

Impact of prenatal multiple micronutrients on survival and growth during infancy: a randomized controlled trial^{1–3}

Dominique Roberfroid, Lieven Huybregts, Hermann Lanou, Laetitia Ouedraogo, Marie-Claire Henry, Nicolas Meda, and Patrick Kolsteren for the MISAME study group

ABSTRACT

Background: Although prenatal multiple micronutrients can improve fetal growth, their benefit on postnatal health remains uncertain.

Objective: We assessed the effect of the UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women (UNIMMAP) compared with the usual iron and folic acid supplement (IFA) on survival, growth, and morbidity during infancy.

Design: In a double-blind, randomized trial, we followed 1294 singleton newborns whose mothers had prenatally received either the UNIMMAP or IFA. We assessed monthly anthropometric measures and health variables up to age 12 mo. Children were assessed again at a mean age of 30 mo. Mixed-effects models accounted for repeated measurements.

Results: The UNIMMAP resulted in a 27% (HR: 0.73; 95% CI: 0.60, 0.87; $P = 0.002$) reduction in the rate of stunting in 15,261 infant-months with a higher length-for-age z score of 0.13 (95% CI: 0.02, 0.24; $P = 0.02$) over the whole observation period. However, by age 30 mo, this difference was not observed. An effect of the UNIMMAP on weight-for-length (P -interaction = 0.004) and head circumference-for-age (P -interaction = 0.03) became apparent by the end of the first year of life. By the age of 30 mo, children from the UNIMMAP group had a higher weight-for-height z score of 0.20 (95% CI: 0.06, 0.34; $P = 0.004$). No difference in mortality or morbidity was identified in groups, except a 14% reduction in reported episodes of fever (95% CI: 1%, 28%; $P = 0.04$).

Conclusions: Improved linear fetal growth with continuation into early life and enhanced postnatal growth were 2 mechanisms that mediated the effect of the prenatal UNIMMAP on infant nutritional status. Additional follow-up to assess long-term effects is warranted. This trial was registered at clinicaltrials.gov as NCT00642408. *Am J Clin Nutr* 2012;95:916–24.

INTRODUCTION

The deleterious effects of an LBW⁴ (weight <2500 g) on child morbidity and survival in developing countries have been well described (1). Therefore, it is expected that improved fetal growth will prevent such negative effects and result in improved growth during infancy. Because multiple micronutrient deficiencies might contribute to LBW (2), UNICEF, WHO, and United Nations University formulated the UNIMMAP, which contains one Recommended Dietary Allowance of 15 micronutrients (Table 1) (3, 4). In a remarkable coordination of in-

ternational research, the evidence base on the UNIMMAP grew rapidly (5). Over the past decade, randomized controlled trials that compared the UNIMMAP with the usual IFA supplement have been carried out in Bangladesh (6), China (7), Indonesia (8, 9), Nepal (10), Pakistan (11), Burkina Faso (12), Guinea-Bissau (13), and Niger (14). Most of these trials have reported a positive effect of the UNIMMAP on birth weight (pooled estimate: +22.4 g; 95% CI: 8.3, 36.4 g; $P = 0.002$) and a reduction in the prevalence of LBW (pooled OR: 0.89; 95% CI: 0.81, 0.97; $P = 0.01$) (15).

In contrast, there is extremely little information about whether such prenatal effects translate into long-term growth and health benefits. A follow-up of the Nepalese study reported that, at a mean age of 2.5 y, children of women who had taken the UNIMMAP were heavier by 204 g (95% CI: 27, 381 g; $P < 0.05$) and had a slightly lower systolic blood pressure than did control subjects, but rates of underweight, stunting, or wasting were not significantly different between the 2 groups (16). In Bangladesh, the prevalence of vitamin B-12 deficiency at 6 mo was lower in the UNIMMAP group (26.1%) than in the IFA group (36.5%) (17), but no difference in the motor development of infants could be observed between the 2 groups when it was evaluated at the age of 7 mo (6). The most striking postnatal effect of the UNIMMAP was observed in the largest UNIMMAP trial carried out in Indonesia, in which infants of women who consumed the UNIMMAP had an 18% reduction in early infant mortality (deaths <90 d postpartum) compared with infants whose mothers had received an IFA supplement (35.5 deaths/1000 live

¹ From the Child Health and Nutrition Unit, Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium (DR and PK); the Center Muraz, Ministry of Health, Bobo-Dioulasso, Burkina Faso (HL, M-CH, and NM); the Institute of Research in Health Sciences, Ministry of Research, Ouagadougou, Burkina Faso (HL and LO); and the Department of Food Safety and Food Quality, Ghent University, Ghent, Belgium (PK and LH).

² Supported by Nutrition Third World and the Belgian Ministry of Development.

³ Address correspondence to D Roberfroid, Child Health and Nutrition Unit, Department of Public Health, Institute of Tropical Medicine, 155, Nationalestraat, 2000 Antwerp, Belgium. E-mail: droberfroid@itg.be.

⁴ Abbreviations used: IFA, iron and folic acid; LBW, low birth weight; MUAC, midupper arm circumference; UNIMMAP, UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women.

Received October 18, 2011. Accepted for publication January 5, 2012.

First published online February 29, 2012; doi: 10.3945/ajcn.111.029033.

TABLE 1
Composition of the UNIMMAP and IFA supplement¹

Nutrient	Form	IFA amount	UNIMMAP amount
Vitamin A (µg)	Retinol	—	800
Vitamin D (IU)	Cholecalciferol	—	200
Vitamin E (mg)	Tocopherol	—	10
Thiamine (mg)	Thiamine HCL	—	1.4
Riboflavin (mg)	Riboflavin	—	1.4
Niacin (mg)	Nicotinamide	—	18
Folic acid (µg)	—	400	400
Vitamin B-6 (mg)	Pyridoxine	—	1.9
Vitamin B-12 (µg)	Cyanocobalamin	—	2.6
Vitamin C (mg)	Ascorbic acid	—	70
Zinc (mg)	Zinc sulfate	—	15
Iron (mg)	Ferrous fumarate	60	30
Copper (mg)	Copper sulfate	—	2
Selenium (µg)	Sodium selenite	—	65
Iodine (µg)	Potassium iodide	—	150

¹ IFA, iron and folic acid; UNIMMAP, UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women.

births compared with 43 deaths/1000 live births, respectively; RR: 0.82; 95% CI: 0.70, 0.95; *P* = 0.010) (9). In contrast, no effect on mortality in the first 2 y of life was identified in Guinea-Bissau, but this study was not powered for the assessment of such an outcome and suffered from an important proportion of loss to follow-up (18). None of these studies assessed infant growth and nutritional status longitudinally.

In 2008, we published the results of an individually randomized, double-blind, controlled trial in Burkina Faso that compared the UNIMMAP to IFA (12). After adjustment for gestational age at delivery, birth weight (52 g; 95% CI: 4, 100 g; *P* = 0.03), birth length (3.6 mm; 95% CI: 0.8, 6.3 mm; *P* = 0.01), arm circumference (1.2 mm; 95% CI: 0.2, 2.3 mm; *P* = 0.02), and chest circumference (2.8 mm; 95% CI: 0.1, 5.6 mm; *P* = 0.02) were all significantly higher in the UNIMMAP group. The aim of this study was to assess whether these differences at birth persist in the postnatal period.

SUBJECTS AND METHODS

Subjects and measurements

From March 2004 to February 2006, 1426 pregnant women in the catchment area of 2 health centers in the Houndé district, Burkina Faso, were randomly assigned to receive daily either IFA or the UNIMMAP up to delivery (12). Participants were also randomly assigned to receive either 300 mg chloroquine once per week, or intermittent, preventive treatment with sulfadoxine (1500 mg) and pyrimethamine (75mg) (once in the second and third trimesters) for malaria prevention. All participants also received albendazole (400 mg) during the second and third trimester for deworming. Twenty-five locally trained home visitors visited every mother of childbearing age monthly for early pregnancy detection. The study purpose and procedures were explained to the mothers in 1 of the 3 local languages (Bwamu, Moré, or Dioula, as appropriate). A unique randomization code generated by a computer program in permuted blocks of 4 was allocated to consenting women. The trial’s staff, health workers,

and mothers remained blinded to the treatment allocation until data analysis. UNIMMAP and IFA tablets were identical in appearance (Scanpharm). The daily supplement intake was directly observed by the project home visitors, whose work was assessed every month on a random day, by using a lot quality survey (19).

After delivery, mothers were invited to monthly visits at the nearest health center for assessment of infant growth and health during the first year of life. In the case of a missed appointment, a home visit was organized to encourage the mother to attend. Lost to follow-up was defined as any living infant who could not be visited ≤1 y of age. This event usually occurred because the mother had left the area. In such cases, data up to the last visit were used in the analysis. After the 12-mo follow-up period of the last newborn had been completed, every family was visited one more time to ascertain the vital status of subjects who had been lost to follow-up and to measure growth variables of all study children (weight, length, and MUAC). Infant length and weight were measured to the nearest 1 mm by using a SECA 207 scale (SECA) and to the nearest 10 g by using a SECA 725 scale (SECA), respectively.

For infants ≥6 mo of age, weight was measured to the nearest 100 g by using a SECA UNISCALE (SECA). Infant occipito-frontal head circumference, thoracic circumference, and MUAC were measured to the nearest 1 mm by using a SECA Girth Measuring Tape (SECA) or a SECA 402 Baby Band (SECA). Head circumference was taken at the maximum occipito-frontal measurement. The MUAC was measured midway between the tip of the olecranon process and the acromion process. The chest was measured at the level of the nipples, midway between inspiration and expiration during quiet breathing. To ensure reliability, all anthropometric variables were measured twice, once by clinic staff and a second time by an anthropometrist hired by the project. The average of the 2 measures was used for analysis. If there was a large discrepancy between the 2 measurements (>200 g for weight or >5 mm for other measurements), the file was reviewed by a supervisor for a consistency check and ascertainment of the valid measurements, if any. All weighing scales were calibrated daily. The accuracy and precision of measurements were established monthly through a standardization session (20) with immediate feedback to the assessors.

At each encounter, we also collected information on diarrhea, which was defined as ≥3 watery stools per 24 h, fever, and cough episodes that had occurred in the 2 wk before the visit. Recommendations about exclusive breastfeeding and, in due time, optimal complementary foods were provided to every woman. Every child was vaccinated according to the national schedule and received vitamin A at 6 mo (100,000 IU) and at 12 mo (200,000 IU). Infants who were sick and/or had lost weight since the previous visit were referred to curative services for appropriate clinical management.

The study was approved by the ethics committees of the Center Muraz, Bobo-Dioulasso, Burkina Faso, and the Institute of Tropical Medicine, Antwerp, Belgium.

Statistical analysis

Intent-to-treat analyses included all singletons born alive who had at least one set of anthropometric measurement taken at or after delivery.



Continuous outcomes included weight-for-age, weight-for-length, length-for-age, MUAC-for-age, and head circumference-for-age *z* scores and chest circumference (mm). The WHO 2006 growth standards served as the reference for computation of *z* scores (21). Because of the repeated measurements at individual levels, we used mixed-effects models with random intercepts (22). These models were quadratic models because growth trajectories are typically nonlinear (ie, growth is fast initially and then slows down). Growth models also included a random slope to account for variations in individual growth trajectories and, hence, to improve the model fit. The random slope allowed for relaxation of the assumption that the individual-specific regression lines were parallel (22). The covariance matrix was unstructured.

For each outcome, the random part of the model included infant identifier, age, and age squared, and the fixed effects were intervention (UNIMMAP compared with IFA), parity (primiparity compared with multiparity), gestational age at delivery, age at measurement, and age squared. To account for study design, malaria prevention (chloroquine compared with sulfadoxine and pyrimethamine) and health center (center 1 compared with center 2) were 2 variables also inserted into every model. We tested the interaction intervention \times age for each outcome variable.

For dichotomous variables such as the occurrence of diarrhea, cough, or fever episodes (yes compared with no) in the 15 d preceding the monthly visit, we used multilevel Poisson's regression with the same strategy modeling, as previously described.

We assessed differences in infant mortality, wasting, underweight, and stunting, which was defined as less than -2 of the respective weight-for-length, weight-for-age, and length-for-age *z* scores with survival analysis. HRs for the UNIMMAP compared with IFA were obtained by Cox proportional hazard models with the time to the first episode as the outcome. The survival analysis was carried out on data generated from the monthly follow-up only (ie, data collected during the final home-based survey were excluded because the time to event could not be ascertained with accuracy in that case). The proportional hazard assumption was visually appraised by inspecting the Kaplan-Meier graphical plots. Infants who did not develop the outcome, because they either died or were lost to follow-up, were censored at the time of their last clinic visit.

Statistical significance was set at $P < 0.10$ for interaction tests and at $P < 0.05$ for all other tests. A cutoff of 0.10 for interaction tests was recommended because of the usual low power of epidemiologic studies for detecting interactions (23, 24). *P* values were adjusted for multiple comparisons by using the false discovery rate method (25). The corrected overall critical $P = 0.04$. All analyses were conducted with Stata 11.0 (StataCorp).

RESULTS

By February 2006, 1426 pregnancies were confirmed by using urine testing and were randomly assigned to receive either the UNIMMAP or IFA. Participants were predominantly young (mean \pm SD age: 24.4 ± 6.3 y) illiterate women (80.1%). Approximately 20.0% of participants were nulliparous. The mean (\pm SD) gestational age at recruitment was 17.3 ± 7.8 wk. Study groups were similar with respect to baseline characteristics (Table 2). Pregnancy outcome could be assessed in 98.1% of cases, which was a proportion slightly higher than was previously reported because the vital status of 22 newborns whose mothers had been lost to follow-up during pregnancy could be clarified by sub-

sequent postnatal home visits (12). The proportion of loss to follow-up was not different between randomization groups, and characteristics of subjects lost to follow-up did not differ from remainders (data not shown). No difference in study duration, tablet intake, gestational length, or place of delivery between intervention groups was observed. Six cesarean deliveries were performed (2 cesarean deliveries in the control group and 4 cesarean deliveries in the intervention group). Three women died before delivery, and one woman underwent a therapeutic abortion (Figure 1). Risk of miscarriage and stillbirth in singleton pregnancies was 2.1% (29 of 1400 singleton pregnancies) and 2.2% (31 of 1400 singleton pregnancies), respectively, with no significant differences between groups.

There were 1294 live births, 18 (1.4%) of whom died in the neonatal period, which left 1276 infants eligible for growth monitoring, which was realized in 91.6% of cases (1169 of 1276 cases), which was a proportion balanced between intervention and control groups. Infants lost to follow-up and those whose growth was monitored presented no significant difference for sex, birth anthropometric measures, or gestational age at delivery (data not shown). One hundred children died during the follow-up period, of which 80 deaths occurred during the first 12 mo postdelivery. The total duration of follow-up was 30,459 infant-months, with 15,261 infant-months during the first year of life. We visited every child an average (\pm SD) of 5.5 ± 3.4 times. The mean age during the last home-based survey was 30.2 ± 8.2 mo.

The linear growth of all participants was suboptimal with a monthly decrease (mean \pm SE) in length-for-age *z* score of 0.06 ± 0.003 ($P < 0.0001$) and an overall stunting rate of 34.6/1000 infant-months (95% CI: 31.3, 38.1/1000 infant-months). Children whose mothers had received the UNIMMAP had a significantly greater length-for-age (0.13 ± 0.06 ; $P = 0.020$) and weight-for-age (0.13 ± 0.05 ; $P = 0.007$) *z* scores (Table 3). Compared with IFA, the UNIMMAP resulted in a 27% (HR: 0.73; 95% CI: 0.60, 0.89; $P = 0.002$) reduction in the rate of stunting during the first year of life (Table 4; Figure 2). Stunting rates were 29.2/1000 child-months in the UNIMMAP group and 39.2/1000 child-months in the IFA group. Thoracic circumference (2.76 ± 1.10 mm; $P = 0.010$), MUAC-for-age *z* score (0.14 ± 0.06 ; $P = 0.020$), and head circumference-for-age (0.10 ± 0.05 ; $P = 0.071$) *z* scores were also higher in the UNIMMAP group than in the IFA group.

TABLE 2
Baseline characteristics of participants by allocation group¹

Characteristics	Control (<i>n</i> = 655)	Intervention (<i>n</i> = 655)
Maternal age (y)	24.3 ± 6.1^2	24.3 ± 6.2
No school education [<i>n</i> (%)]	529 (80.1)	499 (76.2)
Maternal height (cm)	162.0 ± 5.9	162.3 ± 5.8
Maternal BMI (kg/m ²)	20.7 ± 2.0	21.0 ± 2.2
Maternal MUAC ³ (mm)	25.7 ± 2.1	25.9 ± 2.2
Primiparity [<i>n</i> (%)]	125 (19.0)	140 (21.2)
Gestational age at entry (wk)	17.5 ± 7.5	17.7 ± 7.7
Hemoglobin at enrollment (g/dL)	11.1 ± 1.8	10.9 ± 1.6

¹ Only characteristics of women who gave birth to a single infant are presented. Characteristics of the overall study population were presented previously (12). There were no significant differences between the whole study population and participants who were eligible for follow-up.

² Mean \pm SD (all such values).

³ MUAC, midupper arm circumference.

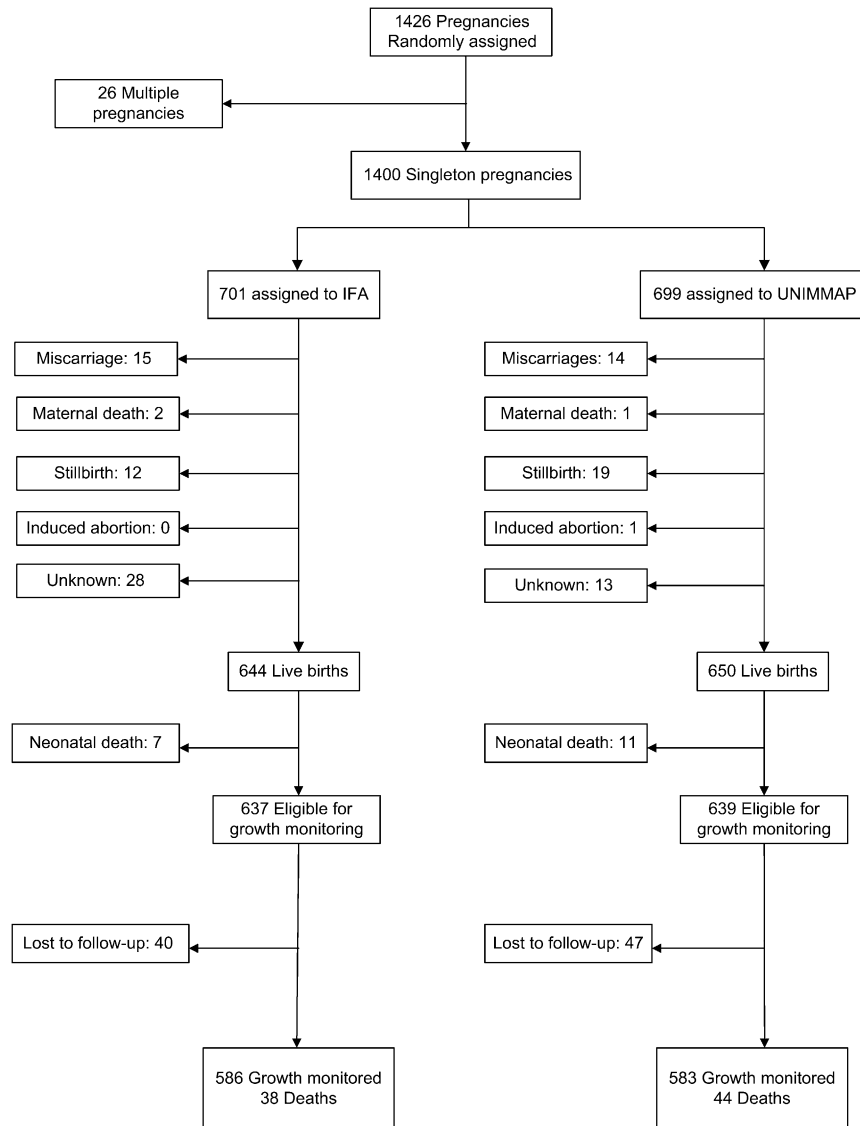


FIGURE 1. Trial profile. Growth monitoring was scheduled monthly from birth to age 12 mo. The survival status was assessed a last time during a home visit at a mean age (\pm SD) of 30.2 ± 8.2 mo. One hundred children died during the follow-up period, of which 80 deaths occurred during the first 12 mo after delivery. The total duration of follow-up was 30,459 infant-months, with 15,261 infant-months during the first year of life. IFA, iron and folic acid; UNIMMAP, UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women.

The difference in length-for-age appeared to level off over time (Figure 3), with a difference in z score of 0.19 (95% CI: 0.07, 0.31; $P = 0.003$) at a younger age [age = (mean - 1 SD); re-centering method] against a z score of 0.10 (95% CI: -0.02, 0.21; $P = 0.093$) at a later age (mean + 1 SD) (Table 5). Eventually, no differences between groups in length-for-age and MUAC were retrieved during the last home-based survey. Weight-for-length presented a different dynamic (Figure 3). We also observed a monthly decrease (z score: 0.13; 95% CI: 0.12, 0.14; $P < 0.001$), but no overall difference between intervention groups in weight-for-length or wasting rates (Tables 3 and 4). The rate of wasting during infancy was 34/1000 infant-months (95% CI: 31, 38). The interaction between intervention and age was highly significant ($P = 0.004$), with a trend toward a higher weight-for-length in the UNIMMAP group at later ages (Table 5). From ≥ 10 mo of age, weight-for-length was higher in the UN-

IMMAP group than in the IFA group, with a difference in z score of 0.20 (95% CI: 0.06, 0.34; $P = 0.004$) measured at the last home visit (Table 3). This corresponded to 178 g (95% CI: 52, 305 g; $P = 0.006$); the prevalence of wasting was 9.7% (45 of 462 subjects) in the IFA group, whereas it was 6.7% (30 of 419 subjects) in the UNIMMAP group ($P = 0.093$) (data not shown). Head circumference-for-age displayed a pattern similar to weight-for-length. Although head circumference-for-age did not differ globally between groups during the observation period ($P = 0.071$), it was higher by a z score of 0.23 (95% CI: 0.04, 0.41; $P = 0.015$) in the UNIMMAP group than in the IFA group at later age (mean + 1 SD) during infancy (P -interaction = 0.033) (Table 5). Such variations over time were not observed for the other indicators.

There was no difference between UNIMMAP and IFA groups in the infant-mortality rate. For morbidity, a 14% (95% CI: 1%, 26%; $P = 0.04$) lower risk of fever was observed in the UNIMMAP

TABLE 3
Effect of prenatal UNIMMAP compared with IFA on child anthropometric measures¹

Outcome	Mean ± SD	Predictor	During the whole observation period		At last home visit only	
			β (95% CI) ²	P	β (95% CI) ³	P
Weight-for-age z score (n = 9037)	−1.06 ± 1.16	UNIMMAP compared with IFA	0.13 (0.04, 0.23)	0.007	0.13 (−0.01, 0.27)	0.077
		Age (mo)	−0.10 (−0.11, −0.09)	<0.0001	0.01 (0.00, 0.02)	0.073
Length-for-age z score (n = 9033)	−1.06 ± 1.24	UNIMMAP compared with IFA	0.13 (0.02, 0.24)	0.02	−0.02 (−0.18, 0.14)	0.77
		Age (mo)	−0.06 (−0.07, −0.06)	<0.0001	−0.02 (−0.03, −0.01)	<0.001
Weight-for-length z score (n = 8960)	−0.50 ± 1.26	UNIMMAP compared with IFA	0.05 (−0.04, 0.15)	0.270	0.20 (0.06, 0.34)	0.004
		Age (mo)	−0.13 (−0.14, −0.12)	<0.0001	0.04 (0.03, 0.04)	<0.001
HC-for-age z score (n = 8167)	−0.51 ± 1.10	UNIMMAP compared with IFA	0.10 (−0.01, 0.20)	0.071	—	—
		Age (mo)	−0.03 (−0.05, −0.01)	0.002	—	—
MUAC-for-age z score (n = 8963)	−0.40 ± 1.15	UNIMMAP compared with IFA	0.14 (0.02, 0.26)	0.020	0.18 (−2.93, 3.29)	0.909
		Age (mo)	−0.14 (−0.15, −0.13)	<0.0001	0.35 (0.15, 0.55)	0.001
TC (mm) (n = 8160)	41.09 ± 4.55	UNIMMAP compared with IFA	2.76 (0.67, 4.85)	0.010	—	—
		Age (mo)	23.48 (22.98, 23.97)	<0.0001	—	—

¹ z scores were calculated from the WHO 2006 reference (21). n includes all measurements from birth to the last home visit. HC, head circumference; IFA, iron and folic acid; MUAC, midupper arm circumference; n, number of measurements; TC, thoracic circumference; UNIMMAP, UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women.

² Estimated from quadratic growth models with a random intercept and random slope (22). Random effects were infant identifier to account for the repeated measurement at the individual level and age and age squared to account for variation in individual growth curves. The covariance matrix was unstructured. Fixed effects were intervention (UNIMMAP compared with IFA), parity (primiparity compared with multiparity), gestational age at delivery, age at time of measurement, and age squared as well as malaria prevention (chloroquine compared with sulfadoxine and pyrimethamine) and health center (center 1 compared with center 2) to account for study design.

³ Estimated from linear regression with adjustment for parity (primiparity compared with multiparity), gestational age at delivery, and age at time of measurement as well as malaria prevention (chloroquine compared with sulfadoxine and pyrimethamine) and health center (center 1 compared with center 2) to account for study design. Data were collected in 911 children during the last home visit that occurred at a mean (±SE) age of 30.2 ± 8.2 mo. Head and thoracic circumferences were not measured during this last home visit.

group than in the IFA group (Table 6). No difference in risk of diarrhea or cough episodes was observed between study groups.

DISCUSSION

The prenatal UNIMMAP reduced the stunting rate by 27% during infancy. Moreover, an effect of the UNIMMAP on weight-for-length and head circumference became apparent by the end of the first year of life. However, infant growth remained generally poor, with only a modest improvement provided by the UNIMMAP compared with IFA.

We observed that the UNIMMAP increased length-for-age from birth onward, which resulted in a lower rate of stunting

during infancy. However, this difference between groups tended to decrease over time. The UNIMMAP also increased weight-for-length compared with that of IFA, but this effect became apparent only a few months after birth. Two main sets of explanations can be proposed for such complex postnatal effects. First, multiple micronutrients improve fetal growth, and that gain would be sustained as such during early life. For instance, zinc, contained in the UNIMMAP, is a necessary component for placental alkaline phosphatase (26) and a regulator of insulin-like growth factor I activity in osteoblast formation (27). Such properties can affect fetal bone growth as shown in a trial in Peru in which the femur diaphysis length was greater in the fetuses of mothers who

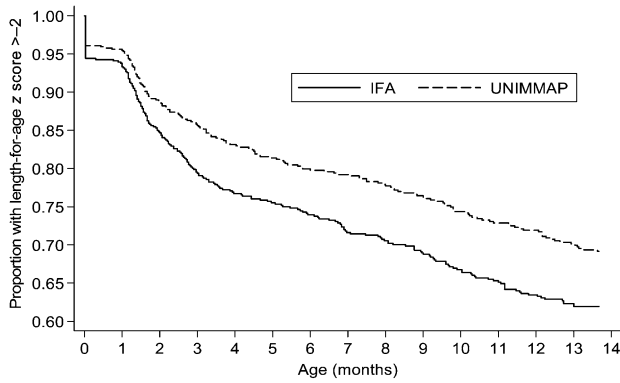
TABLE 4
Effect of prenatal UNIMMAP on the incidence of stunting, wasting, underweight, and death during the first year of life¹

Outcome	IFA		UNIMMAP		HR (95% CI) ²	P
	Exposure ³	Events	Exposure ³	Events		
	<i>Infant-months</i>	<i>n</i>	<i>Infant-months</i>	<i>n</i>		
Underweight	5611	239	5756	211	0.84 (0.70, 1.02)	0.076
Stunting	5845	229	6194	181	0.73 (0.60, 0.87)	0.002
Wasting	6002	194	5704	200	1.10 (0.90, 1.35)	0.334
Death	7665	36	7596	44	1.20 (0.77, 1.88)	0.409

¹ Stunting, wasting, and underweight were defined from length-for-age, weight-for-length, and weight-for-age z scores, respectively, as less than −2 of the reference established by the WHO in 2006 (21). P values were calculated by using Wald's test. IFA, iron and folic acid; UNIMMAP, UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women.

² Computed by using Cox proportional hazards models with time-to-event as the outcome and intervention (UNIMMAP compared with IFA) as the predictor. Malaria prevention (chloroquine compared with sulfadoxine and pyrimethamine) and health center (center 1 compared with center 2) were inserted as covariates in all models to account for study design. Models were further adjusted for parity (primiparity compared with multiparity) and gestational age at delivery. The reference category was the IFA group.

³ For each outcome, infants were censored when they were lost to follow-up, dead, or at the end of the follow-up period.



Numbers at risk	month 0	month 3	month 6	month 9	month 12
IFA	644	502	431	391	347
UNIMMAP	650	496	458	425	384

FIGURE 2. Survival analysis of stunting during infancy. The graph was produced by Kaplan-Meier survival estimates. The main outcome was stunting. Participants were also censored in case of death, loss-to-follow up, or at the end of the follow-up period (last visit to the health center). IFA, iron and folic acid; UNIMMAP, UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women.

received zinc than it was in control subjects (28). Other micronutrients contained in the UNIMMAP, such as vitamin A (29) or D (30, 31) could also have played a role in a better linear growth in the fetal period. We have previously reported that the UNIMMAP resulted in a greater birth length (+3.6 mm; 95% CI: 0.8, 6.3 mm; $P = 0.012$) compared with that of IFA in this study population (12). Differences in length, thoracic circumference, and MUAC between UNIMMAP and IFA groups during infancy observed in this follow-up study were of similar amplitude to the ones observed at birth. However, the difference in length-for-age seemed to level off gradually; and at the age of 30 mo, we did not observe the difference anymore. This result might reflect the predominance of environmental factors on postnatal linear growth (ie, infants exposed to the same suboptimal nutritional

environment after birth end up with a similar growth achievement, whatever their fetal growth had been).

A second hypothesis implies that prenatal micronutrients might be required for enzymatic, hormonal, or immunologic pathways that are important for later growth. Prenatal zinc is illustrative of this mechanistic polymorphism. Prenatal zinc may reduce diarrheal morbidity during infancy, as reported from a trial in Peru (32), and hence, may protect the infants from growth faltering episodes of infectious origin. Prenatal zinc might also be important to ensure hyperplasia in muscle cells that will later grow in size (33). Finally, greater stores at birth could also trigger the production of more growth hormones, such as insulin-like growth factor I, in early life (34). Prenatal selenium (35) and vitamin A (29) could also play a role in postnatal growth.

Experimental studies on the effect of postnatal effect of prenatal micronutrients in humans are scarce, and their results are somehow contradictory. For instance, maternal supplementation with IFA plus zinc resulted in an increased child length in Nepal (36) but not in Bangladesh (37) and Peru (38). In Peru, child weight and arm-muscle area were increased (38) but not in Nepal (36). Varying age at measurement, study design (cross-sectional in Nepal compared with longitudinal in Bangladesh and Peru), zinc dose (30 mg in Nepal and Bangladesh compared with 15 mg in Peru), and variations in the level of micronutrient deficiencies may have contributed to such differences. For multiple micronutrients during pregnancy, there are very few studies against which to compare our results. To our knowledge, postnatal growth after prenatal multiple micronutrient supplements was analyzed in only 3 randomized controlled trials. A study in Tanzania longitudinally monitored the postnatal growth of newborns whose mothers had received multiple micronutrients during pregnancy, but because the supplementation continued during the first 2 y of life, the effect of pre- and postnatal supplementation on growth could not be disentangled (39). The other 2 trials were from Nepal (10, 36). Although carried out in neighboring health districts, the trials reported very different findings. In the first trial, which was carried out, on average, 2.5 y

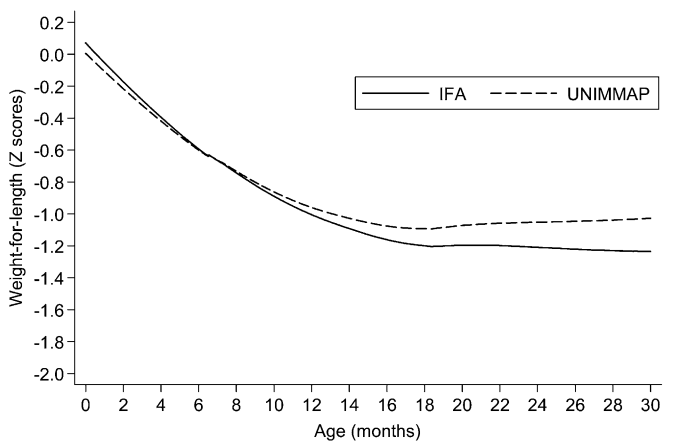
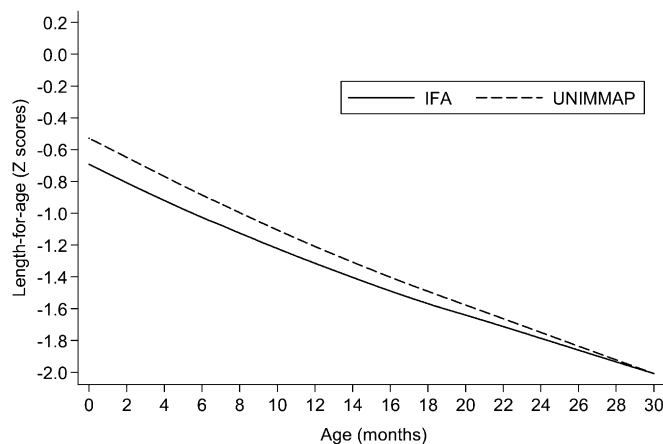


FIGURE 3. Evolution of length-for-age and weight-for-length z scores during the follow-up period. The graphs were produced by locally weighted regression on the predicted values from quadratic growth models with a random intercept and random slope (22). Random effects were infant identifier to account for the repeated measurement at the individual level and age at the time of measurement and age squared to account for variation in individual growth curves. The covariance matrix was unstructured. Fixed effects were intervention (UNIMMAP compared with IFA), parity (primiparity compared with multiparity), gestational age at delivery, age, and age quadratic at the time of measurement, as well as malaria prevention (chloroquine compared with sulfadoxine and pyrimethamine) and health center (center 1 compared with center 2) to account for study design. Models also included an interaction term between intervention and age at the time of measurement. IFA, iron and folic acid; UNIMMAP, UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women.

TABLE 5Effect of prenatal UNIMMAP compared with IFA on child anthropometric measures stratified by infant age at measurement¹

Outcome	Predictor	β coefficient (95% CI) ²	P
Length-for-age <i>z</i> score (<i>n</i> = 9033)	UNIMMAP compared with IFA		0.041 ³
	Age (mean - 1 SD)	0.19 (0.07, 0.31)	0.003
	Age (mean)	0.14 (0.03, 0.25)	0.011
	Age (mean + 1 SD)	0.10 (-0.02, 0.21)	0.093
Weight-for-length <i>z</i> score (<i>n</i> = 8960)	UNIMMAP compared with IFA		0.004 ³
	Age (mean - 1 SD)	-0.05 (-0.17, 0.07)	0.436
	Age (mean)	0.02 (-0.08, 0.12)	0.652
	Age (mean + 1 SD)	0.09 (-0.01, 0.20)	0.069
HC-for-age <i>z</i> score (<i>n</i> = 8167)	UNIMMAP compared with IFA		0.033 ³
	Age (mean - 1 SD)	0.06 (-0.05, 0.17)	0.281
	Age (mean)	0.14 (0.03, 0.26)	0.017
	Age (mean + 1 SD)	0.23 (0.04, 0.41)	0.015

¹ *z* scores were calculated from the WHO 2006 reference (21). *n* includes all measurements from birth to the last home visit that occurred at a mean (\pm SE) age of 30.2 \pm 8.2 mo. Head circumference was not measured during this last home visit. HC, head circumference; IFA, iron and folic acid; *n*, number of measurements; UNIMMAP, UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women.

² Estimated from quadratic growth models with random intercept and random slope (22). Random effects were infant identifier to account for the repeated measurement at the individual level and age and age squared to account for variation in individual growth curves. The covariance matrix was unstructured. Fixed effects were intervention (UNIMMAP compared with IFA), parity (primiparity compared with multiparity), gestational age at delivery, age at time of measurement, and age squared as well as malaria prevention (chloroquine compared with sulfadoxine and pyrimethamine) and health center (center 1 compared with center 2) to account for study design. Strata of infant age were calculated by using the recentring method.

³ *P*-interaction between age at time of measurement and intervention (UNIMMAP compared with IFA).

after birth, children whose mothers had received the UNIMMAP presented greater weight-for-age *z* scores and greater arm, head, and thoracic circumferences than did children whose mothers had been allocated to the IFA group; whereas no difference in length was observed (16). The differences in length-for-age and weight-for-length *z* scores were also close to statistical significance. The direction and amplitude of these results were remarkably close to ours. In contrast, in the second study, in which

a slightly different composition of multiple micronutrients had been used, no differences in anthropometric indicators were observed between the multiple-micronutrient group and children from the IFA or control (folic acid alone) groups when monitored 8 y after birth (36). In that study, children in the IFA plus zinc group had a significantly greater length than did control subjects, but no such results were observed in the group allocated to multiple-micronutrient tablets, although these also contained iron, folic acid, and zinc (36). The authors invoked inhibitory interactions of zinc with other micronutrients or a chance finding to explain such discrepancies.

Our results tend to show that both hypotheses (ie, a gain in fetal growth sustained in early life and enhanced postnatal growth) might be effective, and multiple micronutrients affect both prenatal and postnatal growth. Whether differences in growth of such amplitude are associated with better health is a crucial concern. The rate of fever episodes was reduced by 14%, but incidences of diarrhea and cough episodes were not reduced. There was also no indication toward a reduction in infant mortality. However, it is possible that health had been affected in more subtle ways and/or in the longer term. We measured the incidence of infectious episodes and not their severity. Other physiologic pathways might have been involved. For instance, in Nepal, the systolic blood pressure was slightly lower in children whose mothers had prenatally received the UNIMMAP instead of IFA (16). There is also a growing body of evidence of the inverse association between linear growth and blood pressure, cardiovascular risk factors, and metabolic disorders (40, 41). The main limitation of our study was the lack of measurement of markers that would have allowed a better understanding of intermediary mechanisms. We collected dry blood spots in every infant on 3

TABLE 6Effect of prenatal UNIMMAP on risk of diarrhea, cough, and fever during infancy¹

Outcome ²	IFA	UNIMMAP	Rate ratio (95% CI) ³	<i>P</i>
	No. of events	No. of events		
Diarrhea	375	314	0.96 (0.77, 1.20)	0.73
Cough	354	354	1.04 (0.88, 1.22)	0.62
Fever	474	384	0.86 (0.74, 0.99)	0.04

¹ *P* values were calculated by using Wald's test. IFA, iron and folic acid; UNIMMAP, UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnancy and lactating women.

² Defined as the occurrence (yes compared with no) of diarrhea (defined as ≥ 3 watery stools/24 h), fever, or cough episodes in the 2 wk before the visit. A same event could occur several times in the same infants.

³ Computed with multilevel Poisson regression models. Random effects were infant identifier to account for the repeated measurement at the individual level. Fixed effects were intervention (UNIMMAP compared with IFA), parity (primiparity compared with multiparity), and age as well as malaria prevention (chloroquine compared with sulfadoxine and pyrimethamine) and health center (center 1 compared with center 2) to account for study design. The reference category was the IFA group.

occasions for that purpose; but blood elution failed for an unknown reason. Thus, additional follow-up of this study cohort with more accurate measurement tools is needed.

Finally, the overall child nutritional status of this sample remained poor, even in the UNIMMAP group. By 1 y of age, approximately one-third of infants were stunted, and almost the same proportion had suffered at least one episode of wasting. Prenatal multiple micronutrients may improve health later in life, but they appear globally insufficient to improve nutrition during infancy if they are not accompanied by postnatal measures such as multiple-micronutrient supplements (42).

Members of the Micronutriments et Santé de la Mère et de l'Enfant (MISAME) study group were as follows—analysis and writing team: DR, LH, HL, M-CH, NM, and PK; investigator team: J-P Ki, V Koudougbo, L Toe, E Da, G Lougue, B Negalo, B Hien, and O Guebe; logistic team: S Ouattara, B Bicaba, C Kouakou Yameogo, N Diallo, Michel Sanou, and A Hien; and scientific committee: Jane Kusun (Amsterdam University, Amsterdam Netherlands), Francis Delpuech (Tropical Nutrition Unit in the Institut de Recherche pour le Développement, Montpellier, France), John Van Camp (Department of Food Safety and Food Quality, Bioscience Engineering, Ghent University, Ghent, Belgium), Pierre Bourdoux (Pediatric Laboratory, Université Libre de Bruxelles, Brussels, Belgium), Serge Diabougba (Center Muraz, Bobo-Dioulasso, Burkina Faso), Sylvestre Tapsoba (Ministry of Public Health, Bobo-Dioulasso, Burkina Faso), Mete Boncougou (Ministry of Public Health, Hauts-Bassins, Bobo-Dioulasso, Burkina Faso), and Philippe Nikiema (University of Ouagadougou, Ouagadougou, Burkina Faso).

We thank the families of Karaba and Koho who participated in the study, the health staff of the Houndé district, and, in particular, district directors Pascal Korgo and Noufou Sankara. We also thank the staff of Center Muraz for their logistical and administrative support.

The authors' responsibilities were as follows—PK and DR: designed the study; DR: implemented and followed up the study, undertook analysis and interpretation of the data, and drafted the manuscript; M-CH: made substantial contributions to the execution and supervision of the study; HL: coordinated field investigations; NM: contributed to the execution and supervision of the study; LH: made substantial contributions to the supervision of field investigations and data management; LO: organized the last home-based follow-up visit; and all authors: substantially contributed to the manuscript and saw and approved the final version of the manuscript. None of the authors had a conflict of interest. Supporting agencies had no role in study design, data collection, data analysis, or writing of the report.

REFERENCES

1. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera J. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008;371:243–60.
2. Allen LH. Multiple micronutrients in pregnancy and lactation: an overview. *Am J Clin Nutr* 2005;81:1206S–12S.
3. UNICEF/UNU/WHO. Multiple micronutrient supplementation during pregnancy (MMSDP): a review of progress of efficacy trials. Report of a meeting in Bangkok. New York, NY: UNICEF, 2004.
4. UNICEF/WHO/UNU Study Team. Composition of a multiple micronutrient supplements to be used in pilot programmes among pregnant women in developing countries. Report of a workshop held at UNICEF Headquarters. New York, NY: UNICEF, 1999.
5. Dalmiya N, Darnton-Hill I, Schultink W, Shrimpton R. Multiple micronutrient supplementation during pregnancy: a decade of collaboration in action. *Food Nutr Bull* 2009;30:S477–9.
6. Tofail F, Persson LA, el Arifeen S, Hamadani JD, Mehrin F, Ridout D, Ekström EC, Huda SN, Grantham-McGregor SM. Effects of prenatal food and micronutrient supplementation on infant development: a randomized trial from the Maternal and Infant Nutrition Interventions, Matlab (MINIMat) study. *Am J Clin Nutr* 2008;87:704–11.
7. Zeng L, Dibley MJ, Cheng Y, Dang S, Chang S, Kong L, Yan H. Impact of micronutrient supplementation during pregnancy on birth weight, du-

- ration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial. *BMJ* 2008;337:a2001.
8. Shankar AH, Jahari AB, Sebayang SK, Aditiawarman, Apriatni M, Harefa B, Muadz H, Soesbandoro SD, Tjiong R, Fachry A, et al. Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial. *Lancet* 2008; 371:215–27.
9. Sunawang, Utomo B, Hidayat A, Kusharisupeni, Subarkah. Preventing low birthweight through maternal multiple micronutrient supplementation: a cluster-randomized, controlled trial in Indramayu, West Java. *Food Nutr Bull* 2009;30:S488–95.
10. Osrin D, Vaidya A, Shrestha Y, Baniya RB, Manandhar DS, Adhikari RK, Filteau S, Tomkins A, Costello AM. Effects of antenatal multiple micronutrient supplementation on birthweight and gestational duration in Nepal: double-blind, randomised controlled trial. *Lancet* 2005;365: 955–62.
11. Bhutta ZA, Rizvi A, Raza F, Hotwani S, Zaidi S, Moazzam Hossain S, Soofi S, Bhutta S. A comparative evaluation of multiple micronutrient and iron-folic acid supplementation during pregnancy in Pakistan: impact on pregnancy outcomes. *Food Nutr Bull* 2009;30:S496–505.
12. Roberfroid D, Huybregts L, Lanou H, Henry MC, Meda N, Menten J, Kolsteren P; MISAME Study Group. Effects of maternal multiple micronutrient supplementation on fetal growth: a double-blind randomized controlled trial in rural Burkina Faso. *Am J Clin Nutr* 2008;88:1330–40.
13. Kaestel P, Michaelsen KF, Aaby P, Friis H. Effects of prenatal multi-micronutrient supplements on birth weight and perinatal mortality: a randomised, controlled trial in Guinea-Bissau. *Eur J Clin Nutr* 2005; 59:1081–9.
14. Zagré NM, Desplats G, Adou P, Mamadoultaibou A, Aguayo VM. Prenatal multiple micronutrient supplementation has greater impact on birthweight than supplementation with iron and folic acid: a cluster-randomized, double-blind, controlled programmatic study in rural Niger. *Food Nutr Bull* 2007;28:317–27.
15. Fall CH, Fisher DJ, Osmond C, Margetts BM. Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation. *Food Nutr Bull* 2009;30:S533–46.
16. Vaidya A, Saville N, Shrestha BP, Costello AM, Manandhar DS, Osrin D. Effects of antenatal multiple micronutrient supplementation on children's weight and size at 2 years of age in Nepal: follow-up of a double-blind randomised controlled trial. *Lancet* 2008;371:492–9.
17. Eneroth H, el Arifeen S, Persson LA, Lönnerdal B, Hossain MB, Stephensen CB, Ekström EC. Maternal multiple micronutrient supplementation has limited impact on micronutrient status of Bangladeshi infants compared with standard iron and folic acid supplementation. *J Nutr* 2010;140:618–24.
18. Andersen GS, Friis H, Michaelsen KF, Rodrigues A, Benn CS, Aaby P, Kaestel P. Effects of maternal micronutrient supplementation on fetal loss and under-2-years child mortality: long-term follow-up of a randomised controlled trial from Guinea-Bissau. *Afr J Reprod Health* 2010; 14:17–26.
19. Valadez JJ, Brown LD, Vargas WV, Morley DC. Using lot quality assurance sampling to assess measurements for growth monitoring in a developing country's primary health care system. *Int J Epidemiol* 1996;25:381–7.
20. WHO Multicentre Growth Reference Study Group. Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study. *Acta Paediatr* 2006;450:450:38–46.
21. Mei Z, Grummer-Strawn LM. Standard deviation of anthropometric Z-scores as a data quality assessment tool using the 2006 WHO growth standards: a cross country analysis. *Bull World Health Organ* 2007;85: 441–8.
22. Rabe-Hesketh S, Skrondal A. Multilevel and longitudinal modeling using Stata. 2nd ed. College Station, TX: Stata Press, 2008.
23. Selvin S. Statistical analysis of epidemiologic data. New York, NY: Oxford University Press, 1996.
24. Fleiss JL. Analysis of data from multiclinic trials. *Control Clin Trials* 1986;7:267–75.
25. Benjamini Y, Yekutieli D. False discovery rate-adjusted multiple confidence intervals for selected parameters. *J Am Stat Assoc* 2005; 100:71–81.
26. She QB, Mukherjee JJ, Huang JS, Crilly KS, Kiss Z. Growth factor-like effects of placental alkaline phosphatase in human fetus and mouse embryo fibroblasts. *FEBS Lett* 2000;469:163–7.



27. Matsui T, Yamaguchi M. Zinc modulation of insulin-like growth factor's effect in osteoblastic MC3T3-E1 cells. *Peptides* 1995;16:1063-8.
28. Meriardi M, Caulfield LE, Zavaleta N, Figueroa A, Costigan KA, Dominici F, Dipietro JA. Randomized controlled trial of prenatal zinc supplementation and fetal bone growth. *Am J Clin Nutr* 2004;79:826-30.
29. Prawirohartono EP, Nystrom L, Ivarsson A, Stenlund H, Lind T. The impact of prenatal vitamin A and zinc supplementation on growth of children up to 2 years of age in rural Java, Indonesia. *Public Health Nutr* 2011;14:2197-2206.
30. Viljakainen HT, Korhonen T, Hytinantti T, Laitinen EK, Andersson S, Mäkitie O, Lamberg-Allardt C. Maternal vitamin D status affects bone growth in early childhood—a prospective cohort study. *Osteoporos Int* 2011;22:883-91.
31. Leffelaar ER, Vrijkotte TG, van Eijsden M. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. *Br J Nutr* 2010;104:108-17.
32. Iannotti LL, Zavaleta N, Leon Z, Huasquiche C, Shankar AH, Caulfield LE. Maternal zinc supplementation reduces diarrheal morbidity in peruvian infants. *J Pediatr* 2010;156:960-4, 964.e1-2.
33. Polimeni M, Giorgi S, De Gregorio L, Dragani TA, Molinaro M, Cossu G, Bouché M. Differentiation dependent expression in muscle cells of ZT3, a novel zinc finger factor differentially expressed in embryonic and adult tissues. *Mech Dev* 1996;54:107-17.
34. Roberfroid D, Huybregts L, Lanou H, Henry MC, Meda N, Kolsteren FP. Effect of maternal multiple micronutrient supplements on cord blood hormones: a randomized controlled trial. *Am J Clin Nutr* 2010;91:1649-58.
35. Neville TL, Caton JS, Hammer CJ, Reed JJ, Luther JS, Taylor JB, Redmer DA, Reynolds LP, Vonnahme KA. Ovine offspring growth and diet digestibility are influenced by maternal selenium supplementation and nutritional intake during pregnancy despite a common postnatal diet. *J Anim Sci* 2010;88:3645-56.
36. Stewart CP, Christian P, LeClerq SC, West KP Jr, Khattry SK. Antenatal supplementation with folic acid + iron + zinc improves linear growth and reduces peripheral adiposity in school-age children in rural Nepal. *Am J Clin Nutr* 2009;90:132-40.
37. Osendarp SJM, Baqui AH, Wahed MA, Arifeen SE, van Raaij JMA, Fuchs GJ. A randomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy outcome in Bangladeshi urban poor. *Am J Clin Nutr* 2000;71:114-9.
38. Iannotti LL, Zavaleta N, Leon Z, Shankar AH, Caulfield LE. Maternal zinc supplementation and growth in Peruvian infants. *Am J Clin Nutr* 2008;88:154-60.
39. Villamor E, Saathoff E, Bosch RJ, Hertzmark E, Baylin A, Manji K, Msamanga G, Hunter DJ, Fawzi WW. Vitamin supplementation of HIV-infected women improves postnatal child growth. *Am J Clin Nutr* 2005;81:880-8.
40. Walker SP, Gaskin P, Powell CA, Bennett FI, Forrester TE, Grantham-McGregor S. The effects of birth weight and postnatal linear growth retardation on blood pressure at age 11-12 years. *J Epidemiol Community Health* 2001;55:394-8.
41. Gaskin PS, Walker SP, Forrester TE, Grantham-McGregor SM. Early linear growth retardation and later blood pressure. *Eur J Clin Nutr* 2000;54:563-7.
42. Ramakrishnan U, Goldenberg T, Allen LH. Do multiple micronutrient interventions improve child health, growth, and development? *J Nutr* 2011;141:2066-75.

