S2 Text

Proof of Theorems

Theorem 1 The sufficient conditions for causal effect invariance under different selection mechanisms $\beta_{G,Y|S_2} / \beta_{G,X|S_1} = \beta_{G,Y} / \beta_{G,X}$ from two populations are:

(a) for each valid instrumental variable $G_j$, $S_j \perp G_j$ or $S_j \perp X \mid G_j$ in population I and $S_2 \perp G_j$ or $S_2 \perp Y \mid G_j$ in population II, respectively, or

(b) $G_j \perp Y \mid S_2$ and $G_j \perp Y$ for each valid instrumental variable in population II.

Proof:

For simplicity, each variable is assumed to follow an normal distribution $N(0,1)$. When there is no selection, the causal effect of $X$ on $Y$ is

$$\beta_{GX} = \frac{\partial E(Y \mid G)}{\partial G} / \frac{\partial E(X \mid G)}{\partial G}.$$ 

The causal effect with selection is

$$\beta_{GYS_2} = \frac{\partial E(Y \mid G, S_2)}{\partial G} / \frac{\partial E(X \mid G, S_1)}{\partial G}.$$ 

The partial regression coefficient $\beta_{GX|S_1}$ can be estimated by $\frac{Sd_X \rho_{GX} - \rho_{XS} \rho_{GS_1}}{Sd_G (1 - \rho_{GS_1}^2)}$, where $Sd$ is the standard deviation and $\rho$ is the correlation coefficient. For example, $Sd_X$ is the standard deviation of $X$ and $\rho_{GX}$ is the correlation coefficient between $G$ and $X$. Because both $X$ and $G$ follows standard normal distributions, $Sd_X = Sd_G = 1$, i.e.

$$\beta_{GX|S_1} = \frac{\rho_{GX} - \rho_{XS} \rho_{GS_1}}{1 - \rho_{GS_1}^2}.$$ 

Furthermore, $\rho_{GS_1} = \frac{\text{cov}(G, S_1)}{Sd_G Sd_{S_1}} = \frac{E(GS_1) - E(G)E(S_1)}{Sd_G Sd_{S_1}} = E(GS_1)$.
Assume that $E(G) = E(\rho_{GX} X)$ and $E(S_i) = E(\rho_{XS_i} X)$.

$$E(GS_i) = E(\rho_{GX} \rho_{XS_i} X^2) = \rho_{GX} \rho_{XS_i} E(X^2) = \rho_{GX} \rho_{XS_i}.$$  

Thus, $\beta_{GX|S_i} = \frac{\rho_{GX} - \rho_{XS_i} \rho_{GS_i}}{1 - \rho_{GS_i}} = \frac{\rho_{GX} - \rho_{XS_i}^2 \rho_{GS_i}}{1 - \rho_{GS_i}^2}.$

In addition, $\beta_{GX} = \rho_{GX}, \beta_{XS_i} = \rho_{XS_i}, \beta_{GS_i} = \rho_{GS_i}$ due to the normal distributions of $S_i, G$ and $X$. Therefore, $\beta_{GX|S_i} = \frac{\rho_{GX} - \rho_{XS_i} \rho_{GS_i}}{1 - \rho_{GS_i}^2} = \frac{\beta_{GX} - \beta_{XS_i}^2 \beta_{GS_i}}{1 - \beta_{GS_i}^2} = \frac{\beta_{GX}}{1 - \beta_{GS_i}^2}.$

And yields the bias $\beta_{GX|S_i} - \beta_{GX} = \frac{\beta_{GX} \beta_{XS_i}^2 (\beta_{GX}^2 - 1)}{1 - \beta_{GS_i}^2 \beta_{XS_i}^2}.$

The bias is zero if $S_i \perp G$, that is, $\beta_{GX} \beta_{XS_i} = 0$.

In this situation, we can obtain $E(X | G, S_i = 1) = E(X | G)$ from $\beta_{GX|S_i} = \beta_{GX}$.

If $S_i \perp X | G$, $E(X | G, S_i = 1) = E(X | G)$ can also be obtained.

Thus when $S_i \perp G$ or $S_i \perp X | G$, $E(X | G, S_i = 1) = E(X | G)$. Similarly, when $S_2 \perp G$ or $S_2 \perp Y | G$, we have $E(Y | G, S_2 = 1) = E(Y | G)$. Then we can obtain

$$\frac{\beta_{GY|S_2}}{\beta_{GX|S_i}} = \frac{\partial E(Y | G, S_2 = 1)}{\partial G} / \frac{\partial E(X | G, S_i = 1)}{\partial G} = \frac{\partial E(Y | G)}{\partial G} / \frac{\partial E(X | G)}{\partial G} = \beta_{GY} \beta_{GX}.$$  

On the other hand, if $G \perp Y | S_2$, we have $\frac{\partial E(Y | G, S_2 = 1)}{\partial G} = 0$. If $G \perp Y$, then $\frac{\partial E(Y | G)}{\partial G} = 0$.

We have $\frac{\beta_{GY|S_2}}{\beta_{GX|S_i}} = \frac{\partial E(Y | G, S_2 = 1)}{\partial G} / \frac{\partial E(X | G, S_i = 1)}{\partial G} = 0 = \frac{\partial E(Y | G)}{\partial G} / \frac{\partial E(X | G)}{\partial G} = \beta_{GY} \beta_{GX}$.

The possible causal diagrams are as follows.

When exposure and outcome are binary, traditional MR methods can be used to judge whether there is a causal effect, but cannot estimate causal effect accurately. In this case, Wald
The ratio can be written as \( \log(OR_{G,Y|S_2=1}) / \log(OR_{G,X|S_2=1}) \). In other words, beta-coefficients in linear regression are replaced by \( \log(OR) \)-coefficients in logistic regression. The model of underlying binary variables should be:

\[
\log it[P(Y \mid X, U, G_1, ..., G_j)] = \theta X + U + \sum_{j=1}^{J} \gamma_j G_j \\
\log it[P(X \mid U, G_1, ..., G_j)] = \sum_{j=1}^{J} \alpha_j G_j + U
\]

We also give sufficient conditions for invariance of causal relationship using two-sample MR method on the scale of OR in Theorem 2. Due to the non-collapsibility, \( S_1 \perp G_j \) and \( S_2 \perp G_j \) in condition (a) are replaced by \( S_1 \perp G_j \mid X \) and \( S_2 \perp G_j \mid Y \), respectively. In comparison with the Theorem 1, OR can avoid the influence of selection bias of outcome-dependent, especially in case-control study design. The differences for the DAGs satisfying Theorem 2 are that selection depending on unmeasured confounder no more satisfy the condition (a) in both samples. Instead, selection depending on exposure in sample I and outcome in sample II satisfy condition (a) in Theorem 2.

**Theorem 2** The sufficient conditions for invariance of causal relationship


\[
\log(OR_{G,Y|S_2}) / \log(OR_{G,X|S_2}) = \log(OR_{G,Y}) / \log(OR_{G,X})
\]

from two populations with selection are:

(a) for each valid instrumental variable \( G_j \), \( S_1 \perp G_j \mid X \) or \( S_1 \perp X \mid G_j \) in population I and \( S_2 \perp G_j \mid Y \) or \( S_2 \perp Y \mid G_j \) in population II, respectively, or

(b) \( G_j \perp Y \mid S_2 \) and \( G_j \perp Y \) for each valid instrumental variable in population II.

**Proof** :

(a) The causal effect \( \log(OR_{G,Y|S_2}) / \log(OR_{G,X|S_2}) \) can be written as

\[
\frac{P(Y = 1 \mid G = 1, S_2 = 1)P(Y = 0 \mid G = 0, S_2 = 1)}{P(Y = 1 \mid G = 0, S_2 = 1)P(Y = 0 \mid G = 1, S_2 = 1)} / \frac{P(X = 1 \mid G = 1, S_1 = 1)P(X = 0 \mid G = 0, S_1 = 1)}{P(X = 1 \mid G = 0, S_1 = 1)P(X = 0 \mid G = 1, S_1 = 1)}
\]
For sample I, the $\text{OR}_{\text{GX}\mid S_i}$ can be written as

\[
\text{OR}_{\text{GX}\mid S_i} = \frac{P(X = 1| G = 1, S_i = 1) P(X = 0| G = 0, S_i = 1)}{P(X = 1| G = 0, S_i = 1) P(X = 0| G = 1, S_i = 1)}
\]

Because of $S_i \perp G\mid X$, $P(G, S_i\mid X) = P(S_i\mid X) P(G\mid X)$ can be achieved. Then, we can obtain that

\[
\text{OR}_{\text{GX}\mid S_i} = \frac{P(G = 1, S_i = 1| X = 1) P(X = 1) P(G = 0, S_i = 1| X = 0) P(X = 0)}{P(G = 1, S_i = 1| G = 1) P(G = 0) P(S_i = 1| G = 0) P(G = 1) P(S_i = 1| G = 1)}
\]

Thus, $\text{OR}_{\text{GX}\mid S_i} = \text{OR}_{\text{GX}}$ due to $S_i \perp G\mid X$.

For population I, the $\text{OR}_{\text{GX}\mid S_i}$ can be written as

\[
\text{OR}_{\text{GX}\mid S_i} = \frac{P(X = 1| G = 1, S_i = 1) P(X = 0| G = 0, S_i = 1)}{P(X = 1| G = 0, S_i = 1) P(X = 0| G = 1, S_i = 1)}.
\]

Because of $S_i \perp X\mid G$, we can obtain that

\[
\text{OR}_{\text{GX}\mid S_i} = \frac{P(X = 1| G = 1, S_i = 1) P(X = 0| G = 0, S_i = 1)}{P(X = 1| G = 0, S_i = 1) P(X = 0| G = 1, S_i = 1)} = \text{OR}_{\text{GX}}.
\]

Thus, for population I, we can obtain that $\text{OR}_{\text{GX}\mid S_i} = \text{OR}_{\text{GX}}$ due to $S_i \perp X\mid G$.

Similarly, the $\text{OR}_{\text{GY}\mid S_i}$ can be written as
Because of \( S_2 \perp G \mid Y \), \( P(G, S_2 \mid Y) = P(S_2 \mid Y)P(G \mid Y) \) can be achieved. Then, we can obtain that

\[
OR_{GYS_2} = \frac{P(Y = 1 \mid G = 1, S_2 = 1)P(Y = 0 \mid G = 0, S_2 = 1)}{P(Y = 1 \mid G = 0, S_2 = 1)P(Y = 0 \mid G = 1, S_2 = 1)} \cdot \frac{P(G = 1, S_2 = 1 \mid Y = 1)P(Y = 1 \mid G = 0, S_2 = 1 \mid Y = 0)P(Y = 0 \mid G = 0)}{P(G = 0, S_2 = 1 \mid Y = 1)P(Y = 1 \mid G = 1, S_2 = 1 \mid X = 0)P(Y = 0 \mid G = 1)}.
\]

Thus, \( OR_{GYS_2} = OR_{GY} \) due to \( S_2 \perp G \mid Y \).

For population II, the \( OR_{GYS_2} \) can be written as

\[
OR_{GYS_2} = \frac{P(Y = 1 \mid G = 1, S_2 = 1)P(Y = 0 \mid G = 0, S_2 = 1)}{P(Y = 1 \mid G = 0, S_2 = 1)P(Y = 0 \mid G = 1, S_2 = 1)}.
\]

Because of \( S_2 \perp G \mid Y \), we can obtain that

\[
OR_{GYS_2} = \frac{P(Y = 1 \mid G = 1, S_2 = 1)P(Y = 0 \mid G = 0, S_2 = 1)}{P(Y = 1 \mid G = 0, S_2 = 1)P(Y = 0 \mid G = 1, S_2 = 1)} = OR_{GY}.
\]

Thus, for population II, we can obtain that \( OR_{GYS_2} = OR_{GY} \) due to \( S_2 \perp Y \mid G \).

Therefore, the causal effect \( \log(OR_{GYS_2}) / \log(OR_{GX_2}) \) is s-recoverable from two samples with selection.

(b) Because \( G \perp Y \mid S_2 \), and \( G \perp Y \) for each valid instrumental variable in population II, we can obtain that \( \log(OR_{GY}) = 0 \). Thus,

\[
\log(OR_{GYS_2}) / \log(OR_{GY}) = \log(OR_{GYS_2}) / \log(OR_{GX_2}).
\]
Fig A. The possible causal diagrams for condition (a) of Theorem 2.

Fig B. The possible causal diagrams for condition (b) of Theorem 2.