# Heterogeneous Pathways Characterized in Meta-Analyses of Psychiatric Disorders using Coordinated Epistasis

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[1]Helmholtz Pioneer Campus, Helmholtz Munich, [2]Department of Psychiatry and Psychotherapy, University Medicine Greifswald, [3]German Centre for Neurodegenerative Diseases (DZNE), Site Rostock/Greifswald, [4]Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Mental Health Services of the Capital Region of Denmark, [5]Planck Institute of Psychiatry, Munich, [6]Cluster for Systems Neurology (SyNergy), Institute of Translational Medicine University of Liverpool, [7]University of Chicago

## METHODS

## RESULTS

### COORDINATED EPISTASIS



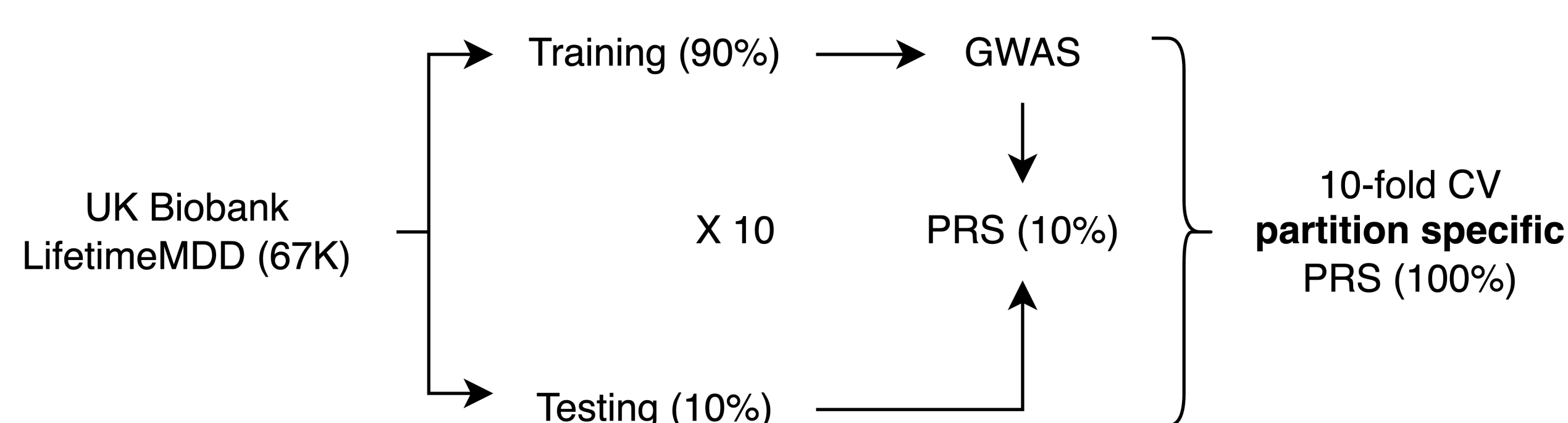**Proof-of-concept: We detect significant negative Coordinated Epistasis between Schizophrenia (SCCZ) and Anorexia (ANO) in iPSYCH.** We combined data in iPSYCH2015i and tested for all chromosome pair interactions between PRSs of SCZ, and ANO, and regressed towards ANO.
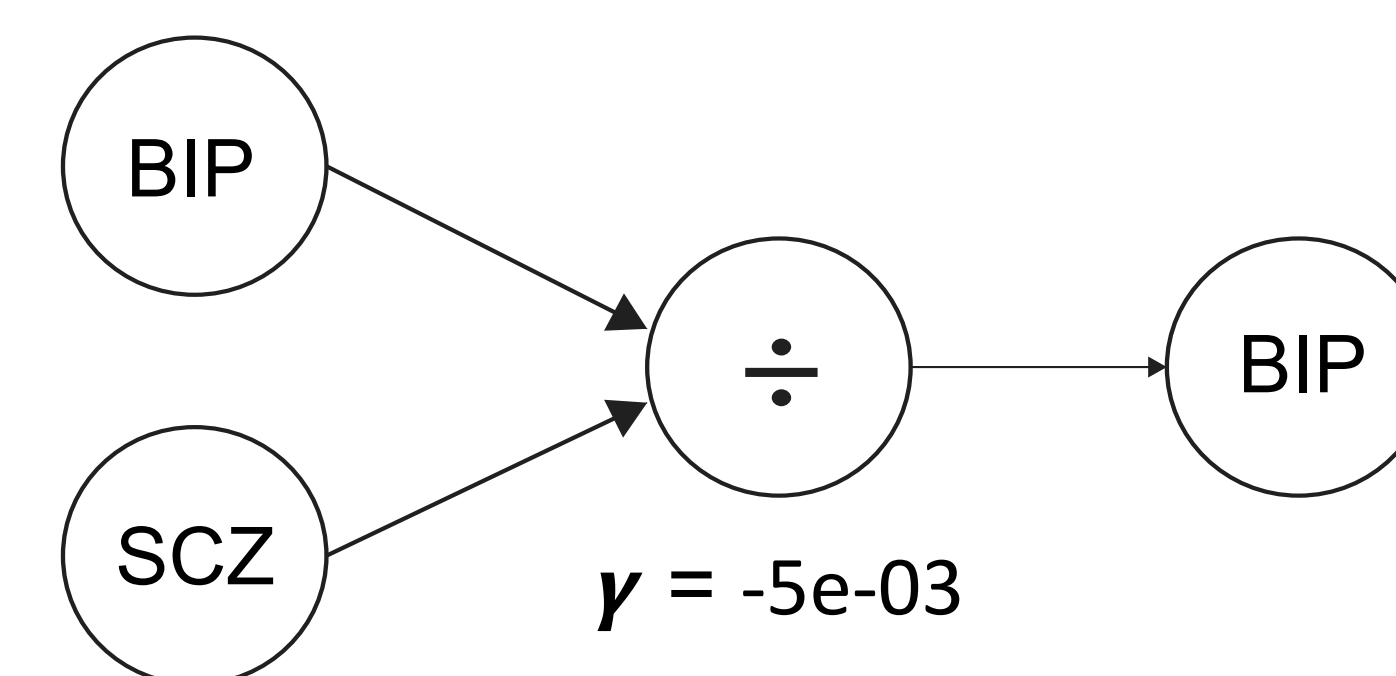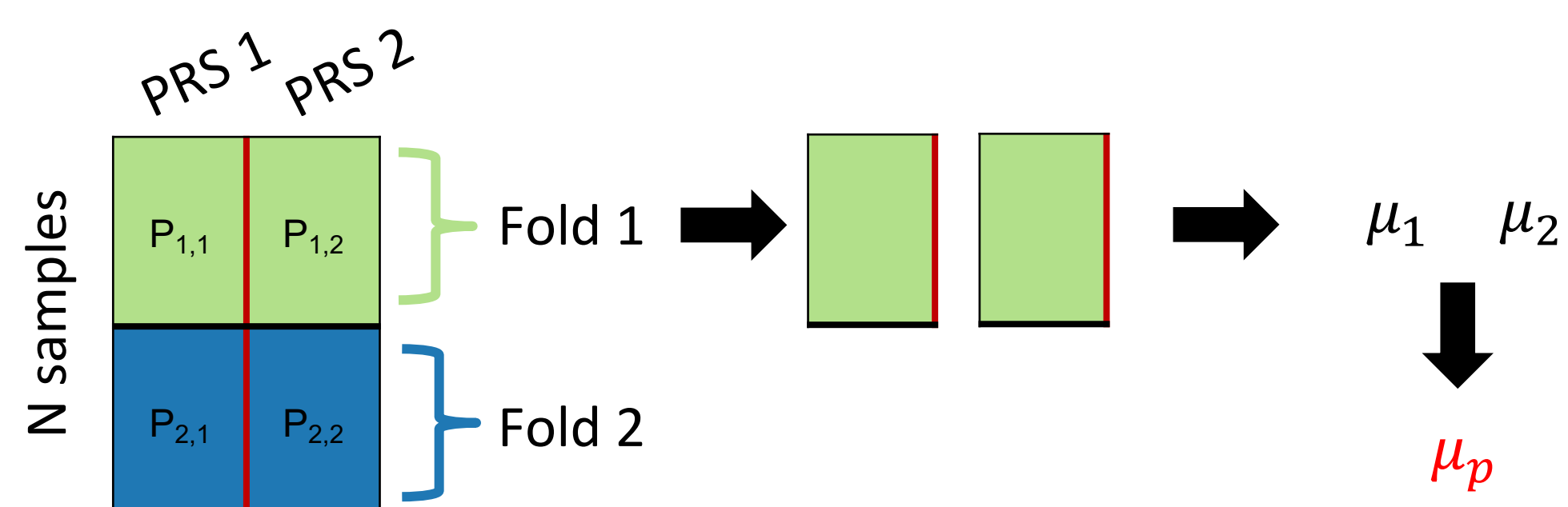


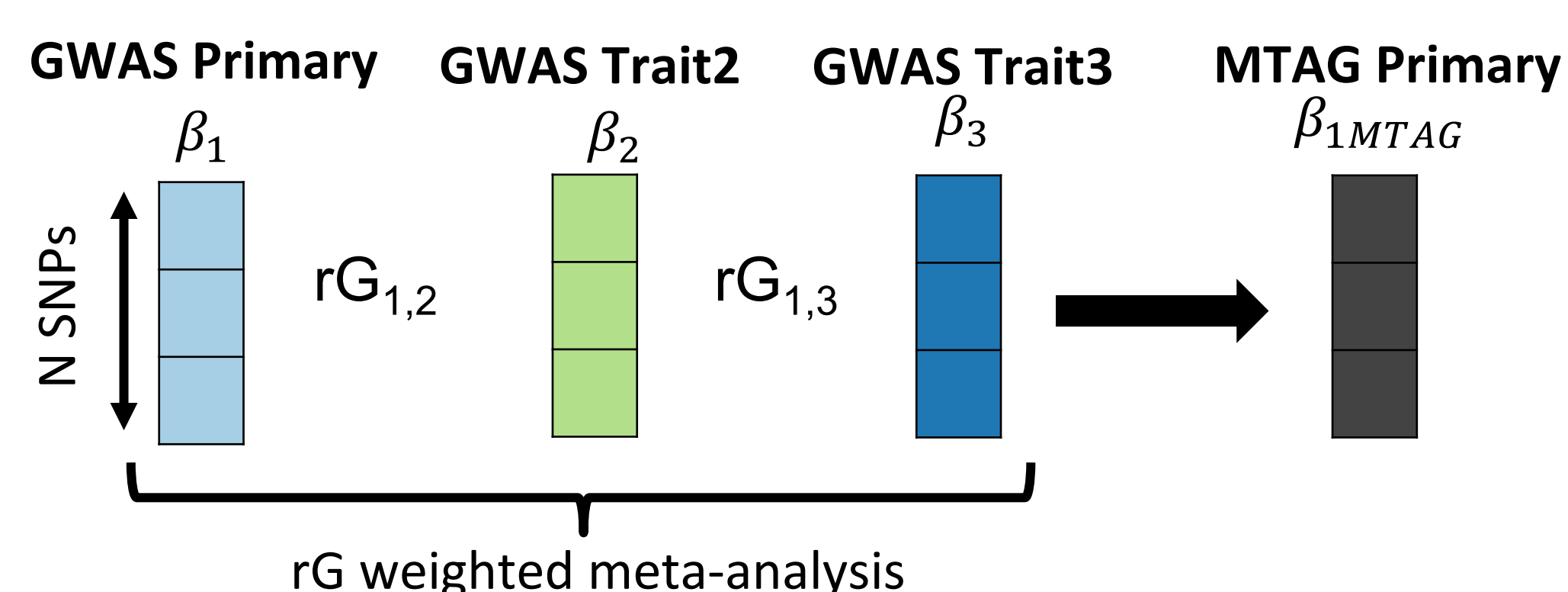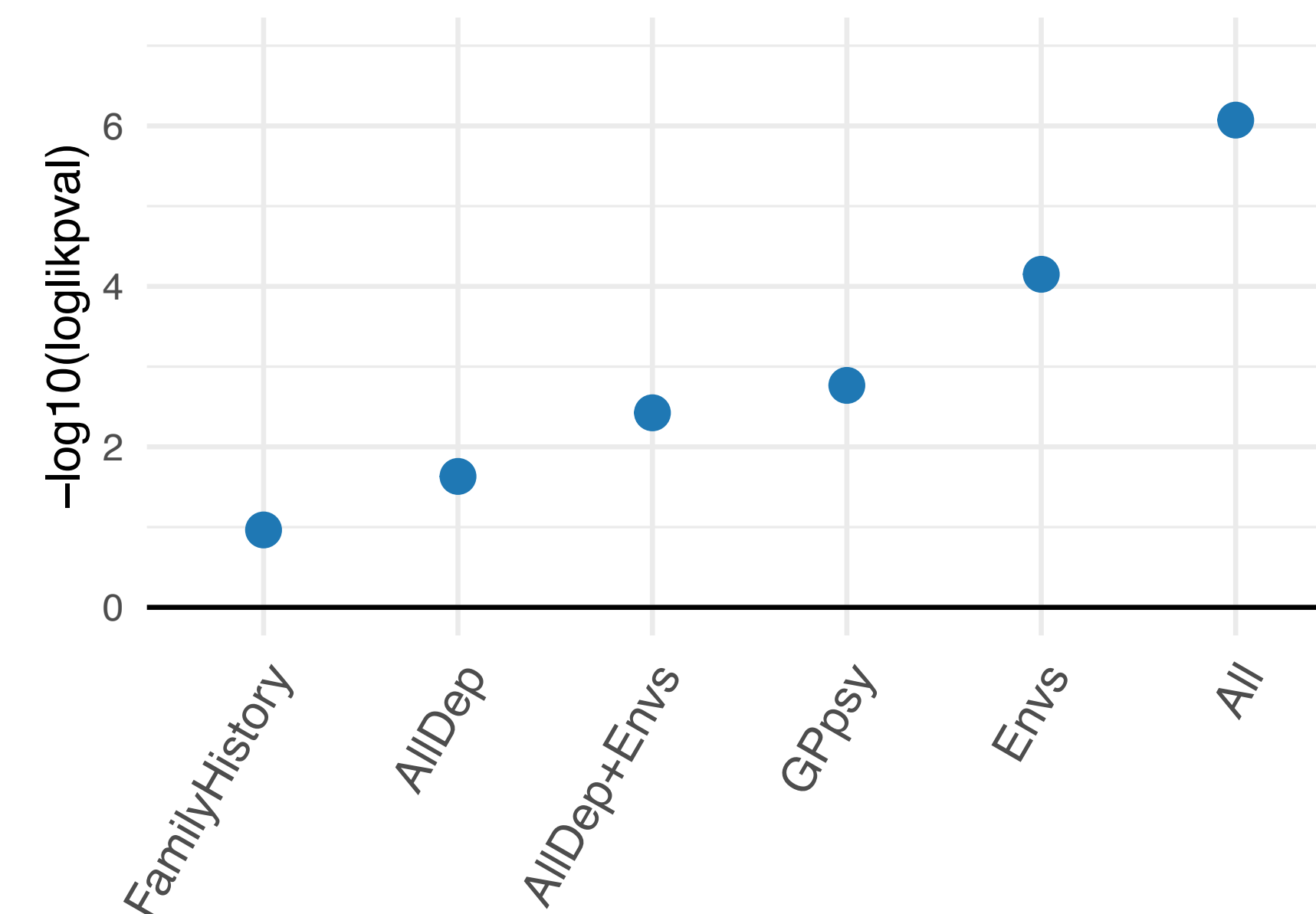| Disorder A | Disorder B | Phenotype | Mean( $\gamma$ ) | P |
|---|---|---|---|---|
| (A) $\gamma_{BIP}$ | SCZ | BIP | $\gamma = $ -5e-03 | 3.3e-08 |

### CROSS VALIDATION



### MUNDLAK



### MTAG



**Coordinated Epistasis with Mundlak correction on 6 different MTAG meta-analysed summary statistics to Major Depressive Disorder in the UK Biobank.** We find polygenic interactions indicative of phenotype heterogeneity.



| Phenotype | N input GWAS | Description |
|---|---|---|
| FamilyHistory | 3 | severe depression in family members |
| AllDep | 5 | Various shallow MDD phenotypes |
| ALLDep+Envs | 9 | Shallow MDD phenotypes and environment variables |
| Gppsy | 1 | Gppsy |
| Envs | 5 | Related environment variables |
| All | 12 | Shallow MDD phenotypes, enivornment variables, family history |

### REFERENCES
1. Sheppard et al. PNAS (2021)
2. Mundlak, Y. Econometrica (1978)
3. Dahl et al. bioRxiv (preprint)
4. Turley et al. Nat Gen (2018)
5. Bybjerg-Grauholm et al. medRxiv (preprint)
6. Sudlow et al. PLoS Med (2015)