

# Severe linear growth retardation in rural Zambian children: the influence of biological variables<sup>1-3</sup>

Jeannine LA Hautvast, Jules JM Tolboom, Emmanuel M Kafwembe, Rosemary M Musonda, Victor Mwanakasale, Wija A van Staveren, Martin A van 't Hof, Robert W Sauerwein, Johannes L Willems, and Leo AH Monnens

## ABSTRACT

**Background:** The prevalence of stunting in preschool children in Zambia is high; stunting has detrimental effects on concurrent psychomotor development and later working capacity.

**Objective:** Our objective was to investigate biological variables that may contribute to linear growth retardation in preschool children in Samfya District, Zambia.

**Design:** Children aged 6–9 mo ( $n = 108$ ) and 14–20 mo ( $n = 102$ ) attending mother-and-child health clinics were included. With a mixed-longitudinal design, they were followed up 9 and 21 mo later. Height and weight of children and their mothers were measured. Biochemical measures (eg, serum zinc, retinol, thyrotropin, iron, and acute phase protein concentrations), malaria parasitemia, and intestinal parasitosis were assessed.

**Results:** Height-for-age  $z$  scores (HAZ) were low, indicating a high prevalence of stunting (36–79%). Ninety percent of the children were anemic, 53–71% had elevated acute phase proteins, and 80% had malaria parasitemia. Regression analyses showed that maternal height predicted the children's height at 6–9 mo (regression coefficient = 0.05; 95% CI: 0.02, 0.08). The children's height at an early age (6–9 and 14–20 mo) showed a strong relation with their height at later ages (22–30 and 34–41 mo). Serum micronutrient status did not show a significant relation with later HAZ.

**Conclusion:** Unlike other studies, we did not identify specific biological factors, such as health and micronutrient status, which contribute to the retardation of linear growth. The normal zinc and iodine statuses of the children suggest that at least these factors are not causal. *Am J Clin Nutr* 2000;71:550–9.

**KEY WORDS** Preschool children, Zambia, height, growth, micronutrients, biochemistry, malaria, maternal nutrition, height-for-age

## INTRODUCTION

In developing countries, linear growth retardation (stunting) is highly prevalent in young children. In sub-Saharan Africa, 42% of the children <5 y of age are stunted (1), indicating that their height-for-age falls below  $-2$  SDs from the median of the National Center for Health Statistics (NCHS) reference population (2). Stunting in childhood is related to concurrent and possibly later delayed mental and motor development (3). The

negative effects in adulthood are limited working capacity because of reduced body mass (4) and increased obstetrical risks in women because of short stature (5). Waterlow (6) and other investigators (7, 8) showed that the process of linear growth retardation starts before or during the second 3 mo of life, a period when breast milk intake declines, supplementary foods are given, and susceptibility to infections starts. Once the height-for-age of these children starts to fall and environmental conditions remain unfavorable, most of them will remain in their acquired growth channel, with limited possibilities for catch-up growth (9).

In Samfya District, northern Zambia, the process of linear growth retardation starts at  $\approx 3$  mo of age and continues into the second year of life (10). At the age of 0–3 mo, 11% of the children are stunted; this incidence increases to 55% and 65% at 6–12 mo and 12–18 mo, respectively. This early stunting places them at high risk of remaining retarded in their linear growth and subject to the negative effects of stunting.

To achieve better understanding of this serious public health problem, we first undertook a study to describe the linear growth pattern of these children during their first 3 y of life. Second, we investigated biological variables contributing to the retardation of linear growth in these children. The following variables were studied: 1) health status [hemoglobin, albumin, C-reactive protein (CRP),  $\alpha_1$ -acid glycoprotein (AGP), and malaria parasitemia], 2) micronutrient status (zinc, retinol, thyrotropin, ferritin, and iron), and 3) maternal nutritional status.

<sup>1</sup>From the Departments of Pediatrics and Medical Microbiology and the Central Clinical Chemical Laboratory of the University Hospital Nijmegen St Radboud, Nijmegen, Netherlands; the Department of Medical Statistics, Faculty of Medicine, Catholic University Nijmegen, Nijmegen, Netherlands; the Division of Human Nutrition and Epidemiology, Wageningen Agricultural University, Wageningen, Netherlands; and the Tropical Diseases Research Centre, Ndola, Zambia.

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<sup>3</sup>Address reprint requests to JJM Tolboom, Department of Pediatrics, University Hospital Nijmegen St Radboud, PO Box 9101, 6500 HB Nijmegen, Netherlands. E-mail: J.Tolboom@ckskg.azn.nl.

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**SUBJECTS AND METHODS**

**Study area**

The study was conducted in Samfya District, a rural area in northeast Zambia (Luapula Province), which covers 10329 km<sup>2</sup> and has 107486 inhabitants (11). A large part of the district is adjacent to Lake Bangweulu. This lake borders a swamp area in the southeast, whereas the main part of the district, with woodland vegetation and marshy flood plains, is located on the western side. The main sources of food and income for the majority of the people are subsistence farming and fishing (12). Maize, cassava, sweet potatoes, pumpkins, groundnuts, beans, and leafy vegetables are common agricultural products (13). The quality of the health-care facilities is poor and the infant mortality rate is high (148/1000 births) in Luapula Province (14).

Within the framework of the Ministry of Health, community health workers provide basic health care services at the village level. This study was implemented with their assistance. Because laboratory facilities, which were needed for our main study, were located in the district headquarters, only villages situated within a 2-h drive from this location were eligible for study. Twelve villages were selected at random for recruitment of children from 37 villages that had a community health worker in the designated study area.

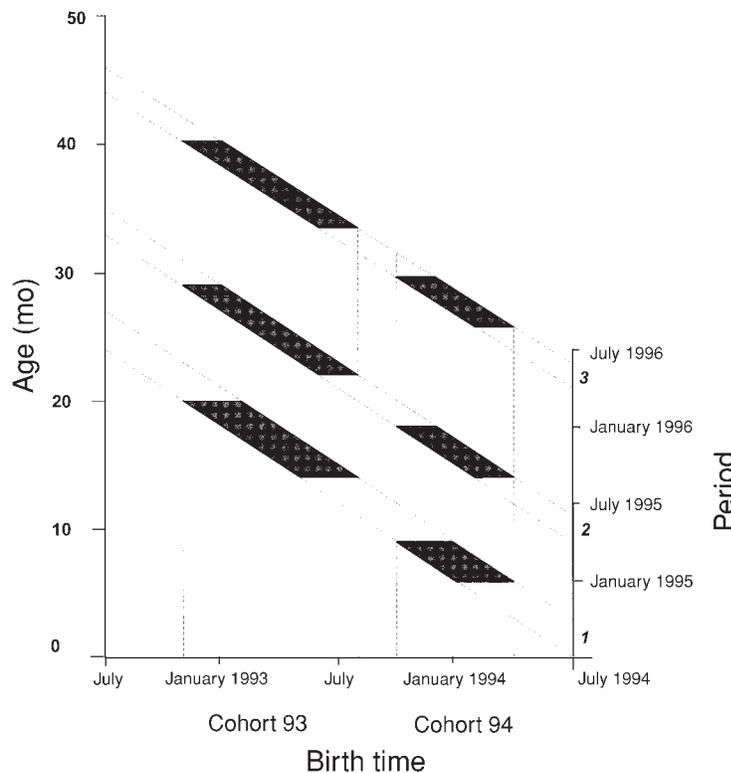
**Design and study population**

A mixed-longitudinal design, that is, a longitudinal study with several birth cohorts, several measurement times, and by conse-

quence several ages (15), was selected for this study. The advantage of the mixed-longitudinal design with overlap in cohorts is that it is possible to distinguish age, cohort, and period effects. Children were examined in period 1 (baseline) and 9 and 21 mo later (periods 2 and 3, respectively). In period 1, children 6–9 mo of age on the day of recruitment (date of birth between 1 October 1993 and 1 April 1994, depending on the date of recruitment) were included in the study; in this report they will be referred to as cohort 94 (**Figure 1**). Children 14–20 mo of age on the day of recruitment (date of birth between 1 November 1992 and 1 August 1993, depending on the date of recruitment) were also included, and will be referred to as cohort 93. As is shown in Figure 1, the age range of cohort 94 in period 2 was the same that of cohort 93 in period 1; this age group will be referred to as age “14–20 mo.” The age range of cohort 94 in period 3 was in the same as that of cohort 93 in period 2; this age group will be referred to as age “22–30 mo.”

**Subjects**

All children 6–9 and 14–20 mo of age who attended the mobile mother-and-child health (MCH) clinics in the selected villages were eligible for participation in the study during the study period. The date of birth of the children was either derived from their clinic card (after verbal verification) or, when the date of birth was unknown, age was estimated by discussion with mothers of age mates with a known date of birth. After the objectives of the study were explained to the mothers by a member of the study team, they were asked to give their written, informed consent for the par-



**FIGURE 1.** Age-period cohort diagram representing the design of the study. The horizontal axis presents the birth time of the cohorts. The left vertical axis indicates the age of the subjects in months; the right vertical axis presents the timing of the 3 periods. The dark parallelograms represent the combination of ages and periods in which the cohorts were examined.

participation of their child in the study. For practical and ethical reasons, children who were not accompanied by their mother or caretaker were excluded. HIV infection is known to be highly prevalent in Zambia (16), and may therefore have acted as a confounder in the design of the study. Because an important symptom of established HIV infection (AIDS) is severe weight loss, we excluded children who were wasted (weight-for-height  $\leq -2$  SD of the median of the NCHS reference population; 2). Initially, 235 children were recorded as eligible; however, 12 were wasted, 13 were excluded for other reasons (5 because the mother or caretaker was absent, 7 because participation was refused, and 1 for another reason). Finally, a total of 108 children were included in cohort 94 and 102 children in cohort 93. In periods 2 and 3, an effort was made to trace all children; 170 (81%) and 137 (65%) children could be located and examined, respectively. Between periods 1 and 3, 7% had died (10 children from cohort 94 and 5 from cohort 93) and 28% were absent because they moved out of the study area or did not show up at the last visit.

Because children enrolled in this study were recruited through MCH clinics, sampling depended on attendance of mothers or caretakers. On the basis of data from the Zambian Ministry of Health (Samfya District Health Management Team, personal communication, 1993), we calculated that we recruited between 75% and 85% of the children in the specific age groups in each catchment area, and thus assume that we included a group of children representative of the mainland area of the district. Because the study area is comparable with other rural areas in Zambia with respect to its ecology, land use, and other population characteristics, the results from this study may also be extrapolated to other rural areas of Zambia.

It is unlikely that selection bias influenced our observations in the follow-up period. The reason is that the baseline (period 1) anthropometric  $z$  scores of children who were traced and examined in period 3 did not differ from the baseline anthropometric  $z$  scores of children who were lost to follow-up or from those who had died.

### Ethics

Ethical approval for this study was obtained from the Ministry of Health and the National Food and Nutrition Commission, Lusaka, Zambia. Permission to anonymously assess HIV status of the children was obtained from the Ethical Committee of the Tropical Diseases Research Centre (TDRC) in Ndola, Zambia.

### Procedures

The study team consisted of the principal investigator (JLAH), 2 qualified staff members from the Ministry of Health, and a research assistant—each of whom was trained for his or her respective tasks during the study visits. All communication with the mothers of the children was made by the local staff of the study team, who were fluent in the local language, Cibemba. Anthropometric measurements were taken in each period (1, 2, and 3). A capillary blood sample was examined for hemoglobin concentration and malaria parasites in each period. A venous blood sample was obtained in period 1 and examined for several biochemical variables. Stool samples were examined for intestinal parasites. In period 2, information on socioeconomic factors was obtained from the mother or caretaker of each child.

### Anthropometry

Anthropometric measurements were performed according to standard procedures (17). Weight of the children, wearing light

clothes only, was measured to the nearest 0.1 kg by using a portable hanging weighing scale (model 235 6S, 0–25 kg; Salter England, West Bromwich, United Kingdom), which was calibrated daily. Recumbent length of the children was measured to the nearest 0.1 cm by using a horizontal measuring board with a sliding foot piece. Length of barefoot children was measured after removal of any headgear and was done by 2 members of the study team cooperatively. Weight of the mothers was measured by using bathroom scales with 0.5-kg accuracy. Standing height was measured to the nearest 0.1 cm by using a length-measuring rod with a sliding head bar fixed against a wall. Members of the study team were trained intensively to minimize interobserver variation in measurements. For all children,  $z$  scores were calculated for height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) by using the NCHS reference (2).

### Biochemical and microbiological variables

Blood sampling was done in a room free from direct light to minimize degradation of retinol. Venous blood samples were collected in aluminum foil-covered tubes and stored in a cool box with ice packs. Thick blood smears were prepared at the study site. The blood samples were centrifuged within 7 h of collection at the Samfya Hospital laboratory and stored at  $-20^{\circ}\text{C}$  until transported to Ndola (for determination of retinol, HIV serology, and malaria parasitemia) or to the Netherlands (for all other analyses). Frozen serum samples were transported to the Netherlands in a cool box with ice packs.

Hemoglobin was assessed at the Samfya Hospital laboratory by using a hemoglobin colorimeter (Ciba-Corning Diagnostics, Alameda, CA). Serum retinol was assessed with HPLC (18) at the Biochemistry Unit of the TDRC in Ndola. The values obtained were 91–106% of the target values of the retinol concentration of the standard serum, as supplied by the Division of Human Nutrition and Epidemiology (Wageningen Agricultural University, Wageningen, Netherlands). The between-day ( $n = 16$ ) CV was 4.3%. HIV serology of the samples was analyzed by the Immunology Unit of TDRC using HIV1/HIV2 Recombigen ELISA (Cambridge Biotechnology, Galway, Ireland) and Recombinant HIV-1 ELISA (International Murex Technologies, Norcross, GA). All positive and discordant samples were confirmed by Western blot analysis (Cambridge Biotechnology). Twenty percent of the samples were retested with an enzyme-linked immunosorbent assay (Abbott Laboratories, Chicago) and immunoblot (Genelabs Diagnostics, Leuven, Belgium) at the Department of Medical Microbiology, University Hospital Nijmegen, Nijmegen, Netherlands (UHN). These results showed that the proportion of false positives was 0% and of false negatives was 2% (1 of 46).

Thyrotropin concentration in serum was determined by a time-resolved fluorescence immunometric assay (Wallac, Turku, Finland) at the Laboratory of Chemical Endocrinology of the UHN. The following biochemical analyses (in serum) were performed at the Central Clinical Chemical Laboratory. Albumin, iron, total-iron-binding capacity (TIBC), and CRP were measured by using a Hitachi 747 apparatus (Boehringer Mannheim, Mannheim, Germany). Albumin measurement was based on a dye binding method using bromocresol green (Boehringer Mannheim). Iron was measured with an assay based on a reaction with guanidine hydrochloride-ferrozine. TIBC was determined with the same method after addition of an excess of iron (19). Transferrin saturation was calculated by dividing serum iron by serum TIBC.

CRP concentration was determined by an immunoturbidimetric assay (Tina-quant; Boehringer Mannheim). The zinc concentration in serum was measured by atomic absorption flame photometry using a Perkin-Elmer model 4100 apparatus (Norwalk, CT). Ferritin was measured in serum by using a microparticle enzyme immunoassay (IMx; Abbott Laboratories). Serum AGP concentration was determined by nephelometry using a Behring BNII apparatus (Behringwerke AG, Marburg, Germany) with DAKO antiserum (Glostrup, Denmark) standardized with CRM 470 reference material (IFCC, Brussels). The CV of the AGP assay was 3.6%.

Thick blood smears were examined for malaria parasites at the Parasitology Unit of TDRC. After staining the smears with Giemsa solution, the species and stage of parasites were determined and the number of malaria parasites was counted per 200 leukocytes. Malaria parasitemia was calculated on the basis of 8000 leukocytes per  $\mu\text{L}$  (20). Duplicates of 20% of the thick smears were reexamined at the Department of Medical Microbiology, UHN. The results showed that the proportion of false positives, false negatives, and difference in species determination were all <5%. Stool samples from children were collected on 3 consecutive days, preserved with sodium acetate-acetic acid-formalin and analyzed at the Parasitology Unit of TDRC. Fecal samples were routinely examined for protozoa and worm eggs. Duplicates of 20% of the feces samples were reexamined at the Department of Medical Microbiology, UHN. The results showed that the proportion of false positives was 0% and of false negatives was 2% (1 of 41).

The following cutoffs were selected to indicate abnormal (low or elevated, depending on the variable) concentrations of each variable: hemoglobin, <110 g/L (21); albumin, <30 g/L (<1 y of age), <33 g/L (1–2 y of age); zinc, <10.3  $\mu\text{mol/L}$  (22); retinol, <0.35  $\mu\text{mol/L}$  (deficient), 0.35–0.70  $\mu\text{mol/L}$  (low; 23); iron, <6  $\mu\text{mol/L}$ ; ferritin, <10  $\mu\text{g/L}$ ; TIBC, >72  $\mu\text{mol/L}$ ; transferrin saturation, <0.12 (24); thyrotropin, >8.2 mU/L (25); CRP,  $\geq 10$  mg/L (26); and AGP, >1.2 g/L (27).

### Socioeconomic information

Because the socioeconomic status of the household may affect the process of linear growth retardation, information on this topic was collected. By use of a structured questionnaire, mothers or caretakers of the children were interviewed on several aspects of their socioeconomic status (28, 29). Through factor analysis, the following list of variables was selected for use in one socioeconomic scale: education (mother and head of household), income (head of household), possessions (radio, bicycle, livestock, water source, agricultural land), and labor capacity (of the household). The reliability of this questionnaire (Cronbach's  $\alpha$ ; 30) was 0.63, which is an acceptable reliability.

### Analysis of period and cohort effects

Period and cohort effects were analyzed in this study because they may be confounders in the estimation of the age effect (15) of anthropometric measurements. We assumed that no differences in environmental living conditions had occurred in the period between the births of the 2 cohorts and that no migration affecting the composition of the population had occurred in that period. Therefore, we assumed that cohort effects did not affect the anthropometric measurements and socioeconomic status in this study. The presence of period effects was analyzed by comparing the mean anthropometric  $z$  scores between the cohorts,

restricted to those children in the same age range (ie, aged 14.7–17.9 mo and 26.0–29.1 mo, *see* Figure 1). Because hemoglobin concentration and malaria parasitemia were used as predictors of future height-for-age in this study, it was not considered relevant to analyze age and period effects of these variables.

### Data analysis

The software package EPI INFO, version 5.01b (31), was used to calculate HAZ, WAZ, and WHZ. SPSS for WINDOWS (version 6.1.4; SPSS Inc, Chicago) was used for further statistical analyses (32). Before analysis, data were checked for normality by examining kurtosis and skewness. Skewed data were log-transformed for further analysis. Comparisons of mean anthropometric  $z$  scores between groups were tested by using Student's  $t$  tests in the situation of 2 groups and by using one-way analysis of variance in the situation of 3 groups. Changes in mean HAZ scores of subsequent visits were tested by using the paired  $t$  test. Results of biochemical tests are presented as means  $\pm$  SDs and as the proportion in the abnormal range. In subsequent analyses, biochemical variables were treated as continuous variables. Pearson's correlation coefficients were calculated to examine relations between continuous variables. The correlation coefficients with a statistically significant ( $P < 0.05$ ) correlation coefficient >0.40 and those that are important for the interpretation of further results are described. Partial correlation coefficients (controlled for age) were calculated of selected biochemical, microbiological, and socioeconomic variables with HAZ obtained during a subsequent visit. Regression analyses were performed with HAZ scores as dependent variables and anthropometric, biochemical, and socioeconomic variables as independent variables. Statistical significance of independent variables was assessed after applying Bonferroni correction for each regression.

## RESULTS

In both cohorts there was a clear decrease in HAZ scores with age (**Table 1**). At baseline, 36% of the children of cohort 94 were stunted (height-for-age  $\leq -2$  SD from the median of the NCHS reference population; 2), increasing to 61% and 75% in periods 2 and 3, respectively. Cohort 93 was 69%, 61%, and 79% stunted in periods 1, 2, and 3, respectively. Baseline anthropometric  $z$  scores (period 1) of those children from cohort 94 and cohort 93 who were traced in period 3 were compared with those who were absent in period 3 and with those who had died before period 3 by using analysis of variance. No significant differences were found between these groups.

### Period effects

Mean anthropometric  $z$  scores were compared between period 1 for cohort 93 ( $n = 58$ ) and period 2 for cohort 94 ( $n = 85$ ) for children aged 14.7–17.9 mo; no significant difference was observed. Comparison of the mean anthropometric  $z$  scores between period 2 for cohort 93 ( $n = 30$ ) and period 3 for cohort 94 ( $n = 60$ ) for children aged 26.0–29.1 mo also did not show a significant period effect. The socioeconomic status scores measured in period 2 did not differ between the 2 cohorts.

### Linear growth pattern

**Figures 2A** and **B** are scatterplots of the HAZ scores of cohort 94 and cohort 93 by age. A clear decrease in HAZ between the first and second cluster of points, which reflect the measurements

**TABLE 1**  
Demographic and anthropometric characteristics of 2 selected cohorts in Samfya District, Zambia<sup>1</sup>

	Cohort 94	Cohort 93
Period 1		
Number	108 (51 M, 57 F)	102 (41 M, 61 F)
Age (mo)	7.3 ± 0.8 <sup>2</sup>	16.4 ± 1.7
Height (cm)	64.4 ± 2.9	72.9 ± 3.5
Weight (kg)	6.9 ± 0.9	8.5 ± 1.2
HAZ	-1.71 ± 1.0	-2.33 ± 1.1
WAZ	-1.28 ± 0.9	-1.98 ± 1.0
WHZ	0.10 ± 0.8	-0.79 ± 0.8
Maternal height (cm)	156.1 ± 6.1	156.3 ± 5.3
Maternal weight (kg)	50.7 ± 7.2	48.4 ± 5.9
Period 2		
Number	85	85
Age (mo)	16.3 ± 0.8	25.3 ± 1.7
HAZ	-2.37 ± 1.1	-2.44 ± 1.1
WAZ	-1.75 ± 1.0	-1.88 ± 1.1
WHZ	-0.43 ± 0.9	-0.52 ± 0.8
Period 3		
Number	67	70
Age (mo)	28.0 ± 0.9	37.0 ± 1.7
HAZ	-2.71 ± 1.2	-2.94 ± 1.3
WAZ	-2.06 ± 1.1	-1.86 ± 1.1
WHZ	-0.52 ± 0.8	-0.19 ± 0.8

<sup>1</sup>Period 2: 9 mo after period 1; period 3: 21 mo after period 1. HAZ, height-for-age  $z$  score; WAZ, weight-for-age  $z$  score; WHZ, weight-for-height  $z$  score.

<sup>2</sup> $\bar{x} \pm SD$ .

in period 1 and period 2, is shown in Figure 2A. With use of the paired  $t$  test, differences between the mean HAZ scores at 2 subsequent visits were tested for those children who were present at both visits. The results showed that the mean HAZ scores in period 1 were significantly higher ( $\alpha < 0.05$ ) than those in period 2 (mean difference: 0.73; SE: 0.08), as were the mean HAZ scores in period 2 compared with those in period 3 (mean difference: 0.34; SE: 0.07). In Figure 2B, a slight decrease in HAZ scores can be seen between the second and third cluster of points, representing the measurements in periods 2 and 3. Analysis by paired  $t$  test showed that the difference between mean HAZ scores in period 1 and period 2 was not significant (mean difference: 0.11; SE: 0.06), whereas the mean HAZ scores in period 2 were significantly higher than those in period 3 (mean difference: 0.36; SE: 0.09).

### Biochemical and microbiological characteristics

In Table 2, biochemical and microbiological characteristics of cohort 94 and cohort 93 in period 1 are presented. Almost all the children of cohort 94 appeared to be anemic (hemoglobin  $< 110$  g/L); 49% of the anemic children had hemoglobin concentrations  $< 90$  g/L. A high proportion of the children of cohort 94 had low serum retinol or low transferrin saturation. One child had a retinol concentration  $< 0.35$   $\mu\text{mol/L}$ , which is considered to indicate severe retinol deficiency. Both acute phase proteins, CRP and AGP, were elevated in a high proportion of the children of cohort 94, suggesting inflammation. Ten percent of the children of cohort 94 had AGP concentrations  $> 2.0$  g/L. In 6% of the children of cohort 94 CRP was  $> 50$  mg/L. CRP and AGP concentrations were significantly correlated ( $r = 0.47$ ,  $P < 0.001$ ).

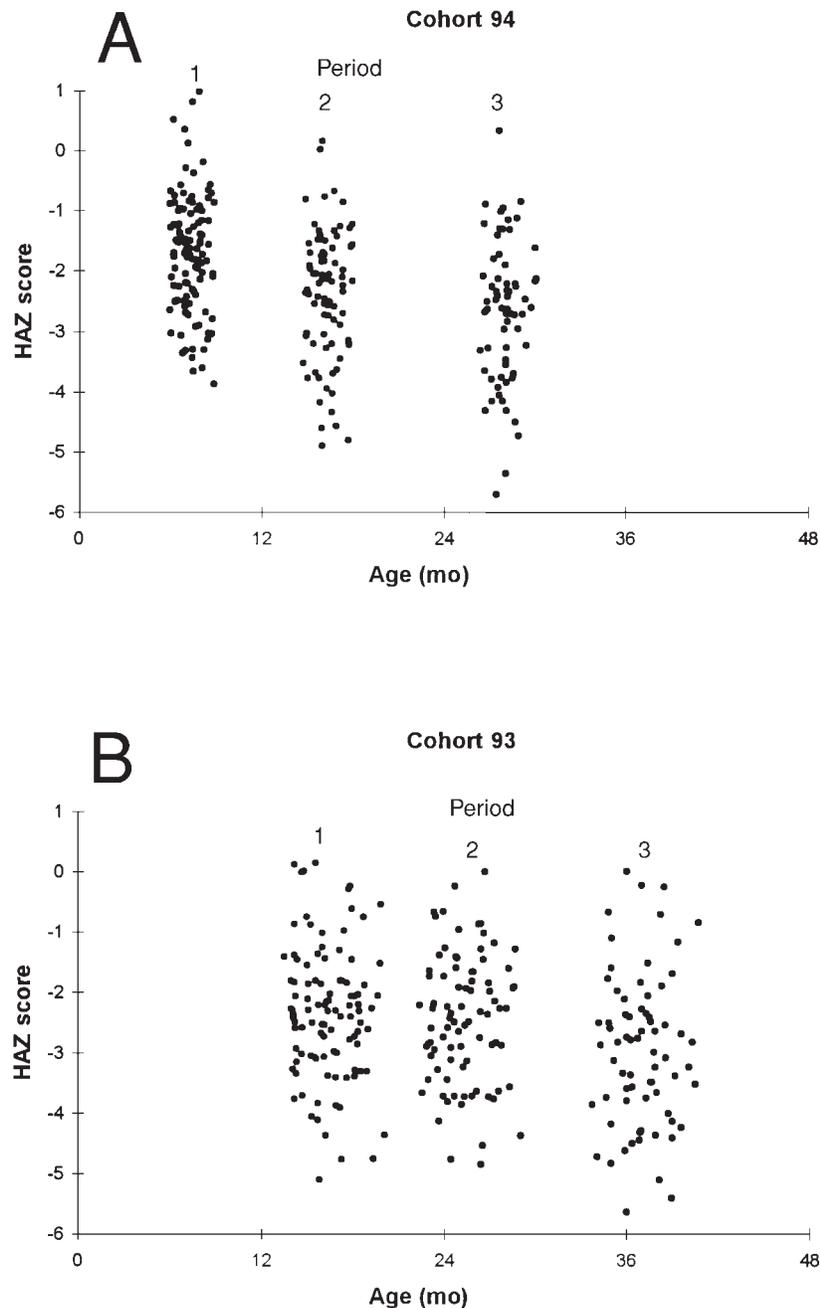
Most of the children of cohort 94 had a positive result for malaria parasites. In the children of cohort 93, the biochemical and microbiological characteristics in period 1 were similar to those observed in cohort 94. In the whole group of children with a positive malaria result, 94% had *Plasmodium falciparum* infection, of which 19% had a mixed *Plasmodium* infection. Of those with a positive malaria result, 64% had low parasite density ( $< 5.0 \times 10^9$  parasites/L) and 36% had a parasite density  $\geq 5.0 \times 10^9$  parasites/L. In the whole group of children with malaria parasitemia, 29% had an elevated serum CRP concentration combined with a malaria parasite density  $\geq 5.0 \times 10^9$  parasites/L. In periods 2 and 3, hemoglobin concentration and malaria parasitemia were assessed (data not shown). The proportion of anemic children in period 2 was 96% for cohort 94 and 95% for cohort 93 and in period 3 was 83% and 78%, respectively. The proportion of children in cohort 94 and cohort 93 with malaria parasitemia in periods 2 and 3 ranged from 89% to 94%. Fecal analysis for the presence of protozoa and intestinal worms showed that 2 subjects in the age range of 14–20 mo had *Ascaris lumbricoides* infection. Examination of HIV serology in all subjects showed that one infant was HIV seropositive.

The calculated Pearson correlation coefficients showed that for both cohorts combined, serum AGP concentrations were negatively associated with serum albumin ( $r = -0.59$ ) and positively associated with serum CRP ( $r = 0.57$ ) and serum ferritin ( $r = 0.43$ ) concentrations. Serum ferritin concentration was associated with serum CRP ( $r = 0.41$ ) and serum iron ( $r = 0.43$ ) concentration. Malaria parasite count (in period 1) showed a significant correlation with hemoglobin ( $r = -0.29$ ), AGP ( $r = 0.23$ ), CRP ( $r = 0.25$ ), ferritin ( $r = 0.17$ ), and iron ( $r = 0.24$ ) concentration. Hemoglobin concentration (in period 1) was significantly correlated with serum AGP ( $r = -0.29$ ), CRP ( $r = -0.28$ ), and retinol ( $r = 0.26$ ) concentration.

In cohort 94, HAZ scores in period 1 were significantly ( $P < 0.05$ ) associated with hemoglobin concentration ( $r = 0.20$ ) and with malaria ( $r = -0.24$ ). HAZ scores of cohort 93 showed significant associations with serum albumin ( $r = 0.23$ ) and CRP ( $r = -0.22$ ) concentrations in period 1. In the total group of children, maternal height was significantly correlated with socioeconomic status scores ( $r = 0.17$ ).

### Predictors of linear growth retardation

To determine the role of measured variables as predictors of height-for-age, partial correlation coefficients were calculated of HAZ with selected variables, corrected for age (Table 3). Maternal height showed a significant positive relation with HAZ at 6–9 mo of age up to 22–30 mo of age. HAZ at 6–9 mo (cohort 94) showed a strong significant positive relation with HAZ in the following 9–21 mo (age 14–20 mo and 22–30 mo). HAZ at 14–20 mo (cohort 93) also showed a strong significant positive relation with HAZ in the following 9–21 mo (age 22–30 mo and 34–41 mo). In cohort 94, serum ferritin concentration at age 6–9 mo showed a significant positive relation with HAZ 9 mo later. However, when calculation of this correlation coefficient was restricted to those children with normal CRP concentrations, it was no longer significant. Malaria parasite count at age 6–9 mo and 14–20 mo showed a significant negative correlation with HAZ at 14–20 mo and 22–30 mo, respectively. In both cohorts, hemoglobin concentration at 14–20 mo was significantly positively associated with HAZ during the following period (age 22–30 mo). Concentrations of albumin, zinc, retinol, thyrotropin,



**FIGURE 2.** Scatterplot of height-for-age z scores of children in cohort 94 (A) and cohort 93 (B) by age in periods 1, 2, and 3, in Samfya District, Zambia.

iron and AGP, as measured in period 1, did not show a significant relation with HAZ during subsequent periods.

Socioeconomic status was not related to HAZ, and neither did it affect the observed relations when it was used as a controller in the calculation of the partial correlation coefficients. Regression analyses with HAZ scores at 6–9, 14–20, 22–30, and 34–41 mo as independent variables (**Table 4**) showed that maternal height predicted HAZ scores at age 6–9 mo in cohort 94 and HAZ scores at age 14–20 mo in cohort 93. HAZ scores at age 14–20, 22–30, and 34–41 mo were predicted by HAZ scores measured at an earlier age.

## DISCUSSION

In our longitudinal study of children aged 6–9 to 34–41 mo in Samfya District, rural Zambia, health and micronutrient status could not be identified as contributing factors to the retardation of linear growth. Only maternal height and the children's heights at early ages predicted height of the children at later ages.

### Validity of results

Because we assumed that there were no cohort effects in our study and because our analyses showed that period effects were not

**TABLE 2**

Biochemical and microbiological characteristics of 2 selected cohorts of children aged 6–9 mo (cohort 94) and 14–20 mo (cohort 93) in period 1 in Samfya District, Zambia<sup>1</sup>

	Cutoff for abnormal results	Cohort 94		Cohort 93	
		<i>n</i>	Value	<i>n</i>	Value
Albumin (g/L)	<30, 33 <sup>2</sup>	108	42.4 ± 3.4 [0] <sup>3</sup>	101	42.1 ± 4.4 [1]
Hemoglobin (g/L)	<110	107	89 ± 12 [95]	101	93 ± 14 [86]
Zinc (μmol/L)	<10.3	108	15.5 ± 2.9 [1]	99	14.8 ± 3.1 [1]
Retinol (μmol/L)	<0.70	107	0.66 ± 0.2 [61]	99	0.70 ± 0.2 [56]
Thyrotropin (mU/L)	>8.2	106	2.1 ± 1.3 [0]	99	2.1 ± 1.3 [0]
Ferritin (μg/L) <sup>4</sup>	<10	51	49.6 ± 55.2 [12]	40	50.9 ± 50.7 [8]
Iron (μmol/L) <sup>4</sup>	<6	50	9.3 ± 3.9 [16]	40	11.1 ± 4.6 [8]
TIBC (μmol/L) <sup>4</sup>	>72	50	72.8 ± 13.0 [54]	40	73.9 ± 12.8 [50]
TS <sup>4</sup>	<12	50	0.135 ± 0.066 [48]	40	0.156 ± 0.073 [38]
CRP (mg/L)	≥10	108	18.0 ± 23.9 [53]	101	26.3 ± 27.9 [60]
AGP (g/L)	>1.2	103	1.4 ± 0.4 [71]	98	1.5 ± 0.5 [61]
Malaria parasites (parasites × 10 <sup>9</sup> /L) <sup>5</sup>	—	108	7.983 ± 10.806 [78]	102	9.384 ± 11.203 [82]

<sup>1</sup>Number of children per variable differs because of missing values due to insufficient serum. AGP, α<sub>1</sub>-acid glycoprotein; CRP, C-reactive protein; TIBC, total-iron-binding capacity; TS, transferrin saturation.

<sup>2</sup>Cutoff <1 y, 30 g/L; 1–2 y, 33 g/L.

<sup>3</sup> $\bar{x} \pm SD$ ; percentage of values in the abnormal range in brackets.

<sup>4</sup>Only for children with CRP < 10 mg/L.

<sup>5</sup>Percentage with positive malaria parasite result presented.

present, we consider the results of the relation of anthropometric measurements with age in our study to be valid. Micronutrient status of the children studied was assessed with TIBC and serum concentrations of zinc, retinol, iron, ferritin, and thyrotropin. Although plasma zinc concentrations in individuals may differ because of various circumstances (33), it was recently shown that mean concentrations may be a useful indicator of zinc status at the population level in a setting with a high prevalence of common

childhood infections (34). Serum retinol concentration has been shown to be an important index of vitamin A status (23). Inflammation, which was highly prevalent in the population studied, may have resulted in low serum iron, low serum TIBC, and increased serum ferritin (24, 35). Therefore, a valid interpretation of iron status is restricted to those children with no inflammation. Serum thyrotropin concentration can be used as an index of impairment of thyroid function resulting from iodine deficiency (36).

**TABLE 3**

Partial correlation coefficients (corrected for age) of maternal height, height-for-age *z* score (HAZ) in periods 1 and 2, and selected variables with subsequent HAZ (at age 6–9 mo to 34–41 mo) of 2 selected cohorts of children in Samfya District, Zambia

Selected variable	HAZ in period											
	Cohort 94						Cohort 93					
	Period 1 (6–9 mo) ( <i>n</i> = 107)		Period 2 (14–20 mo) ( <i>n</i> = 84)		Period 3 (22–30 mo) ( <i>n</i> = 58)		Period 1 (14–20 mo) ( <i>n</i> = 98)		Period 2 (22–30 mo) ( <i>n</i> = 84)		Period 3 (34–41 mo) ( <i>n</i> = 63)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Maternal height	0.33	0.001	0.31	0.004	0.37	0.002	—	—	0.27	0.01	—	—
Period 1 (6–9 mo) <sup>1</sup>												
HAZ	—	—	0.74	<0.001	0.71	<0.001	—	—	—	—	—	—
Serum ferritin	—	—	0.25	0.02	—	—	—	—	—	—	—	—
Malaria parasite count	—	—	–0.30	0.005	—	—	—	—	—	—	—	—
Period 1 (14–20 mo) <sup>1</sup>												
HAZ	—	—	—	—	—	—	—	—	0.87	<0.001	0.77	<0.001
Hemoglobin	—	—	—	—	—	—	—	—	0.23	0.04	—	—
Period 2 (14–20 mo) <sup>2</sup>												
HAZ	—	—	—	—	0.87	<0.001	—	—	—	—	—	—
Hemoglobin	—	—	—	—	0.28	0.03	—	—	—	—	—	—
Malaria parasite count	—	—	—	—	–0.28	0.03	—	—	—	—	—	—
Period 2 (22–30 mo) <sup>3</sup>												
HAZ	—	—	—	—	—	—	—	—	—	—	0.84	<0.001

<sup>1</sup>Correlation coefficients with HAZ in period 2 were calculated for the following selected variables measured in period 1: HAZ, hemoglobin, albumin, zinc, retinol, thyrotropin, iron, ferritin, malaria parasite count, α<sub>1</sub>-acid glycoprotein, and socioeconomic status. Only variables with a significant relation are presented.

<sup>2</sup>Correlation coefficients with HAZ in period 3 were calculated for the following selected variables measured in period 2: HAZ, hemoglobin, malaria parasite count, and socioeconomic status. Only variables with a significant relation are presented.

**TABLE 4**

Results of multiple regression analysis with height-for-age *z* score (HAZ) at age 6–9, 14–20, 22–30, and 34–41 mo as dependent variables and selected independent variables of 2 selected cohorts of children in Samfya District, Zambia<sup>1</sup>

Independent variables	HAZ in period					
	Cohort 94			Cohort 93		
	Period 1 (6–9 mo) ( <i>n</i> = 107)	Period 2 (14–20 mo) ( <i>n</i> = 79)	Period 3 (22–30 mo) ( <i>n</i> = 57)	Period 1 (14–20 mo) ( <i>n</i> = 98)	Period 2 (22–30 mo) ( <i>n</i> = 75)	Period 3 (34–41 mo) ( <i>n</i> = 58)
Maternal height <sup>2</sup>	0.05 (0.02, 0.08) <sup>3</sup>	—	—	0.04 (0.002, 0.08) <sup>4</sup>	—	—
Period 1 HAZ (6–9 mo) <sup>5</sup>	—	0.78 (0.57, 0.99) <sup>3</sup>	0.71 (0.38, 1.05) <sup>3</sup>	—	—	—
Period 1 HAZ (14–20 mo) <sup>5</sup>	—	—	—	—	0.81 (0.68, 0.93) <sup>3</sup>	0.87 (0.65, 1.08) <sup>3</sup>
Period 2 HAZ (14–20 mo) <sup>6</sup>	—	—	0.99 (0.83, 1.14) <sup>3</sup>	—	—	—
Period 2 HAZ (22–30 mo) <sup>6</sup>	—	—	—	—	—	1.01 (0.81, 1.20) <sup>3</sup>

<sup>1</sup>Regression coefficient and 95% CI. Only independent variables with a significant relation are presented; Bonferroni correction was applied for each regression.

<sup>2</sup>Independent variables entered in the regression were age, sex, and maternal height.

<sup>3</sup>*P* < 0.001.

<sup>4</sup>*P* < 0.05.

<sup>5</sup>Independent variables entered in the regression were age, sex, maternal height and socioeconomic status, and as measured in period 1: HAZ, hemoglobin, albumin, zinc, retinol, thyrotropin, iron, malaria parasite count, C-reactive protein, and α<sub>1</sub>-acid glycoprotein.

<sup>6</sup>Independent variables entered in the regression were age, sex, and socioeconomic status, and as measured in period 2: HAZ, hemoglobin and malaria parasite count.

**Etiologies of linear growth retardation**

Studies have shown that linear growth retardation may be caused by single or multiple micronutrient deficiencies, such as zinc, iron, vitamin A, or iodine deficiency (7, 37–40). On the basis of data on the dietary intake of the children studied (41), we expected to find low vitamin A, iron, and zinc statuses. Because of the historical prevalence of iodine deficiency in Zambia, we expected that it may also have been present in the children studied.

Because both serum zinc and thyrotropin concentrations appeared to have been in the normal range for most children, it was unlikely that a relation with linear growth would be observed. In the group of children with normal serum CRP concentrations, serum iron or ferritin concentrations were low in 8–16% of the children, which is a rather low proportion in view of their iron-deficient diet (41). We can only speculate that poor iron status occurred more frequently in the group with elevated serum CRP concentrations. The sample size of children without inflammation was too small to analyze the relation of iron status with linear growth separately. However, in the multiple regression analysis with correction for inflammation, measures of iron status did not show a relation with linear growth. As was expected, serum retinol concentrations were low in a high proportion of the children studied. Because the SD of serum retinol concentrations in our study was 0.2 μmol/L, which is similar to that of normal populations (42), we expect that the heterogeneity of serum retinol was sufficient to detect a possible relation with linear growth; however, no relation was observed.

Because of the well-known nutritional effects of infections (43), we determined the effect of infections on linear growth in the children studied. A high proportion of the children had elevated serum AGP or CRP concentrations, which are both markers of the acute phase response (26, 44). Nevertheless, no relation with linear growth was shown.

If we use the suggestion of McGuire et al (45) that elevated serum CRP concentration in combination with malaria parasitemia >5.0 × 10<sup>9</sup> parasites/L may be considered an index for malarial illness in hyperendemic regions, 29% of the children in

our study with a positive malaria parasite slide (period 1) had malarial illness. The remaining children were either recovering from a recent malarial illness or had another infection combined with asymptomatic malaria parasitemia. Only a small proportion of the children were negative for malaria parasitemia. Within the groups with positive malaria slides, a wide range was observed in the malaria parasite density: the 5th, 50th, and 95th percentiles were 0.418, 4.040, and 35.946 × 10<sup>9</sup> parasites/L, respectively. The results of univariate partial correlations showed that malaria parasite count at 6–9 and 14–20 mo (in cohort 94) predicted HAZ scores at later ages. However, in multiple regression analyses these relations became nonsignificant, which can be explained by the observed relation of malaria parasite count with concurrent HAZ scores. The high prevalence of malaria parasitemia probably explains most of the observed anemia, as has also been described in several other studies (46, 47). In the children studied, univariate analysis showed that hemoglobin concentration predicted HAZ scores at a later age. However, because of the relation between hemoglobin concentration and concurrent HAZ scores, this relation became nonsignificant in multiple regression analyses.

An association between intestinal parasitosis and height in children in developing countries has been described (48, 49). However, in contrast with findings from Zaire (50), the prevalence of intestinal parasitosis was surprisingly low in our study, therefore its possible relation with linear growth could not be determined. Only one infant in our study was HIV-seropositive, from which we may conclude that HIV infection was not a confounder in the study design.

In agreement with the results of several studies (7, 51), we observed a relation between maternal height and height of the child. This relation may be a result of genetic and environmental factors. In a previous study in the same district (10), we showed that at 0–3 mo of age, 11% of the children were stunted. The retarded linear growth in children in the described age range may be due in part to genetic influences. However, the increase in the prevalence of stunting (from 11% at 0–3 mo of age to 55% at 6–12 mo) that was

observed during the first year of life (10) was certainly the result of adverse environmental conditions. Nevertheless, we were not able to detect a relation between socioeconomic status and linear growth. Although the socioeconomic scale, as used in our study, was derived from a variety of items, it may not have been sufficiently specific to describe detailed differences in socioeconomic status.

It is commonly known that inadequate dietary intake may also be a factor involved in the process of linear growth retardation. In the children studied, we observed that median daily energy intake at baseline was below recommended daily intakes (41), which would have contributed to the retarded linear growth.

In general, we consider the heterogeneity of linear growth in these children, based on the SDs of HAZ scores of  $\geq 1$ , sufficiently large to detect any possible relations of specific factors with linear growth. The sample size was sufficiently large to detect significant relations between maternal height and early children's heights with later HAZ scores. That no relation was observed of the low vitamin A status, the suspected low iron status, and the high prevalence of infections with linear growth retardation, can be explained by the fact that almost all children had one or more abnormalities in their health and micronutrient status. Furthermore, looking at the linear growth pattern of these children, it appears that catch-up growth is nearly impossible.

We conclude that in rural Zambia, where stunting is a major public health problem, height of children at 3 y of age is predominantly predicted by maternal height and the children's heights at an early age. We did not, unlike other studies, identify other biological factors, such as health and micronutrient status, which contributed to the retardation of linear growth in this population. The normal zinc and iodine statuses of the children suggest that these factors, at least, are not causal. 

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