Concurrent micronutrient deficiencies in lactating mothers and their infants in Indonesia[1–3]

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ABSTRACT

Background: Deficiencies of vitamin A, iron, and zinc are prevalent worldwide, affecting vulnerable groups such as lactating women and infants. However, the existence of concurrent deficiencies has received little attention.

Objective: The aim was to investigate the extent to which deficiencies of vitamin A, iron, and zinc coexist and the nutritional relation between lactating mothers and their infants.

Design: In a cross-sectional survey in rural West Java, Indonesia, 155 lactating mothers and their healthy infants were assessed anthropometrically and blood, urine, and breast-milk samples were obtained.

Results: Marginal vitamin A deficiency was found in 54% of the infants and 18% of the mothers. More than 50% of the mothers and infants were anemic and 17% of the infants and 25% of the mothers were zinc deficient. There was a strong interrelation between the micronutrient status of the mothers and infants and the concentrations of retinol and β-carotene in breast milk. Vitamin A deficiency in infants led to an increased risk of anemia and zinc deficiency (odds ratios: 2.5 and 2.9, respectively), whereas in mothers the risk of anemia and iron deficiency (odds ratios: 3.8 and 4.8, respectively) increased. In infants, concentrations of insulin-like growth factor I were related to concentrations of plasma retinol and β-carotene but not to zinc.

Conclusions: Micronutrient deficiencies were prevalent in West Java. The micronutrient status of lactating mothers and that of their infants were closely related; breast milk was a key connecting factor for vitamin A status. Furthermore, concurrent micronutrient deficiencies appeared to be the norm. *Am J Clin Nutr* 2001;73:786–91.

KEY WORDS Vitamin A, iron, zinc, deficiency, infants, lactating mothers, anthropometry, plasma, human milk, retinol, β-carotene, retinol binding protein, ferritin, hemoglobin, insulin-like growth factor I, Indonesia

INTRODUCTION

Micronutrient deficiencies are still a major public health problem in many developing countries, with infants and pregnant women especially at risk (1). Infants warrant extra concern because they require extra micronutrients to maintain optimal growth and development. In this context, the nutritional relation between lactating mothers and their infants is of special interest.

Deficiencies of vitamin A, iron, and zinc often coexist and have independent and interacting effects on health, growth, and immunocompetence (2, 3). It is well known that severe vitamin A deficiency leads to xerophthalmia. However, vitamin A is important in many other tissues and metabolic processes and the considerable effects of vitamin A deficiency on morbidity and mortality have become clearer. It is important to note that in populations with only marginal vitamin A deficiency, effects on metabolism and immune function are already present (4). Also, vitamin A deficiency was shown to contribute to the development of anemia and stunting (6, 7). People in developing countries derive most of their vitamin A from provitamin A carotenoids, of which β-carotene is the most important. However, absorption, conversion, and mobilization of carotenoids and retinol are variable and dependent on many factors (8).

Iron deficiency is the most important cause of nutritional anemia and is the most common micronutrient deficiency worldwide; it leads to impairment of health, growth, development, and performance (9). Iron supplementation is currently the most important tool for combating iron deficiency. However, a high intake of iron, especially as a supplement, was shown to be an antagonist to zinc absorption (3, 10).

The extent of zinc deficiency and its consequences are not yet clear. Zinc status is difficult to assess because plasma zinc concentrations do not sufficiently reflect individual zinc status because of strong homeostasis (11). In infants, improved growth performance after zinc supplementation is the most accurate measure of preexisting zinc deficiency but, on a population level, plasma zinc is still the most practical and reliable indicator of zinc status (12).

The manifestations of zinc deficiency range from an increased incidence and severity of infection and impaired growth and development of children to pregnancy complications, low birth weight, and increased perinatal mortality (13–16). Zinc is also thought to play a role in vitamin A and β-carotene metabolism. Zinc supplements were shown previously to improve dark adaptation and intestinal integrity and zinc deficiency was found to aggravate the clinical effects of vitamin A deficiency (2).

Most public health and nutrition programs focus on one micronutrient only, whereas many populations can be expected to be deficient in several micronutrients at the same time. The aim of this study was to investigate the prevalence of concurrent micronutrient deficiencies in lactating mothers and their infants to elucidate the nutritional interrelation between the mothers and their infants and the relation of micronutrient deficiencies with growth.

SUBJECTS AND METHODS

Subjects

One hundred ninety-seven mother-infant pairs (>90% of the eligible population of 2 rural villages in the Bogor District of West Java, Indonesia) were recruited over 2 mo (November and December 1996) by health volunteers to participate in the cross-sectional study. Forty-two of these pairs were excluded because of chronic or severe illness ($n = 2$), severe clinical malnutrition ($n = 2$), congenital anomalies ($n = 2$), fever or other signs of mild systemic acute illness ($n = 15$), twin birth ($n = 1$), or incomplete data ($n = 20$). Complete data sets from 155 mother-infant pairs were available for statistical analyses. The excluded mother-infant pairs did not differ significantly from the subjects for whom data are reported. As is customary in Indonesia, all mothers were breast-feeding their infants but most not exclusively so.

Mothers were informed of the procedures and purpose of the study. After written, informed consent was given by the mothers, infants and mothers were anthropometrically assessed and a short history concerning socioeconomic status, dietary and lactation habits, and health was taken. Furthermore, a series of breast-milk samples from the mothers and blood and urine samples from both the mothers and the infants were obtained as completely as possible. The protocol was approved by the Ethical Committee of the National Health Research and Development Institute of Indonesia and by the Ethical Committee of the Royal Netherlands Academy of Arts and Sciences.

Methods

Anthropometry included measurement of weight, height, and midupper arm circumference by a trained anthropometrist using standard methods; z scores for weight and height [weight-for-age (WAZ), height-for-age (HAZ), and weight-for-height (WHZ)] were calculated by using EPI-INFO (version 6.02; Centers for Disease Control and Prevention, Atlanta) with the use of World Health Organization recommended growth curves (17). A fasting 3-mL venous blood sample was taken from the mothers and a non-fasting 5-mL venous blood sample was taken from the infants. A closed-tube heparin-containing vacuum system was used to avoid zinc contamination. Blood samples were stored immediately at 4 °C to prevent microhemolysis and were separated within 5 h.

Breast milk was obtained from the right breast 45–60 min after the last feeding from that breast. The breast was completely expressed and all milk was collected. The manual breast-milk pumps and containers were washed with acid to prevent zinc contamination (18). Urine samples were collected in acid-washed containers (mothers: midstream samples; infants: samples taken after the genital area was washed).

Zinc in blood, urine, and breast milk was analyzed with flame atomic absorption spectrophotometry (Varian Australia Ltd, Clayton South, Australia) by using certified control sera (J Versieck, Department of Internal Medicine, University Hospital, Gent, Belgium) as a quality control. For plasma and urinary zinc, the interassay CV was typically <5%; however, breast-milk zinc analyses showed more variability (10%), probably because of matrix effects. Urinary zinc concentrations were measured in casual urine samples from 104 infants and 130 mothers.

Retinol and β-carotene were analyzed by using standard HPLC procedures. Hemoglobin concentrations were measured by using the standard cyanoblue method (Humalyzer, Tanusstein, Germany). Hematocrit in blood and creamatocrit in breast milk—a measure of breast-milk fat—were determined according to standard practices. The fat content of breast milk was calculated on the basis of the creamatocrit content according to the method of Lucas et al (19). Ferritin, C-reactive protein (CRP), and insulin-like growth factor I (IGF-I) were measured by using commercial enzyme-linked immunosorbent assay kits (MP-products, Amersfoort, Netherlands). Urinary creatinine was measured colorimetrically (Randox, Antrim, United Kingdom) and retinol binding protein (RBP) turbidimetrically (Behring Diagnostics Benelux NV, Rijswijk, Netherlands). Because a close interrelation between indicators of micronutrient status of mothers and their infants was expected, the relation between hemoglobin and plasma retinol, β-carotene, and zinc concentrations in the mother-infant pairs was examined.

Because many commonly used indicators of micronutrient status [eg, plasma concentrations of zinc, retinol, ferritin, and RBP (20)] are altered by the acute phase response, subjects were screened for the presence of inflammation (12, 20). Because a clinical examination often does not exclude the presence of minor or low-grade chronic infections, subjects with an acute phase response—as indicated by CRP concentrations >10 mg/L or ferritin concentrations >150 μg/L (>400 μg/L in infants aged <6 mo) (21)—were excluded from the statistical analyses.

Statistical analysis

Data were checked for normal distribution by using the Kolmogorov-Smirnov test of normality. Relations were analyzed by using multiple linear regression analysis; confounders were controlled for when necessary by using a backward deletion procedure (threshold: $P > 0.1$). When no confounders were found, Pearson's correlation coefficients were used. Odds ratios and CIs were determined by using chi-square tests. Differences between groups were checked by using Student's t test for parametric or log-transformed variables. Statistical analysis was carried out with EPI-INFO (version 6.04b) and SPSS (version 7.5.2; SPSS Inc, Chicago) software packages.

RESULTS

The infants ranged in age from 2.4 to 10.5 mo (**Table 1**), with an equal age distribution for both sexes; the sample included 78 males and 77 females. The mean HAZ was negative (−0.73) whereas the mean WHZ was positive (0.24), indicating that in general the infants were short but not wasted. Eleven infants

TABLE 1
General characteristics of the study population

	Mothers (n = 155)	Infants (n = 155)
Age[1]	25 y (15–41)	6.6 mo (2.4–10.5)
BMI (kg/m²)[2]	21.2 (19.7–23.0)	—
z Scores[3]		
Weight-for-age	—	−0.36 ± 1.08
Height-for-age	—	−0.73 ± 1.08
Weight-for-height	—	0.24 ± 0.88

[1] Median; range in parentheses.
[2] Median; interquartile range.
[3] $\bar{x}$ ± SD.

(7%) had an HAZ < −2, whereas one infant (0.6%) had a WHZ < −2. An HAZ > 2 and a WHZ > 2 were found in 1% and 3% of the infants, respectively. Furthermore, all z scores were significantly negatively correlated with age after sex was controlled for (HAZ: $r = −0.34$; WHZ: $r = −0.29$; WAZ: $R = −0.48$; $P < 0.01$ for all), implying that growth faltering in these infants started within the first months of life and progressed with age, as is observed frequently in developing countries.

Micronutrient deficiencies were prevalent in both the infants and mothers studied; >50% of the infants and mothers were anemic and >50% of the infants had marginal plasma retinol concentrations (<0.70 μmol/L) (**Table 2**). Seventeen infants and 12 mothers were excluded because of having an acute phase response: either elevated CRP concentrations only or both elevated CRP and ferritin concentrations; none had elevated ferritin concentrations only. As expected, plasma retinol concentrations were significantly lower and plasma ferritin concentrations were significantly higher in the excluded subjects. Plasma zinc and RBP concentrations, however, did not differ significantly in the excluded subjects.

In the infants there was a strong linear correlation between plasma retinol and RBP concentrations ($r = 0.71$, $P < 0.01$; multiple regression analysis, no confounders were found; **Figure 1**).

There was a positive correlation between concentrations of plasma zinc and urinary zinc (related to creatinine) in infants only ($r = 0.23$, $P < 0.05$; Spearman's rank test). The urinary zinc concentration is considered a more sensitive indicator of early zinc deficiency than is the plasma zinc concentration (14); however, in the present study it was found to be less suitable in the field setting, where sampling conditions were difficult. Usually, only casual urine samples can be obtained in a field setting and it is often difficult to obtain samples from young infants. These factors contribute to the large variation in urinary zinc concentrations; therefore, this measure is not very useful as an indicator of zinc status.

There was a strong correlation between concentrations of hemoglobin, plasma retinol, plasma β-carotene, and plasma zinc in the mother-infant pairs (Table 2). Similarly, in lactating mothers, breast milk was an important link between the nutritional status indicators of mothers and infants. Breast-milk concentrations of retinol and β-carotene were significantly correlated with those in the plasma of both mothers and infants (**Table 3**), accounting to a large extent for the strong interrelation between the vitamin A status of the mothers and infants. Concentrations of zinc in breast milk, however, were not significantly correlated with those in the plasma of either the mothers or infants. The fat content of breast milk [calculated on the basis of a median creamatocrit content of 3.7% (interquartile range: 2.8–5.0%)] was significantly positively correlated with both breast-milk retinol and β-carotene concentrations ($r = 0.53$ and $r = 0.24$, respectively; $P < 0.01$ by multiple regression analysis). However, conflicting findings on changes in micronutrient concentrations during lactation were reported previously (22–25). In the present study, there was no significant effect of the duration of lactation on retinol, β-carotene, or zinc concentrations in breast milk.

Vitamin A–deficient infants had a 2.5-fold greater risk of anemia and a 2.9-fold greater risk of zinc deficiency than did nondeficient infants, whereas the vitamin A–deficient mothers were especially at risk of anemia (3.8-fold greater risk) and iron deficiency (4.8-fold greater risk) (**Table 4**).

TABLE 2
Indicators of the micronutrient status of Indonesian infants and their lactating mothers and the prevalence of micronutrient deficiencies[1]

	Infants	Mothers	Correlation between mothers and infants[2]
Plasma retinol (μmol/L)[3]	0.68 ± 0.21[4]	1.09 ± 0.40	0.30
Proportion <0.70 μmol/L (%)	54	18	—
Plasma β-carotene (μmol/L)	0.04 (0.02–0.05)[5]	0.14 (0.09–0.21)	0.42
Plasma lutein (μmol/L)	0.29 (0.20–0.44)	0.41 (0.30–0.57)	—
Plasma retinol binding protein (μmol/L)[3]	0.71 (0.62–0.86)	—	—
Hemoglobin (g/L)	106 ± 12	117 ± 13	0.28
Proportion of anemic subjects (%)[6]	57	52	—
Plasma ferritin (μg/L)[3]	26.9 (10.2–56.3)	13.9 (6.1–30.4)	NS
Proportion of iron-deficient subjects (%)[7]	20	29	—
Plasma zinc (μmol/L)[3]	13.1 (11.5–15.0)	12.6 ± 2.7	0.45
Proportion <10.7 μmol/L (%)	17	25	—
Urinary zinc (μmol/mg creatinine)	17.4 (12.3–26.4)	6.7 (3.8–10.9)	NS

[1] n = 155.
[2] Pearson's correlation coefficient (with linear regression analysis, no confounders were found), $P < 0.01$.
[3] Subjects with an acute phase reaction (17 infants and 12 mothers; 27 mother-infant pairs) were excluded from the statistical analysis.
[4] $\bar{x}$ ± SD.
[5] Median; interquartile range in parentheses.
[6] Anemia was defined as a hemoglobin concentration <110 g/L (in infants) and <120 g/L (in mothers).
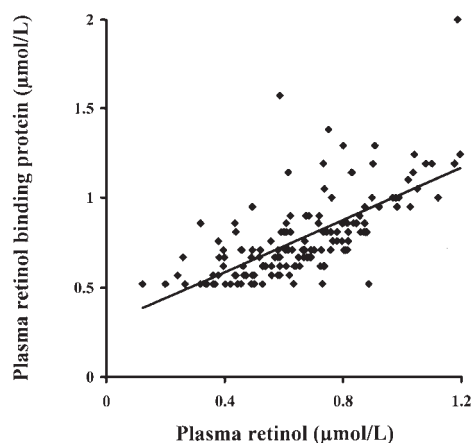[7] Iron deficiency was defined as anemia and a plasma ferritin concentration <15 μg/L.

FIGURE 1. Relation between plasma concentrations of retinol and retinol binding protein in Indonesian infants. $y = 0.73x + 0.30$; $R^2 = 0.46$.

Long-term growth performance can be monitored by taking anthropometric measures, whereas IGF-I concentrations provide a measure of current growth activity. In the infants studied, the median plasma IGF-I concentration was 18.8 μg/L (interquartile range: 10.3–34.7 μg/L) and IGF-I concentrations were negatively correlated with age, as were WAZ, HAZ, and WHZ scores (**Table 5**). Furthermore, a clear relation was observed between IGF-I and plasma retinol and β-carotene concentrations but not with zinc. No relation was found between the indicators of micronutrient status and the anthropometric measurements.

DISCUSSION

This study showed that deficiencies of vitamin A, iron, and zinc occur concurrently in lactating mothers and their infants in rural villages in West Java, Indonesia. Vitamin A–deficient mothers and infants had a 2–3-fold greater risk of also being deficient in iron or zinc than did nondeficient mothers and infants. Furthermore, the interrelation between the micronutrient status of the lactating mothers and that of their infants was shown clearly, with breast milk being a key connecting link, especially for vitamin A nutrition. One of the first effects of suboptimal nutrition in young infants is growth impairment, and the observed relation between plasma concentrations of IGF-I and of retinol and β-carotene was intriguing.

Even though the population studied was not very deprived, merely rural and having traditional habits and diets, they had a high prevalence of marginal-to-severe micronutrient deficiencies, especially of iron and vitamin A. On the basis of the current cutoff indicating zinc deficiency (plasma zinc < 10.7 μmol/L; 26), the prevalence of zinc deficiency in the present study population was almost similar to the prevalence of iron deficiency. This is despite the fact that zinc deficiency is less readily assessed than is iron deficiency. At the population level, the plasma zinc concentration is a useful indicator of zinc status (12). However, current cutoffs for deficiency have been defined without considering the effect of infection on plasma zinc concentrations. Hence, the estimate of zinc deficiency in this population was conservative because subjects with an acute phase response were excluded.

The plasma RBP concentration was advocated recently as an alternative to the plasma retinol concentration for assessing vitamin A status. However, the relation between the plasma retinol

TABLE 3
Relations between concentrations in breast milk and in plasma of retinol, β-carotene, and zinc in Indonesian lactating mothers and their infants

		Correlation with plasma concentration	
	Breast milk[1]	Mother[2]	Infant[3]
Fat (g/L)	21.3 (15.1–30.2)	—	—
Retinol (μmol/L)	0.37 (0.21–0.67)	0.37[4]	0.27[4]
β-Carotene (μmol/L)	0.006 (0.004–0.011)	0.49	0.58
Zinc (μmol/L)	30.3 (20.5–47.2)	NS	NS

[1] Median; interquartile range in parentheses. One hundred fifty breast milk samples were available for vitamin A analyses and 105 of these were analyzed for zinc.

[2] Partial correlation coefficients with control for fat content; no other confounders were found. Subjects with missing creamatocrit values ($n = 12$ mothers) were excluded from the statistical analysis. $P < 0.01$.

[3] Pearson's correlation coefficients with linear regression analysis; no confounders were found. $P < 0.01$.

[4] Subjects with an acute phase reaction were excluded from the statistical analysis ($n = 14$ mothers and 17 infants).

concentration and the retinol-RBP ratio (**Figure 2**) showed that this ratio is constant and close to 1 only above marginal concentrations of retinol: the ratio is <1 at lower plasma retinol concentrations. This lower ratio probably reflects an increase in plasma apo-RBP concentrations in vitamin A deficiency (27). Hence, RBP becomes a less-sensitive indicator of vitamin A status at lower plasma retinol concentrations. Therefore, substituting RBP for retinol as an indicator of vitamin A status may lead to an underestimate of deficiency. Methods that specifically measure holo-RBP circumvent this drawback (28), but are not yet generally available. It is important to establish reliable indicators for micronutrient status, especially when assessing a population for multiple micronutrient deficiencies, because confounding factors such as infection can easily complicate the overall picture.

Micronutrient deficiencies coexist and overlap because of common etiology and underlying mechanisms. For instance, a diet rich in phytate and low in animal proteins, as is common in most developing countries, including Indonesia, predisposes to insufficient intake and absorption of both iron and zinc (14, 29). Also, direct interactions between micronutrients were described previously, such as the positive effect of vitamin A supplementation on iron

TABLE 4
Risk of vitamin A–deficient infants and mothers of having deficiencies of other micronutrients[1]

Micronutrient deficiency indicator	Vitamin A–deficient infants ($n = 138$)	Vitamin A–deficient mothers ($n = 143$)
Anemia[2]	2.5 (1.3, 5.0)	3.8 (1.4, 10.0)
Iron deficiency[3]	2.4 (1.0, 6.0)	4.8 (2.0, 11.6)
Zinc deficiency[4]	2.9 (1.1, 7.8)	1.9 (0.7, 4.6)
Iron, zinc deficiency, or both	2.6 (1.2, 5.5)	2.8 (1.2, 6.8)
Anemia, zinc deficiency, or both	2.6 (1.3, 5.3)	3.1 (1.1, 8.9)

[1] Odds ratios; 95% CIs in parentheses. Subjects with an acute phase response were excluded from the statistical analysis.

[2] Defined as a hemoglobin concentration <110 g/L (in infants) and <120 g/L (in mothers).

[3] Defined as anemia and a plasma ferritin concentration <15 μg/L.

[4] Defined as plasma zinc <10.7 μmol/L.

TABLE 5
Relations between plasma concentrations of insulin-like growth factor I (IGF-I) in infants and indicators of anthropometric and micronutrient status[1]

	r
Age	−0.28[2]
z Scores	
Weight-for-height	0.18[3]
Weight-for-age	NS
Height-for-age	NS
Plasma retinol[5]	0.25[4]
Plasma β-carotene	0.21[4]
Hemoglobin	0.17[3]
Plasma zinc[5]	NS

[1] $n = 155$. The median IGF-I concentration was 18.8 µg/L (interquartile range: 10.3–34.7).

[2] $P < 0.01$ (Pearson's correlation coefficient).

[3] $P < 0.05$ (partial correlation coefficients with control for age).

[4] $P < 0.01$ (partial correlation coefficients with control for age).

[5] $n = 138$ because 17 infants with an acute phase reaction were excluded.

deficiency anemia (6) and the antagonistic effect of iron supplementation on zinc uptake (14). The mechanisms underlying these interactions are not yet fully understood. Focusing on several micronutrients instead of just one is important not only for treating micronutrient deficiencies but also for screening and identifying high-risk groups. This was illustrated clearly by the results reported here. Vitamin A–deficient subjects had a much increased (2.4–4.8) risk of being deficient in iron also. The increased risk of a deficiency of both vitamin A and iron was described previously (30); thus, hemoglobin screening is used to identify people at risk of vitamin A deficiency (6). Furthermore, this study showed an almost 3-fold greater risk of zinc deficiency in vitamin A–deficient infants than in infants without a vitamin A deficiency, whereas there was a tendency toward an increased risk of zinc deficiency in vitamin A–deficient mothers. Whether there is a common underlying cause of these micronutrient deficiencies or whether one micronutrient deficiency leads to another deficiency could not be answered here.

The nutritional status of mothers is an important factor both prenatally and after birth. Prenatal maternal nutritional status affects birth weight, neonatal morbidity and mortality, and the micronutrient status of newborns. Postnatal maternal status can affect the quality of breast milk and thus the nutrient intake of infants (31). In the present study, indicators of the micronutrient status of the lactating mothers were clearly related to those of the infants. Concentrations of hemoglobin, plasma retinol, plasma β-carotene, and plasma zinc were all strongly correlated between the mother-infant pairs. For retinol and β-carotene, this relation was attributable to the breast-milk link referred to above The close relation between maternal vitamin A status and vitamin A concentrations in breast milk was described previously (32, 33), but few data are available on the link between vitamin A concentrations in breast milk and the vitamin A status of infants. The present study showed clearly that the concentrations of vitamin A and β-carotene in breast milk were closely related to those in the plasma of the infants. No relation was found between zinc concentrations in the plasma of the mothers and in breast milk, reflecting earlier evidence that mammary zinc secretion is independent of maternal zinc status (23, 24).

Impaired growth in infants is in itself not hazardous to health but is associated with higher morbidity and mortality and with impaired cognitive and psychomotor development (34). The findings of the present study indicate that growth was suboptimal in these infants, with length more affected than weight. In accordance with findings in similar populations, HAZ scores were lower with increasing age. Growth failure is a consistent sign of zinc deficiency, and zinc supplementation was shown to improve growth, especially in stunted children (35). Ninh et al (36) reported increased IGF-I concentrations after zinc supplementation in stunted Vietnamese infants. In the present study, however, IGF-I was found to be related to plasma concentrations of retinol and β-carotene in the infants, and to a lesser extent to hemoglobin concentrations, but not to plasma zinc concentrations.

There is clear evidence of a direct effect of vitamin A on cellular and tissue growth (37). However, supplementation with either retinol or β-carotene improved growth performance in some studies but not in others, and the underlying mechanisms are not clear (7, 38–40). IGF-I is a relatively new indicator of growth activity and the relation between plasma concentrations of retinol and β-carotene and those of IGF-I has not been reported. Thus, further investigation is required to establish whether this relation can be confirmed and to test whether the effect is causal. Other factors such as infection, nutrient status with respect to other nutrients, and genetic background could also be implicated (41). For instance, vitamin A status has profound effects on morbidity and could thereby indirectly influence growth (4).

The results of this study provide clear evidence that the concurrent occurrence of deficiencies of many micronutrients is the norm rather than the exception. Of special significance is the strong interrelation between the micronutrient status of the mothers and that of their infants; however, the mechanisms involved have not yet been elucidated satisfactorily. In a future trial of β-carotene, iron, and zinc supplementation, we will investigate interactions between vitamin A, iron, and zinc and interrelations between micronutrient deficiencies in infants and pregnant women in West Java, Indonesia.
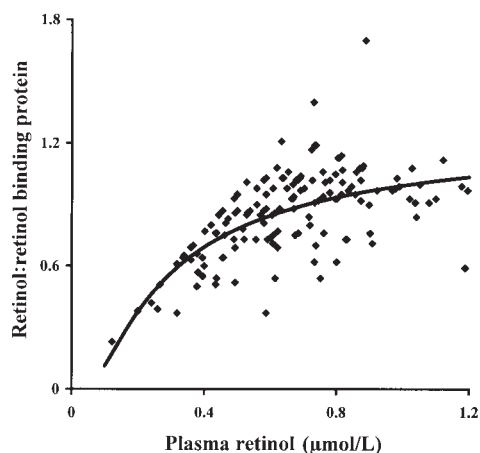
FIGURE 2. Relation between plasma retinol concentrations and the ratio of retinol to retinol binding protein in Indonesian infants. $\ln(y) = 0.24 - 0.24x^{-1}$; $R^2 = 0.54$.

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