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Maternal supplementation with small-quantity Lipid-based Nutrient Supplement compared with multiple micronutrients, but not with iron + folic acid, reduces the prevalence of low gestational weight gain in semi-urban Ghana: A randomized controlled trial[1-8]

Seth Adu-Afarwuah, Anna Lartey, Harriet Okronipa, Per Ashorn, Ulla Ashorn, Mamane Zeilani, Mary Arimond, Stephen A Vosti, Kathryn G. Dewey

[1]From the Department of Nutrition and Food Science, University of Ghana, Legon, Accra, Ghana (SAA, AL, and HO); Center for Child Health Research, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland (PA, UA); Nutriset S.A.S., Hameau du Bois Ricard, PB 35, 76770 Malaunay, France (MZ); Program in International and Community Nutrition, Department of Nutrition, University of California, Davis, USA (MA and KGD); and Department of Agricultural and Resource Economics, University of California, Davis, USA (SAV),

[2]Address correspondence to S Adu-Afarwuah, Department of Nutrition and Food Science, University of Ghana, Legon, Accra, Ghana. Phone: +233 24 914 9385. Email: ct3665@gmail.com. Reprints are not available.

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[4]Running head: MATERNAL SQ-LNS SUPPLEMENTATION IN GHANA.

[5]Abbreviations: BMI, Body Mass Index; GWG, Gestational Weight Gain; IFA, Iron and Folic Acid; iLiNS, International Lipid-based Nutrient Supplements; LNS, Lipid-based Nutrient Supplements; MMN, Multiple Micronutrients; MUAC, Mid Upper Arm Circumference; SQ-LNS, Small-Quantity Lipid-based Nutrient Supplements; TSF, Triceps Skinfold.

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[7]Name for PubMed indexing: Adu-Afarwuah, Lartey, Okronipa, Ashorn Ashorn, Zeilani, Arimond, Vosti, Dewey.

[8]At the time of the study, Mamane Zeilani was an employee of Nutriset S.A.S., which is a commercial producer of lipid-based nutrient supplements. The authors declared no conflicts of interest. The funder of the study had no role in the study design; data collection, analysis, and interpretation; and the preparation of the manuscript.

ABSTRACT

Introduction: It is unclear whether maternal supplementation with small-quantity lipid-based nutrient supplements (SQ-LNS,118 kcal/d) would affect maternal weight.

Objective: We compared several secondary anthropometric measures among 3 groups of women in the iLiNS-DYAD trial in Ghana.

Methods: Women (n=1320; <20 weeks' gestation) were randomly assigned to receive 60 mg Fe + 400 μg folic acid/d (IFA), 18 vitamins and minerals/d (MMN), or 20 g/d SQ-LNS with 22 micronutrients (LNS) during pregnancy, and placebo (200 mg Ca/d), MMN or SQ-LNS, respectively, during 6 mo postpartum. Weight, mid upper-arm circumference (MUAC), and triceps skinfold (TSF) thickness at 36 weeks' gestation and 6 mo postpartum were analyzed, as well as changes from estimated pre-pregnancy values. We assessed the adequacy of estimated gestational weight gain (GWG) by using Institute of Medicine (IOM) and INTERGROWTH-21st guidelines.

Results: Estimated pre-pregnancy prevalence of overweight or obesity was 38.5%. By 36 weeks' gestation, women (n=1015) had a mean ± SD weight gain of 7.4 ± 3.7 kg, and changes of -1.0 ± 1.7 cm in MUAC and -2.8 ± 4.1 mm in TSF. The LNS group had a lower prevalence of inadequate GWG based on IOM guidelines (57.4%) than the MMN (67.2%) but not the IFA (63.1%) groups (P = 0.030), whereas the prevalence of adequate (26.9% overall) and excessive (10.4% overall) GWG did not differ by group. The percentage of normal weight (18.5<BMI<25.0) women (n=754) whose GWG was <3rd centile of the INTERGROWTH-21ST Standards was 23.0%, 28.7% and 28.5% for the LNS, MMN, and IFA groups, respectively (P=0.36). At 6 mo postpartum, the prevalence of overweight or obesity was 45.3%, and the risk of becoming overweight or obese did not differ by group.

Conclusion: SQ-LNS supplementation is one potential strategy to address the high prevalence of inadequate GWG in similar settings, without increasing the risk of excessive GWG.

Clinicaltrials.gov identifier: NCT00970866.

Keywords: gestational weight gain; lipid-based nutrient supplements; maternal supplementation; multiple micronutrient supplementation; iron + folic acid supplementation.

Introduction

In many developing counties, pregnant and/or lactating women often suffer from vitamin and mineral deficiencies (1) commonly as a result of poor diet (2, 3), and the amounts of essential fatty acids available from the food supply may be below the minimum recommended level for pregnant and lactating women (4). Vitamin and mineral deficiencies during pregnancy contribute to intrauterine growth retardation and pregnancy-related and delivery complications (5), and therefore efforts to combat these deficiencies are a global priority (6).

Iron + folic acid supplementation (7) has been the main nutritional supplementation regimen for pregnant women in low income countries for decades, and has been found to reduce the risk of maternal anemia (8, 9) and iron deficiency (9) when compared with no iron or placebo. However, evidence from a recent Cochrane Review (10) suggests that multiple-micronutrient supplementation for pregnant women may be superior to iron supplementation with or without folic acid in terms of reducing the incidence of low birthweight (LBW), small-for-gestational-age (SGA), and stillbirth delivery.

Small-quantity lipid-based nutrient supplements (SQ-LNS) providing 22 vitamins and minerals, including minerals not usually incorporated in multiple micronutrient supplements, offer a relatively new strategy for delivering not only multiple micronutrients, but also essential fatty acids to pregnant and lactating women. Published evidence from our study in Ghana (11) and another study from Bangladesh (12) showed a positive impact of pre-natal SQ-LNS supplementation on fetal growth, particularly among women at a greater risk of delivering infants with intra-uterine growth retardation. Given these results, interest in the use of maternal SQ-LNS supplementation in low income communities might grow.

The Institute of Medicine (IOM) provides recommendations about gestational weight gain (GWG) based on pre-pregnancy body mass index (BMI): underweight women have the greatest recommended weight gain range (12.5-18 kg), followed by normal weight (11.5-16 kg), then overweight (7-11.5 kg) and obese (5-9 kg) women (13). More recently, the INTERGROWTH-21st Project published GWG standards by using data from more diverse populations compared to the IOM's recommendations (14). However, unlike the IOM recommendations, the INTERGROWTH-21st Standards are appropriate for normal weight women only, and therefore the former recommendations may have a greater applicability.

Deviations from GWG recommendations have been associated with adverse consequences for both the mother and child: inadequate GWG is associated with increased risk of low birth weight, whilst excessive GWG is associated with infant macrosomia and maternal postpartum weight retention and development of overweight or obesity (13). Prolonged consumption of SQ-LNS during pregnancy and lactation may affect women's weight, but so far, only one study in Bangladesh (15) has examined this relationship.

In this analysis, we examined several secondary outcomes of our iLiNS-DYAD efficacy trial in Ghana (11), a RCT carried out by the International Lipid-based Nutrient Supplement study group in which mother-child dyads were enrolled. We aimed to determine whether the consumption of SQ-LNS was associated with differences in GWG or maternal anthropometric characteristics, including risk of overweight or obesity, when provided during pregnancy and the first 6 mo postpartum in a semi-urban setting in Ghana, where energy intake among women is generally not limiting and overweight and obesity are matters of growing concern.

Methods

Study setting, design, and participants

We have previously described the setting, design and participants of the iLiNS-DYAD efficacy trial in Ghana (11). Briefly, the study was conducted in a semi-urban settlement (Somanya-Odumase-Kpong area) in the Yilo Krobo and the Lower Manya Krobo districts about 70 km north of Accra, Ghana. It was designed as a parallel, individually randomized, controlled trial with three equal-size groups. The study protocol 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, and was registered at ClinicalTrials.org (Identifier NCT00970866).

Participants were pregnant women attending usual antenatal clinics in the 4 main health facilities in the area between December 2009 and December 2011, who were ≥18 years old; ≤20-weeks gestation; and had antenatal cards complete with history and examination. A woman was excluded if any of the following applied: not residing in the area; intention to move out of the area within the next two years; milk or peanut allergy; unwillingness to receive field workers or take study supplement; participation in another trial; gestational age (GA) >20 weeks before completion of enrolment; and antenatal card indicated HIV infection, asthma, epilepsy, tuberculosis, or malignant disease.

Intervention

We described previously (11) that following baseline assessments, eligible women were randomized to receive one of 3 treatments: (a) 60 mg iron plus 400 μg folic acid/d during pregnancy, and placebo (200 mg Ca/d) during the first 6 mo postpartum (hereafter, IFA

supplement or group); (b) multiple micronutrient capsule containing 18 vitamins and minerals (including 20 mg iron)/d during pregnancy and the first 6 mo postpartum, (hereafter, MMN supplement or group); and (c) 20 g/d of SQ-LNS containing similar micronutrients as the MMN supplement, plus Ca, P, K, and Mg as well as energy (118 kcal/d) and macronutrients (e.g. protein and essential fatty acids) during pregnancy and the first 6 mo postpartum (hereafter, SQ-LNS supplement or LNS group). The LNS (individual 20-g sachets) was supplied by Nutriset S.A.S. (Malaunay, France), and the IFA and MMN (10 capsules/blister pack) by DSM South Africa. We previously published the nutrient contents of all supplements (11), and the rationale for the concentrations of the nutrients (16).

Apart from iron, the vitamin and mineral contents of the MMN and SQ-LNS supplements were either *1x* or *2x* the recommended dietary allowance for pregnancy, or in a few cases, the maximum amount that could be included in the supplement given technical and organoleptic constraints (16). Group allocations were developed by the Study Statistician using a computer-generated (SAS version 9.4) scheme in blocks of nine, and randomization was performed by the Study Nurse who offered 9 sealed, opaque envelopes at a time, one of which was picked by the participant to reveal the allocation. Allocation information was kept securely by one Field Supervisor and the Study Statistician only.

At enrolment, the study nurse gave each woman a two-week supply of the assigned supplement with instructions on how to consume it (IFA and MMN, with water after a meal, one capsule per day; SQ-LNS, mixed with any prepared food, one 20-g sachet per day), and a standard nutrition 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”) designed to reflect Ghana Health Service’s nutritional advice for women during pregnancy

(17) and local food availability. Thereafter, field workers visited women in their homes biweekly, whereupon they delivered fresh supplies of supplement and monitored supplement intakes and monitored morbidity (11).

After birth, field workers visited women and their infants each week, but the delivery of supplement and monitoring of intakes and morbidity were done biweekly as before, until women exited at 6 mo postpartum. During follow-up, women were told not to consume more than one capsule (IFA and MMN groups) or sachet (LNS group) per day, even if they forgot to take the supplement the previous day or days. Women were told to take their assigned supplement with them if they wanted to travel out of the study area. Those who would not return before the next biweekly visit were given an extra supply for the period they intended to be away.

To maintain blinding, the IFA and MMN supplements were color-coded (3 different colors for IFA and 3 for MMN supplements), and were therefore known to the study team and participants only by the colors. It was not possible to blind field workers and participants to the IFA and MMN supplements versus the SQ-LNS supplement due to their apparent differences, but the anthropometrists who measured the women were blinded to the group assignments, and no one apart from the Study Statistician had knowledge of group assignment until all preliminary analyses had been completed.

Outcome measures and procedures

The outcome measures evaluated at 36 weeks' gestation (last laboratory visit before delivery) were: total gestational weight (kg), mid-upper circumference (MUAC, cm) and triceps skinfold (TSF, mm) gain; GWG per week; percentage adequacy of GWG achieved; percentage of women whose GWG was inadequate (< lower cut-off of recommendations), adequate (within

recommended range) or excessive (> upper cut-off of recommendations) according to the IOM GWG recommendations (13); and the percentage of normal weight (18.5<BMI<25.0) women whose estimated GWG was <3rd centile or >97th centile of the INTERGROWTH-21ST Standards (14) . Outcomes evaluated at 6 mo postpartum (maternal endpoint of the study) were weight, MUAC, TSF, and BMI (kg/m^2); change in weight, MUAC, TSF, and BMI from pre-pregnancy; and percentage of women who became overweight or obese out of those who were *not* overweight or obese at pre-pregnancy.

We collected background demographic and socio-economic information at enrolment by using a questionnaire, and completed anthropometric and laboratory assessments at enrolment, 36 weeks gestation, and 6 mo postpartum. Weight (Seca 874; Seca), height (Seca 217; Seca), mid-upper arm circumference, and triceps skinfold (Holtain calipers) were measured using standard procedures. Blood hemoglobin concentration was measured by HemoCue (HemoCue AG, Switzerland), and malaria parasitemia was by a kit (Vision Biotech, South Africa) (11). As described previously (11), gestational age was determined mostly by ultrasound biometry (Aloka SSD 500, Japan).

Sample size and data analysis

The sample size for the iLiNS-DYAD-Ghana study (11) was based on detecting a small-to-moderate (18) effect size (Cohen's d) of 0.3 between any two groups for any continuous outcome measure, with a two-sided 5% test and 80% power. As previously reported (11), a total of 1320 pregnant women were enrolled into the study. We also previously reported (11) a temporary mislabeling of IFA and MMN capsules, as a result of which 170 women who had been assigned to the IFA group inadvertently received the MMN capsule either throughout

pregnancy (n=85) or during part of pregnancy (n=85), before receiving the intended IFA capsule the rest of follow-up, and another 170 women assigned to the MMN group also received the IFA capsule either throughout pregnancy (n=78) or during part of pregnancy (n=92), before receiving the intended MMN capsule. In this current analysis which covered both pre- and post-natal periods of the intervention, we included all of the women enrolled into the study without discarding any data from those who received the unintended supplements, since the unintended exposure occurred only in the pre-natal period. We used this same approach in our previous publication (19) in which we evaluated the impact of the intervention spanning pre- and post-natal periods on the attained growth of 18-mo-old children. We estimated that the actual percentage of follow-up days (13%) during which the women in the IFA and MMN groups had the unintended exposure was relatively small (19), and in addition, no women in the LNS group were exposed to any other supplement apart from the intended SQ-LNS. At 36 weeks gestation and 6 mo postpartum, we had anthropometric data for 1,015 and 1,073 women, respectively. With these sample sizes, we had >97% power to detect an effect size of 0.3 between any two groups for any continuous outcome at each of the time points.

We developed our statistical analysis plan (SAP) and posted it at our web-site (www.ilins.org) before data analysis. The secondary outcomes in the present analysis were pre-specified in the SAP. Statistical analysis was performed on an intention-to-treat basis using SAS for Windows Release 9.4 (Cary, NC, USA). Thus, women were included in the analysis regardless of adherence to treatment. To address the protocol violation as a result of the consumption of mislabeled capsules by some women during pregnancy, we analyzed the data using 2 scenarios as done previously (19): in the first, intervention groups were based on the supplement women were intended to receive when they were enrolled, and in the second,

intervention groups were based on the supplement women actually received when they were enrolled.

The variables used to assess the outcome measures were obtained as follows: first, because it was not possible to obtain women's pre-pregnancy weight (needed to apply the IOM GWG recommendations), we used a third-degree polynomial regression model with one predictor variable (gestational age at enrolment) to estimate pre-pregnancy weight based on weight and gestational age at the time of enrolment. In this case, the shape of the true non-linear response function of maternal weight to gestational age was unknown (or complex), and a polynomial function was a good approximation to the true function (20). The procedure was accomplished, first, by determining the best transformation of the weight at enrolment that achieved a normal distribution, and regressing the transformed weight on gestational age, gestational age squared, and gestational age cubed in order to generate predicted and residual values. We then inspected the regression curve to determine the earliest gestational age before the confidence interval expanded, assuming that weight gain before that time was minimal. Next, we determined the mean of the predicted values at the selected time point in early gestation, added this mean value to the residual for each individual, and then back-transformed the result to obtain the estimated pre-pregnancy weight for the individual. We used the same approach to estimate the pre-pregnancy MUAC and TSF based on the values measured at enrolment. We estimated pre-pregnancy BMI (kg/m^2) as estimated pre-pregnancy weight divided by the square of height measured at the time of enrolment.

We calculated the total GWG, gestational MUAC gain and gestational TSF gain by subtracting the estimated pre-pregnancy values from those measured at the last prenatal visit to the laboratory around 36 weeks gestation, an approach used by other investigators (21). The rate

of GWG by 36 gestational weeks was calculated as total GWG divided by completed weeks of gestation (22). The percentage adequacy of GWG as a continuous variable was calculated by dividing the total GWG by the expected GWG (i.e the amount of weight a woman was supposed to gain according to the IOM recommendation when her weight was measured around 36 weeks gestation) and multiplying the result by 100 (21). For the expected GWG, we used the formula: Expected GWG = Expected 1st trimester total weight gain + [(Gestational age at the last weight measurement around 36 weeks' gestation – 13 weeks) *x* Recommended rate of GWG for 2nd and 3rd trimesters] (21, 23, 24). Expected first-trimester total weight gain was assumed to be 2 kg for underweight and normal-weight women, 1 kg for overweight women, and 0.5 kg for obese women (21), and the recommended rates of GWG for 2nd and 3rd trimesters were 0.5, 0.4, 0.3, and 0.23 kg/week for underweight, normal weight, overweight, and obese women, respectively (25).

Because the IOM recommends a range of total GWG for each pre-pregnancy BMI group, we classified the percentage of weight-gain recommendations met as inadequate, adequate, or excessive (26). For each BMI-specific range, we divided the lower and upper limits of the recommended weight-gain range by the expected weight gain by 40 weeks' gestation and multiplied the result by 100 to obtain the corresponding range of recommended percentage of expected weight gain (26). For example, for women with normal pre-pregnancy BMI, the expected gestational weight gain by 40 weeks' gestation is: 2.0 kg + [(40 weeks – 13 weeks) x 0.4 kg/week] = 12.8 kg. For the IOM's recommended total weight-gain range of 11.5–16 kg, the lower and upper limits of the corresponding range of the recommended percentage of expected weight gain are: 11.5 kg/12.8 kg *x* 100 and 16 kg/12.8 kg *x* 100 = 90% – 125% of the 12.8 kg expected weight gain. Hence we classified inadequate, adequate and excessive weight gain as

<90%, 90–125% and >125% of recommendations, respectively. For a normal-weight woman who gained a total of 9.0 kg and whose weight was last measured at 37 weeks' gestation, the expected GWG would be 11.7 kg, and the percentage of recommendations met would be 9.0 kg/11.7 kg x 100= 77%, which would be classified as inadequate GWG. Changes in weight, MUAC, TSF, and BMI from pre-pregnancy to 6 months postpartum were calculated by subtracting the estimated pre-pregnancy values, from the values measured at 6 months postpartum.

To examine how the GWG assessment using the IOM's recommendation would compare with similar assessment using the INTERGROWTH-21st Standards, we calculated the 3rd and the 97th centiles of expected GWG at the last antenatal measurement around 36 weeks' gestation. For the 3rd centile GWG, we used the formula:

exp({1.382972 - 56.14743 * GA**-2 + 0.2787683 * GA **0.5} + {-1.88 * [0.2501993731 + 142.4297879 * GA **-2 - 61.45345 * GA **-2 * log(GA)]}) - 8.75~~,0.1)~~, where GA = weeks of gestation at the last antenatal measurement (14). For the 97th GWG, we replaced the -1.88 in the formula for the 3rd centile of expected GWG by 1.88 (14). We used actual GWG less than the calculated 3rd centile of the expected GWG as a proxy for inadequate GWG, and actual GWG greater than the calculated 97th centile of expected GWG as a proxy for excessive GWG. Because the INTERGROWTH-21st Standards are appropriate for normal weight women, only women in our sample who had estimated pre-pregnancy BMI between 18.5 and 24.99 kgm^{-2} were included in the analysis involving those standards.

We summarized the background characteristics at enrolment (11), and the number of days from the last prenatal measurements (around 36 weeks' gestation) to delivery as mean ± SD or frequency (%) using the group assignment based on supplements women were intended to

receive when they were enrolled. At 36 weeks' gestation and 6 mo postpartum, we calculated descriptive statistics for the overall sample, before comparing the 3 treatment groups using general linear models (continuous outcomes) and logistic regression models (binary), with Tukey-Kramer adjustment for multiple comparisons. Along with the group comparisons, we calculated pairwise mean differences (continuous outcomes) and relative risks (binary outcomes) with their 95% CI and p-values. Relative risks were calculated using Poisson regression (27). These comparisons were performed twice, first without any covariate adjustments, and then with adjustment for covariates significantly associated ($p<0.10$) with the outcome in question in a bivariate analysis. Potential covariates were specified before analysis, and included primiparity (yes/no), season at enrolment (wet/not wet), anemia (yes/no), age, gestational age at enrolment, and assets index, housing index, and Household Food Insecurity Access Scale (HFIAS) score derived using principal component analysis (28). Finally, as done previously (19) as a possible option for addressing the protocol violation, we performed a secondary analysis of the outcome variables, in which we combined women in the IFA and MMN groups to conduct a 2-group comparison with those who consumed the SQ-LNS. We considered that for these assessments in a clinical trial, in which all of the outcomes were secondary, pre-specified, and highly correlated, correcting for multiplicity was unnecessary (29).

Statistics in the texts are means ± SD (continuous outcomes) or percentages (binary outcomes). Women's adherence to supplement intake, defined as the percentage of follow-up days women self-reported consuming the supplements (pregnancy/lactation) was: 88.1%/85.7 % for the IFA group; 87.0 %/85.0 % for the MMN group; and 83.7 %/80.0 % for the LNS group, as reported previously (30). Data on morbidity have yet to be analyzed, but we reported previously (11, 19) that serious adverse events were evenly distributed across the 3 groups.

Results

Overall sample

The characteristics of the women enrolled, by intervention group, are shown in **Table 1:** on average, the women were aged about 27 y, had 8 y of education, were generally not food insecure, and had a relatively low estimated rate of underweight (3.1%) and a high estimated rate of overweight and obesity (38.5%) at pre-pregnancy. These characteristics were generally balanced across the 3 groups. Number of days from the last prenatal measurement to delivery was 21.8 ± 10.5.

Based on the estimated pre-pregnancy values, the overall GWG at 36 weeks' gestation was 7.4 ± 3.7 kg, which was equivalent to 0.2 ± 0.1 kg per week, and 76.8 ± 43.0% of the expected weight gain according to the IOM's weight-gain recommendation. Women lost 1.0 ± 1.7 cm in MUAC and 2.8 ± 4.1 mm in TSF. The percentages of women in the sample who had inadequate, adequate and excessive GWG at 36 weeks gestation by the IOM recommendations were 62.7%, 26.9% and 10.4%, respectively. On average, 26.8% of women with estimated normal BMI at pre-pregnancy had total GWG <3rd centile of the expected GWG based on the INTERGROWTH-21st Standards, but none had total GWG above the 97th centile of the expected GWG based on the INTERGROWTH-21st Standards.

By 6 mo postpartum, the overall mean ± SD (median) changes in women's anthropometric indices from the estimated pre-pregnancy values were +1.6 ± 4.9 (1.5) kg for weight, +0.4 ± 2.0 (0.3) cm for MUAC, +0.6 ± 5.0 (0.3) mm for TSF, and +0.6 ± 1.9 (0.5) kg/m^2 for BMI. The overall prevalence of underweight (BMI <18.5 kg/m^2) remained relatively low (3.7%), whereas 45.3% of the women were overweight or obese.

Group comparisons

The unadjusted results for the continuous outcome measures for the analysis based on groups according to the supplements women were intended to receive at enrolment are presented in **Table 2.** At 36 weeks' gestation and 6 mo postpartum, the 3 groups did not differ in the unadjusted mean values of the continuous outcome measures, except for a tendency towards a greater percent adequacy of GWG in the LNS group compared to the other groups (Overall P = 0.09). In adjusted analysis controlling for covariates significantly associated with the outcome in question (details not shown), there were trends towards greater mean total estimated GWG (Overall P = 0.07), GWG per week (Overall P = 0.07) and percent adequacy of GWG (P = 0.08) for women in the LNS group compared to those in the other groups. Similar results for both unadjusted (**Supplemental Table 1**) and adjusted (table not shown) analyses were generally observed when groups were examined according to the supplements women actually received when they were enrolled.

When comparing women in the IFA and MMN groups combined versus those in the LNS group (**Supplemental Table 2**), the trends towards greater mean total GWG (P = 0.08) and GWG per week (P = 0.09) for the LNS group paralleled those observed in the 3-group comparison, and mean ± SD percent adequacy of GWG in the LNS group was significantly greater (P = 0.038) than that for the combined IFA + MMN group.

The unadjusted results for the binary outcome measures for the analysis examining groups according to the supplements women were intended to receive at enrolment are presented in **Table 3**. At 36 weeks gestation, the 3 groups did not differ significantly in the percentage of women with adequate or excessive GWG according to the IOM's recommendations, but the percentage of women who had inadequate GWG was significantly lower in the LNS (57.4%)

compared to the MMN (and not the IFA) group (67.2%; Overall P = 0.030 corresponding to RR = 0.85 [95% CI: 0.74, 0.98; P = 0.023]). Among women with estimated normal BMI at pre-pregnancy, the point estimate of the percentage of those whose total GWG was <3rd centile of the expected GWG based on the INTERGROWTH-21st Standards was 23% for the LNS group, compared to 28.5% for the IFA group, and 28.7% in the MMN group, although the differences were not significant. The percentage of women with normal BMI at pre-pregnancy who became overweight or obese by 6 mo postpartum also did not differ significantly among the 3 groups. These results remained unchanged after controlling for pre-specified covariates significantly associated with the outcomes (details not shown). As observed for the continuous outcome variables, similar results for the binary outcome variables were found in the analysis based on the supplements women actually received when they were enrolled (unadjusted, **Supplemental Table 3;** adjusted, table not shown).

In the 2-group comparison (**Supplemental Table 4**), the percentage of women with inadequate GWG was significantly lower (P = 0.016), and the percentage of women with adequate GWG was significantly greater (P = 0.038) in the LNS group compared to the IFA and MMN groups combined. Also, the results from the analysis using the INTERGROWTH-21st Standards mimicked those for the three-group comparison.

Discussion

In the semi-urban setting in Ghana where the iLiNS DYAD study was conducted, we found that at 36 weeks' gestation, women in the LNS, MMN and IFA groups did not differ significantly in most of the secondary anthropometric (weight, MUAC and TSF) outcomes measured. However, by IOM recommendations, the prevalence of inadequate GWG based on estimated pre-pregnancy values was significantly lower in the LNS group compared to the MMN group, and in a 2-group analysis, mean ± SD percent adequacy of GWG was significantly greater, the prevalence of inadequate GWG was significantly lower, and the prevalence of adequate GWG was significantly greater in the LNS group than the non-LNS group (IFA and MMN groups combined). At 6 mo postpartum, the groups did not differ in weight, MUAC, TSF, BMI or changes in these indices from estimated pre-pregnancy values, nor in the percentage of women with excessive GWG, or the percentage of women who had normal BMI at pre-pregnancy but became overweight or obese by 6 mo postpartum.

An estimate of each woman's pre-pregnancy BMI was a pre-requisite for applying the IOM's GWG recommendations. Previously, the proxies used for pre-pregnancy weight or BMI have included weights measured at various times including: first antenatal booking (31), within the previous 12 months of pregnancy (32), in the first trimester (33, 34) and during pregnancy regardless of gestational age (35). As previously noted (36), each of these has its own limitations. We considered our approach to estimate pre-pregnancy weight or BMI (and also MUAC and TSF) using polynomial regression (20, 37, 38) as a good option, for 2 reasons: first, women in this population usually do not know their pre-pregnancy weight. Second, at a mean gestational age of 16.1 wk when women were enrolled, the estimated pre-pregnancy weight of 61.9 ± 11.9 kg implied that the women on average had potentially gained 0.7 kg in weight by the time of

enrollment, and we decided not to ignore this change, as well as those in MUAC and TSF thickness that had occurred. The IOM assumes that women gain 0.5 – 2.0 kg during the first trimester (13), and therefore the average estimated 0.7 kg gain by the time of enrolment would be considered reasonably unbiased.

The estimated pre-pregnancy BMI for women in our study, who were aged 18-45 y, was similar to the mean BMI (24.8 kg/m^2) reported for women 15-49 y of age (excluding those who were pregnant, or had given birth the previous 2 mo) in the 2014 Ghana Demographic and Health Survey (39) for the region of Ghana (Eastern Region) where our study was conducted. Thus, we believe the estimation of pre-pregnancy weight, MUAC and TSF did not generally bias our results.

The losses in MUAC and TSF in the sample at 36 weeks' gestation compared to estimated pre-pregnancy values appear to be characteristic to pregnancy, during which fat is mobilized from the upper body and preferentially deposited over the hips, back, and upper thighs (13, 40). Our results showing the estimated prevalence of inadequate GWG according to IOM recommendation (63%) and percentage of normal weight women whose estimated GWG was less the 3rd centile of expected GWG according to the INTERGROWTH-21st Standards (27%) suggest that low GWG might be a problem in this setting. This observation is consistent with the area being located in the Eastern Region, which has the highest prevalence of low birth weight (14%) among the 10 regions of Ghana (39). Low GWG is associated with low birth weight (41). Elsewhere in Ghana, a low GWG prevalence of 50% based on the IOM's guidelines was reported. Thus, SQ-LNS supplementation during pregnancy might help, albeit modestly, to reduce low GWG in this setting.

Two previous reports may be relevant in relation to our results. In a large cluster-randomized trial in Bangladesh in which women received iron + folic acid or SQ-LNS with similar nutrient content to those provided in this study (15), the provision of SQ-LNS increased maternal weight gain and MUAC only in certain subgroups (for example, women ≥ 25 y of age) but, as in Ghana, it was not associated with excessive GWG. In a Cochrane Review (42), balanced protein-energy supplements (i.e., supplements in which protein provides less than 25% of the total energy content) given to pregnant women increased mean weight gain per week compared to no supplementation, but the daily amounts of energy in those supplements were substantially larger (≥ 400 kcal) than the amount present in SQ-LNS (118 kcal).

Our finding that SQ-LNS supplementation decreased the prevalence of inadequate GWG but was not associated with excessive GWG or risk of overweight and obesity at 6 mo postpartum implies a favorable response to using SQ-LNS, particularly for populations such as that of the study setting where the nutrition transition is underway. The high prevalence of inadequate GWG observed in this cohort, coupled with the 12% prevalence of low birth weight that we previously reported (11), suggest that low energy intake during pregnancy may be an issue of concern in this population, even though a substantial percentage of the women were overweight prior to pregnancy. Low energy intake and low intake of dairy products have been identified as important predictors of inadequate GWG (43-45), along with other biological or metabolic factors (27). SQ-LNS provided a small amount of extra energy, and milk powder was one of the ingredients, which may have contributed to the reduced prevalence of inadequate GWG in the LNS group. The results reported herein are consistent with the previously reported greater mean birth weight and lower prevalence of low birth weight of infants in the LNS group (11).

Because the consumption of SQ-LNS was not associated with greater total gestational weight gain or higher prevalence of excessive gestational weight gain in our sample, it is not surprising that it was also not associated with a greater risk of becoming overweight or obesity by 6 mo postpartum. Women's weight retention by 6 mo postpartum depends not only on dietary factors but also on physical activity and breastfeeding practices. In the study setting, where most women were relatively active (compared to those in, say, urban Accra) and nearly all women breastfed their infants during the first 6 mo postpartum (46), the extra energy provided by SQ-LNS did not exacerbate the already high prevalence (estimated 38.5% at pre-pregnancy) of maternal overweight. This is reassuring but we cannot be sure that this result is generalizable to other contexts.

The iLiNS DYAD Ghana study had several strengths, including using a fully randomized design and having control groups. In addition, all anthropometrists were well-trained and standardized (47) every 6 mo during data collection. Study weaknesses include the inability to fully blind all study staff and participants to the supplementation allocation (due to the obvious differences between the IFA and MMN capsules versus the SQ-LNS sachets), lack of data on women's pre-pregnancy weight, which then had to be estimated, and the exposure of some women to both IFA and MMN supplements during part of pregnancy. It is possible that some of our findings may be due to chance, because of multiple testing (29). However, all anthropometrists and data analysts were fully blinded to the group assignments until analyses were completed, and no women in the LNS group were exposed to any other supplement apart from the intended LNS. We therefore believe that the study weaknesses do not bias the finding of no association of SQ-LNS consumption with excessive GWG or increased risk of overweight or obesity by 6 mo postpartum.

We conclude that daily SQ-LNS supplementation is one potential strategy to address the high prevalence of inadequate GWG in similar settings, without increasing the risk of excessive GWG, or of becoming overweight or obese by 6 months postpartum.

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TABLE 1 Characteristics of women (n = 1320) who participated in a randomized trial of IFA (pregnancy only), MMN (pregnancy and lactation), and LNS (pregnancy, lactation, and infancy) supplementation in a semi-urban setting in Ghana, by intervention group based on intended supplement at enrollment[1]

Characteristics	IFA (n = 441)	MMN (n = 439)	LNS (n = 440)
Age, y	26.4 ± 5.6 (441)	26.9 ± 5.4 (439)	26.9 ± 5.6 (440)
Years of formal education, y	7.8 ± 3.5 (441)	7.6 ± 3.6 (439)	7.6 ± 3.9 (440)
Gestational age at enrolment, weeks	16.0 ± 3.3 (440)	16.2 ± 3.2 (436)	16.1 ± 3.3 (435)
Asset index[2]	0.04 ± 1.03 (433)	0.06 ± 0.97 (431)	-.09 ± 1.00 (432)
Housing index[2]	0.01 ± 1.00 (433)	0.01 ± 1.01 (431)	-.01 ± 1.00 (432)
HFIAS score[3]	2.6 ± 4.4 (434)	2.7 ± 4.3 (431)	2.6 ± 4.0 (432)
Married or co-habiting, *n/N* (%)	408/441 (92.5)	411/439 (93.6)	405/440 (92.0)
Primiparous women, *n/N* (%)	156/441 (35.4)	143/439 (32.6)	147/440 (33.4)
Positive malarial RDT[4], *n/N* (%)	37/440 (8.4)	42/439 (9.6)	54/440 (12.3)
Hb <100 g/L, *n/N* (%)	57/440 (13.0)	68/439 (15.5)	60/440 (13.6)
Weight[5], kg	61.5 ± 11.6 (432)	61.5 ± 12.0 (429)	62.7 ± 12.3 (430)
Body Mass Index[6], kg/m^2	24.4 ± 4.4 (432)	24.4 ± 4.3 (429)	24.8 ± 4.5 (430)
Underweight[6] (<18.5 kg/m^2)	21/432 (4.9)	12/429 (2.8)	7/430 (1.6)
Overweight[6] (25.0-29.9 kg/m^2) *n/N* (%)	113/432 (26.2)	112/429 (26.1)	129/430 (30.0)
Obese[6] (≥ 30.0 kg/m^2) *n/N* (%)	48/432 (11.1)	46/429 (10.7)	49/430 (11.4)
MUAC[5], cm	28.4 ± 4.3 (432)	28.5 ± 4.2 (430)	28.9 ± 4.6 (430)
Triceps skinfold[5], mm	19.8 ± 7.8 (432)	20.1 ± 7.9 (429)	20.7 ± 7.9 (430)
Days from last prenatal measurement to delivery	21.1 ± 9.9 (336)	21.7 ± 11.1 (357)	22.5 ± 10.4 (336)

[1] HFIAS, Household Food Insecurity Access Scale; IFA, Iron + Folic Acid; LNS, Small Quantity Lipid-based Nutrient Supplement; MMN, Multiple Micronutrients; MUAC, Mid Upper Arm Circumference. Unless otherwise indicated, these characteristics were measured at the time of enrolment. Values are mean ± SDs (n), unless otherwise indicated. *n/N* = number of participants whose response was "yes" for the variable in question/*n* of participants analyzed for the variable in question.

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

[3] HFIAS is a proxy indicator for household food insecurity (28); higher values represent higher food insecurity.

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

[5]Pre-pregnancy values estimated from those measured at enrolment by using third-order polynomial regression, with gestational age at enrolment as predictor variable.

[6]Based on pre-pregnancy weight estimated from weight at enrolment using polynomial regression, with gestational age at enrolment as predictor variable.

TABLE 2 Unadjusted continuous anthropometric outcomes of women (n = 1320) who participated in a randomized trial of IFA (pregnancy only), MMN (pregnancy and lactation), and SQ-LNS (pregnancy and lactation) supplementation in a semi-urban setting in Ghana, by intervention group based on intended supplement at enrollment[1]

Outcome variable	IFA[2] (*n*=441)	MMN[2] (*n*=439)	LNS[2] (*n*=440)	P[3]	Comparison of MMN and IFA		Comparison of LNS and IFA		Comparison of LNS and MMN	
					Difference (95 % CI)	P	Difference (95 % CI)	P	Difference (95 % CI)	P
36 weeks gestation										
Total GWG[4], kg	7.3 ± 3.9 (331)	7.2 ± 3.6 (351)	7.7 ± 3.7 (331)	0.18	-0.2 (-0.9, 0.5)	0.79	0.3 (-0.3, 1.0)	0.48	0.5 (-0.1, 1.2)	0.16
Rate of GWG[4], kg/wk	0.2 ± 0.11 (331)	0.2 ± 0.10 (351)	0.2 ± 0.10 (331)	0.19	-0.0 (-0.0, 0.0)	0.76	0.0 (-0.0, 0.0)	0.51	0.0 (-0.0, 0.0)	0.16
Percent adequacy of GWG[5]	76.1 ± 43.6 (331)	73.7 ± 41.0 (351)	80.8 ± 44.2 (331)	0.09	-2.4 (-10, 5.4)	0.75	4.7 (-3.1, 13)	0.33	7.1 (-0.6, 15)	0.08
Total MUAC change[4], cm	-1.1 ± 1.8 (331)	-1.1 ± 1.6 (352)	-0.9 ± 1.6 (332)	0.40	-0.0 (-0.3, 0.3)	0.98	0.1 (-0.2, 0.4)	0.54	0.2 (-0.1, 0.5)	0.41
Total TSF change[4], mm	-2.7 ± 4.2 (331)	-2.9 ± 3.9 (351)	-2.7 ± 4.1 (332)	0.76	-0.2 (-1.0, 0.5)	0.76	-0.0 (-0.8, 0.7)	0.99	0.2 (-0.6, 0.9)	0.84
6 mo postpartum										
Weight, kg	63.6 ± 12.7 (355)	63.0 ± 13.1 (362)	64.2 ± 13.2 (356)	0.52	-0.6 (-2.9, 1.7)	0.81	0.5 (-1.8, 2.8)	0.85	1.1 (-1.2, 3.4)	0.48
MUAC, cm	29.1 ± 4.2 (355)	29.0 ± 4.3 (362)	29.2 ± 4.6 (356)	0.84	-0.1 (-0.9, 0.6)	0.92	0.1 (-0.7, 0.8)	0.98	0.2 (-0.6, 1.0)	0.83
TSF, mm	20.9 ± 7. 6 (355)	20.8 ± 7.8 (362)	21.0 ± 7.8 (356)	0.95	-0.1 (-1.5, 1.3)	0.98	0.1 (-1.3, 1.4)	0.99	0.2 (-1.2, 1.5)	0.95
BMI, kg/m^2	25.2 ± 4.7 (355)	25.0 ± 4.7 (362)	25.4 ± 4.8 (356)	0.67	-0.2 (-1.0, 0.7)	0.90	0.2 (-0.7, 1.0)	0.89	0.3 (-0.5, 1.2)	0.64
Weight change from pre-	1.9 ± 4.7	1.40 ± 5.1	1.4 ± 4.8	0.33	-0.5 (-1.4, 0.4)	0.39	-0.5 (-1.3, 0.4)	0.40	0.0 (-0.9, 0.9)	1.00

Outcome variable	IFA[2] (*n*=441)	MMN[2] (*n*=439)	LNS[2] (*n*=440)	P[3]	Comparison of MMN and IFA		Comparison of LNS and IFA		Comparison of LNS and MMN	
					Difference (95 % CI)	P	Difference (95 % CI)	P	Difference (95 % CI)	P
pregnancy[6], kg	(348)	(356)	(351)							
MUAC change from pre-pregnancy[6], cm	0.6 ± 2.0 (348)	0.3 ± 2.0 (357)	0.3 ± 2.1 (351)	0.12	-0.2 (-0.6, 0.1)	0.24	-0.3 (-0.6, 0.1)	0.14	-0.0 (-0.4, 0.3)	0.95
TSF change from pre-pregnancy[6], mm	0.9 ± 4.9 (348)	0.5 ± 5.0 (356)	0.4 ± 5.0 (351)	0.30	-0.5 (-1.3, 0.4)	0.43	-0.5 (-1.4, 0.3)	0.33	-0.1 (-1.0, 0.8)	0.98
BMI change from pre-pregnancy[6], kg/m^2	0.7 ± 1.9 (348)	0.6 ± 2.0 (356)	0.5 ± 1.9 (351)	0.36	-0.2 (-0.5, 0.2)	0.45	-0.2 (-0.5, 0.2)	0.41	-0.0 (-0.4, 0.3)	1.00

[1]BMI, Body Mass Index; GWG, Gestational Weight Gain; IFA, Iron + Folic Acid; LNS, Small Quantity Lipid-based Nutrient Supplement (SQ-LNS); MMN, Multiple Micronutrients group; MUAC, Mid Upper Arm Circumference; TSF, Triceps Skinfold. IFA group: women were intended to receive 60 mg Fe + 400 mg folic acid/d during pregnancy, and placebo (200 mg Ca/d) during the first 6 mo postpartum; MMN group: women were intended to receive 18 vitamins and minerals (including 20 mg Fe)/d during pregnancy and the first 6 mo postpartum; LNS group: women were intended to receive 20 g/d LNS with the same micronutrients as the MMN group + Ca, P, K, and Mg as well as macronutrients during pregnancy and the first 6 mo postpartum. Results are based ANOVA (SAS PROC GLM).

[2]Values are as Mean ± SD (*n*). Except for weight, MUAC, TSF and BMI at 6 mo postpartum, Mean and SD values are based on pre-pregnancy values estimated from those measured at enrolment, by using third-order polynomial regression with gestational age at enrolment as predictor variable.

[3]P-values compare Mean ± SD of 3 groups, with Tukey-Kramer adjustment for pairwise comparisons.

[4]Observed total gestational weight gain, and MUAC and TSF change were calculated by subtracting the estimated pre-pregnancy weight, MUAC and TSF, respectively from the weight, MUAC and TSF measured at the last prenatal visit (21). Estimated pre-pregnancy weight, MUAC, and triceps skinfold were calculated from baseline values by using third-order polynomial regression with gestational age at enrolment as predictor variable. Rate of GWG was calculated as total GWG at the last pre-natal measurement divided by completed weeks of gestation.

[5]Percent adequacy of GWG (continuous: percentage of weight-gain recommendations met (26)) was calculated by dividing the observed total GWG by the *expected* GWG according to the Institute of Medicine's recommended ranges (25) up to the woman's last prenatal measurement. Expected GWG = expected 1st

trimester total weight gain + [(gestational age at the time of last weight measurement – 13 wk) x recommended rate of GWG for 2nd and 3rd trimesters] (21, 23, 24).

[6]Change from pre-pregnancy to 6 months postpartum was calculated by subtracting the estimated pre-pregnancy values from the values measured at 6 months postpartum.

TABLE 3 Unadjusted binary anthropometric outcomes of women (n = 1320) who participated in a randomized trial of IFA (pregnancy only), MMN (pregnancy and lactation), and LNS (pregnancy and lactation) supplementation in a semi-urban setting in Ghana, by intervention group based on intended supplement at enrollment[1]

	IFA[2] (*n*=441)	MMN[2] (*n*=439)	LNS[2] (*n*=440)	P[3]	Comparison of MMN and IFA[4]		Comparison of LNS and IFA[4]		Comparison of LNS and MMN[4]	
					RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Inadequate GWG[5], %	63.1 (57.8, 68.2) [331]	67.2 (62.1, 72.0) [351]	57.4 (52.0, 62.6) [331]	0.030	1.1 (0.9, 1.2)	0.50	0.9 (0.8, 1.1)	0.29	0.9 (0.7, 1.0)	0.023
Adequate GWG[6], %	25.7 (21.3, 30.7) [331]	24.2 (20.0, 29.0) [351]	31.1 (26.4, 36.3) [331]	0.11	0.9 (0.7, 1.3)	0.90	1.2 (0.9, 1.6)	0.27	1.3 (1.0, 1.7)	0.11
Excessive GWG[7], %	11.2 (8.2, 15.1) [331]	8.5 (6.0, 12.0) [351]	11.5 (8.5, 15.4) [331]	0.38	0.8 (0.4, 1.3)	0.48	1.0 (0.6, 1.7)	0.99	1.3 (0.8, 2.3)	0.41
GWG <10th centile of expected GWG[8], %	28.5 (22.5, 35.4) [186]	28.7 (23.0, 35.2) [209]	23.0 (17.5, 29.6) [187]	0.36	1.0 (0.7, 1.5)	1.00	0.8 (0.5, 1.2)	0.45	0.8 (0.5, 1.2)	0.40
GWW >97th centile of expected GWG[8], %	0	0	0	-	-	-	-	-	-	-
Developed overweight or obesity by 6 months postpartum[9]	20.9 (15.8, 27.2) [196]	15.7 (11.5, 21.2) [216]	17.2 (12.6, 23.0) [204]	0.37	0.8 (0.5, 1.2)	0.36	0.8 (0.5, 1.3)	0.60	1.1 (0.6, 1.8)	0.92
Developed obesity by 6 months postpartum[10]	0.5 (0.1, 3.5) [196]	0.0 (0.0, 100) [216]	0.0 (0.0, 100) [204]	1.00	0.0 (0.0, 0.0)	1.00	0.0 (0.0, 0.0)	1.00	1.0 (0.8, 1.3)	1.00

[1]GWG, Gestational Weight Gain; IFA, Iron + Folic Acid; LNS, Small Quantity Lipid-based Nutrient Supplement (SQ-LNS); MMN, Multiple Micronutrients. IFA group: women were intended to receive 60 mg Fe + 400 mg folic acid/d during pregnancy, and placebo (200 mg Ca/d) during the first 6 mo postpartum; MMN group: women were intended to receive 18 vitamins and minerals (including 20 mg Fe)/d during pregnancy and the first 6 mo postpartum; LNS group:

women were intended to receive 20 g/d LNS with the same micronutrients as the MMN group + Ca, P, K, and Mg as well as macronutrients during pregnancy and the first 6 mo postpartum. Results are based Logistic Regression (SAS PROC GLIMMIX).

[2]Values are percentages (95% CI) [*n*]. Percentages (95% CIs) are based on pre-pregnancy values estimated from those measured at enrolment, by using third-order polynomial regression with gestational age at enrolment as predictor variable.

[3]P-value compares all 3groups, with Tukey-Kramer adjustment for pairwise comparisons.

[4]Relative Risks, RR (95% CI) and their P-values are based on Poisson regression (27)

[5]Below (<) the lower cut-off of Institute of Medicine (IOM)'s recommended range (13).

[6]Within the IOM's recommended range (13).

[7]Above (>) the upper cut-off of Institute of Medicine (IOM)'s recommended range (13).

[8]Based on INTERGROWTH-21st Standards for women whose estimated pre-pregnancy weight was normal (BMI 18.50-24.99). The 3rd centile of expected GWG was calculated as exp((1.382972 - 56.14743 * GA**-2 + 0.2787683 * GA **0.5) + (-1.88 * (0.2501993731 + 142.4297879 * GA **-2 - 61.45345 * GA **-2 * log(GA)))) - 8.75,0.1), where GA = weeks of gestational at the last antenatal measurement (14). The 97th centile of expected GWG was calculated by replacing the -1.88 in the formula for the 3rd centile of expected GWG by 1.88 (14). No woman in the entire sample had total GWG above the 97th centile of the expected GWG based on the INTERGROWTH-21st Standards.

[9]Proportion of women with normal BMI pre-pregnancy who became overweight or obese by 6 mo postpartum.

[10]Proportion of women with normal BMI pre-pregnancy who became obese by 6 mo postpartum.

SUPPLEMENTAL TABLE 1

Unadjusted continuous anthropometric outcomes of women (n = 1320) who participated in a randomized trial of IFA (pregnancy only), MMN (pregnancy and lactation), and SQ-LNS (pregnancy and lactation) supplementation in a semi-urban setting in Ghana, by intervention group based on supplements received at enrollment[1]

Outcome variable	IFA[2] (*n*=441)	MMN[2] (*n*=439)	LNS[2] (*n*=440)	P[3]	Comparison of MMN and IFA		Comparison of LNS and IFA		Comparison of LNS and MMN	
					Difference (95 % CI)	P	Difference (95 % CI)	P	Difference (95 % CI)	P
36 weeks gestation										
Total GWG[4], kg	7.3 ± 3.9 [333]	7.2 ± 3.5 [349]	7.7 ± 3.7 [331]	0.22	-0.05 (-0.72, 0.61)	0.98	0.40 (-0.28, 1.08)	0.34	0.46 (-0.21, 1.13)	0.25
Rate of GWG[4], kg/wk	0.2 ± 0.1 [333]	0.2 ± 0.1 [349]	0.2 ± 0.1 [331]	0.23	-0.00 (-0.02, 0.02)	0.98	0.01 (-0.01, 0.03)	0.36	0.01 (-0.01, 0.03)	0.25
Percent adequacy of GWG[5]	75.0 ± 42.9 [333]	74.7 ± 41.8 [349]	80.8 ± 44.2 [331]	0.12	-0.33 (-8.04, 7.39)	0.99	5.80 (-2.02, 13.6)	0.19	6.12 (-1.61, 13.9)	0.15
Total MUAC change[4], cm	-1.0 ± 1.8 [333]	-1.1 ± 1.6 [350]	-0.9 ± 1.6 [332]	0.29	-0.10 (-0.40, 0.20)	0.70	0.10 (-0.21, 0.40)	0.73	0.20 (-0.10, 0.50)	0.26
Total TSF change[4], mm	-2.8 ± 4.1 [332]	-2.8 ± 4.0 [350]	-2.7 ± 4.1 [332]	0.96	0.03 (-0.71, 0.76)	1.00	0.08 (-0.66, 0.83)	0.96	0.06 (-0.67, 0.79)	0.98
6 mo postpartum										
Weight, kg	63.0 ± 11.8 [355]	63.7 ± 13.8 [362]	64.2 ± 13.2 [356]	0.50	0.64 (-1.63, 2.91)	0.79	1.14 (-1.14, 3.43)	0.47	0.50 (-1.77, 2.78)	0.86
MUAC, cm	29.1 ± 4.1 [355]	29.0 ± 4.5 [362]	29.2 ± 4.6 [356]	0.87	-0.10 (-0.87, 0.67)	0.95	0.08 (-0.70, 0.85)	0.97	0.17 (-0.60, 0.94)	0.86
TSF, mm	21.0 ± 7.5 [355]	20.7 ± 7.9 [362]	21.0 ± 7.8 [356]	0.89	-0.23 (-1.59, 1.12)	0.91	0.02 (-1.34, 1.37)	1.00	0.25 (-1.10, 1.60)	0.90
BMI, kg/m^2	25.1 ± 4.4 [355]	25.1 ± 5.0 [362]	25.4 ± 4.8 [356]	0.73	0.04 (-0.79, 0.88)	0.99	0.26 (-0.57, 1.10)	0.74	0.22 (-0.61, 1.05)	0.81
Weight change from pre-	1.5 ± 4.9	1.8 ± 5.0	1.4 ± 4.8	0.61	0.26	0.76	-0.10	0.96	-0.36	0.60

Outcome variable	IFA[2] (*n*=441)	MMN[2] (*n*=439)	LNS[2] (*n*=440)	P[3]	Comparison of MMN and IFA		Comparison of LNS and IFA		Comparison of LNS and MMN	
					Difference (95 % CI)	P	Difference (95 % CI)	P	Difference (95 % CI)	P
pregnancy[6], kg	[348]	[356]	[351]		(-0.61, 1.12)		(-0.97, 0.77)		(-1.22, 0.51)	
MUAC change from pre-pregnancy[6], cm	0.5 ± 2.0 [348]	0.4 ± 2.0 [357]	0.3 ± 2.1 [351]	0.41	-0.07 (-0.42, 0.29)	0.90	-0.20 (-0.56, 0.16)	0.39	-0.13 (-0.49, 0.22)	0.65
TSF change from pre-pregnancy[6], mm	0.7 ± 4.7 [347]	0.7 ± 5.2 [357]	0.4 ± 5.0 [351]	0.64	0.06 (-0.82, 0.94)	0.99	-0.27 (-1.15, 0.61)	0.75	-0.33 (-1.21, 0.54)	0.65
BMI change from pre-pregnancy[6], kg/m^2	0.6 ± 1.9 [348]	0.7 ± 2.0 [356]	0.5 ± 1.9 [351]	0.60	0.10 (-0.24, 0.44)	0.78	-0.05 (-0.39, 0.30)	0.95	-0.14 (-0.49, 0.20)	0.58

[1]BMI, Body Mass Index; GWG, Gestational Weight Gain; IFA, Iron + Folic Acid; LNS, Small Quantity Lipid-based Nutrient Supplement (SQ-LNS); MMN, Multiple Micronutrients; MUAC, Mid Upper Arm Circumference; TSF, Triceps Skinfold. IFA group: women received 60 mg Fe + 400 mg folic acid/d during pregnancy, and placebo (200 mg Ca/d) during the first 6 mo postpartum; MMN group: women received 18 vitamins and minerals (including 20 mg Fe)/d during pregnancy and the first 6 mo postpartum; LNS group: women received 20 g/d LNS with the same micronutrients as the MMN group + Ca, P, K, and Mg as well as macronutrients during pregnancy and the first 6 mo postpartum. Results are based ANOVA (SAS PROC GLM).

[2]Values are as Mean ± SD (*n*). Except for weight, MUAC, TSF and BMI at 6 mo postpartum, Mean and SD values are based on pre-pregnancy values estimated from those measured at enrolment, by using third-order polynomial regression with gestational age at enrolment as predictor variable.

[3]P-values compare Mean ± SD of 3 groups, with Tukey-Kramer adjustment for pairwise comparisons.

[4]Observed total gestational weight gain, and MUAC and TSF change were calculated by subtracting the estimated pre-pregnancy weight, MUAC and TSF, respectively from the weight, MUAC and TSF measured at the last prenatal visit (1). Estimated pre-pregnancy weight, MUAC, and triceps skinfold were calculated from baseline values by using third-order polynomial regression with gestational age at enrolment as predictor variable. Rate of GWG was calculated as total GWG at the last pre-natal measurement divided by completed weeks of gestation.

[5]Percent adequacy of GWG (continuous: percentage of weight-gain recommendations met (2)) was calculated by dividing the observed total GWG by the *expected* GWG according to the Institute of Medicine's recommended ranges (3) up to the woman's last prenatal measurement. Expected GWG = expected 1st trimester total weight gain + [(gestational age at the time of last weight measurement – 13 wk) x recommended rate of GWG for 2nd and 3rd trimesters] (1, 4, 5).

[6]Change from pre-pregnancy to 6 months postpartum was calculated by subtracting the estimated pre-pregnancy values from the values measured at 6 months postpartum.

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SUPPLEMENTAL TABLE 2

Unadjusted continuous anthropometric outcomes of women (n=1320) who participated in randomized trial of daily IFA (pregnancy only), MMN (pregnancy + lactation) and SQ-LNS (pregnancy + lactation) supplementation in a semi-urban setting in Ghana, by IFA and MMN groups combined versus LNS group[1]

	IFA+MMN[2] (*n*=880)	LNS[2] (*n*=440)	P[3]	Mean difference (95% CI)
36 weeks gestation				
Total GWG, kg	7.24 ± 3.70 (682)	7.67 ± 3.75 (331)	0.08	0.43 (-0.06, 0.92)
Rate of GWG, kg/wk	0.20 ± 0.10 (682)	0.21 ± 0.10 (331)	0.09	0.01 (-0.00, 0.03)
Percent adequacy of GWG	74.9 ± 42.3 (682)	80.8 ± 44.2 (331)	0.038	5.96 (0.32, 11.6)
Total MUAC change, cm	-1.07 ± 1.70 (683)	-0.92 ± 1.64 (332)	0.18	0.15 (-0.07, 0.37)
Total TSF change, mm	-2.79 ± 4.06 (682)	-2.72 ± 4.09 (332)	0.80	0.07 (-0.46, 0.60)
6 mo postpartum				
Weight, kg	63.3 ± 12.9 (717)	64.2 ± 13.2 (356)	0.33	0.82 (-0.83, 2.47)
MUAC, cm	29.1 ± 4.27 (717)	29.2 ± 4.62 (356)	0.66	0.13 (-0.43, 0.68)
TSF, mm	20.8 ± 7.69 (717)	21.0 ± 7.77 (356)	0.79	0.13 (-0.85, 1.12)
BMI, kg/m^2	25.1 ± 4.71 (717)	25.4 ± 4.83 (356)	0.43	0.24 (-0.36, 0.85)
Weight change from pre-pregnancy[4], kg	1.64 ± 4.94 (704)	1.41 ± 4.81 (351)	0.47	-0.23 (-0.86, 0.40)
MUAC change from pre-pregnancy[4], cm	0.45 ± 1.98 (705)	0.29 ± 2.08 (351)	0.21	-0.17 (-0.42, 0.09)
TSF change from pre-pregnancy[4], mm	0.69 ± 4.95 (704)	0.39 ± 4.96 (351)	0.35	-0.30 (-0.94, 0.33)
BMI change from pre-pregnancy[4], kg/m^2	0.64 ± 1.95 (704)	0.54 ± 1.89 (351)	0.45	-0.10 (-0.34, 0.15)

[1]BMI, Body Mass Index; GWG, Gestational weight gain; IFA, Iron + folic acid; LNS, Lipid-based nutrient supplement; MMN, Multiple micronutrients; MUAC, Mid upper arm circumference; SQ-LNS, Small quantity lipid-based nutrient supplement; TSF, triceps skinfold. IFA+MMN = IFA and MMN groups combined: women were intended to receive 60 mg iron + 400 µg folic acid during pregnancy and placebo during the first 6 mo postpartum, or a multiple micronutrient capsule containing 18 vitamins and minerals (including 20 mg iron) during pregnancy and the first 6 mo postpartum; LNS group: women received SQ-LNS-for-women with the same micronutrients as the multiple micronutrients, plus 4 more minerals (Ca, P, K and Mg) as well as macronutrients during pregnancy and the first 6 mo postpartum. All supplements were intended for daily consumption. Results are based ANOVA (SAS PROC GLM). .

[2]Values are Mean ± SD (*n*). Except for weight, MUAC, TSF and BMI at 6 mo postpartum, Mean and SD values are based on pre-pregnancy values estimated from those measured at enrolment, by using third-order polynomial regression with gestational age at enrolment as predictor variable

[3]P-values compare Mean ± SD of two groups.

[5]Based on pre-pregnancy values estimated from values at enrolment by using polynomial regression, with gestational age at enrolment, gestational age at enrolment squared, and gestational age at enrolment cubed as predictors.

SUPPLEMENTAL TABLE 3
Unadjusted binary anthropometric outcomes of women (n = 1320) who participated in a randomized trial of IFA (pregnancy only), MMN (pregnancy and lactation), and LNS (pregnancy and lactation) supplementation in a semi-urban setting in Ghana, by intervention group based on supplements received at enrollment[1]

	IFA[2] (*n*=441)	MMN[2] (*n*=439)	LNS[2] (*n*=440)	P[3]	Comparison of MMN and IFA[4]		Comparison of LNS and IFA[4]		Comparison of LNS and MMN[4]	
					RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Inadequate GWG[5], %	62.8 (57.4, 67.8) [333]	67.6 (62.5, 72.3) [349]	57.4 (52.0, 62.6) [331]	0.023	1.08 (0.94, 1.23)	0.38	0.91 (0.79, 1.06)	0.34	0.85 (0.74, 0.98)	0.017
Adequate GWG[6], %	26.4 (22.0, 31.4) [333]	23.5 (19.3, 28.2) [349]	31.1 (26.4, 36.3) [331]	0.08	0.89 (0.65, 1.21)	0.65	1.18 (0.88, 1.57)	0.38	1.32 (0.98, 1.78)	0.07
Excessive GWG[7], %	10.8 (7.9, 14.6) [333]	8.9 (6.3, 12.4) [349]	11.5 (8.5, 15.4) [331]	0.51	0.82 (0.48, 1.42)	0.68	1.06 (0.63, 1.78)	0.96	1.29 (0.75, 2.22)	0.50
GWG <10th centile of expected GWG[8], %	29.7 (23.6, 36.5) [192]	27.6 (21.9, 34.1) [203]	23.0 (17.5, 29.6) [187]	0.33	0.93 (0.64, 1.35)	0.89	0.77 (0.51, 1.17)	0.30	0.83 (0.55, 1.26)	0.55
GWW >97th centile of expected GWG[8], %	0	0	0	-	-	-	-	-	-	-
Developed overweight or obesity by 6 months postpartum[9]	18.3 (13.6, 24.3) [202]	18.1 (13.4, 23.9) [210]	17.2 (12.6, 23.0) [204]	0.95	0.99 (0.60, 1.61)	1.00	0.94 (0.57, 1.55)	0.95	0.95 (0.58, 1.56)	0.97
Developed obesity by 6 months postpartum[10]	0.0 (0.0, 100) [202]	0.5 (0.1, 3.3) [210]	0.0 (0.0, 100) [204]	1.00	-	1.00	1.00 (0.78, 1.27)	1.00	0.00 (0.00, 0.00)	1.00

[1]GWG, Gestational Weight Gain; IFA, Iron + Folic Acid; LNS, Small Quantity Lipid-based Nutrient Supplement (SQ-LNS); MMN, Multiple Micronutrients. IFA group: women received 60 mg Fe + 400 mg folic acid/d during pregnancy, and placebo (200 mg Ca/d) during the first 6 mo postpartum; MMN group: women received 18 vitamins and minerals (including 20 mg Fe)/d during pregnancy and the first 6 mo postpartum; LNS group: women received 20 g/d LNS with the same micronutrients as the MMN group + Ca, P, K, and Mg as well as macronutrients during pregnancy and the first 6 mo postpartum Results are based Logistic Regression (SAS PROC GLIMMIX).

[2]Values are percentages (95% CI) [*n*]. Percentages (95% CIs) are based on pre-pregnancy values estimated from those measured at enrolment, by using third-order polynomial regression with gestational age at enrolment as predictor variable.

[3]P-value compares all 3groups, with Tukey-Kramer adjustment for pairwise comparisons.

[4]Relative Risks, RR (95% CI) and their P-values are based on Poisson regression (1)

[5]Below (<) the lower cut-off of Institute of Medicine (IOM)'s recommended range (2).

[6]Within the IOM's recommended range (2).

[7]Above (>) the upper cut-off of Institute of Medicine (IOM)'s recommended range (2).

[8]Based on INTERGROWTH-21st Standards for women whose estimated pre-pregnancy weight was normal (BMI 18.50-24.99). The 3rd centile of expected GWG was calculated as exp((1.382972 - 56.14743 * GA**-2 + 0.2787683 * GA **0.5) + (-1.88 * (0.2501993731 + 142.4297879 * GA **-2 - 61.45345 * GA **-2 * log(GA)))) - 8.75,0.1), where GA = weeks of gestational at the last antenatal measurement (3). The 97th centile of expected GWG was calculated by replacing the -1.88 in the formula for the 3rd centile of expected GWG by 1.88 (3). No woman in the entire sample had total GWG above the 97th centile of the expected GWG based on the INTERGROWTH-21st Standards.

[9]Proportion of women with normal BMI pre-pregnancy who became overweight or obese by 6 mo postpartum.

[10]Proportion of women with normal BMI pre-pregnancy who became obese by 6 mo postpartum.

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SUPPLEMENTAL TABLE 4
Unadjusted binary anthropometric outcomes of women (n=1320) who participated in randomized trial of daily IFA (pregnancy only), MMN (pregnancy + lactation) and SQ-LNS (pregnancy + lactation) supplementation in a semi-urban setting in Ghana, by IFA and MMN groups combined versus LNS group[1]

	IFA+MMN[2] [*n*=880]	LNS[2] [*n*=440]	P	Relative Risk (95% CI)[3]
Inadequate GWG[4], %	65.2 (61.6, 68.7) [682]	57.4 (52.0, 62.6) [331]	0.016	0.9 (0.79, 0.98)
Adequate GWG[5], %	24.9 (21.8, 28.3) [682]	31.1 (26.4, 36.3) [331]	0.038	1.3 (1.02, 1.54)
Excessive GWG[6], %	9.8 (7.8, 12.3) [682]	11.5 (8.5, 15.4) [331]	0.42	1.2 (0.80, 1.70)
GWG <10th centile of expected GWG[7], %	28.6 (24.4, 33.3) [395]	23.0 (17.5, 29.6) [187]	0.15	0.80 (0.59, 1.09)
GWW >97th centile of expected GWG[7], %	0	0	-	-
Developed overweight or obesity by 6 months postpartum[8]	18.2 (14.8, 22.2) [412]	17.2 (12.6, 23.0) [204]	0.75	0.94 (0.65, 1.36)
Developed obesity by 6 months postpartum[9]	0.2 (0.0, 1.7) [412]	0.0 (0.0, 100) [204]	0.98	0.0 (0.00, 0.00)

[1]GWG, Gestational weight gain; IFA, Iron + folic acid; LNS, Lipid-based nutrient supplement; MMN, Multiple micronutrients; SQ-LNS, Small quantity lipid-based nutrient supplement; IFA+MMN = IFA and MMN groups combined: women were intended to receive 60 mg iron + 400 µg folic acid during pregnancy and placebo during the first 6 mo postpartum, or a multiple micronutrient capsule containing 18 vitamins and minerals (including 20 mg iron) during pregnancy and the first 6 mo postpartum; LNS group: women received SQ-LNS-for-women with the same micronutrients as the multiple micronutrients, plus 4 more minerals (Ca, P, K and Mg) as well as macronutrients during pregnancy and the first 6 mo postpartum. All supplements were intended for daily consumption. Results are based Logistic Regression models (SAS PROC GLIMMIX).

[2]Values are percentages (95% CI) [*n*]. Percentages (95% CIs) are based on pre-pregnancy values estimated from those measured at enrolment, by using third-order polynomial regression with gestational age at enrolment as predictor variable.

[3]Relative risks and 95% CIs were calculated by using Poisson regression (1)

[4]Below (<) the lower cut-off of Institute of Medicine (IOM)'s recommended range (2).

[5]Within the IOM's recommended range (2).

[6]Above (>) the upper cut-off of Institute of Medicine (IOM)'s recommended range (2).

[7]Based on INTERGROWTH-21st Standards for women whose estimated pre-pregnancy weight was normal (BMI 18.50-24.99). The 3rd centile of expected GWG was calculated as exp((1.382972 - 56.14743 * GA**-2 + 0.2787683 * GA **0.5) + (-1.88 * (0.2501993731 + 142.4297879 * GA **-2 - 61.45345 * GA **-2 * log(GA)))) - 8.75,0.1), where GA = weeks of gestational at the last antenatal measurement (3). The 97th centile of expected GWG was calculated by replacing the -1.88 in the formula for the 3rd centile of expected GWG by 1.88 (3). No woman in the entire sample had total GWG above the 97th centile of the expected GWG based on the INTERGROWTH-21st Standards.

[8]Proportion of women with normal BMI pre-pregnancy who became overweight or obese by 6 mo postpartum.

[9]Proportion of women with normal BMI pre-pregnancy who became obese by 6 mo postpartum.

References

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