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Children with moderate acute malnutrition have inflammation not explained by maternal reports of illness and clinical symptoms: a cross-sectional study in Burkina Faso

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Abstract

Background: Morbidity plays an important role in the development of and recovery from malnutrition. Morbidity in children with moderate acute malnutrition (MAM) has not been described in detail and it is unclear how morbidity compares to serum levels of acute phase proteins (APPs) which indicate systemic inflammation and which can impede response to therapeutic nutritional interventions. The objective of this study was to describe morbidity in children with MAM and to assess to what extent maternally reported and clinically diagnosed morbidity explain the variation in APPs.

Methods: A cross-sectional sub study was conducted as part of a nutrition intervention trial among 6–23 months old children with MAM residing in Burkina Faso. Morbidity data collection at baseline included 2 week maternal recalls and physical examinations. Multivariate ANCOVA models were used to explore the associations between morbidity and C-reactive protein (CRP) as well as α_1-acid glycoprotein (AGP). These models were also used to determine to what extent morbidity explains variation in APPs.

Results: In the 2 weeks prior to the study inclusion visit, 38 % of children were ill according to mothers. Furthermore, 71.8 % of children had a symptom or infection identified during the physical examination and 24.2 and 66.4 % of children had elevated CRP and AGP, respectively. Among children without any identified symptom or illness at the inclusion visit, 10.7 and 46.5 % had elevated CRP and AGP, respectively. History of fever as well as nurse-documented fever, malaria, respiratory tract infections and skin infections were associated with higher levels of both APPs. History of cough and diarrhoea at the inclusion visit was associated with higher α_1-acid glycoprotein only. Overall, morbidity data only explained a small amount of the variation in APP levels (adjusted R^2 below 0.2 in all tested models).

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Conclusion: Morbidity among children with MAM in this setting is common, but maternal reports and clinical examination explained only a small proportion of the variation in APPs, indicating a presence of subclinical inflammation. We recommend further research into the causes of this subclinical inflammation as it could affect nutritional status and success of MAM treatment.

Trial registration: The trial was registered in the International Standard Randomised Controlled Trial Number Register (ISRCTN42569496).

Keywords: Moderate acute malnutrition, Morbidity, Inflammation, Acute phase proteins, Children

Abbreviations: AGP, α_1-acid glycoprotein; ANCOVA, Analysis of covariance; CRP, C-reactive protein; HRP2, Histidine-rich protein 2; IMCI, Integrated Management of Childhood Illness; LRTI, Lower respiratory tract infection; MAM, Moderate acute malnutrition; MUAC, Mid-upper-arm-circumference; RDT, Rapid diagnostic test; WHZ, Weight-for-height z-score

Background

Moderate wasting, defined as a weight-for-height z-score (WHZ) between -2 and -3, affects approximately 33 million children worldwide [1] and is associated with a higher risk of death from infectious diseases compared to children without anthropometric deficits [2].

Malnutrition interacts with infections in a vicious cycle whereby it not only increases the risk and severity of infections, but can also be a result of infection [3]. Early diagnosis and treatment of infections in malnourished children is therefore required, in addition to nutritional treatment, to break this cycle. Morbidity is assessed via a combination of subjective and objective findings through history-taking (relying on recall by the caretaker) and a physical examination carried out by a health professional. In addition, measurement of serum acute phase proteins such as C-reactive protein (CRP) and alpha-1 acid glycoprotein (AGP) can provide objective information about inflammation but are rarely measured in low resource settings. Acute phase proteins rise or fall in response to infection or injury but are not specific to any particular disease [4]. Asymptomatic children can have elevated levels of acute phase proteins [5, 6] indicating the presence of subclinical inflammation, due to conditions that are not captured by patient history or physical examination. Inflammation can affect nutrient intake, nutrient absorption and expenditure [7, 8] and may therefore also play a role in effectiveness of nutrient supplements provided to treat malnutrition and nutrient deficiency disease.

Few studies have reported on morbidity in children with moderate wasting or moderate acute malnutrition (MAM) [9–15] and most based only on symptom-recall. Current case definitions of MAM includes children with moderate wasting and/or a mid-upper arm circumference (MUAC) between 115 and 125 mm [16]. Furthermore, to our knowledge none have compared morbidity data from maternal recall and physical examination to markers of inflammation in children with MAM.

As part of a nutrition intervention trial, we aimed to describe morbidity and inflammation in children with MAM and to assess to what extent morbidity by maternal recall and physical examination explains the variation in markers of inflammation.

Methods

Study area and population

The data for this observational study were collected as part the TreatFOOD trial, a randomised controlled trial investigating effectiveness of six corn-soy blends and six lipid-based nutrient supplements in treating MAM carried out in the Passoré Province, Northern Region, Burkina Faso. This part of Burkina Faso is located in the Sudano-sahelian zone which is characterised by an average yearly rainfall of 600–700 mm [17]. The year is divided into one dry and one rainy season, where the latter runs from approximately mid-May to late October [18]. The catchment area covered a total of 143 villages and a total population of ~258,000.

Children aged 6–23 months with MAM resident in the catchment area and whose parents/guardians consented to participate were included. Screening for participants was carried out by community health workers using MUAC tapes or by designated screening teams using both MUAC and WHZ. In addition, children could be referred from a health centre or could present at site on caretaker's initiative. Recruitment took place from September 2013 until August 2014.

Data collection

Socio-demographic data were collected by trained interviewers. Weight was measured in duplicate to the nearest 100 g with an electronic scale (Seca model 881 1021659). Length was measured in duplicate with a wooden length board to the nearest 1 mm. MUAC was measured to the nearest 1 mm using a standard measuring tape. Morbidity data collection included a patient history based on 14-day

maternal recall of symptoms and a physical examination carried out by study nurses. Study nurses were trained and supervised by a study physician. 2.5 ml of venous blood were collected from the arm. One drop of blood was used for diagnosis of malaria on site using a rapid diagnostic test (RDT) that detects histidine rich protein 2 (HRP2) synthesized by the Plasmodium falciparum malaria parasite (Bioline, Malaria Ag P.f, Standard diagnostics Inc.). The remaining blood from each sample was put into a sample tube with clot activator (BD reference #368492) and transported to the trial laboratory in a cold box at 2–8 °C. Serum was isolated following centrifugation at 3000 RPM for 5 min (EBA 20 S Hettich) and stored at -20 °C until shipment to VitMin Lab in Willstaedt, Germany for analysis. Serum CRP and AGP were determined using a simple sandwich enzyme-linked immunosorbent assay [19]. All samples were measured in duplicate and the intra- and interassay co-efficients of variation were <10 %. Freeze-thaw cycles were avoided during the handling of all samples.

Fever was defined as an axillary temperature ≥ 37.5 °C. Upper and lower respiratory tract infections were diagnosed by experienced nurses based on an adapted version of the Integrated Management of Childhood Illnesses (IMCI) guidelines. Diarrhoea was defined as three or more loose watery stools per day based on information provided by the mother. Malaria diagnosis was based on a positive rapid diagnostic test (RDT) only, and no microscopy was done to establish the level of parasitaemia. Since HRP2, the protein detected by the RDT, can persist in blood for over a month after treatment of malaria [20, 21] positive RDT in absence of clinical findings may be due to either a treated infection or asymptomatic malaria. We therefore present prevalence of children with a positive RDT accompanied by fever in addition to prevalence of positive RDT independent of fever. The thresholds used for defining elevated acute phase protein levels were CRP >10 mg/l [4] and AGP >1 g/l [8].

Two binary composite morbidity variables were generated based on maternal recall and physical examination data. A child was considered ill according to maternal recall if the caretaker reported that their child had, in the previous 2 weeks, any of the following: fever, cough, diarrhoea, vomiting, breathing problems, reduced appetite, rash, pain or swelling. A child was considered ill according to physical examination if he/she had one or more of the following: skin problem (rash, ulcer, infection or other), respiratory tract infections, ear infection, diarrhoea, oral thrush, mouth ulcer, fever and malaria. These two variables were combined to generate 4 illness groups, that is i) no symptom/illness identified, ii) ill according to maternal recall only, iii) ill according to physical examination only, iv) ill according to maternal recall and physical examination.

Data handling and statistical analysis

Data were double entered into EPIDATA 3.1 Software (Epidata Association, Odense, Denmark) and double entry checks were performed on a daily basis. All statistical analyses were carried out using STATA version 12 (StataCorp, College Station TX, USA). *P*-values <0.05 were considered significant.

Baseline characteristics as well as symptoms and illnesses were summarised as percentage, mean (SD), or median (interquartile range). Logistic regression was used to investigate whether morbidity (symptoms and illnesses according to both mother and nurse as well as inflammation) differed according to admission category (low MUAC only, low MUAC and low WHZ or low WHZ only). The models were adjusted for age and sex.

Analysis of covariance (ANCOVA) was used to evaluate differences in mean CRP and AGP levels between illness groups by means of pairwise comparisons while adjusting for age and sex. ANCOVA, in univariate and multivariate models, was used to explore the associations between acute phase protein concentrations and presence of illnesses and to determine the amount of variation in acute phase proteins explained by morbidity data. Six multivariate models were built: two with data from maternal recalls as predictor, two with data from physical examinations and two with data from both sources as predictors and with either CRP or AGP as outcome. All models were adjusted for age and sex. Log transformations were applied to achieve normally distributed variables, if needed, and estimates were subsequently back-transformed [22]. Models were checked using residual and normal probability plots.

Results

Of the 1609 enrolled children 29 % of children were admitted based on MUAC only, 50 % based on MUAC and WHZ and 21 % based on WHZ only as reported previously [23]. Over half (54.6 %) of participants were female. Prevalence of stunting (height-for-age < -2) was 37.7 %. The mean (SD) age was 12.3 (4.8) months (Table 1). Age differed between admission categories, more specifically it was 11 (4.6), 12.6 (4.8) and 13.7 (4.8) months in children admitted based MUAC only, MUAC and WFH and WFH only ($p < 0.001$). Admission categories are presented in order of increasing age for the remainder of this paper. Mothers reported illnesses in the 2 week period prior to admission in 38 % of children. According to the physical examination by the study nurse 71.8 % of children were ill and/or had a positive malaria test on the day of the visit (Table 2). The most prevalent illnesses diagnosed by the nurse were malaria based on positive RDT (40.2 %), lower respiratory tract infections (23.2 %) and upper respiratory tract infections (14.6 %). Fever (without a source on clinical examination)

Table 1 Background characteristics of 1609 6–23 months old children with moderate acute malnutrition

Sex, % female (n)	54.6 (879)
Age, months mean (SD)	12.3 (4.8)
Inclusion category, % (n)	
Low mid-upper-arm circumference only	29 (468)
Low weight-for-height z-score and low mid-upper arm circumference	50 (804)
Low weight-for-height z-score only	21 (337)
Height-for-age z-score < -2, % (n)	37.7 (607)
Mother's education level[a], % (n)	
None	85.5 (1374)
Primary incomplete	7.9 (127)
Primary complete or higher	6.3 (102)
Mother's profession[a], % (n)	
Agriculture	94.3 (1516)
Animal farming	1.6 (25)
Other	4.1 (67)
Mother's ethnic group[a], % (n)	
Mossi	94.1 (1512)
Peulh/Fulani	2.3 (37)
Other	3.6 (58)
Household size, median (interquartile range)	10 (7–16)
Number of children under 5 y in the household, median (interquartile range)	2 (2–4)

[a]Missing data: ethnic group ($n = 1$), education level ($n = 5$), profession ($n = 2$)

was also common (17.7 %). Fever was more common in children with a positive malaria rapid test than those without (21.0 % vs 15.6 %, $p = 0.006$). 31.8 % ($n = 509$) had a positive RDT but no fever and 20.5 % ($n = 329$) had a positive RDT but no other clinical symptoms. Almost a quarter (24.2 %) and two thirds (66.4 %) of children had serum CRP >10 mg/l and serum AGP >1 g/l, respectively (Table 2.). Positive malaria RDTs were more common among children admitted based on MUAC only than children admitted based MUAC and WHZ or WHZ only after adjustment for age and sex. More children had lower respiratory tract infection if they were admitted based on only WHZ compared to only MUAC or MUAC and WHZ after adjustment for age and sex. There was no association between other symptoms, illnesses and acute phase protein levels and admission categories (Table 2).

There was a considerable overlap of children who were ill based on maternal recall, physical examination and elevated acute phase proteins (Fig. 1); however, only 10 % of children for CRP and 24 % for AGP were ill according to all three measures. Among the total study population 2 and 10 % had serum CRP >10 mg/l and AGP >1 g/l, respectively, in the absence of any reported illnesses or symptoms according to the mother and/or the nurse (Fig. 1). A total of 338 (20.8 %) children had no identified symptoms or illnesses according to either maternal recall or physical examination whereas only 302 children (19 %) had normal CRP and 181 children (12 %) had normal AGP in the absence of symptoms. Therefore, of asymptomatic children, 10.7 % ($n = 36$) and 46.5 % ($n = 157$) had a CRP >10 mg/l and AGP >1 g/l, respectively. Mean serum CRP and AGP were higher in children who were ill according to both mother and nurse compared to those who were ill according to the nurse only ($p < 0.05$) (Table 3.). These results remained significant if children with a positive malaria test in the absence of fever were not considered to be ill according to the nurse (data not shown).

The estimates shown in Table 4 correspond to the difference in acute phase protein means between those who had and those who did not have a particular symptom for the two univariate and two multivariate models. Overall, children who had been ill according to either the study nurse and/or maternal recall had a 2.7 mg/l ($p < 0.001$) and 0.33 g/l ($p < 0.001$) higher mean serum CRP and AGP, respectively, compared to those without any reported symptoms.

In univariate models, history of fever and cough were associated with higher serum AGP and CRP; diarrhoea and vomiting were not. In addition, fever, malaria and skin infections diagnosed by the nurse were associated with higher serum CRP and AGP. Lower respiratory tract infection and ear infection were associated with serum AGP but not CRP (Table 4). Differences in means ranged from 1.4 mg/l for skin infections ($p < 0.001$) to 2.86 mg/l ($p < 0.001$) for fever for CRP and from 0.11 g/l for lower respiratory tract infection ($p < 0.001$) to 0.31 g/l ($p < 0.001$) for positive malaria test for AGP (Table 4). Children with malaria but no fever had a 2.8 mg/l and 0.3 g/l higher mean CRP and AGP, respectively, than children without malaria or fever ($p < 0.001$), whereas children with malaria and fever had a 5.9 mg/l and 0.6 g/L higher mean CRP and AGP, compared to children without malaria or fever ($p < 0.001$). In multivariate models, the association between history of cough and serum CRP was lost and history of vomiting became associated with a lower CRP. Diarrhoea on the day of admission and upper respiratory tract infection became associated with serum AGP and both upper and lower respiratory tract infection became associated with serum CRP (Table 4). The adjusted R^2 for serum CRP using morbidity data from maternal recall and physical examination was 0.053 and 0.112, respectively (Table 4) and increased to 0.141 if data from maternal recall and physical examination were included in the same model. The adjusted R^2 for serum AGP using morbidity data from maternal recall and physical examination was 0.103 and 0.152, respectively (Table 4) and increased to 0.186 if

Table 2 Prevalence of symptoms and illnesses according to maternal recall and physical examination by admission criteria

	All	Low Mid-upper arm circumference (MUAC)	Low MUAC and low weight-for-height z-score (WHZ)	Low WHZ	*p*-value
Maternal recall[a], % (n)					
Any symptom	38.0 (608)	34.6 (161)	39.1 (312)	40.2 (135)	0.5
Fever	20 (322)	17.8 (83)	20.3 (162)	22.9 (77)	0.8
Diarrhoea	17.9 (286)	14.8 (69)	19.8 (158)	17.6 (59)	0.9
Cough	9.6 (153)	7.9 (37)	9.5 (76)	11.9 (40)	0.1
Vomiting	6.8 (109)	4.7 (22)	7.4 (59)	8.3 (28)	0.2
Skin infections	0.5 (8)	0.4 (2)	0.5 (4)	0.6 (2)	0.9
Loss of appetite	0.1 (2)	0 (0)	0.1 (1)	0.3 (1)	0.4
Physical examination[a], % (n)					
Any symptom	71.8 (1155)	72.6 (340)	71.9 (578)	74.2 (250)	0.5
Fever	17.7 (285)	15.6 (73)	17.3 (139)	21.7 (73)	0.1
Positive malaria test	40.2 (644)	46 (214)	38.8 (310)	35.6 (120)	<0.001
Without fever	31.8 (509)	38.4 (178)	30.7 (245)	25.6 (86)	<0.001
With fever	8.4 (135)	7.8 (36)	8.1 (65)	10.1 (34)	0.8
Upper respiratory tract infection	14.6 (234)	13.5 (63)	15.8 (127)	13.1 (44)	0.3
Lower respiratory tract infection	23.2 (373)	20.5 (96)	22.4 (180)	28.8 (97)	0.006
Diarrhoea	5.8 (94)	5.1 (23)	6 (48)	6.5 (22)	0.9
Skin[b]	3.9 (63)	4.5 (21)	3.7 (30)	3.6 (12)	0.6
Ear[c]	1.1 (17)	1.1 (5)	0.9 (7)	1.5 (5)	0.7
Acute phase proteins[a]					
Serum C-reactive protein, mg/l,					
Median (interquartile range)	2.3 (0.8–9.4)				
> 10 mg/L, % (n)	24.2 (378)	22.7 (103)	24.2 (190)	26.1 (85)	0.06
Serum α1-acid glycoprotein, g/l,					
Median (interquartile range)	1.2 (0.9–1.6)				
> 1 g/L, % (n)	66.4 (1039)	62.6 (284)	69.4 (544)	64.7 (211)	0.6

[a]Missing data: Maternal recall all symptoms ($n = 9$), fever ($n = 1$), malaria ($n = 8$), Upper respiratory tract infection ($n = 2$), lower respiratory tract infection ($n = 1$), skin infections ($n = 3$), ear infections ($n = 2$), acute phase proteins ($n = 45$)
[b]includes rash, infections, ulcer
[c]includes discharge, pain and other

data from maternal recall and physical examination were included in the same model.

Discussion

In this cross-sectional study we have shown that infections and inflammation in children with MAM are common and largely independent of admission criteria. We have also shown that symptoms and illnesses identified by mothers and by nurses during physical examinations are associated with serum APP levels but that morbidity only explains a small amount of variation in APPs and that even children without any identified symptoms can have elevated APP levels.

This study had a number of limitations. Firstly, the data used were baseline data collected for a randomised controlled trial and data collection was thus not specifically designed for this study. As a result we had no control group and have not been able to compare prevalence of infection and inflammation to children without anthropometric deficits in the same setting. Furthermore, inclusion in the study was based on active case finding by community health workers and study staff or based on mother's initiative and not based on random selection among all children with MAM in catchment area. As such, selection bias cannot be ruled out, which may have led to overestimation of the prevalence of morbidity, since sick children are more likely to have been selected. A further limitation may be the accuracy of lower respiratory tract infection (LRTI) diagnosis by nurses as diagnosis has previously been shown to be unreliable other settings [24, 25]. It is worth mentioning also that although the immune response is altered by malnutrition, a recent review on the immune system in malnourished children concluded that the acute phase response appears intact [6]

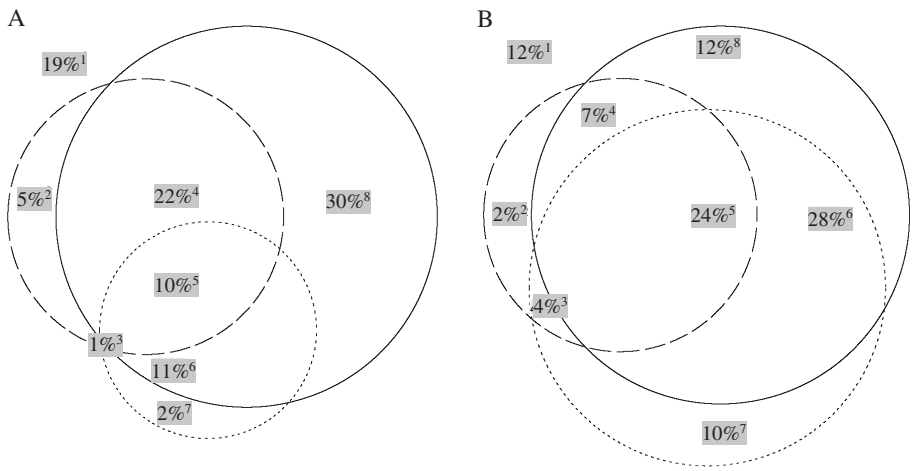

Fig. 1 Overlap between children ill according to maternal recall, physical examination and elevated acute phase proteins. **a** C-reactive protein > 10 mg/l; **b** α1-acid glycoprotein >1 g/l. ___ Any symptom/illness according to physical examination. _ _ _ Any sympton/illness according to maternal recall. …… Elevated acute phase protein. [1] Percentage of children without illness or inflammation; [2] % ill according to maternal recall (MR) only; [3] % with inflammation and ill according MR; [4] % ill according to physical examination (PE) and MR; [5]% with inflammation and ill according to PE and MR; [6]% with inflammation and ill according to PE; [7] % with inflammation only; [8] % ill according to PE only

and we therefore believe that CRP and AGP provide useful information about inflammation in children with MAM.

Our study demonstrates several important points. First, overall more than 80 % of children had an infection and/or inflammation. Considering the interaction between infection and nutrition, treatment of infections may therefore be important as part of MAM treatment in this setting. In Burkina Faso MAM treatment consists mainly of supplementary food and routine medication including deworming and Vitamin A and iron folic acid supplementation. Treatment of asymptomtic malaria is not recommended and little emphasis is placed on identification and treatment of infection [26].

Second, information provided by mothers on children's health status as well as diagnoses made during physical examination appear to be reliable as demonstrated by the association between symptoms and APP levels. Although, as mentioned above there is some concern about reliability of LRTI diagnosis. While data from maternal recall explain less of the variation in APPs than data from physical examinations, both methods are useful and the information they provide is complementary as is also indicated by the higher adjusted R^2 in the models where data from both sources were included. The two acute phase proteins we measured have different properties: CRP responds to infection quickly and reaches its maximum within 24–48 h and drops shortly after while AGP reaches a maximum concentration after 2–5 days and stays elevated longer [27]. It is therefore not surprising that morbidity data explains more of the variation in AGP than CRP. Furthermore, illnesses reported by mothers could have occurred 14 days in the past by which time APPs could have returned back to normal levels which may partly explain why the R^2 for models using recall data is lower than that for models using data from physical examinations. That mothers reported less illness than nurses might be in part due to accuracy of recall data being affected by reporting and recall bias [28, 29], perception of an abnormal situation, or tolerance to discomfort [30]. The latter is likely to be a cause of underreporting in a population such as this one where disease is common and even more so if proxy reporting is used as children may start feeling unwell

Table 3 Mean acute phase protein levels by illness group

	% (n)	Mean level of C-reactive protein mg/l (95 % confidence intervals) [a,b]	Mean α1-acid glycoprotein g/l (95 % confidence intervals) [a,b]
Not ill	21.6 % (345)	1.24 (1.03–1.5)	0.97 (0.92–1.01)
Ill according to mother only	6.6 % (105)	1.68 (1.2–2.35)	1.13 (1.04–1.23)
Ill according to mother and nurse	31.4 % (503)	3.91 (3.35–4.57)	1.4 (1.35–1.46)
Ill according to nurse only	40.4 % (647)	3.1 (2.71–3.55)	1.25 (1.21–1.29)

[a]Means are geometric means

[b]Pairwise comparisons between means adjusted for age and sex showed no significant difference for mean CRP level between children who were not ill and those who were ill according to mother only. All other pairwise comparisons were significant ($p < 0.05$)

Table 4 Morbidity by maternal recall and examination as correlates of serum acute phase proteins

	Serum C-reactive protein[d] (mg/l)				Serum α1-acid glycoprotein (g/l)			
	Univariate model[f]		Multivariate model[f,g]		Univariate model		Multivariate model[f,h]	
	Estimate (95 % confidence interval)[e]	*p*-value	Estimate (95 % confidence interval)[e]	*p*-value	Estimate (95 % confidence interval)[e]	*p*-value	Estimate (95 % confidence interval)[e]	*p*-value
Maternal recall[a]								
Any symptom	1.09 (0.59–1.58)	<0.001			0.21 (0.15–0.26)	<0.001		
Fever	2.68 (2.05–3.31)	<0.001	2.93 (2.26–3.62)	<0.001	0.33 (0.26–0.40)	<0.001	0.30 (0.23–0.38)	<0.001
Diarrhoea	-0.26 (-0.88-0.35)	0.4	-0.59 (-1.30 -0.13)	0.1	0.05 (-0.02-0.13)	0.1	-0.002 (-0.08–0.07)	0.9
Cough	1.36 (0.55-2.17)	0.001	0.53 (-0.36-1.43	0.2	0.27 (0.18–0.36)	<0.001	0.17 (0.07- 0.26)	0.001
Vomiting	-0.74 (-1.69-0.22)	0.1	-1.53 (-2.65- -0.42)	0.007	0.06 (-0.06-0.17)	0.3	-0.06 (-0.17- 0.06)	0.4
Physical examination[a]								
Any symptom	2.68 (2.13–3.22)	<0.001			0.33 (0.27–0.39)	<0.001		
Fever	2.86 (2.20–3.52)	<0.001	2.7 (2.06–3.50)	<0.001	0.26 (0.19–0.33)	<0.001	0.22 (0.15–0.29)	<0.001
Positive malaria test	2.77 (2.25–3.29)	<0.001	3.04 (2.47–3.61)	<0.001	0.31 (0.26–0.37)	<0.001	0.32 (0.26–0.38)	<0.001
Upper respiratory tract infection	0.6 (-0.07-1.3)	0.07	1.03 (0.23-1.82)	0.01	0.06 (-0.02-0.13)	0.1	0.08 (0.003-0.16)	0.04
Lower respiratory tract infection	0.5 (-0.04-1.1)	0.07	0.67 (0.02–1.32)	0.04	0.1 (0.04–0.17)	0.002	0.16 (0.05–0.18)	<0.001
Diarrhoea	0.12 (-0.89-1.12)	0.8	0.78 (-0.39-1.96)	0.2	0.07 (-0.05-0.19)	0.2	0.14 (0.03 -0.26)	0.01
Skin[b]	1.41 (0.20-2.62)	0. 02	1.64 (0.24-3.04)	0.02	0.15 (0.005-0.29)	0.04	0.14 (0.007-0.28)	0.04
Ear[c]	1.75 (-0.58-4.08)	0.1	0.7 (-1.97-3.46)	0.6	0.34 (0.06-0.61)	0.02	0.22 (-0.04-0.49)	0.1
Physical examination[a] & maternal recall								
Any symptom	2.7 (2.09–3.31)	<0.001			0.36 (0.29–0.42)	<0.001		

[a]Missing data: Maternal recall all symptoms ($n = 9$), fever ($n = 1$), malaria ($n = 8$), respiratory tract infection ($n = 6$), skin infections ($n = 3$), ear infections ($n = 2$)
[b]includes rash, infections, ulcer
[c]includes discharge, pain and other
[d]Since it is not possible to take a logarithm of zero, nine CRP values that were equal to zero were replaced with smallest number in the dataset, that is 0.01
[e]Estimates are back-transformed mean differences
[f]Multivariate models for maternal recall included fever, diarrhoea, cough and vomiting as predictors. Multivariate models for physical examination included fever, positive malaria test, respiratory tract infection, diarrhoea, skin and ear infections as predictors. All models are adjusted for age and sex
[g]Adjusted R2 was 0.053 and 0.112 for the multivariate models using maternal recall data and physical examination data, respectively
[h]Adjusted R2 was 0.103 and 0.152 for the multiple regression using recall data and physical examination data, respectively

before mothers notice it. In line with this, we found significantly higher mean serum CRP and AGP levels among children who were ill according to both nurses and mothers compared to those ill according nurses only. This may indicate that infections mothers bring to the nurses attention are more severe than those identified by nurses only. 20 % of children had a positive malaria test but no clinical signs or symptoms. While some of these children may have already been successfully treated for malaria, the higher serum CRP and AGP levels in children with a positive RDT without fever indicate a presence of asymptomatic malaria, which has previously been shown to have health consequences [31].

Third, we have shown that, although morbidity was largely independent of admission criteria, a positive RDT not accompanied by fever was more common among children admitted based on MUAC only and, in contrast, lower respiratory tract infections were most common among children admitted based on only low WHZ after adjustment for age. Asymptomatic malaria in children can persist for a long period of time [32] and we have shown that even a positive RDT without fever is associated with a greater mean difference in APPs. It has been suggested that since amino acid composition of APPs differ from that of muscle, the amount of muscle mobilised to make amino acids available for synthesis of APPs may be quite substantial [33]. Asymptomatic malaria may therefore lead to a greater breakdown of muscle than LRTI and have a greater impact on MUAC. In contrast a more acute condition such as LRTI may be associated with lower WHZ resulting from a short term impact of infection on weight due to anorexia and dehydration. Dehydration has been shown to affect WHZ to a greater extent than MUAC [34]. In addition there was also a non significant trend for other conditions, such as malaria accompanied by fever, to be more common in children with low WFH.

Lastly, we have shown that elevated APP levels in children without identified symptoms are not uncommon and that morbidity data collected explained only a small proportion of the variation, as demonstrated by the adjusted R^2 which was <0.2 in all models, both indicating a presence of subclinical inflammation. We have three possible explanations for the low R^2: Firstly, children may have infections not identified by mothers or nurses that might also have contributed to an increase in serum CRP or AGP. Secondly, acute phase proteins may rise during the incubation phase of a disease before clinical symptoms become apparent and serum AGP remains elevated during convalescence after an acute illness [8]. Thirdly, in addition to infection, there a range of other conditions such as environmental enteric dysfunction (EED), recent vaccinations, cooking with biomass fuels and exposure to toxins that may elicit an acute phase response [4, 8]. EED, previously known as environmental enteropathy or tropical enteropathy, might play an important role as it is believed to be highly prevalent in low-and middle income countries [35]. It is a usually asymptomatic condition characterized by inflammation, altered gut structure and function and is associated with stunting in infants and children [35, 36]. It has been hypothesised that EED may lead to systemic inflammation via increased intestinal permeability and microbial translocation [37], and therefore may be one possible cause of unexplained variation in biomarkers although we did not carry out appropriate tests to determine whether children had EED as part of this study.

Conclusion

Infections in children with MAM in this setting are common and, in addition, children have inflammation not explained by symptoms and illnesses identified during patient histories or physical examinations. We recommend further research to define the role of serum APP in the diagnosis and treatment of childhood infections, into causes of this subclinical inflammation and whether it has an impact on nutritional status and success of MAM treatment.

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Availability of data and materials

Data will be available upon request to the authors.

Authors' contributions

BC, HF, CR conceptualized the study. BC, CF, CWY and RO conducted the research; BC and CR analysed the data and BC wrote the first draft of the manuscript; BC had primary responsibility for final content. CF, CWY, MR, CR, AB, VC, KFM, RO, SF, PA, SS and HF revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests. The funding agencies had no role in the design of study, data collection and analysis, or presentation of the results.

Ethics approval and consent to participate

The study was approved by the Ethics Committee in Burkina Faso and consultative approval was obtained from the Danish National Committee

on Biomedical Research Ethics. Medical treatment was provided free of charge according to an adapted version of the IMCI guidelines and national protocol. Consent was obtained verbally and in writing (signature or fingerprints) from parents or caretakers of the children before inclusion. Caretakers of participants received an information sheet which was explained to them. The information sheet and consent form were translated into local language and back-translated to ensure accuracy. The consent procedure was carried out in the presence of an independent literate witness. Data were kept confidential and in a locked facility. The trial was registered in the International Standard Randomised Controlled Trial Number Register under the number ISRCTN42569496.

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References

1. Black R, Victora C, Walker S, Bhutta Z, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low and middle income countries. The Lancet. 2013;382:427–51.
2. Olofin I, McDonald C, Ezzati M, Flaxman S, Black R, Fawzi W, et al. Associations of suboptimal growth with all-cause and cause-specific mortality in children under five years: A pooled analysis of ten prospective studies. PLoS One. 2013;8(5):e64636.
3. Katona P, Katona-Apte J. The Interaction between Nutrition and Infection. Clin Infect Dis. 2008;46(10):1582–8.
4. Kushner I. Acute phase reactants. In: UpToDate [Internet]. Waltam, MA; 2015. Available from: www.uptodate.com. Accessed 5 Feb 2016.
5. Filteau S, Morris SS, Abbott R, Tomkins A, Kirkwood B, Arthur P, et al. Influence of morbidity on serum retinol of children in a community-based study in northern Ghana. Am J Clin Nutr. 1993;58:192–7.
6. Rytter M, Kolte L, Briend A, Friis H, Christensen V. The immune system in children with malnutrition—A systematic review. PLoS One. 2014;9(8): e105017.
7. Jones K, Thitiri J, Ngari M, Berkley J. Childhood malnutrition: Toward an understanding of infections, inflammation, and antimicrobials. Food Nutr Bull. 2014;35:64–70.
8. Raiten D, Sakr Ashour F, Ross A, Meydani S, Dawson H, Stephenson C, et al. Inflammation and Nutritional Science for Programs/Policies and Interpretation of Research Evidence (INSPIRE). J Nutr. 2015;doi: 10.3945/jn.114.194571.
9. Nikiema L, Huybregts L, Kolsteren P, Lanou H, Tiendrebeogo S, Bouckaert K, et al. Treating moderate acute malnutrition in first-line health services: an effectiveness cluster-randomized trial in Burkina Faso. Am J Clin Nutr. 2014; 100:241–9.
10. LaGrone L, Trehan I, Meuli G, Wang R, Thakwalakwa C, Maleta K, et al. A novel fortified blended flour, corn-soy blend "plus-plus", is not inferior to lipid-based ready-to-use supplementary foods for the treatment of moderate acute malnutrition in Malawian children. Am J Clin Nutr. 2012;95:212–9.
11. Maust A, Koroma A, Abla C, Molokwu N, Ryan K, Singh L, et al. Severe and moderate acute malnutrition can be successfully managed with an integrated protocol in Sierra Leone. J Nutr. 2015;145:2604–9.
12. Usha Devi R, Krishnamurthy S, Vishnu BB. Epidemiological and clinical profile of hospitalized children with moderate and severe acute malnutrition in South India. Indian J Pediatr. 2015;82(6):504–10.
13. Ciliberto M, Sandige H, Nheka M, Ashorn P, Briend A, Ciliberto H, et al. Comparison of home-based therapy with ready-to-use therapeutic food with standard therapy in the treatment of malnourished Malawian children: a controlled, clinical effectiveness trial. Am J Clin Nutr. 2005;81:864–70.
14. Ackatia-Armah R, McDonald C, Doumbia S, Erhardt J, Hamer D, Brown K. Malian children with moderate acute malnutrition who are treated with lipid-based dietary supplements have greater weight gains and recovery rates than those treated with locally produced cereal-legume products: a community-based, cluster-randomized trial. Am J Clin Nutr. 2015;101:632–45.
15. Stobaugh H, Ryan K, Kennedy J, Grise J, Crocker A, Thakwalakwa C, et al. Including whey protein and whey permeate in ready-to-use supplementary food improves recovery rates in children with moderate acute malnutrition: a randomized, double-blind clinical trial. Am J Clin Nutr. 2016;doi: 10.3945/ajcn.115.124636.
16. World Health Organisation. UNICEF, WFP and UNHCR consultation on the programmatic aspects of the management of moderate acute malnutrition in children under five years of age. Geneva: WHO; 2010.
17. FEWSnet. Livelihood zoning and profiling report: Burkina Faso. USAID; 2010.
18. FEWSnet. Burkina Faso Seasonal Calendar, typical year. [Internet]. 2013 [cited 2016 Jan 19]. Available from: http://www.fews.net/west-africa/burkina-faso. Accessed 27 Aug 2016.
19. Erhardt J, Estes J, Pfeiffer C, Biesalsky H, Craft N. Combined Measurement of Ferritin, Soluble Transferrin Receptor, Retinol Binding Protein, and C-Reactive Protein by an Inexpensive, Sensitive, and Simple Sandwich Enzyme-Linked Immunosorbent Assay Technique. J Nutr. 2004;134:3127–32.
20. Swarthout T, Counihan H, Senga R, Van den Broek I. Paracheck-Pf® accuracy and recently treated Plasmodium falciparum infections: is there a risk of over-diagnosis? Malar J. 2007;6(58):doi: 10.1186/1475-2875-6-58.
21. Kyabayinze D, Tibenderana J, Odong G, Rwakimari J, Counihan H. Operational accuracy and comparative persistent antigenicity of HRP2 rapid diagnostic tests for Plasmodium falciparum malaria in a hyperendemic region of Uganda. Malar J. 2008;29(7):221–31.
22. Laursen J, Dalskov S-M, Damsgaard C, Ritz C. Back-transformation of treatment differences - an approximate method. Eur J Clin Nutr. 2014;68:277–80.
23. Fabiansen C, Phelan K, Cichon B, Ritz C, Briend A, Michaelsen K, et al. Short children with a low midupper arm circumference respond to food supplementation: an observational study from Burkina Faso. Am J Clin Nutr. 2016;103:415–21.
24. Bjornstad E, Preidis G, Lufesi N, Olson D, Kamthunzi P, Hosseinipour M, et al. Determining the quality of IMCI pneumonia care in Malawian children. Paediatr Int Child Health. 2014;34(1):29–36.
25. Perkins B, Zucker J, Otieno J, Jafari H, Paxton L, Redd S, et al. Evaluation of an algorithm for integrated management of childhood illness in an area of Kenya with high malaria transmission. Bull World Health Organ. 1997;75(1):33–42.
26. Ministere de la Sante, Burkina Faso. Protocole national: Prise en charge integree de la malnutrition aigue. Burkina Faso: Ministere de la Sante; 2014.
27. Thurnham D, McCabe G. Influence of infection and inflammation on biomarkers of nutritional status with an emphasis on Vitamin A and Iron. In: Priorities in the assessment of vitamin A and iron status in populations, Panama City, Panama, 15-17 September 2010. Geneva: World Health Organisation; 2012.
28. Manesh A, Sheldon T, Pickett K, Carr-Hill R. Accuracy of child morbidity data in demographic and health surveys. Int J Epidemiol. 2008;37:194–200.
29. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemimiology. 1990;43(1):87–91.
30. Das J, Hammer J, Sanchez-Paramo C. The impact of recall periods on reported morbidity and health seeking behaviour. J Dev Econ. 2012;98:76–88.
31. Chen I, Clarke S, Gosling R, Hamainza B, Killeen G, Magill A, et al. "Asymptomatic" malaria: A chronic and debilitating infection that should be treated. PloS Med. 2016;doi:10.1371/journal.pmed.1001942.
32. Franks S, Koram K, Wagner G, Tetteh K, McGuiness D, Wheeler J, et al. Frequent and persistent, asymptomatic plasmodium falciparum infections in african infants, characterised by multilocus genotyping. J Infect Dis. 2001;183:796–804.
33. Reeds P, Fjeld C, Jahoor F. Do the differences between amino acid compositions of acute-phase and muscle proteins have a bearing on nitrigen loss in traumatic states? J Nutr. 1994;124:906–10.

34. Mwangome M, Fegan G, Prentice A, Berkley J. Are diagnostic criteria for acute malnutrition affected by hydration status in hospitalised children? A repeated measures study. Nutr J. 2011;10(92):doi:10.1186/1475-2891-10-92.
35. Crane R, Jones K, Berkley J. Environment enteric dysfunction: An overview. Food Nutr Bull. 2015;36(1):76–87.
36. Prendergast A, Humphrey J. The stunting syndrome in developing countries. Paediatr Int Child Health. 2014;34(4):250–65.
37. Prendergast A, Humphrey J, Mutasa K, Majo F, Rukobo S, Govha M, et al. Assessment of environmental enteric dysfunction in the SHINE trial: Methods and challenges. Clin Infect Dis. 2015;61(S7):S726–32.