The impact of lipid-based nutrient supplement provision to pregnant women on newborn size in rural Malawi: a randomized controlled trial[1–4]

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ABSTRACT

Background: Small birth size, often associated with insufficient maternal nutrition, contributes to a large share of global child undernutrition, morbidity, and mortality. We developed a small-quantity lipid-based nutrient supplement (SQ-LNS) to enrich the diets of pregnant women.

Objective: The objective was to test a hypothesis that home fortification of pregnant women's diets with SQ-LNS would increase birth size in an African community.

Design: We enrolled 1391 women with uncomplicated pregnancies (<20 gestational weeks) in a randomized controlled trial in Malawi. The women were provided with one daily iron–folic acid (IFA) capsule, one capsule containing multiple micronutrients (MMNs), or one 20-g sachet of SQ-LNS (LNS, containing 118 kcal, protein, carbohydrates, essential fatty acids, and 21 micronutrients). Primary outcomes were birth weight and newborn length. Secondary outcomes included newborn weight, head and arm circumference, and pregnancy duration. Analysis was by intention to treat.

Results: The mean ± SD birth weight and newborn length were 2948 ± 432, 2964 ± 460, and 3000 ± 447 g ($P = 0.258$) and 49.5 ± 2.4, 49.7 ± 2.2, and 49.9 ± 2.1 cm ($P = 0.104$) in the IFA, MMN, and LNS groups, respectively. For newborn weight-for-age, head circumference, and arm circumference, the point estimate for the mean was also highest in the LNS group, intermediate in the MMN group, and lowest in the IFA group, but except for midupper arm circumference ($P = 0.024$), the differences were not statistically significant. The prevalence of low birth weight (<2500 g) was 12.7%, 13.5%, and 12.1% ($P = 0.856$), respectively; newborn stunting (length-for-age z score < -2) was 19.2%, 14.0%, and 14.9% ($P = 0.130$), respectively; and newborn small head circumference (head circumference-for-age z score < -2) was 5.8%, 3.0%, and 3.1% ($P = 0.099$), respectively. The associations between the intervention and the outcomes were not modified by maternal parity, age, or nutritional status ($P > 0.100$).

Conclusion: The study findings do not support a hypothesis that provision of SQ-LNS to all pregnant women would increase the mean birth size in rural Malawi. The trial was registered at clinicaltrials.gov as NCT01239693. *Am J Clin Nutr* 2015;101:387–97.

Keywords lipid-based nutrient supplements, home-fortification, intrauterine growth restriction, pregnant women, preterm birth

INTRODUCTION

Child undernutrition and poor growth are common in sub-Saharan Africa and southern Asia, with numerous negative consequences for child development and long-term individual and household welfare (1). To date, few postnatal nutrition interventions have proven successful in preventing linear growth faltering (2, 3). Given that linear growth retardation in low-income countries often starts during the fetal period (4) and the incidence of stunting is also associated with preterm birth (5, 6), interventions during the prenatal period might be more successful. Indeed, a recent systematic review concluded that the incidence of intrauterine growth retardation could be markedly reduced by supplementing maternal diet during pregnancy either with multiple micronutrients or with protein and energy (7). Very few controlled trials have, however, evaluated the impact of combined micronutrient and energy/protein supplementation in pregnancy (8). Even more surprisingly, there have been no attempts since the 1970s to rigorously evaluate the effects of comprehensive nutritional support to the mother-infant dyad throughout pregnancy, lactation, and early childhood (i.e., the 1000-d window of opportunity for the promotion of healthy child growth) (3).

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[3]Supplemental Tables 1 and 2 are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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Lipid-based nutrient supplements (LNSs)[5] are versatile and easy-to-use nutritional products that have been successfully applied to the rehabilitation of children with severe acute malnutrition (7) and may also offer benefits in the promotion of healthy growth (9–11). In the only reported LNS trial targeting the gestational period, infants born to women who, during pregnancy, received a relatively large daily dose (72 g) of a locally made LNS called Fortified Food Supplement had a higher mean birth length than did infants of women who received only multiple micronutrients (MMNs) (12). On the basis of their findings, the authors recommended a targeted nutritional supplementation for pregnant women with suboptimal prepregnancy nutritional status, consisting of MMNs, protein, and energy, as a means to promote child growth in low-income settings (12).

The iLiNS-DYAD-M trial—a trial carried out by the International LIpid-based Nutrient Supplement study group, enrolling mother-child dyads in Malawi—was designed to study the impact on maternal and child health in rural Malawi of an intervention that provides LNSs both to the mothers during pregnancy and early lactation and to their newly born children from 6 to 18 mo of age. Because energy intakes among the target women were assumed to be mostly sufficient but nutrient intakes insufficient (13), we designed a small-quantity LNS (SQ-LNS) that provides only a limited amount of energy (118 kcal/d) but would fortify regular home diets with a full complement of micronutrients and essential fatty acids at a palatable and relatively affordable daily dose of 20 g (14). To facilitate comparison to other recommended antenatal nutritional supplementation schemes, we included 2 control groups, one given iron and folic acid (IFA) and the other given MMNs but no essential fatty acids, sufficient intake of which is considered critical for good pregnancy outcomes (15). In the present communication, we report the intervention effects on the 2 primary birth outcomes, birth weight and newborn length, as well as several secondary variables indicating child size at or soon after birth.

SUBJECTS AND METHODS

Study design, outcomes, and ethics statement

We undertook a randomized, controlled, outcome assessor–blinded clinical trial in rural Malawi. The first study hypothesis was that in the study area, infants born to mothers provided with LNS during pregnancy would on average be bigger than newborns whose mothers received either IFA or MMN supplementation. We used IFA as the first control intervention, because it was the national practice at the study site, and MMN as a second control, because of the existing evidence of its possible benefits over IFA (16). A second set of hypotheses concerned maternal health during pregnancy and early lactation as well as child growth, morbidity, development, and physical activity in the first 18 mo of life. In this article, we report the infant birth outcomes. As exploratory analyses, we also compare the results between the 2 control groups (IFA and MMN).

The trial was performed according to Good Clinical Practice guidelines and the ethical standards of the Helsinki Declaration. The protocol was approved by the College of Medicine Research and Ethics Committee, University of Malawi and the Ethics Committee of Pirkanmaa Hospital District, Finland. Only participants who signed or thumb-printed an informed consent form were enrolled in the study. An independent data safety and monitoring board (consisting of one obstetrician and 2 pediatricians) monitored the incidence of suspected serious adverse events (SAEs) and performed 2 interim analyses for safety. The board members received information about all suspected SAEs on an ongoing basis and met 3 times during the pregnancy part of the trial.

The primary outcome measures were birth weight and newborn length (measured within 6 wk of birth). Secondary birth outcomes included newborn weight, head circumference, midupper arm circumference (MUAC), and the duration of pregnancy, as well as the incidence of maternal or newborn SAEs. The period of postnatal follow-up continued until 6 wk after delivery, because this marks the end of the puerperal period and the agreed time frame for recording maternal mortality.

Study site and participants

The enrollment to the study took place in one public district hospital (Mangochi), one semiprivate hospital (Malindi), and 2 public health centers (Lungwena and Namwera) in Mangochi District, southern Malawi. The Mangochi hospital outpatient clinic served a semiurban population of 100,000; the other sites provided health care to approximately 30,000 people each. All sites were accessible by all-weather roads. The population largely subsisted on farming and fishing. Before commencing, the study team members held numerous discussions with community leaders and organized village meetings to discuss the research objectives and procedures. Pregnant women coming to antenatal visits received further information about the trial.

The target population comprised pregnant women who came for antenatal care at any of the study clinics during the enrollment period and met the following inclusion criteria: ultrasound-confirmed pregnancy of no more than 20 completed gestation weeks, residence in the defined catchment area, availability during the period of the study, and signed or thumb-printed informed consent. Exclusion criteria were age younger than 15 y, need for frequent medical attention due to a chronic health condition, diagnosed asthma treated with regular medication, severe illness warranting hospital referral, history of allergy toward peanuts, history of anaphylaxis or serious allergic reaction to any substance, requiring emergency medical care, pregnancy complications evident at enrollment visit (moderate to severe edema, blood hemoglobin concentration <50 g/L, systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg), earlier participation in the iLiNS-DYAD-M trial (during a previous pregnancy), or concurrent participation in any other clinical trial.

Study interventions

Women in the IFA group, the first control, received standard Malawian antenatal care, including supplementation from enrollment to delivery with one micronutrient capsule/d containing

[5]Abbreviations used: IFA, iron and folic acid; iLiNS, International LIpid-based Nutrient Supplement study group LNS, lipid-based nutrient supplement; MMN, multiple micronutrients; MUAC, midupper arm circumference; SAE, serious adverse effect; SQ-LNS, small-quantity lipid-based nutrient supplement.

60 mg iron and 400 μg folic acid and 2 doses of intermittent preventive malaria treatment with sulfadoxine-pyrimethamine (3 tablets of 500 mg sulfadoxine and 25 mg pyrimethamine orally). One sulfadoxine-pyrimethamine dose was given at enrollment and the other between weeks 28 and 34 of gestation. Participants in the MMN group, the second control, received intermittent preventive malaria treatment and micronutrient capsules that contained IFA and 16 additional micronutrients (14). Because of earlier positive results in Guinea-Bissau with higher-dose micronutrient supplementation (16) and failure to reach desired tissue concentrations among pregnant women provided with the Recommended Dietary Allowances of micronutrients (17), the MMN capsules we used contained twice the amount used in most previous prenatal multiple micronutrient trials for several micronutrients (thiamin, riboflavin, niacin, vitamin B-6, vitamin B-12, vitamin D, vitamin E, zinc, copper, and selenium) (14). Participants in the LNS intervention group received intermittent preventive malaria treatment and sachets of tailor-made SQ-LNS. The daily dose (20 g) was designed to contain the same micronutrients as the MMN capsules, 4 additional minerals, protein, and fat, and it also provided 118 kcal of energy (**Table 1**).

The fat content of the LNS was optimized to provide high amounts of selected essential fatty acids that were thought to be important in pregnancy (15). The iron dose was lower for participants in the MMN and LNS groups (20 mg/d) than for those in the IFA group (60 mg), because the MMN and LNS supplementation was continued during the first 6 mo postpartum, when the recommended nutrient intake for lactating women is much lower than the standard antenatal dose (14). On the basis of a literature review and our estimates of the normal dietary iron intakes among pregnant women in the study area, we considered 20 mg/d a safe and adequate dose to prevent iron deficiency anemia during pregnancy (even for women who would be iron deficient at entry) (14, 20, 21).

The manufacturers packed the IFA and MMN capsules in plastic 10-capsule blister packs and LNS in individual 20-g foil sachets. Data collectors delivered 15 supplement doses (capsules or sachets) fortnightly to each participant until delivery and advised them to consume daily either one micronutrient capsule,

TABLE 1
Nutrient and energy contents of the dietary supplements[1]

				US Dietary Reference Intakes[2]		
Nutrient	IFA	MMN	LNS	AI/RDA pregnancy (19–50 y)	AI/RDA lactation (19–50 y)	UL
Ration	1 tablet	1 tablet	20-g sachet			
Total energy, kcal	0	0	118			
Protein, g	0	0	2.6			
Fat, g	0	0	10			
Linoleic acid, g	0	0	4.59	13*	13*	—
α-Linolenic acid, g	0	0	0.59	1.4*	1.3*	—
Vitamin A, μg RE	0	800	800	770	1300	3000
Vitamin C, mg	0	100	100	85	120	2000
Vitamin B-1, mg	0	2.8	2.8	1.4	1.4	—
Vitamin B-2, mg	0	2.8	2.8	1.4	1.6	—
Niacin, mg	0	36	36	18	17	35
Folic acid, μg	400	400	400	600	500	1000
Pantothenic acid, mg	0	7	7	6*	7*	—
Vitamin B-6, mg	0	3.8	3.8	1.9	2.0	100
Vitamin B-12, μg	0	5.2	5.2	2.6	2.8	—
Vitamin D, μg	0	10	10	15	15	100
Vitamin E, mg	0	20	20	15	19	1000
Vitamin K, μg	0	45	45	90*	90*	—
Iron, mg	60	20	20	27	9	45
Zinc, mg	0	30	30	11	12	40
Copper, mg	0	4	4	1	1.3	10
Calcium, mg	0	0	280	1000*	1000*	2500
Phosphorus, mg	0	0	190	700	700	3500/4000
Potassium, mg	0	0	200	4700*	5100*	—
Magnesium, mg	0	0	65	350/360[3]	310/320[3]	350
Selenium, μg	0	130	130	60	70	400
Iodine, μg	0	250	250	220	290	1100
Manganese, mg	0	2.6	2.6	2.0*	2.6*	11

[1]Where 2 values are given, the first is for pregnancy and the second is for lactation. AI, adequate intakes (denoted with an asterisk); IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrients; RDA, Recommended Dietary Allowances; RE, retinol equivalent; UL, Tolerable Upper Intake Level; —, not determinable or data insufficient.

[2]US Dietary Reference Intakes from reference 18. Historical vitamin D and calcium Dietary Reference Intakes are from Otten et al. 2006 (19).

[3]Values for ages 19–30 y/31–50 y.

to be taken with water after a meal (IFA and MMN groups), or one sachet of LNS, mixed with a small quantity of any food and consumed as one morning dose. At each visit, the data collectors also counted and recovered any unused supplement doses from the participants.

The IFA and MMN capsules were custom-made at and purchased from DSM Nutritional Products South Africa (Pty) Ltd. The LNS was produced and packed by Nutriset S.A.S. Raw ingredients for LNS included soybean oil, dried skimmed milk, peanut paste, mineral and vitamin mix, and sugar (14). At the project office, the research team stored all supplements between 20°C and 40°C in cardboard boxes that protected the supplements from light. At participant homes (maximum storage time 2 wk), the dietary supplements were recommended to be stored indoors, in a dry and as cool place as possible.

During the trial implementation, international organizations involved in medium-quantity LNS distribution to children with acute malnutrition made a recommendation on a new quality assurance procedure for all such products. The recommendation involved the testing of LNS for the presence of *Cronobacter sakazakii* bacteria and in clinical practice withholding of the use of untested products or those that were found to contain any *C. sakazakii*. After consultation with members of the trial's data safety and monitoring board, the study team decided to withhold further distribution of LNS to the iLiNS-DYAD trial participants until the recommended testing had been completed. Because of this episode, a total of 160 pregnant women in the LNS group missed their study supplement for a period ranging from 1 to 20 d between 1 August 2012 and 21 August 2012. Of these women, 127 were provided with IFA capsules (1 capsule/d) while LNS was on hold; the other 33 were not located at their homes during the IFA distribution.

Randomization and enrollment

A study statistician not involved in data collection generated 4 randomization code lists in blocks of 9 (one list for each of the 4 enrollment sites). In the randomization process, each participant number was allocated one of 9 possible letter codes (A, B, C, D, E, H, J, K, or M). Each letter code corresponded to one of the 3 interventions (i.e., each intervention matched with 3 separate letter codes). Another researcher not involved with the iLiNS-DYAD trial then created individual randomization slips, each containing one unique identification number and the corresponding letter code. The researcher sealed the slips into individual opaque randomization envelopes, marked each envelope with the trial name and an individual participant number, and sorted the envelopes in 4 stacks (one for each site), each ordered by the participant number shown on the envelope.

Study nurses and their assistants screened for possible participants among pregnant women who started antenatal care at any of the 4 study sites. They gave a brief introduction on the trial procedures, recorded data on selected "routine antenatal" background variables from all women, and invited the interested women to a more thorough information session about participant eligibility and its assessment. Women who gave a written consent then underwent a full eligibility assessment that included a test dose of LNS to rule out allergic reactivity. Afterward, a study randomizer summarized each person's eligibility and provided further information on the trial implementation to women who were eligible for participation. The women were also given written information on the study and encouraged to discuss possible participation with their family members before their final decision. Before enrollment, the randomizer verified that appropriate information had been provided and obtained the participant's signature or thumbprint on a second consent form.

For the actual enrollment and group allocation, a randomizer picked and shuffled the randomization envelopes for the 6 lowest participant numbers that had not yet been assigned to any participant. He or she then asked the potential participant to choose one, without showing her the envelope identifiers. The number on the envelope chosen by the woman became her participant number, and the contents of the envelope indicated her group allocation (in letter codes). The randomizer then matched the letter code with the actual intervention, gave the participant her first 2-wk ration of trial supplements, instructed her on its use, briefed her about subsequent study visits and supplement delivery, and made her a study identification card. The 5 unused randomization envelopes were returned to the original stack and used (together with a sixth envelope) in the group allocation for the next participant from the same site. The enrollment information that included participant details, her randomization number, and the letter code corresponding to her group allocation (but not the actual intervention) was sent to a study coordinator, who recorded the information in an electronic file that he used to plan subsequent study visits for all participants.

At the enrollment visit, trained anthropometrists measured the participants' weight, height, and MUAC. They did all measurements in triplicate, with high-quality scales (SECA 874 flat scale; Seca GmbH & Co.), stadiometers (Harpenden stadiometer; Holtain Limited), and nonstretchable plastic tapes (Shorrtape; Weigh and Measure LLC), having reading increments of 50 g, 1 mm, and 1 mm, respectively. Research nurses recorded participants' obstetric histories and performed antenatal examinations. They assessed the duration of pregnancy by measuring (in duplicate) the fetal biparietal diameter, femur length, and abdominal circumference (all in millimeters) with ultrasound imagers that used inbuilt Hadlock tables to estimate the duration of gestation (EDAN DUS 3 Digital Ultrasonic Diagnostic Imaging System; EDAN Instruments Inc.). The same nurses measured the women's peripheral blood malaria parasitemia with rapid tests (Clearview Malaria Combo; British Biocell International Ltd.) and hemoglobin concentration with on-site cuvette readers (HemoCue AB; Angelholm). Health facility nurses gave pretest HIV counseling and tested for HIV infection in all participants, except those who opted out or were already known to be HIV infected, by using a whole-blood antibody rapid test (Alere Determine HIV-1/2; Alere Medical Co, Ltd.). If the result was positive, the test was repeated by using another whole-blood antibody rapid test (Uni-Gold HIV; Trinity Biotech plc). If the tests were not available at the health facility on the day of enrollment, the study team arranged the test to be performed as soon as possible thereafter.

Follow-up

Data collectors made home visits biweekly, to deliver the supplements and to collect information on the participant's adherence to the study intervention. The first home visit was implemented within 1–2 wk of enrollment by data monitors, who

recorded the home location with a global positioning system (to facilitate subsequent visits) and interviewed the participants about their demographic, social, and economic background. Data on participant adherence to the study intervention were collected by counting the numbers of delivered and recovered capsules or sachets. For each participant, we calculated an adherence index by using the following formula: adherence index = (number of delivered supplement doses – number of returned doses) ÷ total number of days between enrollment and delivery × 100%. For each participant, we also calculated the percentage of visits when supplements were returned by using the following formula: number of visits when supplements were returned / number of visits done × 100%. Both of these indices provided one data point per participant for the analysis.

Study coordinators invited the participants for follow-up at the study clinic twice during pregnancy (at 32 and 36 gestational weeks) and once after birth (at 1–2 wk after delivery). During the antenatal visits, study anthropometrists measured the participants' weight, height, and MUAC with the same methods as at enrollment, and study nurses carried out standardized obstetric examinations. As soon as possible after birth, research assistants measured the infant's birth weight and interviewed the mother about delivery events; other anthropometric measurements were not taken because this visit was sometimes completed at home. A more thorough postnatal visit was completed when the infant was 1–2 wk old and brought to the study clinic. At this visit, study nurses examined both the mother and the newborn infant. Study anthropometrists measured the infant's length with a high-quality length board (Harpenden Infantometer; Holtain Limited) and recorded it to the nearest 1 mm, weight with an electronic infant weighing scale with a reading increment of 20 g (SECA 381 baby scale; Seca GmbH & Co.), and head circumference and MUAC with the same plastic tapes that were used for maternal anthropometry.

The study team provided all participants with mobile phones and airtime so that they could promptly inform the study coordinators about deliveries that took place outside the study clinics. On notification of a delivery, a study coordinator, a study nurse, or a data monitor visited the woman at her home, health center, or hospital. He or she interviewed the participant about delivery time and events and measured the infant's birth weight with the same electronic scales that were used at the postnatal visit.

Data collectors made tracing home visits if a participant did not come for the scheduled visit within 14 d of the appointment. Information on the participants' hospitalizations and other suspected SAEs was collected actively via interviews at each fortnightly home visit. Study nurses also contacted both hospitals in the study area daily to obtain information on any hospitalizations or deaths among our participants. In addition, the study physicians trained health providers at all the known private and public health facilities in the area to identify the study participants from their iLiNS identification cards and to record information on any nonscheduled visits on structured data collection forms that were collected and reviewed by the study team on a weekly basis. Finally, research assistants made a special home visit at 6 wk after delivery to verify the vital status of the participating woman and infant at the end of the primary follow-up period.

Data on suspected SAEs were recorded on structured adverse event forms. On the first notification, a study physician reviewed each suspected SAE, decided whether the participant could continue receiving the trial intervention, and reported the event to members of the trial's data safety and monitoring board. After the outcome was known, a study physician also made the judgment on the adverse event type, outcome category, and possible relation to the trial interventions.

The study participants attended antenatal and under-5 clinics according to the same schedule as all other Malawian pregnant women and infants and received all normal preventive services provided by the national health system. Study nurses treated participants with documented peripheral blood malaria parasitemia with lumefantrine/artemether, the nationally recommended antimalarial drug. Other medical conditions were treated in the national health system (either in the public or private sector). The study team reimbursed the participants for all medical costs that they incurred during the trial participation.

Quality assurance

We ensured data collection quality through regular staff training and monitoring and the use of written visit guides, instructions about the use of data collection forms, and additional standard operating procedures. Aside from birth weight, anthropometric measurements were taken only by trained personnel whose measurement reliability was verified at the start of the study and at 6-monthly intervals thereafter [with methods modified from the procedures used in the WHO Multi-country Growth Reference Study (22)]. Birth weight could also be measured by study nurses or study coordinators. The anthropometrists calibrated all equipment with standard weights and length rods on a daily basis. An external monitor appointed by the study team did one site monitoring visit during data collection.

The IFA and MMN interventions were provided by using double-masked procedures—that is, the capsules looked identical, and neither the participants nor the research team members were aware of the nutrient contents of the supplement capsules. For the LNS group, we used single-masked procedures—that is, field workers who delivered the supplements knew which mothers were receiving LNS (but not a difference between IFA and MMN), and the participants were advised not to disclose information about their supplements to anyone other than an iLiNS team member. The data collectors who performed the anthropometric measurements or assessed other outcomes were not aware of group allocation. Researchers responsible for the data cleaning remained blind to the trial code until the database was fully cleaned.

Statistical analyses

The target sample size of 1400 participants was based on 2 separate calculations. Our first aim was to detect differences between the 3 groups, assuming an effect size of 0.3 (difference between groups, divided by the pooled SD) for each continuous outcome, assuming 80% power and a 2-sided type I error rate of 5%. This would require 216 participants per group, for a total of 648 subjects. Allowing for up to 25% loss to follow-up, we would have needed to recruit 864 subjects. Our secondary aim was to study the interaction between the maternal intervention and a total of 11 potential effect modifiers. Because the interaction analyses were considered exploratory, the multiple comparisons

were not taken into account in determining the sample size. For each interaction, we assumed an effect modifier prevalence of 25% and an interaction effect size of approximately 0.3, with $P < 0.10$ (2-sided test) and 80% power. With these assumptions, we would have needed approximately 640 participants per group in the analysis. Allowing for 20% missing values, we planned to recruit 2400 participants, which would have given the study 80% power to detect main effects of >0.18 SD. The sample size was, however, subsequently reduced to 1400 because of unexpected budgetary difficulties. The revised final sample size of 370 per group provided the study with 80% power to detect main effects of ≥0.23 SD and an interaction effect of ≥0.47 SD with a 2-sided type I error rate of 5% (corresponding to a difference of approximately 100 g in birth weight or 0.5 cm in newborn length).

All data were initially collected on paper forms from which they were extracted and entered into a tailor-made database through scanning, digital character recognition, and manual verification of critical variables and all suspicious entries. Researchers and research assistants cleaned all data through a number of logic checks. Once the database was considered clean, we broke the code and carried out statistical analysis with Stata 12.1 (StataCorp LP) according to a detailed statistical analysis plan written and published after the onset of the trial but before the code was opened (www.ilins.org). All presented analyses were prespecified either in the trial protocol or in the statistical analysis plan.

We based the analysis on the principle of modified intention to treat—that is, we included all participants randomly allocated in the analyses, with the exceptions that participants with missing data on an outcome variable were excluded from the analysis of that outcome and that 2 participants whose group allocation was incorrectly transcribed and assigned during enrollment were included in the group corresponding to the actual intervention they received throughout the trial. We used data on birth weight as such if measured within 48 h of delivery and back-calculated birth weight from data collected between 6 and 13 d after delivery by using the WHO z scores. If weight was first measured between 2 and 5 d after delivery (when weight loss is typical), we calculated birth weight as a percentage of the actual measured weight (23). We considered birth weight or newborn anthropometric measurements missing if they were collected more than 2 and 6 wk after delivery, respectively. Twelve twin pregnancies were excluded from all main analyses, but we carried out sensitivity analyses that included the twins and used the number of fetuses as a covariate. We carried out a second, "per-protocol," sensitivity analysis that was confined to the most "adherent" participants (participants who received and did not return supplements for more than 80% of the follow-up days). As a third sensitivity analysis, we built Heckman's selection models to explore if loss to follow-up might have biased the results (24, 25). In these models, we included maternal height, maternal BMI, gestational age at enrollment, maternal age, child sex, household assets, number of previous pregnancies, anemia, and study site as potential factors that might have affected loss to follow-up.

We calculated the duration of pregnancy by adding the time interval between enrollment and miscarriage or delivery to the ultrasound-determined gestational age at enrollment and defined preterm delivery as one occurring before 37 completed gestational weeks (259 d) and low birth weight as <2500 g. We calculated age- and sex-standardized anthropometric indices (weight-for-age, length-for-age, weight-for-length, and head circumference-for-age z scores) by using the WHO Child Growth Standards (16) and considered values < -2.0 indicative of underweight, stunting, wasting, or small head circumference, respectively. We considered a birth weight small for gestational age if it was <10th centile of the birth weight for gestational age distribution in an American reference population (26). For all the anthropometric measurements that were completed in triplicate, we used the mean of the first 2 readings if they did not differ by more than a prespecified tolerance limit. If the difference was above the limit, the third measurement was compared with the first and second measurements, and the pair of measurements that had the smallest difference was used to calculate the mean. If there were only one or 2 repeated measurements, the mean of those was used for the analyses.

We estimated the risk ratio for comparison of binary endpoints at a single time point. To prevent inflated type I errors resulting from multiple-group comparisons, we used the close testing procedure (23)—that is, null hypotheses for pairwise comparisons could only be rejected if the global null hypotheses of all 3 groups being identical had also been rejected. We did not adjust for multiplicity in the safety analysis, because this should err on the safe side. We tested the global null hypotheses either with Fisher's exact test (for binary endpoints) or ANOVA (quantitative endpoints) and the pairwise hypotheses with the log-binomial regression model (for binary endpoints) or ANOVA (quantitative endpoints). With the log-binomial regression models for the binary endpoints, we used the software's default setting of Newton-Raphson maximization of the log-likelihood. In case the algorithm failed to converge in the estimation, we used alternative estimation algorithms with iterated reweighted least squares or modified Poisson approximation, in this order (27, 28).

We performed likelihood ratio tests for the interaction between the intervention and maternal characteristics specified in the statistical analysis plan before data analysis and provided stratified analyses in case of a positive interaction text ($P < 0.100$). Variables tested for interaction included maternal age, education, number of previous pregnancies, height, BMI, maternal anemia at enrollment, exposure to the cessation of supplement provision (delivery before or after the temporary suspension of LNS distribution), season of enrollment, gestational age at enrollment, socioeconomic status index (28), and child sex.

Covariates used in the adjusted models were derived from the list of variables that were tested for interaction with the intervention but not selected as effect modifiers. We performed the covariate selection with linear and logistic regression models. All the models were adjusted for the same set of covariates, which were maternal height, maternal BMI, gestational age at enrollment, maternal age, child sex, proxy for socioeconomic status, number of previous pregnancies, maternal anemia at enrollment, and study site.

We recorded and analyzed all SAEs (defined as hospitalizations, life-threatening events, deaths, congenital malformations, or other) for the mothers and infants during pregnancy and until 6 wk after delivery. We categorized deaths of the fetus or child as abortions (fetal loss before 22 completed gestational weeks),

stillbirths (fetal death at or after 22.0 gestational weeks), early neonatal deaths (death to a live-born infant within 7 d of birth), late neonatal death (death at 8–28 d after birth), and infant deaths (death at 29–42 d after birth). Analysis unit was participant, with no adjustment for time in follow-up. Maternal mortality ratio, perinatal mortality rate, and neonatal mortality rate were calculated by using standard definitions.

RESULTS

Between February 2011 and August 2012, the iLiNS team members approached a total of 9310 women at the antenatal clinics of the 4 study sites. Of these, 1391 (14.9%) were enrolled and randomly allocated to one of the 3 intervention arms. The other approached women were excluded because they were not interested, they considered themselves not eligible, or the study team determined that they did not meet all the predefined enrollment criteria (**Figure 1**).

At enrollment, the mean duration of pregnancy was approximately 17 wk in all 3 study groups. The groups were also similar in terms of their average demographic and socioeconomic characteristics, obstetric history, and maternal nutritional status (**Table 2**). The nonenrolled women were similar to the enrolled participants in terms of their mean age, number of completed school years, marital status, home building material, and ownership of phones in the household (**Supplemental Table 1**).

The proportion of biweekly home visits when the study team recovered any unused supplements was higher for the IFA and MMN groups than for the LNS group (40.5% and 41.2% compared with 27.9%, $P < 0.001$). Because of a concern regarding supplement safety, there was, however, a temporary suspension in supplement delivery for the LNS group (see Subjects and Methods). On the basis of the length of follow-up and the number of delivered and returned supplement doses, we estimated that the mean adherence to the intervention (proportion of days when the supplements were consumed) was 84.2%, 83.4%, and 85.7% in the IFA, MMN, and LNS groups, respectively ($P = 0.139$). The proportion of returned supplements did not change during the follow-up in any of the groups ($P = 0.343$ for IFA, 0.283 for MMN, and 0.958 for LNS groups).

We obtained data on the duration of gestation from 94.0% of the women and on birth weight and newborn size from 82.9% and 79.7% of the fetuses, respectively (90.0% and 86.5% of live-born infants) (Figure 1). The success of follow-up was similar between the groups ($P = 0.638$ for birth weight, 0.739 for newborn length and other anthropometrics, and 0.655 for duration of pregnancy). The mean ± SD age of the infants at birth weight and newborn size measurements were 30 ± 50 h and 13 ± 6 d, respectively. Of the recorded birth weights, 89.1% were measured within 48 h, and the rest were back-translated from a measurement within 14 d. Twelve women delivered twins: 3 in the IFA, 1 in the MMN, and 8 in the LNS group. Data collection for the presently reported analyses was completed in June 2013.

The mean ± SD recorded birth weight of singleton infants born to the study participants was 2970 ± 447 g, newborn length was 49.7 ± 2.3 cm, and duration of pregnancy was 39.1 ± 2.9 gestational weeks. The incidence of low birth weight (<2500 g) was 12.8%, low newborn length (<−2.0 z score units) was 16.0%, and preterm delivery was 10.0%. The mean ± SD newborn weight-for-age, length-for-age, weight-for-length, and head circumference z scores were –0.56 ± 1.03, −1.00 ± 1.11, 0.10 ± 1.14, and –0.15 ± 1.09, respectively.

For all the primary continuous outcomes, as well for newborn head and arm circumference, the point estimate for the mean was highest in the LNS group, intermediate in the MMN group, and lowest in the IFA group (**Table 3**). Except for the MUAC results, however, the differences were not statistically significant. The mean (95% CI) MUAC was 0.2 (0.1, 0.3) mm higher in the LNS than in the IFA group ($P = 0.006$). The respective difference between the LNS and MMN groups was 0.1 (−0.0, 0.2) mm ($P = 0.175$).

There were no statistically significant differences between the groups in the incidence of low birth weight, small for gestational age birth weight, or preterm birth, or the prevalence of newborn stunting, underweight or small head circumference (**Table 4**).

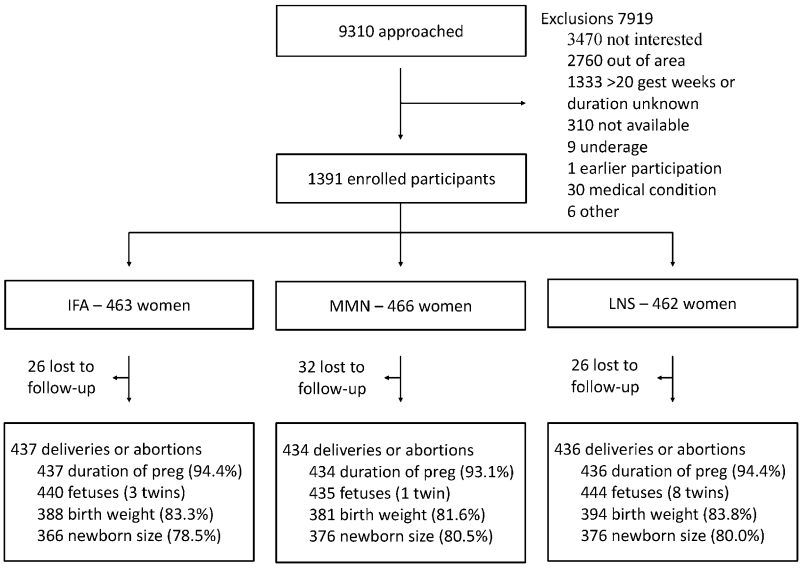

FIGURE 1 Participant flow in Consolidated Standards of Reporting Trials recommended format. gest, gestational; IFA, iron and folic acid group; LNS, lipid-based nutrient supplement group; MMN, multiple micronutrient group; preg, pregnancy.

TABLE 2
Baseline characteristics of the participating women at enrollment, by study group[1]

Characteristic	IFA	MMN	LNS	*P* value
No. of participants	463	466	462	
Maternal age, y	25 ± 6[2]	25 ± 6	25 ± 6	0.768
Maternal education, completed years	3.9 ± 3.4	4.1 ± 3.4	4.1 ± 3.6	0.704
Proportion with severely food insecure households,[3] %	34.7	37.5	35.8	0.686
Gestational age at enrollment, wk	16.8 ± 2.1	16.8 ± 2.1	16.9 ± 2.2	0.931
Number of previous pregnancies	2.1 ± 1.8	2.1 ± 1.8	2.2 ± 1.7	0.715
Proportion of nulliparous women, %	20.4	23.0	22.1	0.607
Height, cm	156.1 ± 5.7	156.0 ± 5.6	156.2 ± 5.7	0.847
Weight, kg	53.9 ± 7.4	54.0 ± 8.1	54.3 ± 8.4	0.719
MUAC, cm	26.4 ± 2.4	26.3 ± 2.8	26.5 ± 2.7	0.477
BMI, kg/m^2	22.1 ± 2.6	22.2 ± 2.9	22.2 ± 3.0	0.795
Proportion of women with a BMI <18.5 kg/m^2, %	5.9	4.6	5.7	0.632
Blood hemoglobin concentration, g/L	111 ± 17	111 ± 16	112 ± 16	0.932
Proportion of anemic women (hemoglobin <100 g/L),[4] %	21.0	19.8	21.2	0.858
Proportion of women with a positive HIV test, %	15.6	11.1	14.4	0.130
Proportion of women with positive malaria test (RDT), %	22.7	24.1	22.8	0.856

[1]*P* values were obtained by ANOVA (continuous variables) or χ^2 test (proportions). IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrients; MUAC, midupper arm circumference; RDT, rapid diagnostic test.
[2]Mean ± SD (all such values).
[3]From Coates et al. (29).
[4]From Nestel (30).

Adjustment of the analyses for selected baseline variables did not markedly change the results (details not shown). An analysis that included the twins and used the number of fetuses as a covariate also gave essentially similar results, and so did the Heckman's selection models that adjusted for the potential correlation between a tendency of missing data on outcome values and their actual values (details not shown). Finally, an analysis that was confined to the most adherent participants (>80% adherence to the intervention) also indicated no statistically significant intergroup differences in the continuous (**Supplemental Table 2**) or dichotomous (details not shown) outcomes.

Tests for interaction indicated that maternal parity, age, nutritional status, exposure to the cessation of supplement provision (delivery before or after the temporary suspension of LNS distribution), and most other tested baseline variables did not modify the associations between the intervention and the study outcomes ($P > 0.100$). Maternal educational achievement modified the association for newborn stunting ($P = 0.018$) but not for the other outcomes. Among women with <4 y of education, the proportion of infants with newborn stunting was 22.5%, 10.3%, and 14.9%, in the IFA, MMN, and LNS groups, respectively ($P = 0.007$). Among women with ≥4 y of education, the respective proportions were 15.3%, 17.0%, and 14.9% ($P = 0.853$).

We recorded a total of 162 SAEs for the women and 256 for the infants by 6 wk after delivery. The number of SAEs and the proportions of participants who died or experienced at least one SAE during the follow-up were roughly equally distributed among the 3 study groups (**Table 5**). There were 8 maternal deaths, 8 abortions (before 22 gestational weeks), 23 stillbirths, and 41 neonatal or infant deaths within 6 wk of birth, resulting in a maternal mortality ratio of 629/100,000 live births, perinatal mortality rate of 45/1000 births, and neonatal mortality rate of 31/1000 live births. The number of stillbirths was higher in the LNS than in the MMN group (Table 5). In the other age brackets, there were no statistically significant intergroup differences in the number of deaths. The perinatal mortality rate per 1000 births was 53, 33, and 49 in the IFA, MMN, and LNS groups, respectively ($P = 0.300$). Of the fetal or infant deaths,

TABLE 3
Continuous birth outcomes by intervention group[1]

	Study group			
Variable	IFA	MMN	LNS	*P* value
Birth weight, g	2948 ± 432	2964 ± 460	3000 ± 447	0.258
Newborn length, cm	49.5 ± 2.4	49.7 ± 2.2	49.9 ± 2.1	0.104
Newborn length-for-age *z* score	−1.10 ± 1.21	−0.98 ± 1.10	−0.93 ± 1.02	0.104
Duration of pregnancy, wk	39.0 ± 2.9	39.2 ± 3.0	39.2 ± 2.9	0.550
Newborn weight-for-age *z* score	−0.64 ± 1.08	−0.57 ± 1.02	−0.48 ± 0.99	0.092
Newborn head circumference-for-age *z* score	−0.24 ± 1.12	−0.14 ± 1.11	−0.06 ± 1.02	0.091
Newborn MUAC	10.5^a ± 1.0	10.6^{a,b} ± 0.9	10.7^b ± 0.9	0.024

[1]Values are means ± SDs. *P* values were obtained by ANOVA. Means sharing different superscript letters are significantly different from each other at the $P < 0.05$ level by ANOVA. IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient; MUAC, midupper arm circumference.

TABLE 4
Dichotomous birth outcomes by intervention group[1]

Variable	Result by study group, *n*/total *n* (%)			*P* value
	IFA	MMN	LNS	
Incidence of low birth weight	49/385 (12.7)	51/379 (13.5)	46/380 (12.1)	0.856
Prevalence of newborn stunting	69/360 (19.2)	52/372 (14.0)	53/357 (14.9)	0.130
Incidence of preterm birth	49/434 (11.3)	41/433 (9.5)	39/428 (9.1)	0.528
Incidence of small-for-gestational age	117/385 (30.4)	109/379 (28.8)	112/380 (29.5)	0.889
Prevalence of newborn underweight	34/362 (9.4)	29/374 (7.8)	22/363 (6.1)	0.250
Prevalence of small head circumference	21/360 (5.8)	11/372 (3.0)	11/359 (3.1)	0.099

[1]*P* values were obtained by Fisher's exact test. IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient.

29 were considered of unknown etiology, followed by infections (14), preterm delivery (12), intrapartum asphyxia (11), maternal bleeding (3), maternal eclampsia (1), fetal malpresentation (1), and cephalopelvic disproportion (1). The trial physicians considered none of the reported SAEs likely to be caused by the trial interventions.

DISCUSSION

The current study tested a hypothesis that provision of LNS rather than IFA or MMN to pregnant women would increase the mean duration of pregnancy and birth size in rural Malawi. Among study infants who were followed up within 6 wk of birth, the mean birth weight and newborn length were approximately 50 g and 4 mm larger in the LNS than in the IFA group. These differences, as well as those for several secondary growth outcomes were, however, not statistically significant. Hence, the study findings do not support the hypothesis that SQ-LNS promotes fetal growth or increases mean birth size, if provided to an unselected group of pregnant women in the study area.

The methodologic strengths of the trial included random group allocation that led to similarity of the intervention groups at enrollment, rigorous quality assurance in data collection, and blinding of the outcome assessors to group allocation. Internal validity could have been compromised by a relatively large number of missing data, delay in anthropometric measurements of some participants, temporary discontinuation of the LNS distribution during the trial, and our inability to directly observe the consumption of the study supplements. Because the results were robust to several sensitivity analyses, we believe these factors did not significantly bias our conclusions. However, the smaller sample size than originally intended (due to budget reduction) limited the statistical power of the study. Therefore, although the results do not support the study hypothesis, they also do not rule out a modest intervention effect on birth size.

We could identify only one published trial on provision of LNS to pregnant women. In Burkina Faso, women who received a much larger daily dose of LNS (72 g compared with 20 g in our study) gave birth to infants whose mean birth weight and length were approximately 10 g and 4 mm greater than that of infants whose mothers had received multiple micronutrients as UNICEF/WHO/UNU international multiple micronutrient preparation (UNIMMAP) capsules (12). There was no IFA control group in that trial, but an earlier publication from the same investigators in the same area suggested that MMNs increased mean birth weight and length by 40 g and 3 mm, respectively, compared with IFA

TABLE 5
Incidence of maternal and infant SAEs by study group[1]

Variable	Result by study group			*P* value
	IFA	MMN	LNS	
Women who experienced SAEs[2]	42/460 (9.1)	46/465 (9.7)	54/454 (11.9)	0.353
Women who were hospitalized	40 (8.7)	41 (8.8)	53 (11.7)	0.242
Women who died	3 (0.7)	4 (0.9)	1 (0.2)	0.550
Infants who experienced SAEs[3]	78/460 (17.0)	79/465 (17.0)	90/454 (19.8)	0.434
Infants who were hospitalized	51 (11.1)	59 (12.7)	65 (14.3)	0.341
Fetal or infant losses (abortion, stillbirth, death)	27 (5.9)	20 (4.3)	25 (5.5)	0.528
Abortions[4]	1/434 (0.2)	4/433 (0.9)	3/428 (0.7)	0.420
Stillbirths	7[a,b] (1.6)	2[a] (0.5)	14[b] (3.3)	0.006
Early neonatal deaths (0–7 d)[5]	16/427 (3.8)	12/430 (2.8)	7/414 (1.7)	0.193
Late neonatal deaths (8–28 d)	2 (0.5)	1 (0.2)	1 (0.2)	0.849
Infant deaths (29–42 d)	1 (0.2)	1 (0.2)	0 (0.0)	1.000

[1]Values are *n* (%) or *n*/total *n* (%). *P* values were obtained by Fisher's exact test. Proportions sharing different superscript letters are significantly different from each other at the $P < 0.05$ level by log-binomial regression. IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient; SAE, serious adverse event.

[2]The denominator includes all enrolled women with a singleton pregnancy.

[3]Also includes fetal losses.

[4]The denominator includes women with a singleton pregnancy for whom the date of abortion or delivery is known.

[5]The denominator includes singleton, live-born infants with a known birth date.

(31). Our point estimates of a 50-g and 4-mm difference in the mean birth weight and length between LNS and IFA groups are thus consistent with those from Burkina Faso.

One intriguing finding from nutrient supplementation trials is the heterogeneity of the treatment effect in different target populations. This has been observed in several earlier trials with multiple micronutrient supplements, indicating a large variation (4–95 g) in the point estimates for the UNIMMAP intervention impact on mean birth weight (31–38). Besides the geographic heterogeneity, several authors have also suggested variation in the effect of dietary supplements on various subpopulations of the target group. For instance, in the trial from Burkina Faso, the treatment effect of LNS was observed among multigravid women and those with anemia or low BMI but not among primigravid participants (12). Although a larger effect in the most undernourished population is logical and also found elsewhere, especially after protein and energy supplementation (3, 39), it has not been consistently documented (8, 40). With multiple micronutrient interventions (without food supplements), a larger treatment effect has actually been documented among the better-nourished pregnant women (16).

In our own trial, maternal age, parity, nutritional status, season of enrollment, or relative wealth did not appear to modify the association between the intervention and the various outcomes. This and the lack of main effect of the intervention suggest that dietary insufficiency may not have been the main or only determinant of poor pregnancy outcomes in this target population. An alternative explanation lies in maternal infections, such as malaria and HIV, which were quite prevalent in this population. Prenatal infections may lead to fetal growth restriction through a multitude of inflammation-related pathways (41, 42), and interventions targeting either maternal malaria or bacterial infections in pregnancy have been associated with improved birth outcomes in sub-Saharan Africa (43, 44). In preliminary analyses from our current study population, maternal malaria, HIV infection, and inflammatory response appeared associated with adverse pregnancy outcomes and also seemed to modify some of the intervention effects on them (details not shown). This supports the idea that maternal infections contribute to fetal growth restriction and preterm onset of labor, but further laboratory analyses are necessary to elucidate the interactions between infection, inflammation, and nutrition in this process.

Previous studies have indicated that LNS supplementation is safe and acceptable to infants and young children (9–11). Our study was not sufficiently powered to test formal hypotheses about the relative safety of the 3 supplementation schemes, but the recorded SAEs do not point to any major safety concerns about LNS provision to pregnant women. The apparent discrepancy between the higher number of stillbirths in the LNS than the in MMN group but no statistically significant differences in perinatal mortality rates probably reflects a difficulty in differentiating the timing of a perinatal death in a low-resource setting. Based on the lower frequency of unused supplement returns, LNS appeared to be somewhat more attractive to the women than IFA or MMN capsules. Unfortunately, this relative benefit may have been offset in our trial by the temporary discontinuation of LNS distribution, which was caused by a sudden change in international recommendations on product quality assurance and led to the withholding of approximately 5% of the intended supplement rations in the LNS group. It is thus possible that our results slightly underestimate the LNS effect. This possibility is also supported by earlier findings from Burkina Faso, indicating that the effect size of multiple micronutrient supplementation is positively correlated with the number of doses given during pregnancy (45).

Taken together, the study findings do not support a hypothesis that provision of SQ-LNS to all pregnant women would increase the mean birth size in rural Malawi. Further studies are needed to understand and identify group-level predictors of fetal growth restriction and to assess the longer-term effect of prenatal LNS provision on subsequent child growth and development.

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The authors' responsibilities were as follows—PA, UA, KGD, AL, SAV, MZ, and KM: designed the research; PA, UA, UH, MN, NP, JP, and KM: conducted the research; PA, LA, and YBC: analyzed data; PA: wrote the manuscript, with critical input and comments from all other authors; and PA and KM: had primary responsibility for final content. All authors read and approved the final manuscript. The findings and conclusions contained within the article are those of the authors and do not necessarily reflect positions or policies of the Bill & Melinda Gates Foundation, USAID, the US government, or the other funders. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. MZ works as a director of research for Nutriset S.A.S., a company that produces and sells lipid-based nutrient supplements and also prepared the LNS supplements purchased for the current trial. The other authors declared no conflicts of interest related to this study.

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