Coordinated Epistasis Detects Heterogenous Pathways Across Psychiatric Disorders and Comorbidities
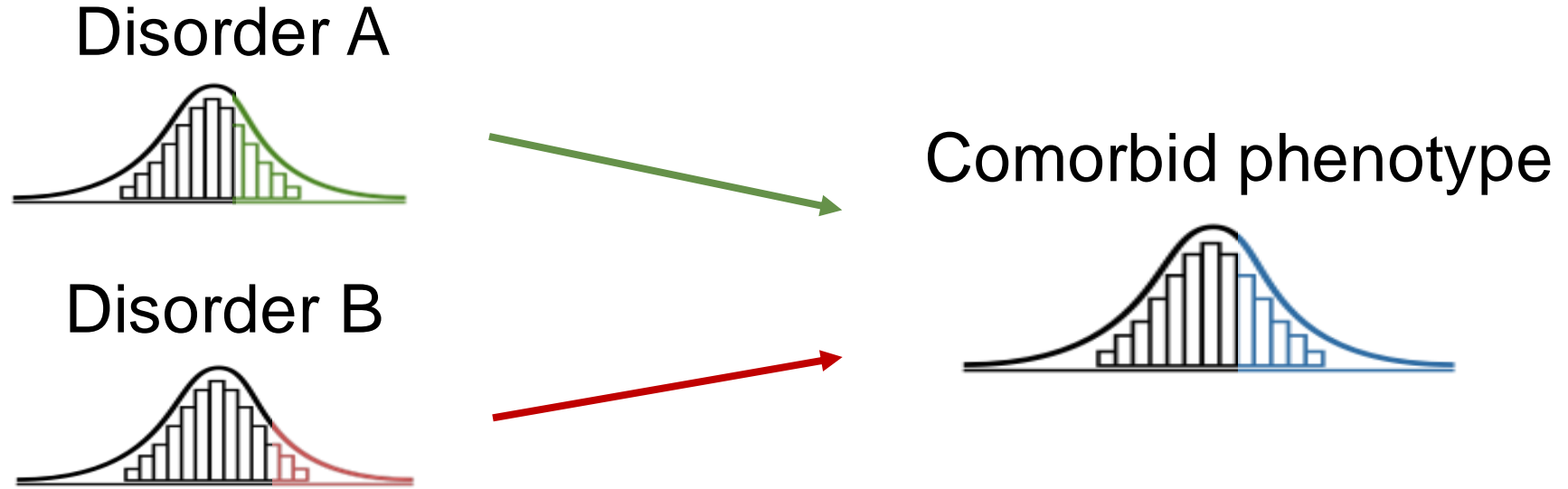
Jolien Rietkerk, Morten Krebs, Lianyun Huang, Kajsa-Lotta Georgii Hellberg, iPSYCH Study Consortium, Thomas Werge, Andrew J. Schork, Andy Dahl, Na Cai
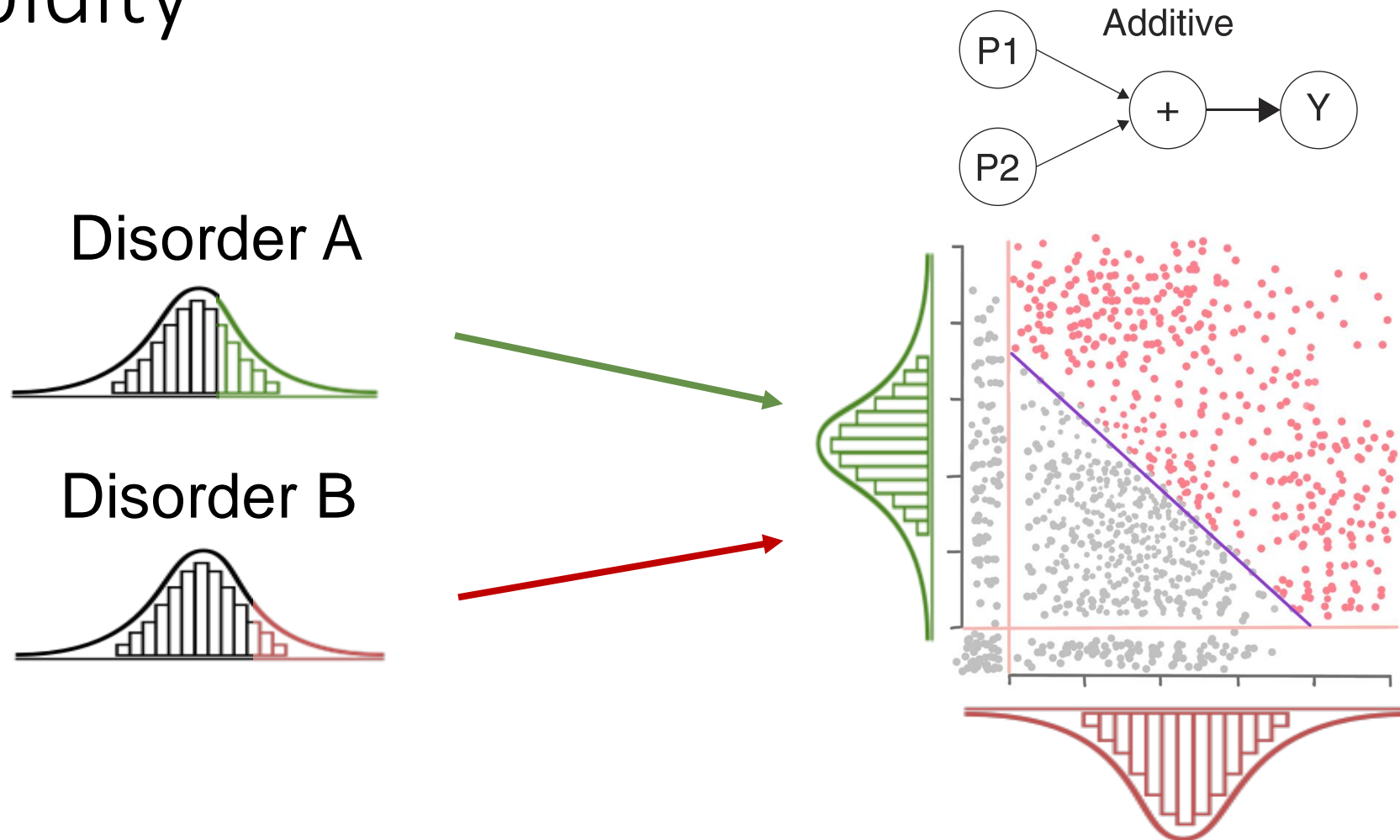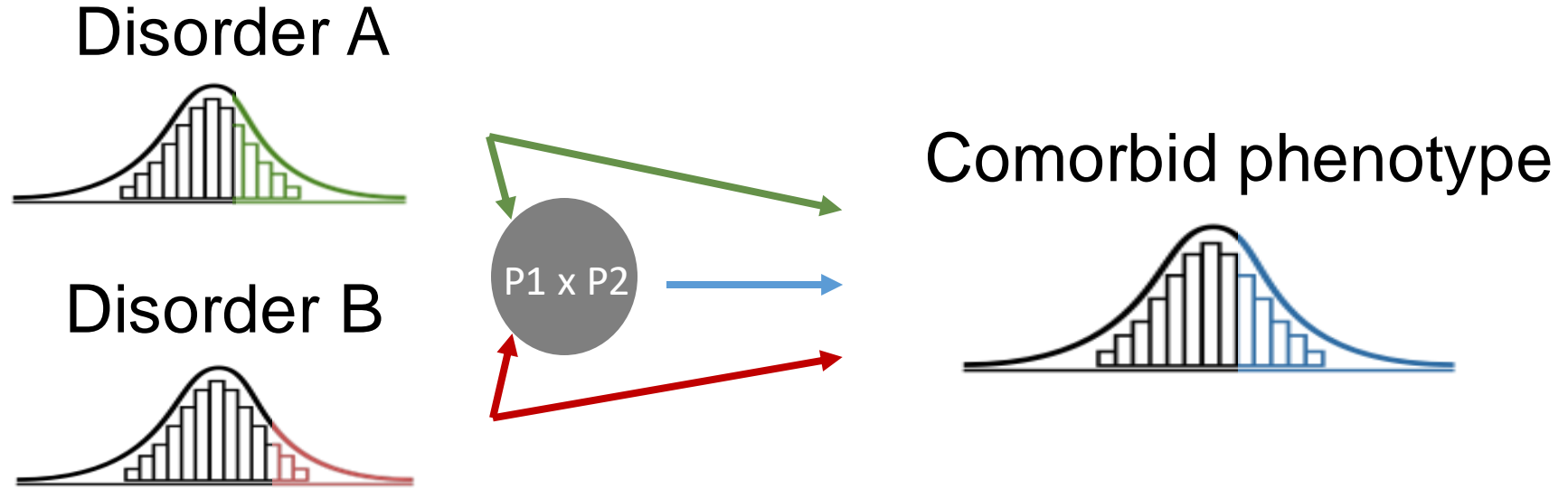
Disclosures

Nothing to disclose

(Psychiatric) Comorbidity
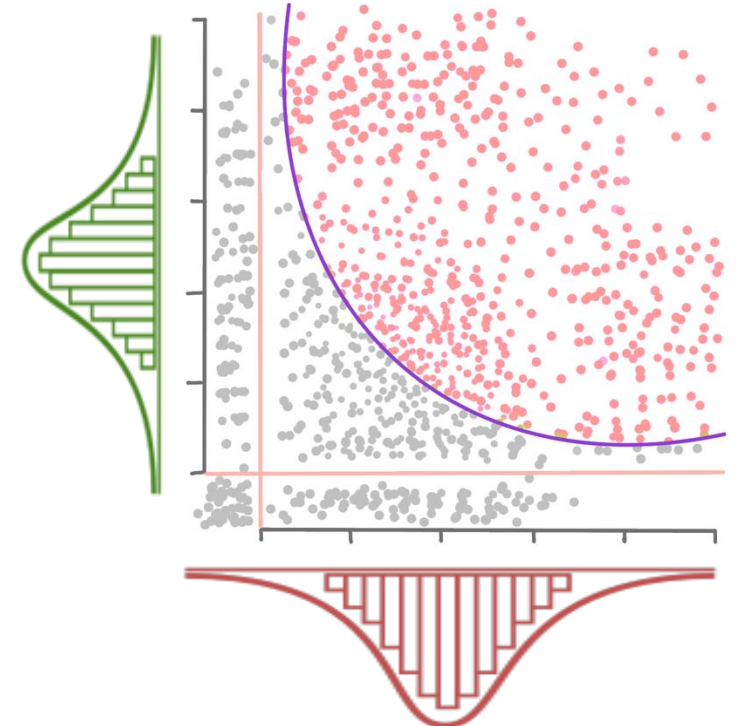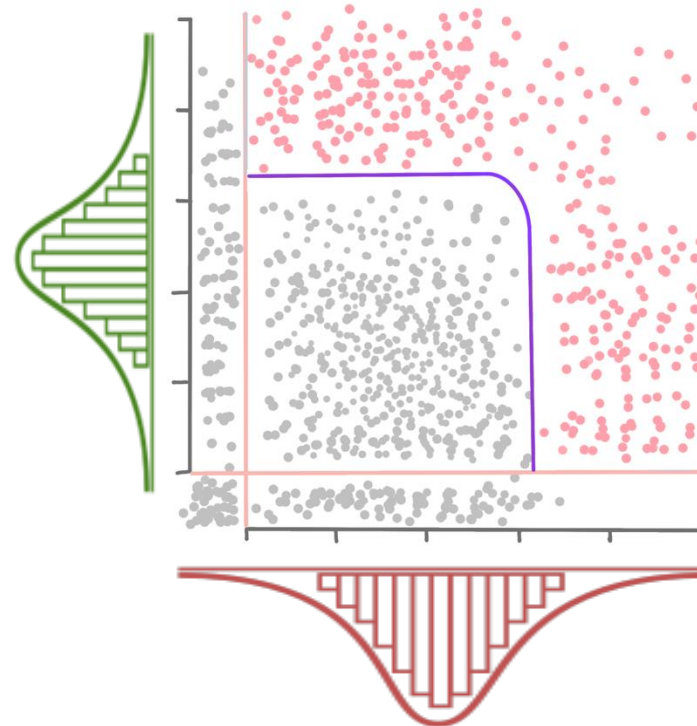
Disorder-specific pathways contributing to comorbidity

Additive

P1
P2
+
Y

Disorder A

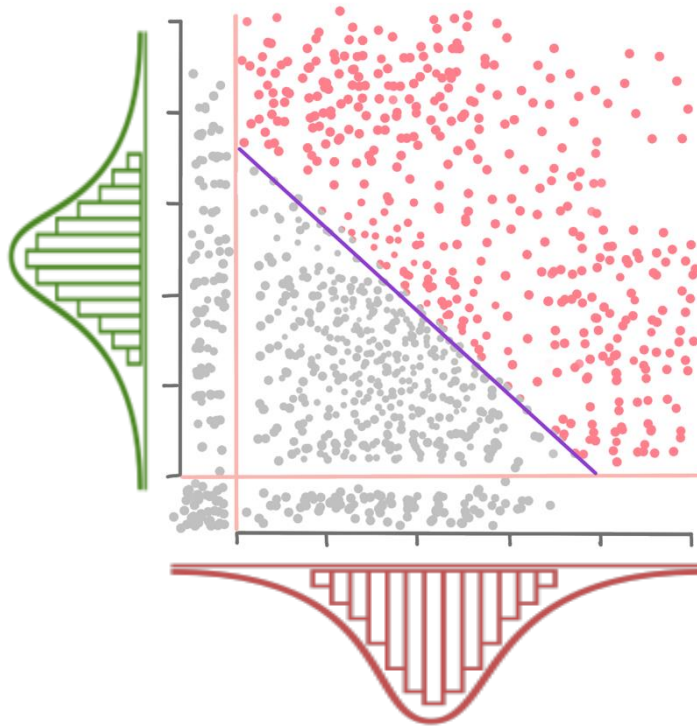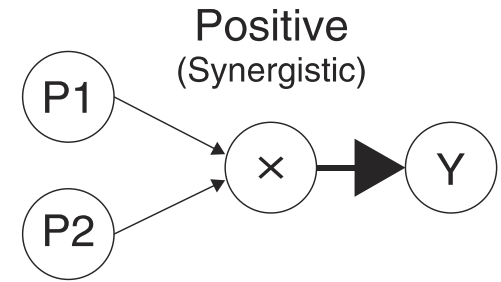Disorder B

Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022

Hypothesis: Disorder-specific pathway interactions contribute to comorbidity

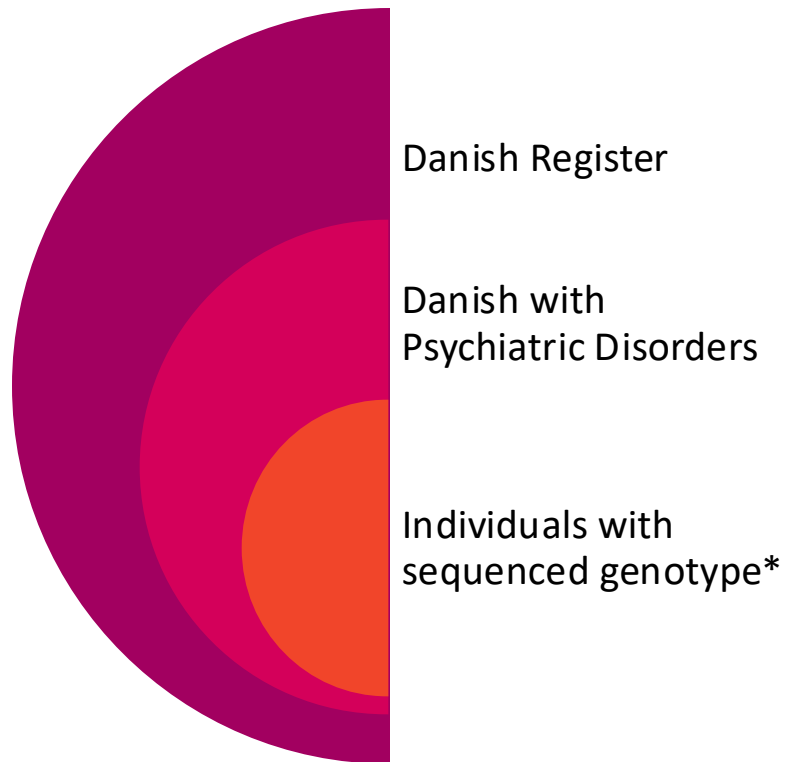Disorder A

Disorder B

P1 x P2

Comorbid phenotype

Negative interaction between pathways
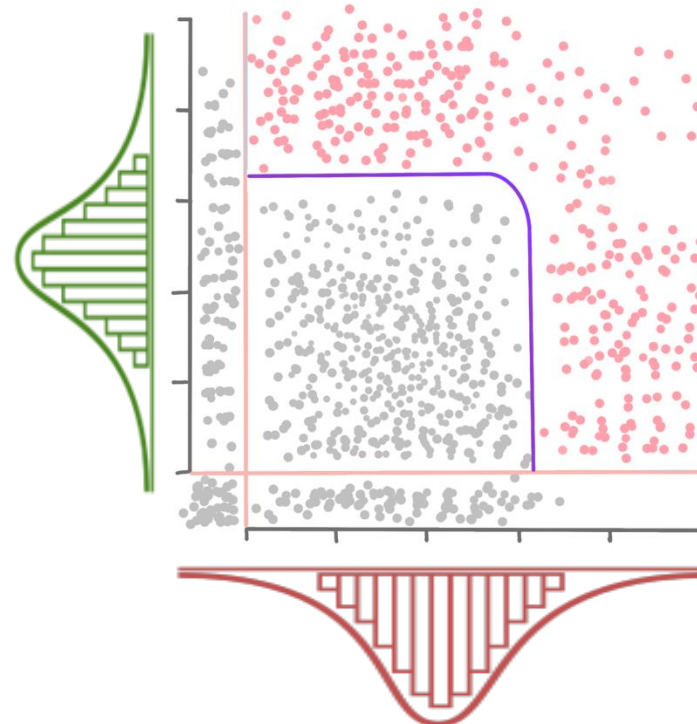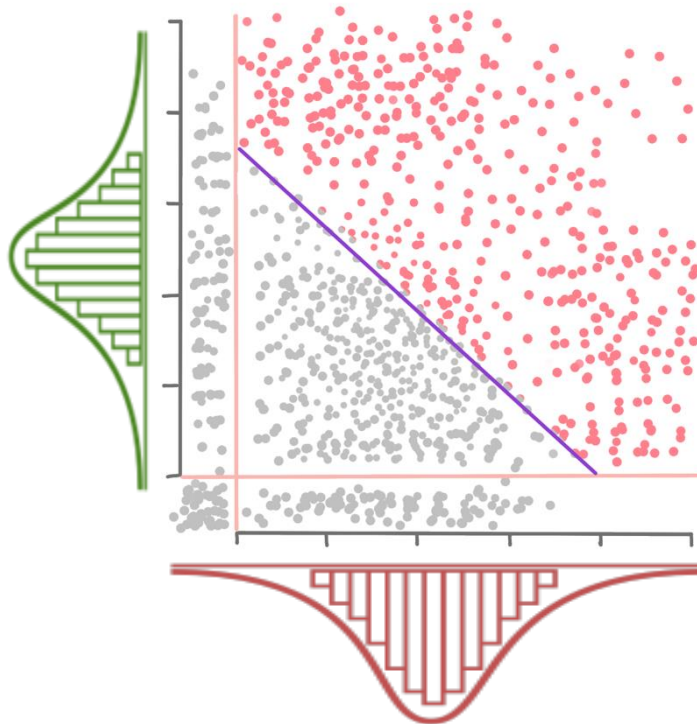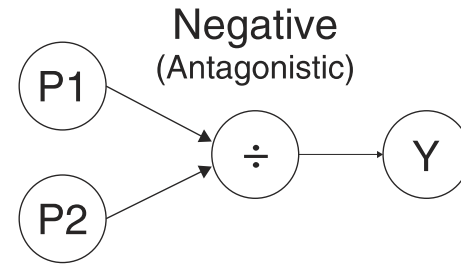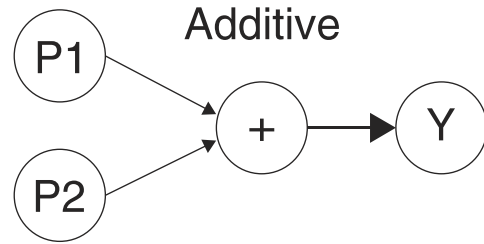
Positive interaction between pathways
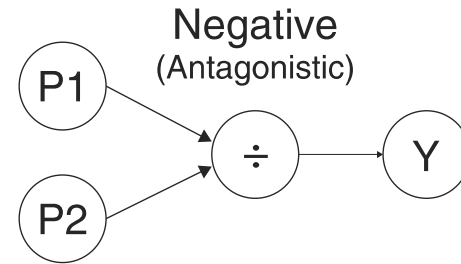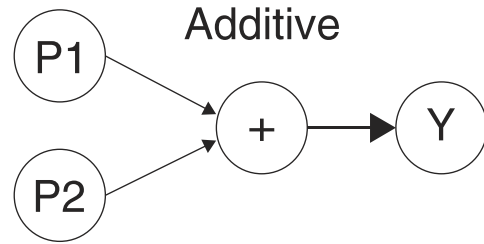
Data: Danish Register and iPSYCH

Danish Register

Danish with
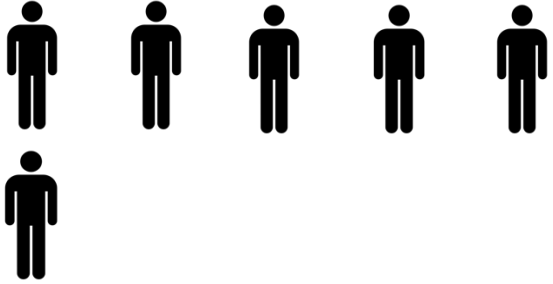Psychiatric Disorders

Individuals with
sequenced genotype*

* Two sequence arrays and separate acertainment gave rise
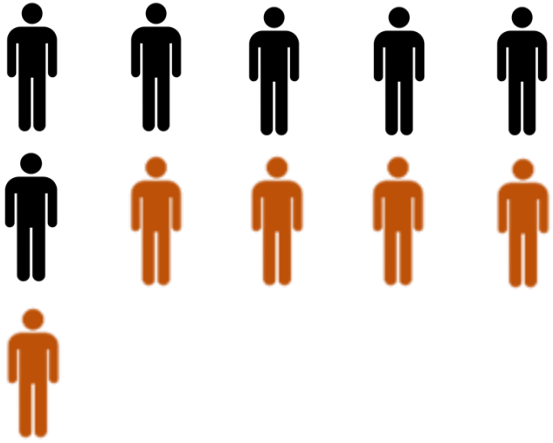to replication cohorts: iPSYCH 2012 and iPSYCH 2015i
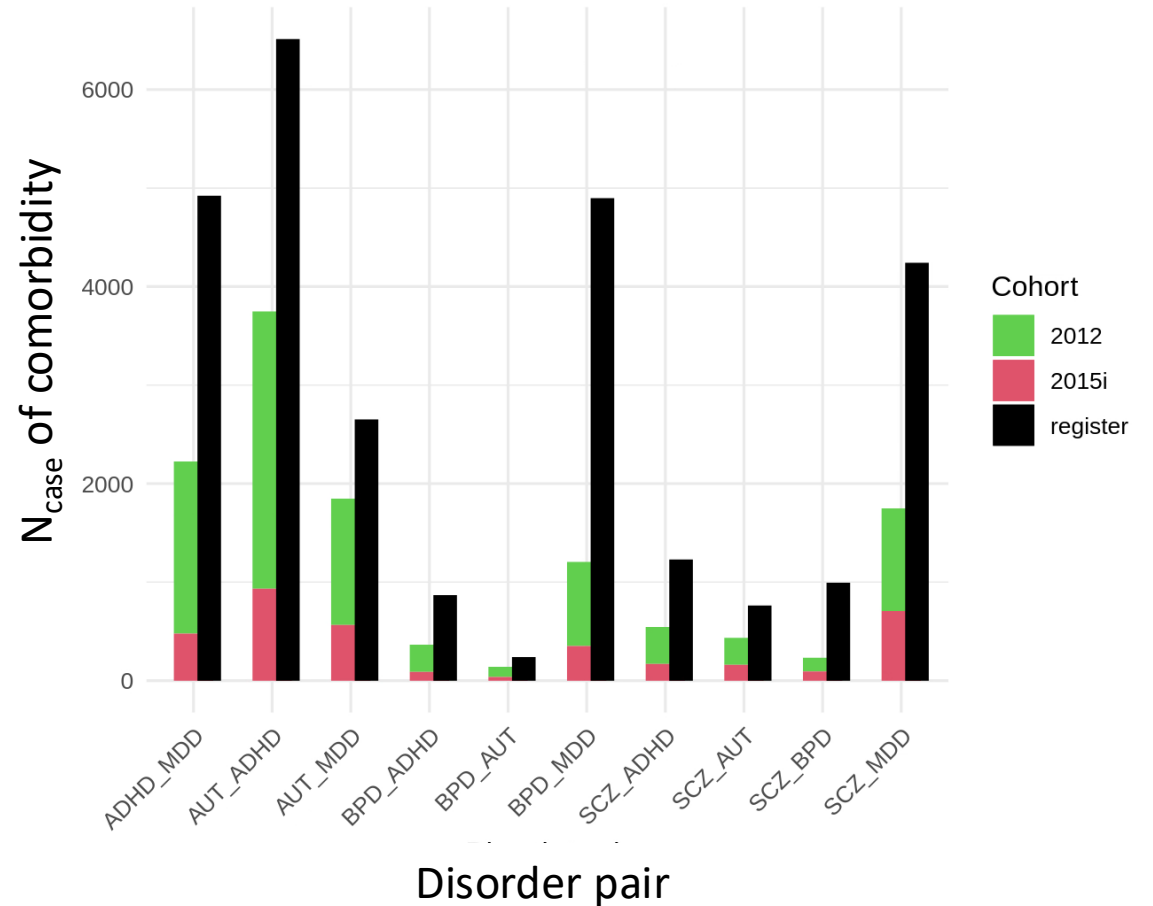
Phenotype definitions: Any

■ Random population controls

Phenotype definitions: Any

■ Random population controls

■ Disorder A

Phenotype definitions: Any

■ Random population controls
■ Disorder A
■ Disorder B

Phenotype definitions: Any

- ■ Random population controls
- ■ Disorder A
- ■ Disorder B
- ■ Comorbid

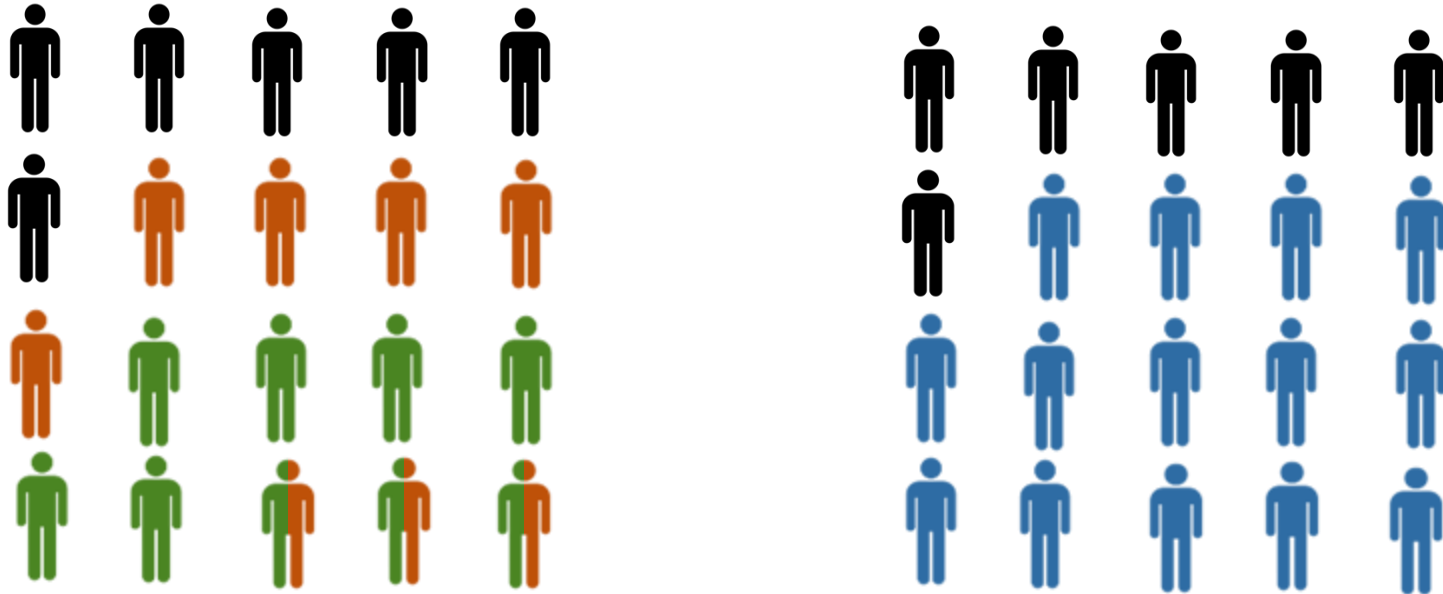# Phenotype definitions: Any

Random population controls

Disorder A

Disorder B

Comorbid

Phenotype cases: Any

Phenotype definitions: Any

Random population controls
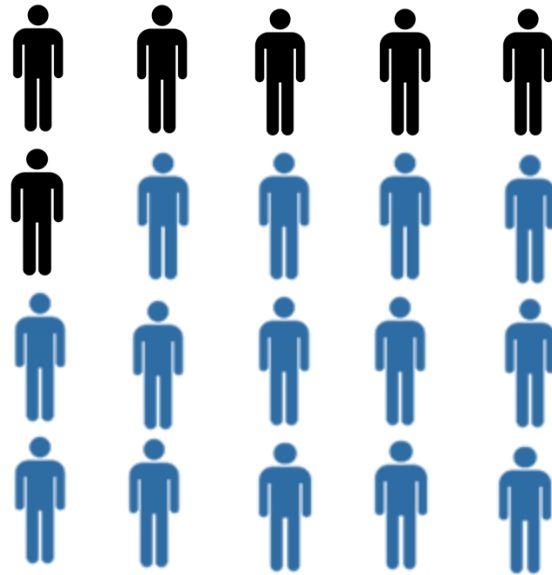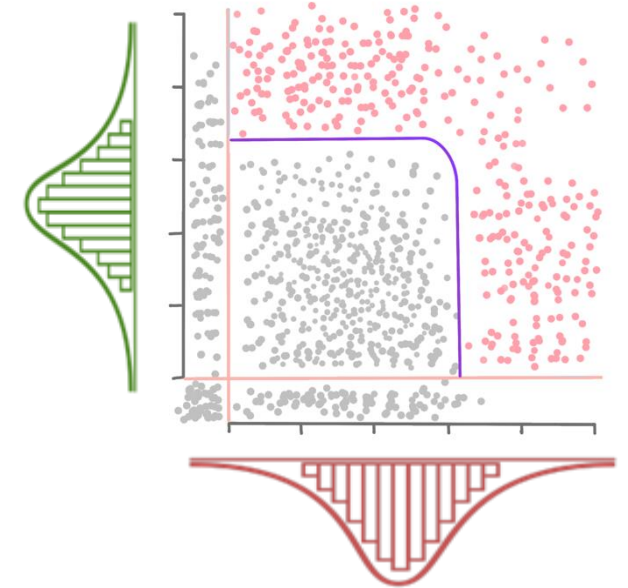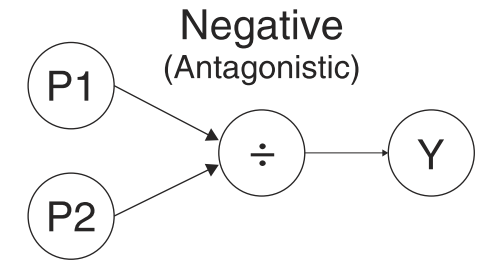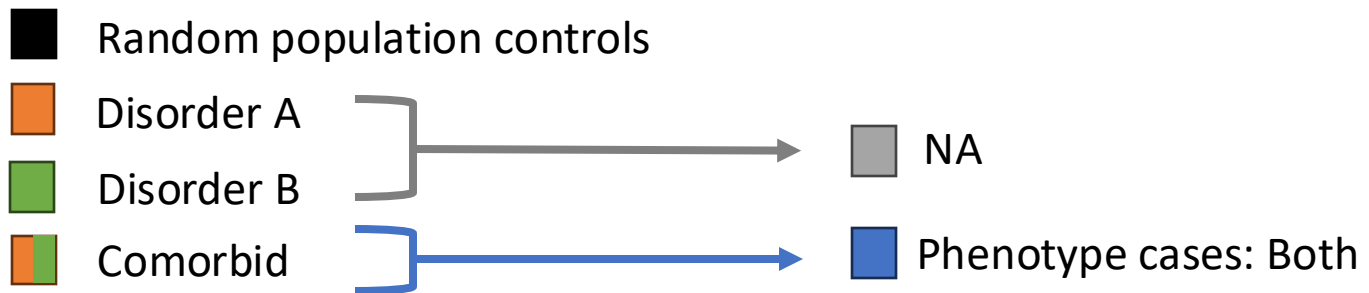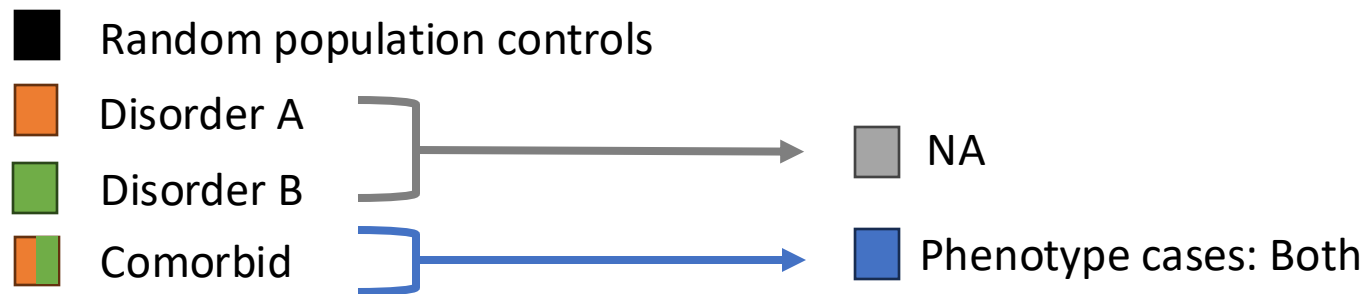Disorder A
Disorder B
Comorbid

Phenotype cases: Any

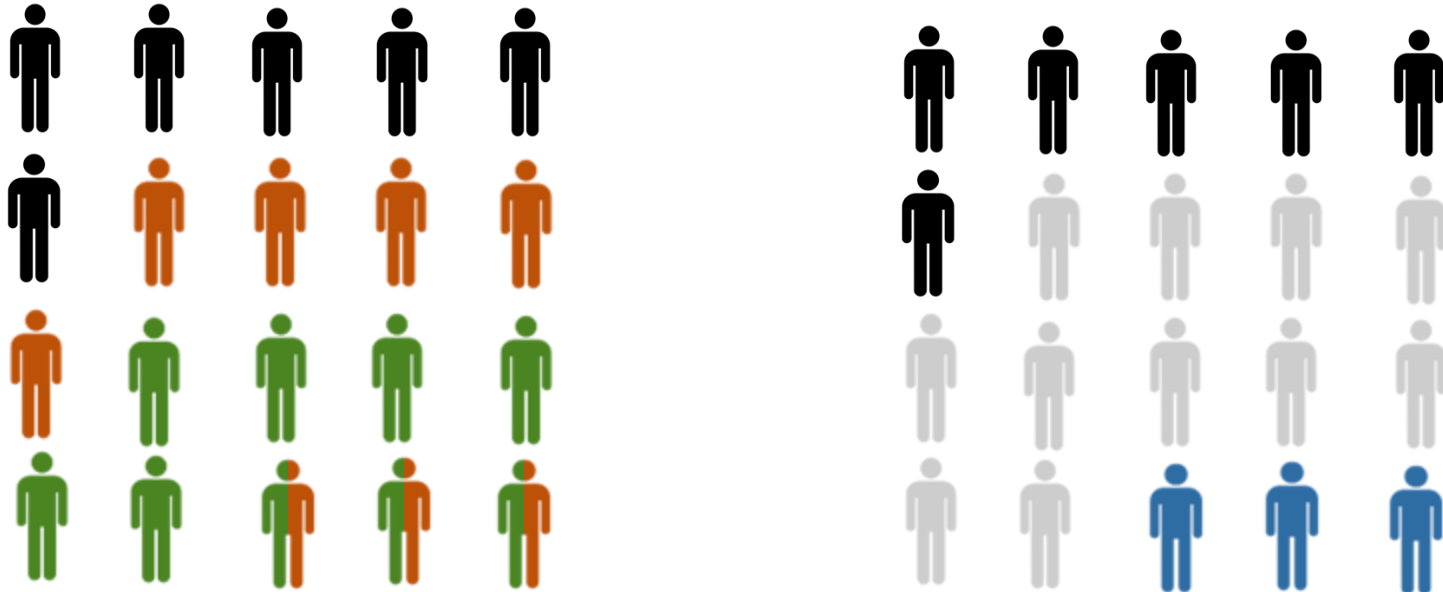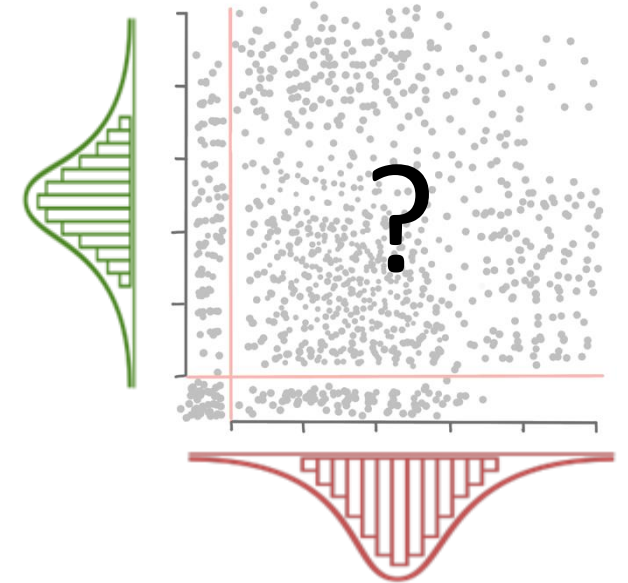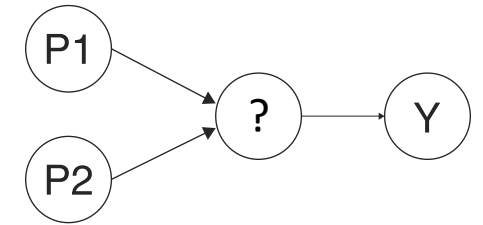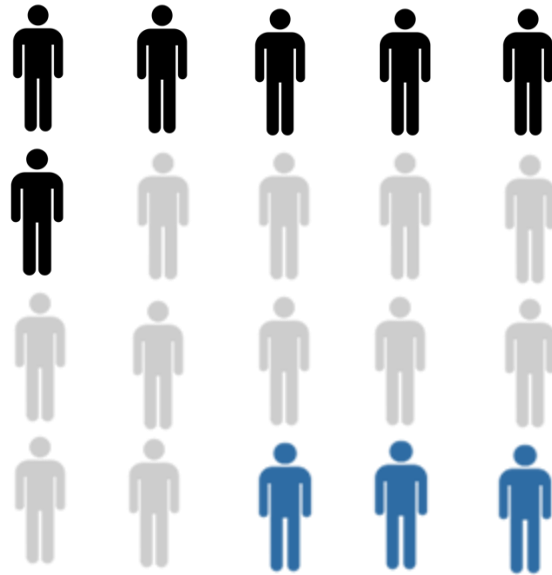# Phenotype definitions: Any

Phenotype definitions: Both

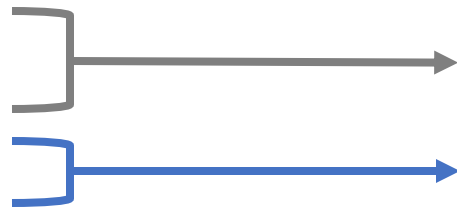# Phenotype definitions: Both

Phenotype definitions: Both

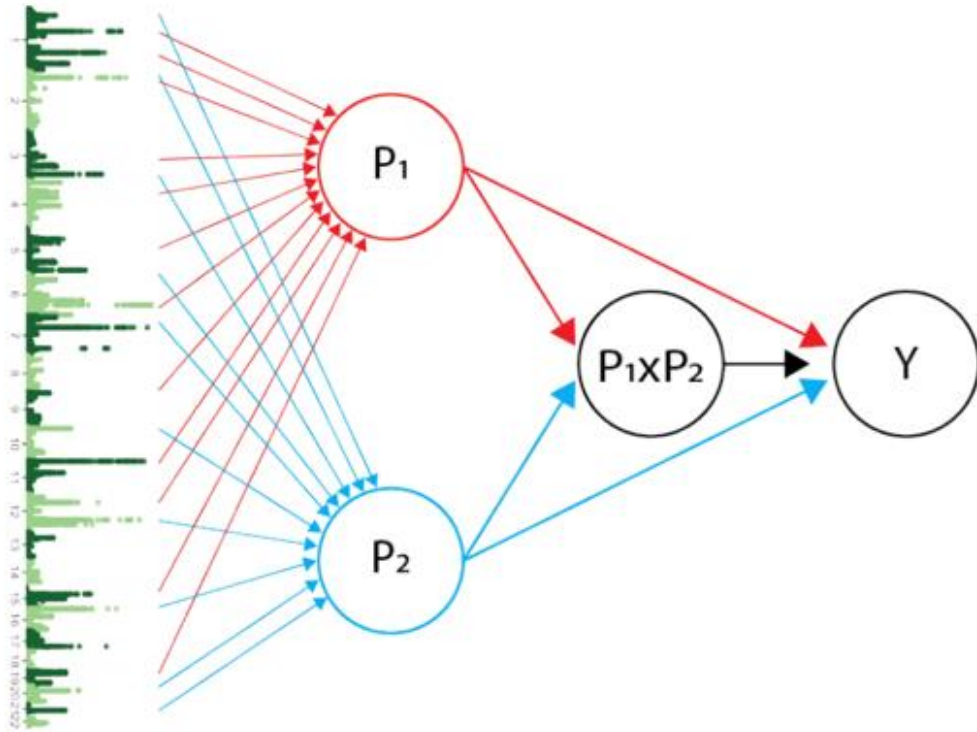Random population controls
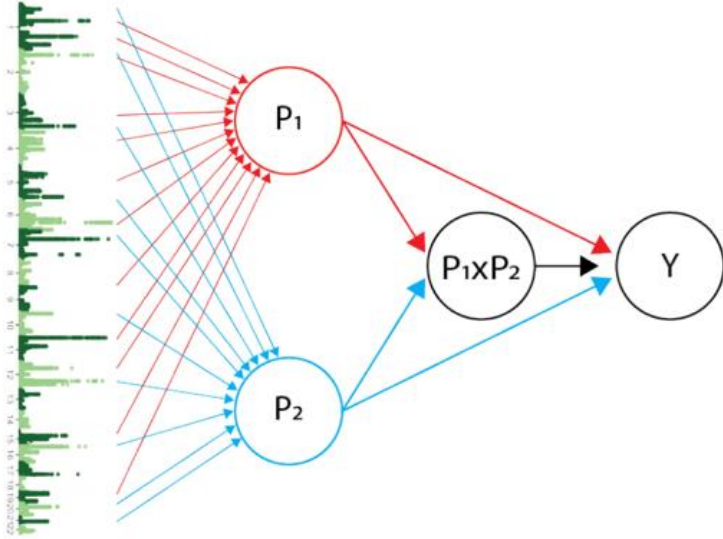Disorder A
Disorder B
Comorbid

NA

Phenotype cases: Both

How to test for disorder-specific pathway interactions?

Coordinated Epistasis (CE)

- $P_1 \approx$ PRS pathway 1
- $P_2 \approx$ PRS pathway 2

Tang D, et al. bioRxiv 2022, Sheppard, B. et al. PNAS 2022

Coordinated Epistasis (CE)

$$y \sim \alpha_i PRS_i + \alpha_j PRS_j + \boldsymbol{\gamma_{i,j}} PRS^* PRS_j$$

PRS = Polygenic Risk Score

i = disorder A

j = disorder B

i ≠ j

Tang D, et al. bioRxiv 2022, Sheppard, B. et al. PNAS 2022

Coordinated Epistasis (CE)

$$y \sim \alpha_i PRS_i + \alpha_j PRS_j + \boxed{\gamma_{i,j}} PRS^* PRS_j$$

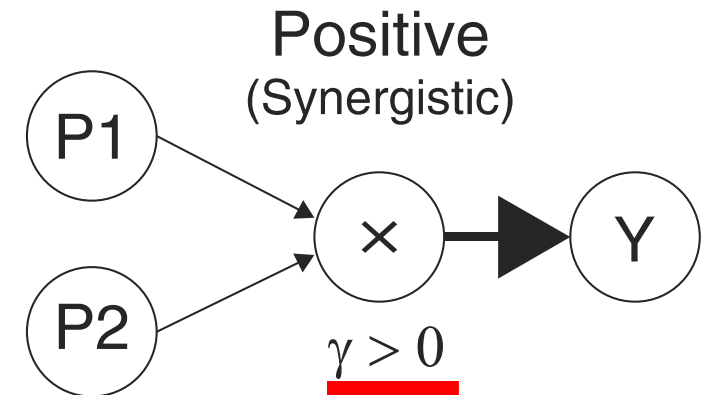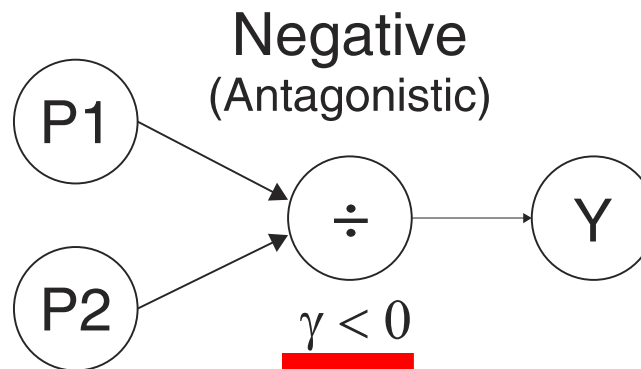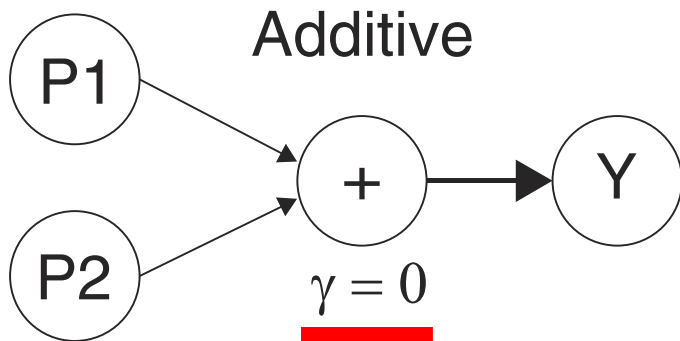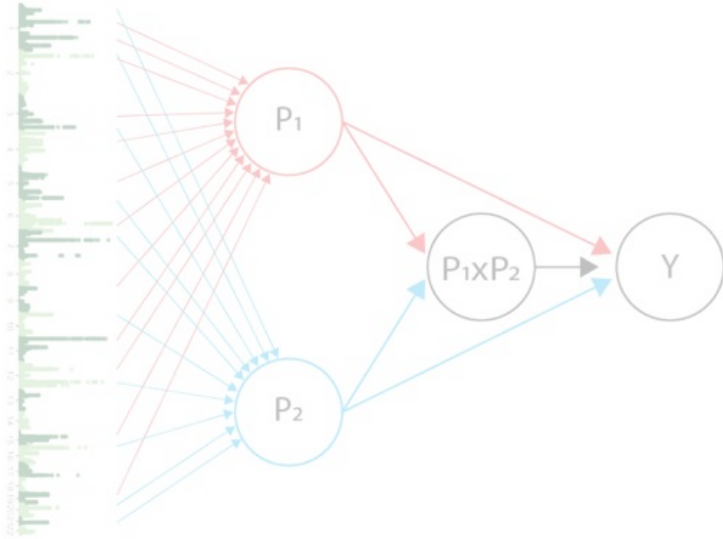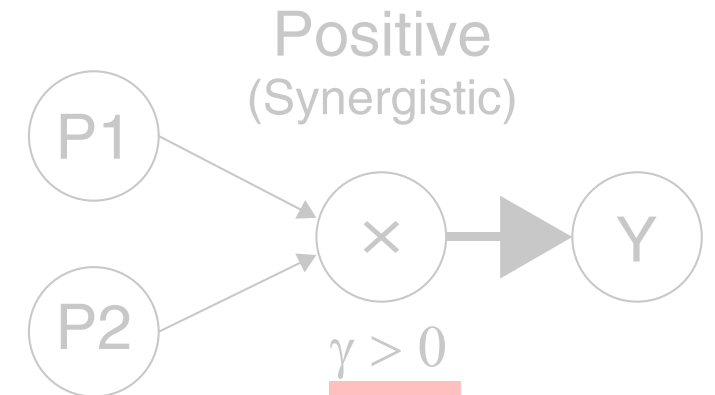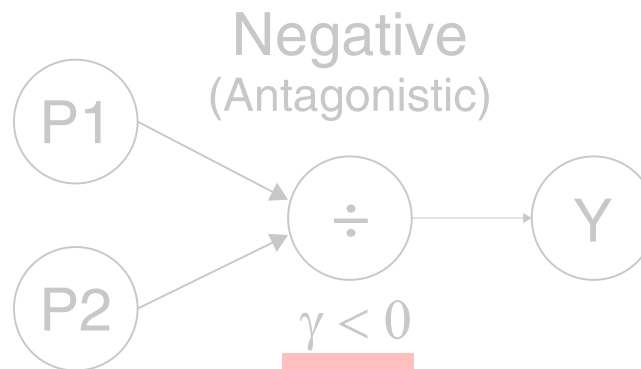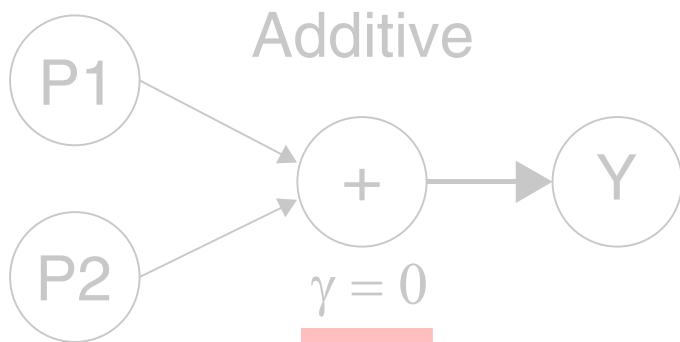PRS = Polygenic Risk Score

i = disorder A

j = disorder B

$i \neq j$

Tang D, et al. bioRxiv 2022, Sheppard, B. et al. PNAS 2022

Coordinated Epistasis (CE)

$$y \sim \alpha_i PRS_i + \alpha_j PRS_j + \boxed{\gamma_{i,j}} PRS * PRS_j$$
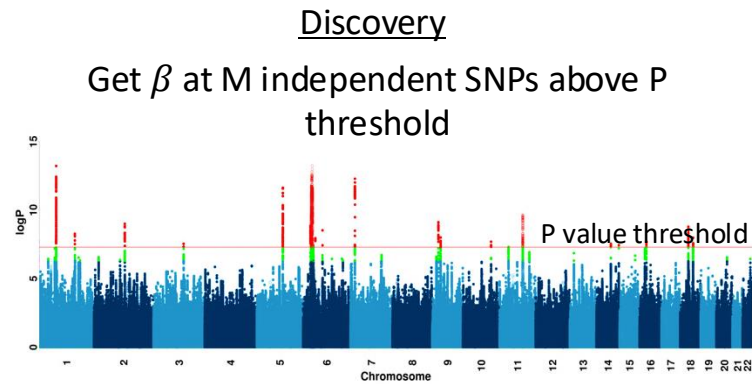
PRS = Polygenic Risk Score

i = disorder A
j = disorder B

i ≠ j

Additive
$\gamma = 0$

Negative
(Antagonistic)
$\gamma < 0$

Positive
(Synergistic)
$\gamma > 0$

Tang D, et al. bioRxiv 2022, Sheppard, B. et al. PNAS 2022

Coordinated Epistasis (CE)

$$y \sim \alpha_i PRS_i \,+\, \alpha_j PRS_j \,+\, \boxed{\gamma_{i,j}}\, PRS^* \, PRS_j$$

PRS = Polygenic Risk Score

i = disorder A
j = disorder B

$i \neq j$

Additive

$\gamma = 0$

Negative
(Antagonistic)

$\gamma < 0$

Positive
(Synergistic)

$\gamma > 0$

Tang D, et al. bioRxiv 2022, Sheppard, B. et al. PNAS 2022

PRS as pathway representation in CE

Polygenic Risk Scores (PRS)

Discovery

Get β at M independent SNPs above P threshold

P value threshold
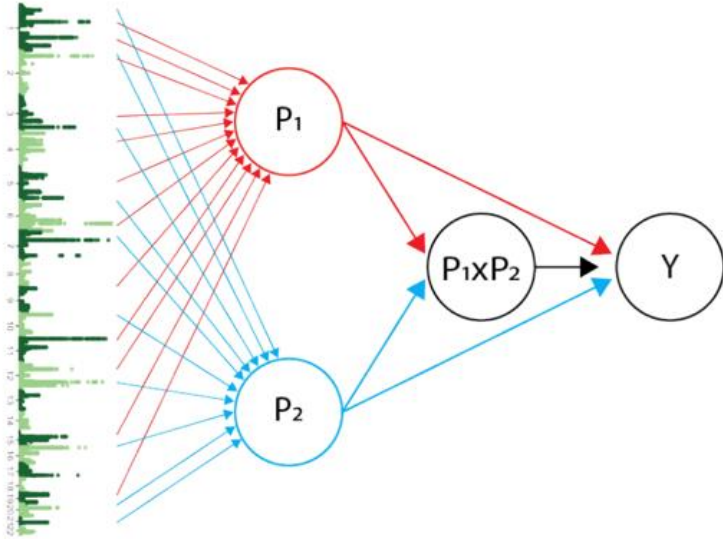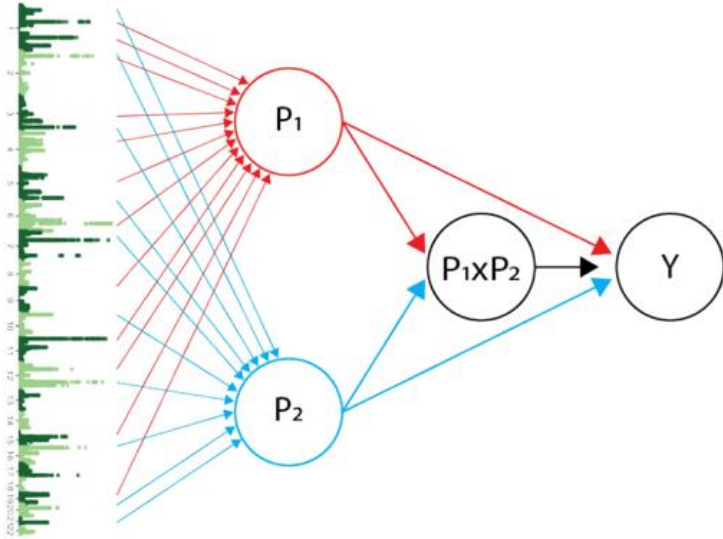
Test

Get **genotypes** at same M independent SNPs X

Get PRS = $\sum_i^M \beta_i X_i$

PA-FGRS as pathway representation in CE

Polygenic Risk Scores (PRS)

Pearson-Aitkens Family Genetic Risk Score (PA-FGRS)
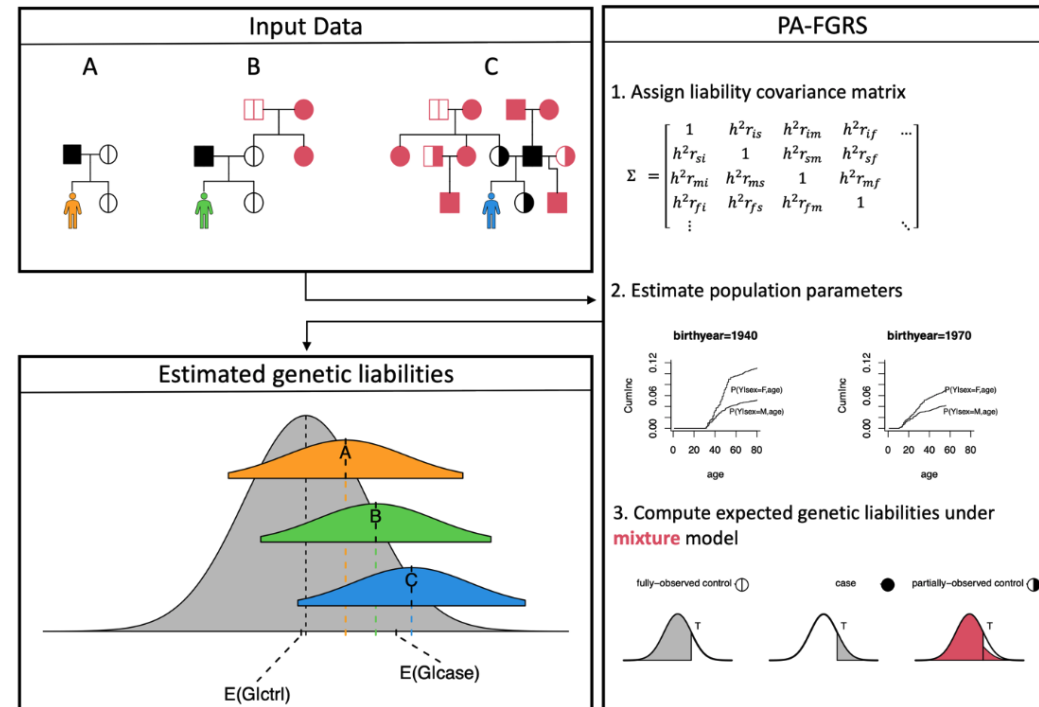
PA-FGRS and PRS capture overlapping and distinct genetic liability

Adjusted Fig. 1A, Krebs et al. MedRxiv 2023
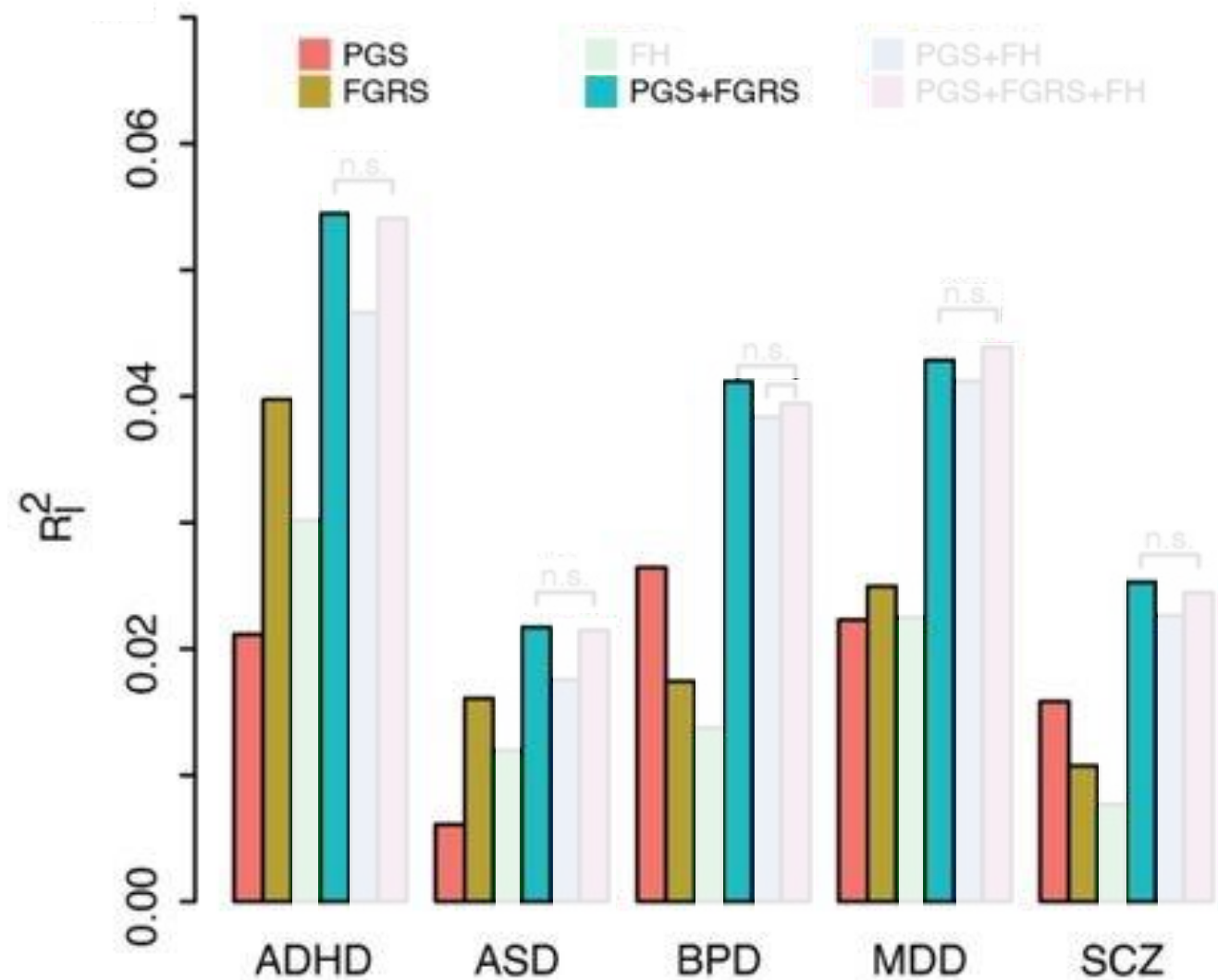
Disorder-specific pathway relations towards comorbidity phenotypes

PRS / PA-FGRS
disorder A

PRS / PA-FGRS
disorder B

$\gamma = ?$

- Any
- Both

Phenotype definitions: Any

Random population controls

Disorder A

Disorder B

Comorbid

Phenotype cases: Any

Negative
(Antagonistic)

P1

P2

÷

Y
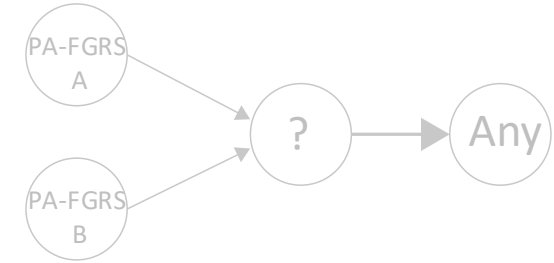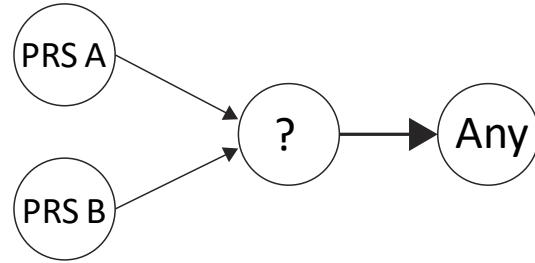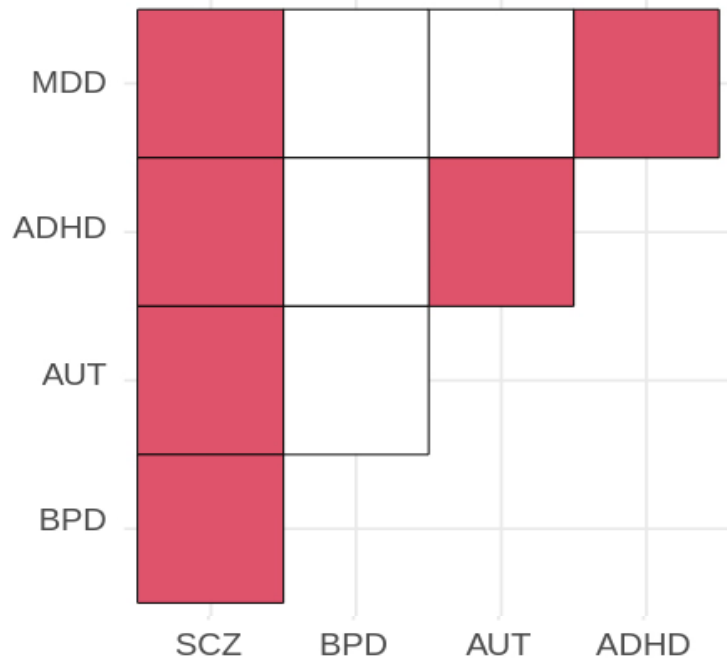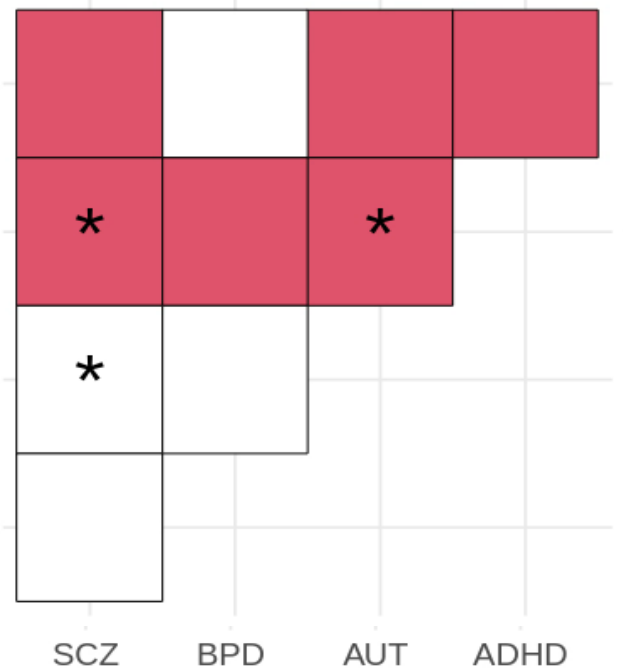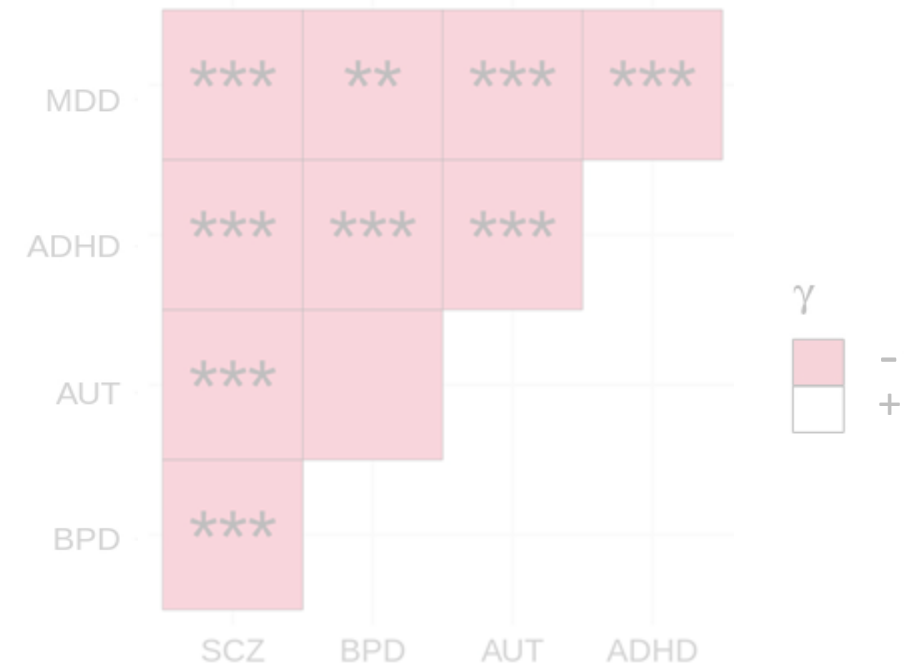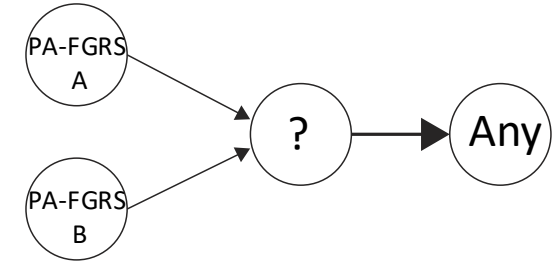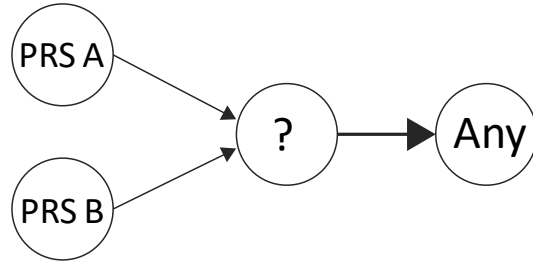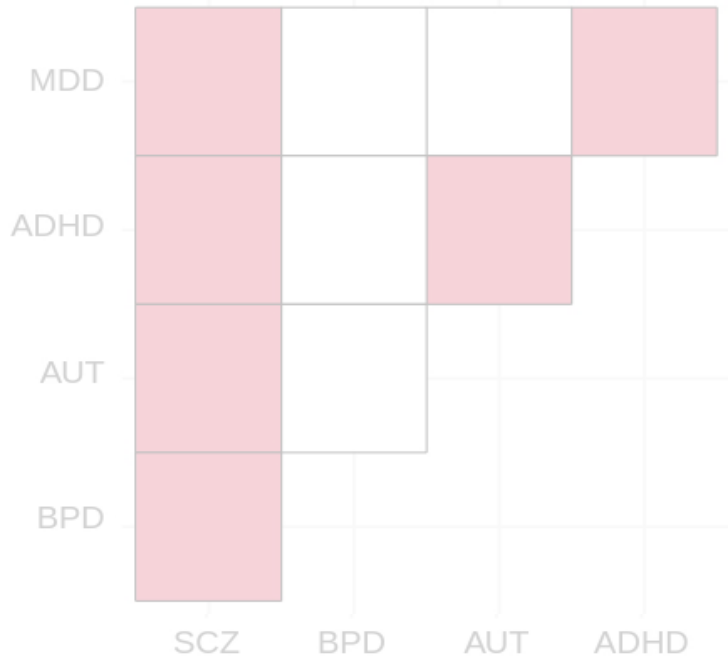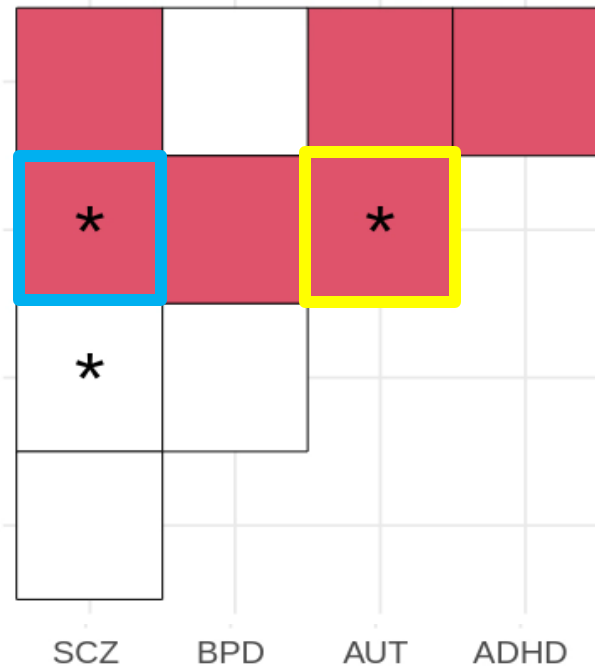
Results: the "any" phenotype
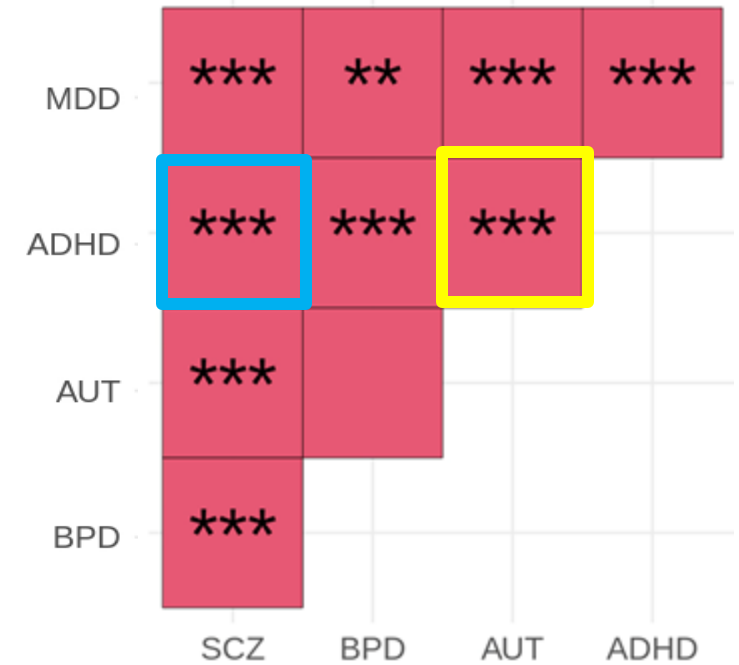
* p < 0.05 ; ** p < 0.005 ; *** p < 0.0005

Results: the "any" phenotype

* p < 0.05 ; ** p < 0.005 ; *** p < 0.0005

Results: the "any" phenotype

* p < 0.05 ; ** p < 0.005 ; *** p < 0.0005

Results: the "any" phenotype

* p < 0.05 ; ** p < 0.005 ; *** p < 0.0005

Results: the "any" phenotype

* p < 0.05 ; ** p < 0.005 ; *** p < 0.0005

Phenotype definitions: Both
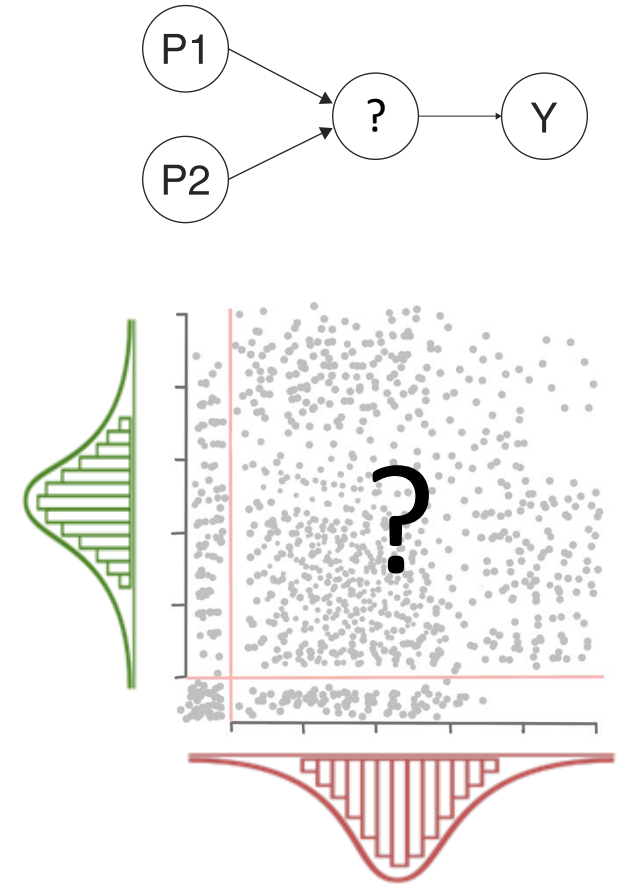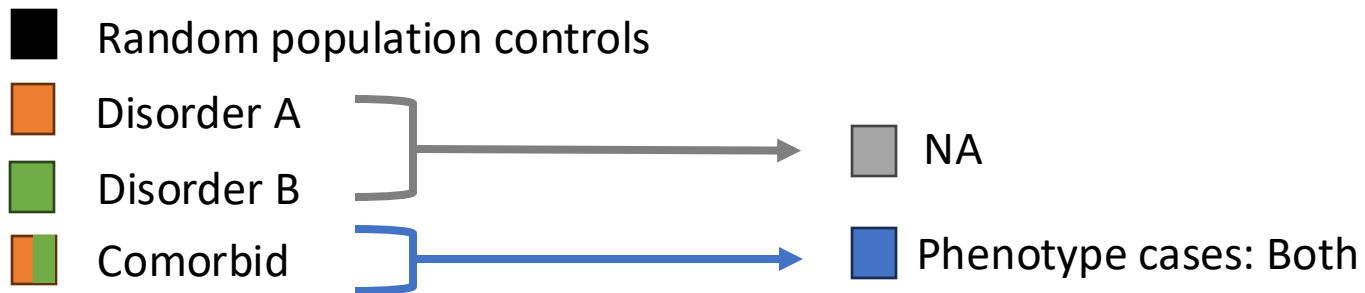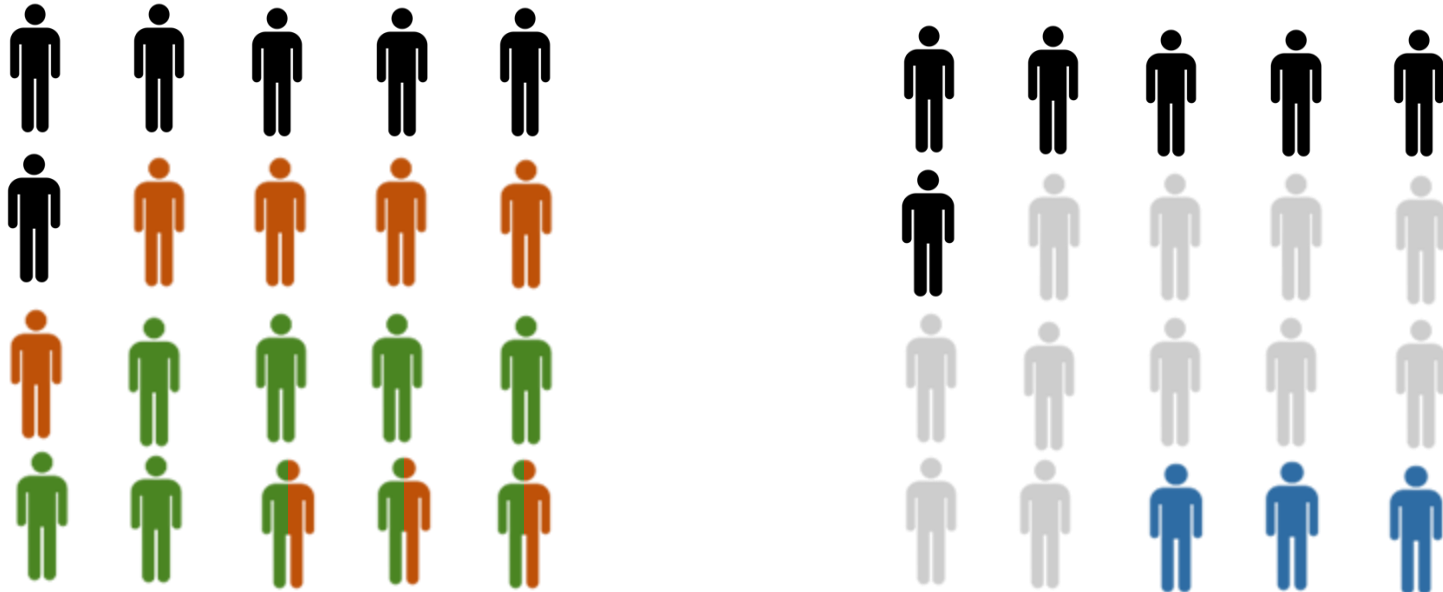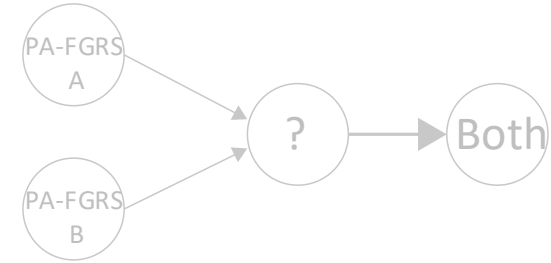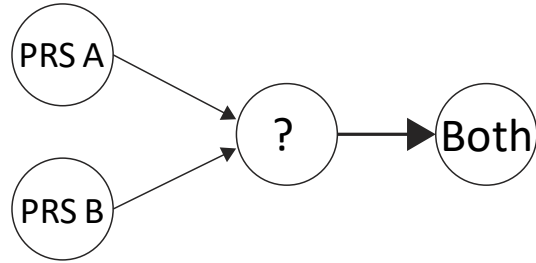
Random population controls

Disorder A

Disorder B

Comorbid

NA

Phenotype cases: Both
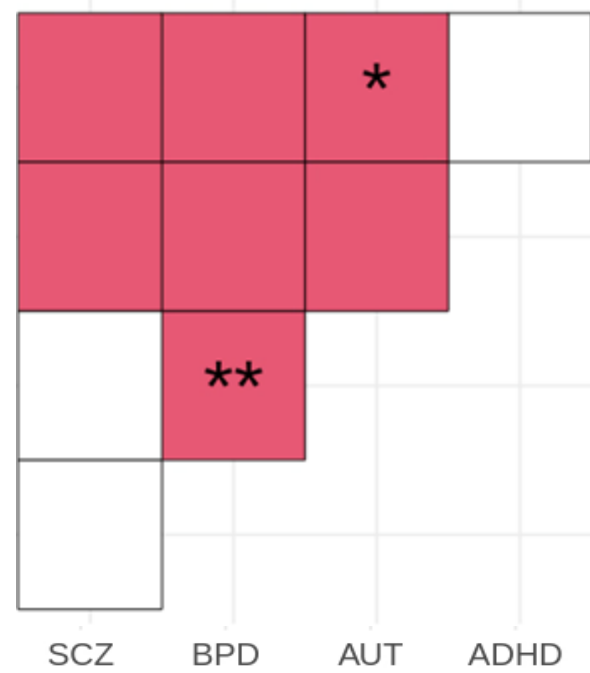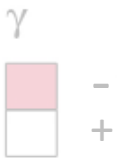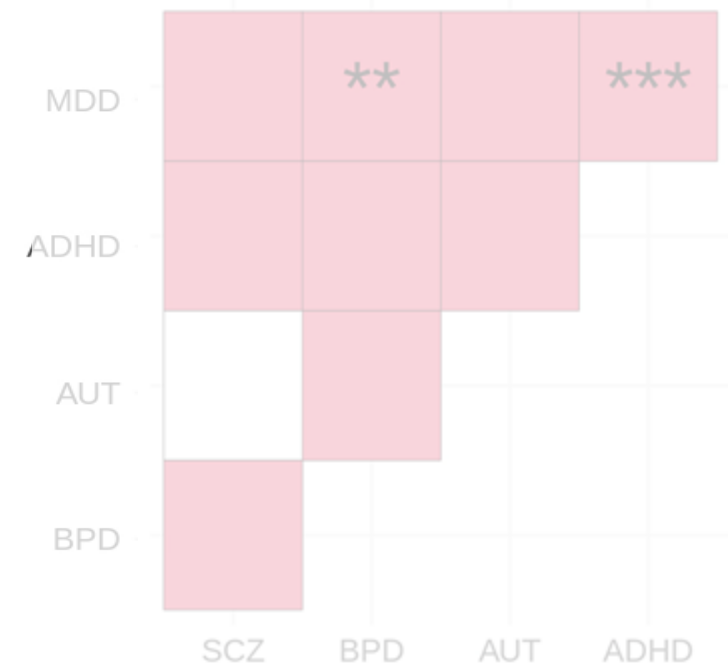
Results: the "both" phenotype
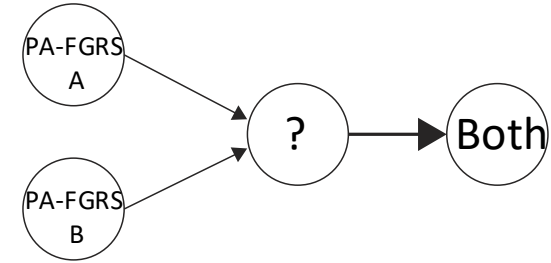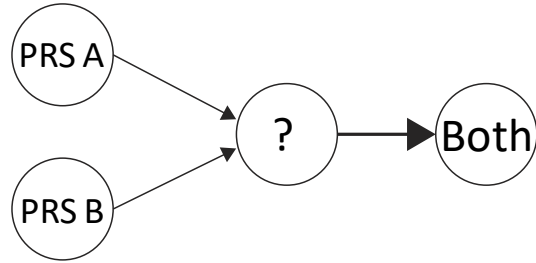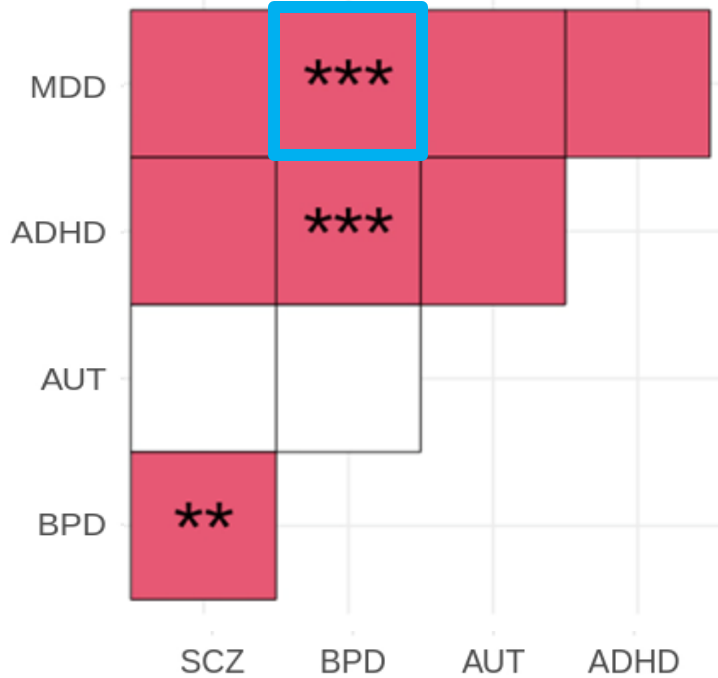
* p < 0.05 ; ** p < 0.005 ; *** p < 0.0005
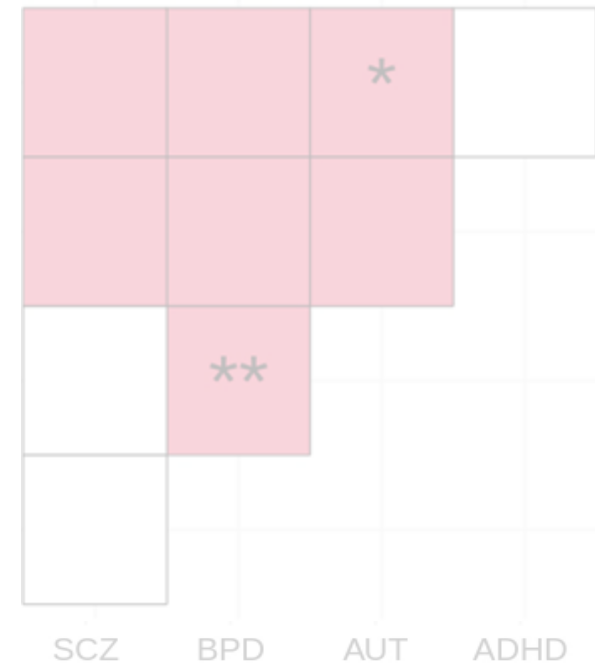
Results: the "both" phenotype
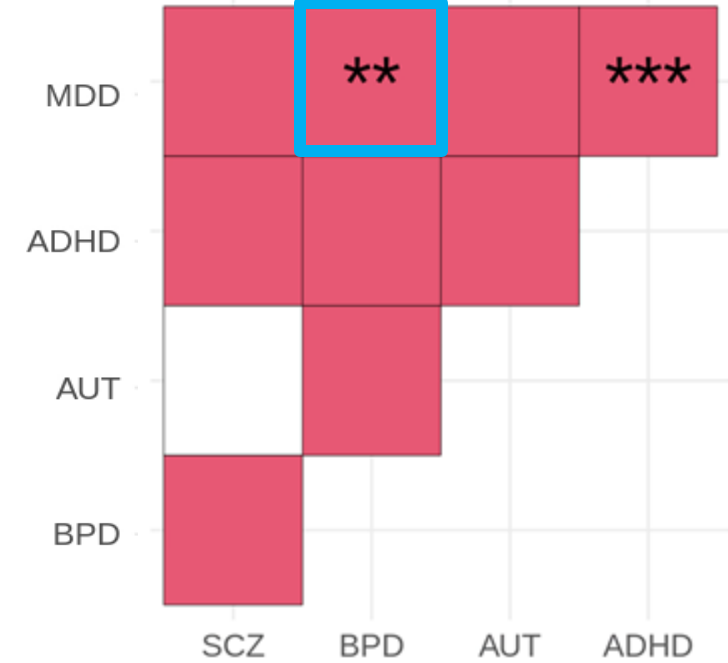
* p < 0.05 ; ** p < 0.005 ; *** p < 0.0005

Meta-analyses using METAL
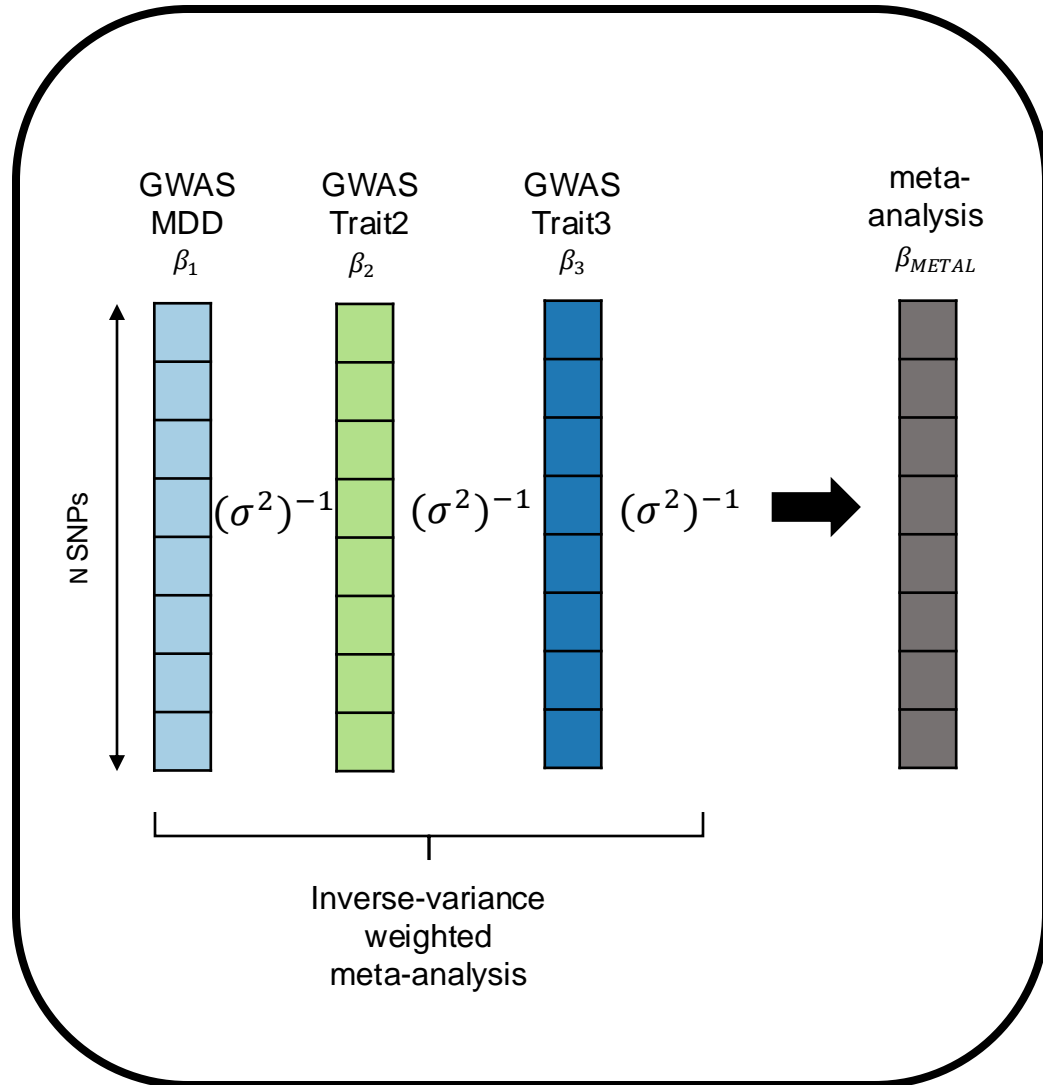
Meta-analyses using METAL and MTAG

Recall: the "any" phenotype results

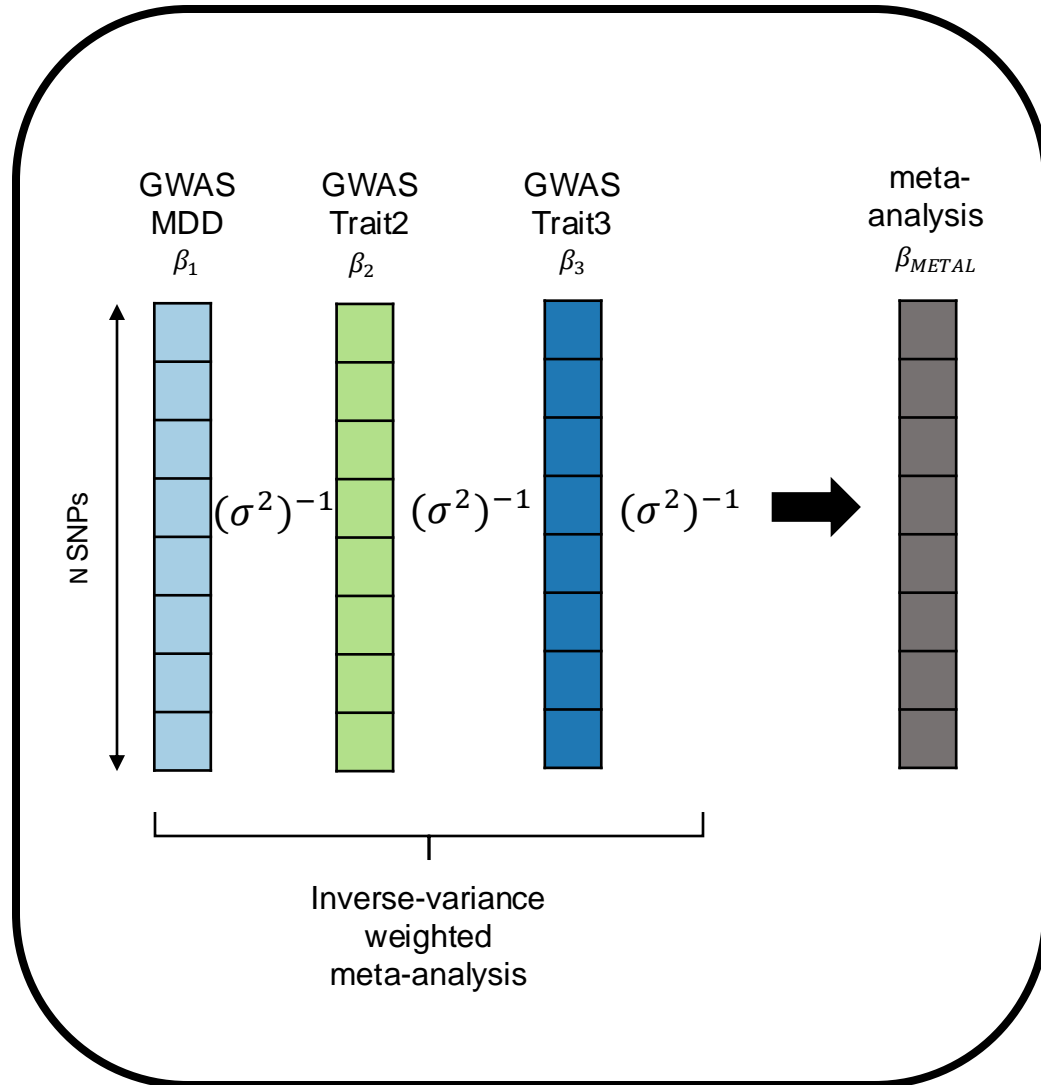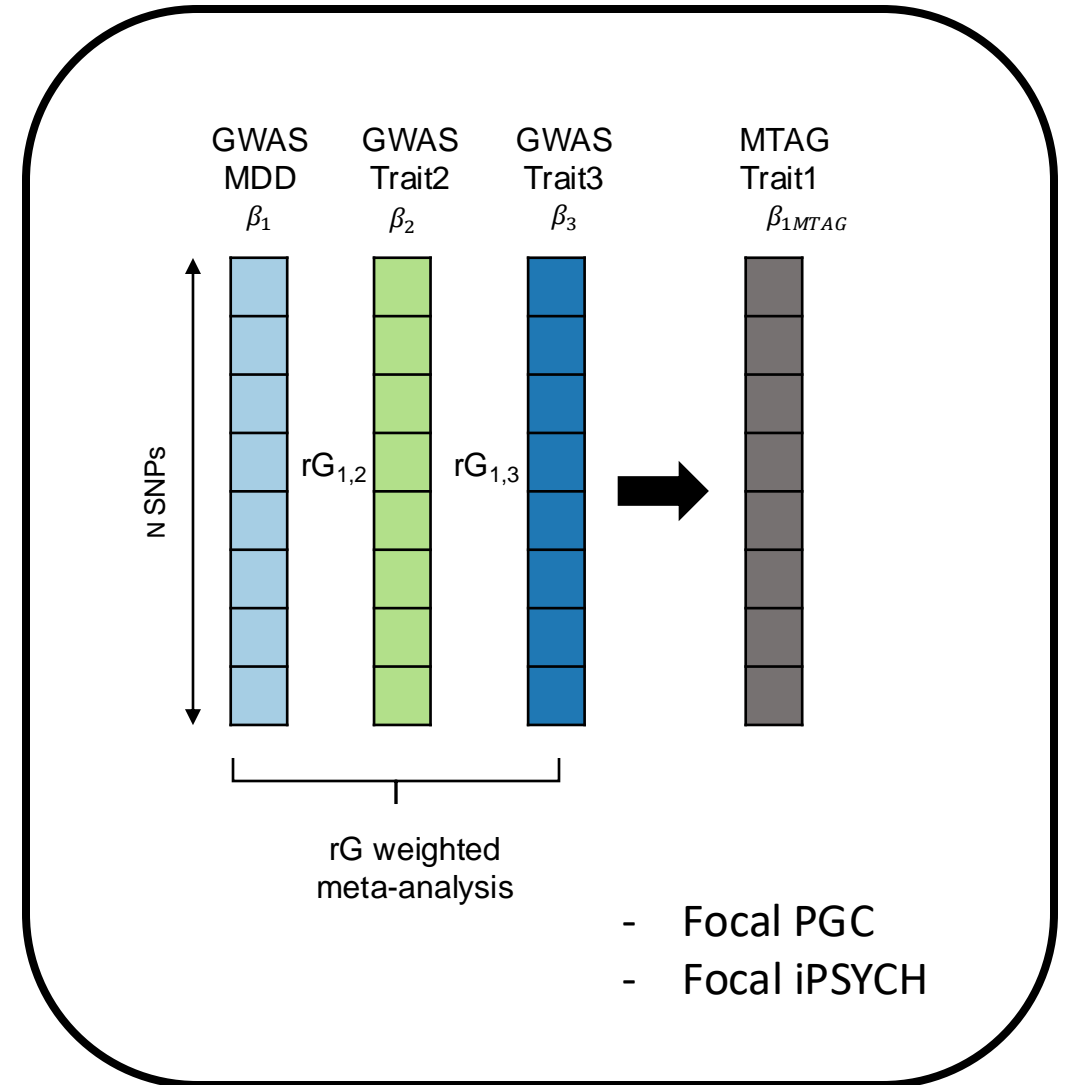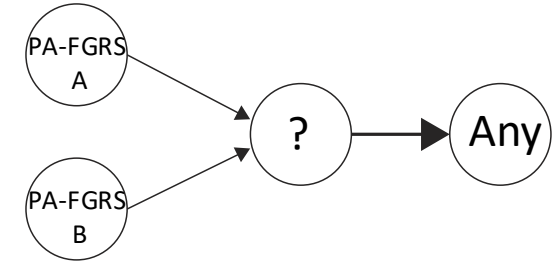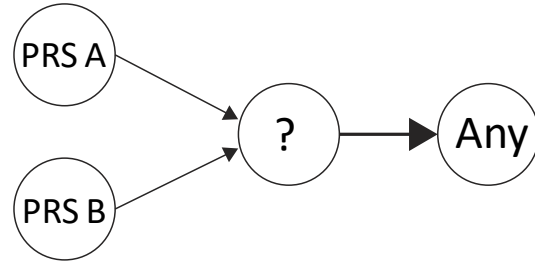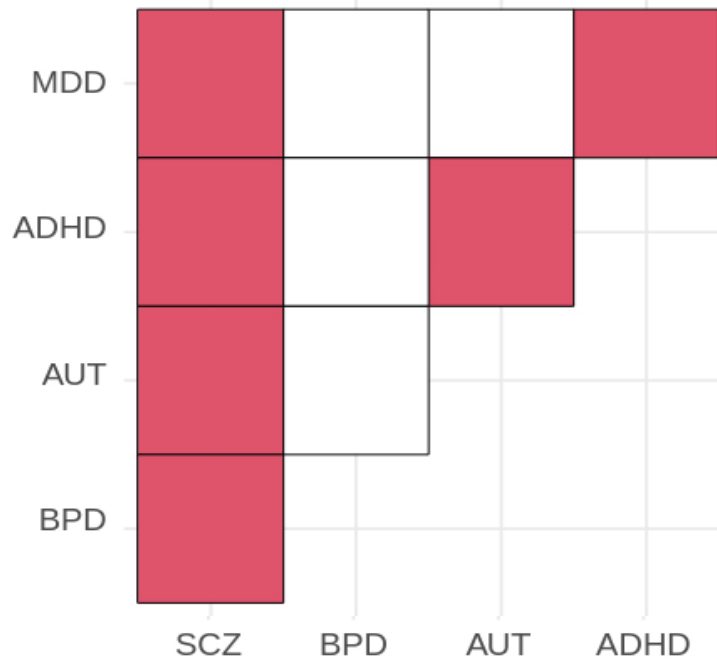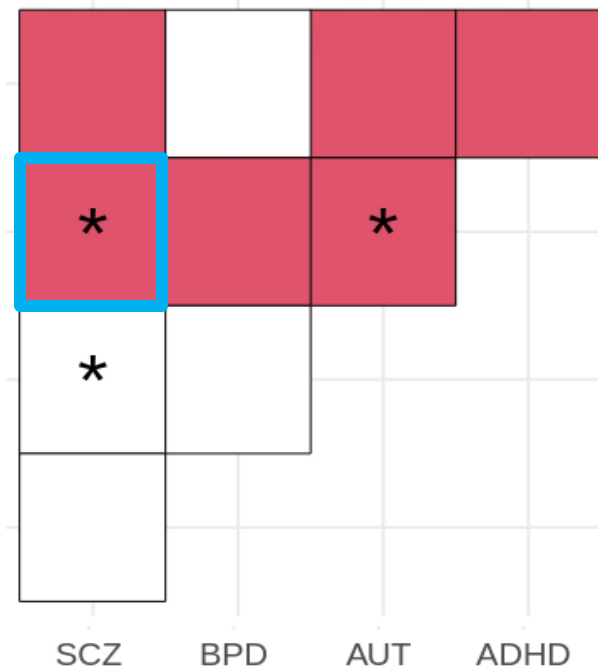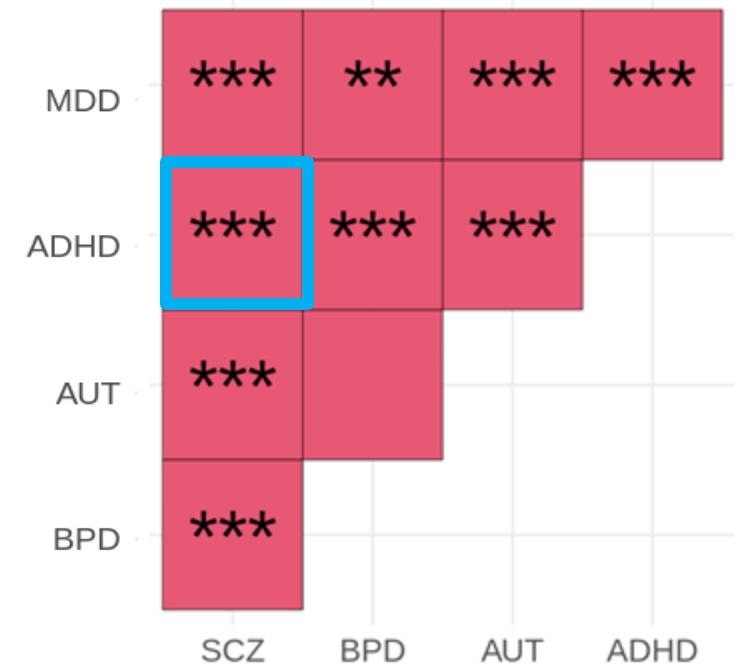* p < 0.05 ; ** p < 0.005 ; *** p < 0.0005

Meta-analyses in CE: consistency is promising

Summary

- We find that disorder-specific polygenic pathway contribute to comorbid phenotypes, through both positive and negative interactions

- We find consistent interaction effects between PRS and PA-FGRS in most instances

- We find PRS trained using meta-analyzed GWAS improve power over single-cohort PRS to detect interactions

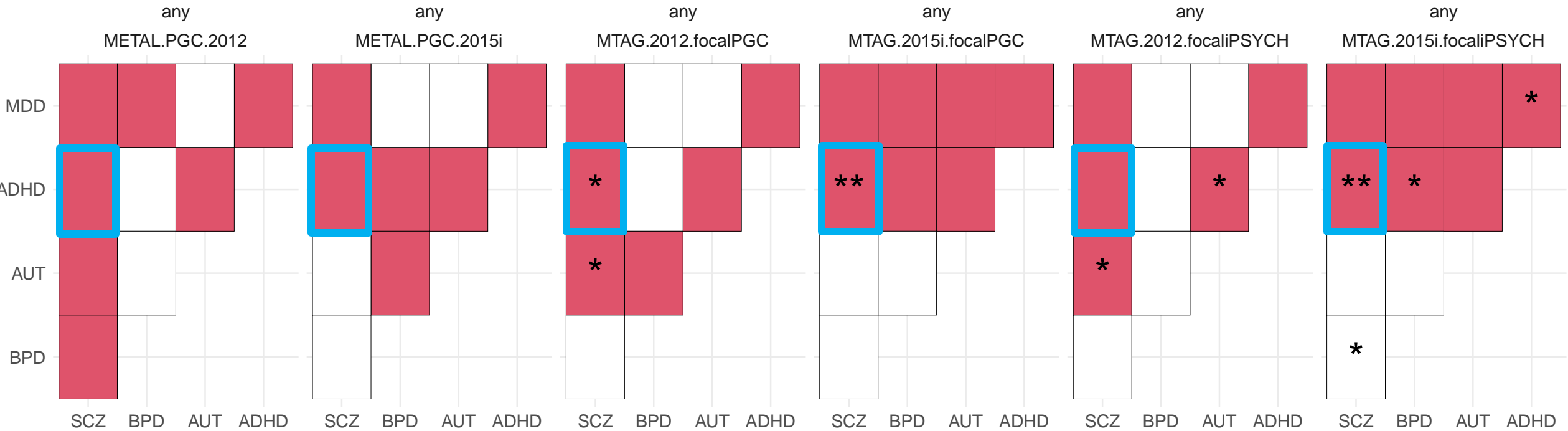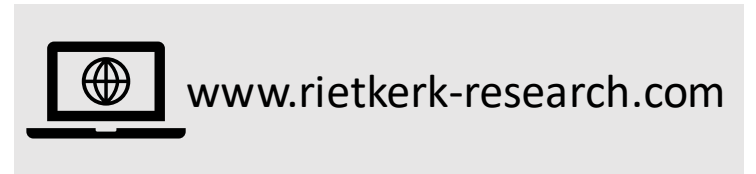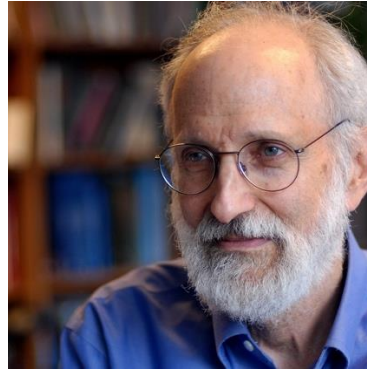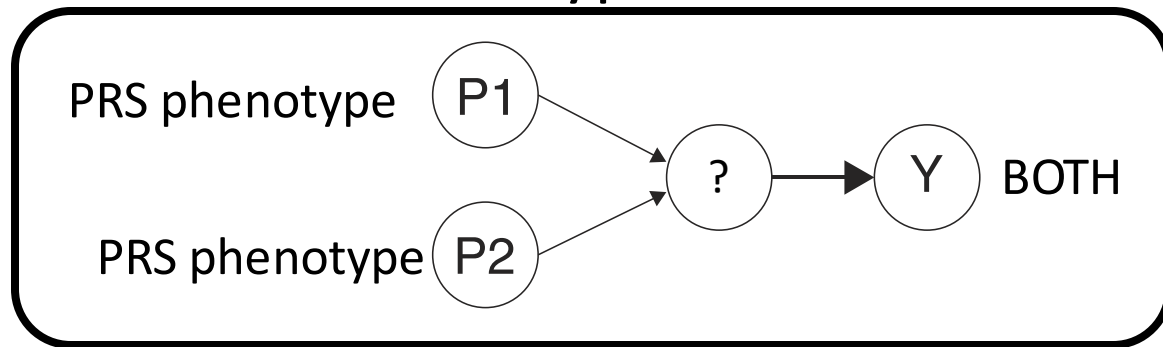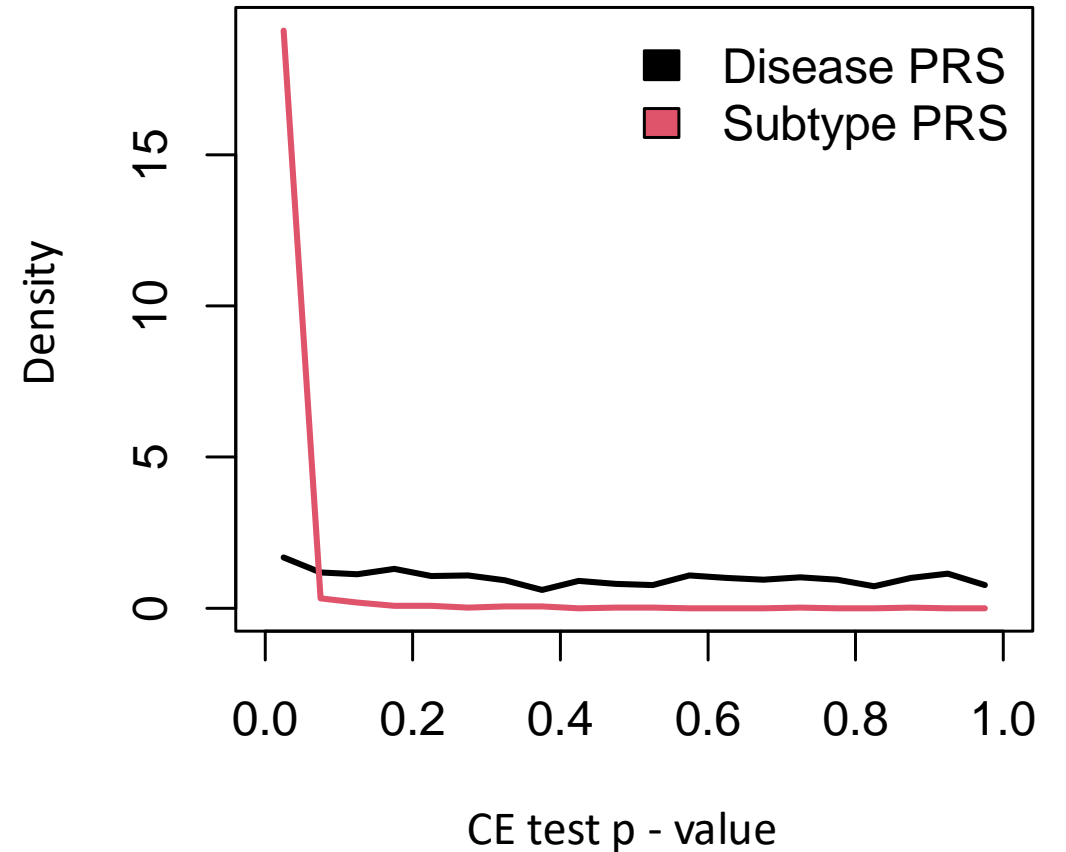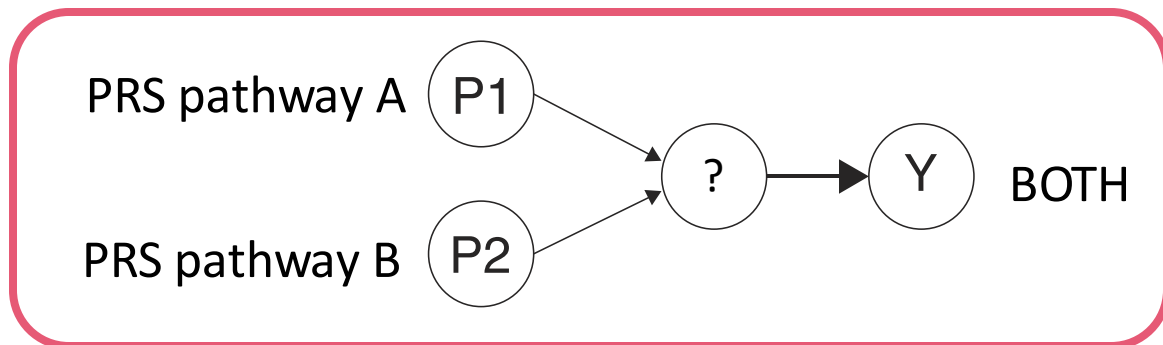# Acknowledgements

Future plans

- Investigate effect of meta-analysis on Coordinated Epistasis
- Investigate differences between PRS and PA-FGRS
- Additional simulations to validate method adjustments

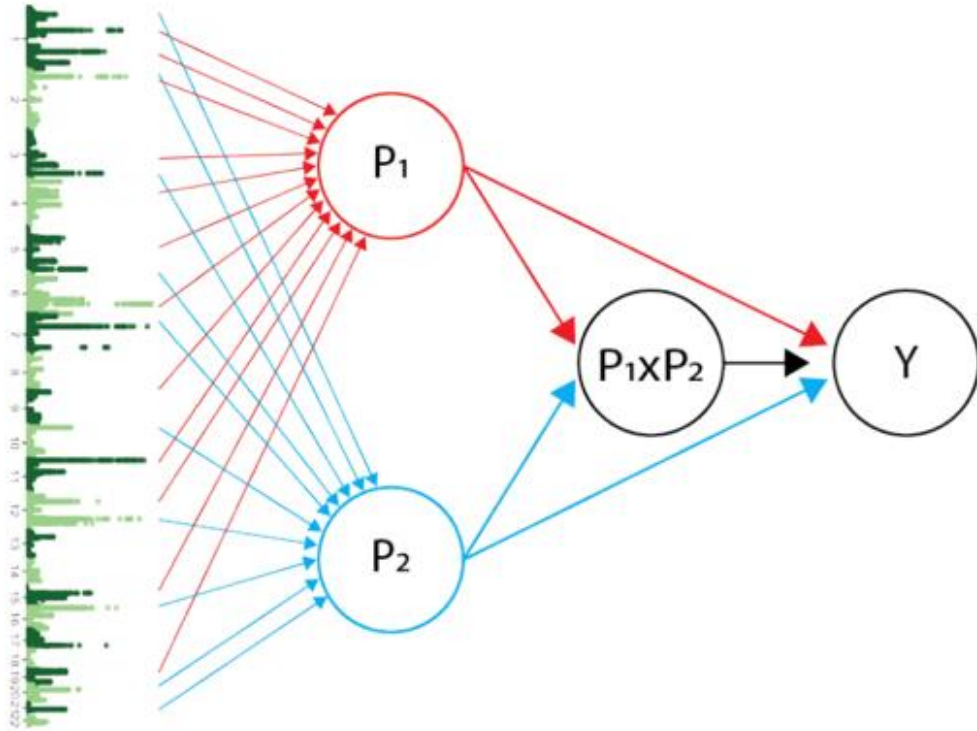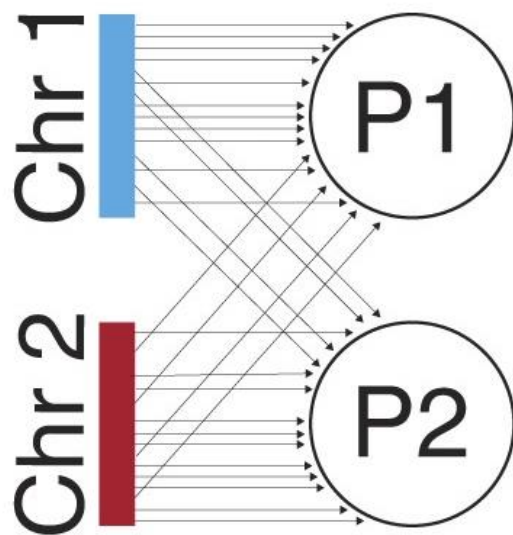# Knowing true subtypes gives highest power

Coordinated Epistasis (CE)

- P$_1$ ≈ PRS pathway 1
- P$_2$ ≈ PRS pathway 2

- Pathway specific variants are distributed across the genome

Tang D, et al. bioRxiv 2022, Sheppard, B. et al. PNAS 2022

Chromosome as partitions

$$y \sim \alpha_i PRS_i + \alpha_j PRS_j + \boldsymbol{\gamma_{i,j}}\ PRS_i{}^* PRS_j$$

$i,j \in \{1..22\}, i \neq j$

In total, 231 pairs of chromosomes

Tang D, et al. bioRxiv 2022, Sheppard, B. et al. PNAS 2022