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Anxiety, Depression and Risk of Cannabis Use: Examining the Internalising Pathway to use among Chilean Adolescents

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Abstract

Background. Adolescents who experience internalising symptoms may be susceptible to the use of alcohol and other substances in an attempt to alleviate or cope with these symptoms. We examined the hypothesised internalising pathway from symptoms of depression, generalised anxiety, social anxiety and panic, to incidence and frequency of cannabis use 18 months later.

Method. Longitudinal cohort study of participants (n = 2,508; 45% female; mean age 14.5 years) recruited from the 9th grade at 22 low-income secondary schools in Santiago, Chile. Baseline internalising symptoms were assessed using the Beck Depression Inventory and the Revised Child Anxiety and Depression Scale. Frequency of cannabis was assessed at baseline, 6 month and 18 month follow-up.

Results. High rates of use were observed in this sample, with 40.3% reporting cannabis use at least once over the study period. Adjusted for baseline cannabis use, symptoms of depression, panic and generalised anxiety were associated with greater cannabis use frequency 18 months later. When all predictors were considered simultaneously, only generalised anxiety symptoms showed an independent association with subsequent cannabis use frequency (OR: 1.23, 95% CI: 1.08 to 1.41). Generalised anxiety symptoms were also associated with a 25% increased risk of transitioning from non-user to use of cannabis during the study (OR: 1.25, 95% CI: 1.09 to 1.44).

Conclusions. Internalising symptoms, and in particular symptoms of generalised anxiety, increase risk of cannabis use during adolescence. Targeted interventions that promote adaptive

anxiety management among high-risk adolescents may represent a promising strategy to prevent uptake of cannabis use during adolescence.

Introduction

Cannabis is the most widely used illicit substance, with a peak in onset and intensity of use occurring during mid to late adolescence (Copeland and Swift, 2009). Global comparisons suggest cannabis use is less prevalent in Latin America compared to more affluent regions such as North America, Europe, Australia and New Zealand (Degenhardt et al., 2008; United Nations Office on Drugs and Crime, 2014). However, national surveys of school students in Chile suggest an upward trend in cannabis use since 2009, increasing to a 12-month prevalence of 30.6% in 2013 (Servicio Nacional para la Prevención y rehabilitación del Consumo de Droga y Alcohol, 2014). This most recent estimate places adolescent prevalence rates in Chile among the highest in the world (Castillo-Carniglia, 2015). This high prevalence is concerning given increasing evidence that adolescent cannabis use can interfere with normal brain development, leading to deficits in cognitive functioning (Bava and Tapert, 2010; Fontes et al., 2011; Squeglia et al., 2009). Furthermore, research suggests substance use patterns established in adolescence tend to predict adulthood problems such as dependence, psychosocial dysfunction, delinquency, and progression to other drug use (Copeland and Swift, 2009; Lynskey et al., 2003; Patton et al., 2007). A promising strategy for reducing these considerable harms is early intervention to prevent cannabis use during adolescence.

Understanding the risk factors that predispose adolescents to cannabis use is an important first step. Developmental models suggest an "internalising pathway" to substance use, whereby adolescents use alcohol and other substances to alleviate psychological symptoms, such as anxiety and depression (also known as the self-medication hypothesis; Hussong et al., 2011; Khantzian, 1997). Evidence of the relationship between internalising symptoms and cannabis use comes predominantly from studies conducted in high-income Western regions. Systematic

reviews indicate a cross-sectional association between cannabis use and symptoms of depression (Degenhardt et al., 2003) and anxiety (Crippa et al., 2009; Kedzior and Laeber, 2014). Furthermore, cohort studies indicate the onset of anxiety and depressive disorders typically precedes that of cannabis use (Agosti et al., 2002; Lopez et al., 2005), lending support to the conceptualisation of internalising symptoms as important triggers for substance use initiation (Clark, 2004; Hussong et al., 2011). However, an alternative explanation is that cannabis use increases vulnerability to anxiety and depression by impairing psychosocial functioning, increasing stress reactivity or directly inducing anxiety symptoms during intoxication or withdrawal (Degenhardt et al., 2013; Wand, 2008; Zvolensky et al., 2008).

Given the potentially bidirectional relationships between cannabis use and mental health symptoms, prospective data are needed to clarify whether internalising symptoms precede cannabis use, and to date the findings have been equivocal. Several prospective studies provide evidence that frequency of cannabis use is associated with prior symptoms of depression (Feingold et al., 2014; Hooshmand et al., 2012; Wittchen et al., 2007) and anxiety (Buckner et al., 2008; Marmorstein et al., 2010b; Wittchen et al., 2007), however other studies found no evidence of an association (Bardone et al., 1998; Bovasso, 2001; Brook et al., 1998; Patton et al., 2002). The variability in results may reflect methodological differences between studies, such as age and gender differences in the sample composition. Studies with adult samples suggest these associations might be moderated by gender: one found that depression was associated with an elevated risk of cannabis use in women but not men (Butterworth et al., 2014), and another that cannabis use is more strongly associated with coping motives in women compared to men (Simons et al., 1998). An analysis of multiple cohort studies suggests there may be age-related

differences in the relationship between depression and cannabis use, with the strongest association observed in mid-adolescence (Horwood et al., 2012). In addition to these methodological considerations, studies investigating the relationship between anxiety and alcohol/substance use have highlighted the importance of distinguishing between subtypes of anxiety (Kaplow et al., 2001; Marmorstein et al., 2010b; McCarty et al., 2012).While some anxiety subtypes such as generalised anxiety may promote substance use to alleviate unpleasant symptoms and tension, others manifestations such as separation or social anxiety may lead to protective behaviours such as staying close to parents and avoiding peer contexts in which substance use is likely (Buckner et al., 2016; Kaplow et al., 2001; McCarty et al., 2012).

Given the high prevalence and upward trend in cannabis use among Chilean adolescents, it is critical to understand factors associated with its use. To inform prevention strategies, an important question is whether internalizing symptoms such as anxiety and depression increase risk of using cannabis during adolescence. As earlier initiation is associated with poorer longer term outcomes (Copeland and Swift, 2009), targeting vulnerability factors to delay onset of use is a promising strategy for reducing drug-related harms. Limited evidence is available about risk factors for cannabis use initiation among adolescents in Latin America, however evidence from studies conducted in Germany and the US suggest that depression, panic disorder and generalised anxiety symptoms increase risk of cannabis use (Feingold et al., 2014; Marmorstein et al., 2010a; Marmorstein et al., 2010b; Wittchen et al., 2007). To our knowledge, this study is the first to examine the internalising pathway to cannabis use in a sample of adolescents in Chile. The association between internalising symptoms and cannabis use was considered in the context of established protective factors, specifically problem-solving ability and sense of school

connectedness, which are both associated with lower incidence of drug use in adolescence (Bond et al., 2007; Jaffee and D'Zurilla, 2009). In view of previous findings indicating moderating effects of age and gender, we also tested the hypothesis that associations between internalising symptoms and cannabis use would decline with age, and be most evident among females. Our study adds to existing research by disentangling the associations between specific subtypes of anxiety and adolescent cannabis use. It explores the independent contribution of depression, generalised anxiety, social anxiety and panic symptoms to predicting new cases of cannabis use and the frequency of use 18 months later. Our hypotheses, derived from review of theory and prior research, were that internalising symptoms, and in particular depression, panic and generalised anxiety, would show independent prospective associations with frequency of cannabis use and transition to use among non-users.

Method

Data for this study were collected between 2009 and 2011 as part of a randomised controlled trial of a school-based prevention program for depression; the full trial protocol and analyses have been published elsewhere (Araya et al., 2013; Araya et al., 2011). In brief, there was no evidence of any effect of the intervention on any depression or substance use outcomes. There was a suggestion of a small beneficial effect on anxiety outcomes at 6 month follow-up, but this was clinically unimportant and was absent at 18 month follow-up. In view of these null results the dataset was used for the present study; analyses were adjusted for trial arm to take into account any residual effects.

Setting and Participants

Twenty-two schools were randomly selected from a sampling frame comprising all Municipal secondary mixed-sex schools with two or more '1^{o} Medio' classes (equivalent to 9th grade) in Santiago, Chile. Municipal schools provide education for most low-income, secondary school students in Santiago. All students attending '1^{o} Medio' grade in the selected schools were invited to participate; all except 4 students consented and signed a written form. In total, 2,508 adolescents were enrolled in the trial at baseline. The study was approved by the Ethics Committee of the Clinical Hospital, Faculty of Medicine, Universidad de Chile. Cannabis use data were available from 2,448 (97.6%) participants at baseline, and 1,933 (77.1%) participants at 18-month follow-up. Table S1 in the supplementary material compares sample characteristics for participants with complete data to those with partial responses.

Measures

Participants provided demographic information and completed the following self-report measures at baseline, then 6 and 18 months later.

Cannabis Use. Participants reported frequency of cannabis use over the past month and past year on a 6-point ordinal scale. Due to small cell count for some response options, prior to analysis responses were collapsed to form a 3-category variable reflecting use in the past year classified as follows: i) No cannabis use; ii) Occasional cannabis use, defined as 9 or less times in past year; iii) Recurrent use, defined as 10 or more times in the past year. Transition from no use at baseline to use over the course of the study was determined based on responses collected at 6 and 18 month follow up. Use of past year reports from both these timepoints enabled us to

capture any new incidents of use occurring over the 18 month course of the study. These responses were used to derive a binary variable indicating no versus any incidence of cannabis use over the entire follow-up period.

Symptom Measures. Depression symptoms were assessed with the adolescent Beck Depression Inventory II (BDI-II; Beck et al., 1996). Symptom scores for social anxiety disorder, generalised anxiety disorder, and panic disorder were measured using 3 of the original 6 subscales of the Revised Child Anxiety and Depression Scale (RCADS; Muris et al., 2002). Both are well-validated continuous measures of clinical symptoms, and the Spanish language versions demonstrate good psychometric properties with adolescent samples (Cumsille and Martinez, 1997; Sandin et al., 2010).

Other Variables. Potential confounding variables were problem-solving style and school connectedness which have both been linked to mental health and substance use (Bond et al., 2007; Jaffee and D'Zurilla, 2009). To assess these constructs we administered the 20-item rationale problem-solving subscale of the Social Problem-Solving Inventory Revised (D'Zurilla et al., 2002), and the 8-item Psychological Sense of School Membership scale (Goodenow, 1993). Two dichotomous variables represented participants' gender and trial allocation. Frequency of alcohol and tobacco use at baseline were also assessed, as there is evidence to suggest shared vulnerability and cross-substance associations (Palmer et al., 2009). A 3-category variable indicated frequency over the past month: i) No use; ii) Occasional use; iii) Recurrent use, defined as weekly or more often.

Data Scoring and Analysis

All analyses were conducted using STATA 13.1. Descriptive statistics were obtained to characterise adolescents at baseline. All analyses used multilevel mixed-effects regression models incorporating a school-level random intercept to take into account non-independence of the data within school groups. First, a series of ordinal logistic regressions (using the Stata meologit command) examined associations between baseline depression and anxiety and frequency of cannabis use 18 months later, adjusted for baseline cannabis use frequency. Second, multilevel logistic regressions (using the Stata xtmelogit command) examined the association between baseline symptoms and new cases of cannabis use over the follow-up period within adolescents who did not report cannabis use at baseline. Collinearity diagnostics indicated acceptable tolerance and variance inflation factor for all analyses (Tabachnick and Fidell, 2001). All continuous predictor variables were standardised. Therefore, odds ratios represent the change in odds related to a one standard deviation increase on the continuous exposure variables. Initially we examined each symptom variable individually; next regression models were adjusted for possible confounders (gender, trial arm, problem-solving, school connectedness). The final model tested the unique contribution of each dimension of anxiety and depression within the context of all other variables. To facilitate interpretation of significant associations from ordinal logistic models, model predicted probabilities for each level of cannabis use were calculated at 1 and 2 standard deviations above and below the symptom variable mean.

Primary analyses were based on complete case data, thus a series of sensitivity analyses examined the impact of response attrition on the results. Analyses were repeated on 50 datasets imputed using multiple imputation by chained equations (Royston, 2009), a recommended approach for handling missing data (Sterne et al., 2009) that assumes data are missing at random

(MAR) conditional on the variables in the imputation model. See Supplementary material for full details.

Results

Sample Characteristics and Prevalence of Cannabis Use

Table 1 presents descriptive characteristics and cannabis use reported by the sample. The sample comprised 2508 adolescents, of which there were marginally more males than females. The mean age for the whole sample at baseline was 14.5 years with a range from 12 to 18 years but with 78% aged 14 or 15 years old. At baseline, 19.0% of the sample reported they had used cannabis in the past year, for the majority (15.4%) this was occasional use, and 3.6% reported use 10 or more times in the past year. Compared to non-users, adolescents who were using cannabis at baseline were older, and had higher panic and depression symptoms. They were also more likely to have used alcohol and tobacco in the past month, and felt less connection to their school.

Insert Table 1

Prospective Associations between Internalising Symptoms and Cannabis Use Frequency

Mean anxiety and depression symptom scores at baseline by cannabis use frequency at 18 month follow-up are presented in Table 2. Adjusted for frequency of baseline cannabis use, odds ratios suggested that baseline symptoms of generalised anxiety, panic and depression were associated with frequency of subsequent cannabis use (see Table 2). Interaction terms revealed

no evidence that the association between symptom variables and frequency was moderated by age or gender. Adjustment for other potential confounders (trial allocation, baseline school-connectedness, problem-solving ability, smoking and alcohol use frequency) had little effect on the association between generalised anxiety and subsequent cannabis use. However, in these adjusted models there was weaker evidence for the association between symptoms of panic and depression and subsequent cannabis use. Within the full multivariable model, increased frequency of cannabis use at 18 month follow-up was associated with baseline generalised anxiety (OR: 1.23, 95% CI: 1.08 to 1.41, $p = 0.002$), frequency of tobacco smoking (OR: 2.46, 95% CI: 1.98 to 3.06, $p < 0.001$) and frequency of alcohol use (OR: 1.46, 95% CI: 1.20 to 1.77, $p < 0.001$). Model predicted proportions were examined to facilitate interpretation of the association between baseline GAD symptoms and cannabis use frequency 18 months later (see Table 3). Adjusted for baseline cannabis use and other covariates, the predicted probability of occasional cannabis use was 39.8% for adolescents with high levels of generalised anxiety symptoms (≥ 2 standard deviations above the mean), compared to 21.1% of adolescents with low levels (≥ 2 standard deviations below the mean) of generalised anxiety symptoms. Model-predicted probabilities of recurrent use were 5.9% and 1.6% respectively for adolescents at high and low levels of generalised anxiety symptoms.

Insert Table 2 & 3

Association between Internalising Symptoms and New Cases of Cannabis Use

Of the 1,972 adolescents who reported no cannabis use in the 12 months preceding baseline assessment, 537 (32.2%) reported use of cannabis within the 18-month follow-up period. Mean anxiety and depression symptom scores for those adolescents who did versus did not transition to cannabis use are presented in Table 4. Multilevel models testing univariable associations indicated that baseline symptoms of generalised anxiety, panic, depression, but not social anxiety, were associated with new incidence of cannabis use over the 18 month study (see Table 4). Interaction terms revealed no evidence that the association between symptom variables and cannabis use was moderated by age or gender. After adjustment for potential confounders, only the association between generalised anxiety and new cases of cannabis use persisted. Within the full multivariable model which adjusted for all depression and anxiety variables, only generalised anxiety symptoms (OR: 1.25, 95% CI: 1.09 to 1.44, $p = 0.001$) accounted for unique variance when predicting subsequent cannabis use. There was also evidence that cannabis use was associated with baseline tobacco use frequency (OR: 2.94, 95% CI: 2.31 to 3.73, $p < 0.001$), alcohol use frequency (OR: 1.86, 95% CI: 1.47 to 2.36, $p < 0.001$), and negatively associated with sense of school connectedness (OR: 0.85, 95% CI: 0.75 to 0.96, $p = 0.009$).

Insert Table 4

Sensitivity Analyses

Results from the fully adjusted analyses using imputed data sets are shown in Table S2 (supplementary material). These analyses confirmed the robustness of the findings; there was no

material difference to the pattern of results derived from imputed data as compared to complete-case analyses.

Discussion

This study examined patterns of cannabis use and the association with internalising symptoms in a sample of Chilean adolescents. At baseline, 19% of the sample reported having used cannabis in the past year, and these adolescents had higher depression and panic symptoms, and were less likely to feel connected to their school. Co-occurrence was observed between high-risk behaviours, with adolescents who used cannabis also more likely to have used tobacco and alcohol. Over the 18-month follow-up period, there were 537 new cases of cannabis use, bringing the total number who had ever reported use to 40.3% of the sample. Longitudinal analyses revealed two main findings. Adjusted for frequency of baseline cannabis use, baseline symptoms of generalised anxiety, panic and depression were associated with higher frequency of cannabis use 18 months later. There was no evidence that these relationships varied according to age or gender. The associations persisted after adjustment for potential confounders, however when the unique contribution of each predictor was tested in the final model, only generalised anxiety symptoms showed an independent association with subsequent cannabis use frequency. For an adolescent with high levels of generalised anxiety symptoms, the predicted probability of occasional use was 39.8%, and predicted probability of recurrent use was 5.9%, compared to 21.1% and 1.6% respectively for adolescents with low levels of generalised anxiety symptoms. A similar pattern of results was found when new cases of cannabis use over the follow-up period

were examined. Again, only generalised anxiety symptoms were independently associated with increased risk of using cannabis. A one standard deviation increase in generalised anxiety symptoms was associated with a 25% increased risk of uptake of cannabis during the follow-up period.

National surveys of school students in Chile have suggested an upward trend in cannabis use since 2009, with the 2013 survey indicating 30.6% of Grade 8 to 12 students had used of cannabis in the past year (Servicio Nacional para la Prevención y rehabilitación del Consumo de Droga y Alcohol, 2014). The rates of use observed in the current study were similar, with 19% reporting past-year use at the baseline assessment (Grade 9) and 32.8% at 18-month follow-up (Grade 11). Our sample was not broadly representative; rather students were recruited from state schools in Santiago. Nonetheless, the current study again conveys the high rates of cannabis use among young Chileans, and in view of the long-term risks associated with early onset cannabis use, highlights the need for effective prevention approaches.

This study has implications for prevention strategy, and suggests that internalising symptoms and generalised anxiety in particular can be seen as a marker by which parents and school communities can identify adolescents at greater risk of cannabis use initiation. In this sample, symptoms of depression, panic and generalised anxiety were associated with initiating cannabis use and greater frequency of use, however the association was most robust for generalised anxiety symptoms. Although the odd ratios were modest in size, these findings are consistent with the hypothesised internalising pathway to substance use (Hussong et al., 2011; Khantzian, 1997), and add to existing data showing that internalising symptoms precede and increase risk for cannabis initiation (Feingold et al., 2014; Marmorstein et al., 2010a; Wittchen et

al., 2007), and predict more frequent use later in adolescence (Marmorstein et al., 2010b; Wittchen et al., 2007). Taken together, these findings suggest that symptomatic adolescents may use cannabis in an attempt to calm anxiety symptoms and tension, cope with negative affect, or avoid ruminative worry. This explanation is consistent with adolescent reports of coping motives for cannabis use (Bottorff et al., 2009; Hides et al., 2008), and studies demonstrating the anxiety-reducing effects of these substances at low doses (see Kushner et al., 2000; Pacher et al., 2006).

There was no evidence that symptoms of social anxiety were associated with increased risk of transitioning to cannabis use or frequency of use. This finding aligns with previous investigations among older samples, which suggest a complex relationship between social anxiety and cannabis use that differs according to the aspect of use under examination: while social anxiety increased risk for cannabis dependence, it was not associated with cannabis use frequency (Buckner et al., 2008; Buckner et al., 2012). A recent study of undergraduate students highlights the importance of context, demonstrating that social anxiety increased risk of solitary cannabis use, but was unrelated to cannabis use frequency in social contexts (Buckner et al., 2016). Buckner and colleagues suggest these findings may be explained by avoidance of social events, with socially anxious young adults electing to engage in solitary cannabis use rather than attend social events. Although these situational factors are yet to be examined among adolescents, there is some evidence that social anxiety protects against frequent alcohol use at this age, possibly because socially anxious adolescents are more inclined to avoid peer contexts involving alcohol and other substance use (Frojd et al., 2011).

Strengths of the current study include the prospective design, developmental approach and use of a large sample drawn from an under-researched population. We also note a number of

limitations. First, our assessment of cannabis use and symptoms of anxiety and depression relied on brief self-report measures, and thus prevalence may be underestimated. The scope of our cannabis measure was limited to frequency of use without assessing related problems or dependence. A second limitation common to most longitudinal studies is missing data, and in this study attrition at 18 month follow-up was 23%. However, we are reassured by sensitivity analyses using multiply imputed data which revealed a pattern of results consistent with complete case analyses. Third, methodological constraints prohibited assessment of externalising symptoms (e.g., hyperactivity, behavioural problems), and family factors such as parental substance use, education, or household income, although we note that the sample was fairly homogeneous in terms of socio-economic standing as state schools in Chile are predominantly attended by low-income adolescents. Without more detailed individual and family data we cannot rule out the possibility that the observed associations between internalising symptoms and cannabis use are explained by unmeasured individual or environmental factors that influence both.

These limitations notwithstanding, our results suggest that symptoms of panic, depression, and most markedly generalised anxiety are prospectively associated with subsequent cannabis use and frequency of use. This study also brings to light new evidence about rates of cannabis use in Chile and is to our knowledge the first to examine the internalising pathway to cannabis use among Chilean adolescents. Importantly, the longitudinal nature of this study allowed for investigation of the temporal sequence and indicated that among adolescents who were not using cannabis at baseline, generalised anxiety symptoms independently predicted subsequent transition to use. Previous evidence suggests cannabis use is associated with a

subsequent increase in internalising symptoms (Degenhardt et al., 2003; Patton et al., 2002), therefore once initiated, cannabis use and internalising symptoms may exacerbate or maintain each other in a vicious cycle (Stewart and Conrod, 2008). Another possibility is that the same risk factors (biological, psychosocial and/or environment), predispose adolescents to both internalising symptoms and cannabis use (Degenhardt et al., 2013; Stewart and Conrod, 2008). At any rate, this study indicates that internalising symptoms can be considered a marker to aid identification of young people at higher risk of cannabis use and who may require additional support. There are clear implications for prevention approaches: providing high-risk adolescents with coping strategies to manage internalising symptoms may help to delay or prevent the onset of cannabis use during this vulnerable developmental stage. Empirical evaluation of preventative programs of this nature is ongoing, but initial results are promising (Conrod et al., 2010). Given earlier age of uptake is associated with negative outcomes including poorer educational performance and ongoing cannabis-related problems, preventative measures at this early stage have the potential to disrupt this trajectory and reduce incidence of substance use disorders into adulthood.

Table 1. Descriptive characteristics at baseline of cannabis users and non-users

Baseline Characteristics	**Total Sample**	**No Cannabis Use**	**Cannabis Use**	**Difference test**[b]
n (%)	2,508 (100%)	1,972 (78.6%)[a]	476 (19.0%)[a]	
Age (years)	14.5 *(0.9)*	14.4 *(0.9)*	15.0 *(0.9)*	$F(6, 2420) = 26.88$, $p < 0.001$
School-Connectedness	18.9 *(3.9)*	19.1 *(3.8)*	18.1 *(4.0)*	$F(41, 2400) = 1.72$, $p = 0.003$
Problem-solving Ability	44.8 *(12.8)*	45.2 *(12.8)*	42.8 *(13.0)*	$F(129, 2318) = 1.19$, $p = 0.080$
Generalised Anxiety	7.5 *(3.6)*	7.4 *(3.6)*	7.6 *(3.5)*	$F(15, 2405) = 0.63$, $p = 0.852$
Panic	4.4 *(3.7)*	4.2 *(3.7)*	5.2 *(3.8)*	$F(15, 2409) = 3.13$, $p < 0.001$
Social Anxiety	7.8 *(3.5)*	7.8 *(3.5)*	7.6 *(3.3)*	$F(15, 2404) = 0.86$, $p = 0.608$
Depression	13.4 *(10.2)*	12.7 *(9.9)*	16.7 *(11.0)*	$F(64, 2382) = 1.91$, $p < 0.001$
Female (*n*, %)	1,115 (44.5%)	863 (43.8%)	228 (47.9%)	$\chi^2(1) = 2.66$, $p = 0.103$
Alcohol Use (*n*, %)				
No	1,814 (72.4%)	1,589 (80.6%)	180 (37.9%)	$\chi^2(2) = 375.6$, $p < 0.001$
Infrequent	532 (21.2%)	313 (15.9%)	206 (43.3%)	
Weekly or more often	155 (6.2%)	66 (3.4%)	89 (18.7%)	
Missing	7 (0.3%)	4 (0.2%)	1 (0.2%)	
Tobacco Use (*n*, %)				
No	1,524 (60.8%)	1,405 (71.3%)	81 (17.0%)	$\chi^2(2) = 472.5$, $p < 0.001$
Infrequent	907 (36.2%)	521 (26.4%)	366 (76.9%)	
Weekly or more often	74 (3.0%)	45 (2.3%)	28 (5.9%)	
Missing	3 (0.1%)	1 (0.1%)	1 (0.2%)	

[a] Cannabis use data was missing at baseline for $n = 60$ (2.4%) participants
[b] Differences in sample characteristics according to cannabis use at baseline were examined using chi-square tests for categorical variables and ANOVA for continuous variables.

Table 2. Univariable and adjusted odds ratios predicting cannabis use frequency within the total sample at 18-month follow-up

Baseline Symptoms	Mean (*sd*)			Adjusted[1]			Adjusted[2]			Adjusted[3]		
	No Cannabis Use	Occasional Cannabis Use	Recurrent Cannabis Use	*n*	OR	*95% CI*	*n*	OR	*95% CI*	*n*	OR	*95% CI*
	(*n* = 1,299)	(*n* = 561)	(*n* = 73)									
Generalised Anxiety	7.3 *(3.6)*	7.9 *(3.5)*	8.3 *(3.6)*	1866	1.22	(1.10, 1.36)	1841	1.22	(1.10, 1.37)	1810	1.23	(1.08, 1.41)
Panic	4.2 *(3.7)*	4.8 *(3.6)*	5.3 *(4.3)*	1869	1.15	(1.04, 1.27)	1843	1.12	(1.00, 1.25)	1810	1.02	(0.89, 1.17)
Social Anxiety	7.8 *(3.5)*	7.9 *(3.4)*	7.7 *(3.2)*	1864	1.04	(0.94, 1.15)	1840	1.05	(0.95, 1.18)	1810	0.93	(0.81, 1.06)
Depression	12.3 *(9.7)*	15.0 *(10.5)*	16.7 *(11.4)*	1887	1.21	(1.09, 1.34)	1860	1.13	(1.01, 1.26)	1810	1.08	(0.94, 1.23)

[1] Adjusted for cannabis use frequency at baseline.
[2] Adjusted for cannabis use frequency and age, gender, trial allocation, school connectedness, problem-solving ability, tobacco and alcohol use frequency at baseline.
[3] Full model with all variables: generalised anxiety, panic, social anxiety, depression, age, gender, trial allocation, school connectedness, problem-solving ability and baseline cannabis, tobacco and alcohol use frequency.
Note. n indicates the sample size for each analysis, which varies somewhat due to missing responses on predictor variables or covariates. All ORs represent the odds of being in a more severe cannabis use category at 18 month follow-up given an increase of one standard deviation on the exposure variable. Occasional use was defined as 9 or fewer times in past year, recurrent use was defined as 10 or more times in the past year. Interaction effects tested within univariate models revealed no evidence that association with cannabis use frequency was moderated by age for generalised anxiety (p = 0.475), panic (p = 0.599), social anxiety (p = 0.864), or depression (p = 0.175). Similar, there was no evidence the association was moderated by gender for generalised anxiety (p = 0.965), panic (p = 0.710), social anxiety (p = 0.735), or depression (p = 0.713).

*Table 3***.** Model predicted probability of cannabis use frequency at 18 month follow-up at varying levels of baseline generalised anxiety symptoms.

	Probability (%) of cannabis use at 18mfu		
Predictor variable	No Cannabis Use	Occasional Cannabis Use	Recurrent Cannabis Use
Generalised Anxiety symptoms			
+2 *SDs*	54.3 [47.5 to 61.2]	39.8 [34.6 to 45.1]	5.9 [3.9 to 7.8]
+1 *SDs*	64.3 [61.6 to 67.0]	30.9 [29.0 to 32.8]	4.7 [3.7 to 5.9]
-1 *SDs*	74.9 [72.4 to 77.3]	22.4 [20.5 to 24.3]	2.7 [2.1 to 3.4]
- 2 *SDs*	77.3 [68.8 to 85.8]	21.1 [13.4 to 29.8]	1.6 [0.9 to 2.4]

Note. This table shows estimated probability of cannabis use (with 95% confidence intervals) at 1 and 2 standard deviations above and below the mean for generalised anxiety symptoms. Estimates are derived from full model adjusted for baseline cannabis use frequency and all other predictors and covariates.

Table 4. Univariable and adjusted odds ratios predicting new cases of cannabis use at 18-month follow-up

Baseline Symptoms	Mean (*sd*)		Unadjusted			Adjusted[1]			Adjusted[2]		
	No Cannabis Use	Cannabis Use at 18mths	*n*	OR	*95% CI*	*n*	OR	*95% CI*	*n*	OR	*95% CI*
	(*n* = 1,131)	(*n* = 537)									
Generalised Anxiety	7.3 *(3.6)*	8.0 *(3.5)*	1645	1.23	(1.10, 1.37)	1631	1.23	(1.09, 1.38)	1602	1.25	(1.09, 1.44)
Panic	4.0 *(3.7)*	4.7 *(3.7)*	1648	1.18	(1.06, 1.32)	1635	1.13	(1.00, 1.27)	1602	1.06	(0.91, 1.23)
Social Anxiety	7.8 *(3.5)*	8.0 *(3.3)*	1649	1.05	(0.94, 1.17)	1635	1.07	(0.95, 1.21)	1602	0.98	(0.85, 1.14)
Depression	11.9 *(9.4)*	13.9 *(10.1)*	1668	1.20	(1.07, 1.34)	1652	1.06	(0.93, 1.20)	1602	0.98	(0.85, 1.14)

[1] Adjusted for, age, gender, trial allocation, and baseline school connectedness, problem-solving ability, tobacco and alcohol use frequency.
[2] Full model with all variables: generalised anxiety, panic, social anxiety, depression, age, gender, trial allocation, school connectedness, problem-solving ability and baseline cannabis, tobacco and alcohol use frequency.
Note. Analysis of new cases conducted only among adolescents who did not report cannabis use at baseline. *n* indicates the sample size for each analysis, which varies somewhat due to missing responses on predictor variables or covariates. All ORs represent the odds of using cannabis over the course of the study given an increase of one standard deviation on the exposure variable. Interaction effects tested within univariate models revealed no evidence that association with transitioning to cannabis use was moderated by age for generalised anxiety ($p = 0.262$), panic ($p = 0.794$), social anxiety ($p = 0.957$), or depression ($p = 0.346$). Similar, there was no evidence the association was moderated by gender for generalised anxiety ($p = 0.584$), panic ($p = 0.407$), social anxiety ($p = 0.154$), or depression ($p = 0.298$).

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Table S1. Demographic characteristics and baseline symptom scores by extent of response attrition

Baseline Characteristics Mean *(sd)*	**Missing Data Status**			
	Total Sample[1]	Complete Case[2]	Partial exposure data[3]	Partial outcome data[4]
	(*n* = 2,508)	(*n* = 1,810)	(*n* = 159)	(*n* = 575)
Age (years)	14.5 *(0.9)*	14.4 *(0.9)*	14.5 *(0.7)*	14.9 *(0.9)*
School-Connectedness	18.9 *(3.9)*	19.1 *(3.8)*	18.9 *(4.1)*	18.3 *(4.0)*
Problem-solving Ability	44.8 *(12.8)*	45.4 *(12.7)*	44.6*(12.2)*	43.1 *(13.0)*
Generalised Anxiety	7.5 *(3.6)*	7.5 *(3.6)*	7.9 *(3.6)*	7.4 *(3.6)*
Panic	4.4 *(3.7)*	4.4 *(3.7)*	4.2 *(3.7)*	4.5 *(3.7)*
Social Anxiety	7.8 *(3.5)*	7.8 *(3.5)*	8.1 *(3.6)*	7.6 *(3.5)*
Depression	13.4 *(10.2)*	13.2 *(10.1)*	12.8 *(9.7)*	14.1 *(10.7)*
Female (*n*, %)	1,115 (44.5%)	846 (46.7%)	62 (39.0%)	219 (38.1%)
Any cannabis use (*n*, %)	476 (19.0%)	296 (16.4%)	24 (24.2%)	161 (28.7%)
Any alcohol use (*n*, %)	687 (27.5%)	466 (25.8%)	36 (23.7%)	193 (33.7%)
Any tobacco use (*n*, %)	981 (39.2%)	636 (35.1%)	58 (37.2%)	305 (53.0%)

[1]Data for entire starting sample of 2,508 adolescents enrolled in the study at baseline.
[2]Complete data for all outcome, covariate and exposure variables. Compared to participants with complete data, those with partial data were significantly older ($p < 0.001$), with higher GAD symptoms ($p = 0.02$), more likely to be female ($p < 0.001$), and more likely to use cannabis ($p < 0.001$), tobacco ($p < 0.001$), and alcohol ($p = 0.002$) at baseline.
[3]Missing data for one or more exposure or covariate variable.
[4]Missing data for one or more outcome (cannabis use or frequency) variable.

Table S2. Odds ratios for the fully adjusted model from sensitivity analyses with multiple imputation datasets and a multilevel logistic model to accommodate clustering at the school level

	Frequency of cannabis use at 18mfu				New cases of cannabis use at 18mfu			
Baseline Symptoms	*n*	*OR*	*95% CI*	*p*	*n*	*OR*	*95% CI*	*p*
Generalised Anxiety	2,508[a]	1.19	(1.06, 1.35)	0.004	2,032[b]	1.19	(1.05, 1.36)	0.009
Panic	2,508[a]	1.06	(0.93, 1.21)	0.362	2,032[b]	1.10	(0.96, 1.26)	0.152
Social Anxiety	2,508[a]	0.93	(0.82, 1.06)	0.290	2,032[b]	0.92	(0.81, 1.05)	0.239
Depression	2,508[a]	1.02	(0.90, 1.16)	0.776	2,032[b]	1.07	(0.93, 1.22)	0.350

[a] Adjusted for baseline cannabis use frequency and age, gender, trial allocation, school connectedness, problem-solving ability, tobacco and alcohol use frequency at baseline. All ORs represent the odds of being in a more severe cannabis use category at 18 month follow-up given an increase of one standard deviation on the exposure variable. Occasional use was defined as 9 or fewer times in past year, recurrent use was defined as 10 or more times in the past year.

[b]Sample size for these analyses is 2,032, as 476 adolescents who reported cannabis use at baseline were excluded from this analysis. Analyses were adjusted for age, gender, trial allocation, school connectedness, problem-solving ability, tobacco and alcohol use frequency at baseline.

Note. To ensure plausibility of the missing at random (MAR) assumption, the imputation model incorporated auxiliary demographic, mental health and substance use variables predictive of incomplete outcome variables and/or missingness (full list available on request). Each data-set entailed 20 cycles of regression switching and predictive mean matching was used for variables that were not normally distributed. Estimates were combined according to Rubin's rules using the "mi estimate" command in Stata. The resulting fraction of missing information (FMI) estimates were no larger than .48, indicating that 50 imputed datasets were sufficient.