# Effects of antenatal multiple micronutrient supplementation on children's weight and size at 2 years: follow-up of a double-blind randomized controlled trial in Nepal

## Authors

Anjana Vaidya, Naomi Saville, Bhim Prasad Shrestha, Anthony M de L Costello, Dharma S Manandhar, David Osrin

UCL Centre for International Health and Development, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK (N Saville PhD, Prof A Costello FRCP, D Osrin MRCP PhD)

Mother and Infant Research Activities (MIRA), PO Box 921, Kathmandu, Nepal (A Vaidya MD, B Shrestha MSc, Prof D Manandhar FRCP)

## Corresponding author

Dr David Osrin. UCL Centre for International Health and Development, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

tel 020 7905 2261, fax 020 7404 2062, d.osrin@ich.ucl.ac.uk

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## Summary

**Background** In an individually randomized, double-blind controlled trial in Dhanusha district, Nepal, 1200 participants received either iron and folic acid or a supplement providing a recommended daily allowance of 15 vitamins and minerals, over the second and third trimesters of pregnancy. Mean birthweight was 77 g (95% CI 24, 130 g) greater in the multiple micronutrient group. We followed up children born in the trial at the age of 2-3 years.

**Methods** Children were visited at home and anthropometric data collected, primary outcomes being weight and height. The study is registered as an International Standard Randomised Controlled Trial, number ISRCTN88625934.

**Findings** 917 children were measured at a mean age of 2.5 years. Mean weights were 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 supplements during pregnancy were a mean 204 g (95% CI 27, 381) heavier than controls. This was accompanied by increments in head circumference (2.4 mm [0.6, 4.3]), chest circumference (3.2 mm [0.4, 6.0]), mid-upper arm circumference (2.4 mm [1.1, 3.7]), and triceps skinfold thickness (2.0 mm [0.0, 0.4]). Systolic blood pressure was slightly lower in the intervention group (2.5 mmHg [0.5, 4.6]).

**Interpretation** In a poor population, the effects of maternal multiple micronutrient supplementation persisted into childhood, with increases in both weight and body size. These increases were relatively small, the mean weight increment representing a 2% increase over the control group. The public health implications of changes in adiposity and blood pressure need to be clarified through further follow-up.

*261 words*

## Introduction

The literature on the burden and effects of low birthweight in developing countries is large. Epidemiological associations and effects on morbidity and survival of a birthweight of less than 2500 g have been well described.[1-3] What is less clear is what to do about it, and what effects interventions might have on subsequent childhood outcomes. Strategies have generally followed from the observation that most low birthweight in poor countries occurs in term, rather than preterm, infants,[4] and that this is a forerunner to childhood malnutrition. Converting a fetal and infant growth agenda into operable public health programmes has been problematic, however, for three reasons. First, the translation of efficacious interventions into effective programmes has eluded us.[5] Second, it does not necessarily follow that increased birthweight will be accompanied by increased survival and reductions in morbidity, in either the newborn period or later childhood. There may even be differential mortality at given weights in different populations.[6] Third, ideas about the fetal or developmental origins of health and adult disease have made us wary of increasing infant weight for its own sake.[7]

In 2005, we published the results of an individually randomized, double-blind controlled trial in Dhanusha district, Nepal.[8] 1200 participants received either routine iron and folic acid supplements or a multiple micronutrient supplement providing a 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 g) and a 25% fall in the proportion of low birthweight. There was no difference in the duration of gestation, infant length, or head circumference.

Nine trials of similar supplementation approaches have been examined in a systematic review whose results are pending.[8-18] It is likely that antenatal multiple micronutrient supplementation does increase birthweight, but it remains unclear whether this translates into either short- or longer-term health benefits. Important questions include whether the effects of antepartum intervention are sustained, and whether micronutrient repletion improves early childhood growth in a way that may confer lasting benefit. To answer these questions, we followed up children, born in the original trial, at the age of 2-3 years.

## Participants and methods

*Study location and population*

The original trial has been described.[8] Briefly, we enrolled participants from an antenatal clinic at Janakpur zonal hospital, Dhanusha, in Nepal's southern *terai* region. The inclusion criteria were (a) gestation of up to 20 completed weeks, based on dates and ultrasound biometry, (b) singleton pregnancy, (c) no notable fetal abnormality on obstetric ultrasound, (d) no existing maternal illness of a severity that could compromise the outcome of pregnancy, and (e) accessibility for follow-up at home. After 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 two weeks, at birth and at one month postpartum. Anthropometric measures were recorded within 72 hours of birth. Allocation was double-blind and randomized 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 $B_1$ 1.4 mg, vitamin $B_2$ 1.4 mg, niacin 18 mg, vitamin $B_6$ 1.9 mg, vitamin $B_{12}$ 2.6 μg, folic acid 400 μg, vitamin C 70 mg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 μg, and iodine 150 μg.[19] All supplements were manufactured by Danish Pharmaceutical Industries Ltd (DK 2750 Ballerup, Denmark).

The trial was approved by the Nepal Health Research Council and the ethics committee of the Institute of Child Health and Great Ormond Street Hospital for Children, UK, and was conducted in collaboration with the Nepal Government Ministry of Health. Benefits to participants included the supply of supplements, free health care, 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 technique involved pilot measurements on 300 non-trial children. We were particularly concerned to minimise inter-observer variation since, for example, it accounted for 23% of the variation in head circumference, while intra-observer variation accounted for 8%. Final study measurements were therefore restricted to two female 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 relocated beyond the possibility of follow-up were visited at home, a process that required up to five visits. The field workers were unaware of the initial supplement allocation as access to

the codes was restricted to principal investigators. With signed consent for the original trial, we obtained 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 for their involvement.

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 Frankfurt plane. Secondary outcomes included head, chest, waist, hip and mid-upper arm circumferences, triceps skinfold thickness and blood pressure. We also collected 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 Printing Ltd, South Shields, Tyne and Wear). Head circumference was taken at the maximum occipito-frontal measurement. Mid-upper arm circumference was measured at a level midway between the tip of the olecranon process and the acromion process. Chest, waist and hip circumferences were measured with a plastic measuring tape accurate to 1 mm. Chest circumference was measured at the level of the nipples, midway between inspiration and expiration during quiet breathing. Waist circumference was measured at the level of the natural waist, and hip circumference at the level of maximum circumference over the buttocks. Triceps skinfold thickness was measured with Harpenden callipers accurate to 1 mm (CEO 120, UK). The measurement was taken midway between the tip of the olecranon process and the acromion process, in the midline of the posterior surface of the extended dominant arm. All measurements except weight and height were made three times and the middle value recorded for analysis.

Blood pressure was measured with the child on her mother's lap, with a portable CE0 197 Omron electronic sphygmomanometer (Japan). We assayed maternal haemoglobin spectrophotometrically on finger-prick blood samples with 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 mortality. 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 0.9 and a two-sided significance level of 0.05, with an allowance for 30% loss to follow-up. The power of the study would be 0.81 if the true difference were equal to the 77 g difference observed. Data were analyzed by intention to treat. We examined 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 and means for continuous variables. Continuous anthropometric outcomes were compared first through t-tests and univariate regression, and subsequently adjusted for potential confounding with multivariate linear regression models. Statistical significance was ascribed at a two-tailed *alpha* of 0.05 and is presented in terms of both *p* values and 95% confidence intervals for means. Total upper arm area was estimated as $(\text{circumference}^2)/4\pi$.[20] Upper arm fat area estimate was calculated as circumference*(triceps skinfold thickness)/2, a model reported as consistent with magnetic resonance images.[21]

*Role of the funding source*

The original study was funded by a project grant from The Wellcome Trust. The follow-up study was conducted under a grant from an anonymous charitable donor. Neither played a part in the study design, the collection, analysis, and 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 located and visited 917 mothers and children from December 2005 to December 2006: 455 in the control group and 462 in the intervention group. Retention rates from enrolment (after discontinuation, fetal loss, stillbirths, infant deaths, post-infancy deaths and loss to follow-up) were 76% and 77% respectively. Retention rates of children who could potentially have been followed up after the neonatal period were 85% in the control and 86% in the intervention group.

At follow-up, we identified a neonatal death in the control group that had occurred beyond our capacity to find it in the first phase. This changes the neonatal mortality rate in the control group (quoted in the original paper as 20.0)[8,22] to 21.8 (95% CI 11.3, 37.8) per thousand live births. 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 below a year of age, with a denominator of live births minus loss to follow-up) were 37.9 (22.6, 59.2) per thousand live births in the control and 43.4 (27.1, 65.6) in the intervention group. Post-neonatal deaths were ascribed to pneumonia (2), diarrhoea (2), meningitis, convulsions (2), measles followed by confirmed tuberculosis, a hepatitic syndrome, complications of cleft palate, a bleeding disorder and sudden unexplained death overnight (2). 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 allocation groups, and in the 147 participants who were lost to follow-up at two years. Inspection suggests that potential confounders were evenly allocated. Compared with the retained groups, women lost to follow-up were more likely to be urban, have 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 between the two allocation groups at follow-up. 43% of women were anaemic. 42% had blood haemoglobin levels below 110 g/L and 1% below 70 g/dL. Just under half of participants had been primigravid in the trial and there were no appreciable differences between maternal anthropometric findings. 94% of infants had been breastfed. The mean ages of introduction of other liquids, cow's milk or regular solids did not differ between the allocation groups. Reported morbidity was common: 35% of children were described as having had fever, and 36% as having had a cough, in the fortnight preceding the interview. We found no difference between the groups in reports of illness in either the preceding 14 days or the first year of life. Immunisation levels were equivalent and high, with reporting of over 90% for BCG, 99% for OPV and DPT 1-3, and 98% for

measles. The most recent inclusion in the schedule – hepatitis B immunisation – was reported at rates of over 93% for all three doses.

For children 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. There was no appreciable difference in this distribution 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 (SD 0.35, range 1.98 – 3.85) in the intervention group. Table 3 presents the anthropometric findings and summarises four analyses. (1) An unadjusted analysis comparing mean measures between the groups. (2) An analysis adjusted for the ages of children when the measurements were made. (3) An 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 recent study from India.[23] (4) An analysis based on a parsimonious model adjusted for age, sex, gestation at birth, maternal weight at enrolment and maternal education. We have used single variables to describe maternal size and social status, based on significance and greatest explanatory effect in univariate analysis. The model explains 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. For this reason, 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 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 did not attain significance at the 5% level, and waist/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 examines prenatal and postnatal differences between the allocation groups by comparing unadjusted mean weight, height and head circumference at birth and at follow-up. Of the 203 g difference between the groups at follow-up, 126 g 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 mmHg (SD 17.54, n=454) in the control group and 99.4 mmHg (SD 13.68, n=460) in the intervention group. Mean diastolic blood pressure was 63.4 mmHg (SD 14.71) in the control group and 62.05 (SD 12.80) in the intervention group. Children of women who had taken

multiple micronutrient supplements during pregnancy had systolic blood pressures a mean 2.5 mmHg (95% CI 0.47, 4.55) lower than controls, but there was no difference in mean diastolic blood pressure (-1.5 mmHg [-3.1, 0.4]).

Table 5 compares weight and height with WHO standards.[24,25] 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 marginally significant increase in weight-for-age (p 0.048) and a non-significant increase in height-for-age (p 0.281), reflected in a non-significant difference in weight-for-height (p 0.097). Defining the cut-offs for underweight, stunting and wasting as 2 Z scores below the medians for weight-for-age, height-for-age and weight-for-height respectively, the overall rate of underweight was 37.2% (340/915), of stunting 58.4% (534/915) and of wasting 5.9% (54/915). None of these rates achieved a significant difference between the two groups. Table 5 presents a detailed categorical breakdown of these indices, which gives the impression that differences between the groups might reflect a reduction in mild degrees of underweight, stunting and wasting. None of the differences was significant. Table 5 also presents estimates of mean total upper arm area (TUA)[20] and mean upper arm fat area estimate (UFE),[21] 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

We followed up children born in a double-blind randomised controlled trial in which their mothers received either iron and folate or multiple micronutrient supplements during pregnancy. At a mean 2.5 years old, children in the multiple micronutrient group were 204 g heavier than controls and, although the difference in height was not significant, their head, chest, hip and mid-upper arm circumferences were larger and their triceps skinfolds thicker. Children in the multiple micronutrient group were less likely to be underweight, stunted or wasted, although these findings did not reach significance.

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

One point of contention is the difference between supplement compositions in a trial that was not placebo-controlled. The supplements were tailored to match those used in other trials to optimise comparability, and there are issues of micronutrient interaction. The iron content of the supplements differed in line with expert opinion (60 mg in the control and 30 mg in the intervention group),[19] which recommended a limitation in iron to avoid a possible negative influence on zinc absorption (although this theoretical concern may not apply in practice[26]). It is also conceivable that the effects we saw 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 remains open.[27]

Our findings suggest that the gains in size at birth afforded by multiple micronutrient supplementation during pregnancy are maintained into childhood. They should, however, be kept in perspective, particularly as regards childhood growth. The adjusted difference in mean weight between control and intervention groups represented an increment of 127 g over the 77 g difference that already existed at birth, and the total 204 g difference translates into a 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). Perspective notwithstanding, we think that the findings raise two interesting questions. First, are the children in the intervention group more healthy? Mothers' recall of their children's illnesses during infancy and the two weeks preceding 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 child development in further follow-up studies. The observed increment in head circumference might reflect 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 growth of 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 is fascinating: might it have implications for the development of adult hypertension? Again, we do not want to over-interpret 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. Recent work, 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 neonatal deaths between the allocation groups.[22] The slight alteration to our original neonatal mortality findings is mildly reassuring, as is the similarity of aggregate infant mortality rates between the allocation groups. However, neonatal mortality remained 40% higher in the intervention group and we emphasise again that mortality needs to be examined in larger datasets.

We are only beginning to unravel the longer-term effects of increasing body mass. Children such as those in our trial may 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.

In a poor southern Nepalese population, the effects of maternal multiple micronutrient supplementation on fetal weight persist into childhood. It appears that both weight and body size are increased. The distal effects on health – cognitive performance, childhood illness and mortality, later blood pressure – may have population benefits, but we need further follow-up and larger studies to confirm our findings.

## Contributors

A Vaidya coordinated the study and data entry, cleaned the data, did the analysis and produced the first draft of the paper. N Saville advised on design and implementation and co-coordinated field and data management. BP Shrestha supervised field activities and was the programme manager in Dhanusha. DS Manandhar, AM Costello and D Osrin were principal investigators. DS Manandhar had overall responsibility for the study in Nepal. AM Costello had overall responsibility for UK partner contributions to the research programme. D Osrin 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. D Osrin had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Figure: Trial profile

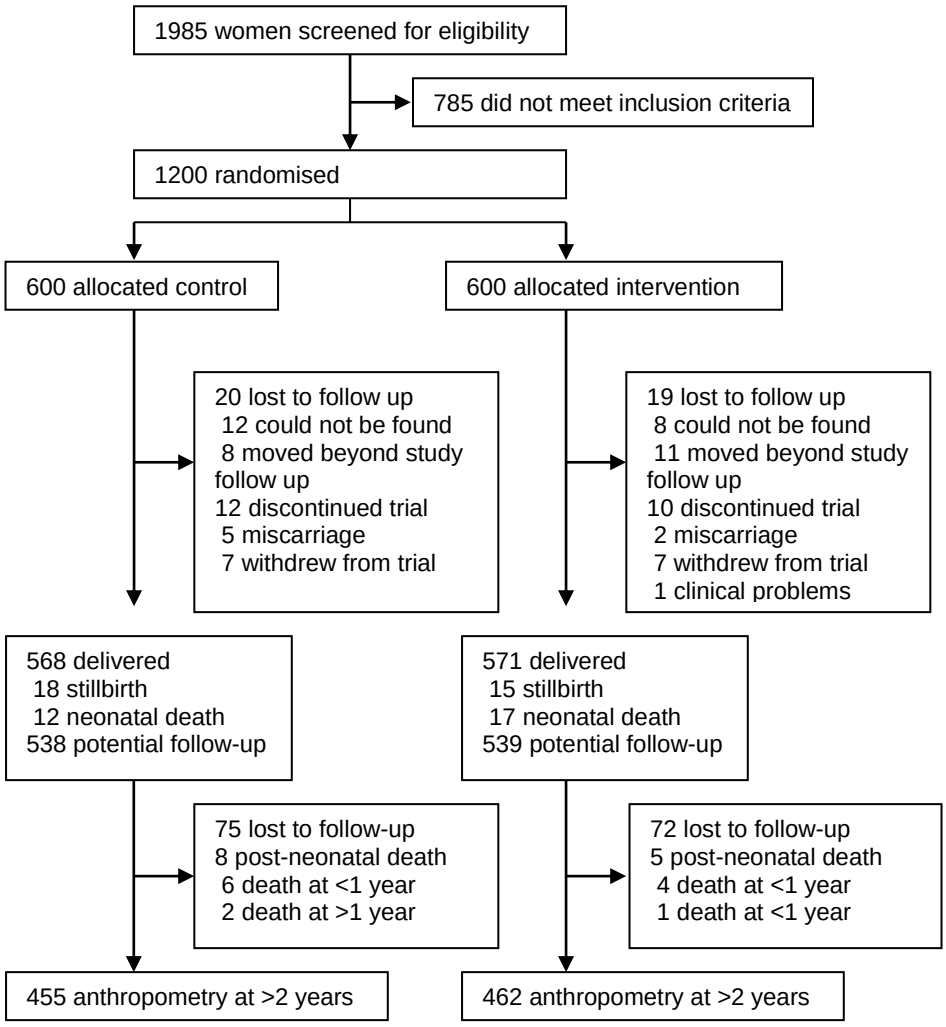

**Table 1: Household and participant characteristics at enrolment, by allocation group**

| | Control (n=455) | Intervention (n=462) | Lost to follow up (n=147) |
|---|---|---|---|
| ***Household*** | | | |
| **Location** | | | |
| Urban | 227 (49.9%) | 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 (55.1%) |
| >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, refrigerator | 243 (53.4%) | 239 (51.5%) | 78 (53.1%) |
| Sewing machine, cassette player, camera, fan, bullock cart | 26 (5.7%) | 18 (3.9%) | 5 (3.4%) |
| Clock, radio, iron, bicycle | 122 (26.8%) | 133 (28.8%) | 42 (28.5%) |
| None of the above | 64 (14.1%) | 73 (15.8%) | 22 (15.0%) |
| ***Participant*** | | | |
| **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 | 135 (29.7%) | 130 (28.1%) | 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%) |

**Table 2: Maternal and child characteristics at follow-up, by allocation group**

| | Control | Intervention |
|---|---|---|
| Mothers | | |
| Age (y) | 24.5 (3.44) [n=455] | 24.6 (3.52) [n=452] |
| Weight (Kg) | 45.8 (7.26) [n=452] | 45.8 (7.38) [n=457] |
| Height (cm) | 150.6 (5.36) [n=452] | 149.8 (5.65) [n=455] |
| Body mass index (Kg/m$^2$) | 20.4 (4.98) [n=452] | 20.4 (2.86) [n=455] |
| Haemoglobin (g/L) | 112.5 (12.7) [n=452] | 112.2 (13.4) [n=456] |
| Had another pregnancy since the trial pregnancy | 159 (34.9%) | 155 (33.5%) |
| Age of infant from subsequent pregnancy in weeks | 29.12 (18.4) | 31.70 (21.3) |
| | | |
| Children | | |
| Breastfed | 432 (94.9%) | 433 (93.7%) |
| Age at introduction of other liquids (months) | 4.04 (2.62) | 4.04 (2.71) |
| Age at introduction of other milk (months) | 8.6 (5.0) | 8.4 (4.9) |
| Age at introduction of regular solids (months) | 8.4 (3.5) | 8.5 (3.3) |
| Reported illnesses in preceding 2 weeks | | |
| Fever | 160 (35.2%) [n=454] | 162 (35.1%) [n=462] |
| Cough | 162 (35.7%) [n=454] | 166 (35.9%) [n=462] |
| Diarrhoea | 66 (14.5%) [n=454] | 59 (12.8)% [n=462] |
| Difficulty breathing | 31 (6.8%) [n=453] | 39 (8.4%) [n=462] |
| Illness in first year | | |
| Less than 5 episodes | 223 (50.5%) [n=442] | 237 (52.4%) [n=452] |
| 5 or more episodes | 219 (49.5%) | 215 (47.6%) |

Data are mean (SD) unless otherwise indicated

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

| | lControl n=455 | Intervention n=462 | Difference between groups (95% CI) | | | |
|---|---|---|---|---|---|---|
| | | | Unadjusted | Adjusted for age at follow-up | Adjusted for age at follow-up, sex, maternal parity, gestation at birth | Adjusted for age at follow-up, sex, gestation at birth, maternal weight at enrolment, maternal education |
| Weight (Kg) | 10.697 (1.383) | 10.900 (1.544) | 0.203 (0.013, 0.393) p 0.036 | 0.204 (0.027, 0.381) p 0.024 | 0.199 (0.027, 0.370) p 0.023 | 0.194 (0.038, 0.350) p 0.015 |
| Height (cm) | 83.76 (4.68) | 84.07 (4.83) | 0.30 (-0.31, 0.92) p 0.33 | 0.31 (-0.20, 0.82) p 0.237 | 0.29 (-0.21, 0.79) p 0.254 | 0.28 (-0.17, 0.73) p 0.226 |
| BMI (Kg/m$^2$) | 15.22 (1.32) | 15.39 (1.47) | 0.17 (-0.01, 0.35) p 0.07 | 0.17 (-0.01, 0.35) p 0.07 | 0.17 (-0.01, 0.34) p 0.07 | 0.16 (-0.01, 0.34) p 0.07 |
| Head Circumference (cm) | 46.40 (1.43) | 46.64 (1.49) | 0.24 (0.06, 0.43) p 0.01 | 0.24 (0.06, 0.43) p 0.01 | 0.23 (0.07, 0.40) p 0.006 | 0.23 (0.07, 0.39) p 0.005 |
| Chest Circumference (cm) | 47.96 (2.26) | 48.28 (2.45) | 0.32 (0.01, 0.66) p 0.04 | 0.32 (0.04, 0.60) p 0.03 | 0.31 (0.03, 0.58) p 0.03 | 0.30 (0.04, 0.56) p 0.02 |
| Waist Circumference (cm) | 46.48 (2.75) | 46.81 (2.84) | 0.33 (-0.03, 0.69) p 0.07 | 0.33 (-0.01, 0.68) p 0.06 | 0.33 (-0.01, 0.67) p 0.06 | 0.32 (-0.01, 0.65) p 0.06 |
| Hip Circumference (cm) | 45.95 (2.68) | 46.34 (2.94) [n=461] | 0.39 (0.03, 0.76) p 0.03 | 0.40 (0.05, 0.74) p 0.02 | 0.39 (0.05, 0.74) p 0.03 | 0.39 (0.06, 0.71) p 0.02 |
| Mid-upper arm circumference (cm) | 14.18 (0.99) | 14.42 (1.07) | 0.24 (0.11, 0.37) P 0.00 | 0.24 (0.11, 0.37) p 0.00 | 0.24 (0.11, 0.37) p 0.000 | 0.24 (0.11, 0.36) p 0.000 |
| Triceps skinfold thickness (mm) | 6.95 (1.45) | 7.15 (1.61) [n=461] | 0.20 (0.00, 0.40) p 0.049 | 0.20 (0.00, 0.40) p 0.049 | 0.20 (-0.005, 0.40) p0.045 | 0.20 (-0.004, 0.40) p 0.045 |

Data are mean (SD) unless otherwise indicated

BMI: body mass index

**Table 4: Mean measurements at birth and at follow-up, with mean and proportional increments, by allocation group**

| | Control n=455 | | | Intervention n=462 | | | Difference between groups (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | At birth | At follow-up | Increment | At birth | At follow-up | Increment | At birth | At follow-up | Increment | Proportional increase over control group at follow-up |
| Weight (Kg) | 2.75 (0.41) | 10.70 (1.38) | 7.95 (1.28) | 2.82 (0.43) | 10.90 (1.54) | 8.08 (1.47) | 0.077 (0.02, 0.13) | 0.203 (0.01, 0.39) | 0.126 (0.05, 0.30) | 1.9% |
| Length/height (cm) | 48.79 (3.23) | 83.76 (4.68) | 34.98 (5.07) | 49.03 (3.14) | 84.07 (4.83) | 35.04 (5.14) | 0.24 (-0.17, 0.65) | 0.30 (-0.31, 0.92) | 0.06 (-0.60, 0.73) | 0.4% |
| Head circumference (cm) | 33.65 (2.21) | 46.40 (1.43) | 12.75 (2.35) | 33.82 (2.24) | 46.64 (1.49) | 12.82 (2.38) | 0.18 (-0.11, 0.47) | 0.24 (0.06, 0.43) | 0.07 (-0.23, 0.38) | 0.5% |

Data are mean (SD) unless otherwise indicated

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

| | Control group (n=453) | Intervention group (n=462) | Difference (95% CI) |
|---|---|---|---|
| Weight for Age Z score (Mean [SD])[1] | -1.76 (0.98) | -1.63 (1.08) | 0.14 (0.001, 0.27) p 0.048 |
| Height for Age Z score (Mean [SD]) [1] | -2.28 (1.06) | -2.20 (1.12) | 0.08 (-0.06, 0.22) p 0.281 |
| Weight for Height Z score (Mean [SD]) [1] | -0.40 (1.05) | -0.28 (1.12) | 0.12 (-0.02, 0.26) p 0.097 |
| Underweight (n [%])[1] | | | |
| Normal (≥ -1 z scores) | 98 (21.6) | 124 (26.8) | |
| Mild underweight (<-1 - -2 z scores) | 184 (40.6) | 169 (36.6) | |
| Moderate underweight (<-2 - -3 z scores) | 125 (27.6) | 125 (27.1) | |
| Severe weight (< -3 z score) | 46 (10.2) | 44 (9.5) | |
| Stunting (n [%])[1] | | | |
| Normal (≥ -1 z scores) | 52 (11.5) | 61 (13.2) | |
| Mild stunting (<-1 - -2 z scores) | 129 (28.5) | 139 (30.1) | |
| Moderate stunting (<-2 - -3 z scores) | 162 (35.7) | 150 (32.5) | |
| Severe stunting(< -3 z score) | 110 (24.3) | 112 (24.2) | |
| Wasting (n [%])[1] | | | |
| Normal (≥ -1 z score) | 331 (73.1) | 354 (76.6) | |
| Mild wasting (<-1 - -2 z score) | 97 (21.4) | 79 (17.1) | |
| Moderate wasting (<-2 - -3 z score) | 19 (4.2) | 25 (5.4) | |
| Severe wasting (< -3 z score) | 6 (1.3) | 4 (0.9) | |
| Total upper arm area ($cm^2$) [2] | 16.07 (2.24) | 16.63 (2.50) | 0.56 (0.25, 0.87) p 0.0004 |
| Upper arm fat area estimate ($cm^2$) [3] | 4.96 (1.23) | 5.20 (1.43) | 0.24 (0.07, 0.41) p 0.007 |

[1] Comparisons with WHO standards.[24,25]

[2] According to equations in [20].

[3] According to equations in [21].