

Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles¹⁻³

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ABSTRACT

Background: Previous analyses derived the relative risk (RR) of dying as a result of low weight-for-age and calculated the proportion of child deaths worldwide attributable to underweight.

Objectives: The objectives were to examine whether the risk of dying because of underweight varies by cause of death and to estimate the fraction of deaths by cause attributable to underweight.

Design: Data were obtained from investigators of 10 cohort studies with both weight-for-age category (< -3 SDs, -3 to < -2 SDs, -2 to < -1 SD, and > -1 SD) and cause of death information. All 10 studies contributed information on weight-for-age and risk of diarrhea, pneumonia, and all-cause mortality; however, only 6 studies contributed information on deaths because of measles, and only 3 studies contributed information on deaths because of malaria or fever. With use of weighted random effects models, we related the log mortality rate by cause and anthropometric status in each study to derive cause-specific RRs of dying because of undernutrition. Prevalences of each weight-for-age category were obtained from analyses of 310 national nutrition surveys. With use of the RR and prevalence information, we then calculated the fraction of deaths by cause attributable to undernutrition.

Results: The RR of mortality because of low weight-for-age was elevated for each cause of death and for all-cause mortality. Overall, 52.5% of all deaths in young children were attributable to undernutrition, varying from 44.8% for deaths because of measles to 60.7% for deaths because of diarrhea.

Conclusion: A significant proportion of deaths in young children worldwide is attributable to low weight-for-age, and efforts to reduce malnutrition should be a policy priority. *Am J Clin Nutr* 2004;80:193-8.

KEY WORDS Underweight, child mortality, diarrhea, pneumonia, malaria, measles, global burden of disease

INTRODUCTION

Previously it was shown that a child's risk of dying as a result of undernutrition, defined as underweight or low weight-for-age, is not limited to only those children with the most severe form of malnutrition (1, 2). Rather, there exists a spectrum of risk associated with all degrees of malnutrition. Although the risk of dying is highest among the severely malnourished, when one considers the elevated risk of mortality associated with moderate malnutrition in combination with their high prevalence worldwide, it becomes clear that much of the burden of deaths as a result of undernutrition in young children is attributable to moderate,

rather than to severe, undernutrition. Pelletier et al (3) estimated that 55% of child deaths worldwide are attributable to undernutrition.

Despite problems in defining cause of death, especially in developing countries in which one would often need to rely on verbal autopsy methods, it is of interest to consider whether the relation between underweight and risk of dying varies by cause of death. For example, are the risks of dying of malaria as a result of undernutrition similar or different from the risks of dying of diarrhea? The purpose of this paper is to describe our analysis of existent data that relate weight-for-age and mortality from diarrhea, pneumonia, measles, and malaria—the principal causes of death of children in developing countries. The goals of the analysis were 1) to derive relative risk (RR) of dying as a result of underweight by cause of death and 2) to combine these estimates with prevalence data to calculate the fraction of deaths attributable to undernutrition during childhood.

SUBJECTS AND METHODS

Two key inputs are necessary to calculate the burden of disease attributable to undernutrition: 1) an estimate of the prevalence of low weight-for-age in young children and 2) the estimated RR of dying associated with child weight-for-age. Prevalences of malnutrition defined by low weight-for-age *z* score in each of 14 World Health Organization (WHO) mortality regions were estimated by analyzing in a standard manner 310 national nutrition surveys compiled in the WHO Global Database on Child Growth and Malnutrition (4). For each region, the average weight-for-age *z* score was calculated, and from this calculation the proportion of children with *z* scores -1.01 to -2.00 SDs, -2.01 to

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TABLE 1Prospective cohort studies with information on weight-for-age *z* score and survival or death by cause

Country	Citation	Age range	Follow-up period	Weight-for-age <i>z</i> score at the start of the follow-up period			
				<−3	>−3 to <−2	>−2 to <−1	>−1
		<i>mo</i>	<i>mo</i>				
Sudan	Fawzi et al (6)	6–72	6	365	985	1123	592
Senegal	Garenne et al (7)	0–59	6	1663	2186	2035	1249
Guinea-Bissau	Andersen (8)	0–59	6–12	1155	4366	7341	2731
Ghana	WHO/CHD (9)	0–12	12	46	183	506	1410
Nepal	West et al (10, 11)	0–72	12	1030	2082	2002	892
Bangladesh	Arifeen et al (12)	0–11	3	79	250	475	478
Pakistan	Khan et al (13), Jalil et al (14)	0–60	120	253	687	1241	1341
India	WHO/CHD (9)	0–12	12	172	639	1259	1295
Indonesia	Sutrisna et al (15)	0–60	18	207	240	797	4856
Philippines	Ricci and Becker (16)	0–59	3	800	3144	4834	5115

−3.00 SDs, and <−3.00 SDs were estimated. In a healthy population, we would expect only 13.6%, 2.1%, and 0.1% of children to be classified into each of these categories, respectively. Weight-for-age was chosen because it is the most widely used indicator of child nutritional status in developing countries, as well as in the studies available for analysis.

We used a variety of approaches to provide information for the second key input. Originally, a survey of the published literature was conducted to gather data to estimate the relation between anthropometric status and cause-specific mortality (5). Because available data were insufficient to accomplish our goal, we contacted investigators with relevant data (published or unpublished) and asked them to contribute specific study results for our analysis. Briefly, on the basis of published reports of studies examining causes of death among children in developing countries, we constructed a list of investigators to be contacted to collaborate in this endeavor. We then augmented this list with knowledge about the existence of other unpublished studies that might provide appropriate data for this purpose and contacted investigators to inquire whether they knew of other studies that might provide appropriate data.

Each investigator was asked to provide the following information: 1) a description of their study; 2) the number of children or child-years of study with weight-for-age *z* scores at the beginning of the follow-up period of <−3.00 SDs, −2.01 to −3.00 SDs, −1.01 to −2.00 SDs, 0.0 to −1.0 SD and >0.0 SDs; and 3) deaths in each category attributable to diarrhea, pneumonia, measles, malaria, other, and total (all cause) during the follow-up period. During analyses, we collapsed the last 2 categories of anthropometric status so that the reference group would comprise those children with weight-for-age *z* scores >−1.0 SD. This collapse was done because the number of deaths by cause for children >−1 SD was limiting in some studies and because the data did not indicate substantial differences in rates of death by cause between those rates with *z* scores −1 to 0 SDs and >0 SDs.

In all, 12 studies were identified, and data from 10 studies were included in the current analysis (6–16). We excluded 2 data sets: one from Peru because the study provided insufficient deaths for the analysis, and one from a case–control study in Brazil because it did not fit the overall analytic approach taken with the other studies, which were prospective cohort designs.

The 10 studies were conducted in sub-Saharan Africa and Asia (Table 1). Each study contributed data about deaths as a result of

diarrhea and pneumonia; however, exposure to infectious diseases such as malaria and measles depends on the ecology of the study setting and health care utilization (ie, measles vaccination rates). Therefore, 6 studies (Guinea-Bissau, Senegal, Ghana, Nepal, Indonesia, and The Philippines) contributed data on deaths as a result of measles, and 3 studies (Guinea-Bissau, Senegal, and Ghana) contributed data on malaria-related deaths. In the study in Guinea-Bissau, deaths as a result of malaria were reported as a result of fever; thus, deaths as a result of febrile illnesses other than malaria were necessarily included.

To estimate the relations between underweight and mortality risk, we followed the analytic procedures used by Pelletier (17). The steps are described briefly here. First, we calculated and then graphed the mortality rates by anthropometric status and cause of death for each study both in simple terms (per 1000) and in proportional terms (as the logarithm of the mortality risk). Second, we compared the results and goodness-of-fit statistics of regression analyses of the natural logarithm of mortality by weight-for-age *z* score category with the results of the simple mortality rates by weight-for-age *z* score category and verified that the models with log mortality rate provided a better fit of the data. For these analyses, we used weighted regression and the weighting scheme of Pelletier (17): [(1/deaths) + (1/children)]. Third, the coefficients from the weighted random effects models for log mortality rate were used to provide global estimates of the RR and 95% CI of mortality for each weight-for-age category. The midpoint of the anthropometric category was used for estimation, and −0.5 SD was considered the value of the reference weight-for-age category of >−1.0 SD. Fourth, we calculated the population attributable fraction (PAF) of deaths by cause for undernutrition (weight-for-age <−1 SD) for each of the 14 WHO regions with use of a standard formula (18) in which the minimal risk exposure or counterfactual exposure distribution was the distribution of weight-for-age in the high-income countries of North America and Western Europe. To obtain a global estimate of the PAF, we used the method described by Vander Hoorn et al (19). We used information on the number of deaths by cause and all-cause mortality for each region (20), calculated the number of deaths attributable to undernutrition, summed across the regions, and divided by the global number of deaths as a result of each cause. For all-cause mortality, we used our estimated risks of overall mortality associated with underweight and regional estimates of total deaths in children aged birth to 4 y.

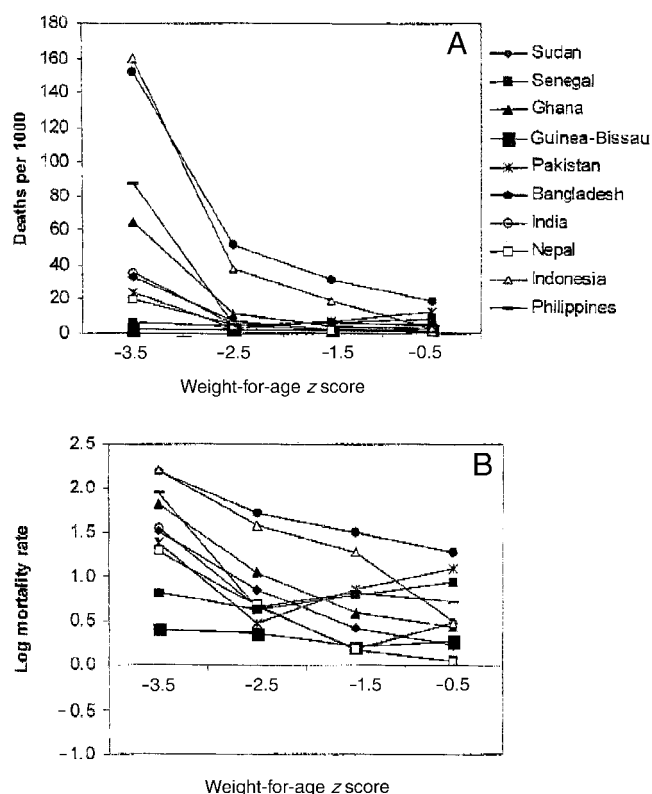


FIGURE 1. Underweight and mortality as a result of pneumonia. A: Deaths per 1000; B: logarithm of deaths per 1000.

SAS (version 8; SAS Institute Inc, Cary, NC) was used for all analyses.

RESULTS

For each study, the absolute mortality rates by weight-for-age category and cause of death were calculated and compared graphically with those relating weight-for-age category and log mortality rate. As shown for mortality as a result of pneumonia in Figure 1, the apparent heterogeneity across study settings in the relations between weight-for-age category and mortality risk in absolute terms (Figure 1A) largely disappears when the relations are regraphed with mortality risk considered in proportional terms (Figure 1B).

The relations between weight-for-age category and log mortality for each cause of death were estimated with use of weighted random effects regression. From these models, RR (95% CI) of dying by cause of death were calculated with use of weight-for-

age > -1.0 SD as the reference category (Table 2). There are significant increased risks of dying associated with low weight-for-age for overall mortality as well as for each cause of death examined. Shown in Table 3 is the estimated mean weight-for-age z scores and prevalence of children in each weight-for-age category in each of the 14 WHO regions. For The Americas A and Europe B regions, the average z score is 0, and the prevalences in each category are those expected in a healthy population. In contrast, the average z scores in sub-Saharan Africa (Afr D and Afr E) and Southeast Asia (Sear B and Sear D) are between -1.35 and -1.90, and prevalences of children with moderate (z scores: -2.01 to -3.00 SDs) or severe (z scores: < -3.00 SDs) malnutrition are quite high.

These 2 pieces of information were combined to estimate the PAF for undernutrition overall and for each WHO region (Table 4). As shown, the PAF for The Americas A and Europe A groups are 0%, whereas the PAF for all-cause mortality for the poorest regions of the world are more than 50%. Overall, it is estimated that 52.5% of deaths in young children worldwide are attributable to undernutrition, with the proportion of deaths varying from 44.8% for measles to 60.7% for diarrhea.

DISCUSSION

These analyses indicate that undernutrition in young children contributes significantly toward the global burden of disease. Indeed, childhood underweight is the leading cause of global burden of disease (21, 22). Deaths attributable to undernutrition encompass 53% of all childhood deaths, echoing the previous estimate of 55% of all deaths to young children (1, 3). Among the principal causes of death in young children, 60.7% of deaths as a result of diarrhea, 52.3% of deaths as a result of pneumonia, 44.8% of deaths as a result of measles, and 57.3% of deaths as a result of malaria are attributable to undernutrition. These attributable fractions are large because undernutrition is the underlying cause for most deaths associated with severe infections and because undernutrition is still highly prevalent in many regions of the world. These numbers place prevention of undernutrition among children as one of the top priorities for action in efforts to reduce child mortality.

It should be emphasized that the calculations made by Pelletier et al (3) related to childhood deaths, ie, deaths among children aged 1-4 y. This specificity was related to the limited availability of data sets with subjects aged younger than 1 y. As shown in Table 1, many of the studies available for our analyses were prospective cohort designs that monitored the vital status of children aged birth to 4 y. Heuristically, one could apply our results to all deaths during infancy, and we have done so. However, it is also understood that a sizable number of deaths during

TABLE 2 Relative risk (95% CI) of mortality overall and by cause associated with low weight-for-age estimated from weighted random effects regression analysis

Cause of death	<3 SDs [†]	-2 to -3 SDs	-1 to -2 SDs	>-1 SDs
Diarrhea	12.50 (7.19, 21.73)	5.39 (3.73, 7.79)	2.32 (1.93, 2.79)	1.0
Pneumonia	8.09 (4.36, 15.01)	4.03 (2.67, 6.08)	2.01 (1.63, 2.47)	1.0
Malaria	9.49 (3.25, 27.66)	4.48 (2.20, 9.15)	2.12 (1.48, 3.02)	1.0
Measles	5.22 (2.29, 11.88)	3.01 (1.74, 5.21)	1.73 (1.32, 2.28)	1.0
All causes	8.72 (5.55, 13.72)	4.24 (3.13, 5.53)	2.06 (1.77, 2.39)	1.0

[†] Calculated at -3.5, -2.5, and -1.5 compared with 0.5 SD weight-for-age from weighted random effects models. A significant test for trend is evidenced by a statistically significant (P < 0.05) coefficient for weight-for-age in each model.

TABLE 3Mean *z* score and percentage of children in each weight-for-age category in each World Health Organization (WHO) region¹

WHO region ²	Mean <i>z</i> score	Prevalence			
		<−3 SDs	>−3 to <−2 SDs	>−2 to <−1 SDs	>−1 SDs
			%		
Africa D	−1.54	7.1	25.1	38.3	29.5
Africa E	−1.5	6.8	24.2	38.3	30.7
The Americas A	0	0.1	2.1	13.6	84.2
The Americas B	−0.35	0.5	4.5	20.8	74.2
The Americas D	−0.84	1.6	10.8	31.3	56.3
Eastern Mediterranean B	−0.6	0.8	7.3	26.3	65.6
Eastern Mediterranean D	−1.33	4.7	20.4	37.8	37.1
Europe A	0	0.1	2.1	13.6	84.2
Europe B	−0.57	0.7	6.9	25.7	66.7
Europe C	−0.05	0.2	2.4	14.5	82.9
Southeast Asia B	−1.35	5.0	20.8	37.9	36.3
Southeast Asia D	−1.9	13.4	32.5	35.8	18.3
Western Pacific Region A	−0.22	0.3	3.5	18.0	78.2
Western Pacific Region B	−1.0	2.3	13.6	34.1	50.0

¹ Expected percentages of children in each weight-for-age category in a healthy population are those reported here for The Americas A and Europe A.² Regions for the Global Burden of Disease project. A indicates very low child mortality and very low adult mortality; B, low child mortality and low adult mortality; C, low child mortality and high adult mortality; D, high child mortality and high adult mortality; E, high child mortality and very high adult mortality.

the neonatal period relate more to events during pregnancy, birth, and the transition to extrauterine life and less to the infectious causes of death studied here.

The studies included here used specific protocols to assess both anthropometric status and cause of death. With minimal training, weight measures are highly accurate and precise; therefore, errors in exposure assessment are unlikely to have affected our results. However, it is also true that the estimates of the weight-for-age distribution for each WHO region were imputed on the basis of the best available information to date; thus, discrepancies with present extent of underweight are possible as new surveys become available. In most cases, cause of death was

determined through verbal autopsy that uses standard protocols (23). Several reasons exist why the results for measles and malaria deaths should be interpreted with caution. First, a reduced number of studies contributed to these analyses, 6 for measles and 3 for malaria. Second, past studies on the influence of low weight-for-age on measles mortality yielded equivocal results (24–26). Third, attributing deaths to malaria is problematic, and, as in the study in Guinea-Bissau, deaths as a result of malaria were not distinguished from deaths as a result of other causes of fever unless these illnesses had symptoms or signs consistent with other causes such as diarrhea or pneumonia. The results for Guinea-Bissau are consistent with those from Senegal, and, although the results from

TABLE 4

Population attributable fraction (PAF) of deaths by cause and World Health Organization (WHO) region

WHO region ¹	PAF by cause of death				
	All causes	Diarrhea	Pneumonia	Measles	Malaria
			%		
Africa D	56.1	64.7	54.6	45.2	57.7
Africa E	55.1	61.7	53.6	44.2	56.7
The Americas A	0.00	0.00	0.00	0.00	0.00
The Americas B	13.2	16.1	12.6	9.3	13.8
The Americas D	32.4	38.1	31.2	24.3	33.7
Eastern Mediterranean B	22.6	27.1	21.7	16.5	23.7
Eastern Mediterranean D	49.7	56.3	48.2	39.2	51.3
Europe A	0.00	0.00	0.00	0.00	0.00
Europe B	21.3	25.5	20.4	15.5	22.3
Europe C	2.2	2.8	2.1	1.5	2.3
Southeast Asia B	50.4	57.1	49.0	39.9	52.0
Southeast Asia D	64.8	71.1	63.4	53.8	66.4
Western Pacific Region A	8.1	10.0	7.7	5.7	8.5
Western Pacific Region B	38.4	44.5	37.1	29.3	39.8
World	52.5	60.7	52.3	44.8	57.3

¹ Regions for the Global Burden of Disease project. A indicates very low child mortality and very low adult mortality; B, low child mortality and low adult mortality; C, low child mortality and high adult mortality; D, high child mortality and high adult mortality; E, high child mortality and very high adult mortality.


Ghana suggest a different pattern of relation between underweight and mortality risk, the number of deaths as a result of malaria is quite small ($n = 8$). Further studies would need to be included to refine these estimates.

It is important to consider that low weight-for-age is commonly associated with deficiencies of micronutrients (27). For example, zinc deficiency contributes to poor growth in young children (28). The association of low weight-for-age with these deficiencies could mean that some of the risk attributed to underweight should be attributable to specific micronutrient deficiencies; however, these other deficiencies also occur in children who are not underweight. Moreover, zinc supplementation in populations that have a moderately high prevalence of zinc deficiency has had similar effects on reducing infectious disease morbidity in children who were classified to be undernourished or not (29), and vitamin A supplementation reduces mortality in vitamin A-deficient populations regardless of anthropometric status (11, 30). Although such evidence is not conclusive, it does suggest that the relations observed here may only in part be attributed to the effects of concurrent micronutrient deficiencies.

Undernutrition contributes to the morbidity burden among children as well, but this contribution is not consistent across illnesses. Although evidence suggests that low weight-for-age increases risk of having pneumonia, diarrhea, or a clinical malarial attack, it may not affect the risk of measles, which is ubiquitous even in well-nourished unvaccinated children (22). The relatively greater risk of dying of infectious disease than for the risk of having the infectious disease is understandable, given the synergy between illness and malnutrition (31, 32). This synergy was most clearly demonstrated for diarrhea illnesses (33), and our analyses suggest an extension to pneumonia, malaria, and measles as well.

It is well understood that young children with moderate-to-severe undernutrition are at increased risk of dying, but note that in these analyses children with weight for age z scores between -1.01 and -2.00 SDs were about twice as likely to die as children with z scores > -1 SD (the reference group). We have labeled this group as likely suffering from mild undernutrition, although some have argued against using this term because one would expect a sizable proportion (13.6%) of a healthy reference population to fall into this category and this expectation needs to be considered during analysis (34). It is important to recognize that in these analyses we have used the expected prevalences from the reference population as the counterfactual, which essentially removes them from the burden estimates, and, thus avoids this problem. We are not arguing for a redefinition of malnutrition to include all children < -1.00 SD, a topic not dealt with in this paper, but our results do emphasize the point that in populations with high prevalences of undernutrition, 30–40% of children have z scores between -1.00 and -2.00 SDs and have small yet significantly increased risk of dying.

These findings underscore the need to make the improvement of the nutritional status of children a priority. In addition to reducing growth faltering, investments in child nutrition programs would support and complement disease-specific prevention and control programs in developing countries. In round numbers, this means that 1 000 000 pneumonia deaths, 800 000 diarrhea deaths, 500 000 malaria deaths, and 250 000 measles deaths could be prevented by eradication of child undernutrition. Although the potential for nutrition programs to reduce diarrhea morbidity and mortality was previously recognized (35), the

result that a large proportion of child deaths as a result of malaria could be prevented by child nutrition interventions is noteworthy. With current programmatic efforts, rates of undernutrition among children are declining in most countries at 1% per year or less (36). We and others argue that this amount of progress is unacceptable (37, 38). Strategies to more effectively reduce child undernutrition by using experiences gained from successful nutrition programmers (39) are urgently needed. 

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