Received: 14 January 2025 | Accepted: 14 April 2025

DOI: 10.1111/acer.70069

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RESEARCH ARTICLE

Multi-ancestry genome-wide association study of topiramate's effects on heavy alcohol use

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Funding information
U.S. Department of Veterans Affairs, Grant/Award Number: I01 BX003341; VISN 4 Mental Illness Research, Education, and Clinical Center

Abstract

Background: Topiramate reduces alcohol consumption in individuals who drink heavily. Candidate gene studies aimed at identifying genetic variants that predict topiramate's effects on drinking have yielded inconsistent findings. To identify genetic variation associated with treatment response, we conducted a genome-wide association study (GWAS) among participants in the Million Veteran Program (MVP) who initiated topiramate treatment.

Methods: Using electronic health records, we identified individuals who were dispensed topiramate for at least 60 days for any indication (i.e., the index event). Alcohol consumption was assessed using Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) scores during the year prior to topiramate exposure (pre index) and at least 60 days after initiating topiramate but within 6 months of drug discontinuation (post index). The final GWAS sample included 8386 individuals who reported alcohol consumption (i.e., AUDIT-C score > 0) during the preceding year. We calculated polygenic scores (PGS) for topiramate treatment response in the Yale-Penn sample ($n = 10{,}275$) and examined associations with 692 phenotypes using a phenome-wide association study.

Results: In the cross-ancestry GWAS meta-analysis, 35 loci had suggestive associations, though none reached genome-wide significance. Topiramate response PGS had nominally significant associations with lower rates of alcohol-related liver disease, older age at alcohol use disorder diagnosis, and higher frequency of alcohol use.

Conclusions: Although no loci reached genome-wide significance, the suggestive variants identified in the cross-ancestry meta-analysis are promising candidates for future investigation. Larger studies are needed to identify significant genetic predictors of topiramate response and advance precision medicine strategies for treating AUD.

KEYWORDS
alcohol use disorder, genome-wide association study, precision medicine, topiramate, treatment response

INTRODUCTION

Pharmacotherapy for alcohol use disorder (AUD) is a critical but underused component of treatment. For example, only 3.4% of patients with AUD in the Veterans Health Administration received medication in 2009 (Harris et al., 2012). Despite low rates of prescribing, several medications have demonstrated efficacy for reducing alcohol consumption and rates of relapse (McPheeters et al., 2023). Currently, three medications—acamprosate, disulfiram, and naltrexone—are approved by the Food and Drug Administration for treating AUD, and several others (e.g., baclofen, gabapentin, varenicline, and topiramate) are prescribed off-label for treating AUD.

Topiramate, which was first approved as an anticonvulsant, subsequently to prevent migraine, and—in combination with phentermine—to promote weight loss, reduces alcohol consumption in individuals with AUD. In a meta-analysis of seven randomized controlled trials (RCTs) comprising 1125 participants with AUD, topiramate was superior to placebo in promoting abstinence and reducing heavy drinking days and the concentration of the hepatic biomarker, gamma-glutamyltransferase (GGT) (Blodgett et al., 2014). A subsequent meta-analysis of 13 placebo-controlled RCTs comprising 1397 participants with AUD showed medium-sized effects of topiramate in increasing the likelihood of abstinence and decreasing the number of heavy drinking days, craving, and GGT concentration (Fluyau et al., 2023). A recent 12-week double-blind, placebo-controlled RCT compared the effects of topiramate with naltrexone—a medication approved to treat AUD—in 147 individuals with the disorder (Morley et al., 2024). Although the two treatments did not differ in reducing heavy drinking days, topiramate was significantly better than naltrexone in reducing the number of drinks per drinking day, craving, and GGT concentrations. These findings support topiramate's efficacy in producing clinically meaningful reductions in alcohol consumption in individuals with AUD.

To evaluate the effects of topiramate on alcohol consumption in real-world clinical settings, we previously used electronic health record (EHR) data from the US Department of Veterans Affairs Health System (VA) (e.g., Kranzler et al., 2022). We compared reductions in Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) scores (Bush et al., 1998) among individuals prescribed the medication for any purpose with a propensity-score matched control group. The analysis showed that individuals with no AUD diagnosis who were prescribed topiramate for other indications showed modest but significant reductions in AUDIT-C score. The effects of topiramate were most pronounced in individuals with a positive baseline AUDIT-C screen (score ≥3 for women and ≥4 for men) and those prescribed >150 mg/day of topiramate. However, there were no significant reductions among individuals with an AUD diagnosis, highlighting potential differences in topiramate's effectiveness when evaluated in controlled research settings compared with routine clinical practice.

Despite the demonstrated efficacy of medications for treating AUD, not all individuals respond to these treatments. Differences in treatment response may be influenced by biological factors, including genetic variation. Recently, the first genome-wide association study (GWAS) of AUD treatment response was conducted in a sample of 1083 individuals treated with acamprosate or naltrexone (Biernacka et al., 2021). In the full sample, a locus on Chromosome 2 was identified in association with time to relapse to heavy drinking. In drug-stratified analyses, two distinct lead single-nucleotide variants (SNVs) were identified for response to naltrexone or acamprosate, suggesting potential medication-specific moderators of treatment.

To date, no GWAS of topiramate treatment response has been conducted. Two pharmacogenetic studies tested the SNV rs2832407 in *GRIK1*, which encodes a kainate receptor subunit, as a moderator of topiramate's reduction of alcohol consumption. In an initial study, a preplanned analysis showed that the SNV significantly moderated topiramate's effects on abstinent and heavy drinking days (Kranzler et al., 2014). However, a subsequent prospective trial that was stratified by genotype failed to replicate these findings (Kranzler et al., 2021). The SNV also failed to moderate treatment response in the trial that compared topiramate with naltrexone (Morley et al., 2024). These inconsistent findings highlight the limitations of candidate gene approaches and the need for hypothesis-free approaches, such as GWAS, to identify genetic predictors of topiramate's effects on alcohol consumption. Although treatment response has a genetic component (Motsinger-Reif et al., 2013), it is a complex trait influenced by multiple genetic variants of small effect (Manolio et al., 2009), making it unlikely that a single, noncoding SNV could be used to personalize treatment. Thus, to identify genetic variants associated with topiramate treatment response, we conducted a GWAS in the Million Veteran Program (MVP) sample among individuals who reported consuming alcohol and initiated topiramate for any indication.

METHODS

This study complies with all relevant ethical regulations regarding human subjects research. It was approved by both the VA Central Institutional Review Board (IRB) and all local site IRBs. All participants provided written informed consent and were not paid to participate.

Participants and phenotyping

Using the VA EHR, we identified MVP participants for whom topiramate prescriptions were dispensed for at least 60 days with no more than a two-week gap in treatment ($n = 53{,}611$; Figure 1). Upon exclusion of individuals without genotype data, 36,521 remained in the analysis sample. Among individuals with multiple exposures to topiramate, only the first was retained. We calculated the median daily prescribed dosage of topiramate during the exposure period.

To assess changes in alcohol consumption, we used AUDIT-C scores, obtained annually during routine health visits for all individuals in VA care. Among the topiramate-exposed sample, 551,013

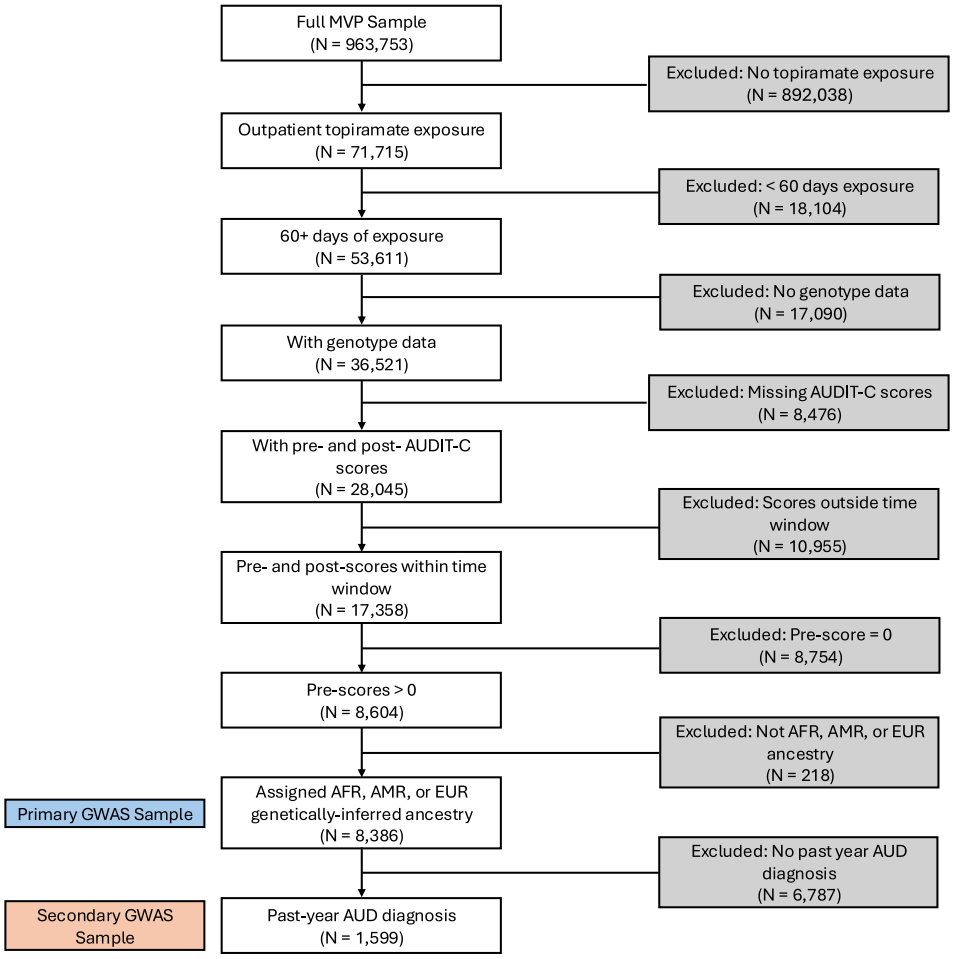

FIGURE 1 Flow diagram of subject selection.

AUDIT-C records were available, which included all AUDIT-C scores obtained prior to the initiation of topiramate (pre index) or at least 60 days after its initiation (post index). The selected pre index scores were those in the past year obtained closest in time and prior to the first topiramate exposure date. For post index scores, we selected AUDIT-C scores obtained at least 60 days after initiating topiramate—the time at which a difference in heavy drinking days emerged between the topiramate and placebo arms of two clinical trials (Kranzler et al., 2014, 2021). From these post index scores, we selected the AUDIT-C score closest in time to the end of the topiramate exposure window and excluded scores obtained more than 6 months after discontinuation. As shown in Figure 1, 17,358 participants had pre- and post index scores that met these thresholds, and 8604 had pre index scores >0, indicating that they had consumed alcohol during the preceding year. The difference between pre- and post index AUDIT-C scores was the outcome examined in the GWAS.

Individuals with genetically inferred ancestry (GIA) assignments of African (AFR), Admixed American (AMR), and European (EUR) were retained ($n = 8386$), forming the primary GWAS sample. Other GIA groups were too small for analysis ($n < 218$). We also identified participants with an International Classification of Diseases (ICD)-9 or ICD-10 diagnosis of AUD in the year prior to initiating topiramate ($n = 1599$) for inclusion in a secondary GWAS. Table 1 provides additional details on the sample.

Genotyping, imputation, and GWAS

MVP samples were genotyped using a custom Affymetrix Axiom Biobank Array. Duplicate samples and those with a sex mismatch, seven or more relatives in MVP (kinship > 0.08), excessive heterozygosity, or a genotype call rate <98.5% were removed. One individual from each pair of close relatives in the MVP sample (kinship ≥ 0.25) was randomly removed. We also removed monomorphic variants and those with high missingness (call rate < 0.95) or a Hardy–Weinberg equilibrium p-value $< 1 \times 10^{-6}$. Genotypes were phased with SHAPEIT4 (Delaneau et al., 2019) and imputed using the Minimac4 software (Das et al., 2016), with biallelic SNVs imputed using a hybrid of the 1000 Genomes Phase 3 (The 1000 Genomes Project Consortium, 2015) and the African Genome Resources reference panel. To infer similarity to reference genomes and generate principal components (PCs) to account for differences in genetic similarity, we calculated GIA composition

TABLE 1 Sample characteristics.

	Full sample ($n=8386$)	AUD cases ($n=1599$)
	Mean (SD) or % (N)	Mean (SD) or % (N)
Age	50.36 (13.03)	49.23 (11.87)
Male	74.03% (6208)	85.37% (1365)
Genetically inferred ancestry		
AFR	24.23% (2032)	30.39% (486)
AMR	12.23% (1026)	13.20% (211)
EUR	63.53% (5328)	56.41% (902)
Current AUD	19.85% (1599)	100% (1599)
Lifetime AUD	31.14% (2479)	100% (1599)
Days on topiramate	204.10 (230.83)	180.80 (193.08)
Maximum daily dose	144.19 (94.32)	142.83 (90.91)
Median daily dose	109.38 (71.92)	105.02 (66.50)
Minimum daily dose	62.90 (39.29)	56.50 (35.11)
Days between topiramate start date and pre index AUDIT-C score	159.95 (99.71)	130.06 (102.27)
Days between topiramate stop date and post index AUDIT-C score	36.73 (93.00)	38.47 (85.93)
AUDIT-C change	−0.91 (2.87)	−2.04 (4.50)
Pre index AUDIT-C score	3.07 (2.88)	6.04 (3.78)
Post index AUDIT-C score	2.16 (2.73)	4.00 (4.04)

(Verma et al., 2023). A random forest classifier was trained on the reference dataset using the first 10 PCs. The algorithm was applied to the MVP PC analysis data, and GIA was inferred when the classifier's predicted probability was greater than 50% (Hunter-Zinck et al., 2020).

We conducted two separate GWAS of the change in AUDIT-C scores—a primary GWAS of the full sample and a secondary GWAS of individuals with a past-year AUD diagnosis. We conducted a separate GWAS for individuals with a past-year AUD diagnosis, as it reflects the individual's status at the time of initiation of topiramate treatment, underscoring its relevance to their treatment response. In contrast, a lifetime AUD diagnosis can be made at any time before treatment initiation and may not be as clinically meaningful, so we chose to include the presence or absence of a lifetime AUD diagnosis as a covariate in the primary GWAS rather than run a separate GWAS among individuals with lifetime AUD.

GWAS were conducted within the three GIA groups (AFR, AMR, and EUR) using linear regression models implemented in PLINK v2.0 (Chang et al., 2015). Covariates included the first 10 within-GIA PCs, age, sex, median topiramate dosage, and pre index AUDIT-C score. Median topiramate dosage was included to account for variability in prescribed dosage throughout the topiramate exposure window, and pre index AUDIT-C score was included to account for baseline differences in alcohol consumption.

Cross-ancestry GWAS meta-analysis

The within-ancestry GWAS results were meta-analyzed using fixed effects inverse-variance weighted meta-analysis in METAL (Willer et al., 2010). Standard genomic control corrections were applied to the summary statistics and to the cross-ancestry meta-analysis results. To identify lead SNPs in the cross-ancestry GWAS meta-analysis, we performed linkage disequilibrium (LD) clumping using the 1000 Genomes Phase 3 ALL reference panel with a window distance of 3000 kb and r^2 threshold of 0.10.

Downstream analyses

To examine potential functional effects of SNVs and map associated genes, we used FUMA (Watanabe et al., 2017). Genes were identified based on position (i.e., nearest gene) and functional effects, including expression quantitative trait loci (eQTLs), which link SNVs to gene activity, and chromatin interaction mapping, which identifies physical connections between genomic regions. After mapping genes for the top SNVs, we queried the GWAS Catalog to examine any previous phenotypic associations with them (Sollis et al., 2023).

Using the EUR and AFR GWAS results, we constructed polygenic scores (PGS) in the Yale-Penn sample ($n=10{,}275$) to perform phenome-wide association studies (PheWAS) and identify additional correlates of genetic liability for topiramate response. PGS were estimated using PRS-CS (Ge et al., 2019), a Bayesian approach that infers posterior SNV effect sizes using GWAS summary statistics and an external LD reference panel (i.e., 1000 Genomes Phase 3). We used linear and logistic regression models to examine associations between the PGS and 692 phenotypes in the Yale-Penn sample. A false discovery rate (FDR) correction was applied to account for multiple testing. Additional details on genotyping and PheWAS procedures in Yale-Penn have been reported previously (Kember et al., 2023).

RESULTS

Participants' mean AUDIT-C pre index score was 3.06 (SD = 2.88) and their post index score was 2.16 (SD = 2.72), an average reduction of 0.90 points. Individuals with a lifetime AUD diagnosis had an average pre index score of 4.92 (SD = 3.64) and a post index score of 3.38 (SD = 3.66)—a difference of 1.64—while those with a past-year AUD had an average pre index score of 5.81 (SD = 3.74) and a post index score of 3.82 (SD = 3.93)—a difference of 1.99 (Figure S1). To evaluate potential confounding from the timing of the post index AUDIT-C measurement, we compared individuals with post index scores obtained before and after the discontinuation of topiramate. These groups did not differ in their average AUDIT-C score reduction ($t(8602)=0.44$, $p=0.66$) or in rates of lifetime ($\chi^2(1)=0.89$, $p=0.35$) or past-year AUD diagnosis ($\chi^2(1)=0.12$, $p=0.72$).

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Primary GWAS

In AFR individuals, no loci were genome-wide significant (GWS). The lead SNV for the top loci was rs451704, with a *p*-value of 9.83×10^{-8}. Forty-two independent loci reached nominal significance ($p<1\times10^{-5}$). In AMR individuals, no loci were GWS. There were 27 independent loci that reached nominal significance ($p<1\times10^{-5}$). In EUR individuals, no loci were GWS. There were 13 independent loci that reached nominal significance ($p<1\times10^{-5}$). Tables S1–S3 and Figures S2–S4 show the ancestry-specific GWAS results.

In the cross-ancestry meta-analysis of AFR, AMR, and EUR individuals (Figure 2 and Figure S5), no loci were GWS, and 38 loci reached nominal significance ($p<1\times10^{-5}$; Table S4). Of the top associations, the lead SNVs for some loci did not have substantial support from nearby variants in LD, suggesting they may be less reliable signals. However, a locus on Chromosome 2 had many nominally significant variants in LD with the lead SNV (rs75813390, $p=2.6\times10^{-7}$), providing greater evidence for a potential association. The nearest gene to the lead SNV was *SGPP2*, previously associated with drinks per week (Saunders et al., 2022). The variant mapped to three additional protein-coding genes—*ACSL3*, *PAX3*, and *CCDC140*—based on chromatin interactions.

Secondary GWAS of individuals with AUD

In AFR individuals, 54 loci reached nominal significance, with none being GWS. Similarly, in AMR individuals, no loci were GWS, though 10 loci reached nominal significance. In EUR individuals, 13 loci were nominally significant, and none were GWS. In the cross-ancestry GWAS meta-analysis of AFR, AMR, and EUR individuals with AUD (Figure 3), 75 independent loci were nominally significant, and none were GWS. Tables S5–S8 and Figures S6–S9 show the ancestry-specific and cross-ancestry GWAS meta-analysis results.

PheWAS in Yale-Penn sample

The topiramate response PGS was associated with 18 traits in EUR individuals (Figure 4A), though none survived multiple testing correction. Among these, higher PGS for topiramate response was associated with fewer years on methadone (beta = −0.02, SE = 0.01, $p=0.006$), higher education (beta = 0.03, SE = 0.01, $p=0.01$), older age of AUD diagnosis (beta = 0.32, SE = 0.13, $p=0.01$), lower rates of alcohol-related liver disease (beta = −0.16, SE = 0.08, $p=0.03$), and higher household income (beta = 0.07, SE = 0.03, $p=0.04$). In AFR individuals, there were 45 significant associations, but none survived multiple testing correction (Figure 4B). Among these, higher PGS was associated with AUD diagnosis (beta = 0.08, SE = 0.03, $p=0.02$) and alcohol use frequency (beta = 0.07, SE = 0.03, $p=0.03$).

DISCUSSION

Using data from the MVP cohort, we conducted the first GWAS of topiramate's effect on reducing alcohol consumption. By going beyond traditional candidate gene approaches, findings from which failed to replicate, the current GWAS—despite failing to identify any GWS loci—provides a foundation for future research on the pharmacogenetics of topiramate for reducing alcohol consumption. Although topiramate treatment was associated with modest reductions in AUDIT-C scores, irrespective of the presence of an AUD diagnosis, among individuals with a past-year AUD diagnosis, there was a nearly 2-point reduction in AUDIT-C scores following topiramate treatment. This finding is consistent with our previous finding in veterans that the drug reduces alcohol consumption more in individuals with higher baseline drinking (Kranzler et al., 2022). Thus, as would be expected, individuals with AUD had higher baseline AUDIT-C scores and change scores than those without AUD, and individuals with current AUD had the highest pre index AUDIT-C

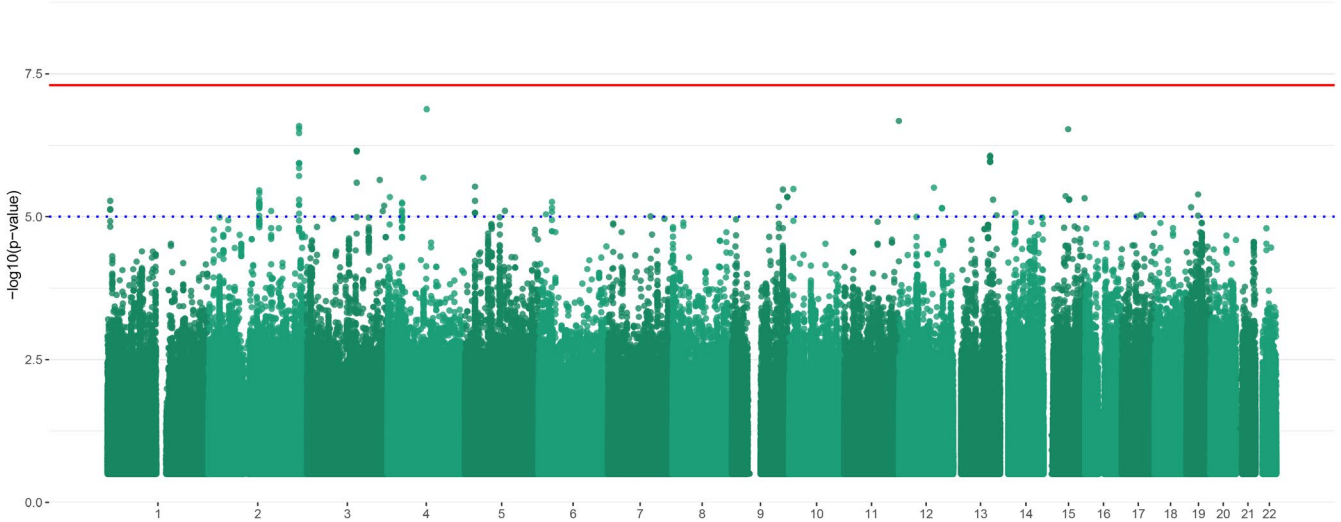

FIGURE 2 Cross-ancestry meta-analysis of topiramate effects on drinking.

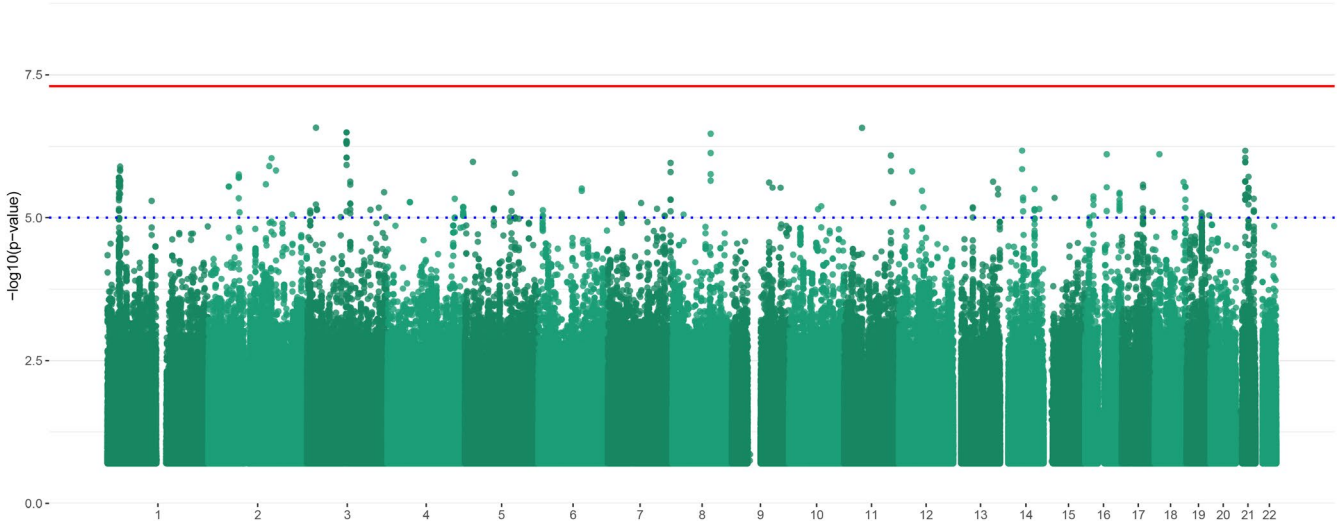

FIGURE 3 Cross-ancestry meta-analysis of topiramate effects on drinking among individuals with alcohol use disorder.

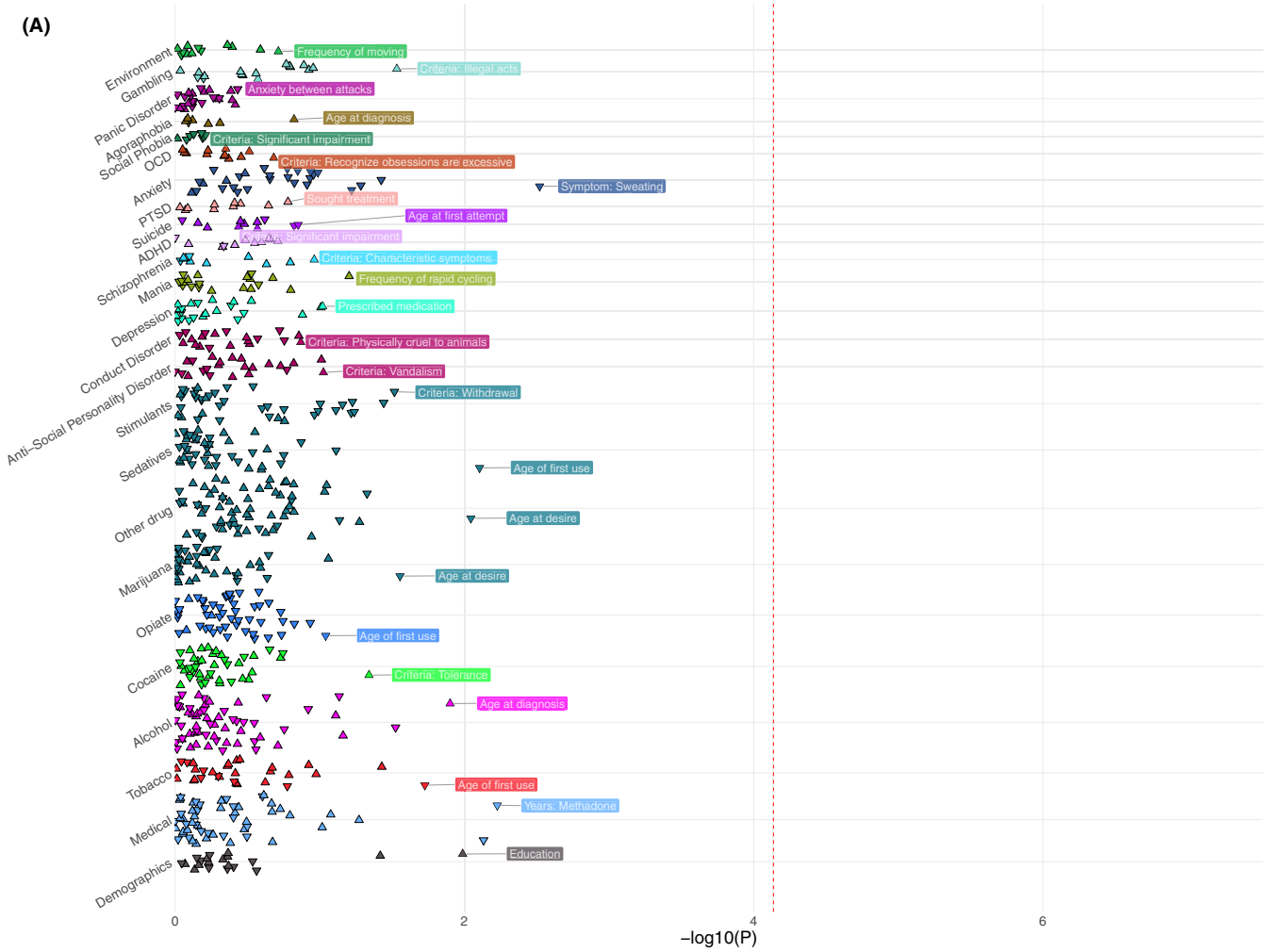

FIGURE 4 Phenome-wide association study of a polygenic score for topiramate reduction in drinking among (A) European-like ancestry individuals and (B) African-like ancestry individuals in the Yale-Penn sample.

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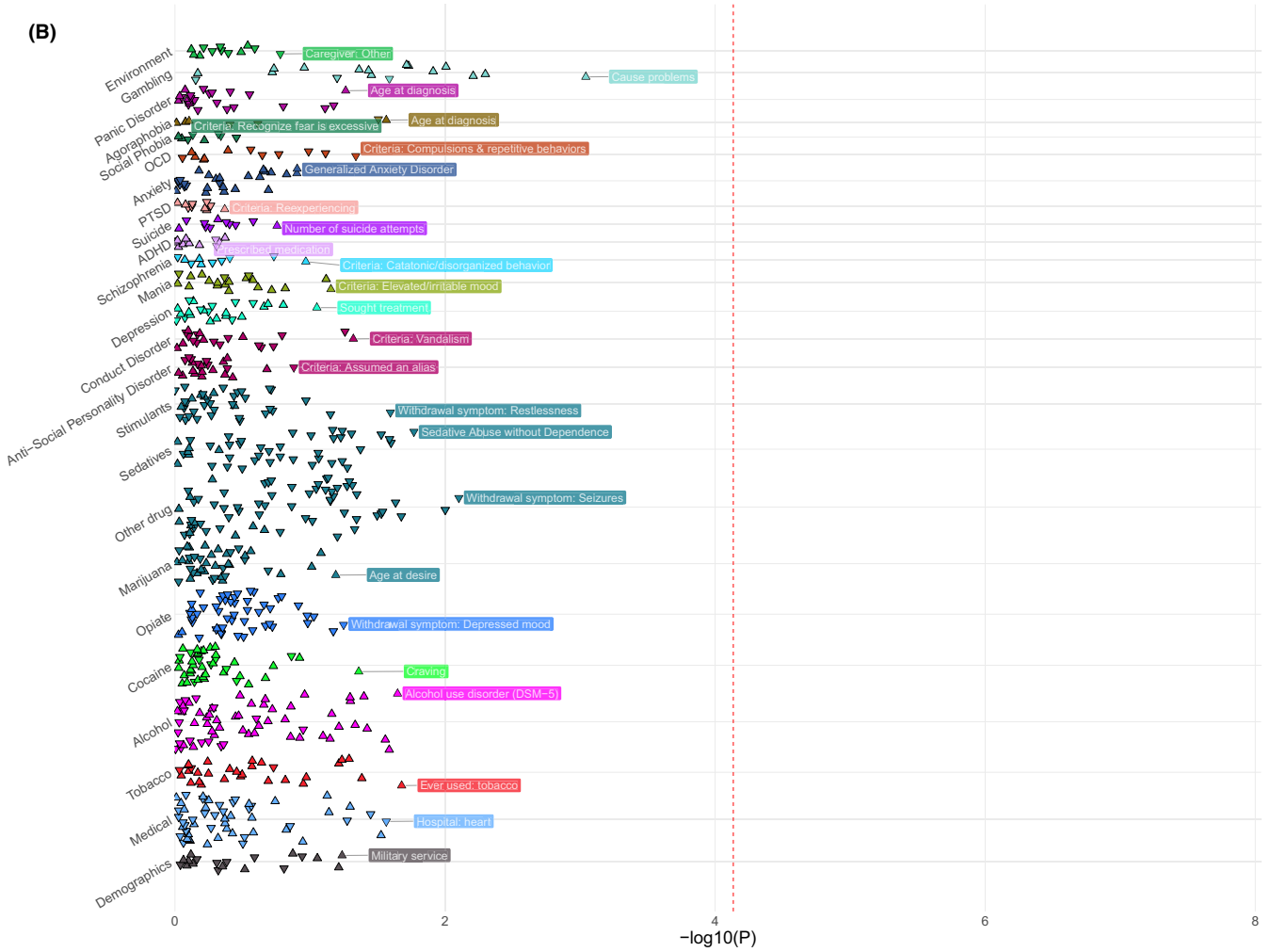

FIGURE 4 (Continued)

score and the greatest reduction associated with topiramate exposure. Together, these results reinforce the value of topiramate as a treatment option for reducing alcohol consumption, while underscoring the need for further research aimed at identifying genetic moderators of its efficacy.

Although we did not identify any GWS variants, many loci reached a less stringent suggestive threshold ($p < 1e\text{-}5$). For example, in the primary cross-ancestry GWAS meta-analysis, a locus on Chromosome 2 (rs75813390, $p = 2.6 \times 10^{-7}$) mapped to *SGPP2*, a gene previously identified in a GWAS of drinks per week (Saunders et al., 2022). Attempts to replicate these suggestive associations in larger samples are needed.

PGS for topiramate treatment response were nominally associated ($p < 0.05$) with several traits in EUR and AFR individuals from the Yale-Penn sample. In EUR individuals, a higher PGS, indicating a greater genetic liability for responding to topiramate, was associated with fewer years on methadone, higher educational attainment and household income, and lower rates of alcohol-related liver disease. In AFR individuals, there were positive associations with AUD diagnosis and alcohol use frequency. These findings may point to broader relationships between topiramate response, socioeconomic status, and health. A review evaluating predictors of AUD treatment outcomes showed that socioeconomic status was consistently associated with better outcomes (Adamson et al., 2009), suggesting that individuals with fewer resources may require additional support to obtain maximum treatment benefit. Consistent with the GWAS findings, these associations should be evaluated in other independent samples.

As with pharmacological treatment responses in general (Motsinger-Reif et al., 2013), topiramate's effects on drinking outcomes likely result from the combined influence of numerous variants, most with small effect sizes. Thus, to identify GWS genetic variants of this effect likely requires GWAS samples that are much larger than that currently available. Nonetheless, research has shown that GWAS offer substantial advantages over candidate gene approaches for identifying novel genetic moderators of treatment response. As of January 2020, only 2% of the SNVs identified in GWAS of treatment response were implicated by candidate gene investigations, while the remaining 98% were novel findings (Linskey et al., 2021). An additional strength of GWAS is that they enable the generation of polygenic scores, which can account for small genetic effects across the genome and thus can be used to predict related

traits in independent samples, such as those demonstrated here in Yale-Penn or those in clinical trials. Despite the difficulty of assembling large samples for pharmacogenetics research, there is a clear need for the use of GWAS and other approaches to advance the precision treatment of AUD with topiramate and other efficacious medications.

Several other limitations should be acknowledged. First, AUDIT-C scores, although often used to screen clinically for hazardous and harmful drinking, may not fully capture topiramate's effects on alcohol-related behaviors, including reduced craving or alcohol-related problems. Second, the variability in real-world EHR data, including medication adherence, prescribed dosages, and psychiatric and physical comorbidities, creates phenotypic heterogeneity that reduces the ability to detect genetic signals. Although we controlled for median dosage, pre index AUDIT-C score, and AUD diagnosis, we could not account for all potential confounders. Finally, although the study sample included individuals from multiple population groups, its size may not have been sufficient to detect the small genetic effects characteristic of highly polygenic traits, such as treatment response. That said, a GWAS of the response to treatment with acamprosate or naltrexone in a total sample of 1083 individuals of European ancestry recruited from clinical trials (Biernacka et al., 2021) identified one GWS SNV in the entire sample and two SNVs associated with medication-specific outcomes—one each for naltrexone and acamprosate. The more rigorous implementation and lower likelihood of erroneous documentation in clinical trials than in routine clinical care appears to limit the use of EHR data for genetic studies of treatment response.

This study also has several key strengths. It is the first GWAS of topiramate treatment effects on alcohol consumption, advancing our understanding of the genetic basis of its effects on that outcome. The use of the MVP cohort, one of the largest and most genetically diverse biobanks, enabled us to include participants of AFR, AMR, and EUR ancestries, addressing the critical need for greater representation of non-EUR individuals in genetics research. We also evaluated the predictive utility of a topiramate treatment response PGS in an independent sample, identifying nominally significant associations that largely aligned with the expected effects. Finally, our findings underscore topiramate's utility for reducing alcohol consumption, even among individuals without AUD.

CONCLUSIONS

As the first GWAS of topiramate treatment effects on alcohol consumption, this study provides a foundation for future pharmacogenomic research on topiramate, with likely applications to other alcohol pharmacotherapies. Although no GWS loci were identified, many loci had suggestive associations, providing candidates for further investigation and replication. Given the highly polygenic nature of treatment response, collaborative efforts to accrue larger multiancestry cohorts are needed to identify significant genetic moderators of topiramate treatment response. Harnessing the power of PGS, genetic liability for a greater response to topiramate had nominal associations in an independent sample, including with lower rates of alcohol-related liver disease. In summary, topiramate is an important medication in the therapeutic armamentarium for AUD, and research that identifies genetic factors that influence its efficacy has the potential to advance precision medicine for AUD.

ACKNOWLEDGMENTS

This work was supported by grants from the US Department of Veterans Affairs Biomedical Laboratory Research and Development Service (no. I01 BX003341 to HRK and ACJ) and the VISN 4 Mental Illness Research, Education, and Clinical Center. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The views expressed in this article are those of the authors and do not necessarily represent the position or policy of the Department of Veterans Affairs or the US Government.

CONFLICT OF INTEREST STATEMENT

Dr. Kranzler is a member of advisory boards for Altimmune and Clearmind Medicine; a consultant to Sobrera Pharmaceuticals and Altimmune; the recipient of research funding and medication supplies for an investigator-initiated study from Alkermes; a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last 3 years by Alkermes, Dicerna, Ethypharm, Imbrium, Indivior, Kinnov, Lilly, Otsuka, and Pear; and an inventor on US provisional patent "Multiancestry Genome-wide Association Meta-analysis of Buprenorphine Treatment Response." The other authors have no disclosures to make.

DATA AVAILABILITY STATEMENT

The cross-ancestry GWAS meta-analysis and within-ancestry GWAS summary-level association data will be made available in dbGaP (https://www.ncbi.nlm.nih.gov/gap/) under accession phs001672 "Veterans Administration (VA) Million Veteran Program (MVP) Summary Results from Omics Studies." Registration and approval are needed following dbGaP's data access process.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Davis, C.N., Jinwala, Z., Justice, A.C., Rentsch, C.T. & Kranzler, H.R. (2025) Multi-ancestry genome-wide association study of topiramate's effects on heavy alcohol use. *Alcohol: Clinical and Experimental Research*, 00, 1–9. Available from: https://doi.org/10.1111/acer.70069