*Psychological Medicine*

**cambridge.org/psm**

## Original Article

**Cite this article:** Na P, Zhou H, Montalvo-Ortiz JL, Cabrera-Mendoza B, Petrakis IL, Krystal JH, Polimanti R, Gelernter J, Pietrzak RH (2023). Positive personality traits moderate persistent high alcohol consumption, determined by polygenic risk in U.S. military veterans: results from a 10-year, population-based, observational cohort study. *Psychological Medicine* **53**, 7893–7901. https://doi.org/10.1017/S003329172300199X

Received: 17 April 2023
Revised: 20 June 2023
Accepted: 29 June 2023
First published online: 29 August 2023

**Keywords:**
Alcohol; alcohol consumption; AUDIT-C; epidemiology; polygenic risk; veteran

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# Positive personality traits moderate persistent high alcohol consumption, determined by polygenic risk in U.S. military veterans: results from a 10-year, population-based, observational cohort study

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## Abstract

**Background.** Understanding the interplay between psychosocial factors and polygenic risk scores (PRS) may help elucidate the biopsychosocial etiology of high alcohol consumption (HAC). This study examined the psychosocial moderators of HAC, determined by polygenic risk in a 10-year longitudinal study of US military veterans. We hypothesized that positive psychosocial traits (e.g. social support, personality traits, optimism, gratitude) may buffer risk of HAC in veterans with greater polygenic liability for alcohol consumption (AC).

**Methods.** Data were analyzed from 1323 European-American US veterans who participated in the National Health and Resilience in Veterans Study, a 10-year, nationally representative longitudinal study of US military veterans. PRS reflecting genome-wide risk for AC (AUDIT-C) was derived from a Million Veteran Program genome-wide association study ($N = 200\,680$).

**Results.** Among the total sample, 328 (weighted 24.8%) had persistent HAC, 131 (weighted 9.9%) had new-onset HAC, 44 (weighted 3.3%) had remitted HAC, and 820 (weighted 62.0%) had no/low AC over the 10-year study period. AUDIT-C PRS was positively associated with persistent HAC relative to no/low AC [relative risk ratio (RRR) = 1.43, 95% confidence interval (CI) = 1.23–1.67] and remitted HAC (RRR = 1.63, 95% CI = 1.07–2.50). Among veterans with higher AUDIT-C PRS, greater baseline levels of agreeableness and greater dispositional gratitude were inversely associated with persistent HAC.

**Conclusions.** AUDIT-C PRS was prospectively associated with persistent HAC over a 10-year period, and agreeableness and dispositional gratitude moderated this association. Clinical interventions designed to target these modifiable psychological traits may help mitigate risk of persistent HAC in veterans with greater polygenic liability for persistent HAC.

## Introduction

Alcohol use is a significant public health concern that accounts for approximately three million deaths worldwide each year (World Health Organization, 2022). Alcohol use disorder (AUD) is highly prevalent in US military veterans. For example, in a nationally representative survey of US military veterans, the lifetime and past-year prevalence of AUD were 42.2% and 14.8%, respectively (Fuehrlein et al., 2016), whereas in the general US adult population, were estimated at 29.1% and 13.9%, respectively (Grant et al., 2015).

Historically, examining the association between biological factors and AUD has been critical in understanding the risk, course, and heterogeneity of AUD (Zucker, 2006). It is well known that a family history of AUD is a strong risk factor for AUD (Deak, Miller, & Gizer, 2019; Kranzler et al., 2019). Over the past decade, genome-wide association studies (GWAS) have implicated an array of genetic variants linked to various alcohol use phenotypes (Deak et al., 2019; Gelernter et al., 2014). A considerable body of evidence suggests a significant contribution of genetic factors to alcohol use phenotypes, such as high alcohol consumption (HAC; defined as a score of 4 or higher on the Alcohol Use Disorders Identification Test–Consumption [AUDIT-C]) and AUD (Deak et al., 2019; Kranzler et al., 2019). Previous research has shown that the genetics of alcohol consumption (AC) tend to differ from those indexing problematic alcohol use (PAU) (Kranzler et al., 2019; Zhou et al., 2020). Extant literature suggests a modest correlation between AC and PAU, suggesting overlapping

but distinct genetic architecture between the phenotypes (Kranzler et al., 2019; Zhou et al., 2020).

Recently, polygenic risk scores (PRS) derived from large-scale GWAS to describe the association between genetic variance and alcohol-related phenotypes have shown significant effects (Gelernter & Polimanti, 2021; Kranzler et al., 2019). However, given the small amount of variance that PRS account for in mental health and alcohol-related phenotypes (Barr et al., 2020; Murray et al., 2021), there is increasing recognition of the importance of understanding genetic susceptibility in the context of environmental and psychosocial factors (Lutz, Mechawar, & Turecki, 2017). A burgeoning body of research examined PRS-by-environmental and psychosocial correlates of psychiatric phenotypes, such as major depressive disorder (Mullins et al., 2016; Musliner et al., 2015), bipolar disorder (Polimanti et al., 2018b), and suicidal thoughts (Na et al., 2022). However, scarce research has examined PRS-by-environmental and psychosocial factors in relation to alcohol use phenotypes (Pasman, Verweij, & Vink, 2019) and to our knowledge, no study has utilized a longitudinal, population-based cohort. Thus, the prospective interactions between polygenic liability of alcohol use and environmental and psychosocial factors in relation to alcohol use phenotypes remain to be elucidated.

Previous research on gene-by-environment interactions in alcohol use phenotypes has disproportionately focused on largely non-modifiable risk factors (e.g. stressful life events, and adverse childhood experiences) (Dick & Kendler, 2012; Polimanti et al., 2018a; Young-Wolff, Enoch, & Prescott, 2011). In contrast, potentially protective factors such as attachment style, purpose in life, gratitude, optimism, and social support, which have been linked to reduced likelihood of HAC and AUD (Fuehrlein et al., 2016; Krentzman, 2017; Na et al., 2021; Straus et al., 2019; Straus, Norman, & Pietrzak, 2020), have received considerably less attention. Characterizing whether such factors may moderate the risk for HAC and AUD determined by PRS will help inform prevention and treatment efforts, especially given that many of them are modifiable (Fava et al., 2004; Hayes, Luoma, Bond, Masuda, & Lillis, 2006; Krentzman, 2017; Seligman, Steen, Park, & Peterson, 2005). In our previous studies using the National Health and Resilience in Veterans Study (NHRVS), we found that lower social support, secure attachment style (Fuehrlein et al., 2016; Na et al., 2023), lower dispositional optimism (Na et al., 2021), and personality factors (i.e. agreeableness, conscientiousness) were associated with probable AUD and excessive AC (Na et al., 2023).

Toward this end, we analyzed data from the NHRVS, a 10-year population-based longitudinal study of US European-American (EUR) veterans to first examine the main effects of PRS derived from a large-scale Million Veteran Program (MVP) GWAS of AUDIT-C scores (Kranzler et al., 2019) as well as a genome-wide meta-analysis of PAU (Zhou et al., 2020). Further, we sought to examine the interactions between AUDIT-C PRS and several psychosocial factors in relation to persistent HAC over a 10-year period. Risk and protective factors examined as potential moderators were selected based on previous work on the correlates of alcohol use phenotypes using the NHRVS, as well as previous genetic and gene-by-environment studies of alcohol-related phenotypes (Dick & Kendler, 2012; Fuehrlein et al., 2016; Kelsall et al., 2015; Krentzman, 2017; Na et al., 2021; Polimanti et al., 2018a; Straus et al., 2019, 2020; Young-Wolff et al., 2011). We hypothesized that AUDIT-C PRS would be associated with persistent and new-onset HAC, and that positive psychosocial factors (i.e. dispositional optimism, gratitude, social support, agreeableness and conscientiousness) would moderate this association.

## Methods

### Participants

Data were analyzed from 1323 EUR veterans who participated in the NHRVS, a 10-year, population-based, longitudinal study of US military veterans. Participants completed a baseline survey and provided a saliva sample for genetic analyses. The baseline assessment was conducted in 2011 and follow-ups were conducted in 2013, 2015, 2018, and 2021 (mean number of completed follow-ups = 2.7, standard deviation [S.D.] = 1.2, range = 1–4). The average age of participants was 63.8 years (S.D. = 13.2: range 24–93); the majority were male (93.1%) and 30.7% were combat veterans. The prevalence of HAC at the baseline assessment did not differ between EUR veterans who did and did not complete follow-up assessments (35.5% *v.* 35.7%, $\chi^2(1) = 0.01$, $p = 0.95$). Participant recruitment is described in detail in the Supplemental Material. The study protocol was approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System, and all participants provided informed consent.

### Assessments

#### High alcohol consumption

HAC was assessed using the AUDIT-C (Bush, Kivlahan, & McDonell, 1998). The AUDIT-C consists of three questions that assess the frequency of AC and binging, and yields a total score ranging from 0 to 12. Higher scores indicate more severe AC. Details of the AUDIT-C are described in the Supplemental Material.

A score of 4 or higher for men and 3 or higher for women was considered positive screens for HAC based on previous recommendations by the World Health Organization and the Veterans Affairs (VA) (VA Health Care, 2013; World Health Organization, 2001). Veterans who consistently screened positive for HAC at the initial assessment and one or more follow-up assessments were classified as having *persistent HAC*. Those who screened negative for HAC at the initial assessment but screened positive at one or more follow-up assessments were classified as having *new-onset HAC*. In contrast, those who screened positive on the initial assessment but negative on all completed follow-up assessments were classified as having *remitted HAC*. Those who consistently screened negative for HAC at initial and all completed follow-up assessments were classified as having *no/low AC*.

### Genotyping

Genotyping was completed at VA Connecticut Healthcare Center (Gelernter lab), as described previously (Na et al., 2022). As part of genotyping quality control, NHRVS participants with mismatched sex or genotype call rate < 95% were excluded from the analysis. Also, we calculated the degree of cryptic relatedness between each pair of individuals in the sample by estimating their identity by descent coefficients. For each pair of related individuals (pihat > 0.2), the individual with the lowest call rate was removed from the analysis. Next, SNPs with genotype call rate < 95% or minor allele frequency (MAF) < 0.01 were removed

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before imputation. Quality control was performed on individual genotypic data using PLINK 1.9 (Purcell et al., 2007). Ancestry assignment was defined via principal component analysis combining NHRVS sample with 1000 Genomes Project reference populations (1000 Genomes Project Consortium, 2015). Since other ancestry groups represented less than 15% of the NHRVS sample, only EUR ancestry was considered for further analyses. Imputation was performed using the genotype imputation software Minimac4 (Fuchsberger, Abecasis, & Hinds, 2015) and the Haplotype Reference Consortium (McCarthy et al., 2016) as reference panel through the Michigan Imputation Server (Das et al., 2016; Michigan imputation server: Free next-generation genotype imputation service). After imputation, we retained a total of 7 974 742 variants with MAF > 1% and INFO score > 0.6.

Principal components were calculated from LD-independent SNPs using the fast PCA approach implemented in PLINK version 2.0 (Galinsky et al., 2016; Purcell et al., 2007). LD Pruning was performed in PLINK ($R^2 < 0.1$ for SNPs < 1 Mb apart) using HapMap3 (The International HapMap Consortium, 2003) (U.S. Utah residents with ancestry from northern and western Europe) as reference.

### Polygenic risk scoring

We calculated AUDIT-C PRS in the NHRVS sample using PRS-CS and PLINK (Ge, Chen, Ni, Feng, & Smoller, 2019; Purcell et al., 2007). We used genome-wide association statistics from a large GWAS of AUDIT-C (as an ordinal trait, as opposed to HAC in the NHRVS sample which used a cutoff to create a binary score based on the same instrument) conducted in EUR participants enrolled in the MVP cohort ($n = 200\,680$) for AUDIT-C PRS (Kranzler et al., 2019). PRS-CS was used to infer posterior effect sizes of SNPs using AUDIT-C GWAS summary statistics and 1000 Genomes Project reference panel for EUR populations (obtained from https://github.com/getian107/PRScs by the authors). Default settings were used with the sample size of AUDIT-C GWAS as input. We then used PLINK (Purcell et al., 2007) for polygenic risk scoring in the NHRVS sample using 1000 Genomes Project EUR as reference panel. In addition, we also calculated PAU PRS with the same methods as above using the genome-wide meta-analysis statistics from PAU conducted in EUR participants ($n = 435\,563$) (Zhou et al., 2020).

### Potential moderating variables

Based on previous work on the correlates of AUD using the NHRVS (Fuehrlein et al., 2018; Na et al., 2021, 2023; Straus et al., 2019, 2020) as well as previous genetic and gene-by-environment studies of relevant psychiatric phenotypes (Dick & Kendler, 2012; Polimanti et al., 2018b; Young-Wolff et al., 2011), we evaluated the role of the following variables as potential moderators, that may interact with AUDIT-C PRS in relation to AC outcomes: two of the Big-Five personality factors (i.e. agreeableness, conscientiousness) (Fuehrlein et al., 2018; Na et al., 2023), attachment style (Fuehrlein et al., 2018; Na et al., 2023), dispositional gratitude (Krentzman, 2017), perceived social support (Fuehrlein et al., 2018), dispositional optimism (Na et al., 2021), combat veteran status (Na et al., 2021), childhood abuse (Dick & Kendler, 2012; Polimanti et al., 2018a; Young-Wolff et al., 2011), lifetime history of major depressive disorder (Fuehrlein et al., 2018) and/or posttraumatic stress disorder (PTSD) (Palmisano, Norman, Panza, Petrakis, & Pietrzak, 2022; Straus et al., 2020). All moderating variables were assessed at the baseline assessment.

### Combat veteran status

Combat veteran status was assessed with the following question: 'Did you ever serve in a combat or war zone?' and the Combat Exposure Scale (Keane et al., 1989), a 7-item self-report measure that assesses wartime stressors experienced by combatants.

### Number of medical conditions

Sum of number of medical conditions endorsed in response to question: 'Has a doctor or healthcare professional ever told you that you have any of the following medical conditions?' (e.g. arthritis, cancer, diabetes, heart disease, asthma, kidney disease) Range: 0–24 conditions.

### Attachment style

Attachment style was assessed with the following options: (a) I am somewhat uncomfortable being close to others (insecure); (b) I find it relatively easy to get close to others (secure); (c) I find that others are reluctant to get as close as I would like (insecure) (Hazan & Shaver, 1990). Secure and insecure attachment styles were dichotomized based on these responses.

### Childhood abuse

The Trauma History Screen (Carlson et al., 2011), a 14-item self-report measure, was used to assess exposure to the lifetime occurrence of child physical and sexual abuse.

### Lifetime major depressive disorder

Lifetime major depressive disorder was assessed using a modified self-report version of the Mini International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 2011).

### Lifetime PTSD

Lifetime PTSD was assessed using a lifetime version of the PTSD Checklist-Specific Stressor version, which assessed PTSD symptoms related to veterans' 'worst' event on the Trauma History Screen; scores $\geq 50$ were indicative of a positive screen (Weathers, Litz, Herman, Huska, & Keane, 1993).

### Agreeableness and conscientiousness

The 'Big Five' personality traits were assessed using the Ten-Item Personality Inventory (TIPI) (Gosling, Rentfrow, & Swann, 2003), a 10-item self-report brief measure on emotional stability (anxious *v.* confident and calm), extraversion (outgoing *v.* reserved), openness to experience (imaginative and inventive *v.* cautious and routine-like), agreeableness (friendly and cooperative *v.* detached), and conscientiousness (efficient and organized *v.* careless). From these five, agreeableness and conscientiousness were selected as possible moderators based on our previous study in the same NHRVS cohort (Na et al., 2023).

### Dispositional gratitude

Score on single-item 7-point Likert scale measure of gratitude from the Gratitude Questionnaire: 'I have so much in life to be thankful for' (rating 1 = strongly disagree to 7 = strongly agree) (Scheier, Carver, & Bridges, 1994).

### Dispositional optimism

Score on single-item 7-point Likert scale measure of optimism from the Life Orientation Test-Revised (Scheier et al., 1994); 'In uncertain times, I usually expect the best' (rating 1 = strongly disagree to 7 = strongly agree).

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### Perceived social support

Score on an abbreviated 5-item version of the Medical Outcomes Study Social Support Scale (Sherbourne & Stewart, 1991) was used to assess perceived social support (sample item: 'How often is each of the following kinds of support available to you if you need it?: Someone to confide in or talk to about your problems'; $\alpha = 0.92$) (Sherbourne & Stewart, 1991). Higher scores indicate greater perceived social support.

### Data analysis

First, we conducted Bonferroni-corrected chi-square tests and univariate analyses of variance to compare sociodemographic, psychosocial, and psychiatric characteristics by AC group (i.e. remitting HAC, new-onset HAC, persistent HAC, and no/low AC). Second, we conducted correlations of AUDIT-C PRS and potential moderating variables. Third, a multinomial logistic regression analysis was conducted to examine associations between AUDIT-C PRS, risk and protective psychosocial factors, and their interaction in relation to persistent HAC, new-onset HAC, remitted HAC, and no/low AC over the 10-year study period. These analyses were adjusted for age, sex, and the top 10 within-ancestry principal components. A backward elimination estimation approach, which assesses the joint predictive ability and retains only the most important explanatory variables (Chowdhury & Turin, 2020), was employed to identify significant PRS × environment interaction terms. Predicted probabilities of persistent HAC were then computed and plotted to illustrate significant interaction effects. All continuous variables were coded continuously, and were not binarized. To evaluate the specificity of the AUDIT-C PRS in predicting HAC group status over the 10-year study period, we additionally examined the relationship between PAU PRS (Zhou et al., 2020) and HAC status. PRS × environment analyses were conducted using IBM SPSS Statistics Version 28 (IBM Corp., 2021).

## Results

Table 1 presents descriptive statistics of the sample by AC status over the 10-year study period. A total of 328 (weighted 24.8%) veterans had persistent HAC; 131 (weighted 9.9%) had new-onset HAC; 44 (weighted 3.3%) had remitted HAC; and 820 (weighted 62.0%) had no/low AC at all assessments (see Fig. 1). Group differences were observed for all of the study variables ($p < 0.05$) except combat veteran status, lifetime major depressive disorder/PTSD, dispositional gratitude and dispositional optimism.

AUDIT-C PRS was not associated with attachment style, combat veteran status, childhood abuse, number of medical conditions, agreeableness, conscientiousness, lifetime major depressive disorder/PTSD, dispositional gratitude, dispositional optimism, or perceived social support ($r$'s < |0.05|, $p$'s > 0.05), thus reducing the potential confounding of PRS-by-environment correlations.

Results revealed that PAU PRS was not associated with new-onset *v.* no/low AC (RRR = 0.94, 95% CI = 0.75–1.17; Wald = 0.33, $p = 0.56$); persistent *v.* no/low AC (RRR = 1.11, 95% CI = 0.96–1.29; Wald = 2.01, $p = 0.16$); or persistent *v.* remitted HAC (RRR = 1.11, 95% CI = 0.77–1.61; Wald = 0.32, $p = 0.57$).

**Table 1.** Sociodemographic, military, and psychiatric characteristics of veterans by alcohol consumption status

| | No/Low AC *N* = 820 (weighted 62.0%) (1) Mean (S.D.) or *N* (%) | Remitting HAC *N* = 44 (weighted 3.3%) (2) Mean (S.D.) or *N* (%) | New-Onset HAC *N* = 131 (weighted 9.9%) (3) Mean (S.D.) or *N* (%) | Persistent HAC *N* = 328 (weighted 24.8%) (4) Mean (S.D.) or *N* (%) | Test of difference ANOVA or $\chi^2$ | Bonferroni-corrected pairwise contrasts |
|---|---|---|---|---|---|---|
| Age | 65.5 (13.1) | 60.3 (14.3) | 57.3 (14.6) | 63.4 (14.1) | 11.44*** | 1,4 > 3 |
| Male sex | 762 (94.1%) | 41 (94.1%) | 109 (80.8%) | 303 (94.5%) | 25.28*** | 1,4 > 3 |
| Combat veteran | 257 (29.3%) | 14 (29.4%) | 47 (40.0%) | 115 (31.1%) | 4.79 | – |
| AUDIT-C PRS | −0.1 (1.0) | −0.2 (0.9) | 0 (1.0) | 0.3 (1.0) | 8.28*** | 4 > 1 |
| Number medical conditions | 3.0 (1.9) | 2.6 (2.0) | 2.0 (1.6) | 2.5 (1.6) | 10.00*** | 1 > 3,4 |
| Secure attachment style | 630 (76.4%) | 30 (61.8%) | 102 (77.8%) | 236 (68.2%) | 10.25* | 1 > 4 |
| Childhood abuse | 167 (20.3%) | 8 (18.2%) | 28 (26.3%) | 97 (32.0%) | 15.73** | 4 > 1 |
| Lifetime PTSD | 67 (8.1%) | 4 (8.8%) | 9 (10.1%) | 25 (6.6%) | 1.34 | – |
| Lifetime MDD | 114 (14.1%) | 7 (20.6%) | 20 (14.1%) | 46 (15.4%) | 1.28 | – |
| Agreeableness | 5.3 (1.2) | 4.9 (1.2) | 5.2 (1.1) | 5.1 (1.1) | 2.93* | 1 > 4 |
| Conscientiousness | 5.8 (1.1) | 5.4 (1.3) | 6.1 (0.8) | 5.7 (1.2) | 4.86** | 3 > 1,2,4 |
| Gratitude | 6.2 (1.1) | 5.9 (1.1) | 6.3 (0.9) | 6.1 (1.2) | 2.02 | – |
| Optimism | 4.8 (1.5) | 4.6 (1.7) | 4.8 (1.4) | 4.8 (1.4) | 0.60 | – |
| Social support | 19.9 (4.5) | 18.4 (5.5) | 20.2 (4.6) | 19.2 (5.4) | 2.74* | 1 > 4 |

ANOVA, analysis of variance; AUDIT-C, Alcohol use disorders identification test-Consumption; AC, alcohol consumption; HAC, high alcohol consumption; MDD, major depressive disorder; PRS, polygenic risk score; PTSD, posttraumatic stress disorder; S.D., standard deviation; * = $p < 0.5$, ** = $p < 0.01$, *** = $p < 0.001$.

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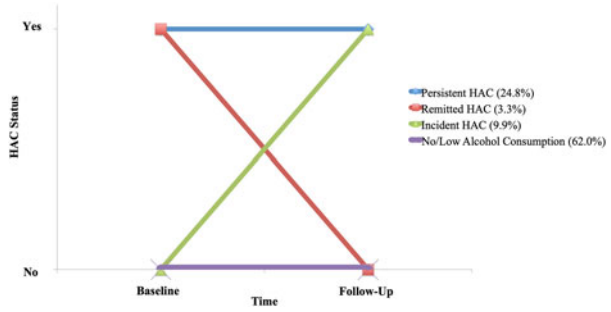


**Figure 1.** Different subgroups of alcohol consumption over the 10-year study period.
*Note*: HAC, high alcohol consumption.

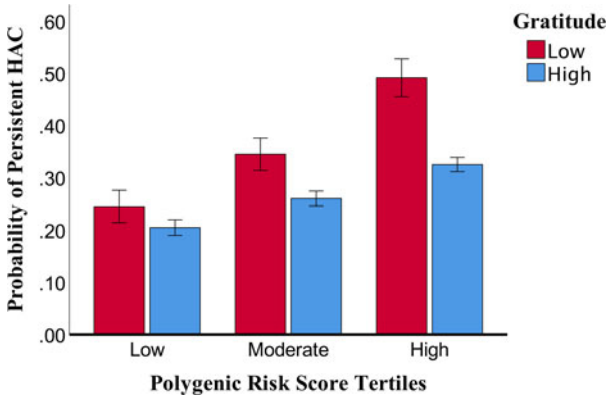


**Figure 2.** Interaction of AUDIT-C PRS and dispositional gratitude in predicting probability of persistent HAC in US military veterans.
*Note*: HAC, high alcohol consumption. Errors bars represent 95% CIs.
Gratitude scores were negatively skewed and kurtotic and thus low and high scores are plotted: Low = Endorsement of 'Strongly disagree' to 'Slightly agree' (Mean = 4.3, S.D. = 1.0, range = 1–5, consistent with mean rating of 'Neither agree nor disagree') *v.* High = Agree or Strongly Agree (Mean = 6.6, S.D. = 0.5, range = 6.0–7.0, consistent with mean rating of 'Agree' to 'Strongly agree').

### *Persistent HAC v. no/low AC*

As shown in Table 2, AUDIT-C PRS and childhood abuse were positively associated with persistent *v.* no/low HAC, while number of medical conditions and agreeableness were negatively associated with this outcome. Significant interactions of AUDIT-C PRS × dispositional gratitude [relative risk ratio (RRR) = 0.77, 95% confidence interval (CI) = 0.64–0.92] and AUDIT-C PRS × agreeableness (RRR = 1.21, 95% CI = 1.05–1.39) were also observed.

Figure 2 illustrates the interaction between AUDIT-C PRS and dispositional gratitude (Low = Endorsement of Strongly Disagree-to-Slightly Agree *v.* High = Agree or Strongly Agree on gratitude measure), which indicated the highest probability of persistent HAC among veterans with high AUDIT-C PRS and low dispositional gratitude. Among veterans in this highest tertile of AUDIT-C PRS, those with high gratitude had 34% lower probability of persistent HAC relative to those with low gratitude. Interactions between AUDIT-C PRS and other potential moderator variables, including lifetime major depressive disorder/PTSD, trauma burden, and combat veteran status, were not significant (all $p$'s > 0.05).

Figure 3 depicts the interaction between AUDIT-C PRS and agreeableness, which indicated the highest probability of persistent HAC among veterans with high AUDIT-C PRS and low agreeableness. The interaction of AUDIT-C PRS × agreeableness

**Table 2.** Results of multinomial logistic regression analyses predicting drinking groups over 10-year follow-up period

| | Persistent HAC *v.* No/Low AC | New-Onset HAC *v.* No/Low AC | Persistent HAC *v.* Remitting HAC | New-Onset HAC *v.* Persistent HAC | New-Onset HAC *v.* Remitted HAC |
|---|---|---|---|---|---|
| | RRR (95% CI) | RRR (95% CI) | RRR (95% CI) | RRR (95% CI) | RRR (95% CI) |
| Age | 0.99 (0.98–1.00) | 0.97 (0.95–0.99)** | 1.03 (0.99–1.07) | 0.97 (0.95–0.99)* | 1.00 (0.95–1.05) |
| Male sex | 1.09 (0.58–2.12) | 4.26 (1.99–9.09)*** | 1.78 (0.31–10.31) | 0.21 (0.08–0.54)** | 0.13 (0.02–0.88)* |
| Combat veteran | 1.14 (0.83–1.59) | 2.17 (1.32–3.58)** | 1.06 (0.44–2.53) | 0.58 (0.33–1.01) | 0.62 (0.22–1.72) |
| AUDIT-C PRS | 1.43 (1.23–1.67)*** | 0.91 (0.72–1.15) | 1.63 (1.07–2.50)* | 0.47 (0.42–0.78)*** | 1.19 (0.71–1.98) |
| Number of medical conditions | 0.85 (0.78–0.93)*** | 0.83 (0.72–0.96)* | 0.85 (0.65–1.11) | 0.99 (0.83–1.18) | 0.84 (0.64–1.12) |
| Secure attachment style | 0.80 (0.53–1.21) | 1.71 (0.85–3.44) | 1.04 (0.39–2.82) | 1.99 (0.96–4.12) | 2.55 (0.63–10.37) |
| Childhood abuse | 1.78 (1.26–2.52)** | 1.18 (0.67–2.08) | 3.41 (1.11–10.42)* | 0.49 (0.25–0.98)* | 1.28 (0.36–4.57) |
| Lifetime PTSD | 0.54 (0.29–1.03) | 0.85 (0.33–2.21) | 1.02 (0.20–5.13) | 1.73 (0.47–6.33) | 1.30 (0.12–14.51) |
| Lifetime MDD | 0.97 (0.60–1.57) | 0.60 (0.26–1.36) | 0.97 (0.32–2.96) | 0.62 (0.26–1.47) | 0.65 (0.18–2.35) |
| Agreeableness | 0.86 (0.74–0.99)* | 0.87 (0.70–1.09) | 0.91 (0.61–1.36) | 0.97 (0.74–1.25) | 0.88 (0.55–1.41) |
| Conscientiousness | 1.01 (0.87–1.17) | 0.70 (0.54–0.91)** | 1.11 (0.76–1.63) | 1.47 (1.09–1.99)* | 1.63 (0.99–2.66) |
| Gratitude | 0.89 (0.75–1.05) | 1.04 (0.78–1.39) | 0.87 (0.56–1.37) | 1.02 (0.74–1.41) | 0.96 (0.51–1.80) |
| Optimism | 1.06 (0.93–1.20) | 0.99 (0.82–1.21) | 1.09 (0.80–1.48) | 0.92 (0.75–1.15) | 0.98 (0.67–1.42) |
| Social support | 1.00 (0.96–1.04) | 1.00 (0.94–1.06) | 1.04 (0.95–1.14) | 1.01 (0.94–1.09) | 1.01 (0.90–1.14) |

AC, alcohol consumption; AUDIT-C, Alcohol use disorders identification test-Consumption; HAC, high alcohol consumption; MDD, major depressive disorder; PRS, polygenic risk score; PRS, polygenic risk score; PTSD, posttraumatic stress disorder; RRR, relative risk ratio; 95% CI, 95% confidence interval.
Significant association: * = $p < 0.5$, ** = $p < 0.01$, *** = $p < 0.001$.

https://doi.org/10.1017/S003329172300199X Published online by Cambridge University Press

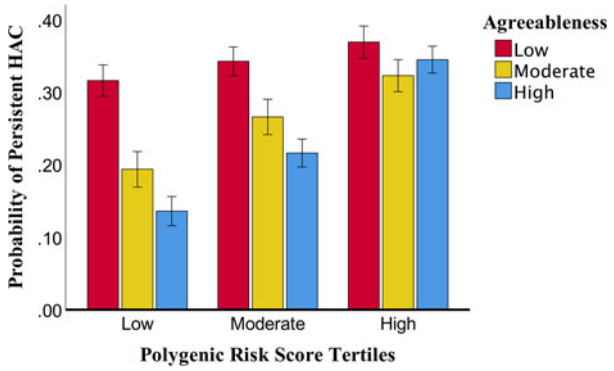


**Figure 3.** Interaction of AUDIT-C PRS and agreeableness in predicting probability of persistent HAC in US military veterans.
*Note*: HAC = high alcohol consumption. Errors bars represent 95% CIs.
Agreeableness scores were stratified into low, moderate, and high levels based on tertiles: Low: Mean = 3.8, S.D. = 0.7, range = 1.0–4.5, consistent with 'Neither agree nor disagree' mean rating; Moderate: Mean = 5.2, S.D. = 0.3, range = 5.0–5.5, consistent with 'Agree a little' mean rating; High: Mean = 6.3, S.D. = 0.4, range = 6.0–7.0, consistent with 'Agree moderately' to 'Agree strongly' mean rating.

was most pronounced at low and moderate AUDIT-C PRS tertiles. Specifically, among veterans with low and moderate AUDIT-C PRS, those with high agreeableness were 57% and 37% less likely, respectively, to have persistent HAC relative to those with low agreeableness. Among veterans with high AUDIT-C PRS, those with moderate agreeableness had 13% lower likelihood of persistent HAC relative to those with low agreeableness.

### *New-onset HAC v. no/low AC*

As shown in Table 2, higher AUDIT-C PRS was not associated with new-onset *v.* no/low HAC. Male sex and combat veteran status were positively associated with new-onset HAC, whereas greater age, number of medical conditions, and conscientiousness were negatively associated with this outcome.

### *Persistent HAC v. remitted HAC*

As shown in Table 2, higher AUDIT-C PRS and child abuse history were positively associated with persistent *v.* remitted HAC. Interaction analyses between AUDIT-C PRS and potential moderating variables were not significant (all $p$'s > 0.09).

### *New-onset HAC v. persistent HAC*

As shown in Table 2, relative to veterans with persistent HAC, those with new-onset HAC were younger, had higher AUDIT-C PRS and conscientiousness scores, and were more likely to be female and less likely to have experienced childhood abuse. Interaction analyses between AUDIT-C PRS and potential moderating variables were not significant (all $p$'s > 0.24).

### *New-onset HAC v. remitted HAC*

As shown in Table 2, relative to veterans with remitted HAC, those with new-onset HAC were more likely to be female, but did not differ with respect to any other variables. Interaction analyses between AUDIT-C PRS and potential moderating variables were not significant (all $p$'s > 0.32).

## Discussion

In this 10-year longitudinal study of US military veterans, we found that greater AUDIT-C PRS derived from a previous large GWAS (Kranzler et al., 2019) was positively associated with persistent HAC. Further, among US military veterans with greater AUDIT-C PRS, the likelihood of persistent HAC was lower among those with higher dispositional gratitude and agreeableness. To our knowledge, this is the first longitudinal study of psychosocial moderators of polygenic liability for longitudinal courses of HAC.

The main effect of AUDIT-C PRS in relation to persistent HAC builds upon previous studies suggesting that the cumulative effects of many common genetic polymorphisms (e.g. *ADH1B*, *ADH1C*, and *SLC39A8*) may contribute to increased risk of HAC (Deak et al., 2019; Kranzler et al., 2019). In a previous study using the same MVP genome-wide association statistics, AUDIT-C PRS was associated with alcohol-related disorders in two independent samples (Kranzler et al., 2019). Our findings expand this previous evidence, highlighting that AUDIT-C PRS was prospectively associated with persistent HAC, and demonstrates potential for further investigation in the application of AUDIT-C PRS in identifying individuals at high risk for persistent HAC (Murray et al., 2021). However, it should also be noted that AUDIT-C scores served as the basis for the GWAS used to generate the PRS; HAC is also derived from AUDIT-C scores. Thus, the GWAS data was a close match for the predicted trait. Of note, PAU PRS was not associated with persistent nor new-onset HAC. This finding aligns with prior work suggesting that PAU and AUD may be genetically different from AC measures (Kranzler et al., 2019; Zhou et al., 2020).

A greater number of medical conditions were inversely associated with persistent HAC relative to no/low AC. One interpretation of this finding is that veterans who had more medical conditions were more likely to refrain from HAC due to actual or perceived negative impact of AC on their physical health (Fuehrlein et al., 2018). Further, greater childhood abuse was positively associated with persistent HAC relative to no/low AC. This finding aligns with previous work showing a robust association between adverse childhood experiences and increased risk of AC (Loudermilk, Loudermilk, Obenauer, & Quinn, 2018; Widom, White, Czaja, & Marmorstein, 2007), as well as substance use disorder (Brems, Johnson, Neal, & Freemon, 2004; Kim, Kim, Chartier, Wike, & McDonald, 2021).

A noteworthy finding of this study was the moderating effect of dispositional gratitude on the relation between AUDIT-C PRS and persistent HAC. Previous work from our and other groups has revealed that gratitude is inversely associated with adverse mental health outcomes, such as current PTSD, major depressive disorder, generalized anxiety disorder, and suicidal thoughts (Emmons & Stern, 2013; Lambert, Fincham, & Stillman, 2012; McGuire, Fogle, Tsai, Southwick, & Pietrzak, 2021). Although not extensively studied, gratitude is a central theme in Alcoholics Anonymous (AA), one of the most commonly utilized behavioral interventions for individuals with alcohol use problems, which defines gratitude as one of the two hallmarks of success within the program (Alcoholics Anonymous, 1953). In the general psychiatric literature, there is considerable evidence suggesting that dispositional gratitude is a modifiable psychological characteristic associated with reduced risk of adverse mental health outcomes (Emmons & Stern, 2013). A recent meta-analysis of 15 studies examining the effect of psychological interventions designed to increase gratitude documented a moderate effect size relative to an

https://doi.org/10.1017/S003329172300199X Published online by Cambridge University Press

alternative-activity condition such as thought recording, group sessions on daily activities, and best possible self-journaling ($d = 0.46$, 95% CI = 0.04–0.58; (Davis et al., 2016). To date, however, limited research has examined the effects of interventions targeting gratitude in individuals with substance use disorders. In a randomized controlled trial of 14-day gratitude exercise [i.e. Three Good Things exercise (Seligman et al., 2005)] that involved six open-ended questions (e.g. please describe three good things that happened to you in the past 24 h) administered daily in individuals with AUD demonstrated an increase in positive affect (e.g. calmness, relaxation) and a decrease in negative affect [e.g. irritability, anger; (Krentzman et al., 2015)]. Given the robust moderating effect of gratitude on polygenic risk for persistent HAC observed in the current study, more research is needed to disentangle the association between gratitude and HAC, and evaluate whether interventions to bolster gratitude may help mitigate risk for HAC. However, it should be noted that enhancement of gratitude in the short term through the aforementioned interventions are not equivalent to establishing the ability to feel grateful on a consistent basis (Emmons & Stern, 2013). Further research is needed to develop psychotherapeutic interventions that foster long-term dispositional gratitude, as well as other positive psychosocial traits.

Greater agreeableness, a personality trait characterized by friendliness and cooperation, was inversely associated with persistent HAC, and moderated the positive association between AUDIT-C PRS and persistent HAC. These findings build upon previous studies that observed strong negative correlations between agreeableness and HAC (Lui, Chmielewski, Trujillo, Morris, & Pigott, 2022). Several mechanisms have been posited for how positive personality traits such as agreeableness may help buffer risk for the development of HAC (Lui et al., 2022). For example, individuals with lower levels of agreeableness may be more likely to become involved in HAC, as they may be less likely to acquire mature roles and responsibilities such as marriage or parenthood (Lee, Ellingson, & Sher, 2015). While agreeableness is largely considered a stable personality trait, there are intensive psychological treatments that may help bolster it (Piedmont, 2001). For example, in a six-week social skills training program in an outpatient rehabilitation treatment setting for 132 substance users, a significant increase in all 'Big 5' personality domains, including agreeableness, was observed (mean Cohen's $d = 0.38$) up until 15 months of follow-up (Piedmont, 2001). In light of our finding that veterans with greater AUDIT-C PRS and low agreeableness had the highest risk for persistent HAC, it is possible that veterans with high genetic liability for HAC and low agreeableness may particularly benefit from such interventions. Further research is needed to evaluate this possibility.

Several limitations of this study must be noted. First, PRS was derived from the largest AUDIT-C GWAS available (Kranzler et al., 2019), while HAC status was dichotomized as a binary outcome from AUDIT-C; nevertheless, latent growth mixture modeling analysis of continuous AUDIT-C scores in this cohort has revealed a similar trajectory of HAC over time (Fuehrlein et al., 2018). Second, although prospective, the relatively small sample size of the NHRVS cohort and low number of persistent and remitted HAC cases may have reduced statistical power in our analyses and limited the ability to detect a broader range of potential moderating effects of AUDIT-C PRS. Third, while the NHRVS cohort is nationally representative, our study sample was comprised entirely of EUR veterans who were predominantly older and male. Given that we could not utilize new analytic tools, such as the PRS-CSx to derive PRS in non-EUR veterans due to the small sample of non-EUR veterans in the NHRVS, it is unclear whether results generalize to more demographically diverse veteran or non-veteran populations. Further large-scale, PRS-by-psychosocial moderator interaction studies are needed to determine whether the findings regarding polygenic risk for AC observed in this study will replicate to more diverse samples. Fourth, the primary outcome used in this study – AUDIT-C scores – does not assess AUD, but rather defines those consuming alcohol above a certain threshold indicative of HAC. Further research using clinical interview-based measures is needed to evaluate the generalizability of the results observed in the current study to AUD diagnoses. Fifth, the self-report of military exposure was not validated, and it is logistically not possible to ascertain whether the veterans who participated in the NHRVS were also included in the MVP cohort. Sixth, although validated in previous studies, the majority of assessments used to measure positive psychosocial traits consisted of brief questionnaires. Nevertheless, there is some evidence to support the use of these brief assessment scales. For example, the TIPI demonstrated high temporal stability, robust correlations with longer measures of personality traits (Gosling et al., 2003; Nunes, Limpo, Lima, & Castro, 2018), and has been replicated in validation studies in different languages and cultures (Nunes et al., 2018). Seventh, the moderating variables were assessed at baseline and we did not look into the stability of the moderating variables throughout the study period; further research is needed to evaluate the stability of these variables and their association with AC trajectories. Lastly, analyses to maximize the longitudinal nature of the data set, such as latent growth mixture modeling, were not employed as the best-fitting solution yielded a 2-class 'extreme groups' solution that was underpowered. Although the prevalence of HAC at the baseline assessment did not differ between veterans who completed follow-up surveys relative to those who did not, it is still possible that heavy drinkers may have been more likely to drop out of the study compared to those who drank less heavily.

Notwithstanding these limitations, results of this 10-year prospective cohort study suggest that polygenic liability for HAC is prospectively associated with increased risk for persistent HAC among US military veterans. Further, it indicates that higher levels of dispositional gratitude and agreeableness may moderate polygenic risk for this outcome. The results suggest the added value of examining polygenic risk along with positive psychosocial factors in building predictive models of HAC. Further research is needed to confirm and extend these results to other, more diverse populations and other alcohol use phenotypes, particularly PAU and AUD; elucidate biopsychosocial mechanisms linking AUDIT-C PRS to alcohol use phenotypes; and evaluate the efficacy of interventions targeting dispositional gratitude and agreeableness in mitigating persistent HAC in veterans with high polygenic risk for alcohol use problems. However, we acknowledge that modifying these positive psychosocial traits may be challenging and thus, early assessments of HAC in veterans will be important in clinical practice.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S003329172300199X.

**Acknowledgements.** We thank the veterans who participated in the National Health and Resilience in Veterans Study.

**Financial support.** Preparation of this report was supported in part by the U.S. Department of Veterans Affairs via 1IK2CX002095-01A1 (J.L.M.O.) and 1IK1CX002532-01 (P.J.N.).

**Competing interest.** Dr Na has received royalty from Wolters Kluwer. Drs Zhou, Montalvo-Ortiz, Cabrera-Mendoza and Pietrzak report no competing interests. Dr Petrakis receives in-kind support (medications) for investigator initiated from Alkermes and BioXcel Therapeutics and a grant funded by BioXcel Therapeutics. Dr Krystal is a scientific advisor to Biohaven Pharmaceuticals, BioXcel Therapeutics, Inc., Cadent Therapeutics (Clinical Advisory Board), PsychoGenics, Inc., Stanley Center for Psychiatric research at the Broad Institute of MIT and Harvard, Lohocla Research Corporation. J.K. owns stock and/or stock options in Biohaven Pharmaceuticals, Sage Pharmaceuticals, Spring Care, Inc., BlackThorn Therapeutics, Inc., Terran Biosciences, Inc. J.K. reports income <$ 10 000 per year from: AstraZeneca Pharmaceuticals, Biogen, Idec, MA, Biomedisyn Corporation, Bionomics, Limited (Australia), Boehringer Ingelheim International, Concert Pharmaceuticals, Inc., Epiodyne, Inc., Heptares Therapeutics, Limited (UK), Janssen Research & Development, L.E.K. Consulting, Otsuka America Pharmaceutical, Inc., Perception Neuroscience Holdings, Inc. Spring Care, Inc., Sunovion Pharmaceuticals, Inc., Takeda Industries, Taisho Pharmaceutical Co., Ltd. J.K. reports income >$10 000 per year from Biological Psychiatry (Editor). J.K. received the drug, Saracatinib from AstraZeneca and Mavoglurant from Novartis for research related to NIAAA grant 'Center for Translational Neuroscience of Alcoholism [CTNA-4] from AstraZeneca Pharmaceuticals. JK holds the following patents: (1) Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. US Patent #:5447948.September 5, 1995; (2) Vladimir, Coric, Krystal, John H, Sanacora, Gerard – Glutamate Modulating Agents in the Treatment of Mental Disorders US Patent No. 8778979 B2 Patent Issue Date: July 15, 2014. US Patent Application No. 15/695164: Filing Date: 09/05/2017; (3) Charney D, Krystal JH, Manji H, Matthew S, Zarate C, – Intranasal Administration of Ketamine to Treat Depression United States Application No. 14/197767 filed on March 5, 2014; United States application or Patent Cooperation Treaty (PCT) International application No. 14/306382 filed on June 17, 2014; (4): Zarate, C, Charney, DS, Manji, HK, Mathew, Sanjay J, Krystal, JH, Department of Veterans Affairs 'Methods for Treating Suicidal Ideation', Patent Application No. 14/197.767 filed on March 5, 2014 by Yale University Office of Cooperative Research; (5) Arias A, Petrakis I, Krystal JH. – Composition and methods to treat addiction. Provisional Use Patent Application no. 61/973/961. April 2, 2014. Filed by Yale University Office of Cooperative Research.; (6) Chekroud, A., Gueorguieva, R., Krystal, J.H. 'Treatment Selection for Major Depressive Disorder' [filing date June 3, 2016, USPTO docket number Y0087.70116US00]. Provisional patent submission by Yale University; (7) Gihyun, Yoon, Petrakis I., Krystal J.H. – Compounds, Compositions and Methods for Treating or Preventing Depression and Other Diseases. U.S. Provisional Patent Application No. 62/444552, filed on January 10, 2017 by Yale University Office of Cooperative Research OCR 7088 US01; and (8) Abdallah, C., Krystal, J.H., Duman, R., Sanacora, G. Combination Therapy for Treating or Preventing Depression or Other Mood Diseases. U.S. Provisional Patent Application No. 62/719935 filed on August 20, 2018 by Yale University Office of Cooperative Research OCR 7451 US01. Drs Gelernter and Polimanti are paid for their editorial work on the journal *Complex Psychiatry*. Dr Polimanti received a grant from Alkermes.

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https://doi.org/10.1017/S003329172300199X Published online by Cambridge University Press