Selection Bias in the Sibling Comparison Design

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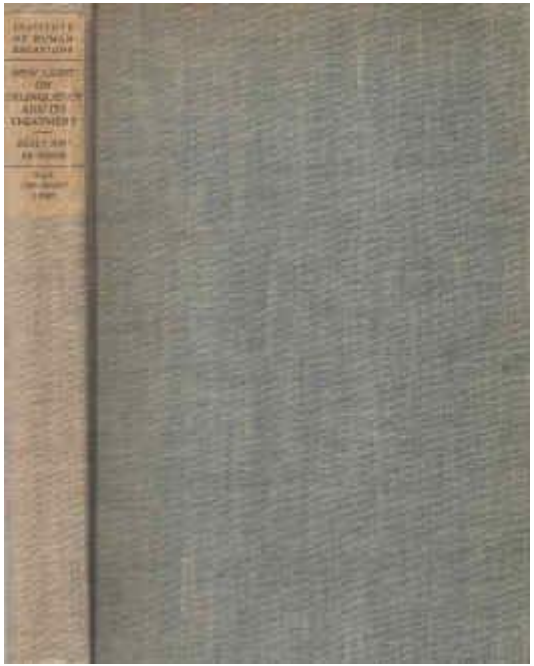
Sibling comparisons have a long history

Healy, W., & Bronner, A.F. (1936). *New Light on Delinquency and its Treatment*. Yale University Press.

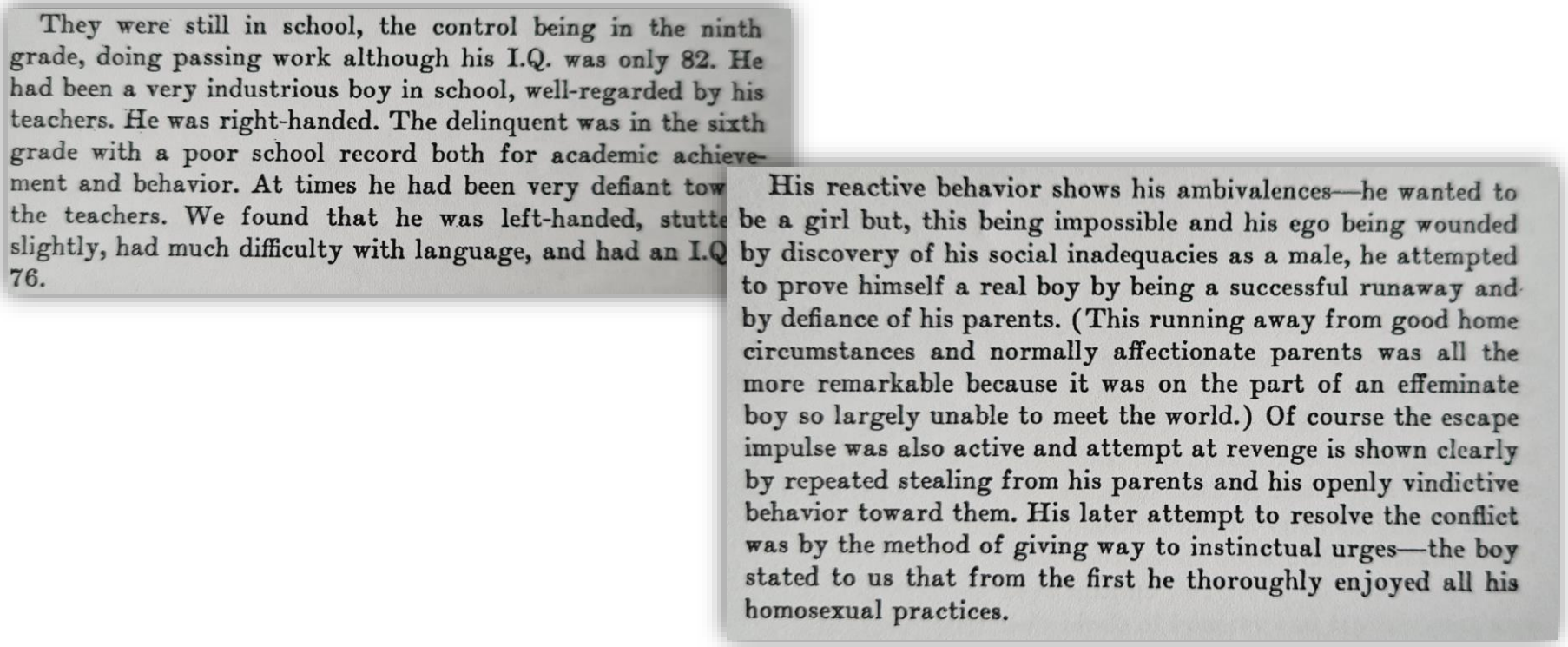
- Compared 105 “delinquents” to their “non-delinquent” siblings
  - → 8 pairs were twins

	Delinquents	*Controls*
Much worry during pregnancy	10	3
Very sickly pregnancy	13	6
Cross, fussy babyhood	14	5
Difficult toilet habit-training	31	13
Much underweight in early childhood	12	5
Many or severe illnesses	28	8
Severe head injuries	5	0

It can be seen at once that many more of the delinquents than of the controls had been subject to interference with healthy normal development. The relationship however be-



Sibling comparisons have a long history



They were still in school, the control being in the ninth grade, doing passing work although his I.Q. was only 82. He had been a very industrious boy in school, well-regarded by his teachers. He was right-handed. The delinquent was in the sixth grade with a poor school record both for academic achievement and behavior. At times he had been very defiant tow the teachers. We found that he was left-handed, stutte slightly, had much difficulty with language, and had an I.Q 76.

His reactive behavior shows his ambivalences—he wanted to be a girl but, this being impossible and his ego being wounded by discovery of his social inadequacies as a male, he attempted to prove himself a real boy by being a successful runaway and by defiance of his parents. (This running away from good home circumstances and normally affectionate parents was all the more remarkable because it was on the part of an effeminate boy so largely unable to meet the world.) Of course the escape impulse was also active and attempt at revenge is shown clearly by repeated stealing from his parents and his openly vindictive behavior toward them. His later attempt to resolve the conflict was by the method of giving way to instinctual urges—the boy stated to us that from the first he thoroughly enjoyed all his homosexual practices.

Healy, W., & Bronner, A.F. (1936). New Light on Delinquency and its Treatment. Yale University Press.

From the Department of Medical Epidemiology and Biostatistics
Karolinska Institutet, Stockholm, Sweden

VIOLENT CRIME: ADDRESSING CAUSATION WITH FAMILY-BASED METHODS

Thomas Frisell

Karolinska Institutet

Stockholm 2012

Svenska Tvillingregistret

Kriminalvården

Psychological Medicine (2011), **41**, 97–105. © Cambridge University Press 2010
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ORIGINAL ARTICLE

Violent crime runs in families: a total population study of 12.5 million individuals

T. Frisell[1,2*], P. Lich

[1] *Department of Medical Ep*
[2] *Centre for Violence Preven*

Background. Etiologi
clusters in families. H

Behav Genet (2012) 42:3–18
DOI 10.1007/s10519-011-9483-0

ORIGINAL RESEARCH

Heritability, Assortative Mating and Gender Differences in Violent Crime: Results from a Total Population Sample Using Twin, Adoption, and Sibling Models

Thomas Frisell · Yudi Pawitan · Niklas Långström · Paul Lichtenstein

Received: 22 September 2010 / Accepted: 29 June 2011 / Published online: 15 July 2011

Causal Inference and Observational Research: The Utility of Twins

5(5) 546–556

DOI: 10.1177/1745691610383511
http://pps.sagepub.com

Matt McGue[1,2], Merete Osler[2,3], and Kaare Christensen[4]

[1]Department of Psychology, University of Minnesota, Minneapolis; [2]Institute of Public Health, University of Southern Denmark, Odense, Denmark; [3]Research Center for Prevention and Health, Glostrup Hospital, Glostrup, Denmark; and [4]The Danish Twin Registry and The Danish Aging Research Center Institute of Public Health, University of Southern Denmark, Odense, Denmark

Abstract

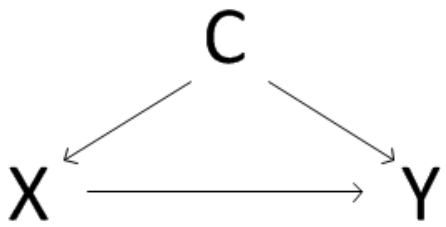
Valid causal inference is central to progress in theoretical and applied psychology. Although the randomized experiment is widely considered the gold standard for determining whether a given exposure increases the likelihood of some specified outcome, experiments are not always feasible and in some cases can result in biased estimates of causal effects. Alternatively, standard observational approaches are limited by the possibility of confounding, reverse causation, and the nonrandom distribution of exposure (i.e., selection). We describe the counterfactual model of causation and apply it to the challenges of causal inference in observational research, with a particular focus on aging. We argue that the study of twin pairs discordant on exposure, and in particular discordant monozygotic twins, provides a useful analog to the idealized counterfactual design. A review of discordant-twin studies in aging reveals that they are consistent with, but do not unambiguously establish, a causal effect of lifestyle factors on important late-life outcomes. Nonetheless, the existing studies are few in number and have clear limitations that have not always been considered in interpreting their results. It is concluded that twin researchers could make greater use of the discordant-twin design as one approach to strengthen causal inferences in observational research.

Correlation does not imply causation

- Counterfactual definition of causality:
  would the outcome have been different had the exposure been different?

- Idealized counterfactual design: same person, same time, different exposure

- 'Mimicking' the counterfactual design
  - → Restriction
  - → Stratification
  - → Multiple regression
  - → Propensity scores
  - → Matching



Matching as a quasiexperiment

- Matching on age and sex is an efficient way of removing confounding from the same factors

- Imagine if we matched on *all* factors except exposure/outcome, wouldn't this give us the counterfactual outcome?

- Sure, but:
  - → can only match on measured variables (or functions thereof)
  - → difficult to find perfect matches

Sibling-matching!

- Siblings (twins!) are perfect matches on all factors shared by siblings, whether we have measured them or not

- Case-control study:
    - pick sibling pairs discordant in outcome and compare their exposure
- Cohort study:
    - pick sibling pairs discordant in exposure and compare their outcome

- The estimates we get from this must be free from confounding by factors notoriously difficult to measure or model
    - parenting, SES, the combined effect of many alleles,…
- Even factors we never suspected of being confounders!

Scandinavian registers: Sweden

Census data, demography

Census every 5th year (1960-1990)

LISA (1990)

Education (1985)

Migrations (1968)

Social services

Sick leave, disability pension (1992)

Financial assistance (1990)

Support for elderly (~2010)

Enlistment

Test results (1969)

Perinatal

Medical Birth Register (1973)

Healthcare

Inpatient (1973 / 1986)

Outpatient, non-primary (2001)

Prescription drugs (2005)

Cancer (1958)

Causes of death (1960)

“Quality” registries (ca 1995)

Crime

Convictions (1973)

Suspicions (1998)

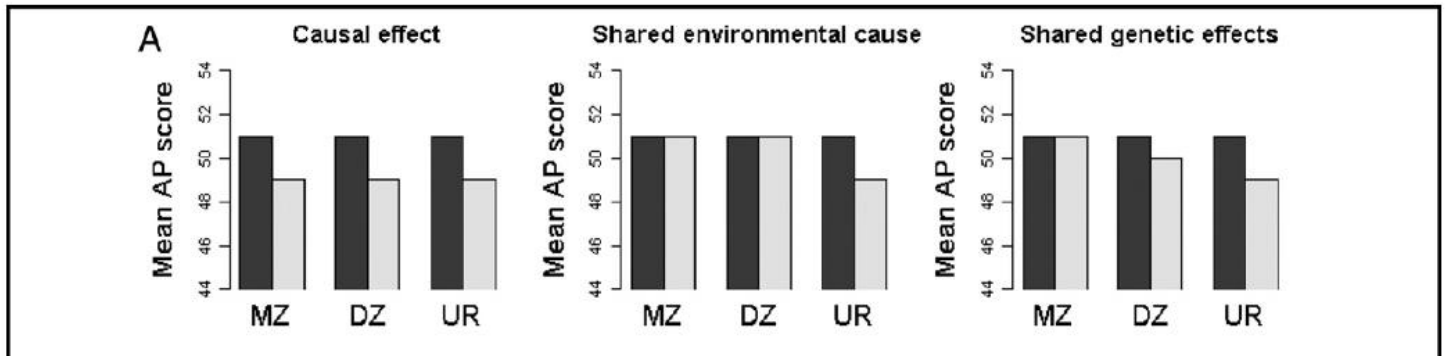
Relatedness

The multigeneration register (1932)

The Swedish Twin register (~1900)

Common interpretation in co-twin control studies

- By comparing the association in general to the association ”within pairs” we can tell whether an association is confounded, and roughly what this confounding is….



Groen-Blokhuis MM, Middeldorp CM, van Beijsterveldt CE, Boomsma DI. Evidence for a causal association of low birth weight and attention problems. *J Am Acad Child Adolesc Psychiatry* 2011; 50(12): 1247-54 e2.

I picked a topic and started analyzing!

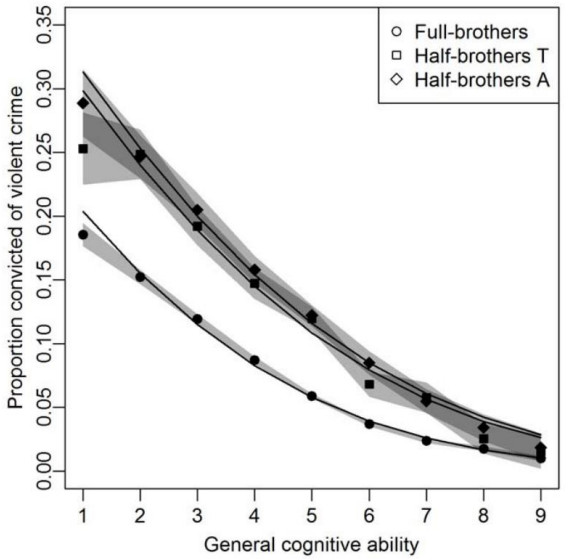


Figure 1. The proportion convicted of violent crime is inversely associated with intelligence. Proportion of men born in Sweden 1961–1975 convicted of one or more violent offences 1973–2009 as a function of stanine general cognitive ability (intelligence), and fit of the probit model. Observed proportions are depicted for full-brothers

OPEN ACCESS Freely available online

PLoS one

Is the Association between General Cognitive Ability and Violent Crime Caused by Family-Level Confounders?

Thomas Frisell[1,2]*, Yudi Pawitan[1], Niklas Långström[1,2]

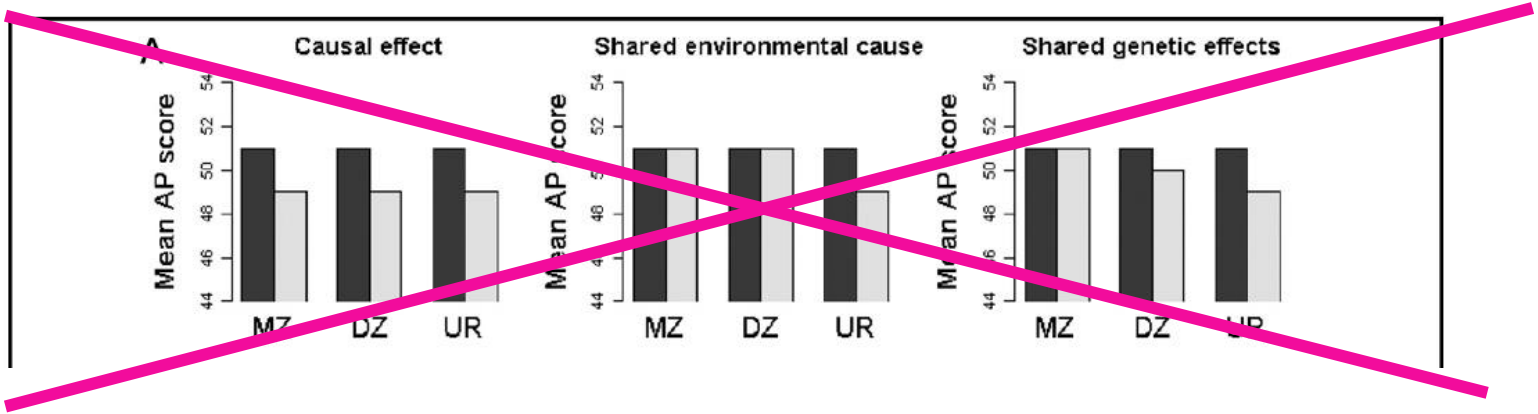
1 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, **2** Centre for Violence Prevention, Karolinska Institutet, Stockholm, Sweden

Abstract

Background: Research has consistently found lower cognitive ability to be related to increased risk for violent and other antisocial behaviour. Since this association has remained when adjusting for childhood socioeconomic position, ethnicity, and parental characteristics, it is often assumed to be causal, potentially mediated through school adjustment problems and conduct disorder. Socioeconomic differences are notoriously difficult to quantify, however, and it is possible that the association between intelligence and delinquency suffer substantial residual confounding.

Common interpretation in co-twin control studies

- By comparing the association in general to the association "within pairs" we can tell whether an association is confounded, and roughly what this confounding is....



- Simplified, vague, and (partly) wrong!

Groen-Blokhuis MM, Middeldorp CM, van Beijsterveldt CE, Boomsma DI. Evidence for a causal association of low birth weight and attention problems. *J Am Acad Child Adolesc Psychiatry* 2011; 50(12): 1247-54 e2.

Siblings are not like other matched controls!

- Matc tatus and r
- Siblir

ORIGINAL ARTICLE

Sibling Comparison Designs

Bias From Non-Shared Confounders and Measurement Error

Thomas Frisell,[a,b] *Sara Öberg,*[c] *Ralf Kuja-Halkola,*[a,b] *and Arvid Sjölander*[a]

- Siblings tend to be similar on all things, yet a sibling comparison depends on the exclusion of sibling pairs which have the same outcome/exposure
- Strong selection, with consequences for the effect estimates!

In this talk

- A brief overview of how to perform a sibling comparison analysis
- Why the ”intuitive” interpretation is wrong, and how sibling comparisons may:
  - → Amplify confounding
  - → Amplify measurement error
  - → Introduce bias from cross-sibling interactions
  - → Reduce generalizability
- Tentative recommendation for use

Statistics for a sibling comparison design

Dichotomous outcome and exposure

- Select sibling pairs that are discordant in exposure

		Exposed sibling Y=1	Exposed sibling Y=0
Unexposed sibling	Y=1	N1	N2
	Y=0	N3	N4

- Turns out only N2 and N3 will influence the within-pair association
  → The 'doubly discordant' pairs

- Historically, analyzed with McNemar's test

Some other historical alternatives

- If either exposure or outcome is dichotomous:
  - → Compare means in exposure (outcome) discordant pairs
  - → Paired t-test

- Model the pair difference
  - → Regress pair difference in outcome on pair difference in exposure

General models

- Fixed effect models, conditional on family
  - → Conditional logistic regression
  - → Stratified Cox regression
  - → …
- ”Between–within” models
  - → GLM framework
  - → Flexible for different types of outcomes and exposures.
- The ‘selection’ of discordant pairs need not be explicit
  - → Only discordant pairs will contribute to ‘effect’ estimates

Between–within model

- Let Y_{ij} and X_{ij} be the outcome and exposure of individual *i* in sibling pair *j*
- Generalized Linear Model:

$$g\{E(Y_{ij}|X_{ij})\} = \alpha + \beta X_{ij}$$

intercept

'effect' of X

- Add the pair mean exposure:

$$g\{E(Y_{ij}|X_{ij}, \overline{X}_i)\} = \alpha_{BW} + \beta_W X_{ij} + \beta_B \overline{X}_i$$

$$or\ (X_{ij} - \overline{X}_i)$$

intercept

'within-pair effect' of X

a weird number

- Works with e.g. linear, logistic, probit, and Poisson regression.

The BW model becomes tedious with many covariates!

$$g\{E(Y_{ij}|X_{ij}, \overline{X}_i)\} = \alpha_{BW} + \beta_W X_{ij} + \beta_B \overline{X}_i + \beta_{cW} C_{ij} + \beta_{cB} \overline{C}_i + \ \ldots$$

Design of sibling comparison studies

- Different terms, essentially the same design
    - Co-twin control study
    - Discordant twin designs
    - Between-within models
    - Family fixed effects models
    - …
- These designs provide a ”within-pair” estimate
- If all confounding is perfectly shared by the pair, and there is no other bias, the within-pair estimate is an unbiased estimate of the causal effect.

So what’s the problem?

The problem is the selection

- Siblings are similar (correlated) on most things
  - → Confounders
  - → But also the exposure and outcome!

- In sibling comparison designs, only sibling pairs that differ (are discordant) in exposure contribute to the within-pair association
  - → An implicit selection of pairs that differ on exposure, despite the fact that siblings tend to be similar on exposure
  - → Thus, we are oversampling pairs that differ in ”factors that make siblings different” in exposure
  - → Thus, exposed and unexposed in the sibling comparison will be more different on ”factors that make siblings different” than unrelated exposed and unexposed in the complete sample
  - → Thus any confounding by such factors will be increased in the sibling comparison

DAG

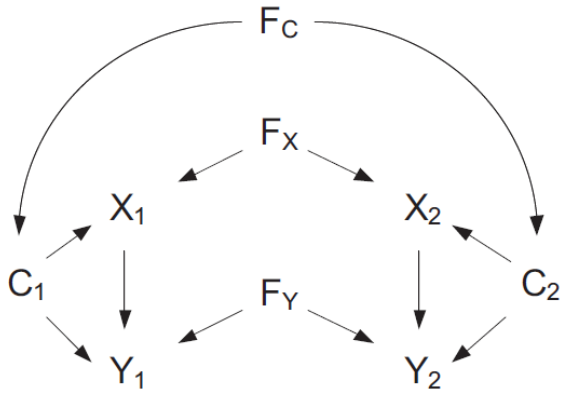
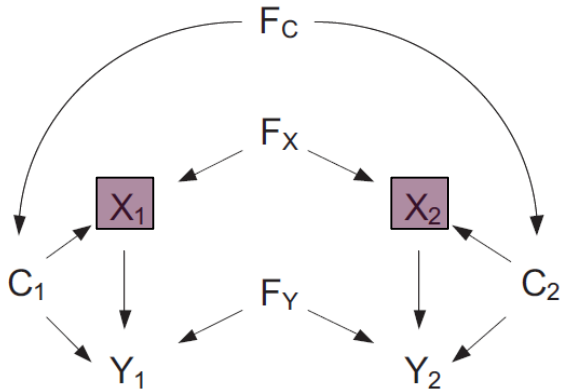


FIGURE. Causal diagram of exposure-outcome association in sibling pairs. X, C, and Y are the exposure, confounder, and outcome, respectively, for individuals 1 and 2. Familial factors (F_X, F_C, and F_Y) cause X, C, and Y to be clustered in families.

DAG



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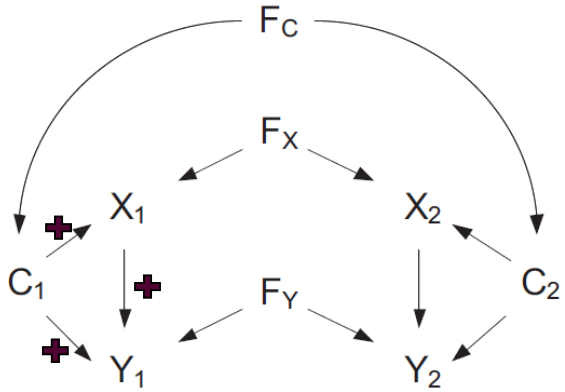
DAG

Strength of confounding depend on strength of correlation between C and X



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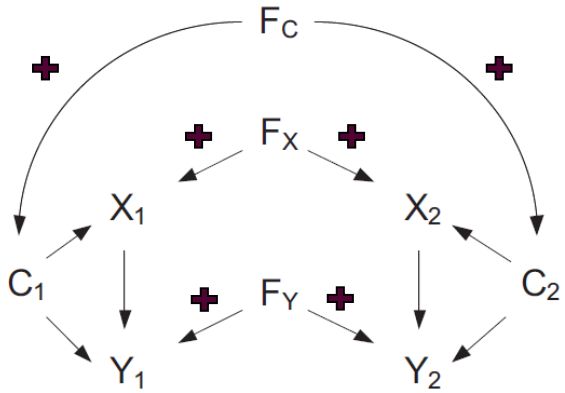

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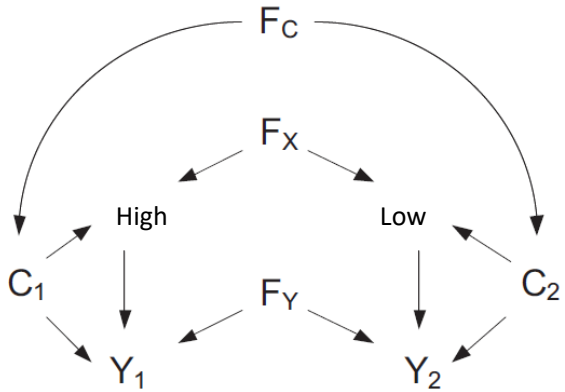

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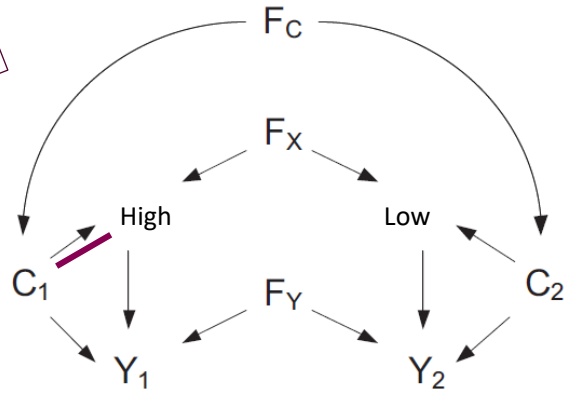
DAG

Strength of confounding depend on strength of correlation between C and X

High X1 tells us C1 is probably high



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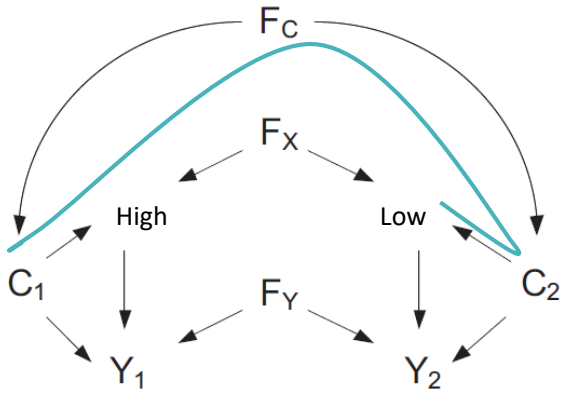
DAG

Low X2 tells us C2 is probably low, and then Fc is probably low, and then C1 is probably low



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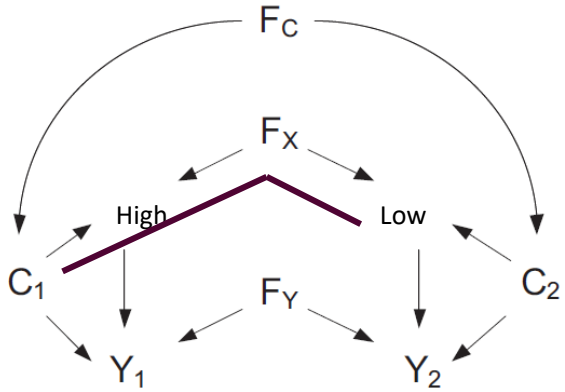
DAG

Low X2 tells us Fx is probably low, and then X1 should have been low, but since it is high then C1 must be high



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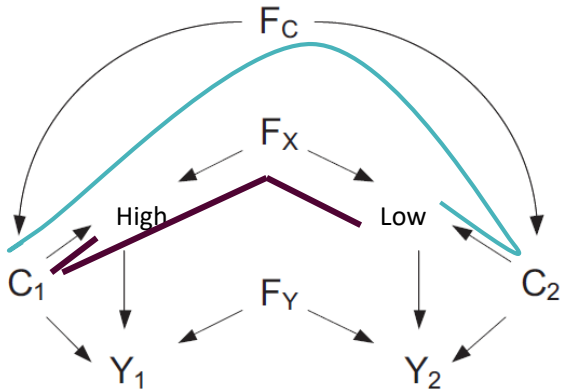
DAG

Strength of confounding depend on strength of correlation between C and X



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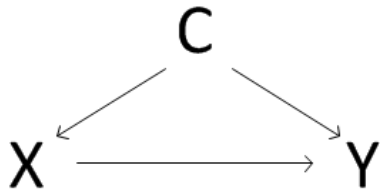
Amplified confounding!

The problem is the effect size



The equation for a simple linear regression coefficient is:

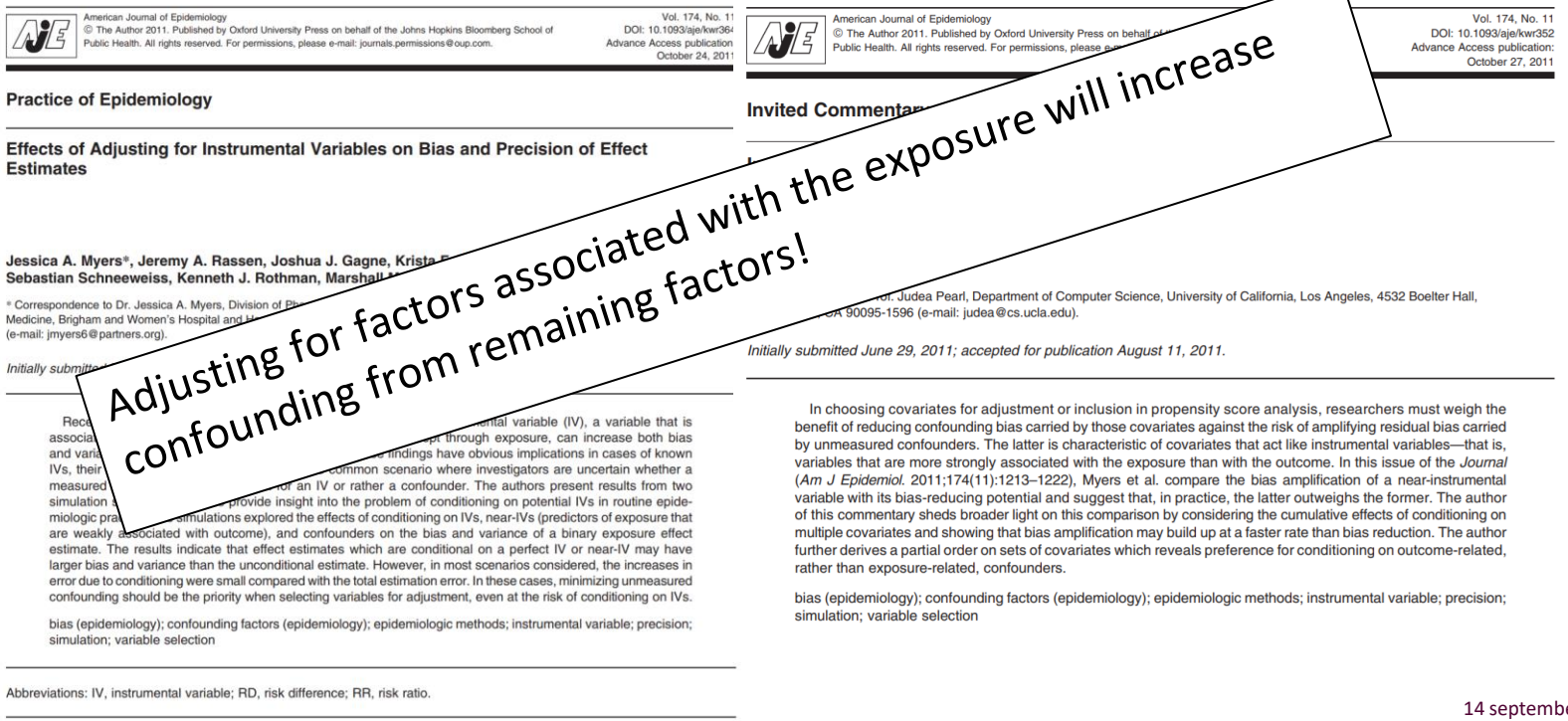
$$\beta = \frac{Cov(X, Y)}{Var(X)}$$

By restricting to sibling pairs, we reduce the variance in exposure, keeping only the within-pair variation

We also reduce the covariance. By how much?

- If the association is completely causal, by an equal proportion
- If the association is completely due to confounders shared by the pair, the covariance within-pair is zero
- What if the association is due to confounders not shared by the pair?

A special case of bias amplification



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Advance Access publication
October 24, 2011

Practice of Epidemiology

Effects of Adjusting for Instrumental Variables on Bias and Precision of Effect Estimates

Jessica A. Myers*, Jeremy A. Rassen, Joshua J. Gagne, Krista F. Sebastian Schneeweiss, Kenneth J. Rothman, Marshall M.

* Correspondence to Dr. Jessica A. Myers, Division of Ph... Medicine, Brigham and Women's Hospital and H... (e-mail: jmyers6@partners.org).

Initially submitte...

Rec... ...ental variable (IV), a variable that is associa... ...pt through exposure, can increase both bias and vari... ...findings have obvious implications in cases of known IVs, their ... ...common scenario where investigators are uncertain whether a measured ... ...or an IV or rather a confounder. The authors present results from two simulation ... ...provide insight into the problem of conditioning on potential IVs in routine epidemiologic pra... ...simulations explored the effects of conditioning on IVs, near-IVs (predictors of exposure that are weakly associated with outcome), and confounders on the bias and variance of a binary exposure effect estimate. The results indicate that effect estimates which are conditional on a perfect IV or near-IV may have larger bias and variance than the unconditional estimate. However, in most scenarios considered, the increases in error due to conditioning were small compared with the total estimation error. In these cases, minimizing unmeasured confounding should be the priority when selecting variables for adjustment, even at the risk of conditioning on IVs.

bias (epidemiology); confounding factors (epidemiology); epidemiologic methods; instrumental variable; precision; simulation; variable selection

Abbreviations: IV, instrumental variable; RD, risk difference; RR, risk ratio.

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October 27, 2011

Invited Commentar...

...ol. Judea Pearl, Department of Computer Science, University of California, Los Angeles, 4532 Boelter Hall, ...A 90095-1596 (e-mail: judea@cs.ucla.edu).

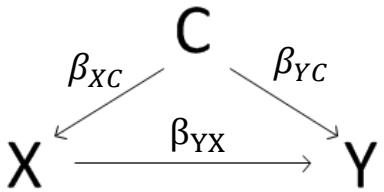
Initially submitted June 29, 2011; accepted for publication August 11, 2011.

In choosing covariates for adjustment or inclusion in propensity score analysis, researchers must weigh the benefit of reducing confounding bias carried by those covariates against the risk of amplifying residual bias carried by unmeasured confounders. The latter is characteristic of covariates that act like instrumental variables—that is, variables that are more strongly associated with the exposure than with the outcome. In this issue of the *Journal* (*Am J Epidemiol.* 2011;174(11):1213–1222), Myers et al. compare the bias amplification of a near-instrumental variable with its bias-reducing potential and suggest that, in practice, the latter outweighs the former. The author of this commentary sheds broader light on this comparison by considering the cumulative effects of conditioning on multiple covariates and showing that bias amplification may build up at a faster rate than bias reduction. The author further derives a partial order on sets of covariates which reveals preference for conditioning on outcome-related, rather than exposure-related, confounders.

bias (epidemiology); confounding factors (epidemiology); epidemiologic methods; instrumental variable; precision; simulation; variable selection

Adjusting for factors associated with the exposure will increase confounding from remaining factors!

Analytically under a linear model



If we let the true causal model (for subject *i* in sib-pair *j*) be

$$Y_{ij} := \beta_{YX} X_{ij} + \beta_{YC} C_{ij} + \epsilon_{Yij}$$
$$X_{ij} := \beta_{XC} C_{ij} + \epsilon_{Xij},$$

the confounded ordinary regression coefficient is $\beta = \frac{Cov(X,Y)}{Var(X)} = \beta_{YX} + \frac{\beta_{YC}\beta_{XC}\sigma_C^2}{\beta_{XC}^2\sigma_C^2+\sigma_{\epsilon X}^2}$,

and the confounded within-pair coefficient is $\beta_W = \frac{Cov(X_{ij}-\overline{X_i},Y)}{Var(X_{ij}-\overline{X_i})} = \beta_{YX} + \frac{\beta_{YC}\beta_{XC}\sigma_C^2}{\beta_{XC}^2\sigma_C^2+\sigma_{\epsilon X}^2}\frac{1-\rho_{\epsilon X}}{1-\rho_C}$

Sibling correlation in exposure

Sibling correlation in confounder

We see that:

ρ_C=1	$\Rightarrow \beta_W = \beta_{YX}$
ρ_C=$\rho_{\epsilon X}$	$\Rightarrow \beta_W = \beta$
$\rho_C < \rho_{\epsilon X}$	$\Rightarrow \beta_W$ more confounded than β

Frisell T, Öberg S, Kuja-Halkola R, Sjölander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012 Sep;23(5):713-20. doi: 10.1097/EDE.0b013e31825fa230. PMID: 22781362.

Simulations under logistic model

Results from between-within model on simulations under a logistic model. Non-confounded causal OR = 5.0.		
Confounding		
Cor(X1, X2)	Cor(C1, C2)	OR
0.6	1	8.0
0.6	0.6	8.0
0.6	0.3	8.0
0.6	0	8.0
0.3	1	8.0
0.3	0.6	8.0
0.3	0.3	8.0
0.3	0	8.0

Frisell T, Öberg S, Kuja-Halkola R, Sjölander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012 Sep;23(5):713-20. doi: 10.1097/EDE.0b013e31825fa230. PMID: 22781362.

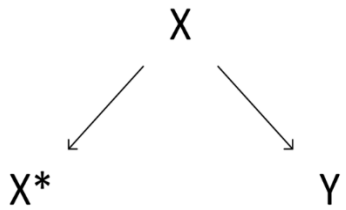
Simulations under logistic model

Results from between–within model on simulations under a logistic model. Non-confounded causal OR = 5.0.			
Confounding			
Cor(X1, X2)	Cor(C1, C2)	OR	OR_W
0.6	1	8.0	5.0
0.6	0.6	8.0	8.0
0.6	0.3	8.0	12.2
0.6	0	8.0	19.9
0.3	1	8.0	5.0
0.3	0.6	8.0	6.5
0.3	0.3	8.0	8.0
0.3	0	8.0	10.1

Frisell T, Öberg S, Kuja-Halkola R, Sjölander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012 Sep;23(5):713-20. doi: 10.1097/EDE.0b013e31825fa230. PMID: 22781362.

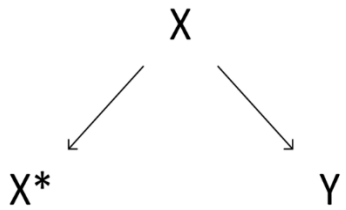
Amplified measurement error!

Random measurement error



- X* is our measure of X
- May contain ”noise”, from factors not associated to the outcome.
- ”Non-differential misclassification”

Random measurement error



- Say X is almost perfectly shared by siblings, but there is substantial random measurement error
- We select sibling pairs discordant in X*
  - → the most likely reason why the siblings are discordant is measurement error

- We have increased the noise in X!

Analytically under a linear model

Let there be random measurement error in X:

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

The ordinary regression coefficient is then

$$\beta^* = Var(X_{ij})/Var(X_{ij}^*)\ \beta_{YX} = \gamma\beta_{YX} = \beta_{YX}(1-(1-\gamma))$$

and under no confounding, the within-pair coefficient is

$$\beta_W^*(\beta_{XC}=0) = \beta_{YX}\left(1 - \frac{1-\gamma}{1-Cor(X_{i1}^*, X_{i2}^*)}\right)$$

where γ is the reliability of our measure of X.

In presence of confounding β_W^* is more complicated, but somewhat more attenuated.

Frisell T, Öberg S, Kuja-Halkola R, Sjölander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012 Sep;23(5):713-20. doi: 10.1097/EDE.0b013e31825fa230. PMID: 22781362.

Simulations under logistic model

Results from between-within model on simulations under a logistic model. Non-confounded causal OR = 5.0.			
Measurement error in exposure			
Sensitivity	Specificity	OR	OR_W
1	1	5.0	5.0
1	0.8	4.4	3.5
1	0.6	3.9	3.0
0.8	1	3.0	2.6
0.8	0.8	2.3	1.9
0.8	0.6	1.8	1.5
0.6	1	2.3	1.9
0.6	0.8	1.7	1.5

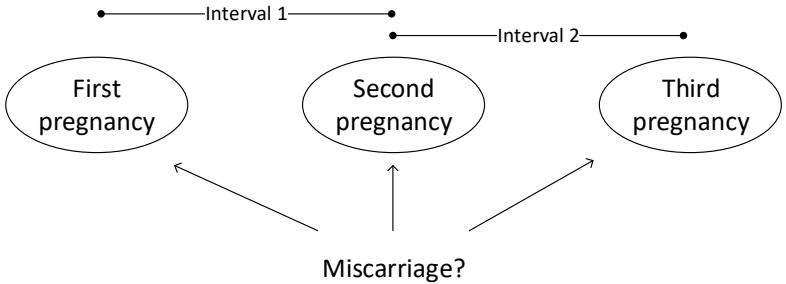
Bias from cross-sibling interactions!

Cross-sibling effects

- Sibling comparison designs assume that the siblings have no causal effects on each other

- What if they do?

Cross-sibling effects

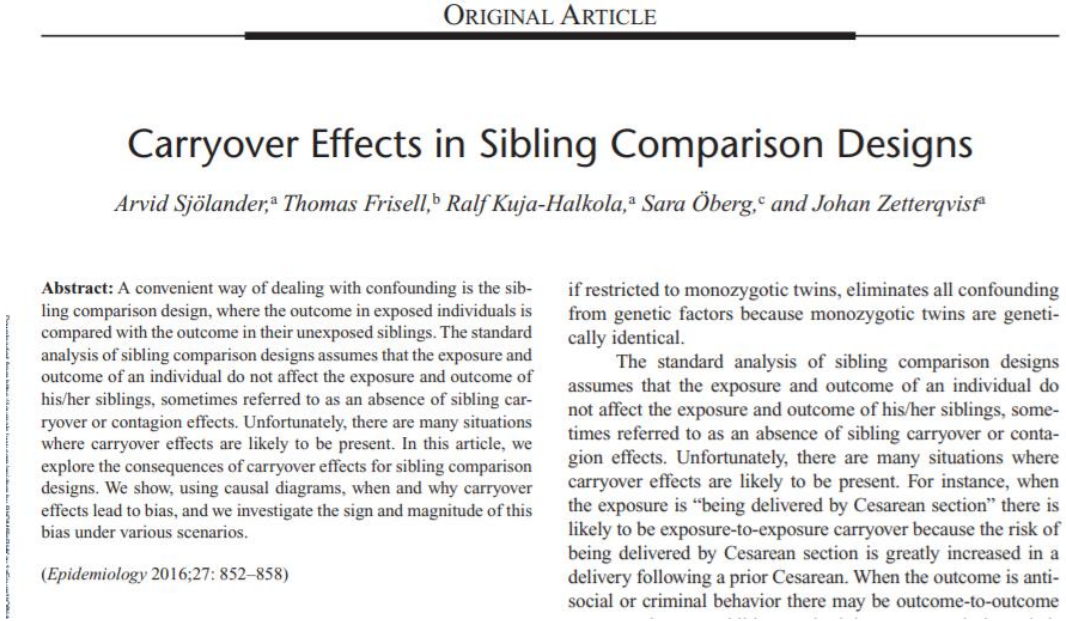


Imagine a sibling study of interpregnancy interval and late miscarriage

- What if women with a late miscarriage wait longer before having their next child than women without a late miscarriage?
- We select only discordant women, so those with late miscarriage in second pregnancy will have longer interval as exposure for their third pregnancy, where there will not be a late miscarriage

→ Longer interpregnancy interval will be associated with fewer late miscarriages among discordant women!

Cross-sibling effects



ORIGINAL ARTICLE

Carryover Effects in Sibling Comparison Designs

Arvid Sjölander,[a] Thomas Frisell,[b] Ralf Kuja-Halkola,[a] Sara Öberg,[c] and Johan Zetterqvist[a]

Abstract: A convenient way of dealing with confounding is the sibling comparison design, where the outcome in exposed individuals is compared with the outcome in their unexposed siblings. The standard analysis of sibling comparison designs assumes that the exposure and outcome of an individual do not affect the exposure and outcome of his/her siblings, sometimes referred to as an absence of sibling carryover or contagion effects. Unfortunately, there are many situations where carryover effects are likely to be present. In this article, we explore the consequences of carryover effects for sibling comparison designs. We show, using causal diagrams, when and why carryover effects lead to bias, and we investigate the sign and magnitude of this bias under various scenarios.

(*Epidemiology* 2016;27: 852–858)

if restricted to monozygotic twins, eliminates all confounding from genetic factors because monozygotic twins are genetically identical.

The standard analysis of sibling comparison designs assumes that the exposure and outcome of an individual do not affect the exposure and outcome of his/her siblings, sometimes referred to as an absence of sibling carryover or contagion effects. Unfortunately, there are many situations where carryover effects are likely to be present. For instance, when the exposure is "being delivered by Cesarean section" there is likely to be exposure-to-exposure carryover because the risk of being delivered by Cesarean section is greatly increased in a delivery following a prior Cesarean. When the outcome is antisocial or criminal behavior there may be outcome-to-outcome

Cross-sibling effects

- The exposure of the first sibling influence the exposure of the second:
  No problem

- The exposure of the first sibling influence the outcome of the second sibling:
  Problem, but often conservative (estimate of causal effect biased towards the null)

- The outcome of one sibling influence the exposure or outcome of the other:
  Big problem

- Good news: you can often assess the presence of cross-sibling effects with observed data

Reduced generalizability!

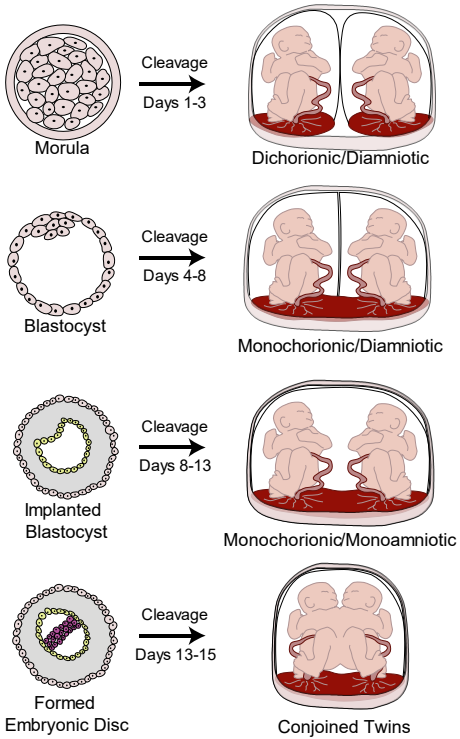
Generalizability

- Are discordant sibling pairs representative of the population?

- NO, that’s the whole point of the sibling comparison!

- Are people with siblings different from those without?
- What about the distribution of effect modifiers?

Are twins generalizable?



Dufendach, K. (Artist). (2008). *Placentation*. [Web]. Retrieved from http://commons.wikimedia.org/wiki/File:Placentation.svg

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International Journal of Epidemiology 2012;**41**:1002–1009
doi:10.1093/ije/dys067

MORE ON TWINS

Twinship influence on morbidity and mortality across the lifespan

Sara Öberg,[1,2]* Sven Cnattingius,[3] Sven Sandin,[1] Paul Lichtenstein,[1] Ruth Morley[4] and Anastasia N Iliadou[1]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA, [3]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden and [4]Clinical Epidemiology & Biostatistics Unit, Murdoch Childrens Research Institute, Melbourne, Australia

*Corresponding author. Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA. Email: oberg@hsph.harvard.edu

Conclusions Despite their adverse intrauterine experience, twins do not seem to fare worse than singletons with respect to adult morbidity and mortality. The findings indicate that the unique experience of twinning does not lead to adverse long-term health outcomes.

Distribution of effect modifiers

- We “select” pairs discordant on exposure/outcome
- Under several plausible scenarios, this may alter distribution of other factors linked to exposure/outcome
- Do income discordant siblings more often come from high income families?
- The target population may not be clear!
  → And are we estimating conditional or marginal effects??

More on generalizability

European Journal of Epidemiology (2022) 37:461–476
https://doi.org/10.1007/s10654-022-00844-x

METHODS

Generalizability and effect measure modification in sibling comparison studies

Arvid Sjölander[1] · Sara Öberg[1] · Thomas Frisell[2]

Received: 27 August 2021 / Accepted: 16 January 2022 / Published online: 21 March 2022

Summary

- The ‘selection’ of discordant pairs will
  - → Remove all confounding by perfectly shared factors
  - → Reduce confounding by factors more shared than the exposure
  - → Amplify confounding by factors less shared than the exposure

  - → Increase attenuation from random measurement error

  - → Possibly introduce bias due to sibling interactions

  - → Raise questions about the generalizability

Where does this leave us?

Conclusions

- Sibling comparisons may both increase and decrease bias compared to the ”unpaired”, cohort estimate

- Even if an association remains unchanged in a sibling/twin comparison, it may be substantially confounded by factors influenced by genetics and family environment
- Even if an association is attenuated in a sibling comparison, it may be completely causal

- Important quantities in a sibling comparison:
  - → Reliability of exposure measurement
  - → The correlation in exposure (different for different relatives!)
  - → The degree that one sibling’s outcome influences the other sibling

- *All this applies equally to other ”within-cluster” analyses, like case-crossover studies*

But perhaps its not that bad?

- Sibling comparisons may:
  - → Amplify confounding
    - But we can adjust for non-shared confounders
  - → Amplify measurement error
    - But we can account for different degrees of error
  - → Introduce bias from cross-sibling interactions
    - But we can assess the asymmetries indicating such interactions
  - → Reduce generalizability
    - But this isn't that big of a deal?

The major problem is the low power?

RESEARCH ARTICLE

Autism Research 13: 134–144, 2020

Familial Confounding of the Association between Maternal Smoking in Pregnancy and Autism Spectrum Disorder in Offspring

Amy E. Kalkbrenner, Sandra M. Meier, Paul Madley-Dowd, Christine Ladd-Acosta, Margaret Daniele Fallin, Erik Parner, and Diana Schendel

Whole-population cohort study in Denmark:
1,294,906 persons, including 993,301 siblings

Adjusted HR: 1.17 (1.13-1.22)
Within sibling: 0.86 (0.64-1.15)

American Journal of Epidemiology

Vol. 190, No. 5
DOI: 10.1093/aje/kwaa182
Advance Access publication: August 24, 2020

Original Contribution

Maternal Prenatal Smoking and Autism Spectrum Disorder in Offspring: A California Statewide Cohort and Sibling Study

Ondine S. von Ehrenstein*, Xin Cui, Qi Yan, Hilary Aralis, and Beate Ritz

* Correspondence to Dr. Ondine S. von Ehrenstein, Fielding School of Public Health, University of California, Los Angeles, P.O. Box 951772, Los Angeles, CA 90095-1772 (e-mail: ovehren@ucla.edu).

Initially submitted January 2, 2019; accepted for publication June 3, 2020.

Statewide population-based cohort and sibling-comparison design using California birth records (n = 2,015,104)

Adjusted OR: 1.15 (1.04-1.26)
Within siblings: 1.03 (0.64-1.68)

Tentative recommendations

- Sibling comparisons may be most useful when you *honestly* suspect that a completely shared factor, e.g. childhood SES, explains the whole association
- Sibling comparisons should still be adjusted for confounders when possible!
- Consider estimating measurement error in exposure, or performing quantitative bias analysis
- Sibling comparisons should not be used when the outcome of one sibling influences the exposure or outcome of the second
- You need well powered studies to separate the different possible explanations!

Thank you for your attention!

References:

- Frisell T. Invited Commentary: Sibling-Comparison Designs, Are They Worth the Effort? Am J Epidemiol. 2021;190(5):738-741
- Sjölander A, Frisell T, Oberg S. Sibling Comparison Studies. ANNUAL REVIEW OF STATISTICS AND ITS APPLICATION 2022 9; 71-94

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