Vitamin A supplementation selectively improves the linear growth of Indonesian preschool children: results from a randomized controlled trial[1–3]

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ABSTRACT

Background: Vitamin A deficiency is associated with stunting and wasting in preschool children, but vitamin A supplementation trials have not shown a consistent effect on growth.

Objective: We examined the effect of vitamin A supplementation on height and weight increments among Indonesian preschool children.

Design: Data were obtained from a randomized, double-masked, placebo-controlled trial of rural Javanese children aged 6–48 mo. Children received 206 000 IU vitamin A (103 000 IU if aged < 12 mo) or placebo every 4 mo.

Results: High-dose vitamin A supplementation modestly improved the linear growth of the children by 0.16 cm/4 mo. The effect was modified by age, initial vitamin A status, and breast-feeding status. Vitamin A supplementation improved height by 0.10 cm/4 mo in children aged < 24 mo and by 0.22 cm/4 mo in children aged ≥ 24 mo. The vitamin A–supplemented children with an initial serum retinol concentration < 0.35 μmol/L gained 0.39 cm/4 mo more in height and 152 g/4 mo more in weight than did the placebo group. No growth response to vitamin A was found among children with an initial serum retinol concentration ≥ 0.35 μmol/L. In non-breast-fed children, vitamin A supplementation improved height by 0.21 cm/4 mo regardless of age. In breast-fed children, vitamin A supplementation improved linear growth by ≈0.21 cm/4 mo among children aged ≥ 24 mo, but had no significant effect on the growth of children aged < 24 mo.

Conclusion: High-dose vitamin A supplementation improves the linear growth of children with very low serum retinol and the effect is modified by age and breast-feeding. *Am J Clin Nutr* 2000;71:507–13.

KEY WORDS Vitamin A, growth, age, breast-feeding, Indonesia, preschool children

INTRODUCTION

Vitamin A deficiency and growth retardation are important public health problems in developing countries (1), including Indonesia. Many cross-sectional studies have linked vitamin A deficiency to a greater risk of being stunted (2, 3) and wasted (2). Additionally, a prospective study conducted in West Java (4) showed that children with mild xerophthalmia have slower rates of weight and height gain than do nonxerophthalmic children.

However, a causal relation between vitamin A status and growth in children has not been conclusively proven in previously reported vitamin A trials. Some have found that vitamin A supplementation improved linear (5, 6) or ponderal (7) growth, but others found no effect (8, 9). These conflicting results are not surprising given the different environments in which children live, with variations in vitamin A status and in other nutrients and changes in nutrient demands associated with age and infectious diseases. In animal models, in which vitamin A was the only growth-stimulating factor manipulated, weight (10) and length (11) gains ceased when liver stores were nearly exhausted. Growth was restored when animals were resupplemented with vitamin A–containing food (12, 13). In vitamin A–deficient populations, children typically have multiple factors limiting their growth. Thus, one must consider the effect of vitamin A supplementation on growth based on different levels of coexisting factors such as initial vitamin A status, initial growth retardation, infection load, dietary vitamin A intake, and other nutritional and nonnutritional factors that might modify growth. Previous studies have not fully considered these potential effect modifiers.

This paper presents the effects of vitamin A supplementation on the linear growth of preschool children in Central Java, Indonesia, where subclinical vitamin A deficiency and stunting are common (14). Because we expected that vitamin A supplementation

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would not have the same effect on growth in all children, we further examined whether the effect of vitamin A supplementation differed by the children's age, sex, initial vitamin A status, breast-feeding status, dietary vitamin A intake, or initial anthropometric status.

SUBJECTS AND METHODS

Study population and design

We analyzed data from the Morbidity and Vitamin A (MORVITA) Study, which was designed to investigate the effect of vitamin A on morbidity, especially respiratory infection and diarrhea. Details of the study design and results are described elsewhere (14, 15), but important aspects of the study are summarized below. The study was conducted by the Johns Hopkins University in collaboration with the Faculty of Medicine, University of Gadjah Mada, from 1989 to 1992. Two rural subdistricts located on the southern coast of Central Java, Indonesia, were selected as the study sites. The study was a randomized, double-masked, placebo-controlled trial and consisted of 6 treatment cycles in which the treatment was given once every 4 mo. Children aged 6–47 mo at the start of each treatment cycle (n = 1407) were randomly assigned to receive either 214 μmol vitamin A (206 000 IU/L, or 107 μmol vitamin A/L if aged < 12 mo) or placebo; this assignment remained fixed for all subsequent treatment cycles. Data were collected for 4430 child-treatment cycles: 2178 from the placebo group and 2252 from the vitamin A group.

The protocol was reviewed and approved by the Committee on Human Research, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore; the Indonesian Vitamin A Research Steering Committee; and the Committee of Ethics in Human Biomedical Research of the Faculty of Medicine, University of Gadjah Mada. Written informed consent was obtained from the guardians of all children before entering the study. A program of community education and meetings with the village headmen was conducted to help people understand the advantages and disadvantages of participating in the study.

Data collection procedures

Anthropometric data

The children's weights and heights were measured by a team of trained anthropometrists. Weight was measured every month in the integrated village health services post, whereas recumbent length was measured only every 4 mo at the start of each cycle in the trial treatment clinic. For children who did not attend the post or clinic, the anthropometric team measured their weights and heights at home. On average, ≈95% of treated children from each cycle completed anthropometric measurements at the start and conclusion of the cycle. The weights of naked or lightly clad children were measured with a suspended Salter spring scale (Salter Industrial Measurement, West Midlands, United Kingdom) and read to the nearest 0.1 kg after the pointer was completely still for ≥2–3 s. The measurements were taken independently ≥3 times and the mean was recorded as the observed value. Recumbent length and standing height were measured to the nearest 1 mm for children aged < 24 and 24–47 mo with a portable wooden board structurally reinforced for increased instrument precision.

Morbidity data

The children's morbidity experience was assessed by trained interviewers who visited the children and their guardians every second day to record symptoms of diarrhea and acute respiratory illnesses. If the children were absent, the interview was attempted at the next scheduled home visit. The longest recall period allowed was 4 d. These morbidity data were collected on standardized precoded forms by using Javanese language with appropriate local terms identified by an anthropologist using focus group discussions and in-depth interviews with village women before data collection.

Episodes of diarrhea were defined as adjoining days on which the child was reported to have ≥3 loose stools/24 h, ending with ≥2 symptom-free or missing data days. Episodes of upper respiratory illness were defined as ≥2 adjoining days on which the child was reported to have a cough, ending with ≥3 symptom-free or missing data days.

Assessment of vitamin A status

Vitamin A status was assessed at the start of each child's first treatment cycle on the basis of their serum retinol concentration. HPLC was used for laboratory analysis. Blood samples were collected from the children by antecubital venipuncture into capped, colored, glass tubes and transported on ice to the field office, where they were centrifuged (1000 × g for 10 min at room temperature) and portioned. On the same day, sera were transported on ice to the laboratory where HPLC procedures were carried out. The samples were handled and processed according to International Vitamin A Consultative Group guidelines (16).

Dietary vitamin A intake

A food-frequency questionnaire was used to characterize the habitual vitamin A intake of individual children. A 1-mo dietary recall was used because the diets of young children change rapidly and because of the seasonal availability of many foods in the study area. The questionnaire covered 57 foods containing vitamin A. Local Javanese terms of all possible vitamin A–containing foods as well as multivitamins were identified by nutritionists during a preliminary survey of the food intake of 156 children near the study area. The frequency of usual consumption of the various foods was recorded in the following categories: ≥4 times/d, 2–3 times/d, 1 time/d, 4–6 times/wk, 2–3 times/wk, 1 time/wk, and 1–3 times/mo. The midpoint of the interval (4 times/d, 2.5 times/d, etc) was used to calculate the frequency of intake. Average portion sizes were determined by interviewing a convenience sample of 150 mothers who lived in villages outside the study area. Mothers were asked about the usual portion sizes their children consumed for all 57 foods. Food models were used in the interview to help identify the usual portion sizes. Separate portion sizes were determined for children aged 6–11 mo, 12–23 mo, and 24–47 mo. An age-specific mean portion size for all food items was then determined based on these interviews. The food-frequency questionnaire was completed by trained high school graduates who were supervised by nutritionists responsible for their training and the editing of forms. Interviews were conducted on the same day or within 2 d of the children's treatment cycle, except for the first cycle, for which 30% of the interviews were conducted ≈1 mo after the trial treatment clinic. Mothers were asked whether their children were breast-fed and whether they received supplementary food at the time of the dietary interviews. Thus, dietary vitamin A intakes were adjusted for the estimated intake of vitamin A from breast milk.

Data management and statistical analysis

Precoded forms with preprinted identification labels were used for data collection. Data were edited by field supervisors before data entry and then entered into the computers by trained computer operators using dSURVEY software (17). Statistical analysis was done by using SAS (version 6.11; SAS Institute, Cary, NC) and STATA 5.0 (STATA Corporation, College Station, TX) software. Anthropometric indicators were calculated by using the World Health Organization (WHO) international growth reference (18) with computer subroutines provided by the US Centers for Disease Control and Prevention (Atlanta). On the basis of the Waterlow classification of malnutrition (19), *stunted* was defined as a height-for-age *z* score < -2 and a weight-for-height *z* score ≥ -2, *wasted* was defined as a weight-for-height *z* score < -2 and a height-for-age *z* score ≥ -2, and *stunted and wasted* was defined as a height-for-age *z* score < -2 and a weight-for-height *z* score < -2.

The comparability between treatment groups was examined by using the chi-square test for general association. Two statistical approaches were used to estimate the effect of vitamin A supplementation on growth. In the first approach, all children's treatment cycles were analyzed and generalized estimating equations (20–22) were used to account for the fact that most children contributed more than one treatment cycle to the analysis. This method accounts for the correlation of the repeated responses within individuals and allowed us to fully use all 4430 treatment cycles. The outcome variable of this analysis was the 4-mo height or weight increment. The explanatory variables included treatment, age, sex, dietary vitamin A intake, initial nutritional status, breast-feeding status, percentage of days with respiratory infections and diarrhea, and season. Because children received different age-specific doses of vitamin A over the course of the study, all models in the analysis were adjusted for the cumulative dose of vitamin A in IUs. This cumulative dose reflected the total dose of vitamin A that had been received by each individual before a cycle-specific treatment. Treatment was handled as a categorical variable: vitamin A or placebo. Age was handled as a dichotomous variable: <24 mo or ≥ 24 mo. Vitamin A intake was handled as a dichotomous variable: below or above the normative requirement [400 retinol equivalents (RE)/d] according to WHO standards (23). Initial anthropometric status was categorized as wasted or nonwasted (19). The percentage of days with respiratory infections and diarrhea were handled as continuous variables. Season was grouped into 3 different categories [season 1 (December to March), season 2 (April to July), and season 3 (August to November)] and handled as 2 dummy variables (seasons 2 and 3). Both the main effect and the treatment interactions of the explanatory variables were considered.

In the second statistical approach, multiple linear regression was used to test whether the effect of vitamin A supplementation on growth was modified by initial vitamin A status. For this analysis, only 1060 child-treatment cycles were used because each child's vitamin A status was assessed only once at the first treatment cycle. Vitamin A status was divided into 3 categories and handled as 2 dummy variables: <0.35 μmol/L, 0.35–0.70 μmol/L, and >0.70μmol/L. All other variables were handled as described for the generalized estimating equations model. Because each child in this subsample had received only one dose of vitamin A and entered the study in different seasons, the model was not adjusted for cumulative doses and seasons. However, the model was adjusted for the season of entry.

RESULTS

Characteristics of treatment groups

The 2 treatment groups had similar distributions of demographic, nutritional, and socioeconomic characteristics (**Table 1**). The study population had a high prevalence of subclinical vitamin A deficiency but a low prevalence of clinical vitamin A deficiency. At entry into the study, 15.4% of the children had very low serum retinol concentrations (<0.35 μmol/L), 52% had low serum retinol concentrations (0.35–0.70 μmol/L), and 32.6% had normal concentrations (>70 μmol/L). Vitamin A deficiency with ocular involvement was almost absent from the study population, with only one case of Bitot spots and no cases of corneal xerophthalmia diagnosed in trial subjects. The prevalence of very low serum retinol concentrations (15.4%) exceeded the WHO criterion indicating vitamin A deficiency as a public health problem, which is 5% of values <0.35 μmol/L (24).

Serum retinol concentrations differed significantly by age group, with a mean (±SD) serum retinol concentration in children aged <24 mo of 0.52 ± 0.1 μmol/L compared with 0.60 ± 0.1 μmol/L in children aged ≥ 24 mo ($P < 0.0001$). Serum retinol also differed significantly by sex, with a mean serum

TABLE 1
Characteristics of study subjects on entry to first treatment cycle[1]

Characteristic	Vitamin A group	Placebo group
	n (%)	
Sex		
Male	351 (49.1)	370 (51.2)
Female	364 (50.9)	352 (48.8)
Age (mo)		
6–12	233 (32.6)	240 (33.2)
13–24	171 (23.9)	176 (24.4)
25–36	155 (21.7)	135 (18.7)
37–48	154 (21.5)	170 (23.6)
>48	2 (0.28)	1 (0.14)
Serum retinol (μmol/L)		
<0.35	94 (13.2)	110 (15.2)
0.35–0.70	339 (47.4)	348 (48.2)
0.71–1.05	197 (27.6)	190 (26.3)
>1.05	22 (3.1)	22 (3.1)
Missing	63 (8.8)	52 (7.2)
Dietary vitamin A intake (RE/d)		
<200	205 (28.7)	188 (26.0)
200–400	198 (27.7)	219 (30.3)
>400	263 (36.8)	266 (36.8)
Missing	49 (6.9)	49 (6.8)
Anthropometric status		
Normal	418 (58.5)	460 (63.7)
Stunted only	245 (34.3)	218 (30.2)
Wasted only	21 (2.9)	19 (2.6)
Stunted and wasted	27 (3.8)	20 (2.8)
Missing	4 (0.6)	5 (0.7)
Mother's education		
None or incomplete primary school	289 (40.4)	301 (41.7)
Complete primary school	252 (35.2)	259 (35.9)
Secondary school	72 (10.1)	58 (8.0)
High school or higher	51 (7.1)	60 (8.3)
Missing	51 (7.1)	44 (6.1)

[1] There were no significant differences between groups (chi-square test). RE, retinol equivalents.

retinol concentration in males of 0.54 ± 0.1 μmol/L compared with 0.59 ± 0.1 μmol/L in females ($P < 0.05$).

Forty percent of the study population had vitamin A intakes above the normative requirement (>400 RE/d) for vitamin A, 31% had vitamin A intakes between the basal and normative requirements (200–400 RE/d), and 29% had daily vitamin A intakes below the basal requirement for vitamin A (<200 RE/d) (23). There were no significant differences in vitamin A intake by treatment group. Average vitamin A intakes were also significantly different by age group. In children aged <24 mo, the mean (±SD) vitamin A intake was 290 ± 239 RE/d compared with 485 ± 291 RE/d in children aged ≥24 mo ($P < 0.0001$). Anthropometric status was comparable between treatment groups (Table 1). In the 2 groups combined, the prevalence of stunting (35.5%) was much higher than the prevalence of wasting (6.1%).

Effect of vitamin A on height and weight increments

On the basis of an analysis of all child-treatment cycles, the vitamin A group had an average 4-mo height increment that was 0.16 cm (95% CI: 0.08, 0.23) greater than that in the placebo group. The effect of vitamin A supplementation on linear growth differed significantly by age group (**Figure 1**). In vitamin A–supplemented children aged <24 mo, the 4-mo height increment was 0.10 cm (95% CI: −0.01, 0.20) greater than that in the placebo group. In vitamin A–supplemented children aged ≥24 mo, the 4-mo height increment was 0.22 cm (95% CI: 0.14, 0.30) greater than that in the placebo group.

The effect of vitamin A supplementation on the height increment was not affected significantly by sex, vitamin A intake, or initial anthropometric status, but was affected significantly by breast-feeding status (**Table 2**). The linear growth responses to vitamin A supplementation in children aged ≥24 mo who were no longer breast-fed, in children aged ≥24 mo who were still breast-fed, and in children aged <24 mo who were no longer breast-fed were similar. In these groups combined, the 4-mo height increment in the vitamin A group was 0.22 cm (95% CI: 0.13, 0.29) greater than that in the placebo group. However, there was no significant difference in the 4-mo height increment between the vitamin A–supplemented children aged <24 mo who were still breast-fed and the placebo group, and the average 4-mo height increment in the vitamin A–supplemented children aged <24 mo was 0.13 cm (95% CI: 0.02, 0.25) less than that in the other vitamin A–supplemented children.

The effect of vitamin A also differed significantly by serum retinol concentration at baseline. In the analyses restricted to the first child-treatment cycles, children with serum retinol concentrations <0.35 μmol/L had a 4-mo height increment 0.16 cm (95% CI: − 0.03, 0.36) less than that in children with serum retinol concentrations >0.70 μmol/L. Children with serum retinol concentrations of 0.35–0.70 μmol/L had a 4-mo height increment that was 0.04 cm (95% CI: −0.23, 0.32) less than that of children with serum retinol concentrations >0.70 μmol/L. This cross-sectional association was borne out in the response to vitamin A. After adjustment for age, sex, anthropometric status before treatment, breast-feeding status, percentage of days with diarrhea and respiratory infection, and season of entry, the positive effect of vitamin A supplementation on linear growth was limited to children who had an initial serum retinol concentration <0.35 μmol/L (**Figure 2**). Specifically, vitamin A–supplemented children who had an initial serum retinol concentration <0.35 μmol/L had a 4-mo height increment 0.39 cm (95% CI: 0.24, 0.53) greater than that in the placebo group.

TABLE 2
Four-month height and weight increments of Indonesian preschool children by treatment group, age, and breast-feeding status[1]

Explanatory variable	Outcome variable	
	Height increment	Weight increment
	cm	*kg*
<24 mo, breast-fed		
Vitamin A group (n = 707)	3.23 (3.12, 3.34)	0.71 (0.62, 0.79)
Placebo group (n = 727)	3.15 (3.07, 3.23)	0.69 (0.63, 0.73)
<24 mo, non-breast-fed		
Vitamin A group (n = 181)	3.08 (2.97, 3.19)	0.55 (0.52, 0.59)
Placebo group (n = 175)	2.88 (2.77, 2.98)	0.56 (0.53, 0.59)
≥24 mo, breast-fed		
Vitamin A group (n = 193)	2.50 (2.39, 2.60)	0.52 (0.48, 0.61)
Placebo group (n = 184)	2.29 (2.16, 2.39)	0.50 (0.45, 0.57)
≥24 mo, non-breast-fed		
Vitamin A group (n = 1133)	2.42 (2.34, 2.50)	0.55 (0.51, 0.58)
Placebo group (n = 1130)	2.21 (2.12, 2.30)	0.52 (0.49, 0.56)

[1] $\bar{x}$; 95% CI in parentheses. Values were derived from multiple linear regression models obtained from generalized estimating equations and adjusted for within-child correlation, sex, initial anthropometric status, percentage of days with diarrhea and respiratory infections, season, and cumulative doses.

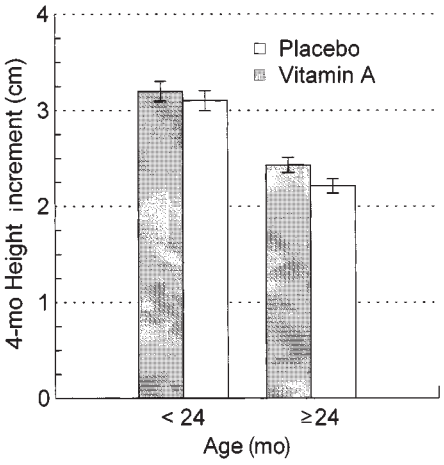

FIGURE 1. Four-month height increments of Indonesian preschool children by age and treatment groups. Values are plotted as means and 95% CIs obtained from a multivariable linear model with generalized estimating equations (GEE) to adjust for within-child correlations (*see* text). A total of 4430 child-treatment cycles (1790 children aged <24 mo: n = 888 in the vitamin A group and 902 in the placebo group; 2640 children aged ≥24 mo: n = 1326 in the vitamin A group and 1314 in the placebo group) were used in the analysis.

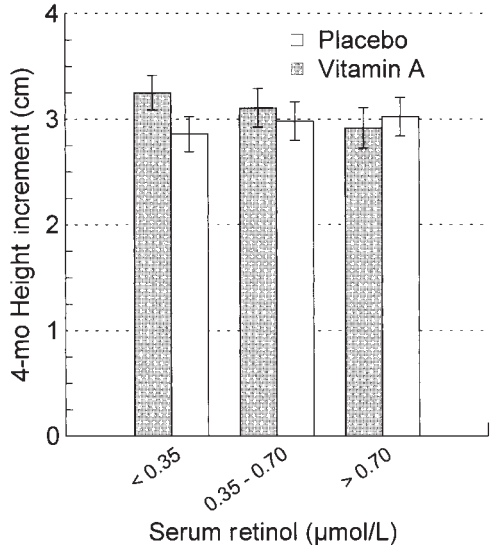

FIGURE 2. Four-month height increments of Indonesian preschool children by initial serum retinol concentrations and treatment groups. Values are plotted as means and 95% CIs obtained from multivariable linear regression models (*see* text). A total of 1060 child-treatment cycles (178 children had serum retinol concentrations <0.35 μmol/L: *n* = 83 in the vitamin A group and 95 in the placebo group; 533 children had serum retinol concentrations of 0.35–0.70 μmol/L: *n* = 271 in the vitamin A group and 262 in the placebo group; and 349 children had serum retinol concentrations >0.70 μmol/ L: *n* = 177 in the vitamin A group and 172 in the placebo group) were used in the analysis.

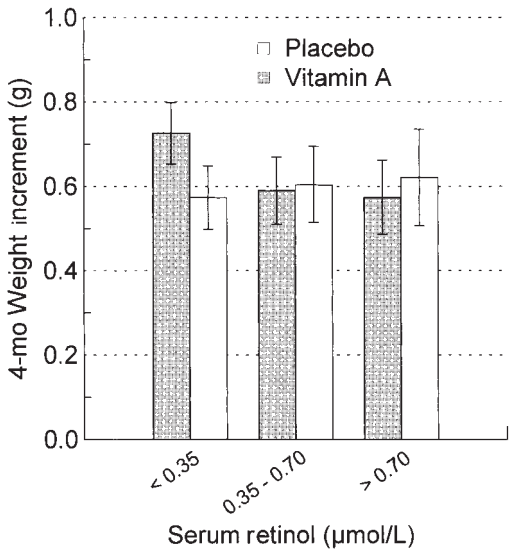

FIGURE 3. Four-month weight increments of Indonesian preschool children by initial serum retinol concentrations and treatment groups. Values are plotted as means and 95% CIs obtained from multivariable linear regression models (*see* text). A total of 1060 child-treatment cycles (178 children had serum retinol concentrations <0.35 μmol/L: *n* = 83 in the vitamin A group and 95 in the placebo group; 533 children had serum retinol concentrations of 0.35–0.70 μmol/L: *n* = 271 in the vitamin A group and 262 in the placebo group; and 349 children had serum retinol concentrations >0.70 μmol/ L: *n* = 177 in the vitamin A group and 172 in the placebo group) were used in the analysis.

There was no overall difference in weight increment between the 2 treatment groups (mean difference: 0.01; 95% CI: −0.02, 0.04), nor was the effect on weight increment significantly different by age, breast-feeding status (Table 2), sex, or initial anthropometric status (data not shown). However, baseline serum retinol again modified the growth effect of vitamin A. In the analyses restricted to the first child-treatment cycles, vitamin A–supplemented children with serum retinol concentrations <0.35 μmol/L had a 4-mo weight increment 67 g (95% CI: −0.9, 143) less than that in vitamin A–supplemented children with serum retinol concentrations >0.70 μmol/L, and vitamin A–supplemented children with serum retinol concentrations of 0.35–0.70 μmol/L had a 4-mo weight increment 17 g (95% CI: −7.3, 107) less than that in vitamin A–supplemented children with serum retinol concentrations >0.70 μmol/L. As seen for linear growth, vitamin A–supplemented children with initially very low serum retinol concentrations (<0.35 μmol/L) had a 4-mo weight increment that was 152 g (95% CI: 97, 207) greater than that in the placebo group (**Figure 3**).

DISCUSSION

Child growth is the product of multiple factors, including both nutritional and environmental factors. Thus, a substantial growth effect should not be expected from a single nutrient intervention such as vitamin A supplementation, except possibly in populations in whom vitamin A deficiency is the strongest growth-limiting factor. Our findings showed that vitamin A supplementation modestly improved overall linear growth, but the effect was predominately in vitamin A–deficient children. Older children and non-breast-fed children also benefited more in linear growth from vitamin A supplementation than did younger children and breast-fed children. There was no overall effect of vitamin A supplementation on ponderal growth, except additional weight gain in severely vitamin A–deficient children (serum retinol concentrations <0.35 μmol/L).

The apparent positive effect on linear growth but not on ponderal growth is consistent with the results from a trial of monosodium glutamate and vitamin A supplementation conducted in West Java (5). Children in villages that received monosodium glutamate and vitamin A supplementation gained more height but not weight than did children in the control villages. This pattern is also consistent with the sequence of changes originally observed in experimental studies with vitamin A–starved rats (25). The rats initially experienced tissue depletion of vitamin A, after which their growth slowed to an eventual plateau (by which time their vitamin A status was very low); only after they became severely depleted of vitamin A did they lose weight. This pattern is also consistent with the results of community-based studies that observed an association between stunting and mild xerophthalmia (2); the severity of stunting was associated with the severity of xerophthalmia (6). In contrast, wasting was only associated with children who had active corneal diseases (2).

Data from the first child-treatment cycles indicated that vitamin A–supplemented children with serum retinol concentrations <0.35 μmol/L had a 4-mo height increment 0.39 cm greater than and a 4-mo weight increment 152 g greater than those in the placebo group. These increments are slightly more than twice the

reductions in 4-mo height (0.16 cm) and 4-mo weight (67 g) increments attributed to severe vitamin A deficiency in the present study. In other words, the first dose of vitamin A caused severely vitamin A–deficient children to gain height and weight at a rate that was higher than that in nonvitamin A–deficient children. The effect of vitamin A that we observed was also greater than that observed by West et al (26) in Nepalese children, assuming that the Indonesian children with serum retinol concentrations <0.35 μmol/L were biologically equivalent to their peers in Nepal with ocular signs and symptoms of vitamin A deficiency. In the Nepalese study, xerophthalmic vitamin A–supplemented children gained ≈1 cm/16 mo (ie, 0.25 cm/4 mo) more height and ≈420 g/16 mo (ie, 105 g/4 mo) more weight than did their counterparts receiving placebo. The fact that the growth effect was not found among children with moderately low and normal serum retinol concentrations suggests that vitamin A deficiency is not growth limiting unless children become severely vitamin A deficient. This is consistent with results of studies with animal models showing that the growth rate, especially ponderal growth, would not be affected unless the vitamin A stores were exhausted (10).

Age-specific differences in growth response to vitamin A have been consistently detected in previous studies: children aged ≥24 mo had a greater response to vitamin A in linear (5) and ponderal (7) growth than did children aged <24 mo. We found that vitamin A–supplemented children aged ≥24 mo gained 0.12 cm/4 mo (≈0.4 cm/y) more than did children aged <24 mo. This effect was not dependent on sex. The mechanism behind the age-specific effect of vitamin A supplementation on growth has not been elucidated. Extended breast-feeding as a protective factor against mild xerophthalmia (27, 28) was assumed to be the major factor associated with a lower growth response to vitamin A among younger children. However, no previous trial has considered breast-feeding as an effect modifier. We found that children aged ≥24 mo who received vitamin A gained significantly more height than their peers receiving placebo, regardless of breast-feeding status. In contrast, in children aged <24 mo, a similar size effect of vitamin A was found only among children who were no longer breast-fed. Among children aged <24 mo who were still breast-fed, the effect of vitamin A supplementation on linear growth was not significant. Others have shown that breast-feeding protects children from vitamin A deficiency (28), although the protection is not absolute (29). Our findings suggest that breast-feeding also protects children from any growth deficit attributable to subclinical vitamin A deficiency.

Unlike serum retinol concentrations, vitamin A intakes from dietary sources seem to not be a predictor of growth benefit from vitamin A supplementation. There was no significant difference in the effect of vitamin A on height and weight increments at different vitamin A intakes. The most likely explanation for this finding is that measurement of a child's typical dietary vitamin A intake is imprecise, which obscures a true relation. In addition, vitamin A losses due to infectious disease might weaken the relation between vitamin A intake and status.

In summary, our findings may be useful in guiding the expectations regarding the effect of vitamin A intervention programs on children's growth. First, in areas where both subclinical vitamin A deficiency and stunting are prevalent, the overall effect of vitamin A supplementation on linear growth is modest, at best. However, in special subgroups, such as children with very low serum retinol concentrations (<0.35 μmol/L), the growth benefit from vitamin A supplementation amounted to ≈11% of the linear growth (0.39 cm/4 mo) observed in the placebo-treated children. This is a sizable benefit because the typical height increment for 1–4-y-old children in normative populations (30) ranges from 2.3 to 3.8 cm/4 mo (7 to 11.5 cm/y). Second, a ponderal increment attributable to vitamin A supplementation may only occur in children with very low serum retinol concentrations. Third, in areas where breast-feeding, subclinical vitamin A deficiency, and stunting are prevalent, breast-feeding protects young children (6–24 mo of age) from the linear growth deficit attributable to vitamin A deficiency.

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