2023). Lastly, we created an interaction term that examined non-zero THC concentrations in the

[2] In each ABCD data release, the data is frozen halfway through an annual follow-up. Thus, in the current data release (5.1), data is frozen midway through the collection of the 4-year follow-up assessment. Thus, we only have ~50 % of the sample for that assessment time point. The total Ns for each follow-up and the corresponding N for this study are presented in Table 1.

presence of dummy-coded CBD to examine whether having measurable CBD concentrations influenced the relationship between THC and outcome variables. While we also include THC x CBD concentration interactions, our focus is here on the presence, rather than concentration, of CBD in hair given the work of prior studies (Morgan et al., 2012) and that therapeutic dosing of CBD is generally much higher than what is available in recreational products (Arnold et al., 2022; ElSohly et al., 2016). In secondary analyses, we fitted models from the prior step in sex-specific models (i.e., for males and females only) consistent with the above methods.

We also fitted two types of exploratory models. To assess whether mental and physical health could have preceded cannabis use, we fitted prospective models from the prior step where mental and physical health variables predicted cannabinoid concentrations one year later. We also fitted concurrent models to examine whether associations existed on a more acute timescale rather than one-year apart.

Lastly, we fitted variations on our primary models to test the robustness of our associations and to address outliers, skew, and bias introduced by the moderating effects of covariates (Lubinski and Humphreys, 1990). In the first variation, data were checked for outliers and winsorized. Results did not change with winsorization, except for one result becoming non-significant (see **Section 3.2**). For parsimony we report the results without outlier correction, except for one model revealed by winsorization (see **Section 3.2**). In the second variation, we confirmed skew was not unduly influencing associations by creating an ordinal variable for THC and CBD concentrations. Both the continuous THC and CBD concentration variables were categorized into four ordinal values based on quartiles within the data. These variables were then used as the "concentration" variables in our primary models. When employing the ordinal cannabinoid variables in our models in place of continuous concentration, results offer largely the same picture regarding directionality. However, one association (strength exercise days) flipped its association ($\beta = 4.80$ to $\beta = -3.10$), while some other associations that were non-significant become significant when using the ordinal versions of the THC and CBD concentrations. Given there is reduced variability from the use of ordinal versus continuous models, we suspect the changes are due to the loss of power to detect differences. For interpretability, however, here we report models with continuous concentration as concentration can better represent a mixture of cannabis frequency (Taylor et al., 2017) and, to some extent, potency (Kroon et al., 2024). See **Table S7** for full results using the ordinal versions of THC and CBD concentrations. In the third variation, we addressed biases introduced by excluding predictor*covariate interactions. Here, we included THC concentration*covariate and CBD concentration*covariate interaction terms within our primary models with hair toxicology predicting mental/physical health. Directionality remained largely the same, though only one significant result remained after the inclusion of all interactions: THC concentration x CBD presence interaction in predicting strength exercise days. Given the number of interactions in the model, it may be that models are insufficiently powered to detect differences. See **Table S8** for full results.

3. Results

3.1. Sample descriptives

Nearly half (49 %) of these youth were female. Regarding race/ethnicity, 66 % were White, 7 % were Black, 20 % were non-White Hispanic, and 8 % identified as a different category. The median household income was $87,500. Sample characteristics for this subsample, including demographics and variables of interest, are presented in Table 1. Descriptive characteristics of our subsample and the entire

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)	2500 - 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 %	^	2 %	^	^	
Black	^	5 %	4 %	^	^	
Hispanic	20 %	17 %	21 %	23 %	20 %	
White	66 %	63 %	63 %	62 %	65 %	
Other	^	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/10 mg)	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						
Any Physical Exercise (%)	92 %	–	92 %	93 %	87 %	
Physical Exercise (days)	4.1 (2.3)	–	3.9 (2.1)	3.9 (2.1)	3.4 (2.1)	0.0–7.0
Any Strength Exercise (%)	74 %	–	66 %	76 %	65 %	
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 (% above clinical cutoffs)	24 %	26 %	22 %	19 %	25 %	
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 (% above clinical cutoffs)	21 %	18 %	17 %	12 %	12 %	
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. Per ABCD Study reporting requirements, cells less than 10 people are obscured (represented by ^). 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.

ABCD Study dataset at Baseline, as well as *t*-test comparisons between the two samples, are presented in **Table S1**. The present subsample relative to the rest of the ABCD Study sample were significantly different by age, income, and prevalence of identifying as White, Black, or Asian, and in reported internalizing symptoms, externalizing symptoms, physical exercise, asthma, and sleep durations.

3.2. Prospective associations in overall sample: Cannabinoid concentrations predicting mental and physical health outcomes

Table 2 shows all the estimated associations in prospective analyses where cannabinoid concentrations predicted mental and physical health outcomes and **Table S3** reports all FDR corrected *p*-values for these associations. In terms of physical health outcomes, higher THC concentration significantly predicted more days of physical exercise, however this association became nonsignificant after FDR correction ($\beta = 2.98$, $p = .02$, FDR $p = .06$). THC concentration also significantly predicted more days of strengthening exercise ($\beta = 4.80$, $p \leq 0.001$, FDR $p < .01$). Independently, CBD concentration predicted fewer strengthening exercise days ($\beta = -1.59$, $p = .002$, FDR $p = .01$). Among individuals with CBD present, higher THC concentration significantly predicted fewer days of strengthening exercise ($\beta = -4.16$, $p = .001$, FDR $p = .01$) and this association remained significant with the inclusion of THC concentration*covariate and CBD concentration*covariate interaction terms ($\beta = -5.27$, $p < .001$). Higher THCCOOH concentration predicted lower average nightly sleep duration ($\beta = -0.20$, $p = .02$, FDR $p = .02$), however this association became non-significant once outlier correction was implemented (winsorized $\beta = -0.15$, winsorized $p = .09$).

In terms of mental health outcomes, CBD concentrations significantly predicted lower internalizing symptoms, however this association became nonsignificant after FDR correction ($\beta = -6.89$, $p = .03$, FDR $p = .09$). All other terms (i.e. coefficients, interactions) in models were nonsignificant.

In a final model including a THC x CBD continuous interaction, higher concentration of both THC and CBD was associated with more weekly sleep, whereas higher THC with lower (or no) CBD was associated with less weekly sleep ($\beta = 0.20$, $p = .02$, FDR $p = .47$). Continuous THC x CBD interactions were not significant in any other models.

3.3. Sex-specific prospective associations: Cannabinoid concentrations predicting mental/physical health outcomes

3.3.1. Prospective associations in males

Table 3 shows all estimated associations for male-specific models, **Table S2** shows male-specific means and standard deviations for outcome variables, and **Table S5** reports all FDR corrected *p*-values for these associations. For physical health measures in males, THC presence was negatively associated with physical exercise days in males, however this association became nonsignificant after FDR correction ($\beta = -0.54$, $p = .04$, FDR $p = .10$). THC concentration was positively associated with physical exercise days ($\beta = 5.31$, $p < .001$, FDR $p < .01$) and strength exercise days ($\beta = 5.81$, $p = .001$, FDR $p = .01$). However, when males had CBD present in their hair, THC concentration was negatively associated with physical exercise days ($\beta = -4.87$, $p = .002$, FDR $p = .01$) and with strength exercise days ($\beta = -5.11$, $p = .005$, FDR $p = .02$).

Lastly, for males and after corrections for multiple comparisons, THC presence and THCCOOH concentration were significantly negatively associated with hours of average nightly sleep duration (THC presence: $\beta = -0.44$, $p = .010$, FDR $p = .03$; THCCOOH concentration: $\beta = -0.23$, $p = .03$, FDR $p = .03$). CBD concentration was significantly positively associated with hours of average nightly sleep duration, but this association was no longer significant after FDR correction ($\beta = 1.98$, $p = .03$, FDR $p = .05$). For mental health outcomes in males, there was a significant negative association between CBD concentration and

Table 2
Full sample cannabis constituents in hair predicting mental and physical health outcomes one year later.

	Outcomes					
	Strength Exercise Coef. (SE) Nobs = 1419	Physical Exercise Coef. (SE) Nobs = 1420	Sleep Duration Coef. (SE) Nobs = 1420	Asthma Presence Coef. (SE) Nobs = 1586	Int. Symptoms Coef. (SE) Nobs = 1482	Ext. Symptoms Coef. (SE) Nobs = 1482
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 Concentrations	0.52 (0.31) $p = .10$ Nobs = 1105	0.45 (0.22) $p = .046$ Nobs = 1106	**−0.20 (0.09)** ***p* = .02** **Nobs = 1106**	0.00 (0.01) $p = .67$ Nobs = 1299	−0.37 (1.35) $p = .78$ Nobs = 1213	0.31 (1.24) $p = .80$ Nobs = 1213

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. 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. Age, household income, and pubertal development were included as covariates within the models. *P*-values with ‡ next to them do not remain statistically significant when FDR correction is implemented. Nobs reported in the first row refer to all of the models except when the predictor is THCCOOH. Nobs for the models where THCCOOH is the predictor are reported inside their respective cells.

Table 3
Cannabis constituents in hair predicting mental and physical health outcomes one year later among males.

	Outcomes					
	Physical Exercise Coef. (SE) Nobs = 754	Strength Exercise Coef. (SE) Nobs = 754	Asthma Presence Coef. (SE) Nobs = 847	Sleep Duration Coef. (SE) Nobs = 754	Int. Symptoms Coef. (SE) Nobs = 793	Ext. Symptoms Coef. (SE) Nobs = 793
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* ≤0.001**	**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 Nobs = 590	0.28 (0.27) *p* = .30 Nobs = 590	0.00 (0.01) *p* = .69 Nobs = 702	**−0.23 (0.10)** ***p* = .03** **Nobs = 590**	−0.44 (1.24) *p* = .72 Nobs = 658	0.46 (1.39) *p* = .74 Nobs = 658

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. 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. Age, household income, and pubertal development were included as covariates within the models. P-values with ‡ next to them do not remain statistically significant when FDR correction is implemented. Nobs reported in the first row refer to all of the models except when the predictor is THCCOOH. Nobs for the models where THCCOOH is the predictor are reported inside their respective cells.

Table 4
Cannabis constituents in hair predicting mental and physical health outcomes one year later among females.

	Outcomes					
	Physical Exercise Coef. (SE) Nobs = 666	Strength Exercise Coef. (SE) Nobs = 665	Asthma Presence Coef. (SE) Nobs = 739	Sleep Duration Coef. (SE) Nobs = 666	Int. Symptoms Coef. (SE) Nobs = 689	Ext. Symptoms Coef. (SE) Nobs = 689
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* ≤0.001**	−0.04 (0.05) *p* = .40	**−3.07 (0.91)** ***p* ≤0.001**	−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* ≤0.001**	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 Nobs = 516	**1.79 (0.56)** ***p* = .001** **Nobs = 515**	**−0.04 (0.01)** ***p* = .02‡** **Nobs = 597**	0.30 (0.47) *p* = .53 Nobs = 516	5.21 (2.89) *p* = .07 Nobs = 555	−2.66 (5.04) *p* = .60 Nobs = 555

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. 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. Age, household income, and pubertal development were included as covariates within the models. P-values with ‡ next to them do not remain statistically significant when FDR correction is implemented. Nobs reported in the first row refer to all of the models except when the predictor is THCCOOH. Nobs for the models where THCCOOH is the predictor are reported inside their respective cells.

Table 5
Mental/physical health variables predicting hair toxicology one year later.

	Outcomes				
	THC Presence Coef. (SE)	THC Concentration Coef. (SE)	CBD Presence Coef. (SE)	CBD Concentration Coef. (SE)	THCCOOH Concentration Coef. (SE)
Physical Exercise (days) Nobs = 1033	**−0.01 (0.01)** **p = .02** **FDR p = .04**	−0.00 (0.01) p = .72 FDR p = .89	0.00 (0.01) p = .73 FDR p = .73	0.00 (0.00) p = .12 FDR p = .15	−0.08 (0.08) p = .33 FDR p = .41 Nobs = 961
Strength Exercise (days) Nobs = 1031	0.00 (0.01) p = .69 FDR p = .69	0.01 (0.01) p = .39 FDR p = .49	−0.00 (0.01) p = .82 FDR p = .82	−0.00 (0.00) p = .16 FDR p = .21	−0.03 (0.07) p = .70 FDR p = .70 Nobs = 959
Asthma Presence Nobs = 1790	−0.05 (0.03) p = .10 FDR p = .17	−0.02 (0.01) p = .11 FDR p = 0.14	−0.03 (0.03) p = .24 FDR p = .30	−0.01 (0.01) p = .11 FDR p = .13	**−0.29 (0.13)** **p = .03** **FDR p = .03** **Nobs = 1591**
Sleep Duration Nobs = 624	−0.02 (0.01) p = .20 FDR p = .33	−0.01 (0.01) p = .45 FDR p = .56	−0.00 (0.01) p = .70 FDR p = .70	−0.00 (0.00) p = 1.00 FDR p = 1.00	0.25 (0.23) p = .28 FDR p = .35 Nobs = 644
Int. Symptoms Nobs = 1789	0.00 (0.00) p = .65 FDR p = .65	−0.00 (0.00) p = .44 FDR p = .44	0.00 (0.00) p = .13 FDR p = .17	0.00 (0.00) p = .36 FDR p = .45	0.03 (0.02) p = .07 FDR p = .09 Nobs = 1589
Ext. Symptoms Nobs = 1789	**0.00 (0.00)** **p = .003** **FDR p = .01**	0.00 (0.00) p = .33 FDR p = .33	**0.00 (0.00)** **p ≤0.001** **FDR p = 0.00**	0.00 (0.00) p = .41 FDR p = .51	0.04 (0.02) p = .07 FDR p = .09 Nobs = 1589

Note. Rows contain predictors and columns represent outcomes. Int = Internalizing, Ext = Externalizing. Each outcome was modeled separately and all predictors were included in one model. THC and CBD Concentrations variables were rescaled via dividing raw values by 100 to ensure coefficients were interpretable. Age, household income, and pubertal development were included as covariates within the models. P-values with ‡ next to them do not remain statistically significant when FDR correction is implemented. Nobs reported in the first column refer to all of the models except when the predictor is THCCOOH. Nobs for the models where THCCOOH is the predictor are reported inside their respective cells.

Table 6
Concurrent analyses: hair toxicology variables predicting MH/PH outcomes.

	Outcomes					
	Physical Exercise (days) Coef. (SE) Nobs = 1356	Strength Exercise (days) Coef. (SE) Nobs = 1356	Asthma Presence Coef. (SE) Nobs = 2005	Sleep Duration Coef. (SE) Nobs = 1448	Int. Symptoms Coef. (SE) Nobs = 2005	Ext. Symptoms Coef. (SE) Nobs = 2005
THC Presence	−0.12 (0.17) FDR p = .47 p = .47	0.00 (0.16) FDR p = .98 p = .98	−0.03 (0.01) FDR p = .18 p = .07	**−0.32 (0.13)** **FDR p = .02** **p = .01**	−0.44 (0.78) FDR p = .79 p = .57	1.17 (0.76) FDR p = .29 p = .12
CBD Presence	−0.43 (0.22) FDR p = .09 p = .055	−0.10 (0.25) FDR p = .98 p = .68	0.01 (0.03) FDR p = .98 p = .84	0.06 (0.19) FDR p = .74 p = .74	−0.32 (1.19) FDR p = .79 p = .79	0.42 (1.05) FDR p = .76 p = .69
THC Concentration	**−0.48 (0.17)** **FDR p = .01** **p = .004**	−0.17 (0.36) FDR p = .98 p = .63	0.02 (0.04) FDR p = .90 p = .63	**−0.52 (0.24)** **FDR p = .04** **p = .03**	**−2.39 (1.20)** **FDR p = .11** **p = .046‡**	−0.81 (1.70) FDR p = .76 p = .63
CBD Concentration	0.20 (0.27) FDR p = .47 p = .44	**−0.41 (0.17)** **FDR p = .09** **p = .02‡**	0.00 (0.02) FDR p = .98 p = .98	−0.25 (0.28) FDR p = .41 p = .37	0.54 (1.77) FDR p = .79 p = .76	−0.71 (1.47) FDR p = .76 p = .63
THC Presence x CBD Presence	0.23 (0.31) FDR p = .47 p = .46	0.09 (0.33) FDR p = .98 p = .78	0.00 (0.03) FDR p = .98 p = .88	−0.26 (0.27) FDR p = .41 p = .34	1.79 (1.56) FDR p = .50 p = .25	2.11 (1.45) FDR p = .29 p = .14
THC Concentration x CBD Presence	**0.48 (0.18)** **FDR p = .02** **p = .008**	0.20 (0.36) FDR p = .98 p = .58	−0.02 (0.04) FDR p = .90 p = .54	**1.03 (0.27)** **FDR p = .00** **p ≤0.001**	2.44 (1.22) FDR p = .11 p = .046	0.83 (1.72) FDR p = .76 p = .63
THCCOOH Concentration	**−0.02 (0.01)** **FDR p = .02** **p = .01** **Nobs = 1456**	−0.01 (0.01) FDR p = .14 p = .055 Nobs = 1456	**−0.00 (0.00)** **FDR p = .02** **p = .01** **Nobs = 1815**	0.02 (0.01) FDR p = .06 p = .06 Nobs = 1332	**0.17 (0.02)** **FDR p = .00** **p ≤0.001** **Nobs = 1815**	**0.14 (0.06)** **FDR p = .02** **p = .02** **Nobs = 1815**

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. 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. Age, household income, and pubertal development were included as covariates within the models. P-values with ‡ next to them do not remain statistically significant when FDR correction is implemented. Nobs reported in the first row refer to all of the models except when the predictor is THCCOOH. Nobs for the models where THCCOOH is the predictor are reported inside their respective cells.

externalizing CBCL scores, which became nonsignificant after FDR correction (β = −9.59, p = .03, FDR p = .11). All other terms (i.e. coefficients, interactions) in models were nonsignificant for males.

3.3.2. Prospective associations in females

Table 4 shows all estimated associations for female-specific models, **Table S2** shows female-specific means and standard deviations for outcome variables, and **Table S4** reports all FDR corrected p-values for these associations. For females, THC presence was negatively associated with strength exercise days (β = −0.70, p = .002, FDR p = .01). THCCOOH concentration was positively associated with strength exercise days (β = 1.79, p = .001, FDR p = .01), as was THC concentration (β = 4.21, p < .001, FDR p = .00). However, in the presence of CBD, THC concentration became negatively associated with strength exercise days for females (β = −4.73, p < .001, FDR p = .00).

In females, THC concentration was significantly negatively associated with hours of average nightly sleep duration (β = −3.07, p < .001, FDR p = .00) and in the presence of CBD, THC concentration was significantly positively associated with average nightly sleep duration (β = 3.74, p = .02, FDR p = .04).

Finally, for asthma presence, THCCOOH concentration was significantly negatively associated with asthma presence in females, however this association became nonsignificant after FDR correction (β = −0.04, p = .02, FDR p = .05). All other terms (i.e., main effects, interactions) in models were nonsignificant.

3.4. Exploratory analyses

3.4.1. Prospective associations in overall sample: Mental/physical health predicting cannabinoid concentrations

Table 5 shows all the estimated associations in prospective analyses where mental and physical health variables predicted cannabinoid presence and concentrations one year later, including all FDR corrected p-values for these associations. Physical exercise days significantly negatively predicted THC presence (β = −0.01, p = .02, FDR p = .04). Externalizing symptoms significantly positively predicted THC presence (β = 0.00, p = .003, FDR p = .01), as well as CBD presence (β = 0.00, p < .001, FDR p = .00). Asthma presence significantly negatively predicted THCCOOH concentration (β = −0.29, p < .03, FDR p = .03). All other terms (i.e. coefficients, interactions) in models were nonsignificant.

3.4.2. Concurrent associations between mental/physical health and cannabinoid concentrations in overall sample

Table 6 shows all the estimated associations in concurrent analyses where cannabinoid concentrations predicted mental and physical health outcomes at the same wave of data collection, including all FDR corrected p-values for these associations. THC concentration significantly negatively predicted days of physical exercise (β = −0.48, p = .004, FDR p = .01), and sleep duration (β = −0.52, p = .03, FDR p = .04). CBD concentration significantly negatively predicted days of strength exercise (β = −0.41, p = .02, FDR p = .08), but this association did not survive FDR correction. In the presence of CBD, THC concentration was significantly positively associated with days of physical exercise (β = 0.48, p = .008, FDR p = .02) and sleep duration (β = 1.03, p < .001, FDR p < .001). THCCOOH concentration was significantly negatively associated with physical exercise days (β = −0.02, p = .01, FDR p = .02) and asthma presence (β = −0.00, p = .01, FDR p = .02), and positively associated with internalizing symptoms (β = 0.17, p < .001, FDR p < .001) and externalizing symptoms (β = 0.14, p = .02, FDR p = .02).

4. Discussion

In a nationwide sample of youth in early adolescence, we examined the prospective associations between cannabinoid concentrations measured via hair toxicology and mental and physical health outcomes one year later. THC concentration positively predicted the number of strengthening exercise days and, prior to multiple comparisons corrections and inclusion of THC*covariate interactions, physical exercise days. However, in the presence of CBD, THC concentration was negatively associated with exercise. CBD concentration alone was associated with fewer exercise days. Further, greater CBD concentration was related to lower internalizing symptoms at the next annual visit, though this was no longer significant after FDR correction. There was also a main, negative effect of THCCOOH concentration and nightly sleep duration. When we conducted sex-stratified analyses to investigate the potential sex-specific effects for males and females, they exhibited the same pattern of results regarding strength exercise. However, for other health outcomes, we observed sex-specific associations between cannabinoid concentrations and mental and physical health. In females, cannabinoid analytes prospectively predicted relationships with sleep duration, and asthma, while in males, analytes uniquely predicted number of physical exercise days and sleep duration, and prior to FDR correction predicted externalizing symptoms. Most relationships we found were modest in effect size and 5 out of 18 relationships were no longer statistically significant after implementing FDR correction, warranting replication and further investigation in future studies where trajectories of symptoms and cannabis use can be modeled over longer periods of time.

We further conducted two exploratory analyses to further characterize the relationships between cannabinoid concentrations and mental/physical health outcomes. A prospective analysis investigating how mental and physical health predicted cannabinoid concentrations measured one year later yielded modest results, revealing only that asthma presence negatively predicted THCCOOH concentration. Concurrent analyses revealed that THC concentration was negatively associated with exercise days and sleep duration, though in the presence of CBD, THC concentration was positively associated with exercise days and sleep duration. As in our primary prospective associations, CBD concentration was related to lower exercise days, however this relationship was no longer significant with FDR correction. THCCOOH concentration was related to fewer exercise days and less asthma presence, as well as greater internalizing and externalizing symptoms.

4.1. Full sample associations between Cannabis use and outcomes one year later and their implications

Overall, we found several notable relationships between cannabinoid concentrations predicted mental health and physical health outcomes one year later. Thus, our results broadly provide evidence for the susceptibility hypothesis, which proposes that substance use contributes to health issues, and extends it to this younger age group.

In terms of our models where cannabinoid concentrations predicted mental health outcomes, higher CBD concentrations predicted fewer internalizing symptoms prior to correcting for multiple comparisons. This was consistent with prior literature that suggested CBD concentrations may modulate the depression and anxiety symptoms that are potentially associated with cannabis use (Morgan et al., 2012; Niesink and van Laar, 2013; Solowij et al., 2018; Xue et al., 2021). CBD also was proposed to have beneficial, therapeutic effects in depression (García-Gutiérrez et al., 2020). We did not find a relationship between THC concentrations and internalizing symptoms one year later, which could suggest the influence of THC operates more acutely.

The relationships between cannabinoid concentrations and physical health outcomes were mixed by analyte and measurement method (i.e., binary presence variables or specific cannabinoid concentrations). Presence alone, a binary indicator not considering concentration, of THC or CBD was not significantly associated with health outcomes. More frequent use or use of higher potency products or individual factors, captured in continuous THC concentrations (Vaiano et al., 2023) may more sensitively relate cannabinoid constituents in hair with health outcomes. Among continuous cannabinoid measures, THC concentrations were positively associated with the number of days of both

physical exercise and strengthening exercise, though results did not withstand FDR corrections or inclusion of THC*covariate interactions indicating that this association may be better explained by the interaction between THC concentrations and covariates (e.g., youth age, pubertal development). Still, it is interesting to note that prior research in adults revealed those who used cannabis were more likely to adhere to the World Health Organization's physical activity guidelines (Vidot et al., 2017). Additionally, cannabis consumption is related to more physical activity when looking at frequent cannabis users (Ong et al., 2021), and, consistent with our study, when measured in days of physical and strengthening activities (French et al., 2021). Though there are potential physical (e.g., respiratory), mental health, and cognitive concerns related to cannabis use in athletes (Huestis et al., 2011), exogenous cannabinoids may replicate the positive effects of endocannabinoids released during acute exercise (Gibson et al., 2024; YorkWilliams et al., 2019). Indeed, studies showed that moderate to frequent cannabis use correlates with enhanced positive moods during exercise (Gibson et al., 2024), heightened self-reported recovery (YorkWilliams et al., 2019), and greater motivation to engage in activity (YorkWilliams et al., 2019). Interestingly, CBD concentrations were negatively associated with strength exercise days. One potential reason for this negative association could be related to exercise-induced muscle damage, as adult elite athletes use CBD in response to injury (Burr et al., 2021), especially following strength training (Cochrane-Snyman et al., 2021; Isenmann et al., 2021). Higher CBD concentrations could, therefore, indicate youth were unable to engage in exercise due to injury and were using CBD in response to injury, though this was not assessed here. Our study served as a novel documentation of the association between cannabis use and exercise in youth. Given the prospective design of our analyses, it was not possible to determine the exact role of THC and/or CBD in later physical activity, warranting future investigation into the underlying mechanisms of this relationship in young adolescents.

Regarding sleep, THCCOOH negatively predicted sleep duration one year later. Cannabis use was linked to disturbed sleep quality (Burr et al., 2021), and limited evidence supports cannabis' efficacy as a potential sleep remedy (Velzeboer et al., 2022). Our findings provided further evidence that cannabis use, and here specifically THCCOOH concentrations, may put individuals at increased risk for decreased duration of sleep.

It is interesting to note that THC and THCCOOH hair concentrations do not always show the same pattern of statistical significance in results. Cannabinoids are incorporated into the hair shaft from the surrounding blood capillaries and from sebum and sweat surrounding the hair shaft (Pragst and Balikova, 2006; Wennig, 2000). Incorporation of THC into hair is higher than that of THCCOOH for physicochemical reasons and because THC in the environment can also be incorporated into hair, while THCCOOH reflects actual cannabis intake (Vaiano et al., 2023). The concentrations of THCCOOH in hair reflect the magnitude of cannabis intake and therefore, better reflect the associations observed in this research. Importantly, among our full sample (Table 2), while patterns of statistical significance for THC and THCCOOH vary, the directionality of associations remained the same, but the magnitude of coefficients were smaller with the THCCOOH concentrations. THCCOOH concentration here is thus likely reflecting more substantial cannabis use, reflected in several more findings for THCCOOH than THC.

4.2. Sex-specific associations between hair toxicology and mental/physical health

Sex-specific models identified differences in directionality by cannabinoid concentrations across several measures. Sex-specific models were fitted to observe differences in health outcomes given the unique trajectories of the ECS and cannabis-behavior associations by sex (Crane et al., 2013; McPherson et al., 2021), with cannabis constituents assessed through hair cannabinoid concentrations.

We limited our discussion of sex-specific associations to the relationships between the continuous measures of cannabinoid concentrations with mental and physical health outcomes, as binary cannabinoid presence was not independently related to outcomes in these models with two exceptions. For males, THC presence was negatively associated with physical exercise, while THC concentrations demonstrated a positive relationship. For females, the same pattern was observed but for strengthening exercise. These results are not wholly unexpected as the two-part regression model provides differential insight that wouldn't be obtained by treating THC or CBD as unidimensional (i.e., only binary) (Dziak and Henry, 2017). Prior studies using this modeling representation found coefficients with opposite signs for smoking status and frequency of smoking on affect, suggesting negative outcomes were most prevalent in those with higher frequency of use (Hedeker et al., 2009, 2012). Given the majority of null findings regarding THC and CBD presence, our results suggest higher THC concentrations—a measure which combines frequency of use or potency of products used, along with individual factors (Vaiano et al., 2023)—may more sensitively identify relationships with health outcomes.

In males, CBD concentrations were negatively associated with externalizing CBCL scores, though this relationship was no longer significant after FDR correction. Cannabis usage, in general, was linked to increased externalizing symptoms (Fergusson et al., 2002; Griffith-Lendering et al., 2011; Monshouwer et al., 2006). However, our findings aligned with emerging research suggesting that CBD may have effects to the contrary. CBD was proposed as a potential treatment for two facets of externalizing symptomatology: substance use disorder (Chye et al., 2019; Navarrete et al., 2021), which includes cannabis use, and behavior in autism spectrum disorder (Ma et al., 2022; Nezgovorova et al., 2021; Poleg et al., 2019). Given the limited prior work in this area, and that the relationship did not survive FDR correction, the role of CBD in specifically modulating externalizing symptoms requires further exploration.

Both male and female young adolescents demonstrated similar patterns between cannabinoids and sleep duration. Overall, THC and THCCOOH were negatively related to sleep duration. Yet CBD, by independent concentrations in males or the presence of CBD in conjunction with THC in females, positively predicted nightly sleep duration. This could suggest a distinct mechanism through which CBD may affect the relationship between THC and sleep duration, possibly mitigating the negative effects of THC in isolation. Notably, the relationship between CBD concentrations and sleep duration in males did not remain significant following FDR correction. However, as there are increasing reports of CBD as a sleep remedy (Moltke and Hindocha, 2021), future work should continue to investigate the content of cannabis in relation to its therapeutic or risk profile.

In terms of physical activity and asthma, males and females displayed similar associations between THC concentrations and strength exercise, but different associations between cannabinoid constituents and physical exercise or asthma. THC concentrations were positively associated with strengthening exercises for both males and females, however, when looking at individuals who also had CBD present, THC concentrations became negatively associated with strengthening exercise for both sexes. Exercise is known to upregulate endocannabinoid activity (Brellenthin and Koltyn, 2016), and thus exogenous cannabinoids may interact and influence the relationship between exercise and the endocannabinoid system (ECS). In terms of physical exercise, males' physical exercise was related to cannabinoid concentrations while female's physical exercise was not. Conversely, THCCOOH concentrations had a stronger association with asthma for females, while asthma presence in males was not related to any cannabinoid concentrations. Given the unique trajectories of the ECS by sex, it will be important to continue to monitor these youth longitudinally with repeated assessments of hair toxicology to assess changes in cannabinoid concentrations and the corresponding impacts on physical health outcomes.

4.3. Exploratory analyses: Testing reverse direction and concurrent associations

In contrast to our primary results where cannabinoid concentrations predicted mental and physical health, we found only one significant relationship when mental/physical health variables predicted cannabinoid concentrations one year later (see Table 5): asthma presence predicted lower THCCOOH concentration, which is plausible considering individuals with asthma might not desire to further compromise their lung health by ingesting cannabis. Importantly, coefficients were close to 0.00, indicating that the one significant association is extremely modest in effect size. The current evidence suggests cannabis constituents in hair are not associated with preceding health issues in this sample.

We identified several concurrent relationships between cannabinoid concentrations and mental/physical health outcomes. This may reflect a more acute influence of cannabis use, supporting the need to consider more proximal outcomes, in conjunction with prospective and longitudinal influences of cannabis use. In our prospective analyses, our predictors and outcomes were spaced one year apart. Future work should look into measuring and analyzing cannabinoid concentrations and mental/physical health factors along a shorter timescale as effects may be present more acutely.

4.4. Strengths and limitations

Our study had many strengths. First, to address some of the limitations of self-report for studying the effects of cannabinoids, we used hair toxicology to objectively measure cannabis constituent concentrations (Johnson, 2014; Wade et al., 2023; Williams and Nowatzki, 2005). Hair toxicology data enabled us to examine specific major cannabinoid concentrations (i.e., CBD, THC, and THCCOOH) in both binary (present/not present) and dose-dependent (continuous) manners. Second, we examined prospective associations between cannabinoids in hair with health outcomes one year later. Third, we were one of the few studies examining sex-specific associations between hair cannabinoid concentrations and mental/physical health one year later. Lastly, we examined all associations among youth during late childhood into early adolescence, a developmental range not usually examined when studying the associations between hair cannabinoid concentrations, cannabis use, and mental/physical health.

Our study also had limitations. First, hair toxicology detects moderate to frequent regular use (Huestis et al., 2007; Taylor et al., 2017), not low infrequent cannabis use which most youth in this age group engage in (Hawes et al., 2019; Sullivan et al., 2022). Combining self-report data with hair toxicology data might mitigate this limitation, however ABCD's self-reported cannabis rates are minimal, usually only indicate one use episode by youth, and do not provide information about cannabinoid concentrations. Thus, our results pertained to the heaviest users, who are at greatest risk for negative outcomes. Relationships in occasional or less frequent users may be different from moderate to heavy users. Second, hair toxicology as a measure is reflective of a mixture of frequency of use, product potency, method of consumption, and individual factors (Vaiano et al., 2023); it was not possible to determine whether the mental and physical health outcomes are related to how often adolescents consume cannabis or how much they are consuming at once. Third, there may be confounders of the prospective associations between cannabinoids and physical and mental health, which limited our ability to make causal statements. Other factors may influence cannabinoid concentration in hair and these relationships (e.g., family history and genetics), and should be assessed in relation to hair cannabinoid concentration and included in future models of these cannabis and health outcome relationships. Future analysis of repeated hair samples in the ABCD Study™ will also allow us to examine change over time with corresponding mental and physical health outcomes to delineate the directionality of associations and whether associations hold across development. Fourth, given limited funding, our sample is a subsample of the ABCD cohort and may not be fully representative of the ABCD cohort, as evidenced by sociodemographic characteristics of those with hair testing versus without from the present analyses. Indeed, the vast majority of hair samples selected for testing were from participants with higher potential risk for substance initiation, including exhibiting characteristics such as externalizing symptoms (Wade et al., 2022). Future ABCD data releases will include hair testing results from a much larger proportion of participants, and these findings should be replicated at that time. While the present subsample may impact generalizability of results given differences in race and ethnicity prevalence in those with assayed hair, we note that prior research indicates there is no difference in hair cannabinoid detection rates by race (Huestis et al., 2007). Fifth, we could not replicate our analyses with other biomarkers collected in ABCD, given differences in collection and measurement between hair cannabinoid concentrations and urine or oral fluid samples. More broad based toxicological testing of urine and oral fluid occurs in later years of the ABCD study. Once those data become available, the current analyses should be replicated to assess these mental and physical health relationships with cannabis use through these biosamples which test for more acute cannabis use. Sixth, as is common in substance use studies, models were skewed due to zero-inflation, which may impact confidence in results. At the same time, models were examined with several alternate methods, and findings were often (though not always) consistent. Seventh, youth reports of internalizing and externalizing symptoms were not included in the current analyses due to youth reports being collected only in select years. Notably, prior literature indicates parental reports of internalizing symptoms are highly predictive of later internalizing diagnoses (Cohen et al., 2019), while other research indicates high concordance in reporting between youth and parent (Rognstad et al., 2022; Stanger and Lewis, 1993). Future research, however, should replicate our findings using youth self-report of internalizing and externalizing symptoms.

5. Conclusion

In a nationwide sample of youth ages 9–15 years old, we found differences in health outcomes varied as a function of dose-dependent cannabinoid concentrations in hair measured one year prior and concurrently. In contrast, we did not find meaningful associations in the reverse direction. This suggested potential differential mechanisms by which THC and CBD influence the ECS and downstream health outcomes. Furthermore, the unique prospective associations of cannabis constituents based on sex underscored the importance of looking at these mechanisms within the context of sex assigned at birth. Given the complexity of characterizing the effects of cannabis use on mental/physical health, leveraging cannabinoid analyte concentrations in hair can highlight important prospective relationships with mental health, physical activity, and sleep measures.

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Data statement

The data used in preparing this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study™ (https://abcdstudy.org), held in the NIMH Data Archive (NDA). The ABCD data used in this article came from the ABCD 5.1 data release (DOI: 10.15154/

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CRediT authorship contribution statement

Isabel R. Aks: Writing – review & editing, Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Herry Patel:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **William E. Pelham:** Writing – review & editing. **Marilyn A. Huestis:** Writing – review & editing. **Natasha E. Wade:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ntt.2025.107433.

Data availability

We used data from the Adolescent Brain Cognitive Development Study, a publicly available dataset.

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