Epidemiologic Evidence for a Potentiating Effect of Malnutrition on Child Mortality

ABSTRACT

Objectives. Despite broad agreement that severe malnutrition contributes to child mortality in developing countries and that malnutrition has a physiologically synergistic relationship with morbidity, evidence of an epidemiologic synergism has been lacking. Also, the literature provides conflicting evidence concerning the existence of elevated mortality among children with mild to moderate malnutrition. A review of published population-based studies of anthropometry–mortality relationships was undertaken to clarify these relationships.

Methods. Six studies with the relevant data were reanalyzed to test for synergism and elevated mortality in mild to moderate malnutrition.

Results. The results demonstrate that mortality increases exponentially with declining weight for age. This effect is consistent across studies and there is no apparent threshold effect on mortality. The primary difference across studies is in baseline levels of mortality, which determine the quantitative impact of malnutrition on mortality in a population.

Conclusions. These results indicate that mild to moderate malnutrition is associated with elevated mortality and that there is an epidemiologic synergism between malnutrition and morbidity. This previously undemonstrated finding has significant implications for child survival policies and research. (*Am J Public Health.* 1993;83:1130–1133)

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Introduction

The relationship between malnutrition and child mortality has been the subject of extensive research and, at times, controversy. The first systematic attempt to estimate the contribution of malnutrition to child mortality indicated that malnutrition was the underlying or contributing cause of death in roughly 55% of 1- to 4-year-olds.[1] Since that time, anthropometric indicators of malnutrition have repeatedly been shown to be predictive of subsequent death in prospective community-based studies from several countries in Africa and Asia.[2] Key objectives of some of these studies and subsequent discussions[3–6] were to describe a threshold effect in the relationship and to estimate stable epidemiologic parameters describing the impact of malnutrition on risk of mortality.

Two key assumptions were implicit in these earlier discussions: (1) that malnutrition is a disease that contributes to mortality in an additive fashion, in such a way that comon epidemiologic parameters (e.g., sensitivity, specificity, attributable risk) can describe the relationship; and (2) that these parameters reflect intrinsic properties of the disease (malnutrition) and can be applied across populations. However, both of these assumptions are at odds with the knowledge from the clinical and biomedical literature,[7] that child mortality is a function of a synergism between malnutrition and morbidity. This paper provides a mathematical description for this synergism that can be tested with available data and applies the model to the results of previously published studies.

Methods

Theoretical Model of Synergism

A simple specification of the synergism between malnutrition and morbidity is that exposure to disease is constant within any given population but the fatality rate per exposure (exposure fatality rate) varies with degree of malnutrition. This would conform to a multiplicative model of the form

$$D_i = \alpha E_i F_i, \quad (1)$$

where D_i = mortality rate (deaths/1000), E_i = disease exposure rate (exposures/1000), F_i = exposure fatality rate (deaths/exposure), and α is a constant, with i indexing populations. It follows that

$$\log(D_i) = \log(\alpha) + \log(E_i) + \log(F_i). \quad (2)$$

According to the latter model, the logarithm of mortality will be linear across different grades of malnutrition and the slopes will tend to be parallel across populations with different disease exposure rates.

For practical purposes it is necessary to rewrite the above expression to apply it to the available data. The model can be rewritten as

$$\log(D_i) = \beta_{0i} + \beta_1 M, \quad (3)$$

where D_i is as defined above and M is the level of malnutrition. This model implies that $\log(D_i)$ is a linear function of malnutrition with slope β_1. This is equivalent to saying that mortality is an exponential function of malnutrition within any given

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This paper was accepted January 12, 1993.

population. Moreover, if the theory of synergism is correct, it is expected that the slopes will tend to be parallel across populations and the intercepts will vary according to disease exposure rates (i.e., levels of morbidity). This is tantamount to saying that the effect of malnutrition on mortality varies according to the baseline level of mortality in the population as reflected among the better-nourished segment, which is a reflection of the disease burden in the population.

If, on the other hand, child mortality conforms to a simple additive function of malnutrition, this could be written as follows:

$$D_i = \beta_{0i} + \beta_1 M. \quad (4)$$

This equation implies that the *observed* mortality rate in a population (rather than the log) increases as a linear function of malnutrition within a given population, and, as above, the intercepts will vary according to disease exposure rates (i.e., levels of morbidity).

Application of the Model to Empirical Studies

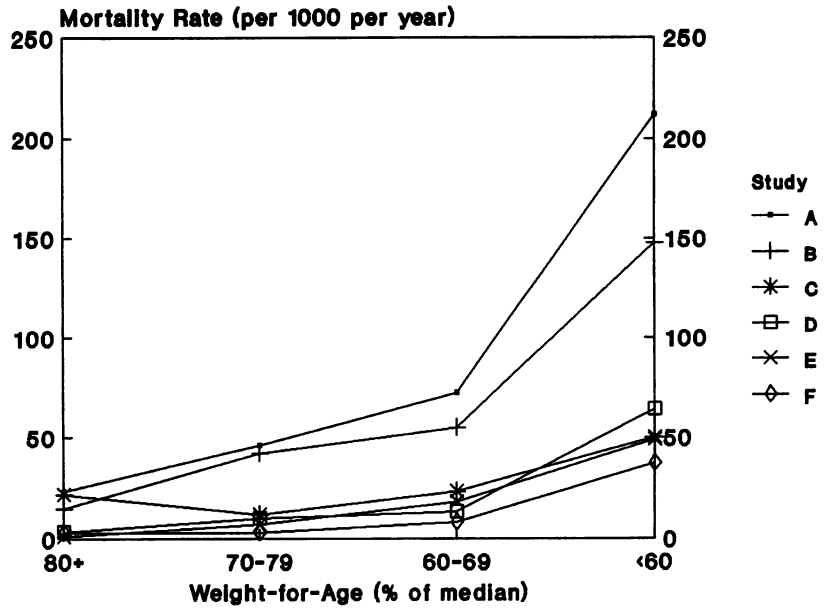
The present paper is based on an analysis of published data from six studies.[8–13] The six studies identified (Table 1) had the published data necessary for cross-study comparison. An additional nine studies have been published on the topic,[2] but their results were presented in noncomparable ways. All studies except one[15] found the expected inverse association between nutritional status and mortality, thereby indicating that the analysis based on these six studies is representative of what would be expected from all available studies. Moreover, the potential selection bias in this body of literature is low, because the large and expensive nature of these studies ensures that both positive and negative results are published.[16] Because of the differences in length of follow-up, all mortality rates in this analysis have been standardized to a 12-month length of follow-up.

The appropriateness of the synergistic model is assessed by comparing the results from equation (3) with those from equation (4). The primary test is to simply compare the parallelism in slopes arising from the two models. In addition, the goodness of fit was described by using an R^2 criterion and by estimating the inter-population variance in parameters estimated from these two equations (attributable risk and relative risk).

TABLE 1—Number of Children (and Deaths, in Parentheses) in the Six Studies Reanalyzed

Study	Location	Length of Follow-Up, mo	Weight-for-Age Category, % of Median[a]			
			<60%	60–69%	70–79%	≥80%
A[8]	Tanzania	12	33 (7)	194 (14)	674 (31)	1551 (36)
B[9]	Papua New Guinea	18	18 (4)	60 (5)	347 (22)	722 (16)
C[10b]	Bangladesh 1	24	387 (39)	735 (34)	644 (15)	232 (10)
D[11]	Bangladesh 2	12	225 (11)	338 (6)	287 (2)	88 (0)[c]
E[12]	Bangladesh 3	6	507 (16)	2591 (17)	4333 (23)	2430 (4)
F[13]	India	12	218 (8)	1025 (8)	2126 (7)	1776 (5)

[a]Studies B and F used the Harvard reference values; all others used values recommended by the World Health Organization.[14]
[b]For comparability purposes, the data were taken from a reanalysis[10] of data originally reported earlier.[3]
[c]An assumed mortality rate of 1/1000 was used for this group in Figure 2 to allow the value to be plotted on a log scale.



Note. Populations and attributable risk (in parentheses) due to severe malnutrition (<60% weight-for-age): A: Tanzania[8] (189); B: Papua New Guinea[9] (133); C: Bangladesh 1[10] (29); D: Bangladesh 2[11] (NA); E: Bangladesh 3[12] (60); F: India[13] (34).

FIGURE 1—Mortality rate (per 1000 children per year), by weight-for-age status, in six studies.

Results

Figure 1 shows the relationship between child weight-for-age and subsequent mortality in six studies from India, Bangladesh, Papua New Guinea, and Tanzania. The studies vary somewhat in the children's age range, although all children were between 6 and 59 months, and the follow-up period ranged from 6 to 24 months. With the exception of one data point (study C), the figure reveals an increase in mortality between 80% weight-for-age or better and 60% weight-for-age, and all studies show a sharp increase in mortality below 60% weight-for-age. Thus, there is an overall increase in mortality with deteriorating nutritional status.

Figure 1, which conforms to the additive model (4), also shows no consistency in the attributable risk due to malnutrition, which is the difference in mortality rates between the well-nourished and a given category of the malnourished. The attributable risk at 60% weight-for-age or less is 5.6 times larger in Tanzania than in India. This lack of consistency in the attributable risk estimates is not surprising if the synergistic model is correct. The in-

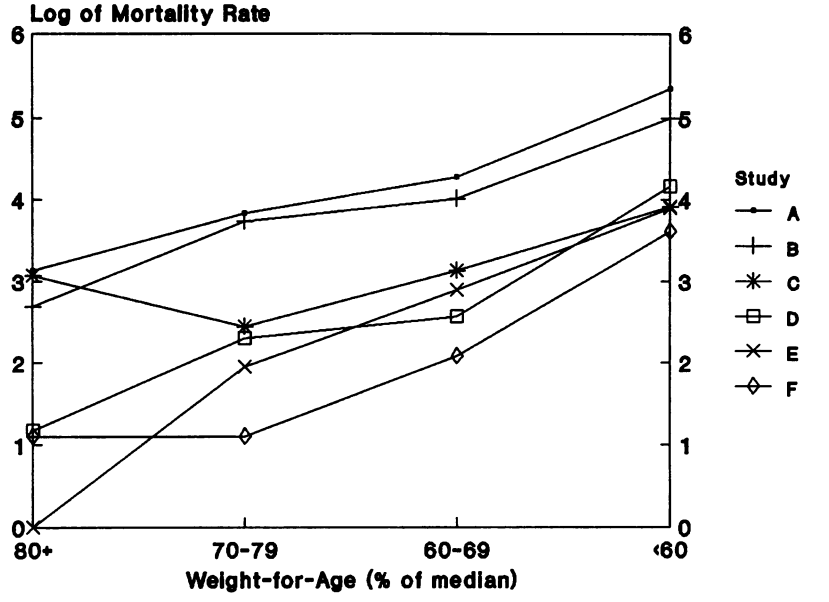


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FIGURE 2—Log of mortality per 1000 children per year, by weight-for-age status.

consistency strongly suggests that a different approach is needed.

When the synergistic model (3) is applied to the available data (Figure 2), the log of mortality is seen to be much more linear across grades of malnutrition and the slopes are much more parallel across populations than in Figure 1. This pattern was confirmed by evaluating goodness of fit for three models in which the observed mortality rate was expressed as different functions of weight-for-age and study: linear, linear and quadratic, and exponential. The resulting coefficients of determination (R^2) were, respectively, .71, .80, and .96. Therefore, the exponential model (equivalent to expressing mortality rate as the logarithm) fits the data very well and requires one degree of freedom less than the other two models.

The exponential model also means that the risk of mortality at a given level of malnutrition, relative to the mortality among the well-nourished, will be more or less constant across populations and is an estimate of the relative risk of the underlying malnutrition-specific fatality rates. Building on the multiplicative model presented above in equation (1), define D_M as the mortality risk at a given level of malnutrition and D_0 as the mortality risk among the well-nourished. Then the relative risk is $D_M/D_0 = (\alpha/\alpha)(E_i/E_i)(F_M F_0)$ and should be constant if this multiplicative model is correct.

The predicted consistency in relative risk when the multiplicative model is used is, in fact, observed. The unweighted average relative risk due to malnutrition is uniform across the five studies that reported deaths in the well-nourished category. The mean relative risk is 11 for severe malnutrition (<60% weight-for-age), 3 for moderate malnutrition (60% to 69%), and 2 for mild malnutrition (70% to 79%). The coefficients of variation for these estimates are .582, .397, and .584, respectively; each of these is much smaller and more consistent than the corresponding coefficient of variation for attributable risk estimates for the three categories of malnutrition (.783, 1.032, and 1.606, respectively), confirming that these data conform to an exponential model more than to an additive model.

The corresponding logistic analysis, which has certain statistical virtues over the simple log transformation in Figure 2, indicates that the odds of dying increase at a compounded rate of 7.3% for each percentage point deterioration in weight-for-age. In this analysis an empirical Bayes method was used to estimate parameters for a two-stage hierarchical model. This model included parameters for weight-for-age (in four categories), among- and within-study variance, and correlation among substudies (levels of weight-for-age) within studies.[17] Note that this 7.3% compounded increase in mortality for each percentage point decline in weight-for-age results in a much larger mortality impact for those populations with relatively high baseline levels of mortality, as would be expected from the theory of synergism.

Discussion

The implications of these results are profound. First, the better fit of the exponential model provides strong evidence that a threshold effect does not exist in the relationship between malnutrition and child mortality, at least over the wide range of nutritional status represented here. Contrary to earlier impressions,[3,4] mild to moderate malnutrition is indeed associated with an elevated risk of mortality, an association that has great policy significance considering the overwhelming number and proportion of children who fall into this category. The result is that 45% to 83% of all malnutrition-related deaths (i.e., the population attributable risk) occur to children in the mild to moderate category (weight-for-age 60% to 80%).[2] These deaths would not be reduced if policies and programs were directed solely toward treatment of the severely malnourished.

The observation that the relationship between mortality and malnutrition is better described by an exponential model than by an additive model might be due to other factors besides changes in the exposure fatality rate. In principle this could result from greater disease exposure and less effective medical care among the malnourished. However, it seems unlikely that these factors would diminish at such similar rates and have such similar exponential effects across populations as weight-for-age decreases. Similarly, these results cannot be due to inadequate sample sizes, underenumeration of mortality, poor measurement of weight-for-age, or even to the possibility that weight-for-age is a poor proxy for malnutrition. All of these factors would tend to bias the slopes in Figures 1 and 2 toward zero (i.e., flatten the relationship, as in the Zairean study[15]) or cause the lines from some studies to intersect those from others. These factors cannot account for the parallelism observed in Figure 2.

A more likely explanation for the consistency in log-transformed results across populations relates to the specified synergy between malnutrition and infection. This synergy means that the mortality rate at a given level of disease exposure depends on a potentiating effect of malnu-

trition, not on an additive effect. Therefore, the epidemiologic statistics pertinent to an additive model as used in the earlier literature (e.g., attributable risk, sensitivity, specificity) have no intrinsic meaning in a heterogeneous population or across countries. More important, the practice of quantifying the relative contribution of various diseases to mortality, as is now commonplace among funding agencies in deciding priorities, is meaningless in such circumstances. It presumes implicitly that malnutrition's contribution is additive and, therefore, that one can partition deaths into those due to malnutrition and those due to other causes. Our findings indicate that such a division is impossible because the relative contribution of malnutrition to mortality depends on morbidity rates, and the contribution of morbidity varies according to the prevalence of malnutrition.

These results highlight the need to elucidate the mechanisms by which malnutrition increases the fatality rate per exposure so that effective intervention strategies can be designed. In principle, malnutrition could operate on the link between exposure and infection or on the link between infection and severity. There are numerous biologic mechanisms by which malnutrition could affect the incidence or severity of infection, including disruption of epidermal integrity and various components of the immune system.[18] However, it is uncertain how these disruptions would be manifested epidemiologically. It is known from epidemiologic studies that malnutrition affects severity of diarrhea much more than it affects incidence of diarrhea.[19] Severity of measles is also markedly affected by malnutrition.[20] It is unclear whether this pattern is generalizable to other types of morbidity, and elucidation of the basis for these differential mechanisms would reveal facts of wider clinical utility. It is also important to note that deficits in the weight-for-age of children may not be caused solely by protein-energy malnutrition but may also arise from associated micronutrient deficiencies.[21–26]

A controlled intervention trial would be a stronger approach for elucidating synergistic relationships of the type discussed here; however, an earlier effort along these lines had very large sample sizes that were still inadequate to permit an examination of synergistic effects on child mortality.[27] Apart from being of questionable feasibility, such studies may not be ethically appropriate today. Thus, the present results represent the strongest available evidence that biological synergism has effects on mortality at a population level and across all grades of malnutrition.

The policy implications are that (1) significant reductions in child mortality can be expected through reductions in morbidity *or* malnutrition—although the greatest impacts can be achieved by addressing both simultaneously—and (2) the greatest impacts can be expected when attention is paid to all grades of malnutrition, and in those populations having the highest baseline levels of morbidity and malnutrition. In contrast to the additive model, which implicitly refers to preventing deaths in different children affected by disease or malnutrition, the synergistic model requires consideration of the relative costs of preventing death in a single child either by preventing exposure to disease or by preventing malnutrition. In practice, preventing both exposure to disease *and* malnutrition in malnourished populations is the most desirable option if one is also concerned about the survivor's quality of life. □

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