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Alimentary Tract

Environmental enteropathy and inflammatory bowel disease are not mutually exclusive ☆

Phoebe Hodges[a,b], Mubbunu Malambo[a], Wamundila Kawana[a], Ellen Besa[a], Monica Mweetwa[a], Violet Kayamba[a], Victor Mudenda[a], Nicholas M. Croft[b], Paul Kelly[a,b,*]

[a] Tropical Gastroenterology & Nutrition group, University of Zambia School of Medicine, Lusaka, Zambia
[b] Blizard Institute, Queen Mary University of London, London, United Kingdom

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ABSTRACT

Background: Environmental enteropathy (EE) is an asymptomatic lesion of the small intestine, likely an adaptive response to environmental noxa, including enteropathogens, leading to recurrent intestinal injury, mucosal inflammation, and microbial translocation. Inflammatory bowel disease (IBD) is increasing in incidence in newly industrialised countries. Given that EE is seen in individuals living in insanitary environments in low-income countries (LICs) and IBD has traditionally been viewed as a disease of developed countries, we hypothesised that these two conditions would not co-exist.
Aims: To investigate whether EE is seen in individuals with IBD living in a low-income country in sub-Saharan Africa.
Methods: Enteropathy was assessed in adult Zambians with IBD and controls from high and low socioeconomic status (SES) groups with duodenal biopsies and biomarkers of intestinal and systemic inflammation. Enteropathogen carriage rates between the groups were compared.
Results: 28 cases and 59 controls (38 high SES and 21 low SES) were included. Histological features of EE were present in all cases and controls, with median villus height to crypt depth ratio <2 in all groups. Enteropathogen carriage was lower in cases (median of 1 pathogen per case to 2 per control).
Conclusion: The co-existence of IBD and EE within the same individuals may prove to be a confounding factor when assessing patients presenting with symptoms suggestive of IBD in this setting and could be interpreted as evidence that improved environmental hygiene does not play a significant role in the emergence of IBD.

1. Background

Originally known as 'tropical enteropathy' due to its predilection for tropical areas, environmental enteropathy is now recognised as an adaptive response of the small intestinal mucosa to enteropathogen exposure in overcrowded insanitary conditions, rather than being dependent on latitude, hence its renaming as environmental enteropathy (EE) [1,2]. EE was originally thought to be a benign lesion but has since been recognised to be associated with malnutrition in children, growth stunting, poor developmental outcomes and reduced efficacy of oral vaccines [3,4]. There is no universally accepted case definition of EE, and histological assessment of small intestinal biopsies remains the gold standard for diagnosis. Histological features of EE are non-specific and include but are not limited to villous atrophy, crypt hyperplasia, increased numbers of intraepithelial lymphocytes, and goblet cell depletion [5].

Inflammatory bowel disease (IBD) has traditionally been regarded as a disease of high-income countries, with the highest prevalence recorded in North America and some European countries although incidence is now rising in newly industrialised countries in Asia and South America [6]. Although data are scarce, incidence of IBD appears to be increasing in Africa [7]. Kaplan has proposed a four-stage epidemiological model for the emergence of IBD in populations during and after industrialization, with countries in the western world being in the 'compounding prevalence' stage where incidence has already plateaued but prevalence is increasing. It is likely that most countries in sub-Saharan Africa are in the first stage of this model, the 'emergence' stage [8].

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* Corresponding author at: Blizard Institute, Barts & The London School of Medicine, Queen Mary University of London, 4 Newark Street, London E1 2AT, United Kingdom.
E-mail address: m.p.kelly@qmul.ac.uk (P. Kelly).

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Improved hygiene has often been cited as an important lifestyle-related factor in the emergence of IBD. Certain hygiene-related factors such as having a pet and contact with farm animals have been shown to have an inverse relationship with risk of IBD, whilst the effect of other factors such as access to a toilet and hot water seem to be influenced by underlying ethnicity [9].

We set out to investigate the hypothesis that EE and IBD would be mutually exclusive due to the opposing lifestyle factors that are thought to contribute to these two conditions, with EE typically being a condition of low-income settings and IBD traditionally being associated with the lifestyle typical of high-income countries. We conducted a case control study of IBD patients living in Zambia, a low-income country in sub-Saharan Africa.

2. Methods

IBD cases and controls were recruited from the gastroenterology outpatient clinic at the University Teaching Hospital (UTH) in Lusaka, from January 2020 to November 2022. UTH is the main government tertiary referral centre in Zambia and patients come from all over the country. Ethical approval for this study was obtained from the University of Zambia Biomedical Ethics Research Committee on 18th February 2020 under reference number 657-2020.

2.1. Recruitment and assessment of cases

Paper records of all IBD patients seen in the clinic exist from 2005 onwards, and all existing patients were contacted by telephone and asked to attend for review. The only inclusion criterion was a confirmed diagnosis of IBD. A guideline for diagnosis of IBD and exclusion of infectious colitis including TB was written for the purposes of this study as well as for use in the GI clinic going forward as existing guidelines largely deal with populations where the likelihood of infectious differential diagnoses would be expected to be low (Supplementary Fig. S1).

An electronic register was created, which was only accessible from the computer in the gastrointestinal clinic and password protected, hence only accessed by study personnel. From the start of the study demographic and clinical details for new patients and any existing patients who attended the clinic were entered into this electronic register.

When patients attended for review, or for new patients at the time of diagnosis, they were invited to participate in the study, and consent sought. Questionnaires were administered for the purposes of collecting relevant information relating to demographics and environmental risk factors, including housing intensity, water and sanitation, educational attainment, and an asset register as indicators of socio-economic status.

2.2. Recruitment and assessment of high SES controls

This control group was recruited from patients attending the GI clinic with symptoms indicating upper GI endoscopy, if they were found to have no pathology at endoscopy and reported no recent history of diarrhoea (within 4 weeks of recruitment). These individuals were invited to participate if they were living in an urban setting and of higher socioeconomic status than the average Lusaka resident (largely determined by residential area). This group will hereafter be described as 'High SES controls'. These individuals were invited to participate prior to endoscopy and asked to bring a stool sample on the day of their endoscopy appointment. They completed the same questionnaires as the cases.

2.3. Recruitment and assessment of low SES controls

These participants were healthy adults recruited from Misisi compound, an unplanned high-density compound in which studies of EE have been carried out over the past two decades. This control group will hereafter be referred to as 'Low SES' controls. Recruitment followed a three stage procedure as previously described [10]. Firstly, an experienced field worker conducted informal door-to-door discussions in Misisi. Secondly a focus group meeting was held, during which a more detailed description was given of the reason for doing the study and of the study procedures and potential participants were invited to ask questions. Thirdly, information sheets in English and Nyanja were provided and read out in English or Nyanja, prior to written consent.

2.4. Exclusion criteria

Exclusion criteria for cases and controls were pregnancy, breastfeeding, antibiotic use within 4 weeks, regular NSAID use within previous 4 weeks, diarrhoea within 4 weeks (in control groups), significant comorbidity precluding endoscopy with sedation, and untreated helminth infection.

2.5. Endoscopic procedures

After an overnight fast, upper GI endoscopy was undertaken in cases, high SES controls and low SES controls. Blood samples were collected into EDTA and plain tubes and intravenous access was obtained prior to the endoscopy. Endoscopy was undertaken under conscious sedation using 2.5–5mg diazepam and 25–50mg pethidine. Oxygen saturations were monitored throughout. Biopsies were taken from the second part of the duodenum, with four biopsies being collected into saline and between two and four biopsies snap frozen in liquid nitrogen. Biopsies collected into saline were oriented under a dissecting microscope in the endoscopy room and fixed in formal saline within 5 min of collection. Blood samples were centrifuged for 15 min at 547g and 4°C following which plasma and serum fractions were frozen at −80°C. Urine samples were frozen at −80°C. Snap-frozen biopsies were transferred from liquid nitrogen to storage at −80°C.

2.6. Enteropathogens

Enteropathogen carriage analysis of stool samples was carried out for cases and high SES controls described above, however, low stool sample volumes in the low SES control group precluded the inclusion of this group in the enteropathogen analysis. Detection of enteropathogens was performed using the xTAG® Gastrointestinal Pathogen Panel (GPP) following the manufacturer's instructions. This is a qualitative nucleic acid multiplex test that provides simultaneous detection and identification of the following multiple bacterial, viral and parasitic nucleic acids: Adenovirus 40/41, *Campylobacter* (*C. coli, C. jejuni* and *C. lari*), *Clostridium difficile* toxin A/B, *Cryptosporidium* (*C. parvum* and *C. hominis*), *Entamoeba histolytica, Escherichia coli* (*E. coli* 0157, enterotoxigenic *E. coli* (ETEC) LT/ST and Shiga-like toxin producing *E. coli* (STEC)), *Giardia lamblia*, Norovirus GI/GII, Rotavirus A, Salmonella, *Shigella, Vibrio cholerae* and *Yersinia enterocolitica*. Data were analysed using TDAS LSM software.

2.7. Analysis of biopsies

Biopsies that had been fixed in formal saline as described were paraffin embedded and stained with haematoxylin and eosin.

Table 1
Demographic and environmental characteristics of participants.

	Cases *n*=28	High SES controls *n*=38	Low SES controls *n*=21
Age (median, IQR)	44	35	32
% female	62	72	43
Highest educational level achieved (n(%))*			
University	6 (21)	21 (55)	0
College	5 (18)	8 (21)	1 (5)
Secondary	7 (25)	6 (16)	14 (67)
Primary	3 (11)	1 (3)	6 (28)
Living environment (n(%))**			
City	21 (75)	28 (74)	21 (100)
Small town	3 (11)	5 (13)	0
Rural village	1 (3.5)	2 (5)	0
Farm	1 (3.5)	1 (3)	0
People per room	0.5	0.7	1.6
No. people sharing toilet facility	4	4	10
No. household commodities in asset register	5	6	3
Drinking water (n(%))***			
Bottled water	7 (25)	12 (32)	0
Borehole	5 (18)	11 (29)	0
Council water	7 (25)	9 (24)	20 (95)
Communal outside tap	2 (7)	2 (5)	1 (5)
Toilet facility (n(%))****			
Flush	19 (68)	35 (92)	2 (10)
Ventilated improved pit latrine	2 (7)	0	12 (57)
Traditional pit latrine	0	0	7 (33)

* Data was missing for 7 cases and 2 high SES controls **Data was missing for 2 cases and 2 high SES controls ***Data was missing for 7 cases and 4 high SES controls ****Data was missing for 7 cases and 3 high SES controls.

Morphometry was performed on biopsy sections where crypts could be seen to have been sectioned along their entire length. Haematoxylin- and eosin-stained slides were imaged on an Olympus VS120 scanning microscope and assessed for villus height, crypt depth, and epithelial surface area in relation to muscularis mucosa length as previously described [11]. (Supplementary Fig. S2.) Mean villus height and crypt depth in each individual were used to calculate the villus height to crypt depth ratio. All biopsies were also assessed by a GI pathologist for features described in the histological index for evaluation of EE [12], and a total score percentage (TSP-5) was calculated based on five of these features as previously described [13].

2.8. Helicobacter pylori *antigen, autoantibodies, biomarkers of translocation, inflammation, and intestinal permeability*

Measurement of *H. pylori* antigen, calprotectin, alpha 1 antitrypsin (A1AT), and polymorphonuclear (PMN)-elastase concentrations in faecal samples and measurement of CRP, sCD163, sCD14, lipopolysaccharide binding protein (LBP), intestinal fatty acid binding (I-FABP), and anti-tissue transglutaminase (TTG) IgA concentrations in plasma was performed by ELISA according to the relevant manufacturer's instructions (see Supplementary Table S1 for further details).

2.9. Cytokines and matrix metalloproteinases

Quantification of cytokines and matrix metalloproteinases in duodenal tissue biopsies was done using a multiplex assay (Luminex® Discovery Assay) according to the manufacturer's instructions (see Supplementary Methods for further details). Snap frozen biopsies from each patient were thawed on ice and weighed then disrupted manually with a pellet pestle in 300 µl PBS with protease inhibitor cocktail (cOmplete^{TM} ULTRA tablets, Mini, Roche) followed by 5–10 passes through a 200 µl pipette tip. Homogenate was obtained by centrifugation at 10000g for 10 min at 4°C and then stored at -80°C [14].

2.10. Statistical analysis

All statistical analysis was performed using SPSS version 28 and R version 4.1.2. Non-parametric tests were used due to relatively small sample sizes and non-normal distribution of many of the data. Values are given as median and interquartile range unless otherwise stated. The Kruskal Wallis H test was used for independent samples and Spearman's rho was used for correlations. Chi square was used for testing the relationship between categorical variables.

3. Results

We recruited 28 patients with IBD (cases) and 59 controls (38 high SES controls and 21 low SES controls). Demographic and environmental characteristics and disease characteristics are shown in Tables 1 and 2 respectively.

3.1. Morphometry and histological scoring

Duodenal biopsies were collected in 22 cases, 30 high SES controls, and 19 low SES controls. In the remainder of participants (8 cases, 8 high SES controls, and 1 low SES control) either there was no consent to GI endoscopy or the procedure was not adequately tolerated to allow collection of biopsies. Biopsies were considered suitable for analysis of morphometry in 19 cases (17 ulcerative colitis, 2 Crohn's colitis), 24 high SES controls and 17 Low SES controls. There was evidence of EE in small bowel biopsies from all cases and controls, including epithelial and lamina propria inflammation, depletion of goblet cells and Paneth cells, and villus blunting (Fig. 1). Crypt depth ($\chi^2(2)$=9.88, $p < 0.01$) and epithelial surface area (($\chi^2(2)$=8.26, $p = 0.02$) were greater in controls from the Low SES group, however there was no significant difference in morphometric parameters between IBD cases and high SES controls (Fig. 2). Normal villus height to crypt depth ratio is likely to be between 3 and 5 [15] whereas medians for villus height:crypt depth in all groups in this study were less than 2, and no participant in this study had a villus height:crypt depth of 3 or more.

Table 2
Disease characteristics.

UC (n(%))	25 (89)	
	Pancolitis	6 (24)
	Left-sided	13 (52)
	Proctitis	6 (24)
Crohn's (n(%))	3 (11)	
	Crohn's colitis	2 (67)
	Ileocaecal disease	1 (33)
Age of onset (n(%))		
	<17 years	1 (4)
	17-40 years	16 (57)
	>40 years	11 (39)
Time from symptom onset to diagnosis (months) (median, IQR)	10 (3,37) Range: 2 months -132 months	
Median time from symptom onset to seeking medical attention (months) (median, IQR)	2 (0.25-5) Range: 1 week – 48 months	
Appendicectomy (n(%))	2 (7)	
Treatment at time of recruitment (n%))	Sulfasalazine	12 (43)
	Corticosteroid	7 (25)
	Azathioprine	2 (7)
	Methotrexate	2 (7)
	Untreated	5 (18)

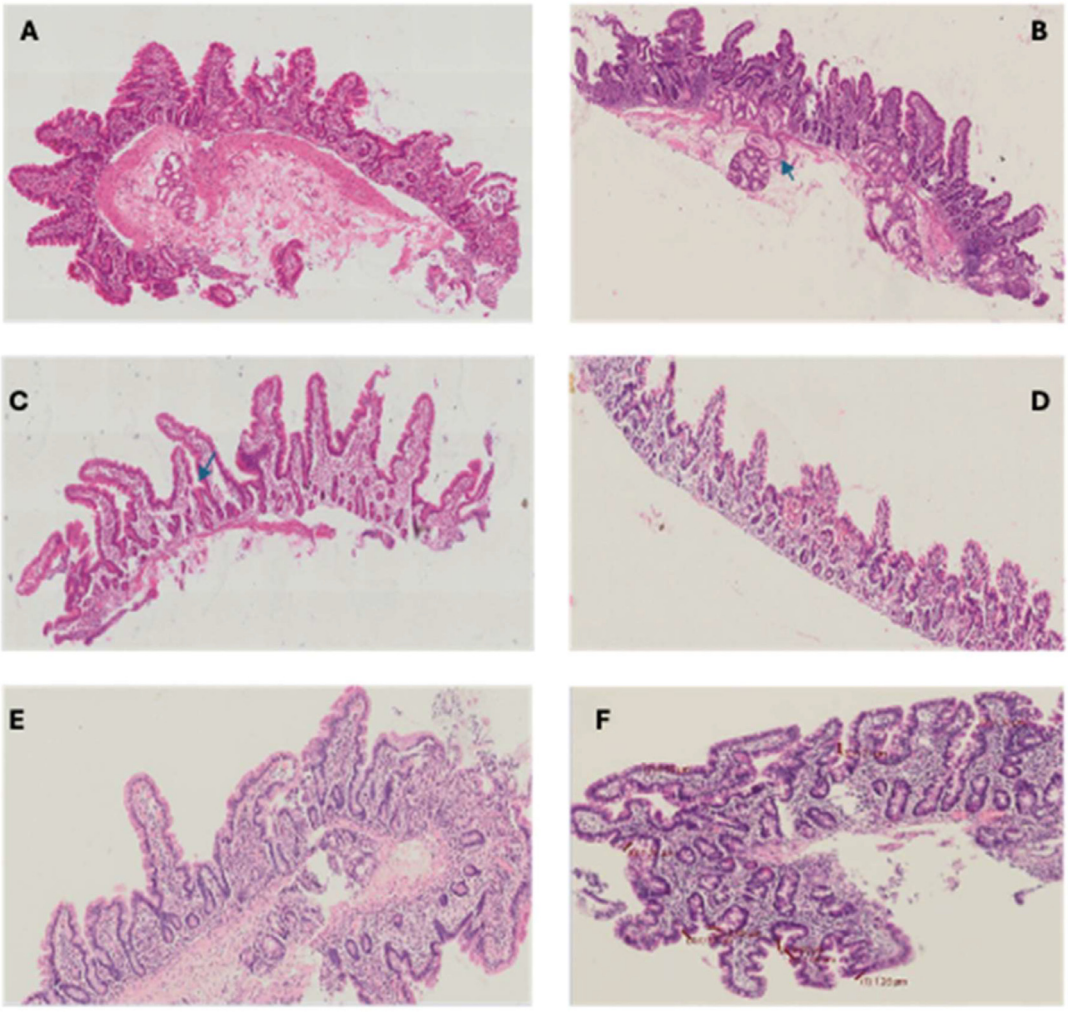

Fig. 1. Duodenal biopsies from cases (A,B), high SES controls (C,D) and low SES controls (E,F). All images show features of environmental enteropathy including villus blunting, crypt hypertrophy, reduced villous height to crypt depth ratio and inflammatory cell infiltrate. Other features include intramucosal infiltration of Brunner's glands (image **b**) and crypt branching (image **c**) (see arrows).

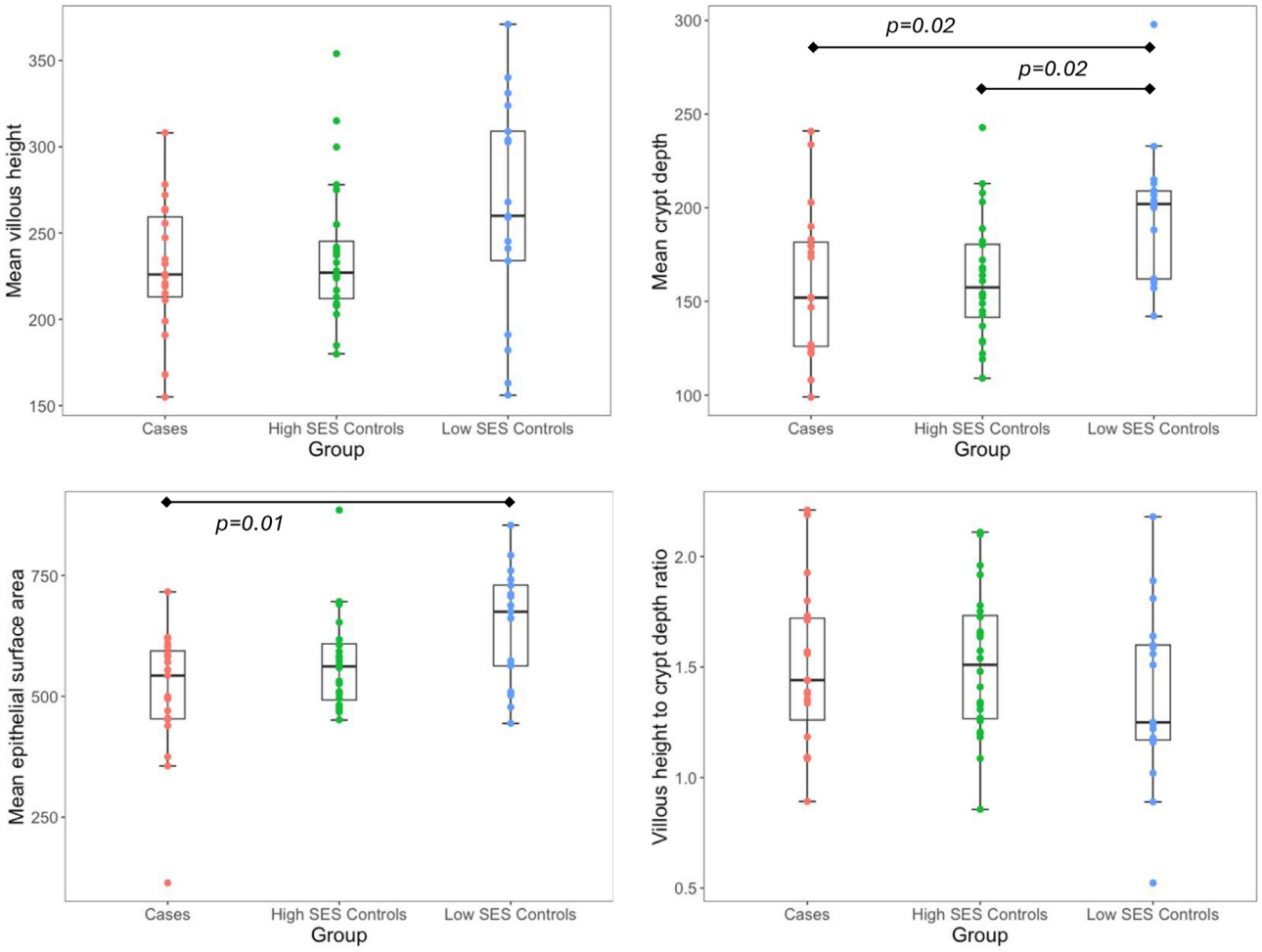

Fig. 2. Boxplots of morphometric measurements. Measurements with significant differences are shown on the graph. All comparisons were made using independent-samples Kruskal Wallis test. Showing median, IQR, range, etc

Table 3
Biopsy scoring for histological features of environmental enteropathy.

Histology feature (score)	Cases $n = 19$ (Median, IQR)	High SES Controls $n = 24$ (Median, IQR)	Low SES Controls $n = 17$ (Median, IQR)	p value
Villus architectural change (0-4)	1 (1, 2.5)	2 (1,2)	1 (1,2)	0.03
Not scorable (n(%))	4 (21)	1 (4)	1 (6)	
Intramucosal Brunner glands (0-3)	3 (2,3)	3 (3,3)	3 (2.5, 3)	0.14
Not scorable (n(%))	3 (16)	5 (21)	1 (6)	
Paneth cell depletion (0-3)	1 (1, 2.75)	1 (1,3)	1 (1,1)	0.01
Not scorable (n(%))	5 (26)	5 (21)	2 (12)	
Goblet cell depletion (0-4)	0.5 (0, 2.75)	1.5 (0.25, 3)	1 (0, 3)	0.41
% not scorable	5 (26)	4 (17)	3 (18)	
TSP-5 (0 %-100 %)	44 (27, 56)	46 (33, 55)	33 (28, 47)	0.29
% not scorable	2 (11)	0	1 (6)	

Biopsies were also assessed for histological scoring parameters as previously described [12,13]. There were no differences found between groups for TSP-5 scores (Table 3).

3.2. Autoantibody concentrations

We also measured anti-tissue transglutaminase IgA antibodies in the plasma of all participants. All results were within the normal range (<10 U ml^{-1}) and there were no significant differences in anti-TTG IgA antibody plasma concentrations between groups. There was no correlation found between anti-TTG IgA concentration and any of the morphometry markers.

3.3. Enteropathogen carriage

As discussed previously, stool volumes in the low SES group were too low to allow of their inclusion in this analysis, hence only results for cases and High SES controls are shown here (Supplementary Fig. S3). Cases were found to carry significantly fewer pathogens than High SES controls, with a median of 1 pathogen per case and 2 per High SES control ($p < 0.01$ using Mann–

Whitney U). One individual in the High SES control group was found to be carrying 5 pathogens simultaneously. There were no significant differences in the numbers of cases or controls reporting past antibiotic use.

There were no incidences of rotavirus, *Campylobacter, V. cholerae* or *Y. enterocolitica* in either group. There was no correlation between total number of enteropathogens carried and any of the morphometric markers of enteropathy.

3.4. Helicobacter pylori

Quantitative measurement of *H. pylori* faecal antigen concentration revealed no statistically significant differences between groups. Using a cut-off of 3ng mL^{-1}, 15% cases were positive, 30% High SES controls were positive, and 44% Low SES controls were positive. Combined positivity rate amongst controls was 36%. Difference in positivity rate between cases and pooled controls was not significant ($\chi^2 = 1.92$, $p = 0.15$).

3.5. Biomarkers of microbial translocation and intestinal inflammation

Plasma concentrations of CRP and sCD14 were higher in cases than in either control group, and plasma LBP levels were higher in cases than in high SES controls (Fig. 3). There was no difference in plasma levels of sCD163 or IFABP between groups. Faecal calprotectin and faecal polymorphonuclear elastase (PMN elastase) concentrations were higher in cases than in controls, although 38% of high SES controls and 29% low SES controls had a faecal calprotectin concentration of >150 µg g^{-1} (generally the upper limit accepted as 'normal' in other settings). Faecal alpha-1 antitrypsin levels were significantly lower in cases, with levels being largely undetectable in cases with the exception of 2 individuals. Correlations between markers of systemic and intestinal inflammation are shown in Supplementary Fig. S4.

3.6. Tissue concentrations of cytokines and matrix metalloproteinases

There were no differences in concentrations of cytokines in homogenates of duodenal biopsies between groups. Concentration of MMP-9 was significantly higher in low SES controls (see Supplementary Fig. S5).

4. Discussion

It is clear that environmental enteropathy and IBD do coexist in this population, with features of enteropathy being present in small bowel biopsies from all cases and controls in this study, and a very high degree of overlap in biomarkers of epithelial damage such as iFABP (see Supplementary Fig. S4). There was perhaps a more severe enteropathy as represented by a greater degree of crypt hypertrophy in the low SES controls, as one might expect consistent with the proposed aetiology of EE, however no difference was found in overall TSP-5 scores between groups. The TSP-5 score provides a percentage score based on five histological parameters: blunted villous architecture; intraepithelial lymphocyto-

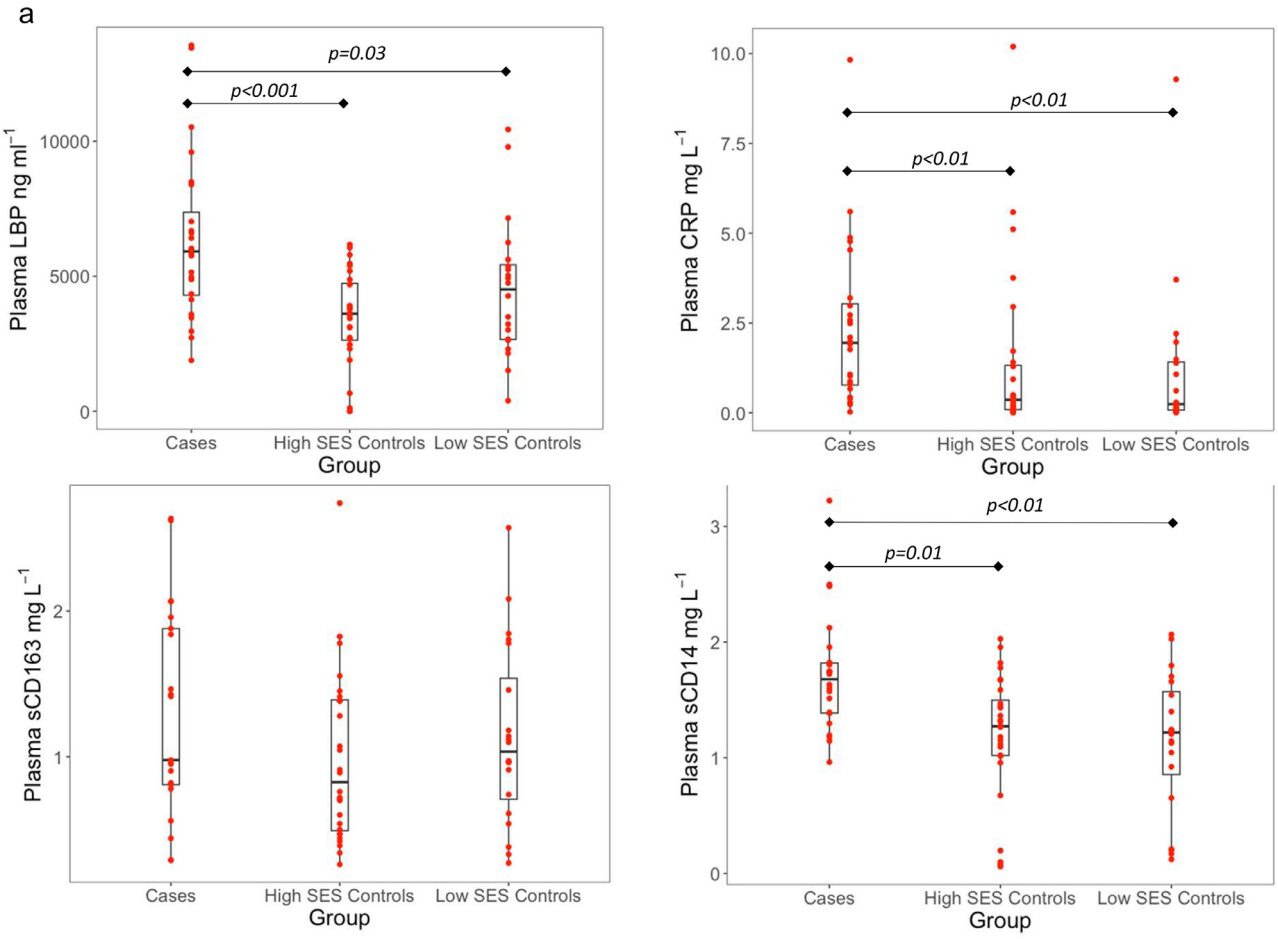

Fig. 3. **a** Biomarkers of systemic and **b** intestinal inflammation. Markers with significant differences are shown on the graph. All comparisons were made using independent-samples Kruskal Wallis test.

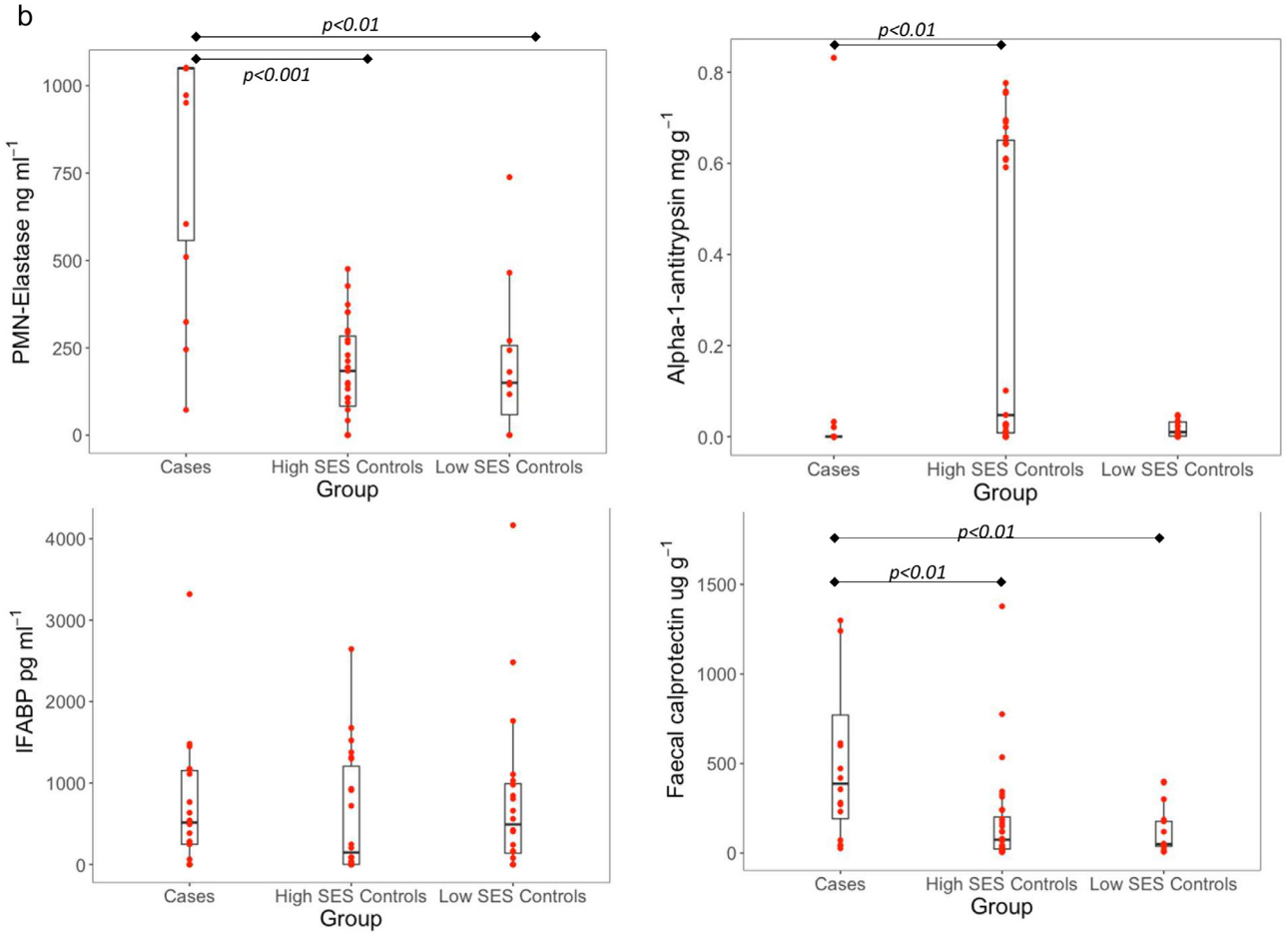

Fig. 3. Continued

sis; Paneth cell depletion; intramucosal Brunner's glands; and goblet cell depletion [13]. This score is given as a percentage of the total possible score, which allows for calculation of a score even when some of these domains are not suitable for scoring in a particularly biopsy, and is able to differentiate between EE and normal biopsies. The score is higher when biopsies are more abnormal. Biopsies from Low SES Controls scored significantly lower for villous architecture and Paneth cell density than high SES controls. (Table 3). For comparison, a median TSP-5 from 44 healthy controls in the US was 11.9 %, with a 95th percentile of 24.6 % [13]. Only 7 of the participants in our study (4 cases, 1 high SES control and 2 low SES controls) had a TSP-5 lower than this. All biopsies scored 0 for intraepithelial lymphocytosis hence this parameter is not included in the table. This is consistent with the finding of lower intraepithelial lymphocyte scores in a cohort of Zambian children with EE (the BEECH study), where the median intraepithelial lymphocyte score was 1, than in children from Pakistan [13].

Cases were found to carry fewer enteropathogens than controls. Although analysis of questionnaire data revealed no difference in antibiotic use between cases and controls, questions related to antibiotic use were general and there is no way of knowing which antibiotics had been prescribed prior to the participant being recruited to the study due to lack of prescribing records in this setting. It seems likely however that metronidazole use in the case group could account for the lack of giardia detected in this group, as this antibiotic is commonly prescribed to people presenting with diarrhoea. Enteropathogen carriage in high SES controls was perhaps higher than expected (median 2 enteropathogens per control) and this may be due to the choice of control group. The high SES control group was selected partially for pragmatic reasons as it was deemed more ethically acceptable to collect endoscopic samples from patients who were undergoing upper GI endoscopy as part of their routine medical care than from asymptomatic healthy individuals, however, this meant that high SES controls were symptomatic (with the major indication for upper GI endoscopy in this group being epigastric pain) hence this may be a confounding factor as enteropathogen carriage may be higher in this group than would be representative of the general (asymptomatic) population. This is a potential flaw of the study design.

Biomarkers of translocation and intestinal inflammation were either found to be higher in IBD cases or not significantly different from controls, although IBD-related inflammation is clearly a confounding factor here. Although faecal calprotectin was significantly higher in the case group, it seems that faecal PMN-elastase may be a more discriminatory test in terms of differentiating between IBD and low-level inflammation resulting from environmental enteropathy in this population. 35% of all controls had a faecal calprotectin concentration of >150 μg g^{-1}, which level is usually used as the cut-off for 'normal' in UK practice. PMN-elastase has not previously been assessed as a biomarker of EE, however, faecal neutrophil elastase activity in UC patients has been found to have similar accuracy in predicting disease activity index as calprotectin [16]. The reference range given as normal for PMN-elastase by the manufacturer of the assay was <62 ng ml^{-1}, however, only 1 individual in this study (a high SES control) had a faecal PMN-elastase concentration that fell within this range. PMN-elastase concentrations in controls however were almost exclusively less than 500 ng ml^{-1}, whereas the median concentration in cases was 1050 ng

ml^{-1}, which was also the upper limit of the measurement range. PMN-elastase may therefore be a promising candidate for a predictive marker in patients presenting with symptoms suggestive of IBD in Africa, as it may have a higher predictive value than calprotectin when triaging patients to colonoscopy in a resource limited setting. This deserves further study.

With the increase in incidence of IBD in populations where it has previously been a rare diagnosis, there is an ongoing need to further understand the environmental factors that influence this. Environmental hygiene factors in childhood offer a possible explanation for IBD in that children raised in sanitary environments are not exposed to a broad range of microbes and therefore do not develop oral tolerance, leading to dysregulated mucosal immune responses which lead to development of IBD. In line with this hypothesis, certain childhood factors such as bed sharing and exposure to pets/farm animals have been shown to be associated with IBD [9]. One might therefore expect that individuals raised in insanitary environments who are persistently exposed to enteropathogens (and therefore more likely to have EE) would be less likely to develop IBD. In terms of histological features, one would expect small intestinal biopsies from people with IBD to score lower for Paneth cell density, villous architectural change, goblet cell density and intraepithelial lymphocyte count, and higher for Brunners glands (which is a reverse scoring system). We did not find this to be the case. One might also expect these biopsies to demonstrate greater villous height and epithelial surface area. Again, our findings were not consistent with this.

5. Conclusions

Inflammatory bowel disease and environmental enteropathy do co-exist in the Zambian population, although IBD patients in this setting carry fewer enteropathogens than controls. This not only contests the role of environmental hygiene factors in the development of IBD but may prove to be a confounding factor when assessing patients presenting with symptoms suggestive of IBD in this setting, as traditional biomarkers such as calprotectin may be of lower predictive value.

Author contributions

PH, NMC and PK conceptualised the study. PH and PK designed the study and acquired funding. PH, MM, WK, VK and PK assessed participants. PH, MM, WK, VK, CM, EB, and VM collected data. PH and MM conducted data analysis. PH and PK wrote the original draft of the manuscript. All authors reviewed and edited the final draft of the manuscript, had full access to all the data in the analysis, and had final responsibility for the decision to submit for publication.

Data sharing

Deidentified data supporting our findings and additional, related documents (i.e., informed consent forms, information sheet, and protocol) are available from the corresponding author upon request from the date of publication.

Conflict of interest

With regards to the above manuscript, the authors declare that they have no conflict of interest related to the content of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.05.001.

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