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# The Birth Weight ''Paradox'' Uncovered?

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Low birth weight (LBW) infants have lower infant mortality in groups in which LBW is most frequent. For example, in 1991, US infants born to smokers had higher risks of both LBW and infant mortality than infants born to nonsmokers. However, among LBW infants, infant mortality was lower for infants born to smokers (relative rate = 0.79). There are competing theories regarding this so-called ''paradox.'' One is that maternal smoking is beneficial for LBW infants. The authors use causal diagrams to show that, even in the absence of any beneficial effect of smoking, an inverse association due to stratification on birth weight can be found. This variable is affected by the exposure of interest and shares common causes with the outcome. That is, LBW infants born to smokers may have a lower risk of mortality than other LBW infants whose LBW is due to causes associated with high mortality (e.g., birth defects). Under realistic causal diagrams, adjustment for birth weight is unwarranted when the analytical goal is to estimate overall effects of prenatal variables on infant mortality. Even for estimating direct effects of prenatal variables, adjustment for birth weight may be invalid when there is an unmeasured common cause of LBW and mortality. An appropriate justification for conditioning on birth weight requires specifying 1) the causal question motivating this analytical approach and 2) the assumptions regarding the proposed underlying biologic mechanisms.

birth weight; confounding factors (epidemiology); infant, low birth weight; infant mortality; smoking

Abbreviations: CI, confidence interval; DAG, directed acyclic graph; LBW, low birth weight.

***Editor's note:*** *An invited commentary on this article appears on page 1121, and the authors' response appears on page 1124.*

Birth weight is a strong predictor of neonatal and infant mortality (1). Probably for that reason, and because birthweight data are readily available, investigators have frequently stratified on birth weight when evaluating the effect of other risk factors (e.g., maternal smoking (2), multiple pregnancies (3), placenta previa (4), Black race (5)) on infant mortality. This stratification often produces a crossover of the birth-weight-specific mortality curves: Low birth weight (LBW) infants in groups with a high prevalence of LBW have a lower mortality rate than LBW infants in groups with a low prevalence of LBW, whereas the opposite is true for normal-weight infants. This phenomenon is known as the ''birth weight paradox,'' and it has been a source of controversy for decades (1). For example, when studies compared mortality rates between LBW infants born to smokers and nonsmokers, infants of smokers had lower mortality rates (2). Although it is widely accepted that infants born to mothers who smoke have lower birth weights and are at higher risk of neonatal mortality (2), it has been suggested that the effect of maternal smoking is modified by birth weight in such a way that smoking is beneficial for LBW babies (6).

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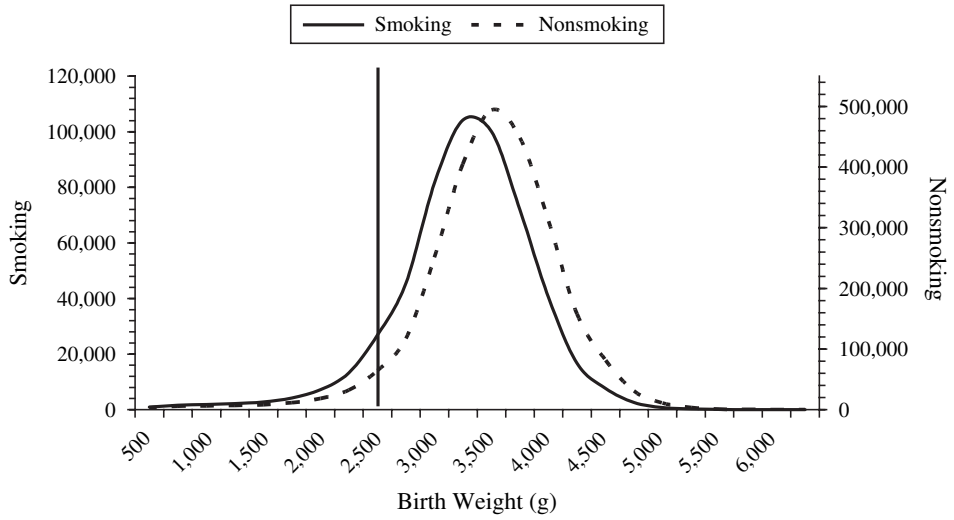


**FIGURE 1.** Distribution of birth weights among infants born to smokers and nonsmokers, United States, 1991 (national linked birth/infant-death data, National Center for Health Statistics). The line at 2,500 g indicates the cutoff point used to define low birth weight.

In this paper, we use national US data to illustrate the birth weight "paradox." We then apply causal diagrams to propose a mechanism, other than effect modification of the effect of smoking by LBW, that may explain the "paradox" for any exposure. We conclude that the apparently paradoxical crossing of curves could be simply the result of selection bias due to stratification on a common effect (7–10).

## MATERIALS AND METHODS

We identified all infants born alive ($n = 4{,}115{,}494$) in the United States in 1991 through the national linked birth/infant-death data sets assembled by the National Center for Health Statistics (11). These data contain information on dates and causes of death, birth weight, maternal smoking, and other medical and sociodemographic characteristics systematically recorded on US birth certificates. The infant mortality rate was defined as number of deaths within the first year of life per 100,000 livebirths. LBW was defined as birth weight below 2,500 g. We excluded from the analyses infants with missing information on birth weight or maternal smoking; California was excluded because of lack of smoking data. The final study population included 3,001,621 livebirths.

We calculated overall and birth-weight-specific (within 250-g categories) infant mortality rates and compared them between infants exposed to smoking during pregnancy and infants nonexposed to smoking during pregnancy. We used logistic regression to estimate infant mortality rate ratios and 95 percent confidence intervals and to control for potential confounders (maternal age, gravidity, education, marital status, race/ethnicity, and prenatal care). Since adjustment for these potential confounders had virtually no effect, we present only the unadjusted rate ratios below. The complex role of gestational age in perinatal research is beyond the scope of this paper (12, 13). Additionally, we will not discuss the potential implications of restricting the analysis to infants born alive (14) or of dichotomizing birth weight (1).

## RESULTS

### The "paradox"

As figure 1 shows, infants born to women who smoked had a lower average birth weight (mean = 3,145 g; prevalence of LBW = 11.4 percent) than infants born to nonsmokers (mean = 3,370 g; prevalence of LBW = 6.4 percent). The infant mortality rate was 1,235 per 100,000 livebirths for infants born to smokers and 805 per 100,000 livebirths for infants born to nonsmokers. Compared with nonsmokers, the infant mortality rate ratio for smokers was 1.55 (95 percent confidence interval (CI): 1.50, 1.59). This rate ratio changed to 1.09 (95 percent CI: 1.05, 1.12) upon adjustment for birth weight.

Infant mortality increased as birth weight decreased among infants born to both smokers and nonsmokers (figure 2). However, the birth-weight-specific mortality rate curve of infants born to smokers crossed over that of infants born to nonsmokers around the interval of 2,000–2,250 g. For babies weighing less than 2,000 g at birth, mortality was higher among infants born to nonsmokers. The infant mortality rate ratio for exposed infants versus nonexposed infants was 0.79 (95 percent CI: 0.76, 0.82) among LBW infants and 1.80 (95 percent CI: 1.72, 1.88) among infants with higher birth weights.

### Causal diagrams

Investigators can use their expert knowledge to propose various hypothetical causal networks linking maternal smoking, birth weight, and infant mortality. Diagrams known as directed acyclic graphs (DAGs) can be used to represent

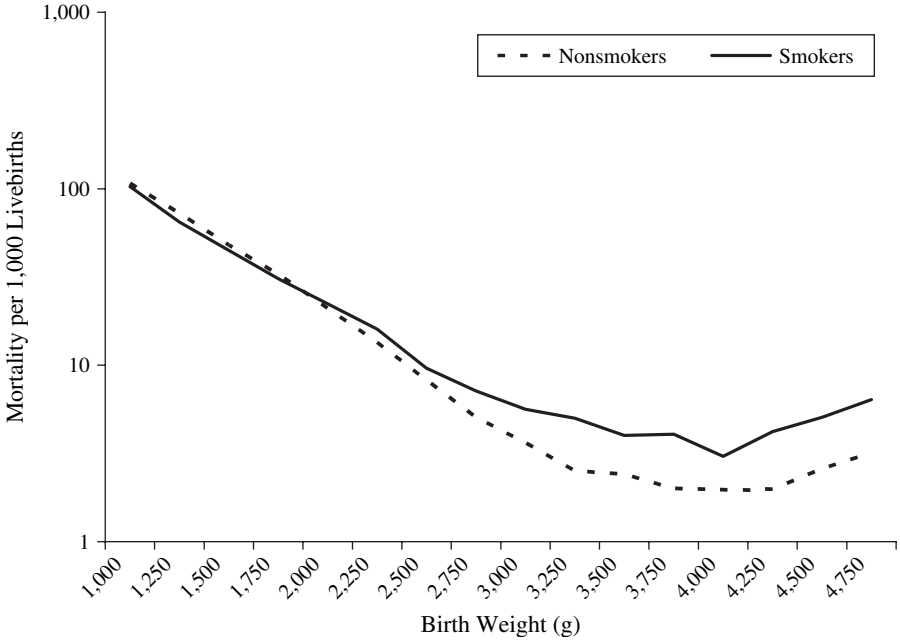


**FIGURE 2.** Birth-weight-specific infant mortality curves for infants born to smokers and nonsmokers, United States, 1991 (national linked birth/infant-death data, National Center for Health Statistics).

those networks (15, 16), as figure 3 shows. The diagrams link variables (nodes) by arrows (directed edges) that represent direct causal effects (protective or causative) of one variable on another. DAGs are acyclic because the arrows never point from a given variable to any other variable in its past (i.e., causes precede their effects); thus, one can never start from one variable and, following the direction of the arrows, end up at the same variable. The absence of an arrow between two variables indicates that the investigator believes there is no direct effect (i.e., a causal effect not mediated through other variables in the DAG) of one variable on the other (15, 17). In this article, we build upon previous publications in which investigators used DAGs to show how standard adjustment (stratification or regression) for variables affected by exposure may create bias by introducing a spurious (noncausal) association between the exposure and the outcome (9, 10, 14).

Figure 3.1 depicts the simplest scenario, in which smoking affects mortality solely through a reduction of birth weight. Under this scenario, the crude mortality rate ratio for smoking would be greater than 1, whereas the adjusted rate ratio and, equivalently, the stratum-specific rate ratios should be 1. Therefore, the proposed DAG in figure 3.1 is not consistent with our findings. Note that there might be common causes of smoking and infant mortality (e.g., socioeconomic factors) that would induce confounding. For simplicity, we assume that our analyses are conducted within levels of those common causes (i.e., there is complete control for confounding) and thus omit them from the graphs.

Alternatively, smoking might affect mortality solely through pathways not mediated by birth weight (figure 3.2). In this case, the crude and adjusted rate ratios would be the same. Again, this is not consistent with our findings.

Figure 3.3 combines the previous two diagrams: The effect of smoking is only partly mediated by birth weight. In this case, the adjusted rate ratio would generally differ from the crude rate ratio and from 1 due to the direct (i.e., not mediated by birth weight) effect of smoking on mortality, which is consistent with our findings. Actually, figure 3.3 would be consistent with any finding, because figure 3.3 is a complete DAG; that is, it does not impose any restrictions on the values of the stratum-specific rate ratios. As a consequence, figure 3.3 is the simplest graphical representation of the theory that there is a qualitative modification of the smoking effect by birth weight. However, most experts would agree that figure 3.3 is an overly simplistic representation of nature. In a more realistic yet still naïve causal diagram (figure 3.4), there would be common causes of LBW and mortality (e.g., birth defects, malnutrition). The presence of these risk factors (*U*), usually unmeasured by the investigator, would generally induce a spurious association between smoking and mortality when the analysis was stratified on birth weight (10, 14, 18). This (selection) bias may explain the "paradox."

We now provide a heuristic explanation of why this type of selection bias arises. To do so, we will use the simplified diagram shown in figure 3.5. This new diagram uses birth defects as the unmeasured variable (*U*) and includes only the three arrows that are necessary for the bias to occur: an arrow from smoking (the exposure) to birth weight (the variable that the analysis is being stratified on), an arrow from birth defects to birth weight, and an arrow from birth defects

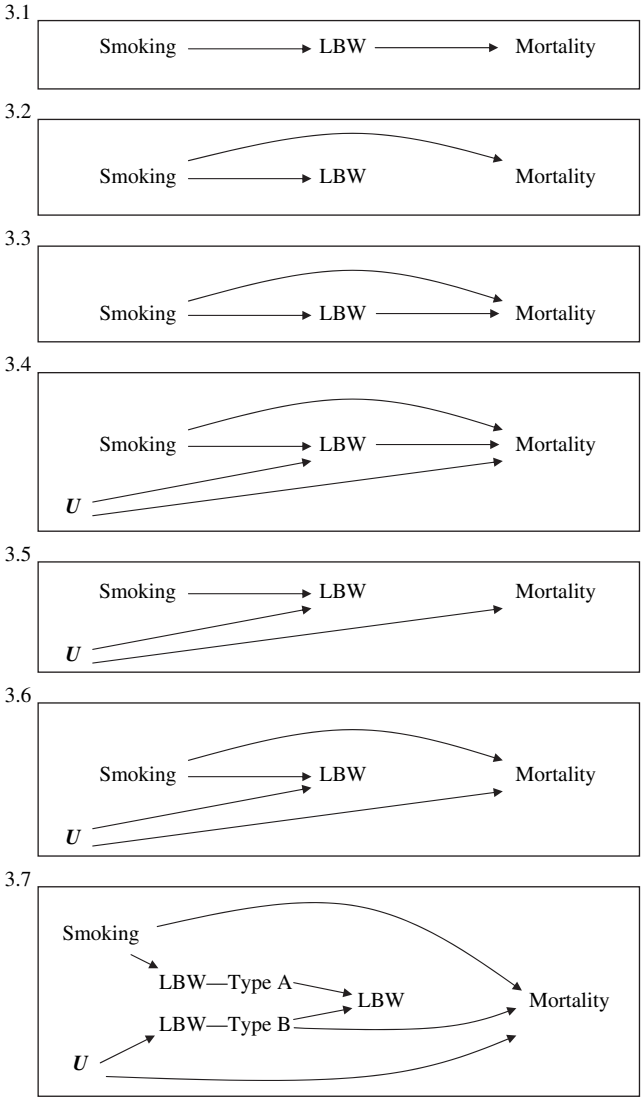


**FIGURE 3.** Causal structure (directed acyclic graph) proposed to represent the role of low birth weight (LBW) in the association between perinatal risk factors and infant mortality. *U*, other unmeasured risk factors (e.g., birth defects).

to mortality (the outcome). For now, let us suppose that maternal smoking and birth defects are the only two independent causes of LBW. In this extreme scenario, all of the LBW infants would have either been exposed to tobacco or had a birth defect (or both). Thus, all LBW infants not exposed to tobacco would necessarily have birth defects, which are associated with a higher mortality than smoking. In other words, there would be an inverse association between maternal smoking and infant mortality among LBW infants. This would be so even if, as in figure 3.5, maternal smoking had no causal effect on mortality.

Figure 3.5 does not include a direct arrow from smoking to mortality and is therefore inconsistent with the unconditional association between smoking and mortality found in the data. However, the rationale of the last paragraph still applies if such an arrow is added. Insofar as there are risk factors for LBW other than smoking that might themselves be associated with a higher mortality, the stratified infant mortality rate ratios for smoking would differ from the crude rate ratio and could be smaller than 1 even if there were no beneficial effect of smoking on mortality for LBW infants. In summary, there will be selection bias when stratifying on a variable that is 1) affected by exposure and 2) shares common causes with the outcome. Such a variable does not need to be on a causal pathway between the exposure and the outcome (i.e., it does not need to be an intermediate variable) (10, 14, 18).

We can now consider more complicated causal structures in which the risk factor also has a direct effect on mortality (e.g., figure 3.6). In this case, the rate ratio adjusted for birth weight would be a combination of 1) the true direct effect of smoking on mortality and 2) the bias resulting from the presence of common causes of LBW and mortality.

Figure 3.7 is an elaboration of figure 3.6 and represents the hypothesis that there are different ways of achieving LBW, so that only the type of LBW caused by certain factors (e.g., birth defects), and not others (e.g., smoking, Black race), increases mortality (1, 2, 19). This causal diagram is also consistent with our results and could represent, for example, how Black LBW infants have better survival than White infants at the same weight. That is, Whites might be born LBW less often than Blacks but, when they are, the etiologies of their LBW (e.g., birth defects) might be associated with a higher mortality (20).

### A general approach to the "paradox"

The "paradox" is not limited to smoking and infant mortality. When studying the association between any prenatal variable (e.g., sex, altitude, race, multiple pregnancy, placenta previa) and any postnatal outcome (e.g., neonatal mortality, cerebral palsy), adjustment for any variable (e.g., birth weight, gestational age) affected by the exposure of interest can introduce bias if the causal relation between these variables resembles that represented in figure 3.5. For example, in words of MacMahon et al., "at any given weight the infant [females] in the series with lower mean weight will have, relative to males, a smaller proportion of members whose weight is reduced by those factors that *are* associated with increased mortality, and the group will consistently have a more favorable mortality rate" (19, p. 259). Likewise, consider the association between altitude and birth weight. Infants born at high altitudes have lower birth weights than but similar mortality rates as (i.e., rate ratio = 1) infants born at lower altitudes in comparable populations (1). However, a rate ratio stratified on birth weight, unlike the crude rate ratio, might indicate a spurious protective effect of altitude on infant mortality for LBW infants. For example, in Denver, Colorado, LBW babies are born LBW because of either the altitude or other factors. However, in Los Angeles, California, all LBW babies are born LBW only because of factors other than the altitude. Since the LBW caused by altitude does not seem to increase mortality, a proportion of LBW babies in Denver will not

have increased mortality, while up to 100 percent of LBW babies in Los Angeles might have increased mortality. That would result in higher mortality for LBW babies in Los Angeles compared with LBW babies in Denver.

In fact, similar ''paradoxes'' can appear in any research field when statistical adjustments ignore the causal relations among variables. For example, consider the association between alcoholism, elevated levels of certain hepatic enzymes, and mortality. Let's assume that there are two major causes of hepatic enzyme elevations, alcoholism and liver cancer. Among patients with elevated levels of hepatic enzymes, alcoholics would probably have a better short-term prognosis than nonalcoholics because the etiology of enzyme elevations among the latter was liver cancer. That is, within patients with elevated hepatic enzyme levels, alcoholism would be associated with a better prognosis (i.e., mortality rate ratio $< 1$). The stratified analyses that lead to these paradoxical (biased) estimates are not only a methodological problem but also a clinical one, given the potentially invalid conclusions and recommendations that might be inferred from such comparisons—for example, if we were to conclude that high alcohol intake is beneficial for patients with elevated hepatic enzyme levels or that maternal smoking is beneficial for LBW babies (6).

## DISCUSSION

Like previous studies, our study showed that LBW infants born to mothers who smoke have lower infant mortality than LBW infants born to nonsmokers. We used causal diagrams to illustrate how, under biologically plausible causal networks, an inverse association between smoking and infant mortality can be found among LBW infants even in the absence of any beneficial effect of smoking. More generally, stratification by birth weight can induce a spurious association between prenatal exposures and postnatal outcomes.

Because adjustment for birth weight may largely explain the birth weight ''paradox'' in the presence of certain causal structures, the first thing to clarify is why one would want to adjust for birth weight (21). When the goal is to estimate the overall effect of prenatal exposures on infant mortality, adjustment for factors that might be on a causal pathway between the exposure and the outcome is unwarranted. Moreover, because prenatal exposures precede birth weight, birth weight is not generally a confounder and adjustment for birth weight is not necessary to reduce confounding bias (14). Therefore, in assessing the overall effect of maternal smoking on infant mortality, adjustment for birth weight is generally inappropriate.

However, when the goal is to estimate the direct causal effect of prenatal exposures on infant mortality (i.e., not mediated by their effects on birth weight), adjustment for birth weight may be justified. Although the causal question is hardly ever stated, we could assume that the authors of some previous articles on the birth weight ''paradox'' were attempting to evaluate the direct effects (not mediated through birth weight) of prenatal factors (e.g., maternal smoking) on mortality. Even if the overall effect might seem of greater interest from a clinical and public health standpoint, identifying the causal pathways (i.e., the role of LBW) may contribute to our understanding of infant mortality and lead to more effective interventions. Unfortunately, standard estimates of direct effects adjusted for birth weight will be biased in the presence of unmeasured common causes of LBW and mortality, such as those shown in figures 3.4–3.7 (7, 9). These common causes must be strongly associated with both birth weight and mortality to produce a substantial bias (17).

In other words, estimating the direct effect of prenatal exposures by adjusting for birth weight implies that the investigators believe that figures 3.1–3.3 are representing the true state of nature. Otherwise, to avoid the bias introduced by stratification, one could measure and adjust for the common causes of LBW and mortality, in addition to birth weight (9). If the common causes are affected by the exposure, methods other than stratification (e.g., G-estimation or inverse probability weighting) are needed (8, 22, 23). However, these common causes are often unknown or unmeasured, and thus this strategy may be unfeasible.

Some authors have solved the paradox of intersecting mortality curves by using population-specific standards for LBW (5) or formulating perinatal risk based on a fetuses-at-risk approach (12). Resolving the paradox by aligning the curves does not necessarily clarify why the curves crossed in the first place and might not result in an estimate of the direct effect, assuming that that was the reason for conditioning on birth weight. However, understanding the origins of the paradox might help us understand the causes and effects of LBW (24). For example, exploring the paradox led Wilcox and Russell (5) to the conclusion that moderate reductions of birth weight do not necessarily increase mortality, and that birth weight and mortality might be associated because some factor(s) affects them both. This conclusion, which explains the crossing of the curves, can be represented with DAGs like the one shown in figure 3.5.

One general limitation of standard causal DAGs is that they do not encode the magnitude or direction of the effects. Therefore, the DAGs we propose as more plausible given our understanding of nature (e.g., figure 3.4) predict that the rate ratio within levels of birth weight will differ from the unconditional rate ratio of mortality for maternal smoking versus no smoking, but they do not predict by themselves that the birth-weight-specific mortality rate curves will cross. This latter result can only be derived by adding quantitative information that is not present in the DAG.

In summary, we propose the use of causal diagrams to provide a conceptual framework for the discussion and interpretation of the birth weight ''paradox,'' as well as for the evaluation of the proposed analytical approaches. We have used causal diagrams to show that this apparent paradox can be conceptualized as selection bias due to stratification on a variable (birth weight) that is affected by the exposure of interest (smoking) and that shares common causes with the outcome (infant mortality). For estimation of overall effects of prenatal variables on mortality, adjustment for birth weight is not only unnecessary but potentially harmful. Even for estimation of direct effects of prenatal variables, adjustment for birth weight is generally not valid when there is an unmeasured common cause of LBW and mortality.

Clarification of the causal question that motivates the analysis and specification of the assumptions regarding the causal structure are prerequisites for any analytical approach.

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