# Causal Effect of Dyslexia on Adult Internalizing Disorders

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## Introduction

Dyslexia is a common neurodevelopmental disorder affecting 5–10% of children, marked by persistent difficulties in word recognition, reading fluency, and spelling despite normal intelligence (Rose, 2009). Beyond academic challenges, longitudinal and meta-analytic studies show that childhood dyslexia is linked to higher risks of depression, anxiety, and low self-esteem in adulthood (Wilmot et al., 2023). Internalizing disorders including major depressive disorder, anxiety, and bipolar disorder account for a substantial share of mental health problems at the population level. While observational studies highlight associations, they remain vulnerable to confounding and reverse causation. To overcome these limitations, Mendelian randomization offers a robust approach to test the causal effect of dyslexia on adult internalizing disorders.

## Materials

**Exposure**: Dyslexia GWAS for top 10K SNPs (Doust et al.,2022)

- 1,087,070 European controls, 51,800 European cases
- How the phenotype was determined: Self-report

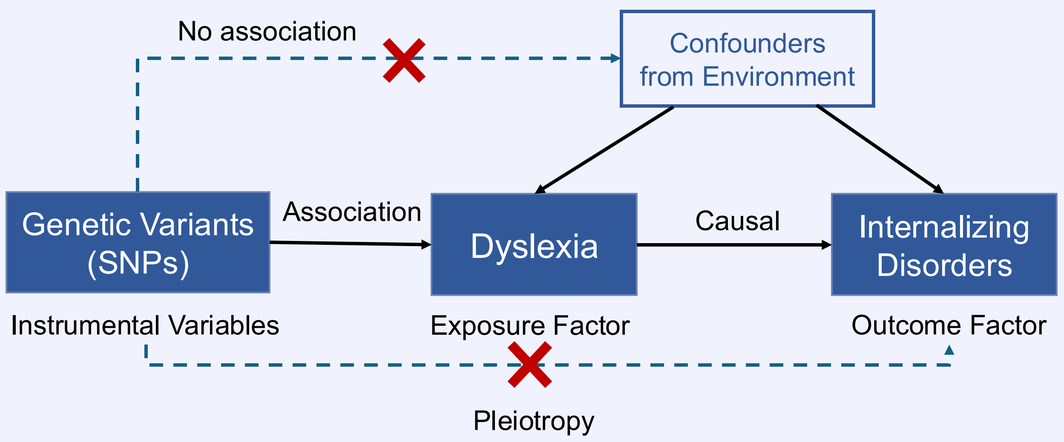
**Outcome**: European GWAS

| Diseases | Major Depressive (Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2025) | Bipolar (O'Connell,2025) | Anxiety (Otowa, 2016) |
|---|---|---|---|
| Case | 525,197 | 58,452 | 7016 |
| Control | 3,362,335 | 778,655 | 14,745 |

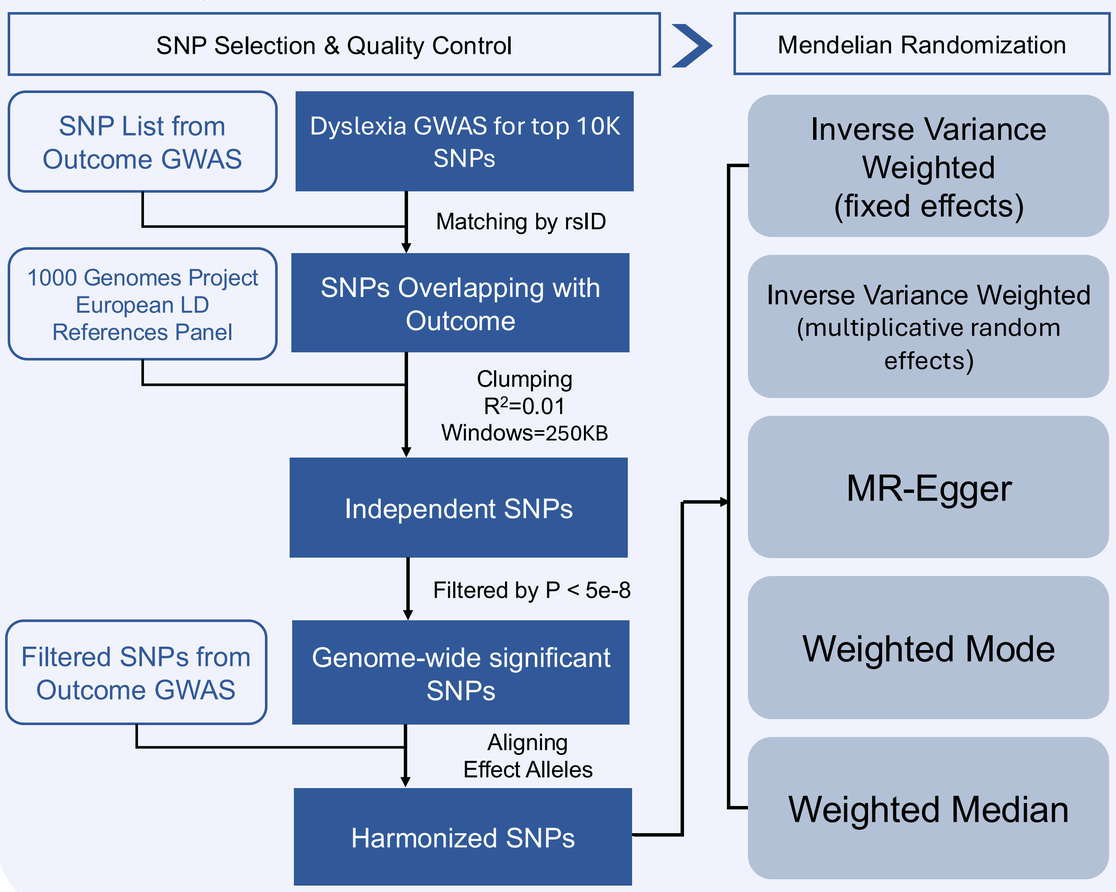
- How these diseases were determined: Clinical diagnoses, Self-report

## Methods

### Mendelian Randomization (MR)




### Study Design

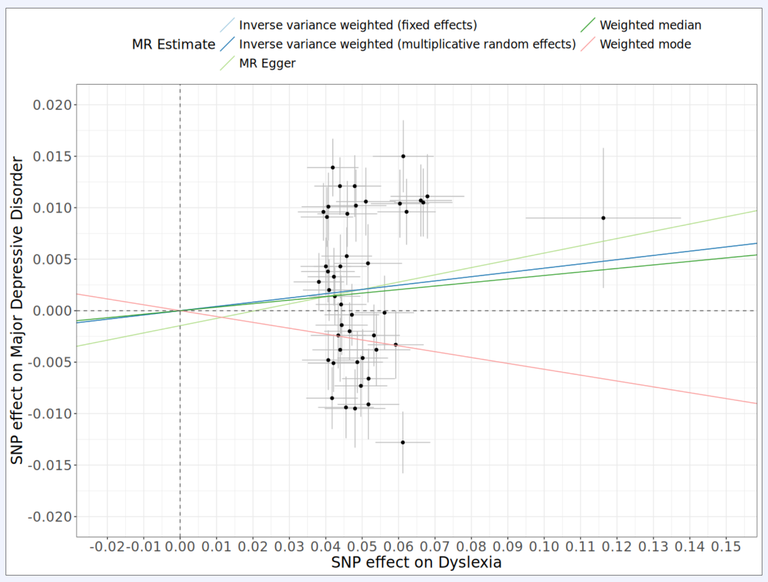



## Results

### Major Depressive Disorder

Overlapped N=6980 → Clumped N=122 → Filtered by P < 5e-8 N=46

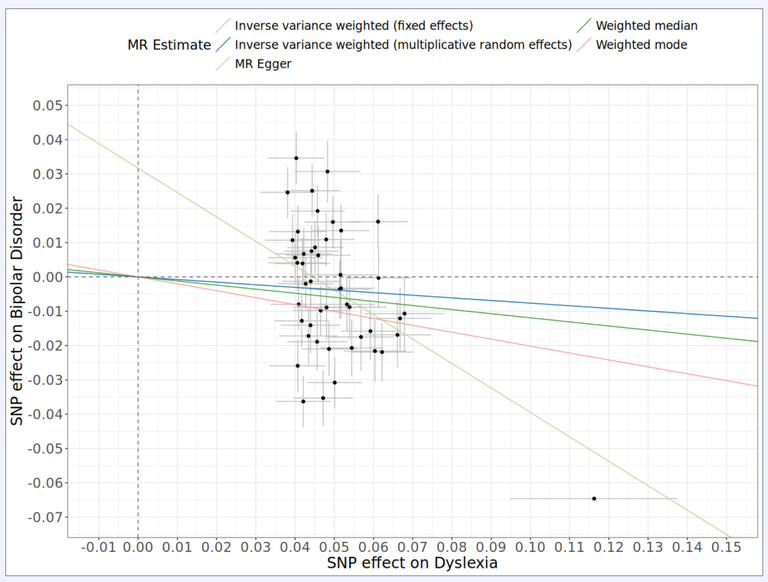
| MR Methods | Effect | P-value |
|---|---|---|
| IVW-fixed | *** 0.041 | 9.8e-6 |
| IVW-MRE | 0.041 | 6.4e-2 |
| MR-Egger | 0.071 | 5.7e-1 |
| Weighted Median | 0.034 | 1.0e-1 |
| Weighted Mode | - 0.057 | 5.6e-1 |
| MR-Egger Interception | | P-value |
| | - 0.00087 | 9.0e-1 |




### Bipolar Disorder

Overlapped N=7566 → Clumped N=126 → Filtered by P < 5e-8 N=47

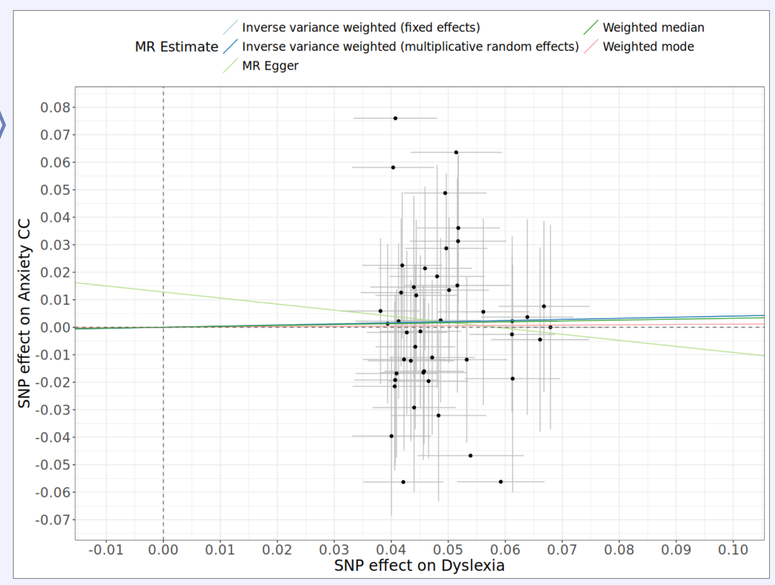
| MR Methods | Effect | P-value |
|---|---|---|
| IVW-fixed | ** -0.076 | 1.6e-3 |
| IVW-MRE | -0.076 | 1.5e-1 |
| MR-Egger | * -0.712 | 1.5e-2 |
| Weighted Median | ** 0.119 | 9.1e-3 |
| Weighted Mode | -0.202 | 8.4e-2 |
| MR-Egger Interception | | P-value |
| | * 0.032 | 2.7e-2 |




### Anxiety Disorder

Overlapped N=8207 → Clumped N=127 → Filtered by P < 5e-8 N=46

| MR Methods | Effect | P-value |
|---|---|---|
| IVW-fixed | 0.041 | 6.5e-1 |
| IVW-MRE | 0.041 | 6.3e-1 |
| MR-Egger | -0.220 | 7.1e-1 |
| Weighted Median | 0.033 | 8.0e-1 |
| Weighted Mode | 0.011 | 9.6e-1 |
| MR-Egger Interception | | P-value |
| | 0.013 | 6.5e-1 |




## Conclusion

- **Dyslexia → MDD**: Evidence for a small positive causal effect, robust against pleiotropy.
- **Dyslexia → Bipolar**: Negative association suggested, but pleiotropy detected.
- **Dyslexia → Anxiety**: Null effects, with no indication of pleiotropic bias.
- Negative association on bipolar may reflect opposite genetic structure on education/ cognition, but pleiotropy indicates bias.

## REFERENCES

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