Letters to the Editor

RE: “ANALYZING RISKS OF ADVERSE PREGNANCY OUTCOMES”

In a recent article, Kramer et al. (1) addressed the “gestational age paradox,” in which an exposure that exerts a harmful influence overall appears protective among babies born preterm. The authors illustrated this phenomenon by comparing the perinatal mortality of singletons with that of twins. They proposed that the observed reversal of comparative risk across the gestational age range is due to a type of selection bias (1). However, their proposed selection bias requires more evidence to be convincing.

We previously suggested a different possible mechanism for this paradox (2, 3). Using simple scenarios, we posited unmeasured factors that could cause both early birth and neonatal death. Such factors would make gestational age at birth a “collider” in the analysis of factors (such as twinning) that also cause early birth. The unmeasured factors would produce a form of selection bias (4), in that babies born early are not a random sample of the population of fetuses. This bias distorts analyses that condition on gestational age at birth. We show explicitly in our scenarios how unmeasured factors can make a harmful exposure appear protective at early gestational ages (2, 3).

Kramer et al. regard our assumption of unmeasured factors as unnecessarily speculative. They prefer their explanation as more parsimonious and thus more plausible. Perhaps they are right—but their own explanation lacks an explicit demonstration. The authors argue indirectly by analogy and by broad resolution of the paradox through fetuses-at-risk analysis. Can they show directly, as we did—in a simple numerical example with realistic parameters—the precise mechanism of the selection bias they propose, and how that mechanism could produce the empirical paradox?

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REFERENCES

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THE AUTHORS REPLY

We thank Wilcox et al. (1) for their comments. In their letter, Wilcox et al. requested an “explicit demonstration” of our explanation for the crossover paradox (2). Again, we do not deny that uncontrolled common causes of preterm birth and neonatal death can create bias in estimates of the association between causes of preterm birth and neonatal death. Basso and Wilcox (3) demonstrated that confounding due to the simultaneous occurrence of 2 rare factors, both of which increase neonatal mortality (one of which also causes a large increase in birth weight, while the other causes a large decrease in birth weight), can bias associations between exposures that cause preterm birth and neonatal death among preterm infants. The possibility that this hypothetical, complicated scenario can lead to an apparently protective effect of the study exposure on neonatal death does not lend it much credibility, in our view.

Instead, we claim that the higher stillbirth and livebirth rates at earlier gestational ages lead to a survivorship bias. Exposed fetuses that survive to later gestational ages are a selected subset of all exposed fetuses who have not succumbed earlier in gestation. Conditioning on survival to a later gestational age ignores earlier deaths. It also removes from the denominator of the risk expression those fetuses that remain unborn at the later gestational age, who will thereby continue their selective