Meta-analysis of Mendelian randomization studies

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Outline

Introduction to MR

Case control study information

Example

Meta-analysis models & results

Summary

Introduction

- Mendelian randomization is an active area of research in genetic-epidemiology.
- Aim: To extend existing meta-analysis models

Mendelian Randomization

- Dates back to [Katan, 1986]
- Recent interest due to the increasing use of genetic data in epidemiology [Katan, 2004]
- Bi-allelic polymorphism - receive one allele from each parent
- Mendel's 2$^{\text{nd}}$ law: genes segregate independently
- Therefore individuals randomized to a genotype at conception
- Randomization by genotype is independent of confounding factors

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- Estimate phenotype-disease effect
- Confounding
- Reverse causation
- [Davey Smith et al., 2005]; phenotype - C-Reactive Protein, disease - hypertension, genetic polymorphism - in the human CRP gene
- Statistically the genotype used as an instrumental variable
- Economics, IVs also applied to;
  - clinical trials [Angrist et al., 1996].
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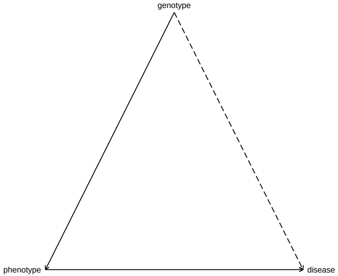

- Use gene-disease & gene-phenotype effect estimates to estimate the phenotype-disease relationship
- Standard IV technique if they were all linear - TSLS
- gene-disease log odds-ratio: θ, difference in mean phenotypes: δ, phenotype-disease log odds-ratio: η
- Ratio of coefficients approach [Thomas and Conti, 2004], for a k-unit change in the mean phenotype difference,

$$\eta_{[k]} \approx \frac{k\theta}{\delta}$$

Information from a case-control study

- A biallellic polymorphism (g,G)
  g: common allele G: risk allele
- 3 genotypes: gg, Gg, GG; $j = 1, 2, 3$
- Observed cases and controls y_{dj}, d = 0,1; control/case
- cell probabilities p_{dj}

	Genotype		
	gg	Gg	GG
Controls	y_{01}, p_{01}	y_{02}, p_{02}	y_{03}, p_{03}
Cases	y_{11}, p_{11}	y_{12}, p_{12}	y_{13}, p_{13}
Mean phenotype levels	μ_1	μ_2	μ_3

- Mean phenotype levels from controls

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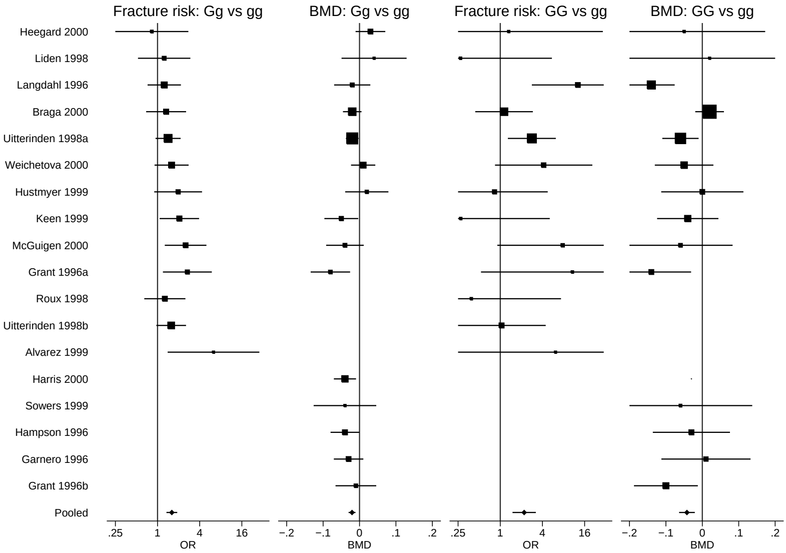
Example meta-analysis

- Mann (2001): Bone mineral denisty (BMD) & risk of osteoporotic fracture
- *COL1A1* gene: codes for collagen
- Average BMD lower for GG versus gg
- Risk of fracture increased for GG versus gg

Meta-analysis results in a four column forest plot



Approach

- Existing meta-analysis models estimate η based on either the Gg versus gg genotype comparison or the GG versus gg comparison, [Thompson et al., 2005].
- Gg vs gg: Bigger sample size; smaller difference in disease risk
- GG vs gg: Smaller sample size; bigger difference in disease risk
- Proposed approach: Estimate η across both genotype comparisons

Modelling assumptions

- phenotype-disease relationship common across studies
- phenotype-disease relationship common across genotype comparisons

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Multivariate meta-analysis models

- Genotype comparison 2:(Gg,gg), 3:(GG,gg)
  for study *i*
  $(\theta_{2i}, \theta_{3i})$: gene-disease log odds-ratios
  $(\delta_{2i}, \delta_{3i})$: difference in mean phenotypes
- Inference at the population level
- Marginal distribution: combine within and between study distributions

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$$\begin{bmatrix}\theta_{2i}\\ \delta_{2i}\\ \theta_{3i}\\ \delta_{3i}\end{bmatrix} \sim \mathrm{MVN}\left(\underline{\psi} = \begin{bmatrix}\eta\delta_2\\ \delta_2\\ \eta\delta_3\\ \delta_3\end{bmatrix}, \mathbf{V}_i + \mathbf{B}\right).$$

$$\mathbf{V}_i = \begin{bmatrix} \mathrm{v}(\theta_{2i}) & 0 & \mathrm{v}(\theta_{2i},\theta_{3i}) & 0\\ 0 & \mathrm{v}(\delta_{2i}) & 0 & \mathrm{v}(\delta_{2i},\delta_{3i})\\ \mathrm{v}(\theta_{3i},\theta_{2i}) & 0 & \mathrm{v}(\theta_{3i}) & 0\\ 0 & \mathrm{v}(\delta_{3i},\delta_{2i}) & 0 & \mathrm{v}(\delta_{3i}) \end{bmatrix}.$$

$$\mathbf{B} = \begin{bmatrix} \eta^2\tau_2^2 & \eta\tau_2^2 & \eta^2\tau_2\tau_3\rho & \eta\tau_2\tau_3\rho\\ \eta\tau_2^2 & \tau_2^2 & \eta\tau_2\tau_3\rho & \tau_2\tau_3\rho\\ \eta^2\tau_2\tau_3\rho & \eta\tau_2\tau_3\rho & \eta^2\tau_3^2 & \eta\tau_3^2\\ \eta\tau_2\tau_3\rho & \tau_2\tau_3\rho & \eta\tau_3^2 & \tau_3^2 \end{bmatrix}.$$

τ_2^2 between-study variance of the δ_{2i}'s

τ_3^2 between-study variance of the δ_{3i}'s

ρ between-study correlation between the δ_{2i}'s and the δ_{3i}'s

Maximum likelihood estimation

- Log-likelihood of the multivariate Normal distribution,

$$\log L \propto \sum_{i=1}^{n} -\frac{1}{2}\log(\det(\mathbf{V}_i+\boldsymbol{\Sigma}))-\frac{1}{2}(\underline{x_i}-\underline{\psi})^T(\mathbf{V}_i+\boldsymbol{\Sigma})^{-1}(\underline{x_i}-\underline{\psi})$$

- Maximisation using the Newton-Raphson algorithm
- Argument for using REML form of the likelihood for marginal models

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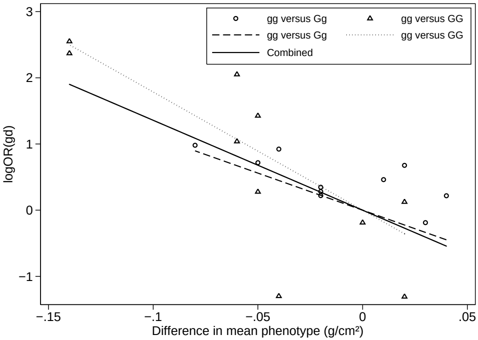
Results

Method of estimation	$OR_{pd,0.05}$	95% C.I./Cr.I.	
Gg vs gg	0.57	0.42	0.77
GG vs gg	0.40	0.28	0.57
Combined	0.50	0.39	0.62

- Gg vs gg expecting narrower CI - but wider
- GG vs gg bigger difference in disease risk - OR_{pd} further from 1
- combined model - weighted average of the separate estimates, with a narrower CI due to increased number of studies
- All results qualitatively the same
- 0.05 unit increase in BMD, implies typical patient at 40% risk of Osteoporotic fracture

Assessment of a common phenotype-disease odds-ratio



- MR assumptions fit straight line through the origin
- η gradient of the line

Incorporating the genetic model-free approach

$$\lambda = \frac{\theta_2}{\theta_3} = \frac{\delta_2}{\delta_3}$$

- Interpretation of λ

λ	Genetic model
0	Recessive
0.5	Co-dominant
1	Dominant
> 1	Over-dominant, heteresis

- Meta-analysis models to estimate λ, [Minelli et al., 2005].

$$\begin{bmatrix}\theta_{2i}\\ \delta_{2i}\\ \theta_{3i}\\ \delta_{3i}\end{bmatrix} \sim \mathrm{MVN}\left(\begin{bmatrix}\eta\lambda\delta\\ \lambda\delta\\ \eta\delta\\ \delta\end{bmatrix}, \mathbf{V}_i + \mathbf{\Sigma}\right),$$

$$\mathbf{\Sigma} = \begin{bmatrix}\eta^2\lambda^2\tau^2 & \eta\lambda^2\tau^2 & \eta^2\lambda\tau^2 & \eta\lambda\tau^2\\ \eta\lambda^2\tau^2 & \lambda^2\tau^2 & \lambda\eta\tau^2 & \lambda\tau^2\\ \eta^2\lambda\tau^2 & \lambda\eta\tau^2 & \eta^2\tau^2 & \eta\tau^2\\ \eta\lambda\tau^2 & \lambda\tau^2 & \eta\tau^2 & \tau^2\end{bmatrix}$$

- τ^2 the between-study variance of the difference in mean phenotypes of the GG versus gg comparison

Bayesian estimation

- Product Normal Formulation [Spiegelhalter, 1998]
- 4 outcomes - univariate Normal distributions

$$\theta_{2i} \sim \mathrm{N}(\eta\lambda\delta_i, v(\theta_{1i})), \qquad \delta_{2i} \sim \mathrm{N}(\lambda\delta_i, v(\delta_{1i}))$$
$$\theta_{3i} \sim \mathrm{N}(\eta\delta_i, v(\theta_{2i})), \qquad \delta_{3i} \sim \mathrm{N}(\delta_i, v(\delta_{2i}))$$

- The correct covariances are induced in the model due to the relationships between the means and the sequential parameter updating under Gibbs sampling
- Prior distributions - vague

$$\delta_i \sim \mathrm{N}(0, 1 \times 10^6), \quad \eta \sim \mathrm{N}(0, 1 \times 10^6), \quad \lambda \sim \mathrm{Beta}(0.5, 0.5)$$

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$$\begin{aligned} \theta_{2i} &\sim \mathrm{N}(\eta\lambda\delta_i, v(\theta_{1i})), & \delta_{2i} &\sim \mathrm{N}(\lambda\delta_i, v(\delta_{1i})) \\ \theta_{3i} &\sim \mathrm{N}(\eta\delta_i, v(\theta_{2i})), & \delta_{3i} &\sim \mathrm{N}(\delta_i, v(\delta_{2i})) \end{aligned}$$

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Results

Method of estimation	$OR_{pd,0.05}$	95% C.I./Cr.I.		λ	95% C.I./Cr.I.	
ML	0.42	0.28	0.61	0.33	0.19	0.47
Bayesian	0.46	0.32	0.61	0.30	0.17	0.45

- Genetic model between recessive and co-dominant

Summary

- Mendelian randomization - depends on random allocation of an individual's genotype
- Genotype used as an instrumental variable
- Meta-analysis model - joint analysis of two genotype comparisons
- Meta-analysis model - incorporating the genetic model-free approach

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