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Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial

The Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT) Study Group‡

Summary

Background

Maternal nutrient supplementation in developing countries is generally restricted to provision of iron and folic acid (IFA). Change in practice toward supplementation with multiple micronutrients (MMN) has been hindered by little evidence of the effects of MMN on fetal loss and infant death. We assessed the effect of maternal supplementation with MMN, compared with IFA, on fetal loss and infant death in the setting of routine prenatal care services.

Methods

In a double-blind cluster-randomised trial in Lombok, Indonesia, we randomly assigned 262 midwives to distribute IFA (n=15 486) or MMN (n=15 804) supplements to 31 290 pregnant women through government prenatal care services that were strengthened by training and community-based advocacy. Women obtained supplements, to be taken daily, every month from enrolment to 90 days post partum. The primary outcome was early infant mortality (deaths until 90 days post partum). Secondary outcomes were neonatal mortality, fetal loss (abortions and stillbirths), and low birthweight. Analysis was by intention to treat. The study is registered as an International Standard Randomised Controlled Trial, number ISRCTN34151616.

Findings

Infants of women consuming MMN supplements had an 18% reduction in early infant mortality compared with those of women given IFA (35·5 deaths per 1000 livebirths *vs* 43 per 1000; relative risk [RR] 0·82, 95% CI 0·70—0·95, p=0·010). Infants whose mothers were

undernourished (mid upper arm circumference <23·5 cm) or anaemic (haemoglobin <110 g/L) at enrolment had a reduction in early infant mortality of 25% (RR 0·75, 0·62—0·90, p=0·0021) and 38% (RR 0·62, 0·49—0·78, p<0·0001), respectively. Combined fetal loss and neonatal deaths were reduced by 11% (RR 0·89, 0·81—1·00, p=0·045), with significant effects in undernourished (RR 0·85, 0·73—0·98, p=0·022) or anaemic (RR 0·71, 0·58—0·87, p=0·0010) women. A cohort of 11 101 infants weighed within 1 h of birth showed a 14% (RR 0·86, 0·73—1·01, p=0·060) decreased risk of low birthweight for those in the MMN group, with a 33% (RR 0·67, 0·51—0·89, p=0·0062) decrease for infants of women anaemic at enrolment.

Interpretation

Maternal MMN supplementation, as compared with IFA, can reduce early infant mortality, especially in undernourished and anaemic women. Maternal MMN supplementation might therefore be an important part of overall strengthening of prenatal-care programmes.

Introduction

Despite great strides in reduction of overall child mortality, fetal loss and infant deaths remain high in the first weeks and months after birth.[1] Infant mortality during this period could be affected by maternal micronutrient deficiencies.[2—4] Increased needs for multiple micronutrients (MMN) during pregnancy and lactation might exacerbate deficiencies and impair fetal and infant development.[5, 6] Results from trials of maternal supplementation with iron, folic acid, retinol, iodine, and zinc, either alone or in combination, have reported improvements in infant and maternal health.[7—10] Although WHO recommends distribution of iron and folic acid (IFA) supplements to pregnant women,[11] the potential benefits of other micronutrients suggest that progressing to maternal MMN supplementation could, along with other interventions,[12] further reduce infant death.[13]

Despite low costs, ease of manufacturing, and widespread use of prenatal MMN supplements in developed countries, formal global policy is still pending, partly because of the paucity of data for the relative benefits of MMN supplementation, compared with IFA, for infant or maternal health.[14] In recognition of this scarcity of data, UNICEF, WHO, and UN University formulated the UN international multiple micronutrient preparation (UNIMMAP)[15] and fostered assessment of the effect of MMN supplementation on birthweight as well as other infant and maternal-health indicators.[16, 17]

Trials on maternal supplementation that compared the UNIMMAP and other MMN formulations, with IFA have been done in Guinea Bissau,[18] Zimbabwe,[19] Tanzania,[20, 21] Dhanusha (Nepal),[22] India,[23] France,[24] and the USA,[25] and have shown improvements in birthweight[18—24] and gestational length,[19] and reductions in prematurity,[20, 25] intrauterine growth retardation,[20, 21] and infant morbidity.[23] However, a study in Mexico[26] reported no effect of prenatal MMN supplements on birth size. Another trial in Sarlahi, Nepal,[27] comparing four maternal micronutrient regimens with retinol alone reported that MMN had no advantage over IFA in increasing birthweight, and a subanalysis, although underpowered, implied that folic acid or MMN might increase perinatal deaths in full-term infants. Overall, although maternal MMN supplementation has tended to improve birthweight, a systematic review concluded that additional evidence was needed to establish the effects of maternal MMN supplements on infant and maternal health and mortality.[14]

Thus, additional findings from studies of maternal MMN supplementation on infant outcomes such as fetal loss and mortality are needed. Moreover, findings obtained in the context of prenatal care delivery systems would provide greater relevance compared with those obtained with unsustainable methods. We therefore undertook the Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT)—a double-blind cluster-randomised trial in Indonesia—to examine the effect of maternal supplementation with MMN, compared with IFA, on fetal loss and infant death in the setting of routine prenatal care.

Methods

Study setting and design

Study enrolment was done between July 1, 2001, and April 1, 2004, on the island of Lombok, Nusa Tenggara Barat Province, Indonesia. The population of Lombok was about 2·7 million, and the infant mortality rate was estimated to be 89 per 1000 livebirths[28] compared with 52 per 1000 for Indonesia.[29] Maternal mortality was also high for this province, with estimated ratios ranging from 400—890 per 100 000 livebirths compared with 390 per 100 000 for Indonesia.[30] The prevalence of wasting (body-mass index <18·5) and anaemia (haemoglobin <110 g/L) for women of reproductive age was reported to be about 15% and 29%, respectively.[31]

Lombok consists of a capital city and 327 villages demarcated into three autonomous districts. Government health services in every district are provided by a hospital and a network of community health centres (known as *Puskesmas*), subcommunity health centres (*Pustu*), and village health clinics (*Polindes*). Trained midwives at community health centres and village health clinics do monthly integrated health posts (*Posyandu*) in every village hamlet to provide immunisations, nutritional support, and prenatal care. Midwives at village health clinics typically maintain a simple birthing room and serve more rural populations, whereas those based at community health centres maintain more advanced facilities and serve more urban or periurban populations. Both sets of midwives provide monthly prenatal care at integrated health posts, and might assist with home deliveries. Pregnant women who self-report to a midwife for prenatal care, usually at the integrated health post but also at village clinics and community centres, routinely receive 90 tablets containing 60 mg iron and 250 µg folic acid as part of the Ministry of Health package of prenatal care. Our trial was done throughout Lombok, apart from the capital city, by collaborating with this prenatal health-care system.

To prepare for the study, midwives at village health centres and community health centres were assigned midwife identification numbers, and an island-wide census of all girls and women aged 10—45 years was completed along with mapping and numbering of their homes. Focus groups with pregnant women were held to identify preferred specifications for the supplements such as halal ingredients, pink hard-gelatine capsules, and packaging in ten-capsule foil blister strips. Two types of identical-looking capsules, either IFA or MMN, were manufactured under good manufacturing practice conditions by a manufacturer approved by UNICEF (PT Soho Pharmaceuticals, Jakarta, Indonesia). The IFA contained 30 mg iron (ferrous fumarate) and 400 µg folic acid, and the MMN was the UNIMMAP formulation[15] containing 30 mg iron (ferrous fumarate) and 400 µg folic acid along with 800 µg retinol (retinyl acetate), 200 IU vitamin D (ergocalciferol), 10 mg vitamin E (alpha tocopherol acetate), 70 mg ascorbic acid,

1·4 mg vitamin B1 (thiamine mononitrate), 18 mg niacin (niacinanide), 1·9 mg vitamin B6 (pyridoxine), 2·6 µg vitamin B12 (cyanocobalamin), 15 mg zinc (zinc gluconate), 2 mg copper, 65 µg selenium, and 150 µg iodine. After recoding to maintain blinding, the manufacturer was required to release data of good manufacturing practice quality assurance for disintegration time, appearance, weight, and amounts of selected nutrients for every production batch. Finished batches were randomly selected and sent to UNICEF, Copenhagen, for testing and met specified composition requirements.

All strips of supplements had an embossed batch number with an embedded digit designating one of eight groups, with four being IFA and the other four MMN. The code to indicate which strip was IFA or MMN was known only by the manufacturing production manager and a quality control officer from UNICEF, Copenhagen, neither of whom had any connection to the study or its personnel. The code was later transmitted in a sealed envelope from the production manager directly to the chairman of the data and safety monitoring board. All study scientists and personnel, government staff, and enrolees were unaware of the allocation.

Before enrolment, midwife identification numbers were sequentially allocated to computer-generated, randomly permuted blocks of groups numbered one to eight, stratified by community health centre or village health clinic. Warehouse staff selected designated supplement batches, relabelled them with the assigned midwife identification number in large black digits, and sent them to midwives. All pregnant women served by the same midwife received supplements with the same midwife identification number, and were of a clustered unit of randomisation. This process resulted in 262 clusters, and from the perspective of midwives, pregnant women, and SUMMIT staff, all distributed supplements were labelled with one of 262 midwife identification numbers.

The study protocol was approved by the National Institute of Health Research and Development of the Ministry of Health of Indonesia, the Provincial Planning Department of Nusa Tenggara Barat Province, and the Johns Hopkins Joint Committee on Clinical Investigation, Baltimore, USA. All data were treated as confidential, and access to archived forms and data was restricted to authorised personnel. Logbooks to record access events were kept and reviewed periodically by the principal investigator and senior information systems officer.

Procedures

Before enrolment, midwives received retraining about micronutrients, prenatal care, and study procedures. They were provided with the supplements labelled with the midwife identification number and a box of sequentially numbered envelopes containing a rapid test for human chorionic gonadotropin in urine (Tulip Diagnostics Ltd, Goa, India), an informed consent form in triplicate with a preprinted unique enrolment identification number, a short enrolment form, a study brochure, and a briefing letter to the head of household.

Pregnant women of any gestational age were eligible to enrol upon self-reporting to a midwife at the integrated health post, village health clinic, or community health centre. If pregnancy was confirmed by physical examination or rapid test, the midwife, and SUMMIT staff if present, would review the informed consent with the woman. Consenting women signed or provided a thumbprint on a consent form that was cosigned by the midwife. Enrollees were

assessed for gestational age by exam and reported last menstrual period, and received 35 supplements with instructions to consume one capsule every day, preferably in the evening with food, and to return every month up to 3 months after birth to replenish the supply. Enrollees were subsequently visited at home within 72 h by a SUMMIT maternal data collector to rereview the study with the woman and family members with use of flipcharts and a facilitated question and answer approach. If consent was reconfirmed, then additional baseline questionnaires were completed to record the last menstrual period, pregnancy history, dietary practices, morbidity history, socioeconomic status, and anthropometrics. A subsample of women provided capillary blood by finger prick for determination of anaemia with a HemoCue portable haemoglobin meter (HemoCue AB, Ängelholm, Sweden).

Maternal data collectors obtained additional data at 36 weeks of gestational age, within 1 week after delivery, and at 12 weeks post partum. If a woman was in labour or had given birth, the midwife or family member would notify the maternal data collector or a SUMMIT community facilitator, who would visit and record the birth outcome and other data for maternal and infant health. When possible, birthweight was recorded within 1 h of birth by a midwife using either an Ministry of Health mechanical infant scale or UNICEF electronic digital scale (Uniscale, UNICEF Supply Division, Copenhagen, Denmark), or by a community facilitator or maternal data collector using a Uniscale or infant digital scale (Tanita model BD585, Tanita Corporation, Tokyo, Japan or Seca model 334, Seca Corporation, Hamburg, Germany). If a death was reported, a specially trained fieldworker did a verbal autopsy. Vital status was finalised on the basis of double confirmation of status from two sources.

Enrollees replenished their supply of capsules every month from midwives who logged the date and previous consumption on the basis of inspection of blister strips. This procedure was assisted by SUMMIT staffs if done at the integrated health post, and the data were obtained every month by a maternal data collector. Midwives submitted requests to replenish supplement stocks as needed. Neither enrollees nor midwives received financial or material incentives to participate in or implement the study. All other health-care delivery and services to pregnant women remained the same. Pregnant women who declined to enrol received the 90-day supply of the standard government IFA tablets along with routine prenatal care according to Ministry of Health guidelines.

To enhance enrolment and encourage regular prenatal care and supplement consumption, we did social marketing activities including radio advertisements, interactive educational games and videos at the integrated health post, promotional banners, promotion of prenatal care through religious meetings, distribution of brochures to women on topics related to pregnancy and child birth, and training of midwives in client service. Additionally, a trained SUMMIT community facilitator visited the enrollees' home every month 1 week before the scheduled integrated health post in her hamlet and provided prenatal health education, inquired about any problems with the pregnancy and discomfort from supplements, and recorded pill consumption counts from inspection of blister strips.

Daily task schedules detailing visits and activities for both community facilitators and maternal data collectors were generated every week from the SUMMIT data management section. Supervisor visitation lists for secondary data verification were generated each night by random

selection of 10% of households. Forms from community facilitators and maternal data collectors were collected every week, logged, and checked for accuracy and completeness. All fieldworkers were required to obtain a knowledge and practice-based certification every 90 days. Data entry staff were required to pass typing accuracy tests daily, and meet monthly accuracy standards on the basis of errors detected by a double data entry process for 10% of forms. The data were entered into a client-server SQL relational database management system (SQL server 7.0, Microsoft Corporation, Redmond, WA, USA) and subjected to range checks and reviewed for completeness and accuracy before being imported into SAS version 9.1 for analysis.

The data and safety monitoring board met on March 12—13, 2004, to do an interim analysis for outcomes for about 23 000 enrollees. The board reported that the study had been undertaken well and recommended continuation and rereview of the data after 12 months, at which time the study enrolment was projected to be about 81 000 women. The general steering committee subsequently concurred with the recommendation of the data and safety monitoring board and endorsed continuation of the study.

However, funding commitments for the planned 5 year duration of SUMMIT had remained about 25% lower than the proposed budget. Thus, despite efforts and anticipation of additional support, by April, 2004, it was clear that needed funds were not forthcoming in sufficient quantity or time to maintain continuity of the fieldwork. The decision was made by the study team to end the study with enrolment of 41 839 women and phase out field activities so that remaining funds could be focused on validation and archiving of data, and to finalise administrative closure. Thus, on April 2, 2004, a letter was sent to all participating district health departments stating that the trial would be terminated.

Statistical analyses

We calculated the sample size on the basis of proportions,[32] since estimates of death rates per person-time were not available, in an intention-to-treat analysis assuming an estimated neonatal mortality ratio of 46 per 1000 livebirths because this figure would accomodate higher ratios of early infant mortality to 12 weeks post partum. The design effect from clustered randomisation was estimated to be 1·20 for 300 clusters, and anticipated loss to follow-up was 10%, with a 15% allowance for abortions and stillbirths. With a power of 80% and a two-sided significance level of 5%, enrolment and follow-up of 36 300 pregnant women and infants would be needed to detect at least a 15% change in the neonatal or postneonatal mortality in the MMN group relative to the IFA group. Stopping rules drafted by the data and safety monitoring board established a minimum meaningful effect as 10%, thereby dictating a provisional sample size of 83 100 enrollees to assess effect of MMN on infant deaths.

Another primary outcome of the study was maternal mortality. On the basis of the above conditions and assuming an estimated maternal mortality ratio of 400 per 100 000 livebirths with an effect size of 30%, the projected sample size was 126 000. However, the data and safety monitoring board indicated in March, 2004, that maternal deaths in the study had fallen to 274 per 100 000 livebirths, which was substantially lower than the ratio for which the trial was designed. This factor and the termination of the study limited conclusions about maternal mortality.

Before breaking the code that indicated which women had received IFA or MMN, the data and safety monitoring board required the SUMMIT Study Group to formally register a detailed analysis plan that would define the primary cohort and the analysis procedures. The primary cohort was defined as women having terminated their pregnancy through abortion, stillbirth, or livebirth, no later than April 1, 2004 (ie, 1 day before notification of termination of the study). Application of this cut-off date uniformly to all clusters, with no other criteria such as enrolment date or location, resulted in a cohort of 31 290 women for analysis of maternal and infant outcomes. The 10 549 remaining pregnant women were excluded from the study. The predetermined primary infant outcome was the intention-to-treat analysis of early infant mortality at the last scheduled visit of the maternal data collector at 12 weeks (90 days) post partum, followed by secondary outcomes including neonatal mortality, early neonatal mortality, late neonatal mortality, perinatal mortality, preterm birth, abortion, stillbirth, and birthweight. After approval of the analysis plan by the data and safety monitoring board and transfer of the cleaned data to them, the code was transmitted to the SUMMIT Study Group on May 2, 2006.

The panel shows the ICD-10 defined outcomes,33 as well as others that were applied as indicated by the analysis plan.

Panel

ICD-10 and SUMMIT definitions that were applied in the study

- Gestational age: the duration of pregnancy in weeks calculated from the first day of last menstrual period
- First trimester: conception to the 14th completed week
- Second trimester: start of the 15th to the end of the 28th week
- Third trimester: start of 29th week to birth
- Preterm birth: birth of a live child at less than 37 weeks of gestational age
- Post-term birth: birth of a live child at more than 42 weeks of gestational age
- Abortion: spontaneous end of confirmed pregnancy before 28 weeks of gestational age
- Stillbirth: spontaneous death of a fetus after 28 weeks of gestational age and occurring in utero before labour or during labour itself and before complete expulsion or extraction
- Perinatal mortality: stillbirth or death of a liveborn infant within 7 days of birth
- Early neonatal mortality: death of a live born child within 7 days of birth
- Neonatal mortality: death within 28 days of birth
- Late neonatal mortality: death after 7 days but within 28 days of birth
- Early infant mortality: death within 12 weeks (90 days) of birth
- Postneonatal mortality: death after 28 days but within 12 weeks (90 days) of birth
- Birthweight: the weight of a living infant taken within 1 h of birth by a midwife or trained SUMMIT staff using either a midwife mechanical child scale or digital scale
- Low birthweight: birthweight less than 2500 g (≤2500 g was used for scales with 100 g increments)
- Compliance: the number of capsules consumed divided by the number of days that capsules should have been consumed since the most recent receipt of supplements
- Loss to follow-up: women or infants in the primary cohort with confirmed migration, drop-out or death, or unsuccessful attempts to obtain data from the relevant health clinic or home visits for 3 months

The analytical procedures were predefined in the analysis plan, which included baseline variables for comparison of homogeneity between groups and for subanalyses of effect-modifiers as suggested at the meeting of UNIMMAP investigators in London, UK, in 2002.17 The relative risk (RR) and 95% CI for dichotomous outcomes were calculated and adjusted for clustered randomisation by hierarchical logistic regression with a mixed effects model with the full likelihood method of SAS PROC NLMIXED by invoking the binary distribution and integration by Gaussian quadrature. This approach allowed the heterogeneity between clusters to be explicitly modelled and was robust to both a wide range of cluster sizes (from 1 to 526) resulting from the cut-off date and different rates of enrolment in every cluster, and to a potentially wide range of intracluster correlations for the various outcomes.34, 35 For comparison, other methods were used including the generalised estimating equations fixed-effects model with SAS PROC GENMOD with the log link function and exchangeable correlation,36, 37 which resulted in similar findings. For continuous variables, such as birthweight, we used analogous hierarchical linear regression models with SAS PROC MIXED with the random effects specification. Differences in effects within subgroups were assessed by addition of the appropriate interaction term to the model and by multiple pairwise comparisons of the estimated rates and confidence intervals.38 The predefined criteria for significance of effect modifiers was p less than 0·10.

Survival of infants to 12 weeks post partum was plotted as a Kaplan-Meier curve and the effect of MMN on infant mortality measured by Cox proportional hazards analysis with SAS PROC PHREG. Parameter estimates were adjusted for intracluster correlation by maximum partial likelihood estimates with an independent working assumption and invoking the robust sandwich covariance matrix estimate.39 Infants were censored at 90 days postnatal if deaths or survival times exceeded 90 days, and those lost to follow-up were censored on the date live status was last known. The exact date of infant death was available for 901 (84%) of deaths, with the remaining 169 (16%) being assigned to intervals of 0—3, 4—7, 8—28, or 29—90 days after birth on the basis of recall of the mother and family. Analyses done with only exact dates or all dates yielded similar and statistically significant effects. The 16% of deaths with estimated dates were excluded from the Kaplan-Meier survival plot. The hazard ratio for infant mortality at 1 year of age was calculated by censoring events that exceeded 52 weeks, and censoring those lost to follow-up before 52 weeks on the date live status was last known.

This study is registered as an International Standardised Randomised Controlled Trial, number ISRCTN34151616.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Overall, 41 839 pregnant women in 262 clusters enrolled in the study, and at the termination date (April 1, 2004) a total of 31 290 women in 262 clusters with 15 486 in the IFA group and 15 804 in the MMN group were deemed to have ended their pregnancy through abortion, stillbirth, livebirth, or death. Birth outcomes were known in 14 633 women in the IFA group and 14 909 women in the MMN group, yielding a 5·0% and

5·7% loss to follow-up during pregnancy and the loss of a one-woman cluster, with an additional loss from livebirth to 12 weeks post partum of 3·9% (n=553) in the IFA group and 4·0% (n=575) in the MMN group.

Figure 1 Full-size image (47K) Download to PowerPoint

Study profile

IFA=iron and folic acid. MMN=multiple micronutrients.

Table 1 shows baseline characteristics related to age, pregnancy history, education, socioeconomic status, and nutritional status. There were 127 clusters ranging from two to 526 enrollees in the IFA group, and 135 clusters ranging from 1 to 420 in the MMN group, with no difference in the distribution of number of small (1—99 women), medium (100—249), or large (≥250) clusters between the IFA and MMN groups. We also compared the baseline characteristics of enrollees lost to follow-up to those completing the study and noted similarity for all variables, suggesting that the few women lost to follow-up would not have disproportionately affected the outcomes. Similarly, the baseline characteristics of the pregnant women excluded due to trial termination were similar for the IFA and MMN groups.

Table 1Table image

Baseline age, pregnancy history, education, socioeconomic status, and nutritional status of pregnant women by treatment group

Active study villages covered 79% of the eligible population of Lombok. On the basis of data from demographic surveillance undertaken by the SUMMIT trial, 41 839 (84%) of an estimated 50 071 pregnant women in these villages enrolled. Comparison of baseline data from enrolees with data from 65 504 women of reproductive age from random household surveys in Lombok from 2001 to 200340 showed similarities in nutrition and health indicators such as proportion of women with mid upper arm circumference less than 23·5 cm (30% *vs* 32%), height less than 145 cm (14% *vs* 14%), BMI under 18·5 (14% [first trimester only] *vs* 15%), anaemia (29% [first trimester only] *vs* 29%), any primary school education (49% *vs* 51%), and previous attended delivery (35% *vs* 40%). Furthermore, analysis of SUMMIT baseline demographic assessment of 543 526 ever married women of reproductive age from 2000 to 2001 showed that 24% reported at least one child death, compared with 28% for enrollees. These data show high

participation rates and suggest enrollees were representative of the general population of Lombok.

The median compliance was 85·0% (85·5% in IFA group, 84·4% in MMN group) as assessed by pill counts at the home and at the integrated health post. 21 847 (70%) women consumed more than half the doses (four or more capsules) per week. Importantly, supplement consumption did not differ between treatment groups.

Table 2 shows the intention-to-treat analysis of infant death and table 3 shows that for fetal loss. We noted an 18% (p=0·010) reduction in early infant mortality in children born to women receiving MMN. A substantial effect of MMN was recorded for postneonatal mortality from 29 to 90 days after birth, when deaths were reduced by 30% (p=0·004). Non-significant reductions of roughly 10% were observed for abortions (p=0·30), stillbirths (p=0·26), perinatal (p=0·12), and neonatal mortality (p=0·19) (table 3). The combined fetal loss and neonatal mortality was reduced by 11% (RR p=0·045; table 2).

Table 2Table image

Effect of maternal MMN supplementation on infant deaths

Table 3Table image

Effect of maternal MMN supplementation on fetal loss and maternal death

The Kaplan-Meier survival curve from birth through the first 90 postnatal days is shown in figure 2. The curves for the MMN and IFA groups were nearly identical for the first 5 postnatal days, after which they progressively diverged. Cox proportional hazards analysis indicated a hazard ratio of 0·82 (95% CI 0·71—0·96, p=0·013) for the MMN group. Additionally, analysis of the effect of MMN on 9528 infants followed up to 1 year showed a hazard ratio of 0·81 (0·69—0·95, p=0·0077), suggesting persistent effects on mortality reduction (data not shown).

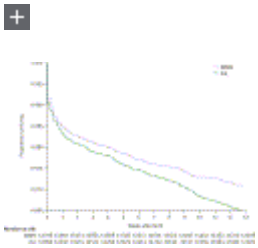

Figure 2 Full-size image (41K) Download to PowerPoint

Kaplan-Meier survival plot for early infant mortality

IFA=iron and folic acid. MMN=multiple micronutrients.

Women of any age, parity, pregnancy history, and gestational age had the opportunity to enrol in the study. Although consistent protective effects of MMN on early infant mortality could be seen across most subgroups, significant reductions were observed for women aged 20—35 years (p=0·011) and those having two or three previous births (p=0·044) (table 4, figure 3). Analysis of gestational age at enrolment suggested reductions in infant deaths for all gestational ages, and a significant reduction of 28% (p=0·018) was seen for third-trimester enrollees. Infants of women who consumed four or more supplements per week had 25% (p=0·0043) fewer deaths, whereas those consuming fewer supplements showed less of an effect (test of interaction p<0·10; table 4).

Table 4Table image

Effect of maternal MMN supplementation on early infant mortality in subgroups

Figure 3 Full-size image (25K) Download to PowerPoint

Effect of maternal MMN supplementation on early infant mortality in subgroups

IFA=iron and folic acid. MMN=multiple micronutrients.

We also examined the effect of MMN on the proportion of preterm or post-term births and noted no effect with 3654/14 053 (26%) and 3736/14373 (26%) livebirths recorded before 37 weeks of gestation in the IFA and MMN groups, respectively. A protective effect of MMN on early infant mortality could be seen in preterm, full term, or post-term births, although the reduction was only significant for full term births (table 4).

Analysis of subgroups by nutritional status showed that MMN supplementation of undernourished women (mid upper arm circumference <23·5 cm) resulted in a 25% (p=0·0021) reduction in early infant mortality (table 4). MMN supplementation of women who were anaemic at enrolment reduced infant deaths by 38% (p<0·0001), which was a stronger effect than was noted in non-anaemic women (test for interaction p<0·05; table 4). We therefore further explored the effect of baseline nutritional status on the significant 11% reduction in combined fetal loss and neonatal death, and observed reductions of 15% (305/4337 *vs* 262/4437, RR 0·85, 95% CI 0·73—0·98, p=0·022) in undernourished women and 29% (223/3993 *vs* 178/4423, RR 0·71, 0·58—0·87, p=0·0010) in anaemic women.

We also examined factors related to the programme, and observed that infants of women obtaining supplements from a midwife at a village health clinics, (ie, the more rural location), had 21% (p=0·010) fewer deaths if the mother received MMN supplementation. Additionally, the effect of MMN on infants with an untrained or trained attendant at delivery tended to be similar, and was significant only with a trained attendant present (p=0·030; table 4).

Lastly, although statistical methods were used to adjust for clustered randomisation, to further rule out the possibility of a potentially dominant cluster affecting the findings, we assessed the effect of MMN on early infant mortality in small, medium, and large clusters. Consistent protective effects were observed across all cluster sizes (table 4).

The cohort for assessment of birthweight included 11 101 infants who were weighed within the required 1 h of delivery. The distribution of baseline characteristics between MMN and IFA groups within this cohort was much the same for all variables. However, in view of the requirements for inclusion in this cohort, a higher proportion in this subgroup than in the remaining intention-to-treat group delivered at a facility (8909/11 076 [80%] *vs* 3842/16 105 [24%]), were primiparous (4368/10 990 [40%] *vs* 6461/19 482 [33%]), and had secondary or higher education (4946/10 942 [45%] *vs* 6176/19 362 [32%]).

As shown in table 5, intention-to-treat analysis indicated a non-significant increase of 21 g in mean birthweight in the MMN group, with a 14% reduction in low birthweight. We also undertook subgroup analyses for nutritional effect modifiers identified above and parity, which are known to affect birthweight. This analysis showed that for women who were anaemic at enrolment, MMN supplementation increased birthweight by 52 g, and reduced low birthweight by 33% (table 5), which was an effect greater than for non-anaemic women (test for interaction p<0·05). By contrast, infants of undernourished women showed little change, whereas those from better nourished women were 37 g heavier with an 18% reduction in low birthweight (table 5).

Table 5Table image

Effect of maternal MMN supplementation on low birthweight and mean birthweight

The early termination of the study and resulting sample size precluded meaningful assessment of the effect of MMN on maternal deaths. Overall, from enrolment to 12 weeks post partum, a similar number of women in the IFA and MMN groups died, suggesting no effect, although the confidence interval is wide (table 3). Formal interpretation of the causes of death from verbal autopsies, including exclusion of accidental deaths, and examination of the effects of MMN supplements on maternal morbidity will be reported elsewhere.

Discussion

Our study suggests that maternal MMN supplementation, compared with IFA, reduced early infant mortality. This effect was seen predominantly after the first 5 days of life, and was most pronounced from days 29 to 90 after birth. Effects were greater in women consuming larger

numbers of supplements and in those who were anaemic or undernourished at enrolment. MMN consumption also resulted in a significant reduction in overall fetal loss and neonatal death, and these effects also tended to be greater in poorly nourished women. Thus, the effects of maternal MMN on infant deaths might be dose and deficiency-dependent, and involve several mechanisms, resulting in perinatal and neonatal effects, and a larger postneonatal effect.

Conclusions about infant death or morbidity from previous studies of maternal MMN supplementation have been hampered by small sample sizes and other design issues. In some cases selective pooling of data sets has been pursued,41 resulting in controversial methods and findings that have stimulated debate.42, 43 Subsequent systematic review of published and unpublished trials drew attention to the few conclusions that could be made about the effects of MMN on mortality because of the small numbers of deaths in many studies that were originally designed to assess birthweight.14

A recent report from Tanzania of around 8500 HIV-negative women suggested that maternal MMN supplements resulted in a 14% (RR 0·86, 95% CI 0·72—1·02, p=0·08) reduction in combined perinatal and neonatal deaths.20 Similarly, MMN supplementation of women infected with HIV-1 also resulted in a 39% reduction in fetal loss (RR 0·61, 0·39—0·94, p=0·02),20 and reduced infant morbidity.44 And in India, prenatal MMN supplementation of 200 women from urban slums reduced early neonatal morbidity by 47% (RR 0·53, 0·29—0·97, p=0·01).23 The full effect of MMN in these, and future studies, might need additional follow-up because of the 30% reduction in postneonatal deaths that we have reported.

Generally, the biological basis for the effects of maternal MMN supplements is probably complex in view of the ubiquitous role of micronutrients in human biology.45, 46 Zinc, retinol, iodine, vitamin D, and folic acid have substantial roles in gene regulation and nucleic acid metabolism that are crucial for embryogenesis. Fetal development along the continuum toward birth and infancy needs precise regulation of both energy metabolism and neurological development that could require vitamins B1, B6, B12, and iron. Immunological maturation and transfer of maternal antibody might be affected by zinc as well,47 and antioxidants such as selenium, vitamin E, ascorbic acid, and riboflavin have been shown to have a role in immune function and cellular viability.48 Thus, adequate availability of many nutrients and improved stores could have pleiotropic effects that produce coordinated physiological and anatomical development of the fetus associated with more robust infant homoeostasis needed to withstand the challenges from birth and early infancy. A deeper understanding of the mechanisms of action is clearly needed.

Furthermore, we could not disaggregate the effects of prepartum and post-partum MMN consumption on infant death. Post-partum consumption could have affected breastmilk quality and competency as a bioregulatory food, thereby improving infant survival.49 Maternal status or intake of several B vitamins, retinol, selenium, and iodine has a strong effect on the breastmilk content of these nutrients.50 Post-partum maternal nutritional supplements have improved infant nutritional status51, 52 and reduced morbidity44, 49, 53 in some, but not all,54 studies.

We had not anticipated the finding that reductions in early infant mortality for first or second trimester enrollees were not clearly greater than those for third trimester enrollees, and this result needs further study. Women presenting for prenatal care later in pregnancy could have poorer health-seeking patterns and health, and have nutrient depletion50 when nutritional needs of the fetus are highest, and possibly benefit most from supplementation. From a public-health perspective, that initiation of supplement consumption even in the third trimester was beneficial for the infant is noteworthy.

The overall effects of maternal MMN supplementation on mean birthweight and low birthweight were comparable with those reported in previous studies,14 including a report from Tanzania suggesting an 18% reduction in low birthweight.21 However, the potential to observe changes in the birthweight cohort of our study could have been restricted because of the high proportion of educated women and deliveries at a birthing facility. Our results might therefore underestimate the effect of MMN supplementation on birthweight in this population. Nevertheless, substantial benefits were seen in infants whose mothers were anaemic at enrolment. It is also notable that no change in birthweight was seen in infants of undernourished women consuming MMN, yet mortality was reduced. An additional reduction in infant mortality and an increase in birthweight was seen when well-nourished women consumed MMN. Thus, amelioration of MMN deficiencies in women with insufficient macronutrient intake could enhance infant physiological, endocrine, or metabolic processes, or optimise fine anatomical structure that promotes survival despite no change in total body mass; whereas sufficient macronutrient intake along with improved MMN status could enable additional changes, such as increased body mass, which further promote survival. The data suggest that birthweight alone might be an inconsistent proxy for assessment of the infant health benefits of maternal MMN supplementation, especially in populations who are poorly nourished.

Generally, the benefits of maternal MMN supplements compared with IFA tended to be greater for infants of women who were anaemic at enrolment. The added value of MMN for this group of women emphasises that anaemia, although frequently identified with iron deficiency or other causes, could be symptomatic for many deficiencies and disorders that are insufficiently treated by only iron and folate. Study of biological and environmental effect modifiers such as maternal and fetal genetics, dietary factors, disease, and behaviour will help to elucidate the qualitative and quantitative factors of the mother and infant dyad that modulate the effects of MMN supplementation.

With respect to maternal deaths, results from our study suggest no effect of maternal MMN supplements. Since the MMN supplements contained retinol, this finding contrasts with a previous report from Nepal showing that retinol supplementation reduced mortality related to pregnancy by more than 40%.8 Additional studies of nutritional factors affecting the health and survival of pregnant women are needed. Further analysis of the cause of death and effects of MMN on maternal morbidity in the SUMMIT trial is in progress.

Our findings for infant mortality might also be applicable to other regions. The infant mortality rate in Lombok in 2001, was reported as 89 per 1000 livebirths and the estimated infant and maternal mortality rate from the SUMMIT baseline was 105 per 1000 and 525 per 100 000

livebirths, respectively. The corresponding values were 58 and 440 for Bangladesh, 70 and 410 for India, and 75 and 540 for Nepal, respectively, and moderate to severe stunting rates in children were 46%, 55%, 52%, and 54%, respectively.29, 55, 56 Location-specific heterogeneity notwithstanding, these data suggest that infants in other regions could also benefit from maternal MMN supplementation.

Lastly, our study strengthened government health infrastructure to distribute supplements, and community facilitators educated pregnant women and encouraged them to visit midwives and obtain and consume supplements. Social marketing promoted the role of midwives, prenatal care, and nutrition. These activities resulted in high participation and compliance rates in this randomised trial, yielding a substantial reduction in early infant mortality because of maternal MMN consumption. Due to the novel design of the SUMMIT as a double-blind, cluster-randomised trial in conjunction with the local health system, we hope that the results will have added relevance for public-health planners and policymakers. The data from our study suggest that maternal MMN supplementation could reduce infant death and potentially be an important complement to overall strengthening of prenatal-care programmes.

The SUMMIT Study Group

Analysis and writing team—A H Shankar (Helen Keller International, Jakarta, Indonesia; Johns Hopkins University, Baltimore, MD, USA) designed the study and protocols, directed and helped execute the study, undertook analysis and interpretation of data, and drafted the manuscript. A B Jahari (Center for Research and Development in Food and Nutrition, Bogor, Indonesia) contributed to the design and helped analyse and interpret data. S K Sebayang made substantial contributions to the design, execution, and supervision of the study, and analysed and interpreted data for birthweight. Aditiawarman, M Apriatni, and B Harefa (SUMMIT, Helen Keller International, Mataram, Indonesia) made substantial contributions to the design, execution, and supervision, and helped analyse and interpret data. H Muadz (University of Mataram, Mataram, Indonesia), S D A Soesbandoro (Mataram General Hospital, Mataram, Indonesia), and R Tjiong (Helen Keller International, Jakarta) helped design and oversee the study, and interpreted data. A Fachry (University of Mataram) helped oversee the study, and analysed and interpreted data. A V Shankar (Johns Hopkins University, Baltimore, MD, USA) helped design the study, and made substantial contributions to data preparation, analysis, and drafting of the manuscript. Atmarita (Directorate of Community Nutrition, Ministry of Health, Government of Indonesia, Jakarta) helped analyse and interpret data. S Prihatini, G Sofia (Center for Research and Development in Food and Nutrition) helped analyse data. All members approved the final report.

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Conflict of interest statement

We declare that we have no conflict of interest.

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