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

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Summary

Background The negative effects of low birthweight on the later health of children in developing countries have been well studied. However, undertaking programmes to address this issue can be difficult since there is no simple correlation between increasing birthweight and improving child health. In 2005, we published results of a randomised controlled trial in Nepal, in which 1200 women received either iron and folic acid or a supplement that provided the recommended daily allowance of 15 vitamins and minerals, over the second and third trimesters of pregnancy. Here, we report on 2–3 years’ follow-up of children born during the trial.

Methods We visited children at home and obtained data for the primary outcomes of weight and height, for childhood illnesses, and maternal blood haemoglobin. The study is registered as an International Standard Randomised Controlled Trial, number ISRCTN88625934.

Findings Between December, 2005, and December, 2006, we assessed 917 children (455 controls, 462 intervention) at a mean age of 2·5 years. Mean birthweight had been 77 g (95% CI 24–130) greater in the micronutrient group than in controls. At 2·5 years old, controls weighed a mean of 10·7 kg (SD 1·38), and those in the intervention group 10·9 kg (SD 1·54). Children of women who had taken multiple micronutrient supplements during pregnancy were a mean 204 g (95% CI 27–381) heavier than controls. They also had greater measurements than controls in the circumference of the head (2·4 mm [95% CI 0·6–4·3]), chest (3·2 mm [0·4–6·0]), and mid-upper arm (2·4 mm [1·1–3·7]), and in triceps skinfold thickness (2·0 mm [0·0–0·4]). Systolic blood pressure was slightly lower in the intervention group (2·5 mm Hg [0·5–4·6]).

Interpretation In a poor population, the effects of maternal multiple micronutrient supplementation on the fetus persisted into childhood, with increases in both weight and body size. These increases were small, however, since those exposed to micronutrients had an average of 2% higher weight than controls. The public-health implications of changes in weight and blood pressure need to be clarified through further follow-up.

Introduction

The negative effects of abirthweight of less than 2500 g on child morbidity and survival in developing countries have been well described.1–4 What is less clear is what effect interventions to raise birthweight might have on child health. Health strategies have generally been based on the observation that in poor countries, low birthweight is more common in babies who are born at full term than in those born prematurely,5 and that low birthweight might lead to childhood malnutrition.

Creating public-health programmes to tackle this issue has been difficult, however, for three reasons. First, we have not yet managed to get potential interventions to women at risk, at a time of life when they might be helpful, and at a population level.6 Second, increased birthweight is not necessarily followed by increased survival and reductions in morbidity in either newborn babies or children—children with similar weights could differ in mortality rates between populations.7 Third, possible associations between fetal and infant growth and adult disease have made us cautious about increasing infant weight.7

In 2005, we published the results of an individually randomised, double-blind controlled trial in Dhanusha district, Nepal.8 1200 women received either routine iron and folic acid supplements or a multiple micronutrient supplement providing the recommended daily allowance of 15 vitamins and minerals, over the second and third trimesters of pregnancy. Mean birthweights were 2733 g (SD 422) in the control group and 2810 g (SD 453) in the intervention group, representing a difference of 77 g (95% CI 24–130) and a 25% fall in the proportion of low birthweight infants. The groups did not differ in the duration of gestation, infant length, or head circumference.

Nine trials of similar supplementation approaches are being systematically reviewed.8–13 Antenatal multiple micronutrient supplementation probably does increase birthweight, but whether this translates into short-term or long-term health benefits remains uncertain. Important questions include whether the effects of antepartum intervention are sustained, and whether micronutrient repletion improves early childhood growth in a way that
could confer lasting benefit. To answer these questions, we undertook a follow-up of children born in the original trial, at the age of 2–3 years.

**Methods**

**Participants**
In the original trial, we enrolled 1200 participants from an antenatal clinic at Janakpur zonal hospital, in Nepal’s Dhanusha district. The inclusion criteria were gestation of up to 20 completed weeks, based on dates and ultrasound biometry; singleton pregnancy; no notable fetal abnormality on obstetric ultrasound; no existing maternal illness of a severity that could compromise the outcome of the pregnancy; and accessibility for follow-up at home.

After providing signed consent, participants received supplements from enrolment (at no earlier than 12 weeks’ gestation) to delivery. The daily micronutrient supplements were provided in monthly allocations. Participants were followed up every 2 weeks, at birth, and at 1 month postpartum. Anthropometric measures were recorded within 72 h of birth. Allocation was double-blind and randomised to two groups of 600 participants. The control group received tablets containing iron (60 mg) and folic acid (400 µg). The intervention group received tablets containing vitamin A (800 µg), vitamin E (10 mg), vitamin D (5 µg), vitamin B1 (1·4 mg), vitamin B2 (1·4 mg), niacin (18 mg), vitamin B6 (2·6 mg), folic acid (400 µg), vitamin C (70 mg), iron (30 mg), zinc (15 mg), copper (2 mg), selenium (65 µg), and iodine (150 µg). All supplements were manufactured by Danish Pharmaceutical Industries Ltd (Ballerup, Denmark).

The trial was approved by the Nepal Health Research Council, and by the ethics committee of the Institute of Child Health and Great Ormond Street Hospital, UK, and was undertaken in collaboration with the Nepal Government Ministry of Health. Benefits to participants included the supply of supplements, free healthcare, and expedited referral in the event of complications. Information provided by participants remained confidential. Access was restricted to supervisory and research staff at the analytical level. No analyses or outputs included the names of participants.

**Procedures**
Children born in the trial were followed-up at 2·5 years of age by five field workers, one of whom acted as coordinator. Training in anthropometric techniques included taking test measurements of 300 children who were not in the trial. We were particularly keen to keep variation between observers to a minimum since, for example, it accounted for 23% of the variation in head circumference, whereas intra-observer variation accounted for 8%. Final study measurements were therefore restricted to two field workers.

Visiting schedules were set according to the ages of individual children and the need to cover flood-prone areas outside the monsoon season. All participants who had not moved home too far for us to travel to were visited at home up to five times. The field workers were unaware of the initial supplement allocation since access to the codes was restricted to principal investigators. We obtained additional informed verbal consent from mothers and family members to collect follow-up information and measurements. Participants received a towel and a sweet as a token of appreciation.

Primary outcomes were weight and height. Weight was measured with Seca 835 electronic scales (Hamburg, Germany) accurate to 10 g. Standing height was measured with a portable Leicester stadiometer accurate to 1 mm, barefoot and with the head in the auriculo-orbital plane. Secondary outcomes included circumferences of the head, chest, waist, hip, and mid-upper arm, triceps skinfold thickness, and blood pressure.

We also obtained information on childhood illnesses and measured maternal blood haemoglobin. Head and mid-upper arm circumferences were measured with disposable insertion tapes accurate to 1 mm (Harlow

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**Figure:** Trial profile

![Trial Profile Diagram](image-url)
Table 1: Household and participant characteristics at enrolment

| Location          | Control (n=455) | Intervention (n=462) | Lost-to-follow up (n=147) |
|-------------------|-----------------|----------------------|--------------------------|
| Urban             | 227 (49.1%)     | 231 (50.0%)          | 96 (65.3%)               |
| Rural             | 228 (50.1%)     | 231 (50.0%)          | 51 (34.7%)               |
| Land owned        |                 |                      |                          |
| None              | 22 (4.8%)       | 23 (5.0%)            | 11 (7.5%)                |
| <10 kattha (0·3 hectares) | 241 (53.0%)   | 267 (57.8%)          | 81 (55.2%)               |
| >10 kattha         | 192 (42.2%)     | 172 (37.2%)          | 55 (37.4%)               |
| Husband’s occupation |                 |                      |                          |
| No work           | 53 (11.7%)      | 51 (11.0%)           | 16 (10.9%)               |
| Farming           | 71 (15.6%)      | 68 (14.7%)           | 19 (12.9%)               |
| Salaried          | 181 (39.8%)     | 203 (43.9%)          | 71 (48.3%)               |
| Small business    | 83 (18.2%)      | 84 (18.2%)           | 32 (21.7%)               |
| Waged labour      | 53 (11.7%)      | 45 (9.8%)            | 5 (3.4%)                 |
| Student           | 7 (1.5%)        | 5 (1.1%)             | 2 (1.4%)                 |
| Out of country    | 7 (1.5%)        | 6 (1.3%)             | 2 (1.4%)                 |
| Consumer durables |                 |                      |                          |
| Motor vehicle, television, or refrigerator | 243 (53.4%) | 239 (51.5%) | 78 (53.3%) |
| Sewing machine, cassette player, camera, fan, or bullock cart | 26 (5.7%) | 18 (3.9%) | 5 (3.4%) |
| Clock, radio, iron, or bicycle | 122 (26.8%) | 133 (28.8%) | 42 (28.5%) |
| None of the above | 64 (14.1%)      | 73 (15.8%)           | 22 (15.0%)               |
| Schooling         |                 |                      |                          |
| None              | 212 (46.6%)     | 219 (47.4%)          | 45 (30.6%)               |
| Primary           | 40 (8.8%)       | 39 (8.4%)            | 21 (14.3%)               |
| Lower secondary or higher | 203 (44.6%) | 204 (44.2%) | 81 (55.1%) |
| Parity at birth of index child |         |                      |                          |
| 0                 | 217 (47.7%)     | 223 (48.3%)          | 71 (48.3%)               |
| 1                 | 335 (73.9%)     | 330 (73.8%)          | 41 (27.9%)               |
| 2                 | 65 (14.3%)      | 63 (13.6%)           | 23 (15.6%)               |
| 3                 | 26 (5.7%)       | 32 (6.9%)            | 9 (6.1%)                 |
| 4                 | 10 (2.2%)       | 9 (2.0%)             | 1 (0.7%)                 |
| ≥5                | 2 (0.4%)        | 5 (1.1%)             | 2 (1.4%)                 |

Blood pressure was measured with the child on her mother’s lap, with a portable CE0 197 Omron electronic sphygmomanometer (Japan). We measured maternal haemoglobin with a spectrophotometer on finger-prick blood samples using a portable HemoCue AB CE201 (Dronfield, UK), with daily calibration checks. We collected information about the number of illnesses in the first year of life and about specific illnesses in the 14 days preceding the interview. Medical reports were examined where available and verbal autopsy questionnaires were completed in the event of death. We defined loss-to-follow-up as confirmed information that a participant had moved beyond the possibility of visiting, usually to India. Information about participants, their progress, and outcomes, was collected in individual files which were manually checked for completeness. Data were entered into a relational database management system with field validity rules (FileMaker Pro 5.5, USA).

Statistical analysis
The original trial sample size was computed to detect a difference in mean birthweight of 100 g at a power of 90% and a two-sided significance level of 0·05, allowing for 30% loss-to-follow-up. The power of the study would be 81% if the true difference were equal to the 77 g difference observed. We assessed outliers in Data Desk 6.2.1 (Ithaca, NY). The rest of the analysis was done in the Statistical Program for the Social Sciences version 11 (SPSS Inc, USA). Baseline confounders were assessed by inspecting proportions for categorical variables and means for continuous variables. Continuous anthropometric outcomes were compared first through t tests and univariate regression, and then adjusted for potential confounding with multivariate linear regression models. Total upper arm area was estimated as the square of the circumference divided by 4π. The upper-arm fat area was calculated as circumference multiplied by triceps skinfold thickness, and then divided by two, a model reported as consistent with magnetic resonance images.

Role of the funding source
The original study was funded by The Wellcome Trust. The follow-up study was funded by a grant from an anonymous charitable donor. Neither played a part in the study design; the collection, analysis, or interpretation of data; the writing of the report; or the decision to submit the paper for publication.

Results
The figure shows the trial profile. We visited 917 mothers and children from December, 2005, to December, 2006: 455 in the control group and 462 in the intervention group. Retention rates in the control and intervention groups (taking into account discontinuation in the study, fetal loss, stillbirths, infant deaths, post-infancy deaths
and losses-to-follow-up) were 76% and 77%, respectively. Retention rates in children who could potentially have been followed up after the neonatal period were 85% and 86%, respectively.

At follow-up, we identified a neonatal death in the control group that we could not have noted in the first phase. This changed the neonatal mortality rate in the control group (quoted in the original paper as 20.0) to 21.8 (95% CI 11.3–37.8) per 1000 livebirths. The rate in the intervention group remains the same as the initial report, at 30.6 (17.9–48.5). We identified six post-neonatal infant deaths in the control group and four in the intervention group. Infant mortality rates (deaths at younger than 1 year, with a denominator of livebirths minus losses-to-follow-up) were 37.9 (22.6–59.2) per thousand livebirths in the control and 43.4 (27.1–65.6) in the intervention group. Post-neonatal deaths were ascribed to pneumonia (two), diarrhoea (two), meningitis (one), convulsion (two), measles followed by confirmed tuberculosis (one), a hepatic syndrome (one), complications of cleft palate (one), a bleeding disorder (one), and sudden unexplained death overnight (two). Four mothers had died between the postnatal period and follow-up, of burns, pesticide ingestion, head injury after a fall, and a possible haematological malignancy.

Table 1 compares household and participant characteristics at enrolment in the two groups, and in the 147 participants who were lost-to-follow-up at 2 years. Investigation suggests that potential confounders were evenly allocated. Compared with the retained individuals, women lost-to-follow-up were more likely to be urban, had husbands who were salaried or ran small businesses, and have gone to school. They were less likely to own land and have husbands who worked in agriculture or as waged labourers.

Table 2 compares maternal and child characteristics at follow-up. 43% of women were anaemic. 42% had blood haemoglobin levels below 6.8 mmol/L and 1% below 4.3 mmol/L. Just under half of participants had been primigravid in the trial and the outcomes appear robust to adjustment. Thus, we dealt with potentially uneven distribution of confounders, investigated potential confounders were evenly allocated. Compared with the retained individuals, women lost-to-follow-up at 2 years. Investigation suggests that potential confounders were evenly allocated. Compared with the retained individuals, women lost-to-follow-up were more likely to be urban, had husbands who were salaried or ran small businesses, and have gone to school. They were less likely to own land and have husbands who worked in agriculture or as waged labourers.

Table 2 shows the anthropometric findings and summarises four analyses: (1) unadjusted analysis comparing mean measures between the groups; (2) analysis adjusted for the ages of children when the measurements were made; (3) analysis adjusted for age, and also for sex, maternal parity, and gestation at birth—this is an intuitive approach similar to that used in a study from India; and (4) analysis based on a parsimonious model adjusted for age, sex, gestation at birth, maternal weight at enrolment, and maternal education. We used single variables to describe maternal size and social status, on the basis of significance and greatest explanatory effect in univariate analysis. The model accounts for 28% of the variance in child weight at follow-up. Tables 1 and 2 suggest that randomisation dealt with potentially uneven distribution of confounders, and the outcomes appear robust to adjustment. Thus, we will discuss the findings as they are presented after adjustment for age at follow-up.

For children who were followed up, mean gestation at birth was 39.38 (SD 1.70) weeks in the control group and 39.58 (1.57) in the intervention group. 468 (51.0%) were boys and 449 (49.0%) girls. This distribution did not differ between either allocation or loss-to-follow-up. Mean age at follow-up was 2.56 (SD 0.35; range 1.98–3.63) years in the control group and 2.56 (0.35; 1.98–3.85) in the intervention group. Table 3 shows the anthropometric findings and summarises four analyses: (1) unadjusted analysis comparing mean measures between the groups; (2) analysis adjusted for the ages of children when the measurements were made; (3) analysis adjusted for age, and also for sex, maternal parity, and gestation at birth—this is an intuitive approach similar to that used in a study from India; and (4) analysis based on a parsimonious model adjusted for age, sex, gestation at birth, maternal weight at enrolment, and maternal education. We used single variables to describe maternal size and social status, on the basis of significance and greatest explanatory effect in univariate analysis. The model accounts for 28% of the variance in child weight at follow-up. Tables 1 and 2 suggest that randomisation dealt with potentially uneven distribution of confounders, and the outcomes appear robust to adjustment. Thus, we will discuss the findings as they are presented after adjustment for age at follow-up.

The mean weight was 10.7 kg (SD 1.38) in the control group and 10.9 kg (SD 1.54) in the intervention group. Children of women who had taken multiple micronutrient

![Table 2: Maternal and child characteristics at follow-up](image-url)
supplements during pregnancy were a mean 204 g (95% CI 27–381) heavier than controls at 2·5 years of age. Their mean heights did not differ, but their head circumferences were a mean 2·4 mm (0·6–4·3) larger, their chest circumferences a mean 3·2 mm (0·4–6·0) larger, and their hip circumferences a mean 4·0 mm (0·5–7·4) larger. A mean 3·3 mm difference in waist circumference was not significant at the 5% level, and waist-to-hip ratios were no different. Mid-upper arm circumference was a mean 2·4 mm (1·1–3·7) larger, and triceps skinfold thickness a mean 2·0 mm (0·0–0·4) greater. Table 4 shows prenatal and postnatal differences between the groups by comparing unadjusted mean weight, height, and head circumference at birth and at follow-up. Of the 203 g difference in weight between the groups at follow-up, 126 g was accrued in early childhood. The incremental differences in height and head circumference were small: 0·6 mm and 0·7 mm, respectively, in early childhood.

Mean systolic blood pressure was 101·9 mm Hg (SD 17·54, n=454) in the control group and 99·4 mm Hg (SD 17·54, n=460) in the intervention group. Mean diastolic blood pressure was 63·4 mm Hg (SD 13·68, n=460) in the intervention group. Mean diastolic blood pressure was 83·76 (SD 14·71) in (SD 13·68, n=460) in the intervention group. Mean diastolic blood pressure was 83·76 (SD 14·71) in the intervention group. Mean diastolic blood pressure was 83·76 (SD 14·71) in the intervention group. Mean diastolic blood pressure was 83·76 (SD 14·71) in the intervention group.

Table 5 compares weight and height with WHO standards.24 Overall, the mean weight-for-age was 1·70, the mean height-for-age 2·24, and the mean weight-for-height 0·34 Z scores below the median. The intervention group showed a slightly significant increase in weight-for-age (p=0·048) and a non-significant increase in height-for-age (p=0·281), which also resulted in a non-significant difference in weight-for-height (p=0·097).

Table 5 presents a detailed categorical breakdown of these indices, which gives the

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### Table 3: Child anthropometry by allocation group, with four analytic models for differences between group means

| Control (n=455) | Intervention (n=462) | Unadjusted (95% CI) | Adjusted for age at follow-up (95% CI) | Adjusted for age at follow-up, sex, maternal parity, gestation at birth (95% CI) | Adjusted for age at follow-up, sex, gestation at birth, maternal weight at enrolment, maternal education (95% CI) |
|----------------|---------------------|---------------------|---------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Weight (kg)    | 10·69 (1·383)       | 10·90 (1·544)       | 0·203 (0·013 to 0·393)                 | 0·204 (0·027 to 0·381)                                                      | 0·199 (0·027 to 0·370)                                                      |
| Height (cm)    | 83·76 (4·68)        | 84·07 (4·83)        | 0·30 (-0·31 to 0·92)                  | 0·31 (-0·20 to 0·82)                                                        | 0·29 (-0·21 to 0·79)                                                        |
| BMI (kg/m²)    | 15·22 (1·32)        | 15·39 (1·47)        | 0·17 (-0·01 to 0·35)                  | 0·17 (-0·01 to 0·35)                                                        | 0·17 (-0·01 to 0·35)                                                        |
| Head circumference (cm) | 46·40 (1·43) | 46·64 (1·49) | 0·24 (0·06 to 0·43)                  | 0·24 (0·06 to 0·43)                                                        | 0·23 (0·07 to 0·39)                                                        |
| Chest circumference (cm) | 47·96 (2·26) | 48·28 (2·45) | 0·32 (0·01 to 0·66)                  | 0·32 (0·04 to 0·60)                                                        | 0·31 (0·01 to 0·58)                                                        |
| Waist circumference (cm) | 46·48 (2·75) | 46·81 (2·84) | 0·33 (-0·03 to 0·69)                  | 0·33 (-0·01 to 0·68)                                                        | 0·32 (-0·01 to 0·67)                                                        |
| Hip circumference (cm) | 45·95 (2·68) | 46·34 (2·94) | 0·39 (0·03 to 0·76)                  | 0·40 (0·05 to 0·74)                                                        | 0·39 (0·06 to 0·74)                                                        |
| Triceps skinfold thickness (mm) | 6·95 (1·45) | 7·15 (1·61) | 0·20 (0·00 to 0·40)                  | 0·20 (0·00 to 0·40)                                                        | 0·20 (-0·005 to 0·40)                                                       |

Data are mean (SD) unless otherwise indicated. BMI=body-mass index. *p<0·05 †n=461.

### Table 4: Mean measurements at birth and at follow-up, with mean and proportional increments

| Control (n=455) | Intervention (n=462) | Difference between groups (95% CI) | Proportional increase over control group at follow-up |
|----------------|---------------------|----------------------------------|--------------------------------------------------|
| Weight (kg)    | 2·75                 | 1·70                             | 7·95                                             | 2·82                             | 10·90                           | 8·08                             | 0·077 (0·02 to 0·13)              | 0·203 (0·01 to 0·29)              | 0·126 (0·05 to 0·30)              | 1·9%                             |
| Length/height (cm) | 48·79               | 48·79                            | 34·98                                           | 49·03                            | 48·07                           | 35·04                                           | 0·24                             | 0·30                             | 0·06                             | 0·4%                             |
| Head circumference (cm) | 73·65               | 73·65                            | 12·75                                           | 73·82                            | 46·64                           | 12·82                                           | 0·18                             | 0·24                             | 0·07                             | 0·5%                             |

Data are mean (SD) unless otherwise indicated.
impression that differences between the groups might indicate a reduction in mild degrees of underweight, stunting and wasting in the intervention group. None of the differences was significant. Table 5 also shows estimates of mean total upper arm area (TUA) and mean upper arm fat area (UFE), both of which were greater in the intervention group. The upper arm fat percentages (UFE/TUA) were 30.1% in the control and 31.3% in the intervention group, a difference of 1.2%.

Discussion

In our study, children aged 2.5 years whose mothers were given multiple micronutrients during pregnancy were 204 g heavier than children in the control group (iron and folate). Although the difference in height was not significant, circumferences of the head, chest, hip, and mid-upper arm in children exposed to micronutrients were larger and their triceps skinfolds thicker than controls. Children in the micronutrient group were also less likely to be underweight, stunted, or wasted, although these findings were not significant.

We think that the only limitations of the study were that the sample size was insufficient to detect small changes in anthropometric categories against international standards, and that field and budgetary constraints precluded more sophisticated assessments of body composition. Retention was satisfactory. Participants lost-to-follow-up were disproportionately likely to come from a mobile, urban group who had moved out of the study area. The balance between potential confounders and the robustness of the findings to adjustment confirmed the value of blinding and random allocation. Anthropometrical assessments were done by only two observers, and systematic error should also have been distributed by randomisation.

One issue that might have affected the results is that supplement compositions differed in this non-placebo-controlled trial. The supplement doses were chosen to match those used in other trials to optimise comparability and to avoid micronutrient interaction. The iron content of the supplements differed (60 mg in the control and 30 mg in the intervention group) in line with expert opinion, to avoid a possible negative influence on zinc absorption (although this concern might not apply in practice). Possibly, the effects we noted were the result not of the addition of vitamins and minerals, but of a reduction in the dose of iron. The question of potential adverse effects of iron supplementation in general remains unanswered.

Our findings suggested that the gains in size at birth because of multiple micronutrient supplementation during pregnancy were maintained into childhood. They should, however, be kept in perspective, particularly with respect to childhood growth. The adjusted difference of 204 g in mean weight between control and intervention groups represented an increment of 127 g over the 77 g difference that already existed at birth—an overall

### Table 5: Underweight, stunting, and wasting according to WHO standards, and estimates of mean upper arm total and fat areas

|                          | Control group (n=453) | Intervention group (n=462) | Difference (95% CI) | p value |
|--------------------------|-----------------------|----------------------------|---------------------|---------|
| Weight-for-age Z score†  | –1.76 (0.98)*         | –1.63 (1.08)*              | 0.14 (0.001 to 0.27) | 0.048   |
| Height-for-age Z score†  | –2.28 (1.06)*         | –2.20 (1.12)*              | 0.08 (0.06 to 0.22)  | 0.048   |
| Weight-for-height Z score†| –0.40 (1.05)*         | –0.28 (1.12)*              | 0.12 (0.02 to 0.26)  | 0.007   |
| Underweight†             |                       |                            |                     |         |
| Normal†                  | 98 (21.6)             | 124 (26.8)                 | –26 (–53 to 1)       |         |
| Mild underweight§        | 184 (40.6)            | 169 (36.6)                 | 15 (–24 to 54)       |         |
| Moderate underweight¶    | 125 (27.6)            | 125 (27.4)                 | 0 (–18 to 18)        |         |
| Severe underweight||     | 46 (10.2)               | 44 (9.5)                |         |
| Stunting†                |                       |                            |                     |         |
| Normal†                  | 52 (11.5)             | 61 (13.2)                  | –9 (–29 to 8)        |         |
| Mild stunting§           | 129 (28.5)            | 139 (30.1)                 | –10 (–29 to 9)       |         |
| Moderate stunting¶       | 162 (35.7)            | 150 (32.5)                 | 12 (–10 to 36)       |         |
| Severe stunting||        | 110 (24.3)             | 112 (24.2)                |         |
| Wasting†                 |                       |                            |                     |         |
| Normal‡                  | 331 (73.1)            | 354 (76.6)                 | –23 (–54 to 8)       |         |
| Mild wasting§            | 97 (21.4)             | 79 (17.4)                  | 18 (–3 to 35)        |         |
| Moderate wasting¶        | 19 (4.2)              | 25 (5.4)                   | –6 (–21 to 8)        |         |
| Severe wasting||         | 6 (1.3)                | 4 (0.9)                   |         |
| Total upper arm area (cm²)**| 16.07 (2.24)          | 16.63 (2.50)              | 0.56 (0.25 to 0.87)  | 0.0004  |
| Upper arm fat area estimate (cm²)††| 4.96 (1.23)         | 5.20 (1.43)                | 0.24 (0.07 to 0.41)  | 0.007   |

*Mean (SD); all other data are n (%). †Comparisons with WHO standards. **Calculated according to equations in reference 20. ††Calculated according to equations in reference 21.
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1.9% gain over the mean control group weight. Likewise, the postnatal increments in height and head circumference were only 0.6 mm and 0.7 mm, respectively (0.4% and 0.5% gains over the control group measures).

We think that the findings raise two key questions. First, were the children in the intervention group more healthy? Mothers’ recall of their children’s illnesses during infancy and the 2 weeks before the interview did not support this hypothesis, but it is quite possible that health had been affected in more subtle ways. We are particularly keen to assess the children’s development in further follow-up studies. The increment in head circumference in the micronutrient group could indicate a difference in brain growth and the potential for improved cognitive performance.28 Equally, it might be explained by extracranial adiposity. A second question is whether the sustained gain in size is associated with physiological changes. This possibility is intriguing given the rapid increase in research into the developmental origins of health and adult disease.29 The small but significant decrease in systolic blood pressure in the multiple micronutrient group suggests it might have implications for the development of adult hypertension. Again, we do not want to over-interpolate a single finding and need to follow up trial cohorts.

Previously, our awareness of the burden of low birthweight and childhood malnutrition would have made us optimistic about the effects of greater fetal, infant, and childhood growth on subsequent illness and mortality. Research over the past decade, however, raises questions about this assumption. We lack evidence to show that increasing weight at birth—and the subsequent tracking shown in this study—will translate into substantial improvements in child survival. We have raised the possibility of an imbalance in stillbirths and substantial improvements in child survival. We have optimistic about the effects of greater fetal, infant, and childhood malnutrition would have to be examined in larger datasets.

Children such as those in our trial might show a predictive adaptive physiological phenotype that turns out to be mismatched with their later nutritional experience.30 In simple terms, South Asian children, though apparently small and thin, may have an intrinsic susceptibility to harmful patterns of fat deposition in situations of nutritional plenty.31 The children born in our study are generally lighter, shorter, and more wasted than children in affluent populations. Has fetal multiple micronutrient supply had generalised effects on growth, with potentially beneficial increments in lean body mass, or has it translated into increased adiposity? The biggest difference between the two groups was in weight for age, and the estimates of upper arm composition suggest a small but significant increase in adiposity.

We are only beginning to unravel the longer-term effects of increasing body mass. Its distal effects on health—cognitive performance, childhood illness and mortality, and later blood pressure—might be beneficial, but we need further follow-up and larger studies to confirm our findings.

Contributors
AV coordinated the study and data entry, cleaned the data, did the analysis, and produced the first draft of the paper. NS advised on design and implementation and co-coordinated field and data management. BPS supervised field activities and was the programme manager in Dhanusha. DSM, AMC, and DO were principal investigators. DSM had overall responsibility for the study in Nepal. AMC had overall responsibility for UK partner contributions to the research programme. DO conceived the study and supervised the analysis. All authors contributed to critique and modification of the manuscript.

Conflict of interest statement
None of the authors has a conflict of interest. DO had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments
We thank the participants and their families for their continuing involvement in the trial; the field-team members, Shiv Shanker Chauhe, Gagan Dev Chauhe, Chandra Maya Thapa, Durna Thapa, and Anupa Regmi, who also entered data; Badri Gyawale for field transport; the staff of the Dhanusha District Public Health Office for their support; the co-investigators on the original trial, Ramesh K Adhikari, Suzanne Filteau, and Andrew Tomkins; and our four anonymous reviewers, whose guidance led to substantial improvements in the paper.

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