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THE INTERRELATIONSHIP OF MALNUTRITION AND DIARRHEA  
IN A PERIURBAN AREA OUTSIDE ALEXANDRIA, EGYPT

By

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<b>13. ABSTRACT (Maximum 200 words)</b>  Background: In the developing world, children are often observed to have both diarrhea and malnutrition. This observation has led many researchers to speculate that diarrhea may produce malnutrition and that malnutrition may predispose to diarrhea. In this study, the interrelationship between diarrhea and malnutrition was investigated among 143 Egyptian children less than 3 years of age. Methods: For 22 months, children were followed for diarrhea at twice weekly home visits and measured for nutritional status at approximately 3-month intervals. Nutritional measurements were converted to z-scores based on the National Center for Health Statistics/World Health Organization (NCHS/WHO) reference population. Results: Three hundred fifty-eight diarrheal episodes were reported with only 1% of episodes lasting 14 days or more. Stunting, wasting, and low weight-for-age were found in 19%, 3%, and 7%, of these children, respectively. When testing whether malnutrition predisposes to diarrhea, a weight-for-age z-score of <-2 standard deviations was associated with increased incidence of diarrhea (RR = 1.7, P < 0.01) but not height-for-age or weight-for-height. Diarrhea itself was associated with a subsequent attack of diarrhea (RR = 2.1, P < 0.001). During short intervals of follow-up (approximately 3 months), an association was detected between diarrhea episodes and growth faltering for height-for-age z-score (-0.16, P < 0.05). This association was reduced, however, when analyzed during 6-month intervals, if no diarrhea was reported in either the first or second half of this interval. Conclusions: In a population with moderate malnutrition, both low weight-for-age and diarrhea itself are associated with increased diarrhea risk. Diarrhea alone does not appear to contribute substantially to malnutrition when children have diarrhea-free time for catch-up growth.			
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## The Interrelationship of Malnutrition and Diarrhea in a Periurban Area Outside Alexandria, Egypt

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### ABSTRACT

**Background:** In the developing world, children are often observed to have both diarrhea and malnutrition. This observation has led many researchers to speculate that diarrhea may produce malnutrition and that malnutrition may predispose to diarrhea. In this study, the interrelationship between diarrhea and malnutrition was investigated among 143 Egyptian children less than 3 years of age.

**Methods:** For 22 months, children were followed for diarrhea at twice weekly home visits and measured for nutritional status at approximately 3-month intervals. Nutritional measurements were converted to z-scores based on the National Center for Health Statistics/World Health Organization (NCHS/WHO) reference population.

**Results:** Three hundred fifty-eight diarrheal episodes were reported with only 1% of episodes lasting 14 days or more. Stunting, wasting, and low weight-for-age were found in 19%, 3%, and 7%, of these children, respectively. When testing

whether malnutrition predisposes to diarrhea, a weight-for-age z-score of  $<-2$  standard deviations was associated with increased incidence of diarrhea (RR = 1.7,  $P < 0.01$ ) but not height-for-age or weight-for-height. Diarrhea itself was associated with a subsequent attack of diarrhea (RR = 2.1,  $P < 0.001$ ). During short intervals of follow-up (approximately 3 months), an association was detected between diarrhea episodes and growth faltering for height-for-age z-score ( $-0.16$ ,  $P < 0.05$ ). This association was reduced, however, when analyzed during 6-month intervals, if no diarrhea was reported in either the first or second half of this interval.

**Conclusions:** In a population with moderate malnutrition, both low weight-for-age and diarrhea itself are associated with increased diarrhea risk. Diarrhea alone does not appear to contribute substantially to malnutrition when children have diarrhea-free time for catch-up growth. *JPGN* 32:189-196, 2001.  
**Key Words:** Children—Diarrhea—Growth—Malnutrition. © 2001 Lippincott Williams & Wilkins, Inc.

For children in developing countries, the average estimated incidence of diarrhea is 2.6 episodes per year, resulting in 2.2 million deaths annually (1). In the same population segment, malnutrition is a considerable health

problem with prevalence rates estimated to range from 4% to 46% with 1% to 10% severely malnourished (2). Based on the coexistence of these two diseases, the interrelationship of diarrhea and malnutrition has been the subject of intensive investigation, particularly in relation to the direction of causality.

Dr. Mourad is deceased (1996).

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Findings from several analytical studies have suggested that diarrhea contributes to malnutrition (3-8). In young Gambian children, weight deficit was shown to correlate directly with the percentage of days of diarrhea during the first year of life (3,4). In a cohort of Colombian children observed from birth to 36 months of age, the number of days with diarrhea was inversely associated with attained height (5).

Without denying that diarrhea may contribute to faltering growth in some circumstances, a few investigators have questioned the clinical significance of this effect (9-13). It has been suggested that catch-up growth may mitigate the transitory effect of diarrhea on nutritional status. Thus, studies designed to measure the effect of diarrhea on malnutrition over short periods have been

criticized, because the effect of subsequent accelerated or catch-up growth is disregarded. In addition, the biological plausibility of the diarrhea-to-malnutrition paradigm has been questioned (9,11), and few studies have clearly established that diarrhea precedes growth retardation.

Stronger empirical evidence indicates that malnutrition predisposes to diarrhea (11). Nevertheless, studies supporting such an association have been criticized because of methodologic flaws and inconsistent findings between studies (14). Specific criticisms have included no controlling for confounders, inadequate adjustment for repeated measures on the same individual, collection of anthropometric data after diarrheal episodes, and inadequate attention to the changing nutritional status of children over time.

In a longitudinal, community-based study of diarrheal diseases in children less than 3 years of age living in rural lower Egypt, periodic anthropometric data were collected to assess the interrelationship between diarrhea and malnutrition in this population. This study was designed to measure the prevalence of malnutrition in this population and to ascertain whether malnutrition predisposes to an increased incidence of diarrhea and whether diarrhea itself predisposes to subsequent diarrheal illness, potentially explaining part of the relationship between malnutrition and diarrhea.

Conversely, the study was designed to ascertain whether diarrhea is associated with malnutrition when allowing for catch-up growth during diarrhea-free time. This is the first study in which these issues have been investigated in Egyptian children.

## MATERIALS AND METHODS

### Study Approval, Location, and Time

This study was approved by the human subjects committees of United States Naval Medical Research Unit 3 (NAMRU-3), Cairo, Egypt, and the Naval Medical Research Center, Bethesda, Maryland, U.S.A. Written informed consent was obtained from a parent or guardian of each enrolled subject.

The study population was drawn from three periurban, agricultural villages located 10 km southwest of Alexandria, Egypt. During the study period of November 1993 through September 1995, at least one full year of diarrheal disease surveillance and periodic anthropometry were performed in these villages for each child.

### Population and Procedures

In November 1993, children from the first village were enrolled, followed by enrollment of children from the second village in January 1994. Children in the third village were enrolled in July 1994. Staggered enrollment reduced supervision and management problems associated with too fast an accrual of children. Before enrollment, villages were mapped and a house-to-house census was performed. Each household was characterized according to selected sociodemographic

variables and household features pertaining to hygiene, water use, and defecation practices. Next, children less than 24 months of age were evaluated for eligibility. Newborns were excluded if a major congenital anomaly or history of severe illness was identified. Children enrolled beyond the first month of life were excluded when evidence of a chronic illness (any illness that required repeated hospital admission) was obtained on screening history or examination.

Each child was visited in the home twice weekly until the third birthday or until study termination in September 1995. At each visit, a trained interviewer asked about any loose or watery stools since the last visit. If one or more loose or watery stools was reported, the mother was queried about the frequency of stools, presence of blood in stool, fever, vomiting, and other clinical characteristics of the child. Oral rehydration therapy was provided. Medical referrals were made for children who needed intravenous fluids, treatment of chronic illnesses and other acute conditions, and for diagnostic and surgical evaluations.

Height and weight measurements were taken every 3 months in a village clinic. For children less than 2 years of age, length was measured with a length board. A height stick was used for older children. Both the length board and the height stick were calibrated in millimeters. Measurements were recorded to the nearest 0.1 cm. Weights were taken using calibrated floor scales. The difference between the weight of a mother alone and a mother with her unclothed or lightly clothed child was recorded to the nearest 100 g.

### Definitions

A "diarrheal day" was defined as the occurrence of at least three unformed stools (or at least one, if bloody) in a 24-hour period. For breast-fed infants, the mother also was asked to indicate increased frequency or decreased consistency of stools from the normal defecation pattern. An episode of diarrhea began on the first diarrheal day after at least three consecutive nondiarrheal days and ended on the last diarrheal day to be followed by at least three consecutive nondiarrheal days.

A household latrine with disposal of waste into a sealed pit or local sewage system was considered a sanitary latrine. Exclusive breast-feeding was defined as receipt of only breast milk from a mother or wet nurse and no other liquids or solids with the exception of drops or syrups consisting of vitamins, mineral supplements, or medicines (15). Exclusive breast-feeding was ascertained during monthly surveys. A child, who was recorded as exclusively breast-feeding at the first but not the subsequent monthly survey, was listed as having discontinued exclusive breast-feeding halfway between the two surveys.

Education consisted of any secular schooling completed at a government or private school. Because educational attainment was limited in adults, mothers were categorized as having any or no education. Socioeconomic status was expressed as a score ranging from 0 to 28 points and based on a sum of the number of expensive items found in the household (washing machine, car or truck, radio, television) and home ownership. Using the index, households in the lowest tertile of the score were categorized as poor relative to other families in the village.

### Nutritional Indices and Use of z-Scores

To indicate a child's nutritional status, anthropometric indices (height-for-age, weight-for-height, weight-for-age) were

expressed as z-scores (16). A z-score is the departure in standard deviation (SD) units of a weight and/or height measurement from the mean of an age- and sex-specific reference population. Anthropometric data from reference populations published by the National Center for Health Statistics (NCHS) and the United States Centers for Disease Control were used as standards (17,18). Anthropometric measures were converted to z-scores using the EPINUT component of the EPI-INFO computer program (19).

The z-score cutoff used to classify moderate malnutrition was SDs below the reference median ( $<-2$  SD). The cutoff for severe malnutrition was considered SDs below the median ( $<-3$  SD).

### Statistical Analysis

To determine whether malnutrition predisposes to diarrhea, follow-up intervals starting at one anthropometric survey and ending with the next consecutive survey were constructed. We then used Poisson regression, first, to model diarrhea incidence (episodes/person days of follow-up) during the intervals as a simple function of malnutrition at the beginning of the interval. Second, we modeled diarrhea incidence as a function of malnutrition at the beginning of the interval, plus confounders and an autoregressive term. The autoregressive term was defined as presence or absence of diarrhea during the previous interval or the 3 months before the first interval. The autoregressive term was used to adjust for the nonindependence of recurrent diarrhea episodes within individual subjects.

Because information from the previous interval was required for the autoregressive term, data for each current interval were paired with episode data from the preceding interval. If episode data were not available from a previous interval because, for example, a child had been recently enrolled, the current interval was excluded from analysis.

Crude and adjusted relative rates (RR) were calculated from model coefficients, and 95% confidence intervals (CI) and probabilities were obtained from the standard errors of the coefficients. Potential confounding variables fit in each model were age, socioeconomic status, mother's education, days of exclusive breast-feeding during the interval, and presence of a sanitary latrine. Malnutrition was defined bivariate as  $<-2$  SD units or  $\geq -2$  SD from the NCHS reference median.

To examine whether the occurrence of diarrhea episodes was associated with worsened nutritional status over short intervals, we used three separate autoregressive models that related the outcome (height-for-age, weight-for-age, or weight-for-height converted to z-scores) at the end of an interval to diarrhea incidence, conditioning on z-score at the beginning of the interval (20). A modification of this model, based on nonlinear regression that allows for unequal times between surveys, was used (21). The use of z-scores as the dependent variable means that population changes in nutritional status were modeled, rather than population changes in heights or weights. Because the frequency of diarrhea episodes was not normally distributed, the number of diarrhea episodes was consistently treated as a categorical variable with none versus one or more. Only multivariate models including potential confounders and incidence of diarrhea were fit. To test whether this autoregressive analysis removed the correlation between repeated measurements on the same child, the residuals were calculated for each

survey. We then used a Pearson product correlation coefficient (22) to test for any statistically significant correlations between the residuals of two consecutive surveys.

To assess whether catch-up growth was sufficient to remove an association between diarrhea and malnutrition, we compared the mean change in z-scores during a 6-month interval between two groups of children. The first group consisted of children who had diarrhea during the first or second half of the interval, but not both halves. The second group comprised children who had no diarrhea during the entire 6-month period. To evaluate the effect of repeated diarrheal episodes on growth, we also compared children who had at least one diarrhea episode in each half of the 6-month interval with children experiencing no diarrhea during the 6 months. Comparisons were made using Student's *t*-test (22).

To control for confounding by age during these comparisons, a second analysis was completed using the autoregressive model with nutritional status as the outcome variable and age, categorized by years, as a confounder. The frequency of diarrhea during the interval was treated as a single ordinal variable where children were categorized as having diarrhea in both halves of the 6 months, diarrhea in the first 3 months only, diarrhea in the second 3 months only, or no diarrhea for 6 months. Because this analysis required children to participate in three consecutive surveys during 6 months, a subset of the total population was included.

All analyses were performed by computer (SAS ver. 6.12) (23).

## RESULTS

### Study Population

The census population in the three villages included in this study was 3111, of whom 50% were male. Of the adult population (over 17 years of age), 63% had no formal education. The most common occupations included housewife (40%), farmer-fisherman (25%), and salaried employee (14%), such as teacher, civil servant, or military serviceman. The proportion of the population less than 5 years of age was 17%.

Most families (69%) resided in village houses (brick homes with cement floors), and the remainder lived in apartments of similar construction. Houses within each village were clustered together, to maximize use of surrounding arable land. Most homes had three to four rooms (60%) and were supplied with electricity (94%). Most homes were equipped with radios (71%), televisions (77%), and washing machines (57%). About 99% of households received water from the municipal water supply. Sanitary latrines were found in 45% of households, and 62% had a garbage container either in or outside the dwelling.

Seven anthropometric surveys were completed. A single planned survey was missed in one village because of concurrent changes in field staff. For implemented surveys, 97% of planned measurements were obtained. There were 496 paired anthropometric measurements, of which 14 were excluded because seven z-scores were

greater than or less than 6 SD units from the reference median. Of the remaining 482 paired measurements or intervals, the median time between measurements was 3.0 months (interquartile range: 2.7–4.0).

The number of children in each survey varied from 61 (February 1994) to 135 (March–April 1995). Differences with passing time in the sample size were due to sequential village enrollment, in- and out-migrations, births, and censoring due to advanced age (>35 months). One hundred forty-three children were included in at least two nutrition surveys.

Ninety-one percent of semiweekly visits for diarrheal disease surveillance were completed in the three villages. There were 358 episodes of diarrhea reported in the cohort over the 22-month study period, corresponding to an incidence rate of 2.6 episodes per child year. The median length of these episodes was 2 days and approximately 1% were longer than or equal to 14 days. The incidence of diarrhea was inversely related to age. In the first, second, and third years of life, children experienced 3.5, 2.5, and 1.2 diarrhea episodes per year during 33.4, 74.8, and 45.3 child-years of follow-up, respectively. During the 482 follow-up intervals, children were diarrhea free throughout 280 (58%) intervals, had one episode during 124 (26%) intervals, and had two to eight episodes during 78 (16%) intervals.

At the time of the fourth anthropometric survey (November 1994), when the children of all three villages were enrolled in the study ( $n = 110$ ), moderate and severe stunting (low height-for-age) was recorded in 14% and 5% of children, respectively. Moderate and severe malnutrition by weight-for-age was documented in 5% and 2% of children, respectively. By weight for height, 3% of children had moderate wasting and none had severe wasting.

### Risk of Diarrhea

When we considered whether malnutrition is responsible for an increased incidence of diarrhea, weight-for-age was a statistically significant predictor of diarrhea (Table 1). The adjusted relative rate ( $RR_a$ ) and 95% confidence intervals (95% CI) for diarrhea among malnourished children from these families was 1.7 (95% CI: 1.2–2.3,  $P < 0.01$ ). In the same model, age and presence of a sanitary latrine were associated with diarrheal incidence. The presence of a sanitary latrine was responsible for almost a 40% reduction in the relative rate of disease ( $RR_a = 0.6$ , 95% CI: 0.5–0.8,  $P < 0.01$ ). Occurrence of diarrhea in the preceding interval was itself associated with an increased incidence of disease ( $RR_a = 2.1$ , 95% CI: 1.6–2.7,  $P < 0.001$ ). No interactions were detected.

Deficits in height-for-age and weight-for-height were not associated with an increased incidence of diarrheal episodes. Children with stunted growth (<–2 SD) had an incidence of 2.6 (49 episodes) versus 2.5 (276 episodes)

per year for children  $\geq -2$  SD above the reference median. The adjusted relative rate was 1.2 (95% CI: 0.9–1.6,  $P = 0.36$ ) and was similar to that of the crude relative rate ( $RR_c = 1.0$ , 95% CI: 0.8–1.4,  $P = 0.84$ ). For weight for height, the incidence of diarrhea in children with moderate or severe wasting (<–2 SD) was 2.3 (21 episodes) compared with 2.5 (304 episodes) per year in those without wasting. The crude relative rate was 0.9 (95% CI: 0.6–1.4,  $P = 0.67$ ), and the adjusted relative rate was 0.7 (95% CI: 0.5–1.1,  $P = 0.13$ ).

### Interrelationship Between Diarrhea and Malnutrition

In multivariate analyses, variables were tested as predictors of change for the three nutritional indices over intervals of approximately 3 months (Table 2). For each of the three models, the residuals were calculated at each survey, and no statistically significant correlations were detected.

Considering height-for-age, both age and the occurrence of one or more episodes of diarrhea during an interval were predictive variables. Diarrhea was associated with a reduction in z-scores of  $-0.16$  ( $P < 0.05$ ). No variables were predictive of changes in weight-for-age. Poverty was the only predictive variable for change in weight-for-height associated with a 0.27 decline ( $P < 0.05$ ) in the corresponding z-score.

### Catch-up Growth

When changes in height-for-age were examined, the age-adjusted analysis did not reveal any differences between those who were free of diarrhea for 3 months, either in the beginning ( $-0.27$ ,  $P = 0.37$ ) or end of the interval ( $-0.58$ ,  $P = 0.09$ ), and those who were diarrhea free for 6 months (Table 3). A marked reduction occurred during 6 months in both the crude analysis ( $-0.66$ ,  $P = 0.02$ ) and age-adjusted analysis ( $-0.53$ ,  $P = 0.07$ ) when children had diarrhea during both halves of the intervals. However children experiencing at least one episode of diarrhea in the second half of the 6-month interval showed a decrease in height-for-age z-scores ( $-0.58$ ,  $P = 0.09$ ) similar to a comparison group with repeated episodes throughout the interval ( $-0.53$ ,  $P = 0.07$ ).

### DISCUSSION

Most studies relating diarrhea and malnutrition have been conducted in economically marginal regions, where young children have high rates of diarrheal diseases and severely faltering growth. The present cohort study was conducted in an agricultural rural community in the Nile delta. The population, although relatively uneducated,

**TABLE 1.** Incidence, crude, and adjusted relative rate of diarrhea by demographic variables and malnutrition by weight-for-age<sup>a</sup> in a cohort of Egyptian children in Abees, Egypt, November 1993 to September 1995

Variables	IR (episodes) <sup>b</sup>	Crude RR (95% CI) <sup>c</sup>	Adjusted RR (95% CI)
Diarrhea during previous interval <sup>d</sup>			
Present	3.5 (243) <sup>e</sup>	2.7 (2.0, 3.4) <sup>f</sup>	2.1 (1.6, 2.7) <sup>f</sup>
Absent	1.3 (82)	1	1
Age in months			
0-11	4.1 (86)	3.4 (2.4, 4.8) <sup>f</sup>	2.6 (1.8, 3.9) <sup>f</sup>
12-23	2.8 (185)	2.3 (1.7, 3.1) <sup>f</sup>	2.0 (1.4, 2.7) <sup>f</sup>
24-35	1.2 (54)	1	1
Gender			
Female	2.4 (160)	0.9 (0.7, 1.2)	1.0 (0.8, 1.3)
Male	2.6 (165)	1	1
Socioeconomic status			
Poor	2.9 (143)	1.3 (1.0, 1.6) <sup>g</sup>	1.3 (1.0, 1.6) <sup>g</sup>
Non-poor	2.3 (182)	1	1
Mother's education			
Any education	2.4 (60)	0.9 (0.7, 1.2)	1.1 (0.8, 1.5)
None	2.5 (265)	1	1
Sanitary latrine			
Present	2.0 (154)	0.6 (0.5, 0.8) <sup>f</sup>	0.6 (0.5, 0.8) <sup>f</sup>
Absent	3.2 (171)	1	1
Days exclusive breast-fed during intervals <sup>h</sup>			
Per day increase from day 0	na <sup>i</sup>	1.004 (1.003, 1.006) <sup>f</sup>	1.002 (0.999, 1.004)
Low weight-for-age			
Yes	4.2 (51)	1.8 (1.3-2.4) <sup>j</sup>	1.7 (1.2, 2.3) <sup>j</sup>
No	2.3 (274)	1	1

<sup>a</sup> Malnutrition by weight-for-age was defined as <-2 standard deviation units from the NCHS median by age and sex.

<sup>b</sup> IR = incidence rate per child-year of follow up.

<sup>c</sup> Relative rate (95% confidence intervals).

<sup>d</sup> An autoregressive term (diarrhea present or absent in previous interval) was included in this model to account for the non-independence of recurrent episodes in the same children. The incidence rates presented are for those children with (present) and without (absent) diarrhea in the previous child-interval of follow up.

<sup>e</sup> The child-years at risk and total episodes were reduced for this analysis when 28 follow-up intervals were dropped because data was not available for the autoregressive term (e.g., presence or absence of diarrhea in previous quarter).

<sup>f</sup>  $P < 0.001$ .

<sup>g</sup>  $P < 0.05$ .

<sup>h</sup> 92 children were exclusively breast feeding during one or more intervals.

<sup>i</sup> na = not applicable for continuous results.

<sup>j</sup>  $P < 0.01$ .

lived well. The villagers frequently owned their small homes or apartments, had access to municipal water, and often had modest luxuries such as radios and televisions. The incidence of diarrhea in children less than 3 years of

age was moderate compared with that in other developing countries, and chronic diarrhea was uncommonly reported. Faltering growth affected a minority of children, with moderate stunting being the most common mani-

**TABLE 2.** Multivariate analysis of relationship between one or more episodes of diarrhea and nutritional outcomes (weight for age, height for age, weight for height) measured in standard deviation units (Z-score) from the NCHS reference median among a cohort of Egyptian children in Abees, November 1993 to September 1995

Variable	Weight-for-age	Weight-for-height	Height-for-age
Intercept	0.15 (-0.14, 0.44) <sup>a</sup>	0.10 (-0.26, 0.46)	-0.07 (-0.30, 0.16)
Age <12 vs. 24-35 mos.	-0.26 (-0.54, 0.01)	-0.11 (-0.46, 0.24)	-0.30 (-0.52, -0.08) <sup>b</sup>
Age 12-23 vs. 24-35 mos.	-0.02 (-0.23, 0.20)	0.04 (-0.22, 0.32)	-0.22 (-0.38, -0.05) <sup>c</sup>
Some caretaker schooling vs. none	0.00 (-0.20, 0.19)	0.09 (-0.15, 0.33)	-0.02 (-0.17, 0.13)
Poor vs. non-poor	0.14 (-0.33, 0.05)	-0.27 (-0.52, -0.02) <sup>b</sup>	0.09 (-0.07, 0.24)
≥1 episode vs. none	-0.07 (-0.26, 0.12)	0.05 (-0.20, 0.29)	-0.16 (-0.31, -0.01) <sup>b</sup>

<sup>a</sup> Coefficient (95% confidence intervals).

<sup>b</sup>  $P < 0.05$ .

<sup>c</sup>  $P < 0.01$ .

**TABLE 3.** Change in standard deviation units (Z-scores) from the NCHS reference median for height for age over two three-month quarters by presence or absence of diarrhea in each three-month quarter

Timing of diarrhea episodes	Number of children	Episodes of diarrhea	Mean change	Mean change adjusted for age
None	26	0	0.09	—
In first quarter only	17	34	-0.25 (p = 0.31)	-0.27 (p = 0.37) <sup>a</sup>
In second quarter only	28	49	-0.52 (p = 0.09)	-0.58 (p = 0.09)
In both quarters	35	162	-0.66 (p = 0.02)	-0.53 (p = 0.07)

<sup>a</sup> All P values are comparisons between the mean change in Z-score in that stratum vs. mean change in Z-score in the two quarters with no diarrhea.

festation. In effect, this cohort presented the opportunity to examine the relationship between diarrhea and malnutrition under conditions in which nutritional deprivation was less pronounced than in most previous investigations, yet diarrhea is still a major cause of morbidity and mortality (24).

#### Malnutrition Associated With Diarrhea

Our first objective was to determine whether malnutrition predisposes to diarrhea. Our findings imply that moderate to severe malnutrition, measured by weight-for-age, predisposes to diarrhea. This association is maintained even after controlling for confounders and repeated measurements on the same child. Height-for-age and weight-for-height were not associated with an increased incidence of diarrhea. However, unlike height-for-age, few children had low weight-for-height. The small number of children who had low weight-for-height may have limited our ability to detect an association between wasting and diarrhea incidence.

Another objective was to test whether a previous episode of diarrhea is associated with an ensuing episode. It was found that a child experiencing diarrhea was twice as likely to have a subsequent episode. This argues that there may be a "diarrhea-to-diarrhea" cycle operative in these children. This observation may have important implications for vaccines directed against specific enteropathogens. It suggests that one or more pathogen-specific vaccines may have a greater impact on the incidence of all-cause diarrhea than the combined reduction predicted by the individual vaccines. Unfortunately, we had insufficient microbiologic data to identify which pathogens may predispose to subsequent diarrhea.

#### Diarrhea Associated With Malnutrition

The second objective of this study was to determine whether diarrhea affects the nutritional status of young Egyptian children. We found that during 3-month intervals, children who experienced diarrhea when compared with those who were diarrhea free showed reduced height velocity. Although not statistically significant,

this association held up using the second regression model that adjusted for age and considered repeat episodes during 6-month intervals. Still, this latter association was not much greater than for those children having diarrhea only during the last 3 months of a 6-month interval. This implies that the reduction in height velocity was due to recent diarrhea episodes and that children may exhibit appropriate catch-up growth if sufficient time elapses without the recurrence of diarrhea. There was an indication, however, that the periods of catch-up growth were longer than 3 months. Although not statistically significant, children with diarrhea only in the first 3-month period of the 6-month interval, still demonstrated reduced growth velocity when compared with those children who were diarrhea free for 6-months. We found no relationship for weight-for-age which was surprising, given that weight-for-age is usually considered a more sensitive indicator of malnutrition. Weight-for-height z-scores and diarrhea were not associated. This was expected, because wasting was a minor problem in this population.

#### Study Limitations

In evaluating our findings, several potential limitations should be considered. Morris found that days ill (days ill with diarrhea/total days of follow-up in period) was a better predictor of weight gain than diarrhea incidence in children in Ghana who frequently experience persistent diarrhea (25). In our study, however, the majority of diarrhea episodes were of short duration (median, 2 days) and diarrhea incidence and days ill were strongly correlated.

There are an increasing number of investigations examining the contribution made by subclinical enteric infections to faltering growth (26,27). This study was limited to investigating clinical diarrhea, and the effects of asymptomatic infections on growth were not considered.

The autoregressive model used for examining whether diarrhea is associated with an increased risk of faltering growth has been applied elsewhere (28), but has been criticized (29). The statisticians who developed this model answered many of these concerns to our satisfac-



tion (30). Still, given that standard methods of analysis have not been generally accepted, we suggest that other statistical methods be used in other studies to corroborate these findings.

Certain biases may have lead to artifactual associations. Interviewer bias may have lead to more intensive interviewing of poor or malnourished children as well as children with a history of diarrhea, leading to a biased correlation between diarrhea and malnutrition and the proposed diarrhea-to-diarrhea cycle. This would be unlikely; staff were unaware we would be studying the interrelationship of malnutrition and diarrhea and were supervised during data collection by trained physicians who were responsible for quality assurance. Recall bias or inability to remember stooling patterns by guardians or missed visits could have led to misclassification of disease or exposure status. Nevertheless, this would most likely bias the relative rate or regression coefficient toward unity (31).

Mismeasurement of weights and heights could have also biased our results. Such errors would probably be random and would thus bias our coefficients toward unity (31). Given that few outliers were detected and excluded and that we found associations between malnutrition and diarrheal illness, it is unlikely that measurements were inaccurate. Still, improvements in obtaining height and weight values such as measuring all children with a length board and averaging triplicate measures for each child may have improved the precision of these values.

Misdiagnosis of diarrhea could have biased the results, although our definition of diarrhea has been empirically evaluated (32). There was no enrollment bias, because 100% of villagers with eligible children were enrolled and participated. Finally, it is recommended that studies of this type have larger sample sizes than in this study. Still, the observed results supported conducting this analysis.

### Implications

The control of diarrhea and the prevention of malnutrition are principal concerns of policy planners in developing countries. Low weight-for-age predisposes to diarrhea, and a reduction in malnutrition could impact on diarrheal diseases. Stunting did not appear to increase diarrhea incidence, which is fortunate, given that stunted growth is the principal nutrition-related problem in this population. Low weight-for-height, which is not a significant problem in these villages, was also not associated with risk of diarrheal diseases. Policy makers should, however, be cautious in generalizing these data to other populations in which a more significant portion of children may have wasting.

Diarrhea itself appears to be associated with subsequent diarrhea episodes. This observation hints that im-

munization programs for enteric diseases may have a broader influence on all-cause diarrhea incidence than predicted.

Our data suggest that the prevention of diarrheal diseases in this population may not substantially impact the prevalence of malnutrition. Diarrhea appears to have some transitory effects on height. Given that this population experiences an incidence of diarrhea lower than many other regions, with few persistent diarrhea episodes, it is safe to conclude that these results may not apply to children experiencing higher incidence rates or frequent chronic disease.

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