SYSTEMATIC REVIEW

Interventions to improve linear growth during complementary feeding period for children aged 6-24 months living in low- and middle-income countries: a systematic review and network meta-analysis [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Optimizing linear growth in children during complementary feeding period (CFP) (6-24 months) are critical for their development. Several interventions, such as micronutrient and food supplements, deworming, maternal education, and water, sanitation and hygiene (WASH), could potentially be provided to prevent stunting, but their comparative effectiveness is currently unclear. In this study, we evaluated comparative effectiveness of interventions under these domains on child linear growth outcomes of height-for-age z-score (HAZ) and stunting (HAZ <-2SD).

Methods: For this study, we searched for low- and middle-income country (LMIC)-based randomized clinical trials (RCTs) of aforementioned interventions provided to children during CFP. We searched for reports published until September 17, 2019 and hand-searched bibliographies of existing reviews. We performed random-effects network meta-analysis (NMA) for HAZ and stunting.

Results: The evidence base for our NMA was based on 79 RCTs (96 papers) involving 81,786 children. Among the micronutrients, compared to standard-of-care, iron + folic acid (IFA) (mean difference =0.08; 95% credible interval [Crl]: 0.01, 0.15) and multiple micronutrients (MMN) (mean difference =0.06; 95%Crl: 0.01, 0.11) showed improvements for HAZ; MMN also reduced the risks for stunting (RR=0.86; 95%Crl: 0.73, 0.98), whereas IFA did not (RR=0.92; 95%Crl: 0.64, 1.23). For food supplements, flour in the caloric range of 270-340 kcal (RR=0.73; 95%Crl: 0.51, 1.00) and fortified lipid-based nutrient supplements (LNS) containing 220-285 kcal (RR=0.80; 95%Crl: 0.66, 0.97) decreased the risk of stunting compared to
standard-of-care, but these interventions and other food supplements did not show improvements for HAZ. Deworming, maternal education, and WASH interventions did not show improvements for HAZ nor stunting.

**Conclusion:** While we found micronutrient and food supplements to be effective for HAZ and/or stunting, the evidence base for other domains in this life stage was limited, highlighting the need for more investigation.

**Registration:** PROSPERO CRD42018110449; registered on 17 October 2018.

**Keywords**
Complementary feeding, low- and middle-income countries, network meta-analysis, height-for-age, stunting, child development

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Introduction
Linear growth is a marker of healthy childhood progression, closely linked with neurodevelopment in early life. Despite global improvements in maternal, newborn, and child health (MNCH), the rate of children that fail to achieve their linear growth potential in low- and middle-income countries (LMICs) is high. Prevention of linear growth faltering, also known as stunting (low height for age), during the complementary feeding period (6 to 24 months of age) is critical, since stunting during this life stage can have immediate, short- and long-term consequences that are difficult to reverse. Continued malnutrition in children experiencing stunting can result in increased susceptibility and frequency to infections, as well as enhanced likelihood of cognitive, motor, and language impairment. In later life, stunted children may also experience reduced life chances such as poor academic performance that may affect future earnings and increased risk for chronic diseases, including obesity if accompanied by excessive weight gain in adulthood.

As children begin to wean off breastfeeding, there is a critical and continual need to ensure proper nutrition, hygiene, control of infectious diseases, and overall care during the complementary feeding period. Despite multiple factors playing a role in child’s linear growth, the majority of the reviews concerning linear growth for children during this life period in the past have focused on a single intervention domain (e.g. micronutrients) (Table 1). The comparative effectiveness of interventions is not clear across multiple domains, such as micronutrients, food supplements, deworming, maternal education, and water, sanitation, and hygiene (WASH) that could be important solutions to optimize linear growth during this life period. Additionally, all of the existing reviews have implemented a traditional pairwise meta-analysis that only allows for comparison between two interventions that have directly been compared head-to-head in clinical trials. Given that the majority of trials have used placebo or other comparators with limited clinical interest, the utility of pairwise meta-analysis can be limiting, particularly when assessing the broad sets of interventions that could be provided during the complementary feeding period.

Network meta-analysis, as an extension of conventional pairwise meta-analysis, allows for comparisons of interventions that have not been directly compared in head-to-head randomized clinical trials within a single analysis. While network meta-analysis is new to MNCH, this technique has been endorsed by the World Health Organization (WHO) to support the development of intervention guidelines in global health, with the past WHO guidelines on HIV drug and behavioral therapies and direct acting agents against hepatitis C having been formulated using network meta-analysis. This study uses a systematic review and network meta-analysis to determine the comparative effectiveness across intervention domains in micronutrient supplements, food supplements, deworming, maternal education, and WASH interventions on HAZ and stunting for children aged 6–24 months living in LMICs.

Methods
The protocol for this study was registered on PROSPERO (CRD42018110449). The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension to network meta-analysis.

Search strategy and selection criteria
Two-way sensitivity searches were conducted for this study. First, key MNCH articles, including Bhutta et al., and the Lancet 2013 umbrella review on evidence-based interventions, were reviewed for relevant systematic reviews and trials. A hand-search of the bibliography of Bhutta et al. was done to identify relevant systematic reviews and trials, and searches were done on PubMed and the Cochrane Database of Systematic Reviews to identify additional reviews that were published after 2013. The list of published reviews relevant to this study is provided in Table 1.

As the second step, a full comprehensive search of literature was conducted from database inception up to September 17, 2019. The Cochrane Central Register of Controlled Trials, Embase, and MEDLINE were searched to identify relevant trials and any additional relevant reviews that were missed in the prior step (search terms are provided in Extended data, Supplementary Tables 1, 2, and 3). Hand searches were done on the reference lists from the relevant reviews identified to improve the sensitivity of this study’s search.

Table 2 summarizes the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) criteria used to guide the study selection for our systematic literature review. In brief, randomized clinical trials that assessed interventions’ comparative effectiveness on HAZ and/or stunting (a HAZ score of less than 2 SDs below the WHO Child Growth Standards median) for children aged 6 to 24 months living in LMICs. The intervention domains of focus included: micronutrient supplements, food supplements, deworming, maternal education, and WASH interventions. Non-English-language studies were excluded. Four reviewers (JJHP, ES, LD, and NEZ) independently reviewed all abstracts and proceedings identified in the systematic search. The same reviewers independently conducted the full-text review. Any discrepancies were resolved by discussion, and if a resolution could not be achieved, a fifth reviewer (KT) settled the disagreements.

Using a standardized data sheet in Microsoft Excel, four investigators (JJHP, ES, LD, and NEZ) independently extracted data for study characteristics, interventions used, participants characteristics at baseline, and outcomes from the final subset of eligible studies. Any discrepancies observed during data extraction were resolved by consensus achieved through discussion.

Data analysis
The network meta-analyses for this study were done using the Bayesian framework in R via the R2WinBUGS v14 package. Bayesian models were performed according to...
**Table 1. Existing reviews on interventions for children aged 6 to 24 months.**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Title</th>
<th>Interventions domains</th>
<th>No of studies</th>
<th>Types of studies included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dangour 2013</td>
<td>Interventions to improve water quality and supply, sanitation and hygiene practices, and their effects on the nutritional status of children (Review)</td>
<td>WASH</td>
<td>14</td>
<td>RCTs, cluster-RCTs, quasi- and non-randomised trials, controlled cohort or cross-sectional studies and historically controlled studies</td>
</tr>
<tr>
<td>Darlow 2016</td>
<td>Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight infants (Review)</td>
<td>Micronutrient: Vitamin A</td>
<td>10</td>
<td>RCTs</td>
</tr>
<tr>
<td>Das 2013</td>
<td>Micronutrient fortification of food and its impact on woman and child health: a systematic review</td>
<td>Micronutrients</td>
<td>201</td>
<td>RCTs, quasi-experimental and before-after studies.</td>
</tr>
<tr>
<td>De-Regil 2011</td>
<td>Intermittent iron supplementation for improving nutrition and development in children under 12 years of age (Review)</td>
<td>Micronutrient: Iron (intermittent)</td>
<td>33</td>
<td>RCTs and quasi-RCTs with either individual or cluster randomisation</td>
</tr>
<tr>
<td>De-Regil 2013</td>
<td>Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age (Review)</td>
<td>Home fortification</td>
<td>8</td>
<td>RCTs or quasi-RCTs</td>
</tr>
<tr>
<td>Gaffey 2013</td>
<td>Dietary management of childhood diarrhea in low- and middle-income countries: a systematic review.</td>
<td>Diet for diarrhea management</td>
<td>29</td>
<td>RCTs</td>
</tr>
<tr>
<td>Gough 2014</td>
<td>The impact of antibiotics on growth in children in low and middle income countries: systematic review and meta-analysis of randomised controlled trials</td>
<td>Antibiotics</td>
<td>10</td>
<td>RCTs</td>
</tr>
<tr>
<td>Imdad 2011</td>
<td>Effect of preventive zinc supplementation on linear growth in children under 5 years of age in developing countries: a meta-analysis of studies for input to the lives saved tool</td>
<td>Micronutrient: Zinc</td>
<td>36</td>
<td>RCTs</td>
</tr>
<tr>
<td>Imdad 2017</td>
<td>Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age (Review)</td>
<td>Micronutrient: Vitamin A</td>
<td>45</td>
<td>RCTs, Cluster-RCTs</td>
</tr>
<tr>
<td>Kristjansson 2015</td>
<td>Food supplementation for improving the physical and psychosocial health of socio-economically disadvantaged children aged three months to five years</td>
<td>Food supplementation</td>
<td>26</td>
<td>RCTs and studies with historical controls</td>
</tr>
<tr>
<td>Lassi 2013</td>
<td>Impact of complementary food and education on complementary food on growth and morbidity of children less than 2 years of age in developing countries: a systematic review</td>
<td>Complementary foods</td>
<td>16</td>
<td>RCTs, nonrandomized trials</td>
</tr>
<tr>
<td>Matsunjo 2017</td>
<td>Lipid-based nutrient supplements and linear growth in children under 2 years: a review</td>
<td>Lipid supplements</td>
<td>7</td>
<td>RCTs</td>
</tr>
<tr>
<td>Mayo-Wilson 2014</td>
<td>Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age (Review)</td>
<td>Micronutrient: Zinc</td>
<td>80</td>
<td>RCTs</td>
</tr>
<tr>
<td>Pasricha 2013</td>
<td>Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials.</td>
<td>Micronutrient: Iron</td>
<td>35</td>
<td>RCTs</td>
</tr>
</tbody>
</table>
Table 2. Population, interventions, comparator, outcomes, and study design (PICOS) criteria.

<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children of age 6 to 24 months, living in low- and middle-income countries</td>
</tr>
<tr>
<td>Intervention</td>
<td>• Micronutrient &amp; calcium supplementation to children • Food supplementation to children • Deworming • Maternal education • Any water, sanitation and hygiene (WASH) intervention</td>
</tr>
<tr>
<td>Comparators</td>
<td>• Placebo • Standard-of-care (if applicable) • No intervention • Any of the interventions listed above as monotherapy or in combination that can be used for indirect comparison</td>
</tr>
<tr>
<td>Outcomes</td>
<td>At least one of the following outcomes (reported after at least 3 months): • Height for age z-score (HAZ) • Proportion of stunted (HAZ &lt; -2SD)</td>
</tr>
<tr>
<td>Study Design</td>
<td>Randomized clinical trials</td>
</tr>
<tr>
<td>Other</td>
<td>Published in the English language</td>
</tr>
</tbody>
</table>

The guideline of NICE Technical Support Document 2 (TSD2)\(^4\). Estimates of comparative effectiveness were measured using mean differences in HAZ with associated 95% credible intervals (95% CrI); and risk ratios (RRs) with associated 95% CrI for the stunting outcome. As heterogeneity was anticipated, random-effects network meta-analysis models were performed. In all models, an empirically informative heterogeneity prior distribution were used, as suggested by Rhodes et al.\(^4\) for continuous outcomes and Turner et al.\(^4\) for dichotomous outcome, to stabilize the estimation of heterogeneity in the face of low number of trials per comparison in the network. The model selection was informed by using the deviance information criterion (DIC) and the deviance-leverage plots that could help identify outlier(s) in terms of model fit, in accordance to the NICE TSD2 recommendations\(^4\). For both HAZ and stunting, the primary analysis included both cluster and non-cluster randomized clinical trials (with the unit of randomization performed at the individual level). To adjust for clustering effects of the cluster trials, a conservative intraclass correlation coefficient of 0.05 was assumed and used inflated variances accordingly for the continuous outcome, and adjusted the sample sizes and the number of cases for the dichotomous outcome, following the principles recommended by Uhlmann et al.\(^4\). Sensitivity analyses were
conducted for each outcome by using non-cluster randomized clinical trials only in the analyses. Full details of the statistical approaches are provided in the Extended data (Supplementary Table and figures file)\textsuperscript{18}.

Risk of bias within and across studies
Each full text article was evaluated for reporting quality according to the Cochrane Risk of Bias Tool\textsuperscript{45}. The risk of bias assessment within and across studies are provided in the Extended data (Supplementary Table 8)\textsuperscript{18}.

Results
A total of 20,511 abstracts was found from our database searches and hand searches of the bibliography of published reviews (Figure 1). Of these, 1,094 studies underwent a full-text review with 96 papers reporting on 79 trials that met the inclusion criteria. The list of included studies is provided in the Extended data (Supplementary Table 4 for included and Table 5 for the list of excluded studies)\textsuperscript{18}. Trial characteristics and participant characteristics of the included studies are provided in the Extended data, Supplementary Tables 6 and 7\textsuperscript{18}, respectively. In total, these trials comprised of 81,786 children who were randomized to 236 unique interventions (Figure 2). Of these trials, 22 were cluster trials with 2,990 clusters (53,057 children) randomized to 80 interventions. The majority of trials were conducted in African (n = 35) and South Eastern Asian (n = 25) countries with double blinding (i.e. blinding of participants and investigators; n = 40) being the most common blinding feature. Micronutrient supplementation was the most common intervention domain studied (n = 50 trials). Only a handful of these micronutrient trials compared interventions from other domains (food supplements: n = 11 trials\textsuperscript{46–56} and maternal education: n = 2 trial\textsuperscript{57,58}). There were four cluster trials on WASH (WASH Benefits Bangladesh\textsuperscript{59}, WASH Benefits Kenya\textsuperscript{60}, SHINE\textsuperscript{61}, and Shafique et al.\textsuperscript{62}), and these trials also included intervention arms that consisted of food supplements (i.e. LNS) or multiple micronutrients (i.e. MMN).

Height-for-age z-score (HAZ)
The network of evidence pertaining to the analysis of the outcome HAZ included 67 trials (69,223 children randomized to 220 intervention arms; Extended data, Supplementary Figure 1)\textsuperscript{18}. Of these, 16 were cluster trials that randomized 1,440 clusters (36,032 children) to 62 intervention arms. Key results of the primary analysis that included both cluster and non-cluster randomized clinical trials are illustrated using a forest plot (Figure 3). Among micronutrient supplementations,
iron + folic acid (IFA) (mean difference = 0.08; 95% CrI: 0.01, 0.15), and multiple micronutrients (MMN) (mean difference = 0.06; 95% CrI: 0.01, 0.11) showed improvements in HAZ in comparison to standard-of-care. Iron (mean difference = 0.03; 95% CrI: -0.02, 0.08) showed a trend towards HAZ improvement versus standard-of-care, but its credible intervals contained the null effect of 0. No food supplements showed improvements for HAZ versus standard-of-care. Similarly, no deworming interventions during the complementary feeding period or WASH interventions showed improvements in HAZ compared to standard-of-care.

Sensitivity analysis for HAZ

The network diagram of the sensitivity analysis restricted to non-cluster randomized clinical trials for HAZ is provided in the Extended data (Supplementary Crosstable and Supplementary Tables and Figures). In comparison to standard of care, IFA showed results highly consistent with the primary analysis (mean difference = 0.08; 95% CrI: 0.00, 0.16). MMN, on the other hand, did not show effectiveness over standard-of-care in the sensitivity analysis, but the trend was similar to the findings from the primary analysis (mean difference = 0.05; 95% CI: -0.03, 0.12). Similar to the primary analysis, no
deworming and food supplements showed improvements in HAZ in comparison to standard-of-care. No WASH interventions were available for the sensitivity analysis, as it was limited to non-cluster trials only.

**Stunting (HAZ < -2SD)**
The network of evidence for the primary analysis of the stunting outcome consisted of 20 trials with 40,193 children randomized to 77 intervention arms (Extended data, Supplementary Figure 3)\(^1\). Of these, 12 were cluster trials with 1,608 clusters (33,660 children) randomized to 50 intervention arms. A forest plot for the comparative effects of interventions on stunting (RRs) is provided in Figure 4. Among micronutrient supplements, MMN (RR: 0.86, 95% CrI: 0.73, 0.98) demonstrated superiority over standard-of-care, whereas IFA (RR: 0.92, 95% CrI: 0.64, 1.23) did not reduce the risks of stunting relative to standard-of-care; however, intake of Iron (RR: 0.91; 95% CrI: 0.76, 1.06) showed trend towards reducing risks for stunting. For food supplements, fortified lipid-based nutrient supplements (LNS) containing 220–285 kcal (RR: 0.80, 95% CrI: 0.66, 0.97) and flour containing 270 – 340 kcal (RR: 0.73, 95% CrI: 0.51, 1.00) showed reduced risks of stunting versus standard-of-care. Among other intervention domains, compared to standard-of-care, Maternal education also showed a trend towards decreasing the risks of stunting (RR: 0.91, 95% CrI: 0.75, 1.08); but no deworming or WASH interventions showed reduced risks for stunting except for WASH combined + fortified LNS containing 118 kilocalories that had showed a trend towards reducing the risks of stunting (RR: 0.91, 95% CrI: 0.73, 1.10).

**Sensitivity analysis for stunting**
The network diagram of the sensitivity analysis for stunting is provided in the Extended data (Supplementary Figure 4)\(^1\). The results of the sensitivity analyses are provided in the Extended data, Supplementary Cross-table file (tab: “Sensitivity, Stunting”)\(^1\). We found several interventions that showed either reduced risks for stunting or trends towards reduced

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**Figure 3. Forest plot for the effects of interventions on HAZ (mean difference), primary analysis.** Vit. vitamin; IFA, iron and folic acid; LNS, lipid-based nutrient supplements; Fort, fortification; MMN, multiple micronutrients; WASH, – water treatment, toilet facilities, and handwashing.
risks. For instance, relative to standard-of-care, MMN (RR: 0.78; 95% CrI: 0.59, 1.00) and fortified LNS 220–285 kcal (RR: 0.80; 95% CrI: 0.62, 1.00) showed reduced risks for stunting. Similarly, iron (RR: 0.89, 95% CrI: 0.74, 1.06) and flour 270–340 kcal (RR: 0.71; 95% CrI: 0.48, 1.02), showed trends towards reducing the risks of stunting versus standard-of-care, but their CrIs contained the null effect of 1. No deworming interventions showed reduced risks for stunting over standard-of-care. Similar to the sensitivity analysis for HAZ, no WASH interventions were available.

Discussion
In this study, systematic literature review and network meta-analysis were used to determine the comparative effectiveness of interventions for linear growth under the domains of micronutrients, food supplements, deworming, maternal education, and WASH interventions for LMIC-based children in the age group of 6 to 24 months. During the complementary feeding period life stage, micronutrient supplements such as IFA and MMN showed improvements for HAZ compared to standard-of-care, with iron showing some trends towards improved HAZ. Deworming, maternal education, food supplements, and WASH interventions, on the other hand, did not show improvements in HAZ versus standard-of-care. For stunting, food supplements of fortified LNS 220–280 kcal and flour 270–340 kcal showed reduced risks of stunting, with other interventions such as iron, MMN, and MMN combined with maternal education, demonstrating trends towards reduced stunting risks, in comparison to standard-of-care.

The key strengths of this study were the consideration of multiple intervention domains and the use of network meta-analysis. The approach undertaken for this study differed from previous reviews (Table 1) that have had limited scopes of single intervention or single intervention domains; these reviews have all used pairwise meta-analysis, thus being limited to
trials and interventions that have only been directly compared to one another. The use of network meta-analysis allowed for consideration of a broader evidence base to estimate the comparative effectiveness of multiple interventions under multiple treatment domains. By incorporating statistical adjustments for clustering effects, this study was able to incorporate cluster randomized clinical trials that mostly did not report information on clustering effects (i.e. ICC or design effects) into the statistical analyses.

Nonetheless, the existing evidence base limited our analyses. The majority of the randomized clinical trial evidence base was confined to the micronutrient supplementation domain (n = 50), and the evidence base for intervention domains for food supplements, deworming, maternal education, and WASH being limited. This imbalance in intervention class could partly be explained by the narrow bounds in the population criterion (i.e. the age criteria of 6 to 24 months) of our PICOS criteria. For instance, there were a number of trials that recruited children using a wider age eligibility criterion (e.g. 6 months up to 5 years of age) that encompassed children in the complementary feeding life stage, but these trials were excluded since growth rates and determinants of children older than 24 months are different than children in the complementary feeding period age group. While this age restriction limited the number of eligible trials for our analysis, it is important to note that the population criteria was determined a priori before the screening was initiated for this systematic review since we recognized that growth determinants and rates can vary substantially for children between these ages.41

This study has shown that the existing evidence base on interventions aimed to improve linear growth in children during the complementary feeding period is limited and inconsistent. Generally, investigation of interventions outside of the domain of micronutrient supplements was limited. There were only two trials on deworming41,46 and four WASH trials, reporting on linear growth outcomes in our analyses. There were eight trials under the maternal education domains, but the components and the delivery of these educational interventions varied considerably between these trials. For food supplement trials, poor adherence and household food insecurity may promote family sharing could influence why these interventions did not show improvements in linear growth. Moreover, the food supplements in these trials were all based on a single type of food, so children may have refused to consume as they have become tired of consuming same type of food over time. There were no trials that investigated nutritional strategies that aimed to improve dietary diversity in order to improve linear growth in children during this life stage, nor were there any trials that aimed to address household food insecurity.

A previous report from Bangladesh has shown that the taste of LNS is generally acceptable, and at least in shorter-term, adherence to LNS was high and sharing of these food supplements could be minimized in the household.3 However, acceptability and adherence to LNS in other settings are not clear; the long-term acceptability and adherence to LNS or other types of food supplements that consist of a single food on daily basis over long-term are also questionable. Additionally, our analysis did not show that supplementing children with high caloric food supplements result in improved linear growth when compared to standard of care or to other lower caloric food supplements. Aside from previously described issues associated with tolerability of nutritional supplementation that may be exacerbated by high caloric formulations, it is possible that in households with food insecurity, caregivers may choose to share these supplements with other children or members of the household who are not enrolled in the trial. Understanding compliance and the influence that this may have on our analyses was not possible, as we found that compliance was usually not measured or reported in the included food supplement trials.72–76

Our findings identified several directions for future research. There is a need to combine interventions across multiple domains as a package. Instead of singling out interventions from one domain, there is a need for comparisons between different packaged interventions because a combined set of interventions will likely result in the greatest improvements in linear growth. Strategies should consider local contexts and challenges. The feasibility of conducting trials that incorporate food supplement strategies aimed to improve dietary diversity and address household food insecurities is undoubtedly difficult. However, it is important to recognize these factors will be important for long-term acceptability and adherence to food interventions, and interventional strategies that incorporate diverse local foods will have higher acceptability and adherence in the long run. Trials with longer follow-up are also needed, as the median follow-up among the trials included for this review was only 6 months. Lastly, there is a need for more innovative trial approaches.77 The majority of the trials identified for this review used a conventional trial approach with a fixed sample size design, where the assessment of interventions occurred only after the number of participants recruited reached the sample size target. It is important to recognize that such approach can be inefficient, and adopting adaptive trial design approaches that allow for pre-specified modifications, with the decision being made based on accumulating trial data may improve both the efficiencies of the trial evaluation in this avenue of research.78

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Extended data
This project contains the following extended data:

- Complementary feeding period NMA - Supplementary Tables and Figures - v2.0
  - Appendix 1. Literature search. (Contains Supplementary Tables 1–3.)
  - Appendix 2. List of included and excluded studies after full-text review. (Contains Supplementary Tables 4 and 5.)
  - Appendix 3. Details of the evidence base. (Contains Supplementary Tables 6 and 7.)
  - Appendix 4. Network for HAZ (Contains Supplementary Figures 1 and 2.)
  - Appendix 5. Network for stunting outcome. (Contains Supplementary Figures 3–9.)

- Complementary feeding period NMA - Supplementary Crosstable - v1.0

Reporting Guidelines


Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

References


Open Peer Review

Current Peer Review Status: ? ✔

Version 1

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In addition to the feedback provided by the other reviewer, we have a few comments for the study author’s consideration.

The study presented was well conducted, with detailed methods provided in the Supplementary Appendices (SA) demonstrating the rigour of the author’s approach. In addition, the registration of the study protocol on PROSPERO and adherence to the PRISMA statement is a strength of the study.

The broad research question, with wide-ranging interventions, led to a high volume of evidence being identified. As noted by the authors, the interventions grouped by domain in this analysis would benefit from an analysis based on individual interventions.

For reproducibility purposes, the manuscript would benefit from clarifying the unexplained discrepancies in the number of trials reported in the SA tables. The PRISMA diagram (Figure 1) states 96 papers were included, representing 79 trials. However, SA Table 4 (list of included studies) lists 91 trials, SA Table 6 (trial characteristics) lists 77 trials, SA Table 7 (patient characteristics) lists 99 trials and SA Table S8 (risk of bias) lists 72 trials. In addition, the asterisk in Figure 3 and 4 should be explained. Finally, in Figure 4 there also appears to be two values of one represented on the x-axis.

Furthermore, given the large volume of evidence reviewed, the GRADE assessment would be useful to rate the certainty of evidence included in this SLR/NMA. The authors should mention the results of their risk of bias assessment for the included trials to elucidate any biases that might be contributing to the heterogeneity or inform future study designs.
As detailed in the SA, the authors may also want to state whether or not it was feasible to conduct any meta-regression or subgroup analyses based on effect modifiers in the main manuscript. This would provide the reader with a sense of what might be the source of the heterogeneity and inform future research in this field. Similarly, with mean differences as an outcome, the length of follow-up time may be a source of heterogeneity and no data on the follow-up time is noted in the main manuscript, but it may enhance the interpretation for the reader. Finally, a brief statement on assessing model convergence and inconsistency in the NMA would be informative in the main manuscript for more technical readers. Overall, the statistical methods of the study were robust and thoroughly reported in the SA document.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**
Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**
Yes

**Is the statistical analysis and its interpretation appropriate?**
Yes

**Are the conclusions drawn adequately supported by the results presented in the review?**
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Systematic literature review and network meta-analysis.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
LAZ)?

2. It would be useful to comment on the clinical relevance of these findings. What would be the expected population level impact on developmental outcomes or survival based on these effect sizes?

3. The authors adhered to the PRISMA guidelines, which is excellent. However, there are few unclear issues with the methods. It appears that the authors searched reviews but then abstracted individual trials? Did the search also focus on individual trials or where these only identified through reviews? If individual trials were included, then these should be listed.

4. Is it possible to include the $I^2$ with the forest plots?

5. I am concerned by the blanket use of am ICC of 0.05. Would it not be preferable to estimate the ICC for each individual study based on similar studies in that environment or with a similar design effect? Perhaps categorizing into 5 different ICCs that could be applied to each? At the very least, it would be useful to conduct a sensitivity analysis where the ICC is varied.

6. The authors note that flour appeared to have an effect on stunting. However, the 95% CI includes 1.0. Should this be considered a significant finding?

7. Some of the grammar in the manuscript could be improved, particularly in the abstract. Please edit for grammar.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Partly

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** infectious disease, nutrition, trials in LMIC settings

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.