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Trauma related drinking to cope: A phenotypic and molecular genetic investigation of the self-medication model

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"Trauma related drinking to cope: A phenotypic and molecular genetic investigation of the self-medication model"

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Abstract

Posttraumatic stress disorder (PTSD) and alcohol use problems (AUP) commonly co-occur, have shared latent genetic risk, and are associated with many negative public health outcomes. Via a self-medication framework, trauma-related drinking to cope (TRD), an unexplored construct to date, may help explain why these two disorders co-occur, thus serving as an essential target for treatment and prevention efforts. The present study aimed to create a novel measure of TRD and examine its psychometric properties, investigate its indirect influences on the association between PTSD and AUP, as well as explore its potential shared molecular genetic risk with PTSD in a genetically-informative study of college students. A sample of 1,896 students with a history of trauma and alcohol use provided genotypic data and completed an online assessment battery. First, the psychometric properties of TRD and how it relates to relevant constructs were examined using descriptive statistics and structural equation modeling. Findings demonstrated support for the external validation of TRD, both with regard to PTSD and alcohol consumption and related problems, and suggested that TRD is a more specific measure of drinking to cope motives compared to the commonly used Drinking Motives Questionnaire coping subscale. Second, results from a correlated multiple mediator model indicated that, while accounting for the effects of generalized drinking motives, TRD partially mediated the relation between PTSD and AUP and that this relationship was stronger for males than for females. Results were substantiated using longitudinal data. Third, univariate and bivariate genotypic analyses were conducted for TRD and PTSD, most of which resulted in null findings likely due to insufficient sample sizes. However, genome wide association analysis identified several significant genetic variants associated with TRD in participants of European Ancestry. Genes associated with TRD included *PRAME*, a protein coding gene with antithetical

effects to genes commonly implicated in alcohol metabolism, as well as several genes implicated in immune system functioning (e.g., *IGH, IGHE, ELK2AP*). Polygenic risk for PTSD was associated with PTSD in the present sample and nominally associated with TRD. Findings are discussed in the context of limitations, clinical implications, and future directions.

Keywords: Self-Medication; PTSD; Alcohol; Trauma-Related Drinking; Drinking-to-Cope

Overall Statement of the Problem

Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) are prevalent (Grant et al., 2015b; Kilpatrick et al., 2013), costly to society (Kessler, 2000), and frequently co-occur (Berenz et al., 2017; Kessler et al., 1997; Pietrzak, Goldstein, Southwick, & Grant, 2011). In fact, nearly half of individuals in treatment for AUD meet diagnostic criteria for current PTSD (Brown, Stout, & Mueller, 1999a). Both PTSD and AUD are moderately heritable (Afifi, Asmundson, Taylor, & Jang, 2010; Verhulst, Neale, & Kendler, 2015) and have overlapping latent genetic risk (Sartor et al., 2011; Xian et al., 2000); however, etiological models examining the shared risk between these phenotypes are lacking. The drinking to cope self-medication model is a promising paradigm to inform research in this area. Although it is well accepted that coping-oriented drinking is linked with problematic alcohol use and increased likelihood of AUD (Carey & Correia, 1997; Kristjansson et al., 2011; Martens et al., 2008), there is a paucity of research examining drinking to cope with trauma-related symptoms specifically. To date, there are no studies, phenotypic or genetic, on trauma-related drinking to cope. The present study sought to fill this void by creating a measure which would assess drinking motives related specifically to coping with symptoms of PTSD, which we named the Trauma Related Drinking Scale, or TRD, and leveraging a genetically informative longitudinal cohort study from a large urban university (NIAAA-R37 AA011408) in order to test the self-medication model from a phenotypic and genotypic perspective. Aim 1 sought to assess the psychometric properties of the brief four-item self-report TRD questionnaire in order to establish the acceptability of this measure in assessing drinking motives related to coping with symptoms of PTSD specifically. We aimed to examine the novel TRD measure in relation to the existing frequently used Drinking Motives Questionnaire coping subscale (DMQ-Cope), trauma exposure, PTSD

symptoms, and alcohol use and related problems (AUP). Aim 2 sought to test the self-medication hypothesis, specifically to determine whether TRD mediated the relationship between PTSD and AUP, above and beyond generalized drinking to cope motives (i.e., DMQ-Cope). Aim 3 sought to identify individual genetic variants (via genome wide association [GWA] analyses) and aggregate genetic risk (via genome wide complex trait analyses [GCTA] and polygenic risk score analyses [PRS]) associated with TRD, PTSD, and shared variation between the two phenotypes (via LD score regression [LDSC]). The results of this study will aid in elucidating shared genetic influences underlying TRD and PTSD, an area which remains poorly understood. The ability to identify individuals with higher biological risk for TRD and PTSD will inform targeted prevention and integrative intervention strategies, particularly among individuals at increased psychosocial risk for problematic alcohol use and PTSD, such as college-age populations.

In the sections that follow, the general epidemiology of trauma exposure and PTSD is presented, followed by a review of the epidemiology of alcohol-related phenotypes and the prevalence and implications surrounding PTSD-AUD comorbidity; a focus on studies of college samples, the population of interest for this study, is given where possible. A discussion of conceptual frameworks for understanding PTSD-AUD comorbidity are presented, including an in-depth review of the self-medication model. Following, common biological underpinnings and related methods for analyzing individual and shared genetic risk for these commonly comorbid phenotypes are reviewed. Then, the aims of the present study are outlined and lead into the related proposed study methods. Lastly, results are detailed and discussed.

Trauma Exposure

Recent findings from the World Mental Health (WMH) Survey Consortium, which includes nationally representative surveys in 24 countries across six continents (Benjet et al., 2016), indicated that, when pooled across countries, 70% of individuals endorsed at least one lifetime traumatic event and approximately one third endorsed four or more traumatic events. According to the Consortium, prevalence rates of trauma exposure vary across countries (ranging from a low of 28.6% in Bulgaria to a high of 84.6% in Ukraine), with the United States ranking third highest in exposure, tied with Columbia, at 82.7% (Benjet et al., 2016). This alarming rate of lifetime trauma exposure in the U.S. is, in fact, lower than the prevalence reported in other national samples of U.S. adults (e.g., 89.7% (Kilpatrick et al., 2013) and 89.6% (Breslau, Kessler, et al., 1998)). However, findings from other widely cited nationally representative samples suggest lower prevalence of U.S. lifetime trauma exposure, with estimated prevalence ranging from approximately 50% for women to 60% for men (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Important methodological factors likely contribute to the wide range of prevalence estimates of exposure to "any traumatic event" found across studies, including breadth of measurement, diagnostic definition requirements of what constitutes a trauma, and modality of assessment.

Breadth of Measurement

The breadth of assessment of trauma type differs substantially across studies. Given that lifetime prevalence rates vary according to trauma type, various methodologies likely result in both over-representative and inconsistent estimated prevalence estimates for lifetime trauma exposure across the literature. For example, in a U.S. epidemiologic sample (Breslau, Kessler, et al., 1998), upwards of 60% of individuals endorsed having experienced the sudden loss of a close

relative or friend, whereas less than 2% endorsed having experienced military combat. Naturally, in the general U.S. population, the probability of experiencing an event like the loss of a loved one is much higher than being exposed to military combat and therefore it follows that assessment batteries including a broad variety of trauma exposures are likely to produce higher estimates.

To that end, findings from a web-based survey of traumatic stress professionals on the use of trauma exposure and posttraumatic assessment instruments (Elhai, Gray, Kashdan, & Franklin, 2005) found that the most commonly used assessment instruments for adult research querying trauma history are the Posttraumatic Diagnostic Scale (PDS; Foa, Cashman, Jaycox, & Perry, 1997; 11%), Conflict Tactics Scale (CTS; Straus, 1990) and Life Events Checklist (LEC; Gray, Litz, Hsu, & Lombardo, 2004b) (both 7%), and Traumatic Life Events Questionnaire (TLEQ; Kubany et al., 2000) and Combat Exposure Scale (CES; Lund, Foy, Sipprelle, & Strachan, 1984) (both 4%). Notably, a majority of these five scales (PDS, LEC, TLEQ) query a broad range of traumatic exposures, including but not limited to natural disasters (e.g., hurricane, flood, earthquake), accidents (e.g., transportation, work injury), interpersonal violence (e.g., physical and sexual assault), serious illness or injury, and military combat. Additionally, each of these batteries provide an optional "Other" category for endorsement of additional events that the participant deemed traumatic that were not captured by other categories in the survey. This option is entirely guided by the responder's subjective experience and could overinflate trauma estimates via inclusion of a broad range of experiences deemed "traumatic" (e.g., loss of a pet, receiving a failing grade). Indeed, even the wording in the LEC prompts broad endorsement, querying "any other very stressful event or experience". Although the CTS and CES are more specialized scales (e.g., family violence, combat experiences, respectively), each contain within

them notable breadth with regard to endorsed trauma type and frequency (e.g., CTS: “my partner insulted or swore at me” vs. “my partner used a knife or a gun on me”; CES: “did you ever go on combat patrols or have other danger duty?”).

Diagnostic Definitions of Trauma

In addition to breadth of events assessed, changes in the definition of traumatic events have been made across versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) as well as the *International Classification of Diseases* (ICD). For instance, according to the fourth edition of the DSM (DSM-IV-TR; American Psychiatric Association, 2000), an event must result in 1) significant threat to life and/or physical integrity and 2) feelings of helplessness, fear, or horror in order to constitute a trauma eligible for PTSD. This same two-part definition is still currently used by the most recent version of the ICD (ICD-10; Organization, 1992). However, the newest edition of the DSM (DSM-5; Association, 2013) eliminated the peritraumatic emotional response criterion for trauma exposure, such that threat to life and/or physical integrity alone is sufficient for an event to be characterized as a trauma. This change has since resulted in higher estimates of traumatic event exposure (Kilpatrick et al., 2013).

Assessment Modalities

Another notable methodological factor contributing to varying trauma prevalence estimates pertains to the means by which trauma is assessed. Research has shown that measures administered via pen-and-paper and measures administered electronically and online are quantitatively comparable (Muehlhausen et al., 2015; Read, Farrow, Jaanimägi, & Ouimette, 2009). However, internet-based surveys offer some strong advantages over other data collection modalities with regard to anonymity, standardization, and eliminating bias (Schlenger & Silver, 2006) and, in fact, have been shown to be preferred over pen-and-paper options when assessing

trauma but not PTSD (Read et al., 2009). Although previous studies have demonstrated positive correlations between different assessment modalities, it is possible that the anonymity and availability of answering questions online versus in a lab setting may influence endorsement of events, and thus, the resulting trauma prevalence estimates.

Sociodemographic Correlates of Trauma Exposure

In addition to notable methodological inconsistencies, lifetime prevalence estimates of trauma exposure vary depending on a number of relevant sociodemographic factors. Notably, most of this research has focused entirely on high resource regions, primarily North America and Europe (Bromet, Karam, Koenen, & Stein, 2018). Prevalence of trauma exposure differs according to sex, such that men are slightly more likely than women to be exposed to trauma overall (Perkonigg, Kessler, Storz, & Wittchen, 2000). Sex differences in trauma prevalence are more notable with regard to trauma type. For instance, men are significantly more likely to experience trauma types including witnessing a death or injury, natural disaster, life-threatening accident, combat experience, threat with a weapon, and captivity (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Moreover, men are approximately twice as likely as women to be exposed to forms of physical assaultive violence (e.g., mugging, threat with a weapon, shot or stabbed, severely injured in a fight), whereas women are approximately three times more likely than men to report rape and sexual violence (Breslau, Kessler, et al., 1998; Frans, Rimmö, Åberg, & Fredrikson, 2005; Kessler et al., 1995). A review of psychosocial determinants of trauma exposure suggests that this pattern of findings is consistent across studies (Hatch & Dohrenwend, 2007). This review also found that low socio-economic status and racial/ethnic minority status were associated with increased risk for trauma exposure, which is consistent with findings published in a seminal study by Breslau and colleagues (1998) demonstrating that

minority racial status, low education, low income, central-city location, and prior marriage increase the likelihood of experiencing an assaultive traumatic event by two-fold. This same study, as well as multiple others, suggests that late adolescence/early adulthood (i.e., age 16-25) may be a critical risk period for trauma exposure, as demonstrated by a drastic increase in prevalence across trauma types during this time (Acierno et al., 2001; Breslau, Kessler, et al., 1998; Norris, 1992).

Trauma Exposure in College Populations

Given that this critical developmental period corresponds with college matriculation for many U.S. individuals, investigation of trauma exposure and related outcomes among college students is imperative. Similar to estimates in the general population, estimates of trauma prevalence in college students vary, ranging between 67% and 84% (Read, Ouimette, White, Colder, & Farrow, 2011). Once more, the variability in these estimates is likely due to numerous methodological factors, including the wide breadth of what constitutes a traumatic event across studies. Further evidence for the increased risk for trauma exposure within this age group was found in Hatch & Dohrenwend's review (2007), which showed an increased risk amongst college-aged individuals for interpersonal violence (i.e., physical and sexual assaults and other acts of violence), specifically. Indeed, findings from a large longitudinal urban college sample showed that nearly one in five (19%) college students will experience sexual assault during college specifically (Conley et al., 2017) and 11% of college students will experience physical assault during their college enrollment period (Overstreet et al., under review). Mirroring general population findings, females within this sample were at significantly higher risk of experiencing sexual assault (23%) than their male counterparts (12%) (Conley et al., 2017) and

males were at significantly higher risk of experiencing physical assault (12%) than their female counterparts (9%) (Overstreet et al., under review).

Trauma Related Outcomes (PTSD)

Increased risk for exposure to trauma among young adults makes this age group particularly vulnerable to the negative consequences associated with trauma exposure. Trauma exposure is related to a variety of internalizing (e.g., generalized anxiety disorder, panic disorder, major depressive disorder; Amstadter, Aggen, Knudsen, Reichborn-Kjennerud, & Kendler, 2013; Pietrzak et al., 2011) and externalizing (e.g., alcohol and substance use disorders; Kilpatrick et al., 2003) mental health disorders. Posttraumatic stress disorder (PTSD), however, is unique from other psychiatric disorders and is often regarded as the "signature" disorder related to trauma exposure, such that exposure to a traumatic event is a required diagnostic criterion for PTSD. Additional criteria for PTSD, per the DSM-5 (Association, 2013), include at least one intrusion symptom (e.g., unwanted trauma-related memories, nightmares), at least one avoidance symptom (i.e., avoiding trauma-related thoughts, feelings, or external reminders), at least two negative alternations in cognitions and mood (e.g., exaggerated blame, anhedonia), and at least two alterations in arousal and reactivity (e.g., difficulty sleeping, hypervigilance). Nationally representative surveys have shown that approximately 3.5% to 9% of individuals will meet lifetime criteria for PTSD (Breslau, Davis, Andreski, Federman, & Anthony, 1998; Kessler, Chiu, Demier, Merikangas, & Walters, 2005; Kessler et al., 1995; Kilpatrick et al., 2013), with the highest conditional risk accounted for by those who have experienced interpersonal traumatic events (Liu et al., 2017; Smith, Summers, Dillon, & Cougle, 2016). The notable discrepancy between ubiquitous estimates of trauma exposure and far lower estimates of PTSD highlight the fact that, in the majority of cases, trauma exposure does not lead to the development of PTSD

(Bonanno, 2004), suggesting that important risk and protective factors exist to influence differential responses to trauma.

PTSD Implications

Identification of risk and protective factors is critical, as PTSD is a detrimental disease, and is associated with significant public health problems. PTSD increases risk for a number of significant mental (e.g., depression, substance use disorders, anxiety; Sareen et al., 2007), physical (e.g., respiratory and cardiovascular diseases, chronic pain; Sareen et al., 2007), and psychosocial (e.g., unemployment and marital instability; Kessler, 2000) health outcomes. In a nationally representative sample of U.S. adults, PTSD was associated with the majority of internalizing and externalizing disorders, including major depressive disorder, dysthymic disorder, bipolar I and II disorders, generalized anxiety disorder, panic disorder, agoraphobia without panic disorder, social and specific phobias, alcohol and drug abuse and dependence, and nicotine dependence (Pietrzak et al., 2011), underscoring the importance of studying comorbidities. Findings such as these highlight a great need for refined understanding of potential transdiagnostic factors related to the etiology and maintenance of PTSD, particularly among college-age individuals who are at increased risk for trauma exposure, which may later be used to inform treatment and prevention efforts.

Cumulative Trauma Load

Cumulative trauma load is one factor that has been highly implicated in deleterious trauma-related outcomes. In fact, exposure to multiple traumas has been shown to predict increased symptom complexity across a number of psychiatric conditions, including PTSD (Cloitre et al., 2009). To that end, multiple meta-analyses have demonstrated that having a history of multiple or repeated traumas significantly increases risk for PTSD (Brewin, Andrews,

& Valentine, 2000; Ozer, Best, Lipsey, & Weiss, 2003). Moreover, having a prior history of exposure to trauma significantly increases an individual's risk of subsequent exposure to trauma (Brewin et al., 2000; Classen, Palesh, & Aggarwal, 2005; Ozer et al., 2003), thereby increasing risk for greater PTSD and other psychological sequelae (e.g., alcohol use) symptom severity (Cloitre et al., 2009; Messman-Moore & Long, 2003). Much of the research surrounding "revictimization" has centered around sexual trauma. Numerous literature reviews on sexual revictimization have summarized evidence for the association between previous and subsequent exposure to sexual trauma (e.g., Arata, 2002; Classen et al., 2005; Messman-Moore & Long, 2003) and meta-analytic techniques have demonstrated a moderate effect size (.59) for the causal relationship between childhood sexual assault and adulthood sexual assault (Roodman & Clum, 2001). Results from Roodman & Clum's (2001) meta-analysis showed that studies with the largest effect sizes included the most restrictive definitions of abuse, providing further support for the influence of broad versus narrow definitions of trauma exposure on outcomes in trauma research. Many of the reviews to date investigating the effects of repeated exposure to trauma on symptom complexity have also found a strong influence of trauma type on subsequent outcomes.

Trauma Type

Trauma type has been shown to have strong effects on the conditional probability of developing PTSD and other negative outcomes following exposure to trauma (Frans et al., 2005). For instance, trauma that is interpersonal in nature is associated with the highest conditional risk for trauma-related outcomes, including PTSD, generalized anxiety disorder, panic disorder, depression, and alcohol and drug misuse (Kilpatrick et al., 2003). Additionally, prior history of interpersonal violence specifically has been evidenced across the literature as a strong predictor of subsequent trauma exposure (Benjet et al., 2016; Messman-Moore & Long, 2003; Ullman &

Vasquez, 2015), which, as previously discussed, in turn increases risk for PTSD. Given evidence for increased risk for interpersonal violence among college-age individuals (Hatch & Dohrenwend, 2007), this age group may be at increased risk for PTSD, creating a critical window for early prevention and intervention. Increased understanding of acute risk and protective factors among this age group is vital in informing said prevention and intervention strategies.

Sociodemographic Correlates of PTSD

A number of demographic and environmental factors have been associated with increased risk for PTSD following trauma exposure. First, women are approximately two times more likely to develop PTSD than their male counterparts (Breslau, Davis, et al., 1998; Kessler et al., 1995). This is particularly notable given the previously described research which suggests that men are more likely to experience exposure to trauma (Perkonigg et al., 2000). In a meta-analysis examining risk factors for PTSD, Brewin and colleagues (2000) offer a number of potential suggestions for this two-fold discrepancy between the sexes. First, they propose that higher PTSD rates among women could potentially result from a higher willingness to report PTSD symptomatology among women than men, though it is unlikely that this would account for a doubling of prevalence estimates between the sexes. Second, and in line with the extant literature, they suggest that higher rates of PTSD in women could result from a cumulative effect of exposure due to prior traumas. Indeed, an overwhelming amount of evidence exists to suggest that women's exposure to childhood sexual abuse, as well as sexual revictimization, for which there is a three-fold increased risk following a prior history of sexual assault (Messman-Moore & Long, 2003), may account for higher rates in PTSD (Kaltman, Krupnick, Stockton, Hooper, & Green, 2005; Kaysen, Rosen, Bowman, & Resick, 2010; Shih, Schell, Hambarsoomian,

Belzberg, & Marshall, 2010). Interestingly, Breslau and colleagues found contradictory evidence for this among a broad epidemiological sample (Breslau, Davis, Andreski, Peterson, & Schultz, 1997), demonstrating that higher incidence of PTSD in women was not attributed to repeated traumatic events within their sample. Instead, after controlling for trauma exposure, they found that childhood trauma was a likely factor influencing PTSD gender discrepancy estimates, emphasizing the importance of trauma timing in the subsequent development of PTSD. Indeed, the meta-analysis by Brewin and colleagues (2000) showed a greater effect size for women when studies included childhood traumas as opposed to studies that examined adult trauma exposure exclusively. In other more recent studies, childhood traumatic events have been associated with greater PTSD symptom severity than traumatic events that occur during adulthood (Ogle, Rubin, & Siegler, 2013). Additionally, as reviewed in a later section, the role of genetic effects may be higher in women than in men for PTSD (Duncan et al., 2016), which may contribute to differential prevalence estimates.

In addition to trauma type, trauma load, and sex, race and ethnicity may influence risk for development of PTSD, although the literature is uncompelling and inconsistent and is likely confounded by a number of relevant factors. Despite little support in the existing literature for ethnic minority status as an independent risk factor for PTSD, meta-analyses have demonstrated significant, albeit low, effect sizes (Brewin et al., 2000) for it as a risk factor for PTSD. However, multiple studies have demonstrated that race/ethnicity does not remain significant when simultaneously accounting for other variables (Breslau, Davis, et al., 1998; Brewin et al., 2000). Small effect sizes and inconsistent findings may reflect the possibility that race and ethnicity are not causally related to PTSD, but instead are likely confounded by multiple sociodemographic factors that put certain individuals at greater risk for repeated interpersonal

trauma exposure (e.g., low income, inner-city urban dwelling; Hatch & Dohrenwend, 2007; Perkonigg et al., 2000). It is these same confounding variables that also likely decrease an individual's access to treatment and/or supportive resources following exposure to a traumatic event (Davis, Ressler, Schwartz, Stephens, & Bradley, 2008; Liebschutz et al., 2007).

Although irrefutably important, demographic and psychosocial factors do not exclusively contribute to the development of PTSD. Indeed, twin studies suggest an etiological role for both environmental and biologic determinants of PTSD, suggesting that PTSD is moderately heritable, with between 35-72% of the variance in PTSD being accounted for by genetic factors (Amstadter et al., 2012; Sartor et al., 2011; Stein et al., 2002; True et al., 1993). Twin studies have also found significant latent gene-by environment (GxE) effects for PTSD (Forresi, Caffo, & Battaglia, 2014), suggesting the importance of both genes and environment in the development and maintenance of PTSD, as well as their interplay. Further details regarding the known molecular bases for PTSD are expanded upon below.

Alcohol Use

Trauma exposure is a transdiagnostic risk factor, and beyond increasing risk for PTSD, trauma is also associated with greater alcohol use (Keyes, Hatzenbuehler, & Hasin, 2011) and alcohol-related phenotypes (e.g., AUD (Kilpatrick et al., 2000), binge drinking (Cerdá, Tracy, & Galea, 2011)). Alcohol use, particularly in late adolescence, has been linked to alcohol dependence, automobile accidents, driving offenses and other criminal convictions, suicide, and mortality (McCambridge, McAlaney, & Rowe, 2011), necessitating the need for early intervention and prevention strategies. Such efforts are particularly crucial among college-aged individuals, as young adulthood represents the age group at highest risk not only of trauma exposure, but also problematic alcohol use. In fact, college aged individuals consume the

highest levels of alcohol and are at highest risk for problematic alcohol use (e.g., binge drinking, heavy alcohol use) compared to any other age group (Ahrnsbrak, Bose, Hedden, Lipari, & Park-Lee, 2017). This is consistent with research on typical alcohol use trajectories, which are characterized by increasing consumption beginning in early adolescence, continued increase until consumption levels peak during the college-age years, followed by a decrease beginning around the mid-twenties (Chen & Jacobson, 2012). Additionally, risk factors specific to college attendance exist, such that college students are at increased risk for problematic alcohol use compared to their same age non-college peers (Barnes, Welte, Hoffman, & Tidwell, 2010; Johnston, O'Malley, Bachman, & Schulenberg, 2013). One possible explanation for this unique college-related risk is demonstrated by study findings which showed that exposure to and initiation opportunities for alcohol use occur frequently on college campuses (Arria et al., 2008). Therefore, unique risk exists in college attendance for increased alcohol use and problematic drinking, risk for developing AUD (Dawson, Grant, Stinson, & Chou, 2004), and negative alcohol-related consequences (e.g., academic impairment, injuries; Perkins, 2002).

Sociodemographic Correlates of AUD

Similar to PTSD, the association of certain sociodemographic factors with alcohol phenotypes and related outcomes have been well-documented. For instance, research suggests that men report higher levels of alcohol consumption, intoxication, alcohol-related problems, and are more than twice as likely as women to develop AUD (Capraro, 2000; Goldstein, Dawson, Chou, & Grant, 2012a). Furthermore, the types of negative consequences associated with consuming alcohol differ by sex. In a review of consequences related to alcohol misuse among college students, Perkins (2002) found that alcohol consumption among males produces more negative consequences involving public deviance (e.g., public risk taking, aggression, property

damage), whereas no sex differences exist with regard to personal and relatively private negative consequences (e.g., blackouts, vomiting, hangovers, unintended sexual activity). Perkins (2002) and other researchers (e.g., RN & Gold, 2010) highlight the need to distinguish sex differences in negative drinking consequences from levels of consumption more generally, positing the two are not directly translatable, given differences in alcohol pharmacokinetics between women and men, such as differences in body weight, fat-to-water ratios and metabolic processing. To that end, strong evidence also exists to suggest that females are more sensitive to the effects of alcohol (Agabio, Campesi, Pisanu, Gessa, & Franconi, 2016) and experience more severe health related consequences compared to men (Arnedt et al., 2011; Nolen-Hoeksema & Hilt, 2006). Interestingly, there have been recent shifts towards more equal levels of consumption, such that high-risk alcohol use and AUD estimates have been increasing at a faster rate among women than men in recent years (Grant et al., 2017) and that the gap between first use of alcohol to AUD onset is shorter for females than it is for males (Agabio, Pisanu, Luigi Gessa, & Franconi, 2017). Regardless, males continue to report higher twelve-month and lifetime prevalence of DSM-5 AUD (Grant et al., 2015b). Just as in PTSD research, these alcohol-related sex discrepancies highlight the need for consideration of sex in both sample ascertainment and data analytic plan in alcohol research.

Moreover, as seen in the PTSD literature, prevalence rates of AUD vary according to race and ethnicity. Native Americans/Alaskan Natives display 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-Sturmhöfel, 2008). These substantial differences in prevalence estimates of AUD between minority groups also demonstrate the importance of examining differences between racial/ethnic minorities, as opposed to simply comparing White versus

"Other" participants (Huang et al., 2006). The failure to account for important variables, such as sex and race/ethnicity, serves to threaten internal validity, conceptualized as the extent to which a study's results are accounted for by the examined independent variable (Kazdin, 2003). In other words, threats to internal validity include factors other than the independent variable that may explain a study's outcomes. Given the known relevance of sex and race/ethnicity in both PTSD and AUD independently, failing to account for these differences when investigating these constructs in conjunction is likely to result in potential confounds. Additionally, failing to account for these crucial sociodemographic factors in research could decrease the applicability and generalization of empirically-based treatments down the line.

PTSD-AUD Comorbidity

As discussed in previous sections, both PTSD and AUD are prevalent and have been independently associated with a number of deleterious outcomes. Moreover, these two conditions frequently co-occur. In fact, nearly half of those seeking treatment for AUD meet *current* criteria for PTSD (Brown et al., 1999a), an estimate more than five times greater than the *lifetime* prevalence of PTSD (e.g., approximately 8%; Kilpatrick et al., 2013). High comorbidity of PTSD-AUD constitutes a public health crisis, such that comorbid PTSD-AUD is associated with higher symptom severity (Najavits et al., 1998; Ouimette, Finney, & Moos, 1999), greater service utilization (Brown, Stout, & Mueller, 1999b), poorer treatment prognosis (Blanco et al., 2013; Ipser, Wilson, Akindipe, Sager, & Stein, 2015; Read, Brown, & Kahler, 2004; Shorter, Hsieh, & Kosten, 2015), shorter time to relapse posttreatment (Bonanno, 2004), poorer physical health (Evren et al., 2011), and higher suicidal ideation and attempts (Rojas, Bujarski, Babson, Dutton, & Feldner, 2014). These high stakes clinical implications warrant increased understanding of factors underlying comorbid PTSD and AUD in order to inform trans-

diagnostic treatment and prevention efforts. In the sections below, models of comorbidity are reviewed.

Pathways Accounting for PTSD-AUD Comorbidity: Conceptual Frameworks

There are four proposed pathways to explain PTSD-AUD comorbidity, including the PTSD susceptibility model (alcohol use increases susceptibility to PTSD), mutual maintenance model (AUD exacerbates PTSD symptoms and vice versa), self-medication model (drinking to cope with PTSD symptoms leads to AUD), and common factors model (shared factors contribute to risk for and maintenance of PTSD and AUD). Each model is discussed in turn, with increased focus on the self-medication and common factors models, as they serve as the primary conceptual frameworks for the present study.

Preliminary Contextual Considerations

Prior to expanding upon some commonly proposed pathways for PTSD-AUD comorbidity, it is important to note that studies of temporal associations between these constructs are more often than not limited with regard to ability to determine causality. In fact, according to a recent review published by Langdon and colleagues (2017), only three studies to date have used longitudinal data to examine the relationship between trauma and PTSD on subsequent alcohol use (Breslau, Davis, & Schultz, 2003; Read et al., 2012; Testa, Livingston, & Hoffman, 2007), each resulting in inconsistent findings. In one case (Breslau et al., 2003), results varied even within the same study sample depending on analytic plan. Disparate findings with regard to the temporal effects of PTSD on subsequent alcohol use or related problems serve as a compelling example that differences in study sample (e.g., trauma type, sex proportions, participant demographics), methodology (e.g., quantification of alcohol use/problems, consideration of covariates), and study design (e.g., longitudinal vs. cross-sectional, timing of

trauma, latency between baseline and follow-up assessments) may contribute to an inconsistent literature.

However, results from a recent national epidemiologic survey (Berenz et al., 2017) suggest bidirectional associations between PTSD and alcohol dependence and that this bidirectionality was stronger for women compared to men. This finding is consistent the majority of studies examining sex differences with regard to comorbid PTSD-AUD, which have demonstrated higher rates in females compared to males (Brady, Grice, Dustan, & Randall, 1993; Brady & Randall, 1999; Kessler et al., 1997; Sonne, Back, Diaz Zuniga, Randall, & Brady, 2003). These findings suggest most often that the presence of PTSD eliminates some of the sex differences with regard to prevalence of AUD, particularly among women. One study, however, showed higher rates among males compared to females (King, Meehan, Trim, & Chassin, 2006), and a large epidemiologic study found no sex differences (Goldstein, Dawson, Chou, & Grant, 2012b). Given sex differences for both phenotypes, examination of etiologic models should incorporate testing for sex differences. Berenz and colleagues (2017) also found that, among individuals with comorbid PTSD and alcohol dependence, initial onset of PTSD was associated initial trauma exposure at a younger age. Important findings such as these not only reiterate the influence of relevant third variables such as sex and trauma timing, but they also proffer that the etiology of PTSD-AUD comorbidity is heterogeneous, and that order of onset may denote various pathways for shared risk.

PTSD Susceptibility Model

The PTSD susceptibility model (see Figure 1) proposes that substance use (e.g., alcohol use) may increase susceptibility to PTSD, either through social (e.g., increased exposure to trauma) or physiological (e.g., impaired homeostatic response to stressors) pathways (Chilcoat &

Breslau, 1998; Danovitch, 2016). One theory proposed in this model suggests that alcohol intoxication may increase the likelihood of trauma exposure, therefore indirectly increase risk for PTSD (Schumm & Chard, 2012). Certainly, alcohol intoxication may increase an individual's risk of experiencing a broad spectrum of potentially traumatic events, such as a motor vehicle collision, sexual assault, or physical assault. In addition to increasing risk for trauma exposure, alcohol use may increase PTSD susceptibility is via its physiological effects, such as sleep disturbance and exaggerated startle response (Schumm & Chard, 2012). However, this increase in susceptibility to PTSD due to physiological effects may be more relevant for other substances, such as opiates. Unlike alcohol, which has stress-response-dampening effects, opiates work to disinhibit the stress response or impair the homeostatic response to stressors (Danovitch, 2016).

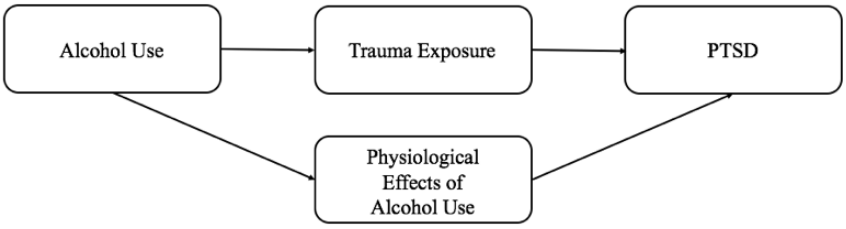

Figure 1. *PTSD Susceptibility Model*

Mutually Inclusive Models

Despite the fact that there are a number of independent proposed pathways to explain the common co-occurrence between PTSD and AUD, it is notable that these various pathways are not mutually exclusive, but instead likely constitute a combination of risk and maintenance processes explaining PTSD-AUD comorbidity (Stewart, Pihl, Conrod, & Dongier, 1998). Several researchers, for example, have suggested mutual maintenance models, such that AUD may exacerbate symptoms of PTSD and vice versa (Danovitch, 2016; Schumm & Chard, 2012; Stewart et al., 1998). For instance, it has already been described how alcohol use may exacerbate symptoms of PTSD by preventing habituation of traumatic memories (Stewart et al.,

1998) and affecting fear conditioning and memory consolidation. Similarly, PTSD may function to exacerbate symptoms of AUD. One mechanism through which PTSD may exacerbate problematic alcohol use is via alcohol withdrawal. Not only does the unpleasant nature of withdrawal symptoms increase motivation for continued alcohol use, but it has been suggested that PTSD may actually exacerbate withdrawal symptoms via an overlap in hyperarousal symptoms (Danovitch, 2016; Jacobsen, Southwick, & Kosten, 2001; Logrip, Zorrilla, & Koob, 2012). Once more, learning-theory offers a framework with which to understand this relationship, such that the overlap between PTSD and withdrawal hyperarousal (e.g., autonomic arousal, irritability, difficulty concentrating, anxious and depressed mood, sleep difficulties) may elicit conditioned responses that trigger substance use (Danovitch, 2016; Stewart et al., 1998) in order to alleviate symptoms (by virtue of the self-medication model). This overlap in conditioned responses exemplifies what previous reviews of PTSD and substance have called "mutual maintenance" (see Figure 2, adapted from Schumm & Chard (2012), for reference) and, as evidenced by the research, is not mutually exclusive from other models of comorbidity, such as the self-medication model.

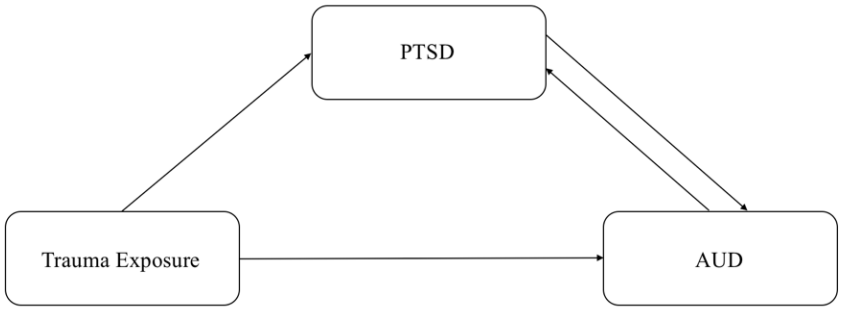

Figure 2. *Mutual Maintenance Model*

Self-Medication Model

Perhaps the most widely accepted explanation for high comorbidity between PTSD and AUD is the self-medication hypothesis. The "drinking to cope" self-medication model (see Figure 3) is a causal model which postulates that individuals with PTSD are more prone to developing problematic drinking behaviors due to a tendency to drink to cope with negative internal experiences (Khantzian, 1999). Examined within a learning-theory framework, the compelling short-term negative reinforcement effects of alcohol may serve to condition the use of alcohol to temporarily alleviate PTSD symptoms and ultimately result in the development of disordered use (Schumm & Chard, 2012). In addition to increasing risk for AUD, use of alcohol to avoid trauma-related memories may also exacerbate or prolong PTSD symptomatology by preventing habituation of traumatic memories (Stewart et al., 1998), which is consistent with evidence for bidirectional causality (Berenz et al., 2017). Furthermore, evidence suggests that consuming alcohol may also interfere with the processing of trauma memories needed for recovery from PTSD on a neurobiological level. For example, both animal and human experimental studies have demonstrated adverse effects of alcohol on fear conditioning and memory consolidation, two processes highly implicated in theories of PTSD development (Kaysen, Bedard-Gilligan, & Stappenbeck, 2017; Tipps, Raybuck, & Lattal, 2014). Taken together, the evidence suggests that models of comorbidity are not mutually exclusive and underscores the clinical significance of the self-medication model, such that drinking to cope with PTSD symptoms may lead to AUD, chronic PTSD, and comorbid PTSD-AUD, which have all been linked with critical public health outcomes, as described in previous sections. Therefore, an empirically substantiated understanding of this model is important.

Evidence from different lines of research may serve to support tenants of the self-medication hypothesis. First, PTSD onset more commonly precedes AUD onset than vice versa, following trauma (Kessler et al., 1995). Further, individuals with PTSD, compared to without, are more likely to endorse drinking to cope with negative affect (though, not PTSD specific symptoms, per se; Waldrop, Back, Verduin, & Brady, 2007). Preliminary support also indicates that coping-oriented drinking may mediate the relationship between PTSD and problem drinking (O'Hare & Sherrer, 2011). Given the self-medication hypothesis is inherently causal, such that PTSD is associated with AUD via coping-related drinking, mediation is the statistical design most fitted to testing this model (i.e., testing the hypothesis that coping related drinking accounts for the variance between PTSD and AUD). However, moderation analyses have also been used to investigate the self-medication hypothesis by testing the interaction between PTSD and drinking coping motives and their joint influence on alcohol outcomes (e.g., that those with high levels of PTSD symptoms and high coping motives would be at increased risk for AUD). Additionally, regression analyses and mean-level differences have been applied in order to examine direct associations or compare mean differences between PTSD, drinking coping motives, and alcohol outcomes. Applications of these approaches across various measures within the PTSD-AUD self-medication literature are discussed below.

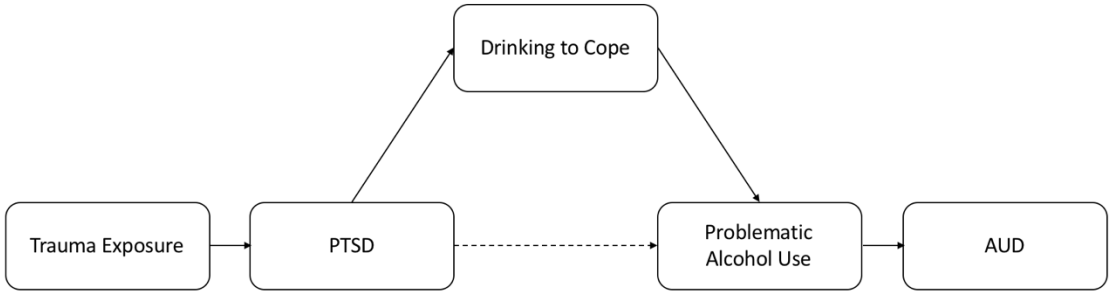

Figure 3. *Self-Medication Model*

An Overview of the Current Self-Medication Literature

(P-)AEQ. A systematic review of the self-medication literature (Hawn et al., in preparation) demonstrated that, by and large, studies assessed a range of generalized drinking motives, tension-reduction strategies, or alcohol expectancies more broadly to infer trauma-related drinking to cope rather than assessing trauma-related drinking to cope specifically. In fact, of the numerous measures used to infer trauma-related drinking, the systematic review produced only one measure that explicitly assessed expectancies for how consuming alcohol would affect PTSD symptoms specifically: the PTSD-Alcohol Expectancies Questionnaire (P-AEQ; Norman, Inaba, Smith, & Brown, 2008). The P-AEQ is a 27-item questionnaire assessing individuals' beliefs regarding the effect of alcohol use on PTSD symptom management based on the fourth edition of the DSM (DSM-IV; Association & Association, 2000) criteria for PTSD. The P-AEQ is comprised of two factors: the positive subscale (indicating the belief that alcohol will reduce PTSD symptoms; e.g. "After a few drinks my flashbacks about past traumatic events would decrease") and the negative subscale (indicating the belief that alcohol will make PTSD symptoms worse; e.g., "After a few drinks my flashbacks about traumatic past events would increase"), assessed on a 5-point Likert scale indicating the extent to which the respondent agrees or disagrees. Although the positive subscale has been associated with alcohol use and alcohol-related consequences across a number of studies (Norman et al., 2008; Pedersen, Myers, Browne, & Norman, 2014; Schaumberg et al., 2015; Vik, Islam-Zwart, & Ruge, 2008), only one study has investigated its mediating effects on the relationship between PTSD and alcohol use, per the self-medication model. Vik and colleagues (2008) failed to find evidence for P-AEQ as a significant mediator or moderator of the relationship between PTSD symptoms and alcohol consumption. One other study examined P-AEQ as a moderator, but not between PTSD and

alcohol use. Instead, Schaumberg et al. (Schaumberg et al., 2015) found that P-AEQ significantly moderated the relationship between impulsivity and alcohol use severity.

In addition to the P-AEQ, there is a non-PTSD specific Alcohol Expectancy Questionnaire (AEQ; Brown, Christiansen, & Goldman, 1987), which assesses expected outcomes related to alcohol consumption across numerous domains, including relaxation and tension reduction scales. The tension-reduction scale (e.g., "If I am tense or anxious, having a few drinks or using drugs makes me feel better") most closely represents drinking to cope with trauma-specific symptoms. However, to date, only two studies have used the tension-reduction scale of the AEQ in their analyses to infer trauma-related drinking to cope (Peters, Khondkaryan, & Sullivan, 2012; Ullman, Filipas, Townsend, & Starzynski, 2005). Both studies found that the tension-reduction scale was significantly associated with both alcohol use and PTSD symptomatology, though Peters and colleagues (2012) did not find support for a significant moderating effect of AEQ tension-reduction expectancies on the relationships between interpersonal violence, PTSD, and problematic alcohol and drug use.

Although the P-AEQ asks about alcohol expectancies with regard to PTSD symptoms specifically, it has been scarcely used to test the veracity of the self-medication hypothesis. Moreover, the P-AEQ assesses alcohol use expectancies as opposed to motives and is therefore does not optimally capture the essence of the self-medication model. Drinking motives fundamentally differ from drinking expectancies in that drinking motives are *reasons* for drinking that are associated with a desired outcome (e.g., change in affect, social rewards; Cooper, 1994), whereas drinking expectancies are *learned connections* between alcohol consumption and either positive or negative outcomes (Anderson, Grunwald, Bekman, Brown, & Grant, 2011). Motives include both the valence and the source of the anticipated outcome and

have been shown to mediate the relationship between expectancies and drinking (Kuntsche, Wiers, Janssen, & Gmel, 2010). Assessing motives is paramount when investigating the self-medication model in order to establish the extent to which an individual's reasons for drinking center around reducing negative affect, or more specifically, mitigating PTSD symptoms.

DMQ-Cope. Among studies that have tested the self-medication model, the predominant measure of choice is the Drinking Motives Questionnaire—Revised (DMQ-R; Cooper, 1994), which is a 20-item self-report measure assessing four distinct drinking motives for alcohol use: coping (i.e., drinking to manage negative emotions), enhancement (i.e., drinking to increase positive emotions or to feel the effects of alcohol ["to get high"]), conformity (i.e., drinking to avoid negative social consequences), and social (i.e., drinking to facilitate social interactions). The DMQ, a three-factor version of the measure created prior to the revised DMQ-R, which subsequently added a conformity subscale, is also often used to infer drinking motives to cope with PTSD symptoms specifically (Cooper, Russell, Skinner, & Windle, 1992). Of the three and four subscales of the DMQ and the DMQ-R, respectively, the coping motives subscale (DMQ-Cope) is by and large the most frequently used subscale for inferring drinking to cope with PTSD symptoms.

Numerous studies have assessed DMQ-Cope in relation to PTSD and alcohol use, though with disparate findings and divergent methods (see Hawn et al., in preparation, for review). Consistent with the conceptual framework of the self-medication model, multiple studies have tested DMQ-Cope as a mediator (Delker & Freyd, 2014; Grayson & Nolen-Hoeksema, 2005; Kaysen et al., 2007; McCabe, Mohr, Hammer, & Carlson, 2018; Tomaka, Magoc, Morales-Monks, & Reyes, 2017), though rarely between PTSD symptoms and alcohol use explicitly. For instance, in a community sample of adults, Grayson and Nolen-Hoeksema (2005) found support

for DMQ-Cope as a mediator between childhood sexual assault and alcohol problems. In another study including women exposed to domestic violence, Kaysen and colleagues (2007) found that DMQ-Cope significantly mediated the relationship between alcohol use predicting trauma symptoms. Alternatively, Delker and Freyd (2014) applied structural equation modeling among a sample of undergraduates and failed to demonstrate significant indirect effects of DMQ-Cope on the relation between PTSD symptoms and substance use more generally, though did find that model fit was substantially improved after including DMQ-Cope as an indicator of the problematic substance use latent variable.

Two studies have explicitly tested the mediating effects of DMQ-Cope on the relation between PTSD symptoms and alcohol consumption and/or problems, both demonstrating evidence supporting this model. The first study, conducted by Tomaka et al. (2017), found that the structural equation model that fit their data best included substance use coping and drinking to cope as mediators of the association between PTSD symptoms and problem drinking, using a sample of municipal firefighters. The second study by McCabe and colleagues (2018) found that coping motives mediated the relation between PTSD symptoms and both alcohol consumption and problems and, further, that this relationship was moderated by perceived friend and familial social support among a sample of U.S. veterans.

Extending beyond mediation models, the DMQ-Cope has been examined in the context of the self-medication model as a potential moderator (Simpson, Stappenbeck, Luterek, Lehavot, & Kaysen, 2014; Stappenbeck, Bedard-Gilligan, Lee, & Kaysen, 2013) and predictor in hierarchical regression models (Dixon, Leen-Feldner, Ham, Feldner, & Lewis, 2009; McDevitt-Murphy, Fields, Monahan, & Bracken, 2015). This snapshot of the DMQ-Cope literature elucidates the fact that conclusions drawn with regard to the self-medication model are often

overgeneralized without explicit investigation into the mediating role of drinking to cope on the relation between PTSD symptoms and alcohol use.

Additionally, the frequency at which the DMQ-Cope is used to infer drinking to cope with PTSD symptoms is problematic because the subscale, which asks on a Likert scale 1-5, "how often do you drink to: 1) forget your worries 2) because it helps you when you feel depressed or nervous 3) to cheer you up when you're in a bad mood 4) because you feel self-confident or sure of yourself 5) to forget about your problems", assesses drinking to cope with negative internal experiences generally, and is not specific to drinking to cope with trauma-related symptoms. Notably, this scale has been refined (Modified DMQ-R; Blackwell & Conrod, 2003) to decompose coping into depression-coping (e.g., "to cheer me up when I am in a bad mood") and anxiety-coping (e.g., "to relax"); however, this modified version is still not specific to symptoms of PTSD and is infrequently used in PTSD-AUD studies. In fact, of the 12 studies that used any iteration of the DMQ to study PTSD-AUD in the review of the PTSD-AUD self-medication literature by Hawn and colleagues (in preparation), only two used the Modified DMQ-R (McDevitt-Murphy et al., 2015; Stappenbeck et al., 2013). Overall, *both* anxiety and depression-coping were significantly higher among individuals with PTSD compared to those without in both studies. Additionally, McDevitt-Murphy and colleagues (2015) found that both the coping-anxiety and coping-depression subscales were significantly correlated with each of the four PTSD symptom clusters, as well as a number of alcohol-related outcomes (e.g., drinking frequency). Moreover, Stappenbeck and colleagues (2013) found that PTSD moderated the association between one's own depression *and* anxiety coping drinking motives and alcohol-related consequences. Specificity of coping related drinking motives is important, as higher coping-anxiety and coping-depression motives have been shown to differentially predict mood-

related alcohol consumption (Grant, Stewart, & Mohr, 2009). Furthermore, there continues to be a lack of research examining drinking to cope in the context of trauma exposure and PTSD specific symptoms (e.g., "to ease intrusive thoughts about your trauma"). Thus, a fallacy exists in the literature that drinking to cope motives are synonymous with drinking to cope with trauma-related symptoms specifically.

Additional Measures. Demonstration of this fallacy in the literature that general drinking to cope motives are synonymous with drinking to cope with trauma-related symptoms specifically extends beyond the prevalent use of DMQ-Cope to other measures assessing general coping motives or alcohol expectancies (e.g., Brief COPE (Carver, 1997), Comprehensive Effects of Alcohol (CEOA; Fromme, Stroot, & Kaplan, 1993), Reasons for Drinking Scale (Beseler, Aharonovich, & Hasin, 2011), and subjective measures of self-medication (Sheerin et al., 2016)). Just as with the (P-)AEQ and DMQ-Cope, results from investigations into the self-medication model using alternative assessment modalities have varied across studies and across measures, even within the same study. For instance, Hruska and Delahanty (2012) included both the Brief COPE, a 28-item measure assessing 14 dimensions of coping among a 1 to 4 Likert frequency scale, and the tension reduction subscale of the CEOA, a 38-item self-report measure that assesses the expected effects of consuming alcohol, and found that the CEOA significantly moderated the relationship between PTSD and alcohol-related problems in a 3-way interaction with sex but the Brief COPE did not. Notably, however, unlike the majority of other studies using Brief COPE which have used one or both items from the substance abuse coping subscale (i.e., "I've been using alcohol or other drugs to make myself feel better", "I've been using alcohol or drugs to help get me through it") to assess use of substances to cope (with inferred traumatic stress/PTSD) (Taylor, 2011; Ullman et al., 2005; Ullman, Relyea, Peter-Hagene, &

Vasquez, 2013b), Hruska and Delahanty (2012) calculated the unweighted sum of items assessing overall avoidance coping, not self-medication specifically, and instead used the CEOA to assess coping drinking motives within a self-medication framework. When applying the substance abuse coping subscale of the Brief COPE, use of substances to cope was found to fully mediate the relationship between PTSD and problem drug use and partially mediate the effect of PTSD on problem drinking (Ullman et al., 2013b). Other studies have more simply examined the direct relationships between the coping motives subscale of the Brief COPE and PTSD and alcohol use, using evidence of association between these constructs as support for the self-medication theory (Taylor, 2011; Ullman et al., 2005).

Similarly, investigation of the self-medication model using the CEOA measure of drinking motives has resulted in inconsistent findings. For instance, one study by Tuliao and colleagues (2016) found that the tension-reduction expectancies subscale of the CEOA did not significantly mediate the relationship between PTSD and three different alcohol measures. Another study, however, by Blumenthal et al. (2015) found that the tension-reduction expectancies subscale did significantly mediate the relation between trauma exposure and alcohol use frequency. Of note, the two described studies differed according to predictor (PTSD vs. trauma exposure). Another study by Creech & Borsari (2014) took a slightly different approach to their analytic plan, using the Brief CEOA (BCEOA; Ham, Stewart, Norton, & Hope, 2005), a 15 item assessment measuring positive (e.g., “It would be easier to talk to people”) and negative (e.g., “I would be clumsy”) alcohol outcome expectancies and valuations of these expectancies (i.e., the degree to which the individual believes that the effect is “good” or “bad”) and found that the positive expectancies subscale of the BCEOA emerged as a significant correlate of problematic drinking, although PTSD symptoms were not related to problematic

drinking. Additionally, the authors found evidence for a significant positive interaction between avoidance coping and positive expectancies predicting problematic drinking.

Additional measures used to infer trauma-related drinking to cope within the context of the self-medication hypothesis include the Reasons for Drinking Scale, which is similar to the DMQ-R in that it is a 35-item Likert-style questionnaire ranging from agree strongly to disagree strongly of drinking motives (Carpenter & Hasin, 1998). Beseler and colleagues (2011) used this scale and found that drinking to cope with negative affect predicted alcohol consumption one week after the terrorist attacks on 09/11/01, but not 16 weeks afterwards. No interactions were observed between drinking motives, proximity to the world trade centers, or lifetime alcohol dependence. Lastly, a systematic review of the literature (Hawn et al., in preparation) found one study applied a subjective measure of self-medication. Sheerin and colleagues (2016) asked participants if they had taken medication or used drugs or alcohol more than once for problems occurring as a result of the traumatic event, producing a dichotomous "yes" or "no" self-medication item. Results showed that AUD was not significantly associated with self-medication, but PTSD was.

Critical Gaps in the Self-Medication Research

A Call for Trauma-Specific Drinking to Cope Measures. As determined by a review of the self-medication literature (Hawn et al., in preparation), with the exception of the P-AEQ which has only been used by two studies to infer trauma-related drinking in the PTSD-AUD literature (Peters et al., 2012; Ullman et al., 2005) and assesses expectations of the effects of alcohol and does not capture the frequency at which an individual uses alcohol to cope with PTSD symptoms, the self-medication model is frequently postulated to explain PTSD and AUD comorbidity in the absence of any explicit validated measure of trauma-related drinking to cope.

Therefore, although it has become well documented that coping-oriented drinking is linked with PTSD, problematic alcohol use, and increased likelihood of AUD, there is a paucity of research examining drinking to cope with PTSD/trauma-related symptoms specifically. This creates an illusion in the literature that drinking to cope motives are synonymous with drinking to cope with trauma-related symptoms specifically, yet in practice drinking to cope is assessed with regard to negative internal experiences more generally (e.g., "To cheer you up when you're in a bad mood"). To date, it appears that no studies have explicitly examined the extent (i.e., frequency, quantity) of drinking to cope with trauma-related symptoms specifically, making this a critical void to fill.

Lack of Mediational Analyses. Provided that the self-medication model is inherently mediational by design, whereby the relationship between PTSD and AUD/problematic alcohol use is explained at least partially by drinking to cope with trauma-related symptoms (see Figure 3 for review), it would follow that the use of mediational analyses to test its validity is imperative. Surprisingly, however, use of mediational analyses in the PTSD-AUD self-medication literature is sparse (Blumenthal et al., 2015; Delker & Freyd, 2014; Grayson & Nolen-Hoeksema, 2005; Kaysen et al., 2007; McCabe et al., 2018; Tomaka et al., 2017; Ullman, Relyea, Peter-Hagene, & Vasquez, 2013a; Vik et al., 2008) and have resulted in disparate findings.

Need for Longitudinal Investigation of the PTSD-AUD Relationship. There have been only a few longitudinal studies published investigating the temporal precedence of PTSD before AUD, a basic assumption of the self-medication model. If alcohol use among individuals with PTSD represents attempts at self-medication of PTSD symptoms, then it stands that problematic alcohol use should develop following trauma exposure and the emergence of PTSD symptoms

(Stewart et al., 1998). Thus, in order to truly test the theory that PTSD increases subsequent risk for AUD (i.e., self-medication), longitudinal research designs are warranted. However, of the 24 studies that met eligibility criteria for a systematic review of the PTSD-AUD self-medication literature (Hawn et al., in preparation), only one was longitudinal in design (Beseler et al., 2011). However, because preliminary analyses failed to show an association between PTSD and alcohol-related outcomes, Beseler and colleagues (2011) did not include any measure of PTSD or traumatic stress in their final analyses.

Methodological Considerations. Differences in both methodology and findings between investigations into the self-medication model illustrate several relevant methodological considerations warranted in the self-medication literature. For instance, some studies do not include any assessment of PTSD in their analyses (e.g., Blumenthal et al., 2015), but instead focus exclusively on trauma exposure and fail to assess trauma-related distress whatsoever. This further generalizes the self-medication model by inferring that trauma exposure is equated with distress, which the discordant prevalence estimates between ubiquitous trauma exposure (Benjet et al., 2016) and low conditional risk for PTSD (e.g., Kilpatrick et al., 2013) suggest is a misconstrued assumption. Additionally, timing of the index trauma regularly differs between studies. For instance, although Grayson & Nolen-Hoeksema (2005), Vik et al. (2008), and Ullman et al. (2013b) all assessed PTSD symptoms in relation to sexual trauma, Grayson and Nolen-Hoeksema assessed sexual trauma occurring prior to age 18, Vik and colleagues assessed PTSD related to any sexual trauma occurring after the age of 12, and Ullman et al. assessed for both child and adult sexual trauma. Given the research on the meaningful differences with regard to PTSD and other deleterious outcomes between child versus adult exposure to sexual trauma (e.g., Cloitre et al., 2009), variations in trauma timing could at least partially explain

some of the inconsistencies in the self-medication literature. Furthermore, whereas the alcohol outcomes included in Grayson and Nolen-Hoeksema (2005) and Ullman et al. (2013b) were computed using diagnostic criteria and alcohol-related consequences, the alcohol outcomes included in Vik et al. (2008) and Blumenthal and colleagues (2015) were computed from quantity/frequency counts of alcohol consumption. Both Grayson & Nolen-Hoeksema and Vik and colleagues used a more general "distress" variable to characterize posttraumatic stress, however, the variable used by Grayson and Nolen-Hoeksema consisted of a composite score of depression and anxiety, whereas the variable used by Vik was composed of items querying specific PTSD symptoms (Impact of Event Scale-Revised; Weiss, 2007). Ullman and colleagues more explicitly tested for PTSD by using the Posttraumatic Stress Diagnostics Scale (Foa, 1995) and Bluementhal and colleagues (2015) failed to incorporate PTSD into their mediational analyses whatsoever. In addition to these methodological inconsistencies, as demonstrated by these study examples, other noteworthy considerations include sample selection and related characteristics, as well as failure to account for relevant factors, such as sex, race/ethnicity, and prior trauma history.

Important Sex Considerations. Just as with PTSD and alcohol use, sex appears to be a relevant consideration with regard to drinking motives, though this literature has proven inconsistent and occasionally contradictory. For instance, in Cooper's seminal paper on the development and validation of the four factor DMQ-R (Cooper, 1994), he found that males reported higher levels of social, enhancement, and conformity motives compared to females, but that neither sex differed significantly with regard to coping motives. Another study testing a five factor DMQ model demonstrated that males endorsed significantly higher levels of social motives than females, but failed to find sex differences across the all other motives (Grant,

Stewart, O'Connor, Blackwell, & Conrod, 2007). Despite some evidence suggesting sex differences in coping-oriented drinking motives may not be meaningful, one study using the substance use subscale of the COPE found that males were more likely to report drinking to cope with a recent stressor than women and women were more likely to report avoidance, emotion-focused, and problem-focused coping rather than drinking-related coping overall compared to men (Park & Levenson, 2002). Results also suggested a crossover effect, such that women who did endorse drinking to cope had higher positive expectancies for alcohol use compared to men. Another study by Fossos and colleagues (Fossos, Kaysen, Neighbors, Lindgren, & Hove, 2011) specifically tested the mediating role of coping-oriented motives, per the DMQ-R, on the relation between sexual assault and problem drinking behaviors for both men and women and found evidence for significant direct and indirect paths between sexual coercion and drinking for men, whereas only indirect paths were found for women. These notable inconsistencies in the drinking motives literature with regard to sex, as well as the methodological considerations expanded upon in the previous paragraphs, highlight the need for more comprehensive and standardized investigation into the mediating role of drinking to cope with trauma-related distress specifically on the relation between PTSD and problematic alcohol use, as potentially moderated by sex.

Common Factors Model

Another model which is not mutually exclusive from the self-medication or other previously discussed models and may help explain the common comorbidity between PTSD and AUD is what Danovitch and colleagues (2016) refer to as the “common factors model”, also known as the “Third Variable Model” (Langdon et al., 2017). Although Danovitch and colleagues present the common factors model in the context of opioid use disorder, the model

itself holds conceptual weight for PTSD-AUD comorbidity as well and therefore warrants discussion. Broadly, the common factors model (Figure 4) posits that shared factors may contribute to increased risk for onset and maintenance of both PTSD and substance use. Indeed, early environmental experiences have been shown to affect physiology in such a way that may increase susceptibility to both PTSD and substance use disorders, such as AUD (Danovitch, 2016). One particularly relevant environmental factor that may confer shared risk for PTSD and substance use more broadly is exposure to stress and trauma. For instance, research suggests that postnatal stress may alter neuroendocrine homeostasis lasting into adulthood (Ábrahám & Kovács, 2000), increasing vulnerability to PTSD, stress-induced substance use relapse, and negative reinforcement behaviors (Henry, Kabbaj, Simon, Moal, & Maccari, 1994), all of which are potential contributing factors to PTSD-AUD comorbidity. Other environmental considerations, such as caregiver support and drug availability, have also been shown to influence risk for comorbidity (Danovitch, 2016; Reddy, Anderson, Liebschutz, & Stein, 2013). Furthermore, there is evidence to support the mutual influence of certain psychological (e.g., impulsivity, distress tolerance; Marshall-Berenz, Vujanovic, & MacPherson, 2011; Schaumberg et al., 2015; Vujanovic, Marshall-Berenz, & Zvolensky, 2011) and personality (Haller & Chassin, 2013; Miller, Vogt, Mozley, Kaloupek, & Keane, 2006) traits in the development and maintenance of both PTSD and AUD. Given that these disorders are moderately heritable, with overlapping heritable influences, genetic factors and downstream biologic risk factors are also possible third variable explanations for PTSD-AUD comorbidity. In the sections that follow, a review of the latent and molecular evidence for each disorder, as well as evidence for their genetic overlap, will be provided.

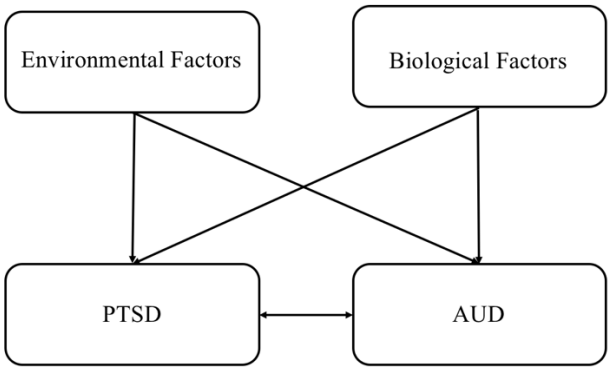

Figure 4. *Common Factors Model*

Genetic Underpinnings of PTSD, AUD, and PTSD-AUD Comorbidity

Heritability

Both PTSD and AUD are moderately heritable, and evidence suggests that this heritability may overlap. Specifically, twin studies, which provide valuable information with regard to the degree of overall genetic and environmental influence on a phenotype of interest by comparing monozygotic (identical; share 100% of their genes) and dizygotic (fraternal; share 50% of their genes) twins, suggest that between 35% to 72% of the variance in PTSD (Amstadter, Aggen, Knudsen, Reichborn-Kjennerud, & Kendler, 2012; Sartor et al., 2011; Stein, Jang, Taylor, Vernon, & Livesley, 2002; True et al., 1993) and approximately 50%-70% of the variance in AUD (Verhulst et al., 2015) is accounted for by genetic factors. Moreover, twin studies suggest that upwards of 30% of genetic vulnerability for PTSD overlaps with genetic vulnerability for AUD (Sartor et al., 2011; Xian et al., 2000).

Sex Differences

To date, the ability to investigate sex differences in the heritability of PTSD within the same sample has been largely underpowered (Sheerin, Lind, Bountress, Nugent, & Amstadter, 2017). However, fragmentary evidence exists from exclusively male and female samples to

suggest that heritability estimates for PTSD may differ as much as two- to three-fold between the sexes. For instance, a sample of all male Veterans produced heritability estimates of approximately 30% (True et al., 1993), whereas an all female civilian sample produced heritability estimates of 72% (Sartor et al., 2011). Unlike the growing PTSD literature, investigations into sex differences in the heritability of AUD have been more plausible due to larger samples sizes, yet have resulted in mixed evidence (see Salvatore, Cho, & Dick, 2017 for review). Although a recent study found that genetic factors accounted for 57%, 95% CI [40%, 69%] of the variance in males' AUD and 22%, 95% CI [7%, 47%] of the variance in females' AUD (Kendler et al., 2016), the majority of studies the literature have failed to find evidence for sex differences (Salvatore et al., 2017). In fact, the most recent meta-analysis of twin and adoption studies of AUD to date (Verhulst et al., 2015) demonstrated heritability estimates of about 50% for both males and females and failed to find evidence for qualitative sex differences as well.

Genetic Variation

Convincing support for moderate heritability has incited research into what specific genetic variants may put an individual at risk for PTSD or AUD. Over the last several decades, due largely to the revolutionary efforts to sequence the human genome in the Human Genome Project (Sawicki, Samara, Hurwitz, & Passaro, 1993), advances in genetic sequencing have allowed researchers to investigate the effects of specific genetic variants on complex psychiatric traits. Most of these investigations have centered around single nucleotide polymorphisms (SNPs; McCarthy et al., 2008). SNPs are the most common form of variation in the DNA sequence. They occur due to point mutations, which result in varying alleles between different members of the same species. Because these variations are easily identifiable, as well as due to

the frequency at which they occur, SNPs have become commonly used markers to map genes that modify susceptibility to diseases or complex traits (Ikegawa, 2012). Therefore, SNPs are commonly used in molecular research to determine whether a significant association exists between a certain genetic variant and a psychiatric trait, either via case versus control status (e.g., PTSD vs. no PTSD) or the degree of association based on a quantitative trait (e.g., PTSD symptom severity). To date, numerous molecular approaches have been taken to investigate the influence of genetic variation on both PTSD and AUD.

Candidate Gene Studies

Candidate gene studies apply an a priori approach in order test associations between hypothesized SNPs and phenotypic traits of interest (e.g., PTSD, AUD; Patnala, Clements, & Batra, 2013). Extant candidate gene studies have identified multiple variants associated with PTSD and AUD, independently (for alcohol review, see Dick & Foroud, 2003; for PTSD review, see Sheerin et al., 2017). However, candidate gene research is characterized by multiple limitations, most notably of which is inconsistent findings across studies (Tabor, Risch, & Myers, 2002). Factors which limit credibility and likely contribute to inconsistent findings in candidate gene research include small sample sizes resulting in low power and increased likelihood of false positives if an effect is found and heterogeneous quality control approaches (e.g., failure to properly control for ancestral influences; Tabor et al., 2002). Another critical limitation is the lack of coherence across particular genes of interest, such that studies commonly examine only specific SNPs of interest within an entire gene. Given increasing awareness of polygenetic contributions to complex traits (Hirshorn & Daly, 2005), candidate gene studies are further limited in that they do not account for the small combined effects of multiple genes on an outcome.

Genome Wide Association Studies (GWAS)

Advances in genomic sequencing, as well as increasing sample sizes due largely to the collaborative efforts of Psychiatric Genomics Consortia (PGC; Nievergelt et al., 2018), have led to a shift in the recent decades in the field of psychiatric genetics away from candidate gene research and towards the application of agnostic approaches, such as genome wide association studies (GWAS; Wilkening, Chen, Bermejo, & Canzian, 2009), which allow for the simultaneous examination of millions of variants (measured or imputed) across the genome to identify potential loci contributing to a phenotype. Specifically, GWAS determine if SNPs occur more frequently based on case status or severity of the trait in question (Risch & Merikangas, 1996). SNPs occurring at higher frequency among cases or in association with increased severity of the trait are implicated as risk factors for the trait of interest.

GWAS apply agnostic approaches by which associations between certain locations on a gene called loci (i.e., fixed position on a chromosome) and the presence/absence or degree of traits of interest are tested. Due to the relevance of loci in GWAS, this method relies largely on linkage disequilibrium (LD). Broadly, LD refers to the non-random association of SNP alleles inherited together within a given population (Bush & Moore, 2012). Populations with longer ancestral histories (i.e., African-descent populations) have lower LD compared to European- and Asian-descent populations due to increased opportunities for recombination over time.

GWAS have been used to gain new insight into the genetic contributions of both AUD and PTSD. GWAS have identified potential sources of genetic variation associated with AUD, the most consistent of which have been identified in the alcohol metabolism genes, alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH*) (Tawa, Hall, & Lohoff, 2016), including *ADH1B* (e.g., Park et al., 2013; Walters et al., 2018) and *ALDH2* (e.g., Polimanti &

Gelernter, 2017). Additionally, specific variants identified in GWAS for AUD have been replicated in independent GWAS studies (e.g., ADH1B, ADH1C, PKNOX2, CPE, KCNB2; Chen et al., 2016; Park et al., 2013; Walters et al., 2018), and across ethnicities (ADH1B, Walters et al., 2018; PTP4A1-PHF3, Zuo et al., 2015). Please refer to Tawa et al., (2016) for a comprehensive overview of the alcohol GWAS literature, although this review does not include the most recent published GWAS of alcohol dependence using AUD-PGC data (Walters et al., 2018).

Compared to the alcohol literature, GWAS of PTSD have been less consistent to date. Although two studies failed to identify SNPs that met genome-wide significance (Ashley-Koch et al., 2015; Wolf et al., 2014), the majority of GWAS have identified significant hits (Almli et al., 2015; Duncan, Ratanatharathorn, et al., 2018; Guffanti et al., 2013; Logue et al., 2013; Nievergelt et al., 2018; Nievergelt et al., 2015; Stein et al., 2016; Xie et al., 2013), some of which have been internally replicated. Although some studies have succeeded in replicating GWAS findings in independent samples (e.g., the RORA variant identified in Logue et al., 2013), others have not (Guffanti et al., 2014). Notably, there has yet to be replication of identified loci across separate GWAS. There are a number of potential explanations for the lack of replication across GWAS, including low power and some of the previously described complex methodological considerations accompanying PTSD research, such as the confounding effects of heterogeneity in trauma type, ancestry, and sex. Despite these inconsistencies, GWAS techniques have resulted in the identification of variants not otherwise explored in candidate gene research which are associated with physiological systems implicated in previous PTSD research (e.g., immune system function; Guffanti et al., 2013; Nievergelt et al., 2018; Nievergelt et al., 2015; Stein et al., 2016).

Aggregate Molecular Genetic Methods

Although GWAS studies to date have helped identify specific genetic variants that confer risk for PTSD and AUD independently, there remains a paucity of research in the genetic literature, beyond twin studies, concerning the genetic overlap of these phenotypes. To start, twin studies have demonstrated that there is etiologic overlap across these phenotypes, such that approximately 30% of the genetic vulnerability to PTSD is shared with AUD (Sartor et al., 2011; Xian et al., 2000). Candidate-gene designs have provided preliminary support for genes related to both PTSD and alcohol use and therefore may offer some potential insight into genes relevant to PTSD-AUD comorbidity; however, it is notable that these genes/SNPs have not been significant in GWAS designs. Specifically, *APOE* and *DRD2* have been associated with both PTSD and harmful drinking behaviors in veteran samples (Kim et al., 2013; Young et al., 2002). Additionally, the *OPRM1* gene, implicated in the stress system, was significantly associated with both PTSD and drinking motives among a sample of individuals with HIV (Nugent, Lally, Brown, Knopik, & McGeary, 2012). This is consistent with previous twin research suggesting that drinking-to-cope motives are moderately (upwards of 42%) heritable (Agrawal et al., 2008; Prescott, Cross, Kuhn, Horn, & Kendler, 2004) and that a significant portion of the genetic risk for alcohol abuse and/or dependence overlaps with "drinking to manage mood states" (Prescott et al., 2004). Moreover, previous research exists supporting the mediating role of drinking-to-cope on latent genetic risk for AUD (Littlefield et al., 2011; Prescott et al., 2004; Young-Wolff, Kendler, Sintov, & Prescott, 2009). Despite evidence from both twin studies and candidate-gene research for shared genetic risk between PTSD and AUD, and evidence supporting the heritability of drinking-to-cope motives, the specific genetic variation underlying PTSD-AUD co-occurrence and shared heritability remains largely unknown. However, recent advances in

statistical procedures offer promising solutions for further analysis of GWAS data, including tests of potential overlap in molecular variation.

Genome-Wide Complex Trait Analysis (GCTA)

Moving beyond twin studies, which have historically been used to inform heritability estimates, recent advances in statistical genetics have led to the emergence of techniques which obtain heritability estimates among unrelated individuals. Among some of the most commonly used of these approaches is genome-wide complex trait analysis (GCTA), which estimates the variance of a particular trait explained by the additive effect of all available SNPs (Yang, Lee, Goddard, & Visscher, 2011). This process is done by regressing a genetic relationship matrix (GRM), which includes correlations between individuals across all available SNPs, onto a phenotype of interest using a restricted maximum likelihood (REML) method, rather than testing the association of any particular SNP with the trait. Because GCTA provides heritability estimates calculated exclusively from information derived from SNPs included on common GWAS arrays, GCTA analyses do not include genetic variation due to rare variants. GCTA also fails to account for dominance effects, epistasis, or gene-by-environment (GxE) effects due to its exclusive reliance on additive SNP effects (Wray et al., 2014; Wray et al., 2013). Such failure to account for anything beyond additive genetic effects likely explains why heritability estimates found in twin studies, which capture all aggregate genetic variation, are often higher than those found in GCTA studies (Trzaskowski, Dale, & Plomin, 2013). To that end, caution is warranted in equating non-significant GCTA findings to a lack of heritability. Additionally, GCTAs are sensitive to sampling and measurement errors and therefore may result in biased estimates (Kumar, Feldman, Rehkopf, & Tuljapurkar, 2016). Despite these methodological limitations, GCTA has become a widely popular method and has been applied across a variety of phenotypes

(e.g., Wray et al., 2014). This popularity, in part, is due to the multiple advantages of GCTA compared to other genetic methods, including ability to conduct analyses in smaller sample sizes than what is needed for GWAS, as well as the availability to examine shared genetic risk between two phenotypic traits among unrelated individuals via bivariate GCTA (Lee, Yang, Goddard, Visscher, & Wray, 2012).

GCTA studies to date suggest that SNP based heritability of alcohol-related phenotypes is moderate. SNP based heritability of alcohol dependence among a Dutch sample suggested that common SNPs jointly capture 33% of the heritability in alcohol dependence, which was approximately half (60%) of the twin-based heritability estimates found within the same sample (Mbarek et al., 2015). A similar pattern of results was demonstrated using a United States sample, wherein GCTA analyses demonstrated that additive SNP effects accounted for 21% and 38% of the heritable variance in alcohol dependence and alcohol consumption, respectively, and biometric twin models resulted in higher heritability estimates overall (56% and 43% for alcohol dependence and consumption, respectively; Vrieze, McGue, Miller, Hicks, & Iacono, 2013). Another study investigating the heritability of assorted substance dependencies, including alcohol, tobacco, cannabis, and illicit drugs, used GCTA estimates to conclude that common SNPs contribute to at least 20% of the variance in substance dependence vulnerability more broadly (Palmer et al., 2015).

Compared to alcohol-related phenotypes, there is a paucity of research on the heritability of trauma-related phenotypes using GCTA methods. As evidenced in the limited research, however, risk for exposure to interpersonal violence has been shown to be moderately heritable (47%; Palmer et al., 2016) and this heritability has been shown to partially overlap with genetic vulnerability to drug dependence, which included alcohol dependence. GCTAs examining

PTSD specifically have been sparse and inconsistent; likely due to differences in sample (e.g., percent male versus female) and in power (i.e., sample size). For instance, Stein and colleagues (2016) did not find evidence supporting significant SNP-based heritability for PTSD using GCTA methods in two European American, primarily male, Veteran samples (n=6,916). Alternatively, the most recent paper published by the PTSD PGC (Nievergelt et al., 2018) indicated that, based on data including individuals of European ancestry and African ancestry for whom the PGC had access to individual-level genotype data (n=47,151, 26.5% PTSD cases), SNP-based heritability estimates for PTSD were significant within the European ancestry subsample (4-5%) but not the African ancestry subsample. However, after stratifying by sex, heritability estimates were significant for both the European ancestry females (8-13%) and African ancestry females (12-18%), but did not statistically differ from zero among males of either ancestral subsample. Heritability estimates varied according to various PTSD prevalence thresholds (i.e., 10%, 30%, and 50%) specified in the analyses. Once more, these disparate findings mirror the trauma/PTSD literature as a whole, which is characterized by heterogeneity (e.g., trauma type and related conditional probability of PTSD, broad variety of assessment measures), as well as highlight the necessity of considering relevant demographic variables, such as sex.

Linkage Disequilibrium Score Regression (LDSC)

Another increasingly popular method for estimating SNP-based heritability estimates among unrelated individuals is linkage disequilibrium score regression (LDSC). LDSC uses regression analyses to examine the associations between SNPs' test statistics derived from GWAS summary statistics and their LD scores. LDSC has several methodological strengths in that it is able to quantify the contribution of polygenicity as well as confounding biases, such as

population stratification and cryptic relatedness (Bulik-Sullivan, Loh, et al., 2015a). Similar to how bivariate GCTA can be used to quantify shared heritability between two traits, LDSC can be applied across traits in order to estimate genetic correlations between traits, an approach termed cross-trait LDSC (Bulik-Sullivan, Finucane, et al., 2015a). Broadly, "the genetic correlation is the additive genetic covariance between two traits scaled by the square root of the product of the genetic variance for each trait" (Ni et al., 2018). Cross-trait LDSC incorporates the LD score derived for each trait in the calculation of this covariance (Bulik-Sullivan, Finucane, et al., 2015a). Like single-trait LDSC, cross-trait LDSC requires only GWAS summary statistics. LDSC and cross-trait LDSC offer notable advantages over GCTA, such that they do not require individual-level genotype data, are not biased by sample overlap or population stratification, and are computationally very fast (Bulik-Sullivan, Finucane, et al., 2015a). Notably, however, some research suggests that GCTA may produce more accurate heritability estimates compared to LDSC (Ni et al., 2018), which could explain why some studies have found lower heritability estimates using GCTA compared to LDSC (e.g., Duncan, Ratanatharathorn, et al., 2018).

The LDSC literature is burgeoning. In the most recent AUD-PGC publication (Walters et al., 2018), LDSC analyses indicated that the SNP-based heritability of alcohol dependence was significant at 9% in a meta-analysis of unrelated European ancestry samples and marginally so in a meta-analysis of unrelated African ancestry individuals. Assuming a population prevalence of 30% after trauma exposure, SNP-based heritability of PTSD was estimated using Freeze 2 summary statistics from the PTSD-PGC European studies (n=174,659, 13.3% PTSD cases) (Nievergelt et al., 2018), which includes data from the UK Biobank (Allen, Sudlow, Peakman, & Collins, 2014), and indicated that overall heritability was significant at 5%. After stratifying by

sex, heritability of PTSD among females was significant at 10% and was not significantly different from zero among males, consistent with the GCTA results.

Cross-trait LDSC studies have documented significant genetic correlations between PTSD and numerous traits, including but not limited to depressive symptoms, schizophrenia, neuroticism, insomnia, smoking behavior, asthma, hip-waste ratio, and coronary heart disease (Nievergelt et al., 2018). Similarly, alcohol dependence has been found to be genetically correlated with traits including schizophrenia, depression, neuroticism, attention deficit-hyperactivity disorder, smoking initiation, lifetime cannabis initiation, and several others (Walters et al., 2018). Of note, there are currently no published studies using LDSC to quantify the genetic correlation between PTSD and alcohol dependence or other alcohol-related phenotypes; however, work by Sheerin and colleagues (Sheerin et al., under review) has found evidence for a modest correlation (r=.35) between PTSD and AUD using data from the PTSD-PGC and SUD-PGC, respectively.

Polygeneic Risk Scores (PRS)

In addition to bivariate GCTA, another widely popular genetic technique for examining genetic covariance between two phenotypes of interest using molecular data from unrelated individuals is through the use of polygenic risk scores (PRS). Unlike GCTA, however, PRS techniques require only summary statistics from a discovery dataset (and genotypic level data from a target dataset) to calculate weighted risk scores using regression analyses to represent an individual's genetic risk for a phenotype (Purcell, 2009). A benefit of PRS over GCTA and LDSC is that, unlike GCTA and LDSC, which assume random SNP effects, PRS accounts for specific SNP effects by weighting scores based on the SNP's effect size from previous a GWAS and then applying p-value thresholds to create multiple scores using SNPs within different

ranges of *p*-values, ranging from very small to encompassing all SNPs. Therefore, this process accounts for likely polygenic effects on a particular trait, such that even SNPs with very small effects may, in tandem with multiple other SNPs, influence a phenotypic trait.

Similar to GCTA and LDSC, PRS has useful bivariate applications, such that weighted genetic risk for one trait (e.g., PTSD) can be used to predict expression of another phenotype (e.g., AUD). Just as it does strengths, PRS shares multiple limitations with GCTA and LDSC, including that analyses are limited by what SNPs are available, do not take into account non-additive effects, GxE, epistasis, or rare variation (Wray et al., 2014; Wray et al., 2013). Furthermore, because PRS are calculated using an original discovery sample, large samples are required in order to produce more accurate estimates (Wray et al., 2014) and replication across studies is difficult (Ware et al., 2017). Although methods have emerged in order to address some of these limitations, (e.g., LDpred (Vilhjálmsson et al., 2015) and PRSice (Euesden, Lewis, & O'Reilly, 2014)), limitations are withstanding and worth mentioning. PRSs have been applied in both the alcohol (Clarke et al., 2016; Salvatore et al., 2014; Vink et al., 2014) and PTSD (Duncan, Ratanatharathorn, et al., 2018; Nievergelt et al., 2015; Solovieff et al., 2014) literatures and, although PRS analyses have provided consistent evidence for aggregate risk across various phenotypes (e.g., PTSD and bipolar disorder (Duncan, Ratanatharathorn, et al., 2018; Nievergelt et al., 2015; Solovieff et al., 2014) and AUD and cigarette use (Clarke et al., 2016; Vink et al., 2014)), no studies to date have used PRS to test aggregate risk for PTSD and AUD.

Summary

Given high prevalence estimates and associated sequela of negative outcomes, PTSD-AUD comorbidity is a major public health concern. Greater understanding of the relationship between PTSD and problematic alcohol use would mitigate this concern by informing

empirically-based treatment and prevention programs. Efforts to increase said understanding have resulted in multiple etiological models that have been proposed to explain PTSD-AUD comorbidity. Although multiple promising models exist, such as the PTSD susceptibility model and common factors model, the most widely accepted model to date appears to be the self-medication model, which assumes that individuals with PTSD are more prone to developing AUD due to a tendency to drink to cope with negative internal experiences (Khantzian, 1999). Despite its popularity, a systematic review of the literature (Hawn et al., in preparation) revealed a lack of rigorous empirical evidence in support of the self-medication model, which is likely due to a number of important methodological considerations. Such considerations include the lack of longitudinal study designs and mediational analyses to account for the temporal and causal assumptions underlying the self-medication model, alcohol assessment heterogeneity, and failure to account for potential confounding variables, such as sample selection (e.g., sex, race/ethnicity) and trauma history and type.

In addition to the limitations reviewed above for the self-medication literature, perhaps the largest limitation is that of measurement of the construct of trauma-related drinking. Given that the basic premise of the self-medication model is that PTSD influences the development of AUD via drinking to cope with unpleasant symptoms of PTSD, failure to explicitly test trauma-related drinking to cope is an irrefutable gap in the current literature. This apparent lack of research examining drinking to cope in the context of trauma exposure and trauma-specific symptoms, as opposed to drinking to cope more broadly, creates a critical void to fill. Because it is likely that trauma-related drinking to cope may help explain the common co-occurrence between PTSD and AUD, further work is needed to create a tailored measure for self-reported trauma-related drinking to cope, which would serve not only to improve methodology by

generating reliability and validity, but also could be useful in targeting individuals with PTSD who may be at increased risk for AUD and therefore lead to improvements in treatment and prevention efforts.

In addition to operationalizing trauma-related drinking to cope, another methodological suggestion that would significantly increase the veracity of the commonly assumed self-medication model would be to increase the amount of mediational research investigating this model. Given the basic causal premise of the self-medication model (i.e., PTSD increases risk for subsequent AUD via trauma-related drinking to cope), the use of longitudinal data to verify mediational analyses would increase understanding with regard to if and how much variance in the relationship between PTSD and AUD is explained by trauma-related drinking to cope, ultimately providing validated, empirical support for the model.

Additionally, inclusion of relevant factors, such as race/ethnicity, sex, trauma type, and trauma history would substantially improve the PTSD-AUD self-medication literature, as well as likely result in more consistent findings across studies. One explanation for the inconsistency of the current literature is that these crucial confounding variables are scarcely accounted for, resulting in skewed findings. This is exemplified by the commonly supported finding that only a percentage of individuals go on to develop problem alcohol use following the onset of PTSD, indicating that there is an array of confounding risk factors necessary to explain the existence of alcohol abuse in association with PTSD. This reiterates the need for this association to be understood in the context of a multifactorial model.

Moreover, given evidence for moderate overlap in genetic variance between PTSD and AUD (e.g., Sartor et al., 2011; Xian et al., 2000), genetically informed research surrounding the self-medication model is warranted. Investigations into the shared genetic risk and biological

underpinnings of comorbid PTSD, AUD, and potential mechanisms through which this comorbidity operates (i.e., trauma-related drinking to cope), would help to further elucidate common etiological pathways underlying PTSD, AUD, and intermediate trauma-related drinking to cope, which is imperative to the development of effective prevention and treatment programs.

Study Aims

Overarching Aims

The present study aimed to address gaps in the current trauma and alcohol literatures by investigating the extent to which trauma-related drinking to cope mediates the distinct relation between PTSD and problematic alcohol use and the extent to which genetic variance for PTSD and trauma-related drinking overlap. This is the first study to investigate trauma-related drinking to cope from a phenotypic or genotypic level of analysis. By assessing drinking to cope motives in relation to PTSD symptoms specifically, the present study aimed to produce detailed and novel data on this unexplored phenotype and provide an innovative approach to studying the self-medication hypothesis. In order to satisfy these objectives, data was leveraged from a unique resource: an ongoing longitudinal, genetically-informative study of college students, which has enrolled five incoming freshman cohorts at a large, diverse urban university ("Spit for Science" [S4S], NIAAA-R37 AA011408). In addition to the existing phenotypic and genotypic data available through S4S, the present study recruited trauma-exposed students with a history of alcohol use to obtain refined phenotypic data ("Life Experience and Alcohol Use" [LEAU] study, F31AA025820; PI: Hawn, P50AA022537, PI: Amstadter). This included a novel measure of trauma-related drinking to cope as well as a more rigorous assessments of PTSD, alcohol consumption and related problems (AUP), and lifetime trauma load in order to address the main research questions. Conducting the present investigation using a college sample is important in

order to elucidate common etiological risk underlying trauma-related drinking to cope, PTSD, and AUP, which is imperative to the development of effective prevention and treatment programs, particularly among young adults who are at increased risk for developing PTSD and AUD.

Aim 1: Psychometric Evaluation of TRD

The present study sought to create a measure which would assess drinking motives related to coping with symptoms of PTSD, which we named the Trauma Related Drinking questionnaire, or TRD. Aim 1 sought to psychometrically evaluate the TRD questionnaire via four sub-aims. First, Aim 1a sought to examine relevant characteristics and distributional properties of TRD and compare them to those of the DMQ-Cope, as well as test omnibus differences in TRD by PTSD and AUP caseness. It was hypothesized that TRD would provide greater specificity than the DMQ-Cope, such that it would be less frequently endorsed and less evenly dispersed among the sample compared to DMQ-Cope and that TRD scores would be higher among PTSD cases versus controls. Second, Aim 1b sought to investigate the factor structure of TRD, determine how it relates to the factor structure of DMQ-Cope, and compare how the two factor structures relate to PTSD using a structural equation modeling (SEM) framework. It was hypothesized that both TRD and DMQ-Cope would demonstrate related, unitary constructs and that PTSD would be more strongly associated with the TRD common factor as compared to the DMQ-Cope common factor. Third, Aim 1c sought to externally validate TRD in relation to PTSD, hypothesizing that each TRD item would be significantly associated with the PTSD symptom cluster (i.e., factor) that it was designed to represent and that each PTSD factor would be significantly associated with the TRD latent factor. For example, it was hypothesized that the arousal factor of the PTSD measure would be most strongly associated

with the TRD item querying frequency of drinking to cope with arousal symptoms when compared to all other PTSD factors and that all PTSD factors would be significantly associated with the TRD common factor. Fourth, Aim 1d sought to externally validate TRD in relation to alcohol consumption and related problems, within the context of PTSD. It was hypothesized that the TRD common factor would be significantly associated with both alcohol consumption and problems.

Aim 2: Investigation of the Self-Medication Model

Aim 2a sought to investigate the self-medication model by testing whether the relation between PTSD and AUP was significantly accounted for by the effects of TRD, while accounting for its relationship with DMQ-Cope. Aim 2b sought to investigate whether this self-medication mediation model was moderated by sex. Aim 2 was conducted both cross-sectionally, using a large sample and comprehensive assessment battery, and longitudinally, using a smaller sample and abbreviated measures from S4S. It was hypothesized that TRD would account for the relation between PTSD and AUP, over and above the effects of DMQ-Cope. Additionally, it was hypothesized that this indirect effect would be stronger for females than males and that this pattern of results would hold across the cross-sectional and confirmatory longitudinal analyses.

Aim 3: Genotypic Investigation into TRD, PTSD, and Their Potential Overlap

Aim 3a was comprised of the univariate genotypic aims, which were three-fold and included conducting genome wide association analyses, specifically univariate GCTA and GWAS, to establish SNP-based heritability and identify genetic variation, respectively, associated with (a) TRD and (b) PTSD. It was hypothesized that both TRD and PTSD would be moderately heritable and that genetic loci of interest would be identified for each phenotype.

Aim 3b sought to examine molecular overlap between TRD and PTSD via cross-trait LDSC and PRS analyses. PRSs were calculated using the summary statistics (*p*-values and coefficients) generated from the Freeze 2 PTSD PGC data (Nievergelt et al., 2018), which is the most highly powered GWAS for PTSD to date (>32,000 cases and >170,000 controls), and was used to assess whether overall molecular risk for PTSD (via PRS) predicted both TRD and PTSD in the present sample. It was expected that TRD and PTSD would demonstrate shared heritable influences and that genetic risk for PTSD from the PGC would significantly predict both TRD and PTSD in the present sample.

Method

Overview of Study Samples

Parent Study Participants and Recruitment: S4S

The present sample was obtained by leveraging a larger, ongoing cohort study from a large urban university that began in 2011 and includes comprehensive genotyping on all willing participants (Spit for Science [S4S]; NIAAA-R37 AA011408). The primary aim of the S4S study is to delineate how genetic and environmental factors contribute to the development of problems associated with use of alcohol and difficulties with emotional health, as youth transition into college life. Each year, freshman from a large Mid-Atlantic university, age 18 or older, are eligible to participate in an online survey. There were four cohorts at the time of recruitment for the present study. Of the 14,959 individuals who were eligible to complete the study's baseline fall assessment, 9,889 participated (cohort 1 entering college in 2011 [n = 2,707], cohort 2 entering college in 2012 [n = 2,481], cohort 3 entering college in 2013 [n = 2,391], cohort 4 entering college in 2014 [n=2,310]). Of these, 38.2% were male, 61.1% were female, and 0.7% declined to identify sex. The sample reflected the population from which it

was drawn: 49.4% White, 18.9% African-American, 16.3% Asian, 6% Hispanic/Latino, and 9.4% other/multi-race/unknown/declined to respond. The average age at baseline assessment was 18.5 years. Those who completed the baseline survey were subsequently invited via email to complete a follow-up assessment between weeks 7 and 14 of the spring semester of their freshman year. Of those who completed the baseline assessment and who were still enrolled at the University, 4,820 also completed the follow-up assessment (59% retention). Individuals were invited to complete a survey during the spring of each subsequent year, even following graduation. For detailed parent study methods, see Dick et al. (2014). Of those individuals who were interviewed in fall of their freshman year, there were no differences between those who were and were not retained in spring of their senior year on race. However, those who were retained more likely to be slightly younger (18.49 versus 18.55, t=5.263, p<.001; Cohen's d: .14) and female (65.8%) compared to those who were not retained (61.6%, χ^2: 4.593, p<.05; Cramer's V: .08). As these effects are small, there is less concern about differences between those retained and not retained. All enrolled participants become part of the S4S registry, are invited to participate in subsequent yearly spring follow up surveys (even post-graduation), and are eligible for spin-off studies.

Parent Study Measures: S4S

Trauma Screening Instrument

Trauma exposure was assessed in the S4S parent study via an abbreviated version of the Life Events Checklist (Gray, Litz, Hsu, & Lombardo, 2004a), which asked participants to report on the occurrence of four different stressful events (i.e., natural disasters, physical assaults, sexual assaults, and transportation accidents). Participants indicated whether they had experienced each event, witnessed the event happening to someone else, or learned about the

event happening to someone close to them. This measure has demonstrated strong interrater (kappa = .61) and test-retest reliability (r = .82, p < .001) (Gray et al., 2004).

Measure Specific Use in Analyses: Responses were used to assess eligibility for participation in the present study by computing a dichotomous trauma exposed versus not trauma exposed variable.

Probable PTSD

If a participant endorsed at least one item on the Life Events Checklist (see above) or at least one item from another instrument assessing additional stressful events (e.g., broken engagement, housing difficulties; Kendler, Karkowski, & Prescott, 1999), they were asked to respond to one of two probable PTSD screeners. Cohorts 1-4 were administered a one item PTSD screener, an abbreviated version of the Primary Care PTSD Screen (PC-PTSD; Prins et al., 2003). The PC-PTSD is a screening instrument with four "Yes/No" items, each representing one of the three *DSM-IV* (Association & Association, 2000) PTSD symptom clusters, with avoidance and emotional numbing separated out into two separate items. The abbreviated screener consisted of one "Yes/No" item, which asked whether the participant had experienced nightmares, attempts to avoid thoughts or reminders of the potentially traumatic experience, hypervigilence, and feelings of detachment. Endorsement of this item was used as indication of a positive lifetime history of probable PTSD. This abbreviated PTSD assessment was administered as part of the year 1 fall survey for cohorts 1-3, year 1 spring survey for cohorts 1-4, year 2 spring survey for cohorts 1-3, year 3 spring survey for cohorts 1-2, and year 4 spring survey for cohort 1. Beginning in 2014 with cohort 4, the full PC-PTSD was administered in order to obtain more comprehensive information with regard to probable PTSD. The full PC-PTSD was administered as part of the year 1 fall and year 2 spring surveys for cohort 4, the year

3 spring survey for cohorts 3-4, and the year 4 spring surveys for cohorts 2-3. Please see Figure 5 for reference.

Measure Specific Use in Analyses: The complete four-item PC-PTSD was used as the independent (time point 1) variable in the longitudinal analysis of the self-medication model (Aim 2).

Alcohol Use and Related Problems

A single item queried whether participants had ever consumed alcohol. Participants who reported having ever consumed alcohol were asked items related to DSM-5 (Association, 2013) AUD criteria (e.g., "Have you ever started drinking and become drunk when you didn't want to?"), with some criteria assessed using multiple items. Criteria were assessed at each time point beginning with the first follow-up survey of cohort 1 (DSM-5 had not yet been published at the time of the cohort 1 initial survey) and all surveys for cohorts 2-4. Language was modified to make the items appropriate for the participants in accordance with IRB guidelines that the language be written at a 10th grade reading level. For all but 2 items, response options were "never," "1–2 times," or "3 or more times," which were scored 1, 2, and 3, respectively. These items were then recoded as 0 or 1 to indicate whether the criterion had been met at least once (no or yes) or three or more times (no or yes) in the past year. Items addressing craving and tolerance had response options of "no" and "yes," coded 0 and 1, respectively.

An AUD count variable for symptoms met at least once in the past 12 months was derived. Given that the sample was comprised of emerging adults, a developmental period which typically precedes the average age of onset for a formal AUD (Grant et al., 2015a), the AUD count variable for symptoms met at least once in the past year was created in an effort to capture subthreshold alcohol-related consequences. Sum scores were created using a missing

data threshold, such that scores were only computed for individuals with data on 6 or more items. Participants were given the option of skipping questions.

Measure Specific Use in Analyses: Any endorsement of lifetime alcohol use deemed participants eligible for participation in the present study. The AUD criterion count variable assessed during the spring of 2017 (year 6, 5, 4, and 3 spring surveys for cohorts 1, 2, 3, and 4, respectively) was included as the outcome variable (time point 3) in the longitudinal analysis of the self-medication model (Aim 2). The AUD criterion count variable assessed at earlier timepoints was included as a covariate at time points 1 and 2 in the longitudinal model to control for previous AUD symptoms (Aim 2). Spring 2018 data was not available at time of analysis. Please see Figure 5 for reference.

DNA Collection and Genotyping

Participants were given the option to provide saliva samples for genotyping (for details, see Webb et al., 2017). DNA was collected via an Oragene kit and isolated via standard procedures. Samples from cohorts 1-3 were genotyped on the Axiom BioBank Array, Catalog Version 2. The array is designed to assay 653K SNPs and InDels including a) 296K common variants that serve as grid for imputation and genome wide association scans and b) 357K likely functional variants from exome studies including non-synonymous, loss of function, known disease, splice altering, eQTL, and pharmacogenetics-related loci. Many of the 'functional' variants are low allele frequency. Therefore, the array allows testing of both common and rare variants. Samples from cohort 4 were completed using the Smokescreen Genotyping Array at RUCDR Infinite Biologics (Piscataway, NJ). The Smokescreen Genotyping Array is a custom array designed to cover SNPs (646,247), genes (n=1,014), and indels related to addiction and smoking-related phenotypes. It covers both common and rare variation and is designed for

African, East Asian, and European populations. The Axiom BioBank Array and Smokescreen Genotyping Array are compatible with one another, enabling imputation of all cohorts to a common 1000 Genomes platform.

Empirical ancestry assignment occurred using genetically informative principal component analysis (PCA). Ancestry principal components (PCs) were estimated using 1000 genomes phase 3 (1KGP; 2,504 samples, 26 populations; Sudmant et al., 2015) as an external reference panel. EIGENSOFT and SmartPCA (Patterson, Price, & Reich, 2006; Price et al., 2006) were used to perform PCA using the 1KGP phase 3 reference panel to determine SNP weights for each eigenvector. This solution was then projected onto the S4S data to generate 10 PCs. Reference population outliers (>4 SD from population median, n=61) were identified by calculating Mahalanobis distance and removed. Following, each S4S sample was assigned to the 1KGP population with the minimum Mahalanobis distance. The S4S samples were then collapsed into their respective super-population assignment. For a more detailed explanation of these methods, please see Peterson et al. (2017). Genotypic data were used in Aim 3 analyses.

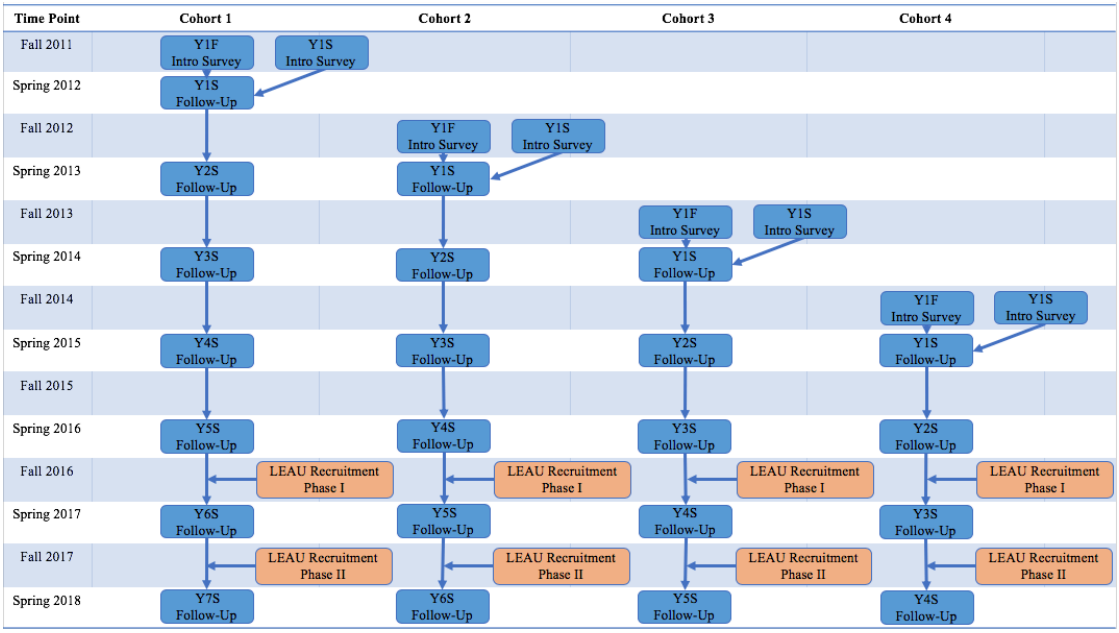

Figure 5. *S4S/LEAU Recruitment Timeline*

Present Study Sample: LEAU

Of the individuals in cohorts 1-4 of the parent study, 7,423 were contacted about participating in a spin-off study, Life Events and Alcohol Use (LEAU; P50AA022537, PI: Amstadter, F31AA025820, PI: Hawn), because they met the following study inclusion criteria: had endorsed at least one lifetime traumatic event during a prior S4S survey (82.8% of total S4S sample) and reported any lifetime alcohol use on a prior S4S survey (88.7% of total S4S sample). The intention of the LEAU survey was to gather more in-depth information about participant PTSD symptoms, trauma history, and trauma-related drinking to cope. Of the 7,423 who were contacted, 2,175 (29%) expressed an interest in participating in this spin-off study and were emailed a survey link to be completed via REDCap (Harris et al., 2009). Of these students, 1,901 (87.4%) enrolled in LEAU. Of all eligible individuals who were contacted regarding participation in LEAU, a significantly higher proportion of those who actually enrolled in LEAU were female (70.18% vs. 61.86%; χ^2=42.139, p<.001; Cramer's V: .08), Asian (28.31%) or

White (23.98%; χ^2=17.530, *p*=.014; Cramer's V: .05), and had endorsed probable PTSD, according to the 1 or 4 item versions of the PC-PTSD screener (28.17% with probable PTSD vs. 22.92% without; χ^2=26.642, *p*<.001; Cramer's V: .06). Additionally, compared to eligible individuals who did not participate, enrolled individuals endorsed significantly higher lifetime traumatic events (*t*=-10.081, *p*<.001; Cohen's d: 0.26), drinking to cope motives (*t*=-7.025, *p*<.001; Cohen's d: 0.19), and AUD symptoms met at least once in the past year (*t*=-4.737, *p*<.001; Cohen's d: 0.13) at any time point. Again, given these are small effects, there is less concern about differences between individuals who did and did not participate. Eligible participants who enrolled, versus those who did not, did not differ significantly according to trauma type (interpersonal [χ^2=0.976, p=0.323] or accidental [χ^2=2.978, *p*=0.084]) or max alcohol consumption (*t*=-2.557, *p*=0.110).

The LEAU survey took approximately 20 minutes to complete, after which participants were given the option to collect $20 compensation via cash in person or electronically via Amazon. The majority of students (60%) preferred to be compensated via cash. Of the 1,901 participants who enrolled, 1,848 completed the survey in full (2.8% began but did not complete the entire survey). The present sample (N=1,896) included LEAU participants who had available data on at least some measures of interest. Of these, 70.18% identified as female. Consistent with the parent study, the LEAU sample was generally representative of the overall university population from which it was recruited with regard to race (49.33% White, 20.00% Black/African American, 16.43% Asian, 5.81% Hispanic/Latino, and 8.43% "Other" or multiracial). There were no differences between those in the larger parent study who were and were not included in LEAU on race. However, those included in LEAU were slightly younger (18.46 vs. 18.51, *t*=4.43, p<.01; Cohens d: .14) and were more likely to be female (70.18% vs.

59.45%; χ^2=74.226, p<.001; Cramer's V: .09) compared to the overall S4S sample. As previously stated, these effects, though significant, were very small and likely not meaningful.

Present Study Measures: LEAU

Trauma Exposure

Trauma history was obtained in LEAU via the Traumatic Life Events Questionnaire (TLEQ; Kubany et al., 2000), a comprehensive assessment of potentially traumatic events. The TLEQ is a 23-item self-report measure which assesses whether and when participants experienced a range of potentially traumatic events (e.g., natural disaster, assault, accidents, illness/injury) and how many times each traumatic event occurred (i.e., allows for calculation of a comprehensive lifetime trauma count for each participant). In addition, for each trauma endorsed, *DSM-IV* PTSD Criterion A1 (i.e., life threat) and A2 (i.e., peritraumatic emotional response of fear, helplessness or horror) were assessed. The TLEQ has evidenced good test-retest reliability (average of 83% agreement across traumas) and good convergent validity with interview assessments of trauma exposure (Kubany et al., 2000).

Measure Specific Use in Analyses: A lifetime trauma load variable was created by summing the frequency endorsements for each trauma included in the TLEQ, which was included as a covariate in analyses for Aims 1 and 2. A dichotomous trauma type variable was also created to reflect endorsement status of having ever experienced an interpersonal (i.e., combat, sudden or unexpected death of a loved one, life-threatening or permanently disabling accident experienced by a loved one, robbery, physical assault, witnessing physical assault, threatened with death or serious physical harm, childhood physical abuse, family and domestic violence, childhood sexual abuse, adult sexual assault, unwanted sexual experience, and stalking) or other (i.e., natural disaster, motor vehicle accident, other accident, miscarriage, abortion, life-

threatening illness, other) type of trauma. This trauma type variable was included as a covariate in Aim 2 analyses.

PTSD

Presence of PTSD symptoms in the past 30 days was assessed using the PTSD Checklist-5 (PCL-5; Weathers et al., 2013). The PCL-5 is a 20-item questionnaire, corresponding to the *DSM-5* symptom criteria for PTSD. The self-report rating scale is 0-4 for each symptom, ranging from "Not at all" to "Extremely". A total symptom severity score (range 0-80) can be obtained by summing the scores for each of the 20 items. The PCL-5 has demonstrated good test-retest reliability (r = .82), and convergent (r's = .74 to .85) and discriminant (r's = .31 to .60) validity (Blevins, Weathers, Davis, Witte, & Domino, 2015). Cronbach's alpha calculated from the LEAU sample suggested high internal consistency (.96).

Measure Specific Use in Analyses: Item level data were used for the structural equation modeling (SEM) analyses in Aim 1. A continuous symptom severity score for PTSD was calculated by summing response items from the PCL-5. A PCL-5 cutoff score of 33 (Bovin et al., 2016) was used to determine PTSD caseness (Aim 1). PCL-5 total score was used as the outcome variable in Aim 2 analyses, as well as the quantitative measure of PTSD in the genetic analyses (Aim 3).

Alcohol Consumption and Related Consequences

Participants reported on their past year alcohol use with ordinal frequency an quantity items from the Alcohol Use Disorders Identification Test (AUDIT), which is a 10-item screening measure developed by the World Health Organization to identify individuals with alcohol problems (Babor, De La Fuente, Saunders, & Grant, 1992). The AUDIT assesses alcohol consumption as well as alcohol-related problems (e.g., consequences related to drinking). There

is a large body of literature attesting to the psychometric properties of the AUDIT (e.g., Saunders, Aasland, Babor, De la Fuente, & Grant, 1993). The AUDIT evidenced good internal consistency in the present sample (α=.82).

Measure Specific Use in Analyses: Item level data were used for the SEM analyses in Aim 1. A continuous symptom severity score for alcohol use problems were calculated by summing response items from the AUDIT. The AUDIT total score, which embodies quantity/frequency of alcohol consumption as well as related-problems, will heretofore be referred to as alcohol use problems (AUP). Past work has indicated that AUDIT total scores of 8 or more are recommended as indicators of hazardous and harmful alcohol use, as well as possible alcohol dependence. Therefore, an AUDIT cutoff score of 8 was used to determine AUP caseness (Aim 1). AUDIT total score was used as the outcome variable in Aim 2 analyses.

General Drinking to Cope Motives

General drinking to cope motives were assessed via the coping subscale of the Drinking Motives Questionnaire-Revised (DMQ-Cope; Cooper, 1994). Participants are asked to rate the frequency of drinking for each of the listed motives on a 1 to 5 scale, on which 1 equals "almost never/never" and 5 equals "almost always". The DMQ-Cope has demonstrated strong test-retest reliability (ICC=.80; Cheng, Phillips, Zhang, & Wang, 2016) and evidenced excellent internal consistency within LEAU (α=.88).

Measure Specific Use in Analyses: Item level data were used for the SEM analyses in Aim 1. Response items from the DMQ-Cope measure were summed to create a continuous score (Aim 2).

Trauma-Related Drinking to Cope

A trauma-related drinking to cope (TRD) measure was created for and administered as part of the LEAU study. Using the same response options from the DMQ-R (i.e., 1 [“almost never/never”] to 5 [“almost always”] Likert scale), frequency of alcohol use to cope with symptoms specific to each PTSD cluster (i.e., re-experiencing [e.g., repeated, disturbing dreams of the traumatic event], avoidance [e.g., avoiding memories, thoughts, or feelings related to the trauma], negative cognitions and mood [e.g., anhedonia] , and arousal [e.g., hypervigilance]) was assessed. Cronbach’s alpha calculated from the LEAU sample suggested the TRD items demonstrated high internal consistency (.88). The TRD screen is presented in Table 1.

Measure Specific Use in Analyses: Item level data were used for the SEM analyses in Aim 1. Response items from the TRD measure were summed to create a continuous score, which was used as the outcome variable in Aim 2 analyses, as well as the quantitative measure of TRD in the genetic analyses (Aim 3).

Table 1.

Trauma-Related Drinking to Cope Questionnaire

How often do you drink alcohol to cope with symptoms including					
	Almost never/ Never	Some of the time	Half of the time	Most of the time	Almost always/ always
Repeated, disturbing, unwanted memories, dreams, or feelings about the stressful experience?	1	2	3	4	5
Avoiding memories, thoughts, feelings, or external reminders of the stressful experience?	1	2	3	4	5
Strong negative beliefs about yourself or the world; feelings of blame, shame, or guilt; loss of interest in activities you used to enjoy; feeling distant or cut off from other people; or trouble experiencing positive feelings?	1	2	3	4	5
Irritability, anger, risk-taking, alertness, jumpiness, difficulty concentrating, or difficulty sleeping?	1	2	3	4	5

Data Analytic Plan

Data Checking

Variables were examined for distributional assumptions prior to analysis. The TRD composite score was significantly skewed (2.68) and kurtotic (7.92) and was therefore log transformed. This score showed improvement in skew (1.78) and kurtosis (2.46), and thus was

used in analyses including the TRD composite score. Lifetime trauma load was also skewed (2.52) and kurtotic (12.00) and was log transformed. This score showed improvement in skew (-.218) and kurtosis (-.648) and was used as a covariate in the mediation analyses (Aim 2). In order to reduce non-essential multicollinearity and increase interpretability of findings (Cohen, 2003), all continuous predictors were centered prior to conducting analyses.

Formatting Note

Due to the computationally complex nature of the analyses, the data analytic plan and relevant results section will be presented separately by aim.

Aim 1: Psychometric Evaluation of TRD

Aim 1 Analytic Plan

Aim 1a. Assess Distributional Properties of TRD, as Compared to DMQ-Cope, and Test Omnibus Differences Between PTSD and at AUP Cases Versus Controls

Descriptive analyses were conducted in R 3.4.4 (Team, 2018). Descriptive statistics (e.g., item category endorsement rates, frequency distributions) were examined for TRD and compared to those for DMQ-Cope. Additionally, frequency distributions for TRD and DMQ-Cope based PTSD diagnostic status and AUP cut-offs were compared. Correlational, chi-square, and t-test analyses were conducted to examine how TRD relates to relevant demographic variables (e.g., sex, race/ethnicity), trauma type, trauma load, DMQ-Cope, PTSD symptoms, and AUP.

Aim 1b. Assess TRD Factor Structure, Determine How it Relates to DMQ-Cope Factor Structure, and Compare How the Two Factor Structures Relate to PTSD

Structural equation modeling (SEM) analyses were performed using M*plus* 8.0 software (Muthén & Muthén, 2017). SEM was used as the primary model building framework to evaluate the TRD items. Given the Likert-type response coding of the TRD, DMQ-Cope, PCL-5, and AUDIT, all item-level variables were treated as ordinal variables in the models. These models introduce latent response variables for each measured item upon which thresholds are estimated distinguishing between the observed categories. The factor models are then fit to the estimated matrix of polychoric correlations, used to measure agreement between ordinal data, among these latent item response variables. This approach mitigates issues of attenuation, whereby correlation coefficients are poorly estimated due to measurement error (Lavrakas, 2008), as is

often the case when using Pearson Product Moment correlations with poorly distributed ordinal variables (e.g., strong positive skewness).

Confirmatory factor analyses (CFA), a form of latent variable modeling, were used to first evaluate the factor structures for the TRD, DMQ-Cope, PCL-5, and AUDIT ordinal item sets. The common factor model is a measurement model that is often used to test for the dimensionality of a set of items developed as indicators of a target construct of interest (DeCoster, 1998). It decomposes the associations among the items into common/shared and item specific latent components, while accounting for random error. Initial CFA models specifying a single factor were fit to each of the instrument item sets to test whether a unidimensional structure was plausible. Poor fit for unidimensional models would suggest there is evidence for multidimensionality and imply more diverse measurement models are needed to adequately account for the associational patterning among the items.

First, TRD and DMQ-Cope were examined as independent common factor models. Second, although a number of different factor structures have been reported for the PCL-5 (Ayer et al., 2011), our CFA modeling followed previous literature (Blevins et al., 2015; Hurlocker, Vidaurri, Cuccurullo, Maieritsch, & Franklin, 2018), which found evidence supporting a 4-factor solution (intrusion, avoidance, alterations in cognition and mood, alterations in arousal and reactivity. The PCL-5 4-factor was compared to a common factor model. Due to the Likert-type ordinal coding of all the items, a limited information weighted least squares mean and variance (WLSMV) adjusted robust estimator was used. The WLSMV robust estimator does not assume normally distributed variables and is well suited for modelling ordinal data (Brown, 2014).

To examine the relationship between TRD and DMQ-Cope, a correlated two-factor model was fit to the TRD and DMQ-Cope item measurement models respectively (Model 1).

Following, both the TRD common factor and DMQ common factor were regressed onto the four oblique PCL-5 common factors in the same model, allowing the TRD and DMQ common factors to correlate (Model 2). Given the previously reported effects of sex and lifetime trauma load on PTSD, the PCL-5 factors were conditioned on the covariates of sex and lifetime trauma load in Model 2.

Multivariate tests of equivalence. A multivariate test of equivalence of the prediction path coefficients was performed to test whether the 4 PCL-5 factors differentially predict variation in the TRD and DMQ-Cope common factors. To evaluate such a test of equivalence, two models are fit and compared. The first model is an unrestricted model allowing path coefficients to be freely estimated. A second restrictive model is then fit that imposes the constraints that the regression coefficients are forced to be invariant within each set of predictions. The restricted model is nested under the unconstrainted model, so a chi-square difference test can be performed to determine whether the restricted model is a statistically significant poorer fit to the data than is the unconstrained model. The difference in degrees of freedom can be used to test this model comparison. For evaluating nested model comparison tests, the adjusted chi-square DIFFTEST feature of M*plus* was used. Here, the adjusted p-value is of primary interest, but the actual chi-square value from the DIFFTEST procedure, although reported, is not informative.

Since the equality constraints involve forcing the magnitudes of the estimated path coefficients to be equal across the correlated PCL factor predictors, for such a test to be meaningful, a common reference unit of measurement is needed. In this application, the PCL-5 common latent factor means and variances were fixed to 0 and 1, respectively, in order to establish a common metric for testing and interpreting the results. In other words, the PCL-5 factor unit is a common standard deviation unit for all PCL-5 factors, and the regression

coefficient magnitudes are in a metric that can be directly compared (i.e., a unit standard deviation change on the latent PCL factor for the corresponding fractional change on the regressed outcomes [e.g., TRD vs. DMQ-Cope common factors]). This not only provides a basis for performing a meaningful comparison of the fitted restricted and unrestricted models but also makes possible an interpretable comparison of the patterning of estimated path coefficients.

Aim 1c. External Validation of TRD in Relation to PTSD

Given our interest in determining how PTSD symptom factors influence motives to use alcohol to cope with said symptoms (TRD), the four oblique PCL-5 common factors were first specified as predictors of each of the TRD items individually while allowing the TRD items to be correlated (Model 3). This structural model provides information about whether and how the PCL-5 factors differentially predict each of the TRD items. A multivariate test of the equivalence of the prediction path coefficients was performed within the full structural model.

Next, the four oblique PCL-5 common factors were used to predict the single TRD latent factor (Model 4). Sex and lifetime trauma load were again included as covariates predicting PCL-5 factors in Models 3 and 4. Once again, a multivariate test of the equivalence of the prediction path coefficients was performed within the full structural model to determine whether the 4 PCL-5 factors differentially predict variation in the TRD latent factor.

Aim 1d. External Validation of TRD in Relation to Alcohol Consumption and Related Problems

CFA modeling for the AUDIT also followed previous literature (e.g., Chung, Colby, Barnett, & Monti, 2002; Doyle, Donovan, & Kivlahan, 2007; Maisto, Conigliaro, McNeil, Kraemer, & Kelley, 2000; Pahlen et al., 2008), which has presented evidence of a best fitting 2-factor model (alcohol consumption and alcohol dependence/consequences). Consistent with the other CFA models, item level responses were treated as ordinal variables Given that our interests

were not only in determining how PTSD symptoms may influence TRD but also how TRD may influence alcohol use, we completed our conceptual model by regressing the TRD factor onto the four oblique PCL-5 common factors as before, as well as regressed the two common factors for the AUDIT onto the TRD factor (Model 5). Given their previously reported effects on PTSD and alcohol use, sex and lifetime trauma load were retained as predictors of both the PCL-5 and AUDIT common factors. A multivariate test of the equivalence of the prediction path coefficients was performed within the full structural model to determine whether the TRD latent factor differentially predicts variation in the 2 AUDIT factors.

Aim 1 Results

Aim 1a: Assess Distributional Properties of TRD, as Compared to DMQ-Cope, and Test Omnibus Differences Between PTSD and at AUP Cases Versus Controls

Relevant Descriptive and Distributional Properties of TRD, as Compared to DMQ-Cope. Descriptive statistics are provided in Table 2, for the full sample as well as for individuals with and without PTSD. The average total scores for TRD, DMQ-Cope, PCL-5, AUDIT, and lifetime trauma load were all significantly higher among individuals exceeding the suggested PCL-5 diagnostic cutoff for PTSD (n = 286; 15.77%) compared to those who did not exceed the threshold. Correlational analyses are provided in Table 3. All study constructs were significantly associated. Notably, TRD and DMQ-Cope were moderately correlated but not multicollinear (r = .60, p<.001). Consistent with the hypothesis that TRD would demonstrate greater specificity compared to DMQ-Cope, whereas an overwhelming majority (72.96%) of participants in the sample endorsed at least some level of drinking to cope per the DMQ-Cope, only around one-third (34.71%) of participants endorsed at least some level of TRD. Comparatively, 40.85% of individuals with at least some symptoms of PTSD (versus no

symptom endorsement) per the PCL-5 (*N*=1523; 82.55% of LEAU sample with available PCL-5 data [*N*=1845]) endorsed at least some level of TRD. Similarly, histograms (Figure 6) revealed that DMQ-Cope was normally distributed, unlike the un-transformed TRD measure, which was positively skewed (2.68) and kurtotic (7.92).

Omnibus Differences Between PTSD and AUP Cases Versus Controls. Results supported the study hypothesis that TRD would be higher among PTSD cases compared to controls (Table 2). Well over half (66.20%) of individuals with suggested PTSD, per the PCL5 cutoff, endorsed at least some level of TRD. Additionally, the distributions of TRD and DMQ-Cope among individuals exceeding the PCL-5 PTSD diagnostic cutoff were substantially more dispersed compared to individuals who did not exceed the cutoff (Figure 7). A similar pattern of findings was seen with the AUDIT (Figure 8), wherein TRD and DMQ-Cope scores were notably more dispersed among AUP cases (*n* = 677; 35.80%) compared to those who did not.

TRD in Relation to Relevant Variables and How it Compares to DMQ-Cope. Unlike PTSD and AUDIT symptom severity, which significantly differed by sex, wherein women endorsed significantly higher levels of PTSD symptoms overall compared to their male counterparts (t=-6.35, p<0.001) and men endorsed significantly higher AUDIT levels compared to females (t=4.35, p<0.001), average TRD did not differ significantly with regard to sex or race (see Table 3). However, endorsement of specific TRD items (each representing one of the four PTSD symptom clusters) did differ significantly by sex. Although a higher proportion of endorsement was demonstrated among women across all four items, this difference was significant for the avoidance (24% vs 19%; χ^2=4.82, p=.03) and negative cognition and mood (25% vs 21%; χ^2=4.14, p=.04) items (Figure 9). This is somewhat consistent with findings relating to PTSD, wherein women endorsed significantly higher symptoms across each of the

four symptom clusters compared to men (p's < 0.001; Figure 10). There were no significant mean differences between sexes across any TRD items and, like TRD, mean differences in DMQ-Cope did not differ by sex.

Correlation tables comparing associations between PTSD symptom cluster count and TRD and DMQ-Cope and frequency endorsement of various trauma types and TRD and DMQ-Cope are presented in Tables 4 and 5, respectively. Correlation coefficients were higher between all PTSD symptom clusters and trauma types and TRD compared to DMQ-Cope. The only correlation coefficient that was higher for DMQ-Cope compared to TRD was that with AUDIT total score. Lastly, individuals endorsing TRD reported significantly higher lifetime trauma load (M = 13.27, SD = *11.89*) compared to individuals who did not endorse TRD (M=7.76, SD=*7.16*; t=-10.32, p < .001).

Table 2.

Descriptive Information on Study Constructs

	Full Sample			Non-PTSD			PTSD			
Variable	Mean (SD)	Skew	Kurtosis	Mean (SD)	Skew	Kurtosis	Mean (SD)	Skew	Kurtosis	*t*
TRD (Range: 4-20)	5.27 (2.51)	2.68	7.92	4.74 (1.55)	3.07	13.83	7.95 (4.15)	0.81	-0.41	-12.88***
DMQ-Cope (Range: 5-25)	8.63 (4.10)	1.60	5.52	8.05 (3.48)	1.68	3.34	11.65 (5.26)	0.69	-0.52	-10.59***
PCL-5 (Range: 0-80)	15.23 (17.03)	1.37	4.37	8.92 (8.92)	0.88	-0.35	47.74 (11.55)	0.75	-0.40	-53.91***
AUDIT (Range: 0-37)	7.00 (5.26)	1.42	5.66	6.62 (4.77)	1.34	2.44	8.97 (6.84)	1.06	0.89	-5.55***
Trauma Load (Range: 0-94)	9.74 (9.5)	2.49	11.05	8.19 (7.40)	1.79	4.03	17.16 (14.12)	2.00	6.24	-10.34***
Log TRD	1.59 (0.34)	1.78	2.46	--	--	--	--	--	--	
Trauma Log	1.85 (0.98)	-0.22	-0.59	--	--	--	--	--	--	

Note: TRD = Trauma-Related Drinking to Cope; DMQ-Cope = Drinking Motives Questionnaire Coping subscale; PCL-5 = Posttraumatic Stress Disorder Symptom Checklist, DSM-5; AUDIT = Alcohol Use Disorders Identification Test

Table 3.

Correlation Table and Group Comparisons of Study Constructs

Variable	1	2	3	4	5	SEX *t-test*	RACE[#] *t-test*
1. TRD	1.00	--	--	--	--	-1.57	[1-4] NS
2. DMQ-Cope	0.60***	1.00	--	--	--	-0.90	[1]3.07** [2-4] NS
3. PCL-5	0.56***	0.42***	1.00	--	--	4.35***	[1-4] NS
4. AUDIT	0.44***	0.48***	0.22***	1.00	--	-6.35***	[1]4.38*** [2]4.18*** [3-4] NS
5. TRAUMA LOAD	0.35***	0.24***	0.43***	0.19***	1.00	-5.81***	[1]-2.19* [2]5.86*** [3]NS [4]-2.02*

Note: TRD = Trauma-Related Drinking to Cope; DMQ-Cope = Drinking Motives Questionnaire Coping subscale; PCL-5 = Posttraumatic Stress Disorder Symptom Checklist, DSM-5; AUDIT = Alcohol Use Disorders Identification Test; *** $p < .001$, ** $p < .01$, * $p < .05$; [#]Race was dummy coded to represent [1]White vs. Black, [2]White vs. Asian, [3]White vs. Hispanic/Latino, and [4]White vs. Other; NS = not significant

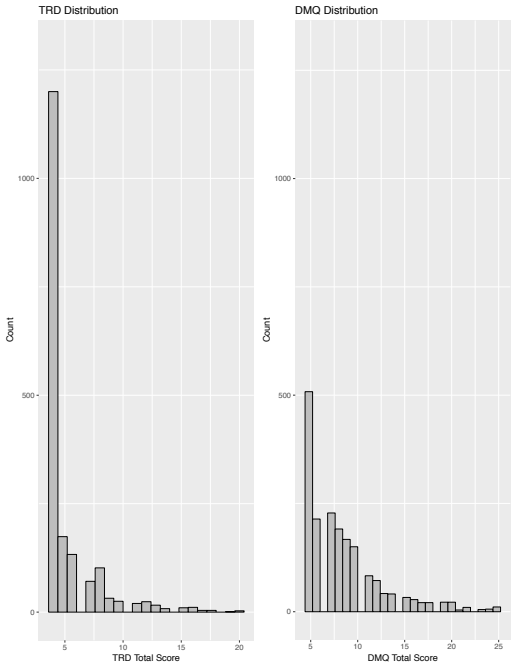

Figure 6. *TRD vs. DMQ-Cope Frequency Distributions*; Note: TRD = Trauma-Related Drinking to Cope; DMQ-Cope = Drinking Motives Questionnaire Coping subscale

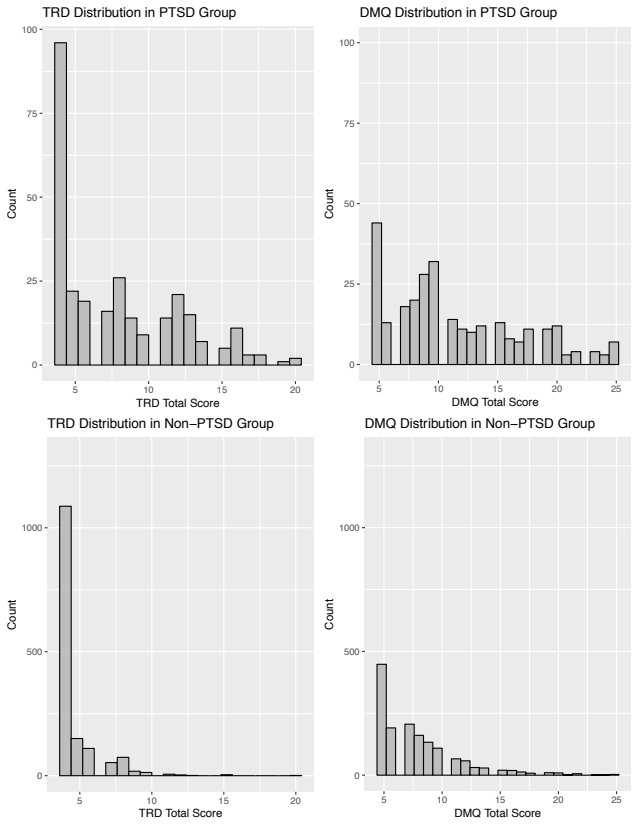

Figure 7. *TRD vs. DMQ-Cope Frequency Distribution by PTSD Diagnostic Cutoff*; Note: TRD = Trauma-Related Drinking to Cope; DMQ-Cope = Drinking Motives Questionnaire Coping subscale; PTSD = Posttraumatic Stress Disorder

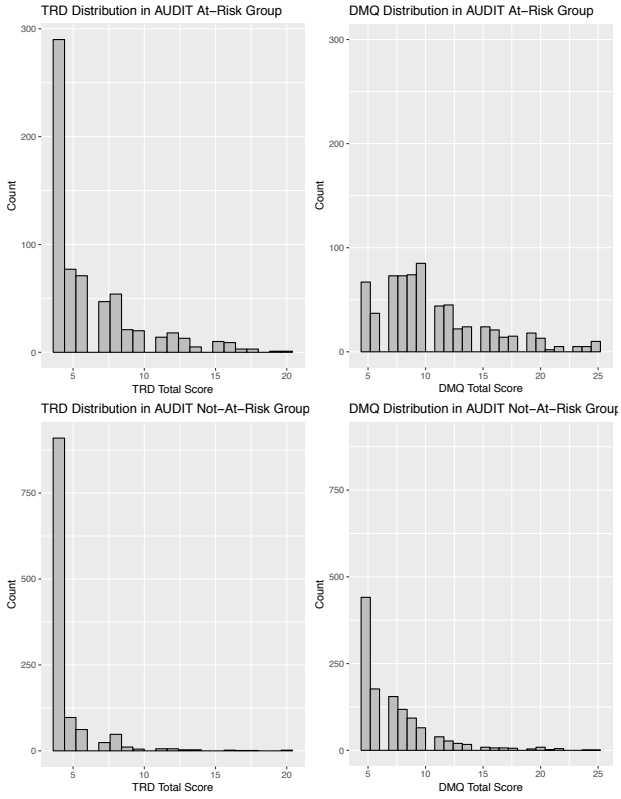

Figure 8. *TRD vs DMQ-Cope Frequency Distribution by AUP Caseness*; Note: TRD = Trauma-Related Drinking to Cope; DMQ-Cope = Drinking Motives Questionnaire Coping subscale; AUP = Alcohol Use Problems

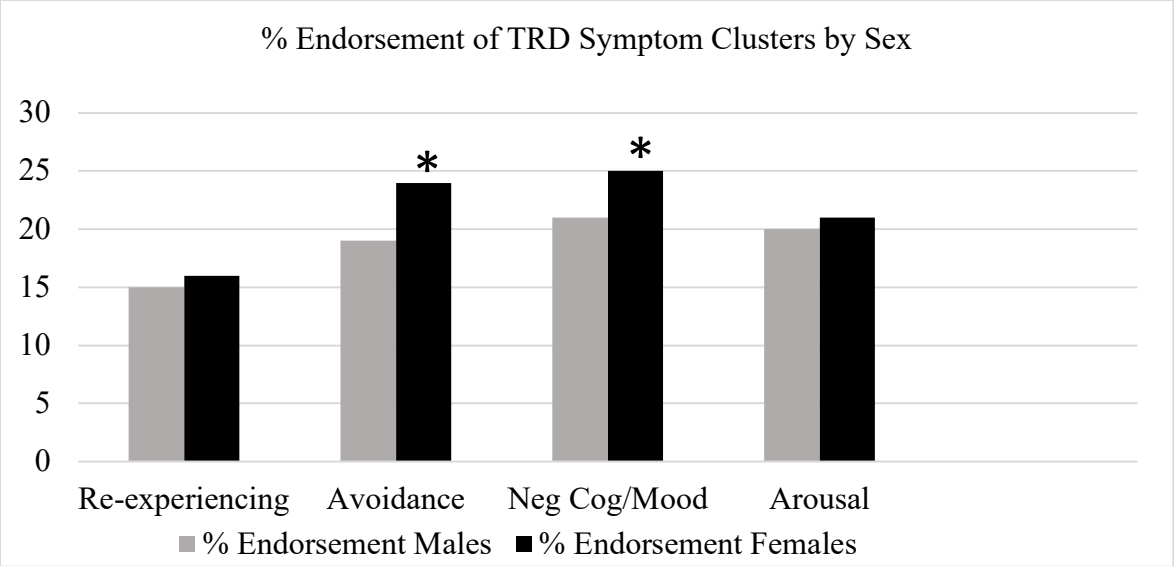

Figure 9. *TRD Item Endorsement by Sex*; Note: TRD = Trauma-Related Drinking to Cope; Neg Cog/Mood = Alterations in negative cognitions and mood

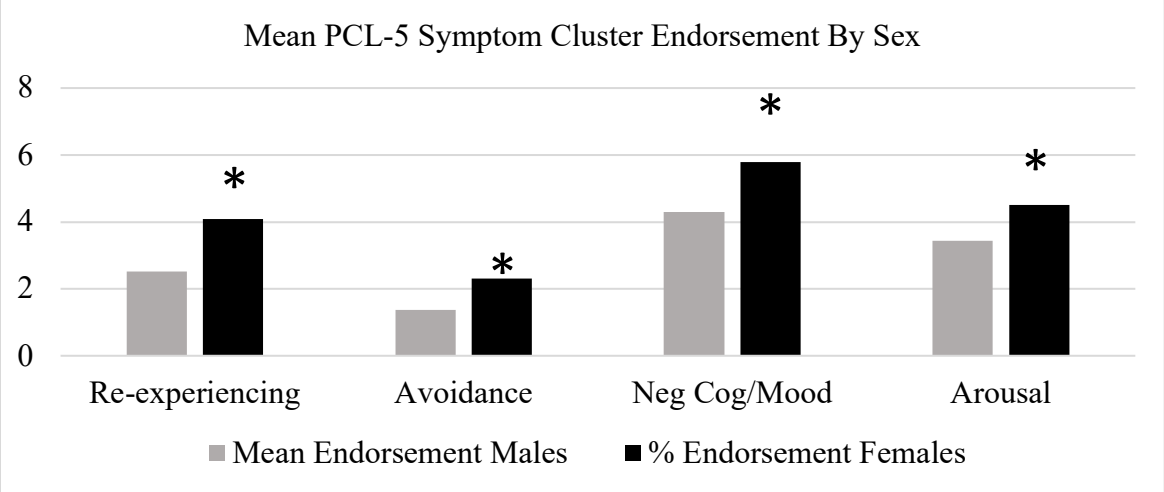

Figure 10. *PTSD Symptom Clusters by Sex*; Note: TRD = Trauma-Related Drinking to Cope; PCL-5 = Posttraumatic Stress Disorder Symptom Checklist, DSM-5; Neg Cog/Mood = Alterations in negative cognitions and mood

Table 4.

Associations Between PTSD Symptom Clusters and Constructs of Interest

	TRD	**DMQ-Cope**	**AUDIT**
AUDIT	.44***	.48***	--
PCL-5 symptom total	.56***	.42***	.22***
Intrusion symptoms	.48***	.33***	.18***
Avoidance symptoms	.43***	.32***	.16***
Negative Cognitions	.53***	.40***	.20***
Arousal symptoms	.55***	.43***	.24***

Note: TRD = Trauma-Related Drinking to Cope; DMQ-Cope = Drinking Motives Questionnaire Coping subscale; PCL-5 = Posttraumatic Stress Disorder Symptom Checklist, DSM-5; AUDIT = Alcohol Use Disorders Identification Test; *** $p < .001$

Table 5.

Associations Between Trauma Load and Type and Constructs of Interest

	TRD	**DMQ-Cope**
Trauma Load	.35***	.24***
IPV	.35***	.27***
Other (non-IPV)	.15***	.04
Overall SA	.30***	.26***
Childhood SA	.21***	.16***
Adult SA	.27***	.26***
Overall PA	.19***	.12***
Childhood PA	.55***	.43***
Accident	.13***	.06**

Note: TRD = Trauma-Related Drinking to Cope; DMQ-Cope = Drinking Motives Questionnaire Coping subscale; IPV = Interpersonal Violence; SA = Sexual Assault; *** $p < .001$, ** $p < .01$

Aim 1b: Assess TRD Factor Structure, Determine How it Relates to DMQ-Cope Factor Structure, and Compare How the Two Factor Structures Relate to PTSD

CFA Dimensionality Testing Results. Model fit indexes for the CFA dimensionality testing for the TRD, DMQ-Cope, PCL, and AUDIT item sets are presented in Table 6. As hypothesized, TRD and DMQ-Cope demonstrated unitary constructs, such that both the TRD and DMQ-Cope common factor models were found to have excellent goodness-of-fit values for the comparative fit indices (CFI's .994 and .992, respectively) and Tucker-Lewis indices (TLI's .982 and .983, respectively). However, rather poor root mean square error of approximation

(RMSEA's .136 and .123, respectively) values characterized these models. This discrepancy has been shown to occur in models with small degrees of freedom, in which cases RMSEA is not recommended as an indicator for model fit (Kenny, Kaniskan, & McCoach, 2015). Single common factor CFA tests of unidimensionality for the 20 item PCL-5 and 10 item AUDIT produced poor omnibus model fit index values (CFI = .0.943, TLI = 0.936, RMSEA = 0.118 and CFI = .0.928, TLI = 0.907, RMSEA = 0.113, respectively). For these measures, more diverse factor structures were investigated[1]. For the 20-item PCL-5, a 4-factor model provided an improved overall fit, $\chi^2(164) = 2381.985$, $p < .001$, compared to the 1-factor model, $\chi^2(170) = 4516.387$, $p < .001$. Therefore, the 4-factor PCL-5 was retained for both statistical and substantive reasons in the PCL model to be used for evaluating the new TRD questionnaire item set. Similarly, the 2-factor model for the AUDIT provided a better overall fit, $\chi^2(34) = 355.795$, $p < .001$, compared to the 1-factor model, $\chi^2(35) = 877.646$, $p < .001$, and was therefore used in the SEM validation analyses. Information on standardized factor loadings and correlations are available in Supplemental Tables 1-7.

Model 1. First, to determine the relatedness of the TRD and DMQ-Cope factors, a correlated two-factor model was fit to the TRD and DMQ-Cope items allowing the two common factors to correlate (Model 1, Figure 11). The model, which demonstrated good fit ($\chi^2(26) = 299.077$, $p < .001$; CFI = .989; TLI = .985; RMSEA = .075), suggested that the latent factors were highly correlated, $\rho = .757$, $p < .001$. This was consistent with the study hypothesis that TRD and DMQ-Cope would be related, but unitary constructs.

Model 2. Next, to test the study hypothesis that PTSD would be more strongly associated with the TRD common factor compared to the DMQ-Cope common factor, the four oblique

[1] As expanded upon in the data analytic section for Aim 1, PCL-5 and AUDIT factor structures recommended in the extant literature were compared to 1-factor structures for parsimony.

PCL-5 common factors were treated as external predictors of both the TRD common factor and DMQ common factor in the same model, allowing the TRD and DMQ common factors to correlate and covarying for sex and lifetime trauma load (Model 2, Figure 12). The model demonstrated good fit ($\chi^2(412) = 2984.451$, $p < .001$; CFI = .964; TLI = .960; RMSEA = .058). Standard deviation scaled effects sizes for this model showed that the arousal factor was the only PCL-5 factor that significantly predicted the TRD common factor (.642, standard error [SE] = .106, $p < .001$) and DMQ-Cope common factor (.579, SE = .093, $p < .001$). A follow up multivariate test of equivalence showed that the PCL-5 factors did not predict the TRD and DMQ-Cope common factors with the similar magnitudes ($\chi^2(4) = 182.942$, $p < .001$; ΔCFI = .007; ΔTLI = .008; ΔRMSEA = -.005), suggesting that the PCL-5 arousal factor more strongly predicted the TRD common factor compared to the DMQ-Cope common factor. The covariate lifetime trauma load had similar positive linear effects on all four PCL-5 common factors. Findings with regard to sex showed that females, compared to males, on average, had higher scores on all four PCL factors, although the sex mean difference for the arousal factor was not significantly different from zero. These covariate effects were consistent across all models.

Table 6.

Confirmatory Factor Analyses: Determining Factor Structures

Model	χ^2	df	*P*	RMSEA	CFI	TLI
TRD One Factor Model	70.051	2	<.001	0.136	0.994	0.982
DMQ-Cope One Factor Model	146.427	5	<.001	0.123	0.992	0.983
PCL-5 One Factor Model	4516.387	170	<.001	0.118	0.943	0.936
PCL-5 Four Factor Model	2381.985	164	<.001	0.086	0.971	0.966
AUDIT One Factor Model	877.646	35	<.001	0.113	0.928	0.907
AUDIT Two Factor Model	355.795	34	<.001	0.071	0.972	0.964

Note: Overall model fit was assessed using omnibus indexes of 1) chi-square test of model-data misfit (χ^2), 2) root mean square error of approximation (RMSEA), 3) comparative fit index (CFI), and 4) the Tucker-Lewis fit index (TLI). Conventional cutoff recommendations were used to evaluate the adequacy of model fit: RMSEA < .05 indicates good fit, < .08 reasonable fit. CFI and TLI values of >.95 are considered relatively good model fits based on comparison with a null model.

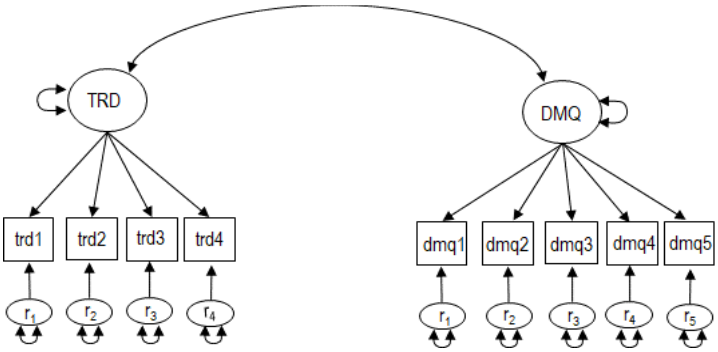

Figure 11. *Model 1: Relationship Between TRD and DMQ-Cope*; Note: TRD = Trauma-Related Drinking to Cope; DMQ = Drinking Motives Questionnaire; Significant association between the two latent factors

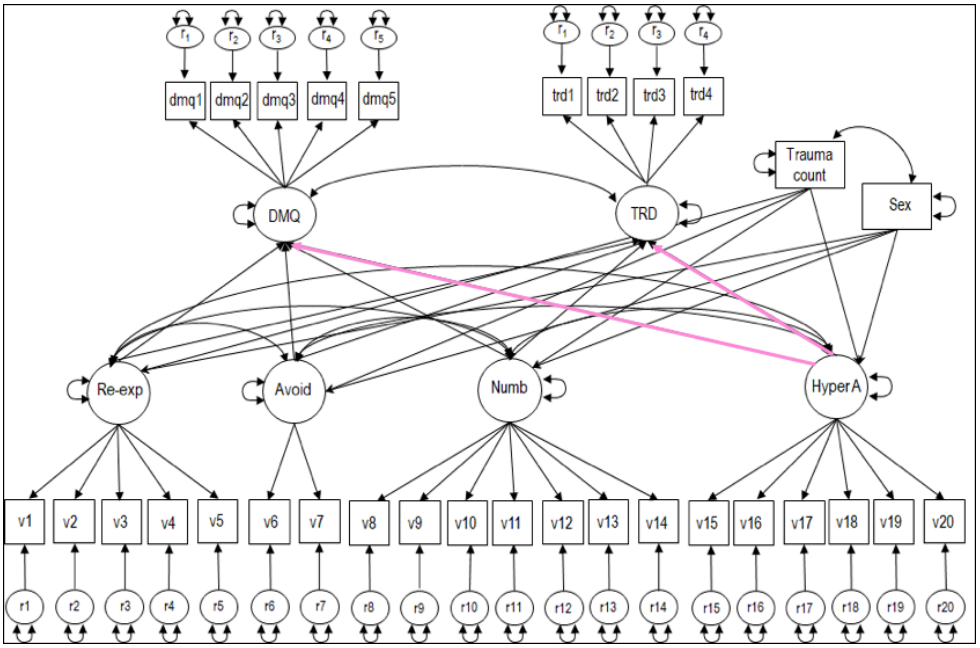

Figure 12. *Model 2: PCL-5 Differential Prediction of TRD versus DMQ-Cope;* Note: TRD = Trauma-Related Drinking to Cope; DMQ = Drinking Motives Questionnaire; Re-exp = Re-experiencing Factor (Factor 1) of PCL-5; Avoid = Avoidance Factor (Factor 2) of PCL-5; Numb = Negative Alterations in Cognition and Mood Factor (Factor 3) of PCL-5; HyperA = Hyperarousal Factor (Factor 4) of PCL-5; Significant paths from hyperarousal factor onto DMQ and TRD.

Aim 1c: External Validation of TRD in Relation to PTSD

Model 3. Given each TRD item was designed to collect information on specific motives for drinking to cope with symptoms specific to each PTSD symptom cluster, the four oblique PCL-5 common factors (i.e., PTSD symptom clusters) were specified as external predictors of each of the new TRD items (Model 3, Figure 13). This was done to test the hypothesis that each TRD item would be significantly associated with the PTSD symptom cluster (i.e., factor). Results from this model, which demonstrated good fit ($\chi^2(268) = 2647.368$, $p < .001$; CFI = .962; TLI = .955; RMSEA = .069), are presented in Table 7. Overall, each of the four PCL-5 common factors significantly predicted their analogous TRD items (i.e., the intrusion PCL factor predicted the TRD item summarizing intrusion symptoms), with the exception of the avoidance factor, which did not significantly predict any of the four TRD items. Instead, the PCL-5 reexperiencing and arousal factors significantly predicted the TRD avoidance item (Item 2).

Model 4. Next, the TRD common factor was regressed onto the four oblique PCL-5 common factors (Model 4, Figure 14). This model also produced good model fits ($\chi^2(282) = 2794.995$, $p < .001$; CFI = .960; TLI = .954; RMSEA = .070). Consistent with results from Model 2, standard deviation scaled effects sizes for this model showed that the arousal factor was the only PCL-5 factor that significantly predicted the TRD common factor (.606, SE = .102, $p < .001$). A follow up multivariate test of the equivalence of the PCL-5 factors' predictions of the TRD common factor, which forced all four PCL-5 prediction paths to be invariant (i.e., equal), provided further evidence that the PCL-5 common factors differentially predicted the TRD common factor ($\chi^2(3) = 38.962$, $p < .001$; ΔCFI = .001; ΔTLI = .002; ΔRMSEA = .002). Thus, the hypothesis that each PCL-5 factor would be significantly associated with the TRD latent factor was not supported.

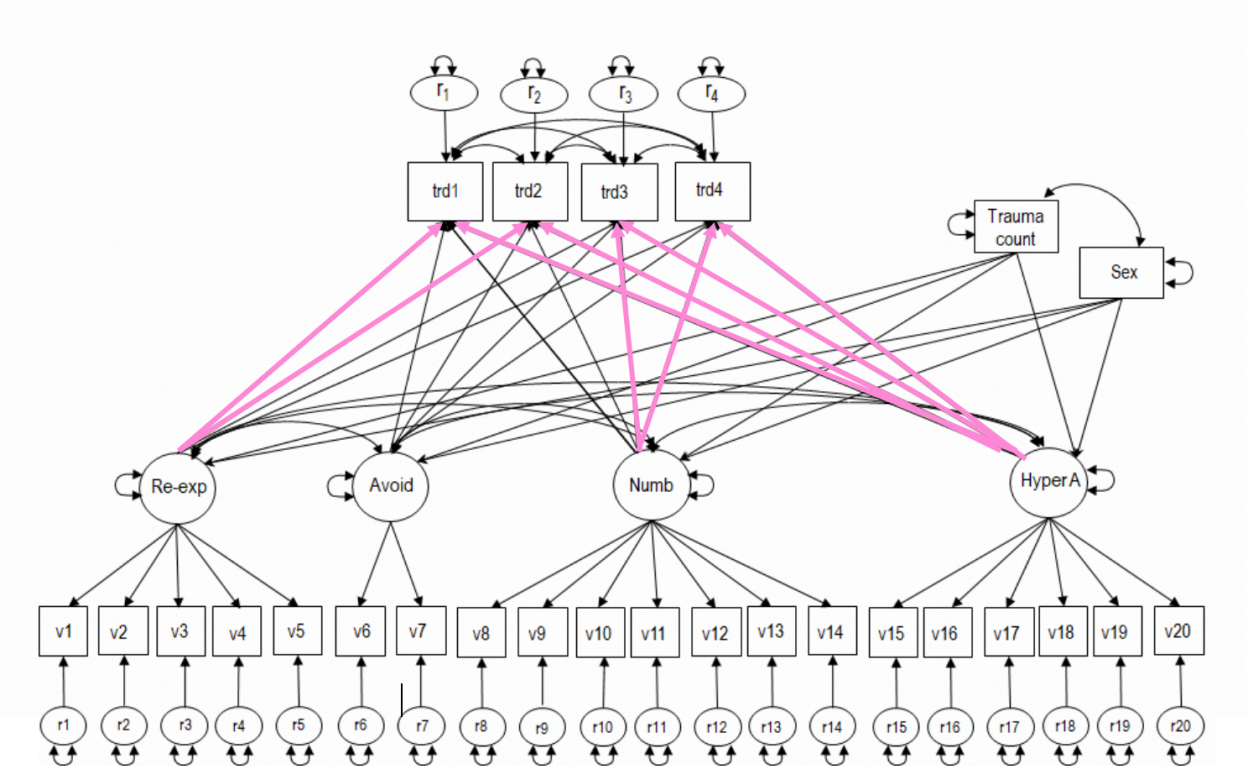

Figure 13. *Model 3: External Validation: How PCL-5 factors load onto TRD Items*; Note: TRD = Trauma-Related Drinking to Cope; Re-exp = Re-experiencing Factor (Factor 1) of PCL-5; Avoid = Avoidance Factor (Factor 2) of PCL-5; Numb = Negative Alterations in Cognition and Mood Factor (Factor 3) of PCL-5; HyperA = Hyperarousal Factor (Factor 4) of PCL-5; Significant paths from re-experiencing factor onto TRD items 1 and 2; Significant paths from negative alterations in cognition and mood factor onto TRD items 3 and 4; Significant paths from hyperarousal factor onto all four TRD items.

Table 7:

External prediction of the four TRD items by the four PCL factors

	PCL Factor 1: Intrusion	PCL Factor 2: Avoidance	PCL Factor 3: Cognitions/Mood	PCL Factor 4: Arousal
Standardized loading (standard error)				
TRD Item 1	.419 (.101)***	-.064 (.109)	-.100 (.113)	.356 (.095)***
TRD Item 2	.195 (.092)*	.155 (.094)	.095 (.096)	.184 (.083)*
TRD Item 3	-.126 (.090)	.010 (.088)	.435 (.090)***	.293 (.082)***
TRD Item 4	-.162 (.102)	.122 (.106)	-.299 (.111)**	.906 (.090)***

Note: TRD = Trauma-Related Drinking to Cope; *** $p < .001$, ** $p < .01$, * $p < .05$

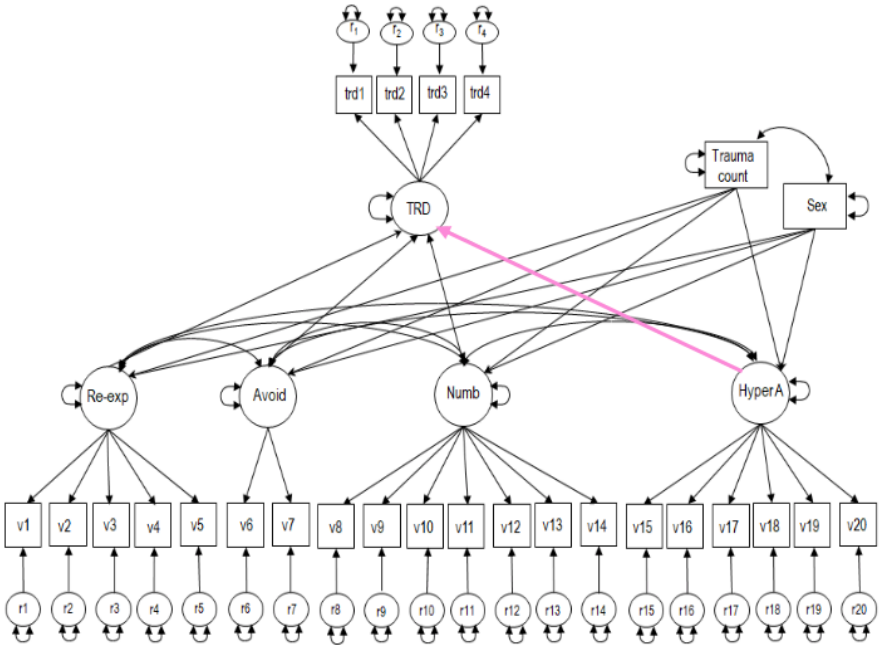

Figure 14. *Model 4: External Validation: How PCL-5 Factors Load Onto TRD Common Factor*; Note: TRD = Trauma-Related Drinking to Cope; Re-exp = Re-experiencing Factor (Factor 1) of PCL-5; Avoid = Avoidance Factor (Factor 2) of PCL-5; Numb = Negative Alterations in Cognition and Mood Factor (Factor 3) of PCL-5; HyperA = Hyperarousal Factor (Factor 4) of PCL-5; Significant paths from hyperarousal factor onto TRD.

Aim 1d: External Validation of TRD in Relation to Alcohol Consumption and Related Problems

Model 5. Finally, although the primary interest was in determining how the PTSD symptom factors predicted the TRD items and common factor, a secondary interest was to investigate how TRD relates to alcohol use and related problems. This model extends the PCL → TRD prediction factor model (Model 4) by adding a 2-factor measurement model with the TRD factor predicting the two AUDIT factors (Model 5, Figure 15). Given their previously reported influences on both PTSD and alcohol use, sex and lifetime trauma load were included as covariates with paths going to the PCL-5 and AUDIT common factors. Overall, this model

demonstrated adequate fit, $\chi^2(572) = 3065.682$, $p < .001$; CFI = .965; TLI = .962; RMSEA = .048. Results from this model are presented in Table 8. Consistent with the previous model, only the PCL-5 arousal factor significantly predicted the TRD factor (.773, SE = .115, $p < .001$), although, unlike the smaller PCL → TRD model, the avoidance factor was nominally predictive of TRD (.231, SE = .125, $p = .064$). Moreover, consistent with study hypotheses, the TRD factor significantly predicted both the consumption (.192, SE = .026, $p < .001$) and the consequences/dependence (.449, se = .038, $p < .001$) factors of the AUDIT, but, with different strengths. A follow up test of the equivalence of the TRD common factor's prediction of the 2 AUDIT factors showed that the TRD common factor does not predict the two AUDIT factors with the similar magnitudes ($\Delta\chi^2(1) = 63.872$, $p < .001$; ΔCFI = -.003; ΔTLI = -.004; ΔRMSEA = -.003). This suggests that TRD more strongly predicted alcohol consequences/dependence compared to general alcohol consumption. As with the previous models, lifetime trauma load had similar positive linear effects on all four PCL-5 common factors and findings with regard to sex showed that females, compared to males, on average, had higher scores on all four PCL-5 factors, although the sex mean difference for the arousal factor was not significantly different from zero. Conversely, however, strong mean differences favoring males were found for the 2 AUDIT factors.

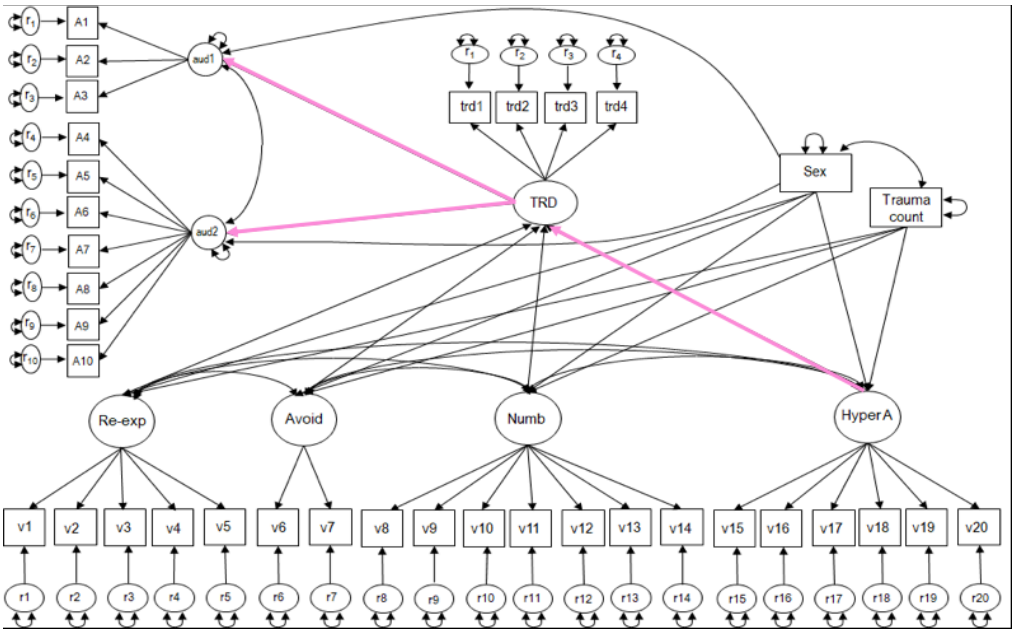

Figure 15. *Model 5: Full Psychometric Validation Model*; Note: TRD = Trauma-Related Drinking to Cope; Re-exp = Re-experiencing Factor (Factor 1) of PCL-5; Avoid = Avoidance Factor (Factor 2) of PCL-5; Numb = Negative Alterations in Cognition and Mood Factor (Factor 3) of PCL-5; HyperA = Hyperarousal Factor (Factor 4) of PCL-5; aud1 = Alcohol Consumption (Factor 1) of AUDIT; aud2 = Alcohol Consequences and Dependence (Factor 2) of AUDIT; Significant paths from hyperarousal factor onto TRD; Significant paths from TRD onto both factors of the AUDIT.

Table 8.

External Validation Prediction Regressions: Full Psychometric Validation Model

	PCL Factor 1: Intrusion	PCL Factor 2: Avoidance	PCL Factor 3: Cognitions/ Mood	PCL Factor 4: Arousal	AUDIT Factor 1: Consumption	AUDIT Factor 2: Consequences/ Dependence
Standardized loading (standard error)						
TRD Common Factor	-.027 (.124)	.231 (.125)	-.103 (.127)	.773 (.115)***	.192 (.026)***	.449 (.038)***
Sex[#]	.366 (.060)***	.365 (.063)***	.133 (.058)*	.074 (.063)	-.423 (.056)***	-.322 (.069)***
Trauma Load	.182 (.010)***	.187 (.011)***	.167 (.010)***	.186 (.011)***	--	--

Note: TRD = Trauma-Related Drinking to Cope[***] $p < .001$, [**] $p < .01$, [*] $p < .05$; [#]Males set as 0

Aim 1 Summary:

- TRD is less commonly endorsed and less evenly distributed compared to DMQ-Cope, suggesting evidence for greater specificity, as hypothesized.
- Results suggested that, broadly, most of the TRD items reflected their synonymous PTSD symptom cluster, as intended, with the exception of the avoidance item (Item 2).
- There is evidence for TRD as a unitary construct and this construct was significantly predicted by the hyperarousal factor of the PCL-5 and nominally by the avoidance factor.
- As hypothesized, TRD also predicted alcohol consumption and consequences/dependence, providing additional evidence for external validation.

Aim 2: Investigation of the Self-Medication Model

Aim 2 Data Analytic Plan

Hypothesis 2a was that TRD would mediate the effect of PTSD symptoms on AUP, over and above the effects of DMQ-Cope and study covariates. It was hypothesized that DMQ-Cope would also mediate this relation, over and above study covariates, but that the mediational effect of TRD would be greater than that of DMQ-Cope. In order to investigate the outlined study hypotheses, a model building approach was used. First, mediation analyses testing TRD and DMQ-Cope as independent mediators of the relation between PTSD and AUP were conducted. Analyses were conducted in *Mplus*, Version 6.12 (Muthén & Muthén, 2012), using the *Model Indirect* command. Second, a correlated mediation model was conducted in *Mplus* in which TRD and DMQ-Cope were both included as mediators and allowed to covary within the same model. This correlated mediation approach was conducted to account for the likely association between TRD and DMQ-Cope.

Hypothesis 2b was that the mediating effects of TRD and DMQ-Cope would be stronger for females compared to males. To test this hypothesis, a moderated mediation model, allowing TRD and DMQ-Cope to covary, while sequentially examining these effects for females and then males, was conducted. In order to test for moderated mediation, interactions between PTSD symptoms and sex to predict TRD and DMQ-Cope, and interactions between TRD and DMQ-Cope and sex to predict AUP were estimated in conjunction with the *Model Indirect* command. *Mplus* uses the product of coefficients strategy to calculate indirect effects (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Preacher & Hayes, 2004).

Missing data on endogenous variables was estimated as a function of the observed exogenous variables under the missingness at random assumption (Schafer & Graham, 2002).

As including covariates may increase the power of a statistical test by minimizing uncontrolled variability and accounting for variance that would otherwise be thought of as error (Turner et al., 2012), several key covariates (i.e., sex, race, cohort, lifetime trauma load, trauma type) were included in the initial study models. Cohort was included based on previous research using this data demonstrating significant differences in AUP between the cohorts (Bountress et al., 2019). Covariates deemed non-significant ($p > .05$) in the initial model were removed in subsequent models in order to improve model fit and parsimony. The study model was assessed for goodness of fit based on whether the values of the following fit indices were consistent with accepted standards (i.e., Hu, 1999): CFI: ≥.95, RMSEA ≤ .06, and Standardized Root Mean Square Residual (SRMR) <.08.

Given the more phenotypically rich LEAU sample was limited by cross-sectional data, the same mediation approach was also applied to data from both LEAU and S4S in order to test the self-medication hypothesis longitudinally (N=899). TRD and DMQ-Cope, assessed in LEAU (Fall 2016), were regressed onto the maximum endorsed probable PTSD score, calculated using the Primary Care PTSD Screen (PC-PTSD; Prins et al., 2003), assessed in the S4S parent study prior to enrollment in LEAU (Fall 2014, Spring 2015). AUD symptoms met at least once in the past 12 months (for full methods see Hawn et al., 2018), assessed the Spring following enrollment in LEAU (Spring 2017), were regressed on TRD, DMQ-Cope, and PC-PTSD. The AUD criterion count variable assessed at earlier timepoints was included as a covariate at time points 1 and 2 in the longitudinal model in order to control for the potential effect of previous AUD symptoms.

Power Calculations

A power analysis was conducted using G*Power software (Faul, Erdfelder, Buchner, & Lang, 2009). The power to detect a small-sized effect (ρ=.10; Cohen, 1988) at an alpha level of .05 in the present study sample of 1896 was determined to be >.99 for the Aim 2 analyses. Given the large sample size available for phenotypic examination, analyses were deemed to be more than adequately powered to examine potential sex effects.

Aim 2 Results

Examination of TRD and DMQ-Cope Separately

Model 6. Row one of Table 9 show the results for the independent regression models conducted using TRD as a mediator. There was a significant indirect effect of PTSD symptoms on AUP (p<0.001) through TRD, which accounted for 87.97% of the total effect. The best fitting model after eliminating non-significant covariates (χ^2 (10) = 20.928, p = .022; CFI: .991, RMSEA: .024; SRMR: .009) included trauma load (β = 0.142, p < .001), trauma type (interpersonal: β = -0.092, p < .001; other: β = -0.049, p = .032), and sex (β = -0.054, p = .006) onto TRD and sex (β = -0.123, p < .001), cohort (cohort 1 vs 2: β = 0.064, p = .012; cohort 1 vs 3: b = 0.080, p = .002; cohort 1 vs 4: β = 0.051, p = .049), and race (White vs Black: β = -0.113, p < .001; White vs Asian: β = -0.103, p < .001; White vs Hispanic: β = -0.019, p = .358; White vs Other: β = -0.032, p = .121) onto AUP.

Model 7. Row two of Table 9 show the results for DMQ-Cope as a mediator. DMQ-Cope was a significant mediator as well, with a significant indirect effect (p<0.001) that accounted 83.33% of the total effect. This model demonstrated good fit to the data after eliminating nonsignificant covariates (χ^2 (6) = 11.851, p = 0.065; CFI: .994; RMSEA: .023;

SRMR: .007). Final covariates included trauma load (β = 0.139, p < .001), trauma type (interpersonal: β = -0.035, p = .231; other: β = -0.110, p < .001), race (White vs Black: β = -0.064, p = .004; White vs Asian: β = 0.004, p = .852; White vs Hispanic: β = -0.024, p = .265; White vs Other: β = 0.004, p = .837), and sex (β = -0.046, p = .032) onto DMQ-Cope and sex (β = -0.115, p < .001), cohort (cohort 1 vs 2: β = 0.061, p = .013; cohort 1 vs 3: β = 0.076, p = .003; cohort 1 vs 4: β = 0.041 p = .105), and race (White vs Black: β = -0.089, p < .001; White vs Asian: β = -0.121, p < .001; White vs Hispanic: β = -0.007, p = .719; White vs Other: β = -0.048, p = .019) onto AUP.

Correlated Mediation Model

Model 8. Given that the indirect pathways through TRD and DMQ-Cope were both significant, and that these constructs were correlated (see Aim 1 Results), a mediation model was fit which included both constructs and allowed them to correlate (Aim 2a). The results of this model are shown in row three of Table 9. The model demonstrated good fit to the data after eliminating nonsignificant covariates (χ^2 (13) = 18.177, p = 0.151; CFI: .998; RMSEA: .014; SRMR: .009). There were significant indirect effects of both TRD and DMQ-Cope (p<0.001). Combined, TRD and DMQ-Cope accounted for 80.34% of the total effect of PTSD symptoms on AUP. A larger proportion of this indirect effect (43.30% of the total effect of PTSD on AUP) was accounted for by TRD, while a slightly smaller portion (37.04% of the total effect) was attributed to DMQ-Cope. However, the indirect effects of TRD and DMQ-Cope were not statistically distinct, b = .007, p = .325, suggesting that neither mediator accounted for statistically more or less of the total effect compared to the other.

Final covariates included trauma load (β = 0.138, p < .001), trauma type (interpersonal: β = -0.090, p = .001; other: β = -0.049, p = .033), and sex (β = -0.053, p = .007) onto TRD; trauma

load (β = 0.137, p < .001), trauma type (interpersonal: β = -0.034, p = .238; other: β = -0.110, p < .001), race (White vs Black: β = -0.059, p = .002; White vs Asian: β = 0.011, p = .553; White vs Hispanic: β = -0.026, p = .151; White vs Other: β = 0.022, p = .232), and sex (β = -0.046, p = .033) onto DMQ-Cope; and sex (β = -0.106, p < .001), cohort (cohort 1 vs 2: β = 0.064, p = 0.008; cohort 1 vs 3: β = 0.073, p = .003; cohort 1 vs 4: β = 0.045, p = .074), and race (White vs Black: β = -0.095, p < .001; White vs Asian: β = -0.118, p < .001; White vs Hispanic: β = -0.103 p = .512; White vs Other: β = -0.039, p = .052) onto AUP.

Moderated Correlated Mediation Model

Model 9. In order to test whether these indirect effects were moderated by sex (Aim 2b), a moderated correlated mediation model was conducted, examining the indirect effect for males and then females. These results are shown in rows four and five of Table 9. The model tested whether sex significantly interacted with PTSD symptoms to influence TRD/DMQ-Cope and whether sex significantly interacted with TRD/DMQ-Cope to influence AUP (see Figure 16 for reference). Results showed significant interactions between sex and PTSD symptoms on TRD and DMQ-Cope (p's < .001) but failed to demonstrate evidence of a significant interaction between sex and TRD or DMQ-Cope on AUP (p's > .30). The model demonstrated good fit to the data after eliminating the nonsignificant interaction terms and nonsignificant covariates (χ^2 (14) = 16.462, p = 0.286; CFI: .999; RMSEA: .010; SRMR: .007). Overall, results showed stronger effects of PTSD symptoms on both TRD and DMQ-Cope for males (β = 0.804 and β = 0.565, respectively, p's < .001) compared to females (β = 0.463 and β = 0.333, p's < .001). With males set as the reference group, TRD and DMQ-Cope accounted for 45.03% and 41.65% of the total effect, respectively. With females set as the reference group TRD and DMQ-Cope accounted for 40.59% and 38.61% of the total effect, respectively.

Final covariates included trauma load (β = 0.146, p < .001), trauma type (interpersonal: β = -0.112, p < .001; other: β = -0.051, p = .025), and sex (β = -0.085, p < .001) onto TRD; trauma load (β = 0.139, p < .001), trauma type (interpersonal: β = -0.042, p = .146; other: β = -0.108, p < .001), race (White vs Black: β = -0.065, p = .001; White vs Asian: β = 0.007, p = .733; White vs Hispanic: β = -0.028, p = .128; White vs Other: β = 0.021, p = .269), and sex (β = -0.0603, p = .006) onto DMQ-Cope; and sex (β = -0.103, p < .001), cohort (cohort 1 vs 2: β = 0.063, p = .009; cohort 1 vs 3: β = 0.075, p = .003; cohort 1 vs 4: β = 0.044, p = .081), and race (White vs Black: β = -0.097, p < .001; White vs Asian: β = -0.120, p < .001; White vs Hispanic: β = -0.013 p = .507; White vs Other: β = -0.040, p = .048) onto AUP.

The moderated mediation analyses were also conducted within a subsample of participants who had endorsed at least 1 item on the PCL-5 (N=1523; 82.55% of LEAU sample with available PCL-5 data [N=1845]). The pattern of results within this subsample was consistent with those found in the overall sample for all primary effects and covariate effects.

Longitudinal Model

A longitudinal model was conducted incorporating data from the S4S parent study. Maximum endorsed PC-PTSD score prior to LEAU enrollment was the time point 1 predictor variable, TRD and DMQ-Cope assessed in LEAU were included as time point 2 mediator variables, and AUD criterion count (AUDIT total not available) assessed following LEAU participation was the time point 3 outcome variable. AUD criterion count assessed at time point 1 was included as a covariate in the model to control for prior symptoms of AUD. Because PC-PTSD was multicollinear (r = .90) with the PC-PTSD X Sex interaction term in the moderated mediation model, the standard errors of the model parameter estimates could not be computed and we were therefore unable to test the moderating effects of sex in the longitudinal model.

These results suggest that the PC-PTSD X Sex interaction term did not provide information over and above the main effects of PC-PTSD and sex. Consistent with findings using the cross-sectional data, both TRD (β = 0.021, p = 0.025) and DMQ-Cope (β = 0.067, p < .001) significantly mediated the relation between PTSD symptoms (per the PC-PTSD) and AUD criterion count. However, unlike the models conducted using the more comprehensive cross-sectional data, results of the correlated mediation model suggested that DMQ-Cope accounted for a significantly (b = -0.076, p = 0.012) larger proportion of the total effect (43.51%) than TRD (13.64%). The best fitting model (χ^2 (6) = 7.832, p = 0.251; CFI: .998; RMSEA: .018; SRMR: .014) accounted for the effect of AUD criterion count assessed at time point 1 on TRD (β = 0.163, p < .001), DMQ-Cope (β = 0.121, p = .001), and AUD post-LEAU (β = 0.333, p < .001), as well as race (White vs Black: β = -0.019, p = .512; White vs Asian: β = -0.029, p = .300; White vs Hispanic: β = -0.003, p = .921; White vs Other: β = -0.064, p = .017) on DMQ-Cope, and sex (β = -0.106, p = .001) and race (White vs Black: β = -0.038, p = .240; White vs Asian: β = -0.100, p = .002; White vs Hispanic: β = -0.063, p = .040; White vs Other: β = -0.008, p = .798) on the AUD outcome variable.

Table 9.

Path coefficients and test statistics for self-medication mediation models

			Total direct effect			Total indirect effect (mediation)			Total effect (indirect + direct)			
	Mediator	Model R^2	β	SE	Ratio	β	SE	Ratio	β	SE	Ratio	Mediated proportion of total effect
Model 6	TRD	0.242	-0.035	0.025	-1.407	0.256	0.016	15.900***	0.220	0.023	9.703***	.8797
Model 7	DMQ-Cope	0.271	0.036	0.022	1.604	0.180	0.013	13.416***	0.216	0.023	9.517***	.8333
Model 8	Correlated mediation	0.309	-0.069	0.024	-2.844**	0.282	0.017	16.603***	0.214	0.023	9.331***	.8034
	TRD	0.334	-	-		0.152	0.016	9.526***	-	-	-	.4330
	DMQ Cope	0.195	-	-		0.130	0.012	10.570***	-	-	-	.3704
Model 9	Moderated mediation	0.307	-0.063	0.024	-2.609**	0.410	0.029	14.183***	0.347	0.030	11.587***	.8668
	TRD	0.351	-	-	-	0.213	0.024	8.798***	-	-	-	.4503
	DMQ Cope (males)	0.205	-	-	-	0.197	0.021	9.553***	-	-	-	.4165
Model 9	Moderated mediation	0.307	-0.064	0.024	-2.676**	0.239	0.017	14.216***	0.175	0.024	7.330***	.7888
	TRD	0.347	-	-	-	0.123	0.014	8.782***	-	-	-	.4059
	DMQ Cope (females)	0.202	-	-	-	0.117	0.012	9.593***	-	-	-	.3861

Abbreviations: TRD = Trauma-related drinking to cope measure (log transformed); DMQ-Cope = Drinking Motives Questionnaire Coping subscale. Note that the ratio column (Z-score) corresponds to the following *p*-values: 1.96* (*p*=0.05); 2.58** (*p*=0.01); 3.29*** (*p*=0.001).

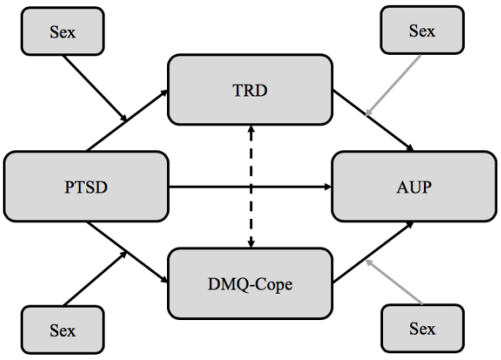

Figure 16. *Moderated Correlated Mediation*; Note: PTSD=Posttraumatic stress disorder; TRD=Trauma related drinking to cope; DMQ-Cope=Drinking motives questionnaire coping subscale; AUP=Alcohol use problems.

Aim 2 Summary:

- While accounting for the effects of DMQ-Cope, TRD partially mediated the relationship between PTSD and AUP and this relationship was stronger for males than for females.
- Results were substantiated using longitudinal data.
- Findings were consistent with the self-medication model, suggesting that drinking to cope motives may serve as a mechanism through which PTSD influences AUP and that trauma-related drinking to cope motives account for a unique proportion of the variance above and beyond general coping motives.

Aim 3: Genotypic Investigation into TRD, PTSD, and Their Potential Overlap

Aim 3 Data Analytic Plan (Table 10)

Data Checking and Missingness

Rigorous quality control (QC) measures (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 have been implemented for the parent study's genetic data, which were used to fulfill Aim 3.

Aim 3a (Univariate) Analytic Plan

The genetic analyses were conducted separately within homogenous ancestral subgroups derived from ancestry principal components (described above in Method section) and then meta-analyzed to increase statistical power, which is the "best practice" that has been implemented by the PGC (Nievergelt et al., 2018). Within ancestry PCs and sex were included as covariates in all genetic analyses.

GCTA. First, in order to establish the heritability of TRD and PTSD independently, a univariate GCTA was conducted for each phenotype using the software program GCTA (Yang et al., 2011). As described previously, GCTA estimates the heritability of a trait based off of the additive effect of all single nucleotide polymorphisms (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. Covariates included top 10 ancestry PCs and sex.

GWAS. GWAS analyses were run using SNPTEST, version 2.5.2 (Marchini, Howie, Myers, McVean, & Donnelly, 2007) to identify specific variants that may be associated with TRD and PTSD. Covariates included within ancestry PCs and sex. GWAS were run under an

additive model only including SNPs with a minimum allele frequency (MAF) of 0.005 and INFO (imputation quality) score of 0.5. Post GWAS filtering applied ancestry specific Hardy-Weinberg Equilibrium (HWE; p-value > $1x10^{-6}$) and sample sized based MAFs (see Webb et al., 2017 for details). Results from the post-filtered European Ancestry (n=~500) and African Ancestry (n=~230) GWASs were meta-analyzed for both TRD and PTSD using METAL (Marchini et al., 2007; Willer, Li, & Abecasis, 2010). The other ancestral groups were not included in the meta-analyses due to low sample size and high inflation. Genomic inflation factors (λ) were estimated in R (Team, 2018) to determine bulk inflation and excess false positives. Manhattan plots were constructed using the qqman package in R (Turner, 2014) and quantile-quantile (QQ) plots were constructed in R using scripts used written by the S4S workgroup. False Discovery Rate (FDR) analysis was performed using the "fdrtool" package (Klaus & Strimmer, 2013) in R, setting a q-value threshold of 0.5, consistent with best practices put forth by the S4S workgroup (Webb et al., 2017). It should be noted that an FDR of 0.5 is very liberal, meaning that approximately half of the values below this cut-off are false positives. Although a more stringent FDR (e.g., 0.05, 5% false positives) is far more statistically rigorous, a threshold of 0.5 allows for further probing of top variants, which was deemed appropriate 1) for the purposes of training and 2) because TRD is a novel phenotype which requires initial broadband exploration to be later followed up with more rigorously by future research. However, in order to characterize genomic bins (i.e., sections of the genome) for follow-up and consistent with S4S practices, all markers with a $q < 0.5$ within 10 kilobases (kb) were collapsed into shared bins for further refinement and rigor. Regions with at least three SNPs within 10kb of one another will be the focus of discussion.

LDSC. In addition to GCTA, a SNP-based heritability estimate for TRD was also estimated using LDSC (Bulik-Sullivan, Loh, et al., 2015b). As described previously, LDSC uses summary-level GWAS data, which are regressed onto LD in order to calculate heritability estimates. Summary statistics for TRD were derived from the GWAS run in the European Ancestry subsample of LEAU. Analysis was restricted to the European Ancestry subsample only, given that LDSC is currently not suitable for populations with recent admixture analyses (e.g., African Ancestry). General instructions for LDSC can be found at https://github.com/bulik/ldsc.

Aim 3b (Bivariate) Analytic Plan

LDSC Cross-Trait. To determine if there is overlap in SNP-based heritability between TRD and PTSD, a cross-trait LDSC was used (Bulik-Sullivan, Finucane, et al., 2015b) to calculate pairwise genetic correlation (r_g) between TRD and PTSD. Summary statistics for TRD were pulled from the European Ancestry GWAS conducted in LEAU and summary statistics for PTSD were pulled from the GWAS meta-analysis of European Ancestry samples conducted by the PGC-PTSD (Nievergelt et al., 2018). Once more, due to the current limitations in applying LDSC across ancestral groups, LDSC cross-trait analyses were conducted using European Ancestry subsamples only.

PRS. Next, polygenic risk scores (PRS) were calculated to estimate whether overall molecular risk for PTSD predicted PTSD and TRD in the present sample. PRS analysis was conducted in PRSice v2.2.0 (Choi & O'Reilly, 2019), using summary statistics generated from the PTSD PGC Freeze 2 European Ancestry meta-analysis as the discovery data and S4S genomic data as the target sample. PTSD diagnostic status, as assessed in LEAU, was included as the binary phenotype in the analysis. Risk scores for each SNP were calculated as the log of

the odds ratio effect from the discovery sample multiplied by number of copies of the risk allele in the target sample. These scores were then summed across all SNPs to create an individual's 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 leading variant (lowest *p*-value) in a given region. PRS are calculated multiple times using various *p*-value thresholds in order to determine the optimal *p*-value threshold in association with the target phenotype. 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. Consistent with previous work (Nievergelt et al., 2018; Power et al., 2015), Nagelkerke's R^2 used as the index for the proportion of variance explained by PRS.

Table 10.

Aim 3 Analytic Plan

Research Question	**Analytic Plan**
Are trauma-related drinking and PTSD heritable?	Univariate GCTA
Are there shared heritable influences?	Cross-Trait LDSC
Are there specific genetic variants for each phenotype independently?	GWAS
Does genetic risk for PTSD predict TRD?	PRS (PGC → S4S)

Power Calculations

First, a GTCA-GREML power calculation (Hemani & Yang) was conducted, based on extant methods (Visscher et al., 2014), for both the univariate and bivariate GTCA analyses. Power calculations were conducted for each TRD and PTSD within each ancestral group (Table 11) and suggest that there is limited power to detect effects within each ancestral group. Given that LDSC uses summary statistics rather than genotypes and because of its robustness to population stratification, LDSC analyses can be expected to be slightly less powered than GCTA and PRS methods, which becomes particularly problematic when working with small samples (Ni et al., 2018). Notably, because TRD has yet to be investigated (phenotypically or genotypically), there are no heritability estimates for TRD to date. Because it is assumed that the heritability for TRD will be smaller than that for AUD, the heritability estimates used to calculate power for the GWAS of TRD conservatively mirrored the lower heritability rates found for PTSD. The effect size (R^2, which we used due to traits analyzed being quantitative) curved for 80% power for GWAS analyses conducted using the complete LEAU sample (N = 1,896) with a genome-wide correction for multiple testing (type I error of $5x10^{-8}$; see Figure 17). However, due to poor inflation among several of the ancestry subgroups, power analyses were recalculated for the actual meta-analyzed sample, which included individuals of European and African decent only (~N=795), which resulted in low power (51%).

Regarding PRS analyses, it is expected that aggregate score approaches will be more highly powered than GWAS analyses using individual variants. It is recognized that power differs as a function of the proportion of genetic variation explained by the PRS and rates of case status. Based on this, it is recommended that the discovery sample, as compared to replication sample, is larger when the goal is prediction (Dudbridge, 2013). Thus, by using a highly

powered sample such as the PTSD PGC as the discovery sample (Nievergelt et al., 2018), the PRS analyses predicting TRD and PTSD in the present sample were deemed to be sufficiently powered. However, a power calculation for a regression analysis with an extremely small effect size (ρ=.005; r^2 =.5%; to account for extremely small variation explained by PRS) was conducted in G*Power (Faul et al., 2009) for the sample of 1,896 participants. The analyses were confirmed to be sufficiently powered (87%).

Table 11.

Power Calculations for Univariate and Bivariate GCTAs of TRD and PTSD by ancestral group

Phenotype	Ancestral Group	N	Power		
			h^2 = .50	h^2 = .20	h^2 = .10
TRD	EUR	539	.136	.063	.053
	AFR	233	.066	.053	.051
	EAS	109	.053	.051	.050
	AMR	101	.053	.051	.050
	SAS	86	.052	.050	.050
PTSD	EUR	533	.135	.063	.053
	AFR	232	.066	.053	.051
	EAS	108	.053	.051	.050
	AMR	101	.053	.051	.050
	SAS	84	.052	.050	.050

Note: TRD = Trauma-related drinking to cope; PTSD = Posttraumatic stress disorder; AFR = African Ancestry; AMR = American Ancestry; EAS = EUR = European Ancestry; SAS=; h^2=SNP-based heritability

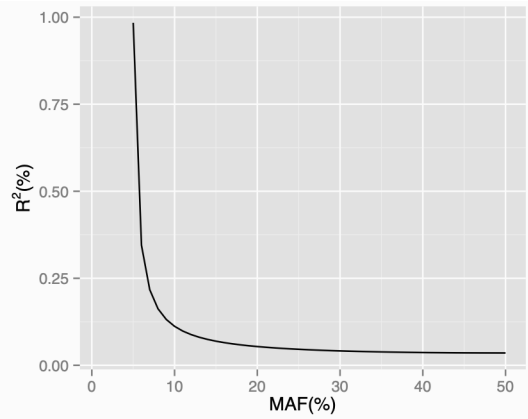

Figure 17. *Variant R^2 Detectable at 80% Power in GWAS for TRD and PTSD in LEAU Sample;* Note: MAF = Minor allele frequency; R^2 = variance explained

Aim 3 Results

Aim 3a: Univariate Analyses

GCTA: SNP-Based Heritability of TRD and PTSD. In order to determine the SNP-based heritability of TRD and PTSD, independently, univariate GCTA analyses were conducted among each ancestral subgroup and then meta-analyzed for each phenotype. Results are shown in Table 12. TRD was found to be heritable among the European subsample (p = .050), however, the heritability estimate was unreliable (h^2 = .999), likely due to large standard error (.754) resulting from low sample size. Given standard error is an indication of the reliability of the mean, small standard error is typically an indication that the sample mean is an accurate reflection of the population mean, such that a standard error of 0 would suggest the statistic has no random error (Field, Miles, & Field, 2012). Therefore, the larger the standard error, the less accurate the statistic. Consistent with the central limit theorem, standard error decreases as sample size increases (Field et al., 2012). None of the remaining GCTA analyses yielded significant

heritability estimates and all produced standard errors that were large. This included the SNP-based heritability estimates derived from the meta-analyses for TRD (h^2 = .654, SE = .573, CI: -0.470 – 1.778) and PTSD[2] (h^2 = .019, SE = .411, CI: -0.787 – 0.825).

LDSC: SNP-Based Heritability of TRD and PTSD. The liability-scale SNP-heritability estimated for TRD was .601 (SE=.854). Unlike the significant heritability estimate produced by the GCTA when conducted with the European Ancestry subsample, the LDSC analysis produced a heritability estimate of TRD that was not significant. Similar to the GCTA analyses, however, the standard error surrounding this estimate was quite large.

[2] Given evidence for sex differences with regard to the heritability of PTSD, as discussed in the Introduction, sub-ancestral and meta-analyzed GCTAs of PTSD were also conducted separately within males and females. Heritability estimates were non-significant for both males and females across GCTAs.

Table 12.

Estimates of SNP-Based heritability for TRD and PTSD Generated Using GCTA

Super-population	N	Covariates	h^2	SE	*p*-value
		TRD			
AFR	233	PCs, sex	.012	1.279	.500
AMR	101	PCs, sex	<.001	1.493	.500
EAS	109	PCs, sex	.999	3.00	.080
EUR	536	PCs, sex	.999	.754	.050
SAS	86	PCs, sex	.999	3.029	.100
		PCL			
AFR	232	PCs, sex	<.001	1.126	.500
AMR	101	PCs, sex	<.001	1.910	.500
EAS	108	PCs, sex	0.999	3.033	.300
EUR	530	PCs, sex	<.001	0.702	.500
SAS	84	PCs, sex	< .001	3.187	.500

Note: TRD=Trauma-related drinking to cope; PTSD = Posttraumatic stress disorder symptom severity; PCs=Top 10 principle components; AFR=African ancestry; AMR=Americas ancestry; EAS=East Asian ancestry; EUR=European ancestry; SAS=South Asian ancestry.

GWAS: Specific Genetic Variation Related to TRD and PTSD.

Meta-Analyzed GWAS. GWAS were conducted using SNPTEST (Marchini et al., 2007) to identify specific genetic variants associated with TRD and PTSD, which were both treated as quantitative variables. Post filtering and meta-analysis, results were available for 8,317,356 and 8,304,361 markers for TRD and PTSD, respectively. Lambda values for TRD (λ=0.989; Figure 18) and PTSD (λ=0.992; Figure 19) were slightly below 1, indicating that the *p*-values resulting from the meta-analyses were underinflated and therefore higher (less significant) than would be expected by chance. FDR analysis indicated that no markers in either the TRD or the PTSD meta-analyzed GWASs had a *q*-value < 0.5. No *p*-values resulting from the meta-analyzed GWASs revealed any genome-wide significant (GWS; $p < 1 \times 10^{-8}$) markers for either phenotype. However, several markers surpassed the suggestive association threshold ($p < 5 \times 10^{-5}$) for both phenotypes (see Figures 20 and 21) and, when investigating the European Ancestry and African Ancestry subsamples separately within the meta-analysis for each phenotype, 102 markers had a *q*-value < 0.5 in the European Ancestry PTSD GWAS. These 102 markers mapped to 29 genomic bins, none of which contained any GWS markers. Given the number of markers passing the FDR threshold among the European subsample only, GWAS results from the European Ancestry and African Ancestry non-meta-analyzed subsamples were examined separately.

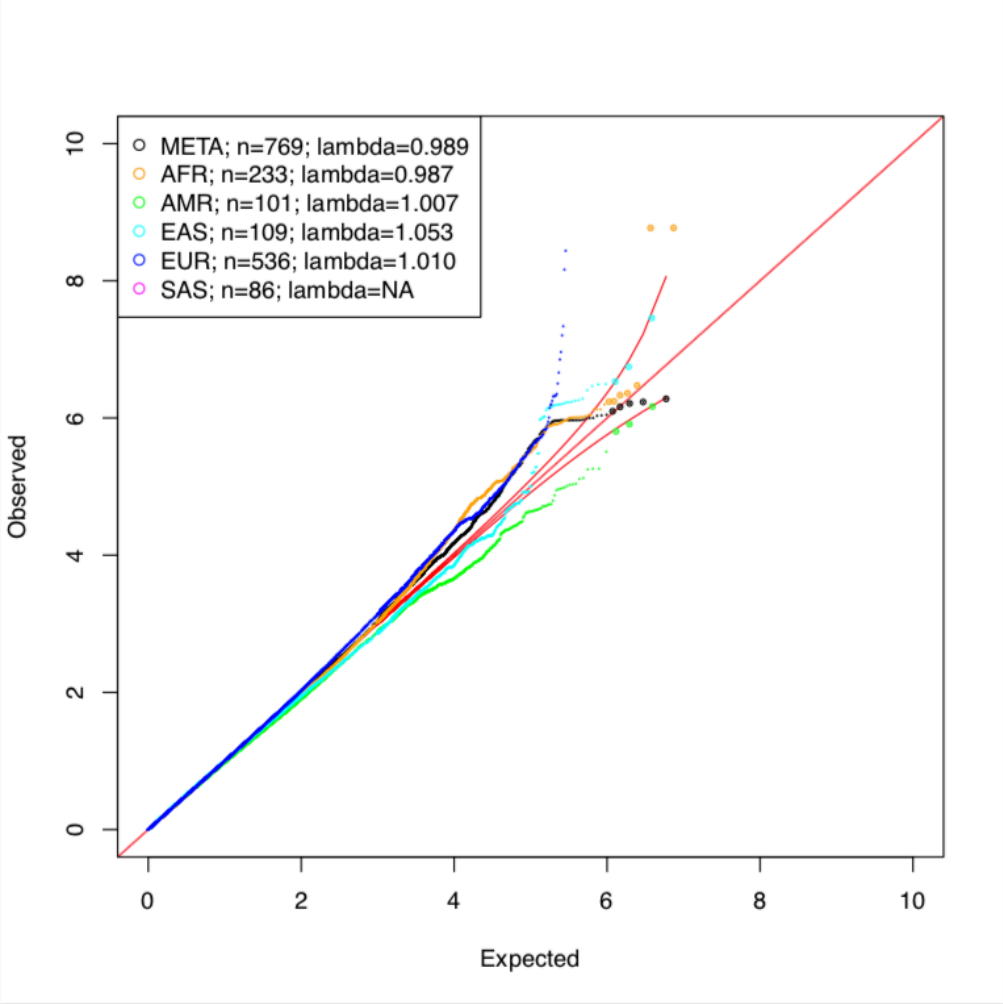

Figure 18. *Q-Q Plot for TRD*; Abbreviations: META=meta-analyzed sample, AFR=African ancestry; AMR=Americas ancestry; EAS=East Asian ancestry; EUR=European ancestry; SAS=South Asian ancestry; Note: The expected distribution of *p*-values is shown on the x-axis, while the observed distribution of *p*-values from GWAS of the TRD is shown on the y-axis for each ancestry subgroup. All *p*-values are represented as –log10(P). The top and bottom red lines represent 95% confidence intervals. Lambdas and *p*-values were not available for SAS because no *p*-values within this subsample met all of the quality control cut-offs (i.e., minor allele frequency, hardy-weinberg equilibrium, imputation quality).

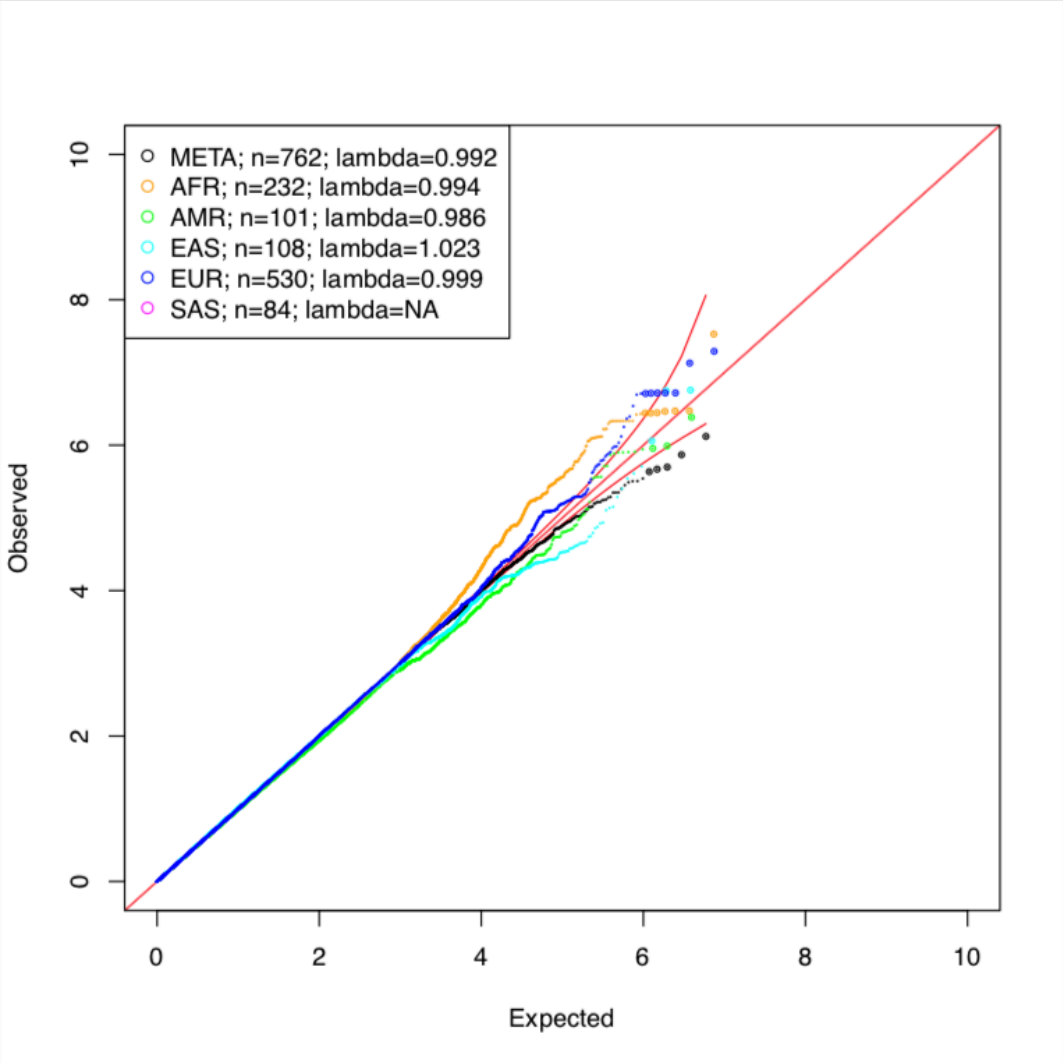

Figure 19. *Q-Q Plot for PTSD;* Abbreviations: META=meta-analyzed sample, AFR=African ancestry; AMR=Americas ancestry; EAS=East Asian ancestry; EUR=European ancestry; SAS=South Asian ancestry; Note: The expected distribution of *p*-values is shown on the x-axis, while the observed distribution of *p*-values from GWAS of the TRD is shown on the y-axis for each ancestry subgroup. All *p*-values are represented as –log10(P). The top and bottom red lines represent 95% confidence intervals. Lambdas and *p*-values were not available for SAS because no *p*-values within this subsample met all of the quality control cut-offs (i.e., minor allele frequency, hardy-weinberg equilibrium, imputation quality).

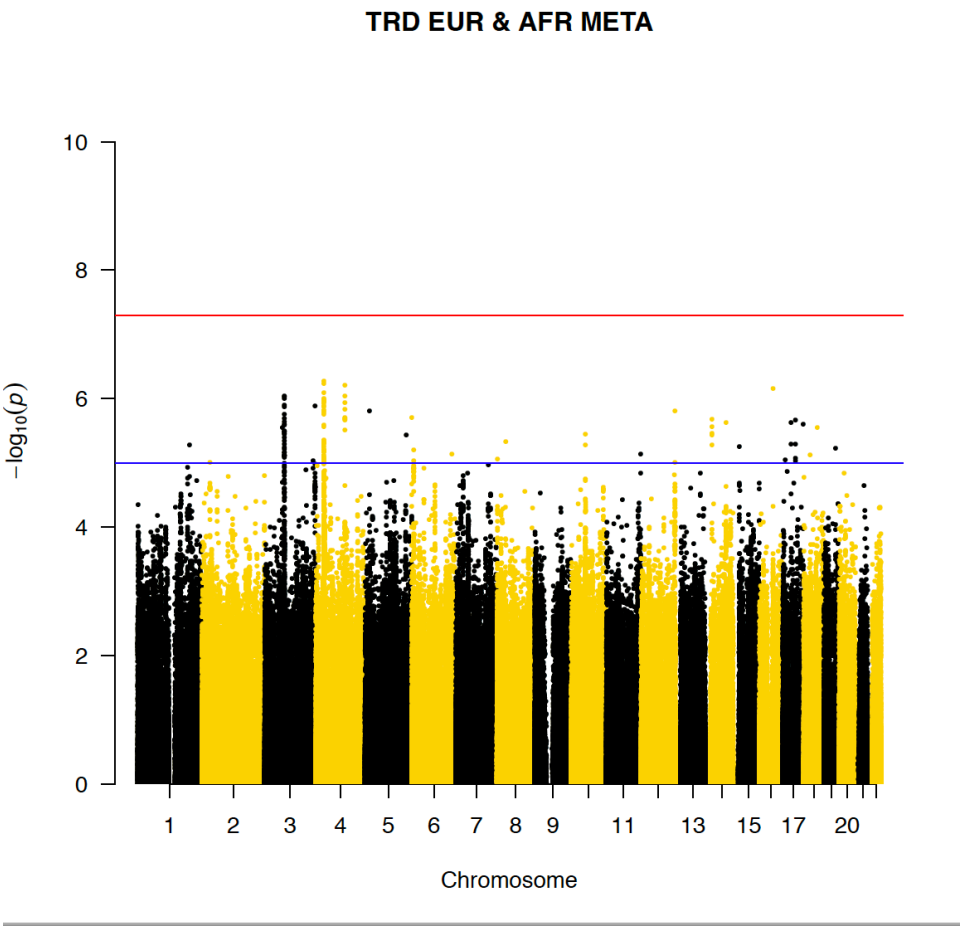

Figure 20. *Manhattan Plot for TRD*; Note: This figure plots the –log10(p) values of associations for TRD by chromosome. The red line represents genome-wide significance ($p = 5x10^{-8}$), while the blue line indicates a suggestive association threshold ($p = 1x10^{-5}$).

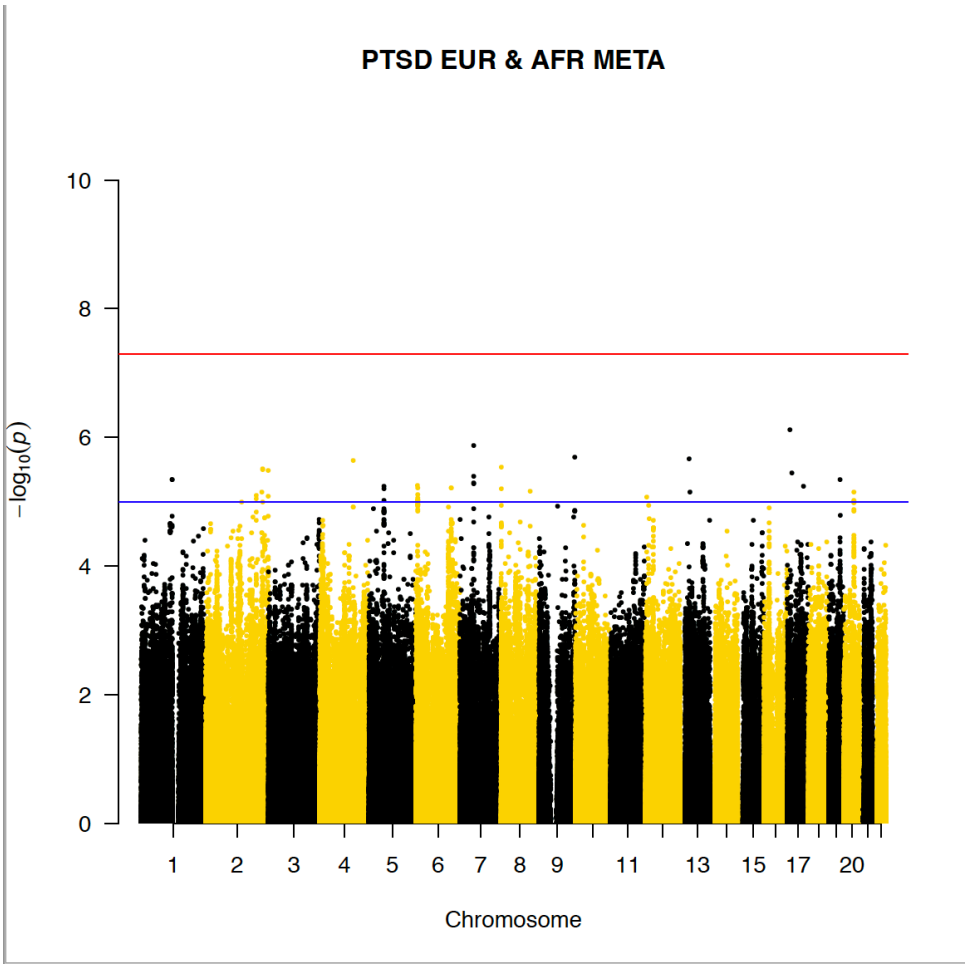

Figure 21. *Manhattan Plot for PTSD*; Note: This figure plots the –log10(*p*) values of associations for PTSD by chromosome. The red line represents genome-wide significance ($p = 5x10^{-8}$), while the blue line indicates a suggestive association threshold ($p = 1x10^{-5}$).

European GWAS for TRD. Post filtering of the European Ancestry GWASs revealed that results were available for 7,470,377 markers for TRD. Lambda values (λ= 1.010) were close to 1, suggesting low bias. However, a lambda value of >1 for TRD suggests that it is possible *p*-values resulting from the GWAS analyses were overinflated and therefore lower (more significant) than would be expected by chance. FDR analysis showed 1306 markers with *q*-

value < 0.5 for TRD. The markers for TRD mapped onto 450 genomic bins, 17 of which contained at least one GWS marker (Table 13), totaling to 28 total GWS markers (Figure 22).

LocusZoom (Pruim et al., 2010), an online plotting program that allows for regional visualization of GWAS results, was used to visualize genes of interest (i.e., genes with >3 SNPs within 10kb from one another) resulting from the TRD GWAS among the European Ancestry sample. –log10P values for SNPs +/- 200 kilobases (kb) from the specified gene of interest were plotted, along with their LD correlations in relation to the index SNP (defined here as the SNP with the lowest *p*-value). The largest number of GWS SNPs (i.e., 8 SNPs: *rs199722259, rs200673580, rs199804610, rs114235862, rs147240636, rs201478890, rs202014912, rs201240393*) were associated with the *preferentially expressed antigen in melanoma gene* (*PRAME*) gene, a protein coding gene that encodes an antigen that is preferentially expressed in human melanomas (Baren, 1998). All but one SNP (*rs114235862*) within the *PRAME* gene were negatively associated with TRD, suggesting that the minor alleles for these SNPs were protective against TRD. A LocusZoom plot (Figure 23) demonstrated several SNPs in high LD with the top SNP (*rs199804610*) associated with *PRAME* resulting from the TRD European Ancestry GWAS.

The second largest number of GWS SNPs (i.e., 5 SNPs; *rs188721059, rs113756886, rs368279732, rs117450256, rs147143502*) were associated not with one gene but with a cluster of genes found on chromosome 14 between base pairs 106145689 and 106162082, most of which are implicated in immune system functioning (e.g., *IGH, IGHE, abParts;* see Table 13). The direction of effect for the minor alleles in association with TRD suggested a mix of risk (*rs113756886, rs368279732, rs117450256*) and protective (*rs188721059, rs147143502*) SNPs

within this region. A LocusZoom plot (Figure 24) showed that the GWS SNPs identified within this genomic region were not in high LD with one another.

Table 13.

Genome-Wide Significant Markers with a False Discovery Rate of q<0.50 for European Ancestry GWAS of Trauma-Related Drinking to Cope

SNP	CHR	BP	A1	A2	Weight (N)	Z-score	P-value	Direction	P-value	start BP	end BP	nSNP	minP	minQ	Gene	Genes local
rs199722259:12993705:G:A	1	1E+07	a	g	536	-10.047	9.43E-24	-	4.58E-18	12993176	12997649	8	8.17E-29	3.05E-22	None	PRAMEF10, PRAMEF22, PRAMEF4, PRAMEF5, PRAMEF6,
rs200673580:12993706:G:A	1	1E+07	a	g	536	-10.047	9.43E-24	-	4.58E-18							
rs199804610:12993674:G:T	1	1E+07	t	g	536	-11.138	8.17E-29	-	3.05E-22							
rs114235862:12993176:A:G	1	1E+07	a	g	536	10.077	6.98E-24	+	3.66E-18							
rs147240636:12995214:C:T	1	1E+07	t	c	536	-9.861	6.13E-23	-	2.54E-17							
rs201478890:12993699:G:C	1	1E+07	c	g	536	-9.699	3.05E-22	-	1.20E-16							
rs202014912:12997649:G:A	1	1E+07	a	g	536	-10.825	2.63E-27	-	4.84E-21							
rs201240393:12993464:C:T	1	1E+07	t	c	536	-10.25	1.18E-24	-	8.00E-19							
rs72490074:89321752:C:T	2	9E+07	t	c	536	-10.772	4.68E-27	-	6.98E-21	89321752	89321752	1	4.68E-27	6.98E-21	abParts	None
rs17005371:26687761:G:A	2	3E+07	a	g	536	-10.567	4.22E-26	-	3.94E-20	26687761	26687761	1	4.22E-26	3.94E-20	OTOF	DRC1, OTOF
rs62274034:147564145:A:G	3	1E+08	a	g	536	5.794	6.89E-09	+	0.00190369	147564145	147564145	1	6.89E-09	0.00190369	None	None
rs78730434:148354984:G:A	3	1E+08	a	g	536	-9.911	3.71E-23	-	1.63E-17	148354984	148354984	1	3.71E-23	1.63E-17	None	TRNA_His
rs62274016:147506715:T:C	3	1E+08	t	c	536	6.635	3.24E-11	+	9.66E-06	147506715	147506715	1	3.24E-11	9.66E-06	None	None
rs62274028:147541217:A:G	3	1E+08	a	g	536	7.001	2.54E-12	+	7.91E-07	147541217	147541217	1	2.54E-12	7.91E-07	None	None
rs10000400:69669309:T:C	4	7E+07	t	c	536	11.955	6.12E-33	+	4.57E-26	69669309	69669309	1	6.12E-33	4.57E-26	None	UGT2B10
rs60721130:64555764:AC:A	7	6E+07	a	ac	536	-10.515	7.34E-26	-	6.09E-20	64555764	64555764	1	7.34E-26	6.09E-20	None	BC044608, CCT6P3, INTS4
rs59268868:9146102:T:C	9	9E+06	t	c	536	5.899	3.66E-09	+	0.00104799	9142493	9161228	10	3.66E-09	0.00104799	PTPRD	None
rs11787886:32299874:A:C	9	3E+07	a	c	536	7.067	1.58E-12	+	5.13E-07	32299874	32299874	1	1.58E-12	5.13E-07	None	None
9:140736922:C:G	9	1E+08	c	g	536	7.091	1.33E-12	+	4.39E-07	140736922	140736922	1	1.33E-12	4.39E-07	None	AK128414, CACNA1B, EHMT1, MIR602
9:19238081:CT:C	9	2E+07	ct	c	536	7.708	1.28E-14	+	4.76E-09	19238081	19238081	1	1.28E-14	4.76E-09	DENND4C	DENND4C, DQ572382
rs12420652:130015292:G:A	11	1E+08	a	g	536	-7.397	1.39E-13	-	4.95E-08	130015292	130015292	1	1.39E-13	4.95E-08	None	APLP2, DQ600312, ST14
rs61953590:63995773:G:C	13	6E+07	c	g	536	-5.466	4.60E-08	-	0.01208814	63995773	63995773	1	4.60E-08	0.01208814	None	None
rs188721059:106145689:C:T	14	1E+08	t	c	536	-10.717	8.46E-27	-	1.05E-20	106145689	106162082	5	3.41E-28	8.49E-22	abParts, DKFZp686O16217, IGH@, IGHE	abParts, DKFZp686O16217, ELK2AP, epsilon
rs113756886:106161852:G:GAC	14	1E+08	g	gac	536	11.01	3.41E-28	+	8.49E-22							
rs368279732:106162082:A:G	14	1E+08	a	g	536	10.609	2.70E-26	+	2.84E-20							
rs117450256:106156655:A:G	14	1E+08	a	g	536	10.189	2.21E-24	+	1.38E-18							
rs147143502:106151934:G:A	14	1E+08	a	g	536	-10.464	1.27E-25	-	9.45E-20							
rs73626693:57397794:T:C	19	6E+07	t	c	536	10.034	1.08E-23	+	5.03E-18	57397794	57397794	1	1.08E-23	5.03E-18	None	MIMT1, PEG3, ZIM2

Note: SNP = Single Nucleotide Polymorphism; CHR = Chromosome; BP = Base Pair; A1 = Effect Allele; A2 = Alternate Allele; nSNP = Number of SNPs in Identified Region; minP = Lowest P-value Detected within Identified Region

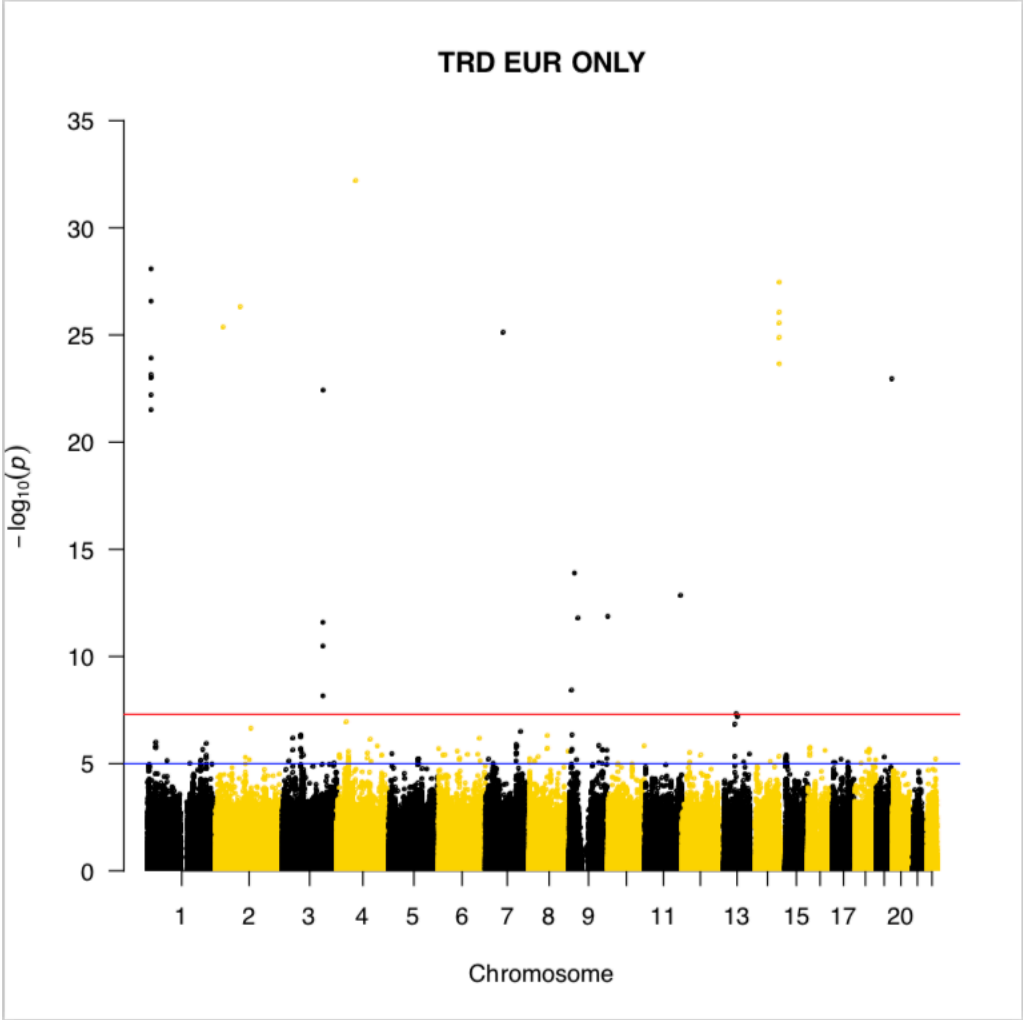

Figure 22. *Manhattan Plot for TRD within the European Ancestry Subsample;* Abbreviations: EUR=European Ancestry subsample; Note: This figure plots the –log10(*p*) values of associations for PTSD by chromosome. The red line represents genome-wide significance ($p = 5x10^{-8}$), while the blue line indicates a suggestive association threshold ($p = 1x10^{-5}$).

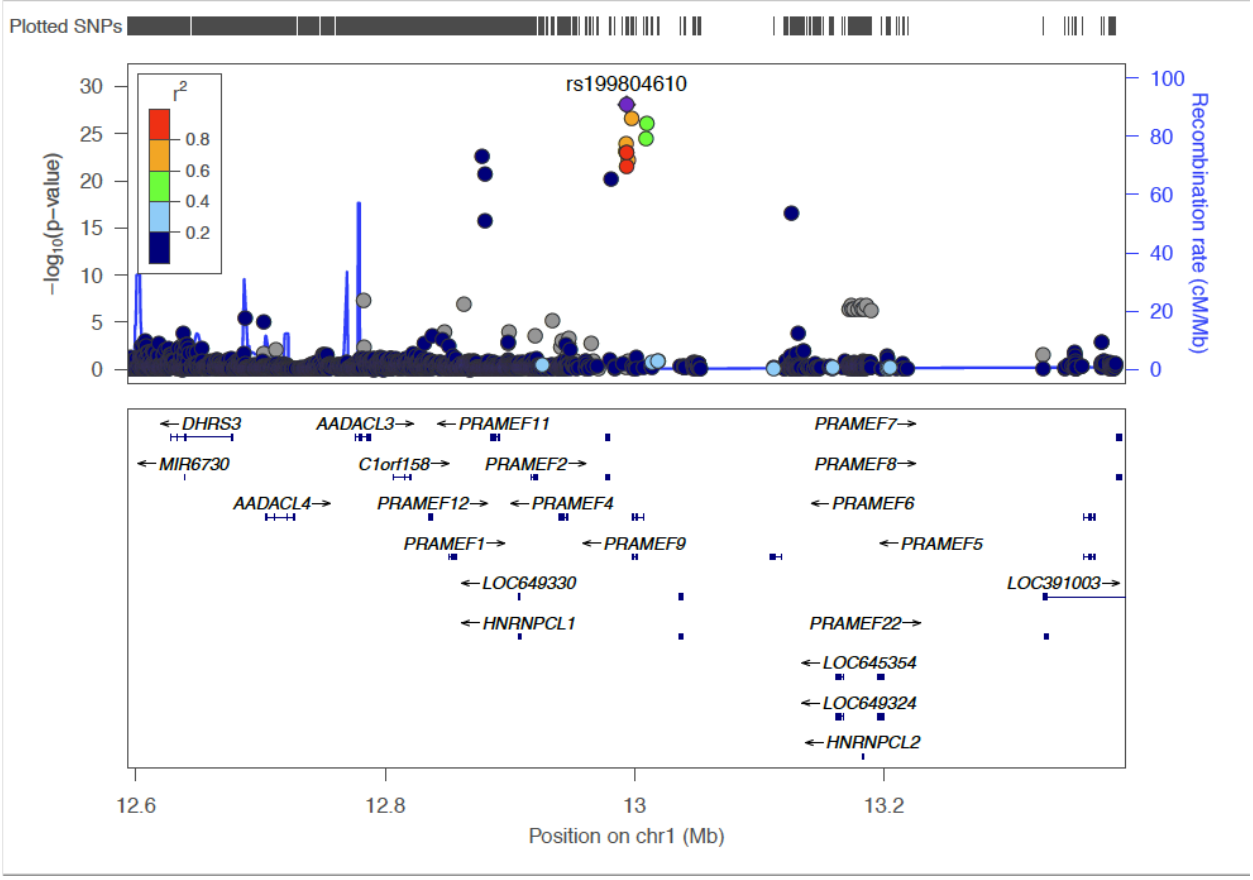

Figure 23. *LocusZoom Plot for TRD Gene of Interest PRAME Among European Ancestry Subsample;* Note: Associations for SNPs within/surrounding the gene of interest *PRAME* (+/- 200 kb) from the TRD European Ancestry GWAS are shown here. Rs19984610, the SNP with the smallest *p*-value, was used as the index SNP. The x-axis shows the position of each SNP, while the y-axis reflects the *p*-value, transformed to –log10(*p*). Magnitude of linkage disequilibrium for each SNP with the index SNP (r2) is represented by different colors, with red being highest and blue being lowest.

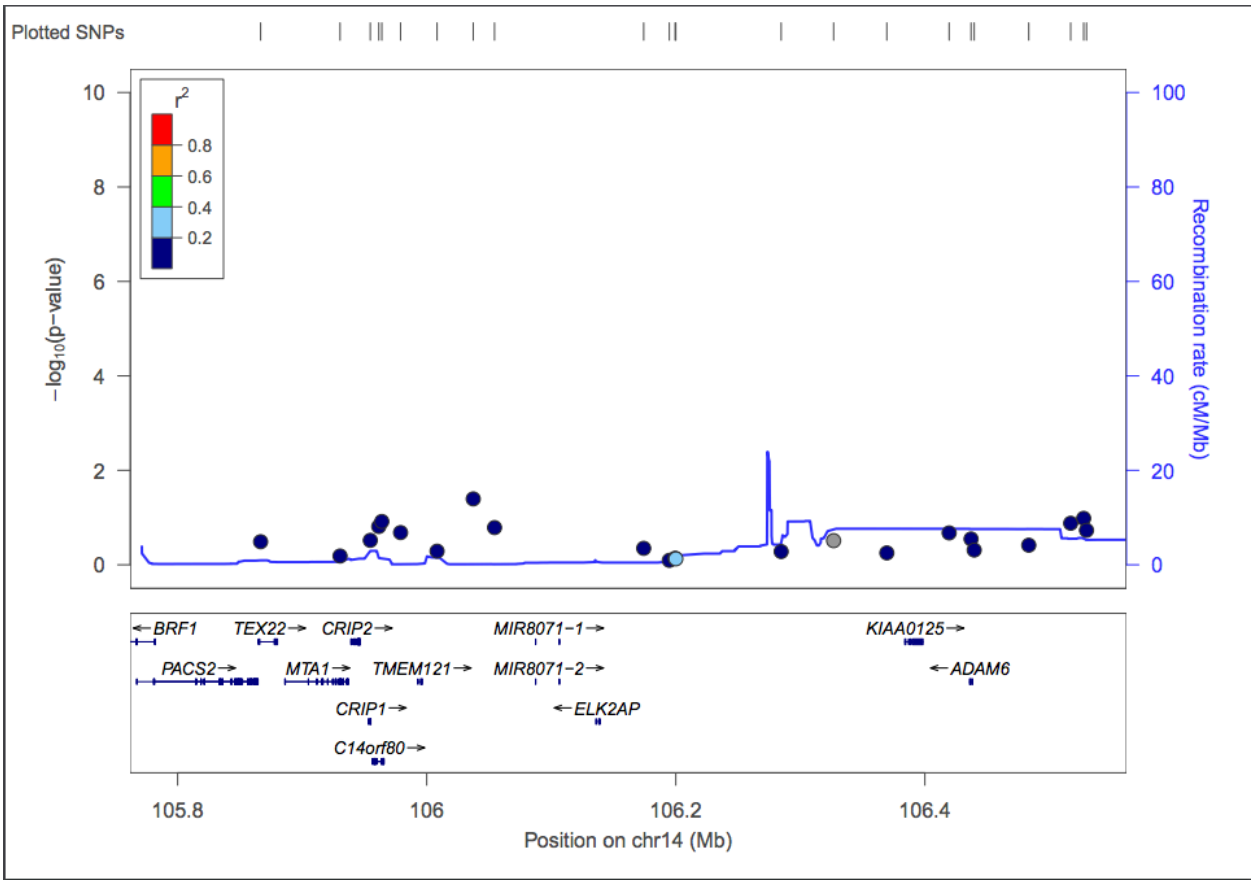

Figure 24. *LocusZoom Plot for TRD Region of Interest on Chromosome 14 Among European Ancestry Subsample;* Note: Associations for SNPs within the region associated with the highest number of GWS SNPs (+/- 200 kb) from the TRD European Ancestry GWAS are shown here. The x-axis shows the position of each SNP, while the y-axis reflects the *p*-value, transformed to –log10(*p*). Magnitude of linkage disequillibrium for each SNP with the index SNP (r2) is represented by different colors, with red being highest and blue being lowest.

European GWAS for PTSD. Post filtering of the European Ancestry GWASs revealed that results were available for 7,460,285 markers for PTSD. Lambda values (λ= 0.999) were close to 1, suggesting low bias. FDR analysis showed 132 markers with *q*-value < 0.5 for PTSD. The markers for PTSD mapped onto 37 genomic bins, zero of which contained at least one GWS marker (Figure 25).

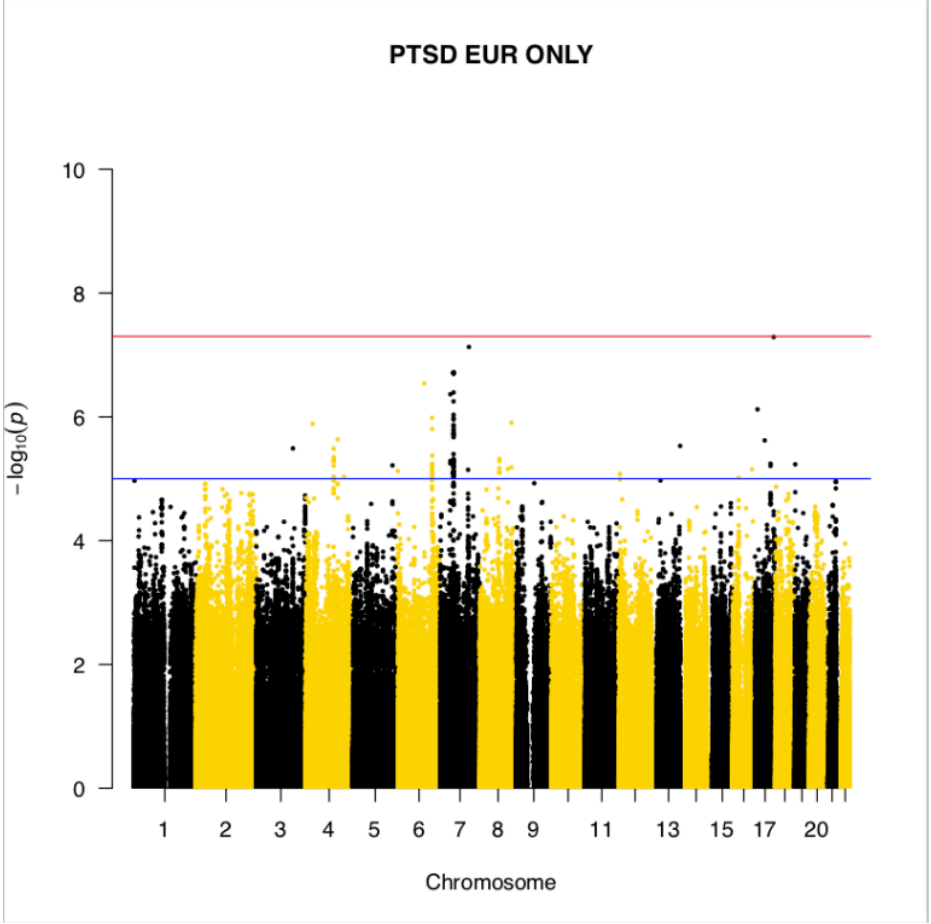

Figure 25. *Manhattan Plot for PTSD within the European Ancestry Subsample*; Abbreviations: EUR=African Ancestry subsample; Note: This figure plots the –log10(*p*) values of associations for PTSD by chromosome. The red line represents genome-wide significance ($p = 5x10^{-8}$), while the blue line indicates a suggestive association threshold ($p = 1x10^{-5}$).

African GWAS for TRD & PTSD. Post filtering of the African Ancestry GWAS revealed that results were available for 7,395,732 and 7,386,457 markers for TRD and PTSD, respectively. Lambda values for TRD (λ=0.987) and PTSD (λ= 0.994) were slightly below 1, indicating that the *p*-values resulting from the GWAS analyses were underinflated and therefore higher (less significant) than would be expected by chance. FDR analysis indicated that the zero markers in either the TRD or the PTSD meta-analyzed GWASs had a *q*-value < 0.50, consistent with findings from the meta-analysis. Manhattan plots for the African subsample are presented for TRD and PTSD in Figures 26 and 27, respectively.

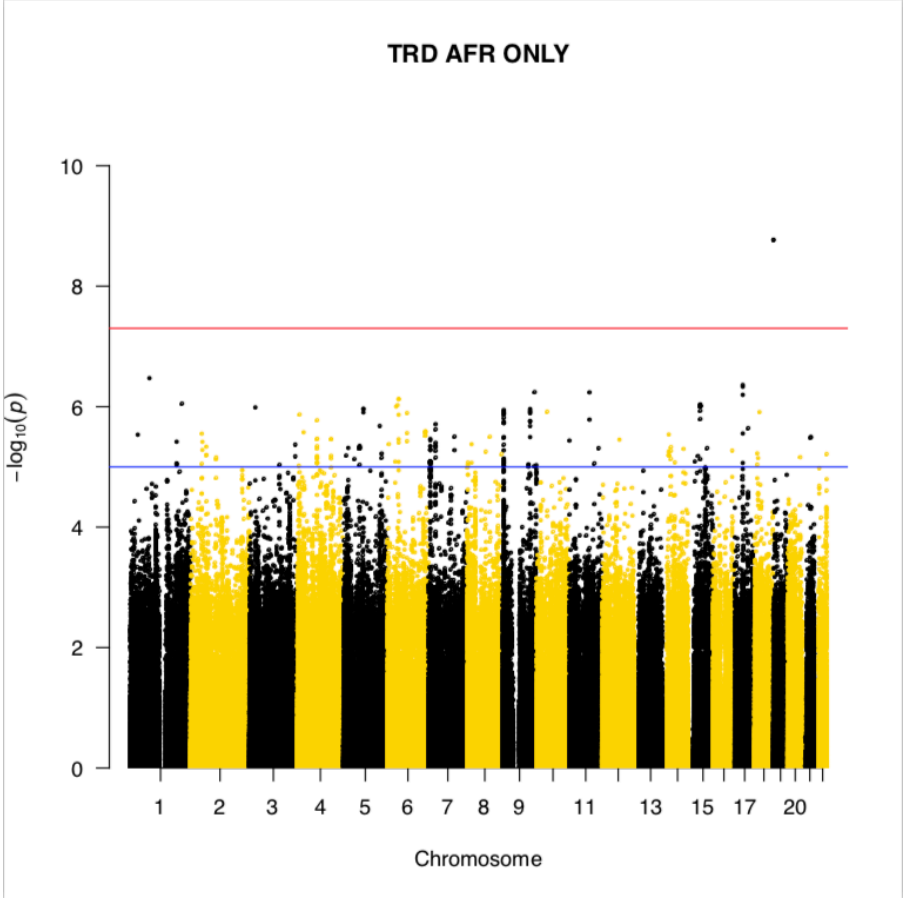

Figure 26. *Manhattan plot for TRD within the African Ancestry Subsample*; Abbreviations: AFR=African Ancestry subsample; Note: This figure plots the –log10(*p*) values of associations for PTSD by chromosome. The red line represents genome-wide significance ($p = 5x10^{-8}$), while the blue line indicates a suggestive association threshold ($p = 1x10^{-5}$).

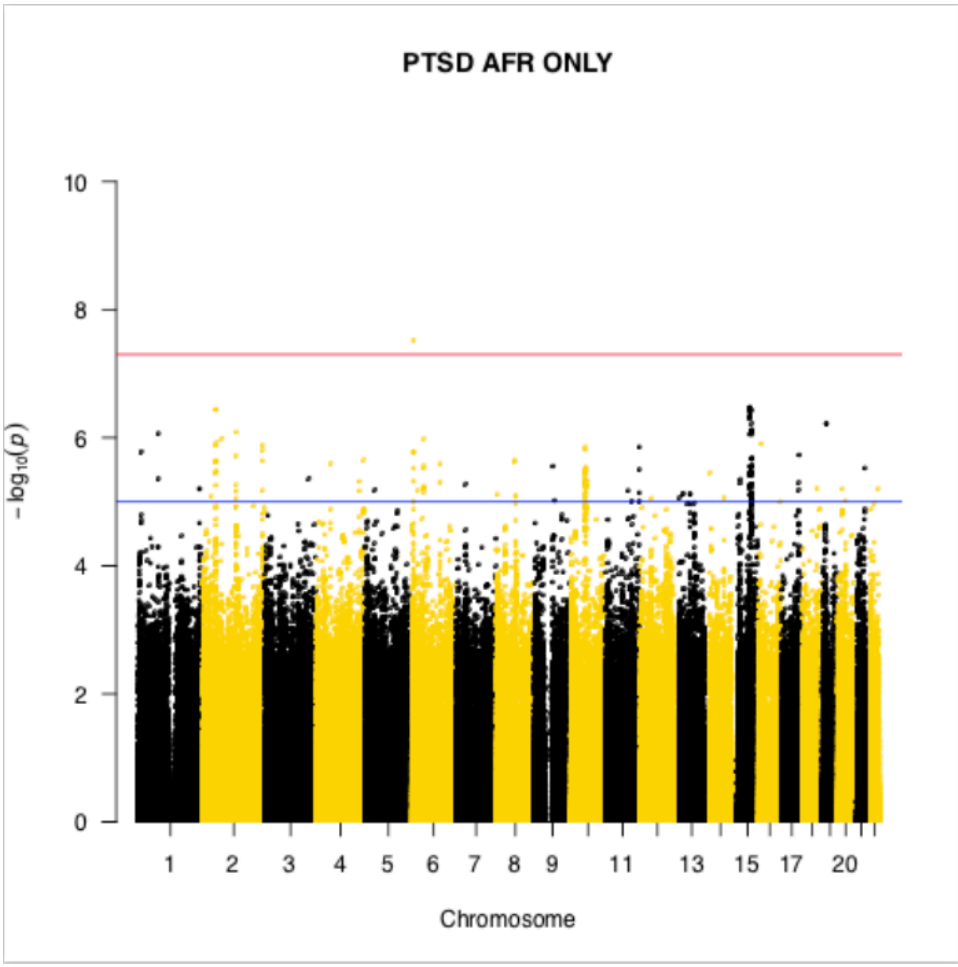

Figure 27. *Manhattan Plot for PTSD within the African Ancestry Subsample;* Abbreviations: AFR=African Ancestry subsample; Note: This figure plots the –log10(*p*) values of associations for PTSD by chromosome. The red line represents genome-wide significance ($p = 5x10^{-8}$), while the blue line indicates a suggestive association threshold ($p = 1x10^{-5}$).

Aim 3b: Bivariate Analyses

Cross-Trait LDSC: Overlap of SNP-Based Heritability between TRD and PTSD. Cross-trait LDSC was used to calculate pairwise genetic correlation (rg) between TRD and PTSD using GWAS summary statistics from the LEAU European Ancestry subsample (TRD) and the PTSD-PGC European Ancestry meta-analyzed sample (PTSD). The genetic correlation between TRD and PTSD was not statistically significant in this sample -.778 (SE = .664), likely due to the unreliable heritability estimate for TRD due to the small sample size of LEAU.

Polygenic Risk Scores. Polygenic risk scores (PRS) for PTSD were calculated using summary statistics from the PTSD-PGC Freeze 2 European meta-analysis (Nievergelt et al., 2018). First, the ability of these PRS to predict PTSD in the LEAU sample was tested. Model fit was optimized at a *p*-value threshold of 0.241 (see Figure 28). Nagelkerke's pseudo-R^2 showed that PRS at this *p*-value threshold explained a maximum variance of 1.35% in PTSD (b = -35.885, SE = 12.259, $p = 0.003$). Notably, PRS values were all negative, which may be an effect of natural selection, wherein effect alleles occur at a lower frequency than non-effect alleles on average, thereby resulting in PRS with a mean negative value (Choi, Mak, & O'Reilly, 2018). For ease of interpretation, PRS were standardized to have a mean score of 0 and standard deviation of 1. There was a strong association between PRS and PTSD symptom severity (β = -1.963, SE = 0.482, $p < .001$), but in the opposite direction than what was expected. There was a nominal association between PRS for PTSD and TRD composite score (β = -0.131, SE = .072, $p = .068$), also in the opposite direction that what was expected.

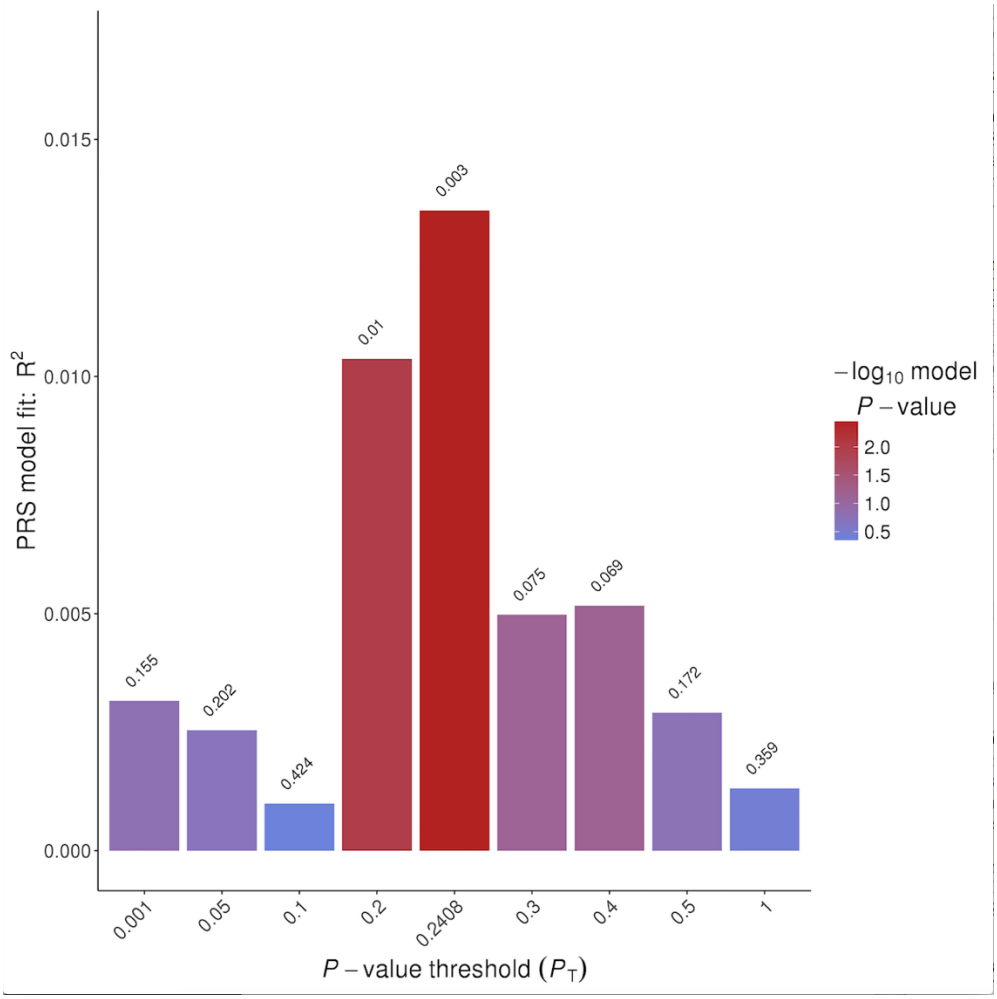

Figure 28. *Bar Plot Displaying Model Fit of the PRS at Various P-value Thresholds*

Aim 3 Summary:

- There was a lack of evidence to suggest that TRD or PTSD were significantly heritable in the present sample, likely due to low power resulting from low sample size.
- A number of genome-wide significant SNPs were associated with TRD in the European Ancestry subsample. The largest groups of genome-wide significant SNPs resulting from the TRD GWAS were associated with gene regions that either had antithetical effects to the gene *ALDH* (*PRAME*) or were implicated in immune system functioning.
- Although the other GWAS analyses (i.e., meta-analysis of both phenotypes, PTSD in the European subsample, TRD in the African subsample, PTSD in the African subsample) did not reveal any genome-wide significant findings, there were a number of nominally significant SNPs and suggestive loci to explore with increased sample sizes.
- Polygenic risk scores for PTSD were strongly associated with PTSD and nominally associated with TRD, although in the opposite direction (protective) than expected.

Discussion

The aims of the present study were threefold. First, the present study examined the psychometric properties of a novel questionnaire designed to assess trauma-related drinking (TRD). Second, the self-medication model was investigated using a mediational framework by testing the indirect effect of PTSD onto AUP via TRD, accounting for DMQ-Cope and as moderated by sex. Third, the present study investigated independent and overlapping genetic risk for TRD and PTSD by testing SNP-based heritability, associations between potential risk variants (SNPs) and both outcomes, and individual polygenic risk for both outcomes. Findings from each aim are discussed in turn.

Aim 1: Psychometric Evaluation of TRD Questionnaire

Overall Summary of Findings

The present study sought to fill a gap in the current literature by creating a measure of drinking motives specific to coping with symptoms of PTSD, which we named the Trauma Related Drinking questionnaire (TRD). Broadly, we found evidence to suggest that TRD is a more specific measure of drinking to cope motives compared to the commonly used DMQ-Cope. Additionally, findings demonstrate support for the external validation of TRD, both with regard to PTSD and alcohol consumption and related problems. Findings from the four aims are discussed in turn.

What are the distributional properties of TRD and how do they compare to DMQ-Cope?

The rates of endorsement of TRD and DMQ-Cope were notably different (34.71% vs. 72.96%), suggesting that TRD is a more specific measure of drinking motives. This was further supported by a higher percentage of TRD endorsement (40.85%) among individuals with any PTSD symptoms. This mirrors the greater PTSD literature, wherein the majority of trauma-exposed individuals do not go on to develop subsequent PTSD (Koenen, Ratanatharathorn, Bromet, Karam, & Stein, 2018) and therefore is conceptually consistent with the idea that the majority of trauma-exposed individuals would not develop problematic drinking related to their PTSD symptoms. This difference between high rates of endorsement of general drinking to cope motives and lower endorsement of drinking to cope with PTSD symptoms specifically confutes the common misconception tainting the self-medication literature to date that drinking to cope with negative affect is synonymous with drinking to cope with trauma-related symptoms specifically. This finding suggests that it is possible the relationship between coping drinking motives and PTSD has been substantially overestimated by previous research (e.g., Grayson &

Nolen-Hoeksema, 2005; Kaysen et al., 2007; McCabe et al., 2018; Tomaka et al., 2017). Moreover, when comparing the frequency distributions of TRD and DMQ-Cope endorsement among PTSD and AUP cases versus controls, the distributions of TRD and DMQ-Cope were substantially more dispersed among cases compared to controls, which demonstrated high positive skewness. This higher endorsement in PTSD and AUP cases versus controls is expected, given that TRD was designed to specifically assess drinking to cope with symptoms related to PTSD and therefore should not be highly endorsed by individuals not experiencing symptoms.

What is the factor structure of TRD, how does it relate to DMQ-Cope, and how do both measures relate to PTSD?

CFA results demonstrated support for TRD as a unitary latent construct, suggesting that the associations among all 4 TRD items were indicators of a single shared component (DeCoster, 1998), thereby providing support for the use of a TRD composite score in the subsequent analyses for Aims 2 and 3. This is consistent with much of the DMQ literature to date, which has broadly found support for the DMQ-Cope subscale as a unitary factor, both in the original three factor DMQ (Cooper et al., 1992) and the four factor DMQ-R (Cooper, 1994). Notably, however, evaluation of the Modified DMQ-R (Blackwell & Conrod, 2003), which extended the DMQ-R by adding items relevant to both coping-anxiety and coping-depression, revealed that a five factor model separating anxiety-coping and depression-coping into separate factors fit the data better than a four factor model, with the coping-anxiety and coping-depression items constrained to load on a single coping factor (Grant et al., 2007). Given TRD was designed to represent one specific type of drinking coping motives (PTSD symptom related), support for a single common factor was found as hypothesized.

As expected, the TRD and DMQ-Cope common factors were correlated. The latent factors were more highly correlated (ρ = .757) compared to the composite scores (r = .60). This discrepancy is not unexpected, as it is often the case that correlations between common factors are higher than correlations between the corresponding composite sum scores, due to the consideration of item specific variance and random error in the calculation of the common factors (Ree & Carretta, 2006). In other words, the common factor version is higher due to the removal of item specific variance and measurement error, which creates a more "purified" measure of variation. When comparing the predictive effects of the four PCL-5 common factors on the TRD and DMQ-Cope common factors in the same model, results showed that only the arousal factor of the PCL-5 significantly predicted either common factor and that this prediction was stronger for TRD compared to DMQ-Cope (see Figure 12 for review). This finding is consistent with the self-medication framework, wherein the stress-response dampening effects of alcohol may be viewed by subjects as particularly effective in alleviating PTSD symptoms related to arousal (e.g., hypervigilance, irritability, poor sleep), therefore reinforcing the use of alcohol to cope. The stronger prediction of PTSD onto TRD compared to DMQ-Cope provides further support for the use of TRD as more specific measure of drinking to cope in the context of PTSD symptoms compared to DMQ-Cope.

How does TRD relate to PTSD?

How well does each TRD item relate to each PTSD symptom cluster?

Findings demonstrated good external validation of the TRD measure at the item level in relation to PTSD symptom clusters, such that each of the four PCL-5 common factors (i.e., symptom clusters) significantly predicted their analogous TRD items, with the exception of the avoidance factor, which did not significantly predict any of the TRD items. In other words, the

PCL-5 factor representing re-experiencing PTSD symptoms significantly predicted the TRD item representing drinking to cope with re-experiencing PTSD symptoms and so on and so forth with the exception of avoidance. Instead, the PCL-5 reexperiencing and arousal factors significantly predicted the TRD avoidance item (Item 2). This suggests that the majority of TRD items are adequately capturing one's propensity to drink to cope with specific PTSD symptoms within this college sample. Conceptually speaking, the lack of direct association between the PTSD avoidance symptom cluster and the TRD avoidance item may not suggest a lack of external validation. For example, if an individual is experiencing high levels of avoidance symptoms related to PTSD (e.g., avoiding crowds, purposely not watching war movies or playing violent video games), it stands that, when examined via a learning theory-informed self-medication framework, the avoidance symptoms themselves may be serving as temporary negative reinforcers of the PTSD-related distress (Foa, Hembree, & Rothbaum, 2007) and, therefore, drinking to cope with said avoidance symptoms may not be necessary nor particularly effective. However, for an individual experiencing high levels of re-experiencing and hyperarousal, it stands that the dampening effects of alcohol related to cognition, memory, and physiology may serve as a powerful negative reinforcer for these symptoms.

How do PCL-5 factors relate to latent TRD?

Consistent with the model in which the PCL-5 common factors were regressed onto both the TRD and DMQ-Cope common factors, the model regressing the PCL-5 common factors onto the TRD common factor only demonstrated that the PTSD arousal factor alone significantly predicted TRD. Once more, this finding could be interpreted via a self-medication framework, wherein the stress-response dampening effects of alcohol may be particularly effective in alleviating PTSD symptoms related to arousal (e.g., hypervigilance, poor sleep), therefore

reinforcing the use of alcohol to cope. This model of reinforcement, otherwise referred to as the self-medication model, could then have subsequent effects on alcohol consumption and related problems. This is consistent with prior experimental research has demonstrated a link between higher alcohol stress-response dampening effects and heightened risk for alcohol use disorder (Sher & Levenson, 1982; Zimmermann et al., 2004). This conceptualization of the present findings provides further support for the use of TRD within trauma populations, which specifically assesses drinking to cope to alleviate symptoms of arousal, as opposed to the more general DMQ-Cope, which assesses broad negative affect and does not consider arousal.

Does TRD predict alcohol consumption and related consequences/dependence?

To that end, TRD significantly predicted both alcohol consumption and related problems while accounting for the effects of the PTSD factors and the covariates of sex and lifetime trauma load in the final model. TRD differentially predicted the two AUDIT common factors, such that it more strongly predicted alcohol consequences/dependence compared to consumption. This is consistent with the broader drinking motives literature, which has demonstrated a stronger association between DMQ-Cope and alcohol problems rather than consumption (Read, Wood, Kahler, Maddock, & Palfai, 2003). This finding may offer additional support for the self-medication model, such that, theoretically, the reinforcing effects of alcohol for the specific purposes of alleviating trauma-related symptoms would more strongly be associated with repeated use that ultimately leads to increased negative consequences and dependence, as opposed to past month consumption generally. Moreover, results suggest TRD may be a clinically useful measure, given its ability to identify problematic alcohol use and dependence. For instance, high levels of alcohol consumption is reasonably normative among college samples, given young adulthood represents the age group with the highest levels of

alcohol consumption (Ahrnsbrak et al., 2017; Chen & Jacobson, 2012). Less normative is a "tipping over" into dependence, represented by the fact that a majority of individuals ages 18 and older in the U.S. consume alcohol (86.40%; Abuse & Administration, 2014) but far fewer meet criteria for alcohol dependence (6.2%; Abuse & Administration, 2014). Thus, the stronger association between TRD and alcohol problems/dependence compared to consumption provides preliminary evidence for the TRD's ability to distinguish between consumption levels and more clinically relevant alcohol-related consequences and dependence within a college sample. However, these findings with regard to differential prediction should be interpreted with some caution given that the alcohol use and consequences/dependence common factors derived from the AUDIT were strongly correlated (r = 0.738) and therefore may have left little variance explained by other variables in the model.

Limitations

Limitations specific to Aim 1 include high correlations between the four PCL-5 factors as well as between the two AUDIT factors, a potential indicator of poor discriminant validity (Kenny, 2012). Furthermore, the association between TRD and the PCL-5 arousal factor only arguably limits the criterion validity of TRD. Criterion validity is defined as the extent to which an individual's score on a measure is associated with other variables one would expect them to be associated with (DeVellis, 2016). Therefore, given the intended purpose of TRD is to measure an individual's drinking motives with regard to alleviating (all) symptoms of PTSD, then the lack of association between TRD and the PCL-5 re-experiencing, avoidance, and negative alternations in cognition and mood factors is potentially problematic. However, given TRD is a new measure and trauma-related drinking to cope motives have yet to be explicitly studied, in addition to the fact that the PCL-5 arousal factor alone predicted DMQ-Cope as well,

it is possible that drinking to cope motives, both general and trauma-specific, are largely driven by arousal states. Further research into the association between TRD and drinking to cope motives more generally and physiological arousal states is warranted, as is replication and extension of the current findings in different samples. Lastly, comparisons were made between TRD and the commonly used DMQ-Cope, but the present study failed to compare the TRD with the anxiety-coping and depression-coping subscales of the more refined Modified DMQ-R (Blackwell & Conrod, 2003). Further investigation into the TRD measure would benefit from examining its associations with anxiety and depression as well as PTSD and future studies should compare the psychometric properties and potential clinical utility between TRD and the anxiety-coping and depression-coping subscales of the Modified DMQ-R.

Clinical Implications and Future Directions

The present study findings show support for the use of TRD as a more specific assessment of trauma-related coping drinking motives compared to frequently used DMQ-Cope. High differential endorsement between endorsement of TRD (one third of sample) and DMQ-Cope (three-fourths of sample) in this representative college sample suggests that the use of TRD as a screening tool among college mental health centers could lead to more accurate identification of individuals drinking to cope with symptoms of PTSD versus drinking to cope for generalized, non-trauma specific motives. Furthermore, given TRD was more strongly associated with alcohol-related consequences and dependence compared to general consumption, the use of TRD as a screening tool would potentially help to disrupt the self-medication process. For example, identification of drinking to cope with symptoms of PTSD would provide a valuable treatment target and opportunity for the introduction of alternative and adaptive coping strategies as well as PTSD treatment, ultimately decreasing one's likelihood of experiencing the

reinforcing effects of alcohol and therefore decreasing one's risk of experiencing negative alcohol-related consequences and/or dependence. The TRD questionnaire used in the present analyses should be evaluated in multiple representative samples to ensure its validity and utility among varying populations.

Aim 2: Investigation of the Self-Medication model

Overall Summary of Findings

The self-medication model is the most predominantly used model to explain PTSD-AUD comorbidity, although the current literature to date has limitations (e.g., lack of trauma-specific drinking to cope measures, failing to employ a mediational statistical design, purely cross-sectional data). This study attempted to address these limitations and in doing so produced three main findings. First, results showed general support for the self-medication model. Second, results showed evidence for key sex differences with respect to the self-medication model, such that males with high levels of PTSD were more likely to drink to cope with trauma-related distress than females. Third, results suggested that general drinking to cope motives (DMQ-Cope) and drinking motives related to coping with trauma-related symptoms specifically (TRD) have unique effects on the relation between PTSD and AUP.

Phenotypic Support for the Self-Medication Hypothesis

Cross-Sectionally

Results from the mediation models were consistent with the self-medication hypothesis, such that TRD explained a significant proportion of the relation between PTSD symptoms and AUP. Moreover, the indirect effect of TRD remained significant when accounting for the indirect effect of DMQ-Cope within the same model. Although follow-up analyses determined the indirect effects for TRD and DMQ-Cope were not significantly different from one another, the mediated proportion of the total effect was greater for TRD (43.30%) than it was for DMQ-Cope (37.04%) when both variables were allowed to correlate within the model. These results suggest that both TRD and DMQ-Cope account for unique variance in the relation between PTSD and AUP, providing further evidence to support that these are associated, yet separate

constructs. Given the TRD measure was created by the study authors to satisfy the lack of explicit measurement of drinking to cope with trauma-related symptoms, these findings are a novel contribution to the self-medication literature. However, present study findings that DMQ-Cope significantly mediated the PTSD-AUP relationship are consistent with prior research finding support for DMQ-Cope as a mediator between trauma exposure and alcohol problems (Grayson & Nolen-Hoeksema, 2005) and PTSD symptoms and problematic drinking (Tomaka et al., 2017). This prior research in combination with the novel TRD findings provide iterative support for the self-medication model. Further, present findings demonstrating a unique effect of TRD on PTSD-AUP comorbidity above and beyond DMQ-Cope support the use of a specific measure of trauma-specific drinking motives moving forward.

Longitudinally

Given the basic causal premise of the self-medication model (i.e., PTSD increases risk for subsequent AUP via trauma-specific drinking to cope), the present study sought to substantiate the primary analyses by conducting follow-up analyses applying longitudinal data to the tested mediation models and found that findings were generally consistent with those generated in the primary correlated mediation model. However, the moderation by sex could not be replicated due to poor model fit and multicollinearity between the PC-PTSD and moderator variables. Similar to the cross-sectional analyses, the overall model was significant and both TRD and DMQ-Cope accounted for significant proportions of the variance between PC-PTSD and AUD. However, unlike the cross-sectional analyses in which the proportion accounted for by DMQ-Cope and TRD did not differ, the proportion accounted for by DMQ-Cope was significantly higher than that accounted for by TRD in the longitudinal model. This finding could potentially be an artifact of our sample, given that college-age predates the average onset of AUD (Grant et

al., 2015a). Relatedly, it is possible that the AUDIT total score used in the cross-sectional analyses provided a more age-appropriate depiction of alcohol use problems, as opposed to AUD criterion count used in the longitudinal analysis. Furthermore, differences in magnitude of effects seen between the cross-sectional and longitudinal analyses could be a product of either phenotypic strength (i.e., the cross-sectional analyses included comprehensive and validated measures of PTSD and alcohol use, whereas the longitudinal analysis included the brief PC-PTSD screen and a summation of items meant to reflect various AUD criteria) or methodological rigor (i.e., the ability to test these relationships temporally in the longitudinal sample). Another notable potential limitation of the supplemental longitudinal analyses is possible overlap between time point 2 (TRD/DMQ-Cope) and time point 3 (AUD). AUD at time point 3 was assessed in the Spring of 2017 and queried symptoms experienced in the past 12 months. TRD at time point 2 was assessed in the Fall of 2016, potentially confounding the temporal precedent of TRD before AUD. Future studies using other samples and more comprehensive measures of PTSD symptomatology should test the mediational effects of TRD within a longitudinal framework, as such research would ultimately decrease bias that accompanies cross-sectional approaches to mediation (Maxwell & Cole, 2007) and provide further validated empirical support for the self-medication model.

Additional considerations

In addition to testing the veracity of our conceptual model within a longitudinal framework, another notable strength of the present study is the inclusion of potentially relevant factors, such as cohort, sex, race, lifetime trauma load, and trauma type. Failure to account for important confounds likely contributes to the inconsistency of the self-medication literature and may result in misleading or skewed findings. This potential for biased results is exemplified by

the commonly supported finding that only a percentage of individuals go on to develop problem alcohol use following the onset of PTSD (Kessler et al., 2005), indicating that there is an array of confounding risk factors necessary to explain the existence of alcohol abuse in association with PTSD. This reiterates the need for consideration of important confounding factors on the indirect effects of drinking to cope on the relation between PTSD and alcohol use problems. Despite the inclusion of many relevant covariates in the model, future studies should also extend additional risk factors to include other psychiatric conditions, particularly given the fact that alcohol abuse is associated with other psychiatric disorders, including panic disorder, major depression and social phobia (McFarlane, 1998).

Important Sex Considerations

Importantly, the present study also found significant sex effects with regard to the self-medication model and TRD specifically. Although TRD did not differ significantly by sex in a univariate analysis, results from the moderated correlated mediation model demonstrated that sex significantly moderated the relation between PTSD symptoms and both TRD and DMQ-Cope, such that the effects of PTSD on TRD and DMQ-Cope were stronger for males than they were for females, contrary to our hypothesis. A test of sex differences with regard to the self-medication model specifically is highly warranted for a number of reasons. First, there is strong and consistent evidence for sex differences in relation to PTSD (Breslau, Davis, et al., 1998; Kessler et al., 1995) and AUD (Capraro, 2000; Goldstein et al., 2012a). Specifically, the contrast between findings suggesting that women are approximately twice as likely to meet criteria for PTSD in their lifetime than men (Breslau, Davis, et al., 1998; Kessler et al., 1995) and that men are almost twice as likely to meet criteria for AUD in their lifetime than women (Grant et al., 2015a) highlights a complicated sex contradiction in need of unpacking in the context of the self-

medication model, which considers both disorders. Second, the current literature surrounding sex differences with regard to coping drinking motives is highly contradictory (e.g., Cooper, 1994; Fossos et al., 2011; Grant et al., 2007; Park & Levenson, 2002) and charged with methodological inconsistencies (e.g., inconsistent measures used to assess drinking to cope, varying data analytic strategies). Third, sex differences with regard to the self-medication model have, to the best of our knowledge, yet to be explicitly tested, particularly within a mediational framework and with the use of a trauma-specific measure of drinking to cope motives.

The present findings suggest that, despite the absence of significant mean differences in TRD or DMQ-Cope between males and females, in the presence of high PTSD symptoms, males are drinking more to cope with their PTSD symptoms compared to their female counter parts. This finding was contrary to study hypothesis, which assumed that females may be more likely to drink to cope with trauma-related symptoms given their higher rates of PTSD compared to males (Breslau, Davis, et al., 1998; Kessler et al., 1995). Our finding that males drank more to cope with PTSD symptoms in the presence of high PTSD could potentially explain the limited research demonstrating higher rates of PTSD-AUD comorbidity among males compared to females (King et al., 2006), however, the overall literature on sex differences with regard to PTSD-AUD comorbidity is inconsistent (Brady et al., 1993; Brady & Randall, 1999; Goldstein et al., 2012a; Kessler et al., 1997; Sonne et al., 2003). Given the mixed literature on this topic to date, we offer this as one potential thread to add to still forming tapestry. With regard to clinical utility, these findings suggest that assessing for TRD among males may be particularly critical in identifying individuals at potential risk of "self-medicating" through the use of alcohol. It is noteworthy, however, that the present study sample was large and the sex effects demonstrated in the moderated correlated mediation model were relatively small. There is much left to be

unveiled with regard to sex differences in the context of the self-medication model, creating a valuable direction for future research.

Comparing TRD to DMQ-Cope

The present study sought to fill a notable gap in the literature by creating a measure of drinking to cope with trauma-related symptoms specifically (trauma related drinking [TRD]). This was done via modification of a prolific measure of general drinking to cope (DMQ-Cope; Cooper, 1994) in order to query the frequency of alcohol use to cope with symptoms specific to each PTSD cluster (i.e., re-experiencing, avoidance, negative cognitions and mood, and arousal). As hypothesized, TRD was significantly associated with PTSD symptom severity, alcohol use severity, and DMQ-Cope. Notably, TRD and DMQ-Cope were moderately correlated but not multicollinear, suggesting that, as expected, they are associated yet distinct constructs. High discrepancy between endorsement rates of DMQ-Cope (72.96%) compared to TRD (34.71%) provide support for TRD as a specific measure of drinking motives. Compared to DMQ-Cope, which captures general drinking motives non-specific to PTSD and was therefore endorsed by a majority of the trauma-exposed sample, endorsement rates of TRD were much more in line with what we would expect conceptually, wherein the majority of trauma-exposed individuals do not develop subsequent symptoms of PTSD or related problematic drinking. The stark contrast between the rate at which participants endorsed general drinking to cope motives versus drinking to cope with PTSD symptoms specifically belies arguably one of the most commonly accepted fallacies in the self-medication literature to date: that drinking to cope with negative affect is synonymous with drinking to cope with trauma-related symptoms specifically. As such, it is plausible that much of the research to date has grossly overestimated the relation between drinking to cope and PTSD.

Clinical Implications

The present findings, which demonstrate that our novel TRD measure is notably more specific than the commonly used DMQ-Cope among a trauma-exposed sample of undergraduates, suggest that this measure might be a better screening tool among college counseling centers for allocation of services in order to best intervene in the developmental trajectory of PTSD symptoms preceding and problem alcohol use, particularly among trauma-exposed men.

The present findings also incite a need for change in the current self-medication literature, which up until now, has as a whole been operating under the assumption that general drinking to cope is synonymous with drinking to cope with trauma-specific symptoms. Given evidence for the misuse of this broad application, increased use of measures that assess PTSD-symptom-specific alcohol expectancy (P-AEQ; Norman et al., 2008) and creation of measures that assess PTSD-symptom-specific alcohol motives and frequency (i.e., TRD) are warranted. Resolution of this misconception has important clinical implications, particularly given the overwhelming rates of PTSD-AUD comorbidity and related public health outcomes (Brown et al., 1999a; Kessler et al., 2005; Kessler et al., 1995). Creation of a gold standard measure for self-reported trauma-specific drinking to cope, which would serve not only to improve methodology by generating reliability and validity, but also could be useful in targeting individuals with PTSD who may be at increased risk for AUD and therefore lead to improvements in treatment and prevention efforts.

Additional Future Directions

Given that TRD did not fully mediate the effect between PTSD and alcohol use severity reinforces that there are likely multiple pathways through which trauma may influence drinking

patterns which are likely not mutually exclusive and that the self-medication model is not the "silver bullet", warranting the need for investigation into additional models of comorbidity to inform clinical intervention. Moreover, given evidence for moderate overlap in genetic variance between PTSD and AUD (Sartor et al., 2011; Xian et al., 2000), genetically informed research surrounding the self-medication model is warranted. Investigations into the shared genetic risk and biological underpinnings of comorbid PTSD and AUD would help to further elucidate common etiological pathways underlying PTSD, AUD, and intermediate trauma-specific drinking to cope, which is imperative to the development of effective prevention and treatment programs.

Aim 3: Genotypic Investigation into TRD, PTSD, and Their Potential Overlap

Overall Summary of Findings

The present study sought to identify potential independent and shared genetic risk for TRD and PTSD. Four statistical genetic techniques were applied to the LEAU data in order to answer questions posed in Table 10. Globally, our findings at this beginning stage of genomic investigation afford only slight insight into the biologic etiology of the phenotypes studied as results were largely underpowered and resulted in null or potentially spurious findings to be interpreted with caution. Findings from each specific sub-aim are discussed in turn within the context of limitations, clinical implications, and future directions.

Are TRD and PTSD Heritable?

Overall, results from the univariate GCTAs conducted for TRD and PTSD, independently, failed to demonstrate significant SNP-based heritability estimates, both within the independent sub-ancestral groups as well as when meta-analyzed across groups. The one exception, which found TRD to be significantly heritable among the European subsample, was likely a spurious finding given notable power concerns. Indeed, the LEAU sample (N=1,896), particularly when analyzed by ancestral subgroup (n's ranging from 84 to 533), is far below the accepted standard for moderate heritability estimates, as demonstrated by our power analyses and substantiated by work by Visscher and colleagues (2014). Another piece of evidence suggesting that our null heritability estimates for TRD, and especially PTSD, may be due to low power is that they are inconsistent with recent GCTA findings demonstrating significant molecular heritability estimates for PTSD (~5%) using data from large and well-powered samples (i.e., the PTSD-PGC; Nievergelt et al., 2018), as well as previous twin studies suggesting that PTSD is moderately heritable, with between 35-72% of the variance in PTSD

being accounted for by genetic factors (Amstadter et al., 2012; Sartor et al., 2011; Stein et al., 2002; True et al., 1993).

Although the null findings resulting from the GCTA analyses are likely a result of low power, it is worth mentioning that the GCTA method uses aggregate SNP data and therefore does not account for variation due to rare variants in its calculation of heritability estimates (Trzaskowski et al., 2013). This explains notable discrepancies between lower heritability estimates derived from aggregate SNP analyses (5%; Nievergelt et al., 2018) compared to those derived from twin studies (35-72%; Amstadter et al., 2012; Sartor et al., 2011; Stein et al., 2002; True et al., 1993). Therefore, the inability to account for other factors (e.g., rare variants) might offer another explanation for the null findings.

Using GCTA methods, one study by Stein and colleagues (2016) did not find evidence of significant SNP-based heritability for PTSD, but this could be the product of lower power or potential sex confounds. For instance, whereas Stein and colleagues conducted GCTA using a sample of primarily male veterans (*N*=6,916) and failed to find significant heritability estimates for PTSD, GCTAs stratified by sex using the PTSD-PGC data (*N*=47,151) demonstrated that the significant heritability estimates were being driven by higher significant heritability among females (8-18%) compared to lower non-significant heritability among males (2-3%) (Nievergelt et al., 2018). This is consistent with previous twin studies of PTSD, which suggest that heritability might be substantially higher among females (72%; Sartor et al., 2011) compared to males (~30%; True et al., 1993). Given this previous research and following the example of the PTSD-PGC, in order to eliminate any potential sex confounds, univariate GCTAs of PTSD were also stratified by sex in the present study. Results remained non-significant in the all-male and

all-female subsamples and standard errors increased, suggesting power may be the larger issue at hand.

Given TRD is a novel measure, there is little research with which to compare this finding. While no studies currently exist that have applied GCTA methods to examine the heritability of drinking-to-cope motives, extant twin research suggests that generalized drinking-to-cope is moderately heritable. Using twin designs to examine the heritability of the popularly used DMQ-R (Cooper, 1994), Agrawal and colleagues (2008) found that genetic factors contributed to 18% of the total variance in coping motives. Similarly, a study by Prescott and colleagues (2004) found that a striking 40% of the variation in "drinking to manage mood states" was attributed to genetic factors across sexes. Although it is well established that heritability estimates derived from twin research are substantially greater than those derived from GCTA methods (Trzaskowski et al., 2013), substantial heritability estimates of generalized drinking-to-cope motives resulting from twin studies, while variable across studies, at the very least suggest that there is a likely genetic component to drinking to cope with PTSD symptoms specifically and, therefore, that the lack of significant TRD heritability is likely due to low power.

Unlike the GCTA finding suggesting significant (yet uninterpretable [h^2=.999, SE=.754]) heritability of TRD among the European Ancestry subsample of LEAU, results of the LDSC failed to demonstrate a significant SNP-based heritability estimate for TRD among the European Ancestry subsample. As with GCTA, results from the LDSC indicated high standard errors, likely resulting from low sample size. Indeed, some work has suggested that LDSC may produce a less accurate heritability estimate compared to GCTA (Ni et al., 2018) and that GCTA should be used instead of LDSC for sample sizes smaller than 3,000 (Bulik-Sullivan, 2015). Once more, the failure of both GCTA and LDSC methods use to account for rare variants, as

well as other important considerations such as dominance effects, epistasis, or gene-by-environment effects, could also be contributing to lack of findings in the present study.

Are There Specific Genetic Variants for Each Phenotype Independently?

Results from the meta-analyzed GWAS were largely driven by the European Ancestry subsample and, therefore, separate GWAS analyses were examined separately among the European Ancestry and African Ancestry non-meta-analyzed subsamples. Although there were nominally significant and suggestive hits across analyses, there were no genome-wide significant variants resulting from the meta-analysis of either phenotype, GWAS of TRD among the African sample, or GWAS of PTSD among either the European or African samples. Significant associations between certain markers (SNPs) and TRD were observed, however, within the European Ancestry subsample. The largest number of GWS SNPs were associated with the *preferentially expressed antigen in melanoma gene* (*PRAME*) gene, a protein coding gene that encodes an antigen that is preferentially expressed in human melanomas (Baren, 1998). It functions as a transcription repressor of retinoic acid, preventing retinoic acid-induced cell proliferation arrest, differentiation and apoptosis, which can impede survival advantages among individuals with cancer (Epping et al., 2005). To the best of our knowledge *PRAME* has not been previously connected to drinking motives, PTSD, or other mental health conditions. Interestingly, however, *PRAME* has antithetical effects to the gene *ALDH1A1*, which is commonly implicated in alcohol metabolism (Edenberg, 2007) and, contradictory to *PRAME,* enhances a cell's capability to metabolize retinal or retinoic acid, inhibiting cell growth and inducing apoptosis of tumor cells (Giannini, Maestro, Vukosavijevic, Pomponi, & Boiocchi, 1997; Simeone & Tari, 2004; Visus et al., 2007). The inverse relationship between the effects of the *PRAME* gene and the effects of a gene commonly implicated in alcohol use disorder (*ALDH*)

make sense within the context of the results, which demonstrated that, with the exception of one, all the SNPs in *PRAME* were inversely associated with TRD, an alcohol-related phenotype (see Table 13).

The second largest number of GWS SNPs resulting from the GWAS of TRD among the European Ancestry sample were associated with a cluster of genes (*IGH, IGHE, abParts, DKFZp686O16217, ELK2AP, epsilon)* found on chromosome 14 between base pairs 106145689 and 106162082, several of which are implicated in immune system functioning. This is overall consistent with much of the PTSD literature, which has identified several loci (none matching those found in the present analyses) within immune system function pathways (Sheerin et al., 2017). In addition to PTSD, genes implicated in the immune system have also been associated with alcohol use (e.g., NFkB, TLRs, IL1b, and TNFa; Crews & Vetreno, 2016; Mayfield, Ferguson, & Harris, 2013; Pascual, Miñarro, & Guerri, 2013) and chronic exposure to alcohol has been shown to negatively affect immune system functioning (Szabo & Banishree, 2015). One significant pseudogene (a section of a chromosome that is an imperfect copy of a functional gene; Tutar, 2012) within this region of particular interest is *ETS Transcription Factor ELK2A, Pseudogene* (*ELK2AP*), which was recently found by McClintick and colleagues (2019) to be differentially expressed between the cells of individuals with alcohol dependence and controls following 48 hour treatment with alcohol.

Therefore, although, to the best of our knowledge, no one specific marker or associated gene identified in the European Ancestry GWAS of TRD has been implicated in prior genetic studies of PTSD or drinking motives, there is a clear connection between the function of the majority of gene regions identified and both PTSD and alcohol use (e.g., immune system functioning). Furthermore, several genes with GWS markers have been either implicated in

alcohol dependence (i.e., *ELK2AP*) or have paradoxical effects to genes implicated in alcohol dependence (i.e., *PRAME*), suggesting a possible link between molecular risk for TRD and other alcohol-related phenotypes. Given these identified associations between the present findings and the extant literature, in addition to the acknowledgement that, as the current state of the literature would suggest (Lambert & Black, 2012), it is very rare that GWAS findings are replicated, future research is warranted and promising.

That said, there are notable limitations of the GWAS analyses conducted for the present study, most notably of which is power. As described in the data analytic plan, there was low power (51%) to detect variants. The ability to detect less common variants and/or variants with small effects using GWAS increases with sample size, particularly when analyzing complex psychiatric traits characterized by a combination of small polygenic effects (Teo, 2008). An effective example of this stems from the various iterations of PGC workgroup publications, each with increasing sample sizes and corresponding increasing number of identified GWS SNPs (e.g., 0 GSW SNPs resulting from N=20,730 transancestry meta-analysis in Duncan, Ratanatharathorn, et al., 2018; 6 GSW SNPs resulting from N=~200,000 in Nievergelt et al., 2018). Phenotype is also an important consideration with regard to power, such that rare traits tend to be stable and have high heritability, both qualities which require smaller samples to detect significant variants (Sham & Purcell, 2014).

Moreover, the significant findings resulting from the GWAS of TRD within the European Ancestry subsample should be interpreted with caution, given the lambda value suggested genomic inflation. Thus, it is probable that the high number of GWS markers resulted from bulk inflation, leading to a higher than expected false positive rate. That said, the lambda value was still close to 1 and did not suggest a high degree of inflation.

Do TRD and PTSD Have Shared Heritable Influences?

Results from the cross-trait LDSC indicated that there was a modest genetic correlation between TRD and PTSD but that, due to sample size, the confidence intervals included zero. As with the univariate analyses, it is likely that the lack of evidence for significant genetic overlap between TRD and PTSD was due to extremely low power resulting from the small European Ancestry subsample (*N*=~500). The large standard error surrounding the TRD estimate derived from the LEAU European Ancestry subsample likely influenced the reliability of the point estimate. TRD is a novel measure, precluding specific comparison of the present findings to extant literature. Additionally, to the best of our knowledge, there are no studies that have looked at potential shared heritability, whether it be via cross-trait LDSC or other bivariate methods, between drinking motives of any kind and PTSD. However, one candidate gene study did demonstrate that the *OPRM1* gene, implicated in the stress system, was significantly associated with both PTSD and drinking motives among a sample of individuals with HIV (Nugent et al., 2012). Moreover, given the known moderate overlap between PTSD and AUD (30% overlap in heritability, per twin research (Sartor et al., 2011; Xian et al., 2000) and a *rg* of .35, per cross-trait LDSC (Sheerin et al., under review)), as well as specific genes that have been associated with both PTSD and alcohol-related phenotypes (e.g., APOE and DRD2 have been associated with both PTSD and harmful drinking behaviors; Kim et al., 2013; Young et al., 2002), it is likely that a genetic correlation between PTSD and TRD does exist but that the current sample is underpowered to detect it.

Does Genetic Risk for PTSD Predict TRD?

The present study sought to assess the predictive value of polygenic risk for PTSD. PRS accounted for approximately 1.35% of the variance in PTSD and was significantly associated

with PTSD and nominally associated with TRD. Although a variance of 1.35% might not seem substantial, it is relatively consistent with the variance explained by PRS for other psychiatric phenotypes (e.g., depression: 0.4-1%, schizophrenia: 3%; Demirkan et al., 2011; Peyrot et al., 2014; Purcell et al., 2009). However, the direction of the PRS effect on PTSD was unexpected such that polygenic risk was inversely associated with PTSD symptom severity. Indeed, this contradicts the current literature to date, which has demonstrated that PRS for PTSD is linked to significant increase in risk (odds ratio = 1.39) for PTSD (Nievergelt et al., 2018). It is possible that the effect of the PRS was made negative due to natural selection, wherein effect alleles occur at a lower frequency than non-effect alleles on average, thereby resulting in PRS with a mean negative value (Choi et al., 2018). Given the strong association, albeit negative, between PRS and PTSD in the present sample, coupled with extant research demonstrating significant *positive* associations between PRS and PTSD (Nievergelt et al., 2018), it is more likely than not that the inverse association demonstrated in the present findings is an artifact of either the data or a flaw in statistical analysis. Furthermore, although sample size is a notable strength of the present analysis, such that the discovery sample was derived from the well-powered PTSD-PGC (Nievergelt et al., 2018), it is possible that highly significant findings can result from subtle confounding when calculating PRS using large sample sizes (Choi et al., 2018). Moreover, differences between discovery and target samples with regard to genetics and environment may confound results and decrease interpretability (Choi et al., 2018).

Despite these limitations of PRS and the notable caution with which the present findings should be interpreted, the clinical implications of PRS are promising and offer an exciting direction for the field of psychiatric genetics as a whole. For instance, recent research has demonstrated that relative risk conveyed to individuals via commonly measured clinical risk

factors (e.g., smoking, blood pressure, cholesterol) and polygenic risk estimation for coronary artery disease is comparable and, when combined, can lead to greater action thresholds (Torkamani, Wineinger, & Topol, 2018). Although PRS is relatively in its infancy and remains simplistic with regard to explanatory power in its current state, efforts are being made to make PRS a more comprehensive clinical tool that can be made generalizable across populations (Duncan, Shen, et al., 2018)

Conclusions

The present study sought to fill a gap in the current literature by creating a measure of drinking motives specific to coping with symptoms of PTSD, which was named the Trauma Related Drinking questionnaire (TRD), in order to help explain the common comorbidity between PTSD and AUP, using both phenotypic and genotypic approaches. The sample consisted of 1,896 college undergraduates from a large public university generally representative of the overall college population. Phenotypically, findings provide evidence to suggest that TRD is a more specific measure of drinking to cope motives compared to the commonly used Drinking Motives Questionnaire coping subscale. Additionally, findings demonstrate support for the external validation of TRD, both with regard to PTSD and alcohol consumption and related problems. Additionally, findings were consistent with the self-medication model, suggesting that drinking to cope motives may serve as a mechanism through which PTSD influences AUP and that trauma-related drinking to cope motives account for a unique proportion of the variance above and beyond general coping motives.

Genotypically, there was a lack of evidence for significant heritability with regard to TRD, PTSD, and their overlap, although this likely resulted from insufficient power due to low sample sizes once the overall sample was stratified by genomic ancestry. GWAS analyses revealed several significant genetic variants associated with TRD within the European Ancestry subsample, some of which conceptually mapped onto prior GWAS of PTSD (e.g., genes implicated in immune system functioning) and alcohol dependence (e.g., genes with antithetical properties to genes implicated in alcohol metabolism). Additionally, there was a nominally significant association between polygenic risk for PTSD and TRD. Interpreting the genetic analyses within the context of the PTSD and AUP literature as a whole suggests that findings

should be interpreted with caution, as they are likely biased by sample specific issues (e.g., power, inflation, heterogeneity).

Overall, findings support the use of TRD in future self-medication research, although TRD should be evaluated in multiple representative sample to ensure its validity and utility among varying populations. Additionally, findings suggest that the use of TRD as a screening tool among college mental health centers could lead to more accurate identification of individuals drinking to cope with symptoms of PTSD versus drinking to cope for generalized, non-trauma specific motives, thereby serving as a crucial treatment target. Mixed genotypic findings warrant additional research with larger samples less biased by the confounds of heterogeneity and population stratification. TRD offers an exciting direction for future research, which is warranted in order to examine both the clinical utility of the TRD questionnaire, as well as TRD as a potential biological mechanism through which PTSD influences AUP.

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