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Alcohol Research Centre

The Difference is Research

Causation in (Quantitative) Science

Ask Questions at any Time!!!

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SCIENTIA

MANU ET MENTE

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What is SCIENCE?

- Science is the measurement of reproducible effect.
- Science allows society and individuals to benefit and plan their existence using reproducible effect.
- To measure reproducible effect – We need to reduce Bias
- Bias:
  - Selection Bias – Need to sample representatively of the population
  - Measurement Error –Keep accurate Measurements (*As the Label on the Jar Says*)
  - Random Chance – Insufficient sample size.
  - Confounding Bias

Reducing Counfounding Bias

Randomised Control Trials (RCTs):

Randomly allocating Interventions to balance confounders between trial groups to reduce bias.

Observational Studies:

Descriptive and interventional: Need to adjust for confounding variables to reduce bias.

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RCTs Not Always!

- Sometimes Unethical
- Balancing confounders is proportional to sample size. Small RCTs don't actually balance for all confounders.
- Treatment non-compliance : Intention to Treat vs As Treated
- Cost
- Inflexibility: Compares few interventions to few outcomes. **New Chemotherapy drug every month. Oh Oh!**
- Cannot personalise treatment to patients.

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RCT Not Always!

Too clean: - cohort is not representative, too many exclusions, too strict inclusion criteria

More Internal consistency, but reduced Generalisability

Challenges in psychotherapy research due to varying therapist client “fit”.

Observational studies

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No RCT	Can’t Balance for Confounders. **So What to Do!!!**
Literature Review	Gather Evidence from Multiple Sources. From tall mountains to small pebbles!
Draw DAG	Directed Acyclic Graph: Draw a mechanism of Causation between predictor and outcome.

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Why the DAG!

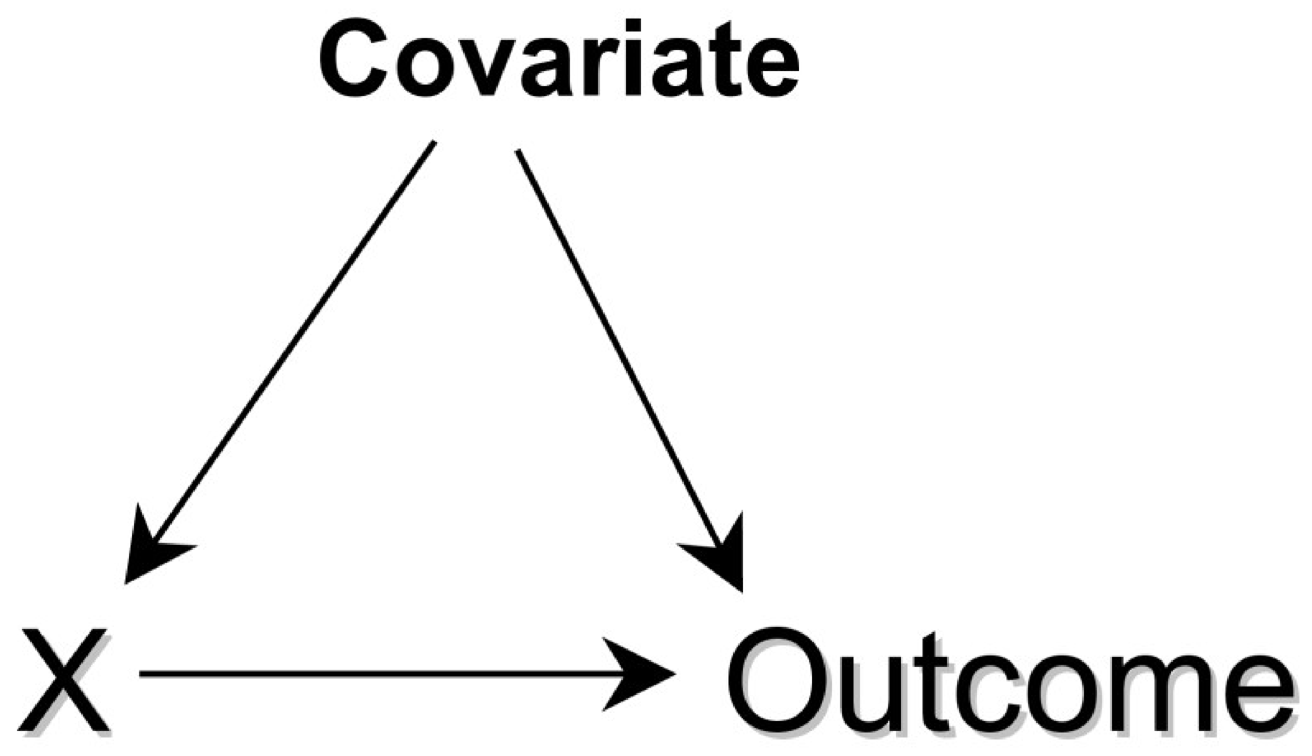
Science Awareness: Accurately portrays the science to the scientist and the reader.(After a good Literature review)

Measuring Causation: By Reducing confounding bias.

Efficiency Gain: DAGs show least confounders required to make causal inference.

Confounding the DAG way

- Predicts both the treatment (X) and the outcome.
- Does not lie on the causal pathway between treatment and outcome (i..e not a Mediator)
- In a DAG arrows only go one way. This causes that. (more details later)



Instrumental Variables: Adjusting For The Unmeasured!

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Hang On!
We didn't measure or don't know what the confounders are.
Intrumental Variables to the Rescue. Assumptions:

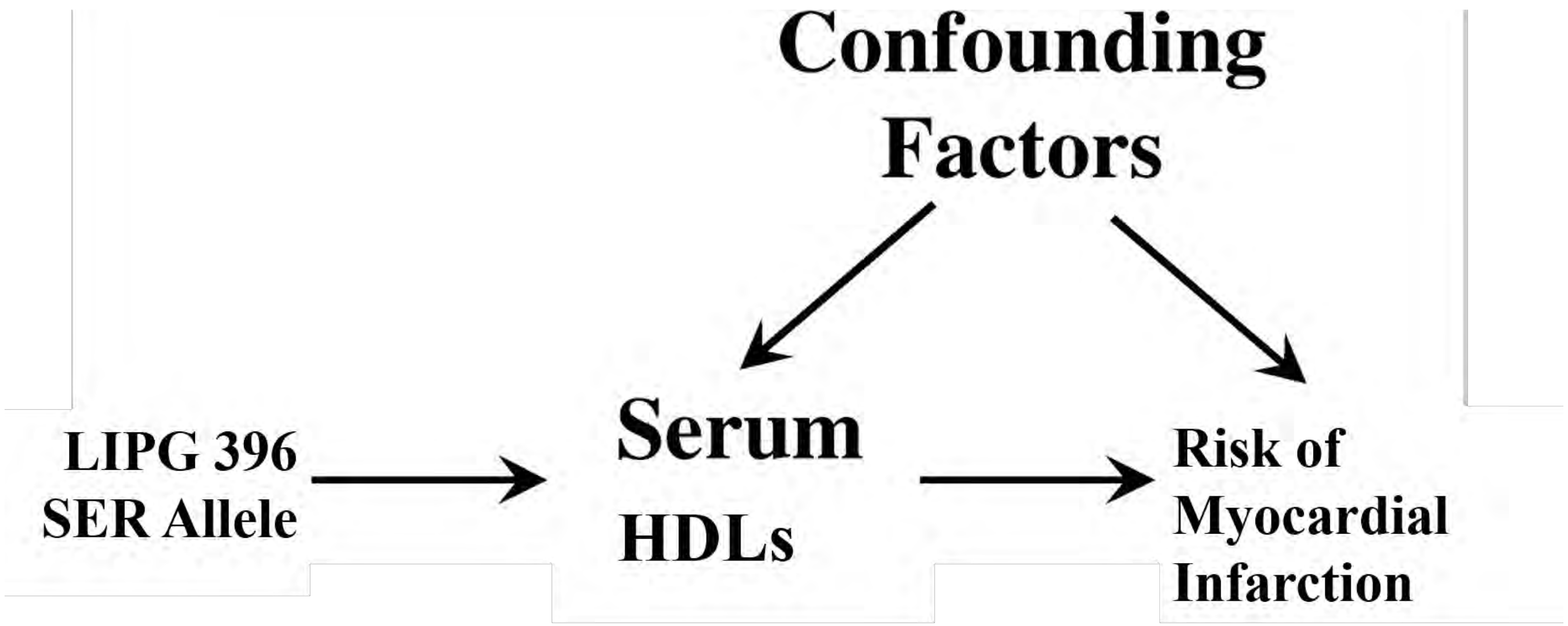
- Not on the causal pathway between treatment and outcome.
- Does Not predict confounders.
- Predicts outcome ONLY through treatment.

Beware: Sample size required is higher for instrumental variables.

Instrumental Variables In Action

No association between HDL and Risk of MI.

Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. The Lancet. 2012;380(9841):572-80.



No instruments! – Adjusting for measured confounders. Collider Bias: traps for young players

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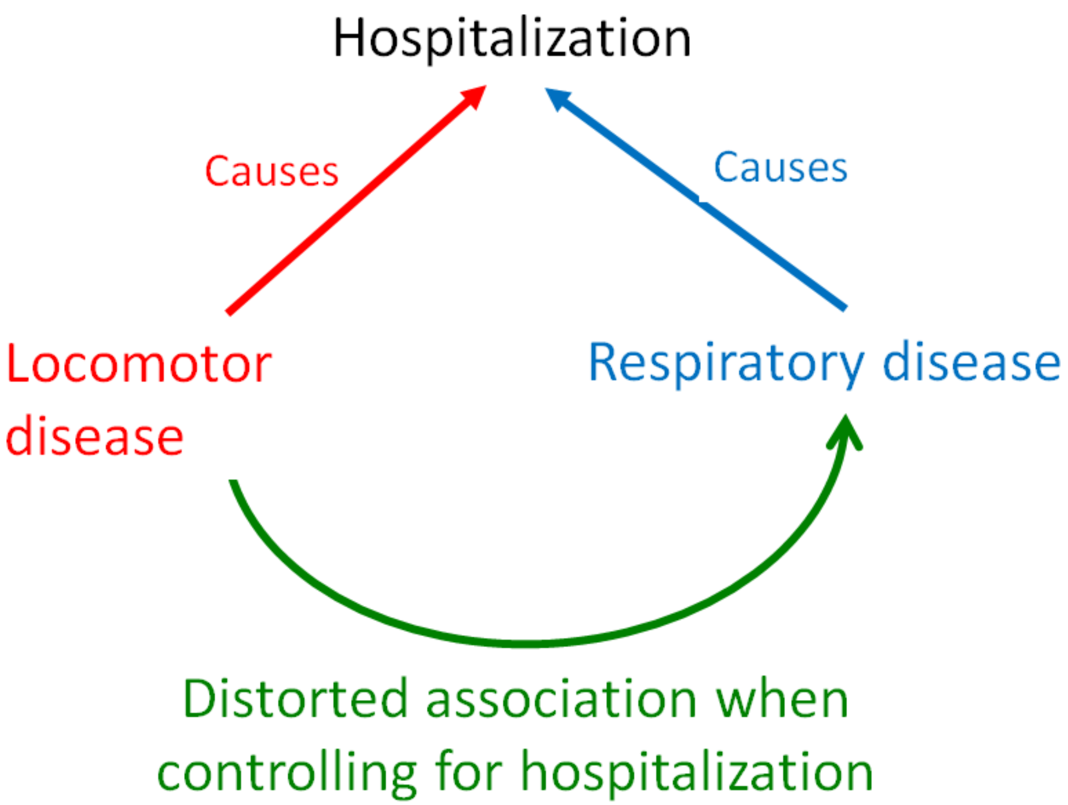


Disease X and Outcome Y might be causally linked.
But adjusting for a collider → increases bias between X & Y.

Hx: That Locomotor Disease reduces mobility and leads to respiratory disease

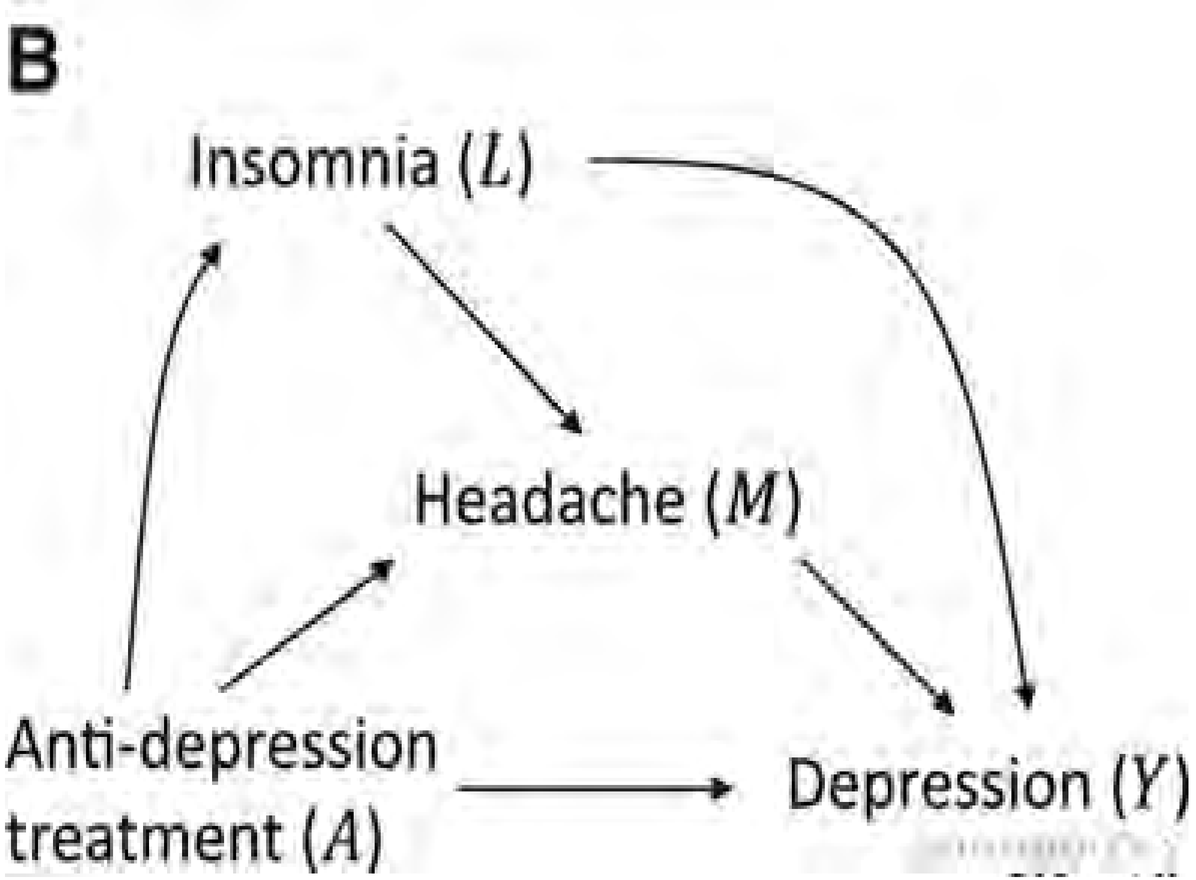
Both cause increased rate of hospitalisation.

Sampling only in hospitals creates a biased association for Hx.

No link seen in general population.

Similar issue seen in general population when adjusting for hospitalisation

Effectiveness Of Antidepressants: An Artificial Scenario



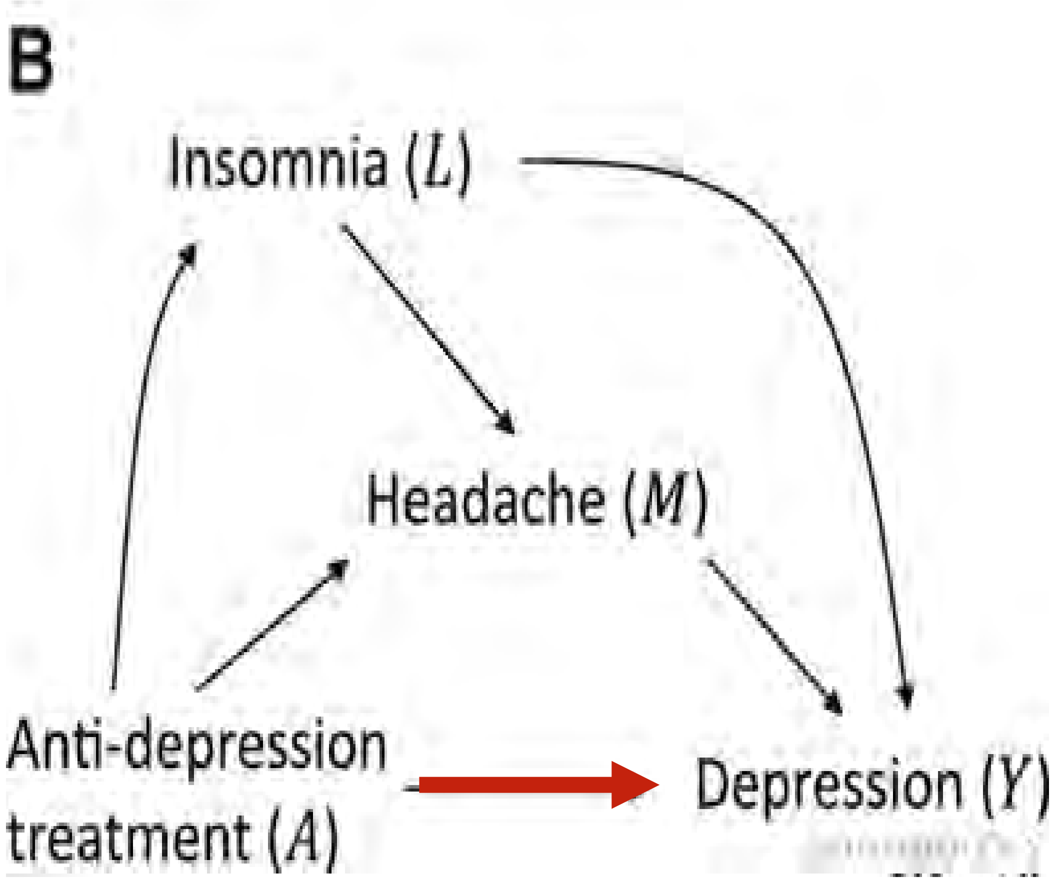
- Antidepressants **Reduce** Depression

- Antidepressants **Increase** Headache
- Headache **Increases** Depression

- Antidepressants **Increase** Insomnia
- Insomnia **Increases** Depression
- Insomnia **Increases** Headache
- Headache **Increases** Depression

A,Y, L, M are all binary variables (Yes or No)

Interventional (I/V) (in)Direct Effects



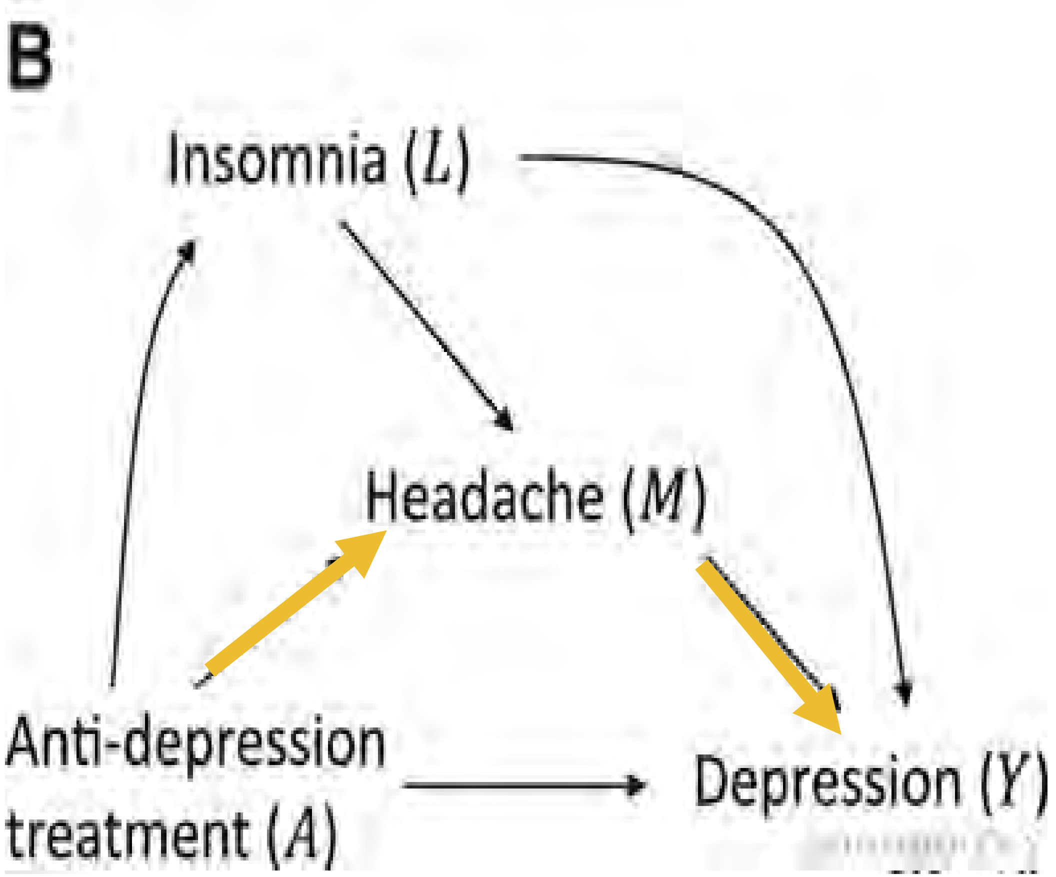
- **Path 1)** Antidepressant to Depression

  A to Y: Interventional Direct Effect

- Path 1 is negative as taking Antidepressants reduce Depression

- Path 1 is the effect of Antidepressants in those who don't have side-effects.

Interventional (I/V) (in)Direct Effects

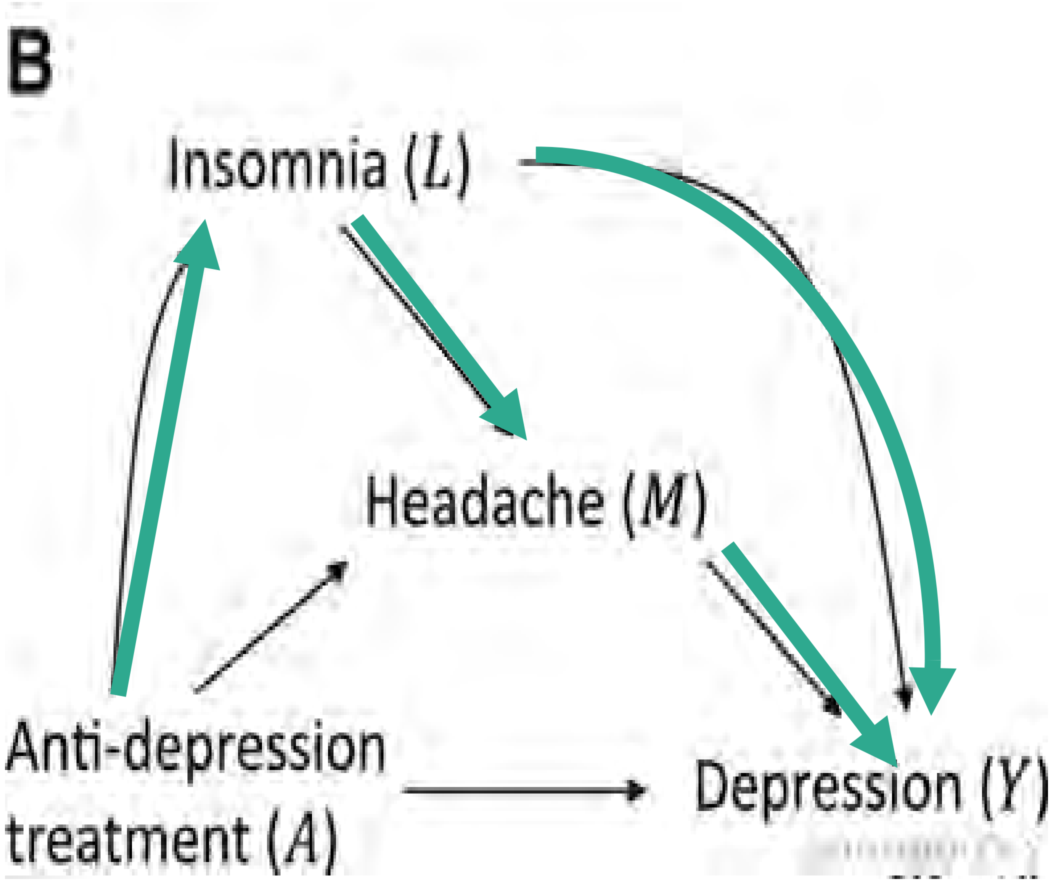


- **Path 2)** Effect Antidepressant on Depression *via Headache*

  A to M to Y: Interventional In-Direct Effect

- Path 2 is positive as Headaches are a side-effect of Antidepressants and headaches increase depression
- Path 2 > 0

Interventional (I/V) (in)Direct Effects



- **Path 3) A→ L→ Y and A→M→L→Y**
- Path 3 has 2 components:
- Antidepressants lead to insomnia. Insomnia leads increases to Depression
- Also: Insomnia makes Headaches worse. Headaches increases Depression
- **Total Effect: Path 1 + Path 2 + Path 3**

Direct effect: Path 1 (A → Y)

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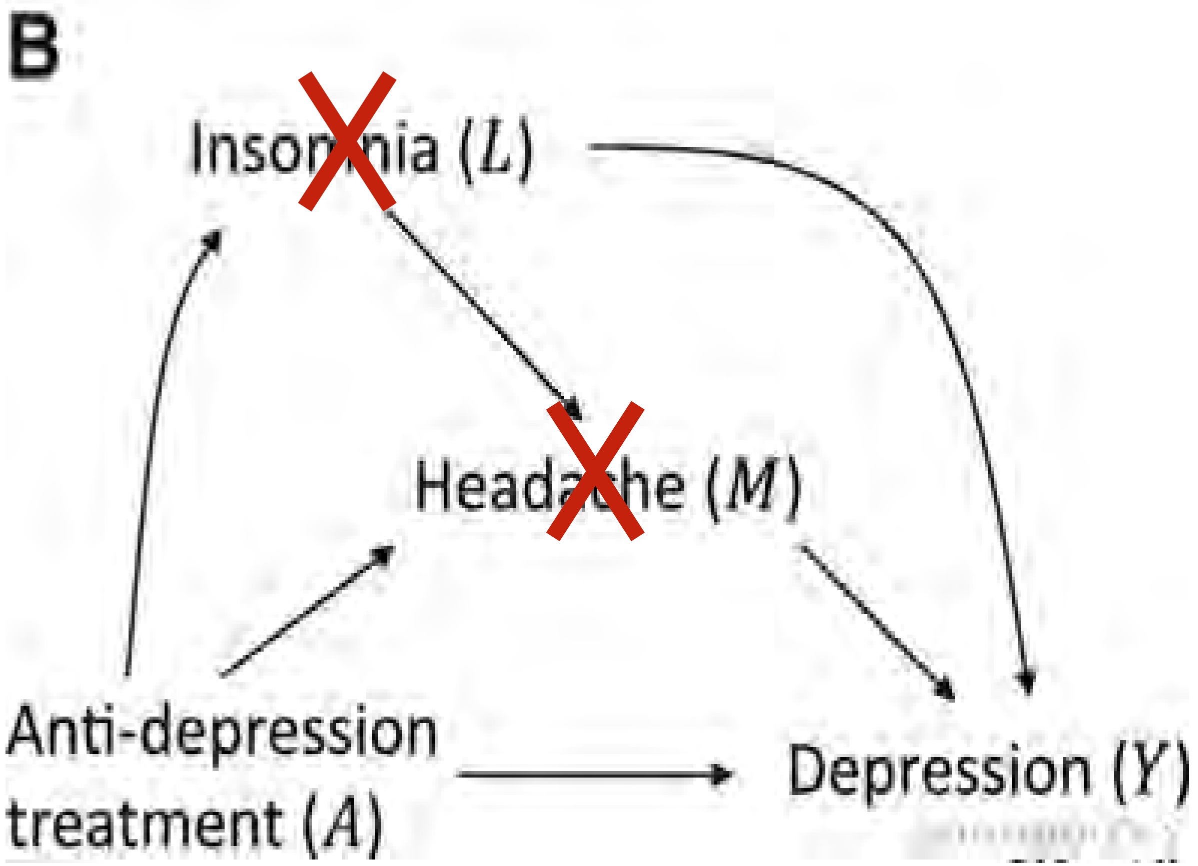
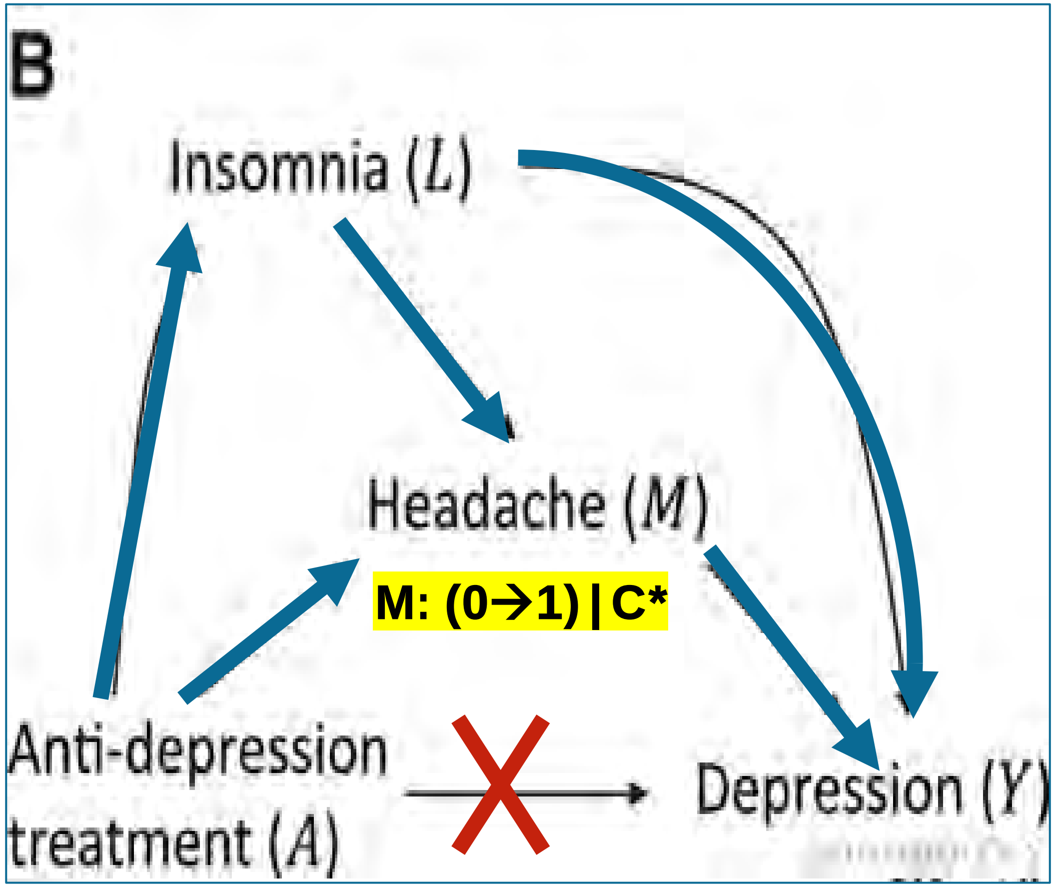
- Fixing **M=0 and L=0** gives direct effect A→Y.
- Effect of Antidepressants on Depression in Patients without the side-effects of insomnia and headache.

A: (0→1)



Indirect effect: via Mediators M(headache) I(insomnia) i.e Path 2 & 3:



Fix A=1: Only Treated Patients

Effect of Headaches and Insomnia on Depression in treated patients.
(Fix A=1)

Effect of Headache (Yes |No) on Depression (Yes|No) for every combination of covariates.(done via bootstrapping)

M: (0→1)|C*

Total Effect = Indirect Effect + Direct Effect

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Effect Decomposition

PATHWAYS	Abbreviation	Odds Ratio
1) Antidepressant to Depression	AY	0.28
2) Antidepressant to Headache to Depression	AMY	1.12
3) Antidepressant to Insomnia to +/- Headache to Depression	ALY & ALMY	1.87
Total Effect	**1) + 2) + 3)**	**0.47**
Treating Insomnia	1) + 2)	0.25
Treating Headache	1) + 3)	0.42
Treating Headache and Insomnia	1)	0.28

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