PATTERNS OF BINGE DRINKING, MARIJUANA USE, AND DEPRESSIVE SYMPTOMS FROM ADOLESCENCE TO YOUNG ADULTHOOD: TESTING THE SELF-MEDICATION AND STRESS MODELS

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ABSTRACT

Andra Lea Wilkinson: Patterns of Binge Drinking, Marijuana Use, and Depressive Symptoms from Adolescence to Young Adulthood: Testing the Self-Medication and Stress Models
(Under the direction of Carolyn T. Halpern)

Understanding the relationships between substance use and depression could inform prevention and treatment efforts. Previous studies provide conflicting support for both depression leading to substance use—the Self-Medication Model—and substance use leading to depression—the Stress Model. Much of this prior literature focuses only on adolescence, examines only one direction, and/or fails to examine potential mediators or whether associations vary by biological sex.

Using data from Waves I, III, and IV of the National Longitudinal Study of Adolescent to Adult Health, mixed effects models were used to test the relationships between depressive symptoms and frequency of alcohol use and marijuana use across development, and whether these associations were moderated by sex. Regression models were used to examine potential mediators and one moderator for both the Self-Medication and Stress Models.

Adolescent depressive symptoms were significantly associated with a steeper predicted increase in marijuana use frequency across development. Further, persistent binge drinking or marijuana use across development were concurrently positively associated with the depressive symptom growth curve, and associations were stronger for females. Results also indicate the association between depressive symptoms and later binge drinking frequency may be mediated by sensation seeking and adherence to gender norms for males and females; adherence to gender

norms also moderated this association for males. For females, the association between depressive symptoms and later marijuana use frequency may also be mediated by sensation seeking.

These results inform how to target and integrate screenings for adolescent substance use and depressive symptoms, both newly covered under the Affordable Care Act. For example, if adolescents screen positive for high or increasing depressive symptoms, it seems they should also be screened for marijuana use. Binge drinking screening could be targeted towards adolescents with higher sensation seeking and depressive symptoms. The findings also indicate substance use and depression prevention and treatment programs should be integrated—as comorbidity is common—and tailored by sex—as the links between substance use and depression seem to differ by sex. Better yet, substance use and mental health programs for youth could challenge the gender norms that promote substance use and self-medication to begin with.

To Darren Lee Legge,
"…That two solitudes shall protect, border, and salute each other." –Rainer Maria Rilke

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LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
ACA	Affordable Care Act
Add Health	National Longitudinal Study of Adolescent to Adult Health
AGB	Adherence to Gender-typical Behavior
BIC	Bayesian Information Criterion
CMS	Centers for Medicare and Medicaid Services
CES-D	Center for Epidemiologic Studies Depression Scale
CRP	High sensitivity C-reactive protein
EBV	Epstein-Barr virus
ICC	Intraclass Correlation Coefficient
SBIRT	Screening, brief interventions, and referral to treatment
SD	Standard deviation
USPSTF	United States Preventive Services Task Force

CHAPTER 1 - INTRODUCTION

Specific Aims

Adolescence is characterized by increasing substance use and depressive symptoms, both of which can have short- and long-term implications.[1–4] Many studies have found strong correlations between substance use and depression, though it is not clear if the association is causal, and if it is, in which direction(s) the process operates. Some studies find that depression leads to substance use, possibly by lowering the accuracy of risk perceptions and decreasing impulse control; we label this pathway the Self-Medication Model.[4–6] Other studies suggest substance use leads to depression.[5,7,8] We label this pathway the Stress Model, as a hypothesized mechanism underlying it involves the stress response, the body's endocrine reaction to novelty exposure, which can be stimulated by risk taking and, when chronic, can lead to depression.[9–13] Complicating potential causal pathways, there are biological sex (sex) differences in the prevalence of substance use and depression, as well as differences in responsiveness to stress.[4,14–16] Findings to date suggest the Self-Medication Model may be more relevant for males, whereas females might be better represented by the Stress Model.[10,11,16–18]

Although there is a vast literature on adolescent substance use, much of the research examining associations between adolescent substance use and depression is cross-sectional, or if longitudinal, is based on non-representative samples, is vulnerable to endogeneity, tests only one direction of association, does not test moderation by sex, does not test mediation, and/or captures time periods limited to adolescence.[6–8,18–23] This project addresses these important limitations by using survey and biomarker data from the National Longitudinal Study of Adolescent to Adult

Health (Add Health), which includes a representative sample of more than 20,000 adolescents in grades 7-12 in the 1994-95 school year who have been followed prospectively for 15 years as they transitioned to young adulthood. Present analyses addressed the following two study aims:

Aim 1. Evaluate empirical support for the Self-Medication and Stress Models by estimating growth curves of alcohol use, marijuana use, and depressive symptoms and testing whether these trajectories are conditioned by biological sex and/or are related to each other.

Aim 2. Using regression models, examine potential mediators (sensation seeking, stress biomarkers, and gender norm adherence) and a moderator (gender norm adherence) of the relationships between substance use and depressive symptoms and whether the relationships differ by biological sex.

Background & Significance

During adolescence, sensation seeking increases while impulse control is still developing; this creates a developmental window where adolescents often experiment with facets of adult behavior, like substance use.[4,24] Risk taking can also facilitate peer group bonding, which is a critical aspect of development as adolescents distance themselves from parents and family.[3] However, too much risk taking, and certain types of risk taking, can be harmful. Most substance use is initiated in adolescence, a developmental period often recognized as lasting from age 12 to 19.[4,15] The trajectory typically begins with alcohol and tobacco use before or early in high school, then may escalate to use of illicit drugs (e.g., heroin) during high school.[4] According to the 2013 Youth Risk Behavior Survey, more than one-third of high school students report current alcohol use, and smoking marijuana (23.4%) is now more common than smoking cigarettes (15.7%) among adolescents.[25] Alcohol and marijuana are the two most commonly used substances among U.S. adolescents, they are both illegal for adolescents, and both can lead to

significant psychological changes.[4,25] Therefore alcohol and marijuana use are the focus of this research project.

The quantity and frequency of alcohol and drug use typically peak between 18-25 years of age in the United States.[4] On average, adolescent males use more substances and use them more frequently than females, though this can vary by age, with females engaging in more substance use than males in early adolescence.[4,25,26] By middle to late adolescence, males are more likely to engage in regular substance use. By comparison, females may accelerate faster than males from initiating use to experiencing problems from use.[4,27] Substance use in adolescence can have significant health effects (e.g., substance dependency or abuse, adverse effects on brain development) as well as deleterious effects on a wide range of developmental outcomes (e.g., educational attainment).[4]

Depression is also prevalent in adolescence. The International Classification of Diseases characterizes depression as including some or all of the following symptoms: a depressed mood, loss of interest and enjoyment, reduced activity, disturbed sleep and appetite, decreased self-esteem, and/or guilt. Diagnoses of mild, moderate, or severe depression depend on the number of symptoms a person experiences and the degree to which a person can continue with their daily activities.[28] A systematic review conducted for the United States Preventive Services Task Force (USPSTF) estimates that the prevalence of current or recent depression in adolescence is 6% and the lifetime prevalence of major depressive disorders among adolescents is as high as 20%.[2] In adolescence and beyond, females are more likely to experience depression than males.[14] Early onset depression (before age 21) is associated with an increased risk of suicide attempts, death by suicide, longer episodes of depression and higher rates of recurrence.[2,29] Adolescent depression can have negative effects in the short-term (e.g., decreased school performance, strained family

relationships) and the long-term (e.g., decreased educational attainment).[1,2,29] At a population level, depression is one of the most burdensome diseases globally because of its early age of onset, tendency to be chronic, impairment of normal activities, and high lifetime prevalence.[22]

Depression and substance use are often comorbid.[23,30] For example, results from the 2013 National Survey on Drug Use and Health revealed 11.8% of 12-17 year-olds without a major depressive episode in the past year reported marijuana use in the past year compared to 25.7% of adolescents who did have a major depressive episode in the past year.[31] Comorbidity of substance use and depression in adolescence is associated with multiple negative outcomes including more severe mental health issues, increases in substance use, delays in substance abuse recovery, longer depressive episodes, and elevated suicide risk.[21] The comorbidity between substance use and depression could indicate several possible relationships between the two. Fleming et al. outlined four possible forms of relationships underlying the comorbidity.[32] First, it is possible the levels of depression and substance use are concurrently associated across time. Second, change in one may be associated with change in the other across development. Third, it is possible the two conditions are only related at specific time points during development. Finally, the relationship may be predictive, meaning one generally precedes and predicts the other; both the Self-Medication and Stress Models are examples of predictive relationships.[32]

Understanding the relationship between substance use and depressive symptoms during development is important because it could inform screening, prevention, and treatment practices. Surveys of physicians indicate approximately less than half screen their patients for substance use or depression, and it is likely even rarer for adolescent patients.[33,34] As a consequence, most cases of substance use problems and depression in adolescence go untreated.[2,33,35] This is a significant missed opportunity to prevent or start treating conditions early, especially as an

estimated 50% of mental health and substance use conditions begin by age 14.[2,35–37] Though the Affordable Care Act (ACA) now ensures insurance companies will cover screening, it does not mandate that physicians provide the screening.[38] Surveys of physicians indicate they feel time constrained and uncomfortable treating or providing referrals for substance use or depression issues.[2,39] Therefore, understanding, for example, that depression generally precedes substance use issues, especially in males, helps physicians target screening and integrate treatment and referral steps accordingly.

Self-Medication Model

The Self-Medication Model, first articulated in the 1990s by Harvard Psychiatrist Dr. Edward Khantzian, holds that people struggling with depression may engage in substance use in an attempt to ameliorate their symptoms.[40–42] This pathway is facilitated by the process of depression impairing cognitive function and memory, decreasing impulse control, and impairing psychosocial functioning, (e.g., motivation), all of which can impair accurate risk perceptions.[4,42] Adolescents may be especially vulnerable to these processes because of existing imbalances between impulsivity and reasoned decisions, and their lesser experience with self-regulation.[24] Evidence for this model includes the finding that adolescents taking antidepressants experience consequent declines in substance use.[43] Expanding beyond depression to internalizing symptoms in general (e.g., anxiety), many studies have connected internalizing symptoms/problems in childhood to substance use in adolescence and young adulthood.[44] Further, studies have found reports of self-medication as a primary reason for addiction among certain populations.[42,44]

Stress Model

Risk taking increases throughout adolescence and can induce stress, which has both short- and long-term health implications.[4] The Stress Model asserts substance use can induce

stress and chronic stress can harm the body; one possible harm is increased depressive symptoms.[45] If the brain perceives risk taking such as substance use as a threat, it stimulates both the sympathetic-adrenal-medullary axis and the hypothalamic-pituitary axis, leading to, among other things, cortisol release.[9,45] Chronically elevated cortisol levels can lead to dysregulated affect, possibly by changing the functional connectivity of the amygdala-ventromedial prefrontal cortex, which is positively associated with depression.[12,13] The stress response also increases inflammation.[46,47] Inflammation can contribute to depression through effects on neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and information processing.[48,49] Past studies have tested whether substance use is associated with later increases in depressive symptoms, but few have articulated conceptual grounding for it.[5–8]

Past Literature

Many prior studies have attempted to tease apart the comorbidity between depression or depressive symptoms and substance use. The bulk of this research has been motivated by the Self-Medication Model, and several longitudinal studies have found support for this model.[6,21,22,42] For example, Burns et al. followed a sample of 64 rural adolescents from ages 12 to 18 and found baseline depression was significantly associated with substance abuse at follow-up, controlling for sex.[50] Henry et al. analyzed a birth cohort of over 700 males and females in New Zealand at ages 11 and 15 and, after stratifying by sex, found baseline depression was associated with later substance use, but only for males.[40] However, using Waves I and II of Add Health, Hallfors et al. found depression did not increase the odds of either experimental or high risk substance use in males, but it did increase the odds of high risk substance use among females already experimenting with substances at Wave I. Contrary to the Self-Medication Model, they

found depression actually decreased the odds of substance use among females abstaining from substances at Wave I.[5]

More recent studies have used methods that allow analysis of individual trajectories (e.g., growth curve and latent growth curve analysis, hierarchical linear modeling, growth mixture modeling). Repetto, Zimmerman, and Caldwell used hierarchical linear models with data from over 600 African American youth surveyed annually for six years to estimate the growth curves of marijuana use and depression and test their inter-relationships as well as potential moderators. One finding, among others, was that higher depressive symptoms predicted increases in later marijuana use, but only for males. For females, those with lower depressive symptoms used more marijuana than those with higher depressive symptoms, somewhat matching the results from Hallfors et al.[5,21] Hooshmand, Willoughby, and Good used latent growth curve models to analyze data from over 4,000 Canadian high school students and found that adolescents with higher depressive symptoms in grade 9 had faster increases in marijuana use frequency during high school, but not the other way around and not for alcohol use.[6]

Studies have also found support for the Stress Model (i.e., substance use associated with later depression). Hallfors et al. tested the Stress Model using Waves I and II Add Health data. They found that high levels of risk taking (i.e., high frequency substance use and sexual risk behavior) increased odds of later depression for males, and both high and experimental risk taking increased odds of later depression for females.[5] Pahl, Brook, and Koppel used growth mixture modeling and found similar results with a sample of over 400 African American and Puerto Rican women who were interviewed five times between the ages of 14 and 32. They found three marijuana use trajectories: "increasers," "quitters," and "nonusers." "Increasers" had higher levels of later depressive symptoms than quitters, supporting a potential causal argument

for the Stress Model.[7] Fergusson et al., with a sample of over 1,000 late adolescents followed into emerging adulthood, tested both potential directions of the association between alcohol abuse or dependence and depression, and found the best fitting model supported a pathway leading from alcohol problems to depression.[51] Three recent reviews found evidence of alcohol or marijuana use being associated with later depression.[52–54]

At least two studies have had more nuanced results. First, Needham used data from Add Health Waves I, II, and III to test sex-stratified latent growth curve models of both directions of the association.[22] Adolescent males and females with higher depressive symptoms at Wave I had higher levels of binge drinking at Wave I but the smallest odds of further increases in binge drinking compared to those with lower depressive symptoms at Wave I. Similarly, adolescent females with higher depressive symptoms at Wave I had higher levels of illicit substance use at Waves I, II, and III though smaller odds of further increases in illicit substance use compared to females with lower depressive symptoms at Wave I. The author interpreted these results as support for the Self-Medication Model, even though she did not find support for an expected accumulation in disadvantage (i.e., increases in substance use over time). Findings for the Stress model followed a similar pattern; adolescents with higher binge drinking or substance use at Wave I had consistently higher depressive symptoms, though they declined at a faster rate, than their peers who were not using any substances at Wave I. The author interpreted the results overall as support for a bi-directional relationship between substance use and depression, though the results could also be interpreted as a concurrent relationship in adolescence that faded with development.[22] Similarly, Costello et al. used latent trajectory analysis to model trajectories of depressive symptoms using Waves I, II, and III of Add Health.[8] They found adolescents who were using alcohol, tobacco, or other drugs on a weekly basis at Wave I were more likely to

show a depressive symptom trajectory characterized by high levels at Wave I that declined over time.[8,22] However, despite the decline, substance using adolescents had consistently higher levels of depressive symptoms compared to adolescents who did not use substances.

Interestingly, another study used longitudinal mixed effects models with Add Health data and found support for a bidirectional relationship.[55] In support of the Self-Medication Model, a five-point increase in depressive symptoms at an earlier wave was significantly associated with approximately a half-day increase in cigarette smoking frequency at a later wave, but only for females. In support of the Stress Model, a 5-day increase in cigarette smoking frequency in the past month at an earlier wave was associated with a 0.02-point increase for males and a 0.05-point increase for females in depressive symptoms at a later wave. Marijuana use and binge drinking were also tested but no significant associations were found.

Finally, at least one analysis has had null findings. Fleming et al. used multivariate latent trajectory modeling with data from over 1,000 males and females surveyed annually from 8th to 11th grade in the Pacific Northwest of the United States to test cross-sectional, concurrent over time (longitudinal), and predictive (e.g., earlier measure predicting a later change) relationships between depressive symptoms and substance use. While they found significant concurrent relationships, perplexingly, they found no significant predictive relationships that supported either Model. However, they did find that higher levels of depressive symptoms predicted a slower increase in alcohol use compared to lower levels of depressive symptoms, which is a challenge to the Self-Medication Model.[32]

Limitations of Past Literature

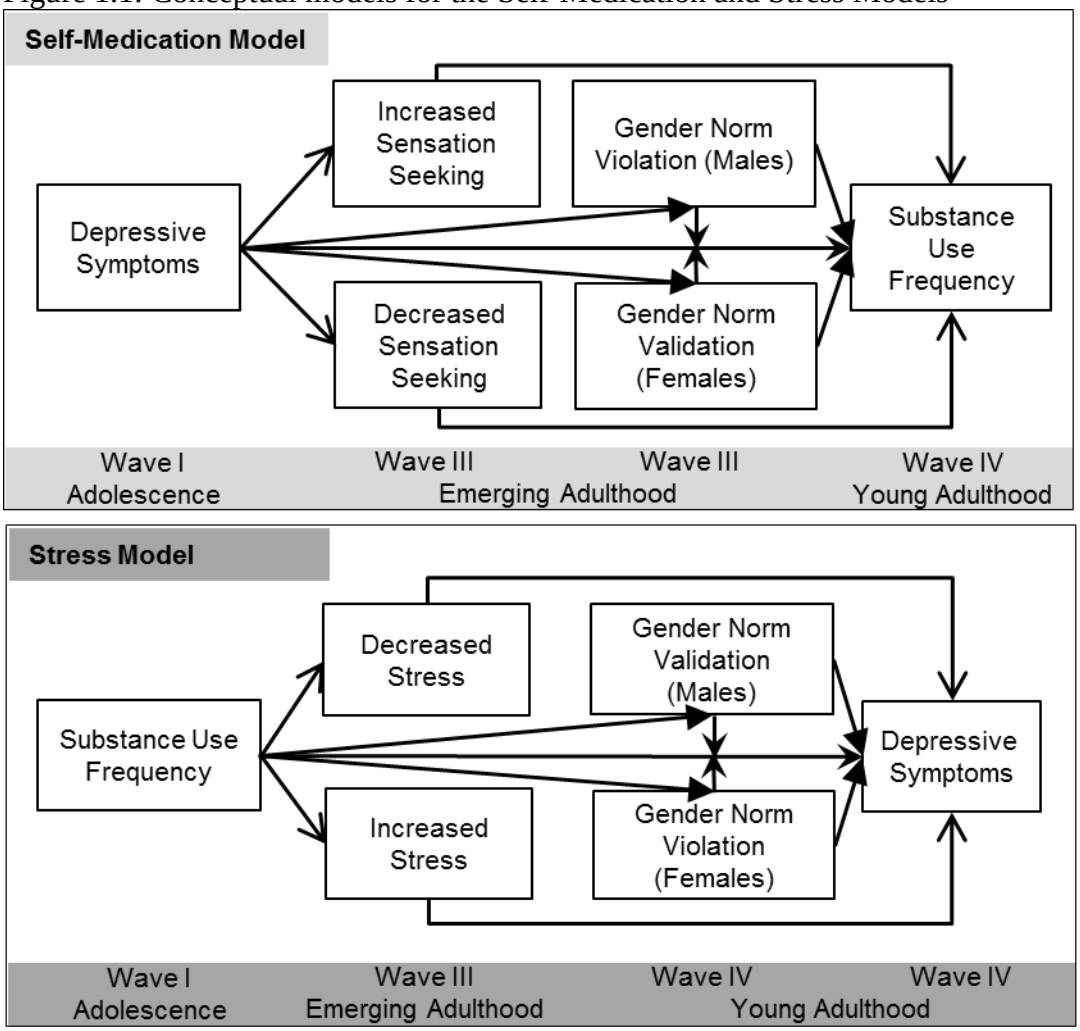
In summary, findings are inconsistent, with mixed support for the Self-Medication and Stress Models. Though studies with strong designs have been done to analyze the directionality

of the relationship between adolescent substance use and depression, they still share many limitations. Prior trajectory analyses in this topic area have disproportionately examined the Self-Medication Model, failing to test the Stress Model. Further, many studies seem restricted to small, non-representative samples (e.g., school- or clinic-based samples) that are followed only during adolescence (e.g., 9th through 12th grade). Also, the studies have been focused on the temporal relationship between substance use and depressive symptoms and therefore have left other relevant research questions like moderation by sex and potential mediators largely untested. In fact, two reviews of this literature have called for more studies examining differences by biological sex.[53,54] The aims of this study address each of these limitations.

Conceptual basis

The current study tested the Self-Medication and Stress Models. These models, and the hypothesized mediating and moderating pathways, are shown in Figure 1.1 below. The models are broadly framed by the Life Course Model. The Life Course Model asserts that human development can be characterized as patterns of transitions or trajectories over time that occur within a social context. Social interactions of individuals within their contexts contribute to cumulative trends over time.[56] The Life Course Model provides a framework for our analysis of adolescent developmental trajectories into adulthood.

Figure 1.1: Conceptual models for the Self-Medication and Stress Models



Self-Medication Model

The top of the figure illustrates the Self-Medication Model. As previously described, the Self-Medication Model holds that adolescents struggling with depression may engage in substance use in an attempt to ameliorate their symptoms.[5,40,41] There is evidence to support people self-medicating with both marijuana and alcohol. Marijuana is generally believed to act as a euphoriant that produces temporary improvements in mood.[57] As such, some researchers interpret the initiation of marijuana use in adolescence as a way to cope with the potential stress of changing roles and increased responsibilities.[21] By comparison, alcohol can provide the

illusion of relieving depressive symptoms such as isolation and emptiness.[42] As such, alcohol use for adolescents could be used to feel relief from social isolation amid new peer groups, for example, and gain a sense of belonging from engaging in a normative activity.[6]

An important potential mediator for the Self-Medication Model is sensation seeking. Sensation seeking has been found to predict alcohol and substance use in adolescents.[58] Sensation seeking has also been implicated in the relationship between depressive symptoms and substance use. Researchers with data from over 4,000 Canadian adolescents who were surveyed each year of high school used latent class growth analysis to determine that adolescents who scored high in sensation seeking were at a higher risk of being in the trajectory of co-occurring depressive symptoms and alcohol use compared to singular trajectories of either one. Further, adolescents who scored low in novelty seeking were much less likely to be in the alcohol use trajectory.[59] Pahl, Brook, and Koppel controlled for sensation seeking when assessing the relationship between marijuana use and depressive symptoms and the relationship persisted, indicating sensation seeking was not confounding the association as a shared predictor.[7] Given this, it seems reasonable to test whether it is a mediator. Adherence to gender norms will be discussed as a potential mediator and/or moderator in a later section.

Stress Model

The Stress Model is illustrated at the bottom of Figure 1.1. According to the Stress Model, risk taking can increase stress, which then has implications for depressive symptoms. As adolescents are negotiating their desire for new experiences along with peer expectations and parental monitoring, even normative experimentation could result in strong stress responses.[5,10] Stress can increase inflammation, which is then associated with depressive symptoms. The physiological mechanism for these associations starts with stress stimulating the sympathetic-

adrenal-medullary axis and the hypothalamic-pituitary axis, which then activates the release of catecholamines and glucocorticoids to ready the body for fight or flight.[45] These responses are acutely adaptive but when repeatedly stimulated can cause the downstream systems to first overcompensate and then dysregulate.[45] In the brain, this can result in remodeling of dendrites and synapses, suppression of new cell growth, and changes in neurotransmitter metabolism and overall neuroendocrine functioning; all of which are implicated in depression.[45,48,49] For example, changes in the metabolisms of serotonin, dopamine, or norepinephrine—the neurotransmitters targeted by depression medications—would likely induce depression.[48] Further, hypersecretion of corticotrophin-releasing hormone—a key regulator of hormonal responses to stress—is often found in patients with depression.[48]

Biological Sex and Gender Differences in Self-Medication and Stress Models

Adolescent females have higher rates of depression and lower rates of risk taking than males, suggesting the possibility that the relationship between substance use and depressive symptoms will differ for males and females. Starting with the Self-Medication Model, we have reason to expect females will be less likely to self-medicate and males will be more likely to. First, using data from over 400 adolescents followed for 16 years as part of the Oregon Adolescent Depression Project, Essau et al. determined females had a higher incidence of depression, a higher chance of recurrence, and, in response to early onset depression, had more subsequent depressive episodes than males.[60] If females experience more severe or chronic depression, they may lack the motivation for sensation seeking and self-medication.[5,21] Second, internalizing emotions like depressive symptoms are considered more compliant with gender norms for females (i.e., in comparison to externalizing behaviors like delinquency), as are most

emotional coping mechanisms and so females, even if they experience depression in similar ways to males, may still have less incentive to use substances in an attempt to self-medicate.[17]

By comparison, we have reason to expect depressive symptoms to have a stronger relationship with sensation seeking and substance use for males. First, compared to females, males are less likely to emotionally regulate and more likely to practice impulsive or reward-seeking behavior, especially drinking alcohol.[17,61,62] Males experiencing depressive symptoms may have or perceive they have no means of regulating or coping with their emotions beyond sensation seeking. In fact, among a sample of social drinkers, males were more likely than females to report drinking in order to regulate negative affect.[63] Second, where depressive symptoms are considered socially acceptable for females, for males they can be perceived as a violation of masculine gender norms like invulnerability.[64] A male experiencing depressive symptoms may feel he is weak or vulnerable due to a perceived lack of emotion regulation tools and/or the perceived violation of masculine norms. From this place of vulnerability, substance use may be an easily accessible means of engaging in risk taking, a key way to demonstrate adherence to masculine gender norms for young men.[22,65]

For the Stress Model, evidence suggests females may be more likely to experience stress and subsequent depression from substance use. Female gender norms can emphasize risk aversion and, to the degree these norms are enforced, this can in turn influence how much stress females may experience from substance use.[18] For example, parental regulation is usually stronger or lasts longer for female children, and so they may come to perceive more negative consequences from risk taking that defies gender norms, and thus may have a stronger stress response to substance use.[10,66] Additionally, females are thought to have both greater sensitivity and stronger negative reactivity to interpersonal stress.[10,11] Therefore, even if both males and

females experienced interpersonal stressors from substance use (e.g., parental or peer disapproval), females may be more likely to perceive the stress and react negatively to it. If substance use increases interpersonal stress with peers, parents, and/or teachers, this process might account for females' greater vulnerability to depressive symptoms.[3,18,67] Finally, females may be more vulnerable to inflammation, strengthening the relationship between stress and depressive symptoms for them compared to males. During adolescence, females develop higher, on average, baseline levels of inflammation compared to males. A cross-sectional analysis of age cohorts spanning from childhood to young adulthood using the National Health and Nutrition Examination Survey found that between ages 16 and 19 a gap emerges in inflammation levels between males and females, with the latter being significantly higher. It is important to note this gap emerges at an unusual time point as it does not coincide with the onset of puberty and thus may be due to behavioral or social, rather than biological, differences in males and females.[68] Therefore, even if risk taking elicits a similar stress response in males and females, with higher baseline inflammation levels, females could still be more vulnerable to a depressive response.[47,68]

In contrast, for males, there are both social and biological reasons to expect less support for the Stress Model. In general, risk taking is much more common among adolescent males compared to adolescent females. For example, young men are less likely to wear bike helmets, more likely to drive recklessly, have more sexual partners on average, and are less likely to seek health care compared to young women.[64,65] This sex disparity in risk taking behavior could be due to the fact that men, on average, perceive less risk than women do when confronted with the same situation.[69] Alternatively, risk taking is a key way for young men to demonstrate adherence to masculine norms (e.g., dominance, denial of vulnerability, emotion and physical control).[65,70] Indeed, several studies have connected measures of men's masculine traits to their

levels of substance use.[71–74] In addition to this social explanation for adolescent males' apparent affinity for risk taking, there is a potential biological explanation. Cortisol, the main hormone of the stress response, is inhibited by testosterone, which is at higher levels in males than females. In fact, one study of 150 young adult males found their cortisol responsiveness to stress varied and those with weaker responses were more likely to engage in high-risk sexual behaviors.[3] Given the prevalence of risk taking behaviors, including substance use, among males and the potential social explanations, it seems reasonable to expect a null or even negative relationship between substance use, stress, and subsequent depressive symptoms for males.[6,42,57,62] Overall, biological sex and/or gender differences could influence the direct associations between depressive symptoms and substance use as well as potential mediation paths in both the Self-Medication and Stress Models.

Aim 1 Methods

Aim 1. Evaluate empirical support for the Self-Medication and Stress Models by estimating growth curves of alcohol use, marijuana use, and depressive symptoms and testing whether these trajectories are conditioned by biological sex and/or are related to each other.

Study Sample

Add Health has to date collected one in-school and four in-home interviews with a nationally representative sample of U.S. adolescents who were in grades 7-12 in the 1994-95 school year. This study used data from Add Health Waves I, III, and IV. The Wave I in-home interview occurred in 1995 when the 20,745 respondents were mostly between ages 12-19. Though twenty years have passed since the Add Health respondents were adolescents, the prevalence of depression and substance use (with the exception of cigarette smoking) have changed little during this time, meaning the adolescent data retain relevance.[31,75] The Wave II

interview data are excluded from these analyses because it was just one year later and by design did not include the Wave I seniors. Wave III interviews (n=15,197) were completed in 2001-02, when respondents were ages 18-26. Response rates exceeded 75% at all waves. Wave IV interviews occurred in 2008-09 when respondents were ages 24-32. An 80% re-interview rate was achieved for Wave IV, yielding information for 15,701 original Add Health respondents.

Aim 1 Measures

Depressive Symptoms: Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D), first created in 1977 it remains a common scale for depression epidemiology.[76] The items in the scale are designed to capture the frequency of types of depression symptoms (e.g., symptoms related to sadness, appetite, being tired, etc.) outlined in the American Psychiatric Association Diagnostic and Statistical Manual, though it is not a diagnostic tool.[76] Nine items from the CES-D were included in the Wave I, III, and IV surveys. Summed scores range from 0-27; higher scores indicate more and/or more frequent symptoms. The CES-D captures depressive symptoms within the past week (e.g., felt sad, tired all the time) (Table 1.1), though 12-month re-test reliability ranges from 0.4-0.7.[76] Adjusting the CES-D scores for participants using antidepressants was not possible, as measures of antidepressant use were only collected at Wave IV, and thus similar adjustments could not be made at all waves of data used in the analysis.

Table 1.1: Depressive symptom items for the CES-D (Waves I, III, and IV)

Item Wording	Item Response
How often was the following true during the past week?	
You felt sad	0: Never or rarely
You felt you were just as good as other people	1: Sometimes
You felt that people disliked you	2: A lot of the time
You felt depressed	3: Most/all of the time
You felt you were too tired to do things	6: Refused
You enjoyed life	8: Don't know

You were bothered by things that usually don't bother you	
You had trouble keeping your mind on what you were doing	
You felt that you could not shake off the blues, even with help from your family and your friends	

Table 1.2 below shows the reliability estimates for the CES-D in this sample, or their coherence in measuring the same thing. The Cronbach's alpha value estimates the proportion of each item's variation that is shared with variation in the latent construct of depressive symptoms.

Table 1.2: Cronbach's alpha for the CES-D for males and females (Waves I, III, and IV)

Wave I CES-D	0.79
Wave III CES-D	0.80
Wave IV CES-D	0.81

Substance Use: For substance use, we focused on the two most commonly used substances (alcohol and marijuana), both of which have in-depth measurement at each wave (Tables 1.3 and 1.4).[25] For marijuana use, at Waves I and III, respondents were asked how many times they used in the past thirty days (e.g., 0 to >900). At Wave IV, the question changed to measure on how many days respondents used marijuana in the past thirty using a 0 to 6 ordinal scale for none to nearly every day. To make the measures of marijuana use frequency comparable at each wave, we derived the number of days of use in a given time period from the times of use reported in Waves I and III (Table 1.5). This derived measure assumes that someone reporting four times of use in the past month at Wave I used about once per week rather than four times in one day, but for this research we care more about the frequency of use and less about the distribution of use.

For alcohol use, as it is a much more commonly reported behavior among adolescents than marijuana, we used a measure of binge drinking frequency to try to capture more proportional levels of risk taking between marijuana and alcohol use.[25] Binge drinking frequency

was assessed for the past year using the same ordinal variable of 0 for none to 6 for nearly every day. At Waves I and III, binge drinking was defined as drinking five or more drinks in a row, but at Wave IV the measure was specified as four or more drinks for women and five or more drinks for men to match the definition of binge drinking from the Centers for Disease Control and Prevention.[77,78] Originally, the measures for both binge drinking and marijuana use were derived as the midpoint from the range of number of days of use, but these measures had too much weight in the tail, so we moved to a rank category measure for marijuana use and kept the ordinal measure for binge drinking frequency. The Bayesian Information Criterion (BIC) model fit index was used to compare the models using the midpoint frequency and rank category measures and they were very similar.

Table 1.3: Binge drinking items (Waves I, III and IV)

Wave I	Wave III	Wave IV
In the past twelve months, on how days did you drink five or more drinks in a row?	In the past twelve months, on how days did you drink five or more drinks in a row?	During the past 12 months, on how many days did you drink [5 or more (males)/4 or more (females)] drinks in a row?
1: Every day/almost	0: None	0: None
2: 3-5 days/week	1: 1-2 days/year	1: 1-2 days/year
3: 1-2 days/week	2: 1 day/month or less	2: 1 day/month or less
4: 2-3 days/month	3: 2-3 days/month	3: 2-3 days/month
5: 1 day/month or less	4: 1-2 days/week	4: 1-2 days/week
6: 1-2 days/year	5: 3-5 days/week	5: 3-5 days/week
7: Never	6: Every day/almost	6: Every day/almost
96: Refused	96: Refused	96: Refused
97: Legitimate skip	97: Legitimate skip	97: Legitimate skip
98: Don't know	98: Don't know	98: Don't know
	99: Not applicable	

Table 1.4: Marijuana use items (Waves I, III, and IV)

Wave I	Wave III	Wave IV
During the past 30 days, how many times have you used marijuana?	During the past 30 days, how many times have you used marijuana?	During the past 30 days, on how many days did you use marijuana?
0: Minimum value	0: Minimum value	0: None
900: Maximum value	999: Maximum value	1: 1 day
996: Refused	9996: Refused	2: 2-3 days
997: Legitimate skip	9997: Legitimate skip	3: 1 day/week
998: Don't know	9998: Don't know	4: 2 days/week
999: Not applicable	9999: Not applicable	5: 3-5 days/week
		6: Every day/almost
		96: Refused
		97: Legitimate skip
		98: Don't know

Table 1.5: Measure transformations for marijuana use

Original Measure (# times/past 30)	Derived Measure (# days/past month)
0	0
1	1: 1 day/month
2,3	2: 2-3 days/month
4,5	3: 1 day/week
6-10	4: 2 days/week
11-25	5: 3-5 days/week
26-900	6: Every day/almost

Confounders:

- Respondent self-identified race/ethnicity from Wave I (Hispanic and non-Hispanic White, Black, Asian, Native American, and Other).
- Parental educational attainment from Wave I (less than high school, high school graduate, some college, or college graduate or higher) as a proxy for socioeconomic status. Though parental education may change at later waves, we are interested in the respondent's

approximate socioeconomic status during adolescence, when they are most likely to still be residing in the parental home.

- Childhood maltreatment, a categorical variable that captures frequency (never; once; twice; three times; four or more times) of experiencing emotional, physical, or sexual abuse before age 18 or physical or supervisory neglect before Wave III by a parent or an adult caregiver. This variable captures frequency of maltreatment rather than type because recent evidence suggests the chronicity of maltreatment is a better indicator of potentially negative consequences than the type.[79] Childhood maltreatment is important to control for as there is evidence it can be a shared risk factor for both substance use and depression in adulthood.[80]
- Levels of the dependent variable before Wave I were included as binary variables; these were constructed from retrospective Wave I measures and included a depression diagnosis, drinking a full alcoholic beverage, and using marijuana.

Aim 1 Analyses

Growth curve modeling enabled us to test both directions of the association over the developmental trajectory and also reduced potential endogeneity by helping to control for time-invariant unobserved individual characteristics.[81] Mixed effects modeling was used to model growth curves of binge drinking frequency, marijuana use frequency, and depressive symptoms from adolescence (Wave I) to emerging adulthood (Wave III) to young adulthood (Wave IV). First, unconditional growth curve models with random intercepts by respondent ID were estimated with just the dependent variable, age, and a measure of age squared. From this first model the intraclass correlation coefficient (ICC) was calculated (formula below) to determine the percentage of variance in the outcome that was due to variance between individuals. We looked for the ICC to be greater than zero, indicating there is individual heterogeneity in the

growth curves over time. The survey weights needed to analyze Add Health data rendered it infeasible to formally test if the ICC was significantly different from zero.[82] Fortunately, it was unlikely for the ICC to be near zero in these models. However, even if the ICC was essentially zero, it would still have provided valuable information because it would demonstrate that the developmental trend, including high-risk periods, are similar across respondents and that respondents' prior values are not predictive of their future values. We calculated the ICC again in the final growth curve model in order to compare the two and see how much variance between individuals had been explained by our predictor variables.

$$Variance\ (Y_{it}) = \tau_{00} + \sigma^2$$
$$ICC = \frac{\tau_{00}}{\tau_{00} + \sigma^2}$$
$$\tau_{00} = Variance\ between\ respondents$$
$$\sigma^2 = Variance\ within\ respondents$$

Second, measures of all of the confounders were added to the model. Third, two models were estimated that allowed the hypothesized coefficients for either age or age squared to randomly vary; at this point we determined whether the growth curve for the variable of interest was best approximated by a linear or quadratic form, judging by the significance of the effect estimate. Typical fit indices (e.g., BIC) are likely invalid due to the sampling weights and so were used with caution, where necessary, for simple comparisons. The fourth set of models tested how the growth curves were moderated by sex by interacting the age and age squared coefficients with sex. If the interaction terms were significant—indicating the slopes of the growth curves for males and females were significantly different from each other—then we did post hoc probing of the moderation. To start, we graphed the growth curves for depressive symptoms, for example, for males and females, with all other covariates at their referent values. Then, we tested the simple slopes to confirm both lines from the model parameters were

significantly different from zero. To reduce possible collinearity with the intercept in the model and to improve interpretability of the moderation results, mean centering variables is encouraged but was not used here. The substance use frequency measures were not centered as the mean value is likely no or little use, and the zero values in these measures are conceptually meaningful. Further, the age variable does not need to be centered because the intercept was interpreted as the average value of the dependent variable at the earliest age. The results from these first four sets of models helped us assess the shapes of the growth curves for binge drinking frequency, marijuana use frequency, and depressive symptoms and whether they were moderated by sex.

The next set of models tested how levels and trends in the key variables of interest are related to the growth curves and whether these relationships are moderated by sex. Keeping with the depressive symptoms example, we next added an adolescent measure of binge drinking frequency (marijuana use frequency was tested in a separate model) to see how it was associated with the intercept, or adolescent measure, of the depressive symptoms growth curve. To test how the starting point in binge drinking frequency was associated with the trend in depressive symptoms, we also tested a model where substance use frequency was interacted with age and age squared. These models tested the relationship between a key variable in adolescence and the intercept and trend of another key variable. These models help address the potentially bidirectional relationships between substance use and depressive symptoms. Again, we tested moderation by sex with the models in both directions to try to address whether there was more support for the Stress Model for females and the Self-Medication Model for males. To illustrate, support for the hypotheses was determined by examining the direction and significance of the interaction term between adolescent substance use frequency and age in the depressive symptom growth curve model. The coefficient was interpreted as whether the slope of depressive

symptoms over time for female respondents varied by binge drinking frequency in adolescence. In this example, we expected this coefficient would be statistically significant or would be larger in magnitude than the sum of this coefficient and the estimate of the interaction term between age, sex, and adolescent binge drinking frequency. The sum is interpreted as whether the slope of depressive symptoms over time for male respondents varies by binge drinking frequency in adolescence. If this latter interaction term were to be significant and the sum of the coefficients smaller than the interaction term for females, this would be interpreted as greater support for the Stress Model among females. An example equation of these models is included below along with some example coefficient interpretations. In practice, the model with three-way interactions with age also included all of the same interactions with age squared, but this was excluded below for simplicity.

Example Equation

$$CES - D_{it} = \beta_{0i} + \beta_{1i}(Age_{it}) + \varepsilon_{it}$$

$$\beta_{0i} = \beta_0 + \beta_2(Male_i) + \beta_3(Race_i) + \beta_4(Parental\ Education_i) + \beta_5(adolescent\ Binge\ Drinking_i) + \beta_6(adolescent\ Binge\ Drinking_i * Male_i) + U_{0i}$$

$$\beta_{1i} = \beta_1 + \beta_7(Male_i) + \beta_8(adolescent\ Binge\ Drinking_i) + \beta_9(adolescent\ Binge\ Drinking_i * Male_i) + U_{1i}$$

$$CES - D_{it} = \beta_0 + \beta_1(Age_{it}) + \beta_2(Male_i) + \beta_3(Race_i) + \beta_4(Parental\ Education_i) + \beta_5(adolescent\ Binge\ Drinking_i) + \beta_6(adolescent\ Binge\ Drinking_i * Male_i) + \beta_7(Age_{it} * Male_i) + \beta_8(Age_{it} * adolescent\ Binge\ Drinking_i) + \beta_9(Age_{it} * adolescent\ Binge\ Drinking_i * Male_i) + U_{0i} + U_{1i}(Age_{it}) + \varepsilon_{it}$$

Example Interpretations

$\beta_1(Age_{it})$ =The slope of depressive symptoms over time for females (assuming sex=1 is male) who reported no binge drinking in adolescence

$\beta_2(Male_i)$ = The association between being male and the intercept of depressive symptoms at the mean age of respondents who reported no binge drinking in adolescence

$\beta_5(adolescent\ Binge\ Drinking_i)$ = The association between adolescent binge drinking and depressive symptoms for female respondents at the mean age

$\beta_5 + \beta_6$ = The association between adolescent binge drinking and depressive symptoms for male respondents at the mean age

$\beta_7(Age_{it} * Male_i)$ = Whether the slope of depressive symptoms over time for respondents who reported no binge drinking in adolescence varies by sex

$\beta_8(Age_{it} * adolescent\ Binge\ Drinking_i)$ = Whether the slope of depressive symptoms over time for female respondents varies by adolescent binge drinking frequency

$\beta_8 + \beta_9$ = Whether the slope of depressive symptoms over time for male respondents varies by adolescent binge drinking frequency

Finally, in the last two sets of models, we used a time-varying measure of binge drinking frequency (and marijuana use frequency in a separate model) instead of the adolescent measures as predictors, and interacted it with age and age squared to see whether binge drinking frequency over time for a respondent was associated with the starting point and trend of their depressive symptoms over time. Next, we again tested the reverse pathways and moderation by sex.

Potential pitfalls in this analytic approach include the complexity of the data leading to models failing to converge, power concerns, and lack of significant results. However, there are

ways to address these issues. First, if some models failed to converge, the model could likely be simplified. For example, it is possible that the growth curve allowing for random variation in the slope for age would not converge, in which case the model could be simplified to allow the age coefficient to have a random intercept and not a random slope. Previous similar analyses have been conducted using the Add Health data set, which gave us confidence that the data had sufficient variability for these complex models.[15] Second, three-way interactions bring up concerns of insufficient power. However, both binge drinking and marijuana use frequencies appeared to have sufficient variability, in both sexes, to allay this concern. Third, if these models produced only non-significant results, this would still likely be a valuable contribution to the field given the plethora of prior conflicting results and the rigor of these analytic methods. Finally, it is also possible that we would find significant results for both pathways, but this would still be informative given the multitude of conflicting results in the field, and it could be further clarified with mediation analysis.

Aim 2 Methods

Aim 2. Using regression models, examine potential mediators (sensation seeking, stress biomarkers, and gender norm adherence) and a moderator (gender norm adherence) of the relationships between substance use and depressive symptoms and whether the relationships differ by biological sex.

Study Sample

The Add Health sample was the study sample for Aim 2, as it was for Aim 1.

Aim 2 Measures

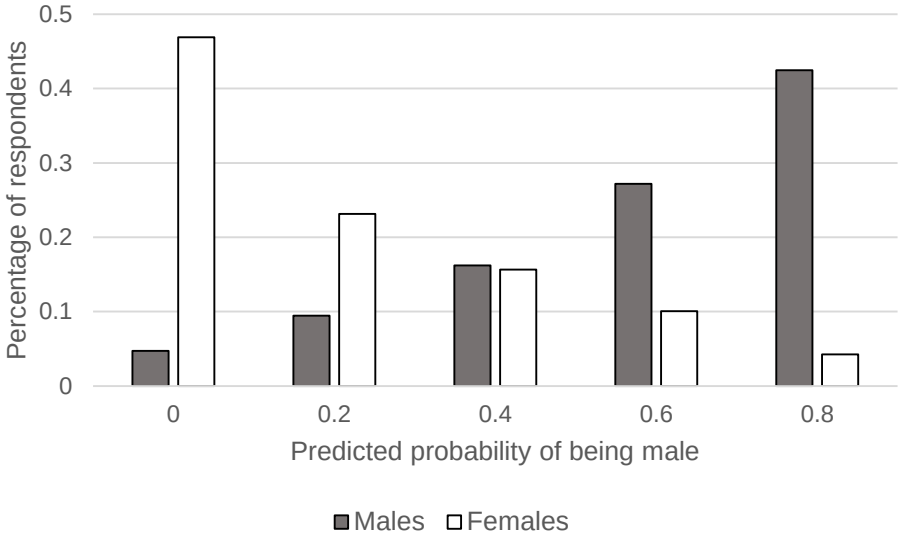
Gender norm adherence: The diversity of items within the Add Health data enabled us to use a unique empirical measure of gendered behavior. Measuring gender as a behavior is

unique because historically gender has been frequently conceptualized as a trait (e.g., masculine personality characteristics) or as an ideology (e.g., beliefs and attitudes about the roles of men and women).[83] Trait measures can conflate biological sex and gender, treat gender as static, and disregard the social aspects of gender that make gender something you do or perform in relation to other people rather than something you are.[84–87] Ideology measures capture only someone's beliefs about gender, or even what they believe are everyone else's beliefs about gender, none of which may correspond to their individual gender expression. Empirically-derived measures of gender can offer a more individual perspective while also capturing developmental and historic changes in gender norms.[64,88] Three prior studies have demonstrated the value of empirically-derived measures of gender based on individual behavior and preferences relative to peers.[89–91]

Using data from respondents interviewed at all four waves of Add Health, Fleming, Halpern, and Harris created the Adherence to Gender-typical Behavior (AGB) score, an empirical measure of behavioral adherence to gender norms.[92] This captures the degree to which respondents' reported behaviors are concordant with those of other Add Health respondents of their same sex within a given interview wave (and thus developmental stage) based on a large pool of behaviors measured at that wave. 'Behaviors' included a range from individual actions (e.g., exercising) to states of being (e.g., weight self-perception) that were shown to be highly correlated with biological sex, these varied slightly across the waves. These variables were then used in a logistic regression model to create predicted probabilities of being a biological sex (e.g., for prediction of being a male, a predicted probability of 0.85 indicates an 85% chance of being male and a 15% chance of being female). Behaviors unique to one sex—for example, experiencing menstruation—were excluded. None of the substance use measures used in these analyses were included as items in the AGB measures.

The process of developing the measure is similar to the methods used by Cleveland et al. in analyses based on Add Health data, but the newer measure includes Waves III and IV and a wider range of variables.[89] Additionally, rather than relying on the predicted probabilities, which were extremely skewed (see Figure 1.3 below), we ranked males and females separately by their adherence scores and used their rank percentile score in our analyses. A higher percentile means greater adherence to the behavior typical of one's own biological sex at a given wave. For example, males with a percentile of 0.95 exhibited strong adherence to male-typical behavior at that wave, and females with a percentile of 0.95 exhibited strong adherence to female-typical behavior at that wave. Two prior analyses tested the relationship between AGB and high frequency substance use in both cross-sectional and longitudinal models with Add Health data. As hypothesized males with higher adherence to male-typical behavior were more likely to report substance use and females with higher adherence to female-typical behavior were less likely to report substance use.[91,93]

Figure 1.2: Distribution of males and females by predicted probability of being male (Wave I)



Inflammation: The stress response is fundamentally an inflammatory process and to measure inflammation we used two biomarkers, the first of which is high sensitivity C-reactive protein (CRP). CRP has been identified as a possible marker for how stress impacts individual disease risk.[47,94] CRP has shown a dose-response relationship with depressive symptoms in both clinical and community settings.[95] The connection between stress and CRP also has longitudinal potency. For example, childhood adversity is positively associated with enhanced inflammatory response to stimuli and elevated CRP and depression risk in adulthood.[48,96–98] Finally, there is evidence that CRP levels are responsive to changes in drinking frequency and marijuana use.[99,100]

Measures of CRP (mg/L) were collected via dried whole blood spots in Wave IV of Add Health. The reliability estimate of CRP was deemed acceptable (ICC = 0.70, 95% CI= 0.59, 0.81).[101] The ICC measure indicates that 70% of the variation in CRP measures is due to variation between, rather than within, individuals. From established guidelines, CRP levels can be broken into three levels: low (<1 mg/L), average (1-3 mg/L), and high (>3 mg/L).[94] But, for mediation analyses, we needed a binary variable so the first and second categories were coded as

'0' and the high category was coded as '1.' It is important to note this category of elevated CRP is a heterogeneous one with values from 3 to 10 mg/L signaling chronic stress, what we are specifically interested in, and values over 10 indicating acute stress (e.g., an infection). The wide range of control variables for analysis of the biomarker variables are intended to adjust for the very high levels of biomarkers, and their coverage for the thirty highest CRP levels was very good. We also re-ran the models excluding those with CRP values over 30 as a sensitivity analysis. Values of CRP that were flagged for inconsistency in measurement were set to missing (n=12).

The second biomarker of inflammation was Epstein-Barr virus (EBV), which captures immune activation. Present in approximately 90% of the world population, EBV is one of the most common human viruses. Most people are infected in adolescence and upwards of 50% of people develop mononucleosis, which resolves within 2 months, but the infection maintains lifelong latency.[102,103] The physiological stress response can reactivate latent viruses. Research from Glaser et al. has connected several psychological stressors to increases in antibody titers to latent EBV, indicating reactivation.[104] Examples of the stressors associated with EBV reactivation include perceived stress, loneliness, discrimination, childhood abuse, medical school exams, marital separation or divorce, and caregiving for someone with Alzheimer's disease.[105] Thus, EBV can be used as an immunological correlate of stress, though the mechanism of this relationship is not well understood.[101,103,106,107] It is important to note that EBV reactivation is usually subclinical, meaning individuals may not experience symptoms though the levels of EBV are physiologically detectable.[102,107] Similar to CRP, there is evidence that EBV levels are responsive to substance use.[108]

EBV was measured via viral capsid antigens (AU/ml) that were also collected through dried whole blood spots in Wave IV. The reliability estimate of EBV is excellent (ICC=0.97, 95% CI =0.96, 0.98).[101] The EBV values are highly skewed and a log transformation of the values improved the distribution by making it more closely resemble a normal distribution (mean=4.8, standard deviation=0.67). So, the log transformed EBV values were used in all analyses, a method which previous studies have also used.[105] Values of EBV flagged for inconsistency in measurement were set to missing (n=2).

Sensation seeking: Wave III had a total of 20 items that have been used alone, or together, to measure the sensation seeking construct. Seven of the items are modified versions of items from the Disinhibition subscale of Zuckerman's sensation seeking scale.[109] However, these items were not presented to all respondents, only a genetic subsample.[110] The other relevant items are aimed at assessing novelty-seeking and impulse control and ask respondents to use a 5-point Likert scale to report how true the statement is for them (e.g., "I often try new things just for fun or thrills, even if most people think they are a waste of time"; Table 1.6).[58] Though impulsivity can be conceptualized as containing both a sensation seeking construct and an impulse control construct, both of which can differentially predict health risk behaviors, exploratory and confirmatory factor analyses of all 16 items in the Add Health Wave III sample found all items loaded onto one factor for sensation seeking.[58] Given these results, in this project, we used nine of the items that were asked of all respondents and that were conceptually similar, reversed coded items as necessary, and created a mean scale (Cronbach's alpha=0.85, min=1, max=5). We created a mean scale rather than a summative scale to decrease the proportion missing, as most respondents were only missing one to two items in the scale, and the patterns of

missing did not vary by respondents' answer to the question "Do you agree or disagree that you like to take risks?" indicating that items in the scale are missing at random.

Table 1.6: Sensation seeking items (Wave III)

Item Wording	Item Response
How true do you think the following statement is of you? I can do a good job of "stretching the truth" when I'm talking to people I can usually get people to believe me, even when what I'm saying isn't quite true I like it when people can do whatever they want, without strict rules and regulations I often follow my instincts without thinking through all the details I often try new things just for fun or thrills, even if most people think they are a waste of time I sometimes get so excited that I lose control of myself When nothing new is happening, I usually start looking for something exciting I often do things based on how I feel at the moment	1: Not true 2: A little true 3: Somewhat true 4: Pretty true 5: Very true 96: Refused 98: Don't know 99: Not applicable
Do you agree or disagree that you like to take risks?	1: Strongly agree 2: Agree 3: Neither agree nor disagree 4: Disagree 5: Strongly Disagree 96: Refused 98: Don't know 99: Not applicable

Confounders: In addition to the confounders listed for Aim 1, the following additional confounders were added for the Aim 2 analyses:

- Wave IV respondent education: Educational attainment of the respondent in young adulthood (less than high school, high school graduate, some college, or college graduate or higher) was used as a proxy for socioeconomic status.
- Wave IV stressful life events (SLE): Exposure to acute and sudden onset events of limited duration was captured through an additive index of over 50 items, compiled in previous

analyses using these data.[61] Example items include becoming disabled, losing a family member or friend, being deployed in a combat zone, and getting arrested. Exposure to SLEs is important to control for because such exposures could increase stress biomarkers and/or depressive symptoms independent of substance use frequency. In this way, SLEs are a potential confounder of the hypothesized relationship between stress biomarkers and depressive symptoms. There appeared to be sufficient variability in the index as it ranges from 0 to 15 (median=1, SD=1.91). The correlations between the SLE index at each wave and substance use frequency at that same wave were assessed to determine if the SLE indices needed to be added as a control variable in the growth curve analyses and the correlations were not sufficiently high to warrant this.

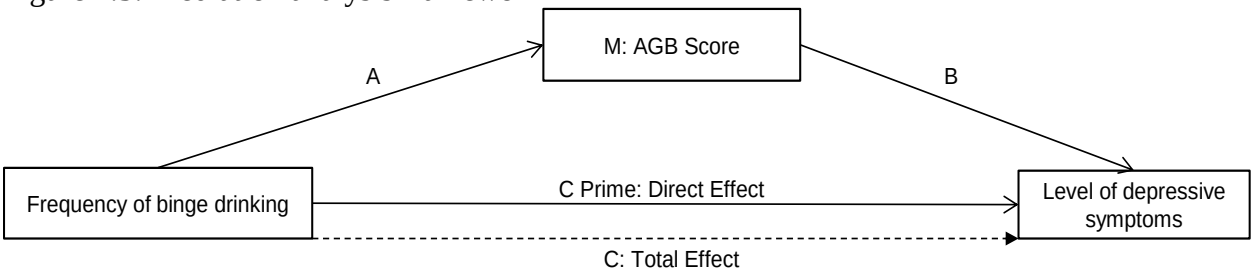
- At a physiological level, the CRP and EBV biomarkers can be influenced by many things. Looking to prior analyses of the biomarkers, we compiled a list of items that are necessary to control for when analyzing them. The same controls were used for both CRP and EBV as they are both part of the same physiological response. These potential confounders included:[101,111,112]
    - Count of subclinical symptoms (0-3)
    - Count of infectious/inflammatory diseases (0-6)
    - Use of NSAID/Salicyate in the past 24 hours and/or in the past four weeks
    - Use of a Cox-2 inhibitor within the past four weeks
    - Use of inhaled corticosteroids in the past four weeks
    - Use of corticotropin/glucocorticoid medication in the past four weeks
    - Use of antirheumatic/antipsoriatic medication in the past four weeks
    - Use of immunosuppressive medication in the past four weeks

- Use of other anti-inflammatory medications
- Currently pregnant
- BMI, derived from measured height and weight
- Cigarette smoking frequency measured as number of days on which a respondent smoked in the past 30 days.
- Vigorous physical activity, a dichotomous variable, assesses whether respondents, in the past 24 hours, did vigorous physical activity for long enough to get out of breath, sweat, or get their hearts thumping. A measure of recent vigorous physical activity is necessary because exercise increases inflammation in the short-term.[113]

Aim 2 Analyses

The mediation analyses for Aim 2 were completed using linear and logistic regression models with the predictor variable measured at Wave I, the hypothesized mediator measured at either Wave III or IV, and the dependent variable measured at Wave IV. All of the mediation analyses followed the same pattern outlined below (see Figure 1.3) using the example of the hypothesized positive relationship between the frequency of binge drinking and depressive symptoms mediated by the AGB score for females. All regression models included the relevant hypothesized confounders as well as a lagged measure of the dependent variable, measured in the most proximal wave, to adjust for prior levels of the dependent variable.

Figure 1.3: Mediation analysis framework



First, we regressed depressive symptoms at Wave IV on binge drinking frequency at Wave I, including a measure of depressive symptoms at Wave III. From this model, we got an estimate of path 'C,' or the total effect. Second, we regressed the AGB score from Wave III on binge drinking frequency at Wave I to get an estimate of path 'A.' Third, we regressed depressive symptoms at Wave IV on binge drinking frequency from Wave I and the AGB score from Wave III, including a measure of depressive symptoms from Wave III. From this final model, we got estimates of paths 'B' and 'C prime.' We looked for the estimates of paths A, B, and C to be statistically significant and the estimate for path C prime to be zero or noticeably smaller than the estimate of path C.[114] This Baron and Kenny approach to mediation has several limitations including limiting power, not computing an estimate of the indirect effect, and missing mediating relationships that can exist even if the A, B, and C path estimates are not statistically significant.[115] However, the more contemporary approach of multiplying the coefficients for the A and B paths together to get a point estimate of the indirect or mediated effect is not feasible as this then requires the use of Sobel's z-score test to determine if the estimated effect is significantly different from zero. Unfortunately, Sobel's test is not well suited for models with binary mediators or models with survey weights. Bootstrapping is another means to test the significance of the indirect effect estimate but is also infeasible with survey weights.[82] For Aim 2, we used a combination of the Baron and Kenny and contemporary mediation

approaches by looking to estimates of the A, B, C, and C' paths to identify mediation but not disregarding models when the C path was not significant but the A and B paths were.

The moderation analyses for Aim 2 tested if the AGB scores moderated either the Self-Medication or Stress Models for males or females. As the AGB score is an innovative new measure, it is not yet clear how the construct it is capturing is involved in the Self-Medication or Stress Models. So, it was tested as a mediator and moderator to inform understanding of the measure. Moderation was tested by creating interaction terms between the independent variable at Wave I and the hypothesized moderator at Wave III and testing the relationship between interaction term and the dependent variable at Wave IV. Moderation models were also tested by interacting an independent variable at Wave III with a hypothesized moderator at Wave III and then assessing the interaction's association with a dependent variable at Wave IV. For example, to test if the Stress Model was better supported for females who are more gender-adherent compared to females who are less gender-adherent, marijuana use frequency at Wave I was interacted with the AGB score at Wave III and then depressive symptoms at Wave IV were regressed on this interaction term for females. If the interaction term was significant and positive and the sum of this coefficient and the coefficient for AGB also positive, it was interpreted as support that the Stress Model was moderated by AGB such that the relationship between marijuana use frequency and later depressive symptoms was more positive for females with higher AGB scores compared to females with lower AGB scores. Next we did post hoc probing of the moderation, first by graphing predicted lines for depressive symptoms—for example, for females with different AGB scores. Next, we tested the simple slopes to confirm the predicted lines from the model parameters were significantly different from zero.

Potential pitfalls of this analytic approach included an inflated the type I error rate, bias, and a lack of significant results. Due to the high number of tests, the analysis plan was at risk of inflating the type I error rate. As a personal benchmark to guard for over interpretation of rare significant results among a large number of tests, the conservative Bonferroni correction for multiple tests was used as a sensitivity analysis for the results. Second, some of the hypothesized mediators were measured only in Wave IV, the same wave as the dependent variable, which could introduce some bias into the models. Simulation models have particularly highlighted problems when the direct or indirect effect is assessed in cross-sectional data.[116] Fortunately, in our analytic plan, only part of the indirect effect was cross-sectional, thereby limiting the potential for bias. However, it is important to note we assumed the relationship between the hypothesized mediator and the dependent variable was instantaneous and did not vary over time.[116] The third potential pitfall of the Aim 2 analyses was a lack of significant results as prior studies have connected ingredients in marijuana with decreased levels of CRP and EBV. However, these studies were testing the effects of specific compounds in marijuana on certain cells and so we hypothesized a broader analytic framework that includes the potential stress from using marijuana would produce different results, especially for females.[100,108]

Sample & Power

The analytic sample for the analyses is restricted to respondents interviewed at Waves I, III, and IV with valid sampling weights and complete data on all variables of interest (n=9,816). For the growth curve models, the data were restructured by age of respondent rather than by interview wave so that we could more accurately examine developmental trajectories.[15] All analyses with Add Health data used weights to adjust for unequal probability of selection into the sample and nonresponse over time. Additionally, variance estimates were adjusted to account for

clustering by primary sampling unit and region. We used Stata, version 14.0 (Stata Corp, College Station TX, 2013) for all regression and mixed effects models.

Table 1.7 below outlines the characteristics of the analytic sample for all of the variables in this project. Some points to note are first that the sample is diverse in race/ethnicity (nearly one third of the sample identifies as non-White) and parental educational attainment (approximately one third of parents had completed college, another third completed some college and another third had a high school degree or less). Second, there is variability in our main measures. For example, 29% of males and 48% of females have elevated levels of CRP. We also see sufficiently high levels of substance use, even at Wave I. Approximately 30% of adolescent males reported binge drinking in Wave I, and this jumps up to about 60% in Waves III and IV; the increase is from 25% to 45% for females. For marijuana use, nearly 15% of males report marijuana use in Wave I, and about 30% report use by Wave III; for females, the increase is from 13% to 20%.

Table 1.7: Characteristics of the analysis sample

Characteristic	Males (n=4323) n (weighted %) or mean (SD)	Females (n=5493) n (weighted %) or mean (SD)
CONTROL VARIABLES		
Race/Ethnicity[a] (WI)		
Hispanic	692 (12.2)	776 (10.7)
Black	721 (12.9)	1206 (15.4)
Asian	318 (3.6)	328 (3.3)
Native American	94 (2.5)	96 (1.9)
Other	38 (1.0)	43 (1.0)
White	2460 (67.9)	3044 (67.9)
Parental Education (WI)		
< High school	475 (10.7)	687 (11.1)
High school	1023 (25.6)	1420 (28.4)
< College	1298 (30.3)	1574 (28.9)
College or higher	1527 (33.4)	1812 (31.6)
Respondent Education (WIV)		
< High school	344 (8.4)	304 (6.4)
High school	762 (19.4)	694 (13.0)

< College	1910 (42.7)	2438 (44.8)
College or higher	1307 (29.5)	2057 (35.8)
Age in years, m		
Wave I	15.5 (1.8)	15.3 (1.8)
Wave III	21.9 (1.9)	21.7 (1.8)
Wave IV	28.4 (1.9)	28.1 (1.8)
Cigarette Use frequency (# days/past 30), m		
Wave I	4.6 (9.8)	4.8 (10.1)
Wave III	9.7 (13.5)	8.6 (13.0)
Wave IV	9.6 (13.3)	7.9 (12.6)
Stressful Life Events Index (0-50) (WIV), m	2.1 (2.0)	1.8 (1.7)
Childhood maltreatment frequency		
Never	1498 (34.8)	1732 (31.5)
Once	427 (9.7)	557 (10.2)
Twice	443 (10.2)	532 (9.4)
Three times	739 (17.1)	1035 (18.5)
Four or more times	1216 (28.3)	1637 (30.4)
BIOMARKER CONTROL VARIABLES		
Count subclinical symptoms, m	0.4 (0.7)	0.5 (0.8)
Count inflammatory diseases, m	0.4 (0.7)	0.5 (0.7)
NSAID/Salicylate (24 hours)	1089 (25.0)	1617 (30.7)
NSAID/Salicylate (4 wks)	104 (2.4)	168 (3.3)
COX-2 Inhibitor (4 wks)	5 (0.0)	7 (0.0)
Inhaled Corticosteroid (4 wks)	11 (0.0)	28 (0.0)
Corticotropin/Glucocorticoid (4 wks)	19 (0.1)	59 (1.2)
Antirheumatic/Antipsoriatic (4 wks)	8 (0.1)	25 (0.4)
Immunosuppressives (4 wks)	4 (0.0)	13 (0.2)
Anti-Inflammatory medications	1149 (26.4)	1734 (32.8)
BMI		
Underweight	31 (0.8)	101 (1.9)
Normal weight	1185 (28.2)	1853 (34.3)
Overweight	1498 (34.0)	1413 (24.6)
Obese	1609 (37.0)	2126 (39.2)
Currently pregnant (WIV)	N/A	345 (6.3)
Vigorous physical activity (yes/no) (24 hours)	2126 (49.7)	1798 (32.7)
HYPOTHESIZED MEDIATORS[b]		
Sensation seeking (1-5) (Wave III), m	3.0 (0.9)	2.4 (0.8)
CRP		

<3 mg/L	3026 (70.0)		2848 (51.8)
>3 mg/L	1297 (30.0)		2645 (48.2)
EBV log AU/ml, m	4.7 (0.7)		4.9 (0.7)
	MALES (n=4323)		
	Wave I	Wave III	Wave IV
Depressive symptoms (0-27), m	5.0 (3.8)	3.9 (3.6)	4.6 (3.7)
Binge drinking frequency			
None	3060 (70.4)	1735(37.2)	1857(40.9)
1 or 2 days/year	388 (9.0)	669 (15.2)	726 (17.3)
Once per month or less	286 (6.5)	511 (12.7)	580 (13.2)
2-3 days/month	238 (5.6)	521 (12.9)	453 (11.0)
1-2 days/week	226 (5.6)	615 (15.6)	448 (11.0)
3-5 days/week	86 (2.1)	223 (5.3)	195 (5.1)
Every day/almost	39 (0.1)	49 (1.2)	64 (1.4)
Marijuana use frequency			
None	3668 (85.4)	3121(71.1)	3394(77.1)
1 day	158 (3.3)	211 (4.9)	171 (3.9)
2 or 3 days	159 (3.4)	201 (4.9)	154 (4.1)
1 day/week	69 (1.7)	118 (3.0)	45 (1.2)
2 days/week	63 (1.5)	107 (2.5)	108 (2.5)
3-5 days/week	88 (2.0)	229 (5.8)	165 (3.8)
Every day/almost	118 (2.7)	336 (7.9)	286 (7.4)
	FEMALES (n=5493)		
	Wave I	Wave III	Wave IV
Depressive symptoms (0-27), m	6.3 (4.5)	4.9 (4.2)	5.6 (4.3)
Binge Drinking frequency			
None	4208 (75.2)	3240(55.4)	3222(56.0)
1 or 2 days/year	557 (10.8)	984 (18.1)	977 (18.9)
Once per month or less	203 (6.1)	537 (11.2)	534 (10.3)
2-3 days/month	203 (3.8)	335 (6.9)	410 (8.0)
1-2 days/week	136 (2.5)	297 (6.3)	247 (4.5)
3-5 days/week	56 (1.1)	82 (1.8)	82 (1.6)
Every day/almost	27 (0.1)	18 (0.2)	21 (0.3)
Marijuana Use frequency			
None	4816(87.2)	4533(80.8)	4840(87.5)
1 day	179 (3.3)	244 (4.8)	159 (3.3)
2 or 3 days	192 (3.8)	192 (3.7)	117 (2.2)
1 day/week	100 (1.6)	116 (2.2)	45 (6.5)
2 days/week	68 (1.3)	114 (2.3)	73 (1.3)
3-5 days/week	81 (1.6)	130 (2.7)	91 (2.0)
Every day/almost	57 (1.3)	164 (3.6)	168 (3.1)

[a]All other race/ethnicities are non-Hispanic

[b]AGB is not included in this table because it is a rank percentile score (e.g., min=0.01, max=0.99, mean=0.5)

Missing Data & Power

The same analytic sample was used for both Aims 1 and 2. This increased the amount of missing data as we used complete case analysis, (i.e., only included respondents with survey weights and complete data on all variables of interest at all waves), an analytic technique recommended for Add Health data.[117] Fortunately, the sampling weights adjust for a respondent's data being missing for an entire wave, which accounts for as much as 25% of the missing data. When we restricted the sample to respondents interviewed at all waves with complete data on all of our variables of interest, we lost 20% of the sample. This proportion missing is not ideal, but the two options for decreasing the proportion missing were not feasible with the complex sampling design of Add Health. First, we considered weighting the respondents who were included in the analytic sample by running a logistic regression to get the response propensity.[118] This method was deemed infeasible as we would have needed to combine the response propensity weight with the existing longitudinal weights in Add Health. Second, we considered multiple imputation through sequential regression to estimate values for AGB or the biomarkers, both of which had the highest proportion missing.[118] This method, however, was also deemed infeasible because the AGB scores are composites of 25 different items at each wave and the biomarkers have very few corresponding variables we could use to reliably impute values. Additionally, as multiple imputation would result in multiple different data sets, it would restrict the complexity of the models we could later run.

Our analyses had power to detect statistically meaningful changes. Using average CES-D scores as the example dependent variable, we would hypothesize that the mean CES-D score would be higher for people engaging in substance use compared to those who are not. Making the conservative estimate of a one-point difference in the mean CES-D score between those

using substances and those not, Add Health has 100% power to detect this difference with the level of significance set at 0.05 for two-sided hypothesis tests. Add Health has 80% power to detect differences as small as a 0.12 point-increase in the CES-D. We used Stata, version 14.0 (Stata Corp, College Station TX, 2013) to perform all of the necessary calculations. As Add Health has a large sample size, even small differences between groups can be statistically significant. To guard against potential over-interpretation of significant p-values, we also looked for differences being conceptually meaningful.

CHAPTER 2 – TESTING RELATIONSHIPS BETWEEN BINGE DRINKING, MARIJUANA USE, AND DEPRESSIVE SYMPTOMS AND MODERATION BY BIOLOGICAL SEX

Overview

Objectives: We examined the longitudinal associations between substance use frequency and depressive symptoms from adolescence into young adulthood, and whether the associations were moderated by sex.

Methods: With data from Waves I, III, and IV of the National Longitudinal Study of Adolescent to Adult Health (n=9816), we used growth curve models to test if depressive symptoms predicted binge drinking or marijuana use frequency or if substance use frequency predicted depressive symptoms. Moderation by sex was tested for both potential pathways.

Results: Higher adolescent depressive symptoms, compared to no symptoms, were associated with a steeper predicted increase in marijuana use frequency from adolescence to young adulthood. Persistent binge drinking or marijuana use had concurrent positive associations with depressive symptoms from adolescence to young adulthood, and these associations were stronger for females.

Conclusions: The results support the self-medication hypothesis for marijuana use but also the reverse pathway, that binge drinking and marijuana use are associated with depressive symptoms, especially for females.

Policy Implications: These results inform prevention and/or treatment steps following adolescent depression or substance use screening, newly covered preventive services under the Affordable Care Act.

Introduction

Both substance use and depressive symptoms increase in adolescence, are often comorbid, and are associated with negative outcomes.[1–4,23,30] Nearly one third of U.S. high school students report current alcohol use, approximately one quarter report current marijuana use, and up to one in five have experienced a major depressive episode.[2,25] Youth with a major depressive episode in the past year are more than twice as likely to report marijuana use compared to youth without a major depressive episode in the past year.[31] Comorbidity between substance use and depression is concerning because it is associated with worse outcomes than either alone, including more severe mental health issues, longer depressive episodes, increases in substance use, delays in substance abuse recovery, and elevated suicide risk.[21]

The comorbidity between substance use and depression indicates there may be a causal relationship between them. Theories suggest alternative directions for this relationship. First, the Self-Medication Model asserts depression leads to substance use as an attempt to ameliorate symptoms.[42] Second, our Stress Model hypothesizes substance use leads to depression by increasing strain in peer and parental relationships and thereby interpersonal stress.[10,11] Processes entailed in these Models are complicated by biological sex, developmental change, and type of substance. In general, adolescent females are more likely to report experiencing depression than males.[60,67] By comparison, adolescent males generally report use of a wider range of substances and at a higher frequency compared to females.[4,25,26] Developmentally, initiation of substance

use is concentrated in adolescence yet the quantity and frequency of substance use typically peak between 18-25 years of age in the United States.[4]

Findings from previous research relevant to the Self-Medication and Stress Models differ across substances and by sex. Starting with the Self-Medication Model, Hooshmand et al. followed 4,000 U.S. adolescents through high school and found those reporting higher depressive symptoms early had faster increases in marijuana use, but found no significant results for alcohol.[6] De Graaf et al., with a sample of over 7,000 late adolescents and young adults found that major depression predicted alcohol dependence. The study found some differences by sex, but did not formally test moderation of the associations by sex.[119] In contrast, a study with a sample of over 600 African American adolescents who were surveyed annually for six years starting in high school found depression predicted marijuana use, but only in males.[21] Mushquash et al. with a sample of 200 undergraduate women found depressive symptoms predicted increases in heavy episodic drinking one week later.[120] However, an analysis using data from the National Longitudinal Study of Adolescent to Adult Health (Add Health) found no evidence for depression predicting increases in substance use or sexual risk behavior, measured in clusters of behavior.[5]

For the Stress Model, evidence is inconsistent for alcohol or marijuana predicting depression and for moderation by sex. In the Add Health study noted above, substance use and sexual risk behavior in adolescence predicted depression in emerging adulthood; this association was present for both experimental (females only) and frequent risk-taking behaviors (males and females).[5] In contrast, a longitudinal survey following over 1,000 African Americans from age six to 42 found increased alcohol or marijuana use (loaded on a single construct) in adolescence predicted psychological distress in young adulthood but only for males.[121] Fergusson et al.

examined only alcohol use, with a sample of over 1,000 late adolescents followed into emerging adulthood, and tested both potential directions of the association between alcohol abuse or dependence and depression, and found the best fitting model was leading from alcohol to depression; a recent review came to the same conclusion.[51,53] In contrast, Mushquash et al. found heavy episodic drinking in a sample of undergraduate women did not predict increases in depressive symptoms one week later.[120] For marijuana, the association appears most robust for frequent marijuana use; two longitudinal studies and a review found an increasing marijuana use trajectory, or at least weekly use, predicted later depression.[7,52,122]

The large literatures on adolescent substance use and depression share several limitations, which this paper aims to address. First, much of the research is cross-sectional, or if longitudinal, is based on non-representative samples, tests only one direction, does not test moderation by sex, and/or captures only adolescence.[6–8,18–23] This project addresses these important limitations by using data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), a nationally representative sample of adolescents who have been prospectively followed into young adulthood. We hypothesized there would be greater evidence for the Self-Medication Model among males compared to females (Hypothesis 1), as a review of sex differences in emotion regulation found males were more likely to engage in impulsive, reward-seeking behavior.[17,62] We also hypothesized the Stress Model would be better supported among females than males (Hypothesis 2), as substance use is less normative for females, and females are generally more sensitive to interpersonal stress than males.[10,11,47,66]

Methods

Sample

Add Health is a longitudinal study that includes a nationally representative sample of U.S. adolescents who were in grades 7-12 in the 1994-95 school year (Wave I). There have been four in-home interviews to date. The present analysis sample is restricted to respondents interviewed at Wave I, Wave III (ages 18 to 26), and Wave IV (ages 24 to 32), with valid sampling weights (N=12,288) and who had complete data on all variables of interest (N=9,816, 80%). Data from Wave II were not used as Wave I seniors were not followed by design. Details of the Add Health study and design are described elsewhere.[78] All Add Health procedures were approved by the Institutional Review Board at the University of North Carolina, Chapel Hill. These analyses were deemed exempt.

Measures

Depressive symptoms were measured using the nine items from the Center for Epidemiologic Studies Depression Scale (CES-D) available at Waves I, III, and IV. The items ask about frequency of symptoms in the past week from rarely (0) to most of the time (3); the summed score for the scale ranges from 0 to 27. Though the items ask about frequency of depressive symptoms in the past week, the 12-month re-test reliability is high.[76] The CES-D is not a diagnostic tool.

The substances measured included alcohol (binge drinking) and marijuana. We measured frequency of substance use rather than ever use to better capture levels of risk taking. In Add Health, substance use frequency is measured with either continuous or ordinal variables with varying time frames. The frequency of binge drinking, defined as consuming 5 or more drinks in

a row, is assessed in the past 12 months with an ordinal variable ranging from 0 (never) to 6 (every day or nearly every day). Marijuana use frequency is assessed in the past 30 days; the measures at Waves I and III were continuous and assessed instances of use. At Wave IV the measure was ordinal and assessed days of use, mirroring the binge drinking frequency measure.[78] To make the marijuana use frequency measures comparable across the waves, the measures at Waves I and III were recoded to capture days of use, assuming an instance of use was equivalent to a day of use, and adapted to match the ordinal measure at Wave IV.

Multiple covariates were included in the model as both depressive symptoms and substance use can vary across several sociodemographic characteristics. The covariates included respondent's self-identified race/ethnicity (Hispanic and non-Hispanic White, Black, Asian, Native American, and Other) and the highest educational attainment of the parents (less than high school, high school graduate, some college, or college graduate or higher) as a proxy for socioeconomic status of the parental home.[4] Frequency of child maltreatment, ranging from never to four or more times, was included as a potential confounder as it can be significantly associated with both depressive symptoms and substance use.[80] Child maltreatment was defined as self-reported emotional, physical, or sexual abuse before age 18 or self-reported physical or supervisory neglect by a parent or adult caregiver at or before the time of the Wave III interview. Finally, binary variables were included to control for levels of the dependent variable at an age before the respondent's age at Wave I, using retrospective measures from Wave I, including a depression diagnosis, drinking a full alcoholic beverage, and using marijuana.

Analysis

The data set was structured by age instead of wave to capture the developmental trajectory from adolescence to young adulthood. Linear mixed effects models were used to

estimate growth curves of the three dependent variables: binge drinking frequency, marijuana use frequency, and depressive symptoms. Nine models were fit for each independent and dependent variable pairing. The first four models were used to estimate the growth curve of the dependent variable, starting with an unadjusted model, adding covariates, testing a random slope by age, then interacting the age and age-squared terms with sex. The next three models test a temporal association, whether an adolescent measure of the hypothesized predictor variable (controlling for pre-Wave I levels) is significantly associated with the starting point and trend in the growth curve of the dependent variable, and whether the association varies by sex. Finally, the last two models test whether a longitudinal measure (i.e., measures across all of the ages rather than at a specific developmental point) of the hypothesized predictor is significantly associated with the growth curve of the dependent variable and whether this association is moderated by sex. These last two models test whether there is a concurrent association (i.e., at each age) between the independent and dependent variables, which serves as a robustness check for the models testing a temporal association by clarifying whether only the adolescent measures of the independent variable are associated with the growth curve of the dependent variable.

For all eligible models, we attempted to fit a random intercept by respondent ID and a random slope by age. We report the variance estimates for the random effects, where applicable. We also calculated the intraclass correlation coefficient (ICC) to get an estimate of the proportion of variance in the outcome that is due to variance between individuals, and report the percent change in the ICC across the models.

Results

Across the developmental trajectory from adolescence to young adulthood in the Add Health sample, the prevalence of binge drinking and marijuana use increases from adolescence to

emerging adulthood and then decreases slightly in young adulthood. For example, from ages 11 to 13, only 9% of respondents report any binge drinking, but this increases to 55% between ages 20 to 22 and then decreases to 38% between ages 32 to 34 (Table 2.1). For marijuana use, the proportion of respondents reporting any use increases from 5% at ages 11 to 13, to 25% at ages 20 to 22, and then decreases to 17% for ages 32 to 34. This pattern is consistent with most previous research on developmental trends in substance use during these stages of the life course.[4] Depressive symptoms follow an opposite pattern, starting higher in adolescence, decreasing in emerging adulthood and then increasing slightly in young adulthood. For example, the mean CES-D for ages 14 to 16 is 5.72; this decreases to 4.28 at ages 23 to 25 but then increases again to 5.08 between ages 29 to 31.

Table 2.1: Characteristics of the analysis sample by age

	Age (years)[a] N (weighted percentage)							
	11-13[a]	14-16	17-19	20-22	23-25	26-28	29-31	32-34
Binge drinking frequency	N=1494	N=5080	N=4276	N=4822	N=4378	N=4517	N=4692	N=189
None	1376 (0.91)	3865 (0.75)	2540 (0.54)	2465 (0.47)	2182 (0.45)	2215 (0.46)	2563 (0.52)	116 (0.62)
1-2 days/year	57 (0.04)	495 (0.10)	560 (0.14)	784 (0.16)	773 (0.18)	809 (0.19)	795 (0.17)	28 (0.13)
≤1 x/month	19 (0.02)	305 (0.06)	382 (0.10)	494 (0.12)	499 (0.12)	530 (0.12)	514 (0.11)	11 0.04)
2-3 days/month	17 (0.01)	176 (0.04)	346 (0.09)	417 (0.09)	396 (0.10)	443 (0.10)	353 (0.08)	12 (0.07)
1-2 days/week	13 (0.01)	140 (0.03)	318 (0.09)	472 (0.11)	363 (0.10)	360 (0.09)	290 (0.07)	13 (0.07)
3-5 days/week	8 (0.01)	63 (0.02)	100 (0.03)	160 (0.04)	130 (0.03)	122 (0.03)	133 (0.03)	8 (0.07)
Every day/almost	4 (0.00)	36 (0.01)	30 (0.01)	30 (0.01)	35 (0.01)	38 (0.01)	44 (0.01)	--[b]
Marijuana use frequency								
None	1430 (0.95)	4390 (0.86)	3412 (0.78)	3705 (0.75)	3534 (0.79)	3733 (0.81)	4006 (0.85)	162 (0.83)
1 day	22 (0.02)	178 (0.03)	201 (0.05)	227 (0.05)	188 (0.05)	142 (0.03)	157 (0.03)	7 (0.03)
2-3 days	22 (0.02)	189 (0.04)	193 (0.05)	201 (0.05)	158 (0.04)	146 (0.04)	104 (0.02)	--
1 day/week	5 (0.00)	88 (0.02)	106 (0.02)	122 (0.03)	84 (0.02)	51 (0.01)	34 (0.01)	3 (0.02)
2 days/week	7 (0.00)	68 (0.01)	89 (0.03)	109 (0.02)	85 (0.02)	89 (0.02)	84 (0.02)	--
3-5 days/week	5 (0.00)	86 (0.02)	129 (0.03)	187 (0.04)	131 (0.04)	116 (0.03)	128 (0.03)	--
Every day/almost	3 (0.00)	81 (0.02)	146 (0.04)	271 (0.06)	198 (0.05)	240 (0.06)	179 (0.04)	11 (0.09)
Depressive symptoms (0-27), m	4.90 (3.87)	5.72 (4.25)	5.66 (4.23)	4.52 (4.07)	4.28 (3.87)	5.12 (4.09)	5.08 (4.10)	6.08 (4.47)

[a]Age is continuous in all of the statistical models but was condensed into categories for this table

[b]Dash indicates fewer than three respondents

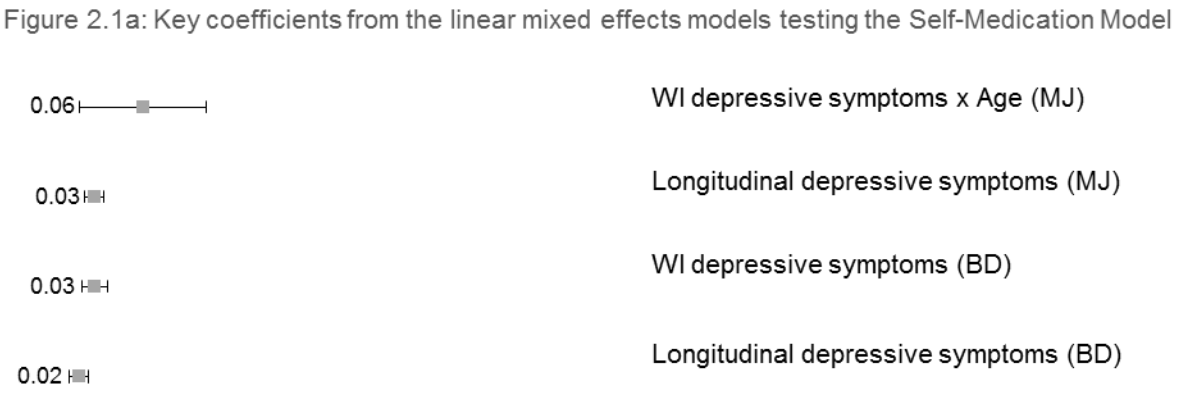
Figure 2.1 is a plot of the key coefficients from the linear mixed effects models (see Appendix 2 for full model results). The data labels show the magnitude of the key coefficients. The coefficients are organized from highest in magnitude, at the top of the figure panel, to lowest in magnitude at the bottom, with a label to the right of the dot identifying the coefficient.

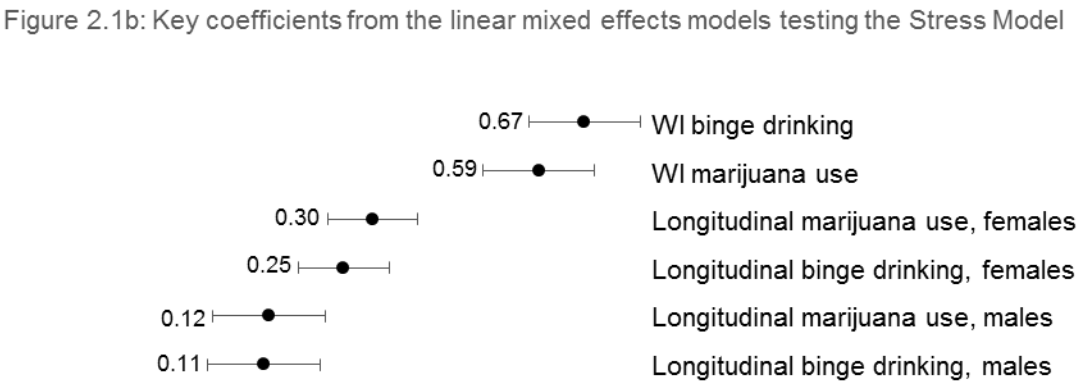
The grey squares in Figure 2.1a show results from models testing the Self-Medication Model (i.e., the independent variable is depressive symptoms). Depressive symptoms in adolescence, a Wave I measure, were significantly associated with the binge drinking growth curve ($b=0.03$, $p<0.001$) with higher depressive symptoms in adolescence associated with higher binge drinking frequency in adolescence. The concurrent relationship across the ages was also significant ($b=0.02$, $p<0.001$). None of the interactions tested with the adolescent or time-varying (longitudinal) measure of depressive symptoms were significant. Depressive symptoms in adolescence were also significantly associated with the marijuana use frequency growth curve, but only when interacted with age ($b=0.06$, $p<0.01$), meaning higher depressive symptoms in adolescence were significantly associated with a steeper slope in marijuana use frequency with increasing age. The concurrent relationship for depressive symptoms and the marijuana use frequency growth curve was also significant ($b=0.03$, $p<0.001$). The interactions between the longitudinal depressive symptom measure and the substance use frequency growth curves were not statistically significant. Self-Medication Models fit with a random slope for age failed to converge.

The black circles in Figure 2.1b show results from analyses testing the Stress Model (i.e., independent variable was substance use frequency). Binge drinking frequency in adolescence was significantly associated with the depressive symptoms growth curve ($b=0.67$, $p<0.001$), with a higher binge drinking frequency in adolescence associated with a higher level of depressive

symptoms in adolescence. The concurrent positive relationship across the ages between binge drinking frequency and the depressive symptom growth curve was also significant and moderated by sex such that the relationship is stronger for females ($b=0.25$, $p<0.001$) compared to males ($b=0.11$, $p<0.01$). Marijuana use frequency in adolescence was also significantly positively associated with the depressive symptom growth curve ($b=0.59$, $p<0.001$). The concurrent relationship across the ages was also significant and moderated by sex, again indicating a stronger relationship for females ($b=0.30$, $p<0.001$) compared to males ($b=0.12$, $p<0.001$). All of the relevant models testing the Stress Model were fit with a random slope for age, allowing further heterogeneity in the growth curves.

Figure 2.1: Key coefficients from the linear mixed effects models[a]

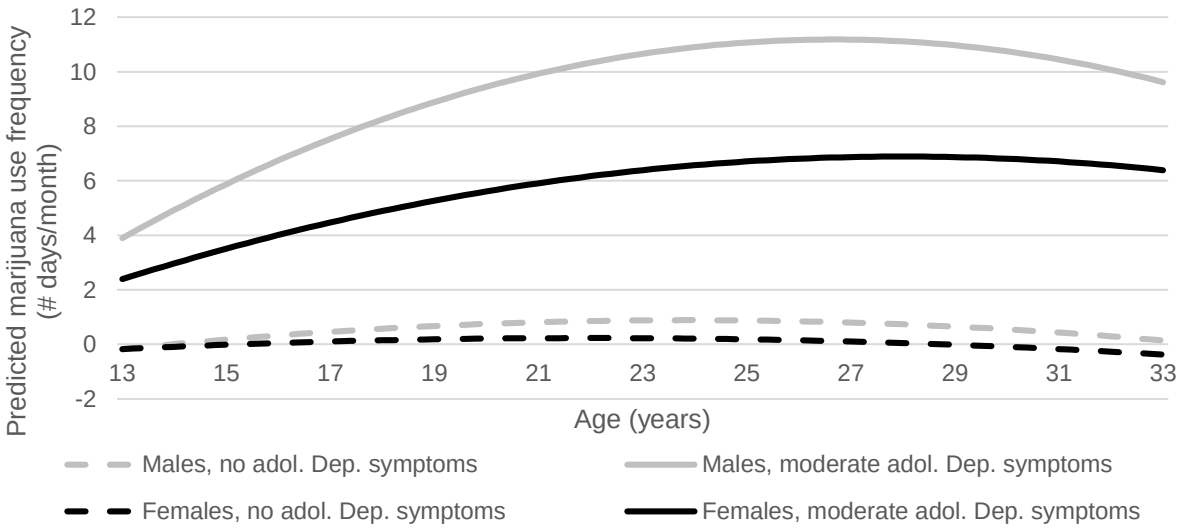




[a] Binge drinking frequency (BD), marijuana use frequency (MJ), Wave I (WI), dependent variable noted with parentheses in Figure 2.1a

Figure 2.2 shows the predicted growth curve of marijuana use frequency across age and how growth varies by sex and depressive symptoms (Self-Medication Model). As can be seen, there is an increase in predicted marijuana use frequency across age for both males and females with moderate depressive symptoms in adolescence, but not for adolescents with no depressive symptoms. Further, the increase in marijuana use frequency among adolescents with moderate depressive symptoms appears greater for males compared to females.

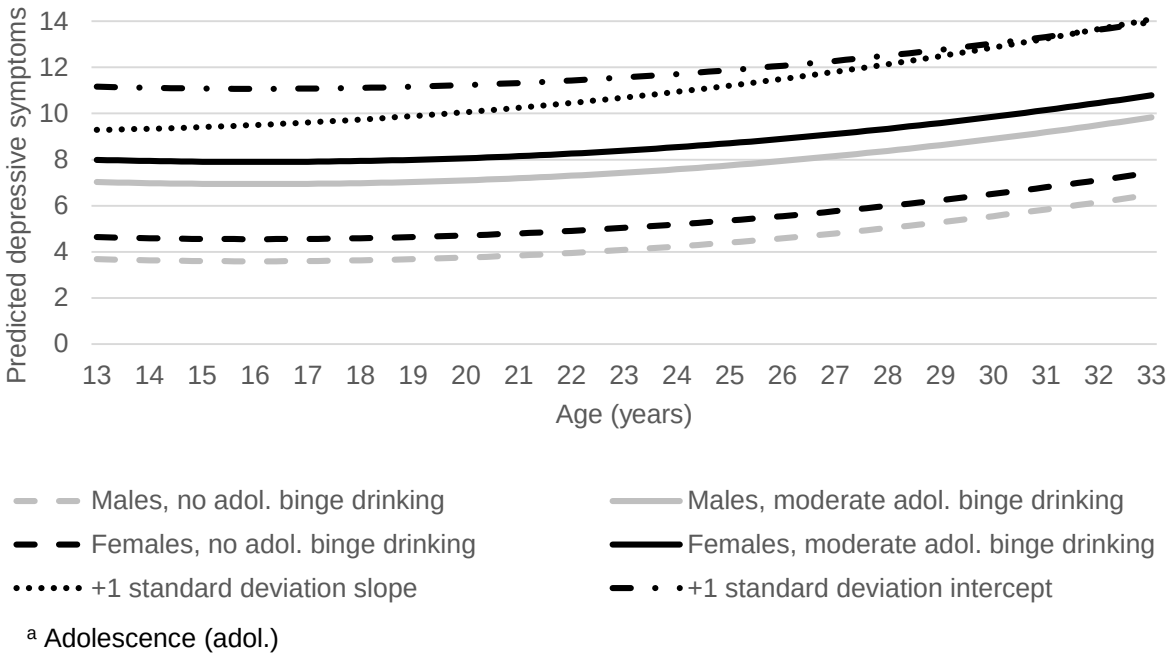
Figure 2.2: Relationship between adolescent depressive symptoms and marijuana use frequency growth curve (Self-Medication Model)[a]



[a] Adolescent (adol), dep (depressive)

Figure 2.3 shows the predicted growth curve of depressive symptoms across age and how growth varies by sex and binge drinking frequency (Stress Model). The figure displays an increase in predicted depressive symptoms in adolescence with an increase in binge drinking frequency in adolescence and a higher starting point in adolescence for females compared to males. Similar results were found for marijuana use frequency. The solid black line in the figure shows the mean predicted depressive growth curve and the top two lines illustrate the variation in the growth curve among females from the random effects in the model. Specifically, the top two lines in the figure show how the predicted depressive symptom growth curve for females shifts if there is a one standard deviation increase in the intercept or the slope; both of the shifts take the predicted depressive symptoms above the threshold for likely depression (10 on the CES-D).

Figure 2.3: Relationship between adolescent binge drinking frequency and depressive symptoms growth curve (Stress Model)[a]



[a] Adolescence (adol.)

There is meaningful within- and between-individual variation in the growth curves. The ICCs decreased across the models when additional predictors were added, indicating the predictor and control variables explained some of the between-individual variation in the outcome, as expected. For example, for the Self-Medication Models, the ICCs decreased by 30% from the unadjusted to fully-adjusted models (0.27 to 0.19) when binge drinking frequency was the dependent variable and by 23% (0.30 to 0.23) when marijuana use frequency was the outcome. For the Stress Models, the ICCs decreased by 18% (0.34 to 0.28).

Discussion

We used Add Health data to fit growth curve models testing both directions of the potential relationship between substance use and depressive symptoms from adolescence to young adulthood; we also tested moderation by sex. The ICCs decreased meaningfully across the

models, indicating our hypothesized predictor and control variables explained considerable variation in growth curves between respondents. Hypothesis 1 asserted there would be greater support for the Self-Medication Model among males compared to females, which was not supported in the current analysis. Rather, the findings support the Self-Medication Model for both males and females. There was a significant relationship between depressive symptoms in adolescence and the slope of marijuana use frequency from adolescence to young adulthood. The remaining significant associations between adolescent and longitudinal measures of depressive symptoms and both marijuana use and binge drinking were all concurrent associations and therefore do not address our directional hypothesis. Hypothesis 2 asserted the Stress Model would be more applicable for females compared to males, and was partially supported. When we tested the association between longitudinal measures of both binge drinking and marijuana use frequency and the depressive symptom growth curve, the association was significantly moderated by sex in both cases, indicating a stronger positive concurrent relationship across the developmental time period for females compared to males. We deem this only partial support for Hypothesis 2 because the associations significantly moderated by sex were concurrent and not directional.

Our results supporting the Self-Medication Model for marijuana are consistent with some past literature as is our lack of significant results for binge drinking. For marijuana use, similar prior studies have found higher depressive symptoms early in adolescence are associated with faster increases in marijuana use during high school; in later adolescence marijuana use can be predicted by depressive symptoms.[6,21] However, other longitudinal studies with dissimilar methods found marijuana use predicted depression and not the other way around, indicating methodological differences may further complicate the evidence for the Self-Medication and

Stress Models.[7,52,122] Our lack of support for moderation by sex is consistent with findings from a study of over 7,000 late adolescents and young adults but inconsistent with findings from a study of over 600 African American adolescents. These patterns suggest future research should examine three-way interactions by age, race, and sex.[21,119] For binge drinking, a review and a similar longitudinal study of early adolescents found no support for self-medication, but two studies of older adolescents found evidence for depressive symptoms predicting binge drinking or heavy episodic drinking.[6,53,120] Results related to the question of sex differences in self-medication with alcohol are unclear. There is more empirical support for males self-medicating, especially with alcohol.[17] However, binge drinking is a normative social activity for males at these ages. If only a minority are self-medicating, the relationship may be hard to find.[62] Further, at least one other similar longitudinal study found evidence for females self-medicating depressive symptoms with alcohol, though only a one-week timespan was examined, a further methodological complication.[120]

Our finding of partial support for the Stress Model among females is consistent with some prior literature. Two similar longitudinal analyses following adolescents into emerging adulthood found both experimental substance use and substance abuse predicted later depression, but the reverse pathway was not supported.[5,51] The Stress Model has also been supported by some reviews of other similar longitudinal study designs.[52–54] Moderation by sex remains unclear. Although an analysis of Add Health data found only high frequency substance use predicted depression in males whereas experimental and high frequency use were predictive of depression in females, race appears to complicate the picture.[5] A longitudinal study of African American and Puerto Rican women followed from adolescence into young adulthood found increasing marijuana use frequency predicted an increase in later depressive symptoms.[7] Yet, a

similar longitudinal study of African American children followed into adulthood found substance use in adolescence predicted psychological distress in adulthood only for males.[121]

The results of this study should be considered in the context of its limitations. First, the ordinal substance use measures were treated as continuous, though various robustness checks indicate the results are stable to variations in the measures (results not shown). Second, though linear mixed effects models remove potential bias from time-invariant unobserved characteristics, the results could still be biased by time-varying unobserved characteristics. Third, the Add Health data allow the developmental time period from adolescence into young adulthood to be studied; however, with only three waves of data (i.e., developmental periods) with the entire sample, it is more difficult to find variation in the growth curves.

This paper addressed several limitations in past literature by using data from a nationally representative sample followed from adolescence into young adulthood and testing both potential directions of the association between substance use and depressive symptoms, as well as possible moderation by sex. The results indicate youth may self-medicate their depressive symptoms with marijuana use and that both marijuana use and binge drinking are concurrently associated with depressive symptoms, especially among females. So, both Models were supported and there was modest evidence suggesting the Stress Model is a better fit for females than males. These results inform efforts to screen adolescents for depression or substance use, now both covered as preventive services under the ACA. For example, youth screening positive for depression or an increase in depressive symptoms should also be screened for marijuana use, and youth, especially females, screening positive for persistent binge drinking or marijuana should be targeted for depression prevention programs or at least flagged as at risk for depressive

symptoms. Future research should examine moderation in these pathways by both sex and race/ethnicity as well as variation in results across different longitudinal methods.

CHAPTER 3 – SENSATION SEEKING, BIOMARKERS OF STRESS, AND ADHERENCE TO GENDER NORMS AS POTENTIAL MEDIATORS OF THE LONGITUDINAL ASSOCIATIONS BETWEEN BINGE DRINKING, MARIJUANA USE, AND DEPRESSIVE SYMPTOMS

Overview

Objectives: We tested potential mediators and moderators of the longitudinal associations between substance use frequency and depressive symptoms from adolescence into young adulthood, and whether the associations differed by sex.

Methods: We used data from Waves I, III, and IV of the National Longitudinal Study of Adolescent to Adult Health (n=9816) to run sex-stratified regression models testing mediation and moderation hypotheses. Specifically, we tested if sensation seeking mediated the association between depressive symptoms and later substance use or if stress biomarkers mediated the association between substance use and later depressive symptoms. Further, we tested whether adherence to gender norms mediated or moderated either association.

Results: The majority of significant results related to mediation and moderation of the association between depressive symptoms and later binge drinking frequency. For both males and females, sensation seeking and adherence to gender norms appear to mediate the association. For males only, adherence to gender norms appears to also moderate the relationship between depressive symptoms and later binge drinking. For females only, sensation seeking also seems to mediate the relationship between depressive symptoms and later marijuana use frequency. No significant results were found for the association between substance use frequency and later depressive symptoms.

Conclusions: Results indicate sensation seeking may mediate the association between depressive symptoms and later binge drinking frequency (males and females) as well as later marijuana use frequency (females only). Also, adherence to gender norms may mediate (in different directions for males and females) and moderate (males only) the association between depressive symptoms and later binge drinking frequency.

Introduction

Depressive symptoms and substance use are often comorbid in adolescence, suggesting a possible causal relationship.[21] Past research examining the directional relationship between substance use and depressive symptoms has yielded mixed findings both in terms of which comes first, depression or substance use, and whether relationships differ by biological sex. Testing potential mediators and moderators of both hypothesized directions of the association could inform our understanding of underlying mechanisms and explain why linkages may vary for males and females.

A predominant hypothesis as to why depressive symptoms may lead to later substance use is the Self-Medication Model, which asserts depressed individuals are motivated to seek novelty (i.e., substances) to ameliorate their symptoms.[42] Therefore, sensation seeking may mediate this relationship. We expect a positive relationship between sensation seeking and later substance use for both males and females, as prior studies have found.[58,59] However, we hypothesize the relationship between depressive symptoms and later sensation seeking will be negative for females and positive for males (Hypothesis 1). First, adolescent females may experience more severe and/or chronic depression, which could dampen motivation to seek novelty.[5,21,60] Second, internalizing symptoms like depression are less socially acceptable for males compared to females, which may motivate sensation seeking in males.[17,64] Further, if

males do feel less masculine when struggling with depression, substance use can be a means of demonstrating adherence to masculine gender norms, which can endorse risk taking.[22,65] Third, males may feel they lack other emotion regulation strategies, as supported in a recent review.[17,61,62] Indeed, a survey of social drinkers revealed males were more likely than females to report drinking to regulate negative affect.[63]

An alternative directional hypothesis about substance use and depression comorbidity is that substance use precedes depression. Past studies have tested whether substance use is associated with later increases in depressive symptoms, but few have articulated conceptual grounding for it.[5–8] We term this the Stress Model because we focus on stress as a potential mediator linking substance use to later depression. We hypothesize stress, which we measure as a physiological stress response, will be positively associated with depression for both sexes.[12,13] However, we hypothesize substance use will be positively associated with stress for females and negatively associated for males (Hypothesis 2). First, substance use, as a risk behavior, does not align with female gender norms, whereas it does align with male norms.[65,71] Second, substance use can be a normative and social behavior in adolescence, especially for males.[6,62] Third, both alcohol and marijuana can give the illusion of relieving depressive symptoms.[42,57] Fourth, females may have learned to expect more negative consequences from violating role norms in general, as parental regulation tends to be stronger and last longer for female children.[66] Fifth, even if males and females have equal strain in parental relationships as a consequence of substance use, females are more perceptive of interpersonal stress and have stronger negative reactivity to it compared to males.[10,11] Thus, we expect females are more likely to experience a stress response from substance use compared to males.

As implied above, adherence to gender norms is an important potential mediator for both the Self-Medication (Hypothesis 3) and Stress Models (Hypothesis 4). For Self-Medication, we hypothesize depressive symptoms will be positively associated with gender norm adherence for both males and females, though for different reasons. For males, we predict depressive symptoms will lead to greater adherence to masculine norms as a means of compensating for the vulnerability of internalizing symptoms.[65] By comparison, for females, we predict depressive symptoms will also lead to greater adherence to feminine norms, but as a means of emotional regulation (e.g., talking with friends) rather than compensating.[123] Because risk taking is "masculine," we expect adherence to gender norms will be positively associated with substance use for males and negatively associated for females.[64] For the Stress Model, we similarly expect substance use will be positively associated with gender norm adherence for males and negatively associated for females and that gender norm adherence will be negatively associated with depressive symptoms for both males and females.

Finally, it also theoretically plausible that adherence to gender norms may moderate rather than mediate the associations between substance use and depressive symptoms. For example, depressive symptoms may be more positively associated with later substance use among males who subscribe more to masculine gender norms and therefore have a stronger incentive to self-medicate. We hypothesize the Self-Medication pathway will be moderated by adherence to gender norms such that the positive association will be stronger for males who are more gender norm-adherent compared to males who are less adherent. For females we hypothesize the negative association between depression and later substance use will be stronger among females who are more adherent compared to females who are less adherent (Hypothesis 5).[64,65] For the Stress Model, substance use may be more strongly associated with later

depressive symptoms for females who are highly adherent to feminine gender norms as they may perceive substance use as antagonistic to these gender norms and thus have a stronger depressive response.[10,11,18] Indeed we hypothesize the positive association between substance use and later depressive symptoms will be stronger for females who adhere more to feminine norms compared to females who are less adherent, and that the overall association will be negative for males and stronger for those who are more adherent to masculine norms compared to those who are less adherent (Hypothesis 6).

Methods

Sample

The National Longitudinal Study of Adolescent to Adult Health (Add Health) is a nationally representative, longitudinal school-based sample of U.S. adolescents who were in grades 7-12 in the 1994-95 school year (Wave I).[78] Four subsequent in-home interviews have followed the respondents into young adulthood. The analysis sample is restricted to respondents interviewed in emerging adulthood (Wave III, ages 18 to 26) and young adulthood (Wave IV, ages 24 to 32) with valid sampling weights (N=12,288) and complete data on all variables of interest (N=9816, 80%). Wave II data were not used as Wave I seniors were excluded by design. Details of the Add Health study and design are described elsewhere.[78] All Add Health protocols were approved by the Institutional Review Board at the University of North Carolina, Chapel Hill. These analyses were deemed exempt.

Measures

Depression: We used the Center for Epidemiologic Studies Depression Scale (CES-D), which measures symptoms but is not a diagnostic tool.[76] Shorter versions of the scale have been previously validated, including a seven-item measure.[124] We used the nine items available at

each wave as prior Add Health analyses have done. Items ask about frequency of symptoms and answers are scored from 0 to 3, indicating rarely to most of the time; the summed score ranges from 0 to 27. Though the measure captures symptom frequency over the past week, the 12-month re-test reliability is high.[76]

Substance use: Substances include alcohol (binge drinking) and marijuana. In Add Health, substance use frequency questions capture use patterns ranging from experimental to heavy. Binge drinking frequency was assessed for the past year with an ordinal variable ranging from 0 (none) to 6 (every day or nearly every day) at each wave. Marijuana use frequency was assessed for the past month with a similar ordinal variable at Wave IV, but with a continuous measure at Waves I and III asking about instances of use rather than days of use. To make the measures of marijuana use frequency comparable across the waves, days of marijuana use were derived (i.e., one instance of use translated to one day of use) at Waves I and III and then these frequencies were made ordinal to align with the measure of marijuana use at Wave IV.

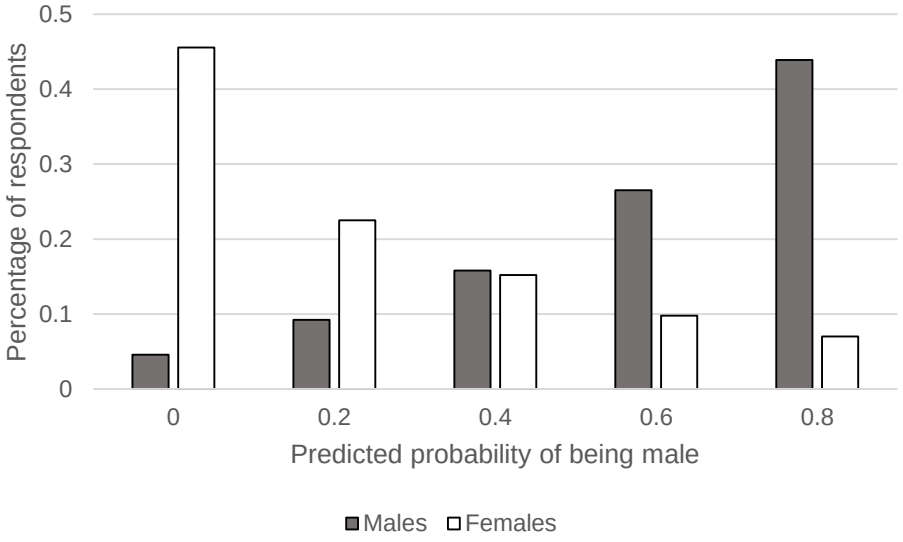
Sensation seeking: Previous exploratory and confirmatory factor analyses of 16 sensation seeking items in Wave III found items all loaded onto one sensation seeking factor.[58] We averaged nine of the items asked of all respondents at Wave III (Cronbach's alpha=0.85, min=1, max=5). Items ask respondents to identify on a 5-point Likert scale how true a statement is for them (e.g., "I often try new things just for fun or thrills, even if most people think they are a waste of time").

Stress: We used two biomarkers as indicators of stress at Wave IV. High sensitivity C-reactive protein (CRP) is a biomarker for inflammation.[48,96,97] Based on established guidelines, we coded CRP levels above 3 mg/L as indicating chronic stress.[94] Epstein-Barr Virus (EBV) is a biomarker of immune function.[78,101] EBV values were left continuous and log transformed to

address negative skew (mean=4.8, standard deviation=0.67), as prior studies have done.[105] Levels of CRP (mg/L) and EBV (AU/ml) were collected via dried whole blood spots in Wave IV of Add Health. The CRP measure has acceptable reliability (ICC = 0.70, 95% CI= 0.59, 0.81) and the EBV measure reliability is excellent (ICC=0.97, 95% CI =0.96, 0.98).[101] A wide range of controls adjusted for health issues or stressful life events that could inflate CRP or EBV (see Chapter 1 for full details).[101]

Adherence to gender norms: Adherence to gender norms was captured with an empirical measure of the degree to which respondents' behaviors were concordant with the most gender-typical behaviors of their same-sex peers at Wave III. This innovative measure, Adherence to Gender-typical Behavior (AGB), was created by Fleming, Halpern, and Harris at all four waves of Add Health data.[92] The items in AGB are highly correlated with biological sex and vary slightly between the waves, allowing for developmental change in the norms. The items include individual behaviors (e.g., exercising) and states of being (e.g., weight self-perception). The items were used in a logistic regression model to create predicted probabilities of being male (e.g., a predicted probability of 0.99 indicates a 99% chance of being male and a 1% chance of being female). This method of measure development has been used previously.[89,91] As the predicted probabilities were skewed, rank percentile scores were created for males and females separately for the analyses (e.g., females with a percentile of 0.85 exhibited greater adherence to female-typical behavior at that wave).

Figure 3.1: Distribution of males and females by predicted probability of being male (Wave III)



Controls: Substance use patterns and depressive symptoms vary by sociodemographics, so we controlled for respondents self-identified race/ethnicity (Hispanic and non-Hispanic White, Black, Asian, Native American, and Other) and educational attainment of both the respondent's parents and the respondent (less than high school, high school graduate, some college, or college graduate or higher). Education is a proxy for socioeconomic status.[4] Respondent's age at the wave at which the dependent variable was measured was included as substance use can vary substantially by age and the age ranges are fairly wide within waves. Also, binary variables indicating levels of the dependent variable before Wave I were created from a retrospective Wave I measure and included drinking an alcoholic beverage, using marijuana, and a depression diagnosis. Finally, frequency of childhood maltreatment (emotional, physical, or sexual abuse and/or supervisory neglect) was included as it can be shared risk factor for both substance use and depression in adulthood.[80]

Analyses

We used linear and logistic regressions to test the mediation and moderation hypotheses. For the mediation models there was a dependent variable measured in young adulthood (Wave IV), an independent variable measured in adolescence (Wave I) and a hypothesized mediator measured in emerging or young adulthood (Wave III or IV). Iterative regression models tested the associations between the independent and dependent variables, independent variable and hypothesized mediator, and all three. We examined the direction and significance of the associations to identify mediation, blending the traditional Baron and Kenny model with the more contemporary approach of assessing only the estimate of the indirect effect.[115] Specifically, we identified mediation as either changes in a significant relationship between the independent and dependent variables or significant relationships between the independent variable and the mediator as well as between the mediator and the dependent variable. For the moderation models, we tested moderation of the relationship between the independent and dependent variables between Waves I and IV as well as between Waves III and IV. We examined the significance of the interaction term to identify moderation, graphed the moderation relationship at typical values, and then tested if these slopes were significantly different from zero. All regression models included a lagged measure of the dependent variable to control for prior levels of the dependent variable.

Results

Table 3.1 outlines characteristics of the analytic sample. Of note, there is meaningful variation in the hypothesized mediators. For example, 30% of males and 48% of females have elevated levels of CRP. Second, females have an average level of depressive symptoms that is at least one point higher than the average for males across the waves. Finally, there are meaningful

levels of substance use, even in adolescence. For example, approximately 30% of adolescent males reported binge drinking in adolescence and 60% report binge drinking in young adulthood; binge drinking increases from 25% to 45% for females.

Table 3.1: Characteristics of the mediation analysis sample

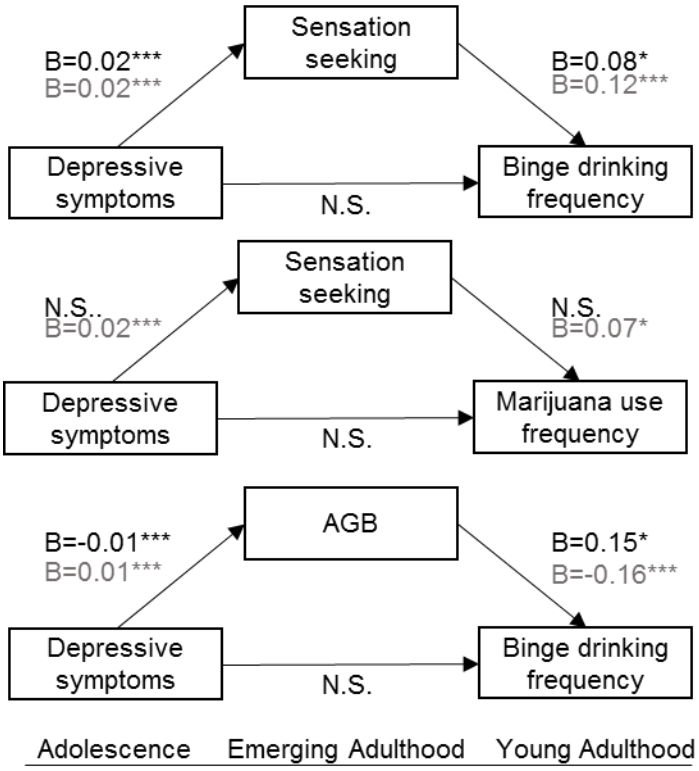
Hypothesized mediator[a]	MALES (n=4323) n (weighted %) or mean (SD)[a]	FEMALES (n=5493) n (weighted %) or mean (SD)
Sensation seeking (Wave III), m	3.0 (0.9)	2.4 (0.8)
CRP (WIV)		
<3 mg/L	3026 (70.0)	2848 (51.8)
>3 mg/L	1297 (30.0)	2645 (48.2)
EBV log AU/ml (WIV), m	4.7 (0.7)	4.9 (0.7)
	MALES (n=4323)	
	Wave I	Wave III	Wave IV
Depressive symptoms (0-27), m	5.0 (3.8)	3.9 (3.6)	4.6 (3.7)
Binge drinking frequency			
None	3060 (70.4)	1735(37.2)	1857(40.9)
1 or 2 days/year	388 (9.0)	669 (15.2)	726 (17.3)
Once per month or less	286 (6.5)	511 (12.7)	580 (13.2)
2-3 days/month	238 (5.6)	521 (12.9)	453 (11.0)
1-2 days/week	226 (5.6)	615 (15.6)	448 (11.0)
3-5 days/week	86 (2.1)	223 (5.3)	195 (5.1)
Every day/almost	39 (0.1)	49 (1.2)	64 (1.4)
Marijuana use frequency			
None	3668 (85.4)	3121(71.1)	3394(77.1)
1 day	158 (3.3)	211 (4.9)	171 (3.9)
2 or 3 days	159 (3.4)	201 (4.9)	154 (4.1)
1 day/week	69 (1.7)	118 (3.0)	45 (1.2)
2 days/week	63 (1.5)	107 (2.5)	108 (2.5)
3-5 days/week	88 (2.0)	229 (5.8)	165 (3.8)
Every day/almost	118 (2.7)	336 (7.9)	286 (7.4)
	FEMALES (n=5493)		
	Wave I	Wave III	Wave IV
Depressive symptoms (0-27), m	6.3 (4.5)	4.9 (4.2)	5.6 (4.3)
Binge drinking frequency			
None	4208 (75.2)	3240(55.4)	3222(56.0)
1 or 2 days/year	557 (10.8)	984 (18.1)	977 (18.9)
Once per month or less	203 (6.1)	537 (11.2)	534 (10.3)
2-3 days/month	203 (3.8)	335 (6.9)	410 (8.0)
1-2 days/week	136 (2.5)	297 (6.3)	247 (4.5)
3-5 days/week	56 (1.1)	82 (1.8)	82 (1.6)

Every day/almost	27 (0.1)	18 (0.2)	21 (0.3)
Marijuana use frequency			
None	4816(87.2)	4533(80.8)	4840(87.5)
1 day	179 (3.3)	244 (4.8)	159 (3.3)
2 or 3 days	192 (3.8)	192 (3.7)	117 (2.2)
1 day/week	100 (1.6)	116 (2.2)	45 (6.5)
2 days/week	68 (1.3)	114 (2.3)	73 (1.3)
3-5 days/week	81 (1.6)	130 (2.7)	91 (2.0)
Every day/almost	57 (1.3)	164 (3.6)	168 (3.1)

[a]AGB is not included in this table because it is a rank percentile score (e.g., min=0.01, max=0.99, mean=0.5)

Figure 3.2 displays the key regression results from all mediation analyses (full results in Appendix 3). There were no significant associations between the independent and dependent variables in any of the models, so results will only be presented if there were significant associations between the hypothesized mediator and both the independent and dependent variables. There were no significant results for the Stress Model. For the Self-Medication Model, in the models testing sensation seeking as a potential mediator, there were significant positive associations between depressive symptoms and sensation seeking and between sensation seeking and later binge drinking frequency for both males and females. There were also significant positive associations between depressive symptoms, sensation seeking and later marijuana use frequency, but only for females. In the models testing AGB as a potential mediator, there were only significant results for binge drinking frequency and not marijuana use frequency. The association between depressive symptoms and AGB was positive for females and negative for males. The association between AGB and binge drinking frequency was positive for males and negative for females.

Figure 3.2: Significant coefficients from the regression models testing mediation

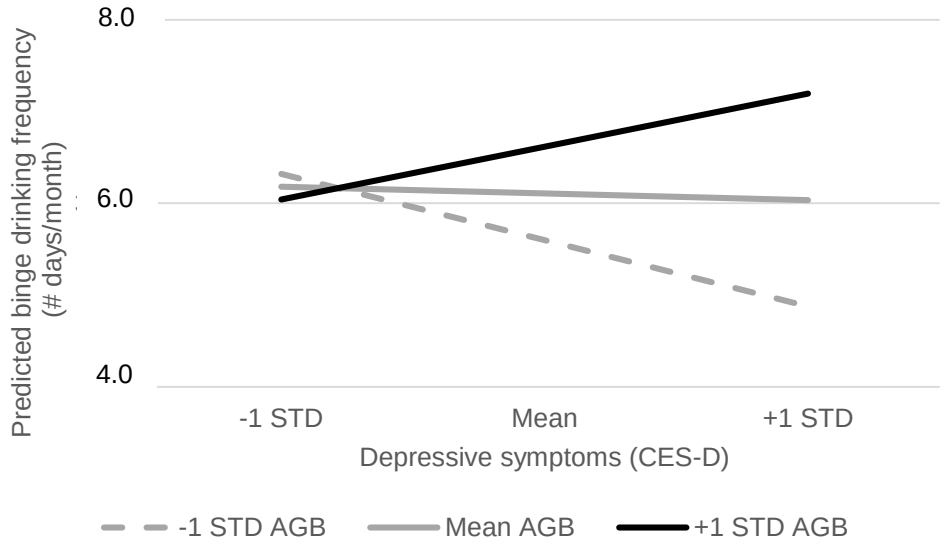


NOTE: Top coefficients with black text represent the regression results for males. Lower coefficients with gray text represent the regression results for females. N.S. = not significant

None of the moderation models tested between adolescence and young adulthood were significant and only one model result was significant for the moderation models tested between emerging and young adulthood. For the latter, the association between depressive symptoms at Wave III and binge drinking frequency at Wave IV is significantly stronger for males with higher AGB scores compared to males with lower AGB scores (see Table 3.7.1). Figure 2 displays the moderation pattern at typical values where the independent variable (depressive symptoms) and moderator (AGB) are graphed at the mean value plus and minus one standard deviation. We tested whether the slope of predicted values was different from zero for each AGB group displayed. The slope for males with a mean AGB value was not significantly different from zero ($F=0.07$, $p=0.79$). However, the slope for males with AGB values one standard deviation below the mean was negative and significantly different from zero ($F=4.14$, $p<0.05$).

For males with an AGB value one standard deviation above the mean the slope was not significantly different from zero (F=2.09, p=0.15), but the relationship is in the expected direction.

Figure 3.3: AGB moderation of the association between depressive symptoms and later binge drinking frequency for males



NOTE: The y axis in the figure was scaled from the ordinal binge drinking frequency measure to approximate days per month to ease interpretation.

Discussion

We used Add Health data to test three hypothesized mediators and one hypothesized moderator of the longitudinal relationships between binge drinking, marijuana use, and depressive symptoms from adolescence to young adulthood. Overall, significant possible mediation and moderation results were found for the Self-Medication Model but not the Stress Model, meaning Hypotheses 2, 4, and 6 were not supported. We found support for the hypotheses (1 and 3) that the relationship between depressive symptoms and later binge drinking frequency is mediated by AGB and sensation seeking. There is also support among males for AGB as a moderator of the relationship between depressive symptoms and later binge drinking

frequency; the relationship is positive for males with higher AGB scores and negative for males with lower AGB scores, supporting our Hypothesis 5 that the Self-Medication Model would be better supported for more gender-adherent males.

The Self-Medication models testing sensation seeking as a mediator supported the hypothesized associations for males but not females. For males, the expected positive associations between depressive symptoms and sensation seeking, and between sensation seeking and substance use were found for binge drinking but not marijuana use. Prior studies have found connections between sensation seeking and alcohol use.[59] Our findings extend that work, suggesting that depressive symptoms may be a proximal cause of sensation seeking. For marijuana use among males, our results do not support sensation seeking as a mediator. This is consistent with a prior analysis that found sensation seeking did not confound the association between depressive symptoms and marijuana use.[7] Contrary to our hypotheses for females, the associations between depressive symptoms and sensation seeking were positive in both the binge drinking and marijuana use models. Sensation seeking was also positively associated with use of both substances, as expected. These results challenge the notion that females would be less likely to experience sensation seeking in response to depression.[5,17,21,60] These results also indicate sensation seeking is a potentially relevant mediator for the relationship between depressive symptoms and marijuana use for females but not males.

Counter to our expectations, no mediation associations were statistically significant for the Stress Model. There are several potential explanations. First, the tests of whether stress biomarkers mediated the association were complicated by the fact that the biomarkers were collected at Wave IV. This means we were testing the association between an independent variable that preceded both the mediator and dependent variable by 14 to 15 years, which was

not the case for the Self-Medication Models. Second, by using continuous measures of the independent and dependent variables, we were testing a subtle relationship that we are assuming is linear. It is possible that variations at the extremes of the distribution are more important. Third, developmental change may explain why depressive symptoms in adolescence were significantly associated with AGB in emerging adulthood and yet AGB in emerging adulthood was not significantly associated with depressive symptoms in young adulthood. Adolescence and emerging adulthood can be a time of gender intensification, where gender roles become rigid as identities are forming, and then later become more fluid in young adulthood.[125] Therefore, depressive symptoms may be more strongly related to gender-typical behavior through adolescence into emerging adulthood as gender identities are solidifying rather than later in development.

In the models testing AGB as a potential mediator of the Self-Medication Model, the support for our hypotheses was mixed. The association between depressive symptoms and AGB was positive for females, as expected, but negative for males—contrary to our hypothesis. The unanticipated negative association between depressive symptoms and later AGB for males could also be explained by gender intensification. From adolescence into emerging adulthood, when males may be expected to increase their gender-adherence, males struggling with depressive symptoms may be less able to do so. They may simply have less motivation or ability to engage in male-typical behaviors. Males may also have less opportunity to engage in male-typical behaviors as a consequence of social isolation that may result from their depressive symptoms. In line with our hypotheses, the association between AGB and binge drinking frequency was positive for males and negative for females.

The moderation results add nuance to the mediation results by suggesting the relationship between depressive symptoms and later substance use significantly varies based on a male's AGB scores. Specifically, the Self-Medication Model for binge drinking may be salient only for gender-adherent males. Perhaps males who are more gender-adherent have stronger incentive to self-medicate depressive symptoms as they, or their peers, may interpret depression as a sign of vulnerability.[64,65] Alternatively, self-medication of depressive symptoms with alcohol may be a reflexive emotion regulation strategy.[17] Males who are less adherent to male-typical behavior are, due to the construction of our measure of gender-adherence, by default more adherent to female-typical behavior, which may include a wider array of emotion regulation tools.

The findings of this study should be considered along with its limitations. First, some of the mediators were measured in emerging adulthood and some only in young adulthood meaning the mediators were not tested in identical temporal circumstances. Further, though we were able to control for prior measures of the dependent variable, we were not able to control for prior measures of the mediators, meaning low AGB in adolescence could precede adolescent depressive symptoms, for example. Second, the ordinal measures of substance use frequency were treated as continuous. However, we repeated the significant mediation models with the ordinal measures translated into an approximately continuous midpoint frequency measure, and the results were consistent. Third, though the length of time between the waves does enable us to examine the entire developmental trajectory from adolescence to young adulthood, it may reduce the likelihood of finding a significant association given the long time period (14 to 15 years) between measures at Waves I and IV, versus the shorter time periods between Waves I and III (approximately 7 years) and Waves III and IV (approximately 6-7 years). Finally, no significant associations were found between the independent and dependent variables in the mediation

models, perhaps due to the long timespan between them. However, several models found significant associations between the independent variable and the mediator and between the mediator and the dependent variable, which is sufficient criteria for assessing potential mediation.[115]

This analysis used longitudinal, nationally representative data to test potential mediation and moderation of the relationship between substance use frequency and depressive symptoms from adolescence to young adulthood. We found support for sensation seeking and AGB as potential mediators in the Self-Medication Model. We also found AGB may act as a moderator of the linkage between depressive symptoms and binge drinking among males. In contrast, we found no evidence to support stress or AGB as potential mediators in the Stress Model.

These findings have implications for public health and future research. First, the USPSTF recently updated its depression screening guidelines to include adolescents, and the ACA lists depression and substance use screening as covered preventive services.[2,38] The results from the Self-Medication mediation models indicate adolescents screening positive for depression or an increase in depressive symptoms could also be screened for sensation seeking to target substance use prevention programs accordingly. Second, the results from the models testing gender adherence as a mediator and moderator indicate depression and substance use prevention/treatment programs could benefit from tailoring on biological sex or even aiming to be gender-transformative by challenging the gender norms that promote substance use and self-medication.[126] Future research should test support for the Stress Model overall as well as other mediators (e.g., indicators of social rather than biological stress).

CHAPTER 4– CONCLUSIONS & IMPLICATIONS FOR CARE

Conclusions

In Chapter 2, linear mixed effects models were used to evaluate the Self-Medication and Stress Models and test whether hypothesized associations are moderated by sex. Findings support the Self-Medication Model for marijuana use for males and females, and provided modest support for the Stress Model for both binge drinking and marijuana use, especially for females. In Chapter 3, regression models stratified by sex were used to test mediation and moderation hypotheses to better understand the processes embedded in the Self-Medication and Stress Models. It appears sensation seeking may mediate self-medication processes involving binge drinking (indirect effect estimate B=0.24) and marijuana (B=0.14) for females, but only binge drinking for males (B=0.16). It remains unclear what mediates self-medication with marijuana in males. Adherence to Gender-typical Behavior also appears to play a role in self-medication with binge drinking for both males (B=-0.012) and females (B=-0.15). The complex sampling design in Add Health precluded testing whether these indirect effect estimates are significantly different from zero and it is possible the estimate for AGB for males is not large enough to indicate mediation. The moderation results help us interpret these mediation results because they indicate the self-medication of depressive symptoms with binge drinking may only be relevant for males with above average adherence to gender norms.

From these findings, the conclusions of these analyses are multiple. First, adolescents may self-medicate depressive symptoms with substance use, possibly via sensation seeking, but this may only be relevant for gender-adherent males. Second, depressive symptoms may increase

gender-adherent behavior for females and decrease it for males, both of which are then likely to decrease later binge drinking. Third, persistent binge drinking or marijuana use from adolescence into young adulthood appears to be concurrently positively linked with depressive symptoms, especially for females.

Across all models, two results were particularly surprising. First, it is not clear why the Self-Medication Model was indirectly supported for binge drinking in the mediation models but not in the growth curve models. However, the lack of significant direct effects between depressive symptoms and later binge drinking in the mediation models still make the results consistent. The results interpreted as support of potential mediation of this relationship by sensation seeking and AGB could instead indicate depressive symptoms are associated with sensation seeking and AGB, which are then associated with binge drinking and that there is in fact no direct relationship between depressive symptoms and later binge drinking. Second, across all models only two results provide modest support for the Stress Model. From the growth curve models, the longitudinal measures of both marijuana use and binge drinking frequencies were positively associated with the depressive symptom growth curve, and this association was significantly moderated by biological sex. These findings indicate significant positive concurrent associations between substance use frequency and depressive symptoms that were stronger for females compared to males. The other result providing modest support for the Stress Model came from the regression models testing if stress biomarkers or AGB mediated the Stress Model. No models yielded significant associations between both the independent variable and mediator, and between the mediator and the dependent variable, but one finding warrants attention. For females, adolescent marijuana use frequency was significantly positively associated with EBV

levels in young adulthood, as we hypothesized, indicating a link between marijuana use and stress for females.

The lack of significant results for the Stress Model is surprising, especially as a prior study using data from Add Health found support for the Stress Model and evidence against the Self-Medication Model. In comparing their methods to the ones used in these papers, one key difference emerges. Their study was examining the relationship between depression and clusters of experimental and higher risk behaviors including both substance use and sexual risk behaviors.[5] It is possible sexual risk behaviors alone were driving the association with later depression or that the combination of sexual risk and substance use are important to the association. In general, another main methodological difference between these and prior analyses is that many papers measured depression or substance use dichotomously, capturing those with real or probable depression diagnoses and/or very high levels of substance use or even abuse/dependence. By using continuous measures of both substance use frequency and depressive symptoms, we were testing for smaller, fine-grained associations that were assumed to be linear across the distributions of each measure (e.g., as binge drinking frequency increases, later depressive symptoms increase linearly). It is possible that the relationship between substance use and depression is not linear across the distribution and that there are points on the distribution at which point the relationship becomes much stronger, something binary measures are better positioned to capture.

Innovation

The analytic methods for this project addressed many existing gaps in the literature. First, the analyses in Chapters 2 and 3 tested both potential directions of the association between substance use and depressive symptoms as well as differences in the association by sex, whereas

the majority of prior studies did not. Second, the use of growth curve analyses in Chapter 2 represents a methodological improvement upon much prior literature. Third, the use of longitudinal data capturing the age range from 11 to 34 enabled us to examine the interplay of substance use and depressive symptoms across the developmental trajectory, where prior studies are heavily concentrated in adolescence. Finally, the use of Add Health data maximized the generalizability of these results for the field as it is a large, diverse, and nationally representative sample.

The use of unique mediators furthered the innovation of this project. A new measure of gendered behavior norms was tested as a potential mediator. Historically, gender has been conceptualized and measured as a trait, an ideology, or even as the stress related to adhering to gender norms.[83] While valuable, static measures miss both developmental and historical changes in gender norms and fail to capture how gender influences behavior at an individual level.[64,88] The AGB measure captures the degree to which respondents' reported behaviors are concordant with those of other Add Health respondents of their same sex at a given point in time.[92] AGB was tested as a potential mediator and moderator in both the Stress and Self-Medication Models and thus helped explain sex differences in the results from Chapter 2. From prior analyses we know the AGB is significantly positively associated with substance use for males and significantly negatively associated with substance use for females; these results align with similar previous analyses using trait or ideology measures of gender thus buffering the construct validity of the measure.[71–74,93] This empirical approach to measuring gender based on individual behavior and preferences relative to peers has been endorsed by previous research in the field.[89–91]

This study also used biomarkers as objective measures of stress, a hypothesized mediator. The biomarker data in Add Health allowed us to measure respondent's inflammation and immune responses as biological indicators of stress. These measures offered insight that is not available through the self-reported measures of perceived stress as prior research shows the level of stress individuals perceive and/or report can be strongly influenced by their sex and the gender norms they are ascribing to.[10,11,69] Biomarker data are able to get beneath the skin and more accurately assess a respondent's stress level and warrant future use, despite the lack of significant findings in this project.

Limitations

The analyses in this project had limitations concentrated in data constraints, analytic constraints, conceptual grounding, and measurement error. First, with observational rather than experimental data, we cannot infer causality from the associations identified. Second, though growth curve models present numerous advantages over both regression and analysis of variance methods, including the ability to examine individual trajectories over time, control for time-invariant unobservables, improved ability to test reciprocal relationships, and increased statistical power, the models are still vulnerable to endogeneity from time-varying unobservables.[6,21,81] For example, a genetic predisposition to substance use and depressive symptoms, if time invariant, was controlled but it is possible that a time-varying unobservable that is associated with both substance use and depressive symptoms could be driving the observed associations. More statistically advanced methods were available to analyze these data; however, these methods did not align with the research questions as well as growth curve modeling. For example, latent class growth analysis and growth mixture modeling are powerful methods for analyzing developmental trajectories over time. However, what distinguishes them from growth curve

analyses is the presence of a categorical latent variable that then enables estimation of different growth curves for different classes of respondents.[127] Examining different growth curve patterns is valuable but did not fit with the aims of this project as the methods are not as well suited for examining relationships between growth curves nor for examining moderation. Further, the models can find local solutions and struggle to converge, and with only three time points of data, it is unlikely we would find curves more diverse than increasing, decreasing, or remaining consistent.[127] The last analytic constraint is that the analyses had 80% power to detect differences in depressive symptoms, for example, as small as 0.12 and smaller differences than this were significant and interpreted. However, the lower power for these smaller differences means there was a higher chance of failing to reject the null hypothesis when it was false (type II error), which is not ideal though tolerable.

Third, the conceptual bases for the analyses were grounded in the Life Course Model, but focused only on individual change over time and did not consider the individual's context, which almost certainly influence the key variables of interest. For example, parental alcohol socialization (e.g., permissive messages, attitude towards children sipping alcohol) can be associated with differentiation in susceptibility to initiation of alcohol use among elementary school children.[128–130] Parental characteristics therefore may increase the risk of alcohol use of Add Health respondents before the Wave I data were collected. Similarly, information on the respondent's peers and their substance use is not included and it likely influences substance use frequency.[131] Though highly relevant for substance use, the individual's context was beyond the scope of the research questions of this project. Fortunately, the growth curve analyses helped control for parental socialization and peer substance use to the extent these factors were time invariant.

A fourth limitation of this work is vulnerability to measurement error. For example, the complete list of items for the CES-D and sensation seeking scale were not available either for the whole sample or at all waves of interest, meaning condensed scales were used. However both measures had high Cronbach's alpha values indicating good reliability/coherence. Also, the substance use frequency measures were originally ordinal or were transformed to be ordinal in the case of marijuana use frequency in Waves I and III and yet were analyzed as continuous measures. This was a constraint in the data but multiple sensitivity analyses using midpoint frequency measures, which were more continuous, and comparing the results or the BIC estimates indicated the measures were comparable. The measures used to capture the frequency of child maltreatment were diverse, though a shared limitation of these measures is that children may not remember it or the maltreatment can happen before children are capable of forming memories, meaning the measure will not control for all child maltreatment. Finally, the index of stressful life events was useful as a control variable for the biomarker mediation analyses, though the measure did not capture how respondents felt about the assumed stressors in their lives (e.g., unplanned pregnancy), nor did it weight some experiences (e.g., being deployed to a combat zone) more than others (e.g., getting arrested). Fortunately, we had repeated measures of most variables, and all of the key variables of interest, which helped to decrease measurement error.[32]

Implications for Health

The conclusions of these analyses, that adolescents—depending on gender-adherence—may self-medicate depressive symptoms with substance use, and that persistent substance use—especially for females—seems concurrently positively linked with depressive symptoms, have implications for health. Specifically, how to target and integrate screening adolescents for

substance use and depressive symptoms as well as how to tailor prevention and/or treatment programs by sex and/or gender.

Screening adolescents for either substance use or depression is uncommon in the United States. A survey of pediatricians revealed fewer than half report screening for substance use and fewer than a quarter felt comfortable providing comprehensive screening or offering a referral to treatment.[33,36] For depression screening, a survey of physicians estimated they screen only 46% of their patients and this statistic is likely much lower for adolescent patients.[34] Infrequent screening means cases are missed and care is not received. Less than 10% of adolescents with substance use problems receive treatment, and a review from the USPSTF in 2009 estimated the vast majority of adolescents with depression received no treatment of any kind.[2,33,35] The lack of screening and treatment for both conditions is problematic. The National Institute of Mental Health estimates half of all substance use and mental health cases begin by age 14, so deficiencies in screening and treatment in adolescence miss opportunities to prevent these conditions or to treat them early.[2,35–37]

The importance of screening adolescents for substance use and mental health issues is not a new concept. In 1998 the Society for Adolescent Medicine published a position paper asserting that the growth of managed care provided an opportunity for adolescent health care to include more screenings, prevention, and coordinated care. Substance use and mental health were included as necessary screens.[132] The American Academy of Pediatrics (AAP), the American Medical Association, the Maternal and Child Health Bureau, the Surgeon General, and the Centers for Medicare and Medicaid Services (CMS) all endorse screening adolescents for substance use and/or mental health issues.[36,37] Fortunately, the ACA recently strengthened the

policy framework to provide screening by covering alcohol, drug use, and depression screening for children and depression and alcohol misuse screening for adults.[38]

However, just because screening services are covered (meaning insurance companies cannot charge a copay for them) does not mean providers will offer the screening.[38] Indeed, other supportive policies existed before the ACA; the AAP includes psychological screening in their Bright Futures screening guidelines from infancy until age 21, and CMS includes substance use and mental health screening under the Early and Periodic Screening, Diagnostic and Treatment benefits for well child exams.[37] Despite these recommendations screening has remained low. Physician knowledge of the screening guidelines is important but not the only barrier. In one study physicians in community health centers *reported* screening 64% of their patients for depression—indicating awareness of the guidelines—but only *documented* screening 3% of them, though these clinics lacked electronic medical records, which likely decreases compliance.[133] Focus groups with pediatricians across a wide range of practice settings identified a lack of time, uncertainty about how to respond to a positive screen, and perceived lack of referral or treatment resources as the main barriers to screening adolescents for both substance use and depression.[2,39] Indeed, a national survey of residency programs found less than one third of pediatric residency programs required training in how to diagnose and treat substance use disorders.[134] Fortunately, both the National Institute on Drug Abuse (NIDA) and the AAP have advocated for training physicians how to provide screening, brief interventions, and referral to treatment (SBIRT) for substance use and depression in adolescents.[36,37] A meta-analysis of brief interventions for heavy alcohol use found brief interventions were as effective as more extensive interventions with a 27% average effect size, which represents the proportion of standard deviation change in alcohol consumption.[135] Further, randomized trials of SBIRT training for

physicians indicate they can be effective in changing physician behavior and that the interventions are implementable.[136]

As more physicians are trained to provide SBIRT and the policy support for screening grows stronger, more cases are likely to be identified, thereby increasing the need to provide and improve treatment. In a sample of adolescents in a managed care plan, 81% who sought substance use treatment had a primary care visit in the previous year so screening in primary care has an opportunity to catch cases.[35] One study of substance use screening of adolescents in primary care found that 15% of patients screened positive for a substance use problem and that the lifetime prevalence of depression among adolescents could be as high as 20%.[2,137] As more adolescents are screened, more cases will likely be detected, and evidence suggests adolescents who screen positive are likely to pursue treatment.[2] More adolescents seeking treatment provides an opportunity to integrate substance use and mental health care. As estimates of comorbidity in clinical samples are as high as 50%, these cases are more the rule than the exception.[33,35] Despite the prevalence of comorbidity, substance use and mental health care are typically isolated from each other in the United States, even though evidence suggests trying to treat the conditions in isolation results in a higher risk of treatment failure.[138,139] Further, integrating substance use and psychiatric care into primary care can produce better outcomes and is even capable of preventing some conditions from developing in the first place.[35] Given this, it is encouraging that many policy and research institutions are advocating for integration (e.g., the Agency for Healthcare Research and Quality, American Society for Addiction Medicine, Substance Abuse and Mental Health Services Administration), and recent Federal parity laws ensure coverage of mental health and substance use treatment equal to the coverage of other medical issues.[35]

While screening all adolescents for all substance use and mental health problems and full integration of care is ideal, the time constraints of physicians and resource constraints in the system remain. Not only are universal programs costly and difficult to implement, the resources are likely better spent on the smaller proportion of adolescents at elevated risk rather than on all adolescents.[36] The results of this study provide insight into how to target screening and integrated care to those most at risk. For example, the findings indicate adolescents screening positive for depression or an increase in depressive symptoms should also be screened for marijuana use and potentially linked to marijuana use programs in addition to depression treatment. Also, it seems screening for binge drinking could be targeted towards youth screening positive in sensation seeking and/or increases depressive symptoms. Sensation seeking screening of pre-adolescents has been recommended as a means of catching those most at risk of substance use and several screening tools exist with good psychometrics and acceptability.[140] If implemented, this could inform further targeting of who to screen for substance use among those who have already screened positive for depression or an increase in depressive symptoms.

The results from this study also inform how substance use and depressive symptoms, and the relationship between them, can function differently for males and females. These differences indicate prevention and treatment programs could benefit from tailoring by sex, as NIDA has indicated.[126] For example, as males tend to have and employ fewer emotional regulation strategies than females, prevention and treatment programs would do well to teach more emotional regulation strategies to males.[17] Also, beyond targeting certain services towards males or females, challenging harmful gender norms could boost overall program efficacy. For example, as adherence to masculine norms can make substance use and self-medication more

likely, programs would do well to try to challenge the links between masculinity and substance use (e.g., "real men can hold their liquor") with gender transformative programs.[64,141]

Increases in screening for substance use and depression and increases in integrated screening, prevention and treatment will increase costs, but they will likely be far cheaper than the costs of maintaining the status quo. The costs of depression in the United States are estimated to be approximately $210 billion annually. Although this cost estimate is not specific to adolescents, it is still relevant as untreated depression is likely to persist or relapse.[142] Underage drinking costs the United States approximately $68 billion per year; drug use among adolescents and adults is estimated to cost $181 billion per year; and adding in lost productivity, social problems (e.g., violence), and broader health implications brings the total cost of alcohol and drug abuse to $600 billion annually.[35,143] To put these numbers in perspective, the Department of Defense budget for 2017 is $582 billion, and this is the largest portion of discretionary spending for the Federal government.[144] In short, we can afford to do better.

APPENDIX 2.1: ANALYSES

The appendices include further detail on statistical analyses and results from Chapters 2 (Appendix 2) and 3 (Appendix 3). This information was not included in the chapters either because it was not central to the research questions posed in the chapters or because space constraints did not allow all of the details to be included.

Cigarette smoking frequency was examined as a potential confounder and, though it is correlated with other forms of substance use, it does not share a strong correlation with depressive symptoms. Further, several of the models were tested with and without a control for smoking frequency and the results changed only very slightly, so smoking frequency was left out as a control variable in these analyses.

Fitting linear mixed effects models is an iterative process, and through this process we tried to find the model that best fit the data. With only three waves of data and measures of substance use frequency with constrained variation, the models testing a random slope by age when substance use frequency measures were the dependent variable did not converge, so we did not proceed to testing random slope by age squared. When depressive symptoms were the dependent variable, the models testing a random slope for age did converge, though the estimate of the variance for age was very small in magnitude, so we also did not test a random slope for age squared in these models.

For testing the simple slopes of the significant and relevant moderation results, the contrast statement was used for interactions with at least one categorical variable. For interactions between continuous variables, it was determined if the slope was significant different from zero by looking to the coefficient for the key predictor in the model before the interaction term was added. The contrast results indicate the interactions between longitudinal

measures of substance use frequency and sex in the depressive symptom growth curve models produced simple slopes for males and females that were both significantly different from zero. When depressive symptoms were tested as a predictor for the marijuana use frequency growth curves (Table 2.3.1), the interaction term between an adolescent measure of depressive symptoms and age was significant ($B=0.06$, $p<0.01$, Model 6), though the coefficient for the adolescent depressive symptom measure in Model 5 was not statistically significant, indicating at certain levels of depressive symptoms the slope would not significantly differ from zero.

APPENDIX 2.2: BINGE DRINKING FREQUENCY GROWTH CURVES

Hypothesis 1.3 for binge drinking, that binge drinking frequency will show a non-linear increase then decrease from adolescence to young adulthood and that it will be moderated by sex such that frequencies will be higher for males compared to females, was supported. In Model 1 (Table 2.2.1) the coefficients for age (B=0.46, p<0.001) and age squared (B=-0.01, p<0.001) were significant and retained significance when the covariates were added in Model 2. Further, the interactions between biological sex and both age (B=0.31, p<0.001) and age squared (B=-0.01, p<0.001) were significant, indicating the gap between male and female binge drinking frequency, on average, increases by a third of a point on the binge drinking frequency category rank measure with each one year increase in age, though this pattern has some non-linearity.

The binge drinking frequency growth curves also revealed significant differences in adolescent (Wave I) levels by sociodemographic characteristics and in different ways than the demographic patterns for the marijuana use frequency and depressive symptom growth curves. Compared to Whites, Black (B=-0.45, p<0.001), Asian (B=-0.36, p<0.001), and Hispanic (B=-0.12, p<0.05) respondents had significantly lower adolescent binge drinking frequencies. For parental educational attainment, only respondents whose parents did not graduate high school had significantly lower adolescent binge drinking frequencies (B=-0.15, p<0.01). Respondents who experienced childhood maltreatment (emotional, physical, sexual, neglect) had significantly higher on average binge drinking frequencies in adolescence, though there did not seem to be a pattern by frequency, from most to least: three times (B=0.17, p<0.001), once (B=0.13, p<0.05), and four or more times (B=0.11, p<0.01). Finally, respondents who reported drinking an alcoholic beverage before Wave I had, on average, a starting binge drinking frequency score that

was 0.66 ($p<0.001$) points higher on the binge drinking category rank score compared to respondents who did report drinking an alcoholic beverage before Wave I.

Table 2.2.1: Linear mixed effects models of binge drinking frequency with depressive symptoms tested as a predictor[a]

	M1: Uncondtl[b]	M2: Covariate[c]	M4: Age x Sex	M5: Dep sympt (WI)	M6: Dep sympt (WI) x Age	M7: Dep sympt (WI) x Age x Sex	M8: Dep sympt (longit)	M9: Dep sympt (longit) x Sex
Age	0.46***	0.45***	0.33***	0.50***	0.56***	0.43***	0.46***	0.46***
	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)
Age^2	-0.01***	-0.01***	-0.01***	-0.01***	-0.01***	-0.01***	-0.01***	-0.01***
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Sex (1=Male, 0=Female)		0.49***	-3.01***	0.49***	0.50***	-2.36***	0.50***	0.55***
		(0.03)	(0.37)	(0.03)	(0.03)	(0.42)	(0.03)	(0.05)
Race/ethnicity (White=referent)								
Hispanic		-0.12*	-0.12*	-0.13**	-0.13**	-0.13**	-0.13**	-0.13**
		(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)
Black		-0.45***	-0.45***	-0.46***	-0.46***	-0.46***	-0.46***	-0.46***
		(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)
Asian		-0.36***	-0.36***	-0.38***	-0.37***	-0.37***	-0.37***	-0.37***
		(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)
Native American		0.11	0.11	0.11	0.11	0.11	0.10	0.10
		(0.09)	(0.09)	(0.09)	(0.09)	(0.09)	(0.09)	(0.09)
Other		-0.13	-0.12	-0.13	-0.13	-0.12	-0.13	-0.13
		(0.17)	(0.17)	(0.17)	(0.17)	(0.17)	(0.17)	(0.17)
Parental education (WI) (college=referent)								
< High school		-0.15**	-0.15**	-0.17***	-0.17***	-0.17**	-0.18***	-0.18***
		(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)
High school		-0.06	-0.06	-0.08*	-0.08*	-0.08*	-0.08*	-0.08*
		(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)
< College		-0.06	-0.07	-0.07	-0.07	-0.07	-0.07*	-0.07*
		(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)

Childhood maltreatment frequency (none=referent)							
Once	0.13*	0.13*	0.13*	0.12*	0.12*	0.12	0.12
	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)
Twice	0.07	0.07	0.06	0.06	0.06	0.05	0.06
	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)
Three times	0.17***	0.18***	0.17***	0.16***	0.17***	0.15***	0.15***
	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)
Four or more times	0.11**	0.12**	0.10**	0.09*	0.10**	0.08*	0.08*
	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)
Drank alcoholic beverage before WI	0.66***	0.66***	0.63***	0.65***	0.65***	0.65***	0.65***
	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)
Age x Sex		0.31***			0.25***		
		(0.04)			(0.04)		
Age^2 x Sex		-0.01***			-0.01***		
		(0.00)			(0.00)		
Depression diagnosis before WI			-0.07	-0.06	-0.06	-0.10	-0.10
			(0.08)	(0.08)	(0.08)	(0.08)	(0.08)
Dep sympt (WI)			0.03***	0.42*	<-0.01		
			(0.00)	(0.19)	(0.21)		
Age x Dep sympt (WI)				-0.04	0.01		
				(0.02)	(0.03)		
Dep sympt (WI) x Sex					0.74		
					(0.40)		
Age x Dep sympt (WI) x Sex					-0.10		

						(0.05)		
Age^2 x Dep sympt (WI)					<0.01	<-0.01		
					(0.00)	(0.00)		
Age^2 x Dep sympt (WI) x Sex						0.003*		
						(0.00)		
Dep sympt (longit)							0.02***	0.02***
							(0.00)	(0.00)
Dep sympt (longit) x Sex								-0.01
								(0.01)
Constant	-4.17***	-4.38***	-2.97***	-5.06***	-5.63***	-4.22***	-4.54***	-4.56***
	(0.18)	(0.18)	(0.24)	(0.18)	(0.20)	(0.24)	(0.18)	(0.18)
Variance estimates (SE)								
Respondent ID	0.56	0.36	0.37	0.37	0.36	0.37	0.36	0.36
	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)
Residual	1.51	1.51	1.49	1.50	1.50	1.48	1.50	1.50
	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Depressive symptoms (Dep sympt), longitudinal measure (longit), standard error (SE) unconditional (uncondtl)

[b]Standard errors are beneath the coefficients in parentheses

[c]A random slope for age was tested, but did not meaningfully improve model fit and so was removed from all models

APPENDIX 2.3: MARIJUANA USE FREQUENCY GROWTH CURVES

Hypothesis 1.3 for marijuana use—that marijuana use frequency will show a non-linear increase then decrease from adolescence to young adulthood, and that it will be moderated by sex such that frequencies will be higher for males compared to females—was supported. In Models 1 and 2 (Table 2.3.1) the coefficients were significant with and without the covariates for age ($B=0.30$, $p<0.001$) and age squared ($B=-0.01$, $p<0.001$). Additionally, the interaction terms between biological sex and age ($B=0.23$, $p<0.001$) and age squared ($B=-0.01$, $p<0.001$) were significant, indicating the gap between male and female marijuana use frequency, on average, increases by a third of a point on the marijuana use frequency category rank score with each one year increase in age, though there is non-linearity.

The marijuana frequency growth curves also showed significant variation by certain sociodemographic characteristics and variation that differed from the binge drinking frequency and depressive symptom growth curves. Only respondents identifying as Asian had significantly different marijuana use frequencies in adolescence compared to Whites ($B=-0.15$, $p<0.01$). Marijuana use frequency in adolescence was not found in our models to significantly vary by parental education. Compared to respondents who reported no childhood maltreatment frequency, those who reported maltreatment happened three times ($B=0.19$, $p<0.001$) or four or more times ($B=0.21$, $p<0.001$) had significantly higher marijuana use frequency in adolescence. Finally, those who reported first using marijuana before Wave I had significantly higher marijuana use frequency in adolescence ($B=1.08$, $p<0.001$).

Table 2.3.1: Linear mixed effects models of marijuana use frequency with depressive symptoms tested as a predictor[a]

	M1: Uncondtl	M2: Covariate[b]	M4: Age x Sex	M5: Dep sympt (WI)	M6: Dep sympt (WI) x Age	M7: Dep sympt (WI) x Age x Sex	M8: Dep sympt (longit)	M9: Dep sympt (longit)x Sex
Age	0.30***	0.30***	0.20***	0.31***	0.33***	0.22***	0.31***	0.31***
	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)
Age^2	-0.01***	-0.01***	-0.005***	-0.01***	-0.01***	-0.005***	-0.01***	-0.01***
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Sex (1=Male, 0=Female)		0.28***	-2.30***	0.29***	0.29***	-2.06***	0.31***	0.30***
		(0.03)	(0.36)	(0.03)	(0.03)	(0.40)	(0.03)	(0.04)
Race/ethnicity (White=referent)								
Hispanic		0.01	0.01	0.01	<0.01	0.01	-0.01	-0.01
		(0.06)	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)
Black		0.03	0.03	0.03	0.03	0.03	0.01	0.01
		(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)
Asian		-0.15**	-0.15**	-0.15**	-0.15**	-0.15**	-0.17***	-0.17***
		(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)
Native American		0.08	0.08	0.08	0.08	0.08	0.07	0.07
		(0.10)	(0.10)	(0.10)	(0.10)	(0.10)	(0.10)	(0.10)
Other		0.03	0.04	0.04	0.03	0.04	0.04	0.04
		(0.14)	(0.14)	(0.14)	(0.14)	(0.14)	(0.13)	(0.13)
Parental education (WI) (college=referent)								
< High school		-0.03	-0.03	-0.04	-0.03	-0.03	-0.07	-0.07
		(0.06)	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)
High school		-0.05	-0.05	-0.05	-0.05	-0.05	-0.06	-0.06
		(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)
< College		-0.01	-0.01	-0.02	-0.02	-0.02	-0.03	-0.03

	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)
Childhood maltreatment frequency (none=referent)							
Once	0.06	0.06	0.06	0.05	0.06	0.04	0.04
	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)
Twice	0.05	0.05	0.04	0.04	0.04	0.02	0.02
	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)
Three times	0.19***	0.19***	0.19***	0.19***	0.19***	0.16**	0.16**
	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)
Four or more times	0.21***	0.21***	0.20***	0.20***	0.20***	0.16***	0.16***
	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)
Marijuana use before WI	1.08***	1.08***	1.07***	1.07***	1.07***	1.06***	1.06***
	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)
Age x Sex		0.23***			0.21***		
		(0.04)			(0.04)		
Age^2 x Sex		-0.005***			-0.004***		
		(0.00)			(0.00)		
Depression diagnosis before WI			0.26*	0.26*	0.26*	0.19	0.19
			(0.12)	(0.12)	(0.12)	(0.12)	(0.12)
Dep sympt (WI)			0.01	-0.45*	-0.44*		
			(0.00)	(0.18)	(0.18)		
Age x Dep sympt (WI)				0.06**	0.06**		
				(0.02)	(0.02)		
Dep sympt (WI) x Sex					-0.38		
					(0.40)		
Age x Dep sympt (WI) x Sex					0.05		

						(0.05)		
Age^2 x Dep sympt (WI)					-0.002**	-0.001**		
					(0.00)	(0.00)		
Age^2 x Dep sympt (WI) x Sex						<0.01		
						(0.00)		
Dep sympt (longit)							0.03***	0.03***
							(0.00)	(0.00)
Dep sympt (longit) x Sex								<0.01
								(0.01)
Constant	-2.67***	-2.97***	-1.92***	-3.13***	-3.33***	-2.19***	-3.16***	-3.16***
	(0.17)	(0.18)	(0.17)	(0.18)	(0.20)	(0.20)	(0.18)	(0.19)
Variance estimates (SE)								
Respondent ID	0.65	0.47	0.48	0.48	0.47	0.48	0.46	0.46
	(0.03)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)
Residual	1.51	1.51	1.49	1.51	1.51	1.49	1.50	1.50
	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Depressive symptoms (Dep sympt), longitudinal measure (longit), standard error (SE), unconditional (uncondtl)

[b]A random slope for age was tested, but did not meaningfully improve model fit and so was removed from all models

APPENDIX 2.4: DEPRESSIVE SYMPTOM GROWTH CURVES

Hypothesis 1.4, that the depressive symptom trajectory will show a decline from adolescence to young adulthood and will be moderated by sex such that the levels of depressive symptoms will be higher among females compared to males, was partially supported.[21] From Model 1 (Table 2.4.1) of the depressive symptom growth curves, the coefficient for age was -0.33 ($p<0.001$), indicating a decline in depressive symptoms from adolescence to young adulthood; this coefficient retained significance when the covariates were added in Model 2. The interaction term between age and sex in Model 4 was not statistically significant, though the coefficient for males was -2.18 ($p<0.05$), indicating the starting points in adolescence for depressive symptoms are significantly different. That the interaction term is not significant means the gap between higher levels for females compared to males does not change with age. Tables 2.4.2 and 2.4.3 outline the full results when binge drinking and marijuana use frequency, respectively, were tested as predictors of the depressive symptom growth curves. These results were discussed in detail in Chapter 2.

The depressive symptom growth curves also revealed significant differences by sociodemographic characteristics and in ways that vary from the binge drinking and marijuana use frequency growth curves. Compared to Whites, with the exception of respondents identifying as an 'Other' race/ethnicity, all racial/ethnic minority groups had higher average adolescent depressive symptoms, from highest to lowest: Asian ($B=0.77$, $p<0.001$), Black ($B=0.65$, $p<0.001$), Native American ($B=0.61$, $p<0.05$), and Hispanic ($B=0.46$, $p<0.05$). Compared to respondents whose parents have a college degree or more, respondents whose parents have lower educational attainment had higher adolescent depressive symptoms, from highest to lowest: less than high school ($B=1.40$, $p<0.001$), high school ($B=0.74$, $p<0.001$), less than college ($B=0.39$,

p<0.001). Compared to respondents who did not report experiencing any childhood maltreatment, increasing frequency of childhood maltreatment showed step-wise increases in adolescent depressive symptom levels. Respondents who experienced maltreatment once had, on average, CES-D score that was 0.60 (p<0.001) points higher. Those who experienced it twice had scores that were 0.82 (p<0.001) points higher; those who experienced maltreatment three times had scores 0.97 (p<0.001) points higher. Those with four or more experiences had scores 1.84 (p<0.001) points higher than the scores for respondents who did not experience childhood maltreatment. Finally, respondents who reported first getting diagnosed with depression at an age before their age at Wave I had, on average, a starting CES-D score that was 2.74 (p<0.001) points higher compared to respondents who did not have a depression diagnosis at all or before Wave I.

Table 2.4.1: Linear mixed effects models of depressive symptoms

	M1: Unconditional	M2: Covariates	M3: Random slope for age	M4: Age x Sex
Age	-0.33***	-0.30***	-0.33***	-0.38***
	(0.05)	(0.05)	(0.05)	(0.07)
Age^2	0.01***	0.01***	0.01***	0.01***
	(0.00)	(0.00)	(0.00)	(0.00)
Sex (1=Male, 0=Female)		-0.86***	-0.86***	-2.18*
		(0.09)	(0.09)	(1.00)
Race/ethnicity (White=referent)				
Hispanic		0.46**	0.45**	0.45**
		(0.17)	(0.17)	(0.17)
Black		0.65***	0.65***	0.65***
		(0.10)	(0.10)	(0.10)
Asian		0.77***	0.77***	0.77***
		(0.15)	(0.15)	(0.15)
Native American		0.61*	0.61*	0.61*
		(0.26)	(0.26)	(0.26)
Other		-0.08	-0.08	-0.07
		(0.44)	(0.44)	(0.44)

Parental education (WI) (college=referent)				
< High school		1.40***	1.40***	1.40***
		(0.18)	(0.18)	(0.18)
High school		0.74***	0.73***	0.73***
		(0.11)	(0.11)	(0.11)
< College		0.39***	0.39***	0.39***
		(0.11)	(0.11)	(0.11)
Childhood maltreatment frequency (none=referent)				
Once		0.61**	0.60**	0.60**
		(0.20)	(0.20)	(0.20)
Twice		0.82***	0.81***	0.81***
		(0.14)	(0.14)	(0.14)
Three times		0.97***	0.97***	0.97***
		(0.12)	(0.12)	(0.12)
Four or more times		1.83***	1.83***	1.83***
		(0.11)	(0.11)	(0.11)
Depression diagnosis before WI		2.74***	2.75***	2.75***
		(0.38)	(0.38)	(0.38)
Age x Sex				0.12
				(0.09)
Age^2 x Sex				<-0.01
				(0.00)
Constant	8.71***	7.23***	7.54***	8.09***
	(0.48)	(0.52)	(0.52)	(0.71)
Variance estimates (SE)[a]				
Respondent ID	5.65	4.20	9.30	9.27
	(0.21)	(0.20)	(2.23)	(2.24)
Residual	10.77	10.70	10.29	10.29
	(0.23)	(0.24)	(0.29)	(0.29)
Age			0.01	0.01
			(0.00)	(0.00)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

Table 2.4.2: Linear mixed effects models of depressive symptoms with binge drinking frequency tested as a predictor[a]

	M5: Binge drinking (WI)	M6: Binge drinking (WI) x Age	M7: Binge drinking (WI) x Age x Sex	M8: Binge drinking (longit)	M9: Binge drinking (longit) x Sex
Age	-0.32***	-0.32***	-0.34***	-0.44***	-0.44***
	(0.05)	(0.05)	(0.06)	(0.05)	(0.05)
Age^2	0.01***	0.01***	0.01***	0.01***	0.01***
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Sex (1=Male, 0=Female)	-0.96***	-0.96***	-1.41	-0.99***	-0.85***
	(0.08)	(0.08)	(0.98)	(0.09)	(0.10)
Race/ethnicity (White=referent)					
Hispanic	0.51**	0.51**	0.51**	0.51**	0.51**
	(0.16)	(0.16)	(0.16)	(0.16)	(0.16)
Black	0.79***	0.79***	0.79***	0.85***	0.86***
	(0.10)	(0.10)	(0.10)	(0.10)	(0.10)
Asian	0.82***	0.82***	0.82***	0.85***	0.85***
	(0.15)	(0.15)	(0.15)	(0.15)	(0.15)
Native American	0.48	0.49	0.49	0.50*	0.49
	(0.25)	(0.25)	(0.25)	(0.25)	(0.25)
Other	-0.09	-0.09	-0.09	-0.10	-0.09
	(0.40)	(0.39)	(0.40)	(0.42)	(0.42)
Parental education (WI) (college=referent)					
< High school	1.40***	1.40***	1.40***	1.52***	1.52***
	(0.16)	(0.16)	(0.16)	(0.16)	(0.16)
High school	0.65***	0.65***	0.65***	0.71***	0.71***
	(0.11)	(0.11)	(0.11)	(0.11)	(0.11)
< College	0.39***	0.39***	0.39***	0.42***	0.42***
	(0.11)	(0.11)	(0.11)	(0.11)	(0.11)
Childhood maltreatment frequency (none=referent)					
Once	0.60**	0.60**	0.60**	0.59**	0.58**
	(0.19)	(0.19)	(0.19)	(0.19)	(0.19)
Twice	0.80***	0.80***	0.79***	0.80***	0.80***
	(0.13)	(0.13)	(0.13)	(0.13)	(0.14)
Three times	0.95***	0.96***	0.95***	0.95***	0.95***
	(0.11)	(0.11)	(0.11)	(0.11)	(0.11)

Four or more times	1.83***	1.83***	1.82***	1.82***	1.82***
	(0.11)	(0.11)	(0.11)	(0.11)	(0.11)
Depression diagnosis before WI	2.79***	2.78***	2.76***	2.83***	2.82***
	(0.37)	(0.37)	(0.37)	(0.37)	(0.37)
Drank alcoholic beverage before WI	<-0.01	<-0.01	-0.01	0.13	0.13
	(0.10)	(0.10)	(0.10)	(0.10)	(0.10)
Binge drinking (WI)	0.67***	-2.27	-7.32		
	(0.05)	(4.26)	(6.22)		
Age x Binge drinking (WI)		0.38	1.08		
		(0.54)	(0.80)		
Binge drinking (WI) x Sex			5.98		
			(8.96)		
Age x Sex			0.05		
			(0.09)		
Age x Binge drinking (WI) x Sex			-0.89		
			(1.13)		
Age^2 x Binge drinking (WI)		-0.01	-0.03		
		(0.02)	(0.03)		
Age^2 x Sex			<-0.01		
			(0.00)		
Age^2 x Binge drinking (WI) x Sex			0.03		
			(0.04)		
Binge drinking (longit)				0.16***	0.25***
				(0.03)	(0.04)
Binge drinking (longit) x Sex					-0.14**
					(0.05)
Constant	7.11***	7.08***	7.25***	8.63***	8.54***
	(0.50)	(0.50)	(0.68)	(0.51)	(0.51)
Variance estimates (SE)					
Respondent ID	10.07	10.05	9.82	11.05	10.79

	(2.25)	(2.26)	(2.25)	(2.30)	(2.29)
Residual	10.01	10.01	10.00	10.13	10.14
	(0.27)	(0.27)	(0.27)	(0.27)	(0.27)
Age	0.01	0.01	0.01	0.01	0.01
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Longitudinal measure (longit), standard error (SE)

Table 2.4.3: Linear mixed effects models of depressive symptoms with marijuana frequency tested as a predictor[a]

	M5: Marijuana use (WI)	M6: Marijuana use (WI) x Age	M7: Marijuana use (WI) x Age x Sex	M8: Marijuana use (longit)	M9: Marijuana use (longit) x Sex
Age	-0.34***	-0.33***	-0.36***	-0.43***	-0.43***
	(0.05)	(0.05)	(0.06)	(0.05)	(0.05)
Age^2	0.01***	0.01***	0.01***	0.01***	0.01***
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Sex (1=Male, 0=Female)	-0.96***	-0.95***	-1.68	-1.00***	-0.89***
	(0.08)	(0.08)	(0.97)	(0.09)	(0.09)
Race/ethnicity (White=referent)					
Hispanic	0.48**	0.48**	0.48**	0.48**	0.48**
	(0.16)	(0.16)	(0.16)	(0.17)	(0.16)
Black	0.77***	0.77***	0.78***	0.77***	0.78***
	(0.10)	(0.10)	(0.10)	(0.10)	(0.10)
Asian	0.79***	0.80***	0.80***	0.83***	0.83***
	(0.14)	(0.14)	(0.14)	(0.15)	(0.14)
Native American	0.43	0.43	0.43	0.45	0.45
	(0.25)	(0.25)	(0.25)	(0.25)	(0.25)
Other	-0.14	-0.14	-0.14	-0.11	-0.11
	(0.39)	(0.39)	(0.39)	(0.39)	(0.40)
Parental education (WI) (college=referent)					
< High school	1.46***	1.46***	1.46***	1.49***	1.50***
	(0.16)	(0.16)	(0.16)	(0.16)	(0.16)
High school	0.70***	0.70***	0.69***	0.71***	0.71***
	(0.11)	(0.11)	(0.11)	(0.11)	(0.11)
< College	0.41***	0.41***	0.41***	0.41***	0.41***
	(0.11)	(0.11)	(0.11)	(0.11)	(0.11)

Childhood maltreatment frequency (none=referent)					
Once	0.60**	0.60**	0.59**	0.60**	0.61**
	(0.19)	(0.19)	(0.19)	(0.19)	(0.19)
Twice	0.80***	0.80***	0.79***	0.80***	0.80***
	(0.13)	(0.13)	(0.13)	(0.13)	(0.13)
Three times	0.96***	0.96***	0.96***	0.94***	0.94***
	(0.11)	(0.11)	(0.11)	(0.11)	(0.11)
Four or more times	1.80***	1.80***	1.80***	1.77***	1.77***
	(0.11)	(0.11)	(0.11)	(0.11)	(0.11)
Depression diagnosis before WI	2.70***	2.70***	2.69***	2.70***	2.68***
	(0.36)	(0.36)	(0.36)	(0.37)	(0.36)
Marijuana use before WI	0.43***	0.44***	0.43***	0.47***	0.47***
	(0.12)	(0.12)	(0.12)	(0.12)	(0.12)
Marijuana use (WI)	0.59***	-1.30	-6.55		
	(0.05)	(5.05)	(6.61)		
Age x Marijuana use (WI)		0.29	1.03		
		(0.63)	(0.84)		
Age x Sex			0.07		
			(0.09)		
Marijuana use (WI) x Sex			5.02		
			(9.69)		
Age x Marijuana use (WI) x Sex			-0.80		
			(1.21)		
Age^2 x Marijuana use (WI)		-0.01	-0.04		
		(0.02)	(0.03)		
Age^2 x Sex			<-0.01		
			(0.00)		
Age^2 x Marijuana use (WI) x Sex			0.03		
			(0.04)		
Marijuana use (longit)				0.19***	0.30***

				(0.02)	(0.04)
Marijuana use (longit) x Sex					-0.18***
					(0.05)
Constant	7.46***	7.37***	7.67***	8.49***	8.43***
	(0.49)	(0.50)	(0.68)	(0.50)	(0.50)
Variance estimates (SE)					
Respondent ID	10.51	10.41	10.33	11.06	11.13
	(2.24)	(2.25)	(2.24)	(2.25)	(2.25)
Residual	10.06	10.07	10.06	10.12	10.11
	(0.27)	(0.27)	(0.27)	(0.27)	(0.27)
Age	0.01	0.01	0.01	0.01	0.01
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Longitudinal measure (longit), standard error (SE)

APPENDIX 3.1: HYPOTHESES

Aim 2. Using regression models, examine potential mediators (sensation seeking, stress biomarkers, and gender norm adherence) and a moderator (gender norm adherence) of the relationships between substance use and depressive symptoms and whether the relationships differ by biological sex.

Self-Medication Model

Hypothesis 2.1: Level of depressive symptoms will be positively associated with the level of sensation seeking for males. The level of sensation seeking for males will be positively associated with the frequency of binge drinking. In this way, the positive relationship between the level of depressive symptoms and frequency of binge drinking will be mediated by the level of sensation seeking. The same hypothesis was tested for marijuana use frequency.[7,17,58,61–63,145]

Hypothesis 2.2: Level of depressive symptoms will be negatively associated with the level of the level of sensation seeking for females. The level of sensation seeking among females will be positively associated with the frequency of binge drinking. In this way, the negative relationship between the level of depressive symptoms and frequency of binge drinking will be mediated by the level of sensation seeking. The same hypothesis was tested for marijuana use frequency.[7,17,58,60,145]

Hypothesis 2.3: Level of depressive symptoms will be positively associated with the AGB score for males. The AGB score for males will be positively associated with the frequency of binge drinking. In this way, the positive relationship between the level of depressive symptoms and frequency of binge drinking will be mediated by the AGB score. The same hypothesis was tested for marijuana use frequency.[17,61–63]

Hypothesis 2.4: Level of depressive symptoms will be positively associated with the AGB score for females. The AGB score for females will be negatively associated with the frequency of binge drinking. In this way, the negative relationship between the level of depressive symptoms and frequency of binge drinking will be mediated by the AGB score. The same hypothesis was tested for marijuana use frequency.[17,60]

Hypothesis 2.5: The positive association between the level of depressive symptoms and binge drinking frequency will be moderated by the AGB score such that the association will be stronger for males who are more gender norm-adherent compared to males who are less adherent.[64,65] The same hypothesis was tested for marijuana use frequency.

Hypothesis 2.6: The negative association between the level of depressive symptoms and binge drinking frequency will be moderated by the AGB score such that the association will be stronger for females who are more gender norm-adherent compared to females who are less adherent.[64,65] The same hypothesis was tested for marijuana use frequency.

Stress Model Hypotheses

Hypothesis 2.7: Frequency of binge drinking will be associated with lower odds of elevated CRP and lower levels of EBV for males. Elevated CRP and EBV levels for males will be positively associated with the level of depressive symptoms. In this way, the negative relationship between the frequency of binge drinking and the level of depressive symptoms will be mediated by elevated CRP and levels of EBV. The same hypothesis was tested for marijuana use frequency.[65,96,101,146]

Hypothesis 2.8: Frequency of binge drinking will be associated with higher odds of elevated CRP and higher levels of EBV for females. Elevated CRP and EBV levels for females will be positively associated with the level of depressive symptoms. In this way, the positive

relationship between the frequency of binge drinking and the level of depressive symptoms will be mediated by elevated CRP and levels of EBV. The same hypothesis was tested for marijuana use frequency.[18,96,101]

Hypothesis 2.9: Frequency of binge drinking will be positively associated with the AGB score for males. The AGB score for males will be negatively associated with the level of depressive symptoms. In this way, the negative relationship between the frequency of binge drinking and the level of depressive symptoms will be mediated by the AGB score. The same hypothesis was tested for marijuana use frequency.[64,65,70,146]

Hypothesis 2.10: Frequency of binge drinking will be negatively associated with the AGB score for females. The AGB score for females will be negatively associated with the level of depressive symptoms. In this way, the positive relationship between the frequency of binge drinking and the level of depressive symptoms will be mediated by the AGB score.[18] The same hypothesis was tested for marijuana use frequency.

Hypothesis 2.11: The negative association between binge drinking frequency and level of depressive symptoms will be moderated by the AGB score such that the association will be stronger for males who are more gender norm-adherent compared to males who are less adherent. The same hypothesis was tested for marijuana use frequency.

Hypothesis 2.12: The positive association between binge drinking frequency and level of depressive symptoms will be moderated by the AGB score such that the association will be stronger for females who are more gender norm-adherent compared to females who are less adherent.[10,11,18] The same hypothesis was tested for marijuana use frequency.

APPENDIX 3.2: ANALYSES

In creating the binary measure for CRP, we included values over 30 mg/L, trusting the numerous control variables would correctly adjust for the very high scores that likely indicate illness. However, as a sensitivity analysis, the relevant mediation models for CRP were repeated with the values over 30 excluded. Fortunately, the results changed very little in both magnitude and significance.

Given the high number of tests employed for Aim 2, we used the conservative Bonferroni correction as a personal guard against over-interpretation of the results. When this was applied to our mediation results, we lost the significant associations between binge drinking frequency and both sensation seeking and AGB for males and also between sensation seeking and marijuana use frequency for females. Given this, the results from the mediation analyses in Chapter 3 should be interpreted with caution and further similar research is needed to buffer these results.

APPENDIX 3.3: SENSATION SEEKING MEDIATION FOR SELF-MEDICATION MODEL

Table 3.3.1 and 3.3.2 include results from the regression models testing Hypotheses 2.1 and 2.2, respectively. Hypothesis 2.1 was partially supported, as depressive symptoms at Wave I were positively associated with level of sensation seeking in Wave III (B=0.02, p<0.001) and the level of sensation seeking was positively associated with binge drinking frequency (B=0.08, p<0.05). Sensation seeking was not significantly associated with marijuana use frequency, contrary to the hypothesis. Hypothesis 2.2 was also partially supported as sensation seeking was positively associated with both binge drinking frequency (B=0.12, p<0.001) and marijuana use frequency (B=0.07, p<0.05), as hypothesized. However, depressive symptoms at Wave I were positively, rather than negatively, associated with sensation seeking (B=0.02, p<0.001).

Table 3.3.1: Linear regression testing mediation of the Self-Medication Model by sensation seeking, Males[a]

	MALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2	M3	M1	M2	M3
Depressive symptoms (WI)	0.01	0.02***	0.01	-0.01	0.02***	-0.01
	(0.01)	(0.00)	(0.01)	(0.01)	(0.00)	(0.01)
Sensation seeking (WIII)			0.08*			0.08
			(0.04)			(0.04)
Binge drinking frequency (WIII)	0.37***		0.36***			
	(0.02)		(0.02)			
Marijuana use frequency (WIII)				0.44***		0.44***
				(0.02)		(0.03)
Age	WIV - 0.12*** (0.02)	WIII - 0.06*** (0.01)	WIV -0.12*** (0.02)	WIV - 0.08*** (0.02)	WIII - 0.06*** (0.01)	WIV - 0.07*** (0.02)

Race/ethnicity (White=referent)						
Hispanic	-0.01	-0.02	-0.01	0.15	-0.02	0.15
	(0.10)	(0.06)	(0.10)	(0.12)	(0.06)	(0.12)
Black	-0.20*	-0.18***	-0.20*	0.12	-0.18***	0.14
	(0.10)	(0.04)	(0.10)	(0.12)	(0.04)	(0.12)
Asian	-0.14	0.04	-0.16	0.06	0.04	0.05
	(0.12)	(0.07)	(0.12)	(0.13)	(0.07)	(0.13)
Native American	0.02	0.21	0.01	-0.38*	0.21	-0.39*
	(0.23)	(0.13)	(0.23)	(0.17)	(0.13)	(0.17)
Other	-0.64*	0.08	-0.64*	-0.17	0.08	-0.18
	(0.30)	(0.15)	(0.29)	(0.24)	(0.15)	(0.23)
Parental education (WI) (college=referent)						
< High school	-0.07	-0.23**	-0.05	-0.28*	-0.23**	-0.27*
	(0.12)	(0.07)	(0.12)	(0.13)	(0.07)	(0.13)
High school	-0.06	-0.08	-0.05	-0.17	-0.08	-0.17
	(0.08)	(0.05)	(0.08)	(0.10)	(0.05)	(0.10)
< College	0.01	-0.04	0.02	-0.06	-0.04	-0.06
	(0.08)	(0.04)	(0.08)	(0.08)	(0.04)	(0.08)
Respondent education (college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	0.04	0.21**	0.01	0.54***	0.21**	0.52***
	(0.14)	(0.07)	(0.14)	(0.14)	(0.07)	(0.14)
High school	0.16	0.06	0.16	0.40***	0.06	0.40***
	(0.10)	(0.06)	(0.10)	(0.10)	(0.06)	(0.10)
< College	0.10	0.07	0.09	0.20*	0.07	0.19*
	(0.07)	(0.05)	(0.07)	(0.08)	(0.05)	(0.08)
Childhood maltreatment frequency (none=referent)						
Once	0.19	0.18**	0.18	0.11	0.18**	0.10
	(0.11)	(0.05)	(0.11)	(0.12)	(0.05)	(0.12)
Twice	-0.06	0.21**	-0.08	-0.00	0.21**	-0.02

	(0.12)	(0.07)	(0.12)	(0.10)	(0.07)	(0.10)
Three times	-0.06	0.23***	-0.07	0.02	0.23***	0.00
	(0.08)	(0.05)	(0.08)	(0.08)	(0.05)	(0.08)
Four or more times	0.01	0.32***	-0.02	0.14	0.32***	0.12
	(0.08)	(0.05)	(0.08)	(0.07)	(0.05)	(0.07)
Drank alcoholic beverage before WI	0.69***		0.69***			
	(0.09)		(0.09)			
Marijuana use before WI				0.68***		0.67***
				(0.12)		(0.12)
Constant	4.06***	4.09***	3.70***	2.25***	4.09***	1.88**
	(0.57)	(0.24)	(0.55)	(0.55)	(0.24)	(0.59)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

[b]M1: Depressive symptoms→Substance use frequency; M2: Depressive symptoms→Sensation seeking; M3: Depressive symptoms→Substance use frequency, controlling for sensation seeking

Table 3.3.2: Linear regression testing mediation of the Self-Medication Model by sensation seeking, Females[a]

	FEMALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2	M3	M1	M2	M3
Depressive symptoms (WI)	-0.00	0.02***	-0.00	0.01	0.02***	0.00
	(0.01)	(0.00)	(0.01)	(0.00)	(0.00)	(0.00)
Sensation seeking (WIII)			0.12***			0.07*
			(0.03)			(0.03)
Binge drinking frequency (WIII)	0.34***		0.32***			
	(0.02)		(0.02)			
Marijuana use frequency (WIII)				0.40***		0.39***
				(0.03)		(0.03)

	WIV -	WIII -	WIV -	WIV	WIII -	WIV
Age	0.10***	0.06***	0.09***	-0.03*	0.06***	-0.03*
	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)
Race/ethnicity (White=referent)						
Hispanic	-0.01	0.01	-0.02	-0.11	0.01	-0.11
	(0.07)	(0.05)	(0.07)	(0.07)	(0.05)	(0.07)
Black	0.17***	-0.00	0.18***	0.11	-0.00	0.10
	(0.05)	(0.04)	(0.05)	(0.06)	(0.04)	(0.06)
Asian	0.02	0.10	-0.00	-0.17*	0.10	-0.18*
	(0.13)	(0.06)	(0.13)	(0.08)	(0.06)	(0.08)
Native American	0.48*	0.13	0.47*	-0.02	0.13	-0.03
	(0.19)	(0.08)	(0.20)	(0.15)	(0.08)	(0.15)
Other	-0.02	-0.14	-0.01	-0.12	-0.14	-0.11
	(0.23)	(0.11)	(0.23)	(0.11)	(0.11)	(0.12)
Parental education (WI) (college=referent)						
< High school	-0.20**	-0.12	-0.19*	0.01	-0.12	0.01
	(0.07)	(0.06)	(0.07)	(0.08)	(0.06)	(0.08)
High school	-0.07	-0.08*	-0.07	-0.02	-0.08*	-0.01
	(0.07)	(0.04)	(0.07)	(0.06)	(0.04)	(0.06)
< College	-0.07	-0.06	-0.06	0.03	-0.06	0.03
	(0.06)	(0.04)	(0.06)	(0.05)	(0.04)	(0.05)
Respondent education (college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	-0.21*	0.15*	-0.24*	0.13	0.15*	0.12
	(0.10)	(0.06)	(0.10)	(0.10)	(0.06)	(0.10)
High school	-0.04	0.09*	-0.06	0.15	0.09*	0.15
	(0.08)	(0.04)	(0.08)	(0.08)	(0.04)	(0.08)
< College	0.03	0.10**	0.02	0.16***	0.10**	0.16***
	(0.05)	(0.04)	(0.05)	(0.04)	(0.04)	(0.04)

Childhood maltreatment frequency (none=referent)						
Once	0.08	0.19***	0.06	-0.02	0.19***	-0.04
	(0.08)	(0.05)	(0.08)	(0.07)	(0.05)	(0.07)
Twice	0.10	0.14*	0.08	-0.02	0.14*	-0.03
	(0.07)	(0.06)	(0.07)	(0.07)	(0.06)	(0.07)
Three times	0.04	0.09*	0.04	-0.01	0.09*	-0.02
	(0.06)	(0.04)	(0.06)	(0.07)	(0.04)	(0.07)
Four or more times	0.04	0.25***	0.02	0.07	0.25***	0.05
	(0.05)	(0.04)	(0.05)	(0.06)	(0.04)	(0.06)
Drank alcoholic beverage before WI	0.59***		0.59***			
	(0.06)		(0.06)			
Marijuana use before WI				0.43***		0.42***
				(0.11)		(0.11)
Constant	3.41***	3.47***	2.95***	0.81*	3.47***	0.53
	(0.33)	(0.24)	(0.35)	(0.33)	(0.24)	(0.35)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

[b]M1: Depressive symptoms→Substance use frequency; M2: Depressive symptoms→Sensation seeking; M3: Depressive symptoms→Substance use frequency, controlling for sensation seeking

APPENDIX 3.4: AGB MEDIATION FOR SELF-MEDICATION MODEL

Tables 3.4.1 and 3.4.2 display the results testing Hypotheses 2.3 and 2.4, respectively. Hypothesis 2.3 was partially supported, as the AGB score for males was positively associated with later binge drinking frequency (B=0.15, p<0.05), though not with marijuana use frequency. Contrary to our hypothesis, depressive symptoms at Wave I were negatively, rather than positively, associated with AGB scores in both the binge drinking and marijuana models (B=0.01, p<0.01). Hypothesis 2.4 was supported. As predicted, depressive symptoms at Wave I were positively associated with AGB scores in Wave III (B=0.01, p<0.001) and the AGB scores were negatively associated with binge drinking frequency (B=-0.16, p<0.001), though not with marijuana use frequency.

Table 3.4.1: Linear regression testing mediation of the Self-Medication Model by AGB, Males[a]

	MALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2	M3	M1	M2	M3
Depressive symptoms (WI)	0.01	-0.01**	0.02	-0.01	-0.01**	-0.01
	(0.01)	(0.00)	(0.01)	(0.01)	(0.00)	(0.01)
AGB (WIII)			0.15*			-0.05
			(0.06)			(0.07)
Binge drinking frequency (WIII)	0.37***		0.36***			
	(0.02)		(0.02)			
Marijuana use frequency (WIII)				0.44***		0.45***
				(0.02)		(0.03)
	WIV	WIII	WIV	WIV	WIII	WIV
	-		-	-		-
Age	0.12***	-0.01*	0.12***	0.08***	-0.01*	0.08***
	(0.02)	(0.01)	(0.02)	(0.02)	(0.01)	(0.02)
Race/ethnicity (White=referent)						
Hispanic	-0.01	0.00	-0.01	0.15	0.00	0.15
	(0.10)	(0.03)	(0.10)	(0.12)	(0.03)	(0.12)
Black	-0.20*	0.03	-0.22*	0.12	0.03	0.12
	(0.10)	(0.03)	(0.10)	(0.12)	(0.03)	(0.12)

Asian	-0.14	-0.09**	-0.14	0.06	-0.09**	0.05
	(0.12)	(0.03)	(0.12)	(0.13)	(0.03)	(0.13)
Native American	0.02	0.03	0.02	-0.38*	0.03	-0.38*
	(0.23)	(0.07)	(0.23)	(0.17)	(0.07)	(0.17)
Other	-0.64*	0.08	-0.65*	-0.17	0.08	-0.16
	(0.30)	(0.11)	(0.29)	(0.24)	(0.11)	(0.23)
Parental education (WI) (college=referent)						
< High school	-0.07	-0.07*	-0.06	-0.28*	-0.07*	-0.29*
	(0.12)	(0.04)	(0.12)	(0.13)	(0.04)	(0.13)
High school	-0.06	0.01	-0.06	-0.17	0.01	-0.17
	(0.08)	(0.03)	(0.08)	(0.10)	(0.03)	(0.10)
< College	0.01	-0.02	0.02	-0.06	-0.02	-0.06
	(0.08)	(0.03)	(0.08)	(0.08)	(0.03)	(0.08)
Respondent education (college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	0.04	0.12*	0.02	0.54***	0.12*	0.54***
	(0.14)	(0.05)	(0.14)	(0.14)	(0.05)	(0.14)
High school	0.16	0.05	0.16	0.40***	0.05	0.40***
	(0.10)	(0.04)	(0.10)	(0.10)	(0.04)	(0.10)
< College	0.10	0.08*	0.09	0.20*	0.08*	0.20*
	(0.07)	(0.03)	(0.07)	(0.08)	(0.03)	(0.08)
Childhood maltreatment frequency (none=referent)						
Once	0.19	0.06	0.18	0.11	0.06	0.11
	(0.11)	(0.03)	(0.11)	(0.12)	(0.03)	(0.12)
Twice	-0.06	0.07	-0.07	-0.00	0.07	0.00
	(0.12)	(0.04)	(0.12)	(0.10)	(0.04)	(0.11)
Three times	-0.06	0.08*	-0.06	0.02	0.08*	0.02
	(0.08)	(0.03)	(0.08)	(0.08)	(0.03)	(0.08)
Four or more times	0.01	0.09***	-0.00	0.14	0.09***	0.14
	(0.08)	(0.03)	(0.08)	(0.07)	(0.03)	(0.07)
Drank alcoholic beverage before WI	0.69***		0.69***			
	(0.09)		(0.09)			
Marijuana use before WI				0.68***		0.68***
				(0.12)		(0.12)
Constant	4.06***	1.10***	3.86***	2.25***	1.10***	2.32***

	(0.57)	(0.14)	(0.57)	(0.55)	(0.14)	(0.55)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

[b]M1: Depressive symptoms→Substance use frequency; M2: Depressive symptoms→AGB; M3: Depressive symptoms→Substance use frequency, controlling for AGB

Table 3.4.2: Linear regression testing mediation of the Self-Medication Model by AGB, Females[a]

	FEMALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2	M3	M1	M2	M3
Depressive symptoms (WI)	-0.00	0.01***	-0.00	0.01	0.01***	0.01
	(0.01)	(0.00)	(0.01)	(0.00)	(0.00)	(0.00)
AGB (WIII)			-0.16***			-0.03
			(0.04)			(0.05)
Binge drinking frequency (WIII)	0.34***		0.33***			
	(0.02)		(0.02)			
Marijuana use frequency (WIII)				0.40***		0.40***
				(0.03)		(0.03)
	WIV	WIII	WIV	WIV	WIII	WIV
Age	-0.10***	0.02***	-0.10***	-0.03*	0.02***	-0.03*
	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)
Race/ethnicity (White=referent)						
Hispanic	-0.01	-0.01	-0.02	-0.11	-0.01	-0.11
	(0.07)	(0.04)	(0.07)	(0.07)	(0.04)	(0.07)
Black	-0.17***	-0.08**	-0.19***	0.11	-0.08**	0.10
	(0.05)	(0.03)	(0.05)	(0.06)	(0.03)	(0.06)
Asian	0.02	-0.14**	-0.01	-0.17*	-0.14**	-0.17*
	(0.13)	(0.04)	(0.13)	(0.08)	(0.04)	(0.08)
Native American	0.48*	-0.05	0.48*	-0.02	-0.05	-0.02
	(0.19)	(0.06)	(0.19)	(0.15)	(0.06)	(0.15)
Other	-0.02	-0.01	-0.03	-0.12	-0.01	-0.12
	(0.23)	(0.08)	(0.22)	(0.11)	(0.08)	(0.12)
Parental education (WI) (college=referent)						
< High school	-0.20**	0.02	-0.19**	0.01	0.02	0.01

	(0.07)	(0.03)	(0.07)	(0.08)	(0.03)	(0.08)
High school	-0.07	0.02	-0.07	-0.02	0.02	-0.01
	(0.07)	(0.03)	(0.07)	(0.06)	(0.03)	(0.06)
< College	-0.07	0.04	-0.06	0.03	0.04	0.03
	(0.06)	(0.02)	(0.06)	(0.05)	(0.02)	(0.05)
Respondent education (college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	-0.21*	0.10**	-0.21*	0.13	0.10**	0.13
	(0.10)	(0.04)	(0.10)	(0.10)	(0.04)	(0.10)
High school	-0.04	0.07*	-0.04	0.15	0.07*	0.15
	(0.08)	(0.03)	(0.08)	(0.08)	(0.03)	(0.08)
< College	0.03	0.05	0.04	0.16***	0.05	0.16***
	(0.05)	(0.03)	(0.05)	(0.04)	(0.03)	(0.04)
Childhood maltreatment frequency (none=referent)						
Once	0.08	-0.03	0.07	-0.02	-0.03	-0.02
	(0.08)	(0.03)	(0.08)	(0.07)	(0.03)	(0.07)
Twice	0.10	-0.02	0.09	-0.02	-0.02	-0.02
	(0.07)	(0.03)	(0.07)	(0.07)	(0.03)	(0.07)
Three times	0.04	0.06*	0.05	-0.01	0.06*	-0.01
	(0.06)	(0.02)	(0.06)	(0.07)	(0.02)	(0.07)
Four or more times	0.04	0.03	0.05	0.07	0.03	0.07
	(0.05)	(0.02)	(0.05)	(0.06)	(0.02)	(0.06)
Drank alcoholic beverage before WI	0.59***		0.59***			
	(0.06)		(0.06)			
Marijuana use before WI				0.43***		0.43***
				(0.11)		(0.11)
Constant	3.41***	0.21	3.45***	0.81*	0.21	0.81*
	(0.33)	(0.12)	(0.33)	(0.33)	(0.12)	(0.33)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

[b]M1: Depressive symptoms→Substance use frequency; M2: Depressive symptoms→AGB; M3: Depressive symptoms→Substance use frequency, controlling for AGB

APPENDIX 3.5: CRP AND EBV MEDIATION FOR STRESS MODEL

Tables 3.5.1 through 3.5.4 display the results for the regression models testing Hypotheses 2.7 and 2.8. Hypothesis 2.7 was not supported; among males there were no significant associations between either binge drinking frequency or marijuana use frequency and CRP or EBV, or between CRP or EBV and depressive symptoms. Hypothesis 2.8 was also largely not supported, as there were no significant associations between substance use frequency and CRP or between CRP and depressive symptoms. However, for EBV, marijuana use frequency was significantly positively associated with later EBV (B=0.02, $p<0.05$), in accordance with our hypothesis, but EBV was not significantly associated with depressive symptoms.

Table 3.5.1: Regression testing mediation of the Stress Model by high sensitivity C-reactive protein, Males[a]

	MALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2[c]	M3	M1	M2	M3
Binge drinking frequency (WI)	0.08	-0.01	0.05			
	(0.05)	(0.04)	(0.05)			
Marijuana use frequency (WI)				0.08	-0.03	0.05
				(0.05)	(0.04)	(0.05)
CRP (>3 mg/L)			-0.04			-0.04
			(0.16)			(0.16)
Depressive symptoms (WIII)	0.40***		0.37***	0.40***		0.37***
	(0.02)		(0.02)	(0.02)		(0.02)
Age	WIV	WIII	WIV	WIV	WIII	WIV
	0.08*	0.02	0.10*	0.09*	0.02	0.10*
	(0.04)	(0.03)	(0.04)	(0.04)	(0.03)	(0.04)
Race/ethnicity (White=referent)						
Hispanic	0.02	-0.02	0.08	0.01	-0.01	0.07
	(0.20)	(0.15)	(0.18)	(0.20)	(0.15)	(0.18)
Black	0.68**	0.19	0.57*	0.66**	0.20	0.55*
	(0.22)	(0.17)	(0.22)	(0.22)	(0.17)	(0.21)
Asian	0.39	-0.35	0.60	0.36	-0.34	0.58

	(0.32)	(0.19)	(0.33)	(0.32)	(0.19)	(0.33)
Native American	0.28	0.28	-0.09	0.28	0.29	-0.09
	(0.38)	(0.34)	(0.34)	(0.38)	(0.34)	(0.34)
Other	-0.62	-0.09	-0.48	-0.64	-0.08	-0.49
	(0.35)	(0.43)	(0.29)	(0.35)	(0.43)	(0.29)
Parental education (WI) (college=referent)						
< High school	0.30	-0.04	0.44	0.31	-0.04	0.44
	(0.23)	(0.19)	(0.23)	(0.23)	(0.19)	(0.23)
High school	0.32	0.11	0.32	0.33	0.11	0.32
	(0.17)	(0.14)	(0.17)	(0.17)	(0.14)	(0.17)
< College	0.18	-0.03	0.19	0.18	-0.04	0.20
	(0.15)	(0.14)	(0.15)	(0.15)	(0.14)	(0.15)
Respondent education (college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	1.14***	0.48*	0.80**	1.14***	0.49*	0.80**
	(0.30)	(0.21)	(0.30)	(0.30)	(0.22)	(0.30)
High school	0.82***	0.46**	0.79***	0.82***	0.47**	0.79***
	(0.20)	(0.16)	(0.21)	(0.20)	(0.16)	(0.21)
< College	0.45**	0.21	0.31*	0.45**	0.21	0.31*
	(0.14)	(0.18)	(0.14)	(0.14)	(0.18)	(0.14)
Childhood maltreatment frequency (none=referent)						
Once	0.34	-0.26	0.21	0.34	-0.26	0.20
	(0.23)	(0.17)	(0.21)	(0.23)	(0.17)	(0.21)
Twice	0.40	0.22	0.23	0.40	0.22	0.23
	(0.23)	(0.17)	(0.24)	(0.23)	(0.17)	(0.24)
Three times	0.97***	-0.18	0.78***	0.97***	-0.18	0.78***
	(0.17)	(0.15)	(0.16)	(0.17)	(0.15)	(0.16)
Four or more times	1.17***	-0.01	0.84***	1.17***	-0.00	0.84***
	(0.20)	(0.12)	(0.19)	(0.20)	(0.12)	(0.19)
Stressful life events scale (WIV)		0.07*	0.32***		0.07*	0.32***
		(0.03)	(0.04)		(0.03)	(0.04)
Count subclinical symptoms		0.34***	0.44***		0.34***	0.44***
		(0.07)	(0.11)		(0.07)	(0.11)
Count infectious/ inflammatory diseases		0.09	0.46***		0.09	0.46***
		(0.08)	(0.10)		(0.08)	(0.10)

NSAID or Salicylate, past 24 hrs		0.52	-0.89		0.53	-0.91
		(0.50)	(0.80)		(0.50)	(0.81)
Past 4 weeks		0.03	-0.35		0.04	-0.37
		(0.28)	(0.36)		(0.28)	(0.36)
COX-2 Inhibitor		-0.22	-4.38***		-0.20	-4.43***
		(1.04)	(0.97)		(1.03)	(0.95)
Inhaled corticosteorids		1.10	-0.19		1.10	-0.20
		(0.76)	(0.91)		(0.76)	(0.91)
Corticotropin or glucocorticoid		0.88	-1.74**		0.90	-1.78**
		(0.62)	(0.64)		(0.62)	(0.63)
Antirheumatic or antipsoriasitic		2.21	2.05		2.20	2.09
		(1.21)	(1.50)		(1.22)	(1.54)
Immunosuppressive		-1.54	0.40		-1.53	0.36
		(1.31)	(1.23)		(1.31)	(1.24)
Anti-inflammatory		-0.25	0.91		-0.26	0.93
		(0.52)	(0.79)		(0.52)	(0.79)
Physical activity past 24 hours		0.02	-0.32*		0.02	-0.31*
		(0.09)	(0.14)		(0.09)	(0.14)
Currently pregnant (WIV)						
BMI (WIV)		0.84***	-0.12		0.84***	-0.12
		(0.07)	(0.10)		(0.07)	(0.10)
Cigarette smoking frequency	WIV	WIII	WIV	WIV	WIII	WIV
	0.02**	0.01*	0.01	0.02**	0.01**	0.01
	(0.01)	(0.00)	(0.01)	(0.01)	(0.00)	(0.01)
Depression diagnosis before WI	1.16		0.67	1.09		0.62
	(0.59)		(0.54)	(0.59)		(0.54)
Constant	-0.84	-4.84***	-1.29	-0.98	-4.86***	-1.39
	(1.14)	(0.69)	(1.16)	(1.14)	(0.71)	(1.13)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

[b]M1: Substance use frequency→Depressive symptoms; M2: Substance use frequency→C-reactive protein (CRP); M3: Substance use frequency→Depressive symptoms, controlling for CRP

[c]M1 and M3 use linear regression and M2 uses logistic regression so the coefficients are log odds

Table 3.5.2: Regression testing mediation of the Stress Model by high sensitivity C-reactive protein, Females[a]

	FEMALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2[c]	M3	M1	M2	M3
Binge drinking frequency (WI)	0.08	-0.04	0.05			
	(0.09)	(0.04)	(0.08)			
Marijuana use frequency (WI)				0.08	-0.04	0.05
				(0.07)	(0.04)	(0.06)
CRP (>3 mg/L)			0.02			0.02
			(0.15)			(0.15)
Depressive symptoms (WIII)	0.35***		0.30***	0.35***		0.31***
	(0.02)		(0.02)	(0.02)		(0.02)
Age	WIV	WIII	WIV	WIV	WIII	WIV
	0.02	-0.03	0.03	0.02	-0.04	0.04
	(0.04)	(0.02)	(0.04)	(0.04)	(0.02)	(0.04)
Race/ethnicity (White=referent)						
Hispanic	0.30	0.09	0.26	0.29	0.10	0.25
	(0.29)	(0.13)	(0.25)	(0.29)	(0.13)	(0.25)
Black	0.55**	-0.07	0.32	0.54**	-0.06	0.32
	(0.20)	(0.12)	(0.19)	(0.20)	(0.12)	(0.20)
Asian	0.64	-0.49**	0.66	0.63	-0.49**	0.66
	(0.37)	(0.17)	(0.34)	(0.37)	(0.17)	(0.34)
Native American	0.61	0.30	0.38	0.61	0.30	0.38
	(0.45)	(0.29)	(0.39)	(0.45)	(0.29)	(0.39)
Other	-0.70	0.58	-0.66	-0.72	0.59	-0.67
	(0.49)	(0.41)	(0.45)	(0.50)	(0.41)	(0.45)
Parental education (WI) (college=referent)						
< High school	0.66	-0.03	0.67*	0.67	-0.03	0.67*
	(0.35)	(0.14)	(0.32)	(0.35)	(0.14)	(0.31)
High school	0.16	-0.02	0.10	0.17	-0.03	0.10
	(0.18)	(0.11)	(0.17)	(0.18)	(0.11)	(0.16)
< College	0.34	-0.07	0.28	0.35	-0.07	0.29
	(0.19)	(0.11)	(0.18)	(0.19)	(0.10)	(0.18)

Respondent education (college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	2.15***	0.06	1.39***	2.16***	0.06	1.40***
	(0.38)	(0.18)	(0.36)	(0.37)	(0.17)	(0.35)
High school	1.15***	0.04	0.83***	1.16***	0.05	0.83***
	(0.21)	(0.15)	(0.22)	(0.21)	(0.15)	(0.22)
< College	0.44**	-0.07	0.19	0.44**	-0.07	0.19
	(0.17)	(0.13)	(0.17)	(0.17)	(0.13)	(0.17)
Childhood maltreatment frequency (none=referent)						
Once	0.58*	-0.00	0.52*	0.58*	-0.00	0.52*
	(0.25)	(0.16)	(0.23)	(0.24)	(0.17)	(0.23)
Twice	0.22	-0.07	0.07	0.23	-0.07	0.08
	(0.25)	(0.14)	(0.24)	(0.24)	(0.15)	(0.23)
Three times	0.67**	-0.19*	0.50*	0.68**	-0.20*	0.50*
	(0.21)	(0.09)	(0.20)	(0.21)	(0.09)	(0.20)
Four or more times	1.13***	-0.23*	0.75***	1.13***	-0.23*	0.75***
	(0.18)	(0.11)	(0.17)	(0.18)	(0.11)	(0.17)
Stressful life events scale (WIV)		-0.00	0.53***		-0.00	0.52***
		(0.03)	(0.05)		(0.03)	(0.05)
Count subclinical symptoms		0.28***	0.70***		0.28***	0.70***
		(0.06)	(0.10)		(0.06)	(0.10)
Count infectious/ inflammatory diseases		-0.02	0.18		-0.02	0.18
		(0.07)	(0.10)		(0.07)	(0.10)
NSAID or Salicylate, past 24 hrs		0.01	-0.32		0.02	-0.33
		(0.33)	(0.63)		(0.34)	(0.64)
Past 4 weeks		0.21	-0.67		0.20	-0.67
		(0.27)	(0.49)		(0.27)	(0.49)
COX-2 Inhibitor		0.11	0.10		0.09	0.14
		(0.75)	(1.44)		(0.75)	(1.43)
Inhaled corticosteorids		0.63	-0.97		0.62	-0.94
		(0.68)	(1.03)		(0.68)	(1.03)
Corticotropin or glucocorticoid		-0.14	-0.38		-0.13	-0.39
		(0.50)	(0.76)		(0.50)	(0.76)

Antirheumatic or antipsoriasitic		-0.10	0.98		-0.08	0.97
		(0.60)	(1.12)		(0.60)	(1.11)
Immunosuppressive		1.05	-2.51		1.02	-2.49
		(0.85)	(1.33)		(0.84)	(1.32)
Anti-inflammatory		0.17	0.86		0.16	0.87
		(0.36)	(0.63)		(0.36)	(0.64)
Physical activity past 24 hours		-0.22*	-0.22		-0.22*	-0.22
		(0.09)	(0.13)		(0.09)	(0.13)
Currently pregnant (WIV)		1.17***	0.18		1.17***	0.18
		(0.16)	(0.26)		(0.16)	(0.27)
BMI (WIV)		1.04***	-0.11		1.04***	-0.11
		(0.05)	(0.09)		(0.05)	(0.09)
Cigarette smoking frequency	WIV	WIII	WIV	WIV	WIII	WIV
	0.01*	-0.00	0.00	0.01*	-0.00	-0.00
	(0.01)	(0.00)	(0.01)	(0.01)	(0.00)	(0.01)
Depression diagnosis before WI	1.90**		1.48*	1.89**		1.47*
	(0.61)		(0.59)	(0.61)		(0.59)
Constant	1.75	-2.42***	1.02	1.63	-2.40***	0.94
	(1.20)	(0.52)	(1.16)	(1.18)	(0.51)	(1.12)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

[b]M1: Substance use frequency→Depressive symptoms; M2: Substance use frequency→C-reactive protein (CRP); M3: Substance use frequency→Depressive symptoms, controlling for CRP

[c]M1 and M3 use linear regression and M2 uses logistic regression so the coefficients are log odds

Table 3.5.3: Linear regression testing mediation of the Stress Model by Epstein-Barr Virus, Males[a]

	MALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2	M3	M1	M2	M3
Binge drinking frequency (WI)	0.08	-0.01	0.05			
	(0.05)	(0.01)	(0.05)			
Marijuana use frequency (WI)				0.08	-0.00	0.05
				(0.05)	(0.01)	(0.05)
EBV			-0.01			-0.01
			(0.08)			(0.08)
Depressive symptoms (WIII)	0.40***		0.37***	0.40***		0.37***
	(0.02)		(0.02)	(0.02)		(0.02)
Age	WIV	WIII	WIV	WIV	WIII	WIV
	0.08*	0.02**	0.10*	0.09*	0.02*	0.10*
	(0.04)	(0.01)	(0.04)	(0.04)	(0.01)	(0.04)
Race/ethnicity (White=referent)						
Hispanic	0.02	0.06	0.08	0.01	0.06	0.07
	(0.20)	(0.05)	(0.18)	(0.20)	(0.05)	(0.18)
Black	0.68**	0.17***	0.57*	0.66**	0.17***	0.55*
	(0.22)	(0.03)	(0.22)	(0.22)	(0.03)	(0.22)
Asian	0.39	0.03	0.61	0.36	0.04	0.59
	(0.32)	(0.05)	(0.33)	(0.32)	(0.05)	(0.33)
Native American	0.28	0.04	-0.10	0.28	0.04	-0.10
	(0.38)	(0.08)	(0.34)	(0.38)	(0.08)	(0.34)
Other	-0.62	-0.04	-0.48	-0.64	-0.04	-0.49
	(0.35)	(0.10)	(0.29)	(0.35)	(0.10)	(0.29)
Parental education (WI) (college=referent)						
< High school	0.30	0.01	0.44	0.31	0.02	0.44
	(0.23)	(0.06)	(0.23)	(0.23)	(0.06)	(0.23)
High school	0.32	0.08*	0.32	0.33	0.08*	0.32
	(0.17)	(0.04)	(0.17)	(0.17)	(0.04)	(0.17)
College	0.18	0.05	0.19	0.18	0.05	0.20
	(0.15)	(0.03)	(0.15)	(0.15)	(0.03)	(0.15)
Respondent education (college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	1.14***	0.02	0.80**	1.14***	0.02	0.80**
	(0.30)	(0.06)	(0.30)	(0.30)	(0.06)	(0.30)
High school	0.82***	0.03	0.79***	0.82***	0.04	0.79***

	(0.20)	(0.05)	(0.21)	(0.20)	(0.05)	(0.21)
College	0.45**	-0.01	0.31*	0.45**	-0.01	0.31*
	(0.14)	(0.04)	(0.14)	(0.14)	(0.04)	(0.14)
Childhood maltreatment frequency (none=referent)						
Once	0.34	-0.07	0.21	0.34	-0.07	0.20
	(0.23)	(0.05)	(0.21)	(0.23)	(0.05)	(0.20)
Twice	0.40	0.01	0.23	0.40	0.01	0.23
	(0.23)	(0.05)	(0.24)	(0.23)	(0.05)	(0.24)
Three times	0.97***	-0.02	0.78***	0.97***	-0.02	0.78***
	(0.17)	(0.04)	(0.16)	(0.17)	(0.04)	(0.16)
Four or more times	1.17***	0.05	0.84***	1.17***	0.05	0.84***
	(0.20)	(0.03)	(0.19)	(0.20)	(0.03)	(0.19)
Stressful life events scale (WIV)		0.00	0.32***		-0.00	0.32***
		(0.01)	(0.04)		(0.01)	(0.04)
Count subclinical symptoms	0.00	0.44***		0.00	0.44***	
	(0.02)	(0.11)		(0.02)	(0.11)	
Count infectious/ inflammatory diseases	0.00	0.45***		0.00	0.46***	
	(0.02)	(0.10)		(0.02)	(0.10)	
NSAID or Salicylate, past 24 hrs		-0.26	-0.90		-0.26	-0.92
		(0.15)	(0.80)		(0.15)	(0.80)
Use in past 4 weeks		-0.01	-0.36		-0.01	-0.37
		(0.11)	(0.36)		(0.11)	(0.36)
COX-2 Inhibitor		-0.80**	-4.39***		-0.79*	-4.43***
		(0.30)	(0.96)		(0.30)	(0.95)
Inhaled corticosteorids		-0.36	-0.20		-0.35	-0.21
		(0.37)	(0.91)		(0.37)	(0.91)
Corticotropin or glucocorticoid		-0.04	-1.75**		-0.04	-1.78**
		(0.18)	(0.63)		(0.18)	(0.63)
Antirheumatic or antipsoriasitic		-0.57**	2.03		-0.57**	2.07
		(0.17)	(1.50)		(0.18)	(1.54)
Immunosuppressive		0.58*	0.42		0.58*	0.38

		(0.26)	(1.23)		(0.26)	(1.24)
Anti-inflammatory		0.27	0.91		0.28	0.93
		(0.16)	(0.78)		(0.16)	(0.78)
Physical activity past 24 hours		-0.02	-0.32*		-0.02	-0.31*
		(0.03)	(0.14)		(0.03)	(0.14)
Currently pregnant (WIV)						
BMI (WIV)		0.04*	-0.13		0.04*	-0.12
		(0.02)	(0.09)		(0.02)	(0.09)
Cigarette smoking frequency	WIV	WIII	WIV	WIV	WIII	WIV
	0.02**	0.00	0.01	0.02**	0.00	0.01
	(0.01)	(0.00)	(0.01)	(0.01)	(0.00)	(0.01)
Depression diagnosis before WI	1.16		0.67	1.09		0.62
	(0.59)		(0.54)	(0.59)		(0.54)
Constant	-0.84	4.00***	-1.25	-0.98	4.05***	-1.34
	(1.14)	(0.19)	(1.15)	(1.14)	(0.20)	(1.12)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

[b]M1: Substance use frequency→Depressive symptoms; M2: Substance use frequency→Epstein-Barr Virus (EBV); M3: Substance use frequency→Depressive symptoms, controlling for EBV

Table 3.5.4: Linear regression testing mediation of the Stress Model by Epstein-Barr Virus, Females[a]

	FEMALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2	M3	M1	M2	M3
Binge drinking frequency (WI)	0.08	0.01	0.05			
	(0.09)	(0.01)	(0.08)			
Marijuana use frequency (WI)				0.08	0.02*	0.05
				(0.07)	(0.01)	(0.06)
EBV			-0.02			-0.02
			(0.09)			(0.09)
Depressive symptoms (WIII)	0.35***		0.30***	0.35***		0.31***
	(0.02)		(0.02)	(0.02)		(0.02)
Age	WIV	WIII	WIV	WIV	WIII	WIV
	0.02	0.01	0.03	0.02	0.01	0.04
	(0.04)	(0.01)	(0.04)	(0.04)	(0.01)	(0.04)

Race/ethnicity (White=referent)						
Hispanic	0.30	0.07	0.26	0.29	0.07	0.26
	(0.29)	(0.04)	(0.25)	(0.29)	(0.04)	(0.26)
Black	0.55**	0.18***	0.33	0.54**	0.18***	0.32
	(0.20)	(0.04)	(0.19)	(0.20)	(0.04)	(0.19)
Asian	0.64	0.02	0.66	0.63	0.02	0.66
	(0.37)	(0.06)	(0.34)	(0.37)	(0.06)	(0.34)
Native American	0.61	0.05	0.38	0.61	0.05	0.38
	(0.45)	(0.10)	(0.39)	(0.45)	(0.10)	(0.39)
Other	-0.70	0.07	-0.65	-0.72	0.07	-0.67
	(0.49)	(0.13)	(0.45)	(0.50)	(0.13)	(0.45)
Parental education (WI) (college=referent)						
< High school	0.66	0.05	0.67*	0.67	0.05	0.67*
	(0.35)	(0.04)	(0.32)	(0.35)	(0.04)	(0.31)
High school	0.16	0.05	0.10	0.17	0.06	0.11
	(0.18)	(0.03)	(0.17)	(0.18)	(0.03)	(0.16)
College	0.34	0.02	0.28	0.35	0.02	0.29
	(0.19)	(0.03)	(0.18)	(0.19)	(0.03)	(0.18)
Respondent education (college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	2.15***	0.05	1.39***	2.16***	0.04	1.40***
	(0.38)	(0.06)	(0.36)	(0.37)	(0.06)	(0.35)
High school	1.15***	0.03	0.83***	1.16***	0.02	0.83***
	(0.21)	(0.04)	(0.22)	(0.21)	(0.04)	(0.22)
College	0.44**	-0.02	0.19	0.44**	-0.02	0.19
	(0.17)	(0.04)	(0.17)	(0.17)	(0.04)	(0.17)
Childhood maltreatment frequency (none=referent)						
Once	0.58*	0.03	0.52*	0.58*	0.03	0.52*
	(0.25)	(0.05)	(0.23)	(0.24)	(0.05)	(0.23)
Twice	0.22	-0.02	0.07	0.23	-0.02	0.08
	(0.25)	(0.04)	(0.24)	(0.24)	(0.04)	(0.23)
Three times	0.67**	-0.00	0.49*	0.68**	-0.00	0.50*
	(0.21)	(0.03)	(0.20)	(0.21)	(0.03)	(0.19)
Four or more times	1.13***	0.01	0.75***	1.13***	0.01	0.75***
	(0.18)	(0.03)	(0.17)	(0.18)	(0.03)	(0.17)
Stressful life events scale (WIV)		0.00	0.53***		-0.00	0.52***
		(0.01)	(0.05)		(0.01)	(0.05)

Count subclinical symptoms		-0.00	0.71***		-0.00	0.71***
		(0.02)	(0.10)		(0.02)	(0.10)
Count infectious/ inflammatory diseases		0.03	0.18		0.03	0.18
		(0.02)	(0.10)		(0.02)	(0.10)
NSAID or Salicylate, past 24 hrs		0.13	-0.32		0.13	-0.32
		(0.10)	(0.63)		(0.10)	(0.64)
Use in past 4 weeks		0.06	-0.67		0.07	-0.67
		(0.07)	(0.49)		(0.07)	(0.49)
COX-2 Inhibitor		0.50	0.11		0.51	0.15
		(0.31)	(1.45)		(0.31)	(1.44)
Inhaled corticosteorids		-0.14	-0.97		-0.13	-0.94
		(0.20)	(1.03)		(0.20)	(1.03)
Corticotropin or glucocorticoid		0.23	-0.38		0.23	-0.38
		(0.12)	(0.76)		(0.12)	(0.76)
Antirheumatic or antipsoriasitic		0.47**	0.99		0.45**	0.98
		(0.16)	(1.12)		(0.16)	(1.11)
Immunosuppressive		-0.66*	-2.52		-0.65*	-2.50
		(0.29)	(1.32)		(0.29)	(1.32)
Anti-inflammatory		-0.13	0.86		-0.13	0.87
		(0.10)	(0.63)		(0.11)	(0.64)
Physical activity past 24 hours		-0.02	-0.22		-0.02	-0.22
		(0.03)	(0.13)		(0.03)	(0.13)
Currently pregnant (WIV)		-0.10*	0.18		-0.10*	0.18
		(0.05)	(0.26)		(0.05)	(0.26)
BMI (WIV)		0.03*	-0.10		0.03*	-0.10
		(0.01)	(0.08)		(0.01)	(0.08)
Cigarette smoking frequency	WIV	WIII	WIV	WIV	WIII	WIV
	0.01*	0.003**	-0.00	0.01*	0.002**	-0.00
	(0.01)	(0.00)	(0.01)	(0.01)	(0.00)	(0.01)
Depression diagnosis before WI	1.90**		1.48*	1.89**		1.47*
	(0.61)		(0.59)	(0.61)		(0.59)
Constant	1.75	4.50***	1.12	1.63	4.52***	1.05

	(1.20)	(0.17)	(1.22)	(1.18)	(0.17)	(1.21)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

[b]M1: Substance use frequency→Depressive symptoms; M2: Substance use frequency→Epstein-Barr Virus (EBV); M3: Substance use frequency→Depressive symptoms, controlling for EBV

APPENDIX 3.6: AGB MEDIATION FOR STRESS MODEL

Tables 3.6.1 and 3.6.2 display the results of the regression models testing Hypotheses 2.9 and 2.10, respectively. Hypothesis 2.9 was largely not supported, as for males there was only one significant association between binge drinking frequency and AGB (B=0.03, p<0.01). Hypothesis 2.10 was also largely not supported, as there was again only one significant association between binge drinking frequency and AGB (B=-0.02, p<0.05). Both of these significant associations were in accordance with our hypotheses, but AGB in emerging adulthood was not significantly associated with depressive symptoms in young adulthood, contrary to the hypothesized pattern.

Table 3.6.1: Linear regression testing mediation of the Stress Model by Adherence to Gender-typical Behavior, Males[a]

	MALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2	M3	M1	M2	M3
Binge drinking frequency (WI)	0.10	0.03**	0.10			
	(0.05)	(0.01)	(0.05)			
Marijuana use frequency (WI)				0.10	0.01	0.11
				(0.05)	(0.01)	(0.05)
AGB3F			-0.21			-0.20
			(0.14)			(0.14)
Depressive symptoms (WIII)	0.41***		0.40***	0.40***		0.40***
	(0.02)		(0.02)	(0.02)		(0.02)
	WIV	WIII	WIV	WIV	WIII	WIV
Age	0.07	-0.02***	0.07	0.08	-0.02**	0.07
	(0.04)	(0.01)	(0.04)	(0.04)	(0.01)	(0.04)
Race/ethnicity (White=referent)						
Hispanic	-0.05	-0.00	-0.04	-0.06	-0.00	-0.06
	(0.20)	(0.03)	(0.20)	(0.20)	(0.03)	(0.20)
Black	0.63**	0.03	0.63**	0.60**	0.02	0.60**
	(0.22)	(0.03)	(0.22)	(0.22)	(0.03)	(0.22)

					-	
Asian	0.38	-0.09**	0.37	0.34	0.10***	0.32
	(0.33)	(0.03)	(0.32)	(0.32)	(0.03)	(0.32)
Native American	0.30	0.01	0.31	0.30	0.02	0.31
	(0.38)	(0.07)	(0.38)	(0.38)	(0.07)	(0.38)
Other	-0.66*	0.08	-0.64*	-0.69*	0.07	-0.67*
	(0.32)	(0.11)	(0.31)	(0.32)	(0.11)	(0.31)
Parental education (WI) (college=referent)						
< High school	0.29	-0.08*	0.27	0.30	-0.08*	0.28
	(0.23)	(0.04)	(0.23)	(0.23)	(0.04)	(0.23)
High school	0.32	0.01	0.32	0.33	0.01	0.33
	(0.17)	(0.03)	(0.17)	(0.17)	(0.03)	(0.17)
< College	0.17	-0.02	0.17	0.18	-0.02	0.18
	(0.15)	(0.03)	(0.15)	(0.15)	(0.03)	(0.15)
Respondent education						
(college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	1.34***	0.09*	1.35***	1.33***	0.10*	1.35***
	(0.29)	(0.05)	(0.29)	(0.30)	(0.05)	(0.30)
High school	0.95***	0.04	0.95***	0.95***	0.04	0.95***
	(0.19)	(0.04)	(0.19)	(0.20)	(0.04)	(0.20)
< College	0.54***	0.07*	0.55***	0.54***	0.07*	0.55***
	(0.14)	(0.04)	(0.15)	(0.14)	(0.04)	(0.15)
Childhood maltreatment frequency (none=referent)						
Once	0.36	0.05	0.38	0.36	0.05	0.37
	(0.23)	(0.03)	(0.23)	(0.23)	(0.03)	(0.23)
Twice	0.43	0.06	0.45	0.42	0.06	0.44
	(0.24)	(0.04)	(0.24)	(0.24)	(0.04)	(0.24)
Three times	0.98***	0.07*	1.00***	0.98***	0.07*	0.99***
	(0.17)	(0.03)	(0.17)	(0.17)	(0.03)	(0.17)
Four or more times	1.21***	0.07**	1.22***	1.20***	0.07**	1.21***
	(0.20)	(0.03)	(0.20)	(0.20)	(0.03)	(0.20)
Depression diagnosis before WI	1.22*		1.21*	1.14*		1.13
	(0.58)		(0.58)	(0.57)		(0.58)
Constant	-0.49	1.25***	-0.14	-0.67	1.16***	-0.37
	(1.15)	(0.15)	(1.17)	(1.14)	(0.14)	(1.16)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)
[b]M1: Substance use frequency→Depressive symptoms; M2: Substance use frequency→Adherence to Gender-typical Behavior (AGB); M3: Substance use frequency→Depressive symptoms, controlling for AGB

Table 3.6.2: Linear regression testing mediation of the Stress Model by Adherence to Gender-typical Behavior, Females[a]

	FEMALES					
	Binge drinking frequency			Marijuana use frequency		
	M1[b]	M2	M3	M1	M2	M3
Binge drinking frequency (WI)	0.10	-0.02*	0.10			
	(0.08)	(0.01)	(0.08)			
Marijuana use frequency (WI)				0.11	0.00	0.11
				(0.07)	(0.01)	(0.07)
AGB3F			0.18			0.17
			(0.16)			(0.16)
Depressive symptoms (WIII)	0.35***		0.35***	0.35***		0.35***
	(0.02)		(0.02)	(0.02)		(0.02)
	WIV	WIII	WIV	WIV	WIII	WIV
Age	0.02	0.03***	0.01	0.02	0.03***	0.02
	(0.04)	(0.01)	(0.04)	(0.04)	(0.01)	(0.04)
Race/ethnicity (White=referent)						
Hispanic	0.21	-0.00	0.21	0.20	-0.00	0.20
	(0.30)	(0.04)	(0.30)	(0.30)	(0.04)	(0.30)
Black	0.47*	-0.08**	0.48*	0.45*	-0.08**	0.47*
	(0.20)	(0.03)	(0.20)	(0.20)	(0.02)	(0.20)
Asian	0.59	-0.13**	0.61	0.58	-0.13**	0.61
	(0.37)	(0.05)	(0.37)	(0.37)	(0.05)	(0.37)
Native American	0.61	-0.05	0.62	0.61	-0.05	0.62
	(0.46)	(0.06)	(0.46)	(0.45)	(0.06)	(0.45)
Other	-0.73	-0.02	-0.72	-0.75	-0.02	-0.75
	(0.48)	(0.08)	(0.48)	(0.49)	(0.08)	(0.49)
Parental education (WI) (college=referent)						
< High school	0.66	0.02	0.66	0.67	0.02	0.66
	(0.35)	(0.03)	(0.35)	(0.35)	(0.03)	(0.35)
High school	0.17	0.03	0.16	0.18	0.03	0.18
	(0.18)	(0.03)	(0.18)	(0.18)	(0.03)	(0.18)
< College	0.35	0.04	0.34	0.36	0.04	0.35
	(0.19)	(0.02)	(0.19)	(0.19)	(0.02)	(0.19)

Respondent education (college=referent)	WIV	WIII	WIV	WIV	WIII	WIV
< High school	2.31***	0.14***	2.31***	2.31***	0.12***	2.30***
	(0.39)	(0.04)	(0.39)	(0.37)	(0.04)	(0.37)
High school	1.26***	0.09**	1.26***	1.26***	0.08**	1.26***
	(0.20)	(0.03)	(0.20)	(0.20)	(0.03)	(0.20)
< College	0.52**	0.05	0.51**	0.52**	0.05	0.51**
	(0.16)	(0.03)	(0.16)	(0.16)	(0.03)	(0.16)
Childhood maltreatment frequency (none=referent)						
Once	0.58*	-0.02	0.59*	0.58*	-0.03	0.59*
	(0.25)	(0.03)	(0.25)	(0.24)	(0.03)	(0.24)
Twice	0.21	-0.00	0.22	0.22	-0.01	0.23
	(0.25)	(0.04)	(0.24)	(0.24)	(0.04)	(0.24)
Three times	0.69**	0.06**	0.68**	0.70**	0.06**	0.69**
	(0.21)	(0.02)	(0.21)	(0.21)	(0.02)	(0.21)
Four or more times	1.15***	0.05*	1.15***	1.15***	0.04	1.16***
	(0.18)	(0.02)	(0.18)	(0.18)	(0.02)	(0.18)
Depression diagnosis before WI	1.97**		1.96**	1.95**		1.94**
	(0.61)		(0.61)	(0.61)		(0.61)
Constant	1.89	0.13	1.90	1.76	0.18	1.76
	(1.19)	(0.12)	(1.19)	(1.17)	(0.12)	(1.16)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

[b]M1: Substance use frequency→Depressive symptoms; M2: Substance use frequency→Adherence to Gender-typical Behavior (AGB); M3: Substance use frequency→Depressive symptoms, controlling for AGB

APPENDIX 3.7: AGB MODERATION OF THE SELF-MEDICATION MODEL

Table 3.7.1 displays the only significant moderation result, which supported Hypothesis 2.5. There was significant interaction between AGB and depressive symptoms at Wave III (B=0.05, p<0.05). Hypotheses 2.6, 2.11, and 2.12 were not supported.

Table 3.7.1: Linear regression testing moderation of the Self-Medication Model for binge drinking frequency by AGB for males[a]

Depressive symptoms (WIII)	-0.04*
	(0.02)
AGB (WIII)	-0.05
	(0.10)
Depressive symptoms (WIII) x AGB (WIII)	0.05*
	(0.02)
Binge drinking frequency (WIII)	0.36***
	(0.02)
Age (WIV)	-0.11***
	(0.02)
Race/ethnicity (White=referent)	
Hispanic	-0.00
	(0.10)
Black	-0.21*
	(0.10)
Asian	-0.11
	(0.12)
Native American	0.01
	(0.22)
Other	-0.64*
	(0.29)
Parental education (WI) (college=referent)	
< High school	-0.04
	(0.12)
High school	-0.06
	(0.08)
< College	0.03
	(0.08)
Respondent education (WIV) (college=referent)	
< High school	0.05
	(0.14)
High school	0.18
	(0.10)
< College	0.10
	(0.07)

Childhood maltreatment frequency (none=referent)	
Once	0.20
	(0.11)
Twice	-0.05
	(0.12)
Three times	-0.05
	(0.08)
Four or more times	0.02
	(0.08)
Drank alcoholic beverage before WI	0.68***
	(0.09)
Constant	3.92***
	(0.56)

*** p<0.001, ** p<0.01, * p<0.05; numbers are regression coefficients, standard errors in parentheses

[a]Wave I (WI), Wave III (WIII), Wave IV (WIV)

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