P17.015.D Impact of control selection strategies on GWAS results: a study of Schizophrenia and Bipolar Disorder in the UK Biobank

Jingzhan Lu[1, 2], Johan H Thygesen[2], Andrew McQuillin[3], Harry D Green[1]

Affiliations: [1]Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK. [2]Institute of Health Informatics, University College London, London, UK. [3]Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, London, UK.

Background

As GWAS studies move from array-based genotyping to whole exome (WES) and whole genome (WGS) sequencing, there is a significant increase in cost. For disease phenotypes, case-control selection may be a useful technique for minimising resource intensity while maintaining statistical power. This is particularly relevant to studies of disease in a general population like the UK Biobank (N=500,000), where there is often a surplus of available healthy controls. This investigation aims to explore the impact of different strategies for control selection on the results and cost- benefit of GWAS studies.

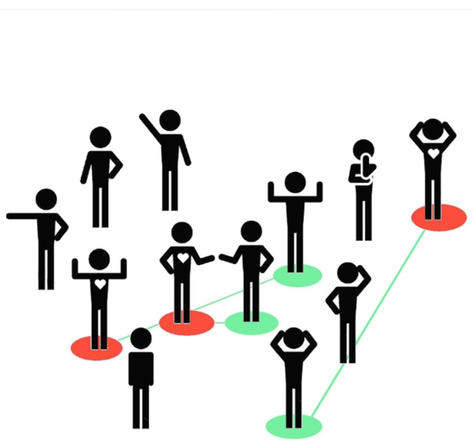
Methods

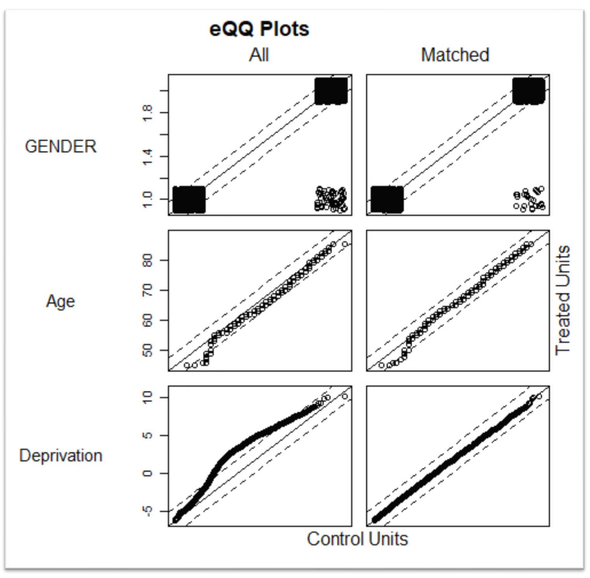
The study included 1,988 Schizophrenia (SCZ) and Bipolar Disorder (BD) cases of European ancestry from the UK Biobank (UKB), with a 1:4 case-to-control ratio. Individual GWAS were conducted under each strategy using REGENIE. We assessed the impact of three control selection strategies on GWAS combining SCZ and BD with covariates: age, gender and deprivation. These $S_{1\text{-}3}$ were:

S1: Random selection without covariates
S2: Case/control matched analysis with covariates
S3: (Another) Random selection with covariates

Results were compared with the Psychiatric Genomics Consortium (PGC 2022), the largest GWAS meta-analysis to date, which was considered the gold standard.

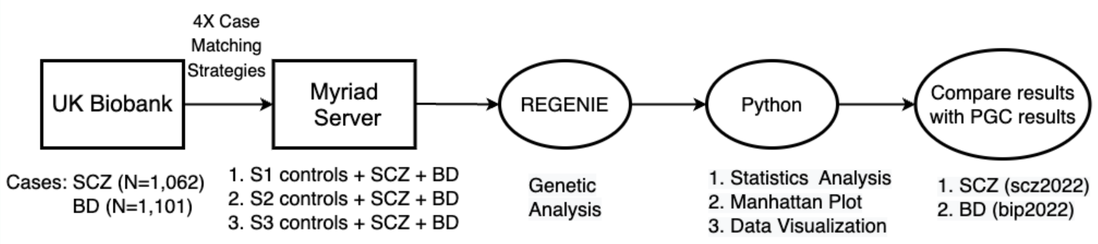
Matching





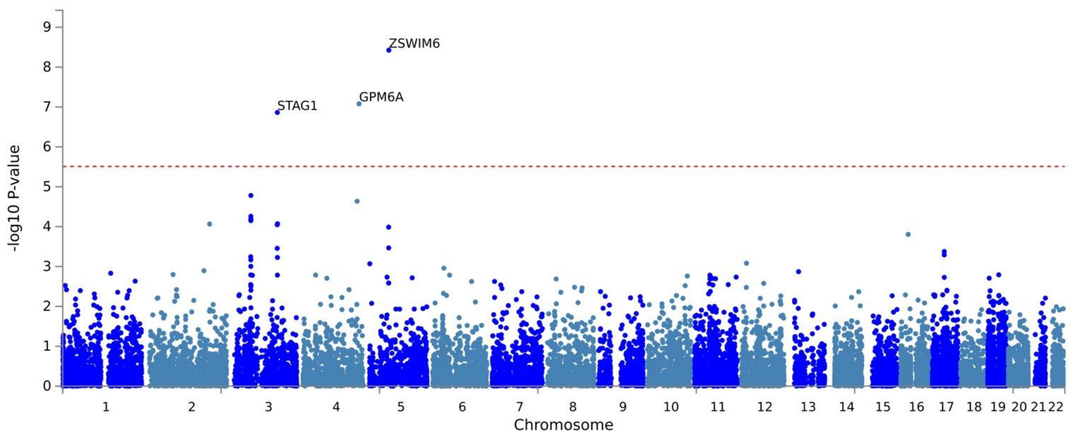
A total of 1,988 SCZ and BD cases were combined in the GWAS. The $S_{1\text{-}3}$ selected 4X controls from the 405,949 available cohort of UKB.

Flowchart

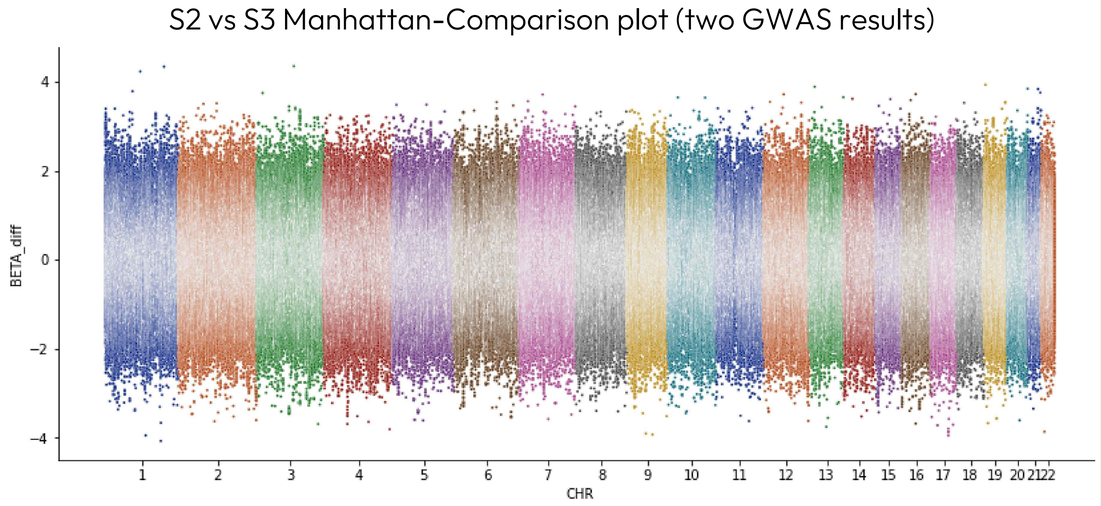


Manhattan-Comparison Plot Development

Example of Manhattan plot (one GWAS result)



S2 vs S3 Manhattan-Comparison plot (two GWAS results)



Results & Discussion

Equation: $\text{p\_diff} = \frac{|(S_{123})_p - PGC_p|}{SNP_{\text{num}}}$, num is the overlapping SNPs

PGC	Compare Items	Strategy 1	Strategy 2	Strategy 3
PGC SCZ				
	p_diff	-0.03	0.0002	-0.021
p mean = 0.426	*p_abs_diff*	0.382	**0.384**	0.375
β mean = -0.002	β_*diff*	0.002	**-0.001**	-0.010
	β_*abs_diff*	0.189	0.419	0.426
PGC BD				
	p_diff	-0.037	-0.003	-0.027
p mean = 0.441	*p_abs_diff*	0.383	**0.387**	0.380
β mean = -0.0016	β_*diff*	**-0.001**	**-0.004**	-0.014
	β_*abs_diff*	0.190	0.430	0.434

Overall, S2 (matching) showed the best performance for GWAS, matching the PGC results the closest. This suggests that the matching process makes the controls and cases more similar at the level of covariates.

Future Plans

This preliminary work shows case-control matching performs better than adjusting the model for the same covariates. Future work will compare case-control matching with using all controls, test in other disease phenotypes, and measure the impact of matching when resource-intensive WGS techniques are used.

@JingzhanLu

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Interested in this project and want to hear more / collaborate or contribute please write to: jl1426@exeter.ac.uk