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Substance Use and Psychological and Physiological Responses to Stress

A dissertation submitted in partial satisfaction of the

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in Psychology

by

Danny Rahal

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ABSTRACT OF THE DISSERTATION

Substance Use and Psychological and Physiological Responses to Stress

by

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Doctor of Philosophy in Psychology

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Professor Andrew J. Fuligni, Co-Chair

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Substance use rapidly increases during adolescence, particularly among youth who experience greater stress and negative emotion. However, limited research has examined whether responses to stress may predict adolescent substance use. Associations between adolescents' responses to acute and daily responses to stress and substance use were tested. Adolescents in the CHAMACOS study completed a social-evaluative stress paradigm at age 14, in which they provided four samples of salivary cortisol, six emotion ratings, and electrocardiogram and impedance cardiogram consistently, and reported whether they had ever used any substances at ages 14 and 16. A community sample of adolescents also reported substance use and completed two weeks of daily reports of emotion and interpersonal conflict, up to three times for every two years, during the transition from adolescence to adulthood. Results indicated that blunted HPA axis responses to stress were related to use of alcohol by age 14, primarily driven by elevated cortisol at baseline, and vaping of nicotine by age 16 among adolescents above the poverty line.

Also, female adolescents with blunted sadness reactivity to stress reported greater use of varied substances, and female adolescents with blunted happiness reactivity reported initiation of substances between ages 14 and 16 (Study 1). Blunted changes in sympathetic and parasympathetic nervous system activity, particularly profiles of coinhibition and reciprocal parasympathetic activation, were related to initiation of substance use among non-users (Study 2). Finally, blunted positive emotion reactivity was related to greater substance use among adolescents irrespective of gender, whereas greater anxious emotion reactivity among female adolescents and blunted depressive emotion reactivity among male adolescents were both related to greater substance use. These results consistently suggest that blunted responses to stress are related to greater substance use across psychological and physiological systems.

The dissertation of Danny Rahal is approved.

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D A N N Y R A H A L

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Research Interests

The effects of social inequality on health and health behaviors, particularly substance use, in adolescents and young adults of diverse socioeconomic and ethnic backgrounds.

Publications

*****Notes co-first authorship.

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Tashjian*, S. M., **Rahal***, **D**., Karan, M., Eisenberger, N., Galan, A., Cole, S. W., Fuligni, A. J. (In Press). Evidence from a randomized controlled trial that altruism moderates the effect of prosocial acts on adolescent well-being. *Journal of Youth and Adolescence.*

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Substance Use and Psychological and Physiological Responses to Stress

Substance use emerges and greatly increases across adolescence, and early substance use and more frequent use are risk factors for substance use disorders in adulthood (Latimer & Zur, 2010; Zapert et al., 2002). In 2018, the percentage of students who had used an illicit drug doubled from 8th to 10th grade, and nearly half of students reported using at least one substance by 12th grade. High substance use in adolescence has been reliably linked with substance use problems and addiction in adulthood (Hingson et al., 2003; Jennison, 2004; Vaillant, 2003). Converging evidence from cross-sectional and prospective studies has indicated that earlier use of alcohol, tobacco, and marijuana during adolescence is a risk factor for more problematic substance use and substance use dependence (e.g., Andersen et al., 2003; DiFranza et al., 2010). Furthermore, youth who engage in substance use broadly have more problems with respect to academics, social function, psychopathology, and the legal system both throughout adolescence and during adulthood (Ellickson et al., 2003; Fergusson et al., 2003). Therefore, it is important to identify youth at heightened risk for substance use. Although stress and distress are consistent risk factors for substance use, few studies have examined whether stress reactivity is related to substance use among adolescents.

Adolescents show neurobiological development, and substances can influence one's neurobiology by altering neural reward circuitry to promote substance dependence and addiction (e.g., Cass et al., 2013; Counotte et al., 2011; Salmanzadeh et al., 2020; Tapert et al., 2002). This substance-induced neural rewiring may be most notable during adolescence, as adolescents experience neurodevelopment and already show increased reward sensitivity relative to children and adults (Caudle & Casey, 2013; Powers & Casey, 2015). Excessive substance use can also reduce executive function and attentional control (e.g., Chin et al., 2010; Hanson et al., 2011;

Koskinen et al., 2011; Orr et al., 2019; Swartzwelder et al., 2017; Tapert et al., 2002). These deficits may cause youth to struggle with academics, and academic motivations and school engagement provide an important buffer for substance use (Hawkins & Weis, 1985; Zimmerman & Schmeelk-Cone, 2003).

Substance use can also manifest in social changes which further promote dependence and risky behavior. For instance, substance use has been linked with increases in impulsivity and sensation seeking and greater involvement with deviant peers during adolescence (Brière et al., 2014; Malmberg et al., 2013). Because youth cannot legally acquire substances, youth may need to identify deviant peers to obtain access, and identification with deviant peers can promote further substance use (Brière et al., 2014). In this way, early substance use can prompt youth to engage with others who promote delinquent behaviors and poorer adjustment (Kandel et al., 1986).

Stress and Substance Use

Adolescents may use substances for varied reasons related to stress. For instance, common motives include to enhance their social and emotional well-being, to reduce distress, and to conform to peer pressure (Hussong et al., 2011; Kuntsche et al., 2015, 2016). Just as substances can influence emotion, emotional states can influence adolescents' inclination to engage in substance use. For instance, substance use is higher on days when individuals experience higher levels of positive emotion as well as negative emotion (Weinstein & Mermelstein, 2013ab). Similarly, daily experiences can also influence one's proclivity for substance use. Daily stressors are generally followed by increased negative emotion and decreased positive emotion, and people turn to substances to mitigate these emotional responses. This may be particularly the case during adolescence, a period when youth experience more

frequent stressors in varied domains (e.g., academic social) as well as enhanced reactivity to stress relative to children and adults (Dahl & Gunnar, 2009; Dorn et al., 2006). Further, adolescents experience greater variability and intensity in emotion relative to adults, such that stressful experiences may be especially distressing (Larson et al., 1980, 2002; Riediger & Klipker, 2014; Shadur et al., 2015). Heightened emotional responses with reduced capacity for regulation can contribute to increased psychopathology broadly during adolescence, including substance use (Dahl & Gunnar, 2009; Kassel et al., 2010; Powers & Casey, 2015).

In addition to emotional responses, stress is followed physiological changes from biological systems that naturally respond to stress. Physiological responses often do not correspond to self-reported emotion, and profiles of psychological and physiological responses together or interactions between systems can impart unique information about adolescents' experiences with stress (e.g., Quas et al., 2014). Two physiological systems that may aid in the identification of at-risk youth are the hypothalamic pituitary adrenal gland (HPA) axis and the autonomic nervous system. Adolescents become more sensitive to social stress following pubertal onset, and the HPA axis is sensitive to social-evaluative stress (Dahl & Gunnar, 2009; Dickerson & Kemeny, 2004). The two branches of the autonomic nervous system—the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS)—jointly alert the body to threat, and they have also been found to relate to impulsivity and emotion regulation, traits relevant for substance use (Krueger et al., 2005; Porges, 2007). People with blunted SNS activity tend to be more impulsive and people with blunted PNS reactivity have poorer mental health and self-regulation (Damasio, 1996; Graziano & Derefinko, 2013; Krueger et al., 2005; Porges, 2007). Although blunted activity across all systems is linked substance use, limited work

has examined whether individuals with dysregulation across systems are at greater risk for substance use.

Limited work has assessed how stress responses reactivity can relate to substance use and behavioral problems concurrently and prospectively. However, among youth with depression, conduct problems, or no psychiatric condition, Brenner and Beauchaine have found that greater increases in SNS activity in response to reward were associated with delinquency, both externalizing and internalizing problems, and anxiety and depressed mood (2011). Moreover, they found that lower SNS reactivity to reward predicted greater alcohol use four and six years later among middle school children (Brenner & Beauchaine, 2011). Yet, no work has assessed links between psychophysiological responses and substance use in middle or late adolescence.

Present Studies

Although substance use often begins in mid-adolescence and increases in frequency during late adolescence, limited work has examined associations between stress responses and substance use onset and frequency in adolescence. Early identification of at-risk youth is imperative as earlier substance use is linked with greater severity of use in adulthood (e.g., Grant & Dawson, 1997). Therefore, this dissertation investigated how stress responses relate to lifetime substance use in middle adolescence among youth with high adversity backgrounds (Studies 1 and 2) and frequency of substance use in late adolescence among a community sample across middle and late adolescence (Study 3). Associations between emotional and cortisol reactivity to stress at age 14 and lifetime substance use at ages 14 and 16 were assessed in Study 1, as well as differences in associations by gender and poverty status. Associations between SNS and PNS reactivity to stress, as well as profiles of responses across the two systems, at age 14 and substance use at ages 14 and 16 will also be assessed in Study 2. In both studies, sensitivity

analyses were limited to adolescents who had never used substances by age 14 to determine whether stress responses were related to use versus initiation specifically. These studies will highlight whether stress reactivity can prospectively predict substance use onset and have utility for identifying at-risk youth. In contrast, Study 3 assessed whether daily emotional reactivity, as opposed to acute reactivity, related to substance use count and frequency of alcohol and marijuana use in late adolescence, as well as whether associations differed by gender. By better understanding pathways that contribute to heightened predisposition for adolescent substance use and which groups of adolescents are at heightened risk for substance use, treatments can be tailored to address aspects of stress regulation among specific populations of at-risk youth.

Study 1: Dampened Psychobiological Responses to Stress and Substance Use in Adolescence

Substance use initiation greatly increases across adolescence (Johnston et al., 2019). Youth with greater internalizing and externalizing problems tend to show high risk for substance use, and differences in the activation of to two key stress response systems—hypothalamic pituitary adrenal (HPA) axis and emotion—have been related to both (e.g., Bai & Repetti, 2018; Hartman et al., 2013). However, limited research has examined whether differences in the biological and psychological responses to stress, with respect to changes in cortisol secretion and emotions following stressor onset and across a recovery period, relate to substance use among adolescents, especially those at heightened risk for substance use. The present study examined how differences in the stress response related to substance use in a sample of Mexican-origin youth growing up in a low-income region with high levels of adversity (Stein et al., 2016). Using a longitudinal study design, we tested whether differences (i.e., exaggerated and blunted) in HPA axis reactivity and emotion and recovery to stress at age 14 were associated with use of alcohol, marijuana, and cigarette use by age 14 (i.e., the substances most commonly used by adolescents); use of alcohol, marijuana, cigarettes, and vaping of nicotine by age 16; and onset of alcohol, marijuana, and cigarette use between ages 14 and 16. Finally, we tested whether associations between stress reactivity, stress, recovery, and substance use varied by poverty status and sex.

Adolescent Substance Use and Stress

Substance use greatly increases during adolescence, as the percentage of students who have used an illicit drug doubles from 8th to 10th grade, and nearly half of students report using at least one substance by 12th grade (Johnston et al., 2019). Although experimentation is common in adolescence, youth who use alcohol, tobacco, and marijuana earlier in adolescence are at higher risk for psychopathology and substance use disorders in adulthood (e.g., Andersen et al.,

2003; Ellickson et al., 2003; Fergusson et al., 2002; Riala et al., 2004; Taylor et al., 2017). Previous research has also consistently found that use of alcohol and marijuana by ages 14 and 16 specifically are related to poorer adjustment and higher use later in adolescence and adulthood (e.g., Colell et al., 2014; DeWit et al., 2000; Duke, 2018; Grant & Dawson, 1997; Grant et al., 2006; Hingson et al., 2006; Strunin et al., 2017; Swift et al., 2008; Wagner et al., 2005). Risk is particularly high for Latinx adolescents, who show higher lifetime use of varied substances by 8th grade and by 12th grade compared to White and Black youth, and tend to begin using cigarettes, alcohol, and other drugs at earlier ages than other ethnic minorities (Johnston et al., 2019; Kann et al., 2018). Furthermore, prior research suggests that Mexican American adolescents, specifically, are more likely to have initiated substance use by the eighth grade than non-Latinx and other Latinx youth (Delva et al., 2005).

Substance Use and Stress Reactivity and Recovery

People generally respond to stress by showing increased negative emotion, decreased positive emotion, and activation of the HPA axis, a biological system especially sensitive to social-evaluative stressors (Dickerson & Kemeny, 2004). Exaggerated emotion reactivity to stress has been related to poorer health (e.g., Uink et al., 2018). However, inability to mount a response or showing blunted reactivity to stress may suggest disengagement and has also been related to poorer well-being (Carroll et al., 2017). Dampened reactivity and recovery following stress (i.e., smaller or no changes in emotion and cortisol secretion following stress onset) have also been related to poorer health including depression and externalizing problems (e.g., Bylsma et al., 2008; Jones et al., 2009; Stadler et al., 2007).

Individuals can show blunted rather than exaggerated stress reactivity and recovery for many reasons (Shirtcliff et al., 2021). Individuals who experience chronic or repeated stress may

initially show heightened emotional and biological stress reactivity and recovery, and these responses may habituate and show a blunted profile over time (Peters & McEwen, 2015). Therefore, whereas unpredictable, acute stressful life events may promote a profile of exaggerated reactivity to stress, living in adversity can serve as a chronic stressor and consequently can promote inflexibility of psychobiological systems over time, such that individuals are incapable of responding to acute stressors (Del Giudice et al., 2011; Shirtcliff et al., 2021). Indeed, youth and adults who experience more adversity generally show blunted rather than enhanced cortisol and heart rate reactivity to acute stress (Carpenter et al., 2007, 2011; Lovallo, 2011; Trickett et al., 2014), as well as reduced activation of neural regions involved in threat such as the amygdala (Ginty et al., 2013; Yang et al., 2015). It has been posited that individuals who experience high levels of adversity may be inclined to disengage from stressors, which can attenuate psychobiological reactivity and recovery (Carroll et al., 2017). Lastly, low reactivity may result from socialization from peers and parents (Chaplin et al., 2018; Guo et al., 2017). For instance, youth who experience adversity may interact with deviant peers or bullies who prompt them to be less responsive to stress and may be socialized by parents to be less affected by daily stressors (Calkins & Hill, 2007; Ouellet-Morin et al., 2011).

Just as heavy substance use can dysregulate HPA axis function (e.g., Koob & Kreek, 2007; Lovallo, 2006), dysregulation of the HPA axis may also contribute to substance use risk. Youth with blunted HPA axis reactivity to stress may lack physiological inhibitory control, such that they may be less inhibited by the social consequences of risk-taking compared to adolescents who show greater cortisol reactivity to stress (e.g., Salis et al., 2016; Wright et al., 2019). Alternatively, adolescents with chronic underarousal may be generally more inclined to pursue risky behaviors to promote physiological arousal (Brewer-Smyth et al., 2004; Ortiz & Raine,

2004; Platje et al., 2013). Youth may not show cortisol reactivity to a stressor because they are not sensitive to that stressor, or because they have already become elevated in anticipation of a stressor (i.e., anticipatory cortisol). That is, certain youth may be more responsive to the threat such that they already show elevated levels of cortisol prior to stress onset and consequently show no further elevation in cortisol thereafter. Both blunted cortisol reactivity and anticipatory cortisol have been associated with more frequent substance use later in adolescence, especially among youth with difficulties in emotion regulation (Evans et al., 2016; Kliewer et al., 2016; Poon et al., 2016). Dysregulation of HPA axis function may similarly promote risk for lifetime substance use during adolescence. Adolescents with higher basal cortisol had earlier onset of substance use, although cortisol was not assessed following stress (Huizink et al., 2006, 2009; Rao et al., 2009), and blunted cortisol secretion in anticipation of a laboratory task has been linked to greater substance use in pre-pubertal boys (Moss et al., 1999). Given the potential for bidirectional associations between HPA axis function and substance use, longitudinal studies are needed to disentangle whether HPA axis reactivity to and recovery from stress relate to risk for substance use onset during adolescence. Specifically, it is well-established that heavy substance use—as opposed to substance use initiation or less frequent substance use—can dysregulate physiology (Koob & Le Moal, 2008; Lovallo, 2006), so researchers may be best positioned to examine the role of physiology on substance use risk during adolescence when youth are initiating substance use but have not yet engaged in heavy substance use.

In addition to cortisol reactivity, emotion reactivity to stress may relate to substance use. There are several emotion-related risk factors for substance use and substance use disorders in both adults and adolescents, including greater negative emotions, emotional lability, and emotional dysregulation (Hersh & Hussong, 2009; Shadur et al., 2015; Shomaker & Reina, 2015;

Simons & Carey, 2002; Simons et al., 2009). Although it is well-established that emotions influence frequency of substance use among users, it remains unclear whether emotion reactivity to stress relate to adolescents' risk for substance use initiation. Emotion reactivity to stress often includes increases in negative emotions of both high arousal (e.g., anger) and low arousal (e.g., sadness) and decreases in positive emotion, and each form of emotional change can have unique implications for health (e.g., Young et al., 2019). Youth with exaggerated and dampened stress reactivity and recovery with respect to emotion may be particularly at risk for earlier onset of substance use, especially for Mexican-heritage adolescents, who experience culturally-specific stressors (e.g., discrimination, acculturation, immigration stressors; Eskenazi et al., 2019). Therefore, research is needed to determine whether emotion reactivity to stress and recovery from stress is related to substance use and the emergence of substance use among these youth.

Sex Differences in Substance Use Motivation

The impact of stress reactivity and recovery on substance use during adolescence may vary by sex. Adolescents' motivations for substance use differ by sex (Becker et al., 2012; Chaplin et al., 2018). Male youth tend to be more motivated to use substances for social enhancement whereas female adolescents are more motivated to use substances to cope with negative emotion and stress (Kuntsche et al., 2015; Pompili & Laghi, 2019). Further, female adolescents show higher comorbidity between substance use and depression relative to male adolescents, suggesting that emotion and stress may be particularly tied to female adolescents' substance use (Latimer et al., 2002). Therefore, although male adolescents tend to show earlier and more frequent substance use relative to female adolescents (Johnston et al., 2019), substance use may be particularly related to the stress response among female adolescents. Indeed, prior research regarding youth who have used substances by age 16 in this cohort of Mexican-origin

adolescents has found that greater cortisol reactivity relates to earlier age of initiation of alcohol use for girls, whereas blunted cortisol reactivity was related to earlier initiation of marijuana use only for boys with less advanced pubertal status (Johnson et al., 2020). It is critical to disentangle whether differences in stress reactivity and recovery precede substance use across the sexes.

Poverty Status Differences in Substance Use Motivation

Poverty status may also moderate associations between responses to stress and substance for two reasons. First, early life adversity including poverty status has been found to influence psychobiology such that youth who experience early life adversity, including youth below the poverty line, tend to show profiles of blunted cortisol responses to stress (e.g., Joos et al., 2019). Because these youth are already at heightened risk for blunted cortisol responses, the association between these responses and substance use may be stronger among these youth. Second, poverty status may influence adolescents' propensity for substance use. Youth below the poverty line may experience earlier exposure to substance use and substance-related crime, more targeted marketing of substances, and lower parental involvement (Biener & Siegel, 2000; Wills et al., 2004). They may also be more motivated to use substances for reasons beyond stress, such as due to boredom, sensation seeking, and pursuit of enhancing effects in order to compensate for a lack of pleasurable substance-free daily activities (Lee et al., 2018; Martz et al., 2018). Poverty status may similarly influence the types of substances that adolescents use. Whereas cigarette use is more common among youth with lower socioeconomic status, marijuana, alcohol, and vaping are generally more prevalent among more affluent youth, potentially due to differences in cost, availability, and social norms (Jones et al., 2016; Melotti et al., 2011; Patrick et al., 2012). As a result, associations between stress reactivity and recovery and certain substances (i.e., cigarettes, marijuana, alcohol, vaping) may differ by poverty status.

Present Study

The present study investigated whether adolescents' HPA axis and emotion responses to the Trier Social Stress Test (TSST), a validated paradigm for eliciting social-evaluative threat, were related to the use of various substances among Mexican-origin youth growing up in a low-income, high-risk agricultural setting (Kirschbaum et al., 1993). Responses to a social stressor were selected because adolescents tend to be particularly responsive to social threats, compared to younger children and adults (Spear, 2009), and youth often use substances in peer contexts to reduce social stress or enhance social experiences. In line with prior research highlighting how people vary in the types of emotions they experience in response to stress (e.g., Duijndam et al., 2020; Habra et al., 2003), we examined changes in three emotions following stress: anger, sadness, and happiness. Discrete emotions have different functional purposes and have unique impacts on cognitions and judgments (cognitive and judgment changes that occur with the experience of discrete emotions (e.g., Lench et al., 2011; Lerner & Keltner, 2001). Therefore, rather than aggregating across emotions, we assessed unique effects of each emotion. We tested whether stress reactivity and recovery related to substance use among adolescents at heightened risk for substance use, in line with previous studies that have examined substance use initiation in high-risk samples (e.g., Moss et al., 1999).

Most prior studies examining stress responses and substance use have been conducted in the context of adult substance users or with cross-sectional designs (see Moss et al., 1999 as an exception). Therefore, we employed a longitudinal design to disentangle whether dampened psychobiological stress reactivity and recovery at age 14 precede the emergence of substance use initiation by age 16. Models examined whether differences in adolescents' HPA axis and emotion reactivity and recovery to the TSST at age 14 were related to a) use of substances by age

14, b) use of substances by age 16, and c) emergence of substance use between ages 14 and 16, excluding youth who had already used by age 14. Given the high levels of adversity in this sample, dampened psychobiological stress reactivity and recovery were predicted to be associated with use of alcohol and marijuana among these youth, in line with previous research (Evans et al., 2012, 2013; van Leeuwen et al., 2011). Although not previously tested with use of cigarettes and vaping, we examined whether dampened psychobiological reactivity and recovery would similarly relate to these substances which are also commonly used in adolescence.

Finally, models examined whether associations between HPA axis and emotion stress reactivity and recovery and substance use differ by sex and poverty status. Given that female adolescents may be more inclined than male adolescents to use substances to reduce negative emotion (Chaplin et al., 2018), we predicted that associations between dampened stress reactivity and recovery and substance use would be stronger for female adolescents than male adolescents. Because poverty status can promote profiles of dampened reactivity and can influence the types of substances that youth use (e.g., Joos et al., 2019; Melotti et al., 2011), we tested whether associations differ by poverty status.

Method

Participants

Participants were recruited as part of the CHAMACOS study, a longitudinal birth cohort study (Eskenazi et al., 2003). The cohort is comprised of Mexican-origin adolescents and their primary caregivers living in the agricultural Salinas Valley in Monterey County, California. The study includes two cohorts: an initial cohort ("CHAM1") of participants followed from birth and a second cohort ("CHAM2") of 9-year-old children recruited part-way through the study.

At the time of CHAM1 enrollment in years 1999-2000, mothers of CHAM1 children were aged 18 or over and pregnant with the target child, under 20 weeks of gestation, eligible for California's low-income health insurance program (Medi-Cal), receiving prenatal care, and planning to deliver at the county hospital. These CHAM1 women were recruited at pregnancy clinics. Originally, 1,130 women were eligible, 601 were recruited, and 531 remained in the study after childbirth. Of their children, 325 CHAM1 remained enrolled in the study until age 14, with the majority of attrition occurring by age 3. Attrition was highest from pregnancy to delivery and was considerably lower since the assessment at age 5 (Eskenazi et al., 2003). A second cohort (CHAM2) of 300 nine-year-old children were recruited between 2009 and 2011, and they and their mothers have completed the same or comparable data collection activities as CHAM1 families since age 9 (Eskenazi et al., 2003). Like the children from CHAM1, the mothers of CHAM2 children were 18 or older when pregnant with the child, primarily Spanish or English-speaking, eligible for Medi-Cal, and received prenatal care in the Salinas Valley. Retention rates for both cohorts were high between ages 9 and 14 (95% for CHAM1, 94% for CHAM2). These cohorts of adolescents were low-income and had high levels of social adversity. As described in detail in previous articles (Hyland et al., 2022; Johnson et al., 2020; Sagiv et al., 2015), roughly 40% of participants experienced an adverse life event between ages of 6 months and 5 years of age, over 60% of participants had a mother with depression at 1 or 3.5 years of age), over one in four adolescents had three or more adverse childhood experiences, and the sample generally reported high numbers of early life events (M = 4.5, SD = 3.3).

Funding was allocated for the experimental component of the study such that the TSST could only be administered to a subset of participants at age 14 data collection. Recruitment was primarily limited to a subset of CHAM1 participants, and few CHAM2 participants also

completed the TSST. All adolescents needed to meet the following criteria to complete the TSST at age 14: completing the visit in-office (as opposed to the at-home visits conducted with families who had moved from the study area), IQ above 70 at age 12, no diagnosis of Autism Spectrum Disorder, no extreme atypical behaviors at past visits, less than three standard deviations above the mean for depressive scores for their age and sex, and no gang involvement in the previous year given the risk for violent responses to the TSST. No participants reported using anabolic steroids. Importantly, participants who completed the TSST at age 14 did not differ from adolescents who completed surveys at age 14 but did not complete the TSST with respect to sex, mother's education, poverty status, or substance use, *p*s > .06. Please see Figure S1 for a full schematic of attrition across the study.

In total, 277 adolescents (53.19% female; 68.35% below the poverty line; 94.15% from CHAM1 cohort) completed the TSST at age 14 (M = 14.11, SD = 0.18), when the majority of participants were in either 8th grade (59.57%) or 9th grade (34.30%). Two years later, 260 of these adolescents (93.86%) completed additional data collection at age 16 (M = 16.45, SD = 0.27). Participants who completed the study at age 16 did not differ from those who did not with respect to sex, mother's education, poverty status, and cigarette use at age 14, *p*s > .15. However, differences did emerge by substance use, such that participants who did not complete the survey at age 16 were more likely to have used alcohol and marijuana at age 14; $\chi 2(1) = 6.71$, $p = .010$, $\chi 2(1) = 4.86$, $p = .028$, respectively.

We examined poverty status as an indicator of relative socioeconomic status. Poverty status was determined using the poverty-income ratio (i.e., family income divided by the poverty line). About two-thirds of participants had family income below the poverty line for their family size (68.35% below the poverty line), and almost all of the remaining participants were below

200% of the poverty line. Household crowding, calculated by dividing the number of family members by the number of rooms in the household, was negatively correlated with poverty-income ratio, $r(267) = -.18$, $p = .0023$. Participants with a poverty-income ratio below 1 were coded as living below the poverty line ($M_{Below} = 0.90$, $SD = 0.50$), and those with a value above 1 were coded as living above the poverty line ($M_{Above} = 1.06$, $SD = 0.47$), and a *t*-test indicated that individuals above the poverty line had significantly higher poverty-income ratio values compared to those below the poverty line. Adolescents who were in also poverty reported lower mother's education ($M_{Below} = 3.09$, $SD = 1.36$; $M_{Above} = 3.47$, $SD = 1.74$; $t(275) = 2.00$, $p = .047$), compared to adolescents who were not in poverty. There was no difference in poverty status between male and female adolescents, $p = .95$, or by grade at age 14, $p = .16$.

Procedure

At age 14, adolescents completed a study visit starting primarily between 3:00 p.m. and 8:00 p.m., in which they completed the TSST, a validated paradigm for eliciting social-evaluative threat (Dickerson & Kemeny, 2004; Kirschbaum et al., 1993). On average, most participants completed the session at 6:05 ($SD = \pm 2$ hours). Adolescents were in the lab space for two hours completing benign surveys and other measures, in order to attenuate arrival effects and ensure participants acclimated to the laboratory environment (Ruttle et al., 2011; Shirtcliff et al., 2014). They then rested for 10 min. prior to the task and watched a 3 min. soothing video of the sea before being instructed to prepare a speech regarding how they are a good friend. They had 3 min. to prepare the speech and then presented the speech for 5 min. to two confederate 'judges' who appeared to be slightly older than the participant and who were described as experts in evaluating task performance. Immediately afterward, participants completed a mental arithmetic task involving serial subtraction for an additional 5 min. The confederates were trained to

maintain neutral emotion and provide no positive feedback, and adolescents were also obtrusively video recorded throughout the speech and math tasks. Participants were debriefed within 15 min. of completing the task to minimize distress.

This protocol differed from the traditional protocol in the following ways for this population of Mexican-origin adolescents from high adversity backgrounds: confederates were from the local Salinas area and who were from Latinx backgrounds, the difficulty of the math task was titrated such that participants would complete slightly easier math tasks if necessary to keep them consistently engaged with the task, participants were debriefed immediately after the TSST rather than after the full recovery period to avoid having participants feel sustained levels of distress, and gang-affiliated youth were not allowed to complete the task due to both emotional outbursts and threats from at least one gang-affiliated youth and staff concerns about safety. An initial subsample of participants still showed a robust cortisol response, similar to that elicited by a traditional TSST, in spite of these modifications, before administering this protocol to the full sample (see Johnson et al., 2017 for a full description).

Measures

Cortisol

Adolescents provided four 1-2 mL saliva samples via passive drool throughout the task. They provided the first sample after spending over two hours in the laboratory environment, during which they completed benign surveys, and then resting in the lab for 10 min. The second sample was collected immediately after the TSST was completed, roughly 15 min. after TSST onset. The third sample was collected 30 min. after TSST onset, and the fourth and final sample was collected 60 min. after TSST onset. This sampling procedure was similar to previous administrations of the TSST (e.g., Chiang et al., 2017; Gunnar et al., 2009; Hostinar et al., 2014;

Natsuaki et al., 2009). By collecting samples immediately after and 30 min. after TSST onset, we were able to collect saliva samples when cortisol levels were expected to increase post-TSST and increased our chances of capturing peak cortisol response in line with previous guidelines (Dickerson & Kemeny, 2004; Goodman et al., 2017). Samples were frozen at -80^{o}C and later thawed and assayed in duplicate using commercially available enzyme immunoassays (Salimetrics, LLC) in the SPIT lab, with low mean inter- and intra-assay coefficients of variation (12.4% and 6.9%, respectively). Samples were assayed again if the optical-density intra-assay coefficient of variation was over 10%.

Emotion

Adolescents also provided emotion ratings throughout the session. They rated the degree to which they felt happy, sad, and angry at four times: at baseline immediately prior to task onset, and at 15, 30, and 60 min. following task onset. Importantly, at 15 min. following task onset, participants completed two reports: they reported how they felt during the TSST, as well as how they felt at that moment. Participants completed two reports at this time point in order to assess emotion felt during the TSST without interrupting the task itself, and because emotion would be expected to change most between baseline and during the task, as opposed to immediately afterward when participants may feel relieved that the task is finished. This resulted in a total of five emotion ratings, all of which were included in analyses. Adolescents reported each form of emotion on a scale from *1* (not at all) to *10* (extremely). Brief and single-item measures of emotion have been commonly used in assessment of emotion responses to stress tasks and throughout the day (e.g., Kelly et al., 2008; Moons et al., 2010; Steptoe et al., 2005).

Substance Use

Adolescents also reported whether they had ever used alcohol, marijuana, and cigarettes in their lifetime at age 14 using items from the Monitoring the Future survey, with separate items for each substance (Johnston et al., 2019). Two years later at age 16, adolescents again reported whether they had ever used alcohol, marijuana, or cigarettes or vaped nicotine in their lifetime.

Analytic Plan

Models tested the association between adolescents' stress reactivity and recovery at age 14 and substance use by age 14, substance use by age 16, and initiation of substance use between ages 14 and 16. Because participants provided multiple cortisol samples and emotion ratings throughout the protocol, we utilized a multilevel framework with observations (Level 1) nested within participants (Level 2). Specifically, saliva samples and emotion ratings were variables at Level 1 and substance use was measured at Level 2. Multilevel models allow for missing data at Level 1, such that participants could be missing data on a sampling occurrence (e.g., provide insufficient saliva for one time point) and still be included in analyses. Models included 905 total observations for cortisol, and 1,299 total observations for emotion. Number of cortisol samples and emotion ratings did not vary by gender, grade, poverty status reported substance use at age 14, and baseline levels of each emotion, all *p*s > .05. Multilevel models also allow for the number of observations and the specific timing of the collection of each saliva sample to vary across participants, so that the cortisol response to stress can be accurately modeled. This framework leveraged all data and enabled both stress reactivity and recovery to be modeled simultaneously. Participants reported substance use at ages 14 and 16, which enabled testing of whether stress reactivity and recovery at age 14 were related to substance use at age 14, substance use at age 16, and substance use initiation over two years among non-users.

Substance use was collected at the level of the participant (Level 2) and was therefore included as a predictor of stress reactivity and recovery (Level 1), and models tested whether differences in the magnitude of stress reactivity and recovery at age 14 related to whether adolescents had ever used each substance (i.e., alcohol, marijuana, cigarettes, vaping nicotine) by ages 14 and 16. It is important to note that we consistently model cortisol and emotion at age 14 as the outcome, even though differences in the stress response (i.e., reactivity and recovery) are thought to be a risk factor for substance use at age 16. This approach is necessary statistically, as other approaches are unable to simultaneously model stress reactivity and recovery with this number of time points. This modeling also allows for piecewise modeling. There are a total of four samples for cortisol and five reports of emotion, both of which allow for piecewise (i.e., non-linear) assessment. Although three time points are generally needed to predict a linear trend, this modeling of all time points allows for HPA axis recovery to be computed using only two time points and for emotion reactivity to be computed using two time points. Alternative approaches include creating another index (e.g., empirical Bayes estimate, change score, regression coefficient) to test as a predictor of substance use, but these indices generally involve exaggerated error terms or violate statistical assumptions by assuming no error for each value (e.g., Liu et al., 2021; Nebebe & Stroud, 1986). Conceptually this model is appropriate because, just as a correlation reflects a bidirectional association, this model tests the association between substance use and differences in stress reactivity and recovery, irrespective of which is the predictor versus outcome. A similar approach has been used in previous papers (e.g., Shirtcliff & Essex, 2008).

Adolescents' substance use was dummy-coded (0 = never used, 1 = had ever used). Separate models predicted cortisol, anger, sadness, and happiness as a function of adolescents'

substance use. Prior research has highlighted that multilevel models are generally robust to violations of assumptions, including having skewed outcome variables (Schielzeth et al., 2020). Piecewise modeling was used so that reactivity and recovery could be modeled simultaneously within the same model, and reactivity and recovery were estimated separately by calculating separate time terms at Level 1 (e.g., Hastings & Kahle, 2019). Reactivity was calculated as the number of minutes before the sample's peak level, and all subsequent values were coded as 0. Recovery was calculated as the numbers of minutes following peak level, and all prior values were coded 0. To examine associations between stress reactivity and recovery with substance use, we included the substance use dummy-code, the reactivity time term, the recovery time term, and the cross-level Substance Use × Reactivity Time and Substance Use × Recovery Time interactions as predictors in the model. The reactivity time and recovery time variables were included as random effects. Models used the following equations:

$$L1\text{: } \widehat{Cortisol\ or\ Emotion}_{ij} = \beta_{0j} + \beta_{1j}(Reactivity\ Time) + \beta_{2j}(Recovery\ Time)$$

$$L2\text{: } \beta_{0j} = \gamma_{00} + \gamma_{01}(Substance\ Use) + \gamma_{02}(Sex) + \gamma_{03}(Poverty\ Status) + \gamma_{04}(Mother's\ Education) + \gamma_{05}(Grade) + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + \gamma_{11}(Substance\ Use) + u_{1j}$$

$$\beta_{2j} = \gamma_{20} + \gamma_{21}(Substance\ Use) + u_{2j}$$

Significant interactions were probed at the two levels of substance use (i.e., never used, had ever used). Because cortisol and emotion were assessed at different time points, the time variables were coded differently for each outcome, as described in the Results section. When interactions were significant, we also probed simple slopes to examined whether there were differences in baseline levels of cortisol and emotion by substance use. These analyses enabled assessment of whether associations were potentially driven by differences at baseline, and whether substance use may also relate to tonic differences in cortisol and emotion.

Next, analyses examined whether stress reactivity and recovery at 14 predicted lifetime use of alcohol, marijuana, cigarettes, and vaping nicotine by age 16. Finally, we repeated these models excluding adolescents who were already using each substance by age 14. This way, models examined whether stress reactivity and recovery were related to emergence of substance use over the next two years. Finally, three-way interaction terms were included in multilevel models predicting cortisol and emotion to test whether associations between substance use and both reactivity and recovery varied by sex (i.e., Substance Use × Reactivity Time × Sex and Substance Use × Recovery Time × Sex) and poverty status (i.e., Substance Use × Reactivity Time × Poverty Status and Substance Use × Recovery Time × Poverty Status). Significant interactions were probed using simple slopes at each level of sex (male, female) and poverty status (below poverty line, above poverty line). These models used the following equations:

$$L1\text{: } \widehat{Cortisol\ or\ Emotion}_{ij} = \beta_{0j} + \beta_{1j}(Reactivity\ Time) + \beta_{2j}(Recovery\ Time)$$

$$L2\text{: } \beta_{0j} = \gamma_{00} + \gamma_{01}(Substance\ Use) + \gamma_{02}(Poverty\ Status) + \gamma_{03}(Substance\ Use * Poverty\ Status) + \gamma_{04}(Sex) + \gamma_{05}(Mother's\ Education) + \gamma_{06}(Grade) + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + \gamma_{11}(Substance\ Use) + \gamma_{12}(Sex) + \gamma_{13}(Substance\ Use * Sex) + u_{1j}$$

$$\beta_{2j} = \gamma_{20} + \gamma_{21}(Substance\ Use) + \gamma_{22}(Poverty\ Status) + \gamma_{23}(Substance\ Use * Poverty\ Status) + u_{2j}$$

$$L1\text{: } \widehat{Cortisol\ or\ Emotion}_{ij} = \beta_{0j} + \beta_{1j}(Reactivity\ Time) + \beta_{2j}(Recovery\ Time)$$

$$L2\text{: } \beta_{0j} = \gamma_{00} + \gamma_{01}(Substance\ Use) + \gamma_{02}(Sex) + \gamma_{03}(Substance\ Use * Sex) + \gamma_{04}(Poverty\ Status) + \gamma_{05}(Mother's\ Education) + \gamma_{06}(Grade) + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + \gamma_{11}(Substance\ Use) + \gamma_{12}(Sex) + \gamma_{13}(Substance\ Use * Sex) + u_{1j}$$

$$\beta_{2j} = \gamma_{20} + \gamma_{21}(Substance\ Use) + \gamma_{22}(Sex) + \gamma_{23}(Substance\ Use * Sex) + u_{2j}$$

All models included the following covariates: sex (0 = male, 1 = female), poverty status at age 14 (below poverty line = 0, above poverty line = 1), parents' education (grand-mean

centered), and grade at age 14 for substance use by age 14 (grand-mean centered, 0 = 8th grade) and grade at age 16 for analyses of substance use by age 16 (grand-mean centered, 0 = 10th grade). All associations were maintained in unadjusted models. Finally, due to concerns regarding skewness of emotion ratings and salivary cortisol, all analyses were repeated after natural log transforming values with extreme skewness (i.e., exceeding 1).

A statistical correction was incorporated for the number of effective tests. The study was designed to test whether (1) HPA axis reactivity and recovery and (2) emotional reactivity and recovery were related to use of different substances. Given that substances have different effects and results may not carryover across substances, analyses of HPA axis and emotional reactivity and recovery for each substance were treated as a separate family of analyses. Three related measures of emotion were administered. Because the emotion items showed a high factor loading using exploratory factor analysis both at baseline and across assessments (eigenvalue = .90), we completed separate analyses of each emotion and incorporated a correction for the degree to which emotion items were related to one another (i.e., the degree to which they were independent analyses; e.g., Purves et al., 2019). The high inter-relatedness of items suggests that analyses are largely non-independent, which resulted in a critical *p*-value of .046.

Results

Most participants had never used each substance by age 14, with 19.26% using alcohol, 17.21% using marijuana, and 7.32% using cigarettes by 14. Use of alcohol (40.24%), marijuana (31.30%), and cigarettes (11.38%) increased by age 16, and the number of youth who had used each substance significantly increased from ages 14 to 16, all McNemar's $\chi^2(1) > 4.5$, *p*s < .05.

Descriptive statistics and figures illustrating changes in cortisol and emotion over time are given in supplementary materials (Tables S1-S4, Figs. S2-S3). Repeated measures ANOVAs

indicated that there was no mean-level change in cortisol levels across the sample, $F(3) = 0.86$, $p = .5$, suggesting that on average participants did not show robust changes in cortisol across the TSST. Repeated measures ANOVAs indicated robust changes in each form of emotion and significant quadratic effects, suggesting that participants on average displayed reactivity in the form of changes between baseline and immediately following the TSST and displayed recovery across the 60 min. following task onset; $F(4) = 184.78$, $F_{quadratic}(4) = 307.95$ for happiness, $F(4) = 93.16$, $F_{quadratic}(4) = 125.10$ for sadness, $F(4) = 25.67$, $F_{quadratic}(4) = 33.85$ for anger, all ps $< .001$. Adolescents' happiness and anger returned to baseline levels by 60 min post-TSST onset, t's $< .6$, $p > .5$, and adolescents were significantly less sad at the end than at the start of the session, $t(249) = 4.23$, $p < .001$. HPA axis reactivity and recovery were generally not related to emotion reactivity and recovery, with the exception that greater cortisol recovery was related to blunted anger reactivity and recovery among adolescents above the poverty line (Table 1).

Cortisol and Substance Use Associations

Piecewise multilevel models were used to examine whether substance use was related to differences in cortisol reactivity and recovery simultaneously. Time was centered at the second cortisol sample, 30 min post-task onset, because salivary cortisol tends to peak 20-30 min following stress onset. Separate time terms were calculated for reactivity and recovery (Hastings & Kahle, 2019). Reactivity time was coded as the number of minutes prior to the 30 min. sample and was coded as 0 for samples following 30 min. post-task onset, and recovery time was coded as the number of minutes following the 30 min. sample and as 0 for samples before 30 min. post-task onset. Coefficients for reactivity time and recovery time represent the change in cortisol per minute. Models tested interactions between substance use and time variables as predictors of cortisol to determine whether the magnitude of cortisol reactivity and recovery differed between

adolescents who had versus had never used each substance by age 14. Models were repeated with substance use at age 16, and interactions were probed to examine cortisol reactivity and recovery at age 14 for adolescents who had versus had never used each substance by age 16.

These models did not suggest that cortisol reactivity or recovery was related to use of alcohol, marijuana, cigarettes, or vaping nicotine use by ages 14 or 16 (Tables S5-S11). There was also consistently no main effect of poverty status on cortisol across all models, *p*s > .05.

Moderation of Associations between Cortisol Reactivity and Recovery and Substance Use

Models then examined moderation of associations by poverty status and sex by including three-way interactions (Tables S12-S18 for poverty status, Tables S19-S25 for sex). There was no significant moderation of associations between either cortisol reactivity or recovery and substance use by sex for any substance, all *p*s > .05. Poverty status significantly moderated associations between cortisol reactivity and alcohol use by age 14 ($B_{\text{Reactivity}}$ = -0.007, *SE* = 0.003, *p* = .010; B_{Recovery} = -0.005, *SE* = 0.003, *p* = .142), alcohol use by age 16 ($B_{\text{Reactivity}}$ = -0.004, *SE* = 0.002, *p* = .042; B_{Recovery} = -0.001, *SE* = 0.003, *p* = .594), and vaping of nicotine by age 16 ($B_{\text{Reactivity}}$ = -0.005, *SE* = 0.002, *p* = .040; B_{Recovery} = -0.003, *SE* = 0.003, *p* = .243). Specifically, there was no association between cortisol reactivity and either use of alcohol by age 14 or vaping nicotine by age 16 for adolescents below the poverty line, *p*s > .4. Among adolescents above the poverty line, blunted cortisol reactivity to the TSST was associated with use of alcohol by 14 and vaping of nicotine by 16. Blunted cortisol reactivity to the TSST—as indicated by smaller increases in cortisol following the TSST at age 14—were observed for adolescents who had used alcohol by 14 and those who proceeded to vape nicotine by 16 compared to those who did not (Fig. 1). This difference appeared to be driven by elevated baseline cortisol among adolescents who used alcohol by 14 and those who proceeded to vape

nicotine by 16. In contrast, adolescents below the poverty line who had used alcohol by 14 or who had vaped nicotine by 16 had significantly blunted cortisol reactivity to the TSST (Supplemental Fig. S2). Despite the significant interaction term for use of alcohol by age 16, associations between cortisol reactivity and alcohol use were non-significant when probing the association between blunted cortisol reactivity and use of alcohol by age 16 at different levels of poverty status.

We also tested whether substance use was related to differences in baseline cortisol. Simple slopes analyses indicated that adolescents who had used alcohol by age 14 had higher cortisol at baseline than adolescents who had not used alcohol by age 14 (B = 0.19, SE = 0.06, p = .003), but that there was no significant difference in baseline cortisol between youth who had and those who had never vaped nicotine by age 16 (B = 0.09, SE = 0.05, p = .095). Associations between cortisol reactivity and alcohol use by age 14 and vaping nicotine by age 16 remained significant when controlling for baseline salivary cortisol. When analyses were repeated covarying for TSST start time, all significant results remained significant. There were 10 cortisol values that were over four standard deviations above the mean and 22 cortisol values that were over three standard deviations above the mean for that time point. The same pattern of associations between cortisol reactivity and recovery and substance use was observed when using unadjusted values, when winsorizing these values to three and four standard deviations, and when excluding these values.

Emotion Reactivity and Recovery and Substance Use by Age 14

Again, reactivity and recovery were modeled simultaneously within the same model using all five reports of emotion, and reactivity and recovery were estimated by calculating separate time terms (Hastings & Kahle, 2019). As expected, participants reported feeling the

most extreme levels of emotion during the TSST using the retrospective report. This report was coded as how participants felt at the midpoint of the TSST, which lasted about 15 min. in total, and each assessment was coded with respect to the number of minutes before or after the middle of the TSST. Therefore, the baseline report was 7.5 min. before the middle of the TSST, and the reports following the TSST were 7.5, 22.5, and 52.5 min. following the middle of the TSST.

For the reactivity time variable, baseline emotion was coded as -7.5 and all subsequent time points were coded as 0, so that this coefficient would only measure changes in emotion between prior to the TSST and during the TSST. Ideally, three or more time points would be used to estimate a linear trajectory. However, within this experimental context, it was not feasible to include another assessment of emotion that would improve estimation of emotion reactivity. For the recovery time variable, the ratings of emotion at baseline and during the TSST were coded as 0, and the subsequent three time points were coded with respect to the number of minutes following the middle of the TSST (i.e., 7.5, 22.5, and 52.5). Coefficients for the time variables represent the rate of change in emotion per minute.

First, models tested whether emotion reactivity to and recovery from the TSST at age 14 were related to whether adolescents had ever used substances by age 14 (Tables S5-S7). Neither changes in anger nor happiness were related to substance use, all *p*s > .07. Sadness reactivity to the TSST was related to marijuana use by age 14 ($B_{\text{Reactivity}}$ = -0.08, *SE* = 0.03, *p* = .023; B_{Recovery} = 0.005, *SE* = 0.004, *p* = .298). Blunted reactivity (i.e., smaller increases) in sadness between pre- and immediately post-TSST was observed in adolescents who had used marijuana relative to adolescents who had not used marijuana by age 14.

Analyses then tested whether emotion reactivity and recovery at age 14 related to lifetime substance use by age 16 (Tables S8-S11). Again, anger reactivity and recovery were not related

to substance use. Sadness reactivity to and recovery from the TSST at age 14 was related to adolescents' marijuana use by age 16 ($B_{Reactivity}$ = -0.07, *SE* = 0.03, *p* = .018; $B_{Recovery}$ = 0.008, *SE* = 0.004, *p* = .044). Smaller increases in sadness immediately following the TSST at age 14 and smaller decreases across the recovery period were found in youth who had used marijuana by age 16 relative to those who had never used marijuana by age 16. However, results were non-significant when excluding individuals who had already used marijuana by age 14, suggesting that the association was driven by adolescents who had used marijuana by age 14 rather than youth who began using marijuana between ages 14 and 16.

Happiness reactivity to the TSST was also associated with adolescents' use of alcohol by age 16 ($B_{Reactivity}$ = 0.09, *SE* = 0.04, *p* = .042; $B_{Recovery}$ = -0.01, *SE* = 0.01, *p* = .195; Fig. 2) and use of marijuana by age 16 ($B_{Reactivity}$ = 0.11, *SE* = 0.05, *p* = .022; $B_{Recovery}$ = -0.004, *SE* = 0.007, *p* = .562). Whereas decreases in happiness in response to the TSST were found for adolescents who did not use alcohol and marijuana by age 16, smaller changes in happiness between before and immediately after the TSST (i.e., blunted happiness reactivity) were found in adolescents who had used alcohol and marijuana by age 16. The association between happiness reactivity to the TSST at age 14 and use of alcohol by age 16 was no longer significant when limiting the sample to participants who had never used alcohol by age 14 ($B_{Reactivity}$ = 0.10, *SE* = 0.05, *p* = .055; $B_{Recovery}$ = -0.008, *SE* = 0.007, *p* = .273). However, the association between happiness reactivity to the TSST at age 14 and use of marijuana by age 16 was maintained when limiting the sample to participants who had never used marijuana by age 14 ($B_{Reactivity}$ = 0.14, *SE* = 0.06, *p* = .014; $B_{Recovery}$ = -0.004, *SE* = 0.009, *p* = .675) suggesting that this association was apparent in youth who initiated substance use between ages 14 and 16.

Moderation of Emotion Reactivity and Recovery and Substance Use Associations

Next, models tested whether associations between emotion reactivity and recovery and substance use varied by poverty status (Tables S12-S18) and by sex (Tables S19-S25). Poverty status moderated associations between sadness reactivity and recovery and adolescents' use of marijuana by age 16 ($B_{\text{Reactivity}}$ = 0.09, *SE* = 0.06, *p* = .1; B_{Recovery} = -0.03, *SE* = 0.01, *p* = .035) and between sadness reactivity, but not recovery, and use of alcohol by age 16 ($B_{\text{Reactivity}}$ = 0.13, *SE* = 0.06, *p* = .028; B_{Recovery} = -0.02, *SE* = 0.01, *p* = .058). However, when probing simple slopes at different levels of poverty status, associations between sadness reactivity and recovery and alcohol use were non-significant, *p*s > .07.

When examining moderation by sex, results suggested that emotion reactivity and recovery to the TSST were related to substance use primarily in female adolescents. First, sex differences emerged in the associations between anger and sadness reactivity and recovery to the TSST and marijuana use by age 14, such that associations were only apparent among female adolescents. Blunted anger reactivity (i.e., smaller increases in anger immediately following the TSST) and recovery (i.e., smaller decreases in anger across the recovery period) were associated with marijuana use by age 14 in female adolescents ($B_{\text{Reactivity}}$ = -0.21, *SE* = 0.10, *p* = .029; B_{Recovery} = 0.03, *SE* = 0.01, *p* = .028; Fig. 3a). Similarly, both blunted sadness reactivity and recovery were associated with marijuana use by age 14 in female adolescents ($B_{\text{Reactivity}}$ = -0.23, *SE* = 0.07, *p* < .001; B_{Recovery} = 0.02, *SE* = 0.01, *p* = .024; Fig. 3b). In contrast, male adolescents' emotion reactivity and recovery were consistently not related to marijuana use by age 14.

Associations between emotion reactivity and recovery to stress at age 14 and substance use by age 16 also emerged in female adolescents. We observed sex differences in associations between sadness reactivity to the TSST at age 14 and alcohol use by age 16 ($B_{\text{Reactivity}}$ = -0.12, *SE* = 0.05, *p* = .035; B_{Recovery} = 0.01, *SE* = 0.01, *p* = .148) and between sadness recovery from the

TSST at age 14 and marijuana use by age 16 ($B_{Reactivity}$ = -0.11, *SE* = 0.06, *p* = .056; $B_{Recovery}$ = 0.02, *SE* = 0.01, *p* = .030). Again, whereas sadness reactivity and recovery were not related to substance use in male adolescents, blunted sadness reactivity was associated with alcohol use by age 16 (Fig. 4a) and blunted sadness recovery was associated with use of marijuana by age 16 in female adolescents (Fig. 4b). However, neither associations was maintained after excluding adolescents who had used each substance by age 14; taken together, there was no evidence that sadness reactivity and recovery were related to the emergence of substance use between ages 14 and 16 among non-users.

Finally, among female adolescents, happiness reactivity to the TSST at age 14 was related to use of cigarettes ($B_{Reactivity}$ = 0.29, *SE* = 0.14, *p* = .039; $B_{Recovery}$ = -0.04, *SE* = 0.02, *p* = .071) and marijuana by age 16 ($B_{Reactivity}$ = 0.26, *SE* = 0.09, *p* = .005; $B_{Recovery}$ = -0.03, *SE* = 0.01, *p* = .050). A similar pattern emerged, as blunted happiness reactivity was related to use of cigarettes and marijuana by age 16 among female but not male adolescents (Fig. 5a,b). These associations remained significant when excluding adolescents who had used each substance by age 14, suggesting that blunted happiness reactivity was related to the emergence of cigarette use and marijuana use between ages 14 and 16 among female non-users. When probing simple slopes to examine differences in baseline emotion, we found that female adolescents who had used cigarettes by age 16 had significantly lower happiness at baseline compared to female adolescents who had never used cigarettes by age 16 (*B* = -2.48, *SE* = 0.94, *p* = .008). Similarly, female adolescents who had used marijuana by age 16 reported marginally lower happiness at baseline at age 14 compared to female adolescents who had never used marijuana by age 16 (*B* = -1.11, *SE* = 0.55, *p* = .046). We therefore re-tested models controlling for baseline happiness, and

associations between happiness reactivity and cigarette and marijuana use by age 16 remained significant.

Variable Transformation

Finally, as a robustness check, we re-tested all models after transforming distributions of outcome variables to account for skew. Cortisol values were positively skewed, as the majority of participants show low levels of salivary cortisol (skewness = 2.58). Happiness was not skewed (skewness = 0.00), but anger and sadness were positively skewed such that participants tended to report very low levels of each emotion (skewness = 2.38 for anger, 3.00 for sadness). Therefore, cortisol, anger, and sadness values were natural log transformed, although anger and sadness distributions remained skewed, albeit to a lower degree (skewness = 0.33 for cortisol, 1.51 for anger, 2.08 for sadness). All associations remained significant with one exception: anger reactivity was no longer significantly related to marijuana use by age 14 among female adolescents, $p = .107$.

Discussion

Although difficulties with stress regulation are related to more frequent substance use among users (e.g., Koob & Kreek, 2007), less is known regarding whether psychobiological responses to stress relate to substance use and precede initiation of use in adolescence. Therefore, the present study investigated whether dampened HPA axis and emotion responses to stress were related to substance use in a sample of Mexican-origin adolescents who had experienced high levels of adversity. Findings suggested that differences in HPA axis and emotion responses to social-evaluative stress relate to—and in some cases temporally precede—substance use among these adolescents, although associations varied by poverty status and sex. Dampened cortisol reactivity was related to use of alcohol by age 14 and vaping nicotine by age 16 among youth

above the poverty line, although there was no evidence that cortisol reactivity related to initiation of use of substances between ages 14 and 16. In turn, dampened emotion responses to stress were related to substance use primarily in female adolescents. Among female adolescents, blunted anger reactivity was related to marijuana use by age 14, and blunted sadness reactivity and recovery were related to use of alcohol by age 16 and use of marijuana by ages 14 and 16. Blunted happiness reactivity was related to use of alcohol by age 16, regardless of sex, and to the emergence of use of marijuana and cigarettes between ages 14 and 16 among female adolescents who had not used these substances by age 14. Differences in associations between stress reactivity and recovery and substance use by poverty status and sex may be due to differences in adolescents' access to substances or differences in motivation for substance use.

Cortisol Responses to Stress and Substance Use among Youth Above the Poverty Line

Dampened cortisol reactivity was related to use of alcohol by age 14 and vaping of nicotine by age 16 for youth above, but not below, the poverty line. These findings align with prior work suggesting that blunted cortisol responses to stress relate to riskier substance use four years later among adolescents (Evans et al., 2016). Differences in stress physiology have been related to greater substance use among users (e.g., Sinha, 2001; Wemm & Sinha, 2019), as well as greater risk for substance use initiation among youth (Evans et al., 2016; Kliewer et al., 2016; Moss et al., 1999; Poon et al., 2016). Inability to elicit a cortisol response from a stressor may suggest inflexibility of the HPA axis, such that people are unable to mobilize biological resources in the context of stress. Dampened cortisol reactivity may be indicative of difficulties with regulating stress, as strategies for emotion regulation have been linked with psychobiological responses to stress (e.g., Lam et al., 2009). For instance, prior studies have found that adolescents and adults with poorer emotion regulation show blunted cortisol reactivity

to stress, often characterized by consistently high levels of cortisol (Ayer et al., 2013; Kliewer et al., 2016; Krkovic et al., 2018). Furthermore, moderate cortisol responses to stress can promote executive function including emotion processing and behavioral inhibition during stress (Peters et al., 2016; Shields et al., 2015). Stress responses may be particularly tied to emotion regulation during adolescence, when youth are particularly sensitive to social threat and are still developing strategies for emotion regulation (Spear, 2009; Zimmermann & Iwanski, 2014). Although associations with alcohol use at age 14 were cross-sectional, most evidence regarding the effect of substance use on HPA axis function has been observed among heavy users (Koob & Le Moal, 2008; Lovallo, 2006), and we do not have heavy use in this sample given participants' age. Therefore, a potentially more probable pathway is that differences in the stress response may confer risk for substance use.

Interestingly, youth above the poverty line who used alcohol by age 14 had higher levels of baseline salivary cortisol compared to youth who had never used alcohol by age 14. Although adolescents had two hours in the laboratory environment to acclimate to space and to rule out an arrival effect (Shirtcliff et al., 2014), there is a chance that adolescents who showed higher levels of salivary cortisol at baseline may have been stressed in anticipation of the TSST, in line with previous findings that adolescents with anticipatory reactivity may be at higher risk for substance use (Evans et al., 2016; Moss et al., 1999). An alternative possibility is that these youth tend to show chronically higher levels of cortisol output as well as dampened reactivity to the task, although this possibility seems somewhat unlikely given that there were no differences in cortisol across the recovery period.

Associations between dampened cortisol responses and substance use only emerged for youth above the poverty line. This finding was particularly interesting given that this sample of

adolescents was very low-income overall (per the selection criteria into the parent study). We assessed differences by poverty status because youth living in poverty often experience additional stressors that can influence their risk for substance use. However, it is important to note that this sample is still low-income overall, such that results may not generalize to differences in socioeconomic status among wealthier (e.g., middle and upper class) adolescents. First, youth who experience relatively more adversity or more challenging home environments are more likely to show blunted cortisol responses to stress (e.g., Joos et al., 2019; Peckins et al., 2016). Therefore, blunted cortisol reactivity to stress may be more consistently related to substance use among youth above the poverty line, whereas blunted responses relate to environmental factors among youth below the poverty line.

Second, associations emerged only for alcohol and vaping nicotine, which tend to be more commonly used among youth with higher family income (Jones et al., 2016; Melotti et al., 2011; Patrick et al., 2012). In this study, adolescents above the poverty line may have been more exposed to alcohol and vaping, specifically, compared to youth below the poverty line. Importantly, irrespective of family poverty status, adolescents may still be able to access substances that they find at home. Third, poverty status may influence adolescents' motivations for substance use; stress may relate to substance use for youth above the poverty line, whereas youth below the poverty line may turn to less costly means of stress relief or may also use substances for alternative reasons. For instance, adolescents with lower parental education engage in fewer pleasurable substance-free activities, and may aim to use substances to amplify positive emotions (Andrabi et al., 2017; Lee et al., 2018). High basal cortisol or dampened cortisol reactivity may be indicative of difficulties with emotion regulation (Krkovic et al., 2018), and difficulties with emotion regulation may more strongly relate to substance use for

youth above the poverty line. Associations between stress responses and substance use may differ by levels of socioeconomic status, and it is important to note that the poverty rate was much higher in the present sample than in the county due to the inclusion criteria of the parent study. Therefore, findings may generalize to families who are lower on the distribution of income, but not to associations between income and substance use among more affluent families. Future research is needed to examine whether adolescents' access to and motivation for substances can explain why associations between dampened cortisol reactivity to stress and alcohol use by age 14 and vaping by age 16 differ by poverty status, and whether similar associations are observed among affluent youth.

Emotion Responses to Stress and Substance Use among Female Adolescents

In addition to HPA axis responses to stress, we found that dampened emotion reactivity to social-evaluative threat was related to alcohol, marijuana, and cigarette use, particularly among female adolescents. Substance use may have been related to dampened rather than exaggerated emotion responses to the TSST because of the nature of this laboratory stressor. Although modified to be culturally sensitive and to avoid eliciting undue distress (Johnson et al., 2017), the TSST can be a particularly taxing stressor. This may have caused youth to disengage rather than actively cope with the task and thereby manifested in dampened stress reactivity (Carroll et al., 2017). Engagement in strategies such as distraction has been related to emotional and behavioral difficulties specifically for youth who show blunted cortisol responses to social stress (Bendezú et al., 2021). Additionally, these youth have backgrounds of high adversity and life stress which may have contributed to dampened emotion responses. Previous research has indicated that youth who experience adversity show reductions in activation of neural regions related to threat and emotion processing (Ginty et al., 2013; Yang et al., 2015).

Several associations between dampened emotion responses and substance use were unique to female adolescents, potentially related to sex differences in adolescents' motivations for substance use (e.g., Chaplin et al., 2018). It is important to note that although emotion responses to stress were more related to substance use in female than in male adolescents, male adolescents tend to be at higher risk for earlier substance use (Johnston et al., 2019). Our results suggest that stress responses may be particularly related to substance use and substance use initiation among female adolescents, although male adolescents may have different motivations that place them at higher risk for substance use more generally. Prior research has found that female adolescents are more motivated to use substances to reduce stress and negative emotion, whereas male adolescents are more motivated to use substances for social benefits (Kuntsche & Müller, 2012; Kuntsche et al., 2015; Pompili & Laghi, 2019), and that stress is more strongly related to substance use in female than in male adolescents (Chaplin et al., 2018; Jun et al., 2015). Future research should investigate the factors that contribute to male adolescents' risk for substance use.

Alcohol and marijuana use may have been more consistently related to emotion responses than cigarettes or vaping because alcohol and marijuana are the most commonly used substances during adolescence and are often used to reduce stress (Cooper et al., 2016). Cigarette use may have only related to happiness reactivity but not sadness or anger reactivity because of the low prevalence of use in this sample, as cigarettes have declined in popularity over time especially among Latinx youth (Miech et al., 2020; Rolle et al., 2015). Emotion reactivity may not have been related to vaping of nicotine because vaping is more frequently used for experimentation and taste rather than to influence stress and emotion (Evans-Polce et al., 2018; Jones et al., 2016;

Temple et al., 2017). Further information on adolescents' motivation for use may provide insight regarding the mechanisms relating substance use and emotion responses to stress.

Finally, sadness and happiness reactivity were more consistently related to substance use than anger reactivity. Anger reactivity was only related to marijuana use by age 14 among female adolescents, and this association was not maintained after transforming the data to account for skew. Studies that examine whether anger reactivity and recovery relate to substance use can consider other paradigms or forms of stress that elicit a more robust change in anger. Substances are commonly used to reduce sadness and stress and to increase positive emotion (e.g., Cooper et al., 2016), which may explain why associations emerged between sadness and happiness reactivity, but not anger reactivity, and substance use. Although prior research has emphasized the role of negative emotions in motivation for substance use (e.g., Gould et al., 2012), dampened happiness reactivity was uniquely related to initiation of cigarette and marijuana use between ages 14 and 16 among female adolescents. We also found that female adolescents who used marijuana and cigarettes by age 16 reported lower levels of happiness at baseline than female adolescents who never used these substances by age 16, but no differences in other emotions. It is possible that these youth use substances to promote positive emotion, or that lower positive emotion reactivity may indicate lower reactivity to other positive daily activities and greater inclination to use substances. Positive emotion has received relatively less attention in the context of stress responses, but the present findings suggest that future studies incorporating social-evaluative threat would be well-positioned to examine how happiness and different dimensions of positive emotion relate to substance use in the context of stress. Further research is needed to understand how dampened positive emotion reactivity may confer risk for substance use in adolescence.

Limitations

Findings must be interpreted within the context of the study design. Results at age 14 may suggest that substance use can influence adolescents' stress reactivity and ability to self-regulate within the context of stress. In turn, stress reactivity at age 14 may relate to substance use at age 16 through various mechanisms, such as through greater inclination to use substances to relieve stress, greater risk-taking, or greater susceptibility to peer pressure, which should be explored in future studies. There were limitations in cortisol assessment. The present study lacked data regarding current use of anxiolytics and antidepressants, both of which could influence cortisol responses. Estimates of cortisol recovery may be affected because participants were debriefed shortly after completing the TSST. Whereas other protocols collect all saliva samples prior to debriefing, the TSST was highly distressing for many participants in this sample, and debriefing occurred earlier to ensure adolescents were not distressed for longer than necessary (detailed in Johnson et al., 2017). This decision may have resulted in higher levels of recovery than would have been experienced otherwise. Although we utilized a social stressor given the high salience of social threats during adolescence, future studies can assess whether similar results are assessed with respect to nonsocial stressors (e.g., physical stressors, stressful film clips or photographs). Also, due to the low number of assessments, we needed to anchor responses at the sample peak rather than at each participant's peak. We could not use analytic techniques such as Landmark registration because we would be unable to assess recovery for a subset of participants who peaked at the fourth time point. Future studies should include multiple assessments of salivary cortisol throughout the recovery period so that this technique can be used.

The present study was limited by the assessment of substance use and emotion. Because adolescents reported whether they had ever used each substance at age 14 and again at age 16, items may assess experimentation, and it is possible that adolescents may have only used a substance once and never again (Kuntsche et al., 2016). Frequency of use over the past month or past year may be a better indicator of adolescents' substance use and risk for problems with substance use in adulthood, although these outcomes had limited variability in the current sample at these ages. Future studies with greater variability in frequency or with slightly older samples should examine how frequency of use is related to differences in the stress response. Furthermore, without items regarding the context of daily use, it is difficult to determine the mechanisms by which differences in stress reactivity relates to substance use. Another important limitation of the present study is that stress responses were measured only at age 14, such that we cannot assess the stability of responses at age 14 and age 16 and cannot determine whether stress responses at age 14 confer risk for substance use at age 16 over and above current concurrent stress responses at age 16.

Additionally, only three discrete emotions were measured, and participants were not able to report how they felt at that moment during the TSST. Potentially by using a different stress paradigm or passive assessment tools, participants could report their emotion as they experienced the stressor rather than immediately afterward in order to limit bias due to retrospective report and maintain consistency across ratings. We also had multiple ratings of emotion across the recovery period, but only one measure of emotion prior to the TSST. Future studies should employ experimental paradigms that allow for incorporation of more assessments of emotion during the stress task and therefore enable better estimation of emotion reactivity to stress. Results could also potentially vary by analytic approach, and other approaches such as

longitudinal structural equation modeling can be used. Given the design of this study, multilevel models allow for all available data to be included, while allowing for timing of individual assessments to vary across participants and allowing for random intercepts and random slopes of reactivity and recovery.

Finally, analyses were tested in a primarily Mexican-origin sample of adolescents with high levels of adversity and poverty, who may be at heightened long-term risk for substance use. We studied youth with high substance use risk because of our interest in how stress responses relate to substance use, as has been done in previous studies (Evans et al., 2016; Moss et al., 1999). We anticipated that the stress responses may be more related to substance use among youth who experience more major negative life events and chronic daily stressors, as these youth may be more inclined to use substances as a means of decreasing negative emotion as opposed to other purposes such as increasing positive emotion compared to other populations (Stein et al., 2016). Therefore, although our results suggest dampened stress responses may predict substance use in this sample, effects may be weaker in other adolescent samples with less adversity. This study was embedded within a larger longitudinal birth-cohort study and therefore limited by attrition. It is possible that mothers who chose to participate in the study and to continue for multiple assessments may have differed from those who did not, although retention since age 9 was around 95%. Given limitations, results should be replicated among diverse populations, as well as other samples of Mexican-origin youth. Lastly, the study was limited to youth who had no gang involvement because of risk for violent responses to the TSST. This criterion may have attenuated associations, as gang members often show greater substance use (Sanders, 2012).

Conclusions

Dampened HPA axis and emotion responses to stress were related to adolescents' substance use for certain groups (i.e., adolescents above the poverty line, female adolescents). These results suggest that dampened stress responses can be a risk factor for adolescent substance use, and may indicate difficulties with responding to stress. Specifically, dampened cortisol reactivity was related to use of alcohol by age 14 and vaping of nicotine by age 16 among adolescents above the poverty line, and dampened happiness reactivity specifically was found to temporally precede initiation of use of cigarettes and marijuana among female adolescents. Poverty status differences may have emerged because early adversity and poverty status can influence HPA axis function, whereas differences by sex may have emerged because female adolescents may be particularly motivated to use substances to relieve stress and influence emotion. Taken together, these findings illustrate how adolescents' capacity for responding to stress can influence substance use and potentially position these adolescents for poorer mental health and long-term outcomes in adulthood.

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Table 1. Correlations between emotion and cortisol reactivity and recovery.

Group (Sample Size)		Happiness Reactivity	Happiness Recovery	Sadness Reactivity	Sadness Recovery	Anger Reactivity	Anger Recovery	Nervous Reactivity	Nervous Recovery
Full Sample (194-210)[a]	Cortisol Reactivity	.03	-.07	-.08	-.02	.15*	-.14*	-.03	-.01
	Cortisol Recovery	-.07	.09	.01	.07	-.09	.09	.05	-.01
Below the Poverty Line (127-137)	Cortisol Reactivity	.09	-.11	-.07	-.01	.04	-.05	.03	-.02
	Cortisol Recovery	-.11	.12	-.04	.09	-.03	.01	.02	.00
Above the Poverty Line (63-70)	Cortisol Reactivity	-.15	.05	-.09	-.06	.33**	-.30*	-.10	.00
	Cortisol Recovery	.02	.03	.08	.09	-.27	.29	.11	.00
Female (116-119)	Cortisol Reactivity	.10	-.14	-.15	.06	.17*	-.13*	.00	-.06
	Cortisol Recovery	-.01	.04	.15	-.04	-.02	.01	.01	.11
Male (78-91)	Cortisol Reactivity	-.01	.00	-.11	.09	-.12	.02	-.07	.08
	Cortisol Recovery	-.16	.17	.19	-.14	.16	-.16	.11	-.15

Note: *$p < .05$, **$p < .01$. Reactivity was calculated as the number of standard deviations change in emotion from baseline to during the task and in cortisol from baseline to 30 min post-task onset, and emotion recovery was calculated as the number of standard deviations change in emotion from during the task to the end of recovery and in cortisol from 30 min post-task to 45 min post-task onset. [a]Sample sizes are provided in parentheses for each group, and ranges are provided to account for participants varying in the number of cortisol samples and emotion surveys they completed.

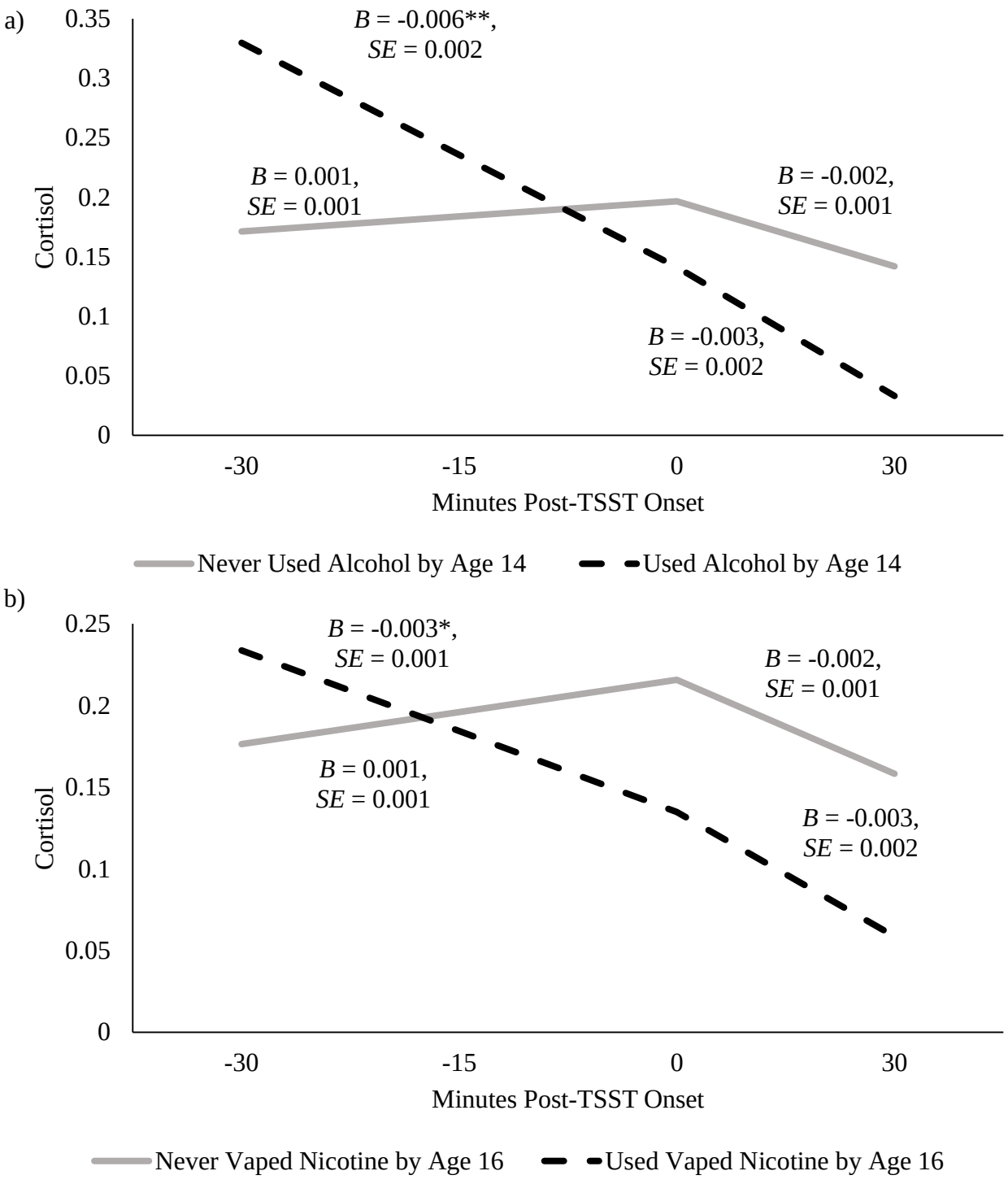

Figure 1. Cortisol responses to the TSST as a function of alcohol use by age 14 (a) and vaping of nicotine by age 16 (b) in youth above the poverty line.
Note: *p<.05, **p<.01.

Figure 2. Happiness responses to the TSST as a function of alcohol use by age 16. Analyses included all participants, regardless of alcohol use by age 14.
Note: ****p*<.001

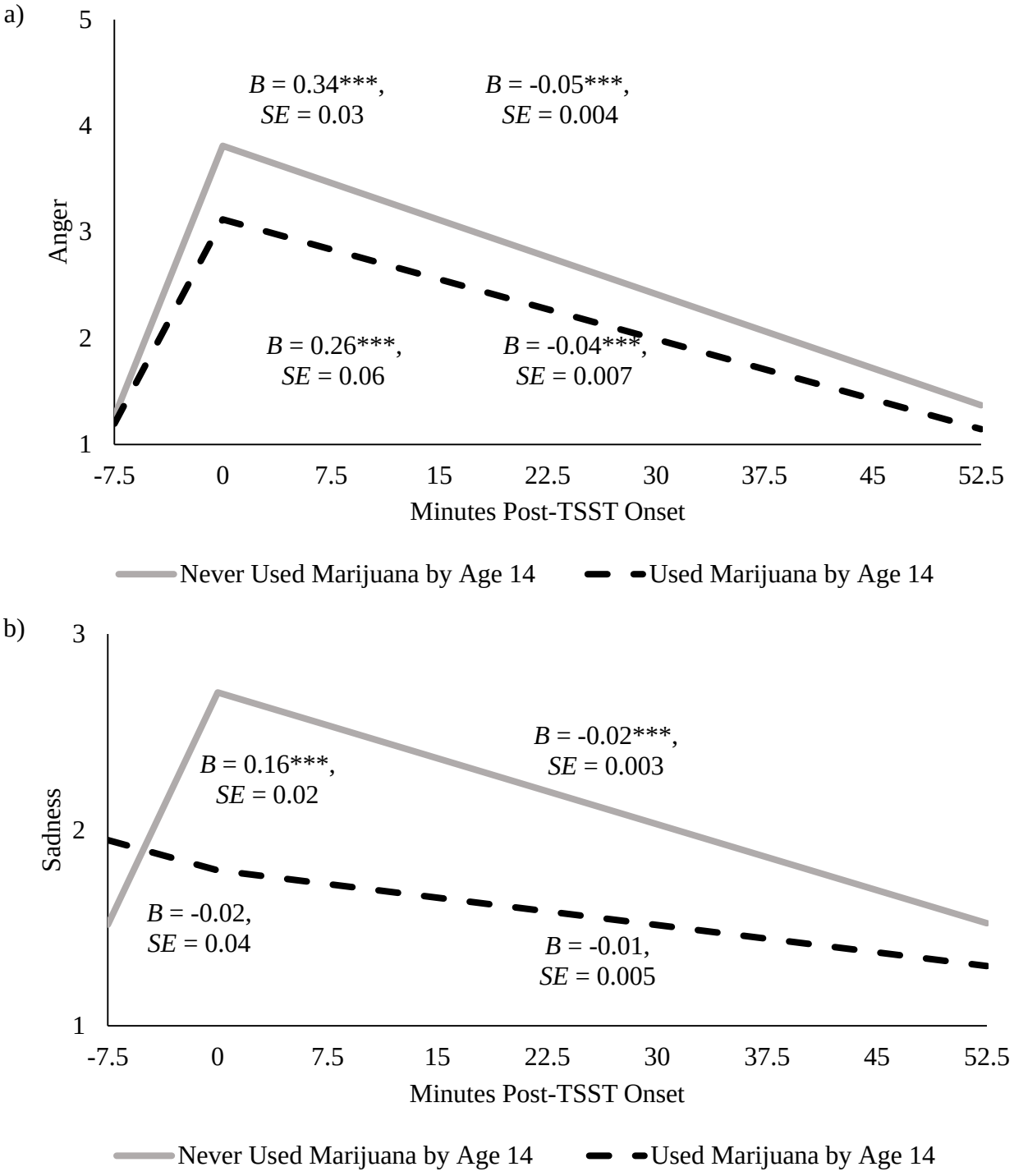

Figure 3. Anger responses (a) and sadness responses (b) to the TSST as a function of marijuana use by age 14 in female adolescents.
Note: *p<.05, ***p<.001.

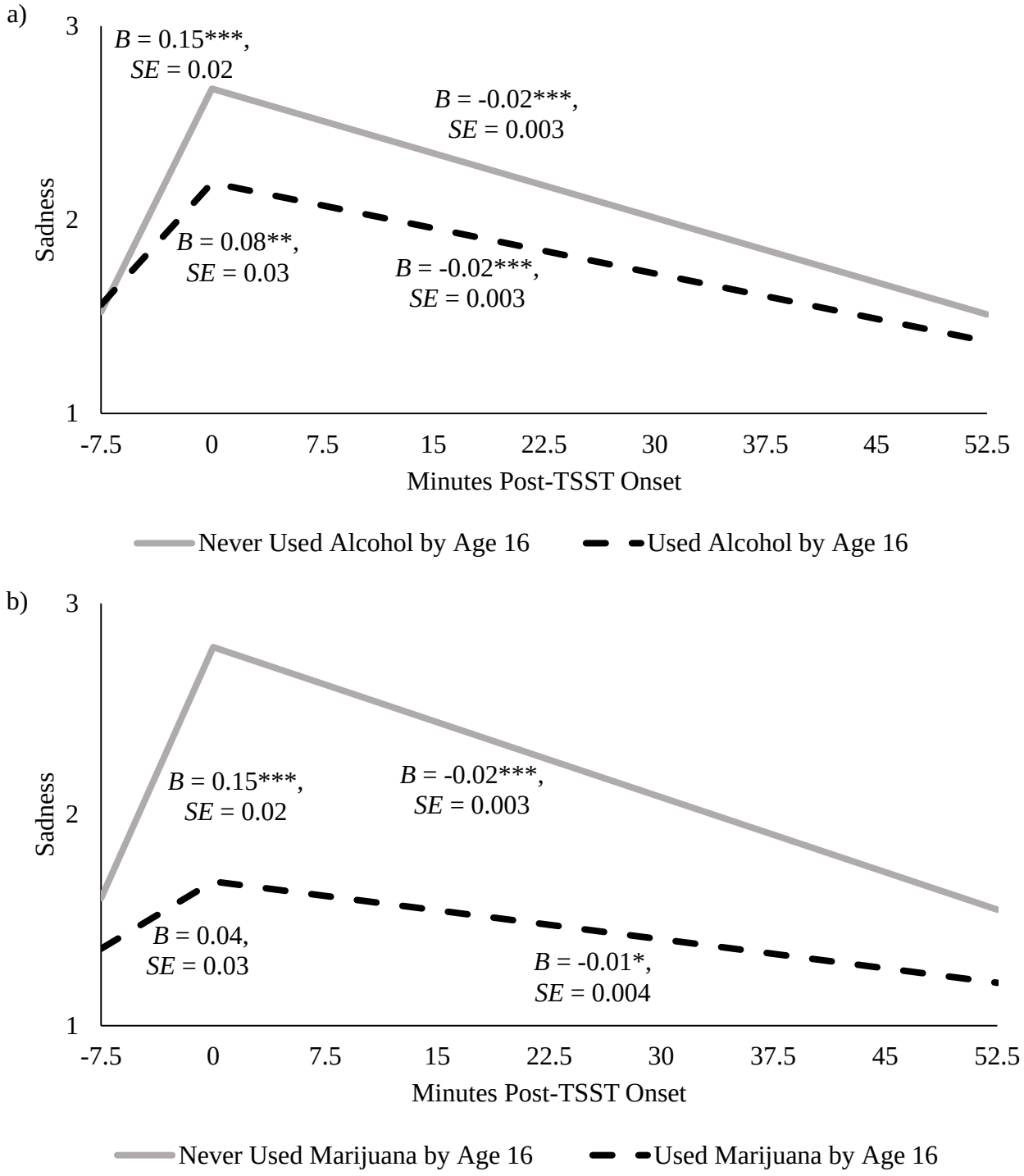

Figure 4. Sadness responses to the TSST as a function of alcohol use by age 16 (a) and marijuana use by age 16 (b) in female adolescents. Analyses included all participants, regardless of substance use by age 14.
Note: *p<.05, **p<.01, ***p<.001.

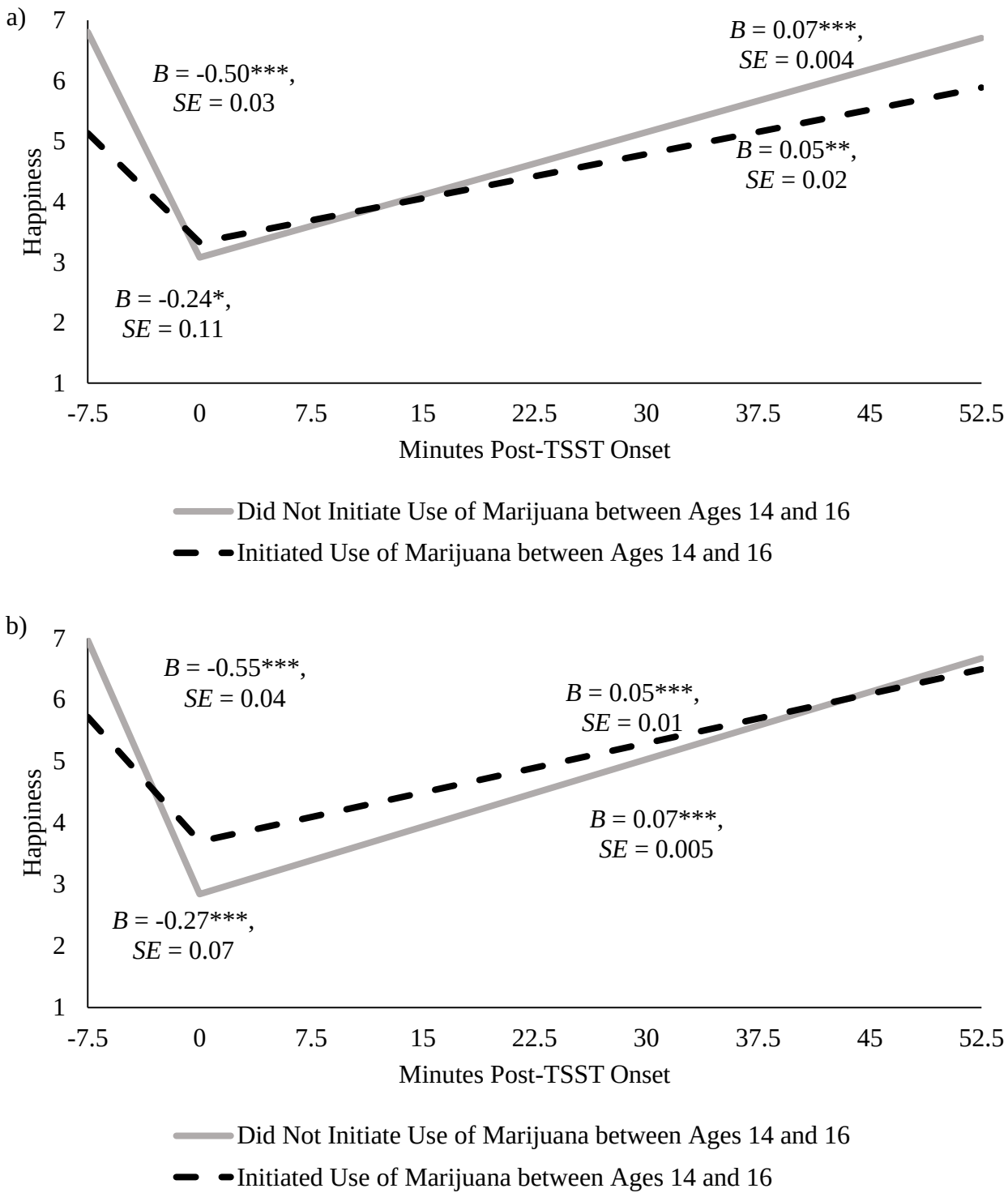

Figure 5. Happiness reactivity to and recovery from the TSST as a function of initiation of cigarettes between ages 14 and 16 (a) and initiation of marijuana between ages 14 and 16 (b) among female adolescents. Analyses excluded participants who used each substance by age 14. Note: *p<.05, **p<.01, ***p<.001.

Study 2: Dampened Autonomic Nervous System Responses to Stress and Substance Use in Adolescence

Substance use greatly increases across adolescence. Hispanic youth are at heightened risk for substance use in the 8th grade relative to White youth and youth with other ethnicities in the United States (Johnston et al., 2019), and risk may be particularly high for Mexican-origin youth (Delva et al., 2005; Kann et al., 2018). Both early use and poly-substance use have been related to heightened risk of substance use-related problems and disorders in adulthood (Latimer & Zur, 2010; Zapert et al., 2002). Studies have shown that Mexican-origin adolescents with both internalizing and externalizing problems are more likely to initiate and escalate substance use (Gonzales et al., 2017), and dampened autonomic responses to stress have been related to greater internalizing and externalizing problems in children (Graziano & Derefinko, 2013). Yet, limited research has examined whether stress physiology may also relate to adolescent substance use.

Dampened cardiovascular reactivity to stress has been consistently related to poorer mental health and greater substance use (e.g., Bibbey et al., 2016; Chaplin et al., 2018; Evans et al., 2016). These dampened responses may suggest conscious and unconscious disengagement with stress (Carroll et al., 2017), heightened risk for depressive symptoms over time (Gentzler et al., 2009), and difficulties with emotion regulation (Phillips et al., 2013), all of which are risk factors for elevated substance use (Wills et al., 1999). Yet, few studies have tested associations during adolescence, when substance use emerges, especially among youth at heightened risk.

The two branches of the autonomic nervous system (ANS)—the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS)—are physiological stress-response systems that may be particularly tied to adolescents' substance use (e.g., Hinnant et al., 2015, 2021). Dampened PNS and SNS responses to stress may indicate impaired ability to regulate one's emotions following stress and consequently may signal risk for use of more substances.

Higher PNS reactivity may suggest greater activation of prefrontal cortical regions and has therefore been considered a marker of greater emotion regulatory capacity (Beauchaine, 2015; Thayer & Lane, 2009). Indeed, dampened parasympathetic responses are associated with poorer mental health, including internalizing and externalizing problems (Graziano & Derefinko, 2013). Similarly, blunted SNS reactivity is consistently related to psychopathology, particularly externalizing problems such as aggression and rule-breaking (Fung et al., 2005; Lorber, 2004).

Furthermore, substance use may relate to profiles of PNS and SNS reactivity. According to the autonomic space model (Figure 1), SNS and PNS responses can show reciprocal activation in the form of reciprocal SNS dominance, which is generally regarded as a classic response to stress and is characterized by increased SNS activity and vagal withdrawal (i.e., decreases in PNS activity), or reciprocal PNS dominance, characterized by decreased SNS activity and vagal augmentation (i.e., increases in PNS activity). The degree of reciprocal activation is measured in terms of cardiac autonomic balance (CAB). There are also non-reciprocal profiles in the forms of coactivation (i.e., both SNS and PNS activity increase) or coinhibition (SNS and PNS activity decrease; Berntson et al., 1994, 2008), and the degree of coactivation is measured as cardiac autonomic regulation (CAR). Non-reciprocal patterns of reactivity suggest lower cross-system coordination. Lower SNS reciprocity and greater coinhibition, or lower activity across systems, suggest that bodily systems are not mobilized to appropriately respond to stress. Indeed, these profiles generally relate to poorer mental health in children and adolescents (e.g., Boyce et al., 2001; Quigley & Moore, 2018). However, few studies measure both SNS and PNS activity and examine minute-by-minute variations in physiology across a task.

Although SNS and PNS activity dynamically develop in early childhood, they stabilize during late childhood and may have predictive utility for adolescents comparable to that for

adults (Gatzke-Kopp & Ram, 2018; Hinnant et al., 2018). Only one study has utilized SNS and PNS activity to predict substance use; in children ages 8-12, dampened SNS reactivity to reward was related to greater alcohol use the next year (Brenner & Beauchaine, 2011). Given that substances are often used to reduce stress and to enhance emotion (Kuntsche et al., 2015), SNS and PNS reactivity to stress may also be predictive markers of substance use during adolescence.

Present Study

The present study examined whether physiological responses to stress were related to the number of substances ever used (i.e., substance use count) in a sample of Mexican-origin adolescents. We examined whether SNS and PNS responses to social-evaluative threat were related to substance use count in adolescence, when substance use often emerges. A sample of Mexican-origin adolescents from high-adversity, low-income backgrounds completed a stress task at age 14 and reported whether they had ever used various substances at age 14 and again two years later at age 16. Given this longitudinal design, we examined how autonomic stress responses at age 14 related to the emergence of substance use by age 16. Because earlier substance use is related to patterns of more frequent and riskier substance use (e.g., Kendler et al., 2008; Richmond-Rakerd et al., 2017), analyses were tested separately among adolescents who had never used any substances by age 14, in order to assess substance use initiation between ages 14 and 16, and among youth who had used substances by age 14, in order to assess escalation of substance use between ages 14 and 16. Adolescents with dampened SNS and PNS responses to stress at age 14 were hypothesized to use more substances by age 16. Further, adolescents with greater cross-system dysregulation (i.e., lower reciprocity and greater coinhibition) were predicted to use more substances by age 16.

Method

Participants. Participants were adolescents from the CHAMACOS study, a longitudinal birth cohort study of over 500 Mexican-origin adolescents living in the agricultural Salinas Valley community (Eskenazi et al., 2003). Mothers were initially eligible to enroll in the study in 1999-2000 if they were age 18 or older and under 20 weeks of gestation, eligible for California's low-income health insurance program, receiving prenatal care, and planning to deliver at a county hospital. For this cohort, there were 1,130 women eligible for the study, of whom 601 were recruited, 531 remained in the study after childbirth, 350 remained in the study at age 5, and 325 remained in the study at age 14. Rates of attrition were highest from pregnancy to delivery and were very low following the age 5 assessment (Eskenazi et al., 2003). A second cohort of 300 9-year-old children were also recruited in 2009, and they and their mothers completed data collection comparable to the original cohort (Sagiv et al., 2015). Retention rates for both cohorts were high between ages 9 and 14 (95% for CHAM1, 94% for CHAM2). The two cohorts did not differ in age at the age 14 and 16 assessments, *p*s > .05. Due to funding constraints, most youth who completed the stress task in the present study were from the original cohort (94.15%).

To participate in the stress task at age 14, adolescents needed to meet the following criteria: IQ above 70 at age 12, no diagnosis of autism spectrum disorder, no extreme atypical behaviors at past visits, within three standard deviations of the mean for depressive scores for their age and sex, and no gang involvement in the previous year. In total, 277 adolescents completed the stress task (59.57% in 8th grade, 67.15% below the poverty line; 45.85% female). Of these adolescents, PNS responses were recorded in 243 adolescents, and SNS responses were recorded in 229 adolescents during the laboratory visit at age 14. Almost all adolescents completed additional data collection at age 16 (97.12%). Participants whose PNS and SNS responses were recorded did not differ in terms of demographics from both the larger cohorts of

participants who had completed assessments at any age (N = 849) and the sample of adolescents who completed an assessment at age 14 but not the stress task (N = 604) with respect to mother's education, sex, poverty status, and substance use count at ages 14 and 16, all ps > .10.

Separate analyses were tested among youth who had never used substances by age 14 (n = 171; 50.88% female, 65.29% below poverty line, 54.97% in 8th grade at age 14) and youth who had used substances by age 14 (n = 72; 54.17% female, 68.57% below poverty line, 63.89% in 8th grade at age 14). Analyses among youth who had never used substances by age 14 tested whether ANS responses were related to substance use initiation between ages 14 and 16, whereas analyses among youth who had used substances by age 14 tested whether ANS responses were related to escalation of substance use. Participants who had used substances by age 14 did not differ from those who did not with respect to mother's education, family income-to-needs ratio, grade at age 14, or grade at age 16, all ps > .232. Participants who used substances by age 14 reported higher substance use count by age 16 (M = 2.25, SD = 1.23) than participants who had not used substances by age 14 (M = 0.69, SD = 0.99), $t(232) = 10.09$, $p < .001$.

Procedure. Adolescents completed the Trier Social Stress Test (TSST), a validated social-evaluative stress paradigm, during the study visit at age 14 (Kirschbaum et al., 1993). The protocol was modified for this population to invoke an appropriate level of distress and challenge (detailed in Johnson et al., 2017). Adolescents rested for 10 min. to acclimate to the space and then watched a 3 min. video as a neutral baseline. Participants stood up and counted to 100 for 2 min. before receiving the instructions regarding the speech and math tasks. Participants then had 3 min. to prepare a speech on how they are a good friend. They then presented the speech for 5 min. to two confederate judges, who were of similar age and ethnicity to participants and were introduced as experts in evaluating the task. After the speech task, youth completed a mental

arithmetic task for an additional 5 min. Confederates were trained to maintain neutral affect and provide no positive feedback, and adolescents were obtrusively video recorded during the tasks. Participants were then debriefed within 15 min. after task completion to minimize distress.

Throughout the task, electrocardiogram (ECG) and impedance measures were continuously monitored. Participants had three spot electrodes on their chest in a lead II configuration to acquire ECG waveforms. Placement of electrodes, data recording, and data reduction followed conventions and published guidelines (Berntson et al., 1997). Impedance was measured using four spot electrodes on the neck and trunk. Impedance cardiography, measured as vascular resistance in the thoracic cavity, was measured using four spot electrodes on the neck, back, and chest (e.g., Paunović et al., 2014). Interbeat intervals (IBIs) were calculated from ECG. IBIs were checked and edited for artifacts using statistical detection algorithms (e.g., Berntson et al., 1990) and visually inspected. The high-frequency variability of IBIs was calculated as a frequency-domain index of respiratory sinus arrhythmia (RSA), controlling for respiration rate. Impedance was calculated from the ECG and impedance waveforms. Pre-ejection period (PEP) was measured as the time between the onset of ventricular depolarization (Q point on the ECG wave) and the onset of left ventricular ejection (B point on the impedance waveform) in milliseconds. Data were processed in one-minute epochs using ensemble averaging (Kelsey & Guethlein, 1990) using Mindware software (mindwaretech.org). The RSA index measures PNS withdrawal with lower RSA indices, and the PEP in milliseconds measures SNS activity, with lower PEP values indicating SNS activation. Both low RSA (withdrawal) and low PEP (activation) increase heart rate.

Finally, at the 14-year visit, adolescents completed items from the Monitoring the Future Survey regarding whether they had used alcohol, marijuana, or cigarettes in their lifetime using a

computer-based survey (Johnston et al., 2019). At the 16-year visit, adolescents reported whether they had ever used cigarettes, marijuana, alcohol, or a vape in their lifetime. For each adolescent, we calculated the number (count) of substances that they had ever used, with a maximum of 3 at age 14 (i.e., use of cigarettes, marijuana, and alcohol in their lifetime) and a maximum of 4 at age 16 (i.e., use of cigarettes, marijuana, alcohol, and vaping nicotine in their lifetime).

Analytic Plan

RSA and PEP responses were modeled using three-level multilevel models with time nested within task segment, nested within adolescents. The TSST comprised five task segments (i.e., baseline, preparation, speech, math, and debriefing), each lasting about 5 min. RSA and PEP were also recorded as participants counted aloud to 100 and received instructions prior to the TSST, each lasting approximately 2 min. These segments were too short to reliably assess associations between physiology and substance use, and reactivity is best examined by comparing segments of similar duration, especially given the rapid habituation of the SNS and PNS. Therefore, RSA and PEP during the counting task and instructions were included in models but were not of primary interest. All variables are described in Table S1.

First, changes in RSA and PEP for the entire sample were modeled across the task (Eq. 1). Task minute and segment were included in descriptive models, with random effects for minute at Level 1 and each segment (i.e., baseline, preparation, speech, math, and debriefing) at Level 2. Each minute of the segment was coded at Level 1 (i.e., the first minute of a segment would be coded as 0) to account for habituation of physiological responses within a segment. Each segment was dummy-coded at Level 2, with baseline as the reference group. Sex (dummy-coded; 0=male, 1=female), poverty status (dummy-coded; 0=below poverty line, 1=above poverty line), and grade at either age 14 for concurrent models (centered at 8th grade) or age 16

for prospective models (centered at 10th grade) were included as control variables at Level 3 in this and all subsequent models (variable coding is summarized in Table S1).

Equation 1:

$$L1: \widehat{RSA}_{tij} \text{ or } \widehat{PEP}_{tij} = \pi_{0ij} + \pi_{1ij}(Minute)$$
$$L2: \pi_{0ij} = \beta_{00j} + \beta_{01j}(Task\ Preparation) + \beta_{02j}(Speech) + \beta_{03j}(Math) + \beta_{04j}(Debrief) + \beta_{05j}(Counting\ Task) + \beta_{06j}(Instructions)$$
$$\pi_{1ij} = \beta_{10j}$$
$$L3: \beta_{00j} = \gamma_{000} + \gamma_{001}(Sex) + \gamma_{002}(Poverty\ Status) + \gamma_{003}(Grade) + u_{00j}$$
$$\beta_{01j} = \gamma_{010} + u_{01j}$$
$$\beta_{02j} = \gamma_{020} + u_{02j}$$
$$\beta_{03j} = \gamma_{030} + u_{03j}$$
$$\beta_{04j} = \gamma_{040} + u_{04j}$$
$$\beta_{05j} = \gamma_{050} + u_{05j}$$
$$\beta_{06j} = \gamma_{060} + u_{06j}$$
$$\beta_{10j} = \gamma_{100} + u_{10j}$$

Next, models examined whether substance use count by age 16 related to adolescents' ANS responses to the task at age 14 among participants who had never used substances (i.e., substance use count = 0 at age 14), so that we could test whether ANS responses related to initiation of substance use over two years. Models predicted RSA and PEP from the task segments, adolescents' substance use count, and interaction terms between the dummy-coded task segments and the number of substances each adolescent had ever used in order to identify whether changes in RSA and PEP across task segments varied by adolescents' substance use count. Although stress responses may theoretically influence substance use count, we consistently modeled substance use count as the predictor and stress responses as the outcome because of the structure of the data (i.e., RSA and PEP values summarized at the level of minutes nested within participants, and substance use count at the level of participants), as has been done in previous research (e.g., Shirtcliff & Essex, 2008). In contrast to other approaches, this statistical technique enabled all minutes of the stress response to be modeled and for assessment of whether the stress response at age 14 systematically differed by adolescents' substance use count. We also conducted models in which segments were dummy-coded with task preparation

as the reference group to represent non-evaluative stress. With this coding, the baseline and debriefing coefficients represented the difference between non-stressful segments (i.e., baseline and debriefing) and non-social evaluative stress (i.e., task preparation). The speech and math coefficients represented the difference between social-evaluative stress and non-evaluative stress and therefore reflect the unique effect of social-evaluation on the stress response. Cross-level interactions between adolescents' substance use count at age 16 at Level 3 and segments at Level 2 tested whether changes in RSA and PEP across the task varied by number of substances used (Eq. 2). Significant interactions between task segments and lifetime substance use count were probed at different levels of substance use count (i.e., 0, 1, 2, 3, or 4 substances used).

Equation 2:

$$L1: \widehat{RSA}_{tij} \text{ or } \widehat{PEP}_{tij} = \pi_{0ij} + \pi_{1ij}(Minute)$$

$$L2: \pi_{0ij} = \beta_{00j} + \beta_{01j}(Task\ Preparation) + \beta_{02j}(Speech) + \beta_{03j}(Math) + \beta_{04j}(Debrief) + \beta_{05j}(Counting\ Task) + \beta_{06j}(Instructions)$$

$$\pi_{1ij} = \beta_{10j}$$

$$L3: \beta_{00j} = \gamma_{000} + \gamma_{001}(Sex) + \gamma_{002}(Poverty\ Status) + \gamma_{003}(Grade) + \gamma_{004}(Substance\ Use) + u_{00j}$$

$$\beta_{01j} = \gamma_{010} + \gamma_{011}(Substance\ Use\ Count) + u_{01j}$$

$$\beta_{02j} = \gamma_{020} + \gamma_{021}(Substance\ Use\ Count) + u_{02j}$$

$$\beta_{03j} = \gamma_{030} + \gamma_{031}(Substance\ Use\ Count) + u_{03j}$$

$$\beta_{04j} = \gamma_{040} + \gamma_{041}(Substance\ Use\ Count) + u_{04j}$$

$$\beta_{05j} = \gamma_{030} + u_{03j}$$

$$\beta_{06j} = \gamma_{040} + u_{04j}$$

$$\beta_{10j} = \gamma_{100} + u_{10j}$$

Next, models were conducted to examine whether coordination between RSA and PEP at age 14 differed by adolescents' substance use count by age 16. The ANS profile of reciprocal SNS activation and PNS withdrawal—generally considered a classic response to stress—is characterized by low RSA and PEP values (i.e., reduced PNS and increased SNS activity, respectively). To determine the specific profiles of ANS activity involved, we calculated CAB (i.e., level of reciprocal activation) and CAR (i.e., level of coactivation) as defined by Berntson and colleagues (1997, 2008). Minute-by-minute RSA and PEP values were *z*-transformed within

each individual. CAB was calculated as the difference between RSA and PEP and indicated the degree of reciprocal activation, with more positive values suggesting greater PNS dominance and more negative values suggesting greater SNS dominance. In turn, CAR was calculated as the sum of RSA and PEP and indicated the degree of coactivation, with more positive values suggesting coactivation and more negative values suggesting coinhibition. Three-level multilevel models examined whether interactions between substance use count at age 16 and task segments predicted CAB and CAR (Eq. 3). Significant interactions would suggest that the profile of ANS responses during that task segment varied with the number of substances adolescents had ever used by age 16. Baseline was consistently used as the reference group, such that coefficients indicate the degree to which CAB and CAR values change from baseline to each task segment.

Equation 3:

$$L1: \widehat{RSA + PEP}_{tij} \text{ or } \widehat{RSA - PEP}_{tij} = \pi_{0ij} + \pi_{1ij}(Minute)$$

$$L2: \pi_{0ij} = \beta_{00j} + \beta_{01j}(Task\ Preparation) + \beta_{02j}(Speech) + \beta_{03j}(Math) + \beta_{04j}(Debrief) + \beta_{05j}(Counting\ Task) + \beta_{06j}(Instructions)$$

$$\pi_{0ij} = \beta_{10j}$$

$$L3: \beta_{00j} = \gamma_{000} + \gamma_{001}(Sex) + \gamma_{002}(Poverty\ Status) + \gamma_{003}(Grade) + \gamma_{004}(Substance\ Use\ Count) + u_{00j}$$

$$\beta_{01j} = \gamma_{010} + \gamma_{011}(Substance\ Use\ Count) + u_{01j}$$

$$\beta_{02j} = \gamma_{020} + \gamma_{021}(Substance\ Use\ Count) + u_{02j}$$

$$\beta_{03j} = \gamma_{030} + \gamma_{031}(Substance\ Use\ Count) + u_{03j}$$

$$\beta_{04j} = \gamma_{040} + \gamma_{041}(Substance\ Use\ Count) + u_{04j}$$

$$\beta_{05j} = \gamma_{030} + u_{03j}$$

$$\beta_{06j} = \gamma_{040} + u_{04j}$$

$$\beta_{10j} = \gamma_{100} + u_{10j}$$

Finally, we repeated analyses to determine whether associations between ANS responses and substance use count were also apparent in youth who had used substances by age 14. First, we included use by age 14 (0 = no substances by age 14, 1 = at least one substance by age 14) as a moderator of associations between substance use count at 16 and RSA, PEP, CAR, and CAB responses in order to determine whether associations differed between adolescents who had and had not used by age 14. If interactions were significant, associations between substance use

count by age 16 and RSA, PEP, CAR, and CAB reactivity were tested for youth who had used substances by age 14. Significant interactions between task segments and substance use count were again probed at different levels of substance use count (i.e., 0, 1, 2, 3, or 4 substances used).

Results

The majority of adolescents (72.1%) did not use substances by age 14, although 15.2% reported using one substance, 9.4% reported using two substances, and 3.3% reporting using all three substances at some point in their lifetime by age 14. Lifetime use of alcohol, marijuana, and cigarettes increased by age 16, $t(219) = 6.89$, $p < .001$. At age 16, 46.3% of youth had never used alcohol, marijuana, or cigarettes and had never vaped nicotine, and 19.1%, 15. 5%, 14.2% and 4.9% reported using one, two, three, and all four substances, respectively, by age 16.

RSA and PEP Responses to Stress

First, multilevel models were used to model RSA and PEP responses to the different segments of the TSST (i.e., baseline, task preparation, speech, math, debriefing; Fig. 2; Table S2). As expected, participants' RSA was highest at baseline. Youth showed vagal withdrawal, such that RSA was relatively lower during task preparation, $B = -0.99$, $SE = 0.05$, $p < .001$, the speech task, $B = -0.70$, $SE = 0.05$ $p < .001$, and the math task, $B = -0.99$, $SE = 0.05$ $p < .001$. RSA increased during debriefing, although it was still lower than at baseline, $B = -0.27$, $SE = 0.05$, $p < .001$. Participants showed lower PEP from baseline to task preparation, $B = -0.85$, $SE = 0.38$, $p = .025$, and from baseline to the speech task, $B = -1.24$, $SE = 0.42$, $p = .003$. PEP during the math task did not differ from baseline, $B = -0.28$, $SE = 0.44$, $p = .5$, and participants showed higher PEP during debriefing than at baseline, $B = 1.16$, $SE = 0.43$, $p = .007$. Responses for adolescents who had and had not used substances by age 14 are presented in in Figure S1.

RSA and PEP Responses to Stress and Initiation of Substance Use by Age 16

Models then tested differences in RSA and PEP responses at age 14 by adolescents' substance use count by age 16 by including interactions between task segments and substance use count (Table S3-S4). Among youth who had never used a substance by age 14, models indicated that greater declines in RSA (i.e., vagal withdrawal) from baseline to task preparation at age 14 were associated with greater substance use count at age 16, B = -0.10, SE = 0.05, p = .049. Specifically, although all youth showed a significant decline in RSA, this decline was smaller for youth who used no substance by age 16, B = -0.91, SE = 0.07, p < .001, relative to youth who went on to use all four substances by age 16, B = -1.32, SE = 0.18, p < .001 (Fig. 3).

RSA and PEP responses to the speech and math portions (i.e., the social-evaluative components) of the TSST at age 14 were also associated with adolescents' substance use count by age 16 among youth who had never used a substance by age 14. Youth who showed greater increases in RSA (i.e., dampened vagal withdrawal) from task preparation to both the speech task and the math task used significantly more substances by age 16, B = 0.14, SE = 0.04, p = .001 for speech, B = 0.14, SE = 0.04, p = .002 for math (Fig. 3). Although participants generally showed increases in RSA from task preparation to the speech task, this increase was smaller for youth who used no substance by age 16, B = 0.19, SE = 0.06, p = .001, than for youth who used four substances by age 16, B = 0.76, SE = 0.15, p < .001. In turn, youth who used no substance by age 16 showed significant declines in RSA from task preparation to the math task, B = -0.16, SE = 0.06, p = .007, whereas youth who initiated use of one or two substances showed no significant change in RSA, ps = .777 and .107, and youth who initiated use of three or four substances showed increases in RSA from task preparation to the math task, B = 0.27, SE = 0.12, p = .020 for three substances, B = 0.41, SE = 0.16, p = .009 for four substances. Changes in RSA between baseline and debriefing were not associated with substance use count at age 16, ps > .1.

Changes in PEP from baseline to the speech task, $B = 1.42$, $SE = 0.41$, $p < .001$, and the math task, $B = 1.58$, $SE = 0.46$, $p = .001$, were associated with substance use by age 16 (Fig. 4a). Specifically, an increase in SNS activity (lower PEP) from baseline to the speech task was observed for youth who abstained from substance use by age 16, $B = -1.80$, $SE = 0.55$, $p = .001$. In contrast, no significant change in SNS activity was observed for 14 year olds who initiated use of one or two substances by age 14, *p*s = .444 and .150, and a significant decrease in SNS activity (i.e., increase in PEP) was observed for youth who initiated three or four substances; $B = 2.46$, $SE = 1.06$, $p = .020$ for three, $B = 3.88$, $SE = 1.44$, $p = .007$ for four. Regarding changes from baseline to the math task, a significant increase in SNS activity was observed for youth who used no substances by age 16, $B = 1.40$, $SE = 0.61$, $p = .021$, no change in SNS activity was observed for youth who used one substance by age 16, $p = .744$, and decreases in SNS activity were associated with initiation of two, three, or four substances; $B = 1.76$, $SE = 0.80$, $p = .029$ for two, $B = 3.34$, $SE = 1.19$, $p = .005$ for three, $B = 4.92$, $SE = 1.62$, $p = .002$ for four substances. Neither changes in RSA between baseline and task preparation nor between task preparation and debriefing were associated with substance use count at age 16, *p*s > .07.

Profiles of RSA and PEP Responses to Stress and Initiation of Substance Use by Age 16

To identify the specific profiles that may contribute to this association, models tested whether CAB and CAR—indicators of the degree of reciprocity and coactivation, respectively—throughout the task were related to substance use count. As before, three-level models predicted CAB and CAR from interactions between task segments and substance use count, and changes in both CAB and CAR were related to substance use count by age 16 (Table S5). Blunted declines in CAB (i.e., reduced reciprocal sympathetic activation) from baseline to the speech task, $B = 0.35$, $SE = 0.09$, $p < .001$, and from baseline to the math task, $B = 0.37$, $SE = 0.10$, $p < .001$, were

related to substance use count. Specifically, greater declines in CAB from baseline to the speech task, B = -1.10, SE = 0.12, p < .001, and from baseline to the math task, B = -1.40, SE = 0.13, p < .001, were associated with abstaining from substance use by age 16, whereas no significant changes in CAB were associated with use of three or four substances between ages 14 and 16, ps = .227 and .851. Changes in CAB reflect the degree of reciprocal SNS dominance, or the degree to which greater SNS activity is accompanied by PNS withdrawal. Therefore, this result suggested that greater reciprocal SNS activation during the math task at age 14 was associated with abstaining from substances by age 16, and a lower degree of reciprocal SNS activation during the math task was associated with use of more substances by age 16 (Fig. S3).

We also found that greater declines in CAR (i.e., greater coinhibition) from baseline to task preparation, B = -0.29, SE = 0.10, p = .004, from baseline to the speech task, B = -0.22, SE = 0.09, p = .020, and from baseline to the math task, B = -0.21, SE = 0.10, p = .028, were related to greater substance use count by age 16. Probing of simple slopes indicated that smaller declines in CAR from baseline to task preparation, the speech task, and the math task were associated with abstaining from substance use by age 16, and larger declines in CAR were associated with initiation of four substances between ages 14 and 16. More negative values of CAR reflect coinhibition, or lower overall SNS and PNS activity, such that greater coinhibition during stress was related to use of more substances by age 16 (Fig. S4).

RSA and PEP Responses to Stress and Escalation of Substance Use between Ages 14 and 16

Finally, we also tested whether ANS responses at age 14 related to substance use count by age 16 among youth who had already begun to use substances by age 14. We tested whether associations between substance use count at age 16 and ANS responses differed by adolescents' use of substances by age 14 by including a three-way Substance Use Count by 16 × Segment ×

Ever Used by 14 interaction. There were no differences in associations for RSA, all *p*s > .15. Rather, the three-way interactions indicated significant differences in associations between substance use count by 16 and PEP during the speech task, *B* = -2.21, *SE* = 0.84, *p* = .008, and the math task, *B* = -2.52, *SE* = 0.98, *p* = .008. We probed simple slopes to examine associations between PEP responses and substance use by 16 among adolescents who had used substances by age 14. Whereas decreased SNS reactivity (i.e., blunted declines in PEP) from baseline to the speech and math tasks were related to greater substance use count by age 16 for youth who had never used substances by age 14, results suggested that greater SNS reactivity (i.e., greater declines in PEP) from baseline to the speech task, *B* = -1.16, *SE* = 0.51, *p* = .022, and math task, *B* = -1.30, *SE* = 0.55, *p* = .018, were related to greater substance use count by age 16 among adolescents who had used substances by age 14 (Fig. 4b).

Results also indicated differences in the degree to which substance use by age 16 was related to changes in CAB from baseline to the speech task, *B* = -0.51, *SE* = 0.15, *p* = .001, and to the math task, *B* = -0.60, *SE* = 0.16, *p* < .001, as well as to changes in CAR from baseline to the speech task, *B* = 0.34, *SE* = 0.16, *p* = .033, and to the math task, *B* = 0.35, *SE* = 0.16, *p* = .031. Although greater declines in CAB and blunted declines in CAR were related to substance use for youth who had not initiated use of substances by age 14, probing of simple slopes indicated that neither changes in CAB nor CAB from baseline to the speech and math tasks were related to substance use among youth who used substances by age 14, all *p*s > .20.

Discussion

The present study investigated whether dysregulation of ANS responses to stress at age 14 were related to substance use count at age 16. Results suggested that dampened SNS and PNS reactivity to social-evaluative threat at age 14 and both lower reciprocity between the SNS and

PNS and greater coinhibition (i.e., lower activity in both systems) were associated with initiation of use of more substances by age 16 among youth who have never used by age 14. Results suggest that dampened ANS responses to stress and profiles of greater coinhibition and reduced reciprocal SNS activation and PNS withdrawal may be risk factors for adolescents' substance use initiation. Interestingly, greater PEP reactivity was also related to greater substance use between ages 14 and 16 among youth who had used substances by age 14.

Dampened PNS responses and SNS responses at age 14 were related to initiation of substance use by age 16 among youth who had not used by age 14, in line with prior work suggesting that both exaggerated and blunted cardiovascular reactivity have been related to poorer mental health (Carroll et al., 2017; Phillips et al., 2013). Greater PNS reactivity to stress has been posited to indicate greater recruitment of cortical regions and thereby signify greater emotion regulatory capacity (Beauchaine, 2015; Thayer & Lane, 2009). Empirically, findings align with past research suggesting that dampened PNS reactivity to a sad film was related to poorer mood repair and greater depressive symptoms in adolescents (Hamilton & Alloy, 2016; Yaroslavsky et al., 2016) and that greater PNS reactivity is related to fewer internalizing and externalizing problems in children (Graziano & Derefinko, 2013), both of which are related to substance use in Latino adolescents (Gonzales et al., 2017). Blunted SNS reactivity to stress has been related to greater depressive symptoms in adults as well as poorer mental health for adolescents living in risky home environments (Erath et al., 2009, 2011; Hinnant et al., 2015; Schwerdtfeger & Rosenkaimer, 2011). It is possible that dampened PNS and SNS reactivity may indicate difficulties with stress regulation, which may be particularly important for youth who experience high levels of adversity (Sagiv et al., 2015) and minority youth who experience marginalization and cultural stressors (Stein et al., 2012). Youth with these responses may be at

heightened risk for using substances to cope with stress (e.g., academic, interpersonal, cultural) or to conform in socially-evaluative circumstances (e.g., social gatherings, parties).

Given that adolescents show heightened sensitivity to peer influence and social status concerns (Blakemore, 2008), it is possible that ANS responses to stress may influence adolescent substance use through peer processes. For example, Latino adolescents with higher family risk (e.g., poorer family relationship quality and conflict) reported associating with more deviant peers, which in turn predicted substance use and risky behavior over time (Gonzales et al., 2017). A previous study found that the consequences of associating with deviant peers on adolescents' own substance use may differ by physiological vulnerability, as adolescents who engaged with deviant peers showed greater substance use if they also showed blunted SNS responses to challenge (Hinnant et al., 2016). Adolescents tend to show heightened reward-sensitivity and to engage in greater risk-taking when being evaluated by peers, such that peers can greatly impact adolescents' inclination to use substances (Chein et al., 2011). Interactions with deviant peers may be stressful for youth (i.e., pressure to conform), and dampened ANS responses to stress may impair adolescents' recruitment of neural regions involved in cognition and decision-making (Weissman et al., 2018). Inability to respond to these situations may heighten adolescents' risk for succumbing to peer influence and initiating substance use, as adolescents who are more easily influenced by peers show greater substance use (Allen et al., 2006).

Adolescents who had ever used more substances by age 16 also showed greater coinhibition and lower reciprocal SNS activation during the speech and math tasks. Participants would be expected to show increases in SNS activity and decreases in PNS activity during stress, as this profile would suggest that they were actively attending to the task (e.g., Salomon et al., 2000) and enables individuals to focus and quickly respond to environmental stimuli (Berntson

et al., 1994; Porges, 2007). In line with previous research suggesting that blunted ANS responses are related to poorer mental health (Graziano & Derefinko, 2013), blunted activity across both systems may be related to greater substance use count. Blunted cardiovascular responses have been posited to indicate unconscious disengagement from a stressor such that individuals are less responsive to their social environment (e.g., Carroll et al., 2017). In contrast, adolescents with a greater degree of reciprocal SNS activation may have been more alert to the math task and attentive to the confederates' cues and thereby been better able to emotionally regulate during stress. Indeed, greater reciprocal sympathetic activation following stress has been found to buffer the negative impacts of conflict on mental health, particularly internalizing and externalizing problems (e.g., Gordis et al., 2010; McKernan & Lucas-Thompson, 2018). Lower reciprocal activation may also indicate impaired ability to regulate stress and therefore greater substance use risk. Importantly, synchrony between the SNS and PNS responses to stress may change throughout development and during adolescence specifically (Gatzke-Kopp & Ram, 2018). Further work should examine stability of SNS-PNS synchrony during adolescence and whether reciprocal ANS responses are similarly relate throughout early and late adolescence.

These findings together suggest that aberrations of ANS responses to stress may be prospective risk factors for adolescent substance use. Previous work has similarly found that dampened and anticipatory cortisol responses precede substance use initiation among adolescents (e.g., Evans et al., 2016; Moss et al., 1999), but few studies have empirically tested temporal associations between ANS responses and substance use outcomes. One study found that preadolescents with blunted sympathetic responses to reward had greater odds of alcohol use the following year (Brenner & Beauchaine, 2011). However, SNS responses to reward have been posited to index impulsivity and inhibition, whereas responses to stress may index regulatory

capacity (Beauchaine, 2015). Hence, this study represents a first step in identifying the role of ANS responses to stress in imposing risk for adolescent substance use.

Interestingly, analyses indicated that profiles of ANS responses at age 14 were not related to substance use count by age 16 among youth who had used a substance by age 14. Further, whereas dampened SNS responses were related to greater substance use count among youth who had not initiated use by 14, the opposite pattern was observed such that greater SNS reactivity was related to higher substance use count by age 16 among youth who had used a substance by age 14. These results highlight how a combination of biological and environmental factors can influence psychological outcomes, supporting the differential susceptibility hypothesis (Belsky, 2016); greater SNS reactivity may not be uniformly associated with substance use for all youth, but may be protective for some youth and a risk factor for substance use for others.

Differences in associations between SNS stress reactivity and substance use by age 14 may emerge for multiple reasons. First, prior research has consistently highlighted the importance of substance use by age 14 as a risk factor for problems with substance use in adulthood (e.g., DeWit et al., 2000; Strunin et al., 2017). Alcohol, nicotine, and cannabis use are highly correlated early in adolescence such that users tend to use multiple substances and non-users tend to fully abstain, and these correlations weaken later in adolescence (Kendler et al., 2008). Therefore, youth who use by age 14 may constitute a high-risk population relative to youth who have not used by age 14, and earlier use may position these youth for trajectories of more frequent or poly-substance use irrespective of physiological responses during stressful conditions. Indeed, earlier use of alcohol, tobacco, and cannabis are associated with greater initial frequency of use of other substances (Richmond-Rakerd et al., 2017), and youth who initiate use at an earlier age tend to use substances alone and engage in riskier use whereas late

initiators tend to use at social gatherings (Kingston et al., 2017). Although dampened reactivity is often a risk factor for poorer mental health, exaggerated SNS reactivity has been previously found in adolescents who experience clinical trauma relative to healthy controls (Schuurmans et al., 2021), and it is possible that exaggerated reactivity may be observed for at-risk youth.

Second, youth who use by age 14 may differ from those who abstain with respect to their access to substances and their motivation for subsequent substance use. Use of one substance by age 14 may relate to use of other substances because of social and familial environmental factors that increase risk of substance use broadly (Kendler et al., 2008). Youth who use a substance by age 14 may live in a community with increased substance use exposure or may befriend deviant peers who are also using at a younger age and thereby develop greater access to and dependence on substances relative to youth who do not use by age 14. Regarding substance use motivation, it has been posited that blunted reactivity may indicate lower sensitivity to social stress and thus greater risk for using substances to promote positive emotion or sociability (Chaplin et al., 2018). In contrast, greater SNS reactivity may suggest greater sensitivity to social stress and may reflect greater risk for using substances to cope with negative emotion or conforming to peer pressure.

Given that ANS responses to stress may precede substance use, ANS activity may be targeted in interventions for reducing substance use. ANS activity has been posited to play a role in substance use treatment given its ties to neural regions involved in emotional regulation and processing (Eddie et al., 2015). For instance, in adults recovering from substance use disorders, daily heart rate variability biofeedback was related to reduced cravings for alcohol (Eddie et al., 2014). Examining profiles of SNS and PNS responses or addressing biofeedback in the context of stressful situations may help to develop effective treatment for adolescent substance users.

Findings must be interpreted within the context of the study design. First, although these results provide temporal precedence for the association between ANS responses and substance use, further research is needed to determine whether ANS responses to stress are causally related to substance use risk. It is possible that both dampened ANS responses and substance use risk may emerge due to aspects of adolescents' home environments, such as adversity (e.g., Dube et al., 2003; McLaughlin et al., 2014). The majority of youth lived in poverty and experienced high levels of adversity (described in Sagiv et al., 2015), which are risk factors for earlier substance use initiation and psychopathology (e.g., Dube et al., 2003; Johnston et al., 2019). As a result, ANS stress responses may not be related to substance use among other populations of youth who experience lower levels of adversity. In turn, other pathways, such as using substances to increase positive emotion, may be more prevalent among other populations of youth.

Conclusions

Substance use greatly increases during adolescence, and use of multiple substances has been related to greater risk of substance use disorders in adulthood (Latimer & Zur, 2010; Zapert et al., 2002). The longitudinal design of this study in high-risk youth enabled us to identify that adolescents with dampened PNS and SNS responses, as well as profiles of coinhibition and lower reciprocal SNS activation, to social-evaluative stress at age 14 initiated use of more substances by age 16, among youth who never used substances previously. These physiological responses may suggest difficulties in emotion regulation following stress. Among youth who had used substances by age 14, exaggerated SNS reactivity to stress was related to greater substance use by age 16. Further research is needed to examine how ANS responses to stress impart risk for substance use during adolescence, whether these responses relate to substance use by

influencing peer processes and susceptibility to peer pressure, and the potential utility of targeting ANS responses in substance use treatments (e.g., biofeedback).

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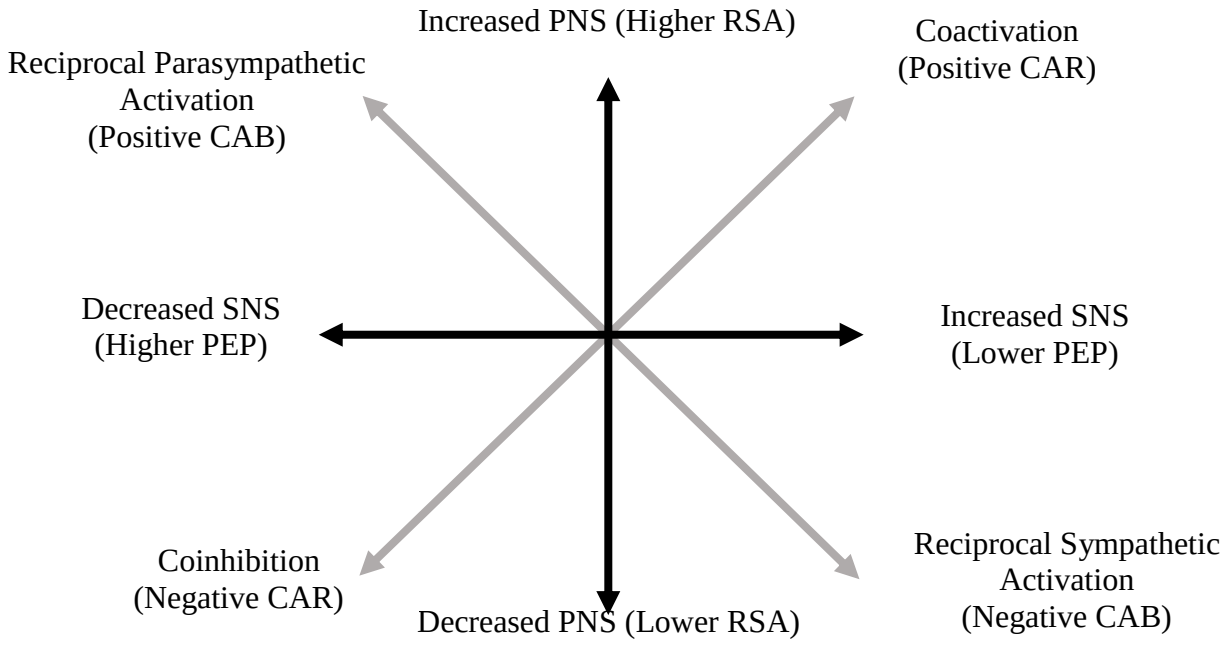

Figure 1. Representation of the autonomic space model (adapted from Berntson et al., 2008, using definitions from Berntson et al., 1991). Associations between parasympathetic activity, as measured by RSA values, and sympathetic nervous system activity, as measured by PEP values are bivariate. Profiles are presented in each quadrant. Associations between the degree of reciprocity, as measured by cardiac autonomic balance, and coactivation, as measured by cardiac autonomic regulation, are also bivariate.
Note: PNS = Parasympathetic Nervous System, SNS = Sympathetic Nervous System, RSA = Respiratory Sinus Arrhythmia, PEP = Pre-Ejection Period, CAB = Cardiac Autonomic Balance, CAR = Cardiac Autonomic Regulation.

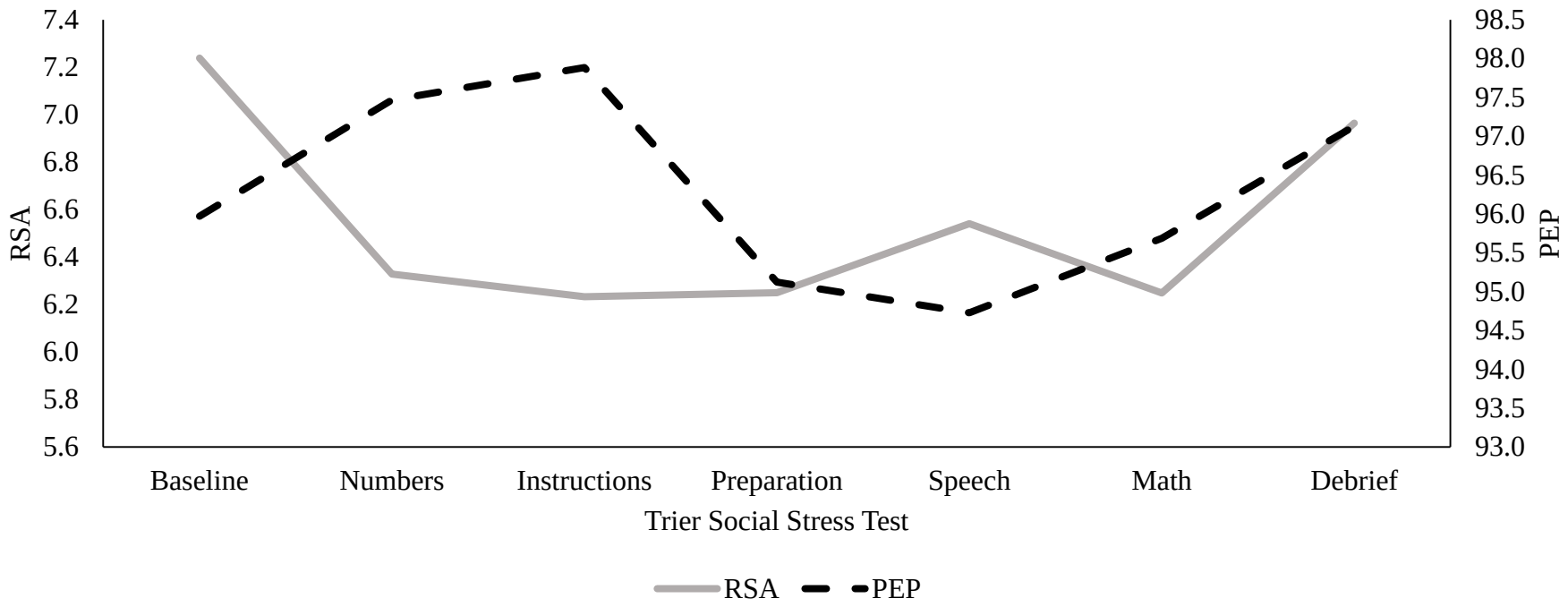

Figure 2. Adolescents' minute-by-minute RSA and PEP responses to the Trier Social Stress Test across the task protocol.
Note: RSA = Respiratory sinus arrhythmia, PEP = Pre-Ejection Period.

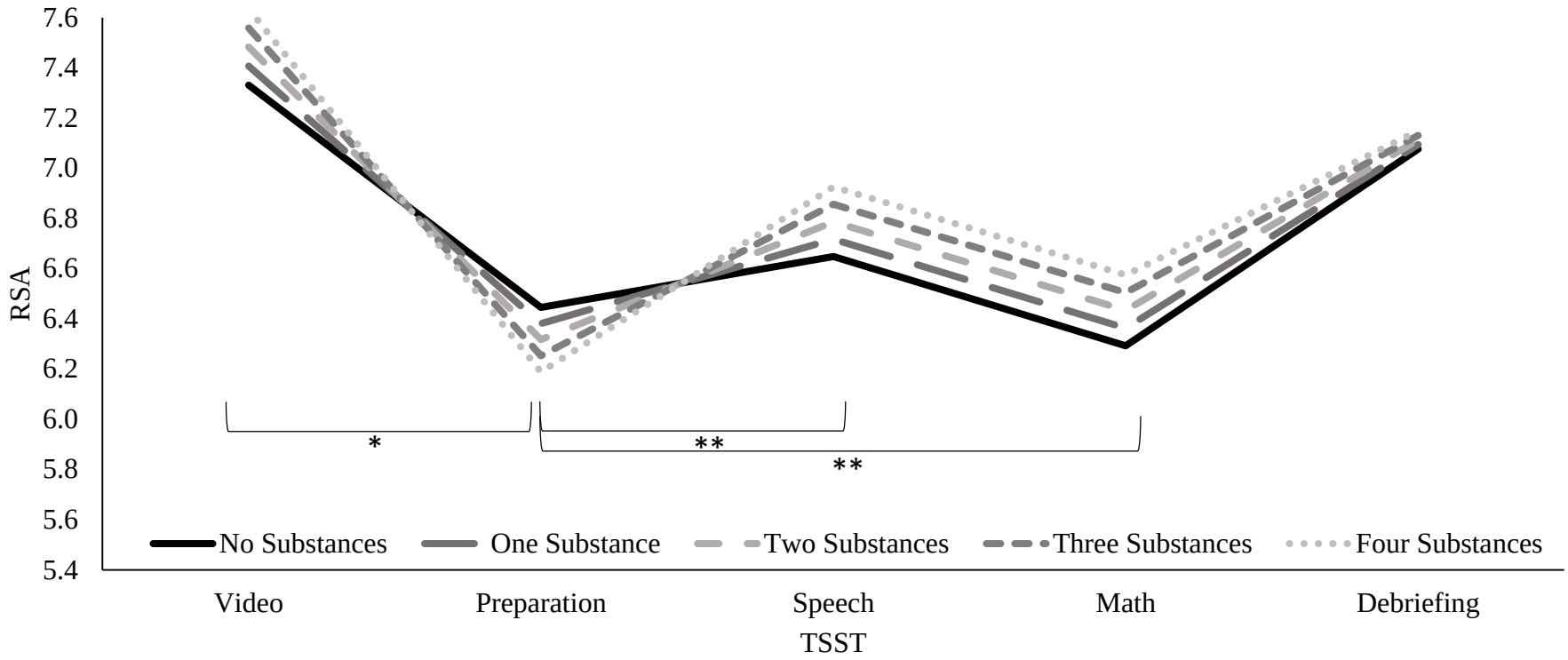

Figure 3. Adolescents' minute-by-minute RSA responses to the Trier Social Stress Test as a function of their substance use count by age 16 among youth who had never used any substances by age 14. Adolescents who used more substances by age 16 showed significantly greater decreases in RSA from baseline to task preparation and significant greater increases in RSA from task preparation to the speech task and the math task (indicated by brackets). Note: RSA = Respiratory sinus arrhythmia, *p<.05 **p<.01.

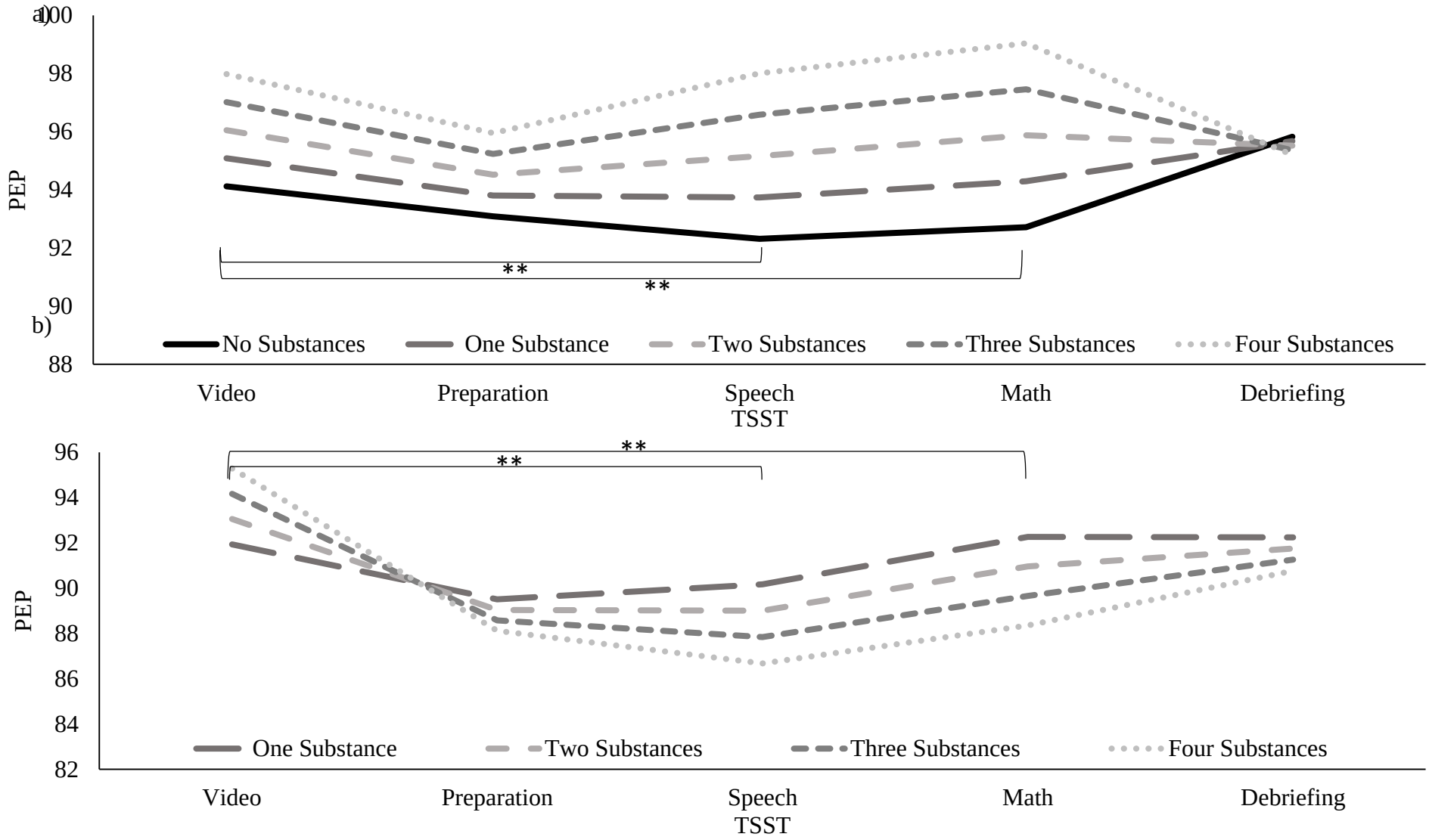

Figure 4. Adolescents' minute-by-minute PEP responses to the Trier Social Stress Test as a function of their substance use count by age 16, among youth who had never used any substances by age 14 (a) and adolescents who had used substances by age 14 (b). Among youth who had never used any substances by age 14, adolescents who used more substances by age 16 showed significantly greater increases in PEP from baseline to the speech and math tasks (indicated by

brackets). Among youth who had used substances by age 14, adolescents who used more substances by age 16 showed significantly greater decreases in PEP from baseline to the speech and math tasks. Note: RSA = Respiratory sinus arrhythmia, $^{**}p<.01$.

Study 3: Associations between Emotional Reactivity and Adolescent Substance Use: Differences by Gender and Valence

Substance use emerges during early and middle adolescence, and frequency of substance use tends to increase during late adolescence and young adulthood (Chen & Jacobson, 2012; Miech et al., 2020). Adolescents have greater access and experience social pressures to engage in substance use, especially in high school and college (Gallegos et al., 2021; Trucco et al., 2011; Yoon et al., 2020). Emotion lability (i.e., fluctuation in emotion) has been identified as a risk factor for greater substance use, in part because youth often use substances to reduce negative emotion and to enhance positive emotion (Siegel, 2015). However, research has not assessed emotional reactivity—the intensity with which an individual emotionally responds to events and experiences (e.g., daily stressors)—as a risk factor for adolescent substance use. Furthermore, emotional reactivity has been posited to differentially relate to substance use by gender (Chaplin et al., 2018) because male and female adolescents show differences in both their daily emotion and their substance use motivations (Frost et al., 2015; Kuntsche et al., 2015), although further empirical research is needed to test these pathways. Therefore, the present study assessed whether daily emotional reactivity to interpersonal conflicts relates to substance use count and frequency across middle to late adolescence, and whether these associations differ by gender.

Adolescent Emotion

Youth experience emotional development during early and middle adolescence. For instance, they show heightened emotional intensity and lability compared to adults and declines in these constructs across adolescence (Bailen et al., 2019; Larson et al., 2002; Maciejewski et al., 2015). Adolescents spend much of their time with friends and family and develop more meaningful peer relationships (Brown & Larson, 2009), and their emotion is highly tied to their interpersonal experiences. Indeed, adolescents tend to report better mental health and well-being

when they experience more positive peer and family interactions and poorer well-being when they have negative social interactions (Fiori & Consedine, 2013; Telzer & Fuligni, 2013). During adolescence, levels of positive emotion tend to decrease whereas levels of negative emotion increases, albeit to a lesser extent (e.g., Frost et al., 2015; Larson et al., 2002; Weinstein & Mermelstein, 2007). Neurobiological development following pubertal onset can promote greater sensitivity to social status and social stressors and greater responsivity to both rewarding and threatening stimuli (Forbes & Dahl, 2010). Adolescents continue to develop strategies to regulate their emotions in response to stress and other stimuli, such that they may show attenuated emotional reactivity as they age (Silvers et al., 2014; Steinberg et al., 2018).

Although there are varied processes related to experiencing extreme emotions, emotional reactivity uniquely relates to emotion involved in the stress process. Following a stressor, people generally experience poorer well-being, characterized by greater negative emotion and decreased positive emotion, and repeated emotional reactivity to daily stressors can gradually degrade physical and mental health (Almeida, 2005). Greater emotional reactivity to negative stimuli is associated with negative health outcomes, including greater depressive symptoms in children and adults (Bai & Repetti, 2018; Bai et al., 2020; Ha et al., 2019; Herres et al., 2016; Myin-Germeys et al., 2003; O'Neill et al., 2004; Parrish et al., 2011). Greater emotion variability and instability have also been associated with depressive symptoms (Kuppens et al., 2007; McConville & Cooper, 1996; Shadur et al., 2015), although more consistently for negative emotion than for positive emotion (Peeters et al., 2006; Thompson et al., 2017). Taken together, greater fluctuations of daily emotion may relate to poorer health, but there is limited empirical evidence regarding heightened emotional reactivity to stress as a risk factor for health during adolescence.

Emotional reactivity and Substance Use

People often use substances because of their effects on emotion, including to promote positive arousal state, to promote sociability, to fit in and conform with peers, and to reduce negative arousal and stress (Kuntsche et al., 2015). Adolescents who are impulsive and feeling positive emotion can use substances to enhance their experiences (Simons et al., 2005), and people with difficulties with coping with negative emotions and stress may be particularly inclined to use substances to dampen negative emotions (e.g., Myers et al., 2003; Shadur & Lejuez, 2015). In addition to these dispositional traits, daily experiences of emotion also contribute to substance use behaviors. Individuals are more likely to use substances and to specifically use substances at an earlier time on days when they feel distressed, nervous, and angry, and often report lower distress immediately following substance use despite showing elevations again later on (Armeli et al., 2007, 2008; Swendsen et al., 2000; Todd et al., 2009). Several studies suggest that college students use substances more on days when they experience greater distress, in line with self-medication models, as well as on days when they experience more positive emotion to enhance their social experiences (Arbeau et al., 2011; Hussong, 2007; O'Hara et al., 2014; Park et al., 2004; Simons et al., 2005, 2010, 2014). Relatedly, greater emotion variability has also been related to substance use among adults (Shadur et al., 2015).

However, most studies only assess daily emotion rather than other daily experiences, such as interpersonal stressors, which may elicit these emotional responses. Stress is consistently related to greater substance use (e.g., Goldbach et al., 2014; Wills et al., 2001), and adolescents and college students experience stressors from multiple domains, including academics, family, and peers (Steinberg et al., 2018). Emotional reactivity is one facet of the stress process, and youth who respond more strongly to these daily stressors and show greater emotional reactivity may also be at heightened risk for substance use. Yet, few studies have tested associations

between emotional reactivity and substance use. One study found that both immediate and sustained emotional reactivity to stress was related to greater tobacco use among college students (Dvorak & Simons, 2008), and this study had participants describe their general responses to stress using psychosocial surveys, which are relatively more susceptible to self-report bias compared to daily reports, rather than incorporate daily reports of emotion and daily stressors.

Furthermore, a number of mental health conditions linked with emotional reactivity have been shown to incur risk for substance use. Substance use initiation has also been consistently related to externalizing problems and, to a lesser extent, internalizing problems (e.g., Gonzales et al., 2017; King et al., 2004). Internalizing problems have been associated with motivation for substances to dampen negative emotion and stress, and externalizing problems have been associated with higher exposure to substances and deviant peers, as well as greater motivation for substances to enhancing emotion and arousal (Brook et al., 2011; Fox et al., 2011). Both internalizing and externalizing problems have also been related to greater emotion lability and use of maladaptive coping strategies including emotion suppression and avoidance have been implicated in both internalizing and externalizing problems (Aldao et al., 2016; Compas et al., 2017), and greater emotional reactivity has been found to temporally precede depressive symptoms (Parrish et al., 2011). Furthermore, depression and substance use are often comorbid (Armstrong & Costello, 2002), and adolescents are at elevated risk for substance use when they have more depressive symptoms (Shore et al., 2018). Emotional reactivity may similarly relate to substance use during adolescence, although this has yet to be explored in the literature.

Gender Differences in Emotion and Substance Use

Emotional reactivity has been posited to differentially relate to substance use among male and female adolescents (Chaplin et al., 2018). First, male and female adolescents frequently

show differences in substance use motivation. Whereas male adolescents tend to use substances for their enhancing effects, female adolescents tend to use substances to reduce negative emotion (Kuntsche et al., 2015). In line with these differences in substance use motives, gender differences have emerged in pathways to substance use. For instance, externalizing problems are more strongly related to substance use among male adolescents than female adolescents (Tarter et al., 1997). Furthermore, during adolescence, female adolescents are particularly vulnerable to poorer mental well-being, including heightened risk for depression, compared to male adolescents, which may predispose them to internalizing problems (Nolen-Hoeksema & Girgus, 1994). In line with these differences in substance use motives, gender differences have emerged in pathways to substance use. Given that exaggerated emotional reactivity is related to depressive symptoms, it may also be related to greater substance use among female adolescents specifically.

Second, male and female adolescents are socialized to experience emotion differently. Due to societal gender norms, male adolescents are often encouraged to be less emotionally responsive to negative events than female adolescents, whereas female adolescents are encouraged to experience their emotions fully (Fivush et al., 2000). Studies also suggest that female adolescents have greater positive and negative emotional variability than male adolescents (e.g., Maciejewski et al., 201). As a result, difficulties with emotion control and expression may be characterized by exaggerated changes in emotion in female adolescents and blunted changes in emotion in male adolescents.

Lastly, pubertal changes during adolescence can influence neural regions related to reactivity, including the amygdala and prefrontal cortex, which may result in sex-specific associations between emotional reactivity and behavioral outcomes including substance use (Hammerslag & Gulley, 2016). A previous study found that harsher parenting was related to

blunted neural activation following negative stimuli in male adolescents and greater neural activation in female adolescents, and greater neural activation predicted substance use risk among only female adolescents (Chaplin et al., 2018). Similarly, substance use elevated has been predicted to relate to heightened emotional reactivity for female adolescents and to blunted stress reactivity for male adolescents (Chaplin et al., 2018). Yet, few studies have tested whether gender differences emerge in associations between substance use and emotional reactivity.

Present Study

The present study investigated whether daily emotional reactivity was related to substance use among male and female adolescents. Adolescents completed a three-wave longitudinal study in which they reported at each wave whether they had ever used varied substances and how frequently they had used alcohol and marijuana over the past year. Participants also reported the number of daily interpersonal conflicts they experienced and their positive, depressive, and anxious emotion each night for 15 days. Because participants may use substances to both promote positive emotion and to reduce negative emotion (Kuntsche et al., 2015), we tested each form of emotion separately. Greater emotional reactivity to stress, characterized by lower levels of positive emotion and higher levels of anxious and depressive emotion on days when they experience more daily stressors, was predicted to be related to greater substance use, with associations strongest among female adolescents in line with previous research (Chaplin et al., 2018). Finally, although daily stressors are one factor that can influence adolescents' emotion, they may show differences in daily emotion due to other factors (e.g., positive experiences, daily activities, sleep, eating). Therefore, we also examined associations between emotion variability (i.e., a measure of fluctuations in emotion, irrespective

of daily stressors) and substance use to determine whether substance use is uniquely related to emotional responses to stress versus general fluctuations in emotion across days.

Method

Participants

The larger study included 350 total participants (55.81% female; *n* = 147 Latino, 42.0%; *n* = 106 European American, 30.3%; *n* = 75 Asian American, 21.43%; *n* = 22 identifying as another ethnicity including Middle Eastern and African American, 6.29%; median annual income of $65,000). Primary caregivers reported the highest level of education achieved by each parents (*1 = some elementary school; 2 = completed elementary school; 3 = some junior high school; 4 = completed junior high school; 5 = some high school; 6 = graduated from high school; 7 = trade or vocational school; 8 = some college; 9 = graduated from college; 10 = some medical, law, or graduate school; 11 = graduated from medical, law, or graduate school*). For youth in two-parent families, parental education was averaged across both parents. Across the sample, 18.45% of participants had parents who did not graduate from high school, 16.37% had parents who graduated high school, 23.81% had parents who graduated from a trade or vocational school, 20.54% had parents who completed some other form of college, and 20.83% had parents who graduated from college or higher education as their highest form of education.

This study used an accelerated longitudinal design, including two cohorts staggered a year apart and followed across three waves, each two years apart. During the first wave of the study, 316 participants were recruited from 10th and 11th grade classrooms at four public high schools in Los Angeles County through in-class presentations, mailings, and flyers from October 2011 to June 2012. Participants then had the option to complete additional waves of data collection two (73.14%) and four years later (64.3%). Because of attrition between the first and

second waves, an additional 34 participants (26 12th graders and eight students who were one-year post-high school) were recruited at the second wave. These participants did not differ from adolescents recruited at wave one with respect to ethnicity, college attendance, or income, all *p*s > .20. By incorporating two cohorts one year apart, with waves staggered two years apart, the study includes data from all years from 10th grade to three-years post-high school.

To be included in the present study, participants needed to both complete reports of substance use in the survey and complete the daily checklist protocol in at least one wave. They also needed to report their age, gender, and parents' education. This resulted in 330 of the 350 participants being retained in analyses (56.4% female; *n* = 138 Latino, 41.8%; *n* = 101 European American, 30.6%; *n* = 72 Asian American, 21.8%; *n* = 19 identifying as another ethnicity including Middle Eastern and African American, 5.8%; median annual income of $65,000). These participants did not differ from the full sample with respect to gender, ethnicity, parents' education, daily emotion, daily conflicts, or substance use, all *p*s > .30.

Procedures

At each wave, research staff visited participants' homes. Both adolescents and a primary caregiver completed online psychosocial questionnaires using an iPad or laptop, and each earned $50, $75, and $120 at each wave of data collection. Caregivers also reported family income and parents' education as part of this survey. All procedures were approved by the UCLA Institutional Review Board. Participants had the option to complete a two-week daily protocol in which they reported whether they experienced varied daily events and reported the extent to which they were feeling positive and negative emotion at bedtime each night for 15 nights. They received an electronic stamper to mark the time at which they completed each checklist. The vast majority of checklists were completed in a timely manner (98%).

Substance Use Measures

Substance Use Count. As part of the psychosocial survey, participants reported whether they had ever used any of the following seven substances: cigarettes, alcohol, marijuana, cocaine, crystal meth, illegal drugs, or any prescription drugs without a valid prescription. Substance use count was calculated as the sum number of substances each participant had ever used (0 = never used any substances, 7 = used all seven substances in their lifetime).

Alcohol Frequency. If participants had drunk alcohol, they reported how many days they had at least one drink of alcohol over the past year using a 10-point scale (1=Never in the past year, 2=1 or 2 days in the past year, 3=3 to 11 days in the past year, 4=one day a month, 5=2 to 3 days a month, 6=one day a week, 7=two days a week, 8=3 to 4 days a week, 9=5 to 6 days a week, 10=Every day). Participants who had never drank alcohol were coded as never using it in the past year (54.7% at first wave, 38.4% at second wave, 21.5% at third wave).

Marijuana Frequency. If participants had used marijuana, they reported how many days they used marijuana over the past year on a 10-point scale (1=Never in the past year, 2=1 or 2 days in the past year, 3=3 to 11 days in the past year, 4=1 day a month, 5=2 to 3 days a month, 6=1 day a week, 7=2 days a week, 8=3 to 4 days a week, 9=5 to 6 days a week, 10=Every day). Participants who had never used marijuana were coded as never using in the past year (75.6% at first wave, 59.8% at second wave, 46.8% at third wave).

Daily Checklist Measures

Interpersonal Conflict. Using the daily checklists, adolescents reported whether they experienced five forms of interpersonal conflict: had an argument or were punished by an adult at school, argued with your mother or father about something, argued with another family member about something, had an argument with a close friend or partner, and were punished or

disciplined by parents (0=no, 1=yes). A sum was calculated for each day for each participant (0 = no conflicts, 5 = all five conflicts), with higher values indicating more daily conflicts. Similar items regarding conflicts have been used to index emotional reactivity to conflicts in married couples (Almeida et al., 2002).

Daily Emotion. Participants reported their daily emotion using items from the Profile of Mood States (POMS; McNair et al., 1989) and Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). Using a scale that ranged from *1* (*not at all*) to *5* (*extremely*), adolescents reported how much they experienced positive mood (*interested, excited, cheerful, enthusiastic, attentive*), anxious mood (*worried, on edge, uneasy, nervous*), and depressive mood (*sad, hopeless, discouraged*). These scales have been used in previous studies of adolescents (e.g., Yip & Fuligni, 2002). Subscales showed moderate reliability across items each day (αs = .65-.81, after standardizing items within each wave for each individual).

Analytic Plan

First, we tested whether participation in the study differed by gender, parents' education, ethnicity, daily emotion, daily conflicts, and substance use outcomes. For each participant, we calculated the percentage of waves they completed out of three possible waves if they initially entered the first wave of the study or out of two possible waves if they initially entered the second wave of the study. We tested the association between the percentage of possible waves and each variable using a *t*-test for gender, ANOVA for ethnicity, correlation for parents' education, and multilevel models for all time-varying variables (i.e., daily emotion, daily conflicts, wave substance use). Because participants were older in each subsequent wave, these multilevel models controlled for age.

Next, we used multilevel models to examine demographic differences in primary study variables: positive emotion, depressive emotion, anxious emotion, daily conflicts, substance use count, frequency of alcohol use, and frequency of marijuana use. Age (grand mean-centered), gender (dummy-coded, male as reference group), ethnicity (dummy-coded, European American as reference group), and parents' education (grand mean-centered) were tested as predictors. Three-level models with days (Level 1) nested within waves (Level 2) within adolescents (Level 3) were used for daily emotion and daily conflicts, and two-level models with waves (Level 1) nested within adolescents (Level 2) were used for substance use variables.

Next, we tested whether emotional reactivity was related to substance use. Three-level multilevel models predicting daily emotion with days (Level 1) nested within years (Level2) within adolescents (Level 3) were used to model emotional reactivity, with separate models for positive, anxious, and depressive emotion. Emotional reactivity was modeled by predicting emotion from daily frequency of interpersonal conflicts. Number of conflicts was reported each day (Level 1) and centered at the participant's mean for that wave. Therefore, this coefficient represented predicted changes in adolescents' emotion on days when they experienced more conflicts. Daily conflict was included as a random effect in all models.

To determine whether emotional reactivity was related to substance use, models tested the cross-level two-way Substance Use (Level 2) × Daily Conflicts (Level 1) interaction as a predictor of daily emotion (Eq. 1). Measures of substance use were reported each wave of the study (Level 2) and were grand mean-centered, with separate models tested for substance use count, frequency of alcohol use, and frequency of marijuana use. Significant interactions would indicate that the degree to which daily emotion related to daily conflicts varied by substance use. Interactions were probed at different level of substance use: one standard deviation below, one

standard deviation above, and at the sample mean. We consistently modeled substance use as the predictor and emotion as the outcome because of the structure of the data (i.e., emotion at Level 1, substance use at Level 2), although emotional reactivity may theoretically influence substance use risk. This approach is necessary statistically, as it allows for all days to be included within the analysis and for accurate error estimation, and has been similarly used in previous research (e.g., Bai et al., 2020; Shirtcliff & Essex, 2008).

Equation 1:

$$L1: \widehat{Affect}_{ij} = \beta_{0j} + \beta_{1j}(Negative\ Events)$$
$$L2: \beta_{0j} = \gamma_{00} + \gamma_{01}(Substance\ Use) + u_{0j}$$
$$\beta_{1j} = \gamma_{10} + \gamma_{11}(Substance\ Use) + u_{1j}$$

Models then tested whether associations between substance use and emotional reactivity differed by gender. Models were repeated including a three-way Gender (Level 3) × Substance Use (Level 2) × Daily Conflicts (Level 1; Eq. 2). Significant three-way interactions would suggest that the Substance Use × Daily Conflicts interaction (i.e., the index of the association between substance use and emotional reactivity) differed between male and female adolescents. Gender was dummy-coded (0 = male, 1 = female), and simple slopes were probed at the level of gender; if a two-way interaction was significant for either male or female adolescents, that interaction was then probed as well.

Equation 2:

$$L1: \widehat{Affect}_{ijk} = \beta_{0jk} + \beta_{1jk}(Negative\ Events)$$
$$L2: \beta_{0jk} = \gamma_{00k} + \gamma_{01k}(Substance\ Use) + u_{0jk}$$
$$\beta_{1jk} = \gamma_{10k} + \gamma_{11k}(Substance\ Use) + u_{1jk}$$
$$L3: \gamma_{00k} = \pi_{000} + \pi_{001}(Gender) + +\pi_{001}(Substance\ Use) + r_{00k}$$
$$\gamma_{01k} = \pi_{010} + \pi_{011}(Gender) + r_{01k}$$
$$\gamma_{10k} = \pi_{100} + \pi_{101}(Gender) + \pi_{101}(Substance\ Use) + r_{10k}$$
$$\gamma_{11} = \pi_{110} + \pi_{111}(Gender) + r_{11k}$$

Parents' education, ethnicity, and age were covaried in all analyses. All models of emotional reactivity controlled for participants' emotion from the previous day, centered at the wave mean.

Finally, models examined associations between emotion variability and substance use. Emotion variability was calculated as the standard deviation of each form of emotion across all days of the wave, such that there was one value of emotion variability per wave for each participant. We used two-level models to predict emotion variability from substance use, with waves nested within adolescents, and then tested for moderation of associations by gender.

Results

Participation Analyses

In total there were 330 participants who completed 658 total assessments at the wave level (M = 1.99, SD = 0.85) and 8773 total observations at the daily level (M = 14.33, SD = 4.71 out of 15 possible per wave; M = 29.58, SD = 11.85 out of 45 possible across all three waves). Because of the longitudinal study design, we tested whether study variables were related to the number of possible waves that participants completed. There were no differences with respect to gender, substance use, emotion, or conflicts, all ps > .05. ANOVA indicated ethnic differences in participation, $F(326,3) = 4.17$, $p = .0064$, and Tukey's post-hoc tests indicated that Asian Americans participated in fewer possible waves than all other ethnic groups; M = 0.58, SD = 0.28 for Asian Americans; Ms = 0.71-0.73, SDs = 0.27-0.28 for other ethnic groups. Lastly, higher parental education was weakly correlated with higher participation, $r(328) = .12$, $p = .03$.

Descriptive Models

First, multilevel models were used to test whether gender, ethnicity, parents' education, and age related to daily emotion, daily conflicts, and substance use. Participants reported low levels of depressive and anxious emotion and high levels of positive emotion across waves, and

levels did not change with age, *p*s > .4. Results indicated male adolescents were higher in positive emotion, *B* = -0.15, *SE* = 0.07, *p* = .026, 95% Confidence Interval (CI) [-0.28, -0.02], and lower in depressive emotion, *B* = -0.09, *SE* = 0.04, *p* = .042, 95% CI [0.003, 0.18], compared to female adolescents. Adolescents with higher parents' education reported higher positive emotion, *B* = 0.04, *SE* = 0.02, *p* = .031, 95% CI [0.004, 0.08], and higher depressive emotion, *B* = 0.03, *SE* = 0.01, *p* = .043, 95% CI [0.0008, 0.05]. Adolescents also consistently reported a low number of conflicts, approximately two per week for each wave. Conflicts became less frequent over time, *B* = -0.03, *SE* = 0.01, *p* < .001, and male adolescents reported significantly more conflicts than female adolescents, *B* = 0.09, *SE* = 0.03, *p* = .004, 95% CI [0.03, 0.14]. Asian American adolescents reported less positive emotion, *B* = -0.23, *SE* = 0.09, *p* = .016, 95% CI [-0.42, -0.04], and fewer conflicts, *B* = -0.11, *SE* = 0.04, *p* = .009, 95% CI [-0.19, -0.03], than European American adolescents.

Substance use count, frequency of alcohol use, and frequency of marijuana use were low at study entry and gradually increased over time (Fig. 1). Male adolescents reported using more substances, *B* = 0.30, *SE* = 0.13, *p* = .020, 95% CI [-0.55, -0.05], and using marijuana more frequently, *B* = 0.47, *SE* = 0.20, *p* = .021, 95% CI [-0.87, -0.07], than female adolescents. Asian American adolescents reported less frequent use of alcohol relative to European American adolescents, *B* = -0.53, *SE* = 0.26, *p* = .043, 95% CI [-1.05, -0.02].

Emotional Reactivity and Substance Use

We investigated whether each form of daily emotional reactivity was related to substance use count, frequency of alcohol use, and frequency of marijuana use using three-level multilevel models. These models included a Substance Use × Daily Conflicts cross-level interaction, which tested whether the daily association between daily conflicts and each form of emotion differed by

adolescents' substance use. We also tested whether associations between daily emotional reactivity and adolescent substance use differed by adolescent gender by testing a three-way Gender × Substance Use × Daily Conflicts interaction.

Positive emotional reactivity (i.e., reductions in positive emotion) was not related to adolescents' substance use count, $B = 0.02$, $SE = 0.01$, $p = .09$. However, positive emotional reactivity was significantly associated with frequency of alcohol use, $B = 0.02$, $SE = 0.01$, $p = .028$, 95% CI [0.002, 0.03], and marijuana use, $B = 0.02$, $SE = 0.01$, $p = .049$, 95% CI [0.00003, 0.03]. Youth who abstained from use of alcohol and marijuana over the past year reported the greatest declines in positive emotion on days when they experienced more conflicts, suggesting that these participants showed the highest degree of positive emotional reactivity to conflicts (Fig. 2). In turn, adolescents who used alcohol and marijuana more frequently reported a smaller decline in positive emotion on days when they experienced more conflicts, such that more frequent use was related to attenuated positive emotional reactivity to conflicts. Associations between substance use and positive emotional reactivity did not differ by gender, ps > .5.

Substance use was related to exaggerated anxious emotional reactivity among only female adolescents. Associations between substance use count and anxious emotional reactivity differed by gender, $B = 0.05$, $SE = 0.03$, $p = .040$, 95% CI [0.002, 0.10]. Simple slopes indicated that greater substance use count was associated with exaggerated anxious emotional reactivity in female adolescents, $B = 0.03$, $SE = 0.01$, $p = .007$, 95% CI [0.008, 0.05], but not male adolescents, $B = 0.00$, $SE = 0.01$, $p = .99$, 95% CI [-0.03, 0.03]. Female adolescents who used more substances showed a significantly larger increase in anxiety on days when they experienced more daily conflicts compared to female adolescents who used no substances (Fig. 3a). Similarly, associations between alcohol frequency and daily anxious emotional reactivity to

conflicts differed by gender, B = -0.04, SE = 0.02, p = .043, 95% CI [-0.07, -0.001]. For female adolescents, more frequent use of alcohol in the past year was associated with greater increases in anxiety on days when they experienced more conflicts, B = 0.02, SE = 0.01, p = .017, 95% CI [0.003, 0.03] (Fig. 3b), and associations were not significant for male adolescents, B = -0.01, SE = 0.01, p = .4, 95% CI [-0.03, 0.01]. Marijuana frequency was not associated with anxious emotional reactivity, p = .8, and this association did not differ by gender, p = .3.

Finally, associations between substance use and daily depressive emotional reactivity differed by gender, B = -0.08, SE = 0.03, p = .002, 95% CI [-0.13, -0.03] for substance use count; B = -0.05, SE = 0.02, p = .006, 95% CI [-0.08, -0.01] for frequency of alcohol use; B = -0.04, SE = 0.02, p = .026, 95% CI [-0.08, -0.005] for frequency of marijuana use. However, in contrast to effects for anxious emotion, we found that greater substance use was consistently associated with blunted depressive emotional reactivity in male adolescents, such that male adolescents with greater substance use count and more frequent use showed smaller increases in depressive emotion on days when they experienced more conflicts; B = -0.05, SE = 0.01, p < .001, 95% CI [-0.08, -0.02] for substance use count, B = -0.03, SE = 0.01, p = .001, 95% CI [-0.04, -0.01] for frequency of alcohol use; B = -0.03, SE = 0.01, p = .001, 95% CI [-0.04, -0.01] for frequency of marijuana use. Although male adolescents generally showed significant increases in depressive emotion on days when they experienced more conflicts, male adolescents who used more substances and used substances more frequently showed the smallest increases in depressive emotion (Fig. 4). Associations were nonsignificant among female adolescents, although substance use count and alcohol frequency were marginally associated with greater depressive mood reactivity in female adolescents in line with associations for anxious emotional reactivity, B = 0.02, SE = 0.01, p = .060, 95% CI [-0.0008, 0.04] for substance use count; B =

0.01, *SE* = 0.01, *p* = .094, 95% CI [-0.002, 0.03] for frequency of alcohol use; *B* = 0.00, *SE* = 0.01, *p* = .620, 95% CI [-0.01, 0.02] for frequency of marijuana use. Female adolescents generally showed increases in depressive emotion on days when they experienced conflicts, and female adolescents who used more substances and used alcohol more frequently showed marginally greater increases in depressive mood. All associations between daily emotional reactivity and substance use remained significant when controlling for emotion variability.

Emotion Variability and Substance Use.

Finally, we examined whether similar associations emerged between emotion variability and substance use to determine whether substance use was uniquely related to responses to stress, or whether similar associations emerged with general fluctuations in emotion. Results indicated that higher anxious and depressive emotion variability was related to higher substance use count; *B* = 0.56, *SE* = 0.16, *p* = .001, 95% CI [0.24, 0.87] for anxious emotion variability; *B* = 0.46, *SE* = 0.16, *p* = .003, 95% CI [0.15, 0.77] for depressive emotion variability. Higher emotion variability was also consistently related to more frequent alcohol use; *B* = 0.80, *SE* = 0.36, *p* = .028, 95% CI [0.09, 1.51] for positive emotion variability; *B* = 0.55, *SE* = 0.24, *p* = .024, 95% CI [0.07, 1.03] for anxious emotion variability; *B* = 0.56, *SE* = 0.24, *p* = .020, 95% CI [0.09, 1.03] for depressive emotion variability. Emotion variability was not related to frequency of marijuana use, *p*s > .15. In contrast to results for emotional reactivity, there were no gender differences in any associations between emotion variability and substance use, *p*s > .08.

Discussion

The present study investigated whether emotional reactivity is related to substance use during middle and late adolescence. Results revealed that associations between substance use and emotional reactivity to daily stress varied by gender and emotional valence. Specifically,

more frequent use of alcohol and marijuana were related to blunted positive emotional reactivity among male and female adolescents. When examining two dimensions of negative emotional reactivity (i.e., anxious and depressive reactivity), we found that exaggerated anxious reactivity to daily conflict was associated with greater substance use count and more frequent alcohol use among female adolescents, whereas blunted depressive reactivity to daily conflict was related to greater substance use count and frequency among male adolescents. When examining emotion variability, we found that higher emotion variability was related to greater substance use count and more frequent alcohol use, irrespective of emotional valence and participant gender. These analyses further suggest that emotional reactivity may be an important dimension for assessment among adolescents at-risk for substance use, distinct from other aspects of emotion variability.

The present findings indicated that substance use is related to both emotional reactivity and emotion variability as unique dimensions of emotion. Previous research has suggested that individuals with difficulties with emotion regulation and heightened chronic negative emotion may turn to substance use either as a means of coping with negative experiences or due to greater exposure to deviant peers (e.g., Goodwin et al., 2004; Myers et al., 2003; Shadur & Lejuez, 2015). Differences in emotional reactivity may similarly relate to use because of coping motives or due to poorer mental health (i.e., greater internalizing and externalizing problems) which are often related to substance use. Regarding peer processes, differences in emotional reactivity may suggest differences in conformity motives, difficulty responding to peer pressure. Furthermore, we observed different patterns of results for associations between emotional reactivity and emotion variability with substance use. These results suggested that, although varied daily experiences can elicit fluctuations in emotion, emotional reactivity to daily interpersonal stress may be uniquely related to adolescent substance use. Whereas higher emotion variability is

consistently related to greater substance use, aspects of both blunted and exaggerated emotion responses related to substance use and these associations varied by sex and emotional valence.

More frequent substance use was associated with blunted positive emotional reactivity for both male and female youth. By using this analytic technique to compare levels of emotion on stressful and non-stressful days, we could assess both levels of emotional reactivity and whether differences were apparent on stressful versus non-stressful days. Although blunted positive emotional reactivity was related to substance use, it is important to note that youth who used substances more frequently specifically showed consistently lower positive emotion, irrespective of daily conflicts, whereas youth who used substances less frequently tended to report higher positive emotion on days when they did not experience conflicts. This research extends previous findings which have focused on associations between substance use and negative emotion (e.g., Myers et al., 2003; Shadur et al., 2015). Whereas chronic negative emotion has been consistently noted as a risk factor for adolescent substance use, we found that chronically low levels of positive emotion were related to substance use. Because reports of positive emotion did not suggest a floor effect for ratings (i.e., participants could have reported lower levels of positive emotion), results suggested that there was also an absence of positive emotional reactivity to daily conflicts in addition to this effect of chronically lower positive emotion among adolescents who used substances more frequently. Blunted emotional flexibility is a symptom of both depression (Coifman & Summers, 2019) and psychopathy (Blonigen et al., 2006), such that youth high in internalizing and externalizing problems, respectively, may show both blunted positive emotional reactivity to conflicts and heightened substance use risk.

Gender differences emerged in associations between anxious and depressive emotional reactivity and substance use. First, exaggerated anxious reactivity was associated with greater

substance use count and more frequent substance use among female adolescents, in line with previous research that exaggerated emotional reactivity is related to more negative health outcomes in adults (e.g., Myin-Germeys et al., 2003) and that emotion instability imposes risk for poorer mental health in adolescence (Aldao et al., 2016). Elevated emotional reactivity is a risk factor for depression, which is both more prevalent and more related to substance use among female than male adolescents (Kuppens et al., 2007; McConville & Cooper, 1996). Gender difference may have emerged because we examined conflicts as a form of interpersonal stress. For instance, female adolescents tend to be more relationally oriented, and more frequent family conflict has been more strongly related to substance use disorders among female than male adolescents (Skeer et al., 2011). Although the associations were marginal, exaggerated depressive emotional reactivity was similarly related to greater substance use count and frequency for female adolescents.

In turn, dampened depressive emotional reactivity was associated with substance use among male adolescents. Blunted depressive emotional reactivity to conflicts may suggest lower sensitivity to interpersonal stressors, in line with research that male adolescents tend to be less affiliative than female adolescents (Feingold, 1994). Blunted emotional reactivity to positive and negative images has also been related to psychopathology including externalizing problems or callous-unemotional traits, both of which tend to be higher in male than in female adolescents and have been related to both greater substance use (Hillege et al., 2010; Truedsson et al., 2019).

This opposite pattern of findings for negative emotional reactivity, such that substance use is associated with exaggerated anxious emotional reactivity among female adolescents and blunted depressive emotional reactivity among male adolescents, may also result from differences in emotion socialization and motive for substance use, in line with theoretical gender

differences in pathways to substance use (e.g., Chaplin et al., 2018). Male and female adolescents show differences in emotion socialization, such that male adolescents are less encouraged to fully express their emotions than female adolescents (Fivush et al., 2000). As a result, difficulties with emotion may be indexed by exaggerated reactivity in female adolescents and blunted reactivity in male adolescents. Blunted emotional reactivity may also suggest emotion suppression, which has been related to both internalizing and externalizing problems (Brenning et al., 2021). Finally, male adolescents tend to be motivated to use substances to promote sociability and positive emotion, whereas female adolescents tend to use substances to reduce negative emotion and social discomfort (Kuntsche et al., 2015). Blunted emotional reactivity may suggest that these youth are less influenced by social stressors, and may use substances impulsively, to promote positive arousal, and to enhance their social experiences. Exaggerated emotional reactivity may in turn suggest being highly influenced by social stressors, and inclined to use substances to reduce negative feelings.

Limitations

The study was limited by assessment of daily emotions and substance use. Although we assess positive, anxious, and depressive emotion, findings could be strengthened by measuring different forms of negative emotion (e.g., anger) and positive emotion (e.g., high- versus low-arousal emotions). Furthermore, we lacked daily reports of substance use, which may produce more accurate estimates of frequency and associations with emotion at the daily level. We also lacked additional information regarding substance use, such as motivation for use, means of access, location of use, and presence of peers or siblings during use.

There were also limitations to the accelerated longitudinal design of the study. There was attrition across assessments, and both youth of lower parental education completed fewer

possible waves of the study and Asian American adolescents completed significantly fewer waves of the study than participants of other ethnic backgrounds. Finally, participants could complete up to three assessments of substance use as part of this study, each two years apart. The timing of assessment precluded rigorous assessment of directionality of associations or trajectories of substance use. Future studies that follow youth with more frequent assessments (e.g., yearly) can assess whether emotional reactivity relates to future substance use.

Conclusion

Although aspects of emotion including emotion variability and chronic negative emotion have been implicated as risk factors of substance use, limited research has examined whether emotional reactivity relates to substance use among adolescents. The present study found emotional reactivity relates to substance use count and frequency during adolescence, a period when youth show escalating levels of substance use. Results indicated that associations differ by gender and emotional valence. More frequent alcohol and marijuana use were related to blunted positive emotional reactivity among male and female adolescents. Interestingly, exaggerated anxious emotional reactivity was related to substance use among female adolescents, whereas blunted depressive emotional reactivity was related to substance use among male adolescents. Also, higher emotion variability was related to higher substance use count and more frequent alcohol use. These findings highlight how emotional reactivity to stress is one aspect of emotion that is tied to substance use, and how gender differences, potentially related to socialization of emotion or substance use motive, may influence the degree to which emotional reactivity relates to substance use. Further research is needed to identify whether emotional reactivity is a risk factor for substance use, or whether there are related factors (e.g., internalizing and externalizing problems) that can account for associations between emotional reactivity and substance use.

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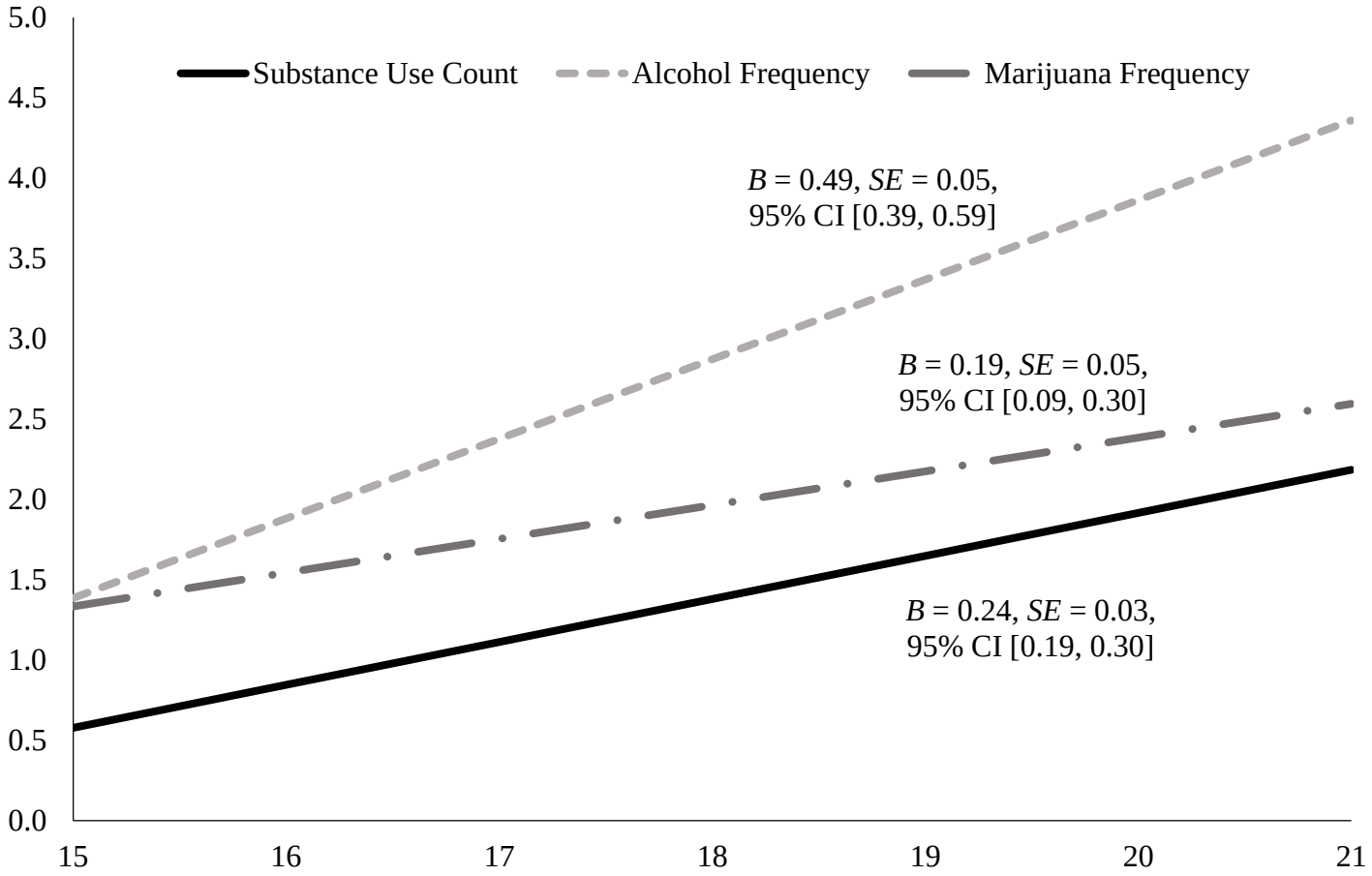


Figure 1. Substance Use as a function of Age. Note: all *p*s < .001. CI = Confidence Interval.

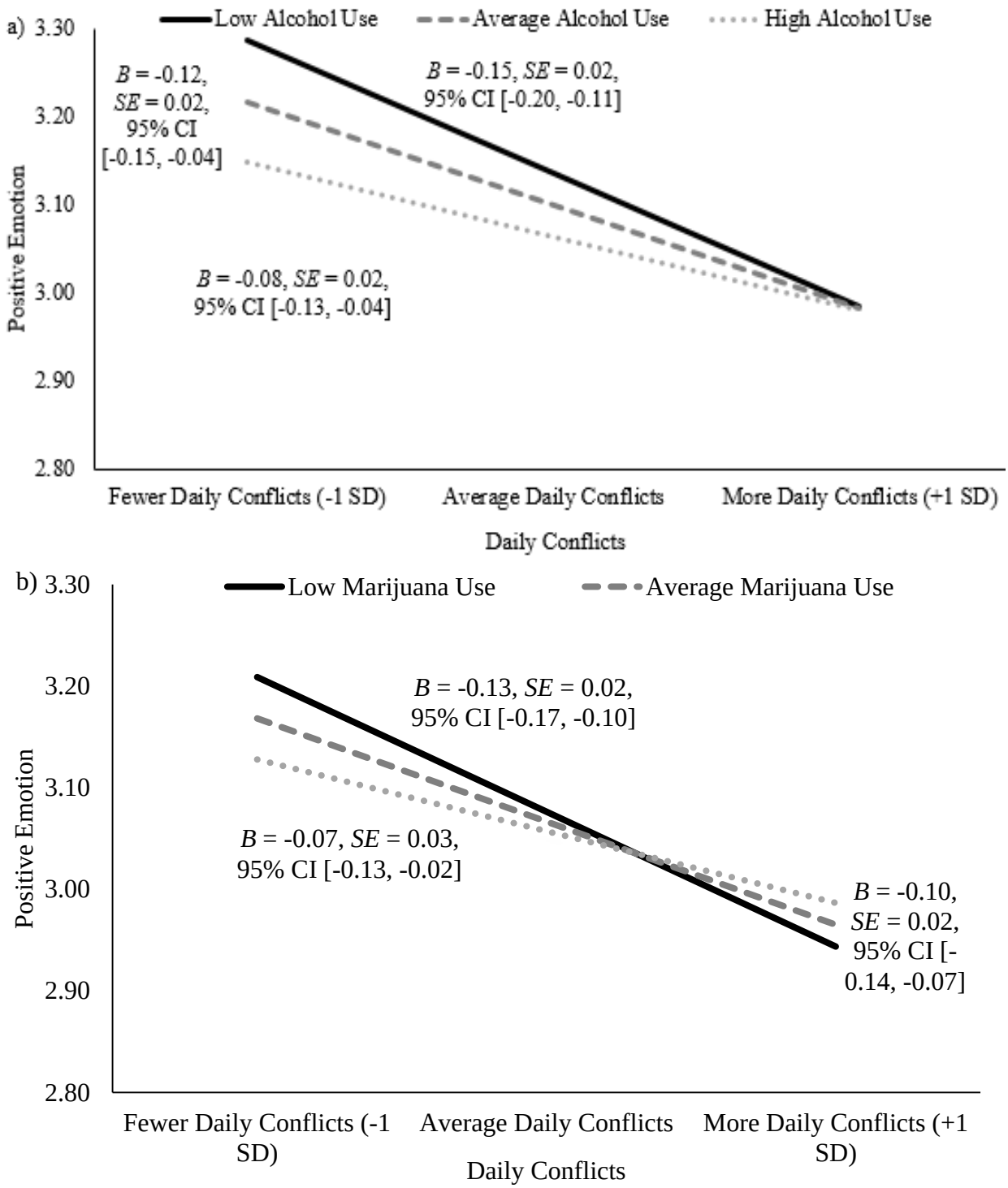
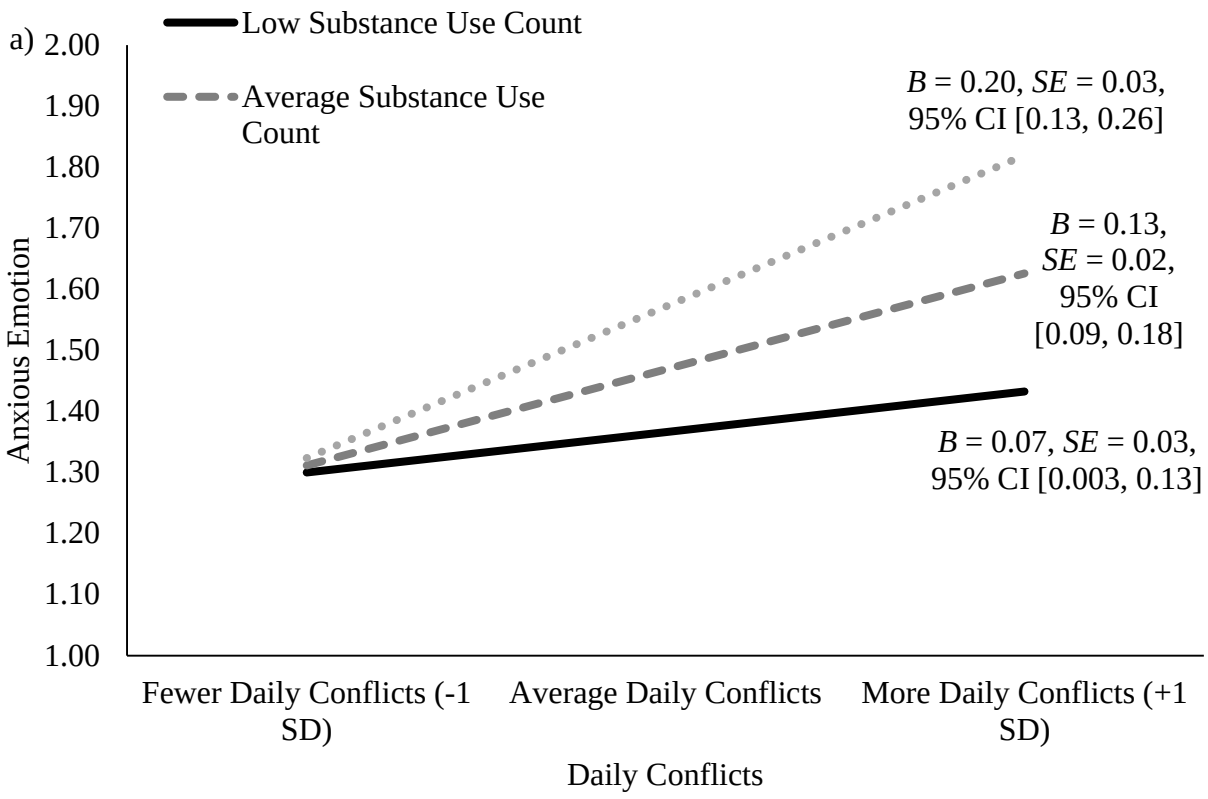
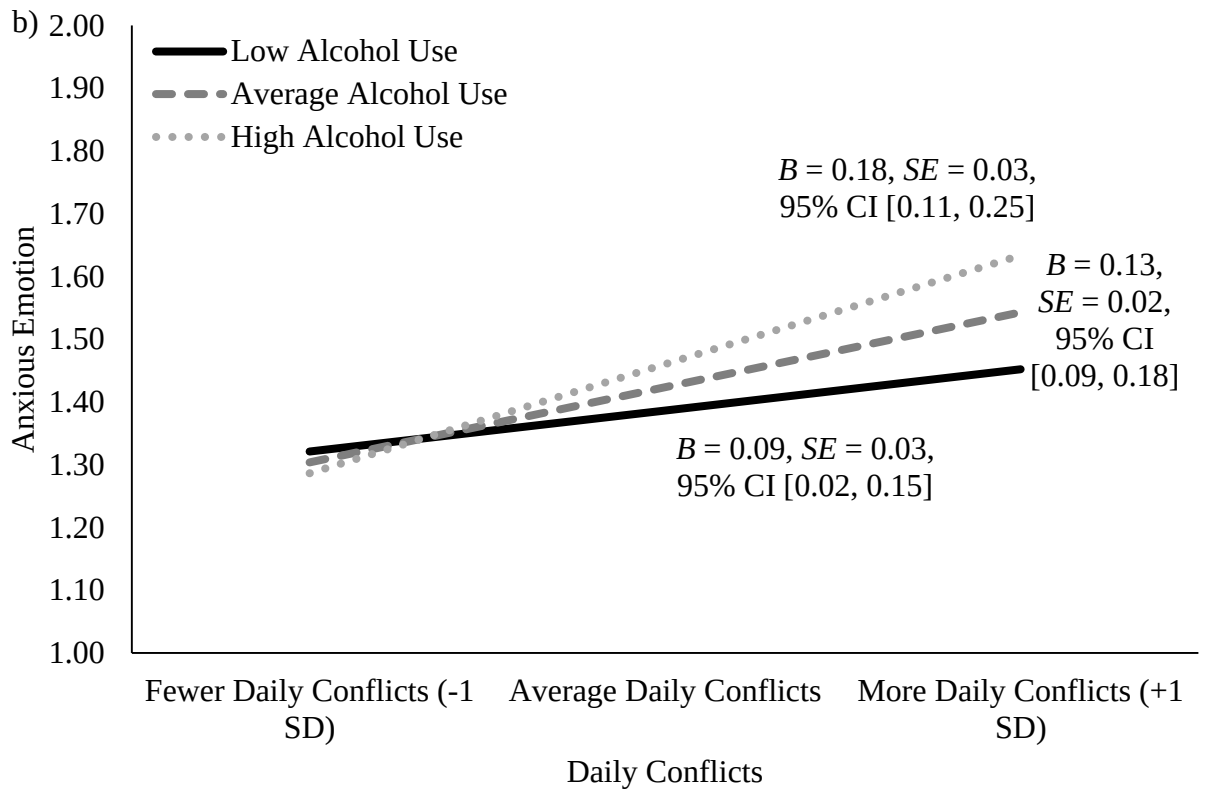


Figure 2. Positive Emotion as a Function of Daily Arguments and Substance Use Count (a) and Frequency of Alcohol Use (b). *p<.05, **p<.01, ***p<.001. CI = Confidence Interval. Associations controlled for age, ethnicity, parents' education, and previous day's emotion. The mean and standard deviation of the sample were used for plotting values.


a)
Low Substance Use Count
Average Substance Use Count
B = 0.20, SE = 0.03, 95% CI [0.13, 0.26]
B = 0.13, SE = 0.02, 95% CI [0.09, 0.18]
B = 0.07, SE = 0.03, 95% CI [0.003, 0.13]
Anxious Emotion
2.00
1.90
1.80
1.70
1.60
1.50
1.40
1.30
1.20
1.10
1.00
Fewer Daily Conflicts (-1 SD)
Average Daily Conflicts
More Daily Conflicts (+1 SD)
Daily Conflicts


b)
Low Alcohol Use
Average Alcohol Use
High Alcohol Use
B = 0.18, SE = 0.03, 95% CI [0.11, 0.25]
B = 0.13, SE = 0.02, 95% CI [0.09, 0.18]
B = 0.09, SE = 0.03, 95% CI [0.02, 0.15]
Anxious Emotion
2.00
1.90
1.80
1.70
1.60
1.50
1.40
1.30
1.20
1.10
1.00
Fewer Daily Conflicts (-1 SD)
Average Daily Conflicts
More Daily Conflicts (+1 SD)
Daily Conflicts

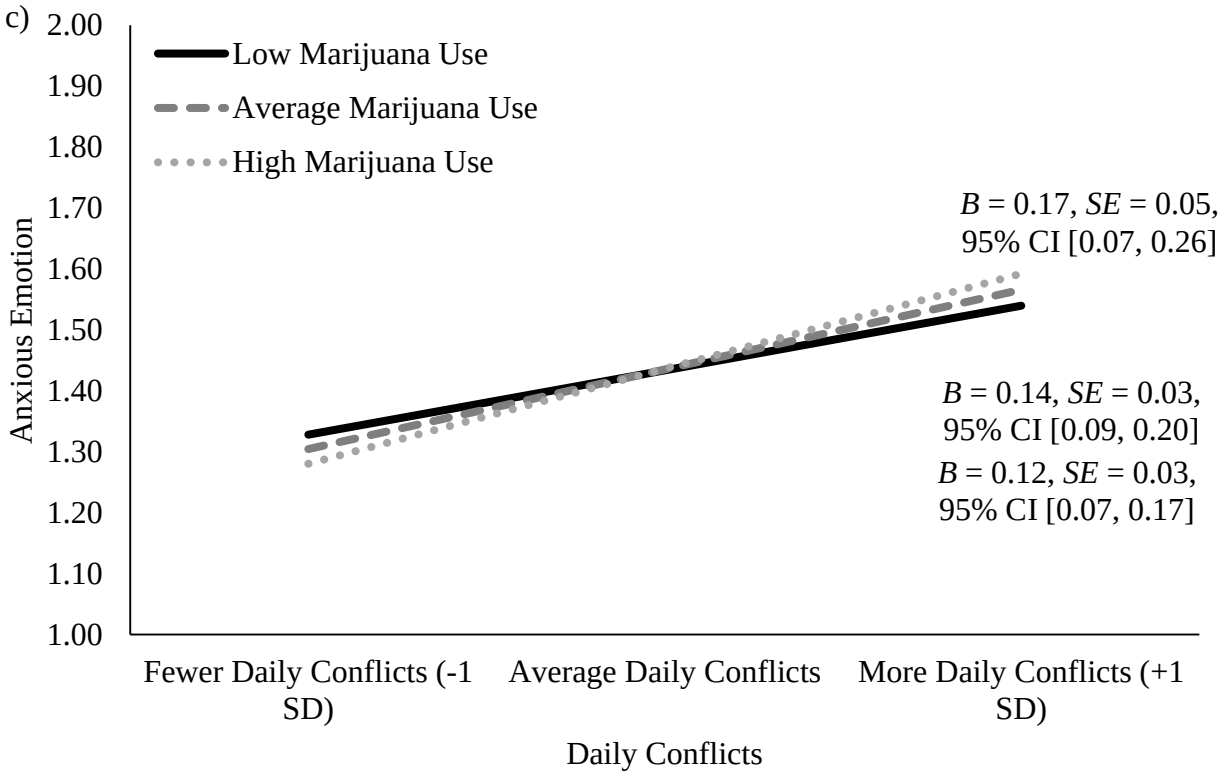
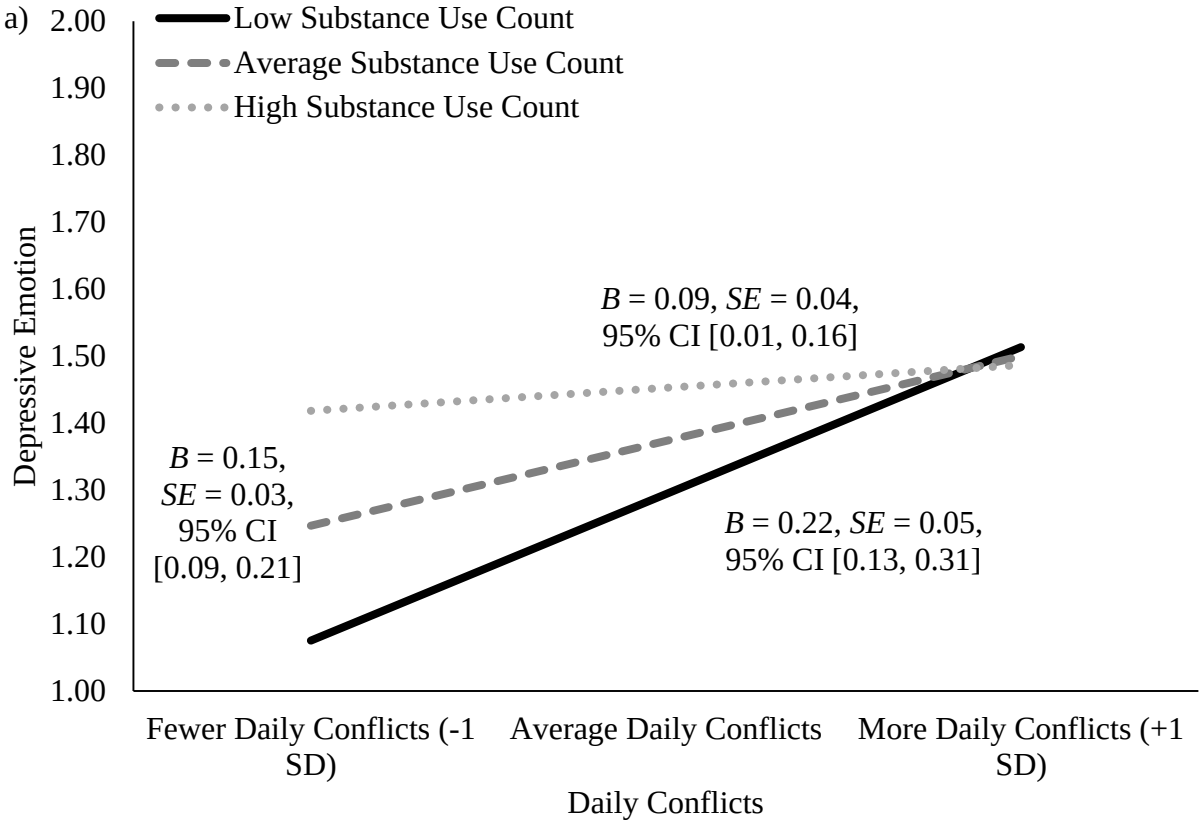
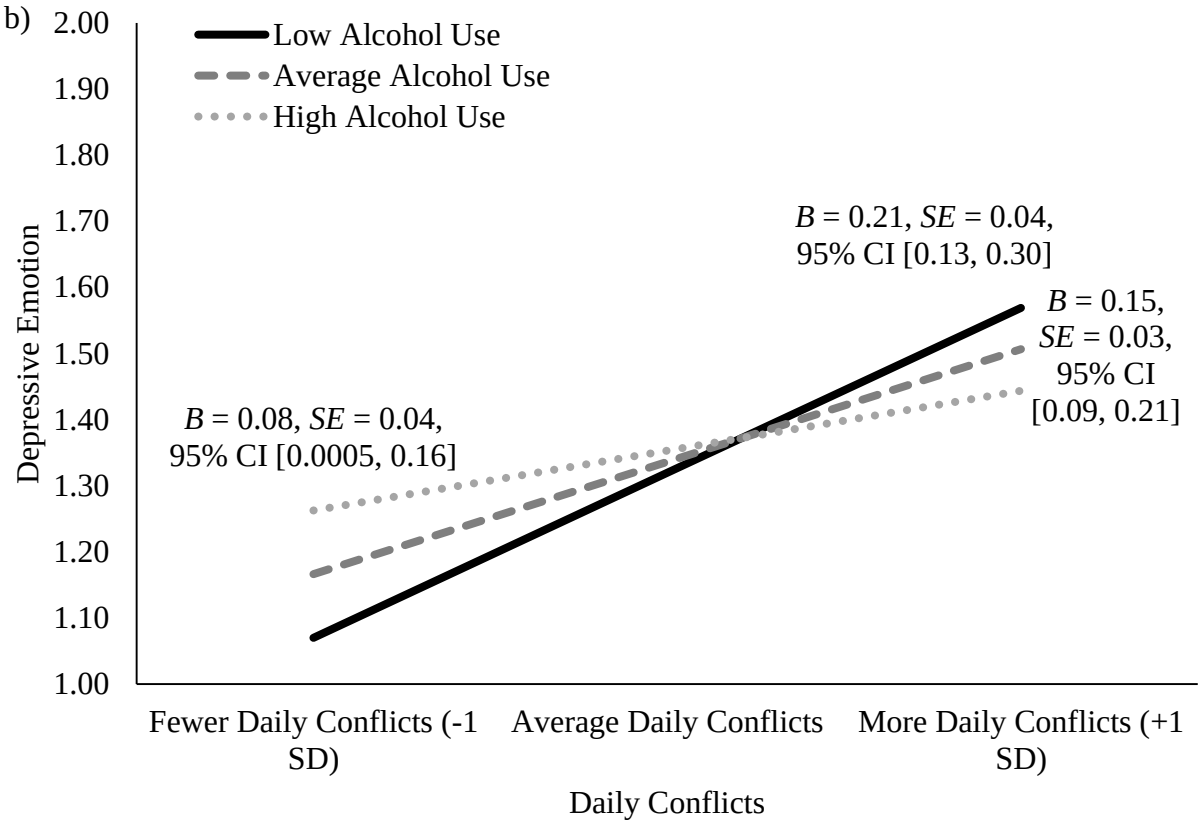


Figure 3. Anxious Emotion as a Function of Daily Arguments and Substance Use Count (a), Frequency of Alcohol Use (b), Frequency of Marijuana Use (c) among female adolescents. **p*<.05, ***p*<.01, ****p*<.001. CI = Confidence Interval. Associations controlled for age, ethnicity, parents' education, and previous day's emotion. The mean and standard deviation of the sample were used for plotting values.


a)
Low Substance Use Count
Average Substance Use Count
High Substance Use Count
Depressive Emotion
2.00
1.90
1.80
1.70
1.60
1.50
1.40
1.30
1.20
1.10
1.00
B = 0.09, SE = 0.04, 95% CI [0.01, 0.16]
B = 0.15, SE = 0.03, 95% CI [0.09, 0.21]
B = 0.22, SE = 0.05, 95% CI [0.13, 0.31]
Fewer Daily Conflicts (-1 SD)
Average Daily Conflicts
More Daily Conflicts (+1 SD)
Daily Conflicts


b)
Low Alcohol Use
Average Alcohol Use
High Alcohol Use
Depressive Emotion
2.00
1.90
1.80
1.70
1.60
1.50
1.40
1.30
1.20
1.10
1.00
B = 0.21, SE = 0.04, 95% CI [0.13, 0.30]
B = 0.15, SE = 0.03, 95% CI [0.09, 0.21]
B = 0.08, SE = 0.04, 95% CI [0.0005, 0.16]
Fewer Daily Conflicts (-1 SD)
Average Daily Conflicts
More Daily Conflicts (+1 SD)
Daily Conflicts

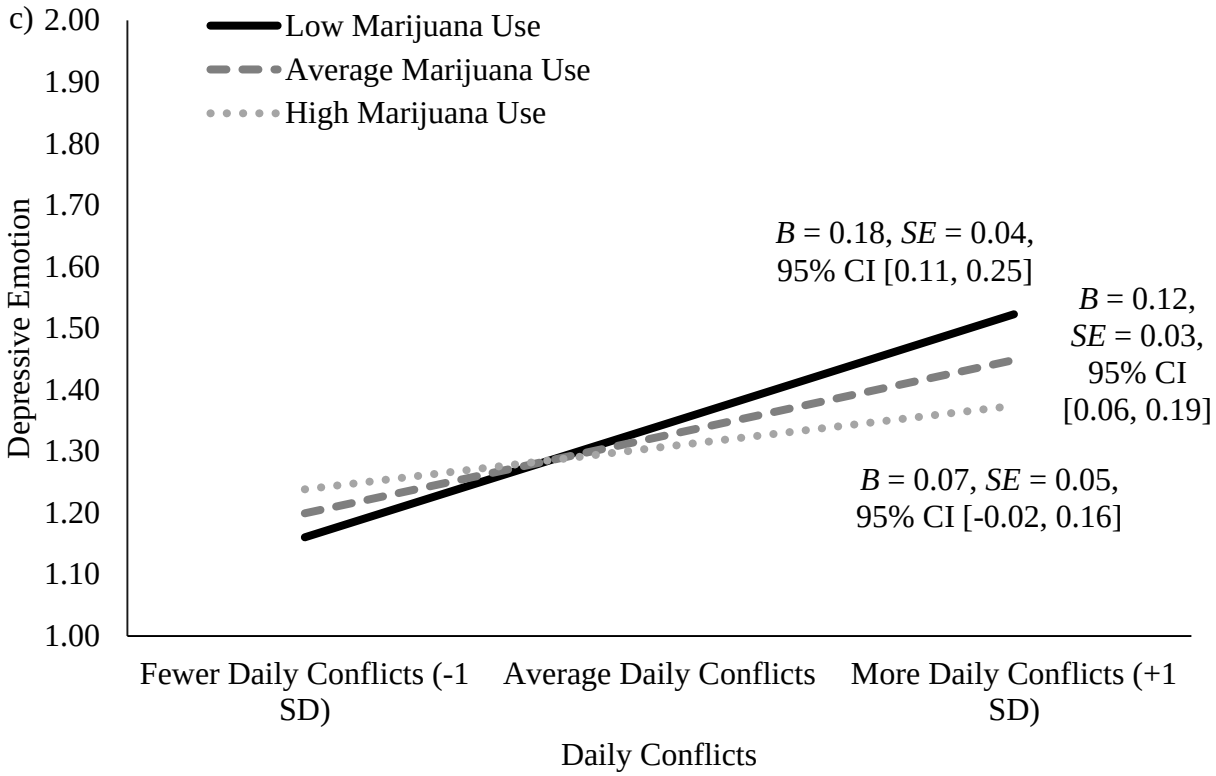


Figure 4. Depressive Emotion as a Function of Daily Arguments and Substance Use Count (a), Frequency of Alcohol Use (b), Frequency of Marijuana Use (c) among male adolescents. **p*<.05, ***p*<.01, ****p*<.001. CI = Confidence Interval. Associations controlled for age, ethnicity, parents' education, and previous day's emotion. The sample mean and SD were used

General Discussion

The present studies rigorously assessed the extent to which differences in the stress response, with respect to HPA axis, emotion, and the ANS, related to substance use across middle and late adolescence. In a sample of high-risk Mexican-origin adolescents with high levels of adversity, blunted emotion responses were related to initiation of alcohol and marijuana use between ages 14 and 16 among female adolescents, and blunted HPA axis responses were related to use of alcohol at age 14 and vaping of nicotine at age 16 among adolescents above the poverty line (Study 1). Similarly, blunted PNS responses, as well as profiles of coinhibition and reciprocal PNS activation, were related to use of more substances between ages 14 and 16 in this same sample (Study 2). Finally, among a community sample of late adolescents, greater substance use was related to blunted positive emotion reactivity to arguments among male and female adolescents, exaggerated anxious emotion reactivity among female adolescents, and blunted depressive emotion reactivity among male adolescents (Study 3). Overall, these results illustrate that psychophysiological responses—particularly blunted reactivity—to stress are related to greater substance use initiation and frequency during adolescence. Importantly, the magnitude of associations differed by system (i.e., HPA axis, ANS, emotion) and participant characteristics (e.g., gender, poverty status), and associations with emotion responses varied by means of assessment (i.e., acute versus daily responses), emotional valence, and period of adolescence.

Across studies, blunted psychophysiological reactivity was consistently a risk factor for substance use among certain groups of adolescents across studies. Associations between blunted reactivity and substance use were somewhat surprising, as heightened negative emotion and emotion variability are common risk factors for adolescent substance use (e.g., McKee et al.,

2020; Shadur et al., 2015; Tschann et al., 1994; Wills et al., 2006), and we also found that heightened emotion variability was consistently related to elevated substance use count and more frequent substance use in Study 3. However, the degree to which emotion reactivity to stress and emotion variability related to substance use differed in both direction and the extent to which there was moderation by gender. These results suggest that aspects of the stress response likely relate to substance use independently of other daily fluctuations in emotion. This finding aligns with previous studies that have examined how emotion responses to stress, as assessed by surveys, and physiological responses to reward relate to substance use risk (Brenner & Beauchaine, 2011; Dvorak & Simons, 2008). Both exaggerated and blunted reactivity to stress may relate to substance use because there are multiple pathways to substance use. Adolescents may use substances to cope with extreme distress such that youth with greater stress reactivity are at heightened risk, but youth may also use substances due to heightened impulsivity and motivation to enhance positive emotion and arousal. Indeed, blunted cortisol responses have been related to greater substance use during adolescence (Evans et al., 2016; Poon et al., & Chaplin, 2016). It is possible that blunted stress responses may suggest greater sensation seeking and motivation for positive emotion, as well as greater susceptibility to peer pressure and conformity for adolescents. Future research should assess adolescents' motivations for substance use to better assess mechanisms by which stress responses relate to substance use.

Still, differences emerged across stress response systems, as cortisol responses were related to substance use among youth above but not below the poverty line, whereas emotion and PNS reactivity were related to substance use more generally. Youth in poverty may have different pathways to substance use compared to youth above the poverty line, such that family and neighborhood exposures may be more related to substance use compared to stress processes

for youth below the poverty line (Biener & Siegel, 2000; Wills & Dishion, 2004). However, this explanation may not be plausible given that associations between PNS and emotion reactivity were not moderated by poverty status. Although poverty status was not related to baseline cortisol, it may have been particularly related to HPA axis reactivity because of the high levels of adversity in the sample. High levels of adversity including poverty status have been consistently related to profiles of blunted HPA axis reactivity to stress (Joos et al., 2019; Peckins et al., 2016). This blunting may have attenuated the association between HPA activity and substance use particularly among youth below the poverty line, who likely experience more adverse circumstances and daily and life stressors compared to youth above the poverty line.

Associations for emotion also differed by adolescent gender for both samples. Associations between emotion responses and substance use were predicted to be stronger for female adolescents because they tend to show greater motivation to use substances as a means of coping relative to male adolescents (Kuntsche & Müller, 2012; Kuntsche et al., 2015; Pompili & Laghi, 2019). Interestingly, blunted acute emotion responses were related to substance use initiation among female adolescents Study 1 whereas exaggerated anxious, and to a lesser degree depressive, emotion reactivity to arguments was related to more frequent substance use among female adolescents in Study 3. It is important to note that positive emotion reactivity to daily arguments among all adolescents and blunted depressive emotion reactivity among male adolescents were related to greater substance use, and youth at higher risk for substance use showed blunted reactivity across systems across all studies.

This difference in blunted versus exaggerated emotion reactivity may be due to the age of participants, as motives for coping tend to relate to frequency rather than initiation of substance use (Wagner et al., 1999), or because of the nature of the stimulus of emotion reactivity, as the

TSST is a cognitively demanding stressor that involves presenting to unfamiliar confederates whereas daily conflicts involves arguments with friends and family. Indeed, acute emotion reactivity relates to daily emotion reactivity to daily demands but not arguments in the community sample of adolescents in Study 3. This difference between unfamiliar confederates and friends and family may be important for emotion responses during adolescence, as female youth are particularly affiliative and impacted by interpersonal interactions and events with family and friends during this period (Cyranowski et al., 2000; Davies & Lindsay, 2004; Feingold, 1994; Telzer & Fuligni, 2013). Therefore, exaggerated emotion reactivity to daily arguments and attenuated emotion reactivity to the TSST may both relate to substance use.

Whereas emotion reactivity was primarily related to lifetime substance use among female but not male youth during middle adolescence in Study 1, blunted depressive emotion reactivity to daily arguments was also related to greater substance use among male adolescents in Study 3. These gender differences align with empirical research suggesting that stress and emotional distress relate to substance use among female adolescents and that female adolescents may be motivated to use substances as a means of coping whereas male adolescents may use substances to enhance their positive emotion, as well as theoretical research suggesting that exaggerated reactivity would relate to substance use in female adolescents whereas blunted reactivity would relate to substance use in male adolescents (Chaplin et al., 2018). It is possible that exaggerated emotion reactivity among female adolescents may suggest greater depressive symptoms, and blunted emotion reactivity among male adolescents may suggest under-arousal or reduced inhibition for risk-taking behaviors (Chaplin et al., 2018; Somers et al., 2018).

It is also possible that exaggerated emotion reactivity among female adolescents and blunted emotion reactivity among male adolescents may both reflect difficulties with mental

health (i.e., internalizing and externalizing problems) and emotion regulation for each gender respectively due to gender differences in emotion socialization (Fivush et al., 2000). Whereas women are encouraged to express their emotions, men are encouraged to mask them (Eisenberg et al., 1999; Fuchs & Thelen, 1988), and extreme levels of either behavior may suggest difficulties with regulating emotion expression. In support of the notion that blunted emotion reactivity may indicate difficulties with mental health, it is important to note that the models used in Study 3 enable assessment of emotion reactivity, as well as differences in emotion on days when a stressor did or did not occur. Although blunted positive emotion reactivity among male and female adolescents and blunted depressive emotion reactivity among male adolescents were related to substance use, results suggested that these youth tended to be chronically lower in positive emotion and higher in depressive emotion. That is, these youth reported poor emotional well-being, regardless of whether they experienced a stressor. Although models accounted for average levels of emotion and indicated a unique association between blunted emotion reactivity and substance use, it is possible that these youth are less emotionally reactive because they have chronically lower emotional well-being generally, in line with research that chronic negative emotion and depression are risk factors for substance use (Goodwin et al., 2004; Myers et al., 2003; Shadur & Lejuez, 2015).

It is possible that blunted positive emotional reactivity in Study 1 and Study 3 is indicative of anhedonia-related process and blunted reward reactivity, as both processes have been implicated in depression and substance use. Youth may be less responsive to stress and daily events, potentially because they are less engaged or less invested in these events, in line with anhedonia (Carroll et al., 2017). Anhedonia is a common symptom of depression which is comorbid with depression, particularly in female adolescents for whom associations were

significant in Study 1 (Latimer et al., 2002). Although blunted reward activity has been related to substance use (Brenner & Beauchaine, 2011; Koob & Kreek, 2007; Koob & Le Moal, 2008), blunted reward activity seems less plausible as a mechanism for the present findings given that associations in Study 3 were limited to reactivity to arguments, and supplemental analyses regarding reactivity to positive events (i.e., getting along with friends and family) indicated that individual differences in positive emotional reactivity were unrelated to substance use. Although youth who used more substances and used substances more frequently showed lower positive emotion on days when they did not experience an argument, it is possible that these youth experience fewer positive daily events such that they may not be less responsive to rewarding experiences.

The assessment of daily versus acute emotion reactivity likely influenced the magnitude of associations across studies. Acute responses may better relate to substance use during middle adolescence due to the academic nature of the TSST. Difficulties with school are a risk factor for substance use (Bryant & Zimmerman, 2002; Cox et al., 2007), so these responses to the TSST may index how participants respond to school assignments. Acute responses may not have related to substance use later in adolescence, when youth have more autonomy over their academic coursework (i.e., electives, major). Finally, it is possible that acute responses uniquely relate to initiation of substance use, potentially through peer processes. For instance, individuals who have difficulties with stress regulation, particularly emotion responses, may be less popular or more inclined to engage with deviant peers who expose them to substances (Lopes et al., 2005). These peer processes may be less related to substance use frequency later in adolescence, when youth develop greater independence and emotion regulatory capacity (Leung et al., 2014).

It is possible that study findings may have clinical implications for identifying youth at early risk of substance use and treating youth. It is not feasible to administer stress protocols to youth as a means of identifying at-risk, although Study 3 assessed conflicts with friends and family as a daily stressor. If indeed stress reactivity is a prospective predictor of substance use, parents may be able to observe their children's general patterns of emotion reactivity to arguments and being punished at home as a proxy measure of individual differences in emotional reactivity. For parents, observing that their female adolescents are highly emotionally reactive and or their male adolescents are clearly less reactive to stress may be reasons for concern regarding substance use risk. For adolescents who are impoverished or who experienced high levels of early life stress, blunted responses may be particularly concerning based on results from Study 1 and Study 2. Because of the difficulties with administering a stress protocol to adolescents, future studies can assess whether parents' and adolescents' reports of emotion reactivity align with estimates of emotion reactivity to acute and daily stress and are similarly related to prospective risk for substance use.

More feasibly, findings provide mechanistic information regarding the pathways that predispose adolescents for substance use and may therefore inform future treatments for adolescent substance use. Specifically, results suggest that substance use treatments for adolescents and anti-substance use programs for at-risk adolescents may be well-positioned to include a focus on appropriate responses to stress and emotion regulation. For instance, these programs can incorporate aspects of mindfulness and acceptance (Broderick, 2013). Given associations between ANS responses and substance use initiation and escalation in Study 2, treatment programs could also incorporate a focus on interoception such that youth can identify and interpret their physiological responses to stress. This treatment may be effective because

chronic underarousal has been related with greater risk-taking (Brewer-Smyth et al., 2004; Ortiz & Raine, 2004; Platje et al., 2013). Biofeedback treatments have proven efficacious in adults and should also be tested in adolescents (Eddie et al., 2014, 2015). Finally, effects were generally small in magnitude, and emotion reactivity should be considered in context with other risk factors for substance use. For instance, results from Study 3 suggested chronic low positive emotion and high depressive emotion as risk factors for more frequent substance use and emotional variability—irrespective of daily stressors—as risk factors for substance use. The results in this dissertation do not detract from the importance of these other aspects of emotionality for substance use risk, but instead highlight the potential importance of emotion reactivity as one aspect of emotion that may confer risk for substance use (Kober, 2014).

Limitations

Studies were limited by aspects of the study design and participant characteristics. Whereas a two-year gap was sufficient for examining whether stress responses related to initiation of substances because most adolescents had not used substances by age 14 during middle adolescence (i.e., Studies 1 and 2), this gap was not sufficient for reasonably testing temporal associations between stress responses and escalation of substance use during late adolescence, and the study design would have resulted in most participants having only one observation in lagged analyses. Study 1 was limited by the administration of emotion items, as opposed to full scales, and Study 3 was missing items for many scales. Furthermore, the paradigm for the TSST in Study 1 was adjusted to ensure that youth did not experience unduly high levels of distress, as described by Johnson and colleagues (2017). This adjustment in paradigm may have also contributed to the overall lack of a robust cortisol response among participants, although anticipated differences in emotion and autonomic activity were observed,

and further complicates the degree to which associations between acute reactivity to stress and substance use can be compared in Studies 1 and 2 versus Study 3. Substance use motivation was not measured across studies, which limits ability to differentiate the mechanisms by which stress responses relate to substance use.

Studies 1 and 2 included a sample of Mexican-origin adolescents with high levels of adversity. In contrast to other ethnic populations, internalizing and externalizing problems have been related to substance use initiation among Latino adolescents, potentially due to ethnic stressors (Gonzales et al., 2017). Therefore, results regarding substance use initiation may not generalize to other ethnic groups. Likewise, Study 3 only included European American and Latino youth, and results may not carryover to Black or Asian youth. Additionally, youth with high levels of adversity were tested in Studies 1 and 2 because these youth may be at higher risk for substance use. However, this sample of youth also showed very low levels of cortisol overall, in line with previous samples of youth with high levels of adversity (Joos et al., 2019; Peckins et al., 2016), which may account for the null associations between substance use and cortisol responses among youth below the poverty line. Finally, different metrics of substance use were used between the two samples. Studies 1 and 2 lacked appropriate variability in frequency outcomes due to the low age of the sample, such that we could not reasonably assess associations between frequent and stress responses in middle adolescence. However, use of substances by ages 14 and 16 have been related to greater substance use and more frequent use later in adolescence (e.g., Colell et al., 2014; DeWit et al., 2000; Duke, 2018; Grant & Dawson, 1997; Grant et al., 2006; Hingson et al., 2006; Strunin et al., 2017; Swift et al., 2008; Wagner et al., 2005). Study 3 had sufficient variation in frequency given the older age of the sample, but had a

smaller number of participants who completed the TSST, which may have contributed to the lack of associations between acute reactivity and substance use in that sample.

Conclusions

In conclusion, stress responses appear to relate to substance use, albeit in different ways across the two samples. Further research is needed to determine how stress processes relate to substance use and the temporality of associations between substance use and stress responses. Future studies can incorporate both diverse paradigms for measuring stress responses (e.g., different types of daily experiences) and diverse sample populations (e.g., ethnic and gender diversity) to further assess the generalizability of results. Also, in addition to measuring the intensity of responses, duration of responses can be measured by incorporating electronic momentary assessment. Regarding clinical implications, differences in responses to stress may provide a means of identifying youth at-risk for substance use, although acute stress responses may be difficult to feasibly measure. Parents and teachers can potentially report whether youth are showing appropriate responses to emotional responses to stress and adolescents can report their own physiological sensations (e.g., heart racing). Treatment programs for at-risk youth may be well-positioned to address emotion regulation and appropriate ways to respond to stress (e.g., accepting emotions, appropriate emotion expression, interpretation of physiological cues) to support youth in abstaining from substance use.

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Appendix

Substance use questions from the CHAMACOS study at age 14 (Studies 1 and 2). Note that other substances were assessed but were not used due to the age and low frequency of use in this sample. Questions with multiple answer options were dichotomized (never vs. used).

Q37.2 Have you ever had any alcoholic beverage to drink- more than just a few sips?

- ❍ **No**
- ❍ **Yes**

Q43.2 Have you ever smoked cigarettes?

- ❍ **Never**
- ❍ **Once or twice**
- ❍ **Occasionally but not regularly**
- ❍ **Regularly in the past**
- ❍ **Regularly now**

Q45.1 On how many occasions (if any) have you used marijuana (weed, pot) or hashish (hash, hash oil) in your lifetime?

- ❍ **0 occasions**
- ❍ **1-2**
- ❍ **3-5**
- ❍ **6-9**
- ❍ **10-19**
- ❍ **20-39**
- ❍ **40 or more**

Have you ever "vaped" using e-cigarettes, e-hookahs, vaping pens, or any other battery-powered device that simulates smoking?

- ❍ **No**
- ❍ **Yes**

Substance use questions from the Family Health Study (Study 3). Only the frequency of use of alcohol and marijuana were used due to low frequency of use of other substances. These questions are bolded and underlined. Substance use count was calculated as the number of substances which adolescents had ever used.

Substance Use

This next section is about your use of different types of substances. Remember your answers are completely confidential and we will not share your answers with anyone.

1. If you have ever smoked more than one or two puffs of a cigarette, how old were you when you smoked that much for the first time?

☐ I have never smoked more than one or two puffs of a cigarette **(SKIP TO QUESTION 2)**
☐ Less than 9 years old
☐ 9 or 10 years old
☐ 11 or 12 years old
☐ 13 or 14 years old
☐ 15 or 16 years old
☐ 17 years old or older

1a. During the past 30 days, how many days did you smoke cigarettes?

☐ 0 days
☐ 1 or 2 days
☐ 3 to 5 days
☐ 6 to 9 days
☐ 10 to 19 days
☐ 20 to 29 days
☐0 All 30 days

1b. During the past 30 days, on the days you smoked, how many cigarettes did you smoke per day?

☐ I did not smoke cigarettes during the past 30 days
☐ Less than 1 cigarette per day
☐ 1 cigarette per day
☐ 2 to 5 cigarettes per day
☐ 6 to 10 cigarettes per day
☐ 11 to 20 cigarettes per day
☐0 more than 20 cigarettes per day

These next few questions ask about drinking alcohol. This includes drinking beer, wine, wine coolers, and liquor such as tequila, rum, gin, vodka or whiskey. But this does not include drinking a few sips of wine for religious purposes.

2. If you have ever had more than a few sips of alcohol, how old were you when you first drank that much alcohol?

☐ I have never had a drink of alcohol other than a few sips **(SKIP TO QUESTION 3)**
☐ Less than 9 years old
☐ 9 or 10 years old
☐ 11 or 12 years old
☐ 13 or 14 years old
☐ 15 or 16 years old
☐ 17 years old or older

2a. During the past 30 days, how many days did you have at least one drink of alcohol?

☐ 0 days
☐ 1 or 2 days
☐ 3 to 5 days
☐ 6 to 9 days
☐ 10 to 19 days
☐0 20 to 29 days
☐ All 30 days

2b. During the past year, on how many days did you have at least one drink of alcohol?

☐ 1 or 2 days in the past year
☐ 3 to 11 days in the past year
☐ one day a month
☐ 2 to 3 days a month
☐ one day a week
☐ two days a week
☐ 3 to 4 days a week
☐ 5 to 6 days a week
☐ Every day

2c. During the past 30 days, how many days did you drink enough to feel pretty high/drunk?

☐ **0 days**
☐ **1 or 2 days**
☐ **3 to 5 days**
☐ **6 to 9 days**
☐ **10 to 19 days**
☐ **20 to 29 days**
☐ **All 30 days**

2d. During the past year, how often did you drink enough to feel pretty high/drunk?

☐ **1 or 2 days in the past year**
☐ **3 to 11 days in the past year**
☐ **one day a month**
☐ **2 to 3 days a month**
☐ **one day a week**
☐ **two days a week**
☐ **3 to 4 days a week**

☐ **5 to 6 days a week**
☐ **Every day**

3. If you have ever tried marijuana (pot, weed, grass, hash, etc.), how old were you when you tried it for the first time?

☐ I have never tried marijuana **(SKIP TO QUESTION 4)**
☐ Less than 9 years old
☐ 9 or 10 years old
☐ 11 or 12 years old
☐ 13 or 14 years old
☐ 15 or 16 years old
☐ 17 years old or older

3a. During the past 30 days, how many times did you use marijuana?

☐ **0 times**
☐ **1 or 2 times**
☐ **3 to 9 times**
☐ **10 to 19 times**
☐ **20 to 39 times**
☐ **40 to 99 times**
☐ **100 or more times**

3b. During the past year, how often did you use marijuana?

☐ **0 days in the past year**
☐ **1 or 2 days in the past year**
☐ **3 to 11 days in the past year**
☐ **1 day a month**
☐ **2 to 3 days a month**
☐ **1 day a week**
☐ **2 days a week**
☐ **3 to 4 days a week**
☐ **5 to 6 days a week**
☐ **Every day**

4. If you have ever tried any form of cocaine, including powder, crack, or freebase, how old were you when you tried it for the first time?

☐ I have never tried cocaine **(SKIP TO QUESTION 5)**
☐ Less than 9 years old
☐ 9 or 10 years old
☐ 11 or 12 years old
☐ 13 or 14 years old
☐ 15 or 16 years old
☐ 17 years old or older

4a. During the past 30 days, how many times did you use any form of cocaine, including powder, crack, or freebase?

☐ 0 times
☐ 1 or 2 times
☐ 3 to 9 times
☐ 10 to 19 times
☐ 20 to 39 times
☐ 40 or more times

4b. During the past year, how often did you use any form of cocaine, including powder, crack, or freebase?

☐ 0 days in the past year
☐ 1 or 2 days in the past year
☐ 3 to 11 days in the past year
☐ 1 day a month
☐ 2 to 3 days a month
☐ 1 day a week
☐ 2 days a week
☐ 3 to 4 days a week
☐ 5 to 6 days a week
☐ Every day

5. If you have ever used crystal meth (also called "ice" or “glass”), how old were you when you used crystal meth for the first time?

☐ I have never tried crystal meth **(SKIP TO QUESTION 6)**
☐ Less than 9 years old
☐ 9 or 10 years old
☐ 11 or 12 years old
☐ 13 or 14 years old
☐ 15 or 16 years old
☐ 17 years old or older

5a. During the past 30 days, how many times have you used crystal meth (also called "ice" or “glass ")?

☐ 0 times
☐ 1 or 2 times
☐ 3 to 9 times
☐ 10 to 19 times
☐ 20 to 39 times
☐ 40 or more times

5b. During the past year, how often have you used crystal meth (also called "ice" or “glass ")?

☐ 0 days in the past year
☐ 1 or 2 days in the past year
☐ 3 to 11 days in the past year
☐ 1 day a month
☐ 2 to 3 days a month
☐ 1 day a week

☐ 2 days a week
☐ 3 to 4 days a week
☐ 5 to 6 days a week
☐ Every day

6. If you have ever used any other type of illegal drug, such as LSD, PCP, ecstasy, mushrooms, speed, or heroin, how old were you when you used them for the first time?

☐ I have never tried any other illegal drugs **(SKIP TO QUESTION 7)**
☐ Less than 9 years old
☐ 9 or 10 years old
☐ 11 or 12 years old
☐ 13 or 14 years old
☐ 15 or 16 years old
☐ 17 years old or older

6a. During the past 30 days, how many times did you use any other type of illegal drug, such as LSD, PCP, ecstasy, mushrooms, speed, heroin, or pills without a doctor's prescription?

☐ 0 times
☐ 1 or 2 times
☐ 3 to 9 times
☐ 10 to 19 times
☐ 20 to 39 times
☐ 40 or more times

6b. During the past year, how often did you use any other type of illegal drug, such as LSD, PCP, ecstasy, mushrooms, speed, heroin, or pills without a doctor's prescription?

☐ 0 days in the past year
☐ 1 or 2 days in the past year
☐ 3 to 11 days in the past year
☐ 1 day a month
☐ 2 to 3 days a month
☐ 1 day a week
☐ 2 days a week
☐ 3 to 4 days a week
☐ 5 to 6 days a week
☐ Every day

7. If you have ever used any prescription drug such Ritalin, oxycotin, adderall, a valium, any narcotic, or any tranquilizer without a prescription, how old were you when you used a prescription drug without a prescription for the first time?

☐ I have never used prescription drugs **(SKIP TO END)**
☐ Less than 9 years old
☐ 9 or 10 years old
☐ 11 or 12 years old
☐ 13 or 14 years old
☐ 15 or 16 years old

☐ 17 years old or older

7a. During the past 30 days, how many days did you use any prescription drug without a prescription?

☐ 0 times
☐ 1 or 2 times
☐ 3 to 9 times
☐ 10 to 19 times
☐ 20 to 39 times
☐ 40 or more times

7b. Duing the past year, how many days did you use any prescription drug without a prescription?

☐ 0 days in the past year
☐ 1 or 2 days in the past year
☐ 3 to 11 days in the past year
☐ 1 day a month
☐ 2 to 3 days a month
☐ 1 day a week
☐ 2 days a week
☐ 3 to 4 days a week
☐ 5 to 6 days a week
☐ Everyday

Negative daily events from daily diaries in the Family Health Study (Study 3). Note, only emotion reactivity to daily arguments was related to adolescent substance use (items bolded).

O argued with your mother or father about something

O argued with another family member about something

O punished or disciplined by parents

O parents had an argument with each other

O had a lot of work at home

O had a lot of demands made by your family

O had an argument or were punished by an adult at school

O someone from school threatened, insulted, or made fun of you

O had a lot of work at school

O had a lot of demands made by your teachers

O had a lot of demands made by friends

O had an argument with a close friend or partner

O had a lot of demands from your supervisor at work

O something bad happened or you were treated poorly because of your race or ethnicity

Emotion rating from daily checklists in the Family Health Study (Study 3). Note: Fatigue, fear, and somatic complaints reactivity were also examined and were not related to substance use.

The following is a list of feelings or experiences. How much did you experience them today?

		Not at all	*A little*	*Moderately*	*Quite a bit*	*Extremely*
Attentive	1	2	3	4	5	
Back, joint, or muscle pain	1	2	3	4	5	
Calm	1	2	3	4	5	
Cheerful	1	2	3	4	5	
Discouraged	1	2	3	4	5	
Enthusiastic	1	2	3	4	5	
Excited	1	2	3	4	5	
Exhausted	1	2	3	4	5	
Fatigued	1	2	3	4	5	
Frightened	1	2	3	4	5	
Happy	1	2	3	4	5	
Headache	1	2	3	4	5	
Hopeless	1	2	3	4	5	
Interested	1	2	3	4	5	
Joyful	1	2	3	4	5	
Nervous	1	2	3	4	5	
On edge	1	2	3	4	5	
Sad	1	2	3	4	5	
Scared	1	2	3	4	5	
Sleepy	1	2	3	4	5	
Threatened	1	2	3	4	5	
Tired	1	2	3	4	5	
Trouble sleeping	1	2	3	4	5	
Unable to concentrate	1	2	3	4	5	
Uneasy	1	2	3	4	5	
Unsafe	1	2	3	4	5	
Worn-out	1	2	3	4	5	
Worried	1	2	3	4	5	