Low Birthweight, Postnatal Growth Failure, and Mortality

David L. Pelletier, Maike Rahn, and Edward A. Frongillo, Jr.

Division of Nutritional Sciences, Cornell University, Ithaca, New York, USA

The effect of malnutrition on child morbidity and mortality in developing countries has been an ongoing concern for decades in international health and nutrition. The synthesis by Scrimshaw et al. (1) has served as a landmark study in this field, drawing together a large body of clinical and laboratory research to establish the existence of physiological synergism between various forms of malnutrition and infectious disease. More recently, the epidemiological evidence on general malnutrition and mortality has been re-examined, confirming that child mortality is associated with malnutrition in a wide variety of settings, that the physiological synergism manifests itself in synergistic effects at the population level, and that the effects are seen in mild to moderate levels of malnutrition as well as in severe forms (2–4). That body of research has led to the estimate that more than half of all child deaths in developing countries are the result of the potentiating effects of malnutrition on infectious disease, a figure roughly 10 times higher than previous estimates based on cause-of-death statistics from clinics and hospitals (5).

Whereas that body of research has helped to clarify and quantify the relation between child malnutrition and child mortality, the results are based largely on a consideration of the nutritional status of children between the ages of 6 and 59 months, who were measured at one point in time and had their vital status determined 12–24 months later. However, this is not the period of highest mortality. The highest risk for mortality occurs in the perinatal period (birth to 7 days) and the neonatal period (birth to 28 days) (6). During these periods, prematurity, congenital defects, and obstetric complications all contribute to mortality, such that it cannot be assumed that malnutrition and infectious disease have the same effects during these periods as they do later in infancy and childhood.

The purpose of this chapter is to examine the role of intrauterine growth and development in relation to mortality during the perinatal, neonatal, and childhood periods. A conceptual framework for examining these relations is provided in the next section, followed by a presentation of a diverse set of empirical findings bearing on these relations. These findings represent work in progress and are offered as suggestive rather than definitive at this stage.
CONCEPTUAL FRAMEWORK

There are many published reports on the relations between maternal characteristics, intrauterine growth and development, and postnatal growth, morbidity, and mortality. For the purposes of this chapter, it is sufficient to summarize some key conclusions emerging from these reports.

- Intrauterine growth and development is influenced by some prepregnancy maternal characteristics and by some factors operating during pregnancy (7,8).
- Therefore, birthweight is a heterogeneous characteristic, reflecting variation in gestational age, rate of growth, and type of growth (linear growth *versus* weight gain) (9); in developing countries, the majority of low birthweight is caused by intrauterine growth retardation (IUGR) as opposed to prematurity (10).
- The consequences of low birthweight on postnatal growth, morbidity, and mortality vary in degree, depending on the extent to which low birthweight reflects shortfalls in gestational age, rate of growth, or linear *versus* ponderal growth (11,12).

Figure 1 depicts some of these relations in the form of a conceptual framework that guides the remainder of this chapter. As shown, birthweight reflects gestational age and birthweight for gestational age, the latter being a function of the rate of intrauterine growth and type of growth (linear *versus* ponderal; note that the distinction between linear and ponderal growth is not shown explicitly in this figure because the studies described here do not have data on these characteristics).

Birthweight is shown having effects on perinatal and neonatal mortality and on child size, although it is considered to be only a proxy for variation in gestational age or birthweight for gestational age in this regard (as indicated by the dashed arrows). This distinction is important because the above studies have shown that prematurity has stronger effects than low birthweight for gestational age (IUGR) on neonatal mortality, whereas IUGR has more persistent effects than prematurity on postnatal growth. Thus, the long-term and short-term consequences of low birthweight are different and depend on the type of low birthweight.

Although the studies described in this chapter are limited to the above variables (namely, birthweight, gestational age, birthweight for gestational age, child size, and mortality in the perinatal, neonatal, and childhood periods), the interpretation of these studies requires consideration of the other factors shown in the conceptual framework. Specifically, a distinction is made between those constitutional factors that may cause low birthweight for gestational age and have relatively attenuated long-term effects (*e.g.*, on infant and child mortality) *versus* those that may have long-term risks. The constitutional ("low risk") causes of small size are hypothesized to be maternal height, maternal birthweight, infant sex, and genetics. The high-risk causes are prepregnant weight or body mass index (BMI), nutrition during pregnancy (including but not limited to weight gain), maternal health during pregnancy (including but not limited to malaria, genital tract infections, hypertension), smoking during pregnancy, and congenital malformations. The implication is that the low-risk causes may contribute to low birthweight and small size or growth postnatally, but owing to the underlying mechanisms, they do not disturb the development of vital organs,
FIG. 1. Conceptual framework for the causes of infant and child mortality.
tissues, and functions (e.g., the immune system). Earlier reports referred to this as a constitutional constraint (13). By contrast, the high-risk causes contribute to low birthweight and small postnatal size and they interfere with normal developmental processes such as the immune system. (Prematurity might be regarded as another example of a “high-risk cause” when viewed from this perspective, although its effects are not mediated through birthweight for gestational age.) These distinctions lead to the hypothesis that in populations where the smallness of children has a large component of the low-risk causes (such as South Asia), there will be a weaker relation between measures of child smallness (such as weight for age) and child mortality.

Finally, although the above discussion focuses on causal pathways mediated through gestational age or birthweight for gestational age, the interpretation of empirical studies also requires attention to various factors operating postnatally. With respect to child mortality, these include the effects of food, health, and care on infant and child growth, the interaction between child size and infection in causing mortality, and the degree of access to good-quality medical care or life-saving technologies (e.g., oral rehydration solutions and antibiotics). With respect to perinatal and neonatal mortality, they include obstetric complications, postnatal infections, and the quality of medical and maternal care in the perinatal and neonatal period.

It is relevant that these postnatal factors are shown not as main effects influencing mortality directly but rather as effect modifiers (interactions) that affect the degree to which gestational age and birthweight for gestational age affect mortality. In other words, they are hypothesized to affect the case fatality rate (where the “cases” are infants with prematurity and low birthweight for gestational age). Thus, mathematically they should express themselves as factors that interact with gestational age and birthweight for gestational age in causing mortality. This logic is a direct extension of that described earlier in relation to the potentiation of infection by malnutrition (2), but in this case, the interaction is between characteristics of the infant and medical technology rather than physiology.

Whereas this conceptual framework is based on an extensive literature on these relations, it is broader in scope than any individual published studies. As such, it leads to some explicit hypotheses that may transcend any one study. The following sections bring together findings from many separate studies bearing on these hypotheses.

CROSS-NATIONAL COMPARISONS

Figure 2 shows scatterplots of the relation between infant (and under 5) mortality and the prevalence of low weight for age among children from birth to 59 months, with separate regression lines for the four world regions. These data are drawn from the World Health Organization global database on child growth and malnutrition (14). The figure reveals the “Asian paradox” mentioned earlier, referring to the fact that the South Asian and Southeast Asian countries tend to have high rates of low weight for age, but their mortality is lower than that seen in other regions. The Asian paradox refers to the unexpected malnutrition–mortality relations described here as well
FIG. 2. Infant and under 5 mortality and child malnutrition in 59 developing countries.
FIG. 3. Infant and under 5 mortality and child malnutrition in countries with high and low incidences of low birthweight (0–9, low incidence; A–J, high incidence).
as the unexpected malnutrition–socioeconomic relations described elsewhere (15). In this chapter, we examine only the mortality aspects, but the “constitutional smallness” hypothesis may account for some of the socioeconomic aspects, as well.

These data were linked to estimates of the incidence of low birthweight at the national level to test the hypothesis that the relations between child size and mortality may partially reflect the effects of “low-risk causes” of low birthweight in these populations, notably low maternal height and low maternal birthweight. In this analysis, the incidence of low birthweight is used as a proxy for maternal stature and maternal birthweight. Figure 3 shows a scatterplot with the 10 countries with the lowest rates of low birthweight (designated by the numbers 0–9 and connected by a polygon) and the 10 countries with the highest rates (designated by the letters A–J and connected by a second polygon). These presentations reveal considerable overlap between the polygons, but the one for low birthweight countries is significantly displaced to the right, indicating a high prevalence of small size in childhood. In addition, three of these countries (India, Bangladesh, and Sri Lanka) have low mortality relative to the prevalence of smallness, especially when considering under 5 mortality. The hypothesized explanation may be that India (I) and Bangladesh (J) have the highest rates of low birthweight (28% and 50%, respectively) and that much of it is associated with low-risk maternal causes. Sri Lanka (C) has a lower rate of low birthweight (18.7%), but its low mortality rates may reflect better coverage of health services than in the other South Asian countries shown here. The proximity of Pakistan (H) to two African countries, Niger (E) and Nigeria (F), despite having a rate of low birthweight similar to that in India (28%), is an apparent exception to the Asian paradox. One might hypothesize that this reflects greater maternal stature (i.e., a higher ratio of high-risk versus low-risk causes of low birthweight) or worse health and nutrition conditions affecting infants and children.

Although these findings are suggestive of the “constitutional causes hypothesis” as it relates to the Asian paradox and more generally, the nature of these data does not lend them to a very firm test of that hypothesis. Work in progress involves testing for an interaction between underweight prevalence and birthweight incidence in regressions predicting infant and child mortality. A more direct test would be to use estimates of maternal height for these countries, but even that will be limited by the ecological nature of these associations. A much stronger test would be to use data from a prospective study with individual-level data on maternal height, birthweight, weight for age, and child mortality.

CROSS-STUDY COMPARISONS OF CHILD SIZE AND CHILD MORTALITY

Another source of support for the Asian paradox and the low-risk causes hypothesis can be gleaned from the earlier work on child size and child mortality, as shown in Fig. 4. The eight studies shown in these figures each represent a prospective study of a cohort of children measured at one point in time, with vital status determined 6–24 months later. Although there is a clear increase in the mortality rate with increasing
FIG. 4. Child mortality and malnutrition in eight prospective studies. [From Pelletier et al. (4)].

severity of weight deficits in each study, a striking feature of these figures is that the four lower curves all are from South Asia (India and Bangladesh) followed by Indonesia (Java). This pattern is consistent with the cross-national evidence of an Asian paradox, with the added feature that the data in Fig. 4 are based on individual children rather than on ecological comparisons. Referring to the conceptual framework in Fig. 1, the interpretation of this may be that the effect of child size on child mortality depends not only on the exposure to infection (2) but also on the ratio of
high-risk *versus* low-risk causes of small size itself. In other words, some of the interstudy variation in baseline mortality in Fig. 4 (mortality rates among the well nourished) may reflect low-risk causes of smallness in Asian populations, with a residual component due to exposure to infection. If this low-risk component in the Asian populations, or some portion of it, results from low maternal stature or low maternal birthweight or both, it suggests that some of the “child malnutrition” in Asian populations actually reflects maternal and intergenerational malnutrition.

**CROSS-STUDY COMPARISONS OF BIRTHWEIGHT AND NEONATAL MORTALITY**

Apart from the above evidence based on child mortality, another test of the constitutional smallness hypothesis may be derived from cross-population patterns in the relation between birthweight and neonatal mortality. The prediction would be that birthweight-specific mortality should be lower in those populations with a higher prevalence of low-risk causes of low birthweight, such as low maternal stature or maternal birthweight. To test this, three data series from developing country studies were identified from published reports, all of which had adequate data on birthweight-specific neonatal mortality. As shown in Fig. 5, these studies are from rural Tanzania (16) and urban Thailand in 1976 and 1996 (17). Bearing in mind the log scale used here for neonatal mortality, the figure shows a marked difference in birthweight-specific mortality across the three series. Thailand (1996) has the lowest mortality at each birthweight. Thailand (1976) has intermediate levels, and Tanzania has the highest mortality rates at all ages. The mortality of “normal birthweight” neonates in Tanzania is at the same level as that observed for 1,000- to 1,500-g neonates in Thailand (1996). Some of this difference is undoubtedly attributable to differences in medical care, but the data from Thailand (1976) are from a hospital 5 years before the introduction of intensive neonatal care. Even this series shows a lower birthweight-specific mortality than Tanzania in 1990. Thus, these data are consistent with the constitutional smallness hypothesis, but this cannot be clearly distinguished from the effects of neonatal care and other factors that may differ among these studies.

**EFFECTS OF GESTATIONAL AGE VERSUS SMALLNESS ON PERINATAL MORTALITY**

A major limitation of the above studies is the inability to distinguish the effects of developmental maturity (as reflected in gestational age) from those of intrauterine growth (as reflected in birthweight for gestational age). As shown in Fig. 1, the available evidence suggests that the effects of nutritional factors on mortality are mediated through birthweight for gestational age rather than gestational age, although the determinants of gestational duration remain largely unknown. None of the studies from developing countries shown in Fig. 5 was able to separate the effects of gestational age from those of birthweight for gestational age on perinatal
or neonatal mortality. Moreover, most of the studies from developed countries have not presented their data in ways that would shed light on the relation between these two factors.

A large study from Norway provides data bearing directly on this question (18). The data represent all singleton live births and fetal deaths in the country from 1967 to 1984 with gestational ages of 28 weeks or more. Perinatal mortality was defined as all fetal deaths plus deaths in the first week of life. The authors adjusted birthweight for gestational age by calculating a $z$ score, using the distribution of birthweight at each week of gestation to calculate the score. In this way, they were able to estimate the associations between perinatal mortality and gestational age versus small size (corrected for gestational age).

By way of making an important methodological comparison, Fig. 6 shows the log of perinatal mortality in relation to birthweight in grams, stratified by gestational age. The characteristic exponential or J-shaped curve is seen with each gestational age, although the absolute level of mortality is higher for those births with shorter gestational ages. Another notable feature of the data presented in this way is that all the gestational age curves progressively converge at lower birthweights. This feature confirms a point made by Kramer et al. (19) and others that much of the mortality associated with low birthweight, especially at very low birthweights, may be due to prematurity rather than smallness per se. If this is so, then nutritional interventions before or during pregnancy may not be effective in reducing perinatal or neonatal mortality.

The use of the birthweight-for-gestational-age $z$ score in the Norway study suggests that this may not be the case, however. Figure 7 shows the relation of the log of perinatal mortality to this birthweight for gestational age index, again stratified by gestational age. As in the previous figure, the characteristic exponential relation is present (bearing in mind the log scale), and the absolute mortality is higher
for those births with shorter gestational ages. However, in this case, the curves do not progressively converge at lower birthweights. On the contrary, they are remarkably parallel and reminiscent of the pattern shown in Fig. 4 for postnatal mortality.

The implications of the patterns in Fig. 7 are potentially quite provocative but are somewhat different from those provided by the authors of the Norway article. Those investigators made three statements that are indicative of an ongoing debate within
the field and can be used to highlight the importance of the interpretation placed on these findings (18):

1. "We have shown that there are two strong and separable factors affecting perinatal survival. One is gestational age, and the other is relative birthweight at any given gestational age."

2. "A baby can benefit as much from an increase in gestational age as from an increase in its weight relative to the weights of others at the same gestational age."

3. "The dominance of birthweight (on mortality) when the ordinary analytic methods are used may have contributed to the current emphasis on low birthweight as a public health problem. Interventions aimed at increasing the size of babies may have little effect on perinatal mortality. Preterm delivery appears as worthy a target for public health intervention as low birthweight and may be more amenable to change."

The latter conclusion is consistent with that drawn by Kramer et al. (19) and the 1985 Institute of Medicine report (20), suggesting that the role of infant size per se has been overemphasized in public health owing to the failure to separate gestational age and size adjusted for gestational age. In contrast to these conclusions, however, the patterns in Fig. 7 and some secondary analysis of the data from that publication seem to support the following conclusions:

- Gestational age and relative weight are both strong factors affecting perinatal survival, but they are not easily separable. Bearing in mind the log scale in Fig. 7, these data reveal that both factors are strongly associated with mortality, but there also is a strong interaction between them. The quantitative effect—that is, the absolute mortality rate—that is, the absolute mortality rate—varies according to gestational age (being greater at earlier ages). Similarly, the quantitative effect of gestational age—that is, the absolute mortality rate—varies according to the relative weight (being greater at lower relative weights).

- Contrary to the statement that the quantitative effects of gestational age and relative weight are the same, re-analysis of the data in Fig. 7 reveals that relative weight has a stronger association with perinatal mortality than gestational age. Preliminary analysis suggests that the relative risks for mortality associated with a deviation in relative weight of 1, 2, and 3 SD from the mean are 2.01, 4.53, and 11.50. By contrast, the relative risks associated with statistically comparable deviations in gestational age (38.5, 37.0, and 35.5 weeks) are 1.63, 2.94, and 5.61.

- In the light of the above, it is apparent that size at birth is a powerful predictor of perinatal mortality, even after adjusting for gestational age. Thus, relative size at birth is an appropriate concern for public health, along with gestational age, and interventions should be sought that can increase relative weight as well as gestational age. A major caveat, as discussed below, is that the arrow of causality is unclear in these data; that is, it is not clear whether small size is contributing to the mortality or is simply a reflection of congenital malformations and complicated pregnancies.
COMMENT

In this chapter, we have sought to explore the relations among intrauterine growth and development, size at birth, and mortality in the perinatal, neonatal, and childhood periods. We have done this by proposing an explicit conceptual framework that gives rise to some testable hypotheses about these relations and by bringing together a diverse set of observations bearing on these hypotheses. Although this work is viewed as exploratory and is still in progress, the findings provide a number of potentially important insights.

The Asian Paradox and the Constitutional Smallness Hypothesis

The results presented here provide some support for a hypothesis that the effects of body size on mortality may vary according to the causes of small size in an individual child or in a particular population. In the present context, it is hypothesized that maternal height and maternal birthweight may impose low-risk constraints on the growth of the fetus, as suggested in the earlier literature (13), but that smallness arising in this way may not carry the same mortality risk as that arising from other factors like poor maternal health and nutritional status in the immediate prepregnancy period and during pregnancy. The lines of evidence supporting this hypothesis are all indirect, including cross-national comparisons, eight prospective studies of child anthropometry and child mortality, and three studies of birthweight-specific mortality in developing countries. Although these studies provide only indirect support, they are consistent in supporting the hypothesis and are sufficient to suggest that more detailed studies should be undertaken to provide more direct evidence bearing on these relations.

Pending the results of such studies, it is important to qualify and delimit the implications and applicability of this hypothesis. First, although the smallness of their children may not be related to mortality as strongly as in other populations, this is not to say it has no effect. The most appropriate way to view these relations is in terms of sources of variance in child size. Specifically, the total variance in child size within a given population (e.g., weight for age) can be conceptualized as having three components: an interindividual genetic component, an environmental component (reflecting the health and nutritional conditions during prepregnancy, pregnancy, and postnatally), and a constitutional component (reflecting maternal size and early development and the health/nutrition conditions in earlier periods). The first two of these are well recognized, whereas the possibility of the constitutional component has received less attention. These three components may have differential effects (relative risks) on mortality, and their relative proportions as causes of small size in childhood may vary across populations, but it is likely that all populations in developing countries have all three components to varying degrees.

Second, although small infant/child size may have only attenuated effects on mortality in populations characterized by short maternal stature and low maternal birthweight, it is important to note that anthropometric characteristics do not reflect all of the potential nutritional problems in a population, and mortality risk is not the only
relevant outcome. Populations, communities, and households with short maternal stature are likely to suffer from a variety of health, nutritional, and social problems—with implications for cognitive development, work capacity, and quality of life—and they should continue to have priority in health, nutrition, and poverty alleviation policies and programs.

Finally, although constitutional smallness is hypothesized here as a partial explanation of the Asian paradox, it is important to note its relation to other empirical and theoretical developments and its potentially broader applicability. The most general statement of the underlying (contingency) theory is that the consequences of small size, or other biological traits, depend upon the causes of the small size itself. To use an analogy, the consequences of fever at the individual or population level depend upon the factors responsible for fever in each setting (e.g., malaria versus viral infection). In other words, small size is only a reflection of earlier developmental processes, some of which may have a higher probability of longer-term functional consequences than others. Although recognizing that the vast majority of the smallness in developing countries is of the high-risk type and that policy in most settings should continue to be based on that knowledge, it also is likely that the ratio of high-risk to low-risk causes may decrease as the food, health, and care situations improve in a country (as, e.g., in some countries in Latin America). In such situations, the low prevalence of traditional indicators makes it increasingly important to target resources to the truly at-risk groups and to the groups most likely to benefit. One of the practical applications of further research guided by contingency theory would be the ability to develop more efficient “indicators of risk” (20), based on an understanding of which subgroups have higher risks. In addition, it is likely that identification of “predictors of benefit” (20) would be enhanced by improving our understanding of the underlying developmental and physiological processes. Thus, it may be useful to view the constitutional smallness hypothesis as simply one example of contingency theory related to causes, indicators, and consequences and to use this construct more broadly in studies of human and public nutrition. This is further illustrated in the discussion of the Norwegian study (18) below.

Relative Size Versus Maturity at Birth

The re-analysis and re-interpretation of the Norwegian study (18) presented in this chapter leads to three important conclusions: Gestational age and birthweight for gestational age both are powerful predictors of perinatal mortality; there is a powerful interaction between gestational age and birthweight for gestational age, such that the quantitative effect of one factor depends on the level of the other factor, and the effect of both factors simultaneously is a function of their product rather than their sum; and in quantitative terms, the main effect for birthweight for gestational age appears stronger than for gestational age, and the size of this difference widens as one considers births further from the mean gestational age and mean birthweight for gestational age. It also is relevant to note that the causes of prematurity remain largely unknown, whereas various determinants of intrauterine growth are well established (such as maternal nutritional status).
These conclusions might appear to support the suggestion that more attention should be given to improving intrauterine growth (e.g., by improving maternal nutritional status); however, consideration of contingency theory and the conceptual framework (Fig. 1) tempers this conclusion. The relevant contextual considerations in this case are that the study comes from a developed country and that nutritional conditions in these countries are generally favorable, the perinatal mortality is low in absolute terms (12.9/1,000), and most of the perinatal deaths in such countries reflect congenital and developmental problems that are unlikely to respond to nutritional improvement. Consideration of these contextual factors suggests that a high proportion of the variance in birthweight for gestational age may be associated with congenital malformations, smoking, and some health conditions during pregnancy, for example, hypertension, with only a minor proportion associated with maternal nutritional status. (The possibility that nutrition may interact with some of these is acknowledged—for example, adequate folate status may avert congenital anomalies like neural tube defects in genetically susceptible individuals, and minerals like calcium and sodium may be involved in gestational hypertension—but the quantitative importance of such examples at a population level is uncertain.) It may be that these and other poorly understood factors are responsible for a variety of developmental and metabolic disruptions in utero that predispose to perinatal death, and the low weight for gestational age at birth is merely a reflection of these disruptions rather than being in the causal pathway leading to death.

Although the above interpretation may hold for the Norwegian context, it also is possible that the relations between gestational age and birthweight for gestational age in that study can provide some insight into biological processes relevant to developing countries. This depends entirely upon the underlying biological theory or mechanisms. For instance, if growth-limiting factors like smoking, gestational hypertension, suboptimal placentation, and other maternal, environmental, or health conditions in Norway operate in part through the common pathway of limiting the flow of blood, oxygen, energy, and nutrients to the fetus, then the growth-limiting factors in developing countries that operate through the same pathway (poor maternal health and nutrition) may have the same or similar effects on perinatal mortality. Indeed, given the much poorer state of perinatal care in developing countries, the effect would be quantitatively much greater. If this is so, then the separation of gestational age effects from birthweight-for-gestational-age effects in Norway suggests that improvement of maternal nutritional status in developing countries may have powerful effects on perinatal survival. However, as noted above, this depends upon the extent to which the underlying biological mechanisms are similar between these diverse settings.

The effect of birthweight for gestational age on mortality in developing countries suggested above has more direct support from the evidence in three studies from developing countries shown in Fig. 5. Indeed, an important conclusion from these results is that the effect of birthweight on neonatal mortality is not eliminated by improvements in the quality of prenatal care. On the contrary, the largely parallel lines in Fig. 5 suggest that neonatal mortality is a function of birthweight and
quality of care, the latter indicated by the absolute level of mortality in each study. (Although these lines are not exactly parallel, it should be noted that neonatal size in these studies was quantified using birthweight rather than birthweight for gestational age; Figs. 6 and 7 from the Norwegian article (18) reveal the same tendency for convergence at very low birthweights in the Norwegian data, but the lines are rendered remarkably parallel when neonatal size is quantified by birthweight for gestational age instead of by birthweight.) Specifically, these lines suggest that neonatal mortality rises exponentially as birthweight declines, but the absolute level of mortality and size of the birthweight effect depend upon country-specific factors that affect mortality even among the normal-weight infants. Consideration of the conceptual framework in Fig. 1 reveals that medical and maternal care and the ratio of high-risk to low-risk smallness are the most likely country-specific factors. Thus, poor neonatal care and the ratio of high-risk to low-risk causes appear to interact with low birthweight to produce multiplicative effects on neonatal mortality. Countries that have improved the quality of neonatal care (17) do reduce the overall level of mortality, but the exponential pattern in birthweight-specific mortality remains in force. This suggests that improvements in maternal health and nutritional status that increase birthweight can be expected to lower the rate of neonatal mortality in all settings, but the greatest impacts can be expected in those settings with poor neonatal care and a high ratio of high-risk to low-risk causes of low birthweight.

REFERENCES

DISCUSSION

Dr. Adair: This is a very interesting set of ideas about the relative importance of low and high risk factors. I’m wondering whether you might be able to test the hypothesis within populations as well, by looking at those infants who are proportionately growth retarded, where there is a strong influence of shot maternal stature. Separating out the high and low risk factors within a population, might actually strengthen your conclusions.

Dr. Pelletier: It’s a good thought. I cannot recall whether things like maternal stature predict proportional IUGR to a greater extent than disproportional. That would be the critical link.

Dr. Adair: The evidence from the Cebu study (1) showed that proportionate growth retardation is much more prevalent in short mothers, and taller maternal stature with poor nutrition is associated with disproportionate growth retardation. So that would be consistent.

Dr. Uauy: Have you attempted to look at population attributable risk, because there will be very few term babies born at -3 SD of weight corrected for gestational age. In addition, malformation would need to be excluded in such analyses.

Dr. Pelletier: That would be one of the next steps for this. Bearing in mind that these relative risks themselves come from the Norway study, I’m a bit uncertain about applying them to the prevalence of IUGR or low birth weight for gestational age in developing countries. That is one of the uncertain things that I still need to work on some more. But that would be one direction to go after this.

Dr. Martorell: In relation to low risk factors, why does small body size constitute a low risk factor? Does this have to do with allowing the fetus to adapt? Does that make it less risky than, say, infection, where there is a sudden change?

Dr. Pelletier: I’m thinking of it more simply than that. If there is physical limitation on the fetus in a small uterus, for example, the internal organs and tissues of the fetus may develop normally, but there is a constraint on the ultimate size.

Dr. Martorell: It could be a constraint on size, but also a small mother has a lower dietary intake, so the nutrient pools are proportionately smaller. What about high altitude? Is that associated with low risk? What are the implications of birth weight differences associated with high altitude?

Dr. Pelletier: That’s a good point. I thought of that rather late and did not put it in the conceptual framework because I wasn’t sure where it would go!
Dr. Ulitaszek: I think it should go into the high risk causes, because it would come into the same category as smoking—that is, hypoxia.

Dr. Stoltzfus: What you've presented makes me think about something that I have wondered about for a while, which is our reliance on the size of the person as a proxy for all the things that we know are associated with small size, such as child development and cognition, morbidity, and mortality. We have strong evidence that small neonates and small children are at higher risk of mortality and delayed development. But, because it is hard to assess child development and it is difficult to assess mortality because it is a rare outcome, we end up by using size as our outcome. But maybe it is not size per se that is important, but all the things that are correlated with size. We rely on growth because we can measure it in relatively small sample sizes and it is easy to assess, but could we be missing other really important things by concentration on growth? Some critical effects may not be reflected in growth—for example, vitamin A deficiency and supplementation. I know there is some evidence that vitamin A supplementation may affect growth, but the mortality effect is not mediated through a growth effect; it bypasses growth entirely. This makes me wonder about birth weight as the primary outcome of so many studies. Could we be missing important effects by assuming that they will all be reflected in growth?

Dr. Pelletier: I agree with you completely. There is a difference between using indicators because they are predictive of something you would like to avoid, and assuming that those indicators are in the causal pathway. Another example is the move toward prescriptive infant growth standards, where what is prescriptive is the input that should go in during infancy, and all we are doing with the standard is showing what kind of growth you get when you follow the prescriptive inputs.

Dr. Lejarraga: In your list of risk factors, you didn't include maternal age. In my country that is strongly related to low birth weight for gestational age and to preterm birth. Could you make any comment about that?

Dr. Pelletier: It certainly is correlated. One could also, for instance, put in parity. But I wonder about the extent to which the effect is due to age per se or to other mechanisms that might be better specified in a more precise way.

Dr. Tudehope: I think this model has great potential for industrialized countries as well. We have found that SGA babies do not divide in a bimodal pattern on ponderal index at all. The proportionate/disproportionate classification is not appropriate for industrialized countries, but this pattern you are describing here has enormous implications for our management, not just for mortality and growth, but even for babies at risk of hypoglycemia and for the way in which we consider supposedly SGA babies. I certainly commend it as a step in the right direction, rather than the inappropriate proportionate/disproportionate, low/normal ponderal index system, which simply does not work. There are other factors we need to look at too, particularly substance use—not just nicotine, but opiates and other drugs as well.

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