Using genome-wide approaches to understand the genetic etiology of suicide-related behaviors and substance use disorders

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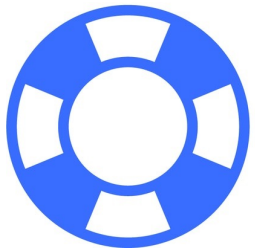


American Foundation for Suicide Prevention

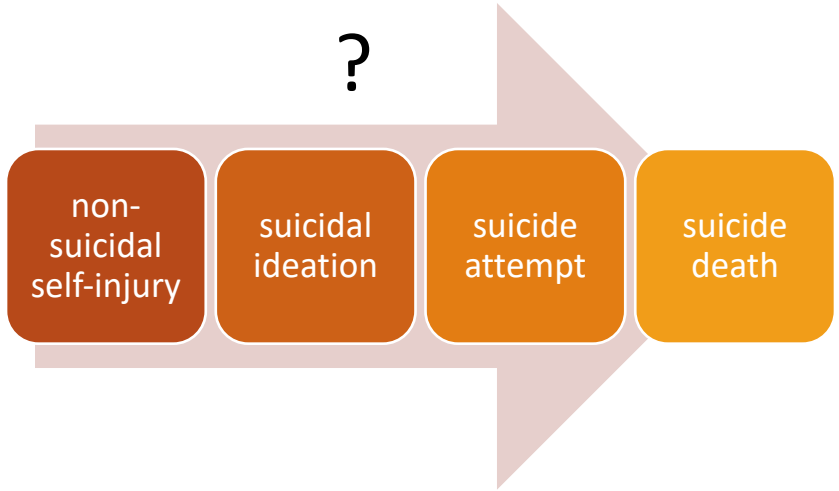
Why genetics?

- Scientific impact: a better understanding of genetic risk, in conjunction with socio-environmental factors → identification of at-risk groups

- Societal impact: a better understanding of genetic and biological mechanisms → reduce stigma around suicide

Background

- Suicidal thoughts and behaviors are **transdiagnostic, heterogeneous, and partly heritable**
- Linear spectrum of liability?



Background

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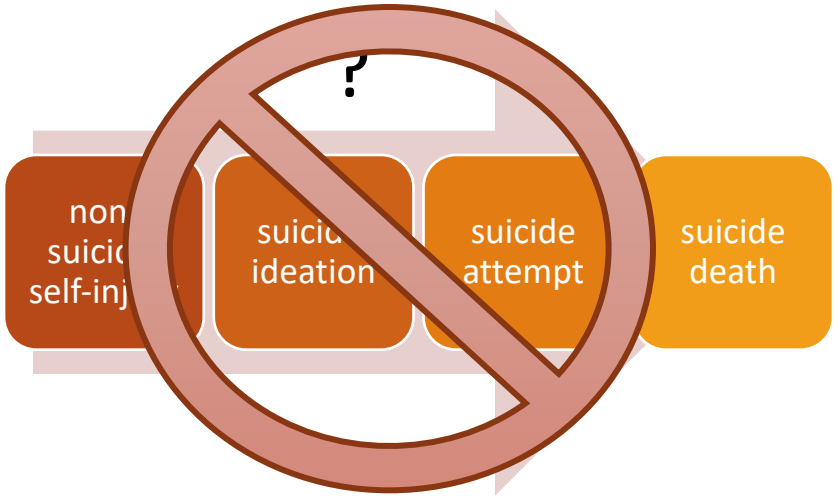
*"The genetic and environmental etiologies of suicide attempt and death are **partially overlapping**, exhibit modest sex differences, and shift across the life course"*
–Edwards et al., 2021



*"While suicide attempt and suicide death are substantially genetically correlated, a model that proposes that they reflect quantitatively different **degrees of severity on the same continuum of liability can be ruled out**"*
–Kendler et al., 2020

Edwards et al., 2021. *American Journal of Psychiatry*
Kendler et al., 2020. *American Journal of Psychiatry*

Outline of today's talk

1. How does genetic predisposition for depression, risk-taking, and cognitive function relate to different suicidal thoughts and behaviors?
2. What are the genetic relationships between suicidal thoughts and behaviors themselves, and substance use disorders?
3. Current directions:
   - Cross-disorder analysis of problematic alcohol use, depression, and suicide attempt
   - Multi-PRS models predicting detailed suicide-related phenotypes

Overarching goal: use genome-wide data to better understand genetic etiology of suicide.

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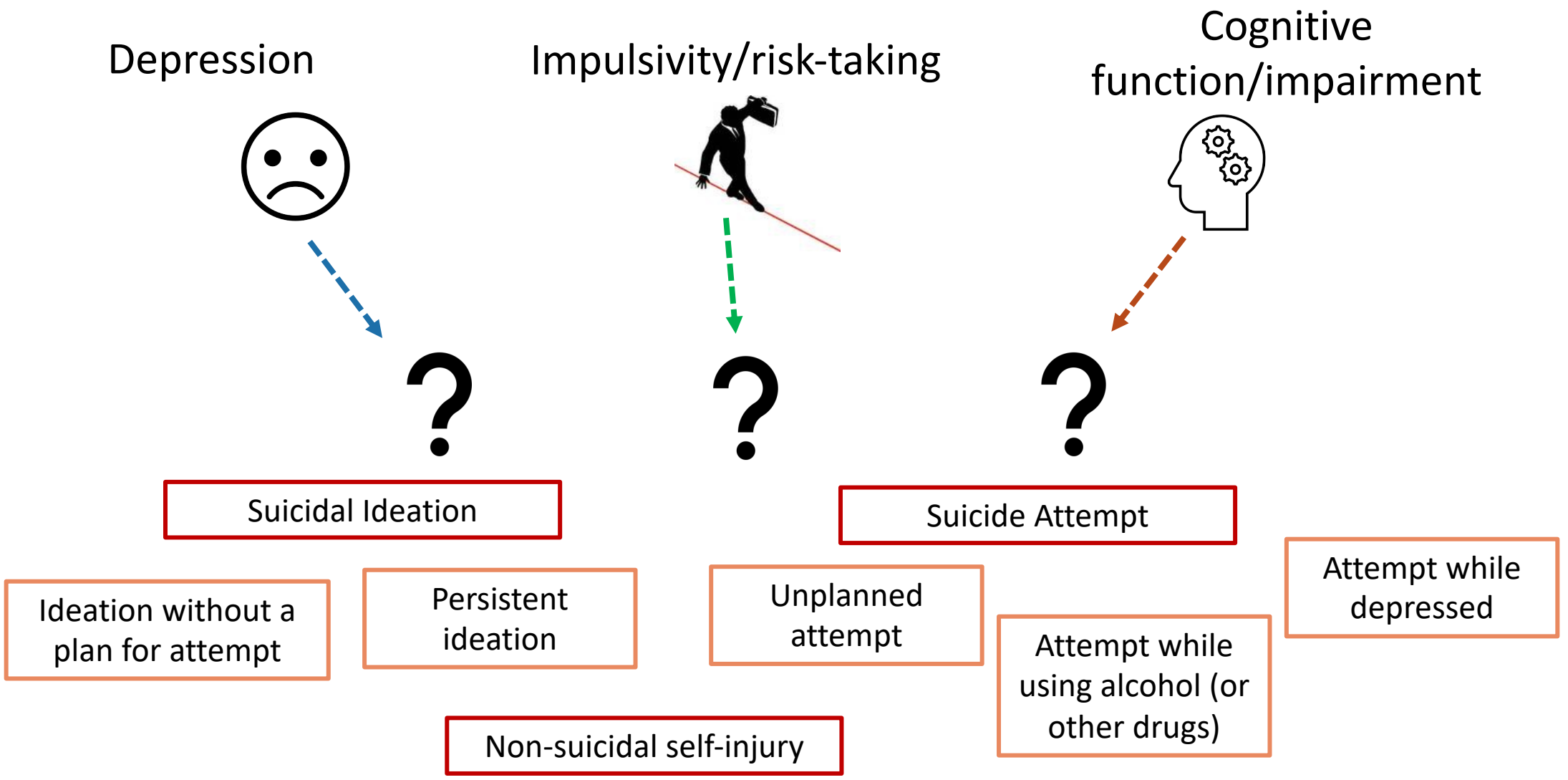


How do depression, risk-taking, and cognitive function relate to suicidal thoughts and behaviors?

Methods: target sample

- We tested whether polygenic scores for depression, risk-taking, and cognitive performance are associated with suicidal thoughts and behaviors and NSSI in a high-risk sample **(N = 10,843)**
- ***Target sample:*** Collaborative Study on the Genetics of Alcoholism (COGA)
  - Case families ascertained for high prevalence of alcohol use disorders
  - Some families have high prevalence of other psychiatric disorders as well

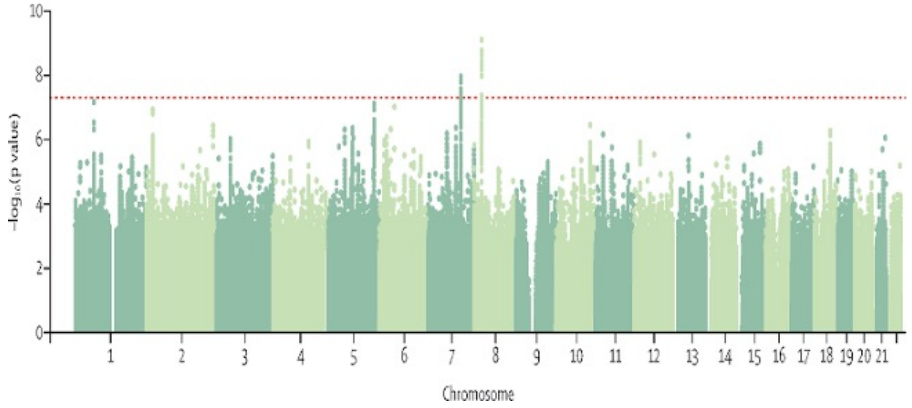
Outcome measure	African-ancestry N reporting 'yes' (% of analytic N)	European-ancestry N reporting 'yes' (% of analytic N)
Suicidal ideation	880 (32.8%)	2,990 (41.5%)
Persistent ideation (7 consecutive days, in those reporting any ideation)	249 (28.3%)	943 (31.6%)
Suicide attempt	300 (11.2%)	776 (10.8%)
Non-suicidal self-injury	149 (6.0%)	548 (8.7%)

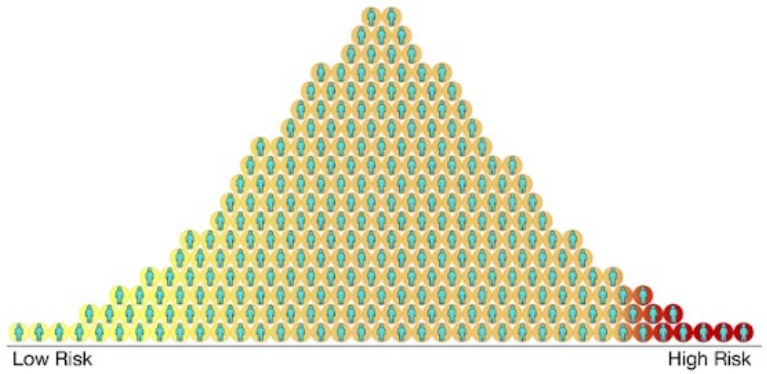
Methods: GWAS for creating polygenic scores

GWAS Phenotype (EA)	GWAS Phenotype (AA)	Sample Size (EA)	Sample Size (AA)
Self-harm (UK Biobank)	NA	N_{cases} = 5,099 $N_{controls}$ = 112,634	NA
Depression meta-analysis (Howard et al., 2019)	Generalized Anxiety Scores (Levey et al., 2020)	N_{cases} = 170,756 $N_{controls}$ = 329,443	N = 24,448
Risk-taking behaviors (Linner et al., 2019)	Self-reported risk taker (Pan UKB)	N = 315,894	N = 6,101
Cognitive performance meta-analysis (Lee et al., 2018)	Fluid intelligence sum score (Pan UKB)	N = 257,828	N = 3,280

Methods: Polygenic score creation

- We used PRS-CS (Ge et al. 2019) and PRS-CSx ('meta' option) to create polygenic scores (**PGS**) in the COGA sample
- Logistic mixed effect regression models controlled for sex, age, array type, AUD case or control family background, and 10 genetic ancestry principal components as fixed effects, and for family ID as a random intercept





Outcome	PGS	Beta	SE	FDR q value	R^2 (%)
Suicidal ideation	Self-harm	0.097	0.027	5.15E−04*	0.24
Persistent ideation	Self-harm	0.128	0.038	0.001*	0.39
Suicide attempt	Self-harm	0.178	0.041	5.29E−05*	0.68
NSSI	Self-harm	0.162	0.051	0.002*	0.50
Suicidal ideation	Depression	0.278	0.028	3.41E−22*	1.96
Persistent ideation	Depression	0.264	0.040	2.18E−10*	1.73
Suicide attempt	Depression	0.339	0.043	4.38E−14*	2.49
NSSI	Depression	0.167	0.054	0.002*	0.58
Suicidal ideation	Risky behaviors	0.124	0.027	2.00E−05*	0.40
Persistent ideation	Risky behaviors	0.125	0.039	0.002*	0.37
Suicide attempt	Risky behaviors	0.174	0.042	1.01E−04*	0.62
NSSI	Risky behaviors	0.132	0.052	0.014*	0.30
Suicidal ideation	Cognitive performance	0.027	0.027	0.360	0.02
Persistent ideation	Cognitive performance	0.026	0.039	0.545	0.01
Suicide attempt	Cognitive performance	−0.159	0.042	3.76E−04*	0.57
NSSI	Cognitive performance	0.006	0.052	0.911	0.00

Not significant when controlling for DSM-IV alcohol dependence and abuse symptom count!

Starred rows indicate significance after multiple testing corrections (FDR < 0.05). COGA, Collaborative Study on the Genetics of Alcoholism; NSSI, nonsuicidal self-injury; PGS, polygenic score.

Summary & limitations

- Genetic liability for depression broadly associated with suicidal thoughts & behaviors
- Genetic predisposition for decreased cognitive performance *only* associated with increased risk of suicide attempts

- No significant PGS associations in the African-ancestry subset of COGA, most likely due to smaller discovery GWAS sample sizes – need larger discovery GWAS in non-European ancestry populations
- PGS not predictive on an individual level

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Sarah Colbert

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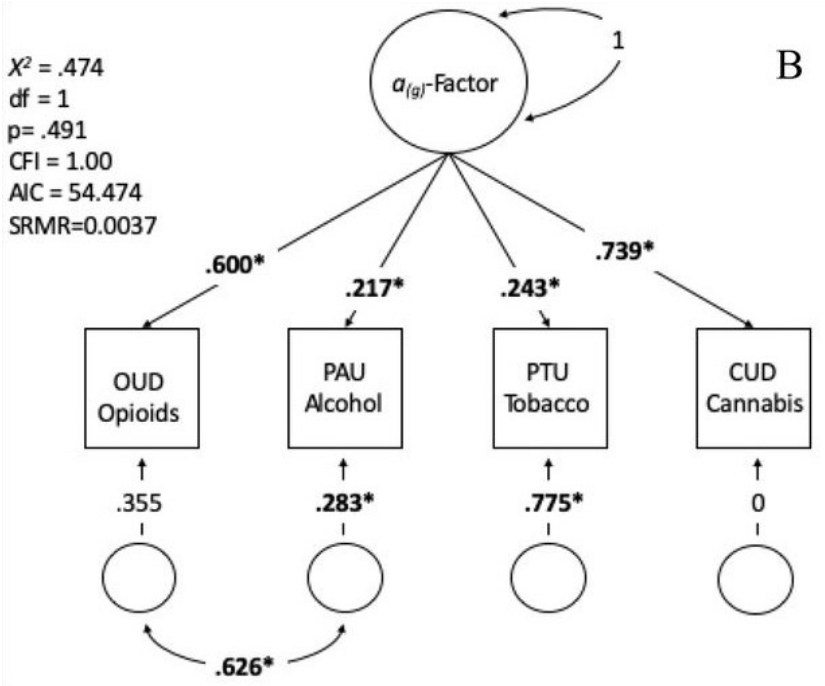
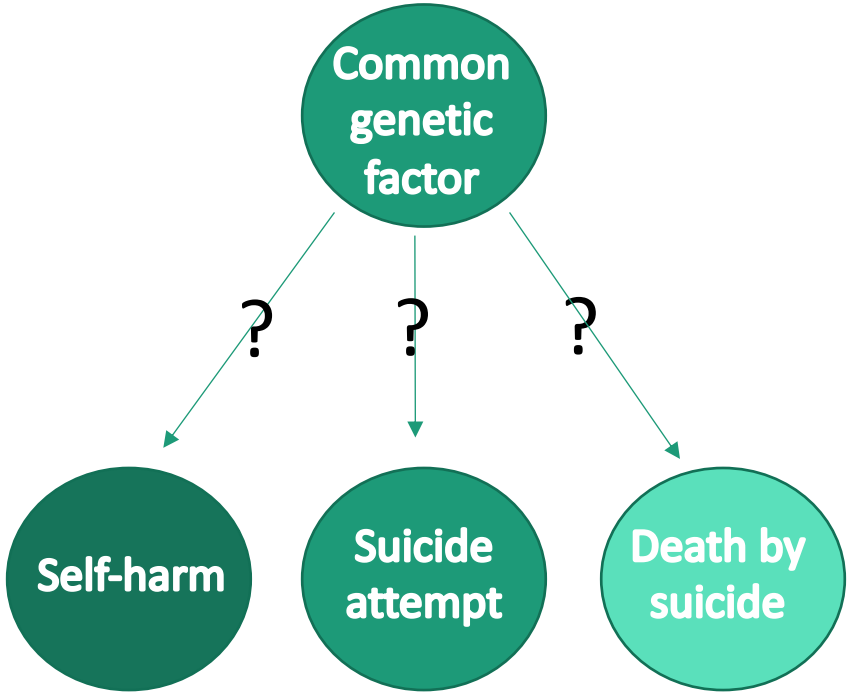
Alexander Hatoum

Background

- It is well established that SUDs load onto common factor
- Genetics of suicide-related behaviors less well-characterized





Hatoum et al. 2021. *Neuropsychopharmacology*
Strawbridge et al. 2019 *EBioMedicine*

Methods

- LD score regression
  - Genetic correlations
- Genomic structural equation modeling (gSEM)
  - Genetic factor structure

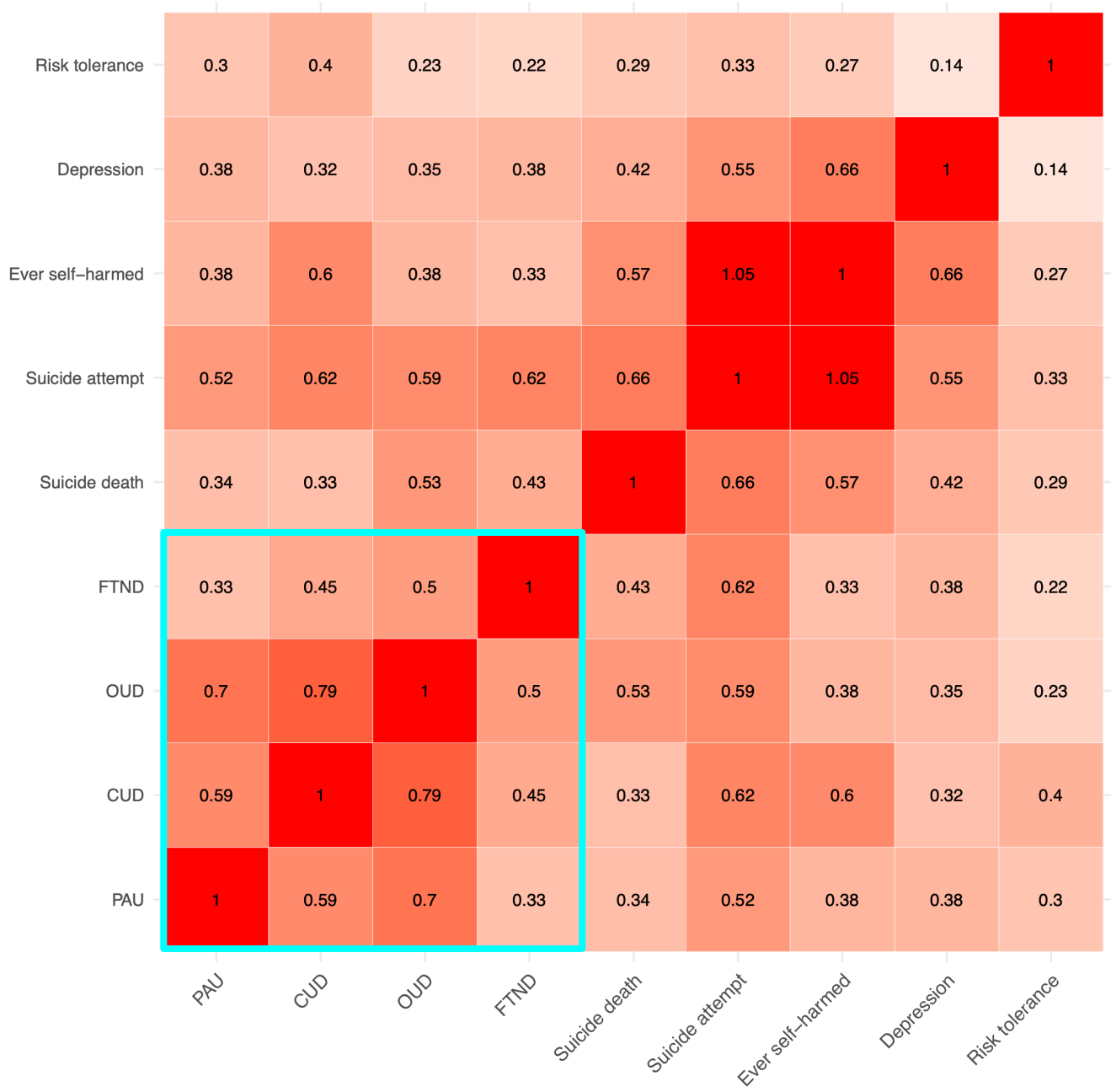
	Phenotype	PMID	Sample Size	SNP-heritability (s.e.)
SUDs	PAU	32451486	N = 435,563	0.07 (0.004)
SUDs	CUD	33096046	N = 358,534; N_{cases} = 14,808	0.12 (0.011)
SUDs	OUD	32492095	N = 82,707; N_{cases} = 10,544	0.11 (0.018)
SUDs	FTND	33144568	N = 46,213	0.09 (0.012)
Suicide phenotypes	Death by suicide	32998551	N = 18,223; N_{cases} = 3,413	0.25 (0.04)
Suicide phenotypes	Suicide attempt	30116032	N = 50,264; N_{cases} = 6,024	0.05 (0.009)
Suicide phenotypes	Ever self-harmed	PMID not available	N = 117,733; N_{cases} = 5,099	0.05 (0.028)
Risk factors	Depression	30718901	N = 500,199; N_{cases} = 170,756	0.09 (0.003)
Risk factors	Risk tolerance	30643258	N = 466,571	0.05 (0.001)

Bulik-Sullivan et al., 2015. *Nature Genetics*
Grotzinger et al., 2019. *Nature Human Behavior*

Genetic correlations

All significant with FDR < 5%

Strong positive correlations among SUDs



Genetic correlations

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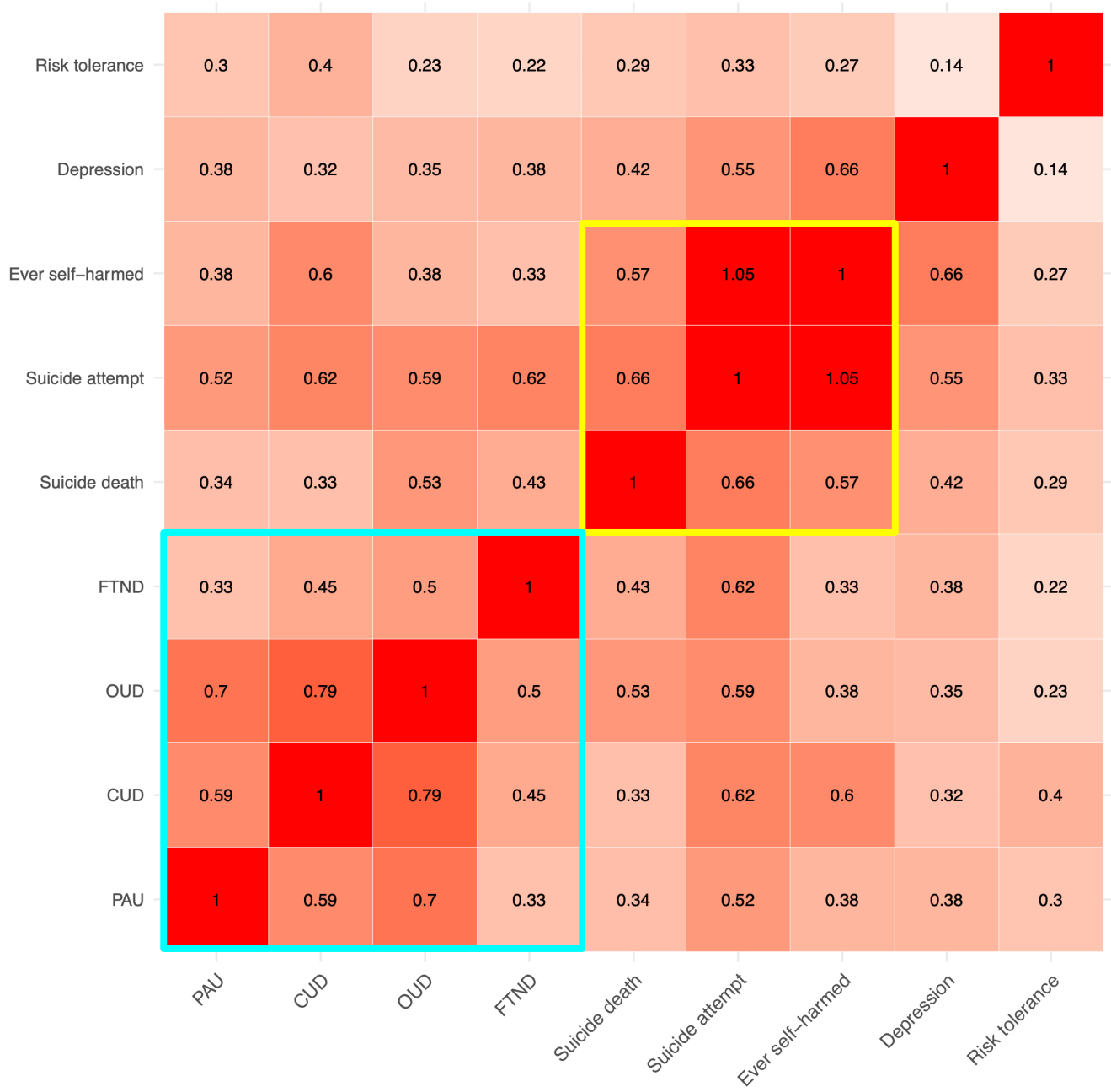
Strong positive correlations among SUDs

Strong positive correlations among suicide-related behaviors



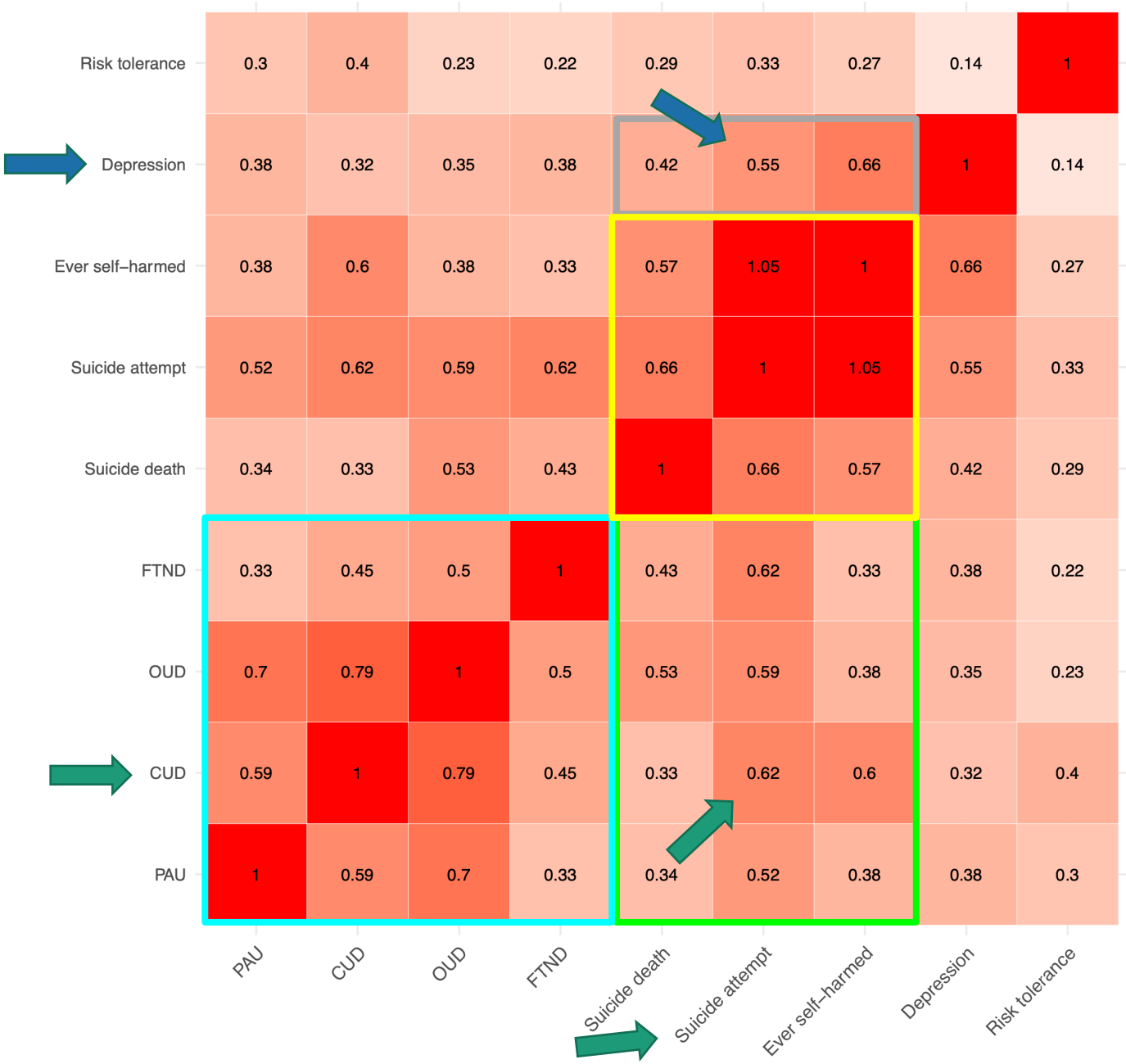
Genetic correlations

All significant with FDR < 5%

Strong positive correlations among SUDs

Strong positive correlations among suicide-related behaviors

Strong positive correlations among SUDs and suicide-related behaviors + comparable to correlations among depression and suicide-related behaviors

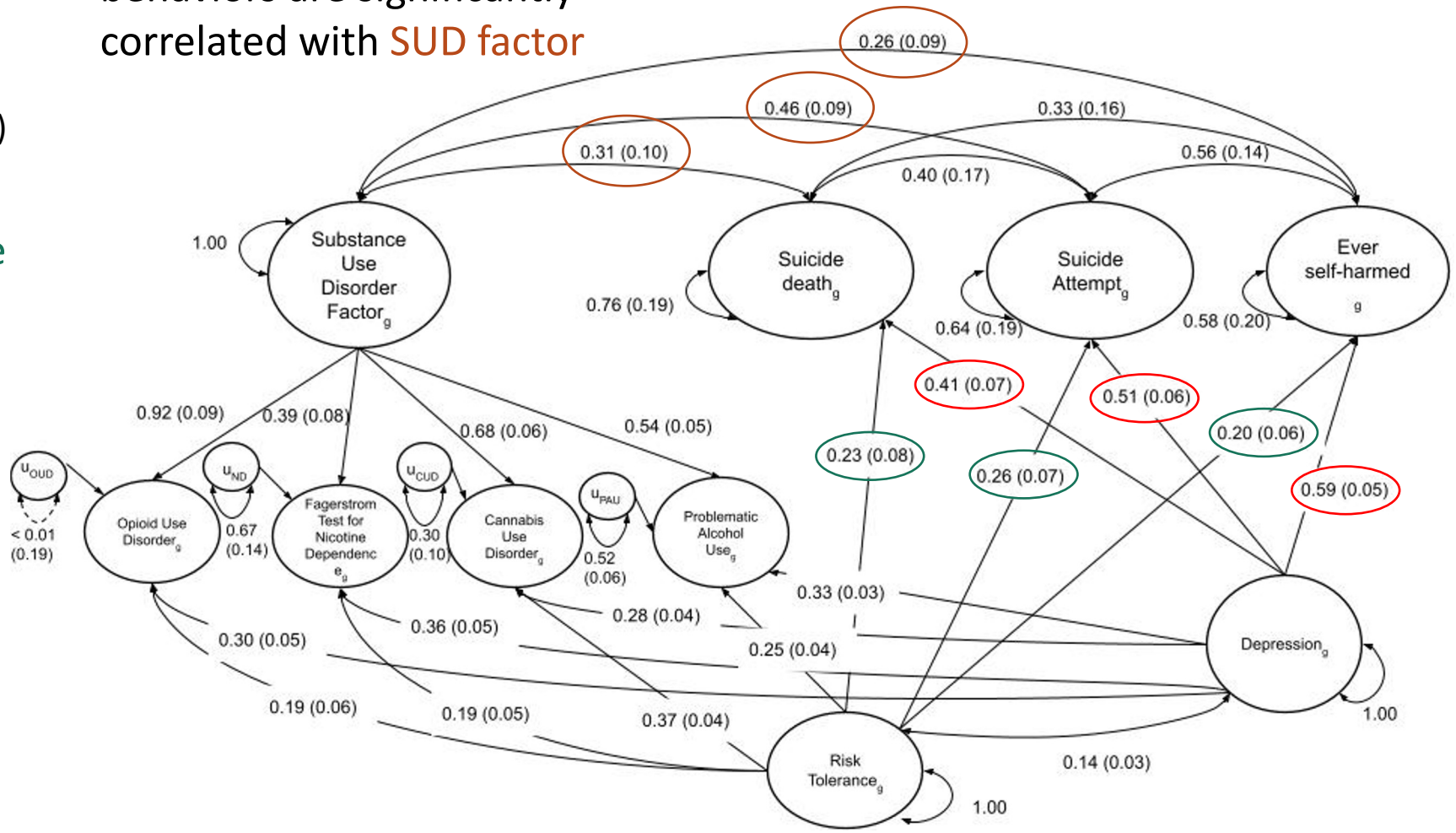


Common SUD and specific suicide-related behaviors model with covariates

Depression was most strongly associated with ever self-harmed and least strongly associated with suicide death. ($\chi^2_{diff}(2) = 13.28$, $p = 0.001$)

Associations between risk tolerance and suicide-related behaviors are somewhat less variable.
($\chi^2_{diff}(2) = 5.17$, $p = .08$)

Even accounting for depression and risk tolerance, suicide-related behaviors are significantly correlated with SUD factor



Model fit statistics:
$X^2 = 11.16$, df = 11, p_$X^2 = 0.43$
AIC = 79.16
CFI = 0.9999
SRMR = 0.0464

Summary & limitations

- We found significant correlations between SUDs and suicide-related behaviors, accounting for depression and risk tolerance
- Interestingly, correlations b/w SUDs and suicide phenotypes rival correlations between depression and suicide
- Limited data on death by suicide and non-suicidal self-injury
- Genetic correlations, but no evidence of causality; larger studies (or alternative designs) needed

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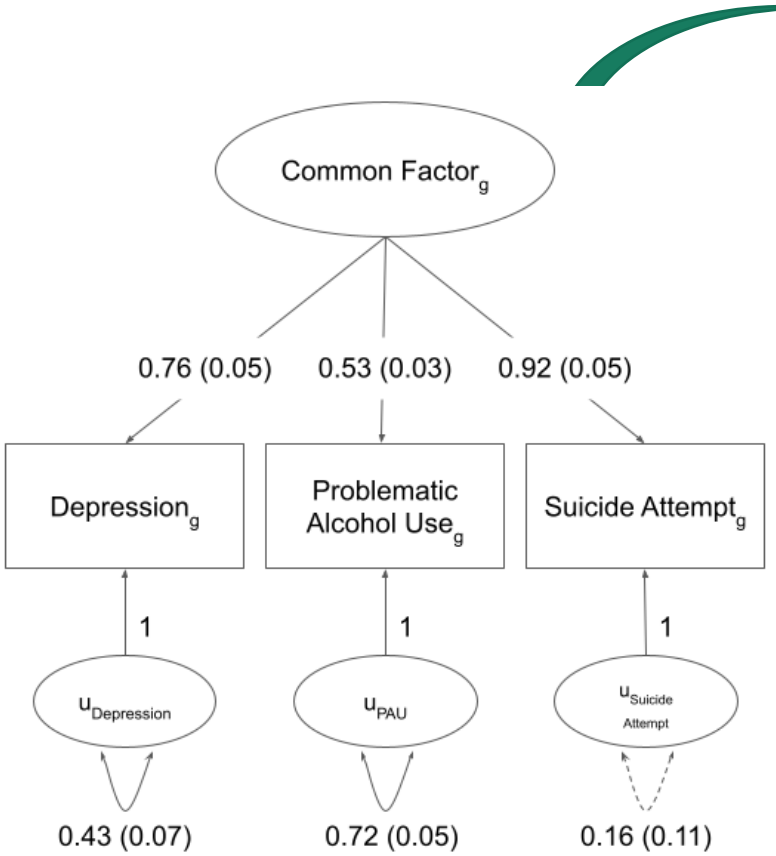
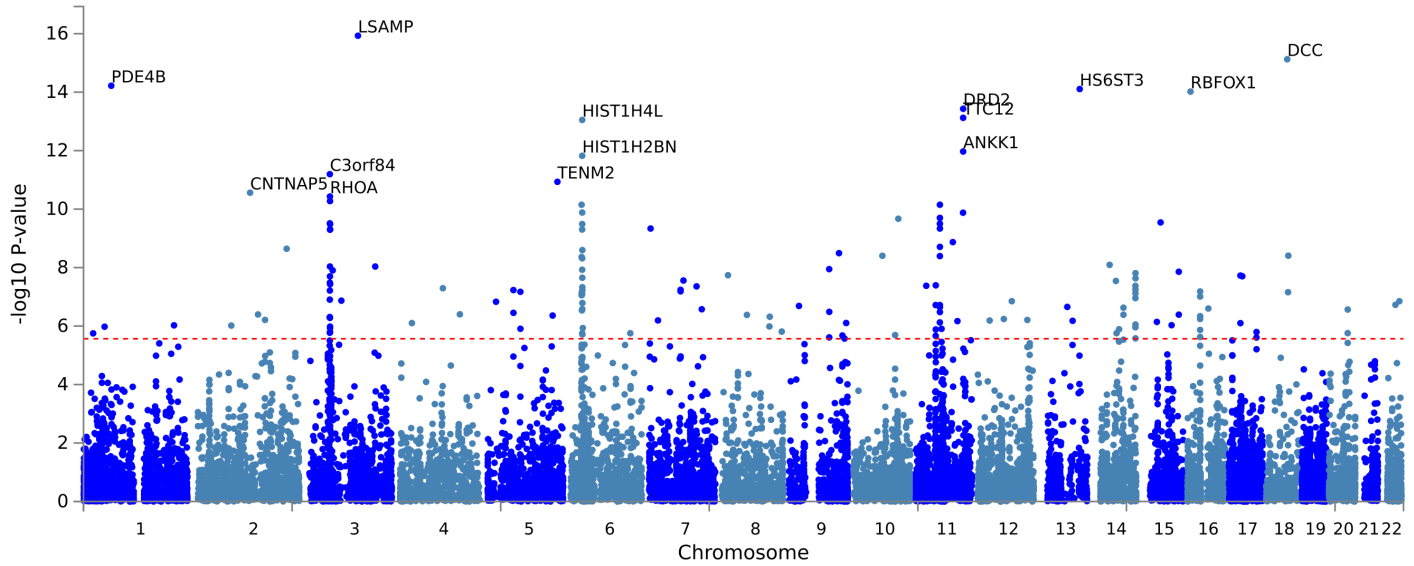
Sarah Colbert

Zooming in on alcohol use, depression, and suicide attempt

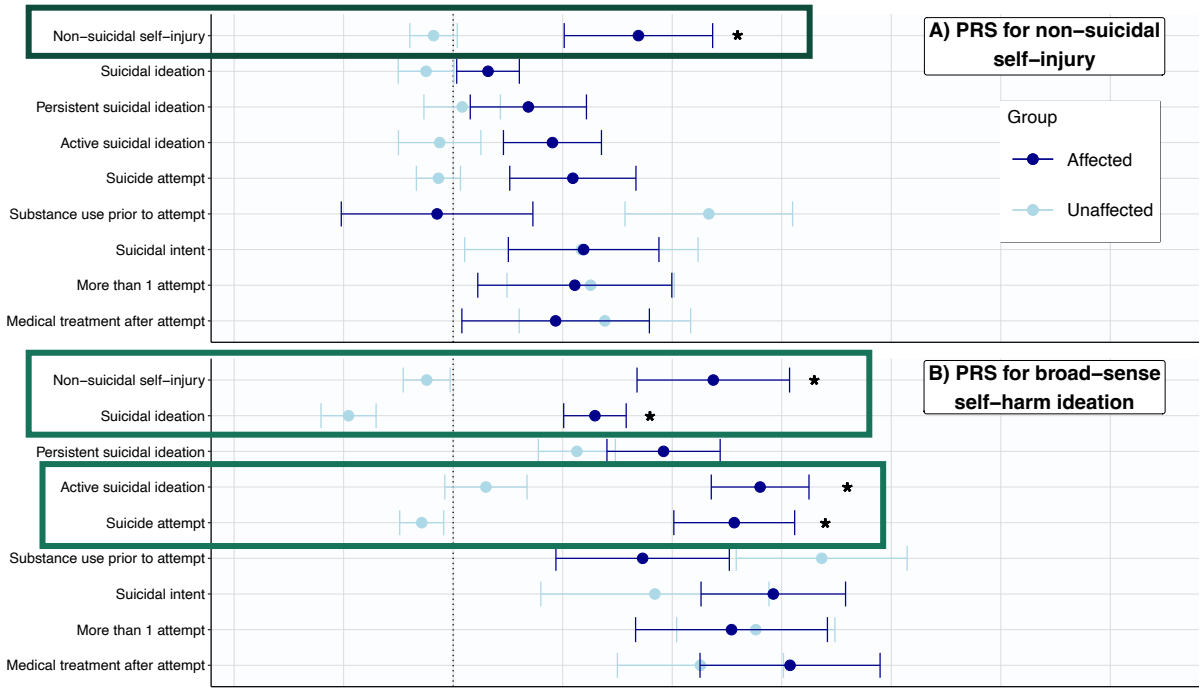


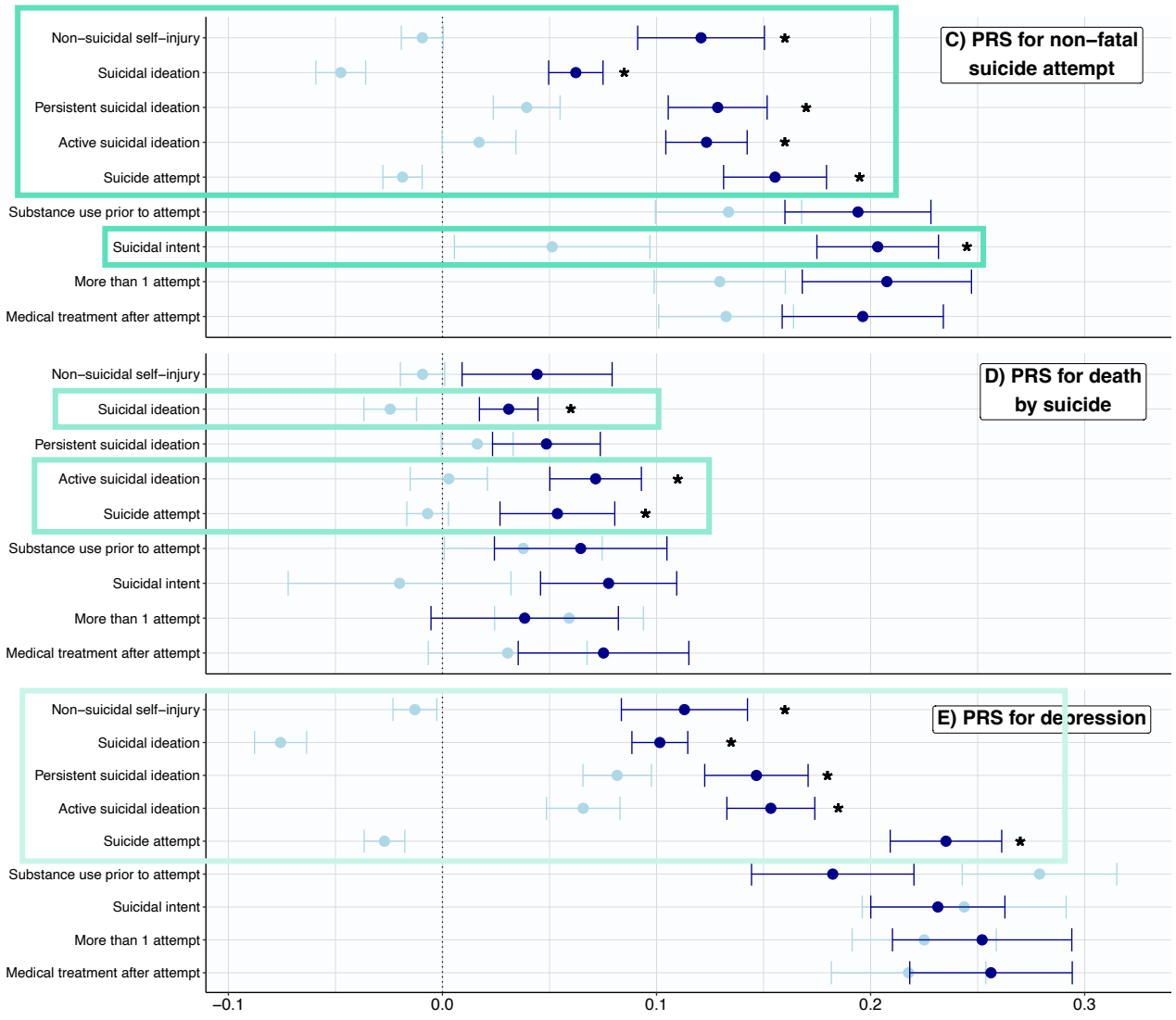
top 14 genes



in prep; Sarah Colbert will be presenting at RSA annual meeting in June 2022

Multi-PRS models in COGA





In follow-up models,

- self-harm ideation, depression, and suicide attempt PRS remained associated w/ **suicidal ideation** in multi-PRS model
- self-harm ideation, depression, suicide attempt, and suicide death PRS remained associated w/ **suicide attempt**

manuscript in prep

Summary

- Suicidal thoughts and behaviors are genetically complex
- Embracing that complexity will lead to better research and better outcomes
- By incorporating this complexity into undergraduate education, we aim to reduce stigma

Thanks

- My AFSP mentor, Dr. Arpana Agrawal
- Collaborators: Sarah Colbert, Alexander Hatoum, Anna Docherty, Hilary Coon, Elliot Nelson, COGA collaborators, PGC-SUD working group
- All the generous participants in these studies
- Past and current funding support from AFSP, BBRF, NIAAA, NIDA, and NIMH

PGC Psychiatric Genomics Consortium

American Foundation for Suicide Prevention

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NIH National Institute on Alcohol Abuse and Alcoholism

NIH National Institute on Drug Abuse

Washington University School of Medicine in St. Louis