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


Allen J. Wilcox, Clarice R. Weinberg, Olga Basso, and Quaker E. Harmon (e-mail: wilcox@niehs.nih.gov)

1 Epidemiology Branch, National Institute of Environmental Health Sciences, Durham, NC
2 Biostatistics Branch, National Institute of Environmental Health Sciences, Durham, NC
3 Department of Obstetrics and Gynecology, McGill University Health Centre, Royal Victoria Hospital, Montreal, QC, Canada
4 Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montreal, QC, Canada

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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
advantage into later gestation. As we have recently pointed out (4), the same phenomenon has been observed with other known causes of preterm birth, including maternal smoking, black (vs. white) race in the United States, twin (vs. singleton) status, primiparity, and maternal short stature.

We do not require hypothetical examples to demonstrate how the bias arises. The attached Table 1 is taken from Tables 1 and 2 in the paper by Joseph et al. (5) and compares birth and neonatal death outcomes at 32–36 completed weeks’ gestation among Canadian twins and singletons born from 1991 to 1997. The livebirth and stillbirth rates are higher among twins, yet the early neonatal (first-week) death rates among the livebirths are lower at each gestational week. When expressed as a proportion of all fetuses at risk (still alive) at the beginning of each week, however, the rate of early neonatal death is higher among twins at each week, thereby demonstrating the bias caused by conditioning on livebirth at that week.

Flanders et al. (6, 7) have demonstrated how earlier mortality can bias later time-specific risks of exposure, and they have recently illustrated the bias with obesity as the exposure, end-stage renal disease as the intermediate event, and subsequent mortality as the outcome. Earlier mortality from any cause results in the appearance of a protective effect of obesity for mortality among persons who develop end-stage renal disease. Just as no uncontrolled confounders of the association between end-stage renal disease and mortality are necessary to bias the effect of obesity on mortality among the obese, none is necessary to bias the effect of preterm birth on mortality among liveborn twins born preterm.

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REFERENCES


Michael S. Kramer1,2, Xun Zhang1, and Robert W. Platt1,2 (e-mail: michael.kramer@mcgill.ca)

1 Department of Pediatrics, Faculty of Medicine, McGill University, Montreal, QC, Canada
2 Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montreal, QC, Canada

Table 1. Birth and Neonatal Death Outcomes at 32–36 Completed Weeks’ Gestation Among Canadian Twins Born From 1991 to 1997 Versus Singletons Born During the Same Perioda

<table>
<thead>
<tr>
<th>Gestational Age, weeks</th>
<th>No. of FAR</th>
<th>No. of Stillbirths</th>
<th>Stillbirth Rate (per 10,000 FAR)</th>
<th>No. of Livebirths</th>
<th>Livebirth Rate (per 10,000 FAR)</th>
<th>No. of ENDS</th>
<th>END Rate (per 1,000 Livebirths)</th>
<th>END Rate Among FAR (per 10,000 FAR)</th>
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</thead>
<tbody>
<tr>
<td><strong>Singletons</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>1,593,933</td>
<td>288</td>
<td>1.8</td>
<td>4,287</td>
<td>26.9</td>
<td>125</td>
<td>29.2</td>
<td>0.8</td>
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<tr>
<td>33</td>
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<td>5,758</td>
<td>36.2</td>
<td>118</td>
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<td>34</td>
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<td>10,661</td>
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<td>144</td>
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<td>2.0</td>
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<td>2.8</td>
<td>41,962</td>
<td>270.1</td>
<td>194</td>
<td>4.6</td>
<td>1.3</td>
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<td>5.5</td>
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<td>28</td>
<td>12.0</td>
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<td>2,307.1</td>
<td>15</td>
<td>2.8</td>
<td>6.4</td>
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<td><strong>Sum</strong></td>
<td>1,688</td>
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<td>80,796</td>
<td>719</td>
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</table>

Abbreviations: END, early neonatal death; FAR, fetuses at risk.

* Based on the paper by Joseph et al. (5).