Disentangling Differing Relationships Between Internalizing Disorders and Alcohol Use

by

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Abstract

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Thesis directed by Assistant Professor Luke M. Evans

Both internalizing disorders and alcohol use have dramatic, wide-spread implications for global health. Previous work has established common phenotypic comorbidity among these disorders, as well as shared genetic variation underlying internalizing and alcohol use. We used genomic structural equation modeling to investigate the shared genetics of internalizing, externalizing, and alcohol use traits, as well as to explore whether specific domains of internalizing symptoms mediate the contrasting relationships with problematic alcohol use compared to alcohol consumption. We also examined patterns of genetic correlations between similar traits within additional Finnish and East Asian ancestry groups. When the shared genetic influence of externalizing psychopathology was accounted for, the effect of internalizing on alcohol use was reduced, suggesting the important role of common genetic factors underlying multiple psychiatric disorders and the genetic influences on comorbidity of internalizing and alcohol use traits. Individual internalizing domains had contrasting effects on frequency of alcohol consumption, which demonstrate the complex system of pleiotropy that exists, even within similar disorders, and can be missed when evaluating only relationships among formal diagnoses. Future work must consider both the broad effects of shared psychopathology and the fine-scale effects of heterogeneity within disorders in order to more fully understand the biology underlying complex traits.

Acknowledgements

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Introduction

Internalizing disorders, including anxiety and depressive disorders, and alcohol use disorder (AUD) are common, often debilitating conditions. Nearly one third of U.S adults experience an anxiety disorder during their lives[1], and approximately 16% of the world's population are affected by either mental or substance use disorders[2]. Excessive alcohol use is one of the leading causes of preventable death in the United States[3], and alcohol use is the leading cause of premature death and disability worldwide for those aged 15-49[4].

Internalizing disorders and AUD are frequently comorbid, co-occurring two to four times more than expected for independently occurring disorders[5–7]. This further confounds diagnosis and treatment of both psychiatric and substance use disorders, which already lack effective treatment options. Along with the observed phenotypic comorbidity between internalizing disorders and AUD, there is substantial evidence of shared genetic factors contributing to comorbidity. Work by Walters et al. found significant positive genetic correlations between alcohol dependence and major depression, depressive symptoms, and neuroticism (r_g = 0.4 - 0.6)[8]. However, there is also evidence that the relationship with internalizing disorders differs depending on the specific alcohol phenotype considered[9,10], while AUD and problematic alcohol use (PAU) metrics are positively genetically correlated with internalizing, alcohol consumption metrics are negatively correlated[9,11].

Further complicating this relationship, there is evidence of underlying heterogeneity in internalizing disorders, with multiple separable genetic factors that do not strictly adhere to clinical diagnostic boundaries. Nitschke et al.[12] used phenotypic factor analysis to expand Watson & Clark's "tripartite model"[13] of anxiety and depression to include four factors: anxious arousal (somatic anxiety), anxious apprehension (cognitive anxiety), depression, and low

positive affect. Recent work by Thorp et al.[14] identified a three genetic factor model of anxiety and depression, with neuroticism traits loading onto either the anxiety factor or the depression factor. These studies demonstrate the multiple, distinguishable phenotypic and genetic factors underlying internalizing disorders, but there has yet to be any analysis of the genetic underpinnings of Nitschke's phenotypic factors or their relationships with alcohol phenotypes.

Here, we use genomic structural equation modeling (GSEM)[15] to further investigate the differing genetic relationships between internalizing disorders and different alcohol use phenotypes. We consider how different specific domains of internalizing traits may influence these relationships, as well as whether the genetic relationship with alcohol use phenotypes is specific to internalizing disorders or shared with other correlated psychopathologies, such as externalizing disorders.

Methods

Phenotypes

We used the largest and most-recent publicly available genome wide association study (GWAS) summary statistics for a range of internalizing and alcohol use traits (Suppl. Table 1 and Suppl. Table 2). Internalizing phenotypes included Generalized Anxiety Disorder two item questionnaire (GAD-2) score from Levey et al.[16], a meta-analysis of lifetime anxiety disorder from Purves et al.[17], a meta-analysis of broad depression from Howard et al.[18], and item-level GWAS of the Generalized Anxiety Disorder seven-item questionnaire (GAD-7) from Brasher et al.[19]. Alcohol use phenotypes included Alcohol Use Disorder (AUD) from Zhou et al.[20], GWAS of Alcohol Use Disorder Identification Test (AUDIT) items and alcohol intake frequency from Colbert et al.[10], and drinks per week (dpw) from Liu et al.[21]. We included an additional

externalizing factor defined by Attention-deficit/hyperactivity disorder (ADHD)[22], antisocial behavior[23], and number of sexual partners[24].

In addition, we performed new GWAS of Patient Health Questionnaire (PHQ-9) depression items and the 12-item EPQ-R neuroticism scale in the UK Biobank[25] (Suppl. Table 2). We treated PHQ-9 items as dichotomous, with an endorsement of experiencing a symptom 'Several days' or more over the last two weeks as a case, following Thorp et al.[14]. Thorp et al. demonstrate that treating symptom-level phenotypes as continuous has been shown to downwardly bias estimates of h^2_{SNP}. Additionally, they showed that for PHQ-9 depression items, genetic correlations between the continuous and dichotomous phenotypes were all >0.95. Neuroticism questionnaire items are dichotomous, with endorsements ("Yes") for an item considered cases for that item. GWAS were performed using BOLT-LMM[26], with MAF and LD-pruned array SNPs (using PLINK2[27]) to account for relatedness. Covariates included sex, age, age^2, education, Townsend deprivation index, assessment center, genotyping batch, and the scores of the first ten genomic principal component (PC) axes. We used the UK Biobank full release of Haplotype Reference Consortium-imputed genotypes[28] for associations, requiring MAF >= 0.0001, genotype missingness < 0.05, Hardy-Weinberg test p-value > 1e-6, and imputation INFO score >= 0.9. Summary statistics for new GWAS will be publically available in the GWAS Catalog[29].

In order to minimize the effects of genetic stratification, all GWAS used in the primary analysis were from individuals of European ancestry, while secondary analyses included individuals of Finnish and East Asian ancestry.

Genetic Correlations

Genome-wide genetic correlations between all pairs of traits were estimated using Linkage Disequilibrium Score Regression (LDSC)[30]. For genetic correlations see Suppl. Figure 1.

Model Testing

To quantify the genetic relationships between our suite of internalizing, externalizing, and alcohol use phenotypes, we used genomic structural equation modeling (GSEM)[15]. GSEM uses GWAS summary statistics to analyze the shared genetic architecture of complex traits. This is done by first calculating the genetic covariances between all pairs of traits implied by the GWAS summary statistics using LDSC. Then parameters of the user-specified model are calculated based on minimizing the discrepancy between the model genetic covariance structure and the empirical genetic covariances.

We used GSEM confirmatory factor analysis to test a hypothesized five factor "base model" (Figure 1), in which the three, correlated alcohol use factors were regressed on the correlated internalizing and externalizing disorder factors. We included three separate alcohol use factors following Colbert et al.[10] due to their demonstrated differing relationships with psychopathologies. The internalizing factor was defined by the GAD-2, lifetime anxiety, and depression GWASs. Problematic alcohol use (PAU) was defined by AUD, and AUDIT items 4, 5, 7, 8, and 10 (AUDIT-P items). Alcohol consumption quantity was defined by AUDIT items 2 and 3 and number of drinks per week. Alcohol consumption frequency was defined by AUDIT 1 and alcohol intake frequency, along with drinks per week, which had loadings on both consumption quantity and frequency. AUDIT items 6 and 9 were not included in this analysis

due to low h^2_{SNP} following Colbert et al.[10] and similar to Mallard et al.[31]. We allowed correlations between all three alcohol factors, as well as between internalizing and externalizing.

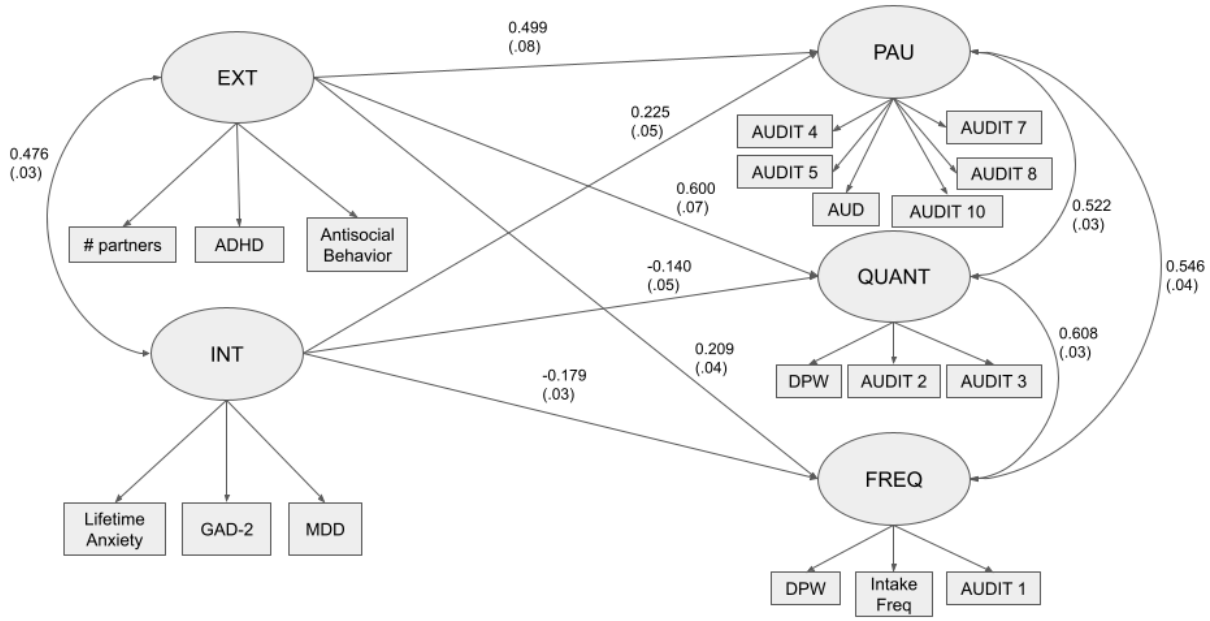

Figure 1. Genomic SEM five factor "base model". Single headed arrows represent regressions, while double headed arrows represent correlations. Internalizing (INT) and externalizing (EXT) were allowed to be correlated, as were all three alcohol factors: problematic alcohol use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). The model used unit variance identification, which constraints the variance of the latent factors to 1. All values are fully standardized estimates with standard errors listed in parentheses. Solid arrows indicate the path coefficient was nominally significant ($p < 0.01$).

We also tested two exploratory models: a four factor model that excluded externalizing phenotypes entirely, as well as a five factor model which did not include externalizing, but did split the internalizing factor into an anxiety factor (GAD-2 and Lifetime anxiety) and a depression factor (MDD). Although fit was slightly better, likely due to less parameters in the model, the models without externalizing were both substantially less interpretable, and anxiety and depression were ultimately combined into a single internalizing factor since the depression factor was defined by only one GWAS.

In order to determine whether any specific domains of internalizing explain the differing relationships between internalizing and PAU versus consumption factors, we ran a series of models that included specific domains of internalizing as mediating factors (see Figure 2 for example). The 28 individual questionnaire items (GAD-7, PHQ-9, neuroticism) were split into four "domains": worry, anxious arousal, general negative affect, and low positive affect (Figure 3), based on the tripartite model of anxiety and depression[13] and the four factor model proposed by Nitschke et al.[12], which added an "anxious apprehension" factor similar to the "worry" domain used here. Some items, such as sleep disturbance from the PHQ-9, were included in multiple domains (low positive affect and anxious arousal) because sleeping too little may indicate more anxious arousal, while sleeping too much may indicate low positive affect. To assess the genetic relationships among these, we ran a correlated four-factor model of the domains themselves (Figure 3, Suppl. Table 3). We tested our hypothesis that the relationship between internalizing disorder and alcohol use traits are mediated by specific internalizing domains by including each domain separately as an additional, mediating factor in the model (e.g., Figure 2). Indirect effects of psychiatric factors on alcohol factors through the mediator were calculated by multiplying the effect of the psychiatric factor on the mediator and the effect of the mediator on the alcohol factor.

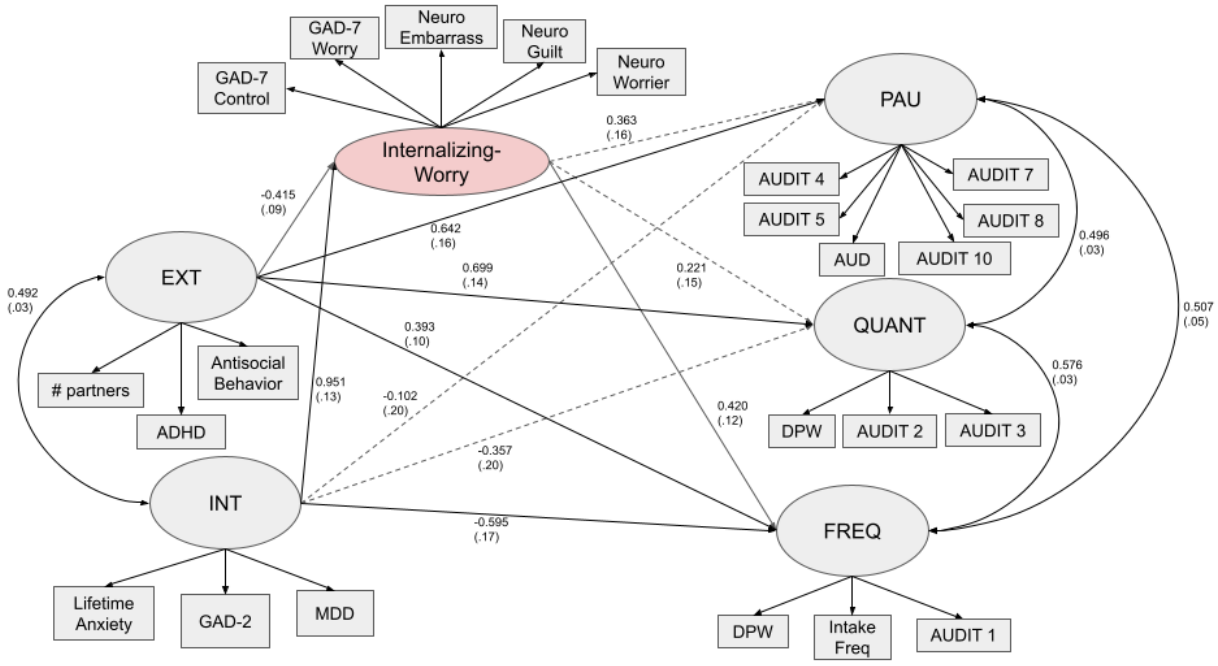

Figure 2. Genomic SEM six factor model with five core factors (INT, EXT, PAU, QUANT, FREQ) and a single specific "worry" factor mediating the relationships between the psychiatric and alcohol use factors. Single headed arrows represent regressions, while double headed arrows represent correlations. Internalizing (INT) and externalizing (EXT) were allowed to be correlated, as were all three alcohol factors: problematic alcohol use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). The model used unit variance identification, which constraints the variance of the latent factors to 1. All values are fully standardized estimates with standard errors listed in parentheses. Solid arrows indicate the path coefficient was nominally significant ($p < 0.01$), while dotted arrows indicate the path did not reach significance.

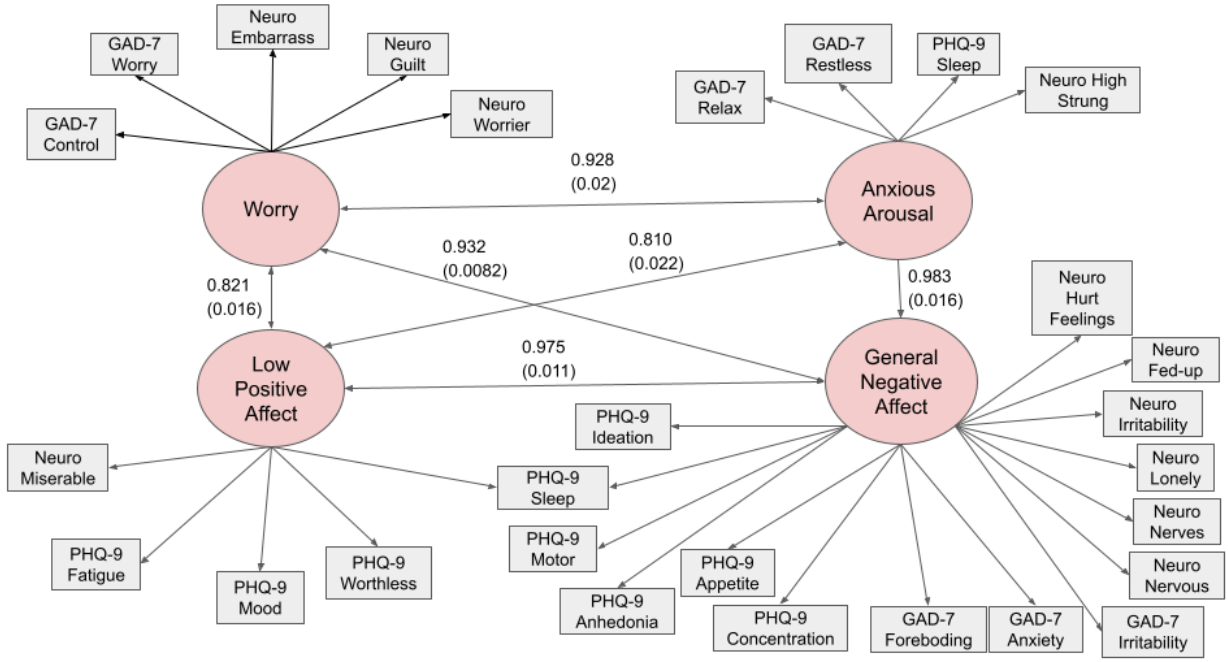

Figure 3. Genomic SEM four correlated factor model relating the four specific domains of internalizing (worry, anxious arousal, low positive affect, and general negative affect). Indicators are item-level GAD-7 anxiety, PHQ-9 depression, and EPQ-R neuroticism questions. Double headed arrows represent correlations between factors. The model used unit variance identification, which constraints the variance of the latent factors to 1. All values are fully standardized estimates with standard errors listed in parentheses. Solid arrows indicate the path coefficient was nominally significant ($p < 0.01$).

Diverse Ancestry Replication

Since the primary GSEM analyses were limited to individuals of European ancestry, we used additional samples to investigate whether patterns of relationships between internalizing, externalizing, and alcohol use differ across diverse ancestry groups. We used summary statistics from studies of individuals of Finnish and East Asian ancestry (Suppl. Table 4), although comparable traits with sufficient sample sizes were not available to fully replicate our analyses in both ancestry groups. We used summary statistics from FinnGen[32] to test a simplified version of our base model in Finnish ancestry individuals, relating an internalizing factor to a problematic alcohol use factor. For East Asian ancestry analyses, we used summary statistics from

GSCAN2[33] and the PCG[34] to consider cross-trait, within-ancestry genetic correlations for pairs of traits using LDSC, which uses GWAS summary statistics and LD information from ancestry-matched references to estimate genetic correlation based on the correlation of SNP effect sizes. For both ancestry groups, ancestry-specific references of HapMap3 SNPs in 1000 Genomes data[35] (Finnish = FIN, East Asian = EAS) were used.

We considered including African American ancestry samples as well, but ultimately did not due to admixture that leads to biased genetic correlation estimates calculated using LDSC[30,36].

Results

Base-model

The five factor model (Figure 1, Suppl. Table 5) relating internalizing, externalizing, and three alcohol use factors fit the data well ($\chi^2(108) = 558.023$, AIC = 648.024, CFI = 0.964, SRMR = 0.102). All indicators had strong, highly significant loadings on their respective latent factors. The three alcohol factors were all strongly correlated (r_g = 0.50-0.60) and internalizing and externalizing were also correlated (r_g = 0.47), as expected. Externalizing was significantly positively predictive of all three alcohol factors (r_g = 0.20-0.60), with the strongest relationship with alcohol consumption quantity. Interestingly, with externalizing included in the model, the genetic effects of internalizing on the alcohol factors were low. The genetic effect of internalizing on PAU was moderately positive (beta = 0.22), but the effects on both alcohol consumption quantity and frequency were significantly negative (beta = -0.14 and -0.18 respectively). This suggests the strong observed phenotypic and genetic relationships between

internalizing and alcohol use may be more due to shared genetic components with other psychopathologies like externalizing traits rather than genetic factors unique to internalizing.

We performed some additional exploratory model testing, including a four factor model excluding externalizing (Suppl. Table 6, Suppl. Figure 2) and a five factor model excluding externalizing and splitting internalizing into separate anxiety and depression factors (Suppl. Table 7, Suppl. Figure 3). Both models also fit the data well ($\chi^2(70) = 313.172$, AIC = 383.172, CFI = 0.979, SRMR = 0.0872 and $\chi^2(67) = 305.473$, AIC =381.473, CFI =0.979, SRMR = 0.0871, respectively), but ultimately we combined the anxiety and depression factors to avoid having a factor defined by only one indicator, and we included externalizing to account for the effect of shared underlying genetic components among psychopathologies. When an externalizing factor was not included in the model, the effects of internalizing on the three alcohol factors were higher, and positive or near zero, rather than negative in the case of both consumption factors (PAU = 0.47, QUANT = 0.15, FREQ = -0.076).

Mediation models

We used four additional factors (worry, anxious arousal, general negative affect, and low positive affect) in a series of models as potentially mediating the relationship between psychiatric factors and alcohol use factors (e.g. Figure 2). For all four mediating factors (Figure 4), the relationship between internalizing and the mediator was high and nominally significant (betas = 0.84-0.99, $p<0.01$), as expected since the mediators were defined to pull out specific domains of internalizing. The externalizing factor was either not or negatively predictive of all four mediators. Across all mediation models, externalizing remained significantly positively

predictive of all three alcohol factors, while internalizing was no longer significantly positively predictive of any alcohol factor in any of the models.

	Base	Worry	GNA	AA	LPA
INT -> Med	NA	0.951 *	0.996 *	0.989 *	0.835 *
EXT -> Med	NA	-0.415 *	-0.243 *	-0.195	-0.081
Med -> PAU	NA	0.363	0.101	0.038	0.121
Med -> QUANT	NA	0.221	0.163	0.155	0.059
Med -> FREQ	NA	0.420 *	-0.104	0.294	-0.174
INT -> PAU	0.226 *	-0.102	0.119	0.184	0.124
INT-> QUANT	-0.140 *	-0.357	-0.355	-0.316	-0.217
INT -> FREQ	-0.179 *	-0.595 *	-0.100	-0.481	-0.049
EXT -> PAU	0.499 *	0.642 *	0.534 *	0.510 *	0.513 *
EXT -> QUANT	0.601 *	0.700 *	0.684 *	0.651 *	0.632 *
EXT -> FREQ	0.209 *	0.393 *	0.189 *	0.272 *	0.205 *
ID INT PAU	NA	0.345	0.101	0.038	0.101
ID INT QUANT	NA	0.210	0.162	0.153	0.049
ID INT FREQ	NA	0.400 *	-0.104	0.290	-0.146 *
ID EXT PAU	NA	-0.150	-0.025	-0.007	-0.010
ID EXT QUANT	NA	-0.092	-0.040	-0.030	-0.005
ID EXT FREQ	NA	-0.174	0.025	-0.030	0.014
INT ~~ EXT	0.476 *	0.492 *	0.525 *	0.5 *	0.502 *

Figure 4. Parameter summaries for the five factor base model and each of the four mediation models. Columns indicate which model values are listed, and rows indicate which model parameter is being shown by describing the corresponding path that would be shown in a path diagram. For example, the "INT -> QUANT" row shows the path coefficients for alcohol consumption quantity regressed on internalizing directly. INT = internalizing; EXT = externalizing; PAU = problematic alcohol use; QUANT = alcohol consumption quantity; FREQ = alcohol consumption frequency; Med = mediator for that particular model (worry, general negative affect, anxious arousal, or low positive affect). The last row (INT ~~ EXT) shows the correlation between the internalizing and externalizing factors, which remains consistent across models.

When mediator "worry" was included, the direct effect of internalizing on alcohol consumption frequency was moderately negative (r_g = -0.59, Figure 4), but the indirect effect of internalizing on frequency mediated by worry was moderately positive and significant (r_g =

0.400, $p < 0.01$). The genetic effect of internalizing on alcohol consumption quantity and frequency was negative in all other models as well, but not nominally significant ($p > 0.01$). Indirect effects of internalizing on alcohol use factors through the other mediators were also non-significant, with the exception of a significant negative indirect effect of internalizing on alcohol consumption frequency when mediated by low positive affect (indirect effect = -0.15, $p < 0.01$). Notably, the shared genetic correlation between internalizing and externalizing remained relatively consistent across all models (r_g = 0.48-0.53). For full mediation model output see Suppl. Tables 8 - 11.

Diverse Ancestry Models

Additional GWAS summary statistics were used to investigate the pattern of relationships between internalizing and alcohol use in individuals of Finnish and East Asian ancestry. In the Finnish population, we tested a reduced version of our base model with two factors: internalizing and problematic alcohol use (Suppl. Figure 4, Suppl. Table 12). None of the available externalizing traits in FinnGen have a sample size sufficient for use with GSEM or LDSC. For each of the two included factors, all indicators had strong, significant loadings. There was a moderate, positive relationship between the internalizing factor and the problematic alcohol use factor (beta = 0.84). This positive relationship is expected, as it matches the relationship observed in European ancestry models between internalizing and alcohol use when genetic variation shared with externalizing is not accounted for, as well as the consistently positive relationship between internalizing and *problematic* alcohol use specifically.

For both ancestry groups we used LDSC to calculate genetic correlations across traits, within each ancestry group (Figure 5, Suppl. Table 13). Since so few summary statistics of

sufficient size were available, particularly for individuals of East Asian ancestry, these results should be interpreted with caution. The correlations between well-powered traits in Finnish individuals were in the expected direction. The two alcohol use traits (AUD and alcohol dependence) were highly correlated (r_g = 1.03, SE = 0.03), as were all three anxiety traits (r_g = 0.97 - 1.15), and depression was most highly correlated with GAD (r_g = 0.95, SE = 0.32). All genetic correlations were moderate to high and positive, which matches the moderately positive relationships between internalizing and specifically *problematic* alcohol use in individuals of European ancestry across all other models.

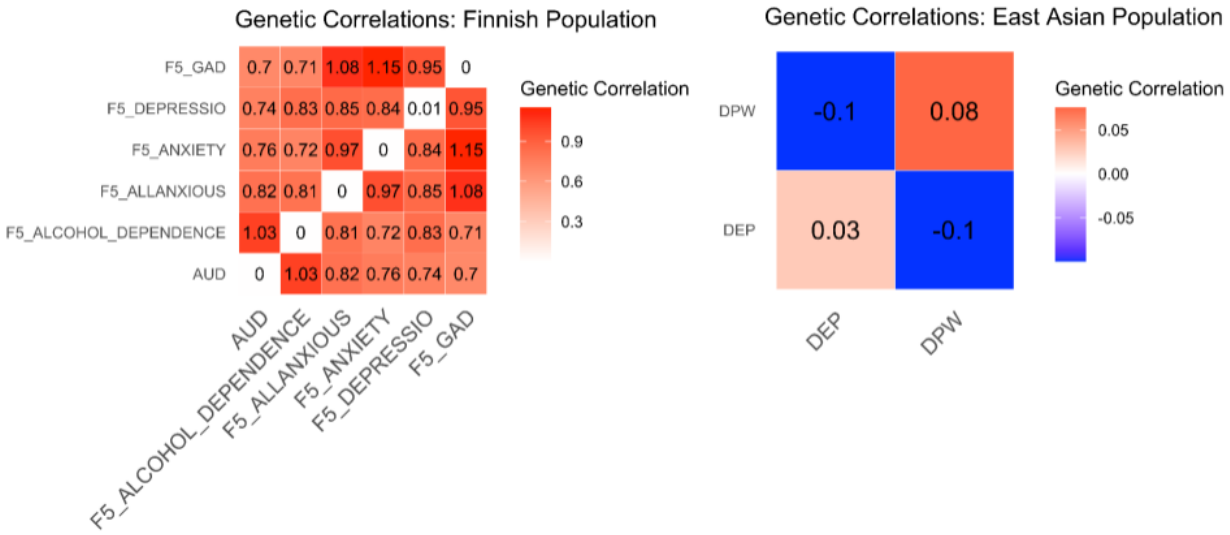

Figure 5. Genetic correlations across traits for two diverse ancestry groups: Finnish (left) and East Asian (right). Off-diagonal elements are genetic correlations and on the diagonal are observed-scale heritabilities, all estimated using LD Score Regression (LDSC). In the Finnish population, note that estimated heritabilities appear as zero due to rounding and were not truly estimated as zero. For a list of GWAS that were included, see Suppl. Table 4.

Only two traits were included for East Asian ancestry analysis: drinks per week and depression. Interestingly, they were slightly negatively, although not significantly correlated (r_g =

-0.10, SE = 0.28, p = 0.72), which is somewhat similar to the negative relationship between internalizing and alcohol intake frequency seen in European ancestry individuals.

Discussion

We used genomic structural equation modeling to test a five factor base model relating internalizing and externalizing disorder factors to three alcohol use factors (problematic use, consumption quantity, and consumption frequency). The internalizing factor was positively related to problematic alcohol use, but negatively related to both alcohol consumption factors, consistent with previous findings[10,11]. Externalizing was significantly positively related to all three alcohol use factors, also consistent with previous findings[37,38]. However, when the externalizing factor was not included in the model, the effects of internalizing on all three alcohol factors increased, and were positive or near-zero, rather than negative, for both alcohol consumption factors. This suggests that the commonly observed phenotypic comorbidity between internalizing traits and alcohol use may be due to underlying genetic variation that is shared among psychiatric disorders, rather than genetic variation unique to internalizing.

Four specific internalizing domains, grouped based on previously proposed phenotypic factors[12,13], were each strongly predicted by the internalizing factor, but largely did not mediate the relationships between internalizing and the three alcohol factors, particularly PAU. This further suggests the importance of shared psychiatric genetic variation, since no domain specific to internalizing fully explained the observed relationships between internalizing and alcohol use traits. However, the indirect effect of internalizing on alcohol consumption frequency *via* the worry factor was significantly positive, and as strong as the direct effect of externalizing on alcohol consumption frequency. Inclusion of the worry mediator led the direct effect of

internalizing on frequency to be even more negative, demonstrating that while genetic influences on "worry" internalizing symptoms, like feelings of embarrassment or guilt and inability to stop worrying, have a positive relationship with alcohol consumption frequency, it is possible other internalizing symptoms may have a more negative relationship with frequency than seen when such subtle variation in internalizing disorders is not accounted for.

Similarly, including a low positive affect factor mediating the relationship between internalizing and the alcohol use factors led to a significantly negative indirect effect of internalizing on alcohol consumption frequency, and a direct effect near zero, consistent with the hypothesis that genetic effects on low positive affect account for at least some of the negative genetic relationship between internalizing and alcohol use frequency. Low positive affect internalizing symptoms, like fatigue and feeling generally miserable, may decrease frequency of alcohol consumption, while some internalizing traits like worry may increase consumption frequency. The relationship between worry and alcohol use has been found in previous phenotypic studies[39,40] but has not been considered at the genetic level or specifically for alcohol consumption frequency.

The mediating effects of the worry and low positive affect factors suggest that even within internalizing, there exists a more complex structure of pleiotropy, in which the genetic variation underlying some specific internalizing traits decreases alcohol consumption, while that underlying others increases it. This is particularly important because the contrasting effects of different internalizing domains can mask each other when internalizing is considered as a whole. For example, recent work by Colbert et al.[10] found slightly negative, but near-zero genetic correlation between internalizing and an alcohol consumption frequency factor when evaluated at a genome-wide level, but variable genetic correlation directions for individual genomic

regions. This could be due to the effects of shared psychopathology that was not accounted for in the model, as well as the heterogeneity of effects within the internalizing disorder factor itself.

While we did see some mediating effects of worry and low positive affect domains, the potential effects of domains themselves may be obscured by heterogeneous effects of traits used to define them. For example, general negative affect was broadly defined, including symptoms from changes in appetite (either loss of appetite or increased appetite) to easily hurt feelings. Some of these symptoms may have important relationships with alcohol use traits such as problematic use, but when combined could not be detected. Similarly, combining anxiety and depression into one internalizing factor may have masked differences. As additional GWAS summary statistics for internalizing disorders become available, anxiety and depression could be considered in models like these separately to gain additional insight into the nuanced relationships between complex traits.

This complex structure of contrasting relationships may also relate to hypothesized mechanisms behind the comorbidity of internalizing disorders and alcohol use disorders. As Stewart and Conrod[41] discuss, comorbid anxiety and substance use disorders may be established and maintained in three ways: 1) through self medication of anxiety symptoms using substances, 2) through the anxiety-inducing effects of substance withdrawal, or 3) not directly causally, but rather due to common basis underlying both anxiety and substance use (for example a shared genetic cause). These hypotheses reflect different types of pleiotropy, or the influence of genetic variation on two or more traits, the first two reflecting vertical pleiotropy and the third horizontal pleiotropy. Here, our analyses cannot determine the causal mechanisms underlying phenotypic comorbidity, but they do support the hypothesis that common genetic variation underlying the comorbidity of internalizing disorders and PAU is shared with other psychopathologies, notably

externalizing disorders, rather than being specific to alcohol use and internalizing disorders, suggesting horizontal pleiotropic effects on at least some aspects of internalizing and alcohol use traits. More generally, these complex relationships between alcohol use and internalizing disorders demonstrate how pleiotropy differs depending on the specific phenotype being considered.

Unfortunately, we were unable to fully replicate our models in additional ancestry groups due to the lack of available GWAS summary statistics with sufficient sample sizes. Some genetic correlations in Finnish and East Asian populations did correspond with what was observed in European ancestry models, such as the positive relationship between problematic alcohol use and internalizing when not accounting for externalizing or other shared psychopathology in Finnish ancestry individuals, and the slight negative correlation between the alcohol intake frequency metric drinks per week and depression in East Asian ancestry individuals. These results should be considered with caution due to low case prevalence in some GWAS, which highlights the critical need for large, publicly available summary statistics from diverse ancestry groups to improve equity in genomic science. We hope that despite the low sample sizes of some available data, inclusion of these non-European ancestry samples provides a starting point[42] to incorporate underrepresented populations into analyses of the comorbidity between internalizing disorders and alcohol use.

Both internalizing and alcohol use disorders have substantial impacts on health worldwide, which are further amplified by their commonly observed comorbidity. In addition to phenotypic comorbidity, internalizing disorders and alcohol use disorders are genetically correlated, although the patterns of genetic correlation depend on the specific psychiatric and substance use traits that are considered. Our results demonstrate the importance of shared

psychopathology (e.g., across both internalizing and externalizing) to this comorbidity, which may be especially important for problematic alcohol use. Notably, this shared genetic influence of psychopathology can be missed entirely when not accounted for in models, leading to misinterpreted relationships between complex traits. By exploring the effects of specific domains of internalizing symptoms, we began to uncover a system of contrasting effects that was previously masked, making some relationships mistakenly appear insignificant. Future work must consider both the broad importance of shared psychopathology, as well as the fine-scale heterogeneity within related disorders in order to work towards a more comprehensive understanding of complex traits and their implications for health and well-being around the world.

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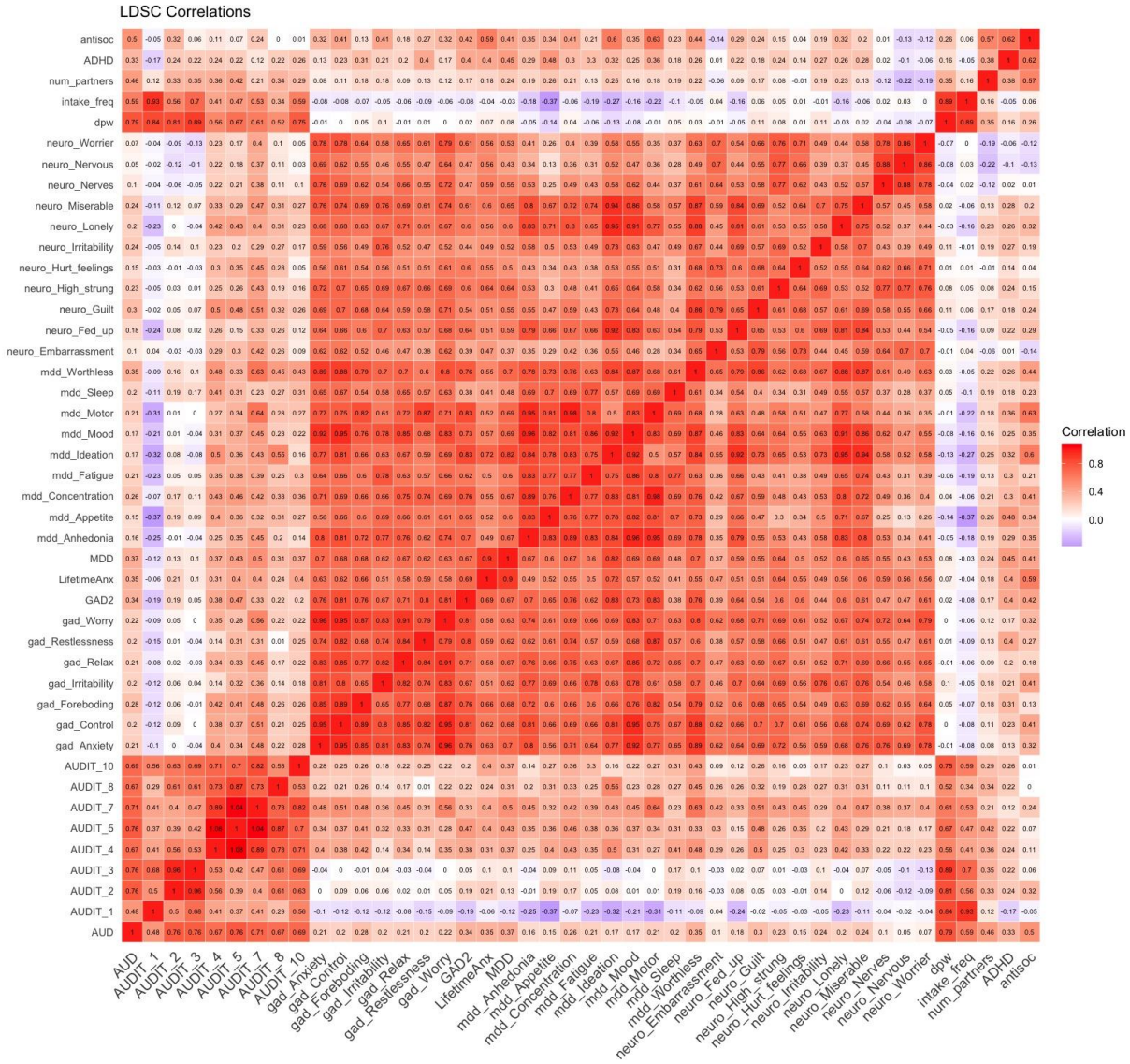
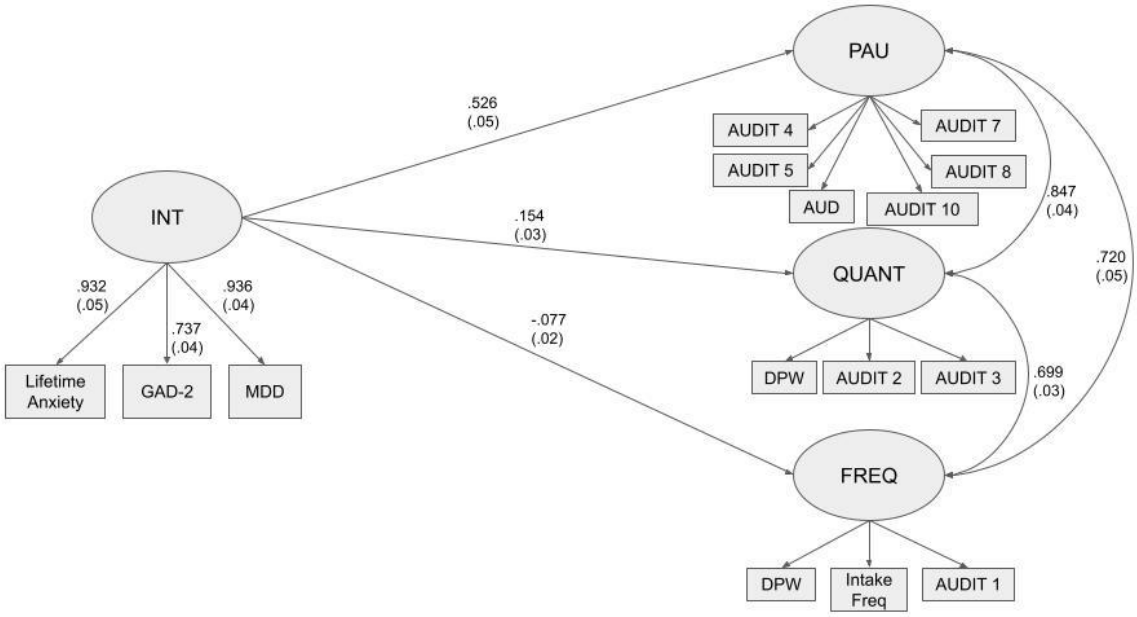
Appendix

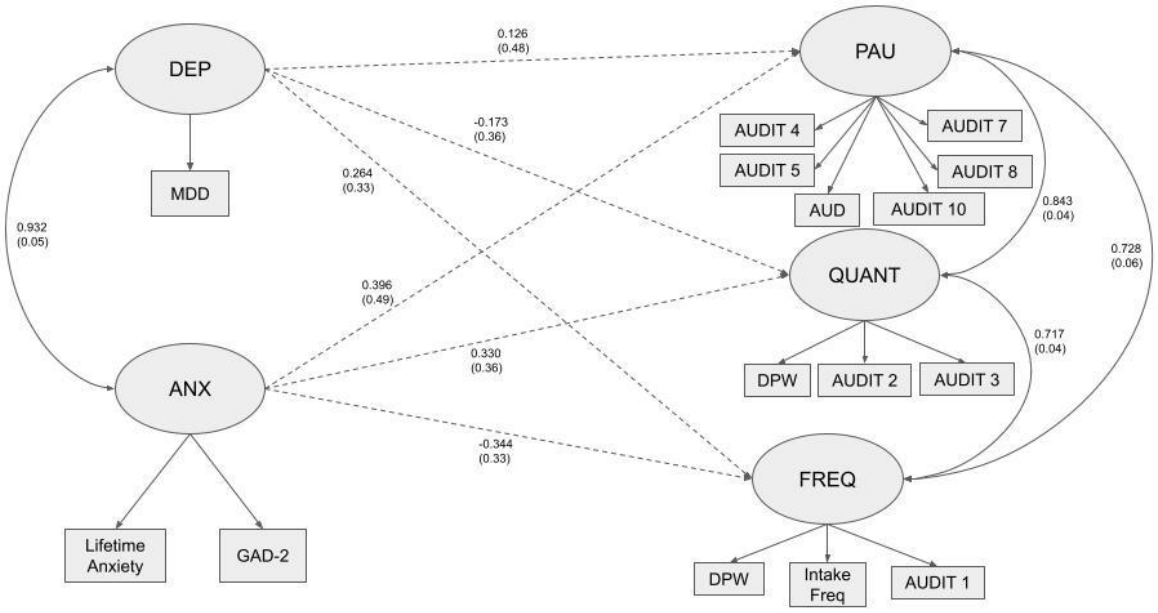
Figures



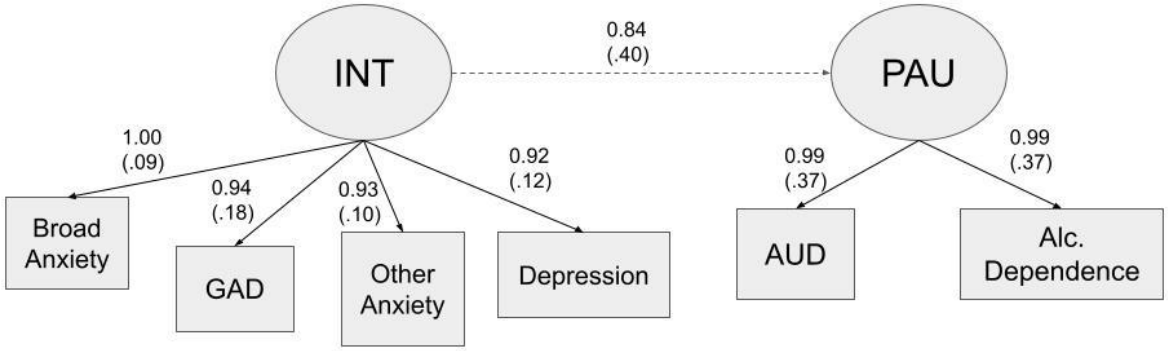
Supplemental Figure 1. Genome-wide genetic correlations for all pairs of traits, including internalizing, externalizing, and alcohol use traits, as well as item-level traits from psychiatric questionnaires (GAD-7 anxiety, PHQ-9 depression, EPQ-R neuroticism). Correlations were calculated using LDSC in individuals of European ancestry.



Supplemental Figure 2. Genomic SEM exploratory four factor model relating internalizing (INT) to three alcohol use factors: problematic alcohol use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). Single headed arrows represent regressions, while double headed arrows represent correlations. All three alcohol factors were allowed to correlate. The model used unit variance identification, which constraints the variance of the latent factors to 1. All values are standardized with respect to the genetic variance of the phenotype, with standard errors listed in parentheses (not fully standardized). Solid arrows indicate the path coefficient was nominally significant ($p < 0.01$).



Supplemental Figure 3. Genomic SEM exploratory five factor model relating separate depression (DEP) and anxiety (ANX) factors to three alcohol use factors: problematic alcohol use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). Single headed arrows represent regressions, while double headed arrows represent correlations. Depression and anxiety were allowed to correlate, as were all three alcohol factors. The model used unit variance identification, which constraints the variance of the latent factors to 1. All values are standardized with respect to the genetic variance of the phenotype, with standard errors listed in parentheses (not fully standardized). Solid arrows indicate the path coefficient was nominally significant ($p < 0.01$), while dotted arrows indicate the coefficient did not reach significance.



Supplemental Figure 4. Genomic SEM two factor reduced base model tested using GWAS summary statistics from individuals of Finnish ancestry from the FinnGen Biobank. The dotted arrow represents problematic alcohol use (PAU) was regressed on internalizing (INT), but did not reach nominal significance ($p < 0.01$). The model used unit variance identification, which constraints the variance of the latent factors to 1. All values are fully standardized estimates with standard errors listed in parentheses. GAD = generalized anxiety disorder; AUD = alcohol use disorder.

Tables

Supplemental Table 1. Description of core genome-wide association studies. N = total sample size, case prevalence reported for case-control studies. PAU = Problematic Alcohol Use; QUANT = Alcohol Consumption Quantity; FREQ = Alcohol Consumption Frequency; INT = Internalizing; EXT = Externalizing

Phenotype	Description	N	Case Prevalence	Factor	Source
Alcohol Use					
AUD	Alcohol Use Disorder	313959	0.183	PAU	Zhou et al. (2020)
AUDIT item 1	How often drink	148222	NA	FREQ	Colbert et al. (2021)
AUDIT item 2	How many drinks in a day	141749	NA	QUANT	Colbert et al. (2021)
AUDIT item 3	frequency of six or more drinks in a day	142034	NA	QUANT	Colbert et al. (2021)
AUDIT item 4	Unable to stop drinking	84621	NA	PAU	Colbert et al. (2021)
AUDIT item 5	Inability to meet expectations due to drinking	84737	NA	PAU	Colbert et al. (2021)
AUDIT item 7	Feelings of guilt after drinking	84675	NA	PAU	Colbert et al. (2021)
AUDIT item 8	Unable to remember due to drinking	84708	NA	PAU	Colbert et al. (2021)
AUDIT item 10	Concern from others about drinking	148185	NA	PAU	Colbert et al. (2021)
Intake freq	Alcohol intake frequency	462016	NA	FREQ	Colbert et al. (2021)
DPW	Drinks per week	537349	NA	QUANT/FREQ	Liu et al. (2019)
Internalizing					
Lifetime Anx	self-reported physician diagnosis of anxiety disorder	83565	0.305	INT	Purves et al. (2019)
GAD-2	Generalized Anxiety Disorder 2-item questionnaire score	175163	NA	INT	Levey et al. (2020)
MDD	Broad depression meta-analysis	322580	0.353	INT	Howard et al. (2019)

Externalizing					
ADHD	Attention-deficit/ hyperactivity disorder diagnosis	35107	0.108	EXT	Demontis et al. (2019)
Antisocial Behavior	Meta-analysis of antisocial behavior phenotypes	16400	NA	EXT	Tielbeek et al. (2017)
# partners	Self-reported number of lifetime sexual partners	370711	NA	EXT	Linner et al. (2019)

Supplemental Table 2. Description of item-level GWAS phenotypes. Summary statistics from Brasher et al. 2022. Includes most questions from Generalized Anxiety Disorder seven-item questionnaire, PHQ-9 depression questionnaire, and 12-item EPQ-R neuroticism questionnaire. GNA = General Negative Affect; W = Worry; AA = Anxious Arousal; LPA = Low Positive Affect

Questionnaire	UKB_ID	Question	N_Total	Case_prevalence	Factor
GAD-7	20505	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Becoming easily annoyed or irritable"	138765	0.28	GNA
GAD-7	20506	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Feeling nervous, anxious or on edge"	138905	0.29	GNA
GAD-7	20509	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Not being able to stop or control worrying"	138880	0.24	W
GAD-7	20512	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Feeling afraid as if something awful might happen"	138760	0.17	GNA
GAD-7	20515	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Trouble relaxing"	139013	0.29	AA
GAD-7	20516	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Being so restless that it is hard to sit still"	139109	0.12	AA

GAD-7	20520	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Worrying too much about different things"	138870	0.32	W
PHQ-9	20510	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Feeling down, depressed, or hopeless"	138965	0.23	LPA
PHQ-9	20511	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Poor appetite or overeating"	139259	0.19	GNA
PHQ-9	20508	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Trouble concentrating on things, such as reading the newspaper or watching television"	139245	0.18	GNA
PHQ-9	20519	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Feeling tired or having little energy"	139167	0.5	LPA
PHQ-9	20513	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Thoughts that you would be better off dead or of hurting yourself in some way"	138392	0.043	GNA

PHQ-9	20518	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual"	139202	0.058	GNA
PHQ-9	20517	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Trouble falling or staying asleep, or sleeping too much"	139155	0.49	AA/ LPA/ GNA
PHQ-9	20507	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Feeling bad about yourself or that you are a failure or have let yourself or your family down"	138784	0.2	LPA
PHQ-9	20514	"Over the last 2 weeks, how often have you been bothered by any of the following problems? Little interest or pleasure in doing things"	139088	0.19	GNA
Neuroticism	2000	"Do you worry too long after an embarrassing experience?"	413198	0.48	W
Neuroticism	1960	"Do you often feel 'fed-up'?"	421783	0.41	GNA
Neuroticism	2030	"Are you often troubled by feelings of guilt?"	419548	0.29	W
Neuroticism	1990	"Would you call yourself tense or 'highly strung'?"	417467	0.18	AA
Neuroticism	1950	"Are your feelings easily hurt?"	418255	0.55	GNA
Neuroticism	1940	"Are you an irritable person?"	411674	0.28	GNA
Neuroticism	2020	"Do you often feel lonely?"	423810	0.19	GNA

Neuroticism	1930	"Do you ever feel 'just miserable' for no reason?"	423410	0.43	LPA
Neuroticism	2010	"Do you suffer from 'nerves'?"	415041	0.21	GNA
Neuroticism	1970	"Would you call yourself a nervous person?"	419463	0.24	GNA
Neuroticism	1980	"Are you a worrier?"	419468	0.57	W

Supplemental Table 3. Full model output for four correlated factor model relating the four specific domains of internalizing: worry (W), anxious arousal (AA), low positive affect (LPA), and general negative affect (GNA). Indicators are the individual items of the GAD-7, PHQ-9, and EPQ-R questionnaires.
Model fit: $\chi^2(316) = 7416.549$, AIC = 7540.549, CFI = 0.8651993, SRMR = 0.1088944

	lhs	op	rhs	Unstand_Est	Unstand_SE	STD_Genotype	STD_Genotype_SE	STD_All	STD_All_SE	p_value
59	W	=~	gad_Control	0.2812062376	0.0100556281	0.954108731	0.03411788846	0.954109 1674	0.034117 88846	4.32E-172
60	W	=~	gad_Worry	0.2701910241	0.009796 083692	0.958876 3089	0.03476515 36	0.958876 321	0.034765 1536	1.85E-167
63	W	=~	neuro_Embarrassment	0.232130 296	0.007662 156657	0.731567 191	0.02414757 898	0.731566 9385	0.024147 57898	1.31E-201
64	W	=~	neuro_Guilt	0.2490359727	0.007358 364652	0.841780 9608	0.02487242 723	0.841781 0415	0.024872 42723	4.46E-251
65	W	=~	neuro_Worrier	0.2807061135	0.007162 433159	0.809645 9242	0.02065874 612	0.809646 1343	0.020658 74612	< 5e-300
2	AA	=~	gad_Relax	0.248345 111	0.009790 965477	0.867000 7658	0.03418148 312	0.867000 1625	0.034181 48312	6.18E-142
3	AA	=~	gad_Restlessness	0.2243490129	0.012404 22676	0.783636 716	0.04332727 645	0.783635 4762	0.043327 27645	4.07E-73
6	AA	=~	mdd_Sleep	-0.066010 30452	0.051465 70726	-0.24129 9796	0.18811798 2	-0.24129 97324	0.188117 982	0.1996296 049
7	AA	=~	neuro_High_strung	0.274651 1779	0.009632 363446	0.809817 9976	0.02840143 214	0.809818 0135	0.028401 43214	8.00E-179
17	GNA	=~	gad_Irritability	0.2358995191	0.009947 865188	0.824920 0953	0.03478681 902	0.824919 362	0.034786 81902	2.61E-124
15	GNA	=~	gad_Anxiety	0.244902 165	0.009427 695062	0.904734 6878	0.03482845 268	0.904734 8543	0.034828 45268	9.04E-149
16	GNA	=~	gad_Forebodin g	0.251815 4977	0.010782 32669	0.816202 6175	0.03494846 009	0.816201 964	0.034948 46009	1.24E-120
21	GNA	=~	mdd_Appetite	0.187353 5892	0.011367 70681	0.634990 1214	0.03852812 448	0.634991 0454	0.038528 12448	5.01E-61
22	GNA	=~	mdd_Concentration	0.203371 4606	0.011102 33276	0.756663 4038	0.04130730 335	0.756664 0521	0.041307 30335	5.96E-75
23	GNA	=~	mdd_Ideation	0.226876 9852	0.015597 19873	0.853723 7476	0.05869133 692	0.853722 7707	0.058691 33692	6.19E-48
24	GNA	=~	mdd_Motor	0.186843 5704	0.013754 10963	0.692321 1251	0.05096385 1	0.692321 3931	0.050963 851	4.94E-42
25	GNA	=~	mdd_Sleep	0.068093 33721	0.085540 36282	0.248905 0564	0.31266417 89	0.248904 9909	0.312664 1789	0.4260102 35
20	GNA	=~	mdd_Anhedonia	0.231012 3789	0.010477 52964	0.790188 2636	0.03583886 577	0.790186 3648	0.035838 86577	9.90E-108
26	GNA	=~	neuro_Fed_up	0.246596 3724	0.006642 710508	0.814310 5179	0.02193555 555	0.814310 4268	0.021935 55555	1.20E-301
27	GNA	=~	neuro_Hurt_feelings	0.219552 3739	0.007315 23872	0.728912 5069	0.02428654 726	0.728912 6302	0.024286 54726	6.64E-198
28	GNA	=~	neuro_Irritability	0.234637 2417	0.007490 578584	0.698921 545	0.02231241 526	0.698921 3724	0.022312 41526	2.18E-215
29	GNA	=~	neuro_Lonely	0.206772 1334	0.007308 781499	0.784046 492	0.02771371 253	0.784046 4671	0.027713 71253	4.47E-176
30	GNA	=~	neuro_Nerves	0.218571 1293	0.007541 704218	0.749669 6166	0.02586703 619	0.749669 7738	0.025867 03619	1.12E-184

31	GNA	=~	neuro_Nervous	0.2322342623	0.007671052277	0.6615316307	0.02185139467	0.6615315246	0.02185139467	2.51E-201
33	LPA	=~	mdd_Fatigue	0.2194782457	0.010038 3759	0.7388267298	0.03379206771	0.7388269931	0.03379206771	5.73E-106
34	LPA	=~	mdd_Mood	0.257597318	0.010163 74897	0.9314623734	0.03675177808	0.9314603486	0.03675177808	1.03E-141
35	LPA	=~	mdd_Sleep	0.1760274431	0.052466 94059	0.6434397394	0.19177797 58	0.6434395 7	0.19177797 58	0.0007936029613
36	LPA	=~	mdd_Worthless	0.255813847	0.010722 53255	0.9570032892	0.04011317 97	0.9570014344	0.04011317 97	8.45E-126
37	LPA	=~	neuro_Miserable	0.2752684 4	0.007758 668915	0.9112832469	0.02568531651	0.9112832681	0.02568531651	1.04E-275
58	W	~~	AA	0.9280805909	0.018142 21461	0.9280843333	0.01814229293	0.9280843333	0.01814229293	< 5e-300
61	W	~~	GNA	0.9316131722	0.008242 546525	0.9316136495	0.00824254 6418	0.9316136495	0.00824254 6418	< 5e-300
62	W	~~	LPA	0.8208825461	0.015593 24477	0.8208844416	0.01559326517	0.8208844416	0.01559326517	< 5e-300
4	AA	~~	GNA	0.982529344	0.015539 20041	0.9825331931	0.01553929707	0.9825331931	0.01553929707	< 5e-300
5	AA	~~	LPA	0.809999756	0.022014 717	0.8100049178	0.02201476891	0.8100049178	0.02201476891	2.34E-296
19	GNA	~~	LPA	0.9754556918	0.010627 12392	0.9754572173	0.01062715623	0.9754572173	0.01062715623	< 5e-300
9	gad_Control	~~	gad_Control	0.007789896536	0.004576 384876	0.08967561465	0.05268276979	0.08967569667	0.05268276979	0.08871893927
14	gad_Worry	~~	gad_Worry	0.006396070277	0.004254 950095	0.08055619907	0.05358928838	0.08055620109	0.05358928838	0.1327857027
47	neuro_Embarrassment	~~	neuro_Embarrassment	0.0467981660 5	0.002934 364068	0.4648101355	0.02914466462	0.4648098146	0.02914466462	2.93E-57
49	neuro_Guilt	~~	neuro_Guilt	0.0255048 3234	0.002698 960983	0.2914046224	0.03083688556	0.2914046782	0.03083688556	3.39E-21
57	neuro_Worrier	~~	neuro_Worrier	0.0414064 7623	0.002965 035952	0.3444729584	0.02466701728	0.3444731372	0.02466701728	2.55E-44
12	gad_Relax	~~	gad_Relax	0.0203730 5676	0.004531 695667	0.2483110637	0.05523209423	0.2483107182	0.05523209423	6.93E-06
13	gad_Restlessness	~~	gad_Restlessness	0.0316302 4364	0.007706 683481	0.3859166616	0.09402685112	0.3859154404	0.09402685112	4.06E-05
45	mdd_Sleep	~~	mdd_Sleep	0.0391366 4737	0.005068 887921	0.5229061283	0.06772597078	0.5229058529	0.06772597078	1.15E-14
50	neuro_High_strung	~~	neuro_High_strung	0.0395898 2711	0.004330 242242	0.3441947715	0.03764658569	0.3441947851	0.03764658569	6.09E-20
11	gad_Irritability	~~	gad_Irritability	0.0261281 2029	0.004735 716424	0.3195086142	0.05791024747	0.3195080462	0.05791024747	3.44E-08
8	gad_Anxiety	~~	gad_Anxiety	0.0132956 6154	0.004334 374334	0.1814547767	0.05915395558	0.1814548435	0.05915395558	0.00215862748

10	gad_Foreboding	~~	gad_Foreboding	0.031774 0261	0.005932 150638	0.333814 8883	0.06232228 491	0.333814 3539	0.062322 28491	8.50E-08
39	mdd_Appetite	~~	mdd_Appetite	0.051952 82565	0.006750 829597	0.596784 6355	0.07754740 153	0.596786 3723	0.077547 40153	1.41E-14
40	mdd_Concentration	~~	mdd_Concentration	0.030879 61167	0.006137 564569	0.427458 7799	0.08496135 062	0.427459 5123	0.084961 35062	4.87E-07
42	mdd_Ideation	~~	mdd_Ideation	0.019149 45047	0.014841 80778	0.271158 0513	0.21015594 89	0.271157 4307	0.210155 9489	0.1969683 618
44	mdd_Motor	~~	mdd_Motor	0.037924 70259	0.011811 03037	0.520690 6856	0.16216135 7	0.520691 0887	0.162161 357	0.0013229 40435
38	mdd_Anhedonia	~~	mdd_Anhedonia	0.032102 34268	0.005749 25043	0.375607 3142	0.06726699 59	0.375605 509	0.067266 9959	2.35E-08
48	neuro_Fed_up	~~	neuro_Fed_up	0.030895 27748	0.002301 081829	0.336898 6042	0.02509220 019	0.336898 5288	0.025092 20019	4.23E-41
51	neuro_Hurt_feelings	~~	neuro_Hurt_feelings	0.042521 41422	0.002679 169106	0.468686 2189	0.02953076 601	0.468686 3775	0.029530 76601	1.00E-56
52	neuro_Irritability	~~	neuro_Irritability	0.057648 87198	0.003276 07658	0.511509 1678	0.02906810 306	0.511508 9152	0.029068 10306	2.60E-69
53	neuro_Lonely	~~	neuro_Lonely	0.026795 82263	0.002701 848834	0.385271 1619	0.03884728 052	0.385271 1374	0.038847 28052	3.49E-23
55	neuro_Nerves	~~	neuro_Nerves	0.037231 8415	0.003166 0617	0.437995 0465	0.03724549 671	0.437995 2302	0.037245 49671	6.30E-32
56	neuro_Nervous	~~	neuro_Nervous	0.069307 14297	0.003726 145533	0.562376 2225	0.03023488 862	0.562376 042	0.030234 88862	3.20E-77
41	mdd_Fatigue	~~	mdd_Fatigue	0.040075 68584	0.004929 723868	0.454134 3505	0.05586320 045	0.454134 6742	0.055863 20045	4.31E-16
43	mdd_Mood	~~	mdd_Mood	0.010124 12928	0.004962 603787	0.132382 1946	0.06488719 626	0.132381 6191	0.064887 19626	0.0413419 4612
46	mdd_Worthless	~~	mdd_Worthless	0.006012 235365	0.005110 711851	0.084148 58083	0.07152556 7	0.084148 25464	0.071525 567	0.2394355 451
54	neuro_Miserable	~~	neuro_Miserable	0.015471 34934	0.003141 734952	0.169562 7975	0.03443215 935	0.169562 8053	0.034432 15935	8.46E-07
66	W	~~	W	1		1		1		NA
1	AA	~~	AA	1		1		1		NA
18	GNA	~~	GNA	1		1		1		NA
32	LPA	~~	LPA	1		1		1		NA

Supplemental Table 4. Diverse ancestry GWAS. Total N is reported, as well as case prevalence for case-control studies. INT = Internalizing; PAU = Problematic Alcohol Use; COMSUM = Alcohol Consumption (quantity and/or frequency).

Phenotype	Description	N	Case Prevalence	Factor	Source
Finnish- all ICD based					
AUD	Alcohol use disorder	429209	0.0417	PAU	FinnGen
F5_ALCOHOL_DEPENDENCE	alcohol dependence	429209	0.026	PAU	FinnGen
F5_ALLANXIOUS	Anxiety disorder, includes GAD, panic, OCD, phobic, other	429209	0.0671	INT	FinnGen
F5_ANXIETY	Other anxiety disorder	429209	0.0459	INT	FinnGen
F5_DEPRESSIO	unipolar depression	429209	0.1158	INT	FinnGen
F5_GAD	generalized anxiety disorder	429209	0.0128	INT	FinnGen
East Asian					
DPW	self-reported average drinks per week	90852	NA	CONSUM	Saunders et al. 2022 (GSCAN2)
DEP	Depression	98502	0.128	INT	Giannakopoulou et al. 2021 (PGC)

Supplemental Table 5. Full model output for base model relating internalizing (INT), externalizing (EXT), and three alcohol use factors- problematic use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). Model fit: $\chi^2(108) = 558.0237$, AIC = 648.0237, CFI = 0.963751, SRMR = 0.101803

	lhs	op	rhs	Unstand_Est	Unstand_SE	STD_Genotype	STD_Genotype_SE	STD_All	STD_All_SE	p_value
29	INT	=~	MDD	0.245166169	0.009203888	0.943784397	0.035431033	0.943784632	0.035431052	2.52E-156
26	INT	=~	GAD2	0.175232506	0.008978858	0.741250238	0.037981444	0.741250413	0.037981443	8.01E-85
28	INT	=~	LifetimeAnx	0.425078474	0.018413086	0.909531738	0.039398129	0.909531615	0.03939812	6.45E-118
16	EXT	=~	num_partners	0.212727167	0.011302981	0.674340778	0.035830203	0.674340724	0.03583018	5.13E-79
13	EXT	=~	ADHD	0.420924986	0.030769132	0.592739305	0.043328536	0.592739242	0.04332835	1.33E-42
14	EXT	=~	antisoc	0.162777852	0.021682119	0.726616696	0.096785904	0.726614639	0.09678591	6.03E-14
33	PAU	=~	AUD	0.175119135	0.012269282	0.732840561	0.051344498	0.951624471	0.06667559	3.23E-46
35	PAU	=~	AUDIT_4	0.099243868	0.010258447	0.586234664	0.060596853	0.761250538	0.07869059	3.88E-22
36	PAU	=~	AUDIT_5	0.080801455	0.009466238	0.581497339	0.068124834	0.755098684	0.08846649	1.39E-17
37	PAU	=~	AUDIT_7	0.111825516	0.010758052	0.593725946	0.057118674	0.770978124	0.07417385	2.62E-25
38	PAU	=~	AUDIT_8	0.104889993	0.010360469	0.537475502	0.053088855	0.697934737	0.0689407	4.32E-24
34	PAU	=~	AUDIT_10	0.104080842	0.009200907	0.638182071	0.056416182	0.828705993	0.07326161	1.14E-29
46	QUANT	=~	dpw	0.127470017	0.010905465	0.568563014	0.04864235	0.679802933	0.05818053	1.46E-31
44	QUANT	=~	AUDIT_2	0.163359167	0.008872828	0.713838036	0.038771926	0.853501649	0.04637454	1.07E-75
45	QUANT	=~	AUDIT_3	0.192034171	0.009564387	0.781730845	0.038934509	0.934676562	0.0465689	1.15E-89
18	FREQ	=~	dpw	0.087510682	0.011578018	0.390329089	0.051642207	0.398375631	0.05270742	4.08E-14
22	FREQ	=~	intake_freq	0.246196761	0.006794419	0.992105381	0.027379654	1.012557323	0.02794249	1.70E-287
17	FREQ	=~	AUDIT_1	0.243045443	0.008366241	0.902884494	0.031079576	0.921497229	0.03172046	1.51E-185
41	PAU	~	INT	0.292992302	0.064767979	0.292993856	0.064767936	0.225632888	0.04987597	6.08E-06
39	PAU	~	EXT	0.647778492	0.103282125	0.647775575	0.103281623	0.498848253	0.07953374	3.57E-10
49	QUANT	~	INT	-0.167826102	0.057359375	-0.167825588	0.057359226	-0.140363356	0.04795582	0.003434939
47	QUANT	~	EXT	0.718511447	0.085159333	0.718509792	0.085159003	0.600936047	0.07119886	3.25E-17
21	FREQ	~	INT	-0.182499572	0.033767166	-0.182499286	0.033767169	-0.178813094	0.03308487	6.49E-08
19	FREQ	~	EXT	0.213001037	0.040119312	0.213000963	0.040119287	0.208698685	0.03930871	1.10E-07

43	PAU	~~	QUANT	0.81025608	0.052039586	0.810255943	0.052039493	0.810255943	0.033504194	1.16E-54
40	PAU	~~	FREQ	0.724114047	0.058195874	0.724114098	0.058195801	0.724114098	0.043909132	1.53E-35
48	QUANT	~~	FREQ	0.742056046	0.035573819	0.74205588	0.035573764	0.74205588	0.029140961	1.25E-96
25	INT	~~	EXT	0.476183008	0.030153033	0.476182979	0.030153015	0.476182979	0.030153009	3.52E-56
31	MDD	~~	MDD	0.007373528	0.004645537	0.109270513	0.068843143	0.109270568	0.068843216	0.112460905
23	GAD2	~~	GAD2	0.025179128	0.00442921	0.450547612	0.079255007	0.450547825	0.079255017	1.31E-08
30	LifetimeAnx	~~	LifetimeAnx	0.037732955	0.020557395	0.172752288	0.094116532	0.172752242	0.094116506	0.066432711
32	num_partners	~~	num_partners	0.054262029	0.005472722	0.545264677	0.054994074	0.545264588	0.054994088	3.58E-23
1	ADHD	~~	ADHD	0.327114183	0.033984882	0.648660329	0.067391224	0.648660191	0.067391208	6.25E-22
2	antisoc	~~	antisoc	0.023688742	0.027921986	0.47203384	0.556374231	0.472031167	0.556374263	0.396220656
3	AUD	~~	AUD	0.005390969	0.003299983	0.09441087	0.057791349	0.094410866	0.057791342	0.102335441
8	AUDIT_4	~~	AUDIT_4	0.012051139	0.004547564	0.420497609	0.158677103	0.420497619	0.158677096	0.008048686
9	AUDIT_5	~~	AUDIT_5	0.008299205	0.004859351	0.429826238	0.25167171	0.429825978	0.25167171	0.087657962
10	AUDIT_7	~~	AUDIT_7	0.014387941	0.004337489	0.405592892	0.122272227	0.405592733	0.122272227	0.000909529
11	AUDIT_8	~~	AUDIT_8	0.019533287	0.004643413	0.512887038	0.121922964	0.512887103	0.121922959	2.59E-05
4	AUDIT_10	~~	AUDIT_10	0.008331757	0.002498686	0.313246712	0.093941745	0.313246377	0.093941747	0.000854667
12	dpw	~~	dpw	0.000178381	0.002715991	0.003547546	0.054034147	0.003547546	0.054034133	0.947634133
6	AUDIT_2	~~	AUDIT_2	0.014220555	0.002604223	0.27153463	0.049726733	0.271534935	0.049726739	4.75E-08
7	AUDIT_3	~~	AUDIT_3	0.007626441	0.002631865	0.126379918	0.043613416	0.126379725	0.043613415	0.003758851
24	intake_freq	~~	intake_freq	-0.001556378	0.002286629	-0.025272337	0.037131855	-0.025272333	0.037131936	0.496097542
5	AUDIT_1	~~	AUDIT_1	0.010930376	0.003123254	0.150842868	0.043101936	0.150842858	0.043101931	0.000465825
27	INT	~~	INT	1		1		1		NA
15	EXT	~~	EXT	1		1		1		NA
42	PAU	~~	PAU	1		1		0.593045173		NA
50	QUANT	~~	QUANT	1		1		0.699505493		NA
20	FREQ	~~	FREQ	1		1		0.960011184		NA

Supplemental Table 6. Full model output for exploratory model relating internalizing (INT) with three alcohol use factors- problematic use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). Model does not include an externalizing factor.
Model fit: $\chi^2(70) = 313.1723$, AIC = 383.1723, CFI = 0.9788987, SRMR = 0.0871512

	lhs	op	rhs	Unstand_Est	Unstand_SE	STD_Genotype	STD_Genotype_SE	STD_All	p_value
18	INT	=~	MDD	0.2423220106	0.01079764891	0.9361585455	0.04170966438	0.9361585391	1.53E-111
16	INT	=~	GAD2	0.1741721308	0.01022561164	0.7367635725	0.04325212561	0.7367635733	4.68E-65
17	INT	=~	Lifetime Anx	0.4350301859	0.02162858795	0.9317359499	0.04631902471	0.9317359368	5.60E-90
22	PAU	=~	AUD	0.1970832786	0.01005845189	0.8269967689	0.04220475752	0.934455834	1.75E-85
24	PAU	=~	AUDIT_4	0.113699407	0.01054968904	0.6730299154	0.06244832489	0.7604830171	4.40E-27
25	PAU	=~	AUDIT_5	0.092961223	0.01007269865	0.6724622094	0.07286352046	0.7598412139	2.73E-20
26	PAU	=~	AUDIT_7	0.1344296601	0.01065139458	0.7246401047	0.05741452823	0.8187991147	1.62E-36
27	PAU	=~	AUDIT_8	0.1199058257	0.01043812969	0.6166910427	0.05368343131	0.6968232071	1.53E-30
23	PAU	=~	AUDIT_10	0.1234559701	0.00879909 8116	0.7774989998	0.05541447737	0.8785264079	1.01E-44
34	QUANT	=~	dpw	0.1361626504	0.01380964867	0.6119483439	0.06141060314	0.6191290644	6.21E-23
32	QUANT	=~	AUDIT_2	0.1957663635	0.00886668 3201	0.8598755572	0.03894465607	0.8699654596	5.05E-108
33	QUANT	=~	AUDIT_3	0.2339488329	0.00910894 5692	0.9597176389	0.037359938	0.9709791015	1.79E-145
11	FREQ	=~	dpw	0.1043128586	0.01340576097	0.4640726269	0.0595181389	0.4654346477	7.18E-15
12	FREQ	=~	intake_freq	0.2464810748	0.00667065 9347	0.9976965816	0.02686420809	0.9976965816	7.27E-299
10	FREQ	=~	AUDIT_1	0.2473636225	0.00851294 7084	0.9197148055	0.03160424649	0.9224138791	1.24E-185
39	intake freq	~~	intake_freq	0.0009999826538	0.00224065 4694	0.00100051 6547	0.03668289946	0.00100051 6547	0.6553874982
28	PAU	~	INT	0.5260930491	0.05086685 82	0.526081878	0.05086460902	0.4655843176	4.52E-25
35	QUANT	~	INT	0.1540350446	0.02682226 6	0.1536426103	0.02674254475	0.1518606501	9.31E-09
13	FREQ	~	INT	-0.07685852494	0.02120932213	-0.07667103488	0.0211345465	-0.07644667025	0.0002902964116
31	PAU	~~	QUANT	0.8464974795	0.03871617713	0.8468069728	0.03868678827	0.8468069728	5.70E-106
29	PAU	~~	FREQ	0.7222639988	0.04654059127	0.7198831266	0.04639483071	0.7198831266	2.58E-54
36	QUANT	~~	FREQ	0.702059737	0.02907619582	0.6992899562	0.0289731785	0.6992899562	8.32E-129
21	MDD	~~	MDD	0.00828471309	0.005411175056	0.1236071913	0.08075077068	0.1236071896	0.1257600719

15	GAD2	~~	GAD2	0.0255471756	0.004800189941	0.457179436	0.08589140385	0.457179437	1.03E-07
20	LifetimeAnx	~~	Lifetime Anx	0.02874422335	0.022745192 37	0.1318681479	0.1043307738	0.1318681441	0.2063199858
9	AUD	~~	AUD	0.007205532554	0.003139308595	0.1267923126	0.05527323539	0.1267922943	0.02171817179
5	AUDIT_4	~~	AUDIT_4	0.01203120027	0.004489775595	0.4216652836	0.1573344646	0.4216655807	0.007369068775
6	AUDIT_5	~~	AUDIT_5	0.00807554737	0.004858759947	0.4226413987	0.2542624734	0.4226413296	0.09650087625
7	AUDIT_7	~~	AUDIT_7	0.0113406764	0.004351192925	0.3295680099	0.12644088	0.3295680098	0.009151629 19
8	AUDIT_8	~~	AUDIT_8	0.01944770093	0.004582890876	0.5144374958	0.1212254806	0.5144374181	2.20E-05
1	AUDIT_10	~~	AUDIT_10	0.005752421636	0.002417017996	0.2281913684	0.09586770033	0.2281913507	0.017314216 34
38	dpw	~~	dpw	0.000412969265	0.002938339975	0.009559935674	0.05884234112	0.00955993593	0.888229327
3	AUDIT_2	~~	AUDIT_2	0.01262305315	0.002572089602	0.2431601174	0.04963299873	0.2431600992	9.21E-07
4	AUDIT_3	~~	AUDIT_3	0.0034207052	0.002694513335	0.05719958879	0.04534010538	0.0571995844	0.204260075 9
2	AUDIT_1	~~	AUDIT_1	0.01087845779	0.003046594463	0.1491527045	0.04202485655	0.1491526356	0.000356036 0976
19	INT	~~	INT	1		1		1	NA
30	PAU	~~	PAU	1		1		0.7832312432	NA
37	QUANT	~~	QUANT	1		1		0.976938343	NA
14	FREQ	~~	FREQ	1		1		0.9941559066	NA

Supplemental Table 7. Full model output for exploratory model including two separate internalizing factors, anxiety (ANX) and depression (DEP), related to three alcohol use factors- problematic use (PAU) , consumption quantity (QUANT), and consumption frequency (FREQ). Model does not include an externalizing factor.
Model fit: $\chi^2(67) = 305.4727$, AIC = 381.4727, CFI = 0.9789053, SRMR = 0.08710279

	lhs	op	rhs	Unstand_Est	Unstand_SE	STD_Genotype	STD_Genotype_SE	STD_All	p_value
1	ANX	=~	GAD2	0.1747230324	0.009734916333	0.7390978156	0.04117776944	0.7390978258	4.97E-72
2	ANX	=~	Lifetime Anx	0.4363892131	0.02341015291	0.9346528317	0.0501368088 2	0.9346528381	1.49E-77
14	DEP	=~	MDD	0.2588527357	0.004867218252	0.9999995089	0.0188030681	0.9999995089	< 5e-300
25	PAU	=~	AUD	0.1979843468	0.010029619 78	0.8307721683	0.0420847591	0.9348354082	9.78E-87
27	PAU	=~	AUDIT_4	0.1141507704	0.010604715 57	0.675705432	0.0627744823 2	0.760344958	5.08E-27
28	PAU	=~	AUDIT_5	0.0931506919 7	0.010075277 9	0.6738342552	0.0728823832 7	0.758239373	2.34E-20
29	PAU	=~	AUDIT_7	0.1347021956	0.010693401 39	0.7261108042	0.0576420053 1	0.8170640829	2.20E-36
30	PAU	=~	AUDIT_8	0.1205099193	0.010445818 93	0.6197964524	0.0537235068 2	0.6974326844	8.62E-31
26	PAU	=~	AUDIT_10	0.1239468909	0.008861943 7	0.7805836839	0.0558106322 5	0.8783602878	1.89E-44
38	QUANT	=~	dpw	0.1351600043	0.013708570 73	0.607542051	0.0609316156 2	0.6172566553	6.23E-23
36	QUANT	=~	AUDIT_2	0.1954632973	0.009164757 921	0.8585806719	0.0402362992 9	0.8723093239	6.28E-101
37	QUANT	=~	AUDIT_3	0.2329345123	0.009259432 154	0.9556052862	0.0379584015	0.9708853639	1.20E-139
17	FREQ	=~	dpw	0.104262214	0.013409267 75	0.4638109992	0.0595131706 7	0.4681398738	7.52E-15
18	FREQ	=~	intake_freq	0.2448901706	0.007465532 936	0.9913204975	0.0300584226 9	0.9913204975	5.38E-236
16	FREQ	=~	AUDIT_1	0.2455320943	0.009016368 456	0.9129773213	0.0334534111	0.9214981473	2.73E-163
44	intake freq	~~	intake_freq	0.000999991 5106	0.002245308 348	0.001000443 435	0.0367508815 7	0.001000443 435	0.656052861 1
31	PAU	~	ANX	0.3959222959	0.488365319 8	0.3959918606	0.4884865675	0.3519111589	0.417532643 9
32	PAU	~	DEP	0.1265626699	0.477992985 7	0.1264863518	0.4781120593	0.1124062464	0.791179449 1
39	QUANT	~	ANX	0.3312470228	0.362445368 8	0.3295158802	0.3612606735	0.3243298583	0.360757504 4
40	QUANT	~	DEP	-0.174190678 2	0.356394970 5	-0.17288236 24	0.355248967	-0.17016148 68	0.625013462 8
19	FREQ	~	ANX	-0.345173842 2	0.331763539 4	-0.34412658 69	0.3308858351	-0.34094447 61	0.298144225 2
20	FREQ	~	DEP	0.2643975205	0.328102874	0.2635517584	0.3272389267	0.2611147165	0.420336691 7
35	PAU	~~	QUANT	0.8428504061	0.038757844 66	0.8431555709	0.0387161342 5	0.8431555709	7.44E-105

33	PAU	~~	FREQ	0.7303790055	0.05597885683	0.7279270743	0.05578552165	0.7279270743	6.57E-39
41	QUANT	~~	FREQ	0.7199417606	0.04124067081	0.7169619509	0.04097932256	0.7169619509	3.04E-68
4	ANX	~~	DEP	0.9323899219	0.04769854139	0.9324040494	0.0476995533	0.9324040494	4.33E-85
22	GAD2	~~	GAD2	0.02535496956	0.00445848511	0.4537343914	0.07977956066	0.4537344039	1.29E-08
23	LifetimeAnx	~~	Lifetime Anx	0.02755994154	0.02479382014	0.1264240704	0.1137314228	0.1264240722	0.266325248
13	AUD	~~	AUD	0.00716492003	0.003228865064	0.1260827632	0.05684970121	0.1260827595	0.02648528228
9	AUDIT_4	~~	AUDIT_4	0.01203748043	0.00450720183	0.4218754686	0.1579449866	0.4218755448	0.007568843591
10	AUDIT_5	~~	AUDIT_5	0.008122145062	0.004861691902	0.425073002	0.2544152144	0.4250730532	0.09479247727
11	AUDIT_7	~~	AUDIT_7	0.01143861835	0.004243126282	0.3324062843	0.1233002734	0.3324062844	0.00702198878
12	AUDIT_8	~~	AUDIT_8	0.01941562206	0.004604946723	0.5135876765	0.1218093314	0.5135876508	2.48E-05
5	AUDIT_10	~~	AUDIT_10	0.005759566282	0.002460435113	0.2284832025	0.09758956901	0.2284832048	0.01923870689
43	dpw	~~	dpw	0.0003567047156	0.002841082388	0.008468838759	0.05689238704	0.008468839595	0.9000862431
7	AUDIT_2	~~	AUDIT_2	0.01241044491	0.002526162733	0.2390764543	0.04874605313	0.2390764435	8.98E-07
8	AUDIT_3	~~	AUDIT_3	0.003431179185	0.002733613663	0.05738161177	0.04600115035	0.05738161014	0.2094131603
6	AUDIT_1	~~	AUDIT_1	0.01100535236	0.003105858294	0.1508412284	0.04284253623	0.1508411646	0.0003949769994
24	MDD	~~	MDD	0		0		0	NA
3	ANX	~~	ANX	1		1		1	NA
15	DEP	~~	DEP	1		1		1	NA
34	PAU	~~	PAU	1		1		0.7897571348	NA
42	QUANT	~~	QUANT	1		1		0.9687710816	NA
21	FREQ	~~	FREQ	1		1		0.9815916666	NA

Supplemental Table 8. Full model output for model that includes a "worry" factor (W) as mediating the relationships between internalizing (INT), externalizing (EXT), and three alcohol use factors: problematic use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). Total effects (TOT) and indirect effects (ID) were calculated using the path coefficients (a = psychiatric factor to mediator; b = mediator to alcohol factor; c = direct path from psychiatric factor to alcohol factor).
Model fit: $\chi^2(193) = 1812.984$, AIC = 1932.984, CFI = 0.931771, SRMR = 0.1023

	lhs	op	rhs	Unstand Est	Unstan d SE	STD_Gen otype	STD_Genoty pe SE	STD All	STD_All SE	p value
38	INT	=~	MDD	0.225452504	0.006789358	0.865216025	0.026055432	0.865215674	0.026055 43	8.60E-242
35	INT	=~	GAD2	0.201352066	0.008288257	0.845212155	0.034791473	0.845212798	0.034791 482	2.29E-130
37	INT	=~	LifetimeAnx	0.407618242	0.016298634	0.870207223	0.034795292	0.870207068	0.034795 296	4.84E-138
16	EXT	=~	num_partners	0.210305344	0.011260268	0.667150147	0.035720851	0.667150179	0.035720 826	7.65E-78
13	EXT	=~	ADHD	0.4252586	0.031137348	0.598848736	0.043847556	0.598848942	0.043847 585	1.82E-42
14	EXT	=~	antisoc	0.164821581	0.021915397	0.713056425	0.094811202	0.713056762	0.094811 249	5.44E-14
45	PAU	=~	AUD	0.159167657	0.013913123	0.66498422	0.058127596	0.903898583	0.079028 569	2.64E-30
47	PAU	=~	AUDIT_4	0.100108214	0.010998373	0.588561529	0.064662333	0.800020924	0.087912 934	8.86E-20
48	PAU	=~	AUDIT_5	0.080124779	0.009881354	0.562938327	0.069424271	0.765190252	0.094387 182	5.12E-16
49	PAU	=~	AUDIT_7	0.116832343	0.011909245	0.611135246	0.062295861	0.830703 92	0.084695 554	1.02E-22
50	PAU	=~	AUDIT_8	0.101582316	0.011130334	0.521514676	0.05714224	0.708883583	0.077688 812	7.07E-20
46	PAU	=~	AUDIT_10	0.096627551	0.009876118	0.584487589	0.059739487	0.794482615	0.081220 049	1.32E-22
59	QUANT	=~	dpw	0.124285027	0.011131557	0.554383396	0.049653072	0.671736672	0.060168 981	6.04E-29
57	QUANT	=~	AUDIT_2	0.161102712	0.009789595	0.7037004	0.042761153	0.852662015	0.051817 528	7.53E-61
58	QUANT	=~	AUDIT_3	0.189648 69	0.010814869	0.770687743	0.043949062	0.933828777	0.053257 039	7.62E-69
18	FREQ	=~	dpw	0.086890652	0.011354532	0.387581077	0.05064761	0.408236763	0.053357 664	1.97E-14
22	FREQ	=~	intake_freq	0.238204582	0.007995411	0.95736326	0.032134288	1.008384573	0.033853 744	4.86E-195
17	FREQ	=~	AUDIT_1	0.235267883	0.009181938	0.872568142	0.034054258	0.919069618	0.035876 431	8.48E-145
72	W	=~	gad_Control	0.152409075	0.014627988	0.522532216	0.050152115	0.938020732	0.090075 77	2.03E-25
73	W	=~	gad_Worry	0.146999312	0.014085541	0.520683763	0.049892431	0.934701966	0.089609 316	1.69E-25
75	W	=~	neuro_Embarrassment	0.128234 71	0.012389257	0.403066381	0.038942037	0.723561941	0.069941 858	4.16E-25
76	W	=~	neuro_Guilt	0.141530 94	0.013630744	0.478329346	0.046067822	0.858669656	0.082740 184	2.96E-25

77	W	=~	neuro_Worrier	0.159065401	0.01457643	0.457349646	0.041910842	0.821008243	0.075273906	1.00E-27
53	PAU	~	INT	-0.139266174	0.26989 2487	-0.139270744	0.269894676	-0.10245 9262	0.198514468	0.60585 0137
51	PAU	~	EXT	0.872710626	0.21144 8182	0.872714017	0.211449695	0.642041764	0.155526912	3.67E-05
56	PAU	~	W	0.274507264	0.12387 6259	0.274508812	0.123876916	0.362532385	0.163646982	0.02669 2899
62	QUANT	~	INT	-0.432666947	0.23722 8828	-0.43267135	0.23723039	-0.35708 3061	0.195769147	0.06817 657
60	QUANT	~	EXT	0.848131615	0.16853 342	0.848132141	0.168534176	0.699962272	0.139079323	4.84E-07
64	QUANT	~	W	0.148895698	0.09789 0046	0.14889787	0.097890366	0.220596585	0.145088652	0.12824 7179
21	FREQ	~	INT	-0.626486802	0.18348 9964	-0.62649037	0.183491701	-0.59479 1574	0.174172076	0.00063 9499
19	FREQ	~	EXT	0.413909091	0.11000 0579	0.413911826	0.110001548	0.392968956	0.104414584	0.00016 8028
23	FREQ	~	W	0.246459626	0.06894 2912	0.246460704	0.068943321	0.420046414	0.117536 81	0.00035 0447
74	W	~	INT	1.708850765	0.23454 0141	1.708856063	0.234541874	0.951932805	0.130586947	3.19E-13
71	W	~	EXT	-0.744695982	0.15886 1043	-0.744699322	0.158862046	-0.41484 1092	0.088450418	2.76E-06
55	PAU	~~	QUANT	0.816986793	0.05679 3718	0.816986293	0.056793718	0.816986293	0.034472568	6.41E-47
52	PAU	~~	FREQ	0.725638084	0.06580 1208	0.725636629	0.065801193	0.725636629	0.045940535	2.81E-28
61	QUANT	~~	FREQ	0.735162623	0.03716 0364	0.735159696	0.037160302	0.735159696	0.029108292	4.13E-87
34	INT	~~	EXT	0.492000983	0.03094 9626	0.492001196	0.030949629	0.492001196	0.030949633	6.67E-57
40	MDD	~~	MDD	0.017069 79	0.00352 8171	0.251402041	0.051962344	0.251401837	0.051962344	1.31E-06
24	GAD2	~~	GAD2	0.016209339	0.00458 9671	0.285614892	0.080872477	0.285615326	0.080872 51	0.00041 2898
39	LifetimeAnx	~~	LifetimeAnx	0.053259619	0.01928 7446	0.242739745	0.087904928	0.242739659	0.087904948	0.00575 6086
44	num_partners	~~	num_partners	0.055141355	0.00542 089	0.554910586	0.054552779	0.554910639	0.054552695	2.64E-24
1	ADHD	~~	ADHD	0.323435345	0.03446 1216	0.641379504	0.068337404	0.641379945	0.068337423	6.26E-21
2	antisoc	~~	antisoc	0.026263058	0.02797 5247	0.491549591	0.523594225	0.491550055	0.523594336	0.34783 5358
3	AUD	~~	AUD	0.010482319	0.00315 7013	0.182967 61	0.055104853	0.182967352	0.055104875	0.00089 9117
8	AUDIT_4	~~	AUDIT_4	0.010414001	0.00447 8348	0.359965191	0.154797179	0.359966521	0.154797207	0.02004 999
9	AUDIT_5	~~	AUDIT_5	0.008396845	0.00484 2021	0.414484 06	0.23901009	0.414483878	0.239010093	0.08288 9481
10	AUDIT_7	~~	AUDIT_7	0.011327035	0.00424 3085	0.309930632	0.116099472	0.309930998	0.116099495	0.00759 5787
11	AUDIT_8	~~	AUDIT_8	0.018874581	0.00462 835	0.497484725	0.121989728	0.497484066	0.121989774	4.54E-05

4	AUDIT_10	~~	AUDIT_10	0.010079579	0.00253 6457	0.3687966 39	0.092806175	0.368797 374	0.092806 175	7.07E-0 5
12	dpw	~~	dpw	0.000120 166	0.00272 6804	0.0023902 96	0.05425435	0.002390 295	0.054254 329	0.96484 9849
6	AUDIT_2	~~	AUDIT_2	0.014306 882	0.00260 103	0.2729672	0.04962655	0.272967 488	0.049626 527	3.79E-0 8
7	AUDIT_3	~~	AUDIT_3	0.007748 908	0.00263 3516	0.1279638 68	0.043490242	0.127963 816	0.043490 214	0.00325 6585
33	intake_freq	~~	intake_freq	-0.00104 2485	0.00228 7656	-0.016839 459	0.03695253	-0.01683 9446	0.036952 529	0.64860 5755
5	AUDIT_1	~~	AUDIT_1	0.011291 027	0.00314 1361	0.1553114 19	0.043210631	0.155311 036	0.043210 608	0.00032 5252
25	gad_Contro l	~~	gad_Control	0.010218 774	0.00562 9153	0.1201170 09	0.066168217	0.120117 106	0.066168 215	0.06947 3126
26	gad_Worry	~~	gad_Worry	0.010069 3	0.00543 3359	0.1263322 74	0.068169087	0.126332 234	0.068169 079	0.06384 8435
41	neuro_Emb arrassment	~~	neuro_Embarr assment	0.048225 96	0.00279 5303	0.4764582 32	0.027616771	0.476458 118	0.027616 77	1.07E-6 6
42	neuro_Guilt	~~	neuro_Guilt	0.022997 484	0.00266 1663	0.2626865 42	0.030402335	0.262686 421	0.030402 349	5.61E-1 8
43	neuro_Worr ier	~~	neuro_Worrier	0.039427 482	0.00313 4344	0.3259454 96	0.02591156	0.325945 466	0.025911 54	2.75E-3 6
31	ID_INT_PA U	:=	a1*b1	0.469091 947	0.19460 5439	0.4690960 48	0.194607548	0.345106 471	0.143138 782	0.01593 1673
69	TOT_INT_ PAU	:=	c1+(a1*b1)	0.329825 773	0.04622 6357	0.3298253 04	0.046226376	0.242647 208	0.034000 769	9.68E-1 3
32	ID_INT_Q UANT	:=	a1*b2	0.254440 528	0.17925 9716	0.2544450 28	0.179261372	0.209993 126	0.147931 362	0.15578 3592
70	TOT_INT_ QUANT	:=	c2+(a1*b2)	-0.17822 6419	0.06419 6046	-0.178226 322	0.06419596	-0.14708 9935	0.052976 447	0.00549 8425
30	ID_INT_FR EQ	:=	a1*b3	0.421162 72	0.15037 5021	0.4211658 68	0.150376659	0.399855 962	0.142738 907	0.00509 8413
68	TOT_INT_ FREQ	:=	c3+(a1*b3)	-0.20532 4082	0.03497 5193	-0.205324 502	0.034975278	-0.19493 5612	0.033198 963	4.34E-0 9
28	ID_EXT_P AU	:=	a2*b1	-0.20442 4456	0.09873 6791	-0.204426 526	0.098737958	-0.15039 3331	0.072624 263	0.03841 5086
66	TOT_EXT_ PAU	:=	c1+(a2*b1)	-0.34369 063	0.32489 0361	-0.343697 271	0.324893589	-0.25285 2593	0.238967 534	0.29011 6307
29	ID_EXT_Q UANT	:=	a2*b2	-0.11088 2028	0.08585 5739	-0.110884 143	0.085856712	-0.09151 2528	0.070851 279	0.19653 3011
67	TOT_EXT_ QUANT	:=	c2+(a2*b2)	-0.54354 8975	0.32143 4261	-0.543555 493	0.321436777	-0.44859 5589	0.265258 538	0.09083 464
27	ID_EXT_F REQ	:=	a2*b3	-0.18353 7493	0.07755 2854	-0.183539 119	0.077553755	-0.17425 2513	0.073614 743	0.01795 1756
65	TOT_EXT_ FREQ	:=	c3+(a2*b3)	-0.81002 4295	0.25419 4618	-0.810029 489	0.254197223	-0.76904 4087	0.241286 445	0.00143 9406
36	INT	~~	INT	1		1		1		NA
15	EXT	~~	EXT	1		1		1		NA
54	PAU	~~	PAU	1		1		0.541230 99		NA
63	QUANT	~~	QUANT	1		1		0.681117 785		NA

20	FREQ	~~	FREQ	1		1		0.90136526		NA
78	W	~~	W	1		1		0.310314179		NA

Supplemental Table 9. Full model output for model that includes a "general negative affect" factor (GNA) as mediating the relationships between internalizing (INT), externalizing (EXT), and three alcohol use factors: problematic use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). Total effects (TOT) and indirect effects (ID) were calculated using the path coefficients (a = psychiatric factor to mediator; b = mediator to alcohol factor; c = direct path from psychiatric factor to alcohol factor).
Model fit: $\chi^2(448) = 6542.752$, AIC = 6702.752, CFI = 0.84497, SRMR = 0.101504

	lhs	op	rhs	Unstand_Est	Unstand_SE	STD_Genotype	STD_Genotype_SE	STD_All	STD_All_SE	p_value
57	INT	=~	MDD	0.229359977	0.00672163	0.875866755	0.025668205	0.875866947	0.025668208	3.40E-255
54	INT	=~	GAD2	0.205323072	0.008663415	0.850600982	0.035890353	0.850600842	0.035890357	3.60E-124
56	INT	=~	LifetimeAnx	0.390134083	0.016241707	0.832160372	0.034643753	0.832160267	0.034643758	1.70E-127
16	EXT	=~	num_partners	0.190752775	0.010570854	0.604809262	0.033516419	0.604809319	0.033516499	8.61E-73
13	EXT	=~	ADHD	0.467437237	0.033339183	0.658163395	0.046942425	0.658163205	0.046942477	1.17E-44
14	EXT	=~	antisoc	0.172746769	0.023628809	0.725901827	0.099290922	0.725901886	0.099291085	2.65E-13
73	PAU	=~	AUD	0.15864843	0.012332154	0.661023773	0.051383646	0.873366768	0.067939759	7.12E-38
75	PAU	=~	AUDIT_4	0.104260257	0.010910783	0.594107796	0.062173412	0.784955144	0.082206415	1.23E-21
76	PAU	=~	AUDIT_5	0.083824426	0.009820148	0.587603222	0.068848215	0.776361301	0.09103205	1.40E-17
77	PAU	=~	AUDIT_7	0.123977932	0.011745052	0.627115771	0.059410252	0.828566185	0.07855282	4.78E-26
78	PAU	=~	AUDIT_8	0.108085355	0.011047301	0.542087318	0.055406542	0.716224136	0.073259127	1.32E-22
74	PAU	=~	AUDIT_10	0.097445635	0.00942947	0.586549498	0.056758732	0.774969258	0.075046992	4.94E-25
87	QUANT	=~	dpw	0.129918326	0.013443928	0.574538825	0.059453679	0.700286547	0.072471807	4.30E-22
85	QUANT	=~	AUDIT_2	0.159090852	0.009435797	0.693389512	0.04112636	0.845149752	0.050130935	8.81E-64
86	QUANT	=~	AUDIT_3	0.185947927	0.010318709	0.751443081	0.041700528	0.915908836	0.050830632	1.35E-72
18	FREQ	=~	dpw	0.078699603	0.014457983	0.348036013	0.063937686	0.355944375	0.065392624	5.23E-08
23	FREQ	=~	intake_freq	0.241765839	0.006777542	0.970093004	0.027195057	0.992136313	0.027813855	1.09E-278
17	FREQ	=~	AUDIT_1	0.248982194	0.008260533	0.920100484	0.030526352	0.941007661	0.031220936	1.40E-199
31	GNA	=~	gad_Irritability	0.104876372	0.014773775	0.367502082	0.051771797	0.819054635	0.115475565	1.26E-12

29	GNA	=~	gad_Anxiety	0.107099333	0.015040006	0.397336033	0.055800617	0.885547067	0.124461731	1.07E-12
30	GNA	=~	gad_Foreboding	0.115809583	0.016213451	0.373817094	0.052337128	0.833128745	0.116736449	9.14E-13
35	GNA	=~	mdd_Appetite	0.097537244	0.013904189	0.328410407	0.046817807	0.731929865	0.104425854	2.30E-12
36	GNA	=~	mdd_Concentration	0.100236879	0.014219602	0.372204695	0.052803285	0.829535141	0.117776336	1.80E-12
37	GNA	=~	mdd_Ideation	0.108686128	0.016119784	0.396932103	0.058873407	0.884645323	0.131315656	1.56E-11
38	GNA	=~	mdd_Motor	0.094178934	0.013977629	0.34642556	0.051417084	0.772081986	0.114684426	1.61E-11
39	GNA	=~	mdd_Sleep	0.079952797	0.011565824	0.291416056	0.042157529	0.649481226	0.094031214	4.75E-12
34	GNA	=~	mdd_Anhedonia	0.112586277	0.015865943	0.385873363	0.054380714	0.859998973	0.121294673	1.28E-12
40	GNA	=~	neuro_Fed_up	0.112469827	0.015328677	0.37107119	0.050576258	0.827009104	0.112808789	2.18E-13
41	GNA	=~	neuro_Hurt_feelings	0.091405797	0.012555516	0.303287898	0.041661628	0.675941063	0.092925083	3.33E-13
42	GNA	=~	neuro_Irritability	0.106652976	0.014626014	0.317072516	0.043484276	0.706662518	0.096990395	3.05E-13
43	GNA	=~	neuro_Lonely	0.098936487	0.013797417	0.376010757	0.052439896	0.838018895	0.116965641	7.46E-13
44	GNA	=~	neuro_Nerves	0.088521712	0.012155279	0.303424172	0.041666354	0.676244283	0.092935601	3.28E-13
45	GNA	=~	neuro_Nervous	0.089092068	0.012088648	0.253452245	0.034391817	0.564871454	0.076709946	1.71E-13
82	PAU	~	INT	0.156775791	0.324927921	0.156759766	0.324944429	0.118646504	0.245751624	0.62945502
79	PAU	~	EXT	0.705642835	0.156552602	0.705654156	0.156559656	0.534087289	0.118403224	6.56E-06
81	PAU	~	GNA	0.059916045	0.125801998	0.059920736	0.125805666	0.101076653	0.212223627	0.63388 0178
91	QUANT	~	INT	-0.43303756	0.301272966	-0.433075933	0.301296916	-0.35531018	0.247161158	0.15061587
88	QUANT	~	EXT	0.833216 67	0.151196803	0.833238576	0.151207665	0.683617181	0.124038841	3.57E-08
90	QUANT	~	GNA	0.089134733	0.107206847	0.089145932	0.107211944	0.163004093	0.196172884	0.40573 2104
22	FREQ	~	INT	-0.10270 4182	0.15601 035	-0.102710 861	0.156017619	-0.10042 8835	0.152543 702	0.51033 48
19	FREQ	~	EXT	0.193790319	0.063871219	0.193791759	0.063873863	0.189486101	0.062451325	0.00241 2713
21	FREQ	~	GNA	-0.04770 9781	0.06282 8476	-0.047705 922	0.062829972	-0.10396 0349	0.137023 1	0.44763 3905
33	GNA	~	INT	2.222060191	0.388656909	2.222117038	0.388682951	0.997042222	0.174253419	1.08E-08
28	GNA	~	EXT	-0.54209 4669	0.18172 5517	-0.542123 287	0.18173665	-0.24324 5426	0.081475 415	0.00285 3998
84	PAU	~~	QUANT	0.831398361	0.057721624	0.831398956	0.05772254	0.831398956	0.035813 34	4.91E-47
80	PAU	~~	FREQ	0.756580736	0.06192 212	0.756582 92	0.061922644	0.756582 92	0.045790 167	2.48E-34

89	QUANT	~~	FREQ	0.779337203	0.03904053	0.77933807	0.039041317	0.77933807	0.031314979	1.17E-88
53	INT	~~	EXT	0.524855912	0.031799593	0.524860223	0.031799833	0.524860223	0.031799761	3.37E-61
63	MDD	~~	MDD	0.015967636	0.003588243	0.23285699	0.052326718	0.232857092	0.052326757	8.59E-06
24	GAD2	~~	GAD2	0.016109308	0.004768649	0.276478299	0.08184136	0.276478208	0.081841397	0.000729699
58	LifetimeAnx	~~	LifetimeAnx	0.067587181	0.019155488	0.307509367	0.087152599	0.30750929	0.087152619	0.000418166
72	num_partners	~~	num_partners	0.06308588	0.004908919	0.63420557	0.049349369	0.634205688	0.049349557	8.46E-38
1	ADHD	~~	ADHD	0.28590485	0.037279463	0.566821521	0.073908013	0.566821195	0.073908165	1.73E-14
2	antisoc	~~	antisoc	0.026790326	0.028220722	0.473066376	0.49831681	0.473066452	0.498316875	0.342460951
3	AUD	~~	AUD	0.013664782	0.003107753	0.237230573	0.053948734	0.237230489	0.053948765	1.10E-05
8	AUDIT_4	~~	AUDIT_4	0.011821178	0.004458512	0.38384555	0.144772484	0.383845422	0.144772481	0.008016528
9	AUDIT_5	~~	AUDIT_5	0.008084414	0.004839316	0.397263038	0.237801577	0.39726313	0.237801556	0.094806703
10	AUDIT_7	~~	AUDIT_7	0.012251689	0.004252373	0.313478335	0.108803201	0.313478077	0.108803191	0.003962375
11	AUDIT_8	~~	AUDIT_8	0.019361627	0.004640591	0.487022888	0.116729514	0.487022987	0.1167295	3.02E-05
4	AUDIT_10	~~	AUDIT_10	0.011024175	0.002614442	0.39942238	0.094725579	0.399422649	0.094725565	2.48E-05
12	dpw	~~	dpw	0.001512901	0.002744987	0.029587321	0.053683675	0.029587321	0.053683681	0.581530578
6	AUDIT_2	~~	AUDIT_2	0.015040945	0.002647567	0.285721895	0.050293888	0.285721897	0.05029389	1.34E-08
7	AUDIT_3	~~	AUDIT_3	0.009865314	0.002658817	0.161111183	0.043421268	0.161111005	0.04342124	0.00020692
52	intake_freq	~~	intake_freq	0.000973085	0.002162316	0.015665534	0.034814157	0.015665536	0.034814157	0.652696088
5	AUDIT_1	~~	AUDIT_1	0.008384756	0.003100397	0.114504606	0.042340002	0.114504581	0.04233999	0.006842496
27	gad_Irritability	~~	gad_Irritability	0.026804767	0.00510469	0.329149977	0.0626829	0.329149505	0.062682902	1.51E-07
25	gad_Anxiety	~~	gad_Anxiety	0.015678513	0.004867181	0.215806076	0.066993978	0.215806392	0.066993978	0.00127623
26	gad_Foreboding	~~	gad_Forebodi ng	0.029358002	0.006298	0.305897082	0.065621631	0.305896494	0.065621634	3.14E-06
60	mdd_Appetite	~~	mdd_Appetite	0.040951244	0.006662885	0.464280432	0.075538895	0.464278673	0.075538895	7.94E-10
61	mdd_Concentration	~~	mdd_Concentration	0.02261754	0.006146488	0.311872079	0.084752215	0.31187145	0.084752216	0.000233462
62	mdd_Ideation	~~	mdd_Ideation	0.016299686	0.014855161	0.217403073	0.198141787	0.217402653	0.198141793	0.272536213
64	mdd_Motor	~~	mdd_Motor	0.029849468	0.011716453	0.403889197	0.158534037	0.403889406	0.158534043	0.010844997
65	mdd_Sleep	~~	mdd_Sleep	0.043519569	0.005173731	0.578174813	0.068735071	0.578174137	0.068735073	4.04E-17

59	mdd_Anhedonia	~~	mdd_Anhedonia	0.02216697	0.00575781	0.260402062	0.06763817	0.260401766	0.067638171	0.000118168
66	neuro_Fed_up	~~	neuro_Fed_up	0.0290337	0.00237399	0.316056417	0.025879757	0.316055942	0.025879751	2.67E-34
67	neuro_Hurt_feelings	~~	neuro_Hurt_feelings	0.049329385	0.00284184	0.543102756	0.0313138	0.543103679	0.031313802	2.19E-67
68	neuro_Irritability	~~	neuro_Irritability	0.056640718	0.0033559	0.500627907	0.029661695	0.500628086	0.029661696	6.54E-64
69	neuro_Lonely	~~	neuro_Lonely	0.020611648	0.002697171	0.297724111	0.038959307	0.297724332	0.038959303	2.14E-14
70	neuro_Nerves	~~	neuro_Nerves	0.046189055	0.003358732	0.542693542	0.039463125	0.54269367	0.039463122	4.96E-43
71	neuro_Nervous	~~	neuro_Nervous	0.0841331	0.004085935	0.680919906	0.033068984	0.68092024	0.033068982	3.31E-94
50	ID_INT_PAU	:=	a1*b1	0.133137059	0.18638828	0.133150887	0.186400781	0.100777691	0.14097125	0.475041987
97	TOT_INT_PAU	:=	c1+(a1*b1)	0.28991285	0.054223066	0.289910654	0.05422403	0.219424195	0.041009325	8.96E-08
51	ID_INT_QUANT	:=	a1*b2	0.198062741	0.22240 7695	0.198092694	0.22242876	0.162521963	0.182462261	0.373176501
98	TOT_INT_QUANT	:=	c2+(a1*b2)	-0.234974818	0.073563646	-0.234983239	0.073566335	-0.192788218	0.060349254	0.001402333
49	ID_INT_FREQ	:=	a1*b3	-0.106014006	0.101102949	-0.106008143	0.101108723	-0.103652857	0.098857061	0.294373853
96	TOT_INT_FREQ	:=	c3+(a1*b3)	-0.208718188	0.033948914	-0.208719004	0.033949366	-0.204081692	0.033193695	7.85E-10
47	ID_EXT_PAU	:=	a2*b1	-0.032480169	0.048494333	-0.032484426	0.04849905	-0.024586434	0.036677959	0.503002855
94	TOT_EXT_PAU	:=	c1+(a2*b1)	0.124295622	0.281596549	0.12427534	0.281614627	0.094060071	0.212979358	0.658926257
48	ID_EXT_QUANT	:=	a2*b2	-0.048319463	0.060898485	-0.048328085	0.060906256	-0.03965	0.049961127	0.427519 89
95	TOT_EXT_QUANT	:=	c2+(a2*b2)	-0.481357023	0.345429049	-0.481404019	0.345460125	-0.394960 18	0.283386991	0.163467207
46	ID_EXT_FREQ	:=	a2*b3	0.025863218	0.023641551	0.025862491	0.023643563	0.025287879	0.023116572	0.273966826
93	TOT_EXT_FREQ	:=	c3+(a2*b3)	-0.076840964	0.152981205	-0.07684837	0.152989614	-0.075140955	0.149582323	0.615463384
55	INT	~~	INT	1		1		1		NA
15	EXT	~~	EXT	1		1		1		NA
83	PAU	~~	PAU	1		1		0.572849684		NA
92	QUANT	~~	QUANT	1		1		0.673111798		NA
20	FREQ	~~	FREQ	1		1		0.956057708		NA
32	GNA	~~	GNA	1		1		0.201322929		NA

Supplemental Table 10. Full model output for model that includes an "anxious arousal" factor (AA) as mediating the relationships between internalizing (INT), externalizing (EXT), and three alcohol use factors: problematic use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). Total effects (TOT) and indirect effects (ID) were calculated using the path coefficients (a = psychiatric factor to mediator; b = mediator to alcohol factor; c = direct path from psychiatric factor to alcohol factor).
Model fit: $\chi^2(173) = 771.5416$, AIC = 887.5416, CFI = 0.959579, SRMR = 0.094138

	lhs	op	rhs	Unstand Est	Unstand SE	STD_Genotype	STD_Genotype_SE	STD_All	STD_All SE	p_value
45	INT	=~	MDD	0.235030465	0.007024222	0.905525843	0.027062937	0.905525832	0.027062959	1.84E-245
42	INT	=~	GAD2	0.19117586	0.008469599	0.807053953	0.035754555	0.807053948	0.035754566	8.17E-113
44	INT	=~	LifetimeAnx	0.40914067	0.016469887	0.874946566	0.035220458	0.874946542	0.035220474	3.18E-136
23	EXT	=~	num_partners	0.203573403	0.010737335	0.645349244	0.034036969	0.645349239	0.034036985	3.69E-80
20	EXT	=~	ADHD	0.441927878	0.031192785	0.622285938	0.043922092	0.622285927	0.043922096	1.45E-45
21	EXT	=~	antisoc	0.162961658	0.021798728	0.721929992	0.096566776	0.721929753	0.096566796	7.68E-14
52	PAU	=~	AUD	0.171524165	0.012318989	0.717650024	0.051540987	0.937818153	0.067386764	4.56E-44
54	PAU	=~	AUDIT_4	0.099920042	0.010328673	0.581468983	0.060106193	0.75985817	0.078585276	3.89E-22
55	PAU	=~	AUDIT_5	0.081353675	0.009536645	0.578428852	0.067804646	0.755885523	0.088650561	1.45E-17
56	PAU	=~	AUDIT_7	0.115054117	0.010926379	0.605095677	0.057463722	0.790733251	0.075130401	6.29E-26
57	PAU	=~	AUDIT_8	0.103597127	0.010408619	0.529215495	0.053170666	0.691573718	0.06951749	2.45E-23
53	PAU	=~	AUDIT_10	0.102669718	0.009223839	0.627163264	0.056344131	0.819570955	0.073666599	8.87E-29
66	QUANT	=~	dpw	0.127513714	0.011623333	0.569928266	0.051608115	0.688454445	0.062354944	5.30E-28
64	QUANT	=~	AUDIT_2	0.161408178	0.009307245	0.708008361	0.040793358	0.855250183	0.049287998	2.26E-67
65	QUANT	=~	AUDIT_3	0.188934194	0.010139006	0.768356699	0.041193192	0.928148976	0.049771014	1.69E-77
26	FREQ	=~	dpw	0.084597149	0.011978424	0.376366191	0.053064682	0.38750354	0.054644851	1.64E-12
30	FREQ	=~	intake_freq	0.240724554	0.007461067	0.9744368	0.030034844	0.9744368	0.030929 1	2.23E-228
25	FREQ	=~	AUDIT_1	0.241317973	0.008784356	0.896160924	0.032539079	0.92267956	0.033507961	3.86E-166
3	AA	=~	gad_Relax	0.103435804	0.021573333	0.362597874	0.075639469	0.863946566	0.180294545	1.63E-06
4	AA	=~	gad_Restlessness	0.10214883	0.021651786	0.3596077	0.076236727	0.856821972	0.18171832	2.38E-06
6	AA	=~	mdd_Sleep	0.068714342	0.014437483	0.250920824	0.052729725	0.597858361	0.125686865	1.94E-06
7	AA	=~	neuro_High_strung	0.109117193	0.023183432	0.322365569	0.068502897	0.768086794	0.163283913	2.52E-06

60	PAU	~	INT	0.240933159	0.39361952	0.240924113	0.393681125	0.184363239	0.301096131	0.540473865
58	PAU	~	EXT	0.666986226	0.141872838	0.666987705	0.141884384	0.510401438	0.108518455	2.59E-06
51	PAU	~	AA	0.020958757	0.152318928	0.020958004	0.152330156	0.038212514	0.277714406	0.890558257
69	QUANT	~	INT	-0.38106997	0.341097078	-0.381715059	0.340995879	-0.315997978	0.282209033	0.26391344
67	QUANT	~	EXT	0.786427568	0.135629666	0.786033541	0.135528962	0.650707914	0.11216593	6.70E-09
63	QUANT	~	AA	0.078375008	0.122891507	0.078585002	0.12281096	0.155005216	0.242277854	0.523631403
29	FREQ	~	INT	-0.497826157	0.272180641	-0.495833957	0.271150783	-0.481583077	0.263296501	0.067395335
27	FREQ	~	EXT	0.280706083	0.08352444	0.27961862	0.083201839	0.271582036	0.08079263	0.000777267
24	FREQ	~	AA	0.12735617	0.090086697	0.126837726	0.089747542	0.293524958	0.207735795	0.157448026
5	AA	~	INT	2.35716151	0.575009199	2.357392635	0.575154611	0.989396312	0.241276999	4.14E-05
2	AA	~	EXT	-0.464438103	0.204269253	-0.464516164	0.204310671	-0.194957163	0.085709279	0.022986651
62	PAU	~~	QUANT	0.816541085	0.056154634	0.816667158	0.05613189	0.816667158	0.035532701	6.67E-48
59	PAU	~~	FREQ	0.742765224	0.066019367	0.740222995	0.065774769	0.740222995	0.048852945	2.30E-29
68	QUANT	~~	FREQ	0.757257188	0.036910205	0.753557696	0.036767631	0.753557696	0.029550587	1.54E-93
41	INT	~~	EXT	0.50043889	0.030899025	0.500443412	0.030899193	0.500443412	0.030899136	5.39E-59
40	intake_freq	~~	intake_freq	0.000999957	0.002231558	0.001000417	0.036532042	0.001000417	0.036532042	0.654082472
47	MDD	~~	MDD	0.012127391	0.003683488	0.180022971	0.054677613	0.180022967	0.054677697	0.000993481
31	GAD2	~~	GAD2	0.019563067	0.004522141	0.348663928	0.080591437	0.348663924	0.080591468	1.52E-05
46	LifetimeAnx	~~	LifetimeAnx	0.051270221	0.019408624	0.234468562	0.088758547	0.234468549	0.088758597	0.008251042
50	num_partners	~~	num_partners	0.058064962	0.005136397	0.583524368	0.051616611	0.583524368	0.051616643	1.25E-29
8	ADHD	~~	ADHD	0.309032047	0.034742668	0.612760246	0.068887068	0.612760225	0.068887078	5.85E-19
9	antisoc	~~	antisoc	0.024397446	0.027931977	0.478817748	0.548178796	0.478817431	0.548178807	0.382412766
10	AUD	~~	AUD	0.006886462	0.003210422	0.120497117	0.056198478	0.120497112	0.056198478	0.031950204
15	AUDIT_4	~~	AUDIT_4	0.012477632	0.004537252	0.422615474	0.153663412	0.422615562	0.153663409	0.005958765
16	AUDIT_5	~~	AUDIT_5	0.008477883	0.004859523	0.428636798	0.24567492	0.428637077	0.245674918	0.081055972
17	AUDIT_7	~~	AUDIT_7	0.013547311	0.004312509	0.374740905	0.119287182	0.374740926	0.119287179	0.00168143
18	AUDIT_8	~~	AUDIT_8	0.019992852	0.004652637	0.521725816	0.121412879	0.521725792	0.121412876	1.73E-05

11	AUDIT_10	~~	AUDIT_10	0.008797439	0.00251 0853	0.3283034 37	0.093694333	0.328303 449	0.093694 332	0.00045 8731
19	dpw	~~	dpw	2.97E-05	0.00273 4067	0.0017429 59	0.054353624	0.001742 96	0.054353 619	0.99132 6499
13	AUDIT_2	~~	AUDIT_2	0.014012 412	0.00261 7288	0.2685473 72	0.050314183	0.268547 125	0.050314 18	8.61E-0 8
14	AUDIT_3	~~	AUDIT_3	0.008437 566	0.00263 3233	0.1385395 95	0.043532484	0.138539 479	0.043532 494	0.00135 4098
12	AUDIT_1	~~	AUDIT_1	0.010867 521	0.00310 7553	0.1486625 34	0.042766615	0.148662 43	0.042766 626	0.00047 029
32	gad_Relax	~~	gad_Relax	0.020632 497	0.00509 8185	0.2535963 38	0.062660835	0.253596 331	0.062660 84	5.19E-0 5
33	gad_Restlessness	~~	gad_Restlessness	0.021447 178	0.00838 0746	0.2658561 35	0.10388304	0.265856 108	0.103883 038	0.01049 4319
48	mdd_Sleep	~~	mdd_Sleep	0.048178 885	0.00560 7991	0.6425654 78	0.074793425	0.642565 38	0.074793 422	8.61E-1 8
49	neuro_High_strung	~~	neuro_High_strung	0.046973 679	0.00478 9042	0.4100426 51	0.041804636	0.410042 676	0.041804 679	1.03E-2 2
38	ID_INT_PAU	:=	a1*b1	0.049403 174	0.24906 1294	0.0494062 43	0.24910814	0.037807 32	0.190522 666	0.84276 5371
75	TOT_INT_PAU	:=	c1+(a1*b1)	0.290336 333	0.05060 7068	0.2903303 56	0.050607608	0.222170 559	0.038707 234	9.63E-0 9
39	ID_INT_QUANT	:=	a1*b2	0.184742 552	0.28776 1148	0.1852557 04	0.287700834	0.153361 589	0.238100 047	0.52087 3421
76	TOT_INT_QUANT	:=	c2+(a1*b2)	-0.19632 7418	0.06532 587	-0.196459 355	0.065271576	-0.16263 6389	0.054021 355	0.00265 2712
37	ID_INT_FREQ	:=	a1*b3	0.300199 062	0.22797 3513	0.2990063 22	0.227133742	0.290412 511	0.220553 424	0.18790 0466
74	TOT_INT_FREQ	:=	c3+(a1*b3)	-0.19762 7095	0.03333 4393	-0.196827 635	0.033196131	-0.19117 0566	0.032236 038	3.05E-0 9
35	ID_EXT_PAU	:=	a2*b1	-0.00973 4045	0.05017 2137	-0.009735 331	0.050184876	-0.00744 9803	0.038381 926	0.84616 573
72	TOT_EXT_PAU	:=	c1+(a2*b1)	0.231199 114	0.33358 3796	0.2311887 82	0.333644039	0.176913 436	0.255177 919	0.48826 1499
36	ID_EXT_QUANT	:=	a2*b2	-0.03640 034	0.06349 7258	-0.036504 004	0.063512373	-0.03021 9377	0.052561 682	0.56646 9713
73	TOT_EXT_QUANT	:=	c2+(a2*b2)	-0.41747 0309	0.39506 2133	-0.418219 063	0.394976416	-0.34621 7356	0.326881 963	0.29063 9103
34	ID_EXT_FREQ	:=	a2*b3	-0.05914 9058	0.05457 9443	-0.058918 174	0.054377008	-0.05722 4793	0.052801 296	0.27848 7147
71	TOT_EXT_FREQ	:=	c3+(a2*b3)	-0.55697 5216	0.30196 0857	-0.554752 131	0.300830075	-0.53880 787	0.292115 339	0.06510 6248
43	INT	~~	INT	1		1		1		NA
22	EXT	~~	EXT	1		1		1		NA
61	PAU	~~	PAU	1		1		0.585582 545		NA
70	QUANT	~~	QUANT	1		1		0.685314 658		NA
28	FREQ	~~	FREQ	1		1		0.943343 592		NA
1	AA	~~	AA	1		1		0.176147 6		NA

Supplemental Table 11. Full model output for model that includes a "low positive affect" factor (LPA) as mediating the relationships between internalizing (INT), externalizing (EXT), and three alcohol use factors: problematic use (PAU), consumption quantity (QUANT), and consumption frequency (FREQ). Total effects (TOT) and indirect effects (ID) were calculated using the path coefficients (a = psychiatric factor to mediator; b = mediator to alcohol factor; c = direct path from psychiatric factor to alcohol factor).
Model fit: $\chi^2(193) = 811.6359$, AIC = 931.6359, CFI = 0.962583, SRMR = 0.09049

	lhs	op	rhs	Unstand Est	Unstand SE	STD_Genotype	STD_Genotype SE	STD_All	STD_All SE	p_value
31	INT	=~	MDD	0.238636763	0.007260816	0.915598249	0.027858186	0.915598134	0.027858178	6.64E-237
29	INT	=~	GAD2	0.194157315	0.008471022	0.813251432	0.035481887	0.813252169	0.035481883	2.92E-116
30	INT	=~	LifetimeAnx	0.394890965	0.016349243	0.844066323	0.034945952	0.844066791	0.034945946	6.87E-129
13	EXT	=~	num_partners	0.201019058	0.010561089	0.637306287	0.0334826	0.63730617	0.03348261	8.93E-81
11	EXT	=~	ADHD	0.446312182	0.031335172	0.628466868	0.044124032	0.628467384	0.044124031	4.94E-46
12	EXT	=~	antisoc	0.166155591	0.021981734	0.733304324	0.097013129	0.733302957	0.097013135	4.07E-14
44	PAU	=~	AUD	0.165852529	0.012215587	0.693989298	0.051114252	0.913896647	0.067348997	5.47E-42
46	PAU	=~	AUDIT_4	0.101218883	0.010404081	0.593745927	0.061033954	0.781887636	0.080419312	2.29E-22
47	PAU	=~	AUDIT_5	0.080932565	0.009513924	0.562815433	0.066160844	0.741156285	0.087174057	1.79E-17
48	PAU	=~	AUDIT_7	0.116291988	0.011041887	0.60580046	0.057520292	0.797762094	0.075789664	6.16E-26
49	PAU	=~	AUDIT_8	0.105849986	0.010525125	0.539604993	0.053655041	0.710591305	0.070696747	8.57E-24
45	PAU	=~	AUDIT_10	0.10291759	0.009313845	0.623627761	0.056436843	0.82123853	0.074362131	2.19E-28
58	QUANT	=~	dpw	0.120771787	0.010876935	0.537642491	0.048421091	0.650648811	0.058633085	1.21E-28
56	QUANT	=~	AUDIT_2	0.162906089	0.009162242	0.712255641	0.040058977	0.861963338	0.048507305	1.01E-70
57	QUANT	=~	AUDIT_3	0.190496915	0.009966429	0.774764392	0.040534104	0.937611135	0.049082617	1.94E-81
16	FREQ	=~	dpw	0.094224243	0.011365063	0.419460758	0.050594129	0.431260278	0.052018197	1.13E-16
17	FREQ	=~	intake_freq	0.24168178	0.006773686	0.972389515	0.027253448	0.999742753	0.028020503	8.22E-279
15	FREQ	=~	AUDIT_1	0.241989882	0.008291863	0.897813071	0.030763892	0.923068707	0.031629745	3.09E-187
34	LPA	=~	mdd_Fatigue	0.149793897	0.011915676	0.507156602	0.04034261	0.841909008	0.067051846	3.04E-36
35	LPA	=~	mdd_Mood	0.153275724	0.011894713	0.567705538	0.044055594	0.942423405	0.073223099	5.39E-38
36	LPA	=~	mdd_Sleep	0.113759075	0.009465067	0.415384239	0.034563125	0.689560838	0.057446001	2.86E-33
37	LPA	=~	mdd_Worthless	0.150129186	0.012129736	0.556905188	0.044995078	0.924491968	0.074784552	3.48E-35

38	LPA	=~	neuro_Miserable	0.159747363	0.012232358	0.529232666	0.040524747	0.878555811	0.067354641	5.62E-39
51	PAU	~	INT	0.162863282	0.168487087	0.162866679	0.168485353	0.123676738	0.127872 23	0.33373 3157
50	PAU	~	EXT	0.676431166	0.114936421	0.676426191	0.114935157	0.513660532	0.087229786	3.97E-09
52	PAU	~	LPA	0.095797 27	0.096876294	0.095796033	0.096875668	0.120760817	0.122200 65	0.32273 0745
60	QUANT	~	INT	-0.26221 6425	0.141174749	-0.262215242	0.141173534	-0.21667 3075	0.116586059	0.06325 5831
59	QUANT	~	EXT	0.764874395	0.098307657	0.764873348	0.098307136	0.632028326	0.081185098	7.23E-15
61	QUANT	~	LPA	0.042947 33	0.075541893	0.042947216	0.075541579	0.058912136	0.103687093	0.56967 9658
19	FREQ	~	INT	-0.05057 3559	0.082653219	-0.050572977	0.082652608	-0.04918 928	0.080390515	0.54061 95
18	FREQ	~	EXT	0.210407417	0.043697636	0.21040673	0.043697449	0.204649919	0.042501285	1.47E-06
20	FREQ	~	LPA	-0.10783159	0.049438963	-0.107831919	0.049438807	-0.17410 9321	0.079920973	0.02917 5622
40	LPA	~	INT	1.387621 72	0.152867293	1.387615257	0.152865725	0.835884608	0.091974612	1.11E-19
39	LPA	~	EXT	-0.13471 1375	0.089094181	-0.134708583	0.08909349	-0.08114 7012	0.053604589	0.13053 1083
55	PAU	~~	QUANT	0.810277538	0.053605979	0.810276711	0.053605787	0.810276711	0.033598 16	1.28E-51
53	PAU	~~	FREQ	0.760448685	0.059538943	0.760447876	0.05953864	0.760447876	0.043949794	2.34E-37
62	QUANT	~~	FREQ	0.750574621	0.037806688	0.750575107	0.037806687	0.750575107	0.030367269	1.04E-87
32	INT	~~	EXT	0.502442 82	0.030837751	0.502441916	0.030837666	0.502441916	0.030837666	1.10E-59
43	MDD	~~	MDD	0.010983089	0.003824256	0.161680099	0.056296569	0.161680058	0.056296527	0.00407 9421
22	GAD2	~~	GAD2	0.019300 78	0.004568767	0.338620296	0.080156867	0.338620 91	0.080156852	2.39E-05
42	LifetimeAnx	~~	LifetimeAnx	0.062938882	0.018989 81	0.287550932	0.086759901	0.287551252	0.086759875	0.00091 8563
78	num_partners	~~	num_partners	0.059081233	0.005059552	0.593841064	0.050854962	0.593840846	0.050854 99	1.67E-31
1	ADHD	~~	ADHD	0.305133885	0.035214 3	0.605027755	0.069824112	0.605028748	0.069824119	4.51E-18
70	antisoc	~~	antisoc	0.023732796	0.028003079	0.462268498	0.545434754	0.462266774	0.545434754	0.39671 2777
10	AUD	~~	AUD	0.009412043	0.003132398	0.164792848	0.054844871	0.164792918	0.054844862	0.00265 808
6	AUDIT_4	~~	AUDIT_4	0.011294969	0.004480784	0.388652648	0.154180598	0.388651724	0.154180 62	0.01171 0261
7	AUDIT_5	~~	AUDIT_5	0.009319 51	0.004848798	0.450688233	0.234486289	0.450687361	0.234486304	0.05460 2657
8	AUDIT_7	~~	AUDIT_7	0.013397897	0.004264193	0.363576345	0.115716185	0.363575642	0.115716208	0.00167 8247
9	AUDIT_8	~~	AUDIT_8	0.019049755	0.004625908	0.495060655	0.120216699	0.495059997	0.120216722	3.82E-05

2	AUDIT_10	~~	AUDIT_10	0.008866858	0.002522004	0.325567788	0.092600937	0.325567277	0.092600947	0.000438434
71	dpw	~~	dpw	0.000185721	0.002713209	0.003679786	0.053769959	0.003679787	0.053769946	0.945426993
4	AUDIT_2	~~	AUDIT_2	0.013445185	0.002578073	0.257019309	0.049282447	0.257019204	0.049282451	1.84E-07
5	AUDIT_3	~~	AUDIT_3	0.00730828	0.002632559	0.120885294	0.043545291	0.120885359	0.043545265	0.005501316
72	intake_freq	~~	intake_freq	3.17E-05	0.002165944	0.000514428	0.035062271	0.000514428	0.035062258	0.988314343
3	AUDIT_1	~~	AUDIT_1	0.010747701	0.003084348	0.147944125	0.042456229	0.147944162	0.042456227	0.000492885
73	mdd_Fatigue	~~	mdd_Fatigue	0.025402913	0.004793767	0.291188774	0.054950323	0.291189223	0.054950327	1.16E-07
74	mdd_Mood	~~	mdd_Mood	0.008152689	0.005437729	0.111838025	0.074589816	0.111838125	0.074589827	0.133769127
75	mdd_Sleep	~~	mdd_Sleep	0.039339094	0.005151405	0.524506243	0.06868335	0.524505085	0.068683357	2.23E-14
76	mdd_Worthless	~~	mdd_Worthless	0.010560114	0.005521206	0.145315177	0.075973855	0.145314602	0.075973862	0.055793361
77	neuro_Miserable	~~	neuro_Miserable	0.020786285	0.003710387	0.228139713	0.040723304	0.228139686	0.040723296	2.12E-08
27	ID_INT_PAU	:=	a1*b1	0.132930373	0.084200768	0.132928036	0.084199576	0.100942108	0.063903539	0.114397745
68	TOT_INT_PAU	:=	c1+(a1*b1)	0.295793655	0.050654748	0.295794715	0.050654379	0.224618846	0.038443993	5.24E-09
28	ID_INT_QUANT	:=	a1*b2	0.059594648	0.087293083	0.059594212	0.087292915	0.049243747	0.072089682	0.494802581
69	TOT_INT_QUANT	:=	c2+(a1*b2)	-0.202621777	0.06588711	-0.20262103	0.065886767	-0.167429328	0.054411347	0.002103
26	ID_INT_FREQ	:=	a1*b3	-0.149629456	0.048882084	-0.149629217	0.048881672	-0.145535302	0.047543927	0.002205781
67	TOT_INT_FREQ	:=	c3+(a1*b3)	-0.200203015	0.031850102	-0.200202193	0.031849961	-0.194724582	0.030978108	3.26E-10
24	ID_EXT_PAU	:=	a2*b1	-0.012904982	0.012828725	-0.012904548	0.012828381	-0.009799379	0.009736178	0.314442387
65	TOT_EXT_PAU	:=	c1+(a2*b1)	0.149958301	0.130922015	0.149962131	0.130920222	0.113877359	0.099362132	0.252042788
25	ID_EXT_QUANT	:=	a2*b2	-0.005785494	0.010709579	-0.005785359	0.010709334	-0.004780544	0.008844114	0.589047552
66	TOT_EXT_QUANT	:=	c2+(a2*b2)	-0.268001919	0.144871041	-0.268000601	0.144869593	-0.221453619	0.11963833	0.064323007
23	ID_EXT_FREQ	:=	a2*b3	0.014526142	0.008260029	0.014525885	0.008259968	0.014128451	0.008033887	0.078644348
64	TOT_EXT_FREQ	:=	c3+(a2*b3)	-0.036047417	0.072985632	-0.036047092	0.072985017	-0.035060829	0.070987524	0.621378613
33	INT	~~	INT	1		1		1		NA
14	EXT	~~	EXT	1		1		1		NA
54	PAU	~~	PAU	1		1		0.576649027		NA
63	QUANT	~~	QUANT	1		1		0.682800812		NA

21	FREQ	~~	FREQ	1		1		0.946027798		NA
41	LPA	~~	LPA	1		1		0.36287289		NA

Table 12. Full model output for the reduced base model in the Finnish population relating internalizing (INT) and problematic alcohol use (PAU).
Model fit: $\chi^2(8) = 3.903019$, AIC = 29.90302, CFI = 1, SRMR = 0.0415988

	lhs	op	rhs	Unstand Est	Unstan d SE	STD_Ge notype	STD_Gen otype SE	STD All	STD_A ll SE	p value
7	INT	=~	F5_ALLANXIOUS	0.123884417	0.01141827138	1.004508049	0.0925842 6737	1.004507 94	0.09258426382	2.00E-27
8	INT	=~	F5_ANXIETY	0.1179540969	0.01312752671	0.9268190716	0.1031489356	0.9268193143	0.1031489353	2.58E-19
9	INT	=~	F5_DEPRESSIO	0.1110803735	0.01427205386	0.9208851365	0.1183190358	0.9208851355	0.1183190343	7.08E-15
10	INT	=~	F5_GAD	0.1040349248	0.01957617259	0.9391876465	0.1767262309	0.9391876144	0.1767262267	1.07E-07
12	PAU	=~	AUD	0.07992361825	0.0301899294	0.5330477502	0.2013506678	0.9875518601	0.3732558164	0.008112288817
13	PAU	=~	F5_ALCOHOL_DEPENDENCE	0.08803746374	0.03261432023	0.5374292457	0.1990958071	0.9956693331	0.3690758123	0.006947507719
14	PAU	~	INT	1.559589278	0.7326078488	1.559589247	0.7326078421	0.841814562	0.3952009842	0.03326926431
3	F5_ALLANXIOUS	~~	F5_ALLANXIOUS	-0.0001374491922	0.001788115019	-0.009036203844	0.1175625596	-0.009036201878	0.1175625751	0.9387283912
4	F5_ANXIETY	~~	F5_ANXIETY	0.002283895509	0.002540039303	0.1410058847	0.1568209709	0.1410059586	0.1568209623	0.3685687491
5	F5_DEPRESSIO	~~	F5_DEPRESSIO	0.002211174837	0.002828750062	0.1519705675	0.1944154874	0.1519705672	0.1944154877	0.4344031802
6	F5_GAD	~~	F5_GAD	0.001446986602	0.007062082256	0.117926633	0.5755449077	0.1179266249	0.5755544903	0.8376540226
1	AUD	~~	AUD	0.0005562082669	0.003057549883	0.02474132383	0.1360052065	0.02474132366	0.1360052151	0.8556509521
2	F5_ALCOHOL_DEPENDENCE	~~	F5_ALCOHOL_DEPENDENCE	0.0002319233635	0.003333049136	0.008642581869	0.1242079078	0.008642583296	0.1242079049	0.9445256146
11	INT	~~	INT	1		1		1		NA
15	PAU	~~	PAU	1		1		0.2913482433		NA

Supplemental Table 13. Full output for cross-trait genetic correlations calculated using LDSC for two separate populations: Finnish and East Asian. For details of diverse ancestry GWAS, see Suppl. Table 3. Columns: rg = genetic correlation; h2_obs = heritability of trait 2; h2_int = LDSC regression intercept for trait 2; gcov_int = cross-trait LDSC intercept

trait 1	trait 2	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se
Finnish Ancestry											
AUD	F5_ALCOHOL_DEPENDENCE	1.0266	0.0322	31.9177	1.52E-223	0.0042	8.00E-04	1.1397	0.0103	0.9593	0.0104
AUD	F5_ALLANXIOUS	0.8168	0.1207	6.7666	1.32E-11	0.0045	8.00E-04	1.1541	0.0099	0.2384	0.0079
AUD	F5_ANXIETY	0.761	0.1331	5.7191	1.07E-08	0.0036	7.00E-04	1.1196	0.0088	0.221	0.0076
AUD	F5_DEPRESSIO	0.7362	0.0912	8.075	6.75E-16	0.0061	0.0011	1.2208	0.0114	0.3246	0.0082
AUD	F5_GAD	0.6953	0.2969	2.3418	0.019193	0.001	7.00E-04	1.0419	0.0076	0.0964	0.0063
F5_ALCOHOL_DEPENDENCE	F5_ALLANXIOUS	0.8103	0.1294	6.2642	3.75E-10	0.0045	8.00E-04	1.1541	0.0099	0.2173	0.0072
F5_ALCOHOL_DEPENDENCE	F5_ANXIETY	0.7189	0.1379	5.2129	1.86E-07	0.0036	7.00E-04	1.1196	0.0088	0.2049	0.007
F5_ALCOHOL_DEPENDENCE	F5_DEPRESSIO	0.8318	0.1143	7.2777	3.40E-13	0.0061	0.0011	1.2208	0.0114	0.291	0.0074
F5_ALCOHOL_DEPENDENCE	F5_GAD	0.7085	0.3168	2.2368	0.025298	0.001	7.00E-04	1.0419	0.0076	0.0862	0.0059
F5_ALLANXIOUS	F5_ANXIETY	0.9724	0.0243	39.9826	0	0.0036	7.00E-04	1.1196	0.0088	0.9723	0.0088
F5_ALLANXIOUS	F5_DEPRESSIO	0.853	0.0802	10.6337	2.08E-26	0.0061	0.0011	1.2208	0.0114	0.5445	0.0079
F5_ALLANXIOUS	F5_GAD	1.0797	0.2942	3.6702	0.00024235	0.001	7.00E-04	1.0419	0.0076	0.5078	0.0067
F5_ANXIETY	F5_DEPRESSIO	0.84	0.0909	9.2414	2.43E-20	0.0061	0.0011	1.2208	0.0114	0.4723	0.0077
F5_ANXIETY	F5_GAD	1.1539	0.3845	3.0007	0.0026934	0.001	7.00E-04	1.0419	0.0076	0.3277	0.0065
F5_DEPRESSIO	F5_GAD	0.948	0.3247	2.9192	0.0035	0.001	7.00E-04	1.0419	0.0076	0.2786	0.006
East Asian Ancestry											
DPW	DEP	-0.0998	0.2777	-0.3592	0.7194	0.0277	0.0105	1.0169	0.0081	-0.0029	0.006