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To the Editor We read with interest the article by Weisz et al[1] evaluating the association between ductal ligation and neurodevelopmental outcome in preterm infants.[1] We fully agree that postnatal events may affect outcome. Although the authors included an extensive list of morbidities and therapies as possible confounders, we suggest nutritional intake should be considered as a covariate for neurodevelopmental outcome.

We previously evaluated neurodevelopmental outcomes of 112 preterm infants at 2 years of corrected age, but related this to protein and energy intake of the first 2 weeks of life.[2] Male sex and patent ductus arteriosus were found to be the greatest negative determinants of neurodevelopment, with an increased risk for adverse outcome. Infants with patent ductus arteriosus received statistically significant less protein and energy during the first 2 weeks compared with infants without patent ductus arteriosus.

While a number of studies, as mentioned by Weisz et al,[1] associated ductal ligation with impaired outcome, none of these studies accounted for nutritional intake. Wickremasinghe et al[3] discontinued enteral feedings in the "early ductal ligation" group, while with the more "selective approach," enteral feedings were continued. Fluid restriction and cautious increment of enteral feeding is a generally accepted measure of conservative treatment of patent ductus arteriosus. In many cases, this is at the expense of the daily required nutritional intake. Ductal ligation usually serves as the last treatment option and thereby prolongs the period of low nutritional intake.

We speculate that the impaired outcome after ductal ligation, as mentioned in many studies, is not only a result of surgery itself but also the consequence of undernutrition in a period of rapid brain growth. Weisz et al[1] did not report nutritional intake; therefore, any effect of nutrition on their positive outcome for ductal ligation compared with other studies remains speculative.

In light of the previously mentioned data, we suggest that future studies should evaluate outcome of prematurity related clinical conditions, such as treatment of patent ductus, in relation to nutritional intake.

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Published Online: August 28, 2017. doi:10.1001/jamapediatrics.2017.2612

Conflict of Interest Disclosures: None reported.

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In Reply We thank Slaughter and Klebanoff for their thoughtful comments regarding possible bias of the association between patent ductus arteriosus ligation and mortality owing to survivor treatment selection. We agree that our subcohort analysis may be undersensitive, although potentially for a reason other than immortal time bias. In our study, survivor treatment selection bias comprises both immortal time bias and bias owing to confounding by contraindication.

Immortal time bias may be mitigated by time-dependent Cox regression (where person-time of ligated infants accrued in the preoperative period is attributed to the medically treated group) when estimating the hazard of in-hospital death, although this analytical method is not readily applicable to the binary primary composite outcome of our study (death or neurodevelopmental impairment at 18- to 24-month follow-up). As suggested, we performed a time-dependent Cox regression analysis post hoc and the hazard of in-hospital death remained significantly lower in ligated infants. We speculate that confounding by contraindication (where medically treated infants with higher illness severity are deemed unsuitable for surgery) accounts for most of the survival bias in our study. A randomized trial of ligation vs conservative treatment may be ideal for unbiased estimation of the effect of ligation on mortality under these conditions because infants whose higher illness severity precludes patent ductus arteriosus surgery would not be enrolled.

Furthermore, we agree that marginal structural models (MSM) are an ideal statistical approach, and we designed this study a priori to use both MSM and multivariable logistic regression. As a first step in MSM analysis, pooled logistic regression was used to estimate stabilized inverse probability of treatment weights, adjusting for antenatal, postnatal, and time-dependent confounders arising prior to ductal closure. Weighted logistic regression analysis was subsequently used to evaluate the association between ligation and outcomes.[1] The associations of ligation and outcomes estimated using MSM were similar to those obtained by multivariable logistic regression analysis, and we presented the latter for analytical parsimony.