LETTER TO THE EDITOR

RE: WHY EVIDENCE FOR THE FETAL ORIGINS OF ADULT DISEASE MIGHT BE A STATISTICAL ARTIFACT: THE "REVERSAL PARADOX" FOR THE RELATION BETWEEN BIRTH WEIGHT AND BLOOD PRESSURE IN LATER LIFE

Tu et al. (1) recently showed how adjustment for current weight tends to increase the inverse association between birth weight and blood pressure. They assumed that current weight is positively correlated with blood pressure and birth weight, and that birth weight and blood pressure are only weakly correlated. They tested the effect of adjustment by simulating different correlation scenarios.

Their argument focuses on how adjusting for current weight alters the association. This depends only on the correlation structure, so the case can be made explicitly, more elegantly and without loss of generality by expressing the three variables as z-scores, i.e. with mean zero and standard deviation one. This avoids the need to specify means and standard deviations for the variables.

Assume that the correlations of birth weight and current weight with blood pressure are r_1 and r_2 respectively, while the birth weight vs current weight correlation is r_{12}. In the z-score regression of blood pressure on birth weight, the unadjusted birth weight coefficient is equal to the correlation r_1, while adjusted for current weight the birth weight coefficient is $\beta_1 = (r_1 - r_2 r_{12}) / (1 - r_{12}^2)$.

The adjusted coefficient is more negative than the unadjusted coefficient (i.e. $\beta_1 < r_1$) if $r_1 < r_2 / r_{12}$, though if r_1 is sufficiently large β_1 may still be positive. The stronger condition $r_1 < r_2 r_{12}$ ensures that $\beta_1 < 0$. Thus under weak conditions the adjustment increases the inverse association between birth weight and blood pressure. This confirms the findings of Tu et al.

Note that r_2 and r_{12} need not be positive. As long as they are of the same sign, either positive or negative, the two conditions hold. So the findings apply quite generally to situations where a covariate correlates in the same direction with birth weight and outcome.

Tu et al. argue that adjusting for a confounder on the causal pathway, i.e. current weight, invalidates the inference that birth weight has an inverse association with blood pressure. The algebra above shows that such an adjustment is very likely to

make the association more negative, but it does not help to decide whether or not such an adjustment is valid. Colleagues and I have argued elsewhere that the change in sign of the weight vs outcome correlation over time indicates the importance of weight change as opposed to birth weight (2, 3).

REFERENCES

1. Tu YK, West R, Ellison GTH, et al. Why evidence for the fetal origins of adult disease might be a statistical artifact: the "reversal paradox" for the relation between birth weight and blood pressure in later life. Am J Epidemiol 2005;161:27-32.

2. Lucas A, Fewtrell M, Cole TJ. Fetal origins of adult disease - the hypothesis revisited. BMJ 1999;319:245-9.

3. Cole TJ, Fewtrell M, Lucas A. Early growth and coronary heart disease in later life. Analysis was flawed [letter]. BMJ 2001;323:572-3.

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