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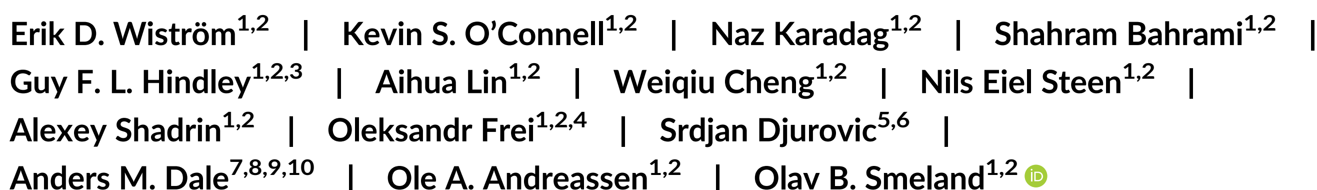
RESEARCH REPORT

ADDICTION SSA

Genome-wide analysis reveals genetic overlap between alcohol use behaviours, schizophrenia and bipolar disorder and identifies novel shared risk loci



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Abstract

Background and aim: Schizophrenia (SCZ) and bipolar disorder (BD) have a high comorbidity of alcohol use disorder (AUD), and both comorbid AUD and excessive alcohol consumption (AC) have been linked to greater illness severity. We aimed to identify genomic loci jointly associated with SCZ, BD, AUD and AC to gain further insights into their shared genetic architecture.

Design: We analysed summary data (*P* values and *Z* scores) from genome-wide association studies (GWAS) using conjunctional false discovery rate (conjFDR) analysis, which increases power to discover shared genomic loci. We functionally characterized the identified loci using publicly available biological resources.

Setting: AUD and AC data provided by the Million Veteran Program, derived from the United States Department of Veterans Affairs Healthcare System. SCZ and BD data provided by the Psychiatric Genomics Consortium, based on cohorts from countries in Europe, North America and Australia.

Participants: AUD (34 658 cases, 167 346 controls), AC (n = 200 680), SCZ (31 013 cases and 38 918 controls), BD (20 352 cases and 31 358 controls). All participants were of European ancestry.

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Measurements: Genomic loci shared between alcohol traits, SCZ and BD at conjFDR <0.05.

Findings: Conditional Q-Q plots showed single-nucleotide polymorphism (SNP) enrichment for both alcohol traits across different levels of significance with SCZ and BD, and *vice versa*. Using conjFDR analysis we leveraged this genetic enrichment and identified several loci shared between SCZ and AUD (n = 28) and AC (n = 24), BD and AUD (n = 2) and AC (n = 8) at conjFDR <0.05. Among these loci, 24 are novel for AUD, 15 are novel for AC, three are novel for SCZ and one is novel for BD. There was a mixture of same and opposite effect directions among the shared loci.

Conclusions: Alcohol use disorder and alcohol consumption share genomic loci with the psychiatric disorders schizophrenia and bipolar disorder with a mixed pattern of effect directions, indicating a complex genetic relationship between the phenotypes.

KEYWORDS

Alcohol consumption, alcohol use disorder, AUDIT-C, bipolar disorder, genetic overlap, GWAS, schizophrenia.

INTRODUCTION

Alcohol is one of the most commonly used psychoactive substances worldwide and alcohol use behaviours have important health-related life outcomes. A total of 5.3% of all deaths globally and 5.1% of the global burden of disease were attributable to harmful use of alcohol in 2016 [1]. Alcohol use behaviours are associated with a wide range of health problems, including cardiovascular and gastrointestinal diseases, injuries, cancers, as well as psychiatric disorders [1–3]. Schizophrenia (SCZ) and bipolar disorder (BD) are severe psychiatric disorders with substantial morbidity and mortality globally [4], and both disorders have a high comorbidity of alcohol use disorder (AUD) and other substance use disorders [5–10]. Importantly, comorbid AUD is associated with a worse prognosis in both SCZ and BD [11–14], and both AUD and higher alcohol consumption (AC) have been linked to greater illness severity and treatment noncompliance in both BD and SCZ [15–20]. Hence, understanding the underlying mechanisms of unhealthy alcohol use in patients with SCZ and BD is of high clinical importance.

Genetic factors influence both AUD and AC, with an estimated heritability from familial studies of around 40% for both phenotypes [21–23], and the heritability accounted for by common genetic variants estimated to be around 4–10% [24–26]. Both SCZ and BD are highly heritable with heritability estimates around 60–80% [27–29], with common variants estimated to account for approximately a half of this heritability [30–33]. To date, genome-wide association studies (GWAS) have identified multiple genetic loci associated with SCZ and BD [32,34–36]. There has also been considerable progress in mapping the genetics of AC, with more than 100 genetic loci identified in recent GWAS [23–25,37]; whereas the yield has been lower in GWAS on AUDs [23,38]. Interestingly, the genetic architectures of alcohol use and abuse appear to be somewhat distinct [39]. For example, in two recent large GWAS on AUD and AC (defined by Alcohol Use Disorders Identification Test-Consumption scores [AUDIT-C]), these two measures had a positive genetic correlation of only 0.52 among European-Americans ($n \sim 200\,000$) [23]. The genetic dissimilarity between alcohol use and abuse is also reflected by their different genetic relationship with SCZ and BD. Although there is a positive genetic correlation between AUD and both SCZ (r_g = 0.34) and BD (r_g = 0.30) [23], studies have found no significant genetic correlations between AC and these disorders [23,24,38–40]. Although environmental factors are likely to contribute to part of the comorbidity between unhealthy alcohol use and SCZ and BD, shared genetic factors may also play a role. Identifying such genetic factors could reveal pathobiological mechanisms and inform development of new prediction tools and therapeutic approaches [41].

Despite the successful progress of recent GWAS in identifying genetic variants influencing AUD [23,38], AC [23–25,37,40], SCZ [34,35,42] and BD [32], much of their genetic architectures remain to be uncovered. In the present study, we aimed to increase discovery of genomic loci jointly influencing these phenotypes to gain further insights into their shared genetic architecture. To this end, we analysed summary statistics from recent GWAS on AUD [23], AC [23], SCZ [34] and BD [32] using the conjunctional false discovery rate (conjFDR) approach. ConjFDR analysis leverages the overlapping genetic associations between phenotypes to improve discovery of shared genomic loci independent of direction [43,44]. This approach has identified overlapping genetic influences between a number of complex human traits and disorders in recent years, beyond genetic correlation [36,44–53].

METHODS AND MATERIALS

Participant samples

We obtained GWAS data in the form of summary statistics (P values and effect sizes) from repositories or publications (Table 1). All

TABLE 1 Summary data from all GWASs used in the present study.

Disorder/trait	*Consortium*	*Sample size, n*	*Ancestry*	*SNPs, n*	*Reference*
Discovery samples					
AUD	MVP	34 658 cases 167 346 controls	European	6 895 250	[23]
AC	MVP	200 680 participants	European	6 898 149	[23]
SCZ	PGC	31 013 cases 38 918 controls	European	15 353 478	[34]
BD	PGC	20 352 cases 31 358 controls	European	13 413 960	[32]
Replication samples					
Alcohol use	GSCAN	941 280 participants	European	11 916 706	[24]
Alcohol use	GSCAN	941 280 participants	European	11 916 706	[24]
SCZ	PGC	22 778 cases 35 362 controls	East Asian	10 694 924	[42]
BD	FINNGEN	4501 cases 192 220 controls	European	14 114 100	Publicly available data (https://r5.finngen.fi)

AUD = alcohol use disorder; AC = alcohol consumption; SCZ = schizophrenia; BD = bipolar disorder; MVP = Million Veteran Program; PGC = Psychiatric Genomics Consortium; GSCAN = GWAS and Sequencing Consortium of Alcohol and Nicotine use; GWAS = genome-wide association study.

participants were of European ancestry to ensure linkage disequilibrium (LD) compatibility across the GWAS, which might otherwise bias the conjFDR analysis, because LD patterns are strongly population-dependent. The GWAS data on AUD and age adjusted AC measured with AUDIT-C scores were obtained from the Million Veteran Program (MVP) [23]. The MVP is an observational cohort study and a biobank supported by the United States (US) Department of Veterans Affairs. The data on AUD comprises 202 004 individuals (34 658 cases, 167 346 controls), whereas the data on AC comprises 200 680 individuals. The AUD diagnosis was identified in participants by examining their electronic health record (EHR) for International Classification of Diseases (ICD) alcohol-related diagnosis codes in the period 2000 to 2018. AUDIT-C scores were collected from the EHR, and consist of the first three questions of the AUDIT, a screening questionnaire for identifying persons with hazardous and harmful alcohol use. AUDIT-C measures AC by asking the individual about the frequency and quantity of their usual drinking, as well as how often they have six or more drinks on one occasion [54].

The GWAS data on SCZ and BD were obtained from the Psychiatric Genomics Consortium (PGC) [32,34]. Because of potential sample overlap between the SCZ [34] and alcohol [23] GWAS, we excluded 2627 cases and 4538 controls from the SCZ GWAS. Because of trans-ancestry LD issues, we excluded all participants of Asian ancestry. The final SCZ sample was based on cohorts from countries in Europe, North America and Australia and contained 29 778 cases with SCZ or schizoaffective disorder and 37 683 controls, as well as three family based association studies containing 1235 parent affected-offspring trios [34], yielding a total of 31 013 cases and 38 918 controls. The data on BD comprised 20 352 cases with BD and 31 358 controls from countries in Europe, North America and Australia [32]. Among the cases, 14 879 had BD type I, 3421 had BD type II, 977 had schizoaffective disorder, bipolar type and the remaining had unspecified BD.

Statistical analysis

We applied the conjFDR method to increase discovery of genomic loci jointly influencing AC, AUD and the two psychiatric disorders [43,44]. The conjFDR approach is an extension of the conditional FDR (condFDR), which leverages cross-trait enrichment between two phenotypes to improve genetic discovery. The condFDR readjusts the test statistics in a primary phenotype (i.e. AUD) by conditioning on single-nucleotide polymorphism (SNP) associations with a secondary phenotype (i.e. SCZ). Inverting the roles of primary and secondary phenotypes gives the inverse condFDR value. The conjFDR, defined in turn as the maximum of the two condFDR values, provides a conservative estimate of the FDR for association with both phenotypes [43,44]. In line with previous literature [52,55,56], we identified shared loci at conjFDR <0.05. The cross-trait enrichment is typically visualized using conditional Q-Q plots, which show the distribution of *P* values for a primary phenotype for all SNPs, and for SNP strata defined by their association with the secondary phenotype. Cross-trait enrichment is evident if there are an increased proportion of lower *P* values in the primary phenotype as a function of association with the secondary phenotype [44]. To control for spurious enrichment, random pruning was averaged over 500 iterations, and one SNP in each LD block (r^2 > 0.1) was randomly selected for each iteration. We excluded SNPs within the major histocompatibility complex (MHC; genome build 19 location 25 652 429–33 368 333), the chromosomal region 8p23 (location 7 200 000–12 500 000) and the gene microtubule-associated protein tau (MAPT) (chr17:40000000–

47 000 000) given their complex LD structures, to avoid biased FDR estimation [57]. All analyses in the present study were conducted in Oslo, Norway. The analysis was not pre-registered and the results should be considered exploratory.

Locus definition

We defined a genomic locus according to the FUMA protocol (http://fuma.ctglab.nl/) [58], an online platform for functional annotation of SNPs and genes. We identified individual significant SNPs based on a conjFDR value <0.05 and being independent from each other with an LD r^2 < 0.6. A subset of these at approximately LD r^2 < 0.1 of each other were considered lead SNPs. Candidate SNPs were defined as all SNPs in LD r^2 ≥ 0.6 with one of the independent significant SNPs in the locus, and determined the borders of each locus. Loci <250 kb apart were merged, with the most significant SNP considered to be the lead SNP of the merged locus. Overlapping signals within complex LD regions were represented by one independent lead SNP only. All LD information was calculated from the 1000 Genomes Project European-ancestry reference haplotype reference panel [59]. We evaluated directional effects of the loci by comparing their *Z* scores and odds ratios.

Replication

To assess the validity of the findings, we used sign tests to compare the overall pattern of consistency in allelic effect directions between the discovery datasets and independent datasets on SCZ (22 778 cases and 35 362 controls) [42], BD (4501 cases and 192 220 controls; https://r5.finngen.fi/) and alcohol use (*n* = 941 240; measured as drinks per week) [24]. The alcohol use phenotype was genetically correlated with both AUD and AC in the MVP cohort ($r_g \sim 0.70$ for both). See Supporting information Supplementary Methods for details. First, we determined the number of lead SNPs in the identified shared loci whose effect directions were the same in the replication datasets. The significance of the observed proportion from chance (50%) was then evaluated using the binomial distribution. Additionally, we evaluated the replicability of individual loci by obtaining the *P* values of the lead SNPs in the replication samples. If a primary lead SNP was missing in the replication dataset, we assigned the next most significant candidate SNP if available.

Functional annotation

Using FUMA [58], we functionally annotated all candidate SNPs with a conjFDR value <0.10 using combined annotation dependent depletion (CADD) scores, which predict how deleterious the SNP effect is on protein structure/function, RegulomeDB scores, which predict regulatory functionality, and chromatin states, which predict transcription/regulatory effects from chromatin states at the SNP locus. Candidate SNPs were then aligned to genes using three different strategies implemented in FUMA. We used positional gene mapping to align SNPs to genes based on physical proximity, expression quantitative trait locus (eQTL) mapping SNPs to the genes whose expression level is influenced by allelic variation at the SNP level, and chromatin states using 3D DNA–DNA interactions to link SNPs to genes. We also used FUMA to evaluate gene ontology gene-set enrichment for the mapped genes. All analyses were corrected for multiple comparisons. See Supporting information for details.

RESULTS

The conditional Q-Q plots demonstrated substantial enrichment of SNP associations with both AUD and AC as a function of increasing levels of SNP associations with SCZ or BD (Fig. 1 a–d). We also constructed reverse conditional Q-Q plots, demonstrating consistent genetic enrichment of SCZ and BD conditional on their association with both alcohol-related phenotypes (Supporting information Fig. S1 a–d). Next, we leveraged this cross-trait enrichment using conjFDR analysis to improve discovery of loci shared between the phenotypes [44]. At conjFDR <0.05, we identified 28 loci significantly associated with both AUD and SCZ, and 24 loci significantly associated with both AC and SCZ (Fig. 2 a,b). Further, we identified two loci jointly associated with AUD and BD, and eight loci associated with AC and BD at conjFDR <0.05 (Fig. 3 a,b). Both of the loci shared between AUD and BD were also linked to SCZ, whereas six of eight loci shared between AC and BD were linked to SCZ.

In total, the conjFDR analysis identified 28 distinct loci linked to AUD and 26 distinct loci linked to AC (Supporting information Tables S1, S2, S3 and S4). Among these, four AUD loci and six AC loci were already identified in the original alcohol GWAS [23], whereas 11 loci have been identified in other alcohol GWAS [24,25,40], yielding 24 novel AUD loci and 15 novel AC loci. Altogether, we identified 44 distinct SCZ risk loci, of which 21 were identified in the original SCZ GWAS [34], whereas 20 were identified in other genetic studies [35,36,50,51,60–63], leaving three novel SCZ loci (near *FABP3* on chromosome 1, near *RP11–254A17.1* on chromosome 5 and at *SCAPER* on chromosome 15) (Supporting information Tables S1 and S3). We identified nine distinct BD risk loci, none of which were identified in the original GWAS study [32]. All but one locus were, however, identified in subsequent genetic studies [36,48,50,64], leaving one novel BD locus near *CRELD2* on chromosome 22 (Supporting information Table S4). Notably, eight of the loci identified for AUD and AC were overlapping. Next, we evaluated the allelic effect directions in the shared loci (Supporting information Tables S1, S2, S3 and S4). Sixteen of the 28 loci (57%) associated with AUD and SCZ had the same effect directions in the phenotypes, meaning that the majority of AUD risk alleles were also associated with higher risk of SCZ. Both of the loci associated with AUD and BD had opposite allelic effect directions. Of the 24 loci associated with AC and SCZ, 10 had same effect directions (42%), whereas five of eight loci (63%) associated with AC and BD had same effect directions.

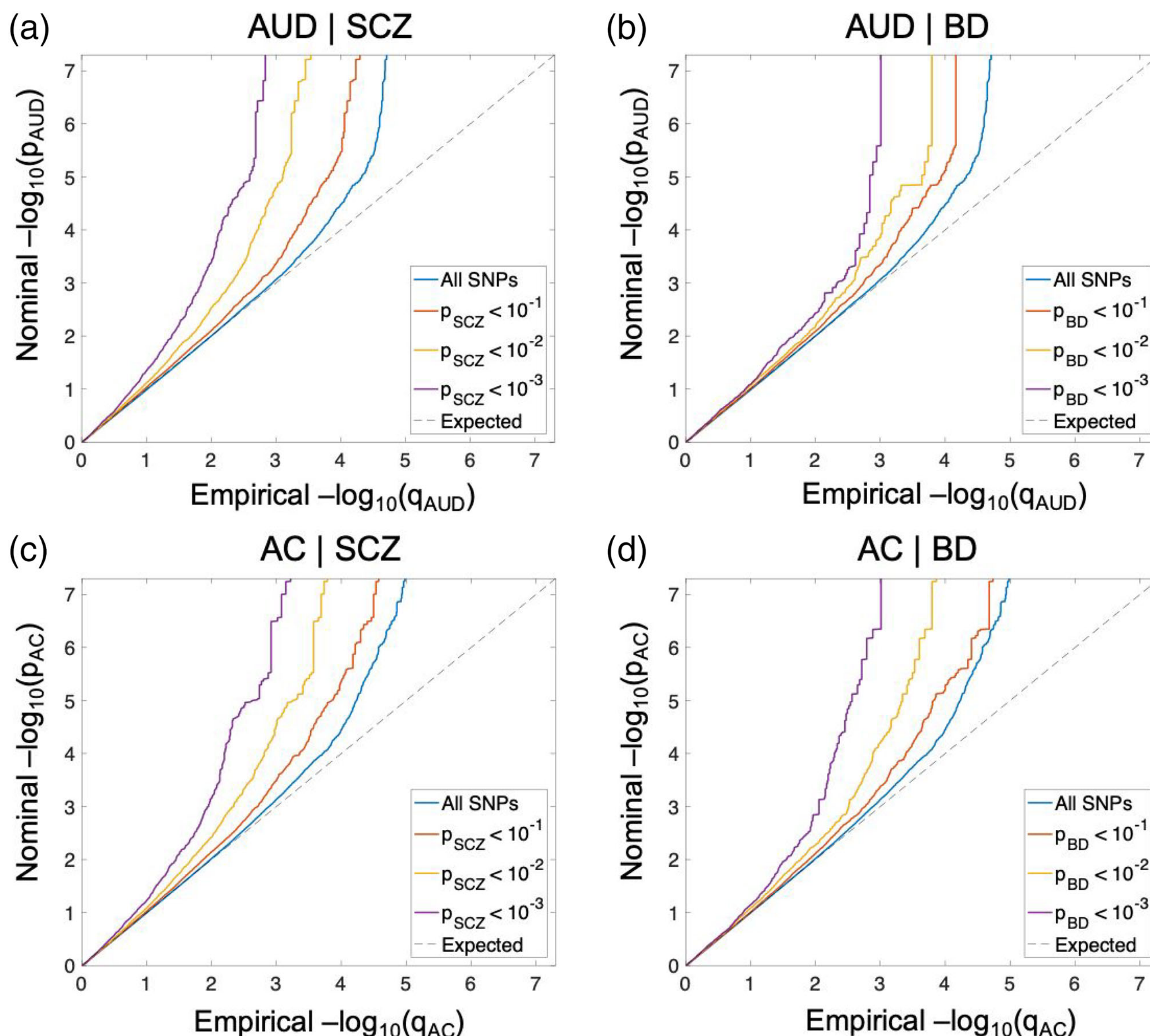

FIGURE 1 Cross-trait enrichment between alcohol use disorder (AUD) and both (a) schizophrenia (SCZ) and (b) bipolar disorder (BD), and cross-trait enrichment between alcohol consumption (AC) and both (c) SCZ and (d) BD. Conditional quantile-quantile plots of nominal versus empirical $-\log_{10}$ *P* values (corrected for inflation) in AUD and AC below the standard genome-wide association study threshold of $P < 5 \times 10^{-8}$ as a function of significance of association with SCZ or BD, at the level of $P < 0.10$, $P < 0.01$ and $P < 0.001$. The blue lines indicate all single-nucleotide polymorphisms (SNPs). The dashed lines indicate the null hypothesis

Among AUD-associated SNPs, 25 of 28 lead SNPs in loci shared between SCZ and AUD (89%; exact binomial $P = 1.37 \times 10^{-5}$) and 2 of 2 lead SNPs in loci shared between BD and AUD (100%; exact binomial $P = 0.25$) were sign concordant in the independent alcohol use GWAS [24] (Supporting information Tables S1 and S2). Of these SNPs, 15 (54%) and 2 (100%), respectively, had $P < 0.05$ in the replication sample. Among AC-associated SNPs, 19 of 23 lead SNPs in loci shared between SCZ and AC (83%; exact binomial $P = 0.001$) and 7 of 8 lead SNPs in loci shared between BD and AC (88%; exact binomial $P = 0.035$) were sign concordant in the replication sample [24] (Supporting information Tables S3 and S4). Of these SNPs, 14 (61%) and 5 (63%), respectively, had $P < 0.05$ in the replication sample. Lead SNP rs9265265 or nearby candidate SNPs lacked summary statistics in the alcohol use replication dataset and its replicability could not be assessed for AC. Among SCZ-associated SNPs, 22 of 27 lead SNPs in loci shared between SCZ and AUD (81%; exact binomial $P = 7.57 \times 10^{-4}$) and 16 of 22 lead SNPs in loci shared between SCZ and AC (73%; exact binomial $P = 0.026$) were sign concordant in the independent SCZ sample [42] (Supporting information Tables S1 and S3). Of these SNPs, 6 (22%) and 6 (28%), respectively, had $P < 0.05$ in the replication sample [42]. Lead SNPs rs72926962, rs9265265 and rs62054433 or nearby candidate SNPs lacked summary statistics in the SCZ replication dataset and their replicability could therefore not be assessed for SCZ. Among BD-associated SNPs, 1 of 2 lead SNPs in

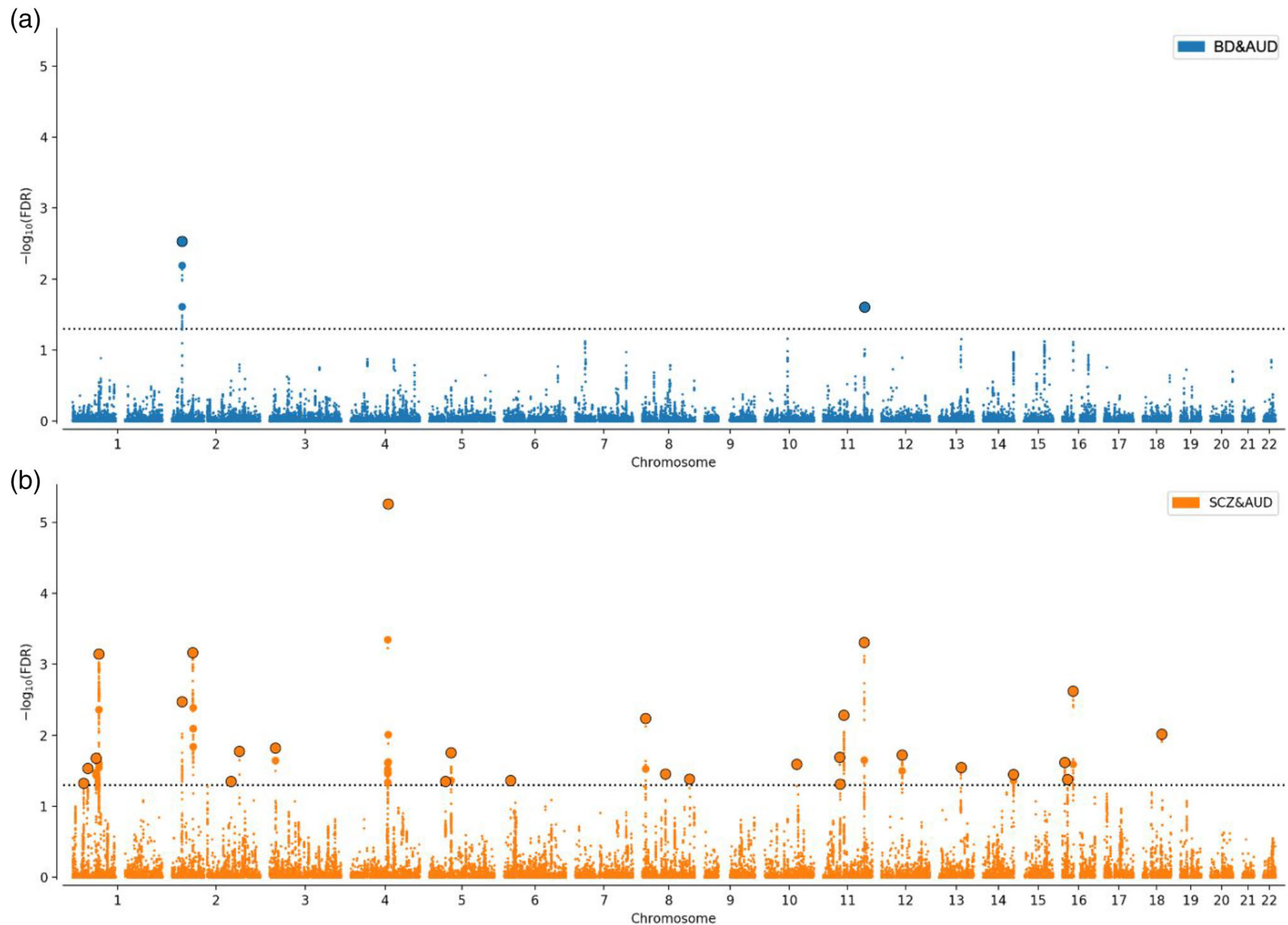

FIGURE 2 Common genetic variants jointly associated with alcohol use disorder (AUD) (n = 202 004) and (a) bipolar disorder (BD) (n = 51 710) and (b) schizophrenia (SCZ) (n = 69 931) at conjunctional false discovery rate (conjFDR) <0.05. Manhattan plots showing the $-\log_{10}$ transformed conjFDR values for each single nucleotide polymorphism (SNP) on the y-axis and chromosomal positions along the x-axis. The dotted horizontal lines represent the threshold for significant shared associations (conjFDR <0.05, i.e. $-\log_{10}$[conjFDR] >1.3). Independent lead SNPs are circled in black. The significant shared signals in the major histocompatibility complex region and region 8p23.1 are represented by one lead SNP only. For further information about the identified variants and loci, see Tables S1 and S2

loci shared between BD and AUD (50%; exact binomial P = 0.750) and 5 of 8 lead SNPs in loci shared between BD and AC (63%; exact binomial P = 0.36) were sign concordant in the independent BD sample (Supporting information Tables S2 and S4). Of these SNPs, 0 (0%) and 2 (25%) lead SNPs, respectively, had P < 0.05 in the replication sample.

Functional annotation of the candidate SNPs in the shared loci in the four analyses revealed that most were intronic and intergenic (Tables S5, S6, S7 and S8) [58]. We found 10 exonic candidate SNPs among the shared loci between AUD and SCZ, six of which were non-synonymous, meaning that these variants change the produced protein's amino acid sequence (Supporting information Table S5). Furthermore, there were four exonic variants within the shared loci between AUD and BD, all of which were non-synonymous (Supporting information Table S6). Within the shared loci between AC and SCZ and AC and BD, 9 of 22 and 4 of 6 exonic variants were non-synonymous, respectively (Supporting information Tables S7 and S8). A CADD-score higher than 12.37 is suggested to reflect deleteriousness [65]. Among the identified shared loci, 26 candidate SNPs shared between AUD and SCZ, seven candidate SNPs shared between AUD and BD, 30 candidate SNPs shared between AC and SCZ and 16 candidate SNPs shared between AC and BD, had a CADD-score higher than 12.37 (Supporting information Tables S5, S6, S7 and S8).

Next, we mapped the identified loci to genes [58]. We identified 335 genes linked to the 28 loci shared between AUD and SCZ (Supporting information Table S9). Thirty of these genes were mapped by all three gene-mapping methods (physical proximity, eQTL associations and chromatin interactions), supporting the link between these genes and loci. Further, we mapped 40 genes to the loci associated with both AUD and BD (Supporting information Table S10), of which seven were mapped by all three methods. We mapped 255 genes to the 24 loci shared between AC and SCZ (Supporting information Table S11), of which 36 were mapped by all three methods. Finally, we mapped 122 genes to the loci shared between AC and BD (Supporting information Table S12), of which 16 genes were

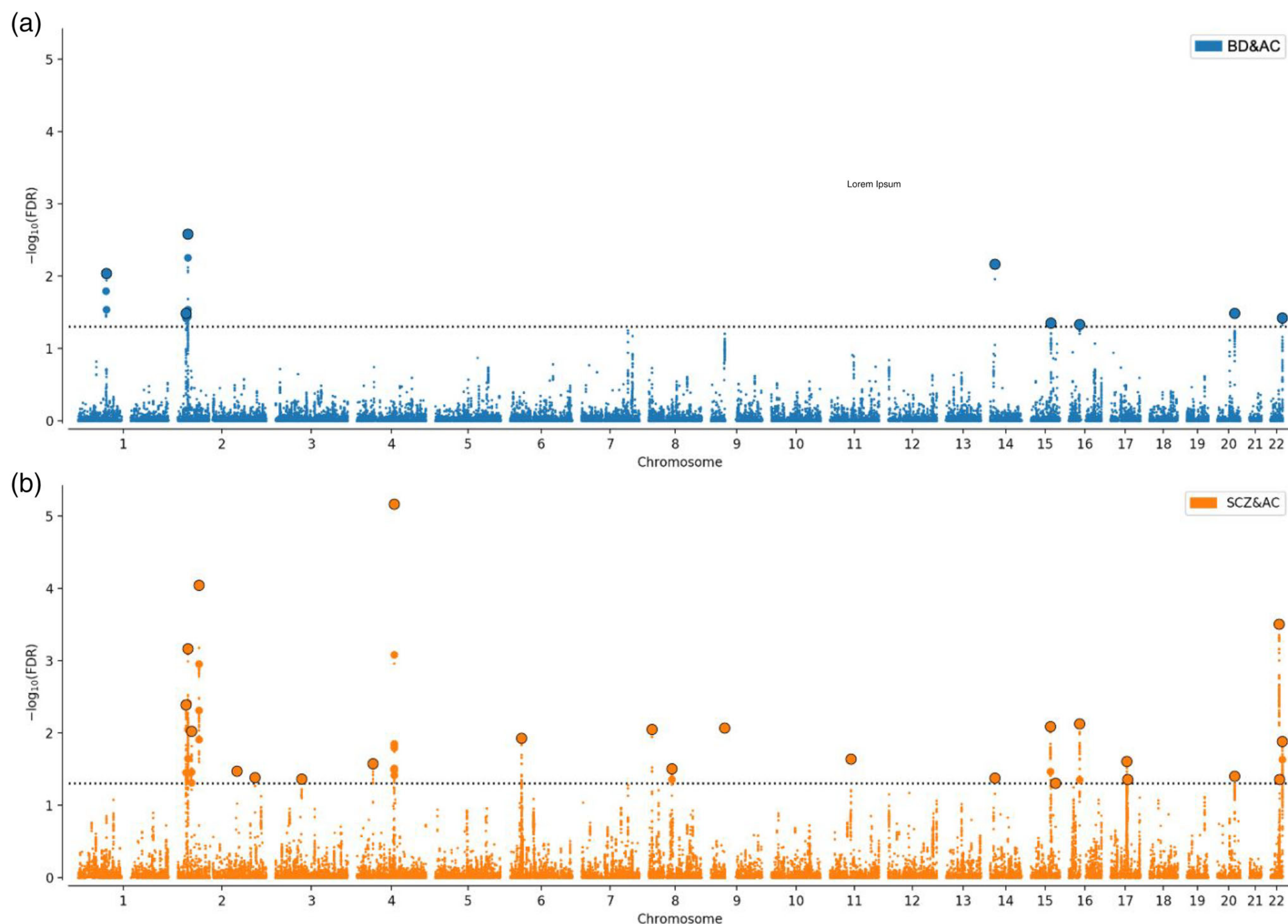

FIGURE 3 Common genetic variants jointly associated with alcohol consumption (AC; n = 202 004) and (a) bipolar disorder (BD; n = 51 710) and (b) schizophrenia (SCZ; n = 69 931) at conjunctional false discovery rate (conjFDR) <0.05. Manhattan plots showing the $-\log_{10}$ transformed conjFDR values for each single nucleotide polymorphism (SNP) on the y-axis and chromosomal positions along the x-axis. The dotted horizontal lines represent the threshold for significant shared associations (conjFDR <0.05, i.e. $-\log_{10}$[conjFDR] > 1.3). Independent lead SNPs are circled in black. The significant shared signals in the major histocompatibility complex region, chromosomal region 8p23.1 and the MAPT region are represented by one lead SNP only. For further information about the identified variants and loci, see Tables S3–S4

implicated by all three methods. No biological pathways were significantly associated with any of the four sets of genes. Using the GTEx expression database [66], we found no significant differential tissue expression for three of the gene sets, whereas the genes implicated by the shared loci between AC and SCZ were found to be downregulated in whole blood (Supporting information Table S13), which may be a coincidental finding.

DISCUSSION

In this study, we demonstrated polygenic overlap between alcohol use behaviours and the psychiatric disorders SCZ and BD. Using the conjFDR method [44], we leveraged the substantial cross-trait enrichment between the phenotypes to increase statistical power for genetic discovery and identified 28 loci shared between AUD and SCZ, two loci shared between AUD and BD, 24 loci shared between AC and SCZ, and eight loci shared between AC and BD (Figs. 2 and 3). In total, we discovered 24 novel loci associated with AUD, 15 novel loci associated with AC, three novel loci associated with SCZ and one novel locus associated with BD (Supporting information Tables S1, S2, S3 and S4). The high degree of sign concordance observed between the independent discovery and replication datasets for the shared loci is highly unlikely to occur by chance (Supporting information Tables S1, S2, S3 and S4), and supports the validity of the findings. Among the shared loci, there was a mixed pattern of allelic effect directions across the phenotypes, indicating a complex genetic relationship between alcohol use behaviours, SCZ and BD. This is in line with an accumulating body of evidence from genetic studies revealing considerable pleiotropy between mental-health related traits and disorders [67], in which many genetic variants are found to influence multiple phenotypes, but to different degrees [41]. The present findings, therefore, increase the understanding of the relationship between SCZ, BD and alcohol-related behaviours and may lead to novel etiological hypotheses about their comorbidity.

Our findings indicate that in some patients, common genetic variants shared by AUD, SCZ and BD may contribute to the comorbidity between these disorders, although environmental factors or rare genetic variants may also play a role. Among the shared loci between AUD and SCZ, there was a slightly larger fraction of loci with same allelic effect directions (57%, Supporting information Table S1), in line with the positive genetic correlation between these phenotypes ($r_g = 0.34$) [23]. However, note that the identified loci only constitute a small fraction of the genetic architectures of the investigated phenotypes [41]. This likely explains why the two loci found to be shared between AUD and BD had opposite effect directions in the phenotypes, contrasting with the positive genetic correlation between these phenotypes [23] (Supporting information Table S2). Given the large variation in alcohol use and abuse among individuals with SCZ and BD, another possibility is the presence of subgroups characterized by shared loci with predominantly agonistic genetic risk variants, leading to higher AC, and other subgroups with a higher occurrence of antagonistic effect directions, explaining a lower alcohol-related behaviour. Our discovery of multiple SCZ and BD risk loci that also influence AC (Fig. 3) indicate polygenic overlap between these phenotypes despite no genetic correlations [23,24,38–40]. Indeed, genetic correlations are unable to capture a mixed pattern of directional effects among shared variants [68], which are increasingly shown to characterize the genetic relationship between many complex human phenotypes [41]. Note that we cannot exclude the possibility that the GWAS samples on AUD and AC include some individuals with BD or SCZ, or that some of the cases in the SCZ and BD GWAS have AUD. These potential confounders, however, cannot explain the findings of mixture of directional effects among the shared loci, but would lead to an excessive concordance of allelic effect directions. Another limitation of our work is that all participants in the discovery samples were of European ancestry, because differences in LD patterns, which are strongly population dependent, may bias the FDR computation. However, the high degree of consistent results for the identified SCZ-risk alleles in the independent SCZ GWAS on East Asian individuals [42] suggests that the findings are also generalizable to this population. Nevertheless, improving the diversity in GWAS populations remains an urgent need for the research community.

Functional characterization of the identified loci revealed several exonic nonsynonymous SNPs with a high probability of deleteriousness (Supporting information Tables S5, S6, S7 and S8). Given that such variants are more likely to substantially impact a phenotype, they are promising candidates for experimental follow-up studies to obtain mechanistic insights into SCZ, BD and alcohol behaviours. However, like in GWAS on other complex human phenotypes [69], most of the identified candidate SNPs reside in non-coding DNA, suggesting a regulatory and more indirect influence on the phenotypes, and follow-up studies are nevertheless needed to determine the specific causal genetic variants underlying the shared loci detected here. To our knowledge, the gene-mapping analysis did not implicate any genes encoding ethanol metabolizing enzymes, which have been strongly linked to alcohol phenotypes in prior GWAS [23,24,38,40], including members of the alcohol dehydrogenase family (*ADH1B* and *ADH1C*) and aldehyde dehydrogenase (*ALDH2*) [70]. This suggests that genetic variants specifically influencing alcohol metabolism are of less importance for SCZ and BD, despite the considerable genetic overlap with alcohol-related traits. Notably, the gene set analysis did not reveal any biological pathways significantly associated with the four sets of genes implicated by the shared loci between alcohol behaviours, SCZ and BD. This may suggest that the shared loci do not influence a distinct biological process, but represent non-specific genetic effects common to these mental-health related phenotypes. However, these negative findings may also reflect insufficient statistical power, or current limitations of the gene-set analysis approach, including uncertainties in translating loci to causal genes or the incomplete characterization of the function of many genes and proteins and their interactions in signalling networks and pathways [71]. The most strongly associated locus shared between SCZ and both AUD and AC was located at chromosome 4, and implicates two genes in particular, *SLC39A8* and *BANK1* (Supporting information Table S9). At this locus, SCZ risk alleles were associated with lower risk of AUD and lower consumption. This highly pleiotropic locus was already identified in both of the original alcohol GWAS and the SCZ GWAS [23,34], and is shown to influence several human traits and disorders [72], including cognitive function and volume of the subcortical brain structure putamen [52,73]. Interestingly, this locus was not significantly associated with BD, illustrating some differences in the genetic makeup of SCZ and BD despite their considerable genetic overlap [36]. At the most strongly associated locus shared between BD and both AUD and AC, which has been associated with all of the phenotypes previously [23,36,60], both BD and SCZ risk was associated with lower risk for AUD and lower AC. This locus on chromosome 2 implicates several genes, with *GCKR* being the gene nearest to the lead SNP rs1260326, a nonsynonymous exonic variant with high probability of deleteriousness (CADD-score = 13.22; Supporting information Tables S6 and S8).

In conclusion, our findings provide new insights into the genetic relationship between alcohol use behaviours and the psychiatric disorders SCZ and BD. Dissecting the genetic relationship between psychiatric disorders and alcohol-related traits is clinically important because it can shed light on the comorbidity between SCZ, BD and unhealthy alcohol use, which negatively affects many individuals suffering from SCZ and BD [15–18]. As such, the present results support the collection and sequencing of DNA in studies on SCZ, BD and alcohol use behaviours to improve risk stratification and obtain biological insights. As GWAS continue to get larger, we expect that more overlapping genomic loci between SCZ, BD and alcohol use behaviours will be uncovered, which may inform the development of new diagnostic tools and therapeutic strategies.

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DECLARATIONS OF INTERESTS

O.A.A. has received speaker's honorarium from Lundbeck and is a consultant for Healthlytix. A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He is also a member of the Scientific Advisory Board of Healthlytix and receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. Remaining authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Erik Wiström: Conceptualization; formal analysis; investigation; project administration. **Kevin S. O'Connell:** Conceptualization; data curation; formal analysis; investigation; methodology; software. **Naz Karadag:** Conceptualization; data curation; formal analysis; investigation. **Shahram Bahrami:** Formal analysis; investigation; methodology; project administration; validation. **Guy F L Hindley:** Conceptualization; data curation; investigation; validation. **Aihua Lin:** Data curation; formal analysis; methodology; software. **Weiqiu Cheng:** Data curation; formal analysis; investigation; methodology; resources; software; validation. **Nils Eiel Steen:** Conceptualization; data curation; funding acquisition; investigation; project administration; resources; supervision; validation. **Alexey Shadrin:** Data curation; formal analysis; investigation; methodology; project administration; software; validation. **Oleksandr Frei:** Data curation; formal analysis; methodology; project administration; resources; software; validation. **Srdjan Djurovic:** Data curation; funding acquisition; investigation; project administration; supervision; validation. **Anders M. Dale:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision. **Ole A. Andreassen:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation. **Olav B. Smeland:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation.

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