Small-quantity lipid-based nutrient supplements increase infants' plasma essential fatty acid levels in Ghana and Malawi: A secondary outcome analysis of the iLiNS-DYAD randomized trials

Seth Adu-Afarwuah[1,*], Charles D. Arnold[2], Anna Lartey[1], Harriet Okronipa[1,2], Kenneth Maleta[3], Per Ashorn[4,5], Ulla Ashorn[4], Yue-Mei Fan[4], Andrew Matchado[3], Emma Kortekangas[4], Brietta M. Oaks[2], Kristina H. Jackson[6], Kathryn G. Dewey[2]

Author Affiliations

[1]Department of Nutrition and Food Science, University of Ghana, Legon, Accra, Ghana; [2]Institute for Global Nutrition, Department of Nutrition, University of California, Davis, CA, USA; [3]University of Malawi College of Medicine, School of Public Health and Family Medicine, Department of Public Health, Blantyre, Malawi: [4]Center for Child, Adolescent and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [5]Department of Pediatrics, Tampere University Hospital, Tampere, Finland; [6]OmegaQuant Analytics, LLC, Sioux Falls, SD, USA

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***Corresponding Author**

Seth Adu-Afarwuah

Department of Nutrition and Food Science, University of Ghana, Legon

Accra, Ghana

Phone: +233 24 914 9385

Email: sadu-afarwua@ug.edu.gh

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SQ-LNS AND INFANTS' PLASMA FATTY ACID PROFILE

Online Supplemental Material

Supplemental Tables 1- 4.

List of abbreviations and their definitions

%C, percent composition; AA, arachidonic acid; ALA, α-linolenic acid; DHA, docosahexaenoic acid; EFA, essential fatty acids; EPA, eicosapentaenoic acid; FA, fatty acids; IFA, Iron and Folic Acid; iLiNS, International Lipid-Based Nutrient Supplements; LA, linoleic acid; LCPUFA, long-chain polyunsaturated fatty acid; LNS, Lipid-based Nutrient Supplements; MMN, Multiple Micronutrient Supplements; SQ-LNS, small-quantity lipid-based nutrient supplements

Authors' last names

Adu-Afarwuah, Arnold, Lartey, Okronipa, Maleta, Ashorn, Ashorn, Fan, Matchado, Kortekangas, Oaks, Jackson, Dewey

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ABSTRACT

Introduction: Small-quantity lipid-based nutrient supplements (SQ-LNSs) may influence infants' plasma fatty acid (FA) profiles, which could be associated with short- and long-term outcomes.

Objectives: We aimed to determine the impact of SQ-LNS consumption on infants' plasma FA profiles in Ghana and Malawi.

Methods: Ghanaian (*n*=1320) and Malawian (*n*=1391) women ≤20 wk pregnant were assigned to consume daily: 60 mg iron and 400 µg folic acid until delivery (IFA group); or multiple micronutrients until 6 mo postpartum (MMN); or SQ-LNSs (~7.8 Linoleic acid:α-Linolenic acid ratio) until 6 mo postpartum (LNS). LNS group infants received SQ-LNS from 6 to 18 mo of age. We compared infant plasma FAs by intervention group in sub-samples (n=379, Ghana; n=442, Malawi) at 6 and 18 mo using ANOVA and Poisson regression models. Main outcomes were mean percent composition (%C, percent FAs by weight) of α-linolenic (ALA), linoleic (LA), eicosapentaenoic (EPA), docosahexaenoic (DHA), and arachidonic (AA) acids.

Results: At 6 mo, LNS infants had greater mean±SD ALA %C in Ghana (0.23±0.08 vs IFA, 0.21±0.06; MMN, 0.21±0.07; P=0.034) and Malawi (0.42±0.16 vs IFA, 0.38±0.15; MMN, 0.38±0.14; P=0.034) and greater AA (6.25±1.24 vs IFA, 6.12±1.13; MMN, 5.89±1.24; P=0.049) in Ghana. At 18 mo, LNS infants had a tendency towards greater ALA (0.32±0.16 vs IFA, 0.24±0.08; MMN, 0.24±0.10; P=0.06) and LA (27.8±3.6 vs IFA, 26.9±2.9; MMN, 27.0±3.1; P=0.06) in Ghana, and greater ALA (0.45±0.18 vs IFA, 0.39±0.18; MMN, 0.39±0.18; P<0.001) and LA (29.7±3.5 vs IFA, 28.7±3.3; MMN, 28.6± 3.4; P=0.011) in Malawi. The prevalence of ALA below the population-specific 10th percentile was lower in the LNS group compared to the MMN group, but not the IFA group. Groups did not differ significantly in plasma EPA or DHA levels.

Conclusion: SQ-LNS increases infants' plasma essential FA levels in Ghana and Malawi, which may have implications for health and developmental outcomes. *Clinicaltrials.gov identifiers:* NCT00970866; NCT01239693.

Keywords: small-quantity lipid-based nutrient supplements; multiple micronutrient supplements; essential fatty acids; plasma fatty acid profile; α-linolenic acid; linoleic acid

INTRODUCTION

Adequate intake of essential fatty acids (EFAs) during the pre- and postnatal periods is fundamental for fetal and child survival, growth, and development (1-3). EFAs (α-linolenic acid, ALA and linoleic acid, LA) serve as precursors for long-chain polyunsaturated fatty acids (LCPUFAs) required as structural and functional components of cell membranes, particularly those of the brain and spinal cord (3, 4), and are needed for the synthesis of prostanoids (prostaglandins and thromboxanes) and leukotrienes essential for many biological processes, including inflammatory reactions, protection of the gastrointestinal mucosa, hemostasis, and maintenance of endothelial function (5-7). In children, the LCPUFA derivatives of EFAs may influence immune function (8-10), lower the risk of allergic disease development (11, 12), and promote better visual acuity (13, 14) and cognitive function (15, 16).

Pregnancy and infancy are associated with high requirements for LCPUFAs due to substantial tissue accretion and rapid development (17); a sufficient intake of EFAs is necessary during these periods to ensure adequate LCPUFA status (18). Meanwhile, analysis of the fatty acid (FA) availability from food supply in 13 low- and middle-income countries suggested that the n-3 FA supply for pregnant and lactating women as well as for infants and young children in these countries may be low (19). There are concerns that low intake of EFAs poses potential risks to child growth (18) development (18, 20).

Collaborators in the International Lipid-based Nutrient Supplements (iLiNS) Project developed small-quantity (20 g/d) lipid-based nutrient supplements (SQ-LNSs) for pregnant and lactating women and for infants (21) with the goal to enrich the usual diets of these vulnerable groups with micronutrients, EFAs, and a small amount of energy (118 kcal/d) and high-quality protein (2.6 g/d). Presently, at least 16 trials have been conducted in 10 countries, in which versions of SQ-LNSs were provided to infants alone during the period 6-23 mo of age (22-33), or to both mothers and infants (34-37) during pregnancy, lactation and infancy. In a recent meta-analysis (38),

the provision of SQ-LNS to infants 6-23 mo of age was found to be associated with positive anthropometric outcomes (including reduction in the prevalence of stunting, wasting and underweight) and a lower prevalence of anemia, when compared with the provision of no intervention, or fortified blended foods, or micronutrient powders. To our knowledge, only one (39) SQ-LNS trial has reported the FA levels in infants: in South Africa, the consumption of SQ-LNSs containing ALA and LA from 6 to 12 mo of age, compared with no supplementation, did not affect infant plasma FA profile, but SQ-LNSs with added AA and DHA increased infant plasma DHA (though not AA) levels. In general, data on the impact of SQ-LNS consumption on the FA profile of infants are limited. Effects on infants' plasma FA levels, particularly EFAs and their most important derivatives, may be associated with nutritional, health and developmental outcomes during infancy and beyond.

This study aimed to determine the plasma FA profiles of infants who participated in the iLiNS-DYAD trials in Ghana (35, 40) and Malawi (37, 41), in which mother-child dyads were enrolled to test the efficacy of 3 micronutrient supplementation regimens. Given that infants' plasma FA profiles may be influenced by maternal FA intake (via placental transfer and breastmilk) and infants' own complementary food intake (3, 42-44), we hypothesized that at 6 and 18 mo of age, plasma levels of EFAs (ALA and LA) and their most important derivatives (eicosapentaenoic (EPA), docosahexaenoic (DHA), and arachidonic (AA) acids) would be greater for infants in the group in which women and their offspring received SQ-LNS, compared with the groups in which women received iron and folic acid or multiple micronutrient supplements and their offspring received no supplementation.

METHODS

Study design, setting, and participants

We previously described the design, settings, and participants of the iLiNS-DYAD trials in Ghana (35, 40) and Malawi (37, 41). Both trials were designed as partially double-blind, parallel, individually randomized, controlled trials with 3 equal-size groups.

In Ghana, the trial (*ClinicalTrials.org* Identifier: NCT00970866) took place in the Somanya-Odumase-Kpong area, a semi-urban setting about 70 km north of Accra. It was approved by the ethics committees of the University of California, Davis; the Ghana Health Service; and the University of Ghana Noguchi Memorial Institute for Medical Research. Women attending routine antenatal clinics in the 4 main health facilities in the area between December 2009 and December 2011 were eligible, provided they were ≥18 y old, ≤20 wk pregnant, and their antenatal cards had all of the information needed to determine eligibility. We included women ≥18 y of age because the legal age of adulthood was 18 y, and the prevalence of pregnancy among girls <18 y at the study site at the time was relatively low. Exclusion criteria were: intention to move out of the area during the period of the intervention; milk or peanut allergy; unwillingness to receive field workers or take study supplement; gestational age (GA) >20 weeks before completion of enrolment; antenatal card indicated HIV infection, asthma, epilepsy, tuberculosis, or malignant disease; known to have previously enrolled in the same trial; or currently taking part in another clinical trial.

The Malawi trial (*ClinicalTrials.org* Identifier NCT01239693) was conducted in the Mangochi District, a largely rural area south of the country. It was approved by ethics committees of the University of Malawi College of Medicine, and the Pirkanmaa Hospital District, Finland. Women attending antenatal clinics at 4 health facilities in the area between February 2011 and August 2012 were eligible if they were ≥15 y old, ≤20 wk pregnant, resident of the catchment area served by the 4 health facilities, had no intention to travel out of the study area during the period of the intervention, and signed or thumb-printed informed consent. In Malawi, we included women ≥15 y of age because the legal age of adulthood was 16 y and teenage pregnancy and marriage were relatively common (45, 46). Exclusion criteria were: requiring medical attention due to a chronic

health condition; known to be asthmatic or allergic to peanuts or to any substance; severe illness warranting hospital referral or emergency medical care; history of anaphylaxis; pregnancy complications at the time of enrolment, including moderate to severe oedema, blood Hb concentration < 50 g /L, systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg; ever enrolled in the present trial during a previous pregnancy; or currently taking part in another clinical trial.

Baseline hemoglobin between 50 and 109 g/L (47) was not an exclusion criterion in either site because the intervention provided at least daily iron and folic acid to all participants, as well as bi-weekly home visits to monitor supplement intakes and morbidity.

Group assignments and randomization

In Ghana and Malawi, pregnant women were randomized after baseline assessments to receive daily: 60 mg iron and 400 µg folic acid during pregnancy and placebo (200 mg Ca) during 6 mo postpartum (IFA supplement or group); or multiple micronutrient supplement containing 18 vitamins and minerals (including 20 mg Fe) during both periods (MMN supplement or group); or 20 g SQ-LNS with the same micronutrients as the MMN group, plus Ca, P, K, and Mg, as well as macronutrients including essential FAs during both periods (SQ-LNS supplement or LNS group). Only infants in the LNS group received supplementation, which consisted of SQ-LNS designed for infants from 6 to 18 mo of age.

The randomization techniques in Ghana (40) and Malawi (41) were similar: the Study Statistician used a computer-generated (SAS version 9.4) scheme to develop the group assignments in blocks of 9 , and each supplement or group was coded with 3 different colors (40) or alphabetical letters (41). Group assignments were placed in opaque envelopes, which were labelled such that the women would never see the labels during randomization, and stacked in increasing order of block numbers. At each enrolment, the randomizer shuffled the 9 (40) or 6 (41) topmost

envelopes in the stack, asked the potential participant to choose one (to determine the group assignment), and then returned the unused envelopes to the top of the stack. This process was repeated until all the envelopes prepared for the enrolment site were used. When there were less than 9 (40) or 6 (41) envelopes left for participants to pick from, the randomizer presented whatever number of envelopes that remained. It was not possible for anyone to guess the group assignments, since none had knowledge of the randomization scheme. Group allocation information was kept only by the field supervisor at the project site, and the Study Statistician at UC Davis.

Micronutrient supplements

The nutrient contents of the supplements are shown in **Table 1.** The IFA reflected the standard micronutrient supplementation for pregnant women in Ghana (48) and Malawi (41) at the time of the trials. As previously described (40), the MMN and SQ-LNS provided either *1x* or *2x* the recommended dietary allowance (RDA) of nutrients for pregnancy (40), but iron was kept at 20 mg/d, assuming that this dose, in addition to the amount from the usual diet, would give a total daily intake close to the United Nations International Multiple Micronutrient Preparation (UNIMMAP) iron content for pregnancy (49) and yet would not greatly exceed the RDA (9 mg/d) for lactation (40, 50). The micronutrient content of the infants' SQ-LNS generally reflected the World Health Organization (WHO)/ Food and Agriculture Organization (FAO) Recommended Nutrient Intake (RNI) for infants 7–12 months of age (51). The oil contents of the SQ-LNS products consisted of soybean oil as well as the oil supplied by the peanut paste ingredient; the ingredients combined were designed to meet the target amounts of ALA and LA in the final products.

TABLE 1

Composition of supplements used in the study[1]

Nutrient	IFA[2]	MMN[3]	SQ-LNS for women[4,5]	SQ-LNS for infants[5,6]
Ration (g/day)		1 tablet	20	20
Total energy (kcal)		0	118	118
Protein (g)		0	2.6	2.6
Fat (g)		0	10	9.6
Linoleic acid (g)		0	4.59	4.46
α-Linolenic acid (g)		0	0.59	0.58
Vitamin A (μg RE)[7]		800	800	400
Vitamin C (mg)		100	100	30
Thiamin (mg)		2.8	2.8	0.3
Riboflavin (mg)		2.8	2.8	0.4
Niacin (mg)		36	36	4
Folic acid (μg)	400	400	400	80
Pantothenic acid (mg)		7	7	1.8
Vitamin B-6 (mg)		3.8	3.8	0.3
Vitamin B-12 (μg)		5.2	5.2	0.5
Vitamin D (IU)[8]		400	400	200
Vitamin E (mg)[9]		20	20	6
Vitamin K (μg)[10]		45	45	30
Iron (mg)	60	20	20	6
Zinc (mg)		30	30	8
Cu (mg)		4	4	0.2
Calcium (mg)		0	280	280
Phosphorus (mg)		0	190	190
Potassium (mg)		0	200	200
Magnesium (mg)		0	65	40
Selenium (μg)		130	130	20
Iodine (μg)		250	250	90
Manganese (mg)		2.6	2.6	1.2

[1]IFA, iron and folic acid capsule; MMN, multiple micronutrient supplement capsule; SQ-LNS, small-quantity lipid-based nutrient supplement. The forms of vitamins and minerals used in the supplement formulations were reported previously (21).

[2]Reflected the standard micronutrient supplementation for pregnant women in Ghana (48) and Malawi (41) at the time of the trials.

[3]Micronutrient content was adapted from the UNICEF/WHO/UNU International Multiple Micronutrient Preparation UNIMMAP (49) formulation and a similar formulation used in Guinea Bissau (52), except iron.

[4]Same micronutrient content as MMN.

[5]Nutrient concentrations include contributions from the ingredients as well as from the multiple micronutrient premix. Oil contents consisted of soybean oil and oil from the peanut paste ingredient, which were combined to meet the target amounts of α-linolenic acid and linoleic acid in the final products.

[6]Daily dose of vitamins and minerals reflected the World Health Organization/ Food and Agriculture Organization Recommended Nutrient Intake for key micronutrients for infants 7–12 months of age, with a few exceptions (21).

[7]As retinyl acetate.

[8]As cholecalciferol (D3).

[9]As DL-alpha-tocopherol acetate.

[10]As phylloquinone 5%.

The IFA and MMN (each in 10-capsule blister packs) were supplied by DSM South Africa, and the SQ-LNSs (individual 20-g sachets for women and 10-g sachets for infants) by Nutriset S.A.S. (Malaunay, France).

Intervention

As reported previously, intervention procedures in Ghana (40) and Malawi (41) were similar. Women received a 2-week supply of the assigned supplement at enrolment, with the advice to those in the IFA and MMN groups to consume only 1 capsule each day with water after a meal, and those in the LNS group to mix the entire content of 1 sachet with a small amount of food each day. In addition, women received the standard message: "Do not forget to eat meat, fish, eggs, fruits, and vegetables whenever you can; you still need these foods even as you take the supplement we have given you". During pregnancy, field workers visited women in the homes biweekly whereupon they delivered supplements and collected information on supplement intakes, including recovering and counting any unused supplements and asking the number of days since the visit or during the past 2 wk when supplements were reportedly consumed. After women gave birth, they continued to receive the assigned supplements or placebo biweekly until they exited at 6 mo postpartum.

During the period from 6 to 18 mo of age, field workers visited all infants weekly and delivered the infants' SQ-LNS to mothers in the LNS group at each of these visits in Ghana and at every other visit in Malawi. Reports of infants' SQ-LNS intakes were collected by recovering and counting any unused supplements and using a calendar grid on which mothers recorded days when

supplements were reportedly given to the infants. At the first delivery of the infants' SQ-LNS, mothers were advised to give the supplements by mixing the entire content of one sachet with 2-3 tablespoons of any food for the infants before feeding additional foods if the infants desired, two times each day. At 6 and 12 mo of age, all mothers received the standard nutrition message: "breastfeed your baby as you did before 6 mo of age; do not forget to give your baby other foods such as meat, fish, eggs, fruits, and vegetables whenever you can because your baby still needs these foods." For mothers in the LNS group, the last part of the message was modified to say; "Your baby still needs these foods even as you give him/her the infants' SQ-LNS."

We could not blind field workers or study participants to those who received the SQ-LNSs, because the capsules (IFA and MMN) and SQ-LNS sachets were dissimilar, and only infants in the LNS group received supplementation. However, the study staff who collected the blood samples as well as the personnel who performed the laboratory analysis did not know the group assignments.

Data on adherence to supplement intake have been reported previously (35, 37, 53). We defined adherence to maternal supplement intake during pregnancy and postpartum as the percentage of days from enrolment to child-birth, and from child-birth to 6 mo postpartum, respectively, when supplement was reportedly consumed by women. Self-reported adherence to supplement intake for women (pregnancy/lactation) was 88%/86% for the IFA group, 87%/85% for the MMN group, and 84%/80% for the LNS group in Ghana, and 92%/97% for the IFA group, 91%/97% for the MMN group, and 94%/96% for the LNS group in Malawi (53). For infants in the LNS group, average adherence (percentage of days from 6 to 18 mo of age when SQ-LNS was reportedly served to the infant) was 74% in Ghana (35) and 77% in Malawi (37).

Procedures and plasma samples analysis

In Ghana (40) and Malawi (41), the baseline assessments included obtaining women's background and household characteristics and determining their weight (Seca 874) and height (Seca 217) using

standard procedures, and malaria parasitemia using a rapid diagnostic test (Vision Biotech, South Africa for the Ghana trial, and Clearview Malaria Combo, British Biocell International Ltd for the Malawi trial). At 6 and 18 mo of age, infants were brought to the laboratory, where venous blood samples were collected into heparin-treated, trace element-free tubes at the laboratory and subsequently centrifuged at 1,252 x *g* for 15 min to obtain plasma samples. These samples were stored temporarily at -33 ºC in Ghana and -80 ºC in Malawi before being air-freighted on dry ice to UC Davis where they were stored at -80 ºC before analysis. Previous results (unpublished) showed no evidence of sample degradation or FA oxidation when plasma samples were stored at -20 ºC versus -80 ºC for up to one year, likely because plasma is relatively stable (54). The mothers typically walked or used public transportation to and from the laboratory (wherever possible, and the project paid any cost of transportation), but when necessary, we used the project vehicles to transport them.

Infants' plasma FA profiles were determined at OmegaQuant Analytics in Sioux Falls, South Dakota, USA, as done previously (55). Plasma was added to a mixture of methanol containing 14% boron trifluoride, toluene, and methanol (35:30:30, v/v/v; Sigma-Aldrich, St. Louis, MO) in a tube, which was then vortexed in a bath at 100 °C for 45 min. Upon cooling, hexane (EMD Chemicals, USA) and distilled water were added, and the samples were vortexed and then centrifuged for 10 minutes. An aliquot of the upper hexane phase was analyzed using a GC-2010 gas chromatograph (Shimadzu Corporation, Columbia, MD) equipped with a 100-m fused silica capillary column (SP-2560: 0.25 mm internal diameter, 0.2 µm film thickness; Supelco, Bellefonte, PA). Plasma samples collected at 6 and 18 mo of age were analyzed at the same time. We expressed FA levels as percent composition (%C) by weight of individual FAs or FA groups relative to the total plasma FAs detected (i.e., % wt/wt), to reflect the amounts of individual FAs and FA groups in relation to other FAs within the plasma FA pool (56). Individual FAs or FA groups expressed as %C of total fat may not reflect absolute concentrations of those FA or FA groups (56, 57).

309

310 **Outcome measures**

311 Given that the participants in the LNS group received EFAs (ALA and LA), we considered the levels
312 of these EFAs and their most important derivatives (EPA, DHA, and AA) at 6 and at 18 mo of age
313 as the main outcome measures in the present analysis. Secondary outcome measures at 6 and 18
314 mo of age were: (a) mean %C of the other individual FAs (besides those listed as main outcomes),
315 (b) mean %C of total FA groups, (c) ratio of n-6 poly-unsaturated FA (PUFA) to n-3 PUFA i.e. FAs
316 with at least 2 double bonds, and (d) percentage of children with a low %C of each EFA and the
317 most important derivatives (ALA, LA, EPA, DHA, and AA). The 7 total FA groups were the sums of
318 all: (i) saturated FA, (ii) monounsaturated FA, (iii) n-3 PUFAs, (iv) n-6 PUFAs, (v) unsaturated FAs
319 (UFA), i.e., FAs with at least one double bond, (vi) PUFAs, i.e., all n-3 and n-6 FAs, and (vii) trans
320 FAs.

321 There are no published or accepted cut-offs for defining low plasma %C of FAs in children
322 6-18 mo of age (58), and in any case, cut-off values based on international or foreign populations
323 might not be appropriate to the Ghanaian or Malawian populations, due to population-specific
324 variations. Thus, as done previously (55), we defined low %C of plasma FAs in Ghana and Malawi
325 as a FA %C below the 10^{th} percentile of %C values in the IFA group, since that group reflected the
326 standard-of-care for pre- and post-natal nutrition intervention in each country. The use of such
327 population-specific cut-offs is common (59), and has been recommended (60).

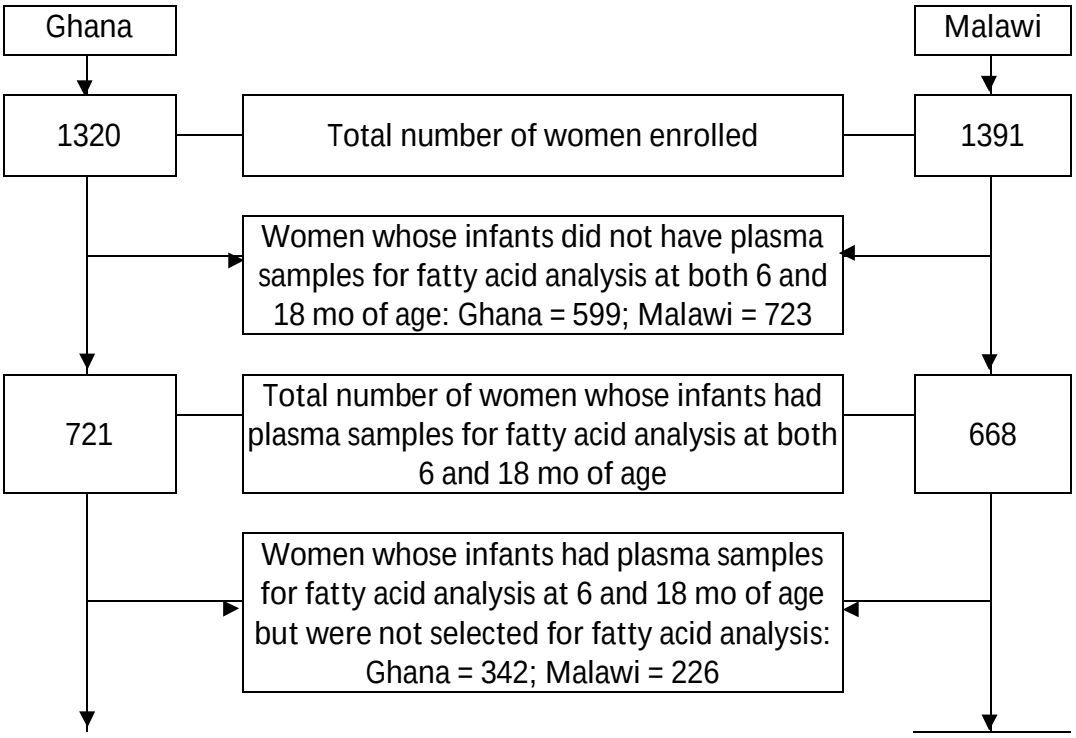
328

329 **Sample size and data analysis**

330 We aimed to analyze plasma samples of infants of approximately 30% of women enrolled in each
331 trial. The resulting sub-sample was larger than the one typically used for most biochemical
332 outcomes in the Ghana and Malawi trials (which was based on detecting Cohen's effect size *d* of
333 0.5 between groups (55, 61-63)), and was intended to give us more statistical power, given the

relatively large number of outcomes being compared. For both trials, infants selected for the analysis had to have plasma samples for fatty acid analysis at both 6 and 18 mo of age, and for the Ghana trial, mothers of the selected infants should have been enrolled after we corrected the mislabeling situation we reported previously (35, 40), so that none of the infants in the IFA and MMN groups was exposed to unintended supplements prenatally or postnatally.

After sorting, infants who had plasma samples for fatty acid analysis at 6 and 18 mo of age (721 in Ghana and 668 in Malawi) were evenly distributed across the intervention groups at each site. We used the XLSTAT's Data sampling function to randomly select the subsets of infants. In Ghana, we selected the infants of 417 women (30% of the 1320 women enrolled, plus another ~5% to compensate for any unsuccessful laboratory test runs). In the later laboratory analysis, infants of 38 women had insufficient (< 0.1 mL) plasma and therefore infants of 379 women (IFA, 124; MMN 130; LNS 125) were included in the present analysis **(Figure 1**). This sample size gave > 93% power to detect an effect size (Cohen's d) of $\geq$ 0.5 between any 2 of the 3 groups, assuming alpha = 0.017 for 3 pairwise comparisons.



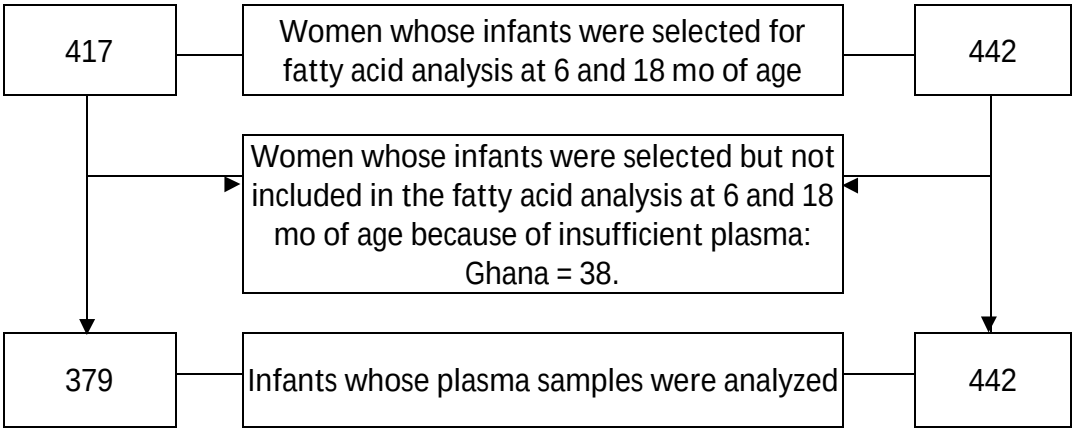


FIGURE 1 Profile for the trials in Ghana and Malawi.

In Malawi, we randomly selected the infants of 442 women (IFA, 146; MMN 149, LNS 147) out of the total 1391 women enrolled **(Figure 1**), using the same procedures as described for the Ghana trial. In the later laboratory analysis, all the selected infants had sufficient plasma (> 0.1 mL) and were included in FA analysis. This sample size gave > 96% power to detect an effect size (Cohen's d) of $\geq$ 0.5 between any 2 of the 3 groups, assuming alpha = 0.017 for 3 pairwise comparisons.

We included measurement of children's EFA status in the trial protocols (registered with ClinicalTrials.gov) as part of the secondary outcomes to be reported separately. In addition, we posted our statistical analysis plan on our website (www.ilins.org) before data analysis.

SAS for Windows version 9.4 (SAS Inst., Cary, NC, USA) was used for data analysis. We applied principal component analysis to create a household assets index (from household ownership of assets such as radio, television, refrigerator, cell phone, and stove) and housing index as proxy indicators for household socioeconomic status, and used the Household Food Insecurity Access Scale, HFIAS as an indicator of household food insecurity (64). Data were analyzed by treatment group as randomized, regardless of any protocol violation, following complete-case intention-to-treat principles.

Descriptive statistics were used to summarize, by group, the background characteristics of the women whose infants were included in the plasma FA analysis. We tested the association between primiparity (which differed among groups in infants selected for the FA analysis) and the FA outcomes, and the pairwise correlations among the FA outcomes by using Pearson correlation analysis. The background characteristics of infants selected for the FA analysis and those not selected were compared using Student's t-test for continuous variables and chi-squared test for binary variables. While the present study was not designed to test differences in FA profiles across study sites (Ghana versus Malawi), we used Cohen's effect size (ES) *d* comparison involving only infants in the IFA groups in the two countries to explore differences in fatty acid levels of infants receiving standard of care in the two countries, i.e., consuming typical diets and receiving no micronutrient supplementation following standard nutritional supplementation (60 mg/d iron and 400 µg/d folic acid) for mothers during pregnancy. We calculated ES *d* as mean %C of fatty acids of infants in the IFA group in Ghana minus those of infants in the IFA group in Malawi divided by the pooled SD for both groups (65). The ES *d* provides the difference in FA levels in Ghana and Malawi expressed in SD units, with a zero value when the null hypothesis (no difference) is true, and some other specific non-zero value when the null hypothesis is false, thereby serving as an index of degree of departure from the null hypothesis (66); the larger the ES *d*, the greater the difference in FA levels between the two sites. We considered ES *d* (i.e., standardized difference between the means of the two sites) of < 0.2 as trivial, 0.2 – 0.49 as 'small', 0.5 – 0.79 as 'medium', and ≥ 0.8 as 'large' (65, 66) .

For each site, we examined continuous outcome variables (individual FAs and total FA groups and ratios at 6 and 18 mo of age) for normal distribution, before analyzing them by ANOVA (unadjusted) and ANCOVA (adjusted) models using the type III tests of fixed effects of the SAS PROC GLIMMIX procedure ("dist = normal). We used untransformed data for the analysis of normally distributed continuous outcome variables. For variables not normally distributed, we

calculated group means (± SD or SE) using untransformed data (17) (to allow for easy interpretation of results) and generated only the p-values for group comparisons using the logarithmically transformed data. The covariates for the ANCOVA models were maternal body mass index (BMI), household assets index, HFIAS, and child sex, which were selected based on the theoretical rationale that they could potentially modify the intervention effects on children's %C of FAs.

We performed unadjusted and covariate-adjusted comparisons of the prevalence of low plasma ALA, LA, EPA, DHA, and AA using a modified Poisson regression model (67). The covariates for the adjusted analysis of the binary outcome variables were the same 4 variables (maternal BMI, household assets index, HFIAS, and child sex) selected for the continuous outcomes.

For the analysis of all outcome variables, we set the level of significance (α) at 0.05 and considered $0.05 < p \leq 0.08$ to show a tendency towards significance (68, 69). Where there was a statistically significant treatment effect at $\alpha = 0.05$, we identified the differing means or percentages by using Tukey-Kramer pairwise comparisons at $\alpha = 0.05$.

RESULTS

The maternal baseline characteristics of the infants in the plasma FA analysis are presented in **Table 2**. In the Ghana trial, maternal age averaged ~28 y, formal education averaged 7 completed y, and mean gestational age and BMI at enrollment were 16 wk and 25.6 kg/m^2, respectively (with prevalence of overweight or obesity being 46%). The average household assets index, housing index, and HFIA score suggest moderate socioeconomic status and low household food insecurity. Mothers of nearly one-half of the infants were enrolled in the dry season, 8% tested positive for malaria, and 20% of the infants were first-born. Intervention groups were similar in background characteristics, except for primiparity (overall P = 0.042), which was not correlated with any of the FA outcomes. Likewise, most of these background characteristics did not differ significantly

between infants selected for the FA analysis compared to those not selected (*n* = 941), except for greater mean ± SD age (27.8 ± 5.4 vs 26.3 ± 5.5; P <0.001), BMI (25.6 ± 4.8 vs 24.4 ± 4.3; P < 0.001), and assets index (0.2 ± 0.9 vs -0.06 ± 1.04; P = 0.001) and lower prevalence of first-time mothers (20% vs 39%) for the former compared with the latter.

TABLE 2 Background characteristics at enrolment of women selected for infants' plasma fatty acid analysis, from the iLiNS-DYAD randomized trials of pre- and post-natal micronutrient supplementation in Ghana and Malawi, by group[1]

Maternal and household characteristics	Ghana			Malawi		
	IFA (n = 124)	MMN (n = 130)	LNS (n = 125)	IFA (n = 146)	MMN (n = 149)	LNS (n = 147)
Age, y	28.0 ± 5.0 (124)	27.4 ± 5.7 (130)	28.1 ± 5.3 (125)	25.1 ± 5.9 (146)	24.7 ± 6.1 (149)	24.9 ± 6.5 (147)
Asset index[2]	0.2 ± 0.9 (124)	0.2 ± 0.8 (130)	0.1 ± 0.8 (125)	-0.1 ± 0.98 (146)	0.0 ± 0.96 (146)	-0.1 ± 0.86 (145)
Housing index[2]	0.10 ± 0.91 (124)	-0.04 ± 1.03 (130)	-0.01 ± 1.04 (125)	-0.16 ± 0.92 (146)	-0.05 ± 0.95 (149)	-0.04 ± 0.92 (143)
HFIA score[3]	3.3 ± 4.8 (124)	2.7 ± 3.9 (130)	2.3 ± 3.4 (125)	5.3 ± 4.2 (146)	5.7 ± 4.8 (147)	4.7 ± 4.3 (145)
Years of formal education, y	7.6 ± 3.5 (124)	7.1 ± 3.4 (130)	7.8 ± 3.8 (125)	3.6 ± 3.5 (145)	3.8 ± 3.5 (149)	3.7 ± 3.4 (145)
Gestational age, wk	15.8 ± 3.3 (124)	16.2 ± 2.9 (130)	16.0 ± 2.9 (125)	16.8 ± 2.1 (146)	17.0 ± 2.1 (149)	16.9 ± 2.2 (147)
BMI, kg/m^2	25.3 ± 4.6 (122)	25.1 ± 4.9 (126)	26.4 ± 4.8 (125)	22.2 ± 2.6 (146)	22.2 ± 2.9 (149)	21.9 ± 2.7 (145)
Season = Dry season *n*/total *n* (%)[4]	70/124 (56.5)	61/130 (46.9)	55/125 (44.0)	73/146 (50.0)	69/149 (46.3)	70/146 (47.9)
Positive malarial RDT, *n*/total *n* (%)[5]	5/124 (4.0)	15/130 (11.5)	11/125 (8.8)	36/146 (24.7)	33/149 (22.1)	33/144 (22.9)
Primiparous women, *n*/total *n* (%)	23/124 (18.5)	35/130 (26.9)	18/125 (14.4)	30/146 (20.5)	33/149 (22.1)	32/146 (21.9)

[1] Total *n*: Ghana, 379; Malawi, 442.. Values are means ± SDs (n) unless otherwise indicated. *n*/total *n* indicates the number of participants whose response was "yes" for the variable in question/total number of participants analyzed for the variable in question. BMI, Body Mass Index; HFIAS, Household Food Insecurity Access Scale; IFA, iron and folic acid; iLiNS-DYAD, International Lipid-based Nutrient Supplements study in which mother-child dyads were enrolled; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient; RDT, Rapid Diagnostic Test.

[2]Proxy indices for household socioeconomic status; higher values represent higher socioeconomic status.

[3]HFIAS is an indicator for household food insecurity (64); higher values represent higher food insecurity.

[4]Season = Dry season: Ghana, November -April; Malawi, May-October.

[5]RDT which detected *P. falciparum* and non-*P. falciparum* histidine-rich protein-2 (Clearview Malarial Combo, Vision Biotech, South Africa).

In Malawi, maternal age averaged ~25 y, formal education averaged 3 completed years, and mean gestational age and BMI at enrollment were 16.9 wk and 22.1 kg/m^2, respectively (with prevalence of overweight or obesity being 12.5%). The average household assets index, housing index, and HFIA score suggested that the women's socioeconomic status was mostly low, and their household food insecurity was generally high. Mothers of nearly one-half of the infants were enrolled in the dry season, 23% tested positive for malaria, and 21.5% of the infants were first-born. The intervention groups were similar in background characteristics. As in Ghana, most of the maternal characteristics compared did not differ significantly between infants selected for the FA analysis compared to those not selected (*n* = 949), except for lower mean ± SD years of formal education (3.7 ± 3.5 vs 4.2 ± 3.4; P = 0.016) and housing score (-0.08 ± 0.93 vs 0.04 ± 1.03; P = 0.036), and a lower percentage of mothers enrolled in the dry season (48% vs 60%) for the selected compared with the unselected infants.

Characteristics of the FA profiles identified in Ghana and Malawi

We present the unadjusted %Cs of 24 individual FAs identified at 6 (**Table 3**) and 18 (**Table 4**) mo of age, along with the sums of FA groups and the n-6 PUFA to n-3 PUFA ratio. The chain lengths of the FAs ranged from 14 to 24 carbon atoms. We do not report plasma mead acid levels of the infants at 6 or 18 mo of age because they were undetectable.

452 **TABLE 3** Unadjusted comparison of mean ± SD percent composition (% of total fat) of individual fatty acids (FAs) and total FA groups and ratios
453 at 6 mo of age, by intervention group in Ghana and Malawi[1]

Individual FAs and total FA groups and ratios		Ghana				Malawi				Effect Size[2]	
		IFA (n = 124)	MMN (n = 130)	LNS (n = 125)	P[3]	IFA (n = 146)	MMN (n = 149)	LNS (n = 147)	P[3]	Positive for Ghana	Positive for Malawi
SFAs											
14:0[4]	Myristic	1.86 ± 0.68	1.93 ± 0.89	1.84 ± 0.67	1.00	4.07 ± 2.07	3.95 ± 2.52	3.76 ± 2.23	0.24		1.4
16:0	Palmitic	26.3 ± 1.4	26.6 ± 1.6	26.2 ± 1.5	0.12	24.7 ± 1.6	24.6 ± 1.8	24.4 ± 1.8	0.43	1.1	
18:0	Stearic	8.24 ± 0.75	8.20 ± 0.73	8.09 ± 0.73	0.26	7.61 ± 0.75	7.58 ± 0.86	7.60 ± 0.82	0.92	0.8	
20:0	Arachidic	0.11 ± 0.03	0.10 ± 0.03	0.11 ± 0.03	0.59	0.13 ± 0.04	0.13 ± 0.04	0.13 ± 0.04	0.84		0.6
22:0[4]	Behenic	0.18 ± 0.06	0.17 ± 0.06	0.18 ± 0.06	0.19	0.21 ± 0.08	0.21 ± 0.09	0.22 ± 0.09	0.34		0.4
24:0[4]	Lignoceric	0.17 ± 0.05	0.17 ± 0.05	0.18 ± 0.05	0.30	0.21 ± 0.08	0.22 ± 0.09	0.23 ± 0.09	0.38		0.6
MUFAs											
16:1n-7[4]	Palmitoleic	1.35 ± 0.35	1.31 ± 0.34	1.34 ± 0.43	0.72	1.44 ± 0.45	1.44 ± 0.46	1.39 ± 0.46	0.45		0.2
18:1n-9	Oleic	22.2 ± 2.3	22.4 ± 2.3	21.9 ± 2.2	0.26	18.2 ± 2.5	17.9 ± 2.8	18.2 ± 2.9	0.50	1.7	
20:1n-9[4]	Eicosenoic	0.17 ± 0.04	0.17 ± 0.04	0.17 ± 0.04	0.77	0.17 ± 0.05	0.17 ± 0.05	0.17 ± 0.05	0.68	0.0	
24:1n-9[4]	Nervonic	0.37 ± 0.15	0.34 ± 0.14	0.36 ± 0.15	0.37	0.34 ± 0.16	0.36 ± 0.18	0.36 ± 0.17	0.33	0.2	
n-3 PUFAs											
18:3n-3[4]	alpha-Linolenic	0.21 ± 0.06[a]	0.21 ± 0.07[a]	0.23 ± 0.08[b]	0.034	0.38 ± 0.15[ab]	0.38 ± 0.14[a]	0.42 ± 0.16[b]	0.034		1.5
20:5n-3[4]	Eicosapentaenoic	0.99 ± 0.58	1.02 ± 0.59	0.99 ± 0.58	0.88	0.52 ± 0.29	0.57 ± 0.39	0.57 ± 0.37	0.54	1.0	
22:5n-3	Docosapentaenoic n-3	0.46 ± 0.13	0.47 ± 0.14	0.47 ± 0.13	0.77	0.53 ± 0.11	0.55 ± 0.17	0.51 ± 0.13	0.054		0.6
22:6n-3	Docosahexaenoic	3.82 ± 0.88	3.81 ± 1.01	3.86 ± 0.83	0.88	3.74 ± 0.91	3.84 ± 0.95	3.77 ± 0.96	0.65	0.1	
n-6 PUFAs											
18:2n-6	Linoleic	25.0 ± 2.5	24.9 ± 2.6	25.4 ± 2.5	0.28	26.7 ± 2.8	27.1 ± 3.5	27.4 ± 3.7	0.17		0.6
20:2n-6	Eicosadienoic	0.23 ± 0.05	0.22 ± 0.04	0.22 ± 0.04	0.43	0.35 ± 0.06[a]	0.34 ± 0.07[ab]	0.33 ± 0.06[b]	0.036		2.2
18:3n-6[4]	g-Linolenic	0.13 ± 0.04	0.13 ± 0.05	0.13 ± 0.04	0.65	0.17 ± 0.08	0.16 ± 0.06	0.16 ± 0.06	0.050		0.6
20:3n-6	Dihomo-g-linolenic	1.26 ± 0.25	1.24 ± 0.29	1.26 ± 0.31	0.79	1.42 ± 0.35[a]	1.34 ± 0.38[ab]	1.31 ± 0.36[b]	0.028		0.5
20:4n-6	Arachidonic	6.12 ± 1.13[ab]	5.89 ± 1.24[a]	6.25 ± 1.24[b]	0.049	8.13 ± 1.63	8.23 ± 1.77	8.05 ± 1.68	0.67		1.4
22:4n-6	Docosatetraenoic	0.14 ± 0.04	0.13 ± 0.04	0.14 ± 0.04	0.65	0.29 ± 0.06[a]	0.27 ± 0.06[b]	0.26 ± 0.05[b]	<0.001		2.9
22:5n-6[4]	Docosapentaenoic n-6	0.12 ± 0.05	0.12 ± 0.05	0.11 ± 0.04	0.42	0.34 ± 0.09	0.33 ± 0.11	0.32 ± 0.10	0.10		3.0
Trans fats											
16:1n-7t[4]	Palmitelaidic	0.09 ± 0.03	0.08 ± 0.03	0.08 ± 0.03	0.12	0.06 ± 0.02	0.06 ± 0.04	0.06 ± 0.03	0.17	1.2	

Individual FAs and total FA groups and ratios	Ghana				Malawi				Effect Size[2]	
	IFA (n = 124)	MMN (n = 130)	LNS (n = 125)	P[3]	IFA (n = 146)	MMN (n = 149)	LNS (n = 147)	P[3]	Positive for Ghana	Positive for Malawi
18:1n-9t[4] Elaidic	0.29 ± 0.13[a]	0.25 ± 0.10[b]	0.29 ± 0.28[ab]	0.026	0.18 ± 0.07	0.19 ± 0.11	0.18 ± 0.08	0.92	1.1	
18:2n-6t[4] Linoelaidic	0.26 ± 0.11	0.23 ± 0.10	0.24 ± 0.10	0.06	0.19 ± 0.07	0.20 ± 0.09	0.20 ± 0.07	0.39	0.8	
Total fatty acid groups and ratios										
SFAs[4, 5]	36.9 ± 1.9	37.1 ± 2.2	36.6 ± 1.9	0.11	36.9 ± 2.9	36.6 ± 3.1	36.4 ± 3.1	0.24	0.0	
MUFAs[6]	24.1 ± 2.5	24.2 ± 2.4	23.8 ± 2.4	0.36	20.2 ± 2.5	19.9 ± 2.9	20.1 ± 3.0	0.60	1.6	
n-3 PUFAs[7]	5.47 ± 1.45	5.51 ± 1.58	5.55 ± 1.40	0.92	5.17 ± 1.19	5.33 ± 1.39	5.26 ± 1.34	0.57	0.2	
n-6 PUFAs[8]	33.0 ± 3.0	32.6 ± 3.3	33.5 ± 3.0	0.08	37.3 ± 3.2	37.8 ± 4.1	37.8 ± 4.1	0.53		1.4
UFAs[4,9]	62.5 ± 1.9	62.3 ± 2.3	62.8 ± 1.9	0.16	62.7 ± 2.8	62.9 ± 3.1	63.2 ± 3.1	0.36		0.1
PUFAs[10]	38.4 ± 3.6	38.1 ± 3.9	39.0 ± 3.4	0.14	42.5 ± 3.7	43.1 ± 4.4	43.1 ± 4.4	0.42		1.1
n-6 PUFAs:n-3 PUFAs ratio[4]	6.45 ± 1.80	6.42 ± 2.15	6.36 ± 1.49	0.92	7.59 ± 1.95	7.53 ± 2.01	7.61 ± 1.94	0.82		0.6
Total trans FAs[4,11]	0.63 ± 0.21[a]	0.55 ± 0.18[b]	0.62 ± 0.33[ab]	0.005	0.42 ± 0.13	0.45 ± 0.19	0.44 ± 0.14	0.36	1.2	

[1]Within country, labeled means in a row without a common letter differ, P<0.05 by ANOVA and Tukey-Kramer tests. FA, fatty acid; IFA, iron and folic acid; LNS, Lipid-based Nutrient Supplements; MMN, Multiple Micronutrients; MUFA, monounsaturated FA; PUFA, polyunsaturated FA; SFA, saturated FA; UFA, unsaturated FA.

[2] Cohen's effect size (ES) *d* (65, 66) is for the difference between study sites (Ghana and Malawi) based on infants in the IFA groups only, who consumed typical diets and received no micronutrient supplementation following standard nutritional supplementation for their mothers during pregnancy. Positive ES indicates that the mean percent composition (%C) of FA level for the site in question is greater than that for the other site. We considered Cohen's *d* of < 0.2 as trivial, 0.2–0.49 as 'small', 0.5–0.79 as 'medium', and ≥ 0.8 as 'large' (66).

[3]P-values compare all 3 group means within country at α = 0.05, by ANOVA.

[4]Log transformed for analysis.

[5]SFAs: Sum of 14:0, 16:0, 18:0, 20:0, 22:0, and 24:0.

[6]MUFAs: Sum of 16:1n-7, 18:1n-9, 20:1n-9, and 24:1n-9.

[7]n-3 PUFAs: Sum of 18:3n-3, 20:5n-3, 22:5n-3, and 22:6n-3.

[8]n-6 PUFAs: Sum of 18:2n-6, 20:2n-6, 18:3n-6, 20:3n-6, 20:4n-6, 22:4n-6, and 22:5n-6.

[9]UFAs: Sum of MUFAs, n-3 PUFAs, and n-6 PUFAs.

[10]PUFAs: Sum of n-3 PUFAs and n-6 PUFAs.

[11]Total trans FAs: Sum of 16:1n-7t, 18:1n-9t, and 18:2n-6t.

475 **TABLE 4** Unadjusted comparison of mean ± SD percent composition (% of total fat) of individual fatty acids (FAs) and total FA groups and ratios
476 at 18 mo of age, by intervention group in Ghana and Malawi[1]

Individual FAs and total FA groups and ratios		Ghana				Malawi				Effect Size[2]	
		IFA (n = 124)	MMN (n = 130)	LNS (n = 125)	P[3]	IFA (n = 146)	MMN (n = 149)	LNS (n = 147)	P[3]	Positive for Ghana	Positive for Malawi
SFAs											
14:0[4]	Myristic	1.52 ± 0.70	1.44 ± 0.81	1.50 ± 0.77	0.40	2.71 ± 1.40	2.84 ± 1.67	2.54 ± 1.59	0.12		1.1
16:0	Palmitic	25.4 ± 1.5[ab]	25.6 ± 1.6[a]	25.0 ± 2.0[b]	0.017	24.5 ± 1.6	24.6 ± 1.9	24.1 ± 2.0	0.11	0.6	
18:0	Stearic	7.70 ± 0.67	7.55 ± 0.69	7.59 ± 0.70	0.22	7.31 ± 0.80	7.19 ± 0.68	7.29 ± 0.68	0.32	0.5	
20:0[4]	Arachidic	0.10 ± 0.03	0.10 ± 0.03	0.10 ± 0.03	0.74	0.12 ± 0.03[a]	0.12 ± 0.04[ab]	0.13 ± 0.04[b]	0.028		0.7
22:0[4]	Behenic	0.18 ± 0.06[ab]	0.17 ± 0.06[a]	0.19 ± 0.07[b]	0.008	0.21 ± 0.07[a]	0.22 ± 0.10[a]	0.25 ± 0.10[b]	0.002		0.5
24:0[4]	Lignoceric	0.19 ± 0.05	0.17 ± 0.05	0.19 ± 0.07	0.06	0.24 ± 0.09[a]	0.25 ± 0.10[a]	0.27 ± 0.11[b]	0.033		0.7
MUFAs											
16:1n-7[4]	Palmitoleic	1.15 ± 0.38	1.17 ± 0.51	1.17 ± 0.59	0.91	1.34 ± 0.57[a]	1.30 ± 0.52[a]	1.18 ± 0.47[b]	0.009		0.4
18:1n-9	Oleic	21.8 ± 3.4	22.1 ± 3.2	22.1 ± 3.1	0.77	18.3 ± 3.4	18.6 ± 3.4	18.5 ± 3.4	0.65	1.0	
20:1n-9[4]	Eicosenoic	0.18 ± 0.05	0.17 ± 0.04	0.18 ± 0.05	0.32	0.17 ± 0.04	0.17 ± 0.06	0.18 ± 0.06	0.60	0.2	
24:1n-9[4]	Nervonic	0.32 ± 0.12	0.30 ± 0.12	0.31 ± 0.12	0.42	0.36 ± 0.16	0.35 ± 0.18	0.36 ± 0.17	0.75		0.3
n-3 PUFAs											
18:3n-3[4]	alpha-Linolenic	0.24 ± 0.08	0.24 ± 0.10	0.32 ± 0.16	0.06	0.39 ± 0.18[a]	0.39 ± 0.18[a]	0.45 ± 0.18[b]	<0.001		1.1
20:5n-3[4]	Eicosapentaenoic	1.13 ± 0.76	1.13 ± 0.82	0.98 ± 0.69	0.14	0.52 ± 0.36	0.55 ± 0.38	0.50 ± 0.40	0.27	1.0	
22:5n-3	Docosapentaenoic -n-3	0.47 ± 0.14	0.49 ± 0.15	0.45 ± 0.13	0.13	0.51 ± 0.13	0.52 ± 0.15	0.48 ± 0.12	0.08		0.3
22:6n-3	Docosahexaenoic	4.13 ± 1.18	4.10 ± 1.12	3.96 ± 1.16	0.47	3.67 ± 1.06	3.65 ± 1.06	3.52 ± 0.95	0.43	0.4	
n-6 PUFAs											
18:2n-6	Linoleic	26.9 ± 2.9	27.0 ± 3.1	27.8 ± 3.6	0.06	28.7 ± 3.3[a]	28.6 ± 3.4[a]	29.7 ± 3.5[b]	0.011		0.6
20:2n-6	Eicosadienoic	0.22 ± 0.05	0.21 ± 0.05	0.21 ± 0.04	0.10	0.32 ± 0.06	0.31 ± 0.06	0.31 ± 0.06	0.08		1.8
18:3n-6[4]	gamma-Linolenic	0.17 ± 0.11	0.18 ± 0.10	0.18 ± 0.11	0.59	0.21 ± 0.11	0.19 ± 0.08	0.20 ± 0.11	0.26		0.4
20:3n-6	Dihomo-g-linolenic	1.14 ± 0.28	1.10 ± 0.25	1.06 ± 0.27	0.11	1.27 ± 0.35[a]	1.19 ± 0.33[ab]	1.16 ± 0.32[b]	0.016		0.4
20:4n-6	Arachidonic	6.05 ± 1.44	5.82 ± 1.37	5.81 ± 1.42	0.31	8.21 ± 1.86	7.95 ± 1.81	7.78 ± 1.99	0.15		1.3
22:4n-6	Docosatetraenoic	0.14 ± 0.05	0.14 ± 0.05	0.14 ± 0.05	0.80	0.28 ± 0.07	0.27 ± 0.07	0.26 ± 0.07	0.06		2.3
22:5n-6	Docosapentaenoic - n6	0.15 ± 0.06	0.15 ± 0.06	0.14 ± 0.06	0.28	0.34 ± 0.10	0.34 ± 0.10	0.33 ± 0.11	0.70		2.3
Trans fats											
16:1n-7t[4]	Palmitelaidic	0.09 ± 0.03	0.09 ± 0.04	0.08 ± 0.03	0.14	0.05 ± 0.02	0.06 ± 0.04	0.06 ± 0.03	0.95	1.6	

Individual FAs and total FA groups and ratios	Ghana				Malawi				Effect Size[2]	
	IFA (n = 124)	MMN (n = 130)	LNS (n = 125)	P[3]	IFA (n = 146)	MMN (n = 149)	LNS (n = 147)	P[3]	Positive for Ghana	Positive for Malawi
18:1n-9t[4] Elaidic	0.30 ± 0.20	0.30 ± 0.22	0.29 ± 0.18	0.72	0.16 ± 0.09	0.17 ± 0.08	0.17 ± 0.07	0.21	0.9	
18:2n-6t[4] Linoelaidic	0.28 ± 0.11	0.27 ± 0.11	0.29 ± 0.13	0.49	0.21 ± 0.09	0.22 ± 0.09	0.22 ± 0.08	0.66	0.7	
Total fatty acid groups and ratio										
SFAs[5]	35.1 ± 1.8	35.0 ± 1.9	34.6 ± 2.3	0.06	35.1 ± 2.2	35.2 ± 2.6	34.6 ± 2.8	0.13	0.0	
MUFAs[6]	23.5 ± 3.5	23.7 ± 3.5	23.8 ± 3.4	0.80	20.1 ± 3.6	20.4 ± 3.6	20.2 ± 3.7	0.77	1.0	
n-3 PUFAs[7]	5.97 ± 1.93	5.96 ± 1.91	5.71 ± 1.83	0.48	5.09 ± 1.41	5.10 ± 1.48	4.96 ± 1.31	0.62	0.5	
n-6 PUFAs[8]	34.8 ± 3.7	34.6 ± 3.6	35.3 ± 4.0	0.31	39.3 ± 3.9	38.9 ± 4.3	39.7 ± 4.6	0.21		1.2
UFAs[9]	64.2 ± 1.8	64.3 ± 1.9	64.8 ± 2.3	0.06	64.5 ± 2.3	64.4 ± 2.5	64.9 ± 2.8	0.13		0.1
PUFAs[10]	40.7 ± 4.6	40.6 ± 4.4	41.0 ± 4.8	0.74	44.4 ± 4.5	44.0 ± 4.6	44.7 ± 5.1	0.40		0.8
n-6 PUFAs:n-3 PUFAs ratio[4]	6.45 ± 2.12	6.38 ± 2.00	6.81 ± 2.31	0.24	8.27 ± 2.22	8.21 ± 2.35	8.50 ± 2.18	0.36		0.8
Total trans FAs[4,11]	0.67 ± 0.25	0.66 ± 0.26	0.66 ± 0.25	0.96	0.43 ± 0.17	0.44 ± 0.17	0.45 ± 0.14	0.47	1.1	

[11]Within country, labeled means in a row without a common letter differ, P<0.05 by ANOVA and Tukey-Kramer tests. FA, fatty acid; IFA, iron and folic acid; LNS, Lipid-based Nutrient Supplements; MMN, Multiple Micronutrients; MUFA, monounsaturated FA; PUFA, polyunsaturated FA; SFA, saturated FA; UFA, unsaturated FA.

[2] Cohen's *d* effect size (65, 66) is for the difference between study sites (Ghana and Malawi), based on infants in the IFA groups only, who consumed typical diets and received no micronutrient supplementation following standard nutritional supplementation for their mothers during pregnancy. We calculated effect size as mean percent composition of fatty acids of infants in the IFA group in Ghana minus those of infants in the IFA group in Malawi divided by the pooled SD for both groups. Positive ES indicates that the mean percent composition (%C) of FA for the site in question is greater than that for the other site. We considered Cohen's *d* of < 0.2 as trivial, 0.2–0.49 as 'small', 0.5–0.79 as 'medium', and ≥ 0.8 as 'large' (66).

[3]P-values compare 3 group means within country at α = 0.05, by ANOVA.

[4]Log transformed for analysis.

[5]SFAs: Sum of 14:0, 16:0, 18:0, 20:0, 22:0, and 24:0.

[6]MUFAs: Sum of 16:1n-7, 18:1n-9, 20:1n-9, and 24:1n-9.

[7]n-3 PUFAs: Sum of 18:3n-3, 20:5n-3, 22:5n-3, and 22:6n-3.

[8]n-6 PUFAs: Sum of 18:2n-6, 20:2n-6, 18:3n-6, 20:3n-6, 20:4n-6, 22:4n-6, and 22:5n-6.

[9]UFAs: Sum of MUFAs, n-3 PUFAs, and n-6 PUFAs.

[10]PUFAs: Sum of n-3 PUFAs and n-6 PUFAs.

[11]Total trans FAs: Sum of 16:1n-7t, 18:1n-9t, and 18:2n-6t.

At 6 mo of age, for all intervention groups, the most abundant plasma FAs in the infants in Ghana were palmitic acid (16:0), followed by LA (18:2n-6), and then oleic acid (18:1n-9), whereas the most abundant FAs in Malawi were LA, followed by palmitic acid, and then oleic acid. Differences between sites in plasma FA %Cs described in terms of Cohen's ES *d* values for the control (IFA) groups (last 2 columns of Table 3), were trivial for eicosenoic acid, DHA, and total saturated FAs (SFAs). Plasma FA %Cs were slightly higher (small effect size) in Ghana (compared with Malawi) for nervonic acid and total n-3 PUFAs, and substantially higher (large effect size) for palmitic and stearic acids, oleic acid, EPA, trans FAs, and monounsaturated FAs (MUFAs). Plasma FA %Cs were slightly higher (small effect size) in Malawi (compared with Ghana) for behenic and palmitoleic acids, and moderately higher (medium-to-large effect sizes) for myristic acid, arachidic acid, lignoceric acid, ALA, docosapentaenoic, the individual and total n-6 PUFAs, total PUFAs, and n-6 PUFA:n-3 PUFA ratio.

At 18 mo of age, for all intervention groups, the most abundant plasma FAs in both Ghana and Malawi were LA, followed by palmitic acid, and then oleic acid. The site differences in the FA profiles observed at 6 mo of age among infants in the IFA groups in Ghana versus Malawi held true at 18 mo of age (last 2 columns of Table 4).

Impact of intervention on FA profile of infants at 6 mo of age

There were several significant differences in the FA profiles among the intervention groups in Ghana and Malawi (Table 3). In Ghana, the LNS group had significantly greater mean ALA %C than the IFA and MMN groups (P = 0.034) and a significantly greater AA %C than the MMN but not IFA group (P = 0.049). There was a tendency towards group differences (P = 0.08) reflecting greater total n-6 PUFA %C in the LNS group than the IFA or MMN group. The 3 groups differed significantly in mean elaidic acid (18:1n-9t) (P = 0.026) and total *trans* FA (P = 0.005) %Cs, but the pairwise tests between the LNS group and the other 2 groups were not significant, whereas the IFA

group had significantly greater mean %Cs than the MMN group. There were no significant differences in mean plasma %Cs of the other individual FAs or sums of FA groups.

In Malawi, infants in the LNS group had significantly greater mean %C of ALA (P = 0.034) than those in the MMN but not the IFA group. There were significant group differences in mean %Cs of 3 FAs considered as secondary outcomes (eicosadienoic acid (20:2n-6); dihomo-g-linolenic acid (20:3n-6); and docosatetraenoic acid (22:4n-6)), and a tendency towards group differences in mean %Cs of 2 other FAs (docosapentaenoic acid (22:5n-3) and g-Linolenic acid (18:3n-6)). In nearly all cases for these secondary outcomes, the IFA group had a greater mean %C than the MMN or LNS groups.

These group differences in Ghana and Malawi at 6 mo of age generally remained unchanged when controlling for maternal BMI, household assets index, HFIAS, and child sex (**Supplemental Table 1**).

The percentages of infants with low plasma %C of EFAs and their most important derivatives are presented in **Supplemental Table 2.** In the unadjusted analysis, the intervention groups in Ghana differed significantly (P = 0.020) in the prevalence of low plasma AA composition, with infants in the LNS group having a lower prevalence than those in the MMN group but not the IFA group. The intervention groups in Malawi, however, did not differ significantly in the prevalence of low plasma %C of any of these FAs. These results remained unchanged in Ghana and Malawi in the adjusted analysis controlling for maternal BMI, household assets index, HFIAS, and child sex.

Impact of intervention on FA profile of infants at 18 mo of age

There were several significant, or tendencies towards significant, differences in the FA profiles among the intervention groups in Ghana and Malawi at 18 mo of age (Table 4). In Ghana, there were tendencies towards significant group differences in %Cs of ALA (P = 0.06) and LA (P = 0.06) reflecting greater levels in the LNS group, compared with the IFA and MMN groups. Besides the

FAs considered as main outcomes, the LNS group had a significantly lower mean palmitic acid (16:0; P = 0.017) %C compared to the MMN group but not the IFA group and a significantly greater mean behenic acid (22:0; P = 0.008) %C compared to the MMN but not IFA group. There were tendencies towards group differences in lignoceric acid (24:04; P = 0.06), total SFAs (P = 0.06), and UFAs (P = 0.06) %Cs reflecting greater lignoceric acid, lower SFA, and greater UFA levels in the LNS group compared with the IFA or MMN group.

In Malawi, the LNS group had significantly greater mean %Cs of ALA (P <0.001) and LA (P = 0.011) levels than the IFA and MMN groups. Among the FAs not considered as main outcomes, the LNS group had significantly greater mean %C of arachidic acid (20:0) than the IFA but not the MMN group (P = 0.028), greater %C of behenic acid (22:0) than the IFA and MMN groups (P = 0.002), greater %C of lignoceric acid (24:0) than the IFA and MMN groups (P = 0.033), lower %Cs of palmitoleic acid (16:1n-7) than the IFA and MMN groups (P = 0.009), and lower %C of dihomo-g-linolenic acid (20:3n-6) than the IFA but not the MMN group (P = 0.016). There were tendencies towards group differences in %Cs of docosapentaenoic (22:5n-3; P = 0.08), eicosadienoic (20:2n-6; P = 0.08) and docosatetraenoic (22:4n-6; P = 0.06) reflecting lower levels in the LNS group compared with the IFA or MMN group.

In both Ghana and Malawi, these group differences in mean plasma %C of FAs at 18 mo of age remained generally unchanged when controlling for maternal BMI, household assets index, HFIAS, and child sex (**Supplemental Table 3**).

Figure 2 shows the percentages of infants with low plasma %C of ALA at 18 mo of age in the intervention groups in Ghana and Malawi, while **Supplemental Table 4** provides detailed results for low plasma %Cs of all the EFAs and their most important derivatives***.*** The Figure shows that the prevalence of low ALA level was significantly lower in the LNS group than the MMN but not the IFA group in both Ghana (P = 0.016) and Malawi (P = 0.023). In Malawi (Supplemental Table 4), other significant differences include a higher prevalence of low AA level in the LNS group

compared with the IFA group but not the MMN group (IFA = 15/146 (10.3%); MMN = 21/149 (14.1%); LNS = 31/147 (21.1%); P = 0.036). As observed at 6 mo of age, these results did not change when controlling for maternal BMI, household assets index, HFIAS, and child sex.

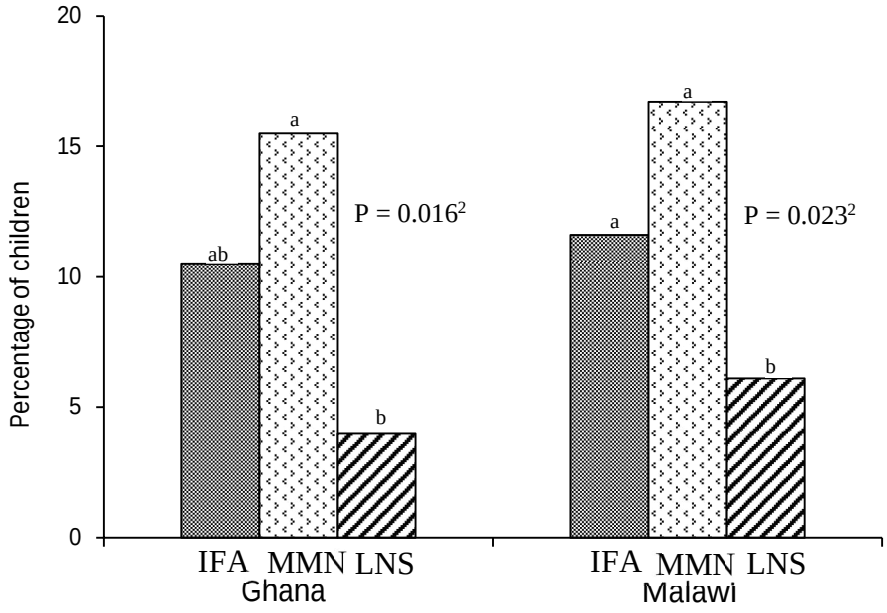


FIGURE 2 Percentage of infants with low plasma percent composition of α-linolenic acid at 18 mo of age, by intervention group in Ghana and Malawi[1]. Total *n*: Ghana, 379 (IFA, 124; MMN 130, LNS 125); Malawi, 442 (IFA, 146; MMN 149, LNS 147). Low plasma percent composition of α-linolenic acid (%C ALA) was defined as %C ALA (% wt/wt of total fatty acids) below the population-specific 10th percentile of %C values in the IFA group (since that group reflected the standard-of-care for pre- and post-natal nutrition intervention in each country). IFA, iron and folic acid; LNS, Lipid-based Nutrient Supplements; MMN, Multiple Micronutrients. [2]Within country, P-value compares all 3 groups at α = 0.05, by a modified Poisson regression (67) and Tukey-Kramer adjustment for pairwise comparisons. Labeled percentages without a common letter differ, P<0.05.

DISCUSSION

Our results show that maternal SQ-LNS consumption increased infants' plasma ALA level in Ghana and Malawi and plasma AA level in Ghana relative to the other FAs in the plasma FA pool at 6 mo of age. At 18 mo of age, the plasma ALA and LA levels of infants in Ghana and Malawi and plasma EPA level of infants in Malawi tended to be greater, or were significantly greater, in the LNS group than in the IFA and/or MMN group, and the prevalence of low plasma ALA level relative to other FAs was significantly lower in the LNS group in both countries. These results support our hypothesis that at 6 and 18 mo of age, the plasma EFA (i.e., ALA and LA) profiles of infants in Ghana and Malawi would differ significantly by intervention group. Except for the group difference in plasma AA in Ghana at 6 mo of age, the data generally did not support the hypothesis that the plasma levels of the most important derivatives of EFAs (i.e., EPA, DHA, and AA) would differ significantly by intervention group. The undetectable levels of plasma mead acid, an indicator of essential fatty acid deficiency (70), in the infants at 6 or 18 mo of age suggests that EFA deficiency was unlikely in the study samples.

Our study has several strengths including the random allocation of participants to intervention groups and blinding of the laboratory analysts to the group assignments. There are potential limitations. First, it is plausible that bias was introduced by selecting infants from a smaller pool (i.e., those who had plasma for fatty acid analysis at both 6 and 18 mo of age) for the FA analysis. In both countries, the infants included in the analysis and those not included differed significantly in certain background characteristics, and therefore the results may not be generalizable to the larger study populations. Second, we collected infants' dietary data (via 24-h recall) at different time points (9 and 15 mo of age) than when blood samples were collected for the fatty acid analysis, and therefore, we did not include infant's background dietary intakes in the present analysis. Nonetheless, because the infants in the FA analysis did not differ significantly between intervention groups in background characteristics, except for primiparity in Ghana (which

was not correlated with any of the FA outcomes), the conclusions about effects of the intervention are unlikely to be biased. Third, plasma fatty acid levels are known to reflect dietary intakes of the past hours to days (plasma triglycerides) or weeks (plasma cholesteryl esters and phospholipids) (71), and therefore may not be adequate to detect the impact of SQ-LNS consumed over a longer duration, as in the Ghana and Malawi trials. However, infants in the LNS group did not stop receiving SQ-LNS until after they had attended the blood draw at 18 mo of age. Last, we tested multiple hypotheses (involving 24 continuous and 5 binary plasma FA variables) at both 6 and 18 mo of age, and therefore, some of the observed differences may be due to chance (72). However, these FAs are generally highly correlated, and under such circumstances, correcting for multiplicity may be unnecessary and counterproductive (73).

Infants' supplement intakes, breastfeeding practices and complementary feeding practices during follow-up may have influenced our results. It was not possible to evaluate whether higher vs. lower adherence to supplements may have modified the results (e.g., in a sensitivity analysis) because only the infants in the LNS group (and not those in the other two groups) received supplementation. In our previous report (74), infants receiving SQ-LNS did not differ significantly in various indicators of infant and young child feeding practices (including breastfeeding and complementary feeding practices) at 18 mo of age in either Ghana or Malawi, compared with those not receiving SQ-LNS. Thus, it is unlikely that infant and young child feeding practices confounded our results regarding intervention group differences in plasma fatty acid levels.

Our results contrast with those of the trial in South Africa (39), which showed no impact on plasma FA profile among infants consuming SQ-LNSs containing ALA and LA from 6 to 12 mo of age, compared with no supplementation. One potential explanation for this difference may be the longer intervention duration of the iLiNS-DYAD trials, in which infants were exposed to SQ-LNS both via maternal supplementation during pregnancy and the first 6 mo postpartum, and directly

from 6 to 18 mo of age. Another potential factor is that the amount of ALA provided by the SQ-LNS in South Africa was less than what was provided in the iLiNS-DYAD trials (0.265 vs. 0.58 g/d).

The FA profiles of the infants in Ghana and Malawi (at both 6 and 18 mo of age) generally mimicked the maternal plasma FA profiles at 36 wk of pregnancy and breastmilk profiles at 6 mo postpartum, which we published previously (55). For example, mothers in Ghana (compared with those in Malawi) had higher levels of palmitic, stearic and oleic acids, as well as EPA, whereas the reverse was true for myristic acid, ALA, and n-6 PUFAs. The pattern of the infants' (as well as the maternal (55)) FA levels in Ghana reflects diets high in palm oil and total fat (75). The majority of women in the Ghana trial typically consumed foods made with red palm oil more than 3 times per wk (76). In Malawi, the plasma FA patterns (e.g., relatively high myristic acid and low oleic acid and stearic acid levels) were attributed to diets high in carbohydrate and low in total fat (77, 78) as well the consumption of *usipa*, a small dried fish from Lake Malawi providing a rich source of AA and DHA (78).

The greater plasma ALA level of the LNS group in Ghana and Malawi at 6 mo of age likely reflects maternal consumption of SQ-LNS, which contains 0.59 g of ALA per daily dose (42-45% of the US Institute of Medicine (IOM) adequate intake for pregnant or lactating women (21)). We previously reported (55) that mothers in the LNS group, compared with those in the IFA and MMN groups, had significantly greater median plasma %C of ALA at 36 wk of pregnancy in the pooled Ghana and Malawi sub-samples, and greater median breast milk %C of ALA in the Ghana sub-sample. Not all of the infants in the present analysis are those of the mothers in the previous analysis (55) because not all of the infants of those mothers had plasma samples at 6 and 18 mo of age available. Nonetheless, the previous maternal results are consistent with the present results for infants. It is likely that during the prenatal period, infants in the LNS group received greater amounts of ALA via placental transfer into fetal circulation (3, 42, 43). During the first 6 mo postpartum,

mothers in the LNS group may have transferred more ALA to their infants via breastmilk as a result of SQ-LNS consumed during both pregnancy and lactation (43, 44).

Infants in the LNS group were also exposed to maternal LA consumption from SQ-LNS (as they were to ALA), and therefore, it is unclear why we found no significant group differences in the levels of that EFA at 6 mo of age. In both Ghana and Malawi, the point estimates of mean %C of LA for the LNS group were slightly higher than those for the other 2 groups, but the differences were not significant, possibly because of the larger plasma pool size for LA (compared with ALA) which may make it more difficult to detect effects of the intervention. In Ghana, another possibility is that the extra LA provided by LNS was converted to AA (3), given that AA level was significantly higher in the LNS group than the other two groups. In Malawi, infants' AA level did not differ significantly between intervention groups, and there was probably less need for LA conversion to AA because the AA levels were relatively high.

At 18 mo of age, the greater mean ALA and LA levels in the LNS group (compared with the other 2 groups) in both Ghana and Malawi are likely due to the provision of these EFAs in the SQ-LNS at doses of 0.58 g/d ALA and 4.46 g/d LA (~82% and ~64%, respectively, of the IOM adequate intakes for infants 12 – 23 mo of age (21)) from 6 to 18 mo of age. The EFA intakes from complementary foods in Ghana and Malawi may be low (19, 79) and therefore, a positive response to SQ-LNS among infants in the LNS group may be expected.

We are not surprised that SQ-LNS had no impact on infants' plasma EPA and DHA levels at 6 or 18 mo of age. This lack of impact is consistent with the results from our previous study among the mothers (55)5 in which SQ-LNS did not affect the median concentration of DHA in plasma (at 36 wk of pregnancy) or breastmilk (at 6 mo postpartum) in Ghana or Malawi. In a systemic review, Brenna et al. (80) identified at least 11 studies in which the impact of ALA supplementation on plasma EPA and DHA was evaluated, mostly among adult participants except for one study (81). In most cases, high-dose (up to 40 g/d) ALA supplementation was associated with a significant

increase in plasma EPA concentration, but had little or no effect on plasma DHA level (80, 82). Although infants may be more efficient than adults at converting ALA to LCPUFA (80), there are several possible reasons for the lack of impact of SQ-LNS on plasma EPA and DHA in our sample, including oxidation of ALA for energy (82, 83), limited conversion of ALA to EPA and DHA (82), and the relatively large size of the plasma DHA pool (84) which means that a small contribution to the pool may be less detectable (80).

Our findings have implications regarding the potential role of SQ-LNS in facilitating healthy child growth and development. First, the positive impact of SQ-LNS on infants' plasma EFA %C suggests that it may help maintain those EFAs at levels necessary for ensuring the adequate synthesis of LCPUFAs (especially DHA and AA) during the prenatal (via placental transfer) and postnatal (via breastmilk and infants' own conversion) periods. Second, SQ-LNS also provides micronutrients and protein, which are important for the efficient synthesis of LCPUFAs and also for normal placental function (85), as well as for the synthesis of FA binding proteins and FA transporters required for the transfer of LCPUFAs from the mother to the fetus during pregnancy, and for the fetus' or infant's own uptake of LCPUFAs (86, 87).

In conclusion, our results show that maternal and child SQ-LNS consumption likely had an impact on infant's EFA profiles in Ghana and Malawi. These findings expand our knowledge regarding the potential impact of SQ-LNS on infant and child outcomes, including growth (38, 88, 89), development (90), mortality (91), anemia and micronutrient status (92). An important next step is to evaluate the extent to which the impact of SQ-LNS on infants' EFA profile may be related to these and other outcomes during the first 1000 days and thereafter. For the Ghana trial, we conducted a follow-up study at age 4–6 y in which we assessed growth (93) cognitive, social-emotional, and motor function (94), and stress and cellular aging (95). We are currently conducting a second follow-up study to examine longer-term health and developmental outcomes at age 10 –

12 y (*ClinicalTrials.org*: NCT00970866), and a similar follow-up study will take place in Malawi. These studies will permit evaluation of outcomes beyond infancy.

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