Original Contribution

Antenatal and Postnatal Iron Supplementation and Childhood Mortality in Rural Nepal: A Prospective Follow-up in a Randomized, Controlled Community Trial

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The long-term benefits of antenatal iron supplementation in child survival are not known. In 1999–2001, 4,926 pregnant women in rural Nepal participated in a cluster-randomized, double-masked, controlled trial involving 4 alternative combinations of micronutrient supplements, each containing vitamin A. The authors examined the impact on birth weight and early infant mortality in comparison with controls, who received vitamin A only. They followed the surviving offspring of these women at approximately age 7 years to study effects of in utero supplementation on survival. Of 4,130 livebirths, 209 infants died in the first 3 months and 8 were lost to follow-up. Of those remaining, 3,761 were followed, 150 died between ages 3 months and 7 years, and 152 were lost to follow-up. Mortality rates per 1,000 child-years from birth to age 7 years differed by maternal supplementation group, as follows: folic acid, 13.4; folic acid-iron, 10.3; folic acid-iron-zinc, 12.0; multiple micronutrients; 14.0; and controls, 15.2. Hazard ratios were 0.90 (95% confidence interval (CI): 0.65, 1.22), 0.69 (95% CI: 0.49, 0.99), 0.80 (95% CI: 0.58, 1.11), and 0.93 (95% CI: 0.66, 1.31), respectively, in the 4 supplementation groups. Maternal iron-folic acid supplementation reduced mortality among these children by 31% between birth and age 7 years. These results provide additional motivation for strengthening antenatal iron-folic acid programs.

child; dietary supplements; folic acid; iron; micronutrients; pregnancy; prenatal care; survival

Abbreviations: CI, confidence interval; RR, relative risk.

Globally, pregnant women and young children are at the highest risk of anemia, with iron deficiency contributing to 50% of this risk (1, 2). The global prevalence of anemia among pregnant women is estimated at 41.8% (1). There exists an international policy for antenatal iron-folic acid supplementation in many developing countries with high rates of anemia and iron deficiency (3). Recent studies have shown antenatal iron (with or without folic acid) to reduce rates of low birth weight (4–6) and preterm birth (6), and anemia during pregnancy is associated with increased risk of perinatal and maternal mortality (7, 8). Recently there has been a global move towards expanding international policy recommendations to promote antenatal multiple micronutrient supplementation. Evidence that micronutrient deficiencies beyond iron-folic acid are common during pregnancy exists but is sparse (9–11). A number of randomized controlled trials of multiple micronutrient supplements versus iron-folic acid have been conducted. Although some results remain unpublished, these studies were recently included in a meta-analysis by Haider and Bhutta (12), who found little benefit of supplementation on pregnancy outcomes, including low birth weight (relative risk (RR) = 0.94, 95% confidence interval (CI): 0.83, 1.06), small-for-gestational-age birth (RR = 1.04, 95% CI: 0.93, 1.17), preterm birth (RR = 0.88, 95% CI: 0.76, 1.03), and perinatal mortality (RR = 1.16, 95% CI: 0.95, 1.42).

In Sarlahi District, Nepal, we conducted a randomized, double-masked trial of administration of 4 alternative combinations of micronutrients during pregnancy (folic acid, folic acid-iron, folic acid-iron-zinc, and a multiple micronutrient supplement that contained the foregoing plus 11 other micronutrients), all including vitamin A, versus
vitamin A alone as the control. We found that iron-folic acid supplementation relative to vitamin A alone significantly reduced the prevalence of low birth weight (<2,500 g) by 16% (RR = 0.84, 95% CI: 0.72, 0.99) (4) and the prevalence of maternal anemia during pregnancy and the postpartum period by approximately 50% (95% CI: 34, 66) (13). The multiple micronutrient supplement also lowered these outcomes but not more so than iron-folic acid. There was no impact on fetal loss, and a small apparent reduction in 3-month infant mortality was not significant (RR = 0.80, 95% CI: 0.55, 1.17) for iron-folic acid (14). The relative risk for the multiple micronutrient supplement was 1.14 (95% CI: 0.82, 1.56) for the 3-month infant mortality outcome, indicating little benefit despite the increase in birth weight (14).

We recently completed a follow-up study of the offspring born to women who participated in the original trial in rural Nepal (4, 14), to examine the long-term impact of antenatal/postnatal micronutrient supplementation on childhood survival, growth, and early clinical and biochemical markers of chronic disease. We examined the effects of this intervention on survival among children through early school age (approximately 7 years).

MATERIALS AND METHODS

In 1999–2001, we conducted a randomized, double-masked controlled community trial of antenatal and postnatal micronutrient supplementation in the rural southern plains district of Sarlahi, Nepal, where we have been conducting research over the past 20 years. Details on the trial were published in previous papers (4, 14). The study area was divided into 426 communities called sectors, which served as the unit of randomization in this cluster-randomized trial. Pregnant women received one of the following 4 daily micronutrient supplements in the form of identically shaped, sized, and colored tablets: folic acid (400 μg), folic acid-iron (60 mg of iron in the form of ferrous fumarate), folic acid-iron-zinc (30 mg of zinc sulfate), or a multiple micronutrient supplement containing folic acid-iron-zinc plus vitamin D (10 μg), vitamin E (10 mg), vitamin B₁ (1.6 mg), vitamin B₂ (1.8 mg), niacin (20 mg), vitamin B₆ (2.2 mg), vitamin B₁₂ (2.6 μg), vitamin C (100 mg), vitamin K (65 μg), copper (2.0 mg), and magnesium (100 mg); all 4 supplements included vitamin A. Women who received vitamin A alone (1,000 μg) served as the control group. The supplements were tested midway through the study, and micronutrient concentrations were found to be within 4% of the concentrations expected.

Women in the study were identified early in pregnancy using a urine test-based pregnancy identification surveillance system. After providing consent, women received their daily allocated supplements throughout pregnancy and until 3 months postpartum from female project workers at twice-weekly home visits. The project workers monitored the women’s compliance using tablet counts at each visit and encouraged regular intake of the supplements. Over 1.5 years, 4,926 pregnancies were included in the trial. The pregnancies resulted in 4,130 livebirths, 34 of which were of liveborn twins. A total of 209 children had died by age 3 months (14). The mean number of pregnant women per sector was 11.6 (standard deviation, 5.6). The mean gestational age at enrollment was 11 weeks (standard deviation, 5.1), and the median percentage of compliance with supplement intake (number of supplements consumed out of the total number of days eligible from pregnancy enrollment to 3 months postpartum) was 82 (interquartile range, 63–101) and comparable across treatment groups.

From September 2006 to March 2008, we conducted a follow-up study of all surviving children of women who had participated in the original trial. Because of our continued research in the same study area in the interim period, we had routinely updated our information on household addresses, tracked moves, and conducted vital surveillance. In addition, 3,857 of the surviving children also participated in a placebo-controlled trial of iron-folic acid and/or zinc supplementation during 2001–2005 (15, 16) and were routinely visited for supplementation and vital status assessment, among other things. Thus, in 2006, at the outset, we generated a list of all surviving children for a systematic cross-sectional follow-up.

Three separate teams visited the homes of the children over a period of approximately 18 months. After obtaining consent, the first team collected basic data on household members and their vital status and socioeconomic status. They also conducted blood pressure measurements, interviewed the parents regarding the child’s schooling, and measured the child’s middle upper arm circumference. A second team of trained anthropometrists measured waist circumference, weight, height, and the triceps and subscapular skinfold thicknesses of the children at a second home visit. Dietary intake was assessed using 1-year and 7-day food frequency questionnaires with a list of selected foods generated from our years of collecting similar data in this study area. A 7-day morbidity history of 10 morbidity symptoms was also elicited. A third team conducted fasting venous blood draws and collected other biologic specimens.

At each visit, migrations, refusals, and deaths were recorded. In the event of death, a short history of the death, including the date of death and a parental report of whether the death was due to injury, severe acute illness, or chronic illness or was a sudden death was ascertained. For deaths that occurred during the follow-up period of the parent trial, a detailed verbal autopsy interview was conducted with the parents, followed by review by 2 physicians and assignment of a consensus cause of death. Cause-of-death information was available for 57 deaths, out of which 11 deaths were assigned an “uncertain” cause. The follow-up study received ethical approval from the institutional review boards at Johns Hopkins School of Public Health (Baltimore, Maryland) in the United States and the Institute of Medicine (Kathmandu) in Nepal.

We compared characteristics of children and their households at the time of follow-up by treatment group. Children’s anthropometric data were converted to weight-for-age, height-for-age, and weight-for-height z scores using the international World Health Organization growth standards (17). Twins were included in the analysis, as was done previously, since their exclusion did not change the results. Analyses
Figure 1. Population follow-up and participation in a controlled trial involving alternative combinations of antenatal micronutrient supplements, Nepal, 1999–2008. Excluded women were those who had a false-positive pregnancy test result, an unknown pregnancy outcome, or an induced abortion.
Table 1. Characteristics of Children and Their Households at Follow-up, by Maternal Antenatal Micronutrient Supplementation Group, Nepal, 1999–2008*  

<table>
<thead>
<tr>
<th>Child characteristics</th>
<th>Controls</th>
<th>Folic Acid</th>
<th>Folic Acid-Iron</th>
<th>Folic Acid-Iron-Zinc</th>
<th>Multiple Micronutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at follow-up, years</strong></td>
<td>749 7.5 (0.4)</td>
<td>681 7.5 (0.4)</td>
<td>689 7.4 (0.4)</td>
<td>731 7.5 (0.5)</td>
<td>761 7.5 (0.4)</td>
</tr>
<tr>
<td><strong>Height-for-age z score</strong></td>
<td>698 -1.93 (0.89)</td>
<td>629 -1.89 (0.83)</td>
<td>639 -1.90 (0.88)</td>
<td>661 -1.83 (0.91)</td>
<td>720 -1.93 (0.89)</td>
</tr>
<tr>
<td><strong>Weight-for-age z score</strong></td>
<td>698 -2.11 (0.88)</td>
<td>629 -2.06 (0.82)</td>
<td>639 -2.07 (0.92)</td>
<td>661 -2.08 (0.90)</td>
<td>720 -2.12 (0.90)</td>
</tr>
<tr>
<td><strong>Body mass indexa for-age z score</strong></td>
<td>698 -1.23 (0.87)</td>
<td>629 -1.19 (0.86)</td>
<td>639 -1.19 (0.88)</td>
<td>659 -1.27 (0.84)</td>
<td>720 -1.23 (0.83)</td>
</tr>
<tr>
<td><strong>Middle upper arm circumference, cm</strong></td>
<td>700 15.4 (1.1)</td>
<td>630 15.4 (1.1)</td>
<td>639 15.4 (1.2)</td>
<td>662 15.4 (1.1)</td>
<td>720 15.4 (1.1)</td>
</tr>
<tr>
<td><strong>Receipt of any schooling</strong></td>
<td>452 62.6</td>
<td>438 66.6</td>
<td>465 68.8</td>
<td>489 69.2</td>
<td>473 63.8</td>
</tr>
<tr>
<td><strong>Literacy</strong></td>
<td>129 17.8</td>
<td>100 15.2</td>
<td>100 14.8</td>
<td>140 19.8</td>
<td>110 14.8</td>
</tr>
<tr>
<td><strong>Morbidity in the past 7 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>56 8.0</td>
<td>57 9.0</td>
<td>61 9.4</td>
<td>66 9.9</td>
<td>79 11.0</td>
</tr>
<tr>
<td><strong>Diarrhea (≥4 watery stools/day)</strong></td>
<td>19 2.7</td>
<td>14 2.2</td>
<td>10 1.6</td>
<td>15 2.3</td>
<td>17 2.4</td>
</tr>
<tr>
<td><strong>Productive cough</strong></td>
<td>23 3.3</td>
<td>24 3.8</td>
<td>35 5.4</td>
<td>28 4.2</td>
<td>26 3.6</td>
</tr>
<tr>
<td><strong>Rapid breathing or grunting</strong></td>
<td>18 2.6</td>
<td>22 3.5</td>
<td>16 2.5</td>
<td>28 4.2</td>
<td>20 2.9</td>
</tr>
<tr>
<td><strong>Food intake (any) in the past 7 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dairy products</strong></td>
<td>587 83.2</td>
<td>505 79.6</td>
<td>501 77.5</td>
<td>527 79.5</td>
<td>570 79.1</td>
</tr>
<tr>
<td><strong>Meat</strong></td>
<td>292 41.5</td>
<td>274 43.2</td>
<td>276 42.6</td>
<td>285 42.9</td>
<td>301 41.8</td>
</tr>
<tr>
<td><strong>Fish</strong></td>
<td>237 33.7</td>
<td>234 36.9</td>
<td>207 31.9</td>
<td>225 33.8</td>
<td>212 29.4</td>
</tr>
<tr>
<td><strong>Eggs</strong></td>
<td>111 15.8</td>
<td>89 14.0</td>
<td>92 14.2</td>
<td>114 17.1</td>
<td>94 13.1</td>
</tr>
<tr>
<td><strong>Dark green leaves</strong></td>
<td>506 72.1</td>
<td>442 69.9</td>
<td>507 78.2</td>
<td>487 73.4</td>
<td>531 73.6</td>
</tr>
<tr>
<td><strong>Tea</strong></td>
<td>236 33.6</td>
<td>179 28.3</td>
<td>208 32.1</td>
<td>228 34.4</td>
<td>217 30.1</td>
</tr>
<tr>
<td><strong>Family characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Religion/caste</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hindu</strong></td>
<td>68 8.7</td>
<td>53 7.4</td>
<td>37 5.2</td>
<td>53 7.0</td>
<td>45 5.7</td>
</tr>
<tr>
<td><strong>Brahmin</strong></td>
<td>65 8.3</td>
<td>34 4.8</td>
<td>67 9.4</td>
<td>57 7.6</td>
<td>49 6.2</td>
</tr>
<tr>
<td><strong>Chettri</strong></td>
<td>439 56.1</td>
<td>476 66.6</td>
<td>487 68.5</td>
<td>493 65.5</td>
<td>521 65.8</td>
</tr>
<tr>
<td><strong>Vaiashya</strong></td>
<td>106 13.6</td>
<td>97 13.6</td>
<td>67 9.4</td>
<td>108 14.3</td>
<td>114 14.4</td>
</tr>
<tr>
<td><strong>Shudra</strong></td>
<td>102 13.0</td>
<td>48 6.7</td>
<td>49 6.9</td>
<td>35 4.6</td>
<td>58 7.3</td>
</tr>
<tr>
<td><strong>Muslim</strong></td>
<td>2 0.3</td>
<td>7 1.0</td>
<td>4 0.6</td>
<td>7 0.9</td>
<td>4 0.5</td>
</tr>
<tr>
<td><strong>Buddhist/Christian</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnic group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pahadi</strong></td>
<td>221 28.3</td>
<td>230 32.2</td>
<td>211 29.7</td>
<td>239 31.7</td>
<td>199 25.1</td>
</tr>
<tr>
<td><strong>Madheshi</strong></td>
<td>559 71.5</td>
<td>483 67.6</td>
<td>497 69.9</td>
<td>512 68.0</td>
<td>591 74.6</td>
</tr>
</tbody>
</table>

were conducted on an intent-to-treat basis. Data on mortality from ages 3 months to 7 years and from birth to age 7 years were examined for each of the treatment groups in comparison with controls. Hazard ratios and 95% confidence intervals for both mortality outcomes were calculated using a Cox proportional hazards model with a robust variance estimator, which uses the independence working model for its correlation structure (18) to account for the cluster-randomization design. The mortality rate in the control group was used as the reference category. We conducted the same analyses to examine treatment effects for iron-folic acid and the multiple micronutrient group by category of birth weight (<2,500 g vs. ≥2,500 g), gestational age (<37 weeks vs. ≥37 weeks), maternal age (<19 years vs. ≥19 years), and body mass index (weight (kg)/height (m)^2; <18.5 vs. ≥18.5) at enrollment in the trial. Interaction terms for these variables and the intervention groups were included in the models and tested at the 10% significance level. In addition, maternal intervention effects were adjusted for iron-folic acid and/or zinc supplementation at preschool age, which occurred as part of the subsequent study that enrolled children included in the current analysis, but the child interventions did not change the hazard ratios and were excluded. We also tested the interaction between maternal and child supplementation but found it to be nonsignificant. Across the 2 interventions, there were many cells, and most of the deaths included in the analysis occurred prior to the start of the child supplementation study.

We plotted Kaplan-Meier survival curves (19) by treatment group to visualize the survival differences by treatment group. For each child, we calculated the duration of follow-up in days, using the date of birth and the date of censorship (date of death for those who died). For those lost to follow-up, the date on which their vital status was last known was used as the date of censorship. Thirteen children had missing dates of death. For these children, age at death in years as reported by the parents was used to calculate age of death, assuming that the death had occurred in the middle of the year.

Analyses were performed using SAS, version 9.0 (SAS Institute Inc., Cary, North Carolina), and Stata, version 10.0 (Stata Corporation, College Station, Texas).
Approximately 7 years of age was 0.69 (95% CI: 0.49, 0.99; matched to treatment groups. Children also did not differ by their dietary micronutrient supplement group. Neither supplement per 1,000 child-years in the period from 91 days to approximately, with 95% confidence intervals that included 1.

We examined cause-of-death assignment by physician review for 46 deaths on which data were recorded previously and type of death (categorized as injury-related, due to severe acute illness, due to long-term illness, or sudden) reported by parents at the time of follow-up for another 90 deaths (Table 3). When we combined acute lower respiratory illness, diarrhea/dysentery, sepsis, hepatitis, and severe acute illness as causes of death, suggestive of an “infection-related/acute” cause, the proportionate mortality ratios in the treatment groups ranged from 0.94 to 0.98, with 95% confidence intervals including 1.0. We also combined only stillbirths ($n = 186$) with child deaths and found the hazard ratio for the iron-folic acid group to be 0.73 (95% CI: 0.54, 0.98).

### DISCUSSION

In this study, we found a 31% reduction in childhood mortality due to maternal antenatal/postnatal supplementation.

**Table 2. Rates of Mortality From Birth to Age 7 Years Among Children of Women Who Received Antenatal Micronutrient Supplements, by Supplementation Group, Nepal, 1999–2008**

<table>
<thead>
<tr>
<th>Supplementation Group</th>
<th>Controls</th>
<th>Folic Acid</th>
<th>Folic Acid-Iron</th>
<th>Folic Acid-Iron-Zinc</th>
<th>Multiple Micronutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths occurring from birth to age 7 years</td>
<td>No. of deaths</td>
<td>5,731</td>
<td>5,203</td>
<td>5,219</td>
<td>5,562</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>87</td>
<td>70</td>
<td>54</td>
<td>67</td>
<td>81</td>
</tr>
<tr>
<td>Rate per 1,000 child-years</td>
<td>15.2</td>
<td>13.4</td>
<td>10.3</td>
<td>12.0</td>
<td>14.0</td>
</tr>
<tr>
<td>HR (95% CI)$^a$</td>
<td>1.00</td>
<td>0.90 (0.65, 1.22)</td>
<td>0.69 (0.49, 0.99)</td>
<td>0.80 (0.58, 1.11)</td>
<td>0.93 (0.66, 1.31)</td>
</tr>
<tr>
<td>Deaths occurring between ages 91 days and 7 years</td>
<td>No. of deaths</td>
<td>5,532</td>
<td>5,201</td>
<td>5,217</td>
<td>5,560</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>38</td>
<td>36</td>
<td>20</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Rate per 1,000 child-years</td>
<td>6.9</td>
<td>6.9</td>
<td>3.8</td>
<td>4.8</td>
<td>5.0</td>
</tr>
<tr>
<td>HR (95% CI)$^a$</td>
<td>1.00</td>
<td>1.05 (0.66, 1.67)</td>
<td>0.58 (0.34, 1.00)</td>
<td>0.74 (0.46, 1.19)</td>
<td>0.76 (0.47, 1.23)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

$^a$ Hazard ratios and 95% confidence intervals were calculated using Cox proportional hazards with a robust estimate of variance.
with iron-folic acid plus vitamin A as compared with vitamin A alone, in a setting where maternal iron deficiency and anemia are common. To our knowledge, this is the first time that the long-term effect of maternal iron-folic acid supplementation, normally a global policy for pregnant women, on childhood survival has been observed. The randomized, controlled design of the study provided statistical strength for making causal inferences regarding this effect. The study also achieved a high rate of follow-up of children.

Intermittent administration of large doses of vitamin A to preschool children has been shown to reduce mortality among children under age 5 years by 30% (20). However, beyond this intervention, few trials have been undertaken to examine the impact of direct supplementation with micronutrients on childhood mortality. Iron-folic acid or zinc supplementation to children from ages 1 month to 36 months in the same population in Nepal had no impact on survival (15, 16). A reduction in mortality resulting from an intervention such as antenatal/postnatal iron-folic acid supplementation, as currently exists in many malnutrition settings, provides a new and previously unreported benefit to offspring during childhood.

While the combination of iron-folic acid also contained vitamin A, the impact on mortality is probably due to iron-folic acid alone, since the control group receiving vitamin A alone had a higher mortality rate. However, a positive interaction between the nutrients cannot be ruled out.

Previously, multiple micronutrients have shown no effect or modest effects on birth weight (12), and based on results from 2 South Asian trials that were not independently powered to find an impact on mortality, administration of multiple micronutrients may elevate risks of neonatal and...
survival is probably due to supplementation mostly during
and survival—a window that may close during the post-
fetal period when iron nutriture can influence future health
it is likely that there exists a critical window of time in the
36 months had no impact on childhood mortality (15, 16),
supplementation to these children from ages 1 month to
plausible mechanisms for iron supplementation’s reduc-
ing mortality relative to iron-folic acid (14, 21, 22). One trial conducted in Indonesia, however, showed a signif-
icant 18% reduction in early infant mortality (<3 months)
that was attributed to antenatal/postnatal micronutrient sup-
plementation, as compared with iron-folic acid (23). In the
present analysis, the hazard ratio for mortality from birth to
age 7.5 years was 0.93 for multiple micronutrients versus controls, suggesting that no long-term adverse effect on
mortality occurred. Similarly, the combination of folic acid-iron-zinc had a hazard ratio of 0.80, suggesting potential
inhibition of iron with zinc, which was also seen with the
birth-weight outcome in the original trial (4). Iron was pres-
ent at the same dosage in all 3 preparations. We have previously suggested a potential role of negative nutrient-
nutrient interactions in causing this (14). The hazard ratio
for folic acid alone was 0.89.

Plausible mechanisms for iron supplementation’s reduc-
ing mortality risk are not known at present, although they
may include its effect on birth outcomes such as decreased
low birth weight (4–6) and preterm birth (6), as well as
increases in infant iron stores (24), all of which may have
an impact on long-term survival. Whether maternal iron
status plays a role in the development of fetal immunity
or early programming is not well established, but the plau-
sibility of such a mechanism cannot be overruled. Given
that in this setting of high iron deficiency, where direct
supplementation to these children from ages 1 month to
36 months had no impact on childhood mortality (15, 16),
it is likely that there exists a critical window of time in the
fetal period when iron nutriture can influence future health
and survival—a window that may close during the post-
natal period. As such, the intervention effect on long-term
survival is probably due to supplementation mostly during
pregnancy, not the postpartum period.

Our study suffered from our being unable to obtain med-
ical diagnoses for causes of death. A medical determination
of cause of death is rare in this environment, where most
deaths occur at home and are unattended by physicians.
Relying on parental recall for verbal autopsies has been
considered valid, and we used these data for deaths when
available. However, since many deaths had occurred several
years prior to follow-up, we were able to use only crudely
categorized causes of death as reported by the parents. How-
ever, the available data seemed to indicate that fewer
infectious and severe acute deaths occurred in the folic
acid-iron group than in the control group; the proportionate
mortality ratios for these deaths were 55 and 74, respec-
tively. We also did not collect data on iron status among
children, although we did not expect iron supplementation
during pregnancy to affect the status of children at school
ages. It is also unlikely that the impact on survival was rel-
ated to the 3 months of postnatal supplementation in
women, since breast milk is a poor source of iron for infants.
Overall, despite the significant findings, the sample size we
had was still limited for observation of mortality outcomes,
and we had 50% power to detect a difference of 30% or
more with α = 0.05, assuming a mortality rate of 100 per
1,000 livebirths. In addition, comparison between treatment
groups could not be done because of the overlapping and
wide confidence intervals. For more efficiency, one could
increase the size of the control arm; however, we did not do
this in the original study, which limited our ability to exam-
ine between-group differences for a rarer outcome such as
mortality.

We undertook sensitivity analyses to examine the impact
of losses to follow-up on the study findings, applying 3
different assumptions regarding the survival of those lost
to follow-up: that all survived, that all died, or that half died.
We had 161 children who were lost to follow-up. The relative risks for iron + folic acid ranged from 0.71 (all lost survived) to 0.73 (all lost died), and the 95% confidence interval around 0.73 was (0.50, 0.99), after adjustment for clustering using generalized estimating equations Poisson regression analysis with exchangeable correlation. This analysis suggests that the approximately 30% reduction in mortality we observed in the iron-folic acid group was a robust estimate and not vulnerable to the uncertain vital experience among children lost to follow-up.

We know of 1 other study which involved follow-up of the offspring (at age 2 years) of women who participated in a multiple micronutrient supplementation trial (25). In that study, Vaidya et al. (25) found small but significant increases in body size and weight among children whose mothers had received multiple micronutrients during pregnancy as compared with iron-folic acid alone. More such follow-ups will be required to examine the long-term effects of maternal nutrient interventions on a range of outcomes. These studies would contribute to our understanding of the role of nutrition in the developmental origins of health and disease.

The findings of this study may be generalizable to a large swath of the South Asian population living on the Indian subcontinent, including northern India and Bangladesh, where similar burdens of maternal malnutrition, low birth weight, and childhood infectious morbidity and mortality exist.

In conclusion, these high-compliance follow-up data from a randomized, placebo-controlled trial cohort provide strong evidence for a beneficial effect of antenatal/postnatal iron-folic acid supplementation on childhood survival through early school age, extending previously observed beneficial effects on birth size, anemia, infant iron status, and early infant survival. Currently, use of antenatal iron and folic acid supplement is low, despite existing policies and persistent maternal iron deficiency and anemia, in many regions of the world. The findings reported here provide new impetus for programs to extend and improve coverage with iron and folic acid supplementation as part of routine antenatal care in undernourished and underserved populations in rural South Asia.

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