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No right answers without knowing your question

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In this issue of *Paediatric and Perinatal Epidemiology*, Basso[1] describes and contrasts the fetuses at risk, or FAR, approach to the "conventional" approach for the evaluation of the effects of perinatal exposures on post-delivery outcomes. Basso provides a thoughtful evaluation of both methods. While the author suggests that both approaches might be problematic for causal inference under different scenarios (of varying likelihood), there was particularly more criticism towards the fetuses at risk approach.

One of our favorite quotes is from the prominent statistician George Box,[2] in which he said, "All models are wrong, but some are useful." Far from an indictment of statistical models, Box's statement can be taken to mean that even when complex realities are not exactly represented by simple fitted models, much can be learned. In this case, neither model (nor any model in general) can guarantee a result with a causal interpretation for every exposure, gestational age, and outcome, whether pre- or post-delivery. Therefore, neither the fetuses at risk nor the conventional method should be considered more causal than the other as a rule. Either can be used to approximate a causal question under certain assumptions and settings, with the appropriate selection heavily dependent on the study-specific objective.

In prior attempts to explain the "birthweight paradox",[3-6] Basso claims this paradox is a result of only an unmeasured strong confounder between live birth and the outcome of interest.[7, 8] As such, the conventional approach, as discussed in Basso's current article,[1] is susceptible to the pitfalls of collider stratification or selection bias.[5] However, the explanation provided for this bias is only partially correct, as has been examined extensively.[3-6, 9] Although the presence of strong confounding is necessary to induce the paradox, it is not sufficient, as previously espoused.[3-6] As we and others proposed over a decade ago, one explanation for crossover paradoxes is conditioning on a collider.[3, 10-13] Thus, to induce such bias one needs unmeasured confounding *coupled with* stratification/

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adjustment for a colliding variable, such as being born. We previously demonstrated that the collider—birth —is a time varying event; selection bias will occur when the exposure of interest either affects or shares causes with the timing of birth.[3] Importantly, however, the issue of selection (i.e., collider stratification) bias in these methods was not discussed by Basso.[1]

To correctly assess a causal question between a perinatal exposure and a postnatal outcome using the conventional method, we previously described three approaches to help draw correct inferences when the effect of interest is such that it may be obtained by conditioning on an intermediate (e.g., live birth).[6] These approaches include conditioning on the predicted risk of the intermediate, conditioning on the intermediate itself through sensitivity analysis, or conditioning on the principal stratum.[6] Furthermore, in certain cases, if the research question concerns time varying confounders affected by prior exposures, a reweighting approach such as marginal structural models[14] or g-estimation[15] can account for the collider stratification bias under certain assumptions and availability of data.

If we are confident that we can correctly specify a model using appropriate methods discussed above, this leads us to question another assumption of Basso's postulate: if the research question focuses on a postnatal outcome (as compared to antepartum stillbirth), Basso criticises the “extension of the fetuses at risk approach to outcomes that can only be defined among live births” to answer causal questions. This debate provides an opportunity to reexamine how we should choose a model based on the specific research question at hand. Is the intended question to ask whether a perinatal exposure causes an outcome only in a live born baby, or is the intended question to ask whether an exposure causes an outcome, which may be hidden in a gestating fetus and is only revealed after delivery of a live baby? In other words, are fetuses *in utero* immune to the outcome of interest while they are *in utero*? For some perinatal outcomes, it may seem far-fetched to consider an unborn fetus at risk.[16] However we must carefully consider the outcome of interest in the context of our causal question; chiefly, we must distinguish our inability to diagnose the outcome from immunity to the outcome (or its biological process) during the time *in utero* and prior to diagnosis.

In other terms, the primary basis of Basso's argument lies in the overly simplified algebraic relationship that equates the probability of the outcome of interest as being directly proportional to the live birth rate at a given week of gestational age. However, this claim neglects the full mathematical expression to calculate the probability of the outcome described by Kramer and colleagues.[17] Specifically, Basso's argument assumes the second term of the conditional probability expression is equivalent to zero (i.e., that those not yet born are immune to the outcome):

$$Pr\,(Yi{=}1|X{=}x) = \underbrace{Pr\,(Yi{=}1|X{=}x, LBi{=}1)\,Pr\,(LBi{=}1)}_{\frac{Y_i}{LB_i}\times\frac{LB_i}{F_i}} + \underbrace{Pr\,(Yi{=}1|X{=}x, LBi{=}0)\,P\,(LBi{=}0)}_{\text{Assumed always 0 by Basso}^1}$$

where Y_i is the outcome at a given gestational age *i*, LB is being born alive, X is the exposure of interest, and F is the fetuses at risk.

To illustrate our logic, consider autism as an example. Autism is currently only diagnosed at or beyond age 2. However, increasing evidence indicates there are very early developmental changes in the brain[18] that are related to autism. Thus, this disease process may occur earlier, but the clinical signs indicative of autistic behavior are evident (and identified) much later. In this case, should all children, versus only those reaching age 2, be in the denominator? The answer to this depends on the specific question being one of diagnosis versus development of the condition. If you systematically exclude those not reaching age 2, you are invoking, rather implicitly, the assumption that children under age 2 are immune from autism (i.e., a form of informative censoring). Whether such an assumption is true or untrue is a topic for another debate; however, the researcher must be aware that this is the assumption being made.

As Hutcheon and Platt[19] eloquently stated, “Perhaps it is time to begin considering each situation individually and to establish the most appropriate denominators based on the research question, the outcome of interest, and the hypothesised timing and mechanism of the exposure.” In epidemiology, this means first framing a specific question of interest, and in the context of that question, carefully considering “who is the source population?” and “who is at risk of the outcome of interest?” In this debate, is being born alive necessary to estimate the effect on the outcome of interest? Or was it merely a selection process on the pathway from exposure to outcome? Ultimately, the only way to derive right answers is to know your specific research question. Thus, neither the conventional nor fetuses at risk method (nor any other method) is globally more correct or more flawed for causal inference regarding effects of perinatal exposures on postnatal outcomes. Can any researcher discount a particular method without a specific question in mind? The determination of which approach is most correct (or least so) for approximating the truth depends on the particular scientific question (i.e., scenario) coupled with a solid understanding of available approaches. Generalisations based on theoretical scenarios should not remain our way of evaluating the utility of different methodologies.

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References

1. Basso O. Implications of using a fetuses-at-risk approach when fetuses are not at risk. Paediatric and Perinatal Epidemiology. 2015 In press.
2. Box GEP. Science and Statistics. Journal of the American Statistical Association. 1976; 71:791–799.
3. Hernan MA, Schisterman EF, Hernandez-Diaz S. Invited commentary: composite outcomes as an attempt to escape from selection bias and related paradoxes. American Journal of Epidemiology. 2014; 179:368–370. [PubMed: 24287470]
4. Hernandez-Diaz S, Schisterman EF, Hernan MA. The birth weight "paradox" uncovered? American Journal of Epidemiology. 2006; 164:1115–1120. [PubMed: 16931543]
5. Hernandez-Diaz S, Wilcox AJ, Schisterman EF, Hernan MA. From causal diagrams to birth weight-specific curves of infant mortality. European Journal of Epidemiology. 2008; 23:163–166. [PubMed: 18224448]
6. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. Epidemiology. 2012; 23:1–9. [PubMed: 22157298]
7. Basso O, Wilcox AJ, Weinberg CR. Birth weight and mortality: causality or confounding? American Journal of Epidemiology. 2006; 164:303–311. [PubMed: 16847040]
8. Basso O. Reproductive Epidemiology in an Evolutionary Perspective: Why Bigger May Not Be Better. Current Epidemiology Reports. 2014; 1:98–101.
9. Whitcomb BW, Schisterman EF, Perkins NJ, Platt RW. Quantification of collider-stratification bias and the birthweight paradox. Paediatric and Perinatal Epidemiology. 2009; 23:394–402. [PubMed: 19689488]
10. Kramer MS, Zhang X, Platt RW. Commentary: Yerushalmy, maternal cigarette smoking and the perinatal mortality crossover paradox. International Journal of Epidemiology. 2014; 43:1378–1381. [PubMed: 25301864]
11. Platt RW, Joseph KS, Ananth CV, Grondines J, Abrahamowicz M, Kramer MS. A proportional hazards model with time-dependent covariates and time-varying effects for analysis of fetal and infant death. American Journal of Epidemiology. 2004; 160:199–206. [PubMed: 15257989]
12. VanderWeele TJ. Commentary: Resolutions of the birthweight paradox: competing explanations and analytical insights. International Journal of Epidemiology. 2014; 43:1368–1373. [PubMed: 25301862]
13. Yerushalmy J. The relationship of parents' cigarette smoking to outcome of pregnancy--implications as to the problem of inferring causation from observed associations. International Journal of Epidemiology. 2014; 43:1355–1366. [PubMed: 25301860]
14. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000; 11:550–560. [PubMed: 10955408]
15. Robins JM, Blevins D, Ritter G, Wulfsohn M. G-estimation of the effect of prophylaxis therapy for Pneumocystis carinii pneumonia on the survival of AIDS patients. Epidemiology. 1992; 3:319–336. [PubMed: 1637895]
16. Paneth N. Invited commentary: the hidden population in perinatal epidemiology. American Journal of Epidemiology. 2008; 167:793–796. author reply 797-798. [PubMed: 18343876]
17. Kramer MS, Zhang X, Platt RW. Analyzing risks of adverse pregnancy outcomes. American Journal of Epidemiology. 2014; 179:361–367. [PubMed: 24287468]
18. Chen JA, Penagarikano O, Belgard TG, Swarup V, Geschwind DH. The emerging picture of autism spectrum disorder: genetics and pathology. Annual Review Pathology. 2015; 10:111–144.
19. Hutcheon JA, Platt RW. The missing data problem in birth weight percentiles and thresholds for "small-for-gestational-age". American Journal of Epidemiology. 2008; 167:786–792. [PubMed: 18343882]