Calculation of Polygenic Scores and its relation to Dyslexia and the clinical practice

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Heritability of traits

- Heritability is estimated in twin studies with the following formula:

$$h^2 = 2(r_{mz} - r_{dz})$$

- This kind of studies have to respect four main assumptions:
  - MZ and DZ twin pairs share their environments to the same extent
  - Gene-environment correlations and interactions are minimal for the trait.
  - Twins are no different from the general population in terms of the trait.
  - Mating in the population occur at random (no assortment).

In the case of reading ability, h^2 estimates go up to 70%

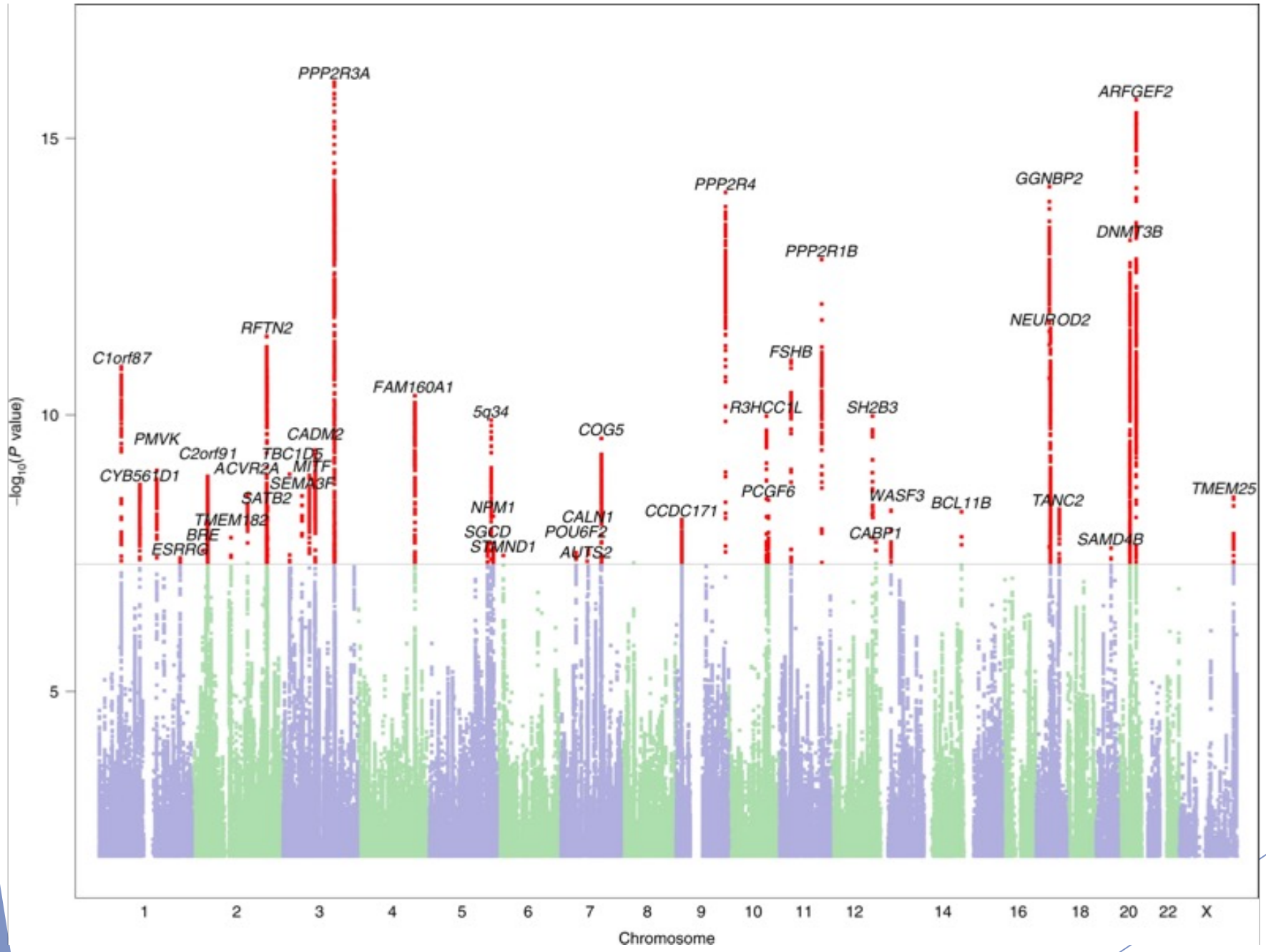
Polygenic Scores

$$PRS_i = \sum_{j=1}^{M} X_{ij}\,\beta_j$$

- When many genes are involved, but each contributes only a small amount, polygenic risk scores are more suitable. They allow the inclusion of a larger number of variations, each with a small individual contribution, thereby incorporating more noisy estimates.
- Polygenic risk scores (PRS) are calculated by summing the individual genetic variants (SNPs) associated with a trait reaching different p-value thresholds and are weighted based on their effect size.
- Effect size and p-values are retrieved from GWAS summary statistics and have to be validated on independent samples.
- Often, these scores are converted into z-scores. Positive z-scores indicate a high chance of developing a particular trait, where 0 represents the average score in the population, and negative scores indicate a lower individual probability of developing it.

Polygenic Scores and Dyslexia:

- Polygenic scores (PGS) are currently used in clinical settings for diseases such as breast cancer, cardiovascular disorders, diabetes, and more (Lambert et al., 2019).
- For dyslexia, several GWAS studies have been conducted to obtain polygenic scores (PGS). The most powerful PGS so far has been derived from Doust et al. (2022), which can explain up to 6% of the variance in reading abilities.
- The sample, representing a 20-fold increase in sample size compared to previous studies, includes 1,087,070 subjects in the control group and 51,800 subjects with a diagnosis of dyslexia.
- 36% of the significant SNPs from Doust et al. (2022) were also found in GWAS (Genome-Wide Association Studies) investigating general cognitive abilities.
- PGS was then validated on four independent cohorts.


PPP2R3A
ARFGEF2
PPP2R4
GGNBP2
DNMT3B
PPP2R1B
NEUROD2
RFTN2
FSHB
C1orf87
FAM160A1
5q34
R3HCC1L
SH2B3
COG5
PMVK
CADM2
C2orf91
TBC1D5
ACVR2A
MITF
SEMA3F
CYB561D1
PCGF6
WASF3
BCL11B
TANC2
TMEM25
SATB2
NPM1
CALN1
CCDC171
TMEM182
BRE
SGCD
POU6F2
CABP1
SAMD4B
ESRRG
STMND1
AVTS2
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−log10(P value)
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2
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18
20
22
X
Chromosome

Article with Edimburgh University

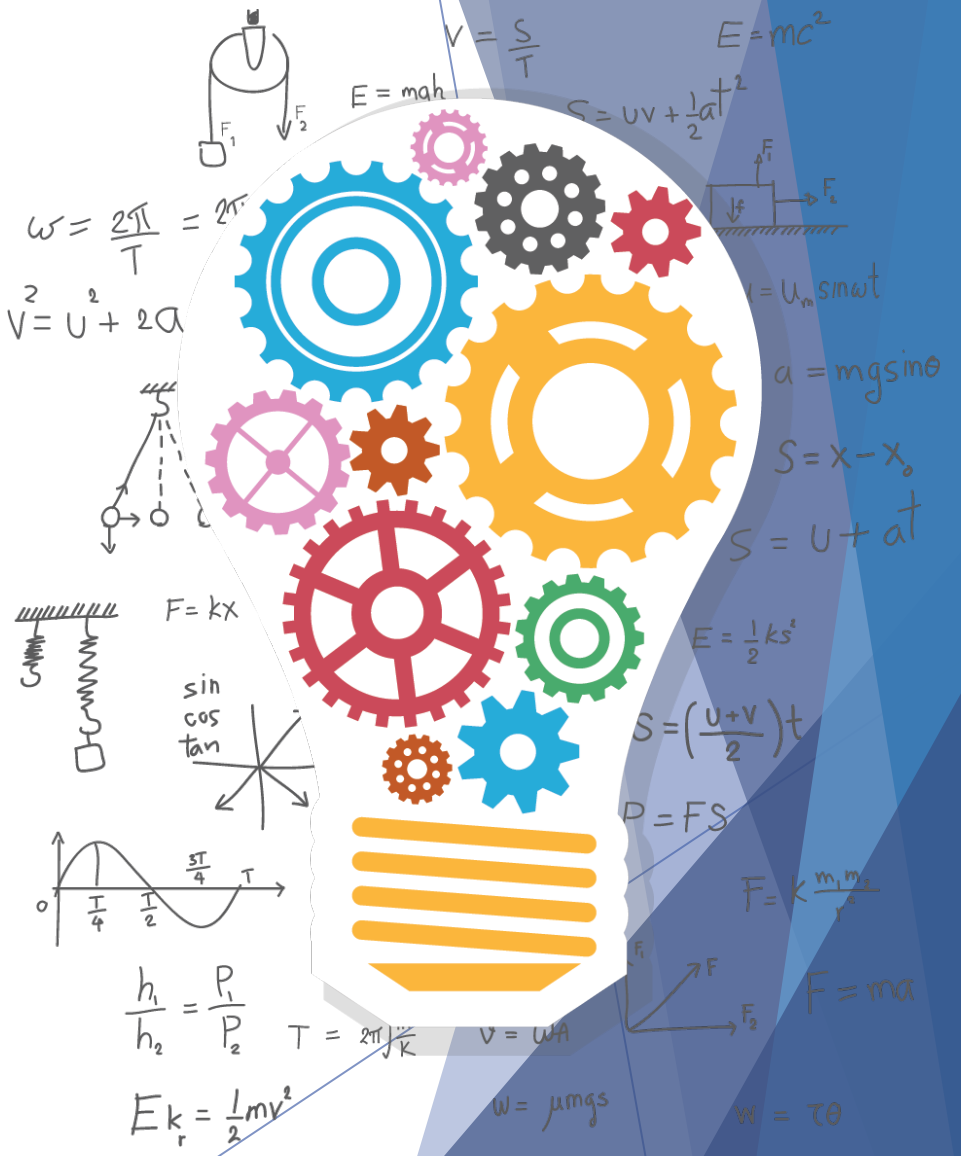
- In the research we conducted on the Australian sample (min n = 734, max n = 1542, mean age = 16.7), the same used as an independent cohort to test the PGS of Doust et al. (2022), we wanted to analyze how the PGS predicted different cognitive abilities:
  - Some subtests of the Multidimensional Aptitude Battery Test (Information, Arithmetic Reasoning, Vocabulary, Spatial, Figure Reconstruction).
  - Some subtests of the WAIS-R itself (Coding, Direct and Indirect Digit Memory, Letter and Number Sequencing).
  - A subtest of the Queensland Core Skill Test (QCST) Create and Present, an index of verbal creativity.
  - Information Processing Speed tests: Inspection Time and Choice Reaction Time.
  - Finally, a test of visuo-spatial working memory: Winnings, which represented the number of wins per accuracy in a spatial delayed response test with and without distractors.

Master's thesis

This research aims to investigate the predictive capabilities of the Polygenic Risk Score for Dyslexia in relation to IQ, Academic Success, and Information Processing Speed.

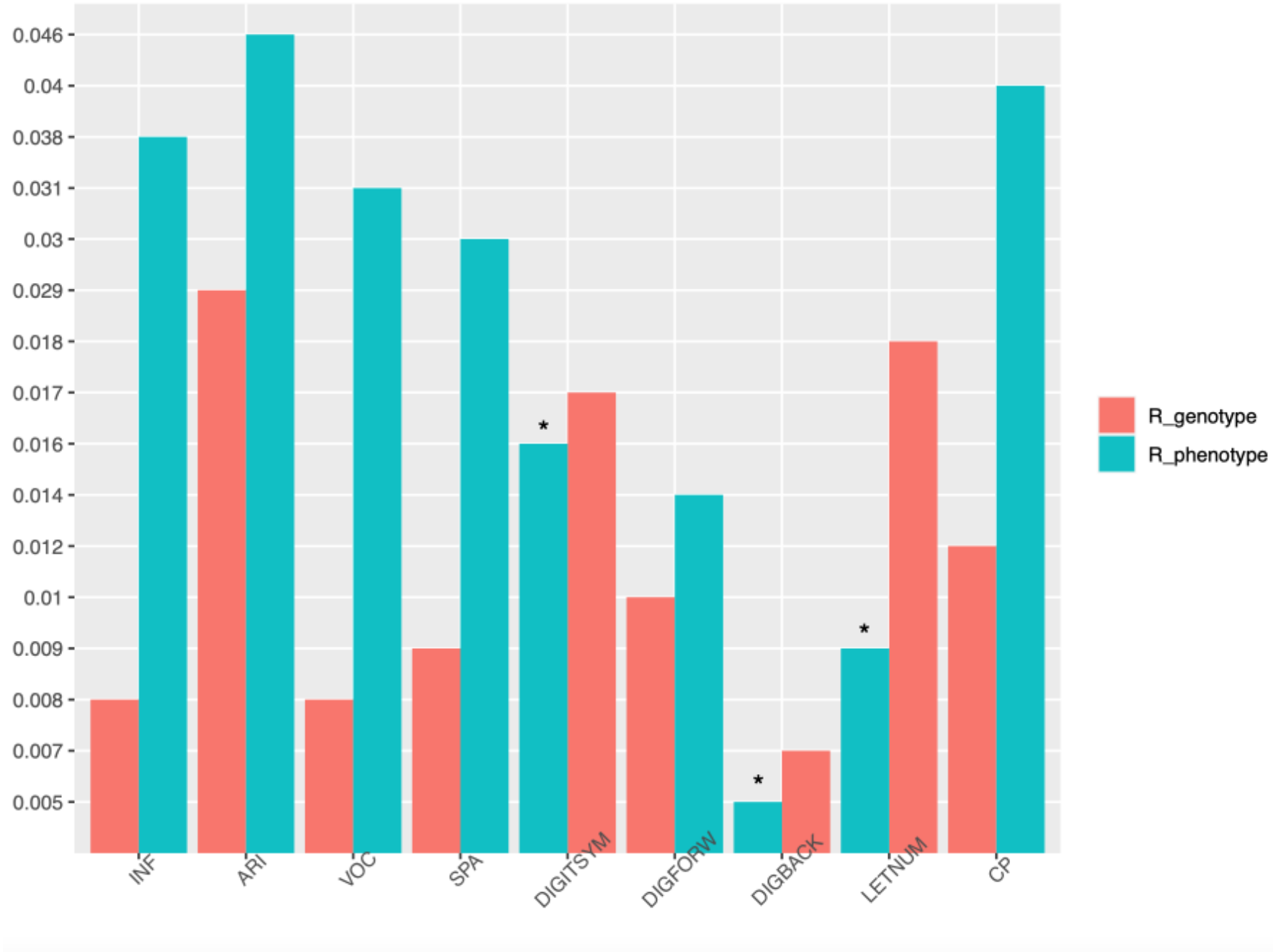
Hypotheses:

1. PRS predicts lower levels of VIQ but not for PIQ.
2. PRS predicts low levels of academic success (Comprehend and Collect) and creativity (Create and Present).
3. Worse response times for Inspection Time and Choice Reaction Time and negative scores for Digit Symbol



Analysis with mixed models and multivariate multilevel models

- In the analyses conducted for the University of Edinburgh, the lme4 package (Bates et al., 2008) was used to run a mixed effect model, specifically with the lmer function.
- In the thesis work, a decision was made to analyze a smaller subset of variables due to their high correlation. Opting for a multivariate and multilevel model allowed us to control the risk of overestimating the model's effect size and enhance the reliability of the estimated parameters.
- Moreover, thanks to the Bayesian approach of the package used, we were able to investigate the model's ability to faithfully reproduce posterior distributions based on observed data and visually represent the effects.


0.046
0.04
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0.031
0.03
0.029
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0.012
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0.005
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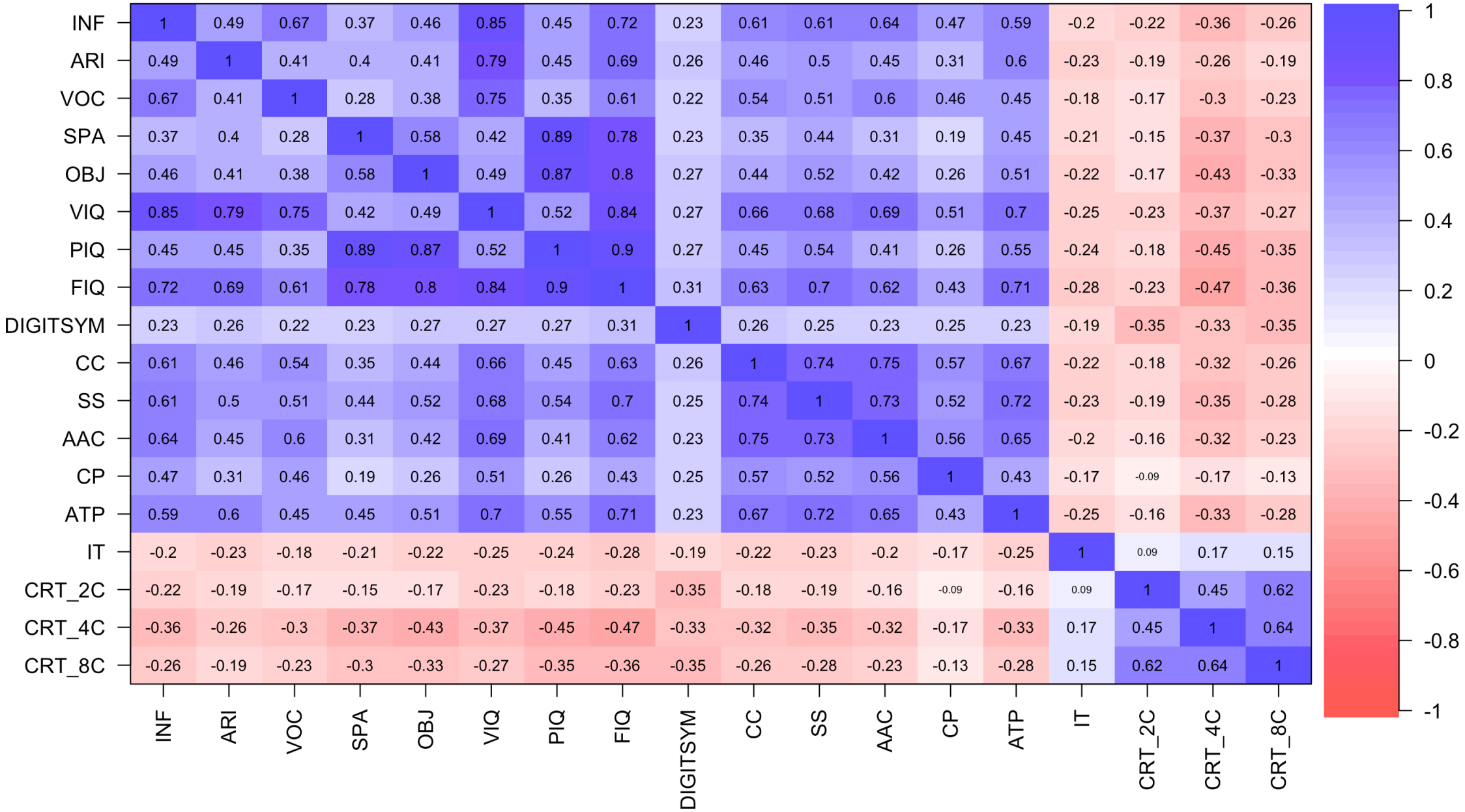
INF
ARI
VOC
SPA
DIGITSYM
DIGFORW
DIGBACK
LETNUM
CP
R_genotype
R_phenotype

Correlation plot



Model Comparison

M0	M1
VIQ~(1|FID)	VIQ~PRS+(1|FID)
PIQ~(1|FID)	PIQ~PRS+(1|FID)
DIGIT~(1|FID)	DIGIT~PRS+(1|FID)
CC~(1|FID)	CC~PRS+(1|FID)
CP~(1|FID)	CP~PRS+(1|FID)
IT~(1|FID)	IT~PRS+(1|FID)
CRT~(1|FID)	CRT~PRS+(1|FID)

- We compared two models: M0, the null model, and M1, the target model. Both models are multivariate and multilevel, involving 7 dependent variables. M0 includes only the random effect, while M1 includes both the random effect and the PRS as a predictor.
- We assessed the comparison of the two models using model weights and R^2 coefficients.

Risultati Model Comparison

M0	M1
0.44	0.56

In comparison, M1 is 1.28 times more plausible than M0. The relative evidence for the PRS is relatively low.

	R^2_{M0}	R^2_{M1}	R^2_{marg}
VIQ	0.10	0.12	0.02
PIQ	0.24	0.24	0.00
DIGIT	0.22	0.24	0.02
CC	0.08	0.08	0.00
CP	0.05	0.06	0.01
IT	0.05	0.05	0.00
CRT	0.27	0.27	0.00

The marginal R^2 show little variance explained by the PGS.

Estimates

The plot displays the estimate values with 95% credibility intervals.

-0.13

-0.05

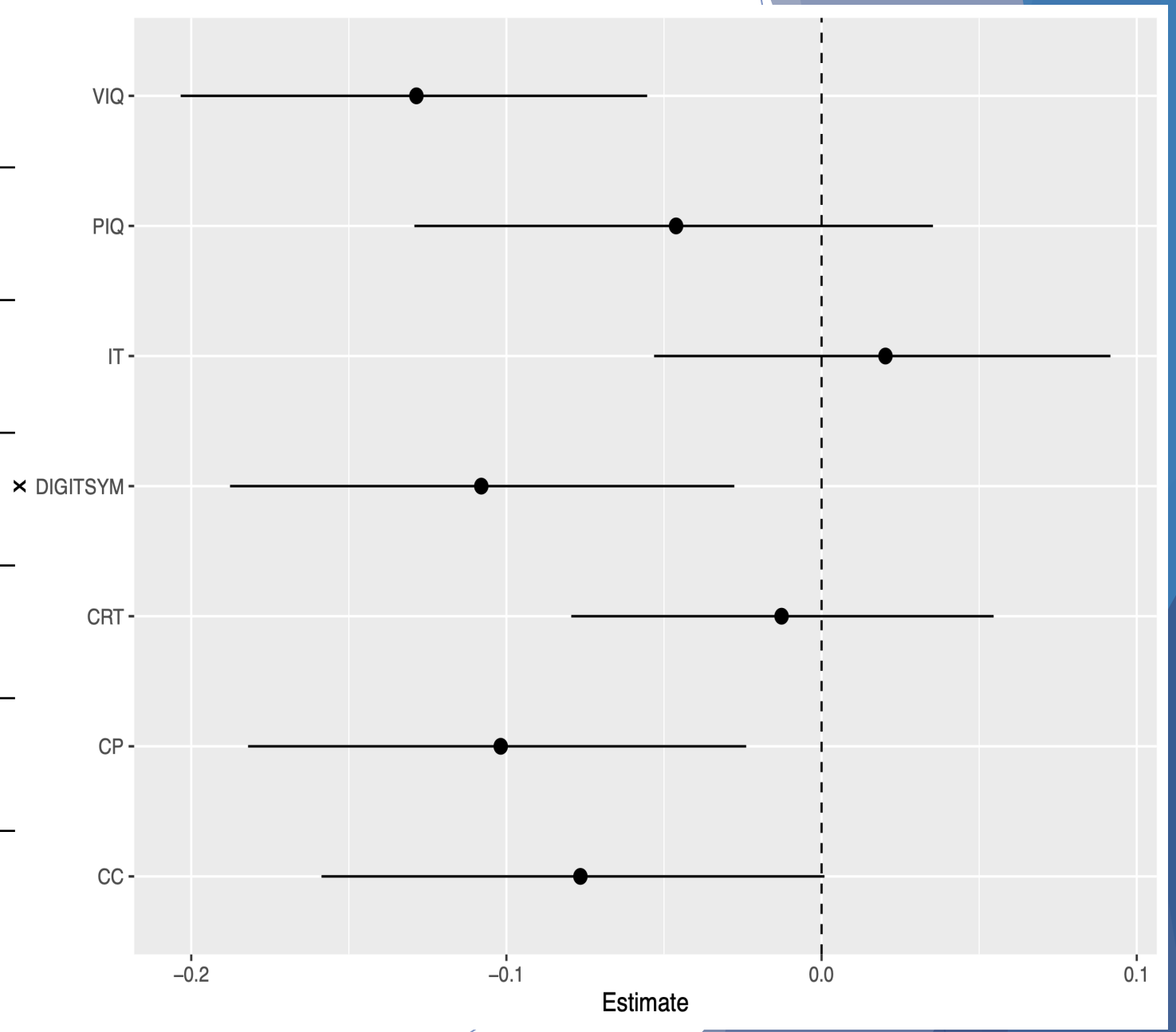
0.02

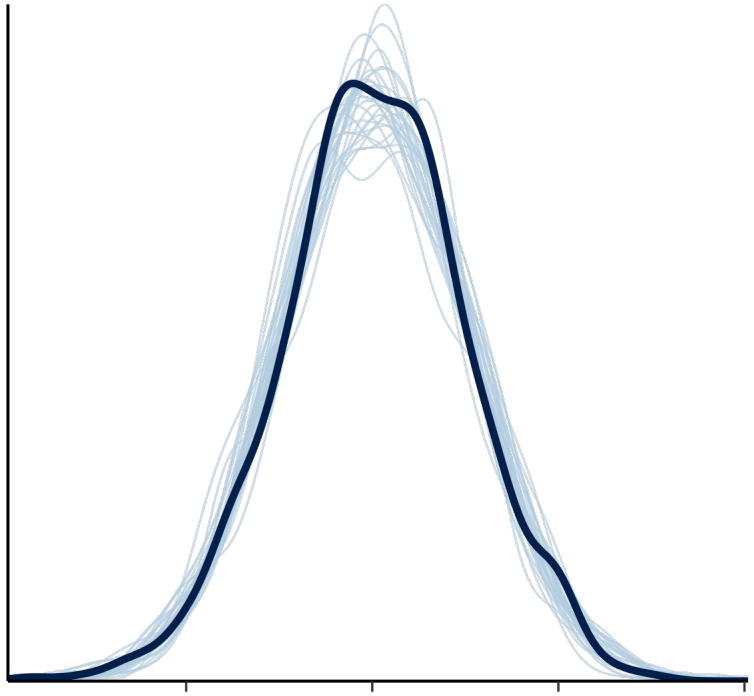
-0.11

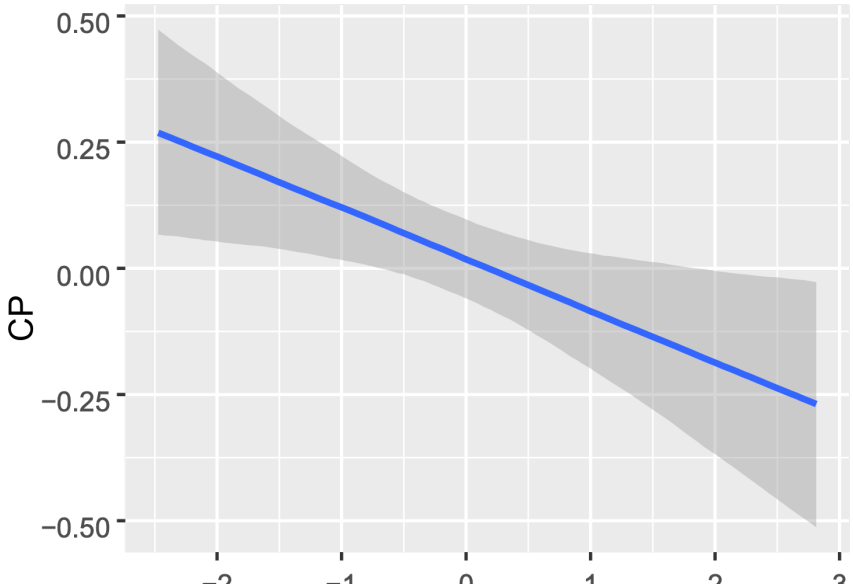
-0.01

-0.10

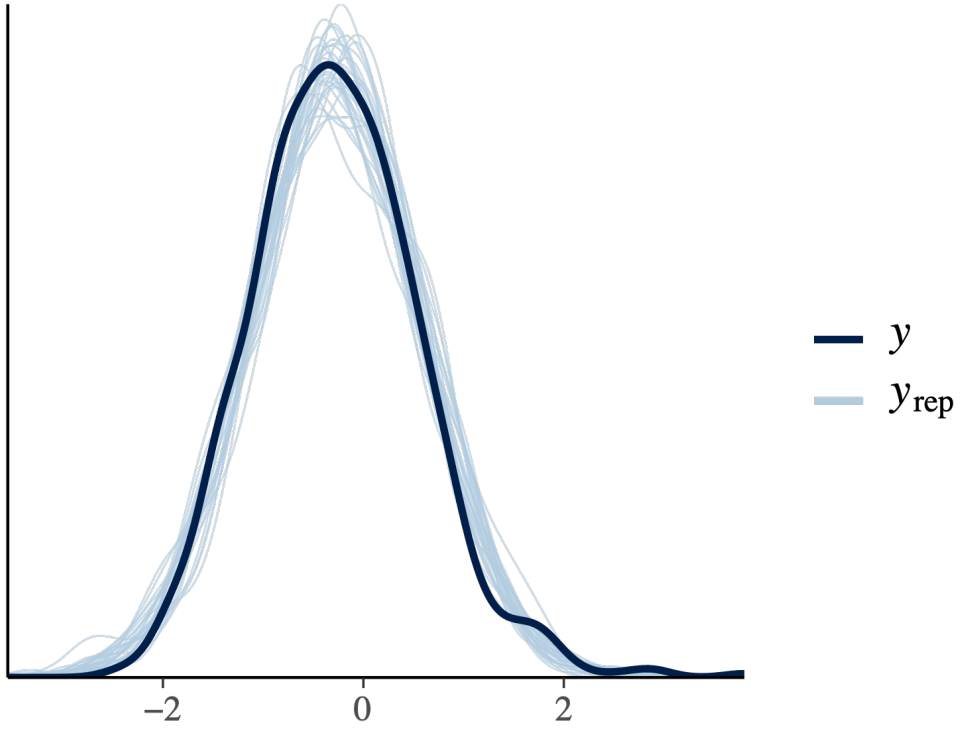
-0.08

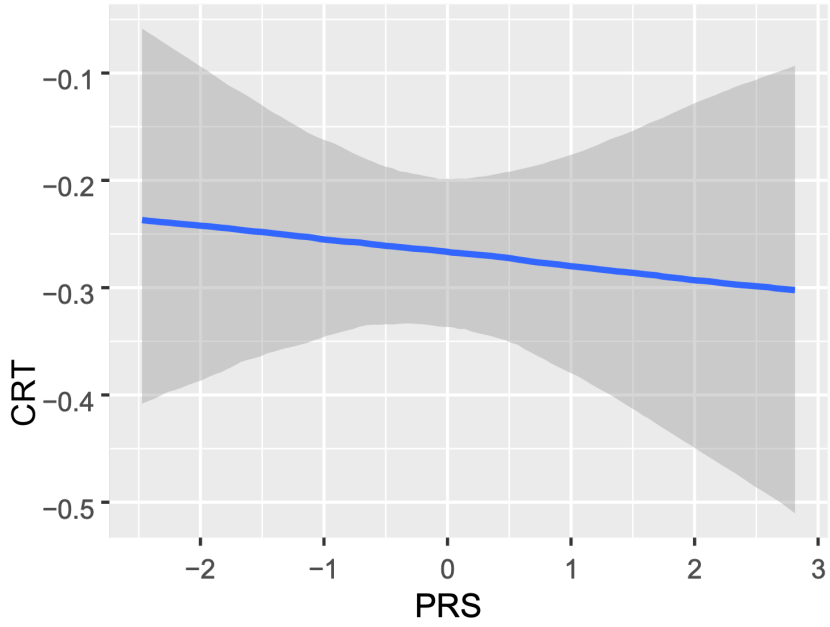




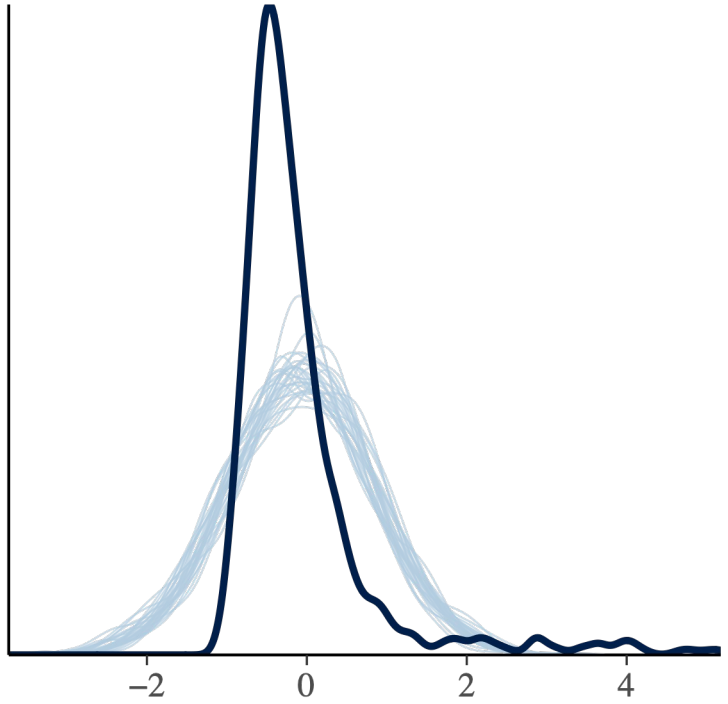


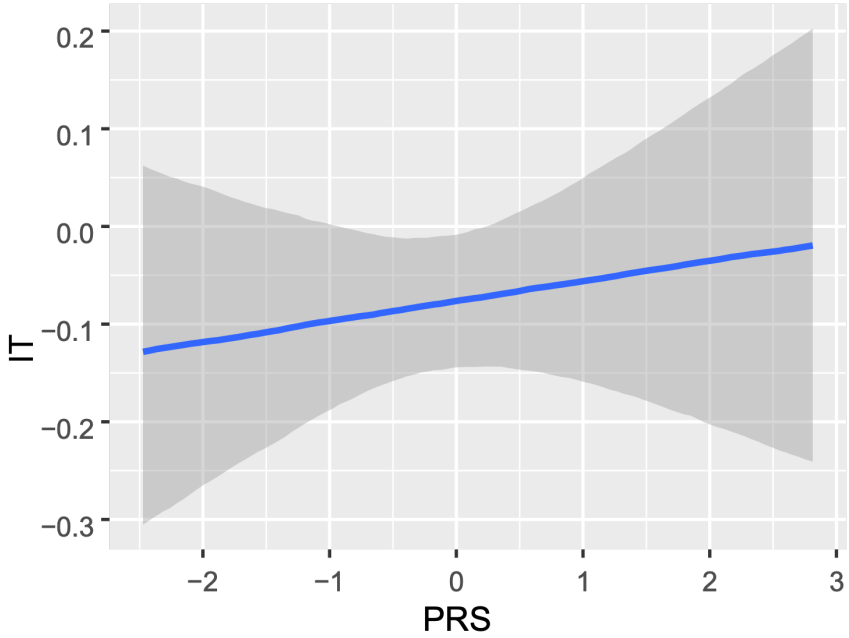
Posterior Predictive Checks & Conditional Effects





Posterior Predictive Checks & Conditional Effects





Posterior Predictive Checks & Conditional Effects

Final considerations

Novel wais to compute PGS are rising and will likely increase predictive performance but part of the research community is skeptical about it's application to estimatebtraits which are not tangible (Penders & Janssens, 2022; Sarkar, 2023). While PGS can be useful in the detection of specific deseases, it is trivial to use it to predict latent constructs which are assessed and evaluated through human-created measures.
In a study on a Danish sample, a polygenic score for school grades correlated with 6 different psychiatric disorders (Rajagopal et al., 2023)

References

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For a more detailed description of the methods avaiable to compute PGS, here some extra References

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