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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