

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

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## METHODS

- **Mundlak method** corrects for 10-fold Cross-Validation induced batch effects by adding covariate of panel means.
- **Coordinated Epistasis** framework tests for polygenic interactions between PRS generated from partitions of the genome (pathway proxies)
- **MTAG** creates heterogeneous summary statistics from multi-trait GWAS weighted on genetic correlation with primary trait.

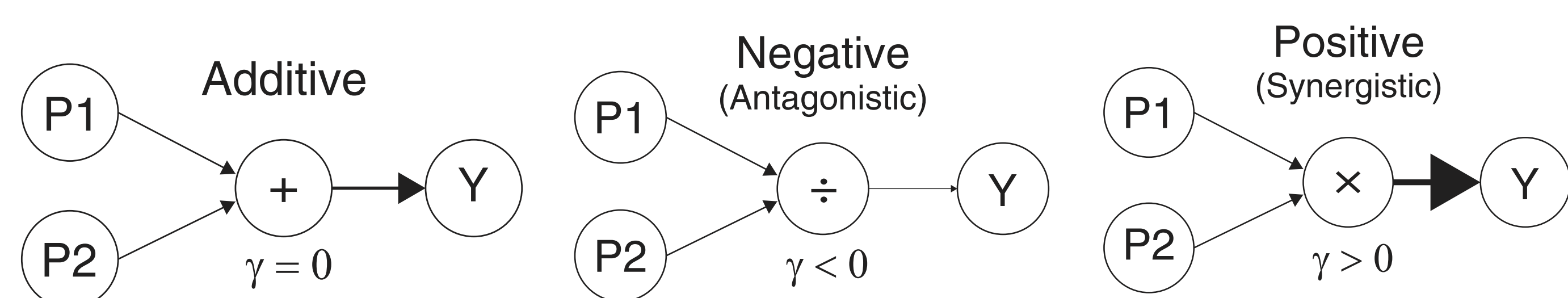
## RESULTS

- Coordinated Epistasis (CE) detects heterogeneity in artificially merged psychiatric disorders
- Mundlak-corrected CE detects pathway architecture in 6 MTAG meta-analyses of Major Depressive Disorder (MDD) in UK Biobank

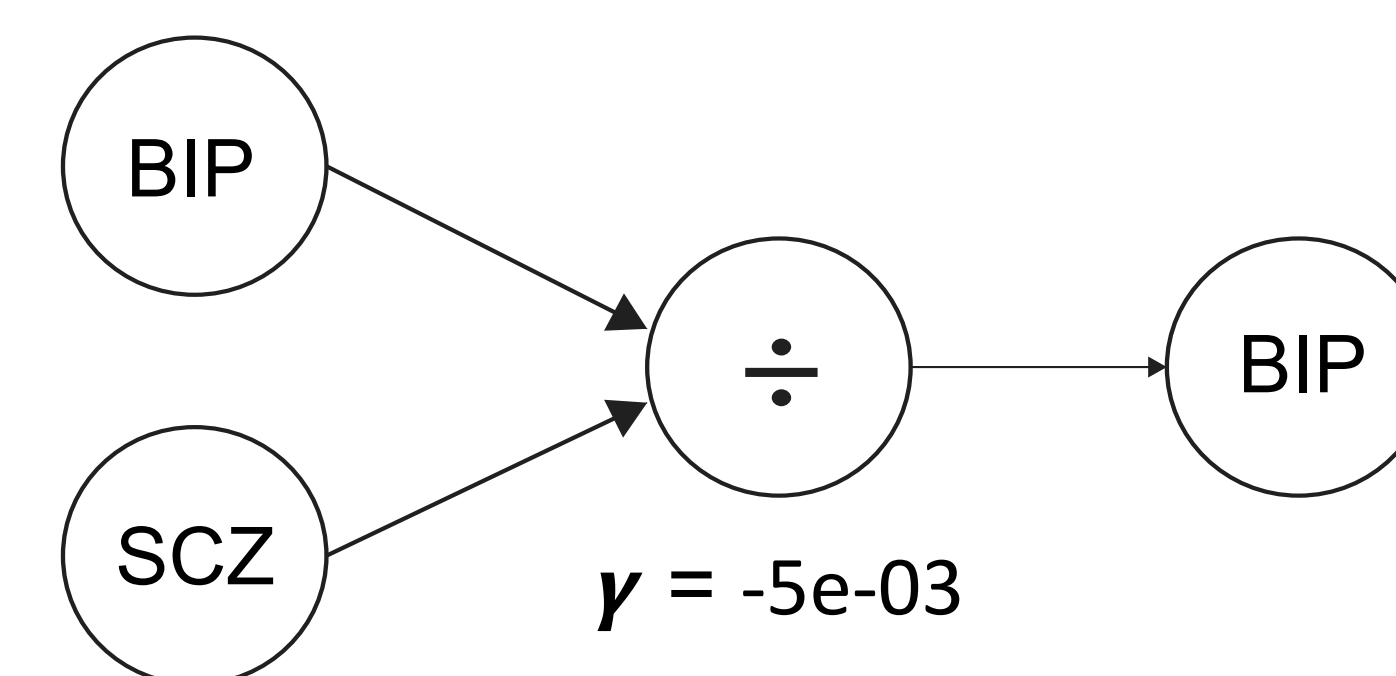
## COORDINATED EPISTASIS

$$Y \sim \text{covariates} + \mu_p + \alpha_i PRS'_i + \alpha_j PRS'_j + \gamma_{i,j} PRS'_i * PRS'_j$$

i = even chromosomes (E)      $\mu_p$  = mean of means  
j = odd chromosomes (O)      $PRS' = PRS - \mu_p$

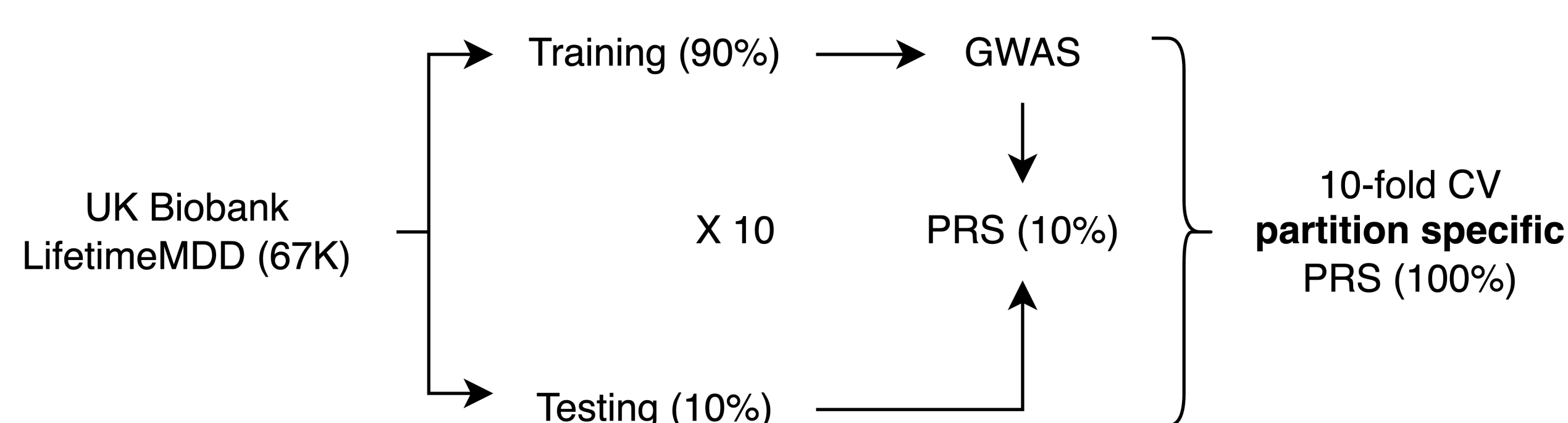


**Proof-of-concept: We detect significant negative Coordinated Epistasis between Schizophrenia (SCZ) and Anorexia (ANO) in iPSYCH.** We combined data in iPSYCH2015i and tested for all chromosome pair interactions between PRSs of SCZ, and ANO, and regressed towards ANO.

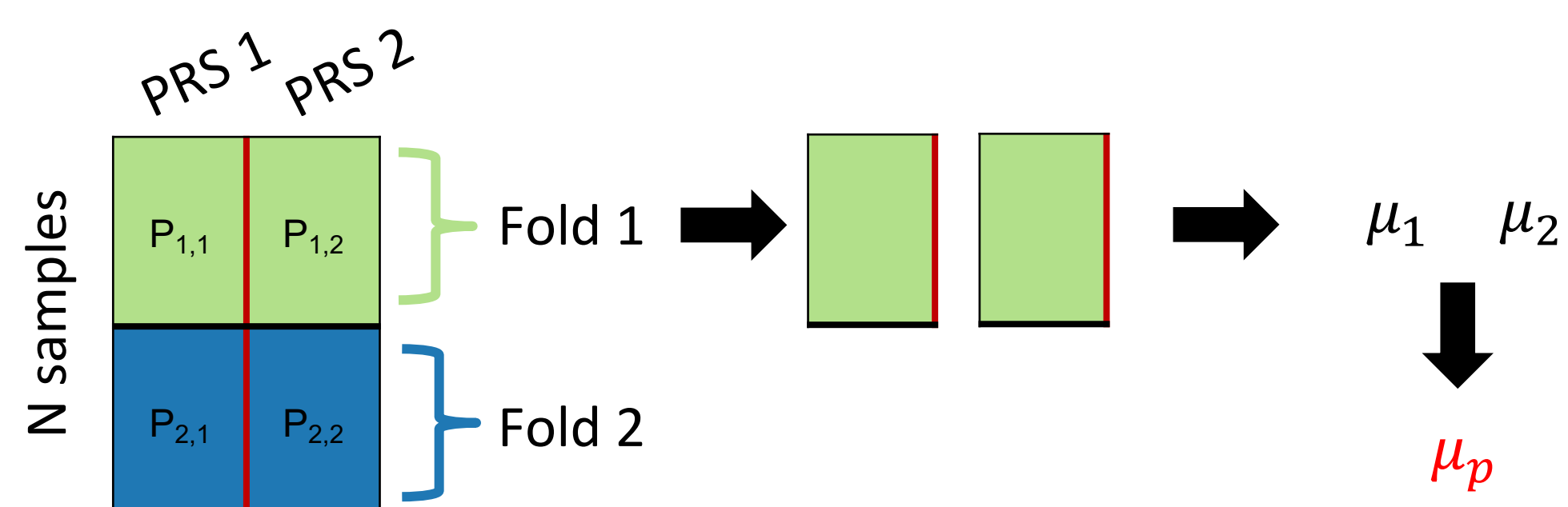


Disorder A	Disorder B	Phenotype	Mean( $\gamma$ )	P
BIP	SCZ	BIP	-5e-03	3.3e-08

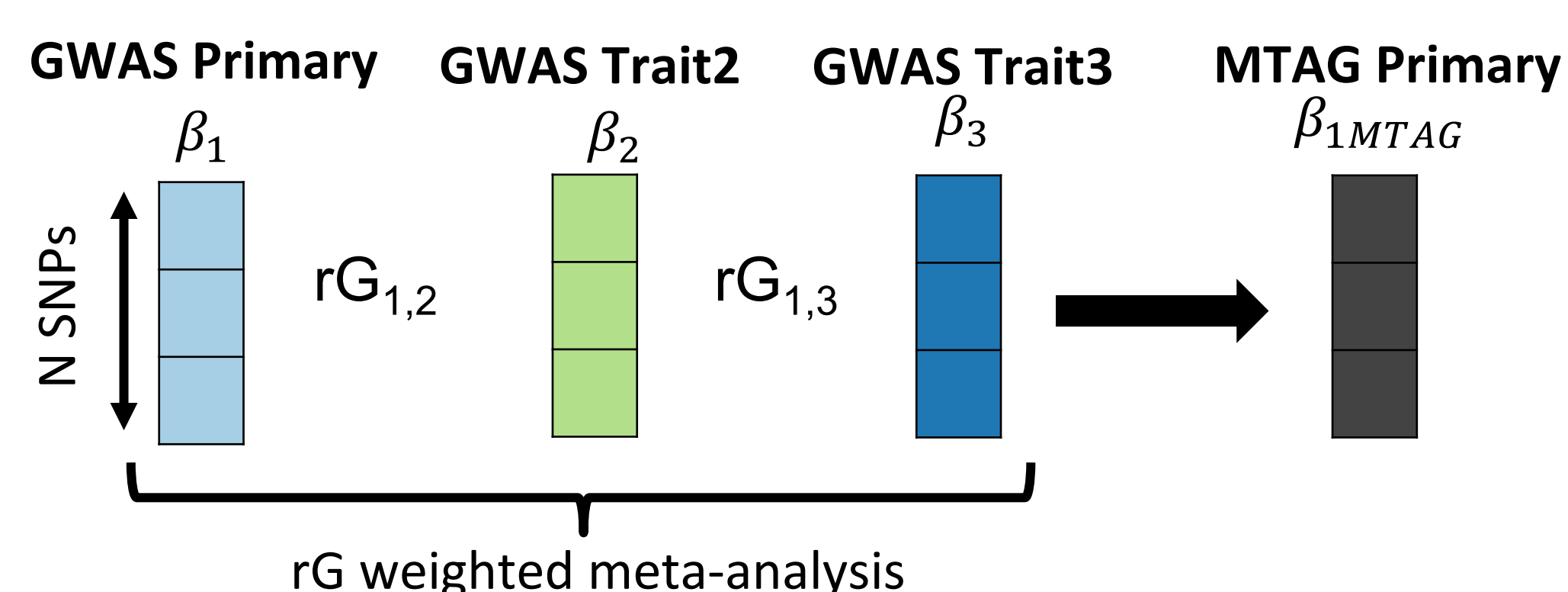
## CROSS VALIDATION



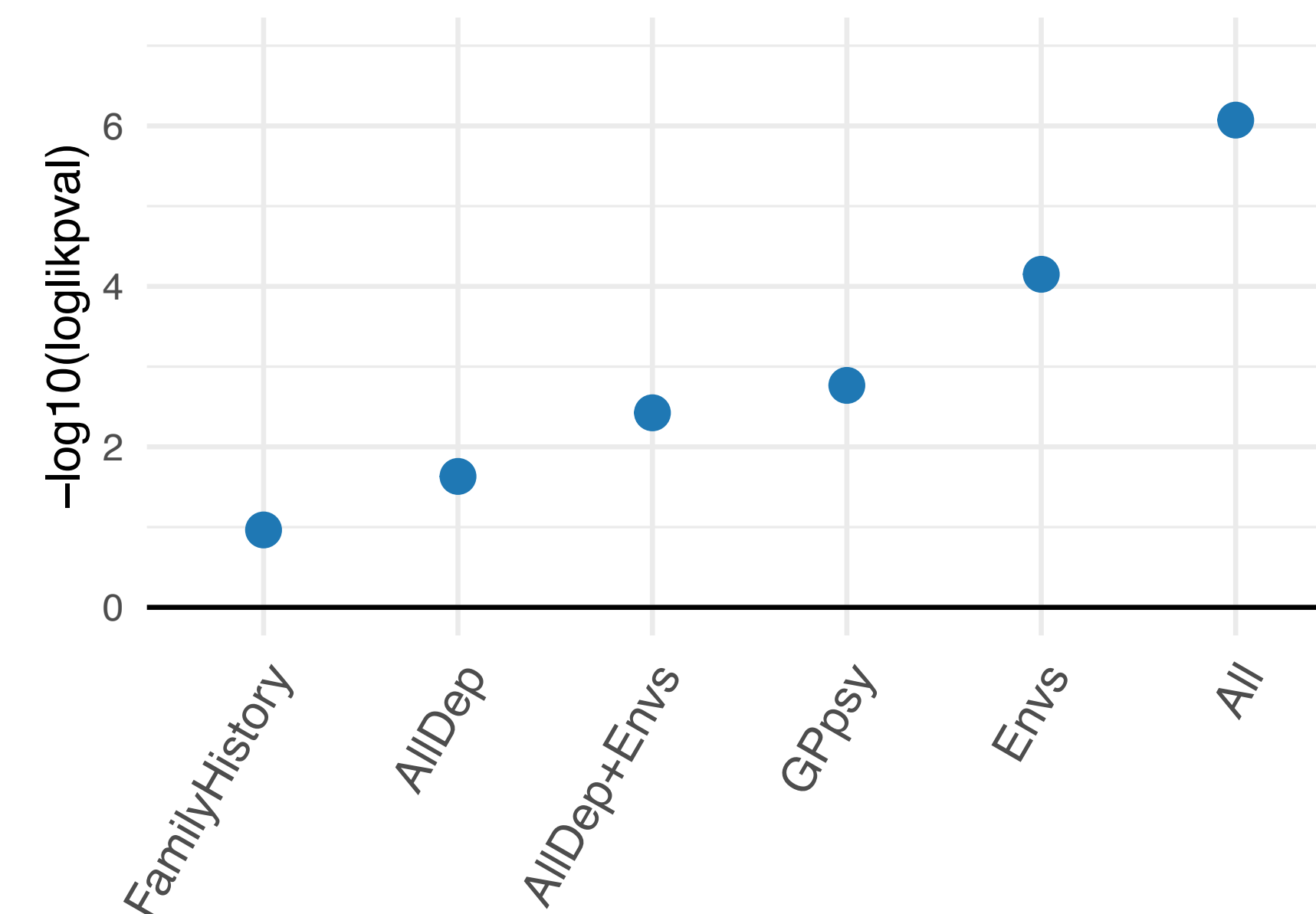
## MUNDLAK



## 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 <sub>input GWAS</sub>	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, environment 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)

