Preventive small-quantity lipid-based nutrient supplements reduce severe wasting and severe stunting among young children: an individual participant data meta-analysis of randomized controlled trials

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ABSTRACT

Background: Meta-analyses show that small-quantity lipid-based nutrient supplements (SQ-LNSs) reduce child wasting and stunting. There is little information regarding effects on severe wasting or stunting.

Objectives: We aimed to identify the effect of SQ-LNSs on prevalence of severe wasting (weight-for-length z score < -3) and severe stunting (length-for-age z score < -3).

Methods: We conducted a 2-stage meta-analysis of individual participant data from 14 randomized controlled trials of SQ-LNSs provided to children 6–24 mo of age. We generated study-specific and subgroup estimates of SQ-LNS compared with control and pooled the estimates using fixed-effects models. We used random-effects meta-regression to examine study-level effect modifiers. In sensitivity analyses, we examined whether results differed depending on study arm inclusion criteria and types of comparisons.

Results: SQ-LNS provision led to a relative reduction of 31% in severe wasting [prevalence ratio (PR): 0.69; 95% CI: 0.55, 0.86; $n = 34{,}373$] and 17% in severe stunting (PR: 0.83; 95% CI: 0.78, 0.90; $n = 36{,}795$) at endline. Results were similar in most of the sensitivity analyses but somewhat attenuated when comparisons using passive control arms were excluded (PR: 0.74; 95% CI: 0.57, 0.96; $n = 26{,}327$ for severe wasting and PR: 0.88; 95% CI: 0.81, 0.95; $n = 28{,}742$ for severe stunting). Study-level characteristics generally

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did not significantly modify the effects of SQ-LNSs, but results suggested greater effects of SQ-LNSs in sites with greater burdens of wasting or stunting, or with poorer water quality or sanitation.
Conclusions: Including SQ-LNSs in preventive interventions to promote healthy child growth and development is likely to reduce rates of severe wasting and stunting. This meta-analysis was registered at www.crd.york.ac.uk/PROSPERO as CRD42019146592. *Am J Clin Nutr* 2022;0:1–20.

Keywords: stunting, wasting, child undernutrition, complementary feeding, severe malnutrition, home fortification

Introduction

The global prevalence of stunting [length-for-age *z* score (LAZ) < −2] among children <5 y of age was estimated to be 22% in 2021 (1), which represents 149 million children. Severe stunting (LAZ < −3) likely affects 40%–50% of that total (2). For wasting [weight-for-length *z* score (WLZ) < −2], the estimated cross-sectional prevalence was 6.7% in 2021 (45.4 million), but that is an underestimate of the total annual burden of wasting because children often cycle in and out of being wasted owing to seasonal and other factors. The total annual burden of wasting may be 3–6 times greater than an estimate based on cross-sectional prevalence, depending on the country and context (3, 4). In a pooled analysis of 21 longitudinal cohorts <2 y of age [the most vulnerable period for wasting (5, 6)], 6.5% of children were wasted at a specific visit but 29.2% experienced ≥1 episode of wasting by 24 mo of age (7). The global prevalence of severe wasting (WLZ < −3) was 2% in 2020 (13.6 million in 2021), but again, this is an underestimate of the total burden which may be as much as 7–10 times higher (4). Risk of mortality is 5.5 times higher among children with severe stunting and 11.6 times higher among children with severe wasting than among children with *z* scores > −1 for LAZ or WLZ, respectively (8). Moreover, severe malnutrition in early life is associated with serious adverse consequences for subsequent health and development (9, 10).

There has been inadequate progress in reducing rates of stunting and wasting, both moderate and severe (1), and in recent years rates of child malnutrition have been rising in areas affected by armed conflict, climate change, and the economic disruptions brought about by the COVID-19 pandemic (6, 11). Thus, there is a pressing need to identify strategies to reduce severe undernutrition among young children. Recent initiatives such as the Global Action Plan on Child Wasting (12) and the development of guidelines for the prevention and treatment of wasting in infants and children (13) reflect the growing awareness of the urgent need for evidence-based actions.

Although the etiology of severe stunting and wasting is complex and multifactorial (14–17), inadequate dietary intake plays a pivotal role. During the complementary feeding period from 6 to 24 mo of age, diets often lack adequate amounts of nutrients that are critical for growth (18), in part because of the high cost of nutrient-rich foods for low-income families. Fortified products, such as fortified blended foods and products used for home fortification including multiple micronutrient powders (MNPs) and small-quantity lipid-based nutrient supplements (SQ-LNSs) (18), can help fill these nutrient gaps. SQ-LNSs provide multiple micronutrients embedded in a small amount of food (∼110–120 kcal/d) that also provides energy, protein, and essential fatty acids (19). SQ-LNSs were designed for the prevention of undernutrition, whereas larger quantities of lipid-based nutrient supplement (LNS) are generally aimed at treatment of moderate and severe wasting. Whereas there have been numerous intervention trials to evaluate treatments of severe wasting, there is very little evidence regarding interventions that are effective for prevention of this life-threatening condition (20, 21).

In a recent individual participant data (IPD) analysis of 14 randomized controlled trials (RCTs), we found a 12%–14% lower prevalence of stunting, wasting, and underweight, as well as reductions in developmental delay, anemia, and micronutrient deficiencies, among children who received SQ-LNSs during the complementary feeding period (22–25). We did not include severe wasting or severe stunting in that set of analyses because we already had a large list of outcomes to examine, and also because a key objective of that work was examining individual-level effect modification, which is problematic for rare outcomes such as severe wasting. However, a previous Cochrane review and meta-analysis of LNSs (including both SQ-LNSs and medium-quantity LNSs) (26) reported on both of these outcomes. The authors reported a 15% reduction in severe stunting (RR: 0.85; 95% CI: 0.74, 0.98) based on 5 studies (6151 participants); they did not find an effect on severe wasting but only 3 studies (2329 participants) included this outcome. Given the strengthened global commitment to combating severe malnutrition, there has been interest in updating the findings for these 2 outcomes using the much larger IPD data set. Therefore, the main objectives for this analysis were to generate pooled estimates of the main effects of SQ-LNSs on severe wasting and severe stunting and identify study-level modifiers of the effect of SQ-LNSs on these outcomes.

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Abbreviations used: GRADE, Grading of Recommendations, Assessment, Development and Evaluations; iLiNS, International Lipid-Based Nutrient Supplements; IPD, individual participant data; IYCF, infant and young child feeding; LAZ, length-for-age *z* score; LNS, lipid-based nutrient supplement; MAM, moderate acute malnutrition; MNP, multiple micronutrient powder; MUAC, midupper arm circumference; MUACZ, midupper arm circumference *z* score; NNT, number needed to treat; *P*-diff, *P* value for the difference in effects of small-quantity lipid-based nutrient supplement between the 2 levels of the effect modifier; PR, prevalence ratio; PROMIS, Innovative Approaches for the Prevention of Childhood Malnutrition; RCT, randomized controlled trial; SAM, severe acute malnutrition; SQ-LNS, small-quantity lipid-based nutrient supplement; WASH, water, sanitation, and hygiene; WLZ, weight-for-length *z* score.
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Methods

The protocol for the IPD meta-analysis was registered as PROSPERO CRD42019146592 (https://www.crd.york.ac.uk/prospero) on 19 November, 2019 (27). The detailed protocol was posted to Open Science Framework (https://osf.io/ymsfu) before analysis and updated after consultations with co-investigators before finalizing the analysis plan (28), and the results are reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-IPD guidelines (29). The analyses were approved by the institutional review board of the University of California, Davis (1463609-1). All individual trial protocols were approved by the relevant institutional ethics committees. The methods were presented in detail previously (23), so are summarized here.

Inclusion and exclusion criteria for this IPD meta-analysis

We included RCTs of SQ-LNSs provided to children age 6–24 mo that met the following study-level inclusion criteria: *1*) the trial was conducted in a low- or middle-income country (30); *2*) SQ-LNS ($< \sim$125 kcal/d) was provided to the intervention group for $\geq$3 mo between 6 and 24 mo of age; *3*) $\geq$1 trial group did not receive SQ-LNS or another type of child supplementation; *4*) the trial reported $\geq$1 outcome of interest; and *5*) the trial used an individual- or cluster-randomized design in which the same participants were measured at baseline (before child supplementation) and again after completion of the intervention (longitudinal follow-up), or different participants were measured at baseline and postintervention (repeated cross-sectional data collection). Trials were excluded if *1*) only children with severe or moderate malnutrition were eligible to participate (i.e., SQ-LNS was used for treatment, not prevention, of malnutrition); *2*) the trial was conducted in a hospitalized population or among children with a pre-existing disease; or *3*) SQ-LNS provision was combined with additional supplemental food or nutrients for the child within a single arm (e.g., SQ-LNS + food rations compared with control), and there was no appropriate comparison group (e.g., food rations alone) that would allow separation of the SQ-LNS effect from effects of the other food or nutrients provided.

Trials in which there were multiple relevant SQ-LNS interventions (e.g., varying dosages or formulations of SQ-LNSs in different arms), which combined provision of child SQ-LNSs with provision of maternal LNSs, or which included other nonnutritional interventions [i.e., water, sanitation, and hygiene (WASH)] were eligible for inclusion. In such trials, all arms that provided child SQ-LNSs were combined into 1 group, and all non-LNS arms (i.e., no LNS for mother or child) were combined into a single comparator group for each trial (herein labeled "control"), excluding intervention arms that received non-LNS child supplementation (e.g., MNP, fortified-blended food). We also conducted a sensitivity analysis restricting the comparison to specified contrasts of intervention arms within multiple intervention trials (described in what follows).

At the individual participant level, we included children if their age at baseline allowed them to receive $\geq$3 mo of intervention (supplementation or control group components) between 6 and 24 mo of age. We considered 3 mo to be the minimum duration for an impact on linear growth.

Search methods and identification of studies

We identified studies cited in a previous systematic review and meta-analysis of child LNSs (26) and through keyword and controlled vocabulary searches of 25 databases, as described in Dewey et al. (23).

Data collection

We invited all principal investigators of eligible trials to participate in the IPD meta-analysis. We provided a data dictionary listing definitions of variables requested for pooled analysis. Those variables were provided to the IPD analyst (CDA) in deidentified IPD sets.

IPD integrity

We conducted a complete-case intention-to-treat analysis (31). We calculated LAZ, WLZ, and midupper arm circumference (MUAC) *z* score (MUACZ) using the 2006 WHO child growth standards and checked the values for acceptable SDs and to be within published WHO acceptable ranges (32). Biologically implausible values were flagged, as recommended by the WHO, in the following way: LAZ < -6 or >6; WLZ < -5 or >5; MUACZ < -5 or >5. These were inspected for errors and either winsorized (33) if anthropometric values were biologically plausible or removed from analysis if values were clearly impossible. Such cleaning was necessary for $<0.5\%$ of participants, with a consistently low rate of implausibility across outcomes and studies. We also checked summary statistics, such as means and SDs, in our data set against published values for each trial.

Assessment of risk of bias in each study and quality of evidence across studies

Two independent reviewers (KRW and CDA) assessed risk of bias in each trial using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (34). The same reviewers also assessed the quality of evidence for anthropometric outcomes across all trials based on the 5 Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria: risk of bias, inconsistency of effect, imprecision, indirectness, and publication bias (35).

Specification of outcomes and effect measures

The statistical analysis plan prespecified severe acute malnutrition (SAM) as an outcome (28) but we did not report it in our previous publication (23) because it is a rare event and thus poses difficulties for effect modification analysis. We updated the analysis plan to include the 4 outcomes reported herein, and added a sensitivity analysis to check the robustness of main effect estimates that excluded trials with 0 events in $\geq$1 comparison group. The 4 outcomes were severe wasting (WLZ < -3 SD), severe stunting (LAZ < -3 SD), SAM (WLZ < -3 SD or MUAC $<$ 115 mm), and very low MUAC (MUACZ < -3 SD or MUAC $<$ 115 mm). The main focus of this analysis was on severe wasting and severe stunting because the sample sizes available for SAM and very low MUAC were considerably smaller. In

addition, we were unable to include bilateral pitting edema as a criterion for SAM because this information was not collected in 5 of the trials, and in the other 9 trials the definition of edema varied (of those trials, 4 reported 0 cases, 4 reported <20 cases, and 1 reported 38 cases of edema). For all 4 outcomes, the principal measure of effect was the prevalence ratio (PR) at endline, which was ≥6 mo after baseline/enrollment. Prevalence at endline was chosen because most of the trials did not conduct frequent interim surveillance, which is necessary to detect incident cases. For descriptive, exploratory purposes, we also examined the endline prevalence of concurrent severe wasting and severe stunting, given that children with both conditions have the highest mortality risk (7).

The treatment of interest was provision of children with SQ-LNS (< ∼125 kcal/d, with or without co-interventions), compared with no intervention or an intervention without any type of LNS or other child supplement. Other types of interventions were delivered with or without LNS, such as WASH interventions and child morbidity monitoring and treatment. In several trials, child LNS was delivered to children whose mothers received maternal LNS during pregnancy and lactation. As described previously (23), we decided that if the main effects did not differ between the child-LNS-only analysis and the all-trials analysis (including maternal plus child LNS arms) by >0.05 for PRs, the results of the all-trials analyses would be presented as the principal findings, in order to maximize sample size. Three additional prespecified sensitivity analyses were also conducted, as described in what follows.

Synthesis methods and exploration of variation in effects

We used R version 4.1.1 (R Core Team, Vienna, Austria) for all statistical analyses. We examined full sample main effects of the intervention for all outcomes and evaluated whether certain characteristics modified the effects of SQ-LNSs on severe wasting or severe stunting. The effect modification analyses focused on study-level characteristics. To be consistent with our previous publications we also examined potential individual-level effect modifiers, but those analyses were considered exploratory because some subgroups have 0 "events" for rare outcomes such as severe wasting, which reduces the number of comparisons available for such outcomes. We used a 2-stage approach for all analyses, which is preferred when incorporating cluster-randomized trials (36). In the first stage, we generated intervention effect estimates within each individual study according to its study design. For longitudinal study designs we controlled for initial child anthropometric status (at baseline or at the start of supplementation if enrollment occurred during pregnancy) when estimating the intervention effect on each outcome, to gain efficiency. To deal with outcome dependence in cluster-randomized trials, we used robust SEs with randomization clusters as the independent unit. In the second stage, we pooled the first stage estimates using inverse variance–weighted fixed effects. We also conducted sensitivity analyses in which we pooled estimates using inverse variance–weighted random effects (37, 38).

To evaluate main effects, we first estimated the intervention effect for each study. We then pooled the first stage estimates to generate a pooled point estimate, 95% CI, and corresponding *P* value. For effect modification analyses, we examined the dichotomous variables shown in **Supplemental Table 1**, as described previously (23). For study-level characteristics, we used random-effects meta-regression to test the association between each effect modifier and the intervention. For individual-level characteristics, we generated pooled intervention effect estimates within each category to determine how the intervention effect in 1 subgroup differed from the intervention effect in the specified reference subgroup.

Heterogeneity of effect estimates was assessed using I^2 and τ^2 statistics, within strata when relevant (39). We used a *P* value of <0.05 for main effects and a *P* value of <0.10 for effect modification—for the difference in effects of SQ-LNS between the 2 levels of the effect modifier (*P*-diff from the random-effects meta-regressions with study-level characteristics or *P*-interaction for individual-level characteristics). Given that the growth outcomes are highly correlated and the effect modification analyses are inherently exploratory, we did not adjust for multiple hypothesis testing because doing so may be unnecessary and counterproductive (40).

For descriptive purposes, we calculated the number needed to avert a single case of severe wasting ["number needed to treat" (NNT)] following the standard approach (41). The equation requires an assumed population prevalence of severe wasting among the untreated, and then the prevalence of severe wasting among the treated is estimated as the prevalence among the untreated multiplied by the PR reduction for severe wasting. These 2 prevalences are then subtracted from one another and inverted. We repeated this calculation for various population prevalences that reflected the range of prevalence of severe wasting in the control groups in the actual trials, to understand how the NNT would vary by context.

Additional sensitivity analyses

As described previously (23), we conducted several prespecified sensitivity analyses:

1) Separate comparisons within multicomponent intervention trials, such that the SQ-LNS against no SQ-LNS comparisons were conducted separately between pairs of arms with the same nonnutrition components (e.g., SQ-LNS + WASH compared with WASH; SQ-LNS compared with control). Infant and young child feeding (IYCF) behavior change communication was not considered an additional component.
2) Exclusion of passive control arms, i.e., when control group participants received no intervention and had no contact with project staff between baseline and endline.
3) Exclusion of intervention arms with SQ-LNS formulations that did not include both milk and peanut.

In addition, we conducted a fourth sensitivity analysis, the "rare events" analysis, in which we included comparisons with 0 event rates within an intervention arm for main effect analysis, to maximize the number of trials included. The primary analytic approach did not produce effect estimates for trials with 0 events in ≥1 arm (3 trials for severe wasting, 1 trial for SAM, 2 trials for very low MUAC, 6 trials for concurrent severe wasting and severe stunting), so an estimate was generated for those trials by adapting the approach described in the *Cochrane Handbook for*

Systematic Reviews of Interventions (34) where an event count of 0.5 is substituted for the 0 event count value observed in the trial.

Results

Literature search and trial characteristics

We identified 15 trials that met our inclusion criteria, 14 of which provided IPD and were included in this analysis (**Table 1**, **Supplemental Figure 1**, **Supplemental Table 2**) (42–56). Investigators for 1 trial were unable to participate (57); binary outcomes were not reported in that trial, so we were unable to insert an estimate from that trial into our analysis. One trial was designed a priori to present results separately for HIV-exposed and HIV-unexposed children, so we present it as 2 separate comparisons (55, 56). Similarly, the 2 PROMIS (Innovative Approaches for the Prevention of Childhood Malnutrition) trials in Burkina Faso and Mali each included an independent longitudinal cohort and repeated (at baseline and endline) cross-sectional samples, so the longitudinal and cross-sectional results are presented as separate comparisons (46, 54). Thus, the 14 trials yielded 17 separate comparisons.

The 14 trials in these analyses were conducted in Sub-Saharan Africa (10 trials in 7 countries), Bangladesh (3 trials), and Haiti (1 trial), and included a total of 37,066 infants and young children with anthropometric data. The majority of trials began child supplementation with SQ-LNSs at 6 mo of age and the intended duration ranged from 6 to 18 mo of supplementation. The SQ-LNSs for children generally provided ∼120 kcal/d and ∼1 RDA of 19–22 micronutrients (23); in 1 trial the ration was ∼120 kcal/d between 6 and 12 mo of age and ∼250 kcal/d between 12 and 24 mo of age (42). Six trials were conducted within existing community-based or clinic-based programs (43, 46, 49, 51, 54–56); in the other trials, all activities were conducted by research teams. All trials provided social and behavior change communication (SBCC) on IYCF to reinforce the normal IYCF messages already promoted in that setting or to go beyond the usual IYCF messaging (23), in addition to information on how to use SQ-LNS for the target child. Three trials included arms with WASH interventions (44, 50, 55, 56). Most trials provided comparisons that included an active control arm (i.e., similar contact frequency as for intervention arms) but 2 were limited to comparisons with a passive control arm (45, 47).

There was variability across trials with regard to screening, referral, and treatment of SAM and moderate acute malnutrition (MAM) among participants (Table 1). In some trials, acute malnutrition at baseline was an exclusion criterion (45, 46, 49, 53, 54), although the definition used for acute malnutrition varied, whereas other trials did not exclude children with SAM or MAM (42, 46, 47, 51, 54–56), or enrollment occurred during pregnancy and thus no such exclusion criteria were applicable (43, 44, 48, 50–52). Once enrolled, most trials included anthropometric assessments of participants in both intervention and control arms on a regular basis [monthly (46, 49, 50, 54); every 3 mo (42); or every 6 mo (43, 48, 52, 53, 55, 56)]. In 2 trials, measurements were conducted only during yearly surveys, in both intervention and control groups (44, 51), and in 3 trials measurements occurred monthly (50) or every 3 mo (45, 47) in the intervention group (and active control group in WASH-Benefits Kenya) but not in the (passive) control group. For children identified with SAM or MAM, 1 trial provided treatment of SAM (but not MAM) directly to participants (42), and all other trials referred children with SAM or MAM to local health facilities for treatment, although the criteria for referral varied. In some sites, treatment of MAM via local programs was available (although coverage may have been low) (46, 52–54), but in most sites MAM treatment was unavailable or unlikely. SAM treatment, however, was reportedly offered in most sites, although referral follow-through and/or availability of ready-to-use therapeutic food may have been limited.

Table 1 shows the prevalences of severe wasting and severe stunting in the control groups at endline. Prevalence of severe wasting ranged from 0% in Haiti and Malawi [iLiNS (International Lipid-Based Nutrient Supplements)-DOSE trial] to 3% in Burkina Faso (iLiNS-ZINC trial). Prevalence of severe stunting ranged from 1% in Ghana to 23% in Madagascar. **Supplemental Table 3** presents additional descriptive information on study-level characteristics. At the study level, 6 sites had a high burden of wasting (≥10% in the control group at endline: Mali, both sites in Burkina Faso, and all 3 sites in Bangladesh) and 8 of the 14 study sites had a high burden of stunting (≥35% in the control group at 18 mo). Country-level malaria prevalence ranged from <1% in Bangladesh and Haiti to 59% in Burkina Faso. Study-specific prevalence of improved water quality ranged from 27% to 100%, and prevalence of improved sanitation ranged from 0% to 97%. Frequency of contact during the study was weekly in 7 trials and monthly in 7 trials. Average estimated reported compliance with SQ-LNS consumption was categorized as high (≥80%) in 7 trials and ranged between 37% and 77% in the other trials. Individual-level characteristics were reported previously (23).

As reported previously (23), we considered the trials to have a low risk of bias for most of the criteria (**Supplemental Figure 2**). For blinding of participants, all trials were judged to have high risk of bias, because blinding was not possible given the nature of the intervention.

Main effects of SQ-LNSs

SQ-LNSs reduced the prevalence of adverse growth outcomes at endline by 31% for severe wasting, 17% for severe stunting, 24% for SAM, and 27% for very low MUAC (**Table 2**, **Figures 1** and **2**, **Supplemental Figures 3** and **4**). Results from the child-LNS-only and all-trials analyses were similar: for all of these outcomes, the PRs for intervention compared with control groups were identical or almost identical when the maternal LNS trials/arms were included (**Figure 3**, **Supplemental Figures 5** and **6**). Therefore, results from the all-trials analyses, inclusive of maternal + child LNS trials/arms, are presented as the principal findings. For all outcomes, fixed-effects and random-effects models generated identical or very similar estimates. We rated the quality of the evidence for all outcomes as high based on GRADE criteria: ≥10 RCTs were available for all outcomes, risk of bias was low, heterogeneity was generally low to moderate (Table 2), precision was rated as high because all but 2 trials had sample sizes > 600, all trials were directly aimed at evaluating SQ-LNSs, and funnel plots revealed no indication of publication bias (35).

Results were similar in most of the sensitivity analyses (Figure 3, Supplemental Figures 5 and 6), including the "rare events" sensitivity analysis (**Supplemental Figure 7** shows a forest plot for severe wasting). However, there was some

TABLE 1 Characteristics of trials included in the individual participant data analysis[1]

Country, years of study, study name, *n*, trial design, authors	Child SQ-LNS supplementation			Prevalence, comparison group at endline		SAM and MAM screening, referral, and treatment			
	Age at start	Duration	Comparison group	Severe wasting, %	Severe stunting, %	Baseline assessment and enrollment criteria	Frequency of anthropometric measurements during intervention	Referral and treatment during intervention	
								Intervention group	Comparison group
Bangladesh, 2012–2014, JiVitA-4, $n = 4218$, cluster RCT, longitudinal follow-up, Christian et al. (42)	6 mo	12 mo[2]	Active control (IYCF counseling; weekly contact)	2.0	12.4	Enrolled children with MAM and SAM	3 mo	No referral. Study implemented Bangladesh guidelines for CMAM for SAM treatment (RUTF provided to children with SAM). No MAM treatment	Same as in intervention group
Bangladesh, 2011–2015, RDNS, $n = 2478$, cluster RCT, longitudinal follow-up, Dewey et al. (43)	6 mo	18 mo	Active control (weekly contact)	1.7	9.1	Not applicable (enrolled during pregnancy)	6 mo	Referred to specific clinics/hospitals if MAM or SAM detected. Treated in local health system. Investigators reported no RUSF/RUTF or F75/100 available. SQ-LNS was not discontinued during treatment unless advised by treatment team	Same as in intervention group
Bangladesh, 2012–2015, WASH-Benefits, $n = 4633$, cluster RCT, cross-sectional surveys, Luby et al. (44)	6 mo	18 mo	Passive control (no intervention) or active control (water, sanitation, and/or hygiene interventions; weekly contact)	1.1	11.8	Not applicable (enrolled during pregnancy)	Year 1 and year 2 surveys in all children	Referred to local health facilities if WLZ < -3 SD and/or bipedal edema. Treated in local health system; investigators reported SAM treatment available in local health facilities, MAM treatment not available. SQ-LNS was not discontinued during treatment	Same as in intervention group

(*Continued*)

TABLE 1 (*Continued*)

Country, years of study, study name, *n*, trial design, authors	Child SQ-LNS supplementation			Prevalence, comparison group at endline		SAM and MAM screening, referral, and treatment			
	Age at start	Duration	Comparison group	Severe wasting, %	Severe stunting, %	Baseline assessment and enrollment criteria	Frequency of anthropometric measurements during intervention	Referral and treatment during intervention	
								Intervention group	Comparison group
Burkina Faso, 2010–2012, iLiNS-ZINC, $n = 2626$, cluster RCT, longitudinal follow-up, Hess et al. (45)	9 mo	9 mo	Passive control (no intervention)[3]	3.0	14.3	Excluded if weight-for-length < 70% of the median of the NCHS/WHO growth reference and/or bipedal edema (national policy at the time)	3 mo in intervention group; none in passive control group	Referred to local health facilities if weight-for-length < 70% of median. Treated in local health system; investigators reported no active SAM treatment programs, limited availability of RUTF. SQ-LNS was not discontinued	No referral in passive control group
Burkina Faso, 2015–2017, PROMIS, $n = 2651$, cluster RCT, longitudinal follow-up and cross-sectional surveys,[4] Becquey et al. (46)	6 mo	12 mo	Active control (standard of care; monthly contact)	1.8 cross-sectional; 0.8 longitudinal	4.8 cross-sectional; 4.7 longitudinal	Cross-sectional surveys: not applicable; longitudinal survey (enrolled at 0–1.4 mo): excluded children with AM	Cross-sectional and longitudinal cohorts: monthly screening if attended well-baby clinic at health center; longitudinal cohort: monthly screening at household (in addition, governmental policy included quarterly door-to-door screening campaigns and passive screening at every contact with health care provider)	MAM and SAM cases referred to local health clinics for nutritional management in accordance with national protocols. MAM and SAM treated with RUSF and RUTF, respectively, in local health system following national protocols (inpatient hospitalization or CMAM program for SAM with no complications and MAM); treatment coverage < 30%; SQ-LNS discontinued during treatment	Same as in intervention group

(*Continued*)

TABLE 1 (*Continued*)

Country, years of study, study name, *n*, trial design, authors	Child SQ-LNS supplementation			Prevalence, comparison group at endline		SAM and MAM screening, referral, and treatment			
	Age at start	Duration	Comparison group	Severe wasting, %	Severe stunting, %	Baseline assessment and enrollment criteria	Frequency of anthropometric measurements during intervention	Referral and treatment during intervention	
								Intervention group	Comparison group
Ghana, 2004–2005, *n* = 194, RCT, longitudinal follow-up, Adu-Afarwuah et al. (47)	6 mo	6 mo	Passive control (no intervention)	1.0	1.0	Enrolled children with MAM and SAM	3 mo in intervention group; none in passive control group (in addition, monthly growth monitoring and nutrition counseling program of the Ghana Health Service was active and had national coverage)	MAM and SAM cases referred to local health facilities for treatment in accordance with national protocols. Treated in local health system. RUSF and RUTF not available in the local health facilities. SQ-LNS was not discontinued	No referral in passive control group
Ghana, 2009–2014, iLiNS-DYAD-G, *n* = 1040, RCT, longitudinal follow-up, Adu-Afarwuah et al. (48)	6 mo	12 mo	Active control (weekly contact)	1.0	1.0	Not applicable (enrolled during pregnancy)	6 mo (in addition, monthly growth monitoring and nutrition counseling program of the Ghana Health Service was active and had national coverage)	SAM cases referred to local health facilities. SAM treated according to national guidelines (Management of Severe Acute Malnutrition); RUTF not available in the local health facilities. MAM cases referred only for intercurrent illness; apparent or underlying illnesses treated for children with MAM in local health facilities; study nurses provided additional nutrition counseling; SQ-LNS was not discontinued	Same as in intervention group

(*Continued*)

TABLE 1 (*Continued*)

Country, years of study, study name, *n*, trial design, authors	Child SQ-LNS supplementation			Prevalence, comparison group at endline		SAM and MAM screening, referral, and treatment			
	Age at start	Duration	Comparison group	Severe wasting, %	Severe stunting, %	Baseline assessment and enrollment criteria	Frequency of anthropometric measurements during intervention	Referral and treatment during intervention	
								Intervention group	Comparison group
Haiti, 2011–2012, $n = 300$, RCT, longitudinal follow-up, Iannotti et al. (49)	6–11 mo	6 mo[5]	Active control (standard of care; monthly contact)	0.0	4.0	Excluded children with SAM (WLZ < -3 SD)	1 mo	Referred to university hospital for treatment of SAM. SAM treated at university hospital with RUTF. SQ-LNS discontinued during therapeutic feeding program for SAM. MAM cases referred to local health clinic program. No MAM treatment available, children continued SQ-LNS supplementation	Same as in intervention group
Kenya, 2012–2016, WASH-Benefits, $n = 6649$, cluster RCT, cross-sectional surveys, Null et al. (50)	6 mo	18 mo	Passive control (no intervention) or active control (water, sanitation, and/or hygiene intervention, or MUAC measurements only; monthly contact)	0.3	9.2	Not applicable (enrolled during pregnancy)	Year 1 and year 2 surveys in all children + monthly MUAC monitoring in intervention and active control groups (none in passive control group)	Referred to local health facilities if WLZ < -3 SD and/or bipedal edema at annual survey and/or if MUAC < 11.5 cm at monthly monitoring. Treated in local health system; investigators reported SAM treatment available in local health facilities, unknown if MAM treatment was available. SQ-LNS was discontinued during SAM treatment	Referred to local health facilities if WLZ < -3 SD and/or bipedal oedema at annual survey only. Treatment same as in intervention group

(*Continued*)

TABLE 1 (*Continued*)

Country, years of study, study name, *n*, trial design, authors	Child SQ-LNS supplementation			Prevalence, comparison group at endline		SAM and MAM screening, referral, and treatment			
	Age at start	Duration	Comparison group	Severe wasting, %	Severe stunting, %	Baseline assessment and enrollment criteria	Frequency of anthropometric measurements during intervention	Referral and treatment during intervention	
								Intervention group	Comparison group
Madagascar, 2014–2016, MAHAY, $n = 3390$, cluster RCT, longitudinal follow-up, Galasso et al. (51)			Active control (standard of care or IYCF counseling; monthly contact)	1.4	23.4	Not applicable (enrolled during pregnancy)	Year 1 and year 2 assessment surveys + community-based monthly growth monitoring in all groups (government program)	MAM cases (11.5 cm < MUAC < 12.5 cm and WLZ ≥ −3 SD and absence of bipedal edema) and SAM cases (MUAC < 11.5 cm and/or WLZ < −3 SD and/or bipedal edema) identified in assessment surveys or during monthly growth monitoring referred to health facilities. SAM treated according to national protocols at health facilities with intensive nutritional rehabilitation centers. RUTF for SAM treatment was available at the nutritional centers. SQ-LNS was discontinued during SAM treatment	Same as in intervention group
Malawi, 2011–2014, iLiNS-DYAD-M, $n = 664$, RCT, longitudinal follow-up, Ashorn et al. (52)	6 mo	12 mo	Active control (weekly contact)	0.7	10.6	Not applicable (enrolled during pregnancy)	6 mo	SAM and MAM cases referred to local health district for nutritional management. CMAM program provided inpatient nutrition rehabilitation (NRU), OTP, and SFP; SQ-LNS discontinued during therapeutic feeding program for SAM, not discontinued during SFP for MAM; district coverage of OTP and SFP >80%	Same as in intervention group

(*Continued*)

TABLE 1 (*Continued*)

Country, years of study, study name, *n*, trial design, authors	Child SQ-LNS supplementation			Prevalence, comparison group at endline		SAM and MAM screening, referral, and treatment			
	Age at start	Duration	Comparison group	Severe wasting, %	Severe stunting, %	Baseline assessment and enrollment criteria	Frequency of anthropometric measurements during intervention	Referral and treatment during intervention	
								Intervention group	Comparison group
Malawi, 2009–2012, iLiNS-DOSE, $n = 943$, RCT, longitudinal follow-up, Maleta et al.[6] (53)	6 mo	12 mo	Active control (weekly contact)	0.0	15.8	Excluded children with MAM and SAM (WLZ < -2 SD and/or edema)	6 mo	SAM and MAM cases referred to local health district for nutritional management. CMAM program provided inpatient nutrition rehabilitation (NRU), OTP, and SFP; SQ-LNS discontinued during therapeutic feeding program for SAM, not discontinued during SFP for MAM; district coverage of OTP and SFP $>80\%$	Same as in intervention group
Mali, 2015–2017, PROMIS, $n = 2937$, cluster RCT, longitudinal follow-up and cross-sectional surveys,[4] Huybregts et al. (54)	6 mo	18 mo	Active control (standard of care + IYCF counseling; monthly contact)	2.2 cross-sectional; 0.0 longitudinal	10.0 cross-sectional; 9.7 longitudinal	Cross-sectional surveys: not applicable; longitudinal survey (enrolled at 6–6.9 mo): excluded children with AM	Cross-sectional and longitudinal cohorts: monthly screening if attended community health volunteer village gathering; longitudinal cohort: monthly screening at household	MAM and SAM cases referred to local health clinics for nutritional management in accordance with national policy. CMAM program provided inpatient nutrition rehabilitation (NRU) or OTP, with RUSF or RUTF for MAM and SAM, respectively; treatment coverage $< 15\%$; SQ-LNS discontinued during MAM or SAM treatment	Same as in intervention group

(*Continued*)

TABLE 1 (*Continued*)

Country, years of study, study name, *n*, trial design, authors	Child SQ-LNS supplementation			Prevalence, comparison group at endline		SAM and MAM screening, referral, and treatment			
	Age at start	Duration	Comparison group	Severe wasting, %	Severe stunting, %	Baseline assessment and enrollment criteria	Frequency of anthropometric measurements during intervention	Referral and treatment during intervention	
								Intervention group	Comparison group
Zimbabwe, 2013–2017, SHINE,[7] $n = 4343$, cluster RCT, longitudinal follow-up, Humphrey et al. (55), Prendergast et al. (56)	6 mo	12 mo	Active control (standard of care; monthly contact)	0.4	9.0	Enrolled children with MAM and SAM	6 mo	SAM and MAM cases referred to local health clinics for nutritional management. Treated in local health system; investigators reported SAM treatment available in local health facilities, likely no MAM treatment. SQ-LNS was not discontinued	Same as in intervention group

[1]AM, acute malnutrition; CMAM, community management of acute malnutrition; IYCF, infant and young child feeding; MAM, moderate acute malnutrition; MUAC, midupper arm circumference; NCHS, National Center for Health Statistics; NRU, nutrition rehabilitation unit; OTP, outpatient therapeutic program; RCT, randomized controlled trial; RDNS, Rang-Din Nutrition Study; RUSF, ready-to-use supplementary food; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; SFP, supplementary feeding program; SHINE, Sanitation Hygiene Infant Nutrition Efficacy; SQ-LNS, small-quantity lipid-based nutrient supplement; WASH, water, sanitation, and hygiene; WLZ, weight-for-length *z* score.

[2]Children 6–12 mo old received 125 kcal/d, children 12–18 mo old received 250 kcal/d of lipid-based nutrient supplement.

[3]All children in the intervention groups, but not the passive control group, received Oral Rehydration Solution (ORS) for diarrhea and treatment of malaria in addition to SQ-LNS.

[4]Cross-sectional and longitudinal cohorts within this trial are considered as separate comparisons in all analyses and the presentation of results. Prevalence estimates of severe stunting and wasting in the comparison group at endline are shown separately for the cross-sectional and the longitudinal cohorts.

[5]Trial also included a 3-mo-duration intervention arm which is excluded from these analyses because there is no comparable control arm available.

[6]Trial is cited as Kumwenda 2014 in Das et al. (26).

[7]Trial was designed a priori to present results separately for HIV-exposed and -unexposed children; thus considered as 2 comparisons in all analyses and the presentation of results. Prevalence estimates of severe wasting and stunting in the comparison group at endline are from the HIV-unexposed cohort. In the HIV-exposed cohort, the prevalence estimates in the comparison group at endline were 0.6% and 15.8% for severe wasting and severe stunting, respectively.

TABLE 2 Main effects of SQ-LNSs on severe wasting, severe stunting, SAM, and very low MUAC[1]

Outcomes	Participants, *n* (comparisons, *n*)	Prevalence ratio SQ-LNSs vs. control (95% CI)	*P* value[2]	Heterogeneity I^2 (*P*-heterogeneity)[3]	Grade
Severe wasting (WLZ < −3 SD)	34,373 (14)	0.69 (0.55, 0.86)	0.001	0.01 (0.856)	High
Severe stunting (LAZ < −3 SD)	36,795 (17)	0.83 (0.78, 0.90)	<0.001	0.58 (<0.001)	High
SAM (WLZ < −3 SD or MUAC < 115 mm)	30,436 (13)	0.76 (0.62, 0.93)	0.008	0.00 (0.892)	High
Very low MUAC (MUACZ < −3 SD or MUAC < 115 mm)	30,069 (12)	0.73 (0.56, 0.94)	0.015	0.24 (0.609)	High
Concurrent severe wasting (WLZ < −3 SD) and severe stunting (LAZ < −3 SD)	27,416 (8)	0.47 (0.30, 0.73)	0.001	0.36 (0.631)	High

[1]LAZ, length-for-age *z* score; MUAC, midupper arm circumference; MUACZ, midupper arm circumference *z* score; SAM, severe acute malnutrition; SQ-LNS, small-quantity lipid-based nutrient supplement; WLZ, weight-for-length *z* score.

[2]*P* value corresponds to the pooled main effect 2-sided superiority testing of the intervention effect estimate and 95% CI presented in the preceding column.

[3]I^2 describes the percentage of variability in effect estimates that may be due to heterogeneity rather than chance. Roughly, 0.3–0.6 may be considered moderate heterogeneity. *P* value from chi-square test for heterogeneity. $P < 0.05$ indicates statistically significant evidence of heterogeneity of intervention effects beyond chance.

attenuation of the effects when passive control arms were excluded; e.g., the PR for severe wasting was 0.74 (95% CI: 0.57, 0.96) and the PR for severe stunting was 0.88 (95% CI: 0.81, 0.95).

For the exploratory analysis of concurrent severe wasting and severe stunting, statistical power was limited because this outcome was rare: endline prevalence in the control group was 0% in 8 of the 17 comparisons, and ranged from 0.2% to 1.8% in the other 9 comparisons. For the 8 comparisons with nonzero events in both arms, SQ-LNS reduced the prevalence of this outcome by 53% (PR: 0.47; 95% CI: 0.30, 0.73) (**Supplemental Figure 8**). Using the "rare events" sensitivity analysis approach,

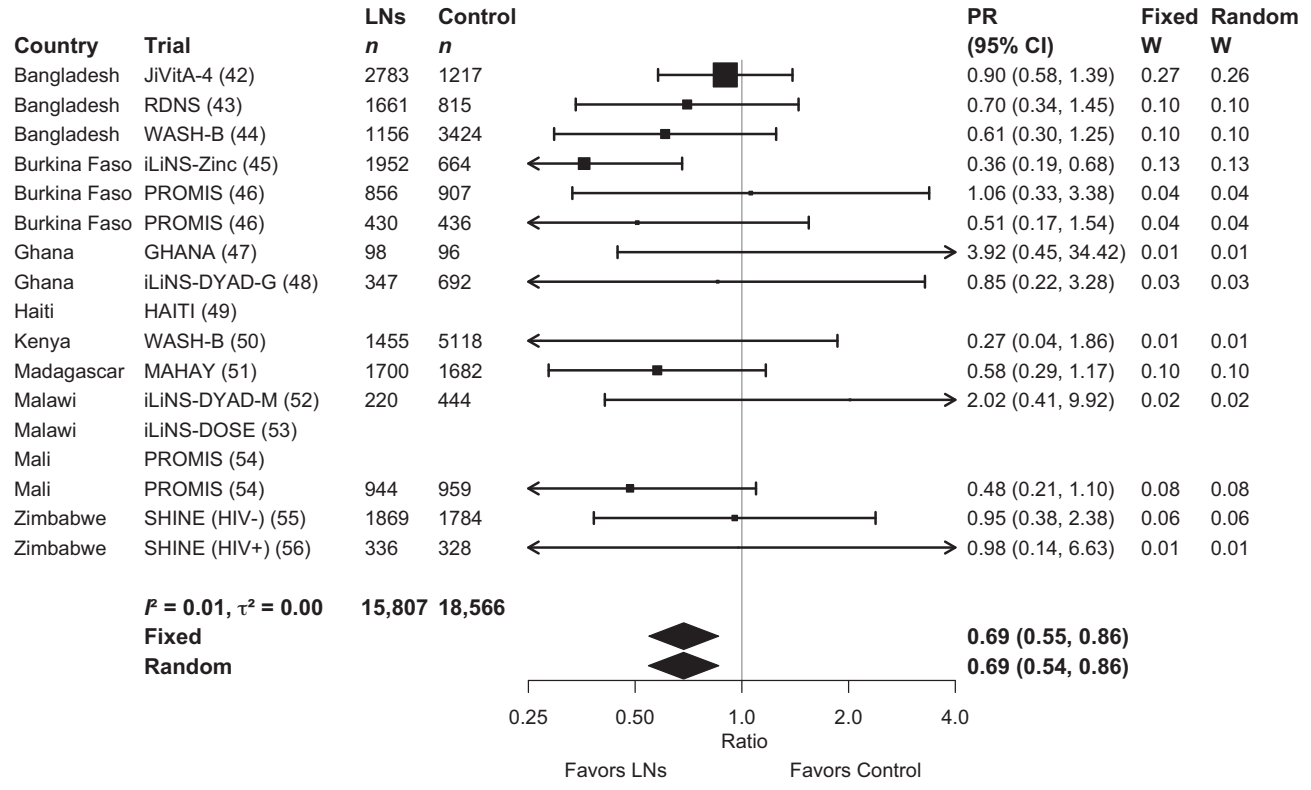

FIGURE 1 Forest plot of effect of small-quantity LNSs on severe wasting prevalence. Individual study estimates were generated from log-binomial regression controlling for baseline measure when available and with clustered observations using robust SEs for cluster-randomized trials. Pooled estimates were generated using inverse-variance weighting with both fixed and random effects. iLiNS, International Lipid-Based Nutrient Supplements; LNS, lipid-based nutrient supplement; PR, prevalence ratio; PROMIS, Innovative Approaches for the Prevention of Childhood Malnutrition; RDNS, Rang-Din Nutrition Study; SHINE, Sanitation Hygiene Infant Nutrition Efficacy; WASH-B, WASH Benefits.

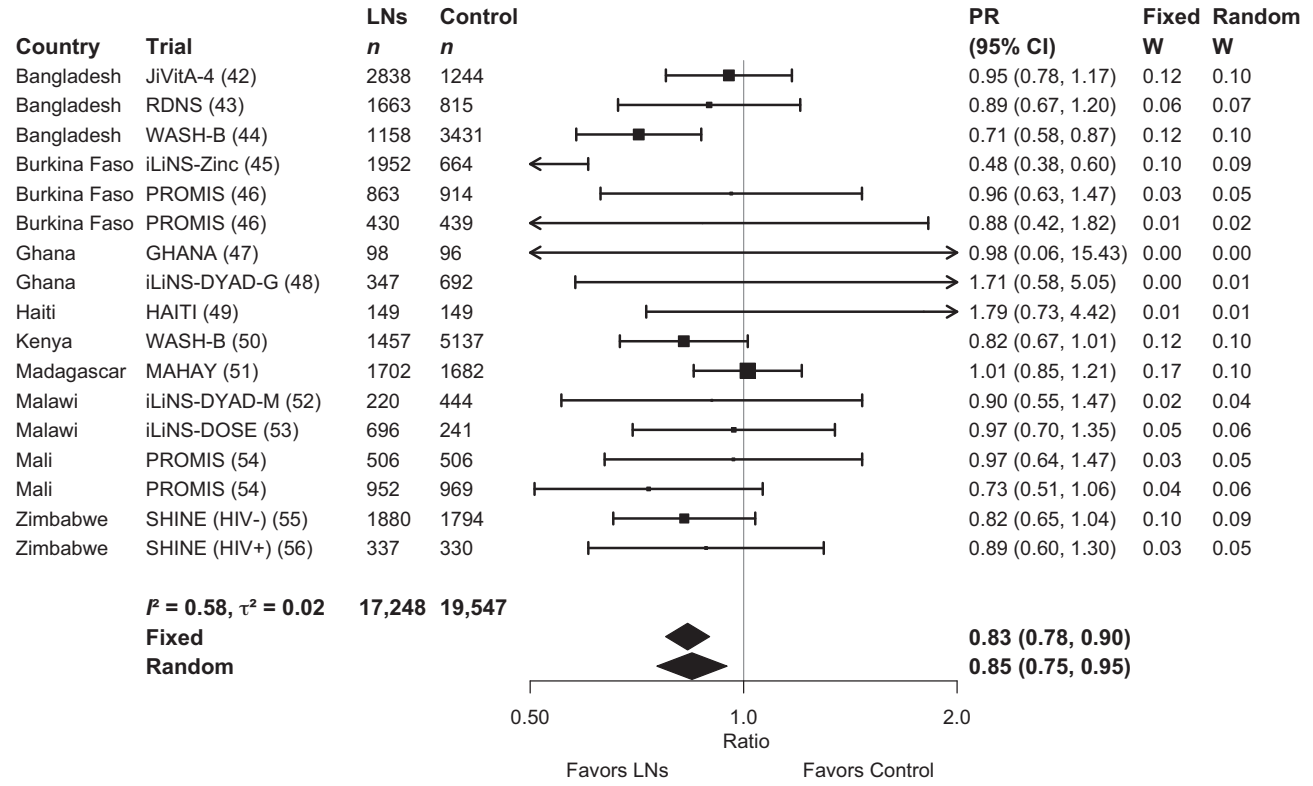

FIGURE 2 Forest plot of effect of small-quantity LNSs on severe stunting prevalence. Individual study estimates were generated from log-binomial regression controlling for baseline measure when available and with clustered observations using robust SEs for cluster-randomized trials. Pooled estimates were generated using inverse-variance weighting with both fixed and random effects. iLiNS, International Lipid-Based Nutrient Supplements; LNS, lipid-based nutrient supplement; PR, prevalence ratio; PROMIS, Innovative Approaches for the Prevention of Childhood Malnutrition; RDNS, Rang-Din Nutrition Study; SHINE, Sanitation Hygiene Infant Nutrition Efficacy; WASH-B, WASH Benefits.

the PR remained the same but the 95% CI was wider (PR: 0.47; 95% CI: 0.22, 1.02), and when passive control arms were excluded, there was some attenuation of the effect of SQ-LNSs (PR: 0.60; 95% CI: 0.36, 1.01).

The number of children who would need to be provided with SQ-LNSs to prevent 1 case of severe wasting (NNT) varied depending on the estimated prevalence of severe wasting in the study area, as shown in **Supplemental Table 4**. The average prevalence of severe wasting in the control groups at endline was ∼1%. At this prevalence, the NNT was 323 assuming a relative reduction of 31% or 385 assuming a relative reduction of 26%. In sites with a higher prevalence, e.g., 3%, the NNT was 108 or 128, assuming relative reductions of 31% or 26%, respectively. If the NNT estimates were based on longitudinal data such as incidence of severe wasting during a 12-mo period, which could be as high as 5%–24% (7, 46, 54), the NNT would range from 13 to 77.

Effect modification

Supplemental Figures 9A–I and **10**A–I present forest plots for severe wasting and severe stunting stratified by study-level effect modifiers, and **Figures 4** and **5** summarize results. For severe wasting, there was a significantly greater effect of SQ-LNSs in sites with unimproved water quality (PR: 0.52; 95% CI: 0.37, 0.73) than in sites with better water quality (PR: 0.86; 95% CI: 0.62, 1.20; *P*-diff = 0.035). For severe stunting, none of the tests for effect modification was statistically significant. For both outcomes, in many cases the differences in PRs between strata were sizable (e.g., >0.10) even though the *P*-diff for interaction was not significant, presumably due to limited statistical power for these types of analyses. For example, the PR for severe stunting was 0.78 (95% CI: 0.65, 0.93) in sites with a wasting burden ≥ 10%, compared with 0.92 (95% CI: 0.83, 1.02) in sites with a lower wasting burden. For severe wasting, notable differences between strata (apart from the water quality interaction noted already) were evident for region (PR: 0.63; 95% CI: 0.45, 0.87 for African sites; PR: 0.78; 95% CI: 0.56, 1.09 for Bangladesh sites), stunting burden (PR: 0.66; 95% CI: 0.51, 0.84 in high stunting burden sites compared with PR: 0.89; 95% CI: 0.48, 1.64 in lower stunting burden sites), wasting burden (PR: 0.64; 95% CI: 0.48, 0.85 in high wasting burden sites compared with PR: 0.81; 95% CI: 0.52, 1.27 in lower wasting burden sites), and sanitation (PR: 0.54; 95% CI: 0.34, 0.87 in sites with unimproved sanitation compared with PR: 0.76; 95% CI: 0.57, 1.02 in sites with better sanitation).

In the exploratory analysis of the potential individual-level modifiers, only a few characteristics significantly modified the effect of SQ-LNSs on severe wasting or severe stunting (**Supplemental Table 5**). As expected, for some characteristics, the number of comparisons available for analysis of effect modification was greatly reduced from the numbers available for analysis of main effects (particularly for severe wasting), so

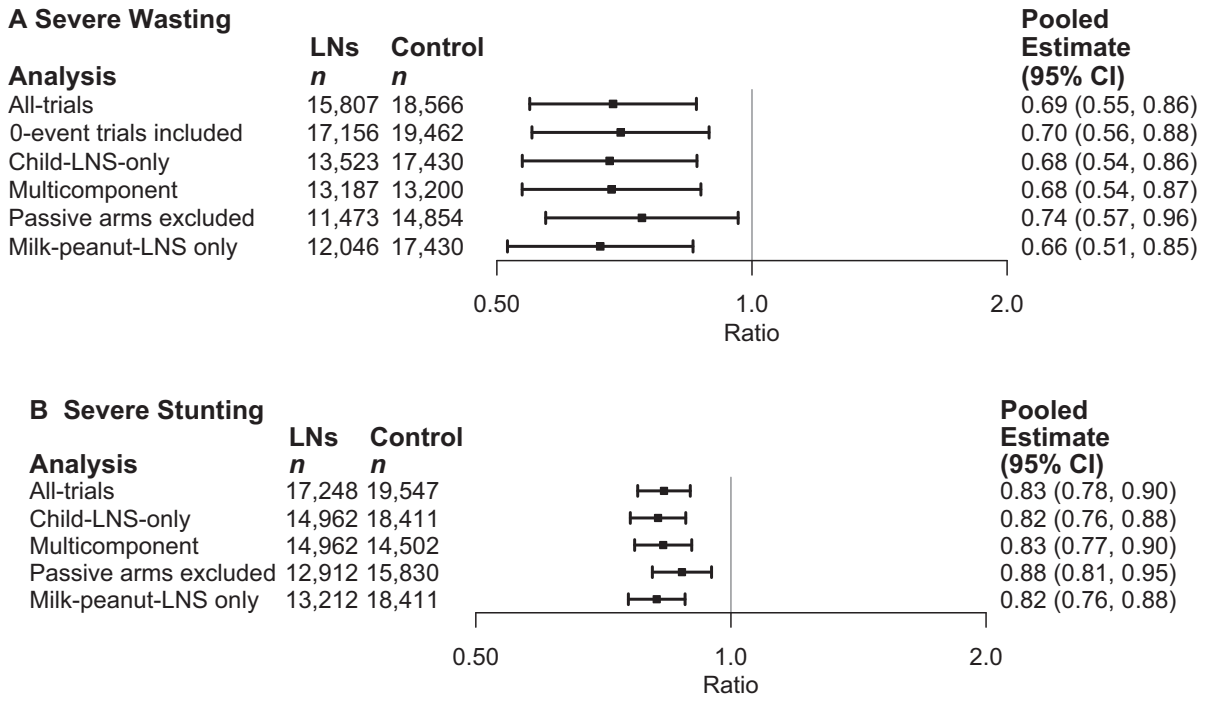

FIGURE 3 Sensitivity analyses of main effects of SQ-LNSs on prevalence ratios for severe stunting (A) and severe wasting (B). All-trial analysis includes all trials; child-LNS-only excludes trial arms that provided both maternal and child LNSs; multicomponent analysis separates comparisons within trials that included multicomponent interventions, so that the SQ-LNS against no SQ-LNS comparisons were conducted separately between pairs of arms that included the same nonnutrition components (e.g., SQ-LNS + WASH vs. WASH; SQ-LNS vs. control); passive arms excluded analysis excludes passive control arms; milk-peanut-LNS only analysis excludes arms with SQ-LNS formulations that were not milk- and peanut-based; "0-events trials included" uses estimates generated for certain trials in which 0.5 is substituted for the 0 value in analysis for severe wasting. Individual study estimates (not shown) were generated from log-binomial regression controlling for baseline measure when available and with clustered observations using robust SEs for cluster-randomized trials. Pooled estimates (shown here) were generated using inverse-variance weighting with both fixed and random effects. LNS, lipid-based nutrient supplement; SQ-LNS, small-quantity lipid-based nutrient supplement; WASH, water, sanitation, and hygiene.

statistical power may be limited. Of the 28 interactions examined (14 individual-level characteristics × 2 outcomes), only 2 (7%) met the criterion of P-interaction < 0.10, which is what could be expected due solely to chance. However, in 1 case the P-interaction was <0.0001, which is less likely to be due to chance: there was a greater effect of SQ-LNSs on severe stunting among later-born children (PR: 0.77; 95% CI: 0.71, 0.84) than among firstborn children (PR: 0.94; 95% CI: 0.84, 1.06).

Discussion

In this large IPD analysis ($n \sim 37{,}000$), the relative reductions in the prevalence of severe adverse growth outcomes at endline, after provision of SQ-LNSs to infants and young children 6–24 mo of age, were 31% for severe wasting and 17% for severe stunting. Results were similar regardless of inclusion/exclusion of arms with maternal plus child SQ-LNS, or arms with nonstandard SQ-LNS formulations, as well as when analyses of multicomponent intervention trials were structured to more specifically isolate the effects of SQ-LNSs. Effects were attenuated, although still significant, when comparisons using passive control arms were excluded, with relative reductions of 26% for severe wasting and 12% for severe stunting. Effects of SQ-LNSs appeared to be greater in sites with greater burdens of stunting or wasting, or with poorer water quality or sanitation, although the only statistically significant study-level effect modifier was water quality: the relative reduction in severe wasting was 48% in sites with unimproved water quality, compared with 14% in sites with better water quality.

Our estimate of the effect of SQ-LNSs on prevalence of severe stunting (17% relative reduction) is similar to the estimated 15% relative reduction reported by Das et al. (26), based on 6151 children in 5 studies that included both SQ-LNSs and medium-quantity LNSs. In their meta-analysis, there was no effect on prevalence of severe wasting but there were only 3 studies and <2500 children. The relatively large reduction in the prevalence of severe wasting in our IPD analysis, restricted to trials that used SQ-LNSs, is thus a novel finding of considerable global health significance and relevant to current initiatives aimed at preventing and treating wasting (11–13). Attenuation of the effect when comparisons using passive control arms were excluded (from a 31% to a 26% relative reduction in severe wasting) is consistent with the results of a previous meta-analysis of effects of LNSs (mostly SQ-LNSs) on all-cause mortality from 6 to 24 mo of age (58). Part of the impact of an SQ-LNS intervention on severe wasting or mortality, when a passive control arm is the comparator, could be due to more frequent contact with a health worker or data collector, which could lead to greater care for the child as well as detection and treatment of acute malnutrition. Nonetheless, the protective effect of SQ-LNSs on severe wasting prevalence is substantial even if this potential phenomenon is taken into account. In areas with a relatively high burden of

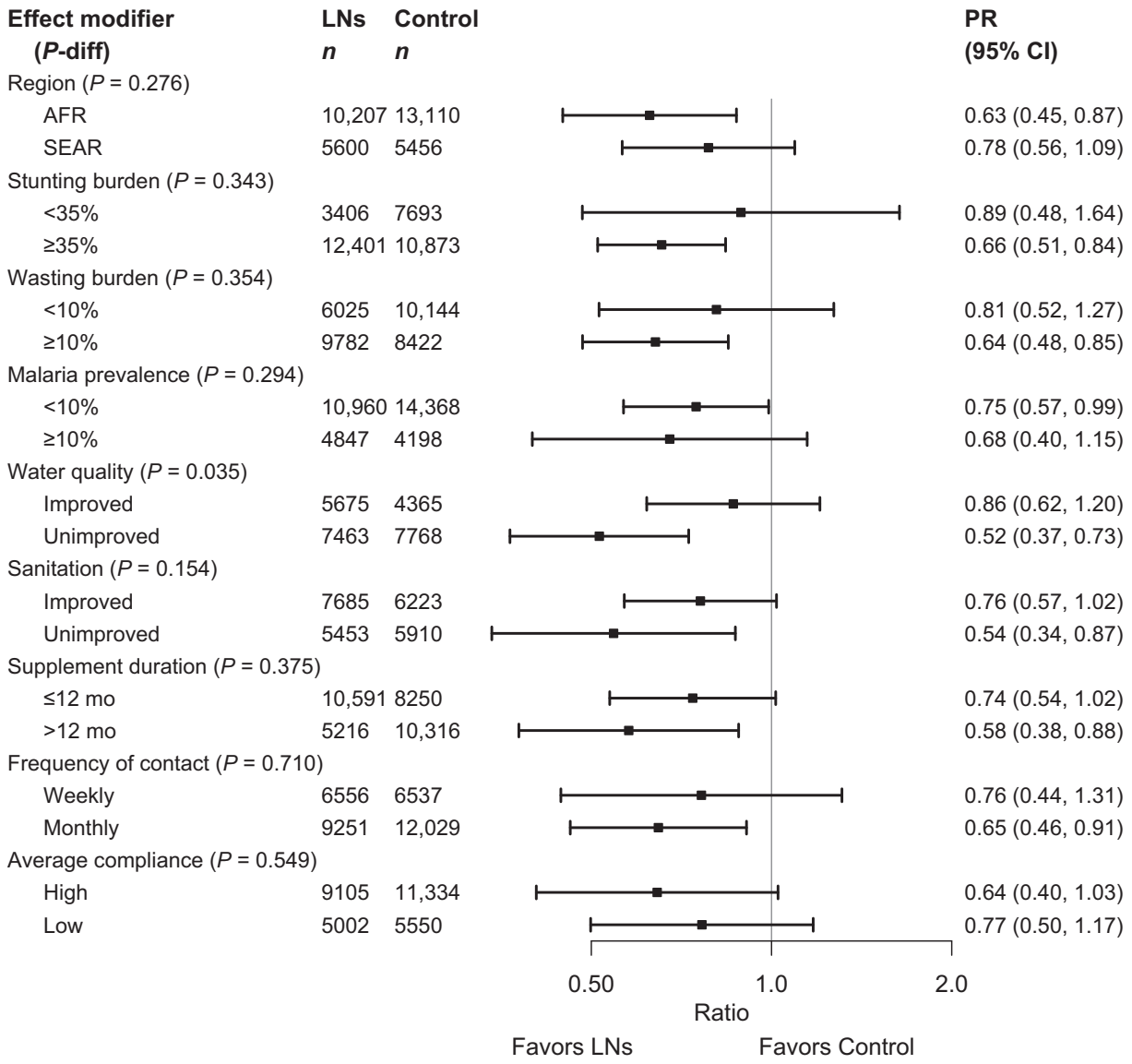

FIGURE 4 Pooled effect of small-quantity LNSs on severe wasting stratified by study-level characteristics. *P*-diff was estimated using random-effects meta-regression with the indicated effect modifier as the predictor of intervention effect size; stratified pooled estimates are presented for each stratum. AFR, African Region; LNS, lipid-based nutrient supplement; *P*-diff, *P* value for the difference in effects of small-quantity lipid-based nutrient supplements between the 2 levels of the effect modifier; PR, prevalence ratio; SEAR, South-East Asia Region.

severe wasting, the number of children who would need to be provided with SQ-LNSs to prevent 1 case of severe wasting, estimated based on a cross-sectional prevalence of 3%, would be ∼108 assuming a relative reduction of 31% and ∼128 assuming a relative reduction of 26%. If estimated based on a 15% incidence of severe wasting over a 12-mo period, the NNT would be ∼22 or ∼26 assuming a relative reduction of 31% or 26%, respectively.

The estimated reduction in severe wasting due to SQ-LNSs in our pooled analyses captures only the impact on prevalence at endline, not on longitudinal prevalence or incidence. In Mali, the SQ-LNS intervention had no effect on the prevalence of SAM in the cross-sectional sample of children but reduced the prevalence of SAM in the longitudinal cohort by 43%, although some of this difference could be due to the season in which the cross-sectional sample was assessed (54). Another consideration is that children who died during the study period did not enter into our calculation of the estimated prevalence of severe wasting at endline. Mortality was lower in the SQ-LNS arms (58), and if severe wasting was associated with mortality then more children with severe wasting could be "missing" from the control arm because they died and were excluded from analysis, which would lead to an underestimate of the effect of SQ-LNSs on severe wasting.

The pooled estimates for relative reductions in severe wasting and severe stunting, across all 14 trials, may also be underestimates of potential effects of SQ-LNSs in the highest-risk populations. Effect modification by study-level characteristics was generally not statistically significant, but statistical power for these analyses was constrained by the limited number of trials. As a result, there may be meaningful differences in effect estimates

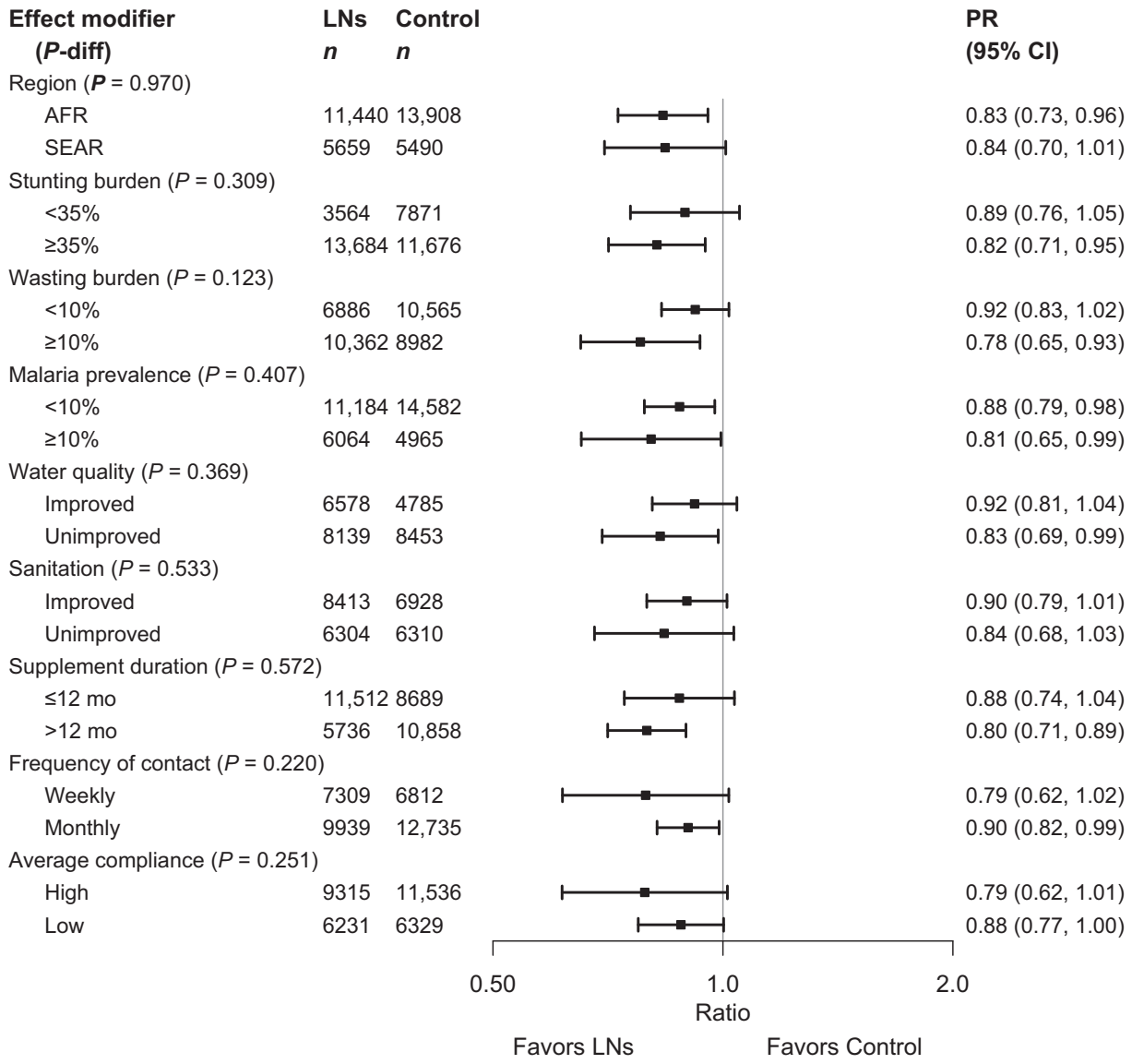

FIGURE 5 Pooled effect of small-quantity LNSs on severe stunting stratified by study-level characteristics. *P*-diff was estimated using random-effects meta-regression with the indicated effect modifier as the predictor of intervention effect size; stratified pooled estimates are presented for each stratum. AFR, African Region; LNS, lipid-based nutrient supplement; *P*-diff, *P* value for the difference in effects of small-quantity lipid-based nutrient supplements between the 2 levels of the effect modifier; PR, prevalence ratio; SEAR, South-East Asia Region.

between categories of trials even if the *P*-diff for the association between the effect modifier and effect size was not significant. For example, the relative reduction in severe stunting due to SQ-LNSs was 22% in sites with a wasting burden ≥ 10%, compared with 8% in sites with a lower wasting burden. For severe wasting, the relative reduction due to SQ-LNSs was 36% in sites with a high wasting burden, 34% in sites with a high stunting burden, 46% in sites with unimproved sanitation, and 48% in sites with unimproved water quality. These findings suggest that targeting preventive SQ-LNSs to high-risk populations may be warranted, which is consistent with the IPD analysis results for developmental outcomes (24) and hemoglobin (25).

The effects on severe wasting reported herein need to be interpreted in the context of how the trials handled children with acute malnutrition at baseline or thereafter. Most of the trials did not exclude children with MAM or SAM from participating (e.g., several trials enrolled during pregnancy), so the results should be generalizable to the general population in those sites. However, most trials did include regular anthropometric assessments of children during the study period and provided treatment or referred children for treatment of acute malnutrition (mainly for SAM, because MAM treatment was less likely to be available locally). Thus, by the time of the endline assessment, such children may no longer have been severely wasted, which could have biased our effect estimates toward the null. For most trials, assessment, referral, and treatment of children with acute malnutrition was the same in both the intervention and control arms, except for the 2 studies in which no active control arm was included (45, 47). The sensitivity analysis excluding passive control arms accounts for the potential bias introduced by those

differences. Provision of SQ-LNSs to children who had MAM or SAM at baseline or during the study may have served to prevent children with MAM from deteriorating to SAM, and to prevent relapse among children with SAM, in addition to preventing development of SAM among children with no history of MAM or SAM.

Strengths of these analyses include the large sample size, the substantial number of high-quality RCTs available, and the high participation rate among investigators invited to contribute data. The 14 study sites were diverse in terms of geographic location, stunting burden, malaria prevalence, water quality, sanitation, and several aspects of study design, which provided heterogeneity for exploration of study-level potential effect modifiers. Six of the 14 trials in this IPD analysis were conducted within existing community-based or clinic-based programs (43, 46, 49, 51, 54–56), so the findings include studies carried out in a real-world context. There are some limitations, however. Bangladesh was the only country represented in the South-East Asia Region, and Haiti was the only country represented in Latin America and the Caribbean. Caution is needed when interpreting the effect modification results because statistical power was limited and many of the study-level characteristics are interrelated (e.g., sites with unimproved water quality also tended to have unimproved sanitation). Thus, attribution of differences in the impact of SQ-LNS to a particular study-level characteristic may not be warranted.

These results add to the body of evidence demonstrating benefits of preventive SQ-LNSs for infants and young children across multiple outcomes, including child growth (23), iron deficiency and anemia (25), child development (24), and child mortality (58). The effects on severe wasting and severe stunting demonstrated herein strengthen our previous recommendation that policymakers and program planners should consider including SQ-LNSs in the mix of interventions to prevent adverse growth outcomes (23). They also provide more evidence for the potential mechanisms by which SQ-LNS reduces child mortality, i.e., via reductions in severe wasting and severe stunting. SQ-LNS is not a stand-alone intervention and should always be accompanied by messaging to reinforce recommended IYCF practices. When included in existing platforms for promoting healthy growth and development, such as community health worker programs, evidence is emerging to suggest that SQ-LNS may be a very cost-effective intervention in terms of costs per disability-adjusted life year (59). The effects on severe wasting are highly relevant to the goals of the UN's Global Action Plan on Child Wasting (12), especially considering the paucity of evidence on effective strategies to prevent severe wasting. An important next step is additional cost-effectiveness analyses of incorporating SQ-LNSs within integrated programs to prevent and treat wasting, taking into account the potential for reducing the number of cases of both moderate and severe wasting that would need treatment with supplemental or therapeutic foods, as well as reduced numbers of children requiring hospitalization.

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Data availability

Data described in the article, code book, and analytic code will not be made available because they are compiled from 14 different trials, and access is under the control of the investigators of each of those trials.

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