

Lecture 2

Dealing with pleiotropic effects

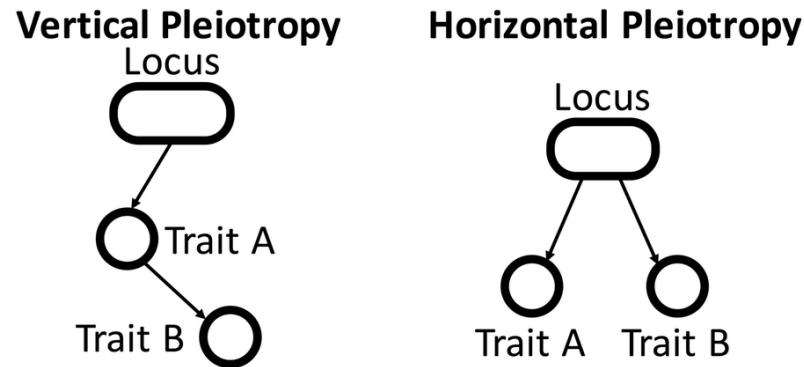
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Feb. 14th, 2024

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)

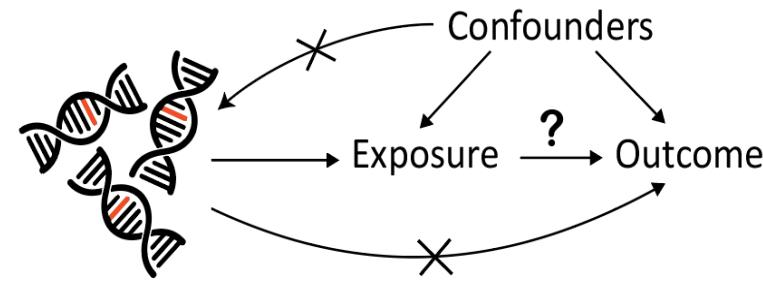
Horizontal pleiotropy

- Horizontal v.s. Vertical pleiotropy



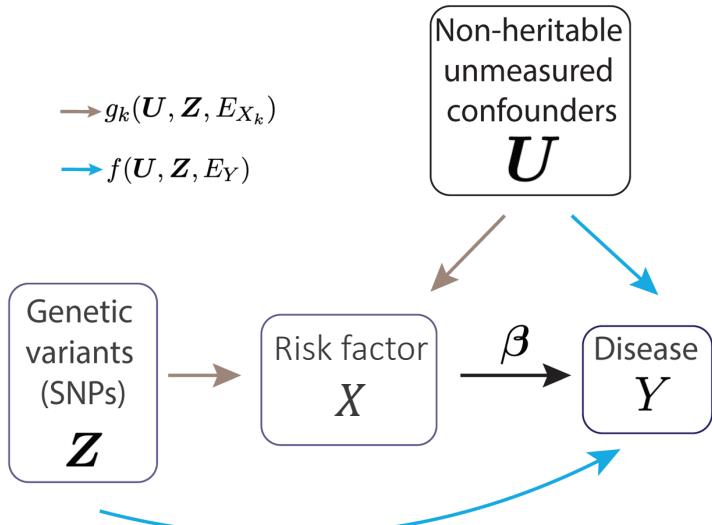
[Figure 1 from Jordan, D.M., Verbanck, M. and Do, R., 2019. HOPS: a quantitative score reveals pervasive horizontal pleiotropy in human genetic variation is driven by extreme polygenicity of human traits and diseases. *Genome biology*, 20(1), pp.1-18.]

- 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 α_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): $\alpha_j = 0$

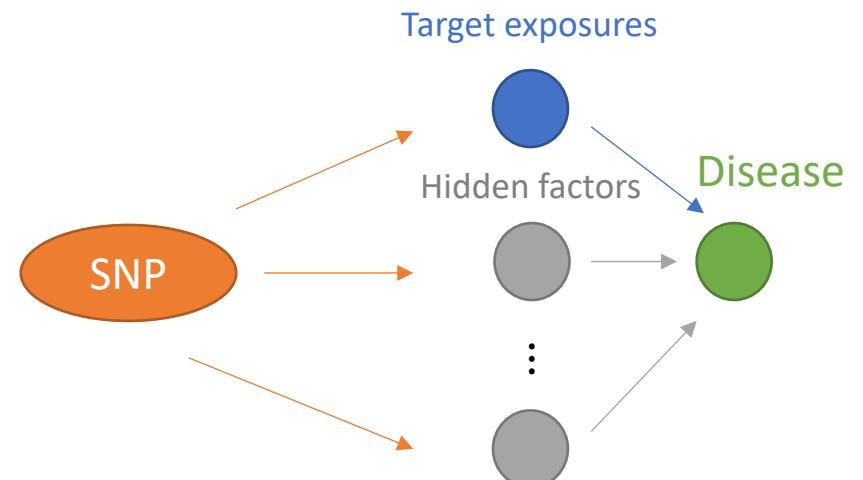
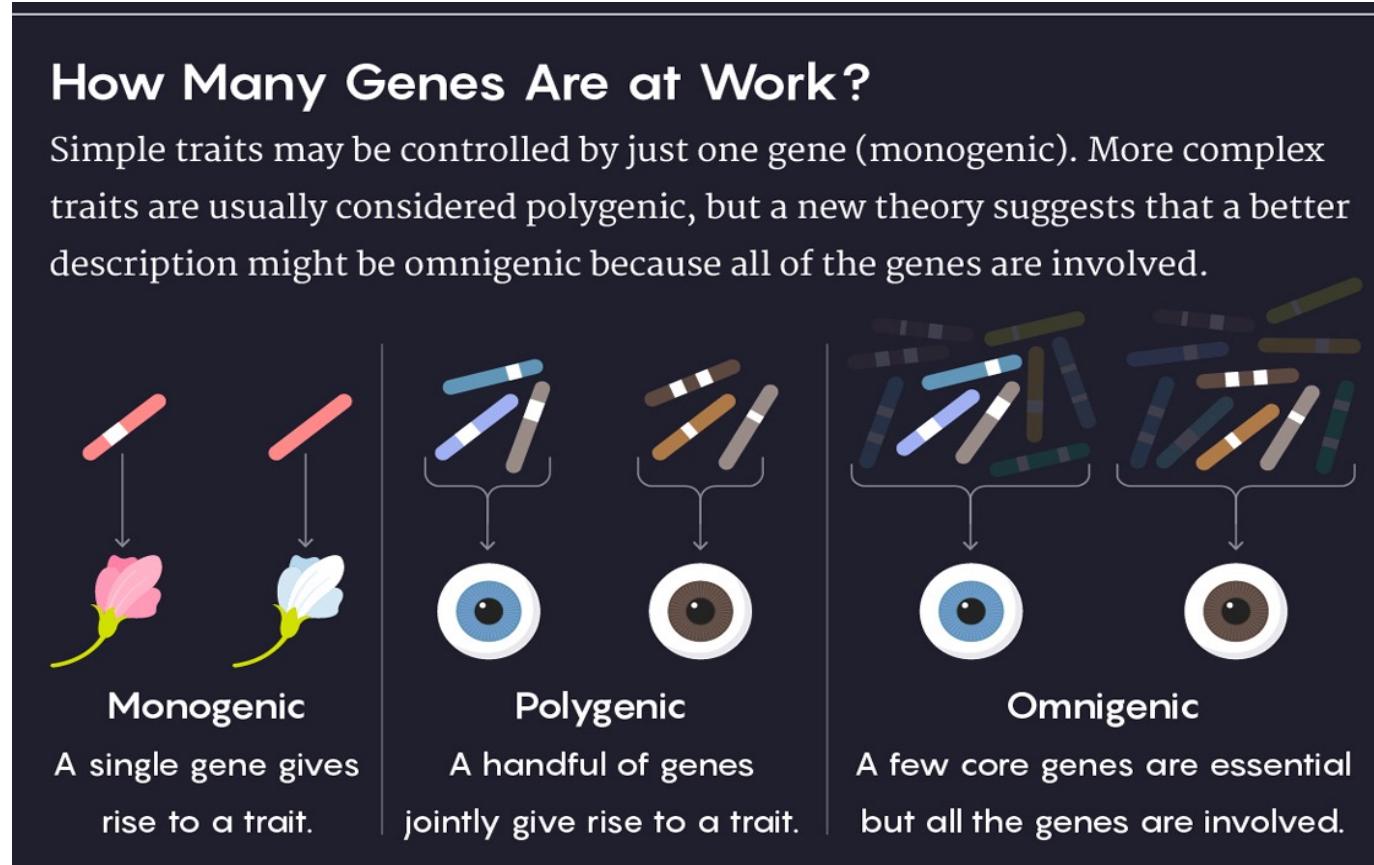
GWAS summary statistics

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

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

Horizontal pleiotropy is a common issue in MR

- Complex traits are extremely polygenic → lead to horizontal pleiotropy



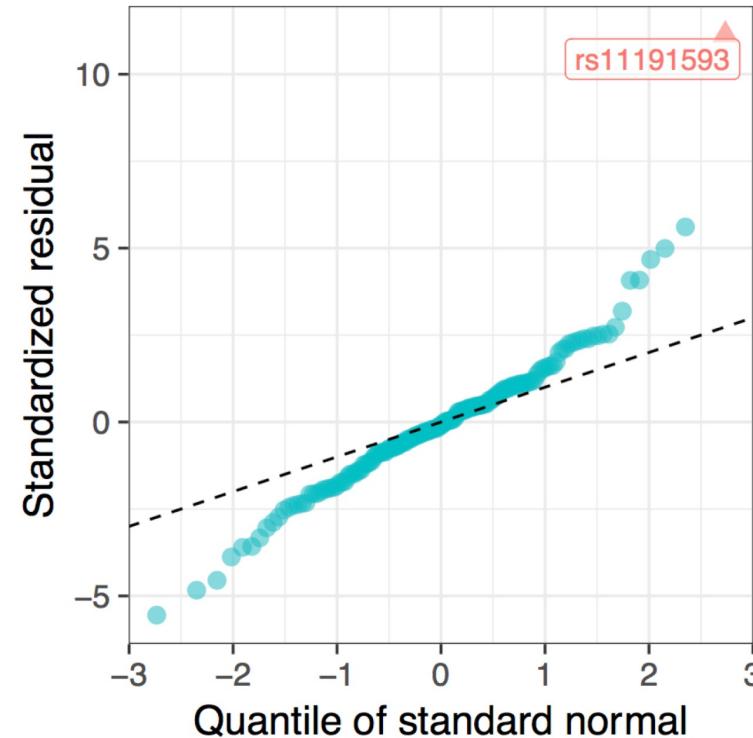
Horizontal pleiotropy is a common issue in MR

- 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

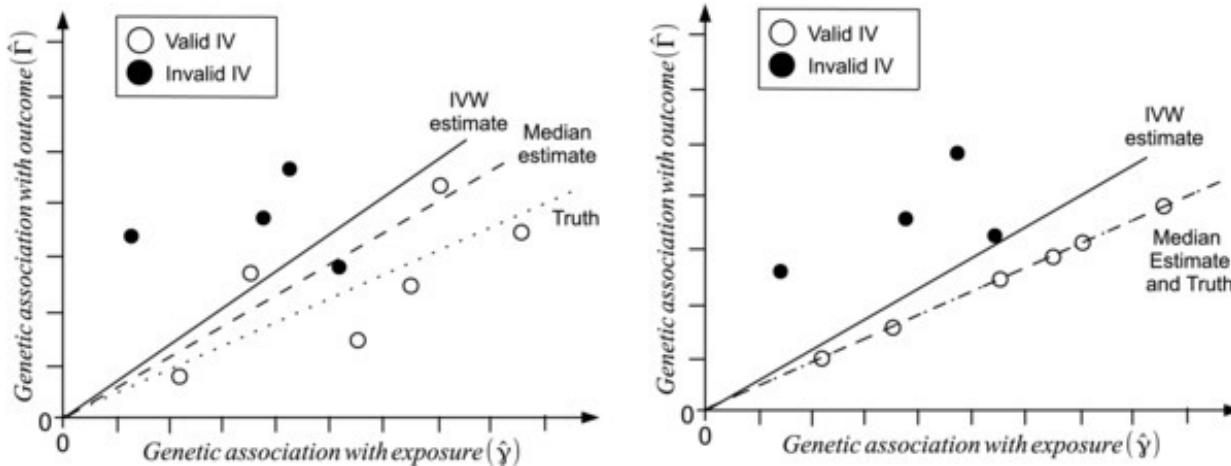
$$\Gamma_j = \beta\gamma_j + \alpha_j: \beta \text{ is not identifiable without additional assumptions on } \alpha_j$$

- 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 β

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

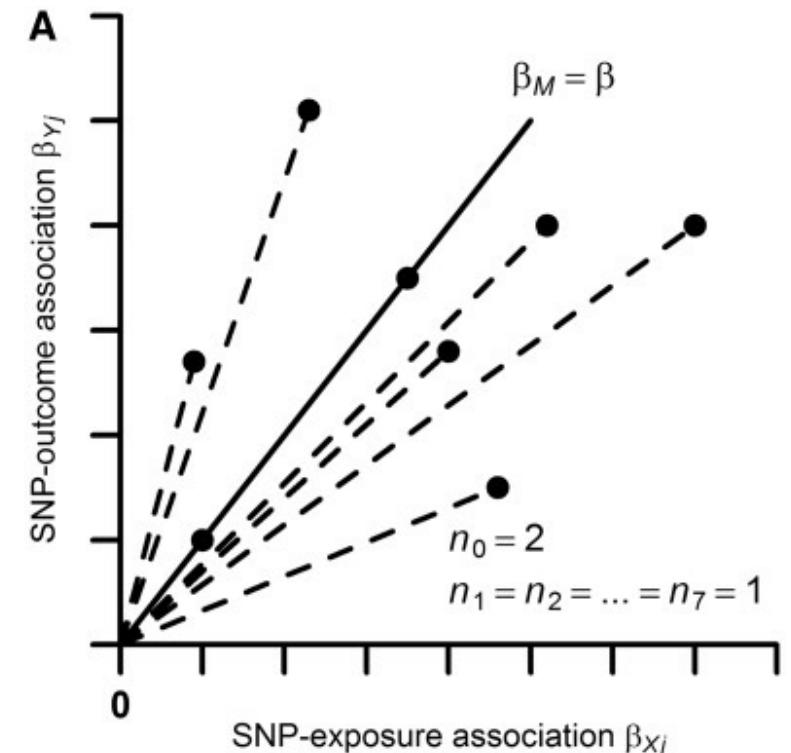
$$w_j^* = \frac{\hat{\gamma}_j^2}{\hat{\sigma}_{Y_j}^{-2}} \times \min(1, 20q_j)$$

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

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

MBE (Hartwig et. al. 2017)

- Let $\frac{\Gamma_j}{\gamma_j} = \beta + \frac{\alpha_j}{\gamma_j}$, define $b_j = \frac{\alpha_j}{\gamma_j}$
- 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:

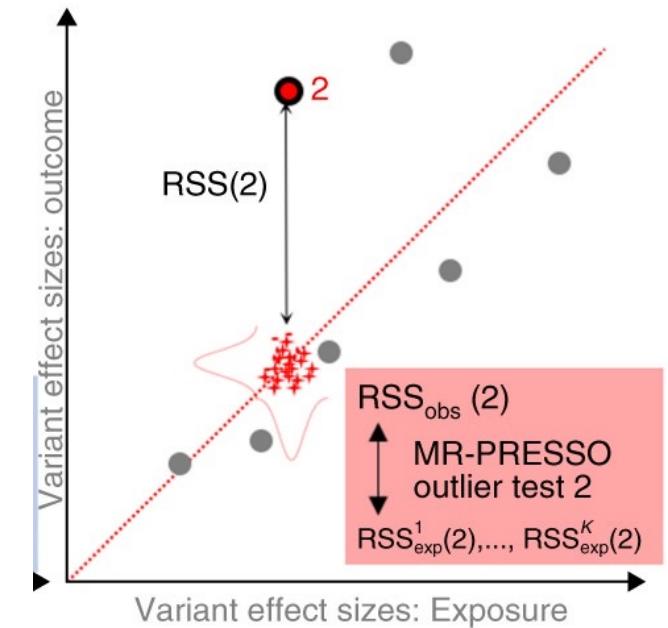
- Detect outliers (invalid IV) by checking whether the standardized leave-one-out residuals are too large

$$r_j = \frac{\hat{\Gamma}_j - \hat{\beta}_{-j}\hat{\gamma}_j}{\sqrt{\hat{\beta}_{-j}^2\hat{\sigma}_{X_j}^2 + \hat{\sigma}_{Y_j}^2}}$$

- 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 β 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):

$$\alpha_j \perp \gamma_j$$

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

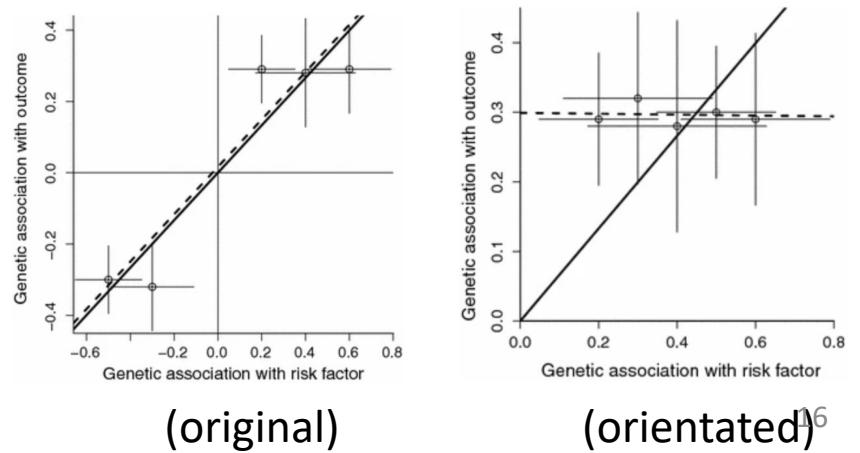
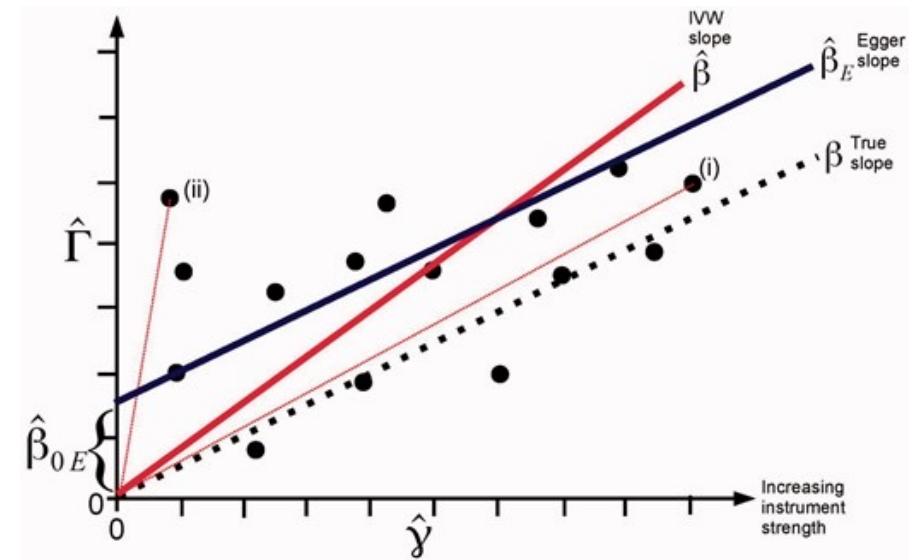
- Allow all SNPs to be invalid IVs
- Roughly, the pleiotropic effects won't cause severe bias in estimating β but would increase uncertainty in the estimates
- Common idea:
model α_j as an additional random effect
- Example methods:
MR-Egger, MR-RAPS, debiased IVW

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

- β 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 β_0 as average pleiotropic effect
- Data-adaptive σ^2 may account for increased uncertainty in $\hat{\beta}$ due to nonzero α_j
- 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

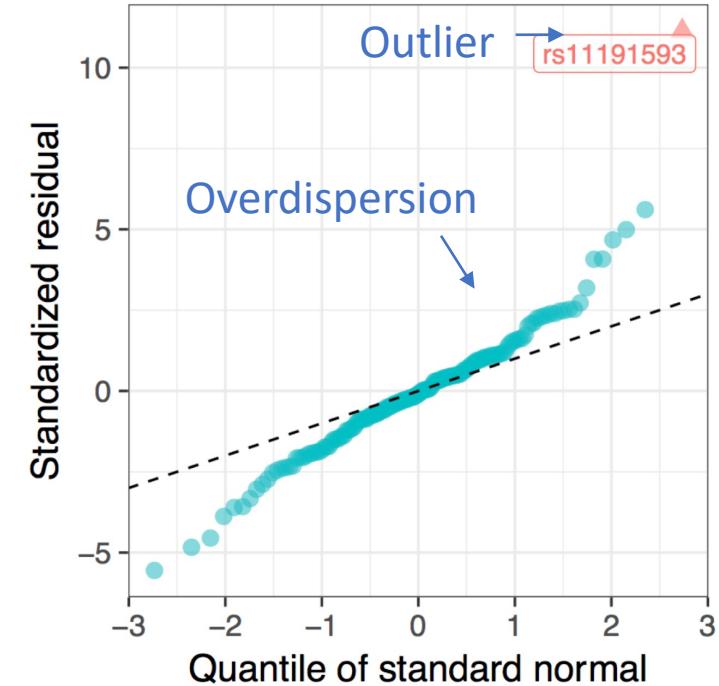


MR-RAPS (Zhao et. al. 2020)

- Model pervasive pleiotropy as random effect

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

- α_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 β and τ^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

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

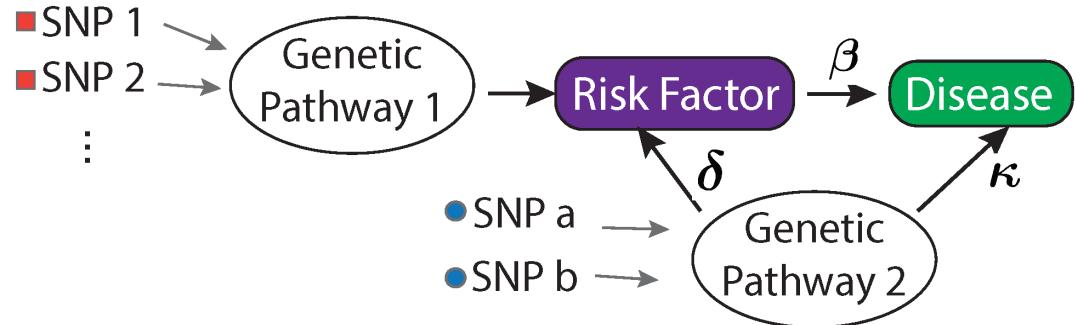
Debiased IVW

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

- 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

● SNP a
● SNP b
⋮

Genetic
Pathway 2

Risk Factor

Disease

■ 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 α_j and γ_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)

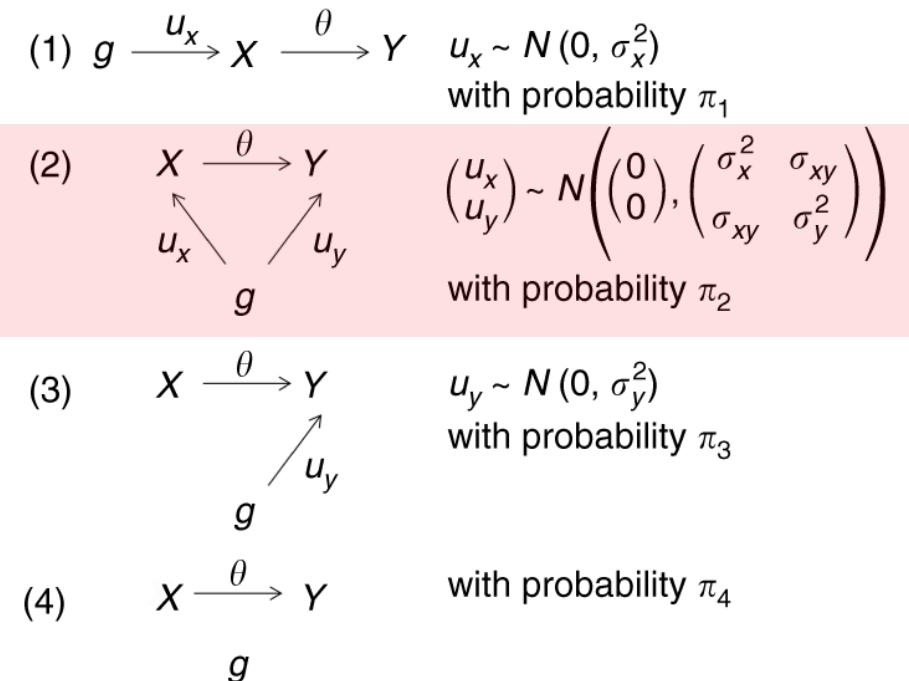
- Assume that there are four types of SNPs

- 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

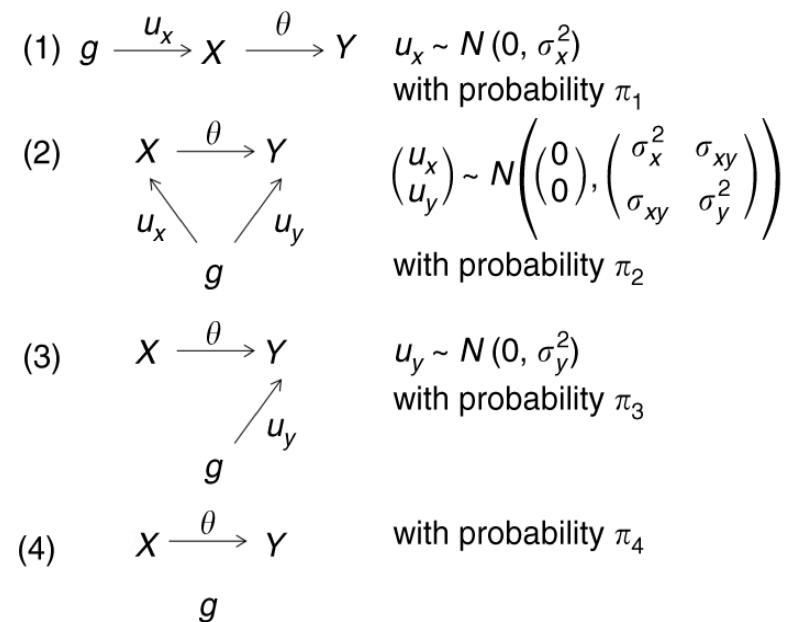
$$\hat{\Gamma}_j - \tilde{\beta} \hat{\gamma}_j \sim \pi_0 N(0, \sigma_{Yj}^2 + \tilde{\beta}^2 \sigma_{Xj}^2) + (1 - \pi_0)N(0, \sigma^2)$$

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

$$\hat{\beta}_j \sim N\left(\beta, \frac{\sigma_{Yj}^2}{\hat{\gamma}_j^2}\right) \quad \text{if } j \text{ is a valid IV}$$

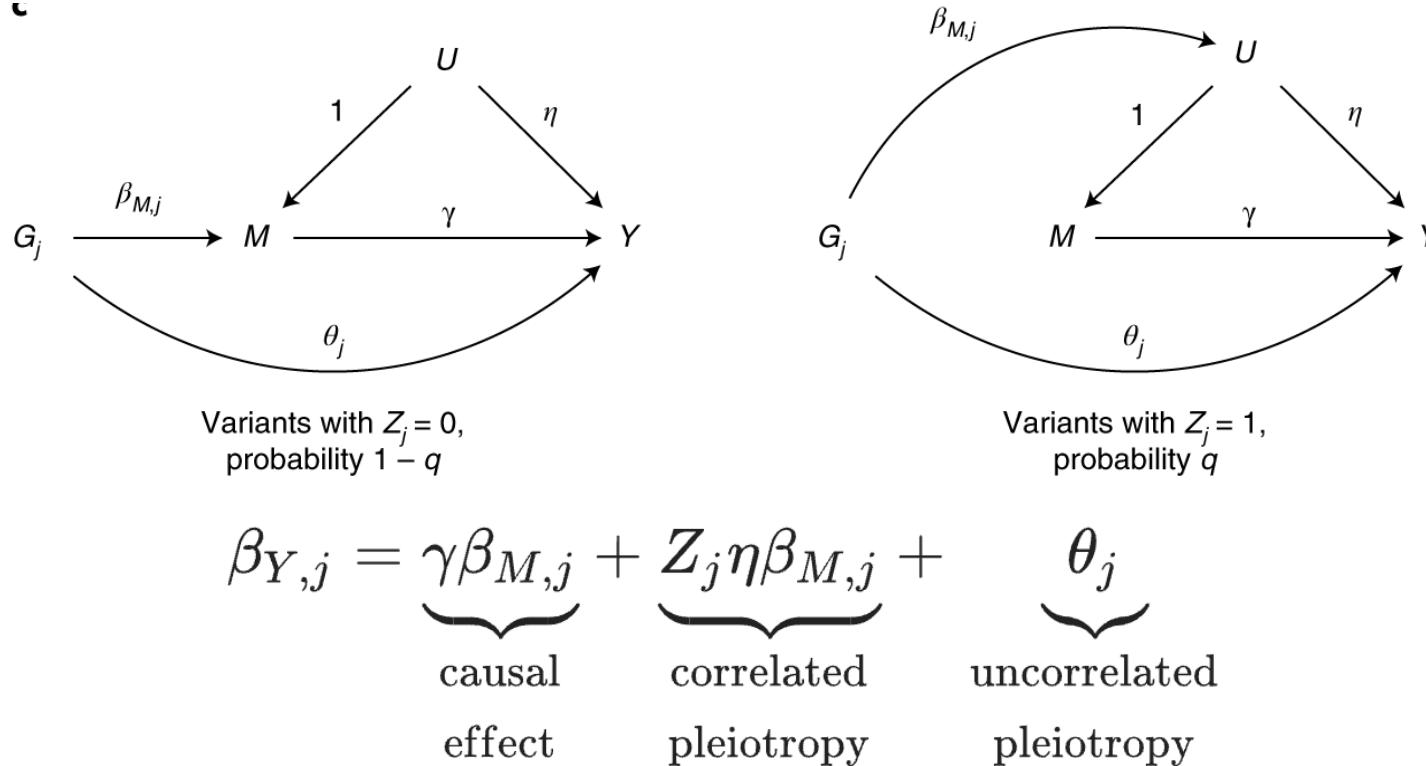
$$\hat{\beta}_j \sim N\left(0, \psi^2 + \frac{\sigma_{Yj}^2}{\hat{\gamma}_j^2}\right) \quad \text{if } j \text{ is an invalid IV}$$

- 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 $\beta_{M,j}$ and θ_j by Gaussian mixtures
- Obtain estimate and credible intervals of the causal effect γ through a Bayesian approach

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

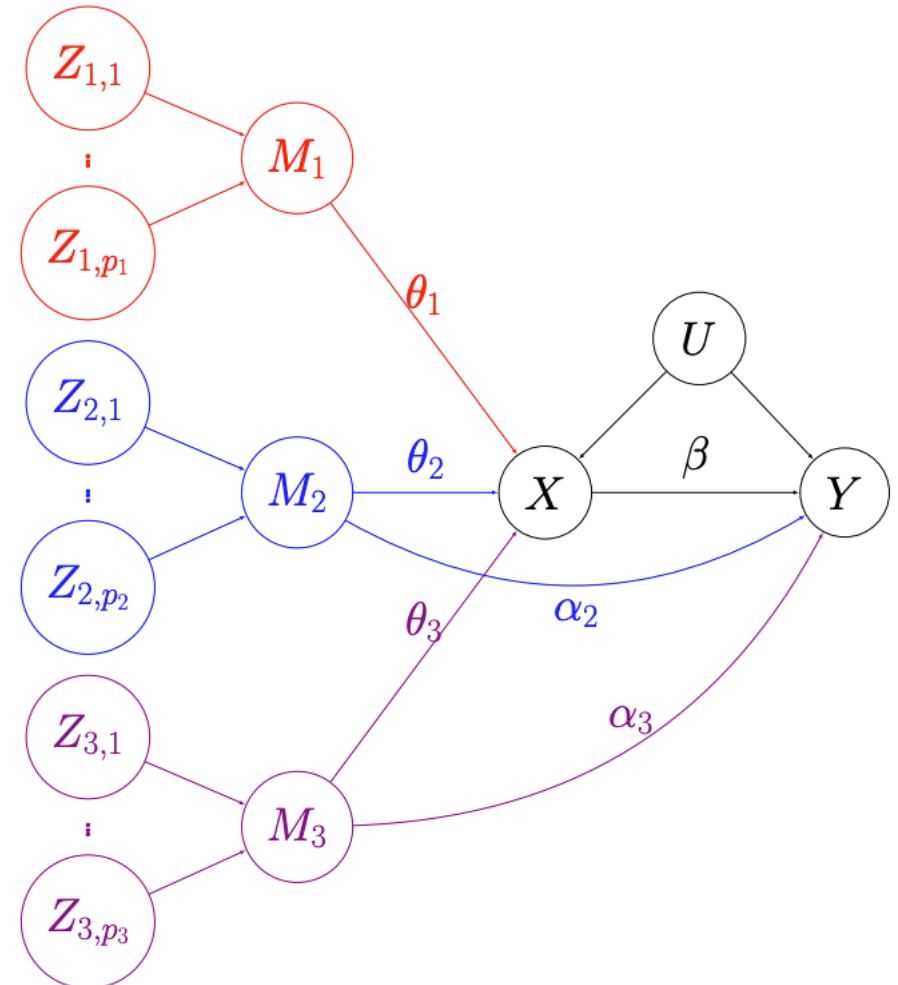
- Model

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

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

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

- 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:

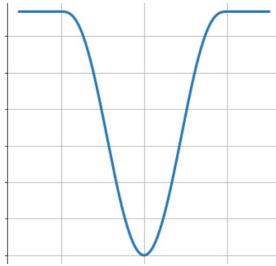
- Residual QQ plot
- Radial plot
- GRAPPLE visualization to detect multiple pleiotropic pathways
- You have learnt most of them in Lecture 1

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

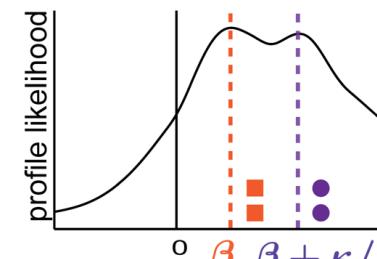
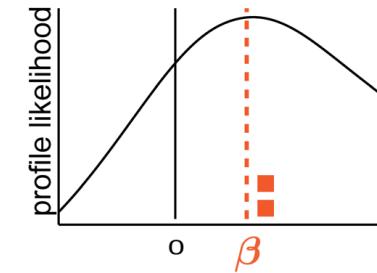


...

- SNP a
- SNP b



MR Short Course, lecture 2



Detect multiple pathways for CRP \rightarrow CAD

CRP: C-reactive protein

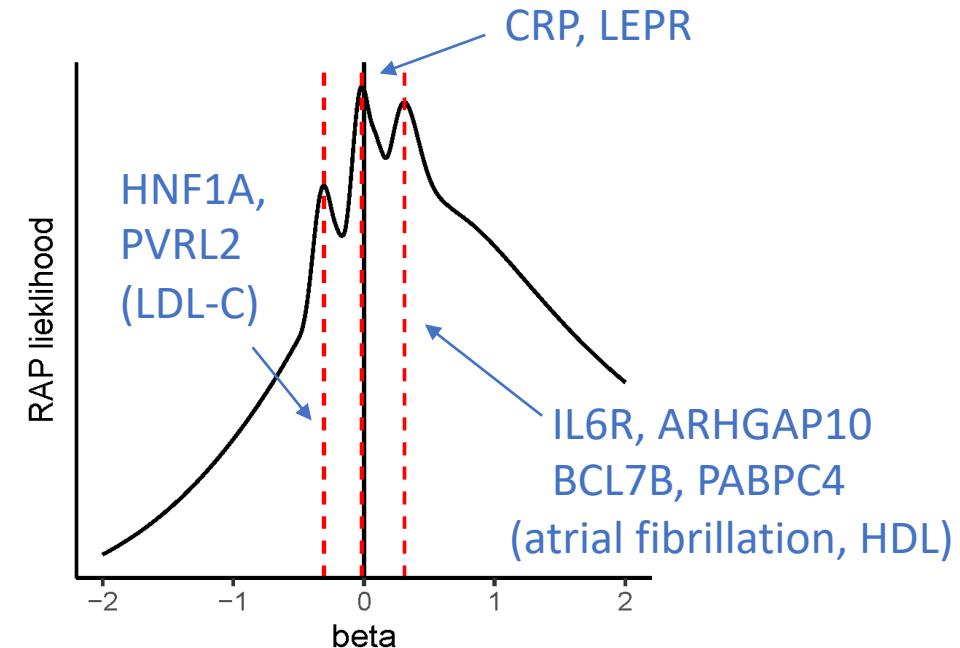
- Find marker SNPs by:

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

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 = β_1	Direct effect = total effect = β_1
Collider	Direct/total effect = β_1	Direct effect = total effect = β_1	Direct effect = total effect = β_1
Mediator	Biased—assumption IV2 is violated	Total effect = $\beta_1 + \alpha\beta_2$	Direct effect = β_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

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

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

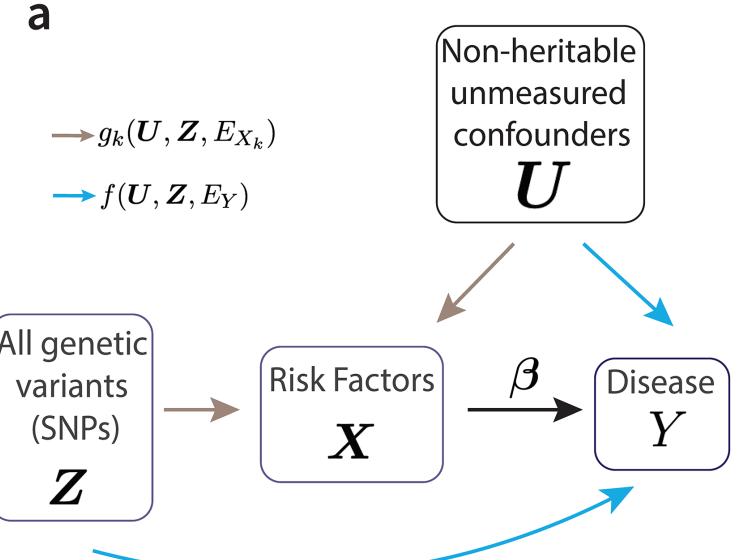
$$X_k = g_k(\mathbf{U}, \mathbf{Z}, E_{X_k}), \quad k = 1, \dots, K$$

- Define marginal effects of each SNP Z_j

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

- α_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 ,

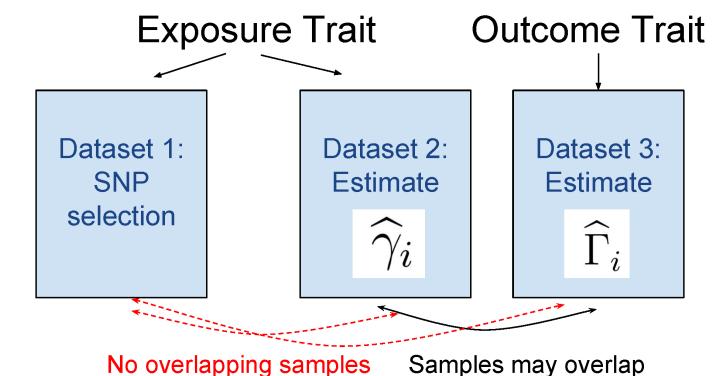
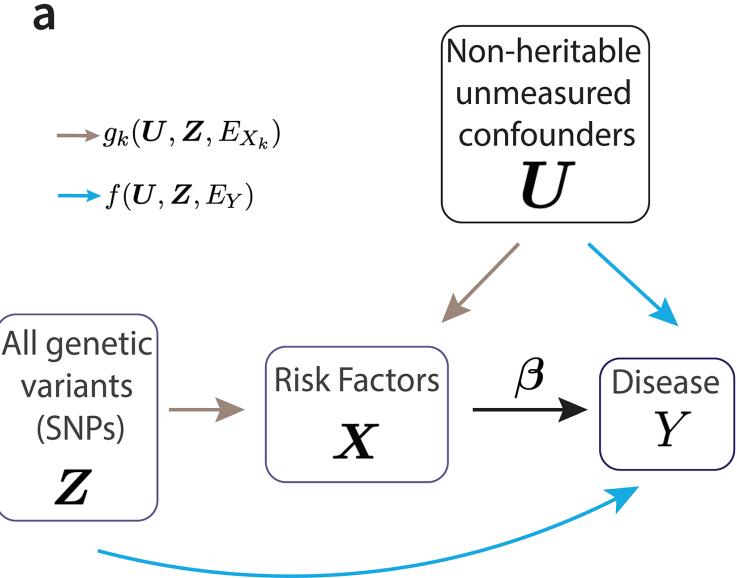
$$\Gamma_j = \boldsymbol{\gamma}_j^T \boldsymbol{\beta} + \alpha_j$$

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.
- **sisVIVE:** Kang, Hyunseung, et al. "Instrumental variables estimation with some invalid instruments and its application to Mendelian randomization." *Journal of the American statistical Association* 111.513 (2016): 132-144.
- **MR-Lasso:** Jessica MB Rees, Angela M Wood, Frank Dudbridge, Stephen Burgess. Robust methods in Mendelian randomization via penalization of heterogeneous causal estimates. *PLoS ONE* 2019; 14(9):e0222362
- **MR-Egger:** Bowden, J., Davey Smith, G., & Burgess, S. (2015). Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *International journal of epidemiology*, 44(2), 512-525.
- **MR-RAPS:** Zhao, Qingyuan, et al. "Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score." *Annals of Statistics* (2020): 1742-1769.
- **Debiased IVW:** Ye, T., Shao, J., & Kang, H. (2021). Debiased inverse-variance weighted estimator in two-sample summary-data Mendelian randomization. *The Annals of statistics*, 49(4), 2079-2100.

List of references

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