






SYSTEMATIC REVIEW

REVISED 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 2; peer review: 3 approved]

Jay J. H. Park^{1,2}, Ofir Harari², Ellie Siden^{1,2}, Louis Dron², Noor-E Zannat², Joel Singer^{3,4}, Richard T. Lester ¹, Kristian Thorlund ^{1,5}, Edward J. Mills ^{1,5}

¹Experimental Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, V6T 1Z3, Canada

²MTEK Sciences, Vancouver, BC, V5Z1J5, Canada

³School of Population and Public Health, University of British Columbia, Vancouver, BC, V6T 1Z3, Canada

⁴Data and Methodology Program, CIHR Canadian HIV Trials Network, Vancouver, BC, V6Z 1Y6, Canada

⁵Department of Health Research Methodology, Evidence, and Impact, McMaster University, Hamilton, ON, L8S 4K1, Canada

v2 First published: 14 Nov 2019, 3:1660
<https://doi.org/10.12688/gatesopenres.13083.1>
 Latest published: 24 Sep 2020, 3:1660
<https://doi.org/10.12688/gatesopenres.13083.2>

Abstract



Background: Optimizing linear growth in children during complementary feeding period (CFP) (6-24 months) is 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 are 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 [CrI]: 0.01, 0.15) and multiple micronutrients (MMN) (mean difference =0.06; 95%CrI: 0.01, 0.11) showed improvements for HAZ; MMN also reduced the risks for stunting (RR=0.86; 95%CrI: 0.73, 0.98), whereas IFA did not (RR=0.92; 95%CrI: 0.64, 1.23). For food supplements, flour in the caloric range of

Open Peer Review

Reviewer Status 

	Invited Reviewers		
	1	2	3
version 2 (revision) 24 Sep 2020	 report		
	↑		
version 1 14 Nov 2019	 report	 report	 report

- Judd L. Walson** , University of Washington, Seattle, USA
- Tara Cowling** , Medlior Health Outcomes Research Ltd, Calgary, Canada
Kelly Larkin-Kaiser, Medlior Health Outcomes Research Ltd, Calgary, Canada
Tayler Scory, Medlior Health Outcomes Research Ltd, Calgary, Canada

270-340 kcal (RR=0.73; 95%CrI: 0.51, 1.00) and fortified lipid-based nutrient supplements (LNS) containing 220-285 kcal (RR=0.80; 95%CrI: 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](https://doi.org/10.1186/1745-2975-449); registered on 17 October 2018.

Keywords

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

Megan Farris, Medlior Health Outcomes Research Ltd, Calgary, Canada

3. **Kenneth Maleta** , University of Malawi, Blantyre, Malawi

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Edward J. Mills (emills@mtksciences.com)

Author roles: **Park JJH:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Harari O:** Formal Analysis, Methodology, Project Administration, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Siden E:** Data Curation, Project Administration, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Dron L:** Data Curation, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Zannat NE:** Data Curation, Project Administration, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Singer J:** Formal Analysis, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Review & Editing; **Lester RT:** Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Review & Editing; **Thorlund K:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Mills EJ:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This study was supported by the Bill & Melinda Gates Foundation (Contract Number: 52565).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2020 Park JJH *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Park JJH, Harari O, Siden E *et al.* **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 2; peer review: 3 approved]** Gates Open Research 2020, 3:1660 <https://doi.org/10.12688/gatesopenres.13083.2>

First published: 14 Nov 2019, 3:1660 <https://doi.org/10.12688/gatesopenres.13083.1>

REVISED Amendments from Version 1

Abstract - grammar has been edited in background section.

Methods section - reported average value of ICC and provided more explanation regarding bias of studies.

Figures - explanations updated for [Figure 3](#) and [Figure 4](#). Horizontal axis amended for [Figure 4](#).

Discussion section - Added more limitations of the paper (Paragraph 3 and 4).

New Supplementary data uploaded - Supplementary Table 4 updated to include 96 studies; Supplementary Table 7 has been updated to reflect 78 trials; Supplementary Table 8 has been updated to reflect 77 trials. Revised link provided under Extended data section.

Reference section - reference no. 18 has been updated to include a revised link for supplementary data file.

Any further responses from the reviewers can be found at the end of the article

Introduction

Linear growth is a marker of healthy childhood progression, closely linked with neurodevelopment in early life¹. 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 high². 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 reverse³⁻⁵. 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^{2,6}. 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^{5,7-9}.

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^{10,11}. 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 health¹¹, with the past WHO guidelines on HIV drug and behavioral therapies and direct acting agents against hepatitis C having been formulated using network meta-analysis¹²⁻¹⁴. 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-analysis¹⁵.

Search strategy and selection criteria

Two-way sensitivity searches were conducted for this study. First, key MNCH articles, including [Bhutta *et al.*¹⁶](#), and the Lancet 2013 umbrella review on evidence-based interventions^{2,17}, were reviewed for relevant systematic reviews and trials. A hand-search of the bibliography of [Bhutta *et al.*¹⁶](#) 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](#))¹⁸. 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)¹⁹ 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

Table 1. Existing reviews on interventions for children aged 6 to 24 months.

Study ID	Title	Interventions domains	No of studies	Types of studies included
Dangour 2013 ²⁰	Interventions to improve water quality and supply, sanitation and hygiene practices, and their effects on the nutritional status of children (Review)	WASH	14	RCTs, cluster-RCTs, quasi- and non-randomised trials, controlled cohort or cross-sectional studies and historically controlled studies
Darlow 2016 ²¹	Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight infants (Review)	Micronutrient: Vitamin A	10	RCTs
Das 2013 ²²	Micronutrient fortification of food and its impact on woman and child health: a systematic review	Micronutrients	201	RCTs, quasi-experimental and before-after studies.
De-Regil 2011 ²³	Intermittent iron supplementation for improving nutrition and development in children under 12 years of age (Review)	Micronutrient: Iron (intermittent)	33	RCTs and quasi-RCTs with either individual or cluster randomisation
De-Regil 2013 ²⁴	Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age (Review)	Home fortification	8	RCTs or quasi-RCTs
Devakumar 2016 ²⁵	Maternal antenatal multiple micronutrient supplementation for long-term health benefits in children: a systematic review and meta-analysis.	Micronutrient: MMS	9	RCTs, cluster-RCTs
Gaffey 2013 ²⁶	Dietary management of childhood diarrhea in low- and middle-income countries: a systematic review.	Diet for diarrhea management	29	RCTs
Gough 2014 ²⁷	The impact of antibiotics on growth in children in low and middle income countries: systematic review and meta-analysis of randomised controlled trials	Antibiotics	10	RCTs
Imdad 2011 ²⁸	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	Micronutrient: Zinc	36	RCTs
Imdad 2017 ²⁹	Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age (Review)	Micronutrient: Vitamin A	45	RCTs, Cluster-RCTs
Kristjansson 2015 ³⁰	Food supplementation for improving the physical and psychosocial health of socio-economically disadvantaged children aged three months to five years	Food supplementation	26	RCTs and studies with historical controls
Lassi 2013 ³¹	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	Complementary foods	16	RCTs, nonrandomized trials
Matsungu 2017 ³²	Lipid-based nutrient supplements and linear growth in children under 2 years: a review	Lipid supplements	7	RCTs
Mayo-Wilson 2014 ³³	Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age (Review)	Micronutrient: Zinc	80	RCTs

Study ID	Title	Interventions domains	No of studies	Types of studies included
Pasricha 2013 ³⁴	Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials.	Micronutrient: Iron	35	RCTs
Petry 2016 ³⁵	The Effect of Low Dose Iron and Zinc Intake on Child Micronutrient Status and Development during the First 1000 Days of Life: A Systematic Review and Meta-Analysis.	Micronutrient: Iron + zinc	90	RCTs or quasi-RCTs
Salam 2013 ³⁶	Effectiveness of micronutrient powders (MNP) in women and children	Micronutrient: Micronutrient powders	17	RCTs
Sguaseero 2012 ³⁷	Community-based supplementary feeding for promoting the growth of children under five years of age in low and middle income countries (Review)	Community-based supplementary feeding	8	RCTs
Taylor-Robinson 2015 ³⁸	Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin and school performance (Review)	Deworming	45	RCTs or quasi-RCTs

Table 2. Population, interventions, comparator, outcomes, and study design (PICOS) criteria.

Category	Inclusion criteria
Population	Children of age 6 to 24 months, living in low- and middle-income countries
Intervention	<ul style="list-style-type: none"> • Micronutrient & calcium supplementation to children • Food supplementation to children • Deworming • Maternal education • Any water, sanitation and hygiene (WASH) intervention
Comparators	<ul style="list-style-type: none"> • 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
Outcomes	At least one of the following outcomes (reported after at least 3 months): <ul style="list-style-type: none"> • Height for age z-score (HAZ) • Proportion of stunted (HAZ < -2SD)
Study Design	Randomized clinical trials
Other	Published in the English language

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, participant 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^{39,40}. Bayesian models were performed according to the guideline of NICE Technical Support Document 2 (TSD2)⁴¹. 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.*⁴² for continuous outcomes and Turner *et al.*⁴³ 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 recommendations⁴¹.

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). Within the cluster trials included in our network meta-analysis, an average value of ICC of 0.0505 was reported. Thus, in order to adjust for clustering effects of the cluster trials, a

conservative intracluster correlation coefficient of 0.05 was assumed and we 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.*⁴⁴ 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)¹⁸.

Risk of bias within and across studies

Each full text article was evaluated for reporting quality according to the Cochrane Risk of Bias Tool⁴⁵. Bias was evaluated using the Cochrane Risk of Bias tool in the areas of selection, performance, detection, attrition, reporting, and other sources of bias. Over 60% of the studies exhibited low bias in terms of attrition, selection, and reporting bias. Sources of detection and performance bias were unclear in about 25–30% of the studies. The risk of bias assessment within and across studies are provided in the *Extended data* (Supplementary Table 8)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

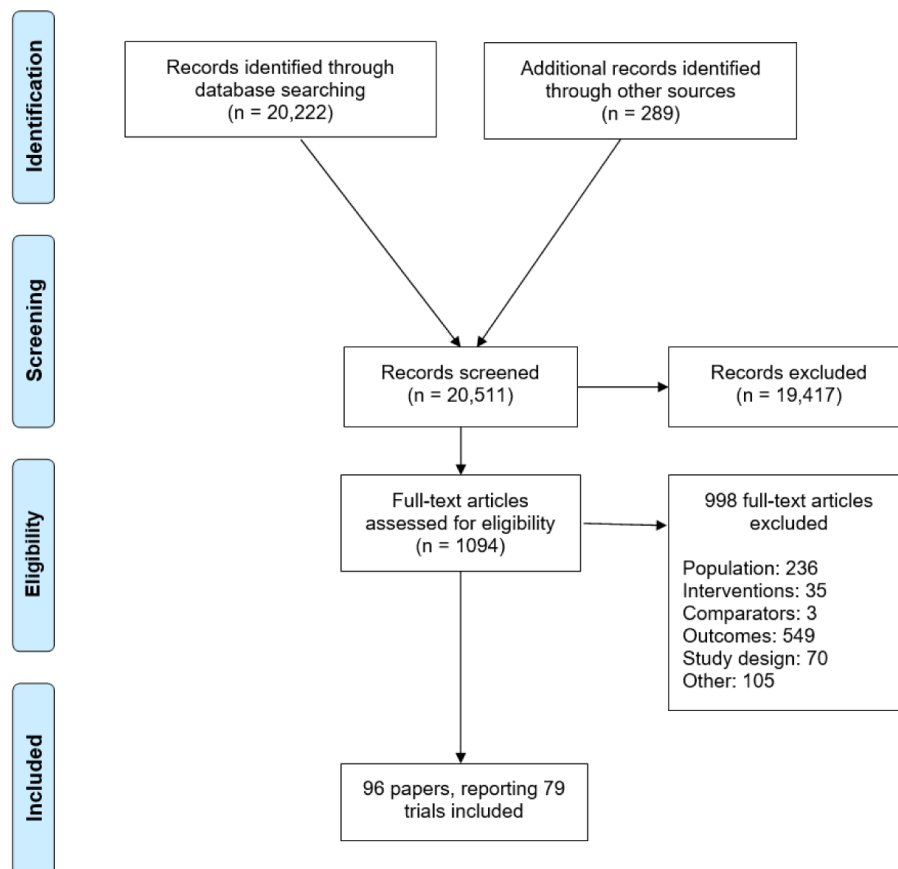


Figure 1. Study selection.

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)¹⁸. Trial characteristics and participant characteristics of the included studies are provided in the *Extended data*, Supplementary Tables 6 and 7¹⁸, 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^{46–56} and maternal education: n = 2 trial^{57,58}). There were four cluster trials on WASH (WASH Benefits Bangladesh⁵⁹, WASH Benefits Kenya⁶⁰, SHINE⁶¹, and Shafique *et al.*⁶²), and these trials also included intervention arms that consisted of food supplements (i.e. LNS) or multiple micronutrients (i.e. MMN).

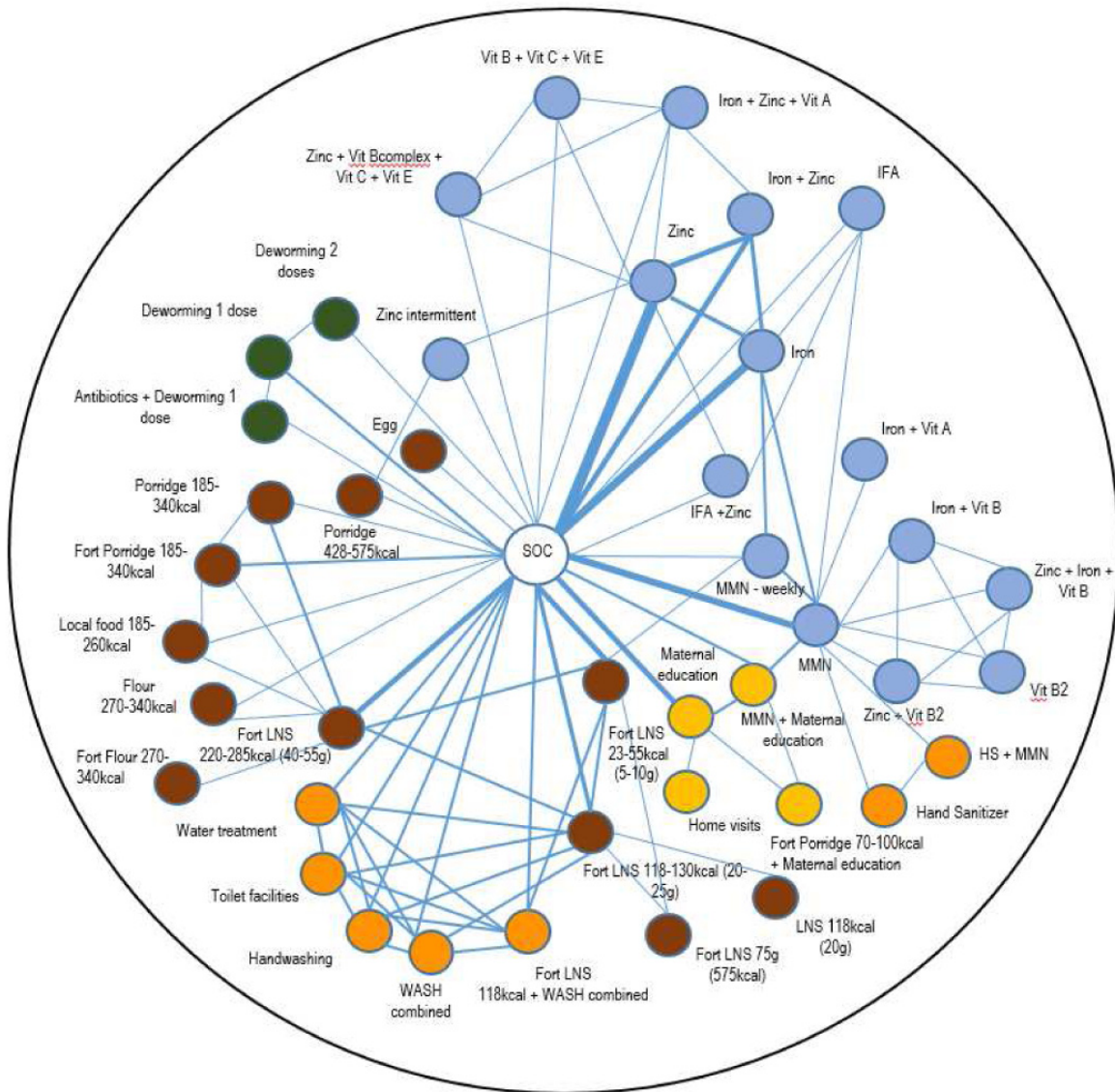


Figure 2. Overall network of the comparisons between interventions for children aged 6 to 24 months. Each node (circle) represents an intervention, each line represents a direct comparison between interventions, with the lines with width representing the number of trials with the direct comparisons in question (i.e. thicker width represents a direct comparison with larger numbers of trials). The different intervention domains are indicated with the following colors: blue for micronutrient supplements; brown for food supplements; yellow for education and counseling interventions; green for deworming interventions; and orange for WASH interventions. Vit. vitamin; IFA, iron and folic acid; LNS, lipid-based nutrient supplements; Fort, fortification; MMN, multiple micronutrients; HS, hand sanitizer.

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)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)¹⁸. 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% CrI: -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.

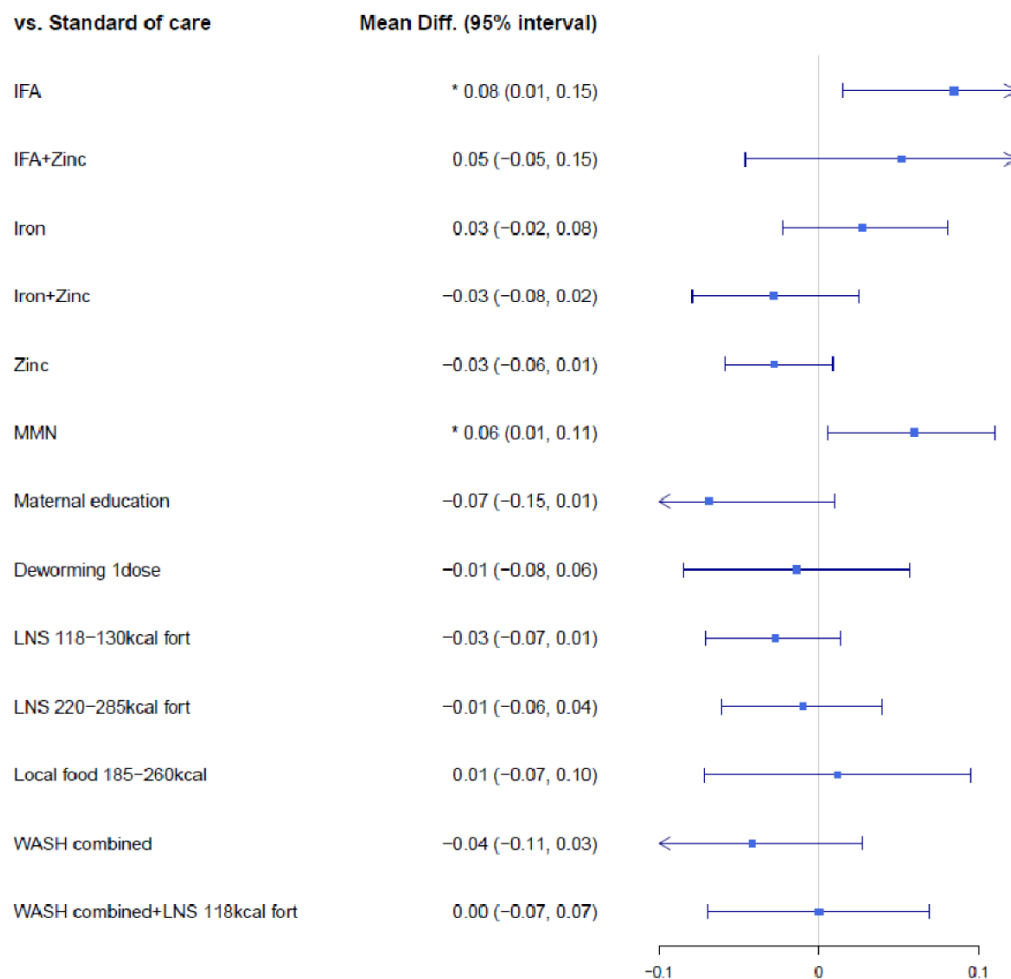


Figure 3. Forest plot for the effects of interventions on HAZ (mean difference), primary analysis. Vit. vitamin; IFA, iron and folic acid; LNS, lipid-based nutrient supplements; Fort, fortification; MMN, multiple micronutrients; WASH, – water treatment, toilet facilities, and handwashing. * Denotes mean difference values that do not contain the null effect of 0.

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)¹⁸. 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)¹⁸. The results of the sensitivity analyses are provided in the *Extended data*, Supplementary Cross-table file (tab: “Sensitivity, Stunting”)¹⁸. We found several interventions that showed either reduced risks for stunting or trends towards reduced risks. For instance, relative to standard-of-care, MMN (RR: 0.78;

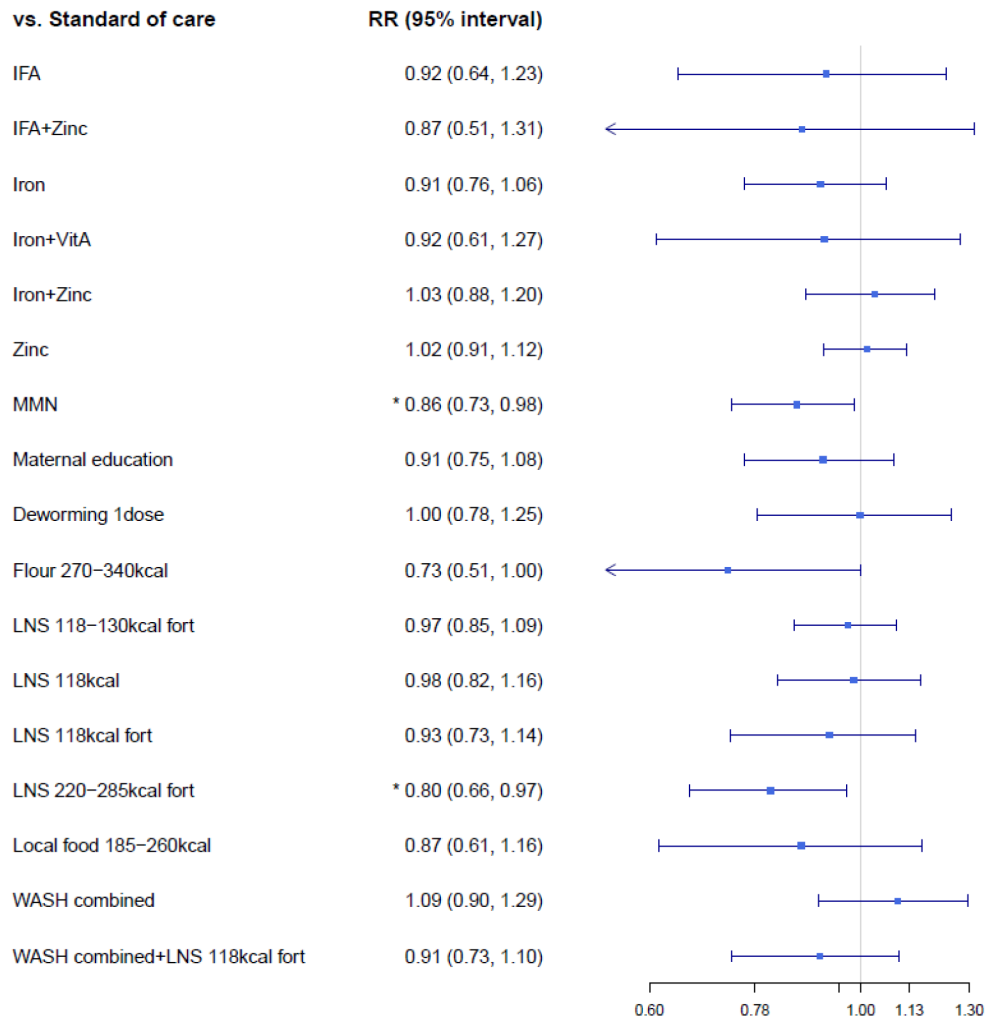


Figure 4. Forest plot for the effects of interventions on stunting (risk ratio), primary analysis. Vit. vitamin; IFA, iron and folic acid; LNS, lipid-based nutrient supplements; Fort, fortification; MMN, multiple micronutrients; WASH, – water treatment, toilet facilities, and handwashing. * Denotes values of risk ratio that do not contain the null effect of 1.

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 ages⁶³. Another limitation related to our categorisation of interventions is that we combined interventions into broad categories to assist with interpretation and acknowledge that a different approach to categorisation might have altered the results.

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 deworming^{64,65} and four WASH trials^{59–62} reporting on linear growth outcomes in our analyses. There were eight trials under the maternal education domains^{57,58,62,66–70}, 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 that 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. It is also important to note that there was randomness in the data as well as substantial heterogeneity observed in the duration of the interventions and the timing of outcome assessments that can be attributed to the variation in impact on HAZ and stunting.

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 household⁷¹. 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 approaches⁷⁷. 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 research⁷⁸.

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

Open Science Framework: 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. <https://doi.org/10.17605/OSF.IO/DTZK7>¹⁸.

This project contains the following extended data:

- Complementary feeding period NMA - Supplementary Tables and Figures - v3.0
 - 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

Open Science Framework: PRISMA checklist for “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.” <https://doi.org/10.17605/OSF.IO/DTZK7>¹⁸.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

Author contributions

JJHP, KT, and EJM conceptualized and designed the study. JJHP, OH, ES, LD, NEZ, JS, RTL, KT, and EJM acquired, analyzed, and interpreted data. JJHP drafted the manuscript. All authors critically revised the manuscript for important intellectual content. JJHP, OH, KT, and EJM did the statistical analysis. EJM obtained funding. JS, RTL, KT and EJM provided administrative, technical, or material support. JS, RTL, KT, and EJM supervised the study. KT and EJM had full access of all of the data in the study. EJM was responsible for the integrity of the data, accuracy of the data analysis, and the final decision to submit for publication.

References

1. Suchdev PS, Boivin MJ, Forsyth BW, *et al.*: **Assessment of Neurodevelopment, Nutrition, and Inflammation From Fetal Life to Adolescence in Low-Resource Settings.** *Pediatrics.* 2017; **139**(Suppl 1): S23–S37. [PubMed Abstract](#) | [Publisher Full Text](#)
2. Black RE, Victora CG, Walker SP, *et al.*: **Maternal and child undernutrition and overweight in low-income and middle-income countries.** *Lancet.* 2013; **382**(9890): 427–51. [PubMed Abstract](#) | [Publisher Full Text](#)
3. de Onis M, Branca F: **Childhood stunting: a global perspective.** *Matern Child Nutr.* 2016; **12** Suppl 1: 12–26. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. Stewart CP, Iannotti L, Dewey KG, *et al.*: **Contextualising complementary feeding in a broader framework for stunting prevention.** *Matern Child Nutr.* 2013; **9** Suppl 2: 27–45. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Mendez MA, Adair LS: **Severity and timing of stunting in the first two years**

- of life affect performance on cognitive tests in late childhood. *J Nutr.* 1999; **129**(8): 1555–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Dewey KG, Mayers DR: **Early child growth: how do nutrition and infection interact?** *Matern Child Nutr.* 2011; **7** Suppl 3: 129–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 7. Perkins JM, Subramanian SV, Davey Smith G, et al.: **Adult height, nutrition, and population health.** *Nutr Rev.* 2016; **74**(3): 149–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 8. Kolđić I: **Double burden of malnutrition: A silent driver of double burden of disease in low- and middle-income countries.** *J Glob Health.* 2012; **2**(2): 020303.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 9. McGovern ME, Krishna A, Aguayo VM, et al.: **A review of the evidence linking child stunting to economic outcomes.** *Int J Epidemiol.* 2017; **46**(4): 1171–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 10. Mills EJ, Thorlund K, Ioannidis JP: **Demystifying trial networks and network meta-analysis.** *BMJ.* 2013; **346**: f2914.
[PubMed Abstract](#) | [Publisher Full Text](#)
 11. Kanters S, Ford N, Druyts E, et al.: **Use of network meta-analysis in clinical guidelines.** *Bull World Health Organ.* 2016; **94**(10): 782.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 12. Kanters S, Vitoria M, Doherty M, et al.: **Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis.** *Lancet HIV.* 2016; **3**(11): e510–e20.
[PubMed Abstract](#) | [Publisher Full Text](#)
 13. World Health Organization: **Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations 2016 update.** World Health Organization; 2016.
[Reference Source](#)
 14. World Health Organization: **Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection.** World Health Organization; 2016.
[Reference Source](#)
 15. Hutton B, Salanti G, Caldwell DM, et al.: **The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations.** *Ann Intern Med.* 2015; **162**(11): 777–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
 16. Bhutta ZA, Das JK, Rizvi A, et al.: **Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost?** *Lancet.* 2013; **382**(9890): 452–77.
[PubMed Abstract](#) | [Publisher Full Text](#)
 17. Ruel MT, Alderman H, Maternal and Child Nutrition Study Group: **Nutrition-sensitive interventions and programmes: how can they help to accelerate progress in improving maternal and child nutrition?** *Lancet.* 2013; **382**(9891): 536–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
 18. Park JJ, Harari O, Siden E, et al.: **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.** 2019.
<http://www.doi.org/10.17605/OSF.IO/DTZK7>
 19. World Health Organization: **Child growth standards: length/height-for-age.** (accessed Aug 15 2017). 2015.
[Reference Source](#)
 20. Dangour AD, Watson L, Cumming O, et al.: **Interventions to improve water quality and supply, sanitation and hygiene practices, and their effects on the nutritional status of children.** *Cochrane Database Syst Rev.* 2013; **(8)**: CD009382.
[PubMed Abstract](#) | [Publisher Full Text](#)
 21. Darlow BA, Graham PJ, Rojas-Reyes MX: **Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight infants.** *Cochrane Database Syst Rev.* 2016; **2016**(8): CD000501.
[PubMed Abstract](#) | [Publisher Full Text](#)
 22. Das JK, Salam RA, Kumar R, et al.: **Micronutrient fortification of food and its impact on woman and child health: a systematic review.** *Syst Rev.* 2013; **2**: 67.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 23. De-Regil LM, Jefferds ME, Sylvetsky AC, et al.: **Intermittent iron supplementation for improving nutrition and development in children under 12 years of age.** *Cochrane Database Syst Rev.* 2011; **2011**(12): CD009085.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 24. De-Regil LM, Suchdev PS, Vist GE, et al.: **Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age (Review).** *Evid Based Child Health.* 2013; **8**(1): 112–201.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Devakumar D, Fall CH, Sachdev HS, et al.: **Maternal antenatal multiple micronutrient supplementation for long-term health benefits in children: a systematic review and meta-analysis.** *BMC Med.* 2016; **14**: 90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 26. Gaffey MF, Wazny K, Bassani DG, et al.: **Dietary management of childhood diarrhea in low- and middle-income countries: a systematic review.** *BMC Public Health.* 2013; **13** Suppl 3: S17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 27. Gough EK, Moodie EE, Prendergast AJ, et al.: **The impact of antibiotics on growth in children in low and middle income countries: systematic review and meta-analysis of randomised controlled trials.** *BMJ.* 2014; **348**: g2267.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 28. Imdad A, Bhutta ZA: **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.** *BMC Public Health.* 2011; **11** Suppl 3: S22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 29. Imdad A, Mayo-Wilson E, Herzer K, et al.: **Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age.** *Cochrane Database Syst Rev.* 2017; **3**(3): CD008524.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 30. Kristjansson E, Francis DK, Liberato S, et al.: **Food supplementation for improving the physical and psychosocial health of socio-economically disadvantaged children aged three months to five years.** *Cochrane Database Syst Rev.* 2015; **2015**(3): CD009924.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Lassi ZS, Das JK, Zahid G, et al.: **Impact of education and provision of complementary feeding on growth and morbidity in children less than 2 years of age in developing countries: a systematic review.** *BMC Public Health.* 2013; **13**(Suppl 3): S13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 32. Matsungu TM, Kruger HS, Smuts CM, et al.: **Lipid-based nutrient supplements and linear growth in children under 2 years: a review.** *Proc Nutr Soc.* 2017; **76**(4): 580–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 33. Mayo-Wilson E, Junior JA, Imdad A, et al.: **Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age.** *Cochrane Database Syst Rev.* 2014; **(5)**: CD009384.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Pasricha SR, Hayes E, Kalumba K, et al.: **Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials.** *Lancet Glob Health.* 2013; **1**(2): e77–e86.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. Petry N, Olofin I, Boy E, et al.: **The Effect of Low Dose Iron and Zinc Intake on Child Micronutrient Status and Development during the First 1000 Days of Life: A Systematic Review and Meta-Analysis.** *Nutrients.* 2016; **8**(12): pii: E773.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 36. Salam RA, MacPhail C, Das JK, et al.: **Effectiveness of Micronutrient Powders (MNP) in women and children.** *BMC Public Health.* 2013; **13**(Suppl 3): S22.
[PubMed Abstract](#) | [Free Full Text](#)
 37. Squassero Y, de Onis M, Bonotti AM, et al.: **Community-based supplementary feeding for promoting the growth of children under five years of age in low and middle income countries.** *Cochrane Database Syst Rev.* 2012; **(6)**: CD005039.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. Taylor-Robinson DC, Maayan N, Soares-Weiser K, et al.: **Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin, and school performance.** *Cochrane Database Syst Rev.* 2015; **(7)**: CD000371.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 39. R Development Core Team: **R: A Language Environment for Statistical Computing.** In: Team RC editor. Vienna, Austria: R Foundation for Statistical Computing; 2017.
[Reference Source](#)
 40. Sturtz S, Ligges U, Gelman A: **R2OpenBUGS: a package for running OpenBUGS from R.** *J Stat Softw.* 2005; **12**(3): 1–16.
[Reference Source](#)
 41. Dias S, Sutton AJ, Ades AE, et al.: **Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials.** *Med Decis Making.* 2013; **33**(5): 607–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 42. Rhodes KM, Turner RM, White IR, et al.: **Implementing informative priors for heterogeneity in meta-analysis using meta-regression and pseudo data.** *Stat Med.* 2016; **35**(29): 5495–511.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 43. Turner RM, Jackson D, Wei Y, et al.: **Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis.** *Stat Med.* 2015; **34**(6): 984–98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 44. Uhlmann L, Jensen K, Kieser M: **Bayesian network meta-analysis for cluster randomized trials with binary outcomes.** *Res Synth Methods.* 2017; **8**(2): 236–50.
[PubMed Abstract](#) | [Publisher Full Text](#)

45. Higgins JP, Thomas J, Chandler J, *et al.*: **Cochrane Handbook for Systematic Reviews of Interventions version 6.0.** Cochrane Reviews; 2019. [Reference Source](#)
46. Skau JK, Touch B, Chhoun C, *et al.*: **Effects of animal source food and micronutrient fortification in complementary food products on body composition, iron status, and linear growth: a randomized trial in Cambodia.** *Am J Clin Nutr.* 2015; **101**(4): 742–51. [PubMed Abstract](#) | [Publisher Full Text](#)
47. Iannotti LL, Dulience SJ, Green J, *et al.*: **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. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Rivera JA, González-Cossio T, Flores M, *et al.*: **Multiple micronutrient supplementation increases the growth of Mexican infants.** *Am J Clin Nutr.* 2001; **74**(5): 657–63. [PubMed Abstract](#) | [Publisher Full Text](#)
49. Krebs NF, Mazariegos M, Chomba E, *et al.*: **Randomized controlled trial of meat compared with multimicronutrient-fortified cereal in infants and toddlers with high stunting rates in diverse settings.** *Am J Clin Nutr.* 2012; **96**(4): 840–7. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. Phu PV, Hoan NV, Salvignol B, *et al.*: **A six-month intervention with two different types of micronutrient-fortified complementary foods had distinct short- and long-term effects on linear and ponderal growth of Vietnamese infants.** *J Nutr.* 2012; **142**(9): 1735–40. [PubMed Abstract](#) | [Publisher Full Text](#)
51. Dewey KG, Mridha MK, Matias SL, *et al.*: **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. [PubMed Abstract](#) | [Publisher Full Text](#)
52. Phuka JC, Maleta K, Thakwalakwa C, *et al.*: **Postintervention growth of Malawian children who received 12-mo dietary complementation with a lipid-based nutrient supplement or maize-soy flour.** *Am J Clin Nutr.* 2009; **89**(1): 382–90. [PubMed Abstract](#) | [Publisher Full Text](#)
53. Jones KDJ, Ali R, Khasira MA, *et al.*: **Ready-to-use therapeutic food with elevated n-3 polyunsaturated fatty acid content, with or without fish oil, to treat severe acute malnutrition: a randomized controlled trial.** *BMC Med.* 2015; **13**(1): 93. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. Phuka JC, Gladstone M, Maleta K, *et al.*: **Developmental outcomes among 18-month-old Malawians after a year of complementary feeding with lipid-based nutrient supplements or corn-soy flour.** *Matern Child Nutr.* 2012; **8**(2): 239–48. [PubMed Abstract](#) | [Publisher Full Text](#)
55. Olney DK, Leroy J, Bliznashka L, *et al.*: **PROCOMIDA, a Food-Assisted Maternal and Child Health and Nutrition Program, Reduces Child Stunting in Guatemala: A Cluster-Randomized Controlled Intervention Trial.** *J Nutr.* 2018; **148**(9): 1493–505. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
56. Smuts CM, Matsungu TM, Malan L, *et al.*: **Effect of small-quantity lipid-based nutrient supplements on growth, psychomotor development, iron status, and morbidity among 6- to 12-month-old infants in South Africa: a randomized controlled trial.** *Am J Clin Nutr.* 2019; **109**(1): 55–68. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
57. Jack SJ, Ou K, Chea M, *et al.*: **Effect of micronutrient sprinkles on reducing anemia: a cluster-randomized effectiveness trial.** *Arch Pediatr Adolesc Med.* 2012; **166**(9): 842–50. [PubMed Abstract](#) | [Publisher Full Text](#)
58. Fink G, Levenson R, Tembo S, *et al.*: **Home- and community-based growth monitoring to reduce early life growth faltering: an open-label, cluster-randomized controlled trial.** *Am J Clin Nutr.* 2017; **106**(4): 1070–7. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
59. Luby SP, Rahman M, Arnold BF, *et al.*: **Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomised controlled trial.** *Lancet Glob Health.* 2018; **6**(3): e302–e315. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. Null C, Stewart CP, Pickering AJ, *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–e329. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
61. Humphrey JH, Mbuya MNN, Ntozini R, *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–e147. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
62. Shafique S, Sellen DW, Lou W, *et al.*: **Mineral- and vitamin-enhanced micronutrient powder reduces stunting in full-term low-birth-weight infants receiving nutrition, health, and hygiene education: a 2 x 2 factorial, cluster-randomized trial in Bangladesh.** *Am J Clin Nutr.* 2016; **103**(5): 1357–69. [PubMed Abstract](#) | [Publisher Full Text](#)
63. Gluckman PD, Hanson MA, Cooper C, *et al.*: **Effect of in utero and early-life conditions on adult health and disease.** *N Engl J Med.* 2008; **359**(1): 61–73. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
64. Goto R, Mascie-Taylor CG, Lunn PG: **Impact of anti-Giardia and anthelmintic treatment on infant growth and intestinal permeability in rural Bangladesh: a randomised double-blind controlled study.** *Trans R Soc Trop Med Hyg.* 2009; **103**(5): 520–9. [PubMed Abstract](#) | [Publisher Full Text](#)
65. Joseph SA, Casapia M, Montresor A, *et al.*: **The Effect of Deworming on Growth in One-Year-Old Children Living in a Soil-Transmitted Helminth-Endemic Area of Peru: A Randomized Controlled Trial.** *PLoS Negl Trop Dis.* 2015; **9**(10): e0004020. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
66. Muhoozi GKM, Atukunda P, Diep LM, *et al.*: **Nutrition, hygiene, and stimulation education to improve growth, cognitive, language, and motor development among infants in Uganda: A cluster-randomized trial.** *Matern Child Nutr.* 2018; **14**(2): e12527. [PubMed Abstract](#) | [Publisher Full Text](#)
67. Nair N, Tripathy P, Sachdev H, *et al.*: **Effect of participatory women's groups and counselling through home visits on children's linear growth in rural eastern India (CARING trial): a cluster-randomised controlled trial.** *Lancet Glob Health.* 2017; **5**(10): e1004–e1016. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
68. Nikiema L, Huybregts L, Martin-Prevel Y, *et al.*: **Effectiveness of facility-based personalized maternal nutrition counseling in improving child growth and morbidity up to 18 months: A cluster-randomized controlled trial in rural Burkina Faso.** *PLoS One.* 2017; **12**(5): e0177839. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. Saleem AF, Mahmud S, Baig-Ansari N, *et al.*: **Impact of maternal education about complementary feeding on their infants' nutritional outcomes in low- and middle-income households: a community-based randomized interventional study in Karachi, Pakistan.** *J Health Popul Nutr.* 2014; **32**(4): 623–33. [PubMed Abstract](#) | [Free Full Text](#)
70. Osei AK, Pandey P, Spiro D, *et al.*: **Adding multiple micronutrient powders to a homestead food production programme yields marginally significant benefit on anaemia reduction among young children in Nepal.** *Matern Child Nutr.* 2015; **11** Suppl 4: 188–202. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
71. Mridha M, Chaparro C, Matias S, *et al.*: **Acceptability of lipid-based nutrient supplements and micronutrient powders among pregnant and lactating women and infants and young children in Bangladesh and their perceptions about malnutrition and nutrient supplements.** Washington, DC: FHI. 2012; **360**. [Reference Source](#)
72. Cohen RJ, Brown KH, Canahuati J, *et al.*: **Determinants of Growth From Birth to 12 Months Among Breast-Fed Honduran Infants in Relation to Age of Introduction of Complementary Foods.** *Pediatrics.* 1995; **96**(3 pt 1): 504–10. [PubMed Abstract](#)
73. Thakwalakwa C, Ashorn P, Phuka J, *et al.*: **A lipid-based nutrient supplement but not corn-soy blend modestly increases weight gain among 6 to 18 month-old moderately underweight children in rural Malawi.** *J Nutr.* 2010; **140**(11): 2008–13. [PubMed Abstract](#) | [Publisher Full Text](#)
74. Oelofse A, Van Raaij JJM, Benade AJ, *et al.*: **The effect of a micronutrient-fortified complementary food on micronutrient status, growth and development of 6 to 12 month-old disadvantaged urban South African infants.** *Int J Food Sci Nutr.* 2003; **54**(5): 399–407. [PubMed Abstract](#) | [Publisher Full Text](#)
75. Lartey A, Manu A, Brown KH, *et al.*: **A randomized, community-based trial of the effects of improved, centrally processed complementary foods on growth and micronutrient status of Ghanaian infants from 6 to 12 mo of age.** *Am J Clin Nutr.* 1999; **70**(3): 391–404. [PubMed Abstract](#) | [Publisher Full Text](#)
76. Kuusipalo H, Maleta K, Briand A, *et al.*: **Growth and change in blood haemoglobin concentration among underweight Malawian infants receiving fortified spreads for 12 weeks: a preliminary trial.** *J Pediatr Gastroenterol Nutr.* 2006; **43**(4): 525–32. [PubMed Abstract](#) | [Publisher Full Text](#)
77. Park JJ, Thorlund K, Mills EJ: **Critical concepts in adaptive clinical trials.** *Clin Epidemiol.* 2018; **10**: 343–51. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
78. Thorlund K, Haggstrom J, Park JJ, *et al.*: **Key design considerations for adaptive clinical trials: a primer for clinicians.** *BMJ.* 2018; **360**: k698. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:   

Version 2

Reviewer Report 24 September 2020

<https://doi.org/10.21956/gatesopenres.14383.r29668>

© 2020 **Walson J.** This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Judd L. Walson 

Department of Global Health, University of Washington, Seattle, WA, USA

The authors have responded clearly to my initial comments.

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.

Version 1

Reviewer Report 19 March 2020

<https://doi.org/10.21956/gatesopenres.14225.r28444>

© 2020 **Maleta K.** This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Kenneth Maleta 

School of Public Health and Family Medicine, University of Malawi, Blantyre, Malawi

The authors tackle an otherwise vexing question of the limited success of interventions to address linear growth faltering and stuntedness by employing network analysis which allowed for assessing multiple interventions and their comparative effects on the outcomes. The statistical approach is very well justified and described. Overall the paper is very well written save for a few

areas where the authors need to clarify or speculate reasons for their findings:

1. The authors should explain why they think certain interventions had an impact on HAZ index (HAZ<-2.0) but not on actual HAZ.
2. Considering that the interventions were of variable duration, did the authors explore sensitivity analyses that limited analyses to intervention domains that were implemented for comparable periods of time (i.e. within each domain)? If not possible then some explanation and concession on how this could have affected the results should be included in the write up.
3. It is commonly accepted that interventions' effects vary depending on context. In the realm of this analysis it seems it is not possible to include effect modification analysis and if that is true, the discussion should highlight the impact lack of such analysis may have had on the findings.
4. I am not entirely clear on the definition of standard of care. In Table 2 this is defined as placebo/no intervention/standard of care/or monotherapy or combination therapy that can be used for indirect comparison. This seems too broad and heterogeneous. Did the authors try narrowing this down further to the placebo/no intervention and rest? How did this very broad categorization affect the findings?

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?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nutrition, Epidemiology, Clinical trials in LMIC.

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.

Author Response 21 Aug 2020

Edward Mills, University of British Columbia, Vancouver, Canada

Dear Dr. Maleta:

Thank you for your thorough review of our manuscript. Our responses to your recommendations and comments are marked with bullets below.

Sincerely,

Edward J. Mills

The authors should explain why they think certain interventions had an impact on HAZ index (HAZ<-2.0) but not on actual HAZ.

- *Thank you for your comment. The observed differences between the impact on HAZ and stunting can be attributed to randomness in the data as well as substantial heterogeneity observed in the duration of the interventions and the timing of outcome assessments. We have amended the discussion section to include this as a limitation.*

Considering that the interventions were of variable duration, did the authors explore sensitivity analyses that limited analyses to intervention domains that were implemented for comparable periods of time (i.e. within each domain)? If not possible then some explanation and concession on how this could have affected the results should be included in the write up.

- *In order to address heterogeneity between different trials, we employed random effects models for our network meta-analyses with empirically informative priors for the heterogeneity variance. We did not conduct analyses that were limited to one specific intervention domain, as this approach would have mimicked a pairwise meta-analysis approach. We considered different random-effects model options with or without baseline adjustments or meta-regression based on baseline characteristics and intervention duration. However, we did not find them to affect our treatment estimates nor did they improve the model fit.*

It is commonly accepted that interventions' effects vary depending on context. In the realm of this analysis it seems it is not possible to include effect modification analysis and if that is true, the discussion should highlight the impact lack of such analysis may have had on the findings.

- *We considered different random-effects model options with or without baseline adjustments or meta-regression based on baseline characteristics and intervention duration. However, we did not find them to affect our treatment estimates nor did they improve the model fit.*

I am not entirely clear on the definition of standard of care. In Table 2 this is defined as placebo/no intervention/standard of care/or monotherapy or combination therapy that can be used for indirect comparison. This seems too broad and heterogeneous. Did the authors try narrowing this down further to the placebo/no intervention and rest? How did this very broad categorization affect the findings?

- *We thank you for this comment. We have acknowledged this as a limitation in our revised manuscript. We have amended the discussion section to include the following:*

“Another limitation related to our categorisation of interventions is that we combined interventions into broad categories to assist with interpretation and acknowledge that a different approach to categorisation might have altered the results.”

Competing Interests: No competing interests were disclosed.

Reviewer Report 13 December 2019

<https://doi.org/10.21956/gatesopenres.14225.r28241>

© 2019 Cowling T et al. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Tara Cowling 

Medlior Health Outcomes Research Ltd, Calgary, AB, Canada

Kelly Larkin-Kaiser

Medlior Health Outcomes Research Ltd, Calgary, Canada

Taylor Scory

Medlior Health Outcomes Research Ltd, Calgary, Canada

Megan Farris

Medlior Health Outcomes Research Ltd, Calgary, Canada

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.

Author Response 21 Aug 2020

Edward Mills, University of British Columbia, Vancouver, Canada

Dear Reviewers:

Thank you for your thorough review of our manuscript. Our responses to your recommendations and comments are marked with bullets below.

Sincerely,

Edward J. Mills

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.

- *Thank you for your comment. The Supplementary Crosstable – v1.0 that we provided captures interactions between individual interventions. The Bayesian network analysis tool that was used to create the cross table can also be used to report analysis based on individual intervention. Given the nature and objective of our paper, we provided a comprehensive framework where comparative effectiveness of multiple interventions under multiple treatment domains can be understood.*

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.

- *Thank you for pointing out the discrepancy. The PRISMA chart shows that we have 96 papers as final includes which consist of both primary and secondary studies. Among the 96 papers, there are 79 unique trials, that is, they exclude secondary studies with the same trial ID. SA Table 4 has now been updated to reflect 96 studies. Please note that the paper Zambrana 2019 is one single primary study, reporting on two separate trials with unique trial registries. As a result, it has been captured as two trials on SA Table 4. Menasria 2018, which was initially part of the final includes, was not included in our analysis since the intervention arms did not consist the usual food/dietary supplements and thus represented as an outlier. Hence, the number of unique trials that were part of the analysis was 78. The updated SA table can be found here: <https://doi.org/10.17605/OSF.IO/DTZK7>.*
- *SA Table 6 includes characteristics from 77 trials. The two trials from Zambrana 2019 have been combined into one here, both clinical trials from this study share similar study characteristics, which is why the number is 77.*
- *SA Table 7 has been updated to reflect 78 trials.*
- *SA Table 8 has been updated to reflect 77 studies. You can find the updated table here <https://doi.org/10.17605/OSF.IO/DTZK7>.*
- *Explanations for Figures 3 & 4 have been updated. The horizontal axis for Figure 4 has been edited.*

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.

- *Thank you for your suggestion. We have updated the bias section of the manuscript to include the following:*

“Bias was evaluated using Cochrane risk-of-bias assessment tool in the areas of selection, performance, detection, attrition, reporting, and other sources of bias. Over 60% of the studies

exhibited low bias in terms of attrition, selection, and reporting bias. Sources of detection and performance bias were unclear in about 25-30% of the studies.”

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.

- *We thank you for this comment. Given the limited evidence base, meta-regression analyses of different potential effect modifiers were not possible. We have checked the model fit using leverage plots and DIC and consistency assumption using consistency plots of indirect and direct evidence. These results can be found in the Supplementary File (Supplementary Figures 5-8).*

Competing Interests: No competing interests were disclosed.

Reviewer Report 26 November 2019

<https://doi.org/10.21956/gatesopenres.14225.r28242>

© 2019 **Walson J.** This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Judd L. Walson 

Department of Global Health, University of Washington, Seattle, WA, USA

This is a very interesting study describing the results of a network meta-analysis of studies of interventions to improve HAZ (and therefore reduce stunting in LMIC settings). There are a number of issues that should be addressed in the manuscript:

1. I find it difficult to reconcile the differences observed in the analyses between changes in HAZ and changes in stunting. I would have expected that the analysis incorporating a continuous variable (HAZ) would have had more power to detect differences than the analysis of stunting as a dichotomous variable? If this is so, what is a reasonable explanation for the finding that interventions would have an impact on stunting but not on HAZ (given that stunting is a function of 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 an 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.

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.

Author Response 21 Aug 2020

Edward Mills, University of British Columbia, Vancouver, Canada

Dear Dr. Watson:

Thank you for your thorough review of our manuscript. Our responses to your recommendations and comments are marked with bullets below.

Sincerely,

Edward J. Mills

I find it difficult to reconcile the differences observed in the analyses between changes in HAZ and changes in stunting. I would have expected that the analysis incorporating a continuous variable (HAZ) would have had more power to detect differences than the analysis of stunting as a dichotomous variable? If this is so, what is a reasonable explanation for the finding that interventions would have an impact on stunting but not on HAZ (given that stunting is a function of LAZ)?

- *Thank you for your comment. The observed differences between the impact on HAZ and stunting can be attributed to randomness in the data as well as substantial heterogeneity observed in the duration of the interventions and the timing of outcome assessments. We have updated the discussion section to include this as a limitation.*

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?

- *We have pointed out in the discussion section that the existing evidence base is limited and does not provide a robust answer in regards to how food and other interventions, such as deworming, maternal, and WASH, impact linear growth outcomes in children in LMICs. As such, there is no strong evidence to report on population level impact on developmental outcomes.*

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.

- *Our search started with a review of systematic reviews before finalizing the study scope in terms of PICOS and the search strategies. For this, we performed a hand-search of the bibliography of Bhutta 2013 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.*
- *For the individual randomized clinical trials for our meta-analyses, a comprehensive search of literature was conducted from the Cochrane Central Register of Controlled Trials, Embase, and MEDLINE database to identify relevant trials and any additional relevant reviews that were missed in the prior step. The database search was complemented by bibliographical review of the published literature reviews to ensure that we did not miss*

any important clinical trials in our evidence base. The list of included and excluded trials are available in the Extended data (Supplementary Table 4 for included and Table 5 for the list of excluded studies). Here is the URL for your reference:

<https://doi.org/10.17605/OSF.IO/DTZK7>.

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

- *In order to address heterogeneity between different trials, we employed random effects models for our network meta-analyses. We used empirically informative priors for the heterogeneity variance for binary outcomes and non-informative priors for continuous outcomes. Since the use of I^2 as a measure of heterogeneity in Bayesian network meta-analysis is uncommon, we have decided to exclude it for the purpose of this study.*

I am concerned by the blanket use of an 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.

- *Thank you for this comment. Within the cluster trials included in our network meta-analysis, an average value of ICC of 0.0505 was reported, so we assumed a conservative value of 0.05 to adjust for the clustering effects of the cluster trials in our analyses. The ICC was used to inflate variance accordingly for the continuous outcome and to down-adjust the sample sizes and the number of cases for the dichotomous outcome, as recommended by Uhlmann 2016 (<https://pubmed.ncbi.nlm.nih.gov/27390267/>). It is expected that in a network meta-analysis with cluster randomized trials, a varying level of ICC would not impact/change results.*

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?

- *The reason why we reported this is because flour showed some reduction in stunting compared to standard of care in contrast to other interventions whose CI completely crossed the null effect of 1.*

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

- *This is now corrected.*

Competing Interests: No competing interests were disclosed.