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Environmental enteric dysfunction: An overview

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Abstract

Background—Environmental enteric dysfunction (EED) refers to an incompletely defined syndrome of inflammation, reduced absorptive capacity, and reduced barrier function in the small intestine. It is widespread among children and adults in low- and middle-income countries. Understanding of EED and its possible consequences for health is currently limited.

Objective—A narrative review of the current understanding of EED: epidemiology, pathogenesis, therapies, and relevance to child health.

Methods—Searches for key papers and ongoing trials were conducted using PUBMED 1966–June 2014; ClinicalTrials.gov; the WHO Clinical Trials Registry; the Cochrane Library; hand searches of the references of retrieved literature; discussions with experts; and personal experience from the field.

Results—EED is established during infancy and is associated with poor sanitation, certain gut infections, and micronutrient deficiencies. Helicobacter pylori infection, small intestinal bacterial overgrowth (SIBO), abnormal gut microbiota, undernutrition, and toxins may all play a role. EED is usually asymptomatic, but it is important due to its association with stunting. Diagnosis is frequently by the dual sugar absorption test, although other biomarkers are emerging. EED may partly explain the reduced efficacy of oral vaccines in low- and middle-income countries and the increased risk of serious infection seen in children with undernutrition.

Conclusions—Despite its potentially significant impacts, it is currently unclear exactly what causes EED and how it can be treated or prevented. Ongoing trials involve nutritional supplements, water and sanitation interventions, and immunomodulators. Further research is

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needed to better understand this condition, which is of likely crucial importance for child health and development in low- and middle-income settings.

Keywords

Environmental enteric dysfunction; environmental enteropathy; malnutrition; stunting

Introduction

Environmental enteric dysfunction (EED) is a poorly understood condition that may have far-reaching impacts on child growth, health, and development in low- and middle-income country settings. Characterized by small intestinal inflammation and strongly associated with stunting (low height-for-age), it is now the subject of significant research interest as investigators seek to define its causes, pathogenesis, consequences, and possible preventive or curative approaches.

The earliest descriptions of EED, previously known as “tropical enteropathy,” date back to the 1960s, when an abnormal microscopic appearance of the small bowel was observed in adults from low- and middle-income countries [1]. It was observed that the villi were blunted and shortened, leading to a decreased surface area for nutrient absorption. Tropical enteropathy was renamed “environmental enteropathy” in the late 2000s in recognition of emerging evidence that the quality of the environment was more important than climate or latitude; EED is not limited to tropical areas, nor does it affect all residents in the tropics. Over the past year, it has been further renamed “environmental enteric dysfunction.”

There is no universally accepted case definition or specific diagnostic criteria for EED, and it does not have immediately apparent clinical symptoms. The key demonstrable histological features (villous flattening, crypt hyperplasia, and lymphocytic infiltration of the lamina propria [2–5]) are not unique to EED. Tropical sprue (a syndrome of chronic diarrhea, malabsorption, and malnutrition seen in residents of tropical countries) and EED were initially thought to be the same process, with symptomatic tropical sprue the most severe pathology but representing the “tip of the iceberg” of largely unrecognized EED, although this distinction remains unclear [6]. There are also some similarities with other chronic gut inflammatory conditions, such as celiac disease and inflammatory bowel disease (Crohn’s disease and ulcerative colitis) [7].

Impact of EED on health and nutrition

Impact on nutrition and development

Childhood EED has been associated with stunting (low height-for-age) for as long as it has been a recognized entity [8–12] although it is not entirely clear which of these two is the primary instigator and which the consequence. A 2008 systematic review of the effectiveness of existing complementary feeding interventions for malnutrition among 6- to 24-month-olds suggested that they had only moderate benefits and that EED may be a key factor limiting effectiveness [13]. Nutritional intervention alone may not be fully addressing the problem of stunting among infants and children in low- and middle-income country settings—with EED possibly explaining this shortfall [14].

There are many ways, other than malabsorption, in which chronic intestinal inflammation could impact growth. One proposed mechanism is appetite suppression, since this—rather than food availability—is often a key factor restricting children's food intake [15]. Proinflammatory cytokines are known to act on appetite centers in the brain [16]. Another proposed mechanism is via negative regulation of systemic inflammatory activation on signaling through the growth hormone–insulin-like growth factor 1 (IGF-1) axis, which has been clearly demonstrated in pediatric Crohn's disease [16, 17]. A similar situation may occur in EED: indeed, higher blood inflammatory markers in Zimbabwean infants were associated with lower levels of IGF-1 and with stunting [18].

Stunting has devastating consequences for child health. Difficult to reverse beyond 2 years of age, it has long-lasting effects on health and development [19, 20]. A meta-analysis in 2007 suggested that each year 200 million children do not reach their developmental potential due to stunting [21]. Certain noncommunicable diseases in adulthood are associated with stunting in childhood, perhaps through epigenetic regulation (which refers to long-term alteration in gene expression) or via chronic inflammation [22].

Impact on immunity

The gut is the site of a highly sophisticated immune surveillance operation, the purpose of which is to detect and destroy potential pathogens and maintain the integrity of host tissues while at the same time avoiding unhelpful immune responses against foods, nonpathogenic microorganisms, and other harmless contents of the gut lumen. The presence of abnormally large numbers of white blood cells in the gut wall of children and adults with EED suggests that this surveillance operation is being stressed. Impaired barrier function (a hallmark of EED) results in luminal contents (including both harmless and potentially pathogenic bacteria) crossing the gut wall itself and activating the immune system. Chronic inflammation is triggered, which may be a direct cause of growth failure (as described above) and may impair antipathogen surveillance capacity. The nature of this chronic inflammation remains poorly understood. This is partly because it is a difficult phenomenon to study, since biopsy samples from children with EED are scarce. However, in recent years there have been a number of fundamental advances in our understanding of mucosal immunity coming from work with mouse models of human disease, and it is possible that approaches utilizing animal model systems will further our understanding of EED and even guide clinical and public health management in the future [23–25]. Lastly, although the exact mechanism is unclear, EED has been implicated in the poor response to oral vaccines (polio and rotavirus) seen in children living in low- and middle-income countries [7, 26–28].

Diagnosis: How do we identify the child with EED?

To confirm the diagnosis of EED beyond doubt requires demonstration of the histological features of EED. This can only be done by endoscopy and small intestinal biopsy. The logistical challenges of this have led investigators to seek simpler biomarkers for EED: less invasive tests that measure proxy biomarkers are used to quantify gut inflammation and reduced barrier function.

The dual sugar absorption tests

To date, the most frequently used tests for EED are the dual sugar absorption tests. The most commonly implemented of these at present is the lactulose:mannitol (L:M) test, although other sugars, such as xylose and rhamnose, can be used. Lactulose is a large sugar that is not normally absorbed by the small intestine. Mannitol is a smaller sugar that is absorbed by the small intestine in proportion to absorptive surface area. In the L:M test, after oral ingestion, both lactulose and mannitol are excreted intact in the urine following minimal metabolism. Urinary mannitol therefore gives an index of absorptive capacity, while the presence of lactulose in the urine indicates impaired barrier function. Higher urinary L:M ratios reflect greater abnormalities of one or both functions [8, 29, 30].

The L:M test requires cooperation and understanding from the participant and the carer, which may present a challenge when the test is performed in very young children. Ensuring complete collection of all urine voided over up to 5 hours and avoiding contamination with feces is difficult in infants and requires parental patience. Measurement of lactulose and mannitol in urine can be performed by enzyme-linked immunosorbent assay (ELISA), anion exchange chromatography, or mass spectrometry. All of these methods require centralized laboratory equipment and expertise, and the results are not always comparable between laboratories.

Emerging biomarkers

New biomarkers of EED are being actively investigated. Current markers of gut inflammation are measured in feces: calprotectin [31–34]; myeloperoxidase, neopterin, and α-1-antitrypsin [35]; mRNA [36]; REG1b [37]; lactoferrin [38]. Markers of gut permeability are measured in blood: zonulin; [39] EndoCAb; [11, 12, 18, 39] soluble CD14 [18]. Lastly, a marker of total enterocyte mass is also measured in blood: citrulline [40].

By investigating and testing markers for their hypothesized roles in the establishment and maintenance of EED, our understanding of the processes causing EED will hopefully improve. For example, small intestinal epithelial cells from a child with EED are assumed to differ in the kinds of proteins they produce from those from a child without EED. Certain mRNA transcripts with roles in inflammatory pathways have been shown to be present more often in the stool of Malawian children with abnormal L:M ratios [36].

Most new markers have been evaluated in association with stunting rather than according to histological changes or the L:M test. Future studies may compare new markers against indicators other than anthropometry, including assessing their abilities to closely reflect short-term changes in EED as defined by a gold standard diagnostic test. Such markers would be useful for evaluating the effects of interventions against EED in trials where follow-up is comparatively brief.

Epidemiology: Who has EED? What are its risk factors?

EED was first recognized in adults. A 1971 study of US Peace Corps volunteers is frequently referred to as the first to demonstrate that EED can be acquired and lost according to environment [41]. Participants were assessed during and after placement in India and

Pakistan. Gut absorptive function tests and biopsies confirmed abnormalities during residence abroad and recovery within 1 or 2 years after return to the United States. At the time, an environmental cause was suggested. A later study of Zambian adults demonstrated the same histological abnormalities, which varied with season, further implying an environmental cause [4]. In the early 1990s, community-wide studies revealed that EED was a widespread and pervasive problem in infants and children. An abnormal L:M test was almost universally acquired by the end of infancy in The Gambia [12, 42, 43] and was associated with stunting among infants and children in many low- and middle-income country settings, including Zambia, Malawi, Bangladesh, India, Nepal, Brazil, and Guatemala and among Aboriginal communities in Australia [5, 8–12, 30, 31, 40, 42–57]. In 1999, a large study measured intestinal permeability and absorptive capacity among asymptomatic adults in 14 countries across the world [58]. Abnormalities of both intestinal absorption and permeability were, in general, found in tropical rather than temperate countries. However, average intestinal absorptive capacity by country also correlated very closely with national gross domestic product per capita, independently of climate, suggesting that poverty may play a more significant role.

Putting these studies together, a consistent picture has emerged: EED seems highly prevalent in low- and middle-income country settings, is acquired during infancy, and persists into adulthood, but can perhaps be cured or improved with change in environment. It is strongly associated with stunting in infants and children.

Etiology: What causes EED?

Nutritional deficiency

Zinc is known to aid recovery of the intestinal mucosa following diarrhea [48] and is recommended as part of standard therapy for diarrhea by the World Health Organization. Zinc deficiency is associated with abnormal L:M ratio in Malawian children [53]. Vitamin A deficiency is associated with abnormal L:M ratio and stunting in Brazilian children [50]. In The Gambia, the least abnormal L:M ratios are observed during the mango season, when vitamin A intake is highest [49]. However, trials of both vitamin A and zinc have had mixed impacts on growth and/or EED markers among children in low- and middle-income countries [47, 49, 50, 52, 59, 60]. Multiple micronutrient supplementation in Zambian adults has yielded improvements in the histological features of EED [61].

Several other nutritional approaches have been proposed to tackle EED, for example, improving the digestibility of food through fermentation, hydrolysis, or enzyme supplementation, or optimizing amino acid profiles to reduce gut inflammation and support repair [62]. Trials of n-3 (omega-3) long-chain polyunsaturated fatty acid (LC-PUFA), a dietary essential fatty acid thought to reduce intestinal inflammation, in The Gambia and of alanyl-glutamine, an essential precursor for rapidly replicating cells such as those lining the small intestine, in Brazil have yielded some positive results (table 1) [31, 51]. These interventional studies and others will improve our understanding of the possible nutritional causes of EED.

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Microorganisms

Nonspecific feco-oral contamination: Role of WASH—Microorganisms in the gut may be important in the establishment and/or maintenance of EED. Their relative importance may differ according to geographic setting, season, age, and feeding practices. Bangladeshi children from cleaner households were observed to have lower risks of both abnormal L:M ratio and stunting than those from less clean households [11]. In Malawian 3- to 5-year-olds, an abnormal L:M test was associated with lack of latrine access and low household water usage [63]. However, a recent systematic review of 14 trials of water, sanitation, and hygiene (WASH) interventions worldwide on anthropometric outcomes for children aged 0 to 18 years suggested a very modest impact of WASH on stunting (with no effect at all among children aged under 2 years) and no impact on underweight or wasting [65]. Observational study of infants and young children in Zimbabwe suggests that a significant proportion of the burden of feco-oral contamination is likely to come not only from well-characterized sources (food, water, and hands) but also from direct eating of soil and animal feces in the course of play and exploration [66]. Several multisite studies are currently ongoing to investigate the effectiveness of different WASH interventions against EED [67–69].

A recent systematic review concluded that good evidence exists for moderate beneficial effects of antibiotics on growth in prepubertal children in low- and middle-income countries [70]. Several antibiotic studies aimed at particular species of pathogen have included EED in their outcomes (table 1).

During the transition period from exclusive breast-feeding to complementary feeding, which frequently occurs much earlier than the recommended 6 months [71], infants are at risk for feco-oral contamination from complementary (weaning) foods. These may be prepared separately from family foods, stored for longer periods, and reheated inadequately [72]. It is during these vital months of high energy demand and immune system development that the benefits of exclusive breastfeeding are lost and a convergence of poor nutrition and feco-oral contamination takes place. The development of EED is also observed during this time. For example, moving from exclusive breastfeeding to mixed feeding and subsequent cessation of breastfeeding altogether are both seen alongside worsening of the L:M ratio in Nepali infants, and early breastfeeding cessation is associated with worse L:M ratio in Guatemalan infants [9, 45]. Although it is difficult to distinguish from the risk of nutritional deficiency that occurs with early cessation of breastfeeding, a possible cause of these observations may be the poor hygiene often associated with complementary feeding.

Specific pathogens—Linear growth-faltering has been linked to concurrent infection with multiple intestinal parasites (*Cryptosporidium* [73], amoeba [74], roundworm [75], and hookworm [76]). Elevated fecal lactoferrin was found among Ghanaian and Brazilian children with enteroaggregative *Escherichia coli* intestinal infection, and in Brazilian children, linear growth impairment was also found [38, 77]. The abnormal histological findings in EED have been linked to infection with hookworm and the bacterium *Citrobacter rodentium* [4]. The parasite *Giardia duodenalis* has been particularly implicated in abnormal L:M ratios in Nepal [9] and acute growth-faltering in Gambian infants [54].

Acute rotavirus infection has been associated with high L:M ratios in Bangladeshi and Peruvian children [48, 78].

More recent advances in molecular pathogen diagnostics, such as the polymerase chain reaction (PCR), have allowed greater range and sensitivity in detecting pathogens. In urban Bangladeshi infants, associations were found between stunting, diarrhea, and EED (measured by EndoCAb, an antibody formed in the bloodstream in response to movement of gut-resident gram-negative bacteria across a leaky gut wall) [39]. Amoeba, *Cryptosporidium*, and enterotoxigenic *E. coli* were important causes of diarrhea in these infants (associations with EED itself were not examined).

The gut microbiome—An imbalance of gut organisms, rather than the presence or absence of specific pathogens, may be important in EED and nutrition. The gut microbiota differs significantly between African and European infants [79] and between malnourished and well-nourished children [80, 81]. Evidence that the microbiome affects nutritional status comes from an experiment where feces from malnourished children were transplanted into gnotobiotic (germ-free) mice that were fed a typical Malawian diet, resulting in the mice becoming malnourished [82]. There are no published studies to date of the gut microbiome in the specific context of EED.

Helicobacter pylori* and small intestinal bacterial overgrowth—Helicobacter pylori* is a bacterial infection best known as a cause of gastric ulcers. It has also been implicated in allowing the passage of live pathogens beyond the stomach through inhibition of stomach acid secretion [83]. In The Gambia, 15% of 0- to 20-month-olds and 46% of 40- to 60-month-olds had evidence of *H. pylori* infection, with higher prevalence among those acutely malnourished or with chronic diarrhea [84–86]. In urban Peru, a high frequency of *H. pylori* infection was noted among children and was associated with a subsequent higher risk of diarrhea [87].

The small intestine is where the majority of nutrient absorption occurs and where the histological abnormalities of EED are seen. In good health, the small intestine is relatively sterile compared with the large intestine. Small intestinal bacterial overgrowth (SIBO) is a condition that can arise secondary to bowel stasis seen, for example, in muscular disorders [88] The gold standard for the diagnosis of SIBO is sampling and culture of fluid from the small intestinal lumen. In the 1970s and 1980s, small intestinal fluid samples from acutely malnourished Indian adults and Gambian and Nigerian children were found to be heavily contaminated with pathogenic bacteria and yeasts regardless of the presence of diarrhea [89–91]. In The Gambia, SIBO was observed in apparently healthy infants, peaking during the first few months of introduction of complementary foods, as exclusive breastfeeding ceases [92].

Testing the hydrogen content of exhaled air is a reasonable method of detecting the presence of bacteria in the small intestine, since the human body does not produce hydrogen except via metabolically active intestinal bacteria [93]. When measured at intervals following ingestion of a sugar substrate, a large, late peak in the hydrogen content of exhaled air indicates metabolism of the sugar by normally resident bacteria in the large intestine. An

earlier, smaller peak indicates abnormal presence of bacteria in the small intestine. This early peak is associated with EED-like small intestinal histologic changes in slum-dwelling Brazilian infants [94], poverty in urban Brazilian children [95], malnutrition and malabsorption in Burmese infants [96], and enteral vaccine failure in Chile [97].

SIBO can be treated successfully with antibiotics [98]. Metronidazole targeted at SIBO (though likely impacting on specific bacterial or parasitic infections, such as *Giardia*, as well) aided recovery from malnutrition in Jamaican children [99], but the nonabsorbable oral antibiotic rifamixin, also targeted at SIBO, was found not to improve L:M ratios in Malawian children [64]. Probiotics have also been investigated, although there is very limited evidence for their effectiveness in treating SIBO [88], and they have not been found to improve L:M ratios in Malawian children [63]. The role of SIBO—and its possible promotion via *H. pylori* infection—in the pathogenesis of EED is therefore still unclear.

HIV enteropathy—Enteropathy, with chronic diarrhea and weight loss, is common in severely immune-suppressed people with HIV infection and those who have progressed to AIDS [100]. The microscopic appearance of the gut in HIV infection is similar to that in EED, especially during late-stage illness. The HIV virus itself may cause direct damage to intestinal epithelium, while also permitting injury by other gut pathogens by weakening host defenses against them. This resultant enteropathy may itself drive HIV disease progression.

Which treatments have already been tried?

Table 1 summarizes selected published trials conducted among children in low- and middle-income country settings where EED has been explicitly targeted. The trials described therein have suggested beneficial effects of zinc, vitamin A, n-3 LC-PUFA, and alanyl-glutamine on L:M ratios. Ongoing studies are now building on these results.

How should our present knowledge of EED affect our practice today?

Testing for EED in a therapeutic context, as part of routine management of moderate acute malnutrition (MAM), severe acute malnutrition (SAM), or stunting, is not presently indicated, since its etiology remains unclear and evidence for benefit from targeted treatments is lacking.

The significant impact of poor WASH on the general health of children is already well established, and there is already evidence that WASH interventions can reduce infectious morbidity and mortality in low- and middle-income country settings [101, 102]. A holistic approach to nutritional rehabilitation that includes attention to minimizing feco-oral contamination in the home or hospital environment should therefore already be prioritized. However, our emerging understanding of the possible benefits of these interventions, perhaps mediated via EED, on nutritional and immune status may further enhance the scale and types of WASH approaches undertaken. As new, noninvasive, cheap, and quick biomarkers of EED and evidence for setting-specific etiology and effective treatments emerge, more specific recommendations will follow.

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Current research, future priorities

There are several ongoing randomized trials of interventions to prevent or treat EED (table 2). Research on EED is a rapidly expanding field. Questions requiring further work include:

» What are the important causes of EED? Is it predominantly due to a specific pathogen, nutritional deficiency, or genetic predisposition?

» How can we diagnose EED using a point-of-use test?

» How prevalent is EED in different settings worldwide?

» What is the impact of EED on child health? How are these effects mediated?

» How can we best prevent EED?

» Once EED is established, is there any role for providing direct (e.g., immunomodulatory) treatment for EED?

Further detailed longitudinal observational studies of EED are needed in varied demographic and geographic settings, focusing on the hypothesized period of establishment of EED (infancy). One ongoing example is the Interactions of Malnutrition & Enteric Infections: Consequences for Child Health and Development (MAL-ED) network: coordinated birth cohorts in Peru, Brazil, Bangladesh, India, Pakistan, Nepal, Tanzania, and South Africa [103]. In addition to repeated measurement of L:M ratios, gut pathogens, and growth, enteral vaccine immunogenicity is being studied within this network.

EED transcends traditional discipline boundaries, so its study requires collaboration among pediatricians, immunologists, gastroenterologists, epidemiologists, water and sanitation experts, nutritionists, and others. The fact that positive findings have been observed in studies investigating a wide range of causes for EED (both nutritional and infective) suggests that EED is likely to be multifactorial in nature and therefore probably not amenable to one single therapy. Understanding this complexity will be crucial to addressing the significant public health issues of childhood malnutrition and susceptibility to infection in low- and middle-income country settings.

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TABLE 1

Selected published trials conducted among children in low- and middle-income country settings where EED has been explicitly targeted[a]

Author and year	Setting	Age group	Intervention and duration	Results: L:M ratio	Results: anthropometry	Notes
Thurnham et al. 2000 [49]	India; rural	2–15 mo	Vitamin A single dose (inpatients) or for 8 wk (outpatients)	Improvement seen within 30 days	Not reported	
Galpin et al. 2005 [63]	Malawi; rural	3–5 yr	*Lactobacillus* 30 days	No difference	No difference	
Lima 2007 [51]	Brazil; rural	7 mo–7 yr	Alanyl-glutamine 10 days	Improvement	Improved WAZ and WHZ but no difference in HAZ	
Trehan et al. 2009 [64]	Malawi; rural	3–5 yr	Rifamixin 7 days	No difference	Not reported	SIBO itself not measured
Goto 2009 [55]	Bangladesh; urban	3–15 mo	Albendazole 3 monthly and secnidazole monthly for 9 mo	No difference	No difference	Possible reason for failure: high *Giardia* reinfection rate
van der Merwe et al. 2013 [31]	The Gambia; rural	3 mo	n-3 LC-PUFA for 6 mo	No difference	Improved MUAC at 9 and 12 mo	Cognition also examined: no difference
Ryan et al. 2014 [47]	Malawi; rural	1–3 yr	Zinc 14 days	Prevented deterioration	No difference	
			Albendazole single dose	Prevented deterioration	No difference	

EED, environmental enteric dysfunction; HAZ, height-for-age z-score; LC-PUFA, long-chain polyunsaturated fatty acid; MUAC, mid-upper-arm circumference; SIBO, small intestinal bacterial overgrowth; WAZ, weight-for-age z-score; WHZ, weight-for-height z-score; WHO, World Health Organization

[a]Searches for key papers and ongoing trials were conducted using PubMed 1966–June 2014, ClinicalTrials.gov, the WHO Clinical Trials Registry, the Cochrane Library, hand searches of the references of retrieved literature, discussions with experts, and personal experience from the field.

TABLE 2

Ongoing randomized trials of interventions to prevent or treat EED[a]

Trial name and design	Setting	Age group	Intervention and duration	Outcomes
Mesalazine in Environmental Enteropathy; double-blind, placebo-controlled, randomized trial	Kenya; urban	1–5 yr (SAM and stunting)	Mesalazine 28 days	Safety, growth, EED biomarkers
WASH Benefits Bangladesh; factorial cluster-randomized trial	Bangladesh; urban	Birth–2 yr	Nutrition and WASH interventions	L:M, growth, diarrhea, neurological development
WASH Benefits Kenya; factorial cluster-randomized trial	Kenya; rural	Birth–2 yr	Nutrition and WASH interventions	Above plus fecal neopterin, α-1-antitrypsin, myeloperoxidase
Sanitation, Hygiene, Infant Nutrition Efficacy Project; factorial cluster-randomized trial	Zimbabwe; rural	Birth–18 mo (plus mothers)	Infant nutrition and household WASH interventions	L:M, growth, fecal neopterin, EndoCAb, sCD14, immune activation markers, IGF-1, IGF-1:IGFBP3
Effectiveness of Micronutrient Supplementation and Fish Oil + Micronutrient Supplementation in the Treatment of Environmental Enteropathy; factorial double-blind, placebo-controlled, randomized trial	Malawi; rural	1–3 yr	Multiple micronutrients and highly purified fish oil 6 mo	L:M, growth, fecal human mRNA
n-3 LC-PUFAs for the Healthy Growth and Development of Infants and Young Children in Southwest Ethiopia; factorial double-blind, placebo-controlled, randomized trial	Ethiopia; rural	6–12 mo (plus breastfeeding mothers)	n-3 LC-PUFA 12 mo	Growth, neurological development
Zinc Resistant Starch Project; single-arm, open label	Malawi; rural	3–5 yr	Resistant starch 28 days	L:M, growth, markers of zinc homeostasis
Intervention and Mechanisms of Alanyl-Glutamine for Inflammation, Nutrition and Enteropathy; factorial double-blind, placebo-controlled, randomized trial	Brazil; urban	2 mo–5 yr	Alanyl-glutamine 10 days	L:M, growth, fecal lactoferrin, fecal cytokines, diarrhea, markers of alanyl-glutamine metabolism

EED, environmental enteric dysfunction; LC-PUFA, long-chain polyunsaturated fatty acid; L:M, lactulose:mannitol; SAM, severe acute malnutrition; WASH, water, sanitation, and hygiene

[a]Trials were ongoing as of June 2014.