

# Daily Supplementation with Iron Plus Folic Acid, Zinc, and Their Combination Is Not Associated with Younger Age at First Walking Unassisted in Malnourished Preschool Children from a Deficient Population in Rural Nepal<sup>1-4</sup>

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## Abstract

A community-based, cluster-randomized, placebo-controlled trial of daily zinc and/or iron+folic acid supplementation was conducted in rural southern Nepal to examine motor milestone attainment among 3264 children 1–36 mo of age between 2001 and 2006. Treatment groups included placebo, zinc (10 mg), iron+folic acid (12.5 mg iron + 50  $\mu$ g folic acid), and zinc +iron+folic acid (10 mg zinc + 12.5 mg iron + 50  $\mu$ g folic acid). Infants received half of these doses. The iron arms were stopped November 2003 by recommendation of the Data Safety and Monitoring Board; zinc and placebo continued until January 2006. A total of 2457 children had not walked at the time of entry into the trial and 1775 were followed through 36 mo. Mean age at first walking unassisted did not differ among groups and was  $444 \pm 81$  d (mean  $\pm$  SD) in the placebo group,  $444 \pm 81$  d in the zinc group,  $464 \pm 85$  d in the iron+folic acid group, and  $446 \pm 87$  d in the iron+folic acid+zinc group. Results were similar after adjustment for age at enrollment, asset ownership, maternal literacy, and prior child deaths in the household and in children who consumed at least 60 tablets. Compared with placebo, iron+folic acid was associated with an adjusted mean delay of 28.0 d (95% CI: 11.3, 44.7) in time to walking among infants and the delay was more pronounced with mid-upper arm circumference (MUAC) < 9.5 cm [60.6 d, (95% CI: 28.5, 92.6)]. Risks and benefits of universal iron+folic acid supplementation of infants beyond improved hematologic status deserve further consideration. *J. Nutr.* 140: 1317–1321, 2010.

## Introduction

Iron and zinc are critical for brain development and deficiencies of these minerals are highly prevalent among preschool age children in low-income countries (1–3). Iron-deficient children score lower on motor development tests (4–6) and have less locomotive activity (7), and anemia was associated with an older age at first walking in both Zanzibari and Nepali children (8,9). Indian children supplemented with zinc in addition to other

micronutrients had higher activity levels than those given micronutrients without zinc (10), and low birth weight infants supplemented with zinc had improved motor development (11). Two large randomized, placebo-controlled,  $2 \times 2$  factorial trials examined the impact of iron+folic acid and zinc supplementation on preschool child mortality in Pemba, Zanzibar (12,13), and rural Sarlahi district in southern Nepal (14,15). Both these populations have high rates of stunting, wasting, and anemia (7,16). Iron+folic acid supplementation had no impact on child survival in Nepal, but hospitalizations and mortality were higher among children receiving iron+folic acid in Zanzibar. Zinc supplementation did not affect overall child survival in either trial.

Each of these trials had a substudy to examine the impact of supplementation on motor milestone attainment. In Pemba, those randomized to receive iron+folic acid supplementation with or without zinc for at least 6 mo walked unassisted a mean of 15 d earlier (17). We examined the effect of iron+folic acid alone, zinc alone, or iron+folic acid and zinc supplementation on

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<sup>3</sup> The trial is registered at clinicaltrials.gov as NCT00109551.

<sup>4</sup> Supplemental Tables 1–6 and Figures 1 and 2 are available with the online posting of this paper at [jn.nutrition.org](http://jn.nutrition.org).

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time to first walking unassisted among children enrolled in the motor milestone substudy in rural Nepal.

## Materials and Methods

Details of the main trial methods have been previously published (14,15). The Nepal Nutrition Intervention Project, Sarlahi was a cluster randomized, population-based,  $2 \times 2$  factorial trial of daily iron+folic acid and/or zinc supplementation conducted in 30 Village Development Committees in the low-lying Sarlahi district of rural southern Nepal. All children 1–35 mo of age in October 2001 were eligible for enrollment. Infants born from this time until January 2006 were also eligible for the trial when they reached 1 mo of age. All children were discharged from the trial at age 36 mo. The study area was divided into 426 geographic sectors that were the units of randomization. The motor milestone substudy was conducted within 1 of the 30 Village Development Committees (Ishwarpur) with 22 sectors. Children received 1 of 4 daily supplements, depending on sector of residence. The supplements with active ingredients contained 12.5 mg of elemental iron as ferrous sulfate + 50  $\mu$ g folic acid, and/or 10 mg of elemental zinc as zinc sulfate. Infants were given one-half this dose. The supplements were made by Nutriset with assistance from the Department of Child and Adolescent Health and Development at the WHO and packaged in blister packs of 14 dispersible tablets. A study worker visited biweekly to give a tablet to the child and left tablets for the mother to give on the days until the next visit. Older children consumed the tablets directly, whereas infants were fed the tablets mixed with breast milk or clean water. Compliance was assessed by counting the difference between tablets provided at each visit and those remaining at the following visit. A treatment code was imprinted on the package, but all tablets looked identical and study staff were unaware of the intervention. Children 6 mo or older were eligible for twice-yearly vitamin A supplements via the Nepal national program.

The Data Safety and Monitoring Board recommended stopping supplementation with the iron+folic acid-containing treatments in November, 2003 due to no survival effect. These sectors were rerandomized to placebo or zinc and children in those sectors received the newly assigned supplements. Children who reconsented and switched from an iron-containing supplement to either zinc or placebo were not included in this analysis. Children who aged into the study after November 2003 received only placebo or zinc supplementation and were included in the placebo vs. zinc comparison. Eleven sectors were initially randomized to receive zinc ( $n = 6$ ) or placebo ( $n = 5$ ) and 11 to iron+folic acid alone ( $n = 5$ ) or iron+folic acid and zinc ( $n = 6$ ). From November 2003, the 11 sectors receiving iron+folic acid were rerandomized to either placebo ( $n = 5$ ) or zinc ( $n = 6$ ) alone. A total of 2274 children living in these 22 sectors were randomized to received only placebo ( $n = 1195$ ) or only zinc ( $n = 1079$ ) (Supplemental Fig. 1). A total of 588 (52.0%) in the placebo group and 539 (53.5%) in the zinc group had not yet started walking unassisted at enrollment. There were 1772 children who were randomized to placebo or iron+folic acid and/or zinc supplements during the earlier part of the trial, prior to rerandomization (Supplemental Fig. 2). Of the participants, 40.0, 40.5, and 36.9% in the placebo, iron+folic acid, and iron+folic acid and zinc groups had not yet walked unassisted at enrollment.

Verbal informed consent was obtained from caregivers of eligible children. Socioeconomic characteristics were collected when children entered the trial. Attainment of 14 motor milestones was assessed weekly via an interview with the child's caregiver. Pictures of the sequential milestones were used to confirm the parental report. The milestones ranged from sitting if pulled up by the arms through crawling, standing, walking, running, and standing on 1 foot. The validity and reliability of this data collection instrument have been reported previously (8,9). The age at which the caregiver said the child had attained that milestone was recorded, with recall being at most 1 wk. Age at first walking unassisted was the main outcome of interest.

The analysis was intent to treat. Because children first enrolling in the study could be 1–35 mo of age, the analysis was confined to those who had not yet started walking unassisted. Chi-square tests were used to compare distributions of adherence to supplement use. The mean difference in age at which children first walked unassisted between each

supplement and placebo group and the relative risk of not yet walking unassisted by 18 mo was calculated with placebo as the reference. This cutpoint was used because it represents the 99th percentile of the upper end of the distribution for normal children, where one might expect a health impact of such extreme delayed milestone attainment (18). Adjusted mean differences and 95% CI in age at first walking and relative risk of not yet walking by 18 mo were estimated using linear and Poisson regressions, respectively. Variables selected for adjustment were those that were imbalanced at baseline and associated with age at first walking. The same analysis was conducted on the subset of children who received at least 60 d of supplementation and among infants. Generalized Estimating Equations (GEE) with robust variance estimates were used to account for the cluster randomization (19). Because certain covariates were strongly correlated with geographic location, some GEE models with binary outcomes would not converge and those covariates were removed from the regressions.

Ethical approval for the trial was obtained from the Nepal Health Research Council, the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health, and the Institutional Review Board of Cornell University. The financial supporters of this trial played no role in the design, conduct, analysis, interpretation of the results, or in the writing, reviewing, or approving of the manuscript.

## Results

**Zinc.** Treatment groups were comparable on many demographic and socioeconomic characteristics at entry into the trial (Supplemental Table 1). However, there was a higher proportion of Muslims, slightly lower parental literacy, and less land ownership but more electricity in the placebo than zinc group.

Children in the placebo group consumed a mean of 11.1 more tablets than those in the zinc group, with 69.5 and 65.9% in the placebo and zinc groups, respectively, having consumed at least 180 tablets (Supplemental Table 2). The age at first walking unassisted was 444 d in both the placebo and zinc groups and the lack of difference remained after adjusting for age at enrollment, asset ownership, maternal literacy, and a history of prior child deaths (Table 1). The proportion of children not walking by 18 mo of age was also similar in the placebo (12.8%) and zinc (11.3%) groups. The results were similar for children under 12 mo of age at the start of the trial, for those under 12 mo with MUAC <9.5 cm and  $\geq 9.5$  cm (Table 1), and for those who consumed at least 60 tablets (data not shown). There was no impact of supplementation on sitting unassisted, running, jumping, and standing on 1 leg (Supplemental Table 3).

**Iron+folic acid and/or zinc.** A higher proportion of children in the iron+folic acid group were lower caste, Hindu, with lower maternal literacy and fewer latrines (Supplemental Table 4). There were no significant differences between the distributions of supplements consumed by treatment arms (Supplemental Table 5). There tended to be a delay in age at first walking of 16.3 d (95% CI: -1.8, 34.1) in the iron+folic acid group compared with the placebo group ( $P = 0.09$ ) (Table 2). Adjustment for age at enrollment, asset ownership, maternal literacy, and a history of prior child death did not modify this difference in a developmentally meaningful way (21.4 d, 95% CI: 2.9, 39.9). There were no differences in time to walking among children who had received at least 60 d of supplementation (data not shown). Similar analyses for sitting unassisted, running, jumping, and standing on 1 leg showed no impact of iron+folic acid and/or zinc supplementation on age at first reaching these milestones (Supplemental Table 6). In children who were <12 mo at entry into the trial, there was a significant delay in time to first walking in the iron+folic acid group (adjusted 28.0-d delay 95% CI: 11.3, 44.7) and the percent of

**TABLE 1** Mean age and proportion >18 mo of age at first walking unassisted among children not yet walking at baseline by zinc and placebo treatment groups<sup>1</sup>

Treatment group	n	Age, d	Mean difference (95% CI)		>18 mo, n (%)	Relative risk (95% CI)	
			Crude	Adjusted		Crude	Adjusted
All children							
Placebo	588	444.2 ± 81.4			75 (12.8)		
Zinc	539	443.7 ± 80.9	-0.5 (-15.8, 14.7)	2.8 (-10.5, 16.0) <sup>2</sup>	60 (11.1)	0.87 (0.63, 1.22)	0.94 (0.67, 1.30) <sup>2</sup>
Children <12 mo of age at baseline							
Placebo	555	439.4 ± 78.6			66 (11.9)		
Zinc	523	441.7 ± 80.2	2.2 (-11.9, 16.4)	3.6 (-10.7, 17.9) <sup>2</sup>	55 (10.5)	0.88 (0.64, 1.22)	0.92 (0.65, 1.31) <sup>2</sup>
Children <12 mo of age and MUAC < 9.5 cm at baseline							
Placebo	158	442.5 ± 81.0			18 (11.4)		
Zinc	166	449.4 ± 86.5	6.9 (-5.9, 19.7)	4.0 (-10.5, 18.5) <sup>2</sup>	22 (13.3)	1.16 (0.63, 2.14)	1.19 (0.55, 2.57) <sup>3</sup>
Children <12 mo of age and MUAC ≥ 9.5 cm							
Placebo	394	438.6 ± 77.8			48 (12.2)		
Zinc	354	437.8 ± 76.9	-0.8 (-18.7, 17.1)	2.8 (-14.5, 20.0) <sup>2</sup>	33 (9.3)	0.77 (0.49, 1.19)	0.83 (0.51, 1.35) <sup>3</sup>

<sup>1</sup> Values are means ± SD, means difference (95% CI), n (%), or relative risks (95% CI).

<sup>2</sup> Adjusted for age enrolled, assets, maternal literacy, and prior child deaths using GEE.

<sup>3</sup> Adjusted for ethnicity, assets, maternal literacy, and prior child deaths using GEE.

children first walking beyond 18 mo of age also was greater than in the placebo group (adjusted relative risk, 4.69; 95% CI: 1.83, 12.01) and to a similar extent in the iron+folic acid and zinc group (adjusted relative risk, 3.41; 95% CI: 1.34, 8.67) (Table 2). This delay was more pronounced among infants with mid-upper arm circumference (MUAC) <9.5 cm (60.6 d, 95% CI: 28.5, 92.6), although the delay was significant in both MUAC strata.

## Discussion

In this trial, where iron and zinc deficiency are endemic (14,15,16) and where age at first walking unassisted is higher than in the United States (9), iron+folic acid and zinc supplementation, alone or in combination, did not affect the age at first

walking unassisted or time to other key motor milestones. Although iron deficiency has been shown to be a risk factor for late attainment of motor milestones (4–9,20,21), few randomized trials of iron+folic acid and/or zinc supplementation have examined locomotor activity or motor milestone attainment as an outcome (10,17). Population and trial characteristics such as age at intervention, dose and adherence, baseline micro and macronutrient deficiencies, and morbidities could lead to varying supplementation effects. The most comparable trial to the one in Nepal was the trial in Pemba, which used the same design and supplement doses (17). That trial did not find an impact of zinc supplementation on time to first walking, but iron+folic acid (with or without zinc) did reduce time to walking by a mean of 15 d compared with those not supplemented with iron+folic acid (17). An analysis restricted to the same age range as the

**TABLE 2** Mean age and proportion >18 mo of age at first walking unassisted among children not yet walking at baseline by iron+folic acid, iron+folic acid and zinc, and placebo treatment groups<sup>1</sup>

Treatment group	n	Age, d	Mean difference (95% CI)		>18 mo, n (%)	Relative risk (95% CI)	
			Crude	Adjusted		Crude	Adjusted
All children							
Placebo	216	447.4 ± 81.2			23 (10.7)		
Iron+folic acid	195	463.6 ± 85.3	16.3 (-1.8, 34.1)	21.4 (2.9, 39.9) <sup>2</sup>	30 (15.4)	1.44 (0.82, 2.53)	2.18 (0.87, 5.44) <sup>3</sup>
Iron+folic acid and zinc	238	446.4 ± 87.1	-0.9 (-18.8, 16.9)	5.5 (-11.6, 22.5) <sup>2</sup>	28 (11.8)	1.10 (0.65, 1.88)	1.72 (0.98, 3.04) <sup>3</sup>
Children <12 mo of age at baseline							
Placebo	183	433.4 ± 72.0			14 (7.7)		
Iron+folic acid	170	454.7 ± 82.2	21.2 (10.6, 31.8)	28.0 (11.3, 44.7) <sup>2</sup>	21 (12.4)	1.61 (1.08, 2.41)	4.69 (1.83, 12.01) <sup>3</sup>
Iron+folic acid and zinc	211	434.9 ± 81.0	1.5 (-13.8, 16.7)	7.1 (-8.8, 23.0) <sup>2</sup>	19 (9.0)	1.18 (0.70, 1.97)	3.41 (1.34, 8.67) <sup>3</sup>
Children <12 mo of age and MUAC <9.5 cm at baseline							
Placebo	28	411.9 ± 50.8			0 (0.0)		
Iron+folic acid	26	457.9 ± 63.4	46.1 (10.4, 81.8)	60.6 (28.5, 92.6) <sup>2</sup>	2 (7.7)	—	—
Iron+folic acid and zinc	33	424.3 ± 75.1	12.4 (-14.7, 39.5)	16.9 (-17.3, 51.2) <sup>2</sup>	2 (6.1)	—	—
Children <12 mo of age and MUAC ≥ 9.5 cm at baseline							
Placebo	153	438.3 ± 74.6			14 (9.2)		
Iron+folic acid	143	454.3 ± 85.6	15.9 (0.2, 31.6)	22.4 (0.6, 44.3) <sup>2</sup>	19 (13.3)	1.45 (0.88, 2.39)	4.28 (1.50, 12.25) <sup>3</sup>
Iron+folic acid and zinc	178	435.8 ± 80.9	-2.6 (-21.6, 16.4)	4.2 (-15.2, 23.6) <sup>2</sup>	16 (9.0)	0.99 (0.51, 1.92)	2.69 (0.94, 7.70) <sup>3</sup>

<sup>1</sup> Values are means ± SD, mean difference (95% CI), n (%), or relative risks (95% CI).

<sup>2</sup> Adjusted for age enrolled, assets, maternal literacy, and prior child deaths using GEE.

<sup>3</sup> Adjusted for ethnicity, assets, maternal literacy, and prior child deaths using GEE.

children in the Pemba trial did not modify the zinc effects but showed a significant delay in time to first walking unassisted for the iron+folic acid group, the opposite of what was found in Pemba.

In the larger Nepal trial, iron+folic acid and/or zinc supplementation had no impact on mortality or morbidity (14,15). In the same subsample of children for whom motor milestones were assessed, there was no impact of iron+folic acid or zinc on nutritional status measured 4 y later (22). Forty-three percent of the children in a small sample of the Nepal trial were iron deficient at baseline (16) and iron+folic acid supplementation reduced iron deficiency anemia after 1 y of supplementation by 84% (iron+folic acid) and 53% (iron+folic acid and zinc) (14). Serum zinc was not measured at baseline, but 16% of the placebo group had serum zinc  $<9.2 \mu\text{mol/L}$  compared with 11% in the zinc group after 12 mo of supplementation (14). Hence, this population was both iron and zinc deficient and supplementation did improve status, but not mortality, morbidity, growth, or motor milestone acquisition. In a subsample of this population, 51% of those 4–17 mo of age fell below  $-2$  Z-scores of weight for age (16). One study suggested that macro- rather than micronutrient deficiency may be the rate-limiting step in achieving age-appropriate motor milestones (23). That trial of energy supplementation with and without iron in Indonesian infants found that those receiving the high energy supplement and iron walked earlier than those who received a lower energy supplement with the same amount of iron. The time to walking in this study (14.8 mo) was  $\sim 1.5$  mo later than that estimated for British and U.S. populations (24,25) and around the 90th percentile of the WHO multicenter growth reference study populations of healthy children (18). This was unlikely due to the exclusion of only those children who had already walked at enrollment, because time to walking was only 2 wk earlier for those  $<12$  mo of age at enrollment compared with children of all ages.

Strengths of this trial include a deficient population with potential to benefit from supplementation, a large sample size, sufficient length of supplementation, and high adherence. Age at first walking unassisted was prospectively collected at weekly visits and easier to measure than tests of motor development. Although the importance of walking 15 d earlier if supplemented with iron+folic acid is unclear, it has been postulated that early acquisition of motor milestones allow children to explore their environment more fully and may solicit more positive interactions from caregivers (26–28). It is not clear whether a 28-d delay in walking, as found in Nepal among those enrolled as infants, has any functional impact on cognition or other developmental outcomes. It is also possible that this finding was due to chance alone and will need to be replicated in other studies. It is also difficult to separate out whether this delay was due to the young age at which supplementation started or the higher cumulative dose received by younger children.

A limitation of this trial is that we do not have baseline and follow-up nutritional and micronutrient status on the specific children for whom we have prospectively collected motor milestones. Hence, we are unable to examine interactions between nutritional status and supplementation on motor milestone acquisition. Another limitation is that only 22 sectors were randomized in this sample of the larger study. There were some baseline differences in the treatment groups and the overlap between certain characteristics such as caste and ethnicity within clusters precluded adjustment for these. Hence, some residual confounding may be present in the estimation of

treatment effects. While motor milestone acquisition is associated with motor development, other more complex tests of motor development are more likely to help in understanding the mechanisms by which iron and zinc affect nervous system development and function. Iron deficiency anemia has been shown to be associated with motor milestone acquisition in this population (9). However, in the current trial, among a malnourished population, iron+folic acid supplementation was not associated with improved survival or time to motor milestone acquisition and was associated with a delay in the time to first walking. The risk and benefit of universal iron+folic acid supplementation of preschool children beyond improvement of hematologic status deserves further consideration.

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