Folate, but not vitamin B-12 status, predicts respiratory morbidity in north Indian children[1–5]

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ABSTRACT

Background: Vitamin deficiencies are often part of malnutrition, which predisposes to acute lower respiratory tract infections.

Objective: The objective was to measure the association between cobalamin and folate status and subsequent respiratory morbidity.

Design: A prospective cohort study was conducted in 2482 children aged 6–30 mo nested in a zinc supplementation trial. We measured plasma concentrations of folate, cobalamin, methylmalonic acid, and total homocysteine (tHcy) and followed the children for 4 mo.

Results: We observed 1176 episodes of acute lower respiratory tract infections. Children with folate concentrations in the lowest quartile (interquartile range: 6.4–20.0 nmol/L) had a 44% higher incidence [adjusted incidence rate ratio (IRR): 1.44; 95% CI: 1.23, 1.70] of acute lower respiratory tract infections than did children in the other 3 quartiles. For tHcy, the IRR was 1.24 (1.07, 1.40) in a comparison of those in the highest quartile with those in the other quartiles. Breastfeeding was associated with high folate concentrations and protection against subsequent respiratory tract infections. This protection was significantly and substantially reduced after adjustment for plasma folate concentrations at baseline. Compared with the children in the other 3 quartiles, the IRR for being in the lowest quartile of cobalamin was 1.13 (0.76, 1.03) and for being in the highest quartile of methylmalonic acid was 1.12 (0.96, 1.31).

Conclusions: Poor folate status appears to be an independent risk factor for lower respiratory tract infections in young children. This study also suggests that the protective effect of breastfeeding is partly mediated by folate provided through breast milk. *Am J Clin Nutr* 2007;86:139–44.

KEY WORDS Children, pneumonia, folate, cobalamin, homocysteine, methylmalonic acid, malnutrition, cohort study, India

INTRODUCTION

In children in developing countries, acute lower respiratory tract infections are among the most common causes of death, claiming ≈2 million lives every year (1). Known risk factors are young age, low birth weight, pollutants, poverty, malnutrition, zinc deficiency, and lack of breastfeeding (2). Therapeutic or prophylactic administration of zinc to young children reduces the risk of acute lower respiratory tract infections and the episode duration (3–6). Whether deficiencies of other nutrients, such as folate or vitamin B-12 (cobalamin), are independent risk factors for lower respiratory tract infections, is not known. The main sources of cobalamin are animal products, of which poor children have a low intake (7). It is therefore plausible that many children of developing countries are cobalamin deficient. Folate deficiency, however, is presumably less prevalent because of the abundance of folate in breast milk and because of the predominantly vegetarian diet in many low-income countries, such as in South Asia (8).

We undertook a prospective cohort study to assess whether poor folate and poor cobalamin status were risk factors for acute lower respiratory tract infections in young children.

SUBJECTS AND METHODS

Study population

This study was nested within a zinc supplementation trial in 2482 children aged 6–30 mo. Assessment of the association between markers of cobalamin and folate status and respiratory illness were predefined secondary objectives in this project. The inclusion and exclusion criteria and the effects of zinc administration are described elsewhere (3). The ethics committee of the All India Institute of Medical Sciences in New Delhi approved the study. Details of the study were given in writing and were also

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[2] The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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read to the parents in the presence of a witness. Signatures or thumb impressions were obtained on a consent form.

Data collection

A study physician interviewed the caretaker, examined the child, and collected a venous blood specimen from the child on enrollment. Fieldworkers visited each child every seventh day for 4 mo. At each visit, the caretakers were asked about fever, cough, and other symptoms of disease and whether they had sought treatment for the child in the previous 7 d. Respiratory rates were counted twice for 1 min, and the temperature was recorded. The caretakers were encouraged to bring their children to the study clinic whenever they were ill. In the field clinic, 2 physicians assessed the child.

Acute lower respiratory tract infection was defined by cough and fast breathing or lower chest indrawing. Fast breathing was defined as 2 counts of ≥50 breaths/min for infants (<12 mo of age) and ≥40 breaths/min for older children. We defined 2 episodes to be distinct from each other when they were separated by >14 continuous days without acute lower respiratory tract infection.

Treatment

Acute illness was treated according to the guidelines of the World Health Organization. Children with acute lower respiratory tract infections received co-trimoxazole, which was substituted with amoxicillin if the child did not respond within 3 d. Children were sent to the hospital if they had signs or symptoms that required referral.

Blood collection and biochemical analyses

We collected samples of nonfasting venous blood (≈5 mL) in heparinized polypropylene tubes (Sarstedt, Nümbrecht, Germany) between 0900 and 1200. The samples were centrifuged (447 × *g*, 10 min, room temperature), and the plasma was divided and stored into polypropylene vials (Eppendorf, Hinz, Germany) at −20 °C until analyzed.

All samples were analyzed at the University of Bergen, Bergen, Norway (Section for Pharmacology, Institute of Medicine). Plasma cobalamin and plasma folate concentrations were estimated by microbiological assays with the use of a chloramphenicol-resistant strain of *Lactobacillus casei* and a colistin sulfate–resistant strain of *Lactobacillus leichmannii*, respectively (9, 10). Both assays were adapted to a microtiter plate format and carried out by a robotic workstation (11). Plasma methylmalonic acid and total homocysteine (tHcy) were analyzed with a modified gas chromatography–mass spectrometry method based on ethylchloroformate derivatizations (12).

Data management and statistical analyses

The data entry forms were designed with FOXPRO for WINDOWS (Microsoft Corporation, Redmond, WA), with range and consistency checks incorporated. Double data entry by 2 data encoders followed by validation was completed within 48 h after the forms were completed in the field. Growth was assessed by calculating height-for-age and weight-for-age, and weight-for-height *z* scores based on the 1978 references with the use of EPIINFO 6 (13, 14).

Summary measures for continuous variables are reported as means or medians as appropriate, and categorical variables are reported as proportions. We used the Mann- Whitney *U* nonparametric test to compare the plasma concentration of folate, tHcy, cobalamin, and methylmalonic acid between age and breastfeeding categories. The number of episodes of acute lower respiratory tract infections was summarized for each child; these summary measures were used as outcome variables. We used negative binomial regression to estimate the incidence rate ratio (IRR) for acute lower respiratory tract infections between categories or units of the exposure variables. The negative binomial distribution was used instead of the Poisson distribution because there was overdispersion in the data. Exposure variables were plasma concentrations of folate, cobalamin, tHcy, and methylmalonic acid at the day of inclusion. These variables were included as dichotomous or continuous variables in generalized linear models and continuous variables in generalized additive regression models with the negative binomial distribution family and a logarithmic link function. We used log (base 2)-transformed values of the exposure variables when they were right-skewed and when entered as continuous variables in the regression models. The exposure variables were also dichotomized into categories above or below the 25th percentile for folate and cobalamin and into categories above or below the 75th percentile for tHcy and methylmalonic acid. We identified predictors for acute lower respiratory tract infections in a stepwise process. We assessed whether these and several other variables confounded the association between folate, tHcy, vitamin B-12, or methylmalonic acid concentrations and respiratory tract infections by adding them to the multiple model one at a time. These variables were height-for-age, weight-for-age, and weight-for-length *z* scores, age, breastfeeding status, sex, season, zinc supplementation status, family type [nuclear or joint (multigenerational)], family size, income, and years of schooling of the mothers and fathers (**Table 1**). Statistical analyses were done with STATA 9.0 sta-

TABLE 1
Variables assessed in the multivariable regression models that measured the association between plasma folate, cobalamin, homocysteine, or methylmalonic acid and the subsequent incidence of acute respiratory tract infections in 2482 Indian children aged 6–30 mo[1]

	Continuous	Categorical
Breastfeeding	—	Yes or no
Age	Months	Infants: yes or no
Sex	—	Male or female
Living in multigenerational families	—	Yes or no
Members in the household	Number	
Years of schooling, mother	Years	School: yes or no
Years of schooling, father	Years	School: yes or no
Weight-for-age *z* score	*z* scores	<−2 WAZ: yes or no
Weight-for-length *z* score	*z* scores	<−2 WHZ: yes or no
Height-for-age *z* score	*z* scores	<−2 HAZ: yes or no
Maternal age	Years	—
Paternal age	Years	—
Income	1000 Indian rupees	—
Time since blood sampling	Days	—
Season	—	3 Categories
Zinc supplementation status	—	Given: yes or no

[1] Interactions assessed: of age with breastfeeding, of age with sex, and of folate, homocysteine, cobalamin, and methylmalonic acid with breastfeeding status and age categories.

TABLE 2
Baseline characteristics of the children in the cohort by breastfeeding status and age[1]

	Breastfed		Not breastfed	
Variable	6–11 mo	12–30 mo	6–11 mo	12–30 mo
No. of subjects [*n* (%)]	854 (34.4)	869 (35.0)	152 (6.1)	607 (24.5)
Boys [*n* (%)]	461 (53.9)	465 (53.5)	79 (52.0)	295 (48.6)
Weight-for-length *z* score	−0.65 ± 0.9[2]	−1.52 ± 0.8	−1.06 ± 0.9	−1.35 ± 0.8
Weight-for-length *z* score <−2 [*n* (%)]	261 (30.6)	559 (64.3)	76 (50.0)	349 (57.5)
Length-for-age *z* score	−1.27 ± 0.9	−1.94 ± 1.1	−1.64 ± 1.1	−1.83 ± 1.2
Length-for-age *z* score <−2 [*n* (%)]	177 (20.7)	392 (45.1)	54 (35.5)	251 (41.4)
Income (in 1000 rupees)	47.2 ± 42.0	44.7 ± 46.8	45.1 ± 32.1	45 ± 32.7
Duration of schooling, mother (y)	5.2 ± 4.5	5.0 ± 4.5	5.4 ± 4.4	5.4 ± 4.7
Duration of schooling, father (y)	8.7 ± 4.0	8.2 ± 4.4	8.5 ± 3.7	8.5 ± 4.1
No. of individuals in household (*n*)	5.9 ± 2.3	5.8 ± 2.4	6.1 ± 2.7	5.9 ± 2.1
Living in multigenerational families [*n* (%)]	449 (52.6)	383 (44.0)	89 (58.6)	310 (51.1)
Cobalamin (pmol/L)[3,4]	184 (120–263)[5]	172 (124–253)	334 (235–463)	261 (194–348)
Folate (nmol/L)[3]	20.2 (11.7–34.4)	11.3 (7.4–17.6)	5.3 (3.4–7.7)	6.5 (4.7–9.2)
tHcy (μmol/L)[3]	12.6 (9.2–18.1)	11.3 (8.7–15.2)	10.7 (8.2–13.9)	9.1 (7.4–11.2)
MMA (μmol/L)[3,6]	1.03 (0.54–2.08)	0.74 (0.42–1.36)	0.45 (0.31–0.71)	0.38 (0.26–0.59)

[1] tHcy, total homocysteine; MMA, methylmalonic acid.
[2] $\bar{x}$ ± SD (all such values).
[3] *P* values were calculated by using the Mann-Whitney *U* nonparametric test. *P* values were < 0.001 for the differences in cobalamin, folate, tHcy, and MMA concentrations between breastfeeding categories in infants and toddlers (children aged ≥12 mo) and between infants and toddlers who were breastfed and those who were not breastfed.
[4] *P* = 0.36 for the comparison of cobalamin concentrations between infants and toddlers who were breastfed.
[5] Median; intraquartile range in parentheses (all such values).
[6] *P* = 0.002 for the comparison of concentrations of MMA between infants and toddlers who were not breastfed.

tistical software (StataCorp, College Station, TX). We also categorized the children by whether they had had at least one episode of pneumonia or not and used this outcome in multivariable logistic regression analyses including the same exposure variables as used in the negative binomial regression models. We used generalized additive models in the statistical software R version 2.0 (The R Foundation for Statistical Computing) to describe nonlinear associations between the exposure variables and acute lower respiratory tract infections after adjustment for potential confounders (15). To measure the extent of the change in the effect estimate of breastfeeding after adjustment for plasma folate concentration, we performed a nonparametric bootstrap analysis with 1000 replications (16). For each bootstrap replicate of the data set, we estimated the model parameters both with and without this adjustment. Bootstrap CIs and *P* values for the change in estimates were then computed from the replicated results.

RESULTS

Demographics and blood indexes

Selected baseline characteristics of the study subjects according to breastfeeding status and age categories are shown in **Table 2**. The mean (±SD) age of the subjects was 15.3 ± 7.5 mo. Fifty-two percent of the subjects were boys, and 69% were breastfed. The median plasma concentrations of cobalamin, folate, tHcy, and methylmalonic acid were 205 (IQR: 141–299) pmol/L, 10.7 (6.4–20.0) nmol/L, 10.9 (8.3–14.9) μmol/L, and 0.65 (0.37–1.30) μmol/L, respectively. The folate concentration was substantially and significantly lower in children that were not breastfed than in those who were breastfed (Table 2).

Risk factors for acute lower respiratory tract infections

During a total of 266 537 d of follow-up, there were 848 children who had 1176 episodes of acute lower respiratory tract infections: 69% of these children had only one episode, 25% had 2 episodes, and 6% had >2 episodes. Not being breastfed, young age, being enrolled in the wet or cool months (June to January) compared with the months of February to May, and a low length-for-age *z* score were all independent risk factors (**Figure 1**, **Table 3**). Socioeconomic factors, however, were not associated with acute lower respiratory tract infections.

Folate and cobalamin status and acute lower respiratory tract infections

In the crude analyses, low folate and high tHcy concentrations were predictors for acute lower respiratory tract infections, whereas low cobalamin and high methylmalonic acid concentrations were not (**Table 4**). After adjustment for potential confounders (listed in Table 1), the associations of folate and tHcy with respiratory tract infections were maintained, whereas plasma methylmalonic acid and cobalamin concentrations remained unassociated with respiratory morbidity (Table 4). Furthermore, methylmalonic acid or cobalamin and acute lower respiratory tract infections were still not associated after inclusion of folate or tHcy concentration in the statistical models.

To avoid overlooking nonlinear associations, we also undertook multivariable analyses with these markers as smooth terms in generalized additive models. In these models, with adjustment for the same variables, both plasma folate (**Figure 2**) and tHcy were predictors of acute lower respiratory tract infections. The inverse association between log IRR and folate concentration was linear at a folate concentration <20 nmol/L (the lowest 3

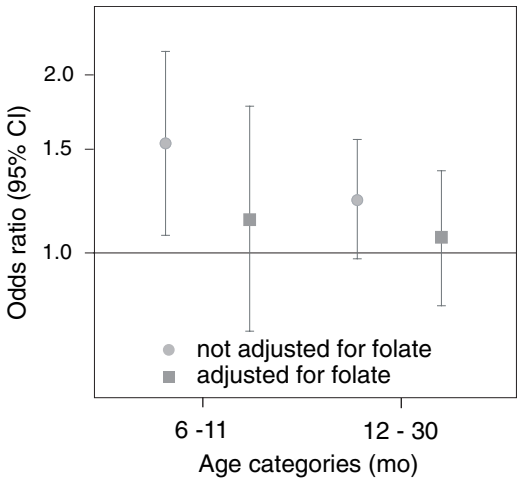

FIGURE 1. Adjusted odds ratios for having ≥1 episode of an acute respiratory tract infection between 2482 Indian nonbreastfed and breastfed infants and children aged 12–30 mo with and without adjustment for plasma folate concentration at enrollment. To estimate the extent to which the effect of breastfeeding was altered after adjustment for plasma folate concentration, we performed a nonparametric bootstrap analysis (16). The estimate for breastfeeding was attenuated 1.34-fold (95% CI: 1.04, 1.76; $P = 0.011$) and 1.17-fold (95% CI: 1.03, 1.32; $P = 0.008$) in infants and older children, respectively.

quartiles). In contrast, there was a linear and positive association between the incidence of respiratory tract infections and tHcy concentrations throughout the whole range of tHcy concentrations. The results from the multivariable generalized additive models confirmed that there were no associations between baseline methylmalonic acid or cobalamin and subsequent acute lower respiratory tract infections.

Children with a folate concentration in the lowest quartile had a 44% (95% CI: 23%, 70%) higher incidence of respiratory tract infections than did those with a folate concentration in the highest 3 quartiles (Table 4). The IRR of acute lower respiratory tract infections was 0.90 (95% CI: 0.84, 0.96) for each doubling [one-unit increase in the log transformed (base 2) value] of folate concentration. Thus, the higher the folate concentration, the lower the incidence.

TABLE 3
Predictors of acute lower respiratory tract infection in 2482 Indian children aged 6–30 mo who were followed for 4 mo[1]

Variable	IRR (95% CI)	*P*
Age		
Per month in breastfed, children	0.96 (0.95, 0.98)	< 0.001
Per month in non-breastfed children	0.99 (0.97, 1.00)	0.015
Interaction of breastfeeding status with age	0.98 (0.96, 0.99)	0.01
Season[2]		
February through May (reference)	1	
June through September	1.59 (1.36, 1.87)	< 0.001
October through January	1.45 (1.22, 1.72)	< 0.001
Height-for-age		
Per *z* score	0.88 (0.83, 0.93)	< 0.001

[1] IRR, incidence rate ratio (calculated by negative binomial regression and adjusted for time of blood sampling, sex, zinc supplementation, and socioeconomic status). The effect of breastfeeding is depicted in Figure 1.
[2] *P* for trend across seasons < 0.001.

Those with a tHcy concentration in the highest quartile had a 24% (95% CI: 7%, 40%) (Table 4) higher incidence than did those with lower concentrations of tHcy. Furthermore, for each doubling in tHcy concentration, the incidence increased by 22% (95% CI: 10%, 36%). Thus, the higher the tHcy concentration, the higher the incidence of acute lower respiratory tract infections.

Inclusion of both folate and tHcy in the models did not alter the estimate of the other compared with when either folate or tHcy was included in the multivariable negative binomial regression model. Furthermore, in the multivariable regression models and in stratified analyses, the associations of acute lower respiratory tract infections with plasma folate, cobalamin, tHcy, or methylmalonic acid were not modified by zinc administration or breastfeeding status. The protective effect of breastfeeding on respiratory tract infections was substantially and significantly reduced when the folate concentration was added to the regression models, particularly in infants (Figure 1).

The effect of poor cobalamin status on plasma folate

In this predominant vegetarian population, the plasma folate concentration may have been high because of cobalamin deficiency, which led to the folate trap phenomenon (17, 18). This may obscure the assessment of folate status in cobalamin-deficient subjects. We therefore depicted the association between plasma cobalamin and plasma folate from continuous generalized additive models. This analysis showed that the plasma folate concentration started to increase when the cobalamin concentration was <250 pmol/L. We therefore investigated the relation between acute lower respiratory tract infections and folate in a subgroup with presumably adequate cobalamin status, ie, plasma cobalamin >250 pmol/L. For these children, the adjusted IRR was 1.53 (95% CI: 1.22, 1.93) in a comparison of the lower (lower 25%) and upper (upper 75%) 3 quartiles of plasma folate. Thus, the association between folate and respiratory tract infections was not significantly different between the subgroups consisting of children with a cobalamin concentration ≤250 pmol/L and those with higher cobalamin concentrations (*P* for interaction = 0.2)

DISCUSSION

Our analyses showed a strong and independent association between low plasma folate concentrations and the risk of acute lower respiratory tract infections. Children in the lowest quartile of plasma folate had an almost 50% greater risk than did the other children. The association between acute lower respiratory tract infections and folate was not altered by adjustment for other risk factors for acute lower respiratory tract infections or other potential confounders that we measured.

Children who were not breastfed had a significantly lower plasma folate concentration than did breastfed children of the same age. This difference was larger in the lowest age categories. In fact, breastfed infants had a median folate concentration that was almost 4 times that of infants who were not breastfed. Our analyses also showed that children who were breastfed had a lower incidence of acute lower respiratory tract infections than did children who were not breastfed. The effect of breastfeeding on respiratory illness was significantly and substantially reduced when the folate concentration was included in the regression

TABLE 4
Associations between concentrations of the plasma markers of folate and cobalamin status and the incidence of acute lower respiratory tract infections in Indian children aged 6–30 mo[1]

	Duration of follow-up	No. of episodes		IRR (95% CI)		
		Total	Per child-year	Unadjusted	Adjusted[2]	*P*
	d					
Folate						
Reference (quartiles 2–4)	187 668	759	1.48	1	1	
Low (quartile 1)	62 761	359	2.09	1.42 (1.23, 1.63)	1.44 (1.23, 1.70)	< 0.001
Cobalamin						
Reference (quartiles 2–4)	185 309	812	1.60	1	1	
Low (quartile 1)	61 403	292	1.74	1.08 (0.93, 1.25)	1.13 (0.76, 1.03)	0.13
Homocysteine						
Reference (quartiles 1–3)	186 665	783	1.53	1	1	
High (quartile 4)	61 296	316	1.88	1.22 (1.06, 1.42)	1.24 (1.07, 1.40)	0.005
Methylmalonic acid						
Reference (quartiles 1–3)	187 140	806	1.57	1		
High (quartile 4)	60 702	293	1.76	1.11 (0.96, 1.29)	1.12 (0.96, 1.31)	0.15

[1] IRR, incidence rate ratio (calculated by negative binomial regression).
[2] Adjusted for age, breastfeeding status, interaction of age with breastfeeding, time of blood sampling, sex, zinc supplementation, nutritional status (height-for-age *z* score), socioeconomic status (income, family, size education of parents, and multigenerational or nuclear family), and season.

models. This indicates that the beneficial effect of breast milk may be due in part to its folate content.

We found that the incidence of acute lower respiratory tract infections increased throughout the whole range of tHcy concentrations. In adults, the plasma tHcy concentration is a good marker of folate status, and it increases with declining folate status (19). Because a low plasma folate concentration was found to be a strong predictor of respiratory tract infections, we anticipated that the tHcy effect would be attenuated after adjustment for folate concentration and vice versa. This was, however, not the case, which suggests that tHcy and folate are independent predictors of acute lower respiratory tract infections. tHcy is not a specific marker of folate status (20), and the plasma folate concentration explained little of the variability of tHcy in our study (data not shown). Indeed, in newborns and breastfed infants, low plasma cobalamin concentrations are more important determinants of tHcy than are low folate concentrations (21, 22). It is therefore surprising that tHcy was associated with acute lower respiratory tract infections, whereas plasma concentrations of cobalamin and methylmalonic acid were not. Notably, tHcy increases with activation of the immune system, particularly the TH1 response (23, 24). A high burden of infectious diseases may therefore cause immune activation and elevated tHcy, which may explain the association between tHcy at baseline and subsequent respiratory morbidity.

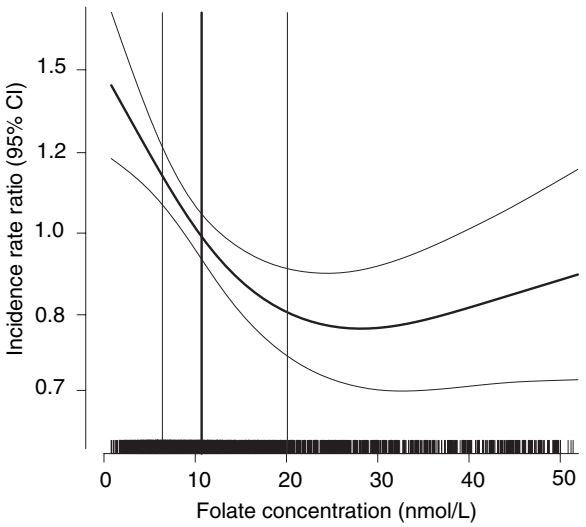

FIGURE 2. Association between plasma folate concentration and the incidence of acute lower respiratory tract infections derived by using generalized additive negative binomial regression models. The vertical lines depict the 25th, 50th, and 75th percentiles for plasma folate concentration. The middle curved line depicts the relation between folate concentration and the incidence rate ratio of acute respiratory tract infection. The outer lines indicate the 95% CIs of the incidence rate ratios. The figure includes the 95% lowest folate concentrations, and the small lines on the *x* axis (bottom) show the distribution of these observations.

It is an inherent weakness of cohort studies that they identify associations rather than causality and that the observed associations can be due to confounding. We therefore undertook several multivariable regression analyses with outcomes as dichotomous (logistic) and count (negative binomial) variables, adjusting for socioeconomic, anthropometric, and clinical variables. In these models, the association between folate or tHcy and subsequent morbidity were not attenuated. However, we cannot rule out that the observed association is confounded by variables that we did not measure. For example, children with low folate concentrations could come from homes with poorer indoor air quality, which is a well-known risk factor for childhood pneumonia (2). However, plasma folate concentration at recruitment was still associated with the risk of acute lower respiratory tract infection after adjustment for family size, income, maternal and paternal education, and type of housing, which are probably related to indoor air pollution. Moreover, the plasma folate concentration could be associated with other nutrients, such as vitamin A, that might be associated with respiratory tract infections (2). In any case, our findings need to be verified in clinical trials to have clinical or public health implications.

The folate trap phenomenon might cause high plasma folate but low cellular folate concentrations in cobalamin-deficient individuals (17, 18). However, elevated plasma folate concentrations in children with plasma cobalamin <250 pmol/L would

then attenuate the folate-respiratory tract infections relation rather than produce false results. This assumption is in line with the observation that neither the cobalamin nor the methylmalonic acid concentration was associated with acute lower respiratory tract infections. Furthermore, the increased risk of acute lower respiratory tract infections in children with low folate concentrations did not change when we excluded children with poor cobalamin status from the analysis.

The defense against respiratory tract infections relies on the ability of the immune cells to proliferate and differentiate and on the effective renewal of the respiratory epithelial linings. Folates play a crucial role in DNA and protein synthesis, which suggests that processes in which cell proliferation is essential may be impaired by poor folate status. Indeed, macroscopic disruption of the epithelial lining occurs with anti-folate treatment (25), and several facets of the immune system are affected by folate deficiency (25, 26). The phagocytic and bactericidal ability of polymorphonuclear leukocytes is poor in individuals with severe folate deficiency and improves with folate replenishment (27). Furthermore, the thymus and cell-mediated immunity, the blastogenic response of T lymphocytes to certain mitogens, and the antibody responses to several antigens is reduced in folate-deficient individuals (25). These changes to the immune system caused by folate deficiency may result in an increased susceptibility to infections.

Some antimalarial drugs act on the folate metabolism of the parasite, and folate administration during sulfadoxine pyrimethamine prophylaxis has been shown to reduce its efficacy (28). This needs to be kept in mind if folate is given to populations in areas where malaria is endemic and sulfadoxine pyrimethamine is commonly used.

Little attention has been paid to folate deficiency as a public health problem in children of developing countries. We found that poor folate status was an independent risk factor for acute lower respiratory tract infections and that the beneficial effect of breastfeeding may in part be explained by the high folate concentrations in breast milk. Conceivably, folic acid given in adequate amounts may counteract some of the negative consequences faced by children that cannot be breastfed, such as orphans or children of HIV-infected mothers. These children may be at increased risk of infections, because of poverty, poor nutrition, and poor access to health care. Supplementation or fortification with folic acid may reduce their burden of infection. This hypothesis, however, should be explored in clinical trials before any public health measures are taken.

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