Cumulative Vulnerabilities: Substance Use in Adolescence and in Recovery

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ABSTRACT

Substance use and substance use disorders (SUDs) pose a significant health and economic concern in the United States. Conditions and comorbidities exist that are associated with substance use onset, continuation, and outcomes. In the theory of Reinforcer Pathology, we can categorize these conditions into *vulnerabilities*, or factors that may be associated with susceptibility to substance use onset and poorer outcomes in substance use recovery. The theory of vulnerabilities and reinforcer pathology is tested through three investigations. The first investigation sought to establish the relationship between cumulative vulnerabilities and adolescent substance use in a cross-sectional analysis. The second investigation evaluates the temporal relationship of cumulative vulnerabilities and substance use among adolescents. The final investigation establishes the relationship of cumulative vulnerabilities and substance use among individuals in recovery from Opioid Use Disorder. Collectively, these reports suggest that the intersection and cumulation of vulnerabilities to substance use and substance use disorders are directly related to substance use outcomes. Future research and reports in the substance use domain should consider these constructs, their accumulation, and their co-occurrence patterns.

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GENERAL AUDIENCE ABSTRACT

Substance use and substance use disorders are a great health and economic concern in the United States. Conditions that are related to trying substances, using substances, and outcomes of this substance use. In the theory of Reinforcer Pathology, we can call these conditions *vulnerabilities*, or conditions that may be associated with the likelihood of starting to use substances and having poorer substance use outcomes in the long-term. Three studies investigate the theory of vulnerabilities and Reinforcer Pathology. First, the relationship between cumulative vulnerabilities and substance use among adolescents is assessed cross-sectionally or simultaneously. The second study examines the relationship between cumulative vulnerabilities and adolescent substance use over time. The third study examines the relationship between cumulative vulnerabilities and substance use among individuals in recovery from Opioid Use Disorder. Collectively, the studies in this report suggest that the overlap and cumulation of vulnerabilities to substance use and substance use disorders is related to substance use outcomes. Future research and other reports in the substance use domain should consider these constructs, their accumulation, and their co-occurrence patterns.

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INTRODUCTION

Cumulative Vulnerabilities: Substance Use in Adolescence and in Recovery

Substance use disorders are diagnosed and characterized by four general criteria in the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5): impaired control of substance use, impaired social skills, risky use, and pharmacologic factors (American Psychiatric Association, 2013). Substance Use Disorders can be diagnosed for a number of substances, including: alcohol, opioids, stimulants (e.g., cocaine, methamphetamine) and tobacco. To meet a diagnosis for a substance use disorder, participants are asked about eleven individual items from the above four criteria. These items include: 1) using substances more or longer than intended, 2) trying to cut down or quit the use of a substance without the ability to do so, 3) experiencing a craving for the substance, 4) developing tolerance (i.e., needing to use more of the substance to obtain a desired effect), 5) developing withdrawal symptoms when not using the substance, 6) spending more time getting, using, and recovering from use, 7) ignoring or neglecting responsibilities (at work, home, or school), 8) continuing use of the substance even when faced with relationship problems, 9) giving up other activities (e.g., social, recreational) because of continued use, 10) using substances in settings that may cause danger (e.g., using and driving), and 11) using despite negative consequences to physical and mental health (American Psychiatric Association, 2013). To receive a diagnosis of a substance use disorder, participants must endorse two to three of the above criteria (mild), four or five of the criteria (moderate), or six or more of the criteria (severe) over the last 12 months.

Substance use disorders were reported to affect 20.4 million Americans aged 12 or older in 2019 (Abuse, n.d.). Substance Abuse and Mental Health Services Administration reports that

of these 20.4 million Americans with a substance use disorder over the past year, 14.5 million individuals had alcohol use disorder, 8.3 million individuals had an illicit substance use disorder, and 2.4 million individuals had both an alcohol use disorder and illicit substance use disorder; these statistics exclude diagnosis of tobacco use disorder (Abuse, n.d.).

Substance use and substance use disorders pose a significant economic burden on the United States. For example, in 2010, excessive drinking cost the United States an estimated $250 billion (Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015). Moreover, in 2017 the cost of substance use disorders in emergency departments and inpatient settings in the United States exceeded $13 billion (Peterson, Li, Xu, Mikosz, & Luo, 2021).

In addition to the economic toll, substance use disorders contribute to many deaths. According to Esser et al. (2022), one in eight deaths among United States adults aged 20 to 64 contributed to excess alcohol consumption, with the percentage increasing to one in five among individuals aged 20 to 49. In addition to these statistics about alcohol consumption, over 100,000 deaths from April 2020 to April 2021 were substance-related overdoses ("Drug Overdose Deaths in the U.S. Top 100,000 Annually," 2021), and the number of overall overdose deaths has quintupled from 1999 to 2020.

Treatment strategies exist to help individuals with substance use disorders. Specifically, treatment strategies such as contingency management (Prendergast, Podus, Finney, Greenwell, & Roll, 2006), cognitive behavioral therapy (Morin, Harris, & Conrod, 2014), and medication-assisted treatment (Connery, 2015) have been reported to help individuals reduce substance use across several substances. In 2019, an estimated 21.6 million Americans needed substance use treatment (i.e., had a substance use disorder in the last year or received treatment in a facility for a substance use disorder in the past year) (Abuse, n.d.). The need for substance use treatment is

high, however, only a portion of individuals needing treatment actually receive treatment. In 2019, only 4.2 million Americans received substance use treatment (defined as treatment received in any location, e.g., hospital, outpatient, jail or prison, self-help group) in the past year compared to the estimated 21.6 million Americans who needed treatment (Abuse, n.d.). Of these 4.2 million individuals, approximately half (2.1 million individuals) received help through a self-help group (i.e., Alcoholics Anonymous, Narcotics Anonymous), while some received help through outpatient rehabilitation services (1.7 million), outpatient mental health centers (1.3 million), inpatient rehabilitation services (1.0 million), and other forms of treatment including private doctors offices, inpatient services at a hospital, the emergency room or jail (Abuse, n.d.). Examining and understanding the antecedents to substance use is pivotal to better prevent and treat substance use disorders. Additionally, understanding the factors associated with substance use and initiation among adolescents may provide more insight into prevention efforts.

Factors associated with substance use among adolescents come in a variety of forms. One categorization of risk factors for adolescent substance use includes the domains: culture and society (e.g., laws favoring substance use), interpersonal (e.g., family and peer relationships), psychobehavioral (e.g., internal factors), and biogenetic (e.g., inherited characteristics) (Newcomb, 1995). Another more recent review categorized factors associated with adolescent substance use into three domains: familial, social, and individual risk factors (Whitesell, Bachand, Peel, & Brown, 2013). Familial risk factors associated with adolescent substance use include, but are not limited to: maltreatment in childhood, familial history of substance abuse, parental education and socioeconomic status, and parental marital status (Whitesell et al., 2013). Evidence exists in the literature that hereditary, genetic factors may be associated with substance use and substance use disorders (for review, see Deak & Johnson, 2021).

In addition to these familial and genetic risk factors, a number of environmental factors associated with substance use exist among adolescents and adults. Whitesell et al. (2013) review social factors that would fall in the environmental domain; these factors include deviant peer relationships, bullying, popularity and peer pressure, and association with gangs. Additionally, other environmental factors, such as drug availability, social norms favorable to substance use, and neighborhood disorganization, are reported to be associated with substance use (Newcomb, 1995). The third general category of factors related to substance use among adolescents, according to Whitesell et al. (2013) is individual risk factors. These factors are internal and include but are not limited to: attention deficit hyperactivity disorder (ADHD), depression, post-traumatic stress disorder (PTSD), and other mental illness or psychiatric disorders (RachBeisel, Scott, & Dixon, 1999; Weinberg, 2001; Whitesell et al., 2013).

One modern theory of addiction, Reinforcer Pathology, posits that substance use disorders, as well as other maladaptive behaviors, are the result of two distinct features: 1) the persistently high valuation for brief and intense reinforcers, and 2) the excessive preference for immediate available rewards despite negative long-term consequences (Bickel, Jarmolowicz, Mueller, & Gatchalian, 2011; Bickel, Johnson, Koffarnus, MacKillop, & Murphy, 2014). The first feature of Reinforcer Pathology Theory can be assessed by measures of substance use valuation, including real administration of substances and hypothetical tasks. The second feature of Reinforcer Pathology can be assessed through the theoretical construct of the temporal window. The temporal window in the theory of Reinforcer Pathology refers to the temporal resolution that individuals can imagine and envision in the future.

To explain the Theory of Reinforcer Pathology more concretely, let us consider two reinforcers: one brief, intense, and immediately available reinforcer, and one variable and

temporally extended reinforcer. The brief, intense, and immediately available reinforcer may represent commodities such as alcohol, cigarettes, or food. The variable, extended reinforcer may represent prosocial reinforcers such as employment or social relationships. If we were to integrate the reinforcing value of the brief, intense, and immediately available reinforcer, we would observe a strong reinforcing value in the short term with the accrual of negative reinforcing value over a longer period of time. On the contrary, we would see more variable reinforcing value over the short term with the variable, extended reinforcer, with the accrual of more positive reinforcing value over a more extended period of time. Reinforcer Pathology postulates that if we can extend the temporal window, we may be able to change the amount of reinforcement obtained through the use of different reinforcers (i.e., brief, intense immediate reinforcers versus the more extended, variable reinforcers).

Taken together, the field of substance use research has established a number of antecedents to substance use. These antecedents to substance use and substance use disorders may also be defined as vulnerabilities or disparities experienced by individuals that may make them more susceptible to substance use and substance use disorders. Through the Theory of Reinforcer Pathology, a vulnerability can be defined as a condition that may be related to or cause a shortened temporal window. Vulnerabilities associated with substance use are also associated with increased rates of delay discounting (i.e., shorter temporal window), including psychiatric symptomatology (for meta-analysis see Amlung et al., 2019), low SES (de Wit, Flory, Acheson, McCloskey, & Manuck, 2007; Oshri et al., 2019; Reimers, Maylor, Stewart, & Chater, 2009), and lower educational attainment (Jaroni, Wright, Lerman, & Epstein, 2004; Reimers et al., 2009).

In addition to literature examining individual vulnerabilities to substance use and substance use disorders, the cumulation of vulnerabilities has been examined. The cumulation of vulnerabilities has been reported to be associated with cigarette use among adults (Gaalema, Leventhal, Priest, & Higgins, 2018; Higgins et al., 2021, 2015, 2016; Leventhal, Bello, Galstyan, Higgins, & Barrington-Trimis, 2019). More specifically, the cumulation of vulnerabilities is associated with: increased risk of smoking initiation (Higgins et al., 2016), the number of cigarettes smoked per day (Higgins et al., 2021), indices of heavy smoking, severity of dependence, and more problems with trying to quit smoking (Leventhal et al., 2019). The literature also reports that these vulnerabilities tend to co-occur. The co-occurrence patterns produce differing risk profiles for cigarette use among adults (Gaalema et al., 2018; Higgins et al., 2015, 2016; Leventhal et al., 2019). In addition to these studies in individuals who smoke cigarettes, other reports indicate that the number of risk factors, or vulnerabilities, that individuals have are associated with the frequency of past 6 month substance use among adolescents (Newcomb, 1995).

Although the literature has examined the relationship between vulnerabilities, their accumulation, and smoking indices among adults and recent substance use among adolescents, a scientific gap remains for the use of other substances associated with cumulative vulnerabilities. Moreover, the literature does not report the association between cumulative vulnerabilities and substance use initiation among adolescents and substance use among individuals in recovery from substance use disorders. The following studies comprise a report that examines the cumulation of vulnerabilities among adolescents and individuals in recovery from opioid use disorders and their relationship to substance use. First, the associations between cross-sectional vulnerabilities and previous substance use in adolescents are identified. Second, the changes in

associations of vulnerabilities and substance use are examined longitudinally in adolescents. Third, lifetime substance use and associations with vulnerabilities are examined cross-sectionally in a sample of individuals previously enrolled in a clinical trial for opioid use disorder. Finally, implications for the results and future directions are discussed. These findings in adolescents across several substances are consistent with previous literature examining both cumulative vulnerability scores and profiles of vulnerabilities in adults who smoke cigarettes.

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MANUSCRIPT 1

Title

Cumulative Vulnerabilities in Adolescents: Associations with Age of First Substance Use, Any Substance Use, and Total Substances Used

Abstract

Aims: Vulnerabilities are associated with the use of substances such as cigarettes in adults. To inform public health policies to reduce substance use and initiation among adolescents, this study examines the associations of cumulative vulnerabilities and substance use among adolescents in the United States.

Design: Data were collected from the Happiness and Health survey, which included participants in 9th grade from 10 schools across Los Angeles County, California in 2013.

Measurements: Participants were asked about substance use and 13 vulnerabilities; the presence of these vulnerabilities was summed to create a *cumulative vulnerability score*. The relationship between *cumulative vulnerability score* with any substance use (binary), total substances used (poisson), and age of first use (ordinal) was evaluated. Latent class analysis was performed on these thirteen vulnerabilities to identify five subgroups of participants in the sample. These subgroups' relationship with any substance use, total substances used, and age of first use were evaluated.

Findings: *Cumulative vulnerability score* was significantly associated with any substance use ($X^2(1) = 194.56$; *p<0.001)*, total substances used ($X^2(1) = 744.24$; *p<0.001)*, and the age of first use ($X^2(1) = 21.36$; *p<0.001)* among adolescents in this sample. Subgroups (i.e., patterns of vulnerabilities) were significantly associated with any substance use ($X^2(5) = 178.38$; *p<0.001)*, total substances used ($X^2(5) = 667.44$; *p<0.001)*, and the age of first use ($X^2(5) = 22.325$; *p<0.001)*. The subgroup with the lowest proportion of vulnerabilities had significantly lower substance use (21.6%) than the subgroup with the highest proportion of vulnerabilities (55.7%); OR: 0.219; $p<0.001$).

Conclusions: The cumulation of vulnerabilities are an important consideration for public health and policy proposals targeting substance use among adolescents because of their relationship with substance use indices.

Keywords: cumulative vulnerabilities, vulnerability, adolescent, substance use

Introduction

In 2020, over 162 million Americans aged 12 or older used a substance in the past month (58.7%) (*2020 NSDUH Annual National Report*, n.d.). Specifically among adolescents ages 12 to 17 in 2020, 12.2 percent indicated using a substance such as alcohol, tobacco, or an illicit drug in the past month (*2020 NSDUH Annual National Report*, n.d.). Research shows that 50% of substance use initiations occur below the age of 20 (Blanco et al., 2018). Substance use among adolescents can have negative long-term consequences, including growth and brain development, co-occurring risky behaviors, and health problems into adulthood (CDC, 2020). Further, the younger the age of substance use initiation is associated with an increased risk of developing a substance use disorder later in life (Viner & Taylor, 2007).

In adolescents, a number of factors that are associated with substance use exist, including familial, social, and individual factors (Whitesell et al., 2013). These factors can be defined as a vulnerability or disparity associated with substance use disorders. These factors (e.g., mental illness, affective disorders), hereby referred to as vulnerabilities, are associated with the use of substances such as cigarettes in adults (Gaalema et al., 2018; Higgins et al., 2015, 2016, 2021; Leventhal et al., 2019).

Vulnerabilities tend to co-occur; individuals facing one vulnerability often experience others, such as poverty, low education, and affective disorders (Gaalema et al., 2018; Higgins et al., 2016, 2021). When examining the co-occurrence of vulnerabilities, different co-occurrence patterns emerge, producing different risk profiles for cigarette use (Gaalema et al., 2018; Higgins et al., 2015, 2016; Leventhal et al., 2019). The cumulation of vulnerabilities are associated with an increased risk of smoking initiation (Higgins et al., 2016), the number of cigarettes smoked per day (Higgins et al., 2021), heavy smoking, the severity of dependence and problems trying to

quit (Leventhal et al., 2019), and poorer cessation outcomes in a clinical trial for smoking cessation (Zvolensky et al., 2023).

To inform public health policies to reduce substance use and initiation among adolescents, this study examines the associations of cumulative vulnerabilities and substance use among adolescents in the United States. The accumulation of thirteen different behavioral, family history, or health-related vulnerabilities are the focus of this study: sleep problems, impulsive behavior (positive and negative urges), inhibitory control, family history of substance use, psychiatric symptoms (of mood disorders, anxiety, depression, panic disorder, social phobia, and obsessive-compulsive disorder), anhedonia, and satisfaction with life. In addition to the comparisons of the cumulation of these vulnerabilities, identifying patterns of vulnerabilities that may lead to increased substance use among adolescents was an aim.

Methods

Participants and procedures

Data were collected in the Happiness & Health Study, a prospective cohort survey of behavioral health aimed at understanding trends across the lifespan, which enrolled 3,396 students in 9th grade from ten schools in Los Angeles County, California in 2013. Participants provided assent and parental consent to be surveyed. The University of Southern California Institutional Review Board approved the data collection. The work herein is an exploratory, secondary analysis of the de-identified data; the reported analyses were not pre-registered. All measures analyzed in the current study were collected at the first time point, in fall 2013 (9th grade). The sample included 2,651 participants who provided answers to all independent variables (demographic and vulnerability measures) and the primary outcome measure (any substance use; details below).

Measures

Demographics

Participants' characteristics, including sex, age, race/ethnicity, speaking language, home language, living situation, parental education, and family history of substance use were collected using self-reports with predefined categories (response options available in **Table 1.1**). Additional demographic variables were collected at a school level, including the number of students receiving free or reduced lunch.

Vulnerabilities (Independent measures)

Twelve vulnerabilities were evaluated, including: the Revised Children's Anxiety and Depression Scale (RCADS) subscales (1-5), the Mood Disorder Questionnaire (MDQ; 6), Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale (UPPS-P) subscales (7, 8), the Early Adolescent Temperament Questionnaire Revised-Inhibitory Control subscale (EATQR-IC; 9), Snaith-Hamilton Pleasure Scale (SHAPS; 10), Satisfaction with Life Scale (SLS; 11), Sleep Problems Questionnaire (SPQ; 12).

Revised Children's Anxiety and Depression Scale (RCADS) subscales. The RCADS is used to assess symptoms of anxiety and depression among children and adolescents (Chorpita et al., 2000, 2005). The RCADS is composed of six subscales; five subscales were used in the present study: Generalized Anxiety Disorder (GAD), Major Depression Disorder (MDD), Panic Disorder (PD), Social Phobia (SP), and Obsessive Compulsive Disorder (OCD). All items of the RCADS are answered on a 4-point Likert scale (0 = never, 3 = always). Scores are summed and compared to a cut-off score (meets criteria for disorder or does not). As defined in Chorpita et al.

(2005), a binary variable of meeting the weighted clinical cut-off for each of the subscales was used for analyses.

Mood Disorder Questionnaire (MDQ). The MDQ is used to screen individuals for Bipolar Spectrum Disorder, which includes Bipolar I, Bipolar II, and Bipolar Not Otherwise Specified (Hirschfeld et al., 2000). The 15 items are answered on a 4-point Likert scale (0 = no problem, 3 = serious problem). Item responses are summed and compared to a cut-off score (meets criteria for mood disorder or does not). A binary variable of meeting the weighted clinical cut-off was used for analyses, as in Hirschfeld et al (2000).

Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale (UPPS-P) subscales. Emotional reactivity to negative and positive experiences was measured using the positive and negative urgency subscales of the UPPS-P (Cyders et al., 2007; Whiteside & Lynam, 2001). The negative urgency subscale consists of 12 items, and the positive urgency subscale consists of 14 items. Items are responded to on a 4-point Likert scale (1 = 'definitely true' to 4 = 'definitely false'). Scores are summed across negative and positive urgency subscales, with higher scores reflecting a more emotion-based rash action. The weighted sum for each subscale was used in the analyses.

Early Adolescent Temperament Questionnaire Revised-Inhibitory Control subscale (EATQR-IC). The EATQR-IC measures an individual's capacity to plan and suppress inappropriate responses (Capaldi & Rothbart, 1992). The subscale comprises five items; items are answered on a 5-point Likert scale (1 = almost always untrue, 5 = almost always true). Responses are summed and divided by the number of items for a mean EATQR-IC score; higher scores reflect a greater ability to plan ahead and suppress inappropriate responses. The mean EATQR-IC was used for analyses.

Snaith-Hamilton Pleasure Scale (SHAPS). The SHAPS measures anhedonia, or the absence of a hedonic tone (Snaith et al., 1995). The SHAPS includes 14 items that are answered on a 4-point Likert scale (1 = strongly disagree, 4 = strongly agree). Scores are compared to a cut off to obtain a clinical level of anhedonia (Snaith et al., 1995). A binary variable of meeting the weighted clinical cut-off was used for analyses.

Satisfaction with Life Scale (SLS). The SLS measures the global cognitive judgments of one's life satisfaction (Diener et al., 1985). The scale contains five items scored on a 7-point Likert scale (0 = strongly disagree, 6 = strongly agree). Scores are summed and divided by the number of items to obtain a mean score; higher scores indicate greater life satisfaction. The mean SLS score was used for analyses.

Sleep Problems Questionnaire (SPQ). The SPQ, also called the Jenkin's Sleep Questionnaire (Jenkins et al., 1988), assesses an individual's sleep disturbances. The SPQ consists of four items about sleeping behaviors in the past month (i.e., 30 days); items were answered on a 5-point scale (1 = not at all, 5 = 22-30 days). Scores of each item are summed; higher scores indicate greater sleep disturbances. The weighted sum of the SPQ was used in analyses.

Cumulative Vulnerability Score. To evaluate the accumulation of vulnerabilities, a global score was created of participants' vulnerabilities for the 12 measures (see above) and family history of substance use. For items with clinical cut-offs, participants' vulnerability scores increased for each cut-off they met. For items with weighted sums or means, a median split was calculated. Participants in the more "vulnerable" median were assigned the vulnerability (e.g., UPPS-P scores greater than the median are assigned the vulnerability). The total number of

vulnerabilities a participant indicated were summed for a vulnerability score hereby referred to as *cumulative vulnerabilities*. The range of cumulative vulnerabilities was 0 to 13.

Substance use measures (Dependent measures)

Participants were asked "How old were you the first time you tried each of the following substances" about 24 substances, including one fictitious substance: a few puffs of a cigarette, a whole cigarette, electronic cigarettes, smokeless tobacco, big cigars, little cigars or cigarillos, hookah water pipe, blunts, other forms of tobacco, marijuana, one full drink of alcohol, inhalants, cocaine, methamphetamine, derbisol (fictitious substance), LSD/mushrooms/or other psychedelics, ecstasy, heroin, salvia, prescription painkillers to get "high", tranquilizers or sedatives, diet pills, prescription stimulant to get "high", and any other pill or illegal drug to get high. Items were answered on a 7-point scale (I've never tried this substance, 8 years or younger, 9-10 years old, 11-12 years old, 13-14 years old, 15-16 years old, 17 years or older). Three participants in the sample (0.11%) indicated derbisol use. These participants were excluded from all analyses, making the analytical sample 2,648 participants. In addition, four participants (0.15%) were removed as they indicated inconsistent ages of first substance use (i.e., ages of first use that were older than their age reported), making the analytical sample 2,644 participants.

Any substance use. Any substance use was defined as a binary outcome if participants had endorsed using any of the 23 substances (after removing derbisol) in their lifetime.

Total substances used. The total number of classes of substances participants endorsed derived from the 23 items (after removing derbisol) were summed up for *total substances used* score. The total substances used scored was calculated by summing the use of the following classes of substances: alcohol, illicit stimulants (i.e., cocaine, methamphetamine, ecstasy), prescription stimulants (i.e., diet pills, prescription stimulants), opioids (i.e., heroin, prescription

painkillers), e-cigarettes, cigarettes (i.e., a few puffs of a cigarette, whole cigarette), cigars (i.e., big cigars, little cigars or cigarillos), marijuana (i.e., blunts, marijuana), smokeless tobacco, hookah water pipe, other forms of tobacco, inhalants, psychedelics, salvia, and tranquilizers or sedatives. The range of *total substances used* was 0 to 15.

Age of first substance use. The *age of first substance use* was defined as the minimum score (i.e., age) participants endorsed across the 23 substance use items. Participants that did not endorse using any substances were excluded from analyses of the age of substance use onset; 1,646 participants did not provide an answer to the age of first substance use question or indicated they had never used a substance previously.

Data analysis

The final analytical dataset for *any substance use* was N = 2,639 (five participants did not provide a response to this question). For *total substances used*, the analytical sample was N = 2,563 (81 participants did not provide a response to one of the classes of substances used to define the total score). The final analytical dataset for the *age of first substance use* was N=998 (1,646 participants did not provide an answer to the age of substance use onset question or indicated they had never used a substance previously). Participants' characteristics were described using mean, standard deviation, and percentages, where appropriate.

All statistical analyses were performed in R version 3.5.1 (Team, 2018). Univariate regression analyses were conducted to determine the relationship between the dependent measures and each of the 13 binary vulnerabilities and the cumulative vulnerability score. To evaluate *any substance use*, a binary generalized logistic regression was performed using the package `stats` (Team, 2018). To evaluate the *total substances used*, a poisson generalized linear regression was performed using the package `stats` (Team, 2018). To evaluate the *age of*

first substance use, an ordinal linear regression was performed using the package `MASS` (Venables & Ripley, 2002).

To further evaluate the classes of cumulative vulnerabilities and their impact on substance use, a latent class analysis (LCA) was performed using the package `poLCA` (Linzer & Lewis, 2011). The LCA was performed with the 13 binary vulnerabilities as indicator variables. The appropriate number of latent classes was determined with Bayesian Information Criterion (BIC); the model with the lowest BIC was considered optimal (k = 6; Weller et al., 2020). Here, k=6 was the optimal number of classes. The relationship between outcome measures and the latent class assignment was performed. Specifically, a binary logistic regression was used to evaluate *any substance use*, a poisson generalized linear regression was used to evaluate *total substances used*, and an ordinal linear regression was used to evaluate the *age of first substance use*. Significance of the model effects was determined using a Type III ANOVA. Pairwise comparisons were performed using estimated marginal means to determine differences between latent classes using the package `emmeans` (Russell, 2019); contrasts were adjusted using the Tukey method to correct for multiple comparisons. Significance in the present report was defined as $p < 0.001$ to adjust for multiple tests.

Results

Cohort characteristics

The demographic characteristics of the sample of participants can be found in **Table 1.1**. The majority of participants were 14 years old (82.9%; age was categorical ranging from <12 to 16 years old), female (55.7%), and a plurality endorsed being multi-ethnic or multiracial (48.9%).

Individual vulnerabilities

Univariate binary logistic regression predicting *any substance use* was performed for all demographic and vulnerability variables (**Table 1.2**). Of note, four demographic variables are significant in predicting *any substance use*: age ($X^2(4)=24.88$, $p<0.001$), living situation ($X^2(8)=46.994$, $p<0.001$), highest parental education ($X^2(6)=58.202$, $p<0.001$) and percentage of students receiving free lunch ($X^2(1)=47.909$, $p<0.001$). All vulnerability variables are significant predictors of *any substance use* (ps<0.001), except for the RCADS Social Phobia ($X^2(1)=1.101$, $p=0.294$) and OCD subscales ($X^2(1)=6.863$, $p=0.009$).

The univariate poisson linear regression predicting *total substances used* (**Table 1.3**) indicated age ($X^2(4)=39.79$, $p<0.001$), speaking language ($X^2(4)=21.416$, $p<0.001$), living situation ($X^2(8)=150.65$, $p<0.001$), highest parental education ($X^2(6)=144.65$, $p<0.001$), the percentages of individuals at the schools that receive free lunch ($X^2(1)=61.607$, $p<0.001$) and all vulnerability variables as significant predictors (ps<0.001). The ordinal linear regression predicting *age of first use* (**Table 1.4**) identified that the demographic variable age ($X^2(3)=49.758$, $p<0.001$) and the vulnerability variables SLS cut off ($X^2(1)=11.793$, $p<0.001$) and RCADS MDD clinical cutoff ($X^2(1)=18.124$, $p<0.001$) as significant predictors.

Cumulative vulnerability score

Similar to the univariate analysis of individual vulnerabilities, the cumulative vulnerability score is a significant predictor of *any substance use* ($X^2(1)=194.56$, $p<0.001$; **Table 1.5**), *total substances used* ($X^2(1) =744.24$, $p<0.001$), and *age of first use* ($X^2(1)=21.36$, $p<0.001$).

Latent class analysis

To identify subgroups of participants based on profiles of vulnerabilities, latent class analysis was performed. The model with the lowest BIC indicated that six latent classes (i.e.,

subgroups) were present across the thirteen vulnerabilities in our sample (**Figure 1.1**). These six subgroups are *Low Vulnerabilities; Anhedonia; Behavioral; Psychiatric, Anhedonia, & Sleeping Problems; Behavioral, Anhedonia, & Sleeping Problems;* and *High Vulnerabilities*. *Low Vulnerabilities,* reported low endorsements of all vulnerabilities and the lowest endorsement of any substance use (21.6%). *Anhedonia* endorsed high levels of anhedonia vulnerabilities (i.e., SHAPS and SLS); 40.0% of individuals in this subgroup endorsed any substance use. *Behavioral* endorsed high levels of behavioral vulnerabilities (i.e., UPPS-P Positive Subscale, UPPS-P Negative Subscale, EATQR-IC) and 41.7% endorsed *any substance use*. *Psychiatric, Anhedonia, & Sleeping Problems* endorsed high levels of the psychiatric (i.e., RCADS and MDQ), anhedonia (i.e., SHAPS and SLS) and sleeping problems (i.e., SPQ) vulnerabilities and 46.8% endorsed *any substance use*. *Behavioral, Anhedonia, & Sleeping Problems* endorsed high levels of the behavioral (i.e., UPPS-P Positive Subscale, UPPS-P Negative Subscale, EATQR-IC) , anhedonia (i.e., SHAPS and SLS) and sleeping problems (i.e., SPQ) vulnerabilities and 55.4% endorsed *any substance use*. *High Vulnerabilities* endorsed high levels of all vulnerabilities and the highest endorsement of *any substance use* (55.7%). The demographic characteristics of each subgroup can be seen in **Table 1.6**. Note significant differences in gender ($p<0.001$), highest parental education ($p<0.001$), the percentage of students receiving reduced lunch at school ($p<0.001$), and race ($p<0.001$) were observed between subgroups.

Next, the relationship between subgroup assignment and outcome measures of interest were assessed (**Table 1.7**). Subgroup assignment was a significant predictor of any substance use ($X^2(5) =178.38$, $p<0.001$), total substances used ($X^2(5)=667.44$, $p<0.001$), and age of first use ($X^2(5)=22.325$, $p<0.001$). Contrast comparisons were performed to see which subgroups differed in their estimates from the *Low Vulnerabilities* subgroup (**Tables 1.8-1.10**). When comparing

any substance use between subgroups, all contrasts were significant (*p*s<0.001; **Table 1.8**). For *total substances used,* all contrasts were significantly different (*p*s<0.001; **Table 1.9**). The contrast comparisons of subgroups for the *age of first use* did not report significant differences (*p*<0.001; **Table 1.10***).*

Discussion

The present study examined the effects of vulnerabilities on any substance use, total substances used, and age of first use in a sample of adolescents in Los Angeles, California. The results of the present study reports: 1) higher cumulative vulnerability scores were associated with higher rates of *any substance use*, higher numbers of *total substances used*, and a lower *age of first substance use*, 2) classes of different vulnerability patterns, and 3) these classes of vulnerabilities are significantly associated with rates of *any substance use*, *total substances used* and *age of first substance use*. These results and future considerations are discussed below.

This study reveals a pattern of substance initiation and use disparity among adolescents with multiple vulnerabilities. Previous literature on the topic of vulnerabilities has reported that the cumulation of vulnerabilities is associated with an increased risk of smoking initiation (Higgins et al., 2016), the number of cigarettes smoked per day (Higgins et al., 2021), measures of heavy smoking, the severity of cigarette dependence and problems trying to quit smoking (Leventhal et al., 2019), and poorer cessation outcomes (Zvolensky et al., 2023). These results extend the literature to include the association between the cumulation of vulnerabilities and *any substance use*, the *total number of substances used*, and the *age of first substance use* among adolescents.

In addition to examining the cumulation of vulnerabilities, the present study examines the latent classes or patterns of vulnerabilities present in the sample of adolescents from California in

the United States. Five distinct classes of individuals with varying degrees of vulnerabilities are reported. Previous literature has examined the intersection of common risk factors and their relation to current smoking status, reporting gradation in vulnerabilities associated with increased current smoking risk (Gaalema et al., 2018; Higgins et al., 2016) and differences in smoking risk with varying combinations of vulnerabilities (e.g., gender and socioeconomic status; Higgins et al., 2015). By examining the co-occurrence of vulnerabilities, researchers and policymakers are better able to tailor treatment and prevention strategies to target populations of individuals most at risk of developing substance use disorders or begin using substances. Without examining intersecting vulnerabilities, we may be ignorant of the individuals who need the most unique and intensive forms of care.

Among the latent class with the fewest vulnerabilities (i.e., *Low Vulnerabilities*), the lowest rates of substance use are observed (**Figure 1.1**). Further, higher proportions of vulnerabilities (i.e., *High Vulnerabilities*) report a higher incidence of substance use (**Figure 1.1**). A moderate amount of substance use is observed in the classes with varying levels of vulnerabilities (i.e., *Anhedonia*; *Behavioral*; and *Psychiatric, Anhedonia, and Sleep*). However, these patterns of vulnerabilities produce similar outcomes (i.e., similar rates of substance use). Additionally, significant associations between the patterns of vulnerabilities (i.e., latent class) and participants' age of first use are observed in this sample. Taken together, the patterns of vulnerabilities observed may inform treatment and prevention strategies unique to groups of adolescents with specific vulnerabilities.

To our knowledge, this is the first investigation of cumulative vulnerabilities and their association with substance use in adolescents. Understanding how these vulnerabilities relate to substance initiation and use throughout adolescence is an important gap with the potential to

inform public health interventions and policies. Adolescence is a period of growth and development associated with increased risk-taking behaviors, emotional reactivity, and autonomy (Casey et al., 2008; Jaworska & MacQueen, 2015). This developmental period is an optimal time for interventions to prevent substance use onset. In addition to this period being developmentally suitable for intervention, adolescents are also in a unique position for interventions when they are enrolled in school. School gives prevention efforts and interventions an ideal physical location to be implemented, as students are present most of the week. These interventions have precedent, as other prevention strategies have taken place in school settings and demonstrated positive outcomes, including interventions for reducing substance use (Das et al., 2016), such as the good behavior game (Kellam et al., 2011). By identifying adolescents or students at risk, we may be able to better help them while they are enrolled in school.

In the present report, the cumulative vulnerability score focused on vulnerabilities related to substance use that may be modifiable, except with a family history of substance use. These modifiable vulnerabilities encompass psychiatric symptomatology, behavioral problems (i.e.,impulsivity), satisfaction with life, and sleeping problems. Although the vulnerabilities defining the cumulative vulnerability score in the present report are heterogeneous, they include factors related to substance use that may also be stigmatized (e.g., family history of substance use and psychiatric symptomatology). These stigmatized variables pose unique opportunities for public health education and de-stigmatizing efforts; perhaps by modifying perceptions and stigma around these vulnerabilities, we can reduce their impact on adolescent substance use. The intersection and culmination of vulnerabilities are important considerations for public health and policy proposals targeting substance use among adolescents because of their role in substance use in this population.

The present study is subject to limitations. First, the cross-sectional design of this study prohibits causal or temporal inferences or conclusions being drawn. Future examinations should investigate the effect of the cumulation of vulnerabilities on substance use over time. Second, the present study did not assess the quantity of substances used, severity, dependence level, or times of use. These varying outcome measures could overlap with vulnerabilities of substance use among adolescents. Third, the measures completed defining our cumulative vulnerability score are self-reports assessed using survey questionnaires and may not capture all aspects of mental health problems or other disorders that may be associated with substance use among adolescents. Further, the cumulative vulnerability score created in this report is by no means exhaustive. Variables that define potentially vulnerable populations, such as physical disability and family income, warrant investigation in future research. For example, previous investigations have examined other vulnerabilities (e.g., employment, educational attainment, income) associated with substance use in adults. These vulnerabilities may not be known or applicable to adolescents still enrolled in high school but may provide further insight into populations of adolescents with unique considerations.

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Table 1.1. Demographic characteristics of the sample.

n	2644
Gender = Male (%)	1171 (44.3)
Age (%)	
12 or younger	1 (0.0)
13	122 (4.6)
14	2193 (82.9)
15	321 (12.1)
16	7 (0.3)
Language Spoken at Home (%)	
English/another language	838 (31.7)
Mostly another language	246 (9.3)
Mostly English	418 (15.8)
Only another language	68 (2.6)
Only English	1074 (40.6)
Speaking Language (%)	
English/another language	1077 (40.7)
Mostly another language	13 (0.5)
Mostly English	599 (22.7)
Only another language	2 (0.1)
Only English	953 (36.0)
Living Situation (%)	
Father	51 (1.9)
Father/stepmother	28 (1.1)
Group Home	51 (1.9)
Mother	361 (13.7)
Mother/Father	1713 (64.8)
Mother/stepfather	194 (7.3)
Other	50 (1.9)
Some Mother/Some Father	145 (5.5)
Someone else	51 (1.9)

Highest Parental Education (%)	
8th or less	81 (3.1)
Advanced degree	466 (17.6)
College graduate	736 (27.8)
Don't know	320 (12.1)
High school graduate	391 (14.8)
Some college	453 (17.1)
Some high school	197 (7.5)
School Free Lunch (mean (SD))	30.03 (19.58)
School Reduced Lunch (mean (SD))	10.02 (5.78)
Race / Ethnicity (%)	
American Indian/Alaska Native	21 (0.8)
Asian	477 (18.0)
Black or African American	121 (4.6)
Multi-ethnic or Multi-racial	1293 (48.9)
Native Hawaiian/Pacific Islander	116 (4.4)
Other	156 (5.9)
White	460 (17.4)
Cumulative Vulnerabilities	3.77 (2.45)
Outcomes	
Any Substance Use = Yes (%)	1026 (38.9)
Total Substances Used (mean (SD))	1.00 (1.87)
Age of First Use (%)	
8 or younger	79 (7.9)
9-10 years old	74 (7.4)
11-12 years old	229 (22.9)
13-14 years old	576 (57.7)
15-16 years old	40 (4.0)

Table 1.2. Chi-Square statistic and p-value from Type III ANOVA on binary generalized logistic regression with demographics and vulnerabilities associated any substance use. Note alpha is 0.001.

Variable	Chi-sq	DF	p-value
Demographics			
Gender	1.842	1	0.175
Age	**24.88**	**4**	**<0.001**
Home Language	2.696	4	0.61
Speaking Language	17.103	4	0.002
Living Situation	**46.994**	**8**	**<0.001**
Highest Parental Education	**58.202**	**6**	**<0.001**
Free School Lunch	**47.909**	**1**	**<0.001**
Reduced School Lunch	2.666	1	0.103
Vulnerabilities (Binary)			
SHAPS	**63.999**	**1**	**<0.001**
SLS	**74.273**	**1**	**<0.001**
MDQ	**43.105**	**1**	**<0.001**
RCADS GAD	**30.295**	**1**	**<0.001**
RCADS MDD	**50.464**	**1**	**<0.001**
RCADS PD	**40.504**	**1**	**<0.001**
RCADS SP	1.101	1	0.294
RCADS OCD	6.863	1	0.009
Fam. Hist. Sub. Use	**83.586**	**1**	**<0.001**
SPQ	**38.607**	**1**	**<0.001**
EATQR-IC	**40.31**	**1**	**<0.001**
UPPSP-Pos	**87.358**	**1**	**<0.001**
UPPSP-Neg	**93.162**	**1**	**<0.001**

Table 1.3. Chi-Square statistic and p-value from Type III ANOVA on poisson generalized linear regression with demographics and vulnerabilities associated with total substances used. Note alpha is 0.001.

Variable	Chi-sq	DF	p-value
Demographics			
Gender	8.042	1	0.005
Age	**39.79**	**4**	**<0.001**
Home Language	10.986	4	0.027
Speaking Language	**21.416**	**4**	**<0.001**
Living Situation	**150.65**	**8**	**<0.001**
Highest Parental Education	**144.65**	**6**	**<0.001**
Free School Lunch	**61.607**	**1**	**<0.001**
Reduced School Lunch	3.559	1	0.059
Vulnerabilities (Binary)			
SHAPS	**273.9**	**1**	**<0.001**
SLS	**329.53**	**1**	**<0.001**
MDQ	**245.96**	**1**	**<0.001**
RCADS GAD	**103.88**	**1**	**<0.001**
RCADS MDD	**249.5**	**1**	**<0.001**
RCADS PD	**210.2**	**1**	**<0.001**
RCADS SP wClinical	**14.371**	**1**	**<0.001**
RCADS OCD	**53.935**	**1**	**<0.001**
Fam. Hist. Sub. Use	**233.97**	**1**	**<0.001**
SPQ	**117.55**	**1**	**<0.001**
EATQR-IC	**103.72**	**1**	**<0.001**
UPPSP-Pos	**361.77**	**1**	**<0.001**
UPPSP-Neg	**367.01**	**1**	**<0.001**

Table 1.4. Chi-Square statistic and p-value from Type III ANOVA on ordinal linear regression with demographics and vulnerabilities associated with age of first substance used. Note alpha is 0.001.

Variable	Chi-sq	DF	p-value
Demographics			
Gender	0.117	1	0.732
Age	**49.758**	**3**	**<0.001**
Home Language	3.636	4	0.458
Speaking Language	8.023	4	0.091
Living Situation	17.439	8	0.026
Highest Parental Education	4.335	6	0.632
Free School Lunch	0.224	1	0.636
Reduced School Lunch	1.273	1	0.259
Vulnerabilities (Binary)			
SHAPS	3.238	1	0.072
SLS	**11.793**	**1**	**<0.001**
MDQ	8.321	1	0.004
RCADS GAD	2.485	1	0.115
RCADS MDD	**18.124**	**1**	**<0.001**
RCADS PD	2.145	1	0.143
RCADS SP wClinical	1.049	1	0.306
RCADS OCD	5.756	1	0.016
Fam. Hist. Sub. Use	5.479	1	0.019
SPQ	1.741	1	0.187
EATQR-IC	2.488	1	0.115
UPPSP-Pos	3.676	1	0.055
UPPSP-Neg	5.709	1	0.017

Table 1.5. Outcome measures predicted by cumulative vulnerabilities. Note alpha is 0.001.

Outcome Measure	**Distribution**	**Chi-Sq**	**DF**	**p-value**
Any substance use	Binary	192.14	1	**<0.001**
Total substances used	Poisson	742.99	1	**<0.001**
Age of first use	Ordinal	22.66	1	**<0.001**

Figure 1.1. Latent class response probabilities for each of the 13 vulnerabilities. The vulnerabilities in the green represent psychiatric symptomatology; red represents behavioral vulnerabilities; pink represents anhedonia; teal is family history of substance use; blue is sleeping problems.

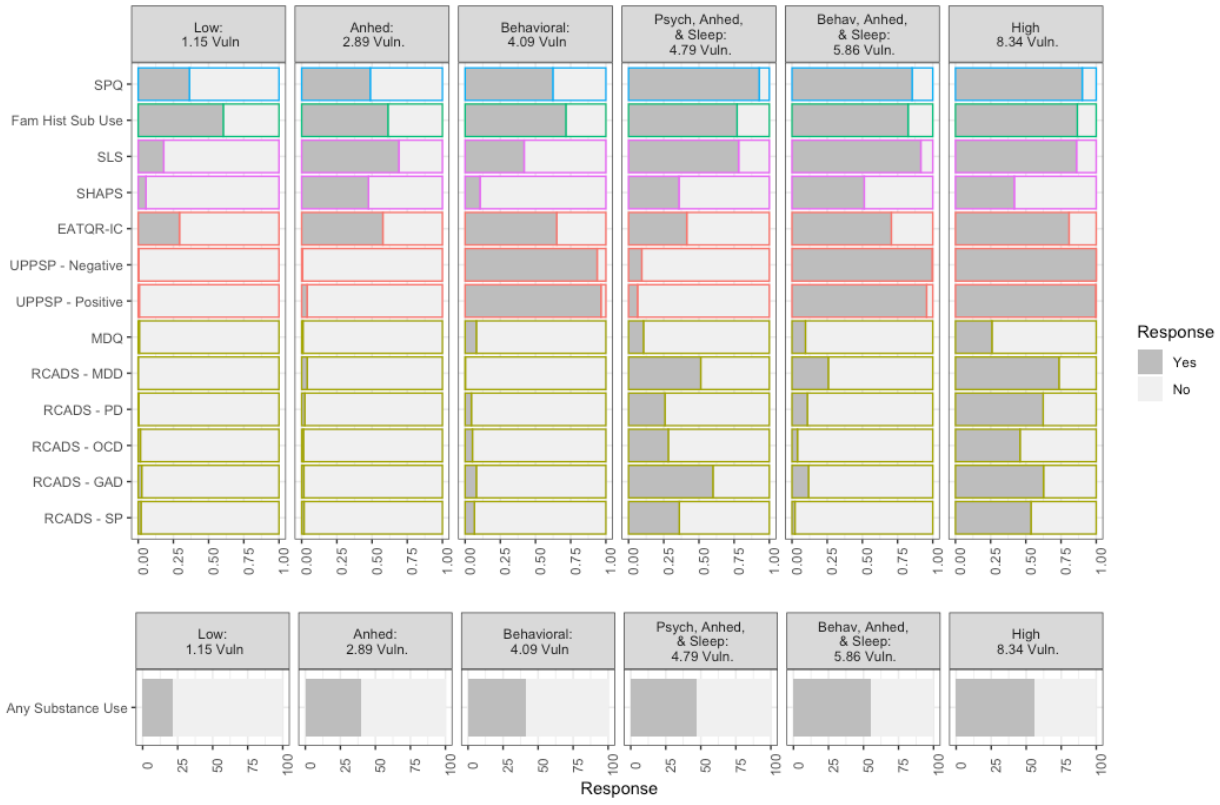

Table 1.6. Outcome measures predicted by latent class. Note alpha is 0.001.

Outcome Measure	Distribution	Chisq	DF	p-value
Any substance use	Binary	178.38	5	**<0.001**
Total substances used	Poisson	667.44	5	**<0.001**
Age of first use	Ordinal	22.325	5	**<0.001**

Table 1.7. Demographics by latent class. Note alpha is 0.001.

	Low	Anhedonia	Behavioral	Psychiatric, Anhedonia, & Sleeping Problems	Behavioral, Anhedonia, & Sleeping Problems	High	p
n	780	346	786	154	287	291	
Gender = Male (%)	370 (47.4)	189 (54.6)	375 (47.7)	51 (33.1)	119 (41.5)	67 (23.0)	<0.001
Age (%)							0.114
12 or younger	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
13	37 (4.7)	18 (5.2)	39 (5.0)	8 (5.2)	9 (3.1)	11 (3.8)	
14	660 (84.6)	265 (76.6)	638 (81.2)	134 (87.0)	248 (86.4)	248 (85.2)	
15	81 (10.4)	61 (17.6)	107 (13.6)	11 (7.1)	30 (10.5)	31 (10.7)	
16	1 (0.1)	2 (0.6)	2 (0.3)	1 (0.6)	0 (0.0)	1 (0.3)	
Language Spoken at Home (%)							0.696
English/another language	258 (33.1)	109 (31.5)	256 (32.6)	41 (26.6)	86 (30.0)	88 (30.2)	
Mostly another language	70 (9.0)	37 (10.7)	72 (9.2)	10 (6.5)	24 (8.4)	33 (11.3)	
Mostly English	109 (14.0)	53 (15.3)	134 (17.0)	29 (18.8)	47 (16.4)	46 (15.8)	
Only another language	17 (2.2)	13 (3.8)	20 (2.5)	2 (1.3)	7 (2.4)	9 (3.1)	
Only English	326 (41.8)	134 (38.7)	304 (38.7)	72 (46.8)	123 (42.9)	115 (39.5)	
Speaking Language (%)							0.007
English/another language	319 (40.9)	146 (42.2)	334 (42.5)	51 (33.1)	113 (39.4)	114 (39.2)	
Mostly another language	4 (0.5)	5 (1.4)	1 (0.1)	0 (0.0)	2 (0.7)	1 (0.3)	
Mostly English	155 (19.9)	77 (22.3)	179 (22.8)	44 (28.6)	68 (23.7)	76 (26.1)	
Only another language	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	
Only English	302 (38.7)	118 (34.1)	272 (34.6)	59 (38.3)	104 (36.2)	98 (33.7)	
Living Situation (%)							0.002
Father	15 (1.9)	7 (2.0)	12 (1.5)	2 (1.3)	6 (2.1)	9 (3.1)	
Father/stepmother	1 (0.1)	2 (0.6)	8 (1.0)	3 (1.9)	4 (1.4)	10 (3.4)	

Group Home	16 (2.1)	8 (2.3)	16 (2.0)	3 (1.9)	3 (1.0)	5 (1.7)	
Mother	85 (10.9)	63 (18.2)	97 (12.3)	28 (18.2)	46 (16.0)	42 (14.4)	
Mother/Father	543 (69.6)	210 (60.7)	534 (67.9)	91 (59.1)	172 (59.9)	163 (56.0)	
Mother/stepfather	54 (6.9)	27 (7.8)	57 (7.3)	8 (5.2)	24 (8.4)	24 (8.2)	
Other	15 (1.9)	6 (1.7)	11 (1.4)	3 (1.9)	5 (1.7)	10 (3.4)	
Some Mother/Some Father	39 (5.0)	18 (5.2)	40 (5.1)	11 (7.1)	19 (6.6)	18 (6.2)	
Someone else	12 (1.5)	5 (1.4)	11 (1.4)	5 (3.2)	8 (2.8)	10 (3.4)	
Highest Parental Education (%)							<0.001
8th or less	19 (2.4)	11 (3.2)	23 (2.9)	4 (2.6)	11 (3.8)	13 (4.5)	
Advanced degree	164 (21.0)	50 (14.5)	149 (19.0)	21 (13.6)	33 (11.5)	49 (16.8)	
College graduate	231 (29.6)	69 (19.9)	243 (30.9)	46 (29.9)	74 (25.8)	73 (25.1)	
Don't know	87 (11.2)	55 (15.9)	83 (10.6)	23 (14.9)	44 (15.3)	28 (9.6)	
High school graduate	116 (14.9)	65 (18.8)	93 (11.8)	21 (13.6)	47 (16.4)	49 (16.8)	
Some college	117 (15.0)	67 (19.4)	141 (17.9)	27 (17.5)	47 (16.4)	54 (18.6)	
Some high school	46 (5.9)	29 (8.4)	54 (6.9)	12 (7.8)	31 (10.8)	25 (8.6)	
School Free Lunch (mean (SD))	29.05 (19.08)	33.04 (19.85)	29.03 (19.40)	32.19 (20.04)	30.20 (19.60)	30.44 (20.49)	0.014
School Reduced Lunch (mean (SD))	10.37 (6.09)	10.93 (6.31)	9.65 (5.50)	10.53 (5.98)	9.65 (5.43)	9.12 (4.97)	<0.001
Race / Ethnicity (%)							<0.001
American Indian/Alaska Native	7 (0.9)	1 (0.3)	7 (0.9)	1 (0.6)	1 (0.3)	4 (1.4)	
Asian	150 (19.2)	51 (14.7)	175 (22.3)	21 (13.6)	40 (13.9)	40 (13.7)	
Black or African American	42 (5.4)	18 (5.2)	30 (3.8)	9 (5.8)	15 (5.2)	7 (2.4)	
Multi-ethnic or Multi-racial	362 (46.4)	206 (59.5)	353 (44.9)	73 (47.4)	157 (54.7)	142 (48.8)	
Native Hawaiian/Pacific Islander	23 (2.9)	7 (2.0)	46 (5.9)	6 (3.9)	5 (1.7)	29 (10.0)	
Other	50 (6.4)	15 (4.3)	42 (5.3)	14 (9.1)	15 (5.2)	20 (6.9)	
White	146 (18.7)	48 (13.9)	133 (16.9)	30 (19.5)	54 (18.8)	49 (16.8)	
Cumulative Vulnerabilities	1.15 (0.74)	2.89 (0.75)	4.09 (1.08)	4.79 (1.48)	5.86 (0.90)	8.34 (1.45)	<0.001
Outcomes							
Any Substance Use = Yes (%)	168 (21.6)	138 (40.0)	327 (41.7)	72 (46.8)	159 (55.4)	162 (55.7)	<0.001

Total Substances Used (mean (SD))	0.40 (0.96)	0.91 (1.71)	1.03 (1.79)	1.13 (1.99)	1.71 (2.37)	1.91 (2.67)	<0.001
Age of First Use (%)							<0.001
8 or younger	12 (7.5)	7 (5.3)	25 (7.8)	5 (7.2)	13 (8.3)	17 (10.8)	
9-10 years old	5 (3.1)	12 (9.0)	20 (6.2)	5 (7.2)	13 (8.3)	19 (12.1)	
11-12 years old	35 (21.7)	32 (24.1)	62 (19.3)	14 (20.3)	39 (25.0)	47 (29.9)	
13-14 years old	99 (61.5)	74 (55.6)	200 (62.1)	44 (63.8)	88 (56.4)	71 (45.2)	
15-16 years old	10 (6.2)	8 (6.0)	15 (4.7)	1 (1.4)	3 (1.9)	3 (1.9)	

Table 1.8. Estimated Marginal Mean Contrasts for any substance use by latent class. The Tukey method was used to adjust for multiple tests. Note alpha is 0.001.

Contrast	Odds Ratio	Z score	p-value
Low and Anhed	**0.413**	**7.13**	**<0.001**
Low and Behav	**0.385**	**8.829**	**<0.001**
Low and Psych, Anhed, & Sleep	**0.314**	**5.449**	**<0.001**
Low and Behav, Anhed, & Sleep	**0.222**	**6.789**	**<0.001**
Low and High	**0.219**	**6.817**	**<0.001**

Table 1.9. Estimated Marginal Mean Contrasts for total substances used by latent class. The Tukey method was used to adjust for multiple tests. Note alpha is 0.001.

Contrast	Ratio	Z score	p-value
Low and Anhed	**0.436**	**-10.16**	**<0.001**
Low and Behav	**0.383**	**-14.141**	**<0.001**
Low and Psych, Anhed, & Sleep	**0.352**	**-10.877**	**<0.001**
Low and Behav, Anhed, & Sleep	**0.232**	**-19.88**	**<0.001**
Low and High	**0.207**	**-21.892**	**<0.001**

Table 1.10. Estimated Marginal Mean Contrasts for age of first use by latent class. The Tukey method was used to adjust for multiple tests. Note alpha is 0.001.

Contrast	Estimate	Z score	p-value
Low and Anhed	0.234	1.001	0.918
Low and Behav	0.112	0.576	0.993
Low and Psych, Anhed, & Sleep	0.246	0.868	0.954
Low and Behav, Anhed, & Sleep	0.472	2.136	0.269
Low and High	0.867	3.982	0.001

MANUSCRIPT 2

Title

Cumulative Vulnerabilities Predict Current and Future Substance Use: A Three Year Study of Adolescents

Abstract

Aims: Vulnerabilities are associated with adult cigarette use. To better understand substance use and initiation among United States adolescents, this study examines the ability of cumulative vulnerability scores to predict substance use longitudinally.

Design: Data were analyzed from the Happiness and Health study; participants were high schoolers from 10 schools across Los Angeles County, California, USA.

Measurements: Participants were asked about substance use and 11 vulnerabilities over time; the presence of these vulnerabilities was summed to create a *cumulative vulnerability score*. The relationship between *cumulative vulnerability score* with any substance use (binary) and total substances used (poisson) was evaluated currently (current) and prospectively (six-months, twelve-months). A principal components analysis and *k*-means clustering was performed to identify subgroups of participants in the sample. These subgroups' relationship with any substance use and total substances used were evaluated.

Findings: *Cumulative vulnerability score* was significantly associated with any substance use at all three-time points (current, six-month, twelve-month; *p*s <0.001). *The cumulative vulnerability score* was also significantly associated with total substances used at all three-time points (*p*s <0.001). Subgroups (i.e., patterns of vulnerabilities) were identified: *Low, Behavioral* and *High.* These subgroups were significantly associated with any substance use and total substances used at each time point (*p*s < 0.001).

Conclusions: The cumulation of vulnerabilities were associated with current substance use and were able to predict substance use prospectively in our sample. The evaluation of these vulnerabilities and their accumulation is an important consideration for policy proposals for adolescent substance use.

Keywords: cumulative vulnerabilities, vulnerability, adolescent, substance use, longitudinal

Introduction

Substance use disorders (SUDs) are reported to affect over 20.4 million individuals aged 12 or older in the United States in 2019 (Abuse, 2020). SUDs pose both an economic and public health burden on the United States and its residents. As an example of economic burdens, in 2010, $250 billion was spent in costs related to excessive drinking alone, including binge drinking and underage drinking (Sacks et al., 2015). Moreover, public health burdens exist for SUDs, including significant medical costs; for example, in 2017 $13 billion were spent in emergency departments and inpatient settings (Peterson et al., 2021).

Several factors are significantly associated with substance use onset, use, and the ultimate development of a substance use disorder, including: culture and society (e.g., laws favoring substance use), interpersonal (e.g., family and peer relationships), psychobehavioral (e.g., internal factors), and biogenetic (e.g., inherited factors), familial, social, and individual risk factors (Newcomb, 1995; Whitesell et al., 2013). Through understanding these factors, we may be better able to prevent SUDs, identify those at risk for the development of SUDs, and treat those with SUDs.

The field of addiction research has identified antecedents to, or factors associated with, substance use, also described as vulnerabilities or characteristics that may be associated with susceptibility to substance use and adverse substance use outcomes. In addition to studying individual vulnerabilities, a body of literature examines the cumulation of these vulnerabilities. Cumulative vulnerabilities, or the presence of a larger number of individual vulnerabilities, are associated with myriad indices of cigarette use among adults, including: increased risk of smoking initiation (Higgins et al., 2016), cigarettes smoked per day (Higgins et al., 2021), measures of heavy smoking, measures of severity of dependence, and indications of more

problems with trying to quit smoking (Leventhal et al., 2019) and worse cessation outcomes (Zvolensky et al., 2023). Additional research reports that the number of cumulative vulnerabilities is significantly and positively correlated with a higher frequency of past 6 month substance use among adolescents (Newcomb, 1995). A cross-sectional analysis of adolescents included in this report demonstrates associations of cumulative vulnerability score and age of first substance use, any substance use, and the total number of substances used in an individual's lifetime.

The present report aims to extend the literature about cumulative vulnerabilities temporally, examining how cumulative vulnerabilities are associated with prospective substance use in a sample of adolescents from California in the United States. The hypotheses are: 1) higher cumulative vulnerability score will be associated with increased substance use cross-sectionally; 2) higher cumulative vulnerability score will predict higher substance use prospectively; 3) patterns of vulnerabilities exist that will be associated with substance use cross-sectionally, and 4) patterns of vulnerabilities will predict substance use prospectively.

Methods

Participants and Procedures

Data were collected in the Happiness & Health Study, a prospective cohort study of behavioral health trends across the lifespan of individuals in Los Angeles County, California, USA. In 9th grade (2013), 3,396 students were enrolled in ten schools throughout the county. Participants provided assent and parental consent before enrolling in the study. Follow-up surveys were conducted semi-annually via paper-and-pencil in the classroom. The University of South California Institutional Review Board approved the study data collection. The work herein is a secondary analysis of the de-identified data. The present report analyzes responses from

seven-time points of data collection over three and a half years: wave 1 (9th grade; fall 2013), wave 2 (9th grade; spring 2014), wave 3 (10th grade; fall 2014), wave 4 (10th grade; spring 2015), wave 5 (11th grade; fall 2015), wave 6 (11th grade; spring 2016), and wave 7 (12th grade; fall 2016). See **Figure 2.1** for more information about time points, waves, and data collected.

Measures

Demographics

Participants' demographic characteristics (i.e., sex, age, race/ethnicity, usual speaking language, usual home language, participant living situation, parental education, and family history of substance use) were collected at wave 1 (fall 2013) using self-report (for response options see **Table 2.1**).

Vulnerabilities (Independent measures)

Participants completed each vulnerability measure at waves 1, 3 and 5 (i.e., fall of 9th, 10th, and 11th grade).

Mood Disorder Questionnaire (MDQ). The MDQ screens individuals for Bipolar Spectrum Disorder, including: Bipolar I, Bipolar II, and Bipolar Not Otherwise Specified (Hirschfeld et al., 2000). The 15-items of the MDQ are answered on a 4-point Likert scale (0 = no problem, 3 = serious problem). Item responses are summed and compared to a cut-off score (i.e., meets criteria for mood disorder or does not). A binary variable of meeting the weighted clinical cut off was used for defining the vulnerability.

Revised Children's Anxiety and Depression Scale (RCADS) subscales. The RCADS assesses symptoms of anxiety and depression in children and adolescents (Chorpita et al., 2000, 2005). The RCADS is composed of six subscales; however, five subscales were used in the present study: Generalized Anxiety Disorder (GAD), Major Depression Disorder (MDD), Panic Disorder

(PD), Social Phobia (SP), and Obsessive Compulsive Disorder (OCD). All items of the RCADS are answered on a 4-point Likert scale (0 = never, 3 = always). Scores are summed and compared to a cut-off score (i.e., meets criteria for disorder or does not). A binary variable of meeting the weighted clinical cut off for each of the subscales was used for defining the vulnerability.

Snaith-Hamilton Pleasure Scale (SHAPS). The SHAPS assesses anhedonia, or the absence of hedonic tone (Snaith et al., 1995). The SHAPS comprises 14 items that are answered on a 4-point Likert scale (1 = strongly disagree, 4 = strongly agree). Scores are compared to a cut-off to obtain a clinical level of anhedonia (Snaith et al., 1995). A binary variable of meeting the weighted clinical cut off was used for defining the vulnerability.

Satisfaction with Life Scale (SLS). The SLS measures the global cognitive judgments of one's life satisfaction (Diener et al., 1985). The scale's five items are scored on a 7-point Likert scale (0 = strongly disagree, 6 = strongly agree). Scores are summed and divided by the number of items to obtain a mean score; higher scores indicate greater life satisfaction. The mean SLS score was used for analyses.

Sleep Problems Questionnaire (SPQ). The SPQ is similar to the Jenkin's Sleep Questionnaire (Jenkins et al., 1988) and assesses an individual's sleep disturbances. The SPQ consists of four items about sleeping behaviors in the past month (i.e., 30 days); items were answered on a 5-point scale (1 = not at all, 5 = 22-30 days). Scores of each item are summed; higher scores indicate greater sleep disturbances. The weighted sum of the SPQ was used in analyses.

Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale (UPPS-P) subscales. The positive and negative urgency subscales of the UPPS-P assess emotional reactivity to negative and positive experiences (Cyders et al., 2007; Whiteside & Lynam, 2001). The negative urgency subscale consists of 12 items, and the

positive urgency subscale consists of 14 items. All items are responded to on a 4-point Likert scale (1 = definitely true to 4 = definitely false). Scores are summed across subscales, with higher scores reflecting a more emotion-based rash action. The weighted sum for each subscale was used in the analyses.

Cumulative Vulnerability Score. To evaluate the accumulation of vulnerabilities, a global score of participants' vulnerabilities for the 11 measures previously described was created for waves 1, 3, and 5. For items with clinical cut-offs (RCADS subscales, MDQ, SHAPS), participants' vulnerability score increased for each cut off they met. A median split was calculated for all other items (SLS, SPQ, UPPS-P subscales). Participants in the more "vulnerable" median were assigned the vulnerability (e.g., UPPS-P subscale scores greater than the median are assigned the vulnerability). The total number of vulnerabilities a participant indicated were summed for a vulnerability score, hereby referred to as *cumulative vulnerability score* at waves 1, 3, and 5. The range of cumulative vulnerabilities was 0 to 11. See **Table 2.2** for the distribution of *cumulative vulnerability scores* and endorsements of individual vulnerability items.

Substance use measures (Dependent measures)

Any substance use*:* At all seven waves, participants were asked "Have you used this substance in the last six months" about 23 substances: a few puffs of a cigarette, a whole cigarette, electronic cigarettes, smokeless tobacco, big cigars, little cigars or cigarillos, hookah water pipe, blunts, other forms of tobacco, cannabis (assessed by "marijuana"), one full drink of alcohol, inhalants, cocaine, methamphetamine, LSD/mushrooms/or other psychedelics, ecstasy, heroin, salvia, prescription painkillers to get "high", tranquilizers or sedatives, diet pills, prescription stimulant to get "high", and any other pill or illegal drug to get high. An additional fictitious substance,

derbisol, was included to test the reliability of answers received by students at each wave. Due to the evolving substance environment, new substances were included at subsequent waves: cannabis edibles (introduced at wave 3), synthetic cannabis (introduced at wave 3), electronic cannabis (introduced at wave 4), bath salts (introduced at wave 4), electronic cigarettes without nicotine (introduced at wave 5), and dabbing (introduced at wave 6). Items were answered as a binary response of "Yes" or "No" for each substance. The outcome of *any substance use* was defined as a binary indication of "Yes" to any of the substances listed above at each wave; see **Table 2.3** for proportions of individuals endorsing "Yes" for at least one substance in the past six months at each wave.

Total substances used*:* At each of the seven waves, the total number of substances participants endorsed derived from the above original 23 substances were summed up for the total substances used score. The total substances used score was calculated by summing the use of the following classes of substances at wave 1 through wave 7: alcohol, illicit stimulants (i.e., cocaine, methamphetamine, ecstasy), prescription stimulants (i.e., diet pills, prescription stimulants), opioids (i.e., heroin, prescription painkillers), e-cigarettes, cigarettes (i.e., a few puffs of a cigarette, whole cigarette), cigars (i.e., big cigars, little cigars or cigarillos), marijuana (i.e., blunts, marijuana), smokeless tobacco, hookah water pipe, inhalants, psychedelics, salvia, and tranquilizers or sedatives. The range of *total substances used* was 0 to 14; see **Table 2.3** for median score and interquartile range at each wave.

Substance use timepoints:

Current substance use. Current substance use was defined as substance use at the waves where vulnerabilities were assessed (i.e., waves 1, 3, and 5; **Figure 2.1**). For example, substance use collected at wave 1 was considered current substance use for wave 1 vulnerabilities. Six-month

substance use was defined as substance use at the data collection time-point immediately following vulnerability assessment (i.e., waves 2, 4, 6; **Figure 2.1**). Similarly, substance use collected at wave 2 was considered six-month substance use for wave 1 vulnerabilities. Twelve-month substance use was defined as substance use at the data collection timepoint one year past the assessment of vulnerabilities (i.e., waves 3, 5, 7; **Figure 2.1**) with substance use collected at wave 3 considered the twelve-month substance use for wave 1 vulnerabilities.

Substance use outcome measures (i.e., binary *any substance use* and poisson t*otal substance used*) were evaluated at current, six-month, and twelve-month time points.

Data analysis

The analytical dataset for the present report was 1,760 individuals who responded to all eleven vulnerabilities at waves 1, 3, and 5. Participants' characteristics were described using mean (standard deviation), median (interquartile range [IQR]), and frequency (percentages) where appropriate.

To evaluate the effect of cumulative vulnerabilities on *any substance use* at each time-point (i.e., current, six-months, and twelve-months), a binary logistic regression with a random effect per participant and unstructured correlation structure was performed. We considered an autoregressive correlation structure at time-point per participant and a random effect per participant. To evaluate the effect of cumulative vulnerabilities on *total substances used* at each time-point, a poisson linear regression with a random effect per participant was performed. We considered both an unstructured correlation structure and an autoregressive correlation structure at time-point per participant. For *any substance use* and *total substances used,* models with and without the autoregressive correlation structure were compared using Bayesian Information Criterion (BIC); the model with the lowest BIC was considered optimal and used for analyses.

For each time point for *any substance use*, the model without the autoregressive correlation structure was considered optimal and was reported. For each time point for *total substances used*, the model with the autoregressive correlation structure was considered optimal and reported. To evaluate the significance of each model, a Type III Sums of Squares ANOVA was performed.

Next, we evaluated the patterns of vulnerabilities present in the model using a principal component analysis (PCA) on the continuous scores of the vulnerabilities (`psych` (Revelle, n.d.)). The optimal number of components was determined by the number of eigenvalues greater than "1" (l=3). Following the PCA, k-means clustering analysis was performed. The optimal number of clusters was determined through the elbow method via the within-cluster sums of squares ("wss") method; the optimal number of clusters (k=3) was determined to assist interpretability while balancing the within-cluster sums of squares. Similarly to the above, we evaluated *any substance use,* and *total substances-used* outcomes predicted by cluster assignment.

To further assess predictive performance of cumulative vulnerabilities and cluster assignment on *any substance use*, a Receiver Operator Characteristic (ROC) curve was evaluated using area under the ROC curve (AUC). A maximum value of 1.0 of AUC indicates a perfect relationship (i.e., 100% specific and 100% sensitive in predicting substance use). In contrast, an AUC value of 0.50 indicates that the model is no better than random (i.e., 50% specific and 50% sensitive). In general, AUC values between 0.70 and 0.80 are considered "acceptable", values between 0.80 and 0.90 are considered "excellent", and those greater than 0.90 are considered "outstanding" (Mandrekar, 2010). In addition to the AUC value, a 95% confidence interval was calculated.

For this analysis, we used the following packages: `lme4` (Bates et al., 2015), `glmmTMB` (Brooks et al., 2017), `car` (Fox, n.d.), `stats` (Team, 2018), `factoextra` (Alboukadel & Fabian, 2020), and `pROC` (Robin et al., 2011). All statistical analyses were performed in R version 3.5.1 (Team, 2018). Significance in the present report was defined as $p < 0.001$ to adjust for multiple tests.

Results

Demographic characteristics

The demographic characteristics of the sample can be seen in **Table 2.1**. Overall, the majority of participants were female (57.9%), 14 years old at wave 1 (84.5%), multi-ethnic or multi-racial (48.8%).

Cumulative Vulnerabilities

The distribution of cumulative vulnerability scores can be seen in **Table 2.2**. When evaluating substance use outcomes (i.e., current, six-months, and twelve-months), significant associations between cumulative vulnerability score and each outcome were observed (**Table 2.4**). Specifically, higher cumulative vulnerability score was significantly associated with higher current *any substance use* (X2(1) = 106.34; $p<0.001$; OR [95% CI] = 1.269 [1.213,1.328]), and predicted higher six-month *any substance use* (X2(1) = 80.04; $p<0.001$; OR [95% CI] = 1.243 [1.185,1.304]), and higher twelve-month *any substance use* (X2(1) = 34.15; $p<0.001$; OR [95% CI] = 1.144 [1.093,1.196]). Moreover, significant associations between higher cumulative vulnerability scores and higher current *total substances used* (X2(1) = 113.08; $p<0.001$), significant predictions of higher six-month *total substances used* (X2(1) = 68.98; $p<0.001$), and higher twelve-month *total substances used* (X2(1) = 21.63; $p<0.001$) were observed.

Patterns of Vulnerabilities

To evaluate the patterns of vulnerabilities present in the sample, a principal components analysis (PCA) was performed. The visualization of factor loadings can be seen in **Figure 2.2**; three components were present in the sample: psychiatric, behavioral, and anhedonia. The results of k-means clustering indicated three subgroups of participants were present in the sample (**Figure 2.3**): *Low Vulnerabilities, Behavioral Vulnerabilities,* and *High Vulnerabilities.* The *Low* subgroup demonstrated low factor loadings on all three components; the *Behavioral* subgroup had high factor loadings on the Behavioral component, and *High* indicated high factor loadings on all three components. Significant associations were observed between the subgroup assignment and each outcome (**Table 2.4**). Specifically, subgroup assignment was significantly associated with current *any substance use* (X2(2) = 93.53; $p<0.001$), and predicted six-month *any substance use* (X2(2) = 81.67; $p<0.001$), and twelve-month *any substance use* (X2(2) = 56.96; $p<0.001$). Additionally, significant relationships between subgroup assignment and *total substances used* were observed (**Table 2.5**), including current *total substances used* (X2(2) = 92.51; $p<0.001$), six-month *total substances used* (X2(2) = 53.44; $p<0.001$), and twelve-month *total substances used* (X2(2) = 41.67; $p<0.001$).

To further evaluate differences between subgroups and substance use outcomes, Tukey-adjusted estimated marginal means comparisons by subgroup were performed for each outcome (current: **Table 2.6**; six-month: **Table 2.7**; twelve-month: **Table 2.8**). Significant differences between the *Low* and *Behavioral* and the *Low* and *High* subgroups for current *any substance use* and current *total substances used* (*p*s <0.001; **Table 2.6**) were observed, where low had significantly lower substance use. For six-month substance use, significant differences in all contrasts (*p*s <0.001; **Table 2.7**) were observed, where *Low* reported lower substance use than *High,* and *Behavioral* reported lower substance use than *High.* The only non-significant contrast

for six-month substance use was the contrast *Low* and *Behavioral* for *total substances used* (p=0.018). For twelve-month *any substance use* (**Table 2.8**), significant differences between *Low* and *Behavioral* and the *Low* and *High* were observed (ps<0.001), where *Low* reported lower substance use than the other subgroups; for *total substances used* at twelve months, the single significant contrast was *Low* and *High* (p<0.001), where low indicated fewer substances used.

Receiver Operator Characteristics for Outcome Measures

To evaluate the predictive ability of our models for *any substance use* at each time point, the area under the Receiver Operator Characteristic (ROC) Curve was evaluated (**Table 2.9**; **Figures 2.4-2.9**). **Figure 2.4** demonstrates the ROC Curve and AUC for current *any substance use* predicted by cumulative vulnerabilities (AUC [95% CI]: 0.947 [0.942-0.952]; "outstanding"); **Figure 2.5** represents six-month *any substance use* by cumulative vulnerabilities (AUC [95% CI]: 0.954 [0.950-0.959]; "outstanding"); and **Figure 2.6** represents twelve-month *any substance use* by cumulative vulnerabilities (AUC [95% CI]: 0.945 [0.940-0.950]; "outstanding"). The AUC for substance use outcomes by subgroup assignment was also evaluated (**Figures 2.7-2.9**). Current *substance use* by subgroup assignment can be seen in **Figure 2.7** (AUC [95% CI]: 0.948 [0.942-0.953]; "outstanding"); while six-month *any substance use* (AUC [95% CI]: 0.956 [0.951-0.960]; "outstanding") and twelve-month *any substance use* (AUC [95% CI]: 0.948 [0.943-0.953]; "outstanding") can be seen in **Figure 2.8** and **Figure 2.9**, respectively.

Discussion

The present report examined the association of a cumulative vulnerability score with substance use outcomes (i.e., any substance use and total substances used) currently, up to six-months, and twelve-months. Consistent with our hypotheses, the main results are: 1) a higher

cumulative vulnerability score is associated with current substance use; 2) a higher cumulative vulnerability score was able to predict increased substance use at six-months and twelve-months; 3) patterns of common vulnerabilities emerged in the sample, and these subgroups are significantly associated with substance use outcomes currently, 4) the subgroups of vulnerabilities were able to predict substance use prospectively. Moreover, the models predicting substance use at each time point had outstanding predictive ability when analyzed using area under the ROC curve. Below, the findings, their relevance, and future directions are discussed.

The results presented herein are consistent with the extant literature in adults who smoke cigarettes (Gaalema et al., 2018; Higgins et al., 2021; Leventhal et al., 2019; Zvolensky et al., 2023), that higher cumulative vulnerability scores are associated with higher substance use, defined in the present report as any substance use and total substances used. The results reported about current substance use are consistent with a cross-sectional analysis of cumulative vulnerability scores and substance use among adolescents from the same sample at the baseline wave. Further, the literature is extended by evaluating these relationships temporally, or prospectively and reporting higher cumulative vulnerability scores are predictive of increased endorsement of any substance use at six- and twelve-months prospectively. Additionally, the present report indicates for the first time that higher cumulative vulnerability scores are associated with increased total substances used both currently and predictive of total substances used prospectively (i.e., six- and twelve-months in the future).

In addition to the cumulative vulnerability score, a principal components analysis and k-means clustering was performed to identify relevant subgroups of participants with similar vulnerabilities in the sample. Consistent with previous literature examining co-occurring vulnerabilities (Gaalema et al., 2018; Higgins et al., 2015), subgroups of participants were

identified with different patterns of vulnerabilities endorsed: *Low*, *Behavioral,* and *High*. Subgroup assignment was significantly associated with current substance use and substance use prospectively across both outcomes: any substance use and total substances used. Moreover, significant differences between the *Low* and *High* subgroups (i.e., current any, current total, six-month any, six-month total, twelve-month any, twelve-month total) were observed in all comparisons. This suggests that both the number of cumulative vulnerabilities and the pattern of those endorsed is an important consideration.

For further investigation of the predictive ability of our models, an analysis of the area under the Receiver Operator Characteristics curve (AUC) was performed for our models evaluating any substance use. All six models provided an "outstanding" predictive ability. The AUCs reported here suggest that the ability of the cumulative vulnerability score is much better than chance to provide a prediction of outcome (i.e., any substance use). The AUCs reported herein extend the literature to provide an estimate of the cumulative vulnerability score's predictive ability in determining adolescent substance use.

Taken together, these results support the notion that cumulative vulnerability scores are related to future substance use. Although the present report did not examine the mechanisms of these relationships, higher cumulative vulnerability scores are associated with a higher incidence of substance use (i.e., any substance use) and a higher total number of substances used temporally can be concluded. Future investigations should consider examining changes in vulnerabilities and changes in substance use. That is, do decreases in cumulative vulnerability scores also associate with or predict decreases in substance use? Dissecting this question may lead to innovation opportunities for identifying individuals at risk for substance use and providing novel tangential treatment targets related to substance use outcomes. Another

worthwhile investigation for future research is understanding the pathway at play in the reported relationship. Possibly the pattern of vulnerabilities is cyclical; that is, increased vulnerabilities leads to increased substance use, that leads to increased vulnerabilities. Parsing out this pattern, and, furthermore, identifying mechanisms that may mediate or moderate this relationship would be novel and necessary pursuits for understanding the causal pathway.

Despite the important findings, limitations of the present work should be acknowledged. First, the definition of our outcome current substance use is a cross-sectional, albeit retrospective, examination of substance use at the same time point when vulnerabilities were assessed. Although causality cannot be implied from these relationships, the cross-sectional association of the cumulative vulnerability score and substance use is important for extending the analysis temporally. A second limitation is that although the waves of data were collected in the fall and spring of school years, the retrospective analysis of 6 months may not completely cover the time elapsed between assessments. Gaps in the assessments could exist, and small gaps in between waves of data may be present (i.e., completed W2 in spring 2014 seven months after W1 in fall 2013). A third important limitation is that data collection is capturing a small snapshot of dynamic and modifiable vulnerabilities at each time point. These scales, symptoms, and assessments could prove to be more dynamic than the rate of assessment (i.e., yearly in the present report). Future research could examine these vulnerabilities in different study designs (e.g., intensive longitudinal design) that would allow for a more fluid analysis of vulnerabilities over the course of adolescence.

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Figure 2.1. Diagram of data collection time points and substance use definitions.

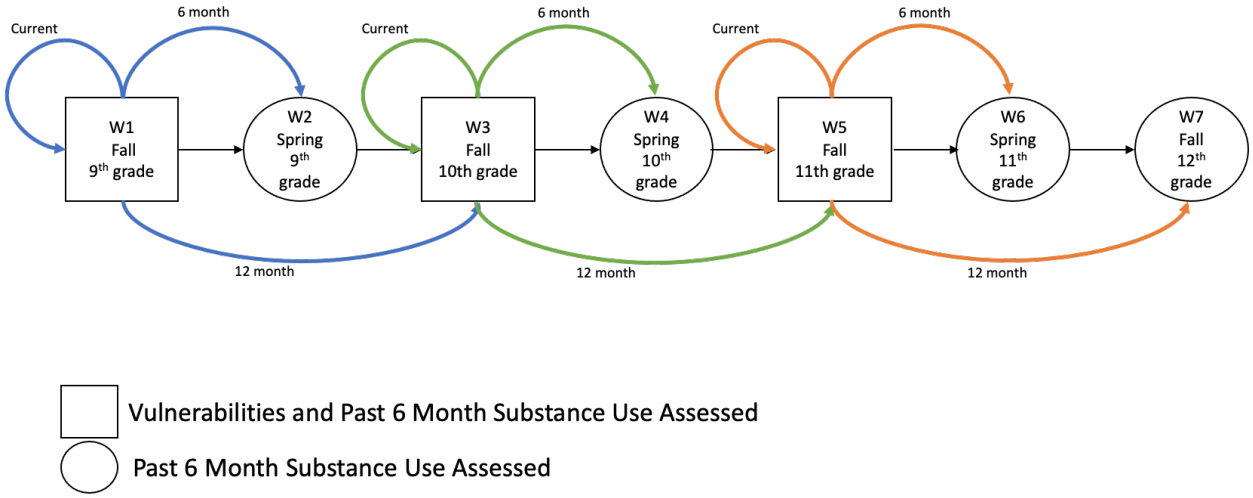

Table 2.1. Demographic characteristics of participants in the sample.

n	1760
Gender = Male (%)	741 (42.1)
Age (%)	
13	81 (4.6)
14	1486 (84.5)
15	187 (10.6)
16	4 (0.2)
Race/Ethnicity (%)	
American Indian/Alaska Native	14 (0.8)
Asian	362 (20.6)
Black or African American	64 (3.6)
Multi-ethnic or Multi-racial	859 (48.8)
Native Hawaiian/Pacific Islander	77 (4.4)
Other	94 (5.3)
White	290 (16.5)
Language Spoken at Home (%)	
English/another language	573 (33.6)
Mostly another language	159 (9.3)
Mostly English	264 (15.5)
Only another language	40 (2.3)
Only English	669 (39.2)
Speaking Language (%)	
English/another language	723 (42.5)
Mostly another language	8 (0.5)
Mostly English	374 (22.0)
Only another language	3 (0.2)
Only English	595 (34.9)
Living Situation (%)	
Father	32 (1.8)
Father/stepmother	15 (0.9)
Group Home	34 (1.9)

Mother	220 (12.6)
Mother/Father	1189 (68.1)
Mother/stepfather	111 (6.4)
Other	28 (1.6)
Some Mother/Some Father	85 (4.9)
Someone else	32 (1.8)
Highest Parental Education (%)	
8th or less	61 (3.5)
Advanced degree	314 (17.8)
College graduate	512 (29.1)
Don't know	207 (11.8)
High school graduate	239 (13.6)
Some college	301 (17.1)
Some high school	126 (7.2)

Table 2.2. Individual vulnerability items and cumulative scores.

Vulnerability Endorsement	Wave 1	Wave 3	Wave 5
SHAPS	420 (23.9)	438 (24.9)	344 (19.5)
MDQ	118 (6.7)	116 (6.6)	75 (4.3)
RCADS GAD	282 (16.0)	245 (13.9)	152 (8.6)
RCADS MDD	259 (14.7)	294 (16.7)	212 (12.0)
RCADS PD	191 (10.9)	196 (11.1)	139 (7.9)
RCADS SP	200 (11.4)	158 (9.0)	180 (10.2)
RCADS OCD	159 (9.0)	158 (9.0)	53 (3.0)
UPPSP Positive Urges	906 (51.5) (median [IQR]: 22.96 [17.36, 30.80])	960 (54.5) (median [IQR]: 17.0 [14.0, 28.0])	932 (53.0) (median [IQR]: 18.0 [14.0, 28.0])
UPPSP Negative Urges	905 (51/4) (median [IQR]: 19.64 [14.73, 26.18])	911 (51.8) (median [IQR]: 22.0 [16.0,30.0])	933 (53.0) (median [IQR]: 24.0 [16.0, 31.0])
SPQ	1076 (61.1) (median [IQR]: 7.0 [5.0, 10.0])	926 (52.6) (median [IQR]: 8.0 [5.0, 11.0])	919 (52.2) (median [IQR]: 8.0 [5.0, 11.0])
SLS	920 (52.3) (median [IQR]: 4.0 [3.0, 4.8])	915 (52.0) (median [IQR]: 3.8 [2.6, 4.8])	940 (53.4) (median [IQR]: 3.6 [2.4, 4.6])
Cumulative Vulnerabilities (%)			
0	251 (14.3)	255 (14.5)	241 (13.7)
1	281 (16.0)	268 (15.2)	315 (17.9)
2	257 (14.6)	287 (16.3)	308 (17.5)
3	274 (15.6)	303 (17.2)	321 (18.2)
4	245 (13.9)	226 (12.8)	246 (14.0)
5	181 (10.3)	170 (9.7)	140 (8.0)
6	110 (6.2)	103 (5.9)	94 (5.3)
7	65 (3.7)	65 (3.7)	48 (2.7)
8	61 (3.5)	37 (2.1)	30 (1.7)
9	20 (1.1)	23 (1.3)	11 (0.6)
10	14 (0.8)	17 (1.0)	4 (0.2)

11	1 (0.1)	6 (0.3)	2 (0.1)

Table 2.3. Substance use outcomes.

	Endorsement (%) / Median [IQR]	Number of missing observations (%)	Time
Wave 1 Past Six-Month Substance Use = Yes (%)	412 (23.5)	6 (0.3)	fall 9th grade
Wave 2 Past Six-Month Substance Use = Yes (%)	625 (36.0)	22 (1.2)	spring 9th grade
Wave 3 Past Six-Month Substance Use = Yes (%)	600 (34.3)	13 (0.7)	fall 10th grade
Wave 4 Past Six-Month Substance Use = Yes (%)	599 (34.5)	22 (1.2)	spring 10th grade
Wave 5 Past Six-Month Substance Use = Yes (%)	624 (35.9)	21 (1.2)	fall 11th grade
Wave 6 Past Six-Month Substance Use = Yes (%)	695 (40.4)	40 (2.3)	spring 11th grade
Wave 7 Past Six-Month Substance Use = Yes (%)	757 (43.8)	30 (1.7)	fall 12th grade
Wave 1 Total Substances Used (median [IQR])	0 [0,0]	91 (5.2)	fall 9th grade
Wave 2 Total Substances Used (median [IQR])	0 [0,1]	41 (2.3)	spring 9th grade
Wave 3 Total Substances Used (median [IQR])	0 [0,1]	32 (1.8)	fall 10th grade
Wave 4 Total Substances Used (median [IQR])	0 [0,1]	56 (3.2)	spring 10th grade
Wave 5 Total Substances Used (median [IQR])	0 [0,1]	38 (2.2)	fall 11th grade
Wave 6 Total Substances Used (median [IQR])	0 [0,1]	125 (7.1)	spring 11th grade
Wave 7 Total Substances Used (median [IQR])	0 [0,1]	161 (9.1)	fall 12th grade

Table 2.4. Outcome measures predicted by cumulative vulnerabilities. Note alpha is 0.001.

Any Substance Use	**Distribution**	**Chisq**	**DF**	**p-value**	**Odds Ratio (95% CI)**
Current any substance use	Binary	106.43	1	**<0.001**	**1.269 (1.213,1.328)**
Six-month any substance use	Binary	80.04	1	**<0.001**	**1.243 (1.185, 1.304)**
Twelve-month any substance use	Binary	34.15	1	**<0.001**	**1.144 (1.093, 1.196)**
Total Substances Used					
Current total substances used	Poisson	113.08	1	**<0.001**	-
Six-month total substances used	Poisson	68.98	1	**<0.001**	-
Twelve-month total substances used	Poisson	21.63	1	**<0.001**	-

Figure 2.2. Principal Components Analysis visualization.

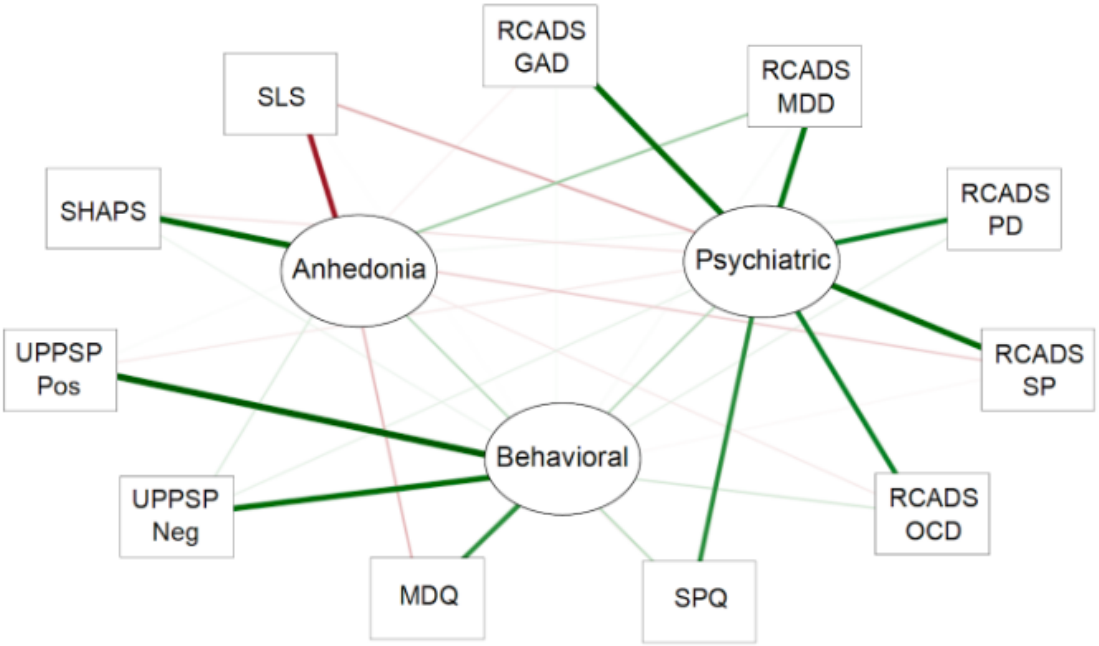

Figure 2.3. Mean factor loadings for the three subgroups identified by k-means clustering.

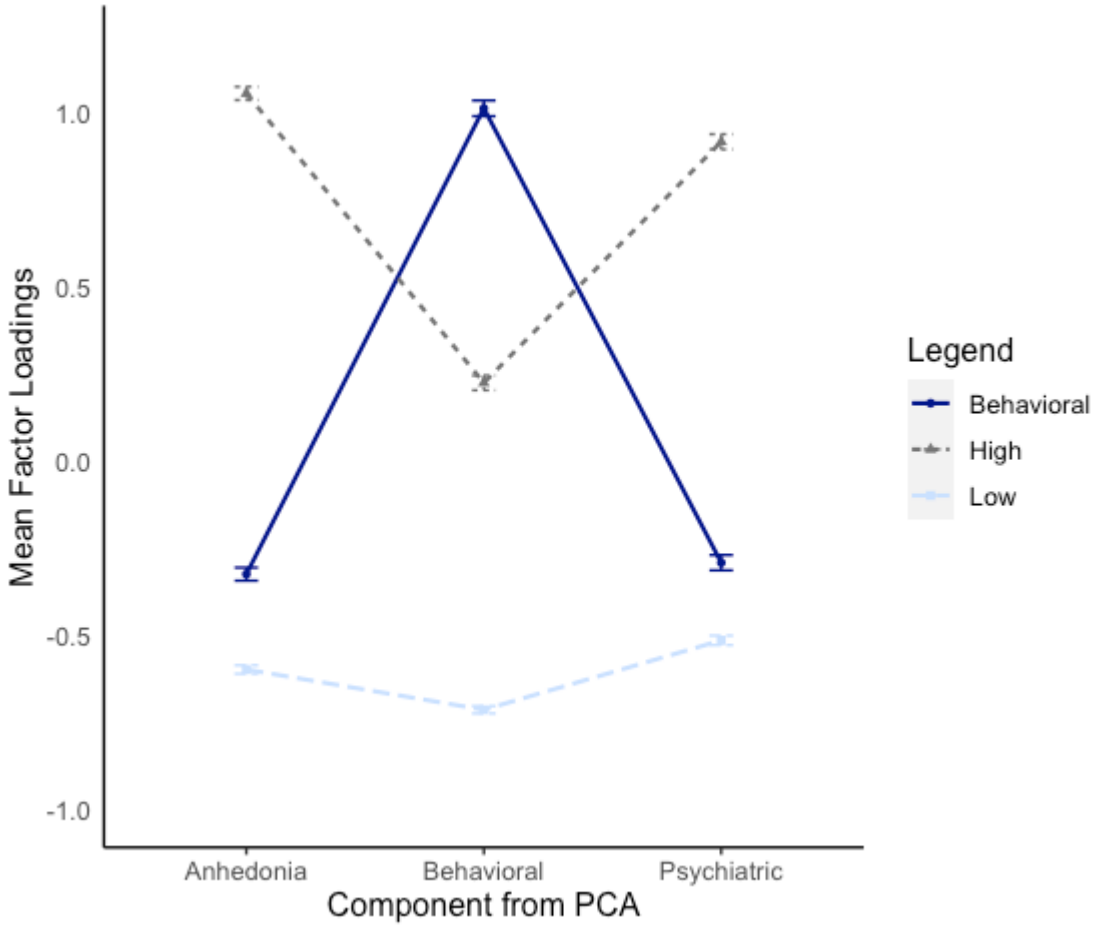

Table 2.5. Outcome measures predicted by cluster assignment. Note alpha is 0.001.

Any Substance Use	**Distribution**	**Chisq**	**DF**	**p-value**
Current substance use	Binary	93.53	2	**<0.001**
Six-month substance use	Binary	81.67	2	**<0.001**
Twelve-month substance use	Binary	56.96	2	**<0.001**
Total Substances Used				
Current total substances used	Poisson	92.51	2	**<0.001**
Six-month total substances used	Poisson	53.44	2	**<0.001**
Twelve-month total substances used	Poisson	41.67	2	**<0.001**

Table 2.6. Estimated Marginal Mean Contrasts for current outcomes by subgroup. The Tukey method was used to adjust for multiple tests. Note alpha is 0.001.

Any Substance Use Contrasts	**Estimate**	**Z Score**	**p-value**
Low and Behavioral	-0.753	-6.176	**<0.001**
Low and High	-1.114	-9.467	**<0.001**
Behavioral and High	-0.361	-2.924	0.01
Total Substances Used Contrasts	**Estimate**	**T Score**	**p-value**
Low and Behavioral	-0.487	-6.284	**<0.001**
Low and High	-0.708	-9.516	**<0.001**
Behavioral and High	-0.221	-3.022	0.007

Table 2.7. Estimated Marginal Mean Contrasts for six-month outcomes by subgroup. The Tukey method was used to adjust for multiple tests. Note alpha is 0.001.

Any Substance Use Contrasts	**Estimate**	**Z score**	**p-value**
Low and Behavioral	-0.653	-5.01	**<0.001**
Low and High	-1.109	-8.973	**<0.001**
Behavioral and High	-0.474	-3.615	**<0.001**
Total Substances Used Contrasts	**Estimate**	**T Score**	**p-value**
Low and Behavioral	-0.19	-2.717	0.018
Low and High	-0.484	-7.182	**<0.001**
Behavioral and High	-0.294	-4.444	**<0.001**

Table 2.8. Estimated Marginal Mean Contrasts for twelve-month outcomes by subgroup. The Tukey method was used to adjust for multiple tests. Note alpha is 0.001.

Any Substance Use Contrasts	**Estimate**	**Z score**	**p-value**
Low and Behavioral	-0.53	-4.38	**<0.001**
Low and High	-0.8712	-7.451	**<0.001**
Behavioral and High	-0.343	-2.731	0.017
Total Substances Used Contrasts	**Estimate**	**T Score**	**p-value**
Low and Behavioral	-0.21	-3.133	0.005
Low and High	-0.408	-6.453	**<0.001**
Behavioral and High	-0.199	-3.08	0.006

Figure 2.4. Area under the Receiver Operator Characteristics Curve for current any substance use predicted by cumulative vulnerabilities.

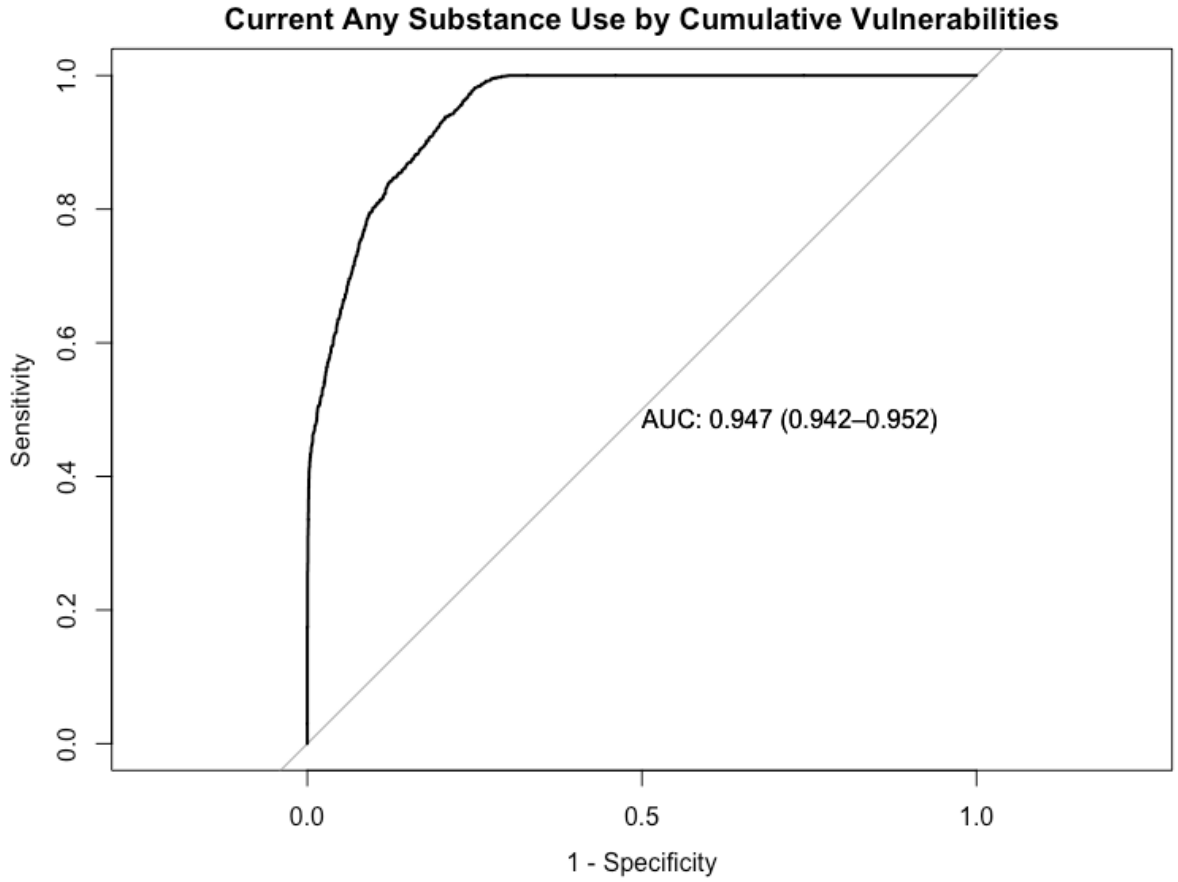

Figure 2.5. Area under the Receiver Operator Characteristics Curve for six-month any substance use predicted by cumulative vulnerabilities.

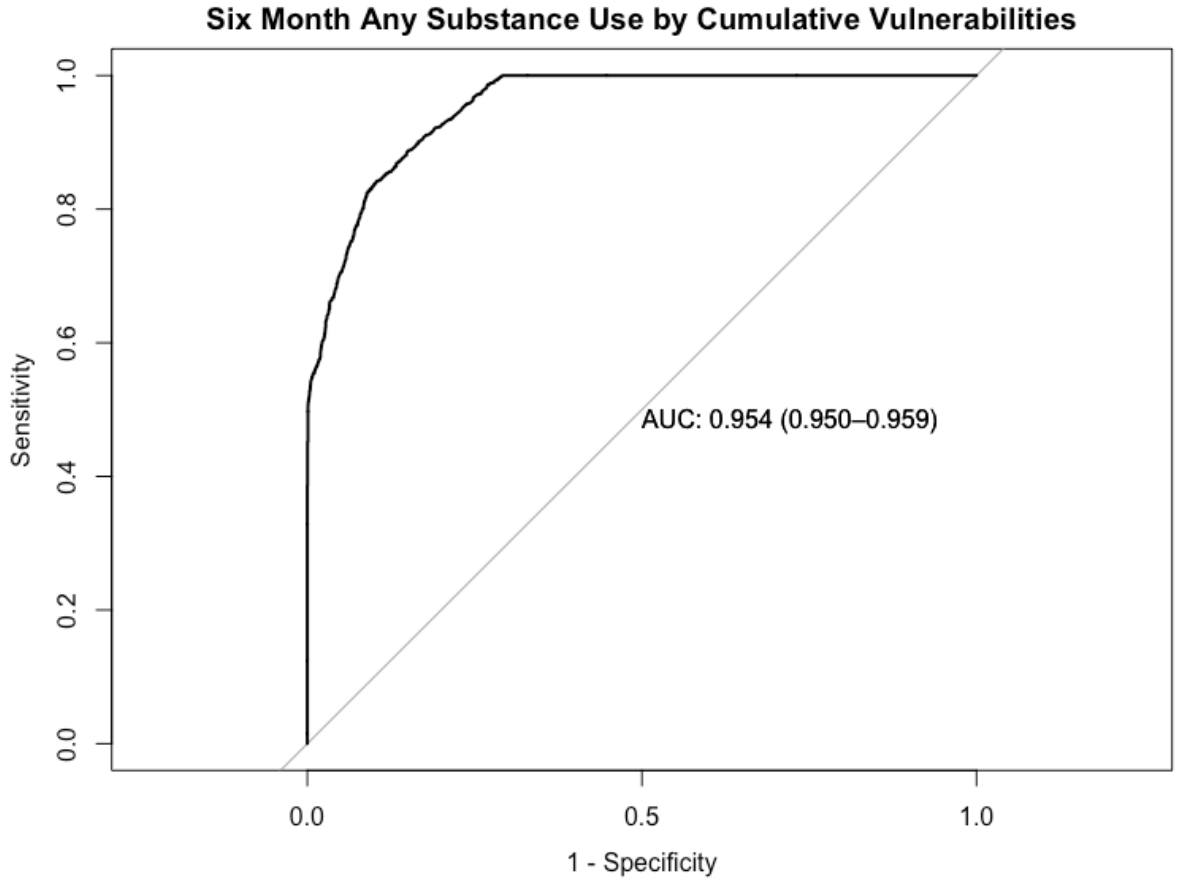

Figure 2.6. Area under the Receiver Operator Characteristics Curve for twelve-month any substance use predicted by cumulative vulnerabilities.

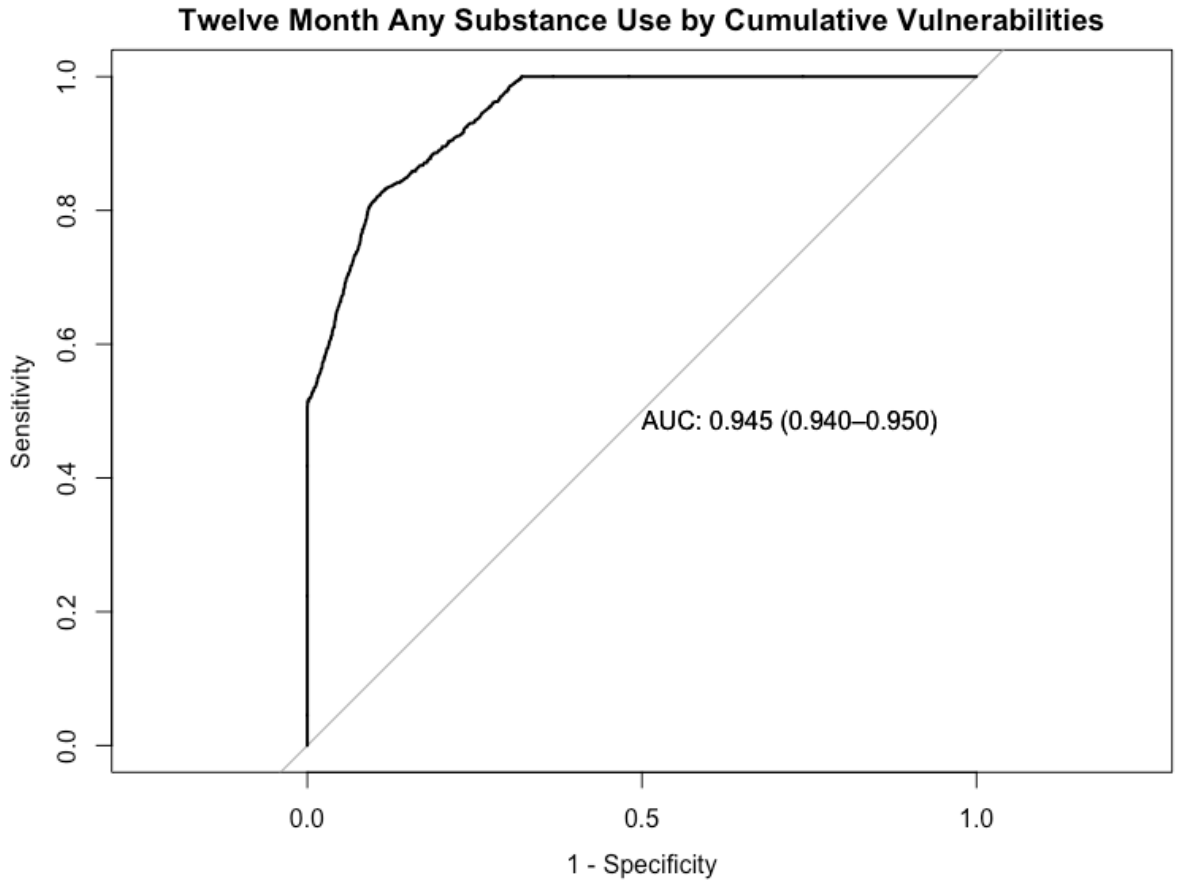

Figure 2.7. Area under the Receiver Operator Characteristics Curve for current any substance use predicted by subgroup assignment.

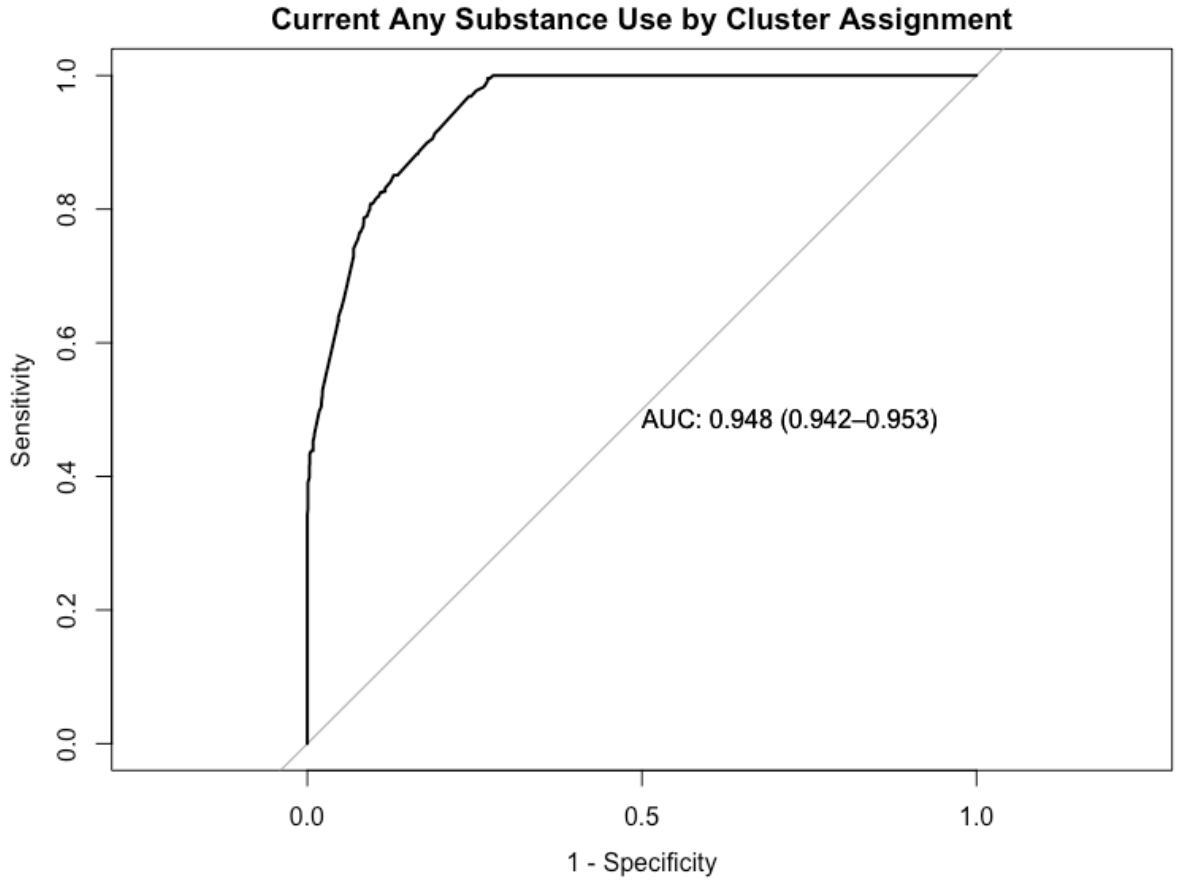

Figure 2.8. Area under the Receiver Operator Characteristics Curve for six-month any substance use predicted by subgroup assignment.

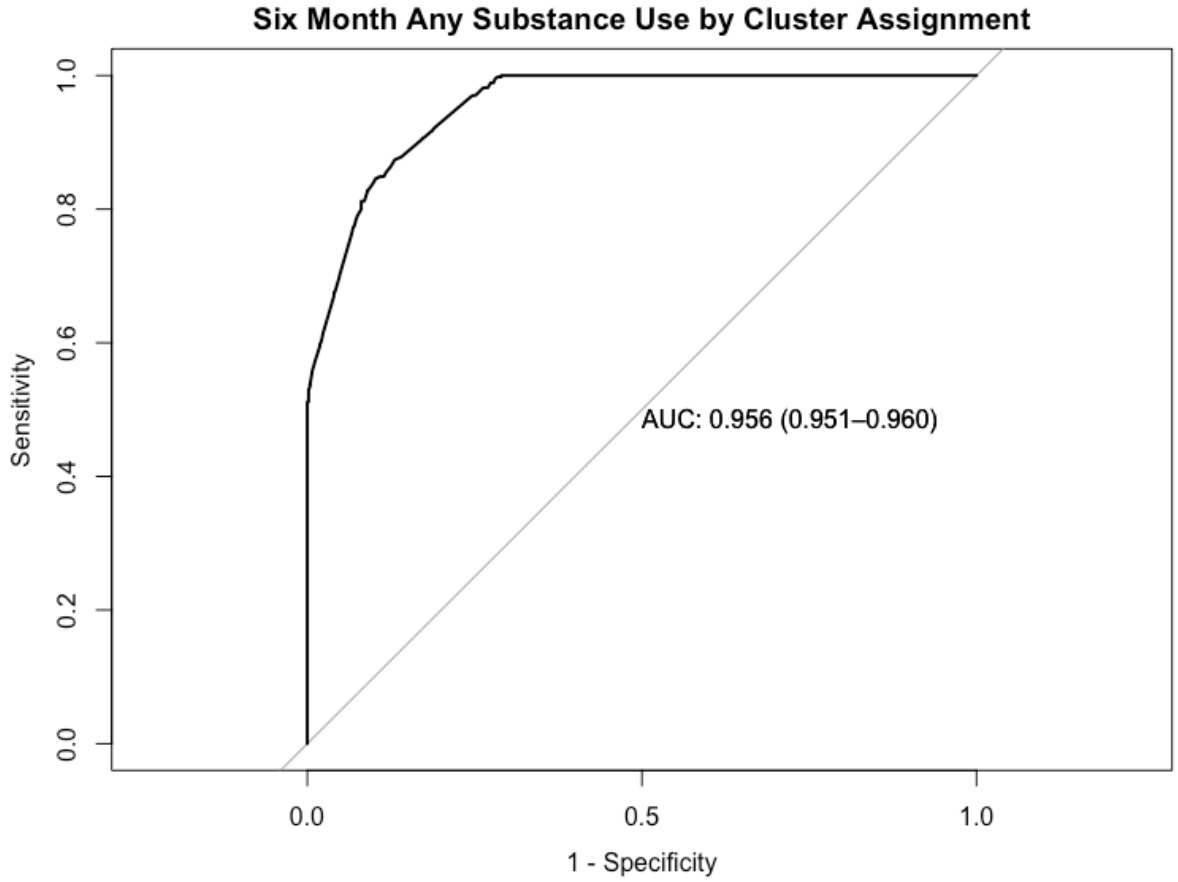

Figure 2.9. Area under the Receiver Operator Characteristics Curve for twelve-month any substance use predicted by subgroup assignment.

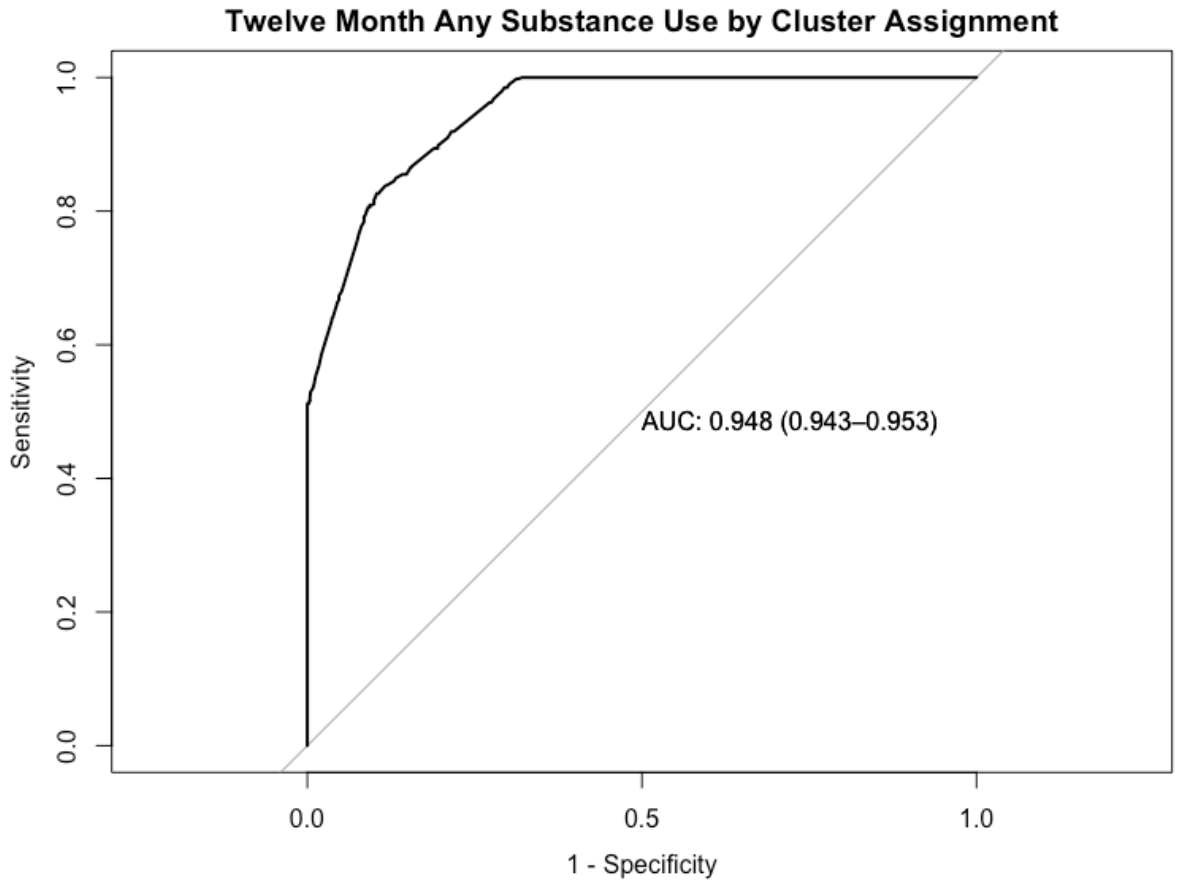

Table 2.9. Area under the Receiver Operator Characteristics Curve (AUC) for any substance use by cumulative vulnerabilities and cluster assignment.

Cumulative Vulnerabilities	**AUC (95% CI)**
Current substance use	0.947 (0.942-0.952)
Six-month substance use	0.954 (0.950-0.959)
Twelve-month substance use	0.945 (0.940-0.950)
Cluster Assignment	
Current substance use	0.948 (0.942-0.953)
Six-month substance use	0.956 (0.951-0.960)
Twelve-month substance use	0.948 (0.943-0.953)

MANUSCRIPT 3

Title

Cumulative Vulnerabilities: An Investigation of Overdose History and Lifetime Substance Use Among Individuals in Recovery from Opioid Use Disorder

Abstract

Aim: The cumulation of vulnerabilities are associated with the initiation, frequency, and cessation of cigarettes. We explored the association of cumulative vulnerabilities and substance use in a sample of individuals in recovery from opioid use disorder (OUD).

Methods: We performed a secondary analysis of data from the Remission from Chronic Opioid Use-Studying Environmental and Socio-Economic Factors on Recovery study of individuals with OUD (NCT03604861; N=348). First, we created a summed cumulative vulnerabilities score composed of 11 factors including history of abuse, mental health conditions (e.g., chronic pain, mood disorder), symptoms of depression, and psychological distress; a higher cumulative vulnerability score indicated participants had more vulnerabilities (range: 0-11). The associations between cumulative vulnerabilities and lifetime substance use outcomes were evaluated using generalized linear regression.

Results: Increased cumulative vulnerability score was associated with an endorsement of previous overdose (OR: 1.300; 95%: 1.184, 1.433). An increase in the cumulative vulnerabilities score was significantly related to endorsement of lifetime use of prescription opioids (OR: 1.114; 95%: 1.005, 1.244), methamphetamine (OR: 1.104; 95%: 1.018, 1.200), misuse of buprenorphine (OR: 1.088; 95%: 1.002, 1.182), crack (OR: 1.104; 95%: 1.015, 1.203), cocaine (OR: 1.131; 95%: 1.004, 1.289), stimulants (OR: 1.097; 95%: 1.011, 1.192), sedatives (OR: 1.111; 95%: 1.022, 1.211), club drugs (e.g., ecstasy, molly; OR: 1.171; 95%: 1.077, 1.276), goofball (methamphetamine-heroin; OR: 1.143; 95%: 1.044, 1.251). Significant associations were not observed between cumulative vulnerability scores and lifetime use of heroin, misuse of methadone, cannabis, inhalants, alcohol, or speedball (cocaine-heroin).

Conclusion: The present report extends the literature on the cumulation of vulnerabilities to

include substance use in individuals in recovery from OUD. We report, consistent with previous literature, an association between substance use and higher cumulative vulnerability scores.

Introduction

Opioid Use Disorder (OUD) is a psychiatric condition that is defined as problematic patterns of opioid use that result in impairment or distress (American Psychiatric Association, 2013; *Opioid Use Disorder: Preventing and Treating*, 2022) . In the midst of the opioid epidemic, over 2.7 million individuals in the United States aged 12 or older are estimated to have had OUD in 2020 (SAMHSA, Center for Behavioral Health Statistics & Quality, n.d.). Efficacious treatments for OUD exist, including buprenorphine, a partial mu-opioid receptor agonist (Bickel & Amass, 1995; Mattick et al., 2014). Through these treatments and other recovery pathways, such as 12-step programs, an estimated 1.2 million Americans report being in recovery from OUD (Hoffman et al., 2020).

While efficacious treatments are available and recovery from OUD is observed, many individuals still relapse during recovery (Smyth et al., 2010). By examining comorbidities and other circumstances that may aid or hinder one's recovery, we may be better able to inform treatments and interventions to help individuals succeed in recovery from OUD. Previous literature has examined the relationship between vulnerabilities (i.e., conditions that may make an individual more susceptible to substance use) and outcomes of cigarette smoking. These studies report that a greater number of vulnerabilities are associated with numerous indices of cigarette smoking, including a greater number of cigarettes smoked per day (Higgins et al., 2021), a higher smoking prevalence (Leventhal et al., 2019), and poorer cessation outcomes among individuals enrolled in a clinical trial for smoking cessation (Zvolensky et al., 2023).

In a sample of individuals in recovery from OUD, the cross-sectional associations of physical and mental health vulnerabilities (e.g., history of abuse, chronic pain, depression) and lifetime substance use are examined. The hypotheses include, consistent with the literature,

greater cumulative vulnerabilities would be associated with a greater incidence of substance use and a higher incidence of overdose.

Methods

Participants

The present report is a secondary analysis of data from the Chronic Opioid Use-Studying Environmental and Socio-Economic Factors on Recovery study of individuals with OUD (RECOVER; NCT03604861; N = total 533; sample analyzed in this paper = 348; details below). See Ling et al. (2019) for a description of the study design and full sample characteristics.

Vulnerabilities

Eleven vulnerabilities to substance use were examined, three assessing history of abuse, six regarding psychological diagnosis, and two examining current psychological symptoms. The vulnerabilities were: 1) physical abuse, 2) sexual abuse, 3) mental abuse, 4) anxiety disorder, 5) mood disorder, 6) bipolar disorder, 7) conduct disorder, anger disorder, or oppositional defiant disorder, 8) insomnia, 9) chronic pain, 10) depression measured by the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), and 11) psychological distress measured by the Kessler Psychological Distress Scale (K6; Kessler et al., 2003). The first nine vulnerabilities were assessed by asking participants if they had ever experienced these or had these conditions, with "Yes" or "No" response options. The final two vulnerabilities were assigned by calculating a median split on these two scales and assigning individuals in the more vulnerable median the vulnerability (i.e., scores higher than the median were assigned the vulnerability). Median splits were calculated on the full sample of participants. Participants who did not provide a response to the vulnerabilities were excluded from this analysis; the final analytical sample was N=348.

Cumulative Vulnerability Score

To evaluate the accumulation of vulnerabilities, a global score of participants' vulnerabilities was created for the 11 vulnerabilities previously described. The total number of vulnerabilities a participant indicated were summed for a total score hereby referred to as *cumulative vulnerabilities*; the range of this score was 0 to 11.

History of overdose

To assess the history of overdose participants were asked: "Have you ever overdosed?", with response options of "Yes" or "No." An overdose is indicated as "1."

Previous substance use

Participants were asked the following question to assess substance use, "Please select which of the following substances you have used in your lifetime, either to get high or to self-medicate a problem using substances that were not approved by your doctor." Participants were instructed to refer to use of substances that were not approved by a medical professional. Participants responded "Yes" or "No" for each of these substances: prescription pain relievers, heroin, methamphetamine, buprenorphine, methadone, cannabis (i.e., assessed using "marijuana"), crack (e.g., rock, pipe), powder cocaine (e.g., snort, freebase), prescription stimulants, prescription sedatives, inhalants (e.g., gassing/huffing), club drugs (e.g., MDMA, Ecstasy, Molly), a hallucinogen (e.g., LSD, mushrooms), alcohol (e.g., beer/wine/spirits), goofball (e.g., methamphetamine, heroin), and speedball (e.g., cocaine and heroin). For all substance use outcomes, the indication of previous use is "1." Please note, the use of any opioid was not evaluated in the present study because of the nature of the sample (individuals in recovery from OUD); opioids were split into more specific categories for this study.

Statistical Analysis

Participants' characteristics were described using mean, standard deviation, and percentages, where appropriate. The statistical analyses in the present report were performed in R version 4.0.2 (Team, 2021). A binary generalized logistic regression was performed using the package `stats` to evaluate the relationship between outcome measures and the cumulative vulnerability score (Team, 2021). Odds ratios (OR) were calculated for each outcome and presented with 95% confidence intervals (CI). Significance was defined as the absence of "*1.000"* in the CI of the OR.

Results

Demographic characteristics

Demographic characteristics of the present sample are visible in **Table 3.1**. Overall, the majority of the sample was male (n=228, 65.5%), White (n=214, 61.5%), and non-Hispanic (n=321, 92.2%). Most participants endorsed completing at least a high school education (n=290, 83.3%), while 14 were currently enrolled as a student. The distribution of cumulative vulnerability scores can also be seen in **Table 3.1** (median [interquartile range]: 2 [1-4]). Proportions of individuals endorsing each vulnerability item are shown in **Table 3.2**.

Vulnerabilities and Outcomes

A significant association between cumulative vulnerability score and endorsement of a previous overdose was observed (OR for every unit increase in cumulative vulnerability score: 1.300; 95%: 1.184, 1.433; **Figure 3.1**). Moreover, significant relationships were observed between an individual's cumulative vulnerability score and lifetime endorsement of: prescription opioids (OR: 1.114; 95%: 1.005, 1.244), methamphetamine (OR: 1.104; 95%: 1.018, 1.200), buprenorphine (OR: 1.088; 95%: 1.002, 1.182), crack (OR: 1.104; 95%: 1.015, 1.203), cocaine

(OR: 1.131; 95%: 1.004, 1.289), stimulants (OR: 1.097; 95%: 1.011, 1.192), sedatives (OR: 1.111; 95%: 1.022, 1.211), club drugs (e.g., ecstasy, molly; OR: 1.171; 95%: 1.077, 1.276), goofball (methamphetamine-heroin; OR: 1.143; 95%: 1.044, 1.251). A significant relationship was not observed between an individual's cumulative vulnerability score and lifetime use of: heroin (OR: 1.087; 95%: 0.969, 1.232), methadone (OR: 0.985; 95%: 0.901, 1.073), cannabis (OR: 1.055; 95%: 0.932, 1.209), inhalants (OR: 1.038; 95%: 0.941, 1.141), alcohol (OR: 1.151; 95%: 0.995, 1.359), speedball (cocaine-heroin; OR: 1.041; 95%: 0.960, 1.131). Odds ratios and 95% confidence intervals are visualized in **Figure 3.1**.

Discussion

The present report extends the literature of associations of cumulative vulnerabilities and substance use metrics among a sample of individuals in recovery from OUD. First, a significant association between cumulative vulnerability score and previous overdose was observed. Second, a significant association between cumulative vulnerability scores and lifetime use of prescription opioids not as prescribed, methamphetamine, buprenorphine not as prescribed, crack, cocaine, stimulants, sedatives, club drugs, and goofball was observed. Contrastly, a significant association was not observed between cumulative vulnerability score and lifetime use of heroin, methadone not as prescribed, cannabis, inhalants, alcohol, or speedball.

A significant association was observed between cumulative vulnerability score and previous overdose. To our knowledge, this is the first report that extends the examination of increased cumulative vulnerabilities to the substance-use related outcome of overdose, providing important contextual information for overdose reduction strategies, interventions, and prevention measures. The results presented herein provide evidence that individuals with more physical and

mental health conditions may be more susceptible to overdose, providing rationale for treatment and prevention strategies targeting individuals with co-occurring conditions.

The significant findings of the association of lifetime substance use and cumulative vulnerabilities are consistent with previous reports of associations of cumulative vulnerabilities and indices of cigarette smoking, including increased risk of smoking initiation (Higgins et al., 2016), current smoking prevalence (Leventhal et al., 2019), and cigarettes per day (Higgins et al., 2021). However, one important difference between published and present reports is the vulnerabilities that compose the cumulative vulnerability score. Previous reports have included vulnerabilities such as education or poverty (Higgins et al., 2021; Leventhal et al., 2019), whereas the vulnerabilities defined in the present report are exclusively psychological and mental health conditions. By examining modifiable, treatable, or intervenable vulnerabilities we may inform treatment strategies for unique subtypes of individuals in recovery from substance use disorders, compared to previously published vulnerabilities that may be more static in adulthood (e.g., education; (Higgins et al., 2021; Leventhal et al., 2019)) or may require a systemic upheaval to address (e.g., poverty, rural residence; (Higgins et al., 2021; Leventhal et al., 2019)).

The non-significant findings of the association between lifetime substance use and cumulative vulnerabilities are inconsistent with previous reports. One explanation is that the proportion of participants who endorsed or did not endorse are high (e.g., alcohol, N = 312, 89.7%) and low (e.g., inhalants, N=75, 21.6%), respectively, suggesting that a majority of participants used and did not use these substances regardless of their vulnerabilities. These proportions could be observed because the sample of individuals in the present report is individuals in recovery from OUD. Replication of the analyses with a larger sample size or in a population of individuals not in recovery from OUD may produce different results.

The present report is not without limitations. First, the present analysis includes a subset of individuals from the total sample who provided complete responses to the items used to define our cumulative vulnerability score. Furthermore, our sample was largely 65.6% male, 61.6% White, and 92.3% non-Hispanic. Future research could replicate these findings in a larger and more diverse sample. Second, the analysis involved the association between lifetime diagnosis of physical and mental vulnerabilities and lifetime use of substances. These findings are cross-sectional and retrospective, limiting our ability to interpret causality. Future investigations should examine the associations of vulnerabilities and substance use temporally, particularly among individuals in recovery from OUD and other substance use disorders.

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Table 3.1. Demographic characteristics of the study participants.

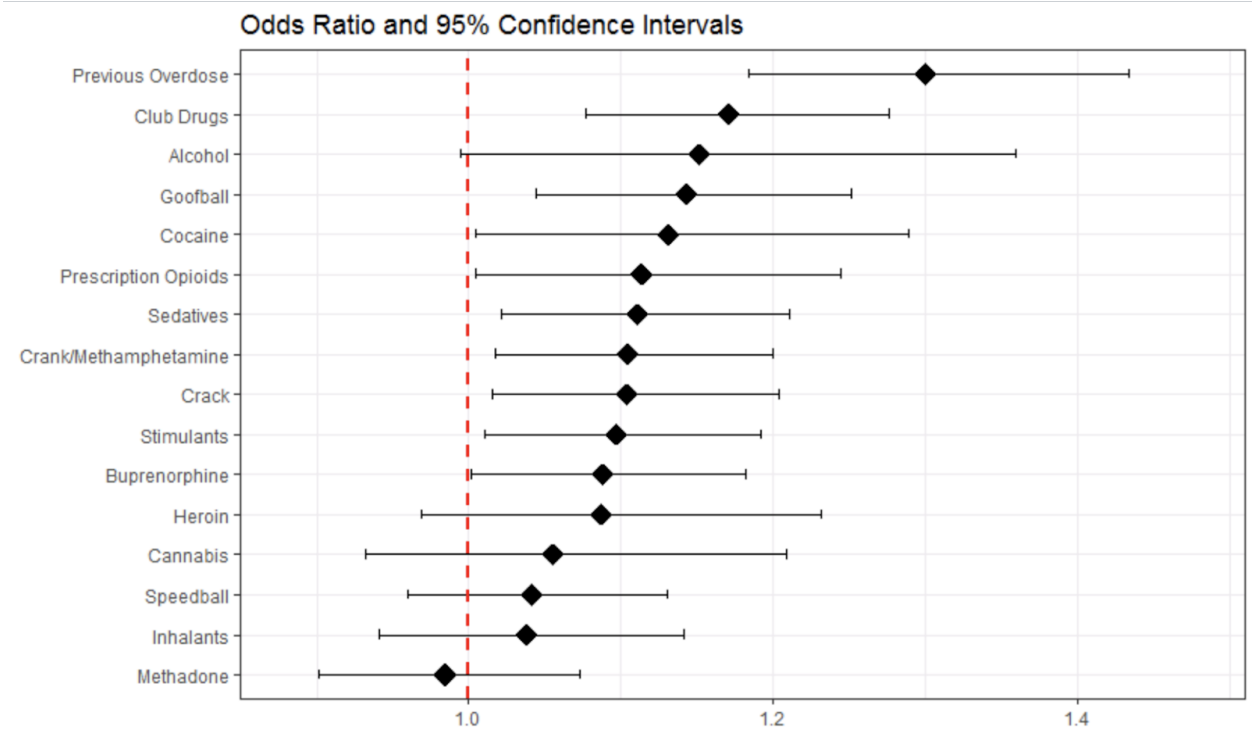
Demographic	**Frequency (%)**
n	348
Sex = Male (%)	228 (65.5%)
Race (%)	
Asian	1 (0.3%)
Black	122 (35.1%)
Native American	11 (3.2%)
Other	13 (3.7%)
White	214 (61.5%)
Ethnicity = Not Hispanic (%)	321 (92.2%)
Education (%)	
Less than High School	58 (16.7%)
High School / GED	235 (67.5%)
College	52 (14.9%)
Professional Degree	3 (0.9%)
Student = Yes (%)	14 (4.0%)
Marital Status (%)	
Divorced	64 (18.4%)
Married	74 (21.3%)
Single	175 (50.3%)
Separated	21 (6.0%)
Widowed	14 (4.0%)
Living Situation	
Alone	50 (14.4%)
Alone with Children	19 (5.5%)
Controlled Environment	7 (2.0%)
Family	73 (21.0%)
Friends	20 (5.7%)
No Stable Environment	8 (2.3%)
Parents	29 (8.3%)
Partner and Kids	85 (24.4%)

Partner without Kids	57 (16.4%)
Live with someone with a drug or alcohol problem = Yes (%)	69 (19.8%)
Can Drive = Yes (%)	199 (57.2%)
Have a Car = Yes (%)	205 (58.9%)
Employment (%) Full Time Looking for a Job Not Looking for a Job Part Time	 109 (31.3%) 96 (27.6%) 96 (27.6%) 47 (13.3%)
Insurance (%) Don't Have Insurance Other Private Public Veteran's	 116 (33.3%) 33 (9.5%) 54 (15.5%) 139 (39.9%) 6 (1.7%)
Cumulative Vulnerabilities 0 1 2 3 4 5 6 7 8 9 10 11	 83 (23.9%) 60 (17.2%) 47 (13.5%) 43 (12.4%) 29 (8.3%) 31 (8.9%) 16 (4.6%) 18 (5.2%) 9 (2.6%) 6 (1.7%) 4 (1.1%) 2 (0.6%)

Table 3.2. Endorsements of individual items composing the cumulative vulnerability score.

Item	**Frequency (%)**
n	348
Physical Abuse	99 (28.4%)
Sexual Abuse	71 (20.4%)
Mental Abuse	121 (34.8%)
Anxiety Disorder	101 (29.0%)
Mood Disorder	42 (12.1%)
Bipolar Disorder	65 (18.7%)
Conduct / Anger / Oppositional Defiant Disorder	9 (2.6%)
Insomnia	50 (14.4%)
Chronic Pain	69 (19.8%)
BDI median split	164 (47.1%)
K6 median split	173 (49.7%)

Figure 3.1. Forest plot of Odds Ratios (OR) and 95% confidence interval for history of overdose and lifetime substance use.[a]



[a] Please note, any prescription is specified as misuse of that medication (i.e., not as prescribed). This includes prescription opioids, buprenorphine, and methadone.

CONCLUSIONS

In the theory of Reinforcer Pathology, vulnerabilities (disparities associated with substance use outcomes or susceptibility to substance use), are also defined as disparities or conditions that may be associated with a constricted temporal window. These individual vulnerabilities (e.g., psychiatric symptomatology, health conditions) and their cumulation have been shown to be related to cigarette smoking outcomes in previous reports. Consistent with these previous reports, the findings extend the Reinforcer Pathology theory of vulnerabilities to include adolescents and individuals recovering from Opioid Use Disorder.

In the first report, cross-sectional associations with age of first substance use, any substance use in an individual's lifetime, and the total number of substances used in an individual's lifetime were significantly associated with cumulative vulnerability scores. In this report, cumulative vulnerability score was composed of the following domains: psychiatric symptomatology, behavioral constructs, anhedonia, sleeping problems and family history of substance use. In addition to the cumulative vulnerability score, the patterns or latent classes of vulnerabilities were significantly associated with age of first substance use, any substance use, and total number of substances used, suggesting that examination of cumulative vulnerability scores and patterns of vulnerabilities may be useful in the prevention of substance use.

The second report extends the first report's findings to examine the longitudinal effects of cumulative vulnerability score on substance use. Consistent with our hypotheses and previous reports, the cumulative vulnerability score is associated with substance use cross-sectionally and prospectively (up to twelve months). The patterns of vulnerabilities, assessed with k-means clustering, were also associated with substance use outcomes cross-sectionally and prospectively.

These results support the idea that the cumulation of conditions related to a shortened temporal window increases substance use over time.

The third report examines the cross-sectional association between a cumulative vulnerability score (composed of physical and mental health conditions) and outcomes in individuals in recovery from Opioid Use Disorder. The outcomes examined included lifetime use of a number of substances and endorsement of experiencing an overdose previously. Although not completely consistent, evidence exists that cumulative vulnerability score is associated with lifetime use of some substances (e.g., heroin, crack) but not others (e.g., alcohol, inhalants). The findings report significant associations between previous overdoses and cumulative vulnerability score. These findings extend the vulnerability theory of Reinforcer pathology to extend to outcomes tangentially related to substance use (i.e., overdose) and may support research into other domains.

Taken together, the three studies reported herein replicate and extend the literature of cumulative vulnerabilities into 1) substance use in adolescents, 2) predicting future substance use in adolescents, and 3) lifetime use and overdose among individuals in recovery from Opioid Use Disorder. The results highlight the importance of considering a number of vulnerabilities and their pattern of occurrence when evaluating substance use outcomes. Future research may elucidate mechanisms by which these vulnerabilities interact with outcomes of interest.