

Developmental Timing of the Reciprocal Associations Between Cannabis Use and Internalizing and Externalizing Symptoms in Early Adolescence

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Abstract

Background. This paper examines the reciprocal associations between specific internalizing and externalizing disorder symptoms and cannabis use during early adolescence with age and sex differences.

Methods. We analyzed youth-reported cannabis use, depressive, anxiety, Attention Deficit/Hyperactivity Disorder (ADHD), Conduct Disorder (CD), and Oppositional Defiant Disorder (ODD) symptoms in 9- to 15-year-old adolescents enrolled in the longitudinal Adolescent Brain and Cognitive Development (ABCD) Study (N=11,868). Multilevel regression models, parsing between- and within-youth effects were fit to examine the association between cannabis use and seven different mental health disorders, both concurrently and prospectively. Age and sex moderations were tested.

Results. Robust reciprocal associations emerged for depression and CD with cannabis use concurrently and prospectively. Youth experiencing more internalizing and externalizing symptoms as they grew older reported more cannabis use concurrently. Female youth experiencing greater internalizing and externalizing symptoms reported greater increases in cannabis use concurrently and prospectively.

Conclusion. In a nationwide sample of adolescents ages 9 to 15 years-old, we found depression and CD symptoms to be most strongly and reciprocally associated with cannabis use concurrently and prospectively. Age moderated the relationship concurrently but not prospectively. Females are generally more vulnerable to increasing cannabis use when experiencing heightened mental health problems. These results suggest associations between cannabis use and internalizing and externalizing disorder symptoms unfold close together in time as youth grow older and are more pronounced in female youth.

Keyword(s): internalizing, externalizing, cannabis use, reciprocal, adolescence

1. Introduction

Cannabis use has long been associated with internalizing and externalizing symptoms, with associations differing by specific internalizing and externalizing disorders. For example, cannabis use has been found to predict anxiety (Duperrouzel et al., 2018; Xue et al., 2021) and vice versa (Beletsky et al., 2024), and a similar reciprocal relationship has been observed for depression (Dierker et al., 2018; Lev-Ran et al., 2014; Pacheco-Colón et al., 2019; Sorkhou et al., 2024). In contrast, Attention Deficit Hyperactivity Disorder (ADHD; Sibley et al., 2014), Conduct Disorder (CD; Fergusson et al., 1993), and Oppositional Defiant Disorder (ODD; Zohsel et al., 2016) tend to predict cannabis use, but less so vice versa. Evidence suggests a reciprocal relationship, where internalizing and externalizing symptoms predict future cannabis use (De Geronimo et al., 2024; Wasserman et al., 2021), and cannabis use precedes internalizing and externalizing symptoms (Girgis et al., 2020). However, little research has examined this reciprocal relationship within the context of development, whereby the relative magnitude of associations and directionality of the relationship may change according to age and sex in early adolescence.

Adolescent development is critical for the onset of cannabis use and internalizing and externalizing symptoms, with onset trajectories differing by age and sex. All adolescents undergo significant neurodevelopmental changes, including synaptic pruning and white matter development. The introduction of outside influences, such as cannabis use, may exert more impact on neurodevelopment, and consequently mental health symptoms, during early adolescence than at other time periods (Lubman et al., 2015). In terms of sex, while comorbid mental illness and cannabis use disorder (CUD) is high in both groups (Khan et al., 2013), males are more likely to have comorbid CUD and schizophrenia, psychotic, or mood disorders, while females are more likely to have comorbid CUD and anxiety or antisocial personality disorders (Kozak et al., 2021). Limited studies have looked at cannabis use and externalizing disorders in adolescent females. Prior studies have found childhood depression and conduct problems predict the onset of cannabis use during early and mid-adolescence among only males (Cerdá et al., 2012), and increases in recent cannabis use and prior years of weekly cannabis use are associated with increases in depression and anxiety among teenage males (Meier et al., 2020). Examining the impact of age and sex differences may offer a more nuanced understanding of the timing, magnitude, and direction of the associations for this reciprocal relationship during development.

Additionally, our understanding of this reciprocal relationship is further complicated by the fact that individuals engaging in cannabis use and/or who have internalizing/externalizing symptoms differ along many other factors (e.g., socioeconomic status, genetics, etc.). Much of the existing literature uses typical standard regression models (De Geronimo et al., 2024; Fergusson et al., 1993; Zohsel et al., 2016), which do not adjust for between-person differences biasing the association. Thus, use of models capable of parsing out the variance from between- and within-person factors (e.g., multilevel modeling) may clarify the association between cannabis use and mental health.

The present study builds on prior literature by examining reciprocal associations between cannabis use and depression, anxiety, CD, ODD, and ADHD symptoms in the context of adolescent development when cannabis use and mental health symptoms are changing rapidly. We leverage longitudinal data from a large, nationwide, young, and initially substance-naive sample of 11,868 adolescents (ages 9 to 15 years-old) enrolled in the Adolescent Brain and Cognitive Development (ABCD) Study. We use multilevel modeling to examine both between-person and within-person associations between cannabis use and depression, anxiety, CD, ODD, and ADHD symptoms. We hypothesize that all mental health symptoms, both internalizing and externalizing, will predict cannabis use according to the self-medication hypothesis (Khantzian, 1997). We also expect reciprocal associations, whereby cannabis use may exacerbate pre-existing mental health symptoms. Lastly, given prior literature (Chaplin & Aldao, 2013; Eaton et al., 2012), we expect stronger reciprocal associations between cannabis use and internalizing symptoms in females, while the association will be stronger with externalizing symptoms in males.

2. Methods

2.1 Participants

Data were acquired from the Adolescent Brain and Cognitive Development (ABCD) Study, a longitudinal study collecting data annually from 21 sites across the United States (Garavan et al., 2018). Participants aged 9 to 10 years-old were recruited from schools between 2016 and 2018, with minimal exclusion criteria, resulting in a baseline sample of 11,880 youth. This study utilizes data from the ABCD 5.1 release (DOI: 10.15154/z563-zd24; Haist &

Jernigan, 2023), which includes data from the baseline visit through the 4-year follow-up. For detailed sample characteristics, see **Table 1**.

2.2 Measures

2.2.1 Mental Health

At each annual visit, from baseline through the 4-year follow-up, parents of youth participants were asked to complete the Child Behavior Checklist (CBCL; Achenbach et al., 2001), a widely used and validated form of assessing psychopathology. The CBCL was administered annually from baseline. Standardized scales were extracted of symptoms for DSM-5 disorders, except for depression and anxiety, which collapsed across multiple disorders (i.e., Dysthymic Disorder and Major Depressive Disorder for depression scores and Generalized Anxiety Disorder (GAD), Separation Anxiety Disorder (SAD), and Specific Phobia for anxiety scores). For all CBCL measures, we utilized age and gender-normed *t-scores* in our analysis.

2.2.2 Cannabis Use

Cannabis use (CU) was assessed annually from baseline. Youth reported on lifetime cannabis use at baseline and were then assessed for past-year cannabis use at each annual follow-up visit. At each visit, youth reported their cannabis use, including form (e.g., flower, edibles, concentrates) and method of administration (e.g., smoking, eating, vaping) to a trained research assistant. We coded cannabis use reported by youth to a binary categorization to indicate any cannabis use (0 = no use in past year, 1 = any use in past year). For a comprehensive description of the ABCD substance use assessment measurements, see Lisdahl et al. (2018).

2.3 Analytic Plan

Data were analyzed in R v4.4 (R Core Team, 2023) by fitting a series of two-level multilevel regression models using the lmerTest package (Kuznetsova et al., 2013). A separate model was fit to examine each association between cannabis use and a specific mental health measure (e.g., depression, anxiety, ADHD, ODD, and CD) concurrently and prospectively (one year apart) to estimate the timescale of any observed relationship. Cannabis use and mental health measures were measured simultaneously at four successive timepoints, 12 months apart.

Our predictor variables were lagged in our dataset to examine prospective associations between cannabis use now and mental health one year later for our prospective models.

2.3.1 Separating Between- and Within-Youth Associations

All models separated between- and within- youth variability in cannabis use to obtain more rigorous tests of a potential causal relationship. Methodologists have recommended this technique as a strategy to reduce confounding bias (Hamaker & Muthén, 2020), and it has been used successfully in prior ABCD data analyses (Aks et al., 2024; Pelham et al., 2022). Each regression follows this general structure for concurrent analyses and for prospective analyses, variables on the right hand side are lagged by one year and represented by $it-1$:

$$cu_{it} = \beta_{0i} + \beta_{between} \times (mh\ outcome_j) + \beta_{within} \times (mh\ outcome_{it} - mh\ outcome_j) + \epsilon_{it}$$

The coefficient $\beta_{between}$ represents whether the average level of cannabis use for a given youth predicts mental health outcomes for that individual. $mh\ outcome$ represents a given mental health outcome tested separately in each model (e.g., depression, anxiety, ADHD, CD, and ODD). If there are systematic differences between youth with low vs. high cannabis use on factors that also affect mental health symptoms (e.g., socioeconomic status, parent substance use), these differences will be represented in a nonzero $\beta_{between}$ coefficient. On the other hand, β_{within} represents the association between within-youth differences in cannabis use and within-youth differences in mental health outcomes over time. A within-person association can not be explained by pre-existing differences between youth with low vs. high cannabis use (which are captured in $\beta_{between}$), and are thus less vulnerable to confounding bias.

2.3.2 Tests of Moderation by Age or Sex

We then tested whether the association between cannabis use and various mental health measures varied by youth age or sex at birth, as age (Leadbeater et al., 2019) and sex (Kozak et al., 2021) are strong predictors of cannabis use and mental health problems per prior work. We performed separate tests for age and sex, achieved by adding a main effect for the moderator and interactions with the $\beta_{between}$ and β_{within} terms. We applied a False Discovery Rate correction (Benjamini & Hochberg, 1995) to the p-values for all tests examining whether age or sex

moderated the within-youth relationship between cannabis use and each mental health measure. If the interaction remained statistically significant, simple slopes were calculated to characterize the interaction.

3. Results

All internalizing results will be presented first, followed by externalizing results. Both sections will follow the same order of presentation with concurrent and prospective mental health → CU first, then concurrent and prospective CU → mental health. Between and within-person coefficients have been plotted for internalizing (**Figure 1**) and externalizing (**Figure 2**) results (full results are included in **Supplemental Tables 1 and 2**). **Table 2** presents multilevel model results adjusted for age and sex interactions in internalizing and externalizing results. **Supplemental Figures 1 and 2** plot the simple slopes for all age interactions, regardless of significance, in each direction (e.g., MH*age → CU, CU*age → MH). **Supplemental Figures 3 and 4** plot the simple slopes for all sex interactions, regardless of significance, in each direction (e.g., MH*sex → CU, CU*sex → MH).

3.1 Cannabis Use and Internalizing Symptoms

3.1.1 Internalizing Symptoms → CU

3.1.1.1 Concurrent Results

All concurrent associations between internalizing symptoms and cannabis use were statistically significant at the between- and within-youth levels ($ps < .001$).

Depression*age (between: $\beta = 0.0475, p < .001$; within: $\beta = 0.1459, p < .001$) and anxiety*age (between: $\beta = 0.0168, p = .001$; within: $\beta = 0.0850, p < .001$) significantly predicted greater cannabis use at the between- and within-youth levels.

Depression*sex significantly predicted cannabis use ($\beta = 0.3571, p < .001$) at within-youth level. All other results were non-significant.

3.1.1.2 Prospective Results

All prospective associations between internalizing symptoms and cannabis use were statistically significant at the between-youth level ($ps < .001$). The only association that remained

significant at the within-youth level was depression predicting cannabis use one year later ($\beta = 0.1078, p = .03$).

Depression*age ($\beta = 0.0627, p < .001$) and anxiety*age ($\beta = 0.0187, p = .03$) significantly predicted cannabis use at the between-youth level only.

No internalizing*sex interactions were significant at either the between- or within-youth level ($ps > .05$).

3.1.2 CU → Internalizing Symptoms

3.1.2.1 Concurrent Results

All concurrent associations between cannabis use and internalizing symptoms were statistically significant at the between- ($ps < .005$) and within-youth levels ($ps < .001$).

Cannabis use*age significantly predicted greater depression symptoms ($\beta = 0.0352, p = .02$) at the between-youth level only. All other age interactions were non-significant ($ps > .05$).

Cannabis use*sex significantly predicted greater depression symptoms ($\beta = 0.0325, p < .001$) and anxiety ($\beta = 0.0183, p < .001$) at the within-youth level only.

3.1.2.2 Prospective Results

All prospective associations between cannabis use and internalizing symptoms were statistically significant at the between-youth level ($ps < .01$). However, none of the associations remained significant at the within-youth level though directionality did change, where cannabis use negatively predicted depression ($\beta = -0.0048, p = .20$) and anxiety ($\beta = -0.0049, p = .18$) one year later.

Cannabis use*age significantly predicted greater depression symptoms ($\beta = 0.0653, p = .004$) at the between-youth level. All other age interactions were non-significant.

No cannabis use*sex interactions were significant at either level for internalizing symptoms.

3.2 Cannabis Use and Externalizing Symptoms

3.2.1 Externalizing Symptoms → CU

3.2.1.1 Concurrent Results

All concurrent associations between externalizing symptoms and cannabis use were significant at the between- ($ps < .001$) and within-youth levels ($ps < .01$).

ADHD*age (between: $\beta = 0.0517, p < .001$; within: $\beta = 0.0811, p = .002$), CD*age (between: $\beta = 0.1046, p < .001$; within: $\beta = 0.3124, p < .001$), and ODD*age (between: $\beta = 0.0611, p < .001$; within: $\beta = 0.1026, p < .001$) significantly predicted cannabis use at the between- and within-youth levels.

CD*sex (between: $\beta = -0.0506, p = .02$; within: $\beta = 0.2381, p = .002$) and ODD*sex (between: $\beta = -0.0431, p = .04$; within: $\beta = 0.1646, p = .03$) significantly predicted cannabis use at the between- and within-youth levels, and ADHD*sex ($\beta = 0.3021, p < .001$) was significant within-youth only.

3.2.1.2 Prospective Results

All prospective associations between externalizing symptoms and cannabis use were statistically significant at the between-youth level ($ps < .001$). Only CD ($\beta = 0.1002, p = .04$) and ODD ($\beta = 0.1324, p = .008$) predicting cannabis use remained significant at the within-youth level.

CD*age (between: $\beta = 0.1267, p < .001$; within: $\beta = 0.1200, p = .005$) and ODD*age (between: $\beta = 0.0805, p < .001$; within: $\beta = 0.0929, p = .03$) significantly predicted cannabis use at the between- and within-youth levels, and ADHD*age ($\beta = 0.0683, p < .001$) was significant between-youth only.

All externalizing symptoms*sex interactions were non-significant.

3.2.2 CU → Externalizing Symptoms

3.2.2.1 Concurrent Results

All concurrent associations between cannabis use and externalizing symptoms were statistically significant at the between- ($ps < .001$) and within-youth levels ($ps < .01$).

CD*age ($\beta = 0.0577, p < .001$) and ODD*age ($\beta = 0.0429, p < .001$) significantly predicted cannabis use at the within-youth level. All other age interactions were non-significant.

ADHD*sex ($\beta = 0.0197, p < .001$), CD*sex ($\beta = 0.0157, p < .001$), and ODD*sex ($\beta = 0.0099, p = .01$) significantly predicted greater cannabis use at the within-youth level only.

3.2.2.2 Prospective Results

All prospective associations between cannabis use and externalizing symptoms were statistically significant at the between-youth level ($p_s < .001$). Only cannabis use predicting CD remained significant within-youth. At the within-youth level, cannabis use negatively predicted ADHD ($\beta = -0.0022, p = .45$), CD ($\beta = -0.0084, p = .003$), and ODD ($\beta = -0.0002, p = .95$) one year later.

CD*age (between: $\beta = 0.0596, p < .001$; within: $\beta = -0.0097, p < .001$) significantly predicted cannabis use at the between- and within-youth levels, whereas ADHD ($\beta = 0.0528, p = .003$) and ODD ($\beta = 0.0531, p = .003$) were significant at the between-youth level only.

All cannabis use*sex interactions were non-significant between- and within-youth.

4. Discussion

Prior literature suggests a reciprocal relationship between internalizing and externalizing symptoms and cannabis use. However, less clear is the presentation of this reciprocal relationship for specific disorder symptoms and cannabis use in the context of early adolescence when cannabis use is considered high risk. We examined these reciprocal associations among a large, sociodemographically diverse sample of youth from 9 to 15 years old. We hypothesized that all internalizing and externalizing disorder symptoms would predict cannabis use, and cannabis use would in turn exacerbate pre-existing mental health symptoms. Strongest support for the reciprocal relationship emerged for concurrent and prospective associations between depression and cannabis use and conduct disorder and cannabis use.

Overall, across our models, we found concurrent within-person associations between cannabis use and all internalizing and externalizing disorder symptoms, but not prospective associations. This implies the relationship between cannabis use and mental health may unfold closer in time to one another rather than cannabis use changing the long-term trajectories of mental health during early adolescence. Though, given our measure of cannabis use assessed potentially low levels of use (e.g., any use in the past year), it may be that initial experimentation does not predict mental health changes, or vice versa, and that only with more frequent and extensive use do stronger relationships appear.

Depression was more strongly associated with cannabis use in both directions (CU→MH and MH→CU) than was anxiety. Our results align with the current literature, which consistently identifies a strong link between cannabis use and depression (Dierker et al., 2018; Lev-Ran et al., 2014; Sorkhou et al., 2024; Womack et al., 2016), but more inconclusive associations with anxiety (Gage et al., 2015; Gobbi et al., 2019). Depression being more strongly associated with cannabis use compared to anxiety may indicate differential mechanisms by which cannabis use is related to different internalizing symptoms.

Conduct disorder (CD) was most strongly and reciprocally associated with cannabis use compared to ADHD and ODD. A strong association between CD and cannabis use has been evidenced in the literature (Fergusson et al., 1993; King et al., 2004; Zohsel et al., 2016), while the literature on the relationship between cannabis use and ADHD (Cassidy et al., 2011; Sibley et al., 2014) and ODD (Morse et al., 2016) has yielded more mixed findings. Reciprocity may be due to CD being highly correlated with delinquency in adolescence (Murray & Farrington, 2010), and delinquency frequently co-occurring with youth cannabis use (Chabrol et al., 2010; White et al., 2019). The negative prospective within-youth association when cannabis use predicted CD symptoms suggests changes in low-level cannabis use may not have a reinforcing effect on changes in CD. Future research should assess the robustness of these findings with regular cannabis use.

4.1 Developmental Timing

We found stronger support for mental health (internalizing and externalizing) predicting any cannabis use than vice versa when adjusting for confounding bias. Youth may increase cannabis use as a short-term coping mechanism during periods of heightened mental health problems (Bonn-Miller et al., 2007). These findings corroborate and extend the existing literature of predominantly concurrent associations between internalizing (Kedzior & Laeber, 2014) and externalizing symptoms (Molinero & Hinckley, 2023) and regular cannabis use to experimentation with cannabis use, given the low level of use in our sample.

4.1.1 Internalizing Symptoms. Depression and anxiety significantly predicted cannabis use as youth grew older but not vice versa, suggesting depression/anxiety may reinforce increasing cannabis use as youth age (i.e., adolescents with depression/anxiety may be more

likely to use cannabis) but increased cannabis use over time does not predict greater depression/anxiety symptoms.

4.1.2 Externalizing Symptoms. Before adjusting for between-youth factors, almost all associations between externalizing symptoms and cannabis use were significant concurrently and prospectively, supporting a robust link between externalizing problems and cannabis use among youth (De Geronimo et al., 2024; Fergusson et al., 1993; Girgis et al., 2020; Zohsel et al., 2016).

However, after adjusting for bias from between-youth factors, we observed significant and reciprocal associations between CD and ODD symptoms and cannabis use as youth grew older, but not ADHD. This may be because, within a given youth, ADHD symptoms (e.g., impulsivity, inattention, etc.) may persist throughout adolescence with little variation over time (Hurtig et al., 2007), whereas CD or ODD symptoms (e.g., delinquency, aggression, etc.) may escalate (Maughan et al., 2004) or transition to other disorders over time. ODD typically precedes CD (Burke, 2021; Rowe et al., 2010) and CD precedes Antisocial Personality Disorder (ASPD; Gelhorn et al., 2007). Interestingly, cannabis use*age negatively predicted CD as youth age, suggesting increased cannabis use predicts little to no change in their typical CD symptom levels, indicating their CD symptoms are unaffected or are minimally impacted by changes in youths' cannabis use. Though, at this developmental time period, increases in cannabis use may indicate initiation into use which may not have meaningful impacts on changes in CD symptoms.

4.2 Sex Differences

Consistent with prior literature (Eaton et al., 2012), males experienced more externalizing symptoms than females. However, no evidence emerged that females experienced more internalizing symptoms compared to males.

4.2.1 Internalizing Symptoms. After adjusting for bias from between-youth factors, females experienced higher-than-average levels of depression (but not anxiety) compared to males, and used more cannabis concurrently, suggesting the presentation of internalizing symptoms among female youth may be more nuanced than previously suggested (McGee et al., 1992). Female youth with higher-than-average levels of cannabis use experience higher levels of depression and anxiety concurrently. Sex moderates the reciprocal relationship between cannabis use and depressive symptoms, but shows only unidirectional moderation for anxiety symptoms.

4.2.2 Externalizing Symptoms. When not adjusting for between-youth factors, female youth with CD and ODD symptoms predict cannabis use concurrently. The lack of significant associations for ADHD symptoms may be due to ADHD being a strong predictor of cannabis use regardless of sex (Wilens et al., 2011). Literature has shown that males tend to experience more externalizing disorders compared to females (Eaton et al., 2012). However, our results indicate that females with CD or ODD may be more likely to use cannabis concurrently.

After adjusting for between-youth factors, for female youth, greater changes in externalizing symptoms and cannabis use seem to be strong predictors of each other. While males have greater CB1 density and binding earlier in life, females typically experience an increase in CB1 density across their lifespan (Crane et al., 2013) within the endocannabinoid system. CB1 receptor density and binding increasing across the lifespan for females may explain the significant sex interactions we see in the current study, as modeling within-youth changes is picking up on this sex-differentiated development of the endocannabinoid system.

4.3 Clinical Implications

Our results may have several clinical implications. The robust and reciprocal relationship between depression, CD and cannabis use compared to other internalizing and externalizing disorders emphasizes the need for prevention efforts, early intervention, and integrated treatment. Given the substantial evidence pointing to depression and CD as being most strongly predictive of early cannabis use, clinicians should specifically focus on symptoms of these disorders as potential risk factors for cannabis use in early adolescence. Cannabis use should also be monitored as potentially reinforcing CD symptoms over time. Preventing and intervening on depression and CD might help mitigate future cannabis use, and intervening on cannabis use may prevent exacerbation in CD symptoms. While this is important in both young females and males, female youth may be more vulnerable to using cannabis as a coping response close to experiencing mental health struggles. Clinicians should thus tailor sex-specific strategies to prevent and intervene on young females' depression and CD symptoms and co-occurring cannabis use.

4.4 Strengths and Limitations

Our study had many strengths. This was the first within-youth longitudinal investigation of reciprocal associations between cannabis use and a range of internalizing (i.e., depression and

anxiety) and externalizing (i.e., ADHD, ODD, CD) disorder symptoms in early adolescence to disentangle the most relevant direction of these associations, as prior literature has typically collapsed across all internalizing and all externalizing symptoms. We examined the impact of age and sex differences to offer a more nuanced understanding of the timing and direction of the associations. We extended findings from prior studies focusing on concurrent associations by examining prospective associations between cannabis use and depression, anxiety, CD, ODD, and ADHD. Using multilevel modeling, we examined both between-person associations, not adjusting for confounding bias, and within-person associations, adjusting for confounding bias, to perform a more rigorous test of reciprocal associations.

Our study also had some limitations. First, while our within-youth model accounted for between-youth bias, other time-varying confounders may still create bias in the within-youth results. Second, parents reported on their children's mental health symptoms, so their reports may not reflect the truest presentation of mental health symptoms being experienced by youth. Though, parents are accurate reporters of their child's mental health (Brown-Jacobsen et al., 2011; Serafimova et al., 2021). Third, our measure of cannabis use is dichotomous and may not capture more graduated increases in frequency. Further research is needed to replicate and extend our findings, especially as youth grow older and start using cannabis more regularly. Fourth, youth may have underreported their cannabis use, potentially limiting our ability to fully assess cannabis and mental health relationships (Wade et al., 2023), and thereby underrepresenting the full extent of cannabis-mental health relationships in early adolescence.

5. Conclusion

Prior literature has indicated a reciprocal relationship between cannabis use and aggregated internalizing and externalizing symptoms. However, less is known about the reciprocal associations between cannabis use and symptoms of specific internalizing and externalizing disorders during early adolescence. In a large nationwide sample, we found depression and CD to be most strongly associated with cannabis use concurrently and prospectively. As youth grow older, internalizing and externalizing symptoms predict more cannabis use than vice versa. Female youth seem more vulnerable to cannabis use during times of heightened mental health symptoms. Clinical intervention and prevention strategies should target age- and sex-specific trajectories of depression and CD as they relate to cannabis use.

Further research is necessary to validate and confirm our findings, and extend to greater cannabis use frequency.

Declaration of Interest Statement. All authors have no conflicts of interest to disclose.

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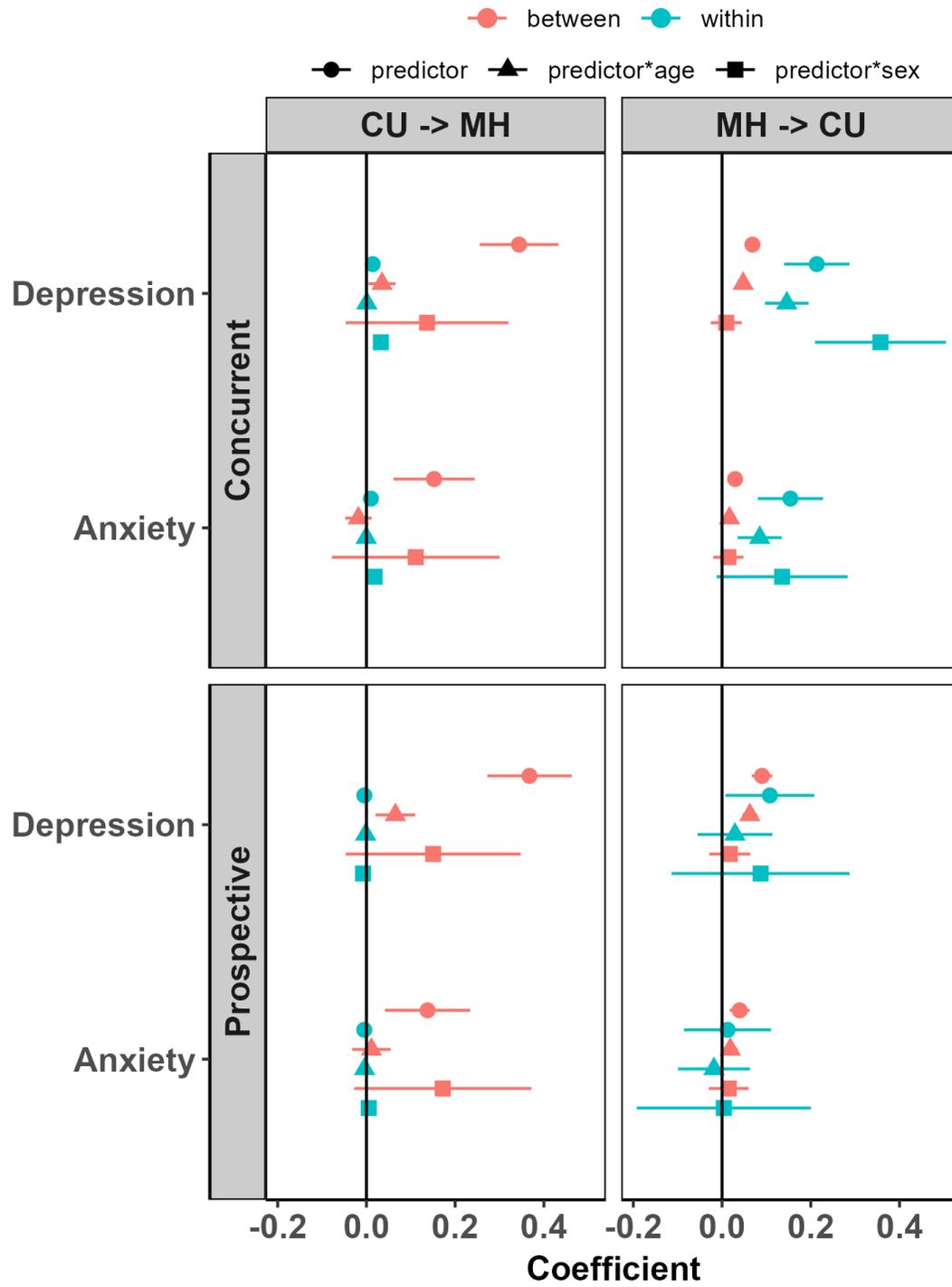
Table 1.
Sample Characteristics at Each Annual Assessment.

	Baseline	1-year follow-up	2-year follow-up	3-year follow-up	4-year follow-up	Range
N	11,868	11,220	10,973	10,336	4,754	-
Age	9.91 (0.62)	10.92 (0.64)	12.03 (0.67)	12.91 (0.65)	14.08 (0.68)	[9-15]
Sex (% Female)	48%					-
Race/Ethnicity						
Black	15%					-
White	52%					-
Hispanic	20%					-
Asian	2%					-
Other	11%					-
CBCL Scores						
Depression	53.60 (5.73)	53.91 (6.08)	53.78 (5.96)	53.98 (6.18)	53.99 (6.39)	[50-100]
Anxiety	53.49 (6.13)	53.54 (6.23)	53.39 (5.92)	53.69 (6.16)	53.48 (5.94)	[50-100]
Attention Deficit Hyperactivity Disorder	53.23 (5.64)	52.99 (5.41)	53.11 (5.34)	53.40 (5.42)	53.07 (5.17)	[50-100]
Conduct Disorder	53.03 (5.53)	52.76 (5.29)	52.39 (4.81)	52.16 (4.41)	51.99 (4.13)	[50-100]
Oppositional Defiant Disorder	53.47 (5.42)	53.26 (5.28)	53.05 (5.04)	52.99 (4.91)	52.60 (4.59)	[50-100]
Cannabis Use Rates	0.08%	0.5%	0.8%	0.9%	3%	-

Note. All variables except for sex and substance use have means and standard deviations presented. Sex and cannabis use rates are percentages.

Figure 1.

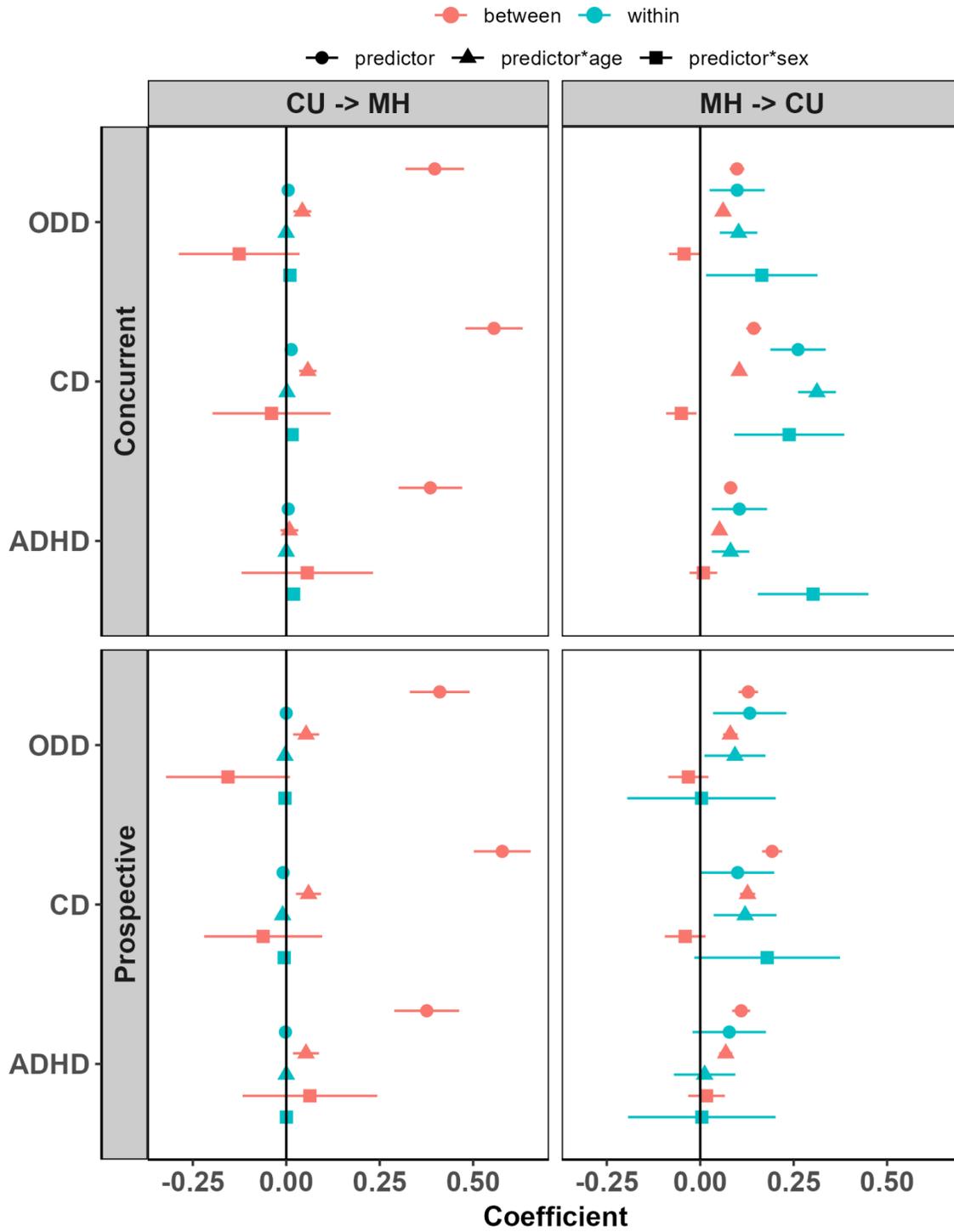
Estimated Reciprocal Associations Between Cannabis Use and Depression and Anxiety Concurrently and Prospectively



Note. Coefficients for between-youth and within-youth estimates from three multilevel models are graphed. For none, coefficient is just the predictor. For age and sex, the coefficient represents the predictor*moderator interaction term. The y-axis is the internalizing disorder, for the CU → MH column it is the outcome, and for the MH → CU column, it is the predictor. The x-axis is the coefficient. For MH→CU analyses, the cannabis score was multiplied by 100 (0 = no use in the past year, 100 = used in the past year) to make coefficients more interpretable. Graph coefficients are reported in Table S1.

Figure 2.

Estimated Reciprocal Associations Between Cannabis Use and ADHD, CD, and ODD Concurrently and Prospectively



Note. Coefficients for between-youth and within-youth estimates from three multilevel models are graphed. For none, coefficient is just the predictor. For age and sex, the coefficient represents the predictor*moderator interaction term. The y-axis is the externalizing disorder, for the CU → MH column it is the outcome, and for the MH → CU column, it is the predictor. For MH→CU analyses, the cannabis score was multiplied by 100 (0 = no use in the past year, 100 = used in the past year) to make coefficients more interpretable. Graph coefficients are reported in Table S2. ADHD = attention deficit hyperactivity disorder, Conduct = conduct disorder, ODD = oppositional defiant disorder.

Table 2.

Multilevel Model Results: Age and Sex Interactions

	Association	Tested Measures	Between-Youth Associations		Within-Youth Associations		N	N _{obs}
			Coef. (SE)	p	Coef. (SE)	p		
Internalizing	Concurrent (MH→CU)	Depression*Age → Cannabis Use	0.0475 (0.005)	<.001	0.1459 (0.0252)	<.001	11864	48582
		Anxiety*Age → Cannabis Use	0.0168 (0.0052)	.001	0.0850 (0.0254)	<.001		
		Depression*Sex → Cannabis Use	0.0095 (0.0179)	.60	0.3571 (0.0753)	<.001	11862	48574
		Anxiety*Sex → Cannabis Use	0.0144 (0.0174)	.41	0.1354 (0.0754)	.07		
	Concurrent (CU→MH)	Cannabis Use*Age → Depression	0.0352 (0.0156)	.02	0.0009 (0.0018)	.62	11864	
		Cannabis Use*Age → Anxiety	-0.0181 (0.0153)	.24	-0.0005 (0.0018)	.80		
		Cannabis Use*Sex → Depression	0.1366 (0.0936)	.14	0.0325 (0.0050)	<.001	11862	48574
		Cannabis Use*Sex → Anxiety	0.1112 (0.0965)	.25	0.0183 (0.0049)	<.001		

	Prospective (MH→CU)	Depression*Age → Cannabis Use	0.0627 (0.0086)	<.001	0.0292 (0.0429)	.50	11516	37003
		Anxiety*Age → Cannabis Use	0.0187 (0.0084)	.03	-0.0182 (0.0414)	.66		
		Depression*Sex → Cannabis Use	0.0174 (0.0236)	.46	0.0868 (0.1024)	.40	11514	36996
		Anxiety*Sex → Cannabis Use	0.0151 (0.0230)	.51	0.0041 (0.1002)	.97		
	Prospective (CU→MH)	Cannabis Use*Age → Depression	0.0653 (0.0229)	.004	-0.0019 (0.0034)	.59	11508	36772
		Cannabis Use*Age → Anxiety	0.0112 (0.0221)	.61	-0.0041 (0.0033)	.21		
		Cannabis Use*Sex → Depression	0.1504 (0.1007)	.14	-0.0077 (0.0080)	.34	11506	36766
		Cannabis Use*Sex → Anxiety	0.1720 (0.1019)	.09	0.0052 (0.0077)	.50		
Externalizing	Concurrent (MH→CU)	ADHD*Age→ Cannabis Use	0.0517 (0.0055)	<.001	0.0811 (0.0256)	.002	11864	48582
		CD*Age → Cannabis Use	0.1046 (0.0064)	<.001	0.3124 (0.0258)	<.001		
		ODD*Age → Cannabis Use	0.0611 (0.0061)	<.001	0.1026 (0.0256)	<.001		

	ADHD *Sex → Cannabis Use	0.0084 (0.0189)	.66	0.3021 (0.0755)	<.001	11862	48574
	CD*Sex → Cannabis Use	-0.0506 (0.0208)	.02	0.2381 (0.0752)	.002		
	ODD*Sex → Cannabis Use	-0.0431 (0.0207)	.04	0.1646 (0.0761)	.03		
Concurrent (CU→MH)	Cannabis Use*Age → ADHD	0.0083 (0.0122)	.49	-0.00003 (0.0014)	.98	11864	48582
	Cannabis Use*Age → CD	0.0577 (0.0120)	<.001	0.0020 (0.0014)	.16		
	Cannabis Use*Age → ODD	0.0429 (.0123)	<.001	-0.0004 (0.0014)	.78		
	Cannabis Use*Sex → ADHD	0.0562 (0.0897)	.53	0.0197 (0.0039)	<.001	11862	48574
	Cannabis Use*Sex → CD	-0.0394 (0.0807)	.63	0.0157 (0.0038)	<.001		
	Cannabis Use*Sex → ODD	-0.1259 (0.0824)	.13	0.0099 (0.0039)	.01		
Prospective (MH→CU)	ADHD*Age → Cannabis Use	0.0683 (0.0090)	<.001	0.0118 (0.0419)	.78	11516	37003
	CD*Age → Cannabis Use	0.1267	<.001	0.1200	.005		

		(0.0104)		(0.0429)			
	ODD*Age → Cannabis Use	0.0805 (0.0098)	<.001	0.0929 (0.0417)	.03		
	ADHD*Sex → Cannabis Use	0.0169 (0.0250)	.50	0.0043 (0.1007)	.97	11514	36996
	CD*Sex → Cannabis Use	-0.0403 (0.0278)	.15	0.1791 (0.0995)	.07		
	ODD*Sex → Cannabis Use	-0.0317 (0.0275)	.25	0.0035 (0.1013)	.97		
Prospective (CU→MH)	Cannabis Use*Age → ADHD	0.0528 (0.0178)	.003	-0.00003 (0.0026)	.99	11508	36772
	Cannabis Use*Age → CD	0.0596 (0.0171)	<.001	-0.0097 (0.0026)	<.001		
	Cannabis Use*Age → ODD	0.0531 (0.0178)	.003	-0.0038 (0.0027)	.16		
	Cannabis Use*Sex → ADHD	0.0632 (0.0919)	.49	0.0003 (0.0061)	.96	11506	36766
	Cannabis Use*Sex → CD	-0.0618 (0.0806)	.44	-0.0055 (0.0059)	.36		
	Cannabis Use*Sex → ODD	-0.1559 (0.0846)	.07	-0.0034 (0.0062)	.58		

Note. CU = cannabis use, MH = mental health, ADHD = Attention Deficit Hyperactivity Disorder, CD = Conduct Disorder, ODD = Oppositional Defiant Disorder, Coef = coefficient, SE = standard error of coefficient. Each between- and within-youth coefficient pair was estimated in a separate regression model. Coefficients are unstandardized. Widely used, validated age and sex-normed t-scores from the CBCL were used for all mental health outcomes. Scores for specific disorders were in accordance with DSM-5 symptoms. Cannabis use was measured as a binary score (0 = no use in past year, 1 = used in past year). For MH→CU analyses, the cannabis score was multiplied by 100 (0 = no use in the past year, 100 = used in the past year) to make coefficients more interpretable.

Supplementary Material

This supplement contains 6 items:

- **Table S1:** *Multilevel Model Results: Internalizing Disorder Symptoms*
- **Table S2:** *Multilevel Model Results: Externalizing Disorder Symptoms*
- **Figure S1:** *Simple Slopes Analysis of Age*Cannabis Use Interactions*
- **Figure S2:** *Simple Slopes Analysis of Age*Internalizing / Externalizing Symptom Interactions*
- **Figure S3:** *Simple Slopes Analysis of Sex*Cannabis Use Interactions*
- **Figure S4:** *Simple Slopes Analysis of Sex*Internalizing / Externalizing Symptom Interactions*

Table S1.*Multilevel Model Results: Internalizing Disorder Symptoms*

Association	Tested Measures	Between-Youth Associations		Within-Youth Associations		N	N _{obs}
		Coef. (SE)	<i>p</i>	Coef. (SE)	<i>p</i>		
Concurrent (MH→CU)	Depression → Cannabis Use	0.0685 (0.0089)	<.001	0.2135 (0.0376)	<.001	11865	48586
	Anxiety → Cannabis Use	0.0294 (0.0087)	<.001	0.1541 (0.0376)	<.001		
Concurrent (CU→MH)	Cannabis Use → Depression	0.3439 (0.0453)	<.001	0.0141 (0.0025)	<.001	11865	48586
	Cannabis Use → Anxiety	0.1525 (0.0467)	.001	0.0101 (0.0024)	<.001		
Prospective (MH→CU)	Depression → Cannabis Use	0.0900 (0.0118)	<.001	0.1078 (0.0511)	.03	11517	37006
	Anxiety → Cannabis Use	0.0397 (0.0115)	<.001	0.0125 (0.0500)	.80		
Prospective (CU→MH)	Cannabis Use → Depression	0.3675 (0.0484)	<.001	-0.0048 (0.0038)	.20	11509	36775
	Cannabis Use → Anxiety	0.1377 (0.0490)	.005	-0.0049 (0.0036)	.18		

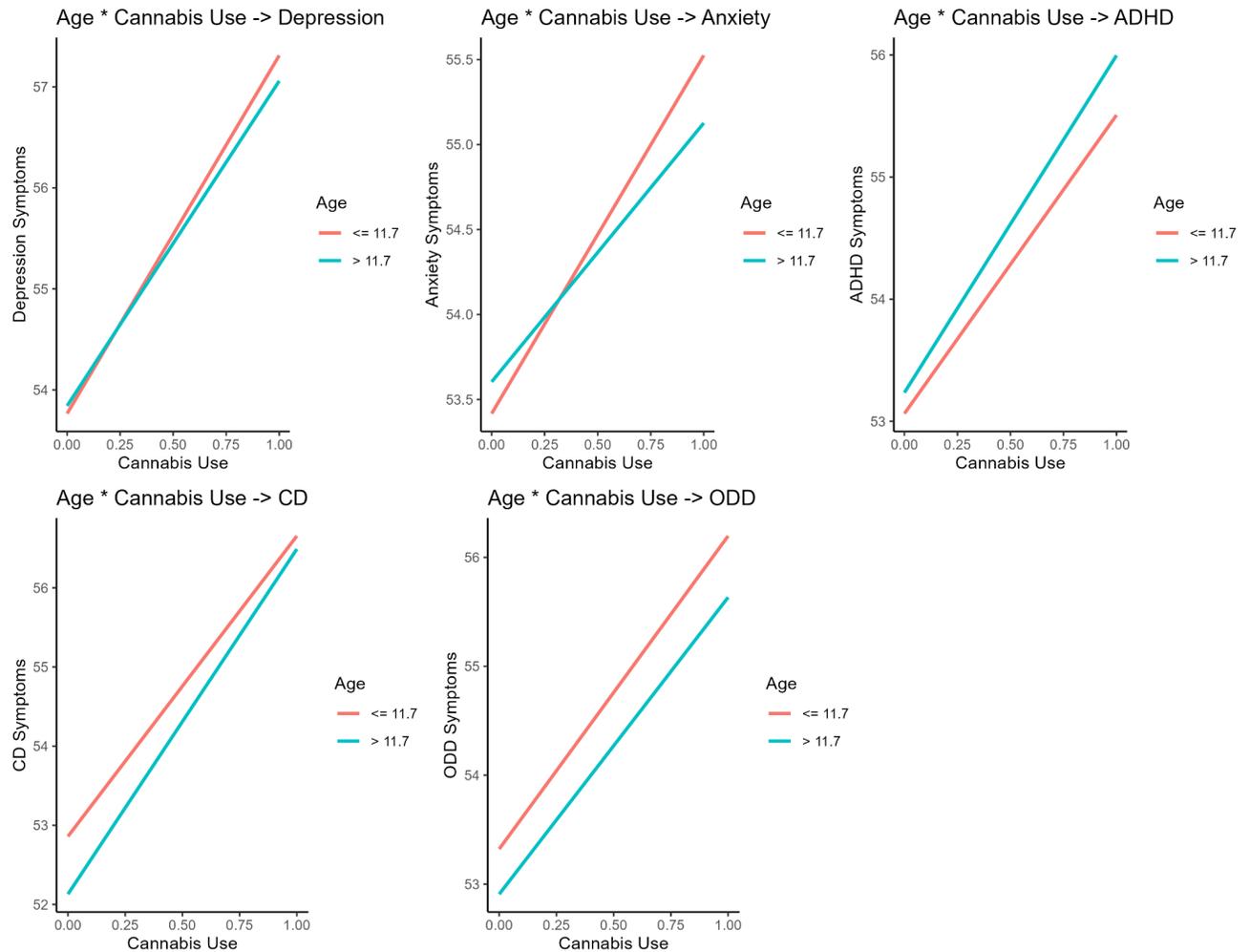
Note. CU = cannabis use, MH = mental health, Coef = coefficient, SE = standard error of coefficient. Each between- and within-youth coefficient pair was estimated in a separate regression model. Coefficients are unstandardized. Widely used, validated age and sex-normed t-scores from the CBCL were used for all mental health outcomes. Scores for specific disorders were in accordance with DSM-5 symptoms. Cannabis use was measured as a binary score (0 = no use in past year, 1 = used in past year). For MH→CU analyses, the cannabis score was multiplied by 100 (0 = no use in the past year, 100 = used in the past year) to make coefficients more interpretable.

Table S2.*Multilevel Model Results: Externalizing Disorder Symptoms*

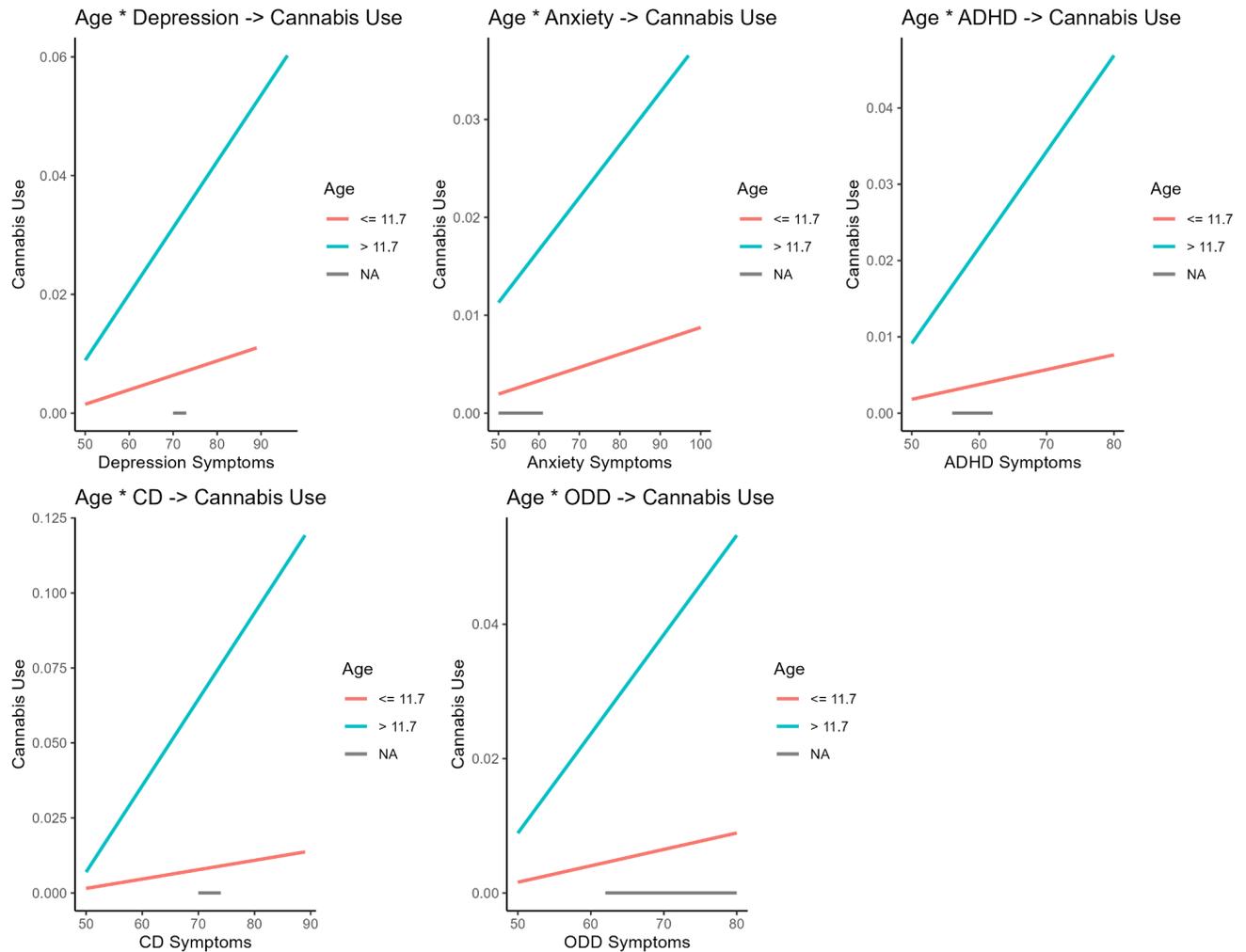
Association	Tested Measures	Between-Youth Associations		Within-Youth Associations		N	N _{obs}
		Coef. (SE)	<i>p</i>	Coef. (SE)	<i>p</i>		
Concurrent (MH→CU)	ADHD→ Cannabis Use	0.0814 (0.0093)	<.001	0.1048 (0.0376)	.005	11865	48586
	CD → Cannabis Use	0.1432 (0.0103)	<.001	0.2617 (0.0378)	<.001		
	ODD → Cannabis Use	0.0983 (0.0101)	<.001	0.0989 (0.0377)	.009		
Concurrent (CU→MH)	Cannabis Use → ADHD	0.3855 (0.0435)	<.001	0.0053 (0.0019)	.006	11865	48586
	Cannabis Use → CD	0.5558 (0.0391)	<.001	0.0133 (0.0019)	<.001		
	Cannabis Use → ODD	0.3973 (0.0400)	<.001	0.0052 (0.0020)	.008		
Prospective (MH→CU)	ADHD → Cannabis Use	0.1096 (0.0123)	<.001	0.0776 (0.0501)	.12	11517	37006
	CD → Cannabis Use	0.1923 (0.0138)	<.001	0.1002 (0.0499)	.04		

	ODD → Cannabis Use	0.1285 (0.0134)	<.001	0.1324 (0.0500)	.008		
Prospective (CU→MH)	Cannabis Use → ADHD	0.3759 (0.0443)	<.001	-0.0022 (0.0029)	.45	11509	36775
	Cannabis Use → CD	0.5779 (0.0388)	<.001	-0.0084 (0.0028)	.003		
	Cannabis Use → ODD	0.4106 (0.0409)	<.001	-0.0002 (0.0029)	.95		

Note. CU = cannabis use, MH = mental health, ADHD = Attention Deficit Hyperactivity Disorder, CD = Conduct Disorder, ODD = Oppositional Defiant Disorder, Coef = coefficient, SE = standard error of coefficient. Each between- and within-youth coefficient pair was estimated in a separate regression model. Coefficients are unstandardized. Widely used, validated age and sex-normed t-scores from the CBCL were used for all mental health outcomes. Scores for specific disorders were in accordance with DSM-5 symptoms. Cannabis use was measured as a binary score (0 = no use in past year, 1 = used in past year). For MH→CU analyses, the cannabis score was multiplied by 100 (0 = no use in the past year, 100 = used in the past year) to make coefficients more interpretable.

Figure S1.*Simple Slopes Analysis of Age*Cannabis Use Interactions*

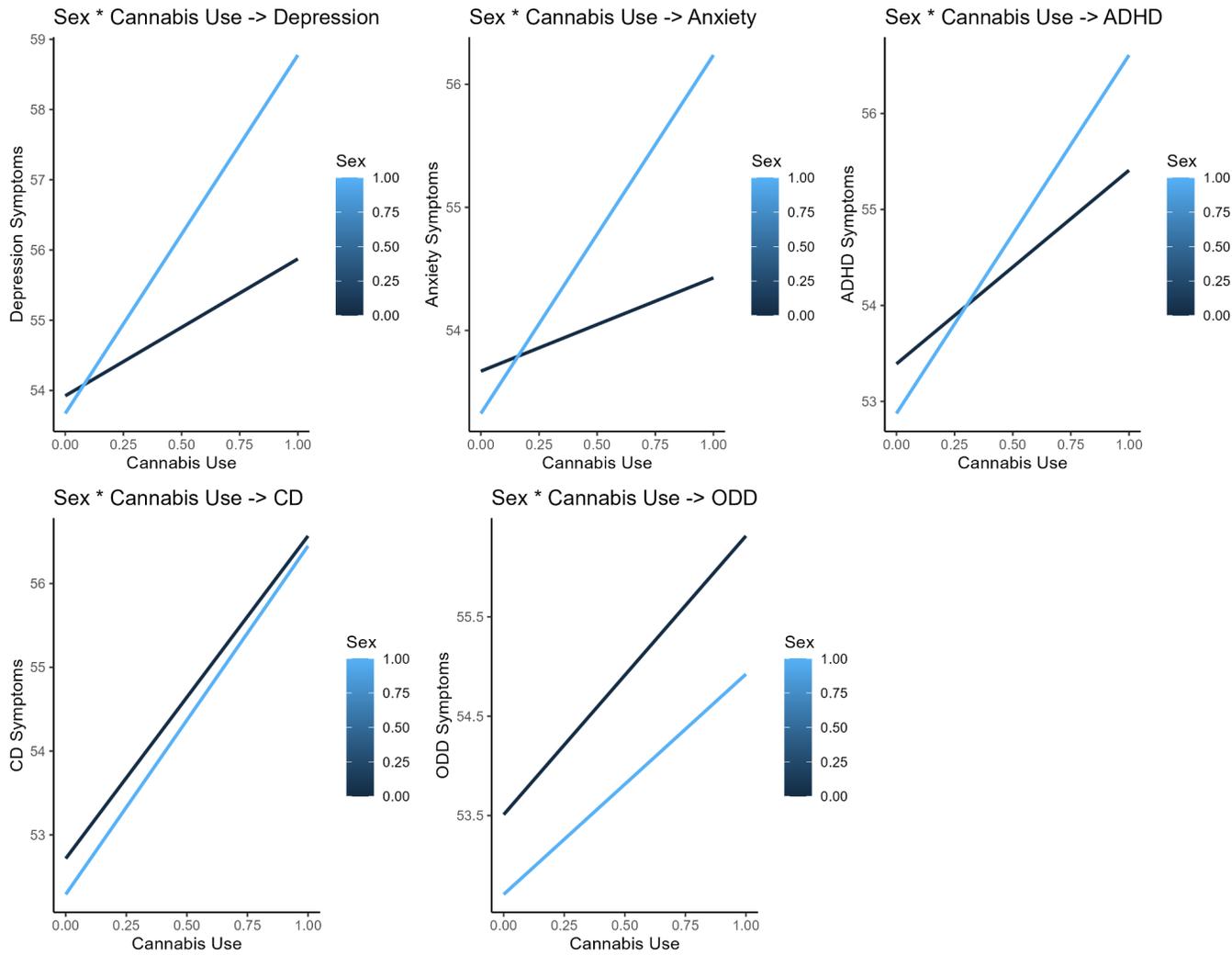
Note. ADHD = Attention Deficit Hyperactivity Disorder, CD = Conduct Disorder, ODD = Oppositional Defiant Disorder. Plot depicts simple slopes for all age*cannabis use interactions. Orange line represents slopes below the mean age (i.e., 11.7 years). Blue line represents slopes above the mean age. Age and sex-normed t-scores from the CBCL were used for all disorders in accordance with DSM-5 symptoms. Cannabis use was measured as a binary score (0 = no use in past year, 1 = used in past year) .

Figure S2.*Simple Slopes Analysis of Age*Internalizing / Externalizing Disorder Symptoms Interactions*

Note. NA = Not Applicable, ADHD = Attention Deficit Hyperactivity Disorder, CD = Conduct Disorder, ODD = Oppositional Defiant Disorder. Plot depicts simple slopes for all age*internalizing and age*externalizing disorder symptom interactions. Orange line represents slopes below the mean age (i.e., 11.7 years). Blue line represents slopes above the mean age. Age and sex-normed t-scores from the CBCL were used for all disorders in accordance with DSM-5 symptoms. Cannabis use was measured as a binary score (0 = no use in past year, 1 = used in past year).

Figure S3.

*Simple Slopes Analysis of Sex*Cannabis Use Interactions*



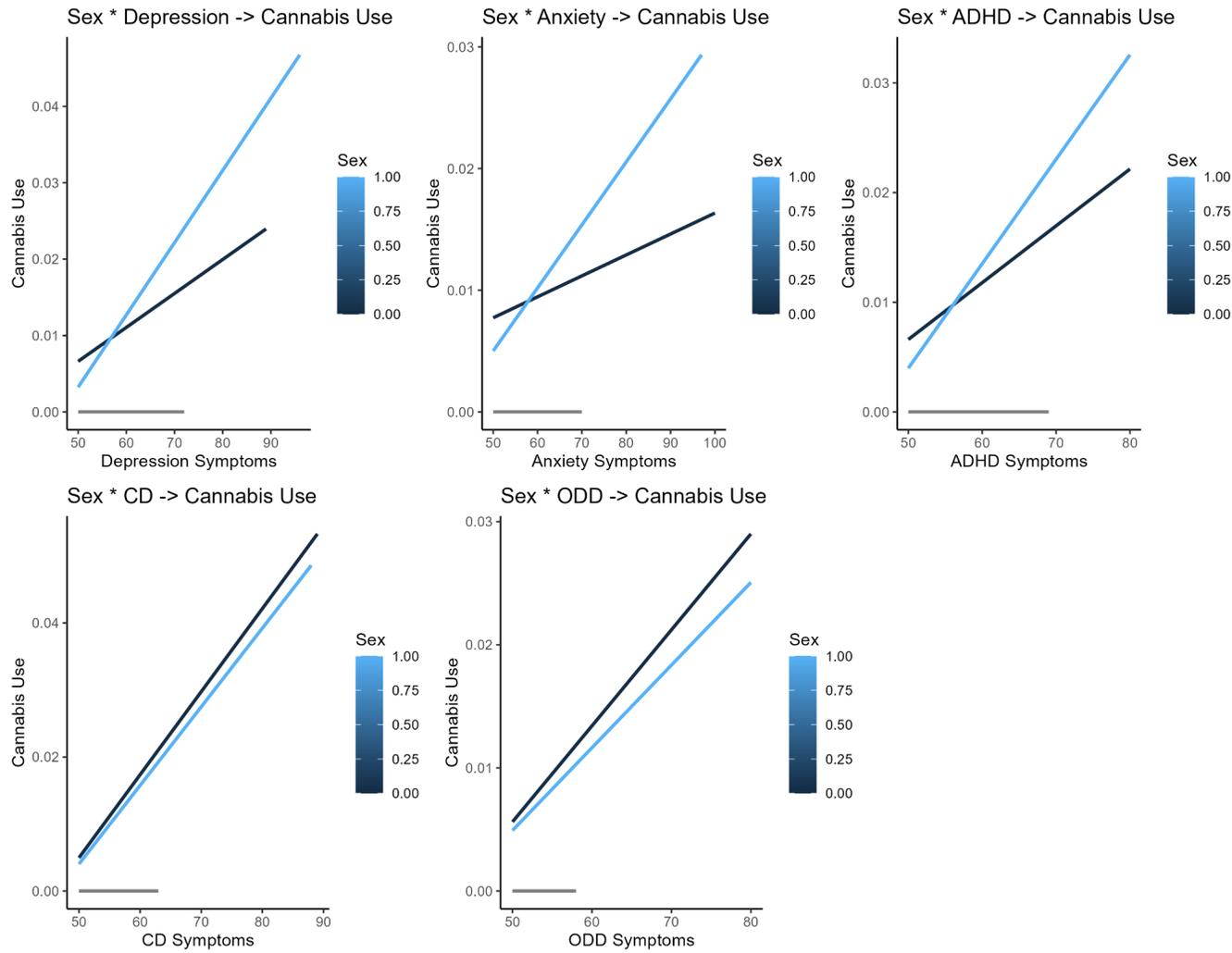
Note. ADHD = Attention

Deficit Hyperactivity Disorder, CD = Conduct Disorder, ODD = Oppositional Defiant Disorder. Plot depicts simple slopes for all

sex*cannabis use interactions. Light blue line represents females (coded as 1), dark blue line represents males (coded as 0). Age and sex-normed t-scores from the CBCL were used for all disorders in accordance with DSM-5 symptoms. Cannabis use was measured as a binary score (0 = no use in past year, 1 = used in past year).

Figure S4.

*Simple Slopes Analysis of Sex*Internalizing / Externalizing Disorder Symptom Interactions*



Note. ADHD = Attention

Deficit Hyperactivity Disorder, CD = Conduct Disorder, ODD = Oppositional Defiant Disorder. Plot depicts simple slopes for all

sex*internalizing and sex*externalizing disorder symptom interactions. Light blue line represents females (coded as 1), dark blue line represents males (coded as 0). Age and sex-normed t-scores from the CBCL were used for all disorders in accordance with DSM-5 symptoms. Cannabis use was measured as a binary score (0 = no use in past year, 1 = used in past year).