Progress in genomics of substance use traits across the genome

Joel Gelernter
Foundations Fund Professor of Psychiatry
Professor of Genetics and of Neuroscience
Director, Division of Human Genetics in Psychiatry
Yale University School of Medicine
VA CT Healthcare Center

COI

- Compensation for editorial work on the journal, Complex Psychiatry.

Psychiatric genomics = Complex trait genomics

- Psychiatric (including substance use) traits are genetically complex: many risk variants, usually of individually small effect
- The best way to identify these risk variants is via genomewide association studies (GWAS)

Genomewide association studies (GWAS) in psychiatry: 2026

- Large studies have had an enormous impact on the field re: risk locus identification.
- First megaanalyses (such as those from the Psychiatric Genomics Consortium, PGC) and now biobanks (such as the UK Biobank, the Million Veteran Program, All of Us, Estonian Biobank, others): larger samples, more discovery.
- What's considered "Large" is evolving rapidly. Samples >1,000,000 are common now! E.g. our 2021 depression study, n=1,200,000; then the 2025 PGC depression CELL paper, n>5,000,000!
- We like to identify gene variants that affect risk; but the ultimate goal is about the biology that comes out of well-powered GWAS… pleiotropy, pathways, mechanisms, better understanding of diagnosis, risk prediction, drug repurposing—i.e. clinical implications

Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7]†

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly. We report a genome-wide screen of 96 cases and 50 controls for polymorphisms associated with AMD. Among 116,204 single-nucleotide polymorphisms genotyped, an intronic and common variant in the complement factor H gene (*CFH*) is strongly associated with AMD (nominal *P* value $<10^{-7}$). In individuals homozygous for the risk allele, the likelihood of AMD is increased by a factor of 7.4 (95% confidence interval 2.9 to 19). Resequencing revealed a polymorphism in linkage disequilibrium with the risk allele representing a tyrosine-histidine change at amino acid 402. This polymorphism is in a region of CFH that binds heparin and C-reactive protein. The *CFH* gene is located on chromosome 1 in a region repeatedly linked to AMD in family-based studies.

Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world. Its incidence is increasing as the elderly population expands (*1*). AMD is characterized by progressive destruction of the retina's central region (macula), causing central field visual loss (*2*). A key feature of AMD is the formation of extracellular deposits called drusen concentrated in and around the macula behind the retina between the retinal pigment epithelium (RPE) and the choroid. To date, no therapy for this disease has proven to be broadly effective. Several risk factors have been linked to AMD, including age, smoking, and family history (*3*). Candidate-gene studies have not found any genetic differences that can account for a large proportion of the overall prevalence (*2*). Family-based whole-genome linkage scans have identified chromosomal regions that show evidence of linkage to AMD (*4*–*8*), but the linkage areas have not been resolved to any causative mutations.

Like many other chronic diseases, AMD is caused by a combination of genetic and environmental risk factors. Linkage studies are not as powerful as association studies for the identification of genes contributing to the risk for common, complex diseases (*9*). However, linkage studies have the advantage of searching the whole genome in an unbiased manner without presupposing the involvement of particular genes. Searching the whole genome in an association study requires typing 100,000 or more single-nucleotide polymorphisms (SNPs) (*10*). Because of these technical demands, only one whole-genome association study, on susceptibility to myocardial infarction, has been published to date (*11*).

Study design. We report a whole-genome case-control association study for genes involved in AMD. To maximize the chance of success, we chose clearly defined phenotypes for cases and controls. Case individuals exhibited at least some large drusen in a quantitative photographic assessment combined with evidence of sight-threatening AMD (geographic atrophy or neovascular AMD). Control individuals had either no or only a few small drusen. We analyzed our data using a statistically conservative approach to correct for the large number of SNPs tested, thereby guaranteeing that the probability of a false positive is no greater than our reported *P* values.

We used a subset of individuals who participated in the Age-Related Eye Disease Study (AREDS) (*12*). From the AREDS

[1]Laboratory of Statistical Genetics, Rockefeller University, 1230 York Avenue, New York, NY 10021, USA. [2]Department of Ophthalmology and Visual Science, Yale University School of Medicine, 330 Cedar Street, New Haven, CT 06520, USA. [3]National Eye Institute, Building 10, CRC, 10 Center Drive, Bethesda, MD 20892–1204, USA. [4]Biological Imaging Core, National Eye Institute, 9000 Rockville Pike, Bethesda, MD 20892, USA. [5]The EMMES Corporation, 401 North Washington Street, Suite 700, Rockville MD 20850, USA. [6]W. M. Keck Facility, Yale University, 300 George Street, Suite 201, New Haven, CT 06511, USA. [7]Department of Epidemiology and Public Health, Yale University School of Medicine, 60 College Street, New Haven, CT 06520, USA.

*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: josephine.hoh@yale.edu

Just about as old as ALBATROS!

This diagram shows all SNP-trait associati

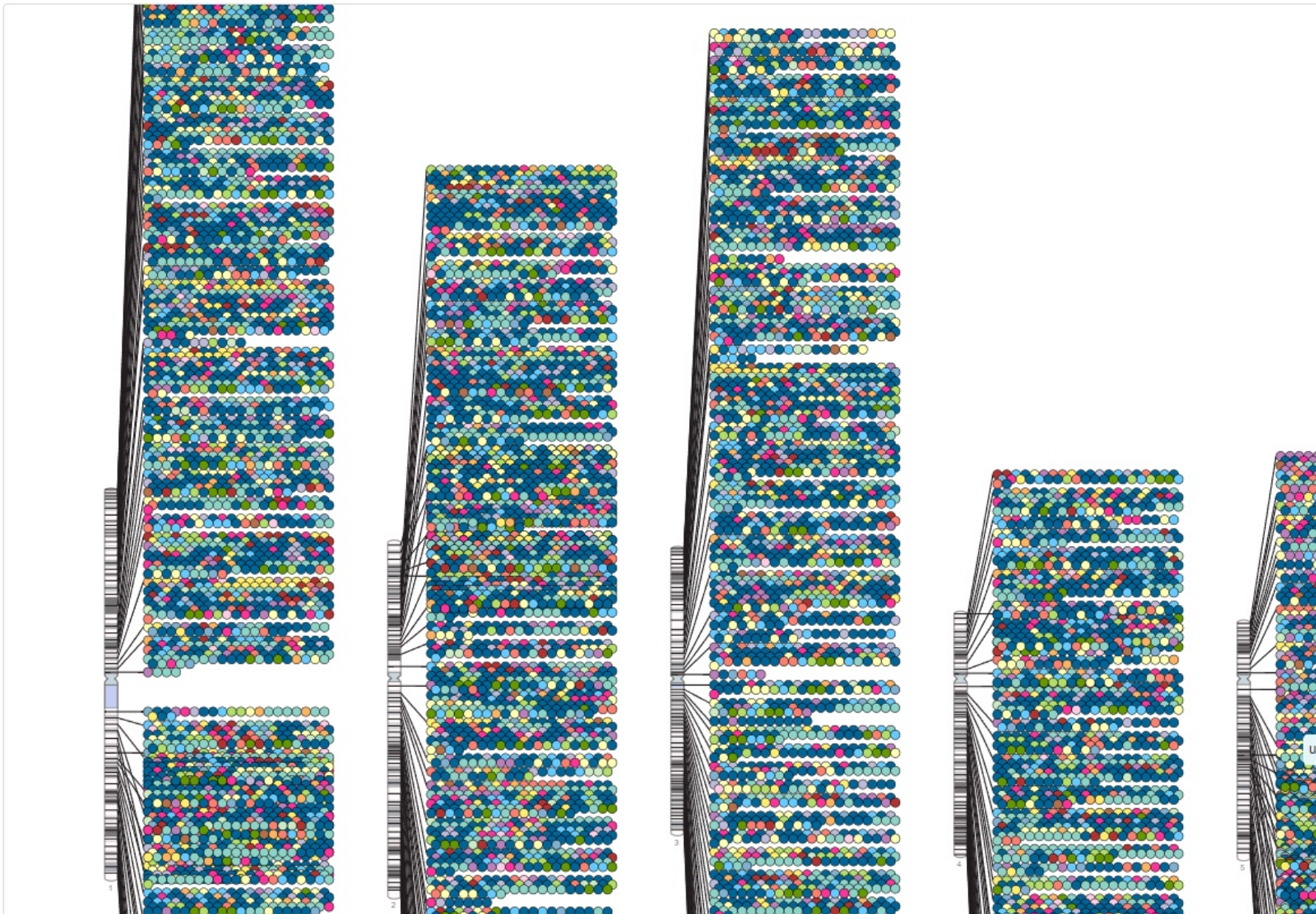
Filter the diagram

Filter by trait

Clear Apply

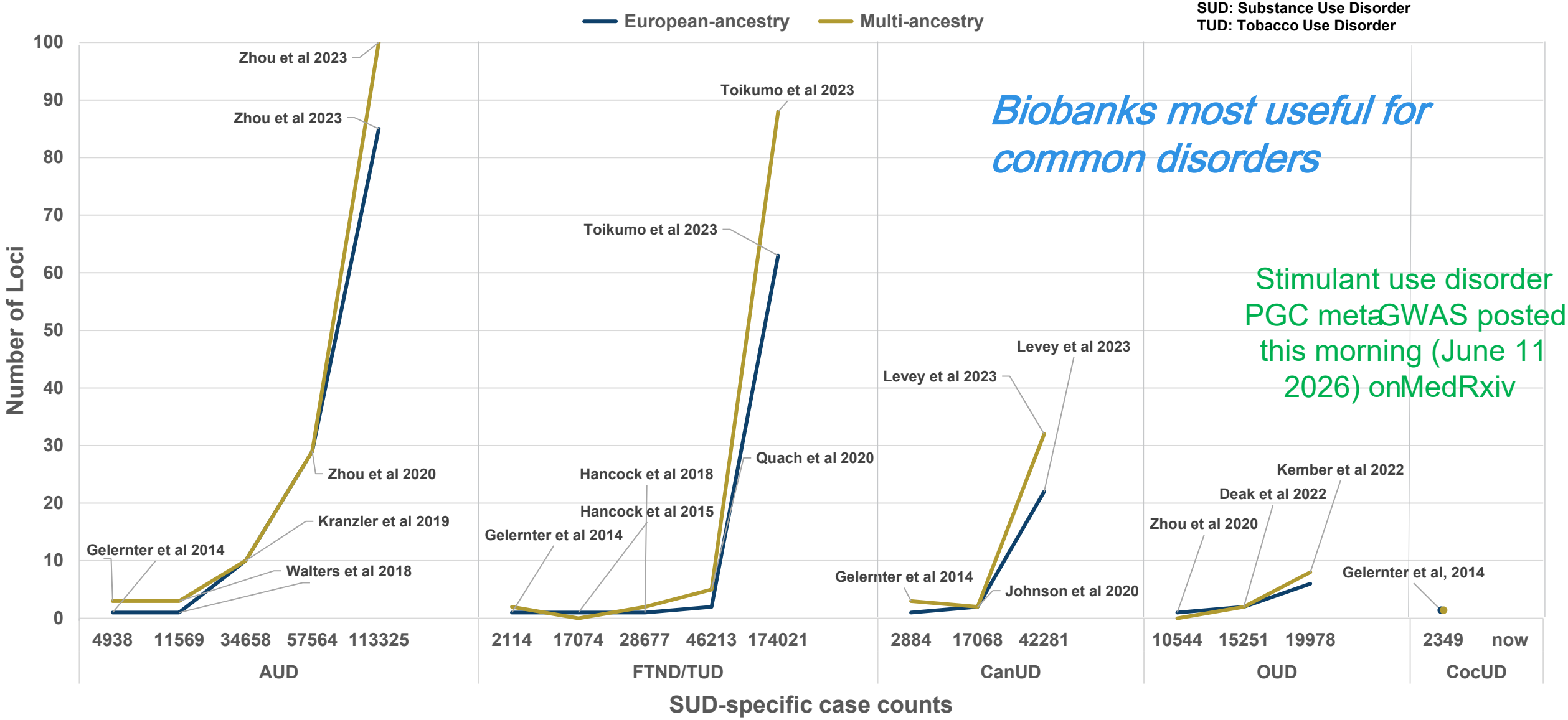
Show SNPs for

- Digestive system disease 570
- Cardiovascular disease 1650
- Metabolic disease 980
- Immune system disease 2068
- Nervous system disease 3289
- Liver enzyme measurement 1363
- Lipid or lipoprotein measurement 2479
- Inflammatory marker measurement 915
- Hematological measurement 10742
- Body weights and measures 3977
- Cardiovascular measurement 1776
- Other measurement 25093
- Response to drug 432



Substance Use Disorder GWAS Progress

AUD: Alcohol Use Disorder
CanUD: Cannabis Use Disorder
CocUD: Cocaine Use Disorder
FTND: Fagerström Test for Nicotine Dependence
OUD: Opioid Use Disorder
SUD: Substance Use Disorder
TUD: Tobacco Use Disorder



Biobanks most useful for common disorders

Stimulant use disorder PGC metaGWAS posted this morning (June 11 2026) onMedRxiv

Figure: Joseph Deak PhD

Alcohol trait genetics: metabolism and genetic polymorphism

"Flushing reaction"
(facial flushing, lightheadedness, palpitations, nausea)

ALSO: GI-tract cancers

Flushing reaction

- Some people – particularly people of Asian ancestry – tend to flush when t eartrate, and sometin
- This is most
- Perceived a
- Increases ri

https://vocal.media/proof/the-science-behind-why-you-turn-red-when-you-drink-alcohol

Molecular Psychiatry (2014) 19, 41–49

www.nature.com/mp

IMMEDIATE COMMUNICATION

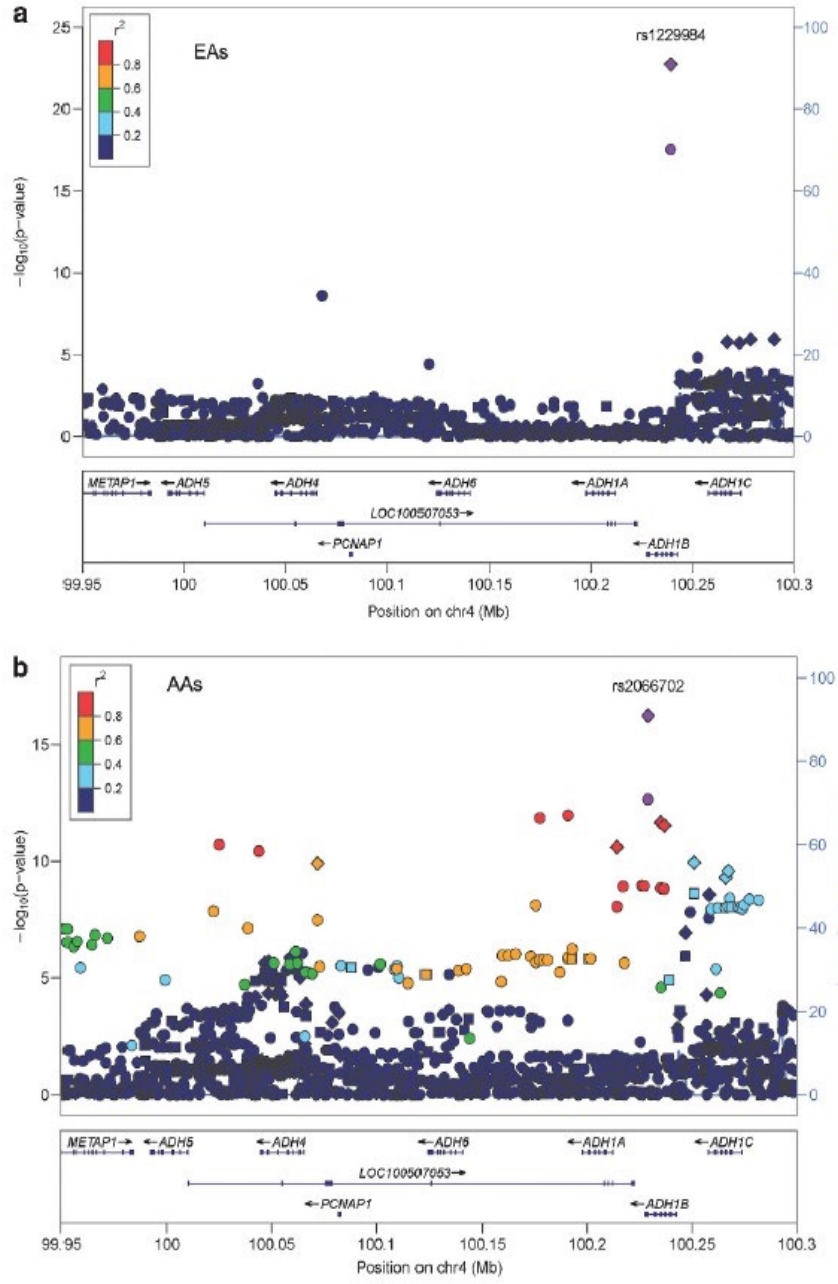
Genome-wide association study of alcohol dependence: significant findings in African- and European-Americans including novel risk loci

J Gelernter[1,2], HR Kranzler[3], R Sherva[4], L Almasy[5], R Koesterer[4], AH Smith[1], R Anton[6], UW Preuss[7], M Ridinger[8], D Rujescu[7], N Wodarz[8], P Zill[9], H Zhao[10,11] and LA Farrer[4,12]

We report a GWAS of alcohol dependence (AD) in European-American (EA) and African-American (AA) populations, with replication in independent samples of EAs, AAs and Germans. Our sample for discovery and replication was 16 087 subjects, the largest sample for AD GWAS to date. Numerous genome-wide significant (GWS) associations were identified, many novel. Most associations were population specific, but in several cases were GWS in EAs and AAs for different SNPs at the same locus,showing biological convergence across populations. We confirmed well-known risk loci mapped to alcohol-metabolizing enzyme genes, notably *ADH1B* (EAs: Arg48His, $P = 1.17 \times 10^{-31}$; AAs: Arg369Cys, $P = 6.33 \times 10^{-17}$) and *ADH1C* in AAs (Thr151Thr, $P = 4.94 \times 10^{-10}$), and identified novel risk loci mapping to the ADH gene cluster on chromosome 4 and extending centromerically beyond it to include GWS associations at *LOC100507053* in AAs ($P = 2.63 \times 10^{-11}$), *PDLIM5* in EAs ($P = 2.01 \times 10^{-8}$), and *METAP* in AAs ($P = 3.35 \times 10^{-8}$). We also identified a novel GWS association (1.17×10^{-10}) mapped to chromosome 2 at rs1437396, between *MTIF2* and *CCDC88A,* across all of the EA and AA cohorts, with supportive gene expression evidence, and population-specific GWS for markers on chromosomes 5, 9 and 19. Several of the novel associations implicate direct involvement of, or interaction with, genes previously identified as schizophrenia risk loci. Confirmation of known AD risk loci supports the overall validity of the study; the novel loci are worthy of genetic and biological follow-up. The findings support a convergence of risk genes (but not necessarily risk alleles) between populations, and, to a lesser extent, between psychiatric traits.

Molecular Psychiatry (2014) **19,** 41–49; doi:10.1038/mp.2013.145; published online 29 October 2013

Keywords: alcohol dependence; alcohol-metabolizing enzymes; complex traits; genome-wide association; population differences; population-specific alleles



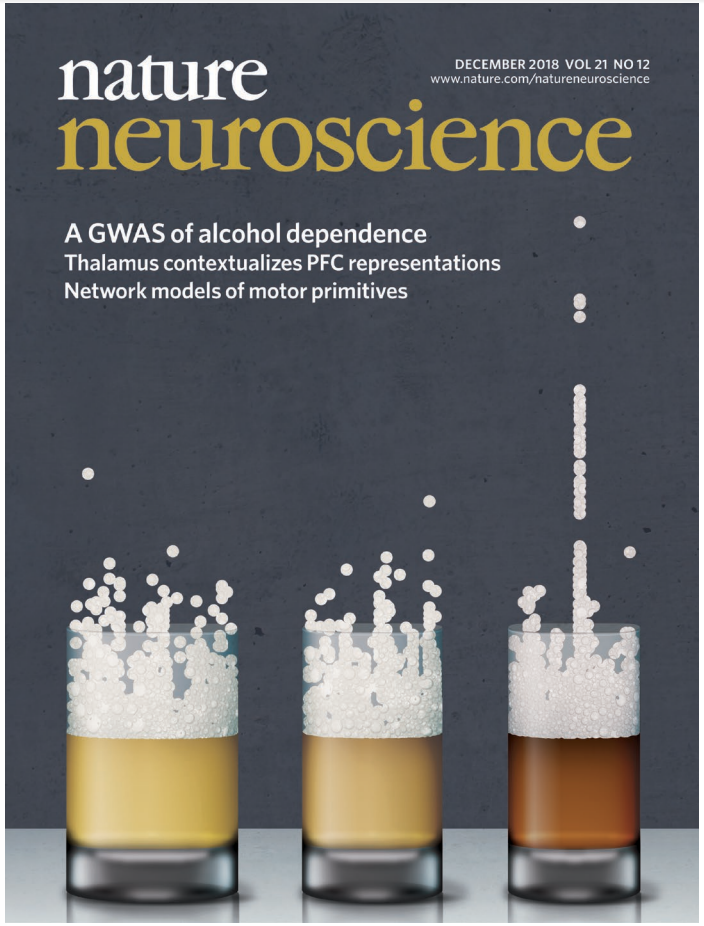
December 2018: One well-replicated locus In European and African-ancestry populations

ARTICLES
https://doi.org/10.1038/s41593-018-0275-1
nature neuroscience

Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders

Liability to alcohol dependence (AD) is heritable, but little is known about its complex polygenic architecture or its genetic relationship with other disorders. To discover loci associated with AD and characterize the relationship between AD and other psychiatric and behavioral outcomes, we carried out the largest genome-wide association study to date of DSM-IV-diagnosed AD. Genome-wide data on 14,904 individuals with AD and 37,944 controls from 28 case-control and family-based studies were meta-analyzed, stratified by genetic ancestry (European, $n = 46,568$; African, $n = 6,280$). Independent, genome-wide significant effects of different *ADH1B* variants were identified in European (rs1229984; $P = 9.8 \times 10^{-13}$) and African ancestries (rs2066702; $P = 2.2 \times 10^{-9}$). Significant genetic correlations were observed with 17 phenotypes, including schizophrenia, attention deficit–hyperactivity disorder, depression, and use of cigarettes and cannabis. The genetic underpinnings of AD only partially overlap with those for alcohol consumption, underscoring the genetic distinction between pathological and nonpathological drinking behaviors.

From the Psychiatric Genomics Consortium



A GWAS of alcohol dependence

Plot glasses: A genome-wide association study of alcohol

2019

nature COMMUNICATIONS

ARTICLE

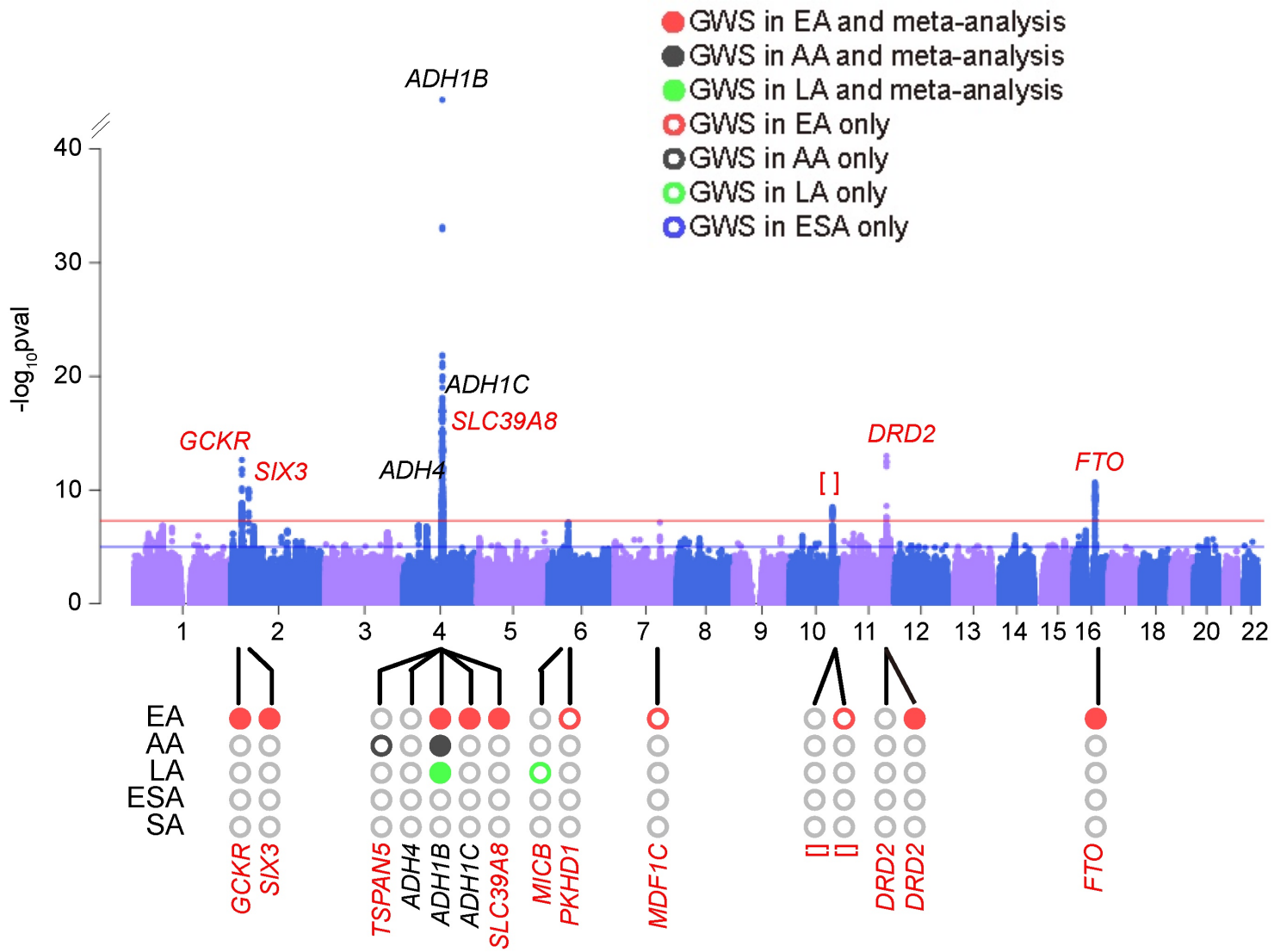
https://doi.org/10.1038/s41467-019-09480-8 OPEN

Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations

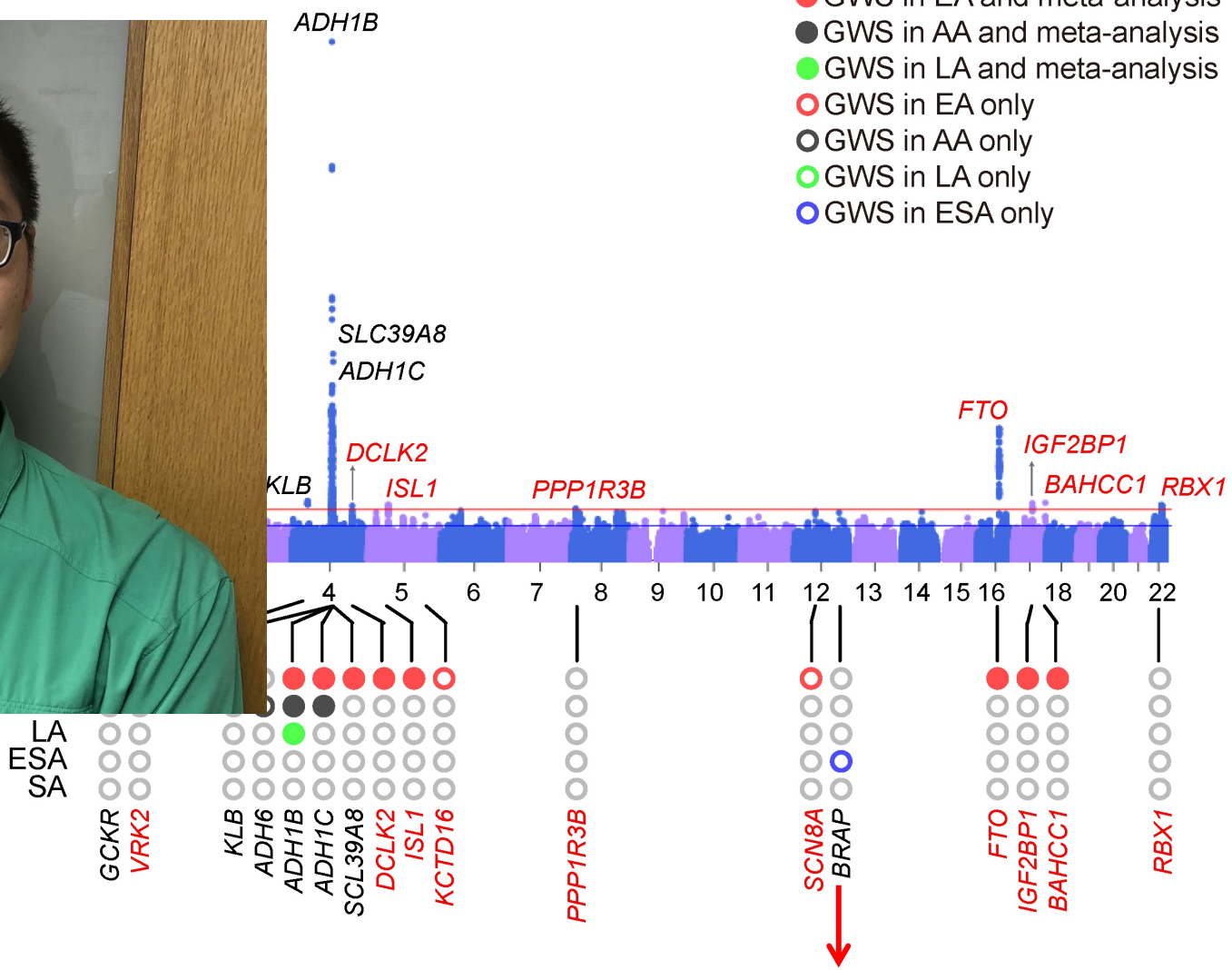
Henry R. Kranzler[1,2], Hang Zhou[3,4], Rachel L. Kember[1,2], Rachel Vickers Smith[2,5], Amy C. Justice[3,4,6], Scott Damrauer[1,2], Philip S. Tsao[7,8], Derek Klarin[9], Aris Baras[10], Jeffrey Reid[10], John Overton[10], Daniel J. Rader[1], Zhongshan Cheng[3,4], Janet P. Tate[3,4], William C. Becker[3,4], John Concato[3,4], Ke Xu[3,4], Renato Polimanti[3,4], Hongyu Zhao[3,6] & Joel Gelernter[3,4]

Alcohol consumption level and alcohol use disorder (AUD) diagnosis are moderately heritable traits. We conduct genome-wide association studies of these traits using longitudinal Alcohol Use Disorder Identification Test-Consumption (AUDIT-C) scores and AUD diagnoses in a multi-ancestry Million Veteran Program sample ($N = 274,424$). We identify 18 genome-wide significant loci: 5 associated with both traits, 8 associated with AUDIT-C only, and 5 associated with AUD diagnosis only. Polygenic Risk Scores (PRS) for both traits are associated with alcohol-related disorders in two independent samples. Although a significant genetic correlation reflects the overlap between the traits, genetic correlations for 188 non-alcohol-related traits differ significantly for the two traits, as do the phenotypes associated with the traits' PRS. Cell type group partitioning heritability enrichment analyses also dif-

Meta-analysis for AUD = *Alcohol Use Disorder*



Meta-analysis for AUDIT-C



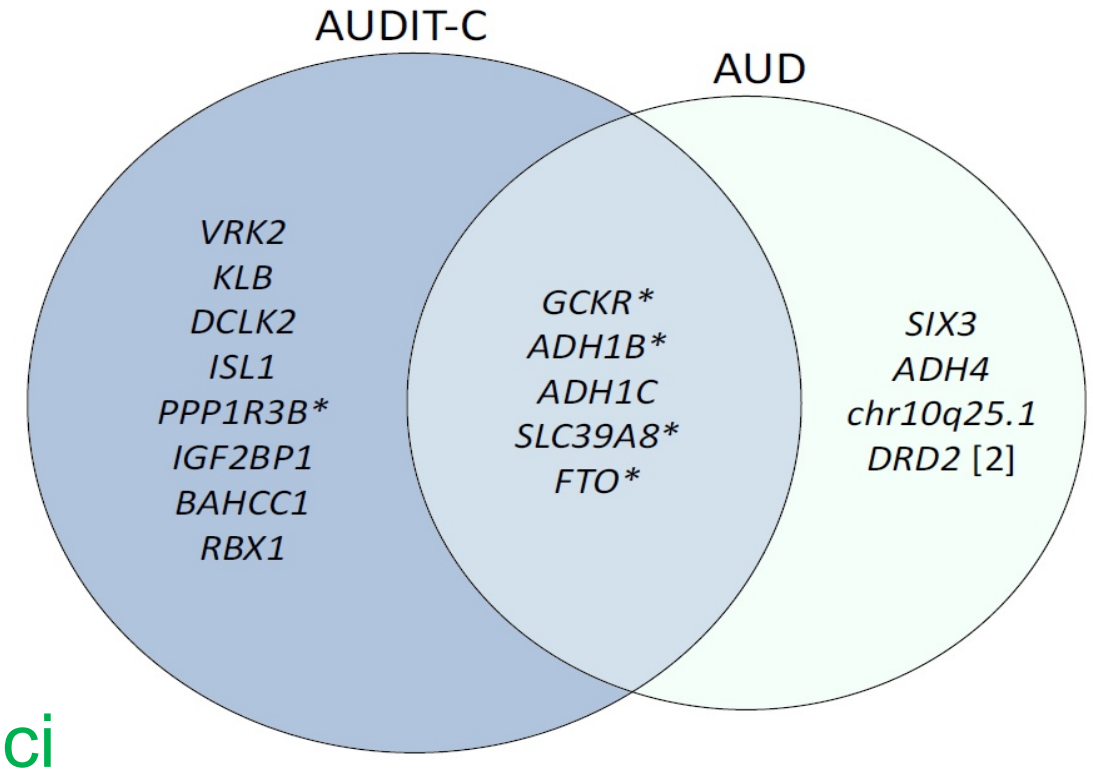
Analysis: Hang Zhao PhD

High LD with *ALDH2*

AUDIT-C: quantity/frequency (state measure)

- **How often did you have a drink containing alcohol in the past year? Consider a "drink" to be a can or bottle of beer, a glass of wine, a wine cooler, or one cocktail or a shot of hard liquor (like scotch, gin, or vodka).**
  - Response options were never (0 points); monthly or less (1 point); 2 to 4 times a month (2 points); 2 to 3 times a week (3 points); 4 to 5 times a week (4 points); or 6 or more times a week (4 points).
- **How many drinks did you have on a typical day when you were drinking in the past year?**
  - Response options were 0 drinks (0 points); 1 to 2 drinks (0 points); 3 to 4 drinks (1 point); 5 to 6 drinks (2 points); 7 to 9 drinks (3 points); or 10 or more drinks (4 points).
- **How often did you have 6 or more drinks on one occasion in the past year?**
  - Response options were never (0 points); less than monthly (1 point); monthly (2 points); weekly (3 points); or daily or almost daily (4 points).

Overlapping and Independent GWS Signals for the two phenotypes (EAs): Alcohol Use Disorder, AUDIT-C



AUD: 10 loci

AUDIT-C: 13 loci

Of which 5 overlap

Now we have full genomewide data for AUD and AUDIT-C. These can be used for downstream analyses…

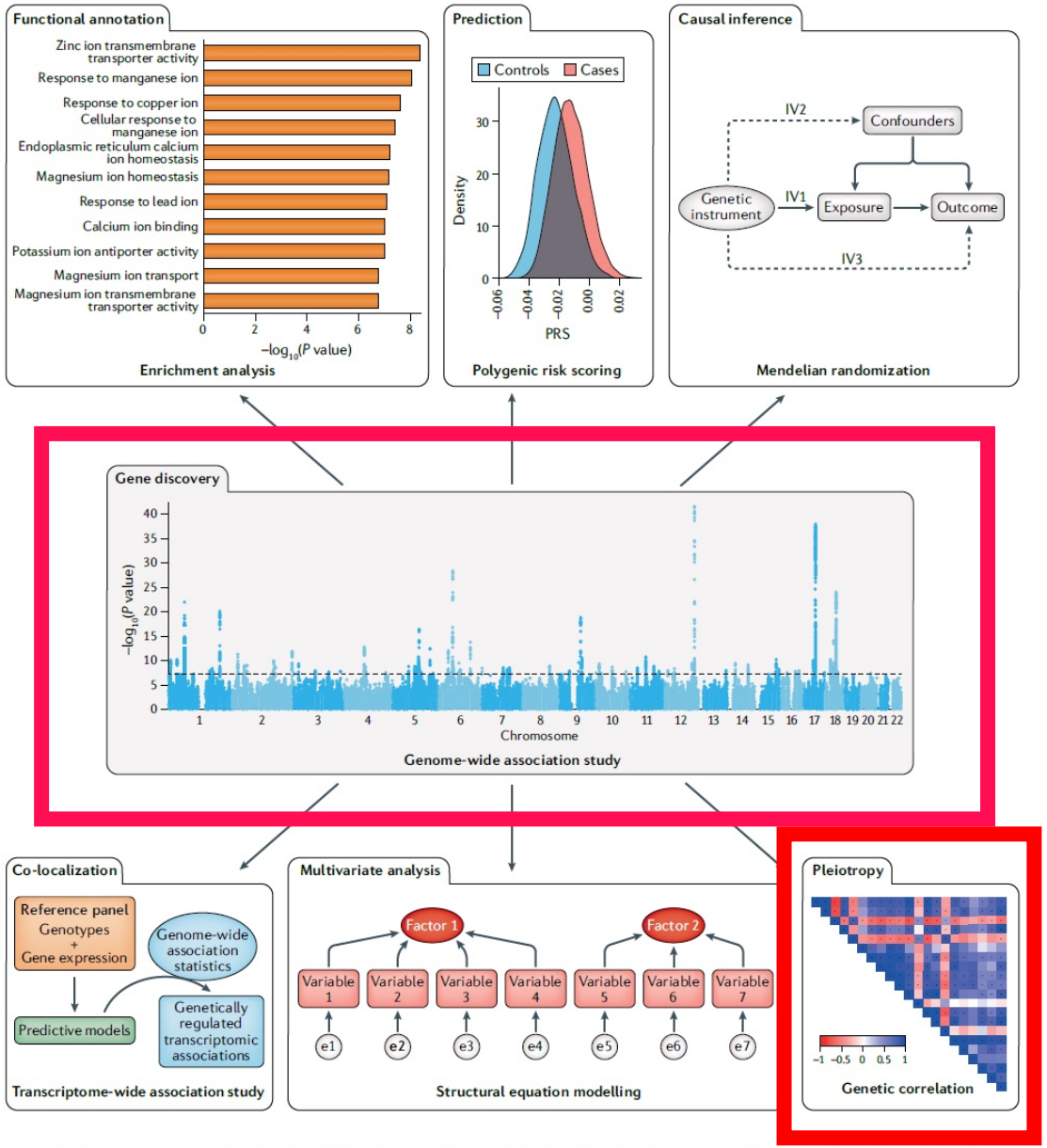
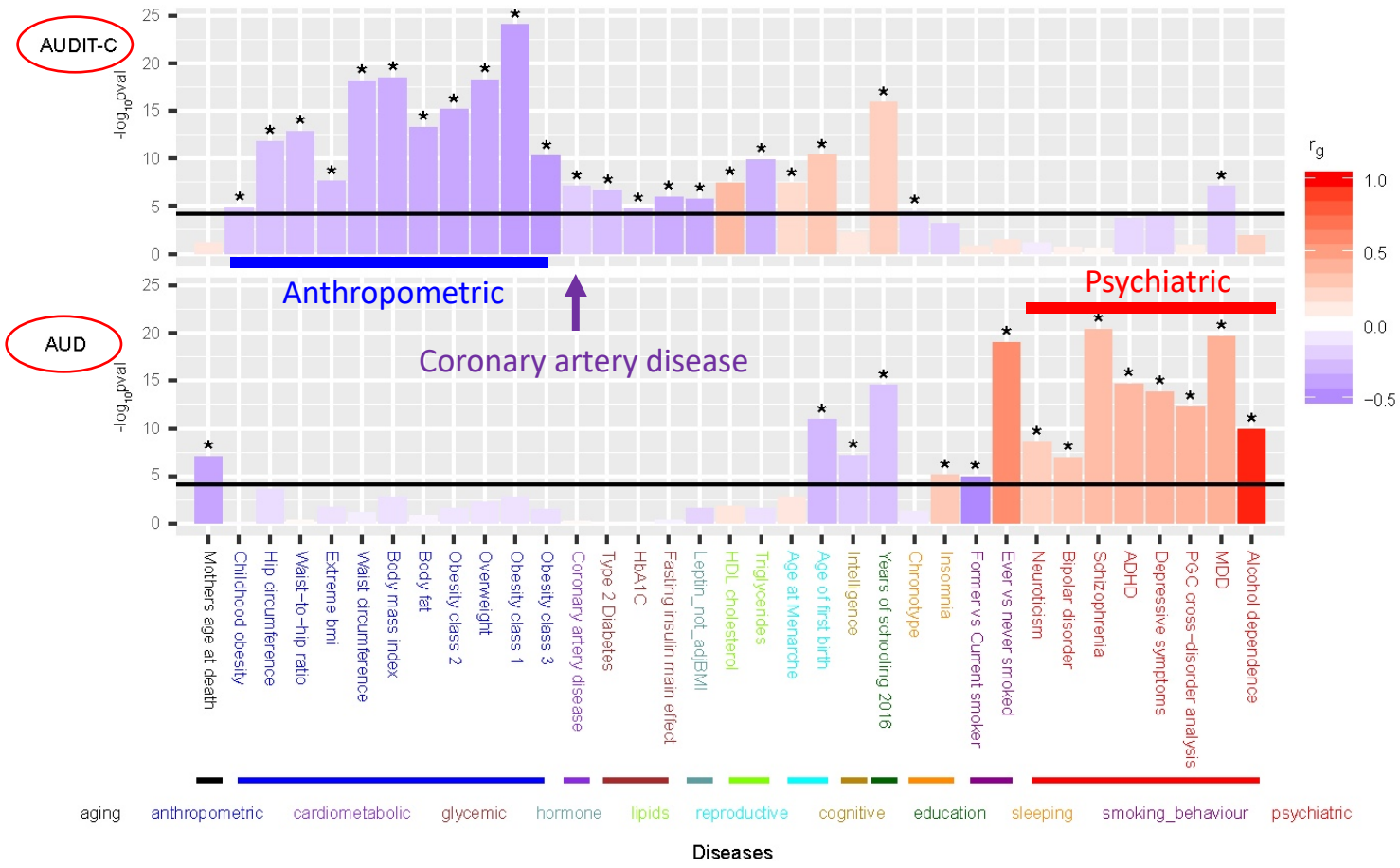


Fig. 1 | **From epidemiology and gene discovery to biology of SUDs.** Genome-wide association data sets can be used as the basis for multiple analytical approaches to disentangle the biology of the traits investigated (for example, cellular processes and molecular functions) and to understand the mechanisms underlying the associations observed in epidemiological studies. IV, instrumental variable assumption; PRS, polygenic risk score; SUD, substance use disorder.

Gelernter & Polimanti, Nature Reviews Genetics, 2021

Genetic correlation, EUR only



Conclusions from MVP Studies: AUD and Related Traits

- Multiple novel loci
  - Some contributed to both traits – AUDIT-C alcohol consumption, AUD risk
  - Others associated with one or the other
  - Heavy drinking, although a necessary precondition for the development of AUD, may not be sufficient to cause it.

- Variation in CNS genes, such as *DRD2*, may be more important for AUD to occur in the context of heavy drinking.

- *Strongest loci (alcohol metabolizing enzyme genes that have survived from the candidate gene era) identified by all of alcohol-related traits*

- *GENETIC DIFFERENCES BETWEEN AUD (DEPENDENCE) AND AUDIT-C (QUANTITY/FREQUENCY)*

- *Huge samples get you a lot more, but it may be important to pay close attention to the phenotypes you're combining and the proxies you may be employing*

Conclusions from MVP Studies: AUD and Related Traits

- Multiple novel loci
  - Some contributed to both traits – AUDIT-C alcohol consumption, AUD risk
  - Others associated with one or the other
  - Heavy drinking, although a necessary precondition for the development of AUD, may not be sufficient to cause it.
- Variation in CNS genes, such as *DRD2*, may be more important for AUD to occur in the context of heavy drinking.
- *Strongest loci (alcohol metabolizing enzyme genes that have survived from the candidate gene era) identified by all of alcohol-related traits*
- *GENETIC DIFFERENCES BETWEEN AUD (DEPENDENCE) AND AUDIT-C (QUANTITY/FREQUENCY)*
- *Huge samples get you a lot more, but it may be important to pay close attention to the phenotypes you're combining and the proxies you may be employing*

Meta-analysis study with new data. *Nature Neuro 2020*

- AUD and closely related traits PROBLEMATIC ALCOHOL USE
  - Fewer studies have focused on AUD than "quantity-frequency" measures
  - Quantity-Frequency measures (like AUDIT-C) get much of their information from normal-range variation
- Only focused on European samples – because of relative lack of other populations to study

nature neuroscience

ARTICLES

https://doi.org/10.1038/s41593-020-0643-5

Check for updates

Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits

Hang Zhou[1,2], Julia M. Sealock[3,4], Sandra Sanchez-Roige[5], Toni-Kim Clarke[6], Daniel F. Levey[1,2], Zhongshan Cheng[1,2], Boyang Li[7], Renato Polimanti[1,2], Rachel L. Kember[8,9], Rachel Vickers Smith[10], Johan H. Thygesen[11], Marsha Y. Morgan[12], Stephen R. Atkinson[13], Mark R. Thursz[13], Mette Nyegaard[14,15,16,17], Manuel Mattheisen[14,18,19], Anders D. Børglum[14,15,16,17], Emma C. Johnson[20,21], Amy C. Justice[2,21,22], Abraham A. Palmer[5,23], Andrew McQuillin[11], Lea K. Davis[3,4,24], Howard J. Edenberg[25,26], Arpana Agrawal[20], Henry R. Kranzler[9,27] and Joel Gelernter[1,2,28] ✉

Problematic alcohol use (PAU) is a leading cause of death and disability worldwide. Although genome-wide association studies have identified PAU risk genes, the genetic architecture of this trait is not fully understood. We conducted a proxy-phenotype meta-analysis of PAU, combining alcohol use disorder and problematic drinking, in 435,563 European-ancestry individuals. We identified 29 independent risk variants, 19 of them novel. PAU was genetically correlated with 138 phenotypes, including substance use and psychiatric traits. Phenome-wide polygenic risk score analysis in an independent biobank sample (BioVU,

Zhou et al, Nature Medicine

nature medicine

Article

https://doi.org/10.1038/s41591-023-02653-5

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

Received: 24 January 2023

Accepted: 18 October 2023

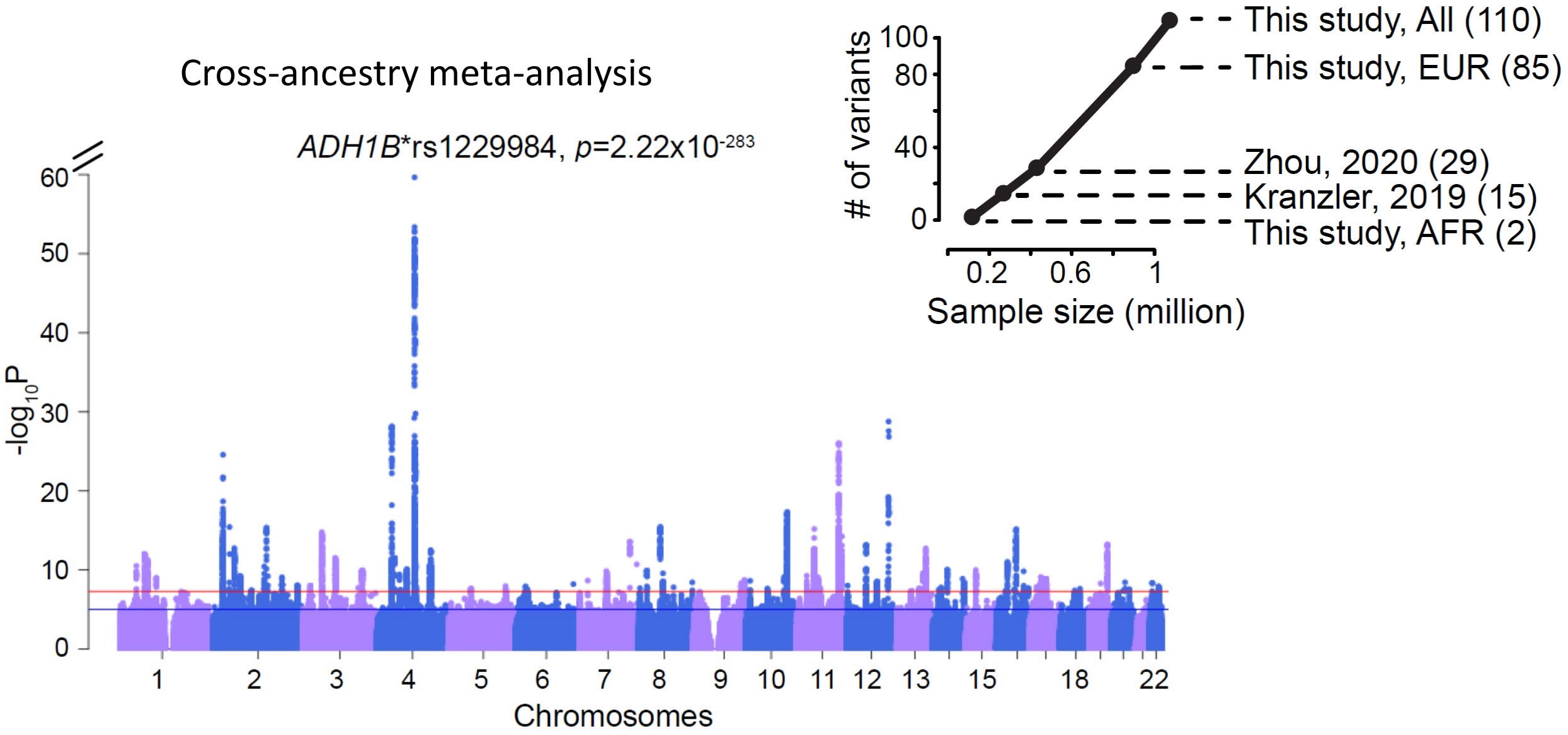
Published online: 7 December 2023

Check for updates

A list of authors and their affiliations appears at the end of the paper

Problematic alcohol use (PAU), a trait that combines alcohol use disorder and alcohol-related problems assessed with a questionnaire, is a leading cause of death and morbidity worldwide. Here we conducted a large cross-ancestry meta-analysis of PAU in 1,079,947 individuals (European, $N = 903,147$; African, $N = 122,571$; Latin American, $N = 38,962$; East Asian, $N = 13,551$; and South Asian, $N = 1,716$ ancestries). We observed a high degree of cross-ancestral similarity in the genetic architecture of PAU and identified 110 independent risk variants in within- and cross-ancestry analyses. Cross-ancestry fine mapping improved the identification of likely causal variants. Prioritizing genes through gene expression and chromatin interaction in brain tissues identified multiple genes associated with PAU. We identified existing medications for potential pharmacological studies by a computational drug repurposing analysis. Cross-ancestry polygenic risk scores showed better performance of association in independent samples than single-ancestry polygenic risk scores. Genetic correlations between PAU and other traits were observed in multiple ancestries, with other substance use traits having the highest correlations. This study advances our knowledge of the genetic etiology of PAU, and these findings may bring possible clinical applicability of genetics insights—together with neuroscience, biology and data science—closer.

Cross-ancestry genetic architecture



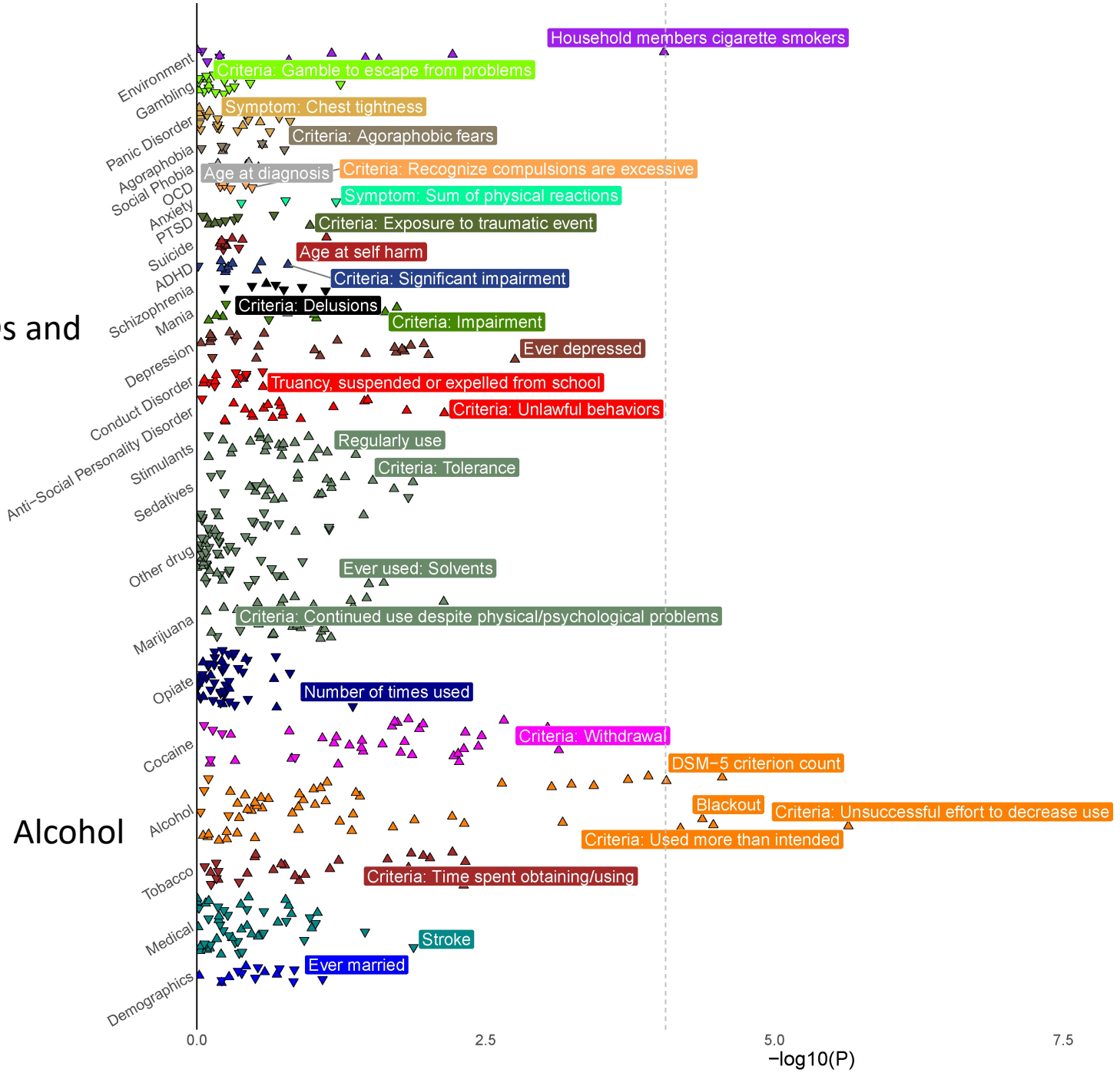
PhewPRS in Yale-Penn

- recruited for genetic studies of SUDs,
- deeply phenotyped
- includes >3500 items
- reliable diagnoses and criterion counts for SUDs and psychiatric disorders

Kember et al., 2023

Base: AFR (N=122,571)

Yale-Penn (N~4,900),
~570 phenotypes



Alcohol

Drug repurposing: Using genomics data to identify existing drugs related to the revealed biology of the trait of interest

- Independent genetic signals from the cross-ancestry meta-analysis were searched in OpenTargets.org for druggability and medication target status based on nearest genes.

- Among them, *OPRM1* implicated naltrexone and *GABRA4* implicated acamprosate, both current treatments for AUD.

- Additionally, the genes *DRD2*, *CACNA1C*, *DPYD*, *PDE4B*, *KLB*, *BRD3*, *NCAM1*, *FTO*, and *MAPT*, were identified as druggable genes.

Alcohol genomics summary

- Cross-ancestry meta-analysis of Problematic Alcohol Use in 1,079,947 individuals
- Shared genetic architecture between EUR and non-EUR
- Cross-ancestry fine-mapping improved the identification of likely causal variants
- Prioritized genes through gene expression and/or chromatin interaction in brain tissues
- Genetic correlations and phenome-wide PRS analyses in AFR
- *Little data in Asian-ancestry subjects*

Fig. 1 | **From epidemiology and gene discovery to biology of SUDs.** Genome-wide association data sets can be used as the basis for multiple analytical approaches to disentangle the biology of the traits investigated (for example, cellular processes and molecular functions) and to understand the mechanisms underlying the associations observed in epidemiological studies. IV, instrumental variable assumption; PRS, polygenic risk score; SUD, substance use disorder.

Gelernter & Polimanti, Nature Reviews Genetics, 2021

Using genomics to answer a clinical question: Alcohol and cognitive function

JAMA 2003 – highly influential article

Prospective Study of Alcohol Consumption and Risk of Dementia in Older Adults

Kenneth J. Mukamal, MD, MPH
Lewis H. Kuller, MD, DrPH
Annette L. Fitzpatrick, PhD
W. T. Longstreth, Jr, MD, MPH
Murray A. Mittleman, MD, DrPH
David S. Siscovick, MD, MPH

Context Alcohol consumption has been associated with complex changes in cerebral vasculature and structure in older adults. How alcohol consumption affects the incidence of dementia is less clear.

Objective To determine the prospective relationship of alcohol consumption and risk of dementia among older adults.

Design, Setting, and Participants Nested case-control study of 373 cases with incident dementia and 373 controls who were among 5888 adults aged 65 years and older who participated in the Cardiovascular Health Study, a prospective, population-based cohort study in 4 US communities. The controls were frequency-matched on age, death before 1999, and their attendance of a 1998-1999 clinic. Participants in this study underwent magnetic resonance imaging (MRI) of the brain and cognitive testing between 1992 and 1994 and were followed up until 1999.

Main Outcome Measures Odds of incident dementia, ascertained by detailed neurological and neuropsychological examinations according to average alcohol consumption, assessed by self-reported intake of beer, wine, and liquor at 2 visits prior to the date of the MRI.

Results Compared with abstention, the adjusted odds for dementia among those whose weekly alcohol consumption was less than 1 drink were 0.65 (95% confidence interval [CI], 0.41-1.02); 1 to 6 drinks, 0.46 (95% CI, 0.27-0.77); 7 to 13 drinks, 0.69 (95% CI, 0.37-1.31); and 14 or more drinks, 1.22 (95% CI, 0.60-2.49; *P* for quadratic term=.001). A trend toward greater odds of dementia associated with heavier alcohol consumption was most apparent among men and participants with an apolipoprotein E ϵ4 allele. We found generally similar relationships of alcohol use with Alzheimer disease and vascular dementia.

Conclusions Compared with abstention, consumption of 1 to 6 drinks weekly is associated with a lower risk of incident dementia among older adults.

DEMENTIA IMPOSES A TREMENdous burden on patients, caregivers, and society. Alzheimer disease alone causes more than 360000 new cases in the United States annually,[1] with a national annual cost of caring for such patients of more than $50 billion.[2] This burden has spurred a search for modifiable factors that cause or prevent dementia.

Atherosclerotic vascular disease may be 1 such risk factor for vascular and nonvascular dementia.[3] Because moderate alcohol consumption is associated with a lower risk of cardiovascular disease in the elderly,[4] such consumption might be expected to lower risk of dementia. However, even moderate alco-

Does this really make sense?

- There are lots of c
- E.g. “sick quitters”
  but who have lifet
- They count in the
  their alcohol-relat
- Maybe the result –
  doesn’t really mak

thebmj

BMJ 2017;357:j2353 doi: 10.1136/bmj.j2353 (Published 6 June 2017)

RESEARCH

Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study

OPEN ACCESS

Anya Topiwala *clinical lecturer in old age psychiatry*[1], Charlotte L Allan *academic clinical lecturer in old age psychiatry*[1], Vyara Valkanova *specialist registrar in old age psychiatry*[1], Enikő Zsoldos *postdoctoral scientist*[1], Nicola Filippini *postdoctoral scientist*[1], Claire Sexton *postdoctoral scientist*[2], Abda Mahmood *research assistant*[1], Peggy Fooks *medical student*[3], Archana Singh-Manoux *professor of epidemiology and public health*[4], Clare E Mackay *associate professor*[1], Mika Kivimäki *professor*[4], Klaus P Ebmeier *professor of old age psychiatry*[1]

[1]Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK; [2]FMRIB Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, OX3 9DU, UK; [3]University of Oxford, Warneford Hospital, Oxford, OX3 9DU, UK; [4]Department of Epidemiology and Public Health, University College London, London, WC1E 6BT, UK

Alcohol and cognitive function: Phenotype study

- Higher alcohol consumption over the 30 year follow-up was associated with increased odds of hippocampal atrophy in a dose dependent fashion.
- There was no protective effect of light drinking (1-<7 units/week) over abstinence
- Higher alcohol consumption over the study predicted faster decline on lexical fluency but not semantic fluency or word recall. Those drinking 7-<14, 14-<21, and >21 units a week declined faster in terms of lexical scores than abstainers.
  - Lexical fluency is the ability to efficiently retrieve words from long-term memory, often measured by generating words starting with certain letters under time constraints

- Topiwala et al 2017… *before rich alcohol trait GWAS results (at this time only confirmed risk genes in European-ancestry mapped to ADH1B)*

Adding genomics: We now have well-powered GWAS for numerous alcohol traits

- Alcohol use disorder and problematic alcohol use; AUDIT-C – our work
- Drinks per week – best data are from GSCAN

- Now that we have GWAS data, we can use the genomewide information to explore how alcohol traits relate genetically to other traits…
- **Collaborations re: dementia traits with Dr Anya Topiwala, Univ. of Oxford**

OPEN ACCESS

Alcohol use and risk of dementia in diverse populations: evidence from cohort, case–control and Mendelian randomisation approaches

Anya Topiwala [1], Daniel F Levey,[2,3] Hang Zhou,[2,3] Joseph D Deak,[2,3] Keyrun Adhikari,[2,3] Klaus P Ebmeier [4], Steven Bell,[5] Stephen Burgess [6], Thomas E Nichols [4,7], Michael Gaziano,[8,9] Murray Stein,[10] Joel Gelernter[3,11]

See more details

- Picked up by **439** news outlets
- Blogged by **9**
- Posted by **284** X users
- On **2** Facebook pages
- Referenced in **2** Wikipedia pages
- Reddited by **7**
- On **1** videos
- Referenced by **73** Bluesky users
- Picked up by **2** podcasts
- **41** readers on Mendeley

11	Total citations
11	Recent citations
n/a	Field Citation Ratio
n/a	Relative Citation Ratio

BMJ EBM study 2025 – Topiwala et al

- **Setting** Two large-scale population-based cohorts: the US Million Veteran Program and UK Biobank. Genetic analyses used summary statistics from genome-wide association studies (GWAS).
- **Participants** 559,559 adults aged 56–72 years at baseline were included in observational analyses (mean follow-up: 4 years in the US cohort; 12 years in the UK cohort). Genetic analyses used summary data from multiple large GWAS consortia (2.4 million participants).
- **Main outcome measures** Incident all-cause dementia, determined through health record linkage, and genetic proxies.

Results

- During follow-up, 14,540 participants developed dementia and 48,034 died.
- Observational phenotype-only analyses revealed U-shaped associations between alcohol and dementia risk: higher risk was observed among non-drinkers, heavy drinkers (>40 drinks per week), and those with alcohol use disorder compared with light drinkers.
- In contrast, Mendelian randomization genetic analysis identified a **monotonic increase in dementia risk with greater alcohol consumption**. A one standard deviation increase in log-transformed drinks per week was associated with a 15% dementia increase (IVW OR=1.15[1.03-1.27]). A two-fold increase in AUD prevalence was associated with a 16% increase in dementia risk (inverse-variance weighted [IVW] OR=1.16[1.03-1.30]).
- Alcohol intake increased dementia, but individuals who developed dementia also experienced a decline in alcohol intake over time, suggesting **reverse causation**—where early cognitive decline leads to reduced alcohol consumption—underlies the supposed protective alcohol effects in observational studies.

Mendelian randomization

- Mendelian randomization uses genes as “natural experiments.”
- Genetic variants are transmitted randomly at conception
- So genetic variants are ***not influenced by lifestyle, environment, or disease***
- That makes them useful as unbiased proxies for certain exposures

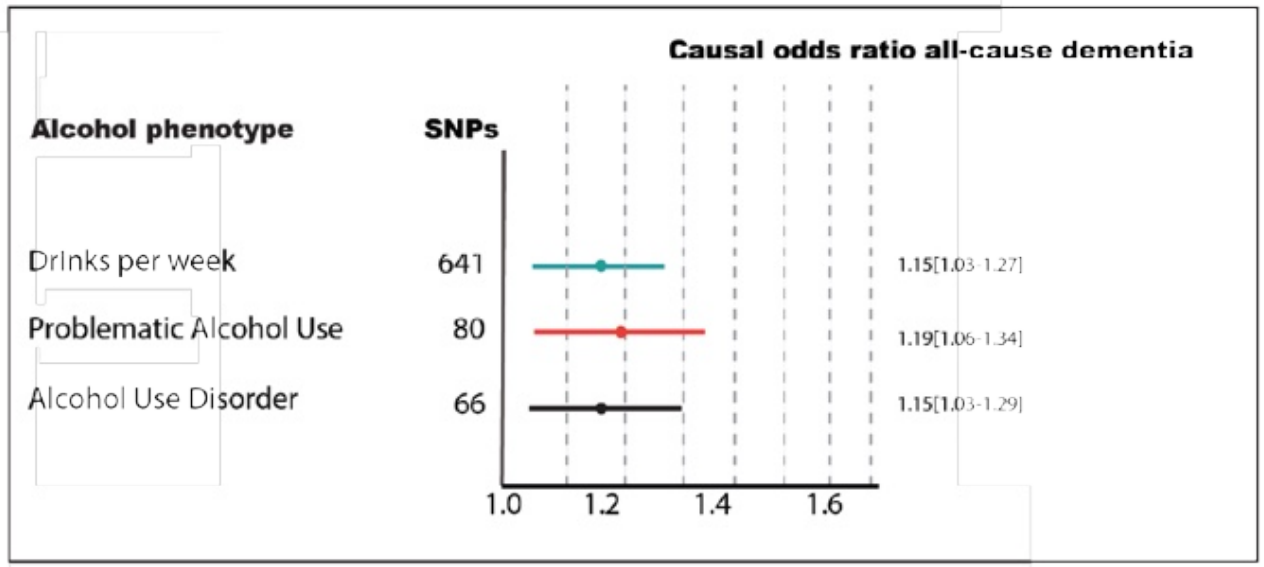
- ***Some genetic variants can be used to predict clinical phenotypes.***

Simple one-variant example

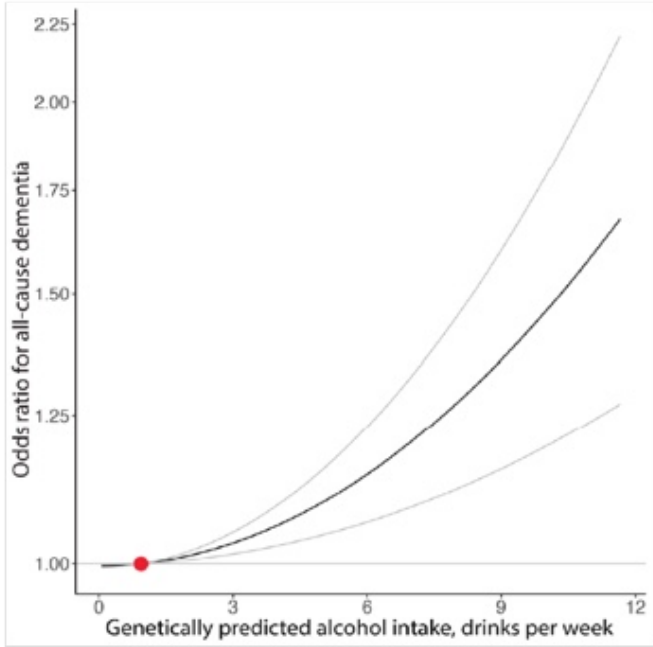
- *MR says:*
- Use **ADH1B genotype** as a proxy for lifetime alcohol exposure
- Why this works:
  - Your genotype is fixed at conception
  - It is **not caused by your behavior or environment**
  - It influences alcohol use behaviors including alcohol use disorder

Mendelian randomization

a) Linear analyses



b) Nonlinear analyses



Results

- During follow-up, 14,540 participants developed dementia and 48,034 died.
- Observational phenotype-only analyses revealed U-shaped associations between alcohol and dementia risk: higher risk was observed among non-drinkers, heavy drinkers (>40 drinks per week; hazard ratio [HR]=1.41, 95% confidence interval[CI] 1.15-1.74), and those with alcohol use disorder (AUD) (HR=1.51[CI 1.42-1.60]) compared with light drinkers.
- In contrast, Mendelian randomization genetic analysis identified a **monotonic increase in dementia risk with greater alcohol consumption**. A one standard deviation increase in log-transformed drinks per week was associated with a 15% dementia increase (IVW OR=1.15[1.03-1.27]). A two-fold increase in AUD prevalence was associated with a 16% increase in dementia risk (inverse-variance weighted [IVW] OR=1.16[1.03-1.30]).
- Alcohol intake increased dementia, but individuals who developed dementia also experienced a decline in alcohol intake over time, suggesting **reverse causation**—where early cognitive decline leads to reduced alcohol consumption—underlies the supposed protective alcohol effects in observational studies.

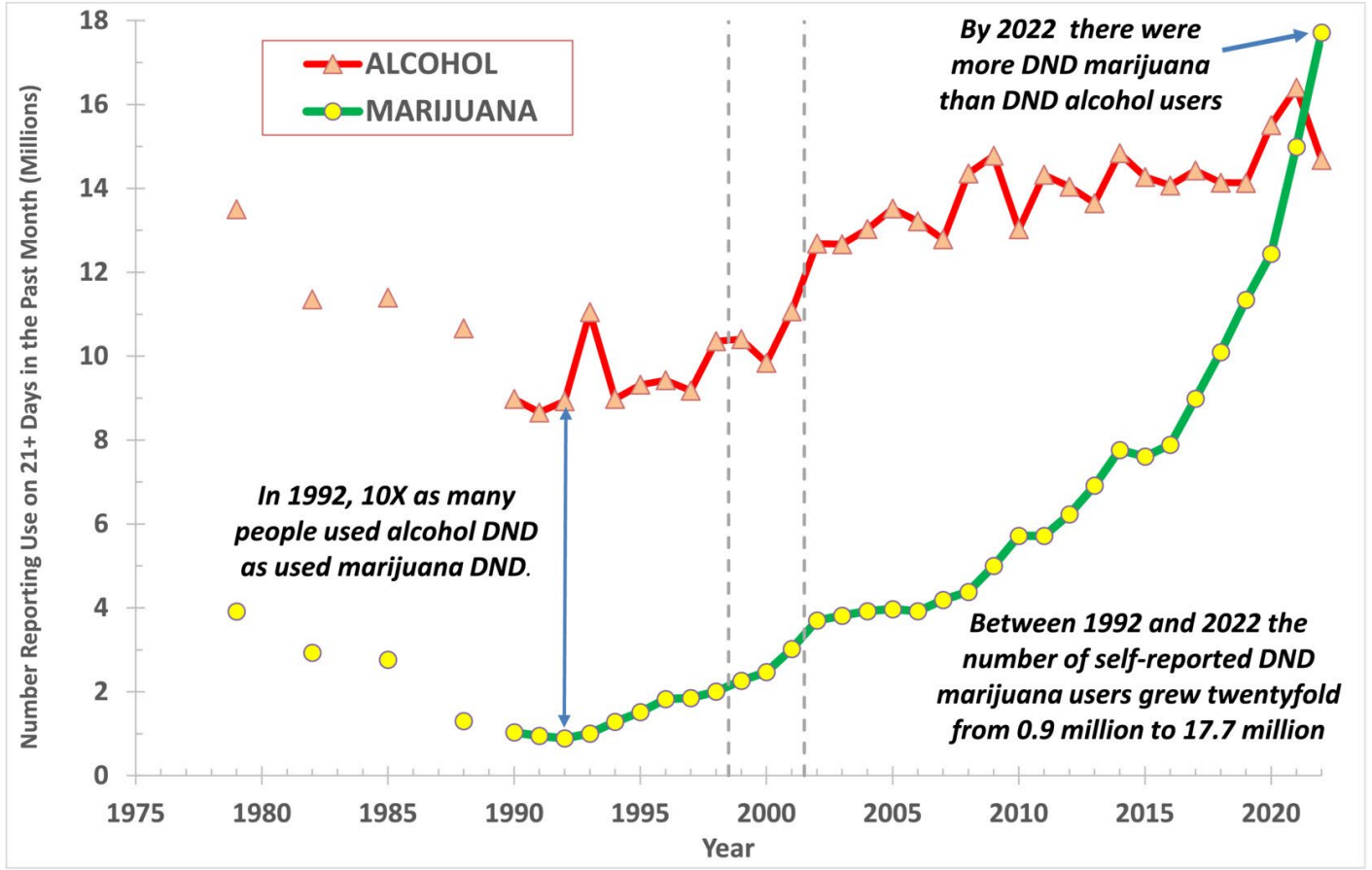
Results

- During follow-up, 14,540 participants developed dementia and 48,034 died.
- Observational phenotype-only analyses revealed U-shaped associations between alcohol and dementia risk: higher risk was observed among non-drinkers, heavy drinkers (>40 drinks per week; hazard ratio [HR]=1.41, 95% confidence interval[CI] 1.15-1.74), and those with alcohol use disorder (AUD) (HR=1.51[CI 1.42-1.60]) compared with light drinkers.
- In contrast, Mendelian randomization genetic analysis identified a **monotonic increase in dementia risk with greater alcohol consumption**. A one standard deviation increase in log-transformed drinks per week was associated with a 15% dementia increase (IVW OR=1.15[1.03-1.27]). A two-fold increase in AUD prevalence was associated with a 16% increase in dementia risk (inverse-variance weighted [IVW] OR=1.16[1.03-1.30]).
- Alcohol intake increased dementia, but individuals who developed dementia also experienced a decline in alcohol intake over time, suggesting **reverse causation**—where early cognitive decline leads to reduced alcohol consumption—underlies the supposed protective alcohol effects in observational studies.

Conclusions: Powerful GWAS results aid in drawing clinically-useful conclusions

- Evidence for a relationship between all types of alcohol use and increased dementia risk.
- While correlational observational data suggested a protective effect of light drinking, this could be in part attributable to reduced drinking seen in early dementia; or current non-drinkers who previously did drink
- Less-confounded genetic analyses did not support this, suggesting that ***any level of alcohol consumption may contribute to dementia risk.***
- Public health strategies that reduce the prevalence of alcohol use disorder could potentially lower the incidence of dementia by up to 16%.

Cannabis use -- US household surveys
DND = daily or near daily



Caulkins, 2024. *Addiction* (PMID 38775461)

nature genetics

Article

https://doi.org/10.1038/s41588-023-01563-z

Multi-ancestry genome-wide association study of cannabis use disorder yields insight into disease biology and public health implications

Received: 26 June 2023

Accepted: 9 October 2023

Published online: 20 November 2023

Check for updates

A list of authors and their affiliations appears at the end of the paper

As recreational use of cannabis is being decriminalized in many places and medical use widely sanctioned, there are growing concerns about increases in cannabis use disorder (CanUD), which is associated with numerous medical comorbidities. Here we performed a genome-wide association study of CanUD in the Million Veteran Program (MVP), followed by meta-analysis in 1,054,365 individuals (n_{cases} = 64,314) from four broad ancestries designated by the reference panel used for assignment (European

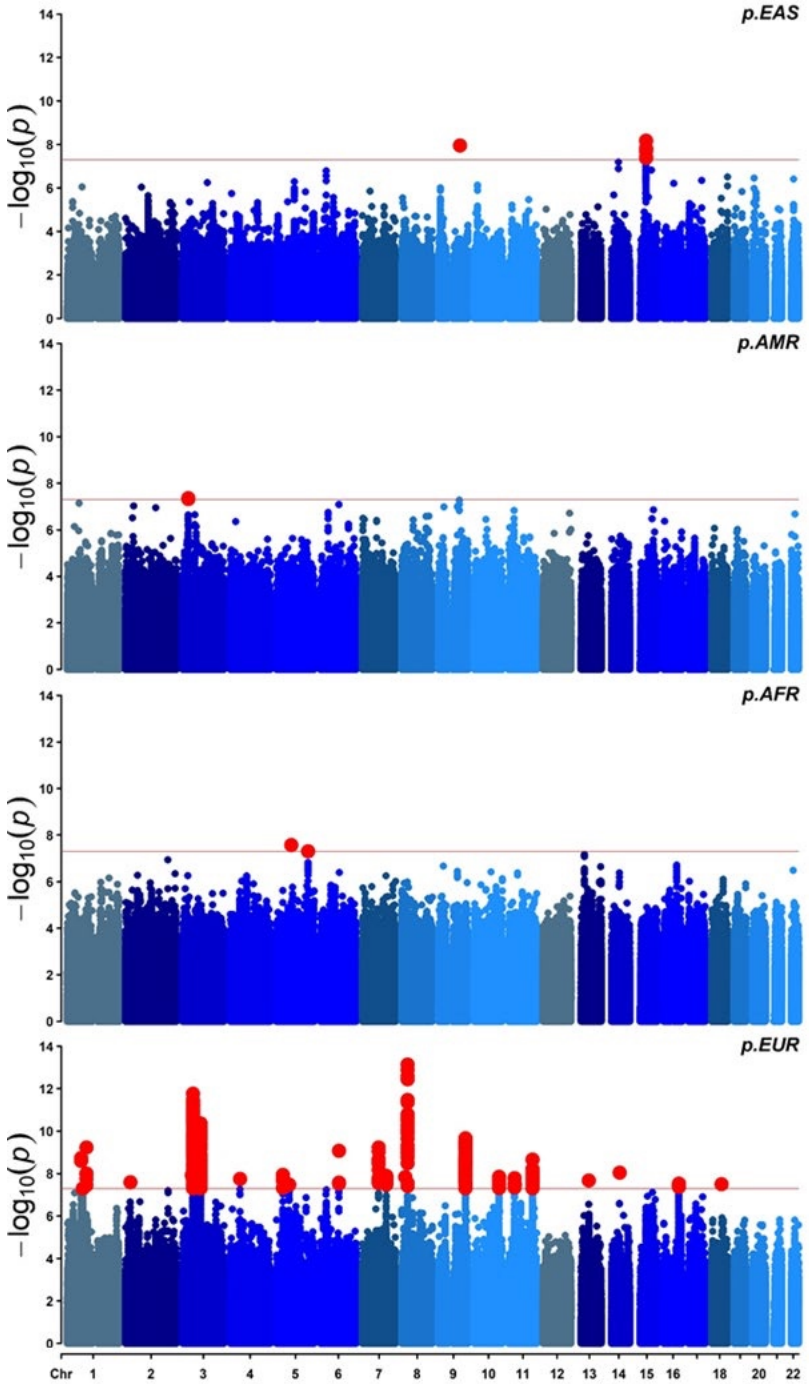
rjun Bhattacharya, Dora Koller,
, Veera M. Rajagopal, Stefany L.
denberg, Arpana Agrawal,
Michael Gaziano, Michael J

EAS	Status	N
MVP	Case	194
6,843	Control	6,649

AMR	Status	N
MVP	Case	2,774
38,289	Control	35,515

AFR	Status	N
Total	Case	19,065
123,208	Control	104,143

EUR	Status	N
Total	Case	42,281
866,025	Control	843,744



GWAS and GWAS meta-analysis stratified by 4 genetic ancestries, labeled by 1000 Genomes reference panel used in the definition:

EAS = East Asian

AMR = Americas
h2=16.8%

AFR = African
h2=12.7%

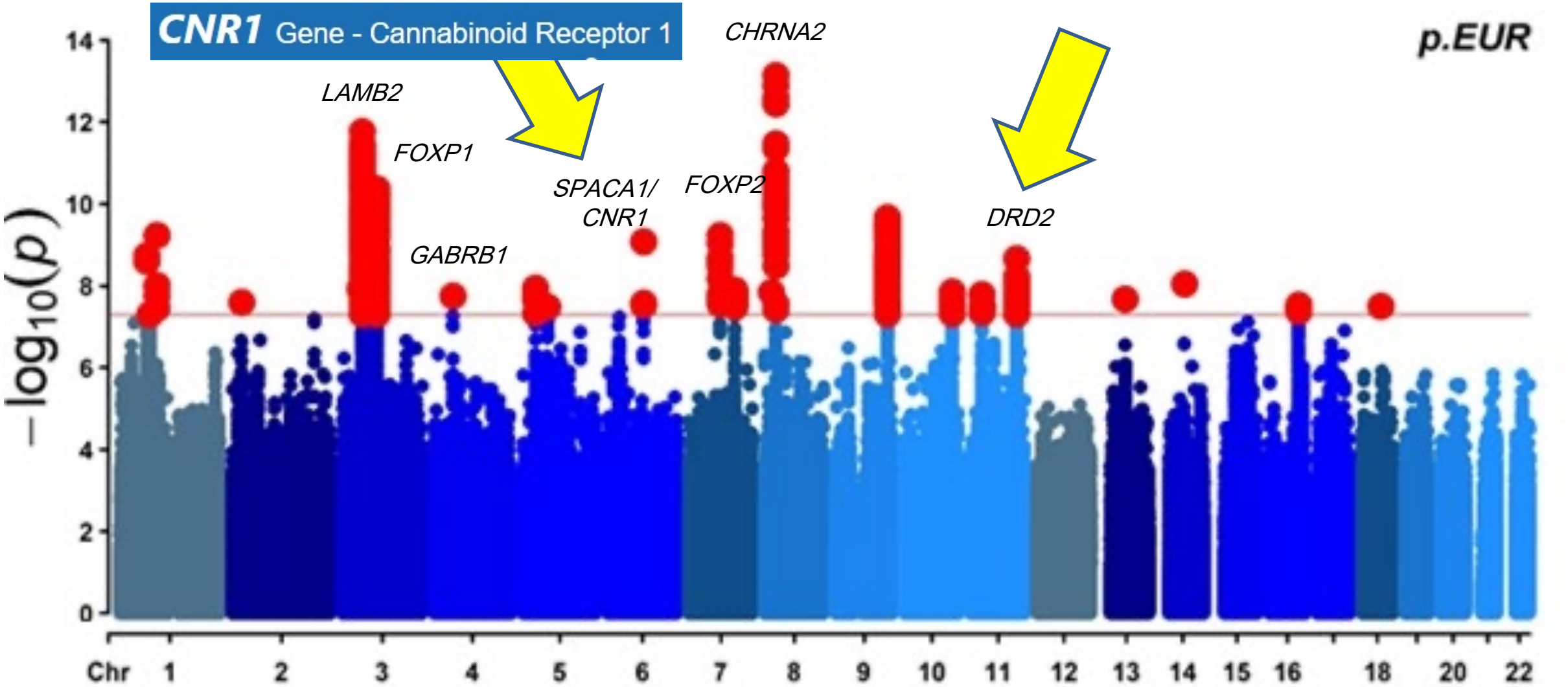
EUR = European
h2=8.5%

Population derived LD scores used to calculate h2 in non-European groups.

Significant heritability in 3 of 4 ancestries

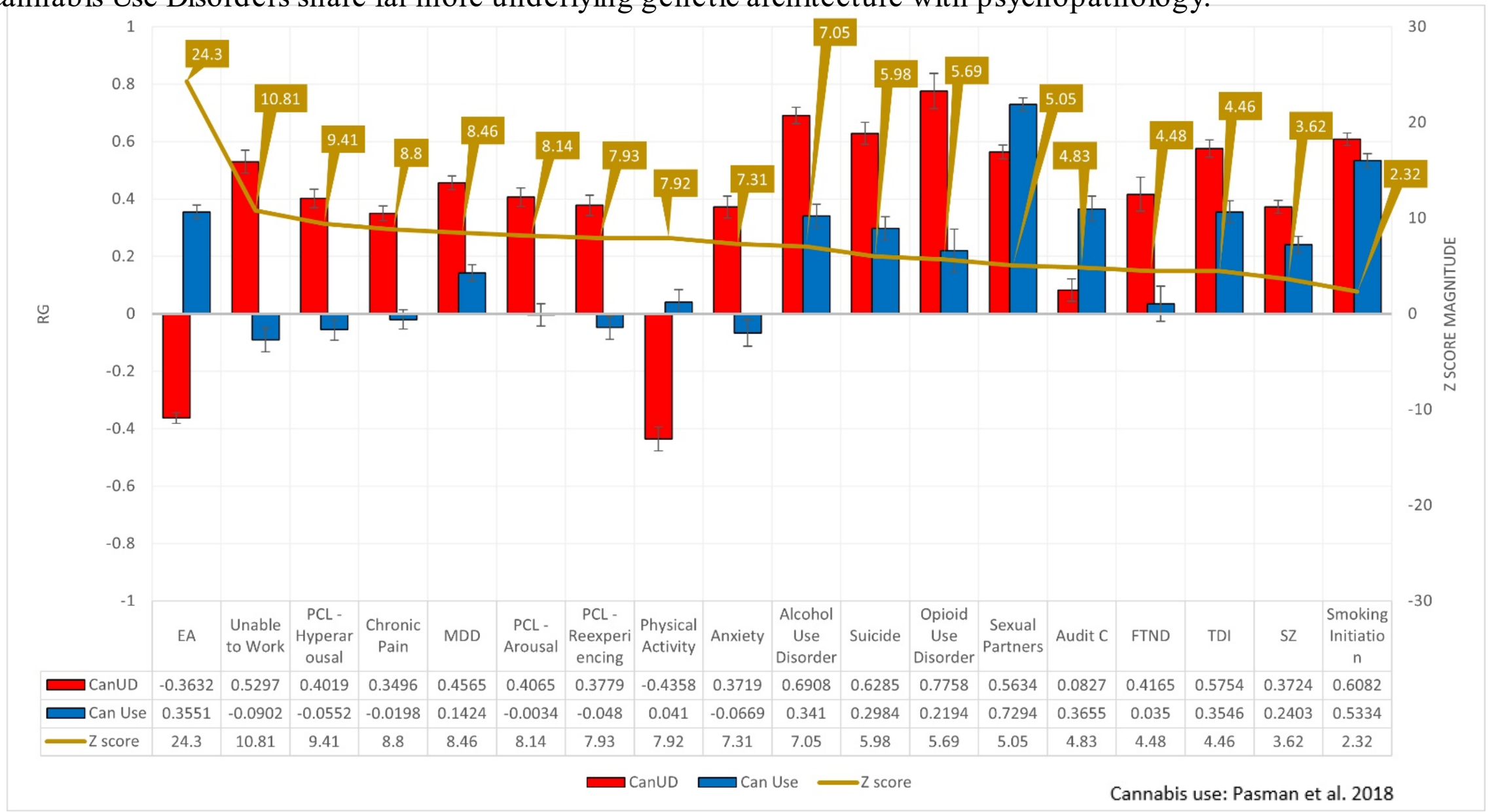
42,281 cases and 843,744 controls
22 Genomic risk loci
25 Independent lead SNPs

Lead SNP is near *CHRNA2*, identical to prior iPSYCH study
SNP near *FOXP2* remains genomewide significant
20 additional novel loci



Comparison of genetic correlations between Cannabis Use (Blue) to Cannabis Use Disorders (Red) and other traits.

Cannabis Use Disorders share far more underlying genetic architecture with psychopathology.



	EA	Unable to Work	PCL - Hyperarousal	Chronic Pain	MDD	PCL - Arousal	PCL - Reexperiencing	Physical Activity	Anxiety	Alcohol Use Disorder	Suicide	Opioid Use Disorder	Sexual Partners	Audit C	FTND	TDI	SZ	Smoking Initiation
CanUD	-0.3632	0.5297	0.4019	0.3496	0.4565	0.4065	0.3779	-0.4358	0.3719	0.6908	0.6285	0.7758	0.5634	0.0827	0.4165	0.5754	0.3724	0.6082
Can Use	0.3551	-0.0902	-0.0552	-0.0198	0.1424	-0.0034	-0.048	0.041	-0.0669	0.341	0.2984	0.2194	0.7294	0.3655	0.035	0.3546	0.2403	0.5334
Z score	24.3	10.81	9.41	8.8	8.46	8.14	7.93	7.92	7.31	7.05	5.98	5.69	5.05	4.83	4.48	4.46	3.62	2.32

Molecular Psychiatry www.nature.com/mp

IMMEDIATE COMMUNICATION OPEN

Check for updates

Genetic influences and causal pathways shared between cannabis use disorder and other substance use traits

Marco Galimberti[1,2], Daniel F. Levey[1,2], Joseph D. Deak[1,2], Hang Zhou[1,2], Murray B. Stein[3,4] and Joel Gelernter[1,2,5]✉

Received: 5 January 2024 Revised: 25 March 2024 Accepted: 28 March 2024
Published online: 05 April 2024

nature mental health

Article

https://doi.org/10.1038/s44220-025-00440-4

The genetic relationship between cannabis use disorder, cannabis use and psychiatric disorders

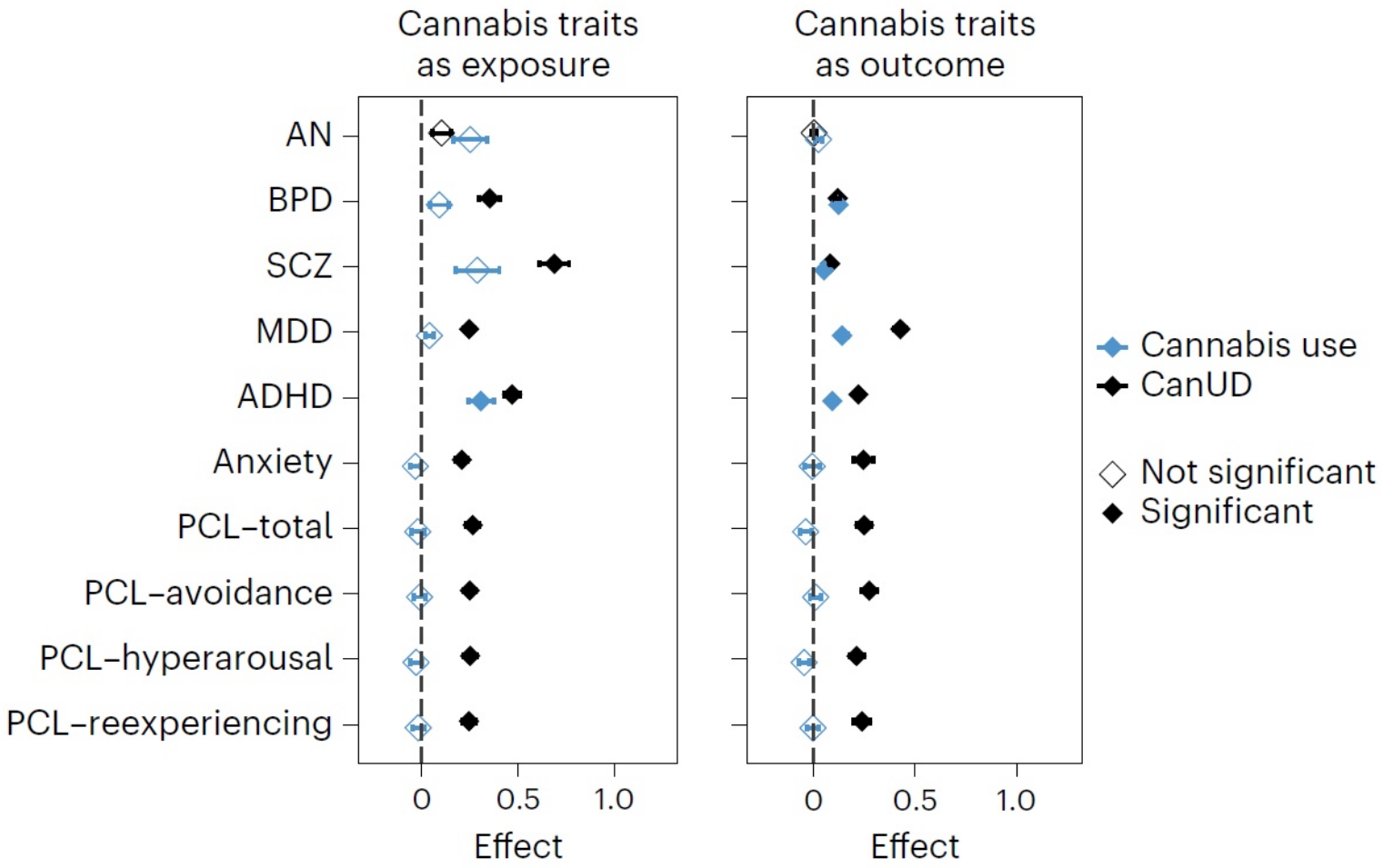
Received: 12 September 2024

Accepted: 22 April 2025

Published online: 29 May 2025

Marco Galimberti[1,2], Cassie Overstreet[1,2], Priya Gupta[1,2], Sarah Beck[1,2], Cecilia Dao[1,2], Joseph D. Deak[1,2], Hang Zhou[1,2], Emma C. Johnson[3], Arpana Agrawal[3,4], Murray B. Stein[4,5], Daniel F. Levey[1,2] & Joel Gelernter[1,2,6]✉

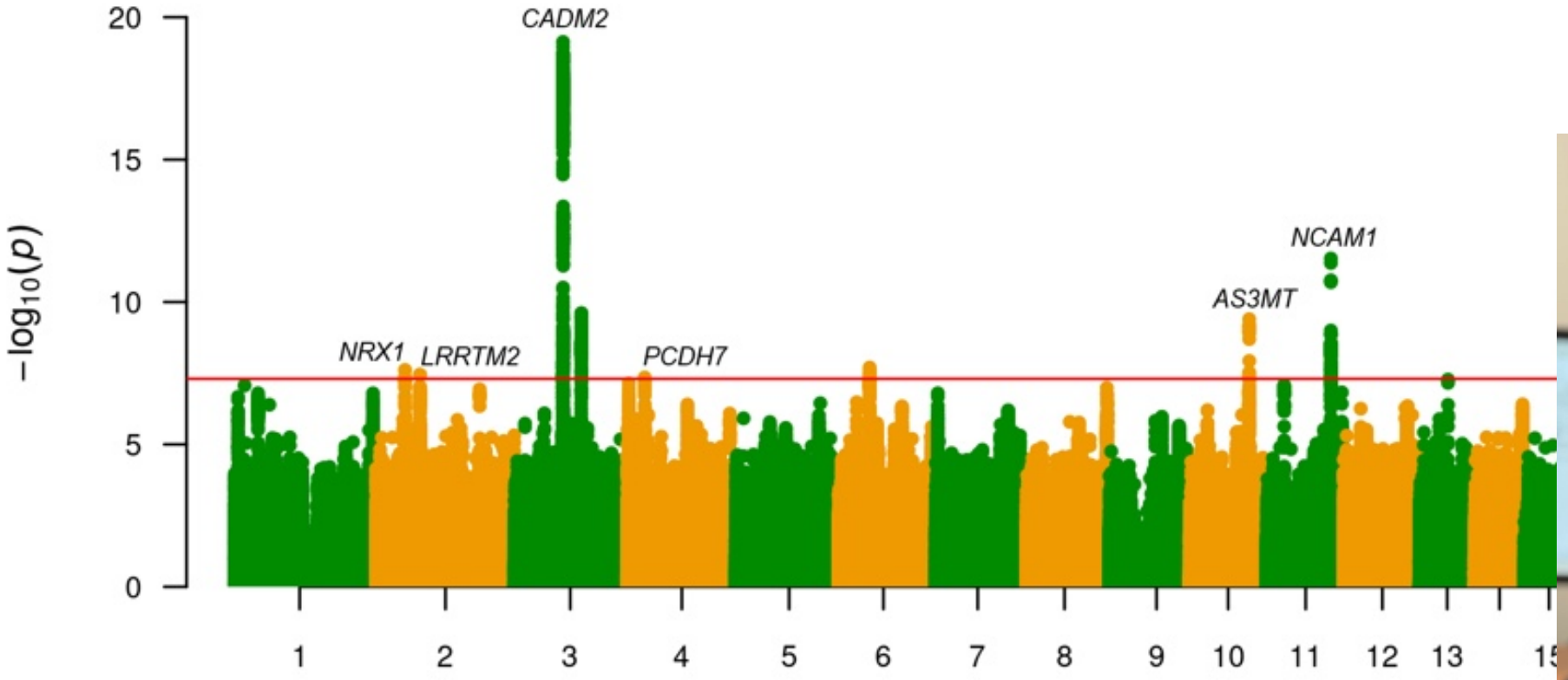
MR analyses of CanUD and cannabis use versus psychiatric disorders

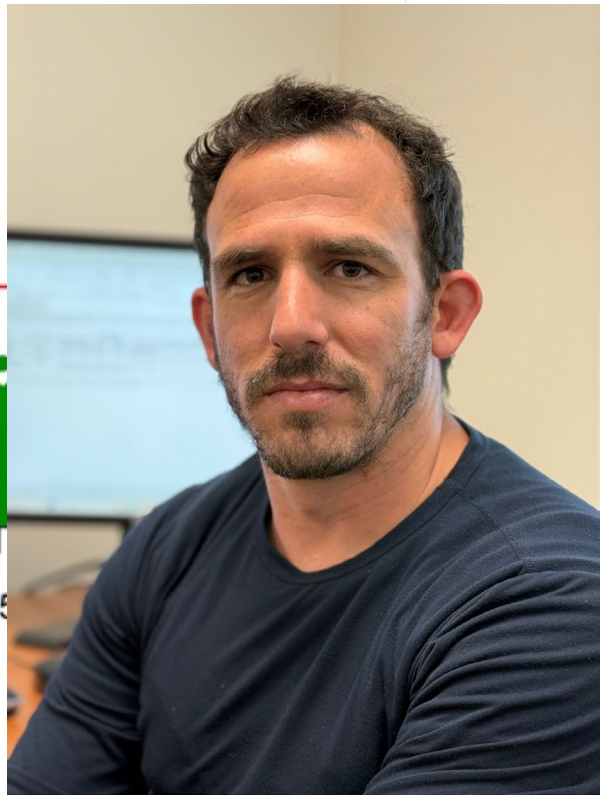


Cannabis use, cannabis use disorder, and other psychiatric traits: conclusions from genomics data

- Increasing evidence for genetic differences between cannabis use and CanUD
- CanUD increases risk of developing SUDs and other psychiatric disorders.
- This is often bidirectional: Multiple psychiatric disorders increase risk for cannabis use traits

CanLU GWAS – EUR (Meta-Analysis)





Genomic Variation Predicts Real-Time Δ^9-tetrahydrocannabinol Response in Humans

Uri Bright[1,2], Suhas Ganesh[1,3,4], Daniel F. Levey[1,2], Priya Gupta[1,2], the Yale THC Studies Consortium, Mohini Ranganathan[1-3], the IOP THC Studies Consortium, Robin M Murray[5], Marta DiForti[6,7], Paul Morrison[8], Deepak Cyril D'Souza[1-3]** Joel Gelernter[1,2,9]**

Why do this work?

- *Genetics studies require large samples and many years of work, so why do them?*
- For psychiatric and SUD traits, genes tend to account for about 50% of the risk – some a little lower, some much higher
- If we understand the genes that predispose to risk, we can understand part of the biology of the disorder
- Once we have genomewide data from GWAS, we can look at the genetic relationships between the disorder of interest and other disorders and traits – pleiotropy analyses, Mendelian randomization, etc… GWAS provides the tools to answer clinically important questions.

Yale University
Daniel F. Levey
Hang Zhou
Uri Bright
Renato Polimanti
Yaira Z. Nunez
Joseph Deak
Marco Galimberti
Hongyu Zhao
D. Cyril D'Souza
Marc Potenza

PGGSUD group
Howard JEdenberg
ArpanaAgrawal
Emma C. Johnson
Alexander Hatoum

University of Pennsylvania
Henry R. Kranzler
Rachel L. Kember
Scott Damrauer

MVP Genisis team

University of Oxford
Anya Topiwala

Funding from…
US NIH:
NIDA
NIAAA
NIMH
US Dept. Veterans Affairs
UKWellcomeTrust

UCSD
Murray B. Stein
Sandra SancheZRoige

BU, Harvard, MVP, MGH
J. Michael Gaziano
Kelly Harrington
Rachel Quaden
Jordan Smoller

And Many More
(please refer to publications)