Genetic Etiology of Alcohol Use Disorder and Related Cancers

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- I have no conflicts of interest to disclose

Alcohol use disorder (AUD)

- Chronic relapsing disease
- Characterized by symptoms like craving, tolerance, etc.
- Comorbid with many adverse medical, psychiatric, and social consequences
- Complex disease with both genetic and environmental components and their interactions

Known genetics of AUD

- AUD is heritable
- The best-fit estimate of the heritability of AUD was 0.49

Psychological Medicine (2015), **45**, 1061–1072. © Cambridge University Press 2014
doi:10.1017/S0033291714002165

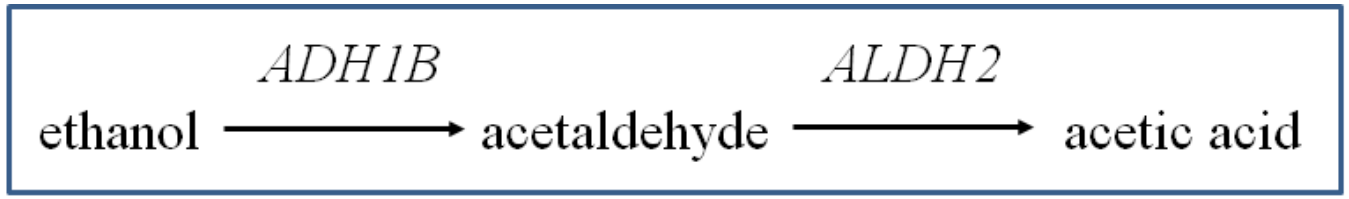
ORIGINAL ARTICLE

The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies

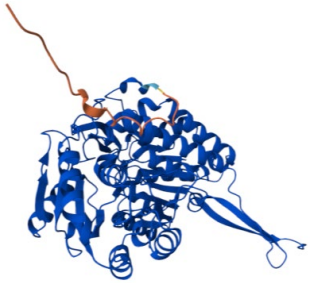
B. Verhulst[1], M. C. Neale[1,2] and K. S. Kendler[1,2]*

Known genetics of AUD

- Known genes and their product (enzymes) in alcohol metabolism
  - *ADH1B* - alcohol dehydrogenase 1B
  - *ALDH2* - aldehyde dehydrogenase 2



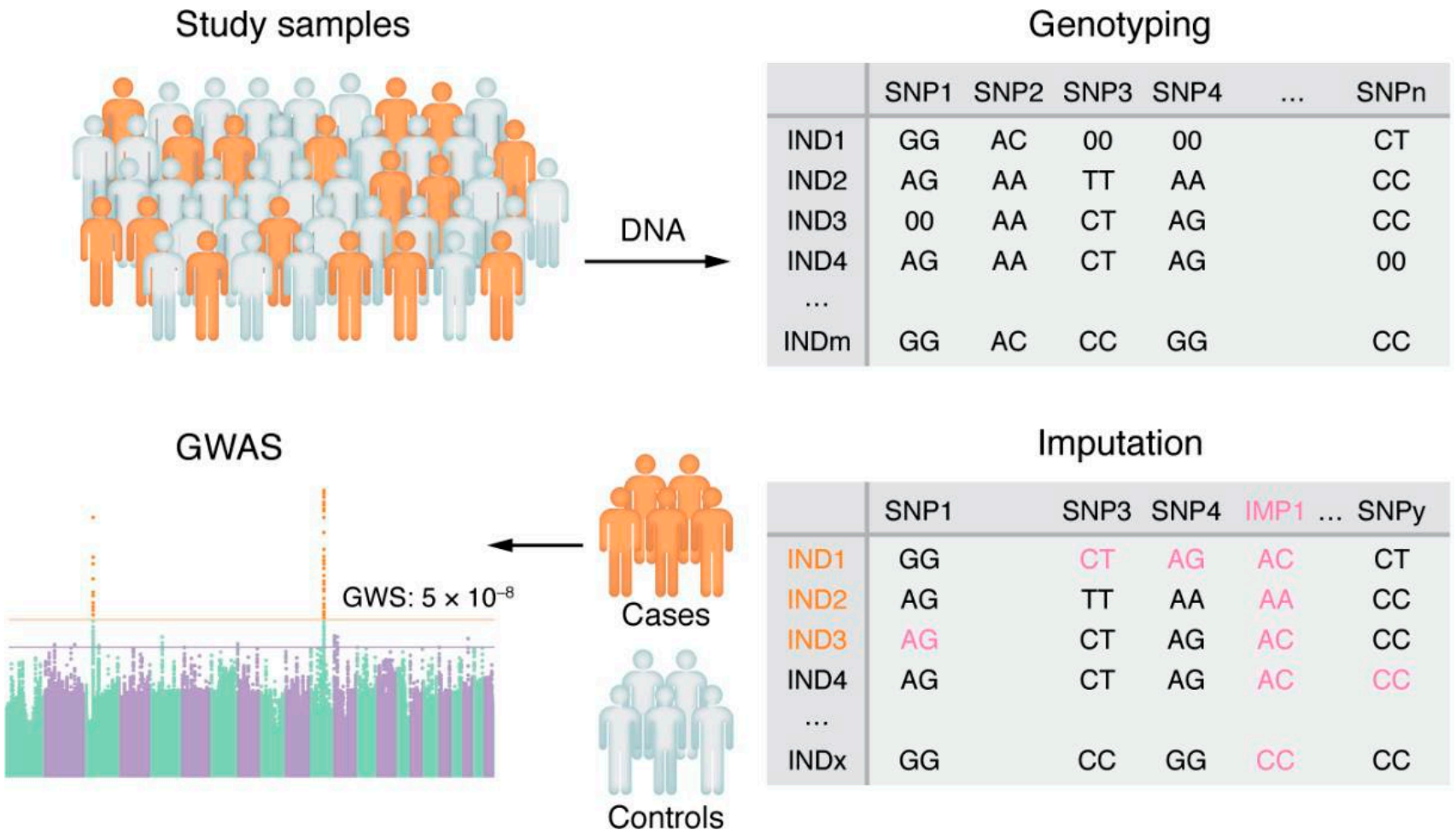
AlphaFold-predicted 3D structure:



- These two genes could not explain all the phenotypic variances (heritability)

- AUD is polygenic - more genetic risk variants need to be discovered

Genome-wide association study (GWAS)



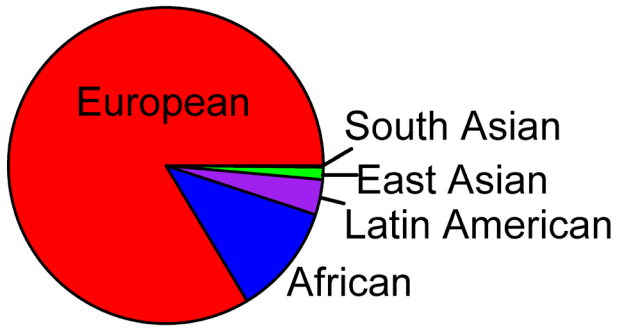
	SNP1	SNP2	SNP3	SNP4	…	SNPn
IND1	GG	AC	00	00		CT
IND2	AG	AA	TT	AA		CC
IND3	00	AA	CT	AG		CC
IND4	AG	AA	CT	AG		00
…						
INDm	GG	AC	CC	GG		CC

	SNP1		SNP3	SNP4	IMP1	…	SNPy
IND1	GG		CT	AG	AC		CT
IND2	AG		TT	AA	AA		CC
IND3	AG		CT	AG	AC		CC
IND4	AG		CT	AG	AC		CC
…							
INDx	GG		CC	GG	CC		CC

Zhou and Gelernter, *J Clin Invest*, 2024

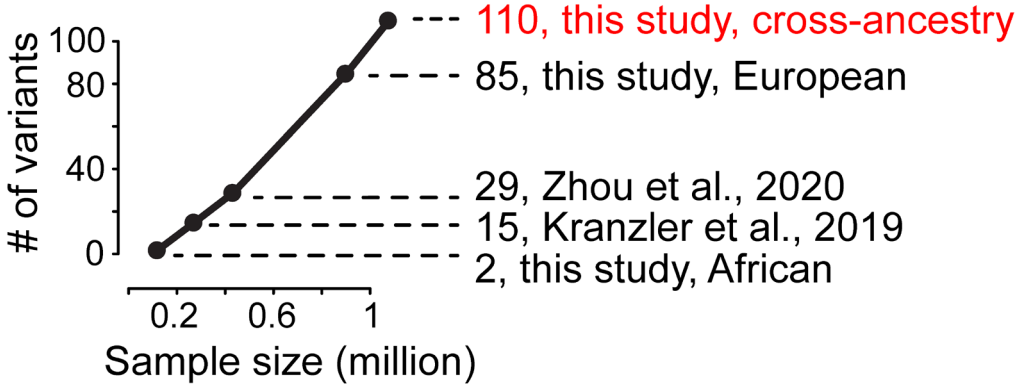
Latest GWAS of AUD (Zhou, 2023)

a. Sample sizes

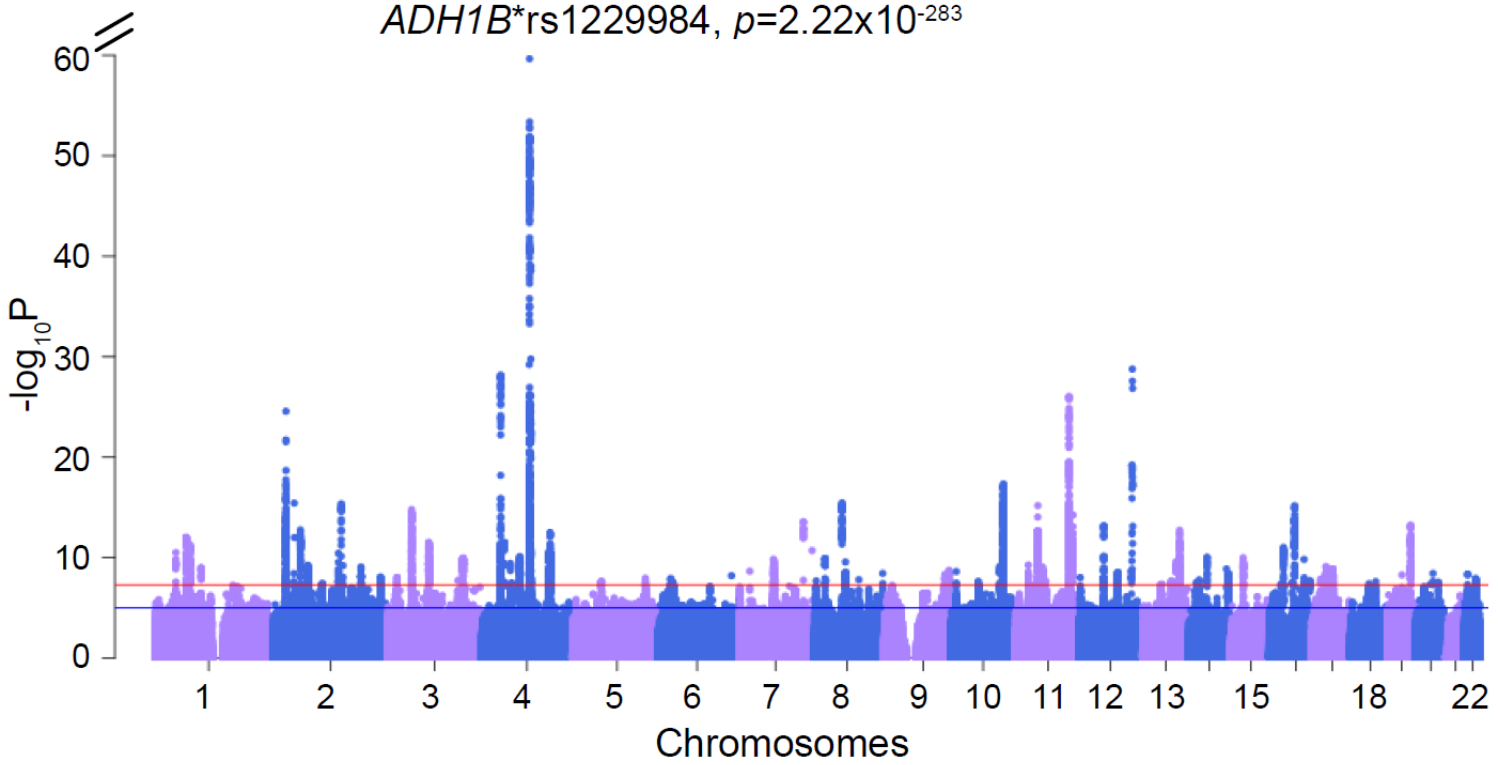


N = 1,079,947

b. Identified risk variants in recent studies



Cross-ancestry meta-analysis

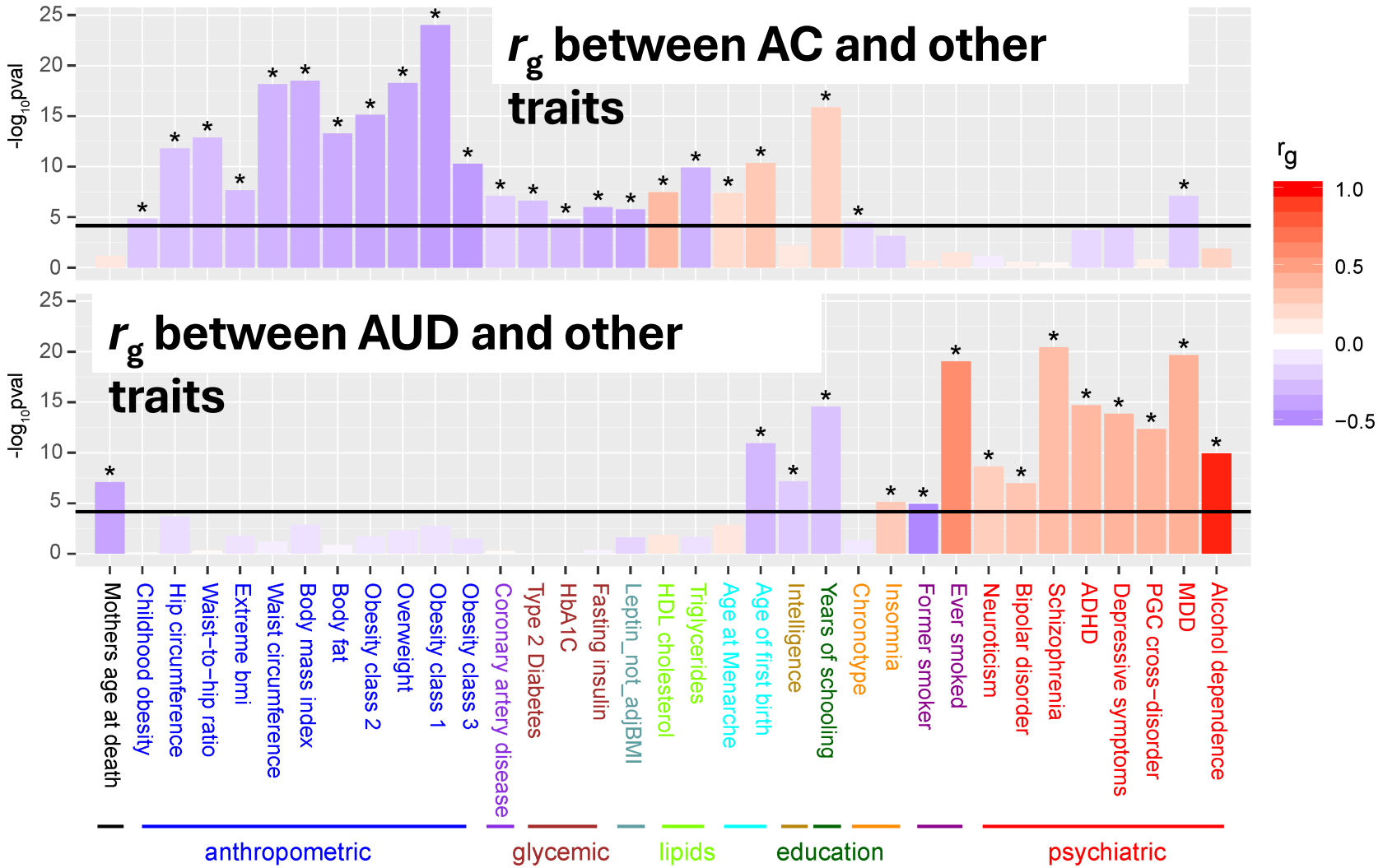


Zhou et al, *Nat Med,* 2023

AUD differs from alcohol consumption (AC) genetically

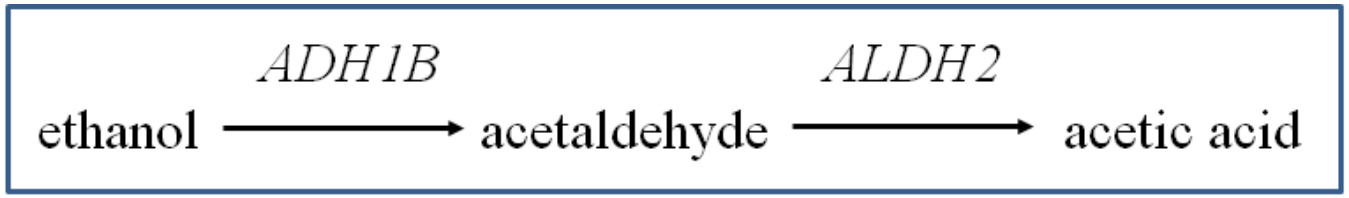
AC, drinking quantity-frequency, e.g., drinks/week

r_g – genetic correlation



Kranzler*, Zhou*, Kember*, 2019

How genetics affect the risk of alcohol-related cancers?



- Acetaldehyde can induce DNA lesions, which can initiate carcinogenesis if unrepaired

Seitz and Stickel. *Nat Rev Cancer*. 2007

Examples:

- Variants in *ADH1B* and *ALDH2* combined with alcohol use in cancer risk (Druesne-Pecollo et al. *Lancet Oncol* . 2009)

- *ADH1B**rs1229984 and *ADH7**rs1573496 are associated with upper aerodigestive cancer risk (Hashibe et al. *Nat Genet*. 2008)

- *ALDH2**rs671 as a genetic risk factor for several cancers, particularly esophageal cancer (Yokoyama et al. *Cancer Epidemiol Biomarkers Prev*. 2002)

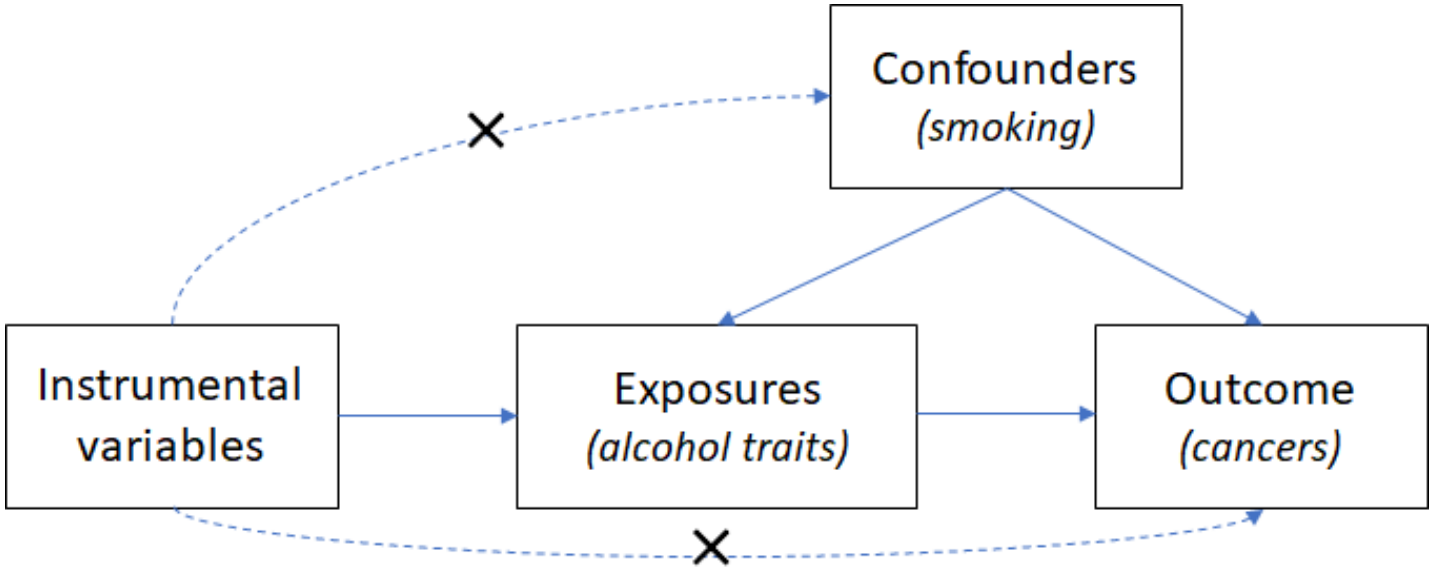
Questions remained

- Both alcohol traits and alcohol-related cancers are highly polygenic – hundreds of genetic variants

- Can we have a more robust causal inference using more genetic variants?
  - Not prone to confounding, measurement error, and reverse causation

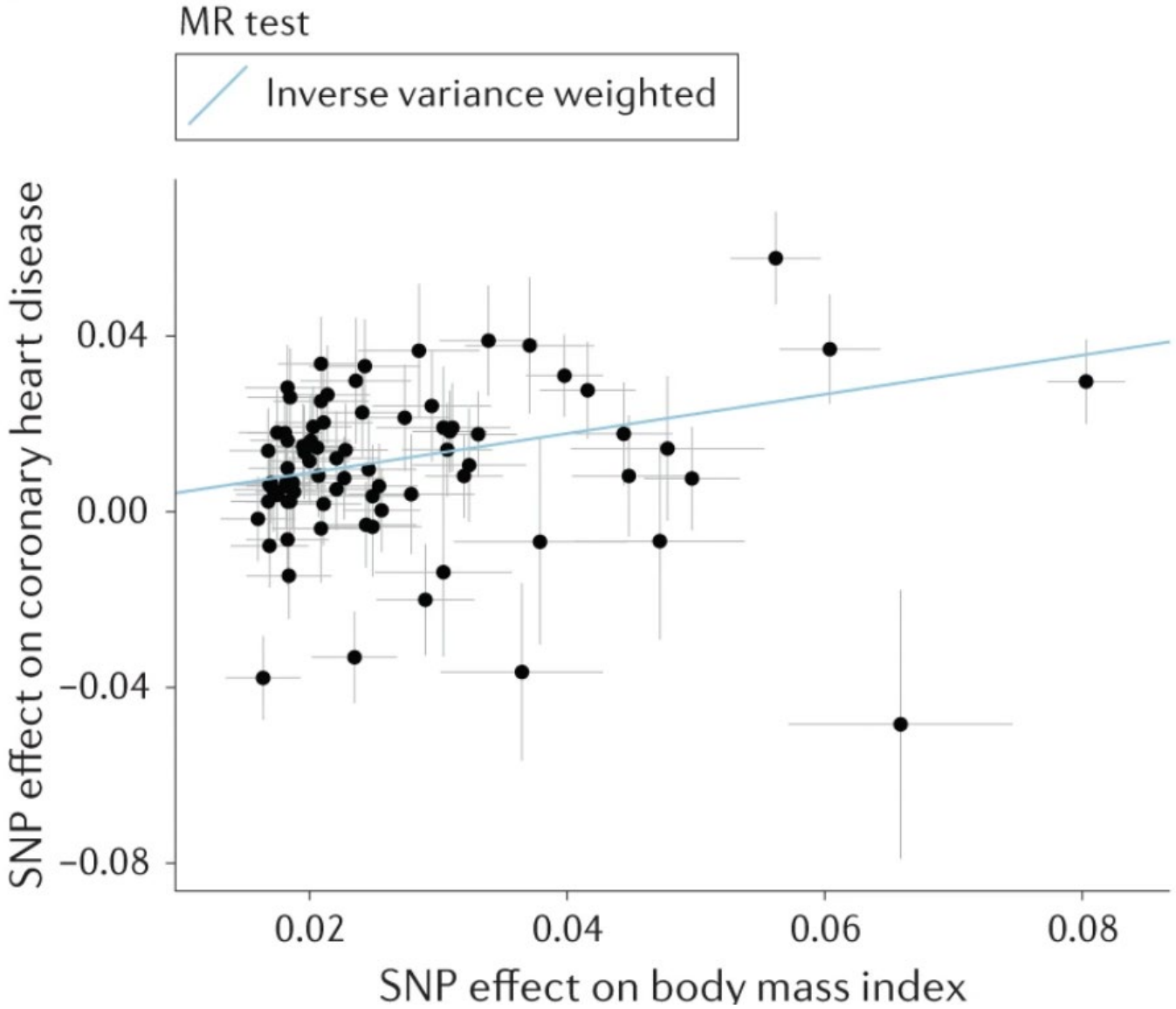
Newly developed tool: Mendelian Randomization (MR)

- MR uses genetic variants (e.g., SNPs) to assess causal relationships



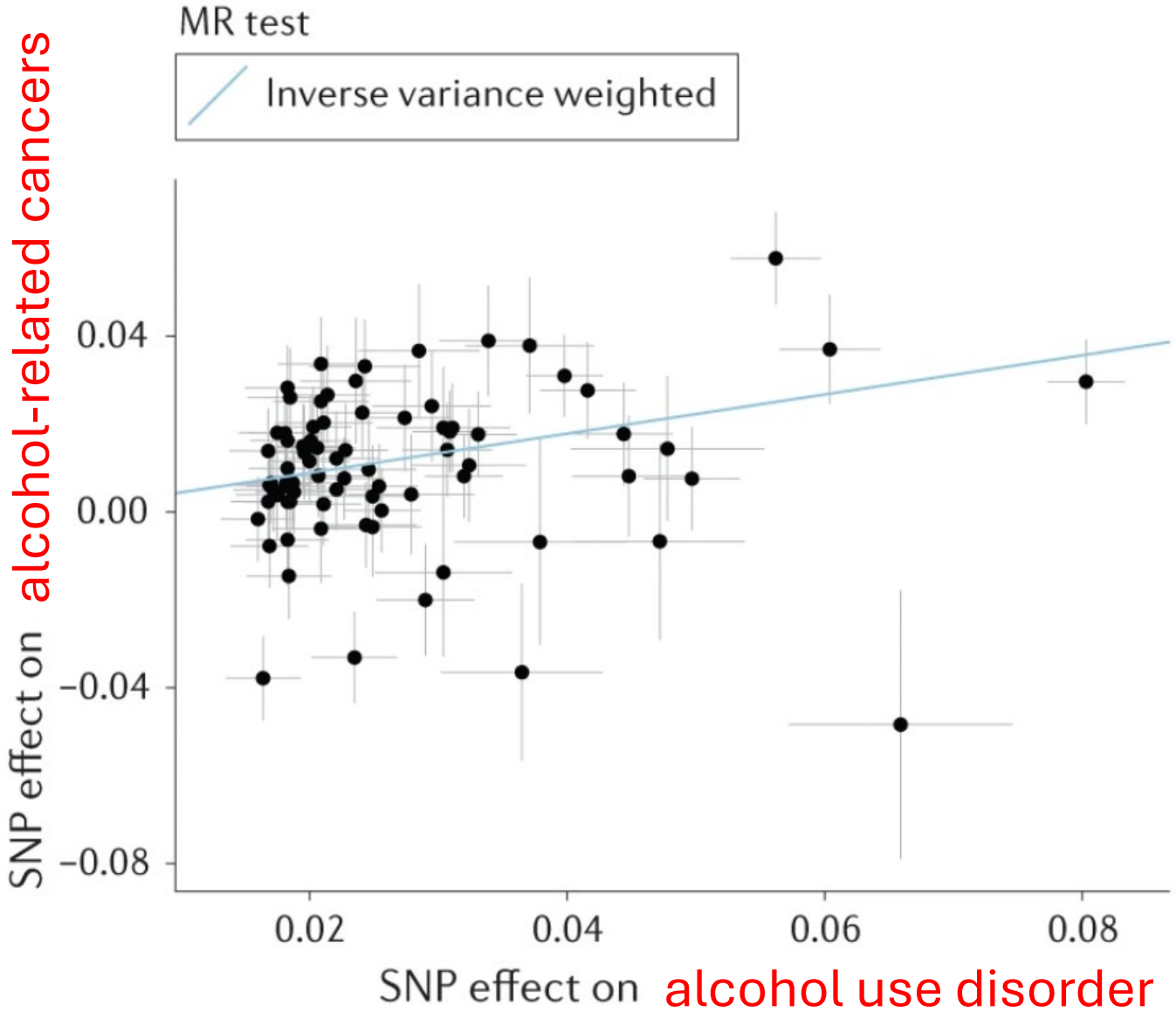
- Genetic instruments: 1) associated with exposure; 2) not associated with confounder; 3) influence the outcome only through the exposure
- Similar to randomized controlled trial (RCT)
- **MR is power-hungry**
- More valid instrumental variables, more robust of the inference

Example



Sanderson et al, *Nat Rev Methods Primers,* 2022

How about AUD and cancers?

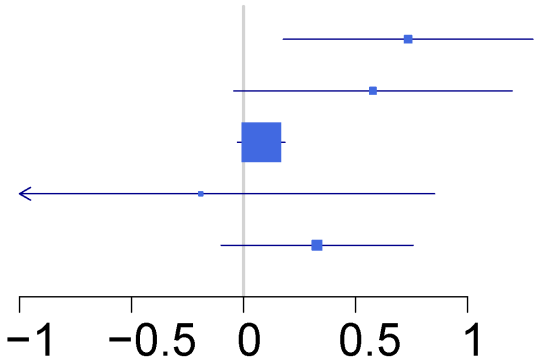


MR results (in European samples)

- Exposures
  - AUD (Zhou et al., 2023)
  - 74 SNPs
- Outcomes - cancers
  - Rashkin et al., 2020
  - Zhang et al., 2020
  - Trepo et al., 2022

AUD

Cancers	**p**
Oral	**9.71×10^{-3}**
Esophageal	0.07
Breast	0.14
Liver	0.72
Colorectal	0.13



Zhou et al., unpublished

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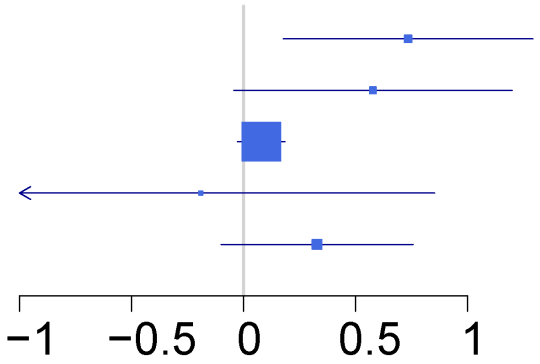
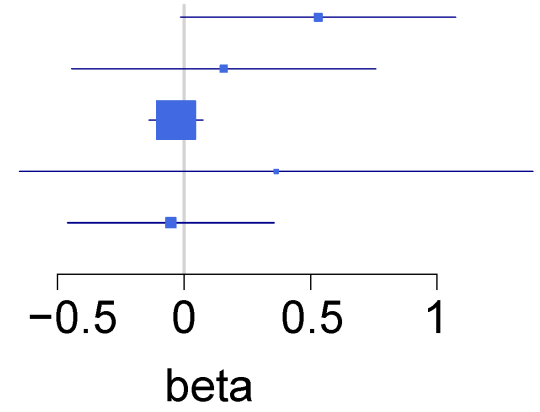


- Exposures
  - Drinks per week (Saunders, et al., 2022)
  - 403 SNPs

DPW

Oral	0.06
Esophageal	0.61
Breast	0.56
Liver	0.48
Colorectal	0.80

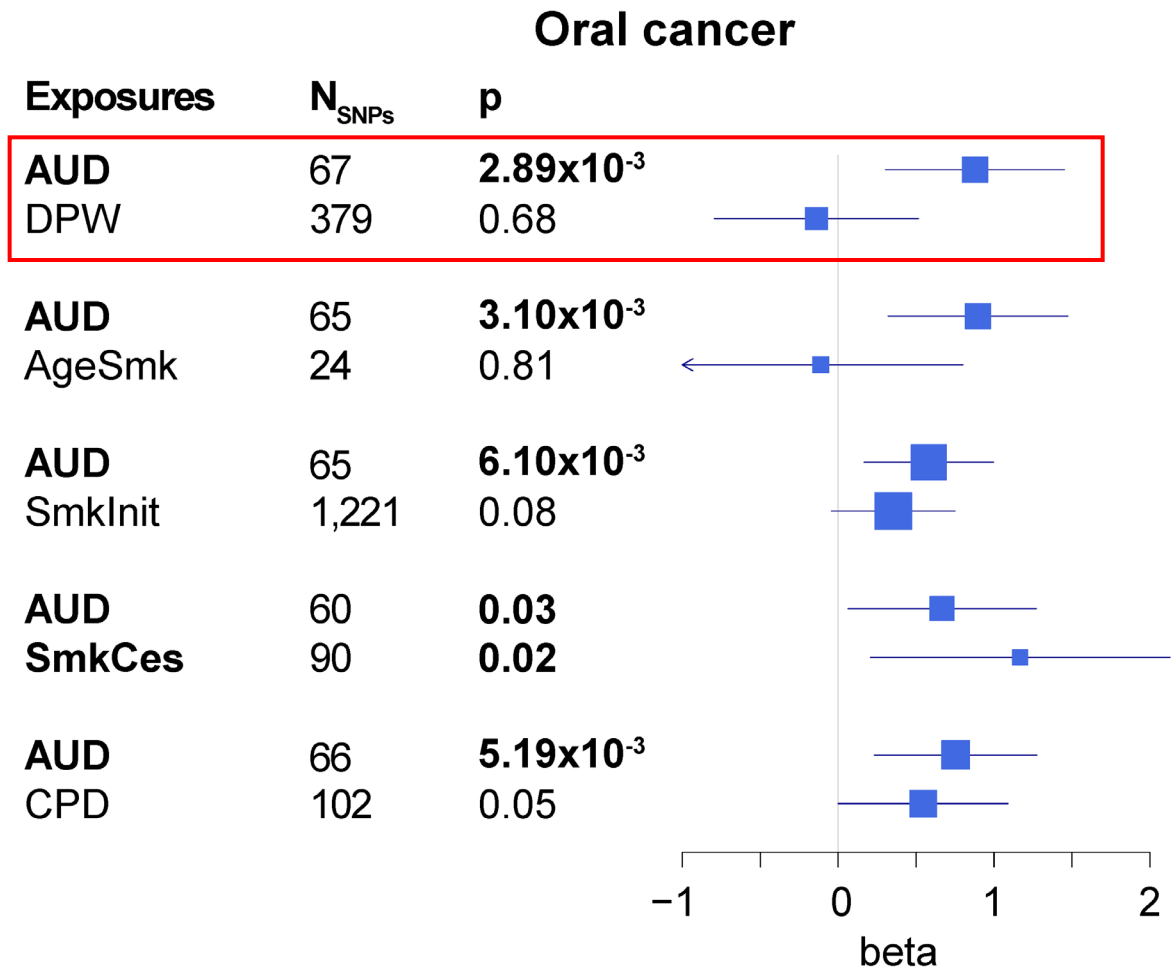


Zhou et al., unpublished

- Both alcohol use and tobacco smoking are related

- Is there a direct effect of AUD on oral cancer, independent from drinks per week or smoking traits?

Multi-variable MR, correcting for alcohol/smoking traits



AgeSmk – age of initiation of regular smoking

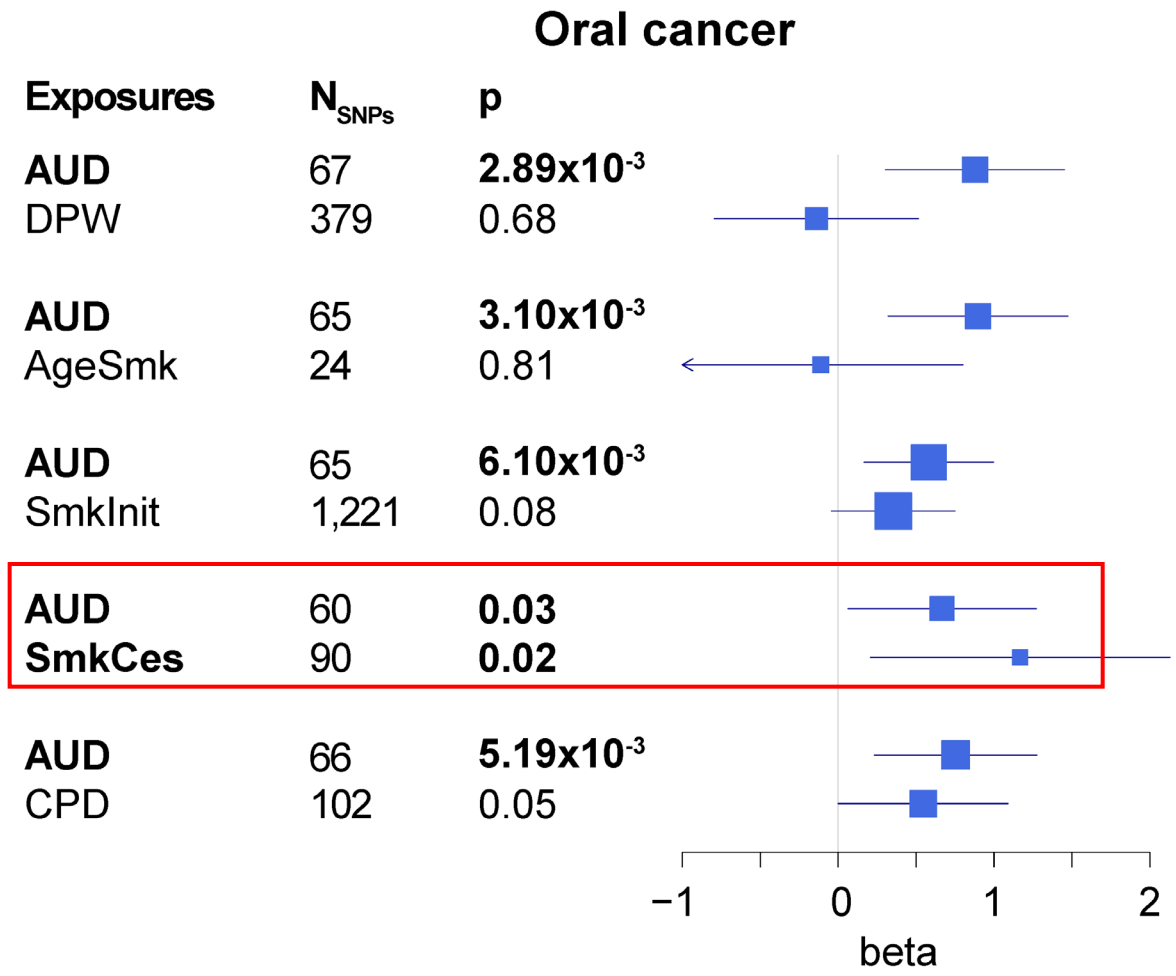
SmkInit – ever smoked regularly

SmkCes – current smoker vs former smoker

CPD – cigarettes per day

Zhou et al., unpublished

Multi-variable MR, correcting for alcohol/smoking traits



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Zhou et al., unpublished

Summary

- Nominally significant genetic causal relationship between AUD and oral cancer
  - Independent from drinks per week
  - Accounting for indirect effects from smoking traits

- **The results should be interpreted with caution**
  - genetic liability to diseases, not the diseases *per se*

- More investigation is warranted, especially in larger GWAS of cancers and in non-European populations.

Zhou et al. *In preparation*

Acknowledgements

- All participants in GWAS
- All collaborators
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Thank you!