Morningness and Related Traits: SNP-heritability, Genetic Correlation, and Causal Effects

25 Fall STAT 605 Final Project

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Questions of Interest

Morningness (also called chronotype) describes an individual's preference of getting up early.

Among 9 sleep/health traits *(BMI, height, obesity, depression, education attainment, blood pressure, smoking, insomnia, and snoring)* around morningness, what are

(i)   SNP-heritability of each trait,

(ii) pairwise genetic correlations,

(iii) causal effects of morningness?

Preliminary: What is GWAS data?

➤ Genome-Wide Association Study

➤ Screening the entire genome of large numbers of individuals to look for **associations between millions of genetic variants and traits**

➤ We can see **effect size, risk measure, and significance** in a GWAS data for one trait.
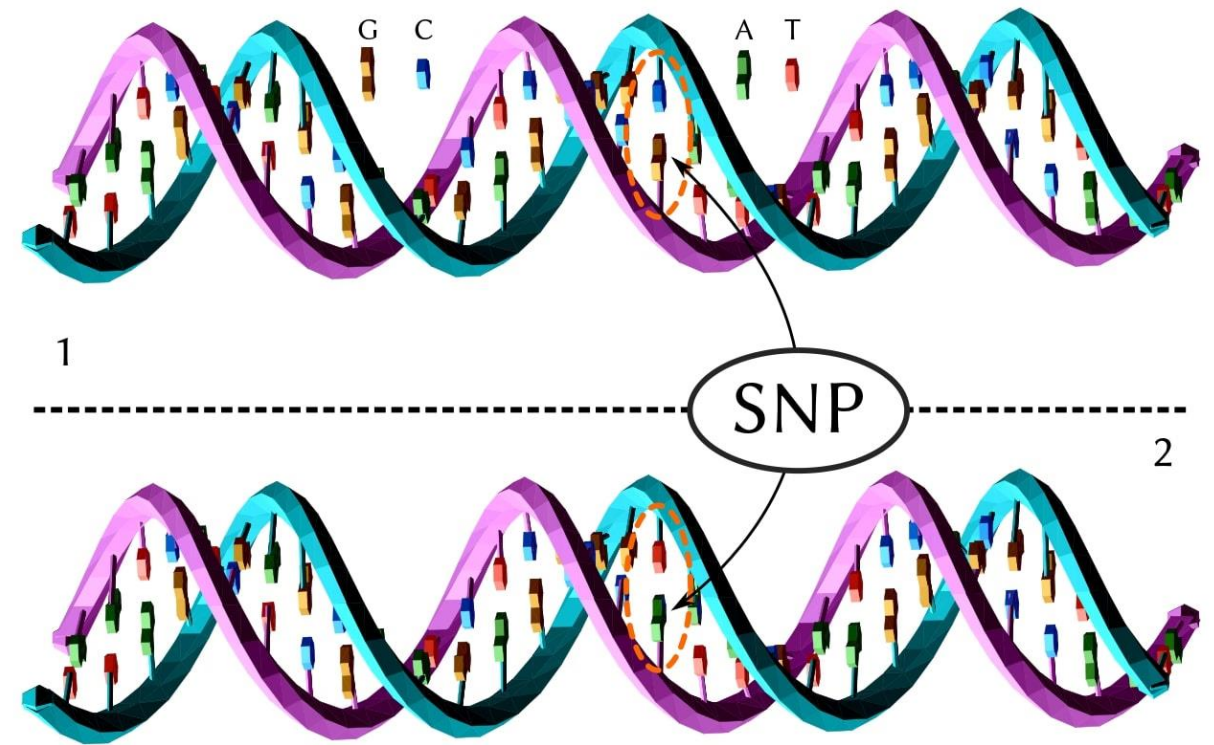
Data

We plan to collect **GWAS** data of 10 traits we previously discussed. These GWAS data can be obtained from GWAS Catalog (https://www.ebi.ac.uk/gwas/home). We have uploaded our data to https://uwmadison.box.com/s/e4yqg7amxiz8w3372te8dpzjkd2i09rw. Take GWAS data of morningness as example, there contains 11 variables:

Variable	Description
SNP	RSID of variant (or CHR:POS_A1_A0 if no RSID available)
CHR	Chromosome number
BP	Chromosomal position (b37)
ALLELE1	Effect allele that LOGOR corresponds to
ALLELE0	Non-effect allele
A1FREQ	Frequency of ALLELE1
INFO	Information metric indicating imputation quality
LOGOR	Log odds ratio for ALLELE1
LOGOR_SE	Standard error of log odds ratio
P_BOLT_LMM	Non-infinitesimal mixed model p-value
HWE_P	Hardy-Weinberg equilibrium test p-value (~380k samples)

Methods

1. SNP-Heritability via LD Score Regression

SNP heritability h^2 quantifies how much of the trait variance can be explained by all common SNPs, it can be computed as the regression slope of **LD Score Regression**,

$$Z_i^2 \sim 1 + \frac{N}{M} \cdot h^2 \cdot LDscore_i$$

where

- Z_i^2 denotes the squared marginal Z-statistic from GWAS data;

- N is the effective sample size;

- M is the number of SNPs contributing to the polygenic architecture;

- $LDscore_i$ captures the amount of heritable variation tagged by SNP (i), which can be downloaded from https://github.com/bulik/ldsc.

10 parallel jobs on CHTC

Methods

2. Pairwise Genetic Correlation via LD Score Regression

Genetic correlation measures the extent to which the same genetic variants influence both traits. It can also be computed by LD score regression,

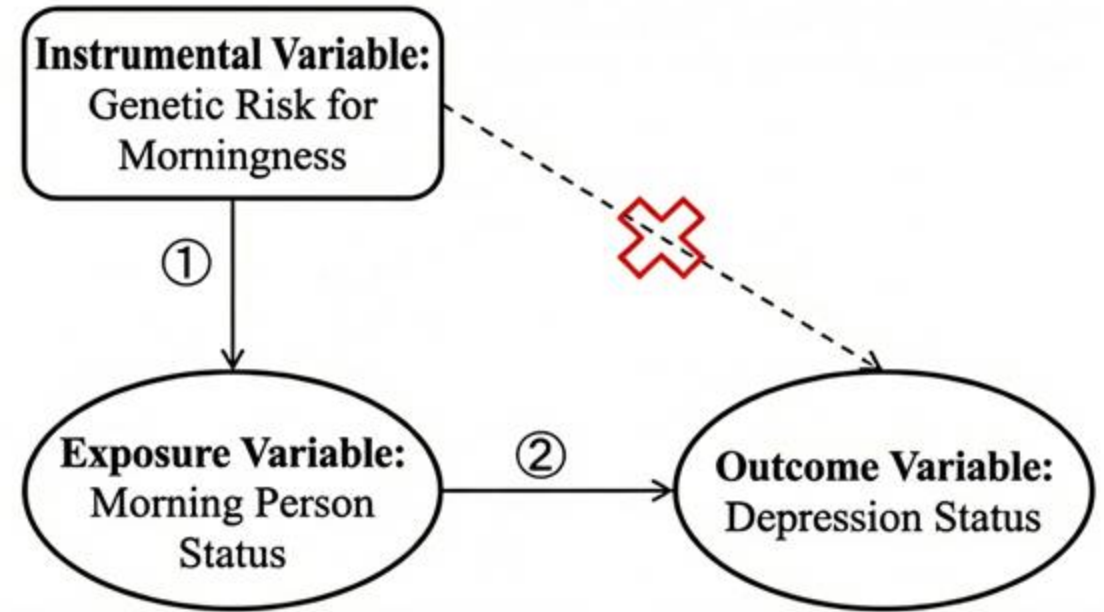$$Z_{i1}Z_{i2} \sim 1 + \frac{\sqrt{N_1 N_2}}{M} \cdot r_g \cdot LDscore_i$$

where

- Z_{i1}, Z_{i2} are Z-scores from two GWAS data;

- N_1, N_2 are sample sizes of two GWAS data;

45 parallel jobs on CHTC

Methods

3. Mendelian Randomization

Mendelian Randomization uses significant genetic variants as **instrumental variables** to infer the causal effect of an exposure on an outcome.

$$① \; Logit\big(\mathbb{P}(morningness = 1)\big) = \alpha_0 + \alpha_1 GeneticRisk + \boldsymbol{\alpha_2^T X} + \epsilon$$

$$② \; Logit\big(\mathbb{P}(depression = 1)\big) = \beta_0 + \beta_1 GeneticRisk + \boldsymbol{\beta_2^T X} + \epsilon$$

Causal Effect of Morningness on Depression: $\dfrac{\beta_1}{\alpha_1}$
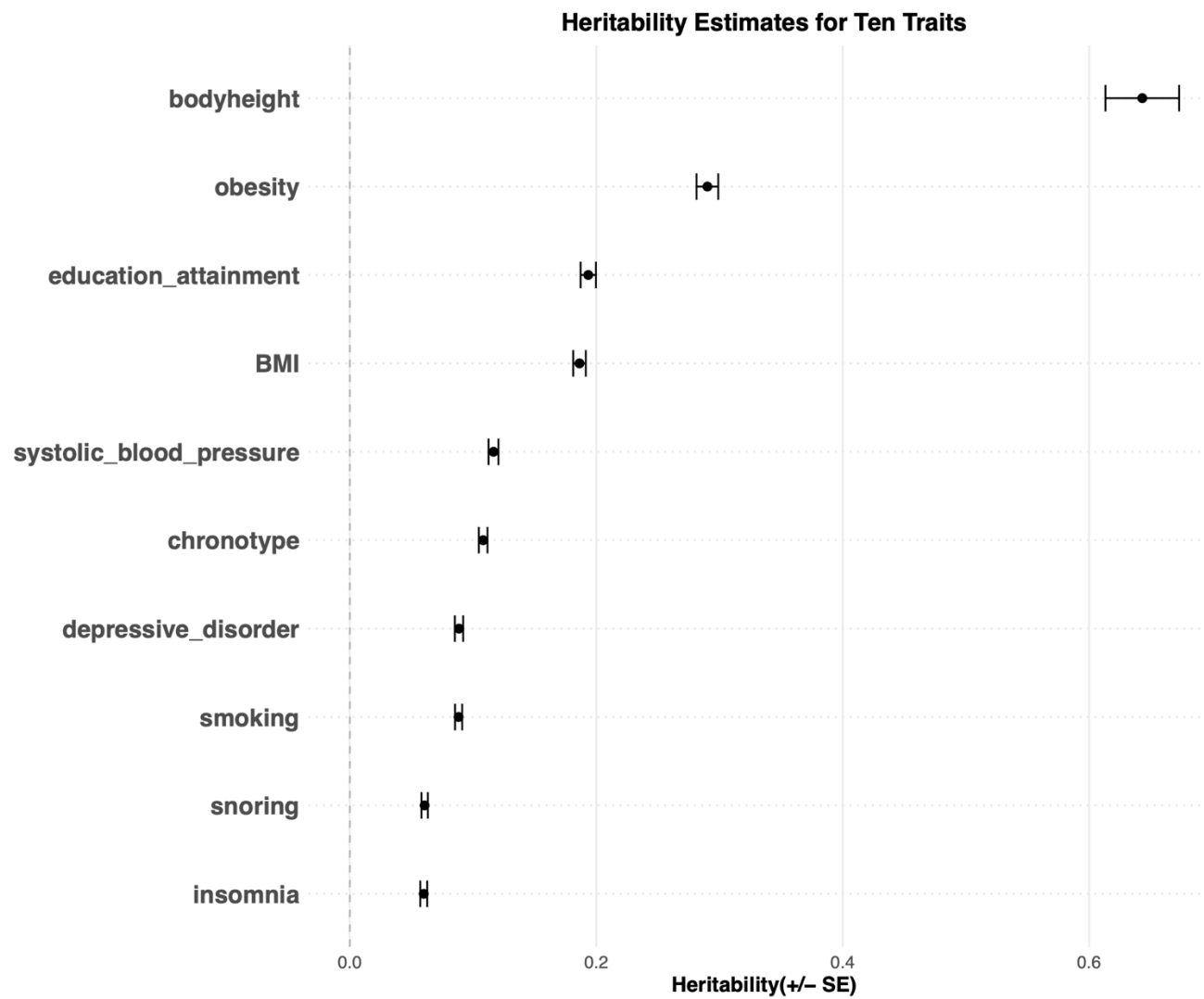
5 parallel jobs on CHTC

Results

O. Manhattan plot of Morningness (chronotype)
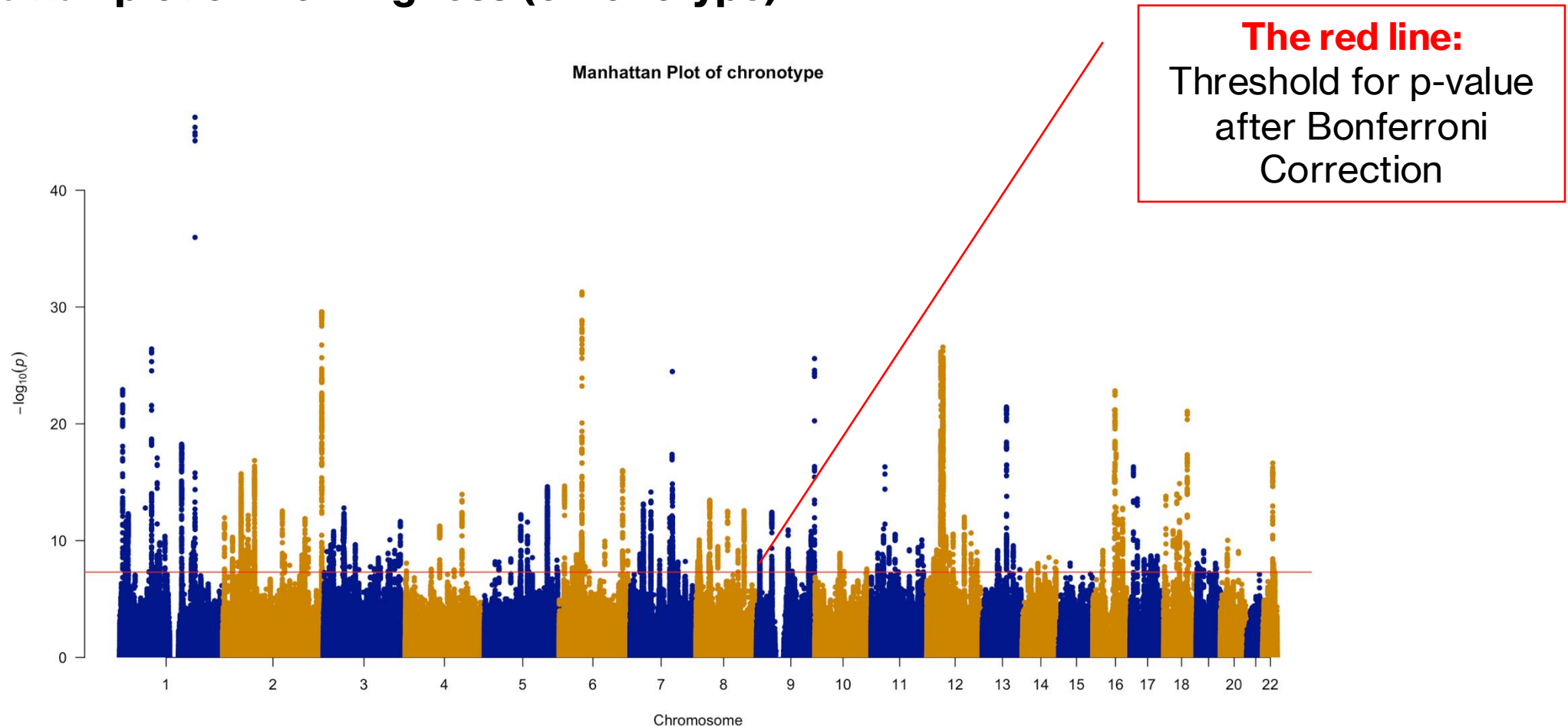
We made Manhattan plot for all ten traits of interest (10 parallel jobs on CHTC). Here we only present one of them for an example.

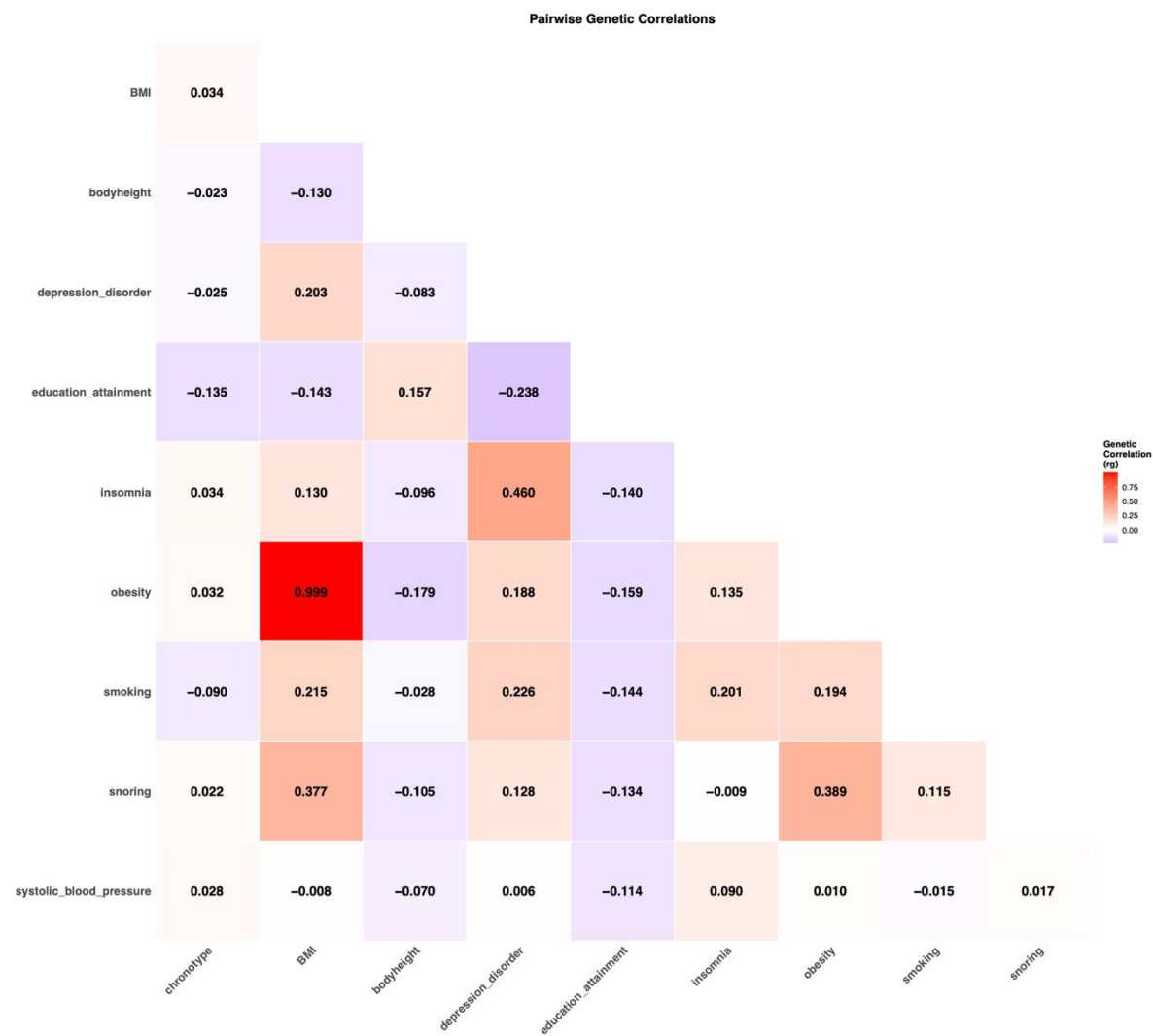# **Results**

1. **Heritability Estimates for Ten Traits**

Heritability Estimates for Ten Traits

| Trait	Heritability (h2)	SE
Body height	0.6431	0.0299
Obesity	0.2902	0.0088
Education attainment	0.1935	0.0062
BMI	0.1864	0.0051
Systolic blood pressure	0.1166	0.0040
Chronotype (Morningness)	0.1082	0.0035
Depressive disorder	0.0886	0.0034
Smoking	0.0883	0.0029
Snoring	0.0607	0.0026
Insomnia	0.0600	0.0028

Results

2.   Pairwise Genetic Correlation

Pairwise Genetic Correlations
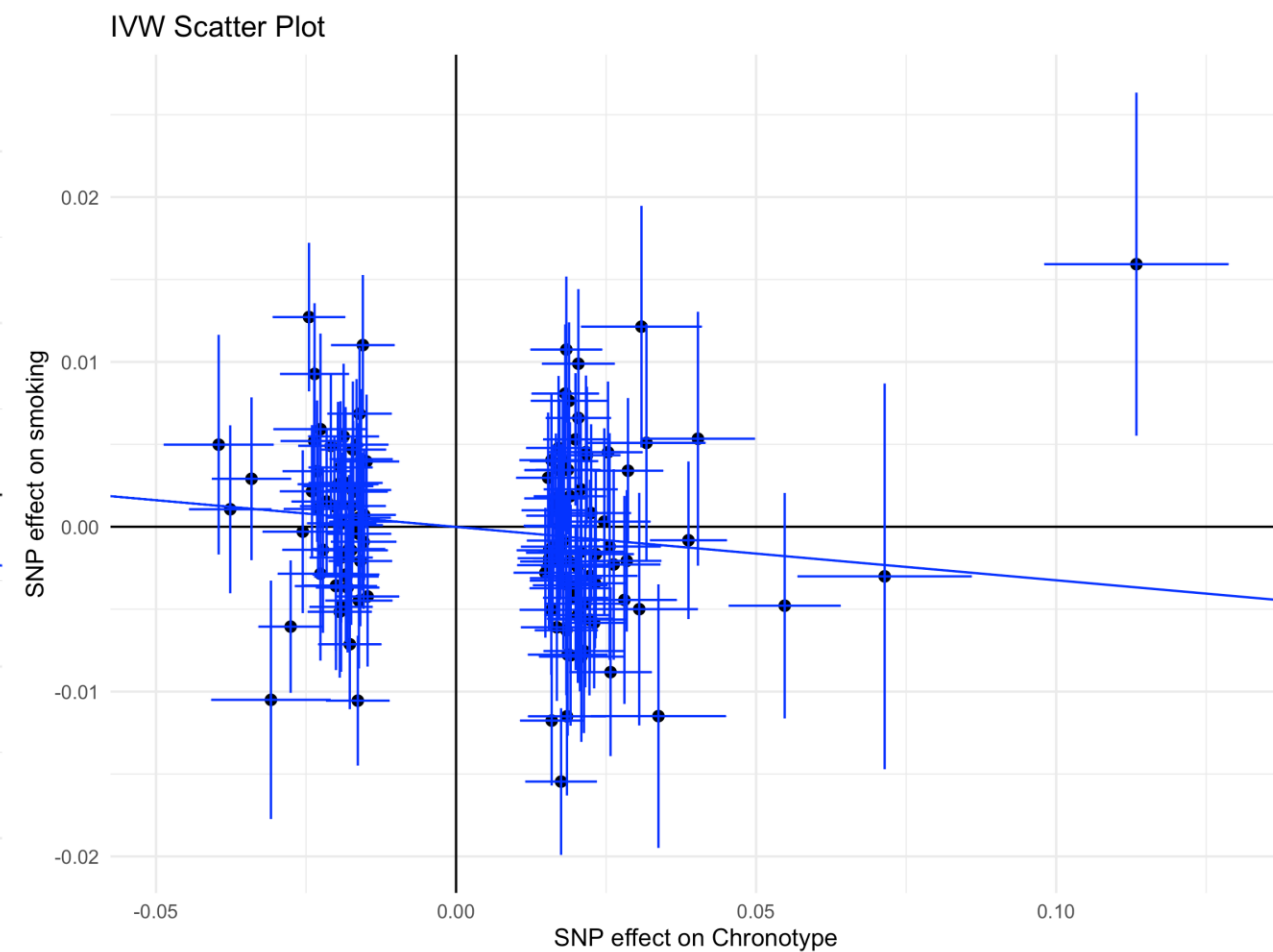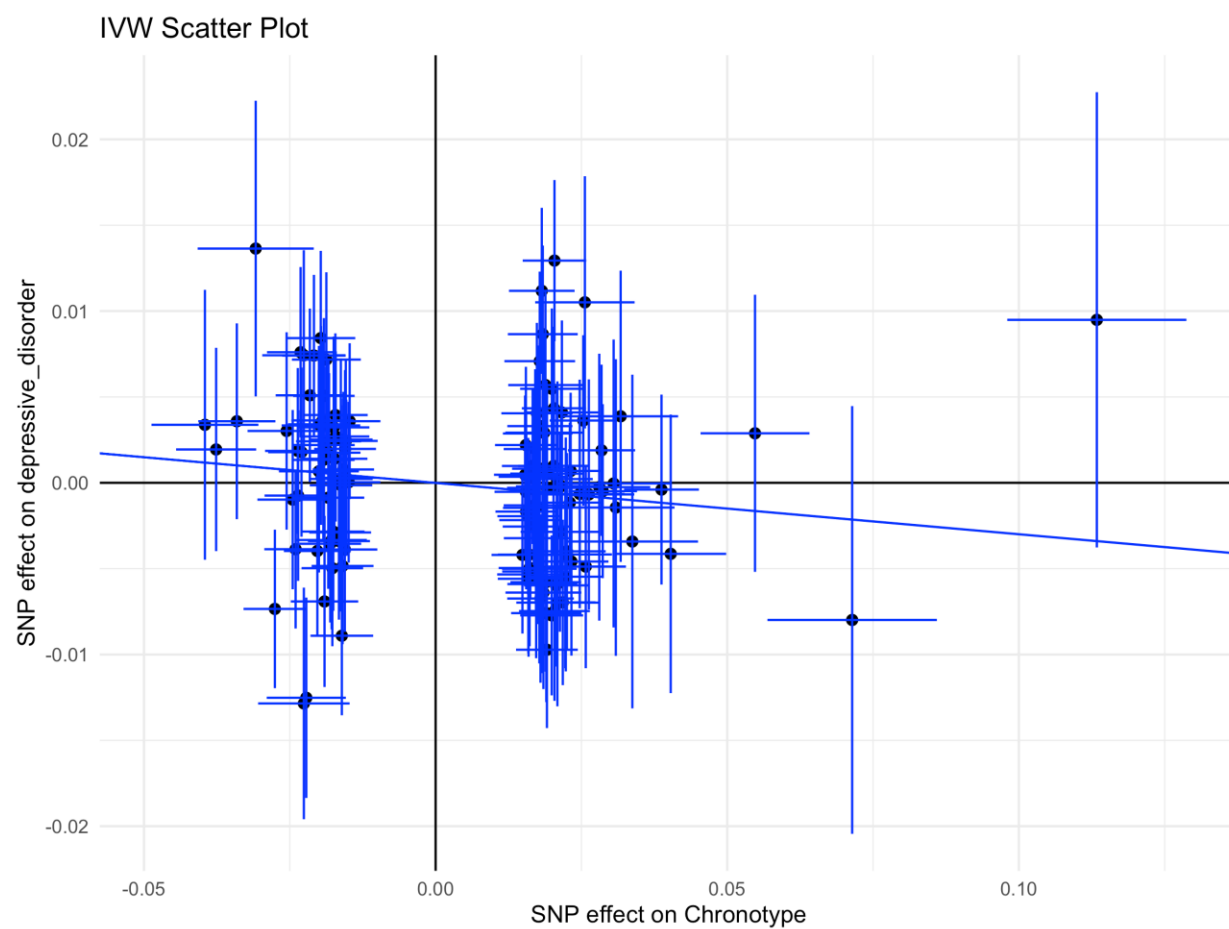
Results
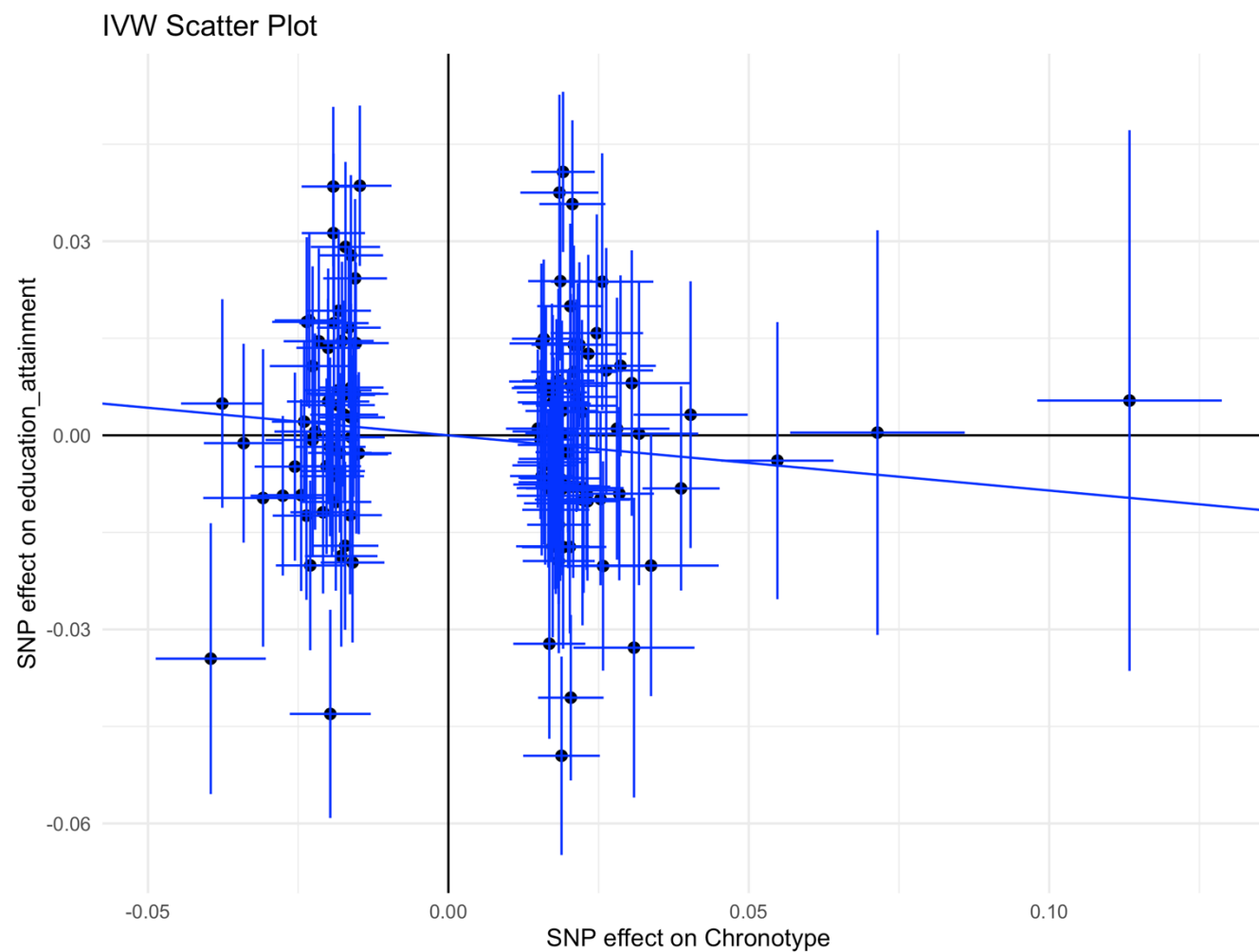
3.1 Causal effect of chronotype on BMI and insomnia
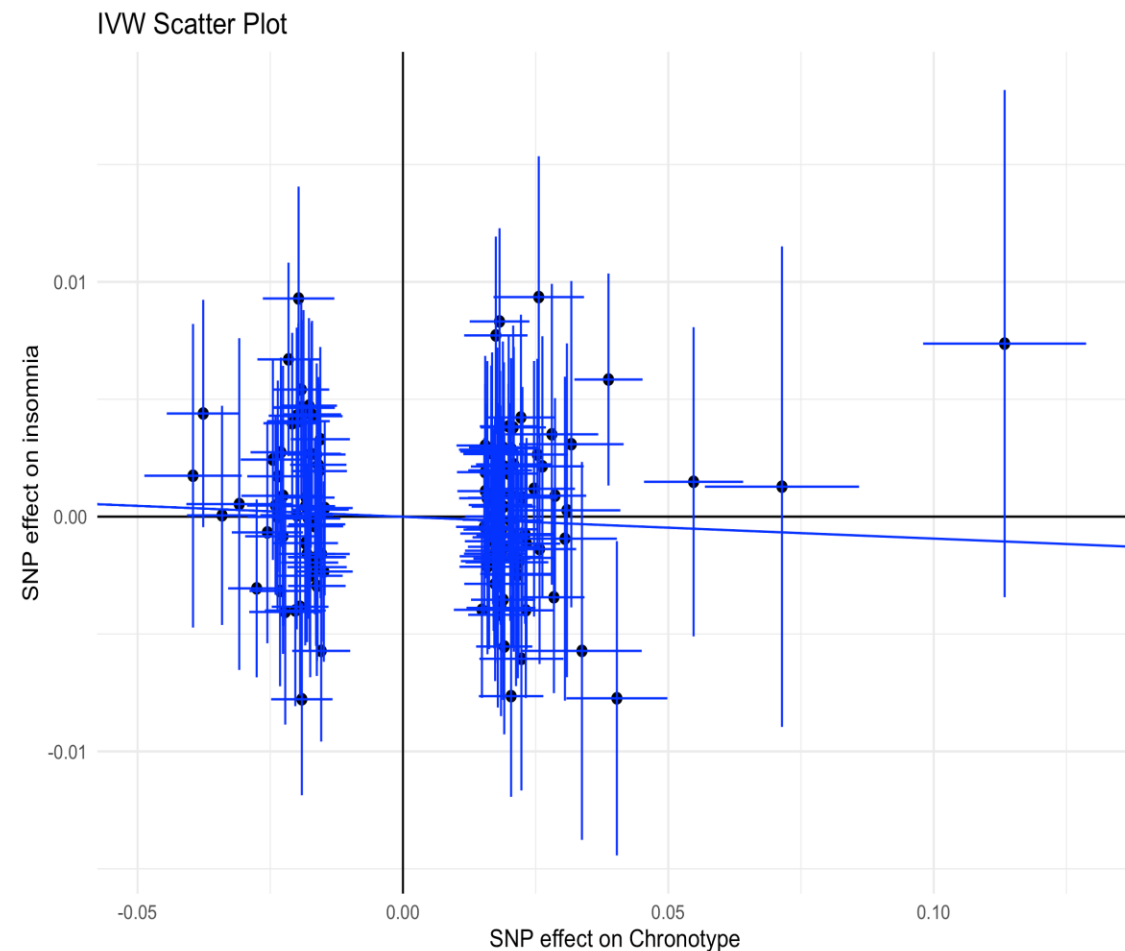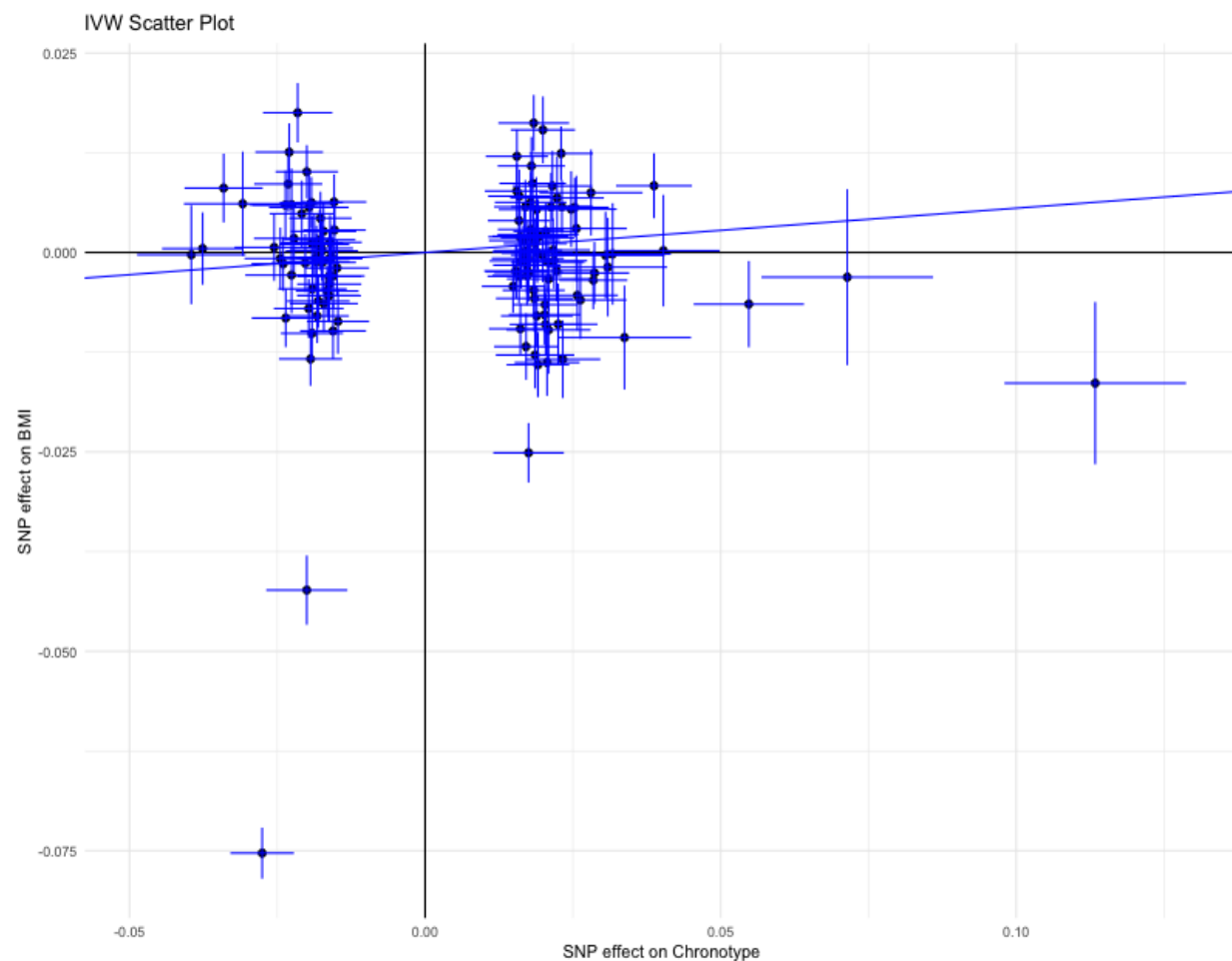
Results

3.2   Causal effect of chronotype on depression and smoking

Results

3.3   Causal effect of chronotype on education attainment

IVW Scatter Plot

Thanks for Listening!

Q & A