Meta-analysis of causal relationships using genetic instrumental variables

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ISCB 2009, 23rd to 27th August 2009
Outline

▶ Introduction to Mendelian randomization
▶ Introduction of Bayesian method through simulated examples
▶ Applying method in one study
▶ Applying method in multiple studies
▶ Conclusion
Mendelian randomization is a technique for using genes (G) as instrumental variables (IV) to assess the true causal association where direct experiment is not possible.
Introduction to Mendelian randomization

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- We use the random allocation of genes at conception in an analogous way to treatment assignment in a randomized control trial.

We seek to estimate the causal effect of change in outcome (Y) for unit increase in phenotype (X) keeping all other factors (U) equal.
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Instrumental variables

\[
\begin{align*}
G &\rightarrow X \\
U &\rightarrow X \\
X &\rightarrow Y \\
Y &\rightarrow G
\end{align*}
\]

**Figure:** DAG of assumptions

- **G** = gene
- **X** = phenotype
- **Y** = outcome
- **U** = confounders
Instrumental variables

Assumptions:

i. the genotype is associated with the phenotype \((G \perp \perp X)\),

Figure: DAG of assumptions

\(G = \text{gene} \)
\(X = \text{phenotype} \)
\(Y = \text{outcome} \)
\(U = \text{confounders} \)
Instrumental variables

Assumptions:

i. the genotype is associated with the phenotype \((G \not\perp \perp X)\),

ii. the genotype is not associated with any confounders \((G \perp \perp U)\),

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G = gene
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Assumptions:

i. the genotype is associated with the phenotype \((G \perp \perp X)\),

ii. the genotype is not associated with any confounders \((G \perp \perp U)\),

iii. the genotype is conditionally independent of the outcome given the phenotype \((G \perp \perp Y \mid X, U)\).
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- measuring over 20 different SNPs, although different studies measure different subsets of these,
- including cohort studies, case-cohort studies, prospective and retrospective case-control studies,
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How to include all of the data?
Existing methodology

Ratio method:
- can be used for one SNP in one study with continuous or binary outcomes.

Two stage least squares:
- for multiple, polychotomous SNPs in one study with continuous outcomes.
- We calculate fitted values of X in the first stage G-X regression.
- We use these fitted values $\hat{X}$ in a second stage X-Y regression.
- Standard error is calculated using sandwich variance estimators.
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Simulated example

Confounded association - for individual $i$:

$$x_i = \alpha_1 g_i + \alpha_2 u_i + \epsilon_{xi}$$
$$y_i = \beta_1 x_i + \beta_2 u_i + \epsilon_{yi}$$
$$u_i \sim \mathcal{N}(0, 1)$$
$$\epsilon_{xi}, \epsilon_{yi} \sim \mathcal{N}(0, \sigma^2)$$
$$g_i \in \{0, 1, 2\}$$
Simulated example

Confounded association - for individual $i$:

\[ x_i = 0.5 g_i + 1 u_i + \epsilon_{xi} \]
\[ y_i = 2 x_i - 3 u_i + \epsilon_{yi} \]
\[ u_i \sim \mathcal{N}(0, 1) \]
\[ \epsilon_{xi}, \epsilon_{yi} \sim \mathcal{N}(0, 0.25) \]
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Simulated examples: Bayesian solution

Re-form the problem as regression with heterogeneous error in $x$ - for genotypic group $j$:

\[ \bar{x}_j \sim N(\xi_j, \sigma^2_{xj}) \]
\[ \bar{y}_j \sim N(\eta_j, \sigma^2_{yj}) \]
\[ \eta_j = \beta_0 + \beta_1 \xi_j \]

We estimate $\sigma^2_{xj}$ and $\sigma^2_{yj}$ for data and set vague priors on all other parameters.

Run in WinBUGS using MCMC sampling.
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- Run in WinBUGS using MCMC sampling.
Simulated examples: Results

<table>
<thead>
<tr>
<th>(true value = 2)</th>
<th>Causal Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak (ratio)</td>
<td>1.637</td>
<td>0.563 to 6.582</td>
</tr>
<tr>
<td>Weak (Bayesian)</td>
<td>1.496</td>
<td>0.536 to 7.190</td>
</tr>
<tr>
<td>Moderate (ratio)</td>
<td>2.555</td>
<td>1.481 to 6.007</td>
</tr>
<tr>
<td>Moderate (Bayesian)</td>
<td>2.417</td>
<td>1.473 to 4.592</td>
</tr>
<tr>
<td>Strong (ratio)</td>
<td>2.139</td>
<td>1.814 to 2.554</td>
</tr>
<tr>
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<td>2.018</td>
<td>1.749 to 2.347</td>
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</table>
Group-based method

\[ \bar{x}_j \sim \mathcal{N}(\xi_j, \sigma^2_{x_j}) \]
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- We extend to use multiple genes, taking each genotype as a separate category in the stratification.
- This gives a more detailed model of the G-X association.
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- We extend to use multiple genes, taking each genotype as a separate category in the stratification.
- This gives a more detailed model of the G-X association.
- If the size of groups are small, exact knowledge of \( \sigma_{xj}^2, \sigma_{yj}^2 \) will not be valid.
Individual- and additive-based methods

We can take population variances $\sigma_x^2, \sigma_y^2$ and model $X$ and $Y$ on an individual level - for individual $i$ in genotypic group $j$:

\[ x_{ij} \sim \mathcal{N}(\xi_j, \sigma_x^2) \]
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We can take population variances $\sigma^2_x, \sigma^2_y$ and model $X$ and $Y$ on an individual level - for individual $i$ in genotypic group $j$:

\[
\begin{align*}
    x_{ij} &\sim N(\xi_j, \sigma^2_x) \\
    y_{ij} &\sim N(\eta_j, \sigma^2_y)
\end{align*}
\]

If we want to introduce an additive model additive across SNPs - for individual $i$ with $G_{ik}$ variant alleles of SNP $k$:

\[
\begin{align*}
    \xi_i &= \alpha_0 + \sum_{k} G_{ik} \alpha_k \\
    x_i &\sim N(\xi_i, \sigma^2_x)
\end{align*}
\]
Bayesian methodology vs Two stage least squares (2SLS)

- Both methods involve fitting a G-X regression, and then using these fitted values in a $\hat{X}$-Y regression.
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- Both methods involve fitting a G-X regression, and then using these fitted values in a \( \hat{X} \)-Y regression
- Bayesian method fits the whole model simultaneously allowing feedback through the joint posterior
- 2SLS uses sandwich variance estimators making assumption of asymptotic normality
- Bayesian method uses MCMC sampling to find standard errors, confidence intervals
Hierarchical meta-analysis

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Fixed/random-effect meta-analysis

Fixed-effect meta-analysis in group based method - for group $j$, study $m$:
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Fixed-effect meta-analysis in group based method - for group $j$, study $m$:

\[ x_{jm} \sim \mathcal{N}(\xi_{jm}, \sigma_{xjm}^2) \]
\[ y_{jm} \sim \mathcal{N}(\eta_{jm}, \sigma_{yjm}^2) \]
\[ \eta_{jm} = \beta_{0m} + \beta_1 \xi_{jm} \quad (1) \]
Fixed/random-effect meta-analysis

Fixed-effect meta-analysis in group based method - for group $j$, study $m$:

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$$y_{jm} \sim \mathcal{N}(\eta_{jm}, \sigma^2_{y_{jm}})$$
$$\eta_{jm} = \beta_{0m} + \beta_1 \xi_{jm} \quad (1)$$

Or for random-effect meta-analysis, line (1) is replaced by:

$$\eta_{jm} = \beta_{0m} + \beta_{1m} \xi_{jm}$$
$$\beta_{1m} \sim \mathcal{N}(\mu_{\beta}, \psi^2)$$
Summary of Bayesian methodology

- We stratify the population into genotypic groups.

- For each genotypic group, we estimate the mean value of phenotype ($\xi_j$) in that group, allowing for an additive structure between these values if appropriate.

- We simultaneously estimate the mean value of outcome ($\eta_j$) in the group under the constraint of a linear relationship between mean phenotype and mean outcome level ($\eta_j = \beta_0 + \beta_1 \xi_j$).

- We set a hierarchical model on our causal parameter between studies.

- We draw samples from the posterior distribution using WinBUGS.
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CCGC study

- We use three SNPs measured in the majority of studies.
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- For participant $i$ in genotypic group $j$ with $N_j$ participants, $n_j$ cases, with $G_{kjm}$ variant alleles of SNP $k$ from study $m$:

\[
\begin{align*}
\xi_{jm} &= \alpha_0 + \alpha_1 G_{1jm} + \alpha_2 G_{2jm} + \alpha_3 G_{3jm} \\
x_{ijm} &\sim \mathcal{N}(\xi_{jm}, \sigma_{xm}^2) \\
n_j &\sim \mathcal{B}(N_j, \pi_j) \\
\eta_j = \logit(\pi_j) &= \beta_0 + \beta_1 \xi_j
\end{align*}
\]
Conclusion

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- The Bayesian method is flexible to deal with situations existing methods cannot deal with:
  - ...meta-analysis, missing data, binary outcomes, uncertainty in haplotype assignment.
References and Acknowledgements


Thanks to:

► The Medical Research Council
► The CRP CHD Genetics Collaboration and especially Frances Wensley for data collation.