Pleiotropy between independent mental health profiles in the UKB

Daniel Roelfs

Background

- Known genetic correlation and loci overlap between psychiatric disorders

- Large clinical overlap between disorders

- What about the overlap in symptom profiles?

RESEARCH ARTICLE SUMMARY

PSYCHIATRIC GENOMICS

Analysis of shared heritability in common disorders of the brain

The Brainstorm Consortium†

INTRODUCTION: Brain disorders may exhibit shared symptoms and substantial epidemiological comorbidity, inciting debate about their etiologic overlap. However, detailed study of phenotypes with different ages of onset, severity, and presentation poses a considerable challenge. Recently developed heritability methods

psychiatric disorders. Understanding the genetic underpinnings and categorical distinctions for brain disorders and related phenotypes may inform the search for their biological mechanisms.

RESULTS: Common variant risk for psychiatric

processes that occur later in life. Extensive simulations were also performed to inform how statistical power, diagnostic misclassification, and phenotypic heterogeneity influence genetic correlations.

CONCLUSION: The high degree of genetic correlation among many of the psychiatric disorders adds further evidence that their current clinical boundaries do not reflect distinct underlying pathogenic processes, at least on the genetic level. This suggests a deeply interconnected nature for psychiatric disorders, in contrast to neurological disorders, and underscores the need to refine psychiatric diagnostics. Genetically informed analyses may provide important "scaffolding" to support such restructuring of psychiatric nosology, which likely

ON OUR WEBSITE

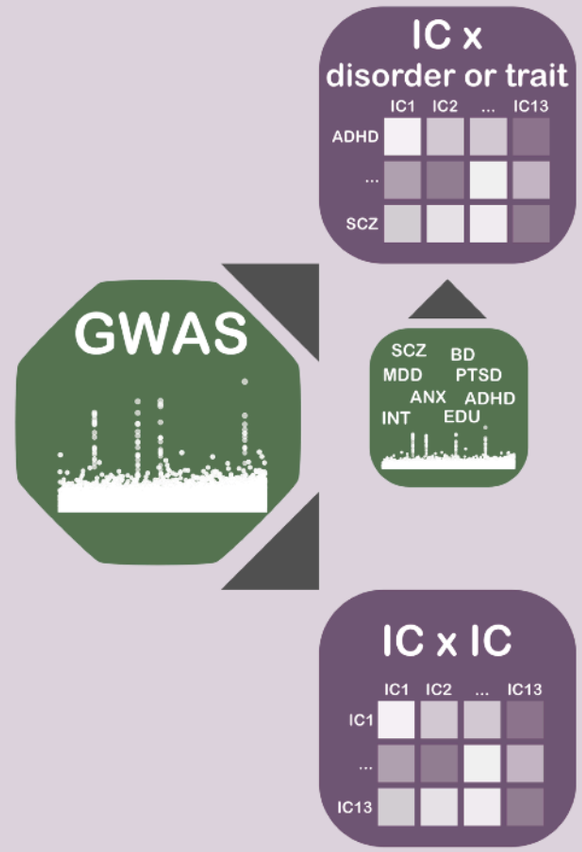
Read the full article at http://dx.doi.org/10.1126/science.aap8757

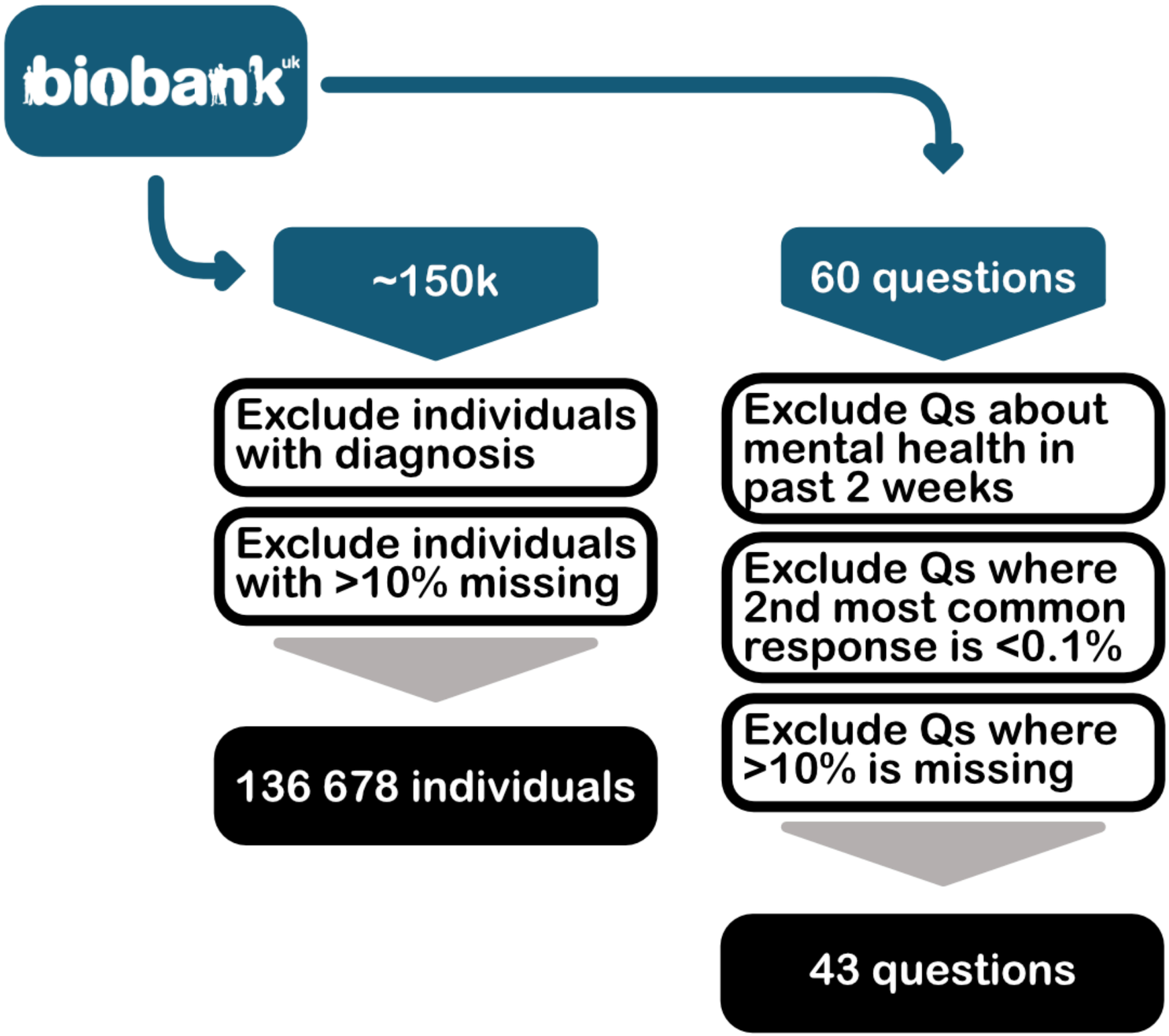
Our approach

Mental health questionnaire from the UK Biobank

Data-driven composition into 13 components

Genetic correlation analysis




biobank uk
~150k
Exclude individuals with diagnosis
Exclude individuals with >10% missing
136 678 individuals
60 questions
Exclude Qs about mental health in past 2 weeks
Exclude Qs where 2nd most common response is <0.1%
Exclude Qs where >10% is missing
43 questions

43 questions
136 678 individuals

Impute missing data (knn = 3)

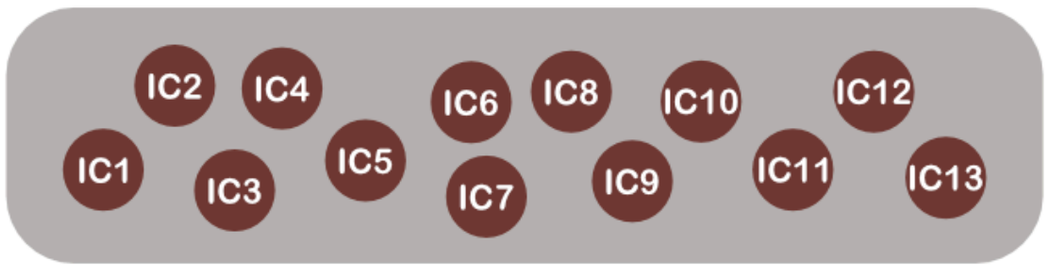
Z-score normalize all scores

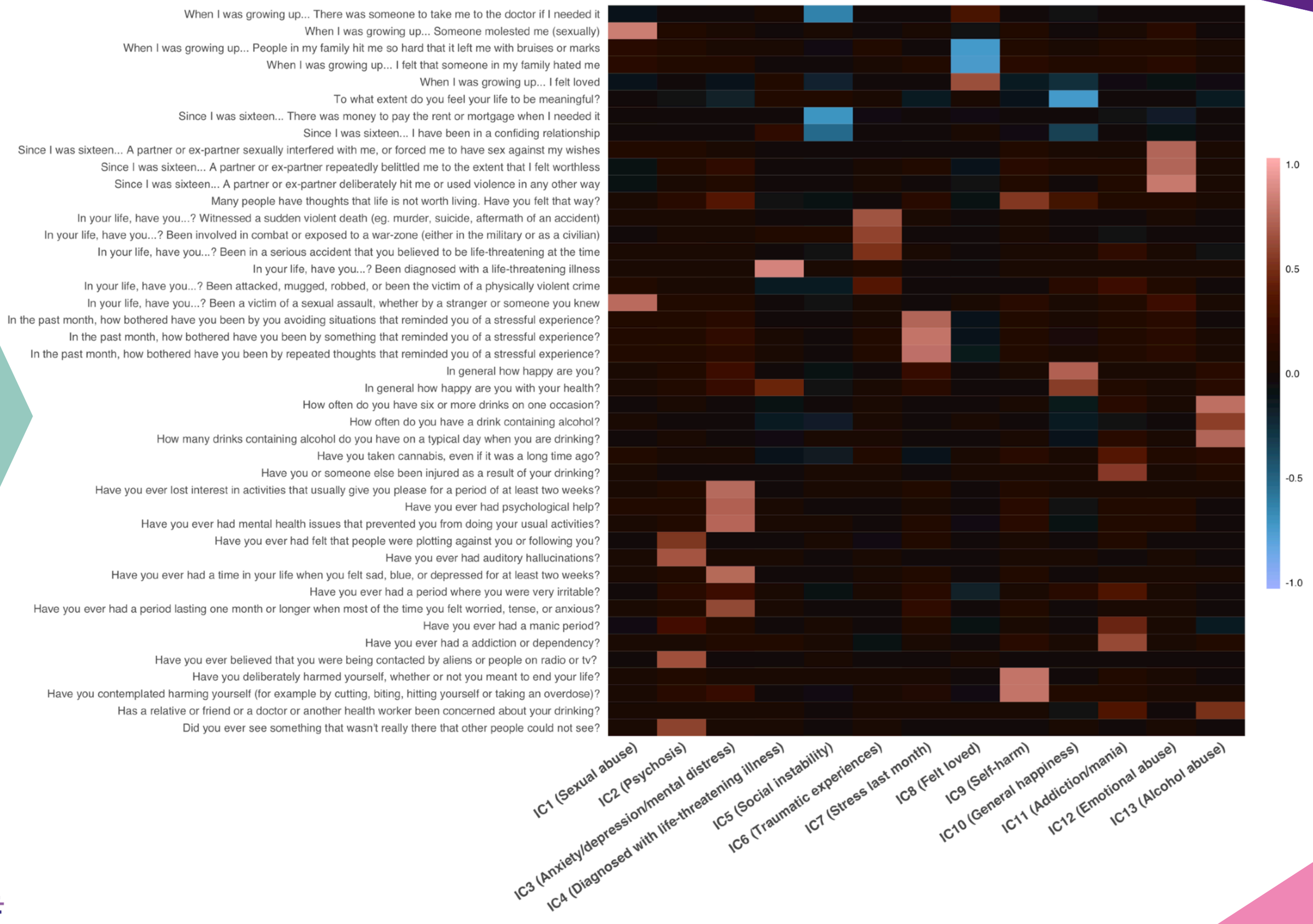
Regress out variables

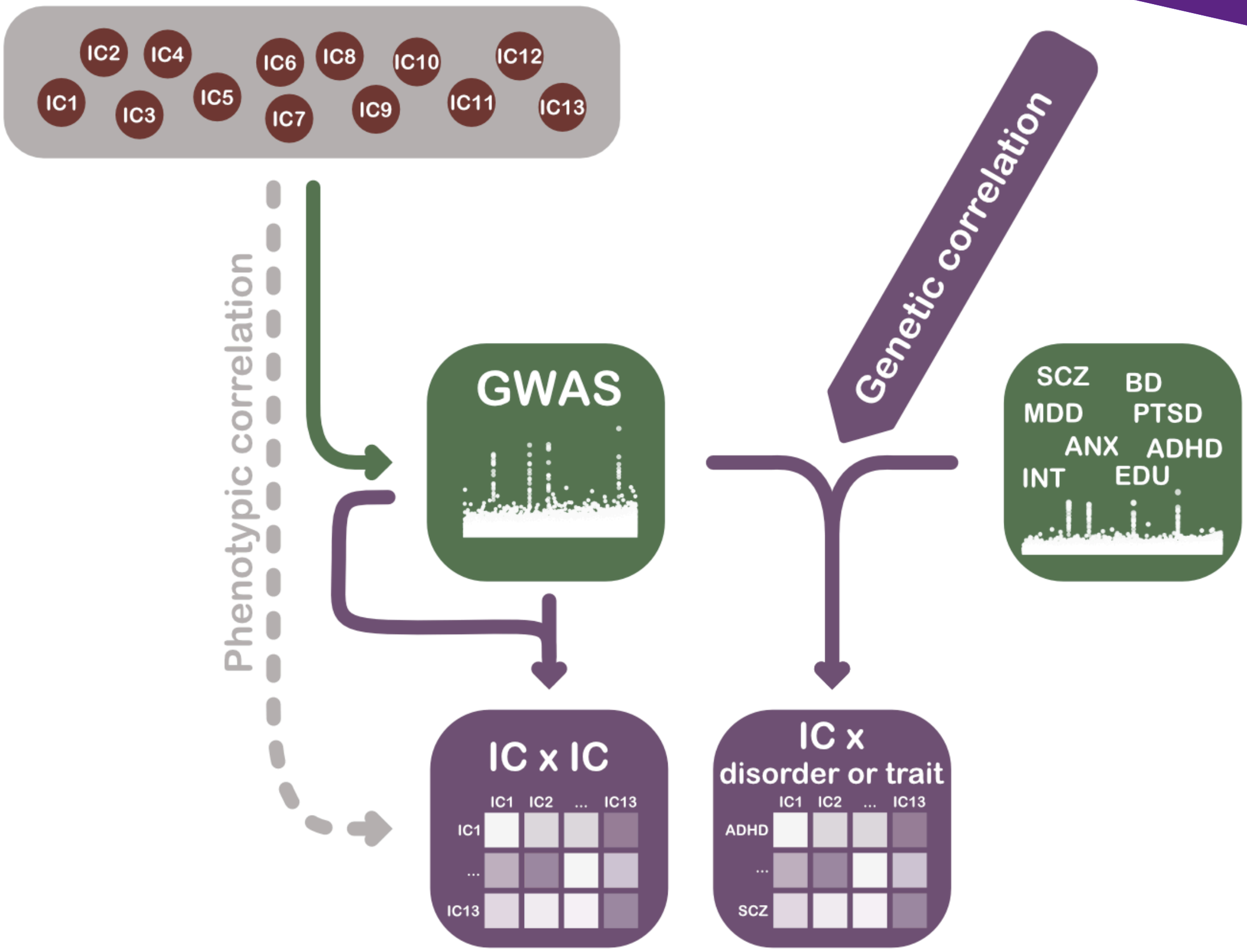
- Age
- Age²
- Sex
- 10 genetic PCs

ICA

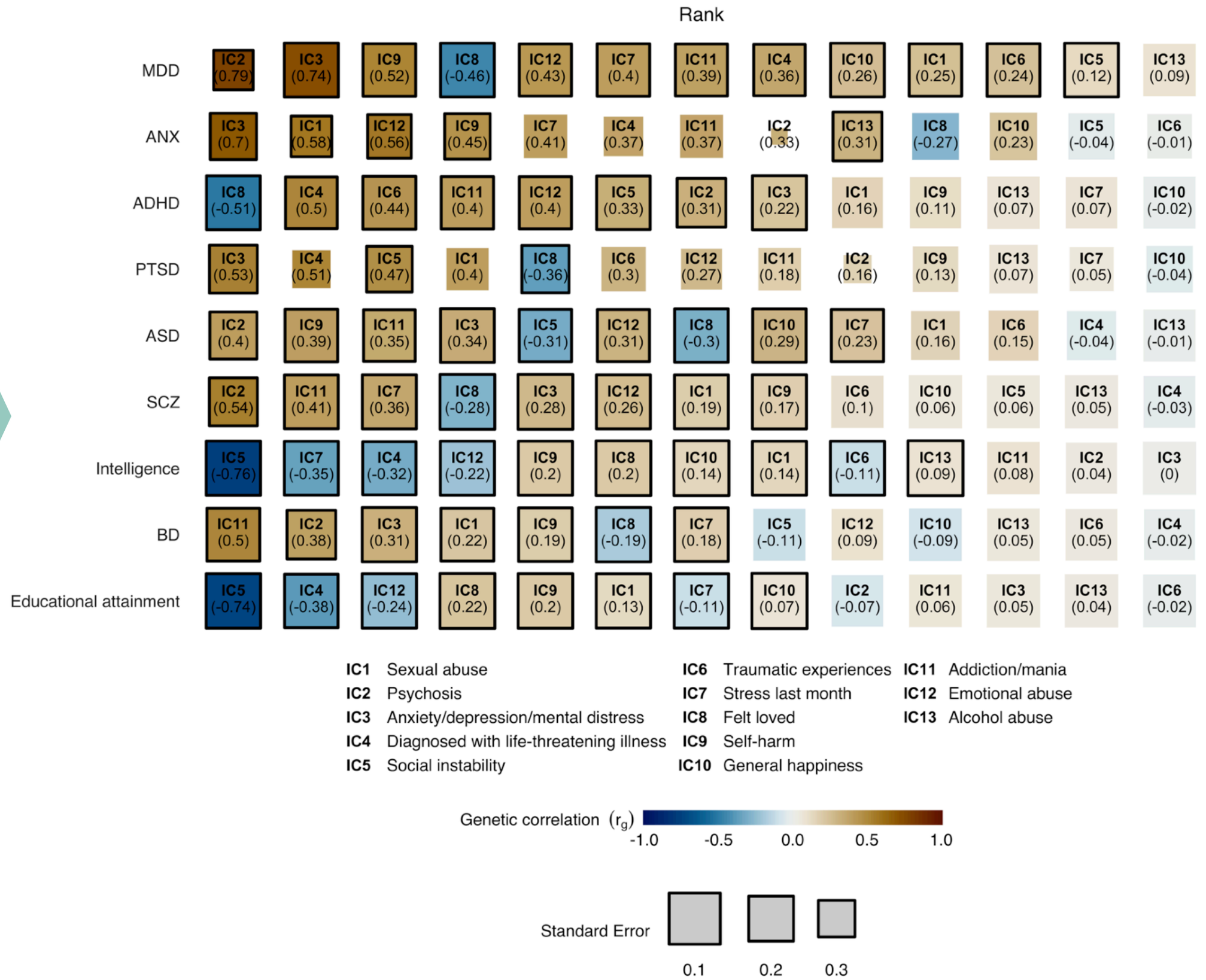
"Get 13 components"




When I was growing up... There was someone to take me to the doctor if I needed it
When I was growing up... Someone molested me (sexually)
When I was growing up... People in my family hit me so hard that it left me with bruises or marks
When I was growing up... I felt that someone in my family hated me
When I was growing up... I felt loved
To what extent do you feel your life to be meaningful?
Since I was sixteen... There was money to pay the rent or mortgage when I needed it
Since I was sixteen... I have been in a confiding relationship
Since I was sixteen... A partner or ex-partner sexually interfered with me, or forced me to have sex against my wishes
Since I was sixteen... A partner or ex-partner repeatedly belittled me to the extent that I felt worthless
Since I was sixteen... A partner or ex-partner deliberately hit me or used violence in any other way
Many people have thoughts that life is not worth living. Have you felt that way?
In your life, have you...? Witnessed a sudden violent death (eg. murder, suicide, aftermath of an accident)
In your life, have you...? Been involved in combat or exposed to a war-zone (either in the military or as a civilian)
In your life, have you...? Been in a serious accident that you believed to be life-threatening at the time
In your life, have you...? Been diagnosed with a life-threatening illness
In your life, have you...? Been attacked, mugged, robbed, or been the victim of a physically violent crime
In your life, have you...? Been a victim of a sexual assault, whether by a stranger or someone you knew
In the past month, how bothered have you been by you avoiding situations that reminded you of a stressful experience?
In the past month, how bothered have you been by something that reminded you of a stressful experience?
In the past month, how bothered have you been by repeated thoughts that reminded you of a stressful experience?
In general how happy are you?
In general how happy are you with your health?
How often do you have six or more drinks on one occasion?
How often do you have a drink containing alcohol?
How many drinks containing alcohol do you have on a typical day when you are drinking?
Have you taken cannabis, even if it was a long time ago?
Have you or someone else been injured as a result of your drinking?
Have you ever lost interest in activities that usually give you please for a period of at least two weeks?
Have you ever had psychological help?
Have you ever had mental health issues that prevented you from doing your usual activities?
Have you ever had felt that people were plotting against you or following you?
Have you ever had auditory hallucinations?
Have you ever had a time in your life when you felt sad, blue, or depressed for at least two weeks?
Have you ever had a period where you were very irritable?
Have you ever had a period lasting one month or longer when most of the time you felt worried, tense, or anxious?
Have you ever had a manic period?
Have you ever had a addiction or dependency?
Have you ever believed that you were being contacted by aliens or people on radio or tv?
Have you deliberately harmed yourself, whether or not you meant to end your life?
Have you contemplated harming yourself (for example by cutting, biting, hitting yourself or taking an overdose)?
Has a relative or friend or a doctor or another health worker been concerned about your drinking?
Did you ever see something that wasn't really there that other people could not see?
1.0
0.5
0.0
-0.5
-1.0
IC1 (Sexual abuse)
IC2 (Psychosis)
IC3 (Anxiety/depression/mental distress)
IC4 (Diagnosed with life-threatening illness)
IC5 (Social instability)
IC6 (Traumatic experiences)
IC7 (Stress last month)
IC8 (Felt loved)
IC9 (Self-harm)
IC10 (General happiness)
IC11 (Addiction/mania)
IC12 (Emotional abuse)
IC13 (Alcohol abuse)


IC1
IC2
IC3
IC4
IC5
IC6
IC7
IC8
IC9
IC10
IC11
IC12
IC13
Phenotypic correlation
GWAS
Genetic correlation
SCZ
BD
MDD
PTSD
ANX
ADHD
INT
EDU
IC x IC
IC1 IC2 ... IC13
IC1
...
IC13
IC x
disorder or trait
IC1 IC2 ... IC13
ADHD
...
SCZ

Results


Rank
MDD
IC2 (0.79)
IC3 (0.74)
IC9 (0.52)
IC8 (-0.46)
IC12 (0.43)
IC7 (0.4)
IC11 (0.39)
IC4 (0.36)
IC10 (0.26)
IC1 (0.25)
IC6 (0.24)
IC5 (0.12)
IC13 (0.09)
ANX
IC3 (0.7)
IC1 (0.58)
IC12 (0.56)
IC9 (0.45)
IC7 (0.41)
IC4 (0.37)
IC11 (0.37)
IC2 (0.33)
IC13 (0.31)
IC8 (-0.27)
IC10 (0.23)
IC5 (-0.04)
IC6 (-0.01)
ADHD
IC8 (-0.51)
IC4 (0.5)
IC6 (0.44)
IC11 (0.4)
IC12 (0.4)
IC5 (0.33)
IC2 (0.31)
IC3 (0.22)
IC1 (0.16)
IC9 (0.11)
IC13 (0.07)
IC7 (0.07)
IC10 (-0.02)
PTSD
IC3 (0.53)
IC4 (0.51)
IC5 (0.47)
IC1 (0.4)
IC8 (-0.36)
IC6 (0.3)
IC12 (0.27)
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ASD
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IC13 (-0.01)
SCZ
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IC1 (0.19)
IC9 (0.17)
IC6 (0.1)
IC10 (0.06)
IC5 (0.06)
IC13 (0.05)
IC4 (-0.03)
Intelligence
IC5 (-0.76)
IC7 (-0.35)
IC4 (-0.32)
IC12 (-0.22)
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BD
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IC1 Sexual abuse
IC2 Psychosis
IC3 Anxiety/depression/mental distress
IC4 Diagnosed with life-threatening illness
IC5 Social instability
IC6 Traumatic experiences
IC7 Stress last month
IC8 Felt loved
IC9 Self-harm
IC10 General happiness
IC11 Addiction/mania
IC12 Emotional abuse
IC13 Alcohol abuse
Genetic correlation (rg)
-1.0
-0.5
0.0
0.5
1.0
Standard Error
0.1
0.2
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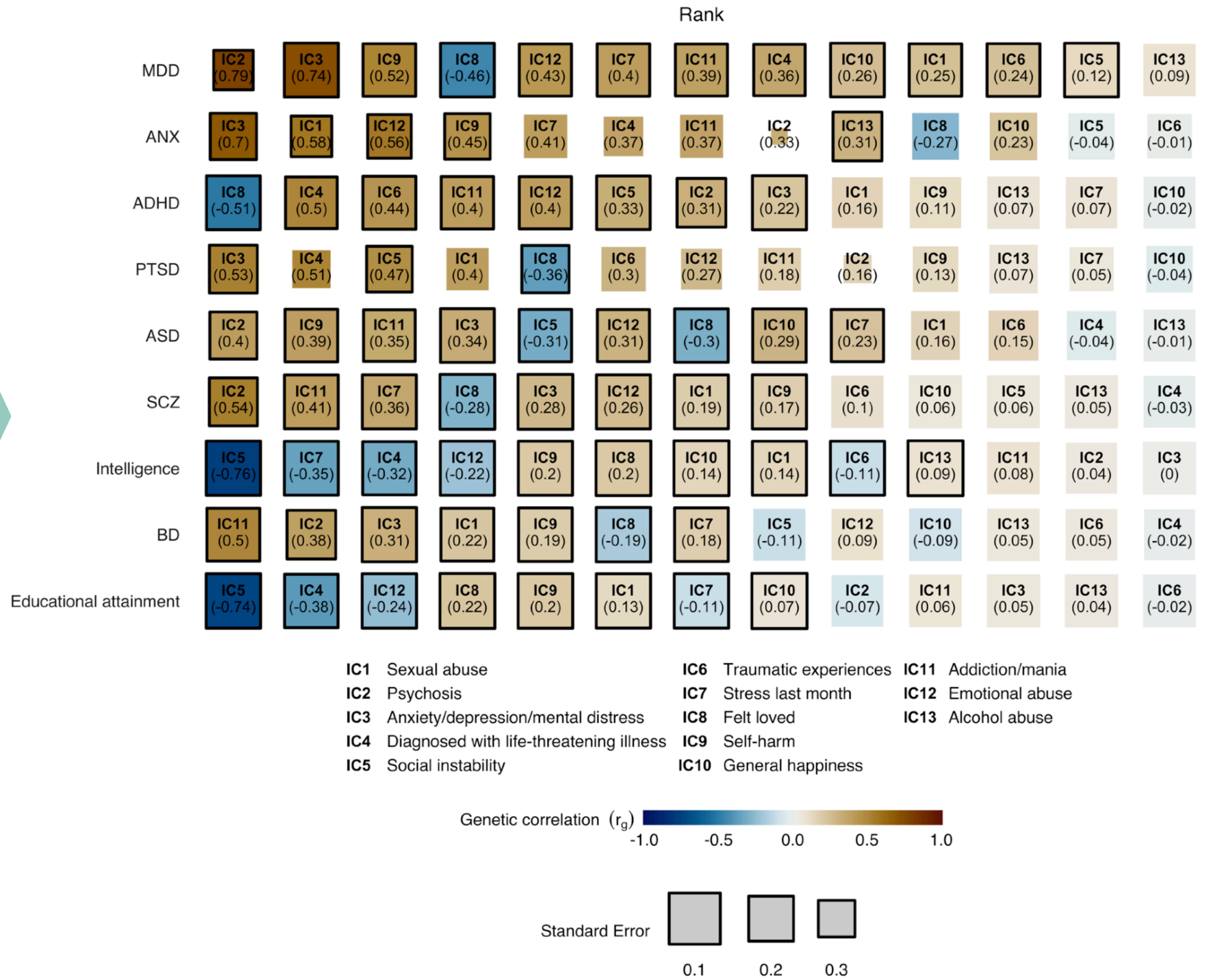
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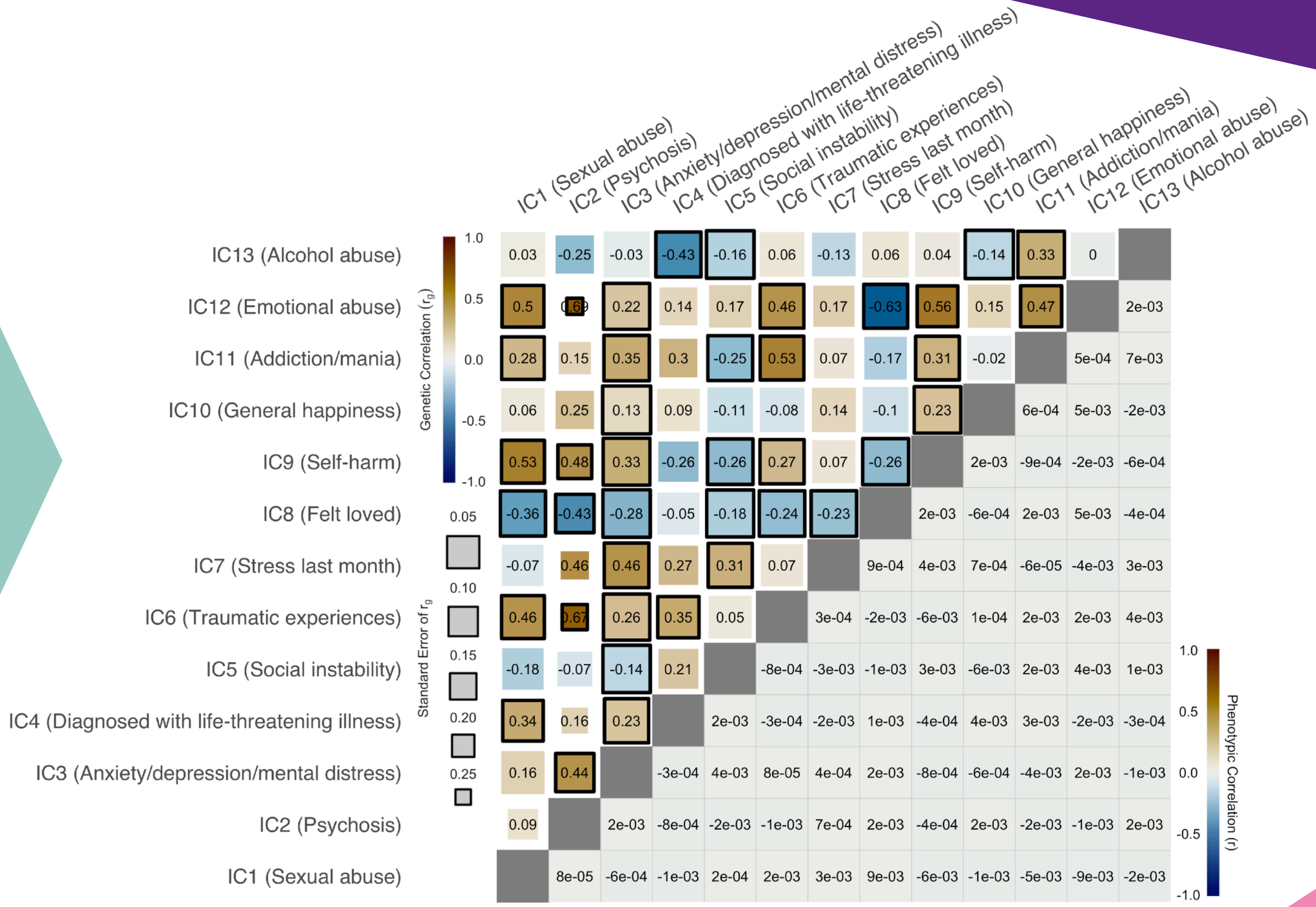
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IC10 (General happiness)
IC11 (Addiction/mania)
IC12 (Emotional abuse)
IC13 (Alcohol abuse)
Genetic Correlation (r_g)
1.0
0.5
0.0
-0.5
-1.0
Standard Error of r_g
0.05
0.10
0.15
0.20
0.25
Phenotypic Correlation (r)
1.0
0.5
0.0
-0.5
-1.0

Conclusions

- Variation in mental health in healthy individuals genetically correlate to psychiatric disorders and cognitive traits
- Pleiotropy between disorders likely not due to overlapping symptoms
- Classical case-control setup in certain situations not the most adequate approach
- Big data 👍

Thanks!

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Ole Andreassen
Lars Westlye

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