Instrumental variable (IV) estimators for the causal effect of an exposure on binary outcome

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Outline

- Introduction
- Instrumental variable (IV) and examples
- IV-methods
- Estimation of causal odds ratio by IV-methods
- Simulation
- Conclusions
bias due to unmeasured confounders

IV-methods consistently estimate the causal effect of exposure on outcome even in the presence of unmeasured confounders

IV-methods have a long tradition in economics and econometrics

they have recently entered the epidemiological and biostatistical literature

mainly in connection with noncompliance adjustment in randomized controlled trial (RCT)

in the context of Mendelian randomization studies
random variable $Z$ such that
- $Z$ is associated with exposure $X$
- $Z$ affects the outcome $Y$ only through $X$ (exclusion restriction)
- no confounding for the effect of $Z$ on $Y$

$U$ represents all confounders (some may be unmeasured)
Example 1: RCT with noncompliance

- a double-blind randomized controlled trial with noncompliance
- randomization is an instrumental variable for the effect of received treatment on outcome

\[ Z = \text{randomization} \quad \rightarrow \quad X = \text{received treatment} \quad \rightarrow \quad \text{outcome} \]
by using an IV, one can estimate the causal effect of a nonrandomized exposure on outcome in the presence of unmeasured confounders
Example 2: observational study

- studies of outcomes associated with exposure to pharmaceutical products (Brookhart et al., 2006)
  - $X$ is Cox-2 selective ($X = 1$) compared with non-selective NSAIDs ($X = 0$)
  - $Y$ is upper GI bleeding within 60 days ($Y = 1$) and 0 otherwise
  - $Z$ is prescribing preference, $Z = 1$ if physician’s prescription preference was Cox-2 and 0 otherwise

Instrumental variable (IV) estimators
We investigate IV-methods for dichotomous outcome

- exact IV-methods which have been proposed in the context of noncompliance adjustment in RCT
  Vansteelandt and Goetghebeur (*JRSSB*), 2003 and
  Robins and Rotnitzky (*Biometrika*), 2004

- approximate IV-methods that have been proposed in the literature on Mendelian randomization
  Thompson, Tobin and Minelli (Technical report GEI), 2003 and
  Thomas and Conti (*Int. J. Epidemiology*), 2004
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Structural mean model (SMM)

- let $Y_{i0}$ denote subject $i$'s potential response to non-selective NSAIDs
- with $Z_i$ the IV (prescribing preference), the model

$$\log\text{it}E(Y_i|X_i, Z_i) - \log\text{it}E(Y_{i0}|X_i, Z_i) = \psi^* X_i$$

then expresses the causal effect of Cox-2 compared to non-selective NSAIDs on GI bleeding risk

- the odds of GI bleeding for subjects on Cox-2 ($X = 1$) would have been $\exp(\psi^*)$ times smaller than had they been on non-selective NSAIDs:

$$\frac{P(Y_i = 1|X_i, Z_i)}{P(Y_i = 0|X_i, Z_i)} / \frac{P(Y_{i0} = 1|X_i, Z_i)}{P(Y_{i0} = 0|X_i, Z_i)} = \exp\{\psi^* X_i\}$$

- this model is called a logistic SMM and $\exp(\psi^*)$ is causal odds ratio

Instrumental variable (IV) estimators
Identification of $\psi^*$

- key to estimation is to choose $\psi^*$ in SMM

$$\logit E(Y_i|X_i, Z_i) - \logit E(Y_{i0}|X_i, Z_i) = \psi^* X_i$$

such that

$$E(Y_{i0}|Z_i) = E(Y_{i0})$$

- to realize this, in addition to SMM, Vansteelandt and Goetghebeur (VG) assume an association model

$$\logit E(Y_i|X_i, Z_i) = \beta_0 + \beta_1 X_i + \beta_2 Z_i + \beta_3 X_i Z_i$$

- $Y_{i0}$ can be predicted as

$$\hat{Y}_{i0}(\psi^*) = \expit(\beta_0 + \beta_1 X_i + \beta_2 Z_i + \beta_3 X_i Z_i - \psi^* X)$$

Instrumental variable (IV) estimators
Estimate of $\psi^*$ by VG

- then we choose $\psi^*$ by solving

$$\sum_i \hat{Y}_{i0}(\psi^*)Z_i - \sum_i \hat{Y}_{i0}(\psi^*)(1 - Z_i) = 0$$

- with dichotomous exposure, closed form solution can be obtained for $\psi^*$
the model used by VG is not guaranteed compatible in the sense that there may be no choice of parameter value for which

\[ E(Y_{i0}|Z_i) = E(Y_{i0}) \]

Robins and Rotnitzky (RR) avoid specifying an association model

they instead postulate a model for

\[ \text{logit}E(Y_{i0}|X_i, Z_i) - \text{logit}E(Y_{i0}|X_i = 0, Z_i) \]

estimation requires solving complex estimating equations
Approximate method 1

to estimate $\psi^*$ in SMM, Thompson et al. (TTM) approximate

$$E[\logit P\{Y = 1|X, Z\}|Z] = \logit P(Y = 1|Z)$$

and

$$E[\logit P\{Y_0 = 1|X, Z\}|Z] = \logit P(Y_0 = 1|Z)$$

so that

$$\logit P(Y = 1|Z) - \logit P(Y_0 = 1|Z) = \psi^* E(X|Z)$$
they obtain an estimate of $\psi^*$ by fitting model

$$\text{logit} P(Y = 1|Z) = \alpha + \psi^* E(X|Z)$$

they then obtain causal odds ratio,

$$\exp(\psi^*) = \exp[\log\{OR(Y|Z)\}/\delta_{xz}]$$

where $$\delta_{xz} = E(X|Z = 1) - E(X|Z = 0)$$

this is the most commonly adopted approach in Mendelian randomization studies

it relies on heavy approximations however.
Approximate method 2

to estimate the causal parameter $\gamma^*$ in the probit SMM

$$\Phi^{-1}\{E(Y|X, Z)\} - \Phi^{-1}\{E(Y_0|X, Z)\} = \gamma^* X$$

$\Phi^{-1}$ is the probit link, an alternative exact method has been developed under the following assumptions that

- $X|Z \sim N(\alpha_0 + \alpha_1 Z, \sigma^2)$
- a probit regression model holds

$$\Phi^{-1}\{P(Y = 1|X, Z)\} = \theta_0^* + \theta_1^* X + \theta_2^* Z$$
Two-stage estimator

- a little algebra shows that under these assumptions
  \[ \exp(\gamma^*) = \exp\left(\frac{\theta_1}{\sqrt{\alpha_1^2 - \theta_1^2 \sigma^2}}\right) \]
  where
  \[ \Phi^{-1}\{P(Y = 1|Z)\} = \theta_0 + \theta_1 Z \]
- this estimator can be obtained in 2 stage
  - by fitting an ordinary regression of \( X \) on \( Z \) to obtain slope \( \alpha_1 \) and residual variance \( \sigma^2 \)
  - by regressing \( Y \) on \( Z \) using the probit link to obtain \( \theta_1 \)
- causal odds ratio is then approximately obtained as
  \[ \exp\left\{\frac{\theta_1}{0.6071 \sqrt{\alpha_1^2 - \theta_1^2 \sigma^2}}\right\} \]
Simulation

- each experiment was based on 1000 samples
  - \( Z \sim Bin(1, 0.67) \)
  - exposure \( X \) is generated for two cases
    - binary: \( X \sim Bin(1, \expit(\alpha_0 + \alpha_1 Z)) \)
    - continuous: \( X \sim N(\alpha_0 + \alpha_1 Z, 1) \)
  - for generating outcome, we assume:
    \[
    \begin{align*}
    \logit E(Y|X, Z) - \logit E(Y_0|X, Z) &= \psi_0 X \\
    \logit E(Y_0|X, Z) - \logit E(Y_0|X = 0, Z) &= X(\eta_0 + \eta_1 Z) \\
    E(Y_0|Z) &= E(Y_0)
    \end{align*}
    \]
these imply that binary outcome $Y$ can be generated by

$$Y \sim Bin(1, \expit(\psi_0 X + (\eta_0 + \eta_1 Z)X + \nu(Z)))$$

where $\nu(Z)$ solves

$$E(Y_0) - \sum_{x=0}^{1} \expit\{x(\eta_0 + \eta_1 Z) + \nu(Z)\}P(X = x|Z) = 0$$
when $\psi_0 = 1$ and $\delta_{xz} = E(X|Z = 1) - E(X|Z = 0) = 0.25$

$\delta_{yz} = E(Y|Z = 1) - E(Y|Z = 0)$

<table>
<thead>
<tr>
<th>$E(Y)$</th>
<th>$\delta_{yz}$</th>
<th>Method</th>
<th>Bias Mean (Median)</th>
<th>M.S.E</th>
<th>SE</th>
<th>% converge</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0.007</td>
<td>VG</td>
<td>-0.88 (-0.66)</td>
<td>3.52</td>
<td>1.65</td>
<td>71.3</td>
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<td>RR</td>
<td>-0.18 (-0.26)</td>
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<td>TTM</td>
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<td></td>
<td>Two-stage</td>
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<td>1.18</td>
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<td></td>
<td></td>
<td>Logis.regr.</td>
<td>-0.90 (-0.92)</td>
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<td>0.25</td>
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<td>0.99</td>
<td>99.2</td>
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<td></td>
<td></td>
<td>RR</td>
<td>0.32 (-0.008)</td>
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<td></td>
<td></td>
<td>TTM</td>
<td>-0.26 (-0.29)</td>
<td>0.50</td>
<td>0.66</td>
<td>100</td>
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<tr>
<td></td>
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<td>-0.89 (-0.90)</td>
<td>0.82</td>
<td>0.16</td>
<td>100</td>
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</tbody>
</table>
when $\psi_0 = 1$ and $\delta_{xz} = E(X|Z = 1) - E(X|Z = 0) = 0.25$

$\delta_{yz} = E(Y|Z = 1) - E(Y|Z = 0)$

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<tbody>
<tr>
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<td>0.06</td>
<td>VG</td>
<td>-0.008 (-0.01)</td>
<td>0.37</td>
<td>0.61</td>
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<tr>
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<td></td>
<td>RR</td>
<td>-0.008 (-0.01)</td>
<td>0.37</td>
<td>0.61</td>
<td>100</td>
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<tr>
<td></td>
<td></td>
<td>TTM</td>
<td>-0.08 (-0.08)</td>
<td>0.30</td>
<td>0.54</td>
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<td>0.61</td>
<td>0.78</td>
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<td></td>
<td>RR</td>
<td>-0.01 (-0.006)</td>
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<td>0.56</td>
<td>100</td>
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<td>TTM</td>
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<td>-0.83 (-0.83)</td>
<td>0.71</td>
<td>0.16</td>
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</tbody>
</table>
Results: Continuous exposure

- when $\psi_0 = 1$ and $\delta_{xz} = E(X|Z = 1) - E(X|Z = 0) = 0.25$

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<th>SE</th>
<th>% converge</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.06</td>
<td>VG</td>
<td>0.07 (0.01)</td>
<td>0.40</td>
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<td>RR</td>
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<td>98.8</td>
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<td>0.42 (0.39)</td>
<td>0.60</td>
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<td>Two-stage</td>
<td>1.39 (0.47)</td>
<td>33.69</td>
<td>5.63</td>
<td>68.1</td>
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<tr>
<td>0.50</td>
<td>0.08</td>
<td>VG</td>
<td>0.06 (0.04)</td>
<td>0.26</td>
<td>0.51</td>
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<tr>
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<td>RR</td>
<td>-0.49 (-0.54)</td>
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<td>0.37</td>
<td>98.4</td>
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<td>TTM</td>
<td>0.29 (0.28)</td>
<td>0.37</td>
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<td>Two-stage</td>
<td>1.12 (0.62)</td>
<td>5.13</td>
<td>1.97</td>
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<td>-1.68 (-1.68)</td>
<td>2.84</td>
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</table>
Conclusions

- VG approach is simpler than RR approach: for binary exposure it even has closed form solution
- with small outcome mean, VG estimator usually has less bias than RR and both usually have less bias than approximate estimators
- for relative large outcome mean with binary exposure, VG and RR estimators are equal in all replications
- we can also handle these estimators with covariate adjustment


