Emerging bias mechanisms in sibling comparison designs

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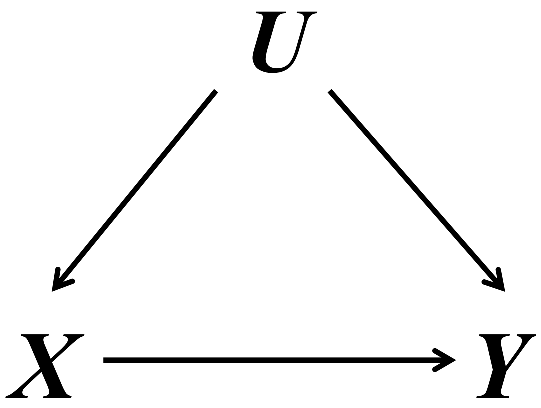
- Frisell Thomas, Öberg Sara, Kuja-Halkola Ralf, Sjölander Arvid. **Sibling Comparison Designs: Bias From Non-Shared Confounders and Measurement Error.** *Epub ahead of print Epidemiology* 2012

Confounding
DAG



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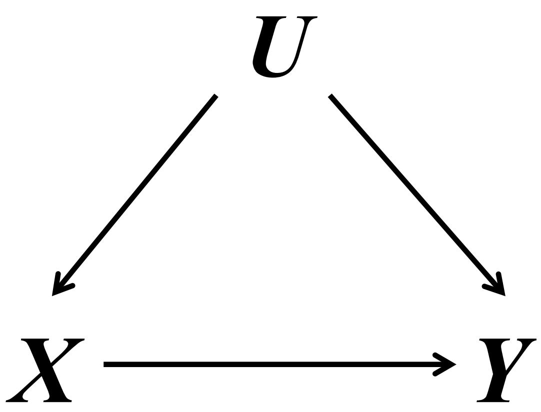

1. Randomize people to different levels of X
2. Measure U and adjust using e.g. regression
3. If U unmeasured, or even unknown, comparing siblings might be a good idea

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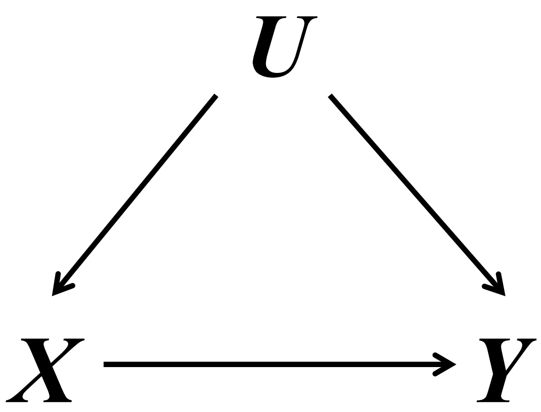

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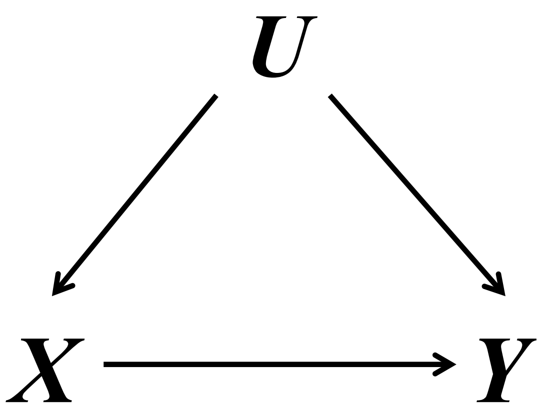

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Sibling comparisons

- Analyses:
  - Generalized Linear Mixed Models
  - Generalized Estimation Equations
  - Conditional regressions
  - Fixed effects (in the econometric/social sciences sense)
  - **Between-Within (BW)**

Within sibling estimate

- Standard model vs. BW model

  - "Cohort" estimate:

$$g(E(Y_{ij} | X_{ij})) = \mu + \beta_C X_{ij} \quad (1)$$

  - Within estimate:

$$g(E(Y_{ij} | X_{ij}, X_{i\cdot})) = \mu + \beta_B X_{i\cdot} + \beta_W X_{ij} \quad (2)$$

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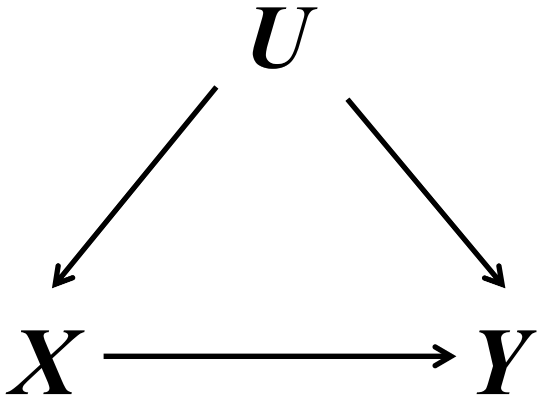
$$g(E(Y_{ij} | X_{ij}, X_{i\cdot})) = \mu + \beta_B X_{i\cdot} + \beta_W (X_{ij} - X_{i\cdot})$$

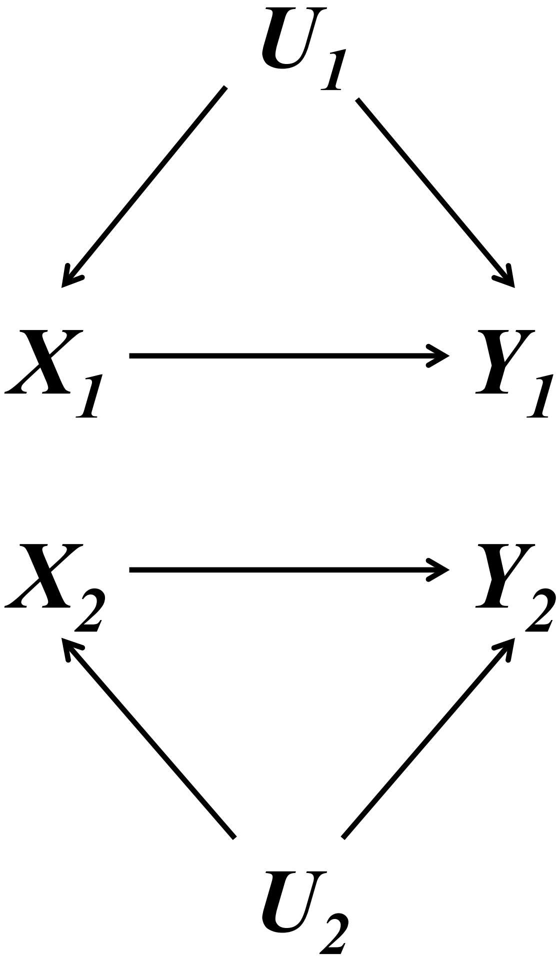
What is the problem then?

- We want to control for unmeasured confounders!
- Inference comes from exposure discordant pairs
- Isn’t the exposure discordant pairs probably less similar in unmeasured confounders than a randomly picked pair of individuals with the same exposure levels?
- Correct inference?!

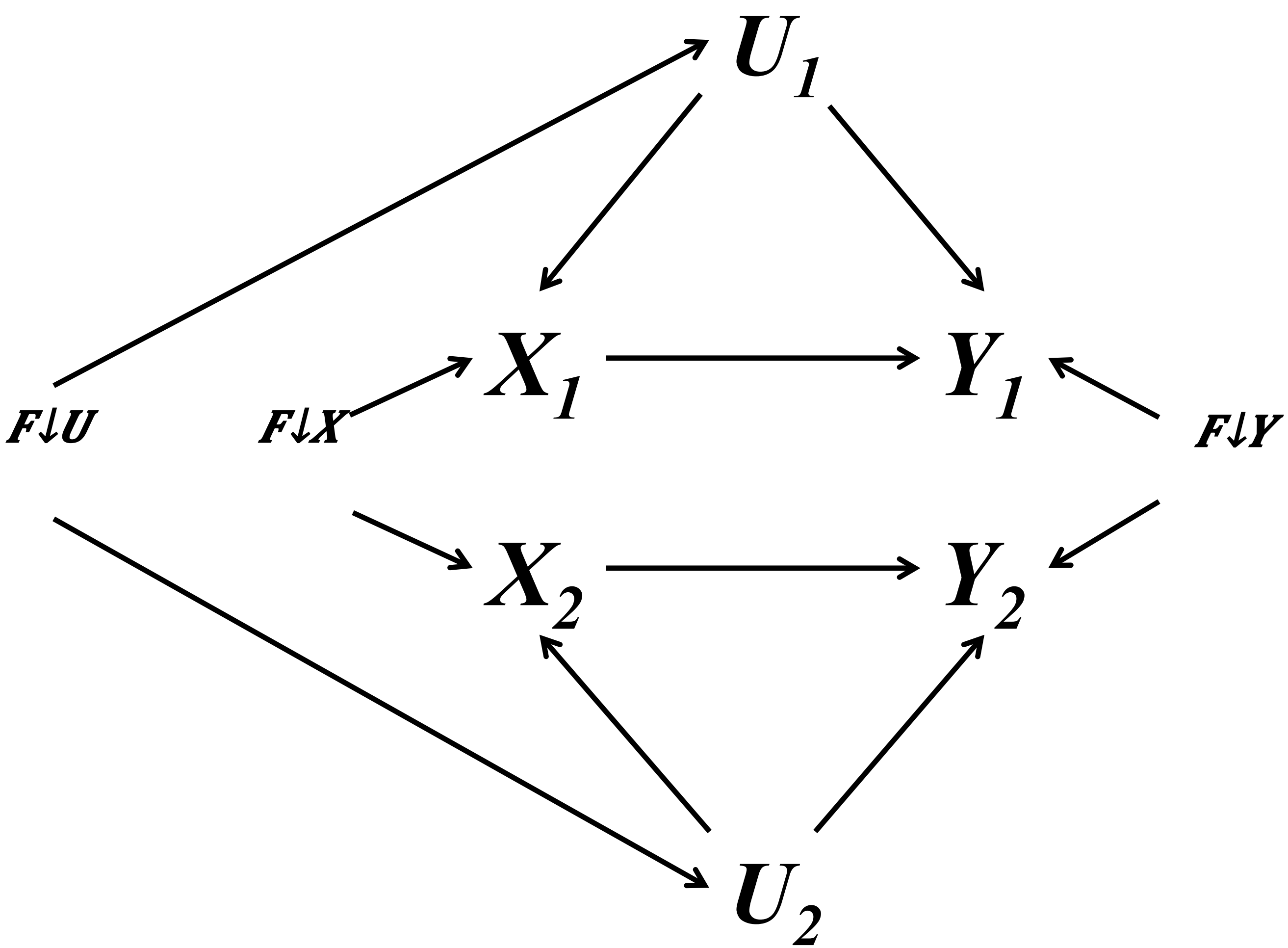
Causality
DAG



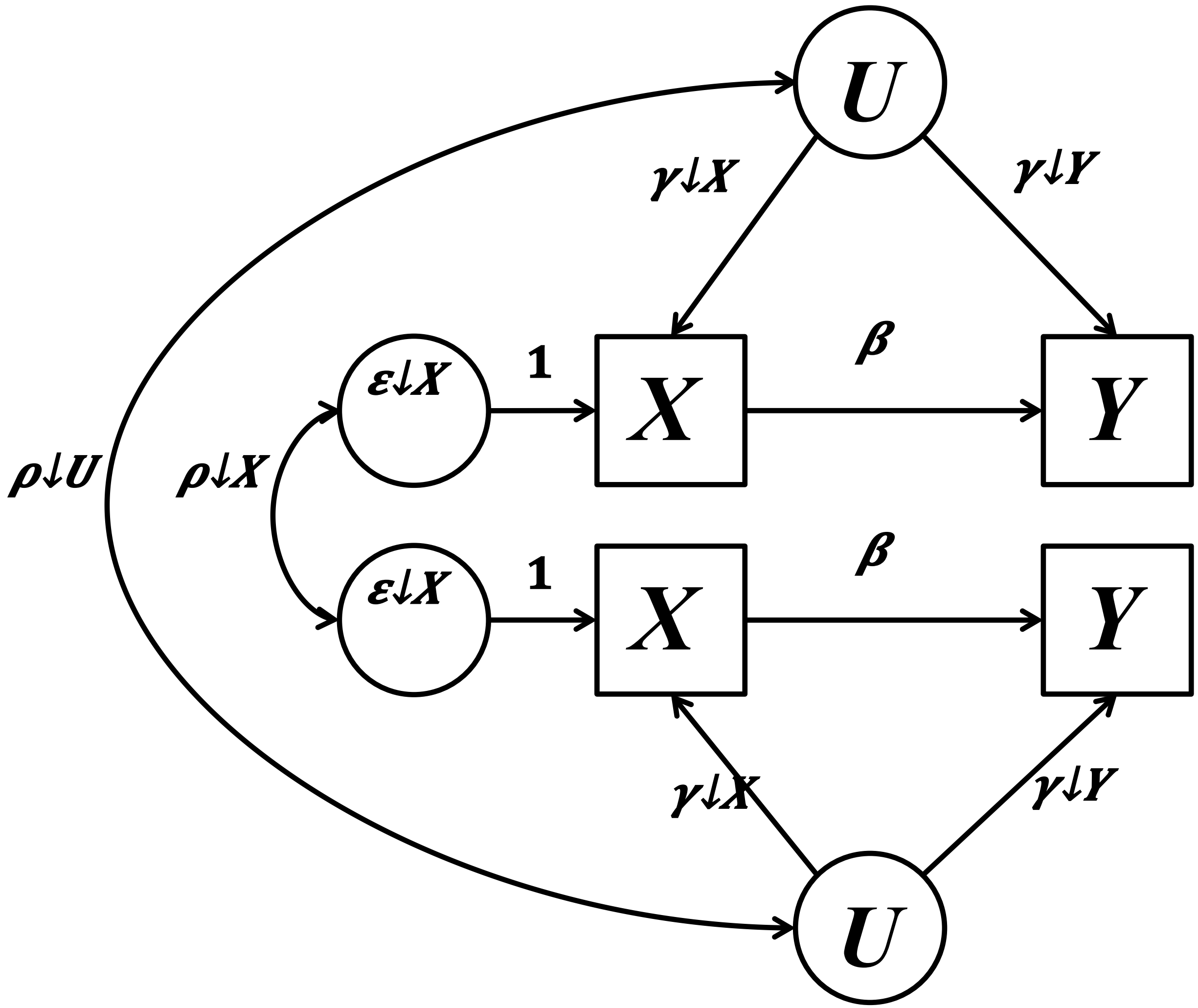
Causality
DAG



Causality
DAG



Causality
Path diagram



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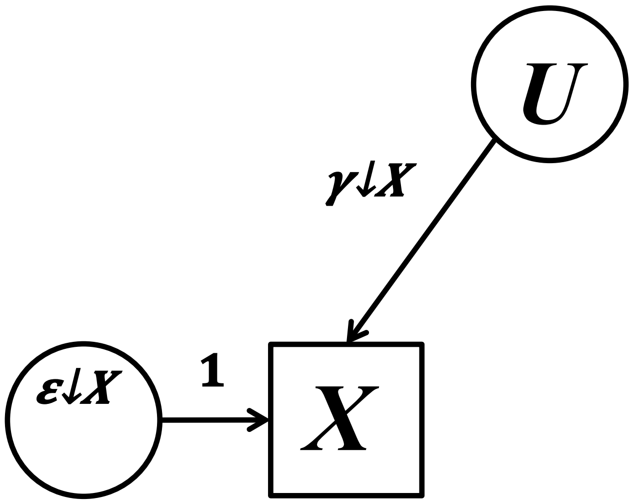
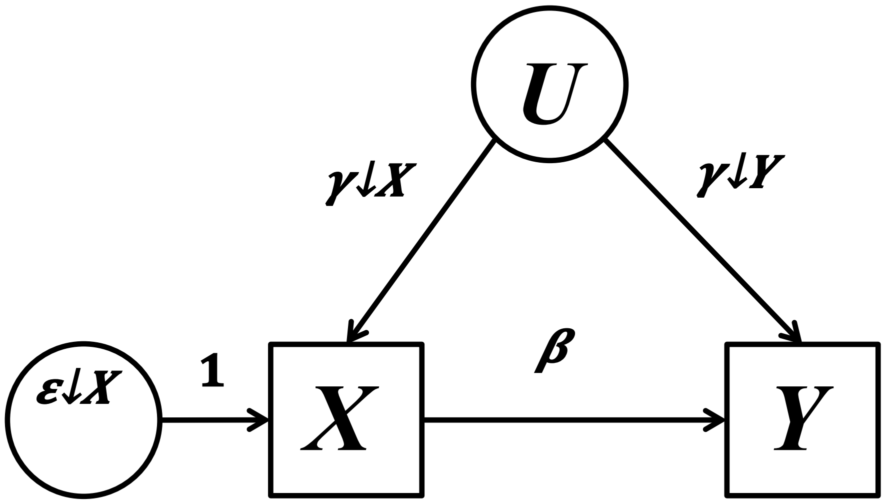


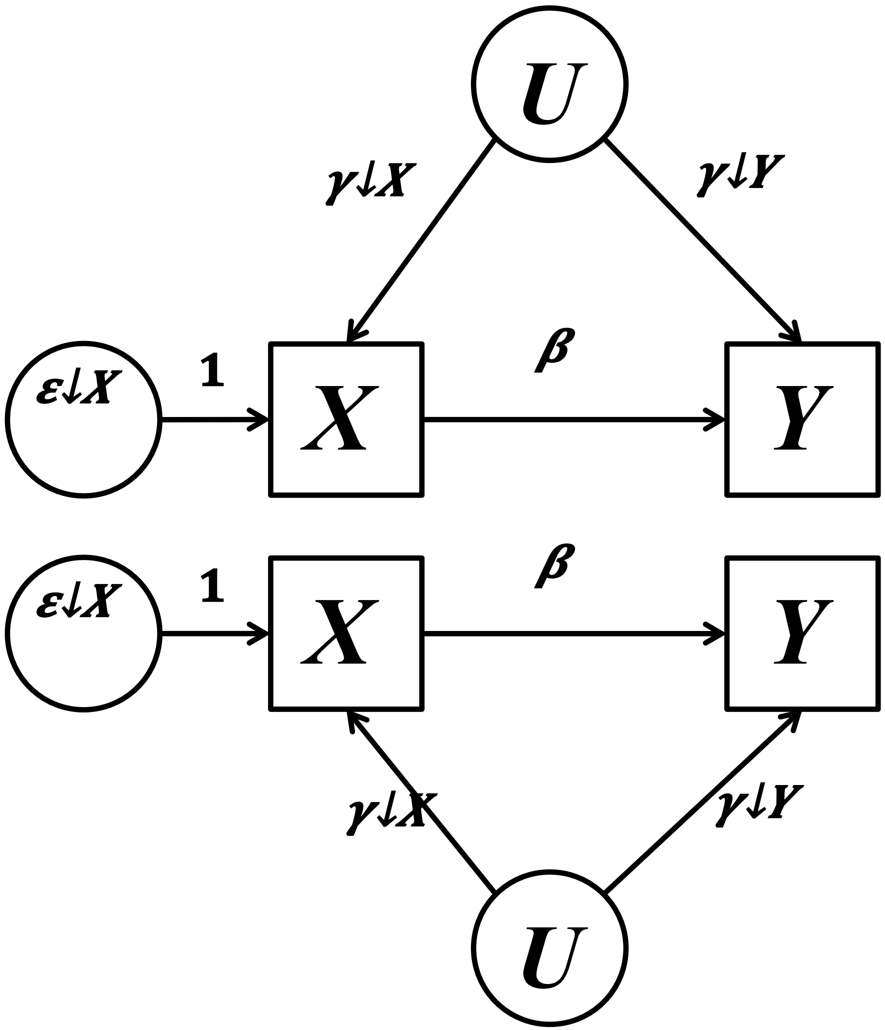
Two processes,
U and ε_X,
which leads to X

Causality
Path diagram



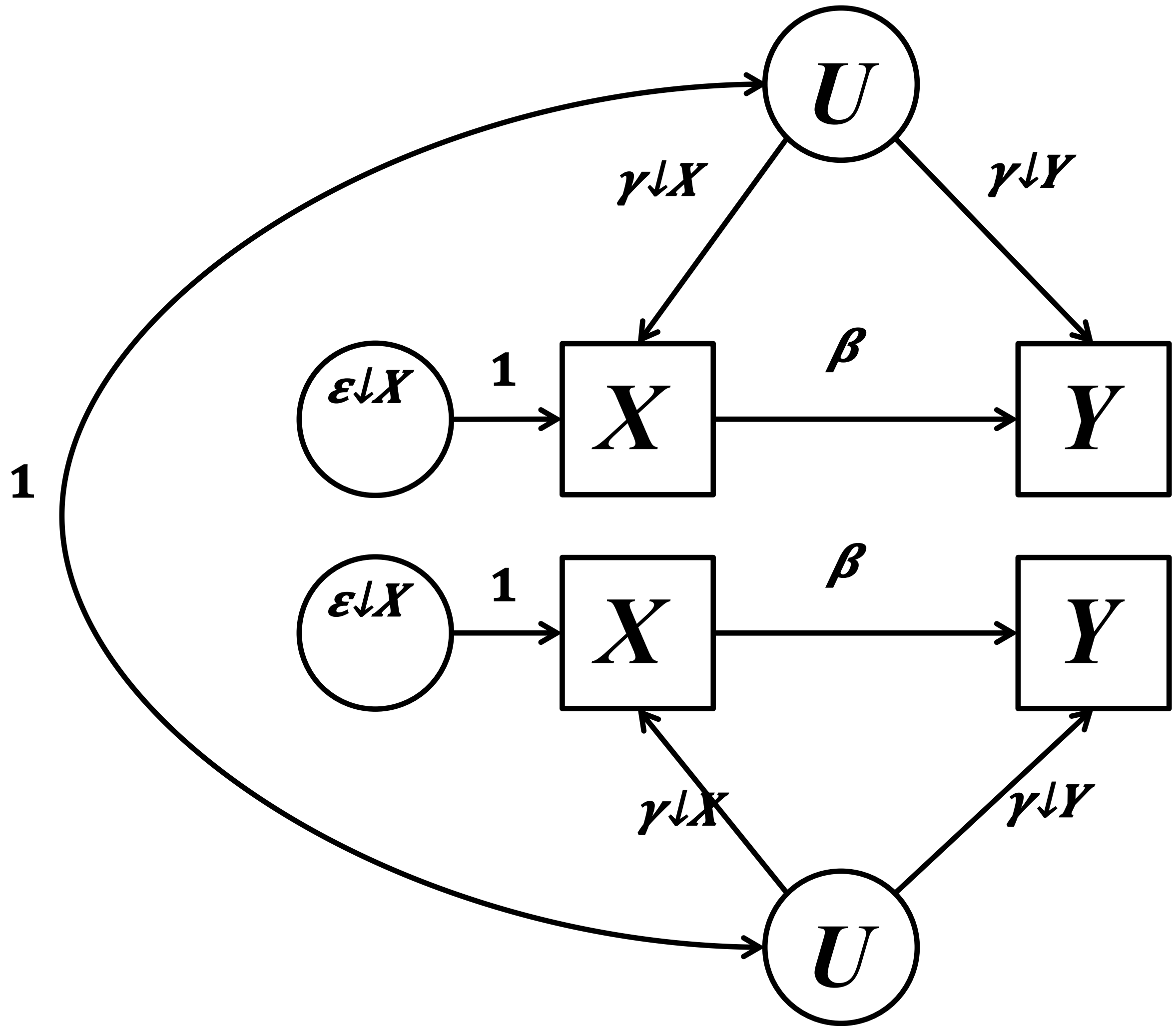
Two processes, U and ε_X, which leads to X and Y

Causality
Path diagram



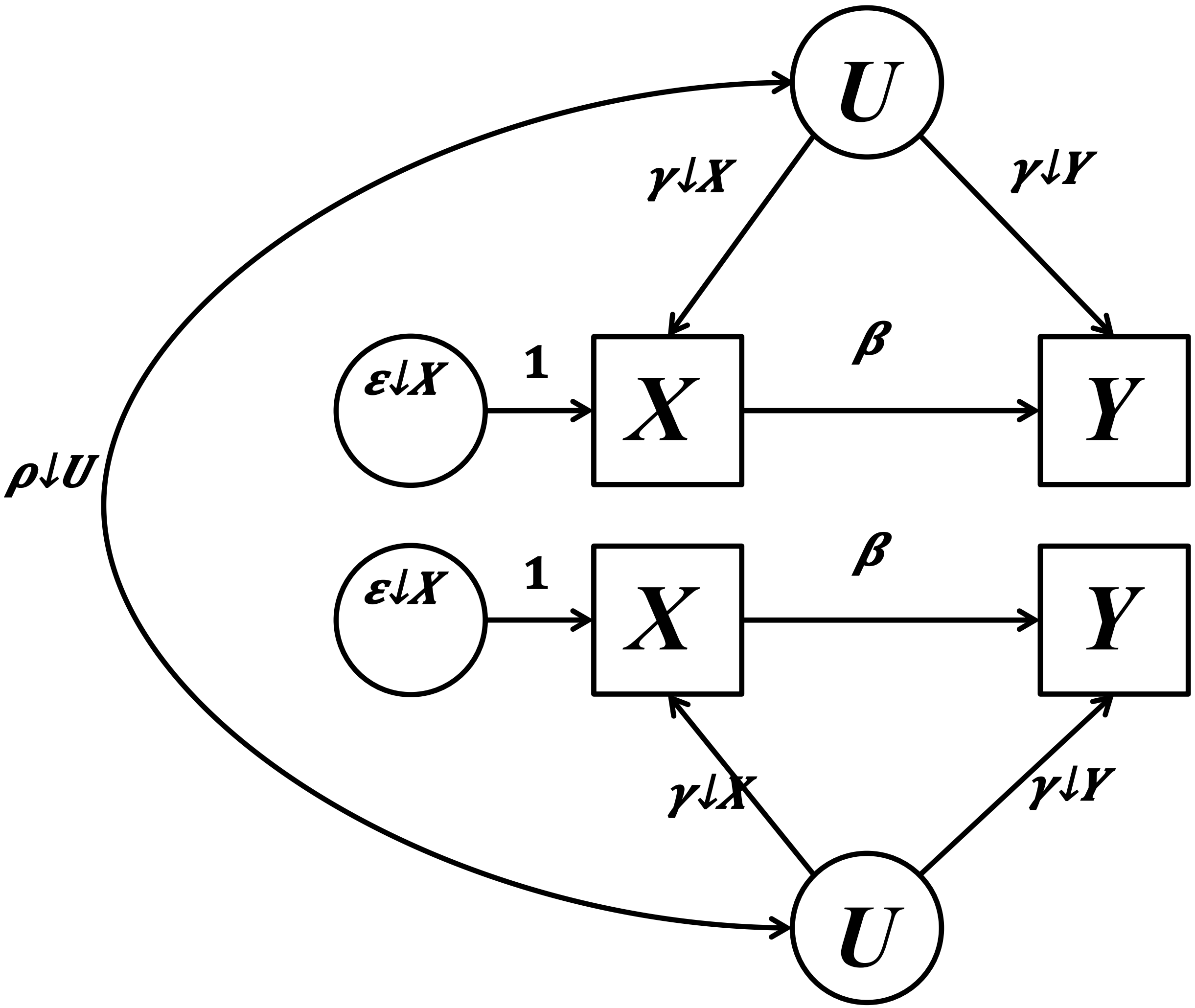
The same process in the other individual in a pair

Causality
Path diagram



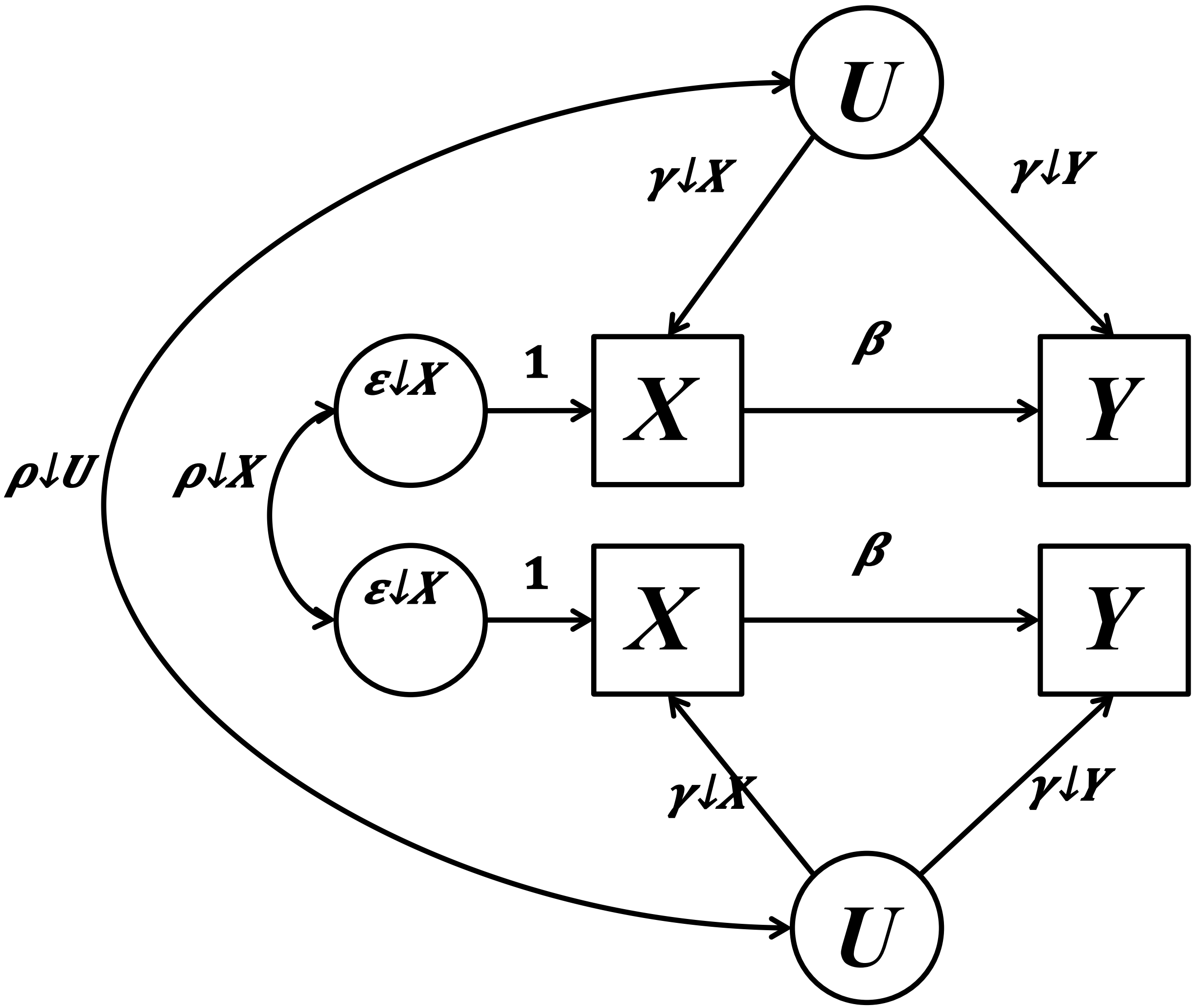
Between-Within analyses assumes *U* to be perfectly shared in pairs…

Causality
Path diagram



… which probably isn't true

Causality
Path diagram



Bias reduction depends on ρ_U and ρ_X

Between-Within

- Data-generating mechanism

$$X_{ij} = \gamma_X U_{ij} + \varepsilon_{Xij}$$

$$g(Y_{ij}) = \beta X_{ij} + \gamma_Y U_{ij} + \varepsilon_{Yij},$$

where $Cor(\varepsilon_{Xi1}, \varepsilon_{Xi2}) = \rho_X$ and $Cor(U_{i1}, U_{i2}) = \rho_U$

- Fitted models:
  - "Cohort" estimate:

$$\text{g}(E(Y_{ij} | X_{ij})) = \mu + \beta_C X_{ij} \quad (1)$$

  - Within estimate:

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Unmeasured confounders

- It can be shown that (if $g(\cdot)$ is the identity link)

$$\beta_C = \beta + \gamma_Y \; \gamma_X \sigma_U^2 \; / \gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon_X}^2$$

and

$$\beta_W = \beta + \gamma_Y \; \gamma_X \sigma_U^2 \; / \gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon_X}^2 \; 1 - \rho_X \; / 1 - \rho_U$$

Unmeasured confounders

- It can be shown that (if $g(\cdot)$ is the identity link)

$$\beta_C = \beta + \frac{\gamma_Y \gamma_X \sigma_U^2}{\gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon_X}^2}$$

and

$$\beta_W = \beta + \frac{\gamma_Y \gamma_X \sigma_U^2}{\gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon_X}^2 \frac{1-\rho_X}{1-\rho_U}}$$

Bias terms

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Bias terms

If $\frac{1-\rho_X}{1-\rho_U} \to 1$ then $\beta_W \to \beta_C$

i.e. when $\rho_X = \rho_U$

Unmeasured confounders

- It can be shown that (if $g(\cdot)$ is the identity link)

$$\beta_C = \beta + \gamma_Y \frac{\gamma_X \sigma_U^2}{\gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon X}^2}$$

and

$$\beta_W = \beta + \gamma_Y \frac{\gamma_X \sigma_U^2}{\gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon X}^2 \frac{1-\rho_X}{1-\rho_U}}$$

Bias terms

If $\frac{1-\rho_X}{1-\rho_U} \to \infty$ then $\beta_W \to \beta$

i.e. when $\rho_U \to 1$

Unmeasured confounders

- It can be shown that (if $g(\cdot)$ is the identity link)

$$\beta_C = \beta + \frac{\gamma_Y \gamma_X \sigma_U^2}{\gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon_X}^2}$$

and

$$\beta_W = \beta + \frac{\gamma_Y \gamma_X \sigma_U^2}{\gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon_X}^2 \frac{1-\rho_X}{1-\rho_U}}$$

Bias terms

When $\rho_X > \rho_U$

β_W is more biased than β_C

Unmeasured confounders

- It can be shown that (if $g(\cdot)$ is the identity link)

$$\beta_C = \beta + \gamma_Y \frac{\gamma_X \sigma_U^2}{\gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon_X}^2}$$

and

$$\beta_W = \beta + \gamma_Y \frac{\gamma_X \sigma_U^2}{\gamma_X^2 \sigma_U^2 + \sigma_{\varepsilon_X}^2} \frac{1-\rho_X}{1-\rho_U}$$

Bias terms

When $\rho_X < \rho_U$

β_W is less biased than β_C

Unmeasured confounders

When $\rho_X > \rho_U$

β_W is more biased than β_C

When $\rho_X < \rho_U$

β_W is less biased than β_C

Measurement error

- Suppose we imperfectly measure X as

$$X_{ij}^{*} = X_{ij} + \varepsilon_{Mij}$$

Measurement error

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- Suppose we imperfectly measure X as

$$X_{ij}^{*} = X_{ij} + \varepsilon_{Mij}$$

- Estimates will be attenuated, the cohort estimate:

$$\beta_{C}^{*} = \lambda \beta_{C}$$

where $\lambda = Var(X)/Var(X)+Var(\varepsilon_{M})$ is the reliability ($0 \leq \lambda \leq 1$)

Measurement error

- The within estimate will be further attenuated

$$\beta_W^{*} = \lambda(\beta\gamma_X^2 \sigma_U^2 (1-\rho_U) + \sigma_{\varepsilon_X}^2 (1-\rho_X) / \gamma_X^2 \sigma_U^2 (1-\lambda\rho_U) + \sigma_{\varepsilon_X}^2 (1-\lambda\rho_X) + \gamma_Y \gamma_X \sigma_U^2 (1-\rho_U) / \gamma_X \sigma_U^2 (1-\lambda\rho_U) + \sigma_{\varepsilon_X}^2 (1-\rho_X))$$

Measurement error

- Suppose $\gamma_X = 0$ then the estimates will be

$$\beta_C^* = \lambda\beta = \beta(1-(1-\lambda))$$

$$\beta_W^* = \beta\left(1 - \frac{1-\lambda}{1-Cor(X_{i1}^*, X_{i2}^*)}\right)$$

- So even with no confounding the within estimate will be further attenuated

Simulations Dichotomous

- Simulated model, Y~Binary, X and U ~MVN:

$\boldsymbol{OR=2}$

$\rho\downarrow U=1$

$\rho\downarrow X=0.5$

$\gamma\downarrow X=0.8$

$\gamma\downarrow Y=0.7$

$\lambda=1$

$\rho\downarrow U=1$

- Result:
    - ”Cohort”: $OR=2.7$
    - BW: $OR\downarrow W=2.0$

Simulations Dichotomous

- Simulated model, Y~Binary, X and U ~MVN:

$\boldsymbol{OR = 2}$

$\rho_U = 0.2$

$\rho_X = 0.5$

$\gamma_X = 0.8$

$\gamma_Y = 0.7$

$\lambda = 1$

$\rho_U < \rho_X$

- Result:
  - ”Cohort”: $OR = 2.7$
  - BW: $OR_W = 2.9$

Simulations
Dichotomous

- Simulated model, Y~Binary, X and U ~MVN:

$\boldsymbol{OR=2}$

$\rho_U = 1$

$\rho_X = 0.5$

$\gamma_X = 0.8$

$\gamma_Y = 0.7$

$\lambda = 0.7$

$\lambda < 1$

- Result:
  - ”Cohort”: $OR = 1.9$
  - BW: $OR_W = 1.3$

Simulations Dichotomous

- Simulated model, Y~Binary, X and U ~MVN:

$\boldsymbol{OR=1}$

$\rho_U = 0.8$

$\rho_X = 0.5$

$\gamma_X = 0.8$

$\gamma_Y = 0.7$

$\lambda = 0.9$

$OR=1$

- Result:
  - ”Cohort”: $OR = 1.4$
  - BW: $OR_W = 1.1$

Simulations

- Simulations in software package R
  - eAppendix to article ”Sibling Comparison Designs: *Bias From Non-Shared Confounders and Measurement Error”* (Frisell *et al* 2012) e-published ahead of print in *Epidemiology*

  - … or ask me and I’ll send some code to you

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Example:
Cognitive ability and violent offending
Frisell et al 2012

- Criminological research has found lower cognitive ability to increase risk for violent behavior
- ~700,000 Swedish males tested for cognitive ability during conscription were assessed for violent criminal convictions
- ~240,000 full brothers, ~18,000 half brothers reared together and ~25,000 half brothers reared apart

Example:
Cognitive ability and violent offending

RESULTS	Cohort	Within
Full	-0.19	-0.10
Half together	-0.18	-0.13
Half apart	-0.18	-0.16

- The authors investigate different plausible explanations:
  - Increased bias? No, based on previous literature
  - Measurement error?

Reliability (λ)	1.0	0.9	0.8	0.7	0.6	0.5
Full	-0.19	-0.17	-0.14	-0.11	-0.07	-0.01
Half together	-0.18	-0.17	-0.16	-0.14	-0.12	-0.09
Half apart	-0.18	-0.17	-0.16	-0.15	-0.14	-0.12

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Full	-0.19	-0.17	-0.14	-0.11	-0.07	-0.01
Half together	-0.18	-0.17	-0.16	-0.14	-0.12	-0.09
Half apart	-0.18	-0.17	-0.16	-0.15	-0.14	-0.12

Example:
Cognitive ability and violent offending

- Test-retest $\rightarrow \lambda = 0.9 - 0.8$
- The authors conclude that there might be a causal effect
- However the association is partly explained by factors shared increasingly by half brothers apart, half brothers together and full brothers

RESULTS	Within
Full	-0.10
Half together	-0.13
Half apart	-0.16

Reliability (λ)	0.9	0.8
Full	-0.17	-0.14
Half together	-0.17	-0.16
Half apart	-0.17	-0.16

Summary

- The bias can both increase and decrease from within sibling comparisons
- The bias reduction (increase) depends on correlation in confounders vs. exposure
- If there is measurement error the within estimate will be more attenuated than the cohort estimate

Recommendations

- Use sibling comparisons!

… but …

- Reason about unmeasured confounders and their stability across siblings (ρ_U vs. ρ_X)
- Is there any information on reasonable values for reliability? In that case use them to see whether that is an alternative explanation

→ Subject matter knowledge

- Frisell Thomas, Öberg Sara, Kuja-Halkola Ralf, Sjölander Arvid. **Sibling Comparison Designs: Bias From Non-Shared Confounders and Measurement Error.** *Epub ahead of print Epidemiology* 2012

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References

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