Associations between stunting, wasting, breastfeeding and body composition: A longitudinal study in 6-15 month-old Kenyan children

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Abstract:	The objective was to assess stunting, wasting and breastfeeding as correlates of body composition in young children. Fat and fat-free mass (FM, FFM) were measured using deuterium dilution technique at age 6 and 15 months (ISRCTN30012997). Among 499 children, breastfeeding declined from 99% to 87%, stunting increased from 13% to 32% and wasting remained at 2-3% between 6 and 15 months. Non-breastfed children had 0.81 (95%CI -0.09;1.52) kg lower FM at 6 months and 0.37 (0.06;0.67) kg lower FFM at 15 months of age. Breastfeeding was not associated with the height-adjusted indices fat or fat-free mass index (FMI, FFMI). Compared to length-for-age Z-score (LAZ) >0, stunted children had 1.12 (0.88;1.36) kg lower FFM at 6 months increasing to 1.59 (1.25;1.94) kg at 15 months, corresponding to deficits of 18% and 17%, respectively. When analysing FFMI, the deficit in FFM tended to be less than proportional to the children's height at 6 months (P ≤ 0.060) and was proportional at 15 months (P >0.40). Stunting was associated with 0.28 (0.09;0.47) kg/m2 lower FM at 6 months. The difference lost significance at 15 months, and stunting was not associated with FMI at any time point. Decreasing WLZ was associated with lower FM, FFM, FMI and FFMI at 6 and 15 months. Deficits in FFM, but not FM, increased with time, while FFMI deficits did not change and FMI deficits generally

	decreased with time. Overall, undernutrition seems to be associated with reduced lean tissue, which may have long-term health consequences.

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Title: Associations between stunting, wasting, breastfeeding and body composition: A longitudinal study in 6-15 month-old Kenyan children

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Short title: Early stunting and body composition

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ABSTRACT

The objective was to assess stunting, wasting and breastfeeding as correlates of body composition in young children. Fat and fat-free mass (FM, FFM) were measured using deuterium dilution technique at age 6 and 15 months (ISRCTN30012997). Among 499 children, breastfeeding declined from 99% to 87%, stunting increased from 13% to 32% and wasting remained at 2-3% between 6 and 15 months. Non-breastfed children had 0.81 (95%CI -0.09;1.52) kg lower FM at 6 months and 0.37 (0.06;0.67) kg lower FFM at 15 months of age. Breastfeeding was not associated with the height-adjusted indices fat or fat-free mass index (FMI, FFMI). Compared to length-for-age Z-score (LAZ) >0, stunted children had 1.12 (0.88;1.36) kg lower FFM at 6 months increasing to 1.59 (1.25;1.94) kg at 15 months, corresponding to deficits of 18% and 17%, respectively. When analysing FFMI, the deficit in FFM tended to be less than proportional to the children's height at 6 months ($P \leq 0.060$) and was proportional at 15 months ($P > 0.40$). Stunting was associated with 0.28 (0.09;0.47) kg/m^2 lower FM at 6 months. The difference lost significance at 15 months, and stunting was not associated with FMI at any time point. Decreasing WLZ was associated with lower FM, FFM, FMI and FFMI at 6 and 15 months. Deficits in FFM, but not FM, increased with time, while FFMI deficits did not change and FMI deficits generally decreased with time. Overall, undernutrition seems to be associated with reduced lean tissue, which may have long-term health consequences.

INTRODUCTION

Malnutrition remains a challenge in many low-income countries [1]. Although stunting has slowly declined over the past decades[1,2], the proportions of wasted and stunted children remain high with 7% of the global population of children below 5 years being wasted and 22% being stunted and with even higher numbers in Africa[1,2]. Stunting and wasting are associated with increased mortality and morbidity as well as long-term consequences including delayed cognitive development in childhood and increased risk of chronic diseases and reduced working capacity in adulthood[1,3,4].

Early growth and specific growth patterns have been associated with risk of obesity and cardio-vascular disease in adulthood [5,6]. This may be mediated by changes in fat mass (FM) and fat-free mass (FFM) composition [7]. Low birth weight is associated with lower FFM at birth, in childhood as well as adulthood [7–9], and subsequent high catch-up growth in childhood may result in accumulation of FM and increased risk of later obesity and metabolic syndrome or cardiovascular disease [7,10].

Only few studies have investigated how growth faltering affects body composition in early life [11-13]. A narrative review based on available data from low- and middle-income countries found that wasting in children with acute malnutrition is associated with large deficits in both FFM and FM [13]. In contrast, stunting is associated with deficits in FFM, which in some cases disappear after adjustment for height, indicating that the deficits are explained by shorter height.

Breastfeeding affects body composition in infancy and young childhood. A meta-analysis based on studies from high-income countries showed that breastfed infants had higher FM than formula-fed infants in the first 6 months[14]. However, at 12 months of age, the difference had switched and formula-fed infants had higher FM than breastfed infants. FFM was higher in formula-fed infants at both 6 and 12 months of age. In a Cambodian study, non-breastfed children had lower FM at 6 and 15 months and slightly higher FFM at 15 months [12].

The aim of the current study was to investigate how stunting, wasting and breastfeeding were associated with changes in FM, FFM and the height-adjusted indices FMI and FFMI as well as skinfolds in Kenyan children followed from 6 to 15 months of age. We hypothesized that these associations change with age.

METHODS

Study design, setting and ethical considerations

The current longitudinal study was nested in a randomized controlled trial (RCT) described in detail elsewhere [15]. The study was conducted from January 2012 to January 2013 at Makunga, Khaunga and Lusheya health centres of Mumias Sub-county in Kakamega County, Western Kenya. In this region, about a quarter of the children below five years are stunted[16]. The area is a rural, malaria-prone, food-insecure and resource-limited locality [17]. As part of the intervention, children received one of three study foods at 200-550 kcal/day, with increasing amount from 6 to 15 months of age [15]. The objectives of this sub-study was to assess stunting, wasting and breastfeeding as correlates of body composition and to investigate if these potential associations change with age. The study was designed similarly to a study we conducted in rural Cambodia among more than 400 6-15 month-old children [12].

Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoNERC-P436/12/2010) approved the study with a further consultative approval obtained from the Danish National Committee on Biomedical Research Ethics. The trial was registered at www.controlled-trials.com (No: ISRCTN30012997). Before infants were enrolled, caregivers gave written informed consent after oral and written information was provided in the local language or Kiswahili. Permission to implement the study was obtained from relevant government line ministries and local authorities.

Study participant recruitment, participant visits, inclusion and exclusion criteria

When infants were 5 months of age, mother-infant dyads were invited to the study from the health facilities they visited for routine monthly growth monitoring. Trained health workers screened infants. Inclusion criteria included caregivers' consent to let their child participate and acceptance to prepare and feed their infants with the assigned complementary food according to the parent randomized controlled trial [15]. Exclusion criteria were clinical signs of vitamin A deficiency, severe anaemia (haemoglobin< 80g/L) and severe acute malnutrition, defined as weight-for-length z-score (WLZ) <-3, pitting oedema or mid-upper arm circumference (MUAC) <11.5 cm. If any of these exclusion criteria were detected, the infant was referred for treatment as per the Kenya Ministry of Health guidelines. Infants with genetic disorders interfering with growth or chronic illness requiring medication were also excluded. Twins were recruited into the study if both were healthy and met the inclusion criteria. All infants were assessed on the recruitment day (a '6-month visit') and 9 months later at a'15-month visit'. Data on breastfeeding, introduction of complementary foods (dietary assessment using the 24 hour recall) and socio-demographic and economic variables were also collected at baseline.

Body composition assessment

As previously described [15], the deuterium dilution technique, which measures total body water (TBW), was used to assess FFM and FM at 6 and 15 months of age. Prior to giving each child an accurately weighed standardized oral dose of deuterium labelled water; a pre-dose sample of about 2 ml of saliva was taken from the child's mouth using a cotton ball. Post-dose saliva samples were taken at 2 hours and 3 hours after intake of the deuterium labelled water [18]. Saliva samples were collected with a syringe into a tightly closed 1.5 mL cryogenic tube by squeezing the saliva from the wet cotton ball removed from the child's mouth. Samples were kept in an iced cooler box and transported the same day to a central collection point at Lusheya health centre where they were stored at -20°C followed by transfer on dry ice to Kenya Medical Research Institute in Nairobi for analysis. A Fourier Transform Infrared spectrophotometer (Shimadzu model 8400s, Shimadzu Corporation, Kyoto, Japan) was used to analyze enrichment of deuterium in the saliva samples and the pre-dose samples were used for background correction. The intention was to take the higher of the two enrichments at 2 and 3 hours, indicating the attainment of peak enrichment at equilibration. Inadvertently, the 2 and 3 hour values were averaged without retaining the raw data. In addition, cases with >50 ppm difference between the 2 and 3 hour samples were considered as poor agreement and discarded from the dataset. Based on field notes, children were excluded from the dataset if there was uncertainty about their ^2H_2O consumption and if the deuterium enrichment in post-dose saliva was less than 600 mg/kg, indicative of issues with dosing [18]. The dilution space and TBW were calculated according to the guideline[18]. FFM was calculated by dividing TBW by an age specific hydration factor as: TBW/0.79 for both sexes. FM was calculated as body weight minus FFM [12,18].The fat-free mass index (FFMI) and the fat mass index (FMI) were calculated by FFM/length^2 (kg/m^2) and FM/length^2 (kg/m^2), respectively. These indices express FFM and FM normalized for length and are expressed in the same unit as BMI. Negative FM values were removed from the dataset, as they were considered to be due to inadequate consumption of the ^2H_2O dose, or inadequate equilibration with body water. As described by others [19], outliers which fitted very poorly with the general association of body water with weight and height were also removed from the dataset. More results were removed at 15 months than 6 months with poor fit likely due to longer equilibration times in older children.

Anthropometry

Trained assistants with previous experience in growth monitoring took the anthropometric measurements in triplicate using standardized anthropometric techniques and calibrated equipment [19]. Length was measured to the nearest 0.1 cm using calibrated length boards, nude weight was measured to the nearest 0.01 kg, using a hanging Seca scale (UniScale) and triceps and subscapular skinfolds were measured to the nearest 0.1 mm using Harpenden skinfold calipers (Crymych, United Kingdom). Head circumference and MUAC were measured to the nearest 0.1 cm using non-stretchable measuring tape (Harlow Printing Limited). Breast-feeding status was determined both at the 6- and 15- month visit. To estimate whether a child was still breastfed, the caregiver was asked ‘Since this time yesterday, has the child been breastfed?’ Finally, some socio-demographic variables were obtained at the 6-month visit.

Data analysis

Collected data were monitored daily and double entered within 2 weeks in Microsoft Excel TM. LAZ and WHZ scores were calculated using WHO AnthroTM v3.2.2 based on the WHO's 2006 Child Growth Standards. LAZ and WLZ<-2 were defined as stunting and wasting, respectively. Statistical analyses were performed with R (R core team, 2017) with the extension packages tukeytrend, lme4 and multcomp. We used χ^2 tests and two-sample t-tests for categorical and continuous variables, respectively, when comparing data by sex and visit. As in our study in Cambodia [12], we fitted separate linear mixed-effects models to FFM and weight, and to FFMI and BMI. FM was subsequently derived from the estimates for FFM and weight, and, similarly, FMI was derived from FFMI and BMI, using a marginal models approach [20]. Age, sex, intervention groups of the original trial design and the interaction between visits and either sex, breast-feeding, LAZ or WLZ categories were included as fixed effects and children and health facility were included as random (intercept) effects. Differences between categories at 6 and 15 months and changes in differences (between categories) from 6 to 15 months were estimated based on test for interaction. For triceps and subscapular skin folds, similar linear mixed-effects models were fitted using the same fixed and random effects as described above. For all analyses, model assumptions were checked using residual and normal probability plots. Missing data were not imputed. A significance level of 5% was used. No adjustments for multiple comparisons were applied since this was primarily an exploratory study.

RESULTS

The study enrolled 499 children out of 527 screened (**Figure 1**). The mean (±SD) age of the children was 6.0 ±0.2 months and approximately half were boys (**Table 1**). Almost all children (99%) were breastfed at 6 months of age and 87% were still breastfed at 15 months (**Table 2**). The stunting prevalence (LAZ<-2) increased from 13% at 6 months to 32% at 15 months (Table 2). In contrast, the wasting prevalence (WLZ<-2) remained low with 3% and 2% at 6 and 15 months of age, respectively. Boys tended to have lower LAZ than girls at 6 (P=0.09) and 15 months (P=0.03) (data not shown).

Deuterium was dosed to 459 (92%) and 385 (90%) of the children present at 6 and 15 months (Figure 1). After laboratory processing and data cleaning, data were available from 442 (89%) of the children at 6 months of age and 288 (67%) at 15 months (Figure 1). The children with or without body composition data did not differ with regards to sex, weight, height, MUAC, LAZ, WLZ, BMI or skinfold thickness at 6 or 15 months (P>0.05, **Supplementary Table 1**). FFM and FFMI increased in both boys and girls from 6 to 15 months (P<0.001, Table 2). However, FM decreased in boys (p=0.002), but not girls (p=0.45) and FMI decreased in both sexes (P<0.001, Table 2). The higher weight and FFM in boys compared to girls persisted when indexed by height as BMI and FFMI (P≤0.05, Table 2). At both 6 and 15 months, boys weighed around 0.5 kg more than girls, which was entirely explained by higher FFM (**Table 3**). Similarly, boys had 0.37 and 0.30 kg/m^2 higher BMI than girls at 6 and 15 months, due to 0.44 and 0.43 kg/m^2 higher FFMI (**Table 4**). Lack of breastfeeding was associated with 0.76 kg and 0.44 kg lower weight at 6 and 15 months of age, respectively. At 6 months, the lower weight in the five non-breastfed children was entirely due to lower FM and at 15 months of age, lower weight in non-breastfed children (n=56) was mainly due to 0.37 kg lower FFM (Table 3). Breastfeeding was not associated with the height-adjusted indexes BMI, FMI or FFMI (Table 4).

Overall, the deficits in weight, FM and FFM were generally greater the lower LAZ scores the children had at both 6 and 15 months (Table 3). Compared to children with LAZ ≥0, stunting was associated with 1.40 kg and 1.88 kg lower weight at 6 and 15 months, mainly explained by 1.12 kg and 1.59 kg lower FFM, respectively (Table 3). The deficits in FFM corresponded to 18% and 17% at 6 and 15 months of age, respectively. In contrast, stunted children had a deficit of 0.28 kg FM at 6 months, corresponding to 15%, which did not change as children grew older ($P_{interaction}$ =0.97). The difference in FM between stunted children and children with LAZ>0 lost significance at 15 months.(P>0.05, Table 3). At 6 months of age, children with LAZ between 0 and -2, had higher BMI and FFMI, and stunted children tended to have higher FFMI than children with LAZ ≥0 (Table 4) At 15 months of age, BMI, FFMI and FMI differed little with LAZ categories.

Children with low WLZ (<0) had not only lower weight, FFM and FM, but also lower BMI, FFMI and FMI compared to children with WLZ >0 (Table 3, 4). Weight and FFM, but not FM deficits generally increased with time for children with WLZ<0. The BMI deficit in children with low WLZ (<0) generally decreased between 6 and 15 months due to a decrease in the FMI deficit. FFMI deficits did not change with time ($P_{interaction}$>0.05) (Table 4). Sensitivity analyses including FFM and FM results from 345 children at 15 months before outliers were removed from the dataset resulted in similar results (**Supplementary table 2, 3**).

Both triceps and subscapular skinfold thickness were lower with lower LAZ and WLZ (**Table 5**). For stunted children, the triceps was 0.9 mm and 1.4 mm thinner at 6 months and 15 months, respectively, corresponding to deficits of 10% and 17% ($P_{interaction}$>0.05). In comparison, the subscapular skinfold was 0.7 mm and 0.6 mm thinner at 6 and 15 months, both corresponding to deficits of 8%.

DISCUSSION

In children from resource-limited rural communities in western Kenya, stunting increased from 13 % at 6 months to 32 % at 15 months, despite a very high prevalence of breastfeeding and supplementation of 200-550 kcal/day throughout the study. The prevalence of wasting remained at 2-3 % throughout the study, which is almost at the level of a normally distributed population following the WHO growth standards.

Stunting and wasting as correlates of body composition

Decreasing LAZ scores were associated with lower FFM and FM at 6 months of age. FFM deficits in children with LAZ below vs. above zero further increased in absolute kilograms from 6 to 15 months, while the FM deficits did not change and lost significance at 15 months, indicating that stunting progressed at the expense of FFM while FM was relatively preserved. Other studies have also quite consistently shown that stunted as well as wasted children seem to lack FFM [12,13, 21–23]. In our parallel Cambodian study, we also found that FFM, but not FM, deficits increased in stunted children between 6 and 15 months of age [12]. In both studies, the FFM deficit increased from 1.1 kg to 1.6 kg, in children with LAZ <-2 compared to children with LAZ ≥0, corresponding to a lack of approximately 20% of the FFM at both time points. However, stunting was associated with the height-adjusted index, FFMI, differently in Kenyan and Cambodian infants. In the current study, the deficits in FFM were lower than proportional to the children's length at 6 months and proportional to their length at 15 months. In the Cambodian study, the FFM deficits were proportional to the children's length at both 6 and 15 months. The populations in the Kenyan and Cambodian studies had comparable stunting prevalences, but the Cambodian population was generally thinner and had a higher prevalence of wasting.

Other studies have found that stunting at an early age may track into later child- or adulthood affecting body composition [23–26]. In a South-African cohort, stunting at 1 year was associated with lower FM at 10 years[23], while stunting at 2 years was associated with lower FFM but not FM at 10 [23] and 22 years [24]. In Nepalese children, stunting at 2 years was associated with reduced amounts of both FM and FFM at 8 years of age[25] and in Brazilian males, stunting at 2 and 4 years was associated with reduced FMI and FFMI (4 years only) at 18 years[27]. Overall, these studies indicated that stunting at an early age was associated with reduced lean and perhaps reduced fat tissue later on. Contrasting results were reported in two Brazilian studies in adolescents from slums in Sao Paolo [27,28]. The first cross-sectional study found that especially stunted adolescent girls had higher weight-for-height than non-stunted adolescents[27]. The second, smaller study followed 11-15 year-old children for 3 years and showed that stunted boys and girls gained less FFM and boys, but not girls, accumulated more FM than controls with normal stature[28].

In the current study, thin children with low WLZ (<0) had both lower FFM, FM, FFMI and FMI at 6 months compared to children with WLZ ≥0. Similar to short children with LAZ<0, FFM deficits of the thin children in absolute kilograms increased between 6 and 15 months, while FM deficits did not change and lost significance in all, but two wasted children. FFMI deficits remained at 15 months whereas the FMI deficits lost significance at 15 months compared to the reference children with WLZ >0. A similar pattern was seen in the Cambodian study, but more clearly due to a higher number of wasted children [12]. In Cambodia, FFMI deficits remained or increased and FMI deficits reduced between 6 and 15 months. This indicates that adipose tissue may be preserved at the expense of fat-free tissue in wasted or mildly wasted children. Lack of one or more growth nutrients, including protein, zinc, magnesium, phosphorus, potassium, and sodium [29] may have resulted in poor accretion of fat-free tissue. As all growth nutrients need to be present in sufficient and balanced amounts to build lean tissue, unbalanced diets with inadequate amounts of one or more growth nutrients will be metabolized and stored as fat tissue [29]. An evolutionary survival strategy aiming at preservation of fat mass tissue at the cost of fat-free tissue could also explain why fat-free tissue seem to be lacking quite consistently in undernourished children [30].

Decreasing LAZ and WLZ was also associated with decreasing skinfolds. For LAZ, deficits in triceps seemed to be worse than deficits in subscapular skinfolds, especially at 15 months. This may indicate that central fat (subscapularis) is preserved over peripheral fat (triceps) during chronic malnutrition. Fat is important for immune function. It provides energy for immune response while also secreting leptin which plays a regulatory role in immune function,[31] and reduced leptin levels have been associated with increased mortality in severely malnourished children[32,33]. However, decreasing WLZ scores was associated with significant reductions in both central and limb skinfolds. As infections are common in wasted children[34], the depletion of both skinfolds in this group is likely to reflect the greater use of fat reserves to fund immune response.

Breastfeeding

Lack of breastfeeding was associated with lower weight at 6 and 15 months of age. The lower weight was due to lower FM at 6 months and lower FFM at 15 months. There were no associations between breastfeeding and BMI, FMI or FFMI at any time points. Only 5 infants were non-breastfed at 6 months, and the results should therefore be considered with reservations. In the Cambodian study, where the children were generally thinner, a lower FM was also found at 6 months among the few, non-breastfed children. The lower FM persisted at 15 months and was more severe, shown as a lower FMI at 6 months reducing to a trend at 15 months[12]. In contrast to the Kenyan children, the non-breastfed Cambodian children had higher

FFM at 15 months and higher FFMI at 6 and 15 months compared to breastfed children. The different associations in the two studies could, among others, be due to differences in the age of introduction and composition and amount of complementary foods. In Cambodia, complementary feeding was reported by the caregiver to start at 5.6 months in average and in Kenya, introduction of foods or liquids was reported to start at a median age of 3 months. In Kenya as well as in Cambodia, traditional complementary foods and feeding practices are generally characterized as insufficient to meet the nutritional needs of young children[35,36].

Strengths and limitations

Due to the practical difficulties, few studies have investigated body composition in young infants in low-income countries. It is a strength that the current study assessed body composition in a large sample of Kenyan infants at both 6 and 15 months of age using the deuterium dilution technique. The study design and the analyses were similar to a study conducted in Cambodia. This made direct comparison between the outcomes possible. The calculation of TBW and FFM based on the average of the 2 and 3 hours post-doses was a limitation of the current study leading to potential overestimation of FFM and underestimation of FM, if equilibrium was not fully obtained. Although negative FM values were rejected, data may still contain some over-inflated FFM and low FM values. In addition, more implausible FFM and FM results were removed from 15 months than 6 months, which could potentially lead to another overestimation of FFM at 15 months. In the current study, an average of the deuterium concentrations measured at 2 and 3 hours postdose was used to calculate FFM and hence FM. However, a study in Burkina Faso later refined the procedure in a local context and found the optimum equilibration time to be 3 hours [37]. As there was no difference in any anthropometric measures between children with or without body composition data at 6 or 15 months, and a sensitivity analysis did not find any differences in results before and after removing FFM and FM outlier values, the influence on the study results is considered to be minor. In addition, the reported findings of the current study are in line with previous studies. Other limitations include the few non-breastfed infants at 6 months of age and the few wasted children at either time point, which affects the certainty of these results. Finally, all children received a food intervention, which may influence the generalizability of the results to communities with no supplementation.

Conclusion

In a population with high breastfeeding, stunting, but not wasting prevalence, we found that stunting was associated with FFM deficits corresponding to 20% of the FFM at 6 and 15 months of age. The deficit was slightly lower than or proportional to the length of the children at 6 months and 15 months, respectively. Low WLZ was associated with deficits in both FFM, FM and the height-adjusted indexes FFMI and FMI at both 6 and 15 months. However, the FMI deficit reduced between the two time points. Undernutrition, in general, seems to be associated with reduced FFM. The proportionality of the FFM deficit with length is suggested to vary between stunted populations. Studies are needed to further explore early changes in body composition and how these changes affect growth and health in the longer term.

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CONFLICT OF INTEREST

None

AUTHORSHIP

HF, KFM, NR and VOO designed the study. SMF reviewed the design. SOK, SAO, JNK and BOO collected data under supervision by BBE and VOO. BG and CR analysed the data and BG, SOK, SMF, JW, HF and NR interpreted the findings. BG and SOK prepared the first draft of the manuscript. SMF, JW, HF and NR contributed to manuscript writing, and BG finalized the manuscript. All authors have read and approved the final manuscript.

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Figure 1

Flow chart

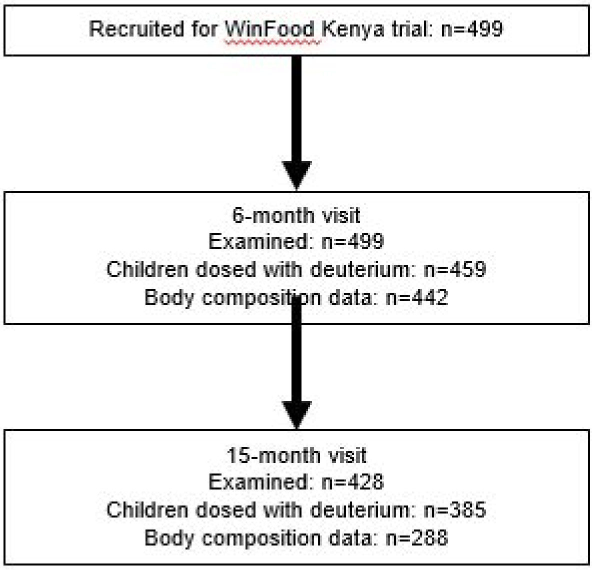

Table 1: Sociodemographic characteristics of 499 Kenyan 6-month-old children

	N	
Child		
Boys	499	240 (48%)
Age at recruitment, months	499	6.0 ±0.2
Birth order		3 [2;5]
Age child introduced to foods or liquid, months		3 [1.5;5]
Caregiver		
Mother is primary caregiver	498	486 (97%)
Caregiver age, years	498	24 [21;29]
Married	499	457 (92%)
Education, primary incomplete or less	499	254 (51%)
Religion		
Father		
Living with the family	419	343 (82%)
Age, years	390	30 [26;37]
Education, primary incomplete or less	411	128 (31%)
Household		
Number of people in the household	499	5 [4;7]
Number of children below 5 years	499	2 [1;2]
Household main income source	487	
Farming		238 (49%)
Self employed		136 (28%)
Salaried employed		73 (15%)
Other		40 (8%)
Drinking water		
Protected (well/borehole/pump/tap)	485	273 (56)

Data are presented as N, n (%), mean (±SD) or median [interquartile range]. For some variables the numbers do not add up to 499 due to missing data.

Table 2. Breastfeeding status, anthropometry and body composition in Kenyan boys and girls at 6 and 15 months of age

	6 months					**15 months**				
	N	Boys	N	Girls	p	N	Boys	N	Girls	p
Breastfeeding, %	240		259		0.93	204		224		0.04
Not breastfed		3 (1%)		2 (1%)			19 (9%)		37 (17%)	
Breastfed		237 (99%)		257 (99%)			185 (91%)		187 (83%)	
Weight, kg	240	7.7±1.0	259	7.2±1.0	<0.001	204	9.9±1.2	224	9.4±1.1	<0.001
Length, cm	240	66.2±2.8	259	64.8±2.8	<0.001	204	75.7±3.0	224	74.5±2.9	<0.001
Mid-upper arm circumference, cm		14.4±1.3	259	14.0±1.2	0.003		14.9±1.2	224	14.7±1.1	0.09
Length-for-age Z, %	240		259		0.43	203		224		0.14
<-2		37 (15%)		28 (11%)			75 (37%)		60 (27%)	
-2≤ and <-1		64 (27%)		69 (27%)			59 (29%)		80 (36%)	
-1≤ and <0		72 (30%)		89 (34%)			50 (25%)		63 (28%)	
≥0		67 (28%)		73 (28%)			19 (9%)		21 (9%)	
Weight-for-length Z, %	240		259		0.19	203		224		0.11
<-2		10 (4%)		6 (2%)			6 (3%)		2 (1%)	
-2≤ and <-1		33 (14%)		23 (9%)			16 (8%)		9 (4%)	
-1≤ and <0		57 (24%)		71 (27%)			55 (27%)		72 (32%)	
≥0		140 (58%)		159 (61%)			126 (62%)		141 (63%)	
Body mass index, kg/m^2		17.6 [16.2;18.6]	259	17.1 [15.9;18.3]	0.02	203	17.1 [16.4;18.1]	224	16.7 [16.0;17.7]	0.05
Fat mass, kg	212	1.6 [1.1;2.0]	230	1.5 [1.1;1.9]	0.17	134	1.3 [0.8;1.7]	154	1.5 [0.8;1.9]	0.21
Fat-free mass, kg	212	6.1±0.8	230	5.7±0.8	<0.001	134	8.5±1.1	154	8.0±1.0	<0.001
Fat mass index, kg/m^2	212	3.6 [2.7;4.6]	230	3.6 [2.6;4.5]	0.69	131	2.3 [1.5;3.1]	150	2.7 [1.3;3.3]	0.24
Fat-free mass index, kg/m^2	212	14.0±1.7	230	13.5±1.5	0.004	131	14.7±1.5	150	14.3±1.5	0.01
Skinfolds										
Triceps, mm	239	8.5 [7.2;10.0]	259	8.1 [6.9;9.5]	0.05	203	7.4 [6.4;8.7]	224	7.3 [6.5;8.4]	0.90
Subscapularis, mm	239	7.8 [6.3;9.2]	259	7.8 [6.7;9.1]	0.80	203	6.7 [5.8;7.8]	224	7.0 [5.9;8.0]	0.06

Data are presented as n (%), mean ± SD or median [IQR] and p-values are calculated using χ^2 tests and two-sample t-tests for categorical and continuous variables.

BMI: Body mass index, FM: Fat mass, FFM: Fat-free mass, FMI: Fat mass index, FFMI: Fat-free mass index, LAZ: Length-for-age z-score, MUAC: Mid-upper arm circumference, N: Number of children in each analysis, WLZ: Weight-for-length z-score.

Table 3. Associations of sex, breastfeeding, length-for age and weight-for-length z-scores with weight, fat-free mass (FFM) and fat mass (FM) in Kenyan children at 6 and 15 months of age

	6 months								15 months							
		Weight, kg			FFM, kg		FM, kg			Weight, kg			FFM, kg		FM, kg	
	N	Δ.	95% CI	N	Δ	95% CI	Δ	95% CI	N	Δ	95% CI	N	Δ	95% CI	Δ	95% CI
Sex[a]																
Boy	240	0.49	0.30;0.69	212	0.46	0.29;0.62	0.04	-0.09;0.17	204	0.53	0.33;0.73	134	0.52	0.32;0.72	0.02	-0.23;0.25
Girl	250	-	-	230	-	-	-	-	224	-	-	154	-	-	-	-
Breastfeeding[b]																
Not breastfed	5	-0.76	-1.39;-0.13	5	0.05	-0.70;0.80	-0.81*	-1.52;0.09	56	-0.44	-0.64;-0.24	31	-0.37	-0.68;-0.06	-0.07	-0.39;0.24
Breastfed	494	-	-	437	-	-	-	-	372	-	-	250	-	-	-	-
Length-for-age Z[c]																
<-2	65	-1.40*	-1.62;-1.18	60	-1.12*	-1.36;-0.88	-0.28	-0.47;-0.09	135	-1.88	-2.14;-1.62	87	-1.59	-1.94;-1.25	-0.29	-0.73;0.16
-2≤ and <-1	133	-0.83	-1.01;-0.65	118	-0.66	-0.86;-0.46	-0.17	-0.33;-0.02	139	-1.03	-1.28;-0.78	93	-0.99	-1.33;-0.65	-0.04	-0.47;0.40
-1≤ and <0	161	-0.41	-0.58;-0.25	141	-0.35	-0.53;-0.16	-0.07	-0.23;0.09	113	-0.67	-0.92;-0.41	71	-0.53	-0.88;-0.18	-0.14	-0.59;0.32
≥0	140	-	-	123	-	-	-	-	40	-	-	25	-	-	-	-
Weight-for-length Z[d]																
<-2	16	-1.75*	-2.06;-1.43	13	-1.17	-1.60;-0.74	-0.57	-0.86;-0.29	8	-2.58	-3.00;-2.16	2	-2.05	-3.10;-1.01	-0.53	-1.00;-0.05
-2≤ and <-1	56	-1.16*	-1.34;-0.97	48	-0.87*	-1.11;-0.64	-0.28	-0.47;-0.10	25	-1.62	-1.87;-1.37	17	-1.41	-1.79;-1.03	-0.21	-0.51;0.09
-1≤ and <0	128	-0.64*	-0.77;-0.51	116	-0.38*	-0.55;-0.22	-0.26	-0.40;-0.11	127	-0.95	-1.08;-0.83	87	-0.88	1.08;-0.69	-0.07	-0.28;0.14
≥0	299	-	-	265	-	-	-	-	267	-	-	170	-	-	-	-

Δ Difference between categories. Separate linear mixed-effects models were fitted to FFM and weight. Age, sex, intervention groups of the original trial design, and the interaction between visit (6 or 15 months) and either [a]sex, [b]breastfeeding, [c]length-for-age or [d]weight-for-length z-score categories were included as fixed effects and children and health centre were included as random (intercept) effects. Estimates for FM were derived from the corresponding estimates for FFM and weight (with error propagation).

* Significant interaction i.e., change in difference between 6 and 15 months (P <0.05)

Table 4. Associations of sex, breastfeeding, length-for-age and weight-for-length z-scores with body mass index (BMI), fat-free mass index (FFMI) and fat mass index (FMI) in Kenyan children at 6 and 15 months of age

	6 months								15 months							
		BMI, kg/m²			FFMI, kg/m²		FMI, kg/m²			BMI, kg/m²			FFMI, kg/m²		FMI, kg/m²	
	N	Δ	95% CI	N	Δ	95% CI	Δ	95% CI	N	Δ	95% CI	N	Δ	95% CI	Δ	95% CI
Sex[a]																
Boy	240	0.37	0.08;0.66	212	0.44	0.15;0.73	-0.07	-0.32;0.18	204	0.30	0.00;0.60	134	0.43	0.07;0.79	-0.13	-0.49;0.23
Girl	250	-	-	230	-	-	-	-	224	-	-	154	-	-	-	-
Breastfeeding[b]																
Not breastfed	5	-0.43	-1.63;0.76	5	0.45	-0.92;1.18	-0.88	-2.20;0.44	56	-0.29	-0.68;0.09	31	-0.39	-0.97;0.18	0.10	-0.37;0.58
Breastfed	494	-	-	437	-	-	-	-	372	-	-	250	-	-	-	-
Length-for-age Z[c]																
<-2	65	0.21	-0.21;0.63	60	0.46	-0.02;0.93	-0.25	-0.66;0.17	135	0.31	-0.18;0.81	87	0.23	-0.45;0.92	0.08	-0.66;0.82
-2≤ and <-1	133	0.38	0.04;0.72	118	0.46	0.07;0.84	-0.07	-0.40;0.25	139	0.61	0.12;1.09	93	0.26	-0.41;0.94	0.34	-0.38;1.06
-1≤ and <0	161	0.45	0.13;0.77	141	0.38	0.01;0.76	0.06	-0.26;0.39	113	0.18	-0.30;0.66	71	0.17	-0.52;0.87	0.01	-0.73;0.74
≥0	140	-	-	123	-	-	-	-	40	-	-	25	-	-	-	-
Weight-for-length Z[d]																
<-2	16	-4.73*	-5.20;-4.26	13	-3.13	-3.87;-2.39	-1.60*	-2.09;-1.11	8	-3.76	-4.41;-3.11	2	-3.55	-5.40;-1.70	-0.21	-0.92;0.50
-2≤ and <-1	56	-3.36*	-3.36;-3.09	48	-2.19	-2.60;-1.78	-1.17	-1.51;-0.83	25	-2.73	-3.11;-2.35	17	-1,94	-2.60;-1.28	-0.79	-1.25;-0.34
-1≤ and <0	128	-2.16*	-2.35;-1.96	116	-1.25	-1.54;-0.96	-0.91*	-1.17;-0.65	127	-1.59	-1.79;-1.40	87	-1.12	-1.46;-0.78	-0.48	-0.78;-0.17
≥0	299	-	-	265	-	-	-	-	267	-	-	170	-	-	-	-

Δ Difference between categories. Separate linear mixed-effects models were fitted to BMI and FFMI. Age, sex, intervention groups of the original trial design, and the interaction between visit (6 15 months) and either [a]sex, [b]breastfeeding, [c]length-for-age or [d]weight-for-length z score categories were included as fixed effects and children and health centre were included as random (intercep effects. Estimates for FMI were derived from the corresponding estimates for BMI and FFMI (with error propagation).

* Significant interaction i.e., change in difference between 6 and 15 months (P <0.05).

Table 5. Associations of sex, breastfeeding, length-for age and weight-for-length z-scores with triceps and subscapular skin folds in Kenyan children at 6 and 15 months of age, including the difference between 6 and 15 months

	6 months					15 months				
		Triceps skinfold, mm		Subscapularis skinfold, mm			Triceps skinfold, mm		Subscapularis skinfold, mm	
	N	Δ	95% CI	Δ	95% CI	N	Δ	95% CI	Δ	95% CI
Sex[a]										
Boy	239	0.36*	0.05;0.67	-0.02	-0.34;0.29	202	-0.03	-0.36;0.30	-0.34	-0.67;-0.01
Girl	259	-	-	-	-	224	-	-	-	-
Breastfeeding[b]										
Not breastfed	5	-0.91	-2.32;0.50	-1.68*	-3.06;-0.30	55	-0.23	-0.68;0.23	-0.06	-0.51;0.39
Breastfed	493	-	-	-	-	371	-	-	-	-
LAZ[c]										
<-2	65	-0.87	-1.35;-0.39	-0.67	-1.16;-0.19	133	-1.42	-2.00;-0.85	-0.55	-1.12;0.03
-2≤ and <-1	132	-1.02	-1.41;-0.63	-0.47	-0.86;-0.08	134	-0.86	-1.42;-0.29	-0.12	-0.68;0.44
-1≤ and <0	161	-0.39	-0.75;-0.02	-0.19	-0.56;0.17	111	-0.84	-1.41;-0.26	-0.04	-0.60;0.53
≥0	140	-	-	-	-	40	-	-	-	-
WLZ[d]										
<-2	15	-1.67	-2.51;-0.84	-1.91	-2.72;-1.11	7	-2.82	-4.02;-1.62	-3.15	-4.30;-2.00
-2≤ and <-1	56	-0.88	-1.34;-0.42	-1.18	-1.62;-0.74	25	-1.64	-2.29;-0.98	-1.57	-2.19;-0.94
-1≤ and <0	128	-0.58*	-0.91;-0.25	-0.89	-1.21;-0.58	126	-1.08	-1.42;-0.74	-1.17	-1.50;-0.85
≥0	299	-	-	-	-	260	-	-	-	-

Δ Difference between categories. Linear mixed-effects models were fitted for triceps and subscapular skinfolds. Age, sex, intervention groups of the original trial design, and the interaction between visit (6 or 15 months) and either [a]sex, [b]breastfeeding, [c]length-for-age or [d]weight-for-age z-score categories were included as fixed effects and children and municipality were included as random (intercept) effects.
* Significant interaction, i.e. change in difference between 6 and 15 months (P < 0.05)

Online supporting material

Supplementary table 1. Comparison of children with and without body composition (BC) data

	6 months			15 months		
	With BC (n=442)	Without BC (n=57)	P	With BC (n=288)	Without BC (n=140)	P
Sex, male %	48	49	0.98	47	50	0.46
Weight (kg)	7.5 ± 1.1	7.4 ± 0.9	0.86	9.6 ± 1.1	9.7 ± 1.4	0.56
Height (cm)	65.4 ± 2.9	65.6 ± 2.6	0.62	75.1 ± 2.9	74.9 ± 3.1	0.54
MUAC (cm)	14.2 ± 1.2	14.4 ± 1.3	0.34	14.7 ± 1.1	14.8 ± 1.3	0.50
Length-for-age Z	-0.71 ± 1.3	-0.56 ± 1.1	0.37	-1.4 ± 1.1	-1.5 ± 1.1	0.81
Weight-for-length Z	0.23 ± 1.2	0.10 ± 1.2	0.41	0.26 ± 0.9	0.38 ± 1.2	0.29
BMI (kg/m2)	17.4 ± 1.8	17.2 ± 1.7	0.51	17.0 ± 1.2	17.2 ± 1.8	0.17
Triceps skinfold (mm)	8.4 ± 1.8	9.0 ± 2.1	0.06	7.5 ± 1.7	7.8 ± 2.0	0.17
Subscapular skinfold (mm)	7.9 ± 1.9	8.2 ± 1.8	0.20	7.1 ± 1.7	7.0 ± 1.8	0.58

Supplementary table 2. Sensitivity analysis showing associations of sex, breastfeeding, length-for age and weight-for-length z-scores with weight, fat-free mass (FFM) and fat mass (FM) in Kenyan children at 6 and 15 months of age, including the difference between 6 and 15 months.

	6 months (n=442)						15 months (n=345)						Differencebetween 6 and 15 months					
	Weight (kg)		FFM (kg)		FM (kg)		Weight (kg)		FFM (kg)		FM (kg)		Weight (kg)		FFM (kg)		FM (kg)	
	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI
Sex[a]																		
Boy	0.49*	0.30;0.69	0.45*	0.28;0.63	0.04	-0.09;0.17	0.53*	0.33;0.73	0.50*	0.31;0.70	0.02	-0.21;0.26	0.03	-0.11;0.18	0.05	-0.16;0.26	-0.02	-0.23;0.19
Girl	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Breastfeeding[b]																		
Not breastfed	-0.76*	-1.39;-0.13	0.02	-0.75;0.78	-0.78*	-1.43;-0.12	-0.44*	-0.64;-0.24	-0.26	-0.54;0.02	-0.18	-0.48;0.11	0.31	-0.31;0.94	-0.28	-1.06;0.51	0.59	-0.08;1.28
Breastfed	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LAZ[c]																		
<-2	-1.40*	-1.62;-1.18	-1.12*	-1.37;-0.87	-0.28*	-0.47;-0.08	-1.88*	-2.14;-1.62	-1.62*	-1,94;-1.29	-0.27	-0.67;0.14	-0.48#	-0.77;-0.19	_-0.49#	-0.89;-0.10	-0.09	-0.52;0.34
-2≤ and <-1	-0.83*	-1.01;-0.65	-0.68*	-0.89;0.48	-0.15	-0.31;0.01	-1.03*	-1.28;-0.78	-1.10*	-1.42;-0.78	0.07	-0.34;0.48	-0.20	-0.47;0.08	-0.42#	-0.79;-0.05	0.22	-0.19;0.64
-1≤ and <0	-0.41*	-0.58;-0.25	-0.36*	-0.57:-0.17	-0.05	-0.21;0.11	-0.67*	-0.92;-0.41	-0.52*	-0.85;-0.19	-0.15	-0.56;0.27	-0.25	-0.54;0.02	-0.16	-0.54;0.22	-0.09	-0.53;0.34
≥0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
WLZ[d]																		
<-2	-1.75*	-2.06;-1.43	-1.17*	-1.62;-0.73	-0.57*	-0.86;-0.29	-2.58*	-3.00;-2.16	-2.30*	-2.94;-1.66	-0.28	-0.87;0.31	-0.83#	-1.32;-0.34	-1.13#	-1.90;-0.36	0.30	-0.33;0.92
-2≤ and <-1	-1.16*	-1.34;-0.97	-0.88*	-1.13;-0.64	-0.27*	-0.46;-0.09	-1.62*	-1.87;-1.37	-1.46*	-1.83;-1.10	-0.16	-0.54;0.23	-0.46#	-0.74;-0.19	-0.58#	-1.01;-0.15	0.12	-0.30;0.54
-1≤ and <0	-0.64*	-0.77;-0.51	-0.40*	-0.57;-0.22	-0.24*	-0.39;-0.10	-0.95*	-1.08;-0.83	-0.91*	-1.10;-0.72	-0.05	-0.24;0.15	-0.31#	-0.48;-0.14	-0.51#	-0.76;-0.26	0.20	-0.04;0.44
≥0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

LAZ, Length-for-age Z, WLZ, Weight-for-length Z.
Separate linear mixed-effects models were fitted to weight and FFM. Age, sex, intervention groups of the original trial design, and the interaction between visit (6 or 15 months) and either [a]sex, [b]breastfeeding, [c]LAZ o [d]WLZ categorieswere included as fixed effects and children and health centre were included as random (intercept) effects. Estimates for FM were derived from the corresponding estimates for BMI and FFMI (with error propagation).
* Significantly different ($p < 0.05$) from the reference category.
# Significant interaction i.e., change in difference between 6 and 15 months ($p<0.05$).

Supplementary table 3. Sensitivity analysis showing associations of sex, breastfeeding, length-for age and weight-for-length z-scores with body mass index (BMI), fat-free mass index (FFMI) and fat mass index (FM in Kenyan children at 6 and 15 months of age, including the difference between 6 and 15 months.

	6 months (n=442)						15 months (n=345)						Difference between 6 and 15 months					
	BMI, kg/m²		FFMI, kg/m²		FMI, kg/m²		BMI, kg/m²		FFMI, kg/m²		FMI, kg/m²		BMI, kg/m²		FFMI, kg/m²		FMI, kg/m²	
	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI	Diff	95% CI
Sex[a]																		
Boy	0.37*	0.08;0.66	0.44*	0.14;0.73	-0.07	-0.32;0.19	0.30*	-0.004;0.60	0.31	-0.02;0.65	-0.01	-0.37;0.35	-0.07	-0.36;0.22	-0.13	-0.55;0.30	0.05	-0.33;0.44
Girl	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Breastfeeding[b] (n=412)																		
Not breastfed	-0.43	-1.63;0.76	0.42	-0.97;1.81	-0.86	-2.17;0.46	-0.29	-0.68;0.09	-0.25	-0.75;0.26	-0.05	-0.52;0.43	0.14	-1.07;1.35	-0.67	-2.13;0.80	0.81	-0.58;2.20
Breastfed	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LAZ[c]																		
<-2	0.21	-0.21;0.63	0.44	-0.05;0.93	-0.23	-0.65;0.19	0.31	-0.18;0.81	0.19	-0.45;0.82	0.13	-0.55;0.80	0.10	-0.46;0.67	-0.25	-1.03;0.52	0.36	-0.39;1.11
-2≤ and <-1	0.38*	0.04;0.72	0.43*	0.03;0.82	-0.04	-0.37;0.29	0.61*	0.12;1.09	0.03	-0.60;0.66	0.57	-0.09;1.23	0.22	-0.31;0.75	-0.39	-1.12;0.34	0.61	-0.09;1.32
-1≤ and <0	0.45*	0.13;0.77	0.36	-0.02;0.74	0.09	-0.24;0.42	0.18	-0.30;0.66	0.15	-0.49;0.80	0.03	-0.64;0.70	-0.27	-0.81;0.28	-0.21	-0.95;0.54	-0.06	-0.79;0.66
≥0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
WLZ[d]																		
<-2	-4.73*	-5.20;-4.26	-3.10*	-3.87;-2.34	-1.62*	-2.12;-1.13	-3.76*	-4.41;-3.11	-3.05*	-4.17;-1.93	-0.71	-1.46;0.04	0.97#	0.20;1.75	0.05	-1.30;1.41	0.92#	0.04;1.80
-2≤ and <-1	-3.36*	-3.36;-3.09	-2.18*	-2.60;-1.76	-1.18*	-1.52;-0.84	-2.73*	-3.11;-2.35	-1.94*	-2.59;-1.29	-0.79*	-1.47;-0.12	0.63#	0.18;1.07	0.24	-0.53;1.01	0.38	-0.37;1.14
-1≤ and <0	-2.16*	-2.35;-1.96	-1.25*	-1.55;-0.95	-0.91*	-1.17;-0.64	-1.59*	-1.79;-1.40	-1.13*	-1.46;-0.80	-0.46*	-0.76;-0.17	0.56#	0.29;0.83	0.12	-0.33;0.57	0.44#	0.05;0.84
≥0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

LAZ, Length-for-age Z, WLZ, Weight-for-length Z.
Separate linear mixed-effects models were fitted to BMI and FFMI. Age, sex, intervention groups of the original trial design, and the interaction between visit (6 or 15 months) and either [a]sex, [b]breastfeeding, [c]LAZ or[d]WLZ categorieswere included as fixed effects and children and health centre were included as random (intercept) effects. Estimates for FMI were derived from the corresponding estimates for BMIand FFMI (with error propagation).
* Significantly different ($p< 0.05$) from the reference category.
# Significant interaction i.e., change in difference between 6 and 15 months ($p<0.05$).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	Suppl table 2-3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Table1-2
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3-5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3-5
		(*b*) Report category boundaries when continuous variables were categorized	Table 3-5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Suppl table 1-3
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.