

# Lecture 2

## Dealing with pleiotropic effects

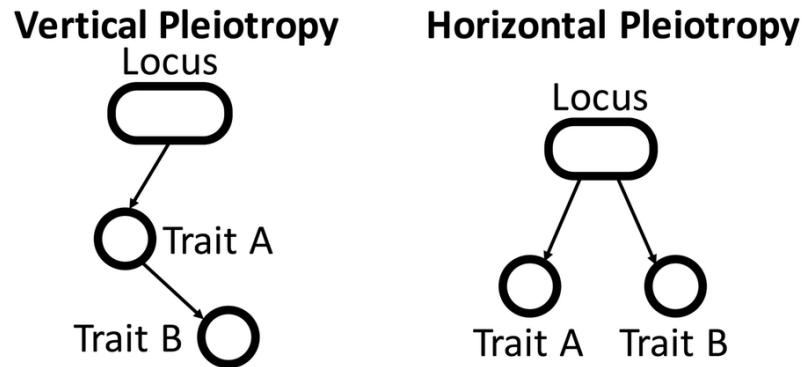
Jingshu Wang  
Feb. 14<sup>th</sup>, 2024

# Outline

- Horizontal pleiotropy and three common types of assumptions
- MR methods under sparsity assumption
- MR methods assuming uncorrelated pleiotropy
- MR methods allowing correlated pleiotropy
- Multivariable MR methods
- Real data example (R notebook)

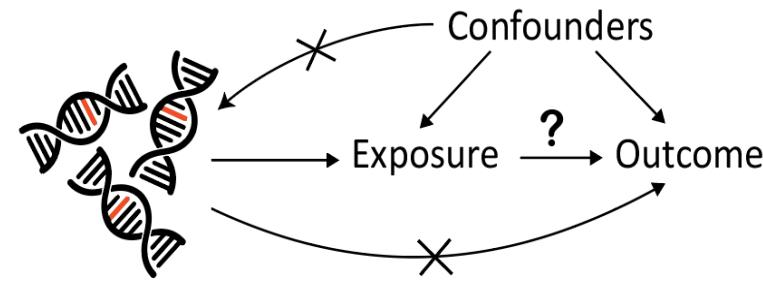
# Horizontal pleiotropy

- Horizontal v.s. Vertical pleiotropy



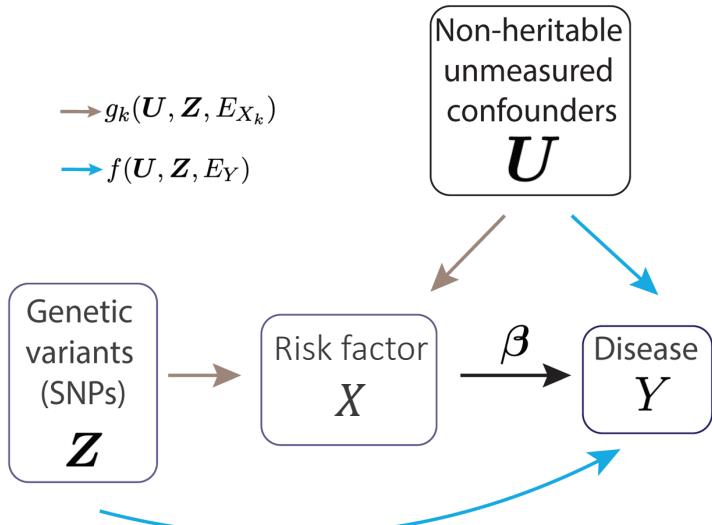
[Figure 1 from Jordan, D.M., Verbanck, M. and Do, R., 2019. HOPS: a quantitative score reveals pervasive horizontal pleiotropy in human genetic variation is driven by extreme polygenicity of human traits and diseases. *Genome biology*, 20(1), pp.1-18.]

- Vertical pleiotropy: SNP influences exposure, thus influence outcome
- Horizontal pleiotropy: SNP influence exposure and outcome through independent pathways



- Horizontal pleiotropy leads to violation of the exclusion restriction assumption in the IV framework
- Can we still perform MR under horizontal pleiotropy?
- Can we diagnose from the data?

# Structural equations allowing pleiotropy



$$Y = X\beta + f(\mathbf{U}, \mathbf{Z}, E_Y)$$

$$X = g(\mathbf{U}, \mathbf{Z}, E_X)$$

- $\mathbf{Z}$ : a vector containing all SNPs
- Random assignment:  $\mathbf{Z} \perp (\mathbf{U}, E_Y, E_X)$
- Causal effects of  $X$  on  $Y$ : assume linearity and homogeneity  
(needed when only GWAS summary statistics are available)
- Flexible assumptions for effects of the SNPs and environmental confounders on traits – no need to assume linear genetic effects

# Model on summary statistics allowing pleiotropy

$$Y = X\beta + f(\mathbf{U}, \mathbf{Z}, E_Y)$$

$$X = g(\mathbf{U}, \mathbf{Z}, E_X)$$

For a particular selected SNP  $Z_j$

- Define marginal effects

$$\Gamma_j = \operatorname{argmin}_\gamma \operatorname{Var}[Y - \gamma Z_j], \quad \gamma_j = \operatorname{argmin}_\gamma \operatorname{Var}[X - \gamma Z_j]$$

- Define  $\alpha_j$ :

$$\alpha_j = \operatorname{argmin}_\alpha \operatorname{Var}[f(\mathbf{U}, \mathbf{Z}, E_Y) - \alpha Z_j]$$

For a SNP  $j$ ,

$$\Gamma_j = \gamma_j \beta + \alpha_j$$

- Exclusion restriction (no horizontal pleiotropy):  $\alpha_j = 0$

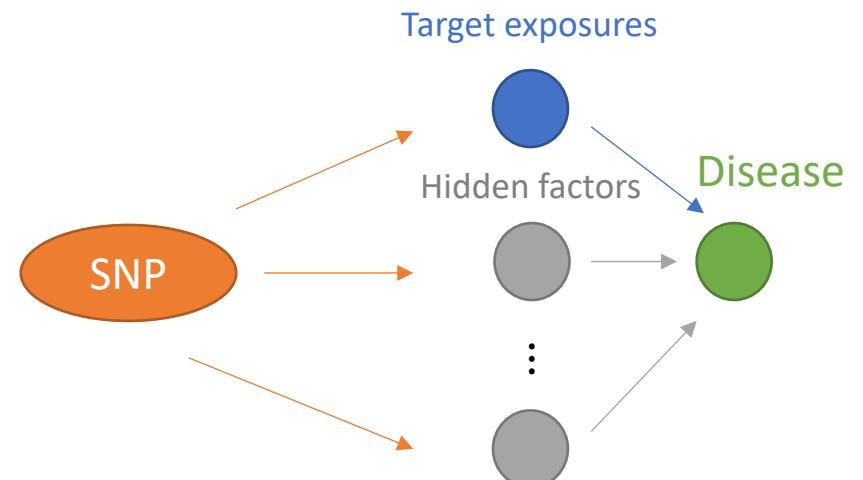
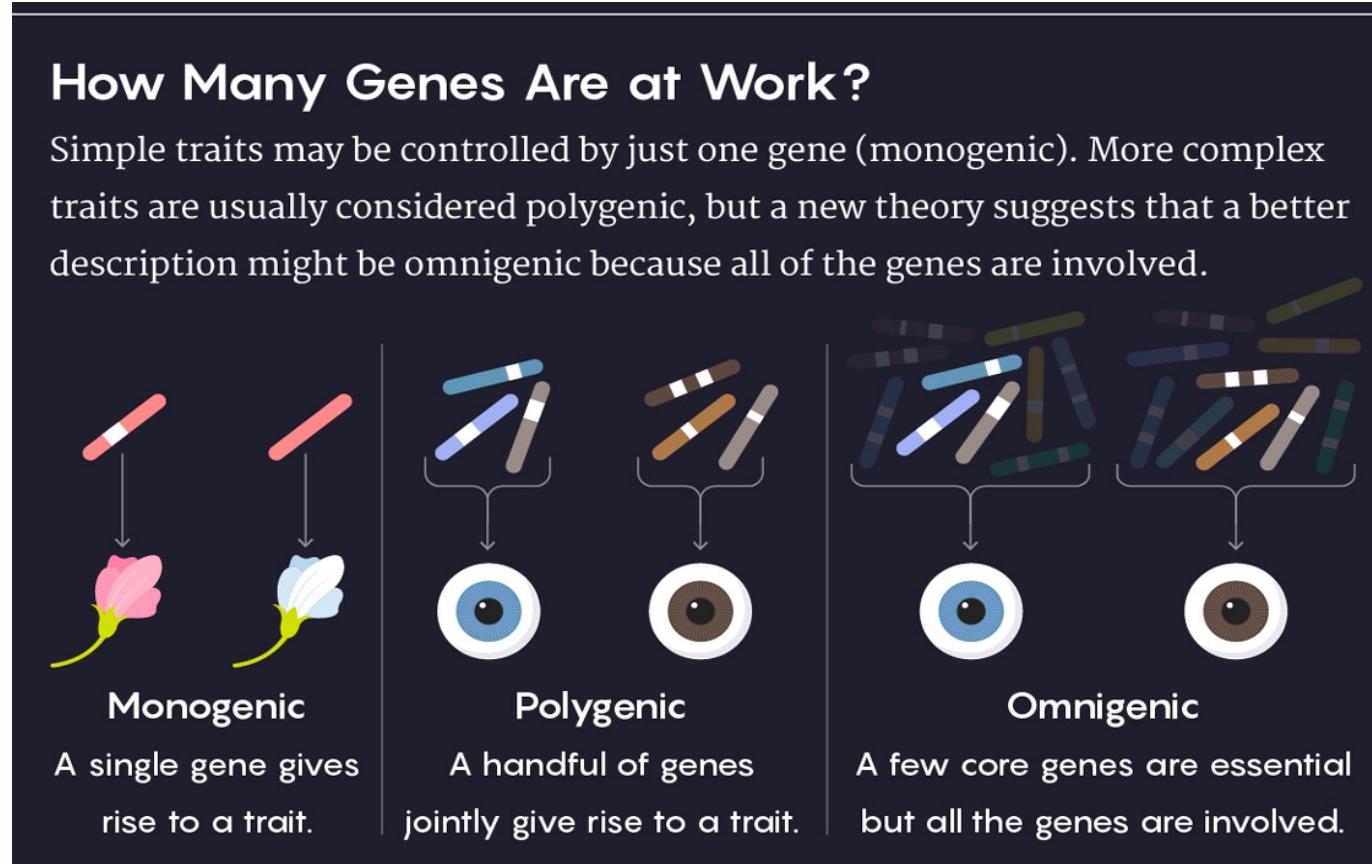
GWAS summary statistics

$$\hat{\Gamma}_j \sim N(\Gamma_j, \sigma_{Yj}^2)$$

$$\hat{\gamma}_j \sim N(\gamma_j, \sigma_{Xj}^2)$$

# Horizontal pleiotropy is a common issue in MR

- Complex traits are extremely polygenic → lead to horizontal pleiotropy



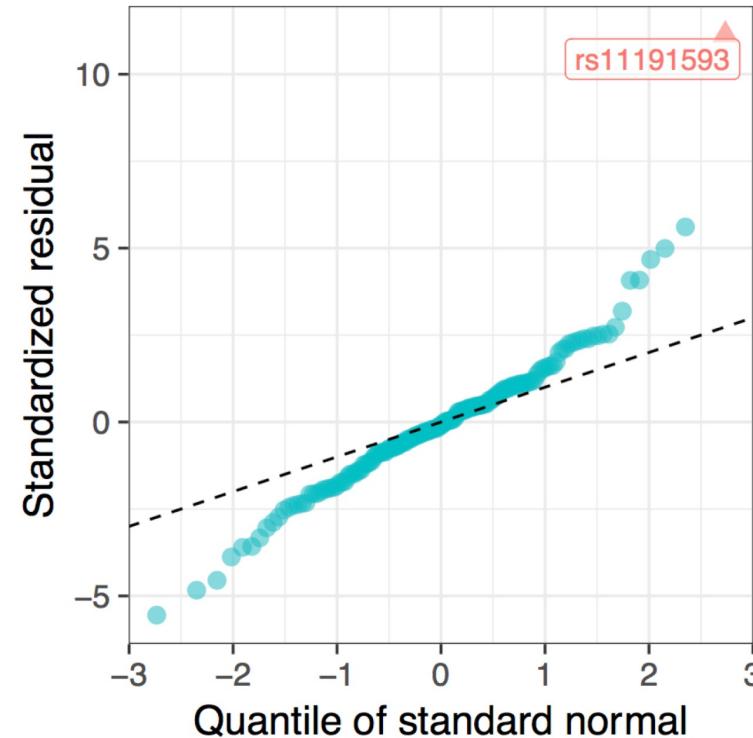
# Horizontal pleiotropy is a common issue in MR

- Empirical evidence: a BMI → SBP example
  - Q-Q plot of the standardized residuals

$$\hat{t}_j = \frac{\hat{\Gamma}_j - \hat{\beta}\hat{\gamma}_j}{\sqrt{\hat{\beta}^2\sigma_{Xj}^2 + \sigma_{Yj}^2}}$$

$$\Gamma_j = \beta\gamma_j + \alpha_j$$

$$\alpha_j = 0 \rightarrow \hat{t}_j \sim N(0, 1)$$



# How to model horizontal pleiotropy?

- MR can not allow for arbitrary pleiotropy

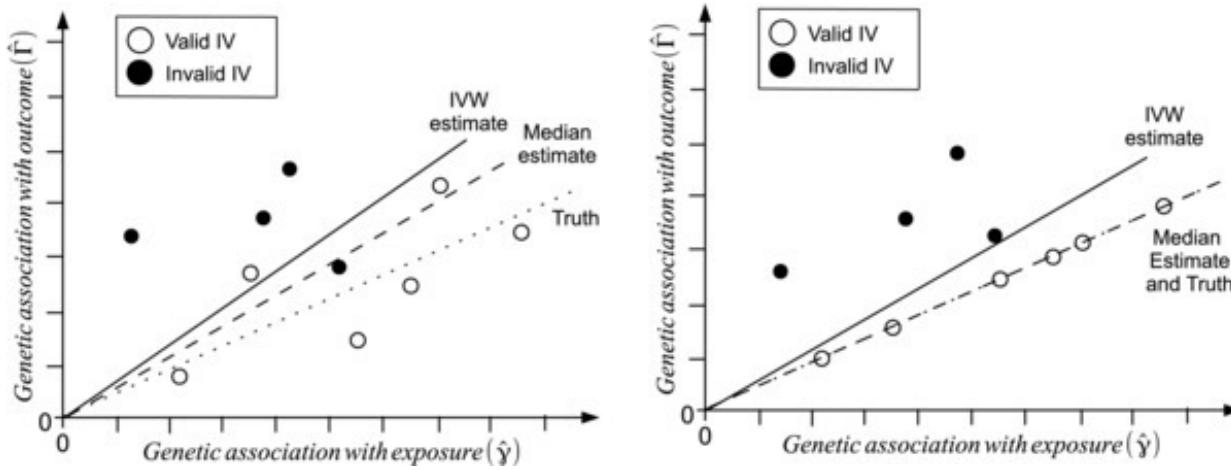
$$\Gamma_j = \beta\gamma_j + \alpha_j: \beta \text{ is not identifiable without additional assumptions on } \alpha_j$$

- Three common types of assumptions:
  - Sparsity
  - Uncorrelated pleiotropy (InSIDE:  $\alpha_j \perp \gamma_j$ )
  - Correlated pleiotropy through hidden confounders

# Sparsity

- Assume that most of the SNPs are valid IV, allow a few SNPs to be invalid
- Minimal requirement: more than 50% are valid IVs
  - Most methods require much more than 50% valid IVs to have good performance
- Common idea:  
outlier detection, or use methods that are robust to outliers
- Example methods:  
sisVIVE, weighted median, MBE, MR-PRESSO, MR-Lasso

# Weighted median estimator (Bowden et. al. 2016)



Core idea:

- SNP-specific estimators  $\left\{ \hat{\beta}_j = \frac{\hat{\Gamma}_j}{\hat{\gamma}_j}, j = 1, \dots, P \right\}$  ordered as  $\hat{\beta}_{(j)}$
- Given weights  $\{w_{(j)}\}$  for the ordered SNP, estimate a distribution  $F$ :
  - Estimate the  $(\sum_{i=1}^{j-1} w_{(i)} + \frac{w_{(j)}}{2})$ th quantile by  $\hat{\beta}_{(j)}$
  - Linearly interpolate other quantiles
- Take the median of  $F$  as estimate of  $\beta$

# Weighted median estimator (Bowden et. al., 2016)

- Choice of weights
  - IVW weights

$$w_j = \frac{\hat{\gamma}_j^2 / \hat{\sigma}_{Y_j}^{-2}}{\sum_l \hat{\gamma}_l^2 / \hat{\sigma}_{Y_l}^{-2}}$$

- Penalized IVW weights

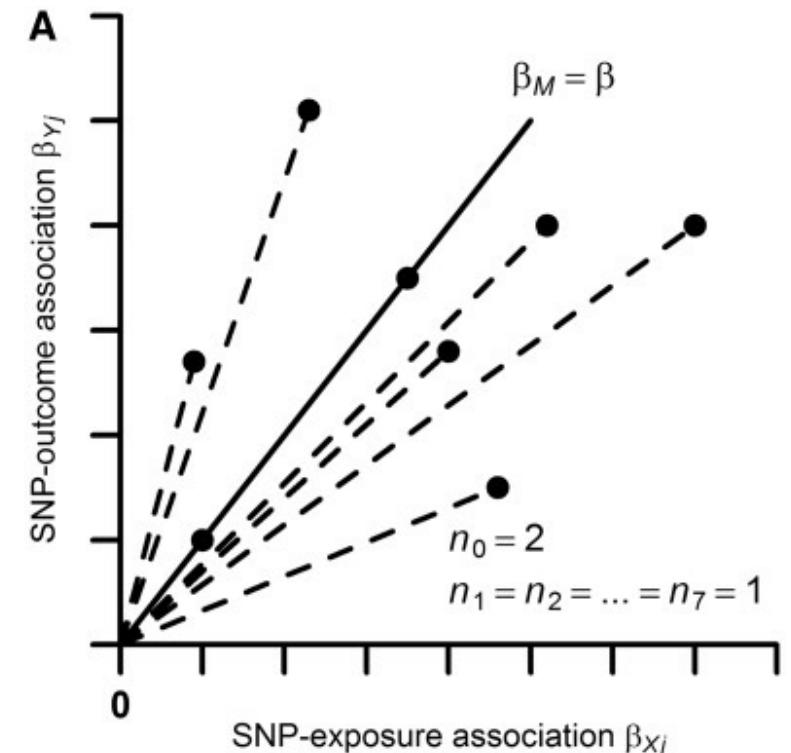
$$w_j^* = \frac{\hat{\gamma}_j^2}{\hat{\sigma}_{Y_j}^{-2}} \times \min(1, 20q_j)$$

where  $q_j$  is a p-value measuring how heterogenous  $\hat{\beta}_j$  is from others

- Use parametric bootstrap to get CI of  $\hat{\beta}$

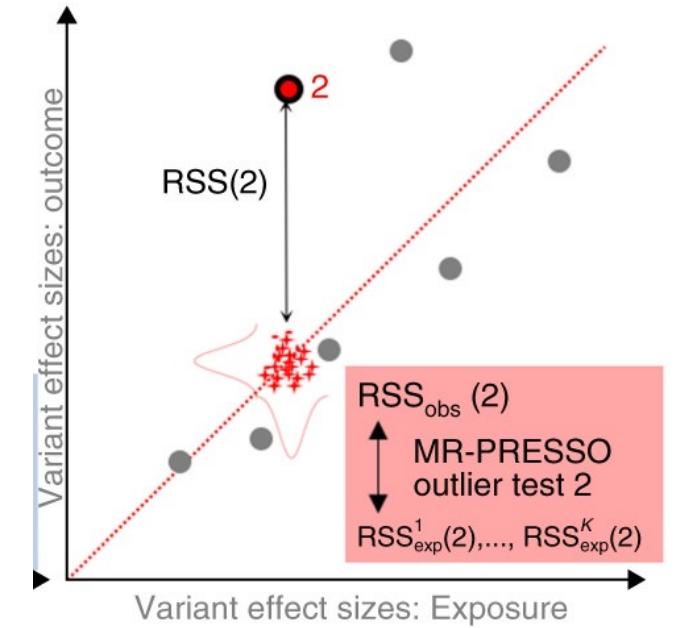
# MBE (Hartwig et. al. 2017)

- Define  $b_j = \frac{\Gamma_j}{\gamma_j} = \beta + \frac{\alpha_j}{\gamma_j}$
- ZEMPA (Zero Modal Pleiotropy Assumption):  
across all instruments, the most frequent value (i.e., the mode) of  $b_j$  is 0
- Simple implementation is to identify the mode of a smoothed empirical distribution of  $\left\{ \hat{\beta}_j = \frac{\hat{\Gamma}_j}{\hat{\gamma}_j}, j = 1, \dots, P \right\}$
- Can also incorporate IVW weights



# MR-PRESSO (Marie et. al., 2018)

- Core idea:
  - Detect outliers (invalid IV) by checking whether the standardized leave-one-out residuals are too large
$$r_j = \frac{\hat{\Gamma}_j - \hat{\beta}_{-j}\hat{\gamma}_j}{\sqrt{\hat{\beta}_{-j}^2\hat{\sigma}_{X_j}^2 + \hat{\sigma}_{Y_j}^2}}$$
  - In the paper, the authors compared observed residuals with simulated residuals  $\hat{\Gamma}_j^{rand} - \hat{\beta}_{-j}\hat{\gamma}_j^{rand}$  where  $\hat{\Gamma}_j^{rand} \sim N(\hat{\beta}_{-j}\hat{\gamma}_j, \hat{\sigma}_{Y_j}^2)$  and  $\hat{\gamma}_j^{rand} \sim N(\hat{\gamma}_j, \hat{\sigma}_{X_j}^2)$ , which is essentially comparing  $r_j$  with  $N(0,1)$
  - Remove detected outliers and use IVW on the rest of SNPs
- Drawback: outlier detection can be challenging if outliers form clusters (outliers masking each other), such as when InSIDE fails



# sisVIVE (Kang et. al., 2016)

- One of the earliest method to deal with invalid IV in MR
- Require running lasso-like regression on individual-level GWAS data

$$(\hat{\alpha}_\lambda, \hat{\beta}_\lambda) \in \operatorname{argmin}_{\alpha, \beta} \frac{1}{2} \|\mathbf{P}_Z (\mathbf{Y} - \mathbf{Z}\alpha - \mathbf{D}\beta)\|_2^2 + \lambda \|\alpha\|_1$$

Exposure  
↓  
Vector of all IVs      Pleiotropic effects

- Identifying  $\beta$  only require 50% SNPs to be valid, but later simulations show that performance can be undesirable if InSIDE fails (Bao et. al. ,2019)

# Uncorrelated pleiotropy

- InSIDE assumption (Bowden et. al. 2015):

$$\alpha_j \perp \gamma_j$$

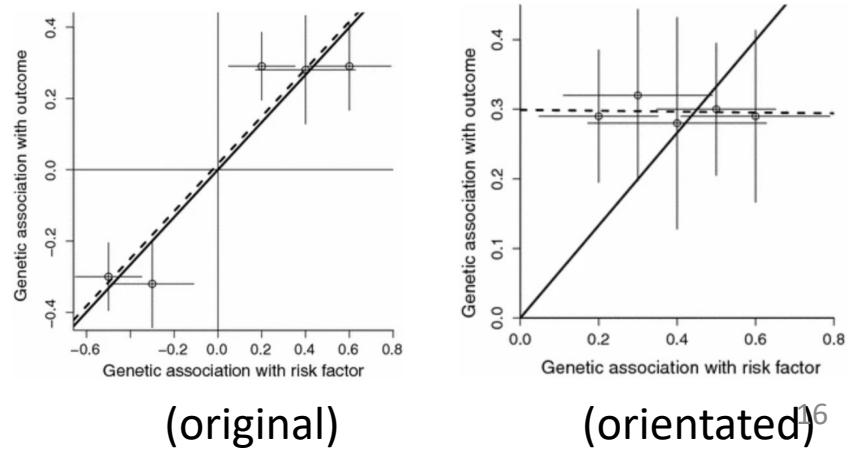
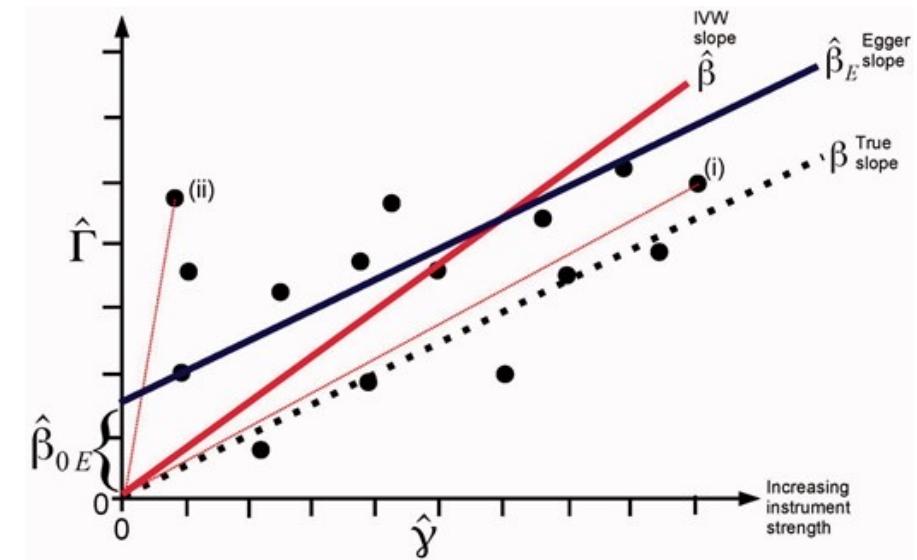
- Allow all SNPs to be invalid IVs
- Roughly, the pleiotropic effects won't cause severe bias in estimating  $\beta$  but would increase uncertainty in the estimates
- Common idea:  
model  $\alpha_j$  as an additional random effect
- Example methods:  
MR-Egger, MR-RAPS, debiased IVW

# MR-Egger (Bowden et. al., 2015)

- $\beta$  is estimated by solving the regression:

$$\hat{\Gamma}_j = \beta_0 + \beta \hat{\gamma}_j + e_j, \quad e_j \sim N(0, \sigma^2 \sigma_{Yj}^2)$$

- Interpretate  $\beta_0$  as average pleiotropic effect
- Dependent on the orientations/coding schemes of SNPs
  - Current practice: orientate the SNPs to be all positively associated with the exposure
  - Can lead to “post-orientation” bias and inflated uncertainty
- Data-adaptive  $\sigma^2$  may account for increased uncertainty in  $\hat{\beta}$  due to nonzero  $\alpha_j$

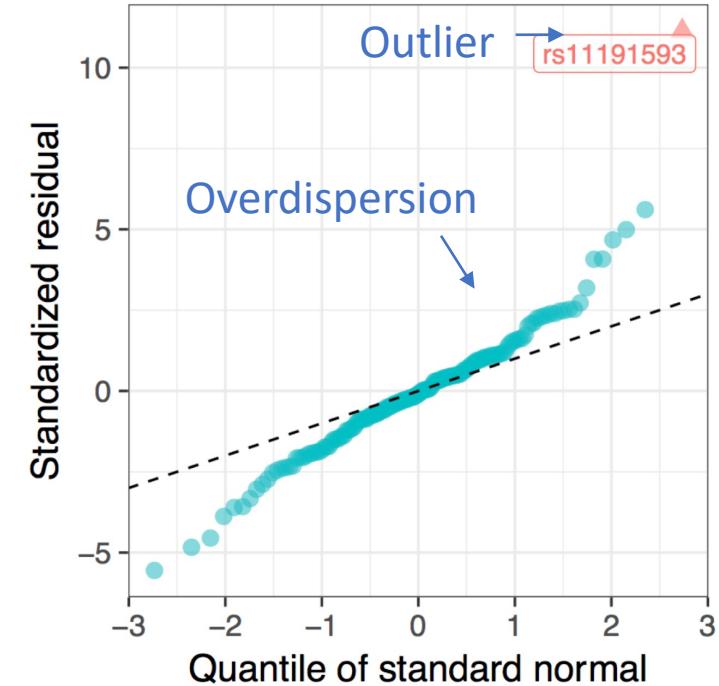


# MR-RAPS (Zhao et. al. 2020)

- Model pervasive pleiotropy as random effect

$$\alpha_j \sim N(0, \tau^2) \text{ i.i.d. for most genetic instruments}$$

- $\alpha_j$  can always have mean 0 after random orientations/coding of the SNPs
- Original idea of model estimation is based on profile-likelihood
- Use robust loss function (such as the Huber loss instead of the L2 loss in the likelihood) to make the solution robust to outlier SNPs
- Have theoretical guarantee for the asymptotic normality of the estimates even when the SNPs are weak instruments



# MR-RAPS

## Robust adjusted Profile score

Most  $\alpha_j \sim N(0, \tau^2)$ , but some  $|\alpha_j|$  might be very large.

- Define standardized residual

$$t_j(\beta, \tau^2) = \frac{\hat{\Gamma}_j - \beta \hat{\gamma}_j}{\sqrt{(\sigma_{Yj}^2 + \tau^2) + \beta^2 \sigma_{Xj}^2}}$$

- Robust adjusted profile score

$$\psi_1^{(\rho)}(\beta, \tau^2) = \sum_{j=1}^p \rho'(t_j) \cdot \frac{\partial}{\partial \beta} t_j,$$

$$\psi_2^{(\rho)}(\beta, \tau^2) = \sum_{j=1}^p \sigma_{Xj}^2 \frac{t_j \cdot \rho'(t_j) - \mathbb{E}[T \rho'(T)]}{(\sigma_{Yj}^2 + \tau^2) + \beta^2 \sigma_{Xj}^2}, \text{ for } T \sim N(0, 1)$$

- Find the roots of the above score equations to estimate  $\beta$  and  $\tau^2$

# Debiased IVW (Ye et. al., 2021)

- Designed to debias IVW when there are many SNPs that are weakly associated with the exposure

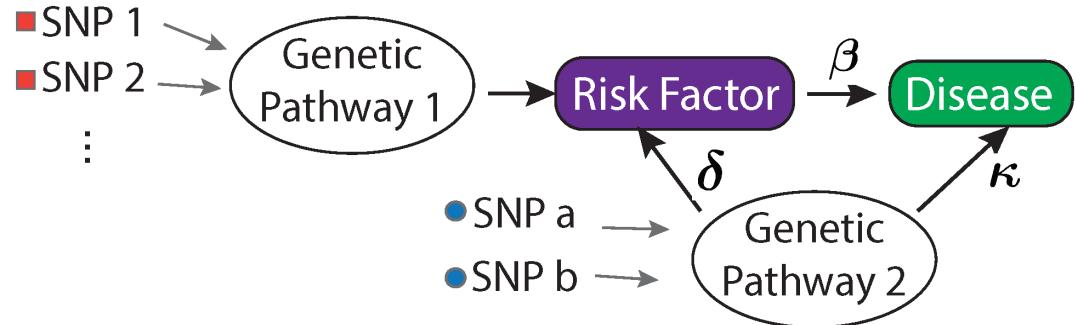
Original IVW       $\hat{\beta}_{\lambda, \text{IVW}} = \frac{\sum_{j \in S_\lambda} \hat{w}_j \hat{\beta}_j}{\sum_{j \in S_\lambda} \hat{w}_j} = \frac{\sum_{j \in S_\lambda} \hat{\Gamma}_j \hat{\gamma}_j \hat{\sigma}_{Yj}^{-2}}{\sum_{j \in S_\lambda} \hat{\gamma}_j^2 \hat{\sigma}_{Yj}^{-2}}, \quad S_\lambda = \{j : |\hat{\gamma}_j^*| > \lambda \hat{\sigma}_{Xj}^*\}$

Debiased IVW       $\hat{\beta}_{\lambda, \text{dIVW}} = \frac{\sum_{j \in S_\lambda} \hat{\Gamma}_j \hat{\gamma}_j \hat{\sigma}_{Yj}^{-2}}{\sum_{j \in S_\lambda} (\hat{\gamma}_j^2 - \hat{\sigma}_{Xj}^2) \hat{\sigma}_{Yj}^{-2}}, \quad S_\lambda = \{j : |\hat{\gamma}_j^*| > \lambda \hat{\sigma}_{Xj}^*\}$

- Debiased IVW can be adjusted to account for pleiotropy under the assumption

$$\alpha_j \sim N(0, \tau^2)$$

# Correlated pleiotropy through hidden confounders



■ SNP 1  
■ SNP 2  
⋮

Genetic  
Pathway 1

Risk Factor

Disease

● SNP a  
● SNP b  
⋮

Genetic  
Pathway 2

■ SNP 1  
■ SNP 2

● SNP a  
● SNP b

$$\Gamma_j = \beta \gamma_j$$

$$\Gamma_j = \beta \delta \tilde{\gamma}_j + \kappa \tilde{\gamma}_j = \left( \beta + \frac{\kappa}{\delta} \right) \gamma_j$$

$$\alpha_j = \frac{\kappa}{\delta} \gamma_j$$

- Common hidden confounding pathways make  $\alpha_j$  and  $\gamma_j$  correlated
- Assumption on the number of hidden confounding pathways
  - Assume only one hidden confounding pathway (at least implicitly)
    - Example methods: MRMix, contamination mixture, CAUSE, cML-MA, MR-CUE
  - Allow/estimate arbitrary number of hidden confounding pathways
    - Example methods: MRClust, MR-PATH

# MRMix (Qi et. al. 2019)

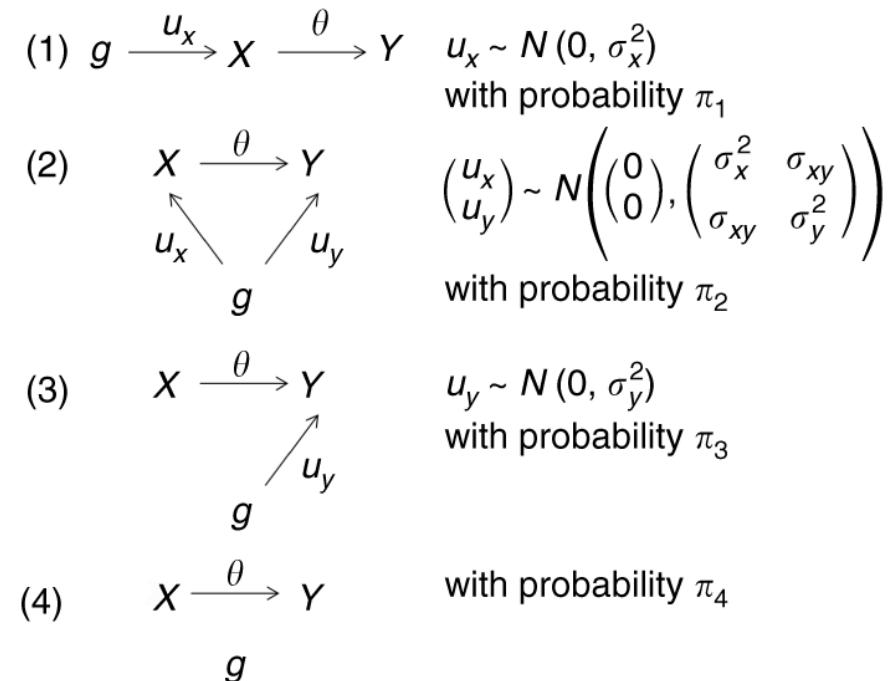
- Assume that there are four types of SNPs

- Marginal association with  $y$  for the second category SNP:

$$u_y + \theta u_x = \left( \theta + \frac{\sigma_{xy}}{\sigma_x^2} \right) u_x + \alpha \text{ where } u_x \perp \alpha$$

Implicitly, these SNPs share the same hidden confounder

- Thus, the model assumes that a group of SNPs are valid and a group of SNPs share the same confounder and has correlated pleiotropy
- Estimating this model is not trivial



# MRMix (Qi et. al. 2019)

- Estimation idea:

- For a fixed  $\tilde{\beta}$ , perform MLE to fit

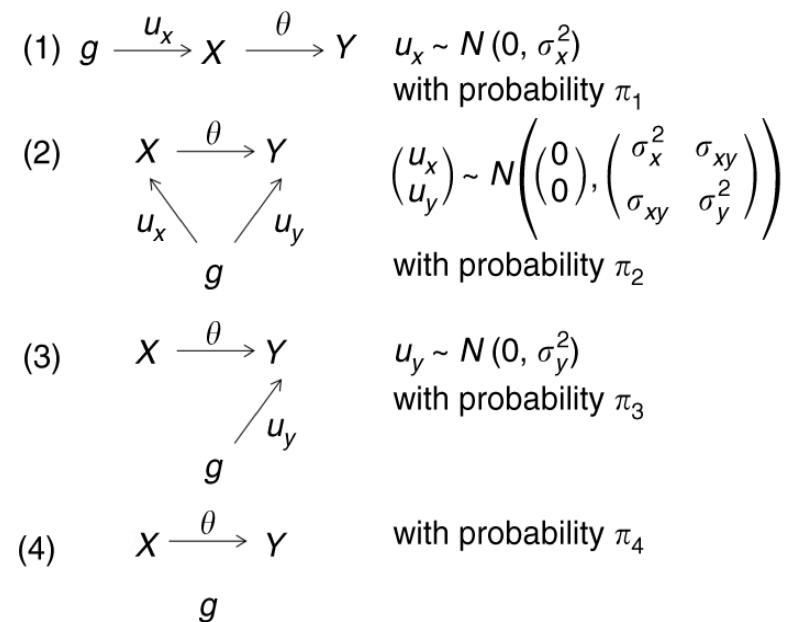
$$\hat{\Gamma}_j - \tilde{\beta} \hat{\gamma}_j \sim \pi_0 N(0, \sigma_{Yj}^2 + \tilde{\beta}^2 \sigma_{Xj}^2) + (1 - \pi_0)N(0, \sigma^2)$$

to get estimates  $\hat{\pi}_0(\tilde{\beta})$

- Search over a grid of  $\tilde{\beta}$  to maximize  $\hat{\pi}_0(\tilde{\beta})$

$$\hat{\beta} = \operatorname{argmin}_{\tilde{\beta}} \hat{\pi}_0(\tilde{\beta})$$

- Use large-sample theory to derive the variance of  $\hat{\beta}$  for inference
- The estimation procedure itself largely rely on the sparsity assumption instead of correlated pleiotropy



# Contamination mixture (Burgess et. al. 2020)

## Core idea

- SNP-specific estimators  $\{\hat{\beta}_j = \frac{\hat{\Gamma}_j}{\hat{\gamma}_j}, j = 1, \dots, P\}$

- Assume the following mixture distributions

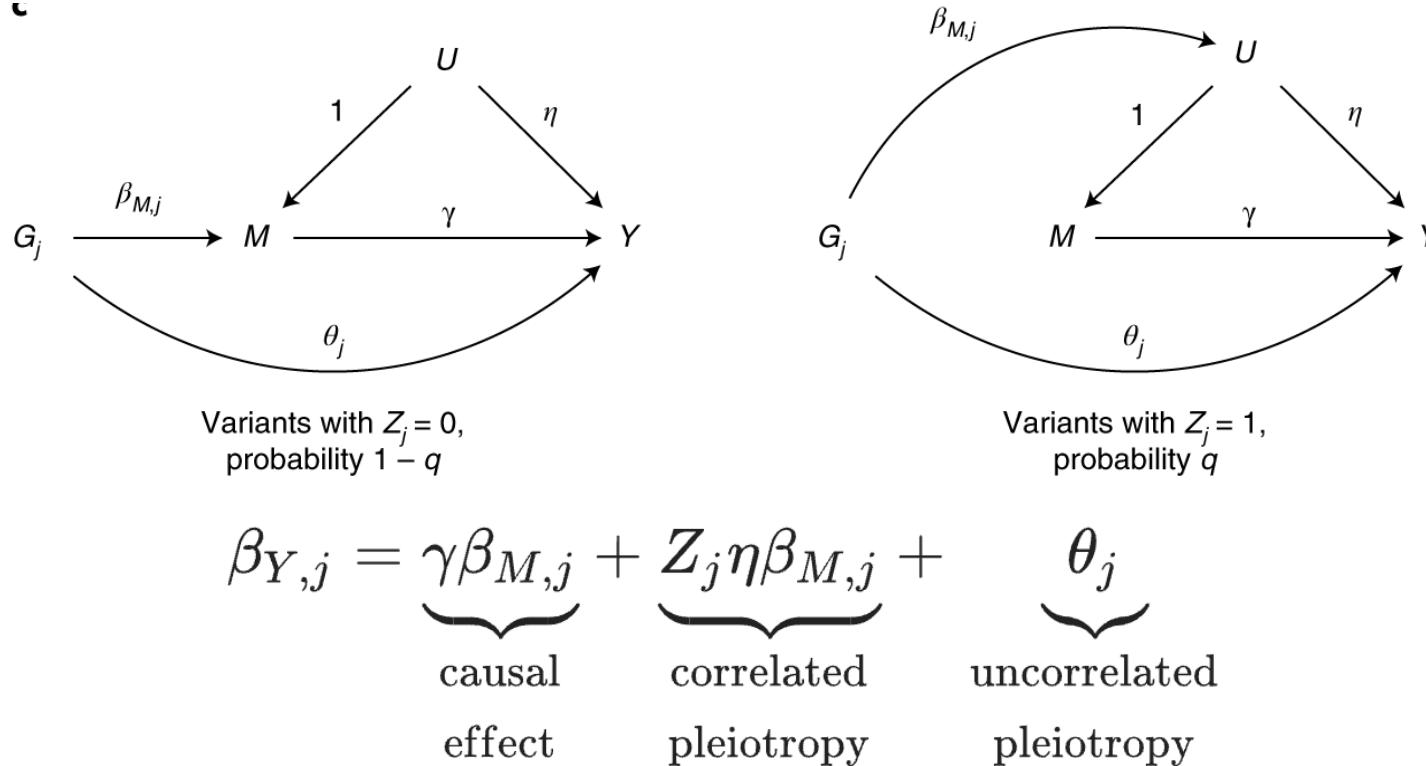
$$\begin{aligned}\hat{\beta}_j &\sim N\left(\beta, \frac{\sigma_{Yj}^2}{\hat{\gamma}_j^2}\right) && \text{if } j \text{ is a valid IV} \\ \hat{\beta}_j &\sim N\left(0, \psi^2 + \frac{\sigma_{Yj}^2}{\hat{\gamma}_j^2}\right) && \text{if } j \text{ is an invalid IV}\end{aligned}$$

- The model assumption allows for correlated pleiotropy for an invalid IV  $j$ :

$$\alpha_j = -\beta\gamma_j + \epsilon_j \quad \text{where } \epsilon_j \sim N(0, \psi^2)$$

- The parameters are solved through a heuristic profile likelihood and the confidence intervals are obtained through inversion of likelihood ratio tests

# CAUSE (Morrison et. al. 2020)



- The model allows both correlated pleiotropy and uncorrelated pleiotropy
- Need to assume that  $P(\eta = 1) < 0.5$  for identifiability
- Model the distributions of  $\beta_{M,j}$  by and  $\theta_j$  by Gaussian mixtures
- Obtain estimate and credible intervals of the causal effect  $\gamma$  through a Bayesian approach

# MR-PATH (Long et. al., 2020)

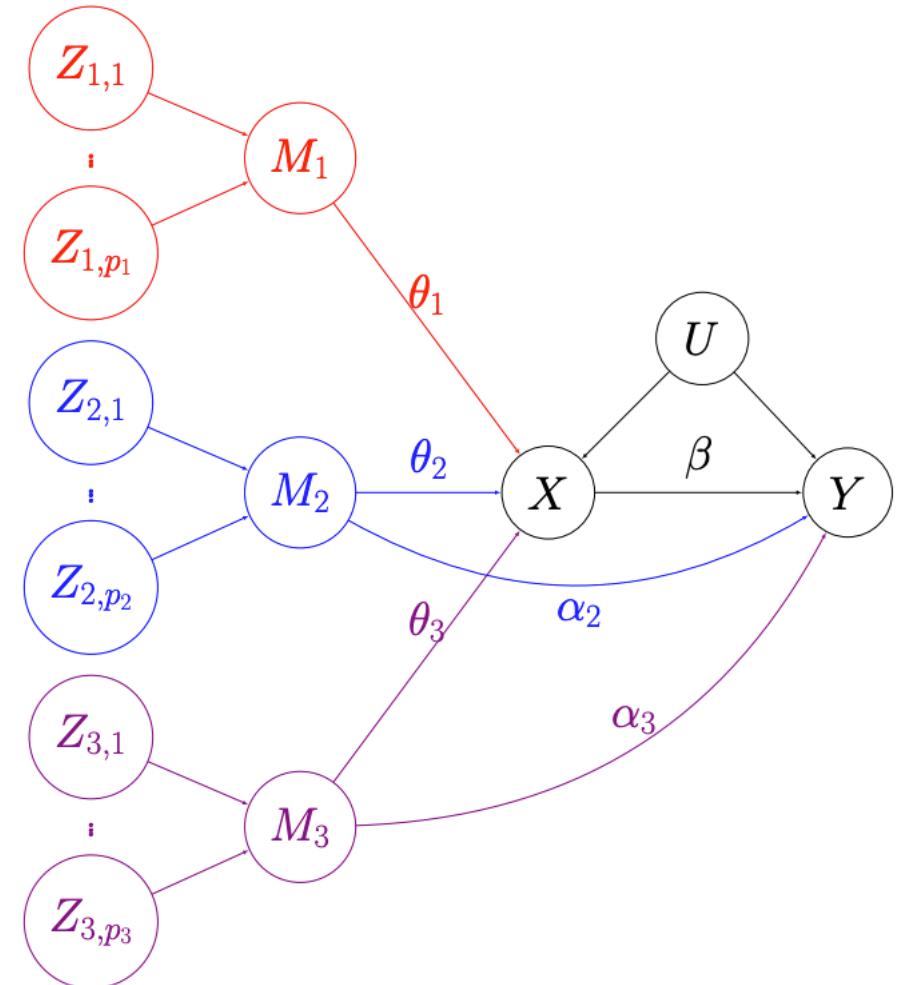
- Model

$$\begin{pmatrix} \hat{\theta}_{X_i} \\ \hat{\theta}_{Y_i} \end{pmatrix} \stackrel{\text{indep.}}{\sim} N\left(\begin{pmatrix} \theta_{X_i} \\ \beta_i \theta_{X_i} \end{pmatrix}, \begin{pmatrix} \sigma_{X_i}^2 & 0 \\ 0 & \sigma_{Y_i}^2 \end{pmatrix}\right) \quad i = 1, \dots, p.$$

$Z_i \sim \text{Categorical } (\pi_1, \dots, \pi_K)$

$\beta_i | Z_i = k \sim N(\mu_k, \sigma_k^2), \quad k = 1, \dots, K.$

- Use Monte-Carlo EM to solve the model and approximate the confidence intervals
- Use modified BIC to select  $K$



# Diagnosis tools for pleiotropic effects

Tests:

- Q test
- MR-PRESSO global test and distortion test

Visualization tools:

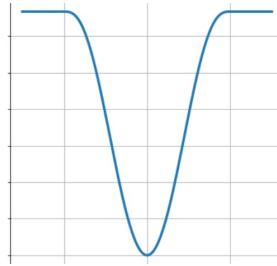
- Residual QQ plot
- Radial plot
- GRAPPLE visualization to detect multiple pleiotropic pathways
- You have learnt most of them in Lecture 1

# GRAPPLE visualization to detect multiple modes to identify pleiotropic pathways

Robust Profile likelihood with  $\tau^2 = 0$ :

$$l(\beta) = - \sum_{j=1}^p \rho \left( \frac{\hat{\Gamma}_j - \beta \hat{\gamma}_j}{\sqrt{\sigma_{Y_j}^2 + \beta^2 \sigma_{X_j}^2}} \right)$$

$\rho(\cdot)$ : Tukey's biweight loss



- SNP 1
- SNP 2 → Pathway 1



...

- SNP 1
- SNP 2 → Pathway 1

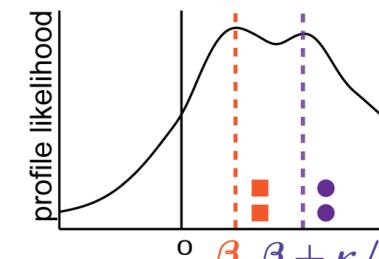
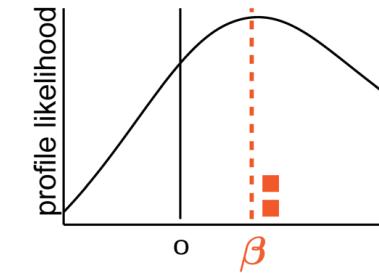


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- SNP a
- SNP b



MR Short Course, lecture 2



# Detect multiple pathways for CRP $\rightarrow$ CAD

CRP: C-reactive protein

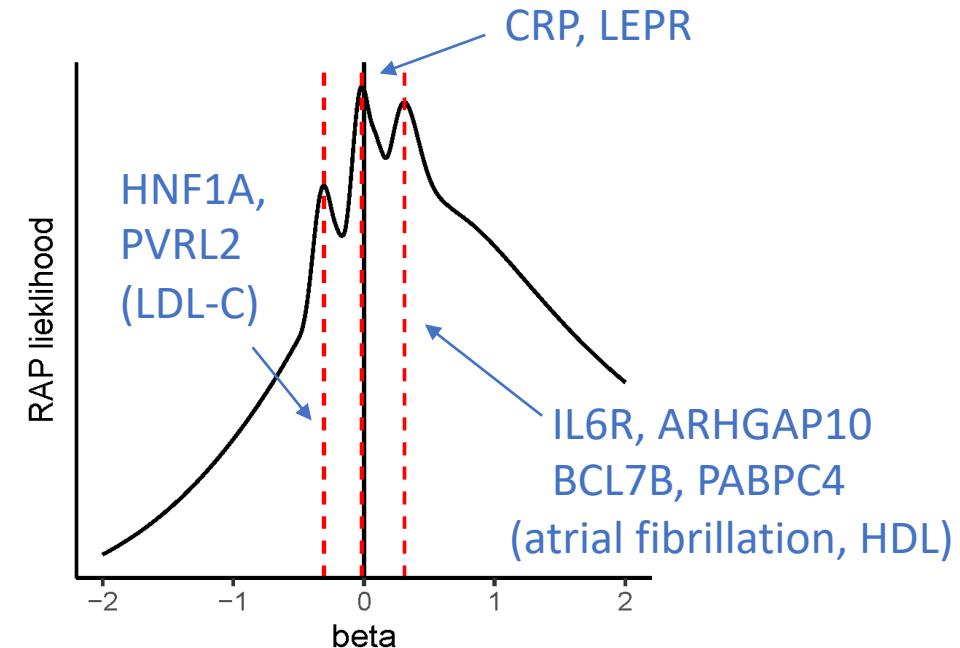
- Find marker SNPs by:

$$t_{j,k} = \frac{\hat{\Gamma}_j - \beta_k \hat{\gamma}_j}{\sqrt{\sigma_{Y_j}^2 + \beta_k^2 \sigma_{X_j}^2}}$$

SNP j is a marker for mode k if

$$|t_{j,k}| < t_1, |t_{j,k'}| > t_2$$

- Map SNPs to genes
- Lookup SNP GWAS associations  
(Query GWAS catalog)



# Multivariable MR (MVMR)

- Simultaneously consider multiple risk factors in MR
- Can adjust for known confounders or estimate direct effects
  - Not affected by collider bias
- Adjust for a small set of known heritable confounders
  - IVW-MVMR, multivariable MR-Egger, MVMR-Horse, GRAPPLE
- Adjust for high-dimensional confounders
  - MR-Reg/Post-reg, MVMR-PRESS

Relationship between $X_2$ and $X_1$	MR—including all SNPs	MR—including SNPs that only affect $X_1$	MVMR
Confounder	Biased—assumption IV2 is violated	Direct effect = total effect = $\beta_1$	Direct effect = total effect = $\beta_1$
Collider	Direct/total effect = $\beta_1$	Direct effect = total effect = $\beta_1$	Direct effect = total effect = $\beta_1$
Mediator	Biased—assumption IV2 is violated	Total effect = $\beta_1 + \alpha\beta_2$	Direct effect = $\beta_1$

(Sanderson 2021)

# IVW-MVMR (Burgess et. al. 2015)

- An extension of IVW to multivariable MR
- Univariable IVW method can be treated as weighted linear regression:
  - Linear regression:  $\hat{\Gamma}_j = \beta \hat{\gamma}_j + \varepsilon_j$
  - Inverse-variance weights for each sample:  $w_i = \hat{\sigma}_{Y_j}^{-2}$
  - The weighted least square solution and variance estimates are the same as IVW
- Straightforward extension of IVW to Multivariable MR
  - Linear regression:  $\hat{\Gamma}_j = \beta_1 \hat{\gamma}_{j1} + \cdots \beta_k \hat{\gamma}_{jk} + \varepsilon_j$
  - Same inverse-variance weights for each sample:  $w_i = \hat{\sigma}_{Y_j}^{-2}$
  - Use weighted least square to find the estimates and standard errors
- Relatively robust to uncorrelated pleiotropy, but sensitive to weak IV bias

# GRAPPLE (Wang et. al. 2021)

- An extension of MR-RAPs to multivariable MR

- Assume the following structural equations on individual-level data

$$Y = \mathbf{X}^T \boldsymbol{\beta} + f(\mathbf{U}, \mathbf{Z}, E_Y) \quad (\text{if } Y \text{ is a continuous trait})$$

$$\text{logit}[P(Y = 1)] = \mathbf{X}^T \boldsymbol{\beta} + f(\mathbf{U}, \mathbf{Z}, E_Y) \quad (\text{if } Y \text{ is a binary trait})$$

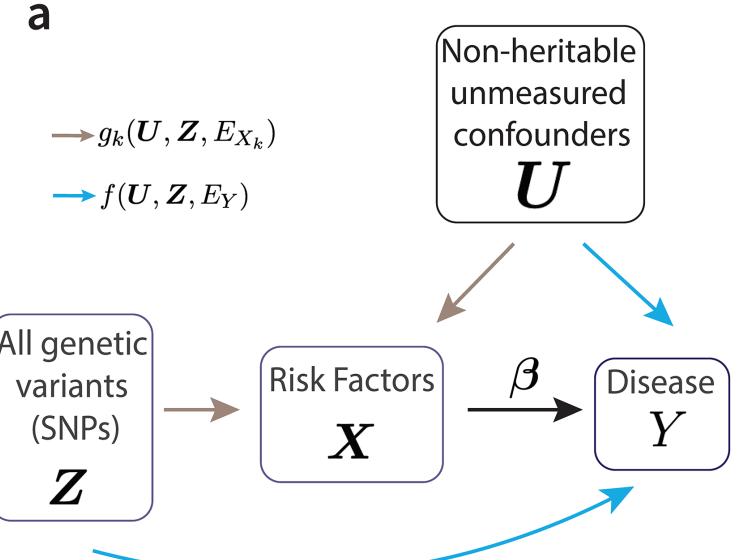
$$X_k = g_k(\mathbf{U}, \mathbf{Z}, E_{X_k}), \quad k = 1, \dots, K$$

- Define marginal effects of each SNP  $Z_j$

$$\Gamma_j = \underset{\gamma}{\operatorname{argmin}} \operatorname{Var}[Y - \gamma Z_j], \quad \gamma_{kj} = \underset{\gamma}{\operatorname{argmin}} \operatorname{Var}[X_k - \gamma Z_j]$$

- $\alpha_j$ : pleiotropic effect of  $Z_j$

$$\alpha_j = \underset{\alpha}{\operatorname{argmin}} \operatorname{Var}[f(\mathbf{U}, \mathbf{Z}, E_Y) - \alpha Z_j]$$



For a SNP  $j$ ,

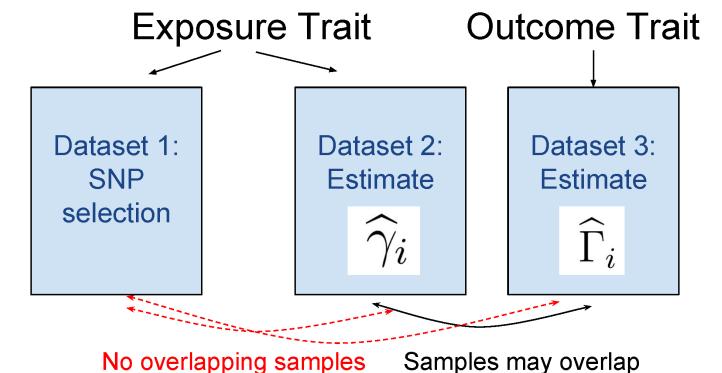
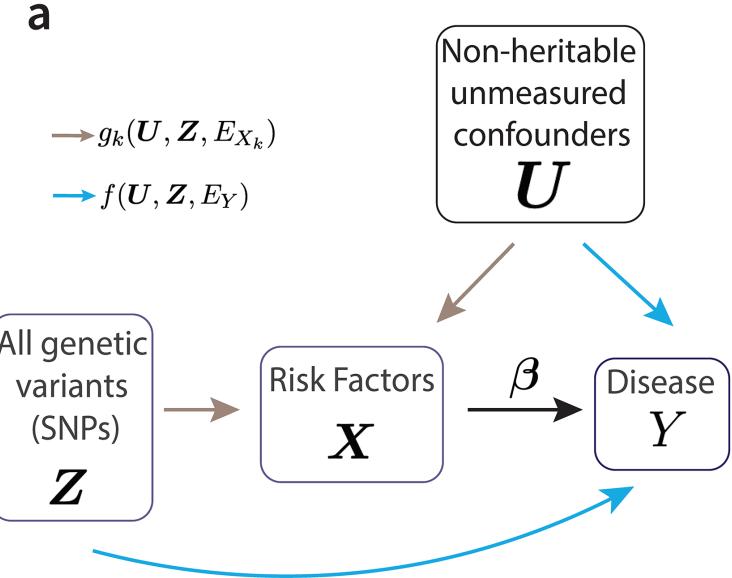
$$\Gamma_j = \boldsymbol{\gamma}_j^T \boldsymbol{\beta} + \alpha_j$$

# GRAPPLE (Wang et. al. 2021)

For a SNP  $j$ ,

$$\Gamma_j = \boldsymbol{\gamma}_j^T \boldsymbol{\beta} + \alpha_j$$

- Same as in MR-RAPs, assume uncorrelated pleiotropy  
Most  $\alpha_j \sim N(0, \tau^2)$ , but some  $|\alpha_j|$  might be very large.
- Use robust adjusted Profile score to get estimates and inference
- Avoids weak instrument bias
- Use three-sample MR



# List of references

- **Weighted median:** Bowden, Jack, et al. "Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator." *Genetic epidemiology* 40.4 (2016): 304-314.
- **MBE:** Hartwig, F. P., Davey Smith, G., & Bowden, J. (2017). Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *International journal of epidemiology*, 46(6), 1985-1998.
- **MR-PRESSO:** Verbanck, Marie, et al. "Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases." *Nature genetics* 50.5 (2018): 693-698.
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