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

CISMAC Webinar

Bergen, 6 March 2019

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Problem

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

$$\mathbf{T} \overset{?}{\rightarrow} \mathbf{O}$$

Problem

Example

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

$T \overset{?}{\rightarrow}$ Mortality

Solution: RCT

T → Mortality

No bias!

Relative risk = 0.8

$p \approx 0.01$

95% confidence interval: 0.7 to 0.9

Another problem

Int. → T → **Mortality**

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

Relative risk = 0.8

$p \approx 0.01$

95% confidence interval: 0.7 to 0.9

Another problem

Int.→ T → Mortality

Can we estimate the true efficacy of the treatment?

Relative risk = ~~0.8~~0.7

$p \approx 0.02$

95% confidence interval: 0.5 to 0.9

Another problem

Int.→ T → Mortality

Can we estimate the true efficacy of the treatment?

Relative risk = ~~0.8~~0.7

$p \approx 0.02$

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**.

$$\mathbf{T} \rightarrow \mathbf{O}$$

A (very brief) primer to IVA

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

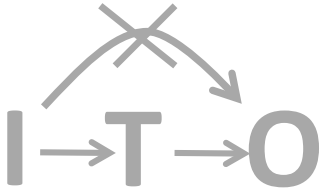
$$\mathbf{I} \rightarrow \mathbf{T} \rightarrow \mathbf{O}$$

A (very brief) primer to IVA

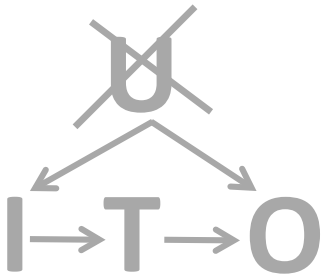
Need assumptions:

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**



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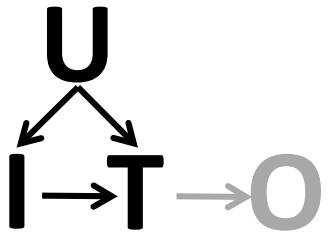

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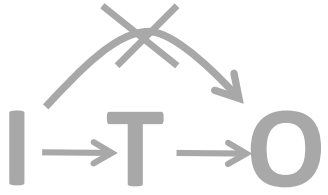

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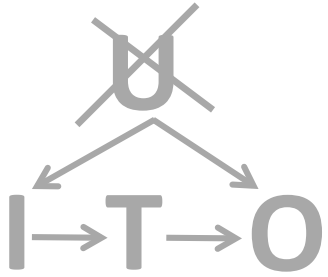

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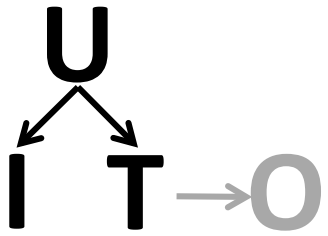
Also OK



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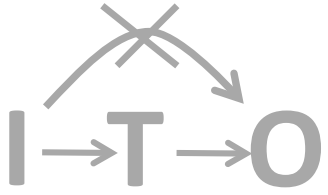

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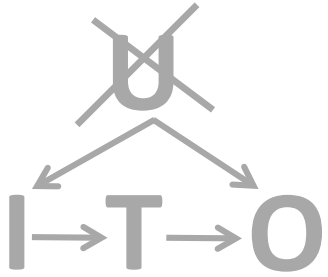

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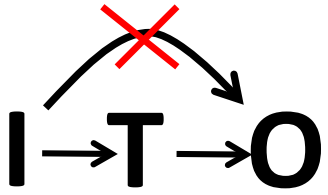

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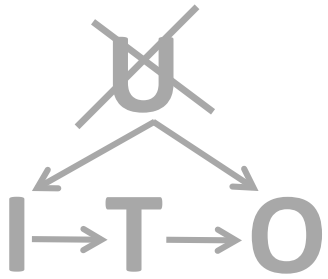

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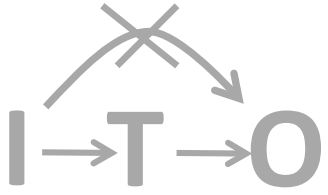

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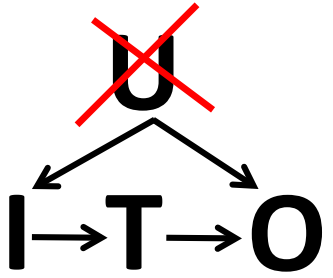
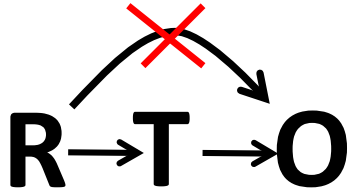


A (very brief) primer to IVA

Randomization is a great instrument!

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

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



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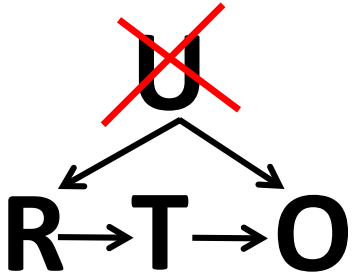

A (very brief) primer to IVA

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

Control arm	Intervention arm
Receive treatment: $P_C(T=1)$	Receive treatment: $P_I(T=1)$
Risk of outcome: $P_C(O=1)$	Risk of outcome: $P_I(O=1)$

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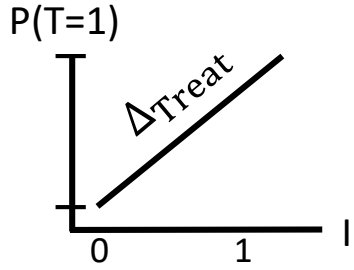
Difference in proportion treated:

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



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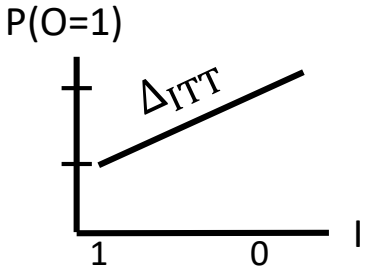
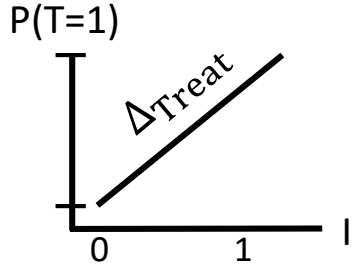
Risk difference between arms:

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





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Risk difference between arms:

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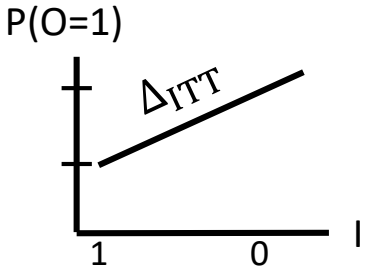
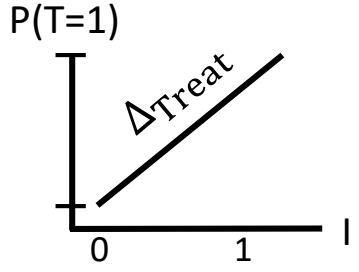
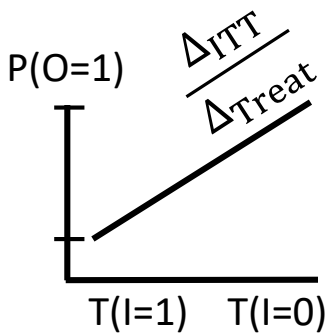
Adjusted risk difference (efficacy):

$$\Delta_{\mathrm{IVA}} = \Delta_{\mathrm{ITT}}/\Delta_{\mathrm{Treat}}$$







IVA with numbers

Control arm

- $P_C(T) = 0\%$
- $P_C(Die) = 4.0\%$ mortality

Intervention arm

- $P_I(T) = 75\%$
- $P_I(Die) = 3.2\%$ mortality

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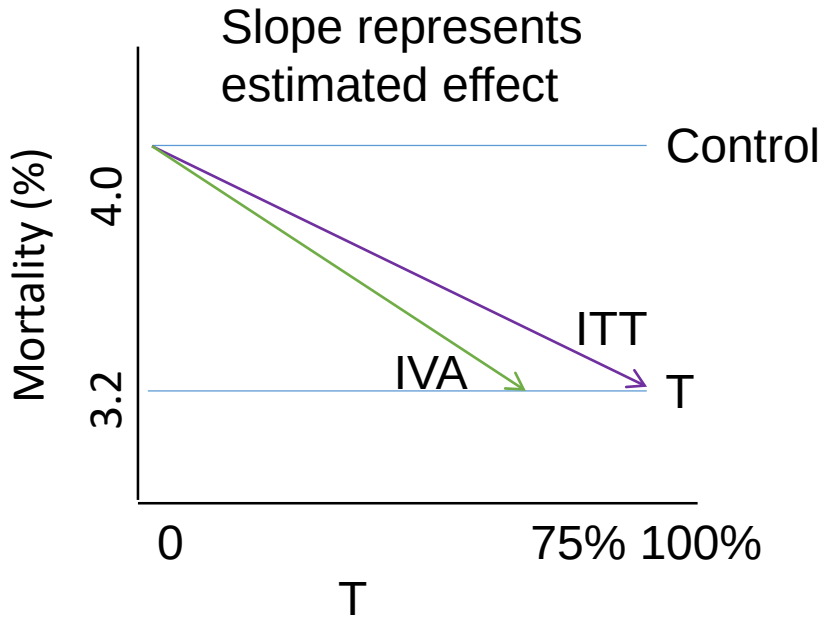
$$\Delta_T = P_I(T) - P_C(T) = 0.75$$



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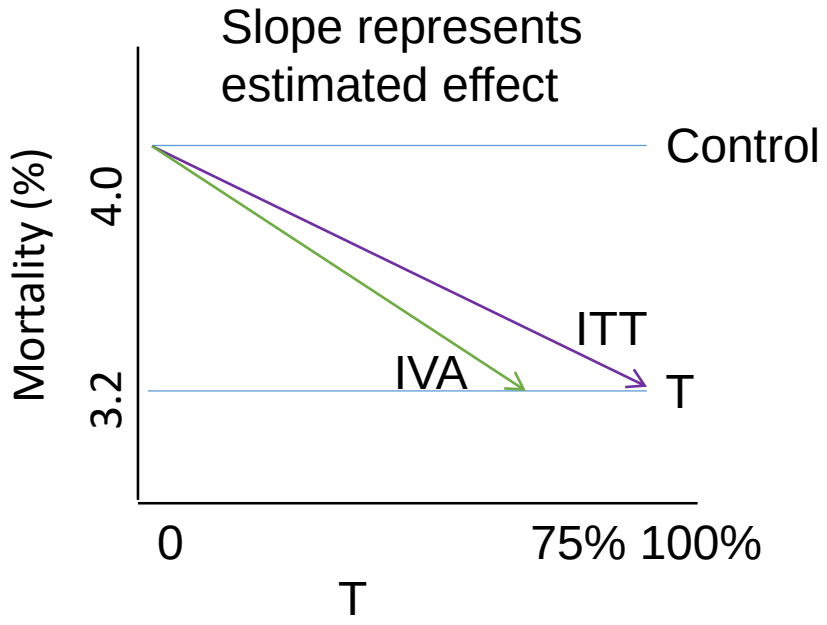
$\Delta_T = P_I(T) - P_C(T) = 0.75$

ITT:

- $\Delta_{ITT} = 0.040 - 0.032 = 0.008$
- $RR_{ITT} = \frac{4.0-0.8}{4.0} = 0.8$



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ITT:

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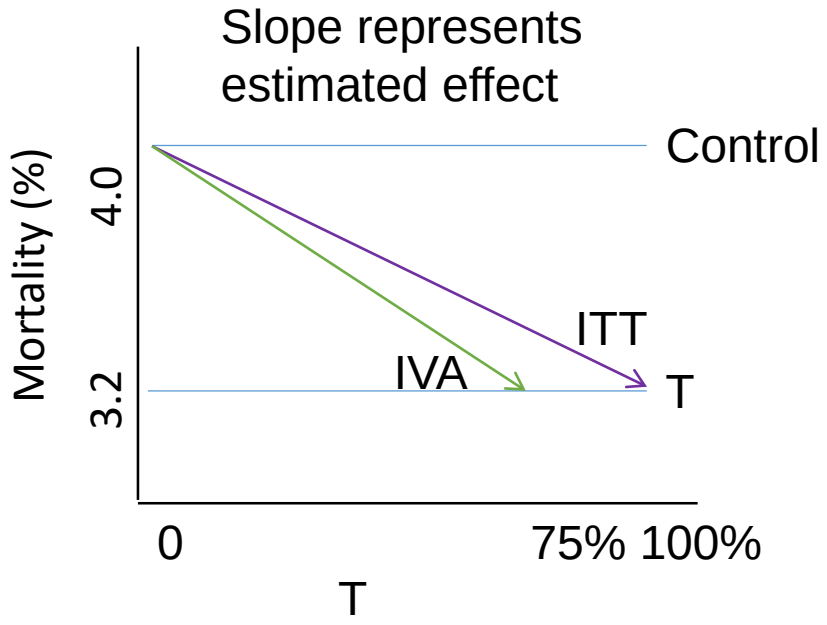
IVA:

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



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?

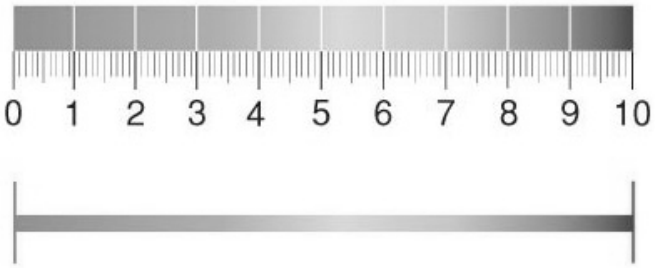
Measuring adherence

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?