Preliminary data analysis using InterMR to identify risk factors with sex-specific effects on ADHD

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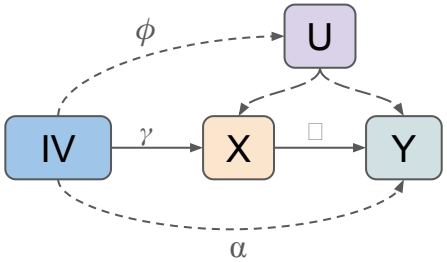
Mendelian randomization and intro to InterMR

- Classical Mendelian randomization (MR) uses genetic variants (SNPs) as instrumental variables (IVs) to detect causal relationships between exposures and outcomes.
- Valid IVs follow 3 assumptions:
  - i. IV is associated with the exposure ($\gamma \neq 0$)
  - ii. IV is associated with the outcome only through the exposure ($\alpha = 0$)
  - iii. IV is not associated with potential confounders ($\phi = 0$)
- Advantages of MR: Robust to confounding and reverse causality, lots of publicly available GWAS for two-sample MR.
- Two problems with MR:
  - Horizontal pleiotropy which leads to invalid IVs
  - Genetic effects that vary significantly significantly among different population groups
- We propose InterMR
  - InterMR jointly analyzes multiple GWAS to detect interaction effects.
  - Knowledge of group label for each individual is not necessary - InterMR uses the distribution of the two groups in summary level data.
  - InterMR is robust to uncorrelated horizontal pleiotropy.



InterMR model overview

- In InterMR we have one exposure GWAS and several outcome GWASs
  - For each outcome GWAS we know the proportion of the sample with the desired characteristic, ρ.
  - In our data analysis we consider ρ to be the proportion of females in the sample.
- We hypothesize that a main causal effect, β, is shared between the two population groups while the causal effect estimate for each GWAS differ by $\beta_{int} \cdot \rho$.
- For a sex-combined GWAS, the j-th SNP can be modeled as:

$$\Gamma_j = (\beta + \beta_{int} \cdot \rho)\, \gamma_j + \alpha_j$$

where Γ_j is the true marginal IV-to-outcome effect, γ_j is the true marginal IV-to-exposure effect, and α_j is the measure of uncorrelated horizontal pleiotropy.

- Single-sex GWAS can have $\rho = 1$ (female) or $\rho = 0$ (male), in which case the j-th SNP can be modeled as:

$$\rho = 1: \ \Gamma_j = (\beta + \beta_{int})\, \gamma_j + \alpha_j$$
$$\rho = 0: \ \Gamma_j = (\beta)\, \gamma_j + \alpha_j$$

- InterMR can be used with two sex-stratified GWASs, but we show that integrating a sex-combined GWAS with larger sample size increases power.
- β and β_{int} are estimated using Gibbs sampling (by extension, $\beta + \beta_{int} \cdot \rho$ can be estimated by combining variables).

Overview of data analysis

- We used InterMR to identify exposures with sex-differentiated effects on Attention-deficit/hyperactivity disorder (ADHD).
  - Diagnosis of ADHD is much more frequent in males (Skogli 2013)
  - Symptoms of ADHD are different in males and females (Skogli 2013)
- Data used:
  - We used 54 GWAS available from the UChicago server for exposures.
    - 14 immunological, 8 metabolic, 7 gastrointestinal, 6 cardiovascular, 4 dermatological, 15 brain related
  - We used ADHD GWAS publicly available from the Psychiatric Genomics Consortium for the outcome.
    - European ancestry meta-analyses
    - Male-only GWAS (Martin 2018)
      - N = 32,102
      - Reference gender: $\rho = 0$
    - Female-only GWAS (Martin 2018)
      - N = 21,191
      - $\rho = 1$
    - Sex-combined GWAS (Demontis 2023)
      - N = 225,534
      - $\rho = 0.4961$
- For each exposure, we applied InterMR twice: first with just the two sex-specific ADHD GWAS and second jointly analyzing all three ADHD GWAS. We show that jointly analyzing all three ADHD GWAS increases the power to detect interaction effects.

Parameters of InterMR ADHD analysis

- IV Selection Criteria
  - p-value threshold of marginal IV-to-exposure effect < 1e-08
  - LD clumping window = 100 kb
  - LD clumping $r^2 < 0.01$
  - Analysis not conducted if number of IVs > 1,000
- InterMR settings
  - Prior settings: $\square = 0$ and $\square_{int} = 0$
    - We opted not to use estimates from other MR methods (IVW, MR-RAPS, etc.) because they may be biased due to pleiotropy or invalid IVs.
  - Number of iterations of Gibbs sampling: number of IVs · 50
    - Each IV adds a dimension, so we scale the number of iterations based on the number of IVs.
  - The first 20% of iterations are discarded (burn-in period), and the remaining 80% of iterations are used to estimate $\square$ (log odds ratio for males), $\square_{int}$ (interaction effect), and $\square + \square_{int}$ (log odds ratio for females).
- Analysis conducted in R

InterMR identified several exposures with sex-differentiated effects on ADHD

- At an alpha value of 0.05, InterMR identified 11 exposures with a statistically significant interaction effect. When only using the two sex-specific GWAS, InterMR identified only 8 such exposures, which were a subset of the 11.

Using all three ADHD GWAS

IV-to-exposure p-value < 1e-08. Clumping window = 100kb. Clumping r^2 < 0.01

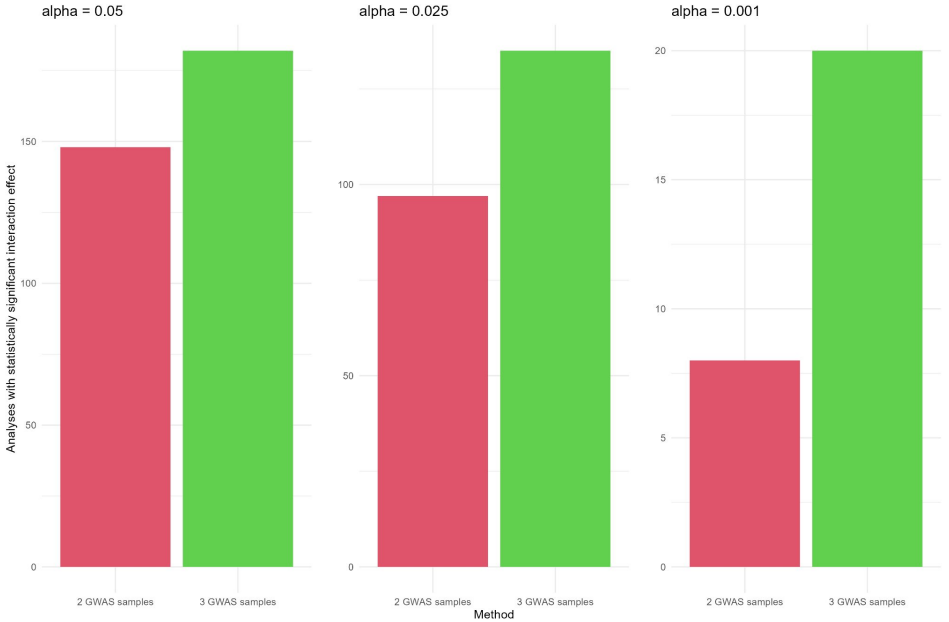
Exposure	Samples	# of IVs	β_int Estimate	β_int p-value	β Estimate	β p-value	β + β_int Estimate	β + β_int p-value
Hypertension	3	311	-0.6004	0.0006	0.6007	<1E-8	0.0003	0.9982
White blood cell count	3	377	0.1203	0.0017	-0.1699	<1E-15	-0.0497	0.1029
Eczema	3	21	0.1134	0.0024	0.0258	0.3906	0.1392	<1E-4
Reticulocyte count	3	479	0.1066	0.0043	-0.0823	0.0003	0.0243	0.3832
Myeloid count	3	321	0.1385	0.0049	-0.1527	<1E-7	-0.0142	0.6995
Granulocyte count	3	309	0.1249	0.0094	-0.1415	<1E-7	-0.0166	0.6382
Neutrophil + Eosinophil count	3	308	0.1182	0.0158	-0.1388	<1E-7	-0.0205	0.5794
High light scatter Reticulocyte count	3	468	0.1020	0.0217	-0.0360	0.1571	0.0660	0.0383
Birth Weight	3	52	0.3262	0.0279	-0.2479	0.0040	0.0783	0.5105
Allergic rhinitis or Eczema	3	250	-0.3672	0.0359	-0.0201	0.8242	-0.3873	0.0043
Psoriasis	3	137	0.2088	0.0414	-0.0205	0.6284	0.1883	0.0192

Using two sex-specific ADHD GWAS

Exposure	Samples	# of IVs	β_int Estimate	β_int p-value	β Estimate	β p-value	β + β_int Estimate	β + β_int p-value
Hypertension	2	311	-0.6021	0.0006	0.6857	<1E-8	0.0836	0.5194
White blood cell count	2	377	0.1045	0.0085	-0.1746	<1E-14	-0.0701	0.0308
Eczema	2	21	0.0881	0.1630	0.0169	0.6971	0.1051	0.0155
Reticulocyte count	2	479	0.0974	0.0248	-0.0915	0.0002	0.0059	0.8602
Myeloid count	2	321	0.1260	0.0099	-0.1626	<1E-8	-0.0366	0.3434
Granulocyte count	2	309	0.1196	0.0128	-0.1552	<1E-6	-0.0356	0.3601
Neutrophil + Eosinophil count	2	308	0.1161	0.0182	-0.1538	<1E-8	-0.0377	0.3885
High light scatter Reticulocyte count	2	468	0.0950	0.0257	-0.0464	0.0820	0.0486	0.1504
Birth Weight	2	52	0.2852	0.0960	-0.2811	0.0082	0.0041	0.9767
Allergic rhinitis or Eczema	2	250	-0.3182	0.0635	0.0053	0.9565	-0.3129	0.0245
Psoriasis	2	137	0.1975	0.0276	-0.0451	0.3614	0.1524	0.0382

InterMR had increased power to detect β_{int} with extra GWAS sample

- InterMR identified three more exposures with statistically significant β_{int} when also using the larger sex-combined GWAS.
- To investigate this difference with more precision, we combined results of different IV selection criteria
  - p-value threshold of marginal IV-to-exposure effect $\in$ {1e-08, 5e-08, 1e-05}
  - Clumping window $\in$ {50 kb, 100 kb, 200 kb}
  - Clumping $r^2 \in$ {0.01, 0.05}
  - This resulted in 1582 total analyses.
- We varied the alpha value from 0.05 to 0.001 and calculated the number of analyses with a statistically significant β_{int} for the two applications of InterMR.
- Our results showed that InterMR had more results with lower p-values when using the third sex-combined GWAS sample.



Conclusion

- Using the proposed InterMR, we identified 11 exposures with sex-differentiated effects on ADHD.
- We showed that InterMR performs better when more outcome GWASs are used.
- Next steps
  - We intend to expand our analysis to other neurological disorders (Alzheimer's disease, Autism spectrum disorder)
  - Compare results of our analysis to what is reported in literature
  - Apply InterMR to other outcomes and covariates

References

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