2024

Alcohol use and alcohol use disorder differ in their genetic relationships with PTSD: A genomic structural equation modelling approach

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Published to Journal of Drug and Alcohol Dependence on March 31, 2022 by Kaitlin E. Bountress, Leslie A. Brick, Christina Sheerin, Andrew Grotzinger, Daniel Bustamante, Sage E. Hawn, Nathan Gillespie, Robert M. Kirkpatrick, Henry Kranzler, Rajendra Morey, Howard J. Edenberg, Adam X. Maihofer, Seth Disner, Allison Ashley-Koch, Roseann Peterson, Adriana Lori, Dan J. Stein, Nathan Kimbrel, Caroline Nievergelt, Ole A. Andreassen, Jurjen Luykx, Arash Javanbakht, Nagy A. Youssef, The Psychiatric Genomics Consortium Posttraumatic Stress Disorder Working Group, Ananda B. Amstadter

Presented by Tulsi Patel
March 27, 2024
Medical Journal Club

Abstract Abstracted

Posttraumatic stress disorder (PTSD) is associated with an increased alcohol use and increased risk of developing alcohol use disorder (AUD). Previous literature suggests that the genetic association between PTSD and alcohol use differs from that between PTSD and AUD. Researchers in this study used a genomic Structural Equation Modeling, genomicSEM, to analyze data from a larger genome-wide association studies (GWAS). Participants in the study were of European descent.

Researchers investigated the genetic association between PTSD, alcohol use, and AUD through these large scale statistical analyses. Researchers observed a significant improvement in model fit ($p < .001$). Genetic correlations (rG) between PTSD and AUD were positive (rG: .36, $p < .001$), while those between PTSD and alcohol use were negative (rG: -0.17, $p < .001$). Researchers observed that when specific variables for alcohol use and AUD were isolated, key differences resulted in genetic association with PTSD, which indicated that the genetic makeup of alcohol-related behaviors is different in individuals with PTSD.

Acronyms

- PTSD: posttraumatic stress disorder
- AUD: alcohol use disorder
- AU: alcohol use
- PGCPTSD: Psychiatric Genomics Consortium Post-Traumatic Stress Disorder
- PCL IV: PTSD Checklist for DSM-IV (updated version DSM-V is now available)
- MVP: Million Veteran Program
- GWAS: genome-wide association studies
- GenomicSEM: genomic Structural Equation Modeling
- PGC-SUD: Psychiatric Genomics Consortium Substance Use Disorder
- DPW: drinks per week
- ICD: International Classification of Diseases

Posttraumatic Stress Disorder

- Posttraumatic stress disorder (PTSD) is a psychiatric disorder that may occur in individuals who have experienced or witnessed a traumatic event.
- These traumatic events can be emotionally and physically harmful, life-threatening, and they often affect physical, mental, and social well-being.
- Symptoms of PTSD can vary based on their severity, but they often include: intrusion, avoidance, and alterations in cognition, mood, and reactivity.
- A Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is frequently used to diagnose individuals with PTSD.

Alcohol Use Disorder

- Alcohol use disorder (AUD) is a brain disorder characterized by an impaired ability to alcohol use despite adverse consequences.
- Clinicians use Diagnostic and Statistical Manual of Mental Disorders (DSM-5) to assess an individual for AUD and to determine its severity if present.
    - Mini International Neuropsychiatric Interview questionnaire (MINI)
- AUD severity can be categorized as mild (2-3 criteria), moderate (4-5 criteria), or severe (6 or more criteria).
- AUD results in lifetime changes in the chemical and physical functioning of the brain, and it’s known to make individuals vulnerable to relapse.

Introduction

- Researchers stated that approximately 50-70% of all individuals have experienced at least one traumatic event over the course of their lifetime.
- Past literature indicates that PTSD often co-occurs with heavy alcohol use (AU) and AUD.
- Twin studies suggested moderate heritability (40–60%) for PTSD, alcohol use, and AUD.
    - Twin studies also indicated a 30% genetic overlap between PTSD and AUD.
- Genetic correlations between PTSD and AUD are significant and positive, while those between PTSD and alcohol use phenotypes are negative or non-significant.

Hypotheses

- The first hypothesis stated that “separating PTSD, AUD, and alcohol use into distinct factors would improve model fit, with positive genetic associations between PTSD and AUD phenotypes and potentially negative associations with alcohol use phenotypes.”
- The second hypothesis proposed that “extracting commonalities among all alcohol items while retaining uniqueness in AUD and alcohol use would further enhance model fit. This anticipated near-zero genetic correlations between PTSD and the common alcohol factor, stronger positive correlations between PTSD and unique AUD, and potentially negative correlations between PTSD and alcohol use.”

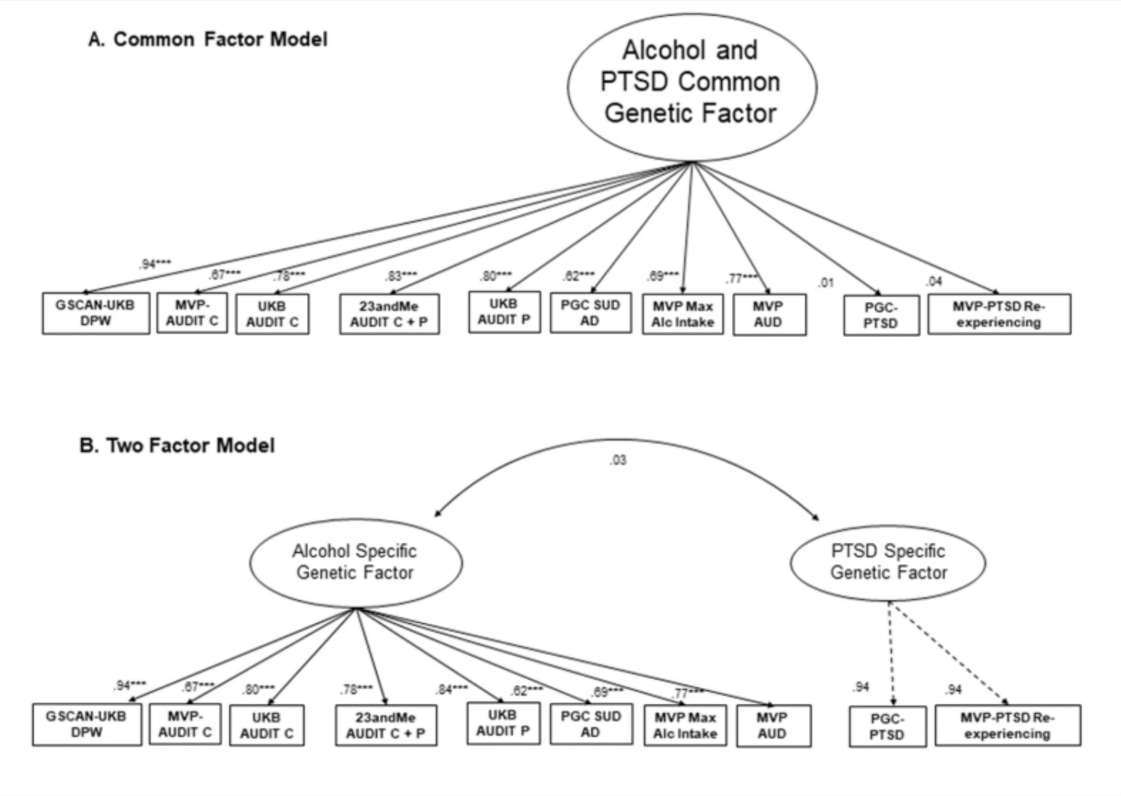
Methods

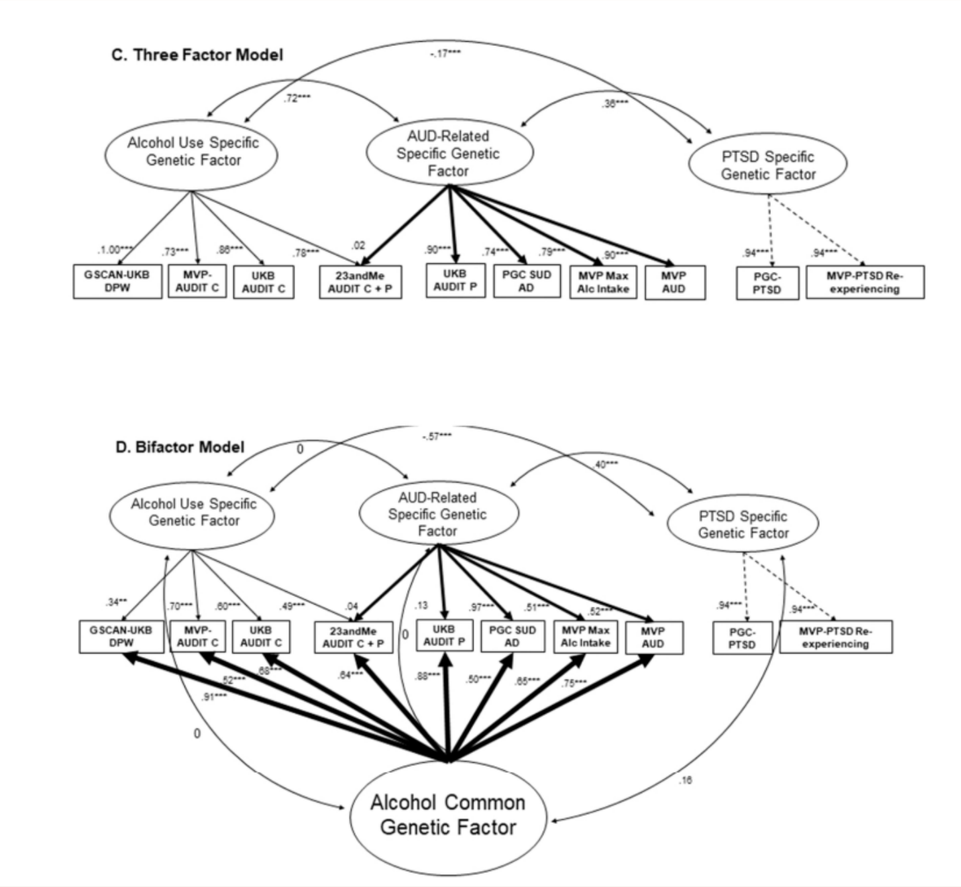
- Summary statistics for PTSD and alcohol use phenotypes were obtained from large-scale datasets, focusing on individuals of European Ancestry.
- PTSD case or control status was sourced from the PGCPTSD Freeze 1.5 (N = 48,471), with re-experiencing symptom severity scores assigned from the PTSD Checklist for DSM-IV (PCL IV) in the MVP (N = 146,660).
- AUD case or control status was derived from the MVP dataset based on ICD-9 or ICD-10 codes for dependence or abuse diagnoses, with cases identified by inpatient or outpatient alcohol-related codes (N = 267,391).
    - Alcohol dependence data came from the PGC-SUD meta-analysis (N = 46,568).
- Drinks per week (DPW) were assessed using data from the GSCAN consortium and UK Biobank (N = 941,280).
    - Various AUDIT scores were used, including AUDIT total score (N = 20,328), AUDIT-C subscale (N = 206,254), and AUDIT-P subscale (N = 121,604), along with a quantitative measure of maximum habitual alcohol use in a typical month (MaxAlc) from the MVP (N = 126,936)."

Analysis

- Four models were estimated and compared for fit, including a common factor model (Model A), a two-factor model (Model B), a correlated three-factor model (Model C), and a bifactor model (Model D).
- The hypothesis suggested that a model with unique factors for PTSD, AUD, and alcohol use would fit the data best, with a stronger and more positive genetic correlation between PTSD and AUD compared to PTSD and alcohol use.
- The bifactor model (Model D) was examined to see if it provided a better fit, allowing for common and specific factors for PTSD and alcohol phenotypes.
    - It was hypothesized that the genetic correlation with the factor would result in positive variance unique to AUD, and negative variance unique to alcohol use.
- Goodness-of-fit indices, including CFI, SRMR, and AIC values, were evaluated to determine the best-fitting model.
- Zero-order genetic correlations between PTSD and alcohol phenotypes were used to inform which alcohol items would load onto the alcohol use-related or AUD-related factors.

Models


A. Common Factor Model
Alcohol and PTSD Common Genetic Factor
.94***
.67***
.78***
.83***
.80***
.62***
.69***
.77***
.01
.04
GSCAN-UKB DPW
MVP-AUDIT C
UKB AUDIT C
23andMe AUDIT C + P
UKB AUDIT P
PGC SUD AD
MVP Max Alc Intake
MVP AUD
PGC-PTSD
MVP-PTSD Re-experiencing
B. Two Factor Model
.03
Alcohol Specific Genetic Factor
PTSD Specific Genetic Factor
.94***
.67***
.80***
.78***
.84***
.62***
.69***
.77***
.94
.94
GSCAN-UKB DPW
MVP-AUDIT C
UKB AUDIT C
23andMe AUDIT C + P
UKB AUDIT P
PGC SUD AD
MVP Max Alc Intake
MVP AUD
PGC-PTSD
MVP-PTSD Re-experiencing


C. Three Factor Model
-.17***
.72***
.36***
Alcohol Use Specific Genetic Factor
AUD-Related Specific Genetic Factor
PTSD Specific Genetic Factor
.1.00***
.73***
.86***
.78***
.02
.90***
.74***
.79***
.90***
.94***
.94***
GSCAN-UKB DPW
MVP-AUDIT C
UKB AUDIT C
23andMe AUDIT C + P
UKB AUDIT P
PGC SUD AD
MVP Max Alc Intake
MVP AUD
PGC-PTSD
MVP-PTSD Re-experiencing
D. Bifactor Model
-.57***
0
.40***
Alcohol Use Specific Genetic Factor
AUD-Related Specific Genetic Factor
PTSD Specific Genetic Factor
.34**
.70***
.60***
.49***
.04
.13
.97***
.51***
.62***
.94***
.94***
0
.68***
.64***
.88***
.50***
.65***
.75***
.91***
0
.16
GSCAN-UKB DPW
MVP-AUDIT C
UKB AUDIT C
23andMe AUDIT C + P
UKB AUDIT P
PGC SUD AD
MVP Max Alc Intake
MVP AUD
PGC-PTSD
MVP-PTSD Re-experiencing
Alcohol Common Genetic Factor

Results

- Model A, representing a common factor model, did not fit the data well ($\chi 2 = 637.67$, AIC = 677.67, CFI = 0.84, SRMR = 0.23). Loadings showed significant influence from alcohol-related factors, with non-significant loadings for PTSD items.
- Model B, a two-factor model, showed slightly better fit but still inadequate ($\chi 2 = 506.97$, AIC = 546.97, CFI = 0.88, SRMR = 0.19). Alcohol items had significant loadings, while PTSD items did not.
- Model C, a three-factor model, demonstrated improved fit ($\chi 2 = 306.97$, AIC = 352.97, CFI = 0.93, SRMR = 0.11). Significant loadings were observed for all factors. A small-to-moderate positive genetic correlation was found between PTSD and AUD ($rG = 0.36$, $p < .001$).
- Model D, a bifactor model, fit the data well ($\chi 2 = 82.99$, AIC = 144.99, CFI = 0.98, SRMR = 0.06). The genetic correlation between PTSD and the common alcohol factor was positive and non-significant ($rG = 0.16$, NS).
    - PTSD's correlation with AUD increased ($rG = 0.40$, $p < .001$), while its correlation with alcohol use became more negative and significant ($rG = -0.57$, $p < .001$), suggesting that extracting commonality increased each phenotype's unique association with PTSD.

Discussion

- Multivariate genetic correlations between PTSD and alcohol factors revealed significant and positive correlations for PTSD-AUD and negative or non-significant correlations for PTSD-alcohol use, aligning with previous findings.
- Neither a common factor model nor a two-factor model adequately fit the data, whereas a three-factor model showed better fit, indicating separate factors for AUD and alcohol use.
- A bifactor model demonstrated improved fit compared to other models, indicating increased unique associations between PTSD and alcohol factors when accounting for shared genetic variance.
- The genetic correlation between PTSD and the common alcohol factor was nonsignificant, while correlations between PTSD and AUD increased, and between PTSD and alcohol use became more negative and significant.
- The study suggests distinct genetic factors contributing to PTSD, AUD, and alcohol use among individuals of European Ancestry.

Limitations

- Limitations include the study's focus on European Ancestry individuals, potential sex differences, and the need for replication across diverse populations.
    - Findings highlight the importance of understanding the genetic architecture of alcohol use and AUD separately, with implications for precision medicine efforts and future research directions.

Discussion Questions

01

How might cultural and social factors influence the genetic associations between PTSD and alcohol use in different populations?

02

How might the findings of this study impact public health initiatives aimed at addressing PTSD and alcohol use disorder?

03

How might the inclusion of diverse populations in genetic studies impact our understanding of the relationship between PTSD and alcohol use?

Citations

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