The American Journal of Clinical Nutrition 123 (2026) 101095

The American Journal of CLINICAL NUTRITION

journal homepage: https://ajcn.nutrition.org/

Original Research Article

Environmental enteric dysfunction, systemic inflammation, growth hormones, and linear growth in infants in western Kenya: a prospective observational cohort study

Mary Iwaret Otiti [1,2], James Dodd [3], Alloys K'Oloo [1], Micah June [1], Miriam Chomba [1], Duolao Wang [2], Kephas Otieno [1], Simon Kariuki [1], Feiko Ter Kuile [1,2], Stephen Allen [2,*]

[1] *Kenya Medical Research Institute (KEMRI), Centre for Global Health Research, Kisumu, Kenya;* [2] *Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom;* [3] *Global Health Trials Unit, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom*

A B S T R A C T

Background: Environmental enteric dysfunction is associated with chronic systemic inflammation that results in growth hormone resistance and impaired growth although associations differ between settings.

Objectives: We aimed to describe the time of onset and progression of intestinal pathology and explore associations between biomarkers of environmental enteric dysfunction, systemic inflammation, growth hormones, and linear growth in infants in western Kenya.

Methods: In this prospective, observational cohort study, analysis is limited to infants recruited to the control arm (no intervention) of the PROSYNK trial between 28 October, 2020, and 13 January, 2022. Biomarkers of environmental enteric dysfunction, systemic inflammation, growth hormones, and infant length were measured at 6 wk and 3, 6, and 12 mo. Associations between biomarkers, growth hormones, and linear growth between time points were explored.

Results: In 149 infants at age 6 wk, fecal myeloperoxidase (a biomarker of intestinal inflammation) was raised (≥0.2 mg/dL) in 47 of 143 (32.9%) and fecal α_1-antitrypsin (intestinal permeability; ≥26.8 mg/dL) in 26 of 142 (18.3%) infants. Chronic systemic inflammation (plasma α_1-acid glycoprotein, >1 g/dL) occurred from age 3 mo (33/140 infants; 23.6%). Once detected, intestinal inflammation, increased intestinal permeability, and chronic systemic inflammation persisted in most infants. Fecal myeloperoxidase, fecal α_1-antitrypsin, and plasma intestinal fatty acid–binding protein (intestinal integrity) were significantly positively associated with chronic systemic inflammation at some time points. Chronic systemic inflammation was significantly negatively associated with insulin-like growth factor 1 and insulin-like growth factor–binding protein 3 at 3, 6, and 12 mo. In multiple regression analysis, fecal α_1-antitrypsin at age 6 mo was negatively associated with subsequent change in length-for-age *z*-score ($n = 124$; coefficient: −0.32; 95% CI: −0.50, −0.13; $P = 0.001$).

Conclusions: Targeting young infants with environmental enteric dysfunction, and especially increased gut permeability, may prevent or ameliorate chronic systemic inflammation and improve growth and development in infants in western Kenya.

The PROSYNK trial was registered at the Pan African Clinical Trials Registry (https://pactr.samrc.ac.za/) as PACTR202003893276712 (https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=9798).

Keywords: environmental enteric dysfunction, biomarkers, systemic inflammation, growth hormones, linear growth, infants, western Kenya

Introduction

Linear growth faltering in childhood remains a persistent challenge and results in stunting (height-for-age *z*-score <−2) in ~1 in 2 children under 5 years old in Asia and 2 of 5 in Africa [1]. Growth faltering occurs early with ~1 in 5 infants (11.8 m infants) in low- and middle-income countries (LMICs) with stunting by age 6 mo [2]. A significant contributing factor to growth faltering may be environmental enteric dysfunction (EED), which is characterized by small intestinal villous atrophy and inflammation and increased mucosal

Abbreviations: AAT, α_1-antitrypsin; AGP, α_1-acid glycoprotein; CSI, chronic systemic inflammation; CRP, C-reactive protein; EED, environmental enteric dysfunction; IFABP, intestinal fatty acid–binding protein; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor–binding protein; PROSYNK, Probiotics and Synbiotics in infants in Kenya.

* Corresponding author.
E-mail address: stephen.allen@lstmed.ac.uk (S. Allen).

https://doi.org/10.1016/j.ajcnut.2025.10.012
Received 11 July 2025; Received in revised form 8 October 2025; Accepted 17 October 2025; Available online 24 October 2025

permeability [3,4]. EED may contribute to growth faltering through malabsorption [5] and increased mucosal permeability resulting in chronic systemic inflammation (CSI) and growth hormone resistance [3,6–11]. In addition, CSI impairs organ development including cognitive development [12–14] and increases risk of longer-term noncommunicable diseases [15]. However, associations between different biomarkers of gut pathology, CSI, growth hormones, and growth differ between settings [4].

EED likely results from pathogen colonization of the gut [4,6,16] and has been reported to occur as early as 4–6 wk in infants in Zimbabwe [9,17] and 12 wk in Bangladesh [18]. The Probiotics and Synbiotics in infants in Kenya (PROSYNK) study was a 4-arm, individually randomized, open study that recruited newborns in western Kenya [19]. The effects of the administration of probiotics/synbiotics on EED, systemic inflammation, and growth hormones were assessed in stool and blood samples collected at ages 6 wk and 3, 6, and 12 mo.

The aim of this analysis was to describe the time course of the onset and progression of EED and CSI during infancy in infants assigned to the control arm of the study and explore associations between these pathologies and growth hormones and growth.

Methods

In the PROSYNK trial, 600 singleton newborns who had birthweight of 2000 g or above, were well, and had taken a breast feed well were recruited within 3 d of birth from Homa Bay County Teaching and Referral Hospital, western Kenya between 28 October, 2020, and 13 January, 2022, and were followed up to age 24 mo. Infants with any acute illness, congenital anomalies that might be life-threatening or impair growth, a potential contraindication to probiotics/synbiotics, whose mother was unlikely to stay in study area for the duration of the study or where there were any concerns of the health or research staff regarding participation in the trial were excluded. Using a computer-generated random sequence, infants were allocated 1:1:1:1 to receive 1 of 3 probiotics/synbiotics or a control group. To minimize risk of colonization of the control infants by the probiotic organisms, probiotic/synbiotic dosing was supervised and recruitment limited to a single infant per household. In this region, stunting (height-for-age *z*-score of <-2) occurs in ~13% of under 5s [20]. Infants allocated to all study arms were visited at home by research staff daily for the first 10 d and then weekly to age 6 mo. In the control arm, some home visits were replaced by mobile phone calls due to COVID-19 restrictions. During these visits and calls, demographic and clinical information was collected by questionnaire and study staff provided mothers/carers with guidance on infant feeding, hygiene, and care and facilitated referral for clinical assessment if the infant was unwell. The infants allocated to the control arm did not receive any other intervention. All infants in the control arm were included in this analysis.

Samples of stool and finger-prick blood were collected using a cool box (temperature range, 9–11 °C) at ages 6 wk and 3, 6, and 12 mo and stored at −20 °C until analysis. Diarrhea stools were not collected; sample collection was deferred until the child's stools had returned to their usual frequency and consistency. Length was measured to the nearest 0.1 cm at these time points using a length board that was calibrated daily. Feeding status was assessed at each scheduled visit using a standardized questionnaire, including whether the child was exclusively breastfed, the age at which anything other than breast milk (recorded in months, weeks, or days) was first received, and current feeds (breast milk, infant formula, water, or other fluids or foods).

Laboratory analyses

The laboratory analyses have been described previously (preprint: https://doi.org/10.21203/rs.3.rs-5929784/v1) and in Supplemental File 1. Briefly, biomarkers of EED included fecal myeloperoxidase (MPO; intestinal inflammation), fecal α_1-antitrypsin (AAT; mucosal permeability), and plasma intestinal fatty acid–binding protein (IFABP; mucosal integrity). Plasma α_1-acid glycoprotein (AGP) assessed CSI, and plasma C-reactive protein (CRP) assessed acute inflammation. Growth hormones were plasma insulin-like growth factor (IGF)-1 and plasma insulin-like growth factor 1–binding protein (IGFBP)3. pH was measured in fresh stool. The cutoffs for the upper and lower limits of the normal range of biomarkers were based on previous studies of EED and systemic inflammation and growth faltering, commonly used reference ranges or manufacturer's guidance (Supplemental Table 1). No cutoff was available for plasma IFABP because a normal range has not been established. We also report biomarker concentrations as continuous values to reflect the continuum of poor gut health and inflammation in LMIC populations. To illustrate range and outliers, boxplots of biomarker concentrations according to time point are shown in Supplemental Figure 1.

Sample size

In the PROSYNK trial, 600 infants (150 per am) would allow the detection of a 50% reduction in the prevalence of CSI at age 6 mo from 35% in the control arm to 17.5% in any of the intervention arms with 80% power and with α of 0.0167 based on the intention to treat population and allowing for 13% dropouts.

Statistical methods

Baseline categorical, demographic and clinical variables were reported as number and percentage and continuous variables as median (IQR) and compared by χ^2 and *t* tests, respectively. No imputation methods were applied to missing data; cases with missing values were excluded from relevant analyses. The onset and time course of raised biomarker concentrations was illustrated in Sankey diagrams.

Given the skewed distribution of most biomarker data, natural log transformation was applied to make the biomarker distributions more symmetric and closer to normal [21]. Pearson correlation coefficients were calculated to assess the relationships between biomarker concentrations at each time point and growth [change in length-for-age *z*-score (LAZ)] over the period until the next time point and between biomarker concentrations at each time point and growth between 12 and 24 mo. The distributions of log-transformed biomarker and growth hormone values according to growth were also illustrated in scatter plots in Supplemental Figures 2, 3 and 4, respectively. To evaluate the possibility that poor growth may precede EED (e.g., EED may result from protein deficiency) [22], we also assessed the association between change in LAZ and biomarker concentration in the period before each biomarker measurement.

To further evaluate the associations between individual biomarkers and growth, univariate and multivariable linear regression models were used, adjusting for potential variables that may affect growth independent of gut health: HIV exposure, residence (rural compared with urban/periurban), season of birth (rainy compared with dry), maternal height, sex, and birthweight.

In this exploratory analysis, a 2-tailed *P* value of <0.05 was considered statistically significant with no correction for multiple analyses. Statistical analyses were performed using STATA v.17.0 (StataCorp LLC).

Ethics approvals

Ethics approvals were secured from the Kenya Medical Research Institute—Scientific and Ethics Review Unit (KEMRI/SERU/CGHR/320/3917), Kenyan Pharmacy & Poison Board, Kenya [PPB/ECCT/20/04/02/2020(063)], National Commission for Science Technology and Innovation, Kenya (NACOSTI/P/24/34212), and the Liverpool School of Tropical Medicine (19-048). The parents/carers of all infants provided informed consent.

Results

The participant flowchart is shown in Supplemental Figure 5. The baseline demographic and clinic information regarding the control group participants is shown in Table 1 and has been published previously (preprint: https://doi.org/10.21203/rs.3.rs-5929784/v1). Briefly, 97 (65%) infants lived in a rural setting and the remainder (52; 35%) in an urban/periurban setting. Most of the mothers were married (118; 79%) and 26 (17%) were HIV positive, but no infant was known to have acquired HIV infection either at recruitment or during follow-up. About half of the infants (83; 56%) were born during a rainy season and were boys (70; 47%). Delivery was by cesarean section for 10 (7%) infants. Mean (SD) birthweight was 3.1 ± 0.41 kg, and 13 (9%) were low birthweight (<2.5 kg). Water, sanitation, and hygiene were generally poor, with 61 (41%) households using an unprotected source for drinking water and 43 (29%) an unimproved lavatory. Mothers reported exclusive breastfeeding in 139 of 146 (95%) infants at age 6 wk, 121 of 140 (86%) at 3 mo, and 62 of 139 (45%) at 6 mo.

TABLE 1
Baseline maternal, delivery, and infant demographic and clinical characteristics.

Variable	Value ($N = 149$)
Residence type	
Rural	97 (65%)
Periurban	43 (29%)
Urban	9 (6%)
Water, sanitation, and hygiene	
Drinking water	
Protected	88 (59%)
Unprotected	61 (41%)
Household lavatory	
Improved	106 (71%)
Unimproved	43 (29%)
Disposal of child stools	
With garbage	136 (91%)
Other	13 (9%)
Mother	
Age (y)	25 ± 6.4
Height (cm)	161 ± 6.0
Weight (kg)	66 ± 12.7
Marital status	
Single	30 (20%)
Married	118 (79%)
Separated/divorced	1 (1%)
Widowed	0 (0%)
Previous number of live births	1.6 ± 1.68
HIV positive	26 (17%)
Well during pregnancy	136 (91%)
Antibiotics in 7 d before delivery	2 (1%)
Delivery	
Rainy season[1]	83 (56%)
Place	
Hospital	136 (91%)
Health center	9 (6%)
Home	4 (3%)
On the way to facility	0 (0)
Mode	
Spontaneous vaginal	139 (93%)
Cesarean section	10 (7%)
Complications	15 (10%)
Delayed cord clamping	133 (89%)
Infant	
Male sex	70 (47%)
Gestational age by Ballard score (wk)	38 ± 1.8
Birth weight (kg)	3.1 ± 0.41
Low birth weight (<2500 g)	13 (9%)
Time of first feed (h)	1.7 ± 1.96

Data are *n* (%) or mean ± SD.
[1] Rainy season: October to December and March to May; dry season: January to February and June to September (https://climateknowledgeportal.worldbank.org/country/kenya/climate-data-historical).

EED biomarkers

Fecal MPO

Median fecal MPO concentrations increased progressively between 6 wk and 3–6 mo and then increased again at 12 mo (Table 2). Approximately 1 in 3 (32.9%) infants had intestinal inflammation (fecal MPO ≥ 0.2 mg/dL) at 6 wk, and the proportion increased progressively to nearly all infants (93.1%) at 12 mo (Table 2). The great majority of infants (≥80.8%) with raised MPO at 1 time point also had raised MPO at the subsequent time point with inflammation resolving in few infants between time points (Figure 1A).

Fecal AAT

Median fecal AAT concentrations were similar between 6 wk and 6 mo but increased by 12 mo (Table 2). About 1 in 5 (18.3%) had raised fecal AAT (≥26.8 mg/dL) at 6 wk, and this increased progressively to 60.3% by age 12 mo (Table 2). In most infants (≥57.9%), raised values at 1 time point persistent to the next (Figure 1B).

Plasma IFABP

Median plasma IFABP was similar at the 6-wk and 3- and 6-month time points but with some increase at 12 mo (Table 2).

Stool pH

Stool pH varied little during infancy with nearly all infants with acidic stools (pH < 7.0) at all time points (Table 2).

Systemic inflammation

Plasma AGP

Median concentrations of plasma AGP rose progressively from age 6 wk to 6 mo with some decrease by 12 mo. No infants had raised AGP at age 6 wk, but AGP was raised in 23.6%, 43.5%, and 42.4% infants at ages 3, 6, and 12 mo, respectively (Table 2). Raised AGP at 3 mo persisted at 6 mo in the great majority of infants (90.6%) and, in most infants (64.4%), between 6 and 12 mo (Figure 2A). AGP showed evidence of a bimodal distribution at age 12 mo (Supplemental Figures 3 and 6). Demographic and clinical variables were similar in infants with lower (<0.75 g/L) and higher (≥0.75 g/L) plasma AGP at 12 mo (Supplemental Table 2).

Plasma CRP

Plasma CRP was raised (>0.45mg/dL) in most infants at all time points, with median concentrations tending to be higher at 3 and 12 mo (Table 2). Raised CRP at 6 wk persisted at 3 mo in the great majority of

TABLE 2
Biomarkers of environmental enteric dysfunction, systemic inflammation, and growth hormones by time point.

Variable	Visit			
	6 wk	3 mo	6 mo	12 mo
Fecal myeloperoxidase (mg/dL)				
n	143	136	130	131
Median (IQR)	0.16 (0.10, 0.24)	0.31 (0.14, 0.47)	0.32 (0.19, 0.55)	0.74 (0.45, 1.02)
No. (%) raised (≥0.2 mg/dL)	47 (32.9)	82 (60.3)	94 (72.3)	122 (93.1)
Fecal α_1-antitrypsin (mg/dL)				
n	142	136	132	131
Median (IQR)	19.3 (12.2, 24.8)	19.7 (12.4, 27.1)	21 (12.5, 37.7)	30.1 (20.5, 38.7)
No. (%) raised (≥26.8 mg/dL)	26 (18.3)	34 (25.0)	48 (36.4)	79 (60.3)
Plasma intestinal fatty acid–binding protein (ng/mL; normal range not established)				
n	145	140	137	132
Median (IQR)	0.95 (0.57, 1.6)	0.76 (0.46, 1.32)	1.0 (0.52, 2.0)	1.22 (0.57, 2.2)
Stool PH				
n	143	136	132	131
Median (IQR)	5.2 (5.0, 5.6)	5.2 (4.8, 5.6)	5.4 (4.8, 6.0)	5.5 (5.2, 6.2)
Plasma α_1-acid glycoprotein (g/L)				
n	146	140	138	132
Median (IQR)	0.29 (0.23, 0.36)	0.61 (0.39, 1.0)	0.86 (0.44, 1.2)	0.61 (0.34, 1.1)
No. (%) raised (>1.0 g/L)	0 (0.0)	33 (23.6)	60 (43.5)	56 (42.4)
Plasma C-reactive protein (mg/dL)				
n	145	139	138	132
Median (IQR)	0.57 (0.25, 1.0)	1.3 (0.69, 2.4)	0.62 (0.38, 1.1)	0.92 (0.40, 1.5)
No. (%) raised (>0.45mg/dL)	75 (51.7)	112 (80.6)	90 (65.2)	91 (68.9)
Plasma insulin-like growth factor 1 (ng/mL)				
n	146	138	137	132
Median (IQR)	59 (22, 129)	42 (20, 114)	31 (16, 101)	97 (37, 161)
No. (%) deficient[1]	20 (13.7)	23 (16.7)	36 (26.3)	5 (3.8)
Plasma insulin-like growth factor–binding protein 3 (mg/L)				
n	146	138	137	132
Median (IQR)	1.2 (0.67, 1.9)	1.1 (0.63, 1.8)	0.88 (0.48, 1.4)	1.1 (0.38, 2.1)
No. (%) deficient at age 12 mo (<0.7 mg/L)[1]	-	-	-	57 (43.2)

[1] Age 0–11 mo: males, <18 ng/mL; females, <14 ng/mL; age 12 mo: males, <14 ng/mL; females, <23 ng/mL (https://pediatric.testcatalog.org/show/IGFGP).

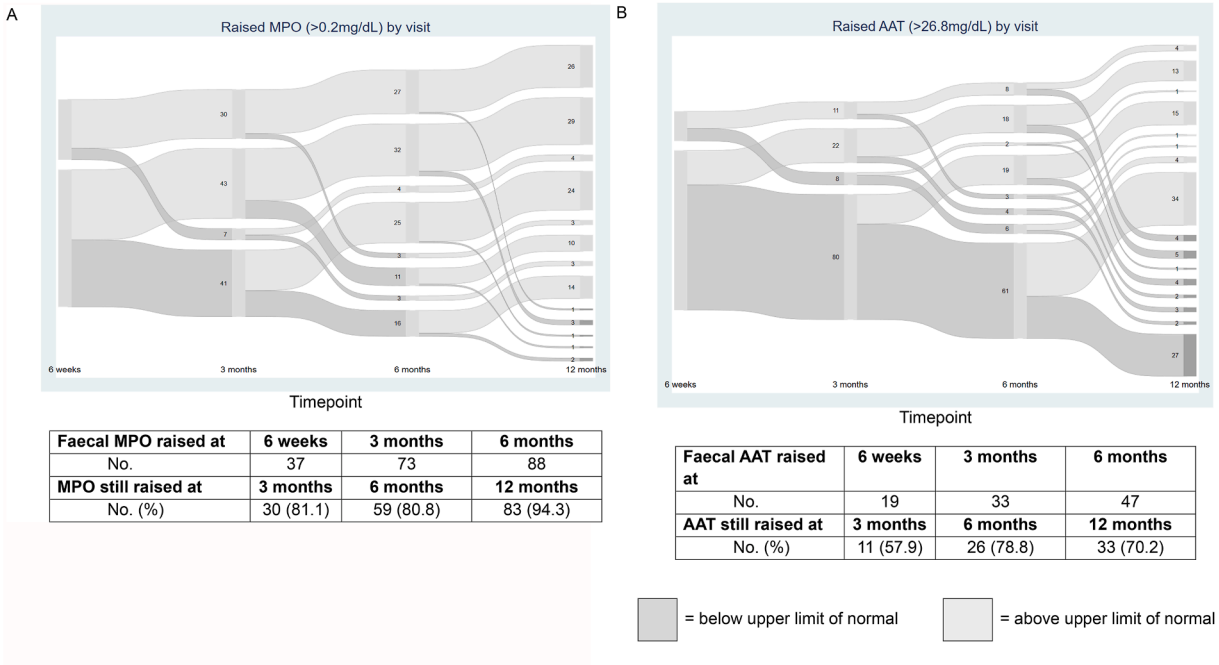
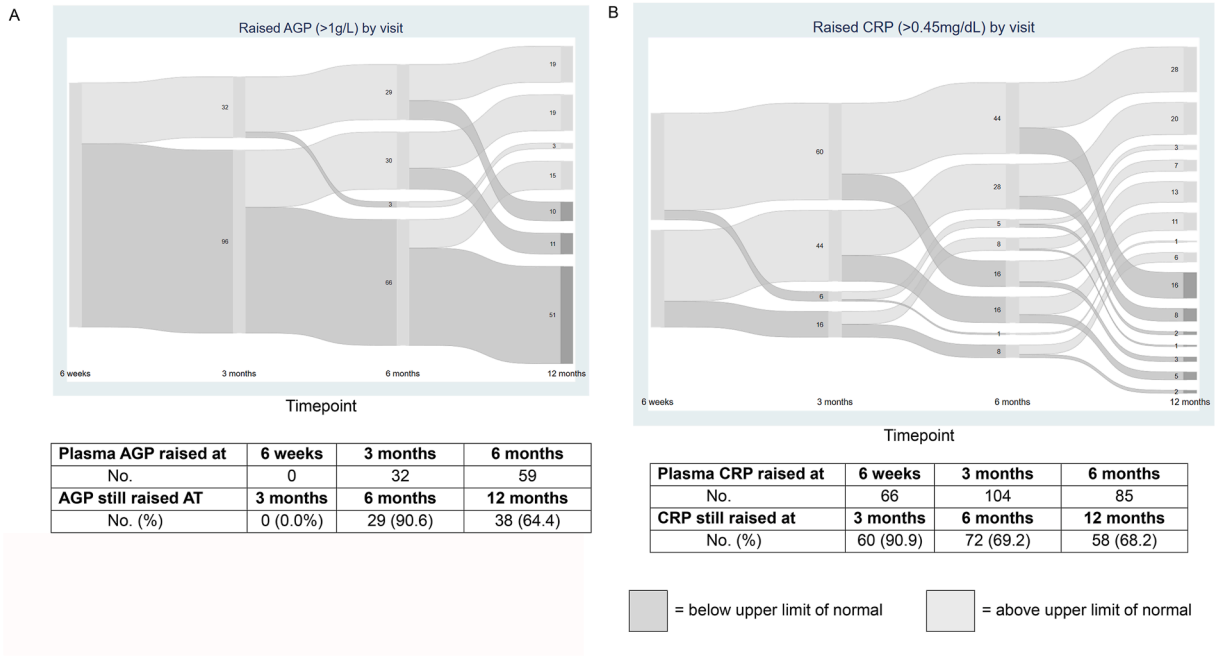


FIGURE 1. Biomarkers of environmental enteric dysfunction during infancy. (A) Fecal myeloperoxidase (MPO). (B) Fecal α_1-antitrypsin (AAT). Notes: only infants with values at all 4 time points are included; numbers show the number of infants at each time point.



Plasma AGP raised at	6 weeks	3 months	6 months
No.	0	32	59
AGP still raised AT	**3 months**	**6 months**	**12 months**
No. (%)	0 (0.0%)	29 (90.6)	38 (64.4)

Plasma CRP raised at	6 weeks	3 months	6 months
No.	66	104	85
CRP still raised at	**3 months**	**6 months**	**12 months**
No. (%)	60 (90.9)	72 (69.2)	58 (68.2)

FIGURE 2. Systemic inflammation during infancy. (A) Plasma α_1-acid glycoprotein (AGP); (B) plasma C-reactive protein (CRP). Notes: only infants with values at all 4 time points are included; numbers show the number of infants at each time point.

infants (90.9%) and in most infants (≥68.2%) between 3–6 and 6–12 mo (Figure 2B).

Growth hormones

Plasma IGF-1

Median plasma IGF-1 concentration was higher at 12 mo than at previous time points. Approximately >1 in 4 (26.3%) infants were IGF-1 deficient at 6 mo, but <1 in 20 (3.8%) at 12 mo (Table 2).

Plasma IGFBP3

Median plasma IGFBP3 concentrations were similar at all time points; 43.2% infants were deficient at age 12 mo (Table 2).

Associations between EED biomarkers and CSI

Statistically significant, weak positive associations (Pearson ρ: <0.4) with plasma AGP were observed between fecal MPO and plasma IFABP at 3 mo, fecal AAT at 6 mo, between all 3 EED biomarkers at 12 mo and a moderate association between plasma AGP and plasma IFABP at age 6 mo (ρ: 0.44; 95% CI: 0.30, 0.57) (Table 3). In multiple regression analysis, significant weak positive associations with plasma AGP were fecal MPO at 3 mo, fecal AAT and plasma IFABP at 6 mo, and plasma IFABP at 12 mo (Table 4).

Associations between plasma AGP and growth hormones

Statistically significant, weak negative associations (ρ: <−0.4) between plasma AGP and plasma IGF-1 and IGFBP3 were observed at

TABLE 3
Associations between biomarkers of EED and plasma AGP according to time point: correlations between plasma AGP and biomarkers of EED (ln values).

Biomarkers	Time point			
	6 wk	3 mo	6 mo	12 mo
Fecal MPO				
n	142	133	129	129
ρ (95% CI)	0.03 (−0.14, 0.19)	0.31 (0.15, 0.45)	0.17 (−0.00, 0.34)	0.20 (0.03, 0.36)
P	0.74	0.0003	0.05	0.021
Fecal AAT				
n	141	133	131	129
ρ (95% CI)	−0.01 (−0.18, 0.15)	0.05 (−0.12, 0.22)	0.21 (0.04, 0.37)	0.24 (0.07, 0.40)
P	0.87	0.58	0.014	0.0063
Plasma IFABP				
n	145	140	137	132
ρ (95% CI)	0.03 (−0.13, 0.20)	0.24 (0.08, 0.39)	0.44 (0.30, 0.57)	0.28 (0.12, 0.43)
P	0.69	0.0045	<0.0001	0.001

ρ refers to the Pearson correlation. *P* value is the significance level of each correlation coefficient (2-sided *t* test).
AAT, α_1-antitrypsin; AGP, α_1-acid glycoprotein; EED, environmental enteric dysfunction; IFABP, intestinal fatty acid–binding protein; MPO, myeloperoxidase.

TABLE 4
Associations between biomarkers of EED and plasma AGP according to time point: multiple regression analysis of EED biomarkers and plasma AGP (ln values).

Biomarkers	Time point			
	6 wk	3 mo	6 mo	12 mo
n	140	133	129	129
Fecal MPO				
Coefficient (95% CI)	0.018 (−0.091, 0.13)	0.20 (0.079, 0.33)	0.043 (−0.079, 0.17)	0.084 (−0.12, 0.29)
P	0.74	0.0015	0.49	0.42
Fecal AAT				
Coefficient (95% CI)	−0.006 (−0.12, 0.11)	−0.027 (−0.17, 0.11)	0.13 (0.016, 0.24)	0.18 (−0.059, 0.42)
P	0.92	0.7	0.026	0.14
Plasma IFABP				
Coefficient (95% CI)	0.008 (−0.080, 0.096)	0.14 (0.006, 0.27)	0.28 (0.19, 0.38)	0.17 (0.057, 0.28)
P	0.86	0.040	<0.0001	0.0033

Independent variables in multiple regression are MPO, AAT, and IFABP. *P* value is at the significance level for regression coefficient (2-sided *t* test). Interpretation of coefficients: for example, for MPO at 6 wk, the multiple variable regression analysis indicated that for every unit rise in ln(mg/dL) MPO, there is a unit change of ln(g/L) AGP of 0.018 (95% CI: −0.091, 0.13; $P = 0.74$).
AAT, α_1-antitrypsin; AGP, α_1-acid glycoprotein; EED, environmental enteric dysfunction; IFABP, intestinal fatty acid–binding protein; MPO, myeloperoxidase.

TABLE 5
Correlation between plasma α_1-acid glycoprotein and growth hormones (ln values) according to time point.

Biomarkers	Time point			
	6 wk	3 mo	6 mo	12 mo
n	146	138	137	132
Plasma IGF-1				
ρ (95% CI)	0.01 (−0.15, 0.17)	−0.24 (−0.39, −0.07)	−0.31 (−0.46, −0.15)	−0.53 (−0.64, −0.39)
P	0.89	0.0049	0.0002	<0.0001
Plasma IGFBP3				
ρ (95% CI)	−0.09 (−0.25, 0.07)	−0.23 (−0.39, −0.07)	−0.20 (−0.35, −0.03)	−0.29 (−0.44, −0.12)
P	0.27	0.0056	0.021	0.0008

ρ refers to the Pearson correlation. *P* value is significance level for regression coefficient (2-sided *t* test). Interpretation of coefficients: for example, for IGF-1 at 6 wk, for every unit rise in ln(ng/mL) IGF-1, there is a unit change of ln(g/L) AGP of 0.01 (95% CI: −0.15, 0.17; $P = 0.89$).
IGF, insulin-like growth factor; IGFBP, IGF-binding protein.

3 and 6 mo and weak and moderate negative associations with IGFBP3 and IGF-1, respectively, at 12 mo (Table 5).

Associations among stool pH, EED biomarkers, systemic inflammation, growth hormones, and linear growth

Mean LAZ declined gradually from age 3 mo and was the lowest at age 24 mo (−0.9; SD: 1.1), when 21 children (15.6%) had at least moderate stunting (LAZ: <−2) (Table 6). From linear regression, there were no significant associations between biomarkers of EED, systemic inflammation, or growth hormones and subsequent change in linear growth at any time point with the exception of fecal AAT at age 6 mo and change in LAZ from 6 to 12 mo (multivariable analysis; coefficient: −0.33; 95% CI: −0.51, −0.14; $P = 0.001$) (Table 7). Assessing the effects of poor gut health in early infancy compared with later growth (12–24 mo), in multivariable regression, fecal pH at 3 mo (coefficient: 1.01; 95% CI: 0.03, 1.98; $P = 0.043$) and fecal AAT at 6 mo (coefficient: 0.17; 95% CI: 0.01, 0.33; $P = 0.035$) were positively associated, and fecal MPO at 6 mo was significantly negatively associated with later growth (coefficient: −0.22; 95% CI: −0.39, −0.05; $P = 0.012$) (Supplemental Table 3). In analysis of poor linear growth as a precursor of gut pathology, change in LAZ between 6 and 12 mo was negatively associated with fecal AAT in univariate analysis (coefficient −0.15; 95% CI: −0.28, −0.03; $P = 0.019$) but no other significant associations were observed (Supplemental Table 4).

TABLE 6
Linear growth according to time point.

Anthropometry	Time point					
	Enrolment	6 wk	3 mo	6 mo	12 mo	24 mo
LAZ (*n*)	149	146	140	139	132	135
Mean (SD)	−0.5 (1.10)	−0.3 (1.03)	−0.1 (1.27)	−0.4 (1.15)	−0.6 (1.08)	−0.9 (1.1)
Stunting, *n* (%)	14 (9.4)	9 (6.2)	9 (6.4)	11 (7.9)	10 (7.6)	17 (12.6)
Moderate	2 (1.3)	2 (1.4)	1 (0.7)	1 (0.7)	2 (1.5)	4 (3.0)

Moderate and severe stunting are defined as LAZ <−2 and ≥−3, and LAZ <−3, respectively (https://www.who.int/tools/child-growth-standards).
LAZ, length-for-age *z*-score.

Discussion

In healthy newborns with birthweight of ≥2kg in western Kenya, evidence of EED was present as early as age 6 wk in ~1 in 3 infants despite exclusive breastfeeding. Biomarkers reflecting different pathologies in EED were significantly associated with CSI which occurred in ~1 in 4 infants from age 3 mo. Once detected, intestinal inflammation, increased mucosal permeability, and CSI persisted in most infants. CSI was significantly associated with reduced growth hormone

TABLE 7
Associations between environmental enteric dysfunction biomarkers, systemic inflammation, growth hormones, and linear growth according to time point.

Variable	Time point			
	6 wk, δLAZ 6 wk–3 mo	3 mo, δLAZ 3–6 mo	6 mo, δLAZ 6–12 mo	12 mo, δLAZ 12–24 mo
Univariate analysis				
Fecal MPO	136; −0.06 (−0.31, 0.19); 0.62	130; 0.15 (−0.08, 0.38); 0.20	124; −0.04 (−0.22, 0.15); 0.69	127; −0.03 (−0.21, 0.15); 0.74
Fecal AAT	135; −0.05 (−0.30, 0.20); 0.69	130; −0.02 (−0.30, 0.26); 0.89	126; −0.27 (−0.43, −0.11); 0.001	127; −0.04 (−0.25, 0.17); 0.72
Plasma IFABP	139; 0.04 (−0.15, 0.22); 0.70	137; −0.11 (−0.35, 0.41); 0.38	129; −0.03 (−0.17, 0.11); 0.68	130; −0.02 (−0.14, 0.11); 0.77
Fecal pH	136; −0.35 (−2.00, 1.31); 0.68	130; −0.46 (−1.89, 0.97); 0.52	126; 0.13 (−0.71, 0.97); 0.76	127; −0.27 (−1.23, 0.69); 0.58
Plasma AGP	140; −0.14 (−0.51, 0.23); 0.46	137; 0.15 (−0.16, 0.46); 0.35	130; −0.01(−0.23, 0.21); 0.94	130; −0.05 (−0.23, 0.12); 0.56
Plasma CRP	139; 0.05 (−0.10, 0.19); 0.53	136; −0.02 (−0.21, 0.16); 0.81	130; −0.10 (−0.24, 0.05); 0.19	130; −0.08 (−0.21, 0.04); 0.17
Plasma IGF-1	140; 0.00 (−0.12, 0.13); 0.96	135; −0.05 (−0.20, 0.10); 0.50	129; 0.09 (−0.02, 0.20); 0.10	130; 0.09 (−0.03, 0.22); 0.15
Plasma IGFB3	140; 0.03 (−0.13, 0.19); 0.73	135; 0.13 (−0.08, 0.35); 0.22	129; 0.08 (−0.06, 0.23); 0.27	130; −0.00 (−0.12, 0.11); 0.96
Multivariable analysis				
Fecal MPO	133; −0.05 (−0.33, 0.23); 0.70	129; 0.15 (−0.12, 0.43); 0.27	124; 0.08 (−0.12, 0.28); 0.42	127; −0.04 (−0.28, 0.21); 0.77
Fecal AAT	133; −0.11 (−0.40, 0.17); 0.44	129; −0.11 (−0.43, 0.21); 0.49	124; −0.33 (−0.51, −0.14); 0.001	127; −0.02 (−0.28, 0.29); 0.97
Plasma IFABP	133; 0.05 (−0.17, 0.27); 0.65	127; −0.12 (−0.40, 0.15); 0.37	124; −0.03 (−0.21, 0.15); 0.74	127; −0.01 (−0.15, 0.13); 0.88
Fecal pH	133; −0.49 (−2.32, 1.30); 0.58	127; −0.73 (−2.24, 0.78); 0.34	124; 0.32 (−0.55, 1.19); 0.46	127; −0.28 (−1.29, 0.72); 0.58
Plasma AGP	133; −0.11 (−0.55, 0.32); 0.60	127; 0.19 (−0.19, 0.56); 0.33	124; 0.10 (−0.18, 0.38); 0.49	127; 0.00 (−0.25, 0.25); 1.00
Plasma CRP	133; 0.06 (−0.11, 0.24); 0.46	127; −0.09 (−0.31, 0.12); 0.40	124; −0.12 (−0.27, 0.03); 0.12	127; −0.04 (−0.20, 0.08); 0.40
Plasma IGF-1	133; 0.01 (−0.14, 0.16); 0.87	127; 0.02 (−0.16, 0.20); 0.82	124; 0.06 (−0.06, 0.19); 0.32	127; 0.07 (−0.10, 0.23); 0.42
Plasma IGFB3	133; −0.02 (−0.21, 0.17); 0.83	127; 0.15 (−0.10, 0.40); 0.23	124; 0.03 (−0.16, 0.21); 0.78	127; −0.04 (−0.16, 0.09); 0.57

Values are n; coefficient (95% CI); *P*. Coefficients from multivariable regression model with change in *z*-score for over the period as outcome variable, and ln-transformed biomarker values, HIV exposure, residence (rural compared with urban/periurban), season of birth (rainy compared with dry), maternal height, sex, and birthweight as explanatory variables. Interpretation of coefficients: for example, for MPO at 6 wk, the univariate analysis indicated that, for every unit rise in ln(mg/dL), MPO there is a unit change in δLAZ of −0.06 (95% CI: −0.31, 0.19; $P = 0.62$).
AAT, α_1-antitrypsin; AGP, α_1-acid glycoprotein; CRP, C-reactive protein; δLAZ, change in length-for-age *z*-score; IFABP, intestinal fatty acid–binding protein; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; MPO, myeloperoxidase.

concentrations. Raised mucosal permeability may be the dominant intestinal pathology driving growth failure during infancy in this population.

Our findings that at age 6 wk, intestinal inflammation was present in ~1 in 3 infants and increased mucosal permeability in ~1 in 5 infants are consistent with other studies. Biomarkers consistent with EED have been reported at age 4 wk in rural Zimbabwe [17] and the multicountry MAL-ED cohorts [23], at 6 wk in HIV-unexposed infants in urban Zimbabwe [9] and in >80% of infants at age 12 wk in an urban slum in Bangladesh [18]. This occurs despite mothers reporting exclusive breastfeeding. Given that the period of highest risk of the onset of stunting after birth is 0–3 mo [24], there is a clear need to start interventions to prevent or ameliorate EED early including in infants who are exclusively breastfed. Unfortunately, concerted efforts to reduce exposure to pathogens through implementation of water, sanitation, and hygiene interventions have either not prevented EED [17] or given equivocal results [25] and have not significantly improved growth so that other approaches are needed [26].

Stool pH was not significantly associated with growth in this study. More acidic stools are considered to be healthy based on a greater abundance of *Bifidobacteria* species and organic acids and protection against enteropathogens [27]. Further research should evaluate these individual components.

The median concentrations of each of the 3 EED biomarkers tended to rise during infancy with the highest concentrations recorded at age 12 mo. Fecal MPO as a marker of intestinal inflammation and fecal AAT as a marker of mucosal permeability and protein loss in stools are measured commonly in studies of EED [4,28]. Once detected, intestinal inflammation and increased permeability persisted in most infants until the next time point. Studies that have reported profiles for EED biomarkers in infants in LMICs show that these differ between populations and geographical regions. In stool collected monthly from a large number of infants from 8 different cohorts in South America, sub-Saharan Africa and Asia, biomarker concentrations were high compared with reference values, but in contrast to our findings, both stool MPO and AAT tended to fall in most of the cohorts over the first year [23]. Fecal MPO concentrations also tended to fall during infancy in rural Zimbabwe [17] and rural Bangladesh [25]. Concentrations of fecal AAT fell during infancy in rural Zimbabwe [17] but, consistent with our findings, tended to increase in rural Bangladesh [25].

Plasma IFABP, present in the cytosol of mature enterocytes, is released into the systemic circulation rapidly following cell damage [29,30]. Although a normal range has not been established for plasma IFABP, concentrations throughout infancy were high compared with studies in the Netherlands that identified 0.40 ng/mL as the upper limit of normal in healthy child volunteers [29] and a cutoff value of 0.22 ng/mL derived for differentiating children with celiac disease from healthy controls [31]. The high median concentration of IFABP at 12 mo in our study (1.22 ng/mL) is very similar to that in HIV-unexposed infants of the same age in urban Zimbabwe (mean: 1.23 ng/mL). Concentrations were lowest at 3 mo in both studies; however, concentrations were lower at ages 6 wk and 3 mo in Zimbabwe than those in our study [9]. Concentrations also fell from 1 to 6 mo in infants in rural Zimbabwe, with only a modest increase by age 12 mo [17]. The marked differences in EED biomarker profiles reflecting different gut pathologies in these studies indicate that the dynamics of gut damage and repair during infancy differ between populations and settings. Similarly, differences in some histopathological features of EED in undernourished children differed between studies in Bangladesh, Pakistan, and Zambia [32].

Unlike EED, CSI was not detected until age 3 mo but occurred in ~1 in 4 infants at that time point and increased to ~1 in 2 infants by age 6 mo. Systemic inflammation has been reported in many studies of growth faltering including in Tanzania [6,33], Zimbabwe [9], Pakistan [7], Peru [34], and the multicountry BRINDA studies [8]. In PROSYNK, in a similar pattern to intestinal inflammation and increased

permeability, once detected, CSI persisted in the great majority of infants. The bimodal distribution of plasma AGP at 12 mo suggested that some infants may have increased susceptibility to CSI. Although demographic and biological variables were similar, 1 or more pathways leading to CSI may differ between those with lower and higher AGP values. A progressive increase in systemic inflammation during infancy has been reported in rural [17] and urban Zimbabwe [9] and in stunted and nonstunted infants in Tanzania [6], but we are not aware that a bimodal distribution for plasma AGP has been reported previously.

The weak but statistically significant associations between EED biomarkers and plasma AGP indicate that the gut pathology in EED contributes to CSI. Multiple regression analysis indicated that the intestinal pathology resulting in CSI may change during infancy with intestinal inflammation prominent at 3 mo, increased permeability at 6 mo and impaired integrity at all 3 time points. There was little consistency in a narrative systematic review of 40 studies of children of different ages in Central and South America, Asia, and Africa, where pathways between gut pathology, systemic inflammation, and growth hormones and growth were assessed by many different biomarkers in stool and blood [4]. Overall, based on the extensive research to date evaluating a wide range of biomarkers, the associations between gut pathology in EED and CSI likely differ at different ages and in different populations.

IGF-1, produced not only by hepatocytes but also locally in several tissues, promotes cell proliferation and tissue-specific cell functions and protects against apoptosis in many cell types. It likely also acts directly on epiphyseal growth plates [10]. IGFBP3 is the major binding protein for IGF-1, prolonging its half-life and modulating its action [35]. CSI impairs growth independently of nutrition by suppression of the growth hormone/IGF-1 axis via several mechanisms. Reduced plasma concentrations of IGF-1 and/or IGFBP3 indicate growth hormone resistance and occurs in conditions characterized by CSI (e.g., Crohn disease, cystic fibrosis, and juvenile idiopathic arthritis) [36]. Consistent with our findings, CSI was associated with reduced concentrations of IGF-1 and/or IGFBP3 in studies in Pakistan [37], Mali [38], Malawi [39], Tanzania [6], and Zimbabwe [9].

In addition to a driver of CSI, fecal AAT, signifying raised mucosal permeability and intestinal protein leak, was a statistically significant predictor of impaired growth in both univariate and multivariable regression analyses. In multivariable regression analysis, every 1.0-mg/L rise in fecal AAT at age 6 mo was associated with a fall in LAZ between 6 and 12 mo of 0.32 (95% CI: 0.50, 0.13). In addition, the significant negative association between linear growth from 6 to 12 mo and fecal AAT concentration at 12 mo, consistent with undernourishment as a cause of enteropathy [22], suggests a vicious cycle between mucosal leakiness and undernutrition. Alongside dietary deficiency, translocation of microbial toxins and possibly whole organisms across the gut barrier may be the dominant pathological pathway that impairs linear growth in this population although this may be restricted to mid-infancy. However, evidence from systematic reviews found variable associations between growth and intestinal permeability assessed mainly by dual sugar absorption tests [40] and between intestinal permeability and bacterial translocation across the intestinal mucosa and permeability and growth using a broader range of biomarkers [4]. In recent studies of children aged 0–36 mo, increased gut permeability assessed by fecal AAT was significantly negatively associated with subsequent linear growth in a periurban setting in Peru and with an interaction with age [41]. In a study of 6-mo-old infants in rural Uganda, evidence of microbial translocation into the lamina propria was associated with lower LAZ score including after controlling for systemic inflammation [42]. In contrast, no significant association was found between fecal AAT and linear growth during infancy in rural Zimbabwe [43].

Additional analyses highlighted the complexity of changes in gut health over time and longer-term linear growth (between 12 and 24 mo). Although fecal MPO concentration at age 6 mo was significantly negatively associated, unexpected findings were that stool pH at 3 mo and fecal AAT at 6 mo were positively associated with later linear growth.

Limitations of our study are that, although we included HIV-exposed infants, newborns who were unwell at screening, were not breastfed or had birthweight of <2000 g were excluded. Although fecal AAT is commonly used as a biomarker of intestinal permeability, the normal range for plasma concentrations is wide and concentrations increase with inflammation; therefore, clearance values may better assess permeability [44]. In addition, production of AAT in hematopoietic cells [45,46] and intestinal epithelium [47] may contribute to fecal concentrations. Reference ranges for biomarker concentrations in healthy infants are not well-established so we cannot assess the effects of age on biomarker profiles. Finally, although no trial intervention was administered, advice and support on childcare, infant feeding, and management during illness provided to mothers/carers during the first 6 mo as part of the clinical trial were more intensive than routinely provided in this region. These factors should be considered in generalizing our findings to all infants in this region.

In conclusion, the findings from this study indicate that interventions to prevent or ameliorate EED early in life, and especially increased mucosal permeability, may improve growth and development in infants in western Kenya through improved gut health and reduced CSI. Generalizability of this approach to different populations and settings needs to consider the variability in the relationships between different elements of gut pathology, CSI, and growth and how these may vary with age.

Author contributions

The authors' responsibilities were as follows – SA, MIO, MJ, DW, KO, SK, FTK: study design; MIO, MJ, MC, KO: conducted the research; JD, AK: data analysis; SA, JD, MIO wrote the article; SA: primary responsibility for the final content; and all authors: have read and approved the final manuscript.

Conflict of interest

SA reports financial support was provided by Children's Investment Fund Foundation. The other authors report no conflicts of interests.

Funding

This study was funded by Children's Investment Fund Foundation and sponsored by Liverpool School of Tropical Medicine (LSTM), Pembroke Place, Liverpool L3 5QA, United Kingdom; E-mail: lstmgov@lstmed.ac.uk). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The sponsor was responsible for trial monitoring but had no other role in undertaking the study and there are no restrictions regarding publication.

Data availability

Data described in the manuscript will be made available upon request pending application and approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2025.10.012.

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