Commentary

No Rates Were Harmed in the Making of This Paper: Response to Critiques

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The debate featured in this issue highlights the complexity of identifying the ‘appropriate’ denominator for estimating gestational-age-specific risk of postnatal endpoints. According to Caughey and Snowden,1 interpretable estimates for most neonatal endpoints can only be obtained with live births as the denominator. Smith2 notes how neither live births nor fetuses perfectly capture the population at risk of neonatal death, although analysis based on the former may be less flawed. As some conditions diagnosed in childhood may nevertheless start in utero,3–5 Schisterman and Lindsey6 emphasize how the ‘correct’ approach can only be evaluated given a specific question. Joseph7 favours fetuses as the denominator in instances involving outcomes with a plausible prenatal origin.

Although most researchers agree on fetuses as the denominator for several endpoints (e.g. antepartum stillbirth, preterm birth, and pregnancy complications), risk of outcomes identified after birth is generally measured among live births, despite the limitations imposed by such a choice.2,8 These ‘conventional’ estimates are predictive and clinically useful but cannot be relied upon for causal interpretation, given how they often result in overall harmful exposures appearing to be protective at preterm weeks. The extended fetuses-at-risk (FAR) formulation is touted as providing causally interpretable estimates,7,9 although what is meant by ‘causal’ is unclear. The aim of my paper8 was to show how, due to their dependence on the probability of live birth, week-specific FAR rates of postnatal endpoints can be higher in pregnancies exposed to a factor that reduces length of gestation, regardless of whether such a factor actually increases risk.8 Given that my demonstration relied entirely on simple algebraic re-formulation of the week-specific FAR rate (as used, e.g., in Joseph et al.9), I was surprised by some of the commentators’ reactions.6,7 There was no model; no rates were harmend, modified, or burdened with assumptions in the making of my paper. All that was done was to multiply both the numerator and denominator of the week-specific FAR rate by the number of live births at that week – that is, multiplication by 1.0 – an accomplishment that can hardly be characterized as ‘courageous’.7 Schisterman and Lindsey criticize my formula as being ‘overly simplified’,7 compared with that of Kramer et al.10 neglecting that the latter measured the composite outcome of stillbirth and neonatal death. My formula, on the other hand, applies to any postnatal outcome, be it cerebral palsy, which often originates prenatally,11 or diaper rash, which – presumably – does not. Regardless, neither can be diagnosed until after live birth. Schisterman and Lindsey’s criticism is puzzling also in light of the fact that Schisterman co-authored a commentary12 to Kramer et al.10’s paper above,10 remarking on how using composite outcomes for competing events changes the question. Unlike Joseph,7 I share this perspective and, with others,1,5 I believe that an association between an exposure and a childhood condition is interpretable only when estimated among those at risk, although assessment of the exposure effect on competing outcomes would be useful.5,8 Knowing the question is thus not only necessary to evaluate whether an answer is correct,8 but also to make sense of it (or it might as well be ‘forty-two’, the answer to the ultimate question that nobody knew13). If we could identify the fetuses that would have developed the endpoint of interest regardless of whether and when they were born, FAR analyses would be appropriate in many situations. In my example, the extended FAR approach applied to a simple scenario failed to yield a causally interpretable answer to a specific question.8 Could it provide the ‘correct’ answer in a different scenario or to a different question? Possibly, but –

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Paediatric and Perinatal Epidemiology, 2016, 30, 25–27
with the appropriate distinctions – my counterexample does to the sweeping claim that the extended FAR approach produces causal interpretable estimates what observing a black swan does to the statement that ‘all swans are white’.

Schisterman and Lindsey note that, in some of my papers, I do not refer to collider-stratification bias when discussing unmeasured confounding of the association between birthweight (or gestational age) and mortality. However, in this context, unmeasured confounding and collider-stratification bias are the same problem, and I prefer to avoid jargon that may be unfamiliar to non-epidemiologists. Nevertheless, we do mention collider-stratification bias when it is central to the discussion.

Not unexpectedly, Joseph disagrees with several things I say (as well as with some I do not say). Although recognizing that my criticism provides insight into FAR rates, his response does not address its broader implications and focuses instead on side issues. For example, he states that stillbirth is not one event but two: fetal death and birth. When writing that antepartum stillbirth (which may indeed be a misnomer) is a single event, I acknowledged that the timing of death may be measured with error. However, unlike cerebral palsy (or autism), fetal death can be detected prior to birth. Joseph likens FAR rates to age-specific mortality rates of cancer. Although that may be an apt analogy for stillbirth, it is not for postnatal events, where rates refer to ‘age’ at birth and not to age at the time of the outcome, which can occur much later. FAR rates of postnatal endpoints are thus comparable with death rates of a given cancer as a function of age at diagnosis, and suffer from the same dangers. As an example, consider two populations with identical underlying age-specific distributions of incidence and mortality of cancer X. The introduction of universal screening leading to earlier diagnosis in only one of the populations will result in the age-specific incidence distribution shifting to younger ages. If early diagnosis has no impact on prognosis, age-specific mortality rates (based on age at death) will remain the same, but mortality rates based on age at diagnosis will shift to younger ages in the screened population, which might be erroneously interpreted as suggesting that screening is associated with earlier death. This is equivalent to the situation where FAR rates are higher in infants exposed to a factor whose sole effect is to cause earlier birth. Yet, Joseph ignores this point and keeps affirming that the extended FAR formulation ‘resolves both the stillbirth and the neonatal mortality crossover’.

I agree with Joseph that it is reasonable for a woman with severe pre-eclampsia to inquire about the potential risk of stillbirth, neonatal death, and cerebral palsy. However, I strongly doubt that such a woman would benefit from learning about risk of neonatal death and cerebral palsy based on fetuses. Indeed, being aware of the dangers of preterm delivery, she would be mystified by the sharply rising rates of these endpoints with increasing gestational age.

Finally, Joseph invokes Whewell’s ‘consilience of inductions’ in support of the extended FAR formulation. First, this criterion applies to a scientific theory, whereas FAR is simply a different way to calculate risk. Second, although antepartum stillbirths would, by definition, be prevented by delivering fetuses as early as possible, nobody would consider such an option, and FAR rates are singularly unhelpful in determining the optimal timing of delivery to reduce neonatal morbidity and mortality. Third, the only difference between the week-specific FAR and conventional relative risks is that the former is multiplied by the ratio of live birth between exposed and unexposed, which goes a long way towards explaining the ‘uncrossing’ of mortality curves with exposures that shorten length of gestation. As long as live birth is necessary for (former) fetuses to contribute to the numerator, the claim that extending the FAR approach to postnatal endpoints will move the field forward remains unsubstantiated.

References

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Paediatric and Perinatal Epidemiology, 2016, 30, 25–27

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