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Original Research Article

Sustained effects of small-quantity lipid-based nutrient supplements provided during the first 1000 days on child growth at 9–11 y in a randomized controlled trial in Ghana

Helena J Bentil [1,*], Seth Adu-Afarwuah [2], Elizabeth L Prado [1,†], Charles D Arnold [1], Paul D Hastings [3], Amanda E Guyer [4], Mavis O Mensah [2], Adom Manu [5], Xiuping Tan [1], Ebenezer Adjetey [2], Benjamin Amponsah [6], Maku E Demuyakor [7], Kathryn G Dewey [1], Brietta M Oaks [8]

[1] *Department of Nutrition, University of California-Davis, Davis, CA, United States;* [2] *Department of Nutrition and Food Science, University of Ghana, Accra, Ghana;* [3] *Department of Psychology and Center for Mind and Brain, University of California-Davis, Davis, CA, United States;* [4] *Department of Human Ecology and Center for Mind and Brain, University of California-Davis, Davis, CA, United States;* [5] *Department of Population, Family & Reproductive Health, School of Public Health, University of Ghana, Accra, Ghana;* [6] *Department of Psychology, University of Ghana, Accra, Ghana;* [7] *McKing Consulting Corporation, Atlanta, GA, United States;* [8] *Department of Nutrition, University of Rhode Island, Kingston, RI, United States*

A B S T R A C T

Background: There is limited research on whether nutritional supplementation in the first 1000 d affects long-term child outcomes. We previously demonstrated that pre- and postnatal small-quantity lipid-based nutrient supplements (SQ-LNS) increased birth weight and child length at 18 mo of age in Ghana.

Objectives: We aimed to investigate the effect of pre- and postnatal SQ-LNS on child growth and blood pressure at 9–11 y.

Methods: In the International Lipid-Based Nutrient Supplements (iLiNS)-DYAD-Ghana trial, 1320 females ≤20 weeks of gestation were randomly assigned to receive daily: iron and folic acid (IFA) during pregnancy and placebo during 6 mo postpartum or multiple micronutrients (MMNs) during pregnancy and 6 mo postpartum, or SQ-LNS during pregnancy and 6 mo postpartum and for their children aged from 6 to 18 mo. We re-enrolled 966 children aged 9–11 y and assessed child blood pressure, height-for-age *z*-score (HAZ), body mass index (BMI)-for-age *z*-score, waist-to-height ratio, triceps skinfold, and midupper arm circumference. We compared SQ-LNS with control (IFA + MMN) groups adjusting for child's age.

Results: Mean (standard deviation [SD]) HAZ in SQ-LNS and control group was −0.04 (0.96) and −0.16 (0.99); $P = 0.060$. There were no indications of group differences in the other outcomes ($P > 0.10$). Effects on HAZ varied by child sex (P-interaction = 0.075) and maternal prepregnancy BMI (kg/m^2; P-interaction = 0.007). Among females, HAZ was higher in the SQ-LNS [0.08 (1.04)] than in the control group [−0.16 (1.01)] ($P = 0.010$); among males, SQ-LNS [−0.16 (0.85)] and control groups [−0.16 (0.96)] did not differ ($P = 0.974$). Among children of females with BMI of <25, HAZ was higher in the SQ-LNS [−0.04 (1.00)] than in the control group [−0.29 (0.94)] ($P = 0.004$); among females with BMI of ≥25, SQ-LNS [−0.04 (0.91)] and control groups [0.07 (1.00)] did not differ ($P = 0.281$).

Conclusions: There is a sustained impact of prenatal and postnatal SQ-LNS on linear growth among female children and children whose mothers were not overweight.

This trial was registered at clinicaltrials.gov as NCT00970866 (https://clinicaltrials.gov/ct2/show/record/NCT00970866).

Keywords: lipid-based nutrient supplements, growth, early adolescence, 1000 days, Ghana

Abbreviations: BAZ, BMI-for-age *z*-score; CESD, Center for Epidemiological Studies – Depression; DBP, diastolic blood pressure; HAZ, height-for-age *z*-score; Hb, hemoglobin; IFA, iron and folic acid; iLiNS, International Lipid-Based Nutrient Supplements; LAZ, length-for-age *z*-score; MC-HOME, Middle Childhood Home Observation for the Measurement of the Environment; MMN, multiple micronutrients; MUAC, midupper arm circumference; SQ-LNS, small-quantity lipid-based nutrient supplements; SBP, systolic blood pressure; TSF, triceps skinfold; WtHR, waist-to-height ratio.

* Corresponding author.

E-mail address: hjbentil@ucdavis.edu (H.J. Bentil).

† Deceased.

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Introduction

The significant effects of nutritional supplementation during both prenatal and postnatal life on child growth and development in early life are well documented. For example, providing small-quantity lipid-based nutrient supplements (SQ-LNS) during pregnancy and the complementary feeding period (6–24 mo) is a proven preventive strategy for undernutrition during the 1000-d window [1–4]. Children who received SQ-LNS had a 12%–14% lower prevalence of stunting, wasting, and underweight than children who did not [5]. However, the long-term effects of exposure to nutritional supplementation during the first 1000 d are less well documented.

Two previous trials of maternal plus child food supplementation conducted in Guatemala [6] and Colombia [7] in the 1970s found long-term positive effects on child height and weight during middle childhood and adolescence. To the best of our knowledge, those 2 studies are the only ones that have included a follow-up evaluation of the growth of children who were exposed to a nutritional supplement during both prenatal and postnatal periods. Evidence suggests that early linear growth predicts adult height [8], and a higher birthweight is consistently associated with a reduced likelihood of short adult stature [8,9]. There is also considerable evidence suggesting that both weight and head circumference at birth are inversely related to systolic blood pressure (SBP) later in life, particularly in adolescence [10], suggesting that blood pressure is another important health indicator to examine as children develop.

We previously have shown positive effects of pre- and postnatal SQ-LNS on weight and head circumference at birth [11], and on length, weight, and stunting prevalence at 18 mo of age [1]. At 4–6 y of age, we found a significant interaction between maternal prepregnancy BMI (kg/m2) and the effect of SQ-LNS on child height: among children of females with a BMI of <25, those who had received SQ-LNS were taller than those who had not (+1.1 cm, $P = 0.017$), whereas there was no significant intervention group difference in height among children of females with a BMI of ≥25 [12]. Additionally, we found no effects of SQ-LNS on blood pressure at 4–6 y [13]; however, evidence [10] suggests that adolescence may be a developmental period in which effects on blood pressure are more likely to emerge. In the present study, we examined the effects of pre- and postnatal SQ-LNS on growth and blood pressure in early adolescence. Our primary outcomes were height-for-age *z*-score (HAZ), SBP, and diastolic blood pressure (DBP) and our secondary outcomes were BMI-for-age *z*-score (BAZ), midupper arm circumference (MUAC), triceps skinfold (TSF), and waist-to-height ratio (WtHR), as well as the prevalence of overweight, obesity, stunting, and high systolic and DBP. We hypothesized that the effects of SQ-LNS on growth in early life would be sustained into early adolescence and that children in the SQ-LNS group would have lower blood pressure than children in the control group.

Methods

Design of the main International Lipid-Based Nutrient Supplements trial (2009–2014)

The International Lipid-Based Nutrient Supplements (iLiNS)-DYAD-Ghana trial was conducted in semiurban communities in the Yilo and Lower Manya Krobo districts of the Eastern Region of Ghana between December 2009 and March 2014. The main trial's study design, randomization, and recruitment details have previously been reported [11]. In brief, the iLiNS-DYAD-Ghana study was a partially double-blind randomized controlled trial with 3 equal-size groups. Participants were 1320 pregnant females aged ≥18 y at ≤20 wk of gestation who were attending antenatal clinics in 4 main health facilities in the study area. Participants were excluded if they had HIV infection, asthma, epilepsy, tuberculosis, or any malignancy, a known milk or peanut allergy, were not residing in the area, had the intention to move within the next 2 y, expressed unwillingness to receive fieldworkers or take the study supplement, or were already participating in another trial. Eligible female participants were randomly allocated to 1 of 3 intervention groups using a computer-generated randomization scheme in blocks of 9. Allocation information was concealed in opaque envelopes with different color codes representing supplements (either iron and folic acid [IFA] or multiple micronutrients [MMNs]) and an "LNS" designation for the lipid-based nutrient supplement group by the study statistician. Each envelope was numbered from 1 to 1320 and, at enrollment, participants would randomly select 1 envelope from a stack that had been shuffled by the study nurse to determine their allocation.

The 3 intervention groups were as follows: *1*) daily IFA tablets consisting of 60 mg iron plus 400 μg folic acid during pregnancy and a 200 mg/d calcium tablet (placebo) during the first 6 mo postpartum and no infant supplementation, *2*) daily MMN tablets consisting of 1–2 Recommended Dietary Allowances of 18 vitamins and minerals during pregnancy and the first 6 mo postpartum and no infant supplementation, or *3*) daily 20 g (118 kcal) SQ-LNS containing the same 18 micronutrients as the MMN group, plus calcium, magnesium, phosphorus, potassium, and macronutrients given during pregnancy and the first 6 mo postpartum followed by infant 20 g/d LNS supplementation from 6 to 18 mo of age. Participants were aware of whether they received SQ-LNS or a capsule because of differences in appearance but remained blind to whether they received IFA or MMN. Field workers who assessed outcomes and collected other data were blinded to all intervention groups.

Recruitment into the 9–11-y follow-up study (2020–2021)

Between December 2020 and December 2021, a follow-up of the iLiNS-DYAD-Ghana trial was carried out. The study children were between 9 and 11 y of age. We sought to locate caregivers of the 1217 known surviving children from the original trial (Figure 1).

Ethical approval for the current follow-up study was obtained from the Institutional Review Board of the University of California-Davis (IRB ID: 1489918) and the Ghana Health Service Ethical Review Committee (GHS-ERC: 027105119). Written informed consent and assent were given by both the primary caregiver and the child before data collection.

Data collection procedures

Each caregiver–child pair received a home visit (~1.5 h) and attended a project office visit (~4 h). During the home visit, data collectors obtained informed consent and assent from both the caregiver and the child as well as sociodemographic information using an interviewer-administered questionnaire. In addition, we assessed the home environment using the Middle Childhood Home Observation for the Measurement of the Environment (MC-HOME) Inventory [14], which consists of 58 items measuring parental responsivity, physical environment, availability of learning materials, level of active stimulation, encouragement of maturity, emotional climate, parental involvement, and family participation. At the project office visit, child anthropometry and blood pressure measurements were completed. Blood pressure was taken by the study nurse using a blood pressure monitor (Omron 10 series, Omron Healthcare). Height was measured using a height board (UNICEF S0114540), weight using a digital

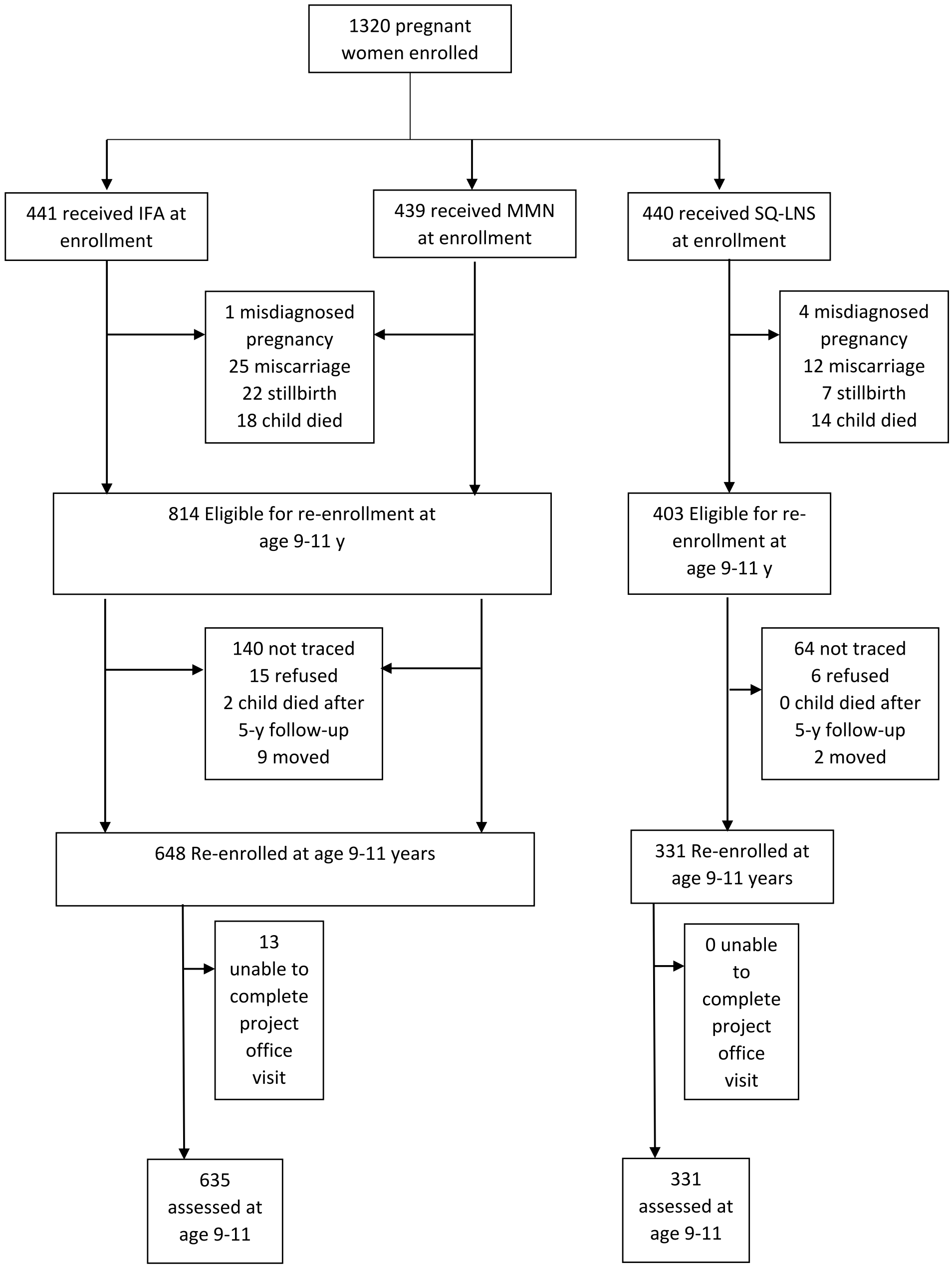

FIGURE 1. Study profile of the International Lipid-Based Nutrient Supplements (iLiNS)-DYAD-Ghana trial. IFA, iron-folic acid; MMN, multiple micronutrients; SQ-LNS, small-quantity lipid-based nutrient supplement.

weight scale (SECA 874, Chino), triceps skin fold (TSF) using Lange skinfold caliper (Beta Technology Inc.), and midupper arm circumference (MUAC) using a MUAC tape. All anthropometric measurements of child growth were taken by trained anthropometrists in duplicate and triplicate if the first 2 measurements differed by a predefined amount: 0.1 kg for weight, 0.5 cm for height and MUAC, and 2 mm for TSF. We also assessed maternal depressive symptoms using the Center for Epidemiological Studies – Depression (CESD) Test [15] and pubertal development using the Petersen Pubertal Development Scale by parent and youth report [16].

Sample size and data analysis

For the current analyses, the sample included 966 (331 LNS and 635 non-LNS) children who had anthropometric data at the 9–11-y follow-up study. This sample size provided 80% power to detect an effect size, that is, a mean difference between 2 groups, of $\geq$0.20 SD for continuous outcomes at a significance level of P value of $<$0.05. A statistical analysis plan was posted to Open Science Framework (https://osf.io/bmv9d/) before conducting analyses. Analyses were performed using SAS Studio version 5.2 (SAS Inst.).

The primary outcomes were continuous HAZ, SBP, and DBP. The secondary outcomes were continuous BAZ score, MUAC, TSF, and WtHR and the prevalence of overweight (BMI-for-age z-score, BAZ $>$ 1 SD), obesity (BAZ $>$ 2 SD), central obesity (WtHR $\geq$ 0.5) [17], stunting (HAZ $<-$2SD), and high systolic and DBP. High systolic or DBP was defined as SBP or DBP $\geq$ 90th percentile of the reference population, respectively, computed using equations provided by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents [18].

Our hypothesis was based on combining the IFA and MMN groups, referred to collectively as the control group, because our own [12] and other previous studies [19] comparing IFA and MMN groups showed no differences in growth outcomes. A sensitivity analysis comparing the maternal intervention groups as randomized was performed nonetheless, to check for any differences between the IFA and MMN groups (Supplemental Table 1). Comparisons reported here are between the child intervention groups, specifically the SQ-LNS and the control (IFA + MMN) groups.

We conducted a complete case intention to treat analysis. To test the effect of the intervention, analysis of covariance (ANCOVA) models were used for continuous outcomes and logistic regression was used for dichotomous outcomes with statistical significance set at P value of <0.05. The primary inference models were only adjusted for the child's age at the age 9–11-y follow-up. In secondary analyses, we estimated adjusted parameters by including characteristics that were strongly associated with the outcome to improve the precision of our estimates (decrease the SEs). In addition to the child's age at follow-up, the second model controlled for prespecified covariates collected upon enrollment into the trial that were significantly associated with the outcomes at P value of <0.10 in a bivariate analysis. Covariates examined for association based on prior literature [5] included maternal age (years), maternal education (year of formal education), marital status (married/cohabiting or single/widowed/separated), household asset index (constructed based on ownership of a set of assets and household characteristics using principal components analysis), household food insecurity access score (z-score), household water source (improved or unimproved water source), household sanitation (improved or unimproved sanitation), maternal height (cm), maternal prepregnancy BMI, maternal hemoglobin concentration (Hb, g/L), and maternal primiparous status (nulliparous or parous). The third model was additionally adjusted for covariates collected at follow-up that were significantly associated at the P value of <0.10 level with the outcome in bivariate analysis. Covariates that were collected at follow-up were first examined for whether they were different between intervention groups at P value of <0.10. None of them differed significantly between the intervention groups (SQ-LNS and control groups). Covariates collected at follow-up based on prior literature [20–22] included home-environment factors (MC-HOME total score), maternal depressive symptoms (CESD Test) score, and child pubertal development score (Petersen Pubertal Development Scale, self-report). Prespecified potential effect modifiers were child sex (male or female), primiparity, baseline maternal education, baseline maternal prepregnancy BMI, and baseline household asset index [5]. These were assessed with an interaction term in the ANCOVA or logistic regression models and significant interactions ($P < 0.10$) were further examined with stratified analyses. In addition, the stratified results were presented not only at 9–11 y but across all time points, including birth, 6 mo, 18 mo, and 4–6 y, to provide contextualization for the findings.

Results

Background characteristics

Out of the total of 1217 children who were eligible to participate in the follow-up study, 979 were enrolled, including 648 in the control group and 331 in the SQ-LNS group (as shown in Figure 1). The reasons for nonparticipation in the follow-up were similar between groups and included the inability to locate the mother ($n = 204$), refusal to take part in the study ($n = 21$), the death of the child ($n = 2$), and no longer residing in the study area ($n = 11$). Of the 979 enrolled, 13 children did not attend the project office visit, all of whom belonged to the control group. Therefore, we were able to obtain measurements for 966 children, which accounted for 79% of the eligible children. Out of these 966 children, 635 belonged to the control group, and 331 were from the SQ-LNS group. The 966 children were similar to the 354 children enrolled in the main trial who were lost to follow-up in terms of baseline characteristics, with the exception of nulliparity (Supplemental Table 2). Those lost to follow-up had a higher proportion of nulliparous females (40% compared with 31%).

Table 1 shows the characteristics of the children's mothers when they were enrolled in the trial during pregnancy. At baseline, the mean maternal age was ~27 y, the mean education was ~8 y, ~94% were married/cohabiting, ~31% were nulliparous, mean maternal height was 159 cm, mean gestational age was 16 wk, and the mean prepregnancy BMI was 25, ~40% were overweight and mean maternal Hb was 111 g/L.

Among those included in the analysis, there were no significant differences in baseline characteristics between the SQ-LNS and control (IFA + MMN) groups, except for household asset score, which was higher in the control group ($P = 0.02$) indicating that females who received SQ-LNS were from poorer households than females in the control group. At the time of the follow-up, there were also no significant differences in child age, sex, or puberty development score between the SQ-LNS and control groups. The mean ($\pm$ SD) age of the children was 9.9 $\pm$ 0.5 y, with boys constituting 48% of the study population.

TABLE 1
Baseline characteristics of females whose children were included in the follow-up, and children in the International Lipid-Based Nutrient Supplements (iLiNS)-DYAD-Ghana trial at follow-up

Characteristic	SQ-LNS ($n = 331$)	Control ($n = 635$)
Maternal characteristics		
Age (y)	27.0 ± 5.5	26.8 ± 5.4
Formal education (y)	7.7 ± 3.8	7.7 ± 3.4
Married or cohabiting (%)	91.8	94.0
Household asset score[1,2]	–0.07 ± 0.97	0.09 ± 0.97
Nulliparous females (%)	30.9	31.7
Height (cm)	159.1 ± 5.4	158.8 ± 5.9
Gestational age (wk)	16.0 ± 3.3	16.2 ± 3.2
Prepregnancy BMI[3], (kg/m^2)	24.9 ± 4.5	24.3 ± 4.4
Overweight/obese (%)	42.7	35.7
Hemoglobin concentration (g/L)	111.5 ± 11.2	111.4 ± 12.6
Child characteristics		
Age of child at follow-up (y)	9.9 ± 0.5	9.9 ± 0.5
Sex of child (% boys)	48.9	48.3
Puberty Development Score at follow-up	7.5 ± 1.1	7.5 ± 1.1

Values are presented as mean ± SD for continuous variables, and % for dichotomous variables.
Abbreviation: SQ-LNS; small-quantity lipid-based nutrient supplement.
[1] Household asset score was constructed based on ownership of a set of assets (radio, television, refrigerator, and stove), lighting source, drinking water supply, sanitation facilities, and flooring materials, developed into an index (with a mean of 0 and SD of 1) using principal components analysis.
[2] Significant at $P < 0.05$.
[3] Estimated prepregnancy BMI was calculated from estimated prepregnancy weight (based on polynomial regression with gestational age, gestational age squared, and gestational age cubed as predictors) and height at enrollment.

Effects of SQ-LNS on growth and blood pressure outcomes

Tables 2 and 3 show the age-adjusted continuous and dichotomous anthropometric and blood pressure measurements at 9–11 y of age by group. HAZ in SQ-LNS and control group was −0.04 (0.96) and −0.16 (0.99); $P = 0.060$. There were no indications of group differences in any of the other outcomes ($P > 0.10$). Adjustment for prespecified covariates did not alter any of the above findings (Supplemental Tables 3 and 4). Both groups were on average close to the median value of 0 as defined by the WHO Child Growth Standards in HAZ [23], and stunting prevalence was only 2%. Ten percent of children were overweight, 3% were obese; and very few had high systolic (0%) or diastolic (1%) blood pressure (Table 3).

Interaction of SQ-LNS with effect modifiers

For HAZ, we found an interaction of the intervention group with child sex (P-interaction = 0.075) and maternal prepregnancy BMI (P-interaction = 0.007) (Figures 2 and 3). Among females, HAZ was higher in the SQ-LNS than control group (mean ± SD; SQ-LNS: 0.08 ± 1.04; control: −0.16 ± 1.01; $P = 0.010$); among males, the SQ-LNS and control groups did not differ (SQ-LNS: −0.16 ± 0.85 and control: −0.16 ± 0.96; $P = 0.974$). Among females with BMI of <25, HAZ was higher in the SQ-LNS than control group (SQ-LNS: −0.04 ± 1.00 and control: −0.29 ± 0.94; $P = 0.004$); among females with BMI of ≥25, the SQ-LNS and control, groups did not differ (SQ-LNS: −0.04 ± 0.91 and control: 0.07 ± 1.00; $P = 0.281$).

Figures 4 and 5 show the length-for-age z-score (LAZ)/HAZ at all time points (birth, 6 mo, 18 mo, 4–6 y, and 9–11 y) by intervention group and child sex or maternal prepregnancy BMI at baseline. The mean LAZ/HAZ was consistently higher in the female SQ-LNS group than in the female control group at all time points. In the subgroup of children born to females with BMI of <25, the mean LAZ/HAZ was consistently higher at all time points in the SQ-LNS group than in the control group.

For other outcomes, we found significant interactions ($P < 0.10$) of the intervention group with *1*) asset index (for WtHR, BAZ, MUAC, and TSF); and *2*) maternal prepregnancy BMI (for DBP and TSF). Results are shown in Supplemental Figures 1–6. All other interactions were non-significant ($P > 0.10$), thus the results are not shown.

Discussion

In this follow-up study, we sought to assess the effect of nutrient supplementation provided to females during pregnancy and the first 6 mo postpartum, and to their children from 6 to 18 mo of age, on child's growth and blood pressure at 9–11 y of age in the iLiNS-DYAD-Ghana cohort. In the full cohort, mean HAZ of children who received pre- and postnatal SQ-LNS did not differ significantly from that of the control group. However, in prespecified subgroup analyses, maternal prepregnancy BMI and child sex modified the effect of the intervention. Among children of females who were not overweight/obese at baseline and among female children, child HAZ was higher in the SQ-LNS group compared with the control group at 9–11 y, whereas there was no difference between intervention groups among children whose mothers were not overweight and among male children. Additionally, we found no differences in blood pressure between the intervention groups.

In our previous follow-up at 4–6 y of age, we also reported a significant interaction between maternal prepregnancy BMI and the effect of SQ-LNS on child HAZ [12]. Our current results, therefore, align with the same pattern observed in the 4–6-y study. One possible explanation for this effect modification could be that children whose mothers were not overweight have greater potential to benefit from nutritional supplementation than children whose mothers were overweight because of greater nutritional deficits in utero in the former subgroup [2,12]. Among the children whose mothers were not overweight, children in the SQ-LNS group began to diverge in linear growth from the control group starting at birth, with differences most apparent at 18 mo and sustained through 9–11 y.

In contrast to our findings at 4–6 y, at 9–11 y we found a significant interaction between child sex and the effect of SQ-LNS on child HAZ. Child HAZ was higher in the SQ-LNS group than in the control group among female children, but there was no effect of SQ-LNS among male children. In an individual participant data meta-analysis of 14 randomized controlled trials in which SQ-LNS was provided to children 6–24 mo of age (n =15,946 to >37,000) greater effects of SQ-LNS on stunting, wasting, MUAC, and head size were found among girls than among boys aged at 18–24 mo [5]. The authors suggested that the difference could be because of a greater potential to respond to nutritional supplementation among girls than among boys, speculating that boys might be more susceptible to unfavorable conditions during their early years, which could also limit their response to nutritional interventions [5]. In a follow-up of one of those randomized trials in Bangladesh, a greater growth response among girls than boys was also evident at 40–52 mo of age [17]. It is unclear why this interaction between child sex and the effect of SQ-LNS on child HAZ was not detected in our cohort at 4–6 y of age, given that it was significant at 9–11 y of age. One possibility is that the females tended to reach puberty earlier than the males, and this influenced the SQ-LNS-related

TABLE 2

Anthropometric and blood pressure measurements of children in the International Lipid-Based Nutrient Supplements (iLiNS)-DYAD-Ghana trial at 9–11 y old

Variable	SQ-LNS (n = 331)	Control (n = 635)	P value	Difference in mean (95% CI)
	M ± SD	M ± SD		
Height-for-age z-score	−0.04 ± 0.96	−0.16 ± 0.99	0.060	0.12 (−0.01, 0.25)
BMI-for-age z-score	−0.43 ± 1.18	−0.50 ± 1.16	0.373	0.07 (−0.08, 0.23)
Weight-to-height ratio	0.43 ± 0.04	0.43 ± 0.04	0.859	0.00 (−0.01, 0.00)
Triceps skinfold (mm)	9.95 ± 5.66	9.66 ± 5.24	0.452	0.27 (−0.44, 0.98)
MUAC (cm)	19.39 ± 2.79	19.15 ± 2.52	0.181	0.23 (−0.11, 0.57)
Systolic blood pressure (mmHg)	89.11± 6.91	89.22 ± 7.17	0.762	−0.14 (−1.08, 0.79)
Diastolic blood pressure (mmHg)	59.80 ± 5.35	59.24 ± 5.49	0.124	0.57 (−0.16, 1.29)

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; MUAC, midupper arm circumference; SQ-LNS, small-quantity lipid-based nutrient supplement.

Values represent mean ± SD and the difference in mean (95% CI). Results are based on an ANCOVA model, adjusted only for child age at follow-up.

TABLE 3
Prevalence of stunting, overweight, obesity, and high blood pressure among children in the International Lipid-Based Nutrient Supplements (iLiNS)-DYAD Ghana trial at 9–11 y

Variable	SQ-LNS (n = 331)	Control (n = 635)	OR (95% CI)	P value
	n (%)	n (%)		
Stunting (HAZ < −2 SD)	6 (1.8)	14 (2.2)	0.82 (0.31, 2.15).	0.684
Overweight (BAZ > 1 SD)	36 (10.9)	67 (10.6)	1.03 (0.67, 1.58)	0.896
Central obesity (WtHR ≥ 0.5)	21 (6.4)	39 (6.2)	1.03 (0.59, 1.78).	0.919
Obese (BAZ > 2 SD)	13 (3.9)	21 (3.3)	1.20 (0.59, 2.43)	0.614
High systolic blood pressure	0 (0.0)	1 (0.2)	—	0.973
High diastolic blood pressure	2 (1.0)	6 (1.0)	0.64 (0.13, 3.19)	0.586

Abbreviations: BAZ, BMI-for-age z-score; CI, confidence interval; HAZ, height-for-age z-score; OR, odds ratio; SQ-LNS, small-quantity lipid-based nutrient supplement; WtHR, waist-to-height ratio.
Results are based on a logistic regression model, adjusted only for child age at follow-up. Reference = control group; control = iron-folic acid group + multiple micronutrients group. High systolic blood pressure (SBP) is defined as SBP ≥ 90th percentile and high diastolic blood pressure defined as diastolic blood pressure ≥ 90th percentile of the reference population, computed using equations provided by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.

height differential. This will be investigated in a further follow-up of this cohort occurring at 11–13 y of age.

Very few studies have investigated the long-term effects of exposure to a fortified nutritional supplement during both pre- and postnatal life on later growth. The 2 previous trials reporting such results, conducted in the 1970s in Guatemala [6] and Colombia [7], both demonstrated sustained long-term effects on growth, consistent with our findings. In Guatemala, 2 pairs of rural villages were provided 1 of the 2 types of supplement: *1*) a high-protein/high-energy drink called "atole" or *2*) a low-energy/no-protein drink called "fresco", with both supplements containing the same amount of micronutrients [6]. Supplements were given from pregnancy to an age of 3 y. A follow-up study conducted when the children were 11–20 y old showed that those from Atole villages were taller than those from Fresco villages [6], and this difference was evident in females but not males. The authors attributed this response to differences that existed at the end of the intervention when the children were 3 y old [6]. The greater response to a nutrition intervention among females is similar to our finding that females who received SQ-LNS had significantly higher LAZ at the end of the intervention, that is, at 18 mo, than females in the control groups (Figure 4), and this difference appears to have persisted to the age of 9–11 y. The intervention group difference in mean height among females in Guatemala at 11–20 y (+2.1 cm) was similar to the difference we observed in Ghana at 9–11 y (+1.8 cm). The Colombia study did not examine differences in intervention effects between males and females [7].

A 2015 World Bank systematic review [24] investigated the long-term effects of early childhood interventions, including nutritional interventions given to either the pregnant mother or infant, on physical outcomes such as (BMI, BAZ, head circumference, HAZ, midupper arm circumference, and weight-for-age z-score). The majority of these studies [9] provided micronutrients, whereas 2 studies provided supplementary feeding and lactation promotion. The authors reported that there was no significant positive effect of the 11 nutrition interventions on any of the physical outcomes measured. They concluded, however, that the effectiveness of nutrition interventions appears to be dependent on both timing and duration, as the only nutrition project that demonstrated lasting effects (the Guatemala trial) [6] was also the only 1 with a sustained intervention from conception to an age of 2 y. Of note, the Guatemala trial was excluded from the physical outcome analysis in that review because of study design limitations, but it was included in all other analyses and was the only nutrition intervention

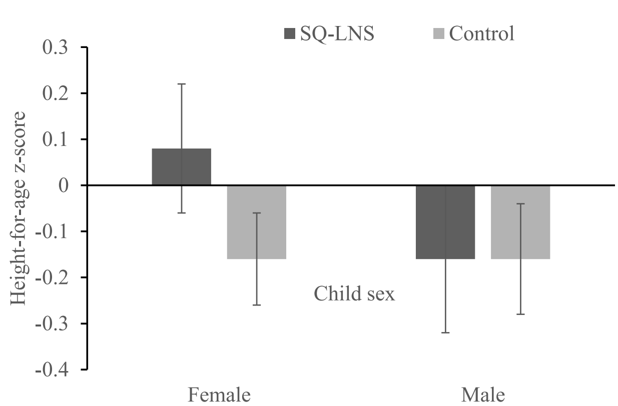

FIGURE 2. Height-for-age z-score by group at age 9–11 y (SQ-LNS compared with control; N = 966), stratified by intervention group and child sex. Values represent mean (95% CI). P-interaction = 0.075. Control = iron-folic acid group + multiple micronutrients group; CI, confidence interval; SQ-LNS, small-quantity lipid-based nutrient supplement.

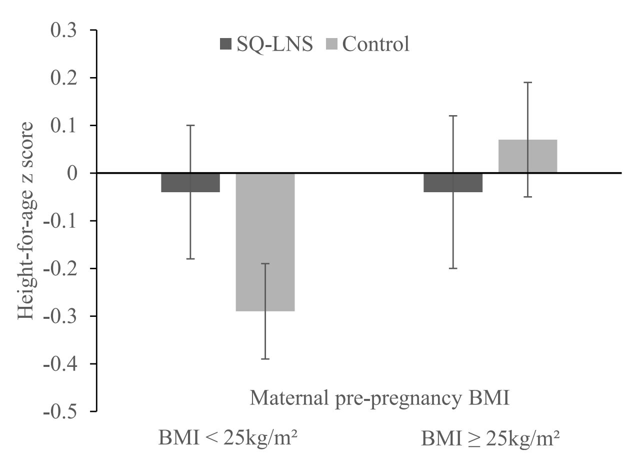

FIGURE 3. Height-for-age z-score by group at age 9–11 y (SQ-LNS compared with control, N = 966), stratified by intervention group and maternal prepregnancy BMI. Values represent mean (95% CI). P-interaction = 0.007. Control = iron-folic acid group + multiple micronutrients group; CI, confidence interval; SQ-LNS, small-quantity lipid-based nutrient supplement.

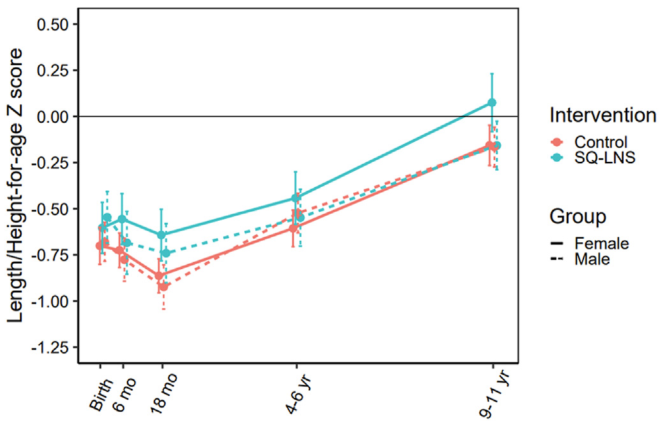

FIGURE 4. Child length/height-for-age *z*-score at birth, 6 mo, 18 mo, age 4–6 y and 9–11 y by intervention group and child sex. Control = iron-folic acid group + multiple micronutrients group; SQ-LNS, small-quantity lipid-based nutrient supplement.

trial that showed long-term effects on other outcomes such as cognitive development, language, and schooling.

Consistent with our findings at 4–6 y, we did not find an effect of SQ-LNS on blood pressure at 9–11 y of age. Similarly, the trial in Guatemala showed no impact of the intervention on SBP or DBP in later adult life (21–29 y) [25]. SQ-LNS improves birth weight and head circumference at birth [11], and both birth weight and head circumference at birth are inversely associated with blood pressure, particularly in adolescence, in previous studies [10]. Thus, it is unclear why we did not observe an effect on blood pressure. Further research is needed to confirm these results.

The strengths of our study include the randomized design of the intervention and the relatively large sample size. Sample retention was high as we assessed 79% of the children born during the main trial who were eligible to be re-enrolled in the follow-up study. Anthropometric assessments were measured by trained and standardized anthropometrists. Data collectors were blinded to group assignments. The study is limited in that those lost to follow-up differed in parity from those included in the analysis. However, the effects of the intervention on the outcomes did not differ by parity. The sample population for this follow-up study was recruited from a specific region in Ghana, which may limit generalizability of the results. However, it is worth noting that the areas included in the study are semiurban, exhibiting

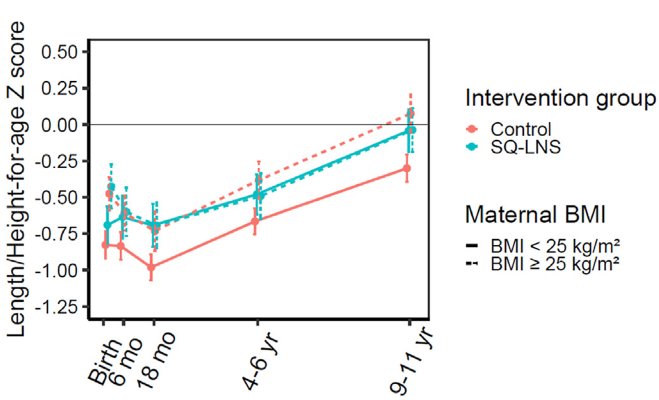

FIGURE 5. Child length/height-for-age *z*-score at birth, 18 mo, age 4–6 y and 9–11 y by intervention group and maternal prepregnancy BMI at baseline. Control = iron-folic acid group + multiple micronutrients group; SQ-LNS, small-quantity lipid-based nutrient supplement.

characteristics that encompass both rural and urban settings and are thus relevant to both urban and rural settings in Ghana.

In conclusion, our study findings demonstrated that provision of SQ-LNS during the 1000-d window, including pregnancy and the first 2 y after birth, promoted long-term linear growth status among female children and children whose mothers were not overweight/obese. Greater stature in females, at the time of childbearing, is likely to reduce small-for-gestational age births and associated adverse consequences. Further research is needed to investigate why females respond more favorably to SQ-LNS than males, in terms of growth.

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Author contributions

The authors' responsibilities were as follows – KGD, SAA, ELP, PDH, AEG, AM, BA, BMO: designed the research; SA-A, EA, HJB, MOM, MED: conducted the research; CDA, XT, HJB: analyzed data; HJB: drafted the manuscript; and all authors: reviewed and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

Deidentified individual participant data (including data dictionaries) used for this current analysis are publicly available at https://osf.io/bmv9d/.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.10.033.

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