Instrumental Variable Analysis: Measuring the ‘true’ effect when trial intervention is not delivered with optimal fidelity. Relevance for CISMAC studies

CISMAC Webinar
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Problem

We want to know the extent to which a treatment, $T$, causally affects an outcome, $O$. 

$T \rightarrow O$
Problem

Example

Does an intervention or treatment (T) reduce child mortality (O)?
Solution: RCT

No bias!

Relative risk = 0.8

$p \approx 0.01$

95% confidence interval: 0.7 to 0.9
Another problem

RR is effect of being in intervention arm (intention to treat), and not the effect of the treatment in itself.

Relative risk = 0.8

p ≈ 0.01

95% confidence interval: 0.7 to 0.9
Another problem

Can we estimate the true efficacy of the treatment?

Relative risk \( = 0.80.7 \)

\( p \approx 0.02 \)

95% confidence interval: 0.5 to 0.9
Another problem

Can we estimate the true efficacy of the treatment?

Int. → T → Mortality

Relative risk = 0.8

p ≈ 0.02

95% confidence interval: 0.5 to 0.9

Note: Often CIs get wider using IVA
Solution: IVA

Want to know the causal effect of $T$ on $O$.

$T \rightarrow O$
A (very brief) primer to IVA

Consider instrument, I, as the exposure in addition to T.

I → T → O
A (very brief) primer to IVA

**Need assumptions:**

1- Causal relationship between $I$ and $T$

2- The effect of $I$ on $O$ is only through $T$

3- No common causes of $I$ and $O$
A (very brief) primer to IVA

Need assumptions:
1- Causal relationship between I and T
   OK

2- The effect of I on O is only through T

3- No common causes of I and O
A (very brief) primer to IVA

Need assumptions:

1- Causal relationship between $I$ and $T$
   Also OK

2- The effect of $I$ on $O$ is only through $T$

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A (very brief) primer to IVA

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A (very brief) primer to IVA

Randomization is a great instrument!

1- Randomization (R) decides intervention status (T)

2- Effect of R on outcome (O) is only through T

3- No common causes of R and O
A (very brief) primer to IVA

Consider scenario with binary exposure, T (e.g., RCT), and binary outcome, O (e.g., death)

<table>
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<tr>
<th>Control arm</th>
<th>Intervention arm</th>
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<td>Receive treatment: $P_c(T=1)$</td>
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A (very brief) primer to IVA

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Difference in proportion treated:

$\Delta_{\text{Treat}} = P_I(T = 1) - P_C(T = 1)$
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$\Delta_{\text{Treat}} = P_I(T = 1) - P_C(T = 1)$

Risk difference between arms:
$\Delta_{\text{ITT}} = P_C(O = 1) - P_I(O = 1)$
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$$\Delta_{\text{Treat}} = P_I(T = 1) - P_C(T = 1)$$

Risk difference between arms:

$$\Delta_{\text{ITT}} = P_C(O = 1) - P_I(O = 1)$$

Adjusted risk difference (efficacy):

$$\Delta_{\text{IVA}} = \Delta_{\text{ITT}} / \Delta_{\text{Treat}}$$
## IVA with numbers

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<td>( P_c(T) = 0% )</td>
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<td>( P_c(Die) = 4.0% ) mortality</td>
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IVA with numbers

Control arm
- $P_C(T) = 0\%$
- $P_C(\text{Die}) = 4.0\%$ mortality

Intervention arm
- $P_I(T) = 75\%$
- $P_I(\text{Die}) = 3.2\%$ mortality

$\Delta T = P_I(T) - P_C(T) = 0.75$

Slope represents estimated effect
Δ_T = P_I(T) - P_C(T) = 0.75

ITT:
- Δ_{ITT} = 0.040 - 0.032 = 0.008
- RR_{ITT} = \frac{4.0 - 0.8}{4.0} = 0.8

**Control arm**
- \( P_C(T) = 0\%
- \( P_C(\text{Die}) = 4.0\% \text{ mortality} \)

**Intervention arm**
- \( P_I(T) = 75\%
- \( P_I(\text{Die}) = 3.2\% \text{ mortality} \)

Mortality (%)

Slope represents estimated effect

Control arm

IVA arm

ITT arm
IVA with numbers

Control arm
- \( P_C(T) = 0\% \)
- \( P_C(\text{Die}) = 4.0\% \) mortality

\[ \Delta_T = P_I(T) - P_C(T) = 0.75 \]

ITT:
- \( \Delta_{ITT} = 0.040 - 0.032 = 0.008 \)
- \( RR_{ITT} = \frac{4.0 - 0.8}{4.0} = 0.8 \)

IVA:
- \( \Delta_{IVA} = \frac{\Delta_{ITT}}{\Delta_T} = \frac{0.008}{0.75} \approx 0.011 \)
- \( RR_{IVA} = \frac{4.0 - 1.1}{4.0} \approx 0.7 \)

Intervention arm
- \( P_I(T) = 75\% \)
- \( P_I(\text{Die}) = 3.2\% \) mortality

Slope represents estimated effect
IVA in general

Similar for continuous outcome, O (e.g., age at first pregnancy)
- Binary exposure (e.g., low vs. high level education)
- Continuous exposure (e.g., years of education)

Slightly different for binary outcome and continuous exposure
Measuring adherence
Measuring adherence

Some treatments are «easy» to measure
- Treatment requiring attendance
- Treatment administered by professionals

CISMAC examples
- BCG vaccine
- B12
- Zinc
- Community initiated kangaroo mother care (ciKMC)?
- Education?
- Postnatal care?
Measuring adherence

Some treatments are «hard» to measure
  - Treatment not requiring attendance
  - Treatment administered by amateurs

CISMAC examples
  - ciKMC?
  - Education?
  - Postnatal care?
Measuring adherence

How?

Suggestions

- Questionnaire
  - «Did you adhere?»
  - «How often did you adhere?»

- Visual scale
  - «How well do you adhere?»
Measuring adherence

Problems

- Treatment arm
  - Introduce recall bias
    (Mortality → Measured adherence)

- Control arm
  - Asking about adherence may affect intervention
    - «Did you get the vaccine?» «No, but perhaps I should!»
Thank you for your Questions or comments?