Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Thymus size in children with moderate malnutrition: a cohort study from Burkina Faso

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BACKGROUND: Moderate acute malnutrition (MAM) affects millions of children, increasing their risk of dying from infections. Thymus atrophy may be a marker of malnutrition-associated immunodeficiency, but factors associated with thymus size in children with MAM are unknown, as is the effect of nutritional interventions on thymus size.
METHODS: Thymus size was measured by ultrasound in 279 children in Burkina Faso with MAM, diagnosed by low mid-upper arm circumference (MUAC) and/or low weight-for-length *z*-score (WLZ), who received 12 weeks treatment with different food supplements as part of a randomized trial. Correlates of thymus size and of changes in thymus size after treatment, and after another 12 weeks of follow-up were identified.
RESULTS: Thymus size correlated positively with age, anthropometry and blood haemoglobin, and was smaller in children with malaria. Children with malnutrition diagnosed using MUAC had a smaller thymus than children diagnosed based on WLZ. Thymus size increased during and after treatment, similarly across the different food supplement groups.
CONCLUSIONS: In children with MAM, the thymus is smaller in children with anaemia or malaria, and grows with recovery. Assuming that thymus size reflects vulnerability, low MUAC seems to identify more vulnerable children than low WLZ in children with MAM.

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IMPACT:

- Thymus atrophy is known to be a marker of the immunodeficiency associated with malnutrition in children.
- In children with moderate malnutrition, we found the thymus to be smaller in children with anaemia or malaria.
- Assuming that thymus size reflects vulnerability, low MUAC seems to identify more vulnerable children than low weight for length.
- Thymus atrophy appears reversible with recovery from malnutrition, with similar growth seen in children randomized to treatment with different nutritional supplements.

INTRODUCTION

Moderate acute malnutrition (MAM), defined as weight-for-length *z*-score (WLZ) between −2 and −3, or a mid-upper arm circumference (MUAC) between 115 and 125 mm affects 10 s of million children,[1] and is estimated to be the underlying cause of >300,000 child deaths per year, most deaths occurring because of reduced resistance to infections. Children with MAM have ~4.7 times higher risk than well-nourished children of dying from pneumonia, and 3.4 times higher risk of dying from diarrhoea.[2] However, children with MAM are a large and heterogeneous group, making it relevant to identify the most vulnerable, and to assess if this vulnerability can be reduced by nutritional interventions.

What makes malnourished children vulnerable to infections is not well understood.[3] One consistently reported abnormality in malnourished children is lymphatic atrophy, particularly of the thymus gland.[4] This has been found in children with malnutrition in autopsy,[5] x-ray[6] and ultrasound studies,[7] and thymus size measured by ultrasound correlated with nutritional status in cohorts of children in Bangladesh[8] and in Guinea Bissau.[9] Also, several studies have found that a large thymus is associated with good health: better nutritional status,[7,9–11] freedom from infections,[12] well-being[13] and lower subsequent mortality.[9,14,15] It therefore seems plausible that a small thymus could be a marker of the immunodeficiency of malnutrition.[16,17]

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The purpose of this study was to assess thymus size in children with MAM; first, to identify characteristics associated with a smaller thymus, and presumably with greater vulnerability; second, to assess how thymus growth is affected by clinical features and nutritional treatment.

METHODS

The study was an observational cohort study done in a sub-sample of children participating in the Treatfood trial, a randomized controlled trial testing different food supplements for treating children with MAM. The Treatfood trial was registered in the Clinical Trial Database ISRCTN, as ISRCTN 42569496. The main outcome of the study was increase in fat-free mass (FFM) index after 12 weeks of intervention, as reported elsewhere.[18]

Study site

Children for the Treatfood study were recruited from September 2013 to August 2014 at five study sites in different departments in the Province of Passoré in northern Burkina Faso, an area with a high prevalence of malnutrition, qualifying for supplementary feeding.[19] The area has a rainy season from May to October, coinciding with a predictable lean season with increased rates of malnutrition.[20]

Study participants

Children at one of the five sites were included in the sub-study assessing thymus size. Children were recruited by active screening in the communities by community health workers using colour-coded MUAC tapes, they could be referred from health centres or caretakers of the children could show up spontaneously at the study site. Only children from one study site was included, as only one ultrasound scanner was available for the study, and thus sample size was determined by pragmatic reasons.

Children were eligible if they were aged 6–23 months at the time of inclusion, and had MAM defined as WLZ between −2 and −3, or MUAC between 115 and 125 mm or both. Children were excluded if they had severe acute malnutrition (SAM) (WLZ < −3 or MUAC < 11.5 cm or bilateral pitting oedema), or illness requiring hospitalization, or had been treated for SAM or admitted to hospital within the past 2 months.

Intervention and other treatments given

As described elsewhere,[18] children were randomized to receive 12 weeks of nutritional supplements with one of 12 products, either lipid-based nutrient supplement (LNS) or corn–soy blend (CSB), each containing either dehulled soy or soy isolate, and 0, 20 or 50% of protein from milk. All products provided 500 kcal/day and complied with WHO's technical note on supplementary foods for children with MAM.[21]

Children came for fortnightly visits during the supplementation period, followed by 12 weeks follow-up period with visits every 4 weeks. On each visit, a study nurse did a medical examination, and illnesses were treated according to Integrated Management of Childhood Illness guidelines and national protocol. On enrolment children were screened for malaria (*Plasmodium falciparum*) by rapid diagnostic test (RDT) (SD Bioline Malaria Ag Pf), and treated if positive. A single dose of Albendazole was given, and vitamin A supplementation, if this had not been given within the past 6 months. Vaccination status was updated at the local health centre, according to the national schedule.

Children who developed SAM during the study stopped receiving experimental supplements, and were treated for SAM, following the national treatment protocol. Children who still had MAM after 12 weeks of supplementation, or who relapsed during the follow-up period, received 4 weeks treatment with ready-to-use therapeutic food (RUTF).

Data collection

On enrolment, the caregiver of the child was interviewed about the family, history of the child, and its symptoms during the past 2 weeks. Weight was measured using an electronic scale (Seca model 881 1021659, Seca GmbH & Co. KG, Hamburg, Germany) with double weighing function, to the nearest 100 g. Length was measured using a length board to the nearest 1 mm, and subtracting 7 mm from measurement in children aged >24 months. WHO tables were used for enrolment on the site and later *z*-scores were calculated using the command "zscore06" in Stata, based on the 2006 WHO growth standards.[22] MUAC was measured using a measuring tape to the nearest 1 mm. Knee–heel length was measured using a digital callipre (Mitutoyo, Germany), mounted with knee and heel caps cast in hard plastic to the nearest 0.01 mm, and skinfold thickness was measured with a Harpenden caliper. Based on MUAC and triceps skinfold, arm muscle area[23] and arm fat area were calculated using the method by Rolland-Cachera.[24] All measurements were done in duplicate, except knee–heel length, which was measured five times, and an average of the measurements was calculated.

Body composition

Body composition was measured by deuterium dilution as described previously.[25] Briefly, a pre-dose saliva sample was collected, then a dose of 5 g of diluted deuterium oxide (D_2O) was given orally, and after a 3-h equilibration period, a second saliva sample was collected. Samples were shipped frozen to St. John's Research Centre, Bangalore, India, where D_2O enrichment was measured using Fourier transform infrared spectrometry (Agilent Technologies, CA, USA). Based on this, the deuterium dilution space and hence total body water were calculated. From this the FFM and fat mass (FM) were estimated.

A standardized physical examination was done on enrolment, including records of vital signs and axillary temperature.

Thymus size

Thymus size was measured with a portable ultrasound scanner (MicroMax, Sonosite) three times during the study: (1) on enrolment, (2) after 12 weeks of supplementation and (3) after 24 weeks, that is, 12 weeks after end of supplementation. The measurements were carried out over a period of one-and a-half year. All examinations were done by S.Z., a nurse trained by M.J.H. R., a medical doctor with experience in ultrasound of the thymus. Measurements were done when the child was lying on the back. The ultrasound transducer was placed on the child's chest, over the sternal bone (not calcified in this age), and the thymus identified as an echo-poor structure in the mediastinum, anterior to and wrapped around the heart and the great vessels (Fig. 1). First, the transversal diameter of the gland from right to left was measured. Second, the transducer was turned 90°, and area of the largest lobe in the perpendicular direction was measured. All measurements were done in triplicate, and the average calculated. The diameter and the area were multiplied to obtain the thymic index (TI) expressed in cm^3, which has been found to correlate with thymus weight in autopsy studies.[26] We also calculated the TI/body weight ratio, expressed in cm^3/kg. Since crying during the examination has been reported to affect the measurements, this was noted.[9]

Ultrasound images were sent to Denmark during the study and reviewed for quality by M.J.H.R. Selected images were discussed with D.L.J., a paediatric cardiologist with extensive experience in ultrasound of the thymus.

The thymus measurements were only recorded for research and not for clinical use.

Blood sampling and analyses

A venous blood sample (2.5 ml) was taken at admission, and haemoglobin concentration and malaria were assessed on site.

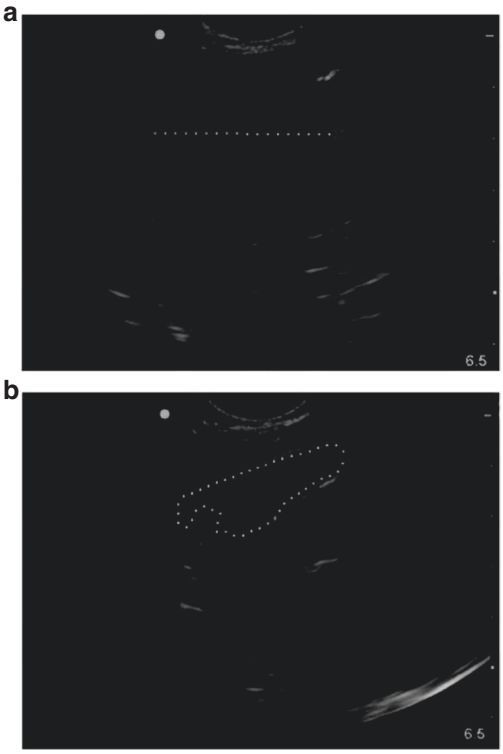

Fig. 1 Ultrasound images of the thymus in a child with MAM. **a** Measurement of transverse diameter. **b** Measurement of area of the largest lobe.

Serum was separated by centrifugation, stored at −20 °C and shipped to VitMin Lab in Germany, where C-reactive protein (CRP), α-1 acid glycoprotein (AGP), serum ferritin, soluble transferrin receptor (sTFR) and retinol-binding protein (RBP) were measured using sandwich enzyme-linked immunosorbent assay.[27] Since serum ferritin is an acute-phase protein, it was adjusted for inflammation using regression models as previously described.[28] When analysing CRP, we used a cut-off of > 5 mg/l to indicate the presence of inflammation, and for sTFR a cut-off at >8.3 mg/l was used to indicate iron deficiency.

Statistical analysis

Data were double entered into Epidata (Odense, Denmark), and analysed using Stata version 12 (StataCorp LP, College Station, TX, USA). Differences between area of the largest thymic lobe, TI and thymus/weight ratio, as well as individual anthropometric child characteristics at different time points, were assessed with paired *t* tests. Correlates of TI on inclusion were analysed by linear regression, first unadjusted, then in two adjusted models: one adjusting for age, sex and body length (since thymus size is proportional to body size), and one adjusting for age, sex and inflammation, measured by serum AGP (since inflammation affects thymus size).[11] Finally, an analysis was done adjusting for age, sex and weight.

Correlates of change in TI were assessed by linear regression of Δ TI adjusted for age, sex and TI at inclusion. All children with available data were included, regardless of whether their treatment at some point had been changed to RUTF (intention-to-treat analysis). When analysing how change in TI correlated with change in FFM and FM, we analysed a model including both body composition parameters together. The same was done in additional analyses of how increases in TI correlated with arm muscle area and arm fat area.

Ethical considerations

The Ethics Committee for Health Research in Burkina Faso approved the study (2012-8-059), and the Danish National Board of Research Ethics gave a consultative approval (1208204). Caretakers of participating children signed an informed consent form, after oral and written information in Mooré. Caretakers who were illiterate signed with their thumbprint.

RESULTS

Of 1609 children included in the Treatfood study, 324 were from the relevant study site, of which 279 were included in the sub-study of thymus size (Fig. 2) The median (interquartile range) age of children was 12.3 (8.2; 16.8) months, and 131 (47%) were girls (Table 1). Ninety-eight (35%) children were recruited based on low WLZ only, 126 (45%) by both low WLZ and low MUAC and 55 (20%) by low MUAC only. Almost all (95%) the children were currently breastfed. Around half of the children had been ill during the preceding 2 weeks, and 125 (45%) had positive malaria RDT. These data were similar to children in the full trial cohort.[18]

The mean ± SD TI on inclusion was 9.5 ± 2.3 cm^3, the area of the largest lobe was 2.6 ± 0.4 cm^2. TI was not associated with crying during examination.

TI was positively associated with age, weight, length and MUAC (Table 2). TI was smaller in girls than in boys, but the association disappeared controlling for age and length. A negative association was seen between TI and WLZ, which was no longer significant when controlling for age, sex and length. Arm muscle area and FFM were positively associated with TI, whereas the relationship with markers of body fatness (FM, skinfolds, arm fat area) disappeared in the adjusted models. All anthropometric associations were not significant when adjusting for body length.

TI (mean ± SD: 8.5 ± 2.3 cm^3) was smallest in children included based on MUAC alone, was intermediate (9.3 ± 2.2 cm^3) in those included by MUAC and WLZ and largest (10.3 ± 2.0 cm^3) in children included by WLZ alone (Fig. 3); all measurements differed significantly from each other. Children included based on MUAC alone were more often girls, and were younger, lighter, shorter, more stunted in length and more often had a positive rapid test for malaria than children included by WLZ only, while those included by WLZ + MUAC were in between (Table 3). After adjusting for age, sex and length, the difference in TI by inclusion criteria was no longer significantly different (Table 2).

TI correlated with blood haemoglobin concentration, and was smaller in children with malaria infection. In the adjusted models, TI correlated negatively with AGP and with ferritin, while an association with inflammation-adjusted ferritin disappeared when controlling for age, sex and weight. In the adjusted models, thymus size was smaller in children with elevated sTFR, indicating iron deficiency. No association was seen with recalled morbidity (reported fever, diarrhoea or cough, data not shown in table), with elevated CRP or with prescription of amoxicillin by the study nurse. When adjusting for age, sex and AGP, a negative association was seen with RBP. TI was smaller in breastfed children, although only 15 children were not breastfed, and these were significantly older, all above 12 months.

TI increased from 9.5 ± 2.3 cm^3 at inclusion to 11.6 ± 1.5 cm^3 after the 12 weeks supplementation ($p < 0.0001$), and to 12.7 ± 1.3 cm^3 after the further 12 weeks of follow-up ($p < 0.0001$). Children also gained weight, with the main increase seen during the supplementation period. However, thymus/weight ratio increased throughout the whole period from 1.4 ± 0.3 to 1.5 ± 0.2 cm^3/kg, and 1.6 ± 0.2 cm^3/kg ($p = 0.0001$) (Table 4). MUAC mainly increased during the supplementation period, with no increase during the follow-up period. Arm fat increased during the supplementation period, but decreased during the follow-up period, while arm muscle area increased throughout both periods.

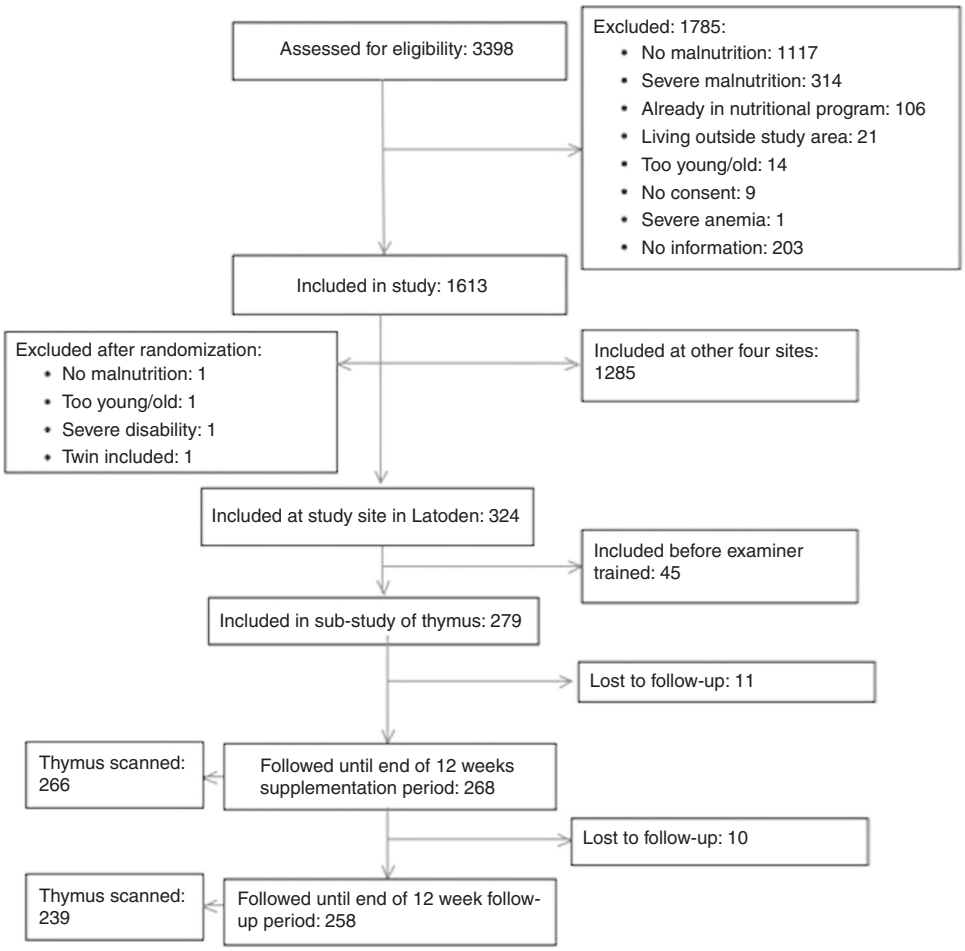

Fig. 2 Flow chart of children assessed and included in study at inclusion, after 12 weeks of supplementation and after another 12 weeks of follow-up.

The increase in thymus size was greater in older children (Table 5), and less increase was seen in children who were most underweight or stunted on inclusion. Higher increases were seen in children with elevated serum AGP at inclusion. Increase in TI correlated with increase in MUAC, WAZ and WLZ during both periods. Over the whole period, increase in TI correlated with increase in knee–heel length. After 12 weeks supplementation, increase in TI correlated with increase in arm fat area (but not arm muscle area), while increase in TI after the whole period correlated with increase in arm muscle area (but not arm fat area). When including both increase in arm muscle area and arm fat area in the regression model, change in TI was not associated with either arm fat or arm muscle change to week 12, while after 24 weeks it correlated with change in arm muscle area ($\beta = 0.20$, CI: 0.05; 0.35, data not in tables). No association was seen with increase in FFM or FM; however, when including both in the model, increase in TI was associated with increase in FFM ($\beta = 0.45$, CI: 0.07; 0.84), but not FM (data not in tables).

The increase in TI was not different in children who received the tested interventions: different levels of milk, different soy quality or food matrix.

DISCUSSION

Our study is the first to measure thymus size specifically in children with MAM. Although one should be cautious comparing measurements obtained in different populations and by different examiners, the mean TI of 9.5 cm^3 measured at inclusion is considerably smaller than the mean TI of 17.3 cm^3 reported in healthy 1-year-old Danish children.[29] Also, the mean area of 2.6 cm^2 of the largest thymic lobe in our study is about twice the area found in children hospitalized with SAM in Uganda, where a control group of healthy children had a median thymic area of 3.5 cm^2.[11] As reported in previous studies, we found that thymus size correlates with measures of body size, and that these were mainly explained by the association with body length. We also, like others, found that thymus size is reduced by infections, in this case particularly malaria, which seemed independent of the association with body size.

Few previous studies have investigated thymus size in relation to body composition. We found thymus to be mainly related to markers of FFM and muscle mass. These associations seemed to be explained by the association of thymus size to body length (which is also linked to muscle mass). In agreement with this, a previous study among children in Burkina Faso found that both arm muscle area and thymus size were smaller in HIV-infected children, despite having a similar body mass index to non-infected children. This study did not report or adjust for children's length.[30] Another study among children with SAM in Bolivia found that zinc supplementation increased both arm circumference and thymus size without affecting weight gain.[31] Probably the relationship of muscle mass with thymus size is not causal, but reflects that muscle mass and thymus size are affected by the same mechanisms. For example, cortisol causes breakdown of muscle tissue, and also causes thymus atrophy.[32] The same could apply to deficiencies of specific type II nutrients.[33] It has previously been

Table 1. Baseline characteristics of 279 children with moderate acute malnutrition.

Age (months)	12.3 (8.2;16.8)
Female sex	47 (131)
Inclusion criteria	
WHZ only[a]	35 (98)
WHZ and MUAC[b]	45 (126)
MUAC only[c]	20 (55)
Socioeconomic data	
Living with both parents	88 (238)
Number of people in household	10 (7;12)
Mother attended school	11 (32)
Father attended school	17 (47)
Currently breastfeeding	95 (264)
Anthropometry	
Weight (kg)	7.0 ± 1.0
Length (cm)	71.1 ± 5.7
Mid-upper arm circumference (mm)	124 ± 5
Weight-for-age *z*-score	−2.6 ± 0.6
Length-for-age *z*-score	−1.7 ± 1.1
Weight-for-length *z*-score	−2.3 ± 0.4
Subscapular skinfolds (mm)	4.9 ± 0.7
Triceps skinfolds (mm)	5.9 ± 0.8
Arm muscle area (cm^2)	8.9 ± − 0.8
Arm fat area (cm^2)	3.7 ± − 0.6
Fat-free mass (kg)	5.8 ± 0.9
Fat mass (kg)	1.2 ± 0.4
Clinical and biochemical data	
Reported ill in past 2 weeks	52 (144)
Measured temperature >37.5	18 (49)
Malaria quick-test positive	45 (125)
Blood haemoglobin (g/dl)	9.9 ± 1.5
Serum C-reactive protein >5 mg/l	39 (108)
Serum α-1 acid glycoprotein (g/l)	1.4 ± 0.7
Serum ferritin (μg/l)	43 (15;89)
Serum ferritin, inflammation adjusted (μg/l)	17 (9;33)
Serum-soluble transferrin receptor >8.3 mg/l	82 (204)
Serum retinol-binding protein (μmol/l)	0.78 ± 0.28

Data are median (IQR), % (*n*) or mean ± SD.
[a]Weight-for-length *z*-score <2 and ≥−3, but mid-upper arm circumference ≥125 mm.
[b]Weight-for-length *z*-score <−2 and ≥−3, and also mid-upper arm circumference ≥115 and <125 mm.
[c]Mid-upper arm circumference ≥115 and <125 mm, but weight-for-length *z*-score ≥−2.

suggested that low leptin associated with low FM mediates thymus atrophy in malnutrition;[16] however, the lack of association with body fat in our population suggests that adipose tissue is less quantitatively important for thymus mass.

Assuming that thymus size reflects vulnerability, MUAC alone seems to identify the most vulnerable children, followed by MUAC + WLZ, while WLZ alone identifies relatively more robust children. The difference seems to be explained by generally smaller body size in the children included by MUAC, as no significant difference was seen after adjusting for age, sex and body length, and it could partly be explained by higher rates of malaria infection in children with low MUAC (Table 3). Even though the association reflects that children included based on MUAC are overall smaller, we still find that it is interesting, and it may give clues to a biological explanation for the previously observed higher risk of death in children identified by MUAC compared to WLZ.[34]

It was somewhat unexpected to find a negative correlation of TI with WLZ. This may reflect that in a population like ours, with a relatively narrow range of weight, children with lower WLZ will be relatively taller. Tall children tend to have larger FFM (because of longer bones and muscles), and indeed the association disappeared when adjusting for length. Similarly, previous studies in healthy children have found negative correlations between muscle mass and WLZ when adjusting for MUAC, so with a fixed MUAC, children with lower WLZ had higher muscle mass.[23]

While having positive malaria RDT was strongly associated with a small thymus, the pattern was less clear for other markers of infection or inflammation. Recalled symptoms of infections (diarrhoea, cough, fever) were not associated with thymus size, neither was elevated CRP, or prescription of amoxicillin. Contrary to expected, body temperature >37.5 was associated with a larger thymus. This could be a chance finding; however, it should be noted that in children with SAM, fever has been found to be marginally associated with survival, perhaps because ability to mount a fever could be a sign of relative health and a functioning immune system.[35] It is also possible that thymus size may react differently depending on the duration of inflammation.

TI correlated to haemoglobin levels, similar to what was found in children with SAM in Uganda.[11] This may be related to infections and malaria, known to induce anaemia, even though an association remained in the inflammation-adjusted model. The effect of anaemia on thymus size deserves further investigation in future studies.

We did not see any clear picture with regards to micronutrient status in relation to thymus size. The negative association with ferritin seemed mainly to be due to ferritin's role as an acute-phase reactant, as there was no association with inflammation-adjusted ferritin. Furthermore, the negative association with elevated sTFR (indicating a smaller thymus in children with iron deficiency) is in the opposite direction as the association with ferritin. It is likely that the associations with haemoglobin, ferritin and sTFR are related to the presence of malaria, to which all are linked. A negative association was seen between TI and RBP, a marker of vitamin A status, when controlling for age, sex and AGP. This was unexpected, because RBP is a negative acute-phase reactant, that is, becoming lower with inflammation. This means RBP would—if anything—be expected to be positively associated with thymus size. This finding should be confirmed in other studies and with other markers before concluding anything about the relationship between vitamin A status and thymus size.

Breastfeeding has previously been associated with a larger thymus;[36] thus, it was unexpected to find a larger thymus size in non-breastfed children. However, only 15 children were not breastfed, and these were among the oldest children in the study. Even adjusting for age it may be difficult to compare them directly to the non-breastfed children. Most studies reporting a larger thymus with breastfeeding were done among well-nourished children, where breastfeeding seemed to have the greatest influence below 6 months of age.[36,37]

It is encouraging that thymus size increased following treatment. Part of this is obviously caused by the children getting older, since thymus size at baseline was associated with ~0.2 cm^3 higher TI per increasing month of age. This linear association with age is different from that observed in well-nourished children, where thymus size seems peak in size ~6 months of age.[8] If this association had remained similar to baseline over time, it would be expected that TI had increased with ~0.6 cm^3 after the supplementation period, and with 1.2 cm^3 after the full study. The observed increase was however much higher (on average 2.1 cm^3

Table 2. Correlates of thymus size on inclusion, in 279 children with moderate acute malnutrition).

	Unadjusted	*P* value	Model 1[a]	*P* value	Model 2[b]	*P* value
Age (months)	0.20 (0.16;0.25)	†	0.003 (−0.09;0.09)	n.s.	0.21 (0.16;0.25)	†
Female sex	−0.78 (−1.31;−0.25)	**	−0.34 (−0.80;0.13)	n.s.	−0.65 (−1.13;−0.16)	**
Inclusion criteria						
WHZ only[c]	Ref.		Ref.		Ref.	
WHZ and MUAC[d]	−1.02 (−1.58;−0.44)	**	−0.37 (−0.90;0.16)	n.s.	−0.56 (−1.11;−0.00)	0.05
MUAC only[e]	−1.86 (−2.57;−1.14)	†	−0.63 (−1.35;0.08)	n.s.	−0.95 (−1.68;−0.22)	*
Currently breastfeeding	−2.32 (−3.47;−1.17)	†	−1.13 (−2.17;−0.09)	*	−1.21 (−2.30;−0.12)	*
Anthropometry						
Weight (kg)	1.16 (0.93;1.39)	†	−0.80 (−1.82;0.22)	n.s.	0.94 (0.47;1.40)	†
Length (cm)	0.21 (0.17;0.25)	†	0.20 (0.12;0.28)	†	0.21 (0.13;0.29)	†
MUAC (mm)	0.13 (0.08;0.18)	†	0.04 (−0.01;0.09)	n.s.	0.08 (0.02;0.13)	**
Weight-for-age *z*-score	0.21 (−0.21;0.63)	n.s.	−0.62 (−1.37;0.13)	n.s.	0.72 (0.34;1.11)	†
Length-for-age *z*-score	0.23 (−0.01;0.47)	n.s.	−0.02 (−0.95;0.99)	n.s.	0.54 (0.32;0.75)	†
Weight-for-length *z*-score	−1.24 (−1.84;−0.64)	†	−0.34 (−0.92;−0.24)	n.s.	−0.55 (−1.14;0.05)	n.s.
Subscapular skinfold	−0.85 (−1.23;−0.46)	†	−0.14 (−0.51;0.23)	n.s.	−0.26 (−0.65;0.12)	n.s.
Triceps skinfolds	−0.30 (−0.61; 0.02)	n.s.	0.14 (−0.14;0.42)	n.s.	0.01 (−0.29;0.31)	n.s.
Arm muscle area	0.96 (0.65;1.27)	†	0.19 (−0.15;0.53)	n.s.	0.49 (0.17;0.81)	**
Arm fat area	−0.12 (−0.58;0.34)	n.s.	0.24 (−0.16;0.63)	n.s.	0.16 (−0.27;0.58)	n.s.
Fat-free mass	1.20 (0.92;1.47)	†	−0.28 (−0.91;0.36)	n.s.	0.64 (0.16;1.11)	**
Fat mass	1.21 (0.53;1.98)	**	0.05 (−0.66;0.77)	n.s.	0.67 (−0.05;1.40)	n.s.
Physical exam						
Measured temp. >37.5	0.58 (−0.12;1.28)	n.s.	0.71 (0.12;1.31)	*	0.74 (0.10;1.38)	*
Biochemical data						
Malaria quick-test positive	−0.81 (−1.34;−0.27)	**	−1.19 (−1.63;−0.75)	†	−1.15 (−1.64;−0.65)	†
Blood haemoglobin (g/dl)	0.15 (−0.03;0.32)	n.s.	0.29 (0.14;0.44)	†	0.26 (0.07;0.44)	**
Serum C-reactive protein >5 mg/l	0.05 (−0.50;0.60)	n.s.	−0.04 (−0.50;0.43)	n.s.	0.36 (−0.25;0.97)	n.s.
Serum α-1 acid glycoprotein (g/l)	−0.02 (−0.43;0.39)	n.s.	−0.36 (−0.71;− 0.01)	*	−0.38 (−0.74;−0.01)	*
Serum ferritin (μg/l)	−0.005 (−0.009;−0.002)	**	−0.005 (−0.009;−0.002)	**	−0.005 (−0.01;−0.001)	**
Serum ferritin, inflammation adjusted (μg/l)	−0.02 (−0.03;−0.004)	**	−0.003 (−0.01;0.01)	n.s.	−0.01 (−0.02;0.004)	n.s.
Serum-soluble transferrin receptor >8.3 mg/l	−0.47 (−1.21;0.27)	n.s.	−0.90 (−1.52; −0.29)	**	−0.71 (−1.35;−0.06)	*
Serum retinol-binding protein (μmol/l)	−0.80 (1.77;0.18)	n.s.	−0.72 (−1.55; 0.11)	n.s.	−0.96 (−1.84;−0.09)	*

Data are regression coefficients (95% CI).
n.s.: $p \geq 0.05$; *$p < 0.05$; **$p < 0.01$; †$p < 0.001$.
[a]Adjusted for age, sex and length.
[b]Adjusted for age, sex and α-1 acid glycoprotein.
[c]Weight-for-length *z*-score 125 mm.
[d]Weight-for-length *z*-score <−2 and ≥−3, and also mid-upper arm circumference ≥115 and <125 mm.
[e]Mid-upper arm circumference ≥115 and <125 mm, but weight-for-length *z*-score ≥−2.

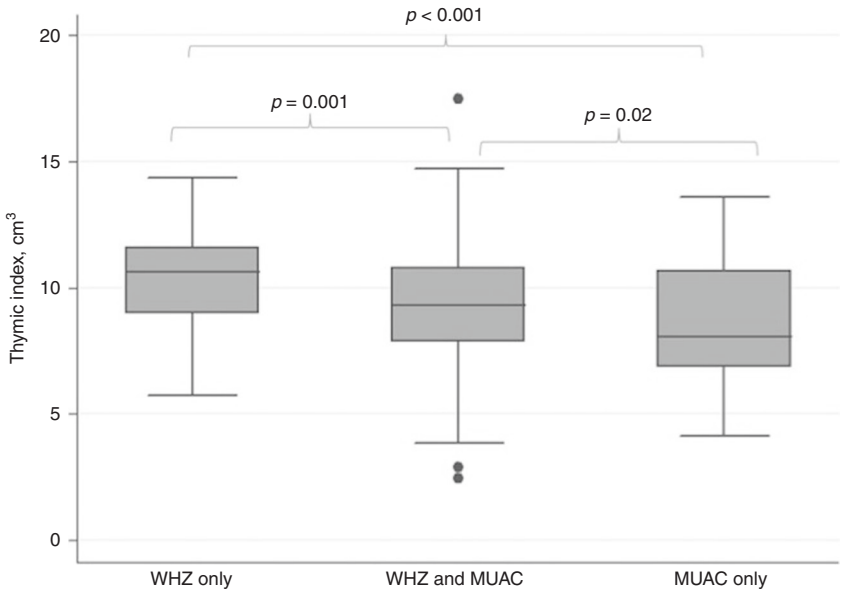

Fig. 3 Thymus size in children diagnosed with malnutrition by different criteria. Unadjusted comparison.

Table 3. Baseline characteristics of 279 children with moderate acute malnutrition, by admission criteria[a].

	WHZ alone[b], $N = 98$	WHZ and MUAC[c], $N = 126$	MUAC alone[d], $N = 55$	P value[e]
Age (months)	14.3 (9.6;18.3)	11.7 (8.4;16.2)	9.6 (6.4;13.5)	0.0001
Female sex	30 (29)	48 (60)	76 (42)	<0.0001
Weight (kg)	7.4 ± 0.9	6.8 ± 0.9	6.7 ± 1.0	<0.0001
Length (cm)	73.7 ± 5.1	70.5 ± 5.2	67.8 ± 5.4	<0.0001
Weight-for-age *z*-score	−2.5 ± 0.6	−2.8 ± 0.6	−2.3 ± 0.5	<0.0001
Length-for-age *z*-score	−1.4 ± 1.2	−1.8 ± 1.1	−1.8 ± 1.0	0.03
Temperature >37.5	21 (21)	14 (17)	20 (11)	0.28
Malaria quick-test positive	32 (31)	49 (62)	58 (32)	0.003
Haemoglobin	10.1 ± 1.4	9.8 ± 1.4	9.6 ± 1.6	0.06
C-reactive protein	1.8 (0.6;7.1)	3.0 (1.0;9.5)	3.2 (1.0;12.0)	0.12
α-1 Acid glycoprotein	1.3 ± 0.6	1.51 ± 0.7	1.4 ± 0.6	0.08
Ferritin	29 (11;55)	50 (17;93)	68 (33;116)	0.0004

[a]Data reported are median (25%;75%), % (*n*) or mean ± SD.
[b]Weight-for-length *z*-score <−2 and ≥−3, but mid-upper arm circumference ≥12.5 cm.
[c]Weight-for-length *z*-score <−2 and ≥−3, and mid-upper arm circumference ≥11.5 and <12.5 cm.
[d]Weight-for-length *z*-score ≥−2, but mid-upper arm circumference ≥11.5 and <12.5 cm.
[e]Test for difference between any of the three groups: ANOVA for normally distributed variables, Kruskal–Wallis test for non-normally distributed variables, χ^2 for categorical variables.

Table 4. Thymus size and other characteristics of children during the study[a].

	Inclusion	After 12 weeks supplementation	After 24 weeks follow-up	Inclusion vs. 12 weeks[c]	12 weeks vs. 24 weeks[c]
N	279	268	258		
Weight (kg)	7.0 ± 1.0	7.9 ± 1.1	8.3 ± 1.1	†	†
Length (cm)	71.1 ± 5.7	73.4 ± 5.7	76.1 ± 5.5	†	†
Mid-upper arm circumference (mm)	124 ± 5	133 ± 7	133 ± 7	†	n.s.
Arm fat area (cm^3)	3.7 ± 0.6	4.4 ± 0.8	4.2 ± 0.8	†	**
Arm muscle area (cm^3)	8.9 ± 0.8	10.0 ± 1.1	10.2 ± 1.0	†	**
Weight-for-age *z*-score	−2.6 ± 0.6	−2.1 ± 0.8	−2.1 ± 0.8	†	*
Weight-for-length *z*-score	−2.3 ± 0.4	−1.5 ± 0.8	−1.6 ± 0.8	†	**
Length-for-age *z*-score	−1.7 ± 1.1	−2.0 ± 1.0	−2.0 ± 1.0	†	n.s.
Recovered[b]	–	68 (182)	68 (175)	†	n.s.
Thymus size					
Area of largest lobe (cm^2)	2.6 ± 0.4	2.9 ± 0.2	3.1 ± 0.2	†	†
Thymic index (cm^3)	9.5 ± 2.3	11.6 ± 1.4	12.8 ± 1.3	†	†
Thymic index/weight ratio (cm^3/kg)	1.4 ± 0.3	1.5 ± 0.2	1.6 ± 0.2	†	†

[a]Data are mean ± SD or % (*n*).
[b]Weight-for-length *z*-score ≥−2 and mid-upper arm circumference ≥125 mm.
[c]*P* values from paried *t* tests: n.s.: $p \geq 0.05$; *$p < 0.05$; **$p < 0.01$; †$p < 0.001$.

during the supplementation period, and 3.3 cm^3 during the full study). Some of this increase was likely caused by regression towards the mean as the children were recruited on a time when they were malnourished, likely to be followed by catch-up growth. It is possible that this may be facilitated by the nutritional supplementation and treatment of infections, but it is difficult to say without an un-supplemented control group.

Thymus growth correlated with increase in MUAC, WLZ, WAZ and marginally with increases in FFM. Interestingly, thymus growth during the first 12 weeks of supplementation correlated with increase in arm fat area, but not arm muscle area. In contrast, during the full observation period, thymus growth correlated with increase in arm muscle area, possibly related to the children gaining arm fat mainly during the supplementation period, but losing arm fat during the following observation period, whereas they gained arm muscle throughout both the observed periods.

We did not find any difference in thymus growth in children randomized to the different nutritional interventions, even though LNS resulted in a higher weight gain.[18] On the other hand, LNS also resulted in higher inflammatory markers after supplementation than CSB,[38] so it is possible that this may have outweighed a possible positive effect of the weight gain. Previous studies have found that other nutritional interventions like zinc supplements to malnourished children,[31] and probiotics to infants[39] resulted in higher increase in thymus size. Our study had limited power, only included a sub-sample of the study, but we did not even see the slightest trend. This suggests that nutrients essential for thymus growth did not differ significantly in the tested supplements.

Table 5. Correlates of change in thymic index after 12 and 24 weeks.

	Change to 12 weeks[a]	*P* value	Change to 24 weeks[b]	*P* value
Data on inclusion				
Age (months)	0.13 (0.10;0.16)	†	0.06 (0.04;0.09)	†
Female sex	−0.47 (−0.75;−0.20)	**	−0.26 (−0.53;0.01)	n.s.
Inclusion criteria				
Only WLZ[c]	Ref.		Ref.	
WLZ and MUAC[d]	0.04 (−0.28;0.36)	n.s.	−0.06 (−0.38;0.25)	n.s.
Only MUAC[e]	0.16 (−0.27;0.59)	n.s.	0.22 (−0.20;0.63)	n.s.
Breastfeeding	0.09 (−0.53;0.72)	n.s.	0.24 (−0.38;0.86)	n.s.
Weight-for-length *z*-score	0.22 (−0.12;0.57)	n.s.	0.02 (−0.32;0.36)	n.s.
Weight-for-age *z*-score	0.35 (0.12;0.57)	**	0.25 (0.03;0.48)	*
Length-for-age *z*-score	0.14 (0.01;0.28)	*	0.16 (0.02;0.29)	*
Mid-upper arm circumference (mm)	0.003 (−0.03;0.03)	n.s.	0.001 (−0.03;0.03)	n.s.
Malaria quick-test positive	0.26 (−0.03;0.55)	n.s.	0.07 (0.21;0.36)	n.s.
Blood haemoglobin (g/dl)	−0.09 (−0.18;0.01)	n.s.	0.005 (−0.09;0.10)	n.s.
Serum c-reactive protein >5 mg/l	0.06 (−0.22;0.34)	n.s.	0.05 (−0.22;0.33)	n.s.
Serum α-1 acid glycoprotein (g/l)	0.23 (0.01;0.44)	*	0.14 (−0.06;0.35)	n.s.
Serum ferritin (μg/l)	0.000 (−0.002;0.002)	n.s.	− 0.000 (−0.002;0.002)	n.s.
Serum retinol-binding protein (μmol/l)	−0.26 (−0.77;0.25)	n.s.	−0.18 (−0.67;0.32)	n.s.
Change in same period of				
Weight-for-length *z*-score	0.19 (0.01;0.38)	*	0.35 (0.19;0.52)	†
Weight-for-age *z*-score	0.31 (0.06;0.56)	*	0.54 (0.31;0.77)	†
Length-for-age *z*-score	0.27 (−0.19;0.72)	n.s.	0.18 (−0.17;0.54)	n.s.
Mid-upper arm circumference (mm)	0.03 (0.004;0.05)	*	0.03 (0.01;0.04)	**
Knee–heel length (mm)	0.01 (−0.02;0.04)	n.s.	0.03 (0.002;0.05)	*
Fat-free mass (kg)	0.31 (−0.04;0.66)	n.s.	–[f]	
Fat mass (kg)	0.16 (−0.20;0.53)	n.s.	–[f]	
Arm muscle area (cm^2)	0.13 (−0.03;0.28)	n.s.	0.20 (0.06;0.33)	**
Arm fat area (cm^2)	0.21 (0.03;0.39)	*	0.12 (−0.05;0.28)	n.s.
Haemoglobin (g/dl)	0.03 (−0.06;0.11)	n.s.	−0.03 (−0.10;0.05)	n.s.
Food supplement				
No milk	Ref.		Ref.	
20% protein as milk	0.02 (−0.32;0.36)	n.s.	0.002 (−0.33;0.33)	n.s.
50% protein as milk	−0.01 (−0.35;0.33)	n.s.	0.04 (−0.29;0.38)	n.s.
Soy isolate vs. dehulled soy	0.06 (−0.21;0.34)	n.s.	0.20 (−0.07;−0.47)	n.s.
LNS vs. CSB	0.03 (−0.24;0.31)	n.s.	0.10 (−0.17;0.37)	n.s.

n.s.: $p \geq 0.05$; *$p < 0.05$; **$p < 0.01$; †$p < 0.001$.
[a]Data are regression coefficients of Δ Thymic index from inclusion to after the supplementation period, adjusted for age, sex and thymus size on inclusion.
[b]Data are regression coefficients of Δ Thymic index from inclusion to after the follow-up period, adjusted for age, sex and thymus size on inclusion.
[c]Weight-for-length *z*-score <−2 and ≥−3, but mid-upper arm circumference ≥12.5 cm.
[d]Weight-for-length *z*-score <−2 and ≥−3, and also mid-upper arm circumference ≥11.5 and <12.5 cm.
[e]Mid-upper arm circumference ≥11.5 and <12.5 cm, but weight-for-length *z*-score ≥−2.
[f]Not measured at this time point.

Strengths of the study include a relatively large sample size, and a well-characterized cohort in terms of anthropometry, body composition and morbidity. The method to measure TI is validated, and has been used previously.

Measuring thymus size by ultrasound is not complicated, and we found that the technique could be learned with a few weeks of training. However, like other ultrasound-based measurements, it has a high degree of inter-observer variability. For this reason, it can be difficult to compare values measured in our study directly to those obtained in studies carried out by different researchers. However, since one person performed all our measurements, inter-observer variability is not a problem within our study.

Another limitation is that the relatively short follow-up period, and low mortality, precluded us from assessing if a small TI was associated with mortality in this cohort, as reported previously.

Generally, the observational nature of our data means that we are not able to draw conclusions about causality, as the associations could be caused by confounding. The exploratory approach also means that we did multiple statistical tests, with the inherent risk of type II errors. For these reasons, our results should mainly serve as hypothesis generation, and should be confirmed in other studies.

Another limitation is that the group is truncated by the different inclusion criteria. This means that baseline associations with WHZ and MUAC should be interpreted with caution.

Finally, it is still unknown to what extent thymus size specifically reflects immune competence. Several studies have found infants with a large thymus to have lower mortality,[9,14,15] and fewer infections.[40] Conflicting data exist on whether TI correlates with white blood cells in peripheral blood, and with other immunological markers.[40] Thus, it is also plausible that the association between thymus size and ability to resist infections is not causal, but that it reflects good health in general, similar to body length, to which it is strongly associated. However, this still makes it a useful marker of robustness in children.

CONCLUSION

Thymus size in children with MAM is reduced in children with low haemoglobin and with malaria infection. Assuming that a small thymus size is a marker of vulnerability, our results suggest that low MUAC identifies more vulnerable children than WHZ, which may provide an explanation for the previously observed higher mortality in children with low MUAC compared to children with low WHZ. Thymus size increases over time with nutritional supplementation, and also during the follow-up period, where thymus growth correlates with increase in anthropometry. Increase in thymus size does not seem to depend on the amount of milk, the quality of soy or whether nutritional supplements are given as LNS or CSB.

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AUTHOR CONTRIBUTIONS

M.J.H.R. designed the study, supervised data collection, analysed and interpreted data, and drafted the first version of the manuscript. B.C., C.F., and C.W.Y. contributed to design of the study, collection of data, interpretation of data and revised the manuscript critically for important intellectual content. S.Z.W. collected data for the study and revised the manuscript critically for important intellectual content. K.F.M., S.F., H.F., A.B. and V.B.C. contributed to design of the study, interpretation of data and revised the manuscript critically for important intellectual content. D.L.J. supervised data collection, contributed to the interpretation of data and revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript to be published.

ADDITIONAL INFORMATION

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Competing interests: K.F.M. has received research grants from US Dairy Export Council and the Danish Dairy Research Foundation, and also has research collaboration with Nutriset, a producer of LNS products; H.F. has received research grants from ARLA Food for Health Centre, and also has research collaboration with Nutriset, a producer of LNS products; S.F. has had research collaboration with Nutriset, a producer of LNS products. None of the other authors have any conflicts of interests to disclose.

Patient consent: Caretakers of all participating children provided informed consent for participation.

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