

# Do effects of early life interventions on linear growth correspond to effects on neurobehavioural development?

## A systematic review and meta-analysis

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### Summary

**Background** Faltering in linear growth and neurobehavioural development during early childhood are often assumed to have common causes because of their consistent association. This notion has contributed to a global focus on the promotion of nutrition during pregnancy and childhood to improve both conditions. Our aim was to assess whether effects of interventions on linear growth are associated with effects on developmental scores and to quantify these associations.

**Methods** In this systematic review and meta-analysis, we included randomised trials done during pregnancy and in children aged 0–5 years that reported effects of any intervention on length-for-age or height-for-age Z scores (LAZ or HAZ) and on any of the following outcomes: motor, cognitive or mental, language, and social-emotional or behavioural development. We searched MEDLINE (Ovid), CINAHL (EBSCO), and PsycINFO (EBSCO) from database inception to June 25, 2019. Study-level data were extracted and, when required, authors were contacted for missing information. We calculated weighted meta-regression coefficients of the association between standardised effect sizes of interventions on LAZ or HAZ and developmental outcome scores and calculated pooled effect sizes for different types of intervention.

**Findings** Of the 7207 studies identified, we included 75 studies with 122 comparisons between intervention and control groups and outcomes reported for 72 275 children. Across all interventions, effect sizes on LAZ or HAZ were significantly associated with effect sizes on social-emotional scores ( $\beta$  0.23, 95% CI 0.05 to 0.41;  $p=0.02$ ), but not on cognitive (0.18,  $-0.36$  to  $0.72$ ;  $p=0.51$ ), language (0.12,  $-0.07$  to  $0.31$ ;  $p=0.21$ ), or motor development scores (0.23,  $-0.05$  to  $0.50$ ;  $p=0.11$ ). In studies that provided nutritional supplements, we observed positive significant pooled effect sizes on all five outcomes of LAZ or HAZ (effect size 0.05, 95% CI 0.01–0.09;  $p=0.01$ ;  $n=50$ ), cognitive or mental (0.06, 0.03–0.10;  $p<0.01$ ;  $n=38$ ), language (0.08, 0.03–0.13;  $p=0.01$ ;  $n=21$ ), motor (0.08, 0.04–0.12;  $p<0.01$ ;  $n=41$ ), and social-emotional (0.07, 0.02–0.12;  $p=0.01$ ;  $n=20$ ) scores. The effect sizes of nutritional supplementation on LAZ or HAZ scores were significantly associated with effect sizes on cognitive ( $\beta$  0.40, 95% CI 0.04–0.77;  $p=0.049$ ) and motor (0.43, 0.11–0.75;  $p=0.01$ ) scores. In the 14 interventions promoting responsive care and learning opportunities, the pooled effect size on LAZ or HAZ score was not significant ( $-0.01$ , 95% CI  $-0.07$  to  $0.05$ ;  $p=0.74$ ), but pooled effect sizes on cognitive, language, and motor scores were 4 to 5 times larger (range 0.38–0.48) than the pooled effect sizes of nutritional supplementation (0.05–0.08).

**Interpretation** In nutritional supplementation interventions, improvements in linear growth were associated with small improvements in child development, whereas nurturing and stimulation interventions had significant effects on child development but no effects on linear growth. The determinants of linear growth and neurodevelopment are only partly shared. To nurture thriving individuals and communities, interventions should specifically target determinants of neurodevelopment and not simply linear growth.

**Funding** University of California Davis, US Department of Agriculture National Institute of Food and Agriculture.

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### Introduction

Globally, an estimated 156 million children younger than 5 years have stunted growth<sup>1</sup> and an estimated 250 million are at risk of not fulfilling their developmental potential.<sup>2</sup> Promoting children's healthy growth and development during early life is essential to the global policy agenda. Global targets for 2030 include reducing stunting in children younger than 5 years by 40%<sup>3</sup> and ensuring that all girls and boys have access to quality early childhood development care.<sup>4</sup>

Stunted growth during early life has been associated with lower than average cognitive scores and school achievement and with health conditions in later life.<sup>5</sup> This association has been influential in prioritising a global agenda to promote nutrition during pregnancy and childhood to reduce linear growth faltering and improve neurobehavioural development. The assumption that a country's progress in reducing infant stunting will correspond to improved brain development and human capital is valid only if the same underlying factors cause

*Lancet Glob Health* 2019;

7: e1398–413

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### Research in context

#### Evidence before this study

Previous meta-analyses have reported pooled effects of specific types of interventions on linear growth and neurodevelopment. However, we are unaware of any study that has done a meta-regression across all types of interventions to examine the associations of effect sizes on length-for-age Z scores or height-for-age Z scores (LAZ or HAZ) with effect sizes on developmental outcomes.

#### Added value of this study

In our systematic review and meta-analysis, we found that effects of early life interventions on length-for-age Z scores or height-for-age Z scores (LAZ or HAZ) were significantly associated with social-emotional, but not cognitive, language, or motor development scores. These findings contradict the assumption that improvements in LAZ or HAZ scores correspond to overall improvements in neurobehavioural development. The majority of studies included (51 of 75) provided maternal or child nutritional supplements. These had small significant positive pooled effects on all five outcomes of LAZ or HAZ, cognitive or mental, language, motor, and social-emotional scores. The second major category of interventions promoted caregiving, with interventions focused on responsive care and learning opportunities (14 of 75 studies). Effects of these interventions on LAZ or HAZ score were not significant, but effects on cognitive, language, and motor development scores were 4 to 5 times larger than the effects of nutritional supplementation, showing that caregiving

had a 4 to 5 times greater effect on developmental outcomes than that of nutritional supplements. Additionally, we stratified nutrition supplementation studies by setting, timing, and type. Small, but significant, positive pooled effects on both LAZ or HAZ and development scores were found in nutrition studies that were done in low-income and middle-income countries, but not in those done in high-income countries; in studies that provided supplementation for children, but not in those providing maternal supplementation; and in studies that provided both macronutrients and micronutrients, but not in those providing micronutrients alone. Therefore, the common nutritional determinant of faltering in both linear growth and development in low-income and middle-income countries seems to be postnatal inadequate dietary intake of macronutrients and micronutrients during early childhood.

#### Implications of all the available evidence

The determinants of linear growth and neurodevelopment are only partly shared. Postnatal macronutrient and micronutrient supplementation might affect both linear growth and development, whereas multiple micronutrient supplementation and responsive care and learning opportunities affect development but not growth. Nutritional programming alone provides only small gains in growth and development. Supporting thriving individuals and communities requires interventions targeting caregiving behaviour and learning opportunities that support cognitive, language, motor, and social-emotional skills.

both linear growth failure and delayed neurodevelopment. The view that stunting is a cause of developmental delay is prevalent among developmental agencies and donors active in nutrition programmes<sup>6</sup> and in scientific publications.<sup>7</sup> However, the causes of faltering in linear growth and neurodevelopment remain poorly understood. Children growing up in the context of poverty face a wide range of risk factors in their environment that might govern growth and development by different or partly overlapping pathways.<sup>8</sup> Different types of intervention might, therefore, affect growth and development to differing degrees (appendix p 24). If so, then a country's progress in reducing stunting might not necessarily result in improved neurodevelopment and human capital.

Therefore, we did a systematic review and meta-analysis of effects of early life interventions on linear growth and neurodevelopment to examine the validity of these assumptions. We aimed to clarify which causes of faltering in growth and neurodevelopment are shared or independent and to quantify the change in neurodevelopment that can be expected to correspond to changes in linear growth. Our hypothesis was that interventions with greater effects on linear growth have greater effects on developmental outcomes than those with lower effects on linear growth. To test this

hypothesis, we used meta regression of the association between effect sizes of interventions on length-for-age or height-for-age Z scores (LAZ–HAZ) and developmental scores, as a primary objective. Our secondary objective was to identify the pooled effect size of different types of interventions on outcomes among all published early-life interventions that measured both LAZ–HAZ and developmental outcomes. Through this analysis, we identified the types of interventions that have a greater effect on linear growth than on development (and vice versa) and the types of interventions that have a similar effect size on both outcomes.

### Methods

#### Search strategy and selection criteria

For this systematic review and meta-analysis, we included only randomised controlled trials reported in English or Spanish. Trials were included only if participants were enrolled during pregnancy or at 0–5 years of age; specifically, trials were included if the minimum age of children at baseline was lower than 60 months and the maximum was lower than 72 months. Any type of intervention or combination of interventions was included—such as nutritional supplementation, promotion of responsive care and learning opportunities,

See Online for appendix

and conditional cash transfer—as long as the study reported effects of the intervention on LAZ–HAZ and any of the following outcomes measured at the same timepoint as LAZ–HAZ: motor (fine and gross), mental, cognitive, language (receptive or expressive), and social-emotional or behavioural development. Control groups in the trials might have received an intervention with fewer components than those of intervention groups or no intervention. Non-randomised comparison groups were not included. No date restrictions were applied.

We searched MEDLINE (Ovid), CINAHL (EBSCO), and PsycINFO (EBSCO) from database inception to June 25, 2019. We also examined the references of included studies and relevant reviews to search for further studies that met the inclusion criteria. The search strategy used the following search terms: (“child” OR “childhood” OR “infant” OR “infancy” OR “pregnancy” OR “pregnant” OR “maternal”) AND (“stunted” OR “stunting” OR “height” OR “length” OR “growth” OR “length-for-age”) AND (“Bayley” OR “PPVT” OR “language” OR “cognitive” OR “socio-emotional” OR “mental development” OR “psychomotor” OR “sensorimotor” OR “intelligence” OR “IQ” OR “executive function” OR “memory” OR “attention” OR “learning” OR “information processing” OR “literacy” OR “reading” OR “math” OR “school readiness” OR “emotion” OR “brain” OR “event-related potential” OR “electroencephalogram”) AND (“trial” OR “intervention” OR “RCT”) AND (“nutrition” OR “supplementation” OR “supplement” OR “food supplements” OR “nutrients” OR “micronutrient” OR “infant food” OR “diet” OR “feeding” OR “iron” OR “iodine” OR “breastfeeding” OR “stimulation” OR “parenting” OR “home visits” OR “home visiting” OR “preschool” OR “foster care” OR “kangaroo care” OR “antibiotic” OR “antiretroviral” OR “cash” OR “cash transfer” OR “conditional cash transfer” OR “water sanitation and hygiene” OR “deworming” OR “malaria treatment” OR “intermittent preventive therapy”).

The age at outcome assessment was not restricted. For the primary analysis, we examined outcomes measured at endline immediately after the intervention period. For studies that reported both LAZ–HAZ and developmental outcomes at multiple timepoints, we selected one timepoint for the primary analyses according to the following criteria: if LAZ–HAZ and developmental outcomes were measured at endline immediately after the intervention period, this timepoint was selected for the primary analysis; if LAZ–HAZ and developmental outcomes were not measured at endline, but were measured at a single timepoint in a follow-up study after the end of the intervention period, this timepoint was selected for the primary analysis; and if LAZ–HAZ and developmental outcomes were not measured at endline, but were measured at multiple timepoints in follow-up studies, we selected the timepoint that was closest to endline. We analysed follow-up studies in a secondary analysis.

## Data collection and analysis

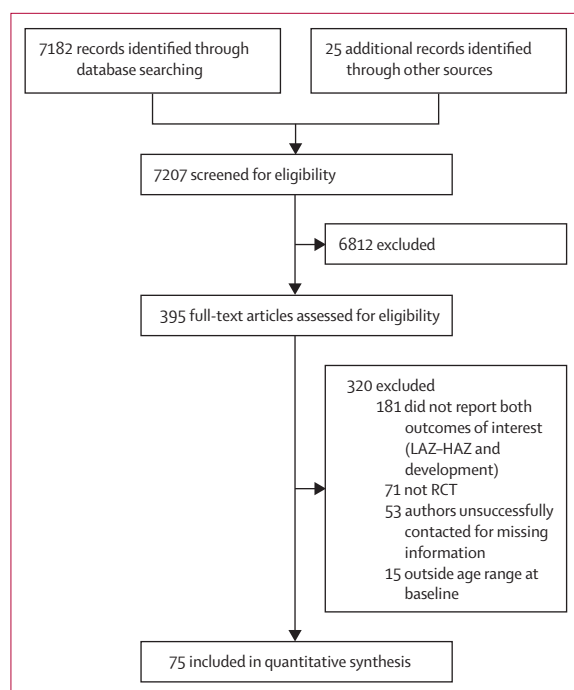
LML, KC, JNK, and ELP (in pairs) screened the title and abstract of each article identified by the search strategy. Abstracts were screened for inclusion criteria on the basis of study design (ie, randomised), population and age group (ie, enrolled pregnant women or children younger than 5 years), and outcomes measured (ie, measured any functional outcome of interest). The full texts of papers identified from the abstract screening were downloaded and assessed for all inclusion and exclusion criteria.

For each study that met the inclusion criteria, three raters independently extracted data and rated the quality. Values that matched between any two raters were used to create the clean database. Any values that did not result in a match were reviewed and resolved through discussion (ELP, LML, and KB). Data extraction tables were created with the following information: study location, study design (including interventions provided to the treatment and control groups and study duration), sample size enrolled and analysed, child age at enrolment and outcome measurements, baseline characteristics (including LAZ–HAZ, cognitive, language, motor, and social-emotional score), mean and SD scores of functional outcomes of interest and measurement tool used, and study quality. We rated the quality of each comparison using the Effective Public Health Practice Project quality assessment tool, on the basis of selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts.<sup>9</sup> Different comparisons within the same study could have different quality ratings because of factors that could vary by intervention group, such as participant masking or imbalance of potential confounders.

We contacted authors of studies with missing information twice to request access to the missing information. Authors of nine studies replied with additional information. Studies were excluded if data were no longer available, no response to inquiries was received, or if the authors did not provide sufficient information to meet inclusion criteria.

We generated meta-regression coefficients and pooled effect sizes in the following way. If intervention studies reported fine and gross motor scores separately, we used gross motor scores. Likewise, if expressive and receptive language scores were reported separately, we used receptive language scores. Mental and cognitive development outcomes were combined. For any social-emotional scores for which a higher score indicated higher behavioural problems, we reversed the effect size and 95% CI to match the direction of the other scores (higher is better).

We presented continuous outcomes as Hedges' *g*, calculated with a pooled SD and with 95% CI.<sup>10</sup> For any trials that did not report endline means by intervention group but reported baseline means and change from baseline to endline, we calculated the endline means by



**Figure 1: Study inclusion flow diagram**

RCT=randomised controlled trial. LAZ or HAZ=length or height-for-age Z scores.

adding the mean change to the baseline mean. We used the SD from the baseline mean and the n of the mean change to calculate the endline 95% CI. Weights were assigned to each study by calculating the inverse variance of the endline scores.

For cluster-randomised trials, we calculated Hedges' *g* and a 95% CI in the same way as individually-randomised trials, without accounting for variance between clusters. We compared our calculated Hedges' *g* and 95% CI with the effect size and 95% CI reported in the corresponding study using statistical methods that adjusted for cluster randomisation. If the results were similar, then we concluded that intracluster correlation coefficients were small and adjustment for cluster design was not necessary. If the results were substantially different, we planned to adjust for cluster design using the method described by Hedges.<sup>11</sup> However, none of the coefficients were substantially different and thus, we did not make this adjustment.

For the meta-regression, we calculated effect sizes separately for each comparison, including studies with multiple intervention versus control group comparisons. To adjust for studies with multiple comparisons, we included a random effect of study. For studies with multiple intervention groups compared with the same control group, we did not divide the number of participants in the control group by the number of comparisons in the main analysis. However, we also did a sensitivity analysis in which we divided the number of participants in the control group, in case the main

analysis overweighted studies with multiple comparisons because of counting participants in the control group more than once.

For the pooled effect sizes, which were calculated separately for each intervention type, we created one comparison per study per intervention type. For studies with multiple intervention groups in the same intervention type, we combined intervention group means and SDs using weighted means by the number of participants per group. For studies with multiple control groups, we combined control group means and SDs in the same way. For the pooled analysis of studies that provided supplementation with a single micronutrient, if the same study included two groups that provided two different micronutrients compared with the same control group, we calculated separate effect sizes and divided the number of participants of the control group between groups to avoid double counting participants in the control group. For pooled effect sizes of nutrition interventions, we excluded comparisons in which the control group received a higher dose or frequency of supplement than the intervention group.

Within each category of intervention, we assessed methodological heterogeneity by describing the methodological similarities and differences between trials. We also described the similarity between the types of participants, interventions, and outcomes. We assessed statistical heterogeneity using a  $\chi^2$  test on the Cochrane's heterogeneity statistic *Q*, and an *I*<sup>2</sup> was also generated. Because of heterogeneity between studies, which was expected given the breadth of interventions included, random effects models were used to create the pooled effect sizes. We created funnel plots to assess publication bias and pooled effect sizes using Stata, version 15.1. Pooled effect sizes were calculated with and without outliers on the basis of these funnel plots.

For the primary objective, we did a meta-regression of the association between effect sizes on LAZ-HAZ and effect sizes on developmental scores weighted by the inverse of the variance, including a random effect of study. After running the meta-regression across all effect sizes in all studies, we then stratified by category of intervention (eg, nutritional supplementation and promotion of responsive care and learning opportunities). We did sensitivity analyses excluding low-quality comparisons and excluding studies in high-income countries. For the meta-regression, we winsorised outliers to the 5th and 95th percentile; however, the forest plot figures show original values.

For the secondary objective, we calculated pooled effect sizes as a weighted mean (ie, the mean of the weighted individual trial effect sizes for each outcome separately). We calculated pooled effect sizes if at least five studies reported an intervention versus control group comparison in any category of intervention (eg, nutritional supplementation and promotion of responsive care and learning opportunities). We applied the same criterion to stratified

# A Prenatal or postnatal maternal interventions and maternal and child interventions

■ Significant positive effect   
 ■ No significant effect   
 ■ Significant negative effect

| Intervention   | Study                             | Country<br>(targeted population,<br>if any)  | Assessed at (age) |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          | Primary analysis<br>outcomes |       |     |           |          | Secondary analysis of<br>outcomes of follow-up<br>studies |       |  |  |  |
|--|-----------------------------------|--|-------------------|---|---|---|----|----|----|----|----|----|---|---|---|---|---|-----|-----|-----------|----------|------------------------------|-------|-----|-----------|----------|---|-------|--|--|--|
|  |                                   |  | In<br>utero       | 3 | 6 | 9 | 12 | 15 | 18 | 24 | 36 | 48 | 5 | 6 | 7 | 8 | 9 | ≥10 | HAZ | Cognitive | Language | Socio-<br>emotional          | Motor | HAZ | Cognitive | Language | Socio-<br>emotional                                       | Motor |  |  |  |
| Maternal<br>DHA/EPA                                    | Tofail et al <sup>49</sup>        | Bangladesh   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
|  | Gonzalez-Casano <sup>57</sup>     | Mexico   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Maternal multiple<br>micronutrients                    | Christian et al <sup>40</sup>     | Bangladesh   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
|  | Nguyen et al <sup>54</sup>        | Vietnam  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
|  | Zhu et al <sup>56</sup>           | China  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
|  | Hanieh <sup>36</sup>              | Vietnam  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Maternal iron or iron<br>plus vitamin A                | Schmidt et al <sup>53</sup>       | Indonesia  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Maternal choline                                       | Jacobson et al <sup>58</sup>      | South Africa (heavy drinkers)  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Maternal zinc  | Hamadani et al <sup>35</sup>      | Bangladesh   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Maternal iodine  | Gowachirapant et al <sup>51</sup> | India, Thailand (mildly iodine<br>deficient women)   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Maternal vitamin B12                                   | Thomas et al <sup>60</sup>        | India  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Maternal fortified milk plus<br>breastfeeding support  | Zhang et al <sup>59</sup>         | Vietnam (pre-pregnancy BMI<br><25 kg/m <sup>2</sup> )  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Maternal and child lipid-based<br>nutrient supplements | Ashorn et al <sup>59</sup>        | Malawi   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
|  | Adu-Afarwah et al <sup>18</sup>   | Ghana  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
|  | Dewey et al <sup>20</sup>         | Bangladesh   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Breastfeeding promotion                                | Tumwine et al <sup>79</sup>       | Uganda, Burkina Faso   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Nutrition and health education                         | Tomlinson et al <sup>78</sup>     | South Africa (women with<br>depression)  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Antimalarials plus azithromycin                        | Hallamaa et al <sup>82</sup>      | Malawi   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Timing of delivery by<br>caesarean section             | Lees et al <sup>80</sup>          | Germany, Italy, UK, the<br>Netherlands, Austria<br>(very preterm foetal<br>growth restriction) |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| WASH   | Gladstone et al <sup>61</sup>     | Zimbabwe   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
|  | Stewart et al <sup>72</sup>       | Kenya  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
|  | Luby et al <sup>73</sup>          | Bangladesh   |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |
| Cash transfer  | Fernald et al <sup>77</sup>       | Ecuador  |                   |   |   |   |    |    |    |    |    |    |   |   |   |   |   |     |     |           |          |                              |       |     |           |          |   |       |  |  |  |

# B Postnatal child interventions with macronutrients or macronutrients plus micronutrients

|   |                                     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|-------------------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| Amino acids   | Blanco et al <sup>8</sup>           | USA (VLBW infants)                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Bellagamba et al <sup>27</sup>      | Italy (preterm VLBW)                     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| DHA   | Van der Merwe et al <sup>29</sup>   | Gambia                                   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Low-dose soybean oil                                  | Ong et al <sup>27</sup>             | USA                                      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fortified milk  | Jeon et al <sup>41</sup>            | South Korea (preterm)                    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Lind et al <sup>51</sup>            | Sweden                                   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Rosado et al <sup>15</sup>          | Mexico                                   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lipid-based nutrient<br>supplements or fortified food | Oelofse et al <sup>52</sup>         | South Africa                             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Nahar et al <sup>48</sup>           | Bangladesh                               |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Smuts et al <sup>52</sup>           | South Africa                             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Husaini et al <sup>50</sup>         | Indonesia                                |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Phuka et al <sup>21</sup>           | Malawi                                   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Maleta et al <sup>27</sup>          | Malawi                                   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Krebs et al <sup>54</sup>           | DR Congo, Zambia,<br>Guatemala, Pakistan |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Bauserman et al <sup>55</sup>       | DR Congo                                 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Faber et al <sup>14</sup>           | South Africa                             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Hess et al <sup>16</sup>            | Burkina Faso                             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Dewey et al <sup>20</sup> (IFA-LNS) | Bangladesh                               |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Stewart et al <sup>22</sup>         | Kenya                                    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Luby et al <sup>23</sup>            | Bangladesh                               |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Gladstone et al <sup>51</sup>       | Zimbabwe                                 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Rosado et al <sup>15</sup>          | Mexico                                   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

(Figure 2 continues on next page)

## C Postnatal child micronutrient interventions

Significant positive effect    No significant effect    Significant negative effect

| Intervention            | Study                     | Country<br>(targeted population,<br>if any) | Assessed at (age) |        |   |   |    |    |    |    |    |       |   |   |   |   |   |     |  | Primary analysis<br>outcomes |           |          |                     |       | Secondary analysis of<br>outcomes of follow-up<br>studies |           |          |                     |       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |    |
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|                         |                           |   | In<br>utero       | Months |   |   |    |    |    |    |    | Years |   |   |   |   |   |     |  | HAZ                          | Cognitive | Language | Socio-<br>emotional | Motor | HAZ   | Cognitive | Language | Socio-<br>emotional | Motor |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |    |
|                         |                           |   |                   | 3      | 6 | 9 | 12 | 15 | 18 | 24 | 36 | 48    | 5 | 6 | 7 | 8 | 9 | ≥10 |  |                              |           |          |                     |       |   |           |          |                     |       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |    |
| Multiple micronutrients | Black et al <sup>12</sup> | Bangladesh                                  |                   |        |   |   |    |    |    |    |    |       |   |   |   |   |   |     |  |                              |           |          |                     |       |   |           |          |                     |       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | </ |

## D Postnatal interventions promoting responsive care and learning opportunities and other interventions

|   |   |  |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|---|--|----------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| Responsive care and learning opportunities                                  | Yousafzai et al <sup>42</sup>             | Pakistan   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Chang et al <sup>54</sup>                 | Jamaica, Antigua, St Lucia   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Nahar et al <sup>48</sup>                 | Bangladesh (child WAZ <-3)   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Hamadani et al <sup>70</sup>              | Bangladesh (child WAZ <-2)   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Tofail et al <sup>71</sup>                | Bangladesh (IDA children)  |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Boivin et al <sup>56</sup>                | Uganda (HIV-exposed uninfected)  |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Responsive care and learning opportunities plus nutrition education         | Singla et al <sup>65</sup>                | Uganda   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Muhoozi et al <sup>67</sup>               | Uganda   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Vazir et al <sup>72</sup>                 | India  |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Aboud et al <sup>69</sup>                 | Bangladesh   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Black et al <sup>69</sup>                 | USA (failure to thrive)  |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Raynor et al <sup>68</sup>                | UK (failure to thrive)   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Rockers et al <sup>73</sup>               | Zambia   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Hamadani et al <sup>74</sup>              | Bangladesh (child WAZ <-2)   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Responsive care and learning opportunities plus nutritional supplementation | Nahar et al <sup>68</sup> (stim plus LNS) | Bangladesh   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | Aboud et al <sup>69</sup>                 | Bangladesh   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Vaccine   | Kjaergaard et al <sup>83</sup>            | Denmark  | At birth |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Erythropoietin  | Natalucci et al <sup>86</sup>             | Switzerland (preterm infants)  | At birth |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Inhaled nitric oxide  | Durrmeyer et al <sup>85</sup>             | Belgium, Finland, UK, France, Germany, Italy, the Netherlands, Spain, Sweden (preterm infants) | At birth |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thyroxine   | Marchal et al <sup>84</sup>               | The Netherlands (Down syndrome)  |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Foster care   | Johnson et al <sup>81</sup>               | Romania (institutionalised children)   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cash transfer   | Fernald et al <sup>66</sup>               | Mexico   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| WASH  | Bowen et al <sup>75</sup>                 | Pakistan   |          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |



analyses (at least five studies). Within nutrition interventions, we considered stratifying by study location (low-income and middle-income countries or high-income countries), timing of supplementation (in pregnant or post-partum women, children, or both), and type of supplement (macronutrients plus micronutrients, macronutrients alone, multiple micronutrients [2 or more], or a single micronutrient). Within interventions promoting responsive care and learning opportunities, we stratified by study location (low-income and middle-income countries or high-income countries). We did sensitivity analyses excluding outliers on the basis of funnel plots and low-quality comparisons. Significance was defined as  $p < 0.05$ . We did the statistical analyses using SAS, version 9.4.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

We identified 7207 studies through the search strategy and review of other meta-analyses and systematic reviews; of those, 395 titles and abstracts were considered relevant. After a review of the full texts, 75 intervention studies were included in the meta-analysis and systematic review (figure 1). Of the 75 studies included, 61 were done in low-income or middle-income countries and 14 in high-income countries. 14 interventions were provided to pregnant or post-partum women, 52 to children, and nine to both. The 75 studies reported 122 comparisons between intervention and control groups and outcomes were reported for 72 275 children. 48 studies reported a single comparison, whereas 27 reported multiple comparisons between intervention and control groups. Of these 27 multi-arm interventions, 20 provided the same category of intervention (eg, nutritional supplementation) to all intervention groups

and seven provided different categories of intervention to different groups (eg, nutritional supplementation or water, sanitation, and hygiene). 51 studies provided nutritional supplementation<sup>12–62</sup> and 14 studies promoted responsive care and learning opportunities.<sup>42,48,63–74</sup> These were the only two categories of intervention that were provided by five or more studies; therefore, analyses of pooled effect sizes focused on these two categories of intervention. Other interventions were water, sanitation, and hygiene (4 studies),<sup>22,23,61,75</sup> cash transfer (2 studies),<sup>76,77</sup> nutrition education (3 studies),<sup>72,78,79</sup> variation of the timing of maternal delivery by caesarean section (1 study),<sup>80</sup> foster care (1 study),<sup>81</sup> provision of antibiotics during pregnancy (1 study),<sup>82</sup> vaccination (1 study),<sup>83</sup> thyroxine supplementation in children with Down syndrome (1 study),<sup>84</sup> provision of nitric oxide to preterm infants (1 study),<sup>85</sup> and newborn erythropoietin treatment (1 study).<sup>86</sup> The majority of studies (52) enrolled community cohorts, whereas 23 targeted specific subgroups, such as underweight or low birthweight infants (12 studies), preterm infants (5 studies), or other categories that applied only to a single study (eg, women with depression or children with Down syndrome).

25 studies reported LAZ–HAZ and developmental outcomes at a timepoint after the end of the intervention, but not immediately after the intervention. These outcomes were included in the primary analyses on endline scores. 12 studies reported LAZ–HAZ and developmental outcomes both at endline and at a subsequent timepoint. These additional timepoints were included in the secondary analyses on follow-up studies. For the primary analysis, the age of children at assessment ranged from 6 months to 12 years. For the secondary analysis of follow-up studies, age at assessment ranged from 12 months to 10 years (figure 2).

For the primary analysis, 62 studies reported cognitive outcomes, 35 reported language outcomes, 59 reported motor outcomes, and 28 reported social-emotional outcomes. The Bayley Scales of Infant Development were the most common measurement tool (used in 42 studies for cognitive outcomes, 14 for language outcomes, 38 for motor outcomes, and 4 for social-emotional outcomes). Other tools measured similar developmental skills and milestones as the Bayley Scales. Among the 13 studies included in the secondary analysis of follow-up studies, 12 measured cognitive outcomes, six measured language outcomes, 11 measured motor outcomes, and five measured social-emotional development outcomes. The Bayley Scales were also the most common tool used in the secondary analysis (used in 7 studies for cognitive outcomes, 4 for language outcomes, and 7 for motor outcomes). All measurement tools and the number of studies that used them are listed in the appendix (pp 1–2).

Most comparisons were given a global quality rating of strong (85 comparisons in 54 studies) or moderate (34 comparisons in 19 studies; appendix pp 3–20). Three comparisons in two studies were rated weak.<sup>61,73</sup>

### Figure 2: Methods of included studies

Shaded area in yellow represents intervention duration and age of participants. If no shaded area is shown, intervention was delivered at birth. Dashed vertical lines represent mean age at baseline. Solid vertical lines represent ages at endline (black) and follow-up (blue) assessments. Outcomes are listed for endline (primary analysis) and follow-up assessments separately. Gladstone et al<sup>61</sup> measured growth at 18 months and development at 24 months. Locks et al<sup>44</sup> measured child development at 15 months and growth at 19 months of age. Singla et al<sup>65</sup> and Thomas et al<sup>60</sup> found significant positive effects on expressive language development, but non-significant effects on receptive language development. BMI=body-mass index. DHA=docosahexaenoic acid. EPA=eicosapentaenoic acid. WASH=water, sanitation, and hygiene. VLBW=very low birthweight. LBW=low birthweight. WAZ=weight-for-age Z score. IDA=iron deficiency anaemia. Stim=psychological stimulation. LNS=lipid-based nutrient supplements. IFA-MNP=iron and folic acid micronutrient powder.

We did not suspect publication bias for several reasons. First, funnel plots did not indicate that effect sizes in published studies were one-sided, thereby indicating absence of bias towards larger effect sizes (appendix pp 25–28). Second, we did not observe an association between smaller sample sizes and larger effect sizes.<sup>88</sup> Third, we did not observe a disproportionately high number of studies reporting *p* values just below the standard level of statistical significance.<sup>88</sup>

Figure 3 shows the forest plots of all 122 comparisons of intervention versus control group, ordered by the magnitude of the LAZ–HAZ effect size. Across all interventions, effect sizes on LAZ–HAZ were significantly associated with effect sizes on social-emotional scores, but not with cognitive, language, or motor scores (table 1). In studies that provided nutritional supplements, effect sizes on LAZ–HAZ were significantly associated with effect sizes on cognitive and motor scores, with each 1 SD difference in effect size of LAZ–HAZ score associated with 0.40 SD difference in cognitive effect size and 0.43 SD difference in motor effect size (table 1), but not with language or social-emotional scores. Sensitivity analyses excluding studies done in high-income countries and low-quality comparisons resulted in similar estimates, as did the analysis for studies with multiple comparisons, which weighted studies dividing the number of participants in the control group by the number of comparisons (appendix p 4). We had an insufficient number of comparisons available to examine associations among other categories of interventions or among follow-up studies.

Among all nutritional supplementation studies, we found positive significant pooled effects on all five outcomes (LAZ–HAZ, cognitive or mental, language, motor, and social-emotional scores), with effect sizes ranging from 0.05 to 0.08 (20–50 studies; table 2; figure 4). In studies done in low-income and middle-income countries, the same pattern of significant positive pooled effect sizes on all outcomes was found (effect size range 0.05–0.08, in 20–44 studies). By contrast, in studies in high-income countries, the pooled effect size of LAZ–HAZ score was significantly negative (6 studies; table 2). We found similar patterns of results in all studies, studies done in low-income and middle-income countries, and studies done in high-income countries when excluding outliers (appendix p 22). Further stratified analyses excluded the six studies done in high-income countries.

On stratification by timing of nutritional supplementation, maternal supplementation during the prenatal or postpartum period (5 to 12 studies) did not result in significant effects on any outcome. By contrast, child supplementation had significant positive effects on all outcomes, with effect sizes ranging from 0.07 to 0.13 (13–30 studies). We did not calculate pooled estimates

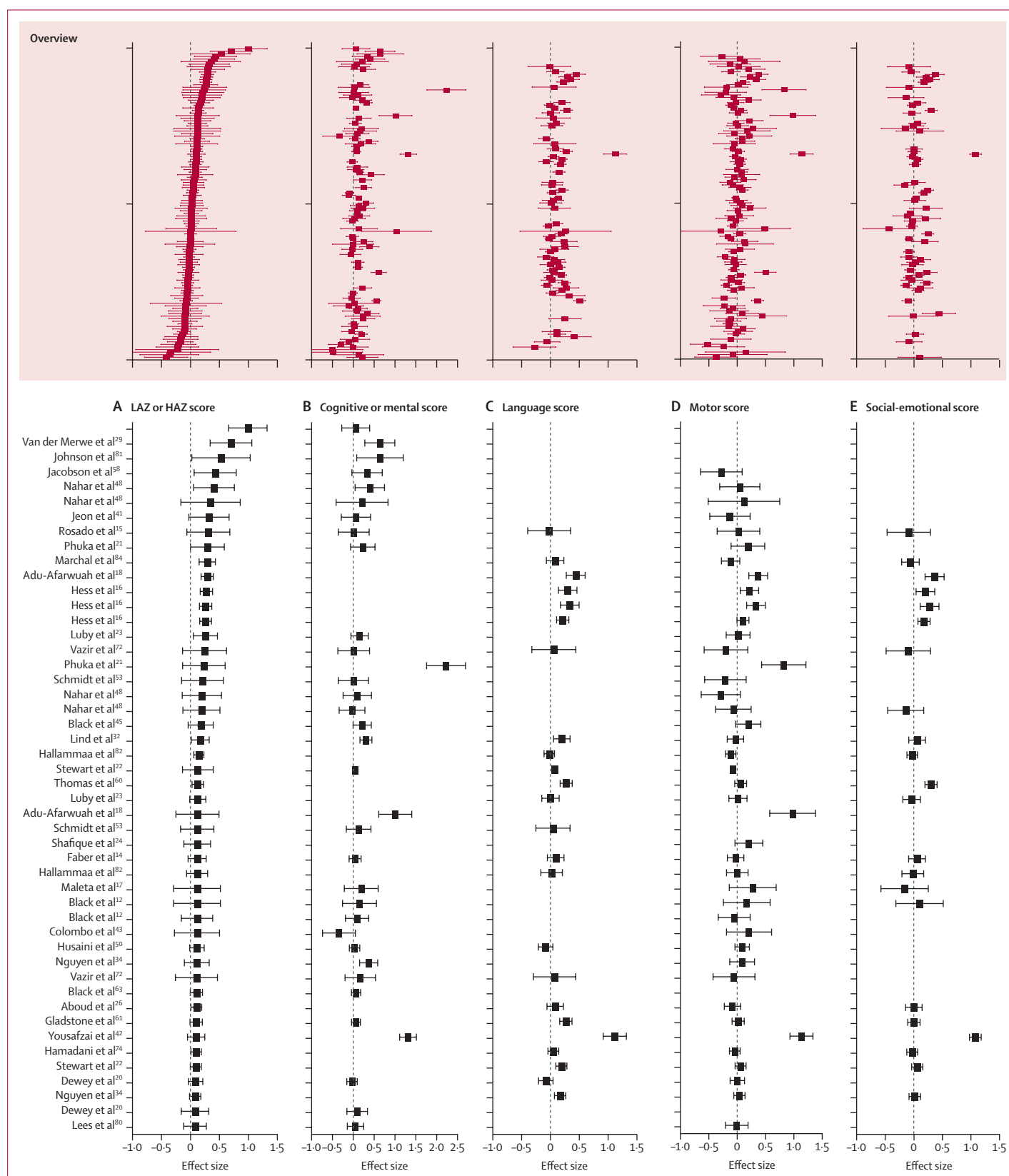
for studies providing both maternal and child supplementation because of the small number of studies (3 studies). Excluding outliers, maternal supplementation had a positive pooled effect on language (effect size 0.05, 95% CI 0.02–0.09; 5 studies) and motor scores (0.09, 0.04–0.15; 5 studies), and findings for child supplementation had a similar pattern to those of the main analysis (significant positive effects on all outcomes, effect size range 0.06–0.11; 8–25 studies; appendix p 22).

On stratification by type of nutritional supplement, the provision of both macronutrients and micronutrients resulted in significant positive effect sizes on LAZ–HAZ, language, motor, and social-emotional scores (effect size range 0.09–0.10; 10–17 studies), but not cognitive or mental score. Supplementation with multiple micronutrients (without macronutrients) positively affected cognitive or mental, language, motor, and social-emotional scores (effect size range 0.08–0.11; 5–13 studies), but not LAZ–HAZ score. Supplementation with a single micronutrient resulted in a significant pooled effect sizes alone (13 studies; table 2). We did not calculate pooled estimates for studies providing macronutrients alone because of the small number of studies (3 studies in low-income and middle-income countries). The pattern of results was similar when outliers were excluded, except that single micronutrient supplementation had a significant positive effect on LAZ–HAZ score (effect size 0.07, 14 studies; appendix p 22). Of the 18 comparisons in which a single micronutrient was provided, eight provided zinc, four iron, three iodine, one choline, one vitamin B12, and one vitamin D. Forest plots for various types of nutritional supplementation are shown in the appendix (pp 29–36).

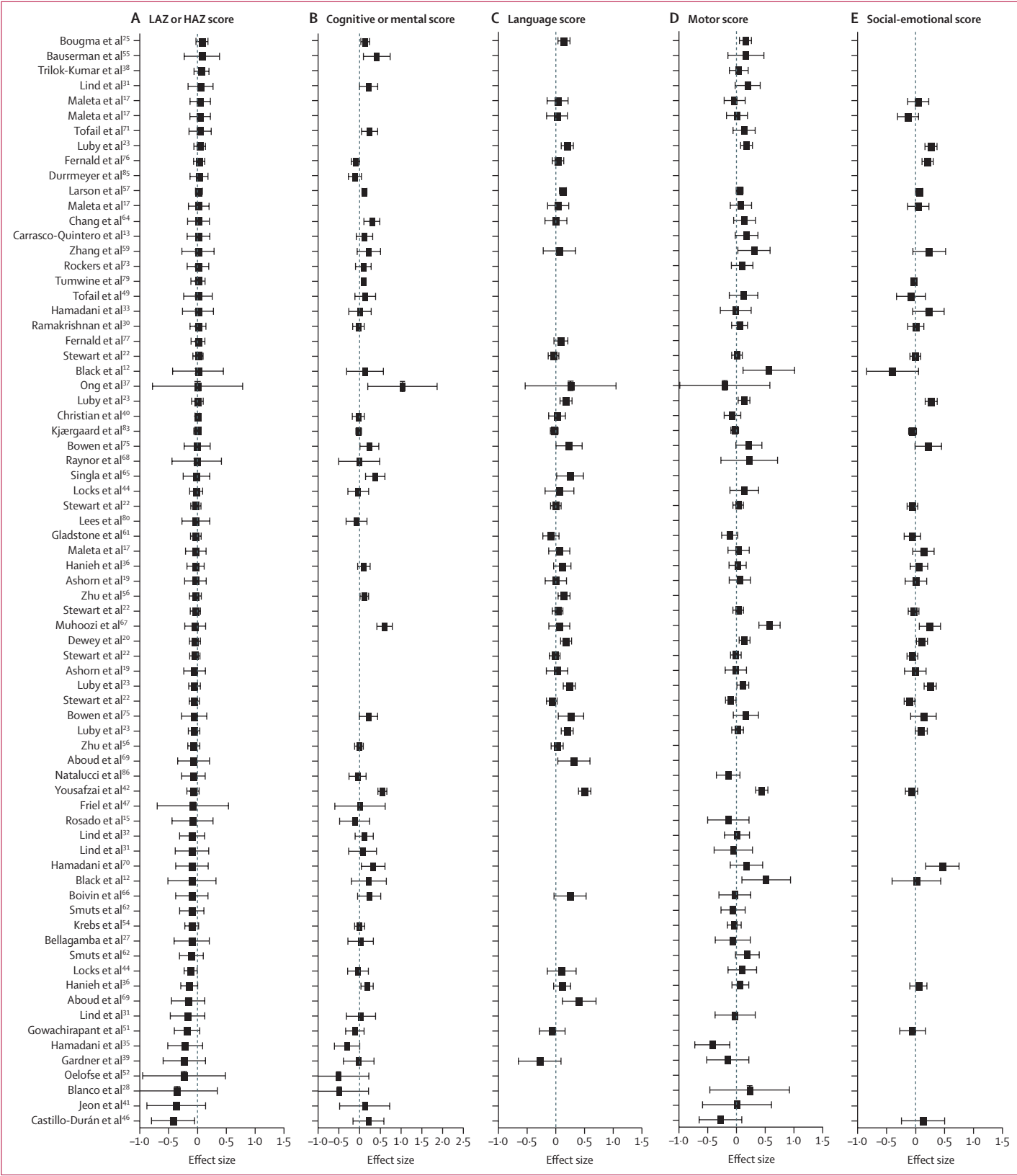
Studies promoting responsive care and learning opportunities resulted in significant positive pooled effect sizes on cognitive (13 studies), language (8 studies), and motor (12 studies) scores, but not LAZ–HAZ score (figure 4; table 3). Only four studies reported social-emotional outcomes, therefore we did not calculate the pooled estimate for this score. Stratifying by study setting, we found that studies done in low-income and middle-income countries showed estimates similar to the unstratified results. Two studies alone were done in high-income countries. Sensitivity analyses excluding outliers and low-quality comparisons resulted in a similar pattern of effects (appendix p 23). Forest plots for studies promoting responsive care and learning opportunities are shown in the appendix (pp 37–38).

In the secondary analysis of follow-up studies, we were only able to calculate five pooled effect sizes because of the small number of studies in each category of intervention (6 nutrition studies and 5 studies promoting responsive care and learning opportunities). None of the pooled estimates were significant. Among follow-up studies of nutritional supplementation, the pooled effect sizes were 0.03 (95% CI –0.05 to 0.11; 6 studies) for LAZ or HAZ score, –0.08 (–0.19 to 0.02; 6 studies) for





(Figure 3 continues on next page)



**Figure 3: Forest plots of effects on each outcome, arranged by the magnitude of the effect on LAZ or HAZ score**

Effect sizes from the same comparison are in the same row across the forest plots, with studies arranged from the most negative effect on LAZ or HAZ score at the bottom of the plot to the most positive effect at the top. If an association between LAZ or HAZ and developmental outcomes existed, we would expect larger negative effect sizes across the bottom of the forest plots and larger positive effect sizes across the top of the forest plots. LAZ or HAZ=length-for-age or height-for-age Z scores.

cognitive score, and  $-0.03$  ( $-0.18$  to  $0.12$ ; 6 studies) for motor score. Among follow-up studies of interventions promoting nurturing care and learning opportunities, the pooled effect sizes were  $0.06$  (95% CI  $-0.12$  to  $0.25$ ; 5 studies) for LAZ or HAZ score and  $0.15$  ( $-0.07$  to  $0.36$ ; 5 studies) for cognitive or mental scores.

## Discussion

In our systematic review and meta-analysis of early life interventions (during pregnancy or in children aged 5 years or younger) that measured both LAZ–HAZ and developmental outcomes (122 intervention versus control group comparisons in 75 studies), we found that effects on LAZ–HAZ scores were not significantly associated with effects on cognitive, language, or motor development scores. These findings contradict the assumption that improvements in LAZ–HAZ correspond to overall improvements in neurobehavioural development.

The majority of studies included (51 of 75) in our review and meta-analysis provided nutritional supplements to mothers, children, or both. This subgroup of nutrition interventions had small, but significant, positive pooled effect sizes on all five outcomes. In the meta-regression of nutrition interventions, each 1 SD difference in effect size of LAZ–HAZ score was significantly associated with 0.40 SD difference in cognitive effect size and 0.43 SD difference in motor effect size. However, given the mean effect size of 0.05 on LAZ–HAZ scores across nutritional interventions, we can expect a small difference of 0.02 SD in cognitive and motor scores with each 0.05 SD difference in LAZ–HAZ score.

The second greatest category of interventions were those promoting responsive care and learning opportunities (14 of 75 studies). This number of studies was insufficient to do meta-regression, but sufficient to

calculate pooled effect sizes. Effects on LAZ–HAZ score were not significant, but the effects on cognitive, language, and motor development scores were 4 to 5 times larger than those resulting from nutritional supplementation. These findings suggest that interventions targeting these aspects of caregiving might have effects on developmental outcomes 4 to 5 times larger than those of interventions providing nutritional supplements.

We stratified nutrition supplementation studies by setting, timing, and type of supplementation. Small, but significant, positive pooled effects on both LAZ–HAZ and development scores were found in studies done in low-income and middle-income countries, but not in those done in high-income countries; studies that provided child supplementation, but not in those providing maternal supplementation; and in studies that provided both macronutrients and micronutrients, but not in those providing micronutrients alone. These findings suggest that the common nutritional determinant of faltering in both linear growth and development in children in low-income and middle-income countries is an inadequate dietary intake of macronutrients and micronutrients during early childhood.

Our findings show that development is more responsive to interventions than linear growth. Several types of interventions had positive effects on developmental scores but not on LAZ–HAZ scores, specifically supplementation with multiple micronutrients and interventions promoting responsive care and learning opportunities. These differences highlight the importance of measuring developmental outcomes of randomised controlled trials, rather than using LAZ–HAZ score as a proxy for development.

Previous meta-analyses<sup>89–91</sup> of effects of postnatal nutritional interventions on LAZ–HAZ score have found effect sizes that were similar to the small effect size that we observed. A meta-analysis<sup>89</sup> of supplementary feeding interventions in children aged 3 months to 5 years found a significant pooled effect on LAZ–HAZ score of 0.15 in nine studies. A meta-analysis<sup>90</sup> of 24 studies of iron supplementation interventions found a non-significant pooled effect on LAZ–HAZ score of 0.01. A meta-analysis<sup>91</sup> of 50 zinc supplementation intervention studies found a positive pooled effect of 0.1 on HAZ score. We found pooled effects on LAZ–HAZ score in a similar range,

|                        | All studies           |                      |         | Nutrition supplementation studies |                       |         |
|------------------------|-----------------------|----------------------|---------|-----------------------------------|-----------------------|---------|
|                        | Number of comparisons | $\beta$ (95% CI)     | p value | Number of comparisons             | $\beta$ (95% CI)      | p value |
| Cognitive score        | 84                    | 0.18 (–0.36 to 0.72) | 0.51    | 54                                | 0.40 (0.04 to 0.77)   | 0.049   |
| Language score         | 66                    | 0.12 (–0.07 to 0.31) | 0.21    | 40                                | 0.16 (–0.12 to 0.44)  | 0.27    |
| Motor score            | 102                   | 0.23 (–0.05 to 0.50) | 0.11    | 69                                | 0.43 (0.11 to 0.75)   | 0.014   |
| Social-emotional score | 58                    | 0.23 (0.05 to 0.41)  | 0.016   | 37                                | –0.04 (–0.37 to 0.29) | 0.83    |

LAZ or HAZ=length-for-age or height-for-age Z scores.

**Table 1: Associations between effect sizes on LAZ or HAZ and effect sizes on developmental outcomes**

|  | LAZ or HAZ score |                           |         | Cognitive or mental score |                          |         | Language score |                         |         | Motor score |                         |         | Social-emotional score |                         |         |
|--|------------------|---------------------------|---------|---------------------------|--------------------------|---------|----------------|-------------------------|---------|-------------|-------------------------|---------|------------------------|-------------------------|---------|
|  | n                | ES (95% CI)               | p value | n                         | ES (95% CI)              | p value | n              | ES (95% CI)             | p value | n           | ES (95% CI)             | p value | n                      | ES (95% CI)             | p value |
| All nutritional supplementation studies                | 50               | 0.05<br>(0.01 to 0.09)    | 0.013   | 38                        | 0.06<br>(0.03 to 0.10)   | 0.0010  | 21             | 0.08<br>(0.03 to 0.13)  | 0.0053  | 41          | 0.08<br>(0.04 to 0.12)  | 0.0003  | 20                     | 0.07<br>(0.02 to 0.12)  | 0.0101  |
| Studies stratified by study setting                    |                  |                           |         |                           |                          |         |                |                         |         |             |                         |         |                        |                         |         |
| Studies in LMICs                                       | 44               | 0.05<br>(0.02 to 0.09)    | 0.0081  | 32                        | 0.07<br>(0.03 to 0.10)   | 0.0010  | 21             | 0.08<br>(0.03 to 0.13)  | 0.0053  | 37          | 0.08<br>(0.04 to 0.12)  | 0.0003  | 20                     | 0.07<br>(0.02 to 0.12)  | 0.0101  |
| Studies in HICs  | 6                | -0.14<br>(-0.17 to -0.10) | 0.0004  | 6                         | -0.02<br>(-0.13 to 0.08) | 0.67    | 0              | ..                      | ..      | 4           | ..                      | ..      | 0                      | ..                      | ..      |
| Studies stratified by study timing                     |                  |                           |         |                           |                          |         |                |                         |         |             |                         |         |                        |                         |         |
| Maternal nutritional supplementation                   | 12               | -0.01<br>(-0.03 to 0.02)  | 0.54    | 11                        | 0.04<br>(-0.03 to 0.11)  | 0.27    | 6              | 0.01<br>(-0.05 to 0.07) | 0.69    | 8           | 0.07<br>(-0.03 to 0.17) | 0.19    | 5                      | 0.04<br>(-0.02 to 0.09) | 0.24    |
| Child nutritional supplementation                      | 30               | 0.07<br>(0.02 to 0.12)    | 0.0063  | 21                        | 0.08<br>(0.05 to 0.11)   | <0.0001 | 13             | 0.13<br>(0.07 to 0.20)  | 0.0011  | 27          | 0.09<br>(0.04 to 0.14)  | 0.0016  | 13                     | 0.09<br>(0.03 to 0.16)  | 0.018   |
| Maternal and child nutritional supplementation         | 3                | ..                        | ..      | 0                         | ..                       | ..      | 3              | ..                      | ..      | 3           | ..                      | ..      | 3                      | ..                      | ..      |
| Stratified by type of nutritional supplement           |                  |                           |         |                           |                          |         |                |                         |         |             |                         |         |                        |                         |         |
| Supplementation with macronutrients and micronutrients | 17               | 0.09<br>(0.04 to 0.14)    | 0.0038  | 7                         | 0.03<br>(-0.06 to 0.12)  | 0.51    | 10             | 0.09<br>(0.03 to 0.16)  | 0.026   | 17          | 0.09<br>(0.02 to 0.16)  | 0.019   | 10                     | 0.10<br>(0.03 to 0.18)  | 0.027   |
| Supplementation with multiple micronutrients           | 14               | 0.00<br>(-0.02 to 0.02)   | 0.99    | 13                        | 0.09<br>(0.04 to 0.14)   | 0.0025  | 9              | 0.11<br>(0.06 to 0.17)  | 0.0026  | 12          | 0.08<br>(0.03 to 0.12)  | 0.0051  | 5                      | 0.08<br>(0.05 to 0.10)  | 0.0025  |
| Supplementation with a single micronutrient            | 18               | 0.01<br>(-0.05 to 0.07)   | 0.77    | 16                        | 0.04<br>(-0.01 to 0.09)  | 0.16    | 6              | 0.01<br>(-0.08 to 0.09) | 0.91    | 13          | 0.09<br>(0.02 to 0.17)  | 0.027   | 6                      | 0.05<br>(-0.06 to 0.16) | 0.43    |

All studies done in LMICs, unless specified otherwise. n indicates the number of comparisons. LAZ or HAZ=length-for-age or height-for-age Z scores. ES=effect size. LMICs=low-income and middle-income countries. HICs=high-income countries.

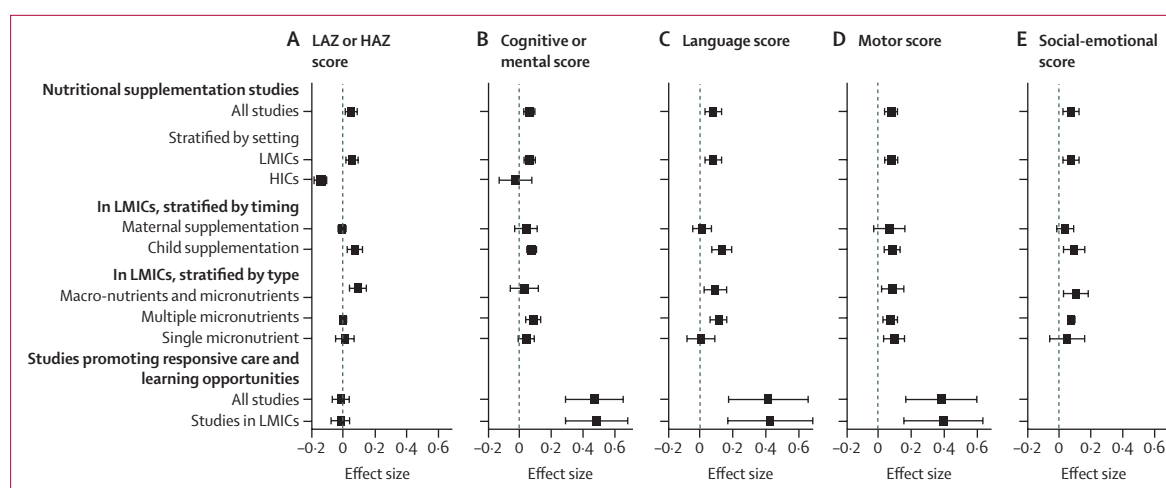
**Table 2: Pooled ES of nutritional supplementation studies**

despite including fewer studies because we restricted our meta-analysis to studies that assessed both LAZ–HAZ and developmental outcomes.

The pooled effects on developmental scores in our meta-analysis were also similar to those of previous meta-analyses.<sup>92,93</sup> A meta-analysis<sup>92</sup> of the effect of nutritional supplementation studies during pregnancy (10 studies) and in children aged 0–2 years (23 studies) on cognitive or mental development outcomes found that maternal supplementation had a non-significant effect, whereas child supplementation had a significant effect size of 0.08. Our finding of the effects of responsive care and learning opportunities on developmental scores is similar to a previous meta-analysis<sup>93</sup> of 21 interventions aimed at enhancing developmental stimulation and 18 interventions that provided nutritional supplementation to children aged 0–2 years. In that meta-analysis,<sup>93</sup> stimulation interventions had an effect size of 0.42 on cognitive development outcomes and 0.47 on language development outcomes, whereas nutritional supplementation had an effect size of 0.09 on cognitive outcomes. Together, these findings highlight the importance of parenting

programmes to encourage responsive care, learning opportunities, and developmental stimulation during early life to support thriving populations.

To our knowledge, this is the first meta-analysis of nutrition supplementation interventions to calculate pooled effects on social-emotional outcomes. We found that effects of interventions on LAZ–HAZ scores were significantly associated with effects on social-emotional scores in the full group of interventions, but not in the subgroup of nutrition supplementation interventions. Because of the small number of studies in categories other than nutrition supplementation interventions, we were unable to assess which type of intervention was driving this association. However, in nutrition supplementation studies, we found positive pooled effects of supplementation with macronutrients and micronutrients and with multiple micronutrients, and supplementation during childhood on social-emotional development. The early development of social-emotional regulation is important to lay the foundation for social-emotional skills during childhood and adulthood, such as the ability to control impulses and



**Figure 4:** Pooled effect sizes on each outcome in stratified analyses

LAZ or HAZ=length-for-age or height-for-age Z scores. LMICs=low-income and middle-income countries. HICs=high-income countries.

|                           | All studies promoting responsive care and learning opportunities |                       |         | Studies promoting responsive care and learning opportunities in LMICs |                       |          |
|---------------------------|--|-----------------------|---------|---|-----------------------|----------|
|                           | n  | Effect size (95% CI)  | p value | n   | Effect size (95% CI)  | p values |
| LAZ-HAZ score             | 14   | -0.01 (-0.07 to 0.05) | 0.74    | 12  | -0.01 (-0.07 to 0.05) | 0.71     |
| Cognitive or mental score | 13   | 0.48 (0.27 to 0.68)   | 0.0003  | 11  | 0.49 (0.27 to 0.72)   | 0.0006   |
| Language score            | 8  | 0.42 (0.13 to 0.72)   | 0.012   | 7   | 0.43 (0.11 to 0.76)   | 0.0018   |
| Motor score               | 12   | 0.38 (0.15 to 0.61)   | 0.0042  | 10  | 0.39 (0.13 to 0.65)   | 0.0084   |
| Social-emotional score    | 4  | ..                    | ..      | 4   | ..                    | ..       |

n indicates the number of comparisons. LMICs=low-income and middle-income countries.

**Table 3:** Pooled effect sizes of studies promoting responsive care and learning opportunities

regulate emotional reactions and social behaviour, which are crucial for mental health, success in school and in the workplace, and healthy peer and family relationships.<sup>34</sup> Our findings suggest that child nutrition supplementation interventions might be part of an effective strategy to support the development of these skills.

Our findings also highlight some research gaps. Numerous risk factors for faltering in linear growth and development during childhood have been identified, including poor quality of water and sanitation, poor health during pregnancy, infrequent infant feeding and low dietary diversity, and childhood diarrhoea incidence.<sup>8</sup> However, few randomised trials of interventions targeting these risk factors have measured both LAZ-HAZ and developmental outcomes. More randomised trials are needed to identify and address the risk factors for poor growth and neurodevelopment in low-income and middle-income countries. Additionally, few randomised trials have done follow-up assessments to assess the sustained effects of early life interventions on growth and development. This type of evidence is important to determine the medium-term and long-term effects of early inputs. Another gap that we identified was the reporting of reliability and validity of developmental assessments in the

local context. Of the 61 studies in low-income and middle-income countries, 60 used tests originally developed and validated in a different country, and only 18 reported any information on reliability and validity in the new context.

Our study had several strengths. These include the comprehensive review of early-life randomised controlled trials that measured LAZ-HAZ and developmental outcomes, the large number of studies and participants included, the low risk of bias, and the moderate to strong quality of all but two studies. Our study also had some limitations. We had sufficient data available to calculate pooled estimates for only two categories of interventions, and the use of study-level data might mask individual-level associations between effects on growth and development. Studies using individual-level data would be able to quantify the proportion of intervention effects on developmental scores that are mediated through effects on LAZ-HAZ.<sup>95</sup>

In conclusion, our findings have shown that we cannot assume that improved growth alone will appreciably improve neurobehavioural development in children. We might expect only small gains in growth and development through nutritional supplementation programming. Beyond nutritional interventions, improvements in neurobehavioural development and human



capital require interventions targeting caregiving behaviour and learning opportunities that support the development of cognitive, language, motor, and social-emotional skills.

#### Contributors

ELP, AHS, and LML designed the study. KC, KB, and JNK contributed to data acquisition. ELP and LML analysed data. ELP wrote the first draft of the manuscript. All authors critically reviewed and edited the manuscript.

#### Declaration of interests

We declare no competing interests.

#### Acknowledgments

This publication was supported by unrestricted research funds to ELP from the Department of Nutrition and College of Agricultural and Environmental Sciences, UC Davis, and the US Department of Agriculture's National Institute of Food and Agriculture (Hatch project number CA-D-NTR-2493-H). Data extraction and study quality ratings were done by Xiuping Tan, Huiyao Xie, Chenxi Zhao, William Hsu, Jennie Davis, Monica Magana, Megan Bragg, Zhijun Chen, Gwen Chodur, Rochelle Werner, Yiwen Bao, Liuzixuan Hu, Addison Montgomery, Kai-An Chu, Alice Hsieh, Yung Yung Lee, Amar Ilyas, Ariana Lawrence, Aya Ead, Zengting He, Diane Han, Daisy Liang, Giovanni Beltran, McKenzie Richard, Jing Peng, Lesley Chang, Catherine Jablonski, Krissa Padilla, Xaudi Wang, Brenda Chaidez, Lihua (Maggie) Zeng, Tinala Wang, and Rosario Lopez. Charles Arnold provided statistical advice.

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