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THE BUFFERING EFFECTS OF RESILIENCE ON ALCOHOL USE: A PHENOTYPIC AND GENOTYPIC INVESTIGATION

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by

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Table of Contents

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List of Tables

List of Figures

List of Abbreviations

AD……Alcohol Dependence
AFR……African
AMR……Admixed from the Americas
ARAS……Adolescent Resilience Attitudes scale
ASPD……Antisocial Personality Disorder
AUD……Alcohol Use Disorder
BRS……Brief Resilience Scale
CAS……College Alcohol Study
CD-RISC……Connor Davidson Resilience scale
cGxE……candidate gene by environment
EAS……East Asian
EUR……European
FDR……false discovery rate
GAD……Generalized Anxiety Disorder
GCTA……genome-wide complex trait analysis
GPA……grade point average
GxE……gene by environment
GWAS……genome-wide association study
HWE……Hardy-Weinberg equilibrium
IBD……identity by descent
LD…….linkage disequilibrium
LEC……Life Events Checklist
MAF……minor allele frequency
MTAG ……multi-trait analysis of GWAS
OR……odds ratio
PC……principal components
PCA……principal components analysis
PGC……Psychiatric Genomics Consortium
PRS……polygenic risk score
PTSD……Posttraumatic stress disorder
QC……quality control
RSES……Response to Stressful Events scale
SAS……South Asian
SNP……single nucleotide polymorphism
SSGAC……Social Sciences Genetic Association Consortium
SUD……Substance Use Disorder
S4S……Spit for Science
TE……traumatic event/trauma exposure
VET……Vietnam Era Twin Registry

Abstract

The college years encompass a time of vulnerability for problematic alcohol use/alcohol use disorder (AUD) and exposure to traumatic events (TE), which is a transdiagnostic risk factor for AUD, posttraumatic stress disorder (PTSD), and comorbid AUD-PTSD. However, not all who experience a TE develop these disorders, highlighting the need to identify factors that impact post-trauma outcomes. Resilience has been shown to be associated with lower alcohol consumption and related problems following TE, though the buffering effects of resilience on alcohol use have not yet been examined. Further, twin studies demonstrate that resilience is moderately heritable, but further research is needed to understand the molecular genetics of resilience (e.g., establishment of molecular heritability, identification of individual variants associated with resilience, examination of overall aggregate genetic risk in relation to AUD, PTSD, and other putative protective factors). Using data of the TE exposed subsample of a larger genetically informative longitudinal cohort study of college students (i.e., Spit for Science, *N*=7,367), the present study had three aims: 1) investigate the buffering effect of resilience against new onset TEs on alcohol use phenotypes; 2) identify individual variants associated with resilience, as well as examine the overall heritability of resilience and 3) examine the aggregate genetic overlap of resilience with alcohol use phenotypes, PTSD, and other protective factors using aggregate risk analyses. First, resilience was examined as a buffer against new onset TE on various alcohol use outcomes using a longitudinal path analysis framework. Findings demonstrated that resilience acts as a buffer in the wake of college onset TE against AUD symptoms, but not for alcohol consumption nor binge drinking status. Second, the genetic underpinnings of resilience were investigated by examining individual variants using genome wide association study (GWAS) analyses, and by calculating the SNP-based heritability via genome-wide complex trait analysis (GCTA). Meta-analyzed GWAS identified no SNPs

meeting genome-wide significance, but revealed 9 SNPs meeting the suggestive of significance threshold that should be examined in future research with larger samples sizes. The majority of these SNPs mapped on to the *SEZ6L* gene, implicated in Bipolar Disorder and seizure activity, as well as a cluster of genes located on chromosome 8 associated with the metabolism of vitamins such as Vitamin B folate and Vitamin E, and as such, implicated in inflammatory response. GCTA estimated modest heritability for resilience, but the estimates did not differ significantly from zero. Lastly, polygenic risk scores (PRS) were used to examine the genetic correlation between resilience and alcohol dependence (AD), alcohol consumption, PTSD, and subjective well-being. Findings support polygenic risk for alcohol consumption as related to resilience in the EUR sub-sample only, and polygenic risk for PTSD as associated with resilience in the AFR sub-sample only. Findings are further discussed in the context of clinical implications, limitations, and future directions.

Chapter 1: Introduction

I. Overall Statement of the Problem

College students, as compared to their same age peers, are at an increased vulnerability for experiencing potentially traumatic events (e.g., Bernat, Ronfeldt, Calhoun, & Arias, 1998), as well as engaging in risky alcohol use (e.g., Schulenberg et al., 2019), both of which are associated with the subsequent development of alcohol use disorder (AUD). Traumatic events, although most commonly thought of as germane to posttraumatic stress disorder (PTSD), also act as a trans-diagnostic risk factor that is associated with psychopathology, such as AUD (e.g., Berenz, et al., 2016). Moreover, AUD is commonly comorbid with PTSD (e.g., Grant, et al. 2015). Given the increased risk of TE, risky drinking, and ensuing development of AUD and/or PTSD, identifying protective factors in this population is imperative. Resilience is a key protective factor to consider, though extant investigations are methodologically limited (for a review, see Cusack & Amstadter, under review) and, as such, there are critical gaps in the literature to be filled.

To date, behavioral genetic (i.e., twin study) designs have established heritability estimates of PTSD (e.g., Stein et al., 2002) and AUD (e.g., Kendler et al., 2016), and an emerging line of behavioral genetic research has also demonstrated a moderate heritability for resilience (e.g., Amstadter, Myers, & Kendler, 2014), though further work is needed. However, little is known about the molecular genetic architecture of resilience, including potential overlap with PTSD and AUD. Thus, the purpose of this dissertation is three-fold: to extend our understanding of how resilience may act as a buffer (i.e., protective in the wake of new onset TE) against adverse outcomes (i.e., AUD, PTSD) in the wake of college onset trauma, to identify individual variants associated with resilience and establish the heritability of resilience, and to examine the molecular overlap of resilience with AUD, PTSD, and other related, protective

phenotypes (e.g., well-being). In the following sections, an overview of the prevalence and correlates of TE, as well as risky alcohol use and AUD, in college students is presented. Next, the extant research examining resilience as a protective factor is reviewed, including a discussion of the various theoretical conceptualizations used to define resilience, demographic correlates of resilience, and methodological limitations of the extant resilience literature. Following, the conceptualization of resilience used in the present study is discussed in detail, followed by a review of studies that examine the genetic components influencing both AUD and PTSD. Lastly, recent innovations in molecular statistical genetics methods will be discussed with particular attention to their application to the data to be analyzed herein. The introduction concludes with an outline of the aims and hypotheses for this dissertation.

II. Prevalence estimates and correlates of alcohol consumption.

a. Prevalence estimates of alcohol use.

Alcohol use in college students has been considered a major public health concern since the mid-1990s (e.g., Dawson, Grant, Stinson, & Chou, 2004; Hingson, Zha, & Weitzman, 2009), and continues to be an increasingly important problem across campuses. Indeed, college is a time of increased vulnerability for problematic alcohol use and AUD. Alcohol use peaks during the college-aged years and decreases to moderate levels in the mid-twenties (Slutske, 2005), although some individuals maintain risky use, and subsequently develop an AUD. Extant research has demonstrated that the first few years following high school are a critical developmental period with notable role changes and experience shifts (e.g., moving out of parent's home and thus lower parental monitoring) that contribute to an increased risk for escalating alcohol use (Patrick, Terry-McElrath, Evans-Polce, & Schulenberg, 2020).

Attending a four-year institution, as opposed to not attending college or attending a two-year institution, is associated with heavier alcohol use prevalence (Carter et al. 2010;

Schulenberg et al., 2019), as well as faster increases in alcohol consumption (Patrick, Terry-McElrath, Kloska, & Schulenberg, 2016). Notably, college students engage in drinking behaviors more often than their same-aged peers (Slutske et al., 2004), whereby approximately 70% of college students report using alcohol in the past month (O'Malley & Johnston, 2002), and nearly half of all college students endorsing at least one heavy drinking episode (i.e., 5+ drinks on one occasion for males, 4+ for a female) in the past two weeks or one month (Substance Abuse and Mental Health Services Administration, 2006). Further, college students experience more alcohol-related consequences, with 18% of U.S. college students (24% of males, 13% of females) suffering from clinically significant alcohol-related problems in the past year, as compared to 15% of their non-college attending peers (Slutske et al., 2005). Examining problematic drinking and related symptoms at the diagnostic level, Caldeira and colleagues (2009) found that nearly half (~44%) of all students in their cohort study met criteria for an alcohol use disorder (i.e., alcohol abuse or dependence) at least once during their first three years of college. Although intervention and prevention efforts have focused on reducing the prevalence of binge drinking, rates have continued to be stable for ~20 years (Wechsler & Nelson, 2008), without any indication of a forthcoming decrease.

Although both males and females endorse engaging in risky drinking behaviors while in college, there are established sex differences in alcohol consumption among college students. Historically, male college students have been consistently shown to consume more alcohol and endorse higher levels of alcohol-related problems than females (e.g., Geisner, Larimer, & Neighbors, 2004), and report more frequent binge drinking and substance-use coping (Harrell & Karim, 2008). However, the magnitude of sex differences in alcohol consumption is rapidly shrinking in recent years (e.g., WHO, 2014), whereby the rate of disordered consumption is

increasingly more rapidly in females, than in males (Grant et al., 2017; Dawson, Goldstein, Saha, & Grant, 2015). More specifically, the prevalence rate of AUD in females has increased by 84% in the past ten years, as opposed to an increase of 34% in males (Grant et al., 2017). Further, females have been shown to demonstrate an accelerated progression from the first use of alcohol to the onset of AUD, and a higher vulnerability to medical consequences related to alcohol use (Agabio, Pisnau, Luigi Gessa, & Franconi, 2017). Given the rapidly evolving nature of evidenced sex differences in alcohol consumption and related problems, further research into sex differences in college students, specifically, is warranted.

In addition to sex differences, there are differences in prevalence rates of AUD according to race and ethnicity whereby Native Americans/Alaskan Natives endorse the highest prevalence of AUD (12.1%), followed by White (8.9%), Hispanic (7.9%), Black (6.9%), and Asian (4.5%) individuals (Falk, Yi, & Hiller-Sturmhofel, 2008). Racial and ethnic differences in alcohol use and AUD in the general population translate to differences in college students specifically. For example, four-year college status is positively associated with heavy alcohol use among white students, but inversely related to drinking among those identifying as black or Asian (Paschall, Bersamin, & Flewelling, 2005). Further, two-year college attendance also reduced the risk for heavy drinking among blacks, Hispanics, and students identifying as Native American or multi-ethnic (Paschall, Bersamin, & Flewelling, 2005).

Risky drinking also seems to occur most amongst those students identifying as White, whereby research has demonstrated that higher rates of alcohol-related blackouts is associated with European American ancestry as compared to Asian and Latinx students (Schuckit, Smith, Goncalves, & Anthenelli, 2016). In an epidemiologic sample of U.S. adults, relative to those identifying as White, non-Hispanics, African American females and Latinx males and females

are at an increased risk for the development of AUD, even at similar levels of alcohol consumption (Grant et al. 2012). The extant research, taken together, supports the idea that differences in consumption and risk for the development of AUD vary across racial and ethnic lines, and that attending college may be a risk factor for those identifying as White, but not for those identifying as ethnic or racial minorities.

b. Correlates of alcohol consumption.

Overview of the Literature. The heavy and problematic alcohol use that is common in college students (e.g., American College Health Association [ACHA], 2016) can lead to a myriad of adverse outcomes ranging from a decline in academic performance to potentially life-threatening outcomes such as physical injury, drunk driving etc. (ACHA, 2016; White & Hingson, 2014). Hingson, Zha, and Smyth (2017) documented that in 2014, 38.8% of emerging adults aged 18-24 reported past-month heavy episodic drinking. In addition to high rates of risky drinking, the authors documented the associated risks, noting that in 2014, there were 2,614 alcohol-related traffic deaths, 4,105 alcohol-related unintentional injury deaths, and 891 alcohol-related overdose deaths, highlighting the significance of drinking as a public health concern on college campuses. Risky drinking behavior is related to, and perhaps a contributing factor of, various academic, emotional, physical, social, and legal problems commonly experienced by undergraduate students (for a review see Boyd, McCabe, & Morales, 2005).

Alcohol and Academic Impairment. Alcohol consumption is strongly linked with impaired academic performance across college campuses. For example, in their longitudinal investigation of the impacts of alcohol use on GPA, Meda and colleagues (2017) found that those students reporting moderate-to-high alcohol consumption had lower GPAs as compared to their non/low alcohol-using peers (Meda et al. 2017). Further, alcohol use has been shown to be

associated with disruptions in college enrollment, or "dropping out" from college (e.g., Arria et al., 2013). This trajectory may ultimately lead to greater likelihood of delayed graduation, or failure to graduate, leading to a cascade of adverse outcomes such as poor employment outcomes and lack of healthcare coverage (Arria, Caldeira, Bugbee, Vincent, & O'Grady, 2013).

Alcohol and Personal Injuries. Harvard's College Alcohol Study (CAS) links increases in average alcohol consumption with a rise in injury rates, suggesting a linear association between average consumption and injury, with every additional drink per drinking occasion in the past month leading to a 3-5% increase in injury rate (Wechsler & Nelson, 2006). Similar to patterns observed between binge drinking and academic performance, students who report alcohol-induced memory blackouts demonstrate an increased vulnerability to experiencing alcohol-related injury in a dose-response manner, whereby risk for personal injury increases with each additional blackout during a 24-month period (Mundt, Zakletskaia, Brown, & Feming, 2012). Further, not only does drinking increase the risk for unintentional injury, it also increases the risk at which unintentional injuries lead to unintentional injury deaths. For example, it was reported that more than 1,800 college students between the ages of 18 and 24 die each year from alcohol-related unintentional injuries, including motor-vehicle crashes (Hingson et al. 2009).

Alcohol and Physical Health. The majority of students who endorse drinking on college campuses report experiencing short-term, health-related consequences such as nausea, vomiting, and headaches, with more than 40% of drinkers having "hangoverlike experiences" (i.e., fatigue, headache, nausea, dehydrated, etc.) at least once over a 14 day period, and after 50% of all drinking episodes (Piasecki, Slutske, Wood, & Hunt-Carter, 2010). A myriad of long-term health consequences of alcohol consumption have been documented throughout the alcohol use literature more broadly, though certainly apply to college student populations as well. According

to the Global Status Report on Alcohol and Health disseminated by the World Health Organization (2019), over 200 health conditions are linked to alcohol use, ranging from liver disease, to cancers, cardiovascular diseases, HIV/AIDS, and obesity. The enormous global burden of disease caused by harmful alcohol use exceeds those caused by many other risk factors and diseases, and as such, problematic alcohol use in any setting, and especially on college campuses, warrants further investigation to inform both intervention and prevention efforts.

Alcohol and Psychopathology. Most mental health disorders have their peak onset during young adulthood, the developmental period of the majority of college students (Pedrelli, Nyer, Yeung, Zulauf, & Wilens, 2015) with ~50% of people aged 18-24 being enrolled in college (Census Bureau US, 2012). As such, college students are at an increased risk for psychiatric disorders (Eisenberg et al. 2007) as compared to their same age non-college peers, which is, perhaps, associated with the fact that college students consume more alcohol than their non-college peers (e.g., Merrill & Carey, 2016). For example, approximately three-fourths of lifetime mood or anxiety disorders begin by age 24, an age that is typical of a college student (Kessler et al. 2005), and 18.5% and 16.7% of college students meet criteria for 12-month mood and anxiety disorders, respectively (Auerbach et al. 2018).

Mental health problems are associated with heavy episodic drinking that occurs on college campuses (Cranford et al. 2009), and those students reporting mental health symptoms are more likely to experience problems related to alcohol use than those without symptoms, regardless of drinking levels (Kenney and LaBrie, 2013; LaBrie, Kenney, & Lac, 2010). More specifically, the risk for experiencing negative alcohol-related outcomes, including development of an AUD, is higher among students experiencing depression (Geisner, Mallett, & Kilmer, 2012), anxiety (Litt, Lewis, Blayney, & Kaysen, 2013), and poor overall mental health more

generally (LaBrie, Kenney, & Lac, 2010). Students experiencing symptoms of psychopathology are more likely to engage in alcohol consumption for several reasons including coping, lowered drinking refusal self-efficacy, and increased salience of alcohol cues, all reasons that exacerbate risk for the development of adverse, alcohol-related consequences (e.g., Ham and Hope, 2003; Park & Grant, 2005). Alcohol consumption on college campuses also increases risk for sexual and physical assault, resulting in an increased risk for the development of PTSD, with rates of PTSD in college samples (i.e., 8-9%) aligning with those in general community samples (e.g., Read, Ouimette, White, Colder, & Farrow, 2011). Indeed, research has shown that the odds of sexual assault perpetration for males with higher bar and party attendance were higher than those for males with lower or no bar and party attendance. Notably, college students are at an increased risk for experiencing TEs as related to their risk drinking, though they are also a population at increased risk of exposure to a TE independent of their alcohol consumption.

III. Environmental influences (i.e., trauma exposure)

a. Prevalence Estimates of Trauma Exposure

College is a time of increased risk for problematic alcohol use, as well as exposure to TEs. This is notable considering that TEs act as a trans-diagnostic risk factor for AUD, and its comorbidities such as PTSD. A TE is defined as a person's subjective response to "exposure to actual or threatened death, serious injury, or sexual violence" (*Diagnostic and Statistical Manual of Mental Disorders [DSM-5]*, 5th ed, APA, 2013, p.271). Per the DSM-5 criterion, a TE can occur through direct experience, witnessing an event in person, learning it has occurred to a loved one, or repeated exposure (e.g., verbally, visually, etc.) to details of the TE. The most common examples of TEs include, but are not limited to, physical assault, sexual assault, motor vehicle accidents, or experiencing a life-threatening illness (e.g., Benjet et al., 2016).

Although TE is common in the general population (e.g., Benjet, et al., 2016), college students report experiencing TEs at higher rates, with exposure estimates ranging from 66% to 85% (e.g., Read, Ouimette, White, Colder, & Farrow, 2011; Smyth, Hockemeyer, Heron, Wonderlich, & Pennebaker, 2008). Indeed, the majority of college students (e.g., 85%) endorse experiencing at least one TE at some point in their lives, with 21% endorsing experiencing one over just a two-month period while enrolled in an undergraduate institution (Frazier et al., 2009). More specifically, 8% of females experience a completed sexual assault in their first semester alone (Carey, Durney, Shepardson, & Carey, 2015).

Using the first cohort from the dataset that will be used for the proposed analyses, "Spit for Science" (S4S), research has evidenced notable rates of past-year TE exposure, with 22% endorsing accidental (i.e., natural disaster, motor-vehicle accident), 5.7% endorsing a physical TE, and 11.3% endorsing a sexual TE (Moore, et al., 2017). Further, research using four cohorts has demonstrated notable rates of initial sexual assault victimization (i.e., 65.2%), a particularly potent TE type, as well as concerning rates of re-victimization over the course of college (i.e., Year 1= 24.0%, 2=28.8%, 3=26.3%, 4=28.8%; Cusack et al., 2019), highlighting the need to examine college onset TE specifically.

As with alcohol consumption, there are important demographic differences in exposure to TEs. In studies of college students, consistent with studies of community samples, male sex is supported as a risk factor for TEs (e.g.,[14]). However, the existing literature on sex differences in college student populations specifically, is mixed. Read, Ouimette, White, Colder, and Farrow (2011) found that females were more likely to report TEs as compared to males, and experienced, on average, more events than men. Similarly, although more general epidemiological work has demonstrated that males are at greater risk for TEs, a number of

studies have reported that females are at greater risk for specific, Criterion A TE, such as sexual assault (e.g., Smyth et al., 2008; Vrana & Lauterbach, 1994).

Race and ethnicity are other important demographic variables to consider when assessing the prevalence rates of TE in college student populations. In college samples, a few studies have found that those identifying as ethnic minorities (i.e., not White), are at an increased risk for stressful life events (e.g., Acierno, Kilaptrick, & Resnick, 1999). Further research into racial and ethnic differences in TE have found that students identifying as Black/African American specifically are at an increased risk for exposure to TEs, as compared to their White peers (e.g., Ai et al. 2011; McGruder-Johnson et al., 2000). In contrast, Read and colleagues (2011) found Non-White ethnicity as not associated with exposure to TEs, broadly. However, their results demonstrated that ethnic minority status was indeed associated with experiencing specific trauma types whereby ethnic minorities reported greater exposure to combat, physical violence, and unwanted sexual experiences.

b. Correlates of TE

TE and Academic Impairment. Both exposure to TEs and the development of PTSD have been shown to play a role in college student dropout rates. For example, Boyraz, Granda, Baker, Tidwell, and Waits (2016) found that those students that endorse a lifetime history of exposure to TEs and PTSD symptoms were less likely to be enrolled at the second year of college due to having a lower grade point average (GPA). Much of the more recent extant literature on TEs and academic performance has focused on specific types of TEs. Results from Jordan, Combs, and Smith (2014) demonstrated that females with prior sexual assault exposure enter college with lower GPA scores and continue to earn lower grades than students without sexual assault exposure, and further, that females assaulted during college tended to have lower

GPAs by the end of the semester than females without a sexual victimization history. The negative impact of TEs on academic outcomes is exacerbated for those students endorsing exposure to multiple events (Mengo & Black, 2016), a notable statistic given the high re-victimization rates in college student populations (e.g., Cusack, et al. 2019).

TE and Physical Health Outcomes. There are a multitude of post-trauma sequela that are associated with both physical and mental health (e.g., AUD, PTSD), making exposure to TEs a significant global public health concern. Although the literature based on TE and physical health outcomes in college student populations specifically is quite sparse, the little evidence there is supports a connection between TEs and poor physical health, whereby poor self-rated health is associated with lifetime PTSD and multiple rape history (Zinzow et al. 2011). The connection between TEs and adverse physical health consequences, more broadly, is well-established, whereby individuals reporting at least one TE are at a greater risk for developing a physical health condition, even after controlling for psychopathology symptoms (Keyes et al. 2013). Individuals who experience TEs, self-report increased health complaints, ranging from minor physical health symptoms such as shortness of breath, to more serious, long-term conditions such as cardiovascular disease (e.g., Flood, McDevitt-Murphy, Weathers, Eakin, & Benson, 2009). In addition to an increased risk for the development of most physical health phenotypes (e.g., arthritis, heart disease, diabetes, etc.), individuals that have experienced eight or more traumatic events report a younger age of onset, 15 years earlier, for a physical health condition than those who did not endorse such a high level of trauma. Taken together, there is sufficient evidence to support a deleterious relationship between TE exposure and physical health outcomes in the general population, which can likely be presumed of college students as well.

TEs and Psychopathology. Perhaps more common than the development of physical health symptoms following exposure to a TE is the development of psychiatric symptoms and related disorders. Generally speaking, trends that have been well-founded in epidemiological samples are consistent with what has been demonstrated with college student samples, whereby exposure to at least one TE increases the likelihood of reporting any mental illness (prevalence of 23.2%) as compared to those who had not been exposed (prevalence rate: 14.3%; Forman-Hoffman, et al. 2012-2016). Consistently, in their sample of college students, subjects reporting at least one lifetime TE, reported higher levels of depression, anxiety, and PTSD symptomatology, as compared to those not endorsing TE exposure. Although PTSD, a stress-related disorder requiring exposure to a TE and characterized by symptoms of re-experiencing, avoidance, and hyperarousal, is most commonly thought of when considering post-trauma psychiatric outcomes, there are many additional psychiatric concerns that often develop following exposure to a TE (e.g., MDD, GAD, AUD).

TEs and Alcohol Use. AUD in particular is a common post-trauma sequela, and is highly comorbid with PTSD (Norman, Haller, Hamblen, Southwick, & Pietrzak, 2018), with lifetime co-morbidity rates ranging from 30-59%. Though, to date, there have been no published prevalence rates of PTSD-AUD co-morbidity at the diagnostic level in college students, the literature base supports that college students with current PTSD evidence greater substance use and abuse than those diagnosed with current social phobia or those classified as “well-adjusted” (McDevitt-Murphy, Murphy, Monahan, Flood, & Weathers, 2010). A lifetime diagnosis of AUD or PTSD are separately associated with poorer health and well-being; extant research indicates that when occurring together, individuals experience higher rates of psychiatric comorbidities (e.g., Bowe & Rosenheck, 2015), physical health problems (e.g., Hoge, Terhakopian, Castro,

Messer, & Engel, 2007; Bowe & Rosenheck, 2015), and psychosocial difficulties (Ouimette, Goodwin, & Brown, 2006). Further, co-morbid AUD and PTSD are associated with worse clinical outcomes such poorer treatment prognosis (Blanco et al., 2013; Isper, Wilson, Akindipe, Sager, & Stein, 2015), shorter time to relapse posttreatment (Bonanno, 2004), and higher suicidal ideation and attempts (Rojas, Bujarski, Babsson, Dutton, & Feldner, 2014). With the notable rates of both TE and risky alcohol consumption, college students represent a population that may be most at risk for developing PTSD, AUD, or PTSD *and* AUD following TE exposure.

IV. Resilience as a protective factor

Although exposure to TE acts as a trans-daignostic risk factor for the development of psychopatholgoy (e.g., AUD, PTSD, etc.), there is hetereogeneity in response to TE, whereby not every person who experiences a TE goes on to develop psychopathology. For example, in epidemiologic samples, upwards of 70% of U.S. adults have expereinced at least one TE in their lifetime (Benjet et al., 2016). However, only 6.7% of Americans meet lifetime diagnostic criteria for PTSD, and even fewer (4.7%) meet past year criteria (Benjet et al., 2016).

Resilience is a key protective factor that has been hypothesized to protect against adverse outcomes following exposure to a TE, potentially contributing to this hetereogeneity in post-trauma sequela. Although there are numerous conceptualizations of resilience used throughout the extant literature, broadly, resilience is defined as a resistance to distress following an adverse life experience, or positive adaption in the face of stressors (e.g., Bonanno, 2004; Connor & Davidson, 2003; Luthar, Cicchetti, & Becker, 2000).

a. Theoretical Conceptualizations

Not surprisingly, given this broad conceptuliazation of resilience (e.g., Bonanno, 2004; Connor & Davison, 2003; Luthar et al., 2000) the concept has been opertationalized in different

ways in the literature. Across this heterogeneous literature resilience is most commonly operationalized as a trait (Connor & Davidson, 2003), outcome (e.g., lack of PTSD symptoms; Bonanno, 2004), or process (Masten & Naryan, 2012).

More specifically, the trait-oriented approach assumes resilience as being an intrinsic and moderately stable attribute, similar to that of a personality trait, that enhances one's ability to adapt in the face of stress or adversity (Block & Block 1980, Connor et al., 2013; Hu et al., 2015). Alternatively, resilience as an outcome refers to conceptualizations that assess mental and/or physical health following significant stress or adversity, whereby an individual is deemed as demonstrating resilience if they are able to maintain or regain their previous mental/physical health status in spite of said adversity (e.g., Kalisch et al., 2017). Using this conceptualization, resilience can only be assessed in the context of the individual having experienced stress, trauma, etc., (Luthar et al., 2000; Masten, 2001), is viewed as modifiable (Masten, 2001), and is thought to be at least partially influenced by resilience or protective "factors" (i.e., internal: epigenetics, personality traits, beliefs, etc.; external: social and material resources, etc.; Fletcher & Sarkar, 2013; Southwick & Charney, 2012; Hobfoll, Stevens, & Zalta, 2015). Lastly, resilience when considered as the dynamic process of adaptation, is understood as a trajectory of recovery following a stressor characterized by a trajectory of stable mental health during or after a period of adversity or by a pattern of temporary disturbance (i.e., symptoms) that is followed by rapid and successful recovery (e.g., Sapienza and Masten, 2011; Windle, 2011; Mancini and Bonanno 2009, etc.).

b. Demographic Correlates

Early work examining demographic differences in resilience has evidenced differences across both sex and racial lines. For example, Bonanno and colleagues (2007), defining

resilience as the absence of PTSD symptoms, found that both sex and ethnicity uniquely contributed to the prediction of resilience levels, whereby females were half as likely to demonstrate resilience as compared to males, and those identifying as Asian were three times as likely to be resilient as those identifying as White. Similarly, in their sample of burn patients, Masood, Masud, and Mazahir (2016) used a self-report measure of both state and trait resilience, and found that males were more likely to demonstrate resilience as compared to females. Although research supports that females typically score lower on measures of resilience as compared to men, this may be a product of current conceptualizations of resilience, and the lack of portrayal of the ways that gender roles, social expectations, and environmental factors interact to shape female and male responses to adversity differently (Hirani, Lasiuk, & Hegadoren, 2016). The research on racial/ethnic differences in resilience is mixed, with some research supporting the tenant that those identifying as racial minorities score higher on measures of resilience (e.g., Bonanno, 2007), and others suggesting that non-Hispanic White individuals score higher (e.g., Herbert, Leung, Pittman, Floto, & Afari, 2018). Nevertheless, both sex and race/ethnicity are important demographic variables to account for in future examinations of resilience.

c. The Buffering Hypothesis.

The buffering hypothesis of resilience is one of the predominant theories used to explain the protective effects of resilience against adverse outcomes. The buffering hypothesis postulates that those with higher levels of resilience should experience less symptoms of psychopathology following exposure to adversity than those with lower levels of resilience, assuming the protective role of resilience (e.g., Sheerin et al., 2018). Indeed, existing research has evidenced the protective effects of resilience whereby those individuals high in resilience, as measured by a

self-report measure (i.e., Resilience Scale for Adults; RSA) remain "unchanged" in terms of depressive, anxiety, and somatic symptoms in the face of adversity (e.g., Hjemdal, Friborg, Stiles, Resenvinge, & Martinussen, 2006).

The existing literature provides a moderate amount of evidence in support of the buffering hypothesis on internalizing symptoms, and less so on externalizing symptoms. For example, Sheerin and colleagues (2018) demonstrated that a discrepancy-based operationalization of resilience (i.e., the difference between the actual and predicted distress score given an individual's stressful life event count) buffered against both Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) at high numbers of past-year stressful life events. Further, Green, Beckham, Youssef, and Elbogen (2014) found evidence to support resilience at baseline, as measured by a self-report measure of perceived coping abilities (i.e., CD-RISC), was associated with alcohol misuse at the one-year follow-up time-point, though the authors did not account for new onset TEs in their analyses.

Much of the extant literature on resilience demonstrates that resilience is negatively associated with internalizing and externalizing outcomes, though this research base is largely cross-sectional in nature. Indeed, resilience (as measured by self-report measures such as: The Response to Stressful Experiences Scale [RSES], CD-RISC, Brief Resilience Scale [BRS], etc.) has been shown to be negatively associated with PTSD symptoms (e.g., Streb, Haller, & Michael, 2014; Zang et al., 2017), anxiety symptoms (e.g., Jones-Bitton, Best, MacTavish, Fleming, & Hoy, 2019), and depressive symptoms (e.g., Tamayo, 2019), etc. The literature on resilience and externalizing symptoms, in comparison, is limited. Broadly, research generally focuses on externalizing behaviors in adolescent populations, and commonly operationalizes resilience as protective factors (i.e., social support, parental monitoring, etc.) that may promote a

resilient response, but are not resilience themselves. However, the research that has been conducted on *resilience* (i.e., not protective factors such as social support) and externalizing factors provides evidence for associations between resilience, as measured by self-report scales, and various externalizing outcomes such as anger levels and expression in adolescents (e.g., Anderson, 2006; Adolescent Resiliency Attitudes Scale [ARAS]), antisocial personality disorder (ASPD; Amstadter, Maes, Sheerin, Myers, & Kendler, 2016; discrepancy-based measure of resilience), lifetime alcohol use problems (Wingo, Ressler, & Bradley, 2014; CD-RISC) and lifetime illicit drug use (Wingo, Ressler, & Bradley, 2014; CD-RISC). Taken together, there is evidence to support resilience as a potential protective factor, though conclusions that can be made about the *buffering* effects specifically are limited due to methodological shortcomings of the extant literature. These shortcomings will, in turn, be discussed.

d. Methodological Limitations

Although, broadly, the existing literature supports resilience as negatively associated with adverse outcomes following exposure to a TE, this literature base is fraught with methodological limitations. Namely, much of the existing literature is cross-sectional in nature, does not test the buffering hypothesis (i.e., moderation analyses), and focuses mainly on internalizing outcomes. If resilience does truly *buffer* against the effects of TEs, to examine the construct validity, resilience at one time point would be hypothesized to protect an individual against the development of symptoms following future TEs, requires the use of longitudinal data. However, in a recent systematic review of the literature (Cusack & Amstadter, in preparation) on resilience and alcohol-related phenotypes, only two of 20 studies identified for inclusion employed a longitudinal research design (Green, Beckham, Youssef, & Elbogen, 2014; Wong et al., 2006). As noted previously, cross-sectional designs, to date, are used more frequently when assessing

the impacts of resilience on psychopathology, thus limiting inferences that can be made about the true buffering effect.

Considering that the buffering hypothesis necessitates a test of moderation by design, whereby resilience affects the impact of new onset trauma on drinking outcomes, it would follow that the use of moderation analyses to test its validity is imperative. Indeed, in the same systematic review of resilience and alcohol-related phenotypes (Cusack & Amstadter, in preparation), only three studies tested a true moderation model (Green et al., 2014; Morgan, Brown, and Bray, 2018; Wingo et al. 2014). However, all three studies tested moderation using cross-sectional data, limiting the inferences that can be made about the buffering effects of resilience. As is the case with longitudinal research designs, the extant literature overwhelmingly tests associations between resilience and phenotype of interest, as opposed to validly testing the buffering hypothesis via moderation analyses.

Third, the focus on internalizing symptoms and disorders (e.g., anxiety, depressive, PTSD symptoms, etc.) limits what is known about resilience and its potential protective effect on externalizing behaviors, such as alcohol consumption. As described in the review of the literature on the buffering hypothesis, much of the research on resilience and externalizing symptoms examines the effects of *protective factors* (e.g., social support, peer influences, etc.) on symptoms in adolescent populations.

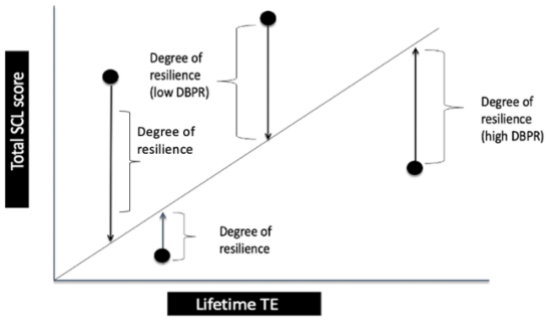
Lastly, research, broadly, has demonstrated that the absence of protective factors such as parental monitoring, or the presence of risk factors such as peer deviance can impact a multitude of psychiatric outcomes, including substance use. However, the extant research on resilience largely ignores these important contextual variables. For example, both parental and peer-group influences early in life have been shown to influence subsequent alcohol consumption in

emerging adulthood (i.e., college-aged years). A general trend emerges throughout the extant literature whereby, broadly speaking, higher parental monitoring, and the presence of a supportive adult in the home is associated with decreased alcohol use (e.g., Veal & Ross, 2006; Hodder et al., 2016; Hodder et al., 2018). Similarly, existing research examining peer influences has found consistent trends whereby the presence of close friends in adolescence, as well as the absence of alcohol use among one's peer group, are key protective factors for alcohol consumption (e.g., Reed, Reno, & Green, 2016).

e. Present Study's Conceptualization of Resilience

The present study uses a "discrepancy-based" measure of resilience that is based off of an individual's lifetime trauma exposure and their reported psychiatric symptoms (see Figure 1). This novel measure of resilience was developed by our research group (Amstadter, Myers, & Kendler, 2014) and has been applied to investigations of resilience and both internalizing (e.g., Sheerin et al. 2018) and externalizing phenotypes (e.g., Amstadter, Maes, Sheerin, Myers, & Kendler, 2016), as well as personality traits (e.g., Amstadter, Moscati, Maes, Myers, & Kendler, 2016). However, the discrepancy-based resilience variable used in the present study varies in key ways from how the variable has been used in prior research (e.g., Amstadter et al., 2014; Amstadter et al., 2016). For example, the variable used in the present study uses lifetime trauma exposure, as opposed to past year, in the calculation of resilience, so perhaps symptoms reported at baseline and used in the calculation variable are less related to the events. However, the variable used in the current study used *trauma* exposure as opposed to stressful life event exposure, which would be hypothesized as having a more enduring influence on outcomes.

Figure 1. *A Theoretical Graphical Representation of the Discrepancy-Based Resilience Variable*.



Note: The black dots on the figure represent an individual's Symptom Checklist (SCL) score. The regression line represents an individual's predicted symptoms based on their TE load. The residual, shown in brackets, is the resilience score.

In contextualizing the variable used in the present study with regards to the most commonly seen conceptualizations of resilience discussed above (i.e., trait, outcome, process), discrepancy-based resilience is most similar to a trait-based conceptualization. Resilience in the present study is theorized to be an interpersonal characteristic that has been shown to be both moderately heritable with the genetic and environmental influences stable over time (Amstadter et al., 2014). However, the genetic influences on discrepancy-based resilience do not account for 100% of the phenotype, and thus, the environment plays a critical role in influencing levels of discrepancy-based resilience. Indeed, the majority of the resilience training literature 1.) views resilience as modifiable (a necessity if assessing the impact of an intervention/prevention protocol) and 2.) addresses resilience "factors" (i.e., coping strategies [Dolbier et al., 2010], problem-solving [Cigrang et al., 2000], cognitive flexibility [Cohn & Pakennham, 2008]) through their trainings in order to improve resilience levels and subsequent outcomes. In relation to enhancing resilience to buffer against alcohol use outcomes, it is imperative that resilience be conceptualized as modifiable.

Studies examining resilience-building interventions and trainings have not yet examined the impacts of training on discrepancy-based resilience. However, extant literature demonstrates that, using trait-based self-report conceptualizations of resilience, an individual's resilience can be increased (e.g., Connor & Davidson, 2003; Bekki, Smith, Bernstein, & Harrison, 2013), suggesting that the buffering capabilities of resilience can be improved through intervention and prevention efforts.

Taken together, there is a dearth of literature examining the buffering capabilities of *resilience* on externalizing behaviors and symptoms, and alcohol-related phenotypes more specifically (e.g., AUD, binge drinking, etc.). Considering the aforementioned methodological limitations, additional research testing the buffering hypothesis of resilience, with longitudinal data, on externalizing phenotypes is highly warranted. As extant research has demonstrated that resilience is modifiable through intervention and prevention efforts, additional research on the buffering effects of resilience on alcohol use outcomes will serve to better inform these efforts.

In addition to the importance of psychosocial moderators of risk, such as resilience, there is a wealth of evidence that genetic risk also influences posttrauma sequela. As such, in the sections that follow, the evidence from twin and molecular studies on AUD and PTSD will be reviewed. Additionally, twin and molecular designs have been used to investigate the etiologic sources of variance for resilience itself, and the following sections review the extant knowledge stemming from that work.

V. Genetic components influence both AUD and PTSD

a. Behavioral genetics

Family and twin studies of AUD and PTSD. Twin and family studies demonstrate that genetic influences are an important etiological risk factor for both AUD and PTSD independently, as well as co-morbid AUD and PTSD. The shared liability model proposes that

AUD and PTSD commonly co-occur due to common familial risk (i.e., genetics factors and shared environment influences; Danovitch et al., 2016; Krueger & Markon, 2006). Twin methodology is commonly used to estimate the proportion of variance within a population attributable to genetic factors, shared environmental influences, and non-shared environmental influences, as well as the proportion of variance from these sources that is unique to versus shared across phenotypes (for a review, see Kendler & Prescott, 2006). As such, twin methodology has been useful in elucidating the genetic and environmental influences on trauma-related and alcohol-related phenotypes.

Although exposure to a TE is often conceptualized as an entirely environmental phenomenon, familial risk for interpersonal TEs (i.e., physical, sexual assault) has been shown to explain significant variance in TE exposure (Kendler, Karkowski, & Prescott, 1999). Further, twin studies have estimated genetic factors to account for 35-47% of the variance in exposure to combat-related trauma (Koenen et al., 2003). Although this heritability is not well understood, exposure to a TE has been demonstrated to be related to both specific familial level factors, such as maternal depression (Koenen et al., 2002), as well as individual level factors (e.g., history of depression, etc.; Koenen et al., 2002).

Additional research has suggested that although the odds of experiencing a TE are influenced by genetic factors, it is more likely that factors that influence an individual's risk for entering into a potentially traumatic situation are heritable (Jang, Stein, Taylor, Asmundson, & Livesley, 2003). Findings from Jang, Stein, Taylor, Asmundson, and Livesley (2003) evidence that genetically based personality factors such as antisocial personality traits, psychoticism, and being open to new ideas and experiences, influence exposure to certain environments that may

increase risk for TE exposure. In other words, findings demonstrate that the genetic influences on TE, in part, are indexed by heritable personality traits.

Genetic influences have been shown to influence not only TE exposure itself, but also common post-trauma sequela, such as PTSD and AUD. Indeed, genetic factors are estimated to account for approximately 24-72% of the variance in PTSD diagnostic status (reviewed in Sheerin, Lind, Bountress, Nugent, & Amstadter, 2017; Daskalakis, Rijal, King, Huckins, & Ressler, 2018). The moderate heritability of PTSD holds when controlling for the genetic influences associated with TEs (True et al. 1993). There are reported sex differences in the heritability of PTSD where heritability estimates in females documented as two to three times higher than that in males (Sartor et al., 2011). More recent research has examined the heritability of PTSD in relation to resilience specifically, demonstrating that PTSD and resilience are moderately correlated, with 59% of the correlation attributed to a single genetic factor, suggesting that PTSD and resilience may be two ends on one single spectrum of traumatic stress (Wolf et al. 2018).

Substance use phenotypes, generally speaking, have demonstrated higher heritability rates as compared to PTSD, though estimates seem to vary based on the developmental stage, whereby phenotypes occurring earlier in life (e.g., substance use initiation in adolescence) tend to be more strongly influenced by shared environmental factors (e.g., peer influences), as opposed to genetic factors (Fowler et al., 2007). AUD, specifically, is approximately 50% heritable (for a meta-analysis, see Verhulst, Neale, & Kendler, 2015). Examining the diagnostic symptoms of alcohol-related problems in a community based-sample of twin pairs, Hardie, Moss, and Lynch (2008) found that three symptoms were heritable in female twins only (i.e., “increased risk of injury or harm”, “emotional problems related to drinking”, and “the desire to

drink"). In male twins, four of the seven symptoms were moderately heritable: "Increased risk of injury or harm", "spending more time using alcohol or getting over its effects", "using larger amounts for longer periods of time than intended", and "the need to use more alcohol to get the same effect". These sex differences suggest that alcohol problems in females and males may have different etiological underpinnings.

Both PTSD and AUD have been shown to be moderately heritable, with heritability rates of AUD being slightly larger than those of PTSD. However, twin studies have demonstrated that the genetic effects associated with PTSD overlap with substance use phenotypes. For example, using data from the Vietnam Era Twin (VET) Registry, Wolf and colleagues (2010) evidenced PTSD as the sole internalizing psychiatric disorder that overlaps with an externalizing factor, that of which includes substance use disorders (Wolf et al. 2010). Findings from Scherrer et al., (2008) support a shared liability between PTSD and alcohol phenotypes more specifically. The authors found that a moderate amount of genetic variance in risk for PTSD overlaps with that for alcohol dependence (i.e., 30%). Twin studies have suggested similar estimates, with 30% of genetic vulnerability for PTSD thought to be overlapping with genetic vulnerability for AUD (Sartor et al., 2011; Xian et al., 2000). Taken together, the evidence from family and twin studies suggest that the genetic liability for PTSD as a post-TE exposure sequela is shared with the liability for alcohol-related phenotypes following TE exposure.

b. Molecular genetic studies

The moderate heritability of both AUD and PTSD is well supported throughout the family and twin literatures. With heritability estimates well-established, research into the genetic etiology of psychiatric disorders (e.g., AUD, PTSD) has shifted to focus on the exploration and elucidation of specific genetic variants that may increase one's risk for development of AUD

and/or PTSD. The majority of this research has focused on single nucleotide polymorphisms (SNPs; McCarthey et al. 2008), and the association of certain SNPs with cases vs. controls (i.e., those that have the psychiatric disorder [e.g., AUD] vs. those that do not). This work has also looked as SNP effects on severity of symptoms (e.g., risk alleles being associated with a total PTSD severity score).

Early research into the genetic etiologies of both AUD and PTSD focused on hypothesis-driven approaches such as main effect and gene-by-environment interaction candidate gene (cGxE) designs (e.g., Mehta & Binder, 2012; Miranda, et al., 2012). In cGxE studies, regions across the genome are selected for examination based on the existing knowledge of underlying genetic mechanisms of the phenotype of interest. Both main effects (i.e., the direct effect of polymorphisms on a phenotype) and cGxE effects (i.e., interaction between environmental risk and/or protective factors and the polymorphisms) have been examined in relation to AUD and PTSD. However, given the limitations of the candidate gene approach, as described below, paired with the decreasing cost of genome-wide arrays, researchers have shifted their focus to agnostic approaches, such as genome-wide association studies (GWAS), that are able to examine millions of variants across the entire genome, as opposed to the gene(s) selected a priori in candidate designs.

Candidate Gene Studies. The candidate gene approach is guided by *a priori* hypotheses about which genes may be of interest to examine in relation to a specific phenotype (i.e., AUD, PTSD, etc.; Patnala, Clements, & Batra, 2013). A priori hypotheses are formed based on prior research findings and resultant knowledge of biological mechanisms. Existing candidate gene studies have identified multiple variants associated with AUD (for a review, see Dick & Foroud, 2003) and PTSD independently (for a review, see Duncan, Cooper, & Shen, 2018). However,

findings from candidate gene studies are inconsistent, likely due to a number of methodological limitations (Tabor, Risch, & Myers, 2002). The reliance on a priori hypotheses to choose which gene(s) and variant(s) to examine, given that our knowledge of the biological etiologic mechanisms behind most psychiatric phenotypes is quite limited, is a weakness of the candidate gene approach. Further, the candidate gene design is methodologically limited by small sample sizes, low power, and subsequent increased likelihood of false positives, leading to inconsistent findings across studies (Tabor, Risch, & Myers, 2002).

Genome Wide Association Studies (GWAS). More recent research into the genetic etiology of various psychiatric disorders (e.g., AUD, PTSD) has taken an agnostic approach, due the aforementioned limitations of the candidate gene design (e.g., sample size, a priori hypothesis driven, etc.). Additionally, advances in the methodology used to genotype arrays and the improved cost-effectiveness of laboratory genome testing, has supported the use of agnostic approaches. GWAS identifies potential variants contributing to a phenotype by comparing the frequencies of millions of common genetic variants across the entire genome and from large-scale populations (Corvin, Craddock, & Sullivan, 2010). More specifically, GWAS determines if SNPs occur more frequently based on case vs. control status, whereby a SNP occurring frequently in cases are deemed risk factors for the phenotype of interest. Alternatively, a SNP occurring frequently in cases may indicate that an is associated with a quantitative trait, such as a risk allele that is correlated with total severity score of AUD.

GWAS have been commonly used to examine the genetic architecture of both AUD and PTSD. Deak, Miller, and Gizer (2019) provide a comprehensive review of the extant GWAS on alcohol phenotypes, noting that GWAS on AUD have suggested hundreds of variants across the genome, though with small effect sizes (e.g., odds ratio [OR] = 1.31; Frank et al. 2012), as

impacting risk for AUD. GWAS significant hits have been found in genes implicated in the alcohol metabolism: alcohol dehydrogenase (*ADH1B;* Gelernter et al. 2014*; ADHIC*; Frank et al. 2012*)* and aldehyde dehydrogenase (*ALDH2;* Polimanti & Gelernter, 2018). Other alcohol phenotypes have also been examined. For example, in their GWAS of alcohol consumption (i.e., *N*=112,117), Clarke and colleagues (2017) found significant associations with 14 variants. Among these loci is replication with variants in the *ADH1B* and *ADH1C* genes, as well as the identification of novel variants in the *GCKR, KLB,* and *CADM2* genes (Clarke et al. 2017).

With the efforts made by the Psychiatric Genomics Consortium Substance Use Disorder (PGC-SUD) Working group (e.g., Agrawal, Edenberg, & Gelernter, 2016), Walters et al. (2018) conducted a GWAS (*N*=14,904 cases, 37,944 controls) of DSM-IV alcohol dependence (AD), and found genome-wide significant effects of variants in *ADH1B* in both European and African ancestries. In the largest GWAS of alcohol consumption and AUD diagnosis to date (*N*=274,424), Kranzler et al. (2019) identified 18 genome-wide significant loci, five of which were associated with both phenotypes, eight associated with consumption only, and five associated with AUD at the diagnostic level. Notably, the genetic etiology of AD and AUD only partially overlap with that of alcohol consumption, highlighting the nuance between diagnostically relevant drinking behaviors and associated problems from those that are not considered pathological.

To date, there have been upwards of 13 GWAS on PTSD published. Taken together, results from these studies have identified 15 SNPs related to PTSD (for a review, see Daskalakis et al., 2018). Results from the majority of the extant GWAS PTSD research have demonstrated SNPs meeting genome-wide significance (i.e., *LINC01090,* Guffanti et al; 2013; *BC036345,* Almli et al., 2015; *ZNRD1-AS1,* Kilaru et al., 2016; *RORA,* Logue et al., 2013; *NLGN1,* Kilrau et

al., 2016; *TLL1*, Xie et al., 2013). More recent investigations have idenfied additional variants associated with PTSD. Namely, Wilker and colleagues (2018) identified a protective association between rs3852144 in PTSD risk and averiseve memory in two independent African samples. Secondly, Wang et al. (2019), in their sample of Danish soldiers, found genome-wide signifcance for a region near the *IL15* gene, implicated in the physiological inflammatory response. PTSD has been shown to be associated with inflammatory medical conditions by way of excess inflammatory actions in an indivdiual's immune system (Gill, Saligan, Woods, & Page, 2009). Using GWAS to examine PTSD on a symptom level, Gelernter et al. (2019) conducted the first GWAS of re-experiencing symptoms, and found three genome-wide significant variants: *CAMKV* and *TCF4*. Lastly, in a recent meta-analysis of PTSD GWAS, using the most recent data freeze from the PGC-PTSD workgroup incuding a multi-ethnic cohort with over 30,000 PTSD cases and 170,000 controls, Nievergelt and colleagues (2019) identified three genome-wide significant loci as associated with increased risk for PTSD, one of which is a gene implicated in Parkinson's disease and involved in dopamine regulation, *PARK2*. The existing and rapidly growing research base of GWAS investigations of PTSD (e.g., the PGC-PTSD is currently funded through NIMH to reach sample sizes of over 100,000 PTSD cases) will enable further clarification of the genetic underpinnings of these debilitating disorders.

VI. Genetic Components Influence Resilience

The research base on the genetic influences on resilience is in its nascence, as compared to that of the genetics of both AUD and PTSD (for a review, see Maul, et al. 2020). As such, most of the knowledge about the genetics of resilience derives mainly from behavioral genetic approaches (i.e., twin studies). There is a need to examine the heritability of resilience from a molecular perspective (i.e., genome-wide complex trait analysis [GCTA]), as well as to examine

the genetic architecture of resilience through examining individual variants associated with the construct (i.e., genome-wide association studies [GWAS].

a. Behavioral Genetics

Twin Studies. Family and twin studies have estimated resilience to be moderately heritable (e.g., Amstadter, Myers, & Kendler, 2014; Wolf et al., 2018), and have demonstrated differences in heritability based on sex (Amstadter et al., 2014), whereby the amount of heritability is consistent across the two sexes, though the genes affecting resilience are not, highlighting the need for molecular genetic investigations. Other twin research has demonstrated that resilience is moderately heritable, but that the heritability is higher among men (h^2 =.52), as compared to females (h^2=.38; Boardman, Blalock, & Button, 2008).

In addition to heritability estimates, twin studies have examined shared genetic factors that contribute to the heritability of resilience and both internalizing and externalizing phenotypes. To this end, Amstadter and colleagues (2016) found that the genetic influences on resilience accounted for 42% of the heritability of MDD, increasing to 46% in a longitudinal model not confounded by measurement error. Further, the authors found 61% of the heritability of GAD is shared with that of resilience, consistent with findings of higher levels of TE in those with GAD as compared to healthy controls (Roemer et al. 1998). Work by this group also suggests that genetic influences on resilience overlap with internalizing phenotypes (i.e., MDD, GAD) more so than externalizing phenotypes (i.e., AAD, 20%; ASPD, 18%; Amstadter et al., 2016). As TE is often associated with the subsequent development of PTSD, Wolf et al. (2018), in a sample of 3,318 male twin pairs, estimated the heritability of resilience at 25%, as compared to that of PTSD at 49%, and further, found that resilience and PTSD were negatively correlated (r=-.59), with 59% of this correlation attributable to a single genetic factor. Findings from twin

studies suggest that resilience is moderately heritable, and that genetic components influencing resilience may overlap with other psychiatric phenotypes, though these findings warrant further investigation into the overlapping genetic components on a molecular level.

b. Molecular Genetics

Candidate Gene Studies. The candidate gene literature on resilience is quite scarce precluding a confident suggestion of any one SNP as associated with resilience. Genetic variants of the noradrenergic, dopaminergic, and serotonergic systems, as well as genes encoding for neurotropic factors or genes related to the HPA axis, have been most extensively studied (e.g., Bruenig et al., 2017) as these systems are implicated in the development of PTSD and MDD, and as such, perhaps in a resilient response to stress. For example, Rana and colleagues (2014), in their candidate gene study of optimism and resilience in older adults, did not find any significant associations for individual SNPs with resilience. In their examination of gene expression variations, Azadmarzabadi, Haghighatfard, and Mohammadi (2018) found that the up-regulation of *DRD1*, *DRD2*, *DRD3*, *DRD1*, *DBH*, *DAT,* and *BDNF*, all implicated in the dopaminergic signaling pathway, and the down-regulation of serotonin transporter, monoamine oxidase A and *COMT,* were associated with stress resilience.

GWAS. To date, there is only one GWAS on resilience, as measured by a 5-item self-report measure (Stein et al. 2019). With a total of 11,492 participants, results revealed a genome-wide significant locus on chromosome 4 in an intergenic region upstream to *DCLK2* (doublecortin-like kinase 2) implicated in the promotion of survival and regeneration of injured neurons (Stein et al. 2019). As such, variation in this gene may be associated with less harmful changes in brain structure and/or cognitive function associated with higher levels of resilience. At gene-wise genome-significance, *KLHL36* (Kelch like family member 36) was significantly

associated with self-report levels of resilience. A SNP in this gene has been shown to be a risk variant for late onset Alzheimer's Disease, perhaps similarly related to changes in brain structure and/or cognitive function. However, the specific role for *DCLK2* and *KLHL36* in resilience requires further investigation, perhaps using more novel molecular genetic techniques. When including only those individuals endorsing the highest levels of deployment stress (*N*=581), a genome-wide significant polymorphism was detected near *SLC15A5* (solute carrier family 15 member 5). Notably, the sample size for this analysis was quite small, relative to what is typically required of GWAS, and as such, this finding should be considered as preliminary, and in need of replication (Stein et al. 2019). Regardless of the well-established co-morbidity between AUD and PTSD, and the likely role of resilience as a protective factor for both disorders, no study to date has examined aggregate risk for all three phenotypes.

Although only one study to date has used GWAS to examine the genetic underpinnings of resilience, a number of studies have used GWAS to examine related constructs that promote adaptation following exposure to a trauma and/or stressor such as positive affect (Wingo et al., 2017), subjective well-being (Okbay et al., 2016; Turley et al., 2018), and IQ (Davies, et al., 2015; Trampush et al., 2017). For example, Wingo and colleagues (2017) found one SNP meeting genome-wide significance (i.e. $10x5^{-8}$; GWS; *rs322931*) associated with positive affect at the GWS level, and further, that a minor allele of this SNP is associated with greater nucleus accumbens reactivity to positive emotional stimuli and enhanced fear inhibition, suggesting that this variant may mediate positive affect via the nucleus accumbens. Additionally, Okbay and colleagues (2016) in their GWAS of subjective well-being (N= 298,420), identified three SNPs meeting GWS. Turley and co-authors (2018), using multi-trait analysis of GWAS (MTAG) identified 49 SNPs associated with subjective well-being (N= 388,538), though none mapped

onto any one clinically relevant gene. Notably the sample sizes of these studies were exponentially larger than that in the present study. Nevertheless, GWAS of related constructs on the well-being spectrum are useful for informing future GWAS of resilience in that they identify genetic variants and regions that may provide insight for such future investigations.

VII. Aggregate Molecular Genetic Approaches

Behavioral genetic approaches have established heritability estimates of AUD, PTSD, and resilience, and have suggested that genetic underpinnings of these phenotypes may overlap. Given these latent genetic findings, the etiologic roots of resilience need to be examined from a molecular standpoint, and particularly among college-aged individuals who represent an important group to study given this period of high-risk for exposure to TEs (e.g., Conley et al., 2017) and subsequent development of AUD (e.g., Dawson, Grant, Stinson, & Chou, 2004) and PTSD (e.g., Read, Ouimette, White, Colder, & Farrow, 2011), making protective factors especially important.

GWAS on AUD (e.g., Kranzler et al., 2019) and PTSD (e.g., Duncan et al., 2018), and the one GWAS on resilience (Stein et al., 2019) have identified variants conferring risk for these phenotypes independently. However, the genetic underpinnings of resilience remain largely unknown, with few studies employing molecular genetic approaches to the study of resilience. No work to date has been conducted to establish the genetic overlap of these phenotypes (i.e., resilience, AUD, PTSD). Prevention and intervention efforts would greatly benefit from molecular genetic investigations of resilience in order to better identify those at risk for the development of psychopathology, and thus inform these efforts. For example, identifying brain regions and neurotransmitter systems that are implicated in both stress and resilience can inform pharmacological interventions. Indeed, recent research in animals has suggested that ketamine,

by acting on the glutamate system, may blunt the biological response to uncontrollable stress, promoting a "resilient" response, as opposed to the development of a stressor-related disorder (e.g., PTSD; Amat, Camps, & Manteca, 2016). Continued identification of relevant neurobiological mechanisms implicated in resilience, through molecular genetic methods, will help to further the development of both pharmacological and non-pharmacological intervention approaches.

a. Novel Statistical Genetic Approaches

Given the large increase in the availability of GWAS data, statistical innovations have rapidly occurred to leverage large-scale molecular data to answer novel questions. In the sections that follow each statistical technique, the mechanics behind it, and the relevant literature for the phenotypes of interest is reviewed.

Genome-Wide Complex Trait Analysis (GCTA). Advancing beyond twin and family studies that provide latent heritability estimates, GCTA provides molecular heritability estimates (referred to as h^2_{SNP}) to be calculated in samples of unrelated individuals using GWAS data. More specifically, GCTA estimates the variance of a phenotype explained by the additive effect of all available SNPS, instead of testing the association of any one SNP with the phenotype (e.g., Yang, Lee, Goddard, & Visscher, 2011). GCTA estimates are created through the use of a genetic relatedness matrix (GRM), which includes the correlations for all individuals across all SNPs. These correlations are then regressed onto a phenotype (e.g., AUD) using a restricted maximum likelihood (REML) method.

Aggregate heritability estimates for drug use, alcohol consumption, AD, nicotine use, and nicotine dependence range from 10-30% (Vrieze, McGue, Miller, Hicks, & Iacono, 2013). Results from GCTA studies of alcohol-related phenotypes more specifically estimate SNP-based

heritability to be moderate. For example, the SNP-based heritability of AD among a Dutch sample was estimated at 33%, nearly half of the twin-based heritability estimates in the same sample (Mbarek et al. 2015). In a more recent examination of the SNP-based heritability of AUD specifically, Palmer and colleagues (2019) found that the SNP-based heritability of DSM-5 AUD varies across the 11 criteria, with the genetic effects on most symptoms largely overlapping. Results also suggest that the AUD factor is more heritable (36%) than symptom count (22%) and diagnosis (14%).

Work by the PGC-PTSD workgroup has allowed for the use of GCTA analyses to examine PTSD SNP-based heritability. To that end, Duncan and colleagues (2018), using the first data freeze (n=20,070), found a joint heritability estimate of 12% for males and females, with 21% for European American females, higher than the estimate for European American males (h^2_{SNP} = 8%, not significantly different from zero). With data from the second PGC-PTSD data freeze, Nievergelt et al. (2018) examined GCTA estimates of PTSD across ancestries, with results suggesting that data were significant for European American females (h^2_{snp} = 10%), but not significantly different from zero in European American males. When stratified by sex, estimates in the African American population were similar to those of the European American. In sum, findings from extant GCTA studies suggest the SNP-based heritability of PTSD to be between 10% and 20%. Only one study to date has applied GCTA to resilience with results suggesting a SNP-based heritability of 16% in a European American sample (Stein et al. 2019).

GCTA, while an exciting tool allowing researchers for the first time to quantify heritability in un-related individuals, has a number of limitations. GCTA relies exclusively on additive SNP effects, meaning that it is unable to include genetic variation due to rare variants, account for dominance effects (i.e., the masking effect of different variants of the same gene on a

particular phenotype), epistasis (i.e., the masking effect of one gene on the phenotype of another gene), or gene-by-environment (GxE) effects (Wray et al., 2014; Wray et al. 2013). Solely accounting for additive genetic effects leads to heritability estimates that are lower than those found in twin studies, which capture all aggregate genetic variation (Trzaskowski, Dale, & Plomin, 2013). As such, a non-significant GCTA heritability estimate should not be equated to a true lack of heritability. Further, there are complex phenotypes with genetic architectures that preclude GCTA to detect heritability, despite the phenotype having large genetic effects (Trzaskowski, Dale, & Plomin, 2013). For example, Trzaskowski, Dale, and Plomin (2013) found that behavior problems in childhood, as rated by parents, teachers, and children themselves, showed no significant genetic influence using GCTA, even though twin estimates of heritability were substantial in the same sample and GCTA estimates of genetic influence for cognitive and anthropometric traits were substantial. This is likely due to the complexity of behavior problems as a phenotype, and the resultant influence of non-additive genetic effects such as GxE, that are not captured by GCTA.

Despite these limitations, GCTA is a popular and powerful tool to estimate molecular heritability across phenotypes. GCTA boasts many advantages when compared to other statistical genetic approaches, such as requiring smaller sample sizes than needed for GWAS, as well as multivariate extensions to the technique which allow for quantification of shared genetic risk between two traits among *unrelated* individuals (Lee, Yang, Goddard, Visscher, & Wray, 2012).

Polygenic Risk Scores (PRS). Polygenic risk scores (PRS) are another popular statistical genetic technique that capture aggregate genetic risk scores for various phenotypes in unrelated individuals using GWAS data. These PRSs can then be used for investigating within-trait, but

cross-sample applications (e.g., does aggregate genetic risk for PTSD from one discovery sample predict PTSD risk in S4S?), as well as cross-trait, aggregate genetic risk extensions (e.g., does risk for PTSD calculated using summary statistics from one sample predict AUD or resilience in S4S?). PRSs which represent the aggregate genetic risk for a phenotype are calculated using summary GWAS statistics from a discovery (i.e., external) dataset to compute a participant's risk for that phenotype in a novel sample (e.g., S4S) using weighted risk scores that sum across the risk alleles across the genome using specified p-value thresholds (e.g., Purcell, 2009). PRS account for aggregate SNP effects, weighting contributions based on effect sizes from GWAS data, as opposed to GCTA, which assumes that SNP effects are random. Indeed, PRS have been applied in both the alcohol (e.g., Salvatore et al., 2014) and PTSD (e.g., Solovieff et al. 2014) literatures, providing consistent evidence for aggregate risk for each phenotype across unrelated individuals.

PRS, similar to GCTA, also has bivariate applications in which weighted genetic risk for one phenotype (e.g., AUD) can be used to predict the expression of another (e.g., PTSD). Extant research using this application demonstrates aggregate risk between AUD and PTSD, and other psychopathologies respectively, whereby the genetic etiology of AUD has been shown to overlap with that of cigarette use (Clarke et al., 2017; Vink et al., 2014). The extant PTSD literature has demonstrated that PTSD overlaps, genetically, with both bipolar disorder and schizophrenia (Misganaw et al., 2019). Only one study to date has used PRS in relation to resilience. Stein and colleagues (2019) computed PRSs for self-report resilience and failed to find a significant correlation between self-assessed resilience and outcome-based resilience in individuals of European ancestry, though all self-report resilience scores were associated with higher odds for outcome-based resilience.

PRS shares many of the same strengths and benefits of GCTA, though also shares multiple limitations. For example, PRS analyses are limited by the reliance on data from available SNPs, and are unable to account for additive effects, GxE, epistasis, or rare variation (Wray et al., 2014; Wray et al., 2013). The use of discovery samples to calculate PRS further limits the technique by requiring large sample sizes (Wray et al., 2014), and complicating replication across phenotypes (Ware et al., 2017).

Utilizing these novel statistical genetic approaches will contribute to the larger need to better understand the moderators of risk for AUD and PTSD, such as resilience, from a genetic standpoint. With further clarification of the genetic etiology of resilience and its overlap with AUD and PTSD, we will be able to better identify those at risk, resulting in far-reaching clinical implications related to prevention and intervention efforts.

VII. Overall Summary and Study Aims

College is a period of increased risk for problematic alcohol consumption and TE exposure, both of which are transdiagnostic risk factors for the development of more severe psychopathology, such as AUD. However, there is an observed heterogeneity in response to TE, and resilience may act to protect against the adverse effects of TE (e.g., AUD, alcohol consumption, PTSD). Further, extant research has demonstrated that resilience is moderately heritable, though this heritability is not well understood. This is the first multi-method longitudinal study of a novel, discrepancy-based measure of resilience, specifically as it relates to alcohol phenotypes in the wake of college-onset TE exposure. Namely, this work expands the buffering hypothesis of resilience to include alcohol outcomes and contribute to the dearth of molecular genetic research on resilience. The present study leverages genome-wide data to better understand the molecular underpinnings of resilience, to estimate the molecular heritability of

resilience, and to examine the genetic overlap between resilience with key outcomes (i.e., alcohol consumption, AUD, PTSD, etc.). To complete these objectives, data was leveraged from TE exposed students enrolled in an ongoing longitudinal, genetically informative study of college students at a large, diverse urban university ("Spit for Science" [S4S], NIAAA-R37 AA011408, PIs: Kendler, Dick).

Aim 1: Investigation of the Buffering Hypothesis

Aim 1 of the present study was to conduct longitudinal analyses to test if resilience buffers the effects of new onset traumatic events on alcohol-related phenotypes (i.e., primary outcome: AUD symptoms; secondary outcomes [alcohol consumption, binge drinking]). It was hypothesized that resilience would buffer against the effect of college onset TE exposure on AUD symptoms and binge drinking status, as markers of problematic consumption, but not alcohol consumption.

Aim 2: Investigation of the Heritability of Resilience

Given the paucity of GWAS investigations into resilience, Aim 2 of the current study was to examine the association of individual genetic variants with the resilience phenotype. Further analyses (i.e., GCTA) were conducted to examine the molecular heritability of a novel discrepancy-based measure of resilience. It was hypothesized that resilience would evidence modest molecular heritability, and that there would be individual variants associated with resilience.

Aim 3: Molecular Investigation of Resilience and Alcohol Phenotypes

As molecular studies of resilience are still in their infancy with no studies to date looking at resilience in the context of or overlapping with AUD, PTSD, and/or other protective phenotypes, the goal of Aim 3 was to examine the genetic correlation between resilience and

AUD, PTSD, and other protective phenotypes (e.g., subjective well-being) using PRSs. It was hypothesized that significant genetic correlations will be found between resilience and alcohol use phenotypes, resilience and PTSD, and resilience and protective phenotypes.

Chapter 2: Methods

I. Participants and Recruitment

The sample included in the present analyses was leveraged from a larger, ongoing cohort study at Virginia Commonwealth University (VCU) in 2011 (Spit for Science [S4S]; NIAAA-R37 AA011408). The overarching aim of S4S is to examine vulnerability factors associated with substance use and emotional health via both genotypic and environmental factors in a college student population. Recruitment efforts start during the summer before an individual's freshman year when all eligible students (i.e., 18 years or older) receive an e-mail inviting them to participate. The e-mail includes a link to an online survey, for which they receive $10 if completed. Participants also have the opportunity to provide a DNA sample for further compensation (for detailed review of study methods, see Dick et al., 2014). Currently, data for four cohorts have been completed, with a fifth cohort currently enrolled. Recruitment and retention rates have been remarkable thus far, with 64% of individuals invited providing year 1 data. At the time of this proposal, 5 cohorts (N=12,365; ~62% female, ~50% European American [EA], ~19% African American [AA], <1% Native American, ~6% Hispanic/Latino, ~15% Asian, 6% Multi-racial, and <1% Native Hawaiian/Pacific Islander) which matriculated in Fall 2011 (Cohort 1; N=2,707), 2012 (Cohort 2; N=2,481), 2013 (Cohort 3; N=2,391), 2014 (Cohort 4; N=2,310), and 2017 (Cohort 5; N=2,476), have been enrolled in the S4S study. All four completed data collection waves (Cohorts 1-4) have successfully recruited over half (~67%) of incoming VCU freshmen to complete the online questionnaire battery, with an average of 91.3% of participants providing a DNA sample. Due to the longitudinal nature of the present

study, only data from cohorts 1-4 was used, as data collection for cohort 5 has not yet been completed.

Those who completed the baseline survey were invited via email to complete subsequent follow-up assessments between weeks 7 and 14 of the spring semester of their freshman year, and every spring semester following. As expected, there is attrition in participation rates across follow-up time-points. The overall retention rate for S4S is ~59%, providing an adequate sample size for the proposed analyses. Of those interviewed in the fall of their freshman year, there were no significant racial/ethnic differences between those who did and did not complete the year 1 spring follow-up assessment. However, there were significant differences in age and sex between those who did complete the follow-up assessment, whereby those who completed the follow-up were slightly younger as compared to those who did not (18.49 year vs. 18.55 years, t= 5.26, p<.001; Cohen's d: .14), and more likely to be female (65.8% vs. 61.6%, x2: 4.59, p<.05; Cramer's V: .08). Additionally, there were significant differences in alcohol consumption between cohorts, whereby those students in cohort 3 endorse consuming more alcohol than those in cohort 1 (F=27.0, p<.001). As such, cohort will be included as a covariate. Notably, these differences are small effects, and as such not considered as having significant implications for analyses. For all Aims, the inclusion criterion requires that participants endorsed experiencing a traumatic event at the baseline time-point (year 1 fall) in order to ensure the valid creation of the proposed resilience variable (N= 7,367).

II. Phenotypic Assessment Measures

All surveys were completed online using the RedCap (Research Electronic Data Capture) system, a secure, web-based application designed to support data capture for research studies.

The S4S assessments are broad and only variables for proposed analyses are discussed below (see Table 1; see Appendix A for item-level information).

Table 1. *Phenotypic Variables for Aim 1 Analyses.*

Variable name	Y1F	Y1S	Y2	Y3	Y4	Covariate?
TEs	X	X	X	X	X	
PTSD	X					X
Resilience	X					
Alc cons		X	X	X	X	
Binge drinking		X	X	X	X	
AUD sx		X	X	X	X	
Age	X					X
Gender	X					X
Race/ethnicity	X					X
Cohort	X					X
Parent	X					X
Peer	X					X
Social support	X					X

Note. Y1F= year 1 fall, Y1S= year 1 spring, Y2= year 2 spring, Y3= year 3 spring, Y4=year 4 spring. Alc cons= alcohol consumption, Parent= parental involvement, Peer= peer deviance.

a. Trauma Exposure

Exposure to a TE is measured by an abbreviated version of the Life Events Checklist (LEC; Gray et al., 2004). The five-item LEC assesses exposure to a range of potentially traumatic events (i.e., natural disaster, sexual assault, physical assault, other unwanted sexual experience, motor vehicle accident) experienced, with a “yes” or “no” response. At the baseline time-point (i.e., year 1 fall), individuals report on lifetime types of traumas experienced before attending VCU, and for each subsequent time-point (e.g., year 1 spring, year 2 spring, etc.), they

report on traumas experienced since the last assessment (i.e., past ~12 month). The TE data was be used in two ways. First, for the creation of the resilience variable, a sum score was used to capture the total load of TEs one experienced before attending VCU. Second, given the hypothesis that resilience will buffer the effect of TE on AUD symptoms, a dichotomous variable capturing whether individuals did or did not experience a TE, with no endorsement coded as "0" and endorsement of at least one new TE as "1", was constructed for each of the four spring follow-up time-points.

b. Internalizing Symptoms (Used in Calculation of Resilience Score)

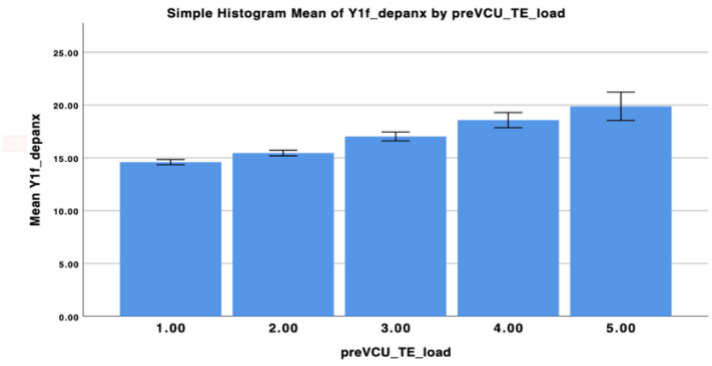
Internalizing symptoms were assessed at the baseline time-point (i.e., year 1 fall, upon entry into VCU) using the Symptom Checklist-90 Short Version (SCL-27; Hardt & Gerbershagen, 2001). The S4S assessment includes four items to assess depressive symptoms (e.g., "feeling low in energy or slowed down"; α =0.89) and four items to assess anxiety symptoms (e.g., "nervousness or shakiness inside"; α =0.85) over the past month. Responses were made on a Likert-type scale of 1 (not at all) to 5 (extremely). A sum score was computed, combining both depressive and anxiety symptoms.

c. Resilience

The discrepancy-based measure of resilience utilized the phenotypic assessment of lifetime TE exposure at baseline (i.e., upon entry into VCU) and internalizing symptoms at baseline. An individual's total score on the SCL-27 was regressed onto their total LEC "lifetime" sum (i.e., year 1 fall total endorsed TE range =1-4). The residual (multiplied by -1 for ease of interpretation such that positive scores will represent degree of 'resilient' responding and negative scores will represent degree of 'non-resilient' responding) was used to quantify resilience as the difference between a participant's actual and expected functioning, based on the

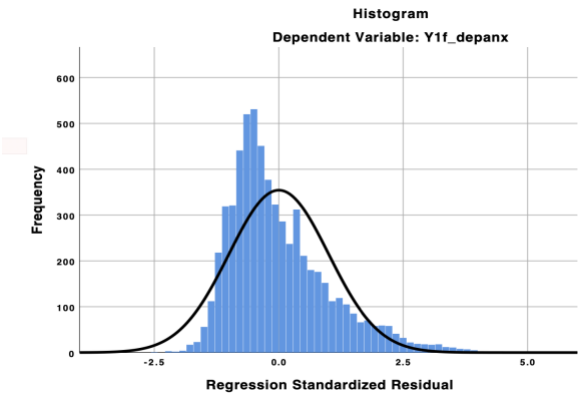
SCL sum score and LEC total, where higher scores represent greater levels of resilience. Given evidence to support resilience as a moderately heritable and moderately stable construct (e.g., Amstadter, Myers, & Kendler, 2014; Connor & Davison, 2003), resilience was measured at the baseline (year 1 fall, upon arrival at VCU) time-point upon a student's entry into college to examine the buffering effects against adverse outcomes (i.e., AUD) in the face of new onset trauma at follow-up time-points. Figure 2 is a histogram that demonstrates the variability in SCL symptoms based on trauma load whereby as trauma load increases, the variability around SCL load increases, as would be expected. Figure 3 presents the distribution of the resilience variable (skewness= -1.21, kurtosis= 1.06).

Figure 2. *Histogram displaying the mean and SD of SCL scores by trauma load*.



Note: Error bars represent standard deviation.

Figure 3. *Distribution of the discrepancy-based resilience variable.*



d. Alcohol Use and Related Phenotypes

The primary alcohol use phenotype, DSM-5 AUD symptoms (e.g., "Have you ever had times where you ended up drinking more, or longer than you intended?"), were assessed for those individuals that endorsed having ever used alcohol use. Symptoms were assessed using items adapted from the Semi-Structured Assessment for the Genetics of Alcoholism (SSGA; Buckholz et al., 1994). Given that the age of the included sample (i.e., emerging adults) typically precedes a formal AUD diagnosis (e.g., Grant et al., 2015a), an AUD symptom count variable for symptoms met within the past 12 months was created for the present study. Symptoms were assessed at each time-point starting with the first spring follow-up time-point for cohort 1, and through all spring follow-up time-points for cohorts 2-4.

Alcohol consumption (i.e., grams of ethanol consumed/month) was calculated using an existing method (Salvatore et al., 2016) with the alcohol frequency and quantity variables. The frequency and quantity items (past 30 days) are from the Alcohol Use Disorder Identification Test (AUDIT; Bohn, Babor, & Kranzler, 1995). Response options for frequency ("How often do you have a drink containing alcohol?") were "never", "monthly or less", "2 to 4 times a month", "2 to 3 times a week", or "4 or more times a week". Response options for quantity ("How many drinks containing alcohol do you have on a typical day when you are drinking?"), were "1 or 2", "3 or 4", "5 or 6", "7", and "10 or more". Alcohol consumption was measured, as a continuous variable, at spring follow-up time points (i.e., year 1 spring, year 2 spring, year 3 spring, and year 4 spring) in order to allow for adequate testing of the buffering hypothesis (i.e., resilience at year 1 fall, new TE at year 1 spring, alcohol consumption at year 1 spring).

Lastly, binge drinking, as defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), is a pattern of drinking that brings blood alcohol concentration (BAC)

levels to 0.08 g/dL. Typically, this BAC occurs after four drinks in a two-hour period for females, and five drinks in a two-hour period for males. Using quantity data, a dichotomous variable (1= 'yes', 0 = 'no') was created for participants at each spring follow-up time point.

e. Covariates

Demographics. Data on participant demographics was drawn from the baseline (year 1 Fall) survey, where participants self-reported on sex, race/ethnicity, cohort, and age. Dummy codes were created for the sex and race variables. For sex, males were coded as "0" and females as "1", in order to compare females and males. For race/ethnicity, three dummy-coded variables were created for White, African American/Black, Asian, and Other (i.e., American Indian/Alaska Native, Hispanic/Latino, Native Hawaiian/Other Pacific, more than race, unknown, and "I choose not to answer"), with White as reference group. The creation of these dummy codes allowed for comparisons between the following groups: White versus African American/Black, White versus Asian, and White versus Other.

Probable PTSD. If a participant endorsed at least one item on the LEC or at least one item on a measure of stressful life events (e.g., broken engagement, housing difficulties, etc., Kendler, Karkowski, & Prescott, 1999), they were administered a PTSD screening measure. DSM-IV PTSD symptoms are measured using the modified version of the Primary Care PTSD Screen (PC-PTSD; Prins et al. 2016). For cohorts one, two, and three, individuals were administered one-item that assess whether the participant has experienced "nightmares, attempts to avoid thoughts or reminders of the potentially traumatic experience, hypervigilance, or feelings of detachment", assessing the PTSD symptom clusters represented in the DSM-IV.

Individuals in cohort four received the four-item version of the PC-PTSD (α =.93). The four items assess whether individuals have experienced nightmares, attempts to avoid thoughts

or reminders of the experience, hypervigilance, and/or feelings of detachment. Given the variation in measures between cohorts, assessments from cohorts one through four were combined to create a dichotomous variable representing the endorsement (i.e., yes/no) of a probable PTSD diagnosis, where a score greater than 0 is classified as probable PTSD. Response options will be coded as "0" and "1", with "0" indicating no probable PTSD, and "1" indicating probable PTSD. For the present analyses, PTSD at baseline (year 1 fall) was included as a time-invariant covariate given that much of the extant literature has demonstrated the use of alcohol to cope with PTSD symptoms (i.e., "trauma-related drinking to cope"; Hawn, Bountress, Sheerin, Dick, & Amstadter, 2020), and as such, PTSD symptoms are a likely confounding variable. The present study aimed to examine resilience as a buffer against alcohol use in the wake of new onset TE above and beyond the influence of PTSD symptoms.

Social Support. Social support (*a*=0.91*)* was measured at baseline (year 1 fall) using three items from the RAND Medical Outcomes Study Social Support Survey (Hays, Sherbourne, & Mazel, 1995). Questions assessed how often some was available to "give advice in a crisis, get together for relaxation, and confide in" in the past 12 months. Answer options were "none of the time", "some of the time", "most of the time", and "all of the time". Items were combined to create a sum score, with higher scores indicating higher levels of social support. Social support as measured at year 1 fall was included as a time-invariant covariate, as social support likely has a protective influence on alcohol use outcomes following new onset TE, and the aim of the present study was to examine resilience above and beyond other putative protective factors.

Peer Deviance. Peer deviance (*a*= 0.89) was measured using items from two instruments (e.g., Johnston, Bachman, & O'Malley, 1982; Tarter & Hegedus, 1991) compiled for use together in Kendler et al. (2008). Baseline surveys (year 1 fall) prompted individuals to report on

high school friends and lifetime engagement in substance use and related consequences. Example items from this measure are as follows: “How many of your high school friends have ever done the following?... smoked cigarettes, got drunk, had problems with alcohol, drunk alcohol, been in trouble with the law, smoked marijuana”. Response options were: “none”, “a few”, “some”, “most”, “all”. Items were reverse coded and compiled to create a sum score, with higher scores indicating higher levels of peer deviance. Similar to social support, peer deviance at year 1 fall was used as a time-invariant covariate for aim 1 analyses to control for the influence of this risk factor, as past research has shown peer deviance is related to college drinking behaviors (e.g., Harford, Wechsler, & Muthen, 2002)

Parenting Style. Parenting style was measured at baseline using the Steinberg Parenting Style Index (Steinberg, Lamborn, Dornbusch, & Darling, 1992). Parental involvement (a=0.68) was assessed with three items: “My parents helped me with schoolwork if there was something I didn’t understand, my parents knew who my friends were, my parents spent time talking with just me”. Participants were asked to respond regarding their parent or guardian during development. Responses options were: “strongly agree”, “agree somewhat”, “disagree somewhat”, “strongly disagree”, or “I choose not to answer”. A sum score was computed, after reverse coding items, with higher scores representing higher levels of parental involvement. Parental involvement was used in the analyses for aim 1 again as a time-invariant covariate given that 1.) We do not expect these responses to have changed once an individual has enrolled in college, and 2.) In order to control for potential protective factors aside from resilience.

III. Genotypic procedures

The following quality control (QC) procedures were conducted for all genetic analyses. Table 2 provides a summary of the proposed genetic analyses, specifying the research question

of interest, analytic plan, and relevant data source for aims 2 and 3 analyses. Detailed analytic plans are provided in Chapter 3, Results, for each aim respectively. Broadly, all individuals who completed the phenotypic online assessment were invited to provide saliva samples for genotyping purposes. DNA was collected via an Oragene kit and isolated via standard procedures. For cohorts 1-3, samples were genotyped on the Axiom BioBank Array, Catalog Version 2. This array is equipped to assay 653K SNPs and InDels including 296K common variants used for imputation and genome wide association scans, and 375K likely functional variants from exome studies including non-synonymous, loss of function, known disease, splice altering, eQTL, and pharmacogenetics-related loci. Given that many of the 375K functional variants are low in allele frequency, the array allows testing of both common and rare variants.

Cohort 4 samples were completed using the Smokescreen Genotyping Array at the Rutgers University Cell and DNA Repository (RUCDR) Infinite Biologics. This array is a custom one designed to cover 646,247 SNPS, 1,014 genes, and indels related to addiction and smoking-related phenotypes. It is applicable to African, East Asian, and European ancestry populations. Similar to the Axiom BioBank Array, the Smokescreen Array covers both rare and common variants. All four cohorts were imputed from their separate arrays to a common 1000 Genomes platform.

S4S has a project specific pipeline that was used to process all saliva samples. For cohorts 1-4, the QC pipeline excluded Off Target Variants found by SNPolisher samples missing >2% of genotypes and SNPs missing >5% of genotypes after sample filtering, similar to the PGC QC pipeline. In other words, processing of genetic samples is susceptible to error from lab processing or from user-error, and as such, individual saliva samples that are missing >2% of genotypes (i.e., within-person missingness across the genome) and individual SNPS missing

>5% of genotypes (i.e., specific loci missingness across the sample) will be removed due to high missingness. Following QC removal, 6,325 samples and 560,138 variants remained for imputation, conducted using SHAPEIT2 and the 1000 genomes phase 3 reference panel (1KGP).

In order to attend to the diversity of the sample with respect to race/ethnicity, population stratification was addressed. Population stratification occurs when both disease prevalence (e.g., AUD) and allelic frequency differences exist in the subpopulation sampled, leading to false positive associations of genetic signals (e.g., Marchini et al., 2016). Since GWAS tests millions of markers across the genome, some will show differences in allele frequency between populations, based on ethnicity (e.g., European American [EUR] vs. African American [AFR]), and the overall distribution of test statistics will be inflated, leading to an increase in false positives (Peterson et al., 2017).

Ancestry assignment was completed using principal component analysis (PCA) with Mahalanobis distance calculations. Variants from the 1KGP phase 3 reference panel were combined with variants present in the cleaned S4S genotypic data. LD-based pruning ($r^2<0.1$) is applied to the matching set of variants. The resulting overlapping marker set of 109,259 variants from 1KGP were then subjected to PCA using the EIGENSOFT (Patterson, Price, & Reich, 2006) and SmartPCA (Zhang, 2009) programs. The 10 resulting ancestry PCs were subsequently projected onto the genotypic data from S4S and sample-specific PCs are created. Finally, each participant is assigned to a 1KGP population on the basis of their minimum Mahalanobis distance. The S4S samples were then collapsed into their respective super-population assignment, which were analyzed separately and then meta-analyzed. Briefly, ancestry super-populations are ancestry groups that subsume populations with smaller numbers of samples to create larger groups that the majority of samples fall into. Five super populations have been

identified within the S4S genotypic data: AFR, admixed from the Americans (AMR), East Asian (EAS), South Asian (SAS), and EUR. For a more detailed explanation of these methods, please see Peterson et al. (2017). For the genetic aims of the present study, only the AFR and EUR sub-samples given that they were the two super populations with the highest number of individuals included, and the other three super populations were significantly underpowered given the size of the sub-sample.

Filtering by Hardy-Weinberg Equilibrium (i.e., the principle that genetic variation in a population will remain constant from one generation to the next in the absence of disturbing factors; HWE), minor allele frequency (MAF), and relatedness were performed within the assigned super-populations. Genome-wide identity by descent (IBD) was calculated using PLINK 1.90 and for each super-population sample, the mean cross-sample genome-wide IBD was calculated to find samples showing excessive relatedness, which is where a sample appears to be a cryptic relative to many other samples but those samples do not appear related to one another (Webb et al., 2017). 194 samples were excluded as outliers for average relatedness with all other samples. Clusters of probable relatives were defined using an IBD of >.01, Zo >= 0.825, and Z1 < 0.175. The best performing sample for each relative cluster was retained, resulting in an additional 180 samples being excluded from the GWAS sample.

Table 2. Proposed Genetic Analyses.

Research Question	**Analytic Plan**	**Data Source**
What specific variants may be associated with resilience? (Aim 2)	GWAS	S4S (EUR, AFR, meta-analysis)
What is the heritability of resilience? (Aim 2)	Univariate GCTA	S4S (EUR and AFR)
What is the molecular overlap between resilience and AUD?	PRS	PGC SUD & S4S (EUR

(Aim 3)		and AFR)
What is the molecular overlap between resilience and PTSD? (Aim 3)	PRS	PGC PTSD & S4S (EUR and AFR)
What is the molecular overlap between resilience and subjective well-being? (Aim 3)	PRS	SSGAC & S4S (EUR)
What is the molecular overlap between resilience and alcohol consumption? (Aim 3)	PRS	UKBB & S4S (EUR)

Note: GWAS= Genome Wide Association Study; GCTA= Genome-wide Complex Trait Analysis; PRS= Polygenic Risk Score(s); S4S= Spit for Science; EUR= European Ancestry; AFR= African Ancestry; PGC SUD= Psychiatrics Genomic Consortium for Substance Use Disorders; PGC-PTSD= Psychiatric Genomics Consortium for Posttraumatic Stress Disorder; SSGAC= Social Science Genetic Association Consortium; UKBB= U.K. BioBank.

Chapter 3: Results

I. Aim 1

a. Aim 1 Data Analytic Plan

The first aim of the present study was to examine resilience as a buffer against alcohol-related outcomes in the face of new-onset TE. It was hypothesized that resilience will buffer the effects of new-onset TE on AUD symptoms and binge drinking status.

A longitudinal path model with moderation was conducted using Mplus Version 8.4 (Muthen & Muthen, 2017; see Figure 4). The model included cohorts 1-4 for which all data is available. The main effects of resilience at year 1 fall (baseline) and new onset trauma at each spring time-point, as well as their interactions were included as predictors of AUD symptoms, the primary alcohol outcome measure (path a1 in Figure 4).

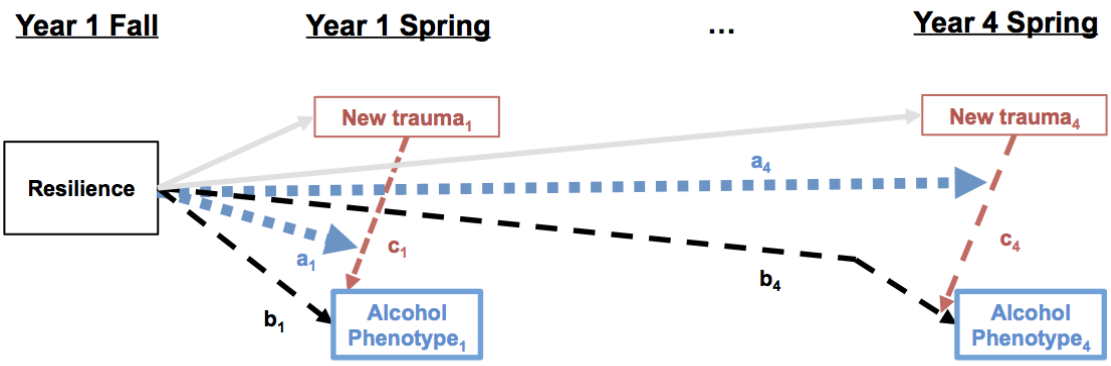


Figure 4. *Longitudinal path model examining the buffering effect of resilience. Note.* All time-points are not shown. The model will be tested across four time-points ranging from spring freshman year to spring senior year. "New trauma" refers to trauma reported between that and the prior assessment period. "b" and "c" paths indicate main effects of resilience and new trauma, respectively. "a" paths indicate tests of resilience moderating impact of new trauma on alcohol phenotypes. Stability paths (e.g., new trauma 1 to new trauma 2) and covariate paths were estimated but are not shown here for ease of interpretation.

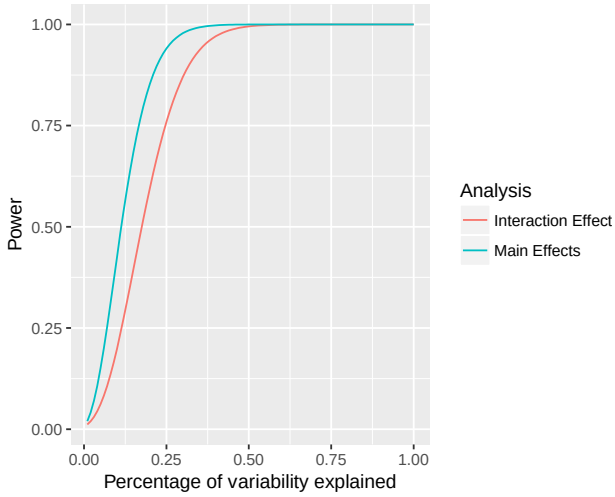
Additional phenotypes of alcohol consumption and binge drinking were examined in subsequent models. Considering the number of alcohol use outcome variables, a Bonferroni correction was applied to provide a conservative correction for multiple testing. Significant interactions were probed using the Johnson-Neyman Regions of Significance Method in order to determine where along the regression lines for the association between resilience and alcohol use phenotype(s) those with versus without new onset trauma significantly differ from one another. Initial zero-order correlations between study variables were examined to determine which covariates (see Table 4) should be included in final models.

Data was examined for outliers, violations of normality, and homogeneity of variance before analysis. A Full Information Maximum Likelihood (FIML) approach was implemented to utilize all available data among individuals who meet inclusion criteria. After a full information model was estimated, T-test and chi square analyses were used to test for differences on study variables between those who do and do not provide data at each spring follow-up time-point.

When these differences are larger than small effects, sensitivity analyses were used, including only those with complete data at the later time-point(s), to test whether study findings replicate or differ from the FIML results. However, none of these differences were larger than small effects, precluding the need to use sensitivity analyses.

A power analysis for Aim 1 demonstrated that power to detect the interaction between resilience and new onset TE is ≥80%, if the interaction explains at least 0.3% of the variance in alcohol consumption (red line/line on right; *Figure 5*), and ≥80% power to detect the main effects of trauma and resilience on alcohol use outcomes, as long as each main effect explains at least 0.2% of the variance (green line/line on left; *Figure 5).*

Figure 5. *Power Analysis for Aim 1 Analyses.*



b. Aim 1 Results

Participant Characteristics. The first sub-sample was created (N=5,346) for the model predicting AUD symptoms and binge drinking status, including only those endorsing lifetime TE and lifetime alcohol consumption. The majority of these individuals identified as White (n=2,870, 53.7%) and as female (n= 3,449, 64.5%). The racial breakdown of the remaining sample was as follows: Black (n=952; 17.8%), Asian (n=719, 13.4%), and Other (n=748,

14.0%). Clinical characteristics for this sub-sample at the Y1 fall and Y1S timepoints are presented in Table 3.

A second sub-sample from the larger S4S sample (N=6,015) includes individuals endorsing lifetime TE exposure at the baseline time-point that were included in the model predicting consumption. Participants included in this sub-sample, for the majority, identified as female (n=3,821, 63.5%) and White (n=3,199, 53.1%). The racial breakdown of the remaining sample is as follows: Black (n=1,100, 18.2%), Asian (n=890, 14.8%) and Other (n=826, 13.7%). Clinical characteristics for this sub-sample at the Y1 fall and Y1S timepoints are presented in Table 3. Differences in clinical and demographic characteristics between the two sub-samples were no larger than a small effect size.

Table 3. *Demographic and Clinical Characteristics of study sub-samples.*

	Sub-sample 1		**Sub-sample 2**	
	M (SD)	**% (n)**	**M(SD)**	**% (n)**
Age	18.5 (0.44)	-	18.5(0.43)	-
Sex (female)	-	64.5% (3,449)	-	63.5% (3,821)
Race (White)	-	53.7% (2,870)	-	53.1% (3,199)
PTSD (probable PTSD)	-	29.0% (1,550)	-	27.6% (1,663)
Parent	9.58 (2.08)	-	9.56(2.10)	-
Peer	9.22 (4.97)	-	8.75 (4.97)	-
Social support	9.49 (2.24)	-	9.47 (2.25)	-
Y1S TE	0.89 (1.14)	39.2% (2,098)	0.88 (1.05)	38.8% (2,333)
Y2S TE	0.64 (.89)	21.3% (1,138)	0.62 (.93)	19.4% (1,157)
Y3S TE	0.53 (.73)	14.3% (765)	0.51 (.84)	13.2% (792)
Y4S TE	0.53 (.77)	12.0% (642)	0.51(.86)	8.5% (510)

Y1S AUD sx	0.54 (1.21)	-	-	-
Y2S AUD sx	1.07 (1.59)	-	-	-
Y3S AUD sx	1.02 (1.50)	-	-	-
Y4S AUD sx	1.14 (1.64)	-	-	-
Y1S Consumption	1.33 (1.36)	-	1.14(1.45)	-
Y2S Consumption	1.50 (1.25)	-	1.33(1.36)	-
Y3S Consumption	1.77 (1.06)	-	1.63(1.18)	-
Y4S Consumption	1.96 (.88)	-	1.95(.89)	-

Note. TE =traumatic event; Both means of new onset trauma load and percentage of those endorsing new onset trauma at each spring time-point are represented. Y1S= Year 1 spring, Y2S= Year 2 Spring, Y3S= Year 3 Spring, Y4S= Year 4 Spring; Sx=Symptoms; Peer= Peer deviance; Parent= Parental involvement

Zero-Order Correlations. Table 4 provides the zero-order Pearson, tetrachoric, and biserial correlations among primary study variables (n= 6,015; second sub-sample). In terms of associations among TE, resilience, and alcohol use outcomes, associations were generally as would be predicted. Specifically, resilience at baseline was significantly, negatively correlated with new onset TE at three follow-up timepoints, with this association strongest at the second time point (Y2S). Resilience was significantly correlated with AUD symptoms at Y1S and Y3S but was not significantly correlated with alcohol consumption at any timepoint.

Table 4. *Correlations among study variables (n=6015).*

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.	25.	26.	27.	28.
1. Age	--																											
2. Sex	.079*	--																										
3. Race: W-B	-.066*	-.093*	--																									
4. Race: W-A	.024	.025	-.186*	--																								
5.Race: W-O	-.007	-.008	-.190*	-.161*	--																							
6.Parent	-.014	-.045*	-.018	-.153*	-.031	--																						
7.Social support	-.038	-.031	-.049	-.069*	-.021	.391*	--																					
8.Peer	-.015	.083*	-.136*	-.161*	.040	-.026	.006	--																				
9. Probable PTSD	.011	-.193*	.012	-.063*	.018	-.096*	-.142*	.104*	--																			
10. Resilience	.002	.166*	.071*	-.013	-.001	.144*	.264*	-.135*	-.264*	--																		
11. Consumption-Y1S	.003	.098*	-.094*	-.154*	.011	.005	.053*	.417*	.042	-.008	--																	
12. Consumption-Y2S	-.024	.120*	-.076*	-.149*	.024	-.006	.062	.373**	.058	-.005	.641*	--																
13. Consumption-Y3S	.059	.110*	-.142*	-.127*	.042	.037	.059	.318*	.057	-.018	.529*	.612*	--															
14. Consumption-Y4S	-.053	.116*	-.109*	-.110*	.009	.037	.092*	.272*	.037	-.022	.488*	.515*	.594*	--														
15. AUD sx-Y1S	.024	.055	-.046	-.035	.008	-.067	-.033	.281*	.078*	-.103*	.266*	.168*	.165*	.206*	--													
16. AUD sx-Y2S	-.008	.056	-.056	-.025	-.017	-.081*	-.056	.285*	.033	-.096*	.278*	.289*	.190*	.230*	.494*	--												
17. AUD sx Y3S	-.019	.095*	-.091*	-.013	.005	-.109*	-.034	.307*	.085	-.134*	.310*	.288*	.321*	.274*	.502*	.574*	--											
18. AUD sx-Y4S	-.041	.089*	-.049	-.501	-.014	-.036	-.034	.261*	.086	-.131*	.304*	.310*	.313*	.374*	.401*	.507*	.570*	--										
19. BD -Y1S	-.005	.038	-.112	-.029	0.38	-	-	.292*	-	.003	.551*	.350*	.358*	.391*	.169*	.158	.194	.232	--									
20. BD – Y2S	-.061	-.342*	.003	-.099*	.032	.040	.069	.152*	.040	.002	.286*	.298*	.230*	.212*	.058	.115*	.090	.100*	.431*	--								
21. BD-Y3S	-.067	.098*	-.101*	-.066	.065	-.030	.068	.235*	.020	-.012	.390*	.467*	.493*	.372*	.132*	.135*	.186*	.228*	.398*	.272*	--							

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.	25.	26.	27.	28.
22. BD-Y4S	-.019	.068	-.073	-.117*	.062	.042	.058	.227*	.023	.012	.376*	.402*	.429*	.477*	.095	.126*	.129*	.233*	.409*	.253*	.458*	--						
23. New onset TE-Y1S	.002	-.042	.016	-.040	-.012	-.052	-.061	.044	.127*	-.044	.064*	.041	.041	.019	.134*	.111*	.095*	.095*	.046	.014	.033	.035	--					
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.	25.	26.	27.	28.
24. New onset TE-Y2S	.034	-.074*	-.021	-.043	.001	-.089*	-.067	.089*	.146*	-.120*	.061	.044	.062	.013	.095*	.146*	.111*	.075	.052	.036	.029	.050	.270*	--				
25. New onset TE-Y3S	-.013	-.057	-.007	-.023	-.036	-.057	-.088*	.068	.118*	-.085*	.105*	.093*	.059	.023	.069	.096*	.171*	.121*	.078	.057	.065	.019	.140*	.250*	--			
26. New onset TE-Y4S	-.046	-.064	-.006	-.036	.039	-.033	-.089	.118*	.119*	-.114*	.100*	.097	.054	.065	.064	.160*	.189*	.221*	-	.107	.056	.071	.144*	.201*	.288*	--		
27. Lifetime trauma load	-.088	-.073*	.004	-.036	.036	-.123*	-.119*	.153*	.398*	-.094*	.077*	.062	.027	.022	.139*	.118*	.106*	.090*	.088	-.012	.063	.041	.229*	.201*	.183*	.160*	--	
28. Anxiety and depressive symptoms	.703	-.156*	-.071*	.018	.007	-.155*	-.272*	.149*	.288*	-.992*	.015	.017	.021	.024	.121*	.102*	.145*	.145*	.015	.001	.017	.001	.071*	.138*	.099*	.140*	.205*	

Notes: *p<.001, Sex is coded 0 for females and 1 for males; For all Race Variables, White=0, African-American, Asian, or Other is coded 1. W-B= White to Black, W-A= White to Asian, W-O= White to Other; Parent= Parental involvement; Peer= Peer deviance; Sx= Symptom; TE= Traumatic event; Y1S= Year 1 Spring, Y2S= Year 2 Spring, Y3S= Year 3 Spring, Y4S= Year 4 Spring; BD= Binge drinking status.

AUD Symptoms Model (n=5,346). The model predicting AUD symptoms with covariates included demonstrated adequate to good fit, χ^2 (116) = 3307.36 , $p < .001$; RMSEA = 0.03, SRMR= 0.05; CFI = 0.85, and TLI = 0.79. To improve model fit, modification indices were considered, and paths recommended to improve model fit were included (i.e., peer deviance with AUD symptoms at year 2, resilience with year 2 TE). The inclusion of these paths significantly improved model fit, χ^2 (96) = 403.59, $p < .001$; RMSEA = 0.03, SRMR= 0.03; CFI = 0.90, and TLI = 0.85. Path coefficients for this model are presented in Table 5.

One significant interaction was found between resilience and new onset trauma exposure at Y4S in predicting Y4S DSM-5 AUD symptoms (see Figure 6), whereby higher levels of new onset TE were associated with higher levels of AUD symptoms at both low (β=.19, $p <.001$), and mean (β=.20, $p =.001$) levels of resilience, but this effect was attenuated at high levels of resilience (β=.07, $p=.051$). The effect of TE on AUD symptoms was significant ($p<.01$) up until 2/5 of one SD above the mean on resilience (see Figure 6). Given the non-significant interaction terms at Y1S, Y2S, and Y3S, main effects were examined in a model without interaction terms. Notably, there were significant main effects of resilience on Y1S and Y3S AUD symptoms, whereby those endorsing higher levels of resilience reported lower AUD symptoms. There were significant main effects of TE on AUD symptoms at Y1S, Y2S, Y3S, and Y4 as well, whereby those reporting higher categories of new onset TE report higher symptoms, as compared to those with less new onset TE (see Table 5).

In terms of covariates, sex, peer deviance, and parental involvement all predicted AUD symptoms at Y1S. More specifically, higher levels of peer deviance, lower levels of parental involvement, and male sex were predictive of increased AUD symptoms.

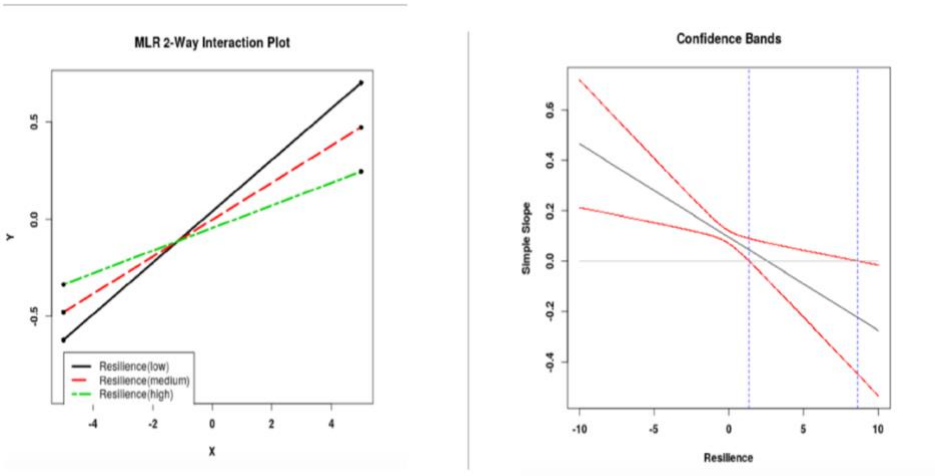
Table 5. Path analysis predicting DSM-5 AUD symptoms and new onset TE (n=5,346).

	AUD Symptoms				**New Onset TE**			
	Y1S	Y2S	Y3S	Y4S	Y1S	Y2S	Y3S	Y4S
Predictor	**B (SE)**	**B (SE)**	**B (SE)**	**B(SE)**	**B (SE)**	**B (SE)**	**B(SE)**	**B(SE)**
Sex (Female)	.06 (.02)**	--	--	--	-.03 (.02)	--	--	--
Age	.02 (.02)	--	--	--	.00 (.02)	--	--	--
Race: White versus Black	.00 (.02)	--	--	--	.00 (.02)	--	--	--
Race: White versus Asian	-.01 (.02)	--	--	--	-.04 (.02)	--	--	--
Race: White versus Other	.00 (.02)	--	--	--	-.02 (.02)	--	--	--
PTSD	.03 (.02)	--	--	--	.10 (.02)**	--	--	--
Parent	-.06 (.02)*	--	--	--	-.04 (.02)	--	--	--
Peer	.27 (.02)**	--	--	--	.04 (.02)	--	--	--
Social support	.03 (.02)	--	--	--	-.03 (.02)	--	--	--
Resilience	-.06 (.02)**	-.05 (.02)	-.07 (.02)**	-.03 (.02)	00 (.02)	-.45 (.05)**	-.06 (.02)	-.09 (.03)*
Y1S TE	.13 (.02)**	--	--	--	--	.26 (.02)**	--	--
Y2S TE	--	.10 (.02)**	--	--	--	--	.26 (.02)**	--
Y3S TE	--	--	.12 (.02)**	--	--	--	--	.30 (.03)**
Y4S TE	--	--	--	.13 (.02)**	--	--	--	--
Y4 INTX	--	--	--	-.07 (.02)*	--	--	--	--

Notes. **p<.01, **p<.001. B= Standardized regression coefficient. *SE*= Standard error; Sex: 1=males, 0=females.; Race: 0=White, 1=Blacks, Asians, or Other for each of the three dummy codes. Y1S= Year 1 spring, Y2S= Year 2 Spring, Y3S= Year 3 Spring, Y4S= Year 4 Spring;

TE= Traumatic event, Peer=Peer deviance, Parent=Parental involvement, PTSD= Probable PTSD, INTX=Interaction term between new onset TE and resilience.

Figure 6. *Interaction plot and regions of significance.*



Note. Regions of significance are presented (p<.01) for the interaction between new onset TE and resilience to predict DSM-5 AUD symptoms. Regression coefficients are nonsignificant at values of the moderator falling within the region (1.4-8.6).

Alcohol Consumption Model (n=6,015). The path analysis predicting alcohol consumption at each spring follow-up timepoint with covariates included produced a decent to good fitting model, χ^2 (140) = 4828.8, p < .001, RMSEA = 0.03, SRMR= 0.03; CFI = 0.89, and TLI = 0.85. To improve model fit, modification indices were considered. Paths that were recommended to improve model fit (i.e., peer deviance with Y2S consumption, resilience with Y2S TE) were incorporated into the model. Including these paths significantly improved model fit, χ^2 (140) = 6007.7, p < .001, RMSEA = 0.03, SRMR= 0.04; CFI = 0.90, and TLI = 0.86. The path coefficients of this model are presented in Table 6.

No significant interaction effects between baseline resilience and new onset TE on alcohol consumption were found for any time-point. Given the non-significant interactions,

interaction terms were removed for supplementary analyses aimed at examining main effects of resilience and new onset TE on alcohol consumption. Results demonstrate no main effect of resilience on alcohol consumption levels. Above and beyond key covariates, there was one significant main effect of Y1S new onset TE on Y1S alcohol consumption, whereby those reporting higher levels of TE endorse consuming more alcohol (see Table 6 for full model results).

A number of covariates were significant predictors of alcohol consumption at Y1S. Identifying as white, as compared to Black/African American or Asian, was associated with higher levels of alcohol consumption. Both social support and peer deviance as contextual factors also significantly predicted alcohol consumption levels whereby higher levels of peer deviance were associated with increased consumption, and interestingly, higher levels of social support were associated with increased consumption as well.

Table 6. Path analysis predicting alcohol consumption and new onset TE (n=6,015).

	Alcohol Consumption				**New Onset TE**			
	Y1S	Y2S	Y3S	Y4S	Y1S	Y2S	Y3S	Y4S
Predictor	**B (SE)**	**B (SE)**	**B (SE)**	**B(SE)**	**B (SE)**	**B (SE)**	**B(SE)**	**B(SE)**
Sex (Female)	.04 (.01)	--	--	--	-.03 (.02)	--	--	--
Age	.01 (.01)	--	--	--	.01 (.01)	--	--	--
Race: White versus Black	-.07 (.01)**	--	--	--	.00 (.02)	--	--	--
Race: White versus Asian	-.12 (.02)**	--	--	--	-.02 (.02)	--	--	--
Race: White versus Other	-.03 (.10)	--	--	--	-.03 (.02)	--	--	--
PTSD	.03 (.02)	--	--	--	.12 (.02)**	--	--	--

Parent	-.01 (.02)	--	--	--	-.03 (.02)	--	--	--
Peer	.42 (.01)**	--	--	--	.05 (.02)*	--	--	--
Social support	.05 (.02)*	--	--	--	-.03(.00)	--	--	--
Resilience	.02 (.02)	-.02 (.01)	-.01 (.02)	-.02 (.02)	.02 (.02)	-.12 (.02)**	-.06 (.02)*	-.09 (.03)*
Y1S TE	.05 (.01)*	--	--	--	--	.28 (.02)**	--	--
Y2S TE	--	.01 (.01)	--	--	--	--	.26 (.02)**	--
Y3S TE	--	--	.00 (.02)	--	--	--	--	.30 (.03)**
Y4S TE	--	--	--	-.02 (.02)	--	--	--	--

Notes. *p<.01, **p<.001. B= Standardized regression coefficient. *SE*= Standard error; Sex: 1=males, 0=females.; Race: 0=White, 1=Blacks, Asians, or Other for each of the three dummy codes. Y1S= Year 1 spring, Y2S= Year 2 Spring, Y3S= Year 3 Spring, Y4S= Year 4 Spring TE= Traumatic event, Peer=Peer deviance, Parent=Parental involvement, PTSD= Probable PTSD.

Binge drinking status model (n=921). Fit for the model predicting binge drinking status was poor to adequate, χ^2 (21) = 114.48, p < .001; RMSEA = 0.07, SRMR=0.05; CFI = 0.84, and TLI = 0.70. Modification indices were considered, and paths recommended to improve model fit were included (i.e., Y4 new onset TE with Y2 new onset TE, Y4 TE with Y2 binge drinking status). However, fit statistics remained poor. Due to missing data patterns (i.e., the binge drinking questions were not asked until 2014 so only cohort 4 had the Y1S timepoint), the path analysis predicting binge drinking status included only the Y2, Y3, and Y4 timepoints, and as such covariates assessed at the baseline timepoint were not included. No significant interaction terms nor main effects were demonstrated for resilience, new onset TE, and binge drinking status (see Table 7). Indeed, the sample included in the analyses predicting binge drinking status was notably smaller than that included in analyses predicting alcohol consumption and AUD symptoms due to missing data patterns. However, the standardized coefficients for the interaction terms predicting binge drinking status were comparable to those for consumption and

AUD symptoms, but were non-significant, and thus, it no meaningful interaction can be inferred even in the context of low power due to sample size (see Table 7).

Table 7. Path analysis predicting binge drinking status and new onset TE (n=921).

Binge Drinking Status				**New onset TE**		
	Y2S	Y3S	Y4S	Y2S	Y3S	Y4S
Predictor	**B (SE)**	**B (SE)**	**B(SE)**	**B (SE)**	**B(SE)**	**B(SE)**
Sex (Female)	--	--	--	--	--	--
Age	--	--	--	--	--	--
Race: White versus Black	--	--	--	--	--	--
Race: White versus Asian	--	--	--	--	--	--
Race: White versus Other	--	--	--	--	--	--
PTSD	--	--	--	--	--	--
Parent	--	--	--	--	--	--
Peer	--	--	--	--	--	--
Social support	--	--	--	--	--	--
Resilience	.02 (.11)	-.07 (.08)	.06 (.05)	-.11 (.04)	-.10 (.05)	-.09 (.05)
Y2S TE	.13 (.06)	--	--	--	.23 (.02)**	--
Y3S TE	--	-.00 (.05)	--	--	--	.23 (.02)**
Y4S TE	--	--	.06 (.06)	--	--	--
INTX	.10 (.09)	.04 (.05)	-.06 (.08)	--	--	--

Notes. *p<.01, **p<.001. B= Standardized regression coefficient. *SE*= Standard error; Y2S= Year 2 Spring, Y3S= Year 3 Spring, Y4S= Year 4 Spring; Peer= Peer deviance; Parent= Parental involvement; TE= Traumatic event. Note: Binge drinking data was not available at the Y1S timepoint. As such, no covariates were included in the present models, as Y1S binge drinking was not included as an outcome.

c. Aim 1 Summary

- Resilience significantly buffered the impact of new onset TE on AUD symptoms and one time-point (Y4S), whereby those endorsing higher levels of resilience reported lower AUD symptoms. Peer deviance levels and parental involvement were both negatively associated with AUD symptoms.
- There were no significant interaction effects between resilience and new onset TE on alcohol consumption levels, nor main effects of resilience on alcohol consumption. Peer deviance and social support were both positively related to consumption levels.
- Model fit for the binge drinking status model was poor due to missing data patterns. Results demonstrate no significant main effects nor interaction effects of resilience on new onset TE or binge drinking status.
- The nuance of resilience as a buffer for AUD symptoms vs. alcohol consumption is likely of clinical importance, and is not surprising given that 1.) alcohol consumption is normative in college student populations, and 2.) the self-medication literature largely posits AUD symptoms as more strongly tied to PTSD than consumption levels alone.

II. Aim 2

The second aim of the current study was to test for individual genetic variants associated with resilience (GWAS) and to examine the molecular heritability of resilience (GCTA). It was hypothesized that there would be individual variants associated with resilience and that resilience would be moderately heritable. Refer to Table 2 for a more detailed explanation of all proposed genetic analyses. As mentioned previously, S4S has implemented rigorous QC procedures (e.g., missing genotype rates, deviations from Hardy-Weinberg equilibrium, inbreeding, excessive

cross-sample relatedness), analyses of ancestry, and suggested best practices for genetic analyses. This QC pipeline was used for data checking, cleaning, etc.

Aim 2 Data Analytic Plan

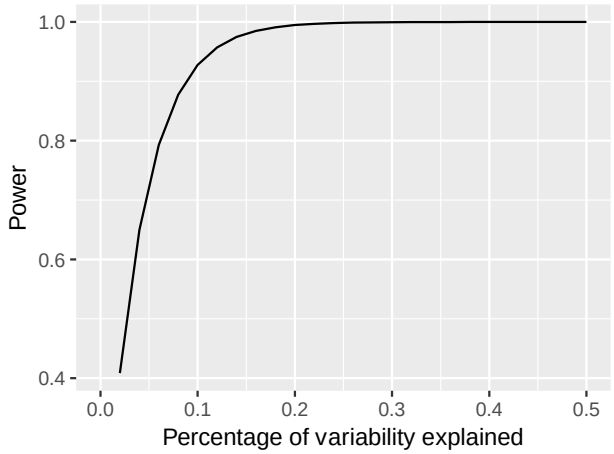
A GWAS was run using PLINK 2.0 (Chang et al., 2015) to identify specific variants that may be associated with resilience, with ancestry PCs and sex included as covariates. The genomic inflation factor (λ) was estimated using R (Team, 2019), and the quantile-quantile (QQ) plots were used to determine and adjust for bulk inflation and excess false positives. False discovery rate (FDR) analysis were used to adjust for multiple testing in all analyses, and to determine what *p*-values are significant or suggestive of significance. Consistent with best practices suggested by the S4S workgroup (Webb et al., 2017), a threshold of 0.5 will be used to determine significance. More specifically, setting an FDR of 0.5 means that approximately half of the values below this cut-off are false positives. A more stringent FDR, such as 0.05, would increase statistical rigor of the proposed GWAS, though a threshold of 0.5 allows for the probing of top variants appropriate for a training exercise. Further, the GWAS was conducted on a novel operationalization of resilience (e.g., Amstadter, Myers, & Kendler, 2014), and as such, a more liberal FDR is warranted. GWAS were conducted for the EUR and AFR sub-samples separately and subsequently meta-analyzed using a program called METAL (Wiler, Li, & Abecasis, 2010), which uses *p*-values from the sub-sample specific analyses, to produce meta-analyzed findings, in order to account for low power due to small sample sizes for each sub-sample.

In order to establish the SNP-based heritability of resilience, a univariate GCTA was conducted. GCTA estimates the heritability of a trait based off of the additive effect of all SNPs. This method creates a genetic relationship matrix (GRM) based on SNPs for all individuals in the sample. The GRM is then used to predict phenotypic relatedness, resulting in an estimate of

the variance in the trait that is due to each phenotype independently.

For Aim 2 analyses, it was estimated that power to detect GWAS or GCTA effects explaining more than 0.1% of the variance in resilience is ≥80% (see *Figure 7*).

Figure 7. *Power Analysis for Aim 2 Analyses*.



a. Aim 2 Results

GWAS, Specific Genetic Variation Related to Resilience.

Meta-Analyzed GWAS. The GWAS was conducted using PLINK 2.0 (Chang, Chow, Tellier, Vattikuti, Purcell, & Lee, 2015) in order to identify specific genetic variants associated with resilience (N= 6,634). Post-filtering, meta-analysis were conducted using METAL (Wiler, Li, & Abecasis, 2010; see Chapter 2, section III, "Genotypic Procedures", for procedure specifics), including sex and top 10 PCs as covariates. Genomic inflation factors (lambda, λ) were estimated in R (Team, 2018). Both Manhattan plots and quantile-quantile (QQ) plots were generated using the qqman package in R (Turner, 2014). Results were available for 3,379,382 markers for resilience. Lambda values for resilience (λ= 0.977, SE= 6.04×10^{-6}; Figure 15,), were slightly below 1 indicating underinflation, and as such *p*-values are higher (less significant) than would be expected by change.

Notably, though, nine SNPs passed the suggestive association threshold ($p < 5x10^{-5}$; see Figure 14; see Table 8 for summary information of these 9 SNPs). LocusZoom (Prium et al., 2010) was used to create plots that allow for visualization of genes of interest from the meta-analyzed GWAS findings. LocusZoom plots -log10P values for SNPs +/- 200 kilobases (kb) from the specified gene of interest, as well as their LD correlations in relation to the index SNP, or the SNP with the lowest *p*-value. The largest number of suggestive SNPs from the meta-analyzed GWAS findings (i.e., three SNPs: *rs2018207, rs7554264, rs7290778*) mapped onto the seizure *related 6 homolog like* (*SEZ6L*, chromosome 22) gene. The majority of the SNPs associated with the *SEZ6L* gene were positively associated with resilience, meaning that increased copies of minor alleles for these SNPs were associated with higher levels of resilience. The LocusZoom plot of *SEZ6L (*see Figure 8*),* demonstrated that two SNPs were in high LD (i.e., correlation between nearby variants) with the reference SNP (*rs2018207*).

Two SNPs (*rs10957272, rs9969662*) were associated with not one gene, but a cluster of genes (*NKAIN3, GGH, TTPA, YTHDF3-AS1)* found on chromosome 8 (see Figure 9) between base pairs 63825092−64225092, which are largely associated with the metabolism of vitamins such as folic acid (B vitamin), vitamin E, potassium, etc. The LocusZoom plot for this area of chromosome 8 demonstrates that these SNPs are in high LD with one another. Findings from the meta-analyzed GWAS suggest a mix of direction of influence with resilience such that *rs10957272* was positively associated with resilience, indicating more copies of minor alleles as related to increased levels of resilience, and *rs9969662* was negatively associated with resilience, meaning more copies of minor alleles being associated with less resilience.

One SNP (*rs74987153)* was associated with the *fyn related src family tyrosine kinase* (*FRK;* chromosome 6; see Figure 11) gene and one SNP (*rs13162155;* see Figure 10) was

associated with the *long intergenic non-protein coding RNA 2112* (*LINC02112*; chromosome 5) gene. Both of these SNPs were negatively related to resilience, suggesting that increased copies of minor alleles for these SNPs are associated with lower resilience. Two SNPs (*rs12719536, rs6578251)* were not associated with any one gene or cluster of genes on a region of chromosome 5 and 11 respectively (see Figures 12 and 13).

Table 8. *Summary Information of SNPs Meeting Suggestive Threshold (Meta-Analyzed).*

SNP	CHR	BP	Ref. allele	Weight (N)	Z-Score	P-Value	Gene
rs10957272	8	64025092	a	3947	4.743	2.11E-06	None
rs9969662	8	64018607	a	3955	-4.633	3.60E-06	None
rs2018207	22	26704363	a	2845	4.586	4.53E-06	SEZ6L
rs12719536	5	104326153	t	3998	-4.575	4.75E-06	None
rs13162155	5	9658482	a	3998	-4.516	6.31E-06	LOC285692
rs7290778	22	26700592	t	2808	-4.51	6.48E-06	SEZ6L
rs75542645	22	26700773	c	2817	4.483	7.37E-06	SEZ6L
rs74987153	6	116318706	t	1132	-4.477	7.66E-06	FRK
rs6578251	11	2268472	t	3976	-4.446	8.77E-06	None

Note. CHR= Chromosome, BP= Position, Ref. allele= Reference allele.

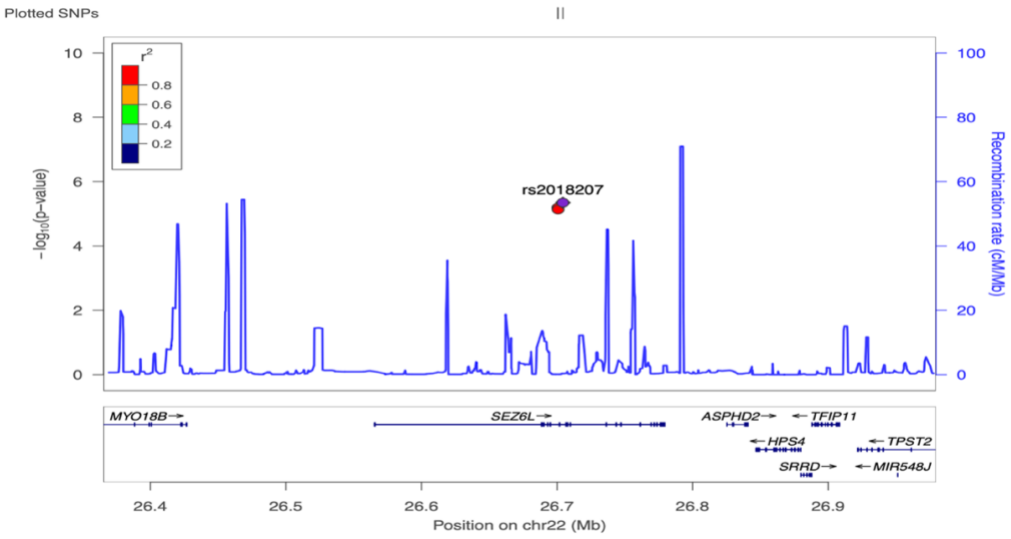


Figure 8. *LocusZoom Plot for Resilience Gene of Interest SEZ6L Among the Meta-Analyzed Sample*. *Note*: Associations for SNPs surrounding *SEZ6L* (+/- 200kb) from the meta-analyzed GWAS are shown here. *Rs2018207* was used as the index SNP, given it is the SNP with the lowest *p*-value. The x-axis illustrates the position of each SNP, and the y-axis shows the *p*-value, log transformed to -log10(p). The size of linkage disequilibrium (LD) for each SNP with the index SNP is represented by different colors.

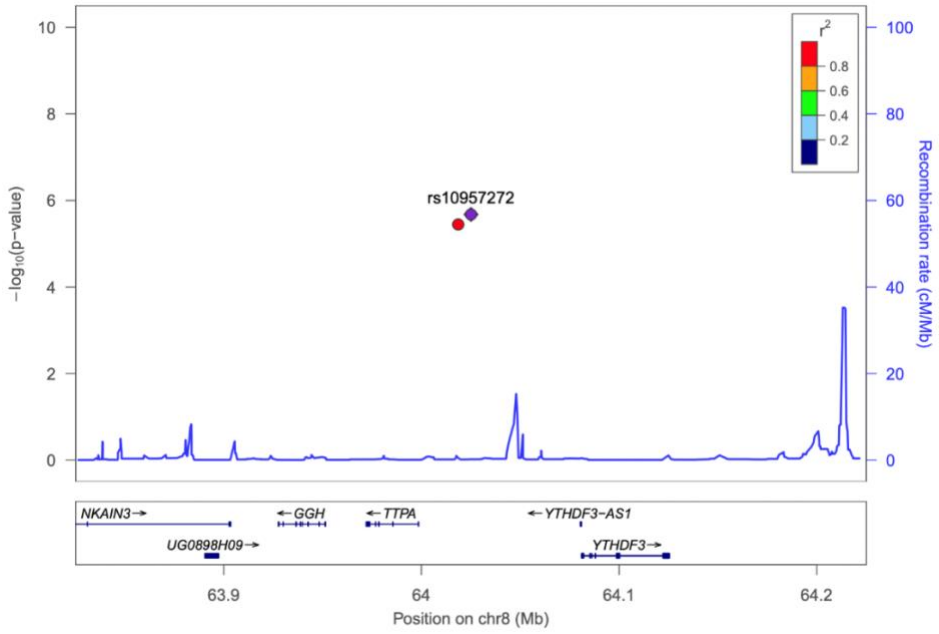


Figure 9. *LocusZoom Plot for Resilience Gene Region of Interest on Chromosome 8 Among the Meta-Analyzed Sample*. *Note*: Associations for SNPs within the region associated with suggestive SNPs are shown here. The x-axis illustrates the position of each SNP, and the y-axis shows the *p*-value, log transformed to -log10(p). The size of linkage disequilibrium (LD) for each SNP with the index SNP is represented by different colors.

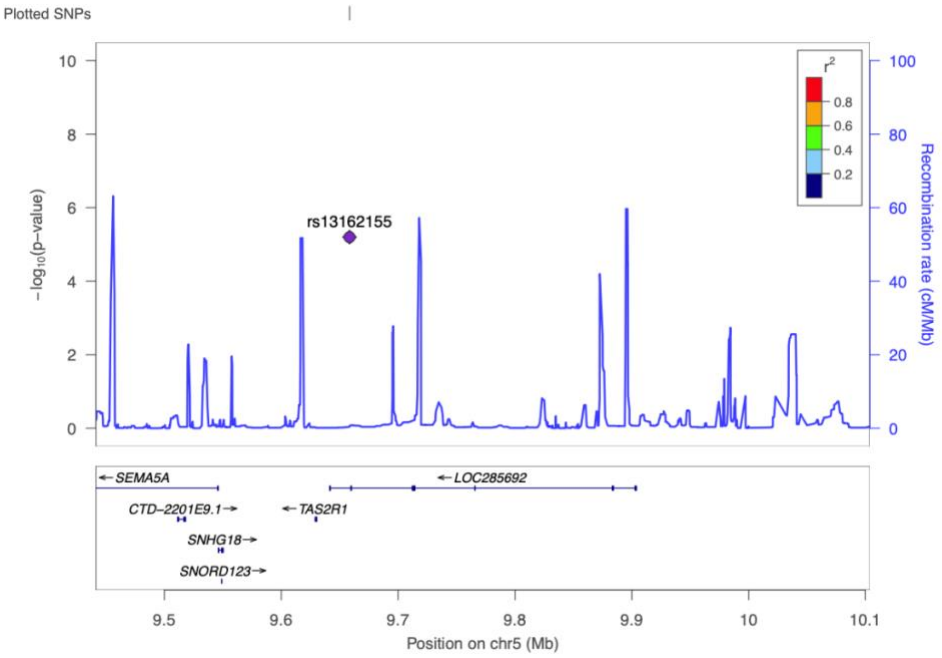


Figure 10. *LocusZoom Plot for Resilience Gene of Interest LOC285692 Among the Meta-Analyzed Sample. Note*: The associations for the SNP surrounding *LOC285692* (+/- 200kb) from the meta-analyzed GWAS are shown here. The x-axis illustrates the position of each SNP, and the y-axis shows the *p*-value, log transformed to -log10(p).

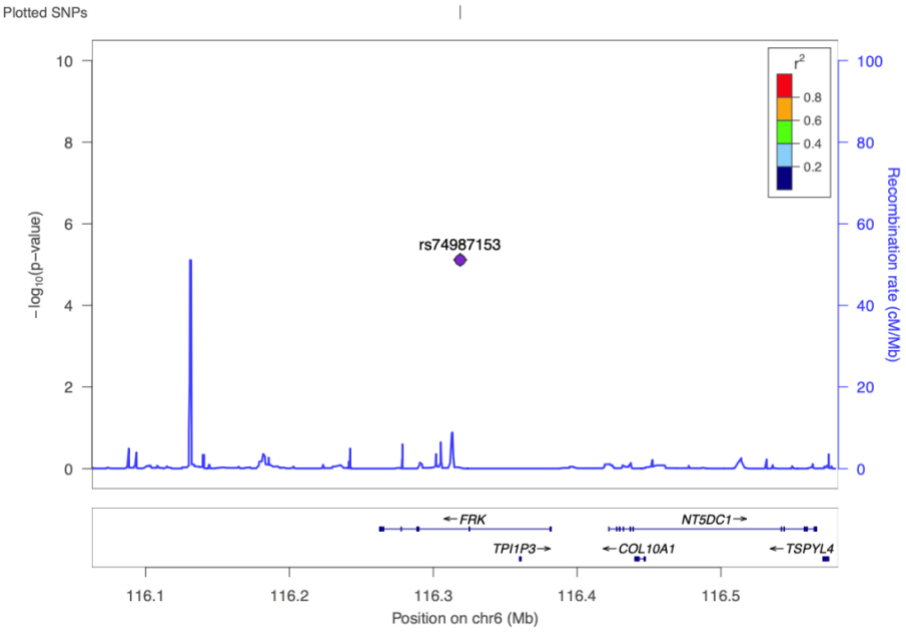


Figure 11. *LocusZoom Plot for Resilience Gene of Interest FRK Among the Meta-Analyzed Sample. Note*: The association for the SNP surrounding *FRK* (+/- 200kb) from the meta-analyzed GWAS are shown here. The x-axis illustrates the position of each SNP, and the y-axis shows the *p*-value, log transformed to -log10(p).

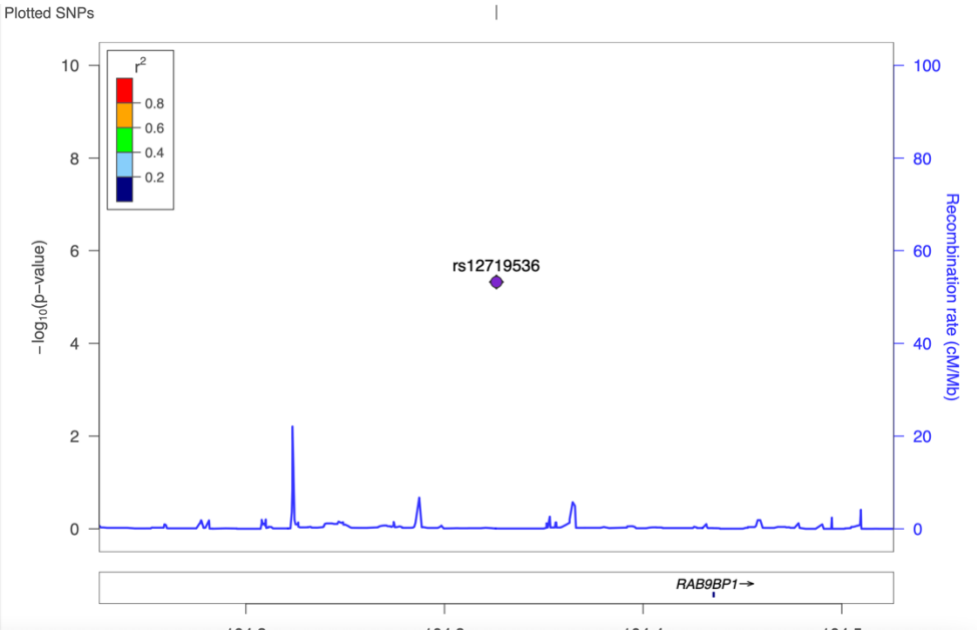


Figure 12. *LocusZoom Plot for SNP rs12719536 Among the Meta-Analyzed Sample. Note*: The association for the SNP *rs12719536* (+/- 200kb) from the meta-analyzed GWAS are shown here. The x-axis illustrates the position of each SNP, and the y-axis shows the *p*-value, log transformed to -log10(p).

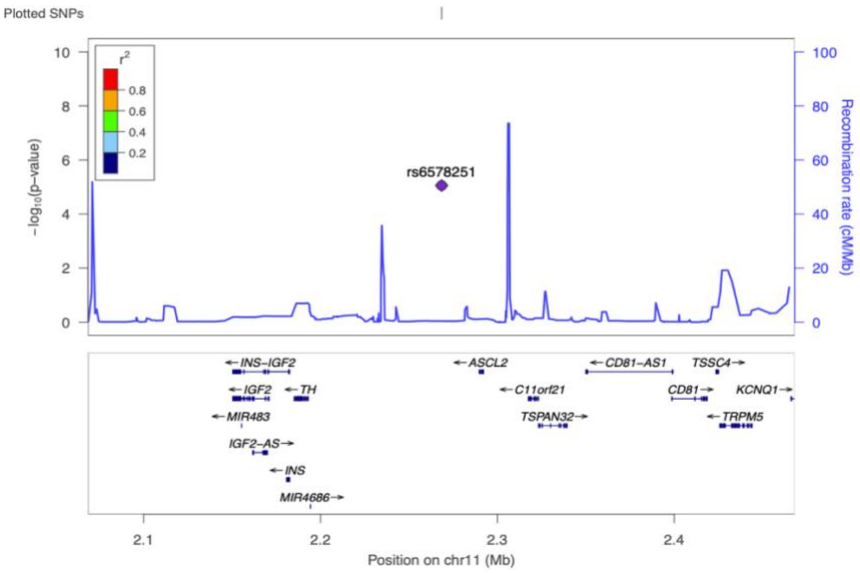


Figure 13. *LocusZoom Plot for SNP rs6578251 Among the Meta-Analyzed Sample. Note*: The association for the SNP *rs6578251* (+/- 200kb) from the meta-analyzed GWAS are shown here. The x-axis illustrates the position of each SNP, and the y-axis shows the *p*-value, log transformed to -log10(p).

Upon investigating the EUR (n= 4,594) and AFR (n= 2,040) subsamples separately within the meta-analysis for resilience, ~16 markers in had a *q*-value threshold of < 0.5. This *q*-value threshold was chosen given recommendations from the S4S genetic workgroup (Webb et al., 2017). Notably a 0.5 threshold is quite liberal, whereby half of the values below this threshold are false positives. Although a more stringent threshold would decrease false positives, and allow for an increase in methodological rigor, 0.5 still allows for further examination of top variants, and is appropriate for the present study given the lack of extant genetic research on resilience, as well as the training aims of the present study. Further, for training purposes, GWAS results from the non-meta-analyzed EUR and AFR sub-samples were examined separately.

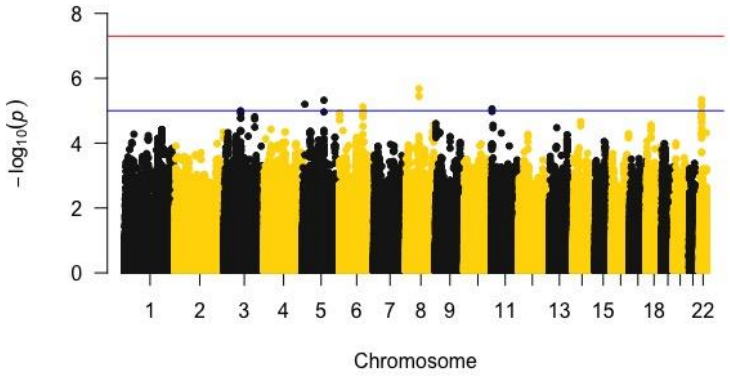


Figure 14. *Manhattan Plot for Resilience (Meta-Analyzed)*; *Note:* This figure plots the -log10(*p*) values of associations for resilience by chromosome. The red line represents genome-wide significance (p=1x10^{-8}), while the blue line indications a suggestive association threshold (p = 1x10^{-5}).

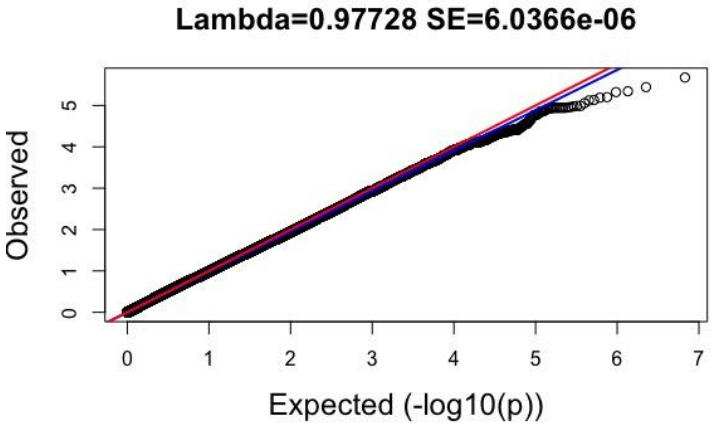


Figure 15. *Quantile-quantile (QQ) plot for Meta-Analyzed Findings; Note*: The expected distribution of p-values is shown on the x-axis, while the observed distribution of p-values from GWAS of resilience is shown on the y-axis. All p-values are represented as –log10(P). The red and blue lines represent 95% confidence intervals.

European GWAS for Resilience. Post-filtering for the EUR ancestry (n=4,594) GWASs revealed that results were available for 2,689,338 markers for resilience, with a lambda value (λ=.971, SE=$9.521x10^{-6}$) close to 1, suggesting slight underinflation (Figure 17). After FDR analysis, no markers met genome-wide significance, however four met the suggestive threshold for significance ($p < 5x10^{-5;}$ Figure 16). Three of the four suggestive SNPs overlapped with SNPs those found to also be suggestive of significance in the meta-analyzed findings (*rs*2018207, *rs7290778*, *rs75542645*), whereas *rs6866409* (*LOC105379111*; chromosome 5) was unique to the EUR analyses. None of the SNPs overlapped with suggestive hits in the AFR sub-sample (see Table 9).

Table 9. *Summary of Suggestive SNPs in EUR sub-sample.*

SNP	CHR	BP	Ref. allele	Obs (N)	Beta(SE)	P-Value	Gene
rs2018207	22	26704363	g	2845	-0.150(0.03)	3.21E-06	SEZ6L
rs7290778	22	26700592	t	2808	-0.149(0.03)	4.64E-06	SEZ6L
rs75542645	22	26700773	g	2817	-0.417(0.03)	5.30E-06	SEZ6L
rs6866409	5	104312745	a	2807	-0.123(0.02)	5.61E-06	LOC285692

Note. CHR= Chromosome, BP= Position, Ref. allele= Reference allele.

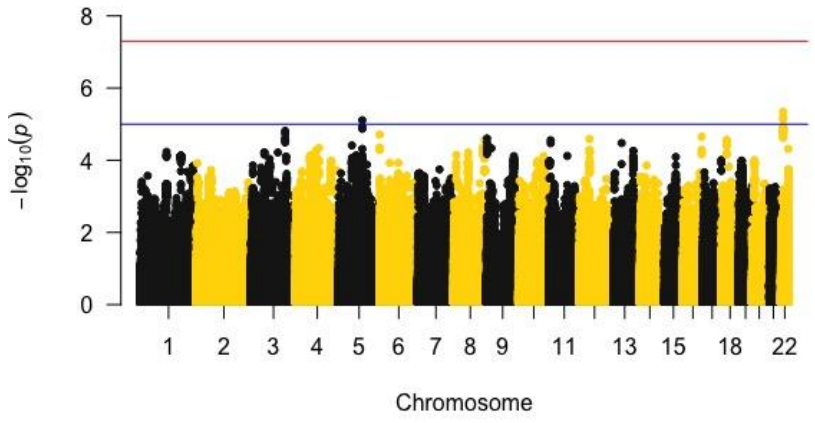


Figure 16. *Manhattan Plot for Resilience within the EUR Sample*; Abbreviations: EUR= European American subsample; *Note*: This figure plots the -log10(*p*) values of associations for resilience by chromosome. The red line represents genome-wide significance (p=1x10^{-8}), while the blue line indications a suggestive association threshold (p = 1x10^{-5}).

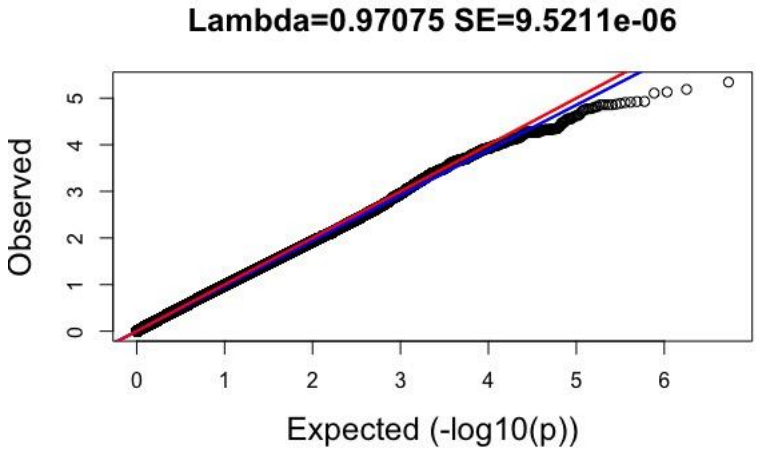


Figure 17. *Quantile-quantile (QQ) plot for Resilience with the EUR Sample;* Abbreviations: EUR= European American subsample. *Note:* The expected distribution of p-values is shown on

the x-axis, while the observed distribution of p-values from GWAS of resilience is shown on the y-axis for the EUR subgroup. All p-values are represented as –log10(P). The red and blue lines represent 95% confidence intervals.

African GWAS for Resilience. Results were available for 2,039,491 markers following filtering for AFR ancestry (n= 2,040), with lambda values close to 1, again, suggesting slight underinflation, meaning that higher *p*-values were found than would be expected by chance (see Figure 19). FDR analyses demonstrated that 0 markers met GWS, however 12 markers met the threshold of suggestive significance ($p< 5x10^{-5}$, see Figure 18). One of these markers (*rs74987153*) overlapped with suggestive hits from the combined, meta-analyzed sample and zero overlapped with suggestive hits from the EUR sample (see Table 10 for summary information). Notably, the AFR sub-sample was 50% of the size of the EUR sub-sample, though findings demonstrate a larger number of suggestive SNPs within the AFR sub-sample. This is possibly due to the effect sizes of the suggestive SNPs being larger in the AFR sub-sample than in the EUR sub-sample.

Table 10. *Summary of Suggestive SNPs in the AFR sub-sample.*

SNP	CHR	BP	Ref. allele	Obs (N)	Beta	P-Value	Gene
rs1937787	1	80839278	t	1120	-0.251(0.05)	4.76E-07	None
rs2897852	12	90768440	t	1276	-0.27(0.06)	1.23E-06	None
rs7296300	12	90768965	g	1129	-0.271(0.06)	1.23E-06	None
rs17435994	1	80808989	t	1119	-0.249(0.05)	1.31E-06	None
rs72675712	1	8080949	t	1119	-0.248(0.05)	1.31E-06	None

rs17488857	1	80808830	a	1120	-0.242 (0.05)	2.63E-06	None
rs4537259	8	27718300	g	1121	-0.241(0.05)	7.23E-06	None
rs74987153	6	116318706	t	1132	-0.34(0.08)	7.57E-06	FRK
rs11651586	17	61825337	c	1133	0.207(0.05)	8.10E-06	CCDC47
rs11730573	4	188079254	g	1119	-0.213(0.05)	8.20E-06	None
rs11870815	17	61834629	g	1135	0.205(0.05)	9.05E-06	CCDC47
rs35844156	17	61837568	g	1135	0.206(0.05)	9.05E-06	CCDC47

Note. CHR= Chromosome, BP= Position, Ref. allele= Reference allele.

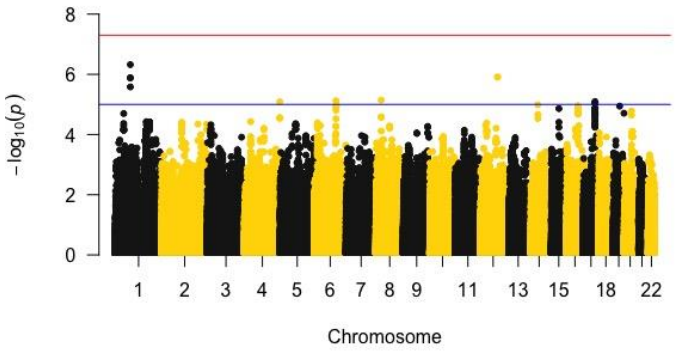


Figure 18. *Manhattan Plot for Resilience within the AFR Sample*; Abbreviations: AFR= African American subsample; *Note*: This figure plots the -log10(*p*) values of associations for resilience by chromosome. The red line represents genome-wide significance (p=1x10^{-8}), while the blue line indications a suggestive association threshold (p = 1x10^{-5}).

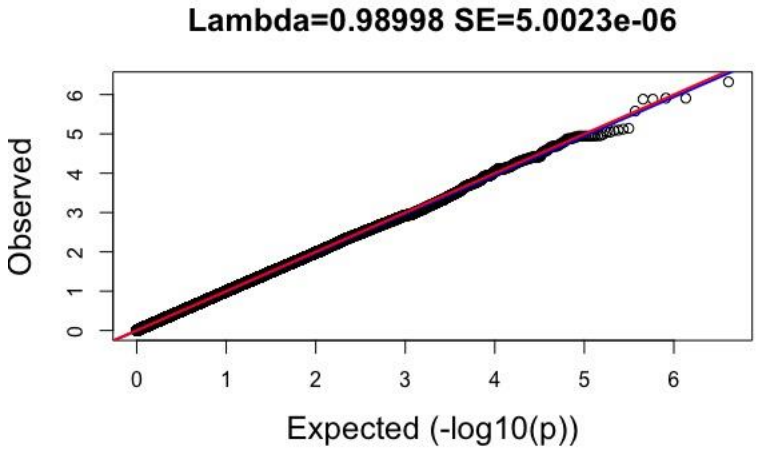


Figure 19. *Quantile-quantile (QQ) plot for Resilience with the AFR Sample;* Abbreviations: AFR= African American subsample; *Note*: The expected distribution of p-values is shown on the x-axis, while the observed distribution of p-values from GWAS of resilience is shown on the y-axis for the AFR subgroup. All p-values are represented as –log10(P). The red and blue lines represent 95% confidence intervals.

GCTA, SNP-based Heritability of Resilience

Univariate GCTA. In order to examine the molecular heritability of resilience, univariate GCTA analyses were conducted separately for EUR and AFR ancestries. Results are shown in Table 11. Resilience was not found to be significantly heritable among the EUR, nor the AFR sub-samples, likely resulting from small sample size. Standard error is used as a metric for indicating how accurately a sample mean reflects the population mean, whereby a standard error of 0 indicates no random error within the sample (Field, Miles, & Field, 2012). Thus, the larger the standard error estimate, the more inaccurate the statistic. Standard error is known to decrease as sample size increases (Field et al., 2012). Given that neither the EUR (h^2= .118, SE=.100, p= .12) nor AFR (h^2= .166, SE= .278, p= .28) analyses yielded significant heritability estimates and

both produced notable standard error estimates (e.g., Visscher & Goddard, 2015), it can be hypothesized that a lack of significant finding is likely due to sample size.

Table 11. *Findings from GCTA of resilience in both sub-samples.*

Super-population	N	Covariates	h^2	SE	*p*-value
AFR	908	PCs, sex	.166	.278	.280
EUR	2371	PCs, sex	.118	.100	.120

Note. SE= Standard error

c. Aim 2 Summary

- Findings from the meta-analyzed GWAS demonstrated that no markers met GWS. Nine markers met the suggestive of significance threshold, with the majority of these markers mapping onto three different genes: *SEZ6L*, *LINC02112*, *FRK*. These loci should be explored with larger sample sizes.
- GWAS findings from the EUR subsample do not reveal any genome-wide significant SNPs associated with resilience. Four SNPs met the suggestive significance threshold.
- No genome-wide significant SNPs were associated with resilience in the AFR subsample. However, 12 SNPs met the suggestive significance threshold, and are suggestive loci to explore with increase sample size.
- There was a lack of evidence to support resilience as significantly heritable in the present sample, likely due to low power resulting from low sample size.

III. Aim 3

To examine the molecular overlap of resilience with alcohol-related phenotypes, PTSD,

and protective phenotypes, PRS scores were generated. It was hypothesized that significant genetic correlations would be found between resilience and alcohol use phenotypes, between resilience and PTSD, as well as between resilience and subjective well-being.

a. Aim 3 Data Analytic Plan

Summary statistics needed for generation of PRS scores came from large-scale archival genetic data that is publicly available to researchers (i.e., UK Biobank [alcohol consumption]; PGC-PTSD [PTSD]: PGC-SUD [AD]; SSGAC [well-being]; see Table 12 for more details). All PRS analyses were analyzed separately, using PLINK, for AFR and EUR ancestries, as they are the largest ancestry populations in S4S and all large-scale consortia contain adequate numbers of EUR and AFR for ancestry specific PRS analyses. Prior to generating PRS, ambiguous SNPs were removed from analysis and LD corrected for by pruning variants nearby (500kb) and in LD ($r^2 > 0.3$) with the reference variant (lowest p-value) in a given region. PRS were calculated multiple times using various *p*-value thresholds in order to determine which *p*-value should be used in the prediction of S4S resilience. Specifically, PRS were generated at the following p-value thresholds: 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4 ,0.5, 1. PRS calculated under the optimal p-value threshold were then used to predict PTSD and TRD symptom severity. The distribution of per-person polygenic risk was normalized by fitting to a standard normal distribution curve, to assist with interpretation of analyses.

Table 12.

Overview of the genetic databases from which summary statistics for PRS analyses were derived.

Phenotype	Source	N (EUR)	N (AFR)	Phenotype measurement
Alcohol Dependence (AD)	PGC-SUD (Walters et al., 2018)	Cases= 8,233 Controls= 18,409	Cases= 2,917 Controls= 1,967	AD diagnostic status (dichotomous)

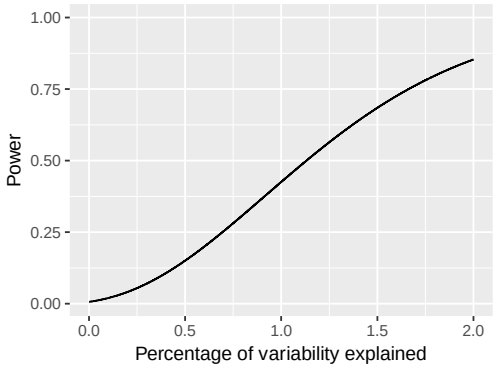
Alcohol consumption	UK BioBank (Clarke et al., 2017)	108,309	N/A	Self-reported units/week
PTSD	PGC-PTSD (Nievergelt et al., 2018)	Cases= 23,185 Controls= 151,309	Cases= 4,363 Controls= 10,976	Lifetime and/or ever diagnostic status
Subjective well-being	SSGAC (Turley et al., 2018)	388,538	N/A	Life satisfaction and positive affect sum score

Following the aforementioned preparatory steps, ancestry specific SNP-level summary statistics from each of the four discovery datasets (AUD, alcohol consumption, PTSD, well-being) were used to create score files using the GWAS data in the S4S dataset to capture aggregate genetic risk of resilience. Each individual in S4S was scored for genetic risk for each phenotype by weighting risk alleles according to the natural log of the odds ratio (OR) from each of the discovery samples for specified *p*-value bins. Given that the optimal *p* -value is unknown a priori, PRS are calculated over a range of thresholds, association with the phenotype of interest tested for each, and the prediction optimized accordingly, resulting in an "optimal" *p*-value threshold. Although multiple testing at many *p*-value thresholds may produce inflated results, there are strategies for avoiding overfitting (e.g., out-of-sample prediction, empirical *p*-values via permutation, etc.), and it is best practice to not select a single, arbitrary *p*-value threshold, as this may lead to underfitting and false conclusions (Choi, Mak, & O'Reilly, 2018). Once PRS were generated from the S4S data, the genetic overlap between resilience and each phenotype was determined using regression analyses, adjusting for sex and ancestry specific PCs.

For Aim 3 analyses, power to detect the effect of the PRS for resilience, if that PRS explains at least 2% of the variance in the four discovery phenotypes (alcohol consumption, AUD, PTSD, well-being; Figure 20), is $\geq$80%. Based on past research examining PRS overlap between externalizing and internalizing disorders, 2% of the variance is plausible (e.g., Salvatore

et al., 2014). It was expected that aggregate score approaches will be more powered than GWAS analyses using individual variants to examine overlap in heritability. By using highly powered samples (e.g., UK BioBank), as the discovery samples, the PRS analyses examining the overlap in heritability between resilience, alcohol consumption, AUD, PTSD, and protective phenotypes in the present sample are maximizing the likelihood that analyses are sufficiently powered.

Figure 20. *Power Analysis for Aim 3 Analyses.*



b. Aim 3 Results

Resilience and Alcohol Dependence (AD*).* S4S genetic data is included in the PGC-SUD summary statistics for AD, and as such, a "leave-one-out" dataset was computed excluding S4S participants as PRS analyses do not allow for sample overlap.

The ability of PRS from the PGC-AD data to predict resilience in the S4S data among the EUR and AFR sub-samples was tested using PRSice 2 (Choi & O'Reilly, 2019). AD summary statistics did not significantly predict resilience in the S4S sample for the EUR sub-sample, nor the AFR sub-sample. Results demonstrated that, for the EUR sub-sample (N cases = 8,233, N controls = 18,409), model fit was optimized at a *p*-value of .20, meaning that at this *p*-value, the capability of AD summary statistics to predict resilience is maximized. Nagelkerke's pseudo- R^2 value showed that PRS at this p-value threshold explained a maximum variance of 0.06% in resilience (b= 2.93, SE= 2.27, *p*= 0.19). Similar patterns were found when examining the ability

of PRS from the PGC-AD data to predict resilience in the S4S data among the AFR sub-sample (N cases = 2,917, N Controls = 1,967) whereby model fit was optimized at a p-value of 0.17, and PRS from the PGC-SUD did not significantly predict resilience (b= -19.25, SE= 14.10, *p*= 0.17) with AD explaining a maximum variance of 0.16%.

Resilience and Alcohol Consumption. Scores were then used to predict resilience within the EUR S4S sub-sample. Polygenic risk for alcohol consumption significantly predicted resilience (b= -46.80, SE=19.81, *p*<.05, see Figure 21), explaining 0.19% of the variance in resilience. The direction of effect is as expected with summary stats for alcohol consumption being negatively related to resilience in the S4S sample. Figure 21 below graphically displays the model fir of the PRS at various p-value thresholds, demonstrating model fit is optimized at *p*= 0.018. PRS analyses for alcohol consumption were used to predict resilience only in the EUR sub-sample, given that summary statistics for consumption from the UK BioBank include EUR individuals only.

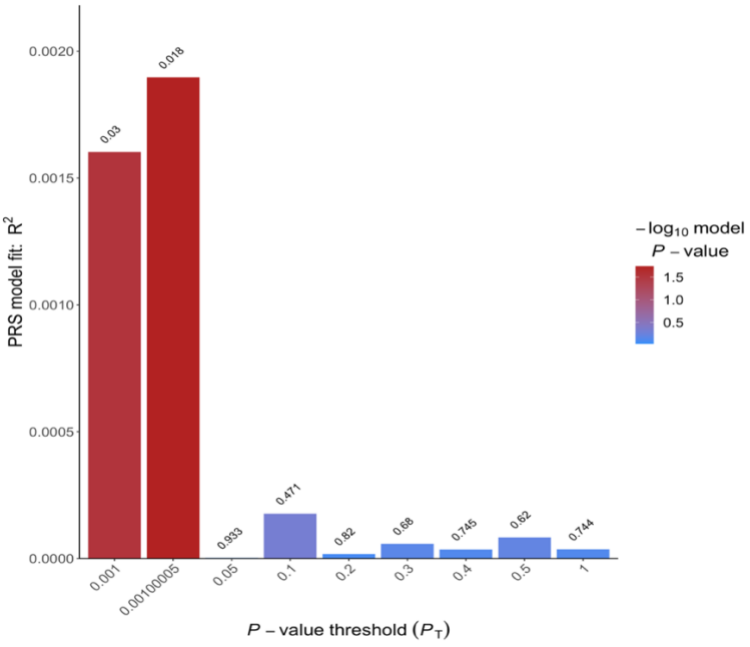


Figure 21. *Bar Plot Displaying Model Fit of the Alcohol Consumption PRS in the EUR Sub-Sample at Various P-value Thresholds.*

Resilience and PTSD. For the EUR sub-sample (N: cases= 23,185, controls= 151,309), there was no significant association between PTSD PRS and resilience (b= -1.92, SE= 1.72, *p*=.10), and the *R2* demonstrated that PTSD at the p-value threshold of .102 explained a maximum variance of 0.09% of resilience. In the AFR sub-sample (N: cases= 4,363, controls= 10,976), there was a significant association between PTSD PRS and resilience (b= 2.94, SE= 0.02, *p*<.05), though in the opposite direction than would be expected such that PTSD-PRS were positively related to resilience (see Figure 22). Given the extant literature demonstrating resilience as protective against internalizing symptoms (e.g., Sheerin et al., 2018, etc.) it would be expected that PTSD and resilience would be negatively related. With p-values optimized at .02, PTSD PRS explained 0.42% of the variance in resilience.

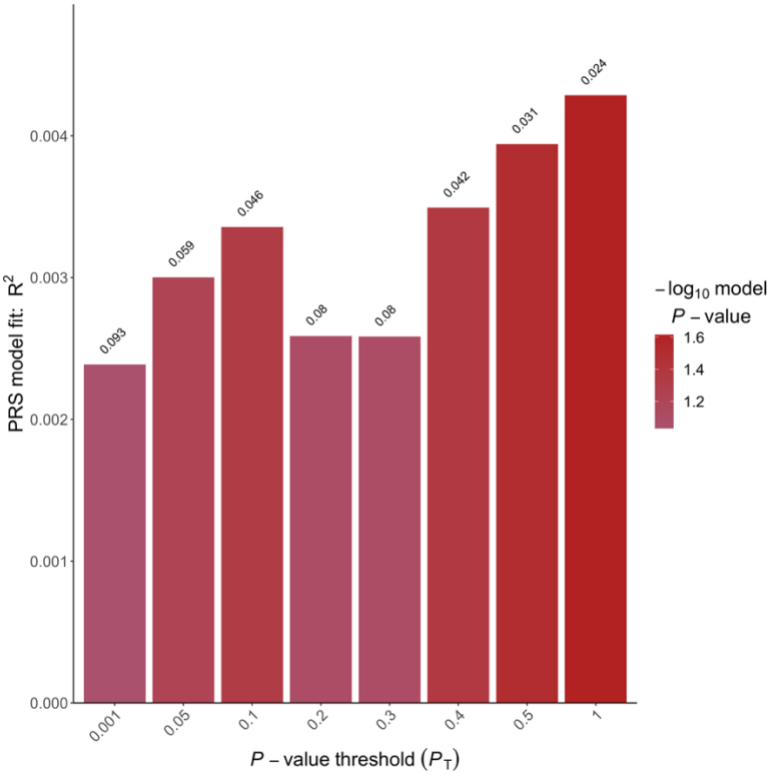


Figure 22. *Bar Plot Displaying Model Fit of the PTSD PRS in the AFR Sub-Sample at Various P-value Thresholds.*

Resilience and Well-being. Polygenic risk scores for subjective well-being were calculated using summary statistics from the SSGAC (N= 388,538, Turley et al., 2018). Subjective well-being was assessed via a combination of measures assessing life satisfaction and positive affect (Okbay et al., 2016; Turley et al., 2018). The ability of the well-being PRS to predict resilience in S4S was tested in the EUR sub-sample, as summary statistics are not available for AFR samples at this time. For the EUR sub-sample, results demonstrated that model fit was optimized at a p-value of .07. There was no significant association between PRS for well-being and resilience in S4S in the EUR sub-sample (b= 49.39, SE= 38.57, p= .20), with the R^2 showing that PRS at this p-value threshold explained a maximum variance of 0.11% of the variance of resilience. Similar to those of alcohol consumption, PRS analyses for well-being were used to predict resilience only in the EUR sub-sample, given that summary statistics for well-being include EUR individuals only

c. Aim 3 Summary

- PRS for AD were not associated with resilience in the S4S sample in either ancestry sub-sample.
- PRS for alcohol consumption were associated with resilience in the EUR sub-sample with alcohol consumption being negatively related to resilience, as would be expected. PRS for alcohol consumption were not tested within the AFR sub-sample as AFR summary statistics are not available.

- PRS for PTSD were not associated with resilience in the S4S sample for the EUR sub-sample but were significantly associated with resilience for the AFR sub-sample, though in the opposite direction than expected (i.e., positively related).
- Well-being was not associated with resilience in the S4S EUR sub-sample, and was not tested in the AFR sub-sample due to lack of AFR summary statistics from the SSGAC.

Chapter 4: Discussion

The present study sought to fill gaps in the literature through three primary aims. First, the present study examined the buffering effect of a discrepancy-based resilience variable on AUD symptoms, alcohol consumption, and binge drinking status in the wake of college onset trauma exposure using longitudinal data. Second, the current study investigated the genetic underpinnings of resilience through testing associations between potential variants and resilience (GWAS), and through calculating the SNP-based heritability of resilience (GCTA). Lastly, the present study examined the shared genetic risk between resilience, alcohol consumption, AD, PTSD, and well-being using polygenic risk score analyses. Findings from each aim are discussed below.

I. Aim I: The Buffering Effect of Resilience on Alcohol Outcomes

Overall Summary of Findings

The first aim of the present study was to examine the buffering effect of resilience on alcohol use phenotypes (AUD symptoms, consumption, and binge drinking status), in the context of new TE experienced over the course of college. There is a large body of literature demonstrating the protective effects of resilience on internalizing disorders, primarily reporting main effects, with only a few examining the longitudinal buffering effects (Sheerin et al., 2018; Ong et al., 2006; Hjemdal, Friborg, Stiles, Rosenvinge, Martinussen, 2006). Amongst the

literature on resilience and alcohol use outcomes, the majority of extant research is cross-sectional in nature (for a review, see Cusack & Amstadter, in preparation). The limited longitudinal work evidences main effects of resilience on alcohol misuse (Green et al., 2014) and on alcohol initiation (Wong et al. 2006). Cross-sectional studies that employ moderation analyses also contribute initial evidence for resilience as moderating the relationship between adversity and harmful alcohol use (Wingo et al. 2014), and alcohol-related consequences (Morgan, Bray, & Brown, 2018).

Findings from the present study largely align with the extant literature and extend findings by examining resilience as a moderator using a longitudinal design. Results demonstrate that resilience interacts with college-onset TE to buffer against AUD symptoms at one time-point (Y4S), but not against alcohol consumption nor binge drinking status. Further, there were main effects of resilience on AUD symptoms at Y1S and Y3S, but not on levels of consumption nor binge drinking status. Specific findings from the three models are discussed in turn.

Resilience as a Buffer Against AUD Symptoms

Resilience was found to exert a main effect on AUD symptoms at Y1S, Y2S, and Y3s, and to interact with new onset TE at Y4S. The main effect of resilience on AUD symptoms is consistent with the prior literature that demonstrates resilience as being negatively related to alcohol phenotypes, such as number of related problems (Weiland et al., 2012), AUD diagnostic status (Long et al., 2017), and lifetime consumption (Alvarez-Aguirre, Alonso-Castillo, & Zanetti, 2014), though these studies are largely cross-sectional in nature.

In line with hypotheses, evidence of a buffering effect was found for AUD symptoms, whereby increased TE exposure led to more AUD symptoms at low and mean levels of resilience, but not at high levels of resilience, highlighting resilience as a key protective factor.

This is consistent with prior research that has found that resilience interacts with number of stressors to predict alcohol related outcomes (Morgan, Brown, & Bray, 2018). Our pattern of findings suggests that resilience does not buffer the impact of TE on AUD symptoms until the end of college (Y4S), and at that point, high levels of resilience are required to impact symptoms, suggesting a pervasive effect of TE on AUD symptoms in college student and that resilience may have an enduring impact on AUD symptoms. Increased TE exposure led to more AUD symptoms for those less than 1.4 SD above the mean on resilience, suggesting that relatively high levels of resilience is needed to see a lack of effect of TE on AUD symptoms.

This finding is also consistent with literature examining the self-medication hypothesis (i.e., the idea that individuals use substances in order to cope with psychiatric symptoms; Khantzian, 1997), specifically in relation to PTSD and alcohol. The literature examining the self-medication hypothesis evidences support for the relation between PTSD and trauma exposure and problematic alcohol use/AUD symptoms (for a review, see Hawn, Cusack, & Amstadter, 2020; Gaher, et al., 2014), though less support is shown for the relation between PTSD and trauma exposure and alcohol consumption (e.g., Bountress, et al., 2019; Possemato et al., 2015). Contextualizing findings from aim 1 of the present study in relation to the self-medication literature, it may be that resilience is most important in buffering against the development of alcohol-related problems in a similar way that PTSD and AUD are more closely linked, compared to PTSD and alcohol consumption.

Resilience as a buffer against alcohol consumption

Resilience was not found to have a main effect on alcohol consumption levels, nor interact with new onset TE to buffer against alcohol consumption. There is a dearth of literature examining resilience in relation to alcohol consumption, and further the extant literature mixed.

In their review of the literature, Cusack and Amstadter (under review) found that three studies found a significant relation between resilience and alcohol use in adolescents specifically (Wong et al., 2006; Alvarez-Aguirre, Alonso-Castillo, & Zanetti, 2014; Jones and Benda 2004. One study using an adult sample found a negative relationship between alcohol consumption and resilience (Unrath et al., 2012). However, on the contrary, in their study of emerging adults, Goldstein, Faulkner, and Wekerle (2013), found that trait-based resilience was not significantly associated with alcohol consumption. The findings from Goldstein and colleagues (2013) taken together with findings from the present study suggest that emerging adulthood (i.e., college years) may be a developmental period in which the relation between resilience and alcohol use differs.

Indeed, college is a developmentally normative time for alcohol consumption, with epidemiologic studies suggesting that drinking increases during adolescence and reaches a peak during young adulthood, specifically through the early 20s (Jackson, Sher, & Park, 2006). However, while some individuals do not reduce their drinking and subsequently develop related problems, most do not develop symptoms of AUD, and as such, not all consumption in college students is problematic. Consistent with this, our findings suggest that resilience may not be an important protective factor against consumption levels, which may not be clinically meaningful for every student. Indeed, prior literature has demonstrated that the *escalation* of drinking across college is a more potent long-term indicator of future problems, as compared to consumption levels alone (Prince, Read, & Colder, 2019).

Resilience as a buffer against binge drinking status

Resilience did not exert a main effect nor interaction effect on binge drinking status, though due to missing data patterns, the model fit for these models was poor. Although the

sample size for these models was much smaller than those for the AUD and consumption models, the standardized coefficients for the interaction terms predicting binge drinking status were comparable to those for AUD symptoms and consumption, but were non-significant, and thus, no meaningful interaction can be inferred even in the context of low power due to sample size.

To the best of our knowledge, no study to date has examined the relationship between resilience and binge drinking status specifically, making it difficult to contextualize findings of the current study. However, research has demonstrated that although college students are at an increased risk for binge drinking due to changes in autonomy, norms, and risky drinking events (e.g., 21st birthday), the use of protective behavioral coping strategies is shown to decrease the likelihood of binge drinking (Krieger, Young, Anthenien, & Neighbors, 2018). The majority of the extant literature on binge drinking in college students has demonstrated that the largest risk factors for binge drinking are related to perceived peer norms around alcohol use and social events related to drinking alcohol (e.g., Kreiger et al., 2018). Given the social nature of these risk factors, individual level resilience may be less important in relation to binge drinking as opposed to the development of clinically relevant AUD symptoms.

Influences of Covariates and Contextual Variables

Both sex and race, included as covariates in the present study, demonstrated significant impacts on AUD symptoms and alcohol consumption levels, respectively. Identifying as being a male was associated with increased AUD symptoms. Identifying as Black, as compared to White, or Asian as compared to White, was associated with increased levels of alcohol consumption.

In terms of sex differences, the finding that male sex is associated with increased AUD symptoms aligns with the extant literature that demonstrates that, historically, male college students have been shown to consume more alcohol and report high levels of alcohol-related problems, as compared to their female counterparts (e.g., Geisner, Larimer, & Neighbors, 2004). However, more recent research has demonstrated that the magnitude of sex differences in alcohol related problems is rapidly shrinking (e.g., WHO, 2014), with rates of AUD in females having increased by 84% in the past ten years, as opposed to an increase of 34% in males (Grant et al., 2017). Given this rapidly evolving nature of sex differences in AUD symptoms and diagnostic status within epidemiological samples, further research is warranted to examine how sex differences in AUD is changing in college student populations specifically.

Identifying as White, as compared to Black or African American or Asian, was associated with increased rates of alcohol consumption in the present study. This finding is consistent with extant literature demonstrating that four-year college status is positively associated with heavy alcohol use among white students, but inversely related to drinking among those identifying as Black or Asian (Paschall et al., 2005).

Work by LaBrie, Lac, Kenney, and Mirza (2011) demonstrated that those identifying as Asian were more likely to endorse using alcohol to cope, as opposed to those students identifying as White. In a trauma-exposed sample, such as the one included in the present study, it may be that differences in alcohol consumption are driven by the tendency of those identifying as racial/ethnic minorities to use alcohol to cope more frequently. Indeed, in the S4S study, there are significant differences in trauma load by race with those identifying as minorities reporting higher levels of trauma exposure, further suggesting they may be drinking more in order to cope with said adversity.

The extant literature examining the impact of resilience on alcohol use outcomes largely ignores contextual factors such as peer and family influences that have been demonstrated as influencing substance use outcomes and tend to be impactful for youth outcomes. For example, Mahedy et al. (2018) found that young adults whose parents engage in moderate or high-risk alcohol consumption are more likely to consume alcohol than those with parents with lower consumption, but this relationship was partly accounted for by higher prevalence of association with peer deviance. Alternatively, parental support and distancing moderates the effects of peer influence on adolescent alcohol use (Marshal & Chassin, 2000). Indeed, findings from the present study demonstrate that parental involvement is negatively related to AUD symptoms in that higher levels of parental involvement are associated with fewer reported AUD symptoms. It is likely that those students reporting higher levels of parental involvement at baseline (i.e., reporting on parental involvement levels before entering college) are also experiencing higher levels of parental involvement while in college, albeit in different forms (e.g., asking about what the individual is learnings vs. being in contact with their teachers directly; Lowe & Dotterer, 2008). As such, these individuals may still be being held things such as grades, work related responsibilities, etc., and so their alcohol use is not as impactful on functional activities.

Secondly, we found that both peer deviance and social support were significant predictors of alcohol consumption levels whereby higher levels of peer deviance and higher levels of social support predicted higher alcohol consumption. Although social support is largely suggested as a protective factor throughout the extant literature (e.g., Gros, et al., 2016; Kahle, Veliz, McCabe, & Boyd, 2019), it may be that students with increased social interaction and contacts are in settings where alcohol consumption is occurring more often. The varied findings with regard to predictors of AUD symptoms vs. consumption levels is not surprising given that consumption is

normative in college students, and that consumption and AUD symptoms look differently in the models included in the current paper. Taken together, such findings highlight the importance of considering the entire picture when investigating contextual factors in relation to alcohol use outcomes. The current study also demonstrated that resilience accounted for variance in AUD outcomes above and beyond these important contextual factors. Our findings, taken together with extant research, highlight low affiliation with deviant peers in high school as a potential protective factor against the development of AUD symptoms. Such factors may be more relevant for substance use or initiation, whereas resilience processes may be more relevant for the development of symptoms subsequent to use.

Limitations and Future Directions

Although the present study makes important contributions to the field of resilience research, findings should be considered in the context of a number of limitations. First, the parent study from which data was used (S4S) prioritizes breadth over depth in terms of assessment measures. Future research should employ more detailed measures of trauma exposure, internalizing symptoms (for calculation of the resilience variable), alcohol use, and related problems to expand upon findings of the present study. Using a more detailed measure of trauma exposure would allow for the examination of resilience as a buffer across trauma types, an important question given that research has demonstrated some trauma types (e.g., sexual assault) as being more potent than others (e.g., motor vehicle accident; Jakob, Lamp, Rauch, Smith, & Buchholz, 2017). With a more detailed assessment of substance use, the buffering hypothesis could be tested in relation to TE and substances aside from alcohol use, such as cannabis, as use is continuing to become increasingly socially acceptable (e.g., Roditis, Delucchi, Chang, & Halper). Further, including PTSD symptoms in the assessment of internalizing symptoms used to

calculate the resilience variable would provide insight into trauma-specific symptoms that are likely more related to trauma exposure, as compared to the abbreviated measures of anxiety and depressive symptoms included in the present study.

Although the resilience variable used in the current study has a number of strengths, it is not without limitations that are inherent when assessing resilience. Resilience, broadly speaking, is a challenging construct to measure, as evidenced by the wide heterogeneity within the extant literature (for a review, see Windle, 2011). In contrast to the assessment of a more straightforward phenotype, such as depression or anxiety, when measuring resilience, there are two potential sources of error: 1.) error in the assessment of the environmental component (e.g., trauma exposure, adversity, stressful life events, etc.,) and 2.) error in the assessment of resilience (e.g., psychiatric symptoms, perceived ability to cope, etc.). In the context of the discrepancy-based resilience variable, both in the current study and in prior research (e.g., Amstadter, Myers, & Kendler, 2014), there is less variability in symptoms for those endorsing one lifetime event as compared to those endorsing three or four events, as would be expected. Although this may suggest that the discrepancy-based conceptualization inherently limits how resilient an individual with only one event can be, the range of symptoms, and subsequent max amount of residual, is the same for everyone, regardless of trauma load. Although the potential range of symptoms is the same for all included individuals, the residual has a restricted range for those endorsing lower levels of TE exposure, given that the residual is the deviation between the predicted and actual symptom score. The actual score has full potential across the sample, but the predicted score is based on the regression, and given that a lower TE load is associated with a lower predicted SCL, the potential range of deviation on the “resilient” side of the regression line is lower. Another example of this principle is demonstrated in research by Gonzalez et al., (2019)

who examined the impact of low SES on cognitive functioning in children, with the relevant question being, if a youth is of higher SES does that mean they are less resilient since they have less environmental stressors and more resources? Although the restricted range of the residual based on stressor load is a limitation inherent in this approach to measuring resilience, it is a larger strength that this conceptualization calculates resilience in a way that thoroughly accounts for trauma or stressor load. resilience variable.

Given the challenges of assessing resilience due to the multiple potential sources of error (e.g., assessment of stressor, trauma, adversity, etc., exposure and assessment of the outcome of interest), future research would benefit from using a multi-modal approach to measuring resilience. For example, combining a self-report, perceived coping scale with a more objective measure (e.g., symptoms, impairment from symptoms, etc.) would provide important information and allow researchers to compare the impacts of resilience as measured objectively (as done in the present study) vs. as measured via self-report, such as the CD-RISC. This comparison would help elucidate which is "more" important (i.e., perceived coping vs. objective outcomes), and may improve error within the measurement of resilience given there are multiple ways measuring the "outcome" piece.

Secondly, the present study uses a college student sample which may limit generalizability (e.g., Peterson & Merunka, 2014). However, notably, the present sample is not a convenience sample, and as such, is less like a "traditional" college population. VCU students, as compared to more "traditional" college samples that are often seen in psychology research are more diverse, more likely to be a first-generation college student, etc., increasing generalizability. The use of a college student population may also be noted as a limitation as related to the examination of AUD symptoms given that the age of participant precedes the

typical age of onset of AUD (e.g., Schukit & Smith, 2011). However, there was sufficient prevalence and variability in symptoms, likely capturing early risk before full development.

Lastly, all assessments were self-report in nature, introducing sources of potential bias that are commonly seen in self-report measurement tools such as social desirability biases (e.g., Van de Mortel, 2008), whereby people respond in a way that they believe will be viewed favorably. Questions regarding alcohol use, particularly in students under the age of 21, are especially vulnerable to this response bias.

Clinical Implications

The nuance between alcohol consumption and AUD symptoms/binge drinking status has important implications for prevention efforts in adolescents prior to entering college, or during the early years of college. Findings from the present study demonstrate a significant interaction between TE and resilience on AUD symptoms at Y4S (an individual's senior year), further highlighting the need to implement prevention efforts in earlier years.

In their review of the literature on resilience building interventions, Chmitorz and colleagues (2018) demonstrate that resilience can potentially be trained, though the methods and concepts (e.g., deeming resilience factors as resilience, not clearly defining resilience ,etc.) that are used in the extant literature limit the ability to assess the efficacy of said training programs. Nevertheless, the existing literature on resilience building intervention provides a place for future development of resilience building interventions to start. For example, Abbott, Klein, Hamiltion, and Rosenthal (2009), in their randomized control trial (RCT) of an internet-based resilience program, found that training on emotion regulation, impulse control, optimism, causal analysis, empathy, self-efficacy, and reaching out improved "resilience", as assessed by happiness, quality of life, and depression, anxiety, and stress levels. Using a trait measure of resilience (i.e., CD-

RISC), Loprinzi, Prasad, Schroeder, and Sood (2011) found their training, "SMART" (Stress Management and Resiliency Training), led to a significant improvement in resilience, perceived stress, anxiety, and overall quality of life for patients with breast cancer. Although the resilience building intervention literature is limited in terms of methodology (for a review see, Chmitorz et al., 2018), it provides support for the idea that, generally speaking, resilience can be improved through training modules targeting things such as coping skills, emotion regulation, attention to and interpretation of stress, etc.

Existing treatment literature, albeit not explicitly targeting resilience, suggests that increased resilience is associated with positive treatment outcomes for comorbid PTSD and substance use disorders (McGuire, Mota, Sippel, Connolly, & Lyons, 2018). School-based interventions aimed at targeting resilience to reduce substance use outcomes have had mixed results, with some studies showing decreased prevalence of alcohol use on year later (Hodder, Daly, Freund, Bowman, Hazell, & Wiggers, 2011), though a meta-analysis of 19 studies found no impact on alcohol use (Hodder et al. 2017).

The extant literature examining the impact of resilience on alcohol use outcomes largely ignores contextual factors such as peer and family influences, potential targets for clinical intervention, that have been demonstrated as influencing substance use outcomes. For example, Mahedy et al. (2018) found that young adults whose parents have moderate or high-risk alcohol consumption are more likely to consume alcohol than those with parents with lower consumption. Further, this relationship was partly accounted for by higher prevalence of association with peer deviance. Contextual factors may also interact in important ways with evidence suggesting that parental support and distancing moderates the effects of peer influence

on adolescent alcohol use (Marshal & Chassin, 2000), highlighting the importance of considering the entire picture when investigating contextual factors in relation to alcohol use outcomes.

Of note, resilience accounted for variance in AUD outcomes above and beyond those of important contextual factors. Though resilience did not exert main or interaction effects on consumption levels, peer deviance levels was a significant predictor of alcohol consumption levels. Our findings, taken together with extant research, highlight low affiliation with deviant peers in high school as a potential protective factor acting in combination with resilience. Such factors may be more relevant for substance consumption levels, whereas resilience processes may be more relevant for the development of symptoms subsequent to use

New onset TE exerted main effects on alcohol consumption at one time-point, and on AUD symptoms at all follow-up timepoints. Indeed, prior work in this sample has demonstrated that those experiencing an interpersonal TE in the first two years, and last two years of college, reported greater increases in symptoms in the first two year, and last two years respectively (Bountress, Bustamante, Sheerin, Dick, Spit for Science Working Group, & Amstadter, 2019). These findings suggest that resilience-focused intervention and prevention efforts should be targeted not only at college student's alcohol consumption and related problems, but also at preventing new onset TE on college campuses**.**

II. Aim 2: GWAS and GCTA of Resilience

Overall Summary of Findings

The second aim of the present study was to examine the genetic etiology of resilience. This aim sought to examine independent SNPs associated with resilience via GWAS, and to determine the SNP-based heritability of resilience using GCTA. Taken together, results from aim 2 provide only modest insight into the genetic etiology of resilience, due to low power,

potentially causing null findings. However, given the nascency of the extant literature on the genetic underpinnings of resilience, results contribute to this growing literature. Findings from the two analyses conducted as part of aim 2 are discussed below within the context of limitations and future directions.

Are there individual SNPs associated with resilience in the meta-analyzed sample?

Separate GWAS analyses were conducted for resilience in the EUR sub-sample and in the AFR sub-sample, and then were meta-analyzed in order to increase power; the meta-analyzed results are therefore considered the primary results. Results from the meta-analyzed GWAS demonstrate that no SNPs met GWS and nine met the suggestive of significance threshold, as compared to four meeting the suggestive threshold from the EUR sub-sample, and 12 meeting the suggestive threshold from the AFR sub-sample. Although the AFR sub-sample was notably smaller than the EUR sub-sample (~50%) more SNPs met the suggestive threshold, likely driven by the fact that the effect sizes of the SNPs from the AFR sub-sample are larger.

The SNPs suggestive of significance from the meta-analyzed GWAS mapped onto three genes: *SEZ6L, LINC02112,* and *FRK*, and one cluster of genes on chromosome 8. The multiple SNPs mapping onto *SEZ6L*, and the SNPs mapping onto chromosome 8, were in high LD with one another, meaning that the nonrandom correlation between the alleles is strong due to physical proximity. The largest number of SNPs (n=3) were associated with the *SEZ6L* gene which is a protein coding gene that may contribute to specialized endoplasmic reticulum functions in neurons (Gorlov, et al., 2007). To the best of our knowledge, *SEZ6L* has not been examined in relation to resilience. However, the *SEZ6L* gene is located on chromosome 22 at what is considered to be a "hotspot" for bipolar disorder (BD; Xu et al., 2013). Indeed, Xu and colleagues found that 27 of 118 SNPs included in their analyses were associated with an

increased risk for bipolar disorder in females (Xu et al., 2013). None of the GWS SNPs found by Xu and colleagues (2013) overlapped with SNPs suggestive of significance in the present study. Similar to the present study the SNPs appear to be in high LD with one another, suggesting that it may not be that each of the 27 SNPs has an independent effect on BD. Genetic variants on chromosome 22 are associated with additional psychiatric disorders such as schizophrenia (Pramparo et al., 2008), as well as seizures in both animal and human studies (Yu et al., 2007). The role of *SEZ6L* in both BD and schizophrenia is further evidenced by the fact that mood disorders often used to treat BD are also anti-epileptics (Leunissen et al., 2011).

Although *SEZ6L* has not been investigated in relation to resilience specifically, the finding that the SNPs in the *SEZ6L* gene were inversely associated with resilience make sense in the context of the gene's association with psychiatric disorders (e.g., increased risk for BD [Xu et al., 2013]; increased risk for schizophrenia [Pramparo et al., 2008]; increased risk for seizure activity [Yu et al., 2007]) in that we would expect a gene whose variants confer risk for various psychiatric disorders to be inversely related to resilience, a potential protective factor against psychiatric disorders. Additionally, it has been demonstrated that trauma exposure is a transdiagnostic risk factor, broadly, for the development of psychopathology (e.g., McLaughlin, Colich, Rodman, & Weissman, 2020), and as such, it is consistent that resistance to stress (i.e., resilience) may also be associated broadly with various psychiatric disorders, such as BD.

Two SNPs from the meta-analysis were associated with a cluster of genes (*NKAIN3, GGH, TTPA, YTHDF3-AS1)* on chromosome 8 implicated in the metabolization and transport of various vitamins and minerals such as Vitamin E, folic acid (Vitamin B), sodium, and potassium. Although not yet studied in relation to resilience, the role of vitamin deficiencies in mental health, more broadly, has been established. Indeed, in their study of vitamin decencies and

mental health symptoms, Ramsey and Muskin (2013) found that both Vitamin B and E deficiencies are implicated in the development of various psychiatric symptoms and diagnoses. Specifically, they demonstrated that Vitamin B folate, for which *GGH* plays a role in the metabolism of, is linked to major depression and BD, and further, that alcohol use impacts risk for developing a folate deficiency.

Vitamin E (*TTPA* gene) has also been implicated in the development of psychiatric symptoms and disorders whereby low levels of Vitamin E may impact the brain via increased inflammation (Ramsey & Muskin, 2013). Although the majority of the extant literature on *TTPA* and vitamin E has focused on cancer, the research on vitamin E and mental health has shown that lower serum vitamin E is associated with depression (e.g., Maes et al., 2000; Ramsey and Muskin, 2013). Although to date no extant literature has examined the role of this cluster of genes in relation to resilience, it is well-established that both trauma and PTSD are linked with increased levels of inflammation, consistent with findings from the present study. More specifically, symptoms of PTSD (e.g., reexperiencing, hyperarousal, etc.) typically prompt activation of the threat response, leading to heightened physiological arousal, and subsequently increasing levels of oxidative stress and inflammation (Miller, Lin, Wolf, & Miller, 2018). Further, PTSD is often linked to physical health comorbidities such as obesity, type 2 diabetes, and cardiovascular complications, conditions all closely related to inflammation (for a review, see Kim, Lee, & Yoon, 2020). This suggestive hit also aligns with current GWAS of PTSD which demonstrate significant hits for genes implicated in the immune system (e.g., Sheerin et al., 2017).

Two SNPs (*rs74987153*, *rs13162155*) were inversely related to resilience. These SNPs were associated with the *LINC02112* and the *FRK* genes, respectively. The *FRK* gene encodes a

protein that belongs to the TYR family of protein kinases. This tyrosine kinase is a nuclear protein that is implicated in growth suppression during the G1 and S phases of the cell cycle (RefSeq, 2008). The potential relation to resilience is unknown, as to date, research on this gene has mostly focused on its role in various types of cancer such as cervical (Zhang et al., 2016), breast (Bagu et al., 2017), and lymphoma (Hu et al., 2018). Lastly, *LINC02112* is an RNA gene that, to date, research has not found to be clinically significant. As such, replication and future investigation into this gene in the context of resilience is warranted.

Are there individual SNPs associated with resilience in the AFR and EUR sub-samples?

Four SNPs met the suggestive of significance threshold in the EUR sub-sample. These SNPs mapped onto the *SEZ6L* gene and the *LINC02112* gene, both of which are discussed in more detail above. From the AFR sub-sample, no SNPs met the GWS threshold, though 12 met the suggestive of significance threshold. One of these 12 mapped on to the *FRK* gene, the only SNP to overlap with findings from the meta-analyzed results. The EUR and AFR sub-samples, when analyzed separately, produced no overlapping SNPS. Three of four SNPs from the EUR sub-sample overlapped with those found to be suggestive of significance within the meta-analyzed findings, and only one marker from the AFR sub-sample overlapped with those of the meta-analyzed GWAS findings, perhaps due to sample size, with more EUR individuals being included in the meta-analysis.

How Do Present Findings Align with the Molecular Genetic Literature on Resilience?

As discussed previously, the extant molecular genetics literature on resilience is in its beginning stages. Only one GWAS of resilience has been conducted to date. Results from Stein and colleagues (2019) demonstrate that among their sample of EUR soldiers, for self-reported resilience, two genes were detected at gene-wise GWS, *doublecortin-like kinase 2* (*DCLK2*) and

kelch-like family member 36 (*KLHL36*). For outcome-based resilience, a measure similar to the one used in the present study as compared to a trait based self-report measure, only one SNP on chromosome 12 downstream from *solute carrier family 15 member 5* (*SLC15A5*) demonstrated GWS. Further, this SNP met GWS only in a sample of soldiers who were exposed to the highest level of deployment stress. The lack of consistent findings in terms of relevant genes associated with resilience between the current study and that of Stein et al., 2019 is likely due to multiple factors such as sample size, sample characteristics (i.e., degree of trauma exposure in civilians vs. soldiers). Further, it is very rare that GWAS findings are replicated due to factors such as insufficient power in the replication study, the original findings being a false positive due to sampling error, differences in the design or trait definition (likely quite relevant with resilience), etc (Kraft, Zeggini, & Ionnidis, 2009).

Although only one GWAS of resilience has been conducted to date, there is a literature examining the genetic underpinnings of traits that may not require adversity to be present, as resilience does, but could be beneficial when adversity occurs. As discussed in their research agenda for psychological resilience, Choi, Stein, Dunn, Koenen, and Smoller (2019) review numerous GWAS examining such traits. For example, research has identified GWS loci associated with factors such as positive affect (Wingo et al., 2017), subjective well-being (Okbay et al., 2016; Turley et al., 2018), and IQ (Davies, et al., 2015, Trampush et al., 2017). Notably, findings from Wingo and colleagues (2017) report two SNPs significantly associated with positive affect that are located in a locus for LINC01221, a gene that is implicated in findings from the present study, suggesting continued research investigating this specific gene and region in relation to resilience.

The largest limitation of the GWAS analyses conducted for the present study is power. As with most statistical approaches, the ability to detect less common variants, or variants that explain only a small amount of the variance in resilience, increases with sample size (Teo, 2008). Indeed, findings from extant literature using big data, such as the PGC, demonstrate this point well in that the number of GWAS SNPs has increased in proportion to increases in their sample sizes. For example, in their GWAS of alcohol dependence using the PGC-SUD data (N=46,568), Walters and colleagues (2018) identified multiple SNPs meeting GWS. However, in their sample of only ~2,000, Bierut et al., (2010) failed to identify any GSW SNPs. This example helps to further contextualize findings as both AUD (e.g., Verhulst, Neale, & Kendler, 2015) and resilience (e.g., Amstader, Myers, & Kendler, 2018) are thought of as being moderately heritable, though the sample size of the present study is more similar to that of Beirut and colleagues (2010), and findings did not produce any GWS SNPs. Although a larger sample size produces an increased number of "true positives", false positives are also less likely to be found as sample size increases (Marigorta, Rodriguez, Gibson, & Navarro, 2018) given that power to detect a true effect is increased. Thus, unfortunately, another limitation related to sample size for the current study is the increased likelihood of suggestive hits being false positives. Notably, though, the heritability of the phenotype of interest also influences statistical power such that the discovery curve in relation to sample size is generally steeper for more heritable phenotypes; in other words, if a phenotype is more heritable increasing sample size "pays off" quicker.

In addition to sample size, phenotype of interest is an important variable to consider in the context of power. Sham and Purcell (2014) note that most diseases have a complex genetic architecture involving various risk loci and environmental factors, but that this level of complexity differs based on the disease. This is demonstrated by the fact that as sample size

increases, the number of SNPs that reaches GWS will also increase, though the rate of this increase differs among diseases (Sham & Purcell, 2014). Resilience is unique in that it is influenced by many contextual factors, making it a complex phenotype, and thus requiring a larger GWAS sample size. Another challenge for the molecular literature on resilience is how it is defined in many different ways across the literature, which could further impact GWAS hits. For example, Stein's (2019) study focused on self-report resilience whereas the present study used a discrepancy-based resilience phenotype (i.e., a mix between trait and outcome. While the discrepancy-based resilience phenotype is a more refined phenotype, it requires precise measurement of both adversity and subsequent symptoms, both of which are likely influenced by genetic factors, whereas an individual's perception of their ability to cope may be influenced by different genetic factors. Indeed, GWAS of outcome-based resilience requires that the sample is conditioned on adversity and/or trauma exposure, excluding a large percentage of people considered as "controls" in extant GWAS, as a trauma exposed sample is more likely to display the disorder of interest. Not only does excluding a large proportion of controls alter the sample, the sample included for a GWAS of outcome-based resilience may also look different given that adversity and/or trauma exposure has a heritable component (e.g., Stein, Jang, Taylor, Vernon, & Livesley, 2002). Additional examples include defining resilience as the absence of a psychiatric disorder (e.g., Bonanno et al., 2007), which would allow for larger sample sizes as compared to outcome-based resilience, for example, and might increase the discovery of GWS SNPS, though may offer limited new insights as this analysis is essentially the inverse of GWAS for the disorder. To improve upon this definition of resilience (i.e., the absence of disorder), future research should focus on gathering genotypic data for one's overall psychiatric profile, as opposed to diagnostic status for one diagnosis. Trauma is a transdiagnostic risk factor (e.g.,

Gibson, Cooper, Reeves, Anglin, & Ellman, 2017) and as such, GWAS of resilience should examine individual SNPs that are potentially associated with a wide variety of psychiatric symptoms in the context of one's exposure to adversity or trauma.

Considering the small sample size of the present study (as compared to what is needed for a well-powered GWAS), and the fact that molecular genetic research on resilience is quite young, follow-up studies are needed with adequate sample sizes for detecting GWS SNPs for resilience. Future research would also benefit from consensus in the field with regards to how to best measure resilience, in terms of both adversity exposure and the outcome variable. This consensus coupled with large, genetic consortia data on resilience would allow for the detection of GWS SNPs for resilience. The detection of GWS SNPs that are associated with resilience will further elucidate the molecular underpinnings of stress-related psychopathology, and specifically, will suggest variants that contribute to health and well-being, as opposed to disease. Identifying SNPs associated with resilience will allow for the development of targeted therapies, including psychotherapy and pharmacotherapy, that directly target the resilience-promoting pathways implicated via GWAS.

Is resilience heritable?

Although very modest estimates of heritability were found in both the EUR (n=2,371) and AFR (n=908) sub-samples, the SEs were such that the heritability estimates were not distinguishable from zero, and as such, were not statistically significant. This is likely due to a lack of power secondary to sample sizes. Indeed, the Spit for Science sample, when analyzed by ancestral sub-groups, is below the reported standard sample size needed to detect moderate heritability estimates (Visscher et al., 2014). More specifically, Visscher and colleagues (2014) note that to detect a heritability estimate of $h^2 = 0.3$ for a quantitative trait (such as resilience in

the present study), one would need ~3000 individuals. The present study was also underpowered to conduct GCTA by sex to examine heritability differences across males and females. However, there are known sex differences in the heritability of resilience whereby the heritability of resilience is thought to be higher among men (h^2 =.52) as compared to women (h^2=.38) in their sample of twins; Boardman, Blalock, & Button, 2098). Sex is a potential confound and may also impact the significance of findings.

Null findings from the GCTA analyses are inconsistent with findings from twin studies for resilience whereby resilience has been found to be moderately heritable. For example, Amstadter, Myers, and Kendler (2018), using a similar discrepancy-based conceptualization of resilience, demonstrated that resilience had a moderate genetic heritability (~31%). Similarly, Wolf and colleagues (2017), assessing resilience via the CD-RISC, found resilience to be 25% heritable.

Although findings from GCTA analyses and twin studies appear to be discrepant, notably, GCTA uses aggregate SNP data and as such, cannot account for variation due to rare variants when calculating heritability (Trzaskowski, Yang, Visscher, & Plomin, 2014). Further, GCTA heritability estimates only capture the additive genetic effects, whereby twin study heritability estimates capture both additive and nonadditive effects (Plomin et al., 2013) such as epistatic effects (i.e., interaction between genes; Cordell, 2002), dominance effects (i.e., one allele masking the effect of another allele and influencing the phenotype of interest; Wilkie, 1994), etc., resulting in higher heritability estimates for traits, broadly. For example, Nievergelt and colleagues (2019) using GCTA methods reported the heritability of PTSD to be between 5 and 20%, varying by biological sex, whereas Wolf and colleagues (2018), using twin study methods, reported the heritability of PTSD to be 49%. Thus, as a whole we'd expect a lower

GCTA heritability estimate compared to that generated for resilience in twin studies. Indeed, this pattern was found, but due to the larger standard error in the GCTA analyses, the estimates were not significant.

While low power due to sample size is a second plausible explanation for the lack of significant findings, findings from the present study, and particularly those within the EUR sub-sample, are consistent with the one GCTA on resilience to date. Indeed, although heritability estimates were not significant, the estimates are consistent with those reported in the one extant study using GCTA to examine resilience. For example, Stein et al., (2019) did not find a significant heritability estimate for outcome-based resilience, a conceptualization that is more similar to the one used in the present study. However, Stein and colleagues (2019), with a sample size 9x larger than the one used in the present study, estimated the SNP-based heritability of self-assessed resilience to be 0.162 (SE=0.05, p= 5.37 x 10^4) in a EUR sample. Another consideration to make in contextualizing findings from the present study is that heritability for resilience may be larger within some groups, such as those with greater trauma exposure or other more clinically acute populations. Indeed, Stein and colleagues (2019) conducted GCTA in a sample of deployed soldiers, who likely have experienced trauma exposure at higher rates than the college student sample used in the present study (Johnson, Graceffo, Hayes, & Locke, 2014). The degree of trauma exposure an individual experiences also likely interacts with genetic influences to increase the heritability of resilience, similar to the finding from Wolf and colleagues (2018) who demonstrated that PTSD is more heritable at higher levels of trauma exposure.

Taken together, the extant literature using molecular genetic methods to examine heritability estimates of resilience, and various conceptualization of, is nascent. As such, future

research is needed to provide additional context for findings from the present study, and to elucidate the SNP-based heritability of resilience. For example, the genetic literature base, similar to the phenotypic literature base, on resilience would greatly benefit from increased clarity with regard to how resilience is being defined. As discussed above, the use of various definitions and measures of resilience like influence genomic findings, limiting the replication and interpretation of these findings. Another recommendation, as posited by Choi and colleagues (2019) in their research agenda for psychological resilience, is to use more nuanced approaches for studying resilience that better account for adversity exposure and emphasize cross-domain and longitudinal investigations. Similar to the phenotypic literature on resilience, prospective studies that adequately account for exposure to adversity and include details measures of outcomes provide the most rigorous design for examining the genetic underpinnings of resilience.

III. Aim 3: Polygenic risk scores

Overall Summary of Findings

The third aim of the present study sought to identify shared genetic "risk" for resilience with that of AD, alcohol consumption, PTSD, and well-being. Polygenic risk score analyses were computed using summary statistics from large consortiums and were subsequently used to predict resilience in the S4S data, by ancestry sub-group. Although at the beginning stages of the investigation of the genetic underpinnings of resilience, our findings support that there may be some shared risk between resilience and alcohol consumption, as well as PTSD. Findings from each PRS are discussed in turn within the context of the limited extant research. Limitations and future directions of PRS analyses as a whole are then reviewed.

Does Genetic Risk for AD Predict Resilience?

The current study used polygenic risk score analyses to assess the value of polygenic risk for AD in predicting resilience. There was no significant association between the AD PRS and resilience for either sub-sample (i.e., EUR and AFR). AD PRS accounted for 0.06% and 0.16% of the variance in resilience in the EUR and AFR sub-samples, respectively. To date, there is no extant literature examining PRS of alcohol related construct(s) in predicting resilience, and as such, findings from the present study are somewhat difficult to contextualize. However, the multivariate twin literature, in examining whether the genetic propensity of AUD is correlated with the genetic propensity for resilience, demonstrates that genetic influences on AUD and resilience are moderately correlated, with estimates around 57% (Long, et al., 2016). Further, the twin literature has demonstrated a moderate degree of genetic correlation (~54%) between psychiatric resilience and alcohol resistance (AR), or the idea that some individuals can drink substantial amounts of alcohol and not develop AUD symptoms, while others develop symptoms (Sheerin, Bustamante, Bountress, Cusack, Aggen, Kendler, & Amstadter, 2021). As findings from the present study are largely inconsistent with the twin literature, it suggests that indeed, null findings are likely due to being underpowered.

Variance estimates for AD are not far from what is reported from studies examining alcohol related phenotypes using polygenic risk scores. For example, Salvatore and colleagues (2018), in their use of PRS to evaluate whether aggregate genetic risk for AUDs differed between clinically ascertained and population-based epidemiological samples, found R^2 estimates of non-significant effects to range from 0.04% to 0.53%. Notably, the authors found that PRS from one population-based sample predicted AUD symptoms in another population-based sample, but not in a clinical sample. The present study, similarly, used a population-based sample (S4S) and a mix of population-based and clinical samples (PGC-SUD) that includes

alcohol-dependent individuals and alcohol-exposed controls, which may explain the lack of significant association.

A second consideration to make in the context of null findings is regarding the statistical power of PRS analyses. Power is significantly influenced by the size of the discovery sample, and subsequent power of the discovery sample (Dudbridge, 2013). Indeed, when examining the sample sizes for the EUR and AFR sub-samples from the PGC-SUD, there were 8,233 cases in the EUR sub-sample, and 2,917 in the AFR sub-sample, as compared to, for example, 23,185 and 4,363 cases of PTSD respectively. The smaller sample size for AD summary statistics may be another explanation for the lack of significant association between AD and resilience.

Does Genetic Risk for Alcohol Consumption Predict Resilience?

Findings demonstrate that alcohol consumption PRS are significantly associated with resilience in the EUR sub-group, explaining 0.19% of the variance in resilience. Although this R^2 estimates may not seem substantial, they are relatively consistent with the variance explained by PRS for alcohol consumption in the literature more broadly, (e.g., 0.11% in drinking behaviors; Mies et al., 2018). Additionally, the direct of the PRS effect on resilience was as expected such that polygenic risk for consumption was inversely associated with resilience. Although the R^2 estimate is consistent with estimates for alcohol consumption in the literature more broadly, PRS from the present study still only explaining much less than 1% of the variance in resilience. As such, given that analyses in the present study are notably underpowered, it is plausible that there is shared genetic risk driving alcohol consumption and resilience that is not captured here.

To the best of our knowledge, this is the first study to use PRS to examine the correlation between the genetic propensity for alcohol consumption and resilience. The majority of the extant multivariate genetic literature has instead focused on the genetic correlation between

resilience, trauma exposure, and PTSD in relation to AUD symptoms and AD (e.g., Sheerin et al., 2021; Long et al., 207; Sartor et al., 2011). Indeed, the self-medication literature largely supports the relationship between PTSD and AUD symptoms (e.g., Gaher et al., 2018), and provides less support for the relationship between PTSD and alcohol consumption (e.g., Possemato et al., 2015). Although the present study did not find a significant relationship between AD and resilience, the discovery sample size for the alcohol consumption summary statistics is significantly larger than that for AD, perhaps explaining findings discrepant from the extant literature.

Future research, including replication of findings from the present study, is needed to clarify how genetic influences may influence the phenotypic expression of resilience as a buffer against alcohol outcomes. Additionally, AFR summary statistics for alcohol consumption were not available. With research in the field of molecular genetics becoming more inclusive, generation of summary statistics for diverse samples will allow for further elucidation into how resilience may be important in the context of alcohol consumption across racial/ethnic lines.

Does Genetic Risk for PTSD Predict Resilience?

Thirdly, the present study sought to assess the association between PTSD PRS and resilience. PTSD PRS were significantly associated with resilience in the AFR sub-sample only, accounting for 0.43% of the variance in resilience. However, PTSD PRS and resilience were positively associated, meaning that PRS for PTSD is linked to an increase in "risk" for resilience ($b = 2.94$, $SE=2.59$, $p<.05$). Although to date, no research has examined PRS for PTSD as predicting resilience, the direction of this finding contradicts the phenotypic literature which largely supports resilience, conceptualized in various ways, as inversely related to PTSD symptoms and diagnostic status (e.g., Bensimon, 2012;), with some researchers defining

resilience as a lack of PTSD symptoms (e.g., Bonanno, Galea, Bucciarelli, & Vlaov, 2007). The multivariate twin literature also provides support for the genetic propensity for PTSD as negatively related to the genetic propensity for resilience (e.g., r = -0.59; Wolf et al., 2017).

One plausible explanation for the direction of this effect is based on the fact that those identifying as Black/African American experience greater cumulative, and continuous, trauma exposure given the systemic racism that exists in our society (e.g., Stevens-Watkins, Perry, Pullen, Jewell, & Oser, 2014). As such, perhaps given this increased trauma load, these individuals are required to "persevere through" constantly, meaning that their genetic risk for PTSD is related to increased levels of resilience through increased trauma exposure, and required "perseverance".

It is also possible that the effect estimate was made positive via effects of natural selection whereby effect alleles occur at a higher frequency than non-effect alleles on average, thereby resulting in a PRS with a mean positive value (Choi et al., 2018). In considering the relatively large test statistic and the extant literature demonstrating an inverse relationship between PTSD and resilience, it is likely that the inverse association is an artifact of the data, such as small sample size, and as such, may not be replicated in a larger sample in which effects are more reliable and stable.

The discrepant findings between the EUR and AFR sub-samples is consistent with the phenotypic literature on PTSD which reports racial differences in lifetime prevalence rates of PTSD (Black/African American [8.7%], non-Latino whites [7.4%]; Roberts et al., 2011). Assuming that the direction of the significant association of PTSD PRS and resilience is indeed an artifact, it follows that, perhaps genetic risk for PTSD influences rates of PTSD in Blacks/African Americans through impacting the genetic capability for resilience, but not for

those identifying as White. However, using a genetic basis to explain higher rates of PTSD in Black/African Americans is problematic due to the fact that although Black/African American individuals report experiencing Criterion A events at lower rates than white individuals (Roberts et al., 2011) they exist in a society that is systemically racist. Although racial discrimination events are not yet considered Criterion A traumas, they have been shown to influence PTSD symptoms in minority populations (Pieterse, A.L., Carter, R.T., Evans, S.A., & Walter, R.A., 2010).

Does Genetic Risk for Well-being Predict Resilience?

PRS calculated from summary statistics for well-being from the SSGAC were used to predict resilience in the S4S EUR sub-sample. PRS were not significantly associated with resilience in the EUR sub-sample. This finding is inconsistent with extant research that examines the relation between resilience and well-being both phenotypically and genotypically. Well-being has been shown to be positively correlated with resilience on a phenotypic level (e.g., Bajaj & Pande, 2016; Satici, 2016). Further, in their recent study using PRS to examine the common underlying genetic factors of well-being and resilience, de Vries et al., (2021) found that PRS for well-being was a significant predictor of resilience, explaining around 1.4-1.8% of the variance. The discrepancy between findings from the present study and that of de Vries and colleagues are likely explained by sample size differences, whereby de Vries and colleagues included 10,876 participants and the present study included only 4,594. Additionally, de Vries and colleagues used summary statistics from a non-clinical sample whereas well-being summary statistics from the SSGAC come from many cohorts, some of which are clinical samples. As such, levels of well-being likely differ between the samples, impacting the subsequent association between well-being and resilience.

Limitations and Future Directions

The use of polygenic risk scores to infer genetic overlap between traits and to predict phenotypes based on the genetic profile of related phenotypes is becoming increasingly popular (Choi et al., 2018). However, PRS analyses are still relatively novel, and as such, there are limited guidelines on how to best perform PRS analyses (Choi et al., 2018; Choi, Mak, & O'Reily, 2020). Although PRS analyses for the present study were conducted in a methodologically rigorous way, there is still room for error that may impact findings and interpretability of said findings. These limitations, as they apply to the current study, will be discussed in turn.

Although sample size is a strength of the PRS analyses, given that summary statistics were derived from large discovery samples such as the PGC-PTSD (EUR and AFR), PGC-SUD (EUR and AFR), etc., it is possible that highly significant findings can result from subtle confounding when calculating PRS using such large sample sizes (Choi, et al., 2018). A second limitation noted by Choi and colleagues (2018) is the idea that differences between discovery and target samples, in terms of their genetic makeup and environmental influences, can confound results and further decrease interpretability. Lastly, PRS analyses test predictive value at many different *p*-value thresholds, which leads to a high probability of inflated results and potentially false conclusions. In order to combat overfit prediction models, it is recommended to perform out-of-sample prediction with a sample independent of the target and base sample (Choi, Mak, & O'Reilly, 2021). While this was not within the scope of the present study, it is an important future direction for validating findings from the present study.

Although PRS analyses have a number of limitations, they offer promising clinical implications. For example, Chang et al., (2019) found that polygenic risk for starting regular

tobacco use was positively associated with alcohol consumption, nicotine dependence, and conduct disorder, suggesting that PRS may be used to identify high-risk individuals for targeted intervention. With continued efforts to standardize analyses and reporting of findings, PRS will become a more comprehensive clinical tool that may be used to identify those at risk and inform prevention and intervention efforts (Duncan et al., 2018).

IV. Conclusions

The current study aimed to address limitations of the current literature through examining resilience as a buffer against alcohol use outcomes using longitudinal data and moderation analyses, as well as examine the individual and shared genetic influences of resilience. Using a sample of ~7,000 undergraduates from a large, public, urban university, findings suggest that resilience acts as a buffer against later AUD symptoms, but not against consumption levels, nor binge drinking status. As such, resilience may be important in protecting against the development of clinically relevant symptoms related to alcohol consumption, as opposed to high consumption levels, which are relatively normative in college student populations.

Genotypically, there were no GWS significant SNPs associated with resilience in the sample, nor was resilience found to be significantly heritable in the present sample. There were nine SNPs meeting the suggestive significance threshold from the meta-analyzed GWAS findings, with the majority of them mapping onto the *SEZ6L* gene and a cluster of genes on chromosome 8. Although, these findings likely result from insufficient power due to low sample sizes subsequent to stratification by ancestry. There was a significant negative association between polygenic risk for alcohol consumption and resilience the EUR sub-samples, and a significant positive association between polygenic risk for PTSD and resilience in the AFR sub-

sample. However, findings should be interpreted with caution given sample specific issues such as low power, potential inflation, heterogeneity, etc.

Taken together, findings suggest that resilience should continue to be examined as a protective influence on alcohol-related outcomes in the context of trauma exposure using methodologically rigorous approaches, such as longitudinal modeling. Indeed, prevention and intervention research efforts should examine including components that may enhance resilience capabilities of students (e.g., coping strategies, etc.) in order to assess the best approaches(s) to "turning up" resilience and how that may impact psychiatric outcomes. In terms of genotypic research, mixed findings suggest that additional research is required to more clearly elucidate the etiological underpinnings of resilience, ideally with larger samples less biased by variables such as heterogeneity (i.e., clinical vs. population based) and population stratification. Nevertheless, resilience is an important protective influence that warrants further research, both of phenotypic and genotypic nature, in order to elucidate how it may be harnessed in intervention and prevention efforts to better improve substance use outcomes in the wake of trauma exposure.

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Appendix A

Demographics:

1. What is your current age?

2. Sex

-Male

-Female

-I choose not to answer

4.Which one of these groups best describes you? (please choose only one)

( ) American Indian/Alaska Native

( ) Asian

( ) Black/African American

( ) Hispanic/Latino

( ) More than one race

( ) Native Hawaiian/Other Pacific Islander

( ) Unknown

( ) White

( ) I choose not to answer

Alcohol Consumption (past 30 days):

1. How often do you have a drink containing alcohol?

-Never

-Monthly or less

-2 to 4 times/month

-2 to 3 times/week

-4+ times/week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

-1 Or 2

-3 or 4

-5 or 6

-7

-10 or more

Alcohol use disorder symptoms

1. In situations where you couldn't drink, did you ever have such a strong desire for it that you couldn't think of anything else?

-Yes

-No

-Don't know
-I choose not to answer

2. Did you ever become tolerant to alcohol; that is, you drank a great deal more in order to get an effect, or found you could no longer get buzzed on the amount you used to drink?

-Yes

-No

-Don't know

-I choose not to answer

3. Have you ever wanted to stop or cut down on drinking (not counting dieting or pregnancy)?

-Never

-1 to 2 times

-3 or more times

-Don't know

-I choose not to answer

4. Have you ever started drinking at times you promised yourself that you wouldn't, or have you ever drunk more than you intended (for example, when you decided to drink two drinks and ended up drinking for our more)?

-Never

-1 to 2 times

-3 or more times

-Don't know

-I choose not to answer

5. Have you ever started drinking and become drunk when you didn't want to?

-Never

-1 to 2 times

-3 or more times

-Don't know

-I choose not to answer

6. Have you ever given up or greatly reduced important activities while drinking (for example, sports, work, or associating with friends or relatives)?

-Never

-1 to 2 times

-3 or more times

-Don't know

-I choose not to answer

7. Has there ever been a period of several days or more when you spent so much time drinking or recovering from the effects of alcohol that you had little time for anything else?

-Never

-1 to 2 times

-3 or more times

-Don't know

-I choose not to answer

8. Have you ever continued to drink even though it was causing you problems (including medical, emotional, or psychological problems)?

-Never

-1 to 2 times

-3 or more times

-Don't know

-I choose not to answer

9. People who cut down, stop, or go without drinking after drinking steadily for some time may not feel well. These feelings are more intense and can last longer than the usual hangover. When you stopped, cut down, or went without drinking, did you ever experience problems like trembling hands, sweating, vomiting, etc. for most of the day for 2 days or longer?

-Never

-1 to 2 times

-3 or more times

-Don't know

-I choose not to answer

Trauma exposure:

Listed below are a number of difficult or stressful things that sometimes happen to people. For each event check one or more of the boxes to indicate if the event happened to you ever in your lifetime, and if it happened to you in the past 12 months.

a. Natural Disaster (for example, flood, hurricane, tornado, earthquake, fire or explosion)

() Ever( ) Past 12 months( ) Never happened to me( ) I choose not to answer.

b. Physical assault (for example, being attacked, hit, slapped, kicked, beaten up, shot, stabbed

( ) Ever ( ) Past 12 months ( ) Never happened to me ( ) I choose not to answer.

c. Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm

( ) Ever ( ) Past 12 months ( ) Never happened to me ( ) I choose not to answer.

d. Other unwanted or uncomfortable sexual experience

( ) Ever ( ) Past 12 months ( ) Never happened to me ( ) I choose not to answer.

e. Transportation accident (for example, car accident, boat accident, train wreck, plane crash)

( ) Ever ( ) Past 12 months ( ) Never happened to me ( ) I choose not to answer

Internalizing symptoms:

The next questions ask about some problems and feelings which people sometimes have. Please give the answer which best describes how much discomfort that problem has caused you during the last 30 days, including today.

a. nervousness or shakiness inside

( ) Not at all ( ) A little bit ( ) Moderately ( ) Quite a bit ( ) Extremely ( ) I choose not to answer

b. scared for no reason

( ) Not at all ( ) A little bit ( ) Moderately ( ) Quite a bit ( ) Extremely ( ) I choose not to answer

c. feeling blue

( ) Not at all( ) A little bit( ) Moderately( ) Quite a bit( ) Extremely( ) I choose not to answer

d. worrying too much about things

( ) Not at all ( ) A little bit( ) Moderately ( ) Quite a bit ( ) Extremely ( ) I choose not to answer

e. feeling no interest in things

( ) Not at all ( ) A little bit ( ) Moderately ( ) Quite a bit ( ) Extremely ( ) I choose not to answer

f. feeling fearful

( ) Not at all ( ) A little bit ( ) Moderately ( ) Quite a bit ( ) Extremely ( ) I choose not to answer

g. feeling hopeless about the future

( ) Not at all ( ) A little bit ( ) Moderately ( ) Quite a bit ( ) Extremely ( ) I choose not to answer

h. spells of terror or panic

( ) Not at all( ) A little bit( ) Moderately( ) Quite a bit( ) Extremely( ) I choose not to answer

Peer deviance (high school):

The following questions are about your friends --friends you would have seen regularly and spent time with in school or outside of school. Please answer for your friends that you spent time with during high school (before starting at VCU). How many of your high school friends have done the following?

1. Smoked cigarettes
   1=None
   2=A few
   3=Some
   4=Most
   5=All
2. Got drunk
   1=None
   2=A few
   3=Some
   4=Most
   5=All

3. Had problems with alcohol
   1=None

   2=A few

   3=Some

   4=Most

   5=All

4. Drunk alcohol
   1=None

   2=A few

   3=Some

   4=Most

   5=All

5. Smoked marijuana
   1=None

   2=A few

   3=Some

   4=Most

5=All

6. Been in trouble with the law
   1=None

   2=A few

   3=Some

   4=Most

   5=All

Social support:

1. Someone available to give good advice about a crisis.
   1=None of the time
   2=Some of the time
   3=Most of the time
   4=All of the time

2. Someone available to get together with for relaxation.
   1=None of the time

   2=Some of the time

   3=Most of the time

   4=All of the time

3. Someone available to confide in or talk about your problems.
   1=None of the time

   2=Some of the time

   3=Most of the time

   4=All of the time

Parental Involvement (reverse coded, higher = more involvement):

1. My parents helped me with my schoolwork if there was something I did not understand.
   1=Strongly agree
   2=Agree somewhat
   3=Disagree somewhat
   4=Strongly Disagree

2. My parents knew who my friends were.
   1=Strongly agree
   2=Agree somewhat
   3=Disagree somewhat
   4=Strongly Disagree

3. My parents spent time just talking with me.
   1=Strongly agree
   2=Agree somewhat
   3=Disagree somewhat
   4=Strongly Disagree

Probable PTSD:

1. Have any of these experiences resulted in any of the following symptoms: Nightmares about it, tried hard not to think about it or went out of your way to avoid situations that reminded you of it, constantly on guard, watchful, or easily startled, or felt numb or detached from others, activities, or your surroundings?

   ( ) Yes( ) No( ) I choose not to answer