

## 1 Multi-ancestry study of the genetics of problematic alcohol use in >1 million individuals

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94 **Abstract**

95 Problematic alcohol use (PAU) is a leading cause of death and disability worldwide. To improve  
96 our understanding of the genetics of PAU, we conducted a large cross-ancestry meta-analysis  
97 of PAU in 1,079,947 individuals. We observed a high degree of cross-ancestral similarity in the  
98 genetic architecture of PAU and identified 110 independent risk variants in within- and cross-  
99 ancestry analyses. Cross-ancestry fine-mapping improved the identification of likely causal  
100 variants. Prioritizing genes through gene expression and/or chromatin interaction in brain  
101 tissues identified multiple genes associated with PAU. We identified existing medications for  
102 potential pharmacological studies by drug repurposing analysis. Cross-ancestry polygenic risk  
103 scores (PRS) showed better performance in independent sample than single-ancestry PRS.  
104 Genetic correlations between PAU and other traits were observed in multiple ancestries, with  
105 other substance use traits having the highest correlations. The analysis of diverse ancestries  
106 contributed significantly to the findings, and fills an important gap in the literature.

## 107 Introduction

108 Alcohol use disorder (AUD) is a chronic relapsing disease associated with a host of  
109 adverse medical, psychiatric, and social consequences<sup>1</sup>. Given observed heritability ( $h^2 \sim 50\%^2$ ),  
110 there has been substantial progress made in genome-wide association studies (GWAS) of AUD  
111 and problematic drinking<sup>3-9</sup>, and also for measures of alcohol consumption<sup>10,11</sup>. A prior GWAS of  
112 problematic alcohol use (PAU, a phenotype based on a meta-analysis of highly genetically  
113 correlated (genetic correlations  $>0.7$ ) AUD<sup>7</sup>, alcohol dependence [AD]<sup>5</sup>, and AUDIT-P [Alcohol  
114 Use Disorders Identification Test-Problem score, a measure of problematic drinking]<sup>4,12</sup>,  
115  $N=435,563$ ) identified 29 independent risk variants, predominantly in European (EUR) ancestry  
116 subjects<sup>6</sup>. Consistent with genetic studies of other complex traits, and the high polygenicity of  
117 PAU, larger and more ancestrally-representative samples need to be examined to outline the  
118 genetic architecture of these alcohol use traits.

119

120 A key finding from recent studies is that both AUD and AUDIT-P differ phenotypically  
121 and genetically from typical alcohol consumption<sup>4,7</sup>. AUD and AUDIT-P index aspects of  
122 disordered alcohol intake and correlate with genetic liability to negative psychiatric and  
123 psychosocial factors (e.g., higher major depressive disorder [MDD], lower educational  
124 attainment). An item-level study of the AUDIT questionnaire confirmed a two-factor structure at  
125 the genetic level, underscoring unique genetic influences on alcohol consumption and alcohol-  
126 related problems<sup>13</sup> and noted that the genetics of drinking frequency were confounded by socio-  
127 economic status. A similar pattern – genetic distinctions between substance use disorder (SUD)  
128 vs. non-dependent use – has also been observed for cannabis use disorder and cannabis use<sup>14</sup>.  
129 Furthermore, aggregating across multiple substance use disorders suggests that problematic  
130 and disordered substance use has a unique genetic architecture that, while shared across  
131 SUDs, does not overlap fully with non-dependent substance use *per se*<sup>15</sup>.

132 Notwithstanding prior discovery of multiple genome-wide significant (GWS) loci for PAU,  
133 there are major gaps in our understanding of its genetic underpinnings. First, the estimated  
134 single-nucleotide polymorphism (SNP)-based heritability ( $h^2$ ) of AUD and PAU ranges from 5.6%  
135 to 10.0%<sup>4-7</sup>, reflecting substantial “missing heritability” compared to estimates based on genetic  
136 epidemiology, which show ~50% heritability<sup>2</sup>. Second, most of the available samples used in  
137 human genetic studies – including for AUD – are of EUR ancestry; lack of ancestral diversity is  
138 a major problem both for understanding the genetics of these traits, and for potential  
139 applications of these genetic discoveries to global populations<sup>16</sup>. Our previous study in the  
140 Million Veteran Program (MVP) analyzed AUD in multiple ancestral groups<sup>7</sup>. However, non-EUR  
141 samples (N=72,387) were far smaller than EUR samples (N=202,004), resulting in inadequate  
142 statistical power and unbalanced gene discovery across ancestral backgrounds, which limits our  
143 understanding of the genetic architecture underlying the trait across populations.

144

145 To improve our understanding of the biology of PAU in multiple populations, we  
146 conducted substantially larger ancestry-specific GWAS of PAU followed by a cross-ancestry  
147 meta-analysis in 1,079,947 individuals from multiple cohorts. We identified 85 independent risk  
148 variants in EUR participants (almost tripling the number identified in previous studies) and 110  
149 in the within-ancestry and cross-ancestry meta-analyses. We investigated the shared genetic  
150 architectures of PAU across different ancestries, performed fine-mapping for causal variants by  
151 combining information from multiple ancestries, and tested cross-ancestry polygenic risk score  
152 (PRS) associations with AUDIT-P in the UK Biobank (UKB) samples<sup>17</sup>. We combined genes  
153 identified by gene-based association analysis, transcriptome-wide association analysis (TWAS)  
154 and brain-chromatin interaction analysis, found dozens of genes linking to brain with convergent  
155 evidence. Drug repurposing analysis identified potential medications for further pharmacological  
156 studies, bringing forward the hope of novel biologically-directed medications strategies with the

157 further potential of personalization. We conducted phenome-wide PRS analyses in biobanks  
158 from the PsycheMERGE Network<sup>18</sup> in AFR and EUR-ancestry samples. We tested the genetic  
159 correlation between PAU and other traits, especially novel with respect to AFR samples where  
160 such analyses could not be conducted previously. These findings substantially augment the  
161 number of loci that contribute to risk of PAU, increasing power to investigate the causal  
162 relationships of PAU with other diseases, and identify novel druggable targets whose  
163 therapeutic potential requires empirical evaluation.

164

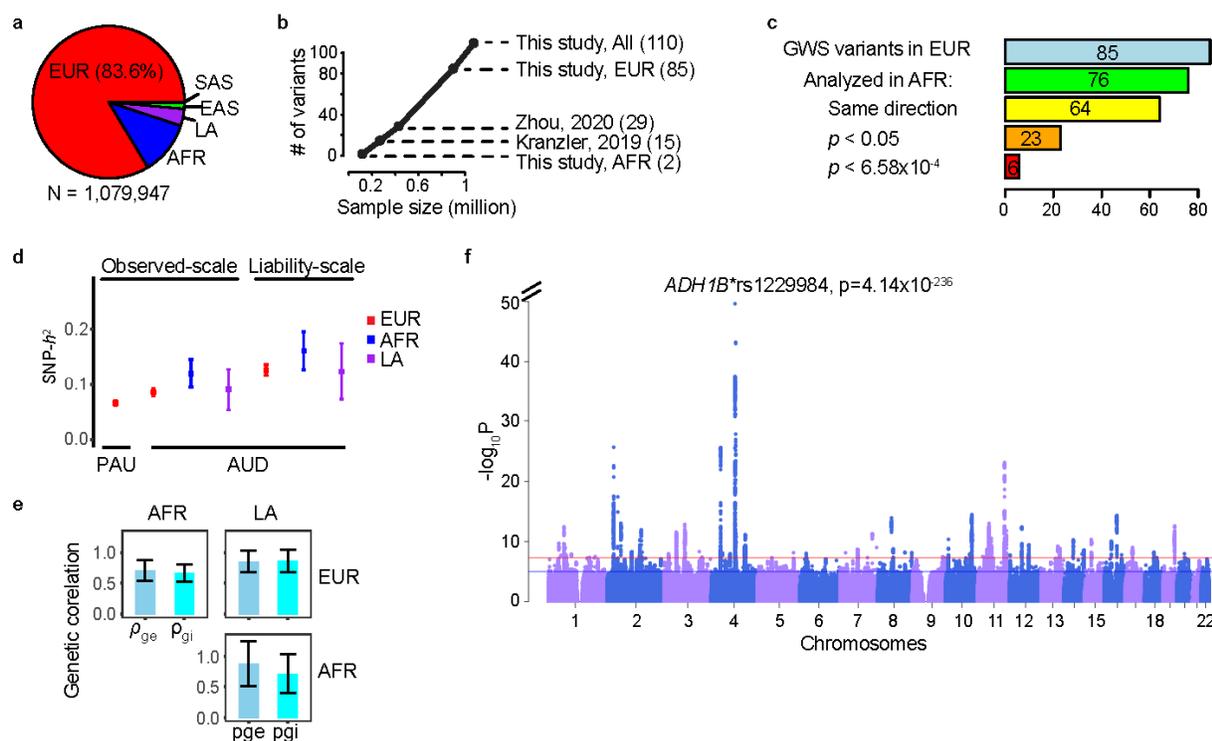
## 165 **Results**

166 **Ancestrally diverse data collection.** We collected newly genotyped subjects (most from MVP)  
167 and previously published data from multiple cohorts (MVP<sup>19</sup>, FinnGen<sup>20</sup>, UKB<sup>17</sup>, Psychiatric  
168 Genomics Consortium (PGC)<sup>5</sup>, iPSYCH<sup>21,22</sup>, Queensland Berghofer Medical Research Institute  
169 (QIMR) cohorts<sup>23-25</sup>, Yale-Penn 3<sup>26</sup>, and East Asian cohorts<sup>27</sup>) resulting in a total of 1,079,947  
170 subjects (Table 1). Five ancestral groups were analyzed (Figure 1a): EUR (N=903,147), AFR  
171 (N=122,571), Latin American (LA, N=38,962), East Asian (EAS, N=13,551, all published in ref.  
172 27), and South Asian (SAS, N=1,716). As in our previous study<sup>6</sup>, we utilized data on  
173 International Classification of Diseases (ICD)-diagnosed AUD (N<sub>case</sub>=136,182; N<sub>control</sub>=692,594),  
174 DSM-IV AD (N<sub>case</sub>=29,770; N<sub>control</sub>=70,282) and AUDIT-P (N=151,119), together defined as  
175 problematic alcohol use (PAU; based on high genetic correlations across these measures). The  
176 total number of AUD and AD cases was 165,952, almost double the 85,391 cases in the  
177 previously largest study<sup>28</sup>.

178

179 **Figure 1. Genetic architecture of problematic alcohol use (PAU).** a, Sample sizes in  
180 different ancestral groups. b, Relationship between sample size and number of independent

181 variants identified. Kranzler et al., 2019: cross-ancestry meta-analysis for AUD; Zhou et al.,  
 182 2020: PAU in EUR. **c**, Lookup for cross-ancestry replication in AFR for the 85 independent  
 183 variants in EUR meta-analysis. Of the 85 variants, 76 could be analyzed in AFR (see Methods).  
 184 Sign test was performed for the number of variants with same direction of effect (64/76,  
 185  $p=1.0 \times 10^{-9}$ ). 23 variants were nominally significant in AFR and 6 were significant after multiple  
 186 correction ( $p < 0.05/76$ ). **d**, Observed-scale and liability-scale SNP-based heritability ( $h^2$ ) in  
 187 multiple ancestries. **e**, Cross-ancestry genetic-effect correlation ( $\rho_{ge}$ ) and genetic-impact  
 188 correlation ( $\rho_{gi}$ ) between EUR, AFR and LA ancestries. Error bar is the 95% confidence interval.  
 189 **f**, Genome-wide association results for PAU in the cross-ancestry meta-analysis. Red line is  
 190 significance threshold of  $5 \times 10^{-8}$ . EUR, European; AFR, African; LA, Latin American; EAS, East  
 191 Asian; SAS, South Asian; GWS, genome-wide significant.



192

193

194 **Table 1. Demographics for cohorts in the meta-analysis of PAU.** Cohorts are described in

195 the Methods. UKB-EUR1: genetically defined White-British by UK Biobank; UKB-EUR2:  
 196 genetically defined European non-White-British participants (see Methods); AGDS, the  
 197 Australian Genetics of Depression Study; TWINS, the Australian twin-family study of alcohol use  
 198 disorder; GBP, the Australian Genetics of Bipolar Disorder Study; iPSYCH1, phase 1 of iPSYCH;  
 199 iPSYCH2, phase 2 of iPSYCH; YP3, Yale-Penn 3;  $N_{\text{effective}}$ , effective sample size; Thai, study of  
 200 the genetics of methamphetamine dependence in Thailand; GSA, Illumina Global Screening  
 201 Array; MEGA, Illumina Multi-Ethnic Global Array; Cyto, Illumina Cyto12 array.

Cohorts	Traits	$N_{\text{case}}$	$N_{\text{control}}$	$N_{\text{total}}$	$N_{\text{female}}$ (%)	$N_{\text{effective}}$	Ref <sup>a</sup>
<b>European ancestry (EUR)</b>							
MVP	AUD	80,028	368,113	448,141	33,345 (7.4)	262,947	[6] and new
FinnGen	AUD	8,866	209,926	218,792	123,579 (56.5)	34,027	New <sup>b</sup>
UKB-EUR1	AUDIT-P	-	-	132,001	74,113 (56.1)	132,001	[6] and new
UKB-EUR2	AUDIT-P	-	-	17,898	10,529 (58.5)	17,898	New
PGC	AD	9,938	30,992	40,930	20,933 (51.1)	23,075	[5] <sup>d</sup>
QIMR_AGDS	AD	6,726	4,467	11,193	8,605 (76.9)	10,737	New
QIMR_TWINS	AD	2,772	5,630	8,402	4,922 (58.6)	7,430	[5] and new
QIMR_GBP	AD	1,287	751	2,038	1,435 (70.4)	1,897	New
iPSYCH1	AD	2,117	13,238	15,355	8,077 (52.6)	7,301	New
iPSYCH2	AD	1,024	5,732	6,756	3,607 (53.4)	3,475	New
YP3	AD	567	1,074	1,641	854 (52.0)	1,484	New
<b>Sub_total</b>	<b>PAU</b>	<b>113,325</b>	<b>639,923</b>	<b>903,147</b>	<b>289,999 (32.1)</b>	<b>502,272</b>	
<b>African ancestry (AFR)</b>							
MVP	AUD	36,330	79,100	115,430	16,084 (13.9)	99,583	[7] and new
PGC	AD	3,335	2,945	6,280	3,124 (49.7)	4,991	[5]
YP3	AD	451	410	861	430 (50.0)	959	New
<b>Sub_total</b>	<b>AUD</b>	<b>40,116</b>	<b>82,455</b>	<b>122,571</b>	<b>19,638 (16.0)</b>	<b>105,433</b>	
<b>Latin American ancestry (LA)</b>							
<b>MVP</b>	<b>AUD</b>	<b>10,150</b>	<b>28,812</b>	<b>38,962</b>	<b>3,731 (9.6)</b>	<b>30,023</b>	[7] and new
<b>East Asian<sup>a</sup> ancestry (EAS)</b>							
MVP	AUD	701	6,254	6,955	747 (10.7)	2,521	[27]
Han Chinese–GSA	AD	533	2,848	3,381	1,012 (29.9)	1,796	
Thai METH–MEGA	AD	794	1,576	2,370	1,008 (42.5)	2,112	
Thai METH–GSA	AD	127	405	532	263 (49.4)	387	
Han Chinese–Cyto	AD	99	214	313	0 (0)	271	
<b>Sub_total</b>	<b>AUD</b>	<b>2,254</b>	<b>11,297</b>	<b>13,551</b>	<b>3,030 (22.4)</b>	<b>7,087</b>	
<b>South Asian ancestry (SAS)</b>							
MVP	AUD	107	389	496	67 (13.5)	336	[7] and new
UKB-SAS	AUDIT-P	-	-	1,220	535 (43.9)	1,220	New
<b>Sub_total</b>	<b>PAU</b>	<b>107</b>	<b>389</b>	<b>1,716</b>	<b>602 (35.1)</b>	<b>1,556</b>	
<b>Total</b>	<b>PAU</b>	<b>165,952</b>	<b>762,876</b>	<b>1,079,947</b>	<b>317,000 (29.4)</b>	<b>646,371</b>	

202 Note: <sup>a</sup>data either published in previous alcohol GWAS or newly included for this project.  
203 <sup>b</sup>FinnGen summary statistics were downloaded from FinnGen data freeze v5  
204 (<https://r5.finnngen.fi/>). <sup>c</sup>Included related subjects from UKB. <sup>d</sup>Reran the PGC AD GWAS in EUR  
205 excluding two Australian cohorts.

206

207 **Genome-wide association results for PAU.** We performed GWAS and within-ancestry meta-  
208 analyses for PAU in five ancestral groups and then completed a cross-ancestry meta-analysis.  
209 In the EUR meta-analysis, 113,325 cases of AUD/AD, 639,923 controls and 149,899  
210 participants with AUDIT-P scores were analyzed (Supplementary Figure 1a). After conditional  
211 analysis, 85 independent variants at 75 loci reached GWS (Methods, Supplementary Table 1)  
212 (see also Figure 1b). Of these variants, 41 are in protein-coding genes; of these, 5 are missense  
213 variants (*GCKR*\*rs1260326; *ADH1B*\*rs75967634; *ADH1B*\*rs1229984; *SCL39A8*\*rs13107325;  
214 *BDNF*\*rs6265).

215

216 Due to the smaller sample numbers, the non-EUR GWAS yielded fewer variants  
217 associated with PAU than did the EUR GWAS (Supplementary Table 1). The AFR meta-  
218 analysis found two independent *ADH1B* missense variants (rs1229984 and rs2066702)  
219 associated with AUD (Figure 1b, Supplementary Figure 1b); these were reported previously<sup>7,26</sup>.  
220 In the LA samples from MVP, only *ADH1B*\*rs1229984 (lead SNP) was identified  
221 (Supplementary Figure 1c). Two independent risk variants, *ADH1B*\*rs1229984 and  
222 *BRAP*\*rs3782886, were reported in EAS previously<sup>27,29</sup>. In the small SAS meta-analysis, one  
223 intergenic variant (rs12677811) was associated with AUD; however, this SNP was present only  
224 in the UKB (Supplementary Figure 1d).

225

226 Of the 85 lead variants identified in the EUR GWAS, 76 were either directly analyzed or  
227 had proxy variants in AFR (Methods, Supplementary Table 2, Figure 1c), 64 of which had the

228 same direction of effect (sign test  $p=1.00\times 10^{-9}$ ). Of these, 23 were nominally associated ( $p<0.05$ )  
229 and 6 were significantly associated with AUD after multiple-testing correction ( $p<6.58\times 10^{-4}$ ). In  
230 LA, 15 of the EUR GWS variants were nominally significant ( $p<0.05$ ) and 2 were significantly  
231 associated with AUD (rs12048727 and rs1229984). In EAS, 5 variants were nominally  
232 significant and two were significantly associated with AUD (rs1229984 and rs10032906). Only  
233 two variants were nominally associated with PAU in SAS (rs1229984 was not present in SAS).

234

235 We estimated the SNP-based heritability ( $h^2$ ) for PAU and AUD (excluding AUDIT-P  
236 from UKB) in EUR, AFR and LA; significant  $h^2$  estimates (range from 0.066 to 0.127) were  
237 observed (Figure 1d, Supplementary Table 3).

238

239 High genetic correlations were observed across the EUR, AFR, and LA ancestries  
240 (Figure 1e, Supplementary Table 4). The genetic-effect correlation ( $\rho_{ge}$ ) is 0.71 (SE=0.09,  
241  $p=6.16\times 10^{-17}$ ) between EUR and AFR, 0.85 (SE=0.09,  $p=3.14\times 10^{-22}$ ) between EUR and LA, and  
242 0.88 (SE=0.18,  $p=1.58\times 10^{-6}$ ) between AFR and LA. The genetic-impact correlation ( $\rho_{gi}$ ) is 0.67  
243 (SE=0.07,  $p=2.78\times 10^{-21}$ ) between EUR and AFR, 0.86 (SE=0.09,  $p=3.52\times 10^{-20}$ ) between EUR  
244 and LA, and 0.72 (SE=0.16,  $p=9.63\times 10^{-6}$ ) between AFR and LA. The estimates involving  
245 smaller study populations were not robust (Bonferroni  $p>0.05$ ).

246

247 In the cross-ancestry meta-analysis of all available datasets, we identified 100  
248 independent variants at 90 loci (Figure 1f, Supplementary Table 1); 80 are novel findings for  
249 PAU. Of these, 53 variants were located in protein-coding genes, of which 9 are missense  
250 variants: *GCKR*\*rs1260326; *ADH1B*\*rs75967634, rs1229984, and rs2066702;  
251 *SCL39A8*\*rs13107325; *OPRM1*\*rs1799971; *SLC25A37*\*rs2942194; *BDNF*\*rs6265; and

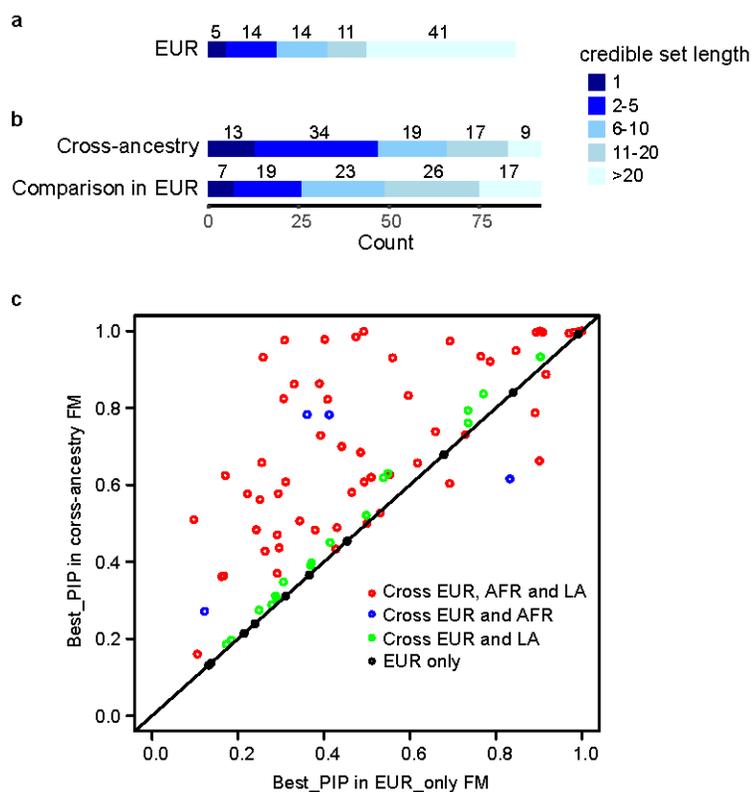
252 *BRAP*\*rs3782886. The cross-ancestry meta-analysis identified 24 more risk variants than the  
253 EUR meta-analysis, but 9 EUR variants fell below GWS (p-values ranging from  $5.26 \times 10^{-6}$  to  
254  $9.84 \times 10^{-8}$ ). In total, 110 unique variants were associated with PAU in either the within-ancestry  
255 or cross-ancestry analyses (Figure 1b, Supplementary Table 1).

256

257 **Within- and cross-ancestry causal variant fine-mapping.** We performed within-ancestry fine-  
258 mapping for the 85 clumped regions with independent lead variants in EUR (Supplementary  
259 Tables 5 and 6). A median number of 115 SNPs were included in each region to estimate the  
260 credible sets with 99% posterior inclusion probability (PIP) of causal variants. After fine-mapping,  
261 the median number of SNPs constituting the credible sets was reduced to 20. Among the 85  
262 regions, there were 5 credible sets that include only a single variant with PIP  $\geq 99\%$  (presumably  
263 indicating successful identification of specific causal variants): rs1260326 in *GCKR*, rs472140  
264 and rs1229984 in *ADH1B*, rs2699453 (intergenic), and rs2098112 (intergenic). Another 19  
265 credible sets contained  $\leq 5$  variants (Figure 2a).

266

267 **Figure 2. Fine-mapping for PAU.** **a**, Fine-mapping of causal variants in 85 regions in EUR. **b**,  
268 92 regions in cross-ancestry analysis were fine-mapped and a direct comparison was done for  
269 these regions in EUR. **c**, Comparison for the highest PIPs from cross-ancestry and EUR-only  
270 fine-mapping in the 92 regions. Red dots are the regions fine-mapped across EUR, AFR, and  
271 LA; blue dots are the regions fine-mapped across EUR and AFR; green dots are the regions  
272 fine-mapped across EUR and LA; black dots are the regions only fine-mapped in EUR. FM, fine-  
273 mapping.



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We performed cross-ancestry fine-mapping to identify credible sets with 99% PIP for causal variants proximate to 92 independent lead variants in the cross-ancestry meta-analysis (Supplementary Tables 7 and 8). The median number of SNPs in the credible sets was 9. 13 credible sets contain only a single variant with  $PIP \geq 99\%$ ; 47 credible sets contain  $\leq 5$  variants (Figure 2b). For example, fine-mapping the region proximate to lead SNP rs12354219 (which maps to *DYPD* on chromosome 1) identified rs7531138 as the most likely potential causal variant ( $PIP=48\%$ ), although this variant and rs12354219 ( $PIP=11\%$ ) are in high linkage disequilibrium (LD) in different populations ( $r^2$  ranges from 0.76 to 0.99). In a cross-ancestry meta-analysis rs7531138 showed significant association with schizophrenia ( $p=1.04 \times 10^{-8}$ ), but rs12354219 ( $p=6.18 \times 10^{-8}$ ) did not<sup>30</sup> (although the two p-values were very similar). rs7531138 is also a lead SNP associated with educational attainment ( $p=1.74 \times 10^{-11}$ ), unlike rs12354219 ( $p > 5 \times 10^{-8}$ )<sup>31</sup>.

288

289 To compare within- and cross-ancestry fine-mapping, we performed fine-mapping for the  
290 above 92 regions using the same SNP sets and EUR-only LD information (Figure 2b & 2c). The  
291 median number of SNPs in the credible sets is 13, with 7 credible sets containing a single  
292 variant and 26 containing  $\leq 5$  variants, indicating that cross-ancestry fine-mapping improved  
293 causal variant identification, consistent with other studies reporting improved fine-mapping by  
294 including other ancestries<sup>11</sup>.

295

296 **Gene-based association analysis.** We used MAGMA<sup>32,33</sup> to perform gene-based association  
297 analyses. 130 genes in EUR, 9 in AFR and 6 in LA (for AFR and LA populations, all mapped to  
298 the ADH gene cluster), and 7 in EAS (mapped to either the ADH gene cluster or the *ALDH2*  
299 region<sup>27</sup>) were associated with PAU or AUD (Supplementary Table 9). There were no significant  
300 findings in SAS.

301

302 **Transcriptome-wide association analyses (TWAS).** We used S-PrediXcan<sup>34</sup> to identify  
303 predicted gene expression associations with PAU in 13 brain tissues<sup>35</sup>. 426 significant gene-  
304 tissue associations were identified, representing 89 unique genes (Supplementary Table 10).  
305 Five genes showed associations with PAU in all available brain tissues, including *AMT*  
306 (Aminomethyltransferase), *YPEL3* (Yippee Like 3), *EVI2A* (Ecotropic Viral Integration Site 2A),  
307 *EVI2B* (Ecotropic Viral Integration Site 2B), and *CTA-223H9.9* (lncRNA). We also observed  
308 associations between PAU and the expression of alcohol dehydrogenase genes (*ADH1B* in the  
309 putamen (basal ganglia), *ADH1C* in 10 brain tissues, and *ADH5* in cerebellar hemisphere and  
310 cerebellum). Among the brain tissues, caudate (basal ganglia) had the most genes whose  
311 expression was associated with PAU (42 genes), followed by the putamen (basal ganglia) (39

312 genes). TWAS that integrated evidence across 13 brain tissues using S-MultiXcan<sup>36</sup> to test joint  
313 effects of gene expression variation identified 121 genes (81 shared with S-PrediXcan) whose  
314 expression was associated with PAU (Supplementary Table 11).

315

316 **Linking risk genes to brain chromatin interaction.** We used H-MAGMA<sup>37</sup> to implicate risk  
317 genes associated with PAU by incorporating brain chromatin interaction profiles. 1,030 gene-  
318 chromatin associations were identified in 6 brain Hi-C annotations, representing 401 unique  
319 genes (Supplementary Table 12). 58 genes showed association with chromatin interaction in all  
320 6 annotations, including *ADH1B*, *ADH1C*, *DRD2*, *EVI2A* and others that also showed evidence  
321 by TWAS in brain tissues.

322

323 **Convergent evidence linking association to brain.** We examined overlapped genes by both  
324 gene-based association analysis and TWAS in brain tissues and/or H-MAGMA analysis using  
325 Hi-C brain annotations. Among the 130 genes associated with PAU in EUR, 60 were also  
326 implicated by TWAS findings either by single brain tissue (S-PrediXcan) or across brain tissues  
327 (S-MultiXcan), 82 have evidence of brain chromatin interaction, and 38 have evidence from both  
328 TWAS and Hi-C annotations including *ADH1B*, *DRD2*, *KLB* and others (Supplementary Table 9).

329

330 **Probabilistic fine-mapping of TWAS.** We performed fine-mapping for TWAS using FOCUS<sup>38</sup>,  
331 a method that estimates credible gene sets predicted to include the causal gene that can be  
332 prioritized for functional assays. We detected 53 credible sets at a nominal confidence level (set  
333 at 90% PIP). These contained 145 gene-tissue associations with an average PIP of 32%  
334 (Supplementary Table 13). For the 19 gene-tissue associations having PIP >90%, 9 are from  
335 brain tissues (e.g., *ZNF184* expression in hypothalamus (PIP=0.94%), *MTCH2* expression in

336 nucleus accumbens (basal ganglia) (PIP=99%), *SLC4A8* expression in dorsolateral prefrontal  
337 cortex (PIP=98%), *YPEL3* expression in cerebellum (PIP=100%), and *CHD9* expression in  
338 dorsolateral prefrontal cortex (PIP=100%).

339

340 **Drug repurposing.** Independent genetic signals from the cross-ancestry meta-analysis were  
341 searched in OpenTargets.org<sup>39</sup> for druggability and medication target status based on nearest  
342 genes. Among them, *OPRM1* implicated naltrexone and *GABRA4* implicated acamprosate, both  
343 current treatments for AUD. Additionally, the genes *DRD2*, *CACNA1C*, *DPYD*, *PDE4B*, *KLB*,  
344 *BRD3*, *NCAM1*, *FTOP*, and *MAPT*, were identified as druggable genes.

345

346 From the drug repurposing analysis using S-PrediXcan results, 287 compounds were  
347 significantly correlated with the transcriptional pattern associated with risk for PAU  
348 (Supplementary Table 14). Of these 287, 141 medications were anti-correlated with the  
349 transcriptional pattern. Of those, trichostatin-a ( $p=3.29\times 10^{-35}$ ), melperone ( $p=6.88\times 10^{-11}$ ),  
350 triflupromazine ( $p=7.37\times 10^{-10}$ ), spironolactone ( $p=2.45\times 10^{-9}$ ), amlodipine ( $p=1.42\times 10^{-6}$ ) and  
351 clomethiazole ( $p=1.30\times 10^{-5}$ ) reversed the transcriptional profile associated with increased PAU  
352 risk, targeted a gene near an independent significant locus in the cross-ancestry GWAS.

353

354 **Cross-ancestry polygenic risk score association.** We tested the cross-ancestry PRS  
355 association with AUDIT-P in UKB using AUD summary data from EUR (leaving out the UKB  
356 AUDIT-P data), AFR, and LA. PRS-CSx was applied to calculate the posterior effect sizes for  
357 each SNP by leveraging LD diversity across discovery samples<sup>40</sup>. We validated the PRS  
358 associations with AUDIT-P in UKB-EUR2 and tested them in UKB-EUR1 (see Table 1). In the  
359 UKB-EUR1 samples, EUR-based AUD PRS is significantly associated with AUDIT-P (Z-

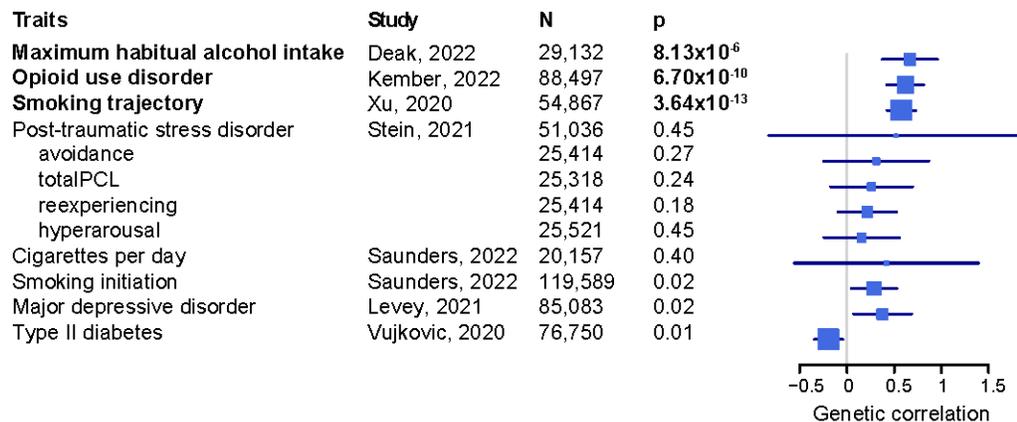
360 score=11.6,  $p=3.14\times 10^{-31}$ ,  $\Delta R^2=0.11\%$ ). By incorporating GWAS data from multiple ancestries,  
361 the AUD PRS is more significantly associated with AUDIT-P and explains more variance (Z-  
362 score=13.6,  $p=2.44\times 10^{-42}$ ,  $\Delta R^2=0.15\%$ ) than the single ancestry AUD PRS.

363

364 **Genetic correlations.** We confirmed significant positive genetic correlations ( $r_g$ ) in EUR  
365 between PAU and substance use and psychiatric traits<sup>6</sup> (Supplementary Table 15). AD<sup>5</sup> showed  
366 the highest correlation with PAU ( $r_g=0.85$ , SE=0.07,  $p=4.49\times 10^{-34}$ ), followed by maximum  
367 habitual alcohol intake<sup>9</sup> ( $r_g=0.79$ , SE=0.03,  $p=1.24\times 10^{-191}$ ), opioid use disorder<sup>41</sup> ( $r_g=0.78$ ,  
368 SE=0.04,  $p=1.20\times 10^{-111}$ ), drinks per week<sup>11</sup> ( $r_g=0.76$ , SE=0.02,  $p<1\times 10^{-200}$ ), smoking trajectory<sup>42</sup>  
369 ( $r_g=0.63$ , SE=0.02,  $p=2.47\times 10^{-176}$ ), and cannabis use disorder<sup>14</sup> ( $r_g=0.61$ , SE=0.04,  $p=4.85\times 10^{-$   
370 <sup>63</sup>). We next tested  $r_g$  between AUD and 13 published traits with large GWAS in AFR (Figure 3,  
371 Supplementary Table 16). As in EUR, the traits with the strongest correlations were substance  
372 use traits. Maximum habitual alcohol intake<sup>9</sup> ( $r_g=0.67$ , SE=0.15,  $p=8.13\times 10^{-6}$ ) showed the  
373 highest correlation with AUD, followed by opioid use disorder<sup>41</sup> ( $r_g=0.62$ , SE=0.10,  $p=6.70\times 10^{-10}$ ),  
374 and smoking trajectory<sup>42</sup> ( $r_g=0.57$ , SE=0.08,  $p=3.64\times 10^{-4}$ ). Major depressive disorder<sup>43</sup> and  
375 smoking initiation<sup>11</sup> showed nominally significant ( $p<0.05$ ) positive correlation with AUD and type  
376 2 diabetes<sup>44</sup> showed a nominally significant negative correlation.

377

378 **Figure 3. Genetic correlations between AUD and traits in AFR.** totalPCL, total index of  
379 recent symptom severity by PTSD checklist for DSM-IV. Traits labeled in bold font are  
380 genetically correlated with AUD after Bonferroni correction ( $p<3.83\times 10^{-3}$ ). Error bar is 95%  
381 confidence interval.



382

383

384 **PRS for phenome-wide associations.** We calculated PRS for PAU (based on the meta-  
 385 analysis of PAU in EUR) in 131,500 individuals of European ancestry, PRS for AUD (based on  
 386 the meta-analysis of AUD in AFR) in 27,494 individuals of African ancestry in 4 biobanks  
 387 (Vanderbilt University Medical Center BioVU, Penn Medicine BioBank, Mount Sinai Icahn  
 388 School of Medicine BioMe<sup>TM</sup>, and Mass General Brigham Biobank) from the PsycheMERGE  
 389 Network, and conducted phenome-wide association studies (PheWAS). After Bonferroni  
 390 correction, 58 of the 1,493 tested phenotypes were significantly associated with the PAU PRS in  
 391 EUR, including 26 mental disorders, 8 respiratory traits, 5 neurological conditions, 4 infectious  
 392 diseases, and 4 neoplasms (Supplementary Table 17, Supplementary Figure 2). For the 793  
 393 phenotypes tested in AFR, alcoholism (OR=1.25, SE=0.04,  $p=2.62 \times 10^{-7}$ ), alcohol-related  
 394 disorders (OR=1.21, SE=0.04,  $p=4.11 \times 10^{-7}$ ), and tobacco use disorder (OR=1.09, SE=0.02,  
 395  $p=6.98 \times 10^{-6}$ ) showed significant association with AUD PRS (Supplementary Table 18,  
 396 Supplementary Figure 3).

397

398 We also conducted PheWAS in Yale-Penn, a deeply phenotyped cohort with  
 399 comprehensive psychiatric assessments (substance use disorders [SUDs] and psychiatric  
 400 disorders) and assessments for physical and psychosocial traits<sup>26,45</sup>. In EUR, the PRS of PAU

401 was associated with 123 traits, including 26 in alcohol, 39 in opioid, 24 in cocaine and 17 in  
402 tobacco categories (Supplementary Table 19, Supplementary Figure 4), indicating high  
403 comorbidity and shared genetic components across SUDs. In AFR, the AUD PRS was  
404 associated with the DSM-5 AUD criterion count, alcohol-induced blackouts, frequency of alcohol  
405 use, and 3 individual AUD criteria: unsuccessful effort to decrease use, used more than  
406 intended, and continued use despite social/interpersonal problems (Supplementary Table 20,  
407 Supplementary Figure 5).

408

## 409 **Discussion**

410 We report here the largest multi-ancestry GWAS for PAU to date, comprising over 1  
411 million individuals and including 165,952 AUD/AD cases, more than double the largest previous  
412 study<sup>28</sup>. Considering the results from this study and previous GWAS, in all ancestral populations,  
413 we observed a nearly linear relationship between sample size and the number of risk variants  
414 discovered.

415 Convergent evidence supports substantial shared genetic architecture for PAU across  
416 multiple ancestries. First, of the 76 independent risk variants detected in EUR and represented  
417 in other populations, the majority have the same direction of effect in AFR (84.2%) and LA  
418 (81.6%). Twenty-three variants (30.3%) in AFR and 15 (19.7%) in LA were nominally replicated  
419 ( $p < 0.05$ ), which is considerable given the appreciably lower sample size of these ancestral  
420 groups. Second, there are high cross-ancestry genetic correlations among EUR, AFR, and LA,  
421 ranging from 0.71 (between EUR and AFR) to 0.88 (between AFR and LA). Third, cross-  
422 ancestry meta-analysis substantially improved the power for gene discovery and resulted in the  
423 identification of 24 additional variants beyond the EUR-only results.

424

425 A total of 110 variants were associated with PAU in either within-ancestry or cross-  
426 ancestry analyses; of these, 9 are missense variants. These include rs1799971 in *OPRM1*  
427 which encodes the  $\mu$  opioid receptor, which plays roles in regulating pain, reward, and addictive  
428 behaviors. This variant was also associated with opioid use disorder (OUD) in multiple large  
429 GWAS<sup>41,46,47</sup>. Previously, there were inconsistent candidate gene association results for  
430 *OPRM1*\*rs1799971 and AUD (reviewed in ref. 48). This is the first GWAS to confirm the  
431 association of rs1799971 in PAU; the risk allele is the same as for OUD. In contrast to an  
432 apparent EUR-specific effect of rs1799971 on OUD, the *OPRM1* association with PAU  
433 ( $p=6.16\times 10^{-9}$ ) was detected in the cross-ancestry meta-analysis. Further investigation in larger  
434 non-EUR samples is needed to assess the association of this SNP with SUDs in different  
435 population groups. Rs6265 in *BDNF* (brain-derived neurotrophic factor) encodes a member of  
436 the nerve growth factor family of proteins and has been investigated intensively in the past  
437 decades<sup>49</sup>; studies showed that this variant is associated with smoking traits<sup>10</sup> and externalizing  
438 behavior<sup>50</sup>. Rs13107325 in *SLC39A8* (Solute Carrier Family 39 Member 8) has been associated  
439 with schizophrenia<sup>51</sup>, substance uses<sup>6,7,10</sup> and many glyceic traits, and is critical for  
440 glycosylation pathways<sup>52,53</sup>.

441  
442 Previous studies have shown that PAU is a brain-related trait with evidence of functional  
443 and heritability enrichment in multiple brain regions<sup>6,7</sup>. We performed gene-based association,  
444 TWAS in brain tissues, and H-MAGMA analysis in brain annotations. We identified 38 genes  
445 that were supported across multiple levels of analysis. For example, *ADH1B* expression in  
446 putamen was associated with PAU by TWAS, and with chromatin interaction in all 6 brain  
447 annotations by H-MAGMA, indicating additional potential biological mechanisms for the  
448 association of *ADH1B* with PAU risk through gene expression and/or chromatin interactions in  
449 brain, potentially independent of the well-known hepatic effect on alcohol metabolism. *DRD2*

450 expression in cerebellar hemisphere and chromatin interaction in all brain annotations were also  
451 associated with PAU risk. Alcohol metabolism, as is well-reported, has affects that modulate  
452 alcohol's aversive and reinforcing effects<sup>54</sup>, but also contributes to brain histone acetylation,  
453 gene expression and alcohol-related associative learning in mice<sup>55</sup>. The detailed molecular  
454 pathways and mechanisms involving changes in human brain need to be elucidated.

455

456 Independent genetic signals supported the two main AUD pharmacological treatments  
457 acamprosate and naltrexone: *GABRA4* is a target of acamprosate while *OPRM1* is a target for  
458 naltrexone. We identified genes known to be druggable; our multivariate analysis also provided  
459 evidence for several repurposable drugs. Trichostatin-a, a histone deacetylase inhibitor, showed  
460 effects on H3 and H4 acetylation and neuropeptide Y expression in the amygdala and  
461 prevented the development of alcohol withdrawal-related anxiety in rats<sup>56</sup>. Clinical trials showed  
462 that melperone, a dopamine and serotonin receptor antagonist, has inconsistent effects on  
463 alcoholic craving<sup>57,58</sup>. Spironolactone, a mineralocorticoid receptor antagonist, reduced alcohol  
464 use in both rats and humans in a recent study<sup>59</sup>. Clomethiazole, a GABA receptor antagonist,  
465 also showed effect of treatment for alcohol withdrawal syndrome<sup>60</sup>. Future clinical trials may use  
466 the evidence from this drug-repurposing analysis to prioritize drugs for further study.

467

468 PAU was positively genetically correlated with many psychiatric and substance use  
469 disorders and negatively with cognitive performance. Most of our genetic correlations with PAU,  
470 and all those in previous studies, were restricted to EUR populations, presumably because of  
471 insufficient statistical power in other populations. The PheWAS PRS also identified associations  
472 with medical phenotypes in EUR. With increasing number of AFR GWAS now published, mainly  
473 from MVP, we were able to estimate genetic correlations between AUD and a limited set of

474 traits in AFR. As in EUR, AUD in AFR was genetically correlated with substance use traits  
475 including OUD, smoking trajectory (which identifies groups of individuals that follow a similar  
476 progression of smoking behavior), and maximum habitual alcohol intake. PheWAS of PRS in  
477 AFR from PsycheMERGE and Yale-Penn confirmed that AUD is genetically correlated with  
478 substance use traits. The lack of a wider set of phenotypes for comparison by ancestry is a  
479 continuing limitation.

480

481 Additional limitations include that the differences in ascertainment and phenotypic  
482 heterogeneity across cohorts might bias the results. Despite the high genetic correlation  
483 between AUD and AUDIT-P, they are not identical traits. Also, differences in ascertainment  
484 amongst the cohorts may have introduced additional biases; for example, considering the QIMR  
485 AGDS and GBP cohorts, the former have high major depression comorbidity, and the latter  
486 have high bipolar disorder comorbidity. (This heterogeneity would, however, have been more  
487 likely to limit discovery than to create false-positives.) Additionally, while we set out to include all  
488 available samples for problematic drinking in multiple ancestries, the sample sizes in the non-  
489 EUR ancestries were still small for gene discoveries and downstream analyses. The collection  
490 of substantial numbers of non-European subjects is a critical next step in this field.

491

492 In summary, we report here a large multi-ancestry GWAS and meta-analysis for PAU, in  
493 which we focused our analyses in three main directions. First, we demonstrated that there is  
494 substantial shared genetic architecture of PAU across multiple populations. Second, we  
495 analyzed gene prioritization for PAU using multiple approaches, including cross-ancestry fine-  
496 mapping, gene-based association, brain-tissue TWAS and fine-mapping, and H-MAGMA for  
497 chromatin interaction. We identified many genes associated with PAU with biological support,

498 extending our understanding of the brain biology that substantially modifies PAU risk and  
499 expands opportunities for investigation using *in vitro* methods and animal models. These genes  
500 are potential actionable targets for downstream functional studies and possible targets of  
501 pharmacological intervention based on the drug repurposing results. Third, we investigated the  
502 genetic relationship between PAU and many traits, which for the first time was possible in AFR  
503 populations. Future increases in sample size will doubtless yield additional gains; this is  
504 particularly needed in non-EUR populations both for primary GWAS analyses and the analysis  
505 of other traits for comparison and to estimate pleiotropy.

506

## 507 **Methods**

508 **Study design.** In the previous PAU study<sup>6</sup>, the  $r_g$  between MVP AUD and PGC alcohol  
509 dependence (AD) was 0.98, which justified the meta-analysis of AUD (includes AUD and AD)  
510 across the two datasets; and the  $r_g$  between AUD and UKB AUDIT-P was 0.71, which justified  
511 the proxy-phenotype meta-analysis of PAU (including AUD, AD and AUDIT-P) across all  
512 datasets. In this study, we use the same definitions, defining AUD by meta-analyzing AUD and  
513 AD across all datasets, and defining PAU by meta-analyzing AUD, AD and AUDIT-P (Table 1).

514

515 **MVP dataset.** MVP enrollment and genotyping have been described previously<sup>19,61</sup>. MVP is a  
516 biobank supported by the US Department of Veterans Affairs (VA) with rich phenotypic data  
517 collected using questionnaires and the VA electronic health record system (EHR). The Central  
518 VA Institutional Review Board (IRB) and site-specific IRBs approved the MVP study. All relevant  
519 ethical regulations for work with human subjects were followed in the conduct of the study and  
520 informed consent was obtained from all participants.

521

522 MVP genotype data were processed by the MVP Release 4 (R4) Data Team. 729,324  
523 samples were genotyped using Affymetrix Axiom Biobank Array. Rigorous sample-level quality  
524 control (QC) served to remove samples with duplicates, call rates <98.5%, sex mismatches, >7  
525 relatives, or excess heterozygosity. After QC, MVP R4 data contains 658,582 participants and  
526 667,995 variants (pre-imputation). Pre-imputation QC removed variants with high missingness  
527 (>1.5%), that were monomorphic, or with Hardy-Weinberg Equilibrium (HWE) p-value  $\leq 1 \times 10^{-6}$ ,  
528 leaving 590,511 variants for imputation. As in our previous work<sup>7</sup>, we ran principal component  
529 analysis (PCA)<sup>62,63</sup> for the R4 data and 1000 Genome phase3 reference panels<sup>64</sup>. The  
530 Euclidean distances between each MVP participant and the centers of the five reference  
531 ancestral groups were calculated using the first 10 PCs, with each participant assigned to the  
532 nearest reference ancestry. A second round PCA within each assigned ancestral group was  
533 performed and outliers with PC scores >6 standard deviations from the mean of any of the 10  
534 PCs were removed. This two-stage approach resulted in the assignment of 468,869 European  
535 ancestry (EUR), 122,024 African ancestry (AFR), 41,662 Latin American (LA), 7,364 East Asian  
536 (EAS) and 536 South Asian (SAS) individuals for analysis.

537

538 Imputation was done by the MVP R4 Data Team. The entire cohort was pre-phased  
539 using SHAPEIT4 (v4.1.3)<sup>65</sup>, then imputed using Minimac4<sup>66</sup> with African Genome Resources  
540 reference panel by Sanger Institute and 1000 Genomes Project phase3 as reference. Single  
541 nucleotide variants with imputation score <0.8, or HWE p-value  $\leq 1 \times 10^{-6}$ , or minor allele  
542 frequency (MAF) lower than the threshold set in each ancestral group based upon their sample  
543 size (EA, 0.0005; AA, 0.001; LA, 0.005; EAA, 0.01; SAA, 0.01) were removed before  
544 association analysis.

545

546 Participants with at least one inpatient or two outpatient International Classification of  
547 Diseases (ICD)-9/10 codes for AUD were assigned as AUD cases, while participants with zero  
548 ICD codes for AUD were controls. Those with one outpatient diagnosis were excluded from the  
549 analysis. In total, 80,028; 36,330; 10,150; 701; and 107 cases were included in EUR, AFR, LA,  
550 EAS, and SAS, respectively; 368,113; 79,100; 28,812; 6,254; and 389 controls were included in  
551 EUR, AFR, LA, EAS, and SAS, respectively. BOLT-LMM<sup>67</sup> was used to correct for relatedness,  
552 with age, sex, and the first 10 PCs as covariates.

553  
554 **UK Biobank (UKB).** UKB released genotype and imputed data for ~500,000 individuals from  
555 across the United Kingdom<sup>17</sup> which were accessed through application 41910. UKB defined  
556 White-British (WB) participants genetically. For the non-WB individuals, we used PCA to classify  
557 them into different genetic groups as for MVP. Subjects with available AUDIT-P score were  
558 included in this study. The final sample included 132,001 WB (hereafter called UKB-EUR1) and  
559 17,898 non-WB Europeans (hereafter called UKB-EUR2), and 1,220 SAS. SNPs with genotype  
560 call rate >0.95, HWE p-value >1×10<sup>-6</sup>, imputation score ≥0.8 and MAF ≥0.001 in EUR1 and  
561 EUR2 and ≥0.01 in SAS were kept for GWAS, BOLT-LMM was used for association correcting  
562 for relatedness, age, sex, and the first 10 PCs.

563  
564 **FinnGen.** Summary statistics for AUD from FinnGen data freeze 5 were downloaded from the  
565 FinnGen website (<http://r5.finnngen.fi/>). Details of the genotyping, imputation and quality control  
566 for FinnGen data were described previously<sup>20</sup>. There were 8,866 AUD cases defined by ICD-  
567 8/9/10 codes and 209,926 controls. Association analysis was performed using SAIGE<sup>68</sup> mixed-  
568 model with age, sex and 10 PCs as covariates. Positions of the variants were lifted over to build  
569 37 (GRCh37/hg19) for meta-analysis.

570

571 **iPSYCH:** The iPSYCH<sup>21,22</sup> samples were selected from a baseline birth cohort comprising all  
572 singletons born in Denmark between May 1, 1981, and December 31, 2008. The iPSYCH study  
573 was approved by the Scientific Ethics Committee in the Central Denmark Region (Case No 1-  
574 10-72-287-12) and the Danish Data Protection Agency.

575

576 AUD was diagnosed according to the ICD-10 criteria (F10.1 – F10.9 diagnosis codes).  
577 The iPSYCH cohort was established to investigate genetic risk for major psychiatric disorders  
578 (i.e., attention-deficit/hyperactivity disorder, schizophrenia, bipolar disorder, major depressive  
579 disorder, autism spectrum disorder) but not AUD (or PAU), so comorbidity of psychiatric  
580 disorders among these AUD cases is higher than expected for cases selected randomly from  
581 the population. Therefore, we generated a control group around five times as large as the case  
582 groups, and to correct for the bias introduced by high comorbidity of psychiatric disorders  
583 among cases, we included within the control group individuals with the above listed psychiatric  
584 disorders (without comorbid AUD) at a proportion equal to what was observed among the cases.

585

586 The samples were genotyped in two genotyping rounds referred to as iPSYCH1 and  
587 iPSYCH2. iPSYCH1 samples were genotyped using Illumina's PsychChip array and iPSYCH2  
588 samples using Illumina's GSA v.2 (Illumina, San Diego, CA, USA). Quality control and GWAS  
589 were performed using the Ricopili pipeline<sup>69</sup>. More details can be found in ref. 70. GWAS were  
590 performed separately for iPSYCH1 (2,117 cases and 13,238 controls) and iPSYCH2 (1,024  
591 cases and 5,732 controls) using dosages for imputed genotypes and additive logistic regression  
592 with the first 5 PCs (from the final PCAs) as covariates using PLINK v1.9<sup>71</sup>. Only variants with a  
593 MAF >0.01 and imputation score >0.8 were included in the final summary statistics.

594

595 **Queensland Berghofer Medical Research Institute (QIMR) cohorts.** The Australian Genetics  
596 of Depression Study (AGDS) recruited >20,000 participants with major depression between  
597 2017 and 2020. Recruitment and subject characteristics have been reported<sup>24</sup>: Participants  
598 completed an online self-report questionnaire. Lifetime AUD was assessed on DSM-5 criteria  
599 using the Composite International Diagnostic Interview (CIDI). A total of 6,726 subjects with and  
600 4,467 without AUD were included in the present study.

601

602 The Australian twin-family study of alcohol use disorder (TWINS, including Australian  
603 Alcohol and Nicotine Studies) participants were recruited from adult twins and their relatives  
604 who had participated in questionnaire- and interview-based studies on alcohol and nicotine use  
605 and alcohol-related events or symptoms (as described in Heath et al.<sup>72</sup>). They were  
606 predominantly of EUR ancestry. Young adult twins and their non-twin siblings were participants  
607 in the Nineteen and Up study (19Up)<sup>25</sup>. 2,772 cases and 5,630 controls were defined using  
608 DSM-III-R and DSM-IV criteria. Most alcohol-dependent cases were mild, with 70% of those  
609 meeting alcohol dependence criteria reporting only three or four dependence symptoms and ≤5%  
610 reporting seven dependence symptoms.

611

612 The Australian Genetics of Bipolar Disorder Study (GBP) recruited >5,000 participants  
613 living with bipolar disorder between 2018 and 2021. The sample's recruitment and  
614 characteristics have been reported<sup>23</sup>: Participants completed an online self-report questionnaire.  
615 Lifetime DSM-5 AUD was assessed using the CIDI.

616

617 Genotyping of QIMR cohorts was performed using Illumina Global Screening Array v2.  
618 Pre-imputation QC removed variants with GenTrain score  $<0.6$ , MAF  $<0.01$ , SNP call rate  $<95\%$ ,  
619 and Hardy-Weinberg equilibrium deviation ( $p < 1 \times 10^{-6}$ ). Variants were then imputed using the  
620 Michigan Imputation Server with the Haplotype Reference Consortium reference panel<sup>66</sup>.  
621 Association analysis was performed using SAIGE and the LOCO=TRUE flag with age, sex, 10  
622 PCs and two imputation variables as covariates. Participants of non-EUR ancestry (defined  
623 as  $>6$  standard deviations from the PC1 and PC2 centroids) were excluded. Association  
624 analyses were limited to variants with a MAF  $\geq 0.0001$ , MAC  $\geq 5$ , and an  $R^2 \geq 0.1$ .

625  
626 **Psychiatric Genomics Consortium (PGC).** Lifetime DSM-IV diagnosis of AD in both EUR and  
627 AFR ancestries were analyzed by PGC, with details reported previously<sup>5</sup>. This included 5,638  
628 individuals from Australia. To avoid overlap with the new QIMR cohorts, we re-analyzed the  
629 PGC data without two Australian cohorts: Australian Alcohol and Nicotine Studies and Brisbane  
630 Longitudinal Twin Study. This yielded 9,938 cases and 30,992 controls of EUR ancestry and  
631 3,335 cases and 2,945 controls of AFR ancestry.

632  
633 **Yale-Penn 3.** There are 3 phases of the Yale-Penn study defined by genotyping epoch; the first  
634 two were incorporated in the PGC study, thus they are included in the meta-analyses. Here, we  
635 included Yale-Penn 3 subjects as a separate sample. Lifetime AD was diagnosed based on  
636 DSM-IV criteria. Genotyping was performed in the Gelernter laboratory at Yale using the  
637 Illumina Multi-Ethnic Global Array, then imputed using Michigan Imputation Server with  
638 Haplotype Reference Consortium reference. We did PCA analyses to classify EAs (567 cases  
639 and 1,074 controls) and AAs (451 cases and 410 controls). Variants with MAF  $>0.01$ , HWE p-  
640 value  $>1 \times 10^{-6}$  and imputation INFO score  $\geq 0.8$  were retained for association analyses using

641 linear mixed models implemented in GEMMA<sup>73</sup> and corrected for age, sex and 10 PCs.

642

643 **East Asian cohorts.** Summary statistics for AUD/AD GWAS from 5 EAS cohorts (MVP EAS,  
644 Han Chinese–GSA, Thai METH–MEGA, Thai METH–GSA and Han Chinese–Cyto) were  
645 included in the cross-ancestry meta-analysis. Analyses of these five cohorts were previously  
646 published and the detailed QC can be found in ref. 27.

647

648 **Meta-analyses.** Meta-analyses were performed using METAL<sup>74</sup> with effective sample size  
649 weighting. For all the case-control samples, we calculated effective sample size as:

650

$$n_{effective} = \frac{4}{\frac{1}{n_{case}} + \frac{1}{n_{control}}}$$

651 For AUDIT-P in UKB, a continuous trait, we used actual sample sizes for meta-analysis. For all  
652 meta-analyses within or across ancestries, variants with a heterogeneity test p-value  $<5 \times 10^{-8}$   
653 and variants with effective sample size  $<15\%$  of the total effective sample size were removed.  
654 For the cross-ancestry and EUR within-ancestry meta-analyses, we required that variants were  
655 present in at least two cohorts. For the AFR and SAS within-ancestry meta-analyses, which are  
656 small samples, this was not required.

657

658 **Independent variants and conditional analyses.** We identified the lead variants using PLINK  
659 with parameters of clumping region 500 kb and LD  $r^2$  0.1. We then ran conditional analyses  
660 using GCTA-COJO<sup>75</sup> to define conditionally independent variants among the lead variants using  
661 the 1000 Genomes Project phase3 as the LD reference panel. Any two independent variants  $<1$   
662 Mb apart whose clumped regions overlapped were merged into one locus.

663

664 **Cross-ancestry lookup.** For the 85 independent variants associated in EUR, we looked up the  
665 associations in non-EUR groups. If the variants were not observed in another ancestry, we  
666 substituted proxy SNPs defined as associated with PAU ( $p < 5 \times 10^{-8}$ ) and in high LD with the EUR  
667 lead SNP ( $r^2 \geq 0.8$ ).

668

669 **SNP-based heritability ( $h^2$ ).** SNP-based  $h^2$  for common SNPs mapped to HapMap3<sup>76</sup> was  
670 estimated in EUR, AFR and LA ancestries using LDSC<sup>77</sup>; corresponding populations in the 1000  
671 Genomes Project phase3 were used as LD reference panels. For PAU in EUR, we only  
672 estimated the observed-scale  $h^2$ . For AUD, both observed-scale  $h^2$  and liability-scale  $h^2$  were  
673 estimated, using population lifetime prevalence estimates of 0.326, 0.220, and 0.229 in EUR,  
674 AFR, and LA, respectively<sup>1</sup>. These prevalence estimates were for lifetime DSM-5 AUD in the  
675 United States, which could introduce bias given the different definitions and prevalence in  
676 different cohorts. By default, LDSC removes SNPs with sample size  $< 90^{\text{th}}$  percentile  $N/2$ . Here  
677 we skipped this filtering and kept all SNPs for analyses because we did basic filtering based on  
678 the number of cohorts and sample size. The final number of SNPs in the analyses range from  
679 527,994 to 1.17 M.

680

681 **Cross-ancestry genetic correlation.** We estimated the genetic correlations between different  
682 ancestries using Popcorn<sup>78</sup>, which can estimate both the genetic-effect correlation ( $\rho_{ge}$ ) as  
683 correlation coefficient of the per-allele SNP effect sizes and the genetic-impact correlation ( $\rho_{gi}$ )  
684 as correlation coefficient of the ancestry-specific allele-variance-normalized SNP effect sizes.  
685 Populations in 1000 Genomes were used as reference for their corresponding population. A  
686 large sample size and number of SNPs are required for accurate estimation<sup>78</sup>, which explains

687 the non-robust estimates for EAS and SAS samples.

688

689 **Within- and cross-ancestry fine-mapping.** We did fine-mapping using MsCAVIAR<sup>79</sup>, which  
690 can leverage LD information from multiple ancestries to improve fine-mapping of causal variants.  
691 To reduce bias introduced by populations with small sample size, here we performed fine-  
692 mapping using summary statistics from the EUR, AFR and LA populations. Three sets of  
693 analyses were conducted. The first is within-ancestry fine-mapping for the 85 regions with  
694 independent variants in EUR using EUR summary data and 1000 Genomes Project phase3  
695 EUR LD reference data. For each region, we selected SNPs which clumped (within 500 kb and  
696 LD  $r^2 > 0.1$ ) with the lead SNP and with  $p < 0.05$  for fine-mapping. We then calculated the pair-  
697 wise LD among the selected SNPs. If two SNPs were in perfect LD ( $r^2 = 1$ , indicating that they  
698 are likely to be inherited together), we randomly removed one from the analysis. The second is  
699 cross-ancestry fine-mapping for the 100 regions with independent variants identified in cross-  
700 ancestry meta-analyses. For each region, we performed clumping (within 500 kb and LD  $r^2 > 0.1$ )  
701 in EUR, AFR, and LA summary data for the lead SNP separately, to select 3 sets of SNPs  
702 ( $p < 0.05$ ) for fine-mapping, corresponding LD reference panels from 1000 Genomes Project  
703 were used. For each set of SNPs, we calculated the pair-wise LD and randomly removed one  
704 SNP if  $r^2 = 1$ . If the lead SNP was not presented in the EUR SNP set, we did not perform fine-  
705 mapping for this region. Loci with limited numbers of variants cannot have convergent results,  
706 so they are not included in the results. After that, this cross-ancestry analysis included 92  
707 regions. For the 10 regions in which the lead SNPs are missing in both AFR and LA populations,  
708 we did within-ancestry fine-mapping in EUR instead to keep the lead SNP (cross-ancestry fine-  
709 mapping will only analyze the SNPs common in analyzed ancestries). Third, because the  
710 credible set length identified is related to the number of variants in the input, to provide a more  
711 direct comparison between the cross-ancestry fine-mapping and the fine-mapping using

712 information only from EUR, we used the same lists of SNPs from the above 92 regions in the  
713 cross-ancestry fine-mapping as for the EUR-only fine-mapping. “Credible set” was defined as  
714 plausible causal variants with accumulated posterior inclusion probability (PIP) > 99%. For each  
715 credible set, we report the variant with the highest PIP. We assumed that each locus contains  
716 only one causal variant by default, and increased to three at maximum if the analysis unable to  
717 converge.

718

719 **Gene-based association analyses.** We performed gene-based association analysis for PAU  
720 or AUD in multiple ancestries using MAGMA implemented in FUMA<sup>32,33</sup>. Default settings were  
721 applied. Bonferroni corrections for the number of genes tested (range from 18,390 to 19,002 in  
722 different ancestries) were used to determine genome-wide significant genes.

723

724 **Transcriptome-wide association study (TWAS).** For PAU in EUR, we performed TWAS using  
725 S-PrediXcan to integrate transcriptomic data from GTEx. With prior knowledge that PAU is a  
726 brain-related disorder (evidenced by significant enrichment of gene expression in several brain  
727 tissues)<sup>6</sup>, 13 brain tissues were analyzed. The transcriptome prediction model database and the  
728 covariance matrices of the SNPs within each gene model were downloaded from the PredictDB  
729 repository (<http://predictdb.org/>). Significance of the gene-tissue association was determined  
730 following Bonferroni correction for the total number of gene-tissue pairs  
731 ( $p < 0.05/166,064 = 3.01 \times 10^{-7}$ ). We also used S-MultiXcan<sup>36</sup> to integrate evidence across the 13  
732 brain tissues using multivariate regression to improve association detection. In total, 18,383  
733 genes were tested in S-MultiXcan, leading to a significance p-value threshold of  $2.72 \times 10^{-6}$ .

734

735 **Association with chromatin interactions in brain.** We used H-MAGMA<sup>37</sup>, a computational

736 tool that incorporates brain chromatin interaction profiles from Hi-C, to identify risk genes  
737 associated with PAU based on EUR inputs. Six brain annotations were used: fetal brain, adult  
738 brain, adult midbrain dopaminergic, iPSC-derived astrocyte, iPSC-derived neuron and cortical  
739 neuron. In total, 319,903 gene-chromatin associations were analyzed across the six brain  
740 annotations. Significant genes were those with a p-value below the Bonferroni corrected value  
741 for the total number of tests ( $p < 0.05/319,903 = 1.56 \times 10^{-7}$ ).

742

743 **Probabilistic fine-mapping of TWAS.** We did fine-mapping for TWAS in EUR using FOCUS<sup>38</sup>,  
744 a method that models correlation among TWAS signals to assign a PIP for every gene in the  
745 risk region to explain the observed association signal. The estimated credible set containing the  
746 causal gene can be prioritized for functional assays. FOCUS used 1000 Genomes Project EUR  
747 samples as the LD reference and multiple eQTL reference panel weights that include  
748 GTEx\_v7<sup>80</sup>, The Metabolic Syndrome in Men<sup>81</sup>, Netherlands Twin Register<sup>82</sup>, Young Finns  
749 Study<sup>83</sup>, and CommonMind Consortium<sup>84</sup>. Under the model of PAU as substantially a brain  
750 disorder, we did fine-mapping while prioritizing predictive models using a brain tissue-prioritized  
751 approach.

752

753 **Drug repurposing.** To match inferred transcriptional patterns of PAU with transcriptional  
754 patterns induced by perturbagens, we related our S-PrediXcan results to signatures from the  
755 Library of Integrated Network-based Cellular Signatures (LINCS) L1000 database<sup>85</sup>. This  
756 database catalogues *in vitro* gene expression profiles (signatures) from thousands of  
757 compounds >80 human cell lines (level 5 data from phase I: GSE92742 and phase II:  
758 GSE70138). Our analyses included signatures of 829 chemical compounds in five neuronal cell-  
759 lines (NEU, NPC, MNEU.E, NPC.CAS9 and NPC.TAK). To test significance of the association

760 between PAU signatures and LINC perturbation signatures we followed the procedure from So  
761 et al<sup>86</sup>. Briefly, we computed weighted (by proportion of heritability explained) Pearson  
762 correlations between transcriptome-wide brain associations and *in vitro* L1000 compound  
763 signatures using the *metafor* package<sup>87</sup> in R. We treated each L1000 compound as a fixed  
764 effect incorporating the effect size ( $r_{\text{weighted}}$ ) and sampling variability ( $se^2$ ) from all signatures of a  
765 compound (e.g., across all time points and doses). We only report those perturbagens that were  
766 associated after Bonferroni correction ( $p < 0.05/829 = 6.03 \times 10^{-5}$ ).

767

768 **Cross-ancestry polygenic risk score.** We used PRS-CSx<sup>40</sup>, a method that couples genetic  
769 effects and LD across ancestries via a shared continuous shrinkage prior, to calculate the  
770 posterior effect sizes for SNPs mapped to HapMap3. Three sets of AUD GWAS summary data  
771 were used as input and corresponding posterior effect sizes in each ancestry were generated:  
772 EUR (without AUDIT-P from UKB,  $N_{\text{effective}}=352,373$ ), AFR ( $N_{\text{effective}}=105,433$ ), and LA  
773 ( $N_{\text{effective}}=30,023$ ). Three sets of AUD PRS based on the posterior effect sizes were calculated  
774 for UKB-EUR1 and UKB-EUR2 individuals using PLINK, following standardization (zero mean  
775 and unit variance) for each PRS. For each related pair ( $\geq 3^{\text{rd}}$ -degree, kinship coefficient  $\geq 0.0442$   
776 as calculated by UKB), we removed the subject with the lower AUDIT-P score, or randomly if  
777 they had the same score, leaving 123,565 individuals in UKB-EUR1 and 17,401 in UKB-EUR2.  
778 Then we ran linear regression for AUDIT-P in UKB-EUR2 as a validation dataset using  $PRS_{\text{EUR}}$ ,  
779  $PRS_{\text{AFR}}$  and  $PRS_{\text{LA}}$  as independent variables. The corresponding regression coefficients were  
780 used as weights in the test dataset (UKB-EUR1) to calculate the final PRS:  $PRS_{\text{final}} =$   
781  $\omega_{\text{EUR}} * PRS_{\text{EUR}} + \omega_{\text{AFR}} * PRS_{\text{AFR}} + \omega_{\text{LA}} * PRS_{\text{LA}}$ . We used linear regression to test the association  
782 between AUDIT-P and  $PRS_{\text{final}}$  after standardization, correcting for age, sex, and the first 10  
783 PCs. We also ran a null model of association between AUDIT-P and covariates only, to  
784 calculate the variance explained ( $R^2$ ) by  $PRS_{\text{final}}$ . For comparison, we also calculated PRS in

785 UKB-EUR1 using only the AUD summary data in EUR using PRS-CS<sup>88</sup>, then calculated the  
786 variance explained by PRS<sub>single</sub>. The improved PRS association was measured as the difference  
787 of the variance explained ( $\Delta R^2$ ).

788

789 **Genetic correlation.** Genetic correlations ( $r_g$ ) between PAU or AUD and traits of interest were  
790 estimated using LDSC<sup>89</sup>. For EUR, we tested  $r_g$  between PAU and 49 traits using published  
791 summary data and the EUR LD reference from the 1000 Genomes Project.  $r_g$ s with p-value  
792  $<1.02 \times 10^{-3}$  were considered significant. For AFR, we tested  $r_g$  between AUD and 13 published  
793 traits in AFR using MVP in-sample LD (most of the analyzed AFR were from MVP) built from  
794 1000 randomly-selected AFR subjects by cov-LDSC<sup>90</sup>.  $r_g$ s with p-value  $<3.85 \times 10^{-3}$  (0.05/13) in  
795 AFR were considered as significant. For comparison, we also tested  $r_g$ s using 1000 Genomes  
796 AFR as LD reference, which showed similar estimates.

797

#### 798 **PAU PRS for phenome-wide associations.**

799 We calculated PRS using PRS-continuous shrinkage (PRS-CS) for PAU (in EUR) and AUD (in  
800 AFR) in four independent datasets [Vanderbilt University Medical Center's Biobank (BioVU),  
801 Mount Sinai (BioMe<sup>TM</sup>), Mass General Brigham Biobank (MGBB)<sup>91</sup> and Penn Medicine Biobank  
802 (PMBB)<sup>92</sup>] from the PsycheMERGE Network, followed by phenome-wide association studies.  
803 Details for each dataset are described below.

804

805 **BioVU:** Genotyping of individuals was performed using the Illumina MEGEX array. Genotypes  
806 were filtered for SNP and individual call rates, sex discrepancies, and excessive heterozygosity  
807 using PLINK. Imputation was conducted using the Michigan Imputation Server based on the

808 Haplotype Reference Consortium reference panel. PCA using FlashPCA2<sup>93</sup> combined with CEU,  
809 YRI and CHB reference sets from the 1000 Genomes Project Phase 3 was conducted to  
810 determine participants of AFR and EUR ancestry. One individual from each pair of related  
811 individuals was removed ( $\pi$ -hat>0.2). This resulted in 12,384 AFR and 66,903 EUR individuals  
812 for analysis.

813

814 *BioMe™*: The *BioMe™* Biobank: The Illumina Global Screening Array was used to genotype the  
815 *BioMe™* samples. The SNP-level quality control (QC) removed SNPs with (1) MAF <0.0001 (2)  
816 HWE p-value  $\leq 1 \times 10^{-6}$  and (3) call rate <98%. The individual-level QC removed participants with  
817 (1) sample call rate <98% and (2) heterozygosity F coefficient  $\geq 3$  standard deviations. In  
818 addition, one individual from each pair of related samples with a genomic relatedness  
819 (proportion IBD) >0.125 was removed (--rel-cutoff=0.125 in PLINK). Imputation was  
820 performed using 1000 Genomes Phase 3 data. Each ancestry was confirmed by the genetic PC  
821 plot. A final sample size of 4,727 AFR and 9,544 EUR individuals were included for this study.

822

823 **MGBB**: Individuals in the Mass General Brigham Biobank (MGBB) were genotyped using the  
824 Illumina Multi-Ethnic Global array with hg19 coordinates. Variant-level quality control filters  
825 removed variants with a call rate <98% and those that were duplicated across batches,  
826 monomorphic, not confidently mapped to a genomic location, or associated with genotyping  
827 batch. Sample-level quality control filters removed individuals with a call rate less than 98%,  
828 excessive autosomal heterozygosity ( $\pm 3$  standard deviations from the mean), or discrepant self-  
829 reported and genetically inferred sex. PCs of ancestry were calculated in the 1000 Genomes  
830 Phase 3 reference panel and subsequently projected onto the MGBB dataset, where a Random  
831 Forest classifier was used to assign ancestral group membership for individuals with a

832 prediction probability >90%. The Michigan Imputation Server was then used to impute missing  
833 genotypes with the Haplotype Reference Consortium dataset serving as the reference panel.  
834 Imputed genotype dosages were converted to hard-call format and subjected to further quality  
835 control, where SNPs were removed if they exhibited poor imputation quality ( $INFO < 0.8$ ), low  
836 minor allele frequency (<1%), deviations from Hardy-Weinberg equilibrium ( $p < 1 \times 10^{-10}$ ), or  
837 missingness (variant call rate <98%). Only unrelated individuals ( $\pi\text{-hat} < 0.2$ ) of EUR ancestry  
838 were included in the present study. These procedures yielded a final analytic sample of 25,698  
839 individuals in the MGBB.

840  
841 **PMBB:** Genotyping of individuals was performed using the Illumina Global Screening Array.  
842 Quality control removed SNPs with marker call rate <95% and sample call rate <90%, and  
843 individuals with sex discrepancies. Imputation was performed using Eagle2<sup>94</sup> and Minimac4 on  
844 the TOPMed Imputation Server. One individual from each pair of related individuals ( $\pi\text{-hat}$   
845 threshold of 0.25) were removed from analysis. PCA was conducted using smartpca<sup>62,63</sup> and the  
846 Hapmap3 dataset to determine genetic ancestry. This resulted in 10,383 AFR and 29,355 EUR  
847 individuals for analysis.

848  
849 **PheWAS:** The AFR AUD PRS and EUR PAU PRS scores in each dataset were standardized  
850 for the PheWAS analyses. International Classification of Diseases (ICD)-9 and -10 codes were  
851 extracted from the electronic health record and mapped to phecodes. Individuals were  
852 considered cases if they had two instances of the phecode. We conducted PheWAS by fitting a  
853 logistic regression for each phecode within each biobank. Covariates included sex, age and the  
854 top 10 PCs. PheWAS results were meta-analyzed within each ancestral group across biobanks  
855 (AFR=27,494, EUR=131,500) using the PheWAS package<sup>95</sup> in R.

856

857 **Yale-Penn:** Quality control and creation of the PheWAS dataset have been described  
858 previously<sup>45</sup>. We calculated PRS for PAU in EUR and AUD in AFR (using summary statistics  
859 that leave out the Yale-Penn 3 and PGC sample which includes Yale-Penn 1 and 2). We  
860 conducted PheWAS by fitting logistic regression models for binary traits and linear regression  
861 models for continuous traits. We used sex, age at recruitment, and the top 10 genetic PCs as  
862 covariates. We applied a Bonferroni correction to control for multiple comparisons.

863

864 **Data Availability:** The full summary-level association data from the meta-analysis are available  
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866

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931

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945 journal *Complex Psychiatry*. J.H.K. has consulting agreements (less than US\$10,000 per year)  
946 with the following: AstraZeneca Pharmaceuticals, Biogen, Idec, MA, Biomedisyn Corporation,  
947 Bionomics, Limited (Australia), Boehringer Ingelheim International, COMPASS Pathways,  
948 Limited, United Kingdom, Concert Pharmaceuticals, Inc., Epiodyne, Inc., EpiVario, Inc.,  
949 Heptares Therapeutics, Limited (UK), Janssen Research & Development, Otsuka America,  
950 Pharmaceutical, Inc., Perception Neuroscience Holdings, Inc., Spring Care, Inc., Sunovion  
951 Pharmaceuticals, Inc., Takeda Industries and Taisho Pharmaceutical Co., Ltd. J.H.K. serves on  
952 the scientific advisory boards of Bioasis Technologies, Inc., Biohaven Pharmaceuticals, BioXcel  
953 Therapeutics, Inc. (Clinical Advisory Board), BlackThorn Therapeutics, Inc., Cadent  
954 Therapeutics (Clinical Advisory Board), Cerevel Therapeutics, LLC., EpiVario, Inc., Lohocla  
955 Research Corporation, PsychoGenics, Inc.; is on the board of directors of Inheris Biopharma,

956 Inc.; has stock options with Biohaven Pharmaceuticals Medical Sciences, BlackThorn  
957 Therapeutics, Inc., EpiVario, Inc. and Terran Life Sciences; and is editor of *Biological Psychiatry*  
958 with income greater than \$10,000. I.B.H. is the Co-Director of Health and Policy at the Brain and  
959 Mind Centre (BMC) University of Sydney. The BMC operates an early-intervention youth  
960 services at Camperdown under contract to Headspace. He is the Chief Scientific Advisor to, and  
961 a 3.2% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of  
962 Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the \$30 M Australian  
963 Government-funded Project Synergy (2017-20; a three-year program for the transformation of  
964 mental health services) and to lead transformation of mental health services internationally  
965 through the use of innovative technologies. J.W.S. is a member of the Leon Levy Foundation  
966 Neuroscience Advisory Board, the Scientific Advisory Board of Sensorium Therapeutics (with  
967 equity), and has received grant support from Biogen, Inc. He is PI of a collaborative study of the  
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