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Title: Longitudinal associations of cannabis, depression and anxiety in heterosexual and LGB adolescents

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Abstract

Cannabis use is linked to symptoms of depression and anxiety, particularly among sexual minorities. This study examines the relationships between cannabis, and depression and anxiety symptoms at 13, 15, and 17 years using cross-lagged models in a predominantly White (n=1430; 92%) subsample of 1548 participants from the Quebec Longitudinal Study of Child Development. Multigroup analyses were conducted to examine the models according to sexual orientation. Demographic covariates were included as control variables, as well as alcohol, cigarette, and other drug use to examine cannabis-specificity. The full sample revealed small bidirectional associations, which remained significant once control variables were included in the model: cannabis at 13 and 15 years predicted anxiety symptoms at 15 and 17 years respectively, and depression symptoms at 15 years predicted cannabis at 17 years. The initial association between cannabis at 13 years and depression symptoms at 15 years was accounted for by other drug use at 13 years. Substantial differences were found between heterosexual participants and sexual minorities: LGB participants presented a substantially larger positive association between depression symptoms at 15 years and cannabis at 17 years, as well as a negative association between anxiety symptoms at 15 years and cannabis at 17 years. Both of these relationships remained significant when accounting for control variables. These results suggest that the relationships between cannabis, and depression and anxiety symptoms are bidirectional across adolescence, albeit small. Sexual minorities present particularly large associations that may represent self-medication efforts for depressive symptoms between 15 and 17 years.

Keywords: Marijuana, youth, mental health, sexual minority, substance use

General Scientific Summary: Throughout adolescence, there is a relationship between cannabis use and symptoms of anxiety and depression. Sexual minority teenagers may be particularly susceptible to using cannabis to cope with symptoms of depression.

Longitudinal associations of cannabis, depression and anxiety in heterosexual and LGB adolescents

Cannabis is one of the most widely used substances (Degenhardt & Hall, 2012), including by adolescents (Leatherdale & Burkhalter, 2012). This may be explained in part by perceptions of cannabis as less harmful than other substances (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). Nonetheless, cannabis use is often associated with mental health issues (Cheung et al., 2010; Fergusson, Horwood, & Swain-Campbell, 2002; Wittchen et al., 2007), including internalizing symptoms such as depression and anxiety. Although the nature and direction of these associations are not well understood, there is evidence they are particularly strong in adolescence (Horwood et al., 2012) and among sexual minority youth (Corliss et al., 2010; Ross et al., 2014). As depression and anxiety both contribute substantially to the global burden of disease (Institute for Health Metrics and Evaluation, 2013), it is imperative to better understand how cannabis use and internalizing mental health issues relate to one another in heterosexual and sexual minority adolescents.

Theoretically, there are several explanations for the relationships between substance use and mental health issues, which may shed light on the cooccurrence of cannabis use and symptoms of depression and anxiety. The Self-Medication (SM) Hypothesis posits that people with psychiatric disorders use certain drugs to alleviate their mental health symptomology (Khantzian, 1985), and thus mental health symptoms would precede later cannabis use. Alternatively, the Secondary Mental Health Disorder (SD) Hypothesis posits that cannabis use may instead precipitate mental health problems, and thus precede them (Santucci, 2012). Furthermore, both hypotheses could coexist, supporting a bidirectional relationship between these variables, which would exacerbate each other across time. It is particularly important to

better understand these relationships during adolescence, which is a formative period during which several developmental milestones occur, in addition to the exploration of new social situations and emotionally-charged experiences. Adolescence is a common period for cannabis initiation (Leos-Toro, Rynard, Murnaghan, MacDonald, & Hammond, 2019) and for the onset of certain depression and anxiety disorders, with earlier onset predicting worse outcomes (Kessler et al., 2005; Wilson, Hicks, Foster, McGue, & Iacono, 2015). However, the relationship between the timing of their onset is poorly understood.

Systematic reviews were conducted to better understand these associations (Gobbi et al., 2019; Esmaelzadeh, Moraros, Thorpe, & Bird, 2018; Lev-Ran et al., 2014; Moore et al., 2007), although all had an exclusive focus on the SD hypothesis. One meta-analysis found the relationship between cannabis use and later depression scores to be dose-dependent (Lev-Ran et al., 2014). Three additional reviews found that cannabis use was a predictor of later depression, but not anxiety, across adolescence and young adulthood (Gobbi et al., 2019; Esmaelzadeh et al., 2018) and in populations of all ages (Moore et al., 2007). Although meta-analyses focused solely on the SD hypothesis, there is some evidence that adolescent depression (Earnshaw et al., 2017; Hawes, Trucco, Duperrouzel, Coxe, & Gonzalez, 2019; Wilkinson et al., 2016; Wittchen et al., 2007) and anxiety (Stapinski, Montgomery, & Araya, 2016; Wittchen et al., 2007) positively predict later cannabis use, supporting the SM hypothesis. To help clarify the direction of the association between cannabis and internalizing symptoms, longitudinal studies consistently looking at bidirectional effects are needed. Furthermore, only a few longitudinal studies explored these relationships across adolescence (e.g., Fleming, Mason, Mazza, Abbott, & Catalano, 2008; Hawes et al., 2019; Meier, Hill, Small, & Luthar, 2015; Stapinski et al., 2016). Examining the relationships between cannabis use, and depression and anxiety repeatedly

throughout adolescence is necessary to understand temporality in onset and the directionality of the associations as well as which theoretical model (the SM or the SD hypotheses, or a combination of the two) can best explain their joint development.

Understanding the associations between cannabis use, and depression and anxiety in sexual minorities is also particularly important, as they report higher rates of cannabis use (Marshal et al., 2008), mental health issues (Marshal et al., 2011) and comorbidity between the two (Espelage, Aragon, Birkett, & Koenig, 2008; Hafeez, Zeshan, Tahir, Jahan, & Naveed, 2017) than their heterosexual counterparts, especially during adolescence (Corliss et al., 2010, Ross et al., 2014). Despite higher rates of cannabis use and mental health issues in sexual minorities, no study to date has evaluated the longitudinal relationships between cannabis use, depression, and anxiety according to sexual minority status in adolescents. Theoretically, a minority stress framework may inform why heterosexual and sexual minority adolescents experience different trajectories with respect to these variables. Minority stress theory (Meyer, 1995; Meyer, 2003) expands stress theory (Lazarus & Folkman, 1984) to explain that chronic stress experienced by a minority group due to stigmatisation and discrimination can accumulate to produce deleterious effects, to which the individual becomes less able to adapt (Institute of Medicine, 2011). In turn, this stress may play an important role in the development of depression and anxiety (Lupien, McEwen, Gunnar, & Heim, 2009) for which substance use has been suggested as a coping tool of choice, particularly in the absence of other coping resources such as access to a supportive environment (Goldbach, Tanner-Smith, Bagwell, & Dunlap, 2014). More specifically, research conducted among adolescents and young adults supports a minority stress framework in describing how minority stressors (e.g., internalized homophobia) predicted both psychological distress and cannabis use, but does not specify directionality between the

latter two variables (Goldbach, Schrage, Dunlap, & Holloway, 2015; Kiekens et al., 2020). Another proposed framework to explain these disparities is the psychological mediation framework proposed by Hatzenbuehler (2009), which extends minority stress theory and posits that minority stressors negatively affect psychological processes, which in turn lead to disparities in psychopathology and substance use. Support for this framework was found by Hatzenbuehler (2009) with minority youth using alcohol for coping purposes at a greater extent than heterosexual youth (supporting indirectly the SM hypothesis). However, another more recent study focusing on cannabis use did not find support for the psychological mediation framework (Kiekens et al., 2020). Although this framework provides some insights as to the potential direction (supports a SM rather than a SD hypothesis) and mechanisms explaining the associations between mental health and substance use problems in sexual minority youth and disparities with heterosexual youth, this literature is still in its infancy and further studies are needed. Key first steps would be: 1) to confirm whether associations between mental health and cannabis use are indeed stronger in sexual minority youth compared with heterosexual youth, as opposed to just a higher prevalence of these problems, and 2) to clarify the direction and nature of these associations.

Accordingly, the present study sought to shed light on the nature of the developmental relationships between cannabis use, and depression and anxiety symptoms across adolescence in heterosexual and sexual minority youth by examining the bidirectional associations over time between these variables assessed at 13, 15 and 17 years. Based on previous empirical findings, we hypothesized that the relationships between cannabis, and depression and anxiety symptoms across adolescence would be bidirectional.

Methods

Sample

Participants were from the Quebec Longitudinal Study of Child Development (QLSCD), a representative sample of 2120 youth born in Québec, Canada in 1997-1998 and followed annually or biennially from infancy to adolescence (Jetté & Des Groseilliers, 2000). Parents were required to speak French or English, and were selected using a stratified procedure based on living area and birth rate via the Québec Birth Registry. Informed written consent from parents and assent from children starting at 13 years was obtained prior to each data collection wave. In adolescence, participants completed a computerized questionnaire. The research protocol was approved by the Québec Institute of Statistics and the Sainte-Justine Hospital Research Centre ethics committees.

Due to attrition and year-to-year variations in participation rates, participants for the present study were a subsample of 1548 participants (1368 heterosexual, 128 sexual minorities, 52 unknown) who reported their cannabis use, depression symptoms, and/or anxiety symptoms at one time point or more. Compared to the remainder of the original sample, participants in the subsample were more likely to be female (OR = 1.6, $p < .001$), have higher family revenue (OR = 1.4, $p = .03$), and have a mother with a university diploma (OR = 1.6, $p = .001$). The samples did not differ on mother's age at birth of the child (OR = 0.9, $p = .18$) or her attainment of a high school diploma (OR = 1.1, $p = .60$). The sample was 51% female. The sample was almost exclusively White (1430; 92%; see Table 1 for full sample racial distribution)

Measures

Main measures

Cannabis use. At 13, 15, and 17 years, adolescents answered the following item based on the Quebec Survey of Tobacco, Alcohol and Drug Use, and Gambling in High School

Students (STADG; Institut de la statistique du Québec, 2007): “During the past 12 months, how often have you used the following drugs: Cannabis?” on a scale from 1 (I did not use) to 7 (Every day).

Due to a pronounced divergence from normality of the cannabis use variable at 13 years (skewness = 7.63, kurtosis = 62.55), we dichotomized this variable ($n = 45$ used in the past year, 3.7%). However, the divergence from normality was lower, and at acceptable levels for the Structural Equation Model (SEM) analyses with the chosen estimator (see analysis section), at 15 years (skewness = 2.29, kurtosis = 4.53) and 17 years (skewness = 1.44, kurtosis = 1.03).

Depression and anxiety symptoms. Past-year depression and anxiety symptoms at 13 years were self-reported using the Child Behavior Checklist (Achenbach & Edelbrock, 1983) on a three-point scale ranging from “Never or not true” to “Often or very true.” There were 3 items on depression (e.g., “I have trouble having fun,” $\alpha = .69$, skewness = 1.44, kurtosis = 2.41) and 4 items on anxiety (e.g., “I am too scared or nervous,” $\alpha = .76$, skewness = .91, kurtosis = .30).

Depression and anxiety symptoms during the past 12 months were self-reported at 15 and 17 years using the Mental Health and Social Inadaptation Assessment for Adolescents (MIA; Côté et al., 2017). This self-report instrument based on the DSM-5 (American Psychiatric Association, 2013) has demonstrated adequate reliability (Côté et al., 2017). Participants answered questions on a three-point scale from “never true” to “always true.” There were 8 items on depression (e.g., “I could not find pleasure in anything, I was not interested in anything,” 15 years $\alpha = .90$, skewness = .55, kurtosis = -.13; 17 years $\alpha = .90$, skewness = .45, kurtosis = -.38) and 9 items on anxiety (e.g., “I had worries that interfered with my everyday life,” 15 years $\alpha = .86$, skewness = .27, kurtosis = -.62; 17 years $\alpha = .84$, skewness = .16, kurtosis = -.56; Fontaine et al., 2019).

Sexual minority status. At 15 and 17 years, participants responded to the following item: “Regarding your attraction and sexual desires, would you say that you are mostly attracted by...” with answer options including attraction to the opposite sex, both sexes, the same sex, or no attraction. Participants were considered part of the lesbian, gay or bisexual (LGB) category if attraction to both genders or to the same gender was reported at 15 and/or 17 years. Analyses showed that participants noting LGB attraction at only one time point closely resembled those who noted so at both time points (i.e., did not differ significantly on any of the variables of interest aside from anxiety at 15 years, with the consistent group reporting a significantly higher mean score than the heterosexual 15/LGB 17 group ($t(90) = 2.14, p=.04$), see Tables S2 and S3 in Supplemental Materials). This is consistent with another study of sexual minority adolescents’ psychological wellbeing and substance use, which showed that results were similar when including adolescents who reported sexual minority status inconsistently or consistently (Kiekens et al., 2020).

Covariates

Mother’s age at the birth of the child and her attainment of a university degree measured at 5 months were included to control for SES as these measures were consistently associated with cannabis use. Household income was not consistently related to any of the study variables, and was thus not included in the models. Sex was consistently associated with depression and anxiety symptoms, and was also included as a control variable.

Other substance use measures

Other substance use was self-reported at 13, 15, and 17 years using items informed by the STADG (Institut de la statistique du Québec, 2007). Alcohol use frequency was assessed for past-year use. Cigarette use frequency was assessed for past-month use. Other drug

experimentation was measured with a dichotomous variable identifying whether any of the following drugs were used in the past year: cocaine, glue or solvents, hallucinogens, heroin, amphetamines, non-prescription medications or others.

Statistical analyses

To examine the bidirectional associations between cannabis use and internalizing symptoms, cross-lag models testing auto-regressive and cross-lagged regression paths were conducted using Mplus 7.4 (Muthén & Muthén, 2012) and maximum likelihood estimation with robust standard errors (MLR). Maximum likelihood can appropriately handle levels of skew and kurtosis of 2 and 7 respectively (Currant, West, & Finch, 1996; Ryu, 2011), and MLR can handle further, even severe, deviations from non-normality (Yuan & Bentler, 2008; Muthén & Asparouhov, 2002). Model fit was evaluated using the model chi-square (χ^2 , acceptable fit $df*3 > \chi^2$), the root mean square error of approximation (RMSEA, acceptable fit < 0.08), the comparative fit index (CFI, acceptable fit $\geq .90$), the Tucker Lewis index (TLI, acceptable fit $\geq .90$) and the standardized root mean square residual (SRMR, acceptable fit < 0.08). 23% of the sample had missing data at 15 and/or 17 years, which were handled using full information maximum likelihood (FIML) under the missing at random assumption. Predictors of missingness within the analysed sample were examined. Sex, mother's education and obtaining a university diploma predicted missingness and were included in all models. Mental health and substance use variables at 13 years did not predict missing data at subsequent follow-up periods.

The first model tested associations between cannabis, and depression and anxiety symptoms at 13, 15, and 17 years while controlling for mother's education and age at birth of the child as well as sex. A multigroup analysis was then conducted to examine these associations in heterosexual and LGB participants. The second and third models incorporated alcohol, cigarette,

and other drug use as controls to examine whether associations were specific to cannabis use in the direction of both the SM and SD hypotheses. That is, in the SM hypothesis model (model 2), cannabis use variables were regressed on other substance use variables from the previous assessment to examine whether cannabis use could still be explained by the mental health variables while accounting for other substance use. In the SD hypothesis model (model 3), the mental health variables were regressed on other substance use variables to examine if relationships were cannabis-specific. These models were also examined in the heterosexual and LGB groups using multigroup analysis. To test whether associations differed by sexual orientation, two approaches were used: 1) the Satorra-Bentler Chi-Square Difference Test (Satorra & Bentler, 2010), which tests moderation by comparing significant change in model fit (chi-square) when the path of interest is constrained to be equal across sexual minority groups, and 2) the Wald test, using the “model test” function in Mplus, which tests whether effect sizes differ significantly across groups.

Results

Descriptive statistics

Among the 1548 participants, 1368 were heterosexual, 128 were sexual minorities, and 52 were unknown due to nonresponse. Of the 128 sexual minority participants, 15 were gay, 15 were lesbian, 22 were bisexual boys and 74 were bisexual girls. As 2 participants had missing information for sex, specific orientation could not be established. For the 6 participants who reported a different minority sexual orientation between both time points, the identity indicated at 17 years was reported. The distribution of sexual minorities differed significantly according to sex ($\chi^2(1, n = 1472) = 18.41, p < .001$), but was similar according to race (exclusively White vs other; $\chi^2(1, n = 1494) = 1.72, p = .19$). Table 1 presents the demographic characteristics of the full

sample as well as by sexual orientation, and Table 2 presents the descriptive statistics of the sample on key variables as well as comparative statistics for heterosexual and LGB participants. The following were higher in LGB participants ($p \leq .05$): depression and anxiety symptoms at every age, the proportion of cannabis users at 13 and 15 years, the proportion of other drug users at every age, mean cigarette use at 13 and 17 years, and frequency of cannabis use at 15 years. Correlations between all variables are reported in supplemental materials (Table S1).

Cross-lag models

Model 1 – Cannabis, depression and anxiety in full sample and by sexual minority status

Figure 1 shows the results of Model 1, which examined the associations between cannabis use, depression symptoms, and anxiety symptoms at 13, 15, and 17 years. The model in the full sample (Figure 1A) had excellent fit: $\chi^2(24) = 68.9$, RMSEA = .04, 90% CI [0.025, 0.045], CFI = .99, TLI = .97, SRMR = .02. The three variables were moderately stable across time, with auto-regressive paths ranging from $\beta = .24$ to $\beta = .56$. Four significant, but small, cross-lagged regression paths between cannabis and mental health symptoms were found: cannabis use at 13 years was positively associated with depression symptoms ($\beta = .08, p = .003$) and anxiety symptoms ($\beta = .05, p = .014$) at 15 years; depression symptoms at 15 years were positively associated with cannabis use at 17 years ($\beta = .13, p < .001$) and cannabis use at 15 years was positively associated with anxiety symptoms at 17 years ($\beta = .06, p = .018$).

Differences according to sexual minority status were examined through a multigroup analysis, depicted in Figures 1B and 1C. Model fit was excellent: RMSEA = .04, CFI = .98, TLI = .96, SRMR = .03. The χ^2 contribution was greater in the heterosexual group (χ^2 contribution = 90.04) than in the LGB group (χ^2 contribution = 23.69), signalling better model fit for the LGB group. Auto-regressive, as well as cross-lagged paths in heterosexual participants were similar to

those found in the full sample. In the LGB group, while auto-regressive paths were similar to the full sample, a different pattern of cross-lagged associations emerged: depression symptoms at 15 years were again positively associated with cannabis use at 17 years, but significantly more strongly than in the heterosexual sample ($\beta = .42, p < .001$; $\chi^2 \text{ diff}(1) = 12.37, p < 0.001$; Wald (1) = 9.71, $p < 0.01$), and anxiety symptoms at 15 years were significantly and negatively associated with cannabis use at 17 years ($\beta = -.25, p = .009$; $\chi^2 \text{ diff}(1) = 6.19, p = 0.013$; Wald (1) = 5.07, $p < 0.05$).

Models 2 and 3 – Cannabis, depression and anxiety in full sample and by sexual minority status, controlling for other substance use.

Models 2 and 3 controlled for alcohol, cigarette, and other drug use to test for cannabis-specificity according to the SM and SD hypotheses, respectively. The results of Model 2 examining the SM hypothesis are presented in Figure 2. The model fit in the full sample (Figure 2A) was excellent: $\chi^2(62) = 217.7$, RMSEA = .04, 90% CI [0.035, 0.046], CFI = .97, TLI = .94, SRMR = .04. Auto-regressive paths were slightly smaller than in Model 1, ranging from $\beta = .18$ to $\beta = .43$. Cross-lagged associations were similar to those in Model 1, with, for example, depression symptoms at 15 years positively predicting cannabis at 17 years, $\beta = .11, p = .006$. However, multigroup analyses showed that this relationship was significant for LGB participants (Figure 2C, $\beta = .38, p < .001$), but non-significant in the heterosexual group (Figure 2B, $\beta = .06, p = .12$; path differed significantly across groups: $\chi^2 \text{ diff}(1) = 10.35, p = 0.001$; Wald (1) = 9.91, $p < 0.01$). All the other paths remained similar to Model 1 when controlling for other drug use.

The results of Model 3 examining the SD hypothesis are presented in Figure 3. The model fit in the full sample (Figure 3A) was good: $\chi^2(52) = 188.94$, RMSEA = .04, 90% CI [0.035, 0.048], CFI = .97, TLI = .93, SRMR = .04. Both paths where cannabis positively

predicted later anxiety symptoms remained significant when controlling for other substance use. However, the positive relationship between cannabis at 13 years and depression symptoms at 15 years found in Model 1 became non-significant ($\beta = .02, p = .48$); instead alcohol use at 13 years predicted depression at 15 years ($\beta = .06, p = .03$). Multigroup analyses showed that in the heterosexual group (Figure 3B), only trends for associations were found between cannabis at 13 years and anxiety symptoms at 15 years ($\beta = .06, p = .08$; χ^2 diff and Wald tests were non-significant) as well as depression at 15 years ($\beta = .05, p = .09$). In the LGB group, cannabis use at 13 was negatively associated with depression symptoms at 15 years ($\beta = -.25, p = .002$; χ^2 diff (1) = 10.35, $p = 0.001$; Wald (1) = 15.03, $p < 0.001$) once alcohol and drug use at 13 years were entered into the model, both of which were significantly and positively associated with depression symptoms at 15 (alcohol use: $\beta = .22, p = .018$; other drug use: $\beta = .22, p = .015$; both χ^2 diff $p < .025$, but Wald tests only at trend level: $p < .057$ and $p = .085$, respectively). Anxiety symptoms at 15 years were significantly predicted only by alcohol use at 13 years ($\beta = .17, p = .042$; χ^2 diff (1) = 5.06, $p = 0.025$; Wald (1) = 3.73, $p = 0.053$) in this group.

Discussion

The main aim of this study was to examine the potential bidirectional relationships between cannabis use and symptoms of depression and anxiety across adolescence in heterosexual and LGB youth, using three time points to parse out the developmental sequence between the variables. A cross-lagged approach was used, which allowed to simultaneously test for predictive relationships between cannabis and mental health symptoms. Results from the full sample provide background on these relationships in adolescents in general. This revealed bidirectional relationships, with cannabis use positively predicting later anxiety symptoms across adolescence, reflecting the SD hypothesis, and depression symptoms at 15 years positively

predicting cannabis at 17 years, consistent with the SM hypothesis. Another positive relationship was initially found between cannabis at 13 years and depression symptoms at 15 years, but this association was accounted for by other substances, namely alcohol use. These findings support our initial hypothesis for adolescents in general, suggesting a complex developmental interplay between cannabis use, and depression and anxiety symptoms, supporting both the SM and the SD hypotheses.

Our findings echo those of another longitudinal study which examined the links between adolescent cannabis use and mental health disorders at 29 years, and found a small relationship between cannabis use (particularly daily use) and later anxiety disorders, but not mood disorders (Degenhardt et al., 2013). As for pathways from internalizing symptoms to cannabis use, we found that symptoms of depression, but not anxiety, predicted later cannabis use, which is partially consistent with another study that found that both mood and anxiety disorders in adolescence predicted cannabis use by young adulthood, with effects being stronger for mood disorders than anxiety disorders, but still small in both cases (Wittchen et al., 2007). These findings suggest substantial differences between the cannabis-depression relationship and the cannabis-anxiety relationship. This signals that the collapsing of anxiety and depression symptoms into the category of “internalizing symptoms,” as is commonly done when studying these disorders, especially in adolescence (Hayatbakhsh et al., 2007), might obscure differences in their unique associations with cannabis use. These should be examined separately in order to clarify associations with cannabis use and potentially other substance use. Furthermore, these relationships may be bidirectional, and future research on these variables should be constructed in a way that allows for bidirectional analyses.

It is important to note that, although our findings on the full sample are consistent with previous research, these bidirectional relationships detected in the full sample were small, and of limited clinical relevance. Instead, it is when we examined the heterosexual and LGB subsamples that the clinical relevance of the associations became clearer. We first note that the cross-lagged links in the heterosexual group were small and overall quite similar to those of the full sample, but lost significance. Indeed, only trends were found in this group for paths supporting the SD hypothesis, i.e., cannabis use at 13 predicting anxiety and depression at 15 years. This differed significantly from associations found in the LGB group, for whom other substance use at 13 years significantly and positively predicted both anxiety and depression at 15 years (alcohol predicted both and other drug use predicted depression only), and cannabis use at 13 negatively predicted depression symptoms at 15 years once alcohol and other drugs were accounted for. This suggests that particular patterns of substance use matter, and different drugs, or their combination, may be differentially associated with mental health issues. Further, the only path congruent with the SM hypothesis found within the full sample (depression symptoms at 15 years positively predicting cannabis use at 17 years) was no longer significant among the heterosexual participants, but was significant and much larger among the LGB participants. Moreover, one new moderate-sized and clinically relevant association emerged in the LGB group: higher anxiety symptoms at 15 years predicted lower cannabis use at 17 years, which is consistent with neither the SM nor the SD hypotheses. This finding is important for a number of reasons. First, the fact that depression and anxiety symptoms were associated with later cannabis use in opposite directions (positively and negatively, respectively), speaks once again to the need to examine these separately. Interestingly, these findings are congruent with a study of substance use in sexual minority men, which report a pathway from internalized homophobia to substance

use through depression, but not through sexual anxiety (i.e., worries around the sexual aspects of one's life; Moody, Starks, Grov, & Parsons, 2018). In the present analysis in LGB youth, depression symptoms emerged as a risk factor for later cannabis use, whereas anxiety symptoms emerged as a protective factor for later cannabis use. This suggests that anxiety and depression may be the reflections of different difficulties related to sexual minority status. For example, among sexual minorities, anxiety has been linked to avoidance of others and close relationships to avoid discovery of their identity, and subsequent rejection (Hatzenbuehler, 2009). This social isolation in sexual minorities could lead to fewer occasions for cannabis use, at least in early to mid-adolescence (the developmental period studied here). While a sizeable minority of youth report using cannabis to cope with their problems, cannabis use in adolescence is mostly a social activity (Terry-McElrath, O'Malley, & Johnston, 2009) and most adolescents do not use alone (Creswell, Chung, Clark, & Martin, 2015). Conversely, depression symptoms could reflect factors such as peer victimization and a diminished sense of belonging (Collier, van Beusekom, Bos, & Sandfort, 2013), as well as feelings of internalized homophobia (Goldbach et al., 2014), and lead to a greater need to dissociate from reality, in this case, by using cannabis. A key factor in these relationships may then be "out" status (i.e., whether one has disclosed sexual minority status or not), which we unfortunately did not document, in determining whether stressors were internal or external. For example, one study found that sexual minority youth whose parents were unaware of their sexual identity had more fear of harassment or rejection by the parents than those whose parents were aware (D'Augelli, Grossman, & Starks, 2005), which could also be a key contributor to anxiety and social isolation. However, another study outlined the risk of "depreciation" (i.e., that the coming out process would have a negative impact on the person's wellbeing). This was linked with more negative feelings toward homosexuality and one's own

sexual orientation and negative social reactions (Solomon, McAbee, Asberg, & McGee, 2015), and may reflect a risk for depression. Another study found that, among bisexual participants, being out was associated with increased cannabis use as well as increased depression (Feinstein et al., 2019), which supports the potential importance of “outness,” particularly among certain sexual minority subgroups. Thus, “outness” (with respect to friends and parents) should be examined in future studies to better understand these differential relationships. Another crucial aspect to examine in future research is the social context, through social norms and networks. Social context may be a particularly important factor in explaining substance use disparities in both sexual minority adults (Cochran, Grella, & Mays, 2012; Hatzenbuehler, Corbin, & Fromme, 2008) and adolescents (Hatzenbuehler, McLaughlin, & Xuan, 2015), as substance use is more widespread and accepted in sexual minority communities. Additionally, one study of sexual minority adolescents found that community connectedness and internalized homophobia were both significant predictors of later cannabis use, but were negatively associated with one another (Goldbach et al., 2015). This may signal two different experiences that could be related to outness, and could potentially explain our finding that depression at 15 years predicted cannabis use at 17 years. Specifically, as mentioned above, peer victimization and internalized homophobia after coming out may be one avenue toward increased cannabis use, while enjoying community connectedness and its associated social norms of increased substance use may be another. These intersections should be explored in future research.

A second implication of this finding is that sexual minority status may exacerbate the relationship between symptoms of depression and cannabis use. One key clinical consideration is that this strong SM relationship between depression symptoms and later cannabis use may signal a lack of alternative coping mechanisms for some sexual minority youth. Indeed, factors that

have been linked to substance use among sexual minorities, such as lower self-efficacy (Tucker, Ellickson, & Klein, 2008), as well as lower life satisfaction and higher stress levels, especially related to the coming out process (Padilla, Crisp, & Rew, 2010; Rosario et al., 2009; Schauer, Berg, & Bryant, 2013), may explain why sexual minority youth would be less likely to possess healthier coping resources such as accessing therapy, or engaging in activities like arts or sports. Accordingly, and relatedly to the hypothesized relationship between cannabis use and depression symptoms as a reflection of internalized homophobia posited above, one study found that participants who declined to disclose their sexual orientation were more likely not to seek treatment for their depression (Rutter et al., 2016). This is detrimental in light of the current findings identifying depression symptoms as an important precursor of cannabis use in this group. Clinicians and support providers should be better trained to recognize important precursors of cannabis use (like depression) and better understand the particular psychosocial challenges that sexual minority teenagers face. Future research should also longitudinally examine the relationships between internalizing symptoms and other substance use, namely alcohol and other drug use, which we found predicted depression and anxiety at age 15 in the LGB group.

While contributing several important results, the present study has certain limitations which must be considered when interpreting the findings. While the initial sample was representative of the broader population, attrition led to a sample that had higher SES (i.e., higher family revenue, and more highly educated mothers) and was composed more prominently of female participants. These were controlled for in analyses, and our findings share some similarities to those of a study that evaluated cannabis, depression, and anxiety in a sample of at-risk youth, and found that that depression, but not anxiety was a predictor of later use (Hawes et

al., 2019). Nonetheless, the generalizability of our findings should be interpreted with caution and may not extend to participants with lower SES and should be examined in more economically diverse populations. The sample was also almost entirely exclusively White (92%), with the LGB group being especially White (95%), including only seven LGB adolescents of colour, and thus results cannot represent the diversity of experiences of other racial groups and should not be generalized to non-exclusively-White LGB adolescents. This is particularly important given that Black, Indigenous and mixed-race adolescents have shown elevated rates of cannabis use when compared with White, Asian and Hispanic adolescents, signaling that cannabis use may function differently in these communities (Wu, Brady, Mannelli, Killeen, & Workgroup, 2014; Wu, Zhu, & Swartz, 2016). In our study, Black and Indigenous identities were only reflected in one participant of the LGB subsample, constituting an important gap. Although we found that there were no statistically significant differences between the distributions of sexual minorities by race, these analyses had limited power, and the examination of all racial minorities as one group did not account for the diversity of their experiences. Unfortunately, with a racial distribution of less than 1% of the sample in each racial minority group, examining each racial group separately was not possible. These distributions and relationships should thus be examined in more racially and economically diverse populations. Furthermore, while this lack of racial diversity in the sample (making it a more homogeneous sample) allowed better isolation of sexual orientation as a minority status, belonging to several minority groups may have additive or interactive effects in terms of the associations between cannabis use and mental health, which could be examined in more diverse samples. Additionally, reflecting the higher proportion of female participants in the general sample, and perhaps also gender norms around sexual fluidity, our sexual minority group had a majority of female participants. Furthermore, while attraction

can be a component of sexual minority status, it is not synonymous with sexual identity nor with other important components such as self-identification and sexual minority behaviours (Lhomond, Saurel-Cubizolles, Michaels, & Group, 2014). The findings from this study may not be generalizable to sexual minorities as operationalized through other definitions. Our study has other methodological limitations, namely that while we could clarify directionality between the variables, all associations remain correlational and do not demonstrate causality. Additionally, although cross-lag models are well suited for examining bidirectional or reciprocal effects across factors longitudinally, cross-lag paths may represent inter-individual differences, as well as intra-individual differences (Hamaker, Kuiper, & Grasman, 2015). Furthermore, the data were self-reported, which may have limited the disclosure of illegal activities (i.e., drug use). However, self-reports were shown to be reliable for substance use (Clark & Winters, 2002). The small size of the LGB group also led to two limitations. First, differences in power between the heterosexual and LGB groups may have made it difficult to detect small sized effects in the LGB group. However, the differences found showing stronger associations in the LGB group remain robust in spite of this limitation. Second, we had to collapse sexual identities. While we did not have sufficient power to stratify our analyses by sex and by sexual orientation, future research should explore these different groups further, as certain groups, i.e., bisexual individuals (e.g., Ross et al., 2014), particularly bisexual women (Schauer et al., 2013) were shown to have substantially higher rates of substance use. Furthermore, gender identity should also be examined, as trans individuals, particularly trans women, also have higher rates of cannabis use and mental health issues (Newcomb et al., 2020; Reisner et al., 2016), and some research suggests that this group may use cannabis as a coping mechanism (Guzman-Parra et al., 2014).

In conclusion, our study detected certain small bidirectional effects between cannabis, and symptoms of depression and anxiety in the general sample. However, once other substance use was accounted for, the associations supporting the SD hypothesis for cannabis and depression were less clear, with results suggesting that these were more consistent for alcohol use and only significant in sexual minority youth. In general, relationships were much larger in LGB youth, who exhibited a considerable and robust SM relationship between depression symptoms and cannabis. We also found support for differential relationships between cannabis and depression symptoms (consistently positive from depression symptoms at 15 years to cannabis at 17 years) versus cannabis and anxiety symptoms (negative prediction from anxiety symptoms at 15 years to cannabis at 17 years) in LGB youth. Our findings provide ground for future studies to explore further the moderating effect not only of sexual minority status, but also of individual orientations and gender identity.

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Figure Captions

Figure 1. Bidirectional associations between cannabis use, depression and anxiety for (A) all participants, (B) heterosexual participants and (C) sexual minority participants. Note: paths in bold and * = $p < .05$. All model coefficients and p values are provided in Supplemental materials Table S4.

Figure 2. Bidirectional associations between cannabis use, depression and anxiety for (A) all participants, (B) heterosexual participants and (C) sexual minority participants, controlling for earlier alcohol, cigarette and other substance use. This model examines cannabis-specificity in the direction of the SM hypothesis. Note: Only cross-lagged paths in the tested direction are included. Paths in bold and * = $p < .05$. All model coefficients and p values are provided in Supplemental materials Table S4.

Figure 3. Bidirectional associations between cannabis use, depression and anxiety for (A) all participants, (B) heterosexual participants, and (C) sexual minority participants, controlling for earlier alcohol, cigarette and other substance use. This model examines cannabis-specificity in the direction of the SD hypothesis. Note: Only cross-lagged paths in the tested direction are included. Paths in bold and * = $p < .05$. All model coefficients and p values are provided in Supplemental materials Table S4.

Table 1. *Demographic characteristics of the sample*

	Full sample (n = 1548)		Hetero (n = 1368)		LGB (n = 128)	
	n	%	n	%	n	%
Sex (female)	796	51.42	682	49.85	89	69.53
Race/ethnicity						
White	1430	92.38	1264	92.40	121	94.53
Black	23	1.49	22	1.61	0	0.00
Latin American	12	0.78	9	0.66	1	0.78
Arabic/West Asian	16	1.03	12	0.88	2	1.56
Southeast Asian	10	0.65	9	0.66	1	0.78
South Asian	6	0.39	6	0.44	0	0.00
East Asian	2	0.13	1	0.07	0	0.00
Indigenous	3	0.19	3	0.22	0	0.00
Other	18	1.16	18	1.32	0	0.00
Unspecified	2	0.13	2	0.15	0	0.00
Mixed	26	1.68	22	1.61	3	2.34
Mother's university degree (% yes)	450	29.09	409	29.92	33	25.78
Mother's age in years (mode)	30-34		30-34		30-34	

Note. LGB= Lesbian, gay and bisexual. Sex was unknown for 24 participants (1.6%). Unknown sexual minority statuses are due to missing data at both 15 and 17 years. Ethnic groups are determined by participants' parents self-report at 5 months with specific groups referring to exclusive identification (e.g., the "Black" group was comprised of participants identifying solely as Black, whereas the mixed group represents participants of various ethnicities).

Table 2

Descriptive Statistics on key variables for the full sample and according to sexual orientation

	Full Sample (n = 1548)		Skew	Kurtosis	Hetero (n = 1368)		LGB (n = 128)		p	Hetero	LGB	p
	M	SD			M	SD	M	SD		# users (n = 1368)	# users (n = 128)	
Variables at age 13												
Cannabis										34	8	.02
Depression	1.56	1.63	1.44	2.41	1.51	1.6	1.94	1.87	.02			
Anxiety	2.42	2.39	0.91	0.30	2.32	2.32	3.25	2.81	.001			
Alcohol	1.39	0.90	2.67	7.62	1.37	0.87	1.5	1.02	.23			
Cigarettes	0.14	0.47	4.53	26.05	0.12	0.43	0.28	0.67	.02			
Other Drugs										14	4	.05
Variables at age 15												
Cannabis	1.64	1.36	2.29	4.53	1.61	1.33	1.98	1.69	.02	298	40	.02
Depression	3.49	2.25	0.55	-0.13	3.39	2.21	4.63	2.34	<.001			
Anxiety	4.10	2.17	0.27	-0.62	4.03	2.17	4.96	2.04	<.001			
Alcohol	2.41	1.34	0.46	-0.71	2.43	1.33	2.36	1.39	.59			
Cigarettes	0.44	0.85	2.44	6.43	0.43	0.83	0.61	1.03	.06			
Other Drugs										72	16	.001
Variables at age 17												
Cannabis	2.16	1.72	1.44	1.03	2.13	1.69	2.49	1.99	.06	463	52	0.45
Depression	3.81	2.32	0.45	-0.38	3.7	2.25	4.99	2.58	<.001			
Anxiety	4.40	2.19	0.16	-0.56	4.3	2.15	5.5	2.23	<.001			
Alcohol	3.27	1.33	-0.29	-0.67	3.29	1.32	3.23	1.39	.68			
Cigarettes	0.67	1.04	1.85	3.02	0.66	1.03	0.85	1.1	.05			
Other Drugs										120	20	.03

Note. M = Mean, SD = Standard deviation, LGB= Lesbian, gay and bisexual. Cannabis was measured by past-year use (yes/no) at 13

years, and frequency of use from 1 (I did not use) to 7 (Every day) at 15 and 17 years. Depression and anxiety symptoms were

measured on a three-point scale of 3 and 4 items, respectively, at 13 years, and 8 and 9 items, respectively, at 15 and 17 years. Alcohol

and cigarette use were assessed as a past-year and past-month frequency, respectively, at all ages. Other drug use was measured by

past-year use (yes/no) at all ages.