GENOMIC PREDICTION OF ALCOHOL-RELATED MORBIDITIES AND MORTALITY

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25/09/2019

Institute for Molecular Medicine Finland

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Building a bridge from discovery to medicine

INTRODUCTION

- Drinking of alcohol (the most harmful of all abused substances) → global morbidity and mortality
- Alcohol-related behavior:
  - strongly affected by genetic factors
  - heritability of alcohol consumption in twin studies has ranged between ~0.35 and ~0.65 (weighted average 0.37)
- Modern large-scale genomic study settings → opportunities to study the heritable component of alcohol-related behavior and harms

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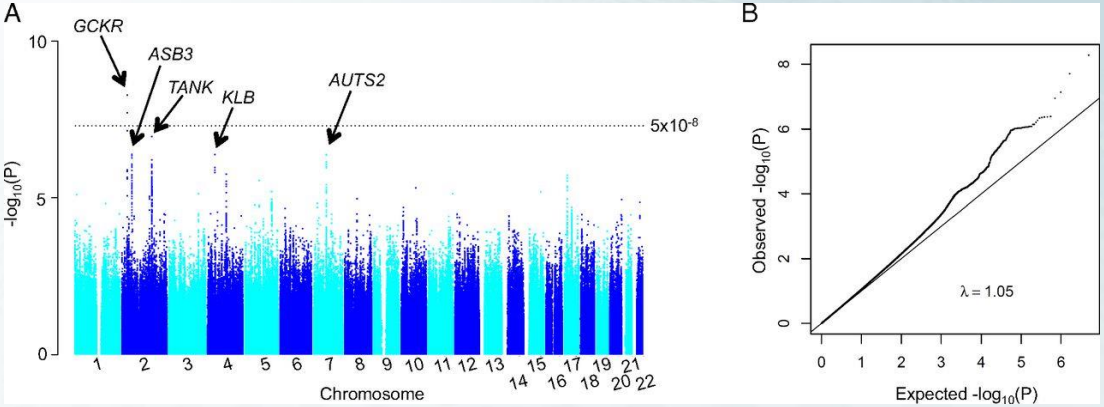
Large scale GWASes: multiple loci associated with alcohol consumption



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Genome-Wide Association Study Meta-Analysis of the Alcohol Use Disorders Identification Test (AUDIT) in Two Population-Based Cohorts

Sandra Sanchez-Roige, Ph.D., Abraham A. Palmer, Ph.D., Pierre Fontanillas, Ph.D., Sarah L. Elson, Ph.D.,
the 23andMe Research Team, the Substance Use Disorder Working Group of the Psychiatric Genomics Consortium, Mark J. Adams, ... **Show all Authors**

Published Online: 19 Oct 2018 | https://doi.org/10.1176/appi.ajp.2018.18040369

MENU

nature neuroscience

Article | Published: 26 November 2018

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

Raymond K. Walters, Renato Polimanti, [...] Arpana Agrawal

Nature Neuroscience **21**, 1656–1669 (2018) | Download Citation
6820 Accesses | **31** Citations | **284** Altmetric | Metrics

New Results Comment on this paper

Meta-analysis of problematic alcohol use in 435,563 individuals identifies 29 risk variants and yields insights into biology, pleiotropy and causality

Hang Zhou, Julia M. Sealock, Sandra Sanchez-Roige, Toni-Kim Clarke, Daniel Levey, Zhongshan Cheng, Boyang Li, Renato Polimanti, Rachel L. Kember, Rachel Vickers Smith, Johan H. Thygesen, Marsha Y. Morgan, Stephen R. Atkinson, Mark R. Thursz, Mette Nyegaard, Manuel Mattheisen, Anders D. Børglum, Emma C. Johnson, the VA Million Veteran Program, Amy C. Justice, Abraham A. Palmer, Andrew McQuillin, Lea K. Davis, Howard J. Edenberg, Arpana Agrawal, Henry R. Kranzler, Joel Gelernter

doi: https://doi.org/10.1101/738088

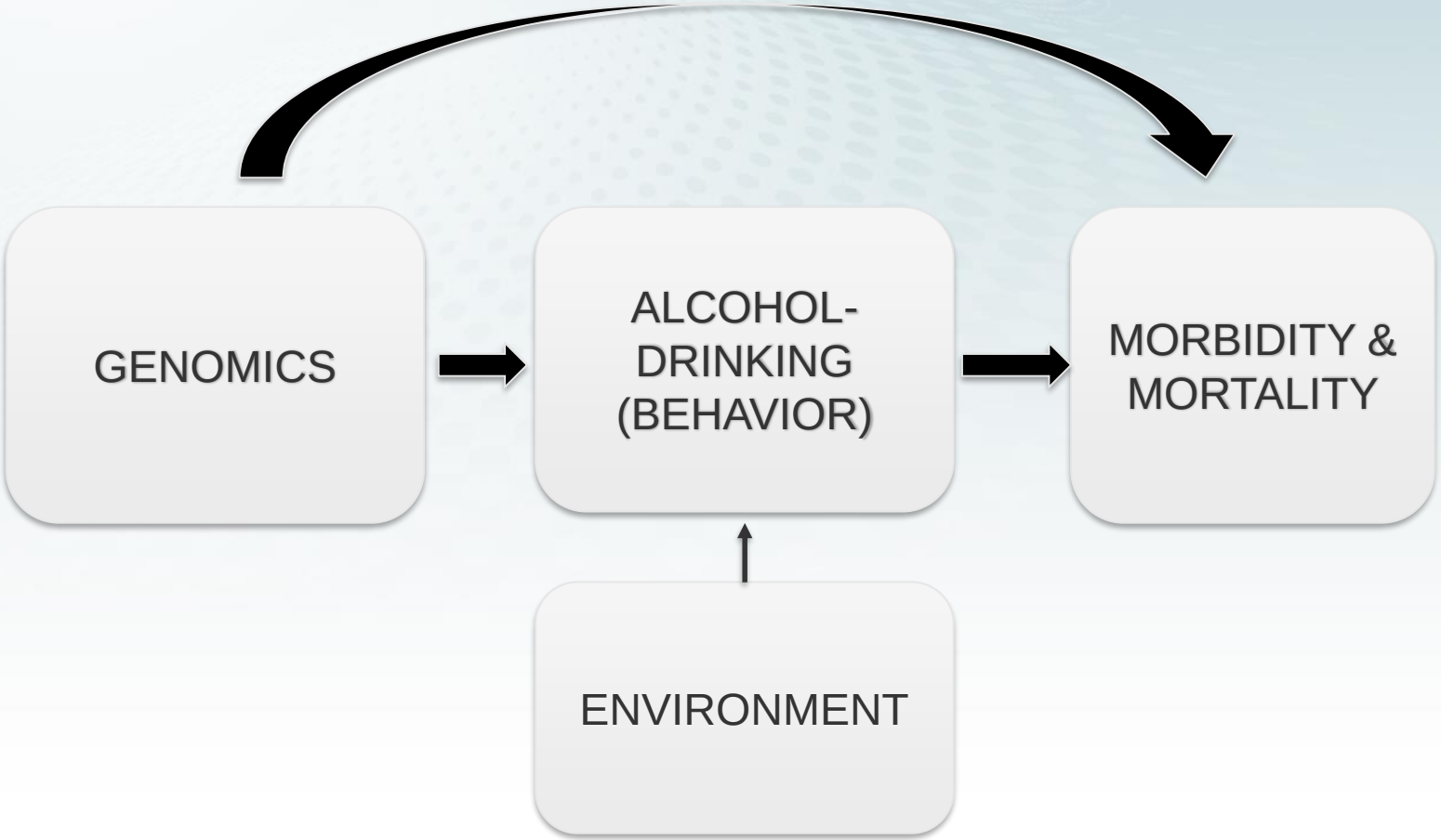
This article is a preprint and has not been certified by peer review [what does this mean?].

Abstract **Full Text** Info/History Metrics Preview PDF

AIMS

- 1) To build polygenic risk score (PRS) derived from alcohol consumption to predict alcohol-related major health events
- 2) To study if the PRS predict events over self-reported alcohol consumption measures?

AIMS


GENOMICS
ALCOHOL-DRINKING (BEHAVIOR)
MORBIDITY & MORTALITY
ENVIRONMENT

New Results

Comment on this paper

Polygenic risk score of alcohol consumption predicts alcohol-related morbidity and all-cause mortality

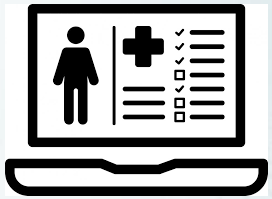
Tuomo Kiiskinen, Nina J. Mars, Teemu Palviainen, Jukka Koskela, Pietari Ripatti, Joel T. Rämö, Sanni Ruotsalainen, FinnGen, GSCAN Consortium, Aarno Palotie, Pamela A.F. Madden, Richard J. Rose, Jaakko Kaprio, Veikko Salomaa, Pia Mäkelä, Aki S. Havulinna, Samuli Ripatti

doi: https://doi.org/10.1101/652396

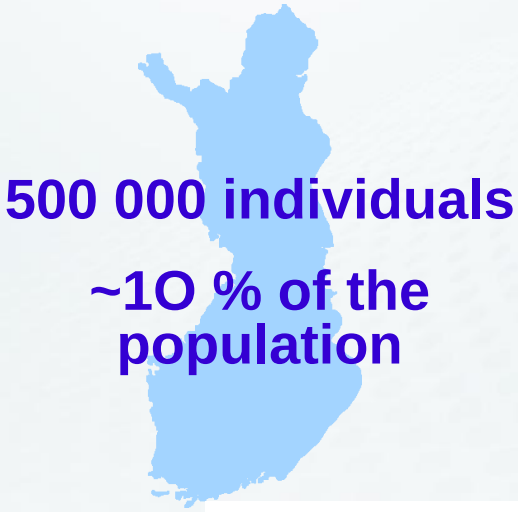
MATERIALS & METHODS

- 1)Datasets:
  - FinnGen R2 (n=96,499)
  - Prospective cohorts (FINRISK, Health 2000, Twin Cohort, n total = 36,499)
- 2) Summary statistics - GWAS meta-analysis of alcohol consumption (GSCAN consortium, n = 527,282 after exclusion of all Finnish samples)
- 3) A genome-wide PRS for alcohol consumption using LDPred (1.1 million genetic variants/SNPs)
- 4) Comprehensive longitudinal nationwide EHR-data
- 5) 21 alcohol-related disease endpoints linked to the cohort baseline data

FinnGen



National Health Register data



500 000 individuals

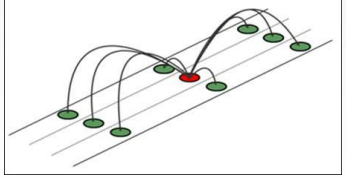
~1O % of the population

500 000 individuals Combined genotype and register data

Association analyses

Axiom GWA array

Imputation



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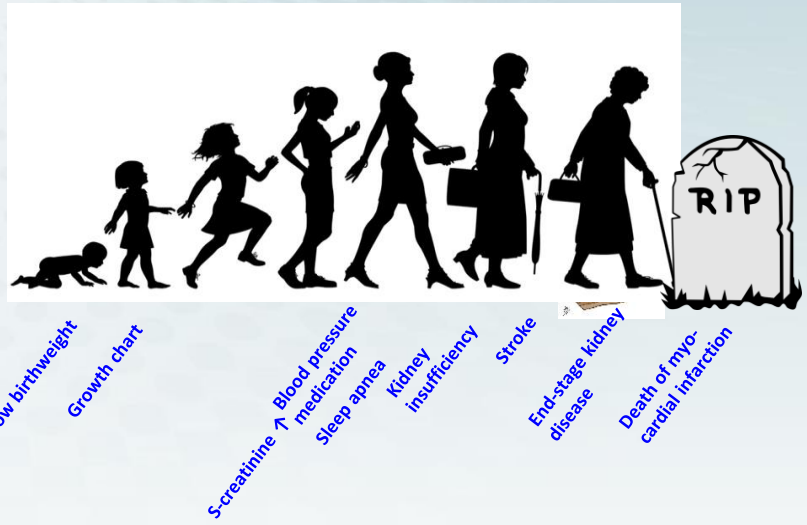
Moving from single time point case collections to a comprehensive view of health and disease

120360-1234

Linkage with person numbers to:

- **Medical Birth Register**
- **Register of Prescription Medicines**
- **National Health Register**
  diagnoses / procedures (ICD codes)
- **Causes of Death Register**
- **Cancer Register**
- **Clinical Laboratory databases**
  via Biobanks



The Nationwide electronic registers provide a unique possibility for data mining
Reconstruction of major life-time events instead of a single-point snapshot

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GSCAN GWAS

MENU

nature genetics

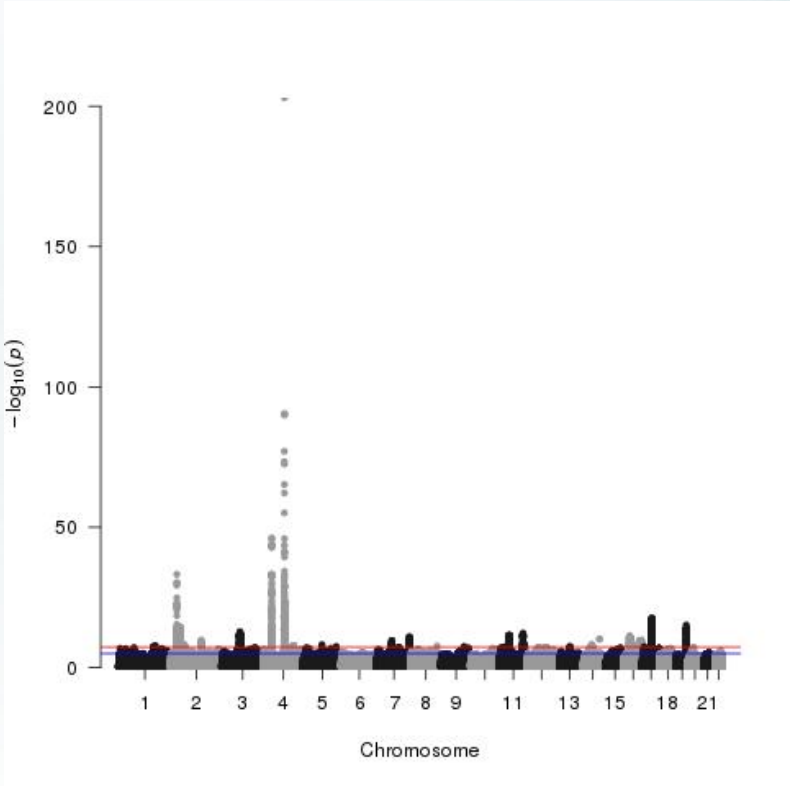
Letter | Published: 14 January 2019

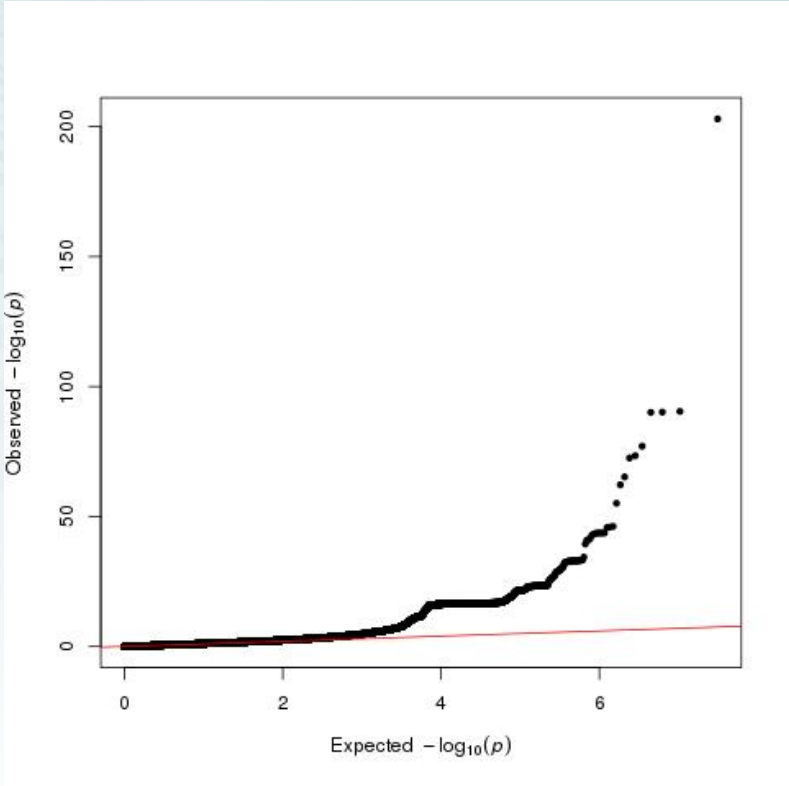
Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use

Mengzhen Liu, Yu Jiang, […] Scott Vrieze

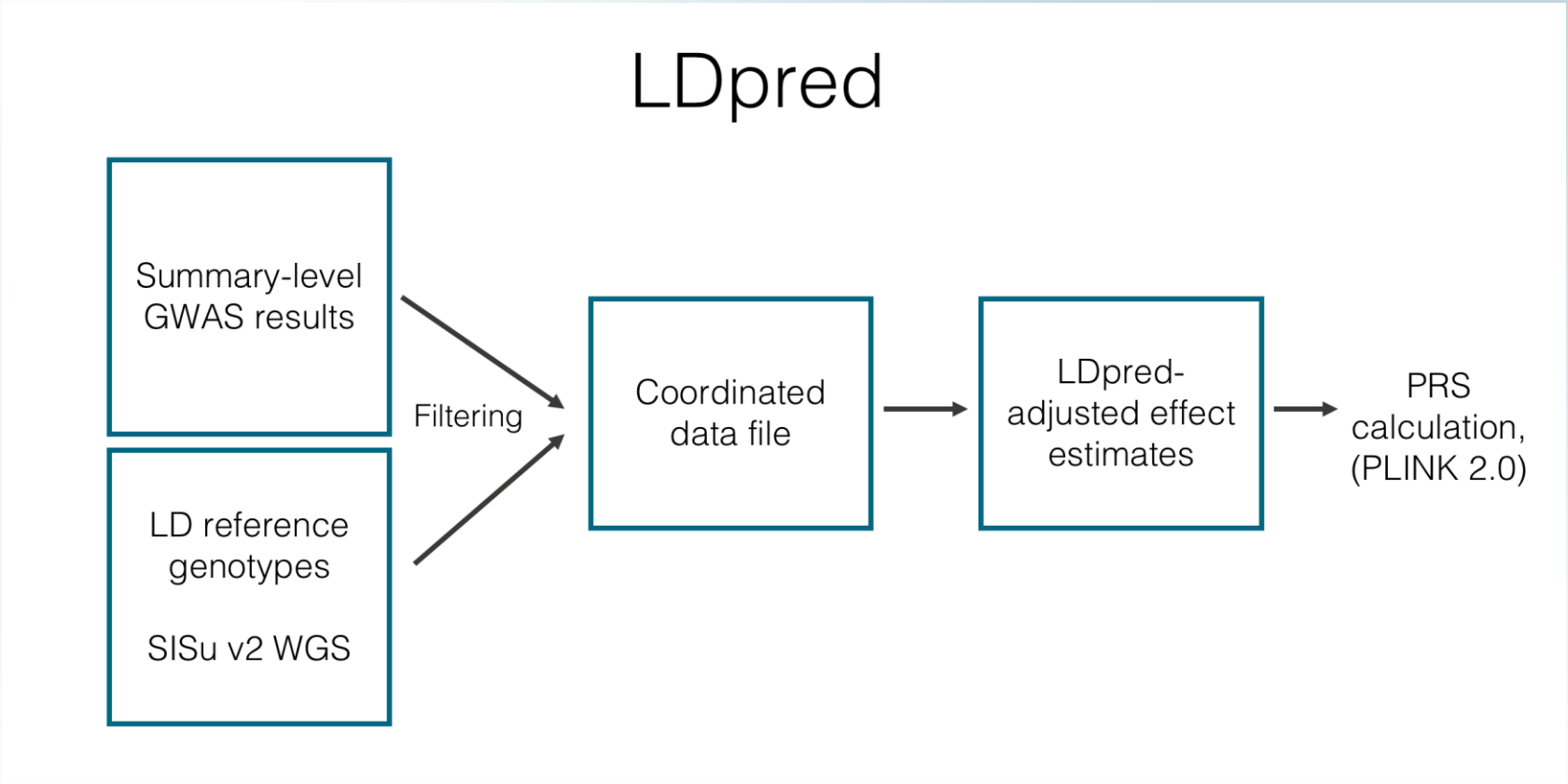
Nature Genetics **51**, 237–244 (2019) | Download Citation

GSCAN Drinks Per Week GWAS results

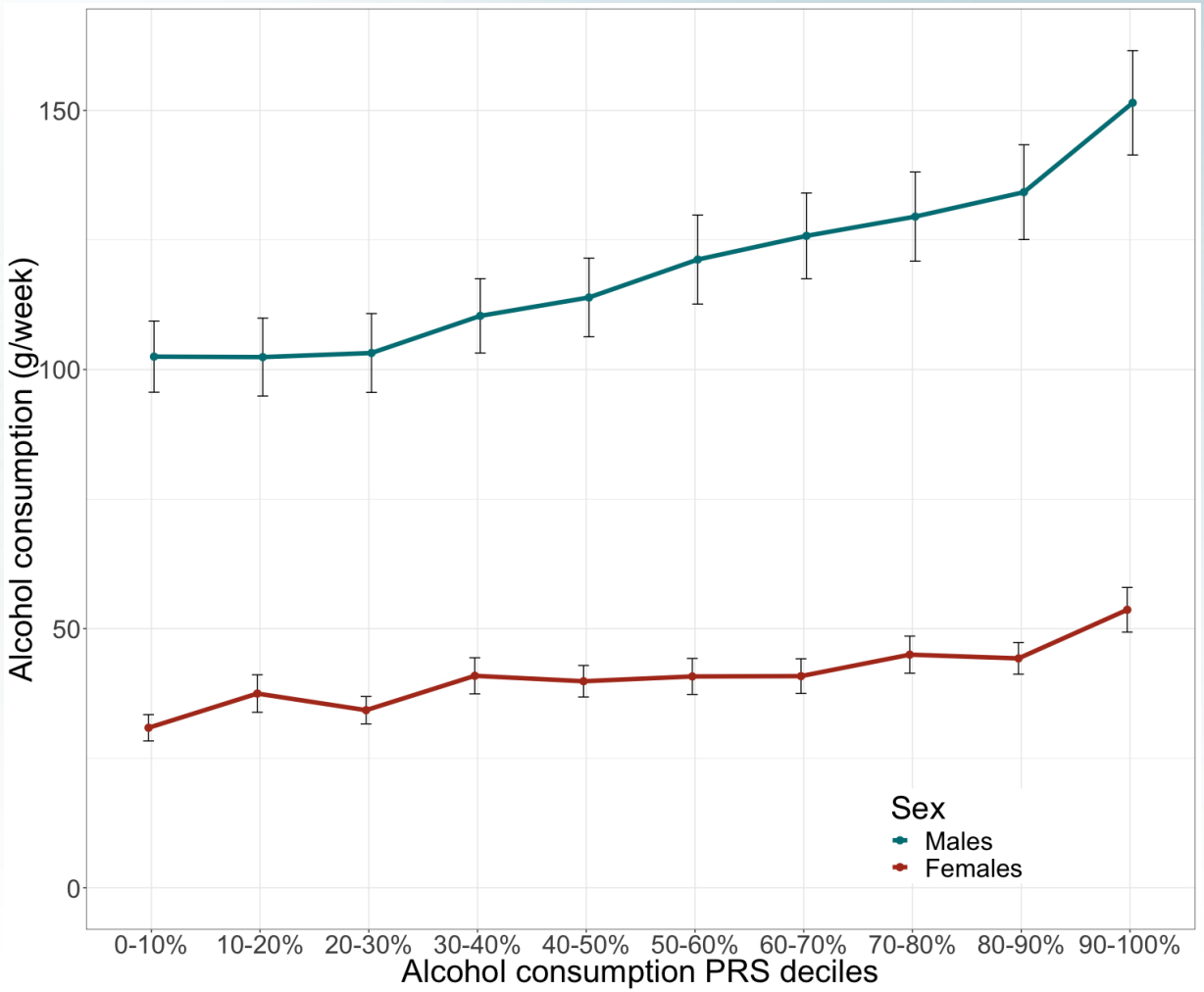




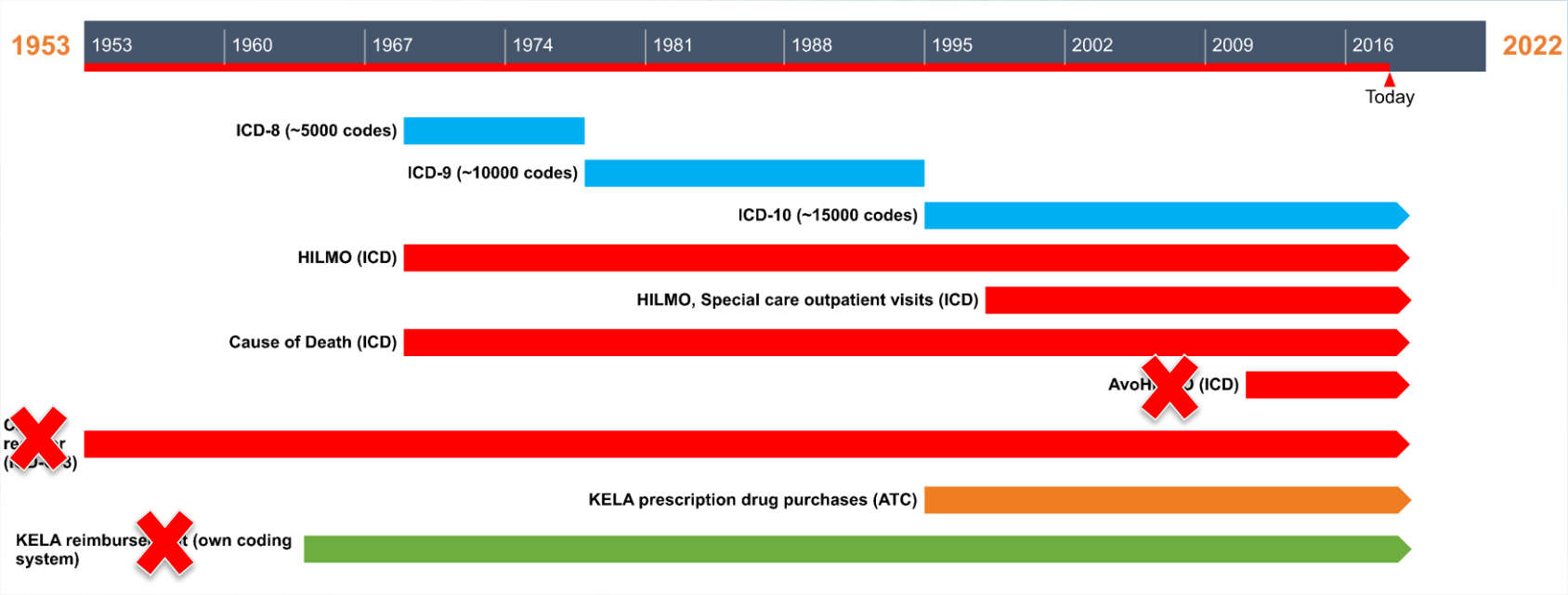
LDPred PRS


LDpred
Summary-level GWAS results
LD reference genotypes
SISu v2 WGS
Filtering
Coordinated data file
LDpred-adjusted effect estimates
PRS calculation, (PLINK 2.0)

PRS ~ Alcohol consumption



Nationwide registries

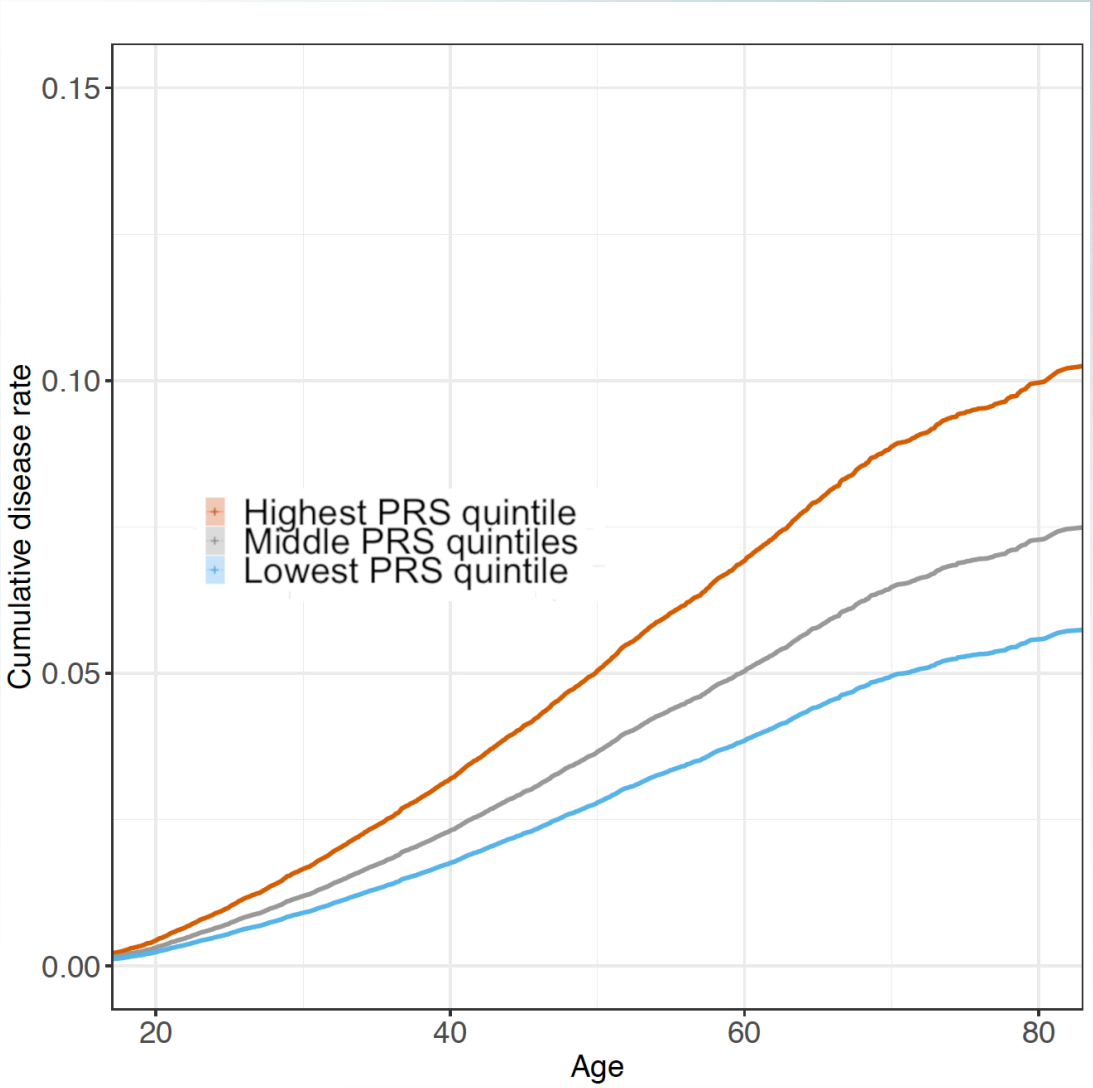


The endpoints

- **Definitions of alcohol-related morbidities endpoints (ICD-10| ICD-9 | ICD-8)**

- 1. Acute alcohol intoxication (F10.0)*, 2. Alcohol intoxication (-|305A) 3. Mental and behavioural disorders due to alcohol, excluding acute intoxication (F10.1-9 | 291,303 | 291,303) 4. Degeneration of nervous system due to alcoho (G31.2) 5. Epileptic seizures related to alcohol (G40.51) 6. Alcohol induced polyneuropathy (G62.1 | 3575A) 7. Alcoholic myopathy (G72.1) 8. Alcoholic cardiomyopathy (I42.6 | 4255) 9. Alcoholic gastritis (K29.3 | 5353A) 10. Alcoholic liver disease (K70 | 5710-3 | 5710) 11. Acohol-induced acute pancreatitis (K85.2 | 5770D-F) 12. Alcohol-induced chronic pancreatitis (K86.0 | 5771C-D) 13. Maternal care for (suspected) damage to fetus from alcohol (O35.4) 14. Fetus and newborn affected by maternal use of alcohol (P04.3 | 7607A)15. Fetal alcohol syndrome (dysmorphic) (Q860) 16. Accidental poisoning by and exposure to alcohol (X45) 17. Guidance and medical advice to a person with alcohol abuse (Z71.4) 18. Alcohol-induced pseudo-Cushing syndrome (E24.4) 19. Toxic effect of ethanol (T51.0| 9800|9800) 20. Toxic effect of unspecified or or other (than ethanol) alcohols (T51.1-9 | 9801-9|9801-9) 21. Use of disulfiram, acamprosate or naltrexone (prescription drug puchases with ATC-codes N07BB01, N07BB02 or N07BB04)

Highest vs lowest 20 %



PRS ~ Alcohol-related morbidities

	Morbidity (alco)	Mortality (alco)	Mortality (all-cause)
FinnGen	Cases=911	Cases=335	Cases=4,125
Basic model with age and sex	HR=1.26 [1.18-1.34],	HR=1.26 [1.13-1.53]	HR=1.11 [1.07-1.14]
Model with alcohol consumption	HR=1.15 [1.08-1.22]	HR=1.13 [1.01-1.26],	HR=1.07 [1.01-1.13]
Fully adjusted model	HR=1.15 [1.08-1.22]	HR=1.11 [0.97-1.24]	HR=1.09 [1.06-1.12]

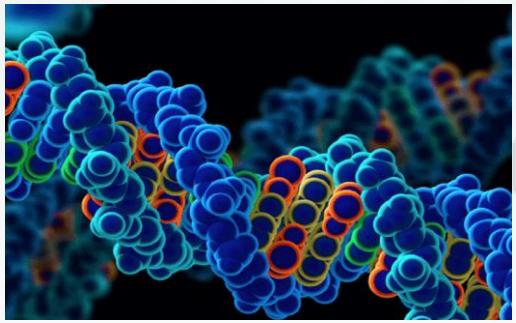
PREDICTION: FR → H2000

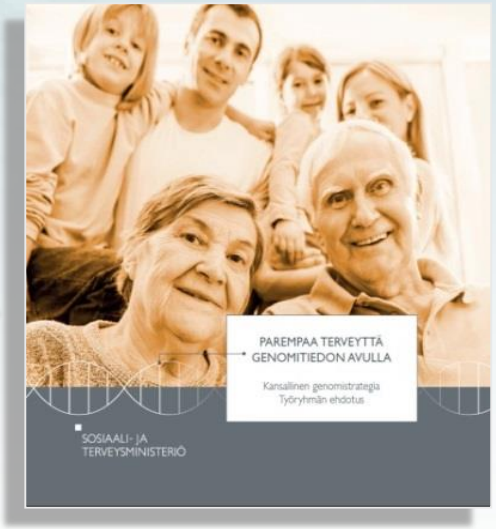
MODEL	C-index improvement by PRS	NRI	IDI
1) Age, sex +PRS	0.02 [0.69 → 0.71] (p = 0.023)	0.29 (p=1.43*10^-3)	0.0026 (p=0.0043)
2) Age, Sex, consumption estimate + PRS	0.002 [0.812→0.814] (p=0.30)	0.34 (p = 0.0051)	0.0024 (p = 0.016)
2) Age, sex, consumption estimate, smoking, marital status, education +PRS	0.0018 [0.847-0.849] (p=0.44)	0.235 (p=0.015)	0.00331 (p=0.048)

Alcohol use disorder (DSM-IV)

- Nicotine Addiction Genetics Family cohort (440 cases, 1,140 controls) + FinnTwin16 cohort (273 cases, 320 controls)
- A meta-analysis of the two cohorts (713 cases) →
- 20 % increase in the prevalence of AUD per 1 PRS SD (OR = 1.20 [1.11-1.31], p = $2.29*10^{-5}$) in the unadjusted model
- Adjusting for marital status, education and smoking explained part of the effect (OR=1.14 [1.02-1.28], p=0.023)
- Further adjusting with maximal amount of drinks taken explained most of the effect (OR=1.06 [0.94-1.19], p=0.35)

HOW TO COMMUNICATE THIS INFORMATION?





Genetic Risk and Health Behavior

Based on previous studies

- Personal disease risk information based on a **few variants with weak effects** does not motivate change in health behavior
- Genetic information based on **single rare DNA variants with a moderately strong effect** on disease risk often prompts health behaviors such as screening, medication and surgery

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Genomic Risk and Health Behavior

The GeneRISK –study (n= ~7,343)

INTENTION
Participants report that personal risk information inspires to improve lifestyle

ACTION
Individuals at high risk take action to lower their risk more often than others

MOTIVATION
Action to lower the risk associates with an increased polygenic load

Elevated genomic risk + interactive tool for communication
= motivation for change

Actions Taken at Follow-up

	CVD-risk > 10% n = 685	CVD-risk < 10% n = 3,996
Sustained weight loss (% of study participants)	15.9 *	12.3
Quit smoking (% of smokers)	14.3	15.3
Seen a physician (%)	20.7 ***	8.3
Any of the above (%)	36.2 ***	20.8

*p=0.01; ***p<0.001

Elisabeth Widén

Attitudes at 1.5 Years of Follow-up (n=5,196)

› My personal risk information was easy to understand	89%
› My results were useful	90%
› My results were unexpected	22%
› My results were concerning	29%
› Genetic factors importantly influence my disease risk	97%
› I can impact on my disease risk through my lifestyle	99%
› My personal risk information motivates me to take better care of my health	89%
› Doctors know how to interpret and utilize genome information	75%

Next steps

- Larger genomic studies with HUGE sample sizes needed (millions)
- Better Polygenic Risk Scores(combining genomic information behind different alcohol-related phenotypes)
- Real-life prospective studies (prediction+diagnosis+prevention)

CONCLUSIONS

- Polygenic risk score for alcohol consumption is strongly associated with increased alcohol consumption and alcohol-related harms
- The PRS predicted alcohol-related major health events over and beyond self-reported baseline alcohol consumption
- Polygenic risk score shows promise in identifying individuals at high risk for alcohol-related morbidities with improved prediction models
- Effect of communicating this information to the public need be carefully and comprehensively studied

THANK YOU

- Nina Mars, Teemu Palviainen, Jukka Koskela, Joel T. Rämö, Pietari Ripatti, Jaakko Kaprio, Veikko Salomaa, Pia Mäkelä, Aki S. Havulinna, Samuli Ripatti
- GSCAN Consortium
- Study participants (FinnGen)

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