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Clarification and justification of within-family analyses of advancing paternal age at childbearing

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Abstract

We appreciate having the opportunity to respond to Sonis' concerns¹ regarding our manuscript on advancing paternal age (APA) at childbearing.² It is important to note that the population and within-family estimates respond to different research questions. The population estimates examine how common it is that offspring born to fathers of different ages have psychopathology. The comparison of differentially exposed siblings and cousins using fixed effects models, on the other hand, examine the magnitude of the risk for psychopathology in offspring associated with paternal age while holding other factors constant.

Sonis¹ states that differences between the fixed effects and both the population and adjusted models (which included covariates) raise concerns about the validity of the fixed effects models. He then argues about bounds on confounding bias by using one confounder (i.e. "stress") as an example. Yet, the fixed effects model adjusts for many confounders; sibling-comparisons account for every factor that makes siblings similar. Thus, even if the effect of each confounder may be small, the accumulated effect may very well be large. Furthermore, our findings are not likely explained by misspecified fixed effects models, as we found commensurate results from sensitivity analyses using a different analytical approach.³

Our findings may be explained by confounders that are positively correlated with the exposure and negatively associated with the outcome, or the other way around. Sonis implies that such confounders are rare. We strongly disagree. Analyses in our appendix illustrated that several covariates in our study that were positively correlated with APA are inversely correlated with psychiatric disorders. Notably, estimates from adjusted models controlling for those covariates went in the opposite direction of the population estimates for several outcomes. For example, see the population and adjusted estimates for substance use problems and suicide attempts. Furthermore, separate studies have found that individuals with ADHD, schizophrenia, and bipolar disorder; their healthy siblings; and men who have children with women with these disorders were more likely to have children as teenagers.⁴ Thus, there are many familial factors that are negatively correlated with APA and positively correlated with psychiatric problems.

The large magnitude of our fixed effects model estimates may be partly explained by the non-collapsibility feature of hazard ratios.⁵ This feature implies that adjusting for (by conditioning on) covariates that are associated with the outcome but independent of the

exposure (i.e. APA) will amplify the magnitude of the statistical association. Because the fixed effects model controls for a large set of (unmeasured) covariates, the potential for “non-collapsibility effects” is large as well. We emphasize that this is not a bias; it simply reflects that parameters in adjusted and fixed effect models have different interpretation than population estimates. We also emphasize that non-collapsibility cannot change the sign of association, or induce an association, only amplify its magnitude.

Sibling-comparisons have a number of weaknesses, as we have acknowledged.^{e.g., 6} Furthermore, quasi-experimental approaches are not RCTs and, thus, cannot rule out all possible confounds. As such, causal inferences regarding APA will require converging evidence from multiple research designs and samples.

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