

## Limitations (With Apologies to Sir Philip Sidney)

It is most true,<sup>1</sup> our study did observe

But a selected few; and that this subpart

Could from the broader population swerve,

Our estimate thus might from truth depart.

It is most true, what we with stats compute,

Confounded is, whence truth cannot be carved;

Adjustment helps, still we do not dispute

Some bias stands; of real truth we are starved.

True, who was exposed is cloaked indeed,

Whereof our measure can be but a shade,

That “Treated” were dosed is not guaranteed;

True, on earth are no firm deductions made,

Skeptics might thus our conclusions reject;

True; and yet true, we hope we are correct.

 **Stephen J. Mooney**

Department of Epidemiology, University of Washington, Seattle, WA

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1. Sidney SP. *Astrophil and Stella 5: It is most true, that eyes are formed to serve*. Poetry Foundation. Available at: <https://www.poetryfoundation.org/>

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[sjm2186@uw.edu](mailto:sjm2186@uw.edu)

Lines: 14 (i.e., a sonnet): The poem is a reference to *Astrophil and Stella 5*: <https://www.poetryfoundation.org/poems/50416/astrophil-and-stella-5-it-is-most-true-that-eyes-are-formed-to-serve>.

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poems/50416/astrophil-and-stella-5-it-is-most-true-that-eyes-are-formed-to-serve. Accessed 27 October 2025.

## Re: Confounders, Mediators, or Colliders

### What Types of Shared Covariates Does a Sibling Comparison Design Control For?

#### To the Editor:

I write regarding Sjölander and Zetterqvist's<sup>1</sup> methodological contribution on sibling comparison designs. While their framework helpfully distinguishes between confounders, mediators, and colliders, their claim that shared family environment may be a mediator does not clearly differentiate between biological mechanisms operating during pregnancy and social pathways operating through postnatal family circumstances. If a researcher's scientific question concerns the biological impact of parental age, then family environment is a confounder, rather than a mediator, and conditioning on it in a sibling design would not remove but rather help isolate the portion of the effect of scientific interest.

Mediators are variables that lie on the causal pathway from exposure to outcome. Sjölander and Zetterqvist write that in a prior sibling study of maternal age and attention deficit hyperactivity disorder (ADHD), attenuated within-family findings might reflect mediation through a shared family

environment: that young maternal age leads to “financially difficult family situations” that increase ADHD risk.<sup>1,2</sup> To classify shared family environment as a mediator, one must posit that parental age causally shapes the environment in which children are raised in a way that itself produces the outcome. But when the biological effects of age are under study—for example, through mechanisms related to gamete quality, placental function, or in-utero biological processes—we generally seek to isolate prenatal pathways that do not plausibly operate through the postnatal family environment. Family environment could potentially modify the magnitude of biological effects (i.e., if the biological impact of maternal age were larger or smaller depending on socioeconomic circumstances), but effect modification would not imply mediation, and would not change its status as a potential confounder, associated with both the exposure and outcome.

If we were interested in the total biological and social effects of maternal age, family environment might constitute a mediator. But that alternative research question would examine maternal age as a social marker rather than a biological exposure. Put another way, for an expectant parent trying to understand biological effects—for example, the ADHD risk for their first child if they give birth at 40 compared to 30, all else equal—adjusting for family environment would remove confounding from socioeconomic factors, providing better estimates of the causal quantity of interest.

Whether a variable acts as a confounder or mediator depends on the specific causal question. For biological hypotheses about maternal age effects (or other prenatal exposures, such as acetaminophen<sup>3</sup>), shared family environment confounds rather than mediates, making sibling comparison designs often well-suited for isolating biological effects.

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Correspondence: Alyssa Bilinski, Brown University School of Public Health, 121 South Main Street, 8th Floor, Providence, RI 02903. E-mail: [alyssa\\_bilinski@brown.edu](mailto:alyssa_bilinski@brown.edu).

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**Alyssa Bilinski**

Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, RI  
Department of Biostatistics, Brown University School of Public Health, Providence, RI

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