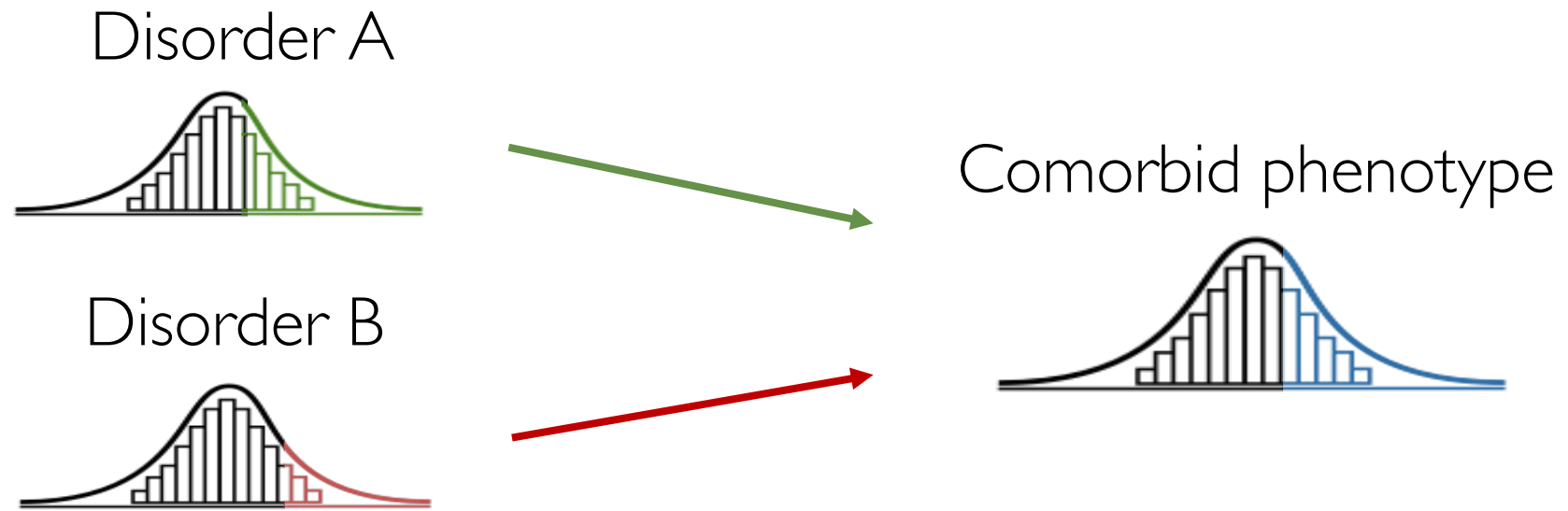


Using Coordinated Epistasis to Investigate Genetic Architecture of Psychiatric Comorbidity

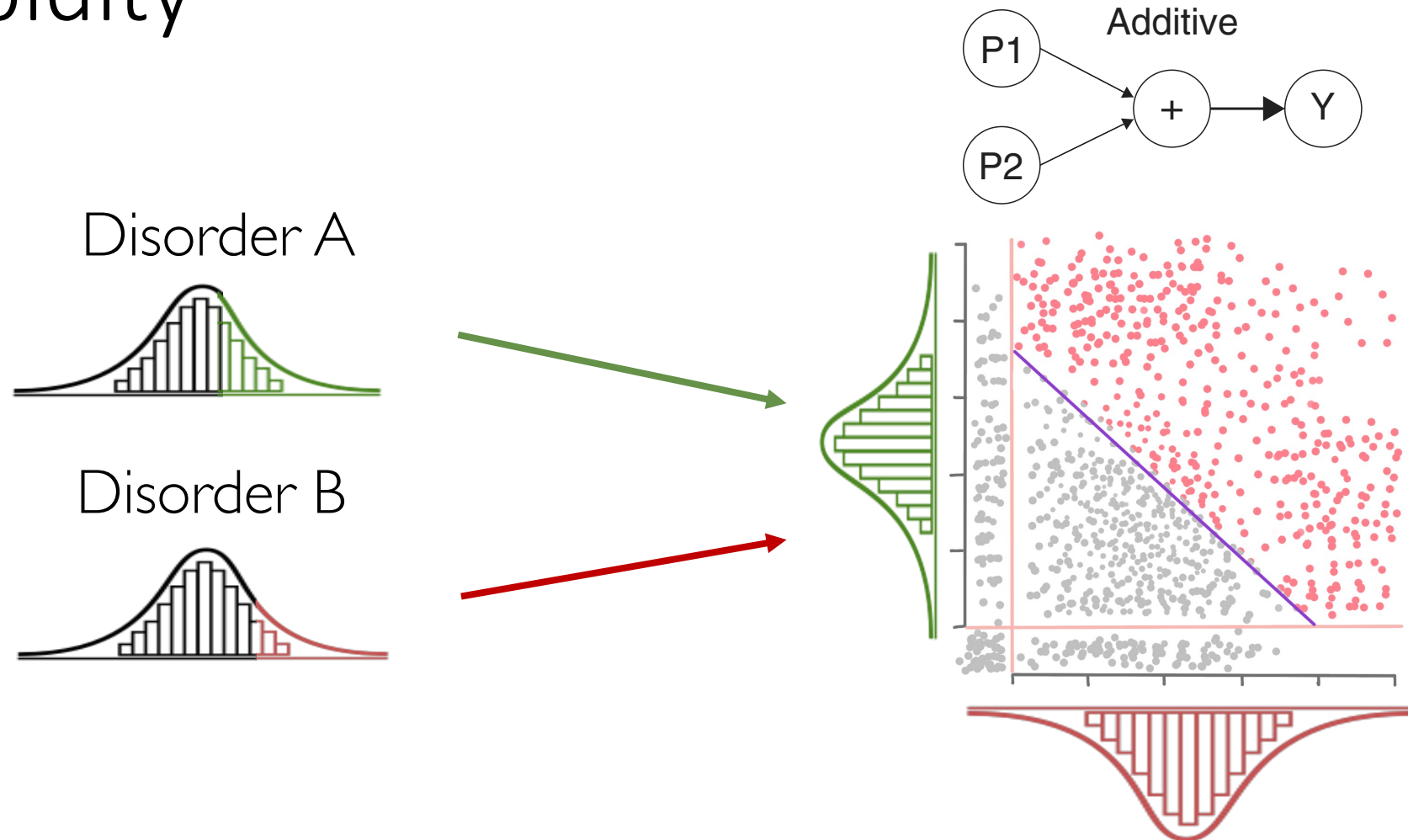
Jolien Rietkerk, Morten Krebs, Lianyun Huang, iPSYCH Study Consortium, Thomas Werge, Andrew J. Schork, Andy Dahl, Na Cai

54th Annual Meeting of the Behavior Genetics Association
June 28th 2024, London

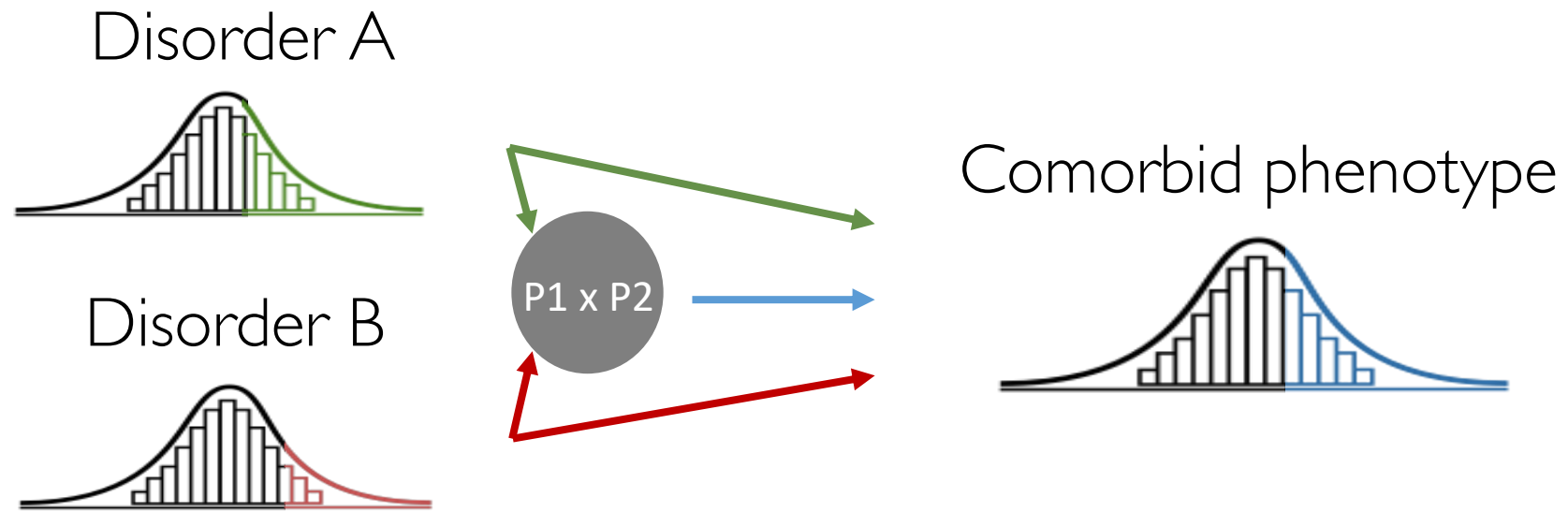
(Psychiatric) Comorbidity



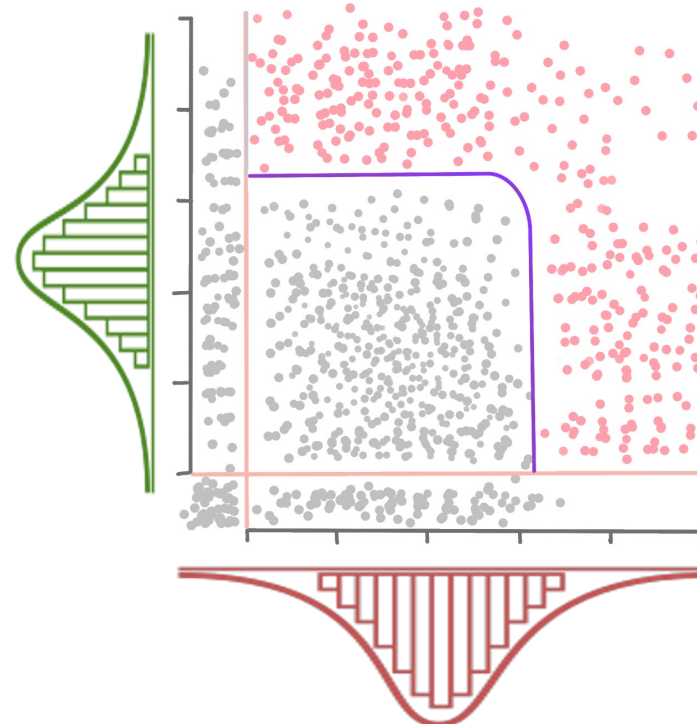
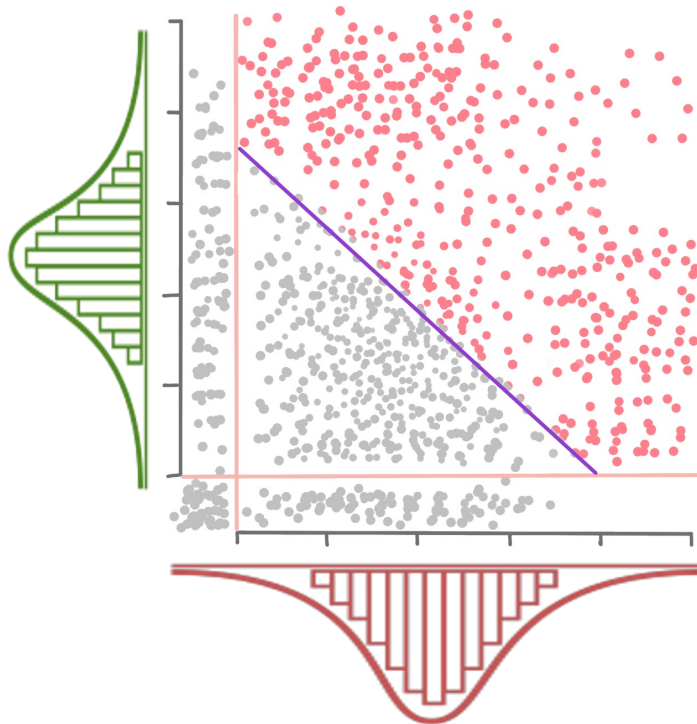
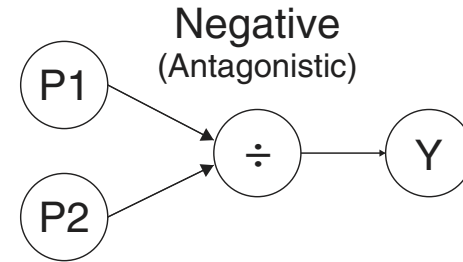
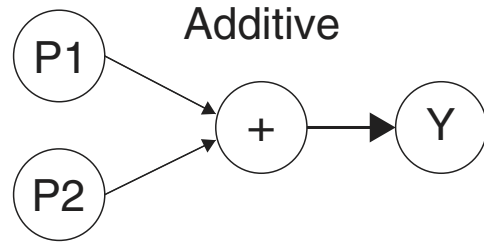
Disorder-specific pathways contributing to comorbidity



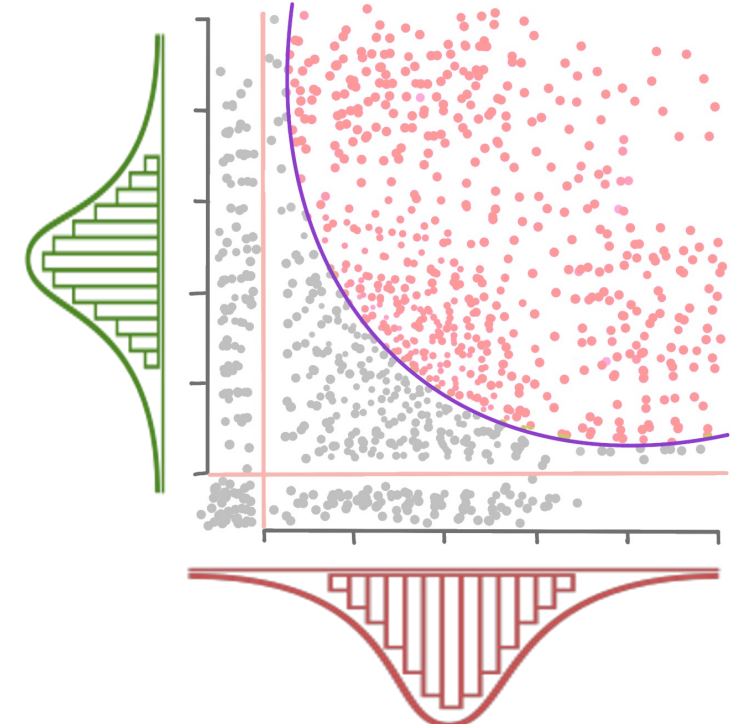
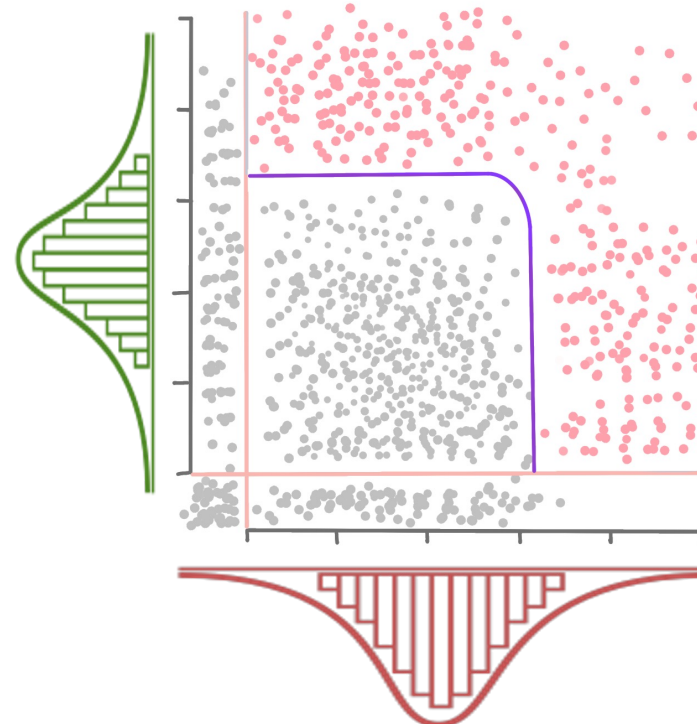
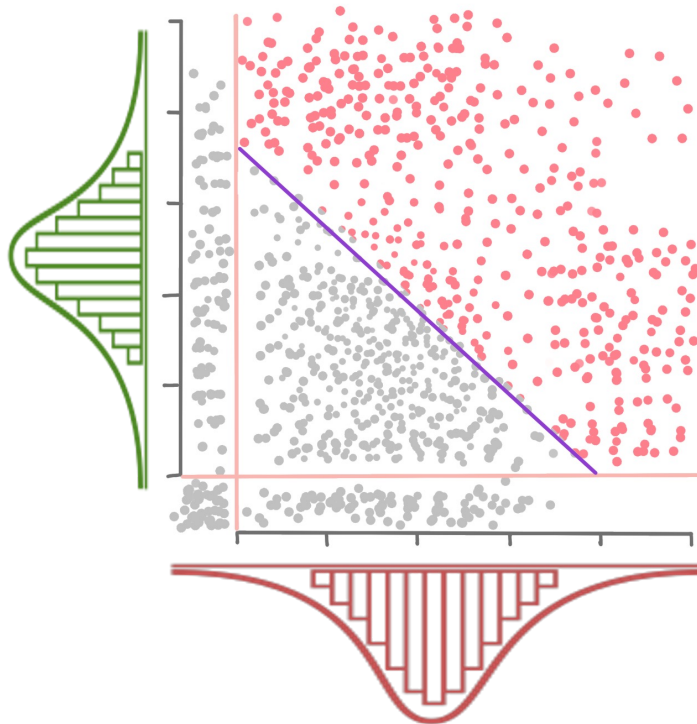
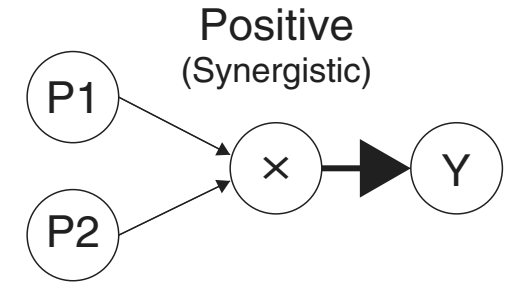
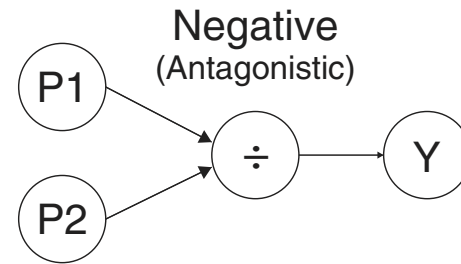
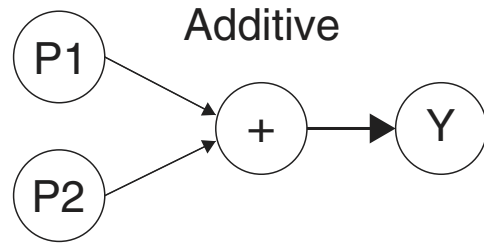
Hypothesis: Disorder-specific pathway **interactions** contribute to comorbidity



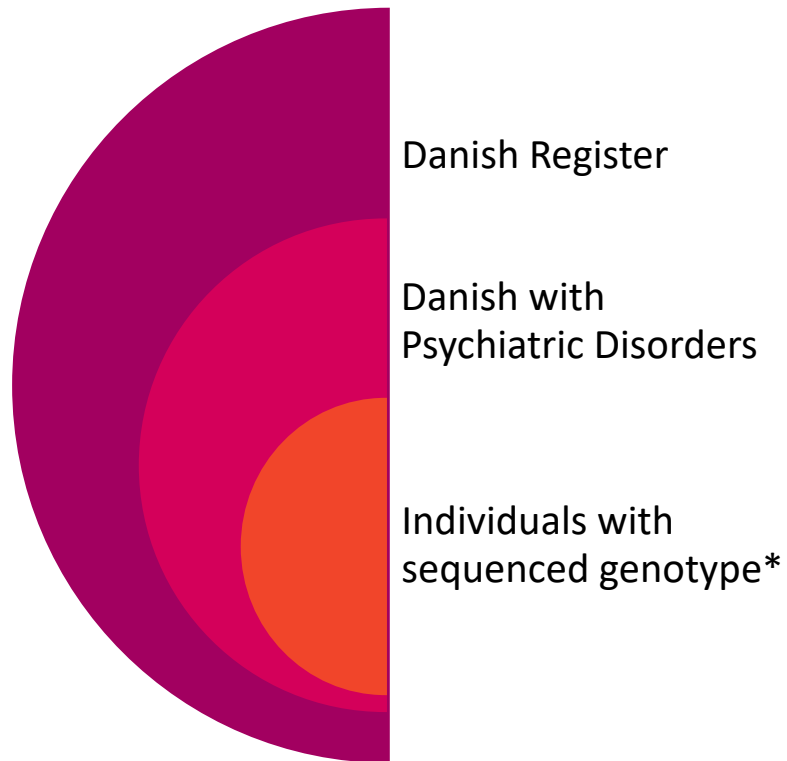
Negative interaction between pathways



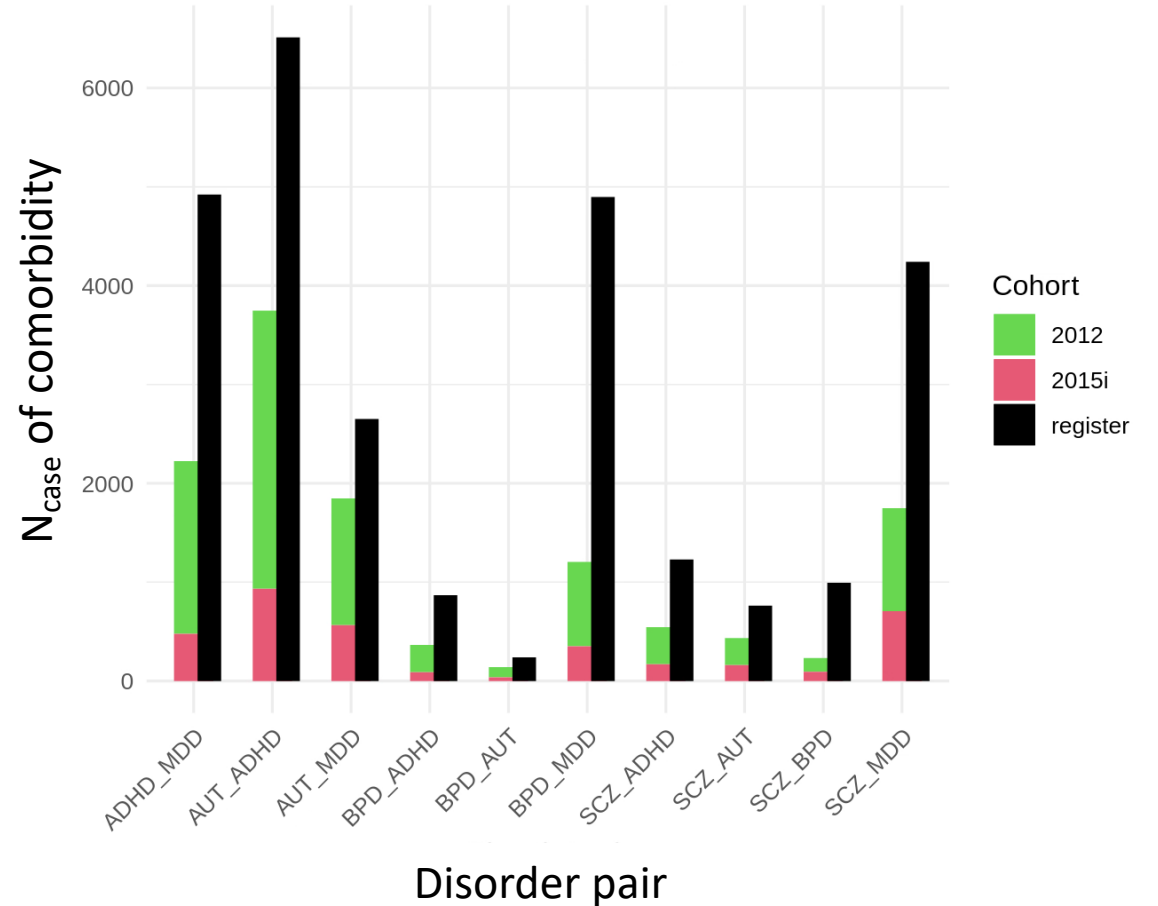
Positive interaction between pathways



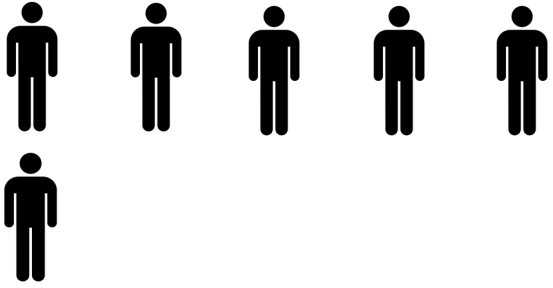
Data: Danish Register and iPSYCH



* Two sequence arrays and separate ascertainment gave rise to replication cohorts: iPSYCH 2012 and iPSYCH 2015i

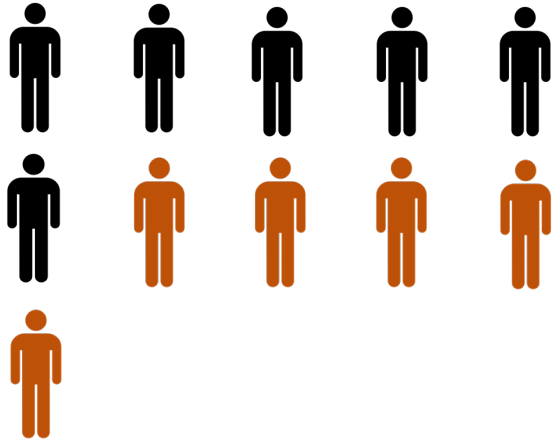


Phenotype definitions



■ Random population controls

Phenotype definitions



■ Random population controls

■ Disorder A

Phenotype definitions



- Random population controls
- Disorder A
- Disorder B

Phenotype definitions



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

Phenotype definitions: Any



■ Random population controls

■ Disorder A

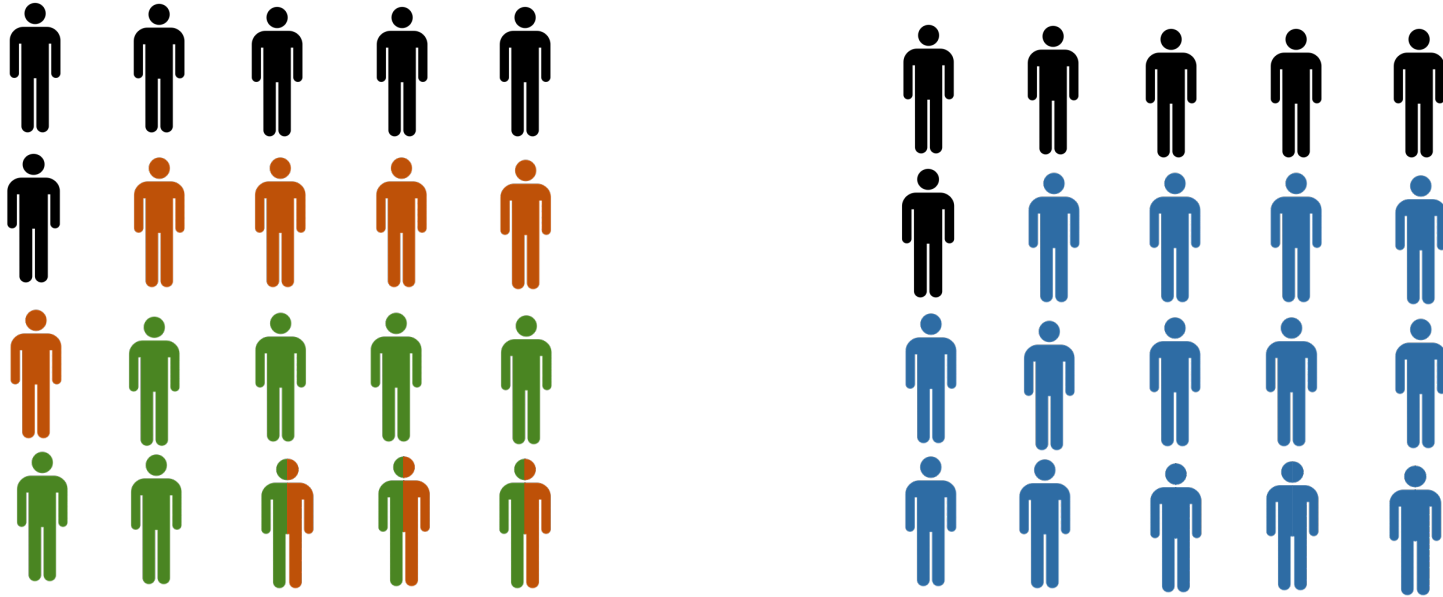
■ Disorder B

■ Comorbid

■ Phenotype cases: Any



Phenotype definitions: Any



■ Random population controls

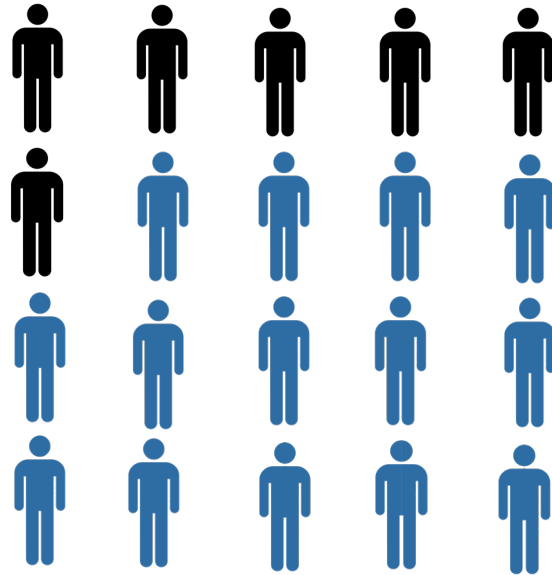
■ Disorder A

■ Disorder B

■ Comorbid

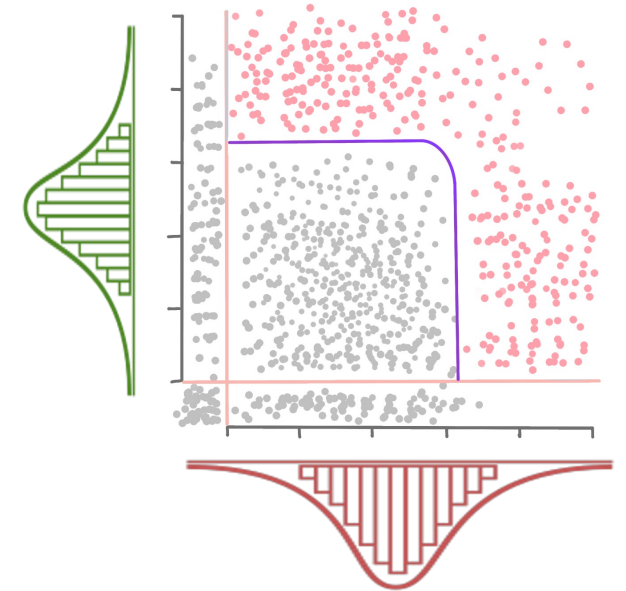
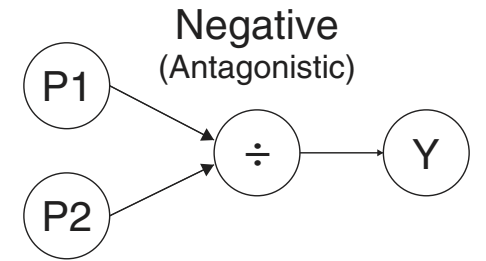
■ Phenotype cases: Any

Phenotype definitions: Any

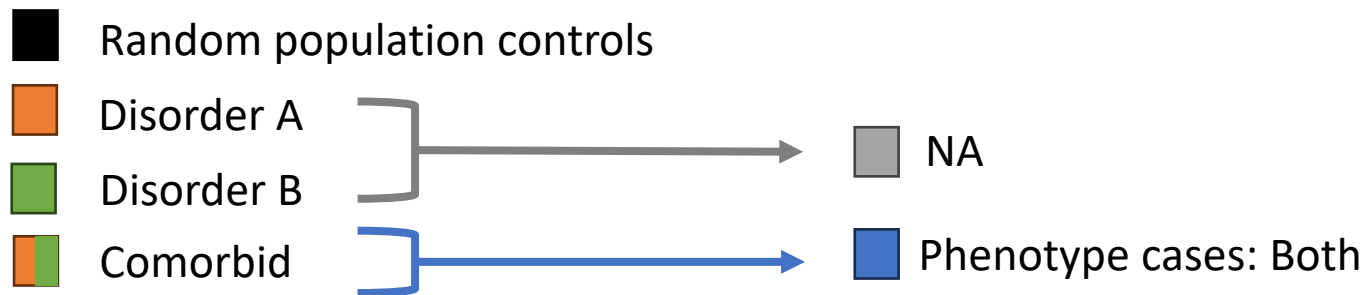


- Random population controls
- Disorder A
- Disorder B
- Comorbid

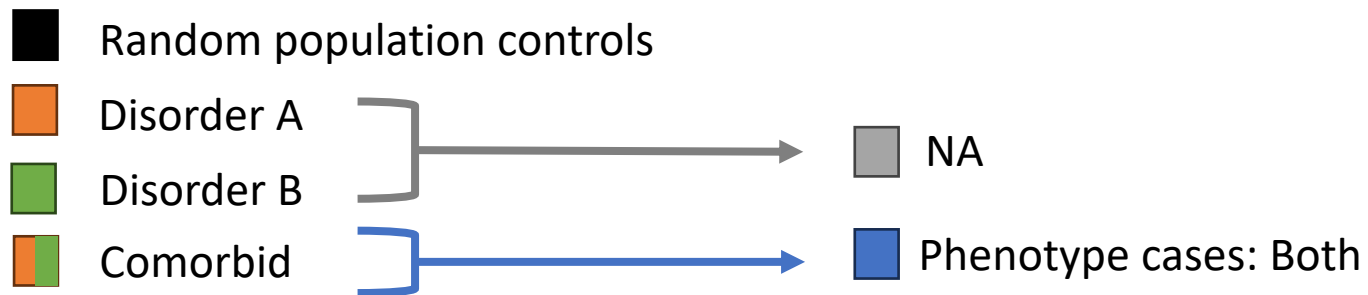
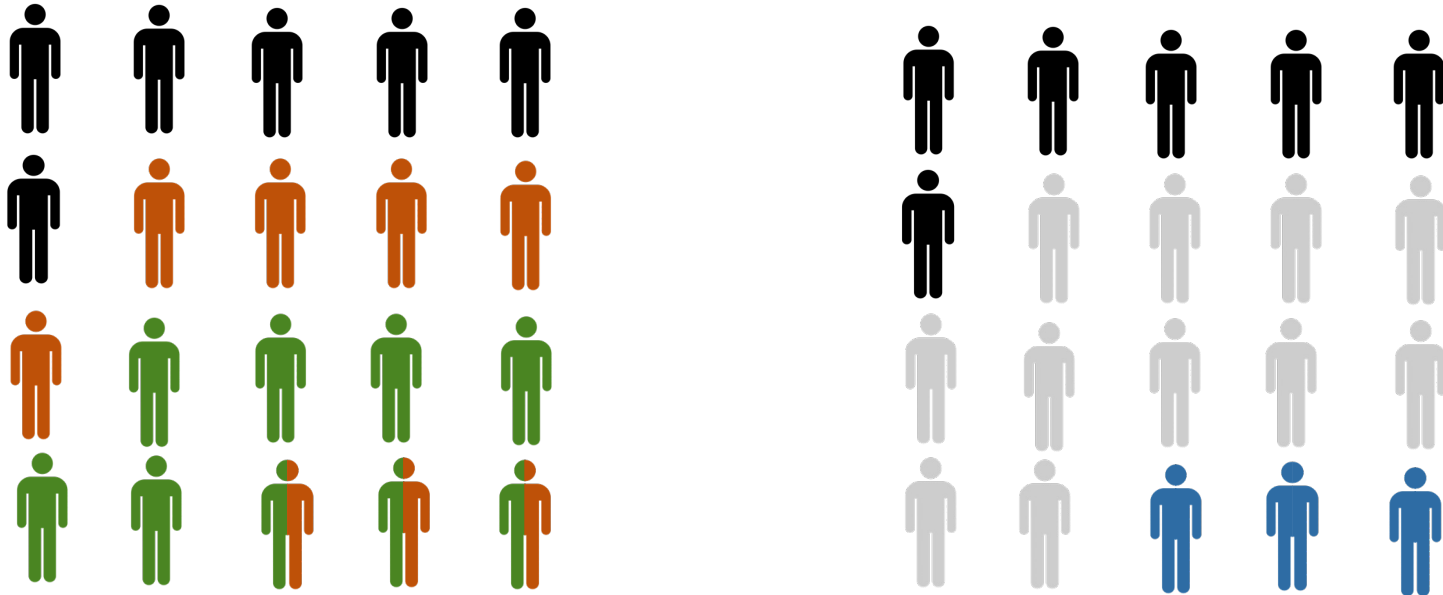
Phenotype cases: Any



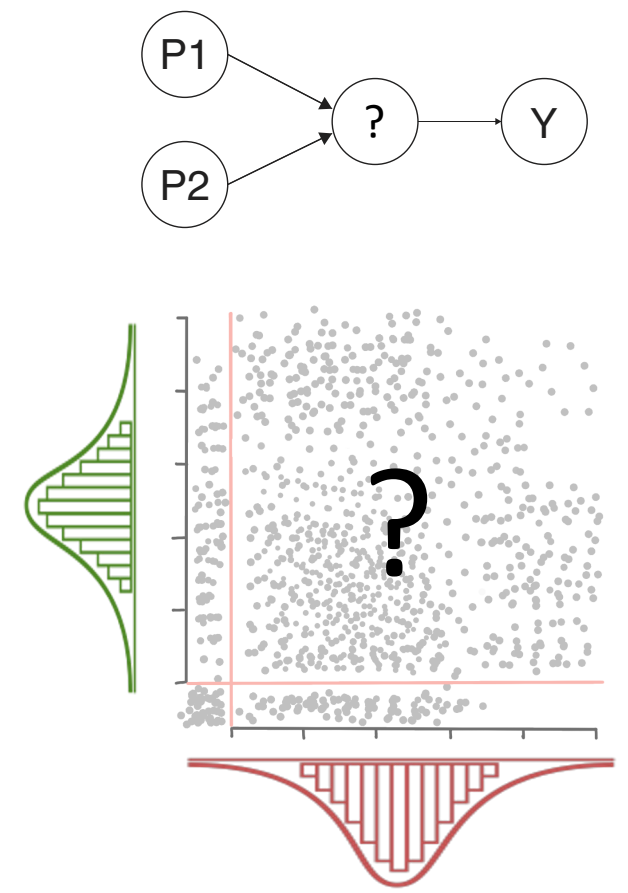
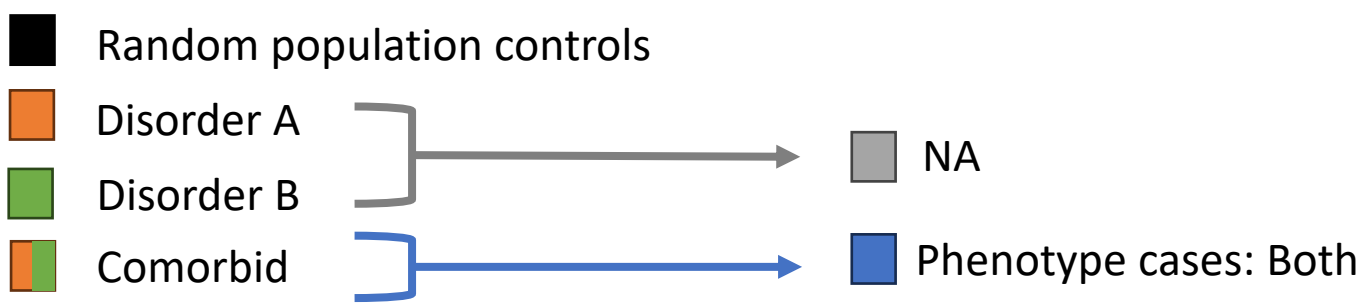
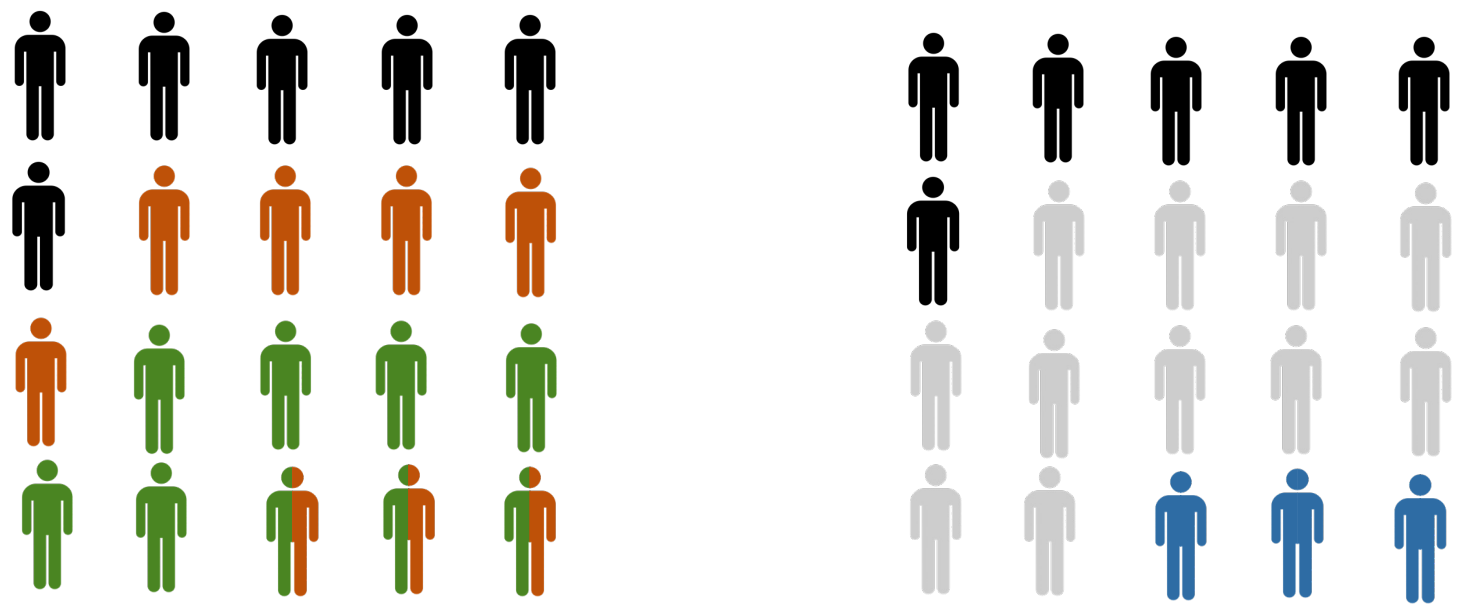
Phenotype definitions: Both



Phenotype definitions: Both

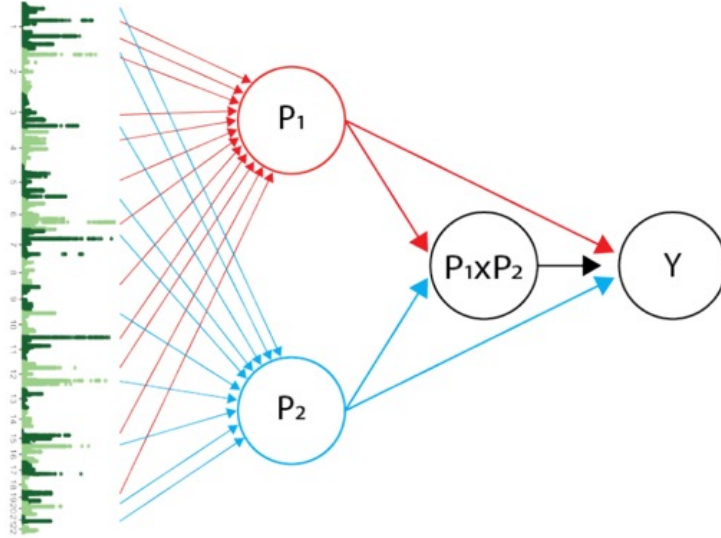


Phenotype definitions: Both



How to test for disorder-specific pathway interactions?

Coordinated Epistasis



$$y \sim \alpha_i GS_i + \alpha_j GS_j + \gamma_{i,j} GS^* GS_j$$

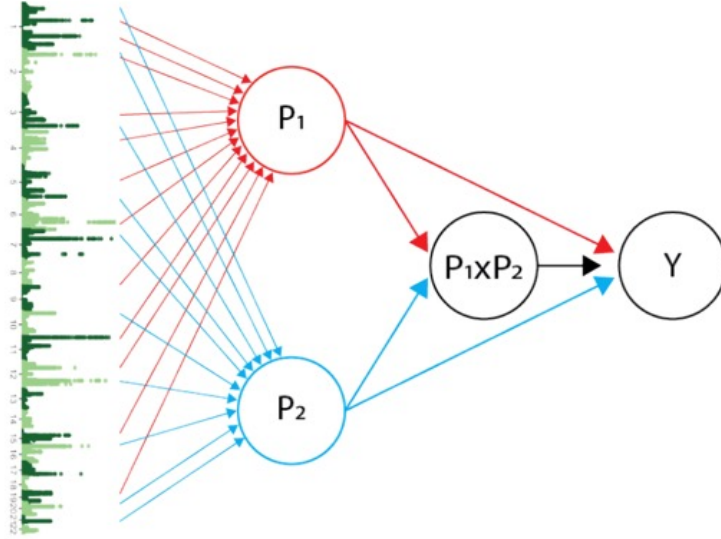
GS = Genetic Score (PRS / PA-FGRS)

i = disorder A

j = disorder B

$i \neq j$

Coordinated Epistasis



$$y \sim \alpha_i GS_i + \alpha_j GS_j + \gamma_{i,j} GS^* GS_j$$

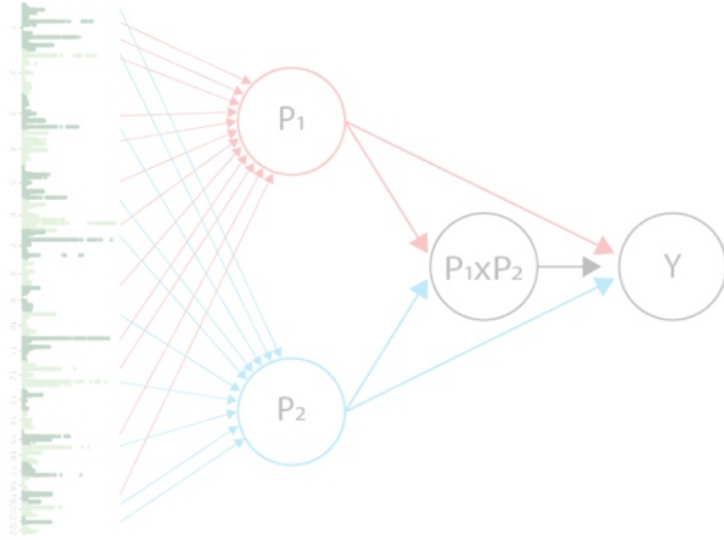
GS = Genetic Score (PRS / PA-FGRS)

i = disorder A

j = disorder B

i ≠ j

Coordinated Epistasis

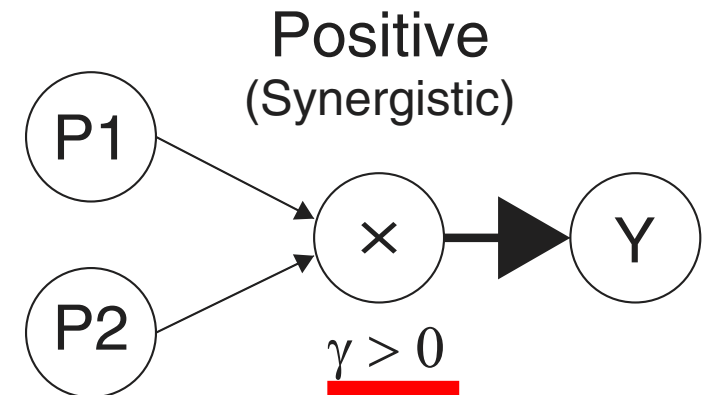
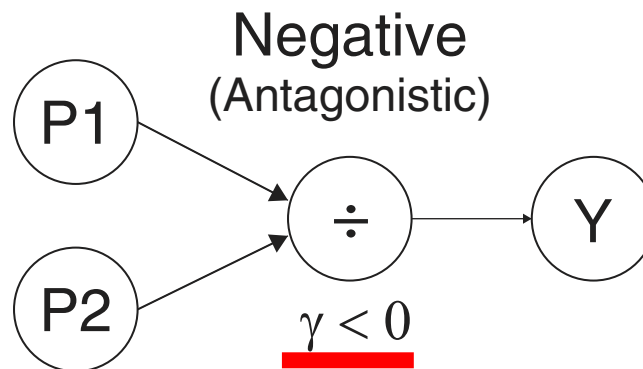
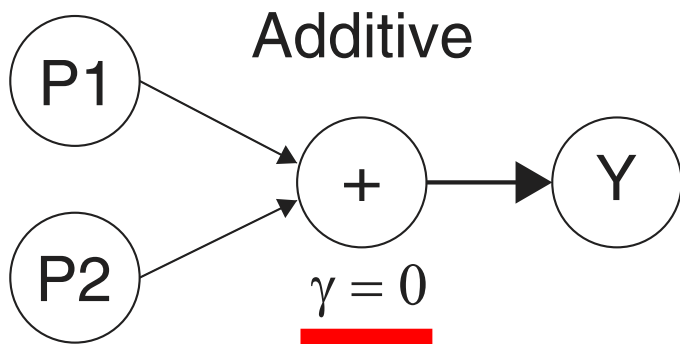


$$y \sim \alpha_i GS_i + \alpha_j GS_j + \gamma_{i,j} GS^* GS_j$$

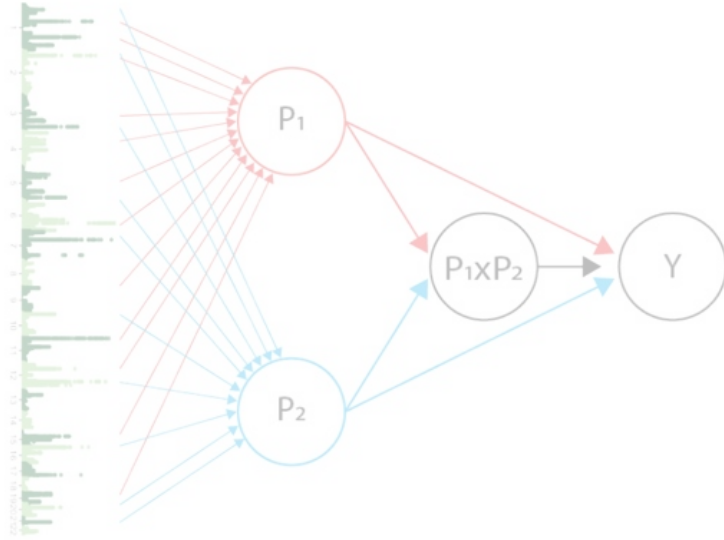
GS = Genetic Score (PRS / PA-FGRS)

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Coordinated Epistasis

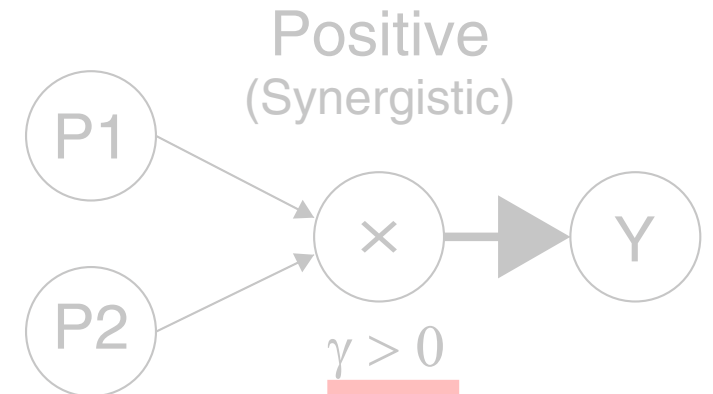
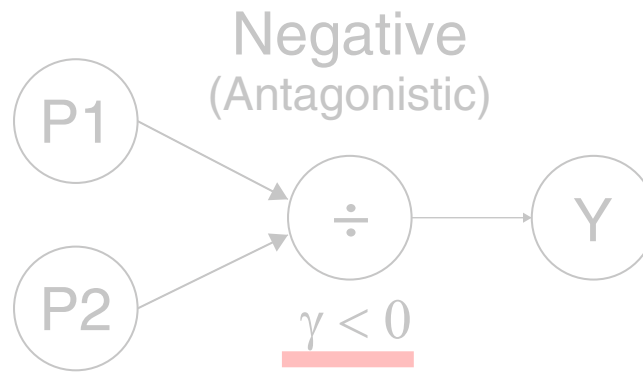
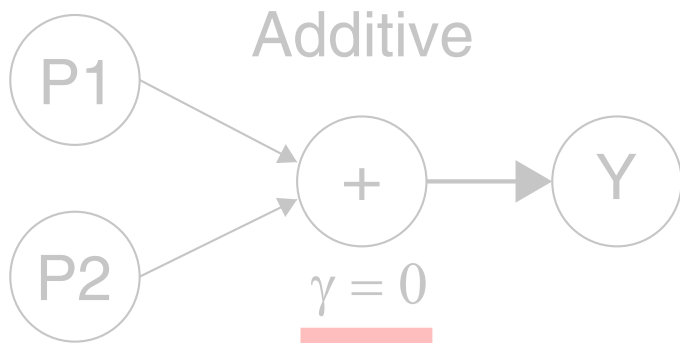


$$y \sim \alpha_i GS_i + \alpha_j GS_j + \gamma_{i,j} GS_i^* GS_j$$

GS = Genetic Score (PRS / PA-FGRS)

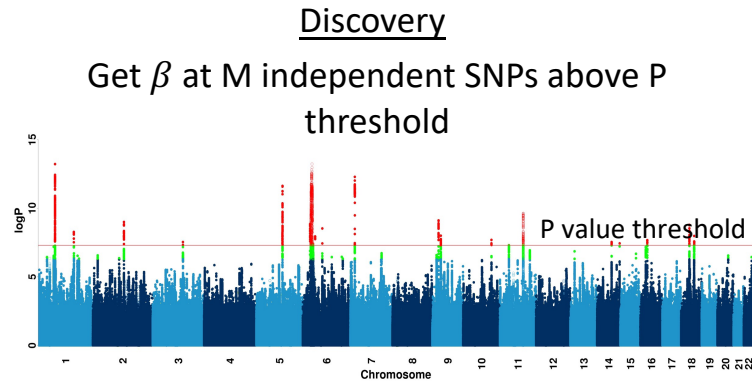
i = disorder A
j = disorder B

$i \neq j$



Genetic Liability Scores

Polygenic Risk Scores (PRS)

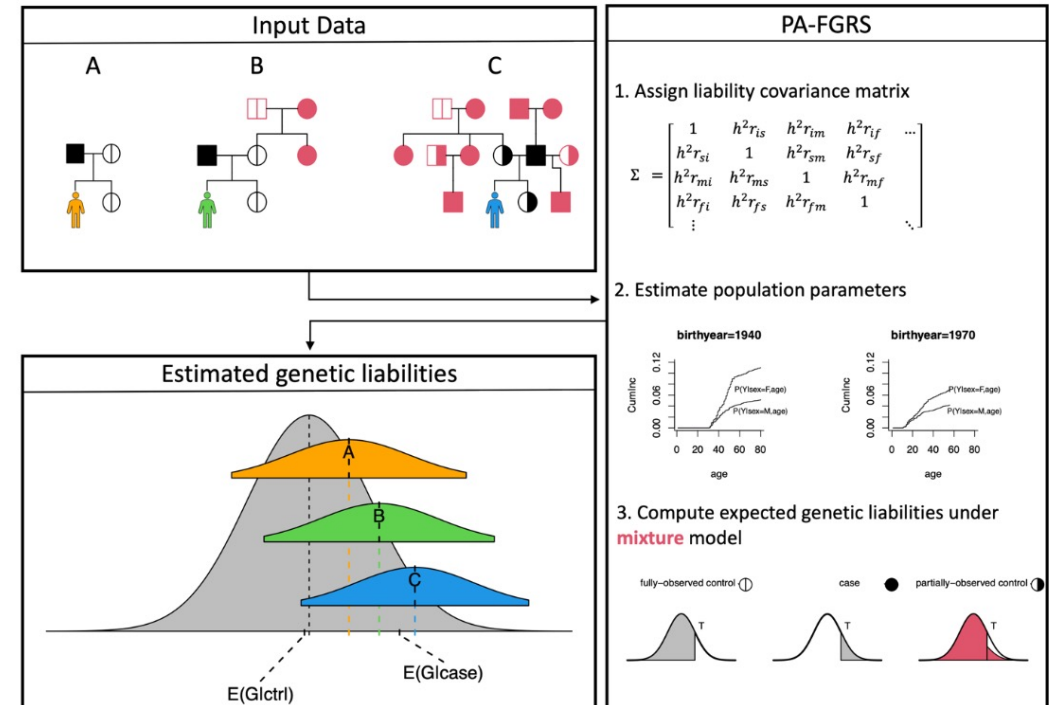


Test

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

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

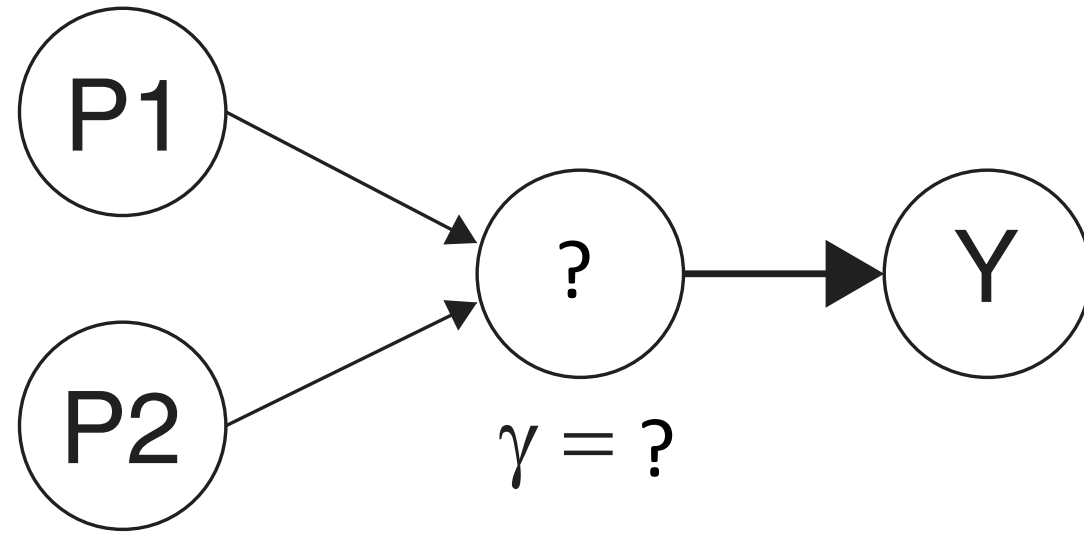
Pearson-Aitkens Family Genetic Risk Score (PA-FGRS)



Disorder-specific pathway realtions towards comorbidity phenotypes

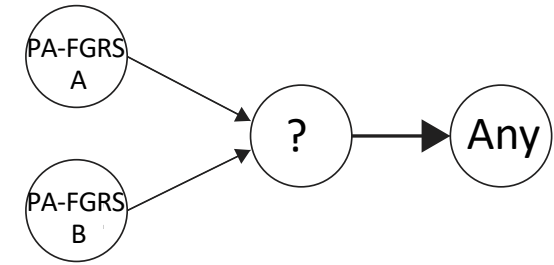
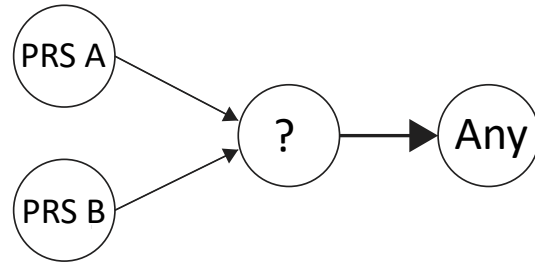
PRS / PA-FGRS
disorder A

PRS / PA-FGRS
disorder B

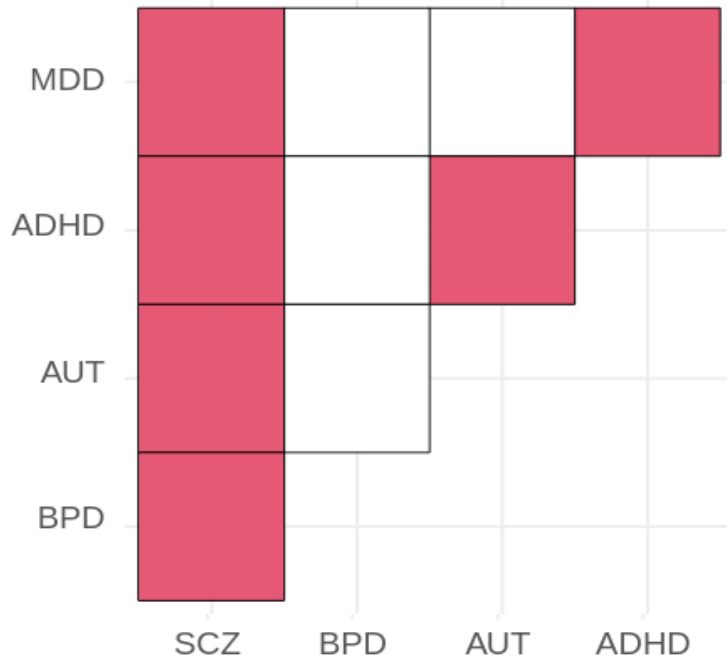


- Any
- Both

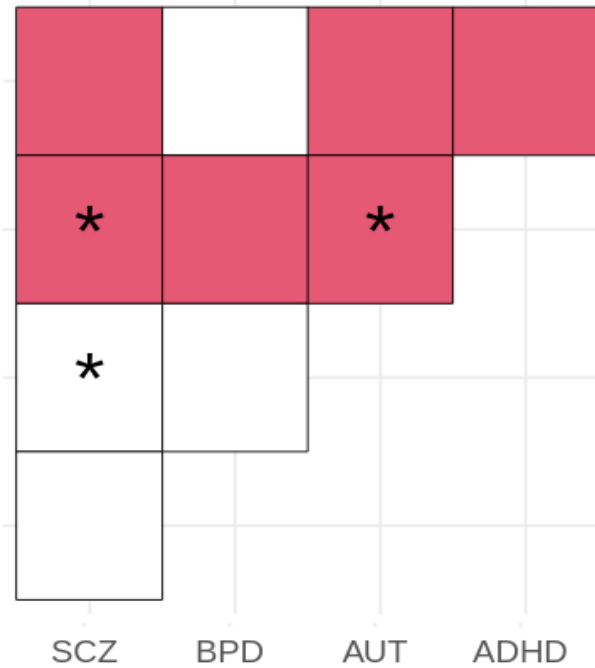
Results: the “any” phenotype



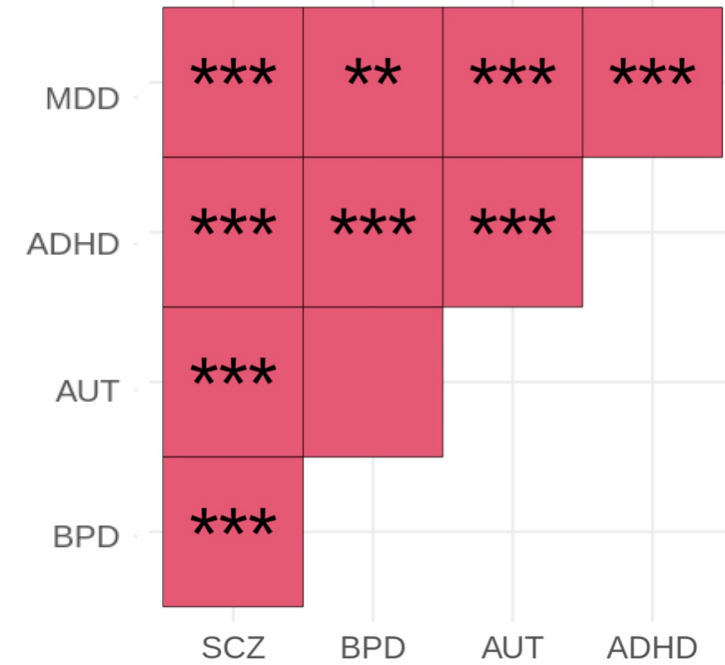
iPSYCH.2012
any



iPSYCH.2015i
any



PA-FGRS
any

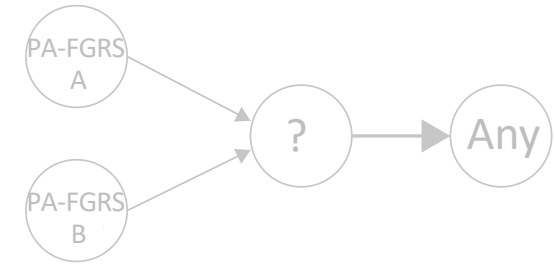
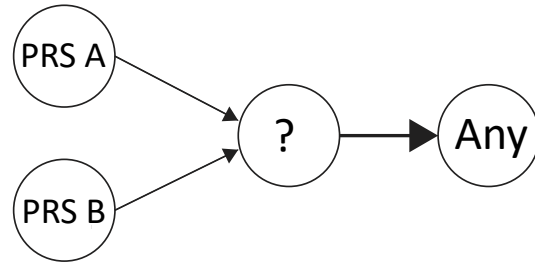


γ

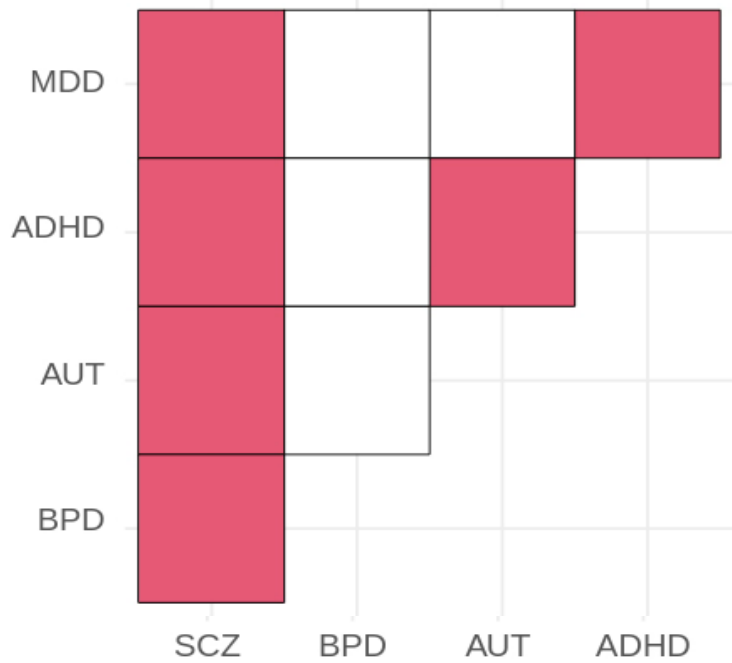
 -
 +

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

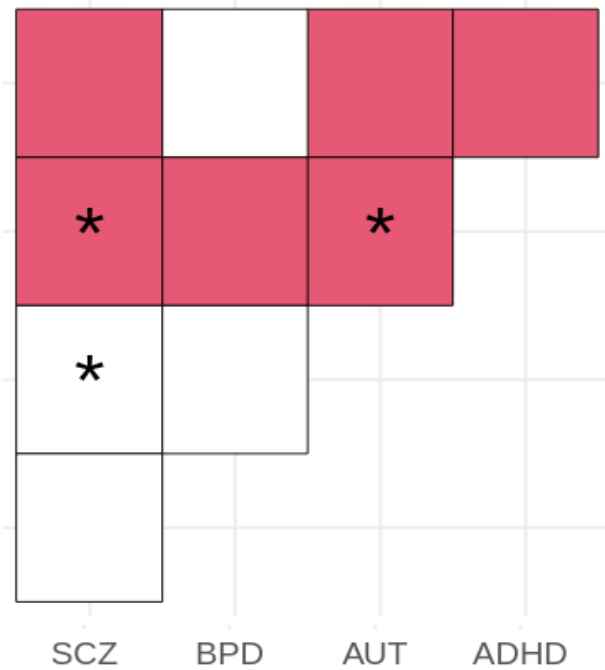
Results: the “any” phenotype



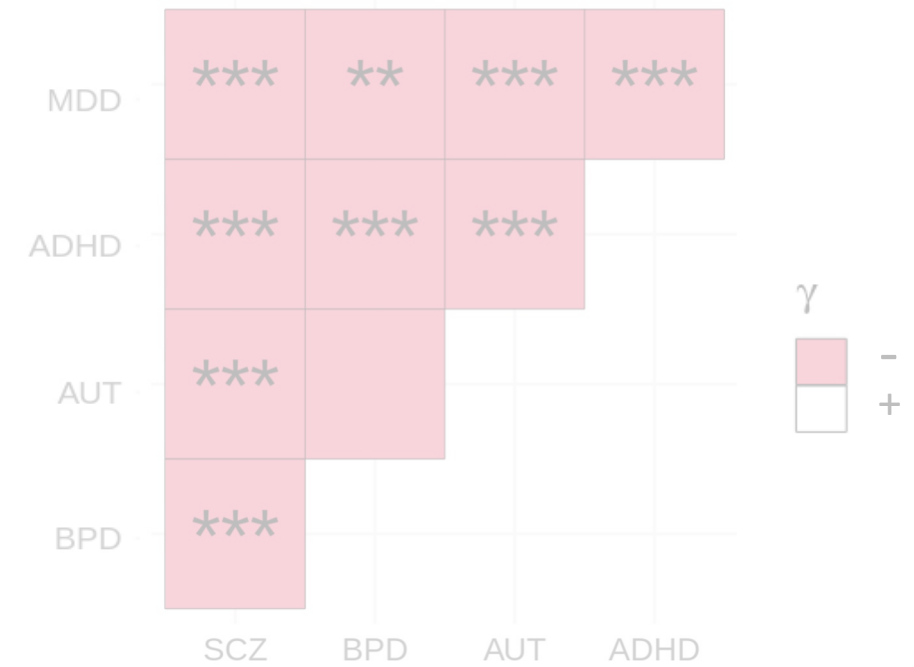
iPSYCH.2012
any



iPSYCH.2015i
any



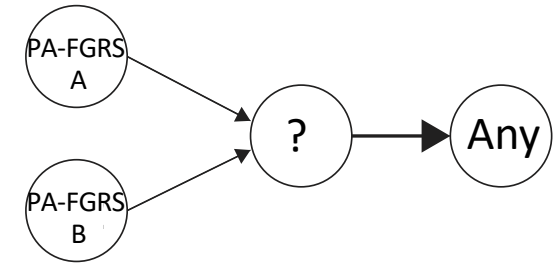
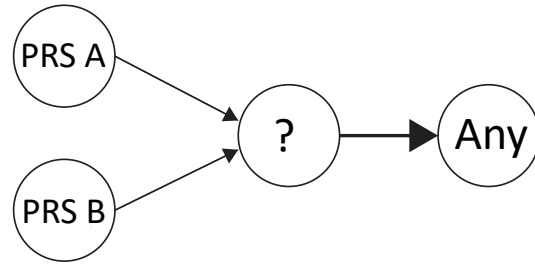
PA-FGRS
any



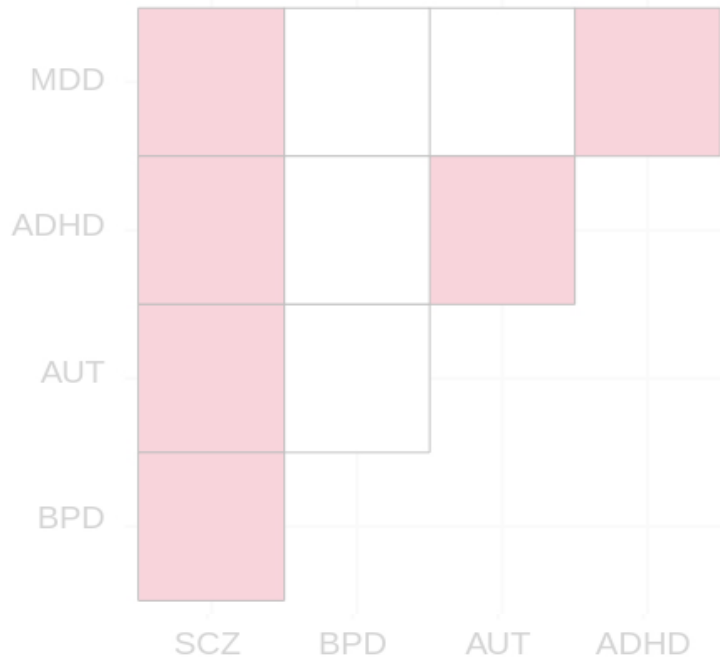
γ
+
-

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

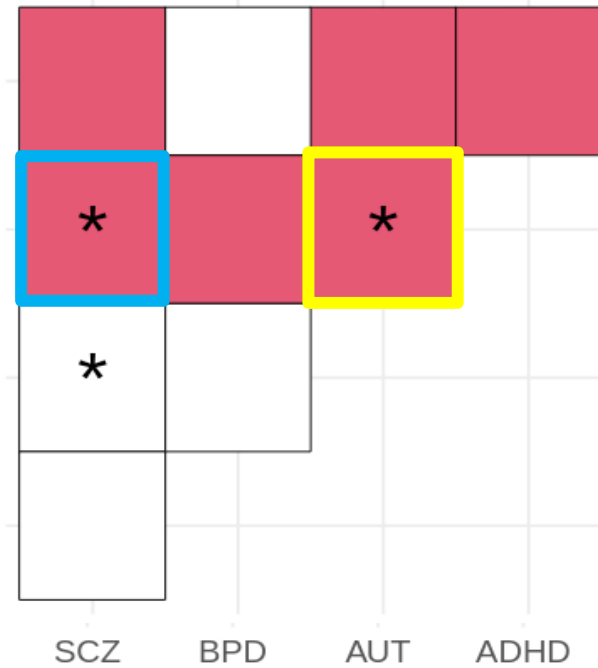
Results: the “any” phenotype



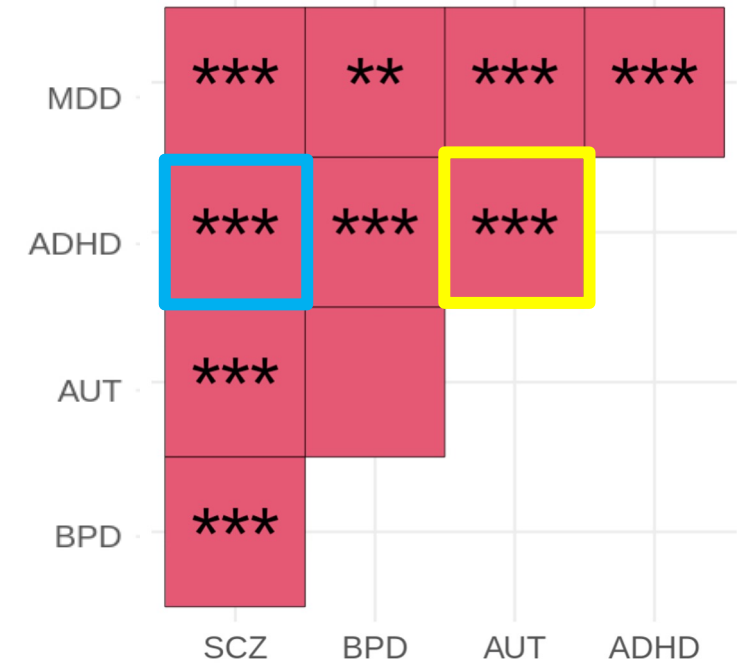
iPSYCH.2012
any



iPSYCH.2015i
any



PA-FGRS
any

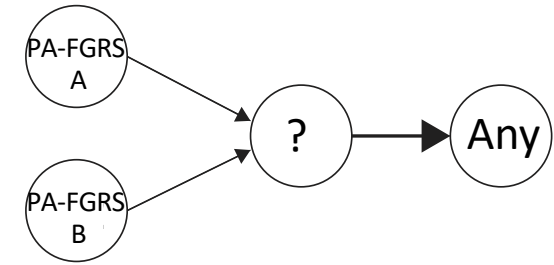
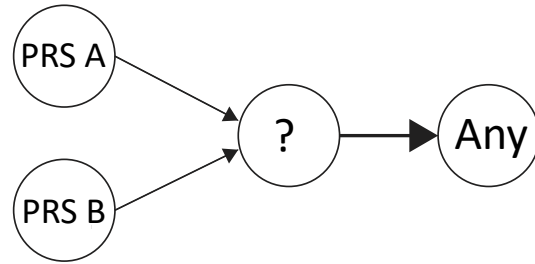


γ

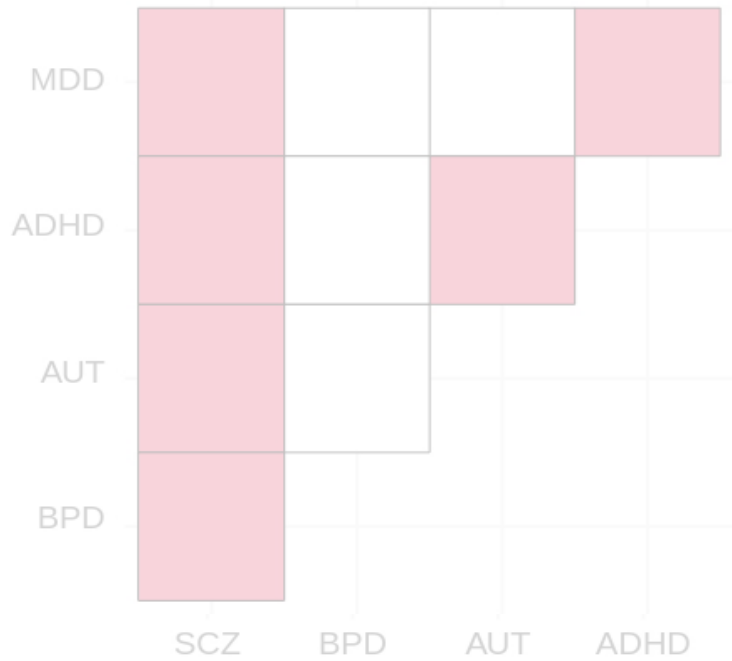
 -
 +

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

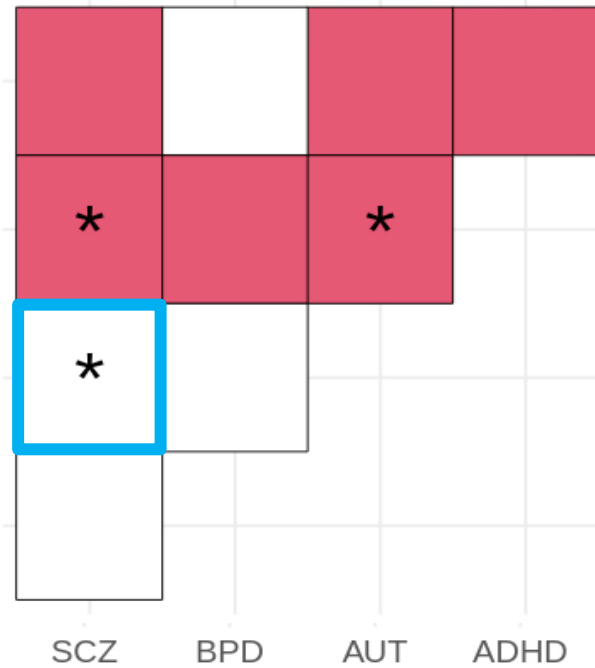
Results: the “any” phenotype



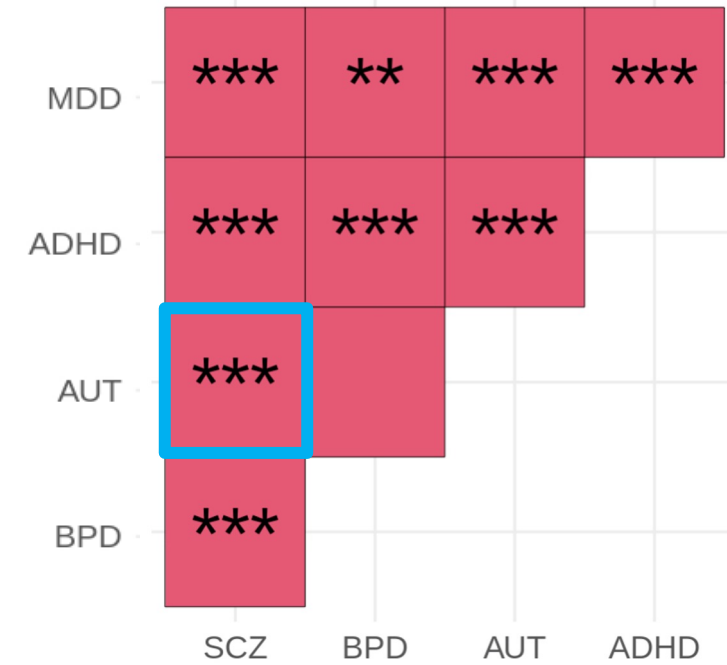
iPSYCH.2012
any



iPSYCH.2015i
any



PA-FGRS
any

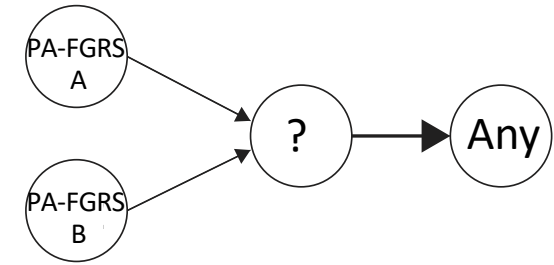
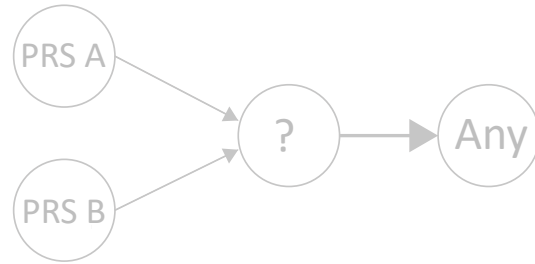


γ

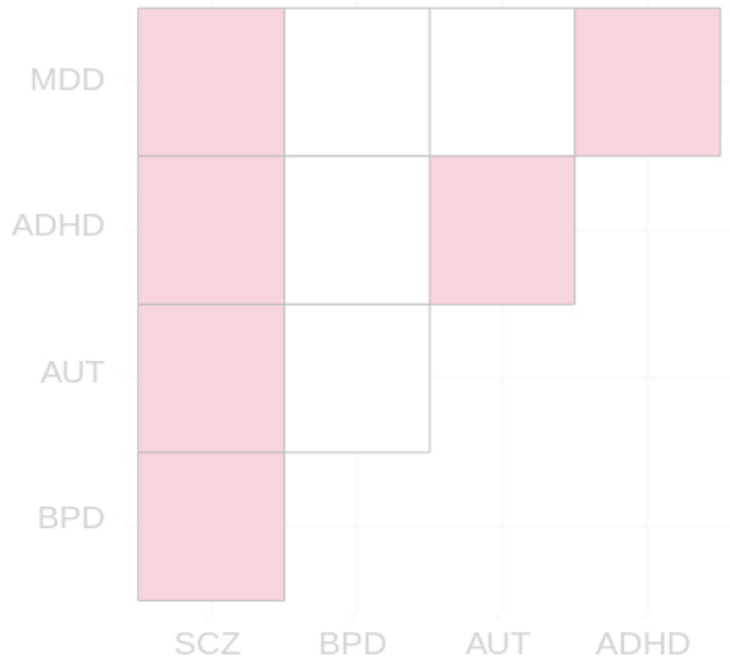
 -
 +

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

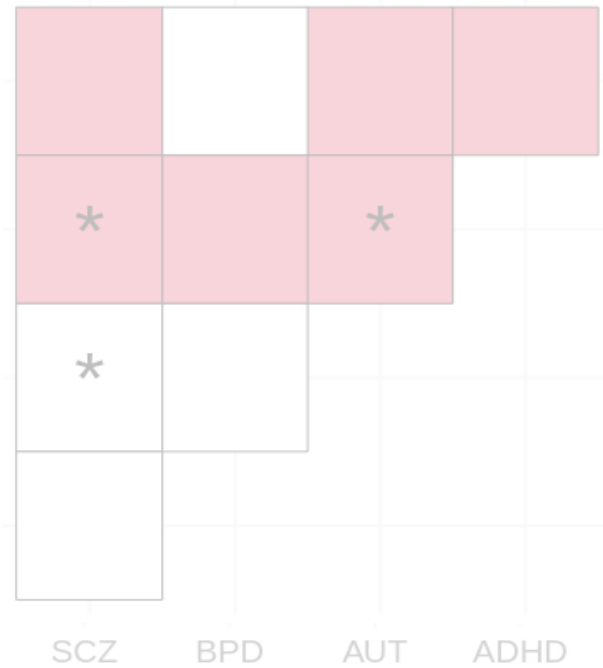
Results: the “any” phenotype



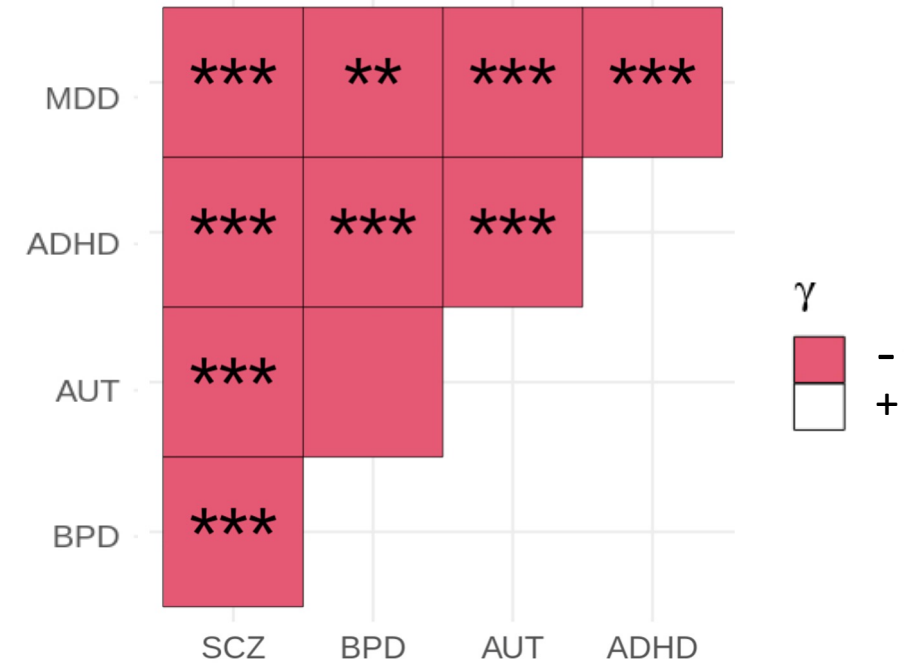
iPSYCH.2012
any



iPSYCH.2015i
any



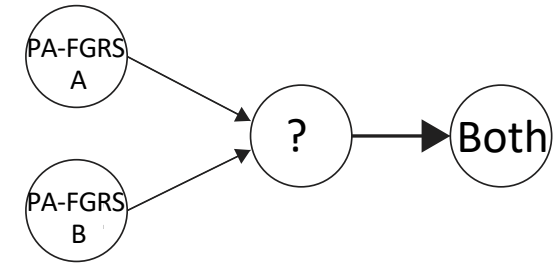
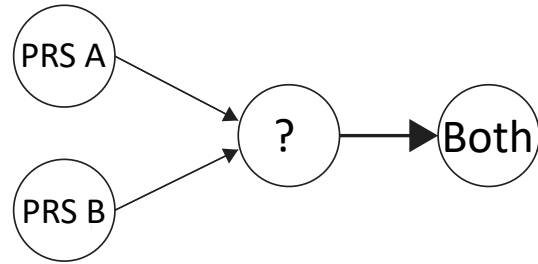
PA-FGRS
any



γ
 -
 +

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

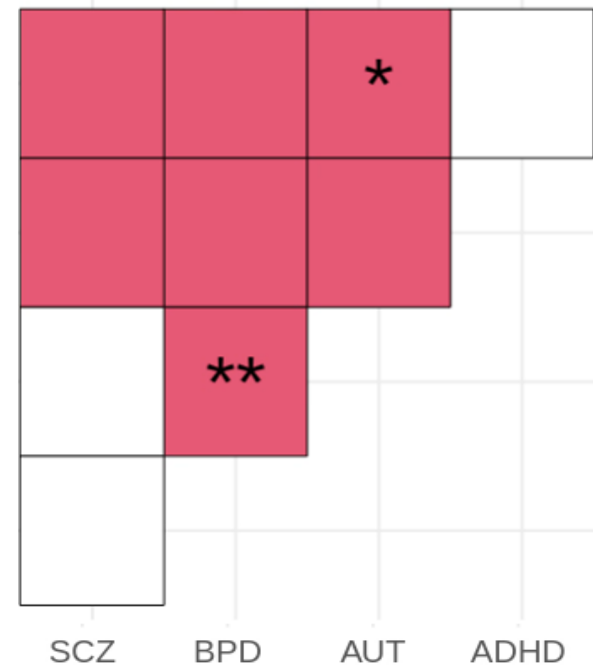
Results: the “both” phenotype



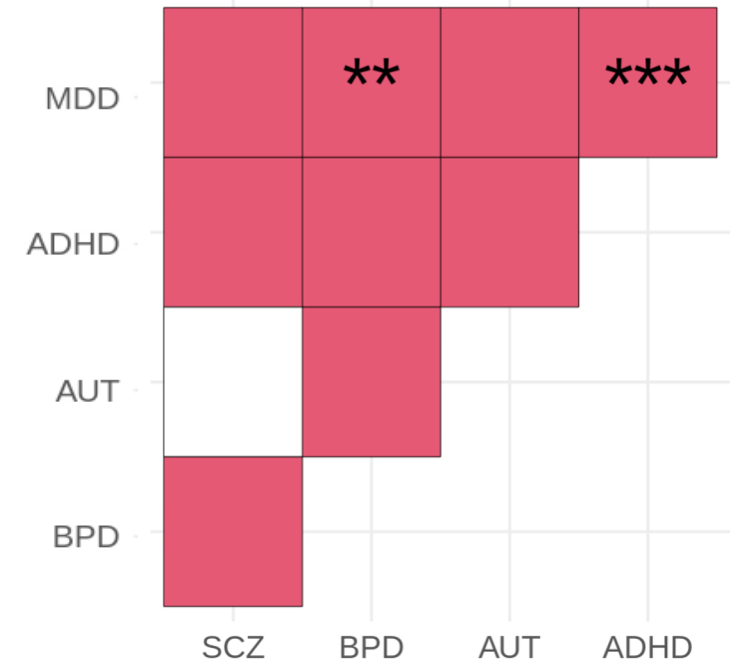
iPSYCH.2012
both



iPSYCH.2015i
both



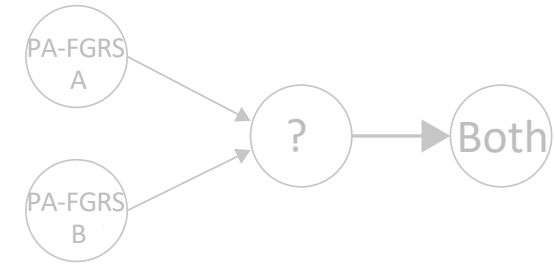
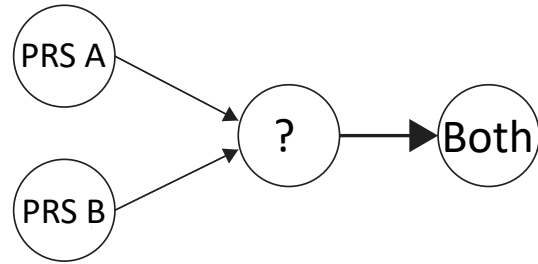
PA-FGRS
both



γ
 -
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* $p < 0.05$; ** $p < 0.005$; *** $p < 0.0005$

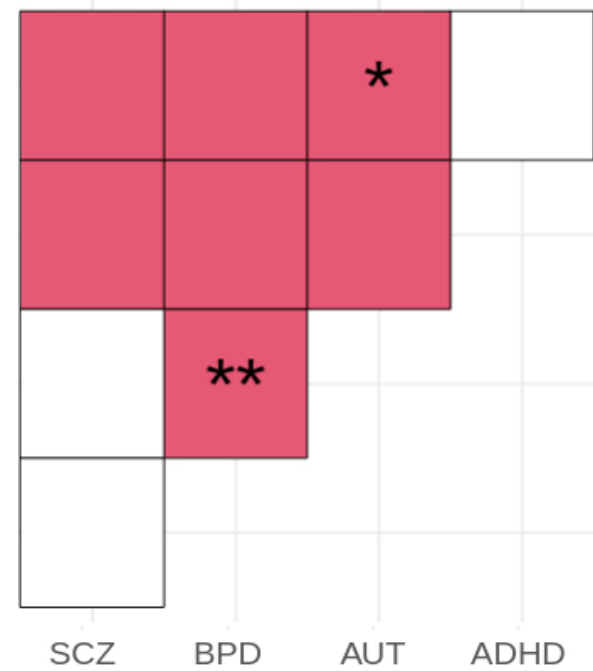
Results: the “both” phenotype



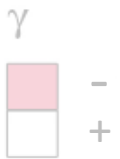
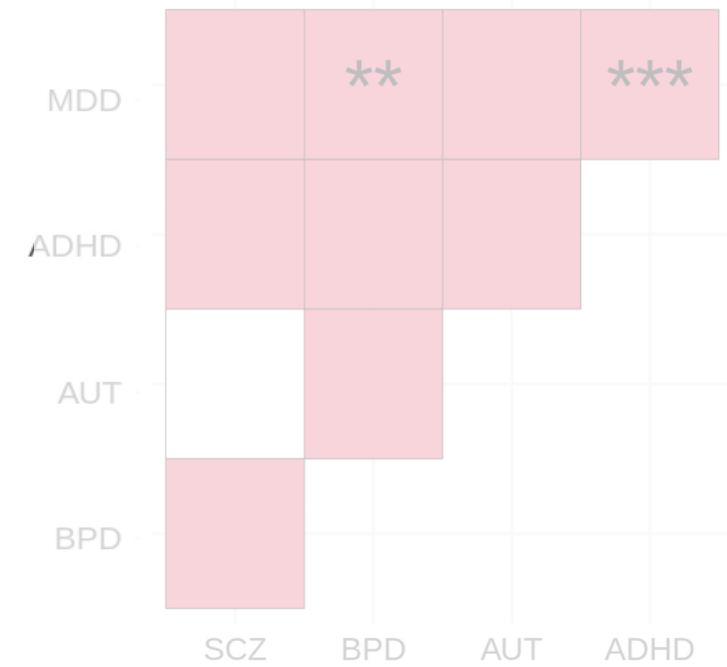
iPSYCH.2012
both



iPSYCH.2015i
both

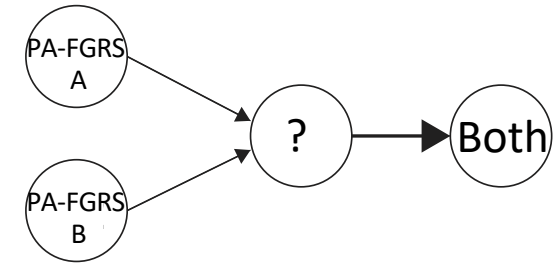
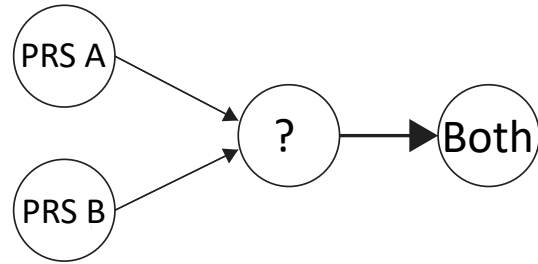


PA-FGRS
both

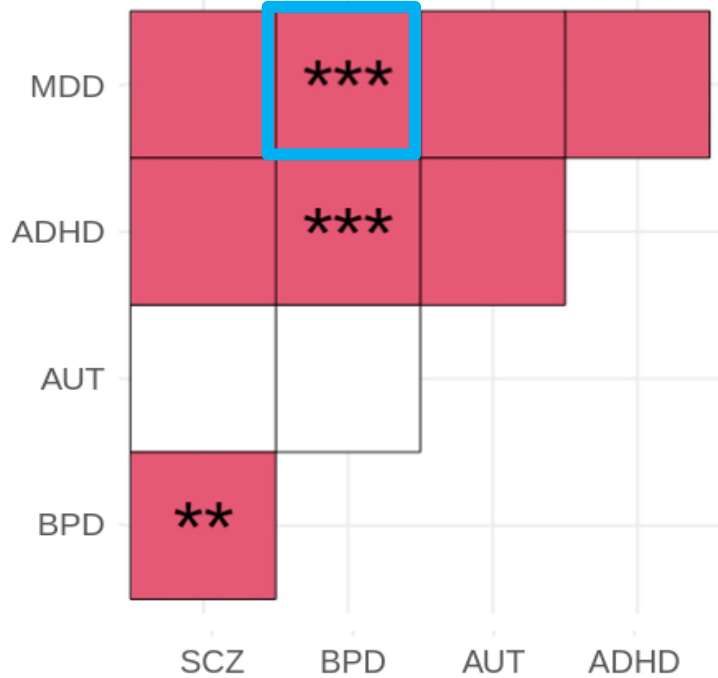


* $p < 0.05$; ** $p < 0.005$; *** $p < 0.0005$

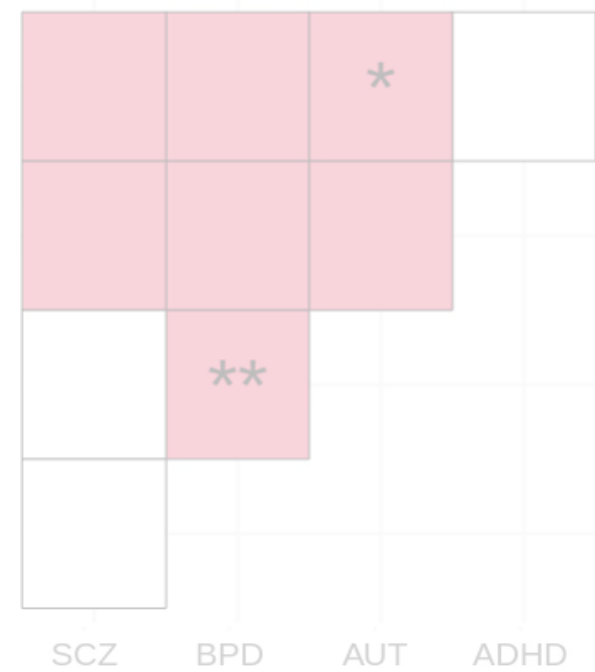
Results: the “both” phenotype



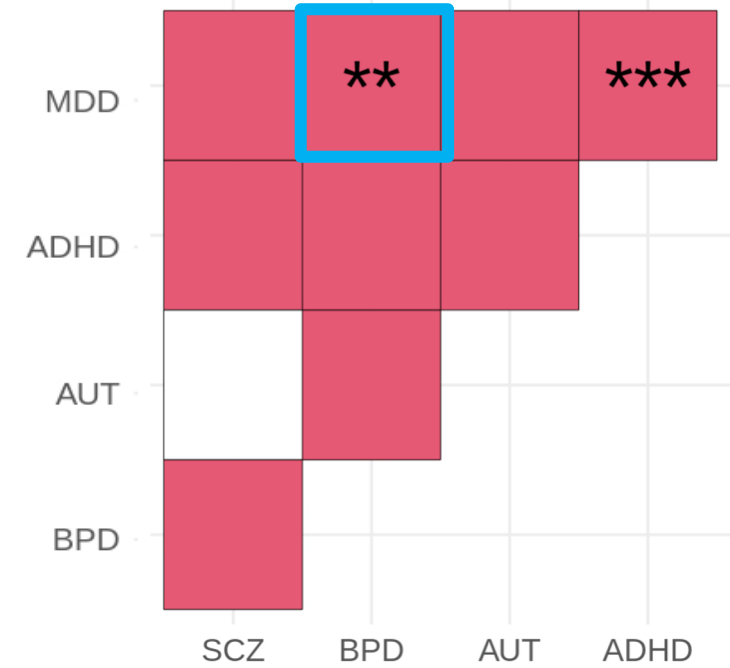
iPSYCH.2012
both



iPSYCH.2015i
both



PA-FGRS
both



γ

 -
 +

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

Conclusions

- 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

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