

1 **Trans-ancestral GWAS of alcohol dependence reveals common genetic**
2 **underpinnings with psychiatric disorders**

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- 177
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179 use, pleiotropy

180 **ABSTRACT**

181 Liability to alcohol dependence (AD) is heritable, but little is known about its complex
182 polygenic architecture or its genetic relationship with other disorders. To discover loci
183 associated with AD and characterize the relationship between AD and other psychiatric
184 and behavioral outcomes, we carried out the largest GWAS to date of DSM-IV
185 diagnosed AD. Genome-wide data on 14,904 individuals with AD and 37,944 controls
186 from 28 case/control and family-based studies were meta-analyzed, stratified by genetic
187 ancestry (European, N = 46,568; African; N = 6,280). Independent, genome-wide
188 significant effects of different *ADH1B* variants were identified in European (rs1229984; p
189 = 9.8E-13) and African ancestries (rs2066702; p = 2.2E-9). Significant genetic
190 correlations were observed with schizophrenia, ADHD, depression, and use of
191 cigarettes and cannabis. There was only modest genetic correlation with alcohol
192 consumption and inconsistent associations with problem drinking. The genetic
193 underpinnings of AD only partially overlap with those for alcohol consumption,
194 underscoring the genetic distinction between pathological and non-pathological drinking
195 behaviors.

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209 INTRODUCTION

210 Excessive alcohol use is a leading contributor to morbidity and mortality. One in 20
211 deaths worldwide is attributable to alcohol consumption, as is 5.1% of the global burden
212 of disease¹. Alcohol dependence (AD), as defined by the Fourth Edition of the American
213 Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-
214 IV)², is a serious psychiatric disorder characterized by tolerance, withdrawal, loss of
215 control over drinking and excessive alcohol consumption despite negative health and
216 social consequences. Among alcohol drinkers, 12% meet criteria for DSM-IV AD during
217 their lifetimes³. In the United States, only 25% of those with AD ever receive
218 treatment^{4,5}.

219

220 AD is moderately heritable (49% by a recent meta-analysis)⁶ and numerous genome-
221 wide association studies (GWAS) have aimed to identify loci contributing to this genetic
222 variance (see⁷ for a review). According to one study, common SNPs are responsible for
223 as much as 30% of the variance in AD⁸, but few have been identified to date. Variants in
224 the genes responsible for alcohol metabolism^{9–19} (*ADH1B* and, to a lesser extent,
225 *ADH1C* and others^{20–22}, e.g., *ADH4*) have been strongly implicated, initially in East-
226 Asians^{9,11,12} and more recently in people of European origin (EU) and in African-
227 Americans (AAs)^{13–15}. The association between AD (and related problem drinking
228 phenotypes) and rs1229984, a missense SNP (Arg48His) in *ADH1B* that affects the
229 conversion of alcohol to acetaldehyde, represents one of the largest common-variant
230 effect sizes observed in psychiatry, with the His48 allele accelerating ethanol
231 metabolism and affording approximately 3-fold reduction in likelihood of AD across
232 numerous studies (e.g.,^{14,23,24}). Another functional polymorphism, rs671 in *ALDH2*
233 (Glu504Lys), strongly affects alcohol metabolism by blocking conversion of
234 acetaldehyde to acetate, but is rare except in some Asian populations^{9–11,17,18}. *ADH1B*

235 and *ALDH2* polymorphisms, however, only explain a small proportion of the heritable
236 variation in AD in populations of European ancestry.

237

238 In this study, we compiled the largest numbers of carefully diagnosed alcohol
239 dependent individuals and alcohol-exposed controls to date, from both case-control and
240 family studies. These included substantial numbers of both European ancestry (EU, N =
241 46,568, including 38,686 unrelated individuals) and African-American ancestry (AA, N =
242 6,280, including 5,799 unrelated individuals) subjects. Each study was subjected to
243 stringent quality control (QC) before conducting GWAS within each population of each
244 study, followed by a genome-wide meta-analysis. We estimated the heritability (SNP- h^2)
245 of AD and examine the extent to which aggregate genetic variation in AD is related to
246 traits from 42 other GWAS, including continuous measures of alcohol consumption.

247

248 **METHODS**

249

250 *Samples:* We collected individual genotypic data from 14 case/control studies and 9
251 family-based studies and summary statistics from GWAS of AD from 5 additional
252 cohorts (**Table 1**; see **Supplementary Information** for cohort descriptions). AD was
253 defined as meeting criteria for a DSM-IV (or DSM-III-R in one instance) diagnosis of AD.
254 Excepting three cohorts with population-based controls (N=7,015), all controls were
255 screened for AD. Individuals with no history of drinking alcohol and those meeting
256 criteria for DSM-IV alcohol abuse were additionally excluded as controls where
257 applicable (**Supplementary Information**).

258

259 *Quality control and imputation:* Data for the genotyped cohorts that shared raw data
260 were deposited to a secure server for uniform quality control (QC). QC and imputation
261 of the 14 case/control studies was performed using the ricopili pipeline
262 (<https://github.com/Nealelab/ricopili>). For 9 family-based cohorts, an equivalent pipeline,

263 picopili (<https://github.com/Nealelab/picopili>), was developed for QC, imputation, and
264 analysis appropriate for diverse family structures, including twins, sibships and
265 extended pedigrees (**Supplementary Information**).

266

267 After initial sample and variant QC, principal components analysis (PCA) was used to
268 identify population outliers for exclusion and to stratify samples in each study by
269 continental ancestry. Identified EU and AA ancestry populations were confirmed by PCA
270 with the 1000 Genomes reference panel²⁵. Final sample and variant QC, including filters
271 for call rate, heterozygosity, and departure from Hardy-Weinberg equilibrium (HWE),
272 was then performed within each ancestry group in each cohort (see **Supplementary**
273 **Information**). Samples were also filtered for cryptic relatedness within and between
274 cohorts and for departures from reported pedigree structures.

275

276 Each cohort was imputed using SHAPEIT²⁶ and IMPUTE2²⁷, using the cosmopolitan (all
277 ancestries) 1000 Genomes reference panel. Consistency of minor allele frequencies
278 (MAF) with the reference panel was verified prior to imputation, with SNPs in EU
279 cohorts compared to MAF in European population samples and AA cohorts compared
280 to MAF in African population samples. Imputed SNPs were then filtered for INFO score
281 > 0.8 and allele frequency > 0.01 prior to analysis.

282

283 *Association Analysis:* A GWAS for AD status was performed within each ancestry
284 stratum of each sample using an association model appropriate for the study design
285 (**Table 1**). For case/control studies, GWAS was performed using logistic regression with
286 imputed dosages. For family-based studies of small, simple pedigrees (e.g., sibships),
287 association with imputed genotypes was tested using generalized estimating equations
288 (GEE). For more complex pedigrees, imputed genotypes were tested using logistic
289 mixed models. Sex was included as a covariate, along with principal components to
290 control for population structure (**Supplementary Information**). Details of the analytic

291 model, software used, effective N, number of SNPs and principal components are
292 presented for each sample in Supplementary **Table S1**.

293

294 In addition to this primary analysis, subsets of genetically unrelated individuals were
295 selected from each family-based cohort (i.e. taking one individual per family) and used
296 to perform a conventional case/control GWAS using logistic regression. This was used
297 in place of the family-based GWAS for estimation of effect sizes and inclusion in
298 estimation of SNP- h^2 and genetic correlations (r_g) using LD score regression analyses.

299

300 *Meta-analysis:* The primary discovery meta-analysis of all ancestry-stratified GWAS
301 ($N_{\text{case}} = 14,904$; $N_{\text{control}} = 37,994$) was conducted in METAL²⁸. As the different study
302 designs (family vs. case-control) produced effect sizes that were not comparable,
303 results were combined using weighting by effective sample size (see **Supplementary**
304 **Information**). Separate ancestry-specific discovery meta-analyses of EU ($N = 46,568$)
305 and AA ($N = 6,280$) cohorts, respectively, were also performed. Heterogeneity was
306 evaluated across all cohorts and between study design subsets (**Supplementary**
307 **Information**). Power analysis was performed using CaTS²⁹ with the estimated effective
308 sample size.

309

310 In addition to the discovery meta-analyses, we conducted meta-analyses for two design
311 subsets. First, we performed sample size weighted meta-analysis of the subset of
312 genetically unrelated individuals in EU ($N = 38,686$) and AA ($N = 5,799$) cohorts for use
313 in LD score regression (LDSR) analysis. Second, we performed inverse-variance
314 weighted meta-analysis of genetically unrelated individuals in genotyped cohorts to
315 estimate within-ancestry effect sizes for EU ($N = 28,757$) and AA ($N = 5,799$). These
316 effect sizes were then used to compare trans-ancestral fine mapping results using
317 inverse-variance weighted fixed effects, random effects³⁰, and Bayesian³¹ models

318 **(Supplementary Information)**. Supplementary **Table S2** provides an overview of the
319 various meta-analytic models that were fitted to data.

320

321 *Heritability and Genetic Correlation Analysis:* LDSR analysis³² was performed to
322 estimate the heritability explained by common SNPs in meta-analyses of unrelated EU
323 and AA samples, respectively. LDSR was performed using HapMap3 SNPs and LD
324 scores computed from 1000 Genomes reference samples corresponding to each
325 population (Supplementary Information). Conversion of h^2_g estimates from observed to
326 liability scale was performed assuming population prevalences of 0.159 and 0.111 for
327 AD in alcohol-exposed EU and AA individuals, respectively³.

328

329 Genetic correlation between AD and 42 traits from LD Hub³³ and other published
330 studies^{34–44} was examined with the same unrelated EU meta-analysis (10,206 cases
331 and 28,480 controls) and precomputed European LD scores using LDSR. To avoid
332 increasing the multiple testing burden, redundant or highly-correlated phenotypes were
333 reduced by manually selecting the version of the phenotype with the greatest predicted
334 relevance to AD, largest sample size, or highest heritability (**Supplementary**
335 **Information**).

336

337 *Replication:* As described below, a locus on chromosome 3 was genome-wide
338 significant (GWS) in the trans-ancestral discovery meta-analysis. The minor allele,
339 associated with lower AD risk in our analysis, had low frequency in all EU samples
340 except the Finnish cohorts; it was also higher in AAs. To seek replication, we examined
341 the association between this locus and DSM-IV AD in two independent AA samples
342 (Yale-Penn 2, n = 911 cases and 599 controls, and COGA AAfGWAS, n = 880 cases
343 and 1,814 controls; Supplementary Information) using GEE (Yale-Penn) and Genome-
344 Wide Association/Interaction Analysis and Rare Variant Analysis with Family Data
345 (GWAF; in COGA) respectively. Association with AD status, broadly defined using

346 hospital and death records, was also examined in the FINRISK cohort (1,232 cases and
347 22,614 controls) using Firth logistic regression⁴⁵.

348

349 RESULTS

350

351 **GWAS meta-analyses:** In both the EU and AA analyses, GWS loci ($p < 5E-8$) were
352 identified in the ADH gene cluster on chromosome 4 (**Figure 1** for Manhattan plot;
353 **Table 2** for top loci; Supplementary **Figure S1** for QQ plot for discovery GWAS showing
354 polygenic signal). Examining individual populations, rs1229984 in *ADH1B* was the
355 strongest associated signal from the analysis in EU ($p = 9.8E-13$), while rs2066702, also
356 in *ADH1B*, was the most significant variant in AA ($p = 2.2E-9$; **Figure 2** shows the
357 regional association plots for the *ADH1B* locus for the discovery, EU, AA and trans-
358 ancestral meta-analysis). Clumping for linkage disequilibrium (LD; $r^2 < .1$ within 500kb)
359 suggested multiple independent signals within this locus in both populations (**Table 2**),
360 with differing leading alleles reflecting different LD structures and allele frequencies in
361 each population (Supplementary **Figure S2A** and **S2B** show LD patterns in the ADH
362 locus, including *ADH1B*, in AA and EU respectively). Conditional analysis controlling for
363 rs2066702 (Supplementary **Figure S3** for results in AA) and rs1229984 (Supplementary
364 **Figure S4** for results in EU) was inconclusive due to limited power, but was tentatively
365 consistent with the existence of additional independent effects in the region
366 (Supplementary **Table S3** shows marginal and conditional effect sizes for genome-wide
367 significant SNPs in the *ADH1B* locus). The most promising support for an independent
368 signal arises from rs894368 (marginal odds ratio = 0.887, $p = 6.9E-7$; conditional odds
369 ratio = 0.890, $p = 6.8E-6$; Supplementary Information). Results from the trans-ancestral
370 meta-analysis reinforced the robust effects of rs1229984 and other *ADH1B* SNPs on
371 liability to AD (regional association plot for rs1229984 in Supplementary **Figure S5A**
372 (inverse-variance weighted), **S5B** (modified random-effects) and **S5C** (Bayesian))
373 across various analytic models.

374

375 We also verified whether variants affecting *ADH1B* expression (eQTLs) were associated
376 with AD. Considering GTEx data V7 (available at <https://www.gtexportal.org/>), 263
377 variants were reported to affect *ADH1B* expression in different human tissues (FDR
378 $q < 0.05$). After LD-informed clumping and the exclusion of variants in LD with the GWS
379 coding alleles (i.e., rs1229984 and rs2066702), three variants (i.e., rs11939328,
380 rs10516440, rs7664780) were considered with respect to their association with AD.
381 SNP rs10516440 showed a genome-wide significant association with AD with
382 contribution from both AA and EU analyses (trans-ancestry $p = 4.72E-8$; EU $p = 3.97E-$
383 6 ; AA $p = 1.97E-3$). In line with the effect of the coding variants where the protective
384 allele is associated with increased *ADH1B* enzymatic activity, the rs10516440*A allele
385 was associated with reduced AD risk and increased *ADH1B* expression, which was
386 consistent across multiple tissues (multi-tissue $p = 1.42E-76$).

387

388 A novel locus on chromosome 3, rs7644567, also achieved GWS in the meta-analysis
389 ($p = 3.03E-8$; Supplementary **Figure S6** for regional association plot), primarily
390 attributable to contributions from the AA samples ($p = 6.64E-6$) with the major, A, allele
391 being associated with AD risk liability. The G allele has an MAF = 0.29 in AA, but
392 MAF < 0.01 in most EU samples, except in FinnTwin (MAF = .032) and NAG-Fin (MAF =
393 0.054). In AA, rs7644567 does not appear to be in high LD with other variants
394 (Supplementary **Figure S6**) and did not replicate in two independent AA samples. In the
395 independent FINRISK cohort (MAF = .045), there was modest evidence for association
396 ($p = 0.019$), but with risk associated with the minor G allele (**Supplementary Table S4**
397 for results in each replication sample).

398

399 Overall, there was limited evidence for heterogeneity across all cohorts, within ancestry,
400 between ancestries, or between study designs within ancestry (**Supplementary**
401 **Information**; Supplementary **Figure S7-S13**). Gene-level association testing with

402 MAGMA⁴⁶ did not identify any additional genes in EU or AA (Supplementary **Table S5**
403 for top 20 genes in EU and AA).

404

405 **Heritability and genetic correlations:** LD score based liability-scale SNP-heritability of
406 AD was estimated at $h^2_g = 0.090$ (SE = 0.019, $p = 8.02E-7$) in the meta-analysis of
407 unrelated EU samples. Exclusion of the *ADH1B* locus did not substantially modify this
408 estimate ($h^2_g = 0.089$, SE = 0.0185). Nominally significant heritability from common
409 variants was also estimated for the meta-analysis of unrelated AA individuals based on
410 LDSR with scores computed from 1000 Genomes African populations ($p = .017$), but the
411 quantitative estimate of h^2_g was unstable depending on the choice of reference panel,
412 reflecting the challenge of correctly specifying LDSR and robustly modelling LD for the
413 admixed AA population (**Supplementary Information**).

414

415 Significant genetic correlation with AD in EU was observed for 16 traits (significant
416 genetic correlations in **Figure 3**; all genetic correlations in Supplementary **Table S6**),
417 after correction for multiple testing ($p = 1.19E-3$ for 42 traits). The largest positive
418 correlations were with ever smoking tobacco ($r_g = .708$, $p = 1.3E-7$) and lifetime
419 cannabis use ($r_g = .793$, $p = 2.5E-4$), and with other psychiatric disorders and traits,
420 especially schizophrenia ($r_g = 0.357$, $p = 3.2E-11$), ADHD ($r_g = .444$, $p = 4.2E-6$), and
421 depressive symptoms ($r_g = .603$, $p = 2.6E-7$). Educational attainment ($r_g = -0.424$, $p =$
422 $6.8E-9$) and age at first birth (higher values indicate that subjects were older when they
423 had their first child, $r_g = -0.63$, $p = 2.0E-9$) showed significant inverse genetic correlation
424 with AD suggesting that liability to AD risk was genetically related to lower educational
425 attainment and lower age at which one had their first child.

426

427 Unexpected patterns of genetic correlation were observed when comparisons were
428 made to other alcohol-related measures. AD was genetically correlated with alcohol
429 consumption in a meta-analysis of the Alcohol Genome-wide Association (AlcGen) and

430 Cohorts for Aging and Research in Genomic Epidemiology Plus (CHARGE+)
431 consortia³⁶ ($rg = .695$, $p = 6.9E-6$) but only modestly with alcohol consumption from the
432 recent large UK Biobank analysis³⁷ ($rg = 0.371$, $p = 5.2E-5$). Liability to AD was not
433 correlated with genome-wide SNPs from a recent GWAS of the Alcohol Use Disorders
434 Identification Test (AUDIT) in 23andMe³⁸ ($rg = 0.076$, $p = 0.65$), perhaps due to the low
435 levels of drinking observed in this population³⁸. Additional analysis indicates AD is
436 genetically correlated with GWAS of delay discounting in the 23andMe sample⁴² ($rg =$
437 0.478 , $p = 6.0E-3$), suggesting behavioral phenotypes in the cohort are still informative
438 to AD.

439

440 **Associations with other GWS loci:** We examined results for the eight independent
441 variants associated at GWS levels with alcohol consumption in the UK Biobank³⁷
442 (**Supplementary Table S7**). Among the UK Biobank findings, three of the four reported
443 variants in the ADH region of chromosome 4 (rs145452708 – a proxy for rs1229984,
444 rs29001570 and rs35081954) were associated in the present study with AD (p ranging
445 from $3.5E-5$ – $2.3E-10$) with sign concordant effects; the remaining variant was
446 excluded from our analysis due to $MAF < 0.01$. The UK Biobank lead variant in *KLB*,
447 rs11940694, was nominally associated with AD ($p = .0097$), though this does not
448 surpass multiple testing correction for the eight GWS alcohol consumption loci. We see
449 little evidence ($p > 0.2$) for association of AD with the reported loci at *GCKR* and
450 *CADM2*, which may be due to differences in power for the given effect size or because
451 these genes exert an influence on liability to consume alcohol but not later problems.
452 The locus on chromosome 18 showed limited regional association with AD, but the
453 index variant was not present in our analysis because it no longer appears in the 1000
454 Genomes Phase 3 reference panel²⁵.

455

456 **Power analysis:** Only 3 additional loci reach $p < 1E-6$ (**Table 2**). Power analyses
457 indicated that the current meta-analysis is expected to have at least 63% power to
458 detect very common variants ($MAF \geq 0.25$) with odds ratios ≥ 1.10 at $p < 1E-6$ (41% for

459 $p < 5E-8$; **Supplementary Figure S14** for power analysis curves). Power is lower for
460 less common variants ($MAF \geq .05$) even with odds ratios ≥ 1.20 at $p < 1E-6$ (60% power)
461 and $p < 5E-8$ (38% power).

462

463 **DISCUSSION**

464

465 To our knowledge, this is the largest GWAS of rigorously-defined AD. We identified loci
466 in *ADH1B* that differed between EU and AA, as well as novel genetic correlations
467 between AD and psychiatric disorders (e.g., schizophrenia), tobacco and cannabis use,
468 and behavioral outcomes (e.g., educational attainment). Analyses also revealed a
469 genetic distinction between GWAS results for alcohol consumption and AD. Although
470 larger sample sizes can be amassed by focusing on quantitative measures of
471 consumption, only the upper tail is relevant to AD (as a medical diagnosis) and even
472 that does not capture other aspects of disordered drinking (e.g., loss of control,
473 withdrawal) directly. Conversely, cases derived from electronic medical records (e.g.,
474 ICD codes) may result in a high rate of false negatives, while self-screening instruments
475 (e.g. AUDIT scores) is best suited to analyses of disordered drinking when a sufficiently
476 high threshold or score cut-off is applied to pinpoint severity. Our study has the
477 advantage of greater diagnostic precision via use of semi-structured interviews to
478 diagnose AD systematically in a majority of the constituent studies.

479

480 The genome-wide significant SNPs reaffirm the importance of functional variants
481 affecting alcohol metabolism to the risk of AD. The top association in *ADH1B*,
482 rs1229984, is a missense variant that is amongst the most widely studied in relation to
483 alcohol use, misuse and dependence. The resulting amino acid substitution (Arg48His)
484 increases the rate at which ADH1B oxidizes ethanol to acetaldehyde^{10,11}. Early studies
485 on Asian populations in which the derived allele is common demonstrated strong
486 protection against the development of AD⁹⁻¹¹. In EUs and AAs, the protective allele is

487 present at much lower frequencies (EU MAF = 3-4%, AA MAF < 1%), but recent large-
488 scale studies have shown an association between this locus and alcohol consumption
489 and problems at GWS levels in EU with similar effect size^{14,15}. The lead variant in AA
490 cohorts, rs2066702 (Arg370Cys), is another functional missense variant in *ADH1B*, and
491 it, similarly, encodes an enzyme with an increased rate of ethanol oxidation^{10,11}. The
492 allele encoding Cys370 is common among AAs, but rare in other populations¹⁰. Our
493 results clearly show that these two different functional SNPs in *ADH1B* both affect risk
494 for alcoholism, with their relative importance dependent upon allele frequency in the
495 population studied. Larger future studies will be needed to evaluate the evidence for
496 additional independent effects in the chromosome 4 locus.

497

498 The only other locus to reach significance was rs7644567 on chromosome 3, primarily
499 driven by AA cohorts due to the variant's very low MAF in EU. This locus did not
500 replicate in independent African or Finnish ancestry samples. We note that the
501 conventional genome-wide significance threshold is derived for European ancestry
502 samples, and thus is likely to be too lenient in GWAS of African-ancestry cohorts due to
503 higher genetic diversity and corresponding increase in the effective number of
504 independent tests in the GWAS^{47,48}. As an illustration, in 4 samples from the current
505 study that included both EU and AA participants, the number of independent SNPs
506 identified upon LD pruning was 1.7- to 2.3-fold greater in AA than EU subjects. Much
507 larger studies in AA and other non-EU populations will clearly be important to elucidate
508 additional loci.

509

510 Despite limited SNP-level findings, there is significant evidence for polygenic effects of
511 common variants in both EU and AA cohorts. The estimated $h^2_g = .09$ for AD in EU is
512 only modestly lower than those recently reported for alcohol consumption ($h^2_g = .13$)³⁷
513 and AUDIT scores ($h^2_g = .12$)³⁸, and comparable to estimates derived for cigarettes-per-
514 day³³. Our h^2_g estimate is lower than a prior report⁸, likely reflecting a combination of
515 differences in estimation method and greater heterogeneity in ascertainment strategy

516 across samples in the current study. The latter is especially relevant given that we
517 incorporated population-based cohorts with a wide range of ages at ascertainment and
518 cultural environments, as well as cohorts enriched for other substance use disorders.

519

520 Comparing our GWAS to recent GWAS of alcohol consumption measures suggests that
521 the liability underlying normative patterns of alcohol intake and AD are only partially
522 overlapping. Genome-wide, we observe only modest genetic correlation (significantly <
523 1) with log-scaled alcohol consumption by participants in AlcGen and CHARGE+
524 Consortia cohorts³⁶ ($r_g = .695$) and in the UK Biobank³⁷ ($r_g = .371$), and no significant
525 correlation with GWAS of log-scaled AUDIT scores in 23andMe participants³⁸ ($r_g =$
526 $.076$). We also observe only partial replication of the 8 loci significantly associated with
527 consumption in the UK Biobank. One key factor in interpreting the differences between
528 these traits and AD is that the distribution of consumption levels and AUDIT scores can
529 be highly skewed in population samples, with most individuals at the low
530 (nonpathological) end of the spectrum. This effect may be especially pronounced
531 among the older, healthy volunteers of the UK Biobank cohort⁴⁹ and the 23andMe
532 cohort, which is more educated and has higher socioeconomic status than the general
533 US population³⁸. We hypothesize that the variants that affect consumption at lower
534 levels may differ substantively from those that affect very high levels of consumption in
535 alcohol dependent individuals, who are also characterized by loss of control over
536 intake⁵⁰. This appears to be the case in one prior study that used specific cut-offs to
537 harmonize AUDIT scores with AD data and noted significant concordance in SNP- h^2
538 estimates⁵¹ – according to that study, the optimal cutoffs for their sample were ≥ 6 and
539 ≥ 9 for women and men respectively. However, there is a need for a further detailed
540 characterization of how AUDIT cut-offs may be applied to maximize concordance with
541 genetic liability to AD diagnosis risk. The strongly negative genetic correlation between
542 educational attainment and AD, in contrast to positive genetic correlations of education
543 with consumption and AUDIT scores, further underscore this distinction between

544 normative/habitual levels of alcohol intake and diagnosed AD, at least in the respective
545 populations studied.

546

547 The current analysis also identified robust genetic correlation of AD with a broad variety
548 of psychiatric outcomes. This correlation is strongest for aspects of negative mood,
549 including neuroticism and major depressive disorder, as also seen in twin studies^{52,53}
550 and through recent specific molecular evidence for pleiotropy^{54,55}. Taken together with
551 evidence from other recent genomic studies⁵⁴, and null correlations for other GWAS of
552 alcohol consumption, these findings suggest that major depression may only share
553 genetic liability with alcohol use at pathological levels.

554

555 AD was also negatively genetically correlated with AFB, which is an indicator of
556 reproductive tempo and correlated with age at first consensual sexual intercourse⁵⁶.
557 This is consistent with evidence of common genetic liability to early, risky behaviors
558 underlying AD and AFB⁵⁷. Nominally significant genetic correlation with delay
559 discounting (i.e. favoring immediate rewards) and the strong genetic correlation of AD
560 with ADHD, cigarette smoking and cannabis use may similarly reflect a shared genetic
561 factor for risk-taking and reduced impulse control.

562

563 Lower genetic correlations were observed for most biomedical and anthropometric
564 outcomes. Liver enzymes GGT and ALT, once proposed as possible biomarkers for
565 alcohol abuse⁵⁸, showed, as expected, nominal evidence for genetic correlation with AD
566 but neither survived multiple testing correction. Notably, we did not find any association
567 between AD and body-mass index (BMI). Negative genetic correlations with BMI were
568 previously reported for both alcohol consumption³⁷ and AUDIT scores³⁸, but there is
569 prior evidence that BMI has differing underlying genetic architecture in the context of AD
570 and outside of that context⁵⁹. The negative genetic correlations observed in those
571 studies are consistent with studies of light to moderate drinking, which is also

572 associated with healthier lifestyle behaviors, while heavy and problematic drinking is
573 typically associated with weight gain⁶⁰.

574

575 This study benefits from precision in diagnostic assessment of AD, known alcohol
576 exposure in a majority of the controls, and careful quality control that excluded overlaps
577 of individuals between studies while combining case-control and twin/family-based
578 study designs. Despite these strengths our sample size was insufficient to identify
579 additional GWS loci robustly. Power analyses indicate that additional SNPs associated
580 with AD are likely to have small effect sizes, consistent with other psychiatric disorders
581 (e.g. depression⁶¹). This supports the pressing need for collection of large numbers of
582 well characterized cases and controls. The differences between our results and the
583 study of AUDIT scores³⁸, however, highlight that ascertainment and trait definition must
584 also be taken into account. Careful study of how screening tools, such as the AUDIT,
585 correlate to genetic liability to AD (as defined by DSM-IV or similar) could substantially
586 boost sample sizes for future AD GWAS. There is also a continued need to characterize
587 the genetic architecture of AD in non-EU populations.

588

589 We show a novel genetic distinction between drinking in the pathological range (AD)
590 and habitual drinking that does not cross the threshold into pathology or dependence.
591 Larger future samples will allow us to uncover additional pleiotropy between
592 pathological and non-pathological alcohol use as well as between AD and other
593 neuropsychiatric disorders.

594

595

596

597

598

Table 1: Descriptive statistics for cohorts in the meta-analysis of AD.

Dataset	PMID	Male (%)	Ages (years)	European (EU)				African - American (AA)			
				N Total		N Unrelated		N Total		N Unrelated	
				Case	Control	Case	Control	Case	Control	Case	Control
Case-control: Logistic Regression											
Comorbidity and Trauma Study (CATS)	23303482	56%	18-67	572	817	572	817	--	--	--	--
Christchurch Health and Development Study (CHDS)	23255320	48%	16-30	112	500	112	500	--	--	--	--
Collaborative Study of the Genetics of Alcoholism - case-control cohort (COGA-cc)	20201924	54%	18-79	583	363	583	363	--	--	--	--
Family Study of Cocaine Dependence (FSCD)	18243582	51%	18-60	266	174	266	174	255	241	255	241
German Study of the Genetics of Alcoholism (GESGA)	19581569	65%	18-84	1314	2142	1314	2142	--	--	--	--
Gene-Environment Development Initiative - Great Smoky Mountains Study (GEDI-GSMS)	8956679	57%	9-26	42	565	42	565	--	--	--	--
Center on Antisocial Drug Dependence (CADD)	25637581	70%	13-20	400	577	400	577	51	51	51	51
Phenomics and Genomics Sample (PAGES)	28371232	57%	18-74	37	523	37	523	--	--	--	--
Collaborative Study on the Genetics of Nicotine Dependence (COGEND Nico)	17158188	34%	25-82	135	272	135	272	46	232	46	232
COGEND - Study of Addiction: Genetics and Environment (COGEND SAGE)	20202923	37%	18-77	311	225	311	225	104	103	104	103
Spit For Science	24639683	36%	>18	252	1863	252	1863	74	841	74	841
National Institute on Alcohol Abuse and Alcoholism Intramural (NIAAA)	n/a	67%	>18	442	206	442	206	404	110	404	110
Mayo Clinic Center for the Individual Treatment of Alcohol Dependence (CITA)	25290263	55%	≥18	378	646	378	646	--	--	--	--
Alcohol Dependence in African Americans (ADAA)	n/a	57%	18-69	--	--	--	--	794	297	794	297
Family-based, twins and sibs: GEE											
Brisbane Longitudinal Twin Study (BLTS)	23187020	43%	18-30	60	938	51	546	--	--	--	--
GEDI - Virginia Twin Study on Adolescent Behavioral Development (GEDI-VTSABD)	9294370	38%	8-32	209	503	188	318	--	--	--	--
Minnesota Center for Twin and Family Research (MCTFR)	23942779	41%	16-21	609	2100	553	1274	--	--	--	--
Center for Education and Drug Abuse Research (CEDAR)	21514569	63%	16-34	59	200	54	152	--	--	--	--
Swedish Twin Registry (STR)	23137839	47%	40-83	76	8311	76	6112	--	--	--	--
Yale-Penn	24166409	58%	16-79	1094	301	1004	252	--	--	--	--
Family-based, large/complex pedigrees: Logistic Mixed Model											
Collaborative Study of the Genetics of Alcoholism - family cohort (COGA-fam)	23089632	45%	12-88	605	682	168	138	--	--	--	--
Australian Alcohol and Nicotine Studies (OZ-ALC-NAG)	21529783	45%	18-82	1571	3069	1111	805	--	--	--	--
Irish Affected Sib Pair Study of Alcohol Dependence (IASPSAD)	15770118	50%	17-84	721	1814	436	1802	--	--	--	--
Yale-Penn	24166409	51%	16-79	--	--	--	--	1607	1070	1263	933
Summary statistics											
Netherlands Study of Depression and Anxiety / Netherlands Twin Registry (NESDA/NTR)	18197199	31%	>18	390	1633	390	1633	--	--	--	--
Finnish Nicotine Addiction Genetics Project (NAG-Fin)	17436240	52%	30-92	439	1137	439	1137	--	--	--	--
FinnTwin12 (FT12)	17254406	47%	20-27	88	874	88	874	--	--	--	--
National Longitudinal Study of Adolescent to Adult Health (Add Health)	25378290	47%	24-34	768	2981	768	2981	--	--	--	--
Helsinki Birth Cohort Study (HBCS)	16251536	43%	56-70	36	1583	36	1583	--	--	--	--
Total				11569	34999	10206	28480	3335	2945	2991	2808

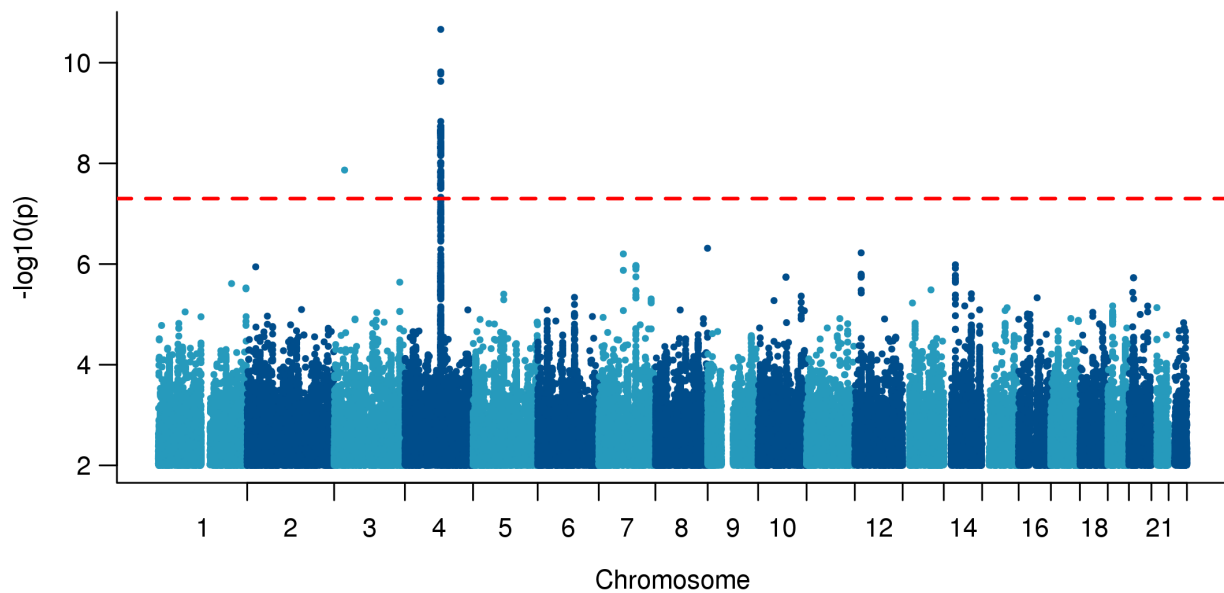
Overview of numbers of alcohol dependent cases and controls from each cohort in the current analysis, including the number of genetically unrelated individuals. Cohorts are listed by study design. Sample sizes are listed after QC exclusions and stratified by ancestry group. PubMed identifiers (PMID) are listed for previous publications describing each cohort, along with the percentage of male samples and the age range in the cohort.

Table 2: Top 10 loci from the discovery meta-analysis of alcohol dependence by ancestry

SNP	CHR	BP	A1	A2	Gene	A1 Allele Freq.		INFO score		Effect size		Discovery meta-analysis p-value		
						EU	AA	EU	AA	EU OR	AA OR	EU	AA	Trans
Trans-ancestral meta-analysis (14,904 cases, 37,944 controls)														
rs1229984	4	100239319	T	C	<i>ADH1B</i>	0.040	0.014	0.904	0.910	0.486	0.912	9.79E-13	3.48E-01	2.18E-11
rs1789912	4	100263942	T	C	<i>ADH1C</i>	0.418	0.132	1.000	1.020	1.106	1.211	1.98E-07	1.32E-03	1.47E-09
rs2066702	4	100229017	A	G	<i>ADH1B</i>	--	0.215	--	0.989	--	0.731	--	2.21E-09	2.21E-09
rs6827898	4	100295863	A	G	--	0.123	0.112	0.963	0.942	1.145	1.270	5.21E-07	9.31E-04	2.97E-09
rs7644567	3	29201672	A	G	<i>RBMS3</i>	--	0.705	--	0.997	--	1.229	--	6.64E-06	1.36E-08
rs894368	4	100309313	A	C	--	0.309	0.386	0.994	0.962	0.887	0.981	1.93E-08	9.73E-01	3.30E-07
rs116338421	8	145761256	C	G	<i>ARHGAP39</i>	--	0.172	--	0.974	--	0.755	--	4.86E-07	4.86E-07
rs79171978	12	17798824	C	G	--	0.099	0.027	0.989	0.986	1.201	1.016	5.47E-08	8.18E-01	5.98E-07
rs2461618	7	68667233	A	G	--	--	0.088	--	0.984	--	0.669	--	6.30E-07	6.30E-07
rs8017647	14	32456358	T	C	--	0.792	0.565	0.998	0.991	0.901	0.923	8.05E-06	4.71E-02	1.03E-06
African ancestry meta-analysis (3,335 cases, 2,945 controls)														
rs2066702	4	100229017	A	G	<i>ADH1B</i>	--	0.215	--	0.989	--	0.731	--	2.21E-09	2.21E-09
rs5781337	1	223883425	CA	C	--	0.263	0.212	0.982	0.927	1.007	0.664	8.85E-01	1.62E-07	6.59E-02
rs116338421	8	145761256	C	G	<i>ARHGAP39</i>	--	0.172	--	0.974	--	0.755	--	4.86E-07	4.86E-07
rs3857224	4	100129685	T	C	<i>ADH6</i>	0.315	0.585	0.994	1.000	0.970	0.814	2.40E-01	5.86E-07	2.36E-03
rs2461618	7	68667233	A	G	--	--	0.088	--	0.984	--	0.669	--	6.30E-07	6.30E-07
rs10784244	12	62035165	G	A	--	0.153	0.484	1.000	0.998	1.041	1.226	6.26E-02	1.04E-06	2.49E-04
rs17199739	16	25444288	G	A	--	0.176	0.096	0.993	0.955	0.994	0.693	4.25E-01	1.11E-06	8.66E-03
rs79016499	11	93010988	T	C	--	--	0.066	--	0.928	--	1.729	--	1.36E-06	--
rs740793	17	3846353	G	A	<i>ATP2A3</i>	0.453	0.350	0.973	0.970	0.996	1.370	4.66E-01	1.48E-06	3.44E-01
rs143258048	3	75982870	A	AC	<i>ROBO2</i>	--	0.028	--	0.879	--	0.490	--	1.86E-06	--
European ancestry meta-analysis (11,569 cases, 34,999 controls)														
rs1229984	4	100239319	T	C	<i>ADH1B</i>	0.040	0.014	0.904	0.910	0.486	0.912	9.79E-13	3.48E-01	2.18E-11
rs894368	4	100309313	A	C	--	0.309	0.386	0.994	0.962	0.887	0.981	1.93E-08	9.73E-01	3.30E-07
rs3811802	4	100244221	G	A	<i>ADH1B</i>	0.454	0.529	0.958	0.956	1.162	0.914	2.40E-08	2.19E-02	1.22E-04
rs79171978	12	17798824	C	G	--	0.099	0.027	0.989	0.986	1.201	1.016	5.47E-08	8.18E-01	5.98E-07
rs1154445	4	100288521	G	T	--	0.425	0.134	0.970	0.986	1.137	1.211	1.80E-07	2.63E-02	1.48E-08
rs6827898	4	100295863	A	G	--	0.123	0.112	0.963	0.942	1.145	1.270	5.21E-07	9.31E-04	2.97E-09
rs4388946	12	17935154	C	A	--	0.240	0.297	0.988	0.976	1.137	0.950	7.14E-07	1.87E-01	7.05E-05
rs1229863	4	100252386	A	T	<i>ADH1B</i>	0.174	0.038	0.990	0.989	1.145	1.254	7.80E-07	4.26E-02	9.28E-08
rs34929220	15	69769635	T	C	<i>DRAIC</i>	0.690	0.937	0.898	0.943	0.893	1.028	1.02E-06	8.38E-01	7.38E-06
rs113659074	4	100252308	T	G	<i>ADH1B</i>	0.068	0.093	0.980	0.947	0.800	1.166	1.54E-06	6.63E-02	2.99E-04

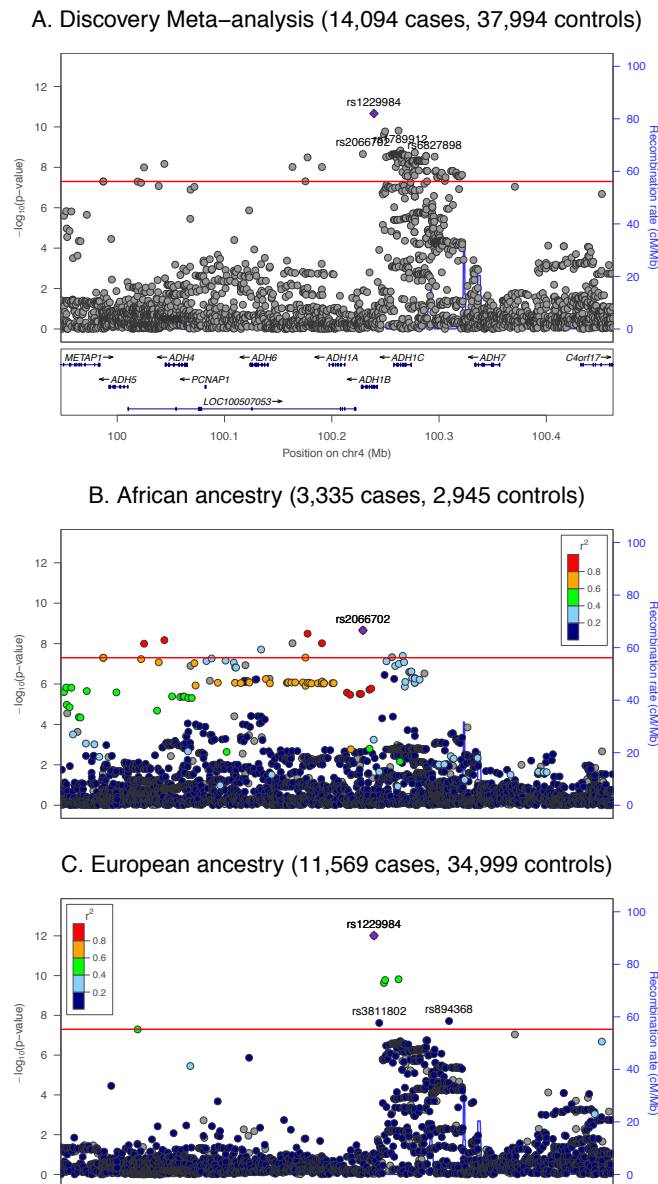
Top 10 nominally independent variants from the discovery trans-ancestral (Trans.) meta-analysis and the discovery meta-analyses in African (AA) and European (EU) ancestry cohorts, respectively. Independent variants are identified based on clumping for LD (pairwise $r^2 < 0.1$) in 1000 Genomes Project Phase 3 data²⁵. EU results are clumped using European (EUR) ancestry reference samples, AA results are clumped using African ancestry reference samples from the American Southwest (ASW), and trans-ancestral results are clumped using merged EUR and African ancestry (AFR) reference samples. Meta-analysis p-values and allele frequencies (Freq.) are reported from full discovery meta-analyses. Bold indicates genome-wide significant p-values ($p < 5e-8$). Odds ratios (OR) and INFO scores are reported from the meta-analyses of the subset of unrelated individuals within each ancestry. Chromosome (CHR) and base pair (BP) position are reported for genome build hg19, with genes annotated by Ensembl VEP⁶². Allele frequency and OR are given with respect to allele 1 (A1).

Figure 1: Manhattan plot of discovery trans-ancestral meta-analysis showing strong evidence for rs1229984 in *ADH1B*.



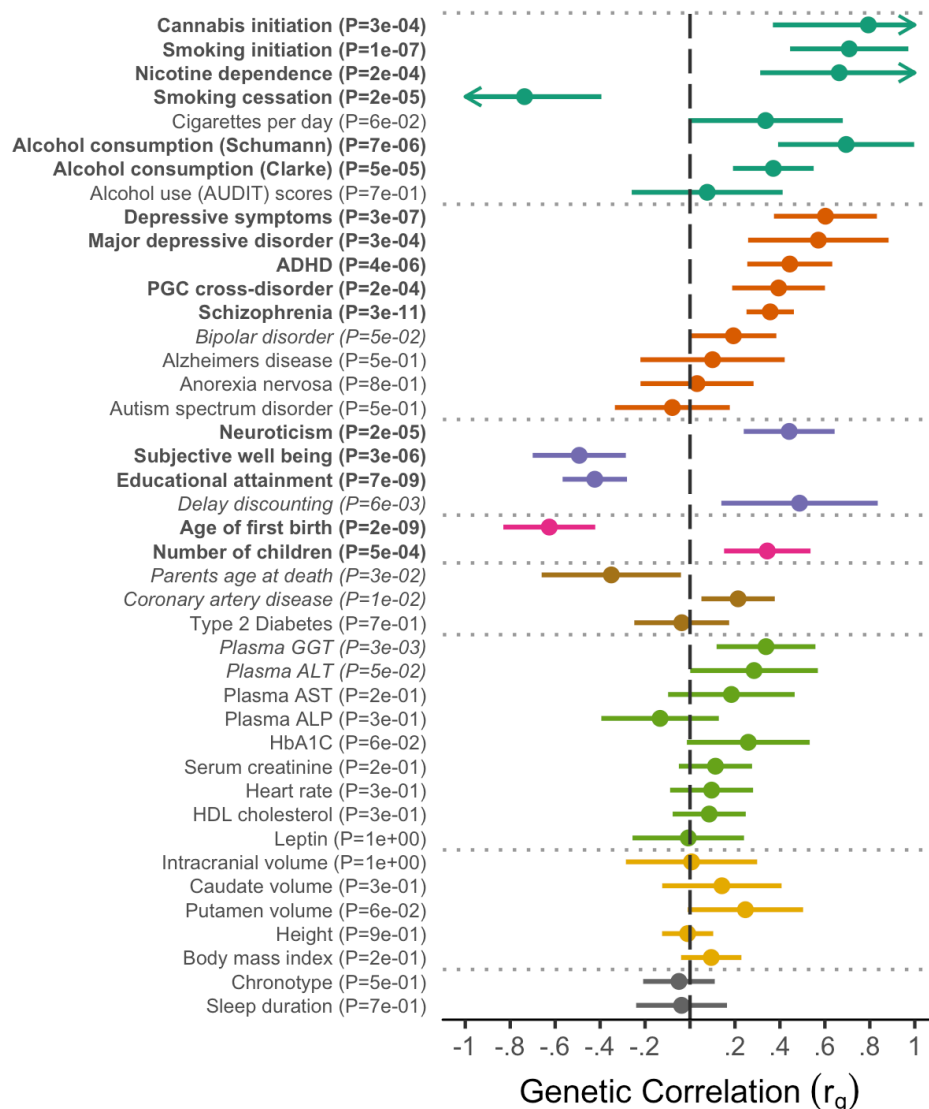
Dashed red reference line indicates genome-wide significance ($p < 5E-8$). Results are from the discovery meta-analysis of all cohorts (14,904 cases, 37,994 controls) under a fixed effects model weighted by effective sample size.

Figure 2: Regional plots for the *ADH1B* locus, rs1229984, in the European (EU), African-American (AA) and trans-ancestral discovery meta-analysis.



Results of meta-analysis with effective sample size weights for the *ADH1B* locus in (A) all cohorts, (B) AA cohorts, and (C) EU cohorts. Red reference line indicates the genome-wide significance threshold ($P < 5e-8$). Within ancestry, colored points reflect the degree of LD (pairwise r^2) to the index variant (indicated by a purple diamond) in 1000 Genomes Project reference data²⁵ for individuals of (B) African or (C) European ancestry, respectively. No reference LD panel exists for the trans-ancestral sample (A).

Figure 3: Genetic correlations between 42 traits and alcohol dependence in Europeans.



Genetic correlation results from LD score regression with the meta-analysis of AD in unrelated EU individuals (10,206 cases, 28,480 controls). After Bonferroni correction, significant correlations are observed with 16 traits and disorders ($p < 1.2E-3$); bold), with nominally significant results for 6 additional traits and disorders ($p < .05$; italics). Error bars indicate 95% confidence intervals, with arrows indicating intervals extending above 1 or below -1. Phenotypes are organized by research domain.

Ethics statement:

This study was approved by the institutional review board (IRB) of Washington University in St. Louis (Human Research Protection Office; number 201512068). Each contributing cohort obtained informed consent from their participants and received ethics approvals of their study protocols from their respective review boards in accordance with applicable regulations.

Contributors:

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Data availability:

Summary statistics from the genome-wide meta-analyses will be made available on the Psychiatric Genomics Consortium's downloads page (<http://www.med.unc.edu/pgc/results-and-downloads>). Individual-level data from the genotyped cohorts and cohort-level summary statistics will be made available to researchers following an approved analysis proposal through the PGC Substance Use Disorder group with agreement of the cohort PIs; contact the corresponding authors for details. Cohort data is also available from dbGaP except where prohibited by IRB or European Union data restrictions (accession numbers to be available before publication).

Code availability:

Code for GWAS of case/control cohorts with ricopili is available at <https://github.com/Nealelab/ricopili>. Code for GWAS of family-based cohorts with picopili is available at <https://github.com/Nealelab/picopili>. Code for LD score regression analyses are available at <https://github.com/bulik/ldsc>. Effective sample size calculations were implemented using PLINK (<https://www.cog-genomics.org/plink2>), and GMMAT (<https://content.sph.harvard.edu/xlin/software.html#gmmat>) and geepack (<https://cran.r-project.org/web/packages/geepack/index.html>) in R (<https://cran.r-project.org/>); example code is available from the first author by request.

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