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Short Communication

Effects of an intervention on infant growth and development: evidence for different mechanisms at work

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Abstract

Millions of children in low-income and middle-income countries falter in linear growth and neurobehavioral development early in life. This faltering may be caused by risk factors that are associated with both growth and development, such as insufficient dietary intake and infection in infancy. Alternatively, these risk factors may be indicative of an environment that constrains both linear growth and development through different mechanisms. In a cluster-randomized trial in Burkina Faso, we previously found that provision of lipid-based nutrient supplements plus malaria and diarrhoea treatment from age 9 to 18 months resulted in positive effects of ~0.3 standard deviation on length-for-age z-score (LAZ) and of ~0.3 standard deviation on motor, language and personal–social development scores at age 18 months. In this paper, we examined whether the effect of the intervention on developmental scores was mediated by the effect on LAZ, or, alternatively, whether the intervention had independent effects on growth and development. For motor, language, and personal–social z-scores, the effect of the intervention decreased from 0.32 to 0.21, from 0.33 to 0.27 and from 0.35 to 0.29, respectively, when controlling for change in LAZ from 9 to 18 months. All effects remained significant. These results indicate that the intervention had independent positive effects on linear growth and development, suggesting that these effects occurred through different mechanisms.

Keywords: infant growth, infant development, infant interventions, growth faltering, low-resource settings, neurobehavioral development.

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Introduction

Children born into disadvantaged circumstances are at risk for falling behind their more advantaged peers in both linear growth and neurobehavioral development early in life, even before they reach age 2 years (Victora *et al.* 2008). Multiple environmental risk factors are associated with early faltering in both growth and development, such as maternal undernutrition, preterm birth, poor care and feeding practices, and clinical and subclinical infection (World Health Organization 2014). In low-income and middle-income countries (LMICs), many studies have found an association between children's growth in height and their cognitive development. A recent meta-analysis reported a pooled estimate of 0.24 standard deviation (SD) difference in cognitive development for every 1 SD difference in length-for-age *z*-score (LAZ) in children under 2 years of age in LMICs (Sudfeld *et al.* 2015). This association between height gain and development is not observed in healthy populations in high-income countries (Belfort & Gillman 2013).

One interpretation of the association between stunting in height and delayed development in LMICs is that exposure to common risk factors, such as insufficient dietary intake and infection before age 2 years, leads to faltering in both linear growth and brain development (Sudfeld *et al.* 2015). A potential implication is that interventions to prevent faltering in linear growth will also prevent faltering in development

(Victora *et al.* 2008). Alternatively, this cluster of risk factors may be indicative of an environment that constrains both linear growth and development through different mechanisms. In this case, interventions that prevent faltering in linear growth might not result in improvements in development. It is also possible that effects of interventions on growth and development may operate through different mechanisms.

We recently conducted a cluster-randomized trial in rural Burkina Faso, in which we observed positive effects on both linear growth (Hess *et al.* 2015) and child development (Prado *et al.* In Press) at age 18 months. In the intervention cohort (IC), 2435 children received 20 g lipid-based nutrient supplements (LNSs) per day containing varying amounts of zinc, as well as weekly diarrhoea and malaria surveillance and treatment, from age 9 to 18 months. In the non-intervention cohort (NIC), 785 children received no intervention during the same period. At age 18 months, children in IC were significantly taller (IC: 77.7 ± 3.0 cm vs. NIC: 76.9 ± 3.4 cm, $P < 0.001$), and stunting prevalence was significantly lower (IC: 29.3% vs. NIC: 39.3%; $P < 0.0001$) (Hess *et al.* 2015). In LAZ units based on World Health Organization norms (WHO Multicentre Growth Reference Study Group 2006), the effect size was 0.31 SDs (95% confidence interval 0.21–0.41). Development was assessed at 18 months in a subgroup ($n = 746$ IC; $n = 376$ NIC) using the Developmental Milestones Checklist-II (Prado *et al.* 2014). Children in IC scored 0.34 (95% confidence interval 0.21–0.46), 0.30 (0.15–0.44) and 0.32 (0.16–0.48) SD higher in motor, language and personal–social development, respectively, than children in NIC (Prado *et al.* In Press).

Participants and methods

The study reported here was embedded in a larger trial, which was part of the International Lipid-Based Nutrient Supplements Project. The objective of the trial was to compare zinc-related functional responses, such as growth and morbidity, among children who received varying doses of zinc in LNSs or as a water-dispersible tablet. The methods of the larger trial and primary outcomes are reported by Hess *et al.* (2015) (Hess *et al.* 2015). First, 34 communities were stratified by selected indicators (population size; proximity to road and the city of Bobo-Dioulasso; and health clinic affiliation) and then were randomly assigned within strata to participate in the IC (25 communities) or in the NIC (9 communities). Second, 2435 nine-month-old children in the IC communities were randomly assigned to one of the following supplement groups: (1) 20 g LNSs/day containing 0 mg added zinc and a placebo tablet (LNS-Zn0), (2) 20 g LNSs/day containing 5 mg added zinc and a placebo tablet (LNS-Zn5), (3) 20 g LNSs/day containing 10 mg added zinc and a placebo tablet (LNS-Zn10) or (4) 20 g LNSs/day containing 0 mg added zinc and a tablet containing 5 mg zinc (LNS-TabZn5). Children in the IC were visited weekly during the 9-month intervention period for the delivery of intervention products and for the collection of morbidity and adherence data. The fieldworker provided treatment for uncomplicated diarrhoea, fever and malaria confirmed by a rapid diagnostic test. Diarrhoea, fever and malaria with complications and any other cases of severe illness were referred to the health centre for evaluation and treatment. In the NIC, 785 nine-month-old children were enrolled in

Key messages

- Millions of children in low- and middle-income countries falter in linear growth and neurobehavioral development early in life.
- We found that an intervention among infants in Burkina Faso had independent effects on linear growth and development.
- The intervention apparently affected growth and development through different mechanisms, suggesting that the underlying causes for the two types of faltering are different.
- It cannot be assumed that interventions that improve growth will always improve developmental outcomes, or vice versa.

the trial. At enrolment, they were screened and treated or referred for any illnesses in the same way as children in the IC. They were subsequently visited after a period of 9 months, during which they did not receive any supplements, visits, morbidity monitoring or treatment from project personnel.

The LNS products were developed and produced by Nutriset SAS (Malaunay, France). Twenty grams of LNSs contained 118 kcal, 2.6 g protein, 9.6 g fat, 4.46 g linoleic acid, 0.58 g α-linoleic acid, 400 µg vitamin A (retinyl acetate), 0.3 mg thiamine, 0.4 mg riboflavin, 4 mg niacin, 1.8 mg pantothenic acid, 0.3 mg vitamin B6, 0.5 µg vitamin B12, 80 µg folic acid (pteroyl monoglutamic acid), 30 mg vitamin C (L-ascorbic acid), 5 µg vitamin D (cholecalciferol), 6 mg vitamin E (DL-alpha-tocopherol acetate), 30 µg vitamin K (phylloquinone 5%), 280 mg calcium (tricalcium phosphate), 0.34 mg copper, 90 µg iodine, 6 mg iron, 40 mg magnesium, 1.2 mg manganese, 190 mg phosphorus, 200 mg potassium and 20 µg selenium.

A subsample of 446 children from NIC and 980 children from three of the four IC groups (LNS-Zn0, LNS-Zn10 and LNS-TabZn5) was randomly selected for motor, language and personal–social assessment at 18 months of age. We were able to obtain developmental assessment data from 346 NIC children and 746 IC children.

Ethical approval for the study procedures was obtained from the Institutional Review Board of the University of California Davis and the Comité d'Ethique Institutionnel du Centre Muraz, Bobo Dioulasso. The study was registered with the US National Institute of Health as a clinical trial (www.ClinicalTrials.gov; NCT00944281).

We examined whether the effect of the intervention on developmental scores was mediated by the effect on LAZ, or, alternatively, whether the intervention had independent effects on growth and development. Because the intervention also reduced wasting and anaemia (Hess *et al.* 2015), we also tested whether the change in weight-for-length z-score (WLZ) or haemoglobin (Hb) mediated the effect of the intervention on development. LAZ and WLZ were calculated based on World Health Organization norms (WHO Multicentre Growth Reference Study Group 2006), and Hb z-score (HbZ) was calculated based on our sample. Changes in LAZ, WLZ and HbZ from baseline to endline were calculated by subtracting values at 9 months from values at 18 months. We included child, maternal and household factors in the model as covariates, as listed in the footnotes of Tables 1 and 2. The analysis included 1112 children for whom complete information was available (741 IC, 371 NIC).

Results

Table 1 shows the association of the 18-month motor, language and personal-social *z*-scores with each baseline measure and with each potential mediator. Change in LAZ from age 9 to 18 months was significantly associated with all three developmental z-scores, indicating that height gain was a potential mediator for all three scores. Changes in WLZ and HbZ from age 9 to 18 months were only associated with motor *z*-scores; therefore, these were potential mediators for motor *z*-scores only.

Table 2 shows the effect of the intervention on each developmental *z*-score in (1) unadjusted models, (2) models adjusting for covariates and (3) models adjusting for covariates and each potential mediator. The final column shows the model adjusted for all potential mediators. None of the potential mediators fully accounted for the effect of the intervention on developmental *z*-scores. For language *z*-scores, the effect of the intervention decreased from 0.33 to 0.27 after controlling for change in LAZ and remained highly significant. Similarly for personal-social *z*-scores, the effect decreased from 0.35 to 0.29, and remained highly significant. For motor *z*-scores, the effect of the intervention decreased from 0.32 to 0.21 when controlling for change in LAZ and decreased further to 0.14 when controlling for all three potential mediators. Although this effect decreased by half, it also remained significant.

Discussion

These results show that the intervention had independent effects on growth and development, suggesting that the intervention affected growth and development

Table 1. Association of each 18-month developmental z-score with each potential mediator adjusting for covariates[1]

	Baseline measure			Potential mediator		
18-month developmental z-score	9-month LAZ	9-month WLZ	9-month HbZ	Change in LAZ 9 to 18 months	Change in WLZ 9 to 18 months	Change in HbZ 9 to 18 months
Language z-score	0.13*** (0.07 to 0.19)	0.07* (0.01 to 0.14)	0.10** (0.03 to 0.18)	0.21*** (0.12 to 0.3)	0.05 (−0.02 to 0.13)	0.04 (−0.02 to 0.10)
Motor z-score	0.27*** (0.22 to 0.32)	0.14*** (0.09 to 0.20)	0.12*** (0.05 to 0.18)	0.41*** (0.33 to 0.49)	0.13*** (0.07 to 0.20)	0.13*** (0.08 to 0.17)
Personal-Social z-score	0.17*** (0.11 to 0.23)	−0.02 (−0.08 to 0.05)	0.06 (−0.02 to 0.14)	0.25*** (0.16 to 0.35)	−0.03 (−0.10 to 0.05)	0.03 (−0.02 to 0.09)

*$P < 0.05$. **$P < 0.01$. ***$P < 0.001$. [1]Covariates were child factors: sex and age at developmental assessment; maternal factors: baseline education and height; household factors: baseline asset index below median, and baseline household food insecurity access index (adjusted for season) above median, 18-month household stimulation index; season during the majority of the enrollment period and data collector. *P*-values were generated in multiple linear regression models with all baseline measures (9-month LAZ, WLZ and HbZ), potential mediators (Change in LAZ, WLZ, and HbZ), and covariates included together in every model. Values show the Estimate (95% confidence interval).
Hbz, Hb z-score; LAZ, length-for-age z-score; WLZ, weight-for-length z-score.

Table 2. Effect of the intervention on each developmental z-score in unadjusted and adjusted models

	Adjusted for cluster randomization	Adjusted for cluster and covariates[1]	Adjusted for cluster, covariates[1] and change in LAZ from 9 to 18 months	Adjusted for cluster, covariates[1] and change in WLZ from 9 to 18 months	Adjusted for cluster, covariates[1] and change in Hb from 9 to 18 months	Adjusted for cluster, covariates[1] and change in LAZ, WLZ, and Hb
Language z-score	0.35*** (0.20 to 0.50)	0.33*** (0.18 to 0.47)	0.27*** (0.13 to 0.42)	–	–	–
Motor z-score	0.38*** (0.21 to 0.55)	0.32*** (0.20 to 0.45)	0.21*** (0.09 to 0.33)	0.29*** (0.16 to 0.41)	0.25*** (0.13 to 0.37)	0.14* (0.01 to 0.26)
Personal-social z-score	0.35*** (0.17 to 0.53)	0.35*** (0.20 to 0.50)	0.29*** (0.14 to 0.44)	–	–	–

***$P < 0.001$. *$P < 0.05$. [1]Covariates were child factors: baseline LAZ, baseline WLZ, baseline HbZ sex, and age at developmental assessment; maternal factors: baseline education and height; household factors: baseline asset index below median, baseline household food insecurity access index (adjusted for season) above median, and 18-month household stimulation index; season during the majority of the enrollment period, and data collector. P-values were estimated using linear mixed models with a random effect of community on intercept, to account for cluster-randomization by community. Values show the Estimate (95% confidence interval). *Note:* Change in WLZ and change in HbZ were not candidates for mediation for language and personal-social scores, since these variables were not associated with these scores.
Hbz, Hb z-score; LAZ, length-for-age z-score; WLZ, weight-for-length z-score.

through different mechanisms. Several factors may account for the independence of these effects. First, the supplements provided to children in IC contained both type I nutrients, such as iron, iodine, selenium and calcium, and type II nutrients, such as zinc, magnesium, phosphorous and potassium. When children are deficient in type I nutrients, tissue concentrations of the nutrient decrease, affecting the metabolic processes that depend on the nutrient, while growth is generally maintained. In contrast, when children are deficient in type II nutrients, tissue concentrations are maintained, while growth is reduced (Golden 1995). Several nutrients that are important for brain development, such as iron, iodine and B-vitamins, are type I nutrients. Thus, it is possible that children who primarily experienced deficiency in these type I nutrients showed greater improvements in development, while children who primarily experienced deficiency in type II nutrients showed greater improvements in growth.

Second, factors that constrain children's growth response to an intervention may be different from those that constrain their response in development. For example, maternal short stature may constrain growth response but not development response. However, in the current dataset, this hypothesis was not supported; in children of both taller and shorter mothers, the effect of the intervention on growth (and development) was consistent. Finally, the window for potential recovery may be different for growth and development. For example, it may be difficult to fully recover from growth faltering that occurs before birth, while the plasticity of the developing brain may enable children to catch up in brain development after an early insult (Kolb & Gibb 2001). Our results suggest that it cannot be assumed that interventions that improve growth will always improve developmental outcomes. Further research is needed to understand the association between linear growth and development and the mechanisms through which interventions may improve each outcome.

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Conflict of interest statement

Kenneth Brown has worked as a consultant and later as an employee for the Bill & Melinda Gates Foundation. None of the other authors have financial relationships or conflict of interest relevant to this article to disclose.

Contributions

KHB and SYH were responsible for the design of the iLiNS-ZINC study and supervised study implementation. SA, EYJ and JWS implemented the study and supervised data collection. EP led the developmental assessments, completed the statistical analyses and drafted the manuscript. KGD supervised EP in the developmental assessments and led the overall iLiNS study. All authors read and approved the final manuscript.

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