

# Lipid-based nutrient supplements and all-cause mortality in children 6–24 months of age: a meta-analysis of randomized controlled trials

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## ABSTRACT

**Background:** Undernutrition is associated with an elevated risk of mortality among children in low- and middle-income countries. Small-quantity lipid-based nutrient supplements (LNS) have been evaluated as a method to prevent undernutrition and improve infant development, but the effects on mortality are unknown.

**Objective:** Our objective was to evaluate the effect of LNS on all-cause mortality among children 6–24 mo old.

**Methods:** We conducted a systematic review and meta-analysis of randomized controlled trials of LNS designed to prevent undernutrition, with or without other interventions. Literature was searched in May 2019 and trials were included if they enrolled children between 6 and 24 mo old and the period of supplementation lasted  $\geq 6$  mo. We extracted data from participant flow diagrams and contacted study investigators to request data. We conducted a meta-analysis to produce summary RR estimates.

**Results:** We identified 18 trials conducted in 11 countries that enrolled 41,280 children and reported 586 deaths. The risk of mortality was lower in the LNS arms than in the non-LNS comparison arms (RR: 0.73; 95% CI: 0.59, 0.89; 13 trials). Estimates were similar when trials with maternal LNS intervention arms were added or when alternative formulations of LNS were excluded. The results appeared stronger in trials in which LNS were compared with passive control arms. Excluding these contrasts and only comparing multicomponent arms with LNS groups and comparison groups that contained all the same components without LNS attenuated the effect estimate (RR: 0.82; 95% CI: 0.61, 1.10).

**Conclusions:** LNS provided for the prevention of undernutrition may reduce the risk of mortality, but more trials with appropriate comparison groups allowing isolation of the effect of LNS alone are needed. This study was registered at [www.crd.york.ac.uk/PROSPERO](http://www.crd.york.ac.uk/PROSPERO) as CRD42019128718. *Am J Clin Nutr* 2020;111:207–218.

**Keywords:** lipid-based nutrient supplement, complementary feeding, child mortality, infants and young children, home fortification

## Introduction

Globally, an estimated 5.5 million children <5 y of age die each year, the majority from preventable causes (1). Undernutrition among infants and children <2 y of age remains common in low- and middle-income countries and is associated with increased risk of mortality, including among children with mild to moderate degrees of undernutrition (2, 3). Among severely or moderately malnourished children, ready-to-use therapeutic and supplementary foods have been found to significantly improve recovery rates and reduce the risk of mortality (4, 5). Lipid-based nutrient supplements (LNS) are available in various quantities and formulations for the prevention or treatment of malnutrition (6) and are designed to provide multiple micronutrients embedded in a food base that also provides energy, protein, and essential fatty acids. Large-quantity LNS are typically used for treatment of severe acute malnutrition and provided in dosages of  $\geq 500$  kcal/d (5). Medium-quantity LNS are generally offered as ready-to-use supplementary food for the treatment of moderate acute malnutrition in dosages of 250–500 kcal/d, and small-quantity LNS are generally given as 100–120 kcal/d for the prevention of undernutrition.

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Supplemental Tables 1–3 and Supplemental Figures 1 and 2 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

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Abbreviations used: CSB, corn–soy blend; IYCF, infant and young child feeding; LNS, lipid-based nutrient supplement(s); MNP, micronutrient powder; WASH, water, sanitation, and hygiene; WSB, wheat–soy blend.

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The primary objective of most trials of small-quantity and some trials of medium-quantity LNS has been to evaluate their efficacy for the prevention of malnutrition, and such trials have therefore focused on linear growth and risk of stunting as their primary outcome measures. Many trials also have evaluated indicators of child development as secondary outcomes. The combination of macro- and micronutrients addresses multiple potential nutritional deficiencies and thus may also reduce child mortality, although none of the trials had been designed with this as an explicit objective. A recently published review considered the impact of small-quantity LNS on a variety of outcomes, including all-cause mortality (7). However, the analysis of the effect on mortality was limited because the authors only included 3 trials, 2 of which reported deaths when children were <6 mo old and therefore too young to have been directly exposed to LNS. The recent publication of a number of additional large trials of LNS provides a larger sample size to examine this outcome. Thus, the objective for this meta-analysis is to evaluate the effect of small- and medium-quantity LNS on child mortality, using an expanded set of trials and restricting the analysis to children who were  $\geq 6$  mo old, i.e., eligible to receive LNS. We hypothesize that children 6–24 mo old who receive LNS for a minimum of 6 mo will have a lower mortality rate than those who do not receive LNS.

## Methods

The study was registered through Prospero (CRD42019 128718) and a detailed statistical analysis plan was developed and posted publicly (<https://osf.io/q76r8/>) before beginning the analysis. The primary and only outcome considered in this analysis was all-cause mortality.

Potential trials for inclusion in the meta-analysis were identified using a systematic review process that mirrored that of the recent meta-analysis of LNS (7). To capture additional, recently published trials, we repeated the search protocol described by Das et al. (7). Specifically, we searched 16 international and 9 regional databases in May 2019 using the keyword and the same controlled vocabulary search terms laid out by Das et al.; reference lists of newly included trials were reviewed to identify any additional trials. The titles and abstracts of all identified records were screened; full-text reports for potentially eligible trials were reviewed using the inclusion and exclusion criteria described below. When only meeting abstracts were identified, we contacted the authors to invite them to share their results.

### Inclusion and exclusion criteria

We restricted this analysis to prospective randomized controlled trials conducted in low- or middle-income countries that were designed such that all enrolled children were eligible to receive  $\geq 6$  mo of supplementation between 6 and 24 mo of age. Trials were excluded if they focused primarily on the treatment, not prevention, of malnutrition. Generally, this was defined as those trials in which severe or moderate malnutrition was an inclusion criterion for children in the trial. We did not include trials that provided  $\geq 500$  kcal LNS/d because such quantities exceed the average energy needed from non-breast-milk sources at 6–12 mo (6) and thus may reduce breast-milk intake and/or lead to incomplete consumption of the daily ration, thereby reducing

the dose of micronutrients and fatty acids received. Both of these consequences could compromise the potential benefits of LNS. Trials that did not formally exclude children with severe or moderate acute malnutrition, as part of the larger sample, were included in this analysis.

Because many trials enrolled children before the supplementation age of  $\geq 6$  mo, we restricted our analysis to children who were still in the trial at the time of initiation of child supplementation. When possible, this restriction was applied through careful extraction of data from publications; when not possible, we reached out directly to investigators.

Our primary comparison was of children in small- and medium-quantity LNS intervention groups with those in non-LNS control groups. If a single trial contained multiple relevant LNS interventions (e.g., varying dosages, formulations, or combinations in different arms), we combined these groups so that there was a single comparison per trial. In some cases, LNS were provided in combination with other interventions within a single intervention arm. All forms of small-quantity and medium-quantity LNS and interventions that included LNS were included as “LNS” in the primary analyses and were differentiated in prespecified sensitivity analyses described below. Non-LNS comparison groups varied by trial. For the primary comparison, we considered all non-LNS arms as a “Control” group for that trial, excluding intervention arms that received other types of (non-LNS) child supplementation, such as micronutrient powder or other fortified blended foods.

Intervention arms that included maternal LNS supplementation, in addition to child LNS, were excluded from the primary analysis. Maternal LNS supplementation may influence infant mortality independently of child LNS supplementation, as suggested by the lower RR for neonatal mortality in a recent meta-analysis of maternal LNS trials (0.72; 95% CI: 0.47, 1.10) (8). Although this was not statistically significant, that analysis was limited in power owing to a relatively small sample size, because only 3 trials were included (8). Our meta-analysis focuses on child mortality after 6 mo of age, when a residual effect of maternal supplementation is less likely. Nonetheless, it is possible that maternal LNS supplementation may affect the risk of mortality after 6 mo, e.g., because of longer-term effects on immune function related to birth size (9). For this reason, we excluded the trials that included maternal LNS from our primary analysis, but included them in a separate sensitivity analysis described below.

### Risk of bias assessment

Risk of bias in the included trials was assessed using the criteria in the Cochrane Handbook for Systematic Reviews of Interventions (10). Two reviewers evaluated each trial against the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, outcome assessment bias, incomplete outcome assessments, selective outcome reporting, and other sources of bias.

### Data extraction

Data were extracted primarily from participant flow diagrams. When insufficient detail was available in the diagram, we

contacted investigators for additional information. If the child supplementation began at enrollment, our denominator for analysis was the number of children enrolled. All deaths after enrollment were considered events. If supplementation began after enrollment (e.g., trials that enrolled during pregnancy), the denominator was the number of children alive and still enrolled when supplementation began. Only deaths that occurred after supplementation began were considered as events. Data extraction was independently replicated.

### Data analysis

Our parameter of interest was the pooled RR of all-cause child mortality comparing LNS with non-LNS intervention groups. We used a patient-weighted random-effects method proposed by Shuster and Walker (11, 12) to include trials in which 1 or both arms had 0 events. We did not adjust our methods for the inclusion of cluster-randomized trials. A recent meta-epidemiological study comparing effect estimates between cluster-randomized trials and individually randomized trials found no systematic differences between the estimation methods and concluded that the 2 types of trials can be safely pooled together for binary outcome meta-analyses (13). Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc.).

We explored trial protocol heterogeneity by summarizing the methods, participants, interventions, monitoring approaches, and potential for bias of each trial. Trials with protocols that differed substantially from the rest triggered discussion of sensitivity analyses, which are described below. For statistical heterogeneity we present  $I^2$  and  $\tau^2$  statistics.

Based on a preliminary literature search, we expected to find  $\geq 18$  trials with  $\geq 32,500$  participants and 400 deaths. Assuming similarly sized trials with equal-sized treatment groups, we would expect to have 80% statistical power to detect an RR of 0.77 between intervention and control groups at the 95% confidence level.

### Sensitivity and secondary analyses

The majority of trials used similar LNS distribution mechanisms [e.g., weekly or monthly rations provided by study staff, community health workers, or other health extension agents together with some infant and young child feeding (IYCF) counseling] and used similar formulations of LNS, specifically peanut- and milk-based products providing  $\sim 1$  RDA of most micronutrients. However, some trials integrated LNS supplementation together with other types of interventions, such as water, sanitation, and hygiene (WASH) or enhanced morbidity monitoring and treatment. The comparison groups also differed between trials. Most had an active control group for which there was a similar visit frequency or set of activities as for the LNS intervention group. However, some trials had a passive control group or nonintervention group, for which there were no contacts between study staff and research participants apart from enrollment and follow-up data collection visits. In addition, some trials provided alternative LNS formulations or supplementation to both the mother and child. These variations in trial design might affect the effect size of the mortality estimates. Therefore, we conducted a series of sensitivity analyses using the following

inclusion and exclusion criteria applied to the data included in the primary analysis:

- 1) Inclusion of intervention arms with maternal supplement components.
- 2) Exclusion of intervention arms with LNS formulations that were not milk- and peanut-based.
- 3) Separate comparison of multicomponent arms with LNS groups and comparison groups that contained all the same components without LNS (e.g., LNS + WASH compared with WASH) and exclusion of trials with only passive control arms.

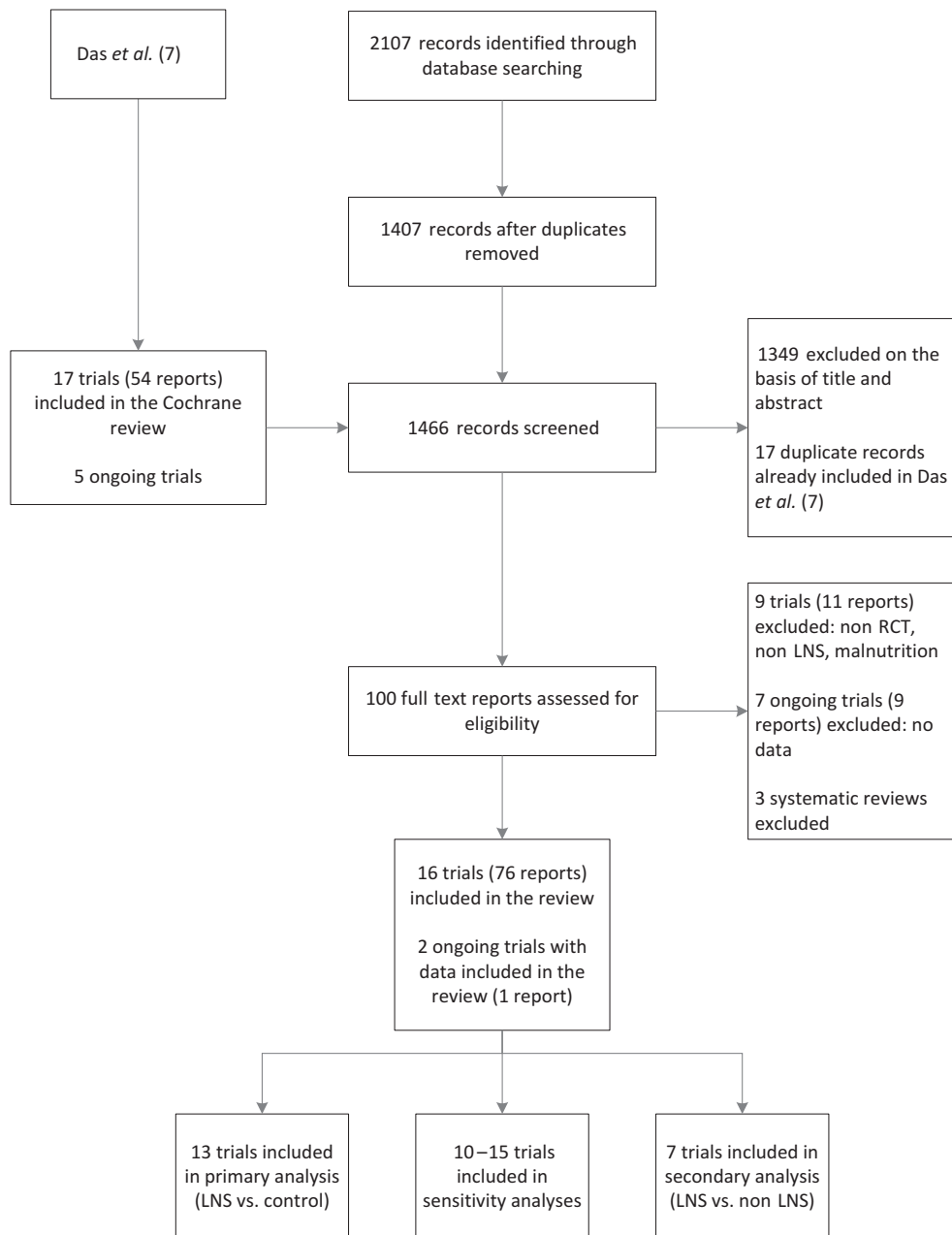
Finally, in a secondary analysis, we conducted a comparison of LNS intervention arms with non-LNS supplementation arms. Some trials included products such as micronutrient-fortified wheat-soy blend (WSB), corn-soy blend (CSB), Nutritabs, or micronutrient powders (MNPs). All of these analyses were considered exploratory.

### Results

We identified 18 trials that met the inclusion criteria for the primary, secondary, or sensitivity analyses (Figure 1). The 18 included trials were conducted in 11 countries, enrolling 41,280 children and recording 586 deaths (14–32). A brief description of each trial is included in Table 1 and information about how each trial was included in each set of analyses is shown in Supplemental Table 1. Trials were considered to generally have a low risk of bias, with the exception of blinding of participants owing to the nature of the intervention (Supplemental Table 2 and Supplemental Figure 1).

In the primary analysis, which included 13 trials with 34,051 participants, there was a 27% lower risk of all-cause mortality (RR: 0.73; 95% CI: 0.59, 0.89;  $I^2 = 23.2\%$ ,  $\tau^2 = 0.044$ ) (Figure 2). All but 2 of the trials had RR point estimates  $< 1$ ; however, only 1 trial was independently statistically significant (iLiNS-Zinc in Burkina Faso). The point estimate of the RR did not differ in sensitivity analyses in which maternal LNS intervention arms were added (Figure 3; 15 trials; 39,903 participants) or when only peanut + milk-based formulations of LNS intervention were included (Figure 4; 12 trials; 30,776 participants).

In a sensitivity analysis in which passive control trials were excluded and multicomponent arms (e.g., WASH + Nutrition) were compared with reference groups with the same components without LNS, the point estimate of the RR shifted toward the null and was no longer statistically significant (0.82; 95% CI: 0.61, 1.10;  $I^2 = 33.3\%$ ,  $\tau^2 = 0.10$ ) (Figure 5; 11 trials; 23,373 participants). To understand this attenuation of the point estimate, we further examined whether the Water, Sanitation, or Handwashing interventions might have had an effect on mortality (Supplemental Table 3). In the Kenya trial, the WASH + Nutrition group had the lowest risk of death (10/1000), followed by the Active Control group (16/1000) and the Water group (19/1000). The Nutrition-only arm had a mortality rate of 24/1000 and all other groups were between 20/1000 and 30/1000. None of the Water, Sanitation, Handwashing, or combined WASH arms had a mortality rate lower than the Active Control arm, even though all arms except for the passive control arm had active visitation. For comparison, in WASH Benefits Bangladesh,



**FIGURE 1** Study flow diagram. LNS, lipid-based nutrient supplement; RCT, randomized controlled trial.

none of the Water, Sanitation, or Handwashing arms, or the combined WASH or WASH + Nutrition arms, had a mortality rate lower than the control group (in this case, passive control); the only arm that had lower mortality was Nutrition (only). In the other WASH + Nutrition trial (the SHINE trial in Zimbabwe), the mortality rate was also lowest in the IYCF arm and was not improved by the addition of WASH.

In a secondary analysis, we compared LNS interventions with other supplement comparison groups (non-LNS, e.g., WSB++, CSB, MNP, or Nutritabs). The results were not statistically significant (RR: 0.76; 95% CI: 0.37, 1.58), but the point estimate was similar to that of the primary analysis (**Supplemental Figure 2**; 7 trials; 8681 participants). There was a much smaller

sample size and larger degree of heterogeneity in these analyses, however ( $I^2 = 52.8\%$ ,  $\tau^2 = 0.384$ ).

## Discussion

These results suggest that LNS supplementation for a minimum of 6 mo among children aged 6–24 mo may reduce the risk of mortality. The estimated reduction of 27% in all-cause mortality between 6 and 24 mo of age in the primary analysis, based on data from 13 trials with 34,051 children, was robust to the inclusion of interventions combined with maternal LNS supplementation or to the exclusion of alternative formulations of LNS. Our primary analysis included all studies and intervention

**TABLE 1** Description of each trial included in the analysis<sup>1</sup>

Authors	Trial name	Country	Intervention groups	Maternal supplement	Infant supplement			Anthropometrics at start of supplementation <sup>2</sup>	
					Age at start	Duration	Outcome ascertainment description	Stunting, %	Wasting, %
Adu-Afarwuah et al. (14)		Ghana	Nutributter (20 g/d; 108 kcal/d) Sprinkles powder Nutritabs (MMN) Passive control (no intervention) LNS: women received SQ-LNS during pregnancy and for 6 mo postpartum, child received SQ-LNS (20 g/d; 118 kcal/d) MMN: women received MMN during pregnancy and 6 mo postpartum, no child supplementation IFA: women received IFA during pregnancy and placebo for 6 mo postpartum, no child supplementation	N	6 mo	Weekly morbidity surveillance in intervention groups	5.4	5.4	
Adu-Afarwuah et al. (15)	iLINS-DYADG	Ghana		Y	6 mo	Weekly morbidity surveillance, trial hotline for participants	—	—	
Ashorn et al. (16)	iLINS-DYADM	Malawi	LNS: women received SQ-LNS during pregnancy and for 6 mo postpartum, child received SQ-LNSs (20 g/d; 118 kcal/d) MMN: women received MMN during pregnancy and 6 mo postpartum, no child supplementation IFA: women received IFA during pregnancy and placebo for 6 mo postpartum, no child supplementation	Y	6 mo	Weekly morbidity surveillance, trial contact with local hospitals	—	—	
Becquey et al. (17)	PROMIS	Burkina Faso	SQ-LNS (20 g/d; 118 kcal/d) Active control	N	6 mo	Monthly home visits by research staff	—	—	
Bisimwa et al. (18)		Democratic Republic of the Congo	RUCF: LNS (50 g/d; 275 kcal/d) UNIMIX: MMN-fortified corn-soy blend (70 g/d; 280 kcal/d) Historical control	N	6 mo	Medical records or verbal autopsy	18.6	5.7	
Christian et al. (19)	JiVrA-4	Bangladesh	Plumpy'Doz (23–46 g/d; 125–250 kcal/d) Chickpea based LNS (23–46 g/d; 125–250 kcal/d) Rice-lentil LNS (28–56 g/d; 125–250 kcal/d) WSB+++; Wheat-soy blend+++ (32–64 g/d; 125–250 kcal/d) Active control	N	6 mo	Twice-weekly morbidity surveillance	25.4	5.8	
Dewey et al. (20)	RDNS	Bangladesh	LNS-LNS: women received SQ-LNS during pregnancy and for 6 mo postpartum, child received SQ-LNS (20 g/d; 118 kcal/d)	Y	6 mo	Home visits every 6 mo by research staff	—	—	

(Continued)



TABLE 1 (Continued)

Authors	Trial name	Country	Intervention groups	Infant supplement			Anthropometrics at start of supplementation <sup>2</sup>		
				Maternal supplement	Age at start	Duration	Outcome ascertainment description	Stunting, %	Wasting, %
Hess et al. (21)	iLINS-Zinc	Burkina Faso	IFA-LNS: women received IFA during pregnancy and 3 mo postpartum, child received SQ-LNS (20 g/d; 118 kcal/d) IFA-MNP: women received IFA during pregnancy and 3 mo postpartum, child received MNP IFA-Control: women received IFA during pregnancy and 3 mo postpartum, no child supplementation LNS-Zn0: LNS (20 g/d; 118 kcal) containing 0 mg Zn/d and placebo tablet LNS-Zn5: LNS (20 g/d; 118 kcal) containing 5 mg Zn/d and placebo tablet LNS-Zn10: LNSs (20 g/d; 118 kcal) containing 10 mg Zn/d and placebo tablet LNS-TabZn5 (20 g/d; 118 kcal) containing 0 mg Zn/d and Zn tablet containing 5 mg Zn/d Passive control (no intervention) IYCF: child received SQ-LNS (20 g/d; 118 kcal/d) WASH: family received ventilated improved pit latrine, handwashing stations, soap, chlorine, child play space WASH and IYCF: child received SQ-LNS (20 g/d; 118 kcal/d), family received ventilated improved pit latrine, handwashing stations, soap, chlorine, child play space Active control (standard of care) SQ-LNS (20 g/d; 118 kcal/d) Active control Nutrifier (20 g/d; 108 kcal/d) for 6 mo Nutrifier (20 g/d; 108 kcal/d) for 3 mo, followed by standard of care Active control (standard of care)	N	9 mo	9 mo	Weekly morbidity surveillance; caregiver interview at endline for passive control group	22.4	16.4
Humphrey et al. (22)	SHINE (HIV-) <sup>3</sup>	Zimbabwe		N	6 mo	12 mo	Monthly reports from village health workers	—	—
Huybregts et al. (23)	PROMIS	Mali		N	6 mo	18 mo	Monthly home visits by research staff	—	—
Iannotti et al. (24)		Haiti		N	6–11 mo	3–6 mo	Monthly trial visit	9.4	2.2

(Continued)

TABLE 1 (Continued)

Authors	Trial name	Country	Intervention groups	Maternal supplement	Infant supplement		Outcome ascertainment description	Anthropometrics at start of supplementation <sup>2</sup>	
					Age at start	Duration		Stunting, %	Wasting, %
Luby et al. (25)	WASH-B	Bangladesh	Nutrition: child received LNS (20 g/d; 118 kcal/d) Water: family received chlorine for drinking water Sanitation: family received upgraded latrine, semi-scoop, and child potty Handwashing: family received handwashing stations with soap Water, sanitation, and handwashing: family received all water, sanitation, and hygiene interventions	N	6 mo	18 mo	Annual caregiver interview	—	—
Maleta et al. (26)	iLINS-DOSE	Malawi	Water, sanitation, handwashing, and nutrition: family received all water, sanitation, and hygiene interventions, child received LNS (20 g/d; 118 kcal/d) Passive control (no intervention) 10 g/d milk LNS (56 kcal/d) 20 g/d milk LNS (118 kcal/d) 20 g/d no-milk LNS (maltodextrin substituted) (118 kcal/d) 40 g/d milk LNS (236 kcal/d) 40 g/d no-milk LNS (maltodextrin substituted) (236 kcal/d)	N	6 mo	12 mo	Weekly morbidity surveillance, trial contact with local health providers	29.3	—
Mangani et al. (27)	LCNI-5	Malawi	Active control Milk-LNS (54 g/d, 285 kcal/d) Soy-LNS (64 g/d, 276 kcal/d) Corn-soy blend (71 g/d, 284 kcal/d)	N	6 mo	12 mo	Weekly morbidity surveillance, trial contact with local health clinics	36.7	1.7
Matias et al. (28)	WASH-B	Peru	LNS: Nutributter (20 g/d, 110 kcal/d) MNP: Sprinkles powder	N	6 mo	6 mo	Not reported	10.0	0.8
Null et al. (29)	WASH-B	Kenya	Nutrition: child received LNS (20 g/d; 118 kcal/d) Water: family received chlorine for drinking water Sanitation: family received upgraded latrine, semi-scoop, and child potty	N	6 mo	18 mo	Monthly reports from child health promoters; annual caregiver interview in passive control group	—	—

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TABLE 1 (Continued)

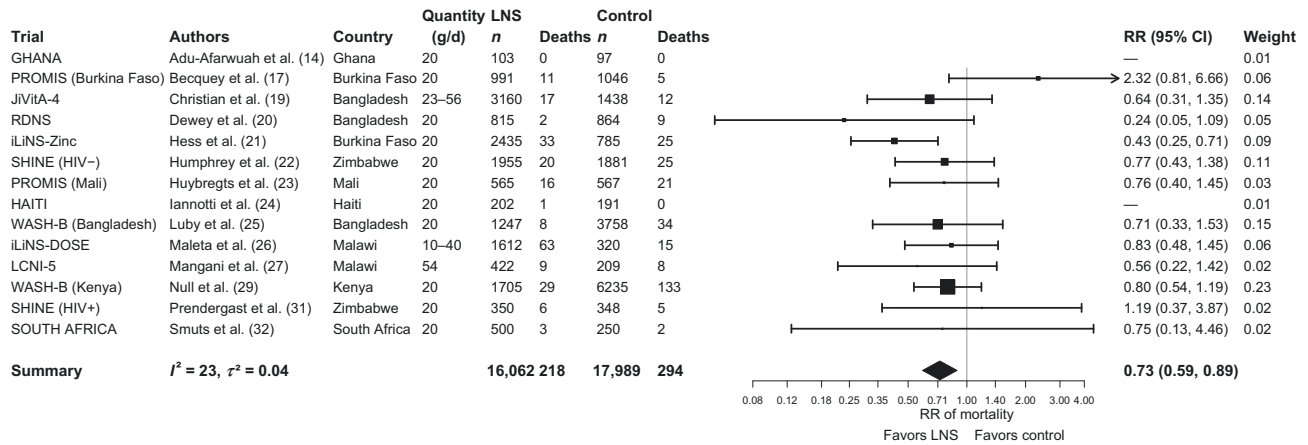
Authors	Trial name	Country	Intervention groups	Maternal supplement	Infant supplement			Anthropometrics at start of supplementation <sup>2</sup>	
					Age at start	Duration	Outcome ascertainment description	Stunting, %	Wasting, %
Phuka et al. (30)		Malawi	Handwashing: family received handwashing stations with soap Water, sanitation, and handwashing: family received all water, sanitation, and hygiene interventions Water, sanitation, handwashing, and nutrition: family received all water, sanitation, and hygiene interventions, child received LNS (20 g/d; 118 kcal/d) Passive control (no intervention) Active control FS-25: micronutrient-fortified spread (25 g/d; 127 kcal/d) FS-50: micronutrient-fortified spread (50 g/d; 256 kcal/d) LP: Likuni Phala, micronutrient-fortified maize-soy flour (71 g/d; 282 kcal/d) IYCF: child received SQ-LNSs (20 g/d; 118 kcal/d)	N	6 mo	12 mo	Weekly morbidity surveillance	—	—
Prendergast et al. (31)	SHINE (HIV+) <sup>3</sup>	Zimbabwe	WASH: family received ventilated improved pit latrine, handwashing stations, soap, chlorine, child play space WASH and IYCF: child received SQ-LNS (20 g/d; 118 kcal/d), family received ventilated improved pit latrine, handwashing stations, soap, chlorine, child play space Active control (standard of care) SQ-LNS (20 g/d; 114 kcal/d) SQ-LNS-plus: SQ-LNS with additional MMN, DHA, AA, L-lysine, and phytase (20 g/d; 113 kcal/d) Active control	N	6 mo	12 mo	Monthly reports from village health workers	—	—
Smuts et al. (32)		South Africa	Active control (standard of care) SQ-LNS (20 g/d; 114 kcal/d) SQ-LNS-plus: SQ-LNS with additional MMN, DHA, AA, L-lysine, and phytase (20 g/d; 113 kcal/d) Active control	N	6 mo	6 mo	Weekly morbidity surveillance	29.5	1.5

<sup>1</sup> AA, arachidonic acid; FS, fortified spread; IFA, iron-folic acid; IYCF, infant and young child feeding; LNS, lipid-based nutrient supplement; LP, Likuni Phala; MMN, multiple micronutrients; MNP, multiple micronutrient powder; RUCF, ready-to-use complementary food; SQ-LNS, small-quantity lipid-based nutrient supplement; WASH, water, sanitation, and hygiene; WSB, wheat-soy blend.

<sup>2</sup> Stunting is defined as length-for-age z score  $\leq -2$  and wasting is defined as weight-for-length z score  $\leq -2$ . Trials that did not report baseline stunting or wasting prevalences are indicated by a dashed line.

<sup>3</sup> The SHINE trial was a single trial published in 2 reports [Humphrey et al. (22) and Prendergast et al. (31)] separately by HIV exposure status of the infant. Data were extracted separately from the 2 reports.



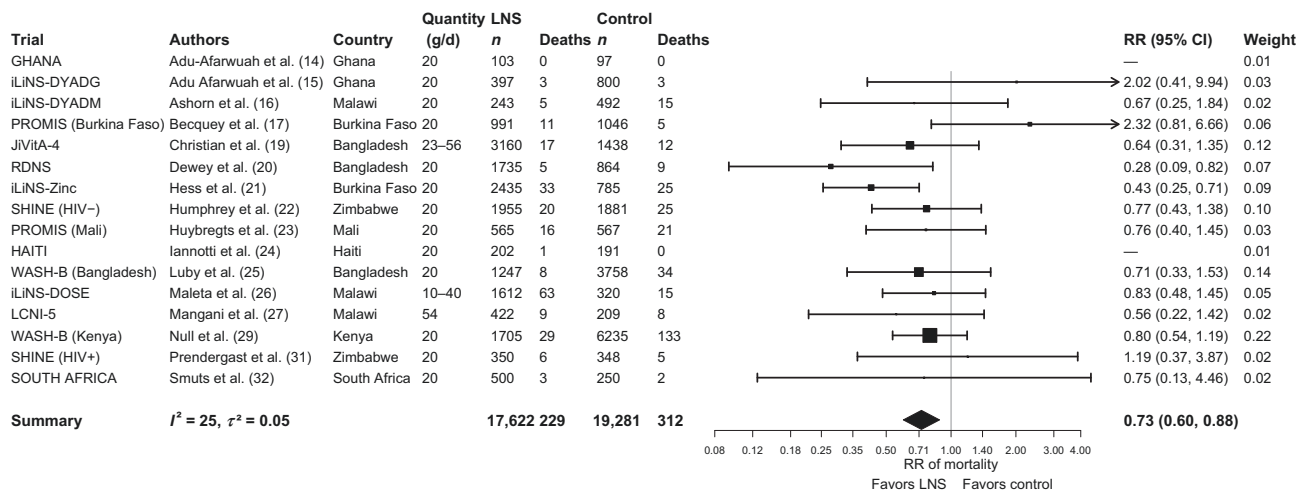


**FIGURE 2** Effect of LNS with or without other interventions on all-cause mortality in children 6–24 mo of age. The SHINE trial presented results in separate reports for children born to HIV+ and HIV– mothers and these have therefore been listed as 2 rows in this figure. LNS, lipid-based nutrient supplement.

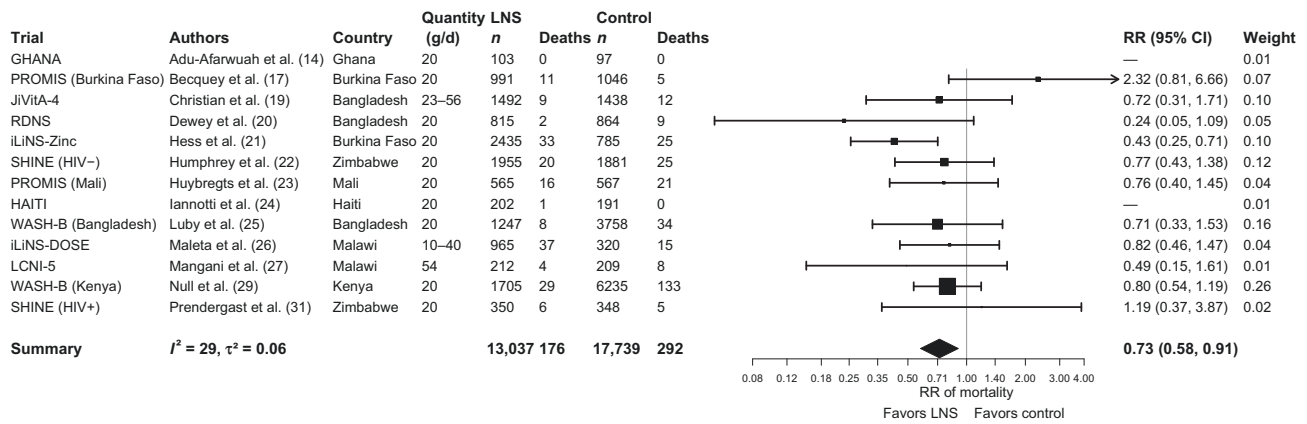
arms containing LNS and compared those with arms without LNS with a goal of maximizing the sample size and power to detect a difference. In a more restrictive sensitivity analysis in which we excluded passive control arms from the analysis and only contrasted LNS groups with comparison groups that contained all the same components without LNS, the estimated risk reduction was reduced to 18% and was no longer statistically significant.

There are a few notable differences in comparing the primary analysis with the latter sensitivity analysis. First, the sensitivity analysis excluded the iLiNS-Zinc trial in Burkina Faso (21) and the Ghana trial (14) completely, which may explain some of the attenuation in effect in this sensitivity analysis. The iLiNS-Zinc trial was the only trial that independently had a significant mortality risk reduction (RR: 0.43; 95% CI: 0.25, 0.71) and it also provided surveillance and treatment of diarrhea and malaria in the intervention groups but not in the passive control group. The second difference was in the contrasts for the 3 WASH + Nutrition trials (WASH Benefits Bangladesh and Kenya and SHINE in Zimbabwe). To isolate the effects of

LNS, this sensitivity analysis compared the LNS arm with the Active Control arm in WASH Benefits Kenya and SHINE and the LNS + WASH arm with the WASH arm in all 3 trials. It also excluded the independent water, sanitation, and handwashing arms from the 2 WASH Benefits trials. The difference in the point estimate in this sensitivity analysis compared with the primary analysis did not appear to be due to a protective effect of the WASH interventions. There was no risk reduction in those arms in either of the WASH Benefits trials. Although the combined LNS + WASH arm had a nonsignificantly lower mortality rate than the LNS arm in Kenya, this was not the case in the other 2 trials. The LNS + WASH arm in WASH Benefits Bangladesh had a higher mortality rate than the LNS group. Similarly, in the SHINE trial, the LNS + WASH group had a higher mortality rate than the LNS group. Lastly, this sensitivity analysis included a smaller sample size (23,373 compared with 34,051 in the primary analysis) and fewer deaths (349 compared with 512), which reduced the power to detect differences.



**FIGURE 3** Sensitivity analysis including arms with combined maternal + child supplementation. The SHINE trial presented results in separate reports for children born to HIV+ and HIV– mothers and these have therefore been listed as 2 rows in this figure. LNS, lipid-based nutrient supplement.



**FIGURE 4** Sensitivity analysis excluding arms that were not peanut- and milk-based LNS. The SHINE trial presented results in separate reports for children born to HIV+ and HIV- mothers and these have therefore been listed as 2 rows in this figure. LNS, lipid-based nutrient supplement.

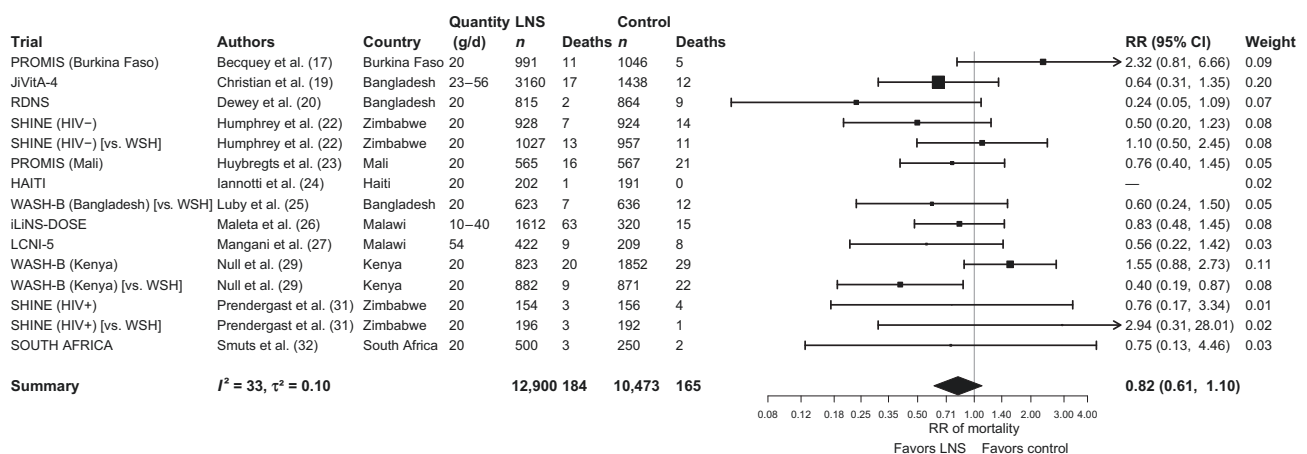
We cannot draw conclusions about the comparison of LNS with alternative products. The sample size in this analysis was small ( $n = 8681$  children and  $n = 72$  deaths) and there was a lot of variation in the comparison products, which likely partly explains the large degree of heterogeneity in the results.

Our estimated effect differs from the RR of 0.93 (95% CI: 0.63, 1.37) recently reported by Das et al. (7) in a number of ways. First, our analysis includes 41,280 children, whereas their analysis included 3321 children. Second, our analysis is restricted to children who were eligible to receive LNS. In the Das et al. review, 2 of the trials were maternal + child LNS trials (15, 16) and mortality outcomes were reported from birth. Thus, some of the deaths occurred before the age of 6 mo when children would have been eligible to first receive LNS directly. Third, in our primary analysis, we combined all groups who received LNS and compared them with all groups who had not received LNS, enabling us to draw more information from the trials.

Our estimated effect size is similar to that reported for the effect of maternal LNS on neonatal mortality (RR: 0.72; 95%

CI: 0.47, 1.10), although this was not statistically significant (8). Nevertheless, the consistency in the direction and magnitude of the effect is notable. Additional trials have been completed since the publication of that review (33), offering additional statistical power to test this hypothesis in the future.

We can only speculate on the potential mechanisms that may explain the observed effect. One possibility is that there was a protective effect through the prevention of wasting. In the Das et al. (7) review, there was an 18% reduction in the prevalence of wasting (RR: 0.82; 95% CI: 0.74, 0.91). Similarly in the PROMIS Mali trial, which was not included in the Das et al. review, there was a risk reduction of 29% in the incidence of acute malnutrition (95% CI: 8%, 46%) (23). Moderate wasting has been associated with a 3.4-fold increased risk of mortality, whereas severe wasting has been associated with >11-fold increased risk (3). Undernutrition is also associated with increased susceptibility to and severity of infections. None of the trials reported cause-specific mortality and, although many reported morbidity outcomes, the results have been inconsistent.



**FIGURE 5** Sensitivity analysis excluding passive control arms and comparing LNS multicomponent arms with reference groups with the same components without LNS. The SHINE trial presented results in separate reports for children born to HIV+ and HIV- mothers and these have therefore been listed as 2 rows in this figure. In the WASH + Nutrition trials, we have included up to 2 sets of contrasts for each trial: LNS compared with active control and LNS + WASH compared with WASH arms. LNS, lipid-based nutrient supplement; WASH, water, sanitation, and hygiene.

One trial in Bangladesh (25) reported a reduction in diarrhea, whereas 6 trials (19, 22, 29, 31, 34, 35) did not find a difference and 2 trials (32, 36) reported an increased risk. Five trials (19, 22, 24, 34, 35) reported no effects on pneumonia or respiratory symptoms, and 2 trials (32, 36) reported a reduction in respiratory symptoms. Five trials (24, 29, 32, 34, 36) reported no effects on malaria or fever, whereas 1 trial (27) reported an increase in malaria-related health center visits. Beyond the common symptoms of infection, other complications of acute undernutrition that may increase the risk of mortality include hypothermia, fluid and electrolyte imbalances, hypoglycemia, and cardiac and respiratory dysfunction (37).

In addition to the biological mechanisms, the intervention may have improved other aspects of caregiving behaviors. Most trials provided counseling by a community health worker or study staff on IYCF or other caregiving messages together with LNS supplementation. It is possible that frequent contact with a health worker could lead to greater care and attention to the child. Most trials included an active control group, in which there was a comparable contact with a health worker. However, there were a few trials with a passive control group. Indeed, when these trials were removed from the analysis, the point estimate shifted toward the null, yet the RR of 0.82 remained of a magnitude of public health importance.

There are some important limitations with this analysis. We lack detailed information on cause-specific mortality, data which could provide insight into possible mechanisms of effect. In addition, the variation in trial design, particularly with respect to passive control groups and multicomponent interventions, complicates the interpretation of results. In the trials with passive controls, there was no contact with participants in the control group yet frequent contact in the intervention groups. The outcome ascertainment may have differed between the arms: retrospective in the control compared with prospective in the intervention groups, which could lead to a biased effect estimate. We would expect this to be minimal for an outcome such as mortality. Yet, active contact with participants could have carried a survival benefit independent of LNS through enhanced care. More trials with a direct comparison of an intervention package with and without LNS are needed.

There are many strengths to this analysis. The sample size was adequate to detect a mortality difference of public health importance. The analytic sample was specific to the period of LNS supplementation, which was achieved by obtaining data from researchers when not available in the publications. All analyses were prespecified and publicly posted. We focused on a single study endpoint and the findings from the sensitivity analyses were generally comparable with that of the primary analysis, suggesting that the results were not due to chance. Overall, there was a generally low degree of heterogeneity across trials in all analyses, as suggested by the  $I^2$  statistics <40% (10). There also was a low risk of bias across the trials on most criteria, with the exception of blinding participants. Nevertheless, mortality is an objective outcome less affected by respondent or interviewer biases. Selective outcome reporting and publication biases were minimized by extracting the data directly from trial flow diagrams and contacting investigators.

Our analyses suggest that the provision of small- and medium-quantity LNS for the prevention of malnutrition likely is associated with a reduction in the risk of all-cause mortality

among children aged 6–24 mo. The trials were conducted in multiple countries in different geographic regions and so these results are likely broadly generalizable to many low- and middle-income country contexts. More research is needed on cause-specific mortality to provide a greater understanding of the causal mechanisms and to incorporate into models such as the Lives Saved Tool (38). Nevertheless, the present analysis provides evidence that reduction in mortality is a likely additional benefit of LNS beyond improvements in growth and micronutrient status.

The authors' responsibilities were as follows—CPS: drafted the manuscript with input from all coauthors; CDA, KRW, KGD, and CPS: wrote the statistical analysis plan; KRW and CDA: extracted the data; CDA: conducted the data analysis; CPS, KGD, LH, PA, EB, and JHH: provided additional data from the PROMIS, SHINE, WASH Benefits, RDNS, and iLiNS trials to support the analysis; and all authors: read, contributed to, and approved the final manuscript. The authors report no conflicts of interest.

## References

1. UN Inter-agency Group for Child Mortality Estimation. Levels and Trends in Child Mortality. New York, NY: UNICEF; 2018.
2. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013;382(9890):427–51.
3. Olofin I, McDonald CM, Ezzati M, Flaxman S, Black RE, Fawzi WW, Caulfield LE, Danaei G; Nutrition Impact Model Study. Associations of suboptimal growth with all-cause and cause-specific mortality in children under five years: a pooled analysis of ten prospective studies. *PLoS One* 2013;8(5):e64636.
4. Picot J, Hartwell D, Harris P, Mendes D, Clegg AJ, Takeda A. The effectiveness of interventions to treat severe acute malnutrition in young children: a systematic review. *Health Technol Assess* 2012;16(19): 1–316.
5. WHO. Guideline: Update on the Management of Severe Acute Malnutrition in Infants and Children. Geneva: World Health Organization; 2013.
6. Arimond M, Zeilani M, Jungjohann S, Brown KH, Ashorn P, Allen LH, Dewey KG. Considerations in developing lipid-based nutrient supplements for prevention of undernutrition: experience from the International Lipid-Based Nutrient Supplements (iLiNS) project. *Matern Child Nutr* 2015;11(Suppl 4):31–61.
7. Das JK, Salam RA, Hadi YB, Sadiq Sheikh S, Bhutta AZ, Weise Prinzo Z, Bhutta ZA. Preventive lipid-based nutrient supplements given with complementary foods to infants and young children 6 to 23 months of age for health, nutrition, and developmental outcomes. *Cochrane Database Syst Rev* 2019;5:CD012611.
8. Das JK, Hoodbhoy Z, Salam RA, Bhutta AZ, Valenzuela-Rubio NG, Weise Prinzo Z, Bhutta ZA. Lipid-based nutrient supplements for maternal, birth, and infant developmental outcomes. *Cochrane Database Syst Rev* 2018;8:CD012610.
9. Moore SE, Collinson AC, Tamba N'Gom P, Aspinall R, Prentice AM. Early immunological development and mortality from infectious disease in later life. *Proc Nutr Soc* 2006;65(3):311–18.
10. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* [Internet]. Version 5.1.0. The Cochrane Collaboration; 2011 [date accessed: October 11, 2019]. Available from: [www.handbook.cochrane.org](http://www.handbook.cochrane.org).
11. Shuster J, Guo J, Skyler J. Meta-analysis of safety for low event-rate binomial trials. *Res Syn Meth* 2012;3:30–50.
12. Shuster J, Walker M. Low-event-rate meta-analyses of clinical trials: implementing good practices. *Statist Med* 2016;35:2467–78.
13. Leyrat C, Caille A, Eldridge S, Kerry S, Dechartres A, Giraudeau B. Intervention effect estimates in cluster randomized versus individually randomized trials: a meta-epidemiological study. *Int J Epidemiol* 2019;48(2):609–19.
14. Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A, Dewey KG. Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. *Am J Clin Nutr* 2007;86(2):412–20.

15. Adu-Afarwuah S, Lartey A, Okronipa H, Ashorn P, Peerson JM, Arimond M, Ashorn U, Zeilani M, Vosti S, Dewey KG. Small-quantity, lipid-based nutrient supplements provided to women during pregnancy and 6 mo postpartum and to their infants from 6 mo of age increase the mean attained length of 18-mo-old children in semi-urban Ghana: a randomized controlled trial. *Am J Clin Nutr* 2016;104(3):797–808.
16. Ashorn P, Alho L, Ashorn U, Cheung YB, Dewey KG, Gondwe A, Harjunmaa U, Lartey A, Phiri N, Phiri TE, et al. Supplementation of maternal diets during pregnancy and for 6 months postpartum and infant diets thereafter with small-quantity lipid-based nutrient supplements does not promote child growth by 18 months of age in rural Malawi: a randomized controlled trial. *J Nutr* 2015;145(6):1345–53.
17. Becquey E, Huybregts L, Zongrone A, le Port A, Leroy JL, Rawat R, Touré M, Ruel MT. Impact on child acute malnutrition of integrating a preventive nutrition package into facility-based screening for acute malnutrition during well-baby consultation: a cluster-randomized controlled trial in Burkina Faso. *PLoS Med* 2019;16(8):e1002877.
18. Bisimwa G, Owino VO, Bahwere P, Dramaix M, Donnen P, Dibari F, Collins S. Randomized controlled trial of the effectiveness of a soybean-maize-sorghum-based ready-to-use complementary food paste on infant growth in South Kivu, Democratic Republic of Congo. *Am J Clin Nutr* 2012;95(5):1157–64.
19. Christian P, Shaikh S, Shamim AA, Mehra S, Wu L, Mitra M, Ali H, Merrill RD, Choudhury N, Parveen M, et al. Effect of fortified complementary food supplementation on child growth in rural Bangladesh: a cluster-randomized trial. *Int J Epidemiol* 2015;44(6):1862–76.
20. Dewey KG, Mridha MK, Matias SL, Arnold CD, Cummins JR, Khan MS, Maalouf-Manasseh Z, Siddiqui Z, Ullah MB, Vosti SA. Lipid-based nutrient supplementation in the first 1000 d improves child growth in Bangladesh: a cluster-randomized effectiveness trial. *Am J Clin Nutr* 2017;105(4):944–57.
21. Hess SY, Abbeddou S, Jimenez EY, Somé JW, Vosti SA, Ouédraogo ZP, Guissou RM, Ouédraogo JB, Brown KH. Small-quantity lipid-based nutrient supplements, regardless of their zinc content, increase growth and reduce the prevalence of stunting and wasting in young Burkinabe children: a cluster-randomized trial. *PLoS One* 2015;10(3):e0122242.
22. Humphrey JH, Mbuya MN, Ntozini R, Moulton LH, Stoltzfus RJ, Tavengwa NV, Mutasa K, Majo F, Mutasa B, Mangwadu G, et al. Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on child stunting and anaemia in rural Zimbabwe: a cluster-randomised trial. *Lancet Glob Health* 2019;7(1):e132–47.
23. Huybregts L, Le Port A, Becquey E, Zongrone A, Barba F, Rawat R, Leroy JL, Ruel MT. Impact on child acute malnutrition of integrating small-quantity lipid-based nutrient supplements into community-level screening for acute malnutrition: a cluster randomized controlled trial in Mali. *Plos Med* 2019;16(8):e1002892.
24. Iannotti LL, Dulience SJ, Green J, Joseph S, Francois J, Antenor ML, Lesorogol C, Mounce J, Nickerson NM. Linear growth increased in young children in an urban slum of Haiti: a randomized controlled trial of a lipid-based nutrient supplement. *Am J Clin Nutr* 2014;99(1):198–208.
25. Luby SP, Rahman M, Arnold BF, Unicomb L, Ashraf S, Winch PJ, Stewart CP, Begum F, Hussain F, Benjamin-Chung J, et al. Effects of water quality, sanitation, handwashing and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomized trial. *Lancet Glob Health* 2018;6(3):e302–e15.
26. Maleta KM, Phuka J, Alho L, Cheung YB, Dewey KG, Ashorn U, Phiri N, Phiri TE, Vosti SA, Zeilani M, et al. Provision of 10–40 g/d lipid-based nutrient supplements from 6 to 18 months of age does not prevent linear growth faltering in Malawi. *J Nutr* 2015;145(8):1909–15.
27. Mangani C, Maleta K, Phuka J, Cheung YB, Thakwalakwa C, Dewey K, Manary M, Puumalainen T, Ashorn P. Effect of complementary feeding with lipid-based nutrient supplements and corn–soy blend on the incidence of stunting and linear growth among 6- to 18-month-old infants and children in rural Malawi. *Matern Child Nutr* 2015;11(Suppl 4):132–43.
28. Matias SL, Vargas-Vásquez A, Bado Pérez R, Alcázar Valdivia L, Aquino Vivanco O, Rodríguez Martín A, Novalbos Ruiz JP. Effects of lipid-based nutrient supplements v. micronutrient powders on nutritional and developmental outcomes among Peruvian infants. *Public Health Nutr* 2017;20(16):2998–3007.
29. Null C, Stewart CP, Pickering AJ, Dentz HN, Arnold BF, Arnold CD, Benjamin-Chung J, Clasen T, Dewey KG, Fernald LCH, et al. Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Kenya: a cluster-randomised controlled trial. *Lancet Glob Health* 2018;6(3):e316–e29.
30. Phuka JC, Maleta K, Thakwalakwa C, Cheung YB, Briend A, Manary MJ, Ashorn P. Complementary feeding with fortified spread and incidence of severe stunting in 6- to 18-month-old rural Malawians. *Arch Pediatr Adolesc Med* 2008;162(7):619–26.
31. Prendergast AJ, Chasekwa B, Evans C, Mutasa K, Mbuya MNN, Stoltzfus RJ, Smith LE, Majo FD, Tavengwa NV, Mutasa B, et al. Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on stunting and anaemia among HIV-exposed children in rural Zimbabwe: a cluster-randomised controlled trial. *Lancet Child Adolesc Health* 2019;3(2):77–90.
32. Smuts CM, Matsungo TM, Malan L, Kruger HS, Rothman M, Kvalsvig JD, Covic N, Joosten K, Osendarp SJM, Bruins MJ, et al. Effect of small-quantity lipid-based nutrient supplements on growth, psychomotor development, iron status, and morbidity among 6- to 12-mo-old infants in South Africa: a randomized controlled trial. *Am J Clin Nutr* 2019;109(1):55–68.
33. Mambidge KM, Westcott JE, Garces A, Figueroa L, Goudar SS, Dhaded SM, Pasha O, Ali SA, Tshetu A, Lokangaka A, et al. A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the Women First trial. *Am J Clin Nutr* 2019;109(2):457–69.
34. Adu-Afarwuah S, Young RR, Lartey A, Okronipa H, Ashorn P, Ashorn U, Oaks BM, Dewey KG. Supplementation with small-quantity lipid-based nutrient supplements does not increase child morbidity in a semi-urban setting in Ghana: a secondary outcome non-inferiority analysis of the iLiNS-DYAD randomized controlled trial. *J Nutr* 2019. In press.
35. Bendabenda J, Alho L, Ashorn U, Cheung YB, Dewey KG, Vosti SA, Phuka J, Maleta K, Ashorn P. The effect of providing lipid-based nutrient supplements on morbidity in rural Malawian infants and young children: a randomized controlled trial. *Public Health Nutr* 2016;19(10):1893–903.
36. Ullah MB, Mridha MK, Arnold CD, Matias SL, Khan MSA, Siddiqui Z, Hossain M, Dewey KG. Provision of pre- and postnatal nutritional supplements generally did not increase or decrease common childhood illnesses in Bangladesh: a cluster-randomized effectiveness trial. *J Nutr* 2019;149(7):1271–81.
37. Brown KH, Nyirandutiye DH, Jungjohann S. Management of children with acute malnutrition in resource-poor settings. *Nat Rev Endocrinol* 2009;5(11):597–603.
38. Clermont A, Walker N. Nutrition interventions in the Lives Saved Tool (LiST). *J Nutr* 2017;147(11):2132S–40S.