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Examining Genetically-Informed Etiologic Models of Co-Occurring Posttraumatic Stress  
Disorder and Recreational Cannabis Use among College Students

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of  
Philosophy at Virginia Commonwealth University

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November 2023

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## Acknowledgement

I must acknowledge and express my deepest gratitude to the unparalleled support system that guided me through my graduate journey. Foremost, my heartfelt appreciation goes to my advisor, Dr. Ananda Amstadter, who has not only served as my professional mentor, but has also been a source of unwavering support over the past several years. I owe a significant part of my personal and professional growth to her tremendous patience, innovative ideas, invaluable feedback, and emotional support throughout my graduate training. I am also deeply grateful for my post-baccalaureate mentor, Dr. Jeannie Beckham, for her unwavering support and guidance, which began during my undergraduate years and continued seamlessly into my graduate journey. Her mentorship, wisdom, and encouragement have been instrumental in shaping my academic path and fostering my growth as a researcher. Drs. Amstadter and Beckham's successful careers will always be a source of hope and inspiration. I am extremely fortunate to have worked with both of them and I look forward to continuing to benefit from their mentorship in my future endeavors.

I am also indebted to the National Institute on Drug Abuse for the funding that made this project and other relevant training experiences possible, which has helped shape the stage for my future as an independent clinical research psychologist. I want to acknowledge my F31 fellowship mentorship team, which includes Drs. Ananda Amstadter, Kaitlin Bountress, Nathan Gillespie, Silviu Bacanu, and Danielle Dick for their collective expertise and exceptional guidance during these formative training experiences. Additionally, my committee members, Drs. Dace Svikis, Amy Adkins, and Bruce Rybarczyk, as well as Drs. Roseann Peterson and Fazil Aliev, who have provided invaluable feedback and instrumental support throughout the

course of this dissertation project, and other essential components of my graduate training, for which I am extremely appreciative.

I am incredibly fortunate to have a circle of friends and family whose unwavering confidence and support have been a constant presence throughout my entire graduate career. To my family members who cheered me on from the sidelines, offering a listening ear, and a shoulder to lean on when the weight of coursework and research felt overwhelming, I am profoundly grateful. To my friends in the VCU psychology doctoral program and my friends in the 2022-2023 San Diego VA/UCSD internship cohort who have been with me through the most challenging moments of these past few years, I am genuinely honored to have shared this arduous journey with you all. Your confidence in my abilities, numerous words of encouragement, and the countless ways in which you have stood by me have made this academic journey all the more rewarding.

Finally, I want to express my deepest appreciation to my mother, Marva Gabriel-Daugherty, and to my father, the late Horace Hicks. Your unwavering belief in me, your sacrifices, and your unconditional love have been the bedrock of my success. I am profoundly grateful for your unending encouragement and for instilling in me the values of education, perseverance, and dedication that have carried me through life. I hope that I continue to make you proud to be my parents. This achievement is as much yours as it is mine, and I look forward to sharing the fruits of our collective journey with you. Thank you from the bottom of my heart.

### List of Abbreviations

<b>AFR</b>	African ancestry
<b>CUD</b>	Cannabis use disorder
<b>DNA</b>	Deoxyribonucleic acid
<b>DSM</b>	Diagnostic and Statistical Manual of Mental Disorders
<b>EMA</b>	Ecological momentary assessment
<b>EUR</b>	European ancestry
<b>GCTA</b>	Genome-wide complex trait analysis
<b>GRM</b>	Genomic relationship matrix
<b>GWAS</b>	Genome-wide association study
<b>ICC</b>	International Cannabis Consortium
<b>IPT</b>	Interpersonal trauma
<b>LD</b>	Linkage disequilibrium
<b>RCU</b>	Recreational cannabis use
<b>MVP</b>	Million Veterans Program
<b>NESARC</b>	National Epidemiologic Survey on Alcohol and Related Conditions
<b>NSDUH</b>	National Survey on Drug Use and Health
<b>PC</b>	Principal component
<b>PGC</b>	Psychiatric Genomics Consortium
<b>PRS</b>	Polygenic risk score
<b>PTSD</b>	Posttraumatic stress disorder
<b>QC</b>	Quality control
<b>S4S</b>	Spit for Science
<b>SAMSHA</b>	Substance Abuse and Mental Health Services Administration
<b>SSAGA</b>	Semi-Structured Assessment for the Genetics of Alcoholism
<b>SNP</b>	Single nucleotide polymorphism
<b>SUD</b>	Substance use disorder
<b>TRD</b>	Trauma-related distress



## Abstract

The college years encompass a period of increased risk recreational cannabis use (RCU), as well as a time of increased risk for trauma exposure and developing posttraumatic stress disorder (PTSD). Given the high co-occurrence between RCU and PTSD, and the potentially negative consequences of the two (e.g., worse academic outcomes), there is a need to understand the etiologic mechanisms of these commonly co-occurring conditions. Two primary phenotypic models exist: self-medication model (i.e., PTSD to RCU) and the high-risk model (i.e., RCU to PTSD). To date, there are two existing studies longitudinally examining the etiologic models proposed to explain co-occurring RCU and PTSD in a college sample, but they are limited to only investigating the first two years of college. Thus, Aim 1 of this study examined these models of co-occurrence in a large, ongoing longitudinal study of college students (Spit for Science [S4S]; NIAAA-R37 AA011408, PIs Kenneth Kendler & Danielle Dick) throughout the first three years of college. Cannabis use and PTSD have been shown to be moderately heritable in twin studies. Thus, Aim 2 conducted aggregate genome-wide analyses (i.e., genome-wide complex trait analysis [GCTA], polygenic risk scores [PRS]) of RCU and PTSD to examine their molecular heritability, as well as the association of aggregate genetic risk with RCU and PTSD. Given evidence of latent heritability, as well as overlapping latent heritability of lifetime cannabis use and PTSD, examination of molecular genetic risk is also needed. Thus, Aim 3 further examined the self-medication and high-risk models by incorporating PRS for lifetime cannabis use and lifetime PTSD as potential influences of same- and cross-phenotype prediction (e.g., PRS for lifetime cannabis use predicting RCU and PTSD in S4S). To limit genetic heterogeneity, study participants were limited to individuals in S4S with European- (n = 3721) and African- (n = 1469) ancestry based off of their genomic super-population assignment. Aim 1

results supported both the self-medication and high-risk model. Aim 2 results did not provide support for significant molecular heritability of RCU or TRD in individuals with European or African ancestry in S4S likely due to low statistical power. Aim 2 results did provide evidence of same-trait prediction of PRS for lifetime cannabis use predicting non-experimental (i.e., use  $\geq 6$  times) cannabis use in individuals with European ancestry in S4S. Aim 3 results did not provide support for significant moderation of PRS for lifetime cannabis use or PRS for lifetime PTSD in the self-medication or high-risk models, respectively. However, Aim 3 results did provide evidence of same-trait prediction of non-experimental cannabis use based on PRS for lifetime cannabis use. Given the relatively small sample size, genotypic results should be interpreted with caution. However, as a whole, these findings provide support for the self-medication and high-risk models explaining the development of co-occurring PTSD and cannabis use. Implications of these findings, in light of study limitations, are discussed.

Keywords: cannabis, substance use, interpersonal trauma, posttraumatic stress disorder, genetics

## **Chapter 1: Introduction**

### **I. Overall Statement of the Problem**

As more states continue to legalize cannabis, a majority of United States (U.S.) adults (91%) say either that cannabis should be legal for medicinal and recreational use (60%) or that it should be legal for medicinal use only (31%; Pew Research Center, 2021), which may be contributing to the increasing and high prevalence of use. Indeed, cannabis is currently the most widely used illicit substance in the U.S. according to the National Survey of Drug Use and Health (NSDUH; Substance Abuse and Mental Health Service Administration, 2020). Currently, the NSDUH survey counts all cannabis use as illegal drug use because despite state specific laws, under federal law, cannabis is illegal throughout the U.S. Cannabis use is common among the general population and among college students (Hasin et al., 2016; Johnston et al., 2016). Of concern, cannabis use is higher among college students than their same-age, non-college peers (Johnston et al., 2016). Most long-term adverse effects of cannabis use are more likely among heavy or chronic users, but short-term impairment across several cognitive domains, including learning, memory, attention, and motor functioning can affect anyone regardless of frequency of use (Kroon et al., 2021). Thus, the identification of etiologic factors associated with cannabis use, particularly among high-risk populations such as college students, are needed to inform prevention and intervention programming.

Two key potential factors associated with cannabis use that warrant increased study are trauma exposure and posttraumatic stress disorder (PTSD), both of which are common among college students (Cusack et al., 2018; Frazier et al., 2009; Read et al., 2011; Scarpa et al., 2002). Further, college students are at higher risk for certain types of traumatic events that have a high likelihood of leading to PTSD, such as interpersonal trauma (IPT; Anders, Frazier, et al., 2012;

Anders, Shallcross, et al., 2012; Edwards et al., 2016). Epidemiological and acute trauma studies suggest that trauma exposure and PTSD are associated with cannabis use and that they frequently co-occur (Cougler et al., 2011; Kevorkian et al., 2015; Vlahov et al., 2002).

There are two phenotypic models posited to explain co-occurring cannabis use and trauma-related phenotypes (e.g., IPT, PTSD). Co-occurrence of these two conditions may begin when a person attempts to self-medicate their post-trauma-related symptoms (Chilcoat & Breslau, 1998). Alternatively, cannabis use could be considered a risk behavior that puts someone at higher risk for trauma exposure and therefore PTSD if the person experiences a traumatic event while under the influence (Chilcoat & Breslau, 1998). There is a need for empirical investigation of these models explaining co-occurring cannabis use and PTSD, particularly as public support for the legalization of cannabis is increasing (Kilmer & MacCoun, 2017), which may promote an increase in the prevalence of cannabis use. Furthermore, given evidence of latent genetic risk for both lifetime cannabis use and PTSD, examination of molecular genetic risk is also needed for a better understanding of whether and how genetic influences may underlie the common co-occurrence of these two phenotypes.

The increasing prevalence of cannabis use and its adverse health effects combined with an increased risk for trauma exposure among college students makes the intersection of cannabis use and PTSD an area in need of future research. Indeed, etiologic models of co-occurring cannabis use and PTSD have not been fully elucidated. Limited epidemiological studies are available on the association between cannabis use and PTSD specifically, as most studies have examined the co-occurrence of PTSD and other substance use disorders such as alcohol use disorder or tobacco use disorder (Debell et al., 2014; Fu et al., 2007). To date, only two studies have examined the association between cannabis use and trauma-related phenotypes (i.e., IPT,

trauma-related distress) longitudinally among college students (Hicks, Bountress, et al., 2022; Hicks et al., 2020). However, there are no studies examining the association between cannabis use and trauma-related phenotypes that have incorporated genetic liability, which will aid in identifying individuals at increased risk to target prevention and intervention efforts.

## **II. Literature Review**

### **A. Importance of Emerging Adulthood**

Emerging adulthood, or the developmental period from the end of adolescence to the young-adult responsibilities of a stable job, marriage and/or parenthood during the mid-to-late twenties (Arnett, 2000), is an important developmental period to study when examining the etiology of co-occurring cannabis use and posttraumatic stress disorder (PTSD) due to the high risk for substance use and trauma exposure (Arnett, 2005). College students encompass a large portion of those in emerging adulthood (i.e., ages 18-25 years old) and colleges across the world are contending with increasing rates of substance use and mental disorders (Auerbach et al., 2018). College students are an important population to study to inform prevention efforts, especially with regard to substance use, because of their size (estimated 19.7 million students in American colleges and universities in fall 2020) and the number of individuals in emerging adulthood (estimated 12.3 million students under age 25; National Center for Education Statistics & US Department of Education, 2020). The college environment poses new challenges to students, as most students are away from home for the first time without parental supervision and are trying to adjust, socialize, and fit in while in a developmental period known for identity exploration and instability, self-focus, and possibilities (Arnett et al., 2014). In addition to adjusting to being away from home, students often attend parties with alcohol and substances, which makes college a potentially dangerous period (Lindo et al., 2018; Marzell et al., 2015).

Therefore, college students are especially vulnerable to new, sometimes prohibited or unsafe, experiences (Martens et al., 2006; Snipes & Benotsch, 2013), as well as traumatic experiences that increase risk for PTSD (Read et al., 2011).

### **B. Prevalence of Cannabis Use**

Cannabis is the world's most commonly used psychoactive substance. Approximately 192 million people, or 3.9% of the world's population between the ages of 15 and 64, reported past-year cannabis use in 2018 (United Nations Office on Drugs and Crime, 2020). The United States (U.S.) is the region with the highest annual prevalence of cannabis use with 8.8% of the population aged 15-64 reporting past-year use (United Nations Office on Drugs and Crime, 2020).

Cannabis use has been consistently increasing in the U.S. over the past decade (Substance Abuse and Mental Health Service Administration, 2020). In 2019, about 35% of young adults aged 18 to 25 reported past-year cannabis use (Substance Abuse and Mental Health Service Administration, 2020). The prevalence of past-year and past-month cannabis use among young adults aged 18 to 25 has increased by over 50% over the past decade to about 35.4%, and the prevalence of daily or near-daily cannabis use (i.e., using on 20 or more occasions in the past 30 days) has doubled to about 9.4%, which is also the highest level ever observed among young adults since the annual survey began three decades ago (Substance Abuse and Mental Health Service Administration, 2020). According to the University of Michigan's Institute for Social Research annual report, *Monitoring the Future* (Schulenberg et al., 2020), past-year and past-month prevalence of cannabis vaping among individuals aged 19–28 years-old, which has more than doubled in the past two years, was reported at 22% and 13%, respectively. The increases were especially large for individuals aged 19-22 years-old, which overlaps with the average age

of college students, which had the highest past-year (24-25%) and past-month (14-15%) prevalence in 2019 (Schulenberg et al., 2020). Almost 6% of full-time college students in the U.S. were daily cannabis users in 2019 (Schulenberg et al., 2020). This is more than triple the number of daily users in this population almost 25 years ago (Schulenberg et al., 2020). Evidence supports increasing rates of cannabis use, however, both the United Nations World Drug Report 2020 and results from the 2019 U.S. National Survey on Drug Use and Health (NSDUH) did not differentiate between medicinal cannabis use and recreational cannabis use (RCU), which is critical because motivation and intention for use are essential to characterizing substance use behaviors, such as whether it is considered problematic or not.

### **C. Medicinal and Recreational Cannabis Use**

Medicinal cannabis is cannabis prescribed by physicians for their patients and recreational cannabis is cannabis used without medical justification. Rates of both medicinal cannabis use and RCU are increasing due, in part, to the continued expansion of legalized medicinal cannabis and recreational cannabis in the U.S. (Hasin, 2018). As of June 2023 (National Conference of State Legislatures, 2023), cannabis is currently approved for medicinal use only in 38 states, three territories, and D.C. Likewise, cannabis is currently approved for recreational use in 23 states, two territories, and D.C. There is increasing empirical support for medicinal cannabis' efficacy for reducing symptoms of a variety of chronic physical and mental health conditions, including, but not limited to PTSD (Kosiba et al., 2019; Orsolini et al., 2019; Walsh et al., 2017). However, increasing research suggests that it is unclear how users of medicinal cannabis differ from users of recreational cannabis.

Research suggests that some medicinal users have had experience as former recreational users (Reinarman et al., 2011). Further, medicinal and RCU may overlap such that individuals

may use both medically and recreationally (Morean & Lederman, 2019). For example, a nationally representative survey found that, among medicinal cannabis users, only 22.5% reported exclusive medicinal use while 77.5% reported also using recreationally (Schauer et al., 2016). Noteworthy, Schauer and colleagues (2016) did not differentiate individuals who were using cannabis to treat a medical condition without physician recommendation from individuals who were using medicinal cannabis legally (i.e., residing in a state in which medicinal cannabis is legal and obtaining medical authorization). A more recent study of overlapping patterns of medicinal and RCU in a large community sample of cannabis users found similar results while distinguishing between authorized and non-authorized medicinal cannabis users (Turna et al., 2020). Specifically, Turna and colleagues (2020) found that among a sample of individuals who endorsed cannabis use in the past 6-months for recreational purposes or some level of medicinal use regardless of medical authorization, 80.6% of medicinal cannabis users also reported using recreationally, and only 23.4% reported authorization from a health professional. In short, research suggests that most individuals who are using medicinal cannabis are also engaging in RCU, similar to the use of other prescriptions drugs for recreational purposes (e.g., opiates, stimulants; United Nations Office on Drugs and Crime, 2020).

The definition of cannabis use and what is considered problematic and/or disordered cannabis use has changed over time. The term “cannabis use” has evolved over the past few decades with the literature using the words “use,” “misuse,” and “abuse” interchangeably as it progressed to the current terms of “recreational cannabis use,” which includes all use without a prescription, and “medicinal cannabis use,” or prescribed cannabis use. Researchers have noted a number of methodological concerns within the growing RCU literature, including variability in what investigators consider problematic cannabis use or cannabis misuse (Asbridge et al., 2014).



The definition provided by the NSDUH currently states that any non-medicinal use (i.e., recreational use) within an individual's lifetime is considered cannabis misuse (Substance Abuse and Mental Health Service Administration, 2020). Any RCU may hardly capture problematic use worthy of clinical attention.

On the opposite end of the RCU spectrum, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for cannabis use disorder (CUD) are thought to identify more accurately those with problematic use. CUD is characterized by the consequences of repeated use, a pattern of compulsive use, and in some cases physiological dependence (American Psychiatric Association, 2013). CUD is only diagnosed when use becomes persistent and causes academic, occupational or social impairment (American Psychiatric Association, 2013). DSM-5 CUD combines the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) categories of cannabis abuse and dependence into a single disorder measured on a continuum from mild to severe. In addition to the DSM-IV abuse and dependence being combined, the symptom of recurrent legal problems has been removed, and the symptom of craving or desire or urge to use has been added. Given the numerous changes in criteria, comparing prevalence of CUD to the prior abuse and dependence diagnoses is difficult. For example, whereas a diagnosis of DSM-IV cannabis abuse previously required only one symptom, mild CUD in DSM-5 requires two to three symptoms from a list of eleven. Therefore, it is currently more difficult to reach the threshold for DSM-5 CUD than DSM-IV. DSM-5 may better capture clinically meaningful disordered RCU; however, the use of strict diagnostic criteria as a means of determining disordered RCU may not aid in identification of individuals exhibiting problematic and subthreshold use. Much less empirical attention has been placed on RCU existing between these two extremes. While the DSM-5 does embrace the consideration of

continuous symptoms with the transition to classification of substance use disorders as mild, moderate, and severe (American Psychiatric Association, 2013), few studies have yet to assess CUD according to the DSM-5 symptomatology.

#### **D. Correlates of RCU**

According to the Monitoring The Future annual survey (Schulenberg et al., 2020), among individuals 19-30 years old, males were more likely to report cannabis use compared to females. Specifically, males were higher than females on prevalence of past year, past month, and near-daily cannabis use, as well as past year and past 30-day cannabis vaping (Schulenberg et al., 2020). The NSDUH found that the prevalence of past-year cannabis use increased for both males and females until 2014, but increases were greater for males than females, leading to a widening of the gender gap over time (Carliner et al., 2017). However, the past-year cannabis use prevalence gender gap for males and females has narrowed since 2016 among individuals aged 19-22 years old, which overlaps with the average age of college students, to 45% and 41%, respectively (Schulenberg et al., 2020). Similar to gender, race and ethnicity are other non-modifiable factors that contribute to an individual's risk for cannabis use.

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; 2002-2002) and NESARC-III (2012-2013) found cannabis use increased over the past decade among all racial/ethnic groups, but also found significant differences between rates of use among Black individuals compared to White individuals, which suggests race as a proxy for better understanding health disparities regarding RCU (Hasin et al., 2019). While gender, race and ethnicity are biologically based factors that cannot be changed, there are also modifiable factors that contribute to an individual's risk for cannabis use, such as other substance use.

Cannabis, alcohol, and nicotine/tobacco are the three most commonly used drugs in the U.S. (Substance Abuse and Mental Health Service Administration, 2020), and research supports that consumption of one of the three substances is associated with increased odds of concurrent (i.e., within close temporal proximity) or simultaneous (i.e., at the same time so the effects overlap) co- and tri-use (Roche et al., 2019). Concurrent use of cannabis and alcohol is one of the most common forms of polysubstance use among college students (Windle et al., 2017). Among a sample of first-year college students from two large public universities, 65.1% of students who reported past-month cannabis use also reported past-month alcohol use and 23.2% of males and 8.5% of females reported using both substances on the same day (Whitehill et al., 2014). Similar to cannabis and alcohol being a common form of polysubstance use, cannabis and nicotine/tobacco is another common form of it. Adult tobacco smokers are approximately 4 to 8 times more likely to report past-month cannabis use than non-smokers (Strong et al., 2018). A study with a different sample of college students found that among individuals who reported both past-three month cannabis and cigarette/e-cigarette use, 17.4% of them reported concurrent (i.e., occurred over a period of time) co-use and 21.7% reported simultaneous (i.e., occurred at the same point in time) co-use (Ruglass et al., 2020). Since RCU is highly associated with alcohol and nicotine/tobacco use (i.e., polysubstance use), they are key variables to control for in future cannabis use research.

### **E. Prevalence of Trauma Exposure and PTSD**

According to the DSM-5 (2013), a traumatic event is defined as “exposure to actual or threatened death, serious injury, or sexual violence,” which includes, but is not limited to, sexual abuse, physical abuse, motor vehicle accidents, natural disasters, suicides, and other traumatic losses. Trauma exposure is universally common among all populations. Twenty-four countries

across six continents assessed trauma exposure with a list of 29 types of traumatic events among a sample of 68,894 adults and over 70% of respondents reported exposure to at least one traumatic event and 30.5% reported exposure to four or more traumatic events (Benjet et al., 2016). The U.S. had the third highest prevalence of trauma exposure (82.7%) of all countries included in the study (Benjet et al., 2016). Consistently, the prevalence of exposure to at least one traumatic event ranged from approximately 55% to 90% in the U.S. according to findings from major general population studies conducted with probability samples of adults (Kilpatrick et al., 2017).

PTSD is a disorder characterized by the following primary symptom areas: exposure to a traumatic event, intrusion or re-experiencing (i.e., recurrent recollections of the event), fear or avoidance behaviors, changes in mood and cognition (i.e., negative alterations in emotions or thoughts), arousal and hyper-reactivity (i.e., agitation, state of constant wakefulness and alertness; American Psychiatric Association, 2013). PTSD is only diagnosed when the symptoms last more than a month, seriously affect an individual's ability to function, and are not due to substance use, medical illness, or anything except the event itself. According to a systematic review of 35 studies investigating PTSD prevalence and trajectories in trauma exposed populations, an estimated 25.4% of those exposed to a traumatic event go on to meet DSM-5 criteria for PTSD one month post-trauma (Santiago et al., 2013). PTSD prevalence rates decrease to 18.8% three months post-trauma and remain steady at twelve months post-trauma (17.7%; Santiago et al., 2013). The National Comorbidity Survey – Replication (NCS-R) estimated the prevalence rate of lifetime PTSD based on the DSM-IV diagnostic criteria to be about 6.8% among a nationally representative sample of U.S. adults (Kessler et al., 2005). The National Epidemiologic Survey on Alcohol and Related Conditions documented similar estimates of

DSM-IV lifetime PTSD (6.4%) among a representative sample of U.S. adults (Pietrzak et al., 2011). PTSD in DSM-5 differs significantly from DSM-IV. The stressor criterion is more explicit regarding what classifies as a traumatic event. Also, the subjective reaction of needing to feel intense fear, helplessness, or horror during the traumatic event has been removed. The three major symptom clusters in DSM-IV (e.g., reexperiencing, avoidance/numbing, and arousal) are now four symptom clusters in DSM-5. The DSM-IV avoidance/numbing cluster is divided into two distinct clusters in the DSM-5: avoidance and negative alterations in cognitions and mood. Negative alterations in cognitions and mood retained most of the DSM-IV numbing symptoms, but also includes new symptoms, such as persistent negative emotional states. Lastly, alterations in arousal and hyper-reactivity retains most of the DSM-IV arousal symptoms, but also includes irritable or aggressive behavior and reckless or self-destructive behavior. Despite these major revisions to what qualifies for a diagnosis of PTSD, the prevalence rates remain relatively similar across the DSM-IV and DSM-5. More recently, results from the National Stressful Events Survey documented similar estimates of DSM-IV lifetime PTSD (10.6%) and DSM-5 lifetime PTSD (9.4%), which sampled a demographically and geographically representative group of U.S. adults (Kilpatrick et al., 2013).

#### **F. Correlates of Trauma Exposure and PTSD**

Many factors play a part in whether an individual will develop PTSD after experiencing a traumatic event. In a meta-analysis across 77 studies examining risk factors for PTSD in trauma-exposed adults, Brewin and colleagues (2000) found pre-trauma (e.g., gender, race, ethnicity, low socioeconomic status), peri-trauma (e.g., trauma severity), and post-trauma (e.g., low social support, subsequent life stress) factors that were associated with a greater likelihood of developing PTSD. In addition to the risk factors Brewin and colleagues (2000) identified,

Kilpatrick and colleagues (2013) found that PTSD was highly associated with interpersonal trauma (IPT; i.e., sexual and physical assault) and combat. Consistent evidence supports IPT being more likely to lead to PTSD than accidental trauma (i.e., motor vehicle accident, natural disaster; Kessler et al., 2017).

Sociodemographic predictors of trauma exposure and PTSD include gender, race, ethnicity, and age. Females are more likely than males to be exposed to intimate partner or sexual violence, but males are more likely than females to experience all other types of traumatic events such as interpersonal violence (i.e., human-perpetrated violence) or being mugged with a weapon (Benjet et al., 2016). Although females are less likely than males to be exposed to any traumatic event, females have a two to three times higher risk of developing PTSD compared to males (Olf, 2017). The lifetime prevalence of PTSD ranges from 10–12% in females and 5–6% in males (Olf, 2017). Racial/ethnic differences in trauma exposure have been investigated among a large, nationally representative sample of U.S. adults (McLaughlin et al., 2019), which found that Asian individuals were most likely to experience organized violence, but had the lowest exposure to all other types of traumatic events. Black individuals had the greatest exposure to participation in organized violence and exposure to sexual violence, Latinx individuals had the highest exposure to physical violence, and White individuals were most likely to experience accidents/injuries (McLaughlin et al., 2019). Research also supports racial/ethnic variation in lifetime PTSD, such that the lifetime prevalence of PTSD was highest among Black individuals, followed by White, Latinx, then Asian individuals likely due to the fact that some racial/ethnic groups are at higher risk for experiencing certain types of traumatic experiences that are more likely to lead to PTSD (McLaughlin et al., 2019). Regarding age as a pre-trauma vulnerability factor for PTSD among adults, the NCS-R found that individuals aged

18- to 29-year olds had the highest odds of a lifetime risk for PTSD compared to 30- to 44-year olds and 45- to 59-year olds (Kessler et al., 2005). College students are in that critical age range for an increased risk for trauma exposure and PTSD (Cusack et al., 2018), and they constitute a sizeable cohort of the U.S. population (National Center for Education Statistics & US Department of Education, 2020). These pre-trauma characteristic differences are attributed to a variety of cultural, socioeconomic, and cohort phenomena.

Psychosocial factors, in addition to demographic variables, contribute to PTSD risk. A meta-analysis across 68 studies examining predictors of PTSD and symptoms in adults found that risk factors for developing PTSD besides low social support had a stronger effect if the index trauma was noncombat interpersonal violence (Ozer et al., 2003). Similarly, Frans and colleagues (2005) examined the lifetime prevalence of traumatic experiences and PTSD and found that the highest risk for developing PTSD was associated with IPT (i.e., sexual and physical assault), robbery, and multiple trauma experiences. Recently, Kilpatrick and colleagues (2013) also found that the prevalence of PTSD was highest among victims of IPT and combat. Consistent evidence supports IPT being more likely to lead to PTSD than accidental trauma. Ozer and colleagues (2003) also found that low perceived social support following a traumatic event was associated with greater development of PTSD. According to Brewin and colleagues (2000), lack of social support and more subsequent life stress were two of the three peri- and post-trauma factors that convey the strongest risk of PTSD. Given the knowledge on pre- peri- and post-trauma risk factors, it is important to investigate trauma exposure and PTSD in high-risk subpopulations (i.e., college students) to better understand the negative effects both acutely and in the longer-term.

## **G. Associations Between RCU and PTSD**

A recent systematic review examining the current state of the literature on the association between RCU and PTSD concluded that a majority of studies included in the review investigating the two commonly co-occurring phenotypes found statistically significant associations between them (Hicks, Zaur, et al., 2022). A majority of studies included in the systematic review utilized a cross-sectional opposed to a longitudinal study design to investigate the association between RCU and PTSD. For example, the NCS-R found significant associations between lifetime and current PTSD and lifetime, current, and daily RCU using a cross-sectional study design (Cogle et al., 2011). Generally, individuals with psychiatric comorbidities have a poorer quality of life compared to those with a single mental health condition (Watson et al., 2011). Further, the symptoms of one condition might negatively interfere with the treatment and management of another (Bonn-Miller et al., 2013; Bonn-Miller et al., 2015).

To best address treatment and management challenges of co-occurring RCU and PTSD, we must understand the etiological and maintenance factors contributing to their onset. There are several models that have been proposed to explain co-occurring RCU and PTSD (Berenz et al., 2019). The self-medication model suggests that individuals with trauma exposure and PTSD are at increased risk for RCU due to repeated use to cope with trauma-related consequences and distress (Khantzian, 1997). The high-risk model suggests that RCU increases risk for trauma exposure and, consequently, PTSD (Brady et al., 2004). The self-medication and high-risk models presume that RCU or PTSD comes before the other, thus a longitudinal study design is needed to investigate the causal relationship between the two phenotypes. All except one of the longitudinal studies included in a systematic review of co-occurring RCU and PTSD found support for a causal relationship between RCU and PTSD (Hicks, Zaur, et al., 2022). The shared



risk model suggests that RCU and PTSD frequently co-occur due to common familial risk (i.e., genetic factors, shared environmental influences; Krueger & Markon, 2006). However, there are no studies that test the shared risk model or how genetic risk for cannabis use and PTSD influences the development of the co-occurring phenotypes (Hicks, Zaur, et al., 2022).

#### **H. The Self-Medication Model**

The self-medication model is the most prominent and widely accepted phenotypic model of comorbidity that is thought to explain the development of co-occurring PTSD and substance use (Khantzian, 1985). The self-medication model purports that individuals with trauma exposure and/or PTSD engage in substance use in an effort to alleviate distressing symptoms stemming from the traumatic experience (i.e., PTSD to substance use). Longitudinal research has found that PTSD symptoms often have an earlier onset than substance use (Bremner et al., 1996), lending support to the purported order of onset of the self-medication model. Another prominent example of the dynamic relationship between PTSD and substance use was found over a 26-week period where increases in PTSD symptoms were positively associated with increases in substance use disorder (SUD) symptoms (Ouimette et al., 2010). Ouimette and colleagues' (2010) research suggests that individuals' SUD symptoms are tied to their PTSD symptoms and that they could be showing signs of using substances in response to their increase in distressing PTSD symptoms. A majority of the PTSD and substance use studies that have attempted to test the tenants of the self-medication model have been conducted on drug use broadly (Reed et al., 2007), alcohol (Breslau et al., 2003; Jacobsen et al., 2001), nicotine/tobacco (Breslau et al., 2003; Cook et al., 2009), or cocaine (Jacobsen et al., 2001), but fewer studies have examined the relationship between PTSD and RCU.

Those exposed to trauma are at a higher risk of using cannabis than individuals without a history of exposure to trauma (Kevorkian et al., 2015). Additionally, individuals with PTSD are at an increased risk for RCU and developing a CUD (Cornelius et al., 2010). Cornelius and colleagues (2010) found that the average age of onset of PTSD was 15.4 +/- 5.6 years and the average age of onset of CUD was 16.7 +/- 2.3 years among trauma-exposed adolescents, which suggests that PTSD may contribute to the etiology of CUD. Further supporting the self-medication model for co-occurring PTSD and RCU, individuals report using cannabis to regulate negative emotions, or help cope with intrusive PTSD symptoms (Bonn-Miller et al., 2011). Recent research among college students suggests that individuals may be using cannabis to self-medicate their PTSD symptoms (Hicks, Bountress, et al., 2022; Hicks et al., 2020), but overall co-occurring PTSD and RCU is an area in need of more research to provide a more comprehensive evaluation of the unique associations between trauma exposure, PTSD, and RCU.

Not all studies have results that are consistent with the self-medication model in relation to co-occurring PTSD and substance use. Breslau and colleagues (2003) did not find supporting evidence for self-medicating relationship between PTSD and alcohol use. Specifically, exposure to trauma in individuals with and without a diagnosis of PTSD did not predict alcohol abuse or dependence in a longitudinal study of young adults (Breslau et al., 2003). In a study examining the relationship between specific PTSD symptom clusters and substance use, Tull and colleagues (2010) found contradicting evidence against the self-medication model. Specifically, no evidence was found for a specific relationship between any of the PTSD symptom clusters and cocaine or alcohol (Jakupcak et al., 2010). Although the self-medication model is the most prominent phenotypic model of co-occurring PTSD and substance use, it is possible for the causal relationship to be in the opposite direction.

## **I. The High-Risk and Susceptibility Models**

The high-risk and susceptibility models are explanations for how co-occurring trauma exposure or PTSD and substance use develop that are based on the opposite causal direction for the relationship compared to the self-medication model (i.e., substance use to PTSD). The high-risk model states substance use behaviors are assumed to increase an individual's risk of exposure to potentially traumatic events and consequentially increases their risk of developing PTSD. Substance use may increase risk for exposure to a traumatic event by placing individuals in high-risk situations or by impairing recognition of danger cues in the environment (Davis et al., 2009; Windle, 1994). The susceptibility model states that substance use increases the likelihood of developing PTSD after being exposed to a traumatic event (Chilcoat & Breslau, 1998). Individuals who use substances may be less able to manage peri- or post-trauma negative emotions because substance use is likely to interfere with their ability to effectively manage increased anxiety and arousal levels or be a method of avoidance and lack of processing (Kaysen et al., 2011; Stewart et al., 1998). For example, individuals with a history of problematic alcohol use were more likely to have more severe PTSD symptoms following an assault compared to those without a history of problematic alcohol use (Kaysen et al., 2006). Research has shown that age of onset of substance use precedes PTSD in cocaine abusing individuals and that the trauma is likely to be associated with the procurement and use of the drug opposed to childhood trauma (Brady et al., 1998). In a study investigating patients with SUD and the association with development of PTSD, cannabis use was the third most commonly reported drug of concern with 36% of the total sample reporting problematic use and 40.9% of those with co-occurring PTSD reported cannabis as their principal drug of concern (Dore et al., 2012). A majority of the supporting studies are cross-sectional and focus on other substances (i.e., alcohol, cocaine)

besides cannabis, which limits the generalizability of their findings. One recent longitudinal study examining the high-risk model among college students found that any amount of cannabis use increased risk for subsequent IPT exposure and trauma-related distress (Hicks et al., under second review), but the study only looked at the first two years of college. Thus, additional longitudinal studies are needed for examining the natural course of associations between trauma exposure, PTSD, and RCU.

### **J. The Shared Risk Model**

Research also suggests that co-occurring PTSD and RCU may represent a shared vulnerability. The shared risk model hypothesizes that individuals with greater common liability for PTSD and RCU are more likely to develop both phenotypes (Krueger & Markon, 2006). Both PTSD and substance use are genetically influenced. In a civilian twin study, Stein and colleagues (2002) found modest heritability for IPT (e.g., robbery, sexual assault), whereas exposure to accidental trauma (e.g., motor vehicle accident, natural disaster) was best explained by environmental influences. Beyond genetic influences on trauma exposure itself, PTSD is also moderately heritable with estimates ranging from 30% (Stein et al., 2002) to 72% (Sartor et al., 2011). Cannabis use phenotypes are also moderately influenced by genetic factors with heritability estimates of 31% for lifetime cannabis use (Ystrom et al., 2014), and ranging from 45-79% for CUD (Agrawal & Lynskey, 2006; Ystrom et al., 2014). Beyond estimation of the individual heritable influences on each phenotype, twin studies also suggest modest overlapping latent genetic risk. Wolf and colleagues (2010) examined the factor structure of PTSD and SUDs in a large study of over 3,000 twin pairs and found that common genetic liability exists between PTSD and SUDs. Xian and colleagues (2000) also investigated whether and to what degree genetic and environmental contributions overlap among PTSD, alcohol use disorders (AUD) and

SUDs in a large study of over 3,000 veteran twin pairs and found that about 15% of genetic risk for PTSD was shared among AUDs and SUDs. Given that cannabis is the most frequently used illicit substance (Substance Abuse and Mental Health Service Administration, 2020), Xian and colleagues' results suggest that PTSD and cannabis use likely share common genetic risk (2000). This shared genetic influence may in part account for co-occurring PTSD and RCU. However, further research is necessary to understand shared risk factors for trauma-related and cannabis use phenotypes, specifically.

### **K. Genetics of Cannabis Use, PTSD, and Cannabis Use-PTSD Co-Occurrence**

Both cannabis use and PTSD are moderately heritable (Minica et al., 2018; Stein et al., 2002), and there is evidence for shared genetic risk between these phenotypes (Xian et al., 2000). Specifically, a meta-analysis of twin studies, which investigate the degree of overall genetic and environmental influences on a phenotype of interest by comparing monozygotic (identical twins; share 100% of their genes) and dizygotic (fraternal twins; share 50% of their genes) twins, found that the proportion of total variance of cannabis use initiation and problematic use accounted for by genes is 48% and 51% for men and 40% and 59% for women, respectively (Verweij et al., 2010). Similarly, a review of six twin studies identified a strong genetic contribution to risk of CUD concluding heritability estimates between 45% and 78% (Agrawal & Lynskey, 2006). In a review summarizing the past three decades of PTSD genetics research, Duncan and colleagues (2018) found that 4 twin study heritability estimates of PTSD ranged from 23.5% to 71%, with 3 of the 4 twin studies having heritability estimates between 38% and 71%. Therefore, the major take-home message from all available twin studies is that cannabis use and PTSD are partially genetically influenced or genetic variation underlies individual differences in risk for cannabis use and PTSD.

Due to the promising results of twin studies on the heritability of cannabis use and PTSD, research aimed at identification of the specific genetic variants that put individuals at risk for cannabis use and PTSD has been conducted as the logical next step. With the collaborative support of big genetic projects, such as the Human Genome Project and the 1000 Genomes Project (Genomes Project et al., 2015; Sawicki et al., 1993), and innovative statistical genetics techniques, researchers have been able to investigate the effects of specific genetic variants called single nucleotide polymorphisms (SNPs) on polygenic (i.e., relating to or determined by multiple genes) psychiatric traits and disorders. SNPs are the most common form of genetic variation in the deoxyribonucleic acid (DNA) sequence that are easily identifiable and occurs due to point mutations, which results in varying alleles between different individuals. SNP variations are used to map genes that modify vulnerability to diseases or polygenic traits because they occur so frequently (Tam et al., 2019). Therefore, SNPs are commonly used in molecular genetic research to determine whether a significant association exists between a certain genetic variant and a psychiatric trait via case versus control status (e.g., case = lifetime cannabis use vs. control = no lifetime cannabis use) or the degree of association based on a quantitative trait (e.g., PTSD symptom severity). To date, numerous molecular approaches have been taken to investigate the influence of genetic variation on both cannabis use and PTSD.

#### ***i. Genome-Wide Association Studies (GWAS)***

The collaborative efforts of large consortia, such as the Psychiatric Genomics Consortium (PGC; Watson et al., 2020), along with advances in genomic sequencing, have paved the way for the application of agnostic approaches using large sample sizes, such as genome-wide association studies (GWAS; Mills & Rahal, 2019), which allow for the simultaneous examination of millions of variants across the genome to identify possible loci contributing to a

phenotype of interest. Specifically, GWASs determine if SNPs occur more frequently based on case status or severity of the trait of interest (Chang et al., 2018). SNPs occurring at a higher frequency among cases or in association with increased severity of the trait are implicated as risk factors for the phenotype of interest. To account for multiple testing in GWASs, a fixed  $p$ -value threshold of  $5 \times 10^{-8}$  is widely used and has been remarkably successful in limiting false positive association discoveries (Hayes, 2013). A large sample size for adequate statistical power is critical to the success of a GWAS's ability to detect causal genes of polygenic phenotypes, such as cannabis use and PTSD (Hong & Park, 2012). GWAS relies largely on linkage disequilibrium (LD). Broadly, LD refers to the non-random association of SNP alleles inherited together within a given population (Reich et al., 2001). Populations with longer ancestral histories (i.e., African-descent populations) have lower LD compared to European- and Asian-descent populations due to increased opportunities for recombination over time.

GWASs have been used to gain new insight into the genetic contributions of cannabis use phenotypes. *Table 1* summarizes the results from the GWAS studies on multiple cannabis use phenotypes. To date, six GWASs of cannabis use phenotypes have been published: a GWAS of cannabis dependence in 708 cannabis-dependent individuals and 2,346 controls (Agrawal et al., 2011); a GWAS meta-analysis of lifetime cannabis use based on two studies with a combined sample size of 10,091 individuals (40.7% cannabis users; Verweij et al., 2013); a GWAS of lifetime cannabis use and age of cannabis use onset based on a sample of 6,744 individuals (20% cannabis users; Minica et al., 2015); a GWAS meta-analysis of lifetime cannabis use from the International Cannabis Consortium (ICC) based on a sample size of 32,330 individuals in the discovery sample along with 5,627 individuals in the replication sample (Stringer et al., 2016); a GWAS meta-analysis of lifetime cannabis use from the Substance Use Disorders Working Group

of the PGC (SUD-PGC) based on a sample size of 184,765 individuals (Pasman et al., 2018); and a GWAS meta-analysis of CUD from the SUD-PGC, iPSYCH, and deCODE based on a sample size of 20,916 individuals with CUD and 363,116 controls (Johnson et al., 2020). Four of the studies did not identify any genome-wide significant associations. This was likely due to the small effect sizes typical of common variants underpinning highly polygenic phenotypes, thereby indicating a need for larger sample sizes. In this context, the success of larger GWASs examining cannabis use phenotypes was encouraging. The remaining two GWAS identified potential sources of genetic variation associated with lifetime cannabis use in eight independent genome-wide significant SNPs (rs2875907, rs1448602, rs7651996, rs10085617, rs9773390, rs9919557, rs10499, rs17761723) in *CADM2*, *ZNF704*, *SDK1*, *NCAMI*, *RABEP2* or *ATP2A1* and *SMG6* on chromosomes 3, 7, 8, 11, 16 and 17 (Pasman et al., 2018), as well as potential sources of genetic variation associated with CUD in two independent genome-wide significant SNPs (rs4732724 and rs7783012) on chromosomes 8 and 7 (Johnson et al., 2020). *CADM2* and *NCAMI* have been identified in multiple GWASs for lifetime cannabis use and have both been associated with alcohol use and risk-taking behaviors (Pasman et al., 2018). Of note, research suggests that lifetime cannabis use and CUD are moderately genetically correlated ( $r_g = 0.5$ ,  $p = 1.50 \times 10^{-21}$ ), but may have different genetic underpinnings (Johnson et al., 2020).

GWAS have also been used to investigate genetic influences of PTSD. *Table 2* summarizes the results from the meta-analytic GWAS studies on PTSD. Several GWASs of PTSD with smaller sample sizes ranging from 147 to 13,690 individuals equating to being underpowered for GWASs of polygenic phenotypes identified potential sources of genetic variation associated with PTSD in several genes (Polimanti & Wendt, 2021), including *RORA* (Logue et al., 2013), *TLL1* (Xie et al., 2013), *lincRNA AC068718.1* (Guffanti et al., 2013),



*PRTFDC1* (Nievergelt et al., 2015), *ANKRD55* (Stein et al., 2016), and *ZNF626* (Stein et al., 2016). To date, 3 meta-analytic GWASs of PTSD have been published by the Posttraumatic Stress Disorder Working Group of the PGC (PTSD-PGC; Duncan, Ratanatharathorn, et al., 2018; Nievergelt et al., 2019) and the United States Veterans Affairs Health Care System's Million Veteran Program (MVP; Stein et al., 2021) as collaborative efforts to achieve an adequate statistical power. Freeze 1 of the PGC-PTSD identified no potential sources of genetic variation associated with PTSD based on 0 independent genome-wide significant SNPs from a meta-analytic sample of 5,183 cases and 15,548 majority trauma-exposed controls (Duncan, Ratanatharathorn, et al., 2018), which was likely due to low power and possibly the inclusion of non-trauma-exposed controls. Freeze 2 of the PGC-PTSD increased their meta-analytic sample size (32,428 cases and 174,227 majority trauma-exposed controls), and thus their statistical power, and identified potential sources of genetic variation associated with PTSD based on 3 independent genome-wide significant SNPs: rs34517852 and rs9364611 on chromosome 6 in individuals with European ancestry, rs115539978 on chromosome 13 in individuals with African ancestry, and an additional locus (rs142174523 on chromosome 6) was found in men when stratified by sex (Nievergelt et al., 2019). Most recently, the MVP analyzed separately by ancestry 36,301 cases and 178,107 controls of European ancestry and 11,920 cases and 39,116 controls of African ancestry, which identified potential sources of genetic variation associated with PTSD based on 5 independent genome-wide significant SNPs: rs10767744 on chromosome 11, and rs137999048 and rs7680 on chromosome 7 in those from European ancestry; and rs4684090 on chromosome 3 and rs112149412 on chromosome 20 in those from African ancestry (Stein et al., 2021). The MVP trans-ancestral meta-analysis (meta-analysis of individuals from both European and African ancestry) included 48,221 cases and 217,223

controls, which identified potential sources of genetic variation associated with PTSD based on 2 independent genome-wide significant SNPs from the same regions in the separate European ancestry analysis: rs137944087 on chromosome 7 and rs10767739 on chromosome 11 (Stein et al., 2021). Notably, rs13262595 and rs11507683 were also found to be significantly associated with PTSD in MVP's replication study using PGC-PTSD as the independent dataset (Stein et al., 2021). Both genes have been associated with risk-taking behaviors, which could increase one's likelihood for experiencing traumatic events and developing PTSD.

a. Table 1: Summary of GWASs for Cannabis Use Phenotypes

Citation	Population Type	Demographics	Cannabis Phenotype	Findings
Agrawal, A., Lynskey, M. T., Hinrichs, A., Grucza, R., Saccone, S. F., Krueger, R., ... & Bierut, L. J. (2011). A genome-wide association study of DSM-IV cannabis dependence. <i>Addiction biology</i> , 16(3), 514-518.	Study of Addiction: Genes and Environment (SAGE), which was one of the eight Phase 1 studies of the Gene Environment Association (GENEVA) consortium	708 cannabis-dependent cases and 2,346 cannabis-exposed controls; 2,019 European ancestry and 1,035 African ancestry	Lifetime DSM-IV cannabis dependence	Non-significant
Verweij, K. J., Vinkhuyzen, A. A., Benyamin, B., Lynskey, M. T., Quaye, L., Agrawal, A., ... & Medland, S. E. (2013). The genetic etiology of cannabis use initiation: a meta-analysis of genome-wide association studies and a SNP-based heritability estimation. <i>Addiction biology</i> , 18(5), 846-850.	Australian and United Kingdom twin registries	10,091 individuals of European ancestry (from 4622 independent families); 4,104 cases & 5,987 controls; 65.2% female	Cannabis use initiation	Non-significant

<p>Minică, C. C., Dolan, C. V., Hottenga, J. J., Pool, R., Fedko, I. O., Mbarek, H., ... &amp; Vink, J. M. (2015). Heritability, SNP- and gene-based analyses of cannabis use initiation and age at onset. <i>Behavior genetics</i>, 45(5), 503-513.</p>	<p>Netherlands Twin Register</p>	<p>Cannabis use initiation: 6,744 related individuals of Dutch ancestry; 1,357 cases &amp; 5,387 controls; 60.9 % female; Age of onset: 5,148 related individuals of Dutch ancestry; 852 cases &amp; 4,296 controls; 62.3 % female</p>	<p>Cannabis use initiation; Age of onset</p>	<p>Non-significant</p>
<p>Stringer, S., Minică, C. C., Verweij, K. J., Mbarek, H., Bernard, M., Derringer, J., ... &amp; Vink, J. M. (2016). Genome-wide association study of lifetime cannabis use based on a large meta-analytic sample of 32 330 subjects from the International Cannabis Consortium. <i>Translational psychiatry</i>, 6(3), e769-e769.</p>	<p>13 discovery samples from Europe, United States, and Australia</p>	<p>Meta-analysis sample: 32,330 individuals of European ancestry; 44.5% cases; 53% female; Replication sample: 5,627 individuals (2,967 European and 2,660 African ancestry)</p>	<p>Lifetime cannabis use</p>	<p>Non-significant; although no individual SNPs reached genome-wide significance, gene-based tests identified four genes significantly associated with lifetime cannabis use: <i>NCAMI</i>, <i>CADM2</i>, <i>SCOC</i>, and <i>KCNT2</i></p>
<p>Pasman, J. A., Verweij, K. J., Gerring, Z., Stringer, S., Sanchez-Roige, S., Treur, J. L., ... &amp; Vink, J. M. (2018). GWAS of lifetime cannabis use</p>	<p>International Cannabis Consortium (North America, Europe, and Australia),</p>	<p>Total sample: 184,765 individuals of European ancestry; International Cannabis Consortium sub-sample: 35,297 individuals of European ancestry; 42.8% cases; 55.5% female;</p>	<p>Lifetime cannabis use</p>	<p>8 independent genome-wide significant SNPs (rs2875907, rs1448602, rs7651996, rs10085617, rs9773390, rs9919557, rs10499, rs17761723) in <i>CADM2</i>,</p>

<p>reveals new risk loci, genetic overlap with psychiatric traits, and a causal effect of schizophrenia liability. <i>Nature neuroscience</i>, 21(9), 1161-1170.</p>	<p>UK-Biobank, and 23andMe</p>	<p>UK-Biobank sub-sample: 22,683 individuals of European ancestry; 43.2% cases; 55.3% female; 23andMe sub-sample: 126,785 individuals of European ancestry; 22.3% cases; 56.3% female</p>		<p><i>ZNF704</i>, <i>SDK1</i>, <i>NCAMI</i>, <i>RABEP2</i> or <i>ATP2A1</i> and <i>SMG6</i> on chromosomes 3, 7, 8, 11, 16 and 17</p>
<p>Johnson, E. C., Demontis, D., Thorgeirsson, T. E., Walters, R. K., Polimanti, R., Hatoum, A. S., ... &amp; Wang, J. C. (2020). A large-scale genome-wide association study meta-analysis of cannabis use disorder. <i>The Lancet Psychiatry</i>, 7(12), 1032-1045.</p>	<p>Psychiatrics Genomics Consortium Substance Use Disorders working group, iPSYCH, and deCODE</p>	<p>Total sample: 384,032 individuals of European ancestry; 20,916 cases &amp; 363,116 controls; Psychiatric Genomics Consortium sub-sample: 8,277 cases &amp; 23,497 controls of European ancestry; 3,848 cases &amp; 5,897 controls of African ancestry; iPSYCH sub-sample: 2,758 cases &amp; 53,326 controls of European ancestry; deCODE sub-sample: 6,033 cases &amp; 280,396 controls of European ancestry</p>	<p>Lifetime DSM-5 cannabis use disorder</p>	<p>2 independent genome-wide significant SNPs (rs4732724 and rs7783012) on chromosomes 8 and 7</p>

b. Table 2: Summary of Meta-Analytic GWASs for PTSD

Citation	Population Type	Demographics	Findings
<p>Duncan, L. E., Ratanatharathorn, A., Aiello, A. E., Almlil, L. M., Amstadter, A. B., Ashley-Koch, A. E., ... &amp; Koenen, K. C. (2018). Largest GWAS of PTSD (N= 20 070) yields genetic overlap with schizophrenia and sex differences in heritability. <i>Molecular psychiatry</i>, 23(3), 666-673.</p>	<p>Psychiatrics Genomics Consortium: Posttraumatic Stress Disorder working group</p>	<p>5,131 cases &amp; 15,092 controls; 9,537 European ancestry, 9,223 African ancestry, 696 Latino/Hispanic ancestry, and 384 South African ancestry</p>	<p>Non-significant</p>
<p>Nievergelt, C. M., Maihofer, A. X., Klengel, T., Atkinson, E. G., Chen, C. Y., Choi, K. W., ... &amp; Koenen, K. C. (2019). International meta-analysis of PTSD genome-wide association studies identifies sex-and ancestry-specific genetic risk loci. <i>Nature</i></p>	<p>Psychiatrics Genomics Consortium: Posttraumatic Stress Disorder working group</p>	<p>European ancestry meta-analyses: 23,212 cases &amp; 151,447 controls; African ancestry meta-analysis: 4363 cases, 10,976 controls</p>	<p>3 independent genome-wide significant SNPs: rs34517852 and rs9364611 on chromosome 6 in individuals with European ancestry, and rs115539978 on chromosome 13 in individuals with African ancestry; an additional locus was found in men when stratified by sex (rs142174523 on chromosome 6)</p>

<i>communications</i> , 10(1), 1-16.			
Stein, M. B., Levey, D. F., Cheng, Z., Wendt, F. R., Harrington, K., Pathak, G. A., ... & Gelernter, J. (2021). Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. <i>Nature Genetics</i> , 53(2), 174-184.	United States Million Veterans Program	European ancestry: 36,301 cases & 178,107 controls; African ancestry: 11,920 cases & 39,116 controls	5 independent genome-wide significant SNPs: rs10767744 on chromosome 11, and rs137999048 and rs7680 on chromosome 7 in those from European ancestry; and rs4684090 on chromosome 3 and rs112149412 on chromosome 20 in those from African ancestry. The trans-ancestral meta-analysis identified 2 independent genome-wide significant SNPs from the same regions in the separate European ancestry analysis: rs137944087 on chromosome 7 and rs10767739 on chromosome 11

## *ii. Genome-Wide Complex Trait Analysis (GCTA)*

Genome-wide complex trait analysis (GCTA) uses individual-level GWAS data from unrelated individuals to create heritability estimates for a specific phenotype (i.e., univariate GCTA) and provides SNP-based heritability estimates ( $h^2_{\text{SNP}}$ ; Yang et al., 2011). There is also a bivariate extension of GCTA that can be used to examine the shared heritability between two different phenotypes by calculating overlapping genetic variance (i.e., genetic correlation [ $r_g$ ]; Lee et al., 2012). GCTA is performed by quantifying the chance of genetic similarity among unrelated individuals and comparing it to their measured similarity on a trait. For example, if two unrelated individuals are relatively similar genetically and have similar trait measurements, then the measured genetic similarity are likely to causally influence that trait, and the correlation can to some degree tell how much. However, there are pros and cons to GCTA just like any statistical analysis. Benefits of GCTA include requiring a smaller sample size compared to a GWAS, the bivariate GCTA extension which can investigate shared genetic risk between two phenotypes (Lee et al., 2012), and the ability to estimate heritability using unrelated individuals (Yang et al., 2011). Limitations of GCTA include disregard of genetic variation due to rare variants since it uses individual-level common GWAS array data. Therefore, GCTA tends to have lower heritability estimates compared to twin studies likely due to the inability to capture all genetic variation (Trzaskowski et al., 2013). GCTA is also sensitive to measurement errors, such as the assessment tool's construct validity, which could result in biased heritability estimates (Kumar et al., 2016). Despite these methodological limitations, GCTA has become a valuable tool in estimating genetic heritability of complex phenotypes, such as cannabis use and PTSD.



GCTA studies suggest that SNP-based heritability of cannabis use phenotypes is small-to-moderate. SNP-based heritability of lifetime cannabis use among a small sample of 7,175 individuals from Australia and 2,916 individuals from the United Kingdom suggested that common SNPs jointly capture 6% of the heritability in lifetime cannabis use (Verweij et al., 2013). In a similar sized sample of distantly related individuals from the Netherlands Twin Registry, Minica and colleagues (2015) found an estimate of 25%. The ICC meta-analyzed genome-wide association data ( $N = 37,957$ ) and found an estimate of 20% (Stringer et al., 2016). This SNP-based heritability estimate is substantially lower than the heritability estimate of about 40% obtained from twin studies (Verweij et al., 2010). As mentioned previously, heritability estimates from twin studies include the effects of all causal genetic variants, while the heritability estimated using GCTA includes only the effects of variants that are in linkage disequilibrium with the SNPs included in the analyses. These SNPs do not capture all genetic variants, especially not rare variants or variants with low minor allele frequencies. Although the SNP-based heritability estimate is somewhat imprecise because of limited power, the result raises the possibility that the role of common genetic variants in the heritability of lifetime cannabis use is small-to-moderate.

GCTA methods have also been utilized to examine the heritability of PTSD. For example, the most recent paper published by the PGC-PTSD found that SNP-based heritability estimates for PTSD were significant within the European ancestry subsample (4-5%), but not the African ancestry subsample (2-4%) based on freeze 2 of their meta-analytic efforts (Nievergelt et al., 2019). However, after stratifying by sex, heritability estimates were significant for both the European ancestry (8-13%) and African ancestry women (12-18%), but were not significant for their male ancestry counterparts. These results are consistent with the broader PTSD literature,

which suggests that the prevalence of PTSD is higher among women compared to men (Olf, 2017). Additionally, PTSD cases vary significantly based on symptom presentation and index trauma or multiple traumas (Zoellner et al., 2014), which contributes to the heterogeneity seen when examining the genetic underpinnings of PTSD.

### *iii. Polygenic Risk Score (PRS)*

A polygenic risk score (PRS) represents an estimate of an individual's aggregate genetic risk for a phenotype that is calculated by adding up the weighted total number of risk-increasing and risk-decreasing alleles using individual-level GWAS data. Some risk alleles do not reach the standard significance  $p$ -value of  $5 \times 10^{-8}$  from GWASs, but the aggregate effect of all potential risk alleles may still influence the phenotype. PRS has become a popular method for risk prediction of human complex traits and psychological disorders due to their polygenic nature. In order to use a PRS for risk prediction, a discovery sample with GWAS summary statistics and an independent target sample with individual-level genotype and phenotype data are needed. The GWAS summary statistics from the discovery sample are used to calculate the weighted total in an independent sample to generate the PRS used to represent an individual's aggregate genetic liability for a phenotype of interest (Dudbridge, 2013). PRSs have the potential to help personalize preventative measures and could soon become part of standard healthcare practice, once some limitations are overcome.

PRSs can also be utilized from a bivariate approach to predict one phenotype (e.g., cannabis use) from aggregate genetic risk of a different phenotype (e.g., PTSD). This bivariate method of PRS enables the genetic covariance between two phenotypes of interest to be examined using molecular data from unrelated individuals, which is a very useful technique. However, PRS is not exempt from limitations. PRS is limited based on what SNPs were

examined in the discovery sample and does not factor in rare variants or potentially non-additive effects, as well as the sensitivity and specificity of the phenotype of interest (Anderson et al., 2019). Replications across studies are difficult partially due to the heterogeneity in measurement of psychiatric phenotypes (Anderson et al., 2019). Furthermore, large samples are required to produce more accurate estimates (Wray et al., 2014). If a study does not have adequate power based on sample size, then PRS cannot be used in cohorts of non-European ancestry unless the discovery GWAS is of the same ancestry (Anderson et al., 2019), but the meta-analytic efforts of the PGC are addressing this concern. PRSs have been applied in both the cannabis (Johnson et al., 2019; Meyers et al., 2019; Winiger et al., 2021) and PTSD (Asch et al., 2021; Duncan, Ratanatharathorn, et al., 2018; Misganaw et al., 2019) literatures separately, but no studies to date have used PRS to test aggregate genetic risk for cannabis use in relation to PTSD.

### **L. Summary**

RCU and its association with PTSD marks an interesting area of research as legal restrictions become less stringent on cannabis (Felson et al., 2019; Hall, 2006). Based on cross-sectional and longitudinal evidence from various populations, PTSD seems to be associated with RCU at a rate higher than chance (Hicks, Zaur, et al., 2022), and their co-occurrence is a growing public health concern as mixed findings suggest inconclusive results about benefits and harms of plant-based cannabis as a treatment for PTSD (Jugl et al., 2021). To best address prevention, treatment, and management challenges of co-occurring RCU and PTSD, we must understand the etiological and maintenance factors contributing to their onset. There are several models that have been proposed to explain co-occurring RCU and PTSD (Berenz et al., 2019). The shared risk model suggests that RCU and PTSD frequently co-occur due to common familial risk (i.e., genetic factors, shared environmental influences; Krueger & Markon, 2006). The self-medication

model suggests that individuals with PTSD are more likely to use cannabis because it serves as a means to cope with trauma-related symptoms (Khantzian, 1997). The high-risk model suggests that RCU increases risk for trauma exposure and, consequently, PTSD (Brady et al., 2004). A systematic review of the literature revealed that the literature to date does provide evidence for the self-medication and high-risk models posited to explain co-occurring RCU and PTSD, but that empirically rigorous investigation of the self-medication, high-risk, and shared risk model is lacking due to numerous methodological limitations (Hicks, Zaur, et al., 2022). Such limitations include the lack of longitudinal designs, as well as not examining longitudinal data thoroughly by testing only one of the self-medication or high-risk models. Specifically, studies should simultaneously test both the self-medication and high-risk models because they are not mutually exclusive, and it is likely that cannabis use and PTSD reciprocally impact one another once developed.

In addition to the limitations reviewed above, perhaps the largest limitation of the RCU and PTSD literature is that there are no genetically-informed studies testing the non-mutually exclusive shared risk model, which suggests that RCU and PTSD co-occur due to common familial risk factors (i.e., shared genes, common environment). This apparent lack of research examining the co-occurrence of RCU and PTSD creates a critical void to fill. Given the evidence for moderate overlap in genetic variance between RCU and PTSD (Xian et al., 2000), genetically-informed research surrounding the co-occurrence of RCU and PTSD is warranted. Investigations into the shared genetic risk and biological underpinnings of co-occurring RCU and PTSD would help to further elucidate common etiological pathways underlying the development of co-occurring RCU and PTSD, which is imperative to the development of effective prevention and intervention programs.

### **III. Study Aims**

#### **A. Aim 1: Phenotypic Investigation of Etiologic Models for Co-Occurring RCU and PTSD**

The goal of Aim 1 was to test phenotypic models of co-occurring RCU and PTSD (i.e., self-medication and high-risk models) across the course of college using data from students enrolled in an ongoing longitudinal, genetically informative study of college students at a large, diverse public university (“Spit for Science” [S4S], NIAAA-R37 AA011408, PIs: Kendler, Dick). Trauma-related distress (TRD) is a term used to describe when an individual experiences any PTSD symptoms. When testing the self-medication model, it was hypothesized that TRD will mediate the relation between new-onset IPT exposure and RCU. When testing the high-risk model, it was hypothesized that new-onset IPT exposure will mediate the relation between RCU and TRD. Additionally, it was hypothesized that a history of IPT exposure will moderate the relationship between new-onset IPT exposure and TRD such that individuals with more IPT exposure will be more likely to report TRD.

#### **B. Aim 2: Genotypic Investigation of RCU and PTSD**

Given that molecular studies of cannabis use are still in their infancy, Aim 2 of the current study was to conduct genome-wide analyses (i.e., GCTA) of RCU and TRD to examine their molecular heritability. Further analyses examined the genetic correlation between lifetime cannabis use and lifetime PTSD using PRSs. It was hypothesized that RCU and TRD will be moderately heritable and that aggregate genetic risk of lifetime cannabis use and lifetime PTSD will predict RCU and TRD in S4S, respectively. Also, it was hypothesized that PRSs for lifetime cannabis use and lifetime PTSD will be correlated.

### **C. Aim 3: Phenotypic and Genotypic Investigation of Etiologic Models for Co-Occurring**

#### **RCU and PTSD**

The goal of Aim 3 was to incorporate aggregate genetic risk for lifetime cannabis use and lifetime PTSD into the phenotypic models of co-occurring RCU and PTSD from Aim 1. It was hypothesized that aggregate genetic risk for lifetime cannabis use will moderate the relationship between TRD and RCU such that individuals with higher PRS for lifetime cannabis use will be more likely to report RCU. Likewise, it was hypothesized that aggregate genetic risk for lifetime PTSD will moderate the relationship between IPT and TRD such that individuals with higher PRS for lifetime PTSD will be more likely to report TRD. It was also hypothesized that individuals with higher aggregate genetic risk for lifetime cannabis use will be more likely to report recent RCU and TRD at subsequent timepoints, and that individuals with higher aggregate genetic risk for PTSD will be more likely to report TRD and RCU at subsequent timepoints.

## **Chapter 2: Methods**

### **I. Participants**

The sample included in the present study was leveraged from an ongoing longitudinal, genetically informative, cohort study of college students (i.e., S4S) at a large public university in the southeast. At the time of this study, five cohorts (N ~ 12,000; ~62% female, ~50% European American, ~19% African American, < 1% Native American, ~6% Hispanic/Latino, ~15% Asian, 6% Multi-racial, and <1% Native Hawaiian/Pacific Islander) had been enrolled in the study. The first cohort of students for the project began in fall 2011 (Cohort 1; N = 2707), and new cohorts were recruited in 2012 (Cohort 2; N = 2481), 2013 (Cohort 3; N = 2391), 2014 (Cohort 4; N = 2310), and 2017 (Cohort 5; N = 2476). The overarching aim of S4S is to examine vulnerability factors associated with substance use and emotional health via both genotypic and

environmental factors in a college student population. Data collection from the parent study is ongoing and has been collected from 2011-present when all incoming students aged  $\geq 18$  years were invited to participate in a university-wide research study on college behavioral health. Approximately 2 weeks before arriving on campus, information was mailed to all incoming students and (separately) to their parents. The week before Welcome Week all eligible students (age 18 or older) received an e-mail through their university e-mail account inviting them to participate in the project. Participants were representative of the broader student population attending a large public university in the southeast, in terms of both gender and race. The university's Institutional Review Board (IRB) approved all study procedures and informed consent was obtained from all study participants. Study data were collected and managed using REDCap (Research Electronic Data Capture), hosted at the university. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to statistical packages; and 4) procedures for importing data from external sources. Participants completed an online survey during the fall of their first year, and each subsequent spring semester in REDCap assessing a variety of factors including childhood experiences, personality, relationships, and behavior, receiving \$10 and a t-shirt as compensation. Participants also have the opportunity to provide a DNA sample for further compensation. Detailed information concerning study methods and recruitment can be found in (Dick et al., 2014).

## **II. Measures**

Given the large-scale nature of the parent S4S study, measures were abbreviated to reduce participant burden. Item response theory modeling was used to justify scale modifications using

data from the first wave of the study. Specifically, by investigating the item characteristic and information curves, items that resembled the calibrating information for estimating subjects' location on the latent factor were removed. If an item was distinct enough compared with the other items included as indicators of the factor and items that optimally functioned on the latent continuum, then they were included in the measures. Therefore, items that provided good discrimination at various locations along the range of the latent factor scale were utilized to make test administration both practical and feasible. Unless otherwise stated, given the longitudinal nature of the dataset, each variable described below was calculated the same way for each time point.

**A. Demographics.** Data regarding demographics were drawn from the baseline (year 1 fall) survey. These questions included self-reported gender, race, cohort, age, and sexual orientation. For gender, males were coded as 0 and females were coded as 1 to compare males to females. For race, 3 dummy coded variables were created for White, Black, Asian, and Other (i.e., American Indian/Alaska Native, Hispanic/Latino, Native Hawaiian/Other Pacific, more than one race, unknown, and I choose not to answer) with White as the reference group to make the following comparisons: White versus Black, White versus Asian, and White versus Other. For cohort, 4 dummy coded variables were created for cohorts one through four with one as the reference group to make the following comparisons: one versus two, one versus three, and one versus four.

**B. Recreational Cannabis Use (RCU).** Lifetime use and total times used was measured using items adapted from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994). Recent cannabis use was assessed using items adapted from Substance Abuse and Mental Health Service Administration (Substance Abuse and Mental Health Service



Administration, 2013). In baseline surveys, participants were asked if they had ever used (yes/no response options) and, if so, how many times (free response). Use 1-5 times was classified as “experimental” use and use 6 or more times was classified as “non-experimental” use, which will be referred to as the “cannabis use threshold” variable. During their follow-up Spring survey the first year, participants were asked the same questions about use “since VCU,” roughly corresponding to past 6 months use. In all other Spring follow-up surveys, participants were asked the same questions about past 12-months use and number of times used. The cannabis use threshold variable was used to represent RCU in the present study.

**C. Interpersonal Trauma Exposure (IPT).** Traumatic event (TE) exposure was assessed at baseline (e.g., year 1 fall) using an abbreviated version of the Life Events Checklist (Gray et al., 2004). Participants were asked to report on the occurrence of five different stressful events: natural disasters, physical assaults, sexual assaults, other unwanted or uncomfortable sexual experiences, and transportation accidents. Response options were “yes” or “no” to items regarding whether each stressful event occurred “before the past 12 months”, “during the past 12 months”, or “never happened to me”. If a participant endorsed that the event occurred either “before the past 12 months”, or “during the past 12 months”, it was considered a positive endorsement of TE exposure prior to college. If a participant did not endorse any of the aforementioned options or reported that the events “never happened to me”, it was considered a negative endorsement of TE history. Categories were further clustered by interpersonal TEs (i.e., physical assaults, sexual assaults, other unwanted or uncomfortable sexual experiences). The clustering created two IPT variables, which were utilized in this study: An IPT endorsement variable (i.e., yes/no) and an IPT category count variable ranging from 0-3 for each type of IPT event. The same items were utilized during yearly spring follow-ups, however, the timeframe of

reference was altered to appropriately capture events occurring “since VCU” and “in the past 12 months”, respectively. The IPT category count variable was used as the secondary trauma-related phenotype in the present study.

**D. Trauma-Related Distress (TRD).** If a participant endorsed a TE on the Life Events Checklist (Gray et al., 2004) or the single item derived from stressful events measure (Kendler et al., 1999) they were prompted to respond to four PTSD screener items (four items;  $\alpha = .93$ ). The PTSD screener items were derived from the Primary Care PTSD Screen (PC-PTSD; Prins et al., 2016), previously used in screening PTSD symptoms in primary care settings. The four items ask whether the participant has ever experienced: nightmares, attempts to avoid thoughts or reminders of the potentially traumatic experience, hypervigilance, and feelings of detachment. The total symptom count (ranging from 0-4) was used as the primary PTSD variable in analyses, and based on standardized scoring for this measure; endorsement of three or more items was used as indication of a positive lifetime history of trauma-related distress (TRD). Cohort 4 is the only cohort that received the four-item measure of TRD. Cohorts 1 through 3 received a version of TRD assessment where all four items were asked in one question and endorsement of any item (e.g., nightmares, attempts to avoid thoughts or reminders of the potentially traumatic experience, hypervigilance, and feelings of detachment) was used as indication of a positive lifetime history of TRD. Assessments for cohorts one through four were combined to create an endorsement of TRD variable (i.e., yes/no), where a score greater than 0 was classified as TRD. Response options were coded as 0 and 1, where 0 is indicative of no TRD and 1 is indicative of TRD. TRD was used as the primary trauma-related phenotype in the present study. Assessments for cohort 5 used the PTSD Checklist (PCL-5; Weathers et al., 2013) and were coded to match

cohorts 1-4 such that a score greater than 0 was classified as TRD for use in GCTA analyses in order to increase sample size for statistical power.

**E. Alcohol Use Frequency.** Average frequency of alcohol use during the past year was assessed using the frequency items from the Alcohol Use Disorder Identification Test (AUDIT; Bohn et al., 1995). Response options for frequency (“How often do you have a drink containing alcohol?”) were “never”, “monthly or less”, “2 to 4 times a month”, “2 to 3 times a week”, or “4 or more times a week.” Response options were coded from 0 to 4, where higher responses were indicative of more frequent alcohol use.

**F. Nicotine Use Frequency.** Nicotine use was assessed across 4 categories: cigarettes, cigars, smokeless tobacco, and hookah. Lifetime use and total quantity consumed was assessed using items adapted from the SSAGA (Bucholz et al., 1994). Recent (past 30 days) frequency of use was measured using items adapted from SAMSHA (Substance Abuse and Mental Health Service Administration, 2013). For each nicotine category, participants were asked how frequently they used the product in the last 30 days. Answer options were “I did not use,” “Once or twice,” “A few days (3 to 4 days a month),” “A couple of days a week (5 to 11 days a month),” “3 times a week (12 to 14 days a month),” “most days of the week (15 to 25 days a month),” and “daily or almost daily (26 to 30 days a month).” Response options specifically for nicotine use were coded from 0 to 6, where higher responses were indicative of more frequent nicotine use.

**G. DNA Collection and Genotyping Procedures.** Participants who completed the phenotypic online assessment were invited to provide saliva samples for genotyping (for details, see Dick et al., 2014; Webb et al., 2017). DNA was collected via an Oragene kit and isolated via standard procedures. Cohorts 1-3 were genotyped on the Axiom BioBank Array, Catalog Version 2. The array is designed to assay 653K SNPs and InDels including a) 296K common variants used for

imputation and genome wide association scans, and 375K likely functional variants from exome studies including non-synonymous, loss of function, known disease, splice altering, eQTL, and pharmacogenetics-related loci. The array allows for testing of both common and rare variants because many of the functional variants have low allele frequency.

Cohorts 4 and 5 were genotyped using the Smokescreen Genotyping Array at the Rutgers University Cell and DNA Repository Infinite Biologics. This array is a custom array designed to cover 646,247 SNPs, 1,014 genes, and indels related to addiction and smoking-related phenotypes. It is applicable to European, African, and East Asian ancestry populations. Similar to the Axiom BioBank Array, the Smokescreen Array covers both rare and common variants. which enabled all cohorts to be imputed from their separate arrays to a common 1000 Genomes platform.

S4S has a project specific pipeline that was used to process all saliva samples. For cohorts 1-4, the quality control (QC) pipeline excluded Off Target Variants found by SNPisher samples missing >2% of genotypes and SNPs missing >5% of genotypes after sample filtering, similar to the PGC QC pipeline. In other words, processing of genetic samples is susceptible to error from lab processing or from user-error, and as such, individual saliva samples that are missing >2% of genotypes (i.e., within-person missingness across the genome) and individual SNPS missing >5% of genotypes (i.e., specific loci missingness across the sample) were removed due to high missingness. Following QC removal, 6,325 samples and 560,138 variants remained for imputation, conducted using SHAPEIT2 and the 1000 genomes phase 3 reference panel (1KGP).

Population stratification was used to account for the racially and ethnically diverse sample. Population stratification occurs when both disease prevalence (e.g., PTSD) and allelic

frequency differences exist in the subpopulation sampled, leading to false positive associations of genetic signals. Since GWAS tests millions of markers across the genome, some will show differences in allele frequency between populations, based on ethnicity (e.g., European-American vs. African-American) and the overall distribution of test statistics will be inflated, leading to an increase in false positives (Peterson et al., 2017).

Ancestry assignment was completed using principal component analysis (PCA) with Mahalanobis distance calculations. Variants from the 1KGP phase 3 reference panel are combined with variants present in the cleaned S4S genotypic data. LD-based pruning ( $r^2 < 0.1$ ) is applied to the matching set of variants. The resulting overlapping marker set of 109,259 variants from 1KGP are then subjected to PCA using the EIGENSOFT (Price et al., 2006) and SmartPCA (Patterson et al., 2006) programs. The 10 resulting ancestry PCs are subsequently projected onto the genotypic data from S4S and sample-specific PCs are created. Finally, each participant was assigned to a 1KGP population based on their minimum Mahalanobis distance. The S4S samples were collapsed into their respective super-population assignment. Briefly, ancestry super-populations are ancestry groups that include populations with smaller numbers of samples to create larger groups that most samples fall into. Five super populations have been identified within the S4S genotypic data: African (AFR), admixed from the Americans (AMR), East Asian (EAS), South Asian (SAS), and European (EUR). Samples were analyzed separately based on their super-populations. Detailed information concerning PCA and genotypic meta-analytic efforts based on super-population assignment in S4S can be found in (Peterson et al., 2017).

GCTA analyses were conducted separately by PC determined ancestry group using METAL (Marchini et al., 2007). PRS analyses used summary statistics from large-scale archival genetic data publicly available to researchers through multiple research consortia, including the

Psychiatric Genomic Consortium (PGC; <https://www.med.unc.edu/pgc/download-results/>) and the International Cannabis Consortium (ICC; <https://www.ru.nl/bsi/research/group-pages/substance-use-addiction-food-saf/vm-saf/genetics/international-cannabis-consortium-icc/>). Summary statistics for lifetime cannabis use (ICC: N = 185k; ~60% endorsing lifetime cannabis use) and PTSD (PGC-PTSD working group: 25k cases and >50k controls) were used to compute PRSs in the S4S database.

### **III. Data Analytic Plan**

**A. Multiple Imputation.** Missing data was imputed using the R package “missForest” (Stekhoven & Buhlmann, 2012). A non-parametric multiple imputation method was applied to estimate missing data in five binary variables of cannabis use from year 1 Fall, year 1 Spring, and year 2 Spring. Eight iterations of the imputation process were performed until reaching an optimal stopping point. The imputation was based on six binary (3 cannabis, 3 alcohol) and nine categorical (3 cannabis, 3 nicotine, and 3 alcohol) variables from years 1 to 2. The overall estimate of imputation error was 0.1459 based on the proportion of falsely classified (PFC) entries, with the PFC of the six binary variables of cannabis use ranging between 0.00 and 0.0002. It is expected that good performance results of imputation with “missForest” will give a value close to 0, in contrast with inadequate results returning values close to 1 (Stekhoven & Buhlmann, 2012). The imputed dataset was used for all analyses.

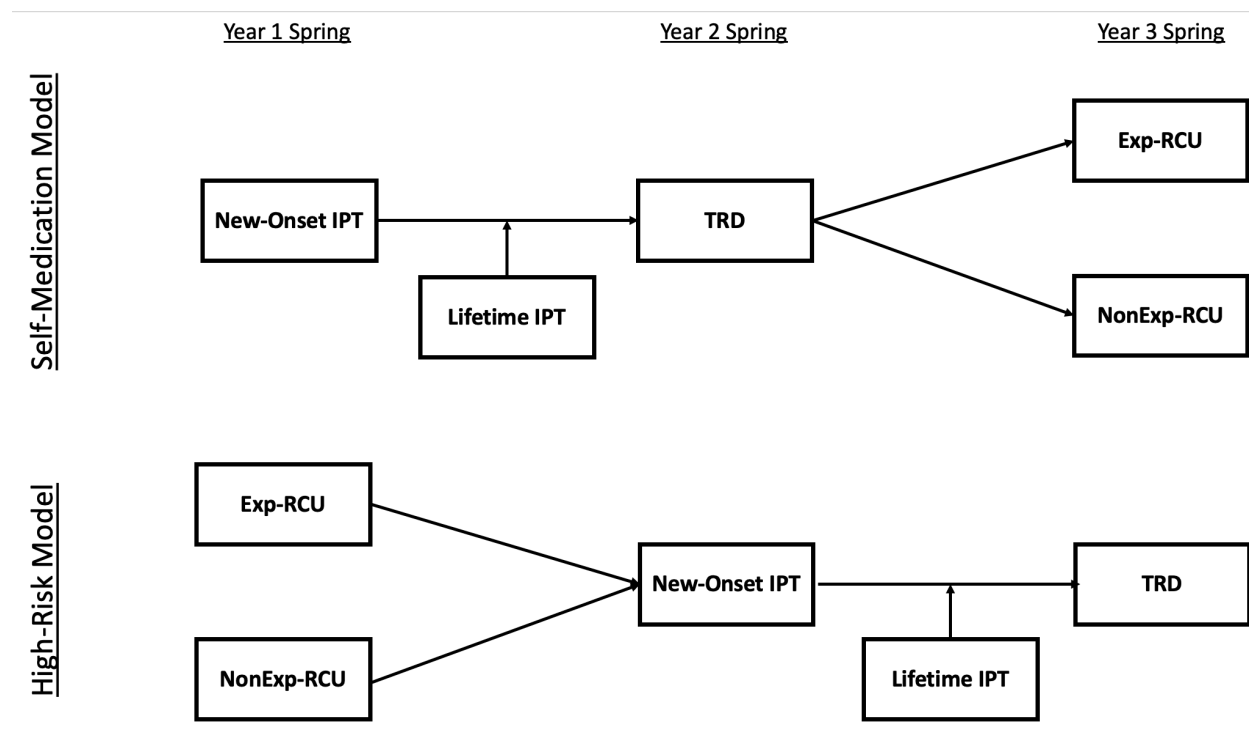
**B. Aim 1.** The first aim of the present study was to test phenotypic models of co-occurring RCU and PTSD (i.e., self-medication and high-risk models) across the course of college using moderated-mediation analyses. Specifically, Aim 1 proposed to model the longitudinal, and indirect, associations among new-onset IPT exposure, TRD, and RCU to test the hypotheses that TRD will mediate the relation between new-onset IPT exposure and RCU (1a; self-medication model) and new-onset IPT exposure will mediate the relation between RCU and TRD (1b; high-risk model). Additionally, it was hypothesized that a history of IPT exposure will moderate the relationship between new-onset IPT exposure and TRD such that the effect of new-onset IPT on TRD will be stronger (and positive) for those with a greater history of IPT. The covariates were age, gender, race, alcohol use frequency, and nicotine use frequency. In order to test study hypotheses, mediation analyses investigated whether the indirect effects of new-onset IPT

exposure on RCU through TRD, as well as RCU on TRD through new-onset IPT exposure were significant.

*Figure 1* illustrates the phenotypic pathways between new-onset IPT, TRD, and RCU to test the self-medication model, as well as between RCU, new-onset IPT, and TRD to test the high-risk model. Two different moderated-mediation analyses (i.e., one for both parts of Aim 1) were run simultaneously using Mplus Version 8.4 (Muthen & Muthen, 2017) and tested (1a) whether new-onset IPT exposure is associated with TRD, and in turn increased RCU (i.e., self-medication model), as well as (1a) whether RCU is associated with new-onset IPT exposure, and in turn TRD (i.e., high-risk model). Any significant interactions ( $p < .05$ ) between lifetime IPT and new-onset IPT were probed using simple slope analyses and/or regions of significance testing (Aiken et al., 1991).



*i. Figure 1: Longitudinal Moderated-Mediation Model Examining Self-Medication and High-Risk Models of Co-Occurring RCU and TRD with History of IPT Exposure as a Moderator*

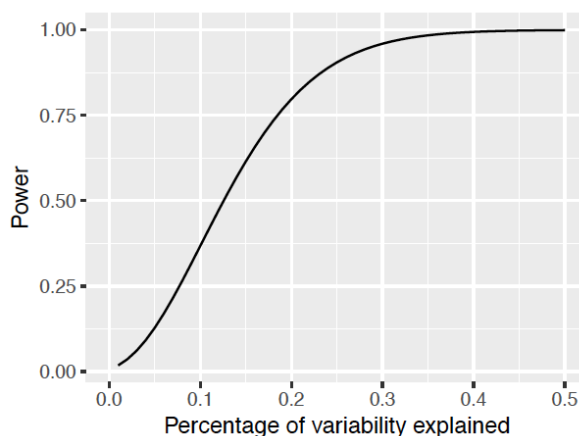


*Note: IPT = interpersonal trauma. TRD = trauma-related distress. RCU = recreational cannabis use. Exp = experimental. NonExp = Non-experimental. Covariates are being included, but are not shown for visual simplicity.*

Hypotheses for Aim 1 were that TRD will mediate the relation between new-onset IPT exposure and RCU (self-medication model), and new-onset IPT exposure will mediate the relation between RCU and TRD (high-risk model). Additionally, it was hypothesized that a history of IPT exposure will moderate the relationship between new-onset IPT exposure and TRD such that the effect of new-onset IPT on TRD will be stronger (and positive) for those with a greater history of IPT. Based on the assumptions of normal distribution of variables, homogenous variances, and homogeneity of variances differences, a power analysis for Aim 1 demonstrated that there is  $\geq 80\%$  power to explain 0.2% or more of the variability explained by

the causal pathways between recent RCU, new-onset IPT, and TRD (i.e., small effect; Cohen, 1992). Prior work has found small to small-medium inter-relations of cannabis use phenotypes and PTSD (Loflin et al., 2017). Thus, we have power to detect even very small effects for Aim 1 (see Figure 2).

*ii. Figure 2: Power Analysis for Aim 1*



**C. Aim 2.** The second aim of the proposed study was to conduct genome-wide analyses (i.e., GCTA) of RCU and TRD to examine their molecular heritability. Additionally, PRSs were calculated to examine the genetic correlation between lifetime cannabis use and PTSD. It was hypothesized that RCU and TRD will be moderately heritable, and that aggregate genetic risk of lifetime cannabis use and PTSD will be positively correlated (i.e., PRSs).

Two univariate GCTAs were conducted. This method creates a genetic relationship matrix (GRM) based on SNPs for all individuals in the sample. The GRM was used to predict phenotypic relatedness. Statistical assumptions that underlie the GCTA power analyses are 1) a conservative heritability estimate of lifetime RCU (51.4%; Verweij et al., 2010), 2) RCU risk in population is about 10.5% (Substance Abuse and Mental Health Service Administration, 2020), and 3) variance of the SNP-derived genetic relationships is  $2e^{-5}$ . A GCTA-GREML power calculation (Yang et al., 2011) was conducted, based on extant methods (Visscher et al., 2014),

which determined that we are not sufficiently powered (< 80%) to detect heritability estimates > 0.

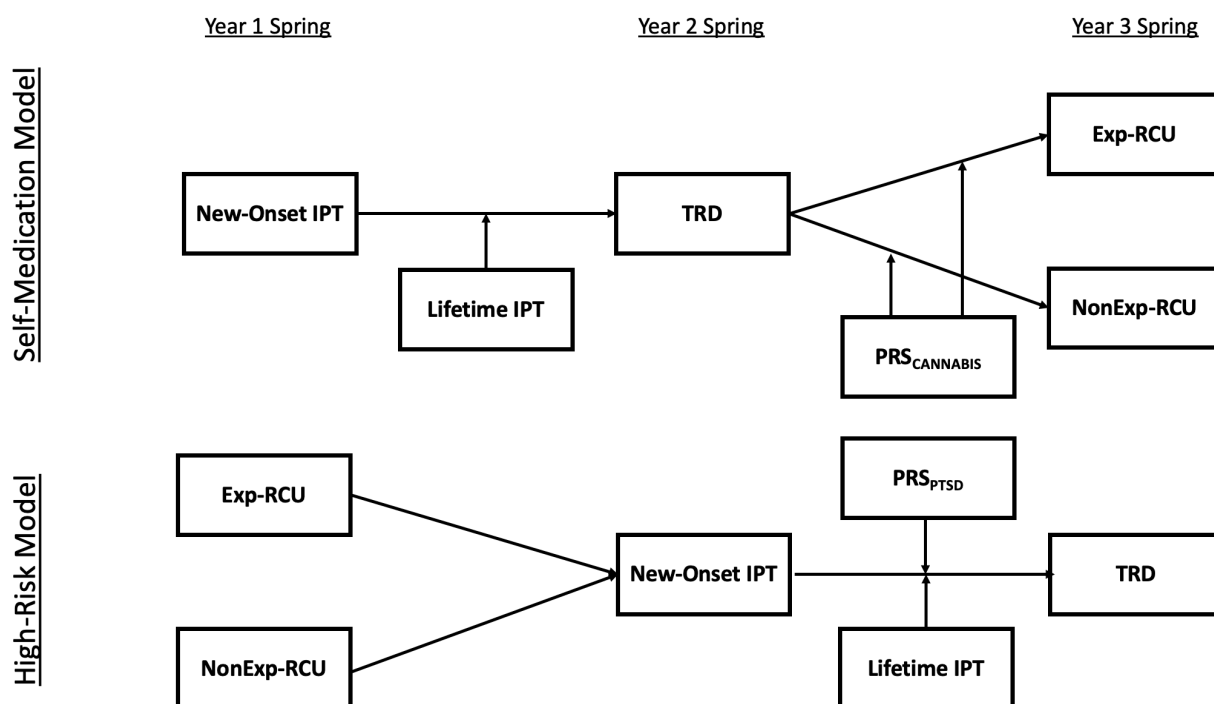
Genetic analyses were analyzed separately by ancestry (EUR and AFR ancestries are the largest ancestry populations in S4S and large-scale psychiatric consortia contain adequate numbers of EUR and AFR for ancestry specific PRS analyses) controlling for PCs and sex. PRS for lifetime cannabis use was calculated using the summary statistics from ICC (N = 184,765; ~60% endorsing lifetime cannabis use) and PRS for PTSD was calculated using the summary statistics from PGC-PTSD (25k cases and >50k controls). Using the PLINK software package, the summary score files from the ICC and PGC-PTSD were used to score each S4S subject's aggregate genetic risk for lifetime cannabis use and PTSD by weighting risk alleles according to the natural log of the odds ratio (OR) from each of the discovery samples for specified *p*-value bins. The resulting PRSs were analyzed via regression analyses; homogenous ancestry populations were analyzed separately.

**D. Aim 3.** The third aim of the proposed study was to incorporate aggregate genetic risk for lifetime cannabis use and PTSD into the phenotypic models of co-occurring RCU and PTSD from Aim 1. It was hypothesized that aggregate genetic risk for lifetime cannabis use will moderate the relationship between TRD and RCU such that individuals with higher PRS for lifetime cannabis use will be more likely to report RCU. Likewise, it was hypothesized that aggregate genetic risk for lifetime PTSD will moderate the relationship between IPT and TRD such that individuals with higher PRS for lifetime PTSD will be more likely to report TRD. It was also hypothesized that individuals with higher aggregate genetic risk for lifetime cannabis use will be more likely to report recent RCU and TRD at subsequent timepoints, and that

individuals with higher aggregate genetic risk for PTSD will be more likely to report TRD and RCU at subsequent timepoints.

*Figure 3* illustrates the phenotypic pathways between new-onset IPT, TRD, and RCU to test the self-medication model, as well as between RCU, new-onset IPT, and TRD to test the high-risk model. Two different moderated-mediation analyses (i.e., one for each model of co-occurring RCU and TRD) were run simultaneously using Mplus Version 8.4 (Muthen & Muthen, 2017) and tested (3a) whether new-onset IPT exposure is associated with TRD, and in turn increased RCU (i.e., self-medication model), as well as does aggregate genetic risk for lifetime cannabis use moderate the causal impact of TRD on RCU. Additionally, we tested (3b) whether RCU is associated with new-onset IPT exposure, and in turn TRD (i.e., high-risk model), as well as does aggregate genetic risk for lifetime PTSD moderate the causal impact of new-onset IPT on TRD. The interaction between PRS for lifetime cannabis use and TRD in the self-medication model, as well as the interaction between PRS for lifetime PTSD and new-onset IPT in the high-risk model were tested as a predictor at subsequent time points. Any significant interactions ( $p < .05$ ) were probed using simple slope analyses and/or regions of significance testing (Aiken et al., 1991). PRS variables for lifetime cannabis use and lifetime PTSD generated in Aim 2 analyses were used for Aim 3 analyses as covariates in order to test same- and cross-phenotype prediction. Specifically, PRS variables for lifetime cannabis use and lifetime PTSD were used as covariates in order to test if individuals at higher aggregate genetic risk for lifetime cannabis use were more likely to report RCU and TRD, and if individuals at higher aggregate genetic risk for PTSD were more likely to report recent TRD and RCU at subsequent timepoints.

*i. Figure 3: Longitudinal Moderated-Mediation Model Examining Self-Medication and High-Risk Models of Co-Occurring RCU and PTSD with History of IPT Exposure and Aggregate Genetic Risk for Lifetime Cannabis Use and Lifetime PTSD as Moderators*

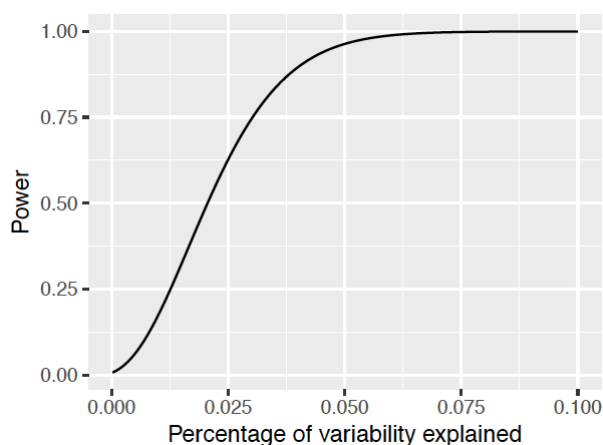


*Note: IPT = interpersonal trauma. TRD = trauma-related distress. RCU = recreational cannabis use. Exp = experimental. NonExp = Non-experimental. PRS = polygenic risk score. PTSD = posttraumatic stress disorder. Covariates are being included, but are not shown for visual simplicity.*

Hypotheses for Aim 3 were that the interaction between PRS for lifetime cannabis use and TRD in S4S will prospectively predict RCU in S4S and that the interaction between PRS for lifetime PTSD and new-onset IPT in S4S will prospectively predict TRD in S4S. Based on the assumptions of effect sizes and standard error of interactions between PRS for lifetime RCU and TRD, as well as between PRS for lifetime PTSD and new-onset IPT being comparable to those of a similar polygenic substance use phenotype, (i.e., problematic alcohol use; Salvatore et al., 2015), *Figure 4* illustrates that there is  $\geq 80\%$  power in Aim 3 to detect moderation effects of PRS for lifetime cannabis use on RCU and TRD in S4S and PRS for lifetime PTSD on TRD and

RCU in S4S when the PRS explains 0.03% or more of the variance in outcomes (Salvatore et al., 2015) (i.e., small effect; Cohen, 1992). Prior work on problematic alcohol use suggests that gene by environment interactions involving PRS are typically small effects (e.g., explaining 0.3% of the variance for problematic alcohol use; Salvatore et al., 2015). Thus, we have sufficient power to detect small effects for Aim 3.

**ii. Figure 4: Power Analysis for Aim 3**



### Chapter 3: Results (Phenotypic)

#### I. Aim 1

##### A. Sample Characteristics

Descriptive statistics are presented in *Table 3*. The majority of participants in the present analytic sample reported that they were White<sup>1</sup> (n = 4956, 72.2%) and female (n = 4266, 62.2%). Participation across all four cohorts was about equal. Almost half of participants reported IPT at year 1 Fall (n = 3380, 49.3%), about a quarter of participants reported IPT at year 1 Spring (n = 1605, 23.4%), and almost a fifth of participants reported IPT at year 2 Spring (n = 1211, 17.6%)

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<sup>1</sup> Due to incorporating those with European and African ancestry in genetic analyses for Aim 3, those self-identifying as White or Black for race were included in analyses from Spit for Science. To limit genetic heterogeneity, we used the largest two sub-populations from Spit for Science. We understand the limitations of this assumption of race and genetic ancestry super-populations.

and year 3 Spring (n = 1152, 16.8%). Almost a third of participants reported TRD at year 1 Fall (n = 1984, 28.9%), year 1 Spring (n = 2045, 29.8%), year 2 Spring (n = 2001, 29.2%), and year 3 Spring (n = 1843, n = 26.9%). Almost half of participants reported cannabis use at year 1 Fall (n = 3424, 49.9%), year 1 Spring (n = 3043, 44.3%), year 2 Spring (n = 3196, 46.6%), and year 3 Spring (n = 3175, 46.3%). At year 1 Fall, the most commonly reported frequency of alcohol use was “monthly or less” (n = 2737, 39.9%), but at year 1 Spring (n = 2371, 34.6%), year 2 Spring (n = 2502, 36.5%), and year 3 Spring (n = 2388, 34.8%), the most commonly reported frequency of alcohol use was “2-4 times a month.” The majority of participants reported no nicotine use at year 1 Fall (n = 3600, 52.5%), year 1 Spring (n = 3613, 52.7%), year 2 Spring (n = 3894, 56.7%), and year 3 Spring (n = 4195, 61.1%).

*i. Table 3: Demographics, Alcohol and Substance Use Prevalence, and Clinical Characteristics for Aim 1 Sub-Sample*

	Overall	Year 1 Fall	Year 1 Spring	Year 2 Spring	Year 3 Spring
	n (%)	n (%)	n (%)	n (%)	n (%)
Race					
White	4956 (72.2%)				
Black	1906 (27.8%)				
Cohort					
1	1918 (28.0%)				
2	1720 (25.0%)				
3	1659 (24.2%)				
4	1565 (22.8%)				
Gender					
Male	2596 (37.8%)				
Female	4266 (62.2%)				
Interpersonal Trauma					
Count by Category					



0	3482 (50.7%)	5257 (76.6%)	5651 (82.4%)	5710 (83.2%)
1	2050 (29.9%)	1170 (17.1%)	1002 (14.6%)	977 (14.2%)
2	887 (12.9%)	319 (4.6%)	165 (2.4%)	150 (2.2%)
3	443 (6.5%)	116 (1.7%)	44 (0.6%)	25 (0.4%)
Trauma-Related Distress				
No	4878 (71.1%)	4817 (70.2%)	4861 (70.8%)	5019 (73.1%)
Yes	1984 (28.9%)	2045 (29.8%)	2001 (29.2%)	1843 (26.9%)
Cannabis Use Threshold				
0	3438 (50.1%)	3819 (55.7%)	3666 (53.4%)	3687 (53.7%)
1	1275 (18.6%)	1380 (20.1%)	1203 (17.5%)	1407 (20.5%)
2	2149 (31.3%)	1663 (24.2%)	1993 (29.0%)	1768 (25.8%)
Alcohol Use Frequency				
0	1122 (16.4%)	914 (13.3%)	899 (13.1%)	503 (7.3%)
1	2737 (39.9%)	2247 (32.7%)	2219 (32.3%)	2037 (29.7%)
2	2103 (30.6%)	2371 (34.6%)	2502 (36.5%)	2388 (34.8%)
3	785 (11.4%)	1164 (17.0%)	1083 (15.8%)	1608 (23.4%)

4	115 (1.7%)	166 (2.4%)	159 (2.3%)	326 (4.8%)
Nicotine Use Frequency				
0	3600 (52.5%)	3613 (52.7%)	3894 (56.7%)	4195 (61.1%)
1	1361 (19.8%)	1346 (19.6%)	1224 (17.8%)	1105 (16.1%)
2	562 (8.2%)	505 (7.4%)	511 (7.4%)	331 (4.8%)
3	323 (4.7%)	320 (4.7%)	267 (3.9%)	250 (3.6%)
4	227 (3.3%)	169 (2.5%)	139 (2.0%)	135 (2.0%)
5	213 (3.1%)	277 (4.0%)	227 (3.3%)	260 (3.8%)
6	576 (8.4%)	632 (9.2%)	600 (8.7%)	586 (8.5%)

*Note:* Interpersonal trauma (IPT) count by category (0 = no IPT, 1 = 1 type of IPT [physical assault, sexual assault, or unwanted/uncomfortable sexual experience], 2 = 2 types of IPT, 3 = 3 types of IPT); Cannabis use threshold (0 = no use, 1 = experimental use [less than 5 times], 2 = non-experimental use [5 or more times]); Alcohol use frequency (0 = never, 1 = monthly or less, 2 = 2-4 times a month, 3 = 2-3 times a week, 4 = 4 or more times a week); Nicotine use frequency (0 = no use, 1 = once or twice, 2 = a few days [3 to 4 days a month], 3 = a couple of days a week [5 to 11 days a month], 4 = 3 times a week [12 to 14 days a month], 5 = most days of the week [15 to 25 days a month], 6 = daily or almost daily [26 to 30 days a month])

## **B. Correlations**

See *Table 4* for correlations between study variables, which ranged between absolute value of  $r = 0.003$  and  $0.299$ . In terms of associations among primary variables of interest, year 1 Spring IPT was positively associated with year 2 Spring TRD, and year 2 Spring TRD was positively associated with year 3 Spring experimental cannabis use. However, there was no significant association between year 2 Spring TRD and year 3 Spring non-experimental cannabis use. Additionally, year 1 Spring non-experimental cannabis, but not experimental cannabis, was positively associated with year 2 Spring IPT, which in turn was positively related to year 3 Spring TRD. These patterns are consistent with the self-medication and high-risk hypotheses.

*ii. Table 4: Correlations among Primary Study Variables for Aim 1 Sub-Sample.*

	1.	2.	3.	4.	5.	6.	7.	8.
1. Y1S IPT	-							
2. Y2S IPT	.218***	-						
3. Y2S TRD	.076***	.209***	-					
4. Y3S TRD	.070***	.099***	.035**	-				
5. Y1S Cann – Exp	-.008	.014	.035**	.045***	-			
6. Y1S Cann – Non-Exp	.117	.055***	.008	.015	-.284***	-		
7. Y3S Cann – Exp	.014	.003	.036**	.032**	.042***	-.118***	-	
8. Y3S Cann – Non-Exp	.042***	.031**	.010	.066***	.029*	.278***	-.299***	-

*Note:* \* = Correlation significant at the .05 level; \*\* = Correlation significant at the .01 level; \*\*\* = Correlation significant at the < .001 level; Y1S = year 1 spring; Y2S = year 2 spring; IPT = interpersonal trauma; TRD = trauma-related distress; Cann – Exp = experimental cannabis use; Cann – Non-Exp = non-experimental cannabis use

### **C. Self-Medication Model**

See *Table 5* for model fitting results. When predicting year 2 Spring TRD, participants reporting more categories of IPT at year 1 Spring were at higher risk of TRD. When predicting year 3 Spring cannabis use, participants with TRD at year 2 Spring were at higher risk for both experimental and non-experimental use. The indirect effect of IPT on non-experimental cannabis use via TRD was not significant (Indirect Effect: .04; 95% CI: .00, .07). However, the indirect effect of IPT on experimental cannabis use via TRD was significant (Indirect Effect: .05; 95% CI: .02, .09), such that those with more IPTs were at higher risk for TRD, which in turn was associated with higher likelihood of experimental cannabis use compared to no use.

*i. Table 5: Final Regression Model Testing Both the Self-Medication and High-Risk Models Simultaneously with Lifetime IPT*

*Exposure as a Moderator (n = 6,862).*

Predictor	Self-medication hypothesis						High-risk hypothesis		
	Year 2 spring TRD		Year 3 spring experimental cannabis use		Year 3 spring non-experimental cannabis use		Year 2 spring IPT	Year 3 spring TRD	
	B (SE)	Odds Ratio	B (SE)	Odds Ratio	B (SE)	Odds Ratio	B (SE)	B (SE)	Odds Ratio
Gender: Female versus Male	-.59 (.06)***	.56	-.16 (.07)*	.85	.20 (.06)**	1.22	-.07 (.01)***	-.17 (.06)***	.76
Age	.19 (.06)**	1.21	-.13 (.08)	.87	-.15 (.07)*	.87	.01 (.02)	.56 (.08)***	1.75
Cohort: 1 versus 2	.27 (.08)***	1.31	.06 (.09)	1.06	.17 (.08)*	1.19	.01 (.02)	.66 (.07)***	1.83
Cohort: 1 versus 3	.38 (.08)***	1.46	.01 (.09)	1.01	-.04 (.08)	.96	.01 (.02)	-.97 (.09)***	.38
Cohort: 1 versus 4	.56 (.08)***	1.74	-.06 (.09)	.94	.19 (.08)*	1.21	.03 (.02)	-1.80 (.11)***	.17
Race: White versus Black	.01 (.06)	1.01	-.09 (.07)	.92	-.00 (.07)	1.00	.00 (.01)	.22 (.07)**	1.25
Year 1 Spring Nicotine	-.06 (.02)***	.94					.02 (.00)***		
Year 2 Spring Nicotine			-.02 (.02)	.98	.09 (.02)***	1.10		-.02 (.02)	1.00
Year 1 Spring Alcohol	.00 (.03)	1.00					.02 (.01)*		
Year 2 Spring Alcohol			.12 (.03)***	1.13	.47 (.03)***	1.60		-.08 (.03)	.94
Year 1 Spring Cann: No Use versus Exp							.03 (.02)	.32 (.08)***	1.44

Year 1 Spring Cann: No Use versus Non-Exp					.06 (02)***	.24 (.08)***	1.38
Lifetime IPT (assessed at Year 1 Fall)	-.03 (.04)	.97				.46 (.04)***	
Year 1 Spring IPT	.20 (.09)*	1.20	.09 (.05)	1.09	.11 (.05)*		1.12
Year 2 Spring IPT						.40 (.09)***	1.62
Year 2 Spring TRD			.21 (.07)**	1.24	.17 (.07)*		1.18
Lifetime IPT X Year 1 Spring IPT	.07 (.05)	1.07					
Lifetime IPT X Year 2 Spring IPT						-.19 (.06)***	

Note: \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ ; B = unstandardized regression coefficient;  $SE$  = standard error; cohort: 1 = 0, and 2, 3, and 4 = 1 for each of the three dummy codes; gender: female = 0, male = 1; race: White = 0, Black = 1; cann = cannabis; exp = experimental use; non-exp = non-experimental use; IPT = interpersonal trauma; TRD = trauma-related distress; note that in predicting TRD and IPT, positive coefficients indicate that a higher value on the predictor is associated with increased likelihood of being a case (i.e., having TRD) or reporting more IPTs; when predicting the cannabis outcomes, positive coefficients indicate that a higher value on the predictor is associated with increased likelihood of being in the never used group, compared to the experimental or non-experimental group; notably, all displayed paths were modeled simultaneously.

In order to test if individuals who reported a history of IPT at college enrollment were more likely to report TRD at year 2 Spring, an ad hoc analysis testing the interaction between lifetime IPT assessed at year 1 Fall and new onset IPT at year 1 Spring was conducted. Results did not find that lifetime IPT moderated the effect of new onset IPT on TRD. Specifically, the effect of lifetime IPT was not significant for those below ( $\beta = .18, p = .04$ ), at ( $\beta = .18, p = .04$ ), or above the mean level of lifetime IPT exposure ( $\beta = .18, p = .04$ ). Results support that new onset IPT is a strong predictor of TRD at all levels of new onset IPT.

### *ii. Covariate Effects*

Identifying as female (compared to male) and belonging to cohorts 2-4 (compared to cohort 1) significantly predicted likelihood of reporting TRD at year 2 Spring. Additionally, those who were older within their cohort and who reported less frequent nicotine use at year 1 Spring were more likely to report TRD. Rates of TRD at year 2 Spring did not differ significantly between White and Black individuals. Alcohol use frequency and lifetime IPT assessed at year 1 Fall also did not impact an individual's likelihood of reporting TRD at year 2 Spring.

When predicting year 3 Spring cannabis use, females (compared to males) were more likely to report experimental cannabis use compared to no use, and males (compared to females) were more likely to report non-experimental cannabis use compared to no use. Individuals with more frequent year 2 Spring alcohol use were more likely to report experimental cannabis use compared to no use. Individuals with more year 1 Spring IPTs, as well as more frequent nicotine or alcohol use at year 2 Spring were more likely to report non-experimental cannabis use compared to no use. Additionally, cohorts 2 and 4 (compared to cohort 1), and those who were younger within their cohort were more likely to report non-experimental cannabis use compared



to no use. Experimental and non-experimental cannabis use at year 3 Spring did not differ significantly between White and Black individuals.

#### **D. High-Risk Model**

See *Table 5* for model fitting results. When predicting year 2 Spring IPT, those who reported non-experimental cannabis use at year 1 Spring were likely to report more IPT, compared to those who had never used cannabis. In predicting year 3 Spring TRD, those who reported more IPTs at year 2 Spring were more likely to meet criteria for TRD. The indirect effect of experimental cannabis use on TRD through IPT was non-significant (Indirect Effect: .01; 95% CI: -.00, .03). The indirect effect of non-experimental cannabis on TRD through IPT was significant (Indirect Effect: .03; 95% CI: .01, .04), such that those who reported non-experimental use (compared to no use) reported more IPTs since beginning college and in turn were at higher risk for TRD.

In order to test if individuals who reported a history of IPT at college enrollment were more likely to report TRD at year 3 Spring, an ad hoc analysis testing the interaction between lifetime IPT assessed at year 1 Fall and new onset IPT at year 2 Spring was conducted. Results found that lifetime IPT significantly moderates the impact of new onset IPT on TRD. Specifically, for a one-unit increase in new onset IPT, individuals below the mean on lifetime IPT reported an increase of .48 in TRD ( $\beta = .48, p < .001$ ). Among those at the mean of lifetime IPT, a one-unit increase in new onset IPT was associated with a .40 increase in TRD ( $\beta = .40, p < .001$ ). Among those above the mean on lifetime IPT, a one-unit increase in new onset IPT was associated with a .32 increase in TRD ( $\beta = .32, p < .001$ ).

### *i. Covariate Effects*

When predicting year 2 Spring IPT, females (compared to males) and those who reported more frequent year 1 Spring alcohol or nicotine use were more likely to report experiencing a greater number of IPT types. Rates of IPT at year 2 Spring did not differ significantly between cohorts 2, 3, and 4 compared to cohort 1, nor did rates of IPT differ between White and Black or older individuals.

When predicting year 3 Spring TRD, females (compared to males), cohort 2 (compared to cohort 1), cohort 1 (compared to cohort 3 and 4), Black individuals (compared White individuals), and older individuals within their cohorts were at increased risk. Alcohol use frequency and nicotine use frequency assessed at year 2 Spring did not impact an individual's likelihood of reporting TRD at year 3 Spring.

## **Chapter 4: Discussion (Phenotypic)**

This study simultaneously examined two potential models posited to explain the development of co-occurring RCU and TRD using longitudinal data and tests of moderated-mediation. Results provided support for both the self-medication and high-risk models posited to explain the development of co-occurring RCU and TRD. Specifically, results demonstrated that IPT predicted experimental RCU, but not non-experimental RCU, via TRD over and above the influences of covariates (i.e., self-medication model). Results also demonstrated that non-experimental RCU, but not experimental RCU, predicted TRD through new-onset IPT above and beyond the influences of covariates (i.e., high-risk model). Results of each model are discussed in turn.

## **I. Self-Medication Model**

This study is an expansion of previous longitudinal work with this sample of college students (Hicks, Bountress, et al., 2022). Briefly, results from Hicks and colleagues supported the self-medication model such that a greater history of IPT exposure prior to college increased the risk for reporting TRD and subsequent non-experimental, but not experimental, cannabis use over the first two years of college. This study is different from previous work such that it is investigating IPT and subsequent TRD and cannabis use over the first three years of college opposed to the first two years. Additionally, as described above, this study is an expansion of previous work done in this sample by looking at the impact of new-onset IPT during the first year of college on subsequent TRD and cannabis use during years two and three of college opposed to the impact of a history of IPT prior to college on subsequent TRD and cannabis use during the first two years of college. Despite the differences, both studies found support for the self-medication model suggesting that college students may be attempting to mitigate their TRD with cannabis use.

This study adds to the rapidly growing literature in support of the self-medication model, such that individuals may be using cannabis recreationally to cope with distressing symptoms resulting from experiencing IPT (Dworkin et al., 2017; McCart et al., 2011; Rohrbach et al., 2009; Sanjuan et al., 2019). In a longitudinal study of sexual minority women, Dworkin and colleagues (2017) found that women with higher overall daily PTSD scores across time had a higher likelihood of using cannabis on any given day. In a longitudinal study of adolescents, McCart and colleagues (2011) found that PTSD was significantly associated with both lifetime cannabis use and lifetime non-experimental cannabis use across a 10-year period. In a longitudinal study investigating the impact of a hurricane on adolescent substance use, Rohrbach

and colleagues (2009) found that PTSD severity score was positively associated with increases in cannabis use during a 7-month follow-up assessment. In a longitudinal study of trauma-exposed pregnant women using ecological momentary assessment, Sanjuan and colleagues (2019) found moderate associations between greater daily peak PTSD symptoms and cannabis use within participants. Similar to 4 of the 5 longitudinal studies referenced above that tested the self-medication model in a systematic review on the association between PTSD and RCU (Hicks, Zaur, et al., 2022), this study's results add a distinct and supportive piece to the PTSD and RCU self-medication literature such that for each additional category of new-onset IPT an individual experienced during their first year of college, their odds of reporting TRD during year two of college increased. Likewise, reporting TRD during year two of college increased the odds of an individual reporting experimental RCU compared to no RCU during their third year of college. Although individuals who reported TRD during year two of college did not have an increased odds of reporting non-experimental RCU compared to no RCU during their third year of college, results overall still support the self-medication model such that individuals with TRD subsequently experimented with RCU. Although McCart and colleagues (2011) found that PTSD was significantly associated with non-experimental cannabis use, participants had a longer time period (i.e., lifetime) to meet their criteria for experimental versus non-experimental cannabis use in their study compared to ours (i.e., 6- or 12-months), which could be a possible explanation for the different findings.

Study results, and the PTSD and RCU self-medication literature, are similar to the broader self-medication literature. Specifically, based on a systematic review by Hawn and colleagues (2020), the more established PTSD and alcohol self-medication literature has a majority of supportive studies with a lack of rigorous empirical evidence that is likely due to lack

of longitudinal study designs and mediational analyses to account for the temporal and causal assumptions underlying the self-medication model.

Findings extend previous research on the self-medication model in numerous ways. First, this study used a longitudinal design, which allowed for a prospective mediational approach to examine the self-medication model. A majority of previous research has typically used cross-sectional designs to examine the associations between IPT, trauma-related psychopathology, and RCU (Hicks, Zaur, et al., 2022). Causality is a fundamental aspect of clinical research, and identifying the direction of effects between variables is critical in clinical research to help establish evidence-based interventions and develop prevention and treatment strategies. Longitudinal studies, accompanied by mediation analyses, offer a more comprehensive approach to unraveling causality in clinical settings.

One of the primary advantages of longitudinal studies lies in their ability to capture temporal order. By observing participants over time, we can determine the sequence of events between the exposure and the outcome. This temporal information is vital in inferring causality and determining the direction of effect. Unlike cross-sectional studies, which merely provide a snapshot of the correlational associations at a specific point in time, longitudinal designs enable us to track the prospective influence of variables, thereby reducing the risk of inferring false causation or direction of effects. By using a longitudinal study design, the current study allowed for suggestions regarding the prediction of RCU based on IPT and TRD, and ultimately a potential direction of effect.

Mediation analyses, a statistical technique frequently employed in longitudinal studies, allow us to explore the underlying mechanisms that mediate the relationship between the exposure and the outcome. These mediating variables serve as intermediate steps in the causal

pathway and play a crucial role in understanding how and why a construct, such as TRD, may lead to a specific outcome, such as RCU. By identifying mediators, we can gain insight into the processes involved in the development of clinical conditions, enhancing our ability to design targeted prevention and intervention efforts.

A second way the current study extends previous research on the self-medication model is that the current study used a moderated-mediational approach to examine the self-medication model. Previous longitudinal research has demonstrated the significant mediational relationship between IPT history prior to matriculating college and RCU during the second year of college through TRD reported during the first year of college (Hicks, Bountress, et al., 2022). While the current study narrows in on the developmental timeline of IPT and subsequent TRD and RCU by focusing on new-onset IPT experienced during the first year of college, it also expands previous research from Hicks and colleagues (2022) by accounting for IPT history prior to college since research supports that trauma history is a strong predictor of future trauma exposure and future PTSD risk (Kessler et al., 2017). Although trauma history has been shown to predict future trauma exposure and future PTSD risk (Kessler et al., 2018), the current study demonstrated that IPT history did not significantly moderate the impact of new-onset IPT on TRD. Results suggest that new-onset IPT is a stronger predictor of TRD compared to lifetime IPT experienced before college.

Another strength of longitudinal studies with mediation analyses lies in their capacity to control for confounding variables more effectively. Cross-sectional studies may suffer from confounding bias due to unmeasured or unknown variables, leading to spurious associations. Longitudinal designs with repeated measurements can account for potential confounders over time, increasing the accuracy of causal inferences and enhancing the internal validity of the

research findings. Since RCU is highly associated with alcohol and nicotine use, the current study was able to determine how cannabis use relates to IPT and TRD above and beyond the effects of alcohol and nicotine use since they were assessed and accounted for consistently throughout the study.

A third way the current study extends previous research on the self-medication model is that the current study sheds new light on how the developmental pathway of IPT on RCU through TRD may be impacted by gender, age, cohort, and race. Specifically, females (compared to males), older individuals, and newer cohorts (compared to cohort 1) may be more likely to develop TRD following new-onset IPT, which has been demonstrated in prior research (Hicks, Bountress, et al., 2022; Olf, 2017). Furthermore, females (compared to males) were more likely to report experimental RCU and males (compared to females) were more likely to report non-experimental RCU following IPT and TRD. Prior research has supported that males were more likely to report RCU than females (Schulenberg et al., 2020), but recent research has shown a surge in cannabis use among females. Specifically, the Brightfield Group, which is a Chicago-based CBD and cannabis-focused market researcher, found that female cannabis consumers skew younger based on their 2021 research (Brightfield Group, 2022). The Brightfield Group's research suggests that females are more likely to use cannabis among younger cohorts of college students, which is consistent with our study results.

## **II. High-Risk Model**

The current study adds to a growing literature in support of the high-risk model explaining the development of co-occurring RCU and PTSD, such that individuals who report RCU may be at higher risk for experiencing subsequent IPT and TRD (Allan et al., 2019; Hicks, Bountress, et al., 2022; Lee et al., 2018). In a longitudinal study of military personnel, Allan and

colleagues (2019) found that more days spent using cannabis predicted increased PTSD symptom severity for individuals with high, but not low, levels of PTSD symptoms. In a longitudinal study of racial and ethnic minority adults, Lee and colleagues (2018) found significant associations with increased likelihood of having PTSD symptoms at age 36 for individuals who reported chronically and moderately using cannabis compared with the no cannabis use group. In a longitudinal study of college students using the same sample as the current study, Hicks and colleagues (2022) found that a history of experimental and non-experimental cannabis use prior to college increases risk for IPT exposure and subsequent TRD over the first two years of college opposed to the current study's trajectory of throughout the first three years of college. Additionally, the current study investigates how recent cannabis use, opposed to a pre-college history of cannabis use, influences risk for IPT exposure and subsequent TRD over the first three years of college. The growing literature supports those individuals who report non-experimental RCU during their first year of college are at an increased risk for experiencing new-onset IPT during their second year of college, and their odds of reporting TRD during their third year of college are increased. These results are consistent with previous research, which suggests that individuals using cannabis are more likely to experience IPT and develop PTSD (Hicks, Zaur, et al., 2022).

Although the high-risk model is not as studied as often as the self-medication model is in the cannabis use and PTSD literature (Hicks, Zaur, et al., 2022), there have been studies that have focused broadly on alcohol and drug use that have found support for the high-risk model. For example, Haller and Chassin's (2014) study used longitudinal data from a community sample to investigate the relationships between pre-trauma substance use problems, trauma exposure, PTSD symptoms, and later alcohol and drug problems. Haller and Chassin's (2014)



study stands out from the more specific cannabis use and PTSD literature because instead of testing only one model, they simultaneously tested four main hypotheses including high-risk, susceptibility, self-medication, and shared vulnerability hypotheses. Regarding the high-risk hypothesis, study results suggests that pre-trauma substance use problems may increase the risk of experiencing assaultive violence in adolescents in addition to supporting the self-medication hypothesis. Similar to our study results, Haller and Chassin's study results also suggest that both the high-risk and self-medication are supported, meaning that there may be a bidirectional impact between PTSD and alcohol and substance use.

Findings extend previous research on the high-risk model in several ways. First, this study used a longitudinal design, which permitted a prospective mediational approach to examine the high-risk model. A majority of previous research has typically used cross-sectional designs to examine associations between RCU, IPT, and trauma-related psychopathology (Hicks, Zaur, et al., 2022). Furthermore, by using a longitudinal design, the current study was able to determine a predictive relationship between RCU and subsequent IPT and TRD, and ultimately establish a potential direction of effect.

Second, the current study used a moderated-mediational approach to examine the high-risk model. Previous longitudinal research has demonstrated the significant mediational relationship between RCU history prior to matriculating college and TRD during second year of college through new-onset IPT during the first year of college (Hicks, Bountress, et al., 2022). While the current study narrows in on the developmental timeline of RCU and subsequent IPT and TRD by focusing on recent RCU during the first year of college and new-onset IPT during the second year of college, it also accounts for IPT history prior to college since research supports that trauma history is a strong predictor of future trauma exposure and future PTSD risk

(Kessler et al., 2017). Although trauma history has been shown to predict future trauma exposure and future PTSD risk, the current study demonstrated that IPT history significantly moderated the impact of new-onset IPT on TRD, but in an unexpected direction. Results suggest that individuals who reported experiencing more lifetime IPT reported less TRD during their third year of college after experiencing a new-onset IPT during their second year of college. There are a couple possible explanations for these findings. First, our large sample size may have led to these results that are significant but potentially not clinically meaningful. Alternatively, results could represent a "steeling effect" (Rutter, 2012), which could be a direction for future research on the moderating impact of prior trauma in the relationship between IPT and TRD as part of the high-risk model. Although studied primarily using animal models (Liu, 2015), the steeling effect states that experiencing and successfully coping with moderate stressful experiences should lead to a decreased negative impact of subsequent stressful experiences by improving resilience resources (Rutter, 2012). Our results are aligned with the steeling effect, such that individuals who reported experiencing more lifetime IPT reported less TRD after experiencing new-onset IPT, which could be due to improving resilience resources based on the steeling effect.

### Implications

The current study offers crucial clinical utility and has implications for both mental health practitioners and policymakers. The support for both the self-medication and high-risk models regarding the association between RCU and PTSD sheds light on the complex relationship between these variables and suggests heterogeneity in the etiologic relationships. Mental health practitioners can now better understand that individuals with PTSD may turn to recreational cannabis as a means of self-medication to cope with their symptoms. This understanding can inform therapeutic interventions, emphasizing the importance of addressing

underlying trauma and offering alternative coping strategies. Additionally, the identification of the high-risk model highlights the potential bidirectional nature of the association, implying that recreational cannabis use might exacerbate PTSD symptoms or act as a risk factor for developing PTSD in vulnerable populations. This knowledge can aid in the early identification of individuals at risk and the implementation of targeted prevention strategies that may help prevent trauma exposure and or PTSD post-trauma. For example, clinicians could incorporate screening for cannabis use and assess the individual's history of traumatic events and PTSD symptoms during intake evaluations in order to aid in early identification of potentially problematic cannabis use and acute post-trauma symptomatology to allow for timely intervention. Furthermore, policymakers can use these findings to develop evidence-based regulations and interventions surrounding cannabis use, particularly in the context of PTSD.

The current status of concurrent treatment for PTSD and CUD involves an integrated and evidence-based approach tailored to address both conditions simultaneously. Treatment typically combines evidence-based therapies, such as cognitive-behavioral interventions, with specialized components that target alcohol and/or substance use. The goal is to address PTSD symptoms while also addressing problematic cannabis use through relapse prevention and coping skills training. Concurrent cognitive-behavioral therapies, such as Concurrent Treatment of PTSD and SUDs using Prolonged Exposure (COPE; Back et al., 2019), that also address coping skills training and relapse prevention have shown positive outcomes in reducing PTSD and substance use symptoms. However, more research is needed to better understand the specific mechanisms and long-term effectiveness of concurrent treatment for individuals with comorbid PTSD and cannabis use disorder. However, results from the current study highlight the bidirectional impact

of trauma exposure/PTSD and cannabis use, and therefore all individuals may benefit from treatment regardless of the timeline of their PTSD and CUD development.

College counseling centers are essential in fostering a safe and supportive campus environment and can play a crucial role in preventing trauma exposure, PTSD, and cannabis use among college students. Implementing comprehensive mental health awareness and educational programs can reduce stigma and encourage prevention and early intervention. By adopting a trauma-informed approach, counseling centers can create a nurturing space for students who have experienced trauma. Offering prevention programs and mental health screenings enables early identification and support for at-risk students. Individual and group counseling services, coupled with evidence-based therapies, such as integrative cognitive-behavioral therapies like COPE, can help address trauma and substance use issues directly. By advocating for campus policies and organizing awareness events, counseling centers can help mitigate the impact of trauma exposure and promote healthier choices on college campuses.

### **III. Study Limitations**

The study has several study limitations that should be noted. First, as concluded in a methodological critique of the cannabis and PTSD literature (Hicks, Zaur, et al., 2022), the assessment tool used to measure cannabis use is not ideal, but the knowledge gained from differentiating between types of RCU (i.e., experimental, non-experimental) is a useful starting point for future research to build off of. For example, research supports that experimental substance use can have different effects on mental health compared to non-experimental substance use (i.e., regular use, risky use, dependence, addiction; Connor et al., 2021; Sznitman et al., 2015), but cannabis use assessment is not currently standardized in a way that allows researchers to compare how types of cannabis use may impact mental health outcomes (Hicks,

Zaur, et al., 2022). Future research investigating the association between RCU and TRD should continue distinguishing between types of cannabis use with the goal of establishing gold standard assessment techniques for types of cannabis use to make it possible to easily compare results across different studies. Second, all IPTs in this study (i.e., physical and sexual assault) were weighted equally regarding their potential impact on the development of subsequent TRD even though the literature shows that some forms of IPT are more likely to lead to distressing symptoms compared to others (Hyland et al., 2017). Spit for Science was developed to collect broad-based information about substance use and mental health outcomes. Therefore, assessment of some constructs, such as IPT and TRD, were not as detailed as they could be based on gold standards of trauma assessment in the PTSD literature, such as the Traumatic Life Events Questionnaire, PTSD Checklist, or Clinician Administered PTSD Scale (Kubany et al., 2000; Weathers et al., 2018; Weathers et al., 2013). Future research should thoroughly assess IPT and TRD to determine if certain types of IPT are more likely to influence the development of co-occurring RCU and PTSD. Lastly, there are additional factors (e.g., genetic influences) that may contribute to risk for cannabis use and PTSD that are excluded from this study. Recent analyses based on linkage disequilibrium score regression have reported that PTSD and lifetime cannabis use are genetically correlated ( $r_g = 0.41$  to  $0.51$ ) with risk taking, which is a risk factor for both PTSD and cannabis use (Strawbridge et al., 2018). Future studies should investigate how genetic risk may influence the development of co-occurring cannabis use and PTSD, which was identified as a major limitation of the co-occurring RCU and PTSD literature in a recent systematic review (Hicks, Zaur, et al., 2022).

#### **IV. Future Directions**

As for future directions, researchers may delve deeper into the underlying mechanisms of self-medication and high-risk models, exploring the specific factors that contribute to these associations. Longitudinal studies that incorporate diverse populations and consider different trauma types can further refine our understanding of the complex interplay between RCU and PTSD, ultimately leading to more tailored and effective prevention and interventions strategies.

Ecological Momentary Assessment (EMA) offers a valuable tool to investigate the developmental direction of PTSD and cannabis use. By capturing real-time data from individuals in their natural environment, EMA allows researchers to assess momentary fluctuations in PTSD symptoms and substance use over time (Lane et al., 2019). This individual-based, micro-level analysis enables the examination of temporal associations between cannabis use and PTSD, shedding light on whether changes in PTSD symptoms precede changes in cannabis use or vice versa (Buckner et al., 2018). EMA also helps identify triggers and coping mechanisms related to substance use in response to acute distress from PTSD symptoms (Possemato et al., 2015). By understanding the dynamic associations between PTSD and cannabis use through EMA, researchers can gain insights into the potential bidirectional relationships and inform the development of targeted preventative measures and interventions for individuals at risk for this comorbidity. Collecting EMA data on PTSD symptoms and cannabis use behaviors can greatly inform a personalized medicine approach to treatment of co-occurring PTSD and CUD by allowing clinicians to tailor interventions targeting specific moments of vulnerability and employ personalized coping strategies (Webb et al., 2022). This approach maximizes treatment effectiveness by addressing individual patterns and needs, ultimately improving outcomes for individuals with co-occurring PTSD and problematic cannabis use.

## Chapter 5: Results (Genotypic)

### I. Aim 2: GCTA of RCU and TRD & PRS of Lifetime Cannabis Use and Lifetime PTSD

#### A. GCTA

There were no univariate outliers based on DFBETAS or multivariate outliers based on studentized deleted residuals (SDRs) (Cohen et al., 2003). The cut-off value for DFBETAS is  $2/\sqrt{n}$ , where  $n$  is the number of observations ( $n = 3721$  [EUR-ancestry sub-sample], 1469 [AFR-ancestry sub-sample]). No cases exceeded a DFBETAS cut-off value of 0.03 (EUR-ancestry sub-sample) or 0.05 (AFR-ancestry sub-sample), but we removed the top three cases with the largest values of DFBETAS from each sub-sample. Since SDRs have a t-distribution, an SDR of magnitude 3 or more in absolute value will be considered an outlier. No cases exceed a SDR cut-off value of 3 in absolute value, but we removed the top three cases with the largest values of SDRs. The model results did not change after the most influential cases were removed. Thus, the confidence in the findings not being driven by single cases was increased.

In order to examine the molecular heritability of cannabis use and TRD, univariate GCTA analyses were conducted separately for EUR and AFR ancestries. Results are shown in *Table 6*. Cannabis use and TRD were not found to be significantly heritable among the EUR, nor the AFR sub-samples. This non-significant heritability, potentially stemming from the constraints of small sample sizes, is reflective of the inherent limitations. Standard error, serving as a metric for gauging the precision with which a sample mean represents the population mean, is instrumental in this context (Field et al., 2012). A standard error of 0 signifies an absence of random error within the sample, with larger standard error estimates indicating greater statistical inaccuracy. As recognized in the literature, standard error tends to decrease with larger sample sizes (Field et al., 2012). In light of the non-significant heritability estimates for both the EUR

( $h^2 = .038$ ,  $SE = .15$ ,  $p = .24$ ) and AFR ( $h^2 = .001$ ,  $SE = .23$ ,  $p = .50$ ) analyses for cannabis use, as well as for both the EUR ( $h^2 = .079$ ,  $SE = .16$ ,  $p = .09$ ) and AFR ( $h^2 = .119$ ,  $SE = .24$ ,  $p = .18$ ) analyses for TRD, coupled with the notable standard error estimates (Visscher & Goddard, 2015), it is reasonable to hypothesize that the lack of significant findings is primarily attributed to the limitations posed by our sample sizes.

***i. Table 6: Findings from GCTA of RCU and TRD in EUR- and AFR-Ancestry Sub-Samples.***

Phenotype	Super- population	N	Covariates	$h^2$	SE	$p$ -value
RCU	EUR	3721	PCs, sex	.038	.15	.24
	AFR	1469	PCs, sex	.001	.23	.50
TRD	EUR	3721	PCs, sex	.079	.16	.09
	AFR	1469	PCs, sex	.119	.24	.18

*Note.* PC = Principal component; SE = Standard error

**B. Polygenic Risk Scores (PRS)**

***i. PRS for Lifetime Cannabis Use Predicting Lifetime RCU in S4S***

The ICC summary statistic data from the EUR sample (N cases = 79,079, N controls = 105,686), resulting from GWAS analyses of lifetime cannabis use (measured on a dichotomous scale; Pasman et al., 2018), were used to generate a  $PRS_{lifetime\ use}$  in S4S. This was done via PRS-CS (Ge et al., 2019). The resulting  $PRS_{lifetime\ use}$  was then used to predict RCU in S4S in the EUR and AFR sub-samples, adjusting for the top three PCs.

The  $PRS_{lifetime\ use}$  was used in the EUR sub-sample (N cases = 3,269, N controls = 452) and in the AFR sub-sample (N cases = 1,209, N controls = 260) of S4S to examine the



relationship between aggregate genetic risk for lifetime cannabis use and the ordinal outcome variable “cannabis use threshold” (categorized as no use, experimental use [use 1-5 times], and non-experimental use [use 6+ times]) via a multinomial logistic regression analysis. This analysis aimed to determine whether higher PRS scores for lifetime cannabis use were associated with a higher likelihood of more frequent RCU.

*Table 7* presents the results of the multinomial logistic regression analysis for the EUR ancestry sub-sample. As shown, higher levels of PRS<sub>lifetime use</sub> were associated with increased odds of non-experimental cannabis use compared to no use. Specifically, for every one-unit increase in PRS<sub>lifetime use</sub>, the odds of reporting non-experimental cannabis use compared to no use increased by 1.23 times (OR = 1.23, 95% CI [1.12, 1.37],  $p < .001$ ). This result suggests that individuals with higher polygenic risk for lifetime cannabis use were more likely to non-experimentally use cannabis within the EUR ancestry sub-sample.

a. Table 7: Multinomial Logistic Regression Model Results for PRS for Lifetime Cannabis Use Predicting Lifetime RCU in S4S with the EUR Ancestry Sub-Sample.

RCU	Variable	$\beta$	Standard Error	$p$ -Value	Odds Ratio	95% Confidence Interval	
Exp.	PRS <sub>lifetime use</sub>	.09	.06	.11	1.10	.98	1.23
Use vs.	PC1	23.83	20.77	.25	2.24 x 10 <sup>10</sup>	4.69 x 10 <sup>-8</sup>	1.08 x 10 <sup>28</sup>
No Use	PC2	16.64	20.92	.43	1.69 x 10 <sup>7</sup>	2.65 x 10 <sup>-11</sup>	1.08 x 10 <sup>25</sup>
	PC3	-5.29	5.18	.31	.005	1.96 x 10 <sup>-7</sup>	130.27
Non-Exp.	PRS <sub>lifetime use</sub>	.21	.05	<.001	1.23***	1.12	1.37
Use vs.	PC1	75.25	35.01	.132	4.79 x 10 <sup>32</sup>	764.10	3.01 x 10 <sup>62</sup>
	PC2	-18.49	20.09	.36	9.37 x 10 <sup>-9</sup>	7.50 x 10 <sup>-26</sup>	1.17 x 10 <sup>9</sup>
No Use	PC3	-9.49	5.83	.10	7.58 x 10 <sup>-5</sup>	8.32 x 10 <sup>-10</sup>	6.92
-2 Log-Likelihood		6665.17					
Likelihood Ratio Test		21.59 (df = 2, $p < .001$ )					

*Note:* RCU = recreational cannabis use; Exp = experimental; PRS = polygenic risk score; PC = principal component; \* = significant at  $p < .001$

The model fit was assessed using the Likelihood Ratio Test, which indicated that the model significantly improved the fit compared to a null model with no predictors ( $\chi^2 = 21.59$ ,  $df = 2$ ,  $p < .001$ ). The Nagelkerke pseudo  $R^2$  was .009, suggesting that the model explained approximately .9% of the variance in cannabis use threshold categories.

*Table 8* presents the results of the multinomial logistic regression analysis for the AFR ancestry sub-sample. Contrary to our hypothesis, higher levels of  $PRS_{\text{lifetime use}}$  were not associated with increased odds of more frequent RCU. Specifically, for every one-unit increase in  $PRS_{\text{lifetime use}}$ , the odds of reporting experimental cannabis use compared to no use ( $OR = .95$ , 95% CI [.82, 1.11],  $p = .55$ ) and reporting non-experimental use compared to no use ( $OR = .97$ , 95% CI [.84, 1.12],  $p = .66$ ) did not significantly change. This result suggests that  $PRS_{\text{lifetime use}}$  did not predict differences in RCU frequency within the AFR ancestry sub-sample.

b. Table 8: Multinomial Logistic Regression Model Results of PRS for Lifetime Cannabis Use Predicting Lifetime RCU in S4S with the AFR Ancestry Sub-Sample.

RCU	Variable	$\beta$	Standard Error	$p$ -Value	Odds-Ratio	95% Confidence Interval	
Exp.	PRS <sub>lifetime use</sub>	-.05	.08	.55	.95	.82	1.11
Use vs.	PC1	31.46	20.09	.12	$4.59 \times 10^{13}$	.00	$5.80 \times 10^{30}$
No Use	PC2	-13.30	42.93	.76	$1.68 \times 10^{-6}$	$4.83 \times 10^{-43}$	$5.84 \times 10^{30}$
	PC3	-4.44	4.14	.28	.01	$3.51 \times 10^{-6}$	39.51
Non-Exp.	PRS <sub>lifetime use</sub>	-.03	.07	.66	.97	.84	1.12
Use vs.	PC1	46.86	18.44	.11	$2.24 \times 10^{20}$	$4.48 \times 10^4$	$1.12 \times 10^{36}$
No Use	PC2	-50.90	39.45	.20	$7.88 \times 10^{-23}$	$2.06 \times 10^{-56}$	$3.02 \times 10^{11}$
	PC3	-4.73	3.90	.23	.01	$4.27 \times 10^{-6}$	18.32
-2 Log-Likelihood		2962.37					
Likelihood Ratio Test		.36 (df = 2, $p = .84$ )					

*Note:* RCU = recreational cannabis use; Exp = experimental; PRS = polygenic risk score; PC = principal component

The model fit was assessed using the Likelihood Ratio Test, which indicated that the model did not significantly improve the fit compared to a null model with no predictors ( $\chi^2 = .36$ ,  $df = 2$ ,  $p = .84$ ). The Nagelkerke pseudo  $R^2$  was 0.011, suggesting that the model explained approximately 1.1% of the variance in cannabis use threshold categories.

### ***ii. PRS for Lifetime PTSD Predicting TRD in S4S***

The PGC-PTSD Freeze 2 summary statistic data from the EUR sub-sample (N cases = 23,185, N controls = 151,309) and AFR sub-sample (N cases = 4,363, N controls = 10,976), resulting from GWAS analyses of lifetime PTSD (Nievergelt et al., 2019), were used to generate

a PRS<sub>lifetime PTSD</sub> in S4S. This was done via PRS-CSx (Ruan et al., 2022). The resulting PRS<sub>lifetime PTSD</sub> was then used to predict TRD in S4S in the EUR and AFR sub-samples, adjusting for the top three PCs.

The PRS<sub>lifetime PTSD</sub> was used in the EUR sub-sample (N cases = 2,595, N controls = 1,138) and the AFR sub-sample (N cases = 1,051, N controls = 420) of S4S to examine the relationship between aggregate genetic risk for lifetime PTSD and TRD via a binary logistic regression analysis. This analysis aimed to determine whether higher PRS scores for lifetime PTSD were associated with an increased likelihood of reporting TRD.

*Table 9* presents the results of the binary logistic regression analysis for the EUR sub-sample. The odds ratio for PRS<sub>lifetime PTSD</sub> was calculated, and it did not reach statistical significance.

a. Table 9: Binary Logistic Regression Model Results of PRS for Lifetime PTSD Predicting Lifetime TRD in S4S with the EUR Ancestry Sub-Sample.

Variable	$\beta$	Standard Error	<i>p</i> -Value	Odds-Ratio	95% Confidence Interval	
PRS <sub>lifetime PTSD</sub>	.03	.04	.41	1.03	.96	1.11
PC1	-52.75	36.12	.14	.00	.00	6.83 x 10 <sup>7</sup>
PC2	7.68	22.36	.73	2154.88	.00	2.33 x 10 <sup>22</sup>
PC3	3.13	5.15	.54	22.96	.00	5.60 x 10 <sup>5</sup>
-2 Log-Likelihood	4573.21					
Hosmer-Lemeshow Test	3.57 (df = 8, <i>p</i> = .89)					

*Note:* PRS = polygenic risk score; PC = principal component

For each one-unit increase in PRS<sub>lifetime PTSD</sub>, the odds of reporting TRD did not statistically change (OR = 1.03, 95% CI [.96, 1.11],  $p = .41$ ). In this study, PRS<sub>lifetime PTSD</sub> did not appear to be associated with a higher likelihood of reporting TRD.

The model fit was assessed using the Hosmer-Lemeshow Test, which indicated that the model did not statistically improve the fit compared to a null model with no predictors ( $\chi^2 = 3.57$ ,  $df = 8$ ,  $p = 0.89$ ). The Nagelkerke pseudo  $R^2$  was .00, indicating that the model explained 0% of the variance in TRD.

Table 10 presents the results of the binary logistic regression analysis for the AFR sub-sample. The odds ratio for PRS<sub>lifetime PTSD</sub> was calculated, and it did not reach statistical significance.

b. Table 10: Binary Logistic Regression Model Results for PRS for Lifetime PTSD Predicting TRD in S4S with the AFR Ancestry Sub-Sample.

Variable	$\beta$	Standard Error	$p$ -Value	Odds-Ratio	95% Confidence Interval	
PRS <sub>lifetime PTSD</sub>	-.09	.07	.20	.91	.79	1.05
PC1	5.55	14.31	.70	255.86	.00	$3.87 \times 10^{14}$
PC2	-7.52	28.65	.79	.00	.00	$1.32 \times 10^{21}$
PC3	-2.52	2.92	.39	.08	.00	24.71
-2 Log-Likelihood	1753.59					
Hosmer-Lemeshow Test	9.83 ( $df = 8$ , $p = .28$ )					

Note: PRS = polygenic risk score; PC = principal component

For each one-unit increase in  $PRS_{\text{lifetime PTSD}}$ , the odds of reporting TRD did not statistically change (OR = .91, 95% CI [.79, 1.05],  $p = .20$ ). In this study,  $PRS_{\text{lifetime PTSD}}$  did not appear to be associated with a higher likelihood of reporting TRD.

The model fit was assessed using the Hosmer-Lemeshow Test, which indicated that the model did not statistically improve the fit compared to a null model with no predictors ( $\chi^2 = 9.83$ ,  $df = 8$ ,  $p = .28$ ). The Nagelkerke pseudo  $R^2$  was .00, indicating that the model explained 0% of the variance in TRD.

## **II. Aim 3: PRS for Lifetime Cannabis Use and Lifetime PTSD Moderation of Self-Medication and High-Risk Models of Co-Occurring RCU and TRD, Respectively**

### **A. Sample Characteristics**

Descriptive statistics are presented in *Table 11*. The majority of participants in the present in the analytic sample reported that they were White<sup>2</sup> ( $n = 3727$ , 71.8%) and female ( $n = 3255$ , 62.7%). Participation across all four cohorts was about equal. Half of participants reported IPT at year 1 Fall ( $n = 2624$ , 50.6%), about a quarter of participants reported IPT at year 1 Spring ( $n = 1260$ , 24.3%), and almost a fifth of participants reported IPT at year 2 Spring ( $n = 927$ , 17.9%) and year 3 Spring ( $n = 889$ , 17.1%). Almost a third of participants reported TRD at year 1 Fall ( $n = 1571$ , 30.3%), year 1 Spring ( $n = 1580$ , 30.4%), year 2 Spring ( $n = 1482$ , 28.6%), and about a quarter of participants reported TRD at year 3 Spring ( $n = 1394$ , 26.9%). About half of participants reported cannabis use at year 1 Fall ( $n = 2640$ , 50.9%), year 1 Spring ( $n = 2339$ ,

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<sup>2</sup> Due to incorporating those with European and African ancestry in genetic analyses for Aim 3, those self-identifying as White or Black for race were included in analyses from Spit for Science. To limit genetic heterogeneity, we used the largest two sub-populations from Spit for Science. We understand the limitations of this assumption of race and genetic ancestry super-populations.

45.1%), year 2 Spring (n = 2440, 47.0%), and year 3 Spring (n = 2423, 46.7%). At year 1 Fall, the most commonly reported frequency of alcohol use was “monthly or less” (n = 2089, 40.3%), but at year 1 Spring (n = 1799, 34.7%), year 2 Spring (n = 1885, 36.3%), and year 3 Spring (n = 1834, 35.3%), the most commonly reported frequency of alcohol use was “2-4 times a month.” The majority of participants reported no nicotine use at year 1 Fall (n = 2743, 52.9%), year 1 Spring (n = 2773, 53.4%), year 2 Spring (n = 2959, 57.0%), and year 3 Spring (n = 3205, 61.8%).



*i. Table 11: Demographics, Alcohol and Substance Use Prevalence, and Clinical Characteristics for Aim 3 Sub-Sample*

	Overall	Year 1 Fall	Year 1 Spring	Year 2 Spring	Year 3 Spring
	n (%)	n (%)	n (%)	n (%)	n (%)
Race					
White	3727 (71.8%)				
Black	1463 (28.2%)				
Cohort					
1	1592 (30.6%)				
2	1162 (22.4%)				
3	1368 (26.4%)				
4	1068 (20.6%)				
Gender					
Male	1935 (37.3%)				
Female	3255 (62.7%)				
Interpersonal Trauma					
Count by Category					

0	2566 (49.4%)	3930 (75.7%)	4263 (82.1%)	4301 (82.9%)
1	1574 (30.3%)	916 (17.6%)	758 (14.6%)	749 (14.4%)
2	704 (13.6%)	251 (4.8%)	134 (2.6%)	116 (2.2%)
3	346 (6.7%)	93 (1.8%)	35 (0.7%)	24 (0.5%)
Trauma-Related Distress				
No	3619 (69.7%)	3610 (69.6%)	3708 (71.4%)	3796 (73.1%)
Yes	1571 (30.3%)	1580 (30.4%)	1482 (28.6%)	1394 (26.9%)
Cannabis Use Threshold				
0	2550 (49.1%)	2851 (54.9%)	2750 (53.0%)	2767 (53.3%)
1	968 (18.7%)	1020 (19.7%)	911 (17.6%)	1065 (20.5%)
2	1672 (32.2%)	1319 (25.4%)	1529 (29.5%)	1358 (26.2%)
Alcohol Use Frequency				
0	842 (16.2%)	687 (13.2%)	672 (12.9%)	370 (7.1%)
1	2089 (40.3%)	1704 (32.8%)	1682 (32.4%)	1511 (29.1%)
2	1574 (30.3%)	1799 (34.7%)	1885 (36.3%)	1834 (35.3%)
3	601 (11.6%)	872 (16.8%)	834 (16.1%)	1229 (23.7%)

4	84 (1.6%)	128 (2.5%)	117 (2.3%)	246 (4.7%)
Nicotine Use Frequency				
0	2743 (52.9%)	2773 (53.4%)	2959 (57.0%)	3205 (61.8%)
1	1032 (19.9%)	978 (18.8%)	930 (17.9%)	828 (16.0%)
2	428 (8.2%)	385 (7.4%)	391 (7.5%)	240 (4.6%)
3	229 (4.4%)	244 (4.7%)	195 (3.8%)	191 (3.7%)
4	170 (3.3%)	132 (2.5%)	95 (1.8%)	97 (1.9%)
5	150 (2.9%)	211 (4.1%)	157 (3.0%)	180 (3.5%)
6	438 (8.4%)	467 (9.0%)	463 (8.9%)	449 (8.7%)

*Note:* Interpersonal trauma (IPT) count by category (0 = no IPT, 1 = 1 type of IPT [physical assault, sexual assault, or unwanted/uncomfortable sexual experience], 2 = 2 types of IPT, 3 = 3 types of IPT); Cannabis use threshold (0 = no use, 1 = experimental use [less than 5 times], 2 = non-experimental use [5 or more times]); Alcohol use frequency (0 = never, 1 = monthly or less, 2 = 2-4 times a month, 3 = 2-3 times a week, 4 = 4 or more times a week); Nicotine use frequency (0 = no use, 1 = once or twice, 2 = a few days [3 to 4 days a month], 3 = a couple of days a week [5 to 11 days a month], 4 = 3 times a week [12 to 14 days a month], 5 = most days of the week [15 to 25 days a month], 6 = daily or almost daily [26 to 30 days a month])

## **B. Correlations**

See *Table 12* for correlations between study variables, which ranged between absolute value of 0.000 and 0.302. In terms of associations among primary variables of interest, year 1 Spring IPT was positively associated with year 2 Spring TRD, and year 2 Spring TRD was positively associated with year 3 Spring experimental cannabis use. However, there was no significant association between year 2 Spring TRD and year 3 Spring non-experimental cannabis use. Additionally, year 1 Spring non-experimental cannabis, but not experimental cannabis, was positively associated with year 2 Spring IPT, which in turn was positively related to year 3 Spring TRD. These patterns are consistent with the self-medication and high-risk hypotheses. Notably, PRS for lifetime cannabis use was positively associated with PRS for lifetime PTSD, as well as year 1 and 3 Spring non-experimental cannabis use.

*i. Table 12: Correlations among Primary Study Variables for Aim 3 Sub-Sample.*

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. Y1S IPT	-									
2. Y2S IPT	.229***	-								
3. Y2S TRD	.091***	.220***	-							
4. Y3S TRD	.075***	.107***	.037**	-						
5. Y1S Cann – Exp	-.004	.012	.046***	.050***	-					
6. Y1S Cann – Non-Exp	.111	.054***	.005	.017	-.289***	-				
7. Y3S Cann – Exp	.012	-.008	.040**	.018	.048***	-.116***	-			
8. Y3S Cann – Non-Exp	.041**	.027	.008	.073***	.024	.286***	-.302***	-		
9. PRS for Lifetime PTSD	.009	.008	.023	.007	-.001	.014	.000	.010	-	
10. PRS for Lifetime Cann Use	.008	.000	.012	-.001	.014	.046***	.003	.032*	.057***	-

*Note:* \* = Correlation significant at the .05 level; \*\* = Correlation significant at the .01 level; \*\*\* = Correlation significant at the < .001 level; Y1S = year 1 spring; Y2S = year 2 spring; IPT = interpersonal trauma; TRD = trauma-related distress; Cann – Exp = experimental cannabis use; Cann – Non-Exp = non-experimental cannabis use; PRS = polygenic risk score

### **C. Self-Medication Model**

See *Table 13* for model fitting results. When predicting year 2 Spring TRD, participants reporting more categories of IPT at year 1 Spring were not at higher risk of TRD. When predicting year 3 Spring cannabis use, participants with TRD at year 2 Spring were at higher risk for both experimental and non-experimental use. The indirect effect of IPT on non-experimental cannabis use via TRD was not significant (Indirect Effect: .03; 95% CI: .00, .06). However, the indirect effect of IPT on experimental cannabis use via TRD was significant (Indirect Effect: .04; 95% CI: .01, .08), such that those with more IPTs were at higher risk for TRD, which in turn was associated with higher likelihood of experimental cannabis use compared to no use. Notably, higher PRS<sub>lifetime PTSD</sub> was not significantly associated with higher risk of TRD at year 2 Spring and higher PRS<sub>lifetime use</sub> was significantly associated with reporting only non-experimental cannabis use compared to no use at year 3 Spring.

*i. Table 13: Final Regression Model Testing Both the Self-Medication Model with PRS for Lifetime Cannabis Use as a Moderator and High-Risk Model with PRS for Lifetime PTSD as a Moderator, Simultaneously (n = 5,190).*

Predictor	Self-medication hypothesis						High-risk hypothesis		
	Year 2 spring TRD		Year 3 spring experimental cannabis use		Year 3 spring non-experimental cannabis use		Year 2 spring IPT	Year 3 spring TRD	
	B (SE)	Odds Ratio	B (SE)	Odds Ratio	B (SE)	Odds Ratio	B (SE)	B (SE)	Odds Ratio
Gender: Female versus Male	-.59 (.07)***	.55	-.16 (.08)*	.85	.19 (.07)**	1.21	-.08 (.02)***	-.13 (.08)	.88
Age	.14 (.07)*	1.15	-.14 (.09)	.87	-.23 (.09)*	.80	.01 (.02)	.57 (.09)***	1.77
Cohort: 1 versus 2	.24 (.09)**	1.27	.09 (.10)	1.09	.28 (.10)**	1.32	.01 (.02)	.74 (.08)***	2.09
Cohort: 1 versus 3	.38 (.09)***	1.46	.01 (.10)	1.01	-.00 (.09)	1.00	-.00 (.02)	-.92 (.10)***	.40
Cohort: 1 versus 4	.49 (.09)***	1.63	-.05 (.11)	.95	.20 (.10)*	1.22	.02 (.02)	-1.79 (.13)***	.17
Race: White versus Black	-.16 (.10)	.85	-.07 (.11)	.93	-.03 (.10)	.98	.00 (.02)	.24 (.12)*	1.27
Year 1 Spring Nicotine	-.07 (.02)***	.94					.02 (.00)***		
Year 2 Spring Nicotine			-.02 (.02)	.98	.10 (.02)***	1.10		.00 (.02)	1.00
Year 1 Spring Alcohol	.02 (.03)	1.02					.02 (.01)**		
Year 2 Spring Alcohol			.12 (.04)**	1.13	.52 (.04)***	1.68		-.06 (.04)	.94
Year 1 Spring Cann: No Use versus Exp							.02 (.02)	.32 (.09)***	1.37

Year 1 Spring Cann: No Use versus Non-Exp					.05 (02)**	.24 (.09)**	1.27	
Lifetime IPT (assessed at Year 1 Fall)	.00 (.05)	1.00						
Lifetime IPT (calculated at Year 1 Spring)						.51 (.04)***	1.66	
Year 1 Spring IPT	.15 (.10)	1.16	.08 (.06)	1.08	.11 (.05)*	1.12		
Year 2 Spring IPT						.42 (.10)***	1.53	
Year 2 Spring TRD			.23 (.08)**	1.26	.15 (.08)*	1.16		
Lifetime IPT X Year 1 Spring IPT	.09 (.06)	1.10						
Lifetime IPT X Year 2 Spring IPT						-.24 (.06)***	.79	
PRS for Lifetime Cann Use	.02 (.03)	1.02	.04 (.04)	1.04	.10 (.04)*	1.11	-.01 (.04)	.99
PRS for Lifetime PTSD	.05 (.03)	1.05	.00 (.04)	1.00	.02 (.04)	1.02	.03 (.04)	1.03
PC1	-38.69 (18.37)	0.00	8.14 (19.46)	3415. 61	-4.00 (16.57)	.02	14.76 (21.17)	.00
PC2	6.73 (9.69)	833.9 1	4.86 (11.90)	129.0 9	-2.61 (10.21)	.07	-24.52 (11.43)	.00
PC3	-2.45 (2.25)	.09	2.89 (2.53)	17.92	-.22 (2.44)	.80	1.21 (2.49)	3.36
PRS for Lifetime Cann			.02 (.07)	1.02	.00 (.06)	1.00		



Use X Year 2 Spring TRD		
PRS for Lifetime PTSD X Year 2 Spring IPT	.00 (.06)	1.00

Note: \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ ; B = unstandardized regression coefficient;  $SE$  = standard error; cohort: 1 = 0, and 2, 3, and 4 = 1 for each of the three dummy codes; gender: female = 0, male = 1; race: White = 0, Black = 1; cann = cannabis; exp = experimental use; non-exp = non-experimental use; IPT = interpersonal trauma; TRD = trauma-related distress; note that in predicting TRD and IPT, positive coefficients indicate that a higher value on the predictor is associated with increased likelihood of being a case (i.e., having TRD) or reporting more IPTs; when predicting the cannabis outcomes, positive coefficients indicate that a higher value on the predictor is associated with increased likelihood of being in the never used group, compared to the experimental or non-experimental group; notably, all displayed paths were modeled simultaneously; PRS = polygenic risk score; PC = principal component;

In order to test if individuals at higher polygenic risk for lifetime cannabis use ( $PRS_{\text{lifetime use}}$ ) were more likely to report experimental or non-experimental cannabis use at year 3 Spring, an interaction between TRD assessed at year 2 Spring and  $PRS_{\text{lifetime use}}$  was included in the model. Results did not find that  $PRS_{\text{lifetime use}}$  moderated the effect of TRD on experimental or non-experimental cannabis use. Specifically, the effect of  $PRS_{\text{lifetime use}}$  was not significant for those below ( $\beta = .23, p = .004$ ), at ( $\beta = .23, p = .004$ ), or above the mean level of  $PRS_{\text{lifetime use}}$  ( $\beta = .23, p = .04$ ) for experimental cannabis use at year 3 Spring. Likewise, the effect of  $PRS_{\text{lifetime use}}$  was not significant for those below ( $\beta = .15, p = .05$ ), at ( $\beta = .15, p = .05$ ), or above the mean level of  $PRS_{\text{lifetime use}}$  ( $\beta = .15, p = .05$ ) for non-experimental cannabis use at year 3 Spring. Results support that TRD is a strong predictor of both experimental and non-experimental cannabis use at all levels of polygenic risk for lifetime cannabis use.

In order to test if individuals who reported a history of IPT at college enrollment were more likely to report TRD at year 2 Spring, an ad hoc analysis testing the interaction between lifetime IPT assessed at year 1 Fall and new onset IPT at year 1 Spring was conducted. Results did not find that lifetime IPT moderated the effect of new onset IPT on TRD. Specifically, the effect of lifetime IPT was not significant for those below ( $\beta = .15, p = .13$ ), at ( $\beta = .15, p = .13$ ), or above the mean level of lifetime IPT exposure ( $\beta = .15, p = .13$ ). Results support that new onset IPT is a strong predictor of TRD at all levels of new onset IPT.

## ***ii. Covariate Effects***

Identifying as female (compared to male) and belonging to cohorts 2-4 (compared to cohort 1) significantly predicted likelihood of reporting TRD at year 2 Spring. Additionally, those who were older within their cohort and who reported less frequent nicotine use at year 1 Spring were more likely to report TRD. Rates of TRD at year 2 Spring did not differ

significantly between White and Black individuals. Alcohol use frequency and lifetime IPT assessed at year 1 Fall also did not impact an individual's likelihood of reporting TRD at year 2 Spring.

When predicting year 3 Spring cannabis use, females (compared to males) were more likely to report experimental cannabis use compared to no use, and males (compared to females) were more likely to report non-experimental cannabis use compared to no use. Individuals with more frequent year 2 Spring alcohol use were more likely to report experimental cannabis use compared to no use. Individuals with more year 1 Spring IPTs, as well as more frequent nicotine or alcohol use at year 2 Spring were more likely to report non-experimental cannabis use compared to no use. Additionally, cohorts 2 and 4 (compared to cohort 1), and those who were younger within their cohort were more likely to report non-experimental cannabis use compared to no use. Experimental and non-experimental cannabis use at year 3 Spring did not differ significantly between White and Black individuals. Individuals with higher PRS<sub>lifetime use</sub> were more likely to report non-experimental cannabis use compared to no use.

#### **D. High-Risk Model**

See *Table 13* for model fitting results. When predicting year 2 Spring IPT, those who reported non-experimental cannabis use at year 1 Spring were likely to report more IPT, compared to those who had never used cannabis. In predicting year 3 Spring TRD, those who reported more IPTs at year 2 Spring were more likely to meet criteria for TRD. The indirect effect of experimental cannabis use on TRD through IPT was non-significant (Indirect Effect: .01; 95% CI: -.00, .03). The indirect effect of non-experimental cannabis on TRD through IPT was significant (Indirect Effect: .02; 95% CI: .01, .04), such that those who reported non-

experimental use (compared to no use) reported more IPTs since beginning college and in turn were at higher risk for TRD.

In order to test if individuals at higher polygenic risk for lifetime PTSD ( $PRS_{\text{lifetime PTSD}}$ ) were more likely to report TRD at year 3 Spring, an interaction between IPT assessed at year 2 Spring and  $PRS_{\text{lifetime PTSD}}$  was included in the model. Results did not find that  $PRS_{\text{lifetime PTSD}}$  moderated the effect of IPT on TRD. Specifically, the effect of  $PRS_{\text{lifetime PTSD}}$  was not significant for those below ( $\beta = .42, p < .001$ ), at ( $\beta = .42, p < .001$ ), or above the mean level of  $PRS_{\text{lifetime PTSD}}$  ( $\beta = .42, p < .001$ ). Results support that IPT is a strong predictor of TRD at all levels of polygenic risk for lifetime PTSD.

In order to test if individuals who reported a history of IPT at college enrollment were more likely to report TRD at year 3 Spring, an ad hoc analysis testing the interaction between lifetime IPT assessed at year 1 Fall and new onset IPT at year 2 Spring was conducted. Results found that lifetime IPT significantly moderates the impact of new onset IPT on TRD. Specifically, for a one-unit increase in new onset IPT, individuals below the mean on lifetime IPT reported an increase of .61 in TRD ( $\beta = .61, p < .001$ ). Among those at the mean of lifetime IPT, a one-unit increase in new onset IPT was associated with a .42 increase in TRD ( $\beta = .42, p < .001$ ). Among those above the mean on lifetime IPT, a one-unit increase in new onset IPT was associated with a .24 increase in TRD ( $\beta = .24, p = .001$ ).

### ***i. Covariate Effects***

When predicting year 2 Spring IPT, females (compared to males) and those who reported more frequent year 1 Spring alcohol or nicotine use were more likely to report experiencing a greater number of IPT types. Rates of IPT at year 2 Spring did not differ significantly between

cohorts 2, 3, and 4 compared to cohort 1, nor did rates of IPT differ between White and Black or older individuals.

When predicting year 3 Spring TRD, females (compared to males), cohort 2 (compared to cohort 1), cohort 1 (compared to cohort 3 and 4), Black individuals (compared White individuals), and older individuals within their cohorts were at increased risk. Alcohol use frequency and nicotine use frequency assessed at year 2 Spring did not impact an individual's likelihood of reporting TRD at year 3 Spring.

## **Chapter 6: Discussion (Genotypic)**

### **I. Aim 2: GCTA and PRS**

#### **A. GCTA**

##### ***i. Overall Summary of Findings***

The second aim of the present study was to examine the genetic etiology of lifetime RCU and PTSD. This aim sought to determine the SNP-based heritability of lifetime RCU and PTSD using GCTA. Taken together, results from Aim 2 provide only small-to-modest insight into the genetic etiology of lifetime RCU and PTSD, due to low power, which potentially may be influencing null findings. However, given the developing literature on the genetic underpinnings of cannabis use and the rapidly growing literature on the genetic underpinnings of PTSD, results contribute to this intersecting area of interest. Findings from the analyses conducted as part of Aim 2 are discussed below within the context of limitations and future directions.

##### ***ii. Are RCU and PTSD Heritable?***

While conducting our analysis on two sub-samples for lifetime RCU and PTSD respectively, EUR (n= 3721) and AFR (n= 1469), we discovered relatively small-to-modest heritability estimates. However, it's important to note that these estimates did not reach statistical

significance due to the high standard error, likely stemming from the relatively small sample sizes. Specifically, when we broke down the S4S sample by ancestral sub-groups, we found that our sample sizes fell short of the recommended standard for detecting moderate heritability estimates, as outlined by Visscher et al. (2014). According to their work, to reliably identify a heritability estimate of  $h^2 = 0.3$  for a quantitative trait, such as lifetime RCU or PTSD in our study, a minimum of approximately 3000 individuals is necessary. Our relatively small sample sizes make it difficult to draw conclusions from our study results, as well as make comparisons across the well-powered genetic heritability literature for lifetime RCU and PTSD.

Previous research with relatively large samples aimed to estimate the heritability of lifetime cannabis use using GCTA, and results are inconsistent with our study's heritability estimates. Specifically, Verweij and colleagues (2013) estimated that 6% of the variance in lifetime cannabis use is explained by aggregated common SNPs using a meta-analysis of a about 10,000 individuals of European ancestry and Minica and colleagues (2015) found a heritability estimate of 25% using a sample of about 7,000 individuals of European ancestry. It is noteworthy that previous research utilizing larger sample sizes than our study reported substantially different heritability estimates for lifetime cannabis use using GCTA methodology. This underlines the significance of continued research in this domain with larger and more diverse samples as cannabis use behaviors continue to become more prevalent, with the goal of yielding more reliable heritability estimates that capture the full spectrum of genetic influences on recreational cannabis use.

Similar to previous research estimating the heritability of lifetime cannabis use using GCTA, there are efforts being made to analyze the heritability of PTSD using relatively large sample sizes, and results are inconsistent with our study's heritability estimates. For instance, in

a large meta-analytic study conducted by the PGC-PTSD group led by first-author Nievergelt (2019), it was observed that the heritability of PTSD appears to be higher among individuals from European ancestry ( $h^2=.05$ ; 95% CI: .02 - .08) compared to individuals from African ancestry ( $h^2=.04$ ; 95% CI: -.06 - .13). Additionally, it was observed that the heritability of PTSD appears to be higher among European-ancestry ( $h^2 =.13$ ; 95% CI: .05 - .20) and African-ancestry ( $h^2 =.18$ ; 95% CI: -.01 - .38) women compared to European-ancestry ( $h^2=.03$ ; 95% CI: -.03 – .08) and African-ancestry ( $h^2=.03$ ; 95% CI: -.21 - .27) men. Taking into account these sex differences is vital since it can serve as a potential confounding factor, influencing the significance of our study's findings. However, our study's sample size was notably underpowered, especially for conducting sex-specific analyses using GCTA, making it challenging to draw meaningful conclusions from. Additionally, there are significant measurement differences between the prior GCTA studies on PTSD which have relied on case-control studies from clinical interviews or from validated self-report instruments versus the abbreviated screening measure used in S4S to assess TRD. Given the complex and multifaceted nature of PTSD, it is imperative to continue research with larger, more diverse sample sizes with detailed measurement of the phenotype. This continued effort will not only enhance the accuracy of heritability estimates, but also deepen our understanding of the genetic underpinnings of PTSD, ultimately guiding future prevention and intervention strategies.

Notably, there are substantial differences between estimations of heritability among GCTA studies and twin studies regarding the heritability of phenotypes, such as lifetime cannabis use and PTSD. For example, Verweij and colleagues (2010) estimated that the proportion of variance accounted for by genetic influences for lifetime cannabis use was 48% for males and 40% for females in a meta-analysis of 28 twin studies. Likewise, Afifi and colleagues

(2010) estimated that the proportion of variance accounted for by genetic influences for PTSD is roughly 30% in a review of twin studies. However, there is a lot of variance when looking at the confidence intervals in these studies ranging from as low as about 18% to as high as 80% in an all-female, high-risk sample. Thus, heritability estimates of PTSD from twin studies should be interpreted with some caution as they may not be the most reliable. These apparent discrepancies are due to methodological differences between GCTA and twin studies. Specifically, GCTA relies on aggregated SNP data, making it unable to consider the variability stemming from rare variants when estimating heritability, as highlighted by Trzaskowski and colleagues (2014). Moreover, it's essential to note that GCTA heritability estimates exclusively encompass the additive genetic effects. In contrast, heritability estimates from twin studies encompass both additive and nonadditive effects, such as epistatic effects, which involve gene-gene interactions (Cordell, 2002), and dominance effects, which is where one allele masks the influence of another allele and affects the observed phenotype (Wilkie, 1994). Consequently, twin studies often yield higher heritability estimates for various traits. Certainly, while this trend was observed with GCTA-based heritability estimates in our study, the lack of statistical significance in the GCTA analyses can be attributed to the greater standard error associated with the estimates.

Although a limited sample size contributes to low statistical power and may offer an alternative explanation for the absence of significant results, the outcomes of this current study align with existing GCTA studies on lifetime cannabis use and PTSD. Indeed, even though the heritability estimates did not attain statistical significance, they are in harmony with the findings reported in previous GCTA studies that explored lifetime cannabis use and PTSD. Collectively, the existing body of literature utilizing molecular genetic techniques to assess the heritability of lifetime cannabis use and PTSD using GCTA remains in its early stages of development.



However, there is a pressing need for future research to provide additional insights into the findings presented in this study and to shed further light on the SNP-based heritability of lifetime cannabis use and PTSD.

## **B. PRS**

### *i. Overall Summary of Findings*

The second aim of the present study aimed to predict RCU and TRD within the S4S dataset using aggregate genetic risk scores computed for lifetime cannabis use and lifetime PTSD. We conducted PRS analyses using data from large consortiums and subsequently applied these scores to predict RCU and TRD within the S4S dataset, stratified by ancestral sub-groups for the two largest ancestral sub-groups in the S4S dataset (i.e., EAU, AFR). Although our investigation into the genetic foundations of RCU and TRD is in its early stages, our results suggest that aggregate genetic risk for lifetime cannabis use is predictive of risk of RCU in the S4S sample. We discuss the findings from each PRS analysis separately, drawing insights from the limited existing research. Additionally, we address the limitations of PRS analyses and propose future research directions in this domain.

### *ii. Does PRS for Lifetime Cannabis Use Predict Lifetime RCU?*

The current study employed PRS analyses to evaluate the predictive value of PRS<sub>lifetime use</sub> in relation to lifetime RCU operationalized as no-use, experimental use, and non-experimental use categories. Our findings revealed a statistically significant association between PRS<sub>lifetime use</sub> and lifetime RCU in the EUR ancestry sub-sample, but not in the AFR ancestry sub-sample. PRS<sub>lifetime use</sub> explained a minimal proportion of the variance in lifetime RCU, accounting for 0.9% in the EUR sub-sample for non-experimental RCU compared to no use and 0.0% in the AFR sub-sample. The study's significant results are likely attributable to the fact that the

construction of the PRS, including the choice of genetic variants and their associated weights, were developed using only European ancestry data, which does not capture the genetic variation relevant to cannabis use as effectively in individuals with African ancestry. The study's lack of significant results in the AFR sub-sample are likely attributable to limited statistical power, low transferability of PRS based on EUR summary statistics to other ancestral groups (Duncan et al., 2019), which is a symptom of a larger problem with regard to the lack of diversity within the larger psychiatric genetics literature (Peterson et al., 2019).

Our study's estimates of odds ratios related to increased risk for more frequent RCU among individuals with European ancestry within S4S demonstrates a noteworthy alignment with limited prior research exploring the predictive power of PRS<sub>lifetime use</sub>. Specifically, our investigation revealed that higher PRS were associated with an increased likelihood of cannabis use, echoing the findings observed in earlier studies. For example, Meyers and colleagues (2019) examined associations of PRS<sub>lifetime use</sub> with cannabis use and DSM-5 CUD symptom count and interactions with trauma exposure among a large sample of individuals of European ancestry from the Collaborative Study on the Genetics of Alcoholism. Their study revealed that in individuals from European ancestry, higher PRS<sub>lifetime use</sub> was linked to an increased probability of cannabis use and the presence of CUD symptoms, with statistical significance at certain thresholds ( $p < 0.05$  and  $p < 0.1$ , respectively). Notably, the influence of PRS<sub>lifetime use</sub> on cannabis use was particularly pronounced in individuals who had experienced trauma, accounting for a greater proportion of the variance ( $R^2: 0.011$ ) compared to those who had not been exposed to trauma ( $R^2: 0.002$ ). The  $R^2$  value in our study ( $R^2 = .007$ ) and Meyers and colleagues' study ( $R^2 = .011$  &  $.002$ ; 2019) demonstrate a comparable level of explained variance, indicating a modest but consistent predictive capacity in both investigations. This congruence underscores the

robustness of the relationship between genetic predisposition, as captured by PRS<sub>lifetime use</sub>, and cannabis use behaviors within this population subgroup. Furthermore, our study contributes to the growing body of evidence supporting the utility of PRS in understanding the genetic underpinnings of cannabis use, providing further validation of the predictive capacity of PRS in identifying individuals at elevated risk for cannabis use within European ancestry populations.

Our study did not observe predictive associations between aggregate genetic risk for lifetime cannabis use and experimental cannabis use compared to no use in individuals of European ancestry. Additionally, we did not observe predictive associations between aggregate genetic risk for lifetime cannabis use and experimental or non-experimental cannabis use compared to no use in individuals of African ancestry. These discrepancies in our study's findings, in contrast to earlier research, may be attributed to methodological variations, particularly in the operational definitions of cannabis use. Specifically, differences in the operational definitions of cannabis use and the variability in the levels of the cannabis use frequency variable across studies may have contributed to these differing outcomes. For instance, Rabinowitz and colleagues (2023) investigated if patterns in cannabis and tobacco use were associated with PRS for lifetime cannabis use and smoking heaviness (i.e., cigarettes per day) among a small sample of African-American individuals in a longitudinal study. Their study revealed odds ratio estimates for significant effects ranging from 1.37 (95% CI: 1.01, 1.86) to 1.40 (95% CI: 1.03, 1.91). Importantly, the authors created their PRS from the same genome-wide meta-analysis of lifetime cannabis use as our study. However, their operational definition of cannabis use included more variability than our study as cannabis use was measured on an 8-point scale ranging from none to 40 or more times in the past year versus our study which measured cannabis on a 3-point scale ranging from none to 6 or more times in the past 6 months.

Our study emphasizes the significance of harmonizing definitions and measurements when investigating the genetic determinants of cannabis use across diverse populations. Future research endeavors should take these methodological nuances into account to ensure a more comprehensive understanding of the genetic underpinnings of cannabis use in individuals of African ancestry.

### ***iii. Does PRS for Lifetime PTSD Predict Lifetime TRD?***

The current study employed PRS analyses to evaluate the predictive value of PRS<sub>lifetime PTSD</sub> in relation to TRD. Our findings revealed no statistically significant associations between PRS<sub>lifetime PTSD</sub> and lifetime TRD in both the EUR and AFR ancestry sub-samples. Although not statistically significant, the direction of effect of PRS<sub>lifetime PTSD</sub> predicting TRD in individuals with EUR ancestry was in the expected direction unlike those with AFR ancestry. Our study's findings are inconsistent with the limited polygenic risk for PTSD predicting trauma-related phenotypes literature, but still warrant attention. For example, Misganaw and colleagues (2019) employed PRS derived from the diverse PGC-PTSD Freeze 1 meta-analytic dataset and conducted a study with a cohort of veterans which yielded noteworthy findings, indicating a significant association between PRS<sub>lifetime PTSD</sub> and both the onset and symptom severity of PTSD. Additionally, Stein and colleagues (2021) utilized PRS derived from the European-ancestry subset of the Million Veteran Program for PTSD diagnosis and PTSD symptoms to predict PTSD diagnosis in the PGC-PTSD Freeze 2 meta-analytic dataset and found that PRS<sub>lifetime PTSD</sub> and PRS<sub>PTSD symptoms</sub> explained approximately 4% and 5.3% of the variance in PTSD diagnosis, respectively. One potential factor contributing to our statistically insignificant results could be the methodological distinction between the variables used. While our PRS were generated based on lifetime PTSD, our analysis focused on predicting a less sensitive trauma-

related variable, or TRD. This methodological difference may account for the unexpected outcomes, as TRD is derived from the screening items of the PC-PTSD which is based off of the four DSM-5 PTSD symptom clusters, but is lower in specificity compared to the diagnostic criteria for PTSD. Basically, anyone who has any symptoms of PTSD will be classified as having TRD, which could lead to more false positives when comparing TRD and PTSD. Therefore, future investigations should consider the nuances of the variables employed in PRS analyses, ensuring alignment with the specific outcomes of interest, to enhance the comparability and interpretability of findings across studies. Overall, the study's lack of significant results are likely attributable to limited statistical power, methodological error, and the lack of diversity within the larger psychiatric genetics literature.

#### ***iv. Summary of PRS Moderation Findings***

The third aim of the present study simultaneously examined two potential models posited to explain the development of co-occurring RCU and TRD using longitudinal data and tests of moderated-mediation. Additionally, this study introduced PRS<sub>lifetime use</sub> and PRS<sub>lifetime PTSD</sub> as moderators in the self-medication and high-risk models from Aim 1, respectively. It is noteworthy that although the PRS moderation was not significant either the self-medication and high-risk models, the outcomes from the current model closely resemble those observed in our earlier analyses from Aim 1, despite the restricted sample. The directional effects remain consistent, demonstrating robustness of study findings. Although the beta weights and standard errors may exhibit slight variations, the persistence of the same directional relationships underscores the reliability and stability of the findings.

### a. Self-Medication Model

Our investigation delved into the potential moderating role of PRS<sub>lifetime use</sub> within the framework of the self-medication model in the context of IPT, TRD, and RCU. While our study did reveal a significant main effect of PRS<sub>lifetime use</sub> on non-experimental cannabis use compared to no cannabis use, contrary to our hypotheses, our findings did not reveal a significant moderation effect on the relationship between IPT and TRD, in the context of predicting RCU. Despite the well-established role of genetics in influencing substance use behaviors (Barr et al., 2020; Kranzler et al., 2023; Schaefer et al., 2023), our results suggest that PRS<sub>lifetime use</sub>, as measured in this study, did not significantly alter the dynamics proposed by the self-medication model in the context of IPT, TRD, and RCU. Results suggest that an individual's level of aggregate genetic risk for lifetime cannabis use did not change the relationship between TRD and RCU in the context of the self-medication model of co-occurring PTSD and cannabis use. These results underscore the complexity of the genetic and environmental factors governing the intricate relationship between IPT, TRD, and cannabis use. These results warrant further scrutiny and emphasize the importance of further investigations to unravel the multifaceted nature of these relationships in the context of the self-medication model for trauma-related phenotypes and cannabis use.

Our results differ from limited previous research, such as Meyers and colleagues (2019), which reported significant moderation effects of PRS<sub>lifetime use</sub> on the relationship between trauma-related phenotypes and cannabis use. Specifically, Meyers and colleagues (2019) found that PRS<sub>lifetime use</sub> only influenced cannabis use among those exposed to trauma compared to those unexposed to trauma. Notably, Meyers' study employed a larger analytic sample of 7591 individuals of European ancestry and 3359 individuals of African ancestry that was recruited

from inpatient and outpatient alcohol use disorder treatment facilities as well as comparison subjects from the same communities, and used lifetime trauma exposure as their trauma-related phenotype compared to our study's more clinical-focused variable of trauma-related distress. The variations in sample size and characteristics, as well as the measures used may account for the differing results observed between our study and previous research. Additionally, the self-medication model's dynamics are multifaceted, influenced by a myriad of factors, including genetic, environmental, and psychological components that are likely unaccounted for in both studies. Our findings underscore the intricate nature of these interactions and highlight the importance of continued research to unravel the complexities of the self-medication model in the context of trauma-related phenotypes and cannabis use.

#### b. High-Risk Model

In our exploration of the high-risk model, which examines the interplay of RCU, IPT, and TRD, we assessed the potential moderating influence of  $PRS_{lifetime\ PTSD}$ . Surprisingly, our results did not reveal a significant main effect of  $PRS_{lifetime\ PTSD}$  on TRD, nor a moderation effect by  $PRS_{lifetime\ PTSD}$  in the relationship between RCU and IPT, within the context of predicting TRD. While genetics plays a moderate role in the prediction of PTSD (Campbell-Sills et al., 2023; Misganaw et al., 2019), our findings suggest that  $PRS_{lifetime\ PTSD}$ , as measured in this study, did not significantly alter the proposed dynamics of the high-risk model in the context of cannabis use and trauma-related distress. Results suggest that an individual's level of aggregate genetic risk for lifetime PTSD did not change the relationship between new-onset IPT and TRD in the context of the high-risk model of co-occurring cannabis use and PTSD. These results underscore the complexity of the genetic and environmental factors governing the complex relationship between cannabis use, IPT, and PTSD. These results warrant further scrutiny and emphasize the

need for further research to comprehensively understand the intricacies of these relationships in the context of the high-risk model for cannabis use and trauma-related distress.

While our study did not unveil a significant moderating effect of PRS<sub>lifetime PTSD</sub>, it is important to recognize that the dynamics of the high-risk model are influenced by a multitude of complex factors, including genetic, environmental, and psychological components. The interplay of these factors, observed across limited previous research of polygenic risk score moderation (Hess et al., 2021; Nelemans et al., 2021; Tonini et al., 2022), underscore the multifaceted nature of gene by environment interactions, which are substance use and trauma-related phenotypes in our study. Our findings are consistent with those of Lipsky and colleagues (2023), who also did not identify significant moderation effects. Contradictory to our study, Lipsky and colleagues (2023) found that PRS<sub>lifetime PTSD</sub> was significantly associated with a diagnosis of PTSD, but they did not find that genetic vulnerability for PTSD was a better predictor of PTSD at higher levels of trauma exposure. Lipsky and colleagues' (2023) study used a sample of Iraq and Afghanistan military service veterans, GWAS summary statistics from the Million Veteran Program, and a clinical diagnosis of PTSD based on medical records, which is different than our study's sample of college students, GWAS summary statistics from a more diverse and representative sample, and broad posttraumatic stress measure. These methodological differences that permeate throughout the literature make it difficult to compare across studies, but also could be contributing to null findings. In light of the infancy of the state of the literature and the methodological inconsistencies observed, our study underscores the critical need for ongoing replication and extension of research efforts, which will undoubtedly deepen our comprehension of the intricate interplay between genetic and environmental factors within the high-risk model of cannabis use and trauma-related phenotypes.



#### ***v. Overall Genetic Analyses Limitations, Future Directions, and Clinical Implications***

Our study demonstrated a notable departure from the significant findings reported in previous research concerning the application of GCTA to assess heritability in the context of lifetime cannabis use and PTSD. In both the European and African ancestry S4S subsamples, our results did not yield statistically significant heritability estimates. Likewise, our study's departure from the findings of previous research on PRS for lifetime cannabis use for the African ancestry subsample, and PTSD and their predictive value among individuals of European and African ancestry warrants careful consideration. Specifically, PRS<sub>lifetime use</sub> predicting cannabis use among individuals from African ancestry and PRS<sub>lifetime PTSD</sub> predicting TRD within S4S were not statistically significant, which is not consistent with limited previous research.

One plausible explanation for the discrepancies observed in our study's findings compared to the extant literature could be the issue of limited statistical power, particularly due to the substantial disparity in sample sizes between the discovery and target samples utilized in the PRS analyses. In a seminal PRS paper by Dudbridge (2013), the focus was on assessing the expected statistical power and predictive accuracy of PRS. Dudbridge's key findings highlighted the alignment between highly significant results observed in PRS association studies and the expected outcomes, taking into account the sizes of the discovery and target samples. Additionally, Dudbridge provided insights into sample size considerations, suggesting that equalizing discovery and target sample sizes optimizes the power of PRS association testing, while maximizing the discovery sample size enhances individual-level predictive accuracy. While our discovery sample boasted a robustly large sample size, the power of PRS analyses is contingent upon both the size of the discovery sample and the target sample. Unfortunately, our target sample was notably smaller, which could have significantly impacted our ability to detect

meaningful associations. The larger discovery sample size may have unearthed genetic variants or associations that, when applied to a smaller target sample, failed to attain statistical significance. It is essential to acknowledge this limitation in terms of sample size, as it underscores the importance of conducting future research with adequately sized target samples to enhance the reliability and generalizability of PRS analyses across diverse populations.

Another reasonable explanation for the discrepancies observed in our study may be attributed to methodological considerations. Notably, the reliance on self-report measures of both cannabis use and trauma exposure/PTSD among college students introduces certain complexities. As our study was conducted in a state where recreational cannabis use was illegal at the time of data collection, participants may have hesitated to provide accurate information, potentially resulting in underreporting of cannabis use. This issue of social desirability bias in self-report measures, particularly in contexts where cannabis use is prohibited (Johnson & Fendrich, 2005), could have affected the precision of our data. Furthermore, variations between measures of trauma-related phenotypes, such as IPT and PTSD, may introduce inconsistencies in the assessment process (Hicks, Zaur, et al., 2022). The multifaceted nature of these constructs, coupled with the potential subjectivity in self-reporting, underscores the importance of refining measurement tools and considering regional variations when examining the relationship between cannabis use and trauma-related phenotypes among college students. Future research should strive to mitigate these methodological challenges to enhance the accuracy and reliability of findings in this context.

The observed disparities in our study's findings, when compared to prior research, may also be attributed to the historical underrepresentation of individuals from non-European ancestry populations in genetic studies. Historically, genomic research has predominantly

focused on individuals of European ancestry, leading to the limited availability of diverse genetic data for other populations (Peterson et al., 2019). This inherent bias in genetic research may contribute to the challenges in extrapolating findings across different ancestral groups. To address these discrepancies and enhance the generalizability of genetic studies, concerted efforts to include more diverse populations in genome-wide association studies and more sophisticated methods are imperative. The ongoing enhancement of reference panels and the increasing representation of diverse global populations in discovery samples mark a pivotal shift in the field of statistical genetics. These advancements pave the way for the future feasibility of innovative analytical methods such as PRS-CSx (Ruan et al., 2022). By transcending the historical focus on European populations and embracing global diversity, genetic research stands to benefit from a more comprehensive and inclusive perspective. As reference panels become more representative and discovery samples mirror the true diversity of the global population, we can anticipate a broader applicability of cutting-edge techniques like PRS-CSx. Such inclusivity will not only aid in elucidating the genetic determinants of complex behaviors and disorders, like cannabis use and PTSD, across diverse backgrounds, but also promote a more equitable and comprehensive understanding of human genetics.

Our study highlights the critical importance of conducting statistical genetic analyses within diverse populations, specifically individuals from non-European ancestry backgrounds. Historically, genetic research has often overlooked or underrepresented individuals from diverse ancestral backgrounds, leading to a substantial gap in our understanding of genetic influences on complex behaviors and disorders, such as cannabis use and PTSD, within these populations. By venturing into underpowered analyses with non-European ancestry individuals, we take a significant step towards addressing this historical inequity. For example, Bountress and

colleagues (2022) used summary statistics from extensive GWAS involving individuals of European and African ancestry to assess the genetic correlations between PTSD and various alcohol phenotypes. Their study results demonstrated that in individuals of European ancestry, there were observed positive genetic correlations between PTSD and alcohol-related problems. Conversely, the genetic correlations between PTSD and alcohol consumption-related characteristics showed negative associations or were not statistically significant. Among individuals of African ancestry, the direction of these correlations occasionally matched that of individuals with European ancestry, but sometimes exhibited inconsistencies, with broader ranges in correlation values. Bountress and colleagues (2022) demonstrated that their preliminary efforts may yield valuable insights, highlighting potential genetic factors that warrant further investigation among individuals from non-European ancestry. Moreover, they lay the foundation for future research endeavors, advocating for increased inclusivity and diversity in genomic studies. While underpowered analyses may not always yield definitive results, they serve as an essential starting point in the journey towards a more inclusive and equitable scientific literature, encouraging a broader perspective on the genetic underpinnings of complex behaviors and disorders across diverse human populations.

The potential for PRS analyses to be equally applicable to individuals of African ancestry, similar to their usability in individuals of European ancestry (Duncan et al., 2019), holds significant clinical implications. Such similarity in the utilization of PRS could usher in a new era of personalized medicine, offering tailored risk assessments and interventions for a broader segment of the global population (Yanes et al., 2020). Equitable access to PRS-based insights would enable healthcare providers to offer more precise risk assessments and early interventions for complex behaviors and disorders, such as problematic cannabis use and PTSD,

influenced by genetics. Racially-equitable utilization of PRS could enable targeted prevention efforts and early interventions for individuals at heightened genetic risk for problematic cannabis use and PTSD. Additionally, tailoring treatment strategies based on an individual's genetic predisposition can potentially enhance treatment efficacy and therapeutic outcomes. Moreover, it would contribute to reducing health disparities by ensuring that individuals from diverse ancestral backgrounds receive equitable access to the benefits of genomic medicine. Thus, the realization of this potential could profoundly impact clinical practice, making genetic risk assessments more comprehensive, equitable, and ultimately more effective in improving individual health outcomes.

### **Chapter 7: Conclusions**

The current study investigated the phenotypic and genotypic etiology of co-occurring TRD and RCU among college students. During this developmental stage, students may encounter new stressors related to academic demands, social pressures, and transitions to independent living. Campus life can also expose them to traumatic events, such as accidents and assaults. Likewise, the college culture of partying and experimentation with substances can also contribute to risky behaviors, making students more susceptible to trauma exposure and potentially using substances as a coping mechanism. The combination of academic stressors, social challenges, and potential traumatic experiences can increase vulnerability to both PTSD and cannabis use. The self-medication hypothesis of co-occurring RCU and PTSD has garnered significant attention in the scientific community. However, as mentioned in a methodological critique of the cannabis use and PTSD literature, it is imperative for future research to address the underlying assumption of PTSD coping-related cannabis use by developing measures that specifically assess if individuals are coping with distressing PTSD symptoms by using cannabis

(Hicks, Zaur, et al., 2022). Similarly, the high-risk hypothesis of co-occurring RCU and PTSD is gaining attention in the scientific community. However, to gain a comprehensive understanding of this intricate relationship, future studies should prioritize investigating the underlying mechanisms, such as short- and long-term impaired cognitive functions (Dellazizzo et al., 2022), that may link cannabis use to increased risk for trauma exposure and developing PTSD. By creating PTSD coping-related cannabis use measures, elucidating the potential pathways of how cannabis use could lead to trauma exposure and PTSD, and highlighting contributing psychiatric and behavioral genetic factors, we can develop more personalized prevention and intervention strategies to support the mental health and well-being of college students.

## Chapter 8: References

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