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# Evaluating risk for alcohol use disorder: Polygenic risk scores and family history

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## Abstract

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All authors have no potential conflicts of interest.

**Background:** Early identification of high-risk individuals for alcohol use disorder (AUD) coupled with prompt interventions could reduce AUD incidence. In this study, we investigated whether Polygenic Risk Scores (PRS) can be used to evaluate the risk for AUD and AUD severity (as measured by the counts of DSM-5 AUD diagnostic criterion), and compared their performance with measures of family history of AUD.

**Methods:** Individuals of European ancestry from the Collaborative Study on the Genetics of Alcoholism (COGA) were studied. DSM-5 diagnostic criteria were available for 7,203 individuals; 3,451 met criteria for DSM-IV alcohol dependence or DSM-5 AUD and 1,616 were alcohol-exposed controls aged 21 years without a history of AUD and drug dependence; 4,842, 2,722, and 336 individuals had positive (FH+), unknown (FH?), and negative (FH−) first-degree family history of AUD, respectively. PRS were derived from a meta-analysis of a genome-wide association study of AUD from the Million Veteran Program and scores from the problem subscale of the Alcohol Use Disorder Identification Test in the UK Biobank. Mixed models were used to test the association between PRS and risk for AUD and AUD severity.

**Results:** AUD cases had higher PRS than controls, and PRS increased with increasing numbers of DSM-5 diagnostic criterion count (P-values 1.85E-05) in the full COGA sample, the FH+ and FH? subsamples. Those in the top decile of PRS had odds ratios of 1.96 (95%CI: 1.54–2.51, P-value=7.57E-08) and 1.86 (95%CI: 1.35–2.56, P-value=1.32E-04) to develop AUD in the full sample and FH+ subsample, respectively, comparable to previously reported odds ratios for the first-degree family history (1.91 to 2.38) estimated from national surveys. PRS were also significantly associated with the DSM-5 AUD diagnostic criterion count in the full sample, FH+ and FH? subsamples (P-values 6.7E-11). PRS remained significantly associated with AUD and AUD severity even after accounting for family history (P-values 6.8E-10).

**Conclusions:** Both PRS and family history were associated with AUD and AUD severity, assessing somewhat distinct aspects of liability.

## INTRODUCTION

Alcohol use disorder (AUD) is one of the most common public health challenges (World Health Organization, 2018). Studies have found that for high-risk individuals, alcohol intervention programs can significantly reduce the incidence of AUD (Kaner et al., 2007, Kaner et al., 2018, Knox et al., 2019, Welter et al., 2020, Solberg et al., 2008, Whitlock et al., 2004, Cronce and Larimer, 2011, Bersamin et al., 2007). Early identification of high-risk individuals, especially prior to the onset of risky alcohol use, could improve the efficiency and effectiveness of these alcohol interventions (Schuckit et al., 2016), and could help the development of novel targeted and personalized prevention strategies.

AUD runs in families with an estimated heritability of 40%–60% (Heath and Martin, 1994, Prescott and Kendler, 1999, Verhulst et al., 2015). First-degree family history of AUD, which encompasses both genetic and shared family environmental factors (Dawson et al.,

1992, Grant, 1998, Dawson, 2000, Dawson and Grant, 1998), has been demonstrated as an AUD risk factor with odds ratios (OR) 1.91–2.38 (Dawson et al., 1992, Karriker-Jaffe et al., 2021). In the U.S., about 19% of adults reported at least one first-degree relative having some alcohol use problems (Karriker-Jaffe et al., 2021). However, not everyone knows or accurately reports their family history (Schuckit et al., 2020); for example, there may be a parent who has a prior history of AUD but is no longer engaging in problem drinking during the observation period. Another issue is that family members carrying high risk may abstain from drinking for religious, health, or other reasons. For complex disorders (i.e., disorders caused by many genes with small effects along with environmental factors) such as AUD, many patients are not expected to have a positive family history, consistent with the polygenic theory (Baselmans et al., 2021, Yang et al., 2010, Wray et al., 2020). For instance, assuming 10% disease prevalence and 50% heritability, up to 65% of patients will not have a positive family history depending on the family size (Yang et al., 2010). Based on a U.S. national survey, about 50% of male and 43% of female patients with AUD did not report a family history of alcohol use problems (Khan et al., 2013). Therefore, relying on family history as the primary predictor of risk to identify those who would benefit from early intervention would miss many high-risk individuals (Wray et al., 2020, Abul-Husn and Kenny, 2019).

For complex disorders, the common genetic variants that contribute to risk have small effect sizes; hence, these variants individually have limited application in disease risk evaluation. However, common genetic variants can be used to calculate polygenic risk scores (PRS), which can be used to evaluate disease risks. PRS are weighted sums of risk alleles across the entire genome, and have shown promise in the identification of high-risk individuals (Abraham et al., 2019, Chatterjee et al., 2016, Craig et al., 2020, Khera et al., 2018, Khera et al., 2019, Niemi et al., 2018, Selzam et al., 2018, Torkamani et al., 2018). For example, in one study, the top 1%, 5%, 10%, and 20% of individuals with high PRS for coronary artery diseases had ORs of 4.83, 3.34, 2.89, and 2.55, respectively, for developing these conditions (Khera et al., 2018). Although some of their functions may be modified by epigenetic mechanisms, genetic variants cannot be changed by environmental factors; therefore, PRS provide a relatively unbiased estimation of genetic risk and may have utility in situations when family history or information on other risk factors are not available. Importantly, like family history, PRS can be evaluated prior to onset of the disorder, allowing individuals to assess their risk for AUD and make informed decisions about their alcohol use (e.g. high risk individuals may choose to abstain from drinking, preventing any possibility of developing AUD).

One source of statistical power in PRS analyses lies in the sample size of the discovery genome-wide association study (GWAS). With the publication of multiple large-scale GWAS of AUD-related phenotypes (Kranzler et al., 2019, Sanchez-Roige et al., 2019, Zhou et al., 2020, Walters et al., 2018), it is now possible to perform PRS analysis of AUD with discovery GWAS of sufficient statistical power. However, current PRS for AUD explained a small proportion of the variance in AUD related traits, and these estimates are often lower than the variance attributable to family history (Kendler et al., 2012, Kiiskinen et al., 2020, Liu et al., 2019, Walters et al., 2018, Wray et al., 2014, Zhou et al., 2020). For example, PRS derived from the largest AUD related GWAS to date only explained   2.12% variations

(Zhou et al., 2020). In this study, we propose a new strategy to calculate PRS using variants that had the same directions of effects in discovery GWAS. Since study-specific variants and variants having small P-values due to random variations were excluded, we hypothesized that the performance of PRS would be improved. We tested for significant differences in PRS between AUD cases and alcohol-using controls, and in individuals with different numbers of lifetime DSM-5 AUD criteria endorsed (as a measure of AUD severity) in target dataset as well as subsamples with positive, unknown, and negative family history of AUD. We then tested whether PRS were associated with AUD diagnosis and AUD severity, and compared the performance of PRS with measures of family history of AUD.

## MATERIALS AND METHODS

### Discovery datasets and meta-analysis

Two large GWAS of AUD-related phenotypes: AUD determined using ICD codes from the Million Veteran Program (MVP-AUD) (Kranzler et al., 2019) and scores derived from the problem subscale (questions 4–10) of the Alcohol Use Disorder Identification Test (AUDIT) from the UK Biobank (UKBB-AUDIT-P) (Sanchez-Roige et al., 2019) were used as the discovery datasets. MVP-AUD (N=202,004; 5,933,416 variants) (Kranzler et al., 2019) were obtained from the database of Genotypes and Phenotypes (dbGaP, phs001672). UKBB-AUDIT-P (N=121,604; 15,312,259 variants) were provided by authors of the original publication (Sanchez-Roige et al., 2019). Only European ancestry samples in both datasets were used due to the limited non-European ancestry samples available (with resultant insufficient statistical power) and complicated linkage disequilibrium structures in admixed populations (e.g., African American, Latinx). A/T or C/G variants were excluded to avoid strand ambiguity. The two GWAS used different phenotypes – one clinically ascribed in healthcare settings (i.e., ICD codes for AUD, requiring one inpatient or two outpatient ICD9/10 codes (Kranzler et al., 2019)) and another via self-report on a questionnaire (i.e., AUDIT) (Sanchez-Roige et al., 2019). Furthermore, the study cohorts differed -while the MVP includes mostly older male veterans with higher likelihood of AUD than the general population, the UK Biobank is a volunteer cohort of older individuals, both female and male, although not socio-economically representative of the UK. These differences could contribute to study-specific signals that may relate to different aspects of drinking, the extent of enrichment for AUD in the study cohort and to study-specific confounding (e.g., via socio-economic factors). Therefore, to minimize study-specific bias, we only retained variants that had the same directions of effects in both GWAS (2,757,680 variants) to exclude study-specific findings and findings due to random variations. These variants explained 23% (SE=0.0042) of variation by using LDSC (LD score regression) (Finucane et al., 2015). On the contrary, using all variants, the variation explained was only 5% (SE=0.002) by using LDSC (Finucane et al., 2015), indicating that many variants with lower P-values were actually study-specific and including them in calculating PRS would introduce noise therefore lower their performance. Metal (Willer et al., 2010) was used for meta-analysis with the effect of each variant weighted by the sample sizes.

### Target dataset

The Collaborative Study on the Genetics of Alcoholism (COGA) was used as the target dataset. We used the European ancestry participants from COGA for PRS analysis in order to remain consistent with the ancestry of the discovery datasets. COGA recruited alcohol dependent probands and their family members from inpatient and outpatient treatment facilities in multiple centers, as well as comparison families in the same areas (Nurnberger et al., 2004, Reich et al., 1998). This study was approved by the Institutional review boards from all centers and every participant provided informed consent. To evaluate alcohol related phenotypes, we used the Semi-Structured Assessment for the Genetics of Alcoholism interview (SSAGA, for age 18) and the child/adolescent version of the SSAGA (for age 17) (Bucholz et al., 1994, Hesselbrock et al., 1999). Only individuals reporting drinking at least one full drink of alcohol in their lifetime were included in analyses. AUD cases were defined as having either lifetime DSM-IV alcohol dependence or DSM-5 AUD. The controls used in this study were defined as follows: 1) 21 years or older; 2) Not meeting any criterion of DSM-IV alcohol dependence or DSM-5 alcohol use disorder during their lifetime; 3) Not having any DSM-IV drug dependence (opioid, cannabis, cocaine, sedative, and stimulant). Those not defined as AUD cases and controls were excluded from the binary AUD diagnosis analysis but were included in analyses of AUD criterion counts. Family history of AUD was obtained from parental interview, family history reports, and respondent reports as described previously (Pandey et al., 2020, Johnson et al., 2019, Bucholz et al., 2017, McCutcheon et al., 2017). In this study, an individual with a positive family history of AUD (FH+) was defined as having at least one first-degree relative with AUD. An individual with a negative family history of AUD (FH−) was defined as all first-degree relatives not having AUD. All others were defined as having unknown family history of AUD (FH?, i.e. no first-degree relatives with AUD but at least one first-degree relative with unknown status).

Genotyping, data processing and quality control information of COGA samples were reported previously (Lai et al., 2019, Lai et al., 2020). Briefly, COGA European ancestry samples were genotyped on different arrays: Illumina Human1M array and OmniExpress 12v1 array (Illumina, San Diego, CA), and the SmokeScreen array (Biorealm LLC, Walnut, CA). To assess the reported family structures, we used a set of 47,000 independent variants (defined as linkage disequilibrium (LD) $r^2 < 0.5$) that were genotyped in all arrays with high genotyping quality (missing rate < 2%, minor allele frequency (MAF) >10%, Hardy-Weinberg Equilibrium (HWE) P-value >0.001), and family structures were updated if necessary. We also used these 47,000 variants to calculate principal components (PC) of population stratification using Eigenstrat (Price et al., 2006). Based on the first two PCs, those clustered with the European samples from the 1000 Genomes Projects were considered as having European ancestry. Before imputation, variants with A/T or C/G alleles, missing rate >5%, MAF <3%, and HWE P-value < 0.0001 were excluded. SHAPEIT2 (Delaneau et al., 2013) was used to phase the haplotypes and Minimac3 (Das et al., 2016) was used for imputation to the 1000 Genomes (Phase 3, version 5, NCBI GRCh 37) separately by array. Variants with imputation quality score $R^2$ 0.3 were kept for analysis.

### PRS calculation

The posterior effect sizes of variants were estimated using PRS-CS (Ge et al., 2019) through a Bayesian regression framework using continuous shrinkage priors. This method models local LD patterns and variants with small effects are excluded from analysis, therefore, neither LD pruning nor P-value thresholding are needed. PRS-CS requires an external LD reference panel and European samples from the 1000 Genomes project (phase 3, NCBI GRCh37) were used. Variants that were present in the discovery datasets, LD reference panel, and the COGA dataset were included (N=2,077,165). Posterior effect sizes were estimated for 326,000 variants by PRS-CS, and these variants were used to calculate PRS using PLINK (Chang et al., 2015, Purcell et al., 2007).

### Statistical analysis

Since COGA is a family cohort, mixed models were used with a random effect to adjust for the family relationships. Linear mixed models were used to compare PRS between AUD cases and controls, as well as in individuals with different counts of DSM-5 AUD diagnostic criterion in COGA full sample, FH+, FH?, and FH− subsamples. To evaluate the risk for AUD and AUD severity, generalized linear mixture models were fit by using the logit link function and the log link function for the status of AUD (yes or no) and DSM-5 AUD diagnostic criterion count (range 0–11), respectively. PRS were dichotomized to facilitate comparison with binary family history measures. As the prevalence of AUD ranges from 3.5% to 14.9% depending on sex and country (World Health Organization, 2018), we assumed an average prevalence of 10% and defined those top 10% of individuals with the highest PRS as the high PRS group and compared with the remaining 90% of individuals. For comparison purposes, we also performed analyses using the original continuous PRS scores (i.e., not dichotomized). For testing the associations between DSM-5 AUD diagnostic criterion count and PRS, continuous PRS scores were used. To test for interactions between PRS and family history, as well as whether PRS were still significant after accounting for family history, we also fit models which included PRS, family history, and their interactions. Sex and birth cohorts (a better predictor of AUD than age in COGA (Grucza et al., 2008, Lai et al., 2020)), and the first 10 principal components of population stratification were included as covariates in all analyses. Birth cohorts were defined based on birth year as follows: 1890–1929, 1930–1949, 1950–1969, 1970. As COGA samples were genotyped on different arrays, genotype array indicator was also included in all PRS analyses. There were two phenotypes (AUD and DSM-5 AUD diagnostic criterion count) and we tested four groups of samples (full sample, FH+, FH?, and FH−); therefore, we adjusted for multiple testing with the significance threshold defined as 0.05/8=6.25E-03 after Bonferroni correction. SAS9.4 (Cary, NC, USA) was used to perform all statistical analyses.

## RESULTS

Demographics of the COGA samples are summarized in Table 1. There were 3,451 cases who met criteria for DSM-IV alcohol dependence or DSM-5 AUD, and 1,616 alcohol-exposed controls (after exclusions for age and other drug dependence diagnoses); 7,203 participants had data on DSM-5 AUD diagnostic criterion count. Given the ascertainment

criteria for the COGA sample, more than half of the participants (N=4,842) had a positive family history of AUD (FH+) with more than half of those being AUD cases (N=2,531).

Average PRS in each group as well as separated by AUD cases and controls were summarized in Table 2. FH+ individuals had higher PRS than individuals in the FH? and FH– subsamples; and FH? had higher PRS than FH–. AUD cases had higher PRS than controls in all four groups of individuals and the differences were significant in the full sample, FH+, and FH? (P-values 1.85E-05) but not in FH– (P-value=0.31) subsamples. Table 3 shows the average PRS in individuals of different DSM-5 diagnostic criterion count. Overall, with the increase of DSM-5 AUD diagnostic criterion count, PRS increased. Again, all were significant (P-values 2.09E-06) except in FH– (P-value=0.89).

Having a first-degree family history of AUD was a significant indicator for AUD risk (OR=2.99, P-value=1.67E-13). PRS was also associated with AUD in the COGA full sample (OR=1.96, P-value=7.57E-08) and in the FH+ subsample (OR=1.86, P=value=1.32E-04) (Table 4). In FH?, while the continuous PRS was significantly associated with AUD (Beta=2.91, SE=0.60, P-value=1.51E-06), the dichotomized PRS (top decile vs remaining 90%) was not (P-value=0.06). Table 5 shows the association results between PRS and DSM-5 AUD diagnostic criterion count. Increasing PRS were significantly associated with greater DSM-5 AUD diagnostic criterion count (P-values 6.04E-16) except in FH– (P-value=0.05).

After adjusting for the first-degree family history, PRS were still significant (AUD: Beta=2.70, SE=0.44, P-value=6.83E-10; AUD diagnosis criterion count: Beta=1.04, SE=0.13, P-value=1.55E-15). The interactions between PRS and the first-degree family history were not significant for either AUD or AUD diagnosis criterion count (P-values=0.60 and 0.22, respectively).

## DISCUSSION

Family studies, twin studies and GWAS have all reiterated the heritability of AUD. For decades, a family history of AUD, which is associated with both genetic and environmental risk, has been used to assess AUD liability. However, accurate family history information may not be available for a variety of reasons. In this study of a large sample enriched for AUD risk, COGA, AUD cases in the full sample, as well as in the subsamples of family history positive (FH+) and family history unknown (FH?) individuals, cases had significantly higher PRS than controls, and individuals with higher DSM-5 AUD diagnostic criteria count had significantly higher PRS. Individuals having high PRS had greater odds of having AUD in the full sample and in the FH+ subsample. PRS were also significantly associated with AUD severity in the full sample, FH+, and FH? subsamples. In addition, PRS were still significant after adjusting for family history. Together, these comparisons demonstrated that family history of AUD assesses part of the genetic risk for AUD, and family history and PRS can be used together to assess the risk for AUD.

In the full sample, FH+, and FH? subsamples, AUD cases had significantly higher PRS than controls, as expected. The average PRS in AUD cases was higher than that in controls in

FH− subsample but not significant, most likely due to the small sample size. Regardless of AUD status, the FH+ subsample had higher PRS than the FH? and FH− subsamples (Table 2). In addition, FH+ (AUD cases and controls combined) had higher PRS than cases in the FH? sample (Table 2). These results also demonstrated that consideration of family history may be critical in the design of future GWAS of AUD. Family history of AUD can be used to help with the identification of potential AUD cases. For example, an individual may stop heavy drinking at early age due to other conditions such as alcohol liver diseases; but if that individual also has a positive family history of AUD, then they may be at elevated genetic risk for AUD and could potentially be used as proxy cases for AUD in GWAS studies. On the other hand, many family history positive individuals do not develop AUD but may be also at elevated genetic risk for AUD. Including these individuals as controls could reduce the statistical power when sample size is mall. Note in this study, we used the first-degree relatives to define the family history because many datasets may not have detailed family history information from distant relatives (Scheuner et al., 2006), and the data for first degree relatives are likely to be more accurate than those of distant relatives. We performed a sensitivity analysis using all relatives to define the family history, which increased the sample size and heterogeneity of FH+ and decreased the sample sizes and heterogeneity of FH? and FH−. All results were similar except that the difference of mean PRS between AUD cases and controls was not significant in FH? subsample, partially due to the dramatically reduced sample size (199 AUD cases and 135 controls).

Compared to PRS, the association between the first-degree family history and AUD was of a greater magnitude (although 95% CI overlapped). This is expected, because the first-degree family history reflects both genetic and shared environmental effects, while PRS estimates only a portion of the genetic component of risk (as captured by common variants). However, the ORs in full sample and FH+ subsample were 1.96 and 1.86, respectively, which are comparable to the estimated ORs of the first-degree family history based on U.S. national surveys (1.91–2.38) (Dawson et al., 1992, Karriker-Jaffe et al., 2021). Therefore, like family history, PRS could be used in evaluating AUD risk. In addition, by adjusting for PRS effects, important non-genetic factors related to AUD can be identified, and interactions between these factors and PRS can also be investigated. These non-genetic factors, combined with PRS, can further improve our ability to evaluate AUD risk. In our dichotomized PRS analysis, we used 10% as the cut-off to define high PRS individuals. For comparison purpose, we also used 5% as the cut-off and results were similar with much wider 95%CI due to the smaller numbers of individuals having high PRS.

This study found that both PRS and family history were effective in evaluating the risk of AUD and AUD severity, however, there were no significant interactions between them, as shown in a previous study (Johnson et al., 2019). In addition, PRS were still significant after adjusting for family history. All of these indicated that while family history includes at least some genetic component of AUD, PRS provided complementary information, and together they improve the ability to evaluate disease risk as having been demonstrated in previous studies (Abraham et al., 2019, Kachuri et al., 2020, Gronberg et al., 2015, Lu et al., 2018, Moll et al., 2020, Hujoel et al., 2021). As noted previously, early alcohol intervention programs with high risk individuals were effective in reducing the incidence of AUD (Kaner et al., 2007, Kaner et al., 2018, Knox et al., 2019, Welter et al., 2020, Solberg et al., 2008,

Whitlock et al., 2004, Cronce and Larimer, 2011, Bersamin et al., 2007), PRS and family history can lead to expedited risk identification, which in turn can guide best practices around these programs, making targeted and personalized prevention strategies possible.

This study has several limitations. First, COGA is a family cohort enriched with AUD cases; thus, our findings may not be widely generalizable. Second, our FH– subsample size was small, therefore, limited statistical power likely contributed to the null findings in that group. Third, we limited our analysis to European ancestry samples only, due to the small sample sizes and therefore limited power in both the discovery and target datasets, as well as complicated LD patterns in admixed populations such as African American and Hispanic populations. Fourth, we adjusted for sex and birth cohorts in our analysis but suspect that there are other important family and environmental factors not evaluated. Fifth, PRS-CS needs an external LD reference panel. Although it is relatively insensitive to the different LD structures between the external reference panel and experimental datasets used, these differences could still potentially cause problems (Ge et al., 2019). Lastly, the PRS we used was from a meta-analysis of MVP-AUD (Kranzler et al., 2019) and UKBB-AUDIT-P (Sanchez-Roige et al., 2019). As noted, these are from somewhat different although correlated phenotypes (Sanchez-Roige et al., 2019) and from different populations, which may reduce the performance of the PRS in our sample even we only kept the variants that have the same directions of effects.

In summary, our study found that PRS could be used to evaluate the risk for AUD and AUD severity. This can be especially useful when family history of AUD is not reported or unavailable. Future studies will aim to further improve the proportion of heritability explained by PRS and the extension to other ancestries. This hopefully would allow PRS, along with non-genetic factors, to more comprehensively characterize liability for AUD and AUD severity.

## ACKNOWLEDGMENTS

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**Table 1:**

Summary of sample for individuals from 1,162 families from the Collaborative Study on the Genetics of Alcoholism (COGA) data used in the current study.

|  | Total | # AUD cases | # controls | # with DSM-5 AUD diagnostic criterion count |
|---|---|---|---|---|
| Male | 3,762 | 2,041 | 422 | 3,400 |
| Female | 4,138 | 1,410 | 1,194 | 3,803 |
| Birth cohort1 | 325 | 82 | 173 | 307 |
| Birth cohort2 | 1,216 | 489 | 462 | 1,188 |
| Birth cohort3 | 2,869 | 1,617 | 515 | 2,804 |
| Birth cohort4 | 3,490 | 1,263 | 466 | 2,904 |
| FH+ | 4,842 | 2,531 | 669 | 4,639 |
| FH? | 2,722 | 850 | 840 | 2,280 |
| FH− | 336 | 72 | 107 | 284 |

**Note:** Alcohol Use Disorder (AUD) was defined as a lifetime diagnosis of DSM-IV alcohol dependence or DSM-5 alcohol use disorder; Controls were individuals aged 21 years or older who had consumed alcohol but did not meet criteria for alcohol or drug use disorders during their lifetimes.

**Table 2:**

Average polygenic risk score (PRS) and stratified by alcohol use disorder case status in full COGA sample as well as FH+, FH−, and FH? subsamples.

| Sample | All | | AUD cases | | Controls | | |
|---|---|---|---|---|---|---|---|
| | Mean PRS | SE | Mean PRS | SE | Mean PRS | SE | P-value |
| FH+ | 0.19 | 0.001 | 0.20 | 0.002 | 0.17 | 0.004 | **1.85E-05** |
| FH? | 0.17 | 0.002 | 0.18 | 0.003 | 0.16 | 0.003 | **6.94E-08** |
| FH− | 0.14 | 0.005 | 0.16 | 0.011 | 0.12 | 0.011 | 0.31 |
| Full sample | 0.18 | 0.001 | 0.19 | 0.002 | 0.16 | 0.002 | **1.96E-14** |

Note: P-values were calculated from linear mixed models to compare PRS between AUD cases and controls. Significant P-values (<6.25E-03) are in bold.

**Table 3:**

Average PRS in individuals stratified by the number of DSM-5 alcohol use disorder criteria endorsed during their lifetimes in the full COGA samples as well as the FH+, FH− and FH? subsamples.

| DSM-5 Criterion count | FH+ | | | FH? | | | FH− | | | Full sample | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | MEAN | SE | N | MEAN | SE | N | MEAN | SE | N | MEAN | SE |
| 0 | 999 | 0.17 | 0.003 | 924 | 0.16 | 0.003 | 139 | 0.13 | 0.009 | 2,062 | 0.16 | 0.002 |
| 1 | 627 | 0.18 | 0.004 | 337 | 0.16 | 0.005 | 39 | 0.15 | 0.016 | 1,003 | 0.17 | 0.003 |
| 2 | 504 | 0.18 | 0.004 | 226 | 0.16 | 0.006 | 34 | 0.16 | 0.016 | 764 | 0.17 | 0.003 |
| 3 | 452 | 0.18 | 0.005 | 181 | 0.17 | 0.007 | 19 | 0.12 | 0.024 | 652 | 0.18 | 0.004 |
| 4 | 351 | 0.19 | 0.005 | 121 | 0.19 | 0.009 | 10 | 0.15 | 0.024 | 482 | 0.19 | 0.004 |
| 5 | 273 | 0.19 | 0.006 | 79 | 0.18 | 0.011 | 10 | 0.16 | 0.030 | 362 | 0.19 | 0.005 |
| 6 | 221 | 0.19 | 0.007 | 79 | 0.18 | 0.009 | 6 | 0.17 | 0.022 | 306 | 0.19 | 0.005 |
| 7 | 182 | 0.20 | 0.008 | 56 | 0.20 | 0.013 | 3 | 0.20 | 0.048 | 241 | 0.20 | 0.007 |
| 8 | 171 | 0.20 | 0.007 | 46 | 0.18 | 0.016 | 5 | 0.16 | 0.047 | 222 | 0.20 | 0.007 |
| 9 | 180 | 0.20 | 0.007 | 63 | 0.18 | 0.012 | 4 | 0.22 | 0.069 | 247 | 0.20 | 0.006 |
| 10 | 234 | 0.21 | 0.007 | 71 | 0.21 | 0.010 | 7 | 0.15 | 0.035 | 312 | 0.21 | 0.006 |
| 11 | 445 | 0.22 | 0.005 | 97 | 0.21 | 0.010 | 8 | 0.18 | 0.035 | 550 | 0.21 | 0.004 |
| P-value | **2.09E-06** | | | **1.59E-08** | | | 0.89 | | | **2.75E-24** | | |

Note: P-values were calculated from linear mixed models. Significant P-values (<6.25E-03) are in bold.

**Table 4:**

Associations between PRS (both continuous and dichotomized (top 10% vs. 90%)) and AUD; also shown is the association between the first-degree family history and AUD.

| sample | Testing variable | Dichotomized PRS | | | Continuous PRS | | |
|---|---|---|---|---|---|---|---|
| | | OR | 95%CI | P-value | beta | SE | P-value |
| having FH information | FH* | 2.99 | 2.23–4.00 | **1.67E-13** | NA | NA | NA |
| FH+ | PRS | 1.86 | 1.35–2.56 | **1.32E-04** | **2.43** | **0.47** | **2.93E-07** |
| FH? | PRS | 1.50 | 0.98–2.29 | 0.06 | **2.91** | **0.60** | **1.51E-06** |
| FH– | PRS | 0.45 | 0.12–1.69 | 0.23 | 2.64 | 1.87 | 0.16 |
| Full sample | PRS | 1.96 | 1.54–2.51 | **7.57E-08** | **3.17** | **0.38** | **2.66E-16** |

Note:

*:
first-degree family history. P-values were calculated from generalized linear mixed models with the logit link function. Significant P-values (<6.25E-03) are in bold.

**Table 5:**

Associations between continuously distributed PRS and DSM-5 AUD criterion count, also shown is the association between the first-degree family history and AUD criterion count.

| samples (N) | Testing variable | beta | SE | P-value |
|---|---|---|---|---|
| having FH information | FH* | 0.25 | 0.06 | **6.04E-06** |
| FH+ | PRS | 0.81 | 0.12 | **4.34E-11** |
| FH? | PRS | 1.65 | 0.25 | **6.70E-11** |
| FH– | PRS | 1.47 | 0.76 | 0.05 |
| Full sample | PRS | 1.35 | 0.13 | **1.68E-26** |

Note:

*: first-degree family history. P-values were calculated from generalized linear mixed models with the log link function. Significant P-values (<6.25E-03) are in bold.