

A NOVEL APPROACH IDENTIFIED SEVEN GENE-ALCOHOL OR GENE-SMOKING INTERACTIONS THAT CONTRIBUTE TO SERUM LIPIDS

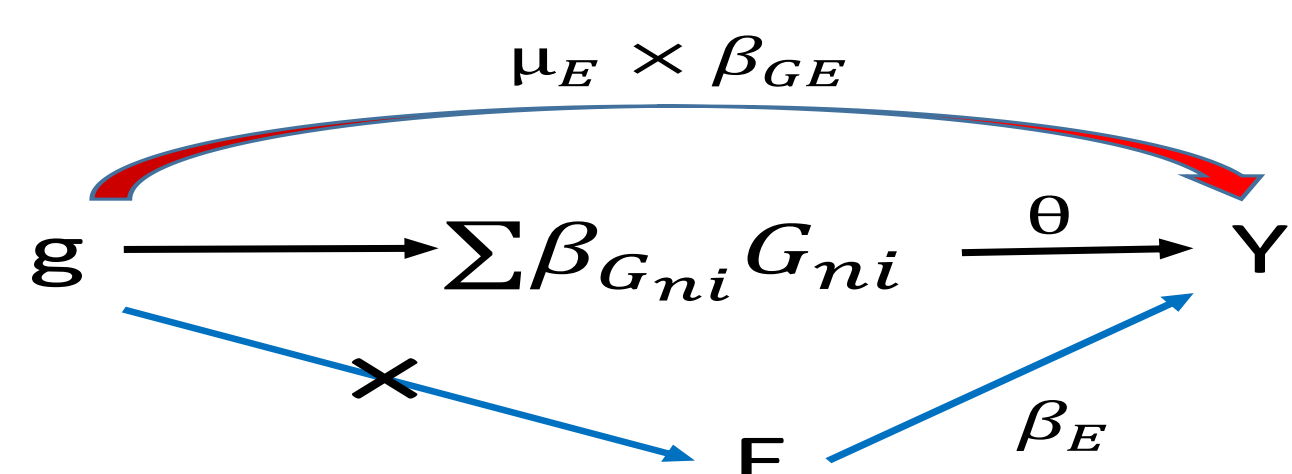
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- 1) Association tests focus on the differences of mean phenotype for different genotype groups
- 2) Mean differences of genotype groups can be affected by environmental factors, i.e. gene by environment interaction (GxE)
- 3) Power to detect GxE requires a large sample size, as demonstrated by multiple large GxE interaction studies in the CHARGE Gene Lifestyle Interactions Working Group

METHODS

G x E study:



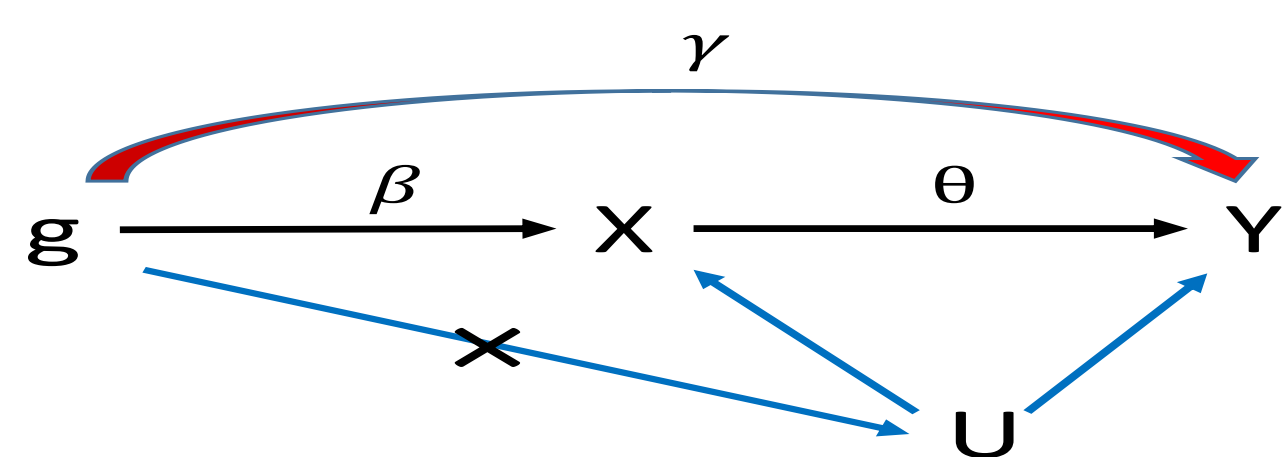
$$Y = \beta_0 + \beta_G g + \beta_E E + \beta_{GE} E \times g + \varepsilon_1$$

$$\text{GWAS: } Y = \alpha_0 + \alpha_G g + \varepsilon_2$$

$$\alpha_G = \beta_G \times 1 + \mu_E \times \beta_{GE}$$

$$\alpha_G = \beta_G \text{ is equivalent to } \beta_{GE}=0$$

Mendelian Randomization (MR)



$$X = \beta g + U + \varepsilon_1$$

$$Y = \theta X + \gamma g + U + \varepsilon_2 = \Gamma g + U + \varepsilon_2'$$

$$\Gamma = \beta \times \theta + \gamma$$

Test pleiotropy by testing $H_0: \Gamma = \beta \times \theta$ (MR-PRESSO, IMRP)

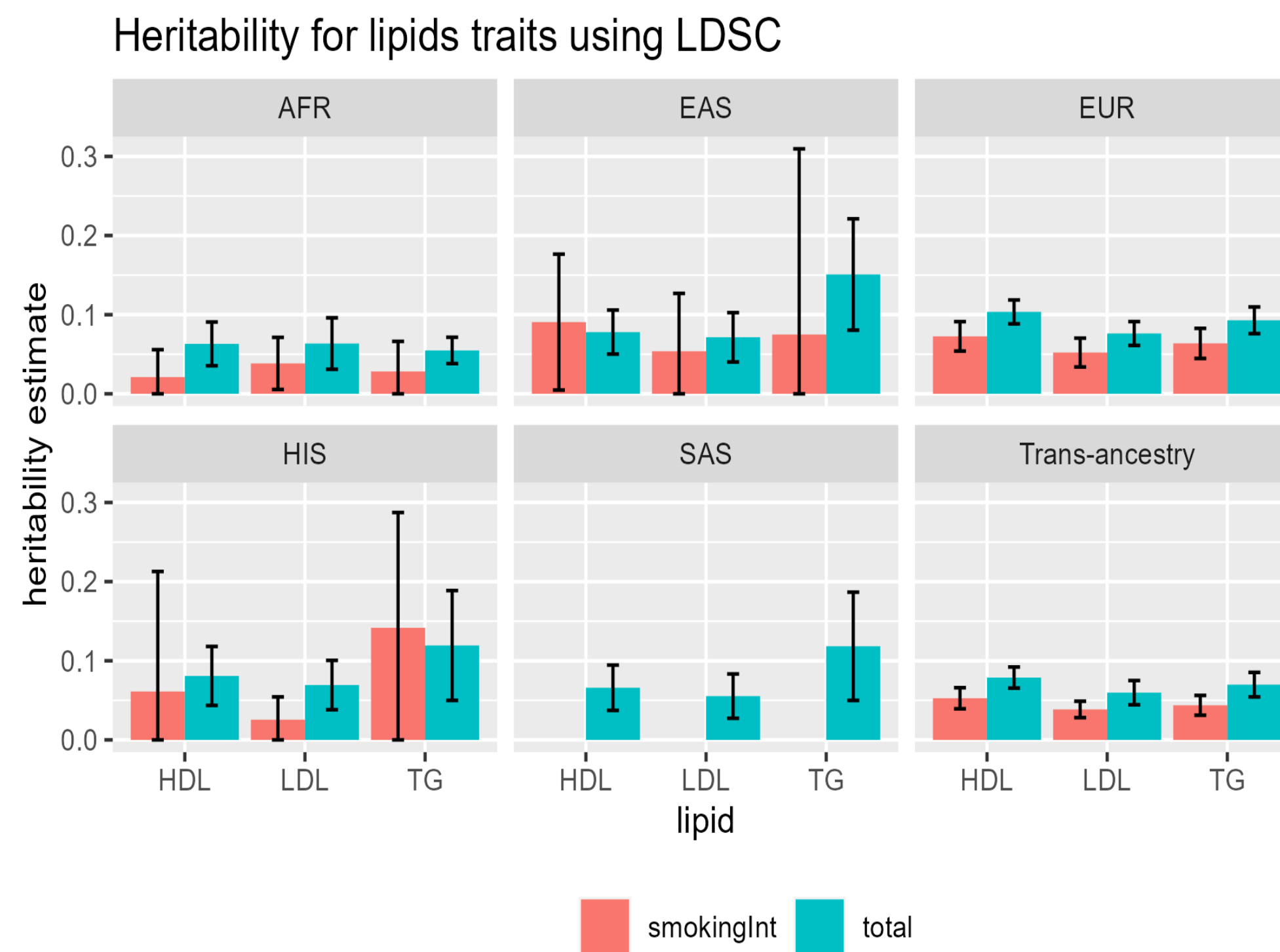
Thus, testing for interaction is similar to testing for pleiotropy in MR

Data: Summary statistics from GLGC GWAS of lipids with 1.5M samples.

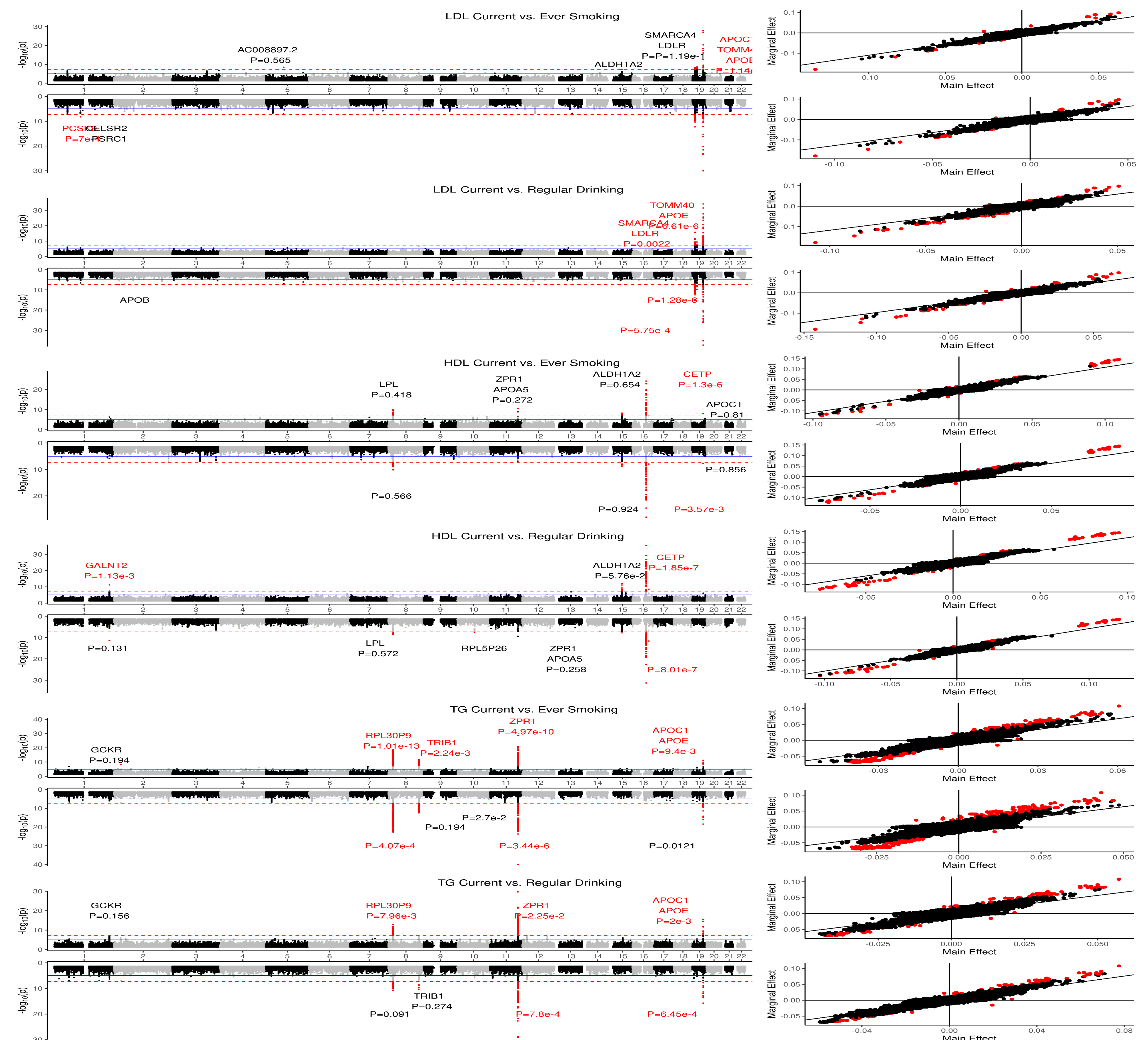
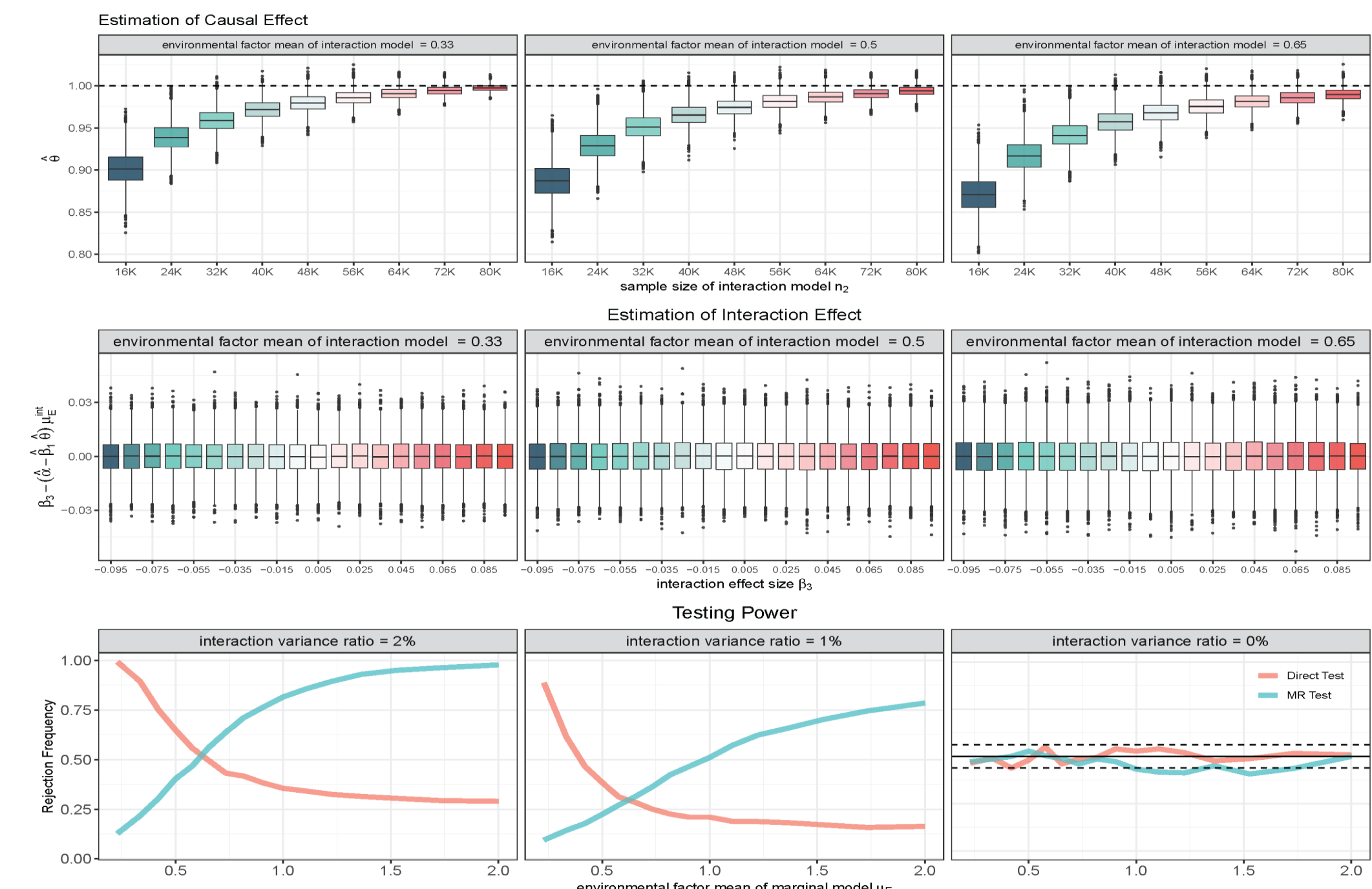
Summary statistics from Gene-lifestyle interactions (gene x smoking and gene x alcohol drinking)

Reference:

SE Graham et al. Nature 2021
AE Bentley et al. 2019, Nat Genet
PS de Vries et al. 2019, Am J Epidemiol
X Zhu et al. 2021. Bioinformatics



SIMULATIONS: ESTIMATE OF θ & INTERACTION EFFECT, POWER AND TYPE I ERROR



Summary:

Gene x alcohol drinking:

LDL-C: *APOE*, *LDLR*, *PCSK9*

HDL-C: *GALNT2*, *CETP*

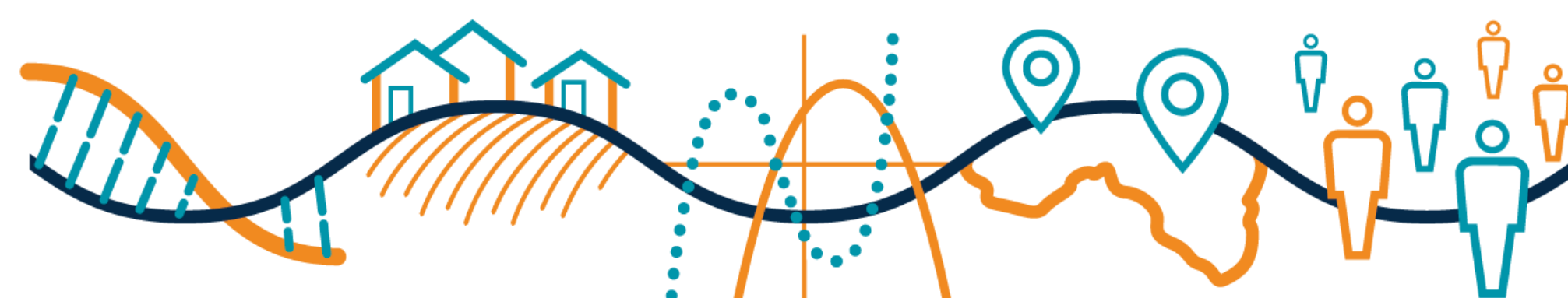
TG: *APOE*, *ZPR1*, *RPL30P9* (*LPL*)

Gene x smoking:

LDL-C: *APOE*

HDL-C: *CETP*

TG: *APOE*, *ZPR1*, *RPL30P9* (*LPL*), *TRIB1*



Contact Us

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