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Exploring Issues of Substance Use Among Special Populations

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Exploring Issues of Substance Use Among Special Populations

by

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Under the Direction of Lucy Popova, PhD

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Abstract

Reducing the burden of tobacco and drug use in the United States (U.S.) is a public health priority. Certain populations are at higher risk of harms associated with tobacco and cannabis use, including youth and people with mental health issues. For tobacco, adults with symptoms of serious psychological distress (SPD) smoke at higher rates than those without SPD. Youth who use tobacco have a greater lifetime risk of serious disease, such as lung cancer compared to youth who do not initiate tobacco use. Some research has shown that cannabis use is associated with risk to youth, including changes in neurodevelopment.

Through three distinct, yet related studies, these topics were explored. The first study was a systematic review and meta-analysis of longitudinal studies looking at the association between cannabis use and depression. We found that the odds of developing depression for cannabis users was 1.36 (95% CI: 1.06, 1.52) compared to non-user controls. The second study took a qualitative approach to explore modification behaviors among adolescent electronic nicotine delivery system (ENDS) users. Our study found that youth are making modifications that are both intended and unintended by the manufacturer. Among our sample, the most mentioned modifications were to the e-liquids. The final paper looked at quit intentions among smokers with SPD through quantitative analyses. For our sample of 1,004 adult smokers, those with SPD were significantly more likely to report intentions to quit smoking and seek counseling than smokers without SPD, controlling for covariates.

The purpose of this dissertation was to address the research questions related to tobacco and cannabis use with special focuses on youth and on mental health with the goal to help reduce the public health burden associated with tobacco and drug use, especially among those who are most vulnerable.

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Dedication

This Dissertation is dedicated to my parents, William and Rose Churchill, who were with me when I started this journey. And to my daughter, Audrey, who is with me at the end.

Acknowledgements

First, I would like to acknowledge my husband, Allen, for all his support throughout this process. Without him, I do not know if I would have been successful in this endeavor. We both made it through the past four years together as a team, and I know we will continue to succeed in the future.

I would like to thank my friends who were there to encourage me, get me out of the house, and let me share my highs and lows: Melissa Schink, Jillian Jantosciak, Aidan O'Connor, and Megan Hanby. I also want to thank my "GSU family" for going through this journey with me – I've learned a lot from all of you!

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Finally, there have been many people in my life that motivated me to get to where I am now, more than I can fit on a single page. I want to acknowledge those that provided support including (but not limited to): Laura Wulach, Kelly Hughes, Mason Betha, and Benita Jackson.

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Chapter 1: Literature Review and Statement of Purpose

Overview

Reducing the burden of tobacco and drug use in the United States (U.S.) is a public health priority.[1] There are currently more than 34 million adult cigarette smokers in the U.S., and cigarette smoking is responsible for almost half a million deaths per year in the U.S. alone.[2] Despite the documented harms of tobacco products, it remains a legal drug worldwide. Cannabis (also commonly called "marijuana") is a drug of mixed legality, both across the globe and within the U.S., though it remains an illegal drug at the U.S. federal level. It is the most commonly used illicit drug in the U.S. and many questions remain about the level of harm associated with its use.[3–6] There are many intricacies of tobacco and cannabis use that need to be considered in research, such as method of use, amount of use, and even the social context in which use occurs. Therefore, in order to reduce the public health impact, it is imperative that researchers understand the complexities of how and why people use drugs such as tobacco and cannabis.[7]

Certain populations are at higher risk of harms associated with tobacco and cannabis use, including youth and people with mental health issues. For tobacco, adults with symptoms of serious psychological distress (SPD) smoke at higher rates than those without SPD.[8] Smokers with SPD have twice the risk of death compared to non-smokers with SPD.[9] Youth who use tobacco have a greater lifetime risk of serious disease, such as lung cancer and chronic obstructive pulmonary disease (COPD), compared to youth who do not initiate tobacco use.[10] While there is still controversy in the field of cannabis, some research has shown that use is associated with risk to youth, including changes in neurodevelopment.[11,12] Some research has been conducted looking at the relationship between cannabis use and mental health disorders. A recently published overview of systematic reviews found that there was a positive association

between cannabis use and mental health disorders, including suicidal ideation, depression, and anxiety, although this review combined cross-sectional and longitudinal studies, so it is difficult to determine if cannabis use was a precursor for mental health disorders, or occurred simultaneously.[13]

This dissertation presents original research on three distinct, yet interrelated topics through three types of analyses. The first study is a systematic review and meta-analysis of cannabis use and depression; the second study is a qualitative study of youth electronic nicotine delivery system (ENDS) users, specifically investigating how and why they make modifications to their devices; the final study is a quantitative analysis that looks at how smokers with SPD differ in their intentions to quit smoking, compared to smokers without SPD. By utilizing different analytic strategies, this dissertation highlights the range of possibilities of study designs in the field of tobacco and substance use research and offers suggestions for future research. Ultimately, the goal of this dissertation is to shine a light on the serious need to minimize harms associated with tobacco and cannabis use.

Study 1: Meta-analysis on cannabis use and depression

Approximately 200 million people worldwide have ever used or are currently using cannabis in some form.[14,15] Laws and practices surrounding cannabis vary greatly by country, and in the U.S. there has been a push for the decriminalization of the medical and retail use of cannabis. Public support of cannabis decriminalization has skyrocketed in recent years, and as of 2021 only 8% of adults in the U.S. believe all cannabis should be illegal.[16] However, cannabis research has faced many challenges that has led to gaps in our knowledge of the consequences and benefits to this drug.

One research gap is in understanding the relationship between cannabis use and mental health, specifically if cannabis use leads to common psychological disorders such as depression. In 2014, Lev-Ran et al. published a meta-analysis investigating the development of depression among cannabis users who were not depressed at baseline.[17] Their systematic review of the literature concluded in December, 2012, and was not limited to any country, language, or age group. They included studies that either assessed the clinical diagnosis or symptoms of major depressive disorder (MDD) or dysthymia (mild chronic depression).[18] The authors identified fourteen studies for their meta-analysis and found that cannabis use was associated with a higher odds of developing depression among adults (OR: 1.17, 95% CI: 1.05, 1.30). This meta-analysis did look at the relationship between heavy vs non-heavy cannabis use and depression, and age of cannabis initiation and depression, but results for both subgroup analyses were underpowered due to the small number of studies included.

Considering the changing landscape of cannabis in the U.S. and globally, an update to the Lev-Ran et al. meta-analysis is warranted. While other meta-analyses have been conducted since 2014, they did not look specifically at the relationship between cannabis use and depression among all ages.[19,20] Furthermore, it is particularly important to address the issue of mental health in the U.S. Studies have shown that rates of depression in the U.S. have increased, especially in the past two years during the COVID-19 pandemic.[21,22] The purpose of this update was to find additional studies since 2013 to add to the original meta-analysis and further explore the relationship between cannabis use and depression.

Study 2: Qualitative analysis on modification behaviors of adolescent ENDS users

The second paper looked at how youth ENDS users modify their devices using qualitative exploration. It is widely accepted that youth vaping is an epidemic in the United

States,[23,24] with current estimates indicating that approximately 27.5% of high school students and 10.5% of middle school students are currently using ENDS products.[25] Understanding how and why youth use ENDS devices is a public health priority. This study was an expansion on previous research on ENDS modifications by our team, specifically a content analysis of YouTube videos about modifications[26], and a qualitative study of modifications among adult ENDS users.[27] The content analysis of YouTube videos laid the foundation for this research, and it involved the coding of 168 videos from YouTube that were related to ENDS modifications. The majority of the videos were "how to" videos (88.1%) providing step-by-step instructions for modifications, and about two-thirds (63.1%) presented modifications as favorable. This study highlighted the fact that YouTube is an easily accessible platform with a plethora of information, including step-by-step videos, on ENDS modifications. What is particularly concerning is that YouTube is social media platform that approximately 85% of children aged 13-17 reported using regularly.[28] Therefore, it is reasonable to assume that at least some of the content about ENDS modifications was being viewed by children. To investigate what ENDS modifications were happening, the next study interviewed adult ENDS users about their modification behaviors. In this study, we found that adults modified several components of their devices, including the battery, the cotton/wick, and the e-liquid. Though this was not a representative sample of adult ENDS users, it did help to elucidate some topics for further research, namely the fact that new ENDS devices were arriving to the market that reduced the need for user-modifications. Based on these findings, the next logical step was to interview youth ENDS users about their modification behaviors and reasonings, which is what this dissertation presents in Chapter 3.

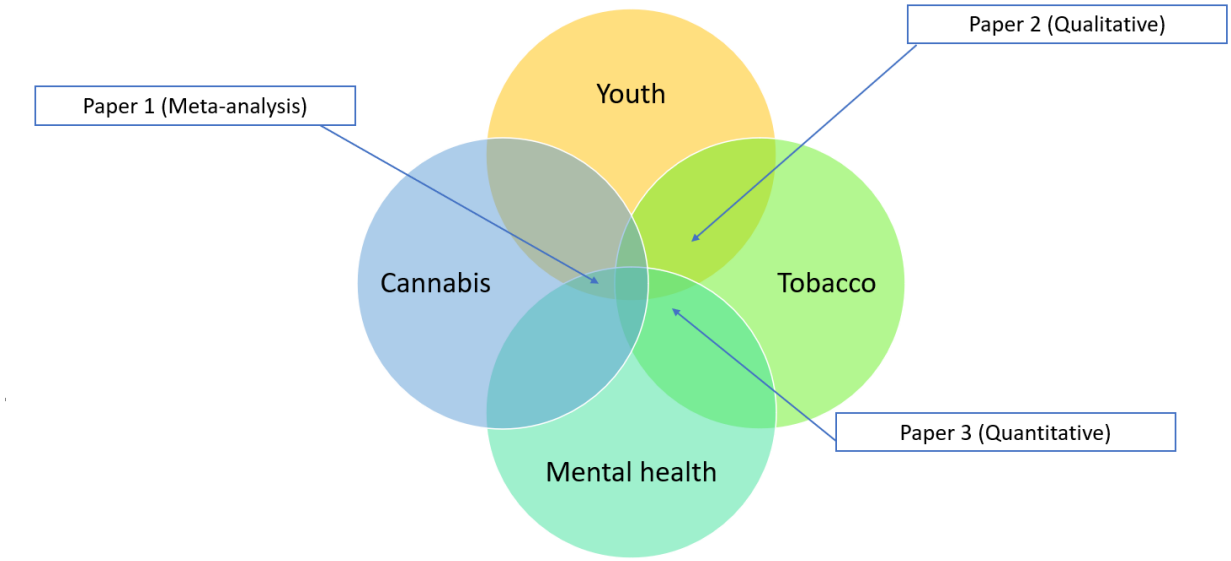
Study 3: Quantitative Analysis

The third paper looked at SPD and quit intentions among adult smokers during the COVID-19 pandemic, in a time when there was debate about how smoking status impacted COVID-19 outcomes.[29–31] Previous research using national cross-sectional data by Kulik and Glantz (2017) found that more smokers with SPD had at least one quit attempt, compared to smokers without SPD;[32] however in their study, past 12-month quit attempts were measured along with past-30 day SPD, which limited the interpretation of the relationship between the two. Yet, it did provide a basis for further investigating how SPD and smoking behaviors were related. In a study by Yang et al., 2019, they explored the role of SPD on quit intentions among current smokers using an online experiment of harm messages.[33] This study found that smokers who had SPD were more likely to report intentions to seek help to quit smoking, compared to smokers without SPD. Their study was conducted prior to the COVID-19 pandemic, and so it is reasonable to reevaluate SPD and quit intentions among smokers since the start of the pandemic. Although the full impact is still not known, the pandemic has had a global impact both on stress[21] as well as on smoking.[34] The third paper in this dissertation examined the prevalence of SPD among current smokers; the associations between SPD, personal characteristics, and smoking and COVID-19 protective behavioral intentions; and whether SPD moderated the effect of messages about risks of smoking and COVID-19.

Statement of Purpose

The overarching theme of this dissertation is to delve deeper into specific issues of tobacco and cannabis use, particularly related to issues of youth use as well as mental health. Through three distinct, yet related studies, these topics were explored. The integration of the themes can be visualized in **Figure 1.1**.

Figure 1.1 Three papers and integration of themes.



The three papers work together to elucidate areas of important research. The meta-analysis and quantitative papers investigate the relationship between mental health and substance use. Based on the theories of comorbidity, as well as previous research in this area, we can hypothesize that psychological disorders can both impact and be impacted by drug use.[35] Youth are also a special population for which there is a need for more substance use-related research. The qualitative paper focused solely on youth behaviors with ENDS, while the meta-analysis paper attempted to explore early onset (i.e., onset of use as a youth) and mental health. Finally, while not a specific focus of this dissertation, it is important to point out that the data collection for the qualitative and quantitative papers occurred during the COVID-19 pandemic, which is a major historical event that has undoubtedly had an influence on substance use behaviors.[36,37]

Chapter 2: Systematic Review and Meta-analysis of Cannabis and Depression

Introduction

Cannabis is the most widely used illicit drug, with approximately 2.5% of people worldwide currently using cannabis in some form.[14,15] In the United States (US), about 18% of Americans aged 12 and older reported having ever used cannabis in 2019[38] and in 2020 there were 2.8 million new cannabis users in the US, of which about 1 million were adolescents aged 12-17, according to the National Survey on Drug Use and Health.[39] Laws and practices surrounding cannabis vary greatly by country, and in the United States there has been a push for the decriminalization of the medical and retail use of cannabis.[40,41] Public support of cannabis decriminalization has skyrocketed in recent years, and as of 2021 only 8% of adults in the U.S. believe all cannabis should be illegal.[16] However, cannabis research has faced many challenges leaving gaps in our knowledge of the consequences and benefits to this drug.

One research gap is in understanding the relationship between cannabis use and mental health, specifically if cannabis use leads to common psychological disorders such as depression. In 2014, Lev-Ran et al. published a meta-analysis investigating the development of depression among cannabis users who were not depressed at baseline.[17] Their systematic review of the literature concluded in December 2012, and was not limited to any country, language, or age group. They included 14 studies that either assessed the clinical diagnosis or symptoms of major depressive disorder (MDD) or dysthymia (mild chronic depression).[18] They found that cannabis use was associated with a higher odds of developing depression among adults (OR: 1.17, 95% CI: 1.05, 1.30). Lev-Ran et al. also conducted meta-regressions on the age of cannabis onset (aged 18 years or younger compared to greater than 18 years) and on heavy cannabis use, but found that both were not significant ($p>0.05$) and underpowered due to the small number of

studies included. Sensitivity analyses showed that the OR for developing depression among heavy cannabis users compared to non-users was also not significant (OR: 1.34, 95% CI: 0.96-1.87).

There have been other systematic reviews and meta-analyses since the Lev-Ran et al. article that explore the relationship between cannabis and mental health. In 2018, Mammen and co-authors (including Lev-Ran) published a study that looked at mental health outcomes among people with anxiety or other mood disorders at baseline. They found that recent cannabis use (within the prior 6 months) was associated with increased levels of mental health symptoms.[19] This offers support for the relationship between cannabis and poor mental health outcomes, although all participants in the Mammen et al. article had a mood disorder at baseline, whereas our meta-analysis looks only at studies that control for depression at baseline. Another meta-analysis published in 2019 explored cannabis use in adolescence and mental health outcomes, including depression, in young adulthood and found a pooled OR of 1.37 (95% CI: 1.16, 1.62).[20] This is further evidence that there is a relationship between cannabis and depression, even though they limited their review to only include studies with adolescent cannabis users.

Considering the changing landscape of cannabis in the U.S. and globally, an update to the Lev-Ran, et al. meta-analysis is warranted. Furthermore, it is particularly important to address the issue of mental health in the U.S. Studies have shown that rates of depression in the U.S. have increased, especially in the past two years during the COVID-19 pandemic.[21,22] The purpose of this article was to update the Lev-Ran et al. meta-analysis by including additional studies published since 2013 and to further explore the relationship between cannabis use and depression. In addition, we conducted meta-analyses looking at the nuanced relationships of early onset cannabis use (i.e., initiating use in adolescence) and depression, as well as heavy

cannabis use and depression. We hypothesized that those who start using cannabis at a younger age will be more likely to develop depression, compared to those who initiate use as adults, which may be due to the psychosocial consequences of early cannabis use that has been demonstrated in the literature.[42] We also expected that heavy cannabis users will be more likely to develop depression, compared to light/occasional users due to the potential for there to be a dose-response relationship between cannabis and depression.

Methods

This review follows the PRISMA 2020 reporting guidelines.[43]

Eligibility criteria

The search for literature concluded April 22, 2022. Initial eligibility criteria were established *a priori*, but additional criteria were added after the literature search began. Articles could originate from any country, as long as they were in English or able to be translated into English. Inclusion criteria we established prior to the literature search were: 1) studies had to report on cannabis use separate from other drug use; 2) studies had to report on depression, separate from any other mental health outcomes; 3) studies had to be longitudinal, with cannabis use measured prior to the outcome of depression. Exclusion criteria were: 1) cross-sectional studies; 2) other systematic review articles; 3) studies that only included populations that were at high-risk for cannabis and/or depression. After the preliminary search, we decided to exclude studies that only focused on special populations that were likely to have higher risk of both cannabis use and depression, in an attempt to reduce confounders. For example, LGBTQ-only studies were excluded[44] as it has been shown that gender and sexual minority populations have higher rates of depression than cisgender and heterosexual populations[45] as well as higher rates of problematic cannabis use.[46] In addition, studies that focused on war veteran-only populations

were excluded[47] because this population also has a unique experience that may lead to differing rates of cannabis use[48] and depression[49] compared to the general population. We excluded studies that only included participants who were seeking treatment for a mental health issue at baseline.[50]

Search strategies

Systematic literature searches were conducted by VC and a student assistant. The initial search started with articles that cited the Lev-Ran et al. meta-analysis. Searches were then conducted in PubMed, Ovid Medline, and Google Scholar. Gray literature was searched using ProQuest for unpublished theses and dissertations. An ancestor search of the Lev-Ran articles was conducted by reviewing all the "Cited By" articles in PubMed. The full search strategy, including key words and limits for each database can be found in **Appendix II**.

Screening

Initial screening following the search was by titles. If the title mentioned cannabis (or synonyms, such as "marijuana") and depression (or mental health or other psychosocial outcomes) it was downloaded to a reference management database. Then the abstracts and the full text of the article were reviewed using the screening tool consisting of five questions: Does it mention cannabis?; Does it mention depression?; Is it a longitudinal study? Does it indicate cannabis use occurred prior to depression? Is it only among a special population? (**Appendix III**). A single-screener (VC) screened all potential studies. The results of the screening process can be found in **Appendix III** along with citations of excluded articles and reasons for exclusion.

Extraction

Study information was independently extracted by V.C., with T.P. serving to assist with extracting data when clarity was needed. The coding sheet can be found in **Appendix IV**. The final codes are detailed below.

Cannabis Measure. Cannabis use in any form was the exposure of interest. Codes specific to cannabis included: how was cannabis use measured (for example, self-reported frequency, or a validated measure such as the Composite International Diagnostic Interview). Specific definitions of exposure were collected. These ranged from ever use to cannabis use disorder. Most of the articles included analyses for different levels of exposure, so these were extracted as separate effects. For example, Pedersen, 2008 reported on participants who had used cannabis 1-10 times in the past 12 months, as well as those who used cannabis 11 or more times in the past 12 months.

While we had intentions to code for method of cannabis use (i.e., edibles, inhaled), this was not available in the eligible studies. However, we were able to code for heavy/problematic use and early onset/adolescent use.

Depression Measure. Outcome was any type of clinical or self-reported depression, including major depressive disorder (MDD), major depressive episode (MDE), and general depressive symptoms. We coded for the specific measure that was used (e.g., Clinical Interview Schedule [CIS]-Revised). We also coded if the depression measure was obtained via self-report survey, structured interview, or indeterminate. Other mental health issues, such as anxiety[51,52] and schizophrenia, were not coded.

Results from Individual Studies. Adjusted odds ratios (ORs) for the depression outcomes were extracted from all studies. If studies reported multiple outcomes for different

exposure categories, we extracted those into separate effects. For example, Feingold, et al. (2015) reported ORs for those who used cannabis less than weekly, weekly to less than daily, and daily users, resulting in three effects for this meta-analysis.[51] Overall, we extracted 1-5 effects from all the articles (median: 2 effects per study). When studies reported multiple ORs for a single effect, we chose the one that was adjusted for the most variables, to maintain consistency across studies. Control variables for each of the studies can be found in **Table 2.3**.

Other Coded Data. For each study, we collected data on setting (years that the study took place, country/state of participants), age of participants at baseline (under 18, over 18, or mix), length of follow-up period, and any adjustments made in the analyses.

Risk of Bias. Risk of bias was assessed using the "Tool to Assess Risk of Bias in Cohort Studies" available from Cochrane (**Appendix V**).[53] We utilized 7 out of the 8 items that were applicable to our systematic review, including "Can we be confident in the assessment of exposure?" We did not use the item that assessed about co-interventions, since it was not appropriate for this systematic review.

Meta-analytic Approach. Rstudio version 1.2 was used to conduct all analyses.[54] We used a random effects model to synthesize the results given the likely variation across studies in population and context. The random effects models were estimated using REML. Many studies reported multiple effect sizes due to subgroup analyses (e.g., different levels of cannabis use, different ages of onset of use); thus, given the presence of dependent effect sizes, we used robust variance estimation for the analysis. We estimated effect size models using a correlated effects model[55] assuming a correlation of 0.8 among dependent effect sizes. For the meta-analyses of early onset and heavy use we examined effect size moderators using meta-regression and the R program robumeta.

Results

Search results

Overall, 1003 titles were initially screened across PubMed (776), MedLine (222), and ProQuest (5). From the ancestor search of the Lev-Ran articles, we screened an additional 969 articles. After duplicates were removed (n=241) there were 1731 articles that were title screened. We excluded 1653 articles based on title screening, leaving 78 articles for abstract/full text screen. The most common reasons for exclusion were review article, included only special populations (i.e., veterans[47], LGBT[56]), study design (i.e., cross-sectional[57]), or did not look at depression separate from other mental health outcomes.[58] In the end, 22 studies were included in the meta-analysis, which included the 14 original articles from the Lev-Ran meta-analysis. Summaries of the included studies can be found in **Table 2.1** and **Table 2.2**. Study selection can be visualized in the PRISMA diagram (**Figure 2.1**).

Study characteristics

Eleven of the studies took place in the United States, three of which were national surveys. The others were based in Sweden (n=2), Australia (n=2); New Zealand (n=2), The Netherlands (n=1), United Kingdom (n=1), Canada (n=1), Switzerland (n=1), and Norway (n=1). The majority (n=12) enrolled participants who were under 18 at the first time point. The median follow-up time was 7 years (interquartile range: 3-16 years).

Meta-analysis

Extracted effects can be found in **Table 2.3**.

Effect Size Calculation. We started with Model A that assumed independence of effect sizes using Metafor with random effects. This model gave us an OR of 1.36 (95% CI: 1.06, 1.52). The T^2, which is an estimate of the variance between studies was 0.0775 (SE = 0.0295)

and the I^2 was 66.17%, suggesting there is substantial heterogeneity in our sample of effect sizes. The Q-test statistic was 119.4903 (df = 50, p-val < .0001), indicating that T^2 is significantly different from 0. The forest plot for the studies can be found in **Figure 2.2**.

Because there were multiple effects per study, we decided to create Model B using a correlated effects model with small-sample correction using robumeta[59] in R. This method allowed us to account for multiple effects nested within studies. This model gave us an estimated mean log-odds of 0.221 (SE = 0.0623, t=3.55, df=14.6) corresponding to an OR of 1.25 (95%CI: 1.09, 1.42). The T^2 was 0.0372 and the I^2 was 56.09%.

We used Model B to create a 95% Prediction Interval of 0.25 to 6.17, which is the likely range of effect size values we would expect a randomly selected new study for the meta-analysis to fall into.[60] This is a wide interval, suggesting a high degree of uncertainty around future predictions.

Sub Meta-Analysis: Early Onset. Table 2.3 indicates the seven effects which were considered as early onset cannabis use (indicated by the superscript "b"). Using a correlated errors model with small-sample corrections in robumeta, we fit a meta-regression with "early onset" as a predictor. The estimated average log-odds for depression among those who were later-onset cannabis users was 0.551 (t=2.73, df = 2.2, p=0.101), corresponding to an odds ratio of 2.74. The coefficient for early onset was -0.299 (odds ratio = 0.74), and was not significant (t=-1.22, df=3.1, p=0.307); furthermore, the degrees of freedom for this analysis was less than 4, indicating that the analysis was unreliable due to the small number of studies included and should not be interpreted further. Thus, the analysis shows no difference in the odds of developing depression between early onset and later onset cannabis users.

Sub Meta-Analysis: Heavy Use. A superscript "c" in **Table 2.3** indicates the 15 effects that were used for the sub-analysis of heavy use. Again, we fit a meta-regression using a correlated effects model with small-sample corrections using robumeta in R. The estimated average log odds for non-heavy use was 0.0736 (t=0.676, df=7.45, p=0.5196) and the coefficient for heavy use was 0.4189 (t=2.214, df=8.94, p=0.0543). These results were not significant (p>0.05). Therefore, we are unable to conclude that heavy cannabis use has a different impact on depression, compared to non-heavy use. The odds of developing depression do not differ among non-heavy and heavy users.

Risk of Bias. Results from this risk of bias tool can be found in **Table 2.4.** Overall, there was a medium risk of bias across all studies with a mean of 2.17 (sd=0.57) on a scale from 1 (low risk of bias) to 5 (high risk of bias). All studies were assigned a "1" for the first question, as they all selected cannabis users and non-users from the same population. The next lowest score was for whether there was adequate control for prognostic variables related to the outcome of depression (mean=2.14), but this one also had the highest variability (sd=1.03). The category that had the highest risk of bias was in the measure of the exposure, with a mean of 2.82 and the lowest variability (sd=0.45). All of the studies relied on self-report from the participants to classify cannabis use. The question that assessed the measurement of the outcome had a moderate level of bias (mean=2.34, sd=0.45) (of note, only one study looked at clinical records to make a determination for depression).[61]

Discussion

This systematic review and meta-analysis was designed to explore the longitudinal relationship between cannabis use and depression. It aimed to update a previous meta-analysis by Lev-Ran et al. (2013). We identified eight additional studies[51,62–68] that we added to the original

studies from the Lev-Ran et al. analysis.[61,69–81] Lev-Ran et al. found that individuals who used cannabis had 1.17 odds of later having depression (95% CI: 1.05-1.30) compared to non-user controls. Our findings were similar with the odds of developing of depression was 1.36 (95% CI: 1.06, 1.52) compared to non-user controls. Though this finding is not surprising, it is noteworthy to mention that the issues identified by Lev-Ran et al. have not been addressed in the subsequent research. Specifically, Lev-Ran et al. indicated a need to look at differences in methods of cannabis use and concentrations. None of the studies we added to the meta-analysis measured type of cannabis, and none mentioned any attempt to look at methods of consumption or concentration level. This highlights an established methodological issue that future research needs to consider.

Also, in line with the results from Lev-Ran et al., our sub meta-analyses did not demonstrate a significant relationship between early onset cannabis use nor heavy cannabis use with depression onset. This lack of statistically significant findings may be due to the high level of heterogeneity across studies. As Lev-Ran et al. pointed out in their discussion, measurements of both the exposure and outcome varied greatly, making it difficult to come to strong conclusions. One of the limitations of meta-analysis is having to decide what meets the definition of the exposure and outcome, and our classification may differ from what other researchers choose. Therefore, while we were justified in our selection of articles and subsequent coding, other meta-analyses on this topic may result in different findings.

Suggestions for future research

Throughout the process, we identified several opportunities for improvement for future research to more clearly determine the relationship between cannabis use and depression.

First, the definition of who is a cannabis user is not consistent across studies. For

example, some studies dichotomize people into cannabis "users" and "non-users". However, even this is not consistent across studies. The article by van Laar, et al. (2007)[81] defined a cannabis user as anyone who used more than 5 times in their lifetime, whereas Manrique-Garcia et al. (2012)[61] defined a cannabis user as anyone who used it at least once. Manrique-Garcia et al. had tried to categorize into more groups, but were unable to due to "the small number of cases,"[61] which is a sentiment that was echoed in other studies. Attempts to label cannabis users as "heavy", "moderate", and "light" were also not consistent. Furthermore, some studies looked at past year to determine heaviness of use, while others looked at lifetime use.

Accordingly, another limitation of the studies is that many of them were not able to consider changes in cannabis use over time. Measuring cannabis use at a single time point may not account for the waxing and waning of use across the lifecycle of an individual. While many cannabis users start in adolescence or young adulthood, there is evidence that some may discontinue the behavior as they "mature out".[82,83] It may be beneficial to explore whether quitting cannabis as an adult reduces the risk of depression to the levels of non-users, or if youth cannabis exposure is enough to elevate the risk of depression despite subsequent non-use. This could have major implications for interventions that aim to delay the onset of cannabis use.

Similar to cannabis use, depression was inconsistently measured across studies. While "major depressive disorder" and "major depressive episode" were commonly cited, other definitions such as "depressive disorder" and "depressive symptoms" were used. Additionally, there were several diagnostic tools and scales used to measure depression across the studies; the most predominant was the DSM. It is not guaranteed that an individual who met the criteria for depression on one measure would meet it on another; therefore, the heterogeneity of the outcome measure is an area of concern that future research needs to consider if we are to gain a better

understanding of the relationship between cannabis and depression.

Conclusions

There is evidence that cannabis use is associated with the onset of depression. While we updated a previous meta-analysis from 2012, and found similar results, it is clear that there are gaps in our understanding of how cannabis affects mental health. The current state of the literature has not kept up with the changing landscape of cannabis use in the U.S. and the world. Although this is partly due to the nature of longitudinal research, we recommend that researchers focus on the following: 1) consider the mode of cannabis use (e.g., edibles, concentrates); 2) find ways to better define cannabis use, specifically definitions of heavy versus light use; and 3) conduct analyses to investigate potential moderators in the relationship between cannabis use and depression (e.g., race, socioeconomic status).

Table 2.1. Summary of studies included in meta-analysis

Article	Study Name	Population	Cohort Demographics	Age Range at Enrollment; Years of enrollment and follow-up
Areseneault, 2002[62]	Dunedin Multidisciplinary Health and Development Study[84]	General population prospective birth cohort in New Zealand	Not reported	Birth; 1972-1999
Blanco, 2016[63]	National Epidemiologic Survey on Alcohol and Related Conditions[85]	Nationally representative sample of US adults	Stratified by state demographics; oversampled for Black and Hispanic individuals and for young adults (aged 18-24)	18 (no upper limit indicated); 2001-2005

Bovasso, 2001[69]*	Baltimore Epidemiological Catchment Area study[86]	Probabilistic sampling of residents from Eastern Baltimore, Maryland	62% female; 63% White; oversampled participants aged 65 and older	18 (no upper limit indicated); 1994-1996
Brook, 2002[70]*	Children in the Community Study[87]	Prospective longitudinal study of children in Albany and Saratoga counties in New York	50% female; 92% white	Between 1 and 10 years of age; 1983-1992
Brook, 2011[71]*	Unique cohort[88]	Four-wave longitudinal study of African-American and Puerto Rican students in Grades 7-10 in New York, US	59% female; 55% African-American; 45% Puerto Rican;	Mean age: 14 years (sd = 1.3) ; 1990-2005
Copeland, 2022[64]	The Great Smoky Mountains Study[89]	Longitudinal prospective representative cohort	48.9% female; 6.9% black; 3.7% American Indian	Age 9, 11, and 13 years; 1993-2015

		study of children in rural North Carolina, US		
Danielsson, 2016[65]	Mental Health, Work, and Relations study[90]	Longitudinal, population-based study of citizens residing in Stockholm, Sweden	57.9% female; Race not reported	Age 20-64; 1998-2000
Degenhardt, 2013[72]*	Unique cohort	Nine-wave prospective cohort study of adolescents and young adults in Victoria, Australia	53% female; Race not reported	Mean age = 14.9; 1992-2008
Feingold, 2015[51]	National Epidemiologic Survey on Alcohol and Related Conditions[91]	Longitudinal and nationally representative of non-institutionalized adults in the US.	55.5% female; 20.1% Black; 18.9% Hispanic; 4.5% Other	18 (no upper age indicated); 2001-2004

Fergusson, 1997[73]*	Christchurch Health and Development Study[92]	Longitudinal birth cohort of children born in Christchurch, New Zealand.	49.8% female; 14.2% Maori/Pacific Islander	Birth; 1977-1995
Gage, 2015[66]	The Avon Longitudinal Study of Parents and Children[93]	Longitudinal prospective population-based birth cohort of infants born in Avon, United Kingdom.	58.5% female; Race not reported	Birth; 1991-1992
Georgiades, 2007[74]*	Ontario Child Health Study[94]	Prospective cohort of children and adolescence living in Ontario, Canada.	48.8% female; Race not reported	Aged 14-16 years; 1983-2001
Harder, 2006[75]*	National Longitudinal Survey of Youth of 1979[95]	Nationally representative longitudinal survey of youth in the US.	50.6% female; Race not reported	Aged 15-22; 1979-1994
Harder, 2008[76]*	Unique cohort	Longitudinal cohort of first-grade children in a	55.3% female; 72.3% black	First-grade students; 1985-2001

		Mid-Atlantic metropolitan area of the US, nested within a randomized trial.		
Hengartner, 2020[67]	The Zurich Study[96]	Stratified population-based longitudinal cohort of young adults from Zurich, Switzerland.	51.6% female; Race not reported	Aged 19 (males) and 20 (females); 1978-2008
Manrique-Garcia, 2012[61]*	Unique cohort	Nationwide survey of Swedish men examined for compulsory military training.	100% male; Race not reported	18-20 years; 1969-2001
Marmorstein, 2011[77]*	Minnesota Twin Family Study[97]	Longitudinal community-based study of twins born in Minnesota.	53.8% female; 98% White	17 years old; 1972-1996
Paton, 1997[78]*	Unique cohort	Representative longitudinal cohort of	Not reported	High school aged; 1971-1972

		adolescents from public high schools in New York, US		
Patton, 2002[79]*	Unique cohort	Stratified cluster sample from schools in Victoria, Australia.	54% female; Race not reported	Aged 18-19; 1992-1998
Pedersen, 2008[80]*	Young in Norway Longitudinal Study[98]	Population-based cohort of students in Norway.	54.8% female; Race not reported	Aged 12-16; 1992-2005
Schaefer, 2021	Minnesota Center for Twin and Family Research[99]	Three longitudinal cohorts of adolescent twins in Minnesota.	Not reported	Age 11 and age 17; 1990-2006
van Laar, 2007[81]*	Netherlands Mental Health Survey and Incidence Study[100]	Longitudinal stratified cohort of adults in the Netherlands.	Not reported	Aged 18-64; 1996-1999

*Notes: * indicates article was included in the Lev-Ran, 2014 meta-analysis.*

Table 2.2. Measurements used in included studies

Article	Exposure (Cannabis)		Outcome (Depression)	
	Measure	Categories	Measure	Definition
Areseneault, 2002[62]	Survey: cannabis use (no timeframe specified)	"Never" or "Once or twice" were considered non-users; "Three times or more" were considered cannabis users.	Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV	Depressive disorder
Blanco, 2016[63]	Interview: cannabis use in the prior 12 months.	No cannabis use in the past 12 months; some cannabis use in the past 12 months, but less than 1 use per month; 1 or more uses per month.	Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS-IV)	Major depressive disorder (MDD)
Bovasso, 2001[69]*	Survey; Diagnostic Interview Schedule (DIS)	Cannabis use disorder	DSM-III	Depressive symptoms
Brook, 2002[70]*	Interview; frequency	Cannabis use on an 8-point scale from never to daily use.	University of Michigan Composite International	MDD

			Diagnostic Interview and modified DSM-IV criteria	
Brook, 2011[71]*	Interview; frequency	Never; a few times a year or less; about once a month; several times a month; once a week or month	Checklist 90-R	Depressive symptoms
Copeland, 2022[64]	Interview; based on DSM-5	Daily cannabis use or cannabis use disorder	DSM-V	Depressive disorder
Danielsson, 2016[65]	Survey; frequency	Ever use; use recency: today, last week, last month, last 12 months, more than 12 months ago.	Major Depression Inventory, based on DSM-IV and International Classification of Diseases (ICD)-9 depressive symptoms	Depressive disorder
Degenhardt, 2013[72]*	Survey; cannabis use in the past 6 months	Non-users; use less than weekly (occasional); weekly or more often (daily)	Clinical Interview Schedule – Revised (CIS-R)	Major depressive episode

	(adolescents) or past 12 months (young adults)			
Feingold, 2015[51]	Survey; lifetime and past-year cannabis use	Cannabis use frequency over the past year ranging from "every day" to "once a year"; number of joints per cannabis-use day	Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS-IV)	MDD
Fergusson, 1997[73]*	Survey; Composite International Diagnostic Interview (CIDI)	Frequency of cannabis use from age 15-16; symptoms of cannabis abuse or cannabis dependence	CIDI	MDD
Gage, 2015[66]	Survey; frequency	Cumulative cannabis use: 0 times; 1-20 times; 21-60 times; more than 60 times	CIS-R	Unipolar depression

Georgiades, 2007[74]*	Survey; frequency of cannabis use in the past 6 months	Cannabis use only in adolescence; cannabis use only in adulthood; cannabis use in both adolescence and adulthood	CIDI-Short Form	MDD
Harder, 2006[75]*	Survey; past year cannabis use	Non-users; light users; heavy users	Center for Epidemiologic Studies Depression Scale (CES-D)	Depressive symptoms
Harder, 2008[76]*	Interview; CIDI	Non-users or non-problematic users; cannabis problems (dependence or nondependent abuse)	DSM-IV	Major depressive episode
Hengartner, 2020[67]	Interview; frequency of cannabis use and age of first use	Age of first use (before or after age 15/16 years); how often cannabis was used in adolescence (less than or equal	DSM-III-R	Major depressive episode

		to 10 times or at least 11 times)		
Manrique-Garcia, 2012[61]*	Survey; frequency of cannabis use	Reported level of cannabis use: never, once, 2-4 times, 5-10 times, 11-50 times, greater than 50 times.	ICD codes from inpatient hospital admissions.	Unipolar depression.
Marmorstein, 2011[77]*	Interview; Substance Abuse Module of the Composite International Diagnostic Interview (CIDI-SAM)	Cannabis use disorder (dependence or abuse); infrequent cannabis users (at least once per year but not more than once per month)	Structured Clinical Interview for DSM-III-Revised	MDD
Paton, 1997[78]*	Survey; ever and past 30 day use of cannabis	Current cannabis user; ever users	Survey; six-item index (not validated)	Depressed mood
Patton, 2002[79]*	Survey; frequency in the past 6 and 12 months	None to less than 5 times in the previous 12 months; 5 times ever to less than weekly;	Computerized Clinical Interview Schedule (CIS)-Revised	"Lower threshold than syndromes of major depression…but one

		1-4 times/week; daily (men); daily (women)		where clinical intervention would still be appropriate.”
Pedersen, 2008[80]*	Survey; lifetime use of cannabis and past 12 month cannabis use	No use through “more than 50 times”	Kandel and Davies’ six-item measure of depressed mood (derived from the Johns Hopkins Symptom Checklist [SCL-90])	Depressed mood
Schaefer, 2021	Computerized Substance Use Inventory (CSU); the Diagnostic Interview for Children and Adolescents (DICA)-Revised or the Substance Abuse Module of the CIDI, or a combination	No use; less than 1 time/month; 1-3 times a month; 1 to 4 times a week; every day or nearly every day; or more than once per day.	Structured Clinical Interview for the DSM (SCID)	MDD

van Laar, 2007[81]*	Interview; frequency of lifetime use during the period of heaviest use	Non-users (less than 5 times in the lifetime); 1-3 days per month; 1-4 days per week; almost every day.	CIDI DMS-III-R	MDD

Notes: * indicates article was included in the Lev-Ran, 2014 meta-analysis.

Table 2.3. Results from the systematic review

Article	Exposed group (control group)	aOR (95% CI)[a]	Control variables
Areseneault, 2002[62]	Cannabis use by age 15 ("never" or "once or twice" users at age 15)	1.02 (0.34, 3.04)	"Childhood psychotic symptoms and use of other drugs in adolescence"
	Cannabis use by age 18 ("never" or "once or twice" users at age 18)	1.62 (1.06, 2.49)	
Blanco, 2016[63]	Cannabis use in the past 12 months (nonusers)	0.8 (0.6, 1.1)	"Risk factors and sociodemographic characteristics"
Bovasso, 2001[69]*	Diagnosis of cannabis abuse at baseline[c] (without a cannabis abuse diagnosis)	4.0 (1.23, 12.97)	"Confounding sociodemographic variables"
Brook, 2002[70]*	Childhood cannabis use[b] (never users)	1.56 (1.10, 2.22)	"Sex, age, parental educational level, family income, prior episodes of MDD"

	Adolescent cannabis use[b] (never users)	1.44 (1.08, 1.91)	
	Adult cannabis use in "early 20's" (never users)	1.17 (0.89, 1.55)	
Brook, 2011[71]*	Maturing-out cannabis use (non- or low-users)	1.5 (0.9, 3.2)	Sex, ethnicity
	Late-onset cannabis use (non- or low-users)	2.3 (1.3, 4.4)	
	Chronic cannabis use[c] (non- or low-users)	2.9 (1.7, 5.7)	
Copeland, 2022[64]	Daily use[c] (cumulative odds)	1.0 (0.6, 1.5)	"Sex and race/ethnicity, childhood psychiatric disorders (mood, anxiety, behavioral and noncannabis substance disorders) and other childhood adversities (low socioeconomic status, familial instability, family dysfunction, maltreatment, and peer victimization)"
	Early onset cannabis use – "before age 16"[b] (non-users)	2.3 (0.7, 7.5)	
	Persistent cannabis use[c] (non-users)	1.6 (0.4, 6.3)	

	Adolescent-only cannabis use[b] (non-users)	1.0 (0.4, 2.7)	
	Adult-onset cannabis use (non-users)	2.1 (0.5, 9.0)	
Danielsson, 2016[65]	Lifetime ever use of cannabis (never users)	0.99 (0.82, 1.17)	"Age, sex, education, place of upbringing, family tension, other illicit drug use, alcohol related problems (AUDIT)"
Degenhardt, 2013[72]*	Occasional cannabis use (no use)	1.2 (0.68, 2.0)	"Sex, non-metropolitan school location, low parental education, parental divorce/separation high-risk alcohol use in the past week and other illicit substance use: any of amphetamine, cocaine or ecstasy use in the past 12 months. and clinically significant depression/anxiety in adolescence"
	Weekly cannabis use (no use)	1.7 (0.76, 3.8)	
	Daily cannabis use[c] (no use)	2.3 (1.1, 4.5)	
	Cannabis dependence[c] (no use)	1.9 (0.87, 4.3)	
Feingold, 2015[51]	Less than weekly cannabis use (cannabis nonusers)	1.04 (0.65, 1.68)	"Socio-demographic variables (sex, age, educational level, household income, marital status, urbanity and region), 12-month alcohol use disorder and other substance use disorders (non-cannabis), 12-month diagnosis of additional psychiatric
	Weekly to less than almost daily use (cannabis nonusers)	0.67 (0.37, 1.22)	

	Daily or almost daily[c] (cannabis nonusers)	0.58 (0.22, 1.51)	disorders at baseline (e.g., personality disorders, anxiety disorders)"
Fergusson, 1997[73]*	Cannabis use (never users)	1.46 (1.0, 2.15)	Maternal age, family socio-economic status, gender, changes of parents, parental history of offending, childhood sexual abuse, IQ, conduct problems, self esteem, novelty seeking, mood disorder, anxiety disorder, alcohol abuse, daily smoking, juvenile offending, parental attachment, deviant peer affiliations
Gage, 2015[66]	Cumulative cannabis intensity (less than 20 times, 21-60 times, greater than 60 times)	1.3 (0.98, 1.72)	"Adjusting for family history of depression, gender, urban dwelling, maternal education, cigarette use, alcohol, and other illicit drug use."
Georgiades, 2007[74]*	Cannabis use only in adolescence[b] (non-users) Cannabis use only in adulthood (non-users)	1.48 (0.65, 3.4) 2.58 (1.67, 3.99)	Family level: SES, single parent home, family functioning, sex; Child level: age, grade failure, medical condition, general health status, externalizing and internalizing syndrome scales

	Cannabis use in adolescence and adulthood (non-users)	4.45 (2.05, 9.66)	
Harder, 2006[75]*	Past-year cannabis user (non-users)	1.13 (0.81, 1.65)	Propensity score weighted
	Heavy cannabis user[c] (non-users)	1.28 (0.72, 2.25)	
Harder, 2008[76]*	Cannabis problems-"dependence or nondependent abuse" among females[c] (no cannabis dependent or abuse – females)	0.7 (0.2, 2.3)	Demographic, socioeconomic status, other drug use, childhood disturbances of psychological well-being, parental monitoring, and behavioral intervention status variables.
	Cannabis problems-"dependence or nondependent abuse" among males[c] (no cannabis dependent or abuse – males)	1.7 (0.8, 3.6)	

Hengartner, 2020[67]	First use in adolescence (younger than age 15/16)[b] (no adolescent use)	1.84 (1.26, 2.7)	"Adjusted for: assessment year (age), sex, family climate (at age 20/21), social support (at age 20/21), parental income (at age 20/21), education level (at age 20/21), drug abuse (time-variant, age 20/21-49/50), and alcohol abuse (time-variant, age 20/21-49/50)"
	First use aged 16-20 years old (no adolescent use)	1.58 (1.04, 2.38)	
	Used 1-10 times (no adolescent use)	1.59 (1.07, 2.36)	
	Used more than 10 times (no adolescent use)	1.9 (1.26, 2.87)	
Manrique-Garcia, 2012[61]*	Ever used cannabis (never use)	1.0 (0.7, 1.2)	"Adjusted for prior personality disorders at conscription, IQ, disturbed behavior in childhood, social adjustment, risky use of alcohol, smoking, early adulthood socioeconomic position, use of other drugs, brought up in a city."
	Used cannabis more than 50 times[c] (never use)	0.9 (0.5, 1.6)	
Marmorstein, 2011[77]*	Infrequent cannabis use (no use)	0.52 (0.19, 1.4)	Adjusted for adolescent MDD, sex/gender, parental MDD, alcohol use disorders by age 17, nicotine dependence by 17, and conduct disorder.
	Cannabis use disorder[c] (no use)	2.62 (1.22, 5.65)	

Paton, 1997[78]*	Current cannabis use, within the past 30 days (no use in the past 30 days)	1.12 (0.87, 1.45)	None
Patton, 2002[79]*	Five times lifetime to less than weekly (none to less than 5 times in the previous 12 months)	0.8 (0.44, 1.5)	Adjusted for parental separation, parental education, current smoking, frequency of drinking, and use of other illicit drugs.
	1-4 times a week (none to less than 5 times in the previous 12 months)	1.1 (0.6, 2.0)	
	Daily (men)[c] (none to less than 5 times in the previous 12 months)	2.2 (0.55, 2.6)	
	Daily (women)[c] (none to less than 5 times in the previous 12 months)	5.6 (2.6, 12.0)	

Pedersen, 2008[80]*	1-10 times in the past 12 months (never use)	1.4 (0.8, 2.1)	"Controlled for age, gender, parental educational level, parents unemployed or receiving social welfare benefits, parental divorce, parental smoking and alcohol problems, parental support and monitoring measured at the age of 16 years, early pubertal maturation, school marks (age 16 years), conduct problems and daily smoking (ages 16 and 21 years), alcohol intoxication (age 16 years), alcohol problems (age 21 years), depression (ages 16 and 21 years), impulsivity (age 21 years), level of education (age 21 years), unemployment and income from social security, marriage/cohabitation and being a parent (age 21 years)."
	11 or more times in the past 12 months (never use)	0.9 (0.4, 2.5)	
Schaefer, 2021	Adolescent cannabis use[b] (cumulative cannabis use)	1.16 (1.07, 1.25)	Age sex, cohort, and zygosity
van Laar, 2007[81]*	1-3 days a month (no cannabis use reported at baseline)	1.49 (0.82, 2.71)	Adjusted for gender, age, education, urbanicity, employment, partner status, neurotic personality, parental psychiatric

1-4 days a week (no cannabis use reported at baseline)	1.79 (0.94, 3.4)	history, traumatic events in childhood, life-time alcohol use disorders or other substance use disorders, life-time psychotic symptoms and life-time anxiety disorders at baseline.
Almost every day[c] (no cannabis use reported at baseline)	1.6 (0.75, 3.42)	

Notes: *included in the initial Lev-Ran et al. article; [a] adjusted for variables in column 4, unless none specified; [b] sub-analysis for early onset; [c] sub-analysis for heavy/problematic use.

Table 2.4. Risk of Bias assessment, average scores ranging from 1 (low risk of bias) to 5 (high risk of bias)

Article	Selection of exposed and non-exposed cohorts[a]	Assessment of exposure[b]	Outcome not present at start of study[c]	Exposed and unexposed matched on prognostic variables[d]	Assessment of prognostic factors[e]	Assessment of outcome[f]	Adequacy of follow-up[g]	Risk of Bias score[h], Mean (*SD*)
Areseneault, 2002[62]	1	2.5	2.5	3.5	3	3	3	2.64 (0.80)
Blanco, 2016[63]	1	2.5	2.5	2	2	1.5	2	1.93 (0.53)
Bovasso, 2001[69]*	1	2	1	2.5	2	2.5	3.5	2.07 (0.89)
Brook, 2002[70]*	1	3	4	1.5	1.5	2.5	2.5	2.29 (1.04)
Brook, 2011[71]*	1	3	4	4	1	2.5	2	2.50 (1.26)

Copeland, 2022[64]	1	2.5	1.75	1	1	2.5	1	1.54 (0.71)
Danielsson, 2016[65]	1	3	3	2	2	2.5	2.5	2.29 (0.70)
Degenhardt, 2013[72]*	1	3	1.75	2.5	2.5	2.5	3	2.32 (0.72)
Feingold, 2015[51]	1	3	1.75	1	2	2	3	1.96 (0.82)
Fergusson, 1997[73]*	1	3	1	4	4	2.5	3	2.64 (1.25)
Gage, 2015[66]	1	3	1.75	2.5	2.5	2.5	3	2.32 (0.72)
Georgiades, 2007[74]*	1	3	1.75	1.5	2	2.5	2	1.96 (0.65)
Harder, 2006[75]*	1	3	1.75	1	2	2.5	2.5	1.96 (0.77)

Harder, 2008[76]*	1	2	2	1.5	2	2	3	1.93 (0.61)
Hengartner, 2020[67]	1	3	1.75	2.5	2	2	2.5	2.11 (0.64)
Manrique-Garcia, 2012[61]*	1	3	3.5	1.5	2	1	1	1.86 (1.03)
Marmorstein, 2011[77]*	1	2.5	1	1.5	2	2	2	1.71 (0.57)
Paton, 1997[78]*	1	4	3	4	4	3	3.5	3.21 (1.07)
Patton, 2002[79]*	1	3	3	2	2	2.5	2	2.21 (0.70)
Pedersen, 2008[80]*	1	3	1.75	1	2	2.5	3	2.04 (0.85)

Schaefer, 2021	1	2	1.75	3	3	2.5	3	2.32 (0.77)
van Laar, 2007[81]*	1	3	1.75	1	2	2	2	1.82 (0.69)
Overall Mean (SD)	**1.0** (0.0)	**2.82 (0.45)**	**2.18 (0.89)**	**2.14 (1.03)**	**2.20 (0.75)**	**2.32 (0.45)**	**2.50 (0.69)**	**2.17 (0.57)**

Low risk of bias | Low-to-medium risk of bias | Medium risk of bias | Medium-to-high risk of bias | High risk of bias

Notes: *indicates article was included in the Lev-Ran, 2014 meta-analysis. Scores were based on the following scale: 1 = "Definitely yes (low risk of bias)"; 2 = "Probably yes"; 3 = "Probably no"; 4 = "Definitely no (high risk of bias)". Half-points were given if the study was deemed to be between two levels in the risk of bias scale. [a]Was selection of exposed and non-exposed cohorts drawn from the same population? [b]Can we be confident in the assessment of the exposure? [c]Can we be confident that the outcome of interest was not present at start of the study? If depression at the start of the study was controlled for, we assigned a score of 1.75. [d]Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? [e]Can we be confident in the assessment of the presence or abssence of prognostic factors? [f]Can we be confident in the assessment of outcome? [g]Was the follow up of cohorts adequate? [h]Assessed using the modified "Tool to Assess Risk of Bias in Cohort Studies" see Appendix IV.

Figure 2.1. PRISMA diagram

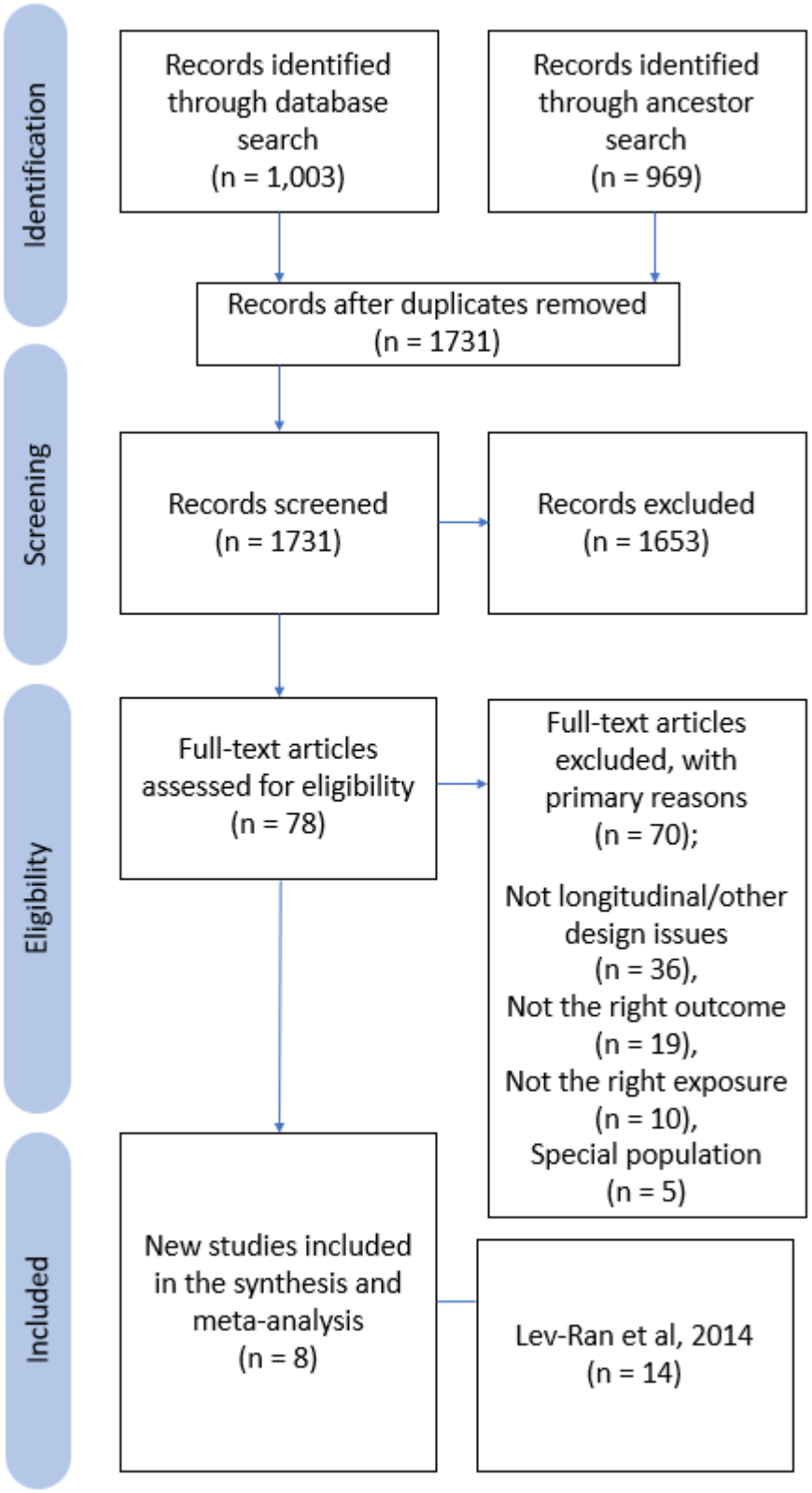
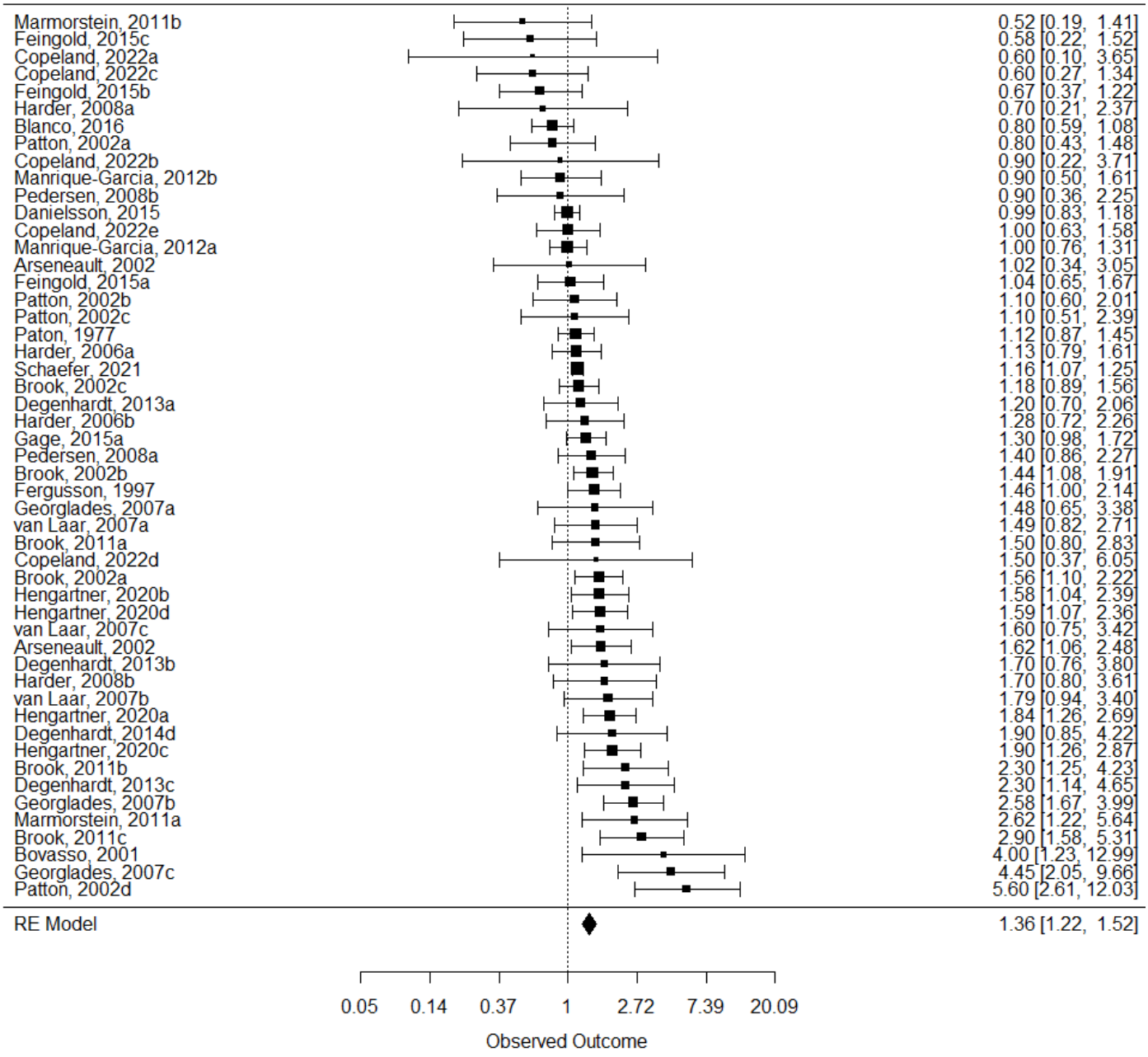


Figure 2.2. Forest plot of studies included in analysis; odds and 95% confidence intervals.



Chapter 3: Qualitative Analysis

Title: "I get the flavors and it makes me love vaping more:" How and why youth users modify electronic nicotine delivery systems (ENDS).

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Abstract

Purpose: Youth in the United States (US) are using electronic nicotine delivery systems (ENDS) at a high rate. Youth ENDS use is associated with negative health consequences. Modifications to ENDS by youth can introduce additional health hazards which have not been previously considered. To better understand these risks, we need more information on what these modifications are, the motivations behind them, and the sources of information on modifications.

Methods: We interviewed 19 youth ENDS users living in the US in 2020-2021 to explore these questions.

Results: The most prominent modification was to the e-liquid; youth indicated that they mixed e-juices to create new flavors and added substances not intended for vaping, as well as illicit drugs such as cannabis and cocaine. Few youths from our sample were interested in achieving a specific nicotine level to vape, and modifications to the battery and coil/wick were less frequently mentioned. Some of these modifications were motivated by a desire to achieve specific experiences with their device. At other times, modifications were made due to necessity because of limited access to ENDS devices and supplies. YouTube and peers were the main sources of information about modifying.

Conclusions: Youth are making modifications that are both intended and unintended by the manufacturer. Adding illicit drugs and other substances not made for vaping is of particular concern. Understanding how youth modify ENDS and how that changes their use is important to guide regulatory policy intended to reduce harm to youth from ENDS use.

Introduction

Electronic nicotine delivery systems (ENDS) were introduced to the US market in 2007 and became popular among youth around 2013,[101] surpassing the use of combustible tobacco products among middle and high school-aged students in 2015.[102,103] In 2019, 27.5% of high school students and 10.5% of middle school students in the US used ENDS.[25] Early exposure to nicotine, which is often used in ENDS devices, can affect cognitive functioning[104,105] and is associated with an increased risk of becoming nicotine dependent later in life.[106–108] Evidence indicates youth may be using ENDS devices as intended by the manufacturer, as well as making modifications to their devices.[109,110] While modifications by adult ENDS users have been studied,[27,111–113] little is known about how youth modify their devices. The few studies that have been published were limited to closed-ended surveys [114] and focused on specific, pre-selected modifications such as vaping cannabis[115] and "dripping."[116] Our study aimed to investigate ENDS modifications by interviewing youth ENDS users to understand how and why youth modify ENDS.

Modifications can be "intended" [26] when they are within the manufacturers' specifications and "unintended" when they differ from what was originally designed by the manufacturer. Common ENDS modifications include changing e-liquid (pre-made liquids or liquids mixed by the user), replacing the coil, or changing the battery.[117] Modifications may be made to extend the life of a disposable device. For example, once the e-liquid is depleted, the battery may still be useable, prompting some users to "hack" into the device to replenish the e-liquid.[118] Unintended modifications, such as adding drugs or other substances not meant for vaping to the e-liquid, or adding extra batteries to increase the power of the device, are

potentially more dangerous and raise significant physical harm or chemical exposure concerns.[119–121]

Given the prevalence of youth ENDS use in the US and the potential harms associated with modifying ENDS, more research is needed to understand how youth are modifying ENDS. Specifically, descriptive research on youth ENDS modifications is needed to identify behaviors that increase population harm (e.g., attracting youth or making harmful chemical exposure more likely). This information would provide valuable insight into prevention efforts and regulatory decision-making about the modifiability of ENDS products. To provide insight into these issues, we conducted in-depth, qualitative interviews with youth current ENDS users in the US. Our study sought to answer three research questions: 1) How do youth modify their ENDS devices?; 2) What are the motivations for these modifications?; and 3) What sources of information, if any, do they use as instructions for these modifications?

Methods

A *qualitative description* approach was used to explore youth ENDS modifications. This approach uses a structured interview guide to understand interviewees' lived experiences.[122,123] Data analysis stays close to the data, with results reported in participants' own words.[123–125] This paper follows the suggested format from Standards for Reporting Qualitative Research (SRQR).[126]

Research Team and Reflexivity

An experienced moderator from a research company (John Snow, Inc [JSI]) conducted all interviews. This moderator was a white, non-Hispanic female in her early 30s with masters' degrees in social work and public health. The rest of the research team all had advanced degrees

and experience working in both tobacco/ENDS research and qualitative research. The JSI moderator was the only person who interacted with participants.

Participants and Procedures

Purposeful and snowball sampling was used to identify and recruit participants.[127] Eligibility criteria were: 13 through 17 years old; had used ENDS in the past 30 days; and were living in the US. Recruitment and the interviews took place in 2020 - 2021. Since this was during the COVID-19 pandemic, all contact with potential participants was done remotely, and the interviews were completed using a web-based conferencing system. We had two recruitment waves. Wave 1 was August-November 2020 and used a nationwide panel research company, resulting in 38 screened, 30 meeting eligibility criteria, but only 2 completed interviews. Wave 2 of recruitment (December 2020 – February 2021) utilized social media postings and sharing study information directly with a youth advisory board in California. We also asked participants to pass the study information to their peers (i.e., snowball sampling). This wave had 72 youth completing the screener, 47 eligible, and 17 completing the interviews. A total of 19 individual interviews were completed. The interviews lasted between 27 and 60 minutes (median time was 44 minutes) and were video and audio recorded. The moderator had her camera on and encouraged the interviewees to also have their cameras on to simulate the in-person experience as much as possible. Other team members observed the interviews but were muted with their cameras off. The Georgia State University Institutional Review Board approved the study, and JSI obtained electronic (screeners) and verbal (interviews) assent from all participants and written consent from the youth's parents or legal guardians.

Data Collection

Before participating in the virtual interview, participants were asked to complete a short online survey to assess their demographics and tobacco use. The research team developed the interview guide based on their previous experience studying ENDS modifications by adult ENDS users.[26,27,113] Example questions in the interview guide included “What type of e-cigarette or vape do you use?" and “How do you tweak your vape (change it, modify it)?” Of note, this article reports on questions related to modifications, whereas future manuscripts from the study will explore reasons for ENDS use in general. Upon completion of the interviews, participants were emailed a fact sheet with information on quitting electronic cigarettes and an incentive of a $50 Amazon or Visa gift card. After the first several interviews, the JSI moderator and GSU observers debriefed and refined the moderator's guide.

Data Analysis

The one-on-one interviews were transcribed and anonymized by JSI before dissemination to the research team. The team had a codebook created from focus groups with adults. Team members (ZBM and LP) added additional codes relevant to youth ENDS use (for example, first time using ENDS) and codes related to the COVID-19 pandemic. RTF and VC independently coded one transcript, then met with ZBM to discuss the minimal discrepancies. RTF and VC split and coded the remaining transcripts in NVivo 13.[128] ZBM, RTF, VC, LP, and DLA reviewed coded transcripts, wrote memos summarizing the results of each code, and discussed those results. VC assigned pseudonyms and synthesized the memos and notes from the discussion into the first draft of the manuscript. All authors contributed and approved the final draft.

Results

Participant demographics and tobacco use are shown in **Table 3.1**. All youth were either 16 or 17 years old; the majority were male (60%) and identified as Black/African American (80%). Since the interviews were remote, we recruited participants from several states. About a third of the youth reported currently living in California (n=6), and about a quarter lived in Texas (n=5).

Modifications to the e-liquids used for vaping were the most mentioned modifications by the youth. Notably, all 19 participants discussed modifications to the e-liquid, such as mixing flavors, adjusting nicotine levels, and adding substances not intended for vaping into their e-liquids. Participants also mentioned adding drugs, most commonly cannabis, to their e-liquids. Some discussed making modifications to the batteries and coils though some youth specified they did not modify batteries or coils due to the perceived danger and/or mess. Friends, family, and online sites were the predominant sources of information for modifications.

Modifications: E-liquids

Mixing Flavors and Refilling Devices. The most common modification to e-liquids was mixing e-juices to create custom flavors and blends. Youth from our study described either mixing liquids on their own or trying e-liquid blends made by their friends. The flavor blend "depends with (sic) the mood" that the youth were in when they vaped or wanted to achieve by choosing certain flavors. For example, Kira (all names are pseudonyms) explained, "I mean, I don't use the same flavors every time. If I'm with my friends maybe we'll put a fruity flavor, compared with I'm alone, when I want to chill." Ethan described "different feelings from different flavors, especially, cinnamon which I like, because it's really revitalizing. It revitalizes your organs in some way. That's how I feel when I use cinnamon. That's why I like it."

Some participants indicated they used food products not intended for vaping to make different e-liquid flavors. Multiple participants mentioned adding easily accessible substances to e-liquids, such as “honey to sweeten [the e-liquid]” or a “bit of lemon [juice].” Trinity discussed how her friends had plans to make e-juice using real strawberries: “I have some friends who are doing research to see how the normal [fruit] juice is made so that we can start from there.” Similar to mixing e-liquids, the addition of food products to e-liquids was described in terms of improving flavors.

Participants also reported mixing flavors because it gave them something to do. That is, mixing was described as a recreational activity they could do on their own or with friends. Participants listed curiosity and a desire to “try out something new” as driving forces behind these modifications. Reflecting about a time she mixed e-liquids with friends, Christina recalled “having a good time. It felt like we were doing a science experiment, but we were being very clean, and everything, because after all, we would be putting this in our bodies.” Based on participants’ descriptions, not only are modifications done to change the vaping experience itself, but they can also be an enjoyable activity.

Participants reported attempting to extend the life of their ENDS devices by fixing or replacing certain parts, even in ENDS devices designed to be disposable, such as Juul and Puff Bar. For instance, Jordan knew of “some people who will open up Puff Bars and then either refill the juice or fix the battery in there, which either one goes first, they'll just fix that. Because usually, if the juice is gone, the battery is still alive” and “people… were trying to get their money's worth” from their devices. Jordan lamented that “pods were expensive and really hard to get when you needed them” and ”if you wanted to use [the ENDS device] you had to do something. And the only thing we had on hand was a bottle of juice and an empty Juul pod,”

suggesting that there are ways to refill closed systems to extend the longevity of their device. Thus, extending device life through modification was a common topic of discussion in interviews.

Adjusting Nicotine Level. Some participants mentioned adding nicotine when they or their friends made e-liquid to get the desired nicotine level. However, nicotine levels did not seem like a major driver behind modifications, and participants seemed willing to use whatever devices or e-liquids were available, regardless of the nicotine level. Christina, who indicated in the interview that her father also vapes, explained, “We didn't add nicotine to [the e-liquid] so obviously that was different. My parents were very happy about that. They were like, ‘we should make it all the time’... But yeah, I liked that it didn't have nicotine but the flavor overall, it just tasted kind of the same as if I had purchased it.” Sydnee described making her own flavored e-liquid with nicotine: “What I mix, it's the nicotine and also the flavor. If I'm going for the strawberry, that's what I'm going to mix with the nicotine. And also, I always ensure that I've measured the... VG [vegetable glycerine], and also the PG [propylene glycol].” When vaping with friends who make their own e-juice Corey reported, “I can't say that I control the amount of nicotine. It's them who control maybe when mixing the e-juice.” Thus, while nicotine was cited as a factor for modifying e-liquids, it did not appear to be as important as other modifications among the participants we interviewed.

Adding Drugs to E-liquids. Cannabis was the most mentioned drug reportedly added to e-liquids. The process of adding cannabis was described in similar detail by multiple participants. Some mentioned using the plant material and adding it to their e-liquids by grinding the plant and then adding it directly into the e-liquid. Braedon explained, “When I have the [cannabis] plant now, I may grind it on my own. You see? Now after grinding, I add on the

liquid. Then after adding on the liquid, now I may smoke it." Braedon further explained that he added cannabis to e-liquids as a flavor. Olivia discussed a similar process for adding plant cannabis to e-liquids. "I have to take off the buds from the plant and then I have to grind them. I have a grinder; it's round you just twist it and then the marijuana comes up really refined." Olivia indicated that she adjusts the potency of the cannabis in her e-liquid by heating it to activate the psychoactive elements of the plant. She explained: "And then depending on how high I want to get, I can decarbonize it with my oven. And then I mix it with my flavor." Olivia further said "Marijuana is really, really... not dangerous, but… you have to measure the amounts you're taking or else you get really, really high. High enough not to function."

Others mentioned using cannabis e-liquid either on its own or with another flavor. Kira talked about vaping with friends: "Sometimes we put the marijuana flavor. Just to relax and listen to soft music. It mimics the real marijuana but it's not the real marijuana." Andre also mentioned using just a "marijuana flavored juice"; however, there was confusion on whether the "marijuana flavor" actually contained the psychoactive component THC or not as it seemed some youth were unsure or unwilling to disclose.

A few participants discussed knowing others who have tried using cocaine in their ENDS devices, though the consensus was that it is dangerous and less acceptable than vaping cannabis. Isaac remembered being "dared" to vape cocaine, recalling it being "very strong," and that he did not want to vape cocaine again. Olivia explained how she watched someone else put cocaine into an e-liquid and was surprised by this behavior, noting that she was "shook" by the incident. Olivia also recounted a friend who added "drinking alcohol" to their e-liquid, and the experience "went really bad" with the friend getting "so high, like too, too high. Very, very high."

Modifications: Coils/wicks

Changing to Improve Taste/flavor. Most of the modifications to the operating mechanisms of the device described by the youth were switching existing coils/wicks with new ones. Several youth mentioned changing coils frequently, motivated mainly by the taste and flavor. After a while, the coils produced a change in flavor that participants described as "burnt" or "just off the usual taste." Some participants also described the coil when it reached the point that it affected the taste as "done." As Andre said, "So I will notice that the smoke... Maybe I'm inhaling less smoke, so maybe my coil is removing a small amount of cloud. So I notice that maybe some coils are burnt, and I have to replace it." Participants also indicated a desire to maintain flavor purity by using different coils for different flavors, "because every coil has its own flavor." Some, like Ethan, had systems to keep from cross contaminating their flavors by storing coils "in a Ziploc, so that [they] can be able to use them at a later time."

Cleaning/disinfecting. Participants described various ways of cleaning and disinfecting ENDS devices. For instance, Olivia shared that "people soak [coils/wicks] in different solutions depending on their preferences." Olivia further explained: "I do the alcohol mostly and for disinfecting, because you can't use actual disinfectant on the wick. Yeah, just some warm water and salt. A lot of salt for it and vinegar." Kira also used "dish soap and warm water" to clean ENDS devices.

Participants mentioned that cleaning helped remove any remaining flavor from the device and helped maintain flavor purity, which was an important factor among the youth we interviewed. Some participants described the process of cleaning their coils as easy and that it did not require any tools ("just your hands'"). Other participants mentioned avoiding coil modifications, including cleaning the coils. Myles shared that "those [ENDS coils] are the kind

of things that if you are to damage you wouldn't have a replacement unless you get another vape pen." Thus, interviews showed that some participants cleaned their devices or device components while others avoided tampering with those device features altogether.

Device Longevity. Being able to replace coils gave youth in our sample the freedom to vape as much as they wanted because it meant they would not have to worry about using up the coil and then not being able to vape. As Darion said, "because if you know how to change your coil and your e-juice you're comfortable even if you vape frequently in a day, you know if it's exhausted you can change it. But if you don't know how to do so, you'll be protective, because you don't want it to end." Jordan confirmed that they too modified the coil in their closed pod system to extend its life: "I have messed with the coils sometimes. If it was with an old Juul, the coils got really burnt so I changed the cotton and then put a new coil just to fix it up, with the help of a friend though."

Modifications: Battery

Unusual Modifications. There were few mentions of battery modifications; however, the ones that were discussed seemed to be experiments to achieve a desired result. Jordan reflected on the time "someone was talking about how she would cook her Juul over a kitchen flame... She said it would fix the battery, which I would never do that." Trinity tried to "[attach] the wires [from the battery] directly to the socket to see if it will last longer when [she charged] it directly, but it didn't really work." After that, she "just decided, 'let me get another one'" rather than continuing her attempt to modify the battery. Myles was inspired by "external power banks" used for phones and tried using one to "extend the usage of the vape pen by just using an external battery."

Reasons Not to Modify

Participants found some modifications, such as replacing e-liquids, to be "messy" and stated they did not want to deal with those modifications. Others said that it is easier to replace parts rather than modify devices. As Myles explained, "if you are to damage [a part] you wouldn't have a replacement unless you get another vape pen." Youth in our sample did express concerns about how modifications affected the safety of their devices. A few participants indicated that they trusted the manufacturers over their own "amateur" modifications. Jonathan went so far as to say, "the manufacturer decided to build this in the safest way possible to use. If they wanted you to use that way then they would let you know." He continued by saying his friends were "so eager to [modify their devices] they might as well just go work in a Juul factory or work on the Juul board to go help them improve their design." Being "young and stupid" and not "know[ing] anything," according to Jonathan, contributed to the concerns about the safety of doing their own modifications.

Youth from our study were not compelled to modify components of their devices because they felt it was unnecessary. For example, Ethan said the "battery is not that expensive," so it is not a "really important" component to modify. Likewise, Christina reported that she keeps "everything very much like how it arrives" and does not "really modify many things."

Sources of Information

Friends/siblings. Most of the youth we interviewed mentioned learning about modifications from friends and had friends who would do the modifications for them. Myles said that "a friend of mine actually showed me, because [modifying] wasn't that easy… I've gotten used to the vaping and the vape pens all over the years, but then I'm not that much into kind of exploring. So a friend of mine actually does that trick [mixing e-liquids] for me." Siblings were

also valuable sources of information. Christina's brother showed her how to modify the coil "a couple of times", but subsequently, she "looked it up on YouTube". She also indicated "A while ago I wanted to change the coil, and I was mad at my brother, so I'm like 'ugh, I can't ask him for help', so I looked that up [online]." Having connections to peers who also used ENDS devices appeared to be a consistent theme among participants.

YouTube. A second major source of information the youth discussed was YouTube. According to our participants, there are thousands of YouTube videos on modifications, and it's easy to "look up how to change a coil on… a vape" and "go on the first video, look at what they're doing" and if it's "too difficult… go on the second one." ENDS users can "have [their] vape right next to [them], as the video is playing" while they work on the modifications. Christina explained that she would "pause the video, do a little bit, pause the video" to complete the modification, though the "whole process [is] definitely not super simple."

Discussion

Youth ENDS users in our sample discussed a wide range of modifications. Changing and mixing e-liquids were the most common modifications mentioned by the youth we interviewed. These modifications occurred with both open and closed-pod systems. Contrasted to earlier research on adult ENDS modifications[26,113] the practices of coil building and cloud blowing were not mentioned by youth in our interviews. Alarmingly, youth also discussed adding illicit drugs such as cannabis and cocaine to e-liquids; the latter has not been examined in the literature but warrants careful monitoring. Together, the results advance our understanding of ENDS modifications among youth ENDS users, a group that deserves greater attention from the research community.

Our interviews showed that having access to such a large variety of e-liquids is appealing to youth, and it gives them ways to interact with friends by sharing flavors. Without a flavor ban, youth may continue to experiment with e-liquids, which may thwart efforts to reduce youth ENDS use. If a flavor ban were to occur, it would likely be on the sale of devices with pre-filled flavored e-liquids and flavored e-juices containing nicotine. In our sample, youth participants predominately described mixing several flavored e-juices rather than creating their own mixes from scratch (as we saw in our research with adult ENDS users).[113] Youth behaviors will need to be monitored, and campaigns discouraging homemade e-liquids will need to be created. As we see in our sample, youth have found ways to modify e-liquids in devices and pods that were not intended to be modified and may be willing to try using non-e-liquid commercial products or other substances to get a desired taste/flavor without considering the potential harms.

Some youth mentioned modifying the battery and coil. However, no youth mentioned building their own coil, which is different from what we saw among adults and in our content analysis of YouTube videos.[26] There was also no mention of "clouds," – which was a driver for modifications among adults and youth in past research,[129,130] but seems to have become less important now among some youth, which is consistent with other recent research.[131] The new generation of ENDS devices may contribute to the youth in our study finding modifications unnecessary due to design features that eliminate the need to change components of the device (e.g., battery and coil).

While the interviews took place during the COVID-19 pandemic, none of the youth suggested they were motivated to clean their devices to minimize disease transmission. Instead, cleaning was described as a way to flush out the old e-liquid flavor before adding a new one. It is unclear if the processes of cleaning/disinfecting the devices, as described in the interviews, are

effective at producing a “clean” device, free from residues from e-liquid flavors or other unwanted substances. Furthermore, it is unclear whether the process of cleaning the devices, especially if it goes against the manufacturer's intent, could be harmful to the user.

Modifications that are not explicitly intended by the manufacturer but are still frequently occurring raise questions about how well these products can be controlled by regulation. For example, while closed pod systems are not created to be refilled with e-liquids, many videos online provide instructions on how to open them up so that the user can add their own e-liquids, extending the life of the product. This may be particularly important to youth who might have difficulty acquiring new pods for their devices.[26] Therefore, it is important to monitor how devices are being used in the real world to inform policies aimed at minimizing harms associated with ENDS products.

Limitations

Our sample is not representative of all youth ENDS users. Due to the difficulty in recruiting underage ENDS users during the COVID-19 pandemic, we used convenience and snowball sampling, which might have further skewed the results because some interviewees were friends or in the same social groups. Therefore, some themes may be disproportionately dominant. Because the interviews were conducted online, there may have been challenges in interpreting the meaning for both the youth and the moderator based on restricted nonverbal communication.[132]

Conclusions

Preventing youth ENDS use is a public health priority. Understanding how youth are modifying ENDS and how that changes their use is important to reduce youth ENDS use. Our research shows that, among the participants we interviewed, youth are modifying their ENDS

devices and e-liquids. Some of these modifications are motivated by a desire to achieve specific experiences with their device, such as adding cannabis to e-liquids to get high. At other times, modifications are made due to necessity because of limited access to ENDS devices and supplies. Since youth are often unable to purchase ENDS devices and e-liquids from an authorized retailer, they may rely on others to procure them. This can lead to a limit on the type of products they can get and may motivate them to make modifications to extend their supplies.

Little published research investigated the riskier modifications made by youth, specifically adding drugs (e.g., cannabis, cocaine) and other substances dangerous to vape (e.g., food products) to their e-liquids. However, the Centers for Disease Control and Prevention (CDC) warn against vaping any products that are not intended for vaping.[133] Research emphasizing understanding how these modifications influence the operation of ENDS devices, the delivery of harmful and potentially harmful constituents, and associated health impacts needs to be prioritized.

In evaluating population-level impacts of specific ENDS devices, the U.S. Food and Drug Administration (FDA) should consider the intended modifications built into the products, as well as how easy it is to modify products not intended to be modified. For example, the ease of opening a closed e-cigarette and replacing the e-liquid should be a factor in determining the appropriateness of the product for the protection of public health. In addition, these modifications may appeal to youth, so FDA should consider mandating better safeguards against these modifications.

Table 3.1. Demographics and smoking/vaping behaviors for youth ENDS users (n=19)

Pseudonym	**Gender**	**Age**	**Race/Ethnicity**	**State**	**Lifetime cigarette count[a]**	**Times used an e-cigarette (lifetime)[b]**	**E-cigarette use frequency**	**Age at first e-cigarette use**	**Type of electronic vapor product used[c]**	**Ever use cannabis or other drug in ENDS**
Aliyah	Female	16	Black/Non-Hispanic	NY	21-99	21-99	Every day	13	1,2,3,4,5	Yes
Andre	Male	17	Black/ Non-Hispanic	TX	21-99	≥100	Some days	12	1,2,3,5	Yes
Braedon	Male	16	Black/ Non-Hispanic	CA	2-20	2-10	Rarely	14	1,2,3,4,5	Yes
Christina	Female	17	White/ Hispanic	TX	0<1	21-99	Some days	16	2,3,5	No
Corey	Male	16	Black/ Non-Hispanic	CA	2-20	11-20	Every day	13	1,2,5	Yes

Darion	Male	17	Black/ Non-Hispanic	TX	21-99	21-99	Some days	14	1,2,3,4,5	Yes
Ethan	Male	17	Black/ Non-Hispanic	NY	21-99	≥100	Every day	14	1,2,5	Yes
Isaac	Male	17	Black/ Non-Hispanic	CA	21-99	21-99	Every day	12	1,2,3,4,5	Yes
Jonathan	Male	16	Black, White/ NH[1]	TX	2-20	≥100	Every day	15	1,5	No
Jordan	Other	16	Asian, White/ Non-Hispanic	MI	0	≥100	Some days	14	2,5	Yes
Kira	Female	17	Black/ Non-Hispanic	CA	≥100	≥100	Every day	15	1,2,3,4,5	Yes
Lucas	Male	17	Black/Hispanic	TX	≥100	≥100	Every day	15	1,2,3,4,5	Yes
Mason	Male	16	White/ Non-Hispanic	NY	21-99	2-10	Some days	6	1	Yes
Myles	Male	17	Black/ Non-Hispanic	GA	0	21-99	Every day	15	2,3,4,5	No

Olivia	Female	17	Black/ Non-Hispanic	CO	≥100	21-99	Some days	14	1,2,3,4,5	Yes
Patrick	Male	16	Black/ Non-Hispanic	FL	21-99	≥100	Every day	11	1,2,5	Yes
Sydnee	Female	16	Black/ Non-Hispanic	GA	0<1	2-10	Some days	15	1,3,5	Yes
Trinity	Female	17	Black/ Non-Hispanic	CA	≥100	≥100	Every day	14	1,2,3,4,5	Yes
Zoe	Female	17	Black/ Non-Hispanic	CA	21-99	21-99	Every day	15	1,2,3,4,5	Yes

[a]Survey question and options were as follows: "How many cigarettes have you smoked in your entire life? A pack usually has 20 cigarettes in it." None; 1 or more puffs but never a whole cigarette; 2-20 cigarettes; 21 to 99 cigarettes (more than 1 pack but less than 5 packs); 100 or more cigarettes (5 packs or more). [b]Survey question and options were as follows: "During your ENTIRE LIFE, about how many times have you used an electronic vapor product?" None; 1 time, even just a few puffs; 2 to 10 times; 11 to 20 times; 21 to 99 times; 100 times or more. [c]Response options were as follows: 1="Ones that look like a cigarette"; 2="Ones to which you can add e-juice"; 3="Ones that allow you to adjust the power setting"; 4="Ones that are home-built from separate parts"; 5="Juul or similar type."

Chapter 4: Quantitative Analysis

Serious psychological distress is associated with higher intentions to quit among smokers during the COVID-19 pandemic

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Abstract

Background: COVID-19 has increased the rates of serious psychological distress (SPD) among the general population. However, the SPD among smokers during the pandemic remains understudied. We examined the prevalence of SPD among current smokers; the associations between SPD, personal characteristics, and smoking and COVID-19 protective behavioral intentions; and whether SPD moderated the effect of messages about risks of smoking and COVID-19.

Methods: 1,004 U.S. adult smokers with and without SPD were randomized to view messages about COVID-19 risk, smoking risk, combined COVID-19 and smoking risk, or control. Outcomes were smoking quit intentions and COVID-19 protective behavior intentions.

Results: 36% of smokers met the criteria for SPD. Older, everyday smokers, who had COVID-19, planned to quit soon, and had poor health and conservative ideology had higher odds of having SPD. Smokers with SPD were significantly more likely to report intentions to quit smoking and seek counseling than smokers without SPD, controlling for demographics, pre-existing smoking quit intentions, and message condition. SPD was not significantly related to COVID-19 protective intentions. The interactions between SPD and messages were nonsignificant.

Discussion: During the pandemic, smokers with SPD may be motivated to quit smoking, which provides an opportunity for targeted interventions to increase quit attempts.

Introduction

The COVID-19 pandemic has brought serious psychological distress (SPD) with widespread symptoms of depression and anxiety [21,22]. Among adults living in the United States (U.S.), severe depression increased from 0.7% between 2017-2018 to 5.1% in 2020 [134–136]. These studies examined stress related to the COVID-19 pandemic among the general population rather than focusing on vulnerable groups whose well-being might be disproportionally affected [137,138]. Current smokers are one such population because they are at a greater risk of severe illness if they get infected with COVID-19 [139,140]. Adults with psychological distress, which is characterized by depression and anxiety symptoms, have a higher smoking prevalence and smoke more than their non-distressed counterparts [32,141,142]. Thus, stress can be a risk factor leading to more tobacco consumption as well as endangering smokers' chance of fighting COVID-19 if they get infected. A recent study among a small convenience sample of smokers found that increased stress during the pandemic was the main reason for increased smoking [143]. Smokers with depression are often motivated to quit smoking and may make more quit attempts but have less success than their non-depressed counterparts [144–146]. Therefore, understanding smoking behaviors during a pandemic is both complex and important to study to help mitigate tobacco-related harms that may arise from this unprecedented time.

Research has not fully investigated to what degree current smokers experience SPD during the COVID-19 pandemic. A study from the United Kingdom showed that psychological distress increased during the pandemic and smoking decreased; however, this study did not examine the relationship between distress and smoking [21]. Our study fills this gap by examining SPD rates among current smokers, how rates of SPD differ by demographic, smoking, and person characteristics, and how SPD is associated with the intentions to quit smoking or seek

help in quitting smoking during the COVID-19 pandemic. Additionally, it is unclear how SPD is related to COVID-protective intentions and behaviors, such as wearing masks and practicing social distancing. Few studies have specifically considered COVID-19 protective behaviors among current smokers finding that current smokers were less likely to wear a mask in public compared to former smokers and non-smokers [147,148]. However, these studies were conducted outside of the U.S. and did not examine differences among the current smokers. We examined COVID-protective behaviors in a context of a study where current smokers were exposed to messages about risks of smoking and COVID-19, and we also assessed whether SPD moderated the effects of these messages on behavioral intentions.

Materials and Methods

Participants, Design, and Procedure

Participants (n=1004) were U.S. adult current smokers (18 years or older, smoked at least 100 cigarettes and were currently smoking every day or some days) recruited through a survey market research company, Toluna, in August 2020. Participants provided informed consent and the study was approved by the authors' Institutional Review Board.

Participants first answered questions measuring SPD, demographics, smoking frequency, pre-existing smoking quit intentions, general health status, self-reported past COVID-19 disease, and political ideology. Next, participants were randomly assigned to one of four news message conditions: 1) COVID-19 risk information; 2) smoking risk information; 3) combined COVID-19 and smoking risk information; 4) non-health related information (control, see **Appendix VII** for message examples). Each condition contained five news messages about health risks (or non-risk control topics) that were modified from real news stories published by major news outlets. Detailed descriptions of the message development process are provided elsewhere.[149]

Participants in each condition were randomly exposed to one of five news messages to eliminate case-category confounding.[150] Participants could view the message as long as they liked. After viewing the message, participants answered questions about their intentions to quit smoking and implement COVID-19-protective behaviors.

Measures

Serious Psychological Distress. Serious Psychological Distress was measured using the Kessler Psychological Distress Scale (K6).[151] The six questions asked how often participants felt very sad, nervous, restless, hopeless, worthless, and that everything was an effort on a scale (0 = "None of the time" and 4 = "All of the time"). Individuals who scored 13 points or higher were classified as having SPD.

Predictors/covariates. Predictors and covariates in **Table 4.1** were measured prior to message exposure and included participants demographics (age, sex, race, and education), smoking frequency ("some days" versus "every day"); pre-existing smoking quit intentions (ranging from 1 = "currently trying to quit," to 5 = "never expect to quit" [152]; general health status (ranging from "excellent" to "poor")[153]; self-reported past COVID-19 disease ("yes" versus "no"), and political ideology (ranging from "very liberal" to "very conservative")[154].

Outcomes. The outcomes in **Table 4.2** were 1) smoking intentions measured with four questions e.g., "How much do you intend to quit smoking in the next month?" (ranging from 0 = "very definitely no" to 10 = "very definitely yes") [155]; "How likely is it that in the next 6 months you will reduce the number of cigarettes you smoke in a day?" (ranging from 1 = "not at all likely" to 9 = "extremely likely")[156] and 2) COVID-19 protective intentions, measured with three questions, "How frequently do you intend to do each of the following in the next 2-weeks if the COVID-19 pandemic continues?" for "wear a face mask", "wash hands with soap and water"

and “practice social distancing.” Responses were on a scale from 1 = “never” to 4 = “always,” with an option for “don’t know,” which was treated as a missing response.

Data Analysis

The first aim was to examine which participant characteristics were associated with increased odds of SPD. Descriptive statistics for demographic variables were calculated overall and stratified by SPD. We performed logistic regression to calculate the odds of SPD (SPD vs. no SPD) for the continuous (age) and categorical covariates (sex [male vs. female], race [White vs. all other races], education [high school or less vs. college or more], smoking frequency [“some days” vs. “every day”], pre-existing smoking quit intentions [“never expect to quit” vs. other response options], general health status [“poor” vs. other options], self-reported past COVID-19 disease [”yes” vs. “no”], and political ideology [“very conservative” vs. other options], controlling for all other variables in the model.

The second aim was to examine the main effect of SPD and the interactions between message conditions and SPD for smoking intentions and COVID-19 protective intentions. The main effects of conditions are reported elsewhere[149]. We ran general linear models (GLM) for each outcome (smoking and COVID-19 protective intentions) with message condition, SPD, and message condition by SPD interaction. All GLM models controlled for age, sex, race, education, smoking frequency, self-reported past COVID-19 disease, pre-existing smoking quit intentions, political ideology, and general health. Data were analyzed using SPSS 25[157] and significance level was set at $p < .05$.

Results

Participants were 40.6 (Standard Deviation [SD] = 15.0) years old on average, 49.8% female, 67% White, 36.8% had a high school degree or less, 79.4% were daily smokers, and

16.5% reported ever having had COVID-19. Pre-existing smoking quit intentions varied from 43.8% for "maybe in the future but not in the next month" to "will quit in the next month" (6.6%). More than a third of participants indicated "moderate" as their political ideology (37.6%) and a third reported their health status as "good" (32.2%). For additional participant characteristics, see **Table 4.1**.

Among participants, 366 (36%) were classified as having SPD. Age, smoking status, smoking quit intentions, political ideology, and general health were all significantly related to SPD (*ps* < .05). The adjusted odds for SPD decreased with age (adjusted odds ratio [aOR]: 0.95; 95% CI: 0.94, 0.96). Participants who reported smoking some days had significantly lower odds of SPD than those smoking every day (aOR: 0.67; 95% CI: 0.47, 0.97). Participants who reported having COVID-19 disease in the past had significantly higher odds of SPD than those who did not (aOR 2.75; 95% CI: 1.88, 4.02). Participants who intended to quit smoking in the next month were significantly more likely to have SPD than those who had no intention to quit (aOR 1.97; 95% CI: 1.02, 3.81). Participants with very conservative political ideology had higher odds of SPD than those with other political ideologies. The adjusted odds of SPD were significantly lower for participants who reported good to excellent general health than those with poor general health (**Table 4.1**).

There were no significant interactions between message conditions and SPD on smoking intentions and COVID-19-protective intentions (**Table 4.3**). Thus, SPD did not change the impact of the messages on smoking and COVID-19-protective behavioral intentions. However, there was a main effect of SPD on two smoking intention outcomes related to quitting smoking (**Table 4.2**). Specifically, compared to participants with no SPD, participants with SPD were significantly more likely to report an intention to quit smoking in the next month (*b*=1.00;

95%CI: 0.25, 1.76), and seek counseling/support to help quit smoking in the next 6 months (*b*=0.81; 95%CI: 0.14, 1.48). SPD was not significantly related to COVID-19-protective intentions in the next two weeks regarding wearing a face mask (*b*=-0.09; 95%CI: -0.30, 0.13), washing hands (*b*=-0.05; 95%CI: -0.22, 0.11), and practicing social distancing (*b*=-0.07; 95%CI: -0.26, 0.11).

Discussion

In our study, 36% of current smokers had SPD, which was higher than the proportion found in previous studies where SPD among smokers ranged from 5.2% [32] to 23.4% [33]. The prevalence of SPD in our study was also higher than that of adults (smokers and non-smokers) in the U.S. during the COVID-19 pandemic (13.6%)[158] and pre-pandemic (3.4%).[159] These comparisons indicate that while SPD has increased among the U.S. adult population during the COVID-19 pandemic, it might be more pronounced among current smokers.

We found there were some sociodemographic characteristics associated with higher odds of SPD among smokers, including younger smokers and those identifying as "very conservative". A recent study also found that psychological distress during the pandemic was higher among younger adults compared to older adults, consistent with our findings.[160] This study suggested that economic factors related to the pandemic, such as job uncertainty, may be part of the reason younger people are experiencing more stress. Other research has attempted to explore the relationship between political ideology and health outcomes, with one study finding those with were "right-leaning" had a higher perception of COVID-19 risk.[161]As the tumultuous political climate in the U.S. continues alongside the pandemic, it will be important to continue to investigate the impact on health, specifically SPD and substance use.

Current smokers with SPD were significantly more likely to report intentions to quit smoking and seek counseling than current smokers without SPD. While the effect size of this association was small, this finding was consistent with previous research showing that intentions to seek help to quit smoking was significantly higher among smokers with SPD than smokers without SPD.[33] A recent study in New Zealand found that high distress and anxiety were associated with increased daily smoking in the context of COVID-19.[162] Coupled with our results, this may indicate that SPD both increases smoking behaviors (e.g., number of cigarettes smoked) while also increasing motivation to take actions to reduce smoking.

Results showed no significant interactions between SPD and message conditions on intentions to quit smoking. Past research found similar lack of interaction.[33] Additionally, we found no significant interaction between message conditions and SPD and no significant main effect of SPD on intentions to implement COVID-19 preventive behaviors. This was likely due to already high intentions for COVID-19 preventive behaviors (ranging from a mean of 3.4 to 3.7 on a 1-4 scale across the conditions).

Limitations include a non-probability sample, which restricts our ability to generalize to the overall population of smokers in the U.S. Outcomes were measured immediately following a single exposure to the message; therefore, we were not able to assess longer-term outcomes. Another limitation was that we measured behavioral intentions rather than actual behaviors, suggesting the need for longitudinal studies to capture behaviors [163]. Finally, the COVID-19 pandemic and its impact on smokers is a rapidly evolving field of research, and it is likely we did not include all relevant studies in our review of the literature at the time of this article's publication. Despite these limitations, our study offers some insights on the relationship between SPD and smoking quit intentions during the COVID-19 pandemic.

While SPD has been largely associated with negative health outcomes [164], we found higher smoking quit intentions among smokers with SPD compared to smokers without SPD during the COVID-19 pandemic. The U.S. has been the hotspot of the COVID-19 outbreak, and its effect has been profound for many Americans, both non-smokers and current smokers. Tobacco control campaigns should capitalize on the COVID-19 pandemic to make further impacts on encouraging current smokers to quit smoking [165,166]. Smoking cessation programs should consider factors associated with the pandemic that might assist smokers (particularly those with SPD) in their quitting journey.

Table 4.1. Participants' demographic and tobacco use characteristics overall and by past-month serious psychological distress (n=1004).

Participant characteristics	**Overall (N=1,004) N (%)**	**SPD (N=366) N (%)**	**No SPD (N=638) N (%)**	**aOR (95% CI)[a]**
Age (years; mean [SD])	40.6 (15.0)	35.1 (12.0)	43.7 (15.7)	**0.95 (0.94, 0.97)***
Sex				
Female	500 (49.8)	181 (36.2)	319 (63.8)	1.14 (0.84, 1.51)
Male	503 (50.1)	185 (36.8)	318 (63.2)	Reference
Race[b]				
Black	174 (17.7)	57 (32.8)	117 (67.2)	0.75 (0.51, 1.12)
American Indian/Alaska Native	40 (4.1)	14 (35.0)	26 (65.0)	0.68 (0.33, 1.39)
Asian	44 (4.5)	17 (38.6)	27 (61.4)	1.15 (0.56, 2.37)
Native Hawaiian/Other Pacific Islander	12 (1.2)	5 (41.7)	7 (58.3)	1.02 (0.29, 3.60)
More than one race	42 (4.3)	19 (45.2)	23 (54.8)	1.19 (0.83, 1.55)
White	673 (68.3)	246 (36.6)	427 (63.4)	Reference
Education				
Some college or more	635 (63.2)	230 (36.2)	405 (63.8)	1.13 (0.83, 1.55)
High school or less	369 (36.8)	136 (36.9)	233 (63.1)	Reference
Smoking frequency				

Some days	207 (20.6)	73 (35.3)	134 (64.7)	0.70 (0.48, 1.02)
Every day	797 (79.4)	293 (36.8)	504 (63.2)	Reference
Had COVID-19				
Yes	166 (16.5)	106 (63.9)	60 (36.1)	**2.90 (1.97, 4.28)***
No	838 (83.5)	260 (31.0)	578 (69.0)	Reference
Readiness to quit smoking				
Preparation[c]	231 (23.0)	96 (41.6)	135 (58.4)	1.35 (0.94, 1.94)
Contemplation[d]	185 (18.4)	68 (36.8)	117 (63.2)	1.20 (0.82, 1.77)
Pre-contemplation[e]	588 (58.6)	202 (34.4)	386 (65.6)	Reference
Political ideology				
Very liberal	114 (11.4)	46 (40.4)	68 (59.6)	**0.52 (0.31, 0.89)***
Somewhat liberal	123 (12.3)	38 (30.9)	85 (69.1)	**0.35 (0.20, 0.62)***
Moderate	378 (37.6)	114 (30.2)	264 (69.8)	**0.41 (0.27, 0.62)***
Somewhat conservative	199 (19.8)	65 (32.7)	134 (67.3)	**0.43 (0.27, 0.69)***
Very conservative	190 (18.9)	103 (54.2)	87 (45.8)	Reference
General health				
Excellent	176 (17.5)	87 (49.4)	89 (50.6)	**0.39**

				(0.17, 0.88)*
Very good	287 (28.6)	90 (31.4)	197 (68.6)	**0.24**
				(0.11, 0.53)*
Good	323 (32.2)	99 (30.7)	224 (69.3)	**0.32**
				(0.15, 0.68)*
Fair	179 (17.8)	69 (38.5)	110 (61.5)	0.56 (0.26, 1.24)
Poor	39 (3.9)	21 (53.8)	18 (46.2)	Reference

[a]Results of a multiple logistic regression. aOR – adjusted Odds Ratio, adjusted for all other variables in the model; [b]Nineteen participants had missing data for race/ethnicity and one participant had missing data for sex; [c]Includes "Will quit in the next month" and "Are currently trying to quit"; [d] Includes "Will quit in the next 6 months"; e Includes "May quit in the future, but not in the next 6 months" and "Never expect to quit"; *Significant at $\alpha = 0.05$

Table 4.2. Mean scores and SD for smoking and COVID-19 protective intentions for those with and without SPD as well as the main effect of SPD on intentions.

Outcome variables	**SPD (N=366)** **Mean (SD)**[a]	**No SPD (N=638)** **Mean (SD)**	**Main effect of SPD (SPD vs no SPD)** **Unstandardized *b* (95% CI)**[b]
Smoking behavioral intentions (post-experiment)			
"How much do you intend to quit smoking in the next month?"[c]	5.54 (3.22)	4.76 (3.25)	**1.00 (0.25, 1.76)**
"Reduce the number of cigarettes you smoke in a day [in the next 6 months]"[d]	6.02 (2.48)	5.98 (2.46)	-0.18 (-0.79, 0.43)
"Seek counseling/support to help you quit smoking [in the next 6 months].[d]	5.26 (2.64)	4.34 (2.77)	**0.81 (0.14, 1.49)**
"Use nicotine gum, nicotine patch, or other forms of nicotine replacement therapy (NRT) [in the next 6 months]."[c]	5.35 (2.66)	4.64 (2.78)	0.56 (-0.14, 1.25)

COVID-protective intentions			
Wear a face mask in public in the next two weeks. [e]	3.39 (0.90)	3.57 (0.78)	-0.09 (-0.30, 0.13)
Wash hands with soap and water in the next two weeks. [e]	3.58 (0.73)	3.74 (0.59)	-0.05 (-0.22, 0.11)
Practice social distancing in the next two weeks. [e]	3.50 (0.76)	3.66 (0.68)	-0.07 (-0.26, 0.11)

Notes.

[a] SD – standard deviation.

[b] The general linear model for the main effect of SPD controlled for age, sex, race, education, smoking frequency, self-reported COVID-19 diagnosis, pre-existing quit intentions, political ideology, general health, message condition and the interaction between message condition and SPD.

[c] On a scale from 0 = "very definitely no" to 10 = "very definitely yes".

[d] On a scale from 1 = "not at all likely to 9 = "extremely likely".

[e] On a scale from 1 = "never" to 4 = "always".

Table 4.3. Interactions between SPD and Risk Messages

Outcome variables	**Interaction: COVID-risk condition x SPD, unstandardized *b* (95% CI)**	**Interaction: Smoking-risk condition x SPD, unstandardized *b* (95% CI)**	**Interaction: COVID+Smoking-risk condition x SPD, unstandardized *b* (95% CI)**
Smoking behavioral intentions			
"How much do you intend to quit smoking in the next month?"	-0.72 (-1.76, 0.32)	-0.90 (-1.96, 0.16)	-0.09 (-1.15, 0.96)
"Reduce the number of cigarettes you smoke in a day [in the next 6 months]"	0.23 (-0.60, 1.06)	0.39 (-0.47, 1.25)	0.21 (-0.64, 1.06)
"Seek counseling/support to help you quit smoking [in the next 6 months]."	-0.10 (-1.01, 0.82)	-0.25 (-1.20, 0.69)	-0.52 (-1.46, 0.42)

"Use nicotine gum, nicotine patch, or other forms of nicotine replacement therapy (NRT) [in the next 6 months]."	-0.28 (-1.22, 0.67)	-0.28 (-1.25, 0.70)	-0.01 (-0.98, 0.96)
COVID-protective intentions			
Wear a face mask in public in the next two weeks.	0.15 (-0.15, 0.44)	-0.03 (-0.33, 0.27)	0.06 (-0.24, 0.36)
Wash hands with soap and water in the next two weeks.	0.03 (-0.19, 0.25)	-0.05 (-0.27, 0.18)	0.01 (-0.22, 0.23)
Practice social distancing in the next two weeks.	0.15 (-0.11, 0.40)	-0.10 (-0.36, 0.16)	0.02 (-0.23, 0.28)

Notes. General linear models controlled for age, sex, race, education, daily smoking, self-reported COVID-19 diagnosis, baseline quit intentions, political ideology, and self-reported health status.

Chapter 5. Summary and Future Directions

Summary

This dissertation aimed to address several topics related to substance use among special populations (i.e., those with mental health issues and youth), with the goals of not only contributing to the current scientific knowledge, but also placing a spotlight on issues that need further examination.

The first study (Chapter 2) confirmed findings from a previous meta-analysis that people who use cannabis had higher odds of experiencing depression, compared to non-users. Eight additional studies, since the conclusion of the Lev-Ran, et al. study in 2012, were identified that provided data on the longitudinal association between cannabis use and depression.

The second and third studies (Chapters 3 and 4) were uniquely within the context of the COVID-19 pandemic. In Chapter 3, we found that youth ENDS users from our sample were consistently making modifications to their devices, specifically the e-liquids, but also to their coils/wicks and batteries. Motivations for modifications were mainly about wanting a customized experience, such as a particular taste/flavor or strength. However, we also saw that youth from our study modified their devices out of necessity based on their limited access to ENDS devices and accessories. Furthermore, many of the youth we interviewed discussed the use of cannabis in their ENDS devices. This is of particular concern, especially considering the possibility of cannabis use being associated with an increased risk of depression, as we found in the meta-analysis (Chapter 2) of this dissertation.

The third study found that smokers with SPD had higher intentions to quit smoking in the next month (b=1.00; 95% CI: 0.25, 1.76), and seek counseling/support to help quit smoking in the next 6 months (b=0.81; 95% CI: 0.14, 1.48) compared to smokers without SPD. Furthermore,

we found that age, smoking status, smoking quit intentions, political ideology, and general health were all significantly related to SPD (*ps* < .05). Smokers who were older had decreased odds of SPD, compared to younger smokers. Those who did not smoke every day, compared to those who reported smoking every day, were less likely to have SPD. Smokers who indicated they intended to quit smoking in the next month were significantly more likely to have SPD than those who had no intention to quit. Smokers with very conservative political ideology had higher odds of SPD than those with other political ideologies (conservative through very liberal). Smokers who considered themselves to be in good to excellent general health were less likely to have SPD, compared to those who identified as being in poor health. Though this analysis was a part of a larger study looking at COVID and smoking messaging, we found that SPD did not change the impact of the messages on smoking and COVID-19-protective behavioral intentions.

Future Directions

Overall, future research on cannabis should consider ways to standardize measurements of cannabis use, which will better enable scientists to make comparisons across studies. In the systematic review of the literature for the meta-analysis, there were several definitions of cannabis use which were identified. This made it difficult to pinpoint what level of cannabis use was more strongly associated with depression. Furthermore, all of the studies in the meta-analysis relied on self-report to quantify cannabis use, which can lead to inaccurate data.[167] Researchers who design studies for cannabis users in the future may want to consider also collecting biomarker data, in order to validate participants' self-reports.

It was beyond the scope of the current project to look at the relationship between cannabis policies and depression; however, this is an area in which future research may be able to elucidate information that could help inform decision-makers going forward. For example, do

cannabis users who live in states where it is legal to purchase have better mental health outcomes, compared to cannabis users in states where cannabis is illegal, and therefore users have difficulty accessing consistent and quality products without fear of prosecution? Many more research questions will emerge as the landscape of cannabis in the U.S., and the world, evolves. The meta-analysis (**Chapter 2**) proposed opportunities for immediate exploration, including looking specifically at the mode of cannabis consumption, and explore potential moderators in the relationship between cannabis use and depression.

The qualitative study presented in this dissertation also offers ideas for future research. As we identified, the youth in our study participated in risky ENDS modification, such as adding drugs (e.g., cannabis, cocaine) and other substances dangerous to vape (e.g., food products) to their e-liquids. While the CDC warns against vaping any products that are not intended for vaping,[133] there is a dearth of information on the actual consequences of vaping unregulated substances. Research should investigate whether these substances cause direct, physical harm to ENDS users from the inhalation of the aerosol, as well as if the substances added cause the devices themselves to be more dangerous (for example, does the build-up from vaping food products such as homemade strawberry juice lead to an increased risk of burns from the affected devices?).

In the quantitative study, we found that approximately one third (36%) of smokers in our study met the cut-off (a score of 13 points or more), based on the Kessler-6, for SPD, which is categorized by feelings of anxiety and depression.[151] Though our study was not a representative sample of adult smokers in the U.S., it is still an alarming finding. Previous conducted national research, found that approximately 3.4% of adults (smokers and non-smokers) in the U.S. met the criteria for SPD.[159] and pre-pandemic estimates among smokers ranged from 5.2% [32] to

23.4%.[33] Therefore, understanding the mechanism between SPD and smoking may help to elucidate ways to reduce the burden of this co-morbidity. For example, are people with SPD more likely to become smokers as a way to manage their stress, or do the harms from smoking lead to increased distress?

Our study found that smokers with SPD were more likely to report intentions to quit smoking and to seek help for quitting smoking. Future research should follow-up with these smokers to see how successful they are at long-term quit attempts, and to find ways to leverage SPD to their advantage. For example, SPD may make a smoker more motivated to quit, but less able to maintain their non-smoking status.

Conclusions

The purpose of this dissertation was to address the research questions related to tobacco and cannabis use with special focuses on youth and on mental health. The goal was to help reduce the public health burden associated with tobacco and drug use, especially among those who are most vulnerable. While the three studies presented represent small steps, they have the potential to inform future studies, ultimately acting as a ripple in the sea of this vital research.

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151. Kessler RC, Andrews G, Colpe LJ, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol Med*. 2002;32(6):959-976. doi:10.1017/s0033291702006074

152. Prochaska JO, DiClemente CC. Self change processes, self efficacy and decisional balance across five stages of smoking cessation. *Prog Clin Biol Res*. 1984;156:131-140.

153. Idler EL, Benyamini Y. Self-rated health and mortality: A review of twenty-seven community studies. *J Health Soc Behav*. 1997;38(1):21-37. doi:10.2307/2955359

154. Napier JL, Jost JT. Why are conservatives happier than liberals? *Psychol Sci*. 2008;19(6):565-572. doi:10.1111/j.1467-9280.2008.02124.x

155. Carpenter MJ, Hughes JR, Solomon LJ, Callas PW. Both smoking reduction with nicotine replacement therapy and motivational advice increase future cessation among smokers unmotivated to quit. *J Consult Clin Psychol*. 2004;72(3):371-381. doi:10.1037/0022-006X.72.3.371

156. Wong NC, Cappella JN. Antismoking threat and efficacy appeals: effects on smoking cessation intentions for smokers with low and high readiness to quit. *J Appl Commun Res*. 2009;37(1):1-20.

157. IBM Corp. Released 2017. *IBM SPSS Statistics for Windows, Version 25.0.* Armonk, NY: IBM Corp.

158. McGinty EE, Presskreischer R, Anderson KE, Han H, Barry CL. Psychological distress and COVID-19–related stressors reported in a longitudinal cohort of US adults in April and July 2020. *JAMA*. 2020;324(24):2555-2557. doi:10.1001/jama.2020.21231

159. Weissman JF, Pratt LA, Miller EA, Parker JD. Serious psychological distress among adults: United States, 2009-2013. NCHS Data Brief. 2015 May;(203):1-8. PMID: 26046826.

160. Breslau J, Finucane ML, Locker AR, Baird MD, Roth EA, Collins RL. A longitudinal study of psychological distress in the United States before and during the COVID-19 pandemic. *Prev Med*. 2021;143:106362. doi:10.1016/j.ypmed.2020.106362

161. Tung HH, Chang TJ, Lin MJ. Political ideology predicts preventative behaviors and infections amid COVID-19 in democracies. *Soc Sci Med*. 2022;308:115199. doi:10.1016/j.socscimed.2022.115199

162. Gendall P, Hoek J, Stanley J, Jenkins M, Every-Palmer S. Changes in Tobacco Use During the 2020 COVID-19 Lockdown in New Zealand. *Nicotine Tob Res*. 2021;23(5):866-871 doi:10.1093/ntr/ntaa257

163. Ajzen I, Brown TC, Carvajal F. Explaining the discrepancy between intentions and actions: The case of hypothetical bias in contingent valuation. *Pers Soc Psychol Bull*. 2004;30(9):1108-1121. doi:10.1177/0146167204264079

164. American Psychological Association. Stress effects on the body. https://www.apa.org. Published November 1, 2018. Accessed February 4, 2021. https://www.apa.org/topics/stress/body

165. Grummon AH, Hall MG, Mitchell CG, et al. Reactions to messages about smoking, vaping and COVID-19: Two national experiments. *Tob Control*. Published online November 13, 2020. doi:10.1136/tobaccocontrol-2020-055956

166. Popova L. Carpe COVID: Using COVID-19 to communicate about harms of tobacco products. *Tob Control*. Published online November 12, 2020:tobaccocontrol-2020-056276. doi:10.1136/tobaccocontrol-2020-056276

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Appendix

Appendix I: Acronyms

aOR	adjusted odds ratio
AUDADIS	Alcohol Use Disorder and Associated Disabilities Interview Schedule
CDC	Centers for Disease Control and Prevention
CES-D	Center for Epidemiologic Studies Depression Scale
CIDI	Composite International Diagnostic Interview
CIS	Clinical Interview Schedule
COPD	Chronic Obstructive Pulmonary Disease
CSU	Computerized Substance Use Inventory
CUD	Cannabis Use Disorder
DICA	Diagnostic Interview for Children and Adolescents
DSM	Diagnostic and Statistical Manual of Mental Disorders
ENDS	Electronic Nicotine Delivery Systems
FDA	U.S. Food and Drug Administration
GLM	general linear models
ICD	International Classification of Diseases
JSI	John Snow, Inc
K6	Kessler Psychological Distress Scale
MDD	Major Depressive Disorder
PG	propylene glycol
SC	Symptom Checklist
SCID	Structured Clinical Interview for the DSM
SD	standard deviation

SPD	Serious Psychological Distress
SRQR	Standards for Reporting Qualitative Research
US	United States
VG	vegetable glycerine

Appendix II: Search terms

PubMed

(cannabis OR marijuana AND depression OR depressive OR MDD AND longitudinal NOT retrospective NOT treatment NOT spatial NOT genetics NOT e-cigarette NOT policy NOT prenatal NOT prevalence NOT market NOT magnetic NOT parental NOT family NOT schizot* NOT schizophren* NOT receptor)

OvidMedline

((AB (cannabis or marijuana or thc or pot or weed or thc or cbd or tetrahydrocannabinol or cannabidiol) AND AB (depression or depressive disorder or depressive symptoms or major depressive disorder) AND AB (longitudinal studies or longitudinal research or longitudinal method)) NOT (self-injurious behavior or self injury or self harm) NOT (sexually transmitted diseases or sexually transmitted infections or sti or std)) NOT AB opioid

GoogleScholar

(cannabis OR marijuana) AND (depression or depress) AND longitudinal

ProQuest Dissertations & Theses A&I

ti(cannabis or marijuana) AND ti(depression or depress); limit to doctoral dissertations only

Appendix III: Screening tool

Original Search

Citation	Does it mention cannabis?	Does it mention depression?	Is it a longitudinal study?	Does it specify cannabis use before depression?	Is it a special population?	Decision	Notes
Hines LA, Freeman TP, Gage SH, et al. Association of High-Potency Cannabis Use With Mental Health and Substance Use in Adolescence. JAMA Psychiatry. 2020;77(10):1044-1051.	yes	yes	yes	yes	**yes - only cannabis users**	exclude	because it only looked at cannabis users for their analysis and did not compare cannabis users vs non users
Gage SH, Hickman M, Heron J, et al. Associations of Cannabis and Cigarette Use with Depression and Anxiety at Age 18: Findings from the Avon Longitudinal Study of Parents and Children. PLOS ONE. 2015;10(4):e0122896. doi:10.1371/journal.pone.0122896	yes	yes	yes	yes	no	include	
Cannabis and anxiety and depression in young adults: a large prospective study.	yes	**yes - but only in combination with anxiety**	yes	yes	no	exclude	does not separate depression from anxiety
Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychological Medicine. 2003;33(1):15-21. doi:10.1017/S0033291702006402	yes	**no**	no	yes	no	exclude	"psychotic symptoms" and not depression
Wittchen HU, Fröhlich C, Behrendt S, et al. Cannabis use and cannabis use disorders and their relationship to mental disorders: A 10-year prospective-longitudinal community study in adolescents. Drug and Alcohol Dependence. 2007;88:S60-S70. doi:10.1016/j.drugalcdep.2006.12.013	yes	yes	yes	**no**	no	exclude	temporal association of cannabis - depression not established
Fergusson DM, Boden JM. Cannabis use and later life outcomes. Addiction. 2008;103(6):969-976. doi:10.1111/j.1360-0443.2008.02221.x	yes	**no**	yes	no	no	exclude	does not look at depression
Blanco C, Hasin DS, Wall MM, et al. Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence From a US National Longitudinal Study. JAMA Psychiatry. 2016;73(4):388-395. doi:10.1001/jamapsychiatry.2015.3229	yes	yes	yes	yes	no	include	it is the same population as Feingold, 2014

Feingold D, Rehm J, Lev-Ran S. Cannabis use and the course and outcome of major depressive disorder: A population based longitudinal study. Psychiatry Research. 2017;251:225-234. doi:10.1016/j.psychres.2017.02.027	yes	yes	yes	**no**	yes - people with major depressive disorder at baseline	exclude	only looked at people with MDD at baseline
Arseneault L. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002;325(7374):1212-1213. doi:10.1136/bmj.325.7374.1212	yes	yes	yes	yes	no	Include	
Hawke LD, Wilkins L, Henderson J. Early cannabis initiation: Substance use and mental health profiles of service-seeking youth. Journal of Adolescence. 2020;83:112-121. doi:10.1016/j.adolescence.2020.06.004	yes	yes	**no**	no	yes - service seeking youth	exclude	cross-sectional and special population
Gunn RL, Stevens AK, Micalizzi L, Jackson KM, Borsari B, Metrik J. Longitudinal associations between negative urgency, symptoms of depression, cannabis and alcohol use in veterans. Experimental and Clinical Psychopharmacology. 2020;28(4):426-437. doi:10.1037/pha0000357	yes	yes	yes	yes	**yes - Iraqi war veterans**	exclude	too niche of a population
Rasic D, Weerasinghe S, Asbridge M, Langille DB. Longitudinal associations of cannabis and illicit drug use with depression, suicidal ideation and suicidal attempts among Nova Scotia high school students. Drug and Alcohol Dependence. 2013;129(1):49-53. doi:10.1016/j.drugalcdep.2012.09.009	**yes, but also other ilicit drugs**	yes	yes, but also concurrent	yes	no	exclude	looked at cannabis use and depression concurrently; longitudinal association was only on groups that used cannabis+other illicit drugs compared to cannabis users
Danielsson AK, Lundin A, Agardh E, Allebeck P, Forsell Y. Cannabis use, depression and anxiety: A 3-year prospective population-based study. Journal of Affective Disorders. 2016;193:103-108. doi:10.1016/j.jad.2015.12.045	yes	yes	yes	yes	no	include	
London-Nadeau K, Rioux C, Parent S, et al. Longitudinal associations of cannabis, depression, and anxiety in heterosexual and LGB adolescents. J Abnorm Psychol. 2021;130(4):333-345. doi:10.1037/abn0000542	yes	yes	yes	**no**	yes	exclude	does not provide needed information on cannabis - depression

Hengartner MP, Angst J, Ajdacic-Gross V, Rössler W. Cannabis use during adolescence and the occurrence of depression, suicidality and anxiety disorder across adulthood: Findings from a longitudinal cohort study over 30 years. Journal of Affective Disorders. 2020;272:98-103. doi:10.1016/j.jad.2020.03.126	yes	yes	yes	**yes**	no	include	
Dyar C, Bradley H, Morgan E, Sullivan PS, Mustanski B. Reduction and Cessation of Alcohol, Cannabis, and Stimulant Use: Prospective Associations With Changes in Depressive Symptoms Across Two Cohort Studies of Sexual and Gender Minorities. J Stud Alcohol Drugs. 2020;81(6):790-797.	yes	yes	yes	yes	**yes**	exclude	looks at changes in use, which is beyond the scope of this review
Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. Addiction. 2005;100(3):354-366. doi:10.1111/j.1360-0443.2005.01001.x	yes	**no**	yes	no	no	exclude	psychotic symptoms but not depression
Feingold D, Weiser M, Rehm J, Lev-Ran S. The association between cannabis use and mood disorders: A longitudinal study. Journal of Affective Disorders. 2015;172:211-218. doi:10.1016/j.jad.2014.10.006	yes	yes	yes	yes	no	include	
Campeny E, López-Pelayo H, Nutt D, et al. The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms. European Neuropsychopharmacology. 2020;33:1-35. doi:10.1016/j.euroneuro.2020.02.003	yes	yes	**no - review**	yes	no	exclude	systematic review
Silins E, Horwood LJ, Patton GC, et al. Young adult sequelae of adolescent cannabis use: an integrative analysis. The Lancet Psychiatry. `2014;1(4):286-293. doi:10.1016/S2215-0366(14)70307-4	yes	yes	**no - review**	yes	no	exclude	meta-analysis of three cohort studies which we already included
Copeland WE, Hill SN, Shanahan L. Adult Psychiatric, Substance, and Functional Outcomes of Different Definitions of Early Cannabis Use. Journal of the American Academy of	yes	yes	yes	yes	no	include	

Child & Adolescent Psychiatry.
2022;61(4):533-543.
doi:10.1016/j.jaac.2021.07.824

Ancestor Search

Parent Article	Citation	Does it mention cannabis?	Does it mention depression?	Is it a longitudinal study?	Does it specify cannabis use before depression?	Is it a special population?	Is it a review article?	Decision	Notes
Bovasso, 2001	Assari S, Mistry R, Caldwell CH, Zimmerman MA. Marijuana Use and Depressive Symptoms; Gender Differences in African American Adolescents. Front Psychol. 2018;9:2135. doi:10.3389/fpsyg.2018.02135	yes	yes	yes	yes	**yes - African American**		exclude	path analysis rather than odds
Bovasso, 2001	Bechtold J, Simpson T, White HR, Pardini D. Chronic adolescent marijuana use as a risk factor for physical and mental health problems in young adult men. Psychol Addict Behav. 2015;29(3):552-563. doi:10.1037/adb0000103	yes	**no**	yes	no	yes - men only		exclude	does not provide depression outcomes
Bovasso, 2001	Bornovalova MA, Verhulst B, Webber T, McGue M, Iacono WG, Hicks BM. Genetic and environmental influences on the codevelopment among borderline personality disorder traits, major depression symptoms, and substance use disorder symptoms from adolescence to young adulthood. Dev Psychopathol. 2018;30(1):49-65. doi:10.1017/S0954579417000463	**no**						exclude	not cannabis
Bovasso, 2001	de Graaf R, Radovanovic M, van Laar M, et al. Early cannabis use and estimated risk of later onset of depression spells: Epidemiologic evidence from the population-based World Health Organization World Mental Health Survey Initiative. Am J Epidemiol. 2010;172(2):149-159. doi:10.1093/aje/kwq096	yes	Yes	**no - cross sectional**	yes	no		exclude	cross-sectional

Bovasso, 2001	Dembo R, Krupa J, Wareham J, Schmeidler J, DiClemente RJ. A Multigroup, Longitudinal Study of Truant Youths, Marijuana Use, Depression, and STD-Associated Sexual Risk Behavior. J Child Adolesc Subst Abuse. 2017;26(3):192-204. doi:10.1080/1067828X.2016.1260510	yes	**yes but not as an outcome**	yes		no	yes - truant youth	exlcude	not focused on cannabis - depression link
Bovasso, 2001	Feingold D, Weinstein A. Cannabis and Depression. Adv Exp Med Biol. 2021;1264:67-80. doi:10.1007/978-3-030-57369-0_5	yes	yes	**no**				exclude	not a study
Bovasso, 2001	Gorka SM, Shankman SA, Seeley JR, Lewinsohn PM. The moderating effect of parental illicit substance use disorders on the relation between adolescent depression and subsequent illicit substance use disorders. Drug Alcohol Depend. 2013;128(1-2):1-7. doi:10.1016/j.drugalcdep.2012.07.011	**no**	yes	yes	no		yes - youth with parents who use drugs	exclude	not the right population
Bovasso, 2001	Kuhns L, Kroon E, Colyer-Patel K, Cousijn J. Associations between cannabis use, cannabis use disorder, and mood disorders: longitudinal, genetic, and neurocognitive evidence. Psychopharmacology (Berl). Published online November 6, 2021. doi:10.1007/s00213-021-06001-8	yes	yes	**no - review article**				exclude	review article
Bovasso, 2001	Lee JY, Brook JS, Kim W. Triple trajectories of alcohol use, tobacco use, and depressive symptoms as predictors of cannabis use disorders among urban adults. Psychol Addict Behav. 2018;32(4):466-474. doi:10.1037/adb00003731. Lee JY, Brook JS, Kim W. Triple trajectories of alcohol use, tobacco use, and depressive symptoms as predictors of cannabis use disorders among urban adults. Psychol Addict Behav. 2018;32(4):466-474. doi:10.1037/adb0000373	yes	yes	yes	**no**			exclude	looks at depression - CUD

Bovasso, 2001	Leventhal AM, Cho J, Stone MD, et al. Associations between anhedonia and marijuana use escalation across mid-adolescence. Addiction. 2017;112(12):2182-2190. doi:10.1111/add.13912	yes	**no**					exclude	anhedonia not depression
Bovasso, 2001	Looby A, Earleywine M. Negative consequences associated with dependence in daily cannabis users. Subst Abuse Treat Prev Policy. 2007;2:3. doi:10.1186/1747-597X-2-3	yes	**no**					exclude	not depression
Bovasso, 2001	Lucatch AM, Coles AS, Hill KP, George TP. Cannabis and Mood Disorders. Curr Addict Rep. 2018;5(3):336-345. doi:10.1007/s40429-018-0214-y	yes	yes	**no**				exclude	review article
Bovasso, 2001	Pahl K, Brook JS, Koppel J. Trajectories of marijuana use and psychological adjustment among urban African American and Puerto Rican women. Psychol Med. 2011;41(8):1775-1783. doi:10.1017/S0033291710002345	yes	yes	yes	**no**	yes - African American and Puerto Rican women		exclude	does not provide data on odds of depression after cannabis use (only average depression score)
Bovasso, 2001	Rey JM, Tennant CC. Cannabis and mental health. BMJ. 2002;325(7374):1183-1184. doi:10.1136/bmj.325.7374.1183	yes	yes	**no**	no			exclude	review article
Bovasso, 2001	Smolkina M, Morley KI, Rijsdijk F, et al. Cannabis and Depression: A Twin Model Approach to Co-morbidity. Behav Genet. 2017;47(4):394-404. doi:10.1007/s10519-017-9848-0	yes	yes	yes	**no**	yes - twins		exclude	does not report cannabis - depression
Bovasso, 2001	Womack SR, Shaw DS, Weaver CM, Forbes EE. Bidirectional Associations Between Cannabis Use and Depressive Symptoms From Adolescence Through Early Adulthood Among At-Risk Young Men. J Stud Alcohol Drugs. 2016;77(2):287-297. doi:10.15288/jsad.2016.77.287	yes	yes	yes	**no**	yes - at risk men		exclude	bidirectional and special population of men who are at risk for depression and cannabis use
Brook, 2002	Brook JS, Stimmel MA, Zhang C, Brook DW. The association between earlier marijuana use and subsequent academic achievement and health problems: a longitudinal study. Am J	yes		**no**				exclude	not depression

	Addict. 2008;17(2):155-160. doi:10.1080/10550490701860930 Brook JS, Zhang C, Leukefeld CG, Brook DW. Marijuana use from adolescence to adulthood: developmental trajectories and their outcomes. Soc Psychiatry Psychiatr Epidemiol. 2016;51(10):1405-1415.								
Brook, 2002	doi:10.1007/s00127-016-1229-0 Chinet L, Plancherel B, Bolognini M, et al. Substance use and depression. Comparative course in adolescents. Eur Child Adolesc Psychiatry. 2006;15(3):149-155.	yes	**no**					exclude	not depression
Brook, 2002	doi:10.1007/s00787-005-0516-1 Chuang CWI, Chan C, Leventhal AM. Adolescent Emotional Pathology and Lifetime History of Alcohol or Drug Use With and Without Comorbid Tobacco Use. J Dual Diagn. 2016;12(1):27-35.	yes	yes	yes	**no**			exclude	looks at depression and cannabis simultaneously
Brook, 2002	doi:10.1080/15504263.2016.1146557 Fairman BJ, Anthony JC. Are early-onset cannabis smokers at an increased risk of depression spells? J Affect Disord. 2012;138(1-2):54-62.	**no**	yes	no				exclude	cross-sectional
Brook, 2002	doi:10.1016/j.jad.2011.12.031 Filipponi C, Petrocchi S, Camerini AL. Bullying and Substance Use in Early Adolescence: Investigating the Longitudinal and Reciprocal Effects Over 3 Years Using the Random Intercept Cross-Lagged Panel Model. Front Psychol. 2020;11:571943.	yes	yes	**no**	yes	no		exclude	cross-sectional
Brook, 2002	doi:10.3389/fpsyg.2020.571943 Gau JM, Stice E, Rohde P, Seeley JR. Negative life events and substance use moderate cognitive behavioral adolescent depression prevention intervention. Cogn Behav Ther. 2012;41(3):241-250.	yes	**no**					exclude	not depression
Brook, 2002	doi:10.1080/16506073.2011.649781 Green KM, Zebrak KA, Fothergill KE, Robertson JA, Ensminger ME. Childhood and adolescent risk factors for comorbid depression and substance use disorders in adulthood.	**No**	yes	no				exclude	RCT and not cannabis
Brook, 2002		yes	yes	**no**	no			exclude	not longitudinal analysis

	Addict Behav. 2012;37(11):1240-1247. doi:10.1016/j.addbeh.2012.06.008 Guttmannova K, Kosterman R, White HR, et al. The association between regular marijuana use and adult mental health outcomes. Drug Alcohol Depend. 2017;179:109-116. doi:10.1016/j.drugalcdep.2017.06.016							
Brook, 2002	McKowen JW, Tompson MC, Brown TA, Asarnow JR. Longitudinal associations between depression and problematic substance use in the Youth Partners in Care study. J Clin Child Adolesc Psychol. 2013;42(5):669-680. doi:10.1080/15374416.2012.759226	yes	**no**				exclude	not depression
Brook, 2002	Poudel A, Gautam S. Age of onset of substance use and psychosocial problems among individuals with substance use disorders. BMC Psychiatry. 2017;17(1):10. doi:10.1186/s12888-016-1191-0	yes	yes	yes	**no**	Yes	exclude	not cannabis - depression and pts are receiving mental health tx
Brook, 2002	Schwinn TM, Schinke SP, Trent DN. Substance use among late adolescent urban youths: mental health and gender influences. Addict Behav. 2010;35(1):30-34. doi:10.1016/j.addbeh.2009.08.005	**no**	no	no			exclude	cross-sectional
Brook, 2002	Wymbs BT, McCarty CA, Mason WA, et al. Early adolescent substance use as a risk factor for developing conduct disorder and depression symptoms. J Stud Alcohol Drugs. 2014;75(2):279-289.	yes	yes	**no**			exclude	cross-sectional
Degenhardt, 2013	Botsford SL, Yang S, George TP. Cannabis and Cannabinoids in Mood and Anxiety Disorders: Impact on Illness Onset and Course, and Assessment of Therapeutic Potential. Am J Addict. 2020;29(1):9-26. doi:10.1111/ajad.12963	**yes but only with alcohol**	yes	yes	yes	no	exclude	doesn't look at cannabis alone
Degenhardt, 2013	Brook JS, Zhang C, Rubenstone E, Primack BA, Brook DW. Comorbid trajectories of substance use as predictors of Antisocial Personality Disorder, Major Depressive Episode,	yes	yes	**no**			Exclude	systematic review
		yes - but with other substances	yes	yes	yes	no	exclude	does not report on cannabis alone

	and Generalized Anxiety Disorder. Addict Behav. 2016;62:114-121. doi:10.1016/j.addbeh.2016.06.003 Hosseini S, Oremus M. The Effect of Age of Initiation of Cannabis Use on Psychosis, Depression, and Anxiety among Youth under 25 Years. Can J								
Degenhardt, 2013	Psychiatry. 2019;64(5):304-312. doi:10.1177/0706743718809339 Keith DR, Hart CL, McNeil MP, Silver R, Goodwin RD. Frequent marijuana use, binge drinking and mental health problems among undergraduates. Am J Addict.	yes	yes	**no**				exclude	systematic review
Degenhardt, 2013	2015;24(6):499-506. doi:10.1111/ajad.12201 Renard J, Krebs MO, Le Pen G, Jay TM. Long-term consequences of adolescent cannabinoid exposure in adult psychopathology. Front	yes	yes	**no**				exclude	cross-sectional
Degenhardt, 2013	Neurosci. 2014;8:361. doi:10.3389/fnins.2014.00361 Rhew IC, Fleming CB, Vander Stoep A, Nicodimos S, Zheng C, McCauley E. Examination of cumulative effects of early adolescent depression on cannabis and alcohol use disorder in late adolescence in a community-based cohort. Addiction.	yes	**yes - but with anxiety**					exclude	does not look at depression alone
Degenhardt, 2013	2017;112(11):1952-1960. doi:10.1111/add.13907 Brook JS, Stimmel MA, Zhang C, Brook DW. The association between earlier marijuana use and subsequent academic achievement and health problems: a longitudinal study. Am J	yes	yes	yes		**no**		exclude	looks at depression - cannabis
Fergusson, 1997	Addict. 2008;17(2):155-160. doi:10.1080/10550490701860930 Goldschmidt L, Richardson GA, Larkby C, Day NL. Early marijuana initiation: The link between prenatal marijuana exposure, early childhood behavior, and negative adult roles.	yes	**yes - with other metal health**	yes	yes	no		exclude	does not separate depression from other mental health
Fergusson, 1997	Neurotoxicol Teratol. 2016;58:40-45. doi:10.1016/j.ntt.2016.05.011 Meier MH, Hill ML, Small PJ, Luthar SS. Associations of	**yes - prenatal exposure**	no					Exclude	prenatal exposure to cannabis
Fergusson, 1997	adolescent cannabis use with	yes	**no**					exclude	"internalizing symptoms"

	academic performance and mental health: A longitudinal study of upper middle class youth. Drug Alcohol Depend. 2015;156:207-212. doi:10.1016/j.drugalcdep.2015.09.010					
Fergusson, 1997	Smolkina M, Morley KI, Rijsdijk F, et al. Cannabis and Depression: A Twin Model Approach to Co-morbidity. Behav Genet. 2017;47(4):394-404. doi:10.1007/s10519-017-9848-0	yes	yes	**no**	exclude	genetic study
Georgiades, 2008	Botsford SL, Yang S, George TP. Cannabis and Cannabinoids in Mood and Anxiety Disorders: Impact on Illness Onset and Course, and Assessment of Therapeutic Potential. Am J Addict. 2020;29(1):9-26. doi:10.1111/ajad.12963	yes	yes	**no - review article**	exclude	review article
Georgiades, 2008	Chadwick B, Miller ML, Hurd YL. Cannabis Use during Adolescent Development: Susceptibility to Psychiatric Illness. Front Psychiatry. 2013;4:129. doi:10.3389/fpsyt.2013.00129	yes	yes	**no**	exclude	not a longitudinal study
Georgiades, 2008	Esmaeelzadeh S, Moraros J, Thorpe L, Bird Y. The association between depression, anxiety and substance use among Canadian post-secondary students. Neuropsychiatr Dis Treat. 2018;14:3241-3251. doi:10.2147/NDT.S187419	yes	yes	**no**	exclude	cross-sectional
Patton, 2002	Fischer AS, Tapert SF, Lee Louie D, Schatzberg AF, Singh MK. Cannabis and the Developing Adolescent Brain. Curr Treat Options Psychiatry. 2020;7(2):144-161. doi:10.1007/s40501-020-00202-2	yes	yes	**no**	exclude	review article
Patton, 2002	Gukasyan N, Strain EC. Relationship between cannabis use frequency and major depressive disorder in adolescents: Findings from the National Survey on Drug Use and Health 2012-2017. Drug Alcohol Depend. 2020;208:107867. doi:10.1016/j.drugalcdep.2020.107867	yes	yes	**no**	exclude	cross-sectional

Patton, 2002	Hall W, Degenhardt L. Cannabis use and the risk of developing a psychotic disorder. World Psychiatry. 2008;7(2):68-71. doi:10.1002/j.2051-5545.2008.tb00158.x	yes	yes	**no - review article**			Exclude	review article
Patton, 2002	Schaefer JD, Hamdi NR, Malone SM, et al. Associations between adolescent cannabis use and young-adult functioning in three longitudinal twin studies. Proc Natl Acad Sci U S A. 2021;118(14):e2013180118. doi:10.1073/pnas.2013180118	yes	yes	yes	yes	yes - twins	include	
Patton, 2002	Schuler MS, Vasilenko SA, Lanza ST. Age-varying associations between substance use behaviors and depressive symptoms during adolescence and young adulthood. Drug Alcohol Depend. 2015;157:75-82. doi:10.1016/j.drugalcdep.2015.10.005	yes	yes	**no**			exclude	cross-sectional
Patton, 2002	Schwinn TM, Schinke SP, Trent DN. Substance use among late adolescent urban youths: mental health and gender influences. Addict Behav. 2010;35(1):30-34. doi:10.1016/j.addbeh.2009.08.005	yes	yes	**no**			exclude	cross-sectional
Patton, 2002	Struble CA, Ellis JD, Cairncross M, Lister JJ, Lundahl LH. Demographic, Cannabis Use, and Depressive Correlates of Cannabis Use Consequences in Regular Cannabis Users. Am J Addict. 2019;28(4):295-302. doi:10.1111/ajad.12889	yes	**no**				exclude	not depression
Patton, 2002	Wilkinson AL, Halpern CT, Herring AH, et al. Testing Longitudinal Relationships Between Binge Drinking, Marijuana Use, and Depressive Symptoms and Moderation by Sex. J Adolesc Health. 2016;59(6):681-687. doi:10.1016/j.jadohealth.2016.07.010	**yes - but with alcohol**	yes	yes			exclude	looked at cannabis and alcohol predicting depression
Patton, 2002	Womack SR, Shaw DS, Weaver CM, Forbes EE. Bidirectional Associations Between Cannabis Use and Depressive Symptoms From	yes	yes	yes	yes	**yes - low SES/WIC receiving**	exclude	limited population

	Adolescence Through Early Adulthood Among At-Risk Young Men. J Stud Alcohol Drugs. 2016;77(2):287-297. doi:10.15288/jsad.2016.77.287								
van Laar, 2007	Chiu ML, Cheng CF, Liang WM, Lin PT, Wu TN, Chen CY. The Temporal Relationship between Selected Mental Disorders and Substance-Related Disorders: A Nationwide Population-Based Cohort Study. Psychiatry J. 2018;2018:5697103. doi:10.1155/2018/5697103	yes	yes	yes	**no**			exclude	depression before cannabis use
van Laar, 2007	Troup LJ, Andrzejewski JA, Braunwalder JT, Torrence RD. The relationship between cannabis use and measures of anxiety and depression in a sample of college campus cannabis users and non-users post state legalization in Colorado. PeerJ. 2016;4:e2782. doi:10.7717/peerj.2782	yes	yes	**no**	no			exclude	cross-sectional
van Laar, 2007	Wright NE, Scerpella D, Lisdahl KM. Marijuana Use Is Associated with Behavioral Approach and Depressive Symptoms in Adolescents and Emerging Adults. PLoS One. 2016;11(11):e0166005. doi:10.1371/journal.pone.0166005	yes	yes	**no**				Exclude	cross-sectional
Brook, 2011	Brook JS, Zhang C, Leukefeld CG, Brook DW. Marijuana use from adolescence to adulthood: developmental trajectories and their outcomes. Soc Psychiatry Psychiatr Epidemiol. 2016;51(10):1405-1415. doi:10.1007/s00127-016-1229-0	yes	**no**					exclude	does not look at depression alone
Brook, 2011	Caldeira KM, O'Grady KE, Vincent KB, Arria AM. Marijuana use trajectories during the post-college transition: health outcomes in young adulthood. Drug Alcohol Depend. 2012;125(3):267-275. doi:10.1016/j.drugalcdep.2012.02.022	yes	**yes - but only provides BDI score**	yes	yes	yes - college students		exclude	does not provide OR information for depression, just average scores
Brook, 2011	Green KM, Doherty EE, Ensminger ME. Long-term consequences of adolescent cannabis use: Examining	yes	**no - anxiety**					exclude	does not look at depression

intermediary processes. Am J Drug Alcohol Abuse. 2017;43(5):567-575. doi:10.1080/00952990.2016.1258706

Appendix IV: Coding sheet with example

Article ID		1
Effect ID		1
Article		Arseneault, 2002
Citation		Arseneault L. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002;325(7374):1212-1213. doi:10.1136/bmj.325.7374.1212
Study years (enrollment – final follow up)		1972-1999
Setting		a general population birth cohort in Dunedin, New Zealand
Country Code		2
1	US	
2	Non-US	
3	Worldwide	
State Code		0
1	National or more than 1 state	
0	Non-US	
Ages of Participants		2
1	Adults only	
2	Under 18 only (at baseline)	
3	Mixed	
4	Unclear	
Depression Definition		1
1	Major Depressive Disorder (MDD)	
2	Major Depressive Episode (MDE)	
3	Depressive symptoms	
4	Depressive disorder, other	

5	Depression, not otherwise specified	
Depression measure (open text)		DSM-IV
Depression measure (code)		1
1	DSM and its derivatives	
2	Symptom Checklist 90-R	
3	Clinical Interiew Schedule (CIS-R)	
4	CES-D	
5	Clinical diagnosis	
6	Symptom Distress Checklist (SCL)	
7	Brief Symptom Inventory (BSI)	
8	Composite International Diagnostic Interview (CIDI)	
9	Other (specify)	
Method of Depression Assessment		1
1	Self-report	
2	Interview	
3	Unclear	
Cannabis Measure Code		3
1	DSM	
2	Frequency (not a validated measure)	
3	Dichotomized or categorizes	
Method of Cannabis Use Assessment		1
1	Self-report	
2	Interview	
3	Unclear	
Population (exposed group) – open text		Cannabis user by age 15

Heavy/Problematic Use		0
1	Heavy/Problematic	
0	Not heavy	
Onset of Cannabis use		1
1	Early	
0	Not early	
Follow-up period (months)		468
Total (N)		759
aOR		1.02
95% Confidence Interval		0.34 – 3.04
Adjustments/Control variables		childhood psychotic symptoms and se of other drugs in adolescence
Risk of Bias results		17.5

Appendix V: Tool to Assess Risk of Bias in Cohort Studies

1. Was selection of exposed and non-exposed cohorts drawn from the same population?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Exposed and unexposed drawn for same administrative data base of patients presenting at same points of care over the same time frame

Examples of high risk of bias: exposed and unexposed presenting to different points of care or over a different time frame

2. Can we be confident in the assessment of exposure?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Secure record [e.g. surgical records, pharmacy records]; Repeated interview or other ascertainment asking about current use/exposure

Examples of higher risk of bias: Structured interview at a single point in time; Written self report; Individuals who are asked to retrospectively confirm their exposure status may be subject to recall bias – less likely to recall an exposure if they have not developed an adverse outcome, and more likely to recall an exposure (whether an exposure occurred or not) if they have developed an adverse outcome.

Examples of high risk of bias: uncertain how exposure information obtained

3. Can we be confident that the outcome of interest was not present at start of study

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: comprehensive matching or adjustment for all plausible prognostic variables

Examples of higher risk of bias: matching or adjustment for most plausible prognostic variables

Examples of high risk of bias: matching or adjustment for a minority of plausible prognostic

variables, or no matching or adjustment at all. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

5. Can we be confident in the assessment of the presence or absence of prognostic factors?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Interview of all participants; self-completed survey from all participants; review of charts with reproducibility demonstrated; from data base with documentation of accuracy of abstraction of prognostic data

Examples of higher risk of bias: Chart review without demonstration of reproducibility; data base with uncertain quality of abstraction of prognostic information

Examples of high risk of bias: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables

6. Can we be confident in the assessment of outcome?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Independent blind assessment; Record linkage; For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture.

Examples of higher risk of bias: Independent assessment unblinded; self-report; For some outcomes (e.g. vertebral fracture where reference to x-rays would be required) reference to the medical record would not be adequate outcomes.

Examples of high risk of bias: uncertain (no description)

7. Was the follow up of cohorts adequate?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring is unlikely to introduce bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a important impact on the

intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is not large enough to have an important impact on the observed effect size; Missing data have been imputed using appropriate methods.

Examples of high risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is enough to induce important bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is large enough to induce clinically relevant bias in the observed effect size.

8. Were co-Interventions similar between groups?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Most or all relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.

Examples of high risk of bias: Few or no relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.

Appendix VI. Risk of Bias Results

Article	1. Was selection of exposed and non-exposed cohorts drawn from the same population?	2. Can we be confident in the assessment of the exposure?	3. Can we be confident that the outcome of interest was not present at start of the study? [if it was controlled for = 1.75)	4.Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?	5. Can we be confident in the assessment of the presence or absence of prognostic factors?	6. Can we be confident in the assessment of outcome?	7. Was the follow up of cohorts adequate?	Mean
Arseneault, 2002	1	2.5	2.5	3.5	3	3	3	**2.64**
Blanco, 2016	1	2.5	2.5	2	2	1.5	2	**1.93**
Bovasso, 2001	1	2	1	2.5	2	2.5	3.5	**2.07**
Brook, 2002	1	3	4	1.5	1.5	2.5	2.5	**2.29**
Brook, 2011	1	3	4	4	1	2.5	2	**2.50**
Copeland, 2022	1	2.5	1.75	1	1	2.5	1	**1.54**
Danielsson, 2015	1	3	3	2	2	2.5	2.5	**2.29**
Degenhardt, 2013	1	3	1.75	2.5	2.5	2.5	3	**2.32**

Feingold, 2015	1	3	1.75	1	2	2	3	**1.96**
Fergusson, 1997	1	3	1	4	4	2.5	3	**2.64**
Gage, 2015	1	3	1.75	2.5	2.5	2.5	3	**2.32**
Georglades, 2007	1	3	1.75	1.5	2	2.5	2	**1.96**
Harder, 2006	1	3	1.75	1	2	2.5	2.5	**1.96**
Harder, 2008	1	2	2	1.5	2	2	3	**1.93**
Hengartner, 2020	1	3	1.75	2.5	2	2	2.5	**2.11**
Manrique-Garcia, 2012	1	3	3.5	1.5	2	1	1	**1.86**
Marmorstein, 2011	1	2.5	1	1.5	2	2	2	**1.71**
Paton, 1977	1	4	3	4	4	3	3.5	**3.21**
Patton, 2002	1	3	3	2	2	2.5	2	**2.21**
Pedersen, 2008	1	3	1.75	1	2	2.5	3	**2.04**
Schaefer, 2021	1	2	1.75	3	3	2.5	3	**2.32**
van Laar, 2007	1	3	1.75	1	2	2	2	**1.82**
Overall	**1**	**2.82**	**2.18**	**2.14**	**2.20**	**2.32**	**2.50**	**2.17**

Appendix VII: Message Conditions

Condition 1: Covid-19 Threat Messages

Minnesota man, 37, dies from coronavirus: 'He died all alone'

A 37-year-old Minnesota man who died from the coronavirus is being mourned by his mother who says she never got to say goodbye to him before his death.

Ann Neville said her son died Saturday, two days after she drove him to the emergency room, the paper reported Friday. He started feeling sick a few weeks earlier.

"It's very hard," she said. "No one was allowed to go in with him or be with him or see him or touch him. He died all alone. I'm still baffled by all of this. I didn't get to say I loved him; I didn't get a hug. Nothing."

Jack Neville was from Stacy, Minn., and the father of a 7-year-old boy. He was also an avid outdoorsman who loved to fish.

There are easy ways that help prevent catching coronavirus. Health experts advise that washing hands with soap and water for at least 20 seconds will get rid of the virus. If you cannot wash your hands, use a hand sanitizer with at least 60 percent alcohol.

Condition 2: Smoking Threat Messages

Smoking: What does it do to your lungs?

No matter how you smoke it, tobacco is extremely dangerous to your health. In the United States, smoking causes an estimated 480,000 deaths each year. In fact, the Centers for Disease Control says smoking is the most "preventable cause of death" in the United States.

When you inhale smoke, you're damaging your lungs. People who smoke have higher risk for lung conditions like emphysema, chronic bronchitis, and chronic lung infections.

Michael (pictured here) was a smoker. Smoking caused a lung infection. Part of his lung had to be surgically removed. Later, his lung collapsed. Now he needs oxygen therapy to breathe. If his oxygen tank fails, Michael could die.

Quitting smoking is difficult, but your doctor can help you make a plan. There are many highly effective medications that can help you quit. You can also use free smoking cessation programs, which have advice, stories from others, and helpful and effective quitting resources.

These resources have helped many Americans to quit smoking. There are now more former smokers than current smokers in the US.

Condition 3: Covid-19 and Smoking Threat Messages

Minnesota man, 27, dies from coronavirus: 'He died all alone'

A 37-year-old Minnesota man who died from the coronavirus is being mourned by his mother.

Ann Neville said her son died Saturday, two days after she drove him to the emergency room. He started feeling sick a few weeks earlier.

"It's very hard," she said. "No one was allowed to go in with him or be with him or see him or touch him. He died all alone. I'm still baffled by all of this. I didn't get to say I loved him; I didn't get a hug. Nothing."

Jack Neville was from Stacy, Minn., and the father of a 7-year-old boy. He was also an avid outdoorsman who loved to fish.

The mother said she was worried about her son having the virus because he smoked.

The coronavirus attacks the lungs and researchers report that smoking increases risk for complications from COVID-19 infection.

Health experts advise smokers to quit smoking to reduce the risk of COVID-19. Quitting tobacco is challenging, but there are free resources available from the CDC and other sources. Smokers can call the Quitline to talk to an expert and choose an effective option to quit smoking or get quitting help online.

Condition 4: Control Messages

Hubble catches interstellar comet as it flies past

The Hubble Space Telescope had a front row seat to capture the best and closest image to date of interstellar comet 2I/Borisov, a visitor that originated from outside of our solar system. On Sunday, the comet passed within 190 million miles of Earth on its closest approach before continuing on through our solar system.

As it got closer to Earth, the icy comet shed more gas and dust evaporating through its tail.

This is only the second interstellar object to cross into our solar system after 'Oumuamua in 2017.

The comet won't remain in our solar system, despite the gravity of our sun, because it's zipping along at 100,000 miles per hour. By June 2020, the comet will be well past Jupiter and on its way back to interstellar space.

New data revealed that the comet is 3,200 feet across -- the length of nine football fields, according to researchers.

Scientists think the comet originated in another star system but was kicked out after a near-miss with a planet.

Outside of its orbit, the comet is very similar to those we find in our own solar system. And it has a similar chemical composition to comets in our solar system.