Progress Report

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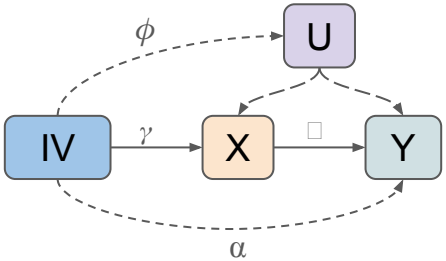
Project 1: Mendelian randomization analysis studying sex-specific effects of 33 complex traits on ADHD

Motivation for Study / Explanation of Mendelian Randomization

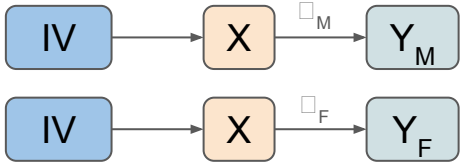
- Studies of ADHD have shown significant differences between sexes.
  - Diagnosis - male ADHD is diagnosed much more often
  - Symptoms - external in men while internal in women
- GWAS summary data was made available for ADHD split by sex
- This allows us to use Mendelian Randomization.



- 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 ($\phi = 0$)
- Correlated horizontal pleiotropy vs Uncorrelated horizontal pleiotropy

Overview of Analysis

- Data
  - GWAS summary statistics for 33 complex traits
  - GWAS summary statistics for ADHD, split by sex
- Goal
  - Identify exposures with sex differentiated effects on ADHD
- IV Selection Criteria
  - p-value of IV-to-exposure effect < 5e-8
  - Clump window = 500 kb
  - Clump $r^2 < 0.05$
- MR Analysis conducted in R with MR-RAPS



Several complex traits had different effects on ADHD for males and females

- Exposures showing non-zero effect in at least one sex
  - Upper section - non-zero effect in both sexes.
  - Lower section - non-zero effect in males only.

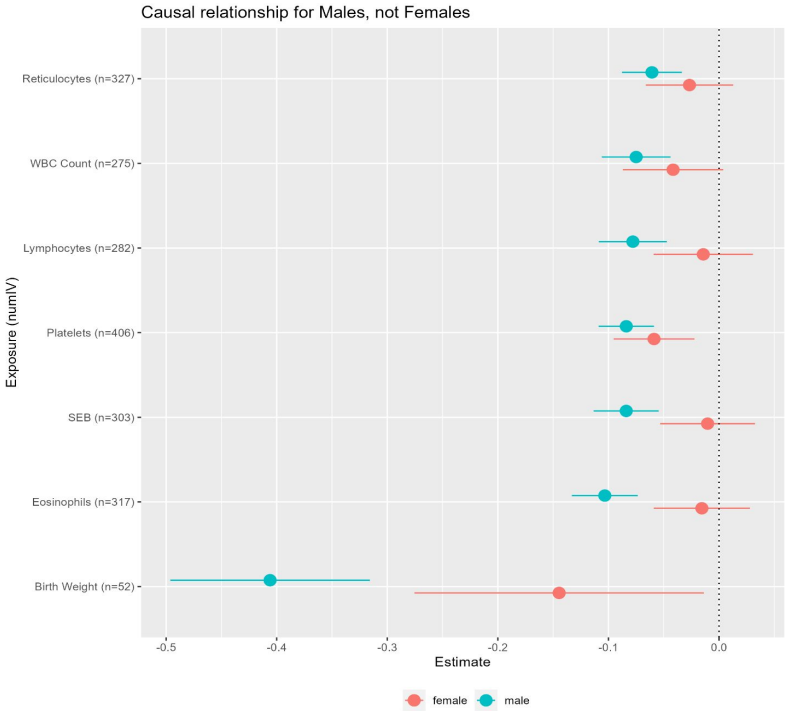
Exposure	# of IVs	Male Estimate	Male p-value	Female Estimate	Female p-value
Eczema	16	0.089	0.016	0.106	0.050
Body Fat	406	0.743	0.000	0.566	0.000
BMI	528	0.650	0.000	0.506	0.000
Neuroticism Score	87	0.164	0.000	0.170	0.001
SLE	81	0.026	0.002	0.028	0.017
Eosinophil Count	317	-0.103	0.001	-0.015	**0.723**
Lymphocyte Count	282	-0.078	0.012	-0.014	**0.752**
SEB	303	-0.084	0.004	-0.010	**0.811**
White Blood Cell Count	275	-0.075	0.016	-0.041	**0.361**
Platelet Count	406	-0.084	0.001	-0.059	**0.108**
Reticulocyte Count	327	-0.061	0.025	-0.027	**0.500**
Birth Weight	52	-0.406	0.000	-0.145	**0.269**

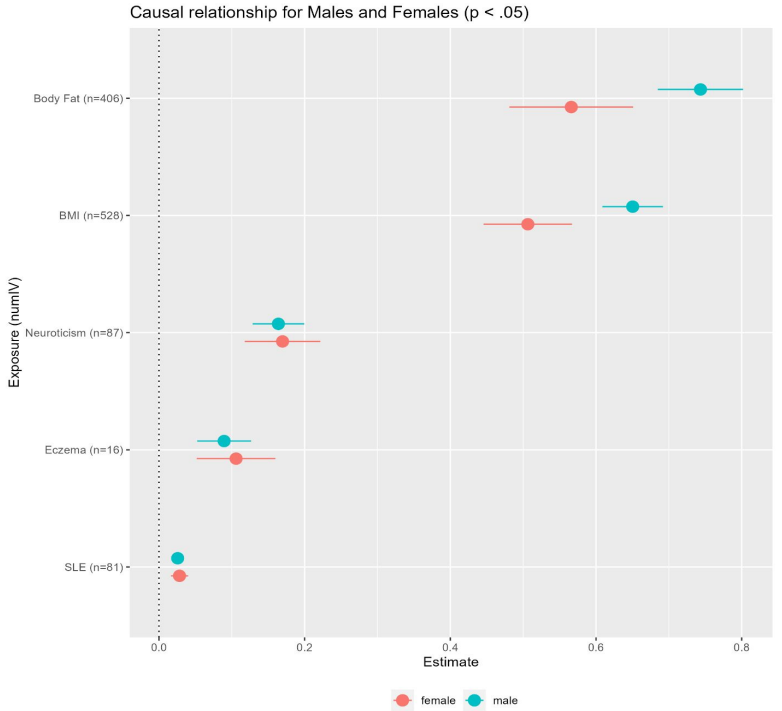
Abbreviations: Systemic lupus erythematosus (SLE), Body mass index (BMI), Sum of Eosinophil and Basophil counts (SEB)

- Birth Weight, White Blood cells (and their parts), and other blood cell related complex traits were showed a causal relationship for males only.
- No complex traits showed a causal relationship for females but not for males.

Plot

- Birth Weight has a much greater difference between sexes.



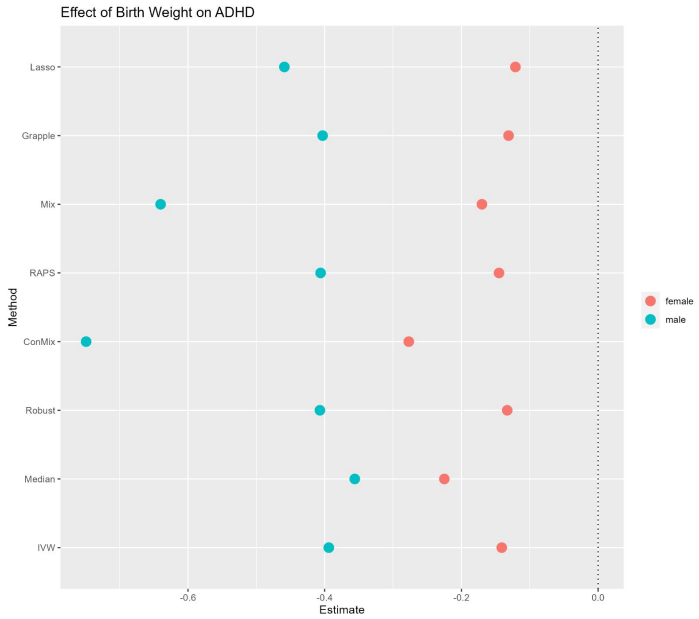


Case Study - Birth Weight
Other MR methods show consistent results

- Several MR other methods used to confirm that Birth Weight has a causal effect for males and not females.

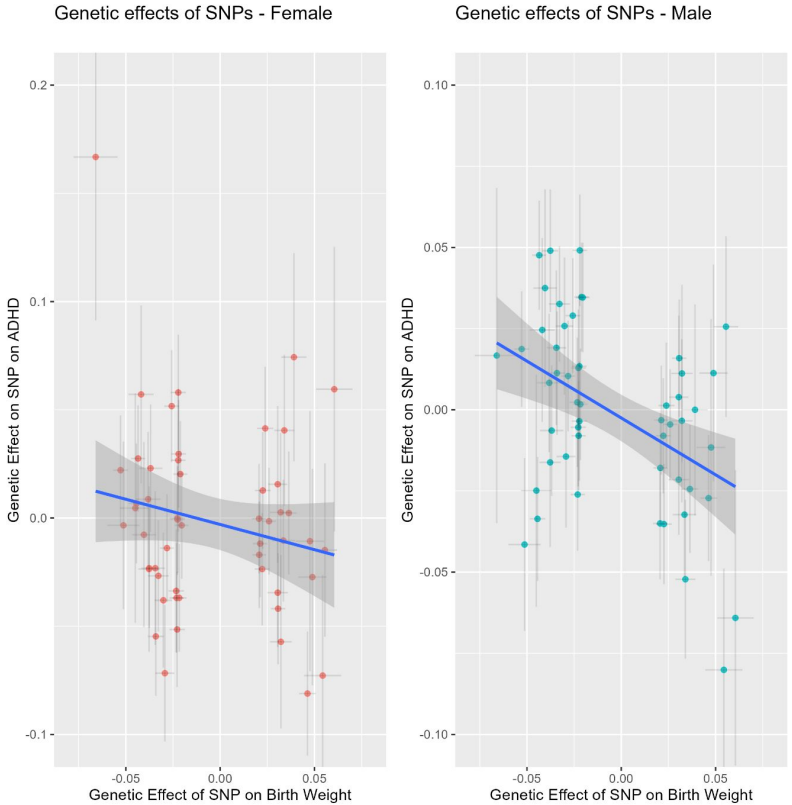
Method	Male Estimate	Male p-value	Female Estimate	Female p-value
IVW	-0.394	**<0.001**	-0.141	0.348
Robust	-0.407	**<0.001**	-0.133	0.383
RAPS	-0.406	**<0.001**	-0.145	0.269
Grapple	-0.403	**<0.001**	-0.131	0.414
Lasso	-0.459	**<0.001**	-0.121	0.377
ConMix	-0.749	**0.001**	-0.277	0.203
Median	-0.356	**0.010**	-0.225	0.262
Mix	-0.640	**0.039**	-0.170	0.564
Mode	-0.403	0.180	-0.227	0.497
Egger	-0.014	0.967	-0.746	0.125

- Mode based estimate was weak but the result is consistent with the other methods.



Case Study - Birth Weight
Scatterplots of effect size of SNPs on BW and ADHD

- Scatterplot shows steeper slope, less variability in the regression line for males, in agreement with previous conclusions.



Literature - Birth Weight

- Martel, 2007
  - Slightly, but not significantly stronger relationship between birth weight and ADHD for boys then for girls.
- Martel, 2013
  - **Sexual Selection Theory**: Higher exposure to prenatal testosterone may cause males to be more susceptible to prenatal stressors, with downstream effects.
- Momany, 2016
  - Significantly stronger interaction between birth weight and ADHD for males relative to females.
- DiPietro & Voegtline, 2017
  - Male fetuses exposed to prenatal and perinatal adversities are more impaired than female fetuses.
  - Male fetuses are more frequently exposed to and more affected by early adversities.
- Dooley, 2022a
  - Sex moderated the effect of birth weight, inverse associations were strongly driven by males.
- Dooley, 2022b
  - Stronger associations between BW and attention/hyperactivity were observed in males
  - Potential difference in US based populations and other populations (Ireland, Sweden, Meta-Analysis)

Conclusions - Project 1

- Several exposures were differentiated by sex in effect on ADHD
  - Exposures with differences between sex were typically causal for males and not females.
  - Birth weight, blood cells.
  - MR analysis consistently showed a much stronger association between BW and ADHD in males compared to females.
    - MR-RAPS: $\theta_M = -0.406$, $p < .0001$ compared to $\theta_F = -0.145$, $p < .27$.
  - Literature support for the conclusion that LBW has a stronger association with ADHD for males than females.
    - Several papers provided theoretical explanations for this effect (such as Sexual Selection Theory).

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Project 2: Multivariable Mendelian randomization analysis mapping risk genes with cell-type-specific effects on Alzheimer's Disease

(Work in progress)

Explanation of Study and Multivariable Mendelian Randomization

- Goals:
  - Map risk genes with cell-type specific effects
  - Compare the results to analysis with bulk tissue
- Inputs
  - sc-eQTL summary statistics from 8 brain cell types from Bryois 2022 study
  - GWAS summary statistics for Alzheimer's Disease
- Multivariable Mendelian randomization
  - MVMR analyzes 8 cell types jointly
- Valid IVs follow 3 assumptions:
  - i. IV is associated with at least one exposure
  - ii. IV is associated with the outcome only through exposures
  - iii. IV is not associated with potential confounders

Overview of Analysis

- We conducted MVMR analyses using the 8 brain cell types from the Bryois study as exposures and Alzheimer's Disease as the outcome.
- IV Selection Criteria
  - p-value of IV-to-exposure effect < 0.005
  - Clump $r^2 < 0.1$
- Genetic variants with significant effect on any exposure were kept for LD clumping.
  - If after IV selection any exposure had 0 IVs, analysis was not conducted.
- MVMR analysis conducted in R with multivariable IVW Mendelian Randomization
- Analysis was conducted restricted to genes in AD-related pathways.
  - Example: Nitric oxide (NO) pathway: dysfunctional endothelial cells decrease NO bioavailability, leading to inflammation. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3721957/)

Found many genes with cell-type-specific effects on Alzheimer's Disease

Pathway	Astrocytes	EndothelialCells	ExcitatoryNeurons	InhibitoryNeurons	Microglia	Oligodendrocytes	OPCsCOPs	Pericytes
NO	1/11	4/12	0/11	0/8	0/8	0/6	0/9	1/8
Cytokine	2/47	6/71	5/46	1/41	3/53	0/22	5/39	4/61
NFKB	3/35	2/38	3/30	2/28	1/35	3/24	2/28	1/28
TNF	3/48	3/57	7/49	2/40	0/41	2/31	2/35	3/38
WNT	8/64	2/61	4/75	2/71	3/35	6/42	9/61	7/45
TGF	0/24	2/33	2/33	3/27	0/18	1/22	4/23	1/26
VEGF	1/22	0/24	3/32	2/29	2/18	2/18	1/21	1/10

Key: 1/11 = Out of 11 genes cell type was present in, 1 showed a significant effect ($p < 0.05$)

- In NO pathway, more genes had cell-type-specific effects in Endothelial cells.
- In TNF pathway, more genes had cell-type-specific effect in Excitatory neurons.
- Other pathways had enrichments of more than one cell type.

Conclusions - Project 2

- Found many genes with cell-type specific effect on Alzheimer's disease.
- Next steps
  - Look at how often a gene had an effect for only one cell type
    - Which cell type has this most often?
    - Or do genes typically have significant effect for multiple cell types?
  - Compare to results from bulk tissue
  - Work with Yihao on applying mintMR with deep multi-view learning methods on integrating sc-eQTL and ct-eQTL data for mapping risk genes.