Original Article

Age-related differences in height gain with dairy protein and micronutrient supplements in Indian primary school children

Tinku Thomas PhD[1], Meenu Singh PhD[2], Sumathi Swaminathan PhD[3], Anura V Kurpad MD, PhD, FRCP[4]

[1]Department of Biostatistics, St. John's Medical College, St. John's National Academy of Health Sciences, Bengaluru, India
[2]Division of Nutrition, St. John's Research Institute, St. John's National Academy of Health Sciences, Bengaluru, India
[3]Division of Nutrition, St John's Research Institute, St. John's National Academy of Health Sciences, Bengaluru, India
[4]Department of Physiology and Division of Nutrition, St. John's Medical College, St. John's National Academy of Health Sciences, Bengaluru, India

Background and Objectives: The efficacy of nutrient interventions to prevent/reverse stunting is considered to be restricted to early life. Whether such interventions are equally effective in later childhood is not clear. The present study evaluated the effect of a food-based high-quality protein and micronutrient intervention on the linear growth of Indian primary school children. **Methods and Study Design:** A secondary analysis of a one-year milk-protein and micronutrient fortified food product intervention (protein-energy ratio: 12.8%) on the height of 550 children aged 6-10 years, of poor-socioeconomic background, was carried out. Height and weight increments were compared between groups of each year of age using multiple linear regression. Comparisons in prevalence of stunting and underweight between these groups was also made. **Results:** The overall mean height increment at the end of 1-year was 6.10±1.07 cm, the highest being for 6-year olds (6.38±0.84 cm). The mean height increments in 6, 7 and 8-year-olds were significantly higher (all $p<0.05$) than the expected median growth. Height-for-age score increased across all age-groups (by 0.14±0.18) and was significantly higher in 6-year olds compared to the rest. Stunting reduced by 12% in 6-year olds in comparison to the older age-groups. No significant association was observed between height gain and gender. The increased BMI-for-age scores were significantly lower for the 6-year olds compared to older children. **Conclusions:** Food supplements containing high-quality protein (like milk) along with micronutrients, can continue to influence height of children even in primary school, although the most effect is seen in younger children.

Key Words: height-for-age (HAZ), linear growth, stunting, micronutrient supplementation, animal source protein

INTRODUCTION

The global burden of childhood stunting remains high at 22.7% in 2017, with a high proportion in South Asia[1] and India.[2] One of the nutrients related to linear growth in infants and young children is high-quality protein.[3-5] Animal protein intake, particularly dairy, has been shown to be significantly associated with increased linear growth in 12 month-old children.[6] Dairy protein intake at 12 months of age was also positively associated with serum growth factor (IGF-1) concentrations at 6 years,[6] and an association between dairy protein intake at 4 years and increased linear growth at that age has been demonstrated in a Danish cohort.[7] The consumption of meat has also been associated with reduced likelihood of stunting in infants and pre-school children.[4,8,9] Micronutrient interventions have also shown some effect on improving height in school children.[10]

The age at which the nutritional intervention is offered

is important. It is clear that nutritional interventions to prevent stunting are most productive in the first 2 years of life, and perhaps up to pre-school age. However, recent evidence from a south Indian cohort shows that children continue to falter in growth well into puberty, albeit with decreasing incidence.[11] In primary school, there are some studies on the effect of dietary protein interventions and its effect on linear growth in primary school children,[12-16] but few in Asian children.[17,18] The question is whether

primary school interventions would be effective, and if so, whether a specific annual age response can be observed.

The objective of this study was a secondary analysis of the linear growth response by year of age, of a one year long milk protein, multiple micronutrient and omega-3 fatty acid intervention[19] in 598 Indian primary school children aged between 6-10 years. This intervention had originally aimed to evaluate the effect of added micronutrients and omega-3 fatty acids on a common base supplement of milk protein on cognitive performance and growth.

METHODS

The CHAMPION Study, (Children's Health and Mental Performance Influenced by Optimal Nutrition)[19] registered at http://www.clinicaltrials.gov (NCT00467909), was undertaken in 2007 to evaluate the efficacy of micronutrient and/or omega-3 fatty acid supplied through a high-protein food product for 1 year, on growth and cognition of 6-10years primary school Indian school children, from a poor socioeconomic background. Children were eligible for inclusion if they were apparently healthy, with no chronic illness or physical or mental handicaps; not severely anaemic (haemoglobin >80 g/L) and not severely undernourished [weight-for-age (WAZ) and height-for-age (HAZ) <-3]. Of the 598 children randomized into the study, 550 completed the study after 1 year and were considered for this secondary analysis (Supplemental Figure 1). The characteristics of the dropout children was comparable to that of the children who completed the study (data not shown). The study design has been published in detail earlier.[19]

The original study used a randomized, double-blind, 2x2 factorial design, with 4 parallel treatment groups providing either high or low (100 or 15% of the RDA[20]) micronutrients (MN) and/or high [900 mg alpha-linolenic acid (ALA) plus 100 mg DHA] or low (140 mg ALA) concentrations of n-3 fatty acids. The high-quality protein and energy content were constant across all groups. Two fortified food products (fruit flavoured wheat biscuit and flavoured milk drink) containing 420 kcal and 13.5 g protein/day (protein energy ratio: 12.8%) and 9.3 g fat/day were provided daily, at mid-morning and mid-afternoon. The composition of the intervention formulations is provided in Supplemental Table 1. The drink was prepared by adding 65 g of the powder to 160 mL water. The children were encouraged to consume their habitual diet (including the mid-day meal) during the intervention period. The habitual diet provided 28±7 g protein per day (protein energy ratio: 10.2%) and this was not different between the age groups of children. Parents were instructed to refrain from providing their children any fortified products or dietary supplements during the study period. According to diet records, the children maintained their regular intake and that the study products did not replace their meals.[19] The children consumed the intervention product under direct supervision of the study team. After consumption, visible leftovers were individually estimated. During school holidays, the children consumed the fortified products at home. Compliance during holidays were captured from returned empty sachets. The compliance of about 73% was similar for all the study groups.[19]

Anthropometric measurements were recorded in duplicate at baseline, 6 and 12 months later, according to standard techniques that have been described earlier.[19] Body weight was recorded to the nearest 0.1 kg with a digital weighing scale (Beurer, Germany) while the subjects were wearing their school uniforms, whereas height was recorded to the nearest 0.1 cm with a locally manufactured stadiometer (Biorad, Mumbai, India). Age and sex standardized scores for BMI (BAZ) and height (HAZ) were computed using the World Health Organization (WHO) growth reference data.[21] Subjects with BAZ and HAZ<-2 were considered thin and stunted, respectively.

The children were grouped based on their completed age at recruitment (eg: children aged 6 years and 1 month to 6 years and 11 months were grouped as 6 years), irrespective of their intervention group (high/low micronutrients and high/low fatty acids), since the protein/energy content of the fortified foods was common for all four groups. All baseline characteristics were compared between the ages using one-way ANOVA for continuous variables and chi-square test for categorical variables. The expected annual rate of growth for children of this age was computed as the annual increase in median height in the WHO growth reference data.[21] The observed increase in height, weight, HAZ and BAZ from baseline to end of one year of intervention for ages 7, 8 and 9 were compared against the increase in age 6 using multiple linear regression adjusting for baseline anthropometry and treatment group. Other social characteristics that were significantly different between the ages were also adjusted for in the regression analysis. The change in stunting and underweight status were compared between ages as the interaction effect of visit and age in generalized estimating equations with logit link function which was specified for the binary outcome. The interaction effect of sex of the child with age on growth was also examined in the regression model. All analyses were performed in Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) and $p < 0.05$ was considered statistically significant.

RESULTS

The screening and inclusion of children has been described earlier.[19] Supplemental Figure 1 shows the recruitment process for the 598 children and 550 who completed the study, whose baseline characteristics and nutritional status are given in Table 1. There was no association between the habitual protein intake and HAZ at baseline (r=0.1, $p > 0.05$). All the ages had an equal distribution of the different interventions (high/low micronutrients and high/low fatty acids). The compliance to intervention (73%) was comparable across the age groups (p=0.467). In the original trial analysis, height gain in the group which received high micronutrient intervention was higher by 0.2 cm (p=0.03) whereas there was no difference between the high and low omega-3 fatty acid groups (p=0.66).[19] This difference between the micronutrient groups was comparable when examined within each age (all $p < 0.05$).

The expected rate of growth of the children at baseline (calculated from the WHO growth standards) is given in

Table 1. Characteristics of subjects by age at baseline

	Completed age at baseline (years)					*p* value
	6, n=44	7, n=130	8, n=160	9, n=115	10, n=101	
Intervention groups (%)						
High Vit High PUFA	26	23	26	28	22	0.79
Low Vit High PUFA	23	25	26	24	23	
High Vit Low PUFA	26	29	21	19	31	
Low Vit Low PUFA	26	23	26	29	23	
Sex						
% Female	36	55	50	57	45	0.101
Maternal education (%)						
Illiterate	35	47	42	45	55	0.593
Primary school	22	22	18	21	18	
Middle school	29	20	23	20	16	
High school	14	11	16	15	11	
Maternal employment (%)	73	62	65	80	75	0.008
Height (cm)[†]						
Male	115 (4.1)	117 (5.1)	121 (5.2)	126 (6.2)	132 (6.2)	<0.001
Female	113 (4.0)	116 (5.1)	122 (5.5)	127 (5.5)	131 (6.2)	<0.001
Weight (kg)[†]						
Male	18.3 (1.8)	19.4 (2.4)	20.3 (2.5)	22.5 (3.6)	25.5 (4.1)	<0.001
Female	17.8 (2.4)	18.7 (2.4)	21.3 (3.5)	23.2 (2.7)	25.1 (3.8)	<0.001
BMI (kg/m^{-2})[†]						
Male	13.8 (1.0)	14.1 (1.2)	13.7 (0.9)	14.0 (1.1)	14.5 (1.6)	0.011
Female	13.9 (1.0)	13.8 (1.1)	14.2 (1.6)	14.3 (1.3)	14.6 (1.3)	0.001
WHO Height for age Z score[†]	-1.07 (0.11)	-1.37 (0.08)	-1.36 (0.07)	-1.41 (0.08)	-1.38 (0.09)	0.26
WHO BMI for age Z score[†]	-1.29 (0.12)	-1.27 (0.08)	-1.46 (0.07)	-1.50 (0.08)	-1.51 (0.10)	0.168
Stunting %	14	21	22	27	29	0.271
Thinness %	19	19	28	28	30	0.172

Vit: Vitamin; PUFA: Polyunsaturated fatty acid; BMI: Body mass index
p value from chi-square test
[†]Values are mean (SD), *p* value from one-way ANOVA.

Figure 1. The yearly expected median growth rate across the ages was similar at about 5.7 cm/year from 6 to 10 years. The mean increase in height observed in the 6, 7- and 8-year olds were significantly higher (all *p*<0.05) than the expected median growth. The overall observed mean increase in height by the end of 12 months intervention period was 6.1 (SD=1.07) cm, the highest being for 6-year olds, 6.38 cm (SD=0.84). The mean (SD) HAZ at baseline was -1.35 (0.89) and this was not significantly different between the five age groups (*p*=0.26). Corresponding to the increase in height over 12 months, there was an increase in HAZ across all age groups, mean (SD)=0.14 (0.18). The increase in HAZ was significantly higher for the 6-year-old subjects compared to the 7, 8, 9 and 10 year old subjects, after adjusting for treatment group and baseline HAZ (Table 2). There was only one child (2%) who remained stunted at the end of 12 months of intervention in the 6 year old children, compared to more than 13% in the older age groups. Thus, there was a 12% point reduction in stunting in the 6 year old children, which was significantly higher than the older age groups. There was no significant interaction of sex with the age of the child, on height gain. The increase in height was not significantly different between children who were stunted and normal at baseline (4.7 cm/year; 95% confidence interval: 4.3 to 5.1 for stunted children versus 5.0 cm/year; 95% confidence interval: 4.7 to 5.4 for normal height children).

The average increase in weight was 1.98 kg/year. The mean (SD) BMI for age (BAZ) at baseline was -1.42 (0.95) and this was not significantly different between the five age groups (*p*=0.168). The observed BMI for age (BAZ) at the end of 12 months was higher than that expected for 6, 7, 8, 9- and 10-year groups (Figure 1B). However, the increase in BAZ was significantly lower for the 6 year old subjects compared to the 8, 9 and 10 year olds even after adjusting for intervention group and baseline BAZ (Table 2). The reduction in the prevalence of thinness was significantly higher for all age groups compared to 6 year group. The thinness prevalence increased by 7% points in the 6 year group.

DISCUSSION

The present analysis was carried out to investigate the effect of a one year dairy protein intervention in school going children in urban India. After one year of intervention in primary school children, it was observed that the 6-year olds had greater increase in height over the intervention period compared to the expected increase for that age group, as well as compared to older children. This resulted in a significant increase in HAZ and consequent reduction in stunting in the 6 year olds, which was greater than the effect observed in the older age groups. The effect on stunting was such that only one child out of 44, remained stunted at the end of one year. In addition, the increase in BAZ was lowest in this age group, indicating a better utilization of the supplemental feeding for height increments.

There are several epidemiological studies and randomized control trials that have suggested that dietary protein
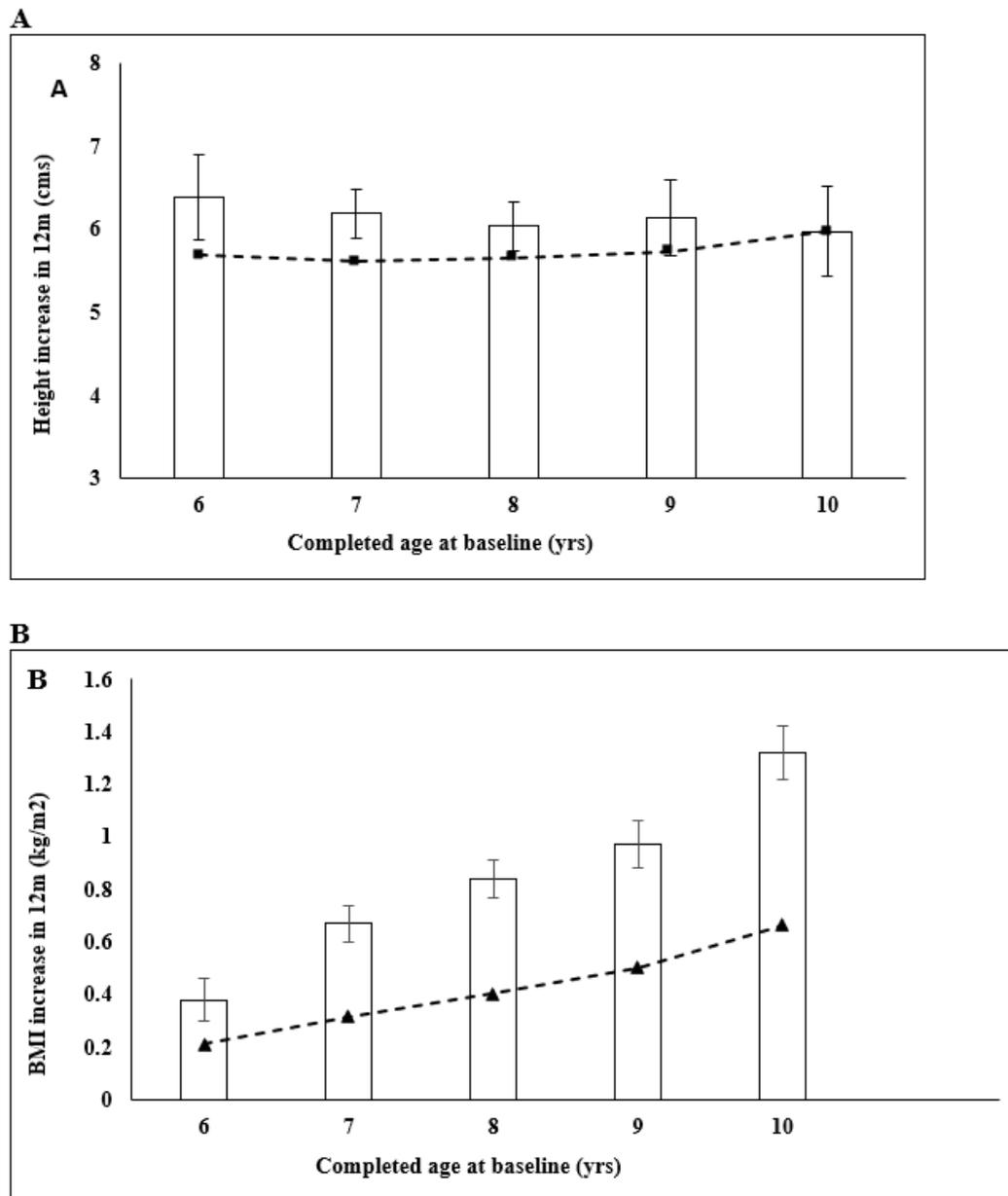
Figure 1. A. Height increase over 12 months of dairy protein intervention by completed age at baseline (n=550). X axis: completed age in years at baseline, Y axis: Increase in height from baseline to 12 months after intervention. Bars represent mean observed increase in height (cms) with 95% confidence interval. Line represent expected increase in height calculated as the difference in median height between adjacent age groups using WHO height for age standard data. The height increase was greater than the expected increase as per WHO standard data for all ages except 10 year old at $p<0.001$. The p value for 10 year old was 0.93. B. Body mass index (BMI) increase over 12 months of dairy protein intervention by age at baseline (n=550). X axis: completed age in years at baseline, Y axis: Increase in BMI from baseline to 12 months after intervention. Bars represent observed increase in BMI (kg/m^2) with 95% confidence interval. Line represent expected increase in BMI calculated as the difference in median BMI between adjacent age groups using WHO BMI for age standard data. The BMI increase was greater than the expected increase as per WHO standard data for all at $p=0.03$ for 6 year olds and $p<0.001$ for other age groups

intake has a role in linear growth in children.[3-6,12,22] Stunted children have lower serum concentrations of all essential amino acids (tryptophan, isoleucine, leucine, valine, methionine, threonine, histidine, phenylalanine, lysine) compared with normal children.[23] A large cohort of pre-menarche girls (9-14 years) showed that those who drank >3 servings per day of milk grew 0.28 cm more in the following year than girls consuming <1 serving per day.[12] An analysis of the macrobiotic diets of nutritionally vulnerable Dutch children (0-8 year old) found that more than 3 servings per day of dairy, compared to 0-2 servings per week, was associated with significantly greater height,

weight and mid-upper arm circumference (MUAC).[24] If there is a burden of co-existing infectious disease, there is a likelihood that this may impose an additional demand on amino acids to support immune function; this may even happen at the expense of growth.[25] This has been demonstrated in an intervention in Bangladesh on mal-nourished children after recovery from shigellosis, where a high-protein diet assisted catch-up growth.[26] Interventions with high dose micronutrient or omega-3 fatty acids supplements were beneficial in reducing duration of common ailments in the same population. The average morbidity rate was about 2 episodes/child/year and was

Table 2. Change in anthropometry at 12 months of dairy protein intervention by age at baseline

	Completed age at baseline (years)[†]				
	6, n=44	7, n=130	8, n=160	9, n=115	10, n=101
Height change, cm[‡]	6.38 (6.12, 6.64)	6.19 (6.04, 6.33)	6.04 (5.89, 6.37)	6.14 (5.91, 6.37)	5.97 (5.70, 6.23)
Height change compared to 6 years[§]	Ref	-0.25 (-0.61, 0.12)	-0.52 (-0.89, -0.14)	-0.53 (-0.96, -0.11)	-0.81 (-1.28, 0.34)
Weight change, kg[‡]	2.64 (2.56, 2.73)	3.13 (3.08, 3.18)	3.54 (3.50, 3.58)	4.03 (3.97, 4.09)	4.91 (4.82, 5.00)
Weight change compared to 6 years[§]	Ref	0.17 (-0.35, 0.69)	-0.67 (-0.59, 0.45)	-0.29 (-0.86, 0.27)	-0.2 (-0.82, 0.41)
HAZ change[‡]	0.22 (0.17, 0.27)	0.18 (0.15, 0.21)	0.14 (0.12, 0.17)	0.12 (0.08, 0.15)	0.07 (0.03, 0.11)
HAZ change compared to 6 years[§]	Ref	-0.05 (-0.11, 0.01)	-0.09 (-0.15, -0.03)	-0.12 (-0.18, -0.06)	-0.16 (-0.22, -0.10)
BAZ difference[‡]	0.122 (-0.01, 0.26)	0.25 (0.16, 0.34)	0.35 (0.26, 0.43)	0.37 (0.28, 0.45)	0.48 (0.39, 0.58)
BAZ change compared to 6 years[§]	Ref	0.13 (-0.05, 0.30)	0.23 (0.06, 0.40)	0.25 (0.07, 0.43)	0.37 (0.19, 0.55)
Difference in % stunted[¶]	-12%	-4% (p=0.026)	-7% (p=0.043)	-6% (p=0.026)	-1% (p=0.01)
Difference in % underweight[¶]	7%	-6% (p=0.02)	-8% (p=0.018)	-9% (p=0.015)	-6% (p=0.023)

HAZ: Height-for-age Z score; BAZ: BMI-for-age Z score
[†]All analysis adjusted for baseline value and intervention group.
[‡]Values are mean (95% confidence interval) change in height (in cm) or weight (in kg) between baseline and endline.
[§]Values are regression coefficients (95% confidence interval) of change in measure from baseline to endline in each age group compared to age group 6 using multiple linear regression adjusted for intervention group and baseline values.
[¶]Values are percentage point change in prevalence of stunting or underweight from baseline to endline in each age group. Negative sign indicates reduction in prevalence and positive sign indicates increase in prevalence. The change from baseline to endline examined using generalized estimation equations with baseline and age group 6 as reference. The p values are for interaction effect of visit and age group with 6 years as reference age.

comparable between the age groups. The duration of morbidity/episode was also comparable.[27]

The protein intervention in this study was dairy protein, and several studies have shown that dairy protein promotes linear growth.[6,7,14] A study from Kenya showed an improvement in height in children 6-14 years when they took a dietary dairy protein supplement. There, the supplement aimed to provide 20% of the required daily energy intake with varying amounts of protein such that the dairy group received 12.7 to 15.2g protein/day,[14] which was comparable to the 13.5g of protein provided in this study. Similarly, younger and stunted children showed a greater rate of height gain in the milk supplemented group in comparison with meat and energy supplemented groups.[14,28] The only evidence on milk protein supplementation from India, although among younger children (1-4 years), showed that children receiving micronutrient supplemented fortified milk powder gained more height in comparison to a control group.[29] Cow milk and dairy products stimulate the release of circulating IGF-I,[30] which positively associates with the increase in linear growth.[31] IGF-1 stimulates proliferation of chondrocytes (cartilage cells), resulting in bone and muscle growth. It stimulates differentiation and proliferation of myoblasts and stimulates amino acid uptake and protein synthesis in muscle and other tissues by binding to the IGF-1 receptor, thereby activating a protein tyrosine phosphorylation signal transduction cascade, similar to the one involved in

insulin action.[32] Plasma IGF-1 levels are affected specifically by protein and energy deficiency but the effect of protein on plasma IGF-1 levels is more pronounced.[33] Linear growth was also shown to be weakly but positively associated with its binding protein-3 (IGFBP-3).[13]

While the impact of quality dietary protein on linear growth is conclusive in pre-school children,[3,28,34] there is very little evidence on the effect of protein intervention on height in children above 6 years. For example, height gains demonstrated in Vietnamese children (aged 7-8 years) supplemented with micronutrient fortified milk, was similar to that in control children.[35] In contrast, in the present study, the increase in height for 6 year old subjects was approximately 0.5 cm greater than that of the older children. Even at 6 months of intervention, the HAZ gain was highest for the 7-year olds (0.06 SD) followed by the 6 and 8 year olds (0.05 SD). The gain in these age groups was greater than that observed in 9 year old children (0.02 SD) and 10 year old children (-0.02 SD).

The height gain observed this study can be attributed to the additional protein intake, but the effect of additional micronutrients is also important. When analysed separately, the height gain in the high micronutrient intervention group was slightly, but significantly, higher than that of other groups. However, within the groups that received high micronutrient supplementation, the effect on height was comparable across all ages, unlike the effect of protein. An important limitation of this secondary analysis is

that there was no control group that did not receive protein supplementation. Thus, the effect of the intervention was examined against cross-sectional growth reference data. However, the nutrition supplements provided for each group were isoenergetic, which facilitated secondary comparisons across years of age for pooled data from four intervention groups. In conclusion, dairy protein and micronutrients can continue to have an effect on linear growth beyond the pre-school age, but the maximal impact might be expected among younger children.

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AUTHOR DISCLOSURES

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Supplemental table 1. Nutritional composition of the intervention products

Nutrients	High micronutrient		Low micronutrient	
	High omega-3	Low omega-3	High omega-3	Low omega-3
Energy (kcal)	420	420	420	420
Protein (g/day)	13.5	13.5	13.5	13.5
Fat (g/day)	9.3	9.3	9.3	9.3
Vitamin A (µg RE/d)	500	500	75	75
Riboflavin (mg/d)	0.9	0.9	0.14	0.14
Vitamin B-6 (mg/d)	1	1	0.15	0.15
Vitamin B-12 (µg/d)	1.8	1.8	0.27	0.27
Folate (µg/d)	300	300	45	45
Vitamin C (mg/d)[2]	227.1	227.1	5.25	5.25
Vitamin E (mg/d)	3.6	3.6	3.6	3.6
Calcium(mg/d)	231	231	105	105
Iodine (µg/d)	100	100	15	15
Iron (mg/d)	18	18	2.7	2.7
Zinc (mg/d)	10.5	10.5	1.7	1.7
Total n-3 (g/d)	1.03	0.14	1.03	0.14
Total n-6 (g/d)	3.7	3.7	3.7	3.7
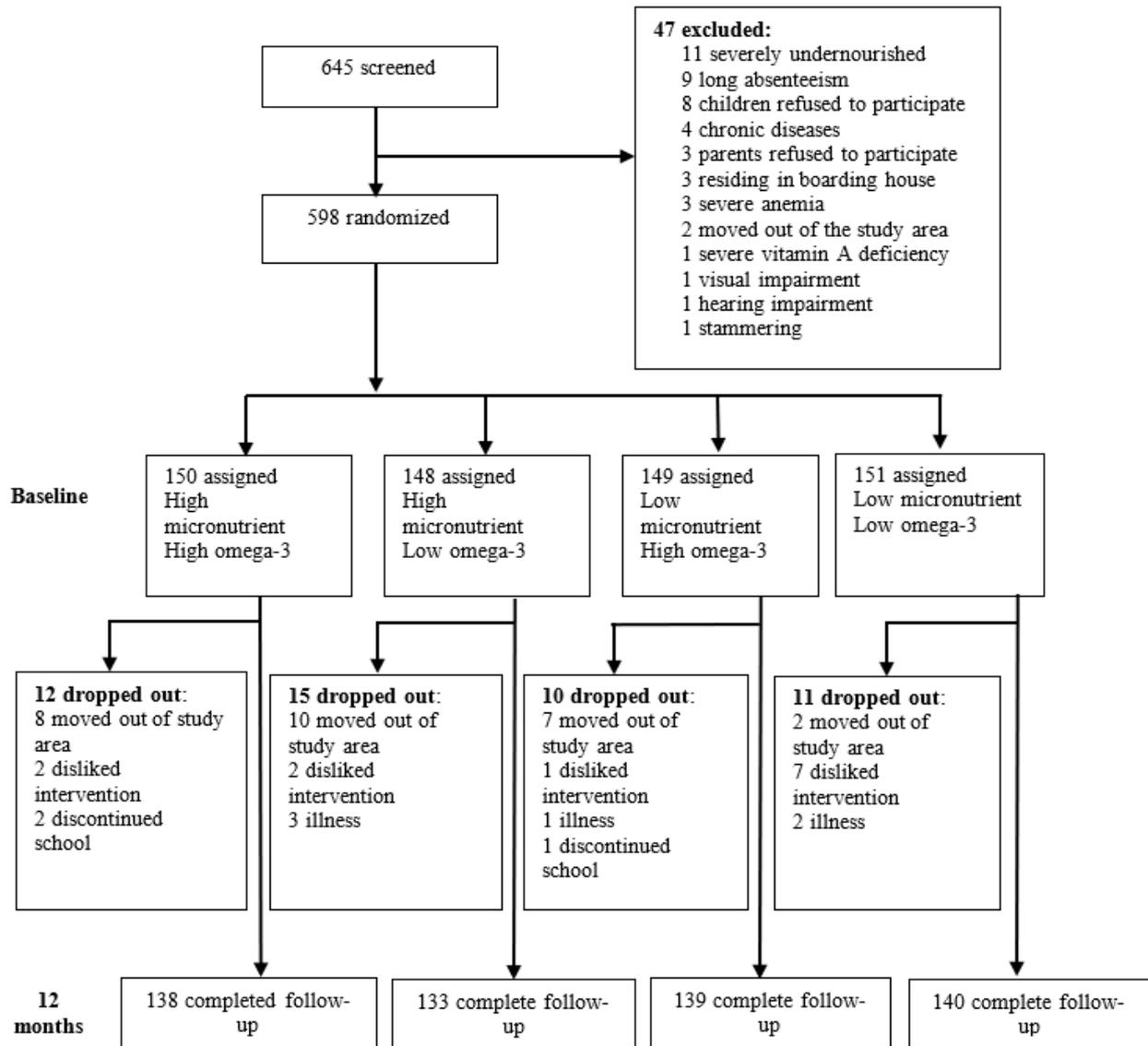
Supplemental figure 1. Participant flow chart.